(Un)erwartete Erweiterungen des Multikatalysekonzeptes

(Un)expected Extensions of the Multicatalysis Concept

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Die vorliegende Arbeit wurde im Zeitraum von Oktober 2010 bis Juli 2016 am Institut für Organische Chemie der Justus-Liebig-Universität Gießen unter der Anleitung von Herrn Prof. Dr. Peter R. Schreiner, Ph.D., angefertigt.

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Ort, Datum Sören Manuel Michael Schuler

Werde, was du noch nicht bist,
Bleibe, was du jetzt schon bist;
In diesem Bleiben und diesem Werden
Liegt alles Schöne hier auf Erden.

Franz Grillparzer (1791-1872)

Für meine Frau

Motivation:

In our highly industrialized era the manufacture of complex products or goods like computers, mobile phones or cars does not take place one by one, but simultaneously and automated. Advantageously, the target products are build-up along an assembly line attaching the corresponding components step by step (Figure 1). Those approaches are especially efficient, effective, and less time-consuming.

Figure 1: Production of VW Beetles.[1]

Based on an analogue concept nature provides a variety of very complex and highly functionalized natural products *via* biosynthesis starting from simple, non-chiral, and easy assessable compounds. One example is the polyketide synthase-mediated macrolactone synthesis. Specialized enzymes fulfill prominent roles performing one step both exclusively and stereoselectively (Figure 2). On the way to the final molecule the corresponding intermediates are passed from one catalytically active unit to the other like in an assembly line (Figure 3).[1]

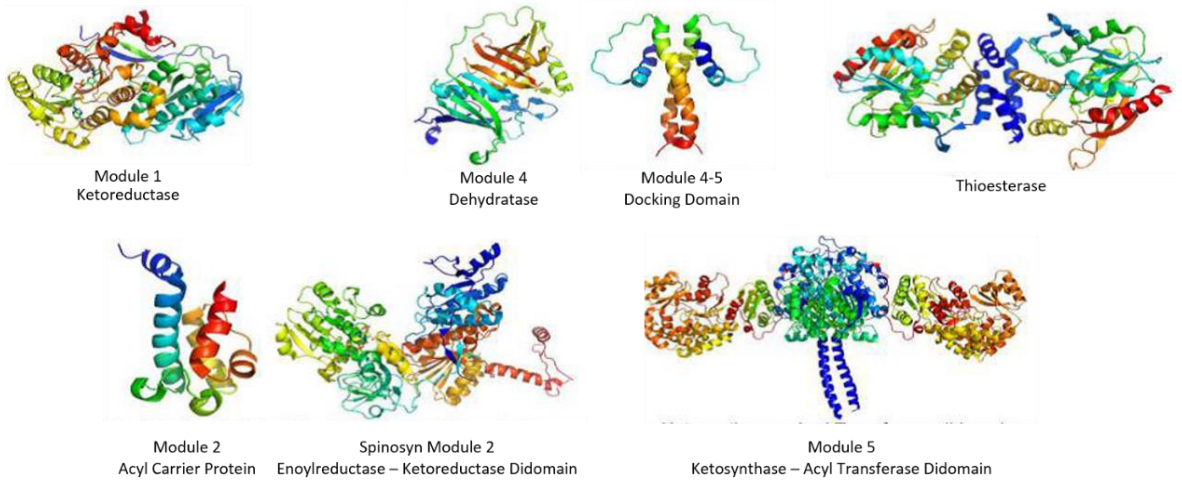


Figure 2: Occurring enzymes.

[1] http://www.welt.de/motor/article118641936/VW-Kaefer-eine-Erfolgsgeschichte-mit-Schatten.html

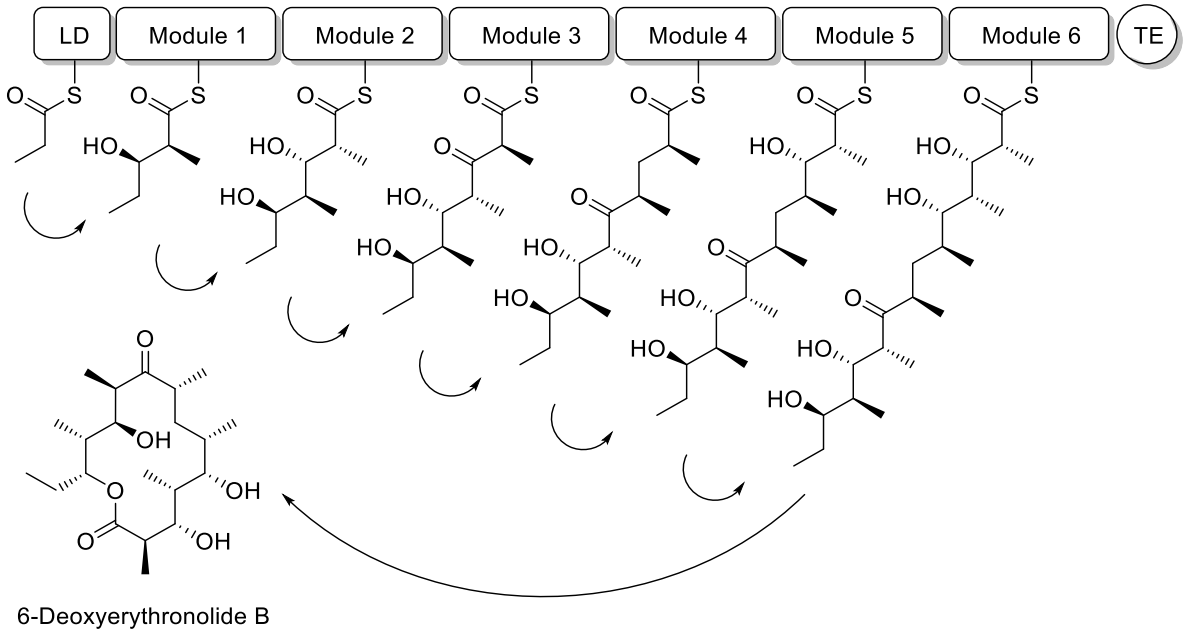


Figure 3: Polyketide synthase.

Since several years, the group of Prof. Peter R. Schreiner is working with peptide-based catalysts. These compounds accelerate also a single reaction exclusively.[2] The combination of different active units separated *via* linkers mimics very, very small enzymes. This approach enables the performance of a special reaction sequence in an assembly line manner. In this context Schreiner *et al.* introduced the terms multicatalyst and retrocatalysis.[3]

Based on previous work the main focus of this thesis is on adding an enantioselective epoxidation to the well-established reaction steps (acylation and oxidation), especially with regard to a new multicatalytic reaction sequence. Therefore, a suitable catalytic moiety has to be identified and incorporated in a peptidic environment. After optimizing the conditions for the separated reaction, the epoxidation should be used as part of the new multicatalytic sequence. Furthermore, starting from generated epoxides a suitable downstream chemistry should be investigated. Lastly, synthesized peptide-based catalysts should also be examined in the context of additional reactions. But, crucial point for all mentioned project is the epoxidation (Figure 4).

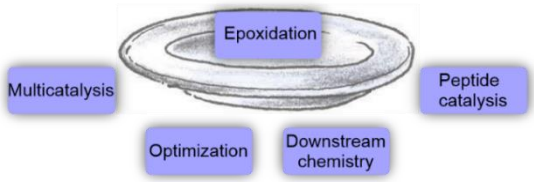


Figure 4: Motivation of this thesis.[2]

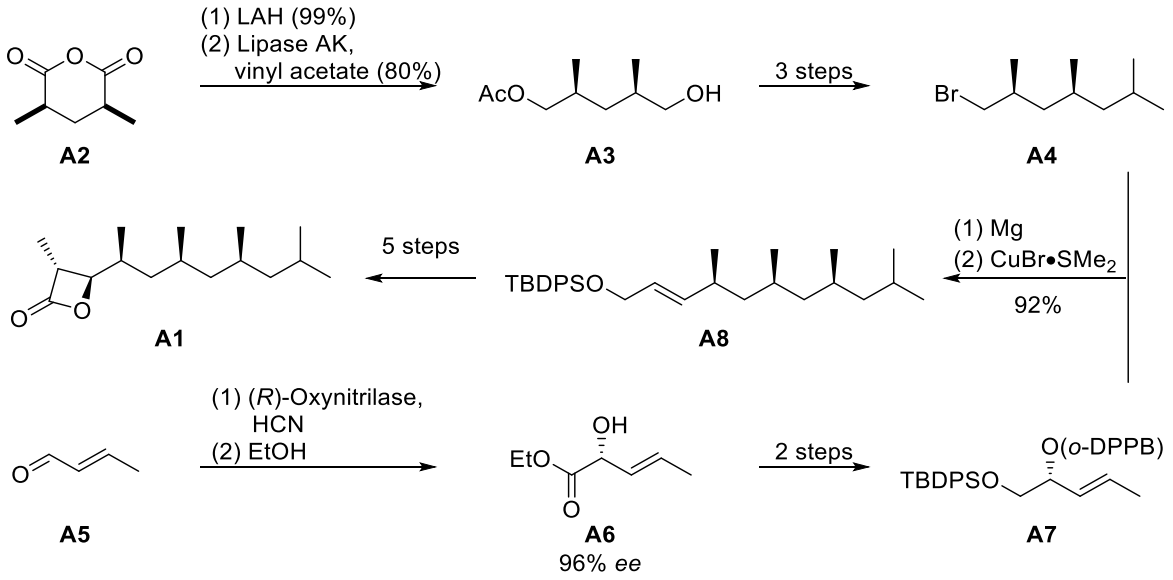
[2] http://www.nibis.de/~niff/material/bild/kueche/original/teller.html

Table of Content

1. Introduction

1.1. Enzyme Catalysis

Enzymes as catalysts are not only used by nature to prepare a necessary molecule. In the meantime, they also find their way into organic laboratories. Especially, due to their high specificity and selectivity they are of high interest for synthetic chemists. In close synergy with typical organic synthesis the enzymatic strategy represents a powerful tool for natural product total synthesis. Associated with complex molecules the mild reaction conditions are a further advantage of this procedure.[4] For example, in 2010 Breit *et al.* published the total synthesis of vittatalactone **A1** combining both strategies (Scheme 1).[5]



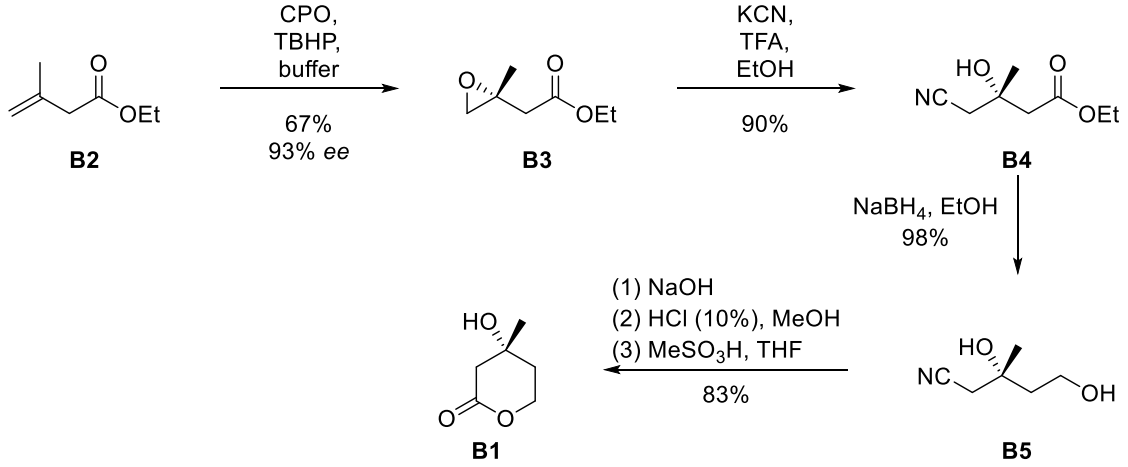
Scheme 1: Total synthesis of vittatalactone **A1**.

In the synthesis of both buildings blocks Breit *et al.* used an enzyme-catalyzed step. After reduction of *meso*-compound **A2** desymmetrization of the formed diol with Lipase AK and vinyl acetate yielded monoacylated product **A3** in 80%. In three additional steps **A3** was transferred into bromide **A4**. The western part of the compound was synthesized *via* hydrogen cyanide addition to crotonaldehyde **A5** in the presence of (*R*)-oxynitrilase. After reaction of the formed cyanohydrin with ethanol ethyl ester **A6** was isolated with an enantiomeric excess (*ee*) of 96%. Starting from this chiral alcohol protected diol **A7** was synthesized in two further steps. Copper-catalyzed allylic substitution provided allylic alcohol **A8** with a yield of 93%. After five additional steps vittatalactone **A1** was obtained with a total yield of 18%.

A variety of different enzymes already find versatile application in their “standard reactions” like esterification or carbon-nitrogen bond formation as well as reduction.

Besides identification of new enzymes for additional transformations investigations of known enzymes in mechanistically related reactions is one of promising aspects for further development in this research area.[6] One growing field with an excellent potential are biocatalytic oxidations. Regarding the aspect of green chemistry due to usage of oxygen or hydrogen peroxide as oxidizing agents this class of reactions can be considered as even more environmentally friendly.[7]

Three different classes of enzymes are capable of epoxidizing carbon-carbon double bonds of aliphatic alkenes: lipases, monooxygenases, and peroxidases.[7] Based on the mechanism lipases provide only the racemic product.[8, 7] In contrast the other ones enable enantioselective reactions. In 1996, Hager *et al.* reported the synthesis of lactone **B1** starting with a peroxidase-mediated epoxidation (Scheme 2).[9]



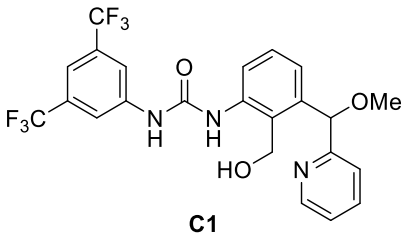
Scheme 2: Synthesis of lactone **B1**.

Epoxidation of **B2** with 0.014 mol% chloroperoxidase (CPO) yielded epoxide **B3** in 67% and with an enantiomeric excess of 93%. Afterwards, epoxide opening and reduction provided γ-hydroxyl nitrile **B5**. Finally, after cyclization lactone **B1** was isolated with a yield of 83%. **B1** was identified to be an important biosynthetic intermediate (IM) in the synthesis of compounds like sterols or terpenes.

Apart from usage in laboratory scale enzymes are also used in industry. Immobilizing those catalysts entails additional advantages like increased stability, recyclability, and continuous product formation. But, a variety of parameters must be taken into account and a direct transfer from one reaction to another might be not possible in some circumstances.[10]

In the field of catalysis chemists can learn a lot from nature. For example, charged intermediates have to be stabilized or the necessary transition state (TS) must be generated. Therefore, plenty

organocatalysts were designed following a model in nature.[11] In 2008, Sakai *et al.* published the trifunctionalized catalyst **C1** containing an oxygen anion-coordinating moiety, a nucleophilic hydroxyl group, and a pyridine unit as base. Thereby, **C1** mimics the active side of a serine hydrolase showing a high catalytic activity (Figure 5).[12]



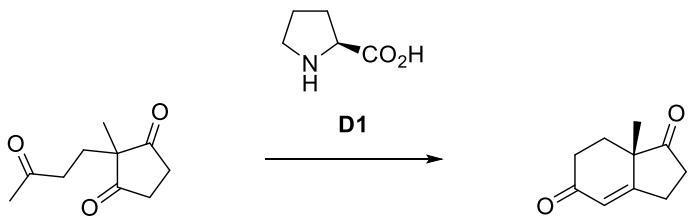
C1

Figure 5: Organocatalyst **C1** mimicking a serine protease.

1.2. Organo-, Peptide and Multicatalysis

1.2.1. Organocatalysis

Apart from already mentioned bio/enzyme and metal catalysis the field of organocatalysis became the third important branch of asymmetric catalysis.[13] It can be divided more precisely by the kind of occurring interactions. Covalent bonds are present, for example, in case of amine or *N*-heterocyclic carbene (NHC) catalysts. On the other hand Brønsted acid or urea species form hydrogen bonds and in case of phase transfer catalysts (PTC) ionic interactions are dominant.[13a, 13b] The phrase 'organocatalysis' was introduced in 2000 by David MacMillan and form the beginning of the 21th century on the activity in the area of organocatalysis and its application started to increase.[14, 13b] Of course, even before 2000 a variety of reactions were performed in the presence of substoichiometric amounts of small organic molecules, which could also be considered as examples for organocatalysis. One very popular example is the proline-catalyzed Hajos-Parrish-Eder-Sauer-Wiechert reaction (Scheme 3). Proline (Pro) **D1** is used to perform an intramolecular aldol reaction. The bicyclic product **D3** was obtained in 70% and with an enantiomeric excess of 97%.[15]



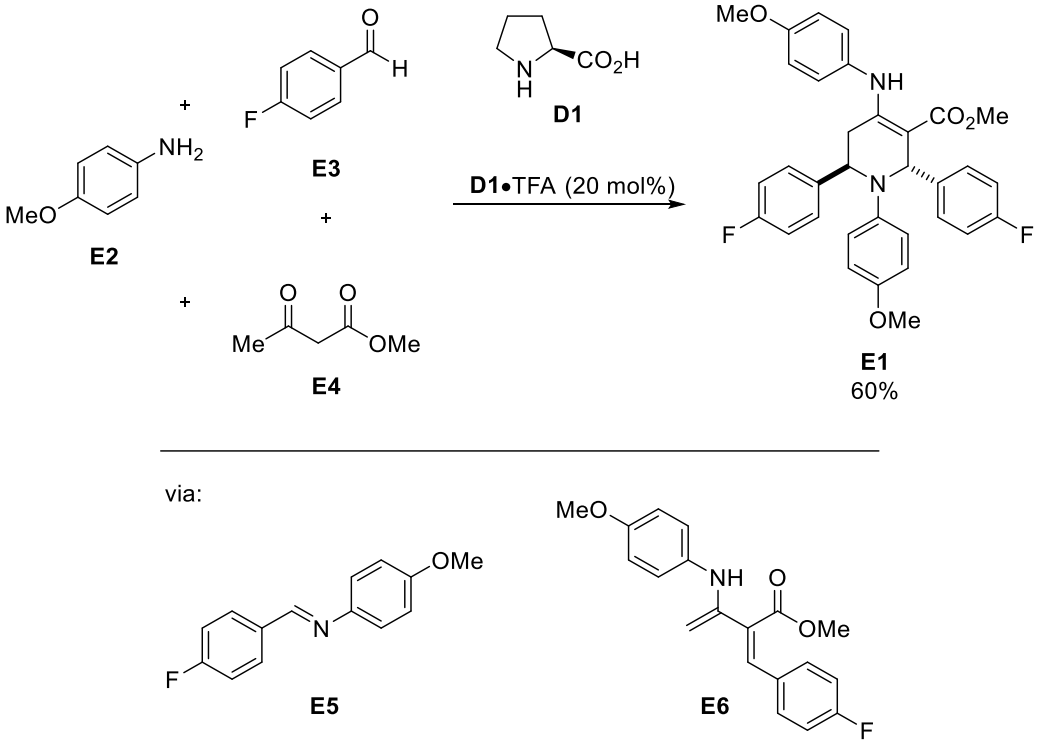
D1

D2

D3
70%
97% *ee*

Scheme 3: Hajos-Parrish-Eder-Sauer-Wiechert reaction.

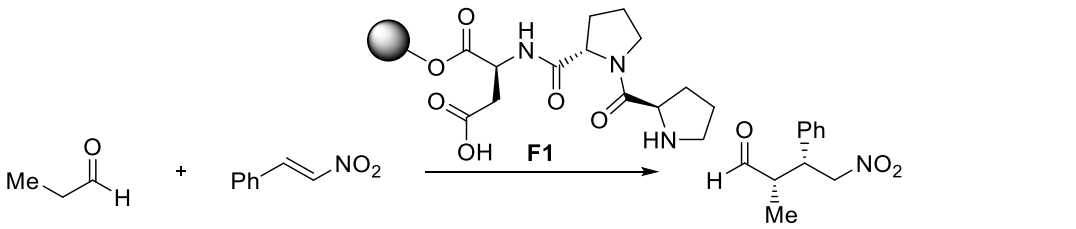
A very important progress was achieved by utilizing organocatalysis in so called domino or multicomponent reactions. Starting from were simple building blocks, which were all added at the same time, highly complex and diverse molecules can be synthesized without isolation of appearing intermediates. Therefore, besides the advantages of organocatalysis (e.g. environment-friendly, enantioselective) these procedures are additionally efficient and atom-economic.[16] Apart from usage in total synthesis organocatalysis is in principle also of interest, for example, for the pharmaceutical industry, because of all the aforementioned properties, but applications are rarely reported.[13c] Using a proline-based approach Tripathi *et al.* synthesized several tetrahydropyridines like **E1**, which have an antimalarial activity (Scheme 4).[17]



Scheme 4: Synthesis of antimalarial agent **E1**.

One equivalent (equiv) aniline **E2** and one equivalent aldehyde **E3** form the corresponding imine **E5**. After enamine formation between **D1**/trifluoroacetic acid (TFA) and **E4**, reaction with aldehyde **E3**, dehydration, and Knoevenagel reaction with aniline **E2** diene **E6** is yielded. After aza-Diels-Alder reaction of building block **E5** and **E6** target compound **E1** was isolated after 18 hours with a yield of 60%. Due to formation of prochiral intermediate **E6 E1** is finally obtained as *trans*-configured racemate. I*n vitro* screening against *Plasmodium falciparum* tetrahydropyridine **E1** showed a 100% inhibition at a concentration (conc.) of 0.09 µg mL^{-1}.

Although, higher amounts of catalysts might still be necessary for some organocatalyzed transformations improvements regarding low-loading were already made.[13a] But, especially to achieve further progress considering scale-up and industrial applications performing reactions in continuous-flow is also an intensively studied aspect in the context of organocatalysis.[18] In 2012, Fülöp *et al.* reported an 1,4-addition of aldehydes like **F2** and nitroalkene **F3** in the presence of immobilized acid catalyst **F1** under continuous-flow conditions (Scheme 5).[19]



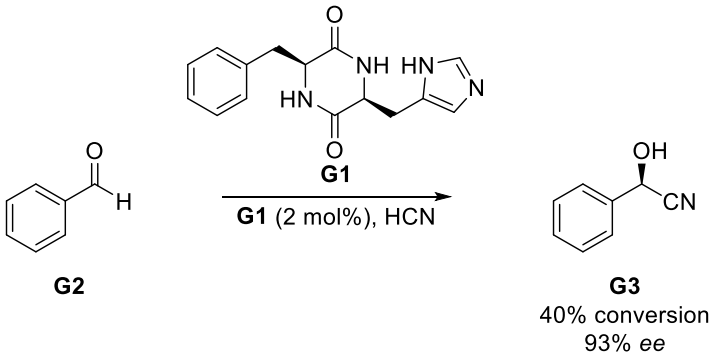
Scheme 5: Immobilized catalyst **F1** in an 1,4-addition utilizing continuous-flow conditions.

After reaction of aldehyde **F2** and olefin **F3** catalyzed by immobilized tripeptides **F1** under continuous-flow-conditions nitro-substituted aldehyde **F4** was isolated with a yield of 91% and an enantiomeric excess of 93% for the major isomer. A simultaneously performed experiment with standard batch conditions produced nearly the same result.

1.2.2. Peptide Catalysis

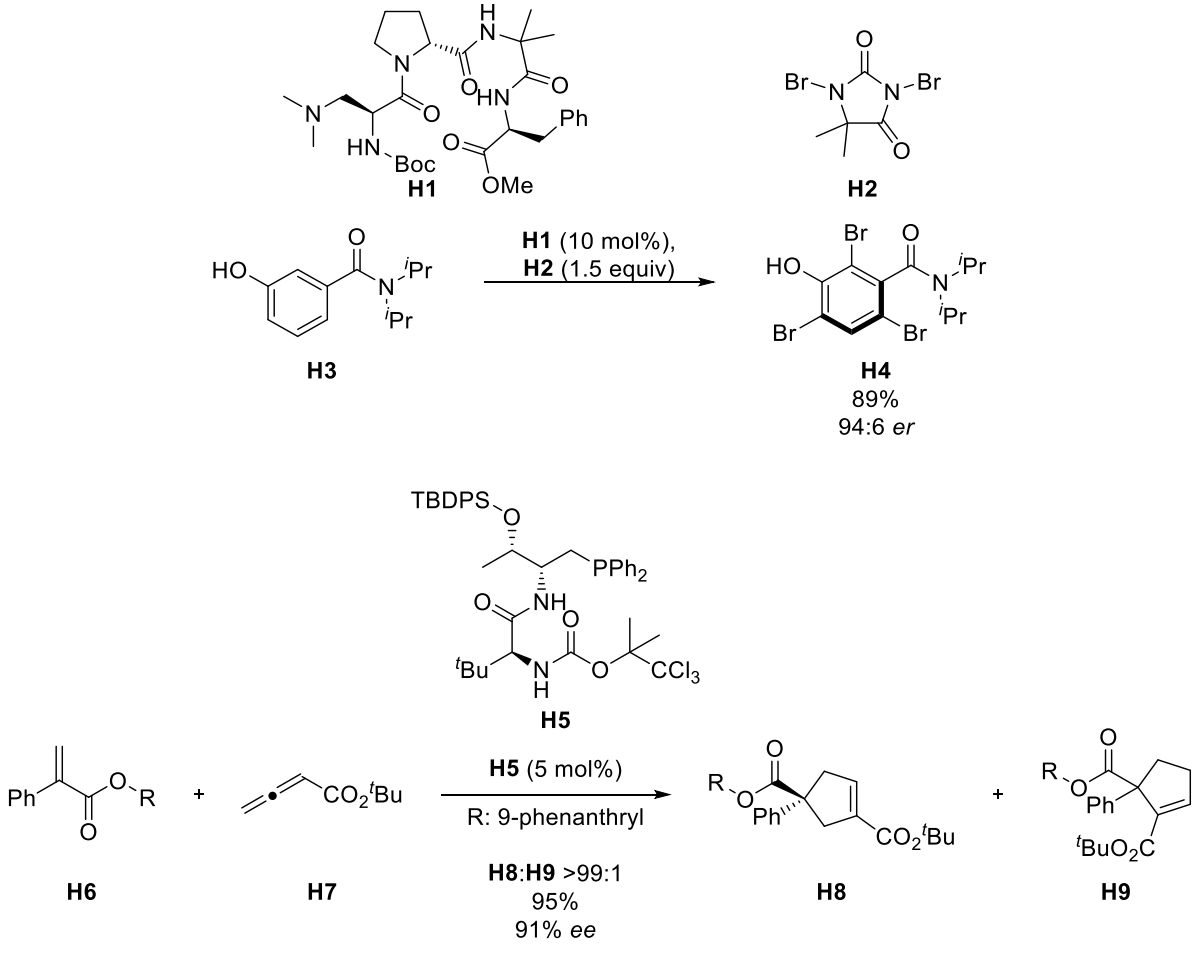
As the last example illustrates, besides amino compounds, Brønsted/Lewis acids and bases, PTCs, *N*-heterocyclic carbene precursors as well as compounds, which can form hydrogen bonds,[13a] peptides can also act as organocatalysts owing of a course a closer resemblance to enzymes. Especially, flexible and modular synthetic availability in combination with the possibility to adopt well-defined secondary structures makes oligopeptides to a potent class of organocatalysts. Their typical chain-length are between 2 and 50 monomers.[20] One of the first examples was the dipeptide-mediated enantioselective synthesis of cyanohydrin reported by Inoue *et al.* in 1979/1981 (Scheme 6).[21]

In the presence of diketopiperazine **G1** addition of HCN on benzaldehyde **G2** takes place. After 30 minutes conversion (conv.) of 40% and an enantiomeric excess of 93% were observed for primary alcohol **G3**. But astonishingly, racemization of cyanohydrin **G3** occurs over time. After 72 hours the conversion increased to 90%, but the enantiomeric excess decreased to only 12%.



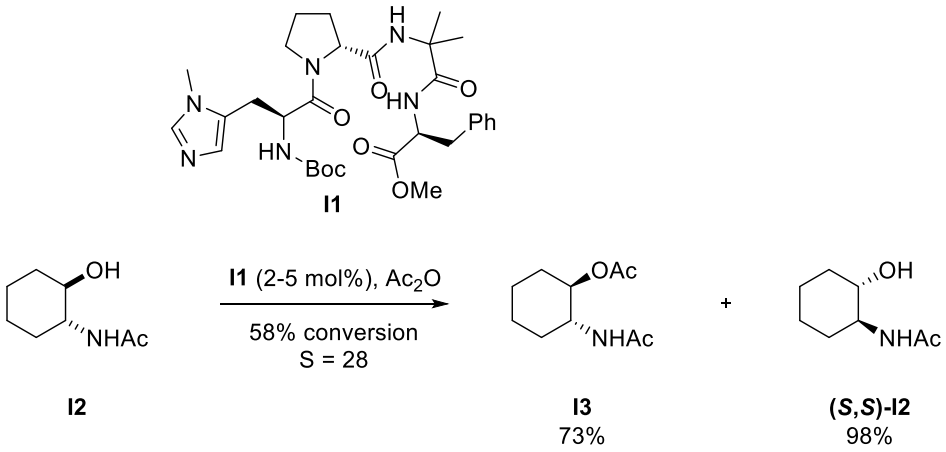
Scheme 6: Diketopiperazine-mediated cyanohydrin synthesis.

Of course, larger systems than dipeptides were considered as well and until now a variety of different reaction types were identified being catalyzed by those systems.[20] The usage of peptide or peptide-based catalysts was, for example, published for Morita-Baylis-Hillman reaction,[22] Friedel-Crafts-type alkylation,[23] and conjugated addition[19, 24] with and without an immobilized system. Catalyzed bromination in the presence of **H1** reported be Miller *et al.* and [3+2] cycloaddition with dipeptide-derived phosphine **H5** described by Lu *et al.* are depicted exemplarily as further possible applications (Scheme 7).[25]



Scheme 7: Two possible examples for peptide-based or peptide-derived catalysts.

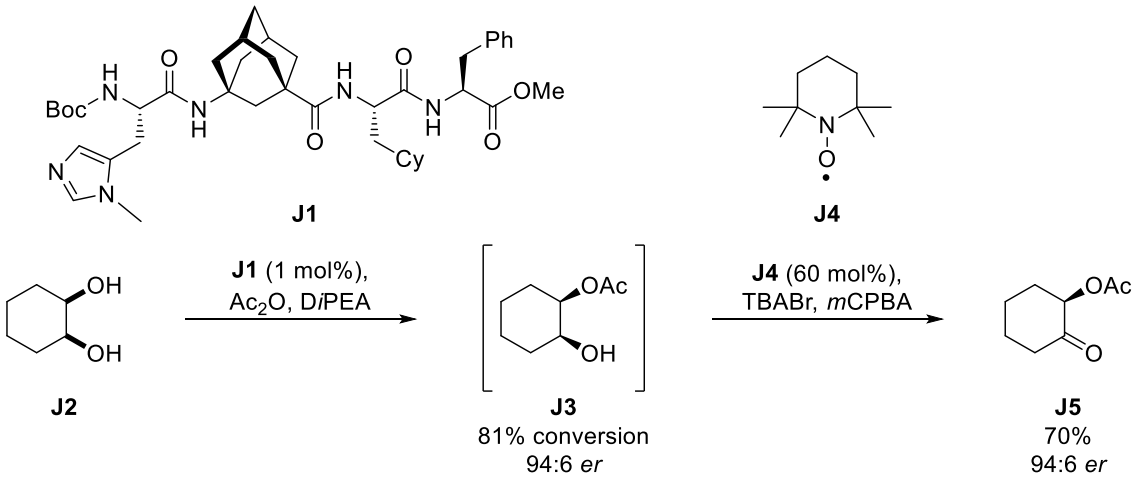
A further very intensively studied example is the peptide-catalyzed acylation of alcohols. This is one type of reaction, which will be important for this thesis. In 1998, Miller *et al.* published the kinetic resolution of *N*-acylated alcohols (Scheme 8).[26] π-Methyl histidine-functionalized (PMH) tripeptide **I1** acts as nucleophilic catalyst. In the same year they reported a similar system and proposed the intermediately formed imidazolium species incorporated in the chiral peptide backbone is essential for transferring the acetyl group onto the free alcohol in a selective way.[27] A selective acylation of alcohols is of great importance for the natural product class of carbohydrates regarding the regioselective introduction of protecting groups (PG). Miller *et al.* transferred their approach onto polyols showing first promising results, but also emphasizing the challenge as well as possible solutions for those substrates.[28]



Scheme 8: Kinetic resolution of *N*-acylated alcohol **I2**.

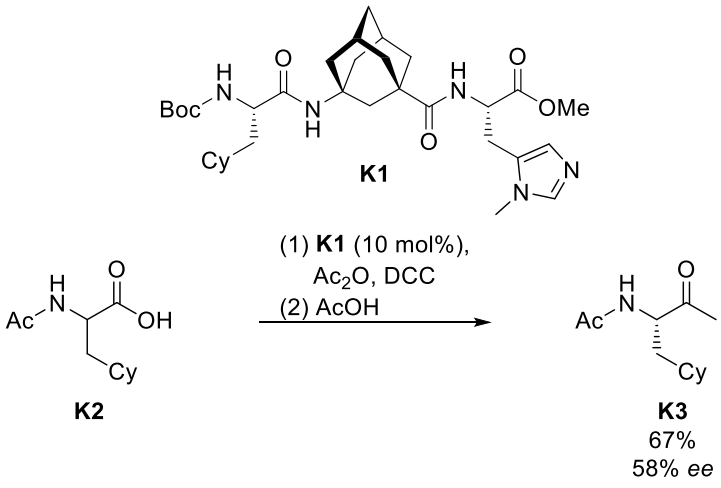
In 2008, Schreiner *et al.* published a catalytic system on basis of PMH, which is able to perform the kinetic resolution of *trans*-cycloalkane-1,2-diols in a highly selective fashion. In contrast to Miller's proline-based catalyst they utilized an *γ*-adamantyl amino acid (AdGly, for the sake of convenience) as core structure. During permutation of the amino acid sequence they identified cyclohexylalanine (Cha) as second unnatural building block necessary for their oligopeptide catalyst. Based on molecular dynamic considerations they concluded that besides hydrogen bonding hydrophobic interactions and a pocket-shaped structure of the oligopeptide are essential for a selective acetyl transfer.[2a] One year later Sunoj *et al.* proofed this observation *via* density functional theory (DFT) calculations.[29] Due to the optimal yield of 50% in case of a kinetic resolution Schreiner *et al.* focused on *meso*-diols because in case of a desymmetrization 100% yield can be achieved. But, they observed that after acylation of **J2** with their already established oligopeptide **J1** monoacylated diol **J3** racemized during purification *via* intramolecular acetyl transfer. To address this finding they performed an add-on oxidation of the remaining hydroxyl group to its corresponding ketone with

substoichiometric amounts of 2,2,6,6-tetramethylpiperidin-1-yl)oxyl **J4** (TEMPO) (Scheme 9).[2b] After purification α-acetoxy ketone **J5** was isolated with a yield of 70%. The enantiomeric ratio (*er*) after oxidation was the same for target compound **J5** compared with its monoacylated non-oxidized derivative **J3**.[2b] Considering the computations of Sunoj *et al.* the proposed *cis*-(1*R*,2*S*)-2-hydroxycyclohexyl acetate **J3** forms preferentially during desymmetrization.[29]



Scheme 9: Desymmetrization of *meso*-cyclohexane-1,2-diol **J2** with peptide-catalyst **J1**.

Schreiner and co-workers extended the application of their catalytic system. In 2010, they published the peptide-mediated Steglich esterification. The necessary anhydride is formed *in situ* from the corresponding carboxylic acid in the presence of a carbodiimide as dehydration and activation agent. Due to this approach acyl species can be transferred to an alcohol which has no stable or commercially available anhydride.[2c] Six years later they used an analogue oligopeptide catalyst in the first enantioselective Dakin-West reaction (Scheme 10).[30]

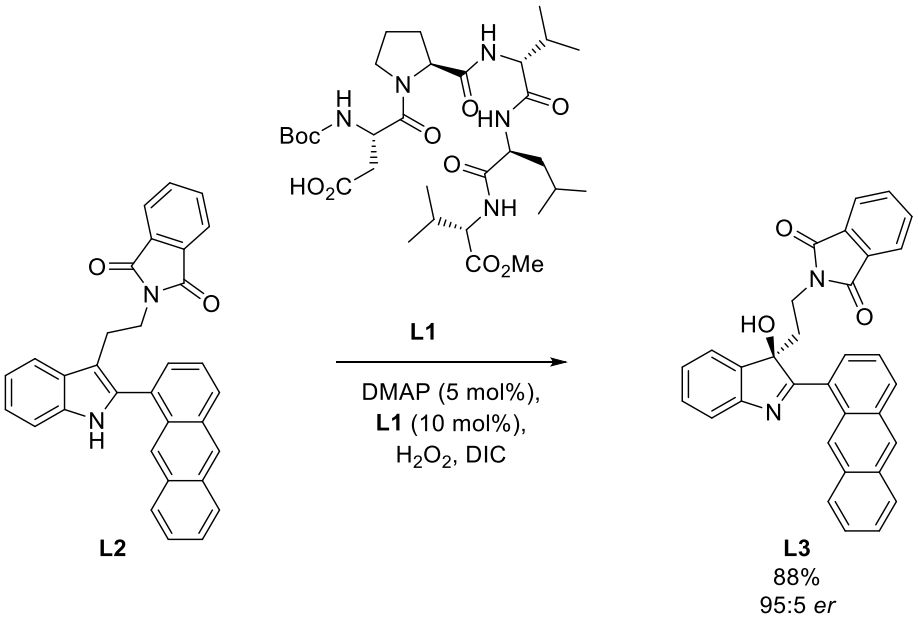


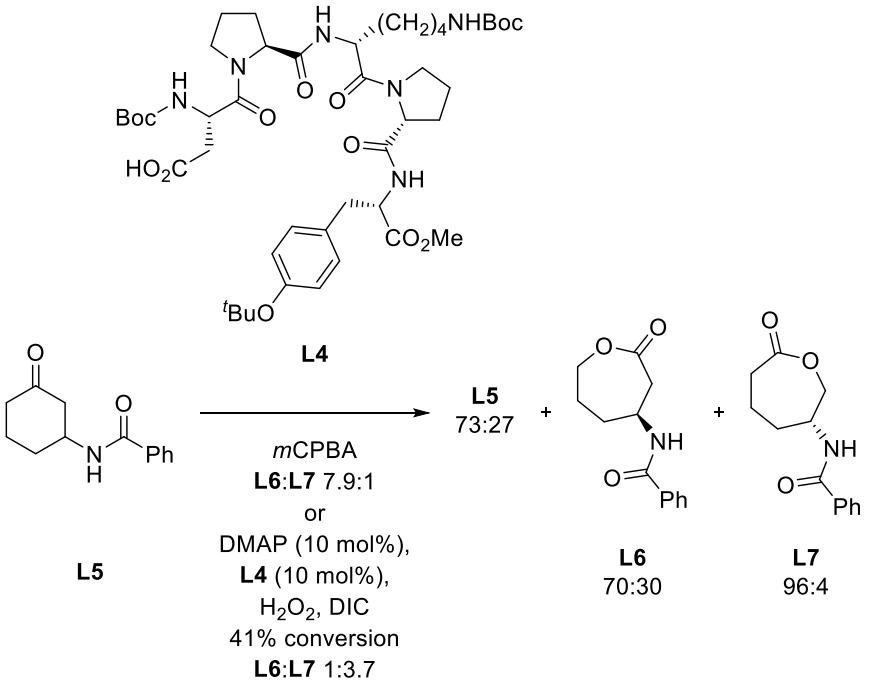
Scheme 10: First enantioselective Dakin-West reaction.

Tripeptide **K1** is involved in the acylation of the formed azlactone and the decarboxylative protonation, which is mechanistically not yet fully understood, yielding final product **K3**. The best result was obtained for cyclohexylalanine, which can be explained by the important role of dispersion interactions between catalytic system and side chain of the amino acid.

The second type of reactions, which is essential for this thesis besides acylations, are oxidation reactions. Epoxidation (Chapter 1.3.) and sulfoxidation (Chapter 5.3.) special types of oxidations are introduced separately. Two additional examples in this context are shown in scheme 11.

In 2011, Miller and co-worker reported the selective oxidation of indoles *via* a peptide catalyst **L1** containing an aspartic acid as catalytically active moiety.[31] The peptidic system is able to oxidize the nitrogen heterocycle **L2** in the presence of catalytic amounts of 4-dimethylaminopyridine (DMAP) both chemo- and enantioselectively (Scheme 11). For years later they used the similar system **L4** for the asymmetric Baeyer-Villiger oxidation (Scheme 11).[32] In this case the introduction of the oxygen proceeded enantio- and regioselectively. They observed a parallel kinetic resolution of both possible products **L6** and **L7** as well as the preferred formation of **L7**, which is the less favored product utilizing *meta*-chloroperoxybenzoic acid (*m*CPBA) as oxidizing agent. They introduced the strategy of carboxylic acid-containing peptides for oxidative reactions firstly in the enantioselective epoxidation of cyclohexene derivatives in 2007 (Chapter 1.3.2.1).[33] In this context the showed a postulated mechanism based on peracid formation *via* carbodiimide activation and hydrogen peroxide addition and explained the role of DMAP in more detail (Chapter 4.3.1).

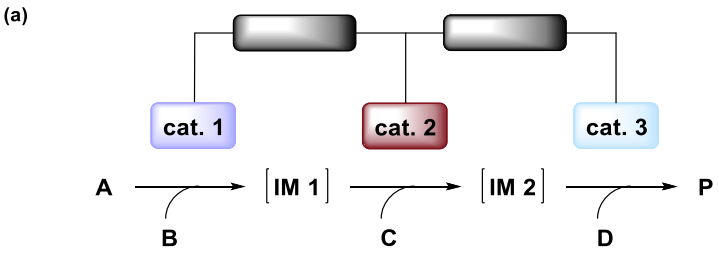




Scheme 11: Examples for peptide-based oxidation reactions.

1.2.3. Peptide-Based Multicalatysis

As shown for the polyketide synthase (Figure 2 and 3)[1] nature can produce complex compounds *via* multistep processes and in a linear manner. Occurring intermediates are passed from one catalytic part to the other. Even if atom, redox-, and step economy are not optimal for all biosynthetic procedures, for synthetic chemists their efficiency is quite high. In 2015, Kirschning *et al.* reviewed these comparable aspects between nature and organic synthesis. They showed, for example, that a domino reaction or a multicatalytic approach are useful tools mimicking natural principles in organic laboratories.[34] Already three years before Schreiner *et al.* published a review focusing more on the synthetic application of multicatalysis with organocatalysts. After describing different models of multicatalytic teamwork they illustrated its potency based on several examples of distinct catalyst combinations. Finally they introduced the concepts of a multicatalyst and retrocatalysis (Figure 6).[3c]



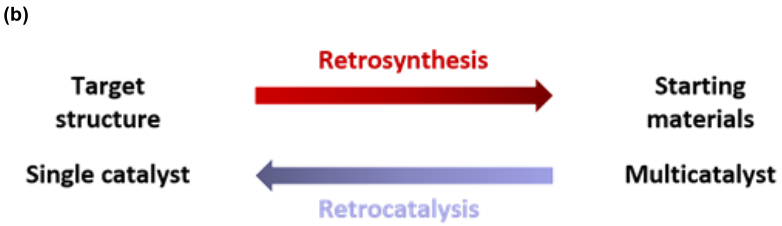


Figure 6: Multicatalyst and retrocatalysis concept.

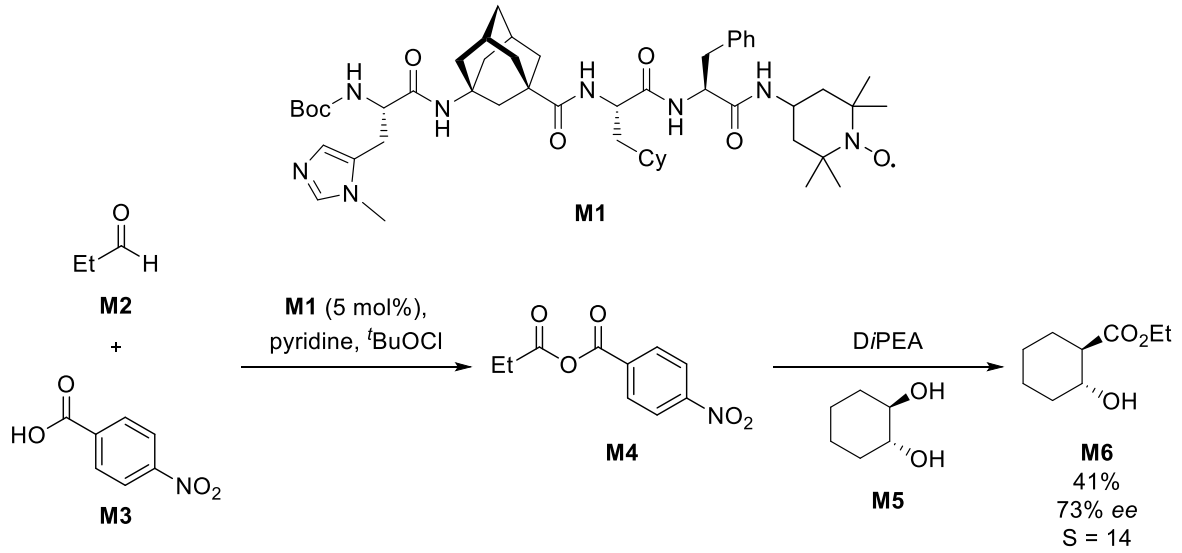
In a multicatalyst all catalytic active moieties or precursors are fixed at one common backbone separated by suitable spacers. The catalyst is present from the beginning while the different reagents are added stepwise. Staring material A is converted into product P *via* intermediates IM1 and IM2, which are not isolated or purified (Figure 6 (a)). Besides simplified dealing with unstable intermediates the multicatalyst approach is also less time and resource-consuming. Furthermore, with regard to reuse only one catalyst has to be recovered.[3c]

A multicatalyst can therefore be considered as an ensemble of single catalysts. Like a target molecule can be divided into its necessary starting materials *via* retrosynthesis the two different catalytic species are connected *via* the concept of retrocatalysis. Both principles can be used in parallel to identify potential educts and an appropriate multicatalyst to obtain the desired target compound (Figure 6 (b)).[3c]

Several requirements must be fulfilled for a multicatalyst to achieve an efficient functioning. Beside an orthogonal reactivity the utilized catalytic moieties are not allowed to interfere or inhibit each other. A suitable spacer and/or backbone have to be identified ensuring a defined structure associated with an asymmetric reaction.[3a]

With a closer look on the desymmetrization-oxidation sequence (Scheme 9) and the "similarity" of oligopeptide catalysts and enzymes in mind it was obvious to fix PMH and the TEMPO moieties on one common peptide backbone. After catalyst screening they identified functionalized peptide **M1** as the catalyst of choice (Scheme 12). They found out that separation of the distinct moieties by three amino acids *via* substitution of the methyl ester of **J1** (Scheme 9) with TEMPO amine has no effect on the three-dimensional structure. With the first organocatalytic multicatalyst **M1** they obtained α-acetoxy ketone **J5** with a yield of 70% and an enantiomeric ratio of 88:12. Astonishingly, the amount of TEMPO catalyst could be reduced from 60 to 5 mol% and only three equivalents of *m*CPBA were necessary to achieve nearly the same result.[3a]

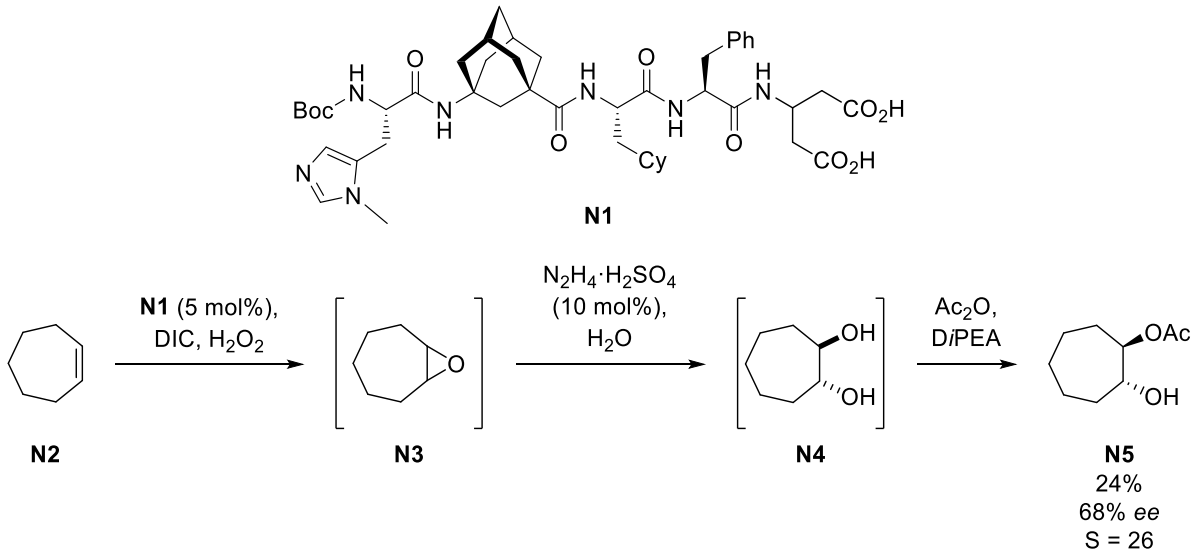
In the next years, Schreiner *et al.* reported three further sequences with a multicatalyst. In 2014, they showed that instead of changing the catalytic moieties in retrocatalytic manner the involved reaction steps can be inverted. The utilized multicatalyst **M1** in an oxidative esterification (Scheme 12).[3d]



Scheme 12: Oxidative esterification with multicatalyst **M1**.

In the first reaction step mixed anhydride **M3** was formed under oxidative conditions starting from aldehyde **M2** and *para*-nitrobenzoic acid (*p*NBA) **M3**. The smaller part of **M3** was finally transferred onto *trans*-diol **M5**. Monoacylated product **M6** was obtained with a conversion of 41% and an enantiomeric excess of 73%. In line with possible acylium sources beginning with anhydride,[2a] acid,[2c] and aldehyde[3d] Schreiner *et al.* also established an "alcohol cross coupling". In 2016, they published the multicatalytic kinetic resolution of *trans*-cyclohexanediols and the corresponding alcohols in the presence of catalytic system **M1**. Different mono- as well as diols were utilized and good yields and enantioselectivities were realized.[35]

It was also possible to extent the kinetic resolution of *trans*-1,2-cycloalkanediols to a multicatalyst approach. In 2012, Schreiner *et al.* published an epoxidation-epoxide opening-acylation sequence. For this three-step procedure they substituted the methyl ester of **J1** *via* a homoaspartic acid motif, which is able to epoxidize the carbon-carbon double bond in the first step (Scheme 13).[3b]



Scheme 13: Kinetic resolution of diol **N4** with multicatalyst **N1** starting from the corresponding olefin **N2**.

Starting form cycloheptene **N2** the diacid moiety mediates the epoxidation to oxirane **N3** by *in situ* formation of its peracid in the presence of diisopropylcarbodiimide (DIC) and hydrogen peroxide. The three-membered ring is opened by the additional catalyst hydrazine sulfate and ten equivalents of water. Finally, the temporarily formed *trans*-diol **N4** is selectively acylated by PMH as catalytically active species. Best results were obtained for the seven-membered system **N5** with an *S*-value of 26. The detailed mechanism was elucidated in 2015 by Schrader *et al. via* MS techniques[36] and the epoxidation part is shown in chapter 4.3.1. in more detail.

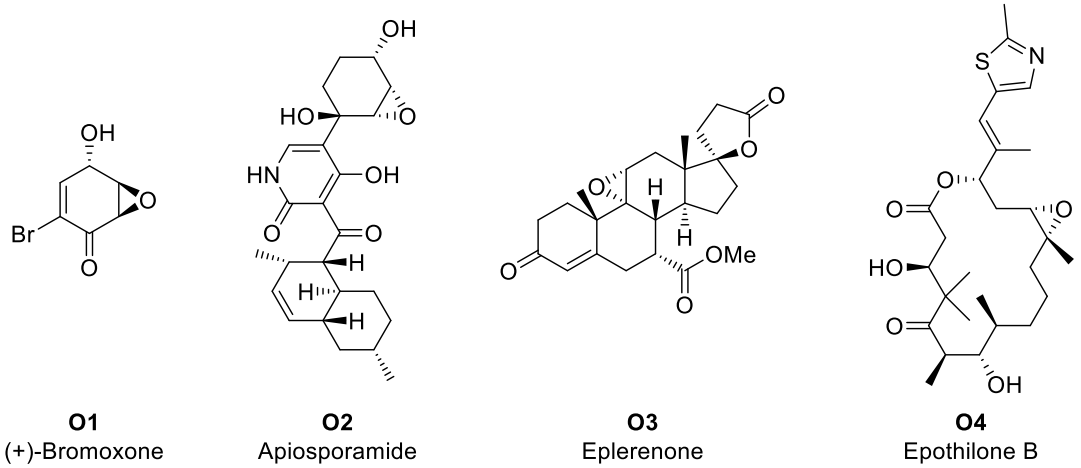
1.3. Epoxidation

In the last-mentioned multicatalytic sequence the asymmetric information was introduced in the acylation step. From a synthetic point of view and considering especially complex target compounds, it would be worthwhile to carry out the first step of a sequence in an enantioselective manner. Therefore, the focus of this thesis lays on the identification of an asymmetric epoxidation strategy based on peptidic platform.

1.3.1. Occurrence of Epoxides

Due to their ring structure epoxides are highly reactive species. Therefore, they are used as a versatile class of starting materials. Besides finding application in polymer chemistry[37] oxiranes can be opened with a variety of different nucleophiles (Nu) using carbon- or heteroatom-based reactants. Depending on the nature of the nucleophilic component, for example, α-halogenated or α-amidated alcohols can be obtained. Moreover, the potential access to two defined stereogenic centers in parallel become important in this regard.[38] In our context the epoxide opening mediated by an organocatalysts is of course of peculiar interest.[38c]

But, besides being starting material or intermediate in a reaction epoxides are also part of different natural products or drugs. Starting from both electron-rich or electron-deficient double bonds one of the possible enantiomers is highly relevant for the corresponding target molecule (Figure 7).



O1 (+)-Bromoxone **O2** Apiosporamide **O3** Eplerenone **O4** Epothilone B

Figure 7: Examples for oxirane-containing natural products or drugs.

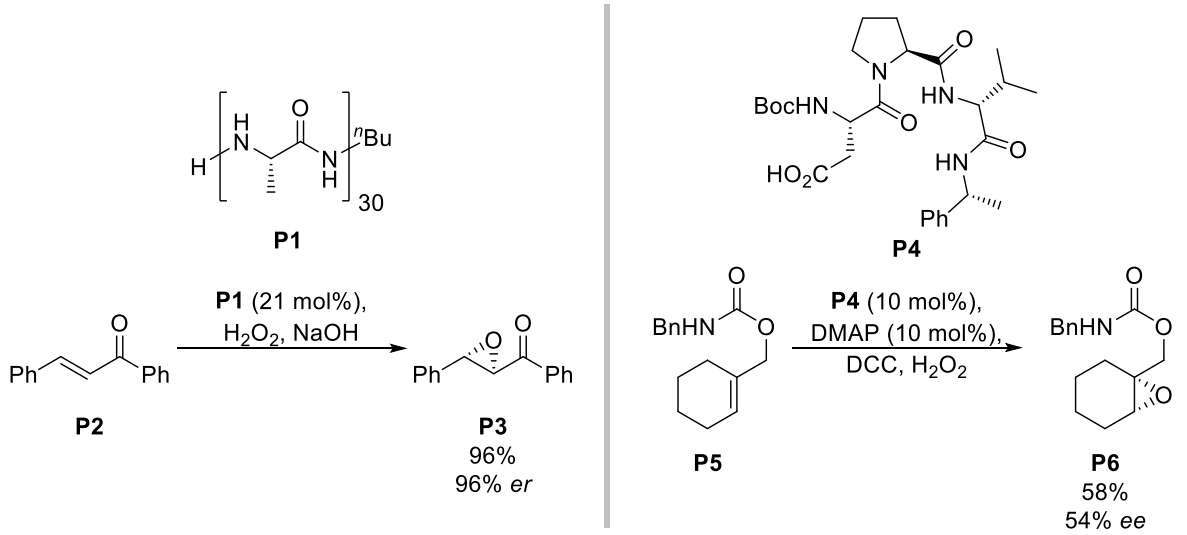
The acetate of bromoxone **O1** was isolated from a marine acorn worm and possesses an antitumor activity. Its total synthesis starting from a chiral building block was reported in 2003 by Kitahara and co-workers.[39] Secondly, the relative and absolute configuration of apiosporamide **O2** was elucidated by Williams *et al.* in 2005 after total synthesis. It is described that their target compound was isolated from a fungus and is both antifungal as well as antibacterial active.[40] Thirdly, Wuts *et al.* synthesized eplerenone **O3** in a chemobiological way in 2008. This compound is utilized for the treatment of hypertension and congestive heart failure.[41] Macrolactone **O4** belongs to a group of similar compounds, which were isolated for myxobacteria *Sorangium cellulosum.* A total synthesis was reported in 2012 by Lin and co-workers. Epothilone B is approved for the treatment of breast cancer and further applications are still under investigation.[42]

1.3.2. Organocatalytic-Based Synthesis of Epoxides

As mentioned in the motivation the main focus of this thesis is on the affiliation of the epoxidation as further type of reaction in context of multicatalysis. In combination with our peptide-based scaffold an organic precursor or catalytic moiety (CM) is preferred. Very prominent strategies are, for example, peptide-, phase-transfer-catalyst-, imine-/enamine-, iminium- and, chiral ketone-based organocatalytic variants.[43] Therefore, those well-established methods are described based on selected examples.

1.3.2.1. Peptide-Based Epoxidation

The first epoxidation, which was carried out with a peptide, was the Juliá-Colonna epoxidation. The polyamino acid-mediated reaction was published in 1982 and is also often denoted as one of the first organocatalyzed reactions (Scheme 14).[44] The second example is the oxirane formation with a carboxylic acid-containing oligopeptide, like it was already introduced in the oxidation of indoles and the Baeyer-Villiger oxidation (Scheme 11). In 2007 Miller *et al.* reported the reaction of substituted olefins to their corresponding oxiranes (Scheme 14).[33]



Scheme 14: Exemplary peptide-based epoxidations.

In the Juliá-Colonna epoxidation polypeptide **P1** catalyzes the reaction of *α,β*-unsaturated ketone **P2** to its oxirane **P3**. The desired product was obtained with a yield of 96% and an enantiomeric excess of 96%. In 2004, Colonna *et al.* showed in mechanistic investigations that the catalyst coordinates the formed hydroperoxide enolate. Afterwards, the oxygen atom is transferred selectively on the double bond.[45, 43e] In case of aspartic acid-containing peptide catalyst **P4** dicyclohexylcarbodiimide (DCC) and hydrogen peroxide form the reactive peracid *in situ*. In contrast to addition of the reactive species on electron-deficient substrate **P2**,[45] the carbon-carbon double bond is epoxidized in a concerted manner (Chapter 4.3.1). Epoxy cyclohexane derivative **P6** was obtained with a yield of 58% and an enantioselective excess of 54%.

1.3.2.2. Phase Transfer Catalysts

With, for example, hydrogen peroxide as oxidizing agent utilized in a biphasic system in the presence of a base the reactive species hydroperoxide enolate has to be transported form the aqueous (aq) to the organic phase. This interfering property is the huge advantage of a PTC

(Figure 8).[43f] Besides epoxidations they are also used, for example, in alkylations, Mannich reactions, and fluorinations.[46]

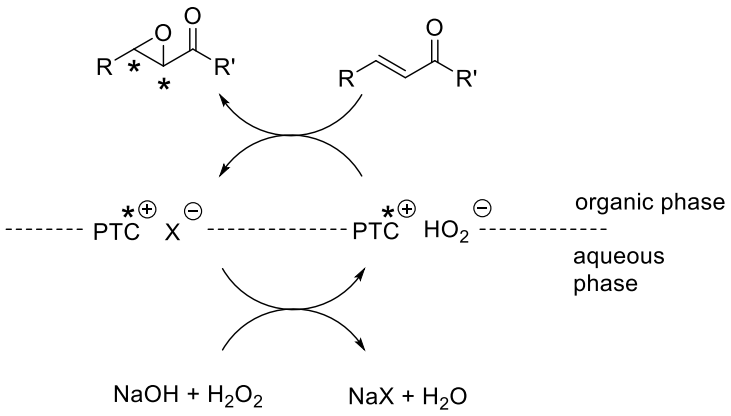


Figure 8: Schematic depiction of the functionality of a PTC.

In the aqueous phase sodium hydroxide deprotonates hydrogen peroxide. By replacement of the anion the formed hydroperoxide enolate is transported into the organic layer by the PTC. In the environment of a chiral cationic counterpart the oxygen is transferred onto the olefin in a selective fashion. Four different types of PTCs are depicted in figure 9 utilizing this concept.

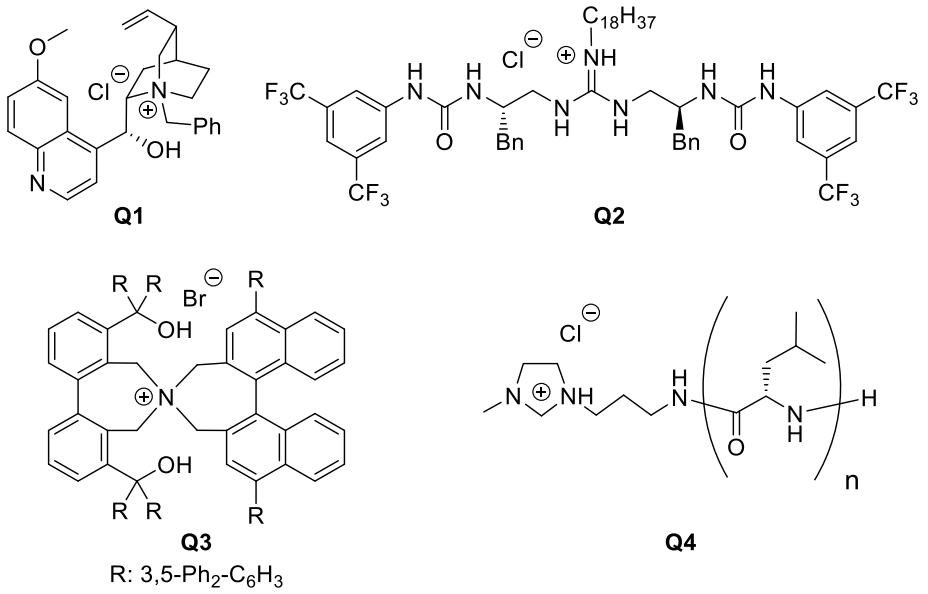


Figure 9: Selected examples of PTCs.

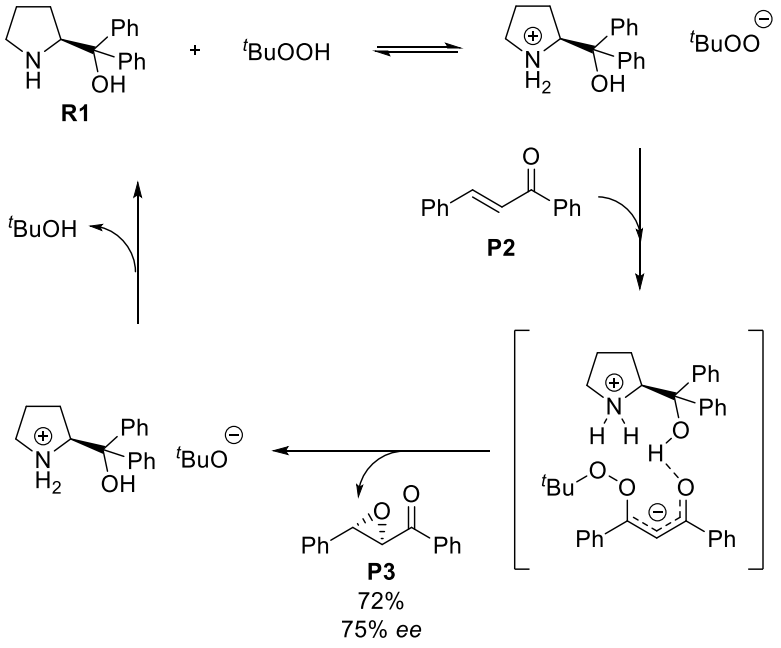
Alkaloid **Q1** was firstly used in the epoxidation of *α,β*-unsaturated alkenes in 1976 by Wynberg and co-workers. They showed that the presence of the salt is necessary for the formation of an enantiomerically enriched product.[47] Bifunctional catalyst **Q2** was reported by Nagasawa *et al.* in 2009. A postulated mechanism bases on the activation and coordination both of olefin and reactive species by either guanidinium or urea unit.[48]

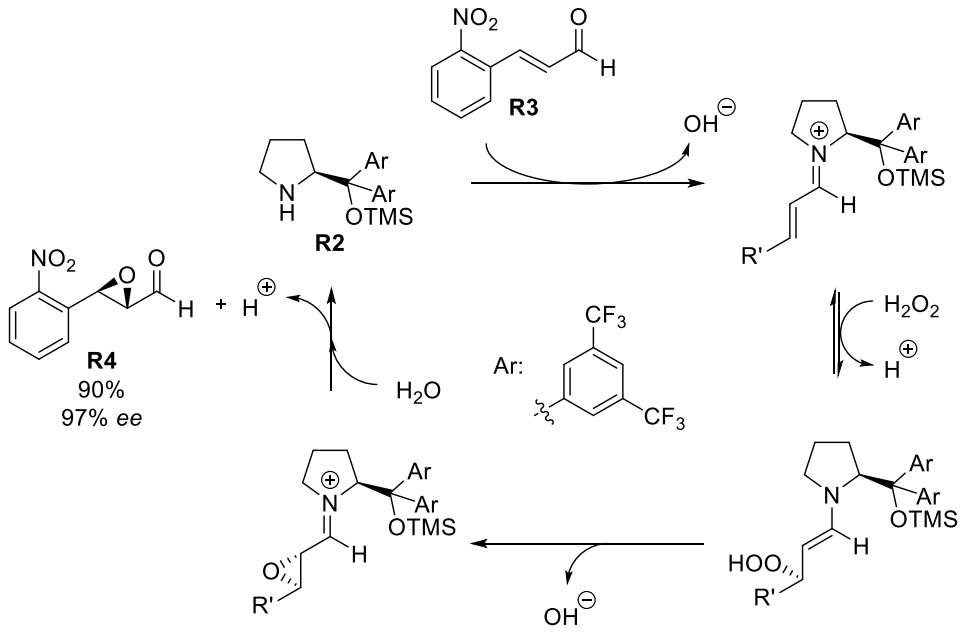
In 2004, Maruoka *et al.* introduced a quaternary ammonium-based PTC **Q3**. They obtained the corresponding epoxides with up to 99% yield and an enantiomeric excess of 96%.[49] Imidazolium-functionalized polypeptide **Q4** was utilized in the Juliá-Colonna epoxidation. Based on a simple recovery catalyst **Q4** was reused in seven cycles without loss of catalytic activity.[50]

1.3.2.3. Proline-Derived Catalysts

A third class of catalysts are systems derived from proline. Both unprotected as well as protected prolinol derivatives can act as catalysts reacting *via* different mechanisms (Scheme 15).

In 2005, Lattanzi published the enantioselective epoxidation with commercially available *α*,*α*-diphenylprolinol **R1**. In their postulated mechanism prolinol **R1** deprotonates *tert*-butyl hydrogen peroxide (TBHP) forming a chiral ion pair with the reactive anion. *n*-Hexane as nonpolar solvent prefers the salt formation additionally. Moreover, the free hydroxyl group activates the carbonyl moiety of *α*,*β*-unsaturated olefin **P2**. For epoxy ketone **P3** they obtained a yield of 72% and an enantiomeric excess of 75%. By release of *tert*-butanol prolinol derivative **R1** can enter the next catalytic cycle.[51]





Scheme 15: Prolinol and prolinol ether catalyzed epoxidations.

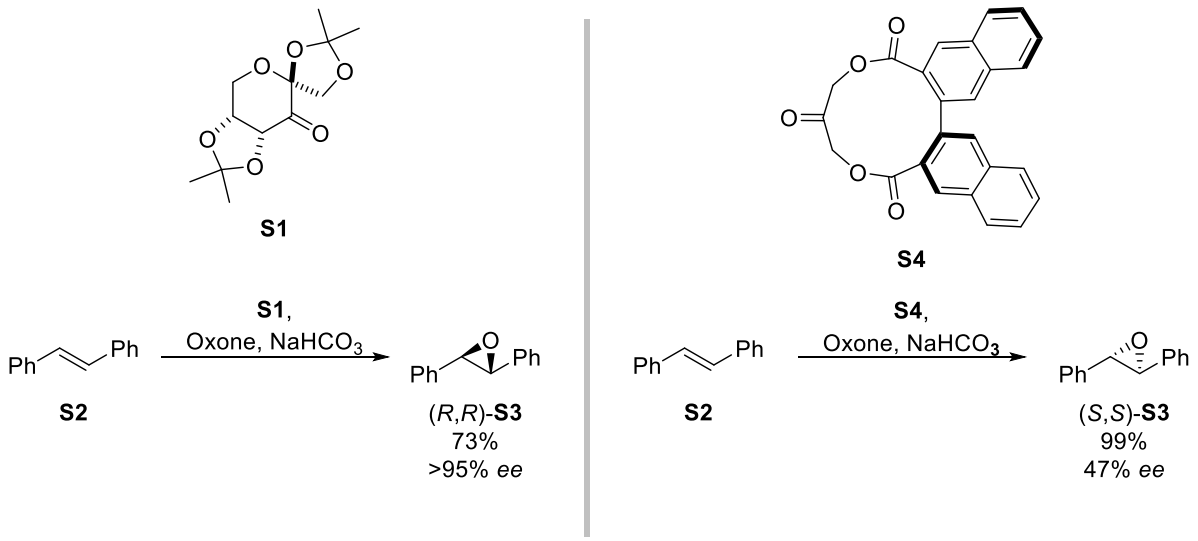
In contrast prolinol ethers, also known as Jørgensen-Hayashi catalysts,[52] have a different mechanism. The first usage in an asymmetric epoxidation of *α,β*-unsaturated aldehydes was published by Jørgensen *et al.* in 2005 including the postulated mechanism.[53] Herein, amine **R2** and aldehyde **R3** form an iminium species, which is afterwards attacked by hydrogen peroxide. Ring closing to the oxirane takes place *via* attack of the *α*-carbon of the enamine on the oxygen atom. After hydrolysis epoxide **R4** was isolated with a yield of 90% and an enantiomeric excess of 97%.

1.3.2.4. Chiral Ketones

Dioxiranes like dimethyldioxirane are standard reagents for the synthesis of epoxides. But, the reactive species can also be generated *in situ* starting form a ketone and an oxidizing agent like Oxone® or hydrogen peroxide. For the corresponding mechanism see chapters 4.4.1. and 4.4.5. In case of a chiral carbonyl component the epoxidation can proceed in an enantioselective manner. Besides C_2-symmetric systems sterically hindered ketones are typical precursors for this kind of epoxidation.[43c, 43d, 43f] Two examples are depicted in scheme 16.

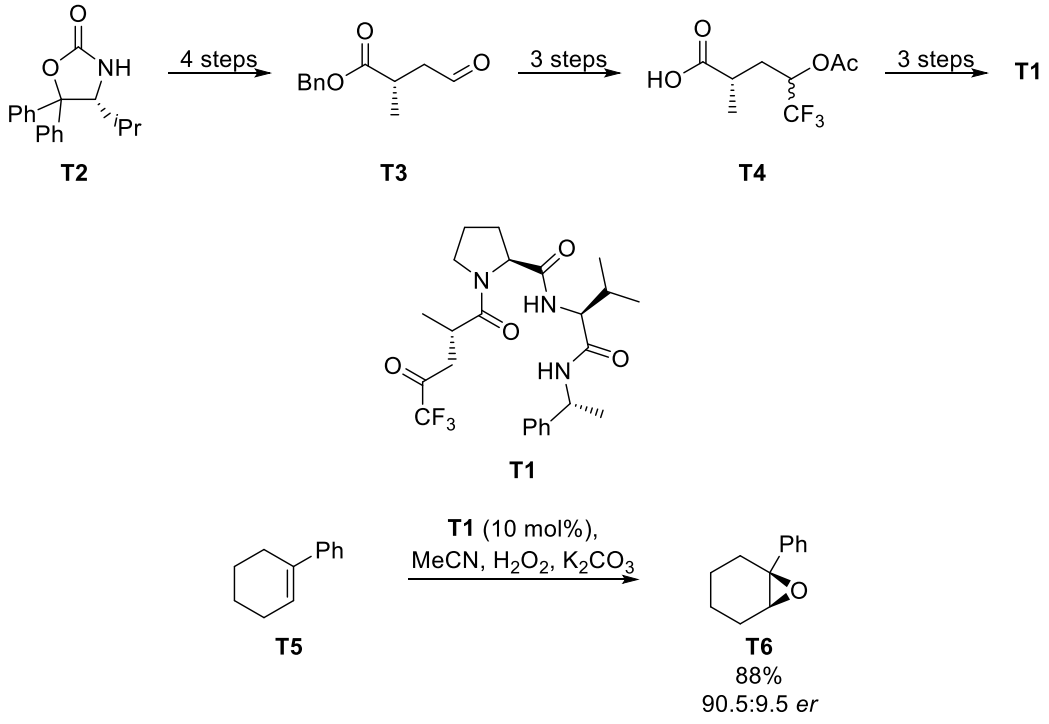
In 1996, Shi *et al.* published the epoxidation with carbohydrate derivative **S1**.[54] In the following year they also reported a catalytic version of their procedure.[55] After transferring one of the dioxirane oxygen atoms onto the carbon-carbon double bond the fructose-derived ketone can enter the catalytic cycle again. Also in 1996, Yang and co-workers introduced C_2-symmetric cyclic ketone **S4** for the asymmetric epoxidation of electron-rich alkenes like **S2**. Moderate to good enantiomeric excesses were achieved for *trans*- as well as trisubstituted

alkenes. A prolonged reaction time was necessary in regard to the usage of catalytic amounts of precursor **S4**.[56]



Scheme 16: *In situ* formation of the active dioxirane species.

Referring to their carboxylic acid-containing peptide catalyst **P4** Miller *et al.* published an oligopeptide functionalized with a trifluoromethyl ketone (TFMK) unit. Oligopeptide **T1** was synthesized in 10 steps beginning with carbamate **T2**, propionyl chloride, and allyl bromide. It was afterwards successfully tested in the enantioselective epoxidation (Scheme 17).[57]



Scheme 17: TFMK-containing peptide **T1** as catalyst in asymmetric epoxidation of **T5**.

Starting from Seebach's auxiliary **T2** aldehyde **T3** was obtained after four steps. **T3** is the key intermediate for the introduction of the trifluoromethyl group. Protected TFMK **T4** was obtained after three additional steps. Finally, **T4** was attached to the *N*-terminal unprotected peptide. Late-stage deprotection and oxidation are the last steps, before the TFMK catalyst **T1** can be used in epoxidation reactions. With 10 mol% of the precursor epoxide **T6** was isolated with a yield of 88% and an enantiomeric ratio of 90.5:9.5.

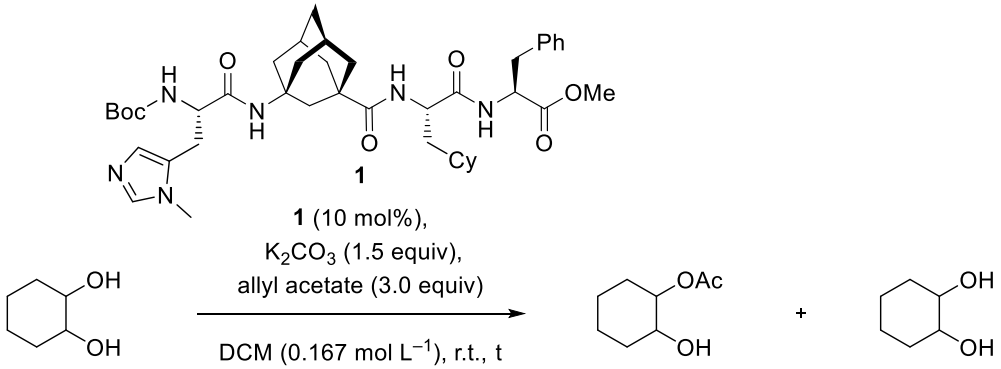
These four selected examples for asymmetric epoxidation reactions with organocatalysts should clarify the enormous potency of this concept. In this thesis we want to combine those strategies with our multicatalyst concept enabling new multicatalytic sequences.

2. Key Step: Acylation

As mentioned and shown in the introduction previous works of our group indicated the key step character of the acylation both in kinetic resolution[2a, 2c, 2d] and desymmetrization (Scheme 9) of 1,2-diols[2b, 2d] as well as in multicatalytic reaction sequences (Chapter 1.2.3.).[3a, 3b] For examining the acylation more intensively, we first tested an alternative acyl source (Chapter 2.1.), a novel application of our catalytic system (Chapter 2.2.), and sulfoximines as a new class of substrates (Chapter 2.3.).

2.1. Alternative Acyl Source

In former experiments acid anhydrides, acyl chlorides, vinyl acetate, and sulfurous- as well as phosphorous-based compounds were tested as electrophiles in combination with peptide catalyst (cat.) **1**. Acetic acid anhydride showed the best results regarding stereo- as well as chemoselectivity.[2d] In 2012, Onomura *et al.* published a Pd-Sn-catalyzed monoacylation of *cis*-cyclohexane-1,2-diol utilizing allyl acetate as acyl source.[58] Due to the good to excellent results based on allyl acetate, peptide catalyst **1** was tested under similar reaction conditions while using K_2CO_3 instead of Cs_2CO_3 as a base (Scheme 18).



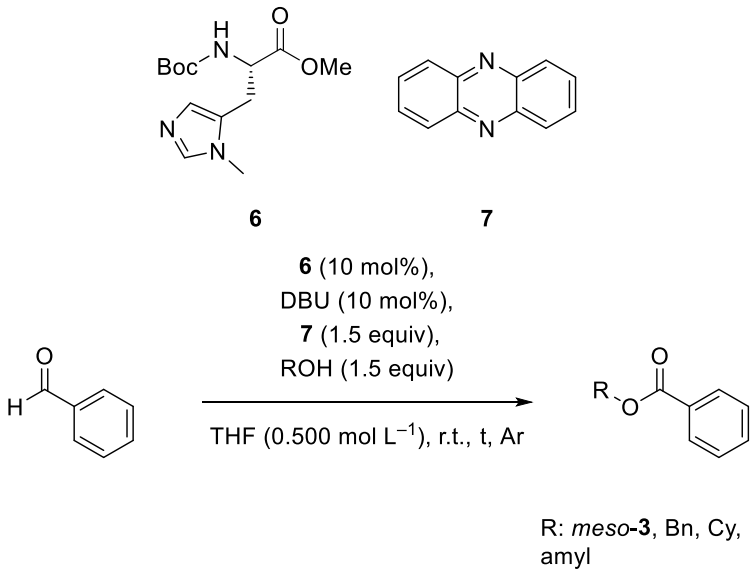
Scheme 18: Allyl acetate as electrophile.

After nearly one day, no conversion to the desired monoacylated product (see **4** and **5** Experimental Section) was observed by GC-MS (gas chromatography-mass spectroscopy) both in the kinetic resolution of *trans*-cyclohexane-1,2-diol (±)-**2** and in the desymmetrization of *meso*-**3**. Compared to its vinyl analog, allyl acetate did not show any reactivity in the acylation with oligopeptide **1**. Therefore, allyl acetate was neglected as acyl source in further investigations.

2.2. Oxidative Esterification

In the previously mentioned experiments the acyl source was added directly at the beginning of the reaction whereas in case of an oxidative esterification the reactive species is rather formed

in situ from the corresponding aldehyde and an oxidizing agent. In 2011, Hui *et al.* established a NHC-catalyzed oxidative esterification of aldehydes with oxygen as oxidizer.[59] One year later, Takemoto and co-workers utilized the same class of catalysts for the reaction of aldehydes and thiols.[60] They identified phenazine **7** as the oxidizer of choice. Combining the strategy of Takemoto and our nucleophilic peptide concept could accomplish an oxidative esterification of alcohols. *tert*-Butyloxycarbonyl-protected (Boc) PMH **6** was chosen as test catalyst and different kind of alcohols as feasible substrates (Scheme 19).



Scheme 19: Oxidative esterification.

meso-1,2-Diol **3** as well as a primary, secondary, and tertiary alcohols were tested, but none of the corresponding esters was observed *via* GC-MS. We assume that either alcohols, in contrast to thiols, are not feasible substrates under these conditions or that our catalyst or the *in situ* generated acid, respectively, is not reactive enough to form the necessary acylium species. Later on, Christine Hofmann was able to perform a peptide-catalyzed oxidative esterification utilizing a combination of TEMPO, *p*NBA, and *tert*-butyl hypochlorite.[3d]

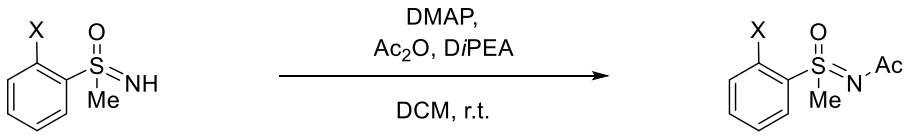
2.3. Sulfoximines as Substrates

Not only reaction conditions were varied in the previously mentioned experiments, but also different kinds of starting materials were employed. As a result, 1,2-diols were identified as the best substrates in combination with the most promising peptide catalyst **1** regarding, for example, reactivity and selectivity.[2d] In collaboration with the group of Professor Michael Harmata (University of Missouri, Columbia), sulfoximines were added to the existing substrate library utilizing our optimized protocol. Harmata *et al.* had already successfully employed the boric acid-catalyzed *N*-acylation of this class of compounds.[61]

2.3.1. Preparation of Racemic Products

Before starting the kinetic resolution of the sulfoximines the desired products were synthesized in racemic form. A protocol based on DMAP as a nucleophilic catalyst in combination with *N*,*N*-diisopropylethylamine (D*i*PEA) was utilized (Table 1).[2a, 62]

Table 1: Syntheses of racemically acylated sulfoximines **9a**, **9b**, and **9c**.



8a: F
8b: Cl
8c: Br

9a: F
9b: Cl
9c: Br

Product	DMAP [equiv]	Ac_2O [equiv]	D*i*PEA [equiv]	t [h]	Yield [%]
9a[(a)]	0.3	1.2	1.1	28	66 (96)[(b)]
9b	0.2	4.0	4.0	24	67
9c	0.4	3.1	3.1	24	55 (85)[(b)]

[(a)]: After 8 h additional 1.1 equiv of Ac_2O and D*i*PEA were added; [(b)]: Yield based on the amount of reisolated starting material.

Acylated sulfoximines **9a**, **9b**, and **9c** could be isolated in preparative yields of up to 67%. Yet, increasing the amount of anhydride, base, and DMAP as well as extending reaction times did not lead to full conversion. Afterwards, the enantiomers of starting material and obtained product were separated *via* chiral GC.

2.3.2. Catalyzed Kinetic Resolution

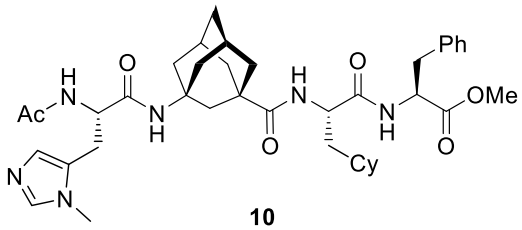
With the analytical data in hand, several types of catalysts were tested in the kinetic resolution of sulfoximines **8a**, **8b**, and **8c**. Apart from peptide catalysts **1**, **10**,[3] and **11** we also used peptide-based catalysts **12**[3] and **13**[3] established by Miller *et al.* for the kinetic resolution of *N*-acylated amino alcohols[26] as well as chiral DMAP catalysts **14**, **15**, and **16** synthesized by Stará *et al.* (Table 2).[63]

For testing the acylation ability of catalysts **1** and **10**-**16** starting from sulfoximines **8a**, **8b**, and **8c** all reactions were carried out under standard conditions optimized for the desymmetrization of *meso*-diol **3**. However, due to the slow and incomplete formation of the racemic products, screening reactions were run at 0 °C and D*i*PEA was added (Table 2). Earlier results showed

[3] Catalyst was synthesized by Dr. Christian E. Müller.

that the reaction proceeds faster and with an increased selectivity in the presence of 5.3 equivalents of base.[2b]

Table 2: Screening results.



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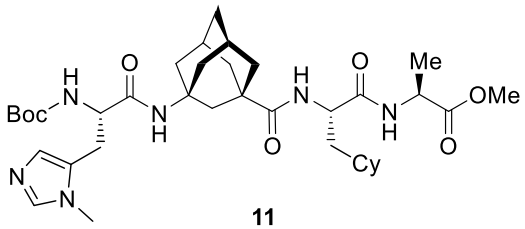

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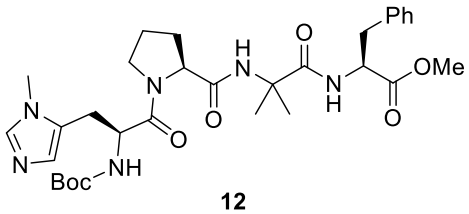

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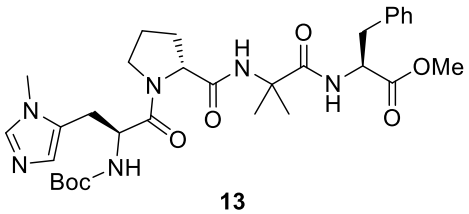

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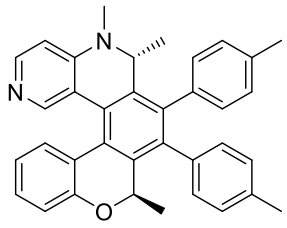

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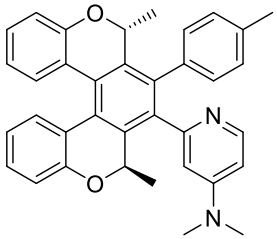

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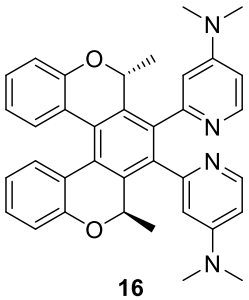

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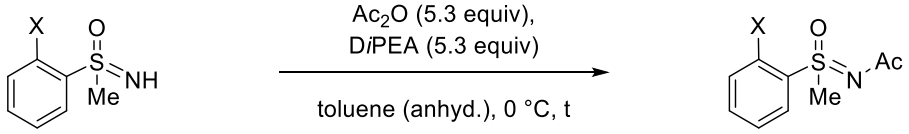


8a: F
8b: Cl
8c: Br

9a: F
9b: Cl
9c: Br

Entry	Product	Cat.	t [h]	Conv.[a] [%]	*S*-value[a]
1	**9a**	**1** [2 mol%]	24	1	1.2
2	**9a**	**1** [4 mol%]	24	13	1.2
3	**9a**	**10** [2 mol%]	24	1	1.4
4	**9a**	**11** [2 mol%]	24	25	1.3
5	**9a**	**12** [4 mol%]	24	traces	1.1
6	**9a**	**13** [3 mol%]	24	3	1.2
7	**9a**	**14** [2 mol%]	48	18	1.0
8	**9a**	**15** [2 mol%]	48	traces	1.2

9	**9a**	**16** [2 mol%]	24	3	1.2
10	**9a**	-	24	2	1.2
11	**9b**	**1** [2 mol%]	24	7	1.5
12	**9b**	**11** [2 mol%]	24	1	1.5
13	**9b**	**12** [3 mol%]	24	27	1.0
14	**9b**	**14** [2 mol%]	24	11	1.1
15	**9b**	**15** [3 mol%]	24	5	1.0
16	**9b**	**16** [2 mol%]	24	1	1.2
17	**9c**	**1** [2 mol%]	24	8	1.5
18	**9c**	**11** [2 mol%]	24	8	1.4
19	**9c**	**12** [2 mol%]	24	65	1.1
20	**9c**	**14** [2 mol%]	24	49	1.1
21	**9c**	**15** [2 mol%]	24	53	1.1
22	**9c**	**16** [2 mol%]	24	48	1.1
23	**9c**	-	24	43	1.0

[a]: Enantiomeric excess of starting material and product were determined *via* chiral GC without internal standard. Conv. and *S*-value were calculated using the procedure of Kagan and Fiaud.[64]

Obtained *S*-values were in the range of 1.0 to 1.5 with a conversion of up to 65%. The high values for the conversion are misleading possibly because the equation of Kagan and Fiaud cannot be used for very low differences in enantiomeric excesses of reactants and products. Obviously, the used catalysts are not able to resolve the three different starting materials in a profitable manner. In most cases reactions were quenched after 24 hours because of very low conversion and no enantiomeric excess. Minimal acylation could also be observed in simultaneously performed background reactions. Hence, it is not completely clear, if product formation results from catalytic activity. Based on these first experimental results, changing either the substitution pattern of the sulfoximines or varying the type of catalyst seems to be less promising. The results indicate that the tested sulfoximines are not feasible substrates in combination with the employed catalysts.

3. New Multicatalytic Sequence

3.1. Combination of Well-Established Procedures

As explained in the introduction, chemical synthesis using a multicatalyst has several advantages. Therefore, one point of interest of this thesis is the development of a further multicatalytic sequence. Using well-established protocols in combination with new reactions leads to extension of our multicatalytic approach. In this context we designed a new catalytic sequence: esterification-epoxidation-epoxide opening (Figure 10).

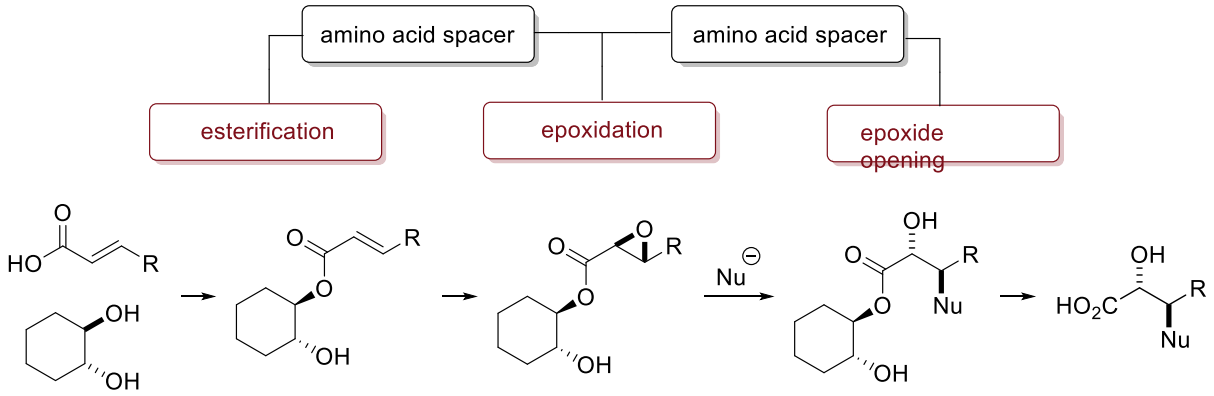


Figure 10: New multicatalytic sequence.

The Steglich esterification of unsaturated carboxylic acids and 1,2-cyclohexanediols is the first step of the sequence. This kind of reaction is intensively studied and should be extended to unsaturated acids under otherwise analogue conditions.[2c] After epoxidation of the unsaturated esters the resulting epoxides will be opened with a nucleophile using the diol motif as auxiliary. For these two steps, feasible catalytic moieties, necessary reagents, and reaction conditions have to be developed. The epoxide opening should be performed following the concept of Tomioka and co-workers (Figure 11). In 1997, the Japanese group published the enantioselective ring opening of epoxides mediated by chiral diether ligands with excellent yields and moderate enantiomeric excesses.[65] One year later, Oguni *et al.* used chiral Schiff bases and salens also based on diol units in the same kind of reaction.[66]

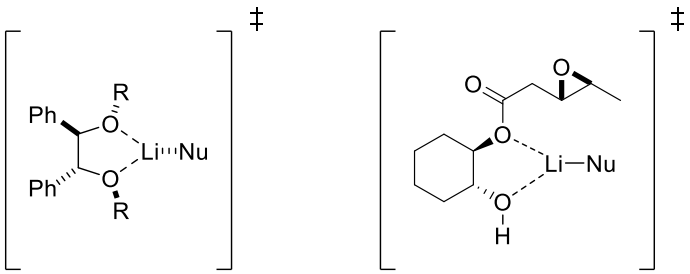


Figure 11: Proposed transition states for the opening of the epoxide based on the results of Tomioka *et al.* (left).

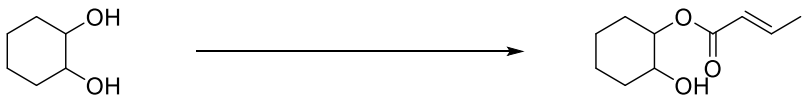
Hydrolysis of the esters results in the formation of carboxylic acids containing two defined stereogenic centers and three functional groups (carboxyl and hydroxyl groups as well as the corresponding nucleophile) enabling a variety of further transformations (e.g., esterification, oxidation). Chiral *α*-hydroxyl carboxylic acids are, for example, present in drugs or natural products.[67]

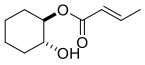
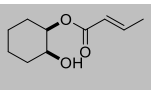
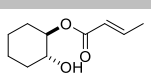
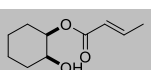
Before establishing a multicatalytic approach all reactions have to be tested with separate peptide catalysts. Moreover, all intermediates and target compounds have to be synthesized as racemates to separate their diastereomers as well as enantiomers for further asymmetric investigations.

3.2. Synthesis of Unsaturated Mono-Esters

For delivering two stereogenic centers in the product the obvious choice as the simplest unsaturated compound was crotonic acid. Based on the modified Steglich protocol utilizing DMAP, *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDAC), and triethylamine (TEA) both *trans*- and *cis*-cyclohexane-1,2-diol **2** and **3** were converted into the corresponding esters **17** and **18** (Table 3).[2c, 68] EDAC was selected as the carbodiimide because removing the generated urea is simpler compared to DIC or DCC.[68] But, due to the low yield of only up to 25%, crotonic anhydride was also tested as an acylium source. Furthermore, a larger amount of DMAP was used and TEA was replaced by pyridine as base.[69] This strategy provided the *α*,*β*-unsaturated products with a yield of 63% (Table 3).

Table 3: Synthesis of crotonic acid esters.



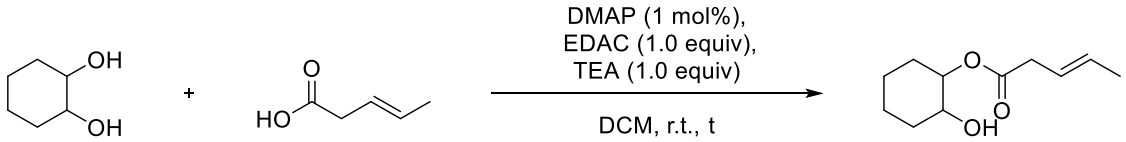
Starting materials			t [h]	Product		Yield [%]
(±)-**2**		Crotonic acid	24	**17**[(a)]		25
meso-**3**		Crotonic acid	22	**18**[(a)]		24
(±)-**2**		Crotonic anhydride	16	**17**[(b)]		63
meso-**3**		Crotonic anhydride	20	**18**[(b)]		63

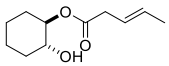
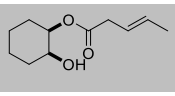
[(a)]: Reaction conditions: DMAP (1 mol%), crotonic acid (1.0 equiv), EDAC (1.0 equiv), TEA (1.0 equiv), diol (1.1 equiv), DCM, r.t.; [(b)]: reaction conditions: DMAP (10-12 mol%), crotonic anhydride (0.9 equiv), diol (1.0 equiv), pyridine (6.0 equiv), DCM, r.t..

The low amount of isolated product starting from crotonic acid can be explained by the mesomeric stabilization of the *α,β*-unsaturated reactant and hence the minimized reactivity considering the formation of the anhydride *in situ*. Due to the lower chemical stability of anhydrides and the easier access to unsaturated acids, crotonic acid was substituted by its homologue.[2c] In 3-pentenoic acid **19a** the mesomeric effect was circumvented by a methylene-spacer.

Using the DMAP, EDAC, and TEA based Steglich protocol, the corresponding esters **20a** and **21a** were synthesized in yields of up to 71% (Table 4).[2c, 68]

Table 4: Steglich esterification with 3-pentenoic acid **19a**.



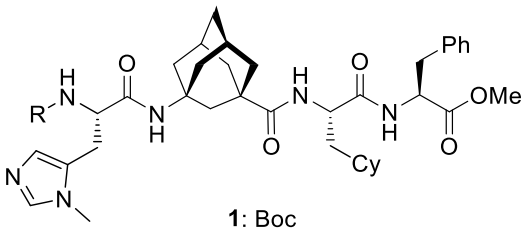
Starting materials		t [h]	Product		Yield [%]
(±)-**2**		25	**20a**[(a)]		71
meso-**3**		24	**21a**[(a)]		54

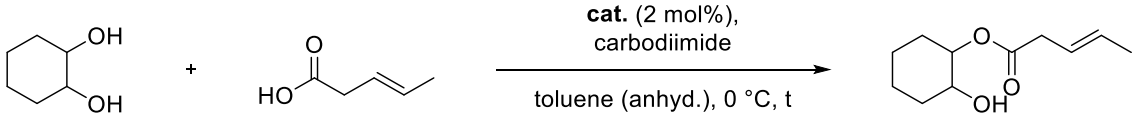
[(a)]: Reaction conditions: DMAP (1-2 mol%), diol (1.0 equiv), 3-pentenoic acid **19a** (1.0 equiv), EDAC (1.0 equiv), TEA (1.0 equiv), DCM, r.t..

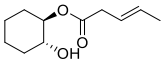
With the racemic compounds in hand, the enantiomers of the esters were separated *via* chiral GC or high-pressure liquid chromatography (HPLC). Afterwards, the Steglich esterification was tested under catalytic conditions utilizing the well-established protocol and tetrapeptide **1** or **10**[4] as catalysts (Table 5).[2c] Both kinetic resolution of (±)-**2** as well as desymmetrization of *meso*-**3** worked very well. As mentioned in literature, the protecting group at the *C*-terminus of the catalyst plays a negligible role comparing oligopeptide **1** and **10**.[2d] Because a combination of EDAC and TEA showed less promising results in simultaneously performed experiments either DIC or DCC are the preferred carbodiimides. Based on these encouraging data, the esterification between diol and unsaturated, but not conjugated acid **19a** is a feasible first step of our new multicatalytic sequence.

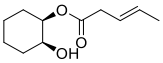
[4] Catalyst was synthesized by Dr. Christian E. Müller.

Table 5: Peptide-catalyzed Steglich esterification.





Starting Materials	t [h]	Carbodiimide [equiv]	Product	*S*-value[(b)]	Conv.[(b)] [%]
(±)-**2**	4	DIC (1.2)	(*R*,*R*)-**20a**[(a)] 	> 50	51

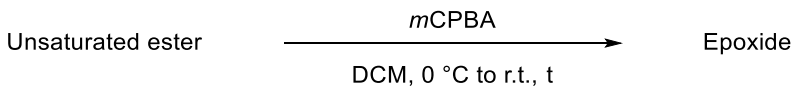
Starting materials	t [h]	Carbodiimide [equiv]	Product	*ee*[(c)] [%]	Conv.[(c)] [%]
meso-**3**	24	DCC (1.0)	(1*R*,2*S*)-**21a**[(a,d)] 	83	55

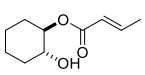
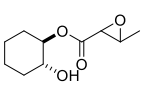
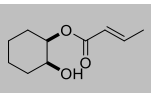
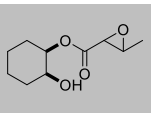
[(a)]: Reaction conditions: **cat.** (2 mol%), diol (1.0 equiv), acid (1.0 equiv), toluene (anhyd., 4.00 mL), 0 °C; [(b)]: *ee* of starting material and product were determined *via* chiral GC without internal standard. Afterwards, conv. and *S*-value were calculated using the procedure of Kagan and Fiaud;[64] [(c)]: *ee* and conv. were determined *via* chiral GC or HPLC without internal standard; [(d)]: cat. **10** was used.

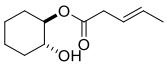
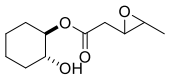
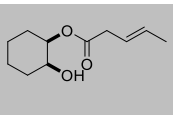
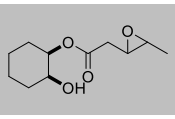
3.3. Synthesis of Epoxides

Now we moved our attention to the second step of the one-pot reaction sequence. All four unsaturated esters were epoxidized racemically including the less promising crotonic acid derivatives. Utilizing a *m*CPBA-based protocol the corresponding oxiranes were isolated in yields of up to 87% (Table 6).[70]

Table 6: Racemic epoxidation of the monoesters.



Unsaturated Ester		Epoxide		t [h]	*m*CPBA [equiv]	Yield [%]
17		**22**		20	1.2	61
18		**23**		24	1.1	72

20a		**24a**		22	1.1	69
21a		**25a**		7	1.1	87

3.4. Synthesis of Functionalized Carbonic Acid Derivatives

3.4.1. Michael-Addition

Simultaneously, for the identification of a possible epoxide opening starting from oxiranes **24a** and **25a**, we also tested the Michael addition for *α*,*β*-unsaturated compounds **17** and **18**. This reaction might also be part of a minimally modified multicatalytic sequence based on an asymmetric acylation of the corresponding starting material. Hydrolysis of the intermediately formed saturated esters would lead to *β*-functionalized carboxylic acids. This kind of compounds are used, for example, as chiral synthons or as receptor antagonists.[71] Sakai *et al.* already described the 1,4-addition of an *in situ* formed diphenylcuprate onto enantiomerically pure crotonic acid derivative **17** providing the product in 66% yield and a diastereomeric ratio of 94:6. The authors assume that coordination of a lithium atom of the dimer by the diol motif generates a chiral environment for the attack of a phenyl group to the double bond (Figure 12).[69]

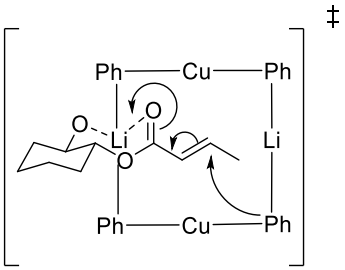
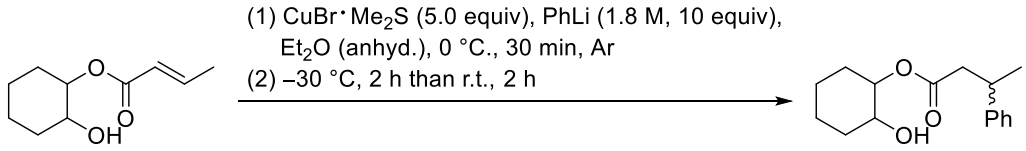


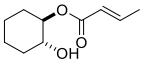
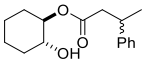
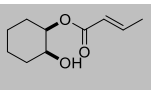
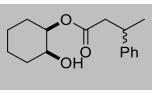
Figure 12: Postulated transition state for the Michael addition.

We tried to reproduce Sakai's result for monoester **17** and to test **18** as further starting material under otherwise identical conditions (Table 7). The necessary Gilman reagent was generated *in situ* starting from copper(I) bromide and phenyllithium. Corresponding Michael addition products **26** and **27** were isolated with a yield up to 48% as a mixture of both diastereomers. An explanation for the lower yield in case of the *cis*-derivative **18** might be the mismatched configuration of the substituents in the transition state (Figure 12). These results show that the 1,4-addition of those compounds is principally possible and could be incorporated into a multicatalytic sequence. But, because of side product formation, purification problems, and less

promising overall yields (Table 3 and 6), no extensive optimization attempts were undertaken until now.

Table 7: Michael addition to crotonic acid derivatives **17** and **18**.



Starting materials		Product		Yield [%]
17		**26**		48
18		**27**		< 10[(a)]

[(a)]: Even after several purification steps *via* column chromatography, the product was not completely pure.

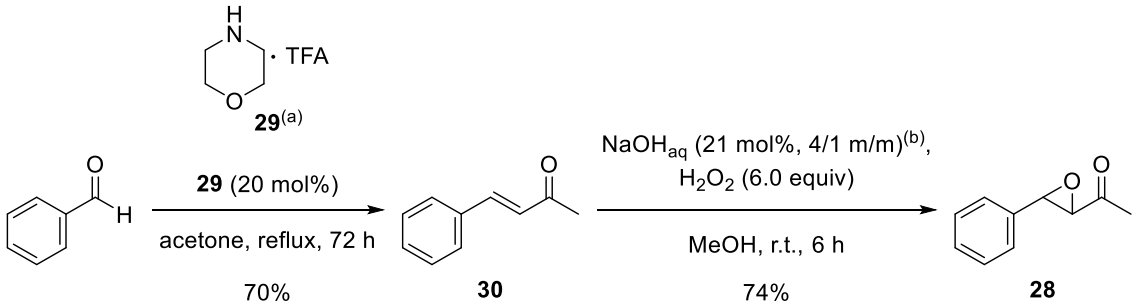
3.4.2. Epoxide Opening

Before performing the epoxidation in an asymmetric and multicatalytic fashion a feasible ring opening reaction and a possible catalytic moiety have to be identified. In 2012, Schreiner *et al.* published a multicatalytic sequence involving an epoxide opening to racemic *trans*-1,2-cyclohexanediol using hydrazine bisulfate as catalyst, which was not fixed at the peptide backbone.[3b] In this thesis, we focused on different nucleophiles introducing a variety of further functional groups. Therefore, several approaches were taken into account (oxirane ring opening with trimethylsilyl cyanide (TMSCN), lithium- as well as copper organyls, and thiols), starting from a racemic mixture of the corresponding epoxides.

3.4.2.1. TMSCN

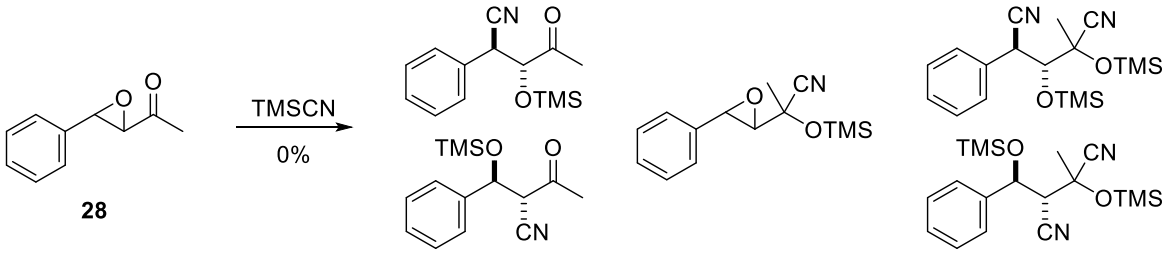
Epoxide opening based on TMSCN is well studied in literature.[72a, 38a, 72b, 72c] Based on this strategy amines, carboxylic acids, nitriles, as well as hydroxyl groups can be installed simultaneously in a molecule. Furthermore, this kind of reaction is utilized in the synthesis of complex compounds.[73] Besides, for example, titanium, ytterbium, and indium species also organic compounds like CBr_4 or a thiourea derivative activate the oxygen ring atom favoring an epoxide opening reaction.[74, 72b, 72c] One drawback of this silyl species is its reactivity towards carbonyl groups. Zhang *et al.* investigated the addition of TMSCN on aldehydes catalyzed by the same thiourea as it was utilized in the ring opening reaction.[75] Considering our developed multicatalytic sequence starting from epoxy esters this chemoselectivity could lead to a variety of potential products. For examining the effect on the functional groups and the catalytic motifs as well as for investigating the reaction conditions more closely, we chose

the epoxide of benzylideneacetone as test substrate. Epoxide **28** was previously synthesized in 53% yield over two steps. After aldol condensation of benzaldehyde and acetone the double bond was epoxidized utilizing typical Weitz-Scheffer conditions (Scheme 20).[76]



Scheme 20: Synthesis of epoxide **28**.
(a): TFA salt **29**: morpholine (1.0 equiv), TFA (1.1 equiv), Et_2O, 0 °C, 1 h, 94%; (b): the same amount of NaOH was added hourly.

With the test substrate in hand, we performed the TMSCN-mediated epoxide opening, theoretically leading to up to five possible products (Scheme 21). Based on the polarization of the carbon atoms the nitrile anion should preferentially attack at the *β*-position. This reactivity applies for all further epoxide opening approaches.



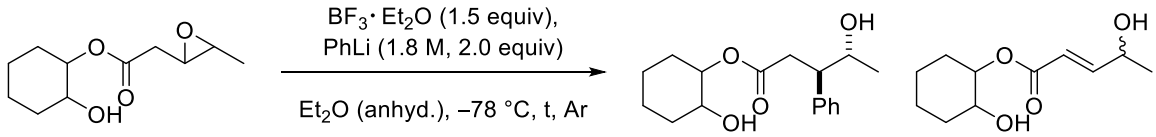
Scheme 21: TMSCN addition on epoxy ketone **28**.

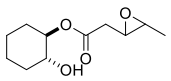
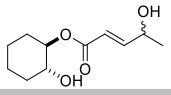
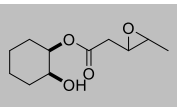
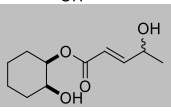
After performing the reaction both with different kind of catalysts ($InCl_3$ and CBr_4) and as a two-step synthesis containing the addition of NaCN followed by protection of the formed alcohol with TMSCl, none of the expected products could be observed *via* nuclear magnetic resonance (NMR) or GC-MS.[74b, 77] In 2011, Fraile *et al.* already described the lower reactivity of *α*,*β*-epoxy ketones in TMSCN-mediated epoxide opening reactions.[72b] Due to the amount and complexity of feasible products as well as the incomplete synthesis of the racemic compounds and the failed identification of a suitable catalytic moiety or reaction conditions, we decided against putting more effort into this reaction as last step of the multicatalytic sequence.

3.4.2.2. Metal Organyls

Ensuing from the arising problems for TMSCN, we chose phenyllithium as an alternate nucleophile, which is also able to form a new carbon-carbon bond during epoxide opening reactions. As already mentioned, the diol motif of our starting material should coordinate the counterion ensuring a preferential trajectory for the attack of the phenyl ion at the epoxide (Figure 11).[65-66] Aside from the oxirane, a carbonyl group and several acidic protons (hydroxyl group as well as *α*-protons) are present in the molecule representing possible reactive centers for the lithium organyl. Therefore, we used directly epoxides **24a** and **25a** as substrates instead of a further test system. We performed the first experiments based on the conditions of Tomioka utilizing two equivalents of the lithium species.[65] The first equivalent should deprotonate the hydroxyl group and the second one should open the epoxide providing the desired product after aqueous work-up (Table 8).

Table 8: Epoxide opening with PhLi.



Starting materials		t [h]	Product		Yield [%]
24a		4	**31**		14
25a		2	**32**		18

During the reactions starting both from *trans*- as well as *cis*-derivative **24a** and **25a** the formation of up to nine new compounds was detected *via* thin-layer chromatography (TLC). Beside small traces of the corresponding starting materials and diols, only elimination products **31** and **32** could be clearly identified *via* NMR or high resolution-MS (HR-MS) (Table 8). These facts and the incorrect mass balance proved the high reactivity of lithium organyls and the possibility of several simultaneously running side reactions.

In contrast to the assumed reaction progress, the second equivalent phenyllithium acts not as nucleophile, but as an additional equivalent of base. Deprotonation in *α*-position followed by a concerted epoxide opening leads to *α*,*β*-unsaturated *γ*-hydroxyl ketones **31** and **32**. Comparison of the postulated TS shows a favored six-membered TS for the formation of allyl alcohols in contrast to the more complex situation in case of the epoxide opening (Figure 13).

Furthermore, the comparable isolated yields clarify the negligible influence of the stereochemistry at the cyclohexyl (Cy) system, because starting from the *cis*-analog should show a better coordination of the lithium cation in case of the epoxide opening.

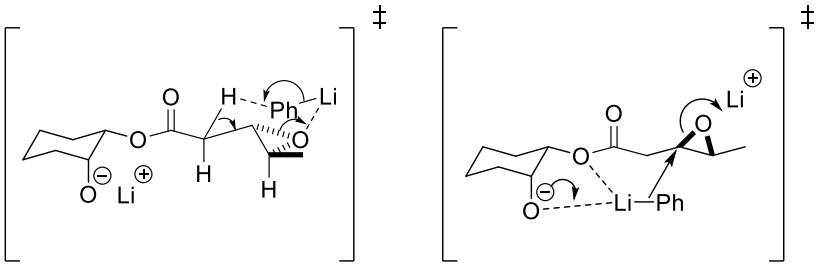
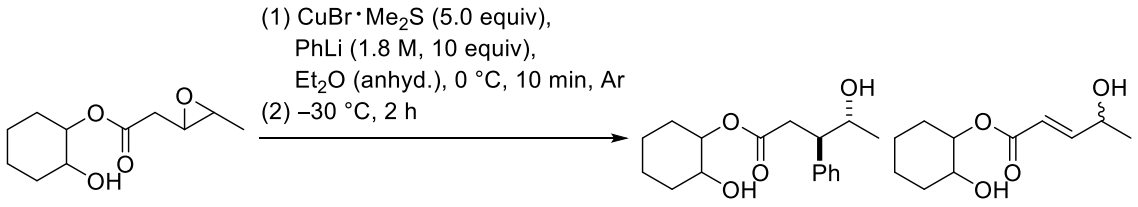
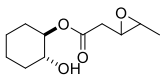
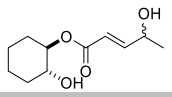
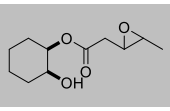
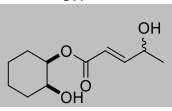


Figure 13: Postulated TSs for elimination and ring opening, respectively.

Substitution of the lithium organyl by its copper analog is one way to overcome the elimination problem. Based on the "hard and soft acid and base (HSAB) concept", cuprates are softer reagents, compared to their lithium analogs. This property can directly be correlated with the basicity and nucleophilicity of these compounds. Moreover, due to an increased reactivity in addition reactions, milder conditions can be utilized. Even if copper organyls react regioselectively in the presence of esters organic copper species provide allyl alcohols as well as ketones as side products.[78] We repeated the test experiments combining the *in situ* generation of lithium diphenylcuprate and its ability in oxirane opening reactions (Table 9).[78, 69]

Table 9: Epoxide opening with Ph_2CuLi.



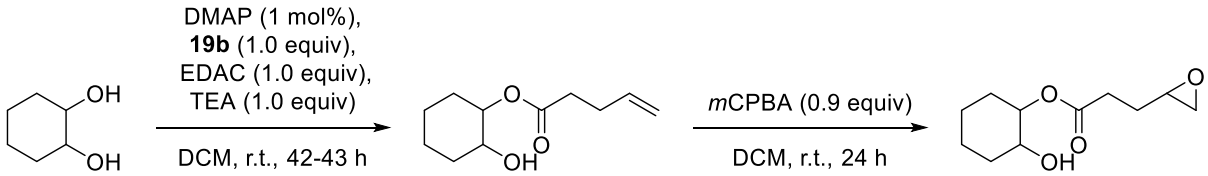
Starting materials		Product		Yield [%]
24a		**31**		15
25a		**32**		4

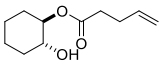
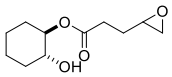
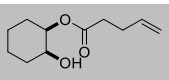
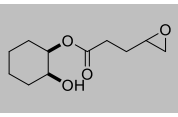
Analogous to phenyllithium a variety of new compounds were observed in the reactions with lithium diphenylcuprate *via* TLC. But, the identification of an epoxide opening product was also not successful. However, allyl alcohols **31** and **32** were isolated with comparable yields of

up to 15% (Table 8 and 9). Even with the less basic copper species formation of the unsaturated system could not be suppressed.

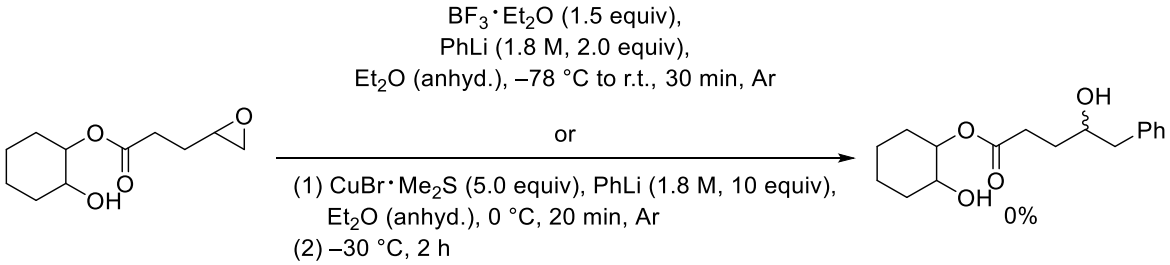
Therefore, we selected the corresponding 4-pentenoic acid derivatives **24b** and **25b** as starting materials. Starting from those oxiranes an epoxide opening to the conjugated compounds is not possible, even if a deprotonation in *α*-position takes place. The epoxy analogs of 4-penonic acid **19b** were synthesized in a total yield of up to 59% utilizing the established protocol mentioned before (Table 10).[2c, 68] To avoid problems with the separation of formed acid only 0.9 equivalents of *m*CBPA were utilized.[70]

Table 10: Synthesis of epoxide **24b** and **25b**.



Educt		Ester	Yield [%]		Epoxide	Yield [%]
(±)-**2**	**20b**		45	**24b**		59
meso-**3**	**21b**		50	**25b**		57

With the necessary oxiranes in hand, the lithium- as well as copper-based ring opening reactions were performed under otherwise identical conditions. Due to polarization of the alkyl chain, the phenyl anion should preferentially attack at the *δ*-position of the epoxy esters **24b** and **25b** (Scheme 22).



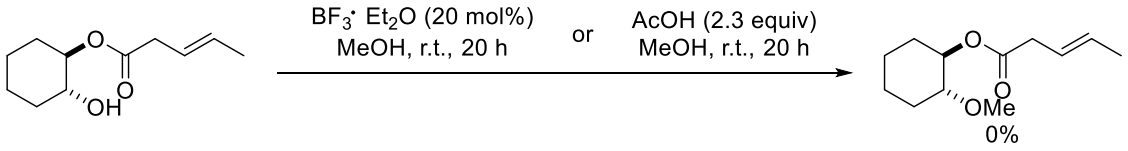
Scheme 22: Organometallic ring opening of terminal epoxides **24b** and **25b**.

Carrying out the reaction both with *trans*- as well as *cis*-analog **24b** and **25b** in combination with the lithium as well as the copper species did not provide the epoxide opening products. Firstly, in all cases a number of new compounds were observable *via* TLC, but could not be

identified clearly *via* NMR or GC-MS. Secondly, only traces of the corresponding reactants could be reisolated. Lastly, a satisfactory mass balance was also not achieved. Introducing a further methylene-spacer did not lead to the desired effect neither for the lithium- or the copper-based strategy.

3.4.2.3. Manipulation of Coordinating Effects

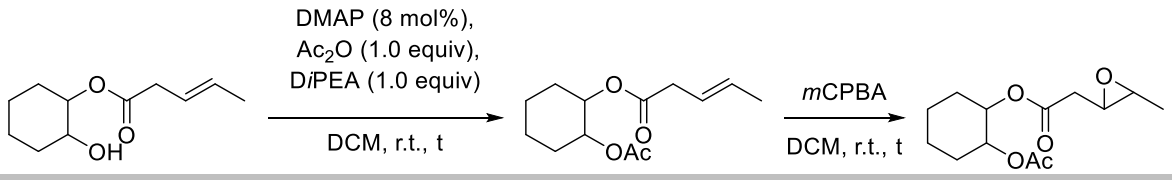
Besides changing the nature of utilized nucleophile and starting material, the coordination properties can also play an important role. For mimicking the diether motif of Tomioka more closely, we first tried to convert the free hydroxyl group into a methyl ether.[65] But astonishingly, neither utilizing a BF_3•Et_2O or an acetic acid-based protocol lead to the methoxy derivative of **20a** (Scheme 23).[79]

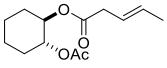
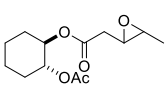
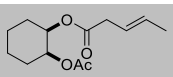
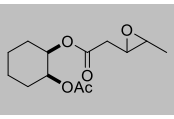


Scheme 23: Introduction of a methyl ether.

During the synthesis of monoesters **20a** and **21a** we also observed the formation of the corresponding diesters. In contrast to an ether, an ester moiety has two oxygen atoms, which can help to coordinate a cation. Based on these two facts, we decided to synthesize the acetoxy-protected derivatives **35** and **36** as starting materials for the ring opening reaction. After a DMAP-catalyzed acylation the double bond was epoxidized with *m*CPBA.[2a, 62a, 70b] Finally, epoxides **35** and **36** were isolated with a total yield of up to 79% (Table 11).

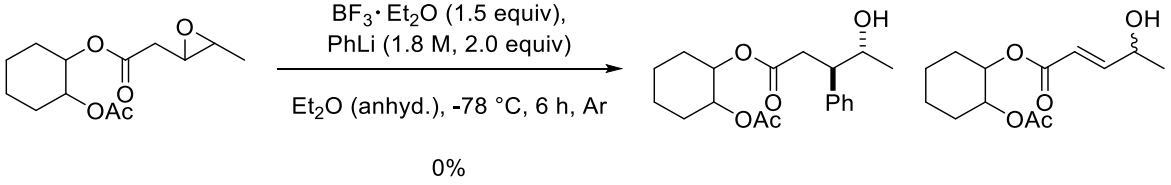
Table 11: Synthesis of acetoxy analogs **35** and **36**.



Educt		Ester	t [h]	Yield [%]		Epoxide	*m*CPBA [equiv]	t [h]	Yield [%]
20a	**33**		31[(a)]	91	**35**		1.1	7	87
21a	**34**		25[(b)]	76	**36**		1.2	7.5	89

[(a)]: 1.0 equiv Ac_2O and D*i*PEA were added after 5.5 h; [(b)]: 1.0 equiv Ac_2O and D*i*PEA were added after 6 h.

Only 1.1 equivalents of the lithium organyl were utilized in the ring opening reactions starting from epoxides **35** and **36** in contrast to their hydroxyl derivatives (Scheme 24). Besides the omission of the acidic hydroxyl group, reduction of phenyllithium should also minimize side-product formation.



Scheme 24: Epoxide opening reaction starting form acetoxy derivatives **35** and **36**.

But, contrary to the assumption, carrying out the reaction with even smaller amounts of the lithium species, up to six different fractions were separated *via* column chromatography. Either for the *trans*- or the *cis*-analog, epoxide opening or elimination product could be identified by NMR- or MS-analysis. Due to this observation we assume protecting the hydroxyl group as acyl ester seems to prohibit even deprotonation in the *α*-position of the epoxide. Furthermore, a second carbonyl species and an *α*-methyl group were incorporated into the molecule as potential additional reaction centers. Nevertheless, regarding the final step of the multicatalytic sequence we stopped further investigations based on metal-containing nucleophiles at this point. Especially, the huge tendency for side reactions, an unpredictable chemoselectivity, and imbalanced mass proportion are disadvantages, which have to be considered.

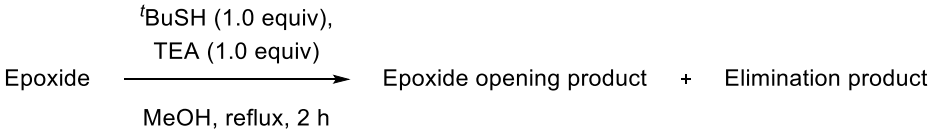
3.4.2.4. Thiols

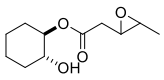
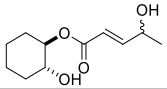
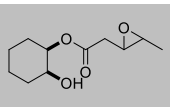
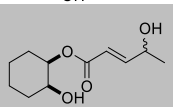
Based on the previous results we replaced the copper reagent by a thiol, which should also act as soft nucleophile, but with a less basic character (pK_a: 11.1[80]). Epoxide opening reactions with sulfur species are widely spread in literature.[81] For example, a combination of thiol and base provides the basis for the ring opening protocols described by Lattanzi and Luly.[82] Our first experiments with epoxides **24** and **25** were performed utilizing the conditions of Luly *et al.* with a combination of *tert*-butyl thiol and TEA (Table 12).[82a] Before adding the epoxide, ^{t}BuSH and TEA were stirred for ten minutes at room temperature (r.t.).

In case of 3-pentenoic acid analogs **24a** and **25a**, the potential ring-opened compound was not observed, but up to 57% of the elimination products **31** and **32** were isolated. This fact indicates that either TEA (pK_a: 10.7) or *in situ* formed *tert*-butyl thiolate removed one of the *α*-protons, thus forming the *α*,*β*-unsaturated products. Starting from 4-pentenoic acid

derivatives **24b** and **25b** also did not provide one of the thioethers, but up to 18% of epoxy methyl ester **37** (Figure 14).

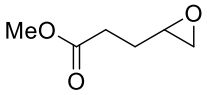
Table 12: Thiolate-mediated epoxide opening.



Starting materials[(a)]		Product		Yield [%]
24a		**31**		57
25a		**32**		48

[(a)]: Results for **24b** and **25b** are not included, because they did not lead to any of the expected products.

Furthermore, in all four reactions the corresponding diols **2** and **3** were identified as side products. Based on these observations, we assume that due to the presence of a protic as well as nucleophilic solvent a transesterification to the corresponding epoxy methyl ester and diol takes place.



37

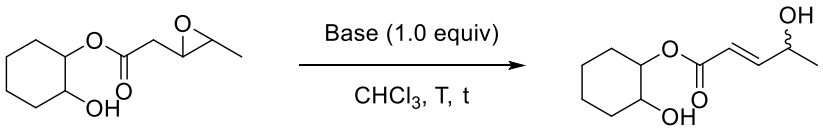
Figure 14: Epoxy methyl ester **37**.

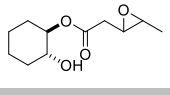
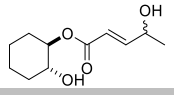
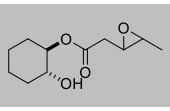
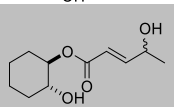
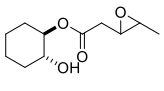
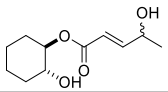
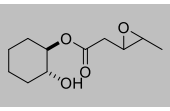
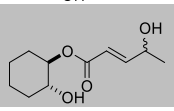
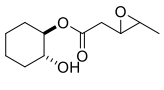
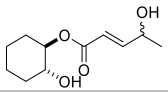
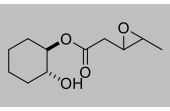
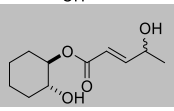
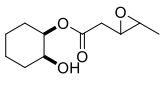
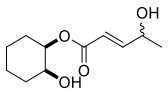
3.4.3. Substitution of the Third Step of the Multicatalytic Sequence

However, even if the desired thioether is not formed, the latter reaction conditions showed a minimized tendency for side product formation in contrast to the organometallic-based ring opening approaches and resulted in an even higher yield of the elimination products. These facts are necessary regarding a multicatalytic procedure. Therefore, considering a modified sequence we focused on the optimization of the elimination generating α,β-unsaturated γ-hydroxyl ketones **31** and **32**, which formed under basic conditions.

For the first test experiment we substituted methanol by chloroform, due to its comparable boiling point. Further reaction parameters were kept constant and were varied afterwards one by one (Table 13).

Table 13: Base-mediated ring opening.



Starting materials[(a)]		Base	T	t [h]	Product		Yield [%]
24a		Imidazole	Reflux	2	**31**		0
24a		TEA	Reflux	2	**31**		37
24a		TEA	r.t.	2	**31**		0
24a		DBU	Reflux	2	**31**		71
24a		DBU	r.t.	2	**31**		52
24a		DBU	r.t.	1	**31**		85
25a		DBU	r.t.	1	**32**		89

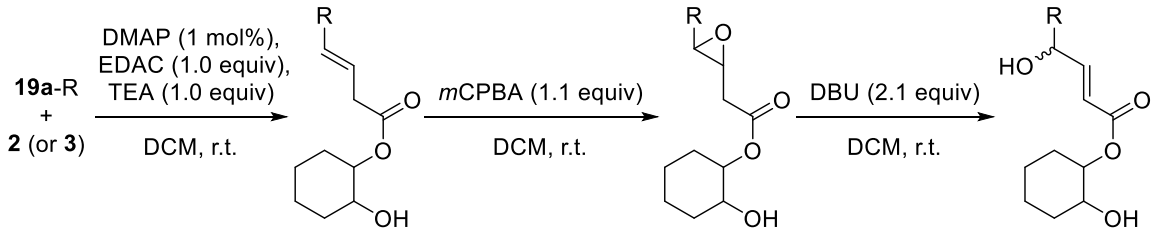
Even at higher temperatures, less basic compounds like imidazole (pK_a: 7.0) and TEA lead to lower isolated yields. The best results both for *trans*- as well as *cis*-derivative **24a** and **25a** were achieved with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (pK_a: 12.0) as base. Stirring for one hour at room temperature resulted in up to 89% of the elimination product. Besides the corresponding diol as result of ester hydrolysis, no further side products were observed. Longer reaction times seem to favor the consumption of the target molecule in this subsequent step. Therefore, stirring a reaction mixture consisting of a 1:1 ratio of epoxide and DBU in chloroform for one hour at room temperature should be the standard conditions for further investigations.

3.4.4. Summary and Outlook

The previous results and especially the problems with a potential epoxide opening reaction suggested a necessary modification of the underlying multicatalytic sequence (Figure 10). Moreover, due to an overall yield of 42% for **31** and **32**, a minimal tendency for side reactions,

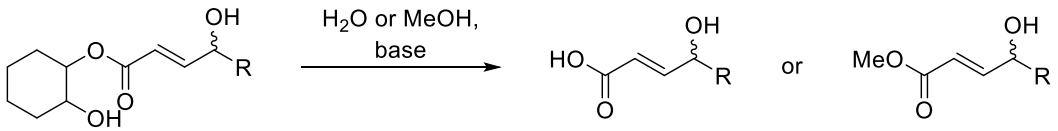
and a more practicable reaction control the acylation-epoxidation-elimination route is more promising.

First of all, an one-pot approach starting from diol and unsaturated acid should be tested. Therefore, the established individual protocols can be combined directly (Scheme 25). Re-optimization concerning, e.g., a consistent solvent or the amount of base for the elimination might be necessary. In additions, more acids can be included in these investigations.



Scheme 25: One-pot acylation-epoxidation-elimination sequence.

Based on the formation of diols **2** and **3** as well as methyl ester **37** (Figure 14) using the thiol-based strategy, a hydrolysis/transesterification procedure should be established simultaneously utilizing either water or methanol as nucleophile under basic conditions. This final step of a four-step sequence would provide free as well as methyl-protected α,β-unsaturated γ-hydroxyl carboxylic acids (Scheme 26). These compounds are, for example, metabolites of biologically active molecules or could be used as starting materials for lactones.[83] Afterwards, this protocol should also be incorporated into the one-pot approach leading to a four-step sequence: acylation-epoxidation-elimination-hydrolysis/trans-esterification.

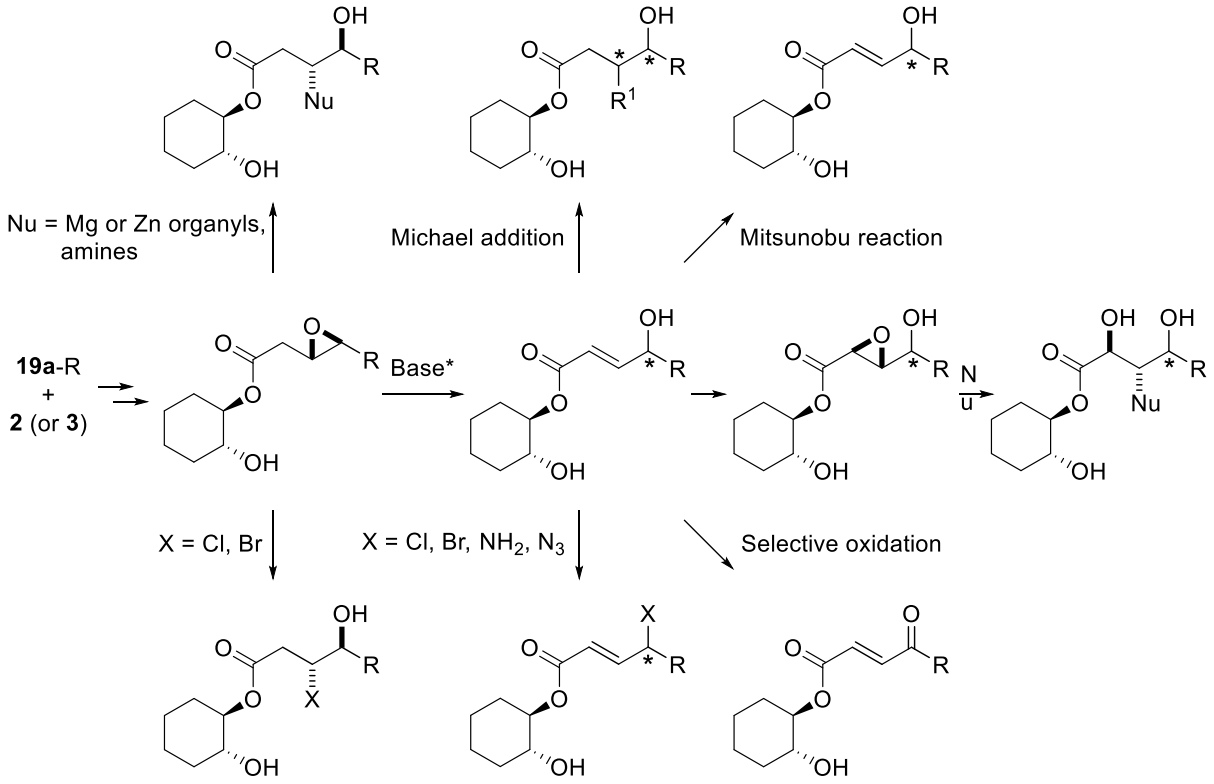


Scheme 26: Envisaged hydrolysis/transesterification step.

However, even in case of a stereoselective variant, before release of the acid derivative further transformations are possible. Hereof, each intermediate might be a potential starting point for an additional functionalization (Scheme 27).

Starting directly from the epoxide zinc[84] as well as magnesium organyls[85] might be utilized as alternatives to their lithium or copper analogs with regard to a higher chemoselectivity (Chapter 3.4.2.2.). These types of nucleophilic carbon species have already been used in epoxide opening reactions, but due to the aforementioned problems these approaches are less promising.

Instead of carbon nucleophiles halogens also induce ring-opening reactions. In 2006, Wu *et al.* established an thiophenol-promoted epoxide opening with elemental iodine.[86] Four years later, Ducho *et al.* published a similar reaction with sodium bromide in the presence of Amberlyst® 15.[87] Installing these functional groups in the molecule enables further transformations such as carbon-carbon bond formation or substitution reactions.



Scheme 27: Further potential functionalization approaches.

Performing either the epoxidation in a stereoselective fashion or the following elimination with a feasible chiral base could provide enantiomerically enriched *α*,*β*-unsaturated *γ*-hydroxyl esters. Referring to crotonic acid derivatives **17** and **18**, these Michael systems might also react in an 1,4-addition. Results of Sakai and of the first experiments (Chapter 3.4.1.) showed the potential of this concept, whereas re-optimization and further investigations are necessary.[69]

Substitution of the allylic hydroxyl group by a bromide, chloride, amine or azide group represents a further attractive opportunity. The corresponding (pseudo)halogen derivatives would enable a variety of consecutive reactions like, e.g., carbon-carbon bond formation or reduction. Introducing, for example, an amine would lead to the synthesis of unsaturated *γ*-amino acids.[88]

Furthermore, configuration of the hydroxyl group can be inverted either by using the reversible configured epoxidation catalyst or base or *via* a subsequent Mitsunobu reaction. A selective

oxidation of the allyl alcohol would provide the corresponding unsaturated 1,4-dicarbonyl compounds.[89] The previous steps can be performed in an achiral way, because the stereo-information gets lost during this reaction anyway.

Finally, α,β-unsaturated γ-hydroxyl esters can be epoxidized under typical Weitz-Scheffer conditions utilizing hydrogen peroxide and sodium hydroxide.[76a] Afterwards, the instantly formed three-membered rings can be opened by nucleophiles. Introducing, for example, a hydroxyl group would lead to triol-substituted carboxylic acids. Uronic and especially glucuronic acid, the C_6-analogs, have versatile applications in industry.[90] In case of an amine moiety an access to β-amino acids with two alcohol groups in α- as well as γ-position would be possible.[88]

Several of the aforementioned pathways lead to the introduction of new hydroxyl groups in the target molecules. After a possible ring closing reaction *via* transesterification between one of the alcohol moieties and the present ester the auxiliary is released and a lactone is formed. These compounds are well known as macrolactones and are intensively utilized as antibiotics.[91]

It has to be investigated in detail if the necessity regarding a cyclohexanediol ligand is really given or if the particular reaction sequence can be performed either with the free acid moiety or in the presence of an alternative and simpler protecting group. Yet, highly functionalized and flexible structured carboxylic acid derivatives can be synthesized based on this strategy.

4. Peptide-Catalyzed Epoxidation

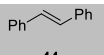
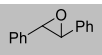
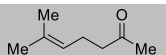
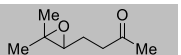
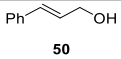
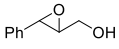
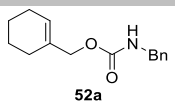
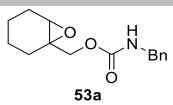
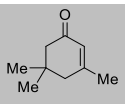
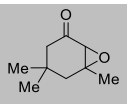
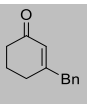
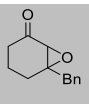
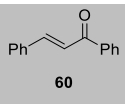
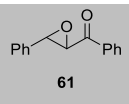
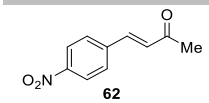
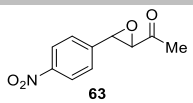
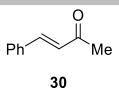
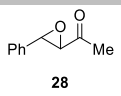
Epoxidation of a carbon-carbon double bond is the second step of the modified multicatalytic sequence as well as of each possible variant (Chapter 3.4.4.). For a multicatalytic approach the early introduction of stereoselectivity favors, e.g., formation of only one diastereomer or potential substrate control in the subsequent steps. Therefore, identification of a feasible catalytic moiety, reaction conditions, and especially an enantioselective version is a further challenge of this thesis.

4.1. Preparatory Work

4.1.1. Substrate Library

Due to the formation of diastereomers epoxidizing alkenes **24** and **25** a substrate library containing a variety of simpler prochiral compounds was established (Table 14). The epoxides were synthesized utilizing typical procedures either with *m*CPBA (Prileschajew epoxidation)[70a] or H_2O_2/NaOH (Weitz-Scheffer epoxidation)[76a] (see Experimental Section).[76b, 70b, 92]

Table 14: Substrate library.

Alkene	Epoxide	Alkene	Epoxide	Alkene	Epoxide
 **38**	 **39**	 **40**	 **41**	 **42**	 **43**
 **44**	 **45**	 **46**	 **47**	 **48**	 **49**
 **50**	 **51**	 **52a**	 **53a**	 **54**	 **55**
 **56**	 **57**	 **58**	 **59**	 **60**	 **61**
 **62**	 **63**	 **30**	 **28**		

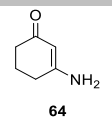
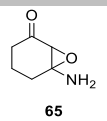
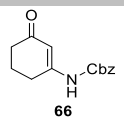
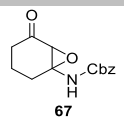
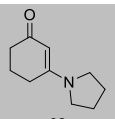
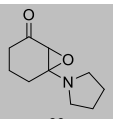
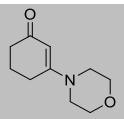
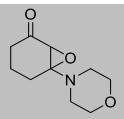
Alkenes **38**, **42**, **44**, **46**, **48**, **50**, **54**, and **56** as well as epoxide **45** are commercially available.

After purification the epoxides were obtained with a yield of up to 89%. The created substrate library includes cyclic and linear compounds, conjugated and isolated double bonds as well as electron-rich and electron-deficient alkenes. Moreover, due to the presence of aromatic and aliphatic substituents as well as hydrogen bonding acceptors and donors π-π-contacts,

dispersion, and hydrogen bonding are later on possible interactions between substrate and catalyst.

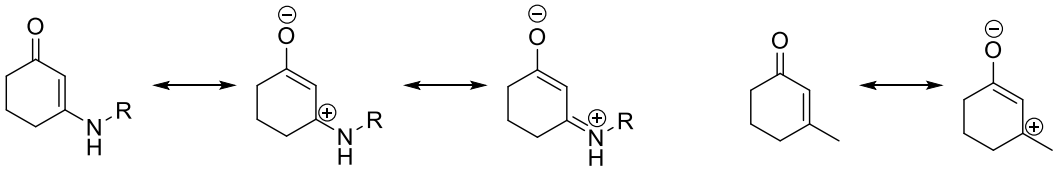
We also want to include nitrogen-containing molecules in further investigations. We chose *α*,*β*-unsaturated alkenes **64**, **66**, **68**, and **70** as further candidates (Table 15).

Table 15: Unsuccessful epoxidation of nitrogen-containing substrates.

Alkene	Epoxide	Alkene	Epoxide
 **64**	 **65**	 **66**	 **67**
 **68**	 **69**	 **70**	 **71**

Alkenes **64**, **68**, and **70** are commercially available.

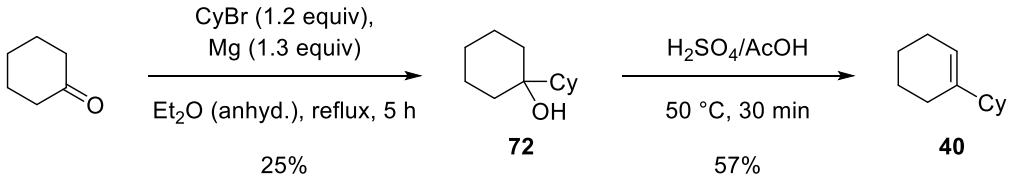
Epoxidation reactions both with sodium hydroxide and hydrogen peroxide as well as *m*CPBA were performed, but none of the desired epoxides was obtained. In literature significantly less examples for epoxidation of nitrogen-substituted alkenes can be found compared with their nitrogen-free analogs. Whereby, Michael systems seem even harder to be epoxidized in contrast to electron-rich systems.[93] We assume that the increased mesomeric delocalization and the further reduced electron density, respectively, is responsible for lower reactivity (Scheme 28). Therefore, we refrain from incorporating this class of substrates into the existing substrate library.



Scheme 28: Comparison of delocalization situations.

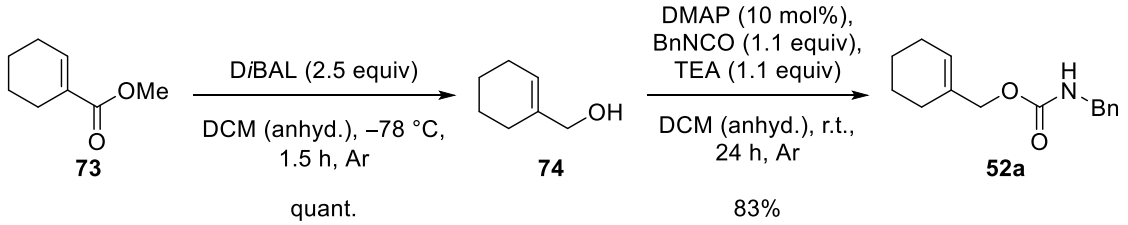
4.1.2. Synthesis of Alkenes

Since not all of the alkenes are commercially available, the corresponding epoxy precursors had to be synthesized previously. Thus, cyclohexyl derivative **40** is accessible *via* a two-step synthesis analogue to its phenyl derivative.[94, 85] After Grignard reaction of cyclohexanone and cyclohexyl bromide water is eliminated from alcohol **72** in the presence of sulfuric acid (Scheme 29). Alkene **40** was obtained with an overall yield of 14%.



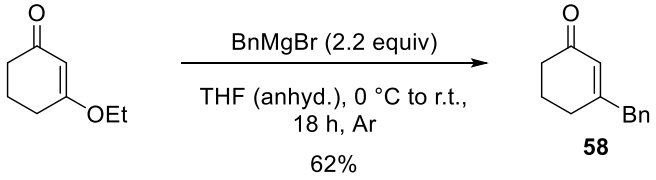
Scheme 29: Synthesis of alkene **40**.

Miller *et al.* utilized carbamate **52a** as test substrate in an enantioselective epoxidation with peracid-bearing peptide catalysts (Scheme 14). They postulated advantageous hydrogen bonding between peptide backbone and the urethane moiety.[33b] Therefore, we used their established protocol to synthesize alkene **52a** for our library. After reduction of methyl ester **73** with diisobutylaluminium hydride (D*i*BAL), the generated allyl alcohol **74** reacted with benzyl (Bn) isocyanate to yield carbamate **52a** in an overall yield of 83% (Scheme 30).[33a]



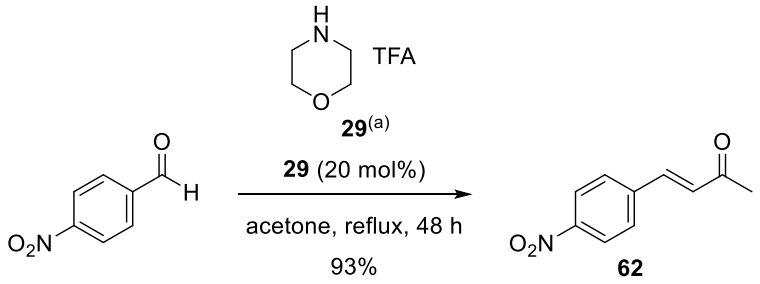
Scheme 30: Synthesis of carbamate **52a**.

Benzyl-substituted cyclohexenone **58** was synthesized using the protocol of List and co-workers.[95] 3-Ethoxy-2-cyclohexen-1-one reacts with benzylmagnesium bromide providing 62% of the *α,β*-unsaturated compound (Scheme 31). The challenging separation of formed benzyl alcohol might be simplified by reducing the amount of Grignard species.



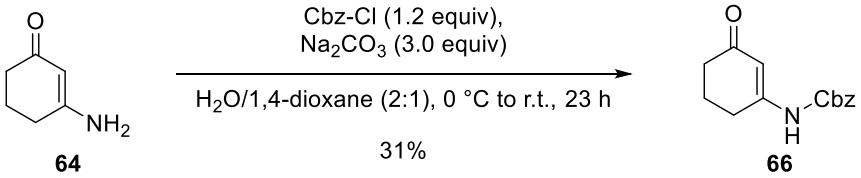
Scheme 31: Synthesis of Michael system **58**.

Analogue to alkene **30** (Scheme 20) we also synthesized an even more electron-deficient derivative *via* introducing a nitro group in *para*-position of the phenyl ring. After aldol condensation of *para*-nitrobenzaldehyde and acetone, substrate **62** was obtained with a yield of 93% after 48 hours (Scheme 32).[76c]



Scheme 32: Synthesis of *α,β*-unsaturated alkene **62**.
(a): TFA salt **29**: morpholine (1.0 equiv), TFA (1.1 equiv), Et_2O, 0 °C, 1 h, 94%.

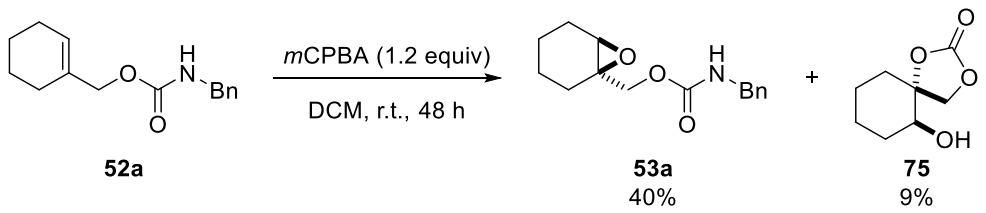
Simultaneously to the epoxidation of alkene **64** containing a free amine group we protected this functional group to avoid its possible interference in the subsequent epoxidation step. For protection we selected a carboxybenzyl (Cbz) group. Therefore, amine **64** reacts with Cbz chloride in the presence of sodium carbonate as base.[96] After purification the Cbz-protected analog was isolated with a yield of 31% (Scheme 33).



Scheme 33: Synthesis of Cbz-protected Michael system **66**.

4.2. Digression I: Access to *α*-Hydroxyl-Carbonates

Epoxidizing carbamate **52a** with *m*CPBA obviously yielded to epoxide **53a**, but also to an unknown side product. After isolation and purification latter compound was examined *via* NMR, infrared (IR), and MS techniques all pointing at carbonate **75** (Scheme 34). The formation of carbonates appearing during the *m*CPBA-mediated epoxidation of (homo)allylic alcohols was investigated by Kocovsky *et al.* in 1990.[97]



Scheme 34: Observation of spiro-carbonate **75**.

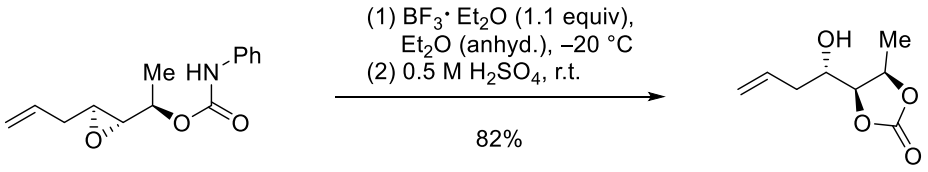
As mentioned in literature, especially IR and ^{13}C-NMR analysis are suitable tools showing characteristic signals for carbonate species.[98] Therefore, comparing our obtained results with data reported in literature showed a good agreement (Table 16). Moreover, a crystal structure of carbonate **75** underpinned the additionally formed by-product (see Experimental Section).

Table 16: Comparison of IR- and NMR-data.

	IR (C=O)	^{13}C-NMR (C=O)
Literature	1800 ± 20 cm^{-1}	152.5 ± 4.5 ppm
Experiment	1777 cm^{-1}	154.9 ppm

Organic carbonates (OC) like **75** are substituted carbonic acid derivatives appearing in a large number of natural products[99, 98] and as intermediates in total syntheses.[100] Based on the substituents on the oxygen atoms OCs can be divided in different classes (e.g., hemi-carbonic acids and carbonates as well as inorganic and organic, saturated and unsaturated, aliphatic and aromatic, linear and cyclic carbonates).[101] Due to their beneficial properties (e.g., high stability, high boiling point, high flash point, low toxicity),[102, 98] (cyclic) carbonates are widely applied,[101, 103, 102] e.g., as solvents,[104] protecting groups,[103] and synthons for typical organic reactions.[103, 102] Besides fixation of carbon dioxide,[105] oxidative carbonylation,[106] and carbonate interchange reactions as well as carbonyl building blocks like phosgene or its derivatives, metal carbonates, and urea[107] are literature-described strategies for the syntheses of OCs.[101, 98] Over the last couple of years organocatalytic approaches were also developed. Plasseraud *et al.* published the carbonate interchange reaction between glycerol and dimethyl carbonate utilizing a zwitterion catalyst in 2009.[108] More recently, Lu *et al.* introduced a carboxylative cyclization of propargylic alcohols catalyzed by a *N*-heterocyclic olefin (NHO).[109]

The aforementioned procedures typically require either high pressure, high temperature or toxic starting materials or catalysts. In 1983, Roush *et al.* published a milder and alternative carbonate formation procedure using Lewis acid boron trifluoride diethyl etherate in anhydrous (anhyd.) diethyl ether (Scheme 35).[110] Afterwards, Roush's protocol[100a, 100c] as well as the unaccompanied carbamate strategy[111] are common in organic synthesis.



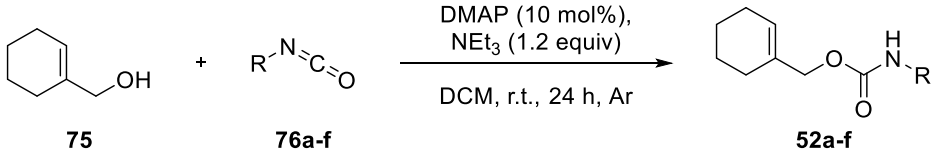
Scheme 35: Carbonate formation reported by Roush.

Phenyl carbamate substituted allyl epoxides were utilized as starting materials. The significance of the neighboring-group effect of this substituent was emphasized by testing various reaction conditions and considering molecular models.[110] During their investigations Roush *et al.*

showed that not only Lewis acid BF_3•Et_2O, but also weak Brønsted acids like acetic acid are able to generate OCs.[110] Therefore, we assume that during epoxidation of alkene **52a** *in situ* generated *meta*-chlorobenzoic acid (*m*CBA) is responsible for the carbonate formation.

Independently from the mechanism, a strong carbon-nitrogen bond must be cleaved during the formation of **75**. By substitution of the benzyl group we hope to favor the cyclization to carbonate **75**. Therefore, further carbamates with both aromatic as well as aliphatic isocyanates were synthesized with a yield of up to 71% using the protocol of Miller (Table 17).[33b] Due to a conjugated system in case of isocyanate **76b** its carbamate **52b** was isolated with a yield of only 52%. The amount of isolated alkenes **52c**-**e** decreased form ethyl to *tert*-butyl caused by an increased steric hindrance. Adamantyl (Ad) analog **52f** was only observed in the NMR spectrum of the crude product in traces, but could not be isolated.

Table 17: Syntheses of carbamates **52a-f**.



75 **76a-f** **52a-f**

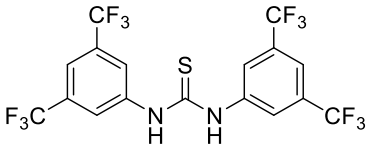
Compound	R	Yield of 52 [%]
a	Bn	83
b	Ph	52
c	Et	71
d	^{i}Pr	64
e	^{t}Bu	14[(b)]
f	Ad	traces[(a), (b)]

[(a)]: Remaining starting material reisolated; [(b)]: observed *via* NMR.

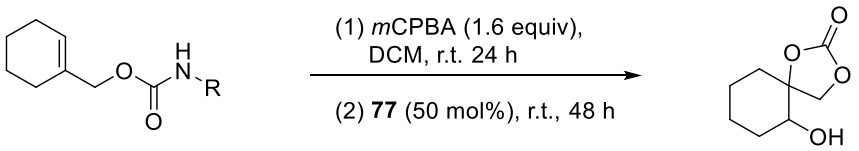
Testing carbamates **52a**-**e** afterwards in the epoxidation-cyclization sequence, product **75** was isolated with a yield of up to 82% (Table 18). In contrast to the synthesis of the epoxide **53a**, 1.6 equivalents of the oxidizer were used for those experiments, because a larger amount of present acid should favor the formation of the spiro compound. Furthermore, after detecting full conversion to the epoxide *via* TLC, thiourea catalyst (TUC) **77**[5] was added to activate either the carbonyl oxygen or the epoxide for the cyclization step.[74c, 75] Taking the first observation of carbonate **75** into account the reaction was stirred for further 48 hours (Scheme 34).

[5] Catalyst was synthesized by Dr. Katharina M. Lippert.

Table 18: Identification of the most feasible leaving group.



77



52a-e **75**

Compound	R	Yield of 75 [%]
a	Bn	75
b	Ph	59
c	Et	82
d	^{i}Pr	82
e	^{t}Bu	78

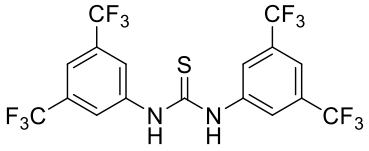
Analogue to its synthesis, phenyl derivative **52b** is less reactive due to mesomeric stabilization. In case of primary, secondary, and tertiary alkyl species the results are comparable indicating minor importance of the generated amine. Ethyl and *iso*-propyl precursors showed the best results. But, we prefer the ethyl derivative for several reasons. Ethyl isocyanate **76c** is less toxic compared to its phenyl, *iso*-propyl, and *tert*-butyl analogs. Furthermore, carbamate **52c** was synthesized with a preparative yield of 71% (Table 17). Moreover, generated ethyl amine is a gas shifting the equilibrium to the product side and simplifying the purification.

In our optimization experiments starting from carbamate **52c** besides thiourea **77** acidic additives nitrilotri(methylphosphonic acid) **78** and *p*NBA were included to cover a broader pK_a-range. Furthermore, variation of solvent, dilution, reaction time of the epoxidation step, and amount of *m*CBPA were also tested (Table 19).

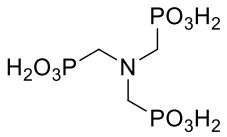
The best result was achieved performing the first step with 1.6 equivalents *m*CPBA for 24 hours in DCM and the second step with only 5 mol% of catalyst **77** (Table 19, Entry 18). Removing *in situ* formed *m*CBA is one of the major challenges. A two-step purification procedure containing solvent evaporation and column chromatography on silica gel with diethyl ether and 0.5% TEA provides **75** with a comparable yield. An increased isolated yield of 11% can be observed utilizing both *m*CPBA/*m*CBA and **77** (Table 19, Entries 18 and 20). Weil *et al.* already

described a cooperative effect between Brønsted and Lewis acids enabling the accelerated formation of the desired product.[74c] Zhang *et al.* investigated this kind of catalysis more detailed using NMR techniques and computational studies.[74c, 75] Both aspects lead to the assumption that a similar effect is responsible for the preferred formation of **75** utilizing a combination of *in situ* generated *m*CBA and catalytic amounts of **77**.

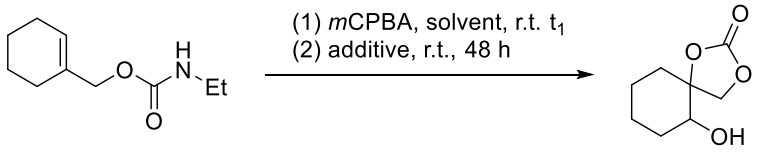
Table 19: Optimization procedure.



77



78



52c **75**

Entry	Solvent	*m*CPBA [equiv]	t_1 [h]	Additive	Additive [equiv]	Yield of 75 [%]
1	DCM	1.1	1	-	-	62
2	DCM	1.1	1	**77**	0.5	71
3	DCM	1.1	1	**78**	0.3	48
4	DCM	1.1	1	*p*NBA	1.0	54
5[(a)]	DCM	1.1	1	-	-	45
6[(a)]	DCM	1.1	1	**77**	0.5	56
7[(a)]	DCM	1.1	1	**78**	0.3	51
8[(a)]	DCM	1.1	1	*p*NBA	1.0	58
9[(a)]	DCM	1.1	8	**77**	0.5	69
10[(a)]	DCM	1.1	14	**77**	0.5	58
11[(a)]	DCM	1.1	24	**77**	0.5	69
12[(a)]	DCM/$PhCH_3$	1.1	8.5	**77**	0.5	67
13[(a)]	DCM/$CHCl_3$	1.1	8.5	**77**	0.5	60
14[(a)]	DCM/^{t}AmylOH	1.1	8.5	**77**	0.5	57
15	DCM	1.6	24	**77**	0.5	73
16	DCM	1.6	24	**77**	0.25	74
17	DCM	1.6	24	**77**	0.1	75
18	DCM	1.6	24	**77**	0.05	78

19	DCM	1.6	24	**77**	0.01	57
20	DCM	1.6	24	-	-	67

[(a)]: Epoxidation was performed with a conc. of 1.0 mol L^{-1} and reaction mixture was diluted after t_1.

To gain a deeper insight into the mechanism of the cyclization, we performed a labeling experiment. Therefore, epoxide **52a** reacts in the presence of *m*CBA and $H_2{}^{18}O$ under otherwise standard conditions for the second step to labeled carbonate **75-^{18}O**. Afterwards, comparison of the IR-spectra of **75** (1792 cm^{-1}) and **75-^{18}O** (1766 cm^{-1}) showed unequivocally that the ^{18}O-atom is located at the carbonyl group (Figure 15).

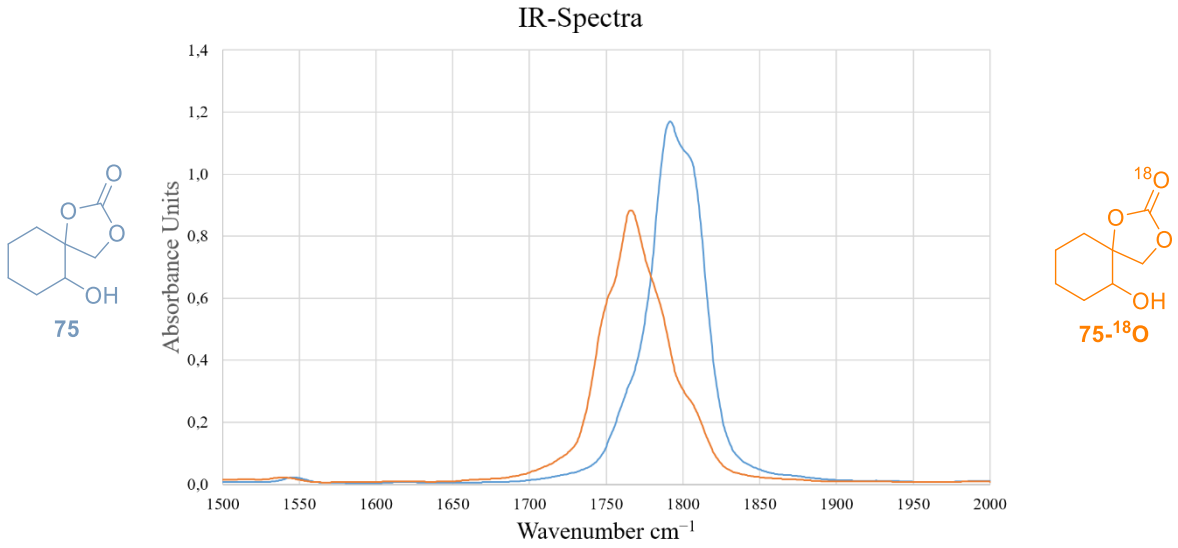
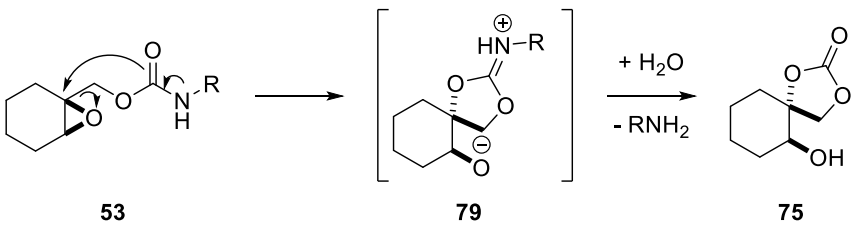


Figure 15: Comparison of the IR-spectra of **75** and **75-^{18}O**.

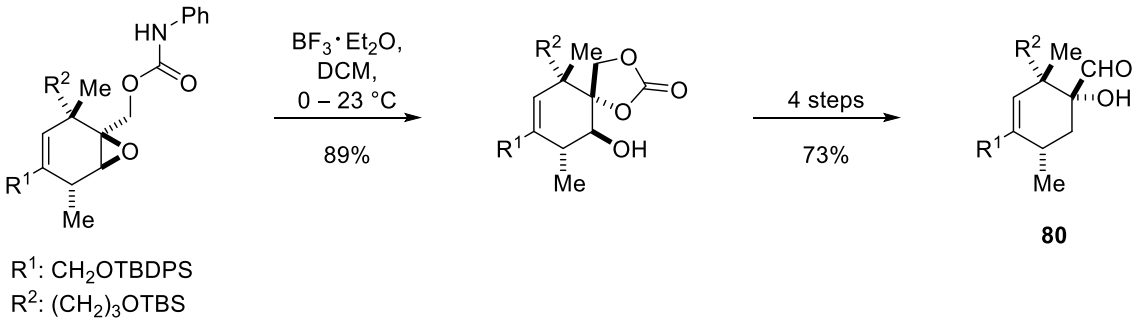
In 2012, Jirgensons *et al.* published the Lewis acid-catalyzed synthesis of *N*-tosyliminocarbonates starting from allylic trichloroacetimidates. From the educt to the desired product they postulated the existence of an ammonium species either by S_N1- or S_N2'-mechanism.[111b] Combining their considerations and our results from IR-analysis, we assume that the *in situ* formed iminium salt **79** is hydrolyzed by water, which is present form the utilized *m*CPBA providing spiro compound **75** (Scheme 36).



Scheme 36: Postulated mechanism for carbonate formation.

In the synthesis of bis-spiro tetronate Roush *et al.* used their protocol to introduce an aldehyde and a hydroxyl group in cyclohexene **80** at the same carbon atom (Scheme 37).[100c]

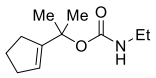
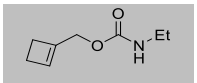
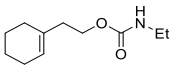
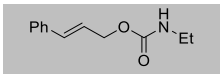
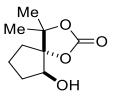
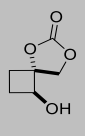
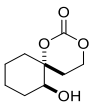
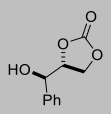
This reaction sequence shows a potential application for this type of reaction even for the synthesis of more complex compounds.



Scheme 37: Synthesis of geminal hydroxyl aldehyde **80**.

Our established protocol provides an access to a spiro center, a carbonate, and a hydroxyl group in one molecule. But before searching for an application, especially the function of thiourea **77** and its interaction with the Brønsted acid has to be studied more intensively. Furthermore, the limitations of this approach have to be identified *via* extension of the substrate scope (Table 20).

Table 20: Potential substrates.

Carbamate				
Carbonate				

Substitution of the isocyanate by its sulfur analog would furthermore provide an access to thiocarbonates. Utilizing an asymmetric epoxidation protocol leading to enantiomerically enriched intermediates in combination with the thiourea-based cyclization results in also enantiomerically enriched spiro compounds. Like Kocovsky, Miller, and Roush showed, the carbamate moiety plays a key role in the epoxidation of this two-step sequence.[110, 97, 33a] All the latter aspects illustrate the relevance of this approach.

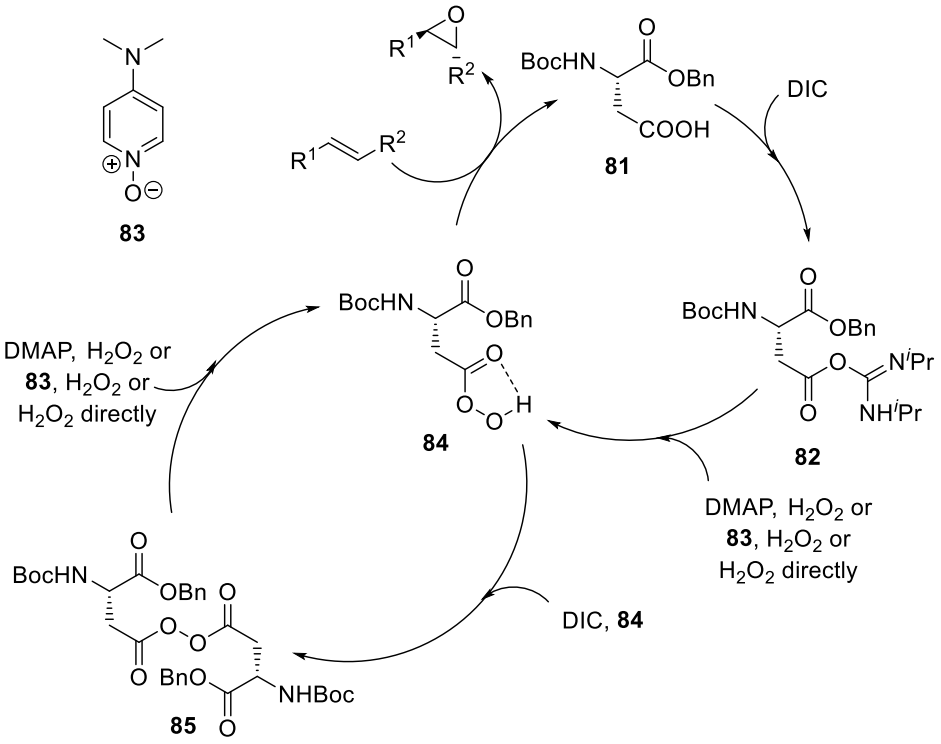
4.3. Peracid-Based Catalysts

One typical procedure for the epoxidation of electron-rich alkenes based on peracids like *m*CPBA. In 1909, Prileschajew mentioned the oxidative ability of peracids for the first time.[70a] We already used this procedure for the syntheses of oxiranes **39**-**53a** (Chapter 4.1.1.). Later on catalytic amounts of the necessary acid precursor in combination with *in situ* generation of the active peracid were intensively examined. For example, Miller and Schreiner utilized this

concept and introduced peptide-based acid catalysts, which are transferred into the reactive peracid species and regenerated after the epoxidation of the carbon-carbon double bond.[33, 31, 3b]

4.3.1. Mechanism

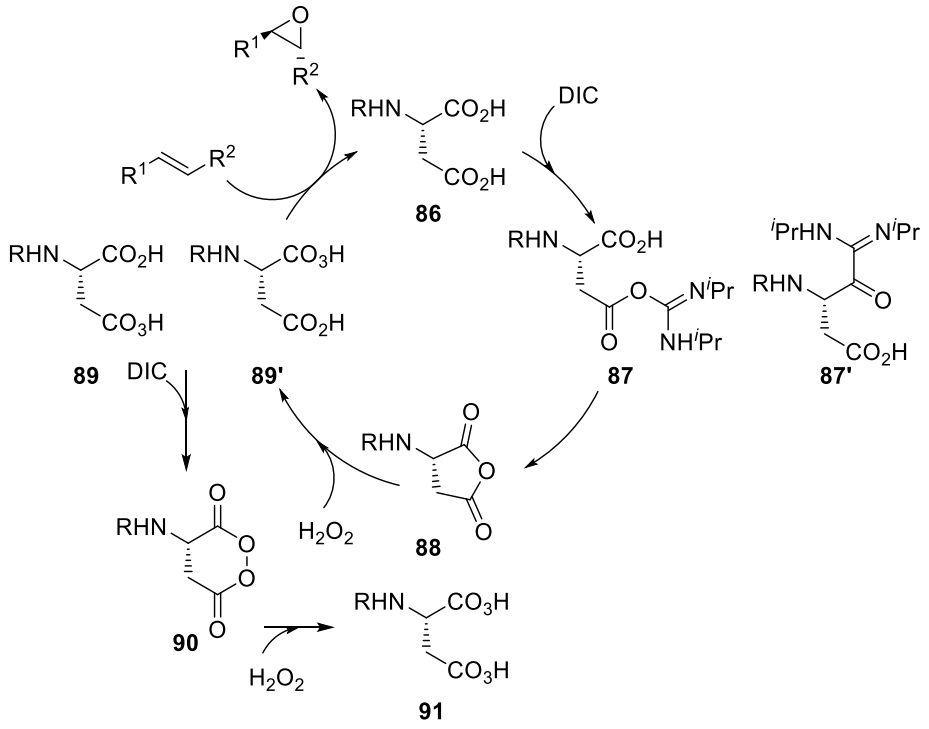
In 2007, Miller *et al.* published a possible catalytic cycle for the *in situ* generation of a peracid-containing peptide catalyst. They showed that a carbodiimide as activating and water-removing agent and DMAP as *N*-oxide equivalent and nucleophilic catalyst are necessary for the oxidation of the carboxylic acid (Scheme 38).[33a, 31]



Scheme 38: Epoxidation *via in situ* generated monoacid peptide catalyst.

Reaction of the carboxylic acid of *C*-terminal benzyl-protected amino acid **81** and DIC provides active ester **82**. The latter intermediate is transferred afterwards into catalytically active peracid **84** *via* nucleophilic attack of hydrogen peroxide. A possible side reaction of **84** is the DIC-mediated formation of aspartic peracid **85**. But, the reaction mixture converts this dimer back into peracid **85**. Miller and co-workers also showed that *N*-oxide **83**, which is also formed *in situ via* oxidation of DMAP, accelerates the whole process.

Instead of a monoacid Schreiner *et al.* utilized a diacid as catalytic moiety.[3b] Based on their previously performed test experiments, they concluded that an intermolecular anhydride is the key intermediate in their reaction cycle (Scheme 39).



Scheme 39: Postulated mechanism for the diacid-based epoxidation.

Similar to Miller's mechanism the first step is the formation of an active ester. At this stage it does not matter, if intermediate **87** or **87'** is generated. Due to the presence of the second acid moiety a cyclization to internal anhydride **88** takes place. Afterwards, the cyclic species is opened *via* hydrogen peroxide, providing peracids **89** and **89'**. If both catalytically active compounds favor the opposite enantiomer of the epoxide, it has to be guaranteed that the opening step should deliver one peracid selectively. Furthermore, activation of the remaining carboxylic acid could lead to intramolecular peracid **90**, analogue to compound **85** (Scheme 38). *Via* ring opening with hydrogen peroxide, diperacid **91** could be generated. Both the selective generation of peracids **89** and **89'** as well as the formation of **91** complicates the establishment of an asymmetric version based on this concept.

In 2015, Schrader *et al.* examined this mechanism in more detail using MS techniques. They identified *in situ* formed peptide species and followed the reaction progress of the epoxidation. But firstly, they started from homoaspartic acid as precursor so both possible peracids are identical. Secondly, diperacid **91** was not observed during their experiments.[36]

After formation of the peracid, the oxygen atom is transferred onto the carbon-carbon double bond in a concerted way.[112] Simultaneously, the peracid is reduced to the corresponding carboxylic acid, which can enter the catalytic cycle again. For the generation of the oxirane two different TSs are under discussion (Figure 16). The TSs **92** and **93** differ in orientation and

angle between alkene and peracid. Several theoretical and computational approaches were performed, but lead to partly opposed results.[113] The butterfly-like spiro structure **93** is the most accepted and commonly depicted TS.[114, 113a] One exception was published by Oshima *et al.* in 2012 examining the epoxidation of a highly crowded fulleroid system. Based on a slightly twisted double bond the spiro TS is inhibited.[112] In 2006, Luthman and co-workers investigated the influence of different alkene substituents on the stereoselective outcome. They observed a huge directing effect of those residues. They also showed that *via* changing the active species the reaction outcome can be inverted.[115] Both examples also illustrate a substrate as well as reagent dependence.

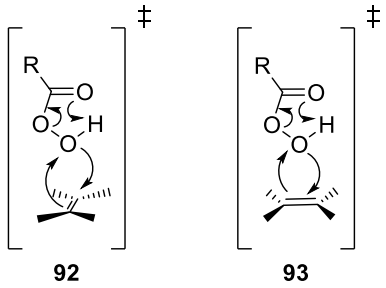
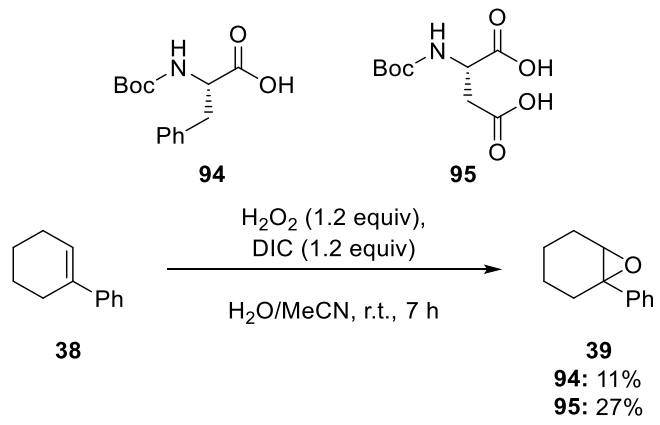


Figure 16: TSs for the peracid-based epoxidation.

4.3.2. Proof of Principle

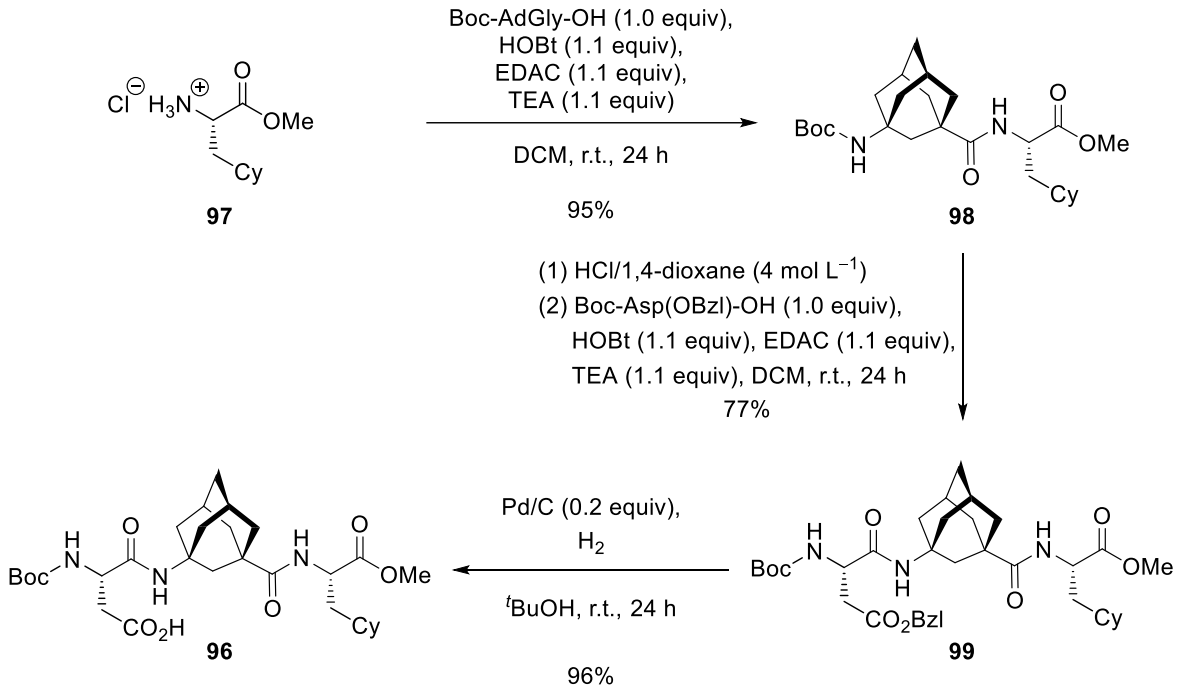
For proofing the concept phenylcyclohexene **38** was epoxidized both with a monoacid- as well as a diacid test catalyst. Under chosen reaction conditions based on Miller *et al.* and Schreiner *et al.* aspartic acid **95** is nearly twice as active as phenylalanine (Phe) **94** (Scheme 40).[33a, 3b] These observation indicate that either two carboxylic moieties react faster than one or the *in situ* generation of an intramolecular anhydride accelerates the whole reaction process. The formation of an activated species was also proofed. In both control experiments without DIC as activating agent no reaction took place.



Scheme 40: Proofing the concept with a mono- as well as a diacid catalyst.

4.3.3. Peptide Catalysts

Taking even the latter results into account mono- as well as diacid-containing peptide catalysts were synthesized. Furthermore, proline and adamantyl glycine were used as structure-giving elements like in the well working systems of Miller and Scheiner.[33, 31, 3b] The synthesis of tripeptide **96** is exemplarily depicted in scheme 41.



Scheme 41: Exemplary synthesis of a peptide catalyst.

Peptide coupling was performed in solution and with 1-hydroxybenzotriazole (HOBt) and EDAC as coupling reagents.[68, 3a] The Boc protecting group was removed by hydrogen chloride in dioxane.[116, 3a] The benzyl ester was cleaved under reductive conditions in *tert*-butanol.[116, 3a] Methanol was not used as solvent because transesterification was observed in previously performed experiments. Finally, tripeptide **96** was isolated with a total yield of 70% after four steps.

Utilizing analogue conditions three additional peptides were synthesized (Figure 17). The aspartic acid moiety at the *C*-terminus of peptide **101** was protected as dimethyl ester. Both protecting groups were removed simultaneously with a sodium hydroxide/ *N*,*N*-dimethylformamide (DMF) protocol.[117] In the end all peptides were isolated in preparative amounts after up to 8 steps.

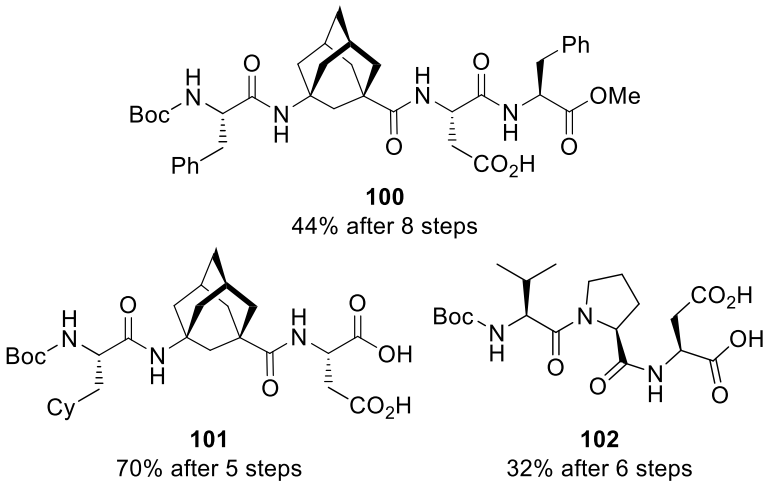
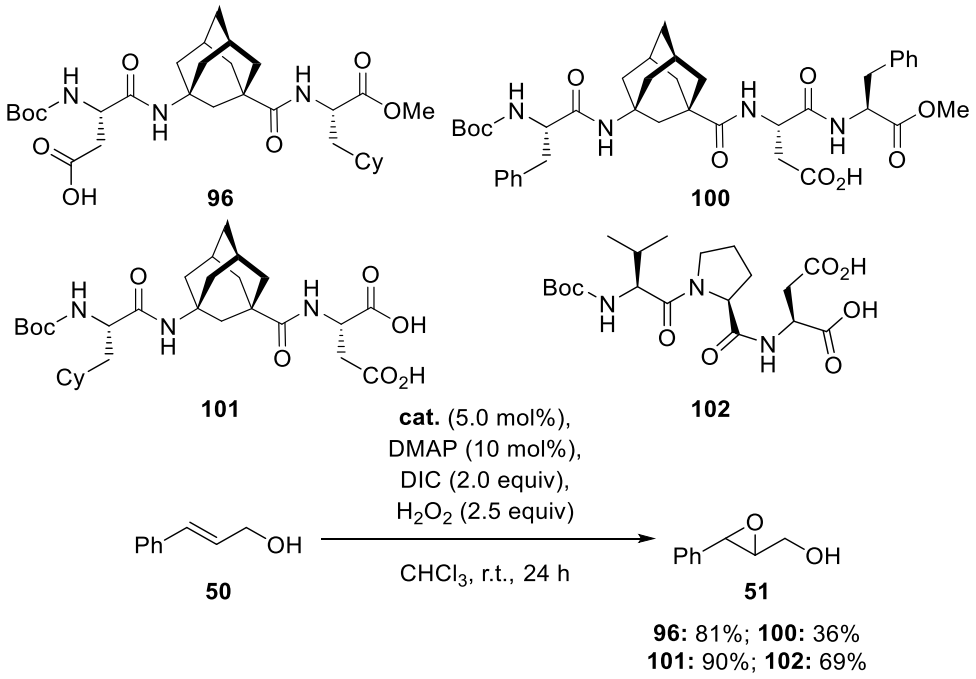


Figure 17: Peptide catalysts **100**, **101**, and **102**.

4.3.4. Optimization of Reaction Conditions

For a better comparison all four catalysts were tested utilizing slightly modified reaction conditions of Miller.[33a] Therefore, in the presence of DIC, DMAP, and H_2O_2 cinnamic alcohol **50** was transferred into its epoxide **51** mediated by a mono- or diacid-containing peptide. A reduced amount of 5 mol% catalyst and chloroform instead of dichloromethane (DCM) was used (Scheme 42).

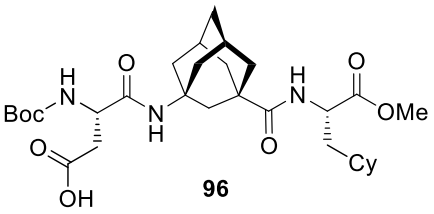


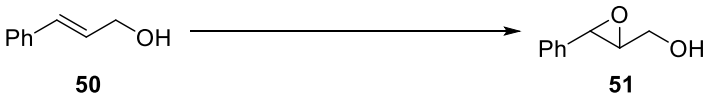
Scheme 42: Comparison experiment.

Comparing the results for **96**, **101**, and **102** a preference for diacid peptide catalysts was not observable. Tetrapeptide **100** showed the lowest conversion after 24 hours. Obviously, based on those first ambiguous results further investigations of the reaction conditions were carried

out. Therefore, the different parameters, e.g., temperature, catalyst loading, and solvent, were varied stepwise. Tripeptide **96** and cinnamic alcohol **50** were chosen as test system. Due to its better solubility in organic solvents without additives compared to EDAC and its simpler dosing compared to DCC we selected DIC as carbodiimide (Table 21).

Table 21: Optimization of peracid-based epoxidation.





Entry[(a)]	96 [mol%]	Solvent	Oxidizer [equiv]	DIC [equiv]	DMAP [mol%]	T [° C]	t [h]	Yield[(d)] [%]
1	0	DCM	H_2O_2 (4.0)	1.2	0	r.t.	48	0
2	2.5	DCM	H_2O_2 (4.0)	1.2	0	r.t.	48	55
3	5.0	DCM	H_2O_2 (4.0)	1.2	0	r.t.	24	80
4	10	DCM	H_2O_2 (4.0)	1.2	0	r.t.	24	66
5	20	DCM	H_2O_2 (4.0)	1.2	0	r.t.	24	36
6	5.0	DCM	H_2O_2 (4.0)	1.2	10	r.t.	24	61
7	5.0	$PhCH_3$	H_2O_2 (4.0)	1.2	0	r.t.	24	67
8	5.0	$CHCl_3$	H_2O_2 (4.0)	1.2	0	r.t.	24	80
9	5.0	$CHCl_3$	H_2O_2 (2 x 2.0)[(b)]	1.2	0	r.t.	24	65
10	5.0	$CHCl_3$	UHP (4.0)	1.2	0	r.t.	24	13
11[(c)]	5.0	$CHCl_3$	H_2O_2 (2.5)	2.0	10	r.t.	24	81
12	5.0	$CHCl_3$	H_2O_2 (2 x 2.0)[(b)]	1.2	0	0	24	16
13[(c)]	5.0	$CHCl_3$	H_2O_2 (2.5)	2.0	10	0	24	37

[(a)]: 0.25 mmol alkene and 2 mL solvent were used; [(b)]: second addition of H_2O_2 (2.0 equiv) after one hour; [(c)]: reaction conditions based on Miller *et al.*; [(d)]: yield determined *via* chiral GC without internal standard.

Varying the catalyst loading showed a maximum yield of epoxide **51** with 5 mol% of tripeptide **96** (Table 21, Entry 3). As expected, without catalyst no reaction took place (Table 21, Entry 1) proofing the necessity for the presence of a carboxylic acid species. For enabling better substrate-catalyst interactions and resulting enantiomeric excess toluene was chosen as solvent,[2c] which did also not show the expected effect (Table 21, Entry 7).

Whereas, chloroform and DCM led to the same results (Table 21, Entries 3 and 8). More polar solvents like THF, 1,4-dioxane ant *tert*-amyl alcohol were also tested, but only traces of the product could be detected (not included in Table 21). Regarding the oxidizing agent a portionwise addition provided epoxide **51** with a minimal reduced yield (Table 21, Entry 9). Whereby, due to its decreased activity urea hydrogen peroxide (UHP) can be neglected as oxidizer (Table 21, Entry 10). A decelerated reaction process was also observed lowering the temperature. Utilizing the conditions of Miller provide the target compound with a higher yield, although the results cannot be compared directly because three parameters differ in these experiments (Table 21, Entries 9 and 11-13). We assume that, especially the increased amount of DIC is coursing this effect, because we were not able to observe the described DMAP dependence utilizing our conditions (Table 21, Entries 3 and 6). Summarizing best results were achieved performing the epoxidation with 5 mol% catalyst in either chloroform or DCM mediated *via* 1.2 equivalents DIC and 4.0 equivalents hydrogen peroxide (Table 21, Entries 3 and 8).

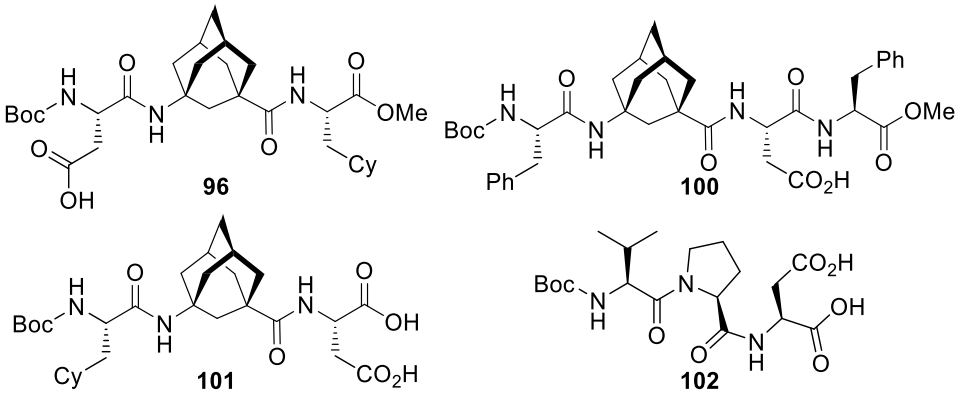
4.3.5. Substrate Scope

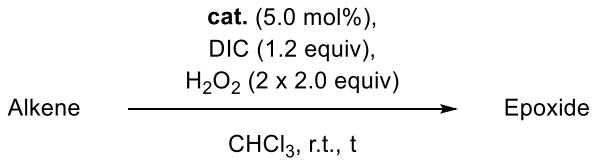
Even knowing that addition of hydrogen peroxide in one portion (Table 21, Entries 8 and 9) and a larger amount of DIC (Table 21, Entries 11 and 13) are favorable for the epoxide formation we selected the conditions mentioned in entry 9 for all further experiments. Regarding the introduction of a stereoinformation we thought slowing down the reaction rate minimally *via* adding the unstable oxidizer portionwise and reducing the amount of reagents present in the reaction mixture are beneficial factors. Hereafter, peptides **96** and **100**-**102** were tested in combination with alkenes **38**, **40**, **44**, and **56** to gain a deeper insight into the catalyst-substrate relationship (Table 22).

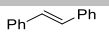
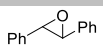
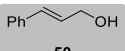
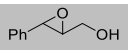
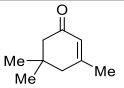
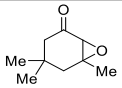
As expected for all catalysts completely conjugated alkene **44** (Table 22, Entries 3, 8, 13, and 18) as well as electron-deficient alkene **56** (Table 22, Entries 5, 10, 15, and 20) showed nearly no reactivity. Only catalyst **96** epoxidized cinnamic alcohol **50** with a preparative yield of 77% (Table 22, Entry 4), while all further catalyst showed a clearly lower reactivity (Table 22, Entries 9, 14, and 19). In contrast substrates **38** (Table 22, Entries 1, 6, 11, and 16) and **40** (Table 22, Entries 2, 7, 12, and 17) were converted into the corresponding epoxides with good to excellent yields. A real catalyst-dependent tendency for the preference of aromatic or aliphatic starting materials is not observable. Compared with the proof of principle experiments diacid catalysts did not show an accelerated epoxidation compared to the monoacid peptides

(Scheme 40). Catalyst **102** containing proline as structure-forming element showed a faster formation of the target oxirane compared to its adamantyl analog **101** maybe coursed by the lower positive inductive (+I) effect or the smaller steric hindrance (Table 22, Entries 11-12 and 16-17). But, none of the tested acid-based catalysts led to an enantiomeric excess for one of the used alkenes.

Table 22: Substrate scope for the peracid-mediated epoxidation.





Entry[(a)]	Cat.	Alkene	Epoxide	t [h]	Yield[(d)] [%]
1	**96**	 **38**	 **39**	72	97
2	**96**	 **40**	 **41**	72	14
3	**96**	 **44**	 **45**	72	6
4	**96**	 **50**	 **51**	72	77
5	**96**	 **56**	 **57**	72	0
6	**100**	**38**	**39**	24	48
7	**100**	**40**	**41**	24	quant.
8	**100**	**44**	**45**	48	11
9	**100**	**50**	**51**	48	0
10	**100**	**56**	**57**	48	0

11	**101**	**38**	**39**	72	24
12	**101**	**40**	**41**	72	63
13	**101**	**44**	**45**	72	1
14	**101**	**50**	**51**	72	33
15	**101**	**56**	**57**	72	0
16	**102**	**38**	**39**	24	36
17	**102**	**40**	**41**	24	68
18	**102**	**44**	**45**	24	1
19	**102**	**50**	**51**	24	5
20	**102**	**56**	**57**	24	0

[a]: 0.25 mmol alkene and 2 mL solvent were used, the second addition was carried out after one hour; [b]: yield determined *via* chiral GC without internal standard.

Comparing the results for alkene **50** based on our (Table 22, Entries 4, 9, 14, and 19) and Miller's conditions (Table 21, Entry 11) showed an obvious preference for the latter ones. For all catalysts higher yields were achieved in a shortened reaction time of only 24 hours. Therefore, our underlying idea was wrong and for all further experiments Miller's conditions should be used.

4.3.6. Summary and Outlook

We synthesized four carboxylic acid peptides containing either mono- or diacids as precursors. Afterwards, those catalysts were tested in epoxidation reactions of several alkenes utilizing our reaction conditions. Electron-rich but unconjugated compounds are the preferred substrates. Even if good to excellent results were achieved very long reaction times were required.

In future experiments additional starting materials from the substrate library should be included. For shortening the reaction time DIC and hydrogen peroxide should be added continuously, for example, *via* syringe pump. Besides further educts and a varied adding procedure, further catalyst-related aspects should be taken into consideration (Figure 18). Due to the advantageous effect of proline this amino acid should be used as structure-forming element. For shortening the distance between peptide backbone and reactive center phthalic acid or 1,2-diamines might be used as key building blocks. In this regard C_2-symmetric systems are accessible. Moreover, these molecules can also help to circumvent the problem of peracid formation. After opening of the *in situ* generated intramolecular anhydride both possible active forms are identical. Therefore, based on the aforementioned results in combination with this outlook regarding a peracid-catalyzed epoxidation a variety of possible changes are still conceivable.

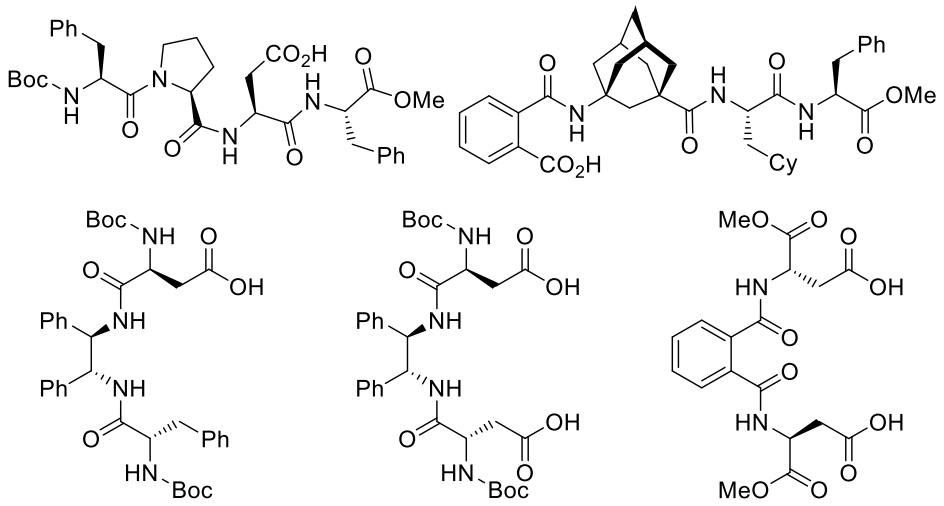


Figure 18: Additional carboxylic acid containing peptide catalysts.

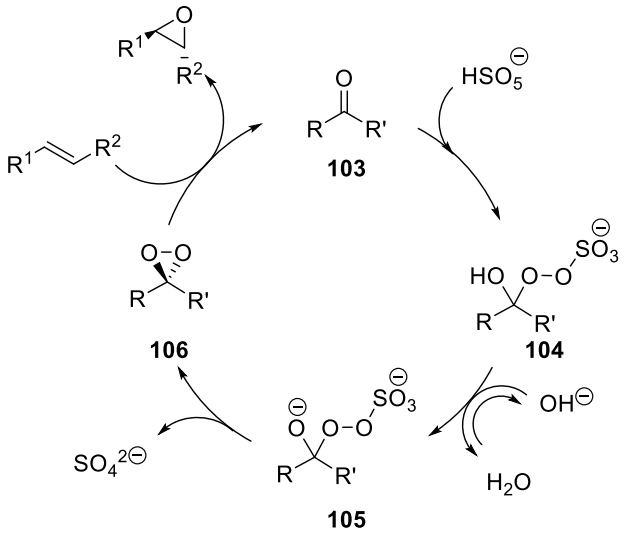
4.4. Dioxirane-Based Catalysts

Besides peracids dioxiranes are also widely used to epoxidize electron-rich alkenes. The reactive intermediate is normally also formed *in situ* starting form a carbonyl precursor and an oxidizing agent like Oxone®. Considering the carbonyl compound both catalytic as well as stoichiometric protocols are described in literature.[118, 43a] The most widely spread stoichiometric versions base on acetone and its derivatives.[119] Using a chiral ketone would enable an asymmetric epoxidation. The most famous catalytic carbonyl precursor in this regard was published by Shi and co-workers (Scheme 16).[54] But, of course there are a variety of further chiral ketone-based systems.[120a-c, 43c, 120d, 43d]

4.4.1. Mechanism

Due to the fact that dioxiranes are an intensively studied class of compounds both *in situ* formation of the active species as well as oxygen transfer are well examined *via* theoretical and experimental studies.[118, 121, 54, 113a, 55] In 1997, Shi *et al.* described the *in situ* formation of the dioxirane species based on their famous fructose-derived catalyst. In basic solution Oxone® was used a oxidizing agent to form the corresponding cyclic intermediate (Scheme 43).[55]

Carbonyl precursor **103** is nucleophilically attacked by peroxomonosulfate the reactive species of Oxone®. Under basic conditions the formed hydroxyl group of oxidized intermediate **104** is deprotonated. Hereafter, generated alkoxide **105** cyclizes under release of one equivalent of sulfate. One of the oxygen atoms of dioxirane **106** is afterwards transferred onto the double bond providing the corresponding epoxide. Thereby carbonyl species **103** regenerates and is available for the next catalytic cycle.



Scheme 43: Oxone®-based epoxidation of carbon- carbon double bonds.

This catalytic cycle helps to understand the presence of electron-withdrawing substituents like fluorine or trifluoromethyl next to the carbonyl group. Due to their electronic properties they lead to a lower electron density at the carbonyl carbon atom, which is therefore activated for the nucleophilic attack of the active species.[119b, 119c, 122a, 120b, 122b, 120c, 57] If there are more potential precursors present in a catalyst those residues help to transfer only this specific atom into the active species.

After formation of the three-membered catalytically active intermediate **106** (Scheme 43) one of the oxygen atoms is transferred onto the alkene. Analogue to peracids a planar **107** as well as a spiro TS **108** are discussed (Figure 19). Both experimental and theoretical investigations proof the prioritization of the spiro TS **108** also for the dioxirane-mediated epoxidation.[113a, 123, 120c]

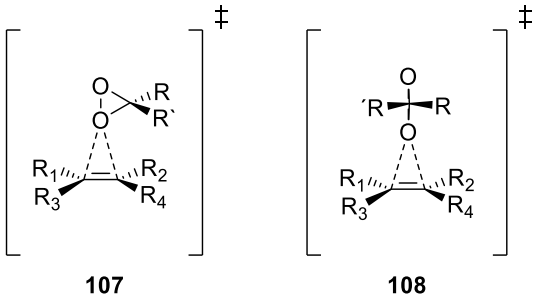


Figure 19: TSs for the dioxirane-mediated epoxidation.

The central quaternary carbon atom of the dioxirane is not chiral because of its two identical substituents (see **106** Scheme 43). For an enantiomeric version two possible strategies can be followed (Figure 20).[120c, 120d] Firstly, one of the substituents must be really crowded shielding one side of the system. Catalysts like Shi's fructose derivative base on this approach allowing

the coordination of the alkene to the catalyst only from the sterically less hindered side (Figure 20, left).[55, 123, 120b, 124, 57] Secondly, if the catalyst possesses a C_2-symmetry both trajectories are identical leading to the same epoxidation product (Figure 20, right).[56, 120a]

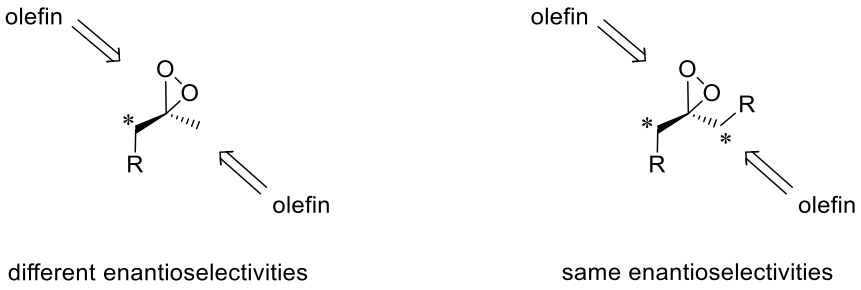


Figure 20: Solution approaches for an enantioselective version.

4.4.2. Identification of a Suitable Moiety

Following the literature, firstly, a sterically hindered and, secondly, an electron-withdrawing substituent at the carbonyl group affects the stereoselective outcome as well as the reactivity of a potential catalyst. In our small combinatorial approach the peptide backbone should block one side of the generated reactive species. Automated peptide synthesis should help to identify the most potential amino acid sequence. However, finding a catalytic moiety is more challenging, because several aspects must be fulfilled. Firstly, the precursor should be commercially available or easily to be synthesized. Secondly, it must be attachable to the peptide backbone. Lastly, carbonyl as well as dioxirane species should show a high reactivity for *in situ* formation of the reactive intermediate and final oxygen transfer. We selected four possible compounds containing TFMKs as precursors and an amide, a bromide or a carboxylic acid as linker (Figure 21).

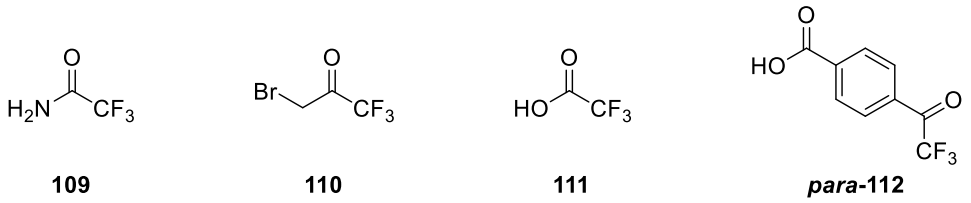
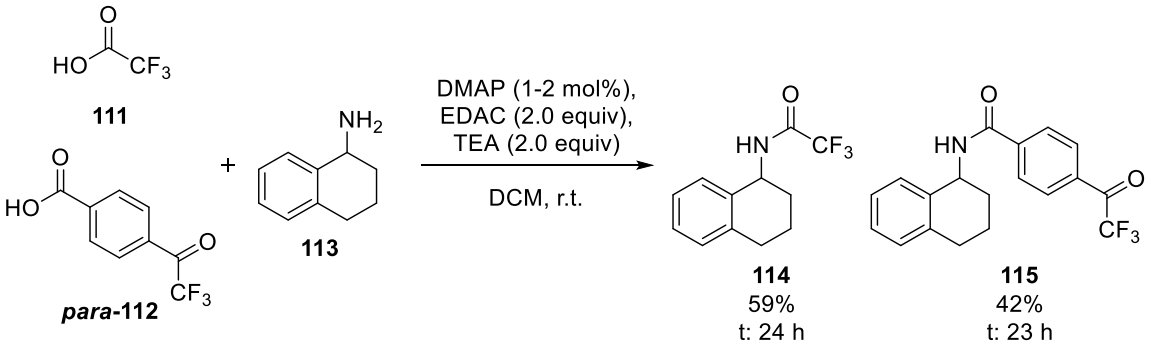


Figure 21: Potential catalytic moieties.

A successful reaction of those motives with a test coupling partner was only observed for acids **111** and ***para*-112**[119c] (Scheme 44). We assume that for **109** and **110** due to the short distance between linking group and trifluoromethyl substituent with its high negative inductive (–I) effect a reaction with their partners was hampered.



Scheme 44: Syntheses of the first test catalysts **114** and **115**.

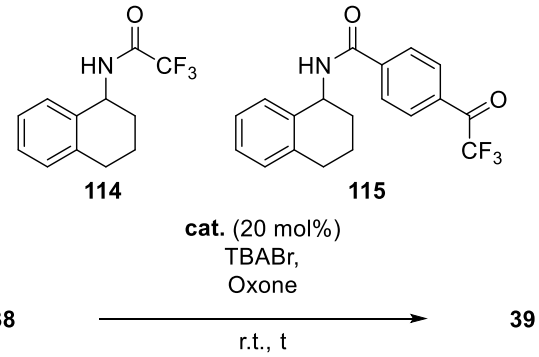
In case of **111** and **112** the amide bond formation was performed with amine **113** utilizing a DMAP/EDAC/TEA protocol.[2c, 68] After isolation compounds **114** and **115** were obtained with a yield of up to 59%. The target molecules were characterized *via* NMR, IR, and MS techniques. The structures of **115** was clearly elucidated *via* NMR, but a difference in mass of 32 units was observed using ESI techniques. By chancing the solvent from methanol to ethanol we saw a mass different of 46 units. Therefore, we concluded that during these analytic experiments an addition of the solvent to the TFMK takes place, which is responsible for the increased mass. In case of **114** the trifluoromethyl group is part of an amide. Therefore, due to the presence of different functional groups the observation was not made for the TFA derivative **114**. We tried to proof this assumption with a NMR experiment. In a NMR tube a 1:1 mixture of compound **115** and methanol in deuterated chloroform was prepared. The spectra measured directly and after two days showed only traces of the addition product indicating that this reaction accompanied with inactivation of the catalyst plays a negligible role under synthetic condition.

With test systems **114** and **115** in hand, we performed the epoxidation reaction of phenylcyclohexene **38** using catalytic amounts of the synthesized carbonyl species (Table 23). As starting point we utilized modified protocols published by Cubillos as well as Shi and Marples.[54, 119c, 125] Oxone® was chosen as oxidizing agents and sodium bicarbonate as buffer system.[125] In the forefront, we identified tetrabutylammonium bromide (TBABr) (compared to, e.g., $TBAHSO_4$ and $BnEt_3NCl$) and DCM (compared to, e.g., toluene) as phase transfer catalyst and solvent of choice for a biphasic system. During those experiments we also observed that without buffer the formed epoxide is immediately opened to the corresponding diol.

Our first results illustrated that both catalysts in combination either with mono- or biphasic systems are able to generate epoxide **39** in up to 96%. Due to byproduct formation with catalyst **114** (Table 23, Entry 1) we focused on precursor **115**. Furthermore, the amount of TBABr has to be reduced because of its own epoxidation ability (Table 23, Entry 3). Utilizing an ultrasonic

bath for mixing the biphasic system did not show the expected effect (Table 23, Entry 7). Identification of a suitable catalytically active motif was the aim of those first coupling and epoxidation experiments. Therefore, based on those encouraging results we could focus on the preparation of chiral catalysts.

Table 23: Test catalysts **114** and **115**.



Entry	Cat.	TBABr [mol%]	Reaction conditions	t [h]	Yield[(g)] [%]
1[(a,b)]	**114**	40	Oxon® (2.0 equiv), $NaHCO_3$ (5%), DCM	1	30[(h)]
2[(a,c)]	**115**	40	Oxon® (2.0 equiv), $NaHCO_3$ (5%), DCM	5	96
3[(a,b,c)]	-	40	Oxon® (2.0 equiv), $NaHCO_3$ (5%), DCM	24	45
4[(d)]	**115**	20	Na_2EDTA (0.2 mmol%); Oxon® (5.0 equiv), $NaHCO_3$ (7.8 equiv), $MeCN/H_2O$	24	56
5[(d,e)]	**115**	-	Na_2EDTA (0.2 mmol%); Oxon® (5.0 equiv), $NaHCO_3$ (7.8 equiv), $MeCN/H_2O$	24	47
6[(b,c,e,f)]	**115**	20	Na_2EDTA (0.2 mmol%); Oxon® (3.1 equiv), $NaHCO_3$ (2.0 equiv), DCM/H_2O	7	70
7[(a,b,c)]	**115**	-	Oxon® (2.0 equiv), $NaHCO_3$ (aq.), DCM, ultrasonic bath	7	0

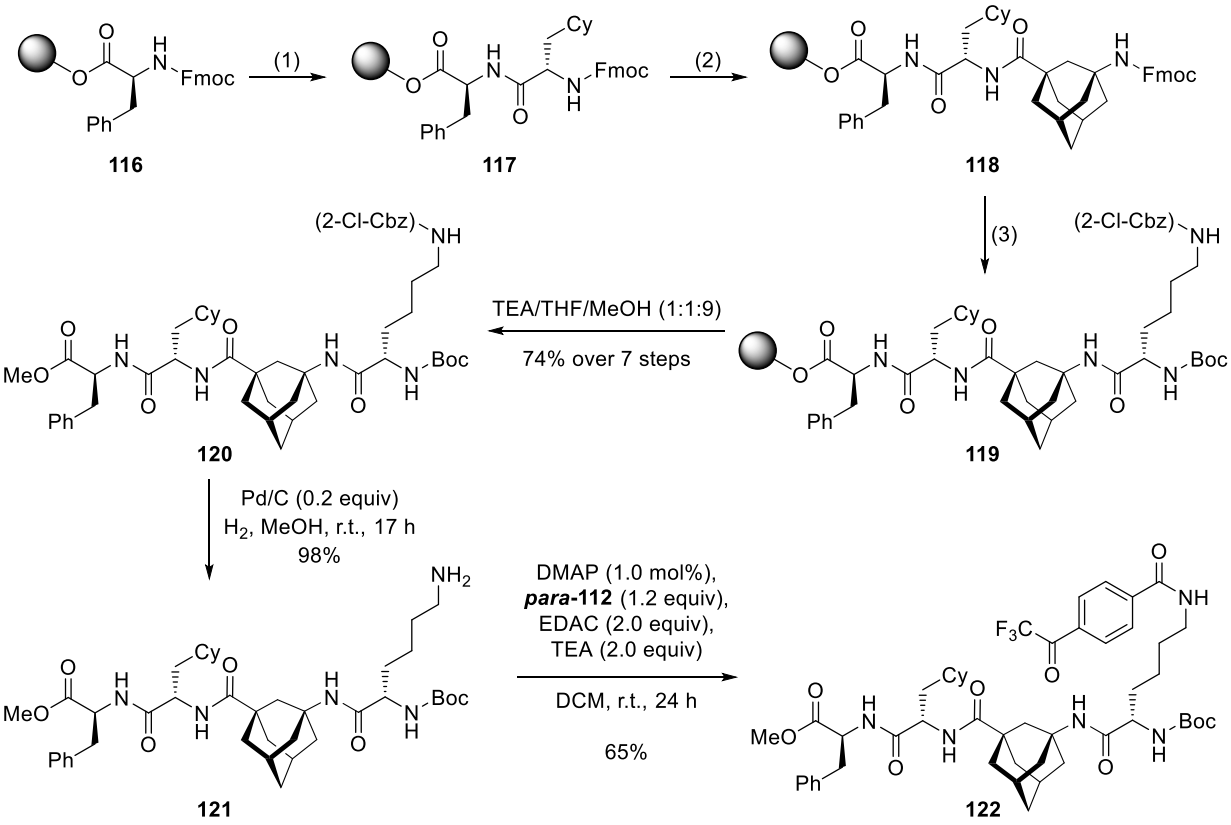
[(a)]: 1.00 mL DCM was used; [(b)]: $NaHCO_3$ (5%) was added to keep the pH at 7; [(c)]: additional amount of Oxon® was added.; [(d)]: $MeCN/H_2O$ 1.50 mL/1.00 mL.; [(e)]: mixture of Oxon® and $NaHCO_3$ was added portionwise; [(f)]: $DCM/NaHCO_3$ (5%) 1.00 mL/1.50 mL; [(g)]: yield determined *via* chiral GC without internal standard; [(h)]: tendency for byproduct formation.

4.4.3. Additional Catalysts

With working epoxidation protocols in hand we drew our attention to the synthesis of peptide-based catalysts to enable a stereoselective version of the epoxidation. Therefore, we followed two strategies. Firstly, we synthesized possible derivatives of the already established and highly selective acylation PMH system **1**.[2d] The catalytic motive PMH has to be replaced by functionalized lysine. Secondly, we focused on C_2-symmetric precursors because of their advantage regarding dioxirane formation.[120c] As key building block we selected a C_2-symmetric amine, which is known, for example, from corresponding TUC.[126]

In our first approach we chose the identical backbone compared to the acylation. The utilized system showed the ability to generate a pocket-shape structure and to perform a stereoselective reaction.[2a, 2d] *Via* automated solid phase peptide synthesis (SPPS) we synthesized the corresponding fundamental unit. Afterwards, either the *N*-terminus or the amino group of lysine acts as linker for attaching the benzoic acid derivative ***para*-112**. After cleavage of the tetrapeptide from the resin deprotection of the amine as well as fixation of the catalytic moiety were carried out in solution. The synthesis is exemplarily shown for functionalized tetrapeptide **122** (Scheme 45).

For SPPS a pre-loaded fluorenylmethyloxycarbonyl (Fmoc)-phenylalanine-Wang-resin **116** was used. After removing of the Fmoc protecting group with piperidine in DMF the coupling of the next Fmoc-protected amino acid was performed *via* a HOBt/ 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluoro-phosphate (HBTU) protocol. After three coupling steps the tetrapeptide was cleaved from the resin utilizing a mixture of tetrahydrofuran (THF), methanol, and TEA.[2a] Afterwards, both hydrogenation as well as fixation of the catalytic moiety starting from methyl ester **120** were carried out in solution under standard conditions.[116, 2c, 68, 3a] Finally, tetrapeptide **122** was isolated with a yield of 47% after nine steps.



Scheme 45: Exemplary synthesis of functionalized tetrapeptides **122**.
After cleavage of the Fmoc-group with piperidine (25%) in DMF, the peptide coupling was performed with Fmoc-amino acid-OH (2 x 2.0 equiv), HOBt (2 x 2.0 equiv), HBTU (2 x 2.0 equiv), and D*i*PEA (2 x 2.0 equiv) in DMF; (1) Fmoc-Cha-OH; (2) Fmoc-AdGly-OH; (3) Boc-Lys(2-Cl-Cbz)-OH.

Based on this protocol additional catalysts **123** and **124** were obtained with up to 50% (Figure 22). Compared to **122** the catalytic moiety was attached at the *N*-terminus in case of peptide **123**. Therefore, the Boc group was removed *via* hydrogen chloride in dioxane before functionalization.[116, 3a] Oligopeptide **124** is a multicatalytic system containing two different catalytic moieties regarding our novel acylation-epoxidation sequence (Chapter 3.1). The PMH moiety is located preferentially at the *N*-terminus of the peptide like in its acylation analog. Hence, the lysine linker as well as the TFMK are incorporated in the middle of the catalyst. Reductive cleavage of the Cbz group and functionalization were performed starting from oligopeptide **125** (see Experimental Section).[116, 2c, 68, 3a]

Analogue to oligopeptide **124** we also synthesized two compounds containing the catalytic moiety at the *C*-terminus. For those approaches we selected an EDAC/HOBt protocol and performed the peptide coupling in solution (Scheme 41).[116, 68, 3a] In the end phenylalanine derivative **126** as well as multicatalytic systems **127** were obtained with a yield of up to 62% (Figure 22).

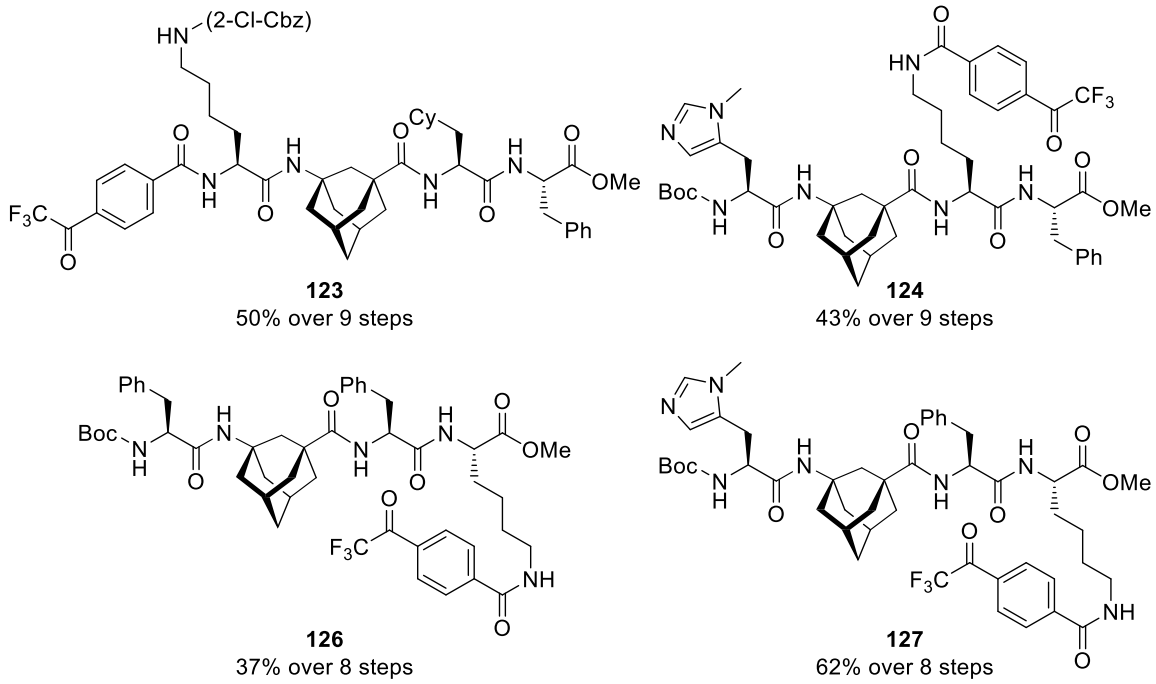


Figure 22: Additional catalysts **123**, **124**, **126**, and **127**.

Comparable to the last mentioned syntheses we also prepared C_2-symmetric diamine-based catalysts **128** and **129** with a yield of up to 47% (Figure 23). In an one-step procedure the corresponding diamine reacts with our selected catalytic moiety ***para*-112** under standard coupling conditions.[2c, 68] In contrast to the aforementioned catalysts the geometric property represents the second possibility for a stereoselective epoxidation compared to the otherwise bulky peptide backbone.

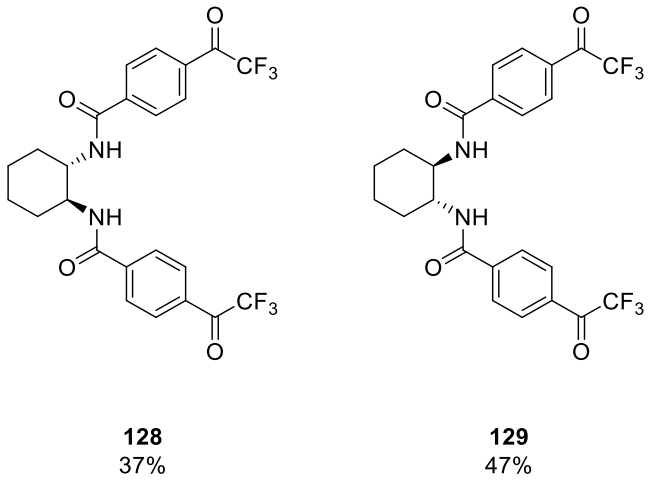
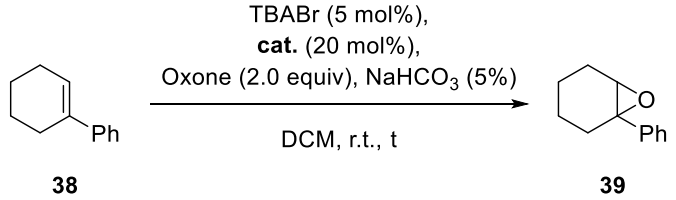


Figure 23: C_2-symmetric diamine-based catalysts **128** and **129**.

With chiral precursors in hand, we wanted to perform the epoxidation in a stereoselective fashion. Therefore, we chose alkene **38** and the Oxon® protocol (Table 23, Entry 2) with only

5 mol% TBABr as our test system (Table 24). But, in contrast to the previous experiment, we used a tenfold dilution because of the concentration dependence in case of the acylation.[2a]

Table 24: Catalyzed epoxidation.



38 **39**

Entry	Cat.	Conc. [mol L^{-1}]	t [h]	Yield[(f)] [%]
1[(a,b)]	**122**	0.025	72	traces
2[(a,b)]	**123**	0.025	24	5
3[(a,b)]	**124**	0.025	24	4
4[(a,b)]	**128**	0.025	24	6
5[(a,b)]	**129**	0.025	24	11
6[(a,b)]	**115**	0.025	24	3
7[(a,b,c,d)]	**128**	0.250	7.5	quant.
8[(a,b,e)]	**126**	0.250	24	15
9[(a,b,e)]	**127**	0.250	24	14

[(a)]: DCM/$NaHCO_3$ (5%) 1.00 mL/1.00 mL; [(b)]: additional amount of Oxone® was added.; [(c)]: $NaHCO_3$ (5%) was added to keep the pH at 7; [(d)]: 20 mol% TBABr were used.; [(e)]: 10 mol% **cat.** were used; [(f)]: yield determined *via* chiral GC without internal standard.

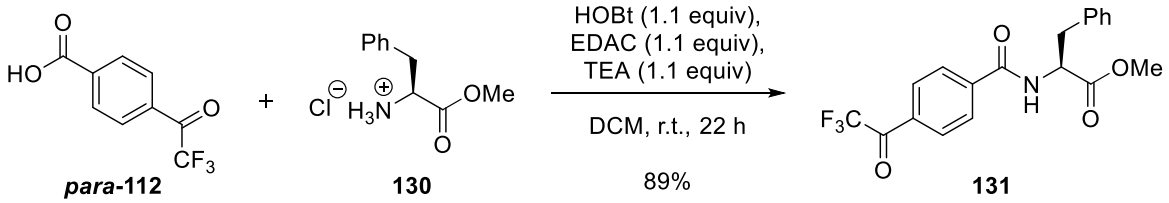
All reactions carried out in a higher dilution showed a decreased yield of epoxide **39** without enantiomeric excess (Table 24, Entries 1-5). For a better comparison we also tested our racemic catalyst **115** under analogue conditions. It also provides the desired product with only 3% yield (Table 24, Entry 6). Subsequently, we used C_2-symmetric diamine **128** exemplarily under aforementioned conditions with a higher concentration. In this case a quantitative yield of oxirane **39** was achieved after 7.5 hours, but also unselectively (Table 24, Entry 7). Reducing the amount of catalyst to 10 mol% decelerates the reaction, even with a concentration of 0.250 mol L^{-1} (Table 24, Entries 8-9).

It is also mentioned in literature that the pH-value is an important factor concerning Oxone® decomposition, catalyst reactivity, and occurrence of Baeyer-Villiger oxidation as possible side reaction.[55] Therefore, we also performed the epoxidation of alkene **38** with an increased pH-value of 8-10. Besides potassium hydroxide or potassium carbonate as base we also varied temperature (e.g., r.t., 0 °C), additives (e.g., Na_2EDTA, TBABr) or catalysts (e.g., **123**, **126**,

127).[55, 123, 43c] Corresponding to the literature we observed a higher yield of up to 94% after four hours, but without enantiomeric excess. The reaction without catalyst is also not negligible.

4.4.4. Re-Optimization with Chiral Test Catalyst **131**

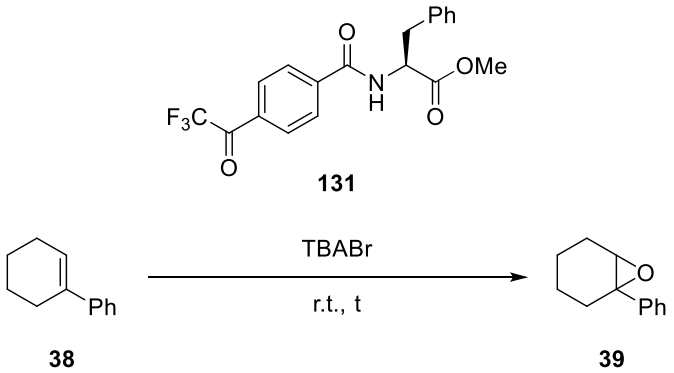
Based on the missing enantiomeric excess and the observed huge influence of several reaction parameters, we took one step back and synthesized a second, chiral, and more peptide-like test catalyst (Scheme 46).



Scheme 46: Chiral test catalyst **131**.

To prevent racemization, which was observed for two of the previously synthesized catalysts, we utilized the EDAC/HOBt-based protocol instead of using a DMAP-mediated one.[68, 3a] Finally, test catalyst **131** was isolated with a yield of 89%. This compound was used afterwards for re-optimization of the catalytic epoxidation instead of the more valuable tetrapeptides. Parameters like catalyst loading and concentration were varied stepwise (Table 25).[123, 119c, 43c, 125]

Table 25: Re-optimization with functionalized amino acid **131**.



Entry	131 [mol%]	TBABr [mol%]	Oxone®/$NaHCO_3$ (s) [equiv/equiv]	Conc.[(h)] [mol L^{-1}]	t [h]	Yield[(i)] [%]
1[(a,b,c)]	20	40	2.0/0.0	0.250	7	94
2[(a,b,d)]	15	15	2.0/0.0	0.250	7	35
3[(a,b)]	11	11	2.0/0.0	0.250	5	17
4[(a,b)]	-	20	2.0/0.0	0.250	7	8

5[e,f]	19	39	3.0/37	0.167	4	quant.
6[e,f]	20	39	1.5/4.7	0.167	2	quant.
7[e,f]	20	38	1.0/3.0	0.167	2	81
8[e,f]	-	41	1.5/4.7	0.167	3	quant.
9[e,f]	-	5	1.6/4.7	0.167	24	17
10[e,f]	-	-	1.6/4.7	0.167	24	8
11[e,f]	20	-	1.5/4.9	0.167	25	25
12[e,f]	20	5	1.5/5.0	0.167	25	23
13[f,g]	20	20	3.0/4.6	0.250	5	95
14[f,g]	20	17	3.0/4.6	0.250	5	71
15[f,g]	20	10	3.0/4.7	0.250	5	41
16[f,g]	21	5	3.0/4.7	0.250	5	34

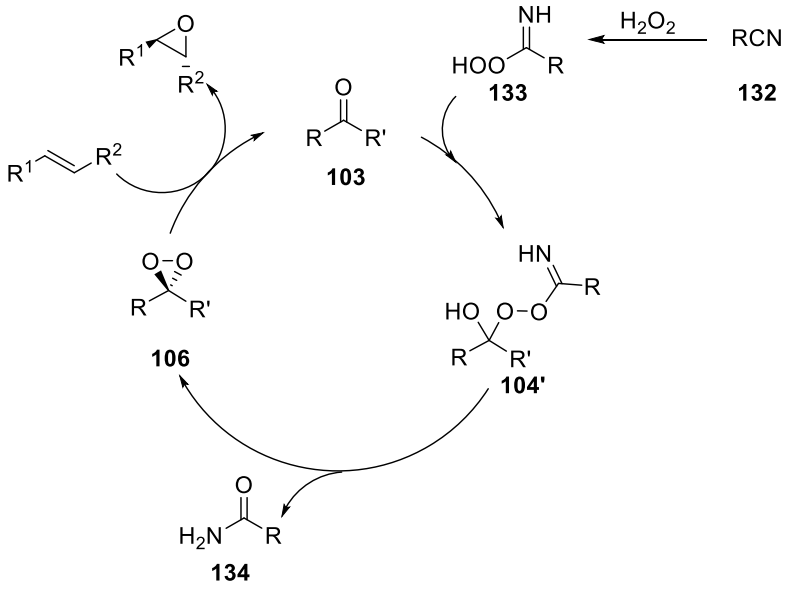
[a]: DCM/$NaHCO_3$ (5%) 1.00 mL/1.00 mL; [b]: additional amount of Oxon® was added.; [c]: $NaHCO_3$ (5%) was added to keep the pH at 7; [d]: a mixture of $NaHCO_3$/Na_2CO_3 was used to keep the pH at 7; [e]: MeCN/H_2O 1.50 mL/1.00 mL, Na_2EDTA were used; [f]: mixture of Oxone®/$NaHCO_3$ (s) was added over around 35 min; [g]: DCM/H_2O 1.00 mL/1.00 mL were used; [h]: with respect to the volume of organic sovent; [i]: yield determined *via* chiral GC without internal standard.

Based on the last results with the peptide catalysts (Table 24) we started our re-optimization. But, for an increased transport of the reactive species we utilized 40 mol% of TBABr as PTC at the beginning. 94% of the desired epoxide **39** were obtained after five hours (Table 25, Entry 1). The whole system is quite sensitive because reducing the amount of catalyst slowed down the reaction distinctly (Table 25, Entries 2 and 3). The background reaction showed that the presence of precursor **131** is necessary (Table 25, Entry 4). Keeping the reaction ongoing and the pH value constant is quite difficult with the aforementioned procedure. Therefore, we decided to mix oxidizing agent and base in solid form beforehand and add the mixture portionwise. We tested a mono- and biphasic system yielding epoxide **39** with up to quantitative yields (Table 25, Entries 5-16). However, the side-reaction of TBABr could not be suppressed and an enantiomeric excess was not observable. We tried to address both problems *via* changing the utilized solvents (e.g., toluene, DMF), but without success. Even with a well-working system in hand (Table 25, Entry 13) we stopped our attempts at this point and draw our attention to a PTC-free approach.

4.4.5. *tert*-Amyl Alcohol and Hydrogen Peroxide Approach

Especially, because of the PTC-mediated background reaction we proceed to a hydrogen peroxide-based protocol form Shi *et al.* published in 2007. Thereby, we want to realize a PTC-free and practically simplified version of our peptide-catalyzed procedure.

Besides dioxirane precursor and oxidizing agent a nitrile source is also required. In their postulated mechanism they showed the *in situ* generation of two reactive intermediates (Scheme 47).[124]



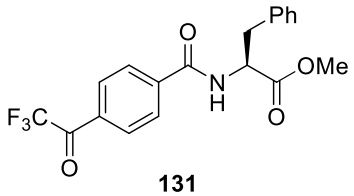
Scheme 47: Postulated reaction mechanism including reactive species **106** and **133**.

Shi *et al.* assume that hydrogen peroxide and nitrile **132** form the reactive peroxyimidic acid **133**. This *in situ* generated species reacts analogously to peroxomonosulfate to peroxy intermediate **104'**. With release of primary amide **134** dioxirane **106** is formed enabling the already mentioned final steps (Scheme 43).

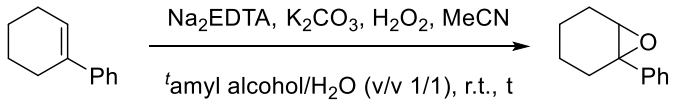
A similar strategy with a peptide-like catalyst was successfully applied by Miller *et al.* in 2012 (Scheme 17).[57] Instead of *n*-butanol they used *tert*-amyl alcohol in combination with water as solvent mixture. Based on those promising results for a comparable system we tested functionalized phenylalanine **131** under analogue conditions (Table 26).

Performing the epoxidation of cyclohexene **38** at room temperature with Miller's reaction conditions provided product **39** with 63% yield, but no enantiomeric excess (Table 26, Entry 1). *Via* omission of either peptide **131** or acetonitrile we get the hints that both components are essential for the formation of the dioxirane (Table 26, Entries 2 and 3). For our system a stepwise addition of hydrogen peroxide and minimizing the equivalents of acetonitrile showed less effect on the reaction outcome compared to lower catalyst loading and concentration (Table 26, Entries 4-8). Utilizing a higher dilution did not only slow the reaction down, but also favored the occurrence of side-reaction (Table 26, Entry 8). Exemplarily GC-determined and isolated yield were compared (Table 26, Entry 4).

Table 26: Hydrogen peroxide-based epoxidation.



131



38 39

Entry	131 [mol%]	K_2CO_3 [equiv]	H_2O_2 [equiv]	MeCN [equiv]	Conc.[f] [mol L^{-1}]	t [h]	Yield[g] [%]
1[a]	10	1.9	8.1	8.0	0.327	5	63
2[a]	-	1.9	8.9	8.0	0.327	25	13
3[a,b]	10	1.8	8.1	-	0.327	23	7
4[a,b]	10	1.8	2.0	8.0	0.327	1	99[d]
5[a,b]	11	1.8	6.0	2.0	0.327	3	quant.
6[a,c]	10	1.8	3.0	2.0	0.327	3	54
7[a,c]	5	1.8	3.0	2.0	0.327	3	18
8[c,e]	11	2.0	4.0	8.0	0.164	4	18

[a]: **38** (0.628 mmol, 1.0 equiv), Na_2EDTA (0.1 mol%), **131**, K_2CO_3, MeCN, H_2O_2, ^{t}amyl alcohol/H_2O 1.92 mL/1.92 mL; [b]: 2.0 equiv H_2O_2 were added hourly; [c]: 1.0 equiv H_2O_2 were added hourly; [d]: 93% isolated yield; [e]: 0.314 mmol (1.0 equiv) **38**, 0.2 mol% Na_2EDTA, **131**, K_2CO_3, MeCN, H_2O_2, ^{t}amyl alcohol/H_2O 1.92 mL/1.92 mL [f]: with respect to the volume of organic solvent; [g]: yield determined *via* chiral GC without internal standard.

4.4.6. Comparison

As a short summary the best conditions both for Oxone® and H_2O_2/MeCN are summarized in table 27. The most important advantages and disadvantages are included as well.

Table 27: Comparison of reaction conditions for the catalytic epoxidation.

Oxone/$NaHCO_3$	H_2O_2/MeCN
20 mol% **131**	10 mol% **131**
Oxone (3.0 equiv)	H_2O_2 (3 x 2.0 equiv), MeCN (2.0 equiv)
$NaHCO_3$ (4.6 equiv)	K_2CO_3 (1.8 equiv),
20 mol% TBABr, CH_2Cl_2/H_2O (1:1)	Na_2EDTA (10^{-4} mol L^{-1}), ^{t}AmylOH/H_2O (1:1)
0.250 mol L^{-1}	0.327 mol L^{-1}

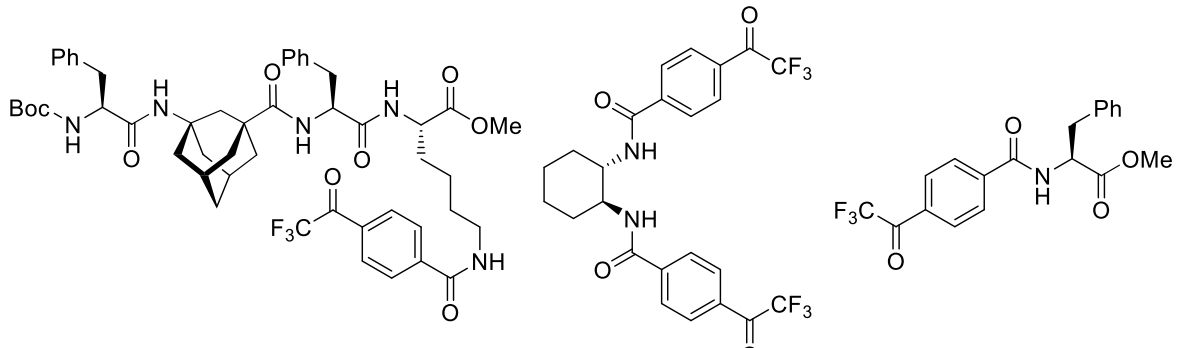
r.t.	r.t.
96% conversion (5 h)	Quant. conversion (3 h)
• Extremely pH-dependent • Mixing Oxone/$NaHCO_3$ and adding portionwise • Fast background reaction • PTC necessary	• H_2O_2 added in portions • MeCN necessary • Less catalyst: slower reaction, but more side reactions • Very slow background reaction • No PTC necessary

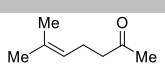
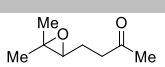
The major differences are catalyst loading, necessity of a PTC, pH-influence, background reaction, and rate of epoxide formation. Based on those observations we used the H_2O_2/MeCN-protocol for testing the peptide catalysts.

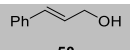
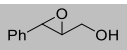
4.4.7. Testing of the H_2O_2/MeCN-Protocol

For those experiments we selected peptide-based and C_2-symmetric catalysts **126** and **128** exemplarily. Those dioxirane precursors showed the best results with the Oxone®-based protocol (Table 24, Entries 7 and 8). We chose alkene **48** for catalyst **126** and cinnamic alcohol **50** for catalyst **128** as substrate building on dispersion and π-π interactions, respectively, as beneficial factors. Due to the negligible effect of the volume of acetonitrile eight equivalents were used. For a direct comparison both reactions were performed with test catalyst **131** simultaneously (Table 28).

Table 28: Epoxidation with catalysts **126** and **128** utilizing the H_2O_2/MeCN-protocol.



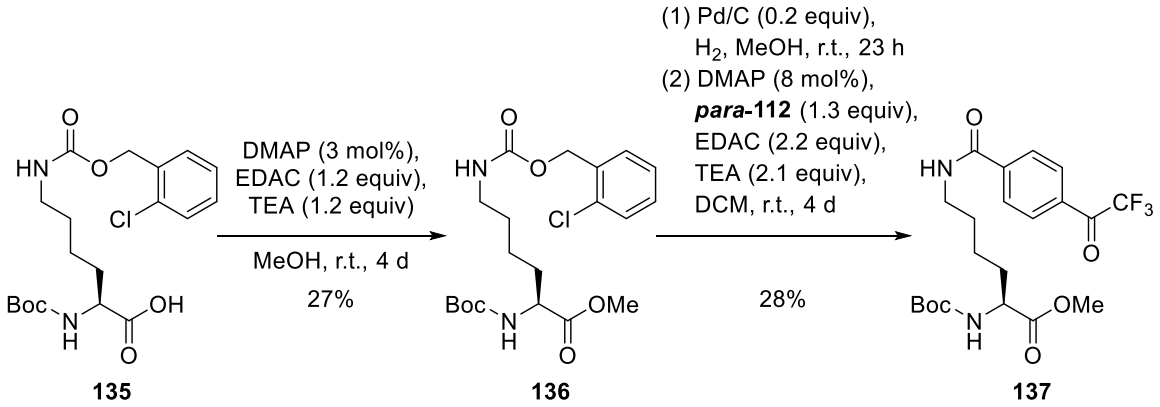
Entry	Cat.	Alkene	Epoxide	H_2O_2[(c)] [equiv]	t [h]	Yield[(d)] [%]
1[(a)]	**126**	 **48**	 **49**	8.0	7	25

2[(b)]	**128**	 **50**	 **51**	2.0	1	quant.
3[(a)]	**131**	48	49	8.0	7	19
4[(b)]	**131**	50	51	6.0	3	quant.

[(a)]: Alkene (0.165 mmol, 1.0 equiv), Na_2EDTA (0.1 mol%), **cat.** (10 mol%), K_2CO_3 (1.8 equiv), MeCN (8.0 equiv), H_2O_2 (8.0 equiv), ^{t}amyl alcohol/H_2O 0.500 mL/0.500 mL; [(b)]: alkene (0.628 mmol, 1.0 equiv), Na_2EDTA (0.1 mol%), **cat.** (10 mol%), K_2CO_3 (1.8 equiv), MeCN (8.0 equiv), H_2O_2 (8.0 equiv), ^{t}amyl alcohol/H_2O 1.92 mL/1.92 mL; [(c)]: 2.0 equiv H_2O_2 were added hourly, [(d)]: yield determined *via* chiral GC without internal standard.

4.4.8. More Efficient Synthetic Procedure

In case of the already shown peptide catalysts the backbone was synthesized initially and functionalized in the last steps. From a synthetic point of view it would be more favorable to have a complete building block in hand enabling a straight forward peptide coupling afterwards. Therefore, we established a three-step process yielding lysine derivative **137** (Scheme 48).



Scheme 48: Synthesis of functionalized lysine **137**.

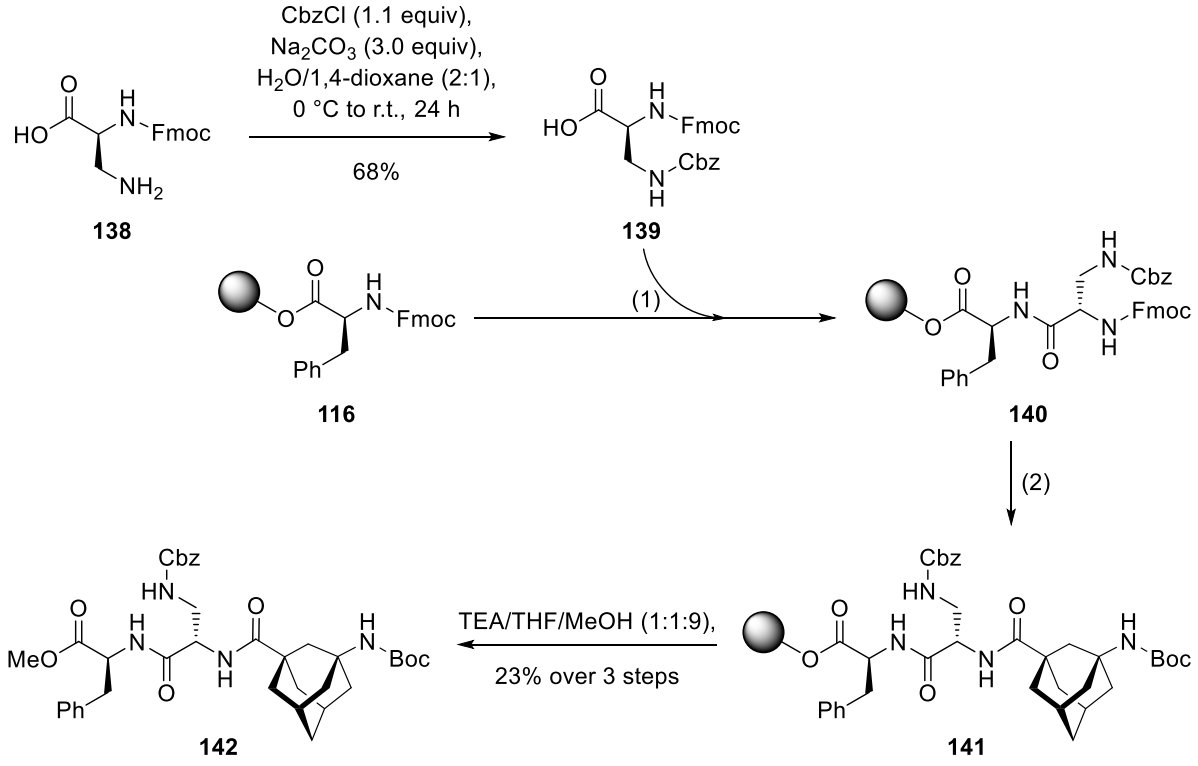
The well-working methyl ester introduction based on thionyl chloride is not possible[127] because the Boc group of orthogonal protected starting material **135** would be cleaved immediately by the *in situ* generated hydrogen chloride. Therefore, we utilized a typically DMAP-mediated esterification protocol with methanol.[2c, 68] Completely protected lysine **136** was isolated with a yield of only 27%. After reductive cleavage of the carbamate group and functionalization of the free amine target compound **137** was finally isolated with a yield of 28% after two steps.[116, 2c, 68, 3a] Purification of the completely protected intermediate and the target product **137** is quite difficult and causes the low overall yield of only 8%. Conclusively, the synthesis of the functionalized building block, which can be utilized in peptide coupling in solution after re-movement of the Boc group, is possible, but for a larger scale not really practicable. In addition to the missing enantiomeric excess, which might be caused by the very flexible alkyl chain, further optimization attempts were stopped.

4.4.9. Missing Enantiomeric Excess

In all catalyzed epoxidation reactions hitherto no enantiomeric excess was observed. For peptide catalyst **123**, C_2-symmetric amines **128** and **129** as well as phenylalanine **131** we assume that the distance between *in situ* generated dioxirane and first chiral center is too large. For further oligopeptides the flexible alkyl chain additionally complicates the formation of a fixed transition state. Therefore, we developed three possible strategies to address these problems. Firstly, we wanted to shorten the linker by utilizing 2,3-diaminopropionic acid (Dap) instead of lysine (Chapter 4.4.9.1.). Secondly, the substitution pattern of the aromatic ring of the catalytic moiety should be changed (Chapter 4.4.9.2.). Finally, an amino acid containing the dioxirane precursor should be synthesized (Chapter 4.4.9.5.).

4.4.9.1. Variation of the Linking Amino Acid

Our first idea to achieve a stereoselective epoxidation based on minimizing the flexibility by reducing the number of CH_2-units between catalytic moiety and peptide backbone. With the already established synthetic route and an orthogonal protecting group strategy in mind we wanted to synthesize the corresponding Cbz-protected Dap derivative **139**, which can afterwards be included in the established SPPS functionalization pipeline (Scheme 49).



Scheme 49: SPPS of Dap-containing tripeptide **142**.
After cleavage of the Fmoc-group with piperidine (25%) in DMF, the peptide coupling was performed with (1) **139** (1.0 equiv), HOBt (3.0 equiv), HBTU (3.0 equiv), and D*i*PEA (3.0 equiv) in DMF and (2) Boc-AdGly-OH (2 x 2.0 equiv), HOBt (2 x 2.0 equiv), HBTU (2 x 2.0 equiv), and D*i*PEA (2 x 2.0 equiv) in DMF.

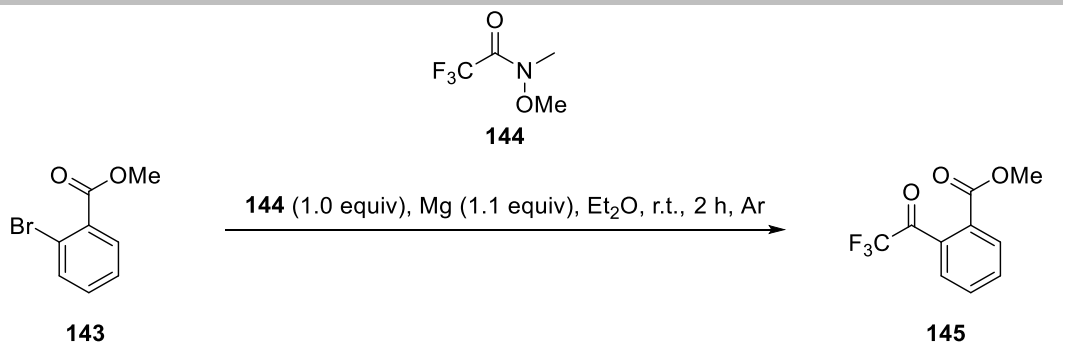
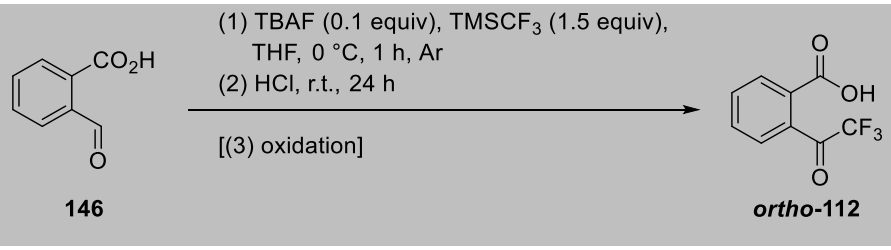
The Cbz protection of Fmoc-Dap **138** was performed with disodium carbonate as base and building block **139** was isolated with a yield of 68%.[96] By analogy with peptide catalyst **124** we synthesized tripeptide **142** under SPPS conditions with 23% yield after three steps.[2a] In combination with a modified catalytic moiety the concept of a shorter linker should enable access to a potent catalytic system.

4.4.9.2. Substitution Pattern of the Aromatic Ring

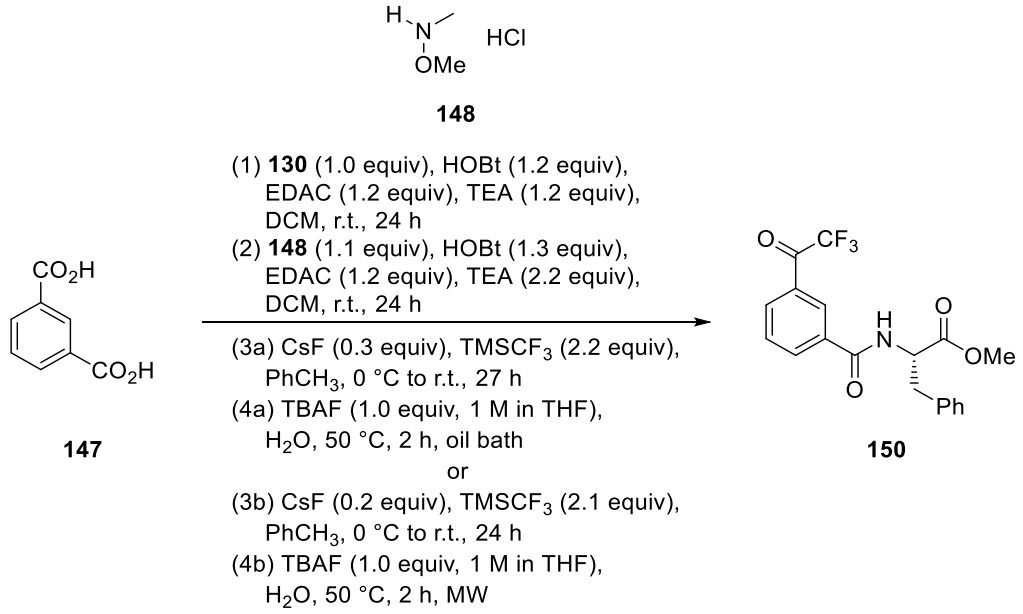
As already mentioned we assume that beside the influence of the flexible alkyl chain combined with the distance between first chiral center and reactive species the substitution pattern of the catalytic moiety plays an important role. Hence, we focused on synthesizing *ortho*- as well as *meta*-substituted derivatives of our identified aromatic catalytic moiety ***para*-112** (Table 29).

In the first place we tried to introduce the TFMK while the starting material already contains the necessary linker.[128] Firstly, based on the protocol of Tuominen *et al.* we performed a Grignard reaction with protected bromide **143** and Weinreb amide **144** to obtain *ortho*-substituted benzoic acid derivative **145** (Table 29, Entry 1).[129] But, during the reaction a reduction took place independently from solvent, temperature as well as inert atmosphere. In contrast to the literature we utilized a substituent with a negative mesomeric (–M) effect, which might have an influence on the reactivity of the aromatic system.

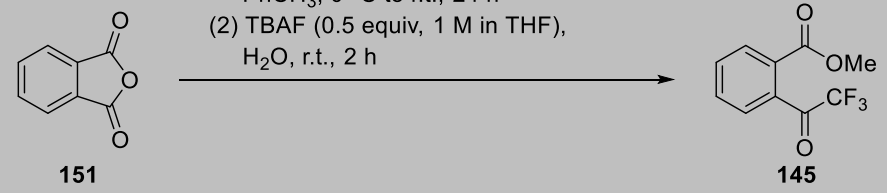
Table 29: Attempts for introducing a TFMKs.

Entry	Conditions
1	
2	

3



4



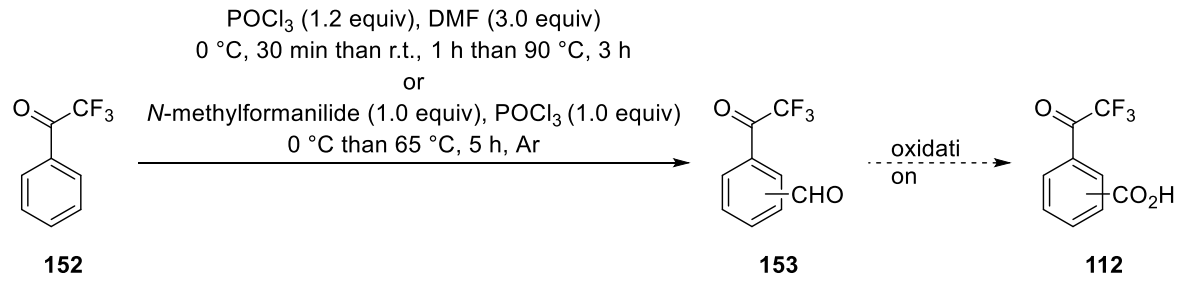
Secondly, utilizing Ruppert-Prakash reagent ($TMSCF_3$),[130] which is a further well-established CF_3-source,[131] in combination with the procedure published by Miller *et al.* we chose carboxybenzaldehyde **146** as educt (Table 29, Entry 2).[57] But, under the selected conditions we could not observe the desired product ***ortho*-112** (Chapter 4.4.9.3).

In 2012, Leadbeeater *et al.* showed that Weinreb amides can also be converted into the TFMKs *via* $TMSCF_3$.[132] Referring to this strategy we thirdly synthesized the Weinreb amide of isophthalic acid, which was coupled with phenylalanine in the forefront (see **149** Experimental Section). Final conversion to the TFMK **150** would directly provide *meta*-analog of **131** (Table 29, Entry 3). We performed the final two-step transformation as published both under standard heating as well as microwave conditions, but we only reisolated the Weinreb amide. Lastly, also testing phthalic acid anhydride **151** with the conditions of the previous experiment does not lead to the corresponding *ortho*-substituted product (Table 29, Entry 4).

Due to the failed aforementioned approaches different starting materials in combination with variation of the reaction conditions could be tested additionally. As further alternative strategy

the DMAP-mediated acylation of aromatic systems with trifluoroacetic anhydride published by Simchen *et al.* in 1996 could be transferred to our starting materials.[133]

As a consequence of the first functionalization attempts we turned our strategy around. We selected trifluoroacetophenone **152** as commercially available starting material and wanted to convert the monosubstituted aromatic system under Vilsmeier conditions to corresponding aldehyde **153**, which should be oxidized finally to the carboxylic acid **112**, which acts afterwards as linking unit (Scheme 50).



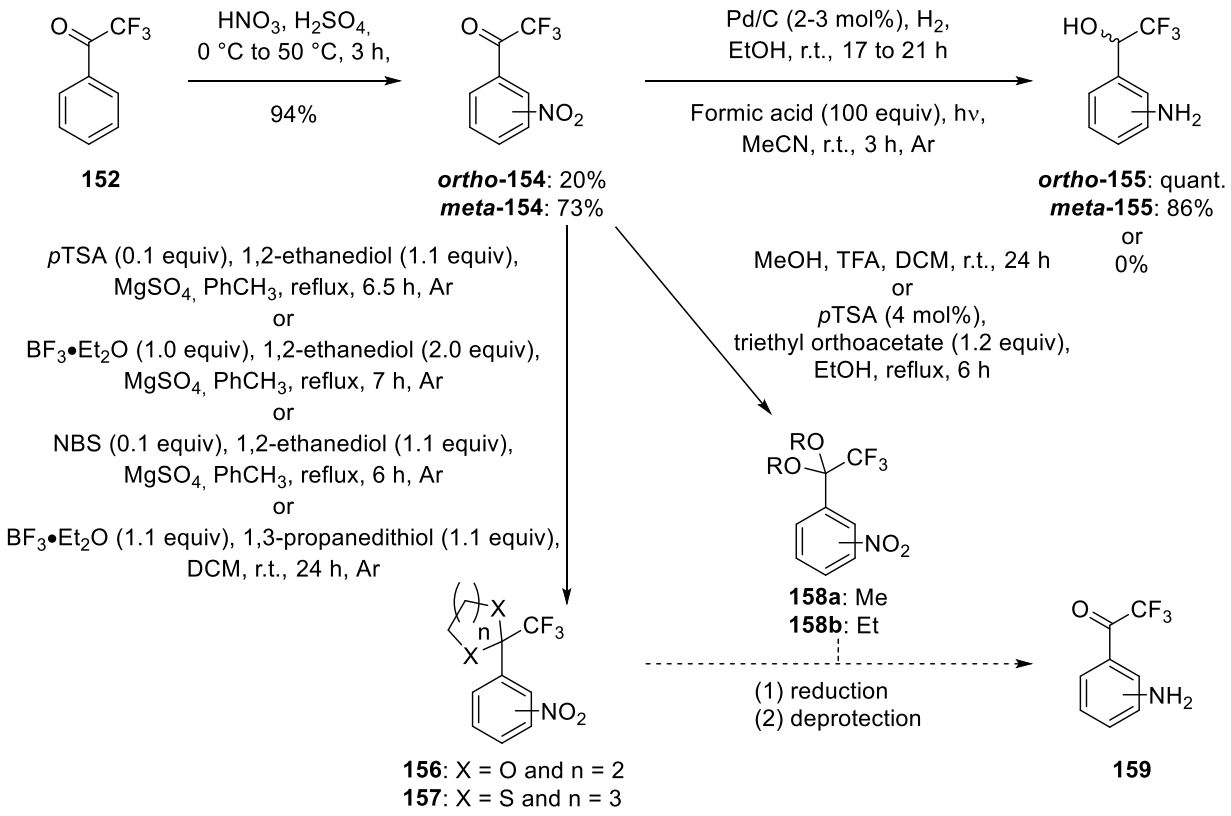
Scheme 50: Vilsmeier reaction.

The reaction was performed both with DMF as well as *N*-methylfomanilide as formylation reagent.[85] But, these typical Vilsmeier conditions did not work for our aromatic system **152** and after aqueous work-up only starting material was reisolated.

Due to the abortive attachment of both a TFMK as well as a carboxylic acid we chose an amino group as potential linker. This functional group should also be introduced *via* an electrophilic aromatic substitution in a two-step sequence of nitration followed by reduction (Scheme 51).

The nitration of trifluoroacetophenone **152** worked excellent under standard conditions with an isolated yield of 94%.[85] It was also possible to separate the majority of both isomers *via* column chromatography. But afterwards, we were not able to reduce the amino group selectively in the presence of the carbonyl with palladium as catalyst under a hydrogen atmosphere even *via* variation of the reaction conditions.[85, 134] We isolated completely reduced amino alcohols **155** with an average yield of 93%.

In 2008, Bonesi *et al.* published the photoreduction of aromatic nitro compounds.[135] Mild conditions and a high functional group tolerance are two advantages of their described protocol. We reisolated quantitative amounts of the starting material after irradiation of our substrate for six hours.



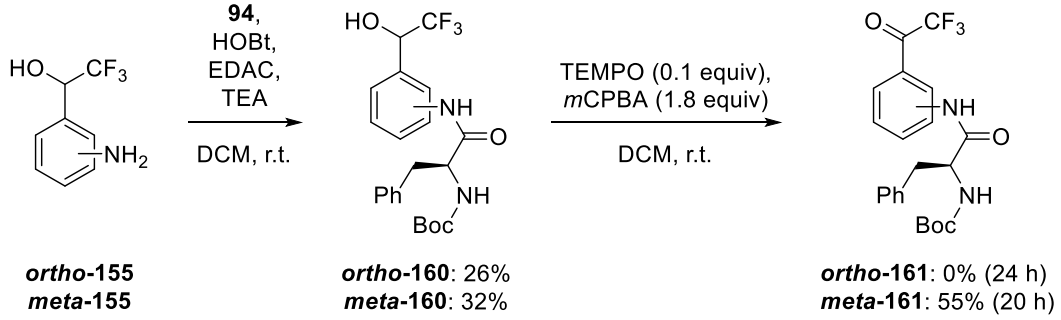
Scheme 51: Synthetic routes for the synthesis of CF_3-derivatives **155** and **159**.

Therefore, we decided to protect the carbonyl before reducing the nitro group. Removing the protecting group would result in attachable amine **159**. We tried to introduce cyclic as well as acyclic acetals even by utilizing different protocols,[116, 136] but we only reisolated or observed unreacted starting material **154**. So we stopped all further attempts to synthesize catalytic moieties **159** at this point.

But, on the other hand we were able to isolate amino alcohols **155** after two steps with a total yield of 87% regarding both isomers. After peptide coupling with phenylalanine **94** and late-stage oxidation these initially unintended compounds would give us *ortho*- and *meta*-substituted analogs of peptide catalyst **131** (Scheme 52).

The formation of the amide bond was performed with the already described HOBt/EDAC-mediated protocol.[68, 3a] Amides **160** were isolated with a yield of up to 32%. One explanation for the reduced amount of product is the disubstituted species, which was separated and identified *via* ESI-MS in case of ***ortho*-155**. Protection of the free hydroxyl group in the forefront could prevent this problem in further experiments. The late-stage oxidation was carried out with TEMPO as catalyst and *m*CPBA as oxidizing agent.[137] The reaction took place successfully for ***meta*-161**, while only starting material was isolated in case of its

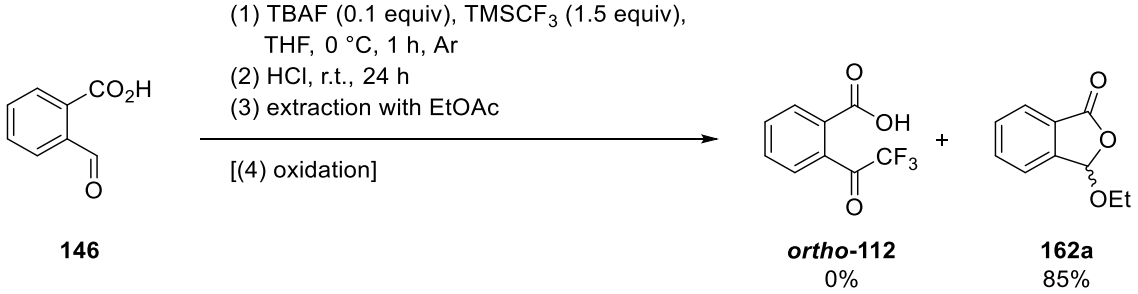
ortho-derivative. The higher steric hindrance of ***ortho*-160** might complicate the formation of the necessary intermediate and thereby prohibit the oxidation. But, with ***meta*-161** in hand a comparison between *para*- and *meta*-substitution pattern in the catalytic epoxidation is possible. If the results show a preference for the *meta*-derivative further optimization efforts will be invested in the synthesis of the corresponding *ortho*-analog.



Scheme 52: Syntheses of *ortho*- and *meta*-substituted analogs of peptide derivative **131**.
Conditions for the amide bond formation: ***ortho*-160**: **94** (1.2 equiv), HOBt (1.3 equiv), EDAC (1.3 equiv), and TEA (0.9 equiv) for 13 h; ***meta*-160**: **94** (1.1 equiv), HOBt (1.1 equiv), EDAC (1.1 equiv), and TEA (1.1 equiv) for 23 h.

4.4.9.3. Digression II: Asymmetric Synthesis of α-Keto Acetals

As mentioned above it was not possible to convert carboxybenzaldehyde **146** into the desired *ortho*-substituted TFMK **112** (Table 29, Entry 2). But, we were able to isolate and characterize α-keto acetal **162a** after work-up with ethyl acetate (Scheme 53).



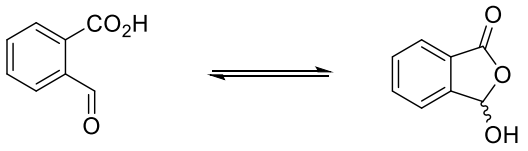
Scheme 53: Observation of the formation of α-keto acetals **162a**.

Firstly, we assume that there must exist a hemiacetal form of starting material **146** in solution. Secondly, the organic solvent is hydrolyzed by hydrochloric acid during extraction of the aqueous layer. Afterwards, the cyclic species is acid-mediately transferred into acetal **162a** *via* reaction with formed ethanol.

Already in 1957, Wheeler *et al.* investigated the open and closed form of carboxybenzaldehyde **146** *via* IR. They reported that both species exist depending on solvent and temperature. Furthermore, it is mentioned that carboxybenzaldehyde **146** possess a reactivity comparable to

an acid chloride or anhydride and a variety of possible reactions were described including the formation of **162a**.[138] For gaining a deeper insight into the real situation in solid state and solution we repeated the IR experiments and performed additional NMR measurements (Table 30).

Table 30: IR and NMR experiments.



146 **163**

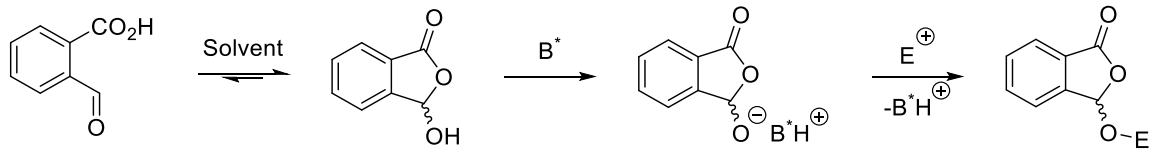
	KBr	**Solution in $CHCl_3$**
C=O (cm^{-1})	1741 1761	1767

Solvent	**^1H**	**^{13}C**	**Ratio or 146:163**
DMSO-d_6	6.68 10.48	98.3 and 168.5 167.6 and 192.9	1:10
$CDCl_3$	6.66	98.0 and 169.7	0:1

Two bands in the IR spectrum showed the presence of carboxybenzaldehyde **146** in the solid state. In contrast all experiments in solution confirmed clearly the closed form **163**. Only in dimethyl sulfoxide (DMSO)-d_6 small traces of the open form were observable. Therefore, a reaction of hemiacetal **163**, which is formed directly during solvation, is possible.

Simultaneously, we performed some test reactions to proof our hydrolysis-acetalization hypothesis. Therefore, we mixed ethyl acetate, diluted hydrochloric acid, and carboxybenzaldehyde **146.** After stirring 17.5 hours we isolated 26% of the ethylated species **162a**. Without acid no reaction took place.

With those information in hand, we postulated that it should be possible to deprotonate generated hemiacetal **163** *in situ* and scavenge the alkoxide subsequently with a suitable electrophile (E^+). Utilizing a chiral base (B*) like an alkaloid should result in chiral intermediate **164**, which should provide target product **162** in a chiral form after reaction with the electrophile (Scheme 54).

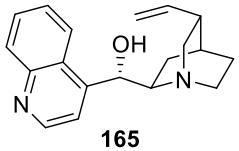


146 163 164 162

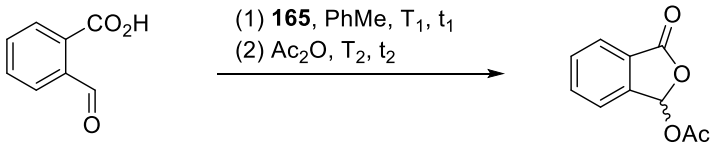
Scheme 54: Postulated sequence for the synthesis of enantiomerically enriched α-keto acetals **162**.

As test system we chose cinchonine **165** as base and acetic anhydride as electrophile referring to our acylation concept. To facilitate the formation of polar intermediate **164** in a defined orientation we selected toluene as solvent, which is also favorable concerning our PMH-mediated acylation (Table 31).[2c]

Table 31: Cinchonine-mediated asymmetric synthesis of enantiomerically enriched α-keto acetals **162b**.



165



146 **162b**

Entry[a]	165 [equiv]	Ac_2O [equiv]	T_2 [°C]	t_1 [h]	T_2 [°C]	t_2 [h]	Yield [%]	*ee*[b] [%]
1	1.0	1.0	r.t.	18	r.t.	6	67	28
2	2.0	1.0	r.t.	18	r.t.	6	79	28
3	1.0	2.0	r.t.	18	r.t.	6	83	28
4	2.0	2.0	r.t.	18	r.t.	6	96	28
5	2.0	2.0	0	24	0	8	88	32

[a]: 0.300 mmol (1.0 equiv) **146**, **165**, and 4.00 mL PhMe than Ac_2O; [b]: *ee* determined *via* chiral GC without internal standard.

Performing deprotonation and protection of hemiacetal **163** with one equivalent base as well as electrophile at room temperature yielded in 67% of acetal **162b** with an enantiomeric excess of 28% (Table 31, Entry 1). Astonishingly, variation of temperature as well as equivalents of base and electrophile did not play such an important role. Yields are always in a good to excellent range and the enantiomeric excess is around 30% (Table 31, Entries 2-5).

In 2008, Yamada *et al.* reported the first catalytic dynamic kinetic resolution for hemiaminals with a very similar structure compared to **163**.[139] With 0.1 to 10 mol% of chiral DMAP catalysts and isobutyric anhydride they obtained excellent yields and good selectivities for the acylated compounds. Utilizing the same procedure they isolated the product of hemiacetal **163** with a nearly quantitative yield and an enantiomeric excess of 40%. But moreover, only a few racemic protocols are described regarding the synthesis of acetate **162b** requiring carbon monoxide and catalytic amounts of a palladium species as well as high temperatures.[140]

Taking this into account and based on only a few very simple experiments we conclude that our approach for the synthesis of α-keto acetals is very promising. Further optimization of the procedure, e.g., catalyst screening, use of additives, different electrophiles, and solvent variation in combination with the substrate scope, is easily possible. Afterwards, enantiomerically enriched compound **162a** can be used as starting material in the synthesis of 3-(heteroaryl)phthalides[140c] or the protocol can help to synthesize chiral esters like the racemic one reported in the biological evaluation of monocyclic β-lactams.[141]

4.4.9.4. Effect on Epoxidation Outcome

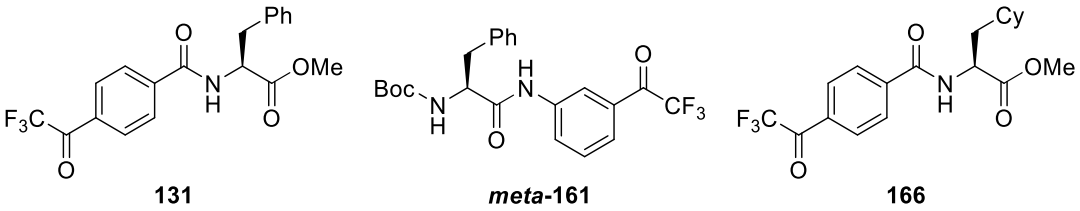
At the end of chapter 4.4.9.2. we showed the successful synthesis of the *meta*-substituted TFMK **161**. With this catalyst and functionalized phenylalanine **131** in hand, it is possible to compare reactivity as well as selectivity of those different substitution pattern. Due to the described synthetic problems the orientation of the amide bond is inverted, which should not play a very important role. In parallel, we wanted to test also the cyclohexylalanine derivative of **131**. **166** was synthesized analogue to **131** (Schema 46; see **166** Experimental Section). Different substituted alkenes were epoxidized in the presence of those three catalysts utilizing the established H_2O_2/MeCN protocol (Table 32).

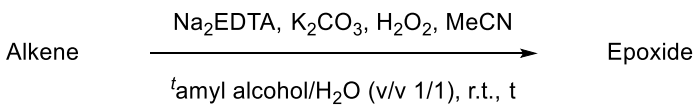
Based on those results we conclude, changing the substitution pattern of the aromatic ring from *para* to *meta* did not lead to an enantioselectively enriched product formation. But, apart from alkenes **40** and **54** (Table 32, Entries 7 and 11) the further epoxides are formed slower with ***meta*-161**. Maybe the increased steric hindrance hampers the generation of the dioxirane in case of ***meta*-161**.

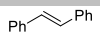
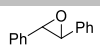
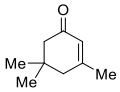
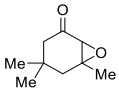
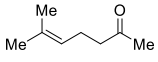
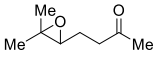
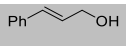
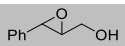
Substitution of phenyl with cyclohexyl did not show a real tendency for either dispersion or π-π-interactions driven reactions. For example, phenylcyclohexene **38** is converted faster by **131** (Table 32, Entries 1 and 12), whereas its cyclohexyl derivative **40** is transferred in an equal manner from both catalysts (Table 32, Entries 2 and 13). Flexible epoxide **49** forms slowly

utilizing all three catalysts (Table 28, Entry 3; Table 32, Entries 9 and 15), but Michael systems **54** and **56** can be epoxidized astonishingly well (Table 32, Entries 4, 5, 11, and 17). The last experiments have to be reproduced and investigated in more detail.

Table 32: Investigation of interaction and substitution pattern.





Entry	Cat.	Alkene	Epoxide	H_2O_2[(c)] [equiv]	t [h]	Yield[(d)] [%]
1[(a)]	**131**	 **38**	 **39**	2.0	1	99
2[(a)]	**131**	 **40**	 **41**	2.0	1	quant.
3[(b)]	**131**	 **44**	 **45**	8.0	7	63
4[(b)]	**131**	 **54**	 **55**	8.0	7	98
5[(a)]	**131**	 **56**	 **57**	8.0	24	36
6[(b)]	***meta*-161**	**38**	**39**	8.0	6	23
7[(b)]	***meta*-161**	**40**	**41**	2.0	1	quant.
8[(b)]	***meta*-161**	**44**	**45**	8.0	7	51
9[(b)]	***meta*-161**	 **48**	 **49**	8.0	7	16
10[(b)]	***meta*-161**	 **50**	 **51**	8.0	6	50
11[(b)]	***meta*-161**	**54**	**55**	8.0	7	98

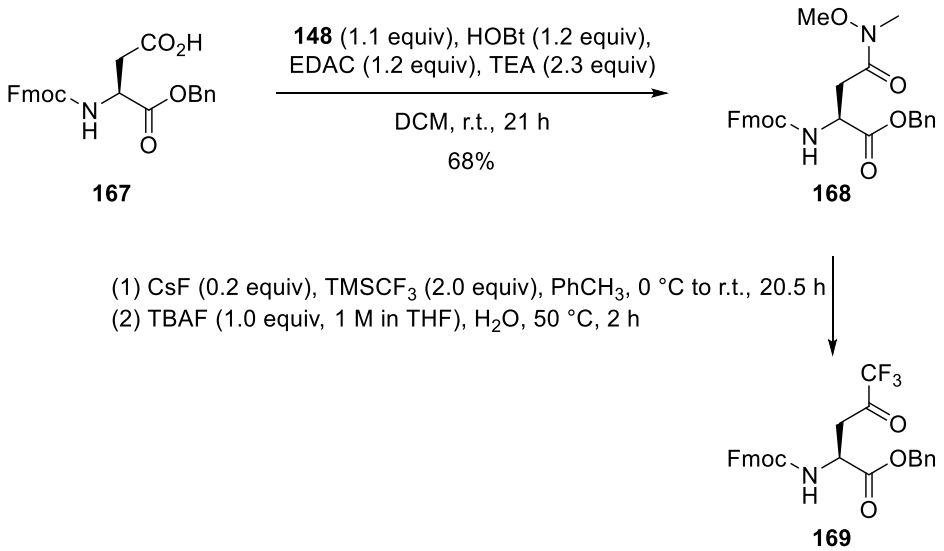
12[a]	**166**	**38**	**39**	8.0	6	55
13[a]	**166**	**40**	**41**	2.0	1	quant.
14[b]	**166**	**44**	**45**	4.0	2	42
15[b]	**166**	**48**	**49**	8.0	24	14
16[b]	**166**	**50**	**51**	8.0	24	20
17[a]	**166**	**56**	**57**	8.0	24	34

[a]: Alkene (0.628 mmol, 1.0 equiv), Na_2EDTA (0.1 mol%), **cat.** (10 mol%), K_2CO_3 (1.8 equiv), MeCN (8.0 equiv), H_2O_2 (8.0 equiv), ^{t}amyl alcohol/H_2O 1.92 mL/1.92 mL; [b]: alkene (0.165 mmol, 1.0 equiv), Na_2EDTA (0.1 mol%), **cat.** (10 mol%), K_2CO_3 (1.8 equiv), MeCN (8.0 equiv), H_2O_2 (8.0 equiv), ^{t}amyl alcohol/H_2O 0.500 mL/0.500 mL; [c]: 2.0 equiv H_2O_2 were added hourly; [d]: yield determined *via* chiral GC without internal standard.

Due to the still absent enantiomeric excess even by varying the substituents at the aromatic ring of the catalytic moiety, we stopped our approach of synthesizing a catalytic moiety before fixation on a peptidic system at this point. Combining the aspect of a shorter linker with a TFMK lead to the synthesis of a functionalized amino acid, which can act as building block in peptide synthesis.

4.4.9.5. TFMK-Based Amino Acid

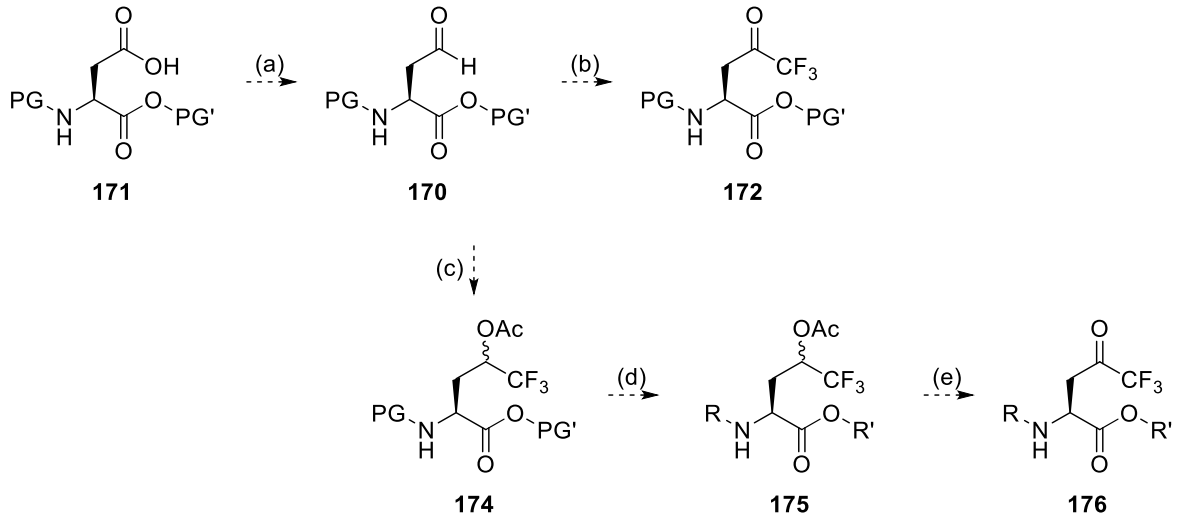
As starting point we wanted to synthesize the TFMK derivative from aspartic acid. To obtain target compound **169** we linked the procedures of synthesized amino acid **139** (Scheme 49) and the Weinreb amid strategy (Table 29, Entry 3).[132] Finally, we would end up with an orthogonally protected and functionalized amino acid, which contains only one CH_2-linker and can be used directly in SPPS (Scheme 55).



Scheme 55: Synthetic approach for amino acid **169**.

The synthesis of Weinreb amid **168** was performed utilizing the EDAC/HOBt-mediated protocol.[68, 3a] After reaction of orthogonal protected carboxylic acid **167** with hydrochloride **148** the target compound was isolated with a yield of 68%. But, the transformation of Weinreb amide **168** to its TFMK analog **169** did not take place and only starting material **168** was reisolated.

Due to the fact that the synthesis of TFMKs *via* their Weinreb amides failed both for substrate **150** (Table 29, Entry 3) as well as for **168** (Scheme 55) we suggest a route starting from an aldehyde. Whereas, the aldehyde of serine is prone to racemize its aspartic acid-derived analog would be our first choice.[142] Two potential approaches are depicted in scheme 56.



Scheme 56: Future approaches for the synthesis of TFMK containing amino acids.
(a): (1) LAH and (2) DMP; (b): (1) **173**, Zn, DMF, −20 °C and (2) DMP; (c): (1) $TMSCF_3$, TBAF, THF, 0 °C and (2) Ac_2O, DMAP, DCM r.t.; (d): deprotection and peptide coupling; (e): (1) LiBr, DBU, MeOH and (2) DMP.

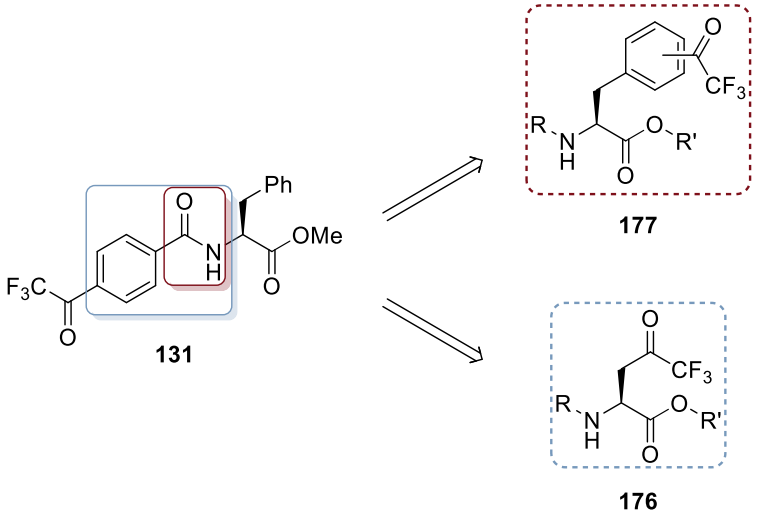
Starting material **170** is commercially available or should be synthesizable in a two-step sequence form aspartic acid **171**.[85] Afterwards, we would firstly utilize the procedure included in the patent of Napper and colleagues[6]. They described the synthesis of **172** *via* addition of trifluoroiodomethane **173** to aldehyde **170** followed by oxidation of the intermediately formed alcohol with Dess-Martin periodinane (DMP). Secondly, we would transfer the strategy established by Miller *et al.* for synthesizing their TFMK containing peptide catalyst to aldehyde **170**.[57] In the first step *in situ* formed trifluoromethyl-substituted alcohol is transferred to acetate derivative **174**. This protected intermediate can be used in the following deprotection

[6] A. D. Napper, R.C. Titmas, M. T. Martin, W. inventors; IGEN International, Inc., assignee. Catalytic antibodies which hydrolyze primary amides and methods for eliciting such antibodies. US 5900237. 1999 May 4.

and coupling steps. After completion of desired target peptide **175** the protecting group has to be removed. Finally, after late-stage oxidation catalyst **176** can be used in epoxidation reactions.

4.4.10. Outlook

After identification of suitable catalytic moiety **112** (Chapter 4.4.2.) we synthesized several peptide-based and C_2-symmetric catalysts containing this dioxirane precursor (Chapter 4.4.3.). For the catalyzed epoxidation we optimized an Oxone®- as well as a H_2O_2/MeCN protocol with less complex chiral test catalyst **131** (Chapter 4.4.6.). To simplify the synthetic procedure of our catalytic systems we prepared functionalized lysine derivative **137** (Chapter 4.4.8.). Unfortunately, none of the performed catalyzed epoxidation reactions provided an enantiomerically enriched product. Therefore, we developed three strategies to address this aspect (Chapter 4.4.9.). While the synthesis of the Dap derivative **139** (Chapter 4.4.9.1.) and *meta*-substituted TFMK **161** worked (Chapter 4.4.9.2.), we were not able to prepare functionalized amino acid **169** yet (Chapter 4.4.9.5.). But, because of synthetic problems concerning the synthesis of catalytic moiety and the still missing enantiomeric excess in the epoxidation (Chapter 4.4.9.4.), we deem it appropriate and the most promising approach to put more effort in the synthesis of amino acid building blocks like **176** and **177** (Scheme 57).



Scheme 57: Potential building blocks **176** and **177**.

In addition to possible synthetic strategies for **176** (Chapter 4.4.9.5) functionalized phenylalanine **177** might be assessable *via* Friedel-Crafts acylation of protected phenylalanine with trifluoroacetic anhydride. The DMAP-mediated synthesis of such aromatic species was published by Simchen *et al.* in 1999.[133] The synthesis of its *para*-substituted analog was described by Hashimoto *et al.* in 2015 utilizing another aromatic substitution approach. After halogen-metal exchange they introduced the TFMK *via* ethyl trifluoroacetate.[143]

The identification of a new and maybe selective catalysts is the key step in this project. While, re-optimization of the established protocols and extending the substrate scope *via* testing the whole substrate library is straight forward.

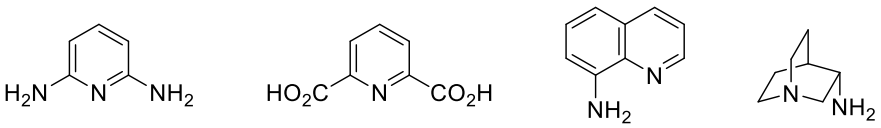
Furthermore, during the attempt to synthesize ***ortho*-112** starting form carboxybenzaldehyde **146** we isolated *α*-keto acetal **162a** (Chapter 4.4.9.3.). Based on this observation we established an alkaloid-mediated asymmetric synthesis of acylated analog **162b**. After only a few reactions we were able to isolate the target compound with 96% yield and an enantiomeric excess of 28%. A variety of parameters like catalyst, temperature or solvent should be varied to refine this very promising approach.

4.5. Peptide-Based Phase Transfer Catalysts

During the first test reactions with catalysts **114** and **115** we saw that TBABr itself is also able to transfer alkene **38** under the chosen reaction conditions in its oxirane (Table 23, Entry 3). Of course a variety of protocols based on the PTC concept for a variety of different reactions in an asymmetric fashion are already described in literature.[46, 43f] Two typical representatives are alkaloid- as well as binaphtyl-based PTCs (Figure 9). The enantioselective epoxidation of electron-deficient alkenes is one intensively studied reactions in the context.[144, 46] Ensuing from our observations and by combining the PTC approach with our peptide concept we wanted to develop a peptide-based PTC, which can be used as third class of catalytically active compounds in epoxidation reactions.

4.5.1. Preliminary Considerations

In first place, we had to find a suitable building block, which could be both incorporated into a peptidic structure and be alkylated in the final step to yield the active species. Based on the good experiences with amide bond formation to connect catalytic moiety and peptide we were looking for carboxylic acid or amine derivatives as potential precursors (Figure 24).



178 **179** **180** **181**

Figure 24: Potential PTC precursors.

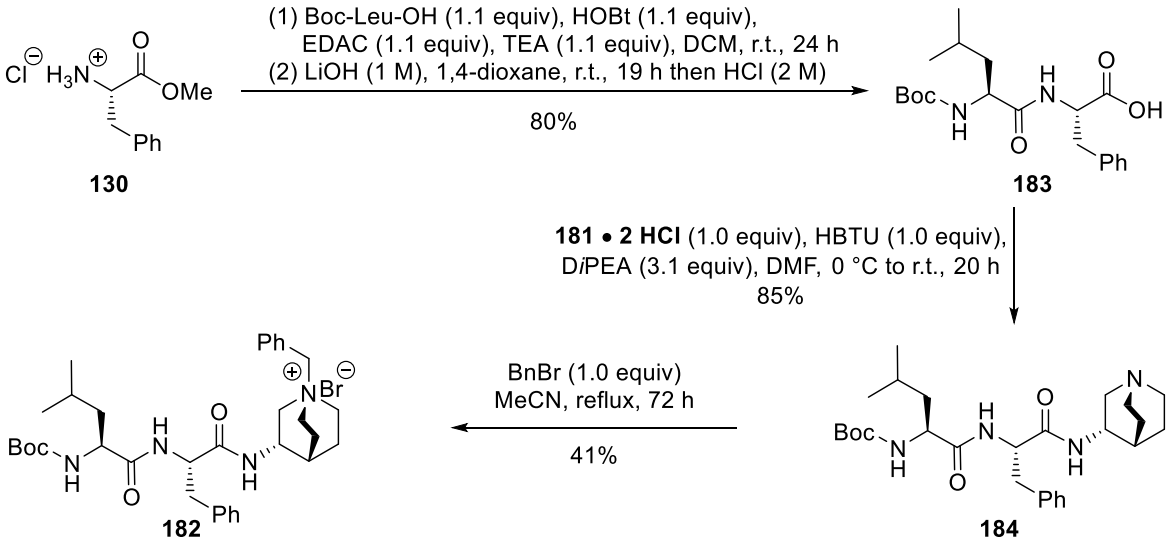
Diamine **178** and diacid **179** were selected to incorporate the PTC precursor in the peptide backbone. Thereby, C_2-symmetric or asymmetric peptides can be obtained. Primary amines **180** and **181** can connected to the *C*-terminus of the peptide or to a carboxylic acid side chain of

aspartic or glutamic acid. In case of **178**, **179**, and **180** we would end up with a pyridine or quinolone-based salt, in which the nitrogen atom is sp^2-hydridized. In contrast, diamine **181** would provide a quaternary ammonium species, which is the typical motif in the already known and established PTCs.

4.5.2. Synthesis of the First Peptide-Based PTC

Our preliminary experiments with **178**, **179**, and **180** showed that formation of an amide bond was indeed only possible for diacid **179** and quinolone derivative **180**,[68, 3a] but the salification did not occur for both species under the selected conditions.[145] Due to its weaker s-character the sp^3-hybridized nitrogen atom of tertiary amine **181** reacts faster in an alkylation than a comparable aromatic sp^2-analog. For example, alkylation of alkaloid **217** (Chapter 5.3.5.3) containing a nitrogen aromatic compound in the presence of a tertiary amine yielded quaternary ammonium salt **218** with 90% utilizing the conditions of Meng.[146] Based on those observation and with the typical used quaternary ammonium salts in mind we focused on tertiary amine **181**. Initial experiments showed that synthesizing the peptide in the typically fashion from *C*- to *N*-terminus starting with diamine **181** lead to purification problems, which were solved by synthesizing the peptide beforehand and attaching the primary amine as last monomer to the final peptide. Due to bad solubility of starting material **181** we also had to change the conditions for its coupling reaction with a *C*-terminal unprotected amino acid. After variation of solvent and addition of base, we were oriented by the conditions of Rogers and co-workers.[147] They reported a procedure with *O*-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium-hexafluorphosphat (HATU) and three equivalents D*i*PEA. Instead of HATU we used HBTU. After late-stage alkylation of the tertiary amine we obtained the desired PTC. The modified synthetic procedure is exemplarily depicted for PTC **182** (Scheme 58).

After peptide coupling utilizing the EDAC/HOBt protocol[68, 3a] the methyl ester was cleaved with lithium hydroxide in 1,4-dioxane.[116] After acidification with hydrochloric acid *C*-terminal unprotected dipeptide **183** was isolated with a yield of 80% after two steps. Based on the HBTU/D*i*PEA protocol we isolated tripeptide **184** with a yield of 85% after 20 hours.[147] Alkylation with benzyl bromide provided target ammonium salt **182** with a yield of 41%.[145] In the end we obtained PTC **182** with an overall yield of 28% after four steps.



Scheme 58: Adapted peptide synthesis for PTC **182**.

Besides the adapted synthetic procedure we included foreknowledge from our initial experiments for designing catalyst **182**. Solubility of the PTC and a faster reaction of the alkene in the afterwards performed epoxidation can be increased by a higher lipophilicity of the catalyst. Therefore, we synthesized a dipeptide consisting of leucine (Leu) and phenylalanine. Furthermore, even if free hydroxyl groups are favorable for an enantioselective epoxidation[49, 148] we refrained from incorporation of unprotected threonine. The free hydroxyl group complicated the purification of the peptides. Of course, one logical alternative would be the use of protected threonine and its deprotection directly before alkylation.

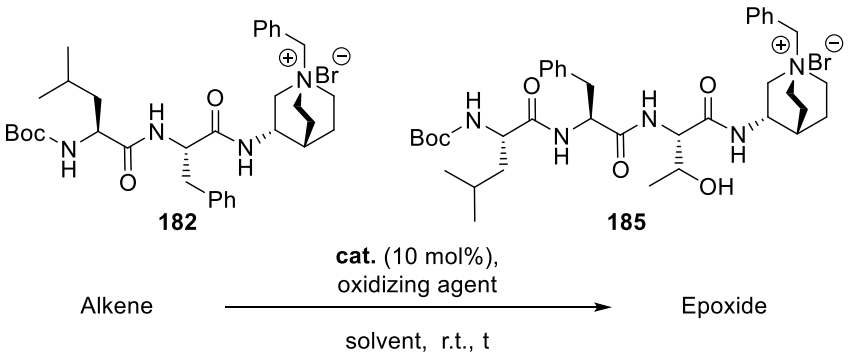
4.5.3. PTC-Based Epoxidation

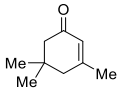
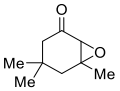
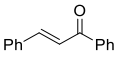
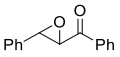
For investigation of the reaction conditions for the catalytic epoxidation we used enone **58** and 10 mol% PTC **185** (see Experimental Section). Due to better solubility properties considering ammonium salt **185** chloroform was chosen as solvent at the beginning. Oxygen sources were selected with respect to literature-known protocols.[49, 148, 76b] Afterwards, the best conditions were directly transferred to further substrates and PTC **182** (Table 33).

Due to a faster reaction in toluene chloroform was substituted in further experiments (Table 33, Entries 3 and 6). In contrast to sodium hypochlorite epoxidation ability of hydrogen peroxide and TBHP are comparable (Table 33, Entries 1, 6, and 8). Increasing the amount of base has no effect on epoxide formation (Table 33, Entries 3 and 4). Based on those results we used toluene in combination with two equivalents of base and ten equivalents hydrogen peroxide for further investigations (Table 33, Entry 6). The background reaction can only be

neglected for alkene **60** (Table 33, Entry 11). Both utilized PTCs showed similar results, but no enantiomeric excess.

Table 33: PTC-based epoxidation of enones.



Entry[a]	Cat.	Alkene	Epoxide	Solvent	t [h]	Yield[f] [%]
1[b]	**185**	 58	 59	$CHCl_3$	23	traces
2[c]	-	**58**	**59**	$CHCl_3$	48	10
3[c]	**185**	**58**	**59**	$CHCl_3$	23	20
4[d]	**185**	**58**	**59**	$CHCl_3$	24	20
5[c]	-	**58**	**59**	$PhCH_3$	23	28
6[c]	**185**	**58**	**59**	$PhCH_3$	24	87
7[e]	-	**58**	**59**	$PhCH_3$	25	4
8[c]	**185**	**58**	**59**	$PhCH_3$	24	71
9[c]	-	 56	 57	$PhCH_3$	24	50
10[c]	**185**	**56**	**57**	$PhCH_3$	23	52
11[c]	-	 60	 61	$PhCH_3$	23	4
12[c]	**185**	**60**	**61**	$PhCH_3$	23	53
13[c]	**182**	**56**	**57**	$PhCH_3$	23	72
14[c]	**182**	**58**	**59**	$PhCH_3$	23	81
15[c]	**182**	**60**	**61**	$PhCH_3$	23	58

[a]: Enone (0.080 mmol, 1.0 equiv), **cat.** (0.008 mmol, 0.1 equiv, 10 mol%), 1.00 mL solvent; [b]: NaOCl (13%) (0.160 mmol, 2.0 equiv); [c]: $NaOH_{aq}$ (2%) (0.160 mmol, 2.0 equiv) and H_2O_2 (30%) (0.800 mmol, 10.0 equiv); [d]: $NaOH_{aq}$ (6%) (0.480 mmol, 6.0 equiv) and H_2O_2 (30%) (0.800 mmol, 10.0 equiv); [e]: $NaOH_{aq}$ (2%) (0.160 mmol, 2.0 equiv) and TBHP (5 M in *n*-decane) (0.800 mmol, 10.0 equiv); [f]: yield determined *via* chiral GC or HPLC without internal standard.

In contrast, for example, to the catalysts of Nagasawa, Maruoka, and Tang our two catalytic systems are inferior considering the epoxidation of olefin **60**.[49-50, 48]

4.5.4. Summary and Outlook

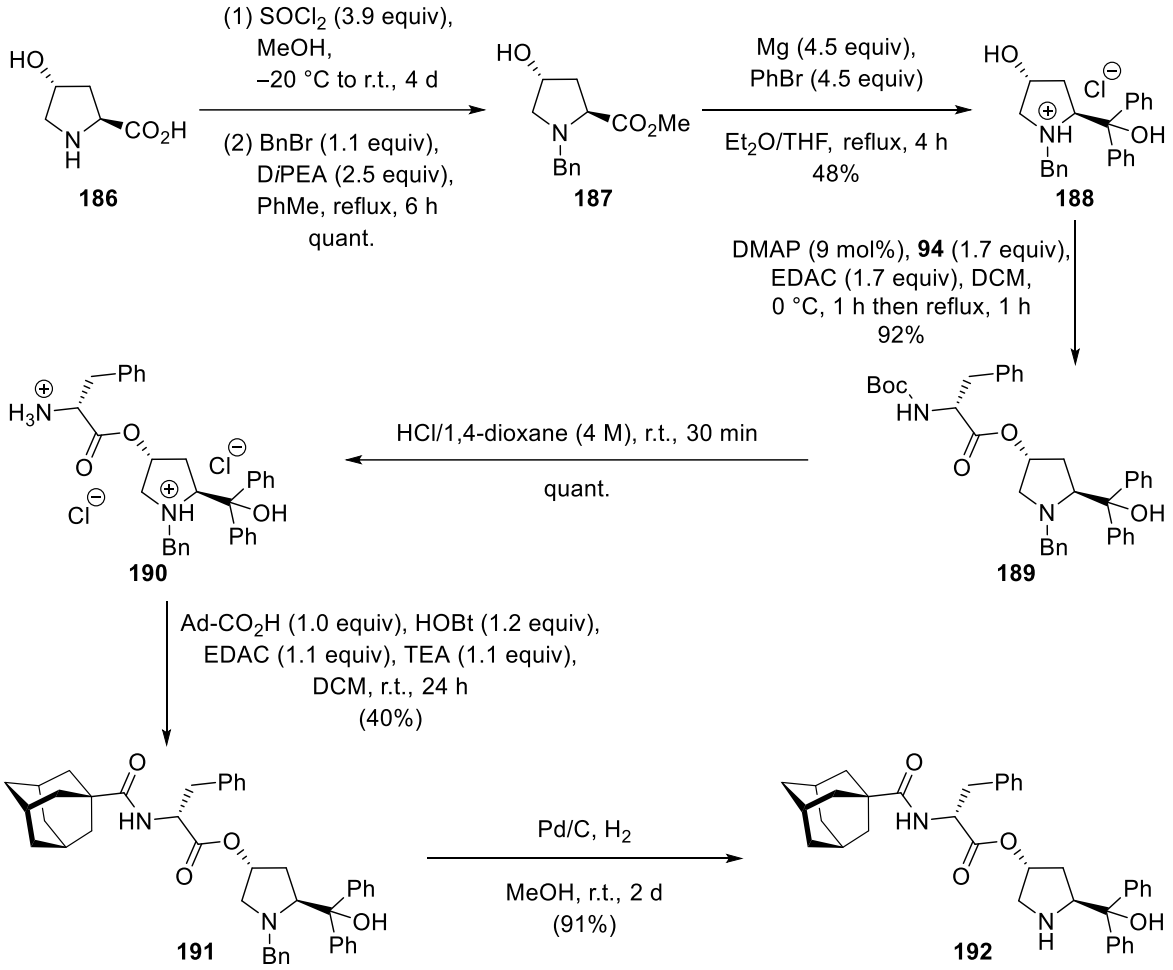
During this project we gained a deeper inside in the field of phase transfer catalysis. After identification of a suitable key building block we were able to synthesize, to the best of our knowledge, the first peptide-based PTCs. Arising problems were solved *via* adaption of the synthetic protocol. As most important aspect we recognized the use of lipophilic amino acids in regard to solubility and epoxidation ability. With those catalysts in hand we tested a protocol starting form literature-known procedures, with which several alkenes were transferred successfully into the corresponding epoxides. But, due to the missing enantiomeric excess, the still difficult synthetic procedure, and especially the excellent working and already published catalysts we stopped further investigations in this direction at this point.

4.6. Prolinol-Based Peptide Catalysts

Besides PTCs *α,α*-diaryl prolinols are also suitable and well-examined catalysts for the epoxidation of *α,β*-unsaturated carbonyl compounds. In 2005, Lattanzi *et al.* published the first prolinol-based enantioselective version of this reaction (Scheme 15).[51] Several years later, Maltsev and Alza described the attachment of hydroxyl prolinol to an ionic liquid and to a polymer, respectively.[149] By containing a linker and a catalytic moiety this prolinol derivative is a perfect motif for our peptide-based approach. Therefore, we wanted to develop this strategy combined with our peptide concept as forth epoxidation procedure.

4.6.1. Synthesis of an Attachable Hydroxyl Prolinol Derivative

Compared to the two last described epoxidation strategies (Chapters 4.4. and 4.5.) we did not have to identify a catalytic moiety in this case because hydroxyl prolinol was already used as catalytic system. Thus, after synthesis and successful coupling with a peptide backbone our preconditions look promising to obtain a functionalized, active, and hopefully selective peptide. For preparation of catalytically active amino acid derivative **188** we oriented ourselves towards the procedures of Maltsev and Alza.[149] Considering a peptide synthesis we selected benzyl as protecting group for the secondary amine. Independently, if SPPS or a peptide synthesis in solution is performed, the benzyl group is orthogonal to the Fmoc and Boc protecting group, respectively. To mimic adamantyl-based catalysts **1** a dipeptide of phenylalanine and adamantyl glycine were bound *via* ester to hydroxyl prolinol **188**. Finally, reductive cleavage of the benzyl group would yield peptide catalyst **192** (Scheme 59).



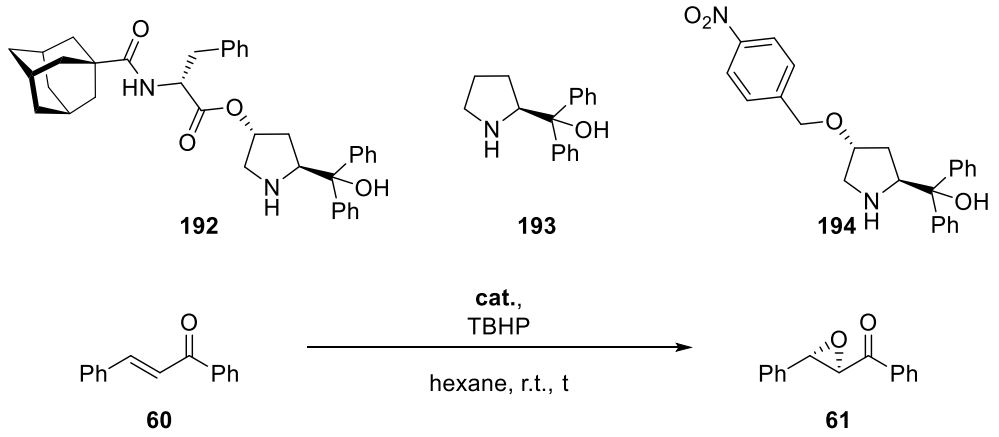
Scheme 59: Synthesis of prolinol-derived peptide catalyst **192**.

Utilizing standard conditions for methyl and benzyl protection of acid as well as amine proline derivative **187** was obtained with a quantitative yield.[127, 149b] The following Grignard reaction was performed in a solvent mixture of THF and diethyl ether, because of solubility problems of the starting materials.[149a] But, tertiary alcohol **188** was only isolated with a yield of 48% as the corresponding hydrochloride. Its presence was elucidated *via* utilizing different solvents for NMR measurements. But, this ionic species was not disadvantageous for the next reaction step and add-on DMAP-mediated coupling yielded functionalized amino acid **189** with 92%.[149a, 68] After removing the Boc group under acidic conditions adamantyl carboxylic acid was coupled.[116, 68, 3a] Even trying to purify product **191** utilizing different procedures could not remove unreacted acid completely (yields in brackets). The mixture of dipeptide and adamantyl carboxylic acid was reduced anyway.[116, 3a] The final step needed a lot of optimization efforts due to incomplete conversion. 27 mol% of Pd/C were necessary to overcome the literature-known catalyst inactivation caused by inhibitors.[150] Unprotected amine **192** contaminated with around 20% carboxylic acid were finally obtained.

4.6.2. Catalysis and Comparison

It is mentioned in literature that the presence of an acid leads to inhibition of the amine catalyst.[151] Protonation of the amine hampers its participation in the catalytic cycle (Scheme 15). Although peptide-bound prolinol **192** still contained adamantyl carboxylic acid, we wanted to perform a proof of principle reaction with this successfully synthesized catalyst. For direct comparison with examples from the literature we used the optimized condition published by Lattanzi (Table 34).[51]

Table 34: Proof of principle experiment with prolinol-based peptide **192**.



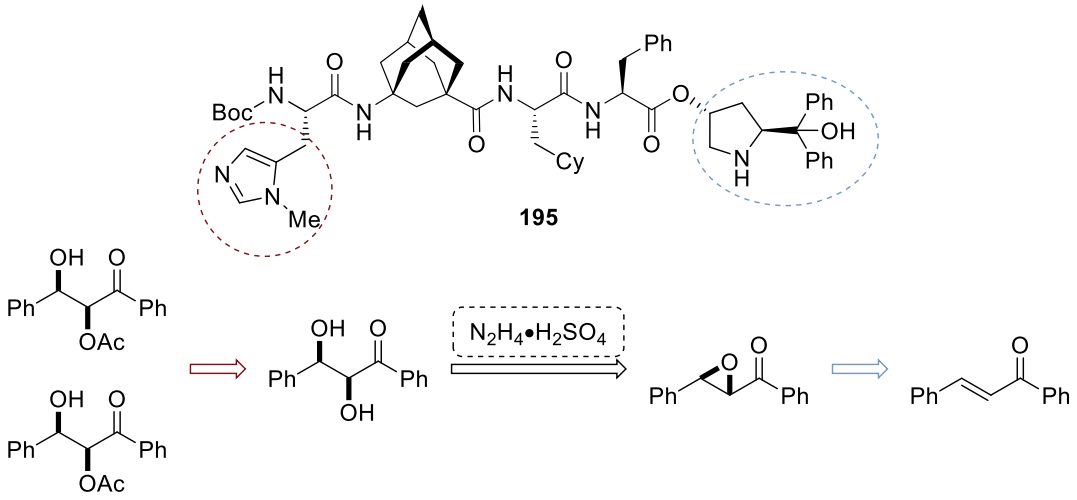
Entry	Cat.	Amount of cat. [mol]	TBHP [equiv]	t [h]	Yield [%]	*ee* [%]
1	**192**	25	1.2	94	4[(a)]	66[(a)]
2	**193**	30	1.2	94	72	75
3	**194**	30	1.3	144	32	80

[(a)]: Yield and enantiomeric excess were determined *via* chiral HPLC without internal standard.

A yield of 72% and an enantiomeric excess of 75% for epoxide **61** are reported for unsubstituted prolinol **193** after 94 hours (Table 34, Entry 2).[51] Such long reaction times in combination with a comparable high catalyst loading are typical for those epoxidation reactions. Introducing a large substituent like a *para*-nitrobenzyl ether in four position of the cyclic system leads to a decreased activity by an unchanged selectivity (**194**: Table 34, Entry 3).[152] As expected, due to inhibition, caused by the still present acid, our catalyst **192** formed epoxide **61** very slowly. Substitution of the pyrrolidine ring decreased the activity additionally. Hence, it is very astonishing that a catalyst loading much lower than 25 mol% generated oxirane **61** with an enantiomeric excess of 66% (Table 34, Entry 1).

4.6.3. Summary and Outlook

We were able to synthesize a prolinol-functionalized peptide mimicking highly selective acylation catalyst **1**. Afterwards, **192** was directly tested successfully in a proof of principle epoxidation under optimized conditions form literature. Especially, in regard to a possible multicatalytic sequence with very flexibly applicable prolinol catalysts further optimizations of the synthetic procedure are useful. After establishing a smoothly working purification procedure acid-free catalysts have to be synthesized and tested in combination with additional substrates to get impression of their real epoxidation ability. Furthermore, a new multicatalytic sequence consisting of epoxidation-epoxide opening-acylation can be investigated. Multicatalyst **195** in combination with hydrazine sulfate[3b] could be used to synthesize acylated α-keto diols (Scheme 60).



Scheme 60: New mutlicatalytic sequence with prolinol-catalyzed epoxidation.

4.7. Summary and Outlook

Considering the second step of our new postulated multicatalytic sequence (Chapter 3.) we created a substrate library containing 14 alkenes and their corresponding epoxides (Chapter 4.1.1.). These less complex unsaturated compounds mimicking the unsaturated esters should facilitate the identification of an asymmetric epoxidation procedure based on peracid- (Chapter 4.3.), dioxirane- (Chapter 4.4.), PTC- (Chapter 4.5.) or prolinol-based catalytic systems (Chapter 4.6.). For dioxirane- and PTC-based strategies we were able to identify a suitable catalytic moiety. After synthesis of peptide-based catalysts containing precursors or catalytic active moieties themselves for all four approaches epoxidation protocols were successfully established. Except for the prolinol-based variant a racemic reaction process

was observed. Although, especially for dioxirane-based systems besides variation of the peptide backbone a lot of effort was invested to synthesize a selective precursor (see Chapter 4.4.9.).

Due to the excellent working PTCs our peptide-based analogs are the less promising approach. On the other hand particularly C_2-symmetric diacid catalysts (Chapter 4.3.6.) and peptides containing a TFMK functionalized amino acid appear to be encouraging (Chapter 4.4.9.5.). The most potent strategy is the prolinol-mediated procedure. A well-working system with intensively studied reaction conditions are optimal requirements. After identification of a suitable peptide backbone in combination with the first promising results this approach should be investigated in more detail.

The last mentioned example illustrates that an alternative to synthesis of catalytic moieties is the use of already discovered ones with optimized reaction conditions and focus on the identification of appropriate peptide backbones in the future examinations. Finding and synthesizing new precursors is very challenging and time-consuming and no warranty is given that they will be active and selective in the end. Therefore, we suggest that, for example, catalytic motifs like Shi's catalysts or alkaloids should be incorporated in peptidic structures providing catalysts like **196** or **197** (Figure 25).

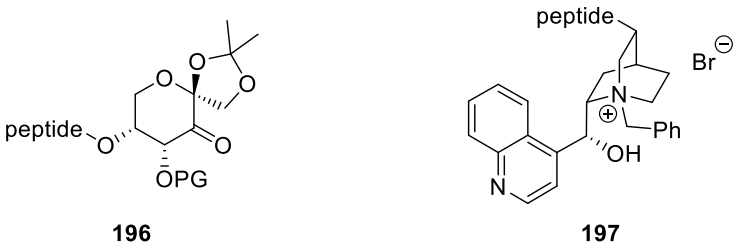


Figure 25: Potential peptide-based systems.

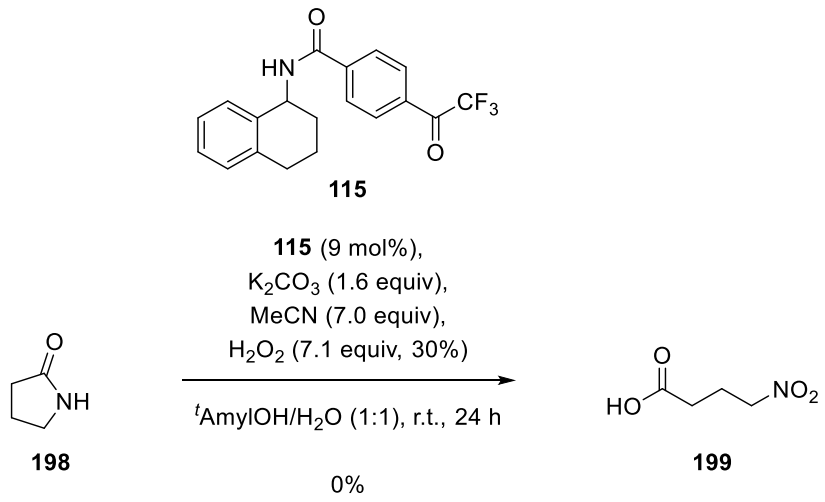
During the synthesis of olefins and modifying TFMK-substituted aromatic systems we discovered both spiro carbonate **75** (Chapter 4.2.) as well as α-keto acetals **162a** (Chapter 4.4.9.3). For the spiro compound the cooperative effect and the substrate scope of the protocol should be investigated in more detail. Considering the α-keto acetals further optimization of the synthetic procedure is necessary to increase the enantioselectivity and include additional substrates and electrophiles in the study.

5. Further Applications for the Available Peptide Catalysts

Besides epoxidation, there are a variety of further reactions, which can be catalyzed, especially by dioxirane- and peracid-based species. Therefore, it is quite obvious to examine the already available catalysts simultaneously starting from literature-known procedures. In this context we tested the oxidative lactam opening (Chapter 5.1.), the synthesis of oxaziridines (Chapter 5.2.), and sulfoxidation (Chapter 5.3.).

5.1. Oxidative Lactam Opening

In 2013, Fusco *et al.* published the oxidative cleavage of lactams. In an aqueous solution trifluoromethyl acetone mediates the ring opening of cyclic amides and provides the corresponding nitro-substituted carboxylic acids in excellent yield. In case of 2-pyrrolidinone **198** Fusco and co-workers isolated over 99% of carboxylic acid **199** after 90 minutes at 0 °C.[153] Based on this observation and with optimized conditions for the dioxirane formation regarding the epoxidation in hand, we tried to combine these strategies. Amide **115** was chosen as the test dioxirane precursor and 2-pyrrolidinone **198** as the substrate (Scheme 61).



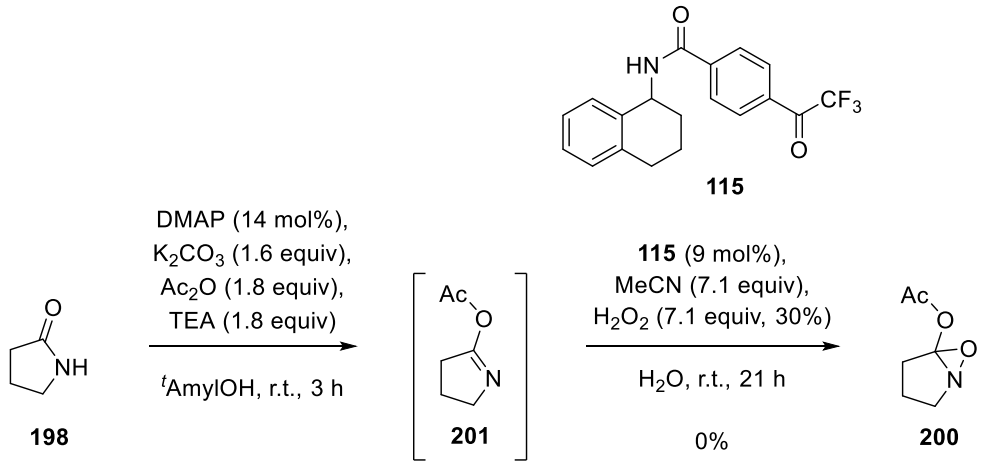
Scheme 61: Oxidative lactam opening.
The reaction was performed in a 0.526 mmol scale with 6.00 mL of solvent; addition of H_2O_2 was split into four portions of 2.0 equiv each, added in 1 hour intervals; reaction progress was monitored by GC-MS.

After a reaction time of 24 hours, no evidence for the formation of carboxylic acid **199** could be found, neither by GS-MS nor NMR analysis. Instead, catalyst **115** and small amounts of lactam **198** were reisolated. Due to the fact that large amounts of starting material **198** are missing we assume that the quite polar byproduct **199**, if formed, might remain in the aqueous phase during work-up. The usage of rather nonpolar starting materials is a possibility to prove this circumstances. However, judging from the less promising test experiment, this reaction was

not studied in more detail, even if a kinetic resolution or desymmetrization of corresponding lactams should be possible using chiral peptide catalyst.

5.2. Synthesis of Oxaziridines

Based on the same starting material we also examined the synthesis of oxaziridine **200** containing an additional quaternary carbon atom. In a two-step sequence, the conjectured intermediary formed *α*-acetoxy imine **201** should be directly epoxidized by the *in situ* generated dioxirane species (Scheme 62). Two papers dealing with one of the reaction steps have already been published. Blanton and co-workers described the synthesis of a comparable acylated compound in 1982,[154] whereas Aue *et al.* established a peracid-based epoxidation protocol of imino ethers in 1973.[155]



Scheme 62: Synthetic approach for oxaziridine **200**.
The reaction was performed in a 0.526 mmol scale with 3.00 mL ^{t}AmylOH and 3.00 mL water; addition of H_2O_2 was split into four portions of 2.0 equiv each, added in 1 hour intervals; reaction progress was monitored by GC-MS.

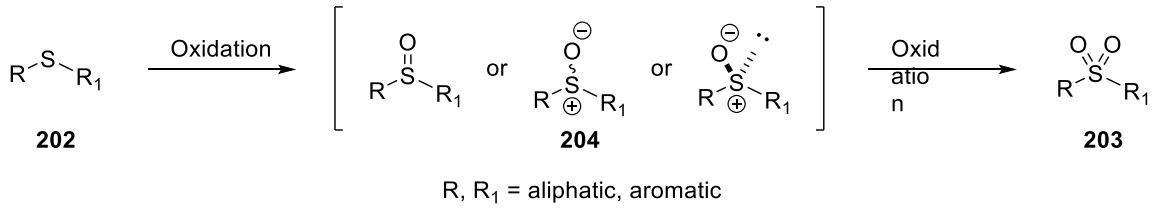
Formation of intermediate **201** was not observable *via* GC-MS. Hence, it was hardly surprising that we reisolated 51% of starting material **198** instead of desired product **200**. Due to the fact that the first step limits the sequence, no further attempts regarding the epoxidation (e.g., use of peracid-based catalysts) were undertaken.

5.3. Sulfoxidation

Comparing nitrogen and sulfur organic compounds of the latter can be chiral. In combination with oxidative conditions suitable catalysts may lead directly to sulfoxidation.

5.3.1. Introduction

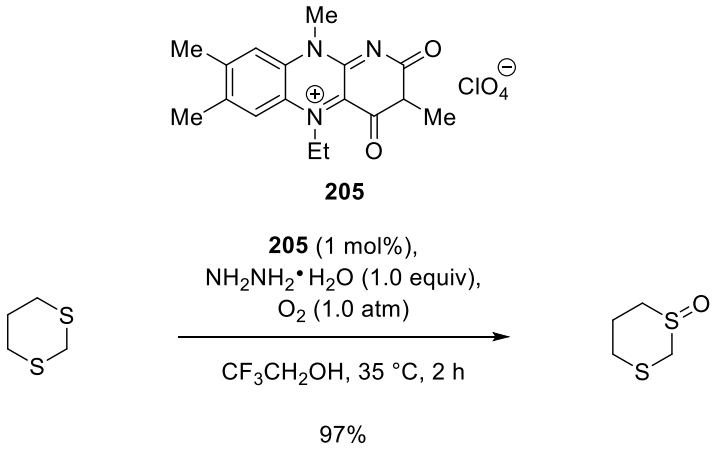
In contrast to sulfides **202** and sulfones **203**, sulfoxides **204** can be chiral if they are substituted with two different residues. Besides the oxygen atom and the two aliphatic and/or aromatic groups, the remaining electron pair counts as the forth substituent (Scheme 63).



Scheme 63: Oxidation states of sulfur.

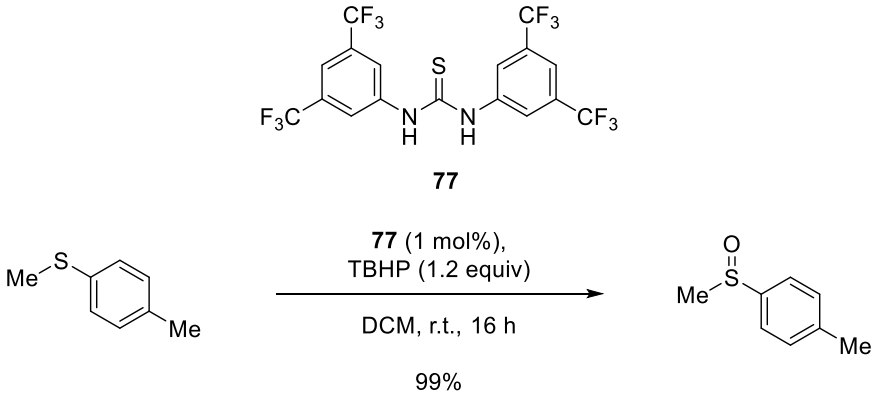
One approach for synthesizing sulfoxides is, for example, a titanium- or vanadium-based oxidation *via* combination of bi-, tri, and tetradendate ligands and a feasible oxidizer.[156] In the mid 1980s, Kagan and Modena independently established protocols for the enantioselective sulfoxidation based on the epoxidation concept of Sharpless.[157] Afterwards, several papers were published using different kind of ligands, oxidizing agents, as well as metals.[156]

Metal-free methods have also been studied intensively during the last years. Besides hypervalent iodine, iminium, and oxaziridine compounds as well as hydroperoxide organocatalysts can be utilized to generate sulfoxides.[158] A combination of a catalyst and a conveniently accessible oxidizer, e.g., Oxone®, oxygen or hydrogen peroxide is favored instead of using stoichiometric amounts of a chiral organic oxidizer, which has to be synthesized beforehand. In 2003, Murahashi *et al.* published the oxidation of sulfides and amines with flavin **205** in an oxygen atmosphere. Water and nitrogen are formed as non-toxic byproducts, thermodynamically favoring the overall process (Scheme 64).[159]



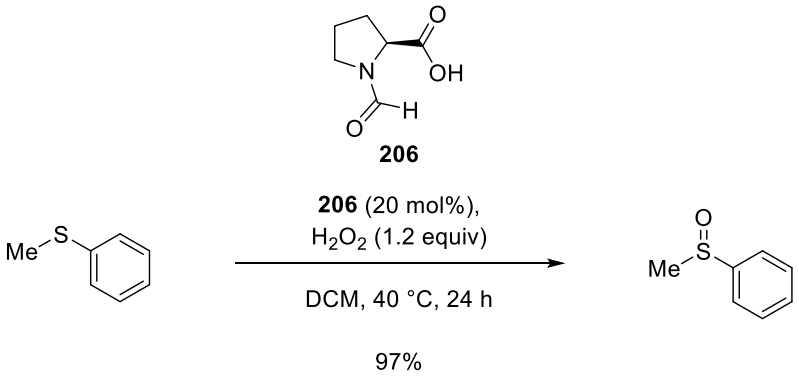
Scheme 64: Flavin-catalyzed sulfoxidation.

Secondly, Lattanzi *et al.* introduced the activation of TBHP *via* TUC **77**. Under these conditions, a variety of sulfides were transferred into their corresponding sulfoxides in good yields and selectivities with a catalyst loading of only 1 mol% (Scheme 65).[160]



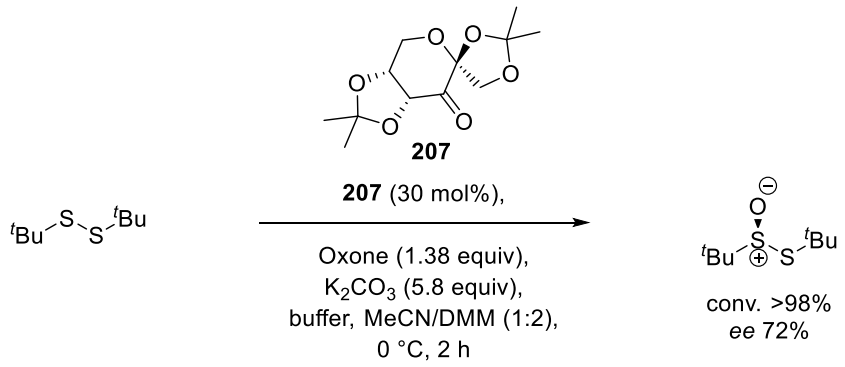
Scheme 65: Sulfoxidation *via* hydrogen bond activation of TBHP.

Amino acids like *N*-protected proline **206** can also act as catalyst in sulfide oxidations. Tsogoeva and co-workers established a protocol providing sulfoxides in good yields up to 97% (Scheme 66). In their postulated mechanistic model, catalyst **206** activates hydrogen peroxide for the nucleophilic attack of the starting material.[161]



Scheme 66: Proline-catalyzed oxidation of sulfides.

Lastly, Colonna and co-workers described the asymmetric sulfoxidation of disulfides with fructose derivative **207** known from the Shi epoxidation. Besides a solvent mixture of acetonitrile and dimethoxymethane (DMM), a 1:1 ratio of starting material, oxidizing agent, and catalyst were chosen providing excellent conversion and good stereoselectivity (Scheme 67).[162]



Scheme 67: Sulfoxidation of disulfides.

The stereoselective mono-oxidation of sulfides catalyzed by metals as well as enzymes plays a key role in the synthesis of biologically active sulfoxides (Figure 26), some of which are already produced on an industrial scale. [163] Esomeprazole **208**, the *S*-enantiomer of omeprazole, a proton-pump inhibitor is used for acid-related diseases.[164] Sulfoxide **209**, derived from the Hantzsch ester, showed good activity as a calcium channel antagonist for the treatment of heart diseases.[165]

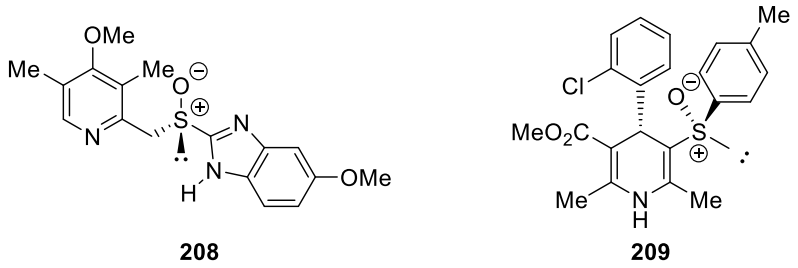
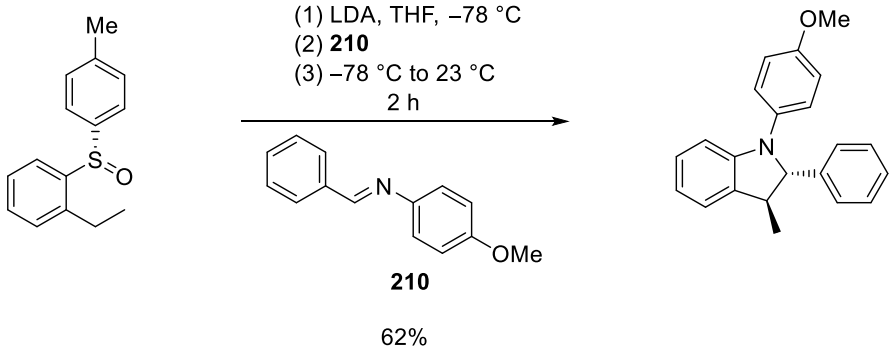
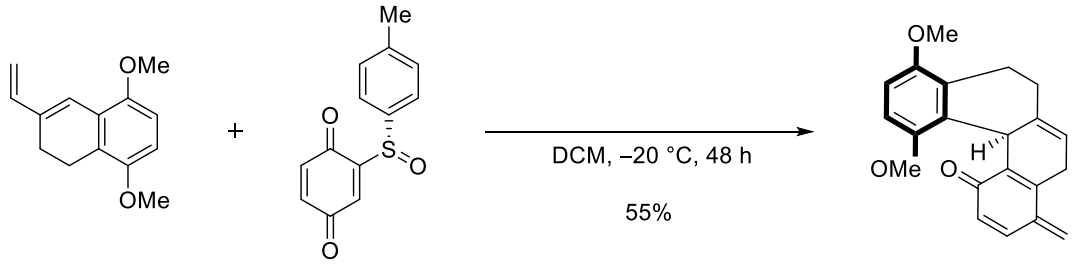


Figure 26: Biologically active sulfoxides.

Furthermore, chiral sulfoxides fulfill a variety of tasks. Over the last years, these compounds have been established as chiral auxiliaries. Owing to their electronic structure as well as flexible substitution pattern, they stabilize TSs of a variety of asymmetric reactions, e.g., carbon-carbon bond formation and cycloadditions, yielding enantiomerically pure products (Scheme 68).[166]





Scheme 68: Sulfoxides as auxiliaries in asymmetric reactions.

Based on their coordinating ability and simple access, sulfoxides are also used as ligands in metal-catalyzed reactions, e.g., 1,2- and 1,4-addition reactions.[167] They provide an alternative to diene as well as phosphane- and amino-olefin ligands. Some examples are depicted in figure 27.[168, 167]

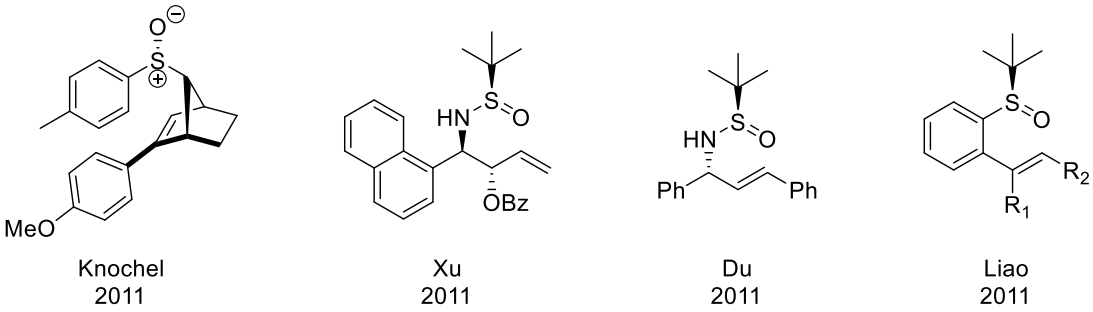


Figure 27: Sulfoxide-olefin ligands.

Substituting an oxygen atom with a sulfinyl moiety in carbohydrates delivers glycosulfoxides. These compounds play a key role as glycosylation donors or as natural carbohydrate mimics, influencing the stability of these molecules (Figure 28).[169] Moreover, glycosulfoxides are pharmaceutically active species for the treatment of , e.g., infectious diseases or cancer.[169d]

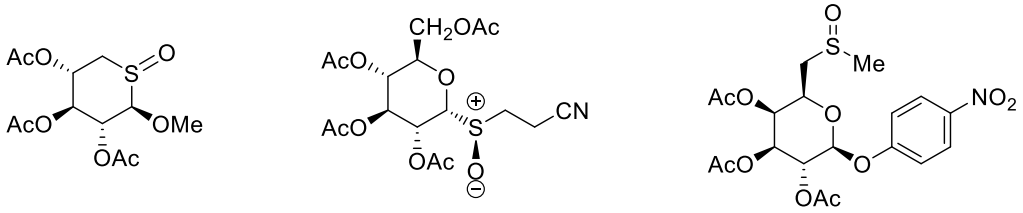


Figure 28: Sulfinyl groups in glycosulfoxides.

Due to the versatility of racemic and especially enantiomerically-enriched sulfoxides we try to establish an organocatalytic and stereoselective synthetic strategy, thus enabling access to this class of compounds.

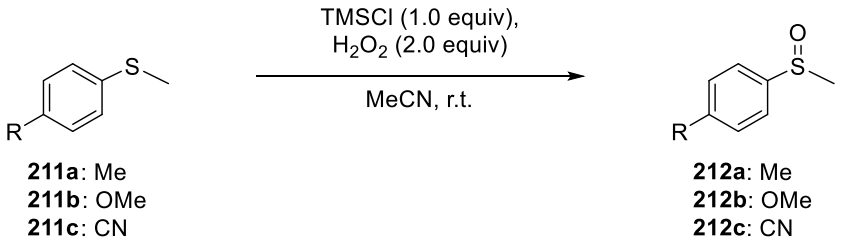
Based on the successful application of TUC **77** (Scheme 65), proline derivative **206** (Scheme 66), and dioxiranes precursor **207** (Scheme 67) as catalysts in sulfide oxidation

reactions, we tested our peptide-based analogs as well as the cooperative catalysis concept of joint phase transfer and thiourea catalysis.

5.3.2. Synthesis of the Racemic Products

Before screening the catalytic reactions, the corresponding products were synthesized as racemic mixtures starting from substituted methyl phenyl sulfides **211a-c**. Both electron-donating as well as electron-withdrawing groups were examined. A procedure based on trimetylsilyl chloride (TMSCl) and hydrogen peroxide in acetonitrile was used leading to the sulfoxides in good to optimal yields (Table 35).[170] The enantiomers were separated afterwards *via* chiral GC.

Table 35: Racemic synthesis of the corresponding sulfoxides.

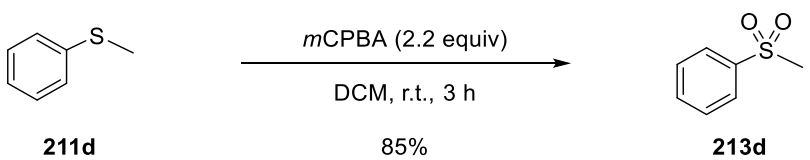


211a: Me
211b: OMe
211c: CN

212a: Me
212b: OMe
212c: CN

Product	t [h]	Yield [%]
212a	17	61
212b	7	86
212c	6.5	85

Methyl phenyl sulfide **211d** was selected as test substrate for the first experiments. The starting material as well as sulfoxide **212d** were commercially available. However, to determine a possible overoxidation, methyl phenyl sulfone **213d** was also synthesized utilizing a *m*CPBA protocol (Scheme 69). Starting with 1.1 equivalents of the oxidizing agent quantitative conversion to the corresponding sulfoxide was observed *via* GC after one hour. With further 1.1 equivalents of *m*CPBA sulfone **213d** was isolated in 85%.[171]



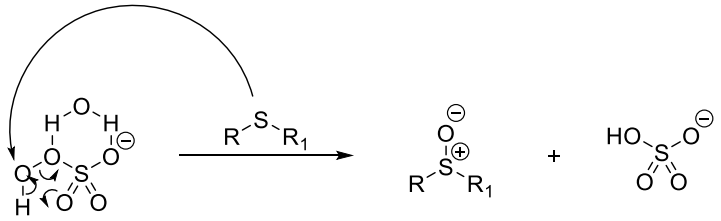
211d 85% **213d**

Scheme 69: Synthesis of sulfone **213d**.

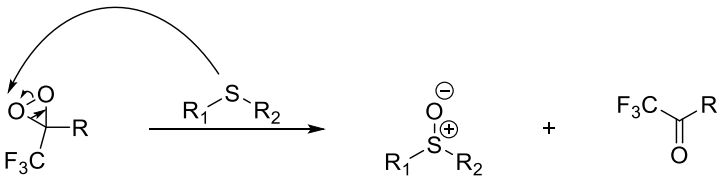
5.3.3. Dioxirane-Based Sulfoxidation

It is known that sulfoxides can be synthesized *via in situ* generated dioxiranes starting from Oxone® and acetone or a carbonyl containing compound.[162, 172] With TFMK catalysts in hand, it is obvious to test them in the mono-oxidation of sulfides as well using the same strategy as for the epoxidation reactions.

With regard to the paper of Yu *et al*. Oxone® was neglected as an oxidizer, because potassium peroxomonosulfate, a feasible oxidizing agent to generate the active species *in situ*, requires the addition of water to prevent solubility problems in most organic solvents. However, Yu *et al.* described that water can activate Oxone®, which transfers an oxygen atom onto sulfides without a further catalyst (Scheme 70).[172] Tugnoli *et al.* used acetone and Oxone to synthesize sulfoxides.[171] These compounds lead to the formation of dimethyldioxirane immediately. We assume that an *in situ* formed dioxirane species transfer one of the oxygen atoms onto the sulfur in a quite comparable manner (Scheme 71).



Scheme 70: Water-based activation of peroxomonosulfate.

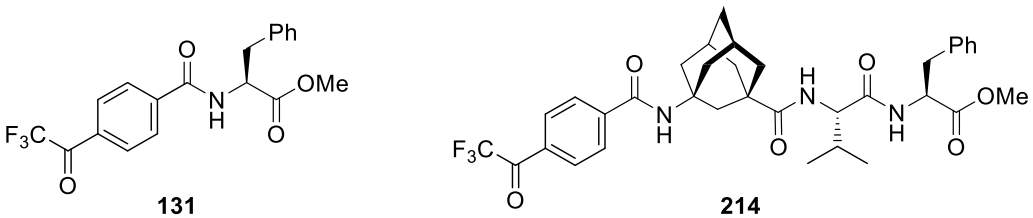


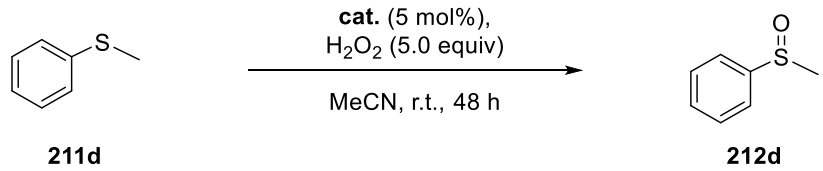
Scheme 71: Postulated dioxirane-based mechanism.

5.3.3.1. Proof of Principle

Consequently, in analogy to the epoxidation the protocol with TFMK precursor, acetonitrile, and hydrogen peroxide was tested in the oxidation of sulfides (Chapter 4.4.). As mentioned in chapter 4.4.5. solvent and oxidizer generate the peroxyimidic acid, which is able to transfer the carbonyl group into the active dioxirane species. For the initial experiments methyl phenyl sulfide **211d** was chosen as substrate and functionalized phenylalanine **131** as well as oligopeptide **214** as catalysts. Both dioxirane precursors led to sulfoxide **212d** in excellent conversions (Table 36). The simultaneously performed background reaction showed only 8% conversion to the product after 24 hours. This approach demonstrates the feasibility to obtain sulfoxides *via in situ* generated dioxirane peptide catalysts.

Table 36: Activity of dioxirane-based catalysts in sulfoxidation reactions.





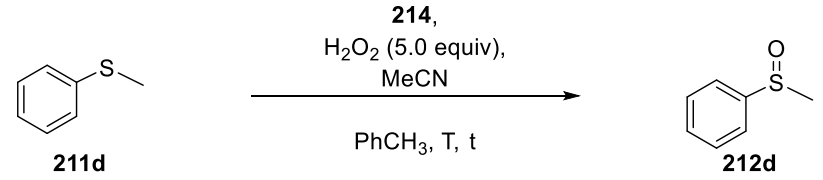
Cat.	212d[(a)] [%]	213d[(a)] [%]
131	87	traces
214	97	traces
-	8[(b)]	0

[(a)]: Conv. was determined using chiral GC without internal standard; [(b)]: 24 hours reaction time.

5.3.3.2. Optimization Process

Concerning a possible enantioselective oxygen transfer catalyst **214** was used for further optimization. Table 37 summarizes the results regarding the variation of catalyst loading, temperature, concentration, and solvent.

Table 37: Optimization of the sulfoxidation.



Entry	214 [mol%]	MeCN [mL]	Toluene [mL]	T [°C]	t [h]	212d[(a)] [%]	213d[(a)] [%]
1	7.5	1.60	-	r.t.	24	89	traces
2	10	1.60	-	r.t.	24	93	1
3	10	3.20	-	r.t.	49	98	traces
4	10	0.800	-	r.t.	24	95	5
5	10	1.60	-	0	46	32	1
6	10	0.800	0.800	r.t.	24	96	2
7	10	0.100[(b)]	1.50	r.t.	48	85	15

[(a)]: Conv. was determined using chiral GC without internal standard; [(b)]: corresponds to 5.0 equiv of MeCN.

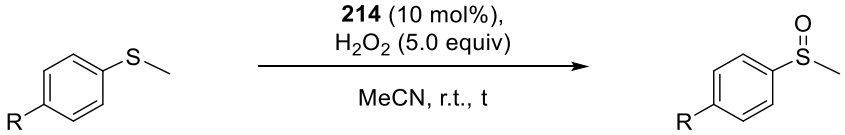
Increasing the amount of catalyst accelerates the reaction and comparable results were achieved after only 24 hours (Table 37, Entries 1 and 2). We refrained from performing the reaction with a smaller amount of catalyst expecting a much longer and unpractical reaction time. Altering the concentration by using 3.20 mL acetonitrile slowed the reaction. A faster reaction was observed in case of 0.800 mL of solvent. One explanation is the necessary encounter of four different compounds to transfer the oxygen atom onto sulfide **211d** (Table 37, Entries 3 and 4). With respect to the missing enantiomeric excess two strategies were examined. Decreasing the temperature to 0 °C did not show the desired result. Obviously, sulfoxide **212d** forms much slower at this temperature and, hence, lower temperatures were not tested (Table 37, Entry 5). Secondly, toluene as nonpolar solvent was added to enable interactions between peptide catalyst and substrate.[2a] Neither a 1:1-solvent ratio nor the addition of 5.0 equivalents of acetonitrile in toluene showed any influence on the reaction outcome (Table 37, Entries 6 and 7).

The variation of parameters had to be performed carefully as overoxidation to the corresponding sulfone **213d** was also observed (Table 37, Entries 5 and 7). Consequently, using 10 mol% catalyst and 1.60 mL of acetonitrile at ambient temperature were selected as the best reaction conditions for further investigations.

5.3.3.3. Substrate Scope

After optimization sulfides **211a-c** with a methyl, methoxy or nitrile substituent in *para*-position were oxidized *via* the established protocol to investigate the influence of electron-donating as well as electron-withdrawing groups (Table 38).

Table 38: Testing of further substrates with peptide catalyst **214**.



R	t [h]	212[(a)] [%]	213[(a)] [%]
Me	24	>99	traces
OMe	24	>99	traces
CN	48	80	traces

[(a)]: Conv. was determined using chiral GC without internal standard.

All substrates were converted into the corresponding products with good to excellent conversions. Substituents in *para*-position with either a +I or a positive mesomeric (+M) effect in conjunction with a −I effect accelerate the formation of sulfides. The nitrile analog reacts more slowly, because the −M effect withdraws electron density from the sulfur atom and decreases its nucleophilic character. The protocol can be carried out with further sulfides, but introducing a residue in *para*-position on the phenyl ring did not lead to an enantiomerically enriched product.

5.3.3.4. Additional Catalysts

Before synthesizing and testing further peptide catalysts a more qualified catalytic moiety has to be found. As mentioned in chapter 4.4.9. two methods have already been tested to obtain a TFMK, which is able to perform a reaction in an enantioselective fashion. Firstly, the substitution pattern of the phenyl ring of the basic moiety was varied from *para* to *meta*. Then, the synthesis of an amino acid containing the dioxirane precursor was studied. After solving this problem, especially *via* the latter approach, further peptide catalysts have to be examined.

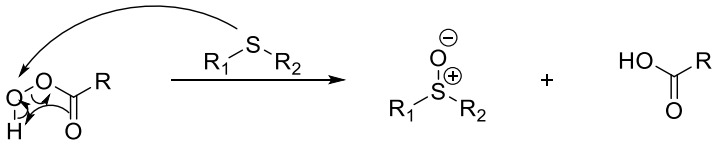
5.3.3.5. Outlook

Three different strategies for an enantioselective version of the sulfoxidation based on *in situ* generated dioxiranes are feasible. Further catalysts have to be synthesized and investigated under analogue conditions. Moreover, additional sulfides have to be tested as starting materials. Finally, a combinatorial approach examining catalysts and starting material has to be established to identify a matching-pair.

5.3.4. Peracid-Based Sulfoxidation

Another access to sulfoxides is based on an oxidation procedure with peracids,[171] as it was published by Barbarella *et al.* and observed during the synthesis of sulfone **213d**. Peracids can be generated *in situ via* a carboxylic acid, hydrogen peroxide, and a carbodiimide as, for example, Miller and Schreiner *et al.* already showed (Chapter 4.3.1.).[33a, 31, 3b] Hence, our carboxylic acid containing peptides should be feasible catalysts for sulfoxidation.

Mechanistically a similar pathway should be followed as mentioned in scheme 70 (Scheme 72). The sulfur atom attacks one of the oxygen atoms of the peracid. Electron transfer provides sulfoxide and acid, which can be transferred into the active species for the next oxidation step.

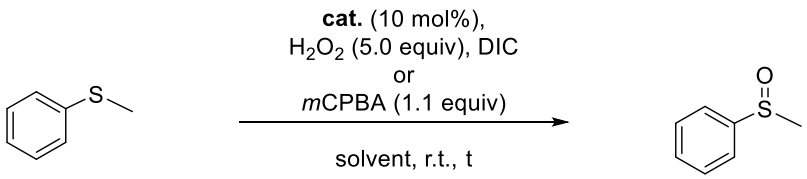


Scheme 72: Postulated mechanism using peracids.

5.3.4.1. Proof of Principle

The synthesis of terephthalic acid analog to peptide catalyst **214** in preparative amounts was troublesome because of solubility problems of the starting material in the reaction mixture and formation of side products involving the two acid moieties. Therefore, the concept was tested utilizing mono- and diacids in combination with hydrogen peroxide and DIC as precursors. Simultaneously, oxidation with *m*CPBA and investigation of a possible background reaction were performed (Table 39).

Table 39: Test experiments for peracid-catalyzed sulfoxidation.



211d **212d**

Entry[a]	Cat.	Oxidizer	DIC [equiv]	t [h]	212d[d] [%]	213d[d] [%]
1[b]	-	*m*CPBA	-	1	94	6
2[b]	benzoic acid	H_2O_2	1.1	48	30	0
3[b]	*m*CBA	H_2O_2	1.1	48	25	0
4[b]	phthalic acid	H_2O_2	1.1	48	90	0
5[c]	phthalic acid	H_2O_2	1.1	24	98	2
6[c]	phthalic acid	H_2O_2	2.5	4	98	traces
7[c]	phthalic acid	H_2O_2	5.0	3	95	3
8[b]	-	H_2O_2	1.1	48	6	0

[a]: The reaction was performed in 1.60 mL solvent; [b]: DCM; [c]: chloroform; [d]: conv. was determined using chiral GC without internal standard.

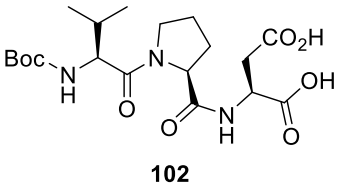
In order to prove the concept the reaction was performed with *m*CPBA as the oxidizer. Sulfoxide **212d** formed quantitatively, but an overoxidation was also observed *via* GC (Table 39, Entry 1). Comparing the dioxirane and the peracid-based sulfoxidation 10 mol% of catalyst and 5.0 equivalents of hydrogen peroxide were used as the initial conditions (Table 37). Benzoic acid as well as *m*CBA in correlation to *m*CPBA were tested and showed a conversion of up to 30% (Table 39, Entries 2 and 3). With phthalic acid as catalyst 90% conversion was

observed (Table 39, Entry 4). In case of monoacids DIC helps to generate an active ester, which is transferred into the reactive species.[33b] Starting from a vicinal diacids, DIC leads to an intramolecular anhydride, which is opened to the peracid *via* hydrogen peroxide (Chapter 4.3.1.).[3b] Upon changing the solvent from DCM to chloroform the procedure of Tugnoli *et al.* accelerates the reaction and a nearly quantitative conversion was observed after 24 hours (Table 39, Entry 5).[171] Increasing the amount of carbodiimide leads to an even faster oxidation (Table 39, Entries 6 and 7). The background reaction is negligible as only 6% of the sulfoxide **212d** formed after 48 hours under the same conditions. Chloroform as solvent and 2.5 equivalents of DIC were utilized for further experiments.

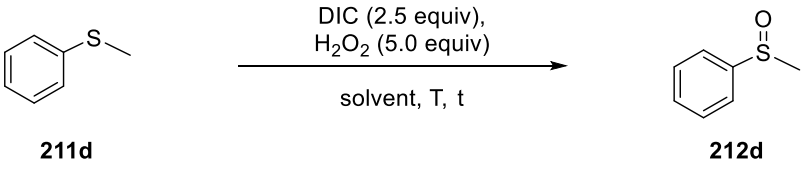
5.3.4.2. Optimization Studies

Peptide catalyst **102** containing proline as structure-forming element and aspartic acid as catalytically active precursor was used for testing the concept and further optimizations. Afterwards, both kind and amount of the solvent, catalyst loading, and temperature were changed (Table 40).

Table 40: Optimization using peptide catalyst **102**.



102



211d **212d**

Entry	102 [mol%]	Solvent [mL]	t [h]	T [°C]	212d[(a)] [%]	213d[(a)] [%]
1	10	$CHCl_3$ (1.6)	3	r.t.	96	4
2	10	$CHCl_3$ (1.6)	4	0	96	2
3	10	$PhCH_3$ (1.6)	7	r.t.	76	15
4	10	$PhCH_3$ (1.6)	25	0	68	13
5	5	$CHCl_3$ (1.6)	1	r.t.	97	2
6	2.5	$CHCl_3$ (1.6)	2	r.t.	97	1

7	1	$CHCl_3$ (1.6)	5	r.t.	89	0
8	-	$CHCl_3$ (1.6)	5	r.t.	2	0
9	2.5	$CHCl_3$ (0.8)	2	r.t.	95	traces
10	2.5	$CHCl_3$ (3.2)	8	r.t.	97	2

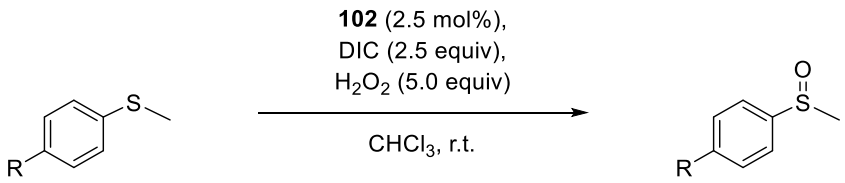
[(a)]: Conv. was determined using chiral GC without internal standard.

Decreasing the temperature did not slow the reaction rate in case of chloroform as solvent. (Table 40, Entries 1 and 2). Replacing chloroform by toluene to promote interactions between substrate and catalyst led to a slower sulfoxidation and favored the formation of sulfone **213d** (Table 40, Entry 3). When performing the reaction at 0 °C a reaction time of 25 hours was necessary to achieve comparable results (Table 40, Entry 4). Yet, an enantiomeric excess was not observed. The catalyst loading could be reduced to 2.5 mol% without influencing the catalytic activity (Table 40, Entries 5-7). The background reaction was very slow and delivered sulfoxide **212d** with a conversion of only 2% after five hours, thereby confirming the need of an acid catalyst (Table 40, Entry 8). While decreasing the amount of solvent did not have a huge influence on the reaction process utilizing a higher dilution delayed the oxidation (Table 40, Entries 9 and 10). The data showed variation of catalyst loading and solvent volume are tunable parameters, whereas temperature seems to have a negligible effect. Hence, 2.5 mol% of catalyst and 1.6 mL of chloroform were used as standard parameters.

5.3.4.3. Substrate Scope

With optimized conditions in hand, substrates **211a-c** were tested to study the effect of the substituents located at the phenyl ring (Table 41).

Table 41: Scope of the reaction.



Sulfide	t [h]	212[(a)] [%]	213[(a)] [%]
Me	1	>99	traces
OMe	2	>99	traces
CN	24	67	traces

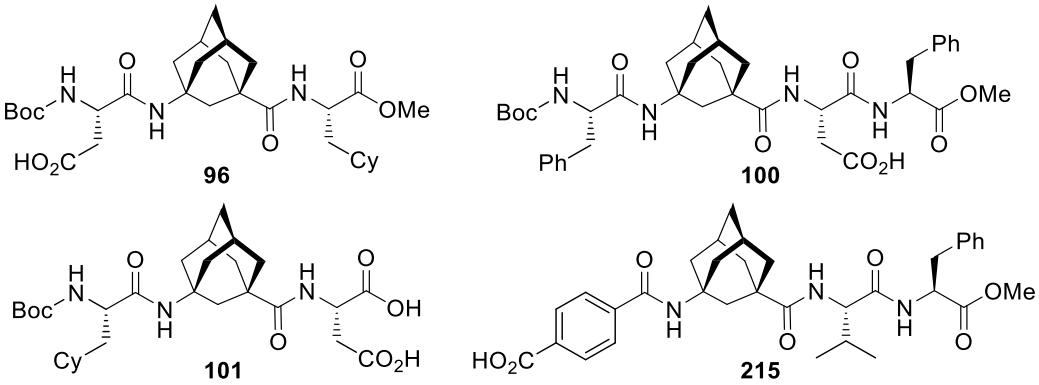
[(a)]: Conv. was determined using chiral GC without internal standard.

In comparison to sulfide **211d**, its *para*-methyl and *para*-methoxy derivatives react faster and its *para*-nitrile congener reacts more slowly in comparison to their sulfoxides **212a-c**. The first mentioned substituents possess either a +I- or a +M/−I-effect, thereby increasing the electron density on the phenyl ring and hence on the sulfur atom. These two sulfides are more active regarding the attack on the peracid (Scheme 72). The nitrile group removes electron density from the phenyl ring and the sulfur atom, thus decreasing the overall nucleophilic reactivity. The same observations were made utilizing the TFMK peptide catalyst **214** (Table 38).

5.3.4.4. Additional Catalysts

Several feasible acid-containing peptides synthesized for the asymmetric epoxidation are available to examine their sulfoxidation ability. The reaction was performed by using optimized conditions and monoacid as well as diacid catalysts (Table 42).

Table 42: Testing further acid peptide catalysts.



Entry	Cat.	t [h]	212d[(a)] [%]	213d[(a)] [%]
1	**96**	24	16	traces
2	**100**	24	31	0
3	**101**	7	94	traces
4	**215**	24	20	0

[(a)]: Conv. was determined using chiral GC without internal standard.

The results of the pre-optimization with benzoic as well as phthalic acid (Table 39) already illustrated that diacid catalysts react faster than monoacids. This observation was confirmed

with the peptide-based species (Table 42, Entries 1, 2, and 4 as well as 3). Astonishingly, tetrapeptide **100** is more active compared to tripeptides **96** and **215**, even if the steric hindrance seems to be larger (Table 42, Entries 1, 2, and 4). 2.5 mol% of satalyst **215**, the acid analog of TFMK peptide **214**, provide sulfide **212d** with a conversion of 20% (Table 42, Entry 4). Aspartic acid catalyst **101** generated 94% of the product after seven hours (Table 42, Entry 3). But, as depicted in the catalytic cycle (Chapter 4.3.1.) and in contrast to C_2-symmetric diacid catalysts in case of a system like **101** two different catalytically active species can be generated preventing a possible stereoselective reaction outcome.

5.3.4.5. Outlook

The optimization procedure demonstrates that sulfoxidations can be carried out *via in situ* generated peracid species and that diacid catalysts are superior to monoacids. Regarding a stereoselective oxidation the employed catalysts and starting materials did not lead to the desired results. Further experiments have to ensure that either one carboxylic acid is transferred selectively into the catalytically active peracid or that either the catalyst or the precursor possesses C_2-symmetry. Besides already synthesized oligopeptides, *β*-aspartic acids described in the publication of Schreiner *et al.* should be incorporated in catalysts.[3b] A short distance between the two carboxylic acid moieties is necessary for a fast process. Furthermore, the existing library of starting materials should be extended and tested utilizing all peptides to identify a suitable combination of catalyst and substrate as well as attractive types of interaction.

5.3.5. Cooperative Thiourea and Phase Transfer Catalysis

5.3.5.1. Concept

Considering the activation model of water and Oxone® a TUC should also be able to activate HSO_5^-. The reaction must be performed in a dry organic solvent to prevent the simultaneous activation by water. The reactive species of the oxidizer should be solved in the organic medium using a PTC. Afterwards, the TUC coordinates and activates the anion before the oxygen atom is transferred onto the sulfide (Figure 29).

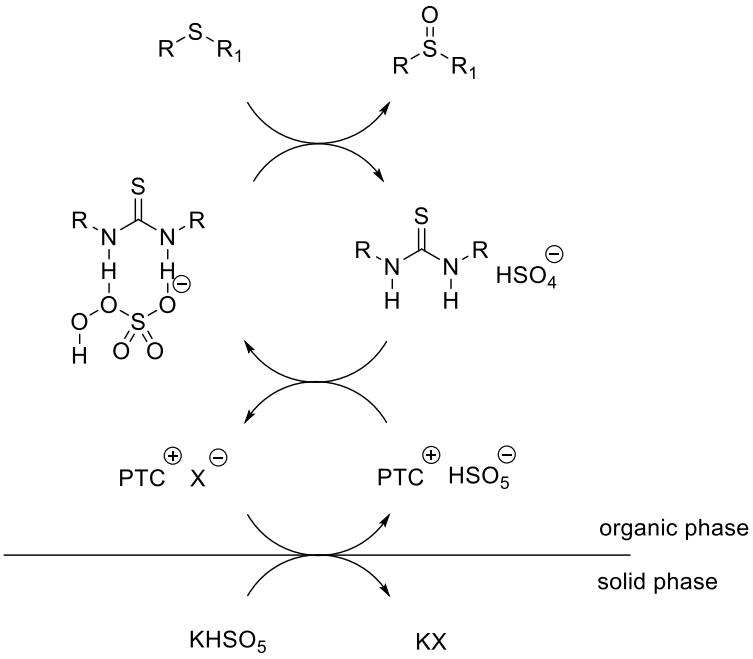
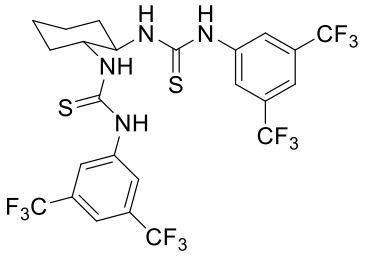


Figure 29: Sulfoxidation using cooperative catalysis.

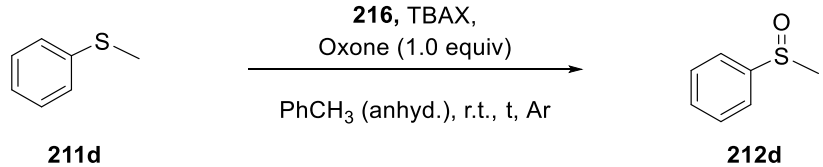
5.3.5.2. Test Experiments

Using a chiral TUC should enable a stereoselective oxidation. Hence, Nagasawa thiourea **216**[7] and TBABr or tetrabutylammonium iodide (TBAI) as a catalytic system and sulfide **211d** as test substrate were chosen for the first experiments (Table 43).

Table 43: Test experiments utilizing cooperative catalysis.



216



211d **212d**

Entry	216 [mol%]	TBABr [mol%]	TBAI [mol%]	t [h]	212d[(a)] [%]
1	0.2	0.2	-	24	0

[7] Catalyst was synthesized by Dr. Katharina M. Lippert.

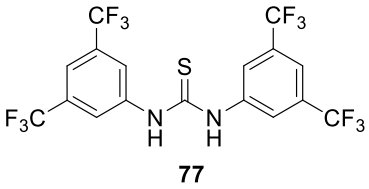
2	0.2	-	0.2	23	0
3	0.2	-	-	25	2
4	-	0.2	-	26	16
5	-	-	0.2	24	0
6	-	-	-	27	6

[a]: Conv. was determined using chiral GC without internal standard.

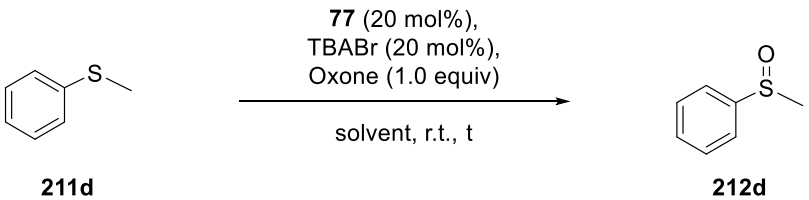
But, reactions involving thiourea **216** did not lead to the desired product (Table 43, Entries 1-3). In contrast oxidation with only TBABr as catalyst led to a conversion of 16% after 24 hours (Table 43, Entry 4). A simultaneously performed background reaction provided 6% of sulfoxide **212d** after 27 hours (Table 43, Entry 6) illustrating that a catalytic intervention of TBABr is not insignificant. The final product is not formed, if bromide is substituted with iodide (Table 43, Entry 5). These experiments confirm the assumption that **216** inhibits the oxidation and that bromide is the preferred counter ion of the PTC.

Based on these first results, **216** was replaced by a more active catalyst to examine the general oxidative ability of TUC. Achiral thiourea **77**[8] possesses two 3,5-bis(trifluoromethyl)phenyl substituents decreasing the electron density of the nitrogen-hydrogen bond. This effect favors the coordination of **77** to HSO_5^-. Furthermore, in the following experiments the influence of the solvent as well as the subsequently added water was investigated (Table 44).

Table 44: Variation of reaction conditions.



77



211d **212d**

[8] Catalyst was synthesized by Dr. Katharina M. Lippert.

Solvent(s)	Product	77/TBABr	77	TBABr	Without catalyst
^{t}AmylOH[(a)]	**212d**	8% (24 h)	34% (24 h) 37% (48 h)	44% (24 h) 56% (48 h)	37% (24 h) 48% (48 h)
$PhCH_3$/water[(b)]	**212d** **213d**	15% (24 h) 10% (24 h)	15% (24 h) 26% (24 h)	19% (23 h) 19% (23 h)	traces (25 h) 30% (25 h)
^{t}AmylOH/water[(b)]	**212d**	61% (4 h)	48% (26 h)	60% (1 h)	62% (25 h)

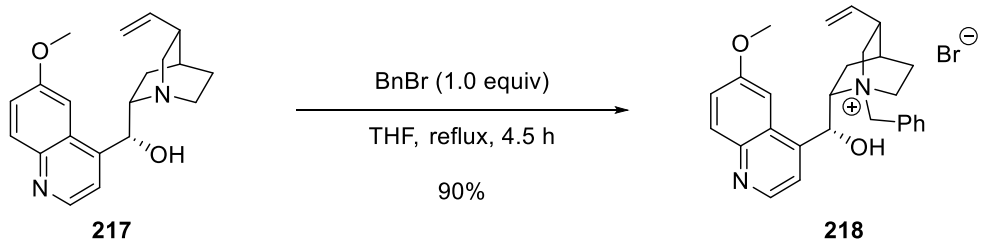
Conv. determined using chiral GC without internal standard; reaction time in parentheses; [(a)]: reaction performed under argon atmosphere; [(b)]: 1:1-mixture of solvent and water.

To increase the formation of sulfoxide **212d** two different strategies were developed. At first, toluene was replaced by the more polar solvent *tert*-amyl alcohol, due to an increased solubility of the oxidizer (Table 44, Line 2). Reactions with separated as well as a combination of catalysts showed better conversions in comparison to the ones performed in toluene (Table 43). The background reaction proceeds quite fast, but the presence of TBABr accelerates the sulfoxidation. Secondly, a biphasic system consisting of toluene and water was tested to enable a liquid-liquid phase transfer catalysis (Table 44, Line 3). The background reaction provided only traces of sulfoxide **212d** after 25 hours. Product **212d** was formed in catalyzed oxidation reactions with a conversion of up to 19%, but the synthesis of sulfone **213d** was even more favored in all experiments. These facts illustrate the catalytically active role of both phase transfer and thiourea species. Substituting toluene with ^{t}AmylOH in the biphasic system necessitates the use of TBABr as PTC (Table 44, Line 4). A fine suspension results from stirring. Even without TUC **77** the product **212d** is formed with a conversion of 62%, thereby decreasing the benefit from this strategy.

It is noticeable that in all cases using a phase transfer catalyst accelerates and a thiourea catalyst inhibits the sulfoxidation compared with the background reaction (Table 43, Entries 1, 3, 4, and 6; Table 44).

5.3.5.3. Single Phase Transfer Catalysis

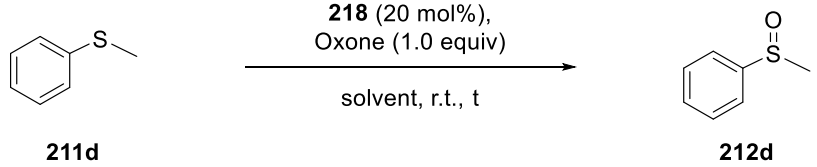
With all these information in hand, compound **218** was synthesized to test a chiral phase transfer catalyst instead of TBABr. The alkylation of quinine **217** with benzyl bromide yielded PTC **218** in 90% (Scheme 73).[146] Regarding our peptide-based PTCs alkaloid-derived system **218** should be utilized as test system in the forefront.



Scheme 73: Synthesis of chiral PTC **218**.

In the following experiments **218** was tested as the chiral version of TBABr. Due to the not promising results of the cooperative catalysis concept, combination with a thiourea catalyst was neglected (Table 45).

Table 45: Chiral PTC **218** in the sulfoxidation of sulfide **211d**.



Solvent(s)	Product	218	TBABr	TBAI	Without catalyst
$PhCH_3$[a]	**212d**	0% (25 h)	16% (26 h)	0% (24 h)	6% (27 h)
$PhCH_3$/water[b]	**212d** **213d**	9% (25 h) 21% (25 h)	19% (23 h) 19% (23 h)	-	traces (25 h) 30% (25 h)
^{t}AmylOH[a]	**212d**	traces (25 h)	44% (24 h) 56% (48 h)	42% (23 h)	37% (24 h) 48% (48 h)
^{t}AmylOH/water[b]	**212d**	78% (25 h)	60% (1 h)	-	62% (25 h)

Conv. determined using chiral GC without internal standard; reaction time in parentheses; [a]: reaction performed under argon atmosphere; [b]: 1:1-mixture of solvent and water.

Quinine-based bromide **218** was tested utilizing all four different solvent combinations. Conversions of up to 78% were obtained, but no enantiomeric excess was achieved. In comparison with TBABr and TBAI catalyst **218** seems to be less reactive except utilizing ^{t}AmylOH. The results concerning the solvents are comparable. ^{t}AmylOH is inferior to toluene and the use of water results in even higher conversion due to the literature-known water-activation of Oxone®.[172]

5.3.5.4. Thiourea-Catalyzed Sulfoxidation

Based on the paper of Lattanzi *et al.* TUC **77** was tested separately in the sulfoxidation. This kind of compound is able to activate TBHP affording oxygen transfer on sulfides (Figure 30).[160]

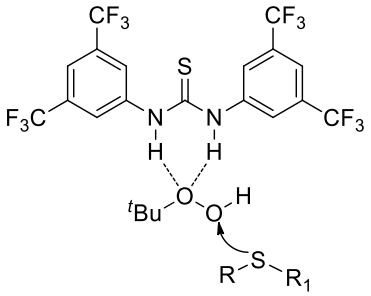
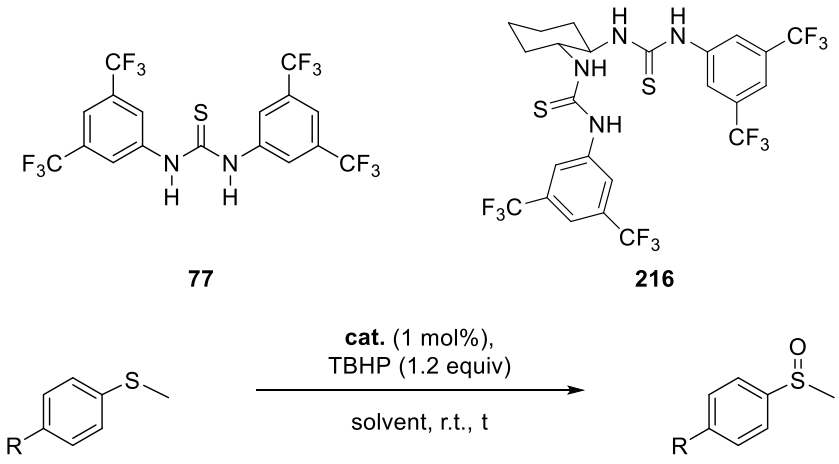


Figure 30: Activation of TBHP *via* thiourea **77**.

At the beginning, the reaction parameters used by Lattanzi and co-workers were chosen to reproduce the results mentioned in the paper. Due to substitution of **77** with **216** under otherwise constant conditions an enantioselective variant of this process should be investigated (Table 46).

Table 46: Sulfoxidation *via* thiourea catalysts **77** and **216**.



Entry	R	Cat.	Solvent	t [h]	212[(a)] [%]	213[(a)] [%]
1	Me	**77**	DCM	53	93	7[(b)]
2	Me	**216**	DCM	54	91	9[(b)]
3	OMe	**216**	DCM	52	97	3[(b)]
4	CN	**216**	DCM	51	91	6[(b)]
5	H	**216**	DCM	51	99	1[(b)]

6	Me	**216**	$PhCH_3$	48	79	2[(b)]
7	Me	**216**	$CHCl_3$	26	73	27[(b)]
8	Me	-	DCM	50	38	traces[(b)]

[(a)]: Conv. was determined using chiral GC without internal standard; [(b)]: identification of the sulfones **213** *via* GC-MS.

First of all, we repeated the experiment of Lattanzi *et al.* with catalyst **77**. But, in contrast to the results mentioned in the original report we needed nearly twice as long to obtain equal amounts of sulfoxide **212a** (Table 46, Entry 1). Furthermore, both the overoxidation to sulfone **213a** as well as the background reaction without catalyst were not negligible (Table 46, Entries 1 and 8). By replacing TUC **77** with **216** we were able to generate mono-oxygenated product **212a** and di-oxygenated by-product **213a** in comparable amounts, but without enantiomeric excess (Table 46, Entry 2). Similar results were observed for starting materials **211b-d** (Table 46, Entries 3-5). Carrying out the reaction in toluene had not a significant influence on the outcome (Table 46, Entry 6), but using chloroform instead accelerated the oxidative process and favored the formation of **213a** (Table 46, Entry 7).

5.3.5.5. Outlook

Combining phase transfer and thiourea catalysis in a cooperative manner does not provide preparative amounts of the sulfoxides. The same observations were made utilizing only a PTC and an oxidizer. However, we were able to reproduce the thiourea-catalyzed protocol established by Lattanzi and co-workers with some discrepancies (formation of sulfone and background reaction), but development of an enantiomeric variant based on Nagasawa's catalyst was not successful. Hence, extending the substrate library and testing further TCUs are the most promising aspects in future experiments beginning with these results.

5.3.6. Summary and Outlook

While carrying out this work, we were able to identify three possible strategies to generate sulfoxides starting from sulfides. Apart from the already established thiourea-based protocol (Chapter 5.3.5.4.), we optimized a dioxirane- (Chapter 5.3.3.) and a peracid-based (Chapter 5.3.4.) sulfoxidation concept (Table 47).

Table 47: Optimized conditions.

	Dioxirane-based Ox.	Peracid-based Ox.	Thiourea-based Ox.[160]
Catalyst loading	10 mol%	2.5 mol%	1 mol%
Solvent	MeCN (1.6 mL)	$CHCl_3$ (1.6 mL)	DCM (0.400 mL)
Oxidizer	H_2O_2 (5.0 equiv)	H_2O_2 (5.0 equiv)	TBHP (1.2 equiv)
Temperature	r.t.	r.t.	r.t.
Additive	-	DIC (2.5 equiv)	-

For dioxirane-based catalysts a more suitable TFMK moiety has to be identified (Chapter 4.4.10.). Afterwards, oligopeptides including this group have to be synthesized utilizing an automated platform, and these new compounds have to be tested under the optimized conditions (Table 47).

Regarding the peracid strategy, we could show that the focus has to lie on C_2-symmetric diacid catalysts with a short acid-acid distance favoring the formation of an intermolecular anhydride. Therefore, further oligopeptides based on these concepts must be synthesized (Chapter 4.3.6) and examined using the aforementioned protocol (Table 47).

TCUs are an intensively studied class of compounds. A variety of catalysts are easily accessible and can be tested afterwards utilizing Lattanzi's protocol (Table 47).

For all three cases further sulfoxides must be synthesized to extent the substrate library, to examine the influence of the substitution pattern, and to get a deeper insight into the interactions between catalyst and sulfide (Figure 31).

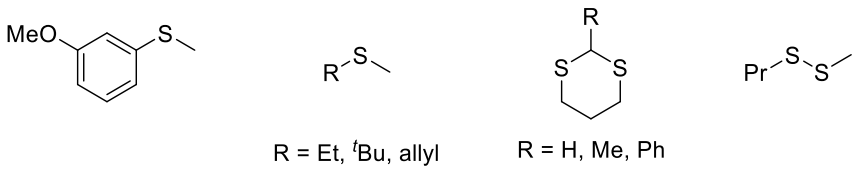


Figure 31: Further possible substrates.

6. Summary and Outlook

6.1. Summary

The aim of this thesis was the establishment of an enantioselective epoxidation in the context of our multicatalysis approach in combination with the already utilized acylation and/or oxidation. As starting point we designed a new sequence consisting of acylation, epoxidation, and epoxide opening (Chapter 3.1.). After epoxidation of the unsaturated side chain the cyclohexanediol moiety should coordinate the nucleophile and enable a selective epoxide opening. After hydrolysis of the auxiliary a carboxylic acid with two stereogenic centers will be yielded.

Considering the already optimized and established enantioselective acylation allyl acetate was tested as further acyl source (Chapter 2.1.). Furthermore, based on phenazine **7** we examined a possible oxidative esterification (Chapter 2.2.) and with sulfoximines **8** we wanted to extent the substrate scope (Chapter 2.3.). But, all three attempts did not show the desired result.

For examination of the single steps of the new multicatalytic sequence we synthesized the racemic products of acylation (Chapter 3.2.) and epoxidation (Chapter 3.3.). Due to synthetic reasons we selected pentenoic acid derivatives as unsaturated components. Promisingly, we were able to obtain the products of *trans*-3-pentenoic acid after both kinetic resolution as well as desymmetrization with the corresponding cyclohexanediol with high selectivities utilizing the Steglich procedure. As alternative to the epoxidation of the crotonic acid monoesters **17** and **18** we tested the Michael addition successfully as potential second step (Chapter 3.4.1.). Both carbon nucleophiles as well as a thiol were used for the possible epoxide opening reaction starting with monoesters **24a** and **25a**. But, independently from the chosen conditions we obtained α,β-unsaturated and γ-hydroxylated esters **31** and **32**. Either protection of the free hydroxyl group or the usage of 4-pentenoic acid led to the desired epoxide opening (Chapter 3.4.2.). After optimization using only DBU as base nearly 90% yield could be achieved for **31** and **32**. Therefore, this step should be included in the multicatalytic sequence enabling a variety of possible transformations based on olefin or alcohol subsequently (Chapter 3.4.3. and 3.4.4.).

For identification and optimization of a feasible epoxidation procedure a substrate library of 14 epoxides was established (Chapter 4.1.1.), because using alkenes **24** and **25** might yield enantiomers as well as diastereomers. A diacid- (Chapter 4.3.), a TFMK- (Chapter 4.4.), a PTC- (Chapter 4.5.), and a prolinol-based epoxidation approach (Chapter 4.6.) were

investigated. Both catalyst synthesis and development of well-working and optimized epoxidation protocols were possible for all four concepts. Generation of an enantiomeric excess was only observable in case of prolinol-based system **192**. Especially, the synthesis of a selective TFMK-derived catalyst was studied very intensively and finally several potential strategies for the synthesis of a directly functionalized amino acid were illustrated (Chapter 4.4.8 and 4.4.9.).

Besides epoxidation dioxirane- (Chapter 5.3.3.) and peracid-based systems (Chapter 5.3.4.) were also tested successfully in the oxidation of sulfides. Starting materials reacted chemoselectively, but not stereoselectively to the corresponding sulfoxides in the presence of both types of catalyst. Simultaneously, a PTC- (Chapter 5.3.5.) and thiourea-based procedure (Chapter 5.3.5.4.) were also studied and an optimized protocol was established for the latter one in regard to further experiments.

During dealing with the main topic of this thesis the formation of spiro carbonate **75** (Chapter 4.2.) and *α*-keto acetal **162a** (Chapter 4.4.9.3.) were observed. For spiro carbonate **75** reaction conditions were optimized starting from carbamate **52c** to obtain the desired product with a yield of 78%. We assume that a cooperative catalysis based on *in situ* generated *m*CBA and TCU **77** takes place. For *α*-keto acetal **162b** we were able to develop an asymmetric access based on literature research and mechanistic considerations. After investigation of the existence of closed form **163** of carboxybenzaldehyde **146** in solution *via* IR and NMR an alkaloid-based procedure was studied. With only a few experiments we found a strategy yielding acylated derivative **162b** with nearly quantitative yield and an enantiomeric excess of up to 32%. Both projects have a huge potency to be investigated in more detail.

6.2. Zusammenfassung

Im Rahmen dieser Arbeit sollte die Epoxidierung als weiterer Reaktionsschritt neben Acylierung und Oxidation für die Multikatalyse zugänglich gemacht werden. Daher wurde eine neue Multikatalysesequenz bestehend aus Acylierung, Epoxidierung und Epoxidöffnung entwickelt (Kapitel 3.1.). Nach Epoxidierung der ungesättigten Ester sollte das Cyclohexandiolmotiv als Auxiliar fungieren und das Nucleophil während der abschließenden Reaktion koordinieren. Nach Esterhydrolyse könnten auf diese Weise Carbonsäurederivate mit zwei stereogenen Zentren erhalten werden.

Für die bereits optimierte und etablierte enantioselektive Acylierung wurde mit Allylacetat eine weitere Acetylquelle (Kapitel 2.1.), unter Verwendung von Phenazin **7** eine oxidative Strategie

(Kapitel 2.2.) und mit den Sulfoximinen **8** weitere Substrate getestet (Kapitel 2.3.). Jedoch konnte in keinem der Fälle das gewünschte Resultat erzielt werden.

Zur genauen Untersuchung der jeweiligen Einzelschritte der neuen Multikatalysesequenz wurden die notwendigen racemischen Acylierungs- (Kapitel 3.2.) und Epoxidierungsprodukte (Kapitel 3.3.) dargestellt. Aus synthetischen Gründen wurden Pentensäurederivate gewählt. Diesbezüglich war es sehr vielversprechend, dass die enantiomerenangereicherten Produkte der *trans*-Pent-3-encarbonsäure sowohl nach kinetischer Racematspaltung, als auch Desymmetrisierung des jeweiligen Cyclohexandiols unter Steglich-Bedingungen in sehr guten Selektivitäten erhalten werden konnten. Als Alternative zur Epoxidierung wurde die Michael-Addition an Crotonsäurederivaten **17** und **18** erfolgreich als möglicher zweiter Sequenzschritt getestet (Kapitel 3.4.1.). Zur Öffnung racemischer Epoxide der ungesättigten Monoester **24a** und **25a** wurden sowohl Kohlenstoffnucleophile, wie auch ein Thiol untersucht. Allerdings wurde jeweils die Eliminierung zu den α,β-ungesättigten und γ-hydroxylierten Estern **31** und **32** beobachtet. Sowohl Schützung der freien Alkoholfunktion, wie auch Verwendung der Pent-4-encarbonsäure führte nicht zur gewünschten Epoxidöffnung (Kapitel 3.4.2.). Nach Optimierung und nur unter Verwendung von DBU war eine Umsetzung zu **31** und **32** mit fast 90% Ausbeute möglich. Dieser Reaktionsschritt sollte als dritter Schritt in die Multikatalysesequenz eingebaut werden, da sowohl mit Doppelbindung, wie auch Hydroxyfunktion vielfältige Folgechemie möglich ist (Kapitel 3.4.3. und 3.4.4.).

Zur Identifizierung und Optimierung der asymmetrischen Epoxidierung wurde eine Substratbibliothek mit 14 prochiralen Epoxiden aufgebaut, da im Falle von Epoxiden **24** und **25** jeweils vier Stereoisomere möglich wären (Kapitel 4.1.1.). Für die katalysierte Epoxidierung wurden Disäure- (Kapitel 4.3.), Trifluormethylketon- (Kapitel 4.4.), PTC- (Kapitel 4.5.) und Prolinol-basierende Strategien (Kapitel 4.6.) untersucht. Katalysatorsynthese mit anschließender Optimierung von gut funktionierenden Epoxidierungsprotokollen wurde realisiert. Dabei wurde allerdings nur mit Prolinol-basierendem Peptide **192** enantiomerenangereichertes Epoxid erhalten. Gerade für die Trifluoromethylketone wurden eine Vielzahl von Synthesestrategien untersucht und am Ende mögliche Syntheserouten aufgezeigt, die zu direkt funktionalisierten Aminosäuren führen sollten (Kapitel 4.4.8 und 4.4.9.).

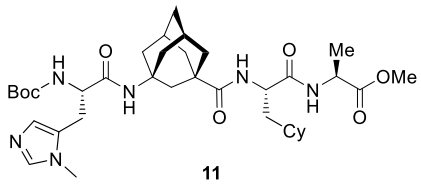
Neben der Epoxidierung wurden Trifluormethylketon- (Kapitel 5.3.3.) und Carbonsäure-basierende Systeme (Kapitel 5.3.4.) auch erfolgreich in Sulfoxidationen getestet. Diese verlief

zwar chemoselektiv zu den entsprechenden Sulfoxiden, aber ohne jegliche Stereoselektivität. Zusätzlich wurden noch PTC- (Kapitel 5.3.5.) und Thioharnstoff-katalysierte Sulfoxidationen (Kapitel 5.3.5.4.) untersucht und für letztgenannten Ansatz ein optimiertes Protokoll für weitere Experimente erarbeitet.

Im Laufe der Arbeit wurde zudem noch die Bildung von Spirocarbonat **75** (Kapitel 4.2.) und α-Ketoacetal **162a** (Kapitel 4.4.9.3.) beobachtet. Für Spirocarbonat **75** wurden die Reaktionsbedingungen soweit optimiert, dass in einem Zweistufenprozess ausgehend von Carbamat **52c** 78% des Carbonats isoliert werden konnten. Es wird dabei eine kooperative Katalyse zwischen *in situ* erzeugter *m*CBA und Thioharnstoff **77** vermutet. Für Ketal **162b** konnte basierend auf Literaturrecherche und mechanistischen Überlegungen ausgehend von Hemiacetal **163**, welches zuvor mittels IR und NMR als in Lösung vorliegende Form identifiziert werden konnte, ein asymmetrischer Zugang entwickelt werden. Auf Basis weniger Experimente wurde eine Alkaloid-basierende Variante erarbeitet, mit der acyliertes Hemiacetal **162b** mit fast quantitativer Ausbeute und einem Enantiomerenüberschuss von bis zu 32% isoliert wurde. In beiden Fällen gibt es noch vielfältige Möglichkeiten, den jeweiligen Ansatz intensiver zu untersuchen.

6.3. Synthesized Compounds

6.3.1. Peptide Catalysts



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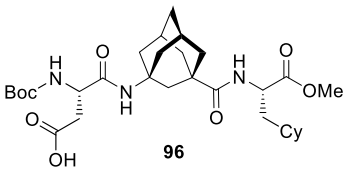

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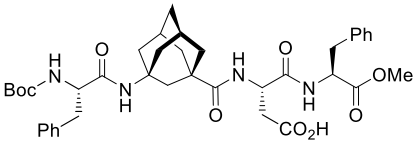

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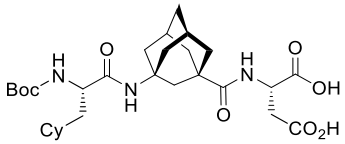

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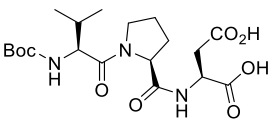

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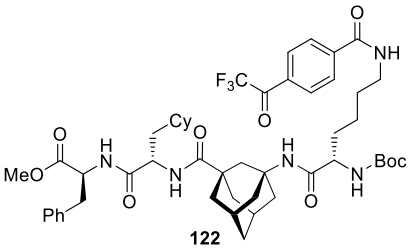

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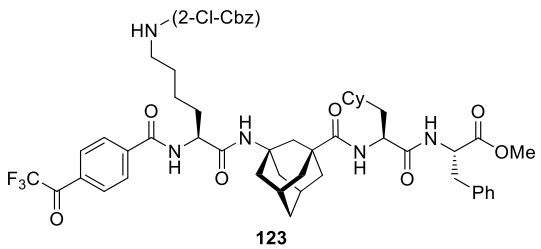

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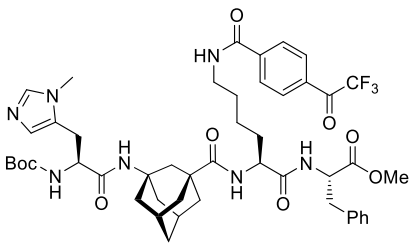

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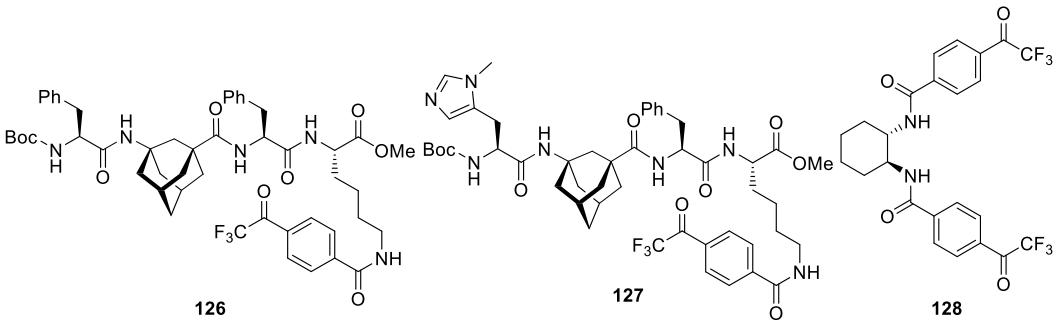
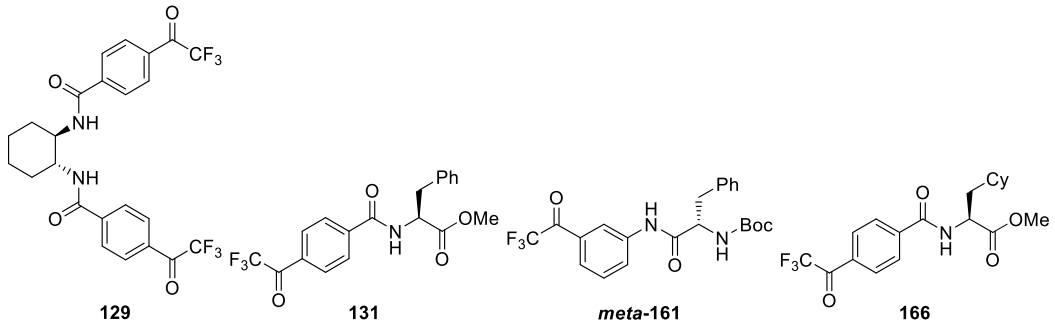
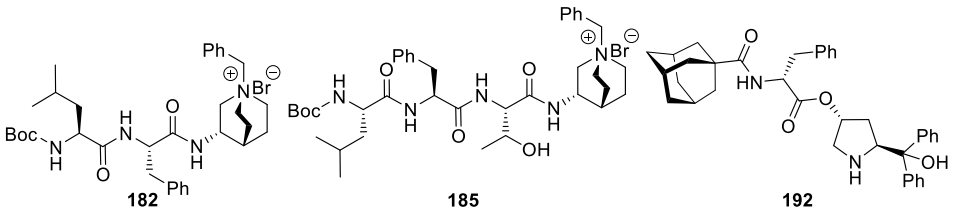


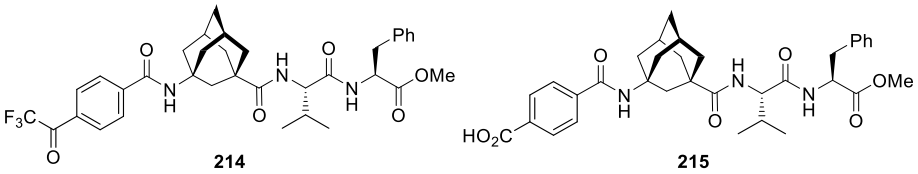
126 **127** **128**



129 **131** ***meta*-161** **166**

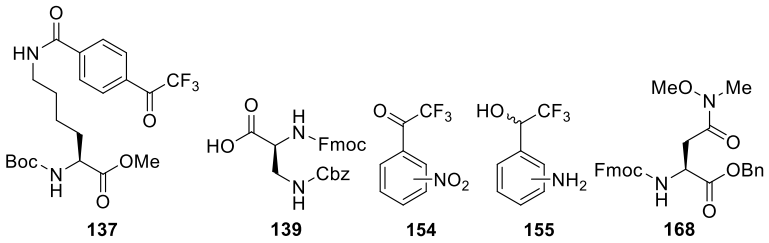


182 **185** **192**



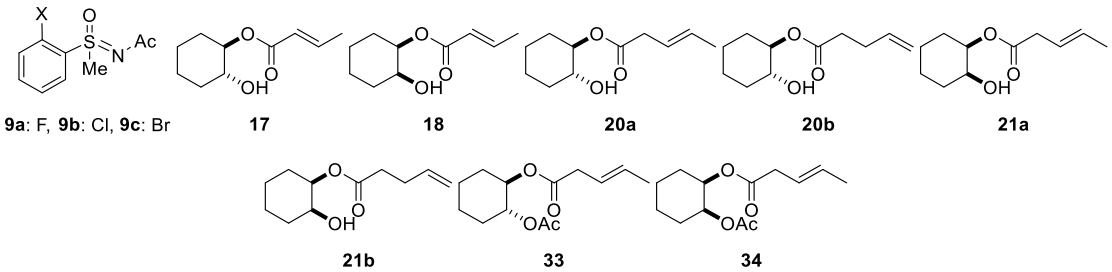
214 **215**

6.3.2. (Towards) TFMKs



137 **139** **154** **155** **168**

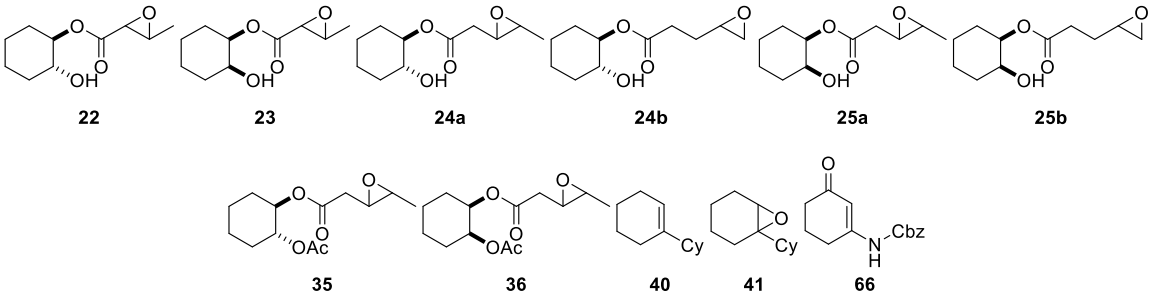
6.3.3. (Mono-)Acylated Compounds



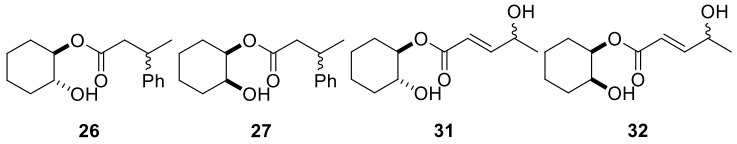
9a: F, **9b**: Cl, **9c**: Br **17** **18** **20a** **20b** **21a**

21b **33** **34**

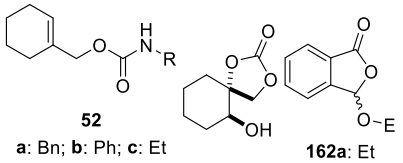
6.3.4. Epoxides and Alkenes



6.3.5. Epoxide Opening Products



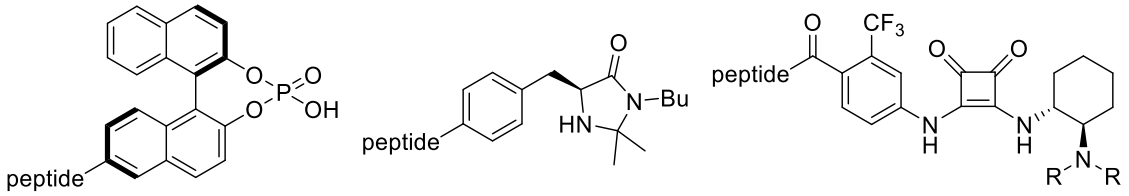
6.3.6. 'Digression' Compounds



6.4. Outlook

With this thesis we gained a deeper insight into the field of multicatalysis identifying challenges, but also possibilities of this approach regarding further developments. Especially, formation of *α,β*-unsaturated and *γ*-hydroxylated esters **31** and **32** enables a very flexible add-on chemistry, which can easily be included in a multicatalytic sequence (Chapter 3.4.4.)**.** Besides synthesis of C_2-symmetric diacids catalysts (Chapter 4.3.6.), we consider the synthetic approach towards directly TFMK-functionalized amino acids (Chapter 4.4.9.5. and 4.4.10.) as most potential regarding an asymmetric epoxidation. Furthermore, utilizing synthesized catalysts in the sulfoxidation showed that it is obvious to test corresponding systems directly in further possible reactions. *Via* investigation of different reaction types in combination with synthesizing new oligopeptides and establishing thereby a catalyst library increases the probability to find an active catalytic system, which acts as starting point for modification. With the optimized protocols for epoxidation and sulfoxidation in hand testing and re-optimizing can be done very quickly. One possible reaction type, which can be included in this context, is the Baeyer-Villiger oxidation referring to the work of Miller and co-workers.[32]

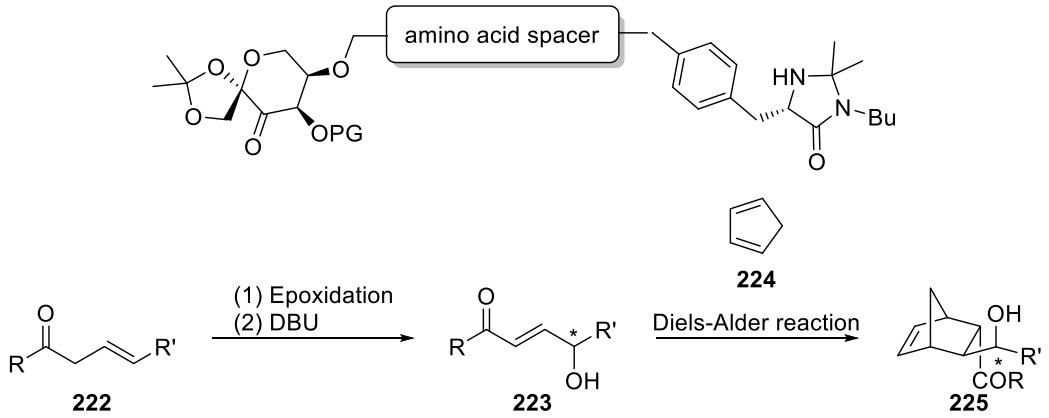
With regard to a new multicatalytic sequence we think it is more promising not to synthesize motifs catalyzing steps of a beforehand determined sequence *de novo*, but to pursue an alternative approach, especially with the results of the prolinol-based epoxidation in mind (Chapter 4.6.2). Based on literature-known catalytically active systems, for which optimized reaction procedures are already reported, a multicatalytic sequence should be developed and the necessary moieties should be combined in a peptide-based catalyst afterwards, because finding a suitable structure-forming element incorporated in a peptidic backbone is challenging enough. Additionally to quoted examples of organocatalysts (e.g., **F1** Scheme 5, **77** and **216** Table 43) and the mentioned motifs **196** and **197** (Chapter 4.7.) additional well-established systems are depicted in figure 32. They were taken from the review of Rüping *et al.* summarizing the progress of organocatalytic-based flow-systems,[18] because substitution of the solid support *via* a peptide would directly yield an functionalized oligopeptidic catalyst.



219 **220** **221**

Figure 32: Potential catalytic motifs for functionalization of peptides.

But, besides chiral organocatalysts also achiral ones (e.g., **77**) can be utilized because the peptidic backbone is responsible for generation of a chiral environment. Based on the huge number of systems enabling a variety of different reactions a wide range of multicatalytic sequences can be realized. One further example additionally to the ones given in chapters 3.4.4. and 4.6.3. is depicted in scheme 74. After epoxidation of olefin **222** with a moiety derived from Shi's catalyst the formed oxirane could be transferred into *α,β*-unsaturated and *γ*-hydroxylated ketone **223** *via* addition of DBU.[54] In the presence of a MacMillan-type motif a Diels-Alder reaction with cyclopentadiene **224** would provide bicyclic product **225**.[14] Besides three stereogenic centers both carbon-carbon double bond as well as ketone or hydroxyl group of the norbornene system can be utilized for further chemical transformations.



Scheme 74: Further postulated multicatalytic sequence.

A combination of a Fmoc protecting group strategy with automated peptide synthesis would be the method of choice for preparation of a larger amount of distinct peptidic backbones. The azide derivative **226** could be a possible alternative for the typically utilized amino acid adamantyl glycine (Figure 33). Firstly, an orthogonal attachment of both functionalized and previously synthesized peptide chains can be achieved *via* azide and carboxylic acid moiety, respectively. Secondly, the *via* click chemistry introduced triazole ring can participate in the interactions between catalyst and substrate in a different way than the replaced amide bond.

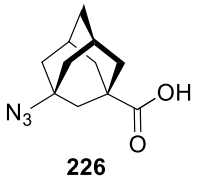


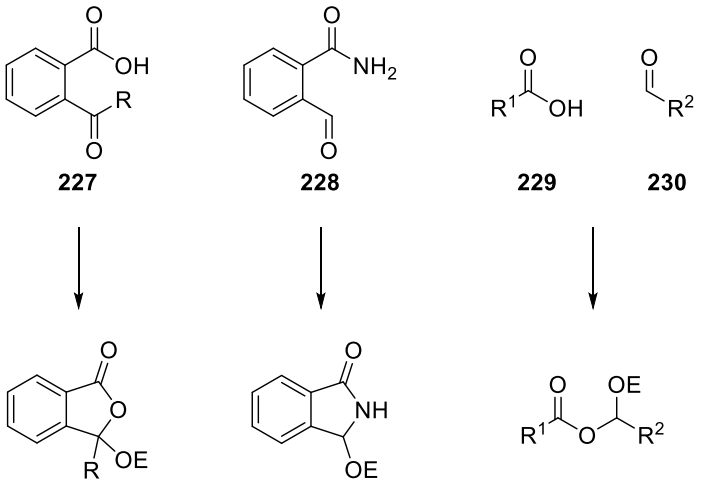
Figure 33: Potential structure-forming unit.

As mentioned in the introduction for enzymes as well as organocatalysts an immobilization approach with peptide and/or multicatalysts should be tested. This strategy implemented in batch or flow conditions would result in a reusable catalytic system.

Apart from the multicatalysis project the synthesis of spiro carbonate **75** can also be investigated further. Especially, synergy of TCU **77** and generated *m*CBA as well as the substrate scope are aspects, which should be considered (Chapter 4.2.).

In case of α-keto acetals **162** first of all the reaction conditions have to be optimized. Therefore, parameters like additional chiral bases (e.g. further alkaloids), different electrophiles (E^+: like further anhydrides or alkylation agent), solvents or temperatures have to be tested. With optimized conditions in hand the substrate scope has to be elucidated. In this regard the

aldehyde moiety can be substituted *via* a ketone, the acid group *via* a primary amide and intramolecular systems *via* intermolecular reaction partners (Scheme 75).



Scheme 75: Possible substrates.

Subsequently, from a multicatalytic as well as synthetic point of view the gained knowledge can lead to further projects or can help to develop approaches in the right direction.

7. Abbreviations

±I effect	Positive or negative inductive effect	LD	Loading didomain
±M effect	Positive or negative mesomeric effect	LDA	Lithium diisopropylamide
anhyd.	Anhydrous	Leu	Leucine
Ac	Acetyl	lit.	Literature
Ad	Adamantyl	m	Multiplet (NMR); medium (IR)
AdGly	γ-Adamantyl amino acid (for the sake of convenience)	M	mol L^{-1}
aq	Aqueous	m.p.	Melting point
Ar	Argon	*m*CBA	*meta*-Chlorobenzoic acid
B^*	Chiral base	*m*CPBA	*meta*-Chloroperbenzoic acid
Bn	Benzyl	Me	Methyl
Boc	*tert*-Butyloxycarbonyl	MHz	Megahertz
bs	Broad signal	mL	Millilitre
calc.	Calculated	MS	Mass spectrometry
cat.	Catalyst	MTBE	Methyl *tert*-butyl ether
Cbz	Carboxybenzyl	NBS	*N*-Bromosuccinimide
Cha	Cyclohexylalanine	NHC	*N*-Heterocyclic carbene
CM	Catalytic moiety	NHO	*N*-Heterocyclic olefin
conc.	Concentration	NMR	Nuclear magnetic resonance
conv.	Conversion	NOESY	Nuclear Overhauser effect spectroscopy
COSY	Correlation spectroscopy	Nu	Nucleophile
CPO	Chloroperoxidase	OC	Organic carbonate
Cy	Cyclohexyl	*o*-DPPB	*o*-Diphenylphosphinobenzoic acid
d	Doublet	PG	Protecting group
Dap	2,3-Diaminopropionic acid	Ph	Phenyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene	Phe	Phenylalanine
DCC	*N*,*N*-Dicyclohexylcarbodiimide	PMH	π-Methyl histidine
DCM	Dichloromethane	*p*NBA	*para*-Nitrobenzoic acid
DEPT	Distortionless enhancement by polarization transfer	ppm	Parts per million
DFT	Density functional theory	Pr	Propyl
D*i*BAL	Diisobutylaluminium hydride	Pro	Proline
DIC	*N*,*N*-Diisopropylcarbodiimide	PTC	Phase transfer catalyst/catalysis
D*i*PEA	*N*,*N*-Diisopropylethylamine	*p*TSA	*para*-Toluenesulfonic acid
DMAP	4-Dimethylaminopyridine	q	Quartet
DMF	*N*,*N*-Dimethylformamide	quant.	Quantitative
DMM	Dimethoxymethane	R	Organic group
DMP	Dess-Martin periodinane	r.t.	Room temperature
DMSO	Dimethyl sulfoxide	resp.	Respectively
E^+	Electrophile	Rt	Retention time
EDAC	*N*-Ethyl-*N*′-(3-dimethylaminopropyl)carbo-diimide hydrochloride	s	Singlet (NMR); strong (IR)

EDTA	Ethylenediaminetetraacetate	sat.	Saturated
ee	Enantiomeric excess	SPPS	Solid phase peptide synthesis
EI	Electron ionization	t	Time; triplet
equiv	Equivalent(s)	T	Temperature
er	Enantiomeric ratio	^{t}Amyl	*tert*-Amyl
ESI	Electron spray ionization	TBA	Tetrabutylammonium
Et	Ethyl	TBDPS	*tert*-Butyldiphenylsilyl
et al.	And others	TBHP	*tert*-Butyl hydroperoxide
eV	Electronvolt	TBS	*tert*-Butyldimethylsilyl
FID	Flame-ionization detector	^{t}Bu	*tert*-Butyl
Fmoc	Fluorenylmethyloxycarbonyl	TE	Thioesterase
GC	Gas chromatography	TEA	Triethylamine
GP	General procedure	TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxy
h	Hour(s)	TFA	Trifluoroacetic acid
HATU	*O*-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium-hexafluorphosphat	TFMK	Trifluoromethyl ketone
HBTU	2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate	THF	Tetrahydrofuran
HMBC	Heteronuclear multiple-bond correlation spectroscopy	TLC	Thin-layer chromatography
HOBt	1-Hydroxybenzotriazole	TMS	Trimethylsilyl; tetramethylsilane
HPLC	High-pressure liquid chromatography	TS	Transition state
HR	High resolution	TUC	Thiourea catalyst
HSAB	Hard and soft acid and base	UHP	Urea hydrogen peroxide
HSQC	Heteronuclear single quantum coherence	UV	Ultraviolet
Hz	Hertz	Val	Valine
IM	Intermediate	vs	Very strong
^{i}Pr	*iso*-Propyl	vw	Very weak
IR	Infrared	w	Weak
J	Coupling constant	wt%	Weigth percent
LAH	Lithium aluminum hydride	δ	Chemical shift

8. Acknowledgment

An erster Stelle bedanke ich mich ganz herzlich bei meinem Betreuer und Doktorvater Prof. Dr. Peter Schreiner für die ständige Unterstützung, sowie das offene und ehrliche Verhältnis während des gesamten Zeitraums meiner Promotion. Vielen Dank insbesondere für die Möglichkeit zur freien Entfaltung und zur stetigen wissenschaftlichen, wie auch persönlichen Entwicklung.

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9. Experimental Section

9.1. General Information

Chemicals were purchased from Alfa Aesar, Acros Organics, Fluka, Fluorochem, Merck, Novabiochem, Roth, Sigma Aldrich, and TCI used without further purification. Solvents for column chromatography, extractions, filtrations, and recrystallizations were distilled prior use. After drying anhyd. solvents using standard procedures they were stored under Ar and over activated molecular sieves (3 Å or 4 Å) or sodium. Column chromatography was carried out with silica gel 60 M (Macherey-Nagel; 0.040 – 0.063 mm, 230 – 400 mesh ASTM). TLC was performed using precoated Machery-Nagel plastic sheets Polygram® SIL G/UV_{254} (Macherey-Nagel; 0.2 mm silica gel layer with fluorescent indicator). For visualization ultraviolet (UV) light (254 nm) or staining solutions (2,4-dinitrophenylhydrazine: 1.0 g hydrazine, 5 mL concentrated H_2SO_4, 8 mL H_2O, 237 mL EtOH; $KMnO_4$: 2.5 g $KMnO_4$, 8.3 g K_2CO_3, 250 mL H_2O; ninhydrin: 0.2 weight percent (wt%) in ethanol; phosphomolybdic acid: 5 wt% in ethanol) were utilized.

All NMR spectra were recorded on Bruker AV 200, AV 400 or AV 600 spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) using either tetramethylsilane (TMS) or the corresponding residual solvent signal as internal standard.[173] Structural assignments were made employing distortionless enhancement by polarization transfer (DEPT) and 2D-NMR spectra (correlation spectroscopy (COSY), heteronuclear multiple-bond correlation spectroscopy (HMBC), heteronuclear single quantum coherence (HSQC), nuclear Overhauser effect spectroscopy (NOESY)). Data are reported as follows: δ, multiplicity (bs: broad signal, s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, or combinations thereof), integration, coupling constant (*J*) in hertz (Hz), assignment. IR spectra were measured on a Bruker IFS25 spectrometer. ESI-MS was performed employing a Finnigan LCQ-Duo spectrometer. HR-MS was performed employing either a Thermo Scientific LTQ FT Ultra (ESI) or a Finnigan MAT95 sectorfield spectrometer (EI). For ESI measurements a methanol solution of the corresponding compound was used. Reaction progress and product formation was monitored by GC-MS analysis with a Hewlett Packard 5890 gas chromatograph with flame-ionization detector (FID) and a Quadropol-MS Hewlett Packard MSD 5971 detector (EI, 70 eV) and a DB-5MS column (30 m x 0.250 mm) was used. Either chiral stationary phase GC analyses on Hewlett Packard 5890 or 6890 gas chromatographs or chiral stationary phase HPLC with a Dionex system (Dionex P680 HPLC pump, Shodex RI-101 detector) were used to monitor enantioselective product formation. Analytic HPLC was performed using a Spectra SP 8700 system and

preparative HPLC utilizing a Knauer system (Knauer HPLC Pump 64, Knauer 2151 Variable Wavelength Monitor). For measurement of melting points (m.p.) a Krüss KSP1N capillary melting point apparatus was utilized. X-ray crystal structures were obtained using either a Bruker/Nonius FR591 rotating anode (Mo-Kα, λ = 0.71073 Å) equipped with a graphite monochromator, a Kappa CCD area detector, and an Oxford Cryostream 600 low temperature unit or a Bruker D8 Venture with dual a Mo/Cu IμS microfocus source (Mo-Kα, λ = 0.71073 Å; Cu-Kα, λ = 1.54178 Å) and a graphite monochromator, equipped with an Oxford Cryostream 700 low temperature unit.

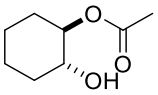
9.2. Racemic Synthesis of Mono-Acylated Compounds

9.2.1. Acyl Derivatives

General Procedure (GP-1):

Catalytic amounts DMAP and 1.0 equiv alcohol were dissolved in DCM. Afterwards 1.0 equiv freshly distilled Ac_2O and 1.0 equiv D*i*PEA were added in one portion and the resulting mixture was stirred at r.t.. At the end of the reaction the solvent was evaporated and the crude product was purified utilizing column chromatography.

***trans*-2-Acetoxycyclohexan-1-ol 4:** (GP-1)



4

The reaction was performed with 0.011 g (0.090 mmol, 5 mol%) DMAP, 0.200 g (1.72 mmol, 1.0 equiv) diol **2**, 0.163 mL (0.176 g, 1.72 mmol, 1.0 equiv) Ac_2O, 0.292 mL (0.222 g, 1.72 mmol, 1.0 equiv) D*i*PEA, and 9 mL DCM. The resulting mixture was stirred for 19 h. After purification *via* column chromatography (EtOAc) 0.133 g (0.841 mmol, 49%) **4** were isolated as colorless oil.

R_f: 0.50 (EtOAc).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 4.61–4.49 (m, 1 H); 3.59–3.47 (m, 1 H); 2.56 (bs, 1 H); 2.11–1.91 (m, 5 H); 1.77–1.61 (m, 2 H); 1.45–1.11 (m, 4 H) ppm.

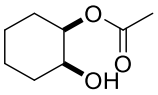
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 171.5; 78.3; 72.8; 33.2; 30.1; 23.8; 24.0; 21.5 ppm.

Analytic data are identical to those reported in literature.[174]

Chiral GC analysis:

Enantiomers of **4** were separated by chiral GC employing a 30 m FS-Hydrodex γ-DiMOM column (Macherey-Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: initial temperature: 100 °C; initial time: 45 min. Retention times: Rt_1 = 42.0 min; Rt_2 = 43.5 min.

***cis*-2-Acetoxycyclohexan-1-ol 5:** (GP-1)



5

The reaction was performed with 0.011 g (0.090 mmol, 5 mol%) DMAP, 0.200 g (1.72 mmol, 1.0 equiv) diol **3**, 0.163 mL (0.176 g, 1.72 mmol, 1.0 equiv) Ac_2O, 0.292 mL (0.222 g, 1.72 mmol, 1.0 equiv) D*i*PEA, and 9 mL DCM. The resulting mixture was stirred for 19 h. After purification *via* column chromatography (EtOAc) 0.178 g (1.13 mmol, 65%) **5** were isolated as colorless oil.

R_f: 0.52 (EtOAc).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.90 (dt, 1 H, *J* = 8.1 Hz, *J* = 2.8 Hz); 3.88–3.85 (m, 1 H); 2.08 (s, 3 H); 1.94 (bs, 1 H); 1.87–1.73 (m, 2 H); 1.67–1.54 (m, 4 H); 1.41–1.33 (m, 2 H) ppm.

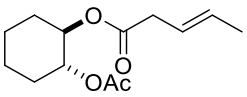
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 170.9; 74.4; 69.2; 30.4; 27.0; 22.2; 21.4; 21.0 ppm.

Analytic data are identical to those reported in literature.[2b]

Chiral GC analysis:

Enantiomers of **5** were separated by chiral GC employing a 30 m FS-Hydrodex γ-TBDAc column (Macherey-Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Condition: initial temperature: 100 °C; final temperature: 140 °C; rate: 2.00 °C/min. Retention Times: Rt_1 = 14.3 min; Rt_2 = 15.2 min.

***trans*-2-Acetoxycyclohexyl (*E*)-3-pentenoate 33:** (GP-1)



33

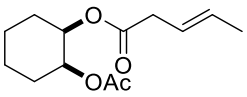
The reaction was performed with 0.003 g (0.020 mmol, 8 mol%) DMAP, 0.050 g (0.252 mmol, 1.0 equiv) monoester **20a**, 24.0 µL (25.9 mg, 0.254 mmol, 1.0 equiv) Ac_2O, 43.0 µL (32.7 mg, 0.253 mmol, 1.0 equiv) D*i*PEA, and 2 mL DCM. Based on TLC further 24.0 µL (25.9 mg, 0.254 mmol, 1.0 equiv) Ac_2O and 43.0 µL (32.7 mg, 0.253 mmol, 1.0 equiv) D*i*PEA were added after 5.5 h. The reaction mixture was stirred 31 h. After purification *via* column chromatography (*n*-hexane:EtOAc 4:1 to 2:1) 0.055 g (0.229 mmol, 91%) **33** were isolated as colorless oil.

R_f: 0.49 (*n*-hexane:EtOAc 2:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.61–5.45 (m, 2 H, C*HCH*); 4.84–4.76 (m, 2 H, C*H*CO); 2.97 (d, 2 H, ^3J = 6.3 Hz, CH_2CHCH); 2.06–2.00 (m, 2 H, H_{Cy}); 2.00 (s, 3 H, CH_3); 1.76–1.70 (m, 2 H, H_{Cy}); 1.69–1.67 (m, 3 H, CHCH_3); 1.44–1.29 (m, 4 H, H_{Cy}) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.7 (*C*O); 170.6 (*C*O); 129.5 (CH$_2$*C*H); 122.8 (CH*C*H); 73.9 (*C*HO); 73.8 (*C*HO); 38.5 (*C*H$_2$CH); 30.3 (*C*H$_2$CHO); 30.2 (*C*H$_2$CHO); 23.57 (*C*H$_2$CH$_2$CH); 23.56 (*C*H$_2$CH$_2$CH); 21.2 (CH_3); 18.1 (CHCH_3) ppm.

***cis*-2-Acetoxycyclohexyl (*E*)-3-pentenoate 34:** (GP-1)



34

The reaction was performed with 0.003 g (0.020 mmol, 8 mol%) DMAP, 0.049 g (0.247 mmol, 1.0 equiv) monoester **21a**, 24.0 µL (25.9 mg, 0.254 mmol, 1.0 equiv) Ac_2O, 43.0 µL (32.7 mg, 0.253 mmol, 1.0 equiv) D*i*PEA, and 2 mL DCM. Based on TLC further 24.0 µL (25.9 mg, 0.254 mmol, 1.0 equiv) Ac_2O and 43.0 µL (32.7 mg, 0.253 mmol, 1.0 equiv) D*i*PEA were added after 6 h. The reaction mixture was stirred 25 h. After purification *via* column chromatography (*n*-hexane:EtOAc 4:1) 0.045 g (0.187 mmol, 76%) **34** were isolated as colorless oil.

R_f: 0.50 (*n*-hexane:EtOAc 2:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.64–5.48 (m, 2 H, C*HCH*); 5.04–5.02 (m, 1 H, C*H*CO); 5.00–4.97 (m, 1 H, C*H*CO); 3.00–3.01 (m, 2 H, CH_2CHCH); 2.02 (s, 3 H, CH_3); 1.88–1.77 (m, 2 H, H_{Cy}); 1.68 (d, 3 H, ^3J = 5.0 Hz, CHCH_3); 1.66–1.58 (m, 4 H, H_{Cy}); 1.51–1.35 (m, 2 H, H_{Cy}) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.6 (*C*O); 170.5 (*C*O); 129.4 (CH_2*C*H); 122.9 (CH*C*H); 71.2 (*C*HO); 71.0 (*C*HO); 38.3 (*C*H_2CH); 27.8 (*C*H_2CHO); 27.6 (*C*H_2CHO); 22.0; 21.6; 21.2; 18.1 (CHCH_3) ppm.

9.2.2. Unsaturated Esters

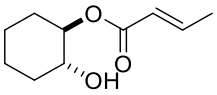
General procedure for the esterification using anhydrides (GP-2):

DMAP and diol were dissolved in DCM. Afterwards pyridine and anhydride were added in one portion. The resulting mixture was stirred at r.t. and the reaction progress was monitored *via* TLC. At the end of the reaction 10 mL of a brine were added. After phase separation, extraction with either DCM or EtOAc (three times 10 mL), and drying over Na_2SO_4 the solvent was evaporated. The crude product was purified utilizing column chromatography.

General procedure using the Steglich protocol (GP-3):

DMAP, EDAC, diol, and solid acids were solved in DCM. Afterwards TEA and liquid acids were added in one portion. The resulting mixture was stirred at r.t. and the reaction progress was monitored *via* TLC. At the end of the reaction sat. $NaHCO_3$ was added. After phase separation, extraction of the aqueous layer with DCM, and drying over Na_2SO_4 the solvent was evaporated. The crude product was purified utilizing column chromatography.

***trans*-2-Hydroxycyclohexyl crotonate 17:** (GP-2)



17

The reaction mixture containing 0.021 g (0.172 mmol, 10 mol%) DMAP, 0.242 mL (0.252 g, 1.63 mmol, 0.9 equiv) crotonic anhydride, 0.202 g (1.74 mmol, 1.0 equiv) diol **2**, 0.840 mL (0.822 g, 10.4 mmol, 6.0 equiv) pyridine, and 4 mL DCM was stirred for 16 h. EtOAc was used for the extraction. After purification *via* column chromatography (*n*-hexane:EtOAc 4:1 to 0:1) 0.188 g (1.02 mmol, 63%) **17** were isolated as colorless oil.

R_f: 0.27 (*n*-hexane:EtOAc 2:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.98 (dq, 1 H, ^3J = 15.5 Hz, ^3J = 6.9 Hz, C*H*CH_3); 5.84 (dq, 1 H, ^3J = 15.5 Hz, ^4J = 1.7 Hz, COC*H*); 4.63–4.58 (m, 1 H, C*H*OCO); 3.59–3.53 (m, 1 H, C*H*OH); 2.44 (bs, 1 H, O*H*); 2.07–2.00 (m, 2 H, H_{Cy}); 1.86 (dd, 3 H, ^3J = 6.9 Hz, ^4J = 1.7 Hz, CH_3); 1.72–1.64 (m, 2 H, H_{Cy}); 1.39–1.18 (m, 4 H, H_{Cy}) ppm.

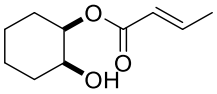
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 166.9; 145.2; 122.8; 78.0; 72.9; 33.1; 30.1; 24.0; 23.8; 18.1 ppm.

IR (Film): ṽ = 3449 (vw); 2939 (w); 2863 (vw); 1718 (w); 1187 (w); 1029 (w); 853 (vw) cm^{-1}.

HR-MS (ESI): m/z: 207.0997 $[M + Na]^+$ (cal. 207.0992); 391.2086 $[2M + Na]^+$ (cal. 391.2091).

Analytic data are identical to those reported in literature.[69]

***cis*-2-Hydroxycyclohexyl crotonate 18:** (GP-2)



18

The reaction mixture containing 0.013 g (0.106 mmol, 12 mol%) DMAP, 0.121 mL (0.126 g, 0.816 mmol, 0.9 equiv) crotonic anhydride, 0.101 g (0.869 mmol, 1.0 equiv) diol **3**, 0.420 mL (0.411 g, 5.12 mmol, 5.9 equiv) pyridine, and 3 mL DCM was stirred for 20 h. DCM was used for the extraction. After purification *via* column chromatography (*n*-hexane:EtOAc 4:1 to 1:1) 0.095 g (0.516 mmol, 63%) **18** were isolated as colorless oil.

R_f: 0.29 (*n*-hexane:EtOAc 2:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.00 (dq, 1 H, ^3J = 15.5 Hz, ^3J = 6.9 Hz, C*H*CH_3); 5.88 (dq, 1 H, ^3J = 15.5 Hz, ^4J = 1.6 Hz, COC*H*); 4.98 (dt, 1 H, ^3J = 7.9 Hz, ^3J = 2.7 Hz, C*H*CO); 3.93–3.85 (m, 1 H, C*H*OH); 1.92–1.86 (m, 4 H, CH_3 and H_{Cy}); 1.82–1.73 (m, 1 H, H_{Cy}); 1.72–1.54 (m, 4 H, H_{Cy}); 1.45–1.30 (m, 2 H, H_{Cy}) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 166.3; 145.3; 122.9; 74.0; 69.5; 30.5; 27.2; 22.1; 21.3; 18.1 ppm.

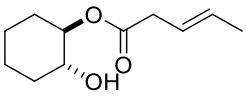
IR (Film): ṽ = 3443 (w); 2941 (m); 2866 (m); 1717 (s); 1185 (m); 972 (m); 850 (w) cm^{-1}.

HR-MS (ESI): m/z: 207.1002 $[M + Na]^+$ (cal. 207.0992); 391.2092 $[2M + Na]^+$ (cal. 391.2091).

Chiral GC analysis:

Enantiomers of **18** were separated by chiral GC employing a 30 m FS-Hydrodex γ-TBDAc column (Macherey-Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: initial temperature: 130 °C; initial time: 55 min. Retention times: Rt_1 = 31.5 min; Rt_2 = 32.2 min.

***trans*-2-Hydroxycyclohexyl (*E*)-3-pentenoate 20a:** (GP-3)



20a

The reaction mixture containing 2.60 mg (0.021 mmol, 2 mol%) DMAP, 0.101 g (0.869 mmol, 1.0 equiv) diol **2**, 0.087 mL (0.086 g, 0.857 mmol, 1.0 equiv) 3-pentonic acid **19a**, 0.165 g (0.861 mmol, 1.0 equiv) EDAC, 0.120 mL (0.087 g, 0.861 mmol, 1.0 equiv) TEA, and 5 mL DCM was stirred for 25 h. The reaction was quenched with 10 mL sat. $NaHCO_3$ and the aqueous layer was extracted with DCM (three times 10 mL). After purification *via* column chromatography (*n*-hexane:EtOAc 3:1 to 0:1) 0.120 g (0.605 mmol, 71%) **20a** were isolated as colorless oil.

$\mathbf{R_f}$: 0.23 (*n*-hexane:EtOAc 2:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.64–5.49 (m, 2 H, C*H*C*H*); 4.60–4.54 (m, 1 H, C*H*OC); 3.60–3.53 (m, 1 H, C*H*OH); 3.09–3.00 (m, 2 H, COCH_2); 2.13 (d, 1 H, ^3J = 3.9 Hz, O*H*); 2.08–1.97 (m, 2 H, H_{Cy}); 1.75–1.63 (m, 5 H, CH_3 and H_{Cy}); 1.40–1.18 (m, 4 H, H_{Cy}) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 172.6 (*C*O); 129.7 (CH_2*C*H); 122.8 (CH*C*H); 78.6 (*C*HOCO); 72.9 (*C*HOH); 38.4 (*C*H_2CH); 33.1 (*C*H_2CHOH); 30.1 (*C*H_2CHOCO); 24.0 (*C*H_2CH_2CHOCO); 23.9 (*C*H_2CH_2CHOH); 18.1 (*C*H_3) ppm.

IR (Film): $\tilde{\nu}$ = 3429 (s); 2939 (s); 2865 (s); 1722 (s); 1261 (s); 854 (m); 574 (w) cm^{-1}.

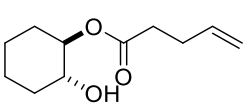
HR-MS (EI): m/z: 198.1239 (cal. 198.1256).

MS (ESI): m/z: 221.1 $[M + Na]^+$ (cal. 221.1); 237.1 $[M + K]^+$ (cal. 237.1); 418.9 $[2M + Na]^+$ (cal. 419.2).

Chiral HPLC analysis:

Enantiomers of **20a** were separated by chiral HPLC employing a 25 cm Chiralpak IA column (4.6 mm ID, Daicel) in combination with an UV-detector (220 nm). Flow = 0.700 mL/min. Solvent mixture: *n*-hexane:isopropanol 90:10. Retention times: Rt_1 = 11.7 min; Rt_2 = 17.7 min.

***trans*-2-Hydroxycyclohexyl 4-pentenoate 20b:** (GP-3)



20b

The reaction mixture containing 0.021 g (0.172 mmol, 1 mol%) DMAP, 2.00 g (17.2 mmol, 1.0 equiv) diol **2**, 1.74 mL (1.71 g, 17.0 mmol, 1.0 equiv) 4-pentonic acid **19b**, 3.32 g (17.3 mmol, 1.0 equiv) EDAC, 2.40 mL (1.74 g, 17.2 mmol, 1.0 equiv) TEA, and 80 mL DCM was stirred for 42 h. The reaction was quenched with 80 mL sat. $NaHCO_3$ and the aqueous layer was extracted with DCM (three times 10 mL). After purification *via* column chromatography (*n*-hexane:EtOAc 2:1) 1.51 g (7.62 mmol, 45%) **20b** were isolated as colorless oil.

R_f: 0.32 (*n*-hexane:EtOAc 2:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.83 (ddt, 1 H, ^3J = 16.4 Hz, ^3J = 10.3 Hz, ^3J = 6.2 Hz, C*H*CH_2); 5.09–5.04 (m, 1 H, CHCH_2); 5.03–5.00 (m, 1 H, CHCH_2); 4.61–4.55 (m, 1 H, C*H*OC); 3.57–3.51 (m, 1 H, C*H*OH); 2.47–2.43 (m, 2 H, COC$H_2$$CH_2$CH); 2.41–2.35 (m, 2 H, C$H_2$$CHCH_2$); 2.15 (bs, 1 H, O*H*); 2.07–1.97 (m, 2 H, H_{Cy}); 1.74–1.64 (m, 2 H, H_{Cy}); 1.39–1.19 (m, 4 H, H_{Cy}) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 173.4 (*C*O); 136.9 (*C*HCH_2); 115.8 (CH*C*H_2); 78.4 (*C*HOCO); 72.9 (*C*HOH); 34.0 (*C*$H_2$$CH_2$CH); 33.1 (*C*$H_2$CHOH); 30.1 (*C*$H_2$CHOCO); 29.2 ($CH_2$*C*$H_2$CH); 24.0 *C*$H_2$$CH_2$CHOCO); 23.9 (*C*$H_2$$CH_2$CHOH) ppm.

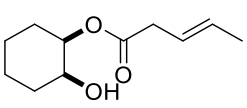
IR (Film): ṽ = 3445 (m); 2940 (vs); 2863 (s); 1733 (vs); 1179 (vs); 852 (w); 568 (vw) cm^{-1}.

HR-MS (EI): m/z: 198.1227 (cal. 198.1256).

Chiral HPLC analysis:

Enantiomers of **20b** were separated by chiral HPLC employing a 25 cm Chiralpak IA column (4.6 mm ID, Daicel) in combination with an UV-detector (254 nm). Flow = 1.00 mL/min. Solvent mixture: *n*-hexane:isopropanol 95:5. Retention times: Rt_1 = 13.4 min; Rt_2 = 14.7 min.

***cis*-2-Hydroxycyclohexyl (*E*)-3-pentenoate 21a:** (GP-3)



21a

The reaction mixture containing 1.05 mg (0.009 mmol, 1 mol%) DMAP, 0.103 g (0.887 mmol, 1.0 equiv) diol **3**, 0.089 mL (0.088 g, 0.876 mmol, 1.0 equiv) 3-pentonic acid **19a**, 0.165 g (0.861 mmol, 1.0 equiv) EDAC, 0.120 mL (0.087 g, 0.861 mmol, 1.0 equiv) TEA, and 4 mL DCM was stirred for 24 h. The reaction was quenched with 10 mL sat. $NaHCO_3$ and the aq layer was extracted with DCM (three times 10 mL). After purification *via* column chromatography (*n*-hexane:EtOAc 2:1 to 0:1) 0.093 g (0.469 mmol, 54%) **21a** were isolated as colorless oil.

R_f: 0.24 (*n*-hexane:EtOAc 2:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.63–5.50 (m, 2 H, C*H*C*H*); 4.92 (dt, 1 H, ^3J = 8.1 Hz, ^3J = 2.8 Hz, C*H*OC); 3.88–3.83 (m, 1 H, C*H*OH); 3.06–3.04 (m, 2 H, COCH_2); 1.92 (bs, 1 H, O*H*); 1.88–1.81 (m, 1 H, H_{Cy}); 1.79–1.72 (m, 1 H, H_{Cy}); 1.71–1.68 (m, 3 H, CH_3); 1.65–1.54 (m, 4 H, H_{Cy}); 1.42–1.31 (m, 2 H, H_{Cy}) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 172.0 (*C*O); 129.7 (CH_2*C*H); 122.8 (CH*C*H); 74.4 (*C*HOCO); 69.3 (*C*HOH); 38.4 (*C*H_2CH); 30.4 (*C*H_2CHOH); 27.0 (*C*H_2CHOCO); 22.1 (*C*H_2CH_2CHOCO); 21.2 (*C*H_2CH_2CHOH); 18.1 (*C*H_3) ppm.

IR (Film): ṽ = 3433 (vs); 2940 (s); 2866 (s); 1719 (vs); 1182 (vs); 887 (m); 596 (w) cm^{-1}.

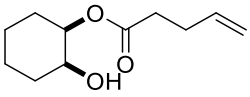
HR-MS (EI): m/z: 198.1240 (cal. 198.1256).

MS (ESI): m/z: 221.0 $[M + Na]^+$ (cal. 221.1); 237.1 $[M + K]^+$ (cal. 237.1); 418.9 $[2M + Na]^+$ (cal. 419.2).

Chiral GC analysis:

Enantiomers of **21a** were separated by chiral GC employing a 30 m Chiraldex G-TA column (Astech). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: Initial temperature: 80 °C; Final temperature: 150 °C; Rate: 1.00 °C/min. Retention times: Rt_1 = 56.5 min; Rt_2 = 57.5 min.

***cis*-2-Hydroxycyclohexyl 4-pentenoate 21b:**



21b

The reaction mixture containing 0.022 g (0.180 mmol, 1 mol%) DMAP, 2.00 g (17.2 mmol, 1.0 equiv) diol **3**, 1.80 mL (1.77 g, 17.6 mmol, 1.0 equiv) 4-pentonic acid **19b**, 3.32 g (17.3 mmol, 1.0 equiv) EDAC, 2.40 mL (1.74 g, 17.2 mmol, 1.0 equiv) TEA, and 80 mL DCM was stirred for 43 h. The reaction was quenched with 80 mL sat. $NaHCO_3$ and the aq layer was extracted with DCM (three times 10 mL). After purification *via* column chromatography (*n*-hexane:EtOAc 2:1) 1.69 g (8.52 mmol, 50%) **21b** were isolated as colorless oil.

R_f: 0.36 (*n*-hexane:EtOAc 2:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.84 (ddt, 1 H, ^3J = 16.3 Hz, ^3J = 10.3 Hz, ^3J = 6.1 Hz, C*H*CH_2); 5.10–5.05 (m, 1 H, CHCH_2); 5.03–5.00 (m, 1 H, CHCH_2); 4.94 (dt, 1 H, ^3J = 8.2 Hz, ^3J = 3.0 Hz, C*H*OC); 3.88–3.83 (m, 1 H, C*H*OH); 2.48–2.45 (m, 2 H, COCH_2CH_2CH); 2.43–2.36 (m, 2 H, CH_2CHCH_2); 1.89 (d, 1 H, ^3J = 4.0 Hz, O*H*); 1.85–1.70 (m, 2 H, H_{Cy}); 1.68–1.54 (m, 4 H, H_{Cy}); 1.43–1.30 (m, 2 H, H_{Cy}) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 172.8 (*C*O); 136.9 (*C*HCH$_2$); 115.8 (CH*C*H$_2$); 74.3 (*C*HOCO); 69.3 (*C*HOH); 33.9 (*C*H$_2$CH$_2$CH); 30.5 (*C*H$_2$CHOH); 29.1 (CH$_2$*C*H$_2$CH); 27.1 (*C*H$_2$CHOCO); 22.1 *C*H$_2$CH$_2$CHOCO); 21.2 (*C*H$_2$CH$_2$CHOH) ppm.

IR (Film): $\tilde{\nu}$ = 3455 (w); 2940 (m); 2863 (w); 1732 (m); 1177 (m); 850 (vw); 601 (vw) cm^{-1}.

HR-MS (ESI): m/z: 221.1158 $[M + Na]^+$ (cal. 221.1148); 419.2411 $[2M + Na]^+$ (cal. 419.2404).

Chiral HPLC analysis:

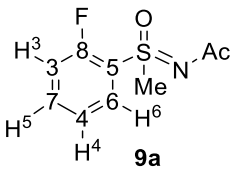
Enantiomers of **21b** were separated by chiral HPLC employing a 25 cm Chiralpak IA column (4.6 mm ID, Daicel) in combination with an UV-Vis-detector (220 nm). Flow = 1.00 mL/min. Solvent mixture: *n*-hexane:*iso*-propanol 97:3. Retention times: Rt_1 = 13.9 min; Rt_2 = 15.5 min.

9.2.3. *N*-Acylated Sulfoximines

General Procedure (GP-4):

Catalytic amounts DMAP and the corresponding sulfoximine were dissolved in 2 mL DCM. Afterwards, freshly distilled Ac_2O and D*i*PEA were added in one portion. The resulting mixture was stirred at r.t. and the reaction progress was monitored *via* TLC. At the end of the reaction 10 mL sat. $NaHCO_3$ were added. After phase separation, washing with DCM, and drying over Na_2SO_4 the solvent was evaporated. The crude product was purified utilizing column chromatography.

1-(*o*-Fluorophenylmethylthioamino)-1-ethanone 9a: (GP-4)



9a

A reaction mixture containing 4.10 mg (0.034 mmol, 27 mol%) DMAP, 22.0 mg (0.127 mmol, 1.0 equiv) sulfoximine **8a**, 0.014 mL (15.1 mg, 0.148 mmol, 1.2 equiv) Ac_2O, and 0.024 mL (18.2 mg, 0.141 mmol, 1.1 equiv) D*i*PEA was stirred for 28 h. After 8 h further 1.1 equiv Ac_2O and D*i*PEA were added. After purification *via* column chromatography (*n*-hexane:EtOAc 1:2 to 1:3) 18.0 mg (0.084 mmol, 66%) **9a** were isolated as colorless oil.

R$_f$: 0.26 (*n*-hexane:EtOAc 1:2).

^{1}H-NMR (^{19}F) (400 MHz, $CDCl_3$): δ = 8.05 (dd, 1 H, ^3J = 8.0 Hz, ^4J = 1.4 Hz, H^6); 7.68–7.64 (m, 1 H, H^5); 7.39 (t, 1 H, ^3J = 7.7 Hz, H^4); 7.25 (d, 1 H, ^3J = 8.6 Hz, H^3); 3.42 (s, 3 H, SCH_3); 2.11 (s, 3 H, COCH_3) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 180.0 (*C*O); 158.4 (C^8, $^1J_{CF}$ = 254.8 Hz); 136.3 (C^7, $^3J_{CF}$ = 8.5 Hz); 130.9 (C^6); 126.4 (C^5, $^2J_{CF}$ = 14.0 Hz); 125.2 (C^4, $^4J_{CF}$ = 3.7 Hz); 117.4 (C^3, $^2J_{CF}$ = 21.3 Hz); 43.4 (S*C*H$_3$, $^4J_{CF}$ = 3.5 Hz); 26.6 (CO*C*H$_3$) ppm.

IR (Film): $\tilde{\nu}$ = 3019 (vw); 2929 (vw); 2090 (vw); 1858 (vw); 1641 (s); 1475 (m); 1263 (s); 1231 (s); 1037 (m); 826 (m); 765 (m) ; 483 (m) cm^{-1}.

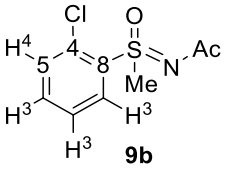
HR-MS (ESI): m/z: 216.0498 $[M + H]^+$ (cal. 216.0489); 238.0314 $[M + Na]^+$ (cal. 238.0308); 453.0725 $[2M + Na]^+$ (cal. 453.0725).

MS (ESI): m/z: 238.1 $[M + Na]^+$ (cal. 238.0); 452.9 $[2M + Na]^+$ (cal. 453.1).

Chiral GC analysis:

Enantiomers of **9a** were separated by chiral GC employing a 30 m FS-Hydrodex γ-TBDAc column (Macherey-Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: Initial temperature: 140 °C; Final temperature: 250 °C; Rate: 2.00 °C/min. Retention times: Rt_1 = 34.0 min; Rt_2 = 35.8 min.

1-(*o*-Chlorophenylmethylthioamino)-1-ethanone 9b: (GP-4)



9b

A reaction mixture containing 4.10 mg (0.019 mmol, 21 mol%) DMAP, 17.0 mg (0.090 mmol, 1.0 equiv) sulfoximine **8b**, 34.2 µL (36.9 mg, 0.362 mmol, 4.0 equiv) Ac_2O, and 61.5 µL (46.7 mg, 0.362 mmol, 4.0 equiv) D*i*PEA was stirred for 24 h. After purification *via* column chromatography (*n*-hexane:EtOAc 1:2) 14.0 mg (0.060 mmol, 67%) **9b** were isolated as colorless oil.

$\mathbf{R_f}$: 0.29 (*n*-hexane:EtOAc 1:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.24–8.22 (m, 1 H, H^4); 7.61–7.51 (m, 3 H, H^3); 3.43 (s, 3 H, SCH_3); 2.11 (s, 3 H, $COCH_3$) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 179.7 (*C*O); 136.2 (C^8); 134.8 (*C*H); 132.2 (*C*H); 131.8 (C^5); 131.1 (C^4); 128.0 (*C*H); 42.0 (SCH_3); 26.4 ($COCH_3$) ppm.

IR (KBr): $\tilde{\nu}$ = 3014 (m); 2931 (m); 2087 (vw); 1948 (vw); 1860 (vw); 1634 (vs); 1475 (m); 1268 (vs); 1213 (vs); 1051 (vs); 969 (vs); 824 (s); 761 (vs); 510 (vs); 465 (s) cm^{-1}.

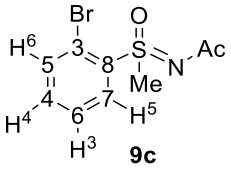
HR-MS (ESI): m/z: 254.0017 $[M + Na]^+$ (cal. 254.0013); 485.0133 $[2M + Na]^+$ (cal. 485.0134).

MS (ESI): m/z: 254.0 $[M + Na]^+$ (cal. 254.0); 485.4 $[2M + Na]^+$ (cal. 485.0).

Chiral GC analysis:

Enantiomers of **9b** were separated by chiral GC employing a 30 m FS-Hydrodex γ-TBDAc column (Macherey-Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: Initial temperature: 140 °C; Final temperature: 250 °C; Rate: 2.00 °C/min. Retention times: Rt_1 = 37.7 min; Rt_2 = 38.8 min.

1-(*o*-Bromophenylmethylthioamino)-1-ethanone 9c: (GP-4)



A reaction mixture containing 3.30 mg (0.027 mmol, 37 mol%) DMAP, 17.0 mg (0.073 mmol, 1.0 equiv) sulfoximine **8c**, 0.021 mL (22.7 mg, 0.222 mmol, 3.1 equiv) Ac_2O, and 0.038 mL (28.8 mg, 0.223 mmol, 3.1 equiv) D*i*PEA was stirred for 24 h. After purification *via* column chromatography (*n*-hexane:EtOAc 1:2) 11.0 mg (0.040 mmol, 55%) **9c** were isolated as colorless oil.

R_f: 0.29 (*n*-hexane:EtOAc 1:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.27 (dd, 1 H, ^3J = 8.0 Hz, ^4J = 1.7 Hz, H^6); 7.76 (dd, 1 H, ^3J = 7.9 Hz, ^4J = 1.2 Hz, H^5); 7.58 (dt, 1 H, ^3J = 7.7 Hz, ^4J = 1.2 Hz, H^4); 7.48 (dt, 1 H, ^3J = 7.7 Hz, ^4J = 1.7 Hz, H^3); 3.45 (s, 3 H, SCH_3); 2.12 (s, 3 H, COCH_3) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 179.7 (*C*O); 137.9 (C^8); 135.8 (C^7); 134.8 (C^6); 132.0 (C^5); 128.6 (C^4); 119.3 (C^3); 41.8 (S*C*H$_3$); 26.4 (CO*C*H$_3$) ppm.

IR (KBr): $\tilde{\nu}$ = 3002 (m); 2922 (s); 2090 (vw); 1871 (vw); 1635 (vs); 1367 (s); 1264 (vs); 1211 (vs); 1045 (vs); 959 (s); 831 (s); 758 (s); 507 (s); 456 (s) cm^{-1}.

HR-MS (ESI): m/z: 297.9514 $[M + Na]^+$ (cal. 297.9508).

MS (ESI): m/z: 297.9 $[M + Na]^+$ (cal. 298.0).

Chiral GC analysis:

Enantiomers of **9c** were separated by chiral GC employing a 30 m FS-Hydrodex γ-TBDAc column (Macherey-Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: Initial temperature: 140 °C; Final temperature: 250 °C; Rate: 2.00 °C/min. Retention times: Rt_1 = 42.3 min; Rt_2 = 43.1 min.

9.3. Catalytic Acylation

9.3.1. Peptide-Based Steglich Esterification of Pentonic Acids and Diols

For the kinetic resolution the reaction vessel was charged with 1.0 equiv diol (±)-**2.** Dissolved cat. **1** (toluene, 2 mol%), 1.2 equiv DIC, and 2.0 equiv pentenoic acid **19a** were rinsed into the reaction vial using 4.40 mL anhyd. toluene. The resulting mixture was cooled to 0 °C. Samples of 0.5 mL were taken, quenched with MeOH, and analyzed directly *via* chiral GC or HPLC.

For the desymmetrization the reaction vessel was charged with 2 mol% cat. **11**, 1.0 equiv DCC, and 1.0 equiv *meso*-**3**. 2.0 equiv pentenoic acid **19a** were rinsed into the reaction vial using

4.00 mL anhyd. toluene. The resulting mixture was cooled to 0 °C. Samples of 0.5 mL were taken, quenched with MeOH, and analyzed directly *via* chiral GC.

9.3.2. Sulfoximines

The reaction vessel was charged with sulfoximine. Freshly distilled Ac_2O, D*i*PEA as well as the corresponding volume of a stock solution containing the cat. were rinsed into the reaction vial using anhyd. toluene. In total 4.00 mL anhyd. toluene were used. The resulting mixture was cooled to 0 °C. Samples of 0.5 mL were taken, quenched with MeOH, and analyzed directly *via* chiral GC.

9.4. Synthesis of Peptide Catalysts

9.4.1. Peptide Synthesis in Solution

Methyl ester protection/Boc deprotection (GP-5):

1.0 equiv of the Boc-protected amino acid was dissolved in MeOH. The resulting mixture was cooled to 0 °C and afterwards $SOCl_2$ was added carefully. After removing the ice bath the solution was stirred for 24 h at r.t.. The solvent was removed under reduced pressure and the crude hydrochloride was used without further purification.

Peptide coupling (GP-6):

1.0 equiv of the *C*-terminal unprotected compound, 1.0 equiv of the hydrochloride, 1.1 equiv HOBt, and 1.1 equiv EDAC were dissolved in DCM. Finally, 1.1 equiv TEA were added and the resulting reaction mixture was stirred at r.t.. The organic layer was diluted with EtOAc, washed three times with citric acid (0.5 M), three times with sat. $NaHCO_3$, and dried over either $MgSO_4$ or Na_2SO_4. Finally, the solvent was removed under reduced pressure and co-evaporated afterwards several times with DCM.

For Boc-PMH-OH 2.0 equiv of EDAC, HOBt, and TEA were utilized.

Removal of the Bzl-/Cbz-/(2-Cl-Cbz)-PG (GP-7):

1.0 equiv of the protected compound was dissolved. After adding catalytic amounts of Pd/C the resulting suspension was stirred at r.t. under a hydrogen atmosphere. After 24 h the reaction mixture was filtered over Celite® and the deprotected product was used directly either for catalytic test reactions or further coupling steps after evaporation of the solvent.

Removal of the Boc-PG (GP-8):

0.500 mmol of the Boc-protected compound were dissolved in 1.00 mL of HCl in 1,4-dioxane (4 M). The vessel was closed with a septum and the generated gas was purged periodically.

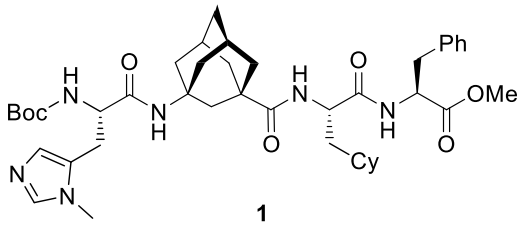
After 1 h remaining HCl was removed in an Ar flow. Finally, the solvent was removed under reduced pressure and co-evaporated afterwards several times with DCM.

Those procedures were repeated until the desired oligopeptide was synthesized. The target compound was purified *via* column chromatography or HPLC.

Removal of the methylester (GP-9):

The methylester derivative was dissolved in DMF and $NaOH_{aq}$ (15%) was added. The resulting reaction mixture was stirred at r.t. for 24 h. Diluted HCl was added to obtain pH 5. The aq layer was extracted with EtOAc. After drying over Na_2SO_4 the solvent was removed under reduced pressure. Remaining DMF was removed under high vacuum.

Boc-PMH-AdGly-Cha-Phe-OMe 1:



1

The synthesis of ClH_3N-Phe-OMe **130** was performed with 2.07 g (7.80 mmol, 1.0 equiv) Boc-Phe-OH **94**, 1.80 mL (2.95 g, 24.8 mmol, 3.2 equiv) $SOCl_2$, and 20 mL MeOH utilizing GP-5. 1.69 g (7.84 mmol, quant.) hydrochloride **130** were obtained as colorless solid.

MS (ESI): m/z: 180.0 $[M + H]^+$ (cal. 180.1).

The synthesis of Boc-Cha-Phe-OMe was performed with 0.610 g (2.83 mmol, 1.0 equiv) hydrochloride **130**, 1.28 g (2.83 mmol, 1.0 equiv) Boc-Cha-OH•DCHA, 0.605 g (3.16 mmol, 1.1 equiv) EDAC, 0.434 g (3.21 mmol, 1.1 equiv) HOBt, 0.432 mL (0.315 g, 3.11 mmol, 1.1 equiv) TEA, and 30 mL DCM utilizing GP-6. After 21 h the reaction mixture was diluted with 300 mL EtOAc. For washing a volume of 25 mL was used. The organic layer was washed additionally with 25 mL brine. 1.18 g (2.73 mmol, 96%) dipeptide were obtained as colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.25–7.13 (m, 3 H and $CHCl_3$); 7.07–7.01 (m, 2 H); 6.48–6.40 (m, 1 H); 4.82–4.71 (m, 2 H); 4.10–4.00 (m, 1 H); 3.64 (s, 3 H); 3.08 (dd, 1 H, ^2J = 13.8 Hz, ^3J = 5.9 Hz); 3.01 (dd, 1 H, ^2J = 13.8 Hz, ^3J = 5.9 Hz); 1.70–1.50 (m, 7 H); 1.37 (s, 9 H); 1.27–1.01 (m, 4 H); 0.94–0.74 (m, 2 H) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 172.4; 171.8; 155.6; 135.9; 129.4; 128.7; 127.2; 80.2; 53.3; 52.6; 52.4; 40.0; 38.1; 34.1; 33.7; 32.7; 28.4; 26.5; 26.3; 26.1 ppm.

MS (ESI): m/z: 455.2 $[M + Na]^+$ (cal. 455.3); 887.1 $[2M + Na]^+$ (cal. 887.5).

The synthesis of ClH_3N-Cha-Phe-OMe was performed with 1.16 g (2.68 mmol, 1.0 equiv) Boc-Cha-Phe-OH and 6.00 mL HCl in 1,4-dioxane (4 M) utilizing GP-8. 1.11 g (3.00 mmol, quant.)[9] hydrochloride were obtained as colorless solid.

MS (ESI): m/z: 333.1 $[M + H]^+$ (cal. 333.2); 355.2 $[M + Na]^+$ (cal. 355.2); 687.1 $[2M + Na]^+$ (cal. 687.4).

The synthesis of Boc-AdGly-Cha-Phe-OMe was performed with 0.989 g (2.68 mmol, 1.0 equiv) hydrochloride, 0.793 g (2.68 mmol, 1.0 equiv) Boc-AdGly-OH, 0.576 g (3.00 mmol, 1.1 equiv) EDAC, 0.412 g (3.05 mmol, 1.1 equiv) HOBt, 0.409 mL (0.298 g, 2.95 mmol, 1.1 equiv) TEA, and 30 mL DCM utilizing GP-6. After 18 h the reaction mixture was diluted with 200 mL EtOAc. For washing a volume of 25 mL was used. The organic layer was washed additionally with 25 mL brine. 1.82 g (2.98 mmol, quant.)[9] tripeptide were obtained as slightly yellowish solid.

MS (ESI): m/z: 610.2 $[M + H]^+$ (cal. 610.4); 632.4 $[M + Na]^+$ (cal. 632.4); 1241.4 $[2M + Na]^+$ (cal. 1241.7).

The synthesis of ClH_3N-AdGly-Cha-Phe-OMe was performed with 1.57 g (2.57 mmol, 1.0 equiv) Boc-Cha-Phe-OH and 5.80 mL HCl in 1,4-dioxane (4 M) utilizing GP-8. 1.80 g (3.30 mmol, quant.)[9] hydrochloride were obtained as slightly yellowish solid.

MS (ESI): m/z: 510.2 $[M + H]^+$ (cal. 510.3); 1019.5 $[2M + H]^+$ (cal. 1019.7) ; 1041.3 $[2M + Na]^+$ (cal. 1041.6).

The synthesis of Boc-PMH-AdGly-Cha-Phe-OMe **1** was performed with 0.411 g (2.58 mmol, 1.0 equiv) hydrochloride, 0.695 g Boc-PMH-OH (2.58 mmol, 1.0 equiv), 0.999 g (5.21 mmol, 2.0 equiv) EDAC, 0.706 g (5.22 mmol, 2.0 equiv) HOBt, 0.717 mL (0.523 g, 5.17 mmol, 2.0 equiv) TEA, and 30 mL DCM utilizing GP-6. After 21 h the reaction mixture was diluted with 200 mL EtOAc. For washing a volume of 25 mL was used. The organic layer was washed additionally with 25 mL brine. Afterwards the aq layer was extracted with 100 mL EtOAc. 0.699 g (0.919 mmol, 36%) tetrapeptide **1** were obtained as slightly brownish solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.57–7.52 (m, 1 H); 7.31–7.21 (m, 3 H and $CHCl_3$); 7.11–7.09 (m, 2 H); 6.86 (s, 1 H); 6.54 (d, 1 H, ^3J = 7.7 Hz); 6.02 (d, 1 H, ^3J = 7.9 Hz); 5.95 (s, 1 H); 5.24 (d, 1 H, ^3J = 8.3 Hz); 4.82–4.77 (m, 1 H); 4.46–4.40 (m, 1 H); 4.25–4.14 (m, 1 H); 3.70 (s, 3 H); 3.62 (s, 3 H); 3.15–3.04 (m, 2 H); 3.00–2.98 (m, 2 H); 2.19 (bs, 2 H); 1.99–1.87 (m, 6

[9] Contains traces of solvent.

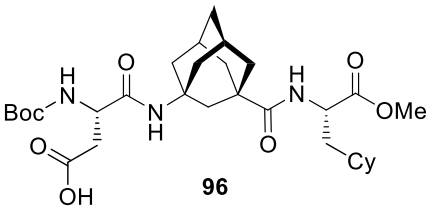
H); 1.72–1.60 (m, 13 H); 1.52–1.46 (m, 1 H); 1.43 (s, 9 H); 1.27–1.07 (m, 4 H); 0.99–0.76 (m, 1 H) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 176.5; 172.0; 171.8; 169.7; 155.5; 138.1; 135.9; 129.4; 128.8; 127.7; 127.5; 127.4; 127.3; 80.7; 53.4; 52.52; 52.48; 50.8; 42.7; 42.3; 40.5; 40.4; 39.6; 38.3; 38.2; 38.0; 35.3; 34.3, 33.6; 32.8; 31.9; 29.22; 29.19; 28.4; 27.1; 26.5; 26.3; 26.2 ppm.

MS (ESI): m/z: 761.5 $[M + H]^+$ (cal. 761.5), 783.5 $[M + Na]^+$ (cal. 783.4); 1521.3 $[2M + H]^+$ (cal. 1521.9); 1543.2 $[2M + Na]^+$ (cal. 1543.9).

For tetrapeptide **1** the analytic data are identical to those reported in literature.[2a]

Boc-Asp(OH)-AdGly-Cha-OMe 96:



96

The synthesis of Boc-AdGly-Cha-OMe **98** was performed with 1.33 g (6.00 mmol, 1.0 equiv) ClH_3N-Cha-OMe **97**, 1.78 g (6.03 mmol, 1.0 equiv) Boc-AdGly-OH, 1.27 g (6.62 mmol, 1.1 equiv) EDAC, 0.890 g (6.59 mmol, 1.1 equiv) HOBt, 0.920 mL (0.671 g, 6.63 mmol, 1.1 equiv) TEA, and 30 mL DCM utilizing GP-6. After 24 h the reaction mixture was diluted with 200 mL EtOAc. For washing a volume of 25 mL was used. 2.63 g (5.68 mmol, 95%) dipeptide **98** were obtained as yellowish solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.93 (d, 1 H, ^{3}J = 8.1 Hz); 4.64 (td, 1 H, ^{3}J = 8.7 Hz, ^{3}J = 5.5 Hz); 4.43 (bs, 1 H); 3.71 (s, 3 H); 2.24–2.18 (m, 2 H); 1.96–1.86 (m, 5 H); 1.80–1.75 (m, 6 H); 1.70–1.61 (m, 9 H); 1.54–1.47 (m, 1 H); 1.42 (s, 9 H); 1.20–1.11 (m, 2 H); 0.98–0.84 (m, 2 H) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 176.3; 173.8; 52.2; 50.8; 49.8; 42.9; 42.6; 40.9; 40.1; 38.2; 35.3; 34.3; 33.4; 32.6; 29.2; 28.4; 26.3; 26.1; 26.0; 14.2 ppm.

The synthesis of ClH_3N-AdGly-Cha-OMe was performed with 2.63 g (5.68 mmol, 1.0 equiv) Boc-AdGly-Cha-OMe **98** and 11.5 mL HCl in 1,4-dioxane (4 M) utilizing GP-8. The crude product was obtained as yellowish solid and used directly without further purification.

The synthesis of Boc-Asp(OBzl)-AdGly-Cha-OMe **99** was performed with the crude product of the hydrochloride, 1.83 g (5.66 mmol, 1.0 equiv) Boc-Asp(OBzl)-OH, 1.20 g (6.26 mmol, 1.1 equiv) EDAC, 0.850 g (6.29 mmol, 1.1 equiv) HOBt, 0.870 mL (0.634 g, 6.27 mmol, 1.1 equiv) TEA, and 30 mL DCM utilizing GP-6. After 24 h the reaction mixture was diluted with 200 mL EtOAc. For washing a volume of 25 mL was used. After purification *via* column

chromatography (DCM:MeOH 30:1) 2.90 g (4.34 mmol, 77%) tripeptide **99** were isolated as colorless solid.

R_f: 0.40 (DCM:MeOH 30:1).

MS (ESI): m/z: 568.3 $[M - Boc + H]^+$ (cal. 568.3); 690.3 $[M + Na]^+$ (cal. 690.4); 1357.0 $[2M + Na]^+$ (cal. 1357.8).

The synthesis of carboxylic acid-containing tripeptide **96** was performed with 0.207 g (0.310 mmol, 1.0 equiv) Bzl-protected compound **99**, 0.066 g (0.007 mmol, 20 mol%) Pd/C (10%), and 25 mL ^{t}BuOH. 0.170 g (0.294 mmol, 95%) tripeptides **96** were obtained as colorless solid. (GP-7)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.49 (bs, 1 H); 6.16 (d, 1 H, *J* = 8.0 Hz); 5.74 (d, 1 H, *J* = 7.1 Hz); 4.63 (td, 1 H, *J* = 8.6 Hz, *J* = 5.5 Hz); 4.40 (bs, 1 H); 3.72 (s, 3 H); 2.94 (dd, 1 H, *J* = 17.0 Hz, *J* = 3.9 Hz); 2.67 (dd, 1 H, *J* = 16.5 Hz, *J* = 6.4 Hz); 2.26–2.19 (m, 2 H); 2.13–2.06 (m, 2 H); 2.06–1.89 (m, 5 H); 1.88–1.74 (m, 5 H); 1.73–1.58 (m, 8 H); 1.55–1.48 (m, 2 H); 1.45 (s, 9 H); 1.25–1.09 (m, 2 H); 1.00–0.80 (m, 1 H) ppm.

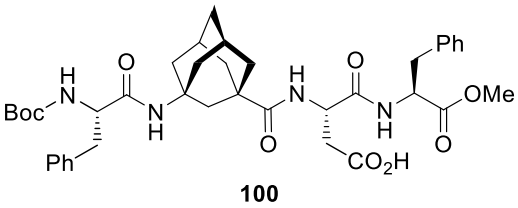
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 179.0; 176.9; 174.0; 170.5; 155.9; 69.6; 52.51; 52.48; 50.1; 42.7; 42.2; 40.5; 40.3; 40.1; 38.28; 38.25; 36.4; 35.3; 34.4; 33.6; 32.7; 31.3; 29.3; 28.4; 26.5; 26.3; 26.2 ppm.

IR (KBr): $\tilde{\nu}$ = 3367 (s); 2922 (vs); 2853 (s); 1659 (vs); 1525 (s); 1450 (m); 1367 (m); 1252 (w); 1169 (m); 1051 (vw); 1025 (vw); 620 (vw) cm^{-1}.

HR-MS (ESI): m/z: 600.3261 $[M + Na]^+$ (cal. 600.3255).

MS (ESI): m/z: 600.3 $[M + Na]^+$ (cal. 600.3); 1177.2 $[2M + Na]^+$ (cal. 1177.7).

Boc-Phe-AdGly-Asp(OH)-Phe-OMe 100:



100

The synthesis of Boc-Asp(OBzl)-Phe-OMe was performed with 0.647 g (3.01 mmol, 1.0 equiv) ClH_3N-Phe-OMe **130**, 0.970 g (3.00 mmol, 1.0 equiv) Boc-Asp(OBzl)-OH, 0.633 g (3.30 mmol, 1.1 equiv) EDAC, 0.509 g (3.76 mmol, 1.3 equiv) HOBt, 0.460 mL (0.335 g, 3.31 mmol, 1.1 equiv) TEA, and 30 mL DCM utilizing GP-6. After 24 h the reaction mixture was diluted with 200 mL EtOAc. For washing a volume of 25 mL was used. 1.31 g (2.71 mmol, 90%) dipeptide were obtained as yellowish oil.

MS (ESI): m/z: 507.1 $[M + Na]^+$ (cal. 507.2).

The synthesis of ClH_3N-Asp(OBzl)-Phe-OMe was performed with 1.31 g (2.71 mmol, 1.0 equiv) Boc-Asp(OBzl)-Phe-OMe and 6.00 mL HCl in 1,4-dioxane (4 M) utilizing GP-8. The crude product was obtained as colorless solid and used directly without further purification. The synthesis of Boc-AdGly-Asp(OBzl)-Phe-OMe was performed with the crude product of the hydrochloride, 0.796 g (2.69 mmol, 1.0 equiv) Boc-AdGly-OH, 0.568 g (2.96 mmol, 1.1 equiv) EDAC, 0.456 g (3.37 mmol, 1.3 equiv) HOBt, 0.413 mL (0.301 g, 2.98 mmol, 1.1 equiv) TEA, and 30 mL DCM utilizing GP-6. After 24 h the reaction mixture was diluted with 200 mL EtOAc. For washing a volume of 25 mL was used. 1.64 g (2.48 mmol, 92%) tripeptide were obtained as yellowish solid.

MS (ESI): m/z: 684.3 $[M + Na]^+$ (cal. 684.3).

The synthesis of ClH_3N-AdGly-Asp(OBzl)-Phe-OMe was performed with 1.64 g (2.48 mmol, 1.0 equiv) Boc-AdGly-Asp(OBzl)-Phe-OMe and 6.00 mL HCl in 1,4-dioxane (4 M) utilizing GP-8. The crude product was obtained as colorless solid and used directly without further purification. The synthesis of Boc-Phe-AdGly-Asp(OBzl)-Phe-OMe was performed with the crude product of the hydrochloride, 0.657 g (2.48 mmol, 1.0 equiv) Boc-Phe-OH **94**, 0.522 g (2.72 mmol, 1.1 equiv) EDAC, 0.420 g (3.11 mmol, 1.3 equiv) HOBt, 0.380 mL (0.277 g, 2.74 mmol, 1.1 equiv) TEA, and 30 mL DCM utilizing GP-6. After 24 h the reaction mixture was diluted with 200 mL EtOAc. For washing a volume of 25 mL was used. After purification *via* column chromatography (DCM:MeOH 40:1) 1.28 g (1.58 mmol, 64%) tetrapeptide were isolated as colorless solid.

MS (ESI): m/z: 831.4 $[M + Na]^+$ (cal. 831.4); 1639.0 $[2M + Na]^+$ (cal. 1639.8).

The synthesis of carboxylic acid-containing tetrapeptide **100** was performed with 1.27 g (1.57 mmol, 1.0 equiv) Bzl-protected tetrapeptide, 0.336 g (0.316 mmol, 20 mol%) Pd/C (10%), and 25 mL ^{t}BuOH. 0.935 g (1.30 mmol, 83%) tetrapeptide **100** were obtained as colorless solid.

R_f: 0.23 (DCM:MeOH 20:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.28–7.10 (m, 10 H and $CHCl_3$); 7.07–7.03 (m, 2 H); 7.00 (d, 1 H, ^3J = 7.4 Hz); 5.55 (bs, 1 H); 4.76–4.68 (m, 2 H); 4.18–4.07 (m, 1 H); 3.60 (s, 3 H); 3.06 (dd, 1 H, ^2J = 13.9 Hz, ^3J = 5.6 Hz); 3.00–2.85 (m, 4 H); 2.61 (dd, 1 H, ^2J = 17.0 Hz, ^3J = 6.1 Hz); 2.10–2.02 (m, 2 H); 1.84–1.67 (m, 6 H); 1.62–1.46 (m, 6 H); 1.33 (s, 9 H) ppm.

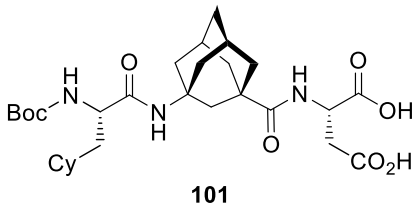
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 177.1; 174.3; 171.7; 170.7; 155.7; 137.0; 135.9; 129.6; 129.4; 128.8; 128.7; 127.2; 127.1; 80.4; 56.6; 53.7; 53.6; 52.5; 52.4; 49.2; 42.6; 42.0; 40.2; 39.0; 37.9; 37.7; 35.6; 35.1; 31.3; 29.11; 29.09; 28.4 ppm.

IR (KBr): $\tilde{\nu}$ = 3329 (m); 3063 (m); 2914 (m); 2853 (s); 1664 (s); 1522 (s); 1455 (m); 1367 (m); 1250 (m); 1170 (s); 1050 (vw); 1022 (vw); 744 (w); 701 (m); 590 (vw); 534 (vw) cm^{-1}.

HR-MS (ESI): m/z: 741.3475 $[M + Na]^+$ (cal. 741.3470).

MS (ESI): m/z: 641.3 $[M – Boc + Na]^+$ (cal. 641.3); 717.2 $[M – H]^–$ (cal. 717.4); 741.3 $[M + Na]^+$ (cal. 741.3).

Boc-Cha-AdGly-Asp(OH)-OH 101:



101

The synthesis of ClH_3N-Asp(OMe)-OMe was performed with 1.34 g (6.00 mmol, 1.0 equiv) H-Asp(OBzl)-OH, 1.50 mL (2.46 g, 20.7 mmol, 3.4 equiv) $SOCl_2$, and 15 mL MeOH utilizing GP-5. After adding $SOCl_2$ to methanol the amino acid was added portionwise. The reaction mixture was stirred for 48 h. After evaporation of the solvent the crude product was used directly without purification. The synthesis of Boc-AdGly-Asp(OMe)-OMe was performed with the crude product of the hydrochloride, 1.77 g (5.99 mmol, 1.0 equiv) Boc-AdGly-OH, 1.27 g (6.62 mmol, 1.1 equiv) EDAC, 1.02 g (7.54 mmol, 1.3 equiv) HOBt, 0.920 mL (0.671 g, 6.63 mmol, 1.1 equiv) TEA, and 30 mL DCM utilizing GP-6. After 24 h the reaction mixture was diluted with 200 mL EtOAc. For washing a volume of 25 mL was used. 2.66 g (6.07 mmol, quant. over two steps) dipeptide were obtained as yellowish solid.

MS (ESI): m/z: 439.0 $[M + H]^+$ (cal. 439.2); 461.1 $[M + Na]^+$ (cal. 461.2).

The synthesis of ClH_3N-AdGly-Asp(OMe)-OMe was performed with 2.63 g (5.99 mmol, 1.0 equiv) Boc-AdGly-Asp(OMe)-OMe and 12 mL HCl in 1,4-dioxane (4 M) utilizing GP-8. The crude product was obtained as colorless solid and used directly without further purification. The synthesis of Boc-Cha-AdGly-Asp(OMe)-OMe was performed with the crude product of the hydrochloride, 2.71 g (5.99 mmol, 1.0 equiv) Boc-Cha-OH•DCHA, 1.27 g (6.62 mmol, 1.1 equiv) EDAC, 1.01 g (7.47 mmol, 1.2 equiv) HOBt, 0.920 mL (0.671 g, 6.63 mmol, 1.1 equiv) TEA, and 30 mL DCM utilizing GP-6. After 24 h the reaction mixture was diluted with 200 mL EtOAc. For washing a volume of 25 mL was used. 3.14 g (5.31 mmol, 89%) tripeptide were obtained as colorless solid.

MS (ESI): m/z: 614.3 $[M + Na]^+$ (cal. 614.3); 1205.0 $[2M + Na]^+$ (cal. 1205.7).

The synthesis of carboxylic acid-containing tripeptide **101** was performed with 2.89 g (4.88 mmol, 1.0 equiv) of the dimethylester, 55 mL $NaOH_{aq}$ (15%), and 80 mL DMF (GP-9). For extraction EtOAc (three times 150 mL) was used. After purification *via* column

chromatography (DCM:MeOH 30:1 to 10:1) 2.17 g (3.85 mmol, 79%) tetrapeptide **101** were isolated as colorless solid.

R_f: 0.41 (DCM:MeOH 10:1).

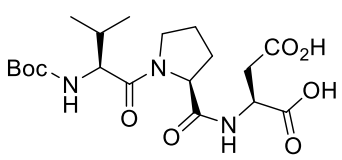
^{1}H-NMR and **^{13}C-NMR** not meaningful.

IR (KBr): $\tilde{\nu}$ = 3337 (m); 2922 (vs); 2853 (s); 1651 (s); 1519 (s); 1449 (m); 1366 (m); 1249 (w); 1169 (m); 1046 (vw); 1022 (vw); 575 (vw) cm^{-1}.

HR-MS (ESI): m/z: 586.3097 $[M + Na]^+$ (cal. 586.3099).

MS (ESI): m/z: 462.2 $[M – Boc – H]^–$ (cal. 462.3); 486.3 $[M – Boc + Na]^+$ (cal. 486.3); 562.2 $[M – H]^–$ (cal. 562.3); 586.2 $[M + Na]^+$ (cal. 586.3); 1149.1 $[2M + Na]^+$ (cal. 1149.6).

Boc-Val-Pro-Asp(OH)-OH 102:



102

The synthesis of Boc-Asp(OBzl)-OBzl was performed with 1.94 g (6.00 mmol, 1.0 equiv) Boc-Asp(OBzl)-OH, 0.624 mL (0.671 g, 6.62 mmol, 1.0 equiv) BnOH, 1.26 g (6.57 mmol, 1.1 equiv) EDAC, 0.890 g (6.59 mmol, 1.1 equiv) HOBt, 0.915 mL (0.667 g, 6.59 mmol, 1.1 equiv) TEA, and 30 mL DCM utilizing GP-6. After 24 h the reaction mixture was diluted with 300 mL EtOAc. For washing a volume of 25 mL was used. 1.54 g (3.72 mmol, 62%) completely protected amino acid were obtained as yellowish oil.

MS (ESI): m/z: 436.1 $[M + Na]^+$ (cal. 436.2).

The synthesis of ClH_3N-Asp(OBzl)-OBzl was performed with 1.49 g (3.60 mmol, 1.0 equiv) Boc-Asp(OBzl)-OBzl and 5 mL HCl in 1,4-dioxane (4 M) utilizing GP-8. The crude product was obtained as slightly yellowish solid and used without further purification. The synthesis of Boc-Pro-Asp(OBzl)-OBzl was performed with the crude product of the hydrochloride, 0.960 g (4.37 mmol, 1.2 equiv) Boc-Pro-OH, 0.940 g (4.90 mmol, 1.4 equiv) EDAC, 0.650 g (4.81 mmol, 1.3 equiv) HOBt, 0.677 mL (0.494 g, 4.88 mmol, 1.4 equiv) TEA, and 30 mL DCM utilizing GP-6. After 22 h the reaction mixture was diluted with 300 mL EtOAc. For washing a volume of 25 mL was used. 1.15 g (2.25 mmol, 63%) dipeptide were obtained as yellowish oil.

MS (ESI): m/z: 533.1 $[M + Na]^+$ (cal. 533.2); 549.0 $[M + K]^+$ (cal. 549.2).

The synthesis of ClH_3N-Pro-Asp(OBzl)-OBzl was performed with 1.15 g (2.25 mmol, 1.0 equiv) Boc-Pro-Asp(OBzl)-OBzl and 4.5 mL HCl in 1,4-dioxane (4 M) utilizing GP-8. The crude product was obtained as yellowish solid and used without further purification. The synthesis of Boc-Val-Pro-Asp(OBzl)-OBzl was performed with the crude product of the

hydrochloride, 0.490 g (2.26 mmol, 1.0 equiv) Boc-Val-OH, 0.470 g (2.45 mmol, 1.1 equiv) EDAC, 0.330 g (2.44 mmol, 1.1 equiv) HOBt, 0.341 mL (0.249 g, 2.46 mmol, 1.1 equiv) TEA, and 30 mL DCM utilizing GP-6. After 15 h the reaction mixture was diluted with 300 mL EtOAc. For washing a volume of 25 mL was used. 1.27 g (2.08 mmol, 92%) tripeptide were obtained as yellowish oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.40–7.27 (m, 10 H); 5.17 (d, 1 H, ^{3}J = 9.4 Hz); 5.11 (s, 2 H); 5.06 (s, 2 H); 4.86 (dt, 1 H, ^{3}J = 9.0 Hz, ^{3}J = 4.7 Hz); 4.54–4.52 (m, 1 H); 4.25 (dd, 1 H, ^{3}J = 9.3 Hz, ^{3}J = 6.0 Hz); 4.54–4.52 (m, 1 H); 3.70–3.64 (m, 1 H); 3.53–3.48 (m, 1 H); 3.05 (dd, 1 H, ^{2}J = 17.2 Hz, ^{3}J = 4.7 Hz); 2.85 (dd, 1 H, ^{2}J = 17.2 Hz, ^{3}J = 4.8 Hz); 2.25–2.18 (m, 1 H); 2.00–1.85 (m, 4 H); 1.43 (s, 9 H); 0.95 (d, 3 H, ^{3}J = 6.8 Hz); 0.86 (d, 3 H, ^{3}J = 6.7 Hz) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 172.4; 171.2; 170.7; 170.4; 156.0; 135.5; 135.3; 128.72; 128.69; 128.56; 128.55; 128.49; 79.7; 67.6; 67.0; 60.0; 56.9; 48.8; 47.6; 36.4; 31.5; 28.5; 27.7; 25.2; 19.6; 17.4; 14.4 ppm.

MS (ESI): m/z: 632.2 $[M + Na]^+$ (cal. 632.3).

The synthesis of carboxylic acid-containing tripeptide **102** was performed with 1.27 g (2.08 mmol, 1.0 equiv) of the Bzl-protected compound, 0.320 g (0.301 mmol, 14 mol%) Pd/C (10%), and 17.0 mL ^{t}BuOH (GP-7). The reaction mixture was stirred for 90 h. 0.780 g (1.82 mmol, 88%) tripeptide **102** were obtained as colorless solid.

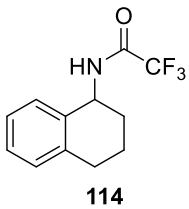
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.69 (d, 1 H, ^{3}J = 8.3 Hz); 7.43 (bs, 2 H); 5.64 (d, 1 H, ^{3}J = 9.2 Hz); 4.88–4.72 (m, 1 H); 4.70–4.53 (m, 1 H); 4.28–4.20 (m, 1 H); 3.89–3.56 (m, 2 H); 3.12–2.96 (m, 1 H); 2.90–2.67 (m, 1 H); 2.27–1.82 (m, 5 H); 1.41 (s, 9 H); 0.97–0.88 (m, 6 H) ppm.

^{13}C-NMR (151 MHz, $CDCl_3$): δ = 174.5; 174.1; 173.1; 171.6; 156.2; 79.9; 60.4; 57.4; 48.6; 48.2; 36.2; 31.2; 28.5; 25.2; 19.4; 17.9 ppm.

HR-MS (ESI): m/z: 452.2026 $[M + Na]^+$ (cal. 452.2003).

MS (ESI): m/z: 452.1 $[M + Na]^+$ (cal. 452.2).

2,2,2-Trifluoro-1-(1,2,3,4-tetrahydronaphth-1-ylamino)-1-ethanone 114:



114

The synthesis of amide **114** was performed with 0.146 mL (0.150 g, 1.02 mmol, 1.0 equiv) amine **113**, 1.70 mg (0.014 mmol, 1 mol%) DMAP, 0.150 mL (0.230 g, 2.02 mmol, 2.0 equiv) TFA **111**, 0.383 g (2.00 mmol, 2.0 equiv) EDAC, 0.279 mL (0.203 g, 2.00 mmol, 2.0 equiv) TEA, and 6 mL DCM. After stirring for 24 h at r.t. the reaction was quenched with sat. $NaHCO_3$. The aq layer was extracted with DCM (three times 10 mL). After drying over

Na_2SO_4 the solvent was evaporated under reduced pressure. After purification *via* column chromatography (*n*-hexane:EtOAc 7:1 to 0:1) 0.148 g (0.599 mmol, 59%) **114** were isolated as slightly yellowish solid.

R_f: 0.33 (*n*-hexane:EtOAc 5:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.25–7.19 (m, 3 H, H_{Ar}); 7.15–7.13 (m, 1 H, H_{Ar}); 6.51 (bs, 1 H, N*H*); 5.23–5.18 (m, 1 H, NHC*H*); 2.90–2.74 (m, 2 H, $CHCH_2CH_2CH_2$); 2.15–2.06 (m, 1 H, $CHCH_2$); 1.95–1.79 (m, 3 H, $CHCH_2CH_2$ and $CHCH_2$) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 159.6 (q, $^2J_{CF}$ = 36.9 Hz, *C*OCF_3); 137.9 (quart., C_{Ar}); 134.5 (quart., C_{Ar}); 129.7 (C_{Ar}); 128.7 (C_{Ar}); 128.2 (C_{Ar}); 126.8 (C_{Ar}); 116.0 (q, $^1J_{CF}$ = 288.2 Hz, *C*F_3); 48.5 (*C*H); 29.6 ($CHCH_2$); 29.1 ($CHCH_2CH_2CH_2$); 19.8 ($CHCH_2CH_2$) ppm.

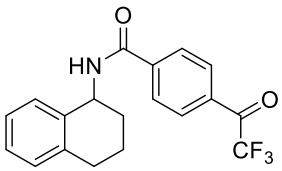
^{19}F-NMR (376 MHz, $CDCl_3$): δ = –75.8 ppm.

IR (KBr): $\tilde{\nu}$ = 3283 (m); 2944 (w); 2090 (vw); 1697 (s); 1183 (s); 746 (m) ; 700 (w) cm^{-1}.

HR-MS (ESI): m/z: 266.0755 $[M + Na]^+$ (cal. 266.0763).

MS (ESI): m/z: 266.0 $[M + Na]^+$ (cal. 266.1).

2,2,2-Trifluoro-1-(*p*-((1,2,3,4-tetrahydronaphth-1-ylamino)carbonyl)phenyl)-1-ethanone 115:



115

The synthesis of amide **115** was performed with 0.220 g (1.01 mmol, 1.0 equiv) acid ***para*-112**, 0.146 mL (0.150 g, 1.02 mmol, 1.0 equiv) amine **113**, 2.88 mg (0.024 mmol, 2 mol%) DMAP, 0.385 g (2.00 mmol, 2.0 equiv) EDAC, 0.279 mL (0.203 g, 2.00 mmol, 2.0 equiv) TEA, and 6 mL DCM. After stirring for 23 h at r.t. the reaction was quenched with sat. $NaHCO_3$. The aq layer was extracted with DCM (three times 10 mL). After drying over Na_2SO_4 the solvent was evaporated under reduced pressure. After purification *via* column chromatography (*n*-hexane:EtOAc 7:1 to 1:5) 0.148 g (0.426 mmol, 42%) **115** were isolated as slightly yellowish solid.

R_f: 0.73 (*n*-hexane:EtOAc 1:5).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.07 (m, 2 H, C*H*C$COCF_3$); 7.90 (m, 2 H, NHCOCC*H*); 7.30–7.27 (m, 1 H, H_{Ar}); 7.22–7.15 (m, 2 H, H_{Ar}); 7.12–7.10 (m, 1 H, H_{Ar}); 6.77 (bs, 1 H, N*H*); 5.34 (dd, 1 H, ^3J = 13.1 Hz, ^3J = 6.2 Hz, NHC*H*); 2.85–2.77 (m, 2 H, $CHCH_2CH_2CH_2$); 2.16–2.09 (m, 1 H, $CHCH_2$); 1.97–1.84 (m, 3 H, $CHCH_2CH_2$ and $CHCH_2$) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 180.1 (q, $^2J_{CF}$ = 35.7 Hz, *C*OCF_3); 165.3 (*C*O); 140.8 (quart., C_{Ar}); 137.8 (quart., C_{Ar}); 136.1 (quart., C_{Ar}); 131.9 (quart., C_{Ar}); 130.4 (2 C, C_{Ar}); 129.5 (C_{Ar});

128.7 (C_{Ar}); 127.8 (2 C, C_{Ar}); 127.7 (C_{Ar}); 126.5 (C_{Ar}); 116.5 (q, $^{1}J_{CF}$ = 291.2 Hz, CF_3); 48.5 (*C*H); 30.1 (CH*C*H$_2$); 29.3 (CHCH$_2$CH$_2$*C*H$_2$); 20.1 (CHCH$_2$*C*H$_2$) ppm.

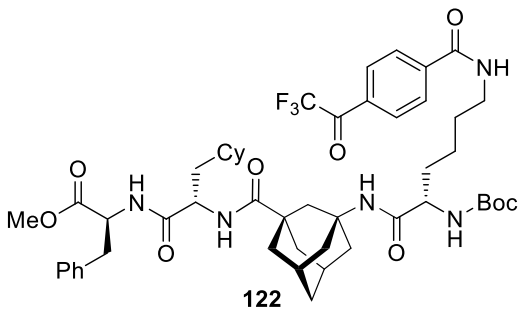
^{19}F-NMR (376 MHz, $CDCl_3$): δ = –71.6 ppm.

IR (KBr): $\tilde{\nu}$ = 3296 (vs); 2933 (m); 1941 (vw); 1723 (s); 1628 (vs); 1536 (vs); 1147 (vs); 1057 (s); 754 (s); 563 (s) cm^{-1}.

HR-MS (ESI): m/z: 402.1296 [M + MeOH + Na]$^+$ (cal. 402.1287); 781.2692 [2M + MeOH + Na]$^+$ (cal. 781.2683).

MS (ESI): m/z: 402.3 [M + MeOH + Na]$^+$ (cal. 402.1); 780.9 [2M + 2MeOH + Na]$^+$ (cal. 781.3) and 416.1 [M + EtOH + Na]$^+$ (cal. 416.1); 808.9 [2M + 2EtOH + Na]$^+$ (cal. 809.3), respectively.

Boc-Lys(CM)-AdGly-Cha-Phe-OMe 122:



122

The synthesis of amine **121** was performed with 0.089 g (0.098 mmol, 1.0 equiv) (2-Cl-Cbz)-protected compound **120**, 23.3 mg (0.022 mmol, 22 mol%) Pd/C (10%), and 3 mL MeOH (GP-7). The reaction mixture was stirred for 17 h. 0.071 g (0.096 mmol, 98%) free amine **121** were obtained as colorless solid.

MS (ESI): m/z: 638.5 [M – Boc + H]$^+$ (cal. 638.4); 738.4 [M + H]$^+$ (cal. 738.5).

The synthesis of Boc-Lys(CM)-AdGly-Cha-Phe-OMe **122** was performed with 0.071 g (0.096 mmol, 1.0 equiv) amine **121**, 27.3 mg (0.125 mmol, 1.3 equiv) acid ***para*-112**, 2.00 mg (0.016 mmol, 17 mol%) DMAP, 0.040 g (0.209 mmol, 2.2 equiv) EDAC, 28.8 µL (21.0 mg, 0.207 mmol, 2.2 equiv) TEA, and 3 mL DCM utilizing GP-3. After 24 h the reaction was quenched with $NaHCO_3$ and the organic layer was extracted with DCM (three times). After purification *via* column chromatography (EtOAc) 0.059 g (0.063 mmol, 65%) **122** were isolated as colorless solid.

R_f: 0.50 (EtOAc).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, 2 H, ^{3}J = 8.0 Hz); 8.00–7.97 (m, 2 H); 7.29–7.20 (m, 5 H + $CHCl_3$); 7.10–7.08 (m, 2 H); 6.84 (bs, 1 H); 6.50 (bs, 1 H); 6.03–5.99 (m, 2 H); 5.17–5.08 (m, 1 H); 4.81–4.76 (m, 1 H); 4.46–4.40 (m, 1 H); 4.02–3.91 (m, 1 H); 3.70 (s, 3 H); 3.56–3.43 (m, 2 H); 3.14–3.03 (m, 2 H); 2.22–2.15 (m, 2 H); 2.06–2.01 (m, 1 H + EtOAc); 1.98–1.93 (m, 4 H); 1.87–1.77 (m, 2 H); 1.75–1.71 (m, 4 H); 1.70–1.59 (m, 13 H); 1.41 (s, 9 H); 1.20–1.07 (m, 3 H); 0.95–0.79 (m, 2 H) ppm.

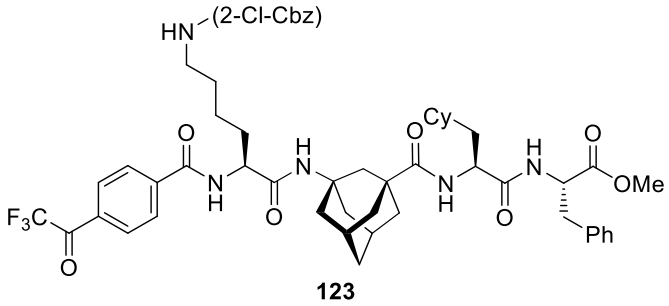
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 180.2 (*C*OCF_3); 176.6; 172.0; 171.7; 171.4; 166.2; 156.1; 140.8; 135.8; 131.9; 130.4; 129.4; 128.8; 128.0; 127.3; 116.6 (*C*F_3); 80.4; 53.4; 52.5; 52.4; 50.8; 42.7; 42.5; 40.6; 40.5; 39.63; 39.57; 38.3; 38.2; 37.9; 35.3; 34.3; 33.6; 32.9; 31.7; 29.2; 28.7; 28.4; 26.5; 26.3; 26.2; 22.7 ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = –71.6 ppm.

HR-MS (ESI): m/z: 992.4972 $[M + MeOH + Na]^+$ (cal. 992.4967).

MS (ESI): m/z: 892.4 $[M – Boc + MeOH + Na]^+$ (cal. 892.4); 992.3 $[M + MeOH + Na]^+$ (cal. 992.5).

CM-Lys(2-Cl-Cbz)-AdGly-Cha-Phe-OMe 123:



123

The synthesis of ClH_3N-Lys(2-Cl-Cbz)-AdGly-Cha-Phe-OMe was performed with 0.137 g (0.151 mmol, 1.0 equiv) Boc-Lys(2-Cl-Cbz)-AdGly-Cha-Phe-OMe **120** and 2 mL HCl in 1,4-dioxane (4 M) utilizing GP-8. The reaction mixture was stirred for 22.5 h. The crude product was obtained as yellowish solid and used without further purification. The synthesis of CM-Lys(2-Cl-Cbz)-AdGly-Cha-Phe-OMe **123** was performed with the crude product of the hydrochloride, 0.038 g (0.174 mmol, 1.2 equiv) acid ***para*-112**, 2.30 mg (0.019 mmol, 13 mol%) DMAP, 0.054 g (0.282 mmol, 1.9 equiv) EDAC, 58.0 µL (42.3 mg, 0.418 mmol, 2.8 equiv) TEA, and 4 mL DCM utilizing GP-3. After 18 h the reaction was quenched with 15 mL $NaHCO_3$ and the organic layer was extracted with DCM (three times 10 mL). After purification *via* column chromatography (*n*-hexane:EtOAc 1:5) 0.104 g (0.103 mmol, 68%) **123** were isolated as colorless oil.

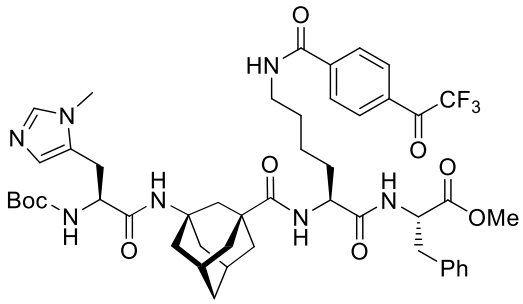
R_f: 0.51 (*n*-hexane:EtOAc 1:5).

^{1}H-NMR and **^{13}C-NMR** not meaningful.

HR-MS (ESI): m/z: 1060.4424 $[M + MeOH + Na]^+$ (cal. 1060.4421).

MS (ESI): m/z: 1028.5 $[M + Na]^+$ (cal. 1028.4); 1060.5 $[M + MeOH + Na]^+$ (cal. 1060.4).

Boc-PMH-AdGly-Lys(CM)-Phe-OMe 124:



124

The synthesis of the free amine was performed with 0.095 g (0.109 mmol, 1.0 equiv) Cbz-protected compound **125**, 24.5 mg (0.023 mmol, 21 mol%) Pd/C (10%), and 5 mL MeOH (GP-7). The reaction mixture was stirred for 19 h. 0.072 g (0.098 mmol, 90%) of the free amine were obtained as yellowish solid.

MS (ESI): m/z: 636.4 $[M - Boc + H]^+$ (cal. 636.4); 736.4 $[M + H]^+$ (cal. 736.4); 758.4 $[M + Na]^+$ (cal. 758.4).

The synthesis of Boc-PMH-AdGly-Lys(CM)-Phe-OMe **124** was performed with 0.072 g (0.098 mmol, 1.0 equiv) of the free amine, 26.0 mg (0.119 mmol, 1.2 equiv) acid ***para*-112**, 2.10 mg (0.017 mmol, 17 mol%) DMAP, 0.039 g (0.203 mmol, 2.1 equiv) EDAC, 27.0 µL (19.7 mg, 0.195 mmol, 2.0 equiv) TEA, and 3 mL DCM utilizing GP-3. After 16 h the reaction was quenched with 15 mL $NaHCO_3$ and the organic layer was extracted with DCM (three times 10 mL). After purification *via* column chromatography ($CHCl_3$:MeOH 9:1 to 5:1) 0.060 g (0.064 mmol, 65%) **124** were isolated as colorless solid.

R_f: 0.35 ($CHCl_3$:MeOH 9:1).

^{1}H-NMR[10] shows traces of racemization and was therefore not evaluable.

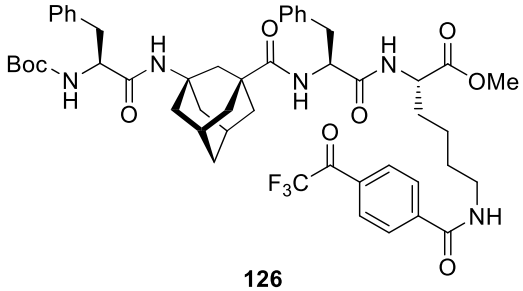
^{13}C-NMR (101 MHz, $CDCl_3$):[10] δ = 180.1 (*C*OCF_3); 176.7; 171.9; 171.7; 169.6; 166.1; 155.4; 140.9; 137.9; 135.7; 131.5; 130.1; 130.1; 129.1; 128.7; 128.0; 127.5; 127.2; 114.3 (*C*F_3); 80.4; 54.4; 53.5; 52.4; 52.2; 52.1; 42.5; 42.1; 40.3; 40.1; 39.7; 38.0; 37.8; 37.5; 35.0; 32.1; 31.6; 29.7; 29.0; 28.3; 26.9; 22.3 ppm.

HR-MS (ESI): m/z: 495.7326 $[M + MeOH + H + Na]^{2+}$ (cal. 495.7316); 990.4566 $[M + MeOH + Na]^+$ (cal. 990.4559).

MS (ESI): m/z: 958.4 $[M + Na]^+$ (cal. 958.4); 968.4 $[M + MeOH + H]^+$ (cal. 968.5); 990.3 $[M + MeOH + Na]^+$ (cal. 990.5); 1006.3 $[M + MeOH + K]^+$ (cal. 1006.4).

[10] Racemization observable.

Boc-Phe-AdGly-Phe-Lys(CM)-OMe 126:



126

The synthesis of ClH_3N-Lys(2-Cl-Cbz)-OMe was performed with 0.402 g (0.969 mmol, 1.0 equiv) Boc-Lys(2-Cl-Cbz)-OH, 0.250 mL (0.410 g, 3.45 mmol, 3.6 equiv) $SOCl_2$, and 6 mL MeOH utilizing GP-5. 0.365 g (0.999 mmol, quant.) hydrochloride were obtained as yellow solid.

The synthesis of Boc-Phe-Lys(2-Cl-Cbz)-OMe was performed with the crude product of the hydrochloride, 0.265 g (0.999 mmol, 1.0 equiv) Boc-Phe-OH **94**, 0.215 g (1.12 mmol, 1.2 equiv) EDAC, 0.153 g (1.13 mmol, 1.2 equiv) HOBt, 0.153 mL (0.112 g, 1.10 mmol, 1.1 equiv) TEA, and 5 mL DCM utilizing GP-6. After 24 h the reaction mixture was diluted with EtOAc. For washing a volume of 20 mL was used. The organic layer was washed additionally with 15 mL brine. 0.549 g (0.953 mmol, 98%) dipeptide were obtained as colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.44–7.40 (m, 1 H); 7.38–7.34 (m, 1 H); 7.28–7.21 (m, 6 H and $CHCl_3$); 7.18–7.16 (m, 3 H); 6.64 (bs, 1 H); 5.28–5.10 (m, 4 H); 4.57–4.49 (m, 1 H); 4.45–4.33 (m, 1 H); 3.69 (s, 3 H); 3.24–3.12 (m, 2 H); 3.11–2.97 (m, 2 H); 1.85–1.74 (m, 1 H); 1.70–1.58 (m, 1 H); 1.52–1.46 (m, 1 H); 1.38 (s, 9 H); 1.30–1.20 (m, 1 H) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 172.3; 171.5; 156.5; 155.7; 136.7; 134.5; 133.6; 129.8; 129.6; 129.4; 128.7; 127.0; 80.4; 64.0, 55.9; 52.5; 52.0; 40.7; 38.2; 32.0; 29.3; 28.4; 22.3 ppm.

MS (ESI): m/z: 498.3 $[M - Boc + Na]^+$ (cal. 498.2); 598.2 $[M + Na]^+$ (cal. 598.2).

The synthesis of ClH_3N-Phe-Lys(2-Cl-Cbz)-OMe was performed with 0.549 g (0.953 mmol, 1.0 equiv) Boc-Phe-Lys(2-Cl-Cbz)-OMe and 2.5 mL HCl in 1,4-dioxane (4 M) utilizing GP-8. The crude product was obtained as colorless solid and used without further purification. The synthesis of Boc-AdGly-Phe-Lys(2-Cl-Cbz)-OMe was performed with the crude product of the hydrochloride, 0.282 g (0.955 mmol, 1.0 equiv) Boc-AdGly-OH, 0.206 g (1.07 mmol, 1.1 equiv) EDAC, 0.148 g (1.10 mmol, 1.1 equiv) HOBt, 0.145 mL (0.106 g, 1.04 mmol, 1.1 equiv) TEA, and 7 mL DCM utilizing GP-6. After 24 h the reaction mixture was diluted with EtOAc. For washing a volume of 50 mL was used. Additionally 10 mL brine were used for washing. 0.669 g (0.888 mmol, 93%) tripeptide were obtained as colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.42–7.40 (m, 1 H); 7.37–7.33 (m, 1 H); 7.29–7.18 (m, 8 H and $CHCl_3$); 6.62–6.55 (m, 1 H); 6.18 (d, 1 H, ^3J = 6.3 Hz); 5.29 (bs, 1 H); 5.24–5.17 (m, 2 H); 4.65–4.59 (m, 1 H); 4.53–4.46 (m, 1 H); 3.70 (s, 3 H); 3.23–3.12 (m, 2 H); 3.11–3.01 (m, 2 H);

2.20–2.10 (m, 2 H); 1.97–1.92 (m, 2 H); 1.91–1.85 (m, 2 H); 1.84–1.76 (m, 3 H); 1.71–1.48 (m, 9 H); 1.41 (s, 9 H); 1.31–1.20 (m, 2 H) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 177.0; 172.2; 171.0; 156.5; 154.3; 136.6; 134.5; 133.6; 129.8; 129.6; 128.8; 127.1; 127.0; 79.2; 64.0; 54.2; 52.5, 52.2; 50.8; 42.8; 42.7; 41.0; 40.7; 38.1; 37.7; 35.4; 31.8; 29.3; 29.2; 28.6; 22.2 ppm.

MS (ESI): m/z: 775.3 $[M + Na]^+$ (cal. 775.3).

The synthesis of ClH_3N-AdGly-Phe-Lys(2-Cl-Cbz)-OMe was performed with 0.669 g (0.888 mmol, 1.0 equiv) Boc-AdGly-Phe-Lys(2-Cl-Cbz)-OMe and 2.5 mL HCl in 1,4-dioxane (4 M) utilizing GP-8. The crude product was obtained as yellow solid and used without further purification. The synthesis of Boc-Phe-AdGly-Phe-Lys(2-Cl-Cbz)-OMe was performed with 0.326 g (0.473 mmol, 1.0 equiv) hydrochloride, 0.128 g (0.475 mmol, 1.0 equiv) Boc-Phe-OH **94**, 0.103 g (0.537 mmol, 1.1 equiv) EDAC, 0.074 g (0.548 mmol, 1.2 equiv) HOBt, 0.072 mL (0.052 g, 0.519 mmol, 1.1 equiv) TEA, and 5 mL DCM utilizing GP-6. After 27 h the reaction mixture was diluted with EtOAc. For washing a volume of 50 mL was used. Additionally 20 mL brine were used for washing. 0.376 g (0.418 mmol, 88%) tetrapeptide were obtained as yellowish solid.

MS (ESI): m/z: 922.4 $[M + Na]^+$ (cal. 922.4); 938.3 $[M + K]^+$ (cal. 938.4).

The synthesis of the free amine was performed with 0.376 g (0.418 mmol, 1.0 equiv) of the (2-Cl-Cbz)-protected compound, 0.090 g (0.085 mmol, 20 mol%) Pd/C (10%), and 10 mL MeOH (GP-7). The reaction mixture was stirred for 22 h. 0.298 g (0.407 mmol, 97%) free amine were obtained as colorless solid.

MS (ESI): m/z: 632.4 $[M – Boc + H]^+$ (cal. 632.4); 732.4 $[M + H]^+$ (cal. 732.4).

The synthesis of Boc-Phe-AdGly-Phe-Lys(CM)-OMe **126** was performed with 0.298 g (0.407 mmol, 1.0 equiv) of the free amine, 0.137 g (0.628 mmol, 1.5 equiv) acid ***para*-112**, 11.5 mg (0.094 mmol, 23 mol%) DMAP, 0.241 g (1.26 mmol, 3.1 equiv) EDAC, 0.171 mL (0.125 g, 1.23 mmol, 3.0 equiv) TEA, and 10 mL DCM utilizing GP-3. After 24 h the reaction was quenched with 30 mL $NaHCO_3$ and the organic layer was extracted with DCM (two times 10 mL). After purification *via* column chromatography (*n*-hexane:EtOAc 1:5 to 1:7) 0.180 g (0.193 mmol, 47%) **126** were isolated as colorless solid.

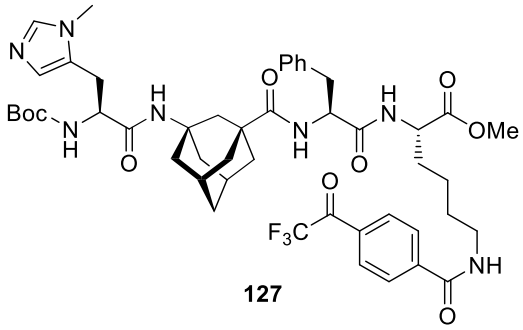
R_f: 0.39 (*n*-hexane:EtOAc 1:5).

^{1}H-NMR and **^{13}C-NMR** not meaningful.

HR-MS (ESI): m/z: 986.4493 $[M + MeOH + Na]^+$ (cal. 986.4497).

MS (ESI): m/z: 986.3 $[M + MeOH + Na]^+$ (cal. 986.4).

Boc-PMH-AdGly-Phe-Lys(CM)-OMe 127:



127

The synthesis of Boc-PMH-AdGly-Phe-Lys(2-Cl-Cbz)-OMe was performed with 0.330 g (0.478 mmol, 1.0 equiv) of the corresponding hydrochloride, 0.131 g (0.486 mmol, 1.0 equiv) Boc-PMH-OH, 0.234 g (1.22 mmol, 2.6 equiv) EDAC, 0.168 g (1.24 mmol, 2.6 equiv) HOBt, 0.166 mL (0.121 g, 1.20 mmol, 1.2 equiv) TEA, and 6 mL DCM utilizing GP-6. After 28 h the reaction mixture was diluted with EtOAc. For washing a volume of 50 mL was used. Additionally 20 mL brine were used for washing. 0.342 g (0.378 mmol, 79%) tetrapeptide were obtained as yellowish solid.

MS (ESI): m/z: 904.4 $[M + H]^+$ (cal. 904.4); 926.3 $[M + Na]^+$ (cal. 926.4).

The synthesis of the free amine was performed with 0.296 g (0.327 mmol, 1.0 equiv) of the (2-Cl-Cbz)-protected compound, 0.074 g (0.070 mmol, 15 mol%) Pd/C (10%), and 10.0 mL MeOH (GP-7). The reaction mixture was stirred for 42 h. 0.235 g (0.319 mmol, 98%) of the free amine were obtained as colorless solid.

MS (ESI): m/z: 368.7 $[M + 2H]^{2+}$ (cal. 368.7); 636.4 $[M – Boc + H]^+$ (cal. 636.4); 736.4 $[M + H]^+$ (cal. 736.4).

The synthesis of Boc-PMH-AdGly-Phe-Lys(CM)-OMe **127** was performed with 0.235 g (0.319 mmol, 1.0 equiv) of the free amine, 0.086 g (0.394 mmol, 1.2 equiv) acid ***para*-112**, 2.4 mg (0.020 mmol, 6 mol%) DMAP, 0.127 g (0.662 mmol, 2.1 equiv) EDAC, 0.090 mL (0.066 g, 0.648 mmol, 2.0 equiv) TEA, and 10 mL DCM utilizing GP-3. After 24 h the reaction was quenched with 10 mL $NaHCO_3$ and the organic layer was extracted with DCM (three times 10 mL). After purification *via* column chromatography (CH_2Cl_2:MeOH 5:1) 0.264 g (0.282 mmol, 88%) **127** were isolated as colorless solid.

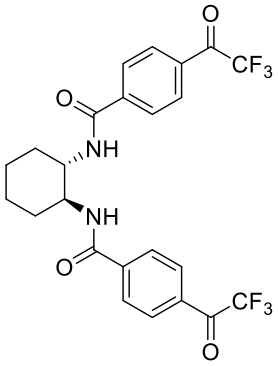
R_f: 0.35 (CH_2Cl_2:MeOH 10:1).

^{1}H-NMR and **^{13}C-NMR** show traces of racemization and are therefore not evaluable.

HR-MS (ESI): m/z: 495.7310 $[M + MeOH + Na + H]^{2+}$ (cal. 495.7316); 990.4565 $[M + MeOH + Na]^+$ (cal. 990.4559).

MS (ESI): m/z: 968.3 $[M + MeOH + H]^+$ (cal. 968.5); 990.3 $[M + MeOH + Na]^+$ (cal. 990.5).

1-(*p*-(((1*S*,2*S*)-2-(*p*-(2,2,2-Trifluoroacetyl)benzoylamino)cyclohexylamino)carbonyl) phenyl)-2,2,2-trifluoro-1-ethanone 128:



128

The synthesis of C_2-symmetric cat. **128** was performed with 0.105 g (0.920 mmol, 1.0 equiv) of the corresponding diamine, 0.394 g (1.81 mmol, 2.0 equiv) acid ***para*-112**, 4.5 mg (0.037 mmol, 4 mol%) DMAP, 0.504 g (2.63 mmol, 2.9 equiv) EDAC, 0.365 mL (0.266 g, 2.63 mmol, 2.9 equiv) TEA, and 8 mL DCM utilizing GP-3. After 47 h the reaction was quenched with 30 mL $NaHCO_3$ and the organic layer was extracted with DCM (three times 20 mL). After purification *via* column chromatography (EtOAc) 0.174 g (0.338 mmol, 37%) **128** were isolated as yellow solid.

R_f: 0.55 (EtOAc).

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.02 (d, 4 H, ^3J = 8.2 Hz); 7.85 (d, 4 H, ^3J = 8.4 Hz); 6.95 (d, 2 H, ^3J = 6.3 Hz, N*H*); 4.11–4.03 (m, 2 H, C*H*NH); 2.26–2.24 (m, 2 H, H_{Cy}); 1.91–1.90 (m, 2 H, H_{Cy}); 1.53–1.44 (m, 4 H, H_{Cy}) ppm.

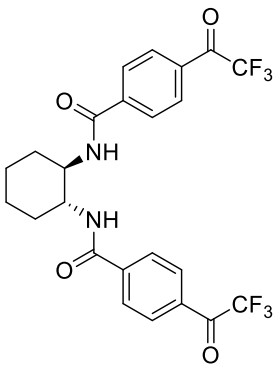
^{13}C-NMR (151 MHz, $CDCl_3$): δ = 180.0 (q, $^2J_{CF}$ = 35.6 Hz, *C*OCF_3); 166.8; 140.1; 132.1; 130.5; 127.7; 116.5 (q, $^1J_{CF}$ = 291.4 Hz, CO*C*F_3); 55.1 (*C*HNH); 32.3 (*C*H_2CHNH); 24.9 (*C*$H_2$$CH_2$CHNH) ppm.

IR (KBr): $\tilde{\nu}$ = 3276 (w); 2943 (vw); 1726 (m); 1634 (m); 1541 (m); 1143 (m); 944 (w); 694 (vw) cm^{-1}.

HR-MS (ESI): m/z: 601.1747 $[M + 2MeOH + Na]^+$ (cal. 601.1744); 1179.3559 $[M + 2MeOH + Na]^+$ (cal. 1179.3595).

MS (ESI): m/z: 579.2 $[M + 2MeOH + H]^+$ (cal. 579.2); 601.3 $[M + 2MeOH + Na]^+$ (cal. 601.2); 1178.9 $[2M + 2MeOH + Na]^+$ (cal. 1179.4).

1-(*p*-(((1*R*,2*R*)-2-(*p*-(2,2,2-Trifluoroacetyl)benzoylamino)cyclohexylamino)carbonyl) phenyl)-2,2,2-trifluoro-1-ethanone 129:



129

The synthesis of C_2-symmetric cat. **129** was performed with 0.057 g (0.499 mmol, 1.0 equiv) of the corresponding diamine, 0.225 g (1.03 mmol, 2.1 equiv) acid ***para*-112**, 3.2 mg (0.026 mmol, 5 mol%) DMAP, 0.287 g (1.50 mmol, 3.0 equiv) EDAC, 0.208 mL (0.151 g, 1.50 mmol, 3.0 equiv) TEA, and 6 mL DCM utilizing GP-3. After 67 h the reaction was quenched with 15 mL $NaHCO_3$ and the organic layer was extracted with DCM (three times 10 mL). After purification *via* column

chromatography (*n*-hexane:EtOAc 1:5) 0.120 g (0.233 mmol, 47%) **129** were isolated as colorless solid.

R*f*: 0.45 (*n*-hexane:EtOAc 1:5).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.80–7.75 (m, 8 H); 7.41 (d, 2 H, ^{3}J = 7.4 Hz, N*H*); 4.22–4.12 (m, 2 H, C*H*NH); 2.26–2.22 (m, 2 H, H_{Cy}); 1.95–1.93 (m, 2 H, H_{Cy}); 1.67–1.55 (m, 2 H, H_{Cy}); 1.52–1.41 (m, 2 H, H_{Cy}) ppm.

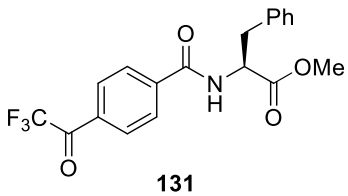
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 179.7 (q, $^{2}J_{CF}$ = 35.8 Hz, *C*$COCF_3$); 166.8; 140.0; 131.9; 130.2; 127.6; 116.4 (q, $^{1}J_{CF}$ = 291.1 Hz, CO*C*F_3); 54.9 (*C*HNH); 32.2 (*C*H_2CHNH); 25.0 (*C*H_2CH_2CHNH) ppm.

IR (KBr): $\tilde{\nu}$ = 3275 (w); 2943 (w); 1726 (m); 1634 (m); 1540 (m); 1143 (m); 944 (w); 693 (w) cm^{-1}.

HR-MS (ESI): m/z: 601.1747 $[M + 2MeOH + Na]^+$ (cal. 601.1744); 1179.3566 $[M + 2MeOH + Na]^+$ (cal. 1179.3595).

MS (ESI): m/z: 579.2 $[M + 2MeOH + H]^+$ (cal. 579.2); 601.3 $[M + 2MeOH + Na]^+$ (cal. 601.2); 1178.9 $[2M + 2MeOH + Na]^+$ (cal. 1179.4).

Methyl (2*S*)-3-phenyl-2-(*p*-(2,2,2-trifluoroacetyl)benzoylamino)propionate 131:



131

The synthesis of functionalized Phe **131** was performed with 0.301 g acid ***para*-112** (1.38 mmol, 1.0 equiv), 0.338 g (1.57 mmol, 1.1 equiv) ClH_3N-Phe-OMe **130**, 0.297 g (1.54 mmol, 1.1 equiv) EDAC, 0.212 g (1.57 mmol, 1.1 equiv) HOBt, 0.210 mL (0.153 g, 1.51 mmol, 1.1 equiv) TEA, and 13 mL DCM utilizing GP-6. After 22 h the reaction mixture was diluted with EtOAc. For washing a volume of 33 mL was used. Additionally 25 mL brine were used for washing. After purification *via* column chromatography (*n*-hexane:EtOAc 1:1) 0.466 g (1.23 mmol, 89%) **131** were isolated as colorless solid.

R*f*: 0.34 (*n*-hexane:EtOAc 1:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, 2 H, ^{3}J = 8.0 Hz, $H_{Ar\text{-}COCF3}$); 7.79–7.77 (m, 2 H, $H_{Ar\text{-}COCF3}$); 7.26–7.17 (m, 3 H, H_{Ar} and $CHCl_3$); 7.06–7.04 (m, 2 H, H_{Ar}); 6.62 (d, 1 H, ^{3}J = 7.4 Hz, N*H*); 5.02 (dt, 1 H, ^{3}J = 7.5 Hz, ^{3}J = 5.6 Hz, C*H*); 3.73 (s, 3 H, CH_3); 3.25 (dd, 1 H, ^{2}J = 13.9 Hz, ^{3}J = 5.7 Hz, CH_2); 3.16 (dd, 1 H, ^{2}J = 13.9 Hz, ^{3}J = 5.5 Hz, CH_2) ppm.

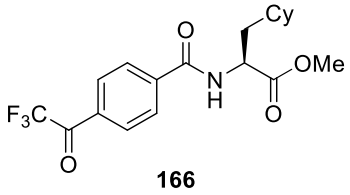
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 180.1 (q, $^{2}J_{CF}$ = 35.7 Hz, *C*$COCF_3$); 171.9; 165.4; 140.0; 135.6; 132.3; 130.5; 129.4; 128.9; 127.8; 127.5; 116.6 (q, $^{1}J_{CF}$ = 291.1 Hz, CO*C*F_3); 53.8; 52.8; 37.8 ppm.

IR (KBr): $\tilde{\nu}$ = 3300 (m); 2959 (vw); 1755 (m); 1737 (m); 1647 (s); 1546 (s); 1141 (s); 942 (m); 699 (m) cm^{-1}.

HR-MS (ESI): m/z: 434.1191 $[M + MeOH + Na]^+$ (cal. 434.1186); 845.2478 $[2M + 2MeOH + Na]^+$ (cal. 845.2479).

MS (ESI): m/z: 412.1 $[M + MeOH + H]^+$ (cal. 412.1); 434.1 $[M + MeOH + Na]^+$ (cal. 434.1).

Methyl (2*S*)-3-cyclohexyl-2-(*p*-(2,2,2-trifluoroacetyl)benzoylamino)propionate 166:



166

The synthesis of functionalized Cha **166** was performed with 0.300 g acid ***para*-112** (1.38 mmol, 1.0 equiv), 0.339 g (1.53 mmol, 1.1 equiv) ClH_3N-Cha-OMe, 0.298 g (1.55 mmol, 1.1 equiv) EDAC, 0.214 g (1.58 mmol, 1.1 equiv) HOBt, 0.230 mL (0.168 g, 1.66 mmol, 1.1 equiv) TEA, and 12 mL DCM utilizing GP-6. After 27.5 h the reaction mixture was diluted with EtOAc. For washing a volume of 45 mL was used. 0.514 g (1.33 mmol, 97%) **166** were obtained as a yellowish oil. The crude product was used without further optimization.[11]

R_f: 0.40 (*n*-hexane:EtOAc 1:1).

^{1}H-NMR (600 MHz, MeOH-d_4): δ = 7.89 (d, 2 H, ^3J = 7.9 Hz, $H_{Ar\text{-}COCF3}$); 7.72 (d, 2 H, ^3J = 7.9 Hz, $H_{Ar\text{-}COCF3}$); 4.71 (dd, 1 H, ^3J = 8.7 Hz, ^3J = 6.1 Hz, C*H*CH_2); 3.74 (s, 3 H, CH_3); 1.85 (d, 1 H, J = 12.6 Hz); 1.78–1.70 (m, 5 H); 1.66 (d, 1 H, J = 10.4 Hz); 1.44 (bs, 1 H); 1.32–1.17 (m, 3 H); 1.02 (q, 1 H, J = 11.8); 0.95 (q, 1 H, J = 11.8) ppm.

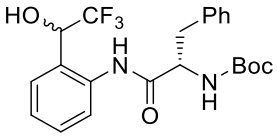
^{13}C-NMR (151 MHz, MeOH-d_4):[12] δ = 174.9; 170.0; 139.8; 136.3; 129.5; 128.3; 124.3 (q, $^1J_{CF}$ = 287.2 Hz, CO*C*F_3); 97.7 (q, $^2J_{CF}$ = 31.6 Hz, *C*$(OH)_2CF_3$); 52.7; 52.1; 39.7; 35.7; 34.8; 33.2; 27.5; 27.3; 27.2 ppm.

HR-MS (ESI): m/z: 440.1655 $[M + MeOH + Na]^+$ (cal. 440.1655); 857.3416 $[2M + 2MeOH + Na]^+$ (cal. 857.3418).

MS (ESI): m/z: 440.2 $[M + MeOH + Na]^+$ (cal. 440.2); 856.9 $[2M + 2MeOH + Na]^+$ (cal. 857.3).

[11] Decomposition over time to the hydrate observed.
[12] Formation of the hydrate in MeOH-d_4 observable. Not observable in MS (ESI).

(1*S*)-1-Benzyl-2-oxo-2-(*o*-(2,2,2-trifluoro-1-hydroxyethyl)phenylamino)ethylamino-2,2-dimethyl-propionate *ortho*-160:



***ortho*-160**:

The synthesis of amino alcohol ***ortho*-155** was performed with 0.335 g (1.53 mmol, 1.0 equiv) nitro compound ***ortho*-154**, 0.042 g (0.039 mmol, 3 mol%) Pd/C (10%), and 7 mL EtOH (GP-7). The reaction mixture was stirred for 21 h. The crude product was utilized without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$ and MeOD-d_4): δ = 7.17 (d, 1 H, ^{3}J = 7.0 Hz); 7.11 (t, 1 H, ^{3}J = 7.6 Hz); 6.76–6.67 (m, 2 H); 5.06–4.97 (m, 1 H, C*H*OHCF$_3$); 3.65 (bs, 3 H, N*H* and O*H*) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$ and MeOD-d_4): δ = 145.4; 129.8; 129.5; 125.3 (q, $^{1}J_{CF}$ = 282.8 Hz, CHOH*C*F$_3$); 119.4; 118.8; 117.8; 71.3 (q, $^{2}J_{CF}$ = 32.4 Hz, *C*HOHCF$_3$) ppm.

IR (ATR): ṽ = 3397 (vw); 3075 (vw); 2289 (vw); 1609 (vw); 1496 (vw); 1294 (vw); 1180 (w); 1112 (w); 758 (w) cm^{-1}.

HR-MS (ESI): m/z: 214.0463 [M + Na]$^+$ (cal. 214.0450).

The synthesis of ***ortho*-160** was performed with 0.139 g (0.727 mmol, 1.0 equiv) ***ortho*-155**, 0.232 g (0.874 mmol, 1.2 equiv) Phe **94**, 0.175 g (0.913 mmol, 1.3 equiv) EDAC, 0.127 g (0.940 mmol, 1.3 equiv) HOBt, 0.088 mL (0.064 g, 0.634 mmol, 0.9 equiv) TEA, and 10 mL DCM utilizing GP-6. The resulting mixture was stirred for 13 h. For washing a volume of 30 mL was used. After purification *via* column chromatography (*n*-hexane:EtOAc 5:1 to 0:1) 0.072 g (0.164 mmol, 26%) ***ortho*-160** were isolated as colorless solid.

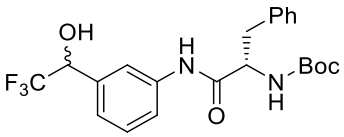
R$_f$: 0.57 (*n*-hexane:EtOAc 1:5).

IR (ATR): ṽ = 3294 (vw); 2928 (vw); 1669 (vw); 1496 (vw); 1160 (w); 751 (vw); 698 (vw) cm^{-1}.

HR-MS (ESI): m/z: 461.1662 [M + Na]$^+$ (cal. 461.1659); 899.3433 [2M + Na]$^+$ (cal. 899.3425).

MS (ESI): m/z: 461.1 [M + Na]$^+$ (cal. 461.2).

(1*S*)-2-(*m*-(2,2,2-Trifluoro-1-hydroxyethyl)phenylamino)-1-benzyl-2-oxoethylamino-2,2-dimethyl propionate *meta*-160:



***meta*-160**

The synthesis of amino alcohol ***meta*-155** was performed with 0.194 g (0.885 mmol, 1.0 equiv) nitro compound ***meta*-154**, 17.7 mg (0.017 mmol, 2 mol%) Pd/C (10%), and 4.5 mL EtOH (GP-7). The reaction mixture was stirred for 17 h.

After purification *via* column chromatography (*n*-hexane:EtOAc 2:1 and 0.25% TEA) 0.144 g (0.761 mmol, 86%) ***meta*-155** were isolated as yellow oil.

R_f: 0.46 (*n*-hexane:EtOAc 1:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.18 (t, 1 H, ^3J = 7.8 Hz); 6.84 (d, 1 H, ^3J = 7.2 Hz); 6.76 (s, 1 H, C(CHOHCF$_3$)C*H*C(NO$_2$)); 6.73–6.67 (m, 1 H); 4.91–4.85 (m, 1 H, C*H*OHCF$_3$); 3.58 (bs, 3 H, N*H* and O*H*) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 146.6; 135.5; 129.7; 124.4 (q, $^1J_{CF}$ = 281.9 Hz, CHOH*C*F$_3$); 118.0; 116.5; 114.0; 73.0 (q, $^2J_{CF}$ = 32.1 Hz, *C*HOHCF$_3$) ppm.

IR (ATR): ṽ = 3408 (vw); 3116 (vw); 1614 (vw); 1255 (w); 1101 (m); 791 (w); 706 (m) cm^{-1}.

HR-MS (ESI): m/z: 214.0453 $[M + Na]^+$ (cal. 214.0450).

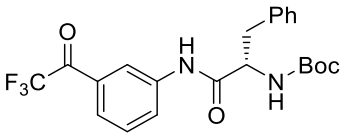
The synthesis of ***meta*-160** was performed with 0.141 g (0.738 mmol, 1.0 equiv) ***meta*-155**, 0.215 g (0.810 mmol, 1.1 equiv) Phe **94**, 0.160 g (0.835 mmol, 1.1 equiv) EDAC, 0.114 g (0.844 mmol, 1.1 equiv) HOBt, 0.113 mL (0.082 g, 0.814 mmol, 1.1 equiv) TEA, and 10 mL DCM utilizing GP-6. The resulting mixture was stirred for 23 h. For washing a volume of 175 mL was used. After purification *via* column chromatography (DCM:MeOH 50:1 to 30:1) 0.104 g (0.237 mmol, 32%) ***meta*-160** were isolated as yellowish foam.

R_f: 0.23 (DCM:MeOH 30:1).

HR-MS (ESI): m/z: 461.1668 $[M + Na]^+$ (cal. 461.1659); 899.3450 $[2M + Na]^+$ (cal. 899.3425).

MS (ESI): m/z: 461.0 $[M + Na]^+$ (cal. 461.2).

(1*S*)-1-Benzyl-2-oxo-2-(*m*-(2,2,2-trifluoroacetyl)phenylamino)ethylamino-2,2-dimethyl propionate *meta*-161:



***meta*-161**

0.086 g (0.196 mmol, 1.0 equiv) alcohol ***meta*-160** and 3.58 mg (0.023 mmol, 0.1 equiv, 12 mol%) TEMPO were dissolved in 10 mL DCM. Afterwards 0.088 g (0.357 mmol, 1.8 equiv) *m*CPBA (70%) were added and the resulting reaction mixture was stirred for 20 h at r.t.. The organic layer was washed portionwise with 200 mL sat. $NaHCO_3$ and dried afterwards over Na_2SO_4. After purification *via* column chromatography (*n*-hexane:EtOAc 2:1) 47.2 mg (0.108 mmol, 55%) ***meta*-161** were isolated as yellow oil.

R_f: 0.23 (*n*-hexane:EtOAc 2:1).

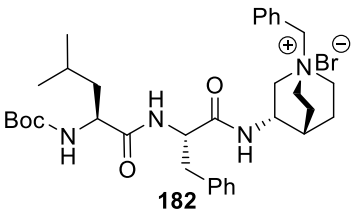
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.81 (bs, 1 H, N*H*); 8.02 (s, 1 H, C(COCF$_3$)C*H*C(NO$_2$)); 7.77–7.65 (m, 2 H); 7.39–7.31 (m, 1 H); 7.28–7.19 (m, 5 H and $CDCl_3$); 5.41 (d, 1 H, ^3J = 7.3

Hz, N*H*); 4.64 (bs, 1 H, C*H*CH_2); 3.19–3.16 (m, 1 H, CHC*H*$_2$); 3.08 (dd, 1 H, ^2J = 13.7 Hz, ^3J = 7.9 Hz, CHC*H*$_2$); 1.41 (s, 9 H, C(C*H*$_3$)$_3$) ppm.

^{13}C-NMR (151 MHz, $CDCl_3$): δ = 180.1 (q, $^2J_{CF}$ = 35.2 Hz, *C*OCF_3); 170.7 (NH*C*OCH); 156.5 (NH*C*OO C$(CH_3)_3$); 138.6 ($C_{quart.}$); 136.4 ($C_{quart.}$); 130.5 ($C_{quart.}$); 129.7; 129.3; 128.9; 127.3; 126.8; 125.8; 121.0; 119.5; 116.5 (q, $^1J_{CF}$ = 291.2 Hz, CO*C*F_3); 81.1 (*C*$(CH_3)_3$); 56.8 (*C*HCH_2); 38.5 (CH*C*H_2); 28.4 (C(*C*H_3)$_3$) ppm.

MS (ESI): m/z: 491.0 $[M + MeOH + Na]^+$ (cal. 491.2).

Boc-Leu-Phe-((3*S*)-*N*-benzylquinuclidinium) bromide 182:



182

The synthesis of Boc-Leu-Phe-OMe was performed with 0.220 g (1.02 mmol, 1.0 equiv) hydrochloride **130**, 0.250 g (1.08 mmol, 1.1 equiv) Boc-Leu-OH, 0.210 g (1.12 mmol, 1.1 equiv) EDAC, 0.150 g (1.11 mmol, 1.1 equiv) HOBt, 0.153 mL (0.112 g, 1.10 mmol, 1.1 equiv) TEA, and 15 mL DCM utilizing GP-6. After 24 h the reaction mixture was diluted with 150 mL EtOAc. For washing a volume of 30 mL was used. The organic layer was washed additionally with 100 mL brine. 0.350 g (0.892 mmol, 87%) dipeptide were obtained as colorless solid.

After dissolving 0.350 g (0.892 mmol, 1.0 equiv) dipeptide in 15 mL 1,4-dioxane 15 mL $LiOH_{aq}$ (1 M) were added. The resulting reaction mixture was stirred for 19 h at r.t. and was acidified afterwards with HCl (2 M) until a pH-value of 5 was reached. The unprotected dipeptide was dissolved in 100 mL EtOAc. The organic layer was washed with 50 mL brine. This aq layer was again extracted with 50 mL EtOAc. After washing the second organic layer with 50 mL brine, both organic layers were combined, and dried finally over $MgSO_4$. After evaporation of the solvent under reduced pressure 0.310 g (0.819 mmol, 92%) Boc-Leu-Phe-OH **183** were obtained as colorless solid.

To a suspension of 0.310 g (0.819 mmol, 1.0 equiv) unprotected dipeptide **183** in 20 mL DMF 0.426 mL (0.324 g, 2.50 mmol, 3.1 equiv) D*i*PEA were added. After stirring the resulting solution for 5 min at r.t. 0.170 g (0.858 mmol, 1.0 equiv) **181** • 2 HCl were added. After stirring for additional 10 min at r.t. the reaction mixture was cooled to 0 °C and 0.310 g (0.818 mmol, 1.0 equiv) HBTU were added. After stirring the reaction mixture for 24 h at r.t. the solvent was evaporated under reduced pressure. The residue was dissolved in 50 mL $CHCl_3$/MeOH (9:1). The organic layer was washed with 30 mL sat. $NaHCO_3$. The aq solution was extracted two times with 25 mL $CHCl_3$/MeOH (9:1). The combined organic layers were washed with 30 mL

birne and dried over $MgSO_4$. After purification *via* column chromatography ($CHCl_3$:MeOH 7:3) 0.340 g (0.696 mmol, 85%) Boc-Leu-Phe-((3*S*)-*N*-benzyl-quinuclidine) **184** were isolated as colorless solid.

R_f: 0.34 ($CHCl_3$:MeOH 7:3).

MS (ESI): m/z: 487.5 $[M + H]^+$ (cal. 487.3).

To a solution of 0.340 g (0.696 mmol, 1.0 equiv) Boc-Leu-Phe-((3*S*)-*N*-benzyl-quinuclidine) **184** in 10 mL MeCN 0.083 mL (0.119 g, 0.698 mmol, 1.0 equiv) BnBr were added. After refluxing the resulting solution for 72 h the solvent was evaporated under reduced pressure. The residue was dissolved in 5 mL MeCN and the crude product precipitated by addition of Et_2O. After filtration and washing with Et_2O the crude product was dried over night in the desiccator. After purification *via* column chromatography ($CHCl_3$:MeOH 4:1) 0.190 g (0.289 mmol, 41%) **182** were isolated as colorless solid.

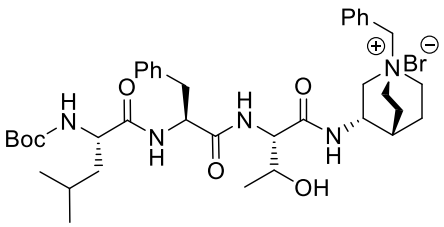
R_f: 0.34 ($CHCl_3$:MeOH 7:3).

^{1}H-NMR (400 MHz, MeOD-d_4): δ = 7.62–7.51 (m, 5 H); 7.24–7.14 (m, 5 H); 4.48–4.37 (m, 3 H); 4.05–4.00 (m, 2 H); 3.83–3.79 (m, 1 H); 3.64–3.58 (m, 1 H); 3.56–3.37 (m, 3 H); 3.14 (bs, 1 H); 3.05 (dd, 1 H, ^2J = 13.3 Hz, ^3J = 6.8 Hz); 2.98–2.89 (m, 1 H); 2.70 (bs, 1 H); 2.11 (bs, 1 H); 2.03 (bs, 2 H); 1.78 (bs, 2 H); 1.67–1.59 (m, 1 H, C*H*$(CH_3)_2$); 1.50–1.39 (m, 11 H); 1.18 (td, 2 H, ^3J = 7.5 Hz, J = 1.5 Hz); 0.94–0.89 (m, 6 H, CH(C*H*$_3)_2$) ppm.

^{13}C-NMR (101 MHz, MeOD-d_4): δ = 175.5; 173.6; 158.0; 138.1; 134.4; 132.0; 130.5; 129.7; 128.2; 128.0; 80.7; 68.9; 60.9; 58.3; 55.9; 55.8; 54.9; 54.6; 46.9; 42.0; 39.0; 28.7; 26.0; 25.9; 23.6; 23.4; 21.9; 19.5; 18.4 ppm.

MS (ESI): m/z: 577.4 $[M]^+$ (cal. 577.4).

Boc-Leu-Phe-Thr-((3*S*)-*N*-benzylquinuclidinium) bromide 185:



185

To a suspension of 1.32 g (6.02 mmol, 1.0 equiv) Boc-Thr-OH in 20 mL DMF 3.10 mL (2.36 g, 18.2 mmol, 3.0 equiv) D*i*PEA were added. After stirring the resulting solution for 5 min at r.t. 1.20 g (6.06 mmol, 1.0 equiv) **181** • 2 HCl were added. After stirring for additional 10 min at r.t. the reaction mixture was cooled to 0 °C and 2.28 g (6.01 mmol, 1.0 equiv) HBTU were added. After stirring the reaction mixture for 24 h at r.t. the solvent was evaporated under reduced pressure. The residue was dissolved in 50 mL $CHCl_3$/MeOH (9:1). The organic layer was

washed with 30 mL sat. $NaHCO_3$. The aq solution was extracted two times with 25 mL $CHCl_3$/MeOH (9:1). The combined organic layers were washed with 30 mL birne and dried over $MgSO_4$. 1.47 g (4.49 mmol, 75%) Boc-Thr-((3*S*)-*N*-benzylquinuclidine) were isolated as orange oil. The crude product was used without further purification.
MS (ESI): m/z: 328.1 $[M + H]^+$ (cal. 328.2); 350.1 $[M + H]^+$ (cal. 350.2).

The synthesis of ClH_3N-Thr-((3*S*)-*N*-benzylquinuclidinium) chloride was performed with 1.47 g (4.49 mmol, 1.0 equiv) Boc-Thr-((3*S*)-*N*-benzylquinuclidine) and 6.3 mL HCl in 1,4-dioxane (4 M) utilizing GP-8. The crude product was used without further purification or analytics. To a suspension of 0.500 g (1.88 mmol, 1.3 equiv) Boc-Phe-OH **94** in 20 mL DMF 0.640 mL (0.486 g, 3.76 mmol, 2.5 equiv) D*i*PEA were added. After stirring the resulting solution for 5 min at r.t. 0.450 g (1.50 mmol, 1.0 equiv) ClH_3N-Thr-((3*S*)-*N*-benzylquinuclidinium) chloride were added. After stirring for additional 10 min at r.t. the reaction mixture was cooled to 0 °C and 0.710 g (1.87 mmol, 1.2 equiv) HBTU were added. After stirring the reaction mixture for 24 h at r.t. the solvent was evaporated under reduced pressure. The residue was dissolved in 50 mL $CHCl_3$/MeOH (9:1). The organic layer was washed with 30 mL sat. $NaHCO_3$. The aq solution was extracted two times with 25 mL $CHCl_3$/MeOH (9:1). The combined organic layers were washed with 30 mL birne and dried over $MgSO_4$. 0.720 g (1.52 mmol, quant.) Boc-Phe-Thr-((3*S*)-*N*-benzylquinuclidine) were isolated as orange oil. The crude product was used without further purification.
MS (ESI): m/z: 475.4 $[M + H]^+$ (cal. 475.4).

The synthesis of ClH_3N-Phe-Thr-((3*S*)-*N*-benzylquinuclidinium) chloride was performed with 0.720 g (1.52 mmol, 1.0 equiv) Boc-Phe-Thr-((3*S*)-*N*-benzylquinuclidine) and 2.1 mL HCl in 1,4-dioxane (4 M) utilizing GP-8. The crude product was used without further purification and analytics. To a suspension of 0.400 g (1.73 mmol, 1.3 equiv) Boc-Leu-OH in 20 mL DMF 0.545 mL (0.414 g, 3.20 mmol, 2.4 equiv) D*i*PEA were added. After stirring the resulting solution for 5 min at r.t. 0.600 g (1.35 mmol, 1.0 equiv) ClH_3N-Phe-Thr-((3*S*)-*N*-benzylquinuclidinium) chloride were added. After stirring for additional 10 min at r.t. the reaction mixture was cooled to 0 °C and 0.610 g (1.61 mmol, 1.2 equiv) HBTU were added. After stirring the reaction mixture for 24 h at r.t. the solvent was evaporated under reduced pressure. The residue was dissolved in 50 mL $CHCl_3$/MeOH (9:1). The organic layer was washed with 30 mL sat. $NaHCO_3$. The aq solution was extracted two times with 25 mL $CHCl_3$/MeOH (9:1). The combined organic layers were washed with 30 mL birne and dried

over $MgSO_4$. 0.840 g (1.43 mmol, quant.)[13] Boc-Leu-Phe-Thr-((3*S*)-*N*-benzylquinuclidine) were isolated as orange oil. The crude product was used without further purification.

MS (ESI): m/z: 588.4 $[M + H]^+$ (cal. 588.4).

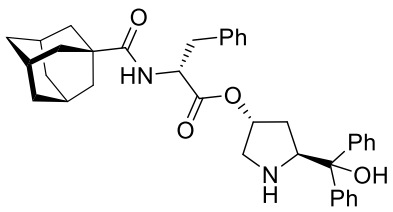
To a solution of 0.450 g (0.766 mmol, 1.0 equiv) Boc-Leu-Phe-Thr-((3*S*)-*N*-benzylquinuclidine) in 10 mL MeCN 0.092 mL (0.132 g, 0.774 mmol, 1.0 equiv) BnBr were added. After refluxing the resulting solution for 72 h the solvent was evaporated under reduced pressure. The residue was dissolved in 5 mL MeCN and the crude product precipitated by addition of Et_2O. After filtration and washing with Et_2O the crude product was dried over night in the desiccator. After centrifugation and decantation with Et_2O 0.180 g (0.237 mmol, 31%) **185** were isolated as fawn solid.

^{1}H-NMR (400 MHz, MeOD-d_4): δ = 7.70–7.45 (m, 5 H); 7.39–7.17 (m, 5 H); 4.70–4.41 (m, 3 H); 4.38–4.13 (m, 3 H); 4.11–3.83 (m, 2 H); 3.73–3.46 (m, 5 H); 3.42–3.28 (m, 2 H and MeOH); 3.27–3.13 (m, 1 H); 3.11–2.96 (m, 1 H); 2.37–2.16 (m, 2 H); 2.15–2.02 (m, 2 H); 2.00–1.87 (m, 1 H); 1.75–1.54 (m, 1 H); 1.52–1.31 (m, 10 H); 1.27–1.06 (m, 5 H); 1.04–0.81 (m, 6 H, $CH(C\mathit{H}_3)_2$) ppm.

^{13}C-NMR (101 MHz, MeOD-d_4): δ = 176.4; 173.6; 172.7; 158.0; 138.1; 134.3; 131.8; 130.4; 129.6; 128.2; 127.9; 80.9 ($\mathit{C}(CH_3)_3$); 69.0 ($\mathit{C}H_2$); 68.2; 66.9 ($\mathit{C}H_2$); 60.8 ($\mathit{C}H_2$); 60.3; 56.5; 55.4 ($\mathit{C}H_2$); 55.3 ($\mathit{C}H_2$); 54.9; 46.9; 41.9 ($\mathit{C}H_2$); 37.9 ($\mathit{C}H_2$); 28.8 ($C(\mathit{C}H_3)_3$); 26.2; 25.8; 23.6 ($\mathit{C}H_2$); 23.3 ($CH(\mathit{C}H_3)_2$); 22.0 ($CH(\mathit{C}H_3)_2$); 20.5; 19.7 ($\mathit{C}H_2$); 15.5 ppm.

MS (ESI): m/z: 678.4 $[M]^+$ (cal. 678.4).

Ad-Phe-((2*S*,4*R*)-4-oxy-2-pyrrolidinyl)diphenylmethanol 192:



192

0.011 g (0.090 mmol, 0.1 equiv, 9 mol%) DMAP and 0.321 g (1.67 mmol, 1.7 equiv) EDAC were dissolved in 56 mL DCM. After cooling the reaction mixture to 0 °C 0.400 g (1.01 mmol, 1.0 equiv) hydrochloride **188** were added over 10 min and the resulting mixture was stirred for 1 h at this temperature. After addition of 0.444 g (1.67 mmol, 1.7 equiv) Boc-Phe-OH **94** the reaction mixture was refluxed for an additional hour. The reaction mixture was washed with citric acid (0.5 M) as well as sat. $NaHCO_3$ (three times 56 mL). After drying over Na_2SO_4 the solvent was removed under reduced pressure. After purification *via* column chromatography (*n*-hexane:EtOAc 3:1)

[13] Contains traces of solvent.

0.566 g (0.933 mmol, 92%) Boc-Phe-((2*S*,4*R*)-4-oxy-2-pyrrolidinyl)diphenylmethanol **189** were isolated as colorless foam.

R_f: 0.52 (*n*-hexane:EtOAc 3:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, 2 H, ^3J = 7.5 Hz); 7.57 (d, 2 H, ^3J = 7.4 Hz); 7.34–7.27 (m, 8 H); 7.24–7.15 (m, 7 H); 7.00 (d, 2 H, ^3J = 6.4 Hz); 5.02–5.00 (m, 1 H, CO_2CH); 4.81 (s, 1 H, O*H*); 4.58–4.53 (m, 1 H, CH_{Phe}); 4.20 (t, 1 H, ^3J = 8.0 Hz, $CHC_{quart.,OH}$); 3.30–3.20 (m, 2 H, $CH_{2,Bn}$); 3.12–3.02 (m, 3 H, $CH_{2,Phe}$ and CH_2N_{Bn}); 2.64 (d, 1 H, ^2J = 12.3 Hz, CH_2N_{Bn}); 1.92–1.85 (m, 1 H, $CH_2CHC_{quart.,OH}$); 1.80–1.75 (m, 1 H, $CH_2CHC_{quart.,OH}$); 1.44 (s, 9 H, $C(CH_3)_3$) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.8 (CO_2CH); 155.2 ($COC(CH_3)_3$); 147.5 ($C_{quart.,Ph}$); 145.7 ($C_{quart.,Ph}$); 139.3($C_{quart.,Ph}$); 136.2 ($C_{quart.,Ph}$); 129.4 (CH_{Ph}); 128.8 (CH_{Ph}); 128.41(CH_{Ph}); 128.37 (CH_{Ph}); 128.3 (CH_{Ph}); 127.23 (CH_{Ph}); 127.18(CH_{Ph}); 126.8(CH_{Ph}); 126.6 (CH_{Ph}); 125.7 (CH_{Ph}); 125.5 (CH_{Ph}); 80.2 ($C(CH_3)_3$); 76.8 ($C_{quart.,OH}$); 75.3 (CO_2CH); 70.6 ($CHC_{quart.,OH}$); 61.2 ($CH_{2,Bn}$); 59.1 (CH_2N_{Bn}); 54.7 (CH_{Phe}); 38.7 ($CH_{2,Phe}$); 35.5 ($CH_2CHC_{quart.,OH}$); 28.4 ($C(CH_3)_3$) ppm.

IR (ATR): $\tilde{\nu}$ = 3352 (vw); 2978 (vw); 2249 (vw); 1708 (m); 1494 (w); 1162 (m); 729 (s); 697 (s) cm^{-1}.

HR-MS (ESI): m/z: 607.3179 $[M + H]^+$ (cal. 607.3166); 629.3003 $[M + Na]^+$ (cal. 629.2986).

MS (ESI): m/z: 607.4 $[M + H]^+$ (cal. 607.3); 629.4 $[M + Na]^+$ (cal. 629.4).

The synthesis of hydrochloride **190** was performed with 0.566 g (0.933 mmol, 1.0 equiv) Boc-Phe-((2*S*,4*R*)-4-Oxy-2-pyrrolidinyl)diphenylmethanol **189** and 1.87 mL HCl in 1,4-dioxane (4 M) utilizing GP-8. 0.507 g (0.934 mmol, quant.) hydrochloride **190** were obtained as orange oil.

MS (ESI): m/z: 507.3 $[M + H]^+$ (cal. 507.3).

The synthesis of Bn-protected amine **191** was performed with 0.507 g (0.934 mmol, 1.0 equiv) hydrochloride **190**, 0.168 g (0.932 mmol, 1.0 equiv) Ad-CO_2H, 0.197 g (1.03 mmol, 1.1 equiv) EDAC, 0.157 g (1.16 mmol, 1.2 equiv) HOBt, 0.143 mL (0.104 g, 1.03 mmol, 1.1 equiv) TEA, and 10 mL DCM (GP-6). After 24 h the reaction mixture was diluted with DCM. For removing the unreacted acid the organic layer was washed three times with Na_2CO_3. After purification *via* column chromatography (*n*-hexane:EtOAc 3:1) 0.309 g of a redish foam consisting of **191** and Ad-CO_2H (around 20%) were obtained.

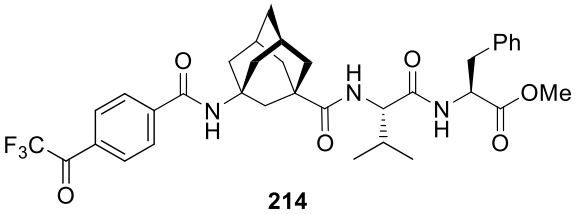
R_f: 0.19 (*n*-hexane:EtOAc 3:1).

MS (ESI): m/z: 669.5 $[M + H]^+$ (cal. 669.4); 691.5 $[M + Na]^+$ (cal. 691.4); 1359.4 $[M + 2Na]^+$ (cal. 1359.7).

The synthesis of Ad-Phe-((2*S*,4*R*)-4-oxy-2-pyrrolidinyl)diphenylmethanol **192** was performed with 0.092 g of acid-impured Bn-protected amine **191**, 0.040 g Pd/C (10%), and 10 mL MeOH (GP-7). The reaction mixture was stirred for 2 d. 0.072 g of a colorless solid consisting of **192** and Ad-CO_2H (around 20%) were obtained.

MS (ESI): m/z: 579.4 $[M + H]^+$ (cal. 579.3); 601.4 $[M + Na]^+$ (cal. 601.3).

CM-AdGly-Val-Phe-OMe 214:



214

The synthesis of Boc-Val-Phe-OMe was performed with 0.506 g (2.35 mmol, 1.0 equiv) hydrochloride **130**, 0.510 g (2.35 mmol, 1.0 equiv) Boc-Val-OH, 0.504 g (2.63 mmol, 1.1 equiv) EDAC, 0.359 g (2.66 mmol, 1.1 equiv) HOBt, 0.360 mL (0.262 g, 2.59 mmol, 1.1 equiv) TEA, and 9 mL DCM utilizing GP-6. After 16.5 h the reaction mixture was diluted with EtOAc. For washing a volume of 20 mL was used. 0.682 g (1.80 mmol, 77%) dipeptide were obtained as colorless solid.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.27–7.12 (m, 3 H and $CHCl_3$); 7.10–6.99 (m, 2 H); 6.26 (d, 1 H, ^3J = 6.8 Hz, N*H*); 4.95 (d, 1 H, ^3J = 8.3 Hz, N*H*); 4.80 (dt, 1 H, ^3J = 7.8 Hz, ^3J = 6.0 Hz); 3.83 (dd, 1 H, ^3J = 8.6 Hz, ^3J = 6.2 Hz); 3.64 (s, 3 H, OCH_3); 3.08–3.01 (m, 2 H, CHCH_2); 2.15–1.92 (m, 1 H, C*H*(CH_3)$_2$); 1.38 (s, 9 H, C(CH_3)$_3$); 0.85 (d, 3 H, ^3J = 6.8 Hz, CH(CH_3)$_2$); 0.79 (d, 3 H, ^3J = 6.7 Hz, CH(CH_3)$_2$) ppm.

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 171.9; 171.4; 155.8; 135.8; 129.4; 128.8; 127.3; 80.9; 60.0; 53.2; 52.5; 38.1; 31.0; 28.4; 19.3; 17.8 ppm.

MS (ESI): m/z: 401.1 $[M + Na]^+$ (cal. 401.2).

The synthesis of ClH_3N-Val-Phe-OMe was performed with 0.661 g (1.75 mmol, 1.0 equiv) Boc-Val-Phe-OMe and 3.6 mL HCl in 1,4-dioxane (4 M) utilizing GP-8. The crude product was obtained as colorless solid and used without further purification.

MS (ESI): m/z: 279.0 $[M + H]^+$ (cal. 279.2).

The synthesis of Boc-AdGly-Val-Phe-OMe was performed with the crude product of ClH_3N-Val-Phe-OMe, 0.517 g Boc-AdGly-OH (1.75 mmol, 1.0 equiv), 0.372 g (1.94 mmol, 1.1 equiv) EDAC, 0.268 g (1.98 mmol, 1.1 equiv) HOBt, 0.270 mL (0.197 g, 1.95 mmol, 1.1 equiv) TEA, and 20 mL DCM utilizing GP-6. After 24.5 h the reaction mixture was diluted

with 200 mL EtOAc. For washing a volume of 50 mL was used. After purification *via* column chromatography (DCM:MeOH 30:1 to 20:1) 0.764 g (1.37 mmol, 79% over two steps) tripeptides were isolated as colorless solid.

R_f: 0.22 (DCM:MeOH 30:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.25–7.14 (m, 3 H and $CHCl_3$); 7.05–7.01 (m, 2 H); 6.35–6.25 (m, 1 H, N*H*); 6.08 (d, 1 H, ^3J = 8.3 Hz, N*H*); 4.78 (dt, 1 H, ^3J = 7.6 Hz, ^3J = 6.2 Hz); 4.40 (d, 1 H, ^3J = 5.1 Hz, N*H*); 4.23–4.16 (m, 1 H); 3.64 (s, 3 H, OCH_3); 3.08–2.98 (m, 2 H, CHCH_2); 2.14 (bs, 2 H); 2.04–1.96 (m, 1 H, C*H*(CH_3)$_2$); 1.92 (bs, 2 H); 1.90–1.79 (m, 4 H); 1.74–1.67 (m, 4 H); 1.61–1.53 (m, 2 H); 1.36 (s, 9 H, C(CH_3)$_3$); 0.84–0.80 (m, 6 H, CH(CH_3)$_2$) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 176.6; 171.8; 171.1; 154.2; 135.7; 129.3; 128.8; 127.4; 79.1; 57.9; 53.3; 52.5; 50.9; 43.2; 42.9; 41.0; 38.4; 38.0; 35.4; 31.2; 29.3; 28.6; 19.2; 18.2 ppm.

MS (ESI): m/z: 556.2 $[M + H]^+$ (cal. 556.3); 578.4 $[M + Na]^+$ (cal. 578.3); 594.3 $[M + K]^+$ (cal. 594.3).

The synthesis of ClH_3N-AdGly-Val-Phe-OMe was performed with 0.764 g (1.37 mmol, 1.0 equiv) Boc- AdGly-Val-Phe-OMe and 3 mL HCl in 1,4-dioxane (4 M) utilizing GP-8. The crude product was obtained as colorless solid and used without further purification.

MS (ESI): m/z: 456.1 $[M + H]^+$ (cal. 456.3); 478.3 $[M + Na]^+$ (cal. 478.3); 911.3 $[2M + H]^+$ (cal. 911.6).

The synthesis of CM-AdGly-Val-Phe-OMe **214** was performed with 0.115 g (0.234 mmol, 1.0 equiv) hydrochloride, 61.9 mg (0.284 mmol, 1.2 equiv) ***para*-112**, 51.4 mg (0.268 mmol, 1.1 equiv) EDAC, 38.3 mg (0.283 mmol, 1.2 equiv) HOBt, 35.6 µL (26.0 mg, 0.256 mmol, 1.1 equiv) TEA, and 3 mL DCM utilizing GP-6. After 24 h the reaction mixture was diluted with 30 mL EtOAc. For washing a volume of 7 mL was used. After purification *via* column chromatography (*n*-hexane:EtOAc 1:3) 69.8 mg (0.106 mmol, 45%) functionalized tripeptides **214** were isolated as colorless solid.

R_f: 0.40 (*n*-hexane:EtOAc 1:3).

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.04 (d, 2 H, ^3J = 8.1 Hz, $H_{Ar\text{-}COCF3}$); 7.79 (d, 2 H, ^3J = 8.4 Hz, $H_{Ar\text{-}COCF3}$); 7.22–7.20 (m, 2 H and $CHCl_3$, H_{Ph}); 7.17–7.15 (m, 1 H, H_{Ph}); 7.04–7.03 (m, 2 H, H_{Ph}); 6.45 (d, 1 H, ^3J = 7.8 Hz, N*H*CHCH_2); 6.19 (d, 1 H, ^3J = 8.5 Hz, N*H*CHCH(CH_3)$_2$); 5.95 (s, 1 H, N*H*AdGly); 4.78 (dt, 1 H, ^3J = 7.9 Hz, ^3J = 6.2 Hz, C*H*CH_2); 4.23 (dd, 1 H, ^3J = 8.4 Hz, ^3J = 6.7 Hz, C*H*CH(CH_3)$_2$); 3.63 (s, 3 H, OCH_3); 3.06 (dd, 1 H, ^2J = 13.9 Hz, ^3J = 6.0 Hz, CHCH_2); 3.01 (dd, 1 H, ^2J = 13.9 Hz, ^3J = 6.4 Hz, CHCH_2); 2.22 (bs, 2 H, H_{Ad}); 2.16–2.11

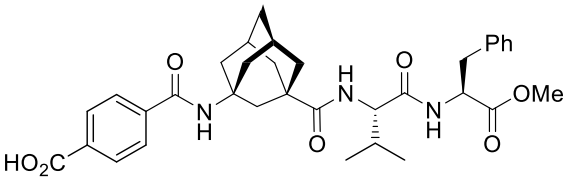
(m, 4 H, H_{Ad}); 2.02–1.97 (m, 3 H, H_{Ad} and CH(CH$_3$)$_2$); 1.82–1.77 (m, 2 H, H_{Ad}); 1.76–1.72 (m, 2 H, H_{Ad}); 1.68 (d, 1 H, J = 12.7 Hz, H_{Ad}); 1.60 (d, 1 H, J = 12.6 Hz, H_{Ad}); 0.84 (d, 3 H, ^3J = 6.8 Hz, CH(CH_3)$_2$); 0.82 (d, 3 H, ^3J = 6.8 Hz, CH(CH_3)$_2$) ppm.

^{13}C-NMR (151 MHz, CDCl$_3$): δ = 180.1 (q, $^2J_{CF}$ = 35.6 Hz, COCF$_3$); 176.4 (CO); 171.9 (CO); 171.1 (CO); 165.3 (CO); 141.9 ($C_{quart.}$); 135.7 ($C_{quart.}$); 131.8 ($C_{quart.}$); 130.45 (CH$_{Ar\text{-}COCF3}$); 130.44 (CH$_{Ar\text{-}COCF3}$); 129.3 (CH$_{Ph}$); 128.8 (CH$_{Ph}$); 127.7 (CH$_{Ar\text{-}COCF3}$); 127.4 (CH$_{Ph}$); 116.6 (q, $^1J_{CF}$ = 291.1 Hz, COCF$_3$); 57.9 (CHCH(CH$_3$)$_2$; 53.31 (CHCH$_2$); 53.27 ($C_{quart.,\ Ad}$); 52.5 (OCH$_3$); 43.0 ($C_{quart.,\ Ad}$); 42.9 (CH$_{2,Ad}$); 40.5 (CH$_{2,Ad}$); 38.5 (CH$_{2,Ad}$); 38.4 (CH$_{2,Ad}$); 38.0 (CHCH$_2$); 35.3 (CH$_{2,Ad}$); 31.4 (CHCH(CH$_3$)$_2$; 29.4 (CH$_{Ad}$); 19.2 (CH(CH$_3$)$_2$); 18.2 (CH(CH_3)$_2$) ppm.

HR-MS (ESI): m/z: 710.3027 [M + MeOH + Na]$^+$ (cal. 710.3024).

MS (ESI): m/z: 710.4 [M + MeOH + Na]$^+$ (cal. 710.3); 1397.1 [2M + 2MeOH + Na]$^+$ (cal. 1397.6).

Terephthalic acid-AdGly-Val-Phe-OMe 215:



215

The synthesis of terephthalic acid-AdGly-Val-Phe-OMe **215** was performed with 0.116 g (0.236 mmol, 1.0 equiv) hydrochloride, 44.0 mg (0.265 mmol, 1.1 equiv) terephthalic acid, 51.6 mg (0.269 mmol, 1.1 equiv) EDAC, 36.1 mg (0.267 mmol, 1.1 equiv) HOBt, 71.2 µL (51.9 mg, 0.513 mmol, 2.2 equiv) TEA, and 3 mL DCM utilizing GP-6. After 25 h the reaction mixture was diluted with 30 mL EtOAc. The organic layer was only washed with citric acid (0.5 M) (three times 7 mL). After purification *via* column chromatography (DCM:MeOH 30:1 to 30:1) 0.054 g (0.089 mmol, 38%) functionalized tripeptides **215** were isolated as colorless solid.

R$_f$: 0.53 (DCM:MeOH 7:1).

^{1}H-NMR (600 MHz, CDCl$_3$): δ = 9.36 (bs, 1 H, COOH); 8.04 (d, 2 H, ^3J = 8.0 Hz, $H_{Ar\text{-}COOH}$); 7.65 (d, 2 H, ^3J = 8.0 Hz, $H_{Ar\text{-}COOH}$); 7.27–7.22 (m, 2 H and CHCl$_3$, H_{Ph}); 7.21–7.17 (m, 1 H, H_{Ph}); 7.12–7.08 (m, 2 H, H_{Ph}); 7.06 (bs, 1 H, NHCHCH$_2$); 6.97 (d, 1 H, ^3J = 8.6 Hz, NHCHCH(CH$_3$)$_2$); 5.98 (bs, 1 H, NHAdGly); 4.89–4.85 (m, 1 H, CHCH$_2$); 4.40–4.33 (m, CHCH(CH$_3$)$_2$); 3.70 (s, 3 H, OCH_3); 3.15 (dd, 1 H, ^2J = 13.9 Hz, ^3J = 5.8 Hz, CHCH_2); 3.08 (dd, 1 H, ^2J = 13.9 Hz, ^3J = 6.6 Hz, CHCH_2); 2.27 (bs, 2 H, H_{Ad}); 2.25–2.18 (m, 4 H, H_{Ad}); 2.13–2.03 (m, 3 H, H_{Ad} and CH(CH$_3$)$_2$); 1.93–1.86 (m, 2 H, H_{Ad}); 1.86–1.77 (m, 2 H, H_{Ad}); 1.73 (d, 1 H, J = 11.8 Hz, H_{Ad}); 1.68 (d, 1 H, J = 11.6 Hz, H_{Ad}); 0.93–0.91 (m, 6 H, CH(CH_3)$_2$) ppm.

^{13}C-NMR (151 MHz, $CDCl_3$): δ = 177.2 (*C*O); 172.4 (*C*O); 171.6 (*C*O); 168.7 (*C*OOH); 166.1 (*C*O); 139.9 ($C_{quart.}$); 135.7 ($C_{quart.}$); 132.6 ($C_{quart.}$); 130.3 ($CH_{Ar\text{-}COOH}$); 129.3 (CH_{Ph}); 128.8 (CH_{Ph}); 127.3 (CH_{Ph}); 126.9 ($CH_{Ar\text{-}COOH}$); 58.7 ($CHCH(CH_3)_2$; 53.6 ($CHCH_2$); 53.1 ($C_{quart.,\ Ad}$); 52.5 (OCH_3); 43.0 ($C_{quart.,\ Ad}$); 42.5 ($CH_{2,Ad}$); 40.6 ($CH_{2,Ad}$); 40.5 ($CH_{2,Ad}$); 38.7 ($CH_{2,Ad}$); 38.3 ($CH_{2,Ad}$); 37.9 ($CHCH_2$); 35.3 ($CH_{2,Ad}$); 30.9 ($CHCH(CH_3)_2$; 29.4 (CH_{Ad}); 29.3 (CH_{Ad}); 19.3 ($CH(CH_3)_2$); 18.7 ($CH(CH_3)_2$) ppm.

HR-MS (ESI): m/z: 626.2833 $[M + Na]^+$ (cal. 626.2837).

MS (ESI): m/z: 602.3 $[M - H]^-$ (cal. 602.3).

9.4.2. SPPS

Fmoc-deprotection (GP-10):[14]

A syringe (reaction vessel) was charged with preloaded *N*-terminally Fmoc-protected polystyrene Wang resin. The deprotection was performed by shaking the solid support two times for 30 min in 6 mL (2 mL) piperidine (25% in DMF). Afterwards the resin was washed five times each with 6 mL (1.5 mL) DMF, DCM, and DMF.

Peptide coupling (GP-11):[14]

The peptide coupling was performed by shaking the reaction mixture containing *N*-terminal deprotected resin, Fmoc-protected amino acid, HOBt, HBTU, and D*i*PEA for 1 h in 3.6 mL (volume depending on the conc. of the used amino acid) DMF. After filtration of the first coupling solution the procedure was repeated. In case of Boc-protected PMH the reaction time was prolonged to 2 h. After filtration of the second coupling solution the resin was washed five times each with 6 mL (1.5 mL) DMF, DCM, and DMF.

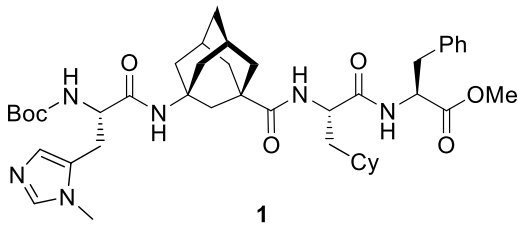
Both procedures were repeated until the desired oligopeptides were synthesized. The final washing step was carried out five times each with 6 mL (1.5 mL) DMF, DCM, and Et_2O.

Peptide cleavage (GP-12):[14]

For cleavage of the peptide from the resin the reaction mixture was shaken two times for 2 d in 6 mL (2 mL) of a TEA-THF-MeOH solation (1:1:9; v/v). After filtration of the second cleavage solution the resin was washed four times with 4 mL (0.5 mL) DCM. After removing the solvent under reduced pressure and co-evaporating several times with DCM the target compound was purified *via* HPLC.

[14] Data in brackets belong to the automated peptide synthesis.

Boc-PMH-AdGly-Cha-Phe-OMe 1:

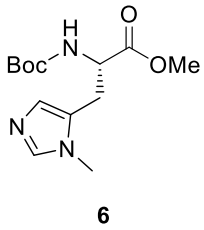


1

The synthesis of Boc-PMH-AdGly-Cha-Phe-OMe **1** was performed using GP-10, GP-11, and GP-12. 0.455 g (0.300 mmol) of preloaded Fmoc-Phe-Wang resin **116** were utilized. One coupling step was performed with 0.237 g (0.603 mmol, 2.0 equiv) Fmoc-Cha-OH or 0.251 g (0.602 mmol, 2.0 equiv) Fmoc-AdGly-OH as well as 0.092 g (0.681 mmol, 2.3 equiv) HOBt, 0.228 g (0.600 mmol, 2.0 equiv) HBTU, 0.204 mL (0.151 g, 1.17 mmol, 3.9 equiv) D*i*PEA. In case of Boc-PMH-OH 0.122 g (0.451 mmol, 1.5 equiv) were used. After purification *via* HPLC (eluent: TBME/MeOH 93:7; 5 mL min^{-1}; UV detector 254 nm, column: l = 250 mm, d = 8 mm; LiChrosorb Diol (7 µm, Merck); Rt = 3.6 min) 0.054 g (0.071 mmol, 24%) tetrapeptide **1** were obtained as colorless solid.

For analytic data see synthesis of tetrapeptide **1** in solution.

Boc-PMH-OMe 6:



6

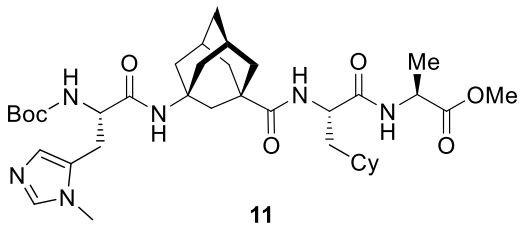
During purification of tetrapeptide **1** *via* HPLC 0.017 g (0.060 mmol, 3%) fully protected amino acid **6** were obtained as colorless oil (eluent: TBME/MeOH 93:7; 5 mL min^{-1}; UV detector 254 nm, column: l = 250 mm, d = 8 mm; LiChrosorb Diol (7 µm, Merck); Rt = 5.9 min).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.39 (s, 1 H); 6.77 (s, 1 H); 5.25–5.16 (m, 1 H,); 4.55–4.50 (m, 1 H); 3.73 (s, 3 H); 3.57 (s, 3 H); 3.11 (dd, 1 H, ^{2}J = 15.3 Hz, ^{3}J = 5.7 Hz); 3.04 (dd, 1 H, ^{2}J = 15.4 Hz, ^{3}J = 6.0 Hz); 1.41 (s, 9 H) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.8; 155.2; 138.5; 128.3; 126.6; 80.4; 53.2; 52.7; 31.5; 28.4; 27.0 ppm.

Analytic data are identical to those reported in literature.[22]

Boc-PMH-AdGly-Cha-Ala-OMe 11:



11

The synthesis of Boc-PMH-AdGly-Cha-Ala-OMe **11** was performed using GP-10, GP-11, and GP-12. 0.750 g (0.300 mmol) of preloaded Fmoc-Ala-Wang resin were utilized. One coupling step was performed with 0.237 g (0.603 mmol, 2.0 equiv) Fmoc-Cha-OH or 0.251 g (0.602 mmol, 2.0 equiv) Fmoc-AdGly-OH as well as 0.092 g (0.681 mmol, 2.3 equiv) HOBt, 0.228 g (0.600 mmol, 2.0 equiv) HBTU, 0.204 mL (0.151 g,

1.17 mmol, 3.9 equiv) D*i*PEA. In case of Boc-PMH-OH 0.122 g (0.451 mmol, 1.5 equiv) were used. After purification *via* HPLC (eluent: TBME/MeOH 90:10; 5 mL min^{-1}; UV detector 254 nm, column: l = 250 mm, d = 8 mm; LiChrosorb Diol (7 µm, Merck); Rt = 8.6 min) 0.043 g (0.063 mmol, 21%) tetrapeptide **11** were obtained as colorless solid.

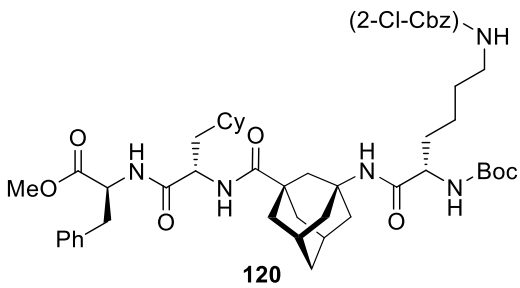
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.42 (s, 1 H); 7.07 (d, 1 H, ^{3}J = 7.3 Hz); 6.82 (s, 1 H); 6.29 (d, 1 H, ^{3}J = 8.0 Hz); 6.23 (s, 1 H); 5.37 (bs, 1 H); 4.53–4.45 (m, 2 H); 4.23 (bs, 1 H); 3.71 (s, 3 H); 3.57 (s, 3 H); 2.95–2.94 (m, 2 H); 2.16 (bs, 2 H); 1.97–1.89 (m, 4 H); 1.81–1.69 (m, 6 H); 1.68–1.57 (m, 8 H); 1.39 (s, 9 H); 1.35 (d, 3 H, ^{3}J = 7.2 Hz); 1.26–1.10 (m, 5 H); 0.97–0.75 (m, 2 H) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 176.7; 173.2; 172.3; 170.0; 155.5; 138.1; 128.0; 127.5; 80.4; 54.4; 52.5; 52.4; 50.7; 48.1; 42.6; 42.4; 40.4; 40.2; 39.8; 38.3; 38.2; 35.2; 34.2; 33.6; 32.8; 31.6; 29.18; 29.16; 28.7; 28.4; 27.1; 26.5; 26.3; 26.2; 18.0 ppm.

MS (ESI): m/z: 685.4 $[M + H]^+$ (cal. 685.4), 707.4 $[M + Na]^+$ (cal. 707.4).

HR-MS (ESI): m/z: 354.2123 $[M + H + Na]^{2+}$ (cal. 354.2088) 685.4289 $[M + Na]^+$ (cal. 685.4283).

Boc-Lys(2-Cl-Cbz)-AdGly-Cha-Phe-OMe 120:

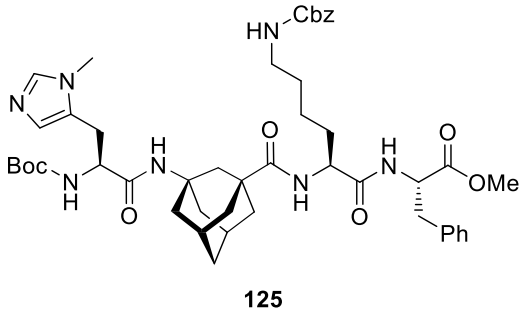


120

The synthesis of Boc-Lys(2-Cl-Cbz)-AdGly-Cha-Phe-OMe **120** was performed using GP-10, GP-11, and GP-12. 0.155 g (0.102 mmol) of preloaded Fmoc-Phe-Wang resin **116** were utilized. One coupling step was performed with 0.087 g (0.220 mmol, 2.2 equiv) Fmoc-Cha-OH, 0.086 g (0.202 mmol, 2.0 equiv) Fmoc-AdGly-OH or 0.091 g (0.219 mmol, 2.2 equiv) Boc-Lys(2-Cl-Cbz)-OH as well as 0.028 g (0.207 mmol, 2.0 equiv) HOBt, 0.077 g (0.203 mmol, 2.0 equiv) HBTU, 0.100 mL (0.076 g, 0.588 mmol, 5.8 equiv) D*i*PEA. After removing the solvent under reduced pressure and high vacuum 0.067 g (0.074 mmol, 74%) tetrapeptide **120** were obtained as yellow oil.

MS (ESI): m/z: 928.5 $[M + Na]^+$ (cal. 928.5).

Boc-PMH-AdGly-Lys(Cbz)-Phe-OMe 125:

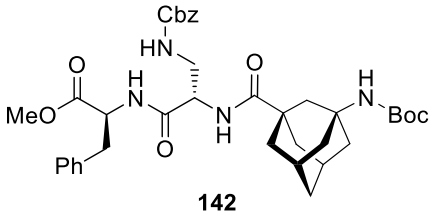


125

The synthesis of Boc-PMH-AdGly-Lys(Cbz)-Phe-OMe **125** was performed using GP-10, GP-11, and GP-12. 0.154 g (0.102 mmol) of preloaded Fmoc-Phe-Wang resin **116** were utilized. One coupling step was performed with 0.104 g (0.206 mmol, 2.0 equiv) Fmoc-Lys(Cbz)-OH, 0.086 g (0.206 mmol, 2.0 equiv) Fmoc-AdGly-OH or 0.058 g (0.215 mmol, 2.1 equiv) Boc-PMH-OH as well as 0.027 g (0.203 mmol, 2.0 equiv) HOBt, 0.077 g (0.203 mmol, 2.0 equiv) HBTU, 0.100 mL (0.076 g, 0.588 mmol, 5.8 equiv) D*i*PEA. After removing the solvent under reduced pressure and high vacuum 0.064 g (0.074 mmol, 73%) tetrapeptide **125** were obtained as yellow oil.

MS (ESI): m/z: 870.4 $[M + H]^+$ (cal. 870.5), 892.3 $[M + Na]^+$ (cal. 892.5).

Boc-AdGly-Dap(Cbz)-Phe-OMe 142:



142

The synthesis of Boc-AdGly-Dap(Cbz)-Phe-OMe **142** was performed using GP-10, GP-11, and GP-12. 0.539 g (0.350 mmol) of preloaded Fmoc-Phe-Wang resin **116** were utilized. The first coupling step was performed only one time with 0.161 g (0.350 mmol, 1.0 equiv) Fmoc-Dap(Cbz)-OH **139**, 0.142 g (1.05 mmol, 3.0 equiv) HOBt, 0.401 g (1.06 mmol, 3.0 equiv) HBTU, 0.183 mL (0.136 g, 1.05 mmol, 3.0 equiv) D*i*PEA in 3 mL DMF. HOBt and HBTU were dissolved in 3 mL DMF. The second coupling step was performed with 0.208 g (0.703 mmol, 2.0 equiv) Boc-AdGly-OH, 0.102 g (0.755 mmol, 2.2 equiv) HOBt, 0.270 g (0.712 mmol, 2.0 equiv) HBTU, 0.122 mL (0.091 g, 0.700 mmol, 2.0 equiv) D*i*PEA in 2 mL DMF. HOBt and HBTU were dissolved in 2 mL DMF. After purification *via* column chromatography (DCM:MeOH 15:1) 54.4 mg (0.080 mmol, 23%) **142** were isolated as colorless solid.

R_f: 0.65 (DCM:MeOH 7:1).

^{1}H-NMR (400 MHz, $CDCl_3$):[15] δ = 7.31–7.11 (m, 9 H and $CHCl_3$); 7.03–6.96 (m, 3 H); 5.55–5.44 (m, 1 H); 5.04 (s, 2 H); 4.80–4.65 (m, 1 H); 4.40–4.30 (m, 2 H); 3.62 (s, 3 H); 3.54–3.36

[15] Racemization observable.

(m, 2 H); 3.05 (dd, 1 H, ^{2}J = 13.9 Hz, ^{3}J = 5.6 Hz); 2.93 (dd, 1 H, ^{2}J = 14.0 Hz, ^{3}J = 7.1 Hz); 2.12–2.07 (m, 2 H); 1.91–1.76 (m, 6 H); 1.65–1.50 (m, 6 H); 1.35 (s, 9 H) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$):[6] δ = 178.1; 171.7; 170.1; 158.2; 154.1; 136.3; 136.0; 129.3; 128.68; 128.65; 128.3; 128.1; 127.2; 79.0; 67.2; 54.9; 53.5; 52.5; 50.8; 43.0; 42.7; 42.6; 40.8; 38.04; 37.96; 37.8; 35.3; 29.2; 28.6 ppm.

MS (ESI): m/z: 699.3 $[M + Na]^+$ (cal. 699.3).

HR-MS (ESI): m/z: 699.3375 $[M + Na]^+$ (cal. 699.3364).

9.5. Epoxidation

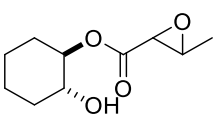
***m*CPBA-based epoxidation (GP-13)**:

The alkene was dissolved in DCM and the resulting solution was cooled to 0 °C. At this temperature *m*CPBA (70%) was added portionwise. Performing the epoxidation in a smaller scale, the oxidizer was added without using an ice bath. The resulting mixture was stirred at r.t. and the reaction progress was monitored *via* TLC. For removing remaining *m*CBA the organic layer was washed several times with sat. $NaHCO_3$. After combining and drying the organic layers over Na_2SO_4 and $MgSO_4$, resp., the solvent was evaporated. The crude product was purified utilizing column chromatography.

$NaOH/H_2O_2$-based epoxidation (GP-14):

1.0 equiv alkene was dissolved in MeOH or EtOH. The reaction was started *via* addition of $NaOH_{aq}$ and H_2O_2 (30%) and the resulting mixture was stirred afterwards. The reaction progress was monitored *via* TLC. After diluting the reaction mixture with brine or water the aq layer was extracted three times. After drying the organic layer over Na_2SO_4 the solvent was evaporated and the crude product was finally purified.

***trans*-2-Hydroxycyclohexyl 3-methyl-2-oxiranecarboxylate 22:** (GP-13)



22

0.080 g (0.434 mmol, 1.0 equiv) ester **17** were dissolved in 4 mL DCM. Afterwards 0.121 g (0.540 mmol, 1.2 equiv) *m*CPBA were added. The resulting mixture was stirred for 20 h. 10 mL brine were added and the aq layer was extracted with DCM (three times 10 mL). After purification *via* column chromatography (*n*-hexane:EtOAc 3:1 to 2:1) 0.053 g (0.265 mmol, 61%) **22** were isolated as slightly yellowish oil. Both diastereomers were obtained with a 2:1 ratio.

Diastereomer 1 (0.017 g):[16]

[16] Minimal traces of *m*CBA present in the spectrum.

R_f: 0.13 (*n*-hexane:EtOAc 2:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.70–4.64 (m, 1 H); 4.34 (bs, 1 H, O*H*); 3.65–3.55 (m, 1 H); 3.32–3.22 (m, 2 H); 2.10–2.00 (m, 2 H, H_{Cy}); 1.76–1.68 (m, 2 H, H_{Cy}); 1.40 (d, 3 H, ^3J = 5.1 Hz, CH_3); 1.36–1.23 (m, 4 H, H_{Cy}) ppm.

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 169.6; 79.4; 72.7; 54.8; 54.3; 33.3; 30.0; 23.9, 23.8; 17.3 ppm.

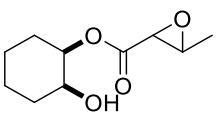
Diastereomer 2 (0.036 g):[17]

R_f: 0.09 (*n*-hexane:EtOAc 2:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.68–4.61 (m, 1 H); 3.98 (bs, 1 H, O*H*); 3.61–3.55 (m, 1 H); 3.25–3.19 (m, 2 H); 2.09–2.00 (m, 2 H, H_{Cy}); 1.74–1.67 (m, 2 H, H_{Cy}); 1.38 (d, 3 H, ^3J = 5.1 Hz, CH_3); 1.33–1.20 (m, 4 H, H_{Cy}) ppm.

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 169.4; 79.5; 72.4; 54.8; 54.3; 33.1; 30.0; 23.9, 23.9; 17.2 ppm.

***cis*-2-Hydroxycyclohexyl 3-methyl-2-oxiranecarboxylate 23:**[17,18] (GP-13)



23

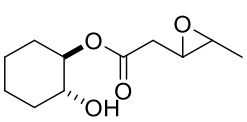
0.108 g (0.586 mmol, 1.0 equiv) ester **18** were dissolved in 4 mL DCM. Afterwards 0.160 g (0.649 mmol, 1.1 equiv) *m*CPBA were added. The resulting mixture was stirred for 24 h. 5 mL brine and 10 mL water were added and the aq layer was extracted with DCM (three times 10 mL). After purification *via* column chromatography (*n*-hexane:EtOAc 3:1 to 2:1) 0.084 g (0.420 mmol, 72%) **23** were isolated as colorless oil.

R_f: 0.13 (0.08) (*n*-hexane:EtOAc 2:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.98 (dt, 1 H, *J* = 7.8 Hz, *J* = 2.4 Hz,); 3.91–3.85 (m, 1 H); 3.49 (bs, 1 H, O*H*); 3.25–3.20 (m, 2 H); 1.91–1.83 (m, 1 H, H_{Cy}); 1.81–1.72 (m, 1 H, H_{Cy}); 1.70–1.52 (m, 4 H, H_{Cy}); 1.38–1.33 (m, 5 H, CH_3 and H_{Cy}) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 169.1 (169.0); 75.55 (75.59); 68.98 (68.95); 54.8 (54.9); 54.2 (54.3); 30.3; 26.9 (27.0); 22.0 (21.9); 21.0 (21.1); 17.23 (17.21) ppm.

***trans*-2-Hydroxycyclohexyl (3-methyl-2-oxiranyl)acetate 24a:** (GP-13)



24a

0.051 g (0.257 mmol, 1.0 equiv) ester **20a** were dissolved in 2 mL DCM. Afterwards 0.070 g (0.284 mmol, 1.1 equiv) *m*CPBA were added. The resulting mixture was stirred for 22 h. 8 mL brine and 10 mL water were added and the aq layer was extracted with DCM (three times 6 mL).

[17] Minimal traces of *m*CBA present in the spectrum.
[18] Data referring to the second diastereomer are given in brackets.

After purification *via* column chromatography (*n*-hexane:EtOAc 2:1) 0.038 g (0.177 mmol, 69%) **24a** were isolated as colorless oil. The diastereomers were separated *via* HPLC.

Diastereomer 1:

R_f: 0.10 (*n*-hexane:EtOAc 2:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.65–4.59 (m, 1 H, C*H*OC); 3.58–3.52 (m, 1 H, C*H*OH); 3.02 (dt, 1 H, ^3J = 5.3 Hz, ^3J = 2.2 Hz, CH_2CH); 2.89 (dq, 1 H, ^3J = 5.2 Hz, ^3J = 2.2 Hz, C*H*CH_3); 2.71 (dd, 1 H, ^2J = 15.7 Hz, ^3J = 5.0 Hz, C*H*$_2$CH); 2.59 (dd, 1 H, ^2J = 15.7 Hz, ^3J = 5.7 Hz, C*H*$_2$CH); 2.48 (bs, 1 H, O*H*); 2.08–2.00 (m, 2 H, H_{Cy}); 1.74–1.70 (m, 2 H, H_{Cy}); 1.39–1.24 (m, 7 H, C*H*$_3$ and H_{Cy}) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 170.4 (*C*O); 79.0 (*C*HOC); 72.8 (*C*HOH); 55.0 (CH_2CH); 54.7 (*C*HCH_3); 37.6 (*C*H_2CH); 32.9 (*C*H_2CHOH); 30.1 (*C*H_2CHOC); 24.0 (*C*H_2CH_2CHOC); 23.9 (*C*H_2CH_2CHOH); 17.4 (*C*H_3) ppm.

IR (Film): $\tilde{\nu}$ = 3407 (m); 2938 (m); 1702 (m); 1274 (m); 1182 (m); 857 (vw) cm^{-1}.

MS (ESI): m/z: 237.1 $[M + Na]^+$ (cal. 237.1); 451.2 $[2M + Na]^+$ (cal. 451.2); 665.3 $[3M + Na]^+$ (cal. 665.4).

Diastereomer 2:

R_f: 0.10 (*n*-hexane:EtOAc 2:1).

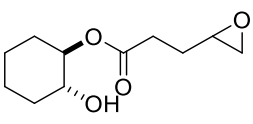
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.65–4.59 (m, 1 H, C*H*OC); 3.59–3.53 (m, 1 H, C*H*OH); 3.03–3.00 (m, 1 H, CH_2CH); 2.87 (dq, 1 H, ^3J = 5.2 Hz, ^3J = 2.1 Hz, C*H*CH_3); 2.63–3.52 (m, 2 H, C*H*$_2$CH); 2.33 (bs, 1 H, O*H*); 2.10–1.99 (m, 2 H, H_{Cy}); 1.78–1.68 (m, 2 H, H_{Cy}); 1.40–1.20 (m, 7 H, C*H*$_3$ and H_{Cy}) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 170.7 (*C*O); 78.9 (*C*HOC); 72.7 (*C*HOH); 55.2 (CH_2CH); 54.8 (*C*HCH_3); 38.1 (*C*H_2CH); 33.1 (*C*H_2CHOH); 30.1 (*C*H_2CHOC); 24.0 (*C*H_2CH_2CHOC); 23.9 (*C*H_2CH_2CHOH); 17.5 (*C*H_3) ppm.

IR (Film): $\tilde{\nu}$ = 3435 (s); 2939 (vs); 1732 (vs); 1262 (s); 1186 (vs); 864 (m) cm^{-1}.

MS (ESI): m/z: 237.1 $[M + Na]^+$ (cal. 237.1); 451.3 $[2M + Na]^+$ (cal. 451.2).

***trans*-2-Hydroxycyclohexyl 3-(2-oxiranyl)propionate 24b:** (GP-13)



24b

0.216 g (1.09 mmol, 1.0 equiv) alkene **20b** were dissolved in 4 mL DCM. Afterwards 0.245 g (0.990 mmol, 0.9 equiv) *m*CPBA were added. The resulting mixture was stirred for 24 h. After diluting with 20 mL EtOAc the work-up was performed with $NaHCO_3$ (five times 20 mL) and

brine (one time 20 mL). After purification *via* column chromatography (*n*-hexane:EtOAc 1:2) 0.126 g (0.588 mmol, 59%) **24b** were isolated as colorless oil.

R_f: 0.08 (*n*-hexane:EtOAc 2:1).

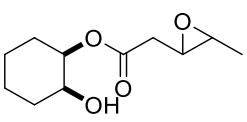
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.65–4.59 (m, 1 H, C*H*OC); 3.60–3.52 (m, 1 H, C*H*OH); 3.05–2.98 (m, 1 H, C*H*OCH_2); 2.79–2.76 (m, 1 H, CHOC*H*$_2$); 2.69 (dd, 1 H, ^3J = 14.5 Hz, ^4J = 3.4 Hz, CHO*H*); 2.56–2.52 (m, 1 H, CHOC*H*$_2$); 2.51–2.42 (m, 2 H, COC*H*$_2$$CH_2$CH); 2.13–1.96 (m, 3 H, $COCH_2$C*H*$_2$CH and H_{Cy}); 1.79–1.67 (m, 3 H, $COCH_2$C*H*$_2$CH and H_{Cy}); 1.39–1.19 (m, 4 H, H_{Cy}) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 173.2 and 172.9 (*C*O); 78.60 and 78.59 (*C*HOC); 72.85 and 72.82 (*C*HOH); 51.74 and 51.68 (*C*HOCH_2); 47.12 and 47.09 (CHO*C*H$_2$); 33.1 and 33.0 (*C*H_2CHOH); 31.30 and 31.26 (COC*H*$_2$$CH_2$CH); 30.2 and 30.1 (*C*$H_2$CHOC); 28.0 and 27.9 ($COCH_2$*C*$H_2$CH); 24.0 (*C*$H_2$$CH_2$CHOC); 23.9 (*C*$H_2$$CH_2$CHOH) ppm.

IR (Film): $\tilde{\nu}$ = 3453 (m); 2939 (s); 1732 (vs); 1258 (s); 1181 (m); 840 (w) cm^{-1}.

HR-MS (ESI): m/z: 215.1282 $[M + H]^+$ (cal. 215.1278); m/z: 237.1103 $[M + Na]^+$ (cal. 237.1097); m/z: 451.2305 $[2M + Na]^+$ (cal. 451.2302).

***cis*-2-Hydroxycyclohexyl (3-methyl-2-oxiranyl)acetate 25a:** (GP-13)



25a

0.104 g (0.525 mmol, 1.0 equiv) ester **21a** were dissolved in 5 mL DCM. Afterwards 0.144 g (0.584 mmol, 1.1 equiv) *m*CPBA were added. The resulting mixture was stirred for 7 h. 4 mL brine were added and the aq layer was extracted with DCM (three times 6 mL). After purification *via* column chromatography (*n*-hexane:EtOAc 1:1) 0.098 g (0.457 mmol, 87%) **25a** were isolated as colorless oil. The diastereomers were separated *via* HPLC.

Diastereomer 1:

R_f: 0.11 (*n*-hexane:EtOAc 2:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.99–4.97 (m, 1 H, C*H*OC); 3.84–3.82 (m, 1 H, C*H*OH); 3.02 (dt, 1 H, ^3J = 5.5 Hz, ^3J = 2.2 Hz, CH_2C*H*); 2.86 (dq, 1 H, ^3J = 5.2 Hz, ^3J = 2.2 Hz, C*H*CH_3); 2.68 (dd, 1 H, ^2J = 16.0 Hz, ^3J = 5.1 Hz, C*H*$_2$CH); 2.58 (dd, 1 H, ^2J = 16.0 Hz, ^3J = 6.0 Hz, C*H*$_2$CH); 2.22 (bs, 1 H, O*H*); 1.93–1.80 (m, 1 H, H_{Cy}); 1.77–1.49 (m, 5 H, H_{Cy}); 1.43–1.24 (m, 5 H, C*H*$_3$ and H_{Cy}) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 170.1 (*C*O); 74.8 (*C*HOC); 69.1 (*C*HOH); 55.1 (CH_2*C*H); 54.7 (*C*HCH_3); 37.8 (*C*H_2CH); 30.4 (*C*H_2CHOH); 27.2 (*C*H_2CHOC); 21.9 (*C*$H_2$$CH_2$CHOC); 21.4 (*C*$H_2$$CH_2$CHOH); 17.4 (*C*$H_3$) ppm.

IR (Film): $\tilde{\nu}$ = 3446 (w); 2938 (m); 1733 (m); 1263 (m); 1183 (m); 863 (vw) cm^{-1}.

HR-MS (ESI): m/z: 237.1101 $[M + Na]^+$ (cal. 237.1097).

MS (ESI): m/z: 237.1 $[M + Na]^+$ (cal. 237.1); 451.3 $[2M + Na]^+$ (cal. 451.2); 665.3 $[3M + Na]^+$ (cal. 665.4).

Diastereomer 2:

R_f: 0.11 (*n*-hexane:EtOAc 2:1).

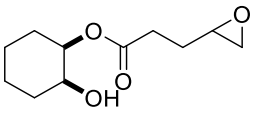
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.98–4.95 (m, 1 H, C*H*OC); 3.87–3.84 (m, 1 H, C*H*OH); 3.00 (dt, 1 H, ^3J = 5.8 Hz, ^3J = 2.1 Hz, CH_2CH); 2.85 (dq, 1 H, ^3J = 5.2 Hz, ^3J = 2.2 Hz, C*H*CH_3); 2.70–2.51 (m, 2 H, CH_2CH); 2.12 (bs, 1 H, O*H*); 1.92–1.82 (m, 1 H, H_{Cy}); 1.79–1.70 (m, 1 H, H_{Cy}); 1.69–1.52 (m, 4 H, H_{Cy}); 1.45–1.28 (m, 5 H, CH_3 and H_{Cy}) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 170.3 (*C*O); 74.8 (*C*HOC); 69.1 (*C*HOH); 55.1 (CH_2*C*H); 54.8 (*C*HCH_3); 38.1 (*C*H_2CH); 30.4 (*C*H_2CHOH); 27.1 (*C*H_2CHOC); 22.0 (*C*H_2CH_2CHOC); 21.3 (*C*H_2CH_2CHOH); 17.4 (*C*H_3) ppm.

IR (Film): $\tilde{\nu}$ = 3433 (m); 2938 (s); 1716 (s); 1271 (m); 1182 (m); 864 (wv) cm^{-1}.

MS (ESI): m/z: 237.1 $[M + Na]^+$ (cal. 237.1); 451.0 $[2M + Na]^+$ (cal. 451.2); 665.3 $[3M + Na]^+$ (cal. 665.4).

***cis*-2-Hydroxycyclohexyl 3-(2-oxiranyl)propionate 25b:** (GP-13)



25b

0.210 g (1.06 mmol, 1.0 equiv) alkene **20b** were dissolved in 6 mL DCM. Afterwards 0.230 g (0.930 mmol, 0.9 equiv) *m*CPBA were added. The resulting mixture was stirred for 24 h. After diluting with 20 mL EtOAc the work-up was performed with $NaHCO_3$ (five times 20 mL) and brine (one time 20 mL). After purification *via* column chromatography (*n*-hexane:EtOAc 1:2) 0.114 g (0.532 mmol, 57%) **25b** were isolated as colorless oil.

R_f: 0.08 (*n*-hexane:EtOAc 2:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.96–4.94 (m, 1 H, C*H*OC); 3.92–3.86 (m, 1 H, C*H*OH); 3.06–2.98 (m, 1 H, C*H*OCH_2); 2.79–2.77 (m, 1 H, CHOCH_2); 2.58–2.44 (m, 3 H, CHOCH_2 and COCH_2CH_2CH); 2.30 (dd, 1 H, ^3J = 13.0 Hz, ^4J = 4.5 Hz, CHO*H*); 2.13–2.03 (m, 1 H, $COCH_2$CH_2CH); 1.92–1.82 (m, 1 H, CH_2CHOC); 1.80–1.71 (m, 2 H, $COCH_2$CH_2CH and CH_2CHOH); 1.70–1.53 (m, 4 H, H_{Cy}); 1.43–1.31 (m, 2 H, H_{Cy}) ppm.

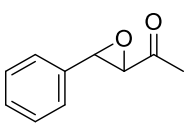
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 172.7 and 172.5 (*C*O); 74.64 and 74.58 (*C*HOC); 69.1 (*C*HOH); 51.70 and 51.66 (*C*HOCH_2); 47.11 and 47.06 (CHO*C*H_2); 31.3 and 31.2

(COCH$_2$CH$_2$CH); 30.5 (*C*H$_2$CHOH); 28.0 and 27.9 (COCH$_2$*C*H$_2$CH); 27.1 (*C*H$_2$CHOC); 22.22 and 22.17 (*C*H$_2$CH$_2$CHOC); 21.2 (*C*H$_2$CH$_2$CHOH) ppm.

IR (Film): $\tilde{\nu}$ = 3471 (vw); 2938 (m); 1731 (m); 1259 (w); 1180 (m) cm^{-1}.

HR-MS (ESI): m/z: 215.1282 [M + H]$^+$ (cal. 215.1278); m/z: 237.1103 [M + Na]$^+$ (cal. 237.1097); m/z: 451.2304 [2M + Na]$^+$ (cal. 451.2302).

1-(3-Phenyl-2-oxiranyl)-1-ethanone 28: (GP-14)



28

The reaction was performed with 0.700 g (4.79 mmol, 1.0 equiv) enone **30**, 2.93 mL (30%, 28.7 mmol, 6.0 equiv) H_2O_2, in total 0.201 mL (4/1 m/m, 1.01 mmol, 0.2 equiv) $NaOH_{aq}$ and 20 mL MeOH for 6 h at r.t.. The reaction was started *via* addition of 0.035 equiv $NaOH_{aq}$ (4/1 m/m) and 1.0 equiv H_2O_2 (30% in water). Further 0.035 equiv $NaOH_{aq}$ (4/1 m/m) were added hourly. For the work-up 30 mL EtOAc and 30 mL brine were used. In the end 0.577 g (3.56 mol, 74%) **28** were isolated as yellow oil starting to crystallize after some time. The crude product was utilized without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.36–7.33 (m, 3 H); 7.28–7.26 (m, 2 H); 4.00 (d, 1 H, ^3J = 1.8 Hz); 3.49 (d, 1 H, ^3J = 1.8 Hz); 2.18 (s, 3 H) ppm.

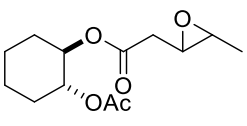
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 204.2; 134.9; 128.9; 128.6; 125.6; 63.4; 57.7; 24.7 ppm.

Analytic data are identical to those reported in literature.[76b]

Chiral GC analysis:

Enantiomers of **28** were separated by chiral GC employing a 30 m FS-Hydrodex γ-TBDAc column (Macherey-Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: Initial temperature: 120 °C; Initial time: 30 min. Retention times: Rt_1 = 24.5 min; Rt_1 = 25.2 min.

***trans*-2-Acetoxycyclohexyl (3-methyl-2-oxiranyl)acetate 35:** (GP-13)



35

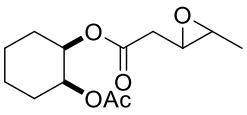
0.054 g (0.225 mmol, 1.0 equiv) alkene **33** were dissolved in 2 mL DCM. Afterwards 0.061 g (0.247 mmol, 1.1 equiv) *m*CPBA were added. The resulting mixture was stirred for 7 h. After diluting with 10 mL DCM the work-up was performed with $NaHCO_3$ (three times 10 mL) and DCM (two times with 10 mL). After purification *via* column chromatography (*n*-hexane:EtOAc 5:1) 0.050 g (0.195 mmol, 87%) **35** were isolated as colorless oil.

R_f: 0.28 (*n*-hexane:EtOAc 2:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.87–4.77 (m, 2 H, C*H*CO); 2.98–2.93 (m, 1 H, CH_2CH); 2.80 (dq, 1 H, ^3J = 5.2 Hz, ^3J = 2.1 Hz, C*H*CH_3); 2.56–2.44 (m, 2 H, C*H*$_2$CHOCH); 2.09–1.97 (m, 5 H, C*H*$_3$ and H_{Cy}); 1.74–1.67 (m, 2 H, H_{Cy}); 1.43–1.32 (m, 3 H, H_{Cy}); 1.32–1.28 (m, 4 H, CHC*H*$_3$ and H_{Cy}) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$):[19,20] δ = 170.6 (*C*O); 170.0 and 169.9 (*C*O); 74.32 and 74.29 (*C*HO); 73.7 and 73.6 (*C*HO); 54.95 and 54.92; 54.5; 38.02 and 37.97 (*C*H$_2$CH); 30.23 and 30.22 (CH_2CH_2*C*HO); 23.5 (*C*H$_2$CH$_2$CHO); 21.3 (C*H*$_3$); 17.4 (CHC*H*$_3$) ppm.

***cis*-2-Acetoxycyclohexyl (3-methyl-2-oxiranyl)acetate 36:** (GP-13)



36

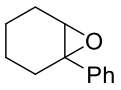
0.043 g (0.179 mmol, 1.0 equiv) alkene **34** were dissolved in 1.5 mL DCM. Afterwards 0.051 g (0.207 mmol, 1.2 equiv) *m*CPBA were added. The resulting mixture was stirred for 7.5 h. After diluting with 10 mL DCM the work-up was performed with $NaHCO_3$ (three times 10 mL) and DCM (two times with 10 mL). After purification *via* column chromatography (*n*-hexane:EtOAc 5:1) 0.041 g (0.160 mmol, 89%) **36** were isolated as colorless oil.

R$_f$: 0.30 (*n*-hexane:EtOAc 2:1).

^{1}H-NMR (400 MHz, $CDCl_3$):[19] δ = 5.14–5.07 (m, 1 H, C*H*CO); 5.04–4.99 (m, 1 H, C*H*CO); 3.01–2.97 (m, 1 H, CH_2CH); 2.83 (dq, 1 H, ^3J = 5.2 Hz, ^3J = 2.6 Hz, C*H*CH_3); 2.65–2.47 (m, 2 H, C*H*$_2$CHOCH); 2.04 (2.03) (m, 3 H, C*H*$_3$); 1.92–1.74 (m, 2 H, H_{Cy}); 1.69–1.59 (m, 4 H, H_{Cy}); 1.49–1.37 (m, 2 H, H_{Cy}); 1.33 (d, 3 H, ^3J = 5.2 Hz, CHC*H*$_3$) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$):[20] δ = 170.5 (*C*O); 170.0 and 169.8 (*C*O); 71.5 and 71.4 (*C*HO); 71.1 and 71.0 (*C*HO); 55.1 and 55.0; 54.53 and 54.51; 38.1 and 38.0 (*C*H$_2$CH); 27.9 and 27.8; 27.7 and 27.6; 22.0 and 21.9; 21.7 and 21.5; 21.3; 17.5 ppm.

1-Phenyl-7-oxabicyclo[4.1.0]heptane 39: (GP-13)



39

0.098 mL (0.097 g, 0.613 mmol, 1.0 equiv) alkene **38** were dissolved in 4 mL DCM. Afterwards 0.168 g (0.681 mmol, 1.1 equiv) *m*CPBA were added. The resulting mixture was stirred for 4 h. The reaction was quenched with 5 mL $NaHCO_3$. The aq layer was extracted with DCM (three times 10 mL). After purification *via* column chromatography (*n*-hexane:EtOAc 5:1 to 2:1) 0.088 g (0.505 mmol, 82%) **39** were isolated as colorless liquid.

R$_f$: 0.46 (*n*-hexane:EtOAc 5:1).

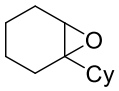
[19] Data referring to the second diastereomer are given in brackets.
[20] Without definite allocation of the signals to one diastereomer.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.32–7.24 (m, 4 H); 7.21–7.16 (m, 1 H); 3.02–3.00 (m, 1 H); 2.21 (ddd, 1 H, *J* = 14.3 Hz, *J* = 8.6 Hz, *J* = 5.4 Hz); 2.05 (dt, 1 H, *J* = 14.8 Hz, *J* = 5.3 Hz); 1.95–1.86 (m, 2 H); 1.58–1.46 (m, 2 H); 1.44–1.36 (m, 1 H); 1.30–1.17 (m, 1 H) ppm.
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 142.7; 128.4; 127.3; 125.4; 62.1; 60.4; 29.0; 24.9; 20.3; 19.9 ppm.

Analytic data are identical to those reported in literature.[175]

Chiral GC analysis:
Enantiomers of **39** were separated by chiral GC employing a 30 m FS-Hydrodex *β*-6-TBDM column (Macherey-Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: Initial temperature: 100 °C; Final temperature: 152 °C; Rate: 2.00 °C/min. Retention times: Rt_1 = 23.7 min; Rt_2 = 24.4 min.

1-Cyclohexyl-7-oxabicyclo[4.1.0]heptane 41: (GP-13)

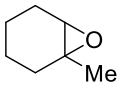


41

0.103 g (0.627 mmol, 1.0 equiv) alkene **40** were dissolved in 6 mL DCM. Afterwards 0.174 g (0.706 mmol, 1.1 equiv) *m*CPBA were added. The resulting mixture was stirred for 7 h. The organic layer was washed with sat. $NaHCO_3$ (five times 20 mL). After purification *via* column chromatography (*n*-hexane:EtOAc 20:1) 0.082 g (0.455 mmol, 73%) **41** were isolated as colorless liquid.
R_f: 0.38 (*n*-hexane:EtOAc 20:1).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.92 (dd, 1 H, ^3J = 3.3 Hz, ^3J = 1.1 Hz, C*H*OC); 1.96–1.89 (m, 1 H, H_{Cy}); 1.79–1.72 (m, 6 H, H_{Cy}); 1.67–1.63 (m, 2 H, H_{Cy}); 1.48–1.34 (m, 2 H, H_{Cy}); 1.25–1.05 (m, 8 H, CH_2CHCH_2 and H_{Cy}) ppm.
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 63.2 (CHO*C*); 58.3 (*C*HOC); 46.0 (CH_2CHCH_2); 28.1 (CH_2); 27.8 (CH_2); 26.6 (CH_2); 26.4 (CH_2); 26.2 (CH_2); 25.3 (CH_2); 25.0 (CH_2); 20.6 (CH_2); 19.9 (CH_2) ppm.
IR (Film): $\tilde{\nu}$ = 2928 (vs); 2854 (s); 2669 (vw); 1722 (vw); 1449 (m); 874 (w); 847 (w); 768 (w) cm^{-1}.
HR-MS (EI): m/z: 180.1511 (cal. 180.1514).

Chiral GC analysis:
Enantiomers of **41** were separated by chiral GC employing a 30 m FS-Hydrodex *β*-6-TBDM column (Macherey-Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: Initial temperature: 100 °C; Final temperature: 150 °C; Rate: 2.00 °C/min. Retention times: Rt_1 = 22.6 min; Rt_2 = 22.8 min.

1-Methyl-7-oxabicyclo[4.1.0]heptane 43: (GP-13)



43

6.17 mL (5.00 g, 0.052 mol, 1.0 equiv) alkene **42** were dissolved in 130 mL DCM. Afterwards 12.8 g (0.052 mol, 1.0 equiv) *m*CPBA were added. The resulting mixture was stirred for 24 h. After deluting with EtOAc the organic layer washed with sat. $NaHCO_3$ (eight times 50 mL). After purification *via* destillation (123 mbar, 70 to 75 °C) 1.84 g (0.016 mol, 32%) **43** were isolated as colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.95 (d, 1 H, *J* = 3.4 Hz); 1.93–1.79 (m, 3 H); 1.69–1.62 (m, 1 H); 1.46–1.35 (m, 2 H); 1.29 (m, 3 H); 1.27–1.23 (m, 1 H); 1.22–1.12 (m, 1 H) ppm.

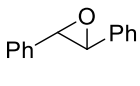
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 59.7; 57.7; 30.0; 24.9; 24.1; 20.2; 19.8 ppm.

Analytic data are identical to those reported in literature.[8]

Chiral GC analysis:

Enantiomers of **43** were separated by chiral GC employing a 30 m FS-Hydrodex *β*-6-TBDM column (Macherey-Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: Initial temperature: 60 °C; Initial time: 20 min. Retention times: Rt_1 = 14.1 min; Rt_2 = 16.0 min.

2,3-Diphenyloxirane 45:

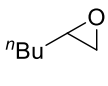


45

Chiral GC analysis:

Enantiomers of **45** were separated by chiral GC employing a 30 m Chiraldex G-TA column (Astech). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: Initial temperature: 160 °C; Initial time: 24 min. Retention times: Rt_1 = 21.7 min; Rt_2 = 22.1 min.

1-(2-Oxiranyl)butane 47: (GP-13)



47

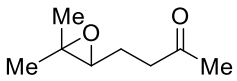
3.00 mL (2.03 g, 0.024 mol, 1.0 equiv) alkene **46** were dissolved in 35 mL DCM. Afterwards 6.45 g (0.026 mol, 1.1 equiv) *m*CPBA were added. The resulting mixture was stirred for 5 h. The organic layer washed with sat. $NaHCO_3$ (230 mL in total). After purification *via* destillation 1.03 g (0.010 mol, 43%) **47** were isolated as colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.92–2.87 (m, 1 H); 2.73 (dd, 1 H, *J* = 5.0 Hz, *J* = 4.0 Hz); 2.45 (dd, 1 H, *J* = 5.0 Hz, *J* = 2.7 Hz); 1.55–1.48 (m, 2 H); 1.47–1.31 (m, 4 H) ; 0.90 (t, 3 H, *J* = 7.1 Hz) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 52.5; 47.2; 32.3; 28.2; 22.6; 14.1 ppm.

Analytic data are identical to those reported in literature.[8]

4-(3,3-Dimethyl-2-oxiranyl)-2-butanone 49: (GP-13)



49

2.00 g (0.016 mol, 1.0 equiv) alkene **48** were dissolved in 60 mL DCM. Afterwards 3.06 g (0.012 mol, 0.8 equiv) *m*CPBA were added. The resulting mixture was stirred for 5 h. The organic layer washed with sat. $NaHCO_3$ (230 mL in total). After purification *via* column chromatography (*n*-hexane:EtOAc 2:1 to 1:2) 0.034 g (0.239 mmol, 2%[176]) **49** were isolated as colorless liquid.

R_f: 0.14 (*n*-hexane:EtOAc 2:1).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.72 (dd, 1 H, *J* = 7.9 Hz, *J* = 4.6 Hz); 2.64–2.57 (m, 2 H) ; 2.16 (s, 3 H); 1.98–1.83 (m, 1 H); 1.71–1.57 (m, 1 H); 1.29 (s, 3 H); 1.26 (s, 3 H) ppm.

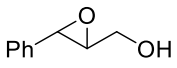
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 208.0; 63.5; 59.0; 40.4; 30.1; 24.9; 23.1; 18.8 ppm.

Analytic data are identical to those reported in literature.[177]

GC analysis:

Enantiomers of **49** were separated by chiral GC employing a 30 m FS-Hydrodex *β*-6-TBDM column (Macherey-Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: Initial temperature: 110 °C; Initial time: 8 min. Retention times: Rt_1 = 6.0 min; Rt_2 = 6.2 min.

(3-Phenyl-2-oxiranyl)methanol 51: (GP-13)



51

0.110 g (0.820 mol, 1.0 equiv) alkene **50** were dissolved in 6 mL DCM. Afterwards 0.212 g (0.860 mol, 1.0 equiv) *m*CPBA were added. The resulting mixture was stirred for 3 h. The reaction was quenched with 2 mL sat. $NaHCO_3$. The organic layer washed with sat. $NaHCO_3$ (three times 10 mL) and brine (three times 10 mL). After purification *via* column chromatography (*n*-hexane:EtOAc 3:1) 0.051 g (0.349 mmol, 41%) **51** were isolated as colorless oil.

R_f: 0.28 (*n*-hexane:EtOAc 3:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 5 H); 4.05 (dd, 1 H, *J* = 12.8 Hz, *J* = 2.1 Hz); 3.93 (d, 1 H, *J* = 2.1 Hz); 3.81 (dd, 1 H, *J* = 12.8 Hz, *J* = 3.4 Hz); 3.23 (dt, 1 H, *J* = 3.8 Hz, *J* = 2.3 Hz); 1.96 (bs, 1 H) ppm.

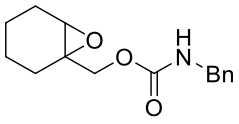
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 136.6; 128.5; 128.3; 125.7; 62.4; 61.2; 55.5 ppm.

Analytic data are identical to those reported in literature.[175]

Chiral GC analysis:

Enantiomers of **51** were separated by chiral GC employing a 30 m FS-Hydrodex γ-TBDAc column (Macherey-Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: Initial temperature: 120 °C; Initial time: 45 min. Retention times: Rt_1 = 39.6 min; Rt_2 = 40.5 min.

Benzylamino (7-oxabicyclo[4.1.0]hept-1-yl)acetate 53a: (GP-13)



53a

0.214 g (0.872 mol, 1.0 equiv) alkene **52a** were dissolved in 15 mL DCM. Afterwards 0.215 g (0.959 mol, 1.1 equiv) *m*CPBA were added. The resulting mixture was stirred for 5.5 h. The organic layer was diluted with 90 mL MTBE and washed with sat. $NaHCO_3$ (three times 30 mL). After purification *via* column chromatography (Et_2O) 0.180 g (0.689 mmol, 79%) **53a** were isolated as colorless oil.

R_f: 0.20 (*n*-hexane:EtOAc 3:1).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.41–7.18 (m, 5 H); 5.12 (bs, 1 H); 4.37 (d, 2 H, *J* = 6.0 Hz); 4.12 (d, 1 H, *J* = 11.6 Hz); 3.98 (d, 1 H, *J* = 11.8 Hz); 3.11 (d, 1 H, *J* = 2.0 Hz); 2.05–1.62 (m, 4 H) 1.57–1.10 (m, 4 H) ppm.

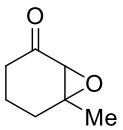
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 156.2; 138.3; 128.6; 127.5; 68.4; 57.9; 56.5; 45.1; 25.2; 24.2; 19.6; 19.4 ppm.

Analytic data are identical to those reported in literature.[33a]

Chiral HPLC analysis:

Enantiomers of **53a** were separated by chiral HPLC employing a 25 cm Chiralpak IB column (4.6 mm ID, Daicel) in combination with an UV-detector (220 nm). Flow = 1.00 mL/min. Solvent mixture: *n*-hexane:*iso*-propanol 90:10. Retention times: Rt_1 = 10.7 min; Rt_2 = 11.9 min.

6-Methyl-7-oxabicyclo[4.1.0]heptan-2-one 55: (GP-14)



55

The reaction was performed with 0.206 mL (0.200 g, 1.82 mmol, 1.0 equiv) enone **54**, 1.10 mL (30%, 10.8 mmol, 5.9 equiv) H_2O_2, 0.128 mL (4/1 w/w, 0.608 mmol, 0.3 equiv) $NaOH_{aq}$, and 10 mL MeOH for 4 h at r.t.. Before deluting the reaction mixture a small volume of acetic acid was added. 20 mL Et_2O were used for work-up. After purification *via* column chromatography (*n*-hexane:EtOAc 3:1) 0.049 g (0.388 mmol, 21%) **55** were isolated as colorless oil.

R_f: 0.12 (*n*-hexane:EtOAc 2:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.03 (s, 1 H); 2.45 (dt, 1 H, *J* = 17.6 Hz, *J* = 4.5 Hz); 2.11–1.80 (m, 4 H); 1.64–1.57 (m, 1 H); 1.41 (s, 3 H) ppm.

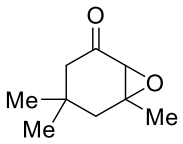
^{13}C-NMR (101 MHz, $CDCl_3$): 206.8; 62.5; 62.0; 35.8; 28.4; 22.3; 17.2 ppm.

Analytic data are identical to those reported in literature.[178]

Chiral GC analysis:

Enantiomers of **55** were separated by chiral GC employing a 30 m FS-Hydrodex *β*-6-TBDM column (Macherey-Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: Initial temperature: 100 °C; Final temperature: 140 °C; Rate: 2.00 °C/min. Retention times: Rt_1 = 7.9 min; Rt_2 = 8.8 min.

4,4,6-Trimethyl-7-oxabicyclo[4.1.0]heptan-2-one 57: (GP-14)



57

The reaction was performed with 2.00 mL (1.84 g, 13.3 mmol, 1.0 equiv) enone **56**, 2.30 mL (30%, 22.5 mmol, 1.7 equiv) H_2O_2, 2.00 mL (9/1 w/w, 5.00 mmol, 0.4 equiv) $NaOH_{aq}$, and 20 mL EtOH for 1 h at 35 °C and 30 min at r.t.. The solution of $NaOH_{aq}$ and H_2O_2 was added over 20 min. After diluting with 15 mL H_2O 25 mL $CHCl_3$ and 20 mL H_2O were used for the work-up. After purification *via* column chromatography (*n*-pentane:EtOAc 9:1) 1.83 g (11.9 mmol, 89%) **57** were isolated as colorless liquid.

R_f: 0.44 (*n*-pentane:EtOAc 9:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.03 (s, 1 H); 2.59 (d, 1 H, *J* = 13.3 Hz); 2.06 (d, 1 H, *J* = 14.9 Hz); 1.79 (ddd, 1 H, *J* = 13.3 Hz, *J* = 2.0 Hz, *J* = 0.9 Hz); 1.67 (dd, 1 H, *J* = 14.9 Hz, *J* = 2.0 Hz); 1.40 (s, 3 H); 1.00 (s, 3 H); 0.89 (s, 3 H) ppm.

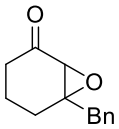
^{13}C-NMR (101 MHz, $CDCl_3$): 209.0; 64.3; 61.4; 48.0; 42.7; 36.1; 30.8; 27.8; 24.0 ppm.

Analytic data are identical to those reported in literature.[179]

Chiral GC analysis:

Enantiomers of **57** were separated by chiral GC employing a 30 m Chiraldex G-TA column (Astech). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: Initial temperature: 100 °C; Final temperature: 136 °C; Rate: 2.00 °C/min. Retention times: Rt_1 = 13.2 min; Rt_2 = 15.2 min.

6-(Phenylmethyl)-7-oxabicyclo[4.1.0]heptan-2-one 59: (GP-14)



59

The reaction was performed with 0.170 g (0.913 mmol, 1.0 equiv) enone **58**, 0.170 mL (30%, 1.66 mmol, 1.8 equiv) H_2O_2, 0.500 mL (9/1 w/w, 1.25 mmol, 1.4 equiv) $NaOH_{aq}$, and 2 mL MeOH for 2 h at r.t.. The solution of $NaOH_{aq}$ and H_2O_2 was added over 20 min. After diluting with 11 mL H_2O 20 mL $CHCl_3$ and 20 mL H_2O were used for the work-up. After purification *via* column chromatography (*n*-pentane:EtOAc:Et_2O 4:1:1) 0.070 g (0.346 mmol, 38%) **59** were isolated as colorless oil.

R_f: 0.42 (*n*-pentane:EtOAc:Et_2O 4:1:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.33–7.23 (m, 3 H); 7.22–7.20 (m, 2 H); 3.11 (s, 1 H); 2.98 (s, 2 H); 2.48 (dt, 1 H, *J* = 17.4 Hz, *J* = 4.5 Hz); 2.11–1.79 (m, 4 H); ; 1.65–1.57 (m, 1 H) ppm.

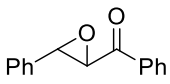
^{13}C-NMR (101 MHz, $CDCl_3$): 206.5; 135.4; 129.5; 128.5; 127.0; 65.2; 60.4; 42.2; 35.9; 26.3; 17.2 ppm.

Analytic data are identical to those reported in literature.[180]

Chiral GC analysis:

Enantiomers of **59** were separated by chiral GC employing a 30 m FS-Hydrodex *β*-TBDAc column (Macherey-Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: Initial temperature: 100 °C; Final temperature: 210 °C; Rate: 1.60 °C/min. Retention times: Rt_1 = 56.3 min; Rt_2 = 56.8 min.

Phenyl(3-phenyl-2-oxiranyl)formaldehyde 61: (GP-14)



61

0.116 g (0.560 mmol, 1.0 equiv) alkene **60** were dissolved in 4 mL MeOH and the resulting mixture was cooled to 0 °C. After adding 0.410 mL (0.455 g, 4.01 mmol, 7.2 equiv) H_2O_2 (30%) and 0.156 mL (37.4 mg, 0.936 mmol, 1.7 equiv) NaOH (6 M) the reaction mixture was stirred for 1 h at 0 °C. The reaction was quenched with 1 trop glacial acetic acid. After diluting the reaction mixture with 20 mL brine Et_2O (three times 25 mL) was used for the extraction. After purification *via* column chromatography (*n*-hexane:EtOAc 4:1) 0.061 g (0.270 mmol, 49%) **61** were isolated as colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.04–7.98 (m, 2 H); 7.67–7.58 (m, 1 H); 7.54–7.45 (m, 2 H); 7.45–7.33 (m, 5 H); 4.31 (d, 1 H, *J* = 1.9 Hz); 4.08 (d, 1 H, *J* = 1.8 Hz) ppm.

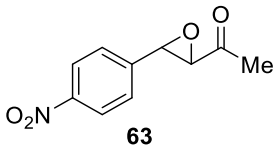
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 193.2; 135.6; 135.5; 134.1; 129.2; 129.0; 128.9; 128.5; 125.9; 61.1; 59.5 ppm.

Analytic data are identical to those reported in literature.[181]

Chiral HPLC analysis:

Enantiomers of **61** were separated by chiral HPLC employing a 25 cm Chiralpak IC column (4.6 mm ID, Daicel) in combination with an UV-detector (254 nm). Flow = 1.00 mL/min. Solvent mixture: *n*-hexane:*iso*-propanol 90:10. Retention times: Rt_1 = 20.7 min; Rt_2 = 22.8 min.

1-(3-(*p*-Nitrophenyl)-2-oxiranyl)-1-ethanone 63: (GP-14)



63

The reaction was performed with 0.120 g (0.628 mmol, 1.0 equiv) enone **62**, 0.385 mL (30%, 3.77 mmol, 6.0 equiv) H_2O_2, 9.00 µL (4/1 m/m, 0.045 mmol, 0.1 equiv) $NaOH_{aq}$, and 10 mL MeOH for 1.5 h at 0 °C. Before deluting with 15 mL brine the reaction was quenched with one trop glacial acetic acid. For the work-up 15 mL Et_2O were used. After purification *via* column chromatography (*n*-hexane:EtOAc 3:1) 0.012 g (0.058 mmol, 9%) **63** were isolated as slightly yellow solid.

R_f: 0.23 (*n*-hexane:EtOAc 3:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.13–8.11 (m, 2 H); 7.41–7.38 (m, 2 H); 4.08 (d, 1 H, ^3J = 1.6 Hz); 3.41 (d, 1 H, ^3J = 1.8 Hz); 2.14 (s, 3 H) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 202.9; 148.0; 142.3; 126.4; 123.7; 63.1; 56.3; 24.7 ppm.

Analytic data are identical to those reported in literature.[182]

Chiral GC analysis:

Enantiomers of **63** were separated by chiral GC employing a 30 m FS-Hydrodex *β*-6-TBDM column (Macherey-Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: Initial temperature: 200 °C; Initial time: 30 min. Retention times: Rt_1 = 28.7 min; Rt_2 = 29.6 min.

9.6. Catalytic Epoxidation

9.6.1. Peracid-Based Epoxidation

0.250 mmol (1.0 equiv) alkene and 0.013 mmol (0.05 equiv, 5 mol%) **cat.** were dissolved in 2.00 mL chloroform. Afterwards 46.5 µL (0.038 g, 0.300 mmol, 1.2 equiv) DIC and 2 × 51.1 µL (2 × 0.058 g, 2 × 0.500 mmol, 2 × 2.0 equiv) H_2O_2 (30%) were added. The resulting reaction mixture was stirred at r.t.. The second addition was carried out after 1 h. Small samples were taken, diluted with DCM, dried over Na_2SO_4, and analyzed directly *via* chiral GC.

9.6.2. Dioxirane-Based Epoxidation (Oxone®)

0.050 mmol (0.2 equiv, 20 mol%) TBABr and 0.050 mmol (0.2 equiv, 20 mol%) **cat.** were dissolved in 1.00 mL DCM. Afterwards 0.250 mmol (1.0 equiv) alkene and 1.00 mL H_2O were added. A mixture of 0.750 mmol (3.0 equiv) Oxone® and 1.15 mmol (4.6 equiv) $NaHCO_3$ (s) was prepared beforehand and added portionwise. The resulting biphasic reaction mixture was stirred at r.t.. Small samples were taken, diluted with DCM, dried over Na_2SO_4, and analyzed directly *via* chiral GC.

9.6.3. Dioxirane-Based Epoxidation (H_2O_2/MeCN)

0.1 mol% Na_2EDTA, 0.063 mmol (0.1 equiv, 10 mol%) **cat.**, and 1.15 mmol (1.8 equiv) K_2CO_3 were dissolved/suspended in 1.92 mL ^{t}AmylOH. Afterwards 0.628 mmol (1.0 equiv) alkene, 1.92 mL H_2O, and 5.05 mmol (8.0 equiv) MeCN were added. Every hour 1.26 mmol (2.0 equiv) H_2O_2 (30%) were added (maximal 8.0 equiv in total). The resulting suspension was stirred at r.t.. Small samples were taken, diluted with DCM, dried over Na_2SO_4, and analyzed directly *via* chiral GC.

9.6.4. PTC-Based Epoxidation

0.080 mmol (1.0 equiv) enone and 0.008 mmol (0.1 equiv, 10 mol%) **cat.** were dissolved/suspended in 1.00 mL toluene. Afterwards 0.800 mmol (10.0 equiv) H_2O_2 (30%) and 0.300 mL NaOH (2% in H_2O) were added. The resulting solution was intensively stirred at r.t.. Small samples were taken, dried over Na_2SO_4, and analyzed directly *via* chiral GC and HPLC, resp..

9.6.5. Prolinol-Based Epoxidation

0.022 mmol (0.3 equiv, 25 mol%) **cat.** were dissolved in 0.435 mL *n*-hexane. Afterwards 0.087 mmol (1.0 equiv) enone and 0.104 mmol (1.2 equiv) TBHP were added. The resulting solution was stirred at r.t. and small samples were analyzed directly *via* chiral HPLC.

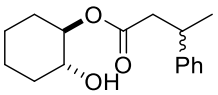
9.7. Michael Addition

General procedure (GP-15):

5.0 equiv CuBr•Me_2S were suspended in anhyd. Et_2O. Under an Ar atmosphere the resulting mixture was cooled to 0 °C. At this temperature 10 equiv PhLi (1.8 M solution in dibutylether) were added and the resulting mixture was stirred afterwards for 30 min. Before adding the *α,β*-unsaturated ester dissolved in anhyd. Et_2O the mixture was cooled to −30 °C. The reaction mixture was stirred 2 h at −30 °C and then 2 h at r.t.. The reaction was quenched by adding

15 mL sat. NH_4Cl. After phase separation the aq layer was extracted with 7 mL Et_2O and the combined organic layers were dried over Na_2SO_4. After evaporation of the solvent the crude product was purified *via* column chromatography.

***trans*-2-Hydroxycyclohexyl 3-phenylbutyrate 26:** (GP-15)



26

The reaction was performed with 0.366 g (1.78 mmol, 5.0 equiv) CuBr•Me_2S dissolved in 7 mL Et_2O, 1.96 mL (3.53 mmol, 10 equiv) PhLi, and 0.065 g (0.353 mmol, 1.0 equiv) ester **17** dissolved in 2 mL Et_2O. After purification *via* column chromatography (*n*-hexane:EtOAc 8:1 to 2:1) 0.045 g (0.170 mmol, 48%) **26** were isolated as slightly yellowish oil.

R_f: 0.28 (*n*-hexane:EtOAc 2:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.33–7.29 (m, 2 H); 7.24–7.19 (m, 3 H); 4.50–4.41 (m, 1 H); 3.46–3.33 (m, 1 H); 3.31–3.22 (m, 1 H); 2.72–2.56 (m, 2 H); 2.00–1.81 (m, 3 H); 1.68–1.58 (m, 2 H); 1.33–1.08 (m, 8 H) ppm.

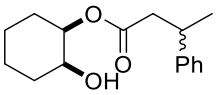
^{13}C-NMR (101 MHz, $CDCl_3$):[21] δ = 172.4 (172.6); 145.6 (145.4); 128.7 (128.8); 126.8 (126.9); 126.7 (126.8); 78.3; 72.5 (72.6); 43.0 (43.6); 36.7 (37.4); 32.8 (32.7); 29.9 (30.0); 24.0; 23.8; 22.4 ppm.

IR (Film): $\tilde{\nu}$ = 3450 (w); 3028 (vw); 2936 (m); 2863 (w); 1731 (m); 1452 (w); 1268 (m); 1171 (m); 700 (w) cm^{-1}.

HR-MS (EI): m/z: 262.1560 (cal. 262.1569).

Analytic data are identical to those reported in literature.[69]

***cis*-2-Hydroxycyclohexyl 3-phenylbutyrate 27:** (GP-15)



27

The reaction was performed with 0.561 g (2.73 mmol, 5.0 equiv) CuBr•Me_2S dissolved in 8 mL Et_2O, 3.10 mL (5.58 mmol, 10 equiv) PhLi, and 0.100 g (0.543 mmol, 1.0 equiv) ester **18** dissolved in 2 mL Et_2O. After purification *via* column chromatography (*n*-hexane:EtOAc 8:1 to 3:1) 13.7 mg (0.052 mmol, < 10%[22]) **27** were isolated as colorless oil.

R_f: 0.22 (*n*-hexane:EtOAc 2:1).

^{1}H-NMR (400 MHz, $CDCl_3$):[22] δ = 7.34–7.30 (m, 2 H); 7.25–7.19 (m, 3 H); 4.83–4.79 (4.84–4.86) (m, 1 H); 3.62–3.59 (3.72–3.69) (m, 1 H); 3.33–3.22 (m, 1 H); 2.73–2.58 (m, 2 H); 1.77–1.69 (m, 1 H); 1.66–1.56 (m, 2 H); 1.54–1.41 (m, 3 H); 1.33–1.24 (m, 6 H) ppm.

[21] Data referring to the second diastereomer are given in brackets.
[22] Even after performing the column chromatography several time traces of impurities could not be removed.

^{13}C-NMR (101 MHz, $CDCl_3$):[23] δ = 172.1 (172.0); 145.5 (145.7); 128.7; 127.0 (126.8); 126.8; 74.3; 69.0 (69.2); 43.5 (43.1); 37.4 (36.8); 30.4; 26.9; 22.4; 22.2; 21.0 ppm.

IR (Film): $\tilde{\nu}$ = 3458 (w); 3062 (vw); 2938 (m); 2866 (m); 1948 (vw); 1731 (m); 1451 (m); 1269 (m); 1171 (m); 701 (w) cm^{-1}.

HR-MS (EI): m/z: 262.1552 (cal. 262.1569).

9.8. Synthesis of Alkenes

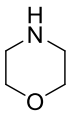
General procedure (GP-16):

1.0 equiv aldehyde and 20 mol% **29** were dissolved in acetone. The resulting mixture was refluxed and the reaction progress was monitored *via* TLC. The solution was diluted either with DCM or EtOAc and was washed afterwards with sat. $NaHCO_3$. After phase separation the aq layer was extracted three times with DCM and EtOAc, resp., and the combined organic layers were dried over Na_2SO_4. After evaporation of the solvent the crude product was purified *via* column chromatography if necessary.

General Procedure (GP-17):

In an Ar atmosphere the corresponding alcohol was dissolved in anhyd. DCM. Afterwards DMAP, isocyanate, and TEA were added and the resulting mixture was stirred for 24 h at r.t.. At the end of the reaction Et_2O was added and the organic layer was washed with aq $NaHSO_4$ (10%). The aq layer was extracted with Et_2O. After combining the organic layers they were washed with sat. $NaHCO_3$ and dried over $MgSO_4$ and Na_2SO_4, resp.. After evaporating the solvent the crude product was purified *via* column chromatography.

(*E*)-4-Phenyl-3-buten-2-one 30: (GP-16)



29

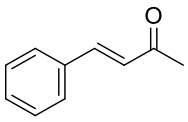
3.00 g (0.034 mol, 1.0 equiv) morpholine were dissolved in 50 mL Et_2O and the resulting mixture was cooled to 0 °C. At this temperature a solution of 2.92 mL (4.32 g, 0.038 mol, 1.1 equiv) TFA and 25 mL Et_2O was added over 10 min. The reaction mixture was stirred for 1 h at 0 °C. The formed colorless solid was filtered and washed with 50 mL Et_2O and *n*-pentane. After drying over paraffin 6.51 g (0.032 mol, 95%) **29** were isolated as colorless solid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 9.06 (s, 2 H); 3.76 (t, 4 H, ^{3}J = 5.0 Hz); 3.10 (t, 4 H, ^{3}J = 5.0 Hz) ppm.

^{13}C-NMR (101 MHz, DMSO-d_6): δ = 63.2; 42.7 ppm.

[23] Data referring to the second diastereomer are given in brackets.

Analytic data are identical to those reported in literature.[76c]


30

The reaction mixture containing 1.91 mL (2.01 g, 0.019 mol, 1.0 equiv) benzaldehyde, 0.758 g (3.77 mmol, 0.2 equiv, 20 mol%) **29**, and 48 mL acetone was refluxed for 72 h. For the work-up 50 mL EtOAc and 50 mL $NaHCO_3$ were used. After purification *via* column chromatography (*n*-hexane:EtOAc 6:1) 1.94 g (0.013 mol, 70%) **30** were isolated as yellow oil.

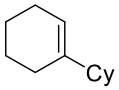
R_f: 0.21 (*n*-hexane:EtOAc 6:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.54–7.48 (m, 3 H); 7.40–7.37 (m, 3 H); 6.70 (d, 1 H, ^3J = 16.3 Hz); 2.37 (s, 3 H) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 198.2; 143.3; 134.2; 130.4; 128.8; 128.1; 127.0; 27.3 ppm.

Analytic data are identical to those reported in literature.[76c]

1-Cyclohexylcyclohexene 40:


40

A round-bottom flask was charged with 1.51 g (0.062 mol, 1.3 equiv) magnesium and 8 mL anhyd. Et_2O. A solution of 7.52 mL (10.0 g, 0.061 mol, 1.2 equiv) CyBr and 17 mL anhyd. Et_2O was added over 45 min. Afterwards the mixture was refluxed for 1 h. Before adding a solution of 5.03 mL (4.82 g, 0.049 mol, 1.0 equiv) cyclohexyanone and 18 mL anhyd. Et_2O carefully over 15 min, the mixture containing the *in situ* formed Grignard species was cooled for several minutes. After refluxing the reaction mixture for further 3 h 9 g ice and later sat. NH_4Cl and Et_2O were added. After phase separation the organic layer was washed with sat. $NaHSO_3$ and $NaHCO_3$ and finally with water. After drying over Na_2SO_4 the solvent was removed under reduced pressure. After purification *via* column chromatography (*n*-hexane:EtOAc 15:1) 2.22 g (0.012 mol, 25%) alcohol **72** were isolated as colorless solid.

R_f: 0.59 (*n*-hexane:EtOAc 5:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.82–1.77 (m, 4 H); 1.67–1.48 (m, 8 H); 1.43–1.36 (m, 2 H); 1.28–1.08 (m, 6 H); 1.06–0.96 (m, 2 H) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 73.1; 48.4; 34.4; 27.0; 26.74; 26.68; 26.1; 22.1 ppm.

Analytic data are identical to those reported in literature.[183]

2.22 g (0.012 mol, 1.0 equiv) alcohol **72** were dissolved in 2.20 mL sulfuric acid and 8.40 mL acetic acid. The resulting mixture was warmed to 65 °C. After 30 min the black and biphasic system was carefully poured on a mixture of Et_2O and water. After phase separation the organic

layer was washed carefully with sat. $NaHCO_3$ (55 mL in total). After purification *via* column chromatography (*n*-hexane:EtOAc 20:1) 1.14 g (6.94 mmol, 57%) **40** were isolated as yellowish liquid.

R_f: 0.61 (*n*-hexane:EtOAc 50:1).

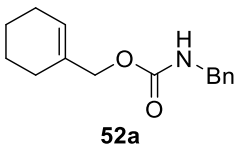
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.45–5.37 (m, 1 H, CH_2CCH); 2.00–1.98 (m, 2 H, H_{Cy}); 1.94–1.89 (m, 2 H, H_{Cy}); 1.76–1.64 (m, 6 H, CH_2CHCH_2 and H_{Cy}); 1.63–1.51 (m, 4 H, H_{Cy}); 1.31–1.07 (m, 5 H, H_{Cy}) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 143.3 (CH_2CCH); 118.8 (CH_2CCH); 46.0 (2 C, CH_2CHCH_2); 32.1 (2 C, CH_2); 27.0 (2 C, CH_2); 26.9 (CH_2); 26.7 (CH_2); 25.4 (CH_2); 23.4 (CH_2); 23.0 (CH_2) ppm.

IR (Film): ṽ = 2925 (vs); 2853 (s); 2853 (s); 2667 (vw); 1662 (vw); 1448 (m); 919 (vw); 801 (vw) cm^{-1}.

HR-MS (EI): m/z: 164.1566 (cal. 164.1565).

Cyclohex-1-en-1-ylmethyl benzylcarbamate 52a:



52a

In an Ar atmosphere 1.62 mL (1.67 g, 11.9 mmol, 1.0 equiv) ester **73** were dissolved in 20 mL anhyd. DCM. The reaction mixture was cooled to −78 °C and 27.7 mL (29.8 mmol, 2.5 equiv) D*i*BAL (1.0 M in hexane) were added slowly. After stirring the solution for 90 min at −78 °C the reaction was quenched with 20 mL of a potassium-sodium-tartrate solution (0.25 M). Then, the mixture was allowed to warm-up to r.t. and stirred for further 30 min. Afterwards the solution was diluted with 300 mL Et_2O, dried over $MgSO_4$, and filtered over a frit containing $MgSO_4$. After evaporation of the solvent 1.36 g (11.9 mmol, quant.) of the crude product **74** were obtained as colorless liquid, which was used without further purification.

R_f: 0.20 (toluene:Et_2O 9:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.72−5.63 (m, 1 H); 3.97 (s, 2 H); 2.10−1.96 (m, 4 H); 1.34 (bs, 1 H); 1.72−1.53 (m, 4 H) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 137.5; 123.0; 67.7; 25.6; 24.9; 22.5; 22.4 ppm.

For the synthesis of **52a** 1.34 g (11.9 mmol, 1.0 equiv) alcohol **74**, 0.145 g (1.19 mmol, 0.1 equiv) DMAP, 1.68 mL (1.81 g, 13.6 mmol, 1.14 equiv) BnNCO **76a**, 1.88 mL (1.37 g, 13.6 mol, 1.14 equiv) TEA, and 26 mL anhyd. DCM were used (GP-17). The reaction mixture was diluted with 100 mL Et_2O. Afterwards the organic layer was washed with 100 mL $NaHSO_4$ (10%) and the aq layer was extracted with 100 mL Et_2O. After purification *via* column

chromatography (toluene: Et_2O 9:1) 2.41 g (9.82 mmol, 83%) carbamate **52a** were obtained as colorless solid.

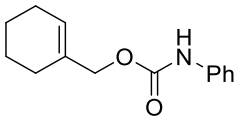
R_f: 0.50 (toluene:Et_2O 9:1).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.40−7.21 (m, 5 H); 5.74 (s, 1 H); 4.99 (s, 1 H); 4.47 (s, 2 H); 4.38 (d, 2 H, *J* = 6.0 Hz); 2.10−1.89 (m, 4 H); 1.70−1.51 (m, 4 H) ppm.

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 156.8; 138.7; 133.5; 128.8; 127.61; 127.55; 126.0; 69.6; 45.2; 25.9; 25.1; 22.5; 22.3 ppm.

Analytic data are identical to those reported in literature.[33a]

Cyclohex-1-en-1-ylmethyl phenylcarbamate 52b:



52b

For the synthesis of **52b** 0.300 g (2.67 mmol, 1.0 equiv) alcohol **74**, 0.033 g (0.267 mmol, 0.1 equiv) DMAP, 0.331 mL (0.363 g, 3.04 mmol, 1.14 equiv) isocyanate **76b**, 0.376 mL (0.405 g, 3.04 mol, 1.14 equiv) TEA, and 6 mL anhyd. DCM were used (GP-17). The reaction mixture was diluted with 22 mL Et_2O and the layers were washed and extracted, resp., with 22 mL $NaHSO_4$ (10%), 22 mL Et_2O, and 22 mL $NaHCO_3$. After recrystallization (*n*-hexane) 0.323 g (1.39 mmol, 52%) carbamate **52b** were obtained as colorless solid.

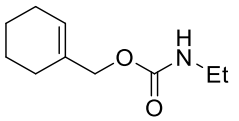
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.37−7.15 (m, 4 H); 7.05−6.90 (m, 1 H); 6.62 (s, 1 H); 5.78−5.64 (m, 1 H); 4.46 (s, 2 H); 2.06−1.87 (m, 4 H); 1.68−1.43 (m, 4 H) ppm.

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 153.6; 138.0; 133.1; 129.1; 126.6; 123.4; 118.7; 69.7; 25.9; 25.0; 22.4; 22.1 ppm.

HR-MS (EI): m/z: 231.1254 (cal. 231.1259).

Analytic data are identical to those reported in literature.[33a]

Cyclohex-1-en-1-ylmethyl ethylcarbamate 52c:



52c

For the synthesis of **52c** 0.300 g (2.67 mmol, 1.0 equiv) alcohol **74**, 0.033 g (0.267 mmol, 0.1 equiv) DMAP, 0.241 mL (0.216 g, 3.04 mmol, 1.14 equiv) isocyanate **76c**, 0.420 mL (0.308 g, 3.04 mol, 1.14 equiv) TEA, and 6 mL anhyd. DCM were used (GP-17). The reaction mixture was diluted with 22 mL Et_2O and the layers were washed and extracted, resp., with 22 mL $NaHSO_4$ (10%), 22 mL Et_2O, and 22 mL $NaHCO_3$. After column chromatography (*n*-hexane:EtOAc 3:1) 0.345 g (1.90 mmol, 71%) carbamate **52c** were obtained as colorless liquid.

R_f: 0.33 (*n*-hexane:EtOAc 3:1).

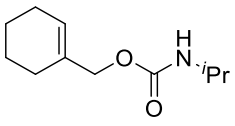
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 5.73−5.70 (m, 1 H, C*H*); 4.65 (bs, 1 H, N*H*); 4.42 (s, 2 H, CH_2O); 3.24−3.19 (m, 2 H, CH_2CH$_3$); 2.05−2.00 (m, 2 H, CH_2CCH); 1.99−1.95 (m, 2 H, CH_2CCH$_2$O); 1.66−1.61 (m, 2 H, CH_2CH$_2$CCH$_2$O); 1.60−1.55 (m, 2 H, CH_2CH$_2$CCH); 1.13 (t, 3 H, ^3J = 7.3 Hz, CH_3) ppm.

^{13}C-NMR (151 MHz, $CDCl_3$): δ = 156.7 (*C*O); 133.7 (*C*CH); 125. 9 (C*C*H); 69.3 (*C*H$_2$O); 36.0 (*C*H$_2$CH$_3$); 25.9 (*C*H$_2$CCH$_2$O); 25.1 (*C*H$_2$CCH); 22.5 (*C*H$_2$CH$_2$CCH$_2$O); 22.3 (*C*H$_2$CH$_2$CCH); 15.4 (C*H*$_3$) ppm.

IR (Film): $\tilde{\nu}$ = 3334 (w); 2931 (m); 1698 (m); 1535 (m); 1252 (m); 1017 (w) cm^{-1}.

HR-MS (ESI): m/z: 206.1157 [M + Na]$^+$ (cal. 206.1151); m/z: 389.2413 [2M + Na]$^+$ (cal. 389.2411).

Cyclohex-1-en-1-ylmethyl isopropylcarbamate 52d:



52d

For the synthesis of **52d** 0.300 g (2.67 mmol, 1.0 equiv) alcohol **74**, 0.033 g (0.267 mmol, 0.1 equiv) DMAP, 0.299 mL (0.259 g, 3.04 mmol, 1.14 equiv) isocyanate **76d**, 0.376 mL (0.405 g, 3.04 mol, 1.14 equiv) TEA, and 6 mL anhyd. DCM were used (GP-17). The reaction mixture was diluted with 22 mL Et_2O and the layers were washed and extracted, resp., with 22 mL $NaHSO_4$ (10%), 22 mL Et_2O, and 22 mL $NaHCO_3$. After column chromatography (*n*-hexane:EtOAc 3:1) 0.336 g (1.71 mmol, 64%) carbamate **52d** were obtained as colorless solid.

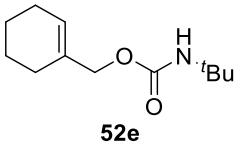
R$_f$: 0.37 (*n*-hexane:EtOAc 3:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.74−5.68 (m, 1 H, C*H*); 4.52 (bs, 1 H, N*H*); 4.40 (s, 2 H, CH_2O); 3.87−3.74 (m, 1 H, C*H*(CH$_3$)$_2$); 2.06−2.02 (m, 2 H, CH_2CCH); 1.99−1.94 (m, 2 H, CH_2CCH$_2$O); 1.68−1.61 (m, 2 H, CH_2CH$_2$CCH$_2$O); 1.59−1.54 (m, 2 H, CH_2CH$_2$CCH); 1.14 (d, 6 H, ^3J = 6.5 Hz, CH(CH_3)$_2$) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 155.9 (*C*O); 133.7 (*C*CH); 125.9 (C*C*H); 69.2 (*C*H$_2$O); 43.1 (*C*H(CH$_3$)$_2$); 25.9 (*C*H$_2$CCH$_2$O); 25.1 (*C*H$_2$CCH); 23.2 (CH(*C*H$_3$)$_2$); 22.5 (*C*H$_2$CH$_2$CCH$_2$O); 22.3 (*C*H$_2$CH$_2$CCH) ppm.

HR-MS (ESI): m/z: 220.1310 [M + Na]$^+$ (cal. 220.1308); m/z: 417.2734 [2M + Na]$^+$ (cal. 417.2724).

Cyclohex-1-en-1-ylmethyl *tert*-butylcarbamate 52e:



52e

For the synthesis of **52e** 0.273 g (2.43 mmol, 1.0 equiv) alcohol **74**, 0.033 g (0.268 mmol, 0.1 equiv) DMAP, 0.317 mL (0.275 g, 2.78 mmol, 1.14 equiv) isocyanate **76e**, 0.390 mL (0.283 g, 2.80 mol, 1.15 equiv)

TEA, and 5.5 mL anhyd. DCM were used (GP-17). The reaction mixture was diluted with 22 mL Et_2O and the layers were washed and extracted, resp., with 22 mL $NaHSO_4$ (10%), 22 mL Et_2O, and 22 mL $NaHCO_3$. After column chromatography (*n*-hexane:EtOAc 5:1) 71.2 mg (0.337 mmol, 14%) carbamate **52e** were obtained as colorless oil. The remaining alcohol was reisolated.

R_f: 0.40 (*n*-hexane:EtOAc 5:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.74−5.69 (m, 1 H, C*H*); 4.64 (bs, 1 H, N*H*); 4.37 (s, 2 H, CH_2O); 2.07−2.01 (m, 2 H, CH_2CCH); 2.00−1.95 (m, 2 H, CH_2CCH$_2$O); 1.67−1.61 (m, 2 H, CH_2CH$_2$CCH$_2$O); 1.60−1.54 (m, 2 H, CH_2CH$_2$CCH); 1.31 (s, 9 H, (CH_3)$_3$) ppm.

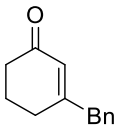
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 155.2 (*C*O)[24]; 133.8 (*C*CH); 125.8 (C*C*H); 68.8 (*C*H$_2$O); 50.4 (*C*(CH$_3$)$_3$); 29.1 (C(*C*H$_3$)$_3$); 26.1 (*C*H$_2$CCH$_2$O); 25.1 (*C*H$_2$CCH); 22.5 (*C*H$_2$CH$_2$CCH$_2$O); 22.3 (*C*H$_2$CH$_2$CCH) ppm.

IR (KBr): $\tilde{\nu}$ = 3333 (s); 2934 (s); 1697 (vs); 1535 (s); 1274 (vs); 1078 (s) cm^{-1}.

HR-MS (ES): m/z: 211.1569 (cal. 211.1572).

Crytal structure: see Chapter 10.

3-Benzyl-2-cyclohexen-1-one 58:



58

In an Ar atmosphere a three-neck round-bottom flask was charged with 43.0 mL (43.0 mmol, 2.2 equiv) benzylmagnesium chloride (1.0 M in Et_2O). After cooling this solution to 0 °C a solution of 2.70 mL (2.78 g, 19.8 mmol, 1.0 equiv) 3-ethoxy-2-cyclohexen-1-one in 15 mL anhyd. THF was added dropwise and the resulting mixture was stirred for 18 h at r.t.. The reaction was quenched carefully with 100 mL HCl (1 M) and extracted afterwards with Et_2O (five times 25 mL). The organic layer was washed with 50 mL sat. $NaHCO_3$, H_2O, and brine. After drying over $MgSO_4$ the solvent was removed under reduced pressure. After purification *via* column chromatography (*n*-pentane:EtOAc:Et_2O 4:1:1 and *n*-pentane:Et_2O 1:1) 2.28 g (12.2 mol, 62%) **58** were isolated as yellowish oil.

R_f: 0.26 (*n*-pentane:EtOAc:Et_2O 4:1:1) and 0.22 (*n*-pentane:Et_2O 1:1).

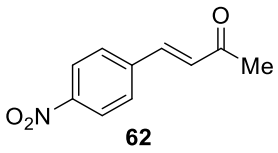
^{1}H-NMR (400 MHz, $CDCl_3$):[25] δ = 7.37–7.22 (m, 3 H); 7.17–7.14 (m, 2 H); 5.86 (s, 1 H); 3.50 (s, 2 H); 2.36–2.33 (m, 2 H); 2.27 (t, 2 H, *J* = 6.0 Hz); 1.98–1.92 (m, 2 H) ppm.

[24] Can be observed in the HMBC spectra.
[25] Traces of BnOH remained even after two times of purification.

^{13}C-NMR (101 MHz, $CDCl_3$):[26] δ = 199.9; 164.7; 136.9; 129.0; 128.6; 126.8; 44.4; 37.2; 29.2; 22.6 ppm.

Analytic data are identical to those reported in literature.[184]

(*E*)-4-(*p*-Nitrophenyl)-3-buten-2-one 62: (GP-16)



62

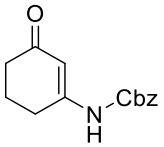
The reaction mixture containing 1.00 g (6.62 mmol, 1.0 equiv) *p*-nitrobenzaldehyde, 0.266 g (1.32 mmol, 0.2 equiv, 20 mol%) **29**, and 17 mL acetone was refluxed for 48 h. For work-up 17 mL DCM and 17 mL sat. $NaHCO_3$ were used. 1.17 g (6.12 mol, 92%) **62** were isolated as yellow solid, which was used without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.26–8.24 (m, 2 H); 7.70–7.68 (m, 2 H); 7.53 (d, 1 H, ^3J = 16.3 Hz); 6.81 (d, 1 H, ^3J = 16.3 Hz); 2.42 (s, 3 H) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 197.5; 148.6; 140.6; 140.0; 130.3; 128.8; 124.2; 28.0 ppm.

^{1}H-NMR data are identical to those reported in literature.[76c]

1-(Benzyloxycarbonylamino)-1-cyclohexen-3-one 66:



66

0.201 g (1.81 mmol, 1.0 equiv) alkene **64** and 0.575 g (5.43 mmol, 3.0 equiv) Na_2CO_3 were suspended in 12 mL of a solvent mixture (H_2O/1,4-dioxane 2/1). After cooling the suspension to 0 °C 0.300 mL (0.359 g, 2.10 mmol, 1.2 equiv) Cbz-Cl were added. The cooling bath was removed after 30 min and the resulting mixture was stirred for 22.5 h at r.t.. Subsequently, the reaction mixture was diluted with H_2O, the aq layer was extracted with DCM (two times 50 mL), the organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. After purification *via* column chromatography (*n*-hexane:EtOAc 2:1 to 0:1) 0.137 g (0.559 mol, 31%) **66** were isolated as colorless solid.

R_f: 0.43 (EtOAc).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.36–7.31 (m, 5 H, H_{Ph}); 7.04 (bs, 1 H, N*H*); 6.40 (s, 1 H, C*H*); 5.15 (s, 2 H, CH_2Ph); 2.50 (t, 2 H, *J* = 6.0 Hz, CH_2); 2.32 (t, 2 H, *J* = 6.5 Hz, CH_2); 2.01–1.95 (m, 2 H, CH_2) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 199.6; 156.0; 152.0; 135.4; 128.79; 128.75; 128.6; 110.4; 67.8; 36.7; 28.3; 21.6 ppm.

IR (KBr): $\tilde{\nu}$ = 3445 (vw); 2958 (vw); 1874 (vw); 1750 (w); 1619 (w); 1524 (w); 1219 (w) cm^{-1}.

[26] Traces of BnOH remained even after two times of purification.

HR-MS (ESI): m/z: 246.1136 $[M + H]^+$ (cal. 246.1125); m/z: 268.0951 $[M + Na]^+$ (cal. 268.0944); m/z: 491.2185 $[2M + H]^+$ (cal. 491.2177); m/z: 513.2006 $[2M + Na]^+$ (cal. 513.1996); m/z: 758.3021 $[3M + Na]^+$ (cal. 758.3048).

Crytal structure: see 10.11.

9.9. *α,β*-Unsaturated *γ*-Hydroxyl Ketones

General procedure with PhLi (GP-18):

1.0 equiv epoxide was dissolved in anhyd. Et_2O. In an Ar atmosphere this solution was cooled to –78 °C. At this temperature firstly 2.0 equiv PhLi (1.8 M in dibutyl ether) and secondly 1.5 equiv BF_3•Et_2O were added. After stirring for 2 to 4 h the reaction was quenched by adding sat. $NaHCO_3$. After extracting the aq layer three times with Et_2O the combined organic layers were washed with $NaOH_{aq}$ (9/1 m/m) and brine and finally dried over Na_2SO_4. After evaporation of the solvent the crude product was purified *via* column chromatography.

General procedure with Ph_2CuLi (GP-19):

5.0 equiv CuBr•Me_2S were suspended in anhyd. Et_2O. Under an Ar atmosphere the resulting mixture was cooled to 0 °C. At this temperature 10 equiv PhLi (1.8 M solution in dibutyl ether) were added and the resulting mixture was stirred afterwards for 10 min. Before adding slowly 1.0 equiv epoxide dissolved in anhyd. Et_2O the mixture was cooled to −30 °C. At this temperature the reaction mixture was stirred 2 h. The reaction was quenched by adding sat. NH_4Cl and the biphasic system was stirred until the copper salts were dissolved. After phase separation the aq layer was extracted with Et_2O and the combined organic layers were dried over Na_2SO_4. After evaporation of the solvent the crude product was purified *via* column chromatography.

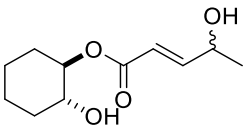
General procedure with TEA/^{t}BuSH (GP-20):

A solution consisting of 1.0 equiv ^{t}BuSH, 1.0 equiv TEA, and methanol was stirred for 20 min at r.t.. After adding 1.0 equiv epoxide dissolved in methanol the resulting mixture was refluxed for 2 h. The reaction progress was monitored *via* TLC. After evaporation of the solvent the crude product was purified *via* column chromatography.

General procedure with DBU (GP-21):

1.0 equiv epoxide was dissolved in 5 mL chloroform. After addition of 1.0 equiv DBU the mixture was stirred for 1 h at r.t.. After evaporation of the solvent the crude product was purified *via* column chromatography.

***trans*-2-Hydroxycyclohexyl (*E*)-4-hydroxy-2-pentenoate 31:** (GP-21)



31

The reaction was performed with 0.100 g (0.467 mmol, 1.0 equiv) epoxide **24a** and 69.8 µL (71.2 mg, 0.468 mmol, 1.0 equiv) DBU. After purification *via* column chromatography (*n*-hexane:EtOAc 1:7) 0.085 g (0.397 mmol, 85%) **31** were isolated as colorless oil.

R_f: 0.38 (*n*-hexane:EtOAc 1:7).

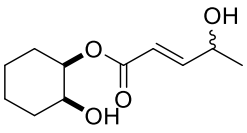
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.99 (dd, 1 H, ^3J = 15.7 Hz, ^3J = 4.6 Hz, COCHC*H*); 6.05 (dd, 1 H, ^3J = 15.7 Hz, ^4J = 1.6 Hz, COC*H*CH); 4.68–4.62 (m, 1 H, C*H*OC); 4.53–4.47 (m, 1 H, C*H*OHCH$_3$); 3.63–3.57 (m, 1 H, C*H*OH); 2.08–2.02 (m, 2 H, H_{Cy}); 1.98 (bs, 2 H, O*H*); 1.75–1.71 (m, 2 H, H_{Cy}); 1.40–1.24 (m, 7 H, H_{Cy} and CH_3) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 166.9 (*C*O); 151.6 (COCH*C*H); 119.7 (CO*C*HCH); 78.5 (*C*HOCO); 73.0 (*C*HOH); 67.3 (*C*HOHCH$_3$); 33.1 (*C*H$_2$CHOH); 30.1 (*C*H$_2$CHOCO); 24.0 (*C*H$_2$CH$_2$CHOCO); 23.9 (*C*H$_2$CH$_2$CHOH); 22.8 (*C*H$_3$) ppm.

IR (Film): ṽ = 3409 (vs); 2939 (vs); 2864 (vs); 1701 (vs); 1273 (vs); 1182 (vs); 857 (m); 597 (w) cm^{-1}.

HR-MS (ESI): m/z: 237.1104 [M + Na]$^+$ (cal. 237.1097); 451.2303 [2M + Na]$^+$ (cal. 451.2301).

***cis*-2-Hydroxycyclohexyl (*E*)-4-hydroxy-2-pentenoate 32:** (GP-21)



32

The reaction was performed with 0.102 g (0.476 mmol, 1.0 equiv) epoxide **25a** and 69.8 µL (71.2 mg, 0.468 mmol, 1.0 equiv) DBU. After purification *via* column chromatography (*n*-hexane:EtOAc 1:7) 0.089 g (0.413 mmol, 89%) **32** were isolated as colorless oil.

R_f: 0.43 (*n*-hexane:EtOAc 1:7).

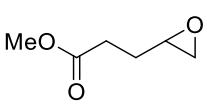
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.98 (dd, 1 H, ^3J = 15.7 Hz, ^3J = 4.6 Hz, COCHC*H*); 6.06 (dd, 1 H, ^3J = 15.7 Hz, ^4J = 1.6 Hz COC*H*CH); 5.00 (dt, 1 H, ^3J = 7.7 Hz, ^3J = 2.6 Hz, C*H*OC); 4.52–4.46 (m, 1 H, C*H*OHCH$_3$); 3.90–3.87 (m, 1 H, C*H*OH); 2.13 (bs, 2 H, O*H*); 1.93–1.84 (m, 1 H, H_{Cy}); 1.80–1.68 (m, 1 H, H_{Cy}); 1.68–1.52 (m, 5 H, H_{Cy}); 1.45–1.36 (m, 2 H, H_{Cy}); 1.34 (d, 3 H, ^3J = 6.6 Hz, CH_3) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 166.4 (*C*O); 151.6 (COCH*C*H); 119.7 (CO*C*HCH); 74.4 (*C*HOCO); 69.5 (*C*HOH); 67.3 (*C*HOHCH$_3$); 30.4 (*C*H$_2$CHOH); 27.2 (*C*H$_2$CHOCO); 22.8 (*C*H$_3$); 22.0 (*C*H$_2$CH$_2$CHOCO); 21.3 (*C*H$_2$CH$_2$CHOH) ppm.

IR (Film): ṽ = 3425 (vs); 2939 (vs); 2864 (s); 1715 (vs); 1273 (vs); 1179 (vs); 980 (s); 888 (m); 595 (w) cm^{-1}.

HR-MS (ESI): m/z: 215.1283 $[M + H]^+$ (cal. 215.1278); 237.1104 $[M + Na]^+$ (cal. 237.1097); 451.2307 $[2M + Na]^+$ (cal. 451.2301).

Methyl 3-(2-oxiranyl)propionate 37: (GP-20)



37

Using the TEA/^{t}BuSH-procedure methyl ester **37** was isolated as side-product starting from epoxides **24b** and **25b**.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.68 (s, 3 H); 3.00–2.95 (m, 1 H); 2.77–2.74 (m, 1 H); 2.49 (dd, 1 H, ^3J = 4.9 Hz, ^3J = 2.7 Hz,); 2.46 (t, 2 H, ^3J = 7.4 Hz), 2.01–1.93 (m, 1 H); 1.80–1.71 (m, 1 H) ppm.

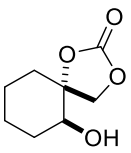
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 173.3; 51.7; 51.2; 47.0; 30.1; 27.6. ppm.

HR-MS (ESI): m/z: 153.0519 $[M + Na]^+$ (cal. 153.0522).

Analytic data are identical to those reported in literature.[185]

9.10. Synthesis of Carbonate **75**

6-Hydroxy-1,3-dioxaspiro[4.5]decan-2-one 75:



75

24.3 mg (0.133 mmol, 1.0 equiv) carbamate **52c** were dissolved in 1.33 mL DCM. Afterwards 47.7 mg (0.213 mmol, 1.6 equiv) *m*CPBA were added. After stirring the resulting mixture for 24 h at r.t. 3.39 mg (0.007 mmol, 5 mol%) TUC **77** were added. After stirring for additional 48 h at r.t. the solvent was evaporated and the crude product was purified *via* column chromatography (Et_2O and 0.5% TEA). Finally, 17.7 mg (0.103 mmol, 78%) carbonate **75** were obtained as colorless solid.

R_f: 0.33 (Et_2O).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.60 (d, 1 H, ^2J = 8.1 Hz, CH_2O); 4.09 (d, 1 H, ^2J = 8.1 Hz, CH_2O); 3.84 (dt, 1 H, ^3J = 10.2 Hz, ^3J = 4.1 Hz); 2.71 (d, 1 H, ^3J = 3.6 Hz, O*H*); 2.03−1.96 (m, 2 H, H_{Cy}); 1.82−1.66 (m, 3 H, H_{Cy}); 1.42−1.14 (m, 3 H, H_{Cy}) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 155.1 (*C*O); 86.0 ($C_{quart.}$); 71.6 (*C*HOH); 69.0 (*C*H_2O); 34.1; 30.7; 22.6; 22.2 ppm.

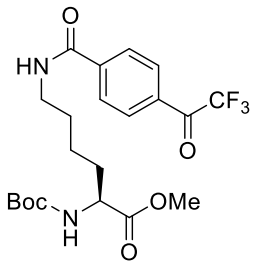
IR (ATR): $\tilde{\nu}$ = 3409 (vw); 2935 (vw); 1777 (m); 1396 (w); 1202 (w); 1168 (m); 1065 (s); 727 (w) cm^{-1}.

HR-MS (EI): m/z: 173.0808 $[M + H]^+$ (cal. 173.0808).

Crytal structure: see 10.11.

9.11. Synthesis of (Functionalized) Amino Acids

Boc-Lys(CM)-OMe 137:



137

The reaction mixture containing 3.00 mg (0.026 mmol, 3 mol%) DMAP, 0.402 g (0.969 mmol, 1.0 equiv) Boc-Lys(2-Cl-Cbz)-OH **135**, 0.228 g (1.19 mmol, 1.2 equiv) EDAC, 0.166 mL (0.121 g, 1.20 mmol, 1.2 equiv) TEA, and 6 mL MeOH was stirred for 4 d at r.t. (GP-3). The solvent was removed under reduced pressure and the residue was dissolved in DCM and H_2O. The aq layer was extracted with DCM (three times 15 mL). The organic layer was dried over Na_2SO_4. After purification *via* column chromatography (EtOAc and *n*-hexane:EtOAc 2:1 to 1:2) 0.114 g (0.266 mmol, 27%) **136** were isolated as slightly yellow oil.

R_f: 0.53 (*n*-hexane:EtOAc 1:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.43–7.39 (m, 1 H, H_{Ar}); 7.38–7.35 (m, 1 H, H_{Ar}); 7.28–7.23 (m, 2 H and $CHCl_3$, H_{Ar}); 5.20 (s, 2 H, CH_2Ar); 5.08 (d, 1 H, ^3J = 7.2 Hz, N*H*); 4.89 (bs, 1 H, N*H*); 4.31–4.26 (m, 1 H, C*H*); 3.73 (s, 3 H, CH_3); 3.22–3.17 (m, 2 H, CHCH_2) 1.85–1.75 (m, 1 H, CH_2); 1.69–1.59 (m, 1 H, CH_2); 1.58–1.48 (m, 2 H, CH_2); 1.43 (s, 9 H, C(CH_3)$_3$); 1.38–1.30 (m, 2 H, CH_2) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 173.4; 156.4; 155.6; 134.5; 133.7; 129.9; 129.6; 129.5; 127.0; 80.1; 64.0; 53.3; 52.4; 40.8; 32.5; 29.4; 28.4; 22.5 ppm.

MS (ESI): m/z: 451.1 $[M + Na]^+$ (cal. 451.2).

The synthesis of the free amine was performed with 0.100 g (0.233 mmol, 1.0 equiv) (2-Cl-Cbz)-protected compound **136**, 0.051 g (0.048 mmol, 20 mol%) Pd/C (10%), and 5 mL MeOH (GP-7). The reaction mixture was stirred for 23 h. The crude product was utilized without further purification. The synthesis of Boc-Lys(CM)-OMe **137** was performed with 2.20 mg (0.018 mmol, 8 mol%) DMAP, 0.065 g (0.298 mmol, 1.3 equiv) acid ***para*-112**, 0.097 g (0.506 mmol, 2.2 equiv) EDAC, 0.068 mL (0.050 g, 0.490 mmol, 2.1 equiv) TEA, and 7 mL DCM for 4 d at r.t. (GP-3). The reaction mixture was washed with sat. $NaHCO_3$ (two times 15.0 mL). The aq layer was extacted with DCM (three times 10.0 mL). The organic layer was dried over Na_2SO_4. After purification *via* HPLC (eluent: TBME/MeOH 98:2; 5 mL min^{-1}; UV detector 254 nm, column: l = 250 mm, d = 8 mm; LiChrosorb Amino (7 µm, Merck); Rt = 14.1 min) 0.030 g (0.065 mmol, 28%) **137** were isolated as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, 2 H, ^3J = 8.0 Hz, C*H*CCOCF_3); 7.94 (d, 2 H, ^3J = 8.5 Hz, NHCOCC*H*); 6.66 (bs, 1 H, N*H*); 5.16 (d, 1 H, ^3J = 8.0 Hz, N*H*); 4.34–4.24 (m, 1 H,

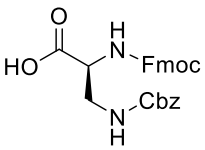
C*H*); 3.73 (s, 3 H, CH_3); 3.52–3.42 (m, 2 H, CHCH_2); 1.88–1.77 (m, 1 H, CH_2); 1.73–1.61 (m, 3 H, CH_2); 1.50–1.41 (m, 2 H, CH_2); 1.38 (s, 9 H, C(CH_3)$_3$) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 180.1 (q, $^2J_{CF}$ = 35.6 Hz, *C*OCF_3); 173.3 (*C*O_2CH_3); 166.3 (NH*C*OC_{Ar}); 155.8 (NH*C*OO); 140.9 (NH*C*O*C*$_{Ar}$); 131.9 (*C*OCF_3); 130.42 (*C*HCOCF_3); 130.40 (*C*HCOCF_3); 127.9 (NHCOC*C*H); 116.6 (q, $^1J_{CF}$ = 291.2 Hz, CO*C*F_3); 80.1 (*C*(CH_3)$_3$); 53.1 (*C*HCH_2); 52.5 (*C*H_3); 40.0 (CH*C*H_2); 32.8 (*C*H_2); 28.7 (*C*H_2); 28.4 (C(*C*H_3)$_3$); 22.7 (*C*H_2) ppm.

IR (Film): ṽ = 3344 (w); 2935 (w); 1723 (s); 1723 (s); 1695 (s); 1173 (s); 1057 (m); 737 (w) cm^{-1}.

HR-MS (ESI): m/z: 515.1974 $[M + MeOH + Na]^+$ (cal. 515.1976); 1007.4026 $[2M + 2MeOH + Na]^+$ (cal. 1007.4059).

Fmoc-Dap(Cbz)-OH 139:



139

0.200 g (0.613 mmol, 1.0 equiv) Fmoc-Lys(NH_2)-OH **138** and 0.198 g (1.86 mmol, 3.0 equiv) Na_2CO_3 were suspended in 2 mL H_2O and 1 mL 1,4-dioxane. After cooling to 0 °C 0.100 mL (0.120 g, 0.701 mmol, 1.1 equiv) CbzCl were added. After 15 min the cooling bath was removed and the suspension was stirred for 24 h. After 2 h further 2 mL H_2O and 1 mL 1,4-dioxane had to be added. The reaction mixture was diluted wit 100 mL H_2O, extracted with with 20 mL Et_2O, and acidified with HCl. The aq layer was extracted with EtOAc (three times 27 mL). The organic layer was dried over Na_2SO_4. After purification *via* column chromatography (DCM:MeOH 10:1) 0.193 g (0.419 mmol, 68%) **139** were isolated as colorless solid.

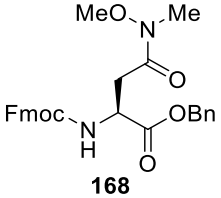
R_f: 0.50 (DCM:MeOH 7:1).

^{1}H-NMR and **^{13}C-NMR** not meaningful.

MS (ESI): m/z: 483.1 $[M + Na]^+$ (cal. 483.2); 499.0 $[M + K]^+$ (cal. 499.1).

Analytic data are reported in literature.[186]

Benzyl (2*S*)-4-(*N*-methylmethoxyamino)-2-((9*H*-fluoren-9-yl)methoxycarbonylamino)-4-oxo-butyrate 168:



168

The synthesis of Weinreb amide **168** was performed with 1.00 g (2.24 mmol, 1.0 equiv) **167**, 0.250 g (2.56 mmol, 1.1 equiv) *N*,*O*-dimethylhydroxylamine hydrochloride **148**, 0.524 g (2.73 mmol, 1.2 equiv) EDAC, 0.368 g (2.72 mmol, 1.2 equiv) HOBt, 0.720 mL (0.525 g, 5.19 mmol, 2.3 equiv) TEA, and 20 mL DCM utilizing GP-6. After 21 h the reaction mixture was

diluted with EtOAc. For washing a volume of 65 mL was used. After purification *via* column chromatography (*n*-hexane:EtOAc 1:1 to 1:3) 0.747 g (1.53 mmol, 68%) **168** were isolated as colorless foam.

R_f: 0.21 (*n*-hexane:EtOAc 1:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, 2 H, ^3J = 7.5 Hz); 7.60 (d, 2 H, ^3J = 7.5 Hz); 7.40 (t, 2 H, ^3J = 7.4 Hz); 7.35–7.27 (m, 7 H); 6.12 (d, 1 H, ^3J = 9.0 Hz, N*H*); 5.24 (d, 1 H, ^2J = 12.3 Hz, CH_2Ph); 5.18 (d, 1 H, ^2J = 12.3 Hz, CH_2Ph); 4.75–4.72 (m, 1 H, C*H*CH_2CO); 4.43 (dd, 1 H, ^2J = 10.3 Hz, ^3J = 7.1 Hz, CHCH_2OCO); 4.29 (dd, 1 H, ^2J = 10.3 Hz, ^3J = 7.6 Hz, CHCH_2OCO); 4.21 (t, 1 H, ^3J = 7.3 Hz, C*H*CH_2OCO); 3.63 (s, 3 H, CH_3); 3.29 (dd, 1 H, ^2J = 17.4 Hz, ^3J = 3.7 Hz, CHCH_2CO); 3.16 (s, 3 H, CH_3); 2.97 (dd, 1 H, ^2J = 17.3 Hz, ^3J = 3.5 Hz, CHCH_2CO) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.5 (*C*O); 171.3 (*C*O); 156.4 (*C*O); 144.1 ($C_{quart.}$); 143.9 ($C_{quart.}$); 141.4 ($C_{quart.}$); 141.3 ($C_{quart.}$); 135.6 ($C_{quart.}$); 128.6; 128.4; 128.2; 127.80; 127.78; 127.19; 127.18; 125.4; 125.3; 120.1; 67.5 (*C*H_2Ph); 67.4 (CH*C*H_2OCO); 61.3 (*C*H_3); 50.5 (*C*HCH_2CO); 47.2 (*C*HCH_2OCO); 34.8 (CH*C*H_2CO); 32.0 (*C*H_3) ppm.

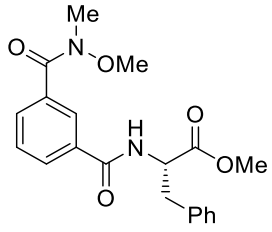
IR (ATR): ṽ = 3326 (vw); 2940 (vw); 1719 (m); 1651 (m); 1500 (m); 1449 (m); 1188 (m); 738 (s) cm^{-1}.

HR-MS (ESI): m/z: 511.1846 $[M + Na]^+$ (cal. 511.1840).

MS (ESI): m/z: 511.3 $[M + Na]^+$ (cal. 511.2); 499.0 $[M + K]^+$ (cal. 499.1).

9.12. Synthesis of *ortho*- and *meta*-Substituted TFMKs

Methyl (2*S*)-2-(*m*-((*N*-methylmethoxyamino)carbonyl)benzoylamino)-3-phenyl-propionate 149:



149

The synthesis of *m*-(((1*S*)-1-methoxycarbonyl-2-phenylethylamino)-carbonyl)benzoic acid **149** was performed with 0.840 g (3.89 mmol, 1.0 equiv) ClH_3N-Phe-OMe **130**, 0.655 g (3.94 mmol, 1.0 equiv) isophthalic acid **147**, 0.920 g (4.80 mmol, 1.2 equiv) EDAC, 0.655 g (4.85 mmol, 1.1 equiv) HOBt, 0.650 mL (0.474 g, 4.68 mmol, 1.2 equiv) TEA, and 25 mL DCM utilizing GP-6. After 24 h the reaction mixture was diluted with EtOAc. The organic layer was washed with citric acid (0.5 M, in total 300 mL). As crude product 1.06 g (3.24 mmol, 83%) of the Phe derivative were obtained as a colorless solid.

The synthesis of Weinreb amide **149** was performed with 1.06 g (3.24 mmol, 1.0 equiv) of the free carboxylic acid, 0.353 g (3.61 mmol, 1.1 equiv) *N*,*O*-dimethylhydroxylamine

hydrochloride **148**, 0.760 g (3.96 mmol, 1.2 equiv) EDAC, 0.548 g (4.06 mmol, 1.3 equiv) HOBt, 1.00 mL (0.729 g, 7.20 mmol, 2.2 equiv) TEA, and 20 mL DCM utilizing GP-6. After 24 h the reaction mixture was diluted with 70 mL EtOAc. For washing a volume of 30 mL was used. After purification *via* column chromatography (*n*-hexane:EtOAc 2:1 to 1:5) 0.369 g (0.996 mmol, 31%) **149** were isolated as colorless oil.

R_f: 0.36 (*n*-hexane:EtOAc 1:5).

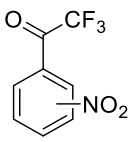
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.12 (s, 1 H, C(COR)C*H*C(COR)); 7.92–7.86 (m, 2 H, C*H*CHC*H*); 7.53–7.49 (m, 1 H, CHC*H*CH); 7.39–7.30 (m, 3 H, H_{Ph}); 7.26–7.24 (m, 2 H, H_{Ph}); 7.14 (bs, 1 H, N*H*); 5.17–5.12 (m, 1 H, C*H*CH_2); 3.83 (s, 3 H, CH_3); 3.59 (s, 3 H, CH_3); 3.42 (s, 3 H, CH_3); 3.37 (dd, 1 H, ^2J = 13.9 Hz, ^3J = 5.7 Hz, CHCH_2); 3.28 (dd, 1 H, ^2J = 13.8 Hz, ^3J = 6.4 Hz, CHCH_2) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 172.0 (*C*O); 168.8 (*C*O); 166.2 (*C*O); 136.0 ($C_{quart.}$); 134.3 ($C_{quart.}$); 133.7 ($C_{quart.}$); 131.3 (*C*HCHCH); 129.3 (CH_{Ph}); 129.2 (*C*HCHCH and CH_{Ph}); 128.5 (2 C, CH_{Ph}); 128.3 (CH*C*HCH); 127.1 (CH_{Ph}); 126.7 (C(COR)*C*HC(COR)); 61.1 (CH_3); 53.7 (*C*HCH_2); 52.4 (CH_3); 37.8 (CH*C*H_2); 33.5 (CH_3) ppm.

IR (Film): ṽ = 3322 (m); 2952 (w); 2236 (vw); 1745 (vs); 1647 (vs); 1213 (vs); 987 (m); 728 (s) cm^{-1}.

HR-MS (EI): m/z: 370.1510 (cal. 370.1539).

2,2,2-Trifluoro-1-(nitrophenyl)-1-ethanone 154:



154

After cooling 0.800 mL (0.992 g, 5.70 mmol, 1.0 equiv) trifluoroacetophenone **152** to 0 °C a mixture of 1.80 mL HNO_3 and 1.60 mL H_2SO_4, which was also cooled to 0 °C, was added carefully. The resulting mixture was stirred 15 min at 0 °C, 15 min at r.t., and 3 h at 50 °C and afterwards poured on 30 mL icy water. The aq layer was extracted with 30 mL Et_2O. The organic layer was washed with sat. $NaHCO_3$ (totally 150 mL) as well as 20 mL water and was dried finally over Na_2SO_4. After purification *via* column chromatography (*n*-hexane:EtOAc 5:1 to 1:1) 1.21 g (5.52 mmol, 97%) **154** were isolated (***ortho*-154**: 0.262 g, 1.20 mmol, 21%, yellowish oil; ***meta*-154**: 0.948 g, 4.33 mmol, 76%, yellowish solid)[27].

***ortho*-154**:

R_f: 0.33 (*n*-hexane:EtOAc 2:1).

[27] Exact ratio of isomers determined *via* NMR.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.43–8.19 (m, 1 H); 7.99–7.71 (m, 2 H); 7.67–7.43 (m, 1 H) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 184.2 (q, ^2J = 38.6 Hz, *C*$COCF_3$); 146.3 (*C*NO_2); 135.4; 132.9; 130.4; 128.7; 124.6; 115.6 (q, ^1J = 290.5 Hz, CO*C*F_3) ppm.

***meta*-154**:

R_f: 0.18 (*n*-hexane:EtOAc 2:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.90 (s, 1 H, C($COCF_3$)C*H*C(NO_2)); 8.59–8.56 (m, 1 H, C*H*C(NO_2)); 8.43–8.37 (m, 1 H, C*H*C($COCF_3$)); 7.82 (t, 1 H, ^3J = 8.1 Hz, CHC*H*CH) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 179.0 (q, ^2J = 36.4 Hz, *C*OCF_3); 148.8 (*C*NO_2); 135.4 (q, ^5J = 2.1 Hz, *C*HC($COCF_3$)); 131.3 (*C*$COCF_3$); 130.8 (CH*C*HCH); 129.8 (C*H*C(NO_2)); 125.1 (q, ^5J = 2.2 Hz, C($COCF_3$)*C*HC(NO_2)); 116.4 (q, ^1J = 290.8 Hz, CO*C*F_3) ppm.

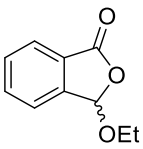
IR (Film): ṽ = 3449 (s); 3095 (m); 2876 (w); 1732 (vs); 1535 (vs); 1353 (vs); 1191 (vs); 712 (vs) cm^{-1}.

HR-MS (ESI): m/z: 274.0299 $[M + MeOH + Na]^+$ (cal. 274.0298).

Crytal structure: see Chapter 10.

9.13. Synthesis of *α*-Ketoacetale

3-Ethoxyphthalide 162a:



162a

0.045 g (0.301 mmol, 1.0 equiv) carboxybenzaldehyde **146** were dissolved in 2.60 mL EtOAc. Afterwards 1.30 mL diluted hydrochloric acid were added and the resulting reaction mixture was stirred for 17.5 h at r.t.. The organic layer was diluted with 20 mL EtOAc and washed with 10 mL H_2O. Befor drying the organic layers over Na_2SO_4 the aq one was extracted with 10 mL EtOAc. After purification *via* column chromatography (*n*-hexane:Et_2O 1:1 to 0:1) 14.0 mg (0.079 mmol, 26%) **162a** were isolated as colorless liquid.

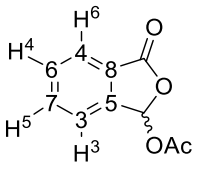
R_f: 0.43 (*n*-hexane:Et_2O 1:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.90–7.88 (m, 1 H); 7.73–7.69 (m, 1 H); 7.59 (t, 2 H, ^3J = 7.6 Hz); 6.37 (s, 1 H); 4.03–3.96 (m, 1 H); 3.91–3.83 (m, 1 H); 1.33 (t, 3 H, ^3J = 7.1 Hz) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 168.9; 145.2; 134.5; 130.9; 127.4; 125.6; 123.6; 102.5; 66.1; 15.3 ppm.

Analytic data are identical to those reported in literature.[187]

3-Phthalideyl acetate 162b:



162b

0.045 g (0.300 mmol, 1.0 equiv) carboxybenzaldehyde **146** and 0.088 g (0.300 mmol, 1.0 equiv) amine **165** were dissolved in 4 mL PhMe. The resulting reaction mixture was stirred 18 h at r.t.. After addition of 28.4 µL (30.6 mg, 0.300 mmol, 1.0 equiv) Ac_2O stirring was continued for 6 h. The solvent was removed under reduced pressure. After purification *via* column chromatography (EtOAc) 0.036 g (0.202 mmol, 67%, 28% *ee*) **162b** were isolated as colorless solid.

R_f: 0.61 (EtOAc).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, 1 H, ^3J = 7.6 Hz, H^6); 7.74 (td, 1 H, ^3J = 7.5 Hz, ^4J = 1.0 Hz, H^5); 7.64 (t, 1 H, ^3J = 7.3 Hz, H^4); 7.59 (d, 1 H, ^3J = 7.6 Hz, H^3); 7.41 (s, 1 H, C*H*$(OR)_2$); 2.18 (s, 3 H, CH_3) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 169.4 (*C*OCH_3); 167.8 (*C*O lactone); 144.7 (C_8); 134.8 (C_7); 131.2 (C_6); 126.4 (C_5); 125.7 (C_4); 123.5 (C_3); 92.6 (*C*H$(OR)_2$); 20.7 (CH_3) ppm.

HR-MS (EI): m/z: 192.0422 (cal. 192.0423).

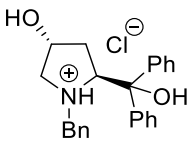
Analytic data are identical to those reported in literature.[140c]

Chiral GC analysis:

Enantiomers of **162b** were separated by chiral GC employing a 30 m FS-Hydrodex *β*-TBDAc column (Macherey-Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: Initial temperature: 100 °C; Final temperature: 190 °C; Rate: 2.00 °C/min. Retention zimes: Rt_1 = 40.4 min; Rt_2 = 40.8 min.

9.14. Synthesis of Hydroxyl Prolinol Moiety

((2*S*,4*R*)-1-Benzyl-4-hydroxy-2-pyrrolidinyl)diphenylmethanol 188:



188

The synthesis of ClH_3N-Pro-OMe was performed with 1.00 g (7.63 mmol, 1.0 equiv) H_2N-Pro-OH, 2.16 mL (3.54 g, 29.8 mmol, 3.9 equiv) $SOCl_2$, and 8 mL MeOH utilizing GP-5. At the beginning the reaction mixture was cooled to −20 °C. The reaction mixture was stirred for 4 d. 1.39 g (7.65 mmol, quant.) ClH_3N-Pro-OMe were obtained as colorless solid.

^{1}H-NMR (400 MHz, D_2O): δ = 4.73–4.68 (m, 2 H); 3.85 (s, 3 H); 3.53 (dd, 1 H, *J* = 8.9 Hz, *J* = 3.8 Hz); 3.44–3.40 (m, 1 H); 2.53–2.47 (m, 1 H); 2.34–2.27 (m, 1 H) ppm.

^{13}C-NMR (101 MHz, D_2O): δ = 170.2; 69.4; 58.1; 53.8; 53.4; 36.6 ppm.

MS (ESI): m/z: 146.1 $[M + H]^+$ (cal. 146.1).

Analytic data are identical to those reported in literature.[188]

0.150 g (0.826 mmol, 1.0 equiv) ClH_3N-Pro-OMe, 0.108 mL (0.155 g, 0.908 mmol, 1.1 equiv) BnBr, and 0.352 mL (0.268 g, 2.07 mmol, 2.5 equiv) D*i*PEA were dissolved in 5 mL PhMe. The resulting reaction mixture was refluxed for 6 h. The biphasic system was diluted with 5 mL sat. $NaHCO_3$ and extracted with EtOAc (three times 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. 0.195 g (0.829 mmol, quant.) benzyl-protected Pro **187** were obtained as brownish oil. The crude product was used without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.32–7.26 (m, 5 H); 4.47–4.42 (m, 1 H); 3.91 (d, 1 H, *J* = 12.8 Hz); 3.69–3.60 (m, 2 H); 3.65 (s, 3 H); 3.33 (dd, 1 H, *J* = 10.2 Hz, *J* = 5.7 Hz); 2.49 (dd, 1 H, *J* = 10.2 Hz, *J* = 3.8 Hz); 2.29–2.22 (m, 1 H); 2.12–2.05 (m, 1 H) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 173.9; 137.8; 129.1; 128.3; 127.3; 70.2; 63.6; 61.1; 58.1; 51.8; 39.6 ppm.

Analytic data are identical to those reported in literature.[149b]

20% of a solution consisting of 0.403 mL (0.601 g, 3.83 mmol, 4.5 equiv) PhBr in 2 mL anhyd. Et_2O were added to 0.093 g (3.83 mmol, 4.5 equiv) Mg and a little amount of iodine stirred in 9 mL anhyd. Et_2O. The mixture was refluxed and the rest of the bromide solution was added once a misting was observable. After the Mg reacted completely 0.200 g (0.850 mmol, 1.0 equiv) of the Bn-protected Pro **187** dissolved in 5 mL THF was added slowly. After 4 h the reaction was quenched with 10 mL sat. NH_4Cl and the aq layer was extracted with EtOAc (three times 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. After purification *via* column chromatography (DCM:EtOAc 3:1) 0.162 g (0.409 mmol, 48%) hydrochloride **188** were isolated as orange oil.

R_f: 0.06 (DCM:EtOAc 3:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, 2 H, *J* = 8.5 Hz); 7.60–7.58 (m, 2 H); 7.30–7.09 (m, 9 H); 7.04–7.02 (d, 2 H); 4.95 (s, 1 H); 4.45–4.35 (m, 1 H); 4.28–4.22 (m, 1 H); 3.31 (s, 2 H); 3.08 (dd, 1 H, *J* = 11.1 Hz, *J* = 4.6 Hz); 2.52 (ddd, 1 H, *J* = 11.2 Hz, *J* = 4.0 Hz, *J* = 1.1 Hz); 1.88 (s, 2 H); 1.56 (s, 1 H) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 147.7; 146.0; 139.5; 128.5; 128.3; 128.2; 128.1; 126.9; 126.6; 126.4; 125.6; 125.4; 76.8; 70.9; 70.4; 62.1; 61.2; 38.7 ppm.

MS (ESI): m/z: 360.2 $[M + H]^+$ (cal. 360.2).

Analytic data are identical to those reported in literature.[149a]

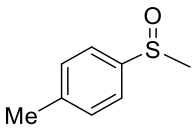
9.15. Sulfoxidation

9.15.1. Racemic Synthesis of Sulfoxides

General Procedure (GP-22):

1.0 equiv sulfide was dissolved in 4 mL acetonitrile. 1.0 equiv TMSCl and 1.0 equiv H_2O_2 (30%) were added in one portion. The resulting mixture was stirred at r.t. until observing full conv. *via* TLC. The reaction was quenched by adding water and DCM. After phase separation, washing with DCM, and drying over Na_2SO_4 the solvent was evaporated under reduced. The crude product was purified *via* column chromatography.

1-Methyl-4-(methylsulfinyl)benzene 212a: (GP-22)



212a

The reaction was performed with 0.097 mL (0.100 g, 0.721 mmol, 1.0 equiv) sulfide **211a**, 0.092 mL (0.079 g, 0.725 mmol, 1.0 equiv) TMSCl, and 0.148 mL (0.049 g, 1.24 mmol, 2.0 equiv) H_2O_2 (30%) for 17 h. For quenching 10 mL water and 10 mL DCM were used. After purification *via* column chromatography (*n*-hexane:EtOAc 1:5 to 1:15) 67.8 mg (0.440 mmol, 61%) **212a** were isolated as colorless oil.

R_f: 0.10 (n-hexane:EtOAc 1:5).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.48−7.44 (m, 2 H); 7.27−7.23 (m, 2 H); 2.62 (s, 3 H); 2.33 (s, 3 H) ppm.

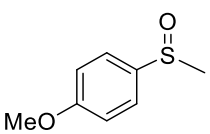
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 142.4; 141.5; 130.0; 123.5; 44.0; 21.4 ppm.

Analytic data are identical to those reported in literature.[189]

Chiral GC analysis:

Enantiomers of **212a** were separated by chiral GC employing a 30 m FS-Hydrodex γ-TBDAc column (Macherey-Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: Initial temperature: 130 °C; Initial time: 40 min. Retention times: Rt_1 = 33.2 min; Rt_2 = 35.0 min.

1-Methoxy-4-(methylsulfinyl)benzene 212b: (GP-22)



212b

The reaction was performed with 0.090 mL (0.100 g, 0.648 mmol, 1.0 equiv) sulfide **211b**, 0.082 mL (0.070 g, 0.646 mmol, 1.0 equiv) TMSCl, and 0.132 mL (0.044 g, 1.29 mmol, 2.0 equiv) H_2O_2 (30%) for 7 h. For quenching 5 mL water and 4 mL DCM were used. After purification *via* column chromatography (*n*-hexane:EtOAc 2:1 to 1:15) 95.0 mg (0.558 mmol, 86%) **212b** were isolated as colorless oil.

R_f: 0.30 (n-hexane:EtOAc 1:5).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.52−7.50 (m, 2 H); 6.96−6.94 (m, 2 H); 3.77 (s, 3 H); 2.62 (s, 3 H) ppm.

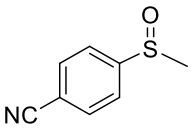
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 161.9; 136.5; 125.4; 114.8; 55.5; 43.9 ppm.

Analytic data are identical to those reported in literature.[189]

Chiral GC analysis:

Enantiomers of **212b** were separated by chiral GC employing a 30 m FS-Hydrodex *γ*-TBDAc column (Macherey-Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: Initial temperature: 170 °C; Initial time: 30 min. Retention times: Rt_1 = 17.1 min; Rt_2 = 17.5 min.

4-(Methylsulfinyl)benzonitrile 212c: (GP-22)



212c

The reaction was performed with 0.103 g (0.690 mmol, 1.0 equiv) sulfide **211c**, 0.085 mL (0.073 g, 0.670 mmol, 1.0 equiv) TMSCl, and 0.136 mL (0.045 g, 1.33 mmol, 1.9 equiv) H_2O_2 (30%) for 6.5 h. For quenching 5 mL water and 4 mL DCM were used. After purification *via* column chromatography (*n*-hexane:EtOAc 2:1 to 1:10) 94.0 mg (0.569 mmol, 85%) **212c** were isolated as colorless solid.

R_f: 0.33 (n-hexane:EtOAc 1:5).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.80−7.78 (m, 2 H); 7.74−7.72 (m, 2 H); 2.72 (s, 3 H) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 151.5; 133.0; 124.3; 117.7; 114.7; 43.8 ppm.

IR (KBr): $\tilde{\nu}$ = 2992 (w); 2235 (s); 1488 (m); 1082 (vs); 1048 (vs); 832 (s); 553 (s) cm^{-1}.

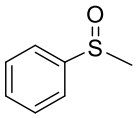
HR-MS(EI): m/z = 165.0240 (calc.: m/z = 165.0248).

Analytic data are identical to those reported in literature.[189]

Chiral GC analysis:

Enantiomers of **212c** were separated by chiral GC employing a 30 m FS-Hydrodex *γ*-TBDAc column (Macherey-Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: Initial temperature: 180 °C; Initial time: 30 min. Retention times: Rt_1 = 23.9 min; Rt_2 = 24.9 min.

(Methylsulfinyl)benzene 212d:



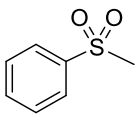
212d

Chiral GC analysis:

Enantiomers of **212d** were separated by chiral GC employing a 30 m FS-Hydrodex *γ*-DiMOM column (Macherey-Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: Initial temperature: 100 °C; Final temperature: 170 °C; Rate: 2.00 °C/min. Retention times: Rt_1 = 28.2 min; Rt_2 = 34.2 min.

9.15.2. Overoxidation to Sulfone **213d**

Methylsulfonyl benzene 213d:



213d

After dissolving 0.126 g (0.563 mmol, 1.1 equiv) *m*CPBA in 3.2 mL DCM 58.6 µL (61.9 mg, 0.499 mmol, 1.0 equiv) sulfide **211d** were added. Further 0.123 g (0.549 mmol, 1.1 equiv) *m*CPBA were added after 1 h. After an additional hour the reaction mixture was diluted with 22 mL Et_2O. The organic layer was washed with sat. $NaHCO_3$ (three times 22 mL). The combined aq layers were extracted with 22 mL Et_2O. After drying the combined organic layers over Na_2SO_4 the solvent was removed under reduced pressure. After purifaction *via* column chromatography (Et_2O) 66.0 mg (0.422 mmol, 85%) sulfone **213d** were isolated as colorless oil.

R_f: 0.72 (EtOAc).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.94−7.90 (m, 2 H); 7.69−7.51 (m, 3 H); 3.04 (s, 3 H) ppm.

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 140.6; 133.8; 129.4; 127.4; 44.5 ppm.

Analytic data are identical to those reported in literature.[190]

Chiral GC analysis:

213d was also injected on the chiral GC employing a 30 m FS-Hydrodex *γ*-DiMOM column (Macherey-Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: Initial temperature: 100 °C; Final temperature: 170 °C; Rate: 2.00 °C/min. Retention time: Rt = 35.8 min.

9.16. Catalytic Sulfoxidation

9.16.1. Dioxirane-Based Sulfoxidation

Before adding 1.0 equiv sulfide and 5.0 equiv H_2O_2 (30%) the utilized **cat.** was dissolved in MeCN or a mixture of toluene and MeCN. The resulting reaction mixture was stirred at r.t. and small samples were taken and analyzed directly *via* chiral GC.

9.16.2. Peracid-Based Sulfoxidation

The used **cat.** was dissolved in the corresponding solvent before adding 1.0 equiv sulfide. The reaction was started with the addition of DIC and 5.0 equiv of H_2O_2 (30%). Afterwards the resulting reaction mixture was stirred at r.t. or 0 °C. Small samples were taken and analyzed directly *via* chiral GC.

9.16.3. Cooperative Catalysis Concept and PTC-Based Sulfoxidation

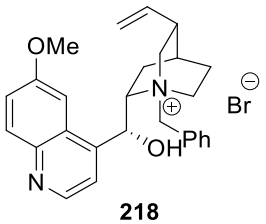
1.0 equivalent Oxone® and 0.2 equiv of PTC and/or 0.2 equiv TUC were suspended in 1 mL anhyd. solvent or in 2 mL of a 1:1-mixture of distilled solvent and water. If the reaction was performed in the absence of water besides anhyd. solvent the reaction vessel was fluted with Ar. After adding 1.0 equiv sulfide the reaction mixture was stirred at r.t.. Small samples were taken and investigated directly *via* chiral GC.

9.16.4. Thiourea-Based Sulfoxidation

0.1 equiv of the TUC were dissolved in the corresponding anhyd. solvent before adding 1.0 equiv sulfide. The reaction was started by addition of 1.2 equiv of *tert*-butyl hydroperoxide (5.0-6.0 M in decane). Afterwards the resulting reaction mixture was stirred at r.t.. Small samples were taken and analyzed directly *via* chiral GC.

9.17. Synthesis of PTC **218**

(1S,2S,4S,5R)-1-benzyl-2-((R)-hydroxy(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidin-1-ium bromide 218:



218

11.5 g (0.035 mol, 1.0 equiv) tertiary amine **217** were dissolved in 350 mL THF. Afterwards 4.00 mL (5.75 g, 0.034 mol, 1.0 equiv) BnBr were added. The resulting mixture was refluxed for 4.5 h. While pouring the solution in 900 mL Et_2O a colorless solid formed, which was separated *via* filtration and washed with 200 mL Et_2O. The crude product was dissolved in 250 mL boiling MeOH. After reaching 40 °C 130 mL Et_2O were added and the product started to crystallize. The crystals were filtered, washed with Et_2O, and dried over night in vacuum. The reaction mixture and the mother liquor were concentrated and the formed solid was treated in the aforementioned way. 15.1 g (0.030 mol, 90%) bromide **218** were obtained as a slightly purple solid.

m.p.: 167.5−169.1 ° C (lit.: 168−170 °C).

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.81 (d, 1 H, *J* = 4.5 Hz); 8.02 (d, 1 H, *J* = 9.2 Hz); 7.76 (d, 1 H, *J* = 4.5 Hz); 7.74−7.66 (m, 2 H); 7.62−7.54 (m, 3 H); 7.50 (dd, 1 H, *J* = 9.2 Hz, *J* = 2.4

Hz); 7.40 (d, 1 H, *J* = 2.2 Hz); 6.71 (d, 1 H, *J* = 3.8 Hz); 6.63−6.56 (m, 1 H); 5.74 (ddd, 1 H, *J* = 17.3 Hz, *J* = 10.4 Hz, *J* = 6.9 Hz); 5.44 (d, 1 H, *J* = 12.1 Hz); 5.11 (d, 1 H, *J* = 17.2 Hz); 5.00 (d, 1 H, *J* = 10.5 Hz); 4.72 (d, 1 H, *J* = 12.2 Hz); 4.31−4.19 (m, 1 H); 4.02 (s, 3 H); 3.92−3.83 (m, 1 H); 3.76−3.65 (m, 1 H); 3.30 (d, 1 H, *J* = 12.1 Hz); 3.26−3.14 (m, 1 H); 2.75−2.64 (m, 1 H); 2.23 (dd, 1 H, *J* = 10.7 Hz, *J* = 4.0 Hz); 2.14 (dd, 1 H, *J* = 15.8 Hz, *J* = 9.6 Hz); 2.04−1.96 (m, 1 H); 1.83 (t, 1 H, *J* = 10.2 Hz); 1.45 (t, 1 H, *J* = 11.8 Hz) ppm.

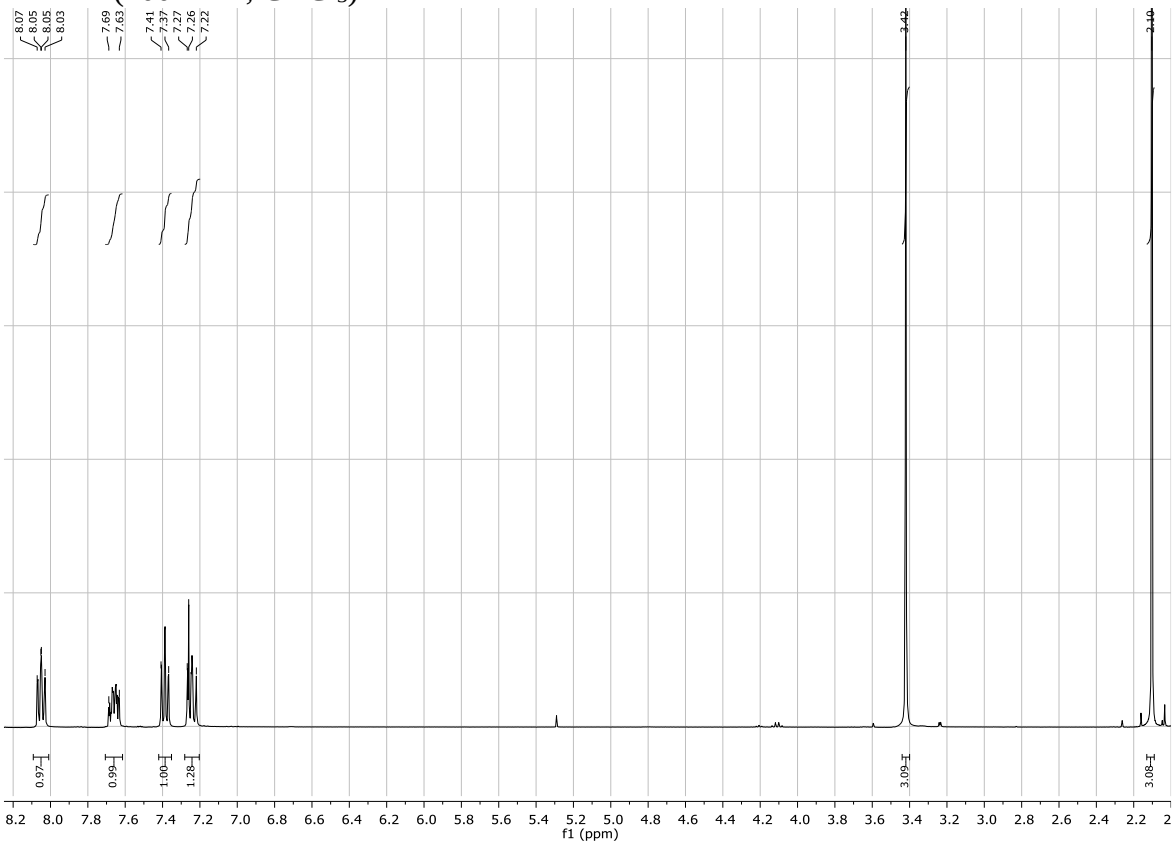
^{13}C-NMR (100 MHz, DMSO-d_6): δ = 157.4; 147.5; 143.8; 143.7; 138.0; 133.6; 131.5; 130.2; 129.1; 127.9; 125.4; 121.5; 120.3; 116.6; 102.1; 68.4; 63.6; 63.3; 59.1; 55.6; 50.7; 37.0; 26.0; 24.2; 20.3 ppm.

Analytic data are identical to those reported in literature.[146]

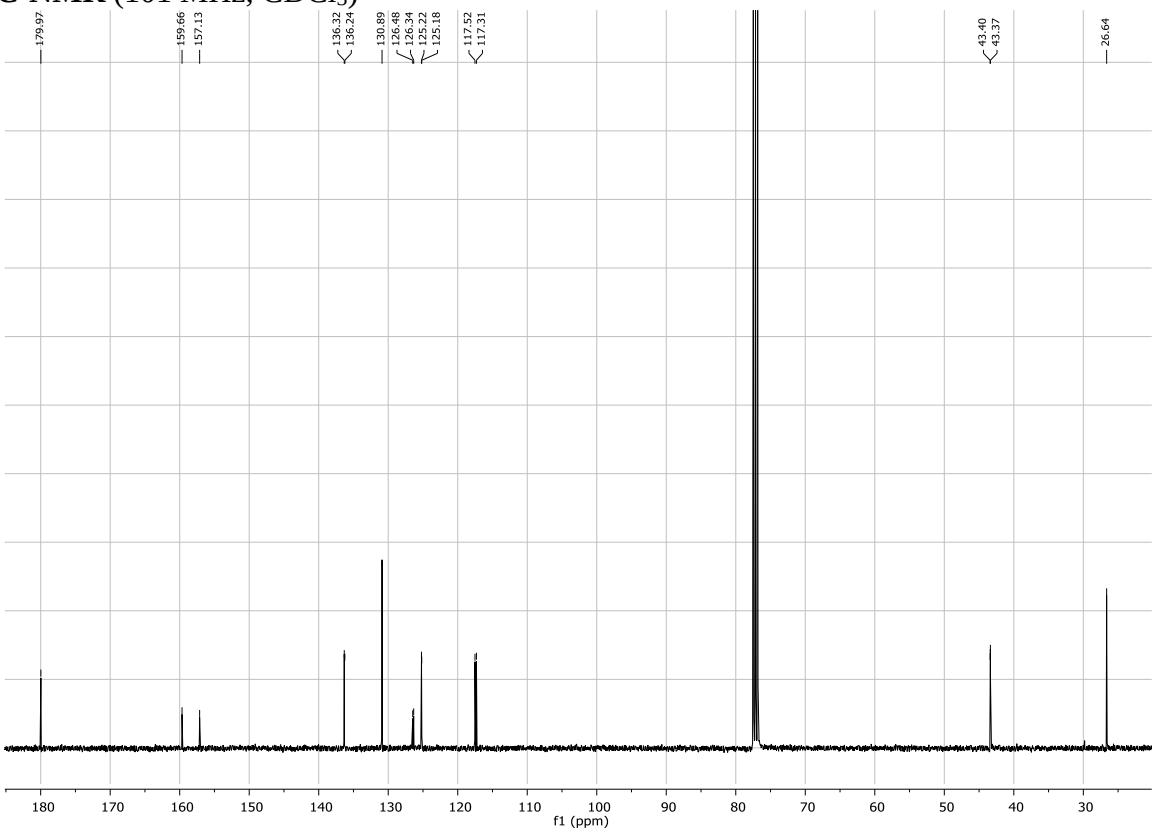
10.NMR spectra

1-(*o*-Fluorophenylmethylthioamino)-1-ethanone 9a:

^{1}H-NMR (400 MHz, $CDCl_3$)

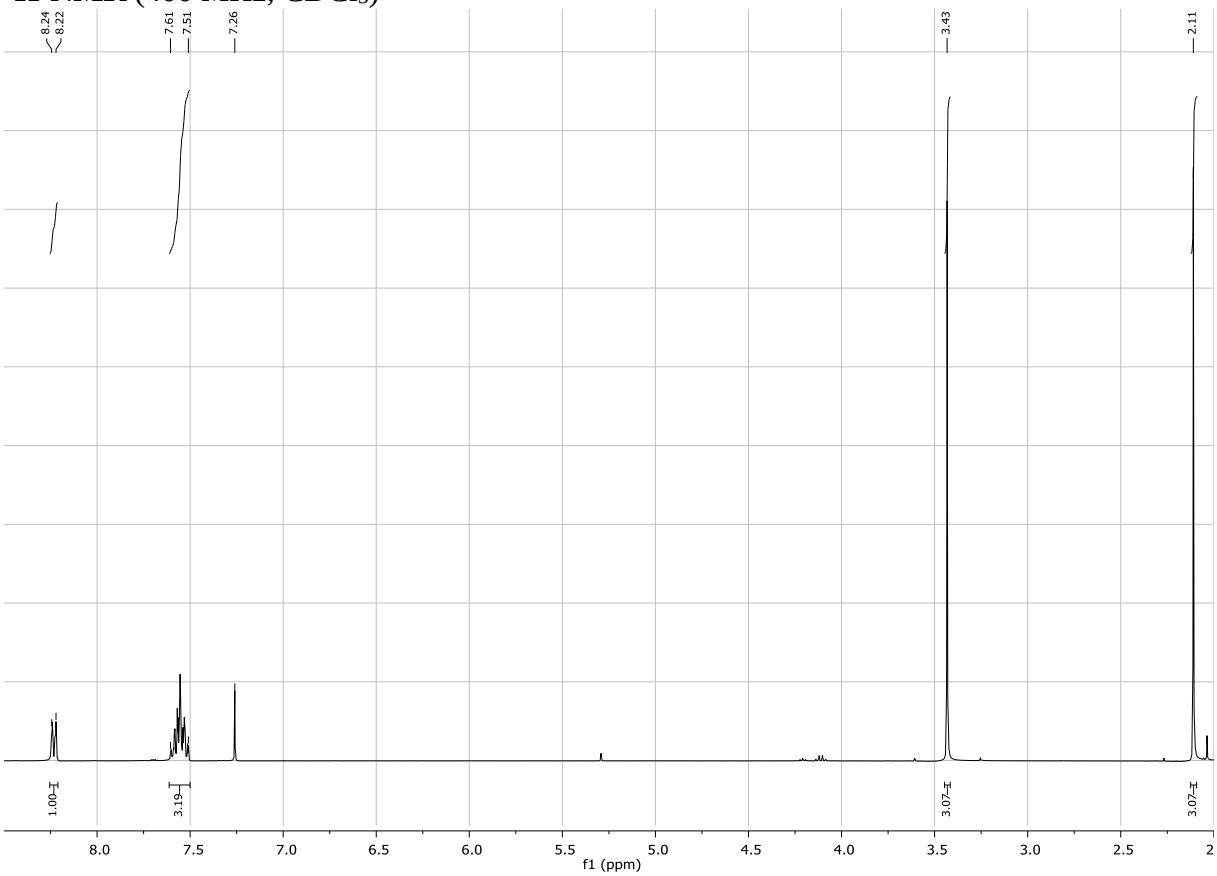


^{13}C-NMR (101 MHz, $CDCl_3$)

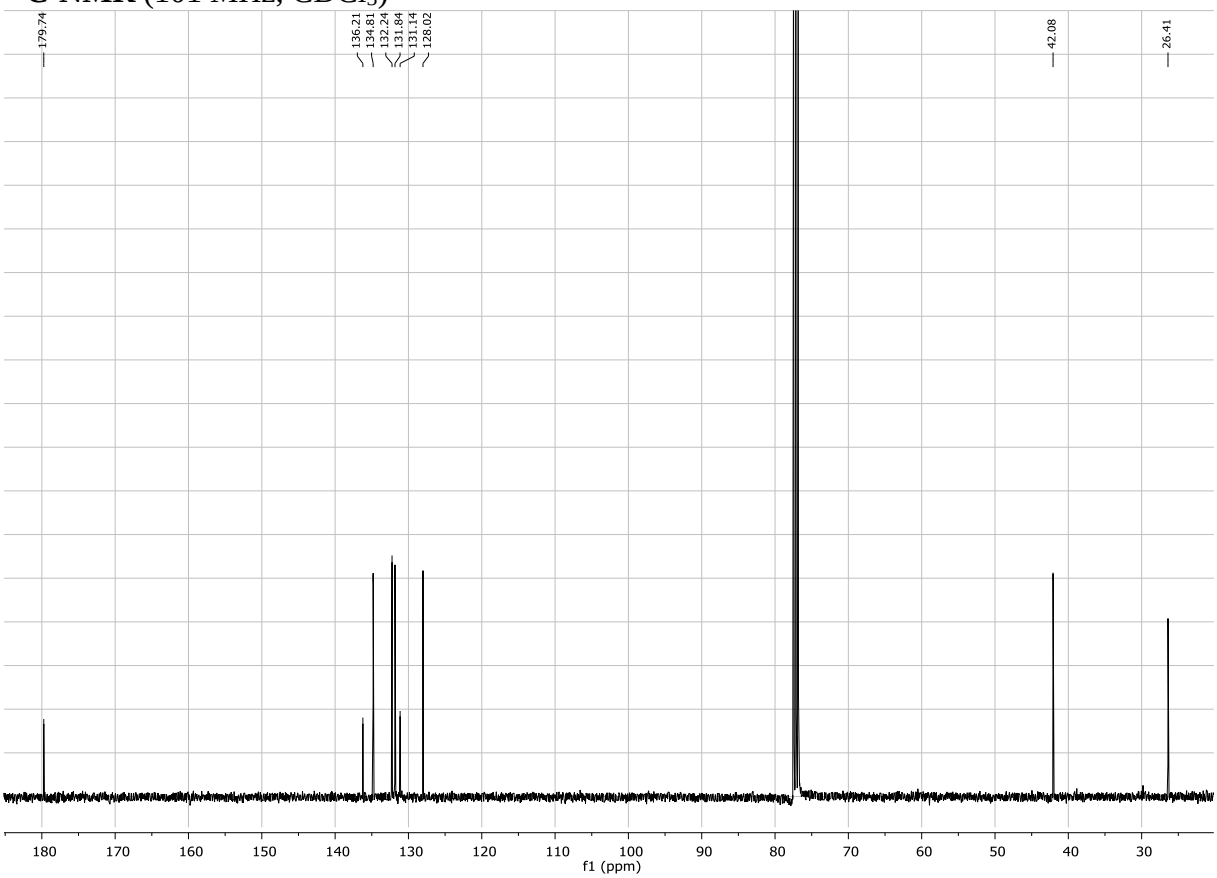


1-(*o*-Chlorophenylmethylthioamino)-1-ethanone 9b:

^{1}H-NMR (400 MHz, $CDCl_3$)

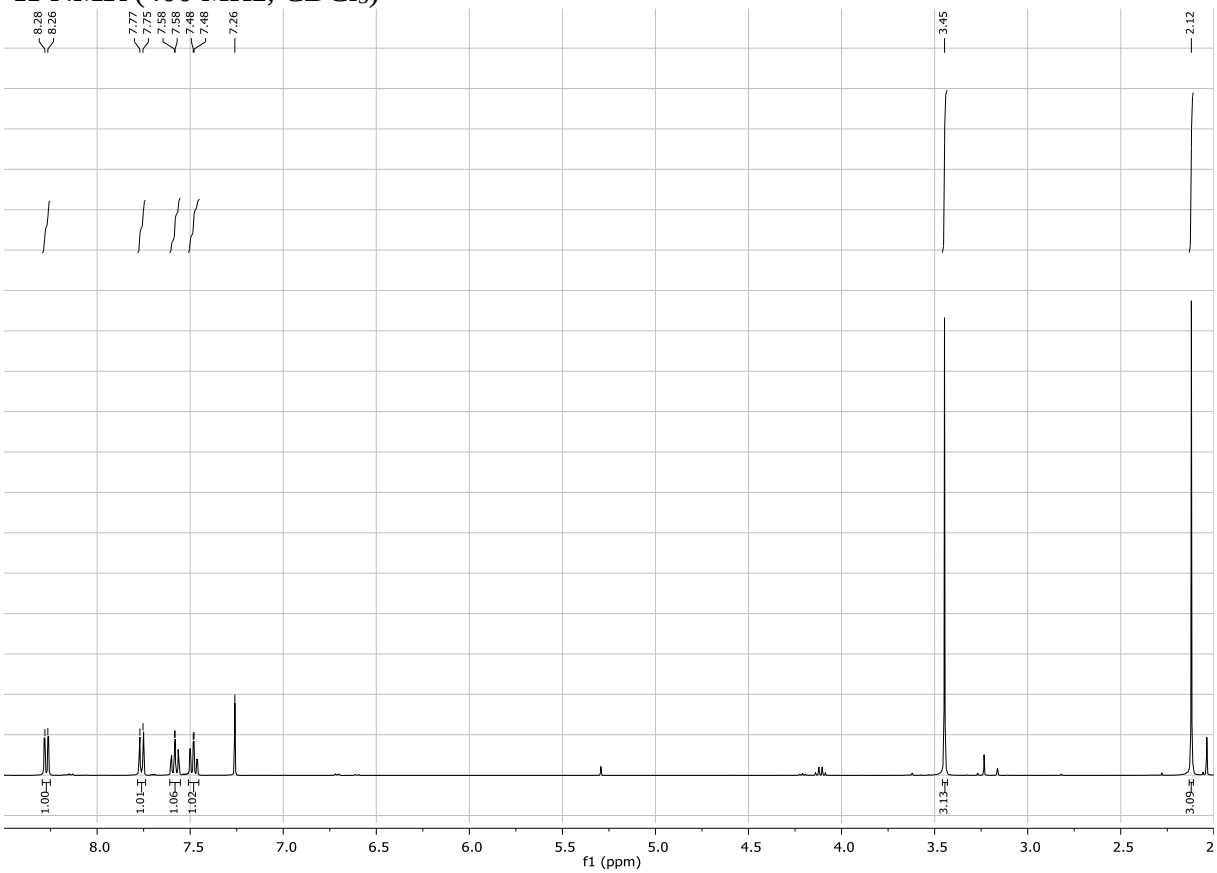


^{13}C-NMR (101 MHz, $CDCl_3$)

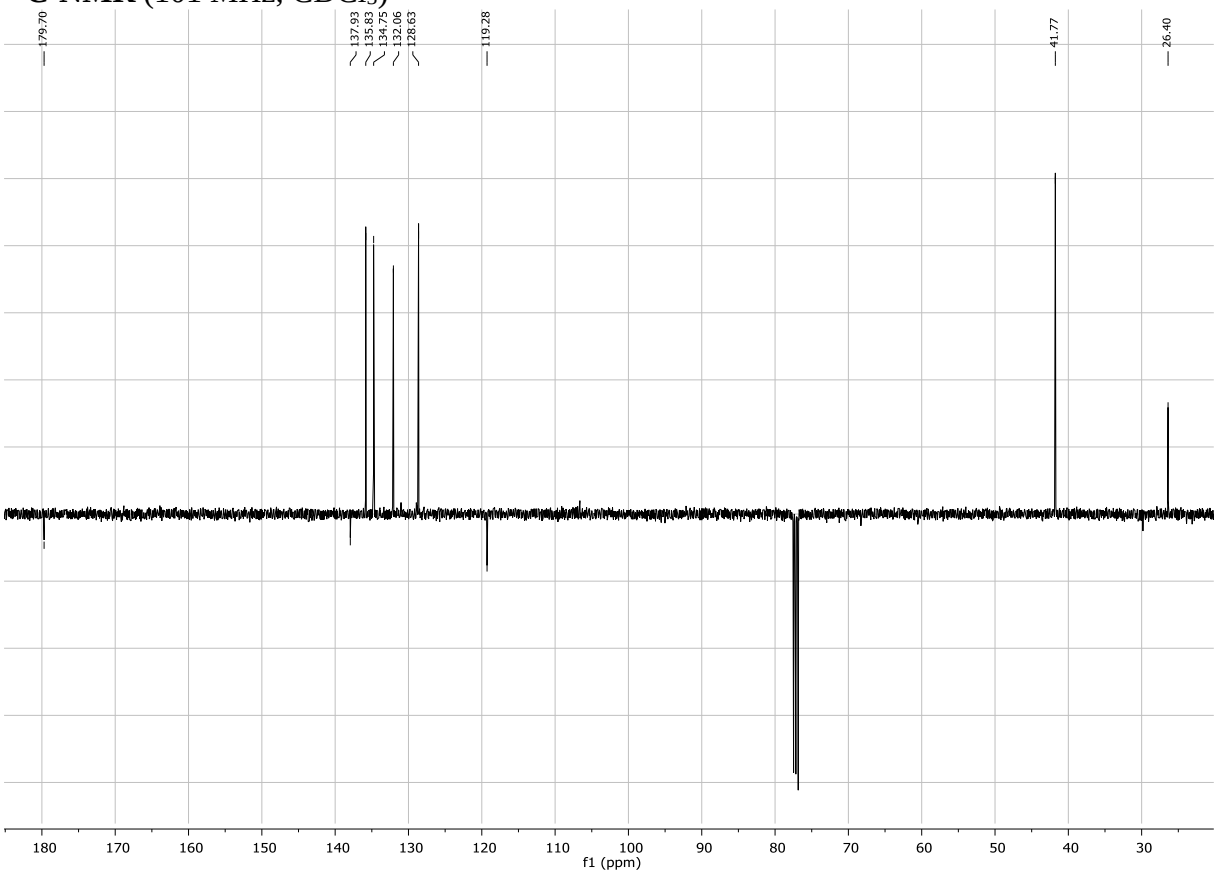


1-(*o*-Bromophenylmethylthioamino)-1-ethanone 9c:

^{1}H-NMR (400 MHz, $CDCl_3$)

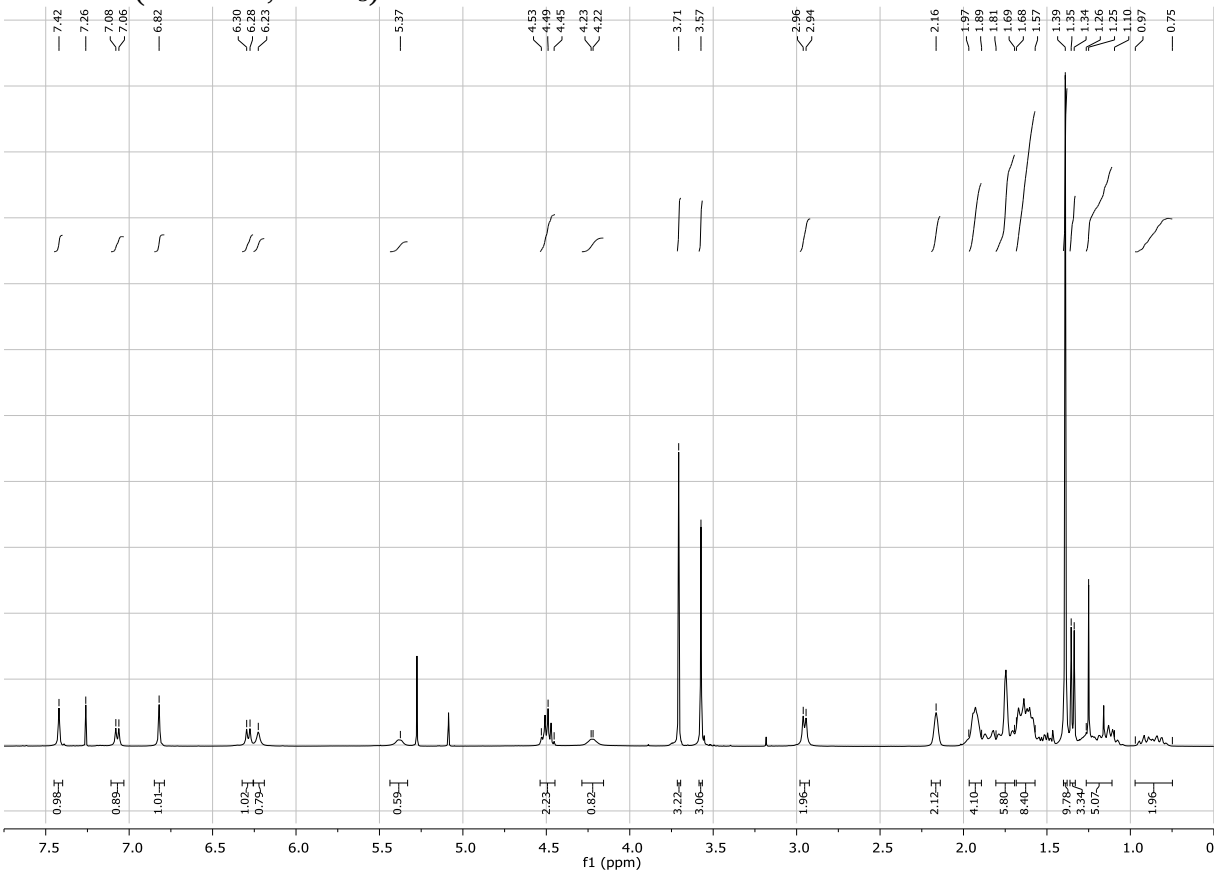


^{13}C-NMR (101 MHz, $CDCl_3$)

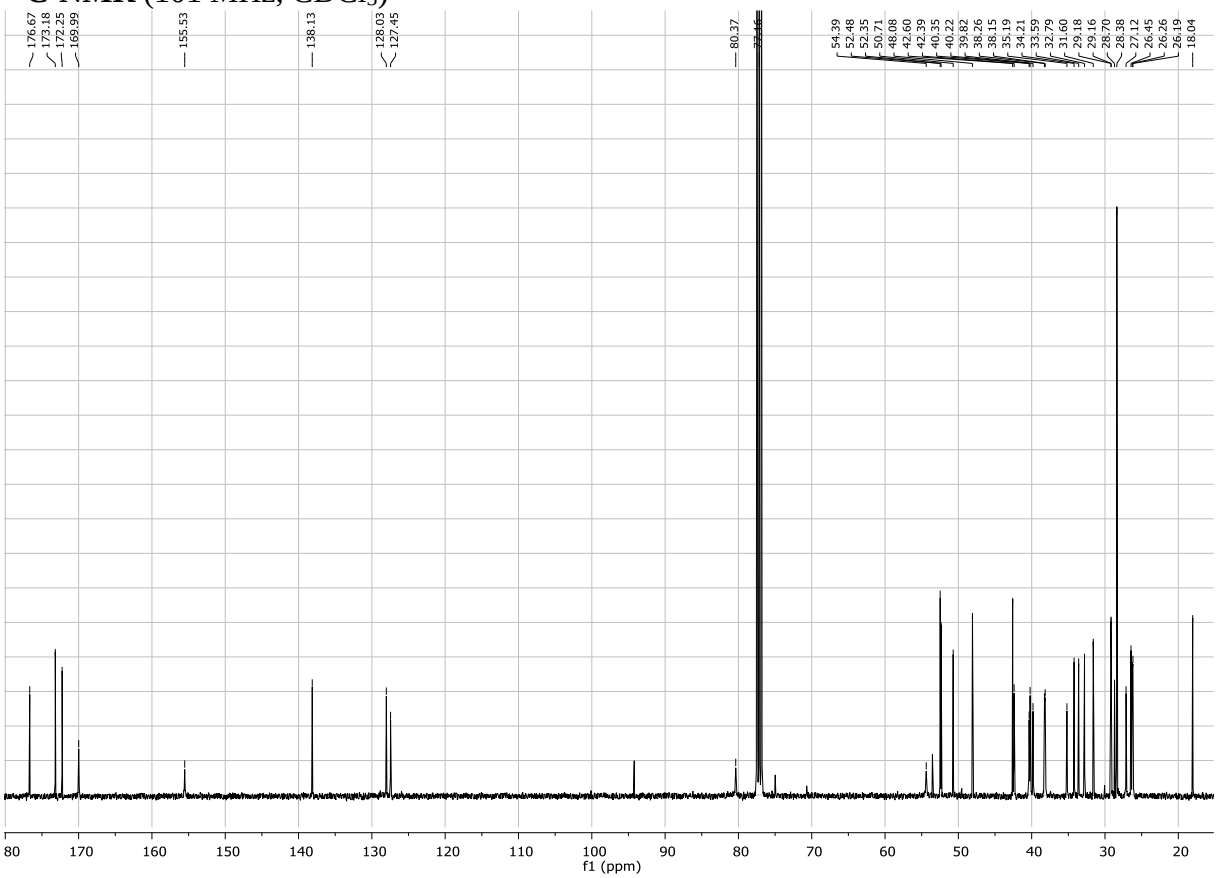


Boc-PMH-AdGly-Cha-Ala-OMe 11:

^{1}H-NMR (400 MHz, $CDCl_3$)

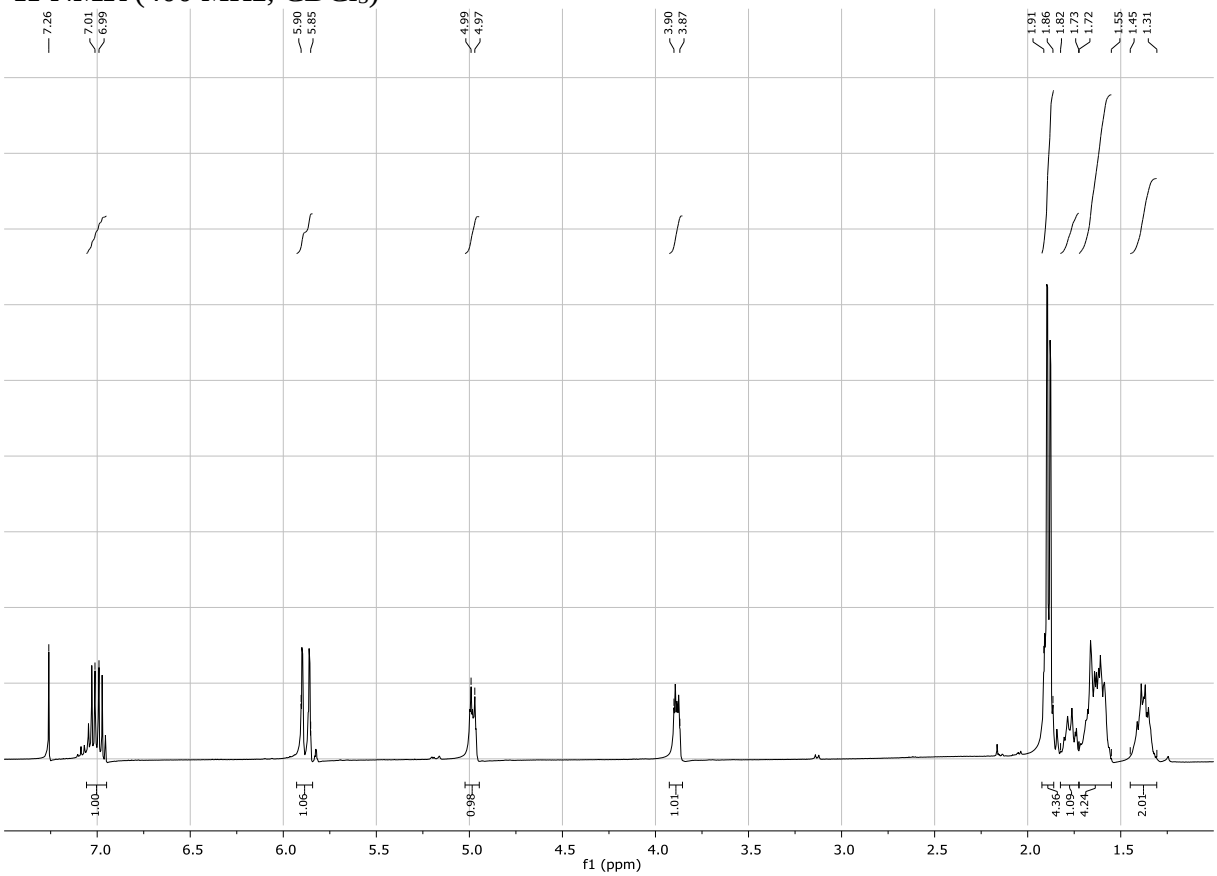


^{13}C-NMR (101 MHz, $CDCl_3$)

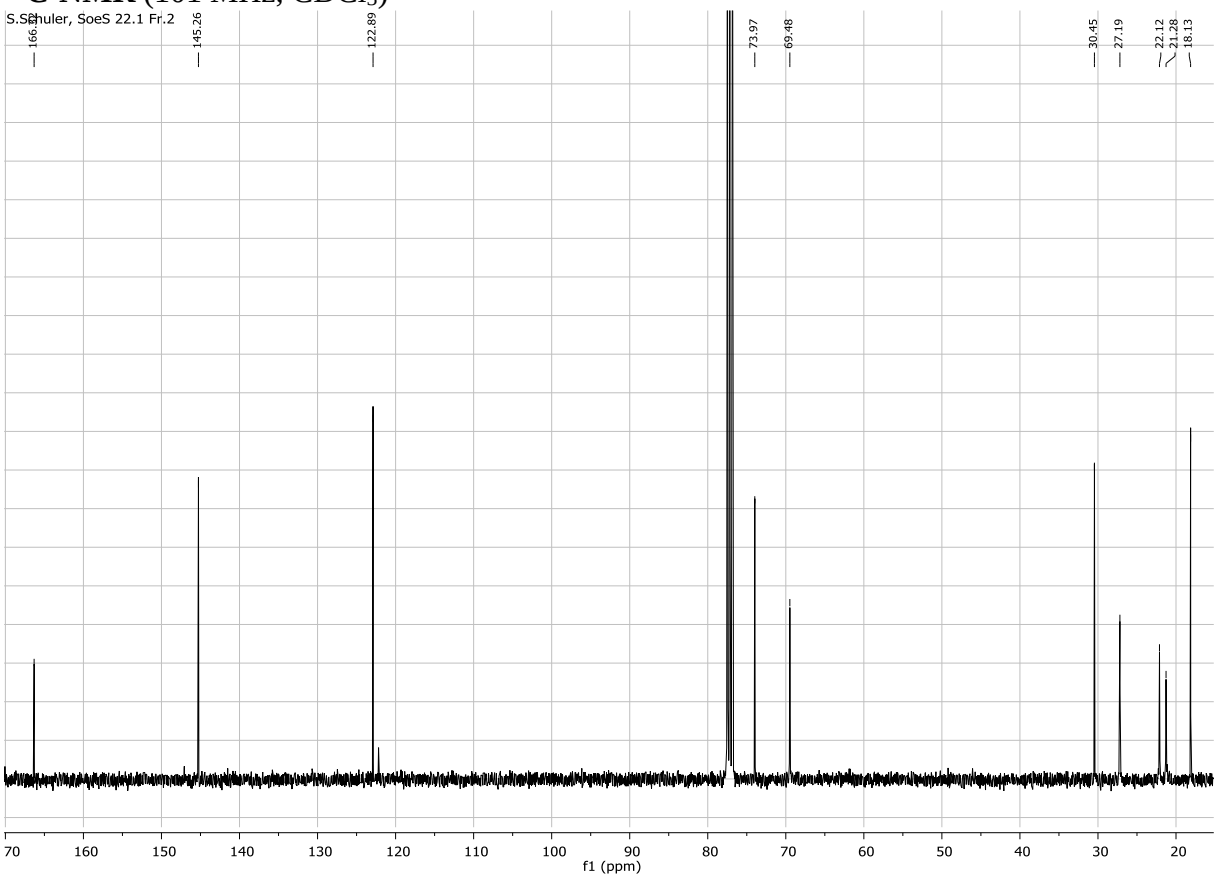


***cis*-2-Hydroxycyclohexyl crotonate 18:**

^{1}H-NMR (400 MHz, $CDCl_3$)

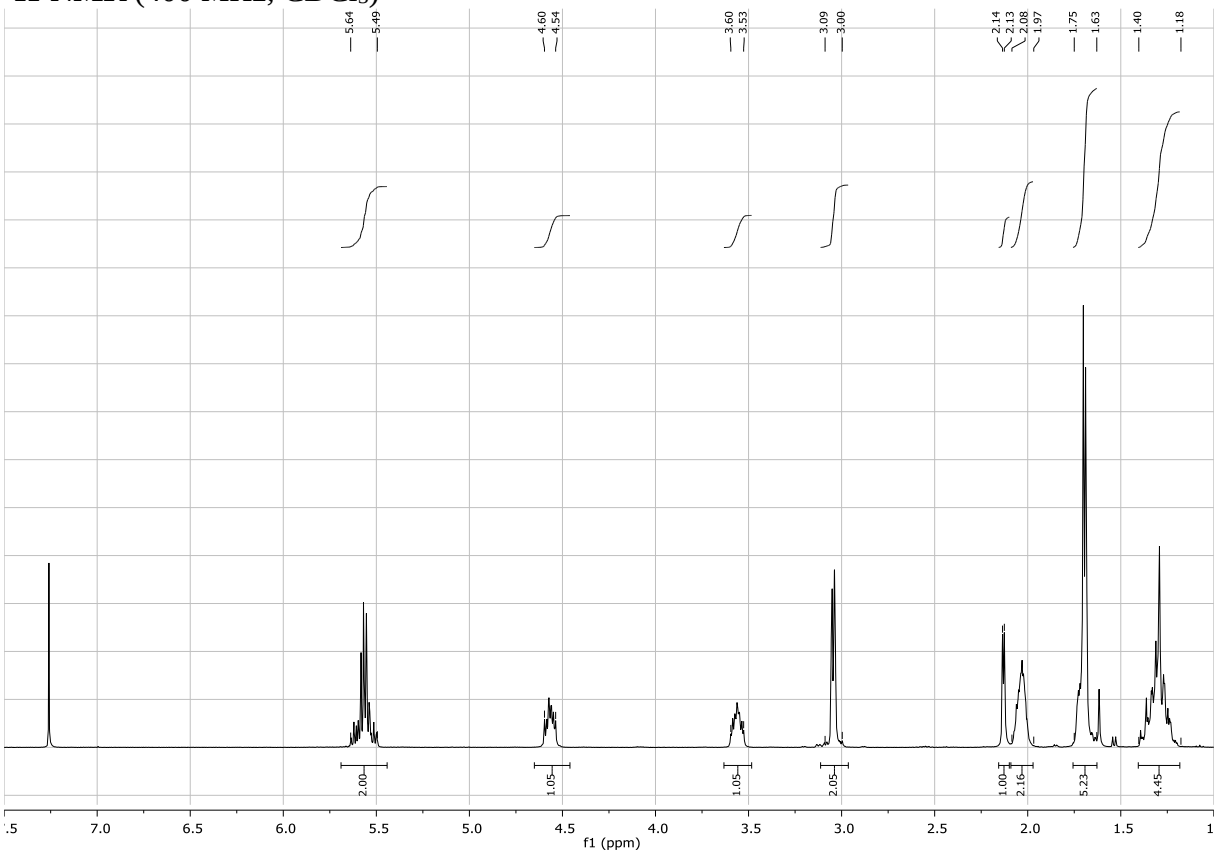


^{13}C-NMR (101 MHz, $CDCl_3$)

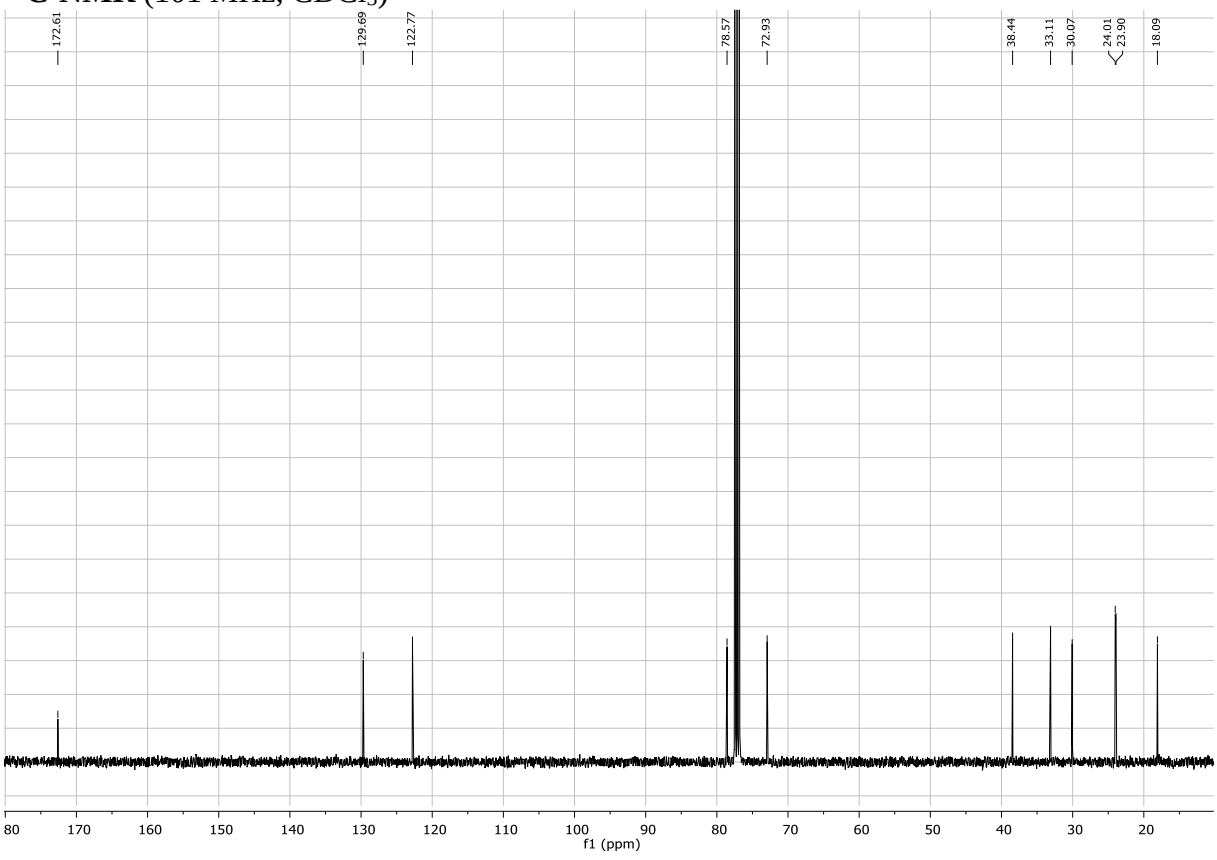


***trans*-2-Hydroxycyclohexyl (*E*)-3-pentenoate 20a:**

^{1}H-NMR (400 MHz, $CDCl_3$)

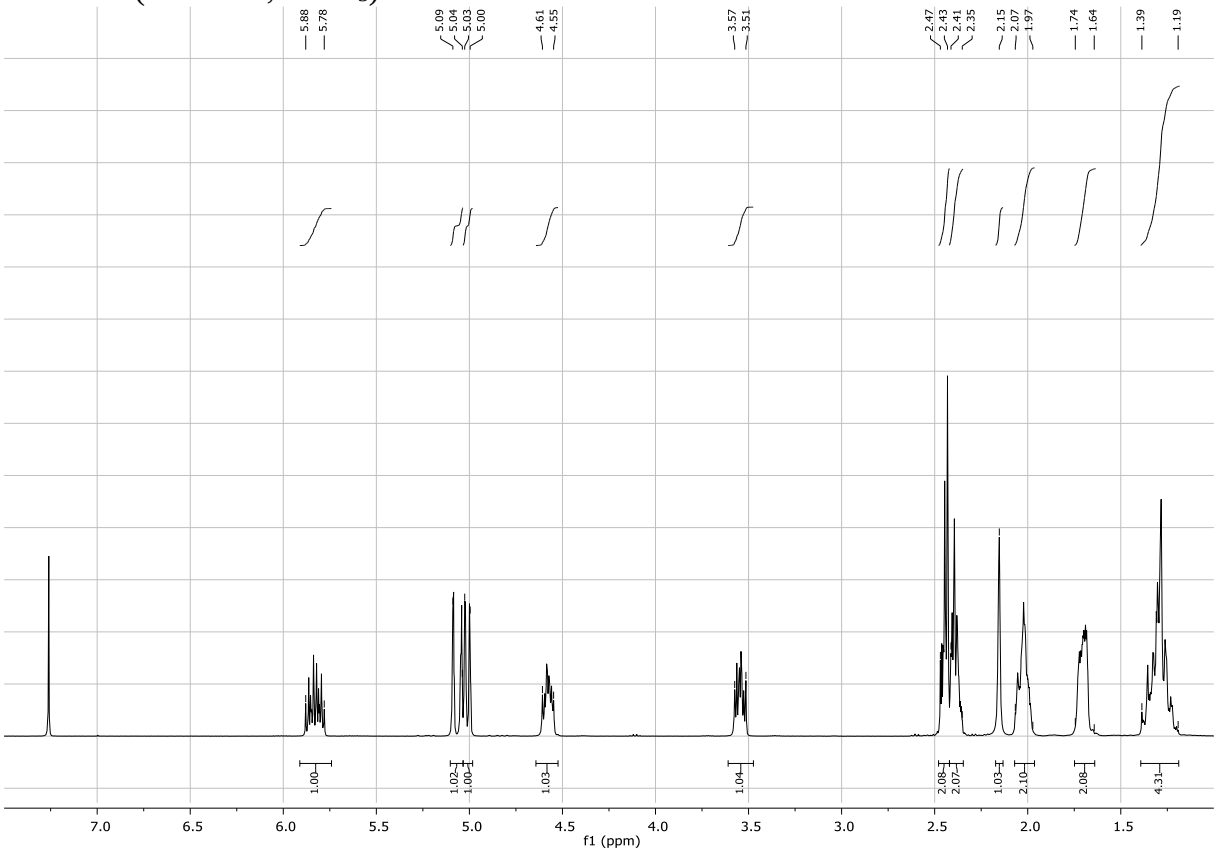


^{13}C-NMR (101 MHz, $CDCl_3$)

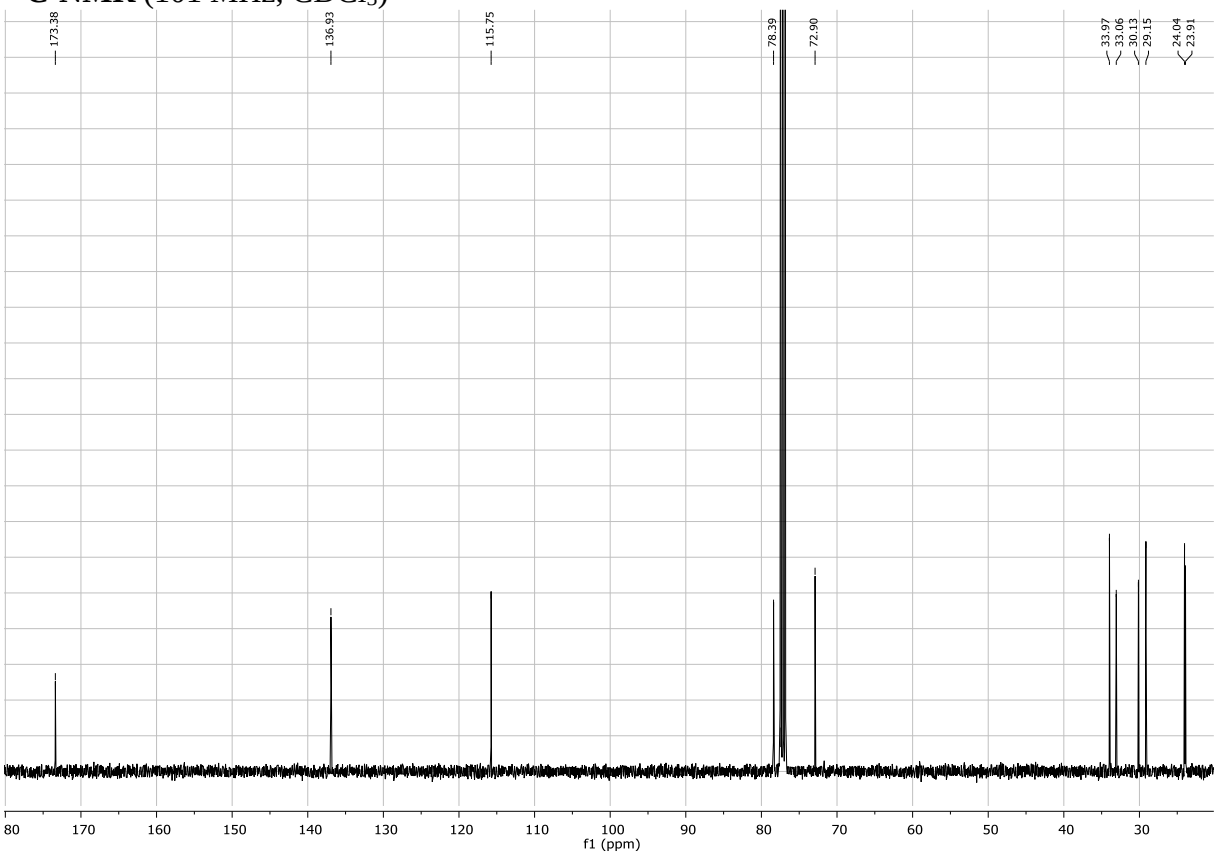


***trans*-2-Hydroxycyclohexyl 4-pentenoate 20b:**

^{1}H-NMR (400 MHz, $CDCl_3$)

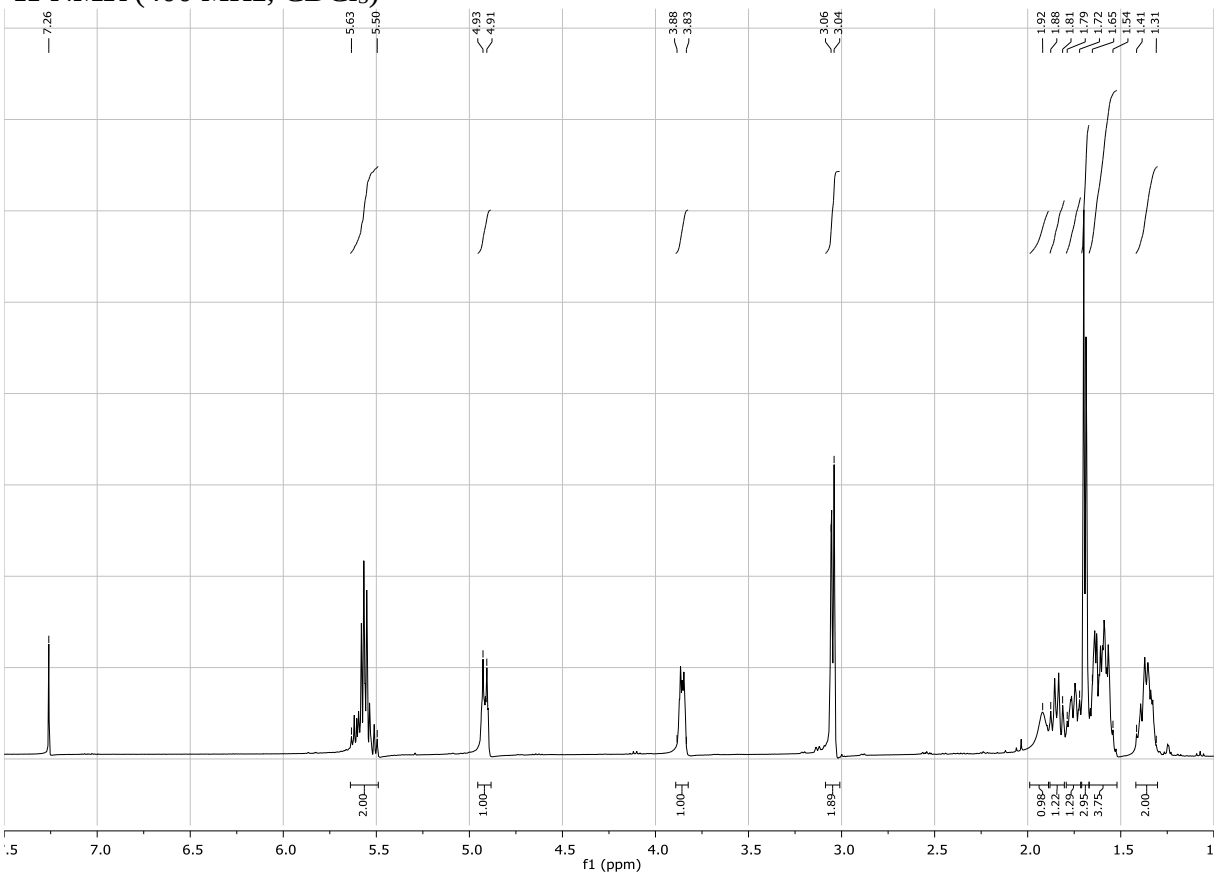


^{13}C-NMR (101 MHz, $CDCl_3$)

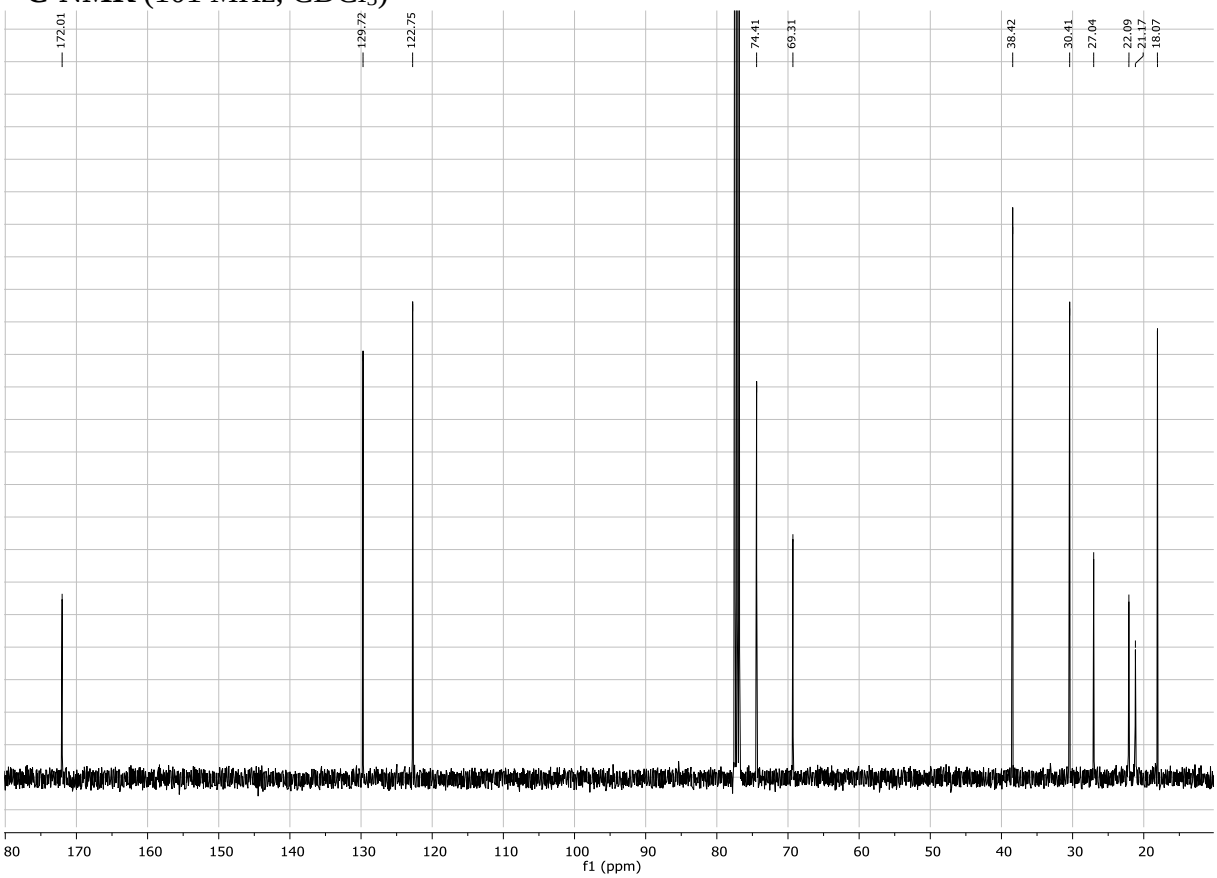


***cis*-2-Hydroxycyclohexyl (*E*)-3-pentenoate 21a:**

^{1}H-NMR (400 MHz, $CDCl_3$)

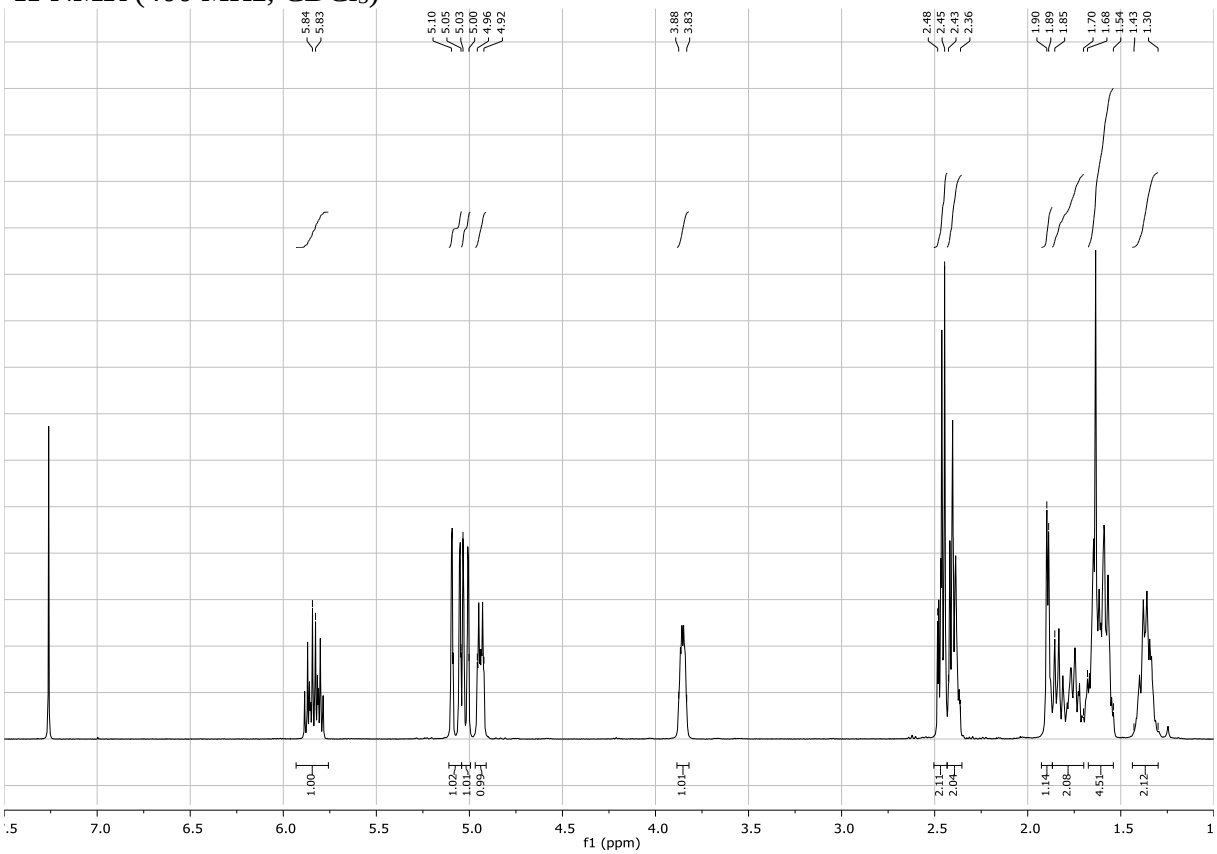


^{13}C-NMR (101 MHz, $CDCl_3$)

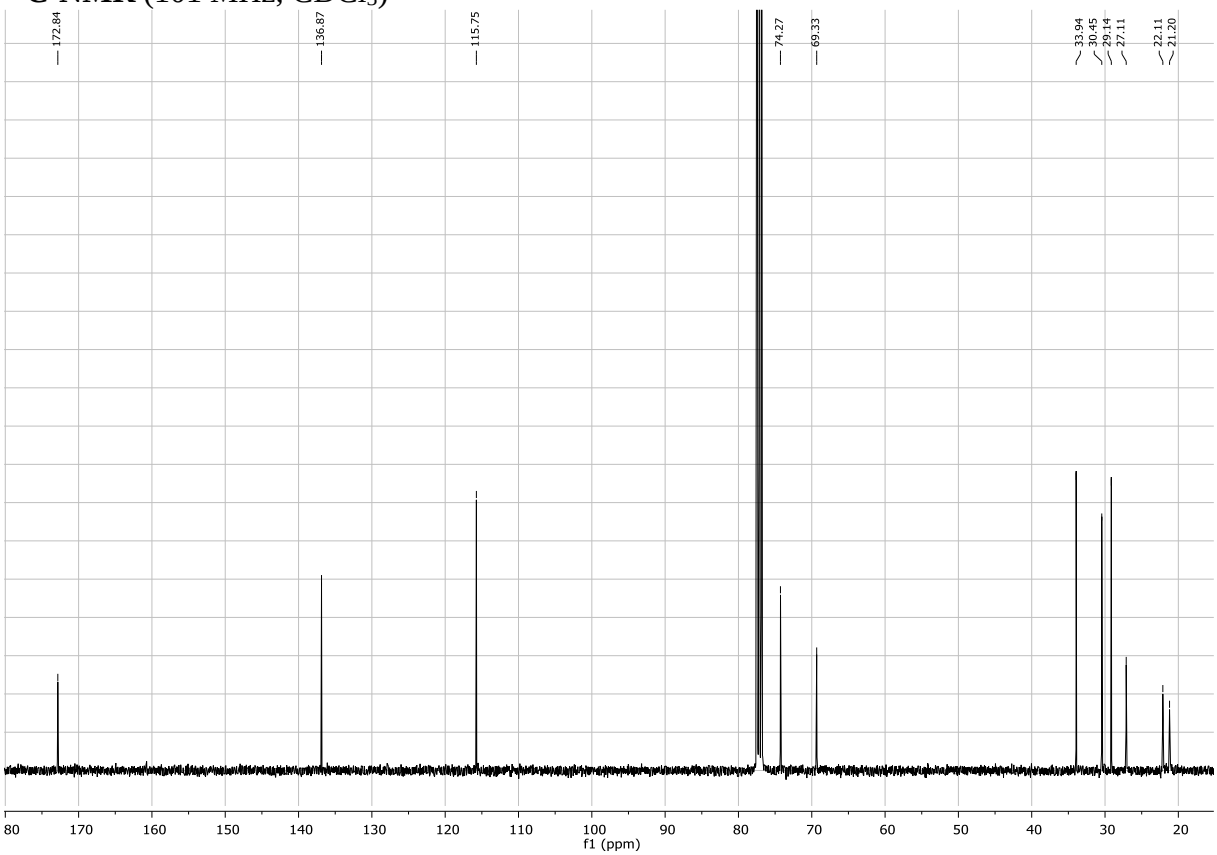


***cis*-2-Hydroxycyclohexyl 4-pentenoate 21b:**

^{1}H-NMR (400 MHz, $CDCl_3$)

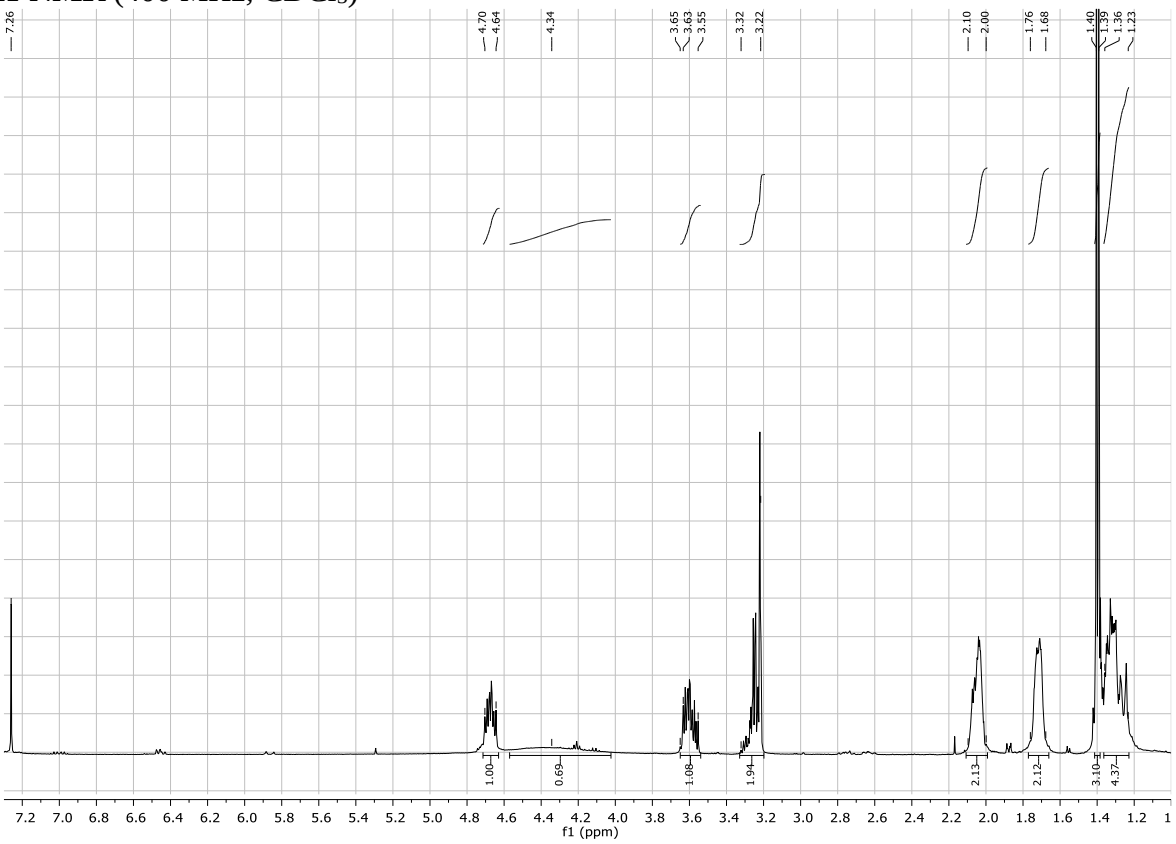


^{13}C-NMR (101 MHz, $CDCl_3$)

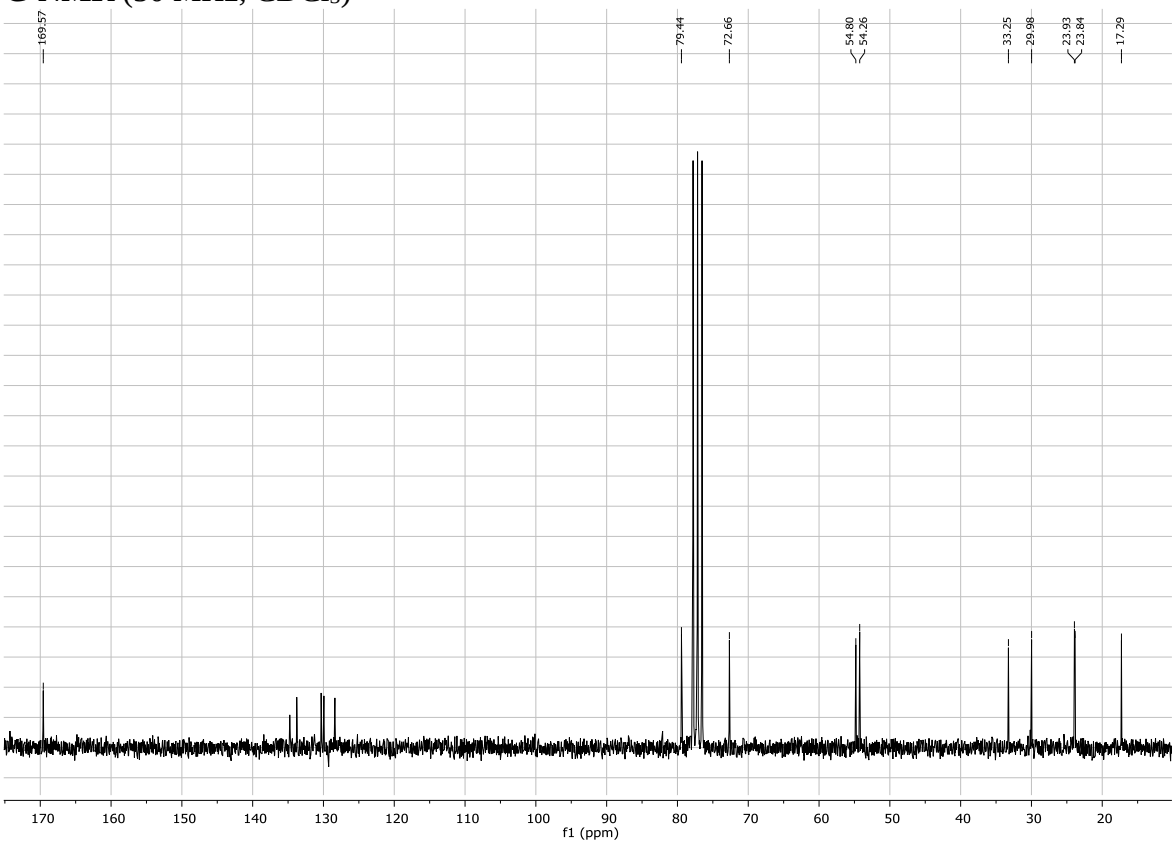


***trans*-2-Hydroxycyclohexyl 3-methyl-2-oxiranecarboxylate 22:[28] (DS1)**

^{1}H-NMR (400 MHz, $CDCl_3$)



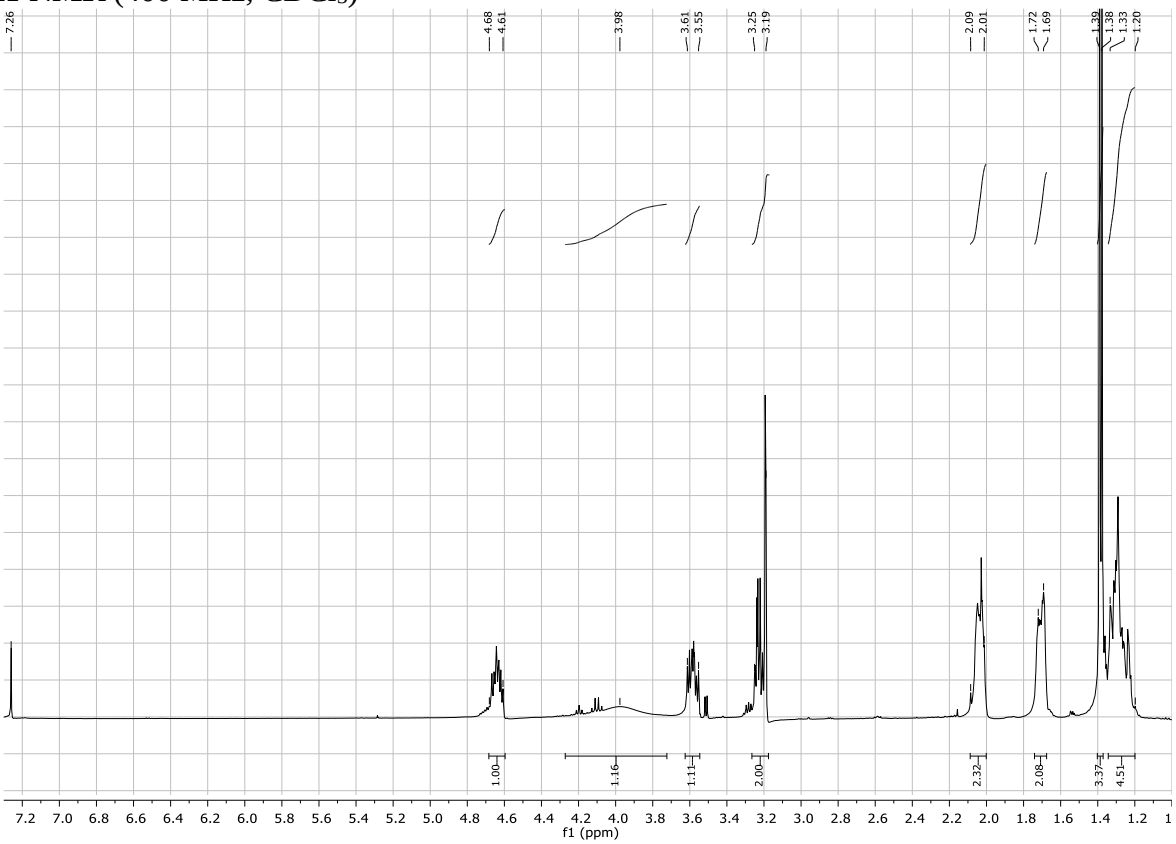
^{13}C-NMR (50 MHz, $CDCl_3$)



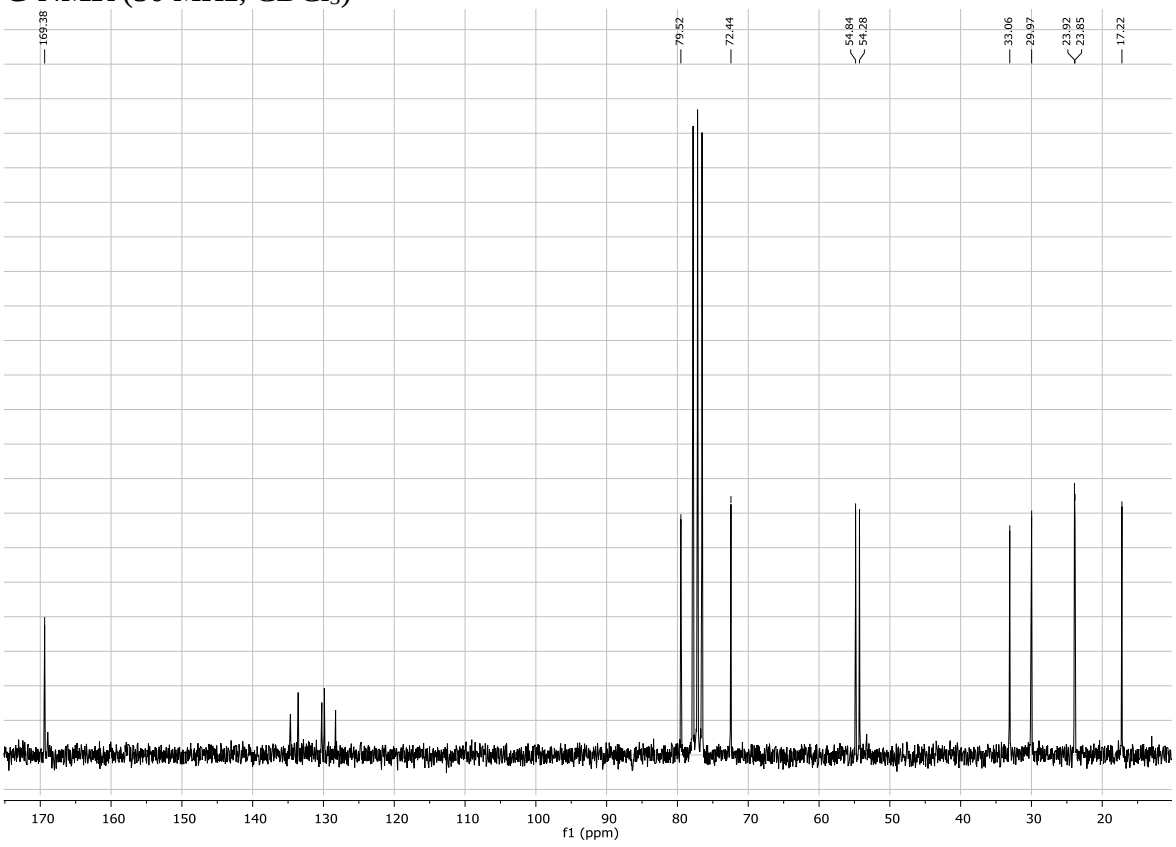
[28] Minimal traces of *m*CBA present in the spectrum.

***trans*-2-Hydroxycyclohexyl 3-methyl-2-oxiranecarboxylate 22:[29] (DS2)**

^{1}H-NMR (400 MHz, $CDCl_3$)



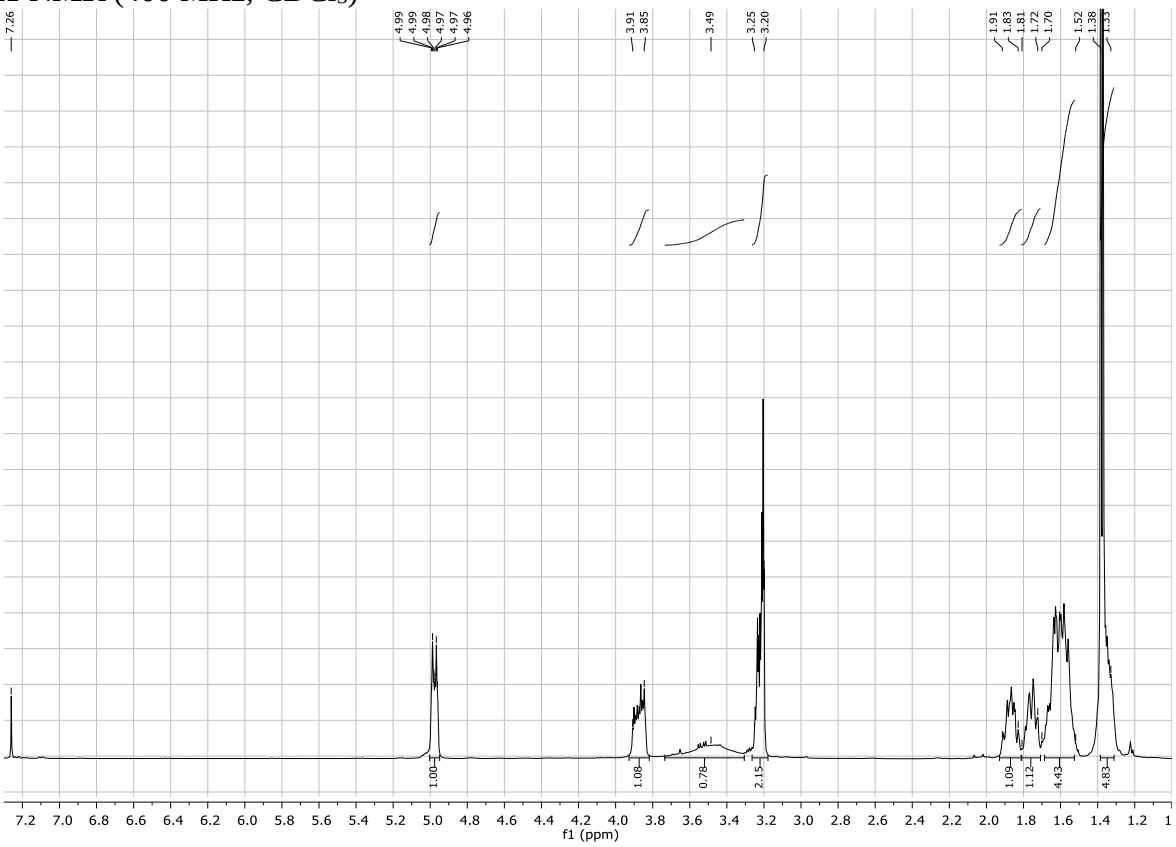
^{13}C-NMR (50 MHz, $CDCl_3$)



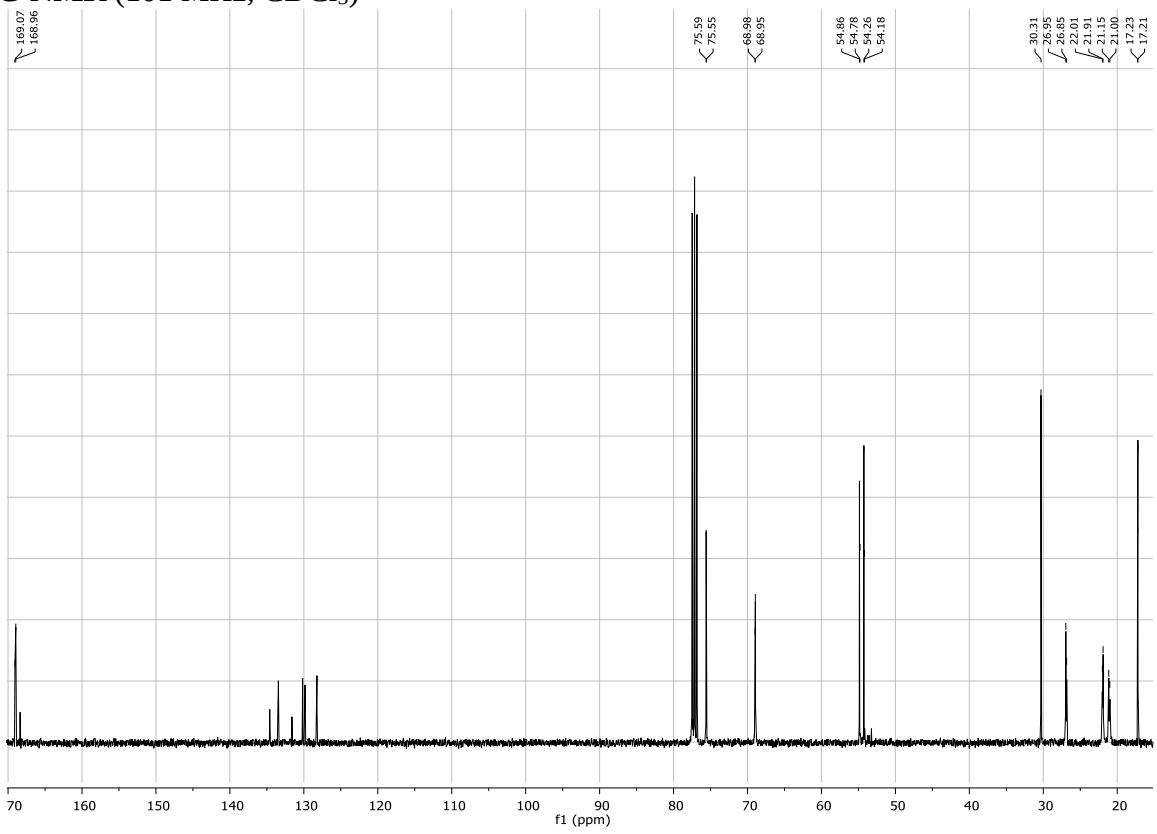
[29] Minimal traces of *m*CBA present in the spectrum.

***cis*-2-Hydroxycyclohexyl 3-methyl-2-oxiranecarboxylate 23:**[30]

^{1}H-NMR (400 MHz, $CDCl_3$)



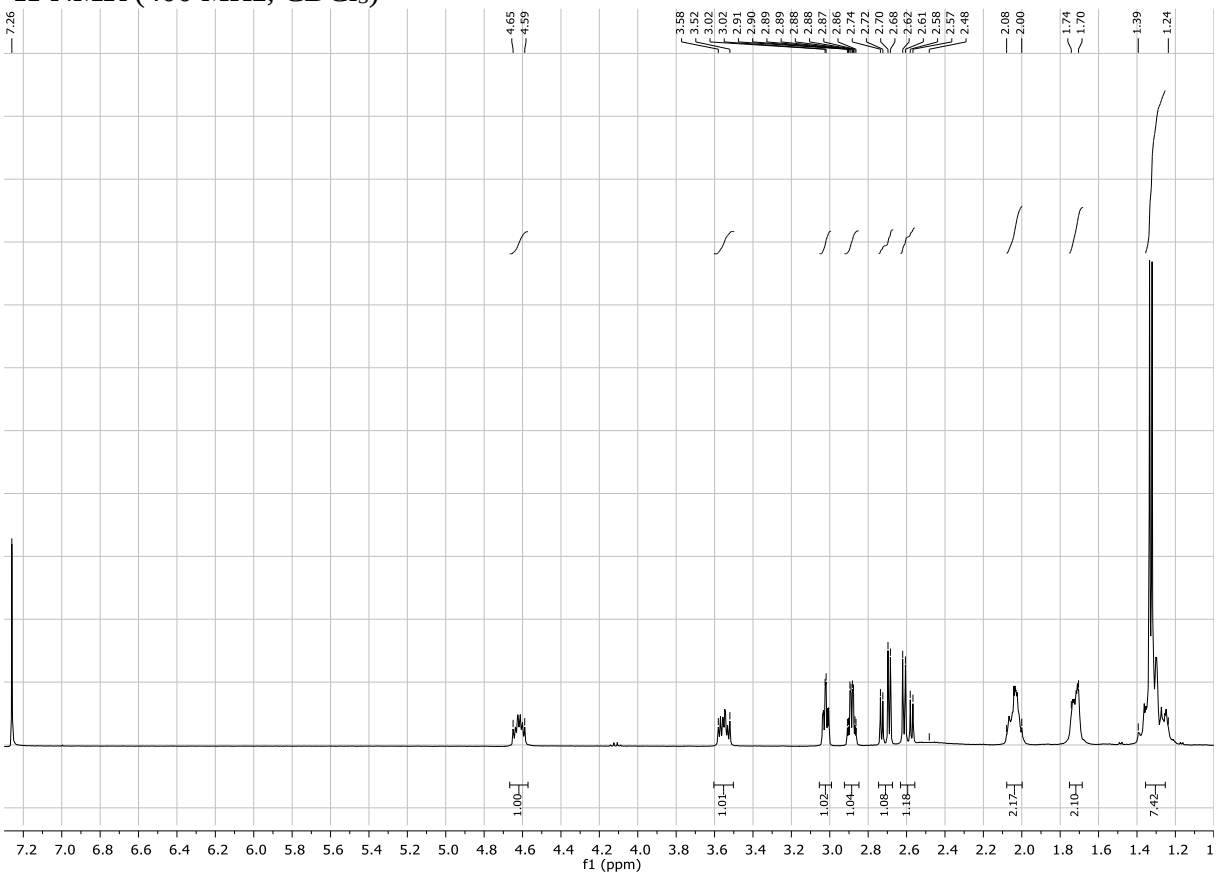
^{13}C-NMR (101 MHz, $CDCl_3$)



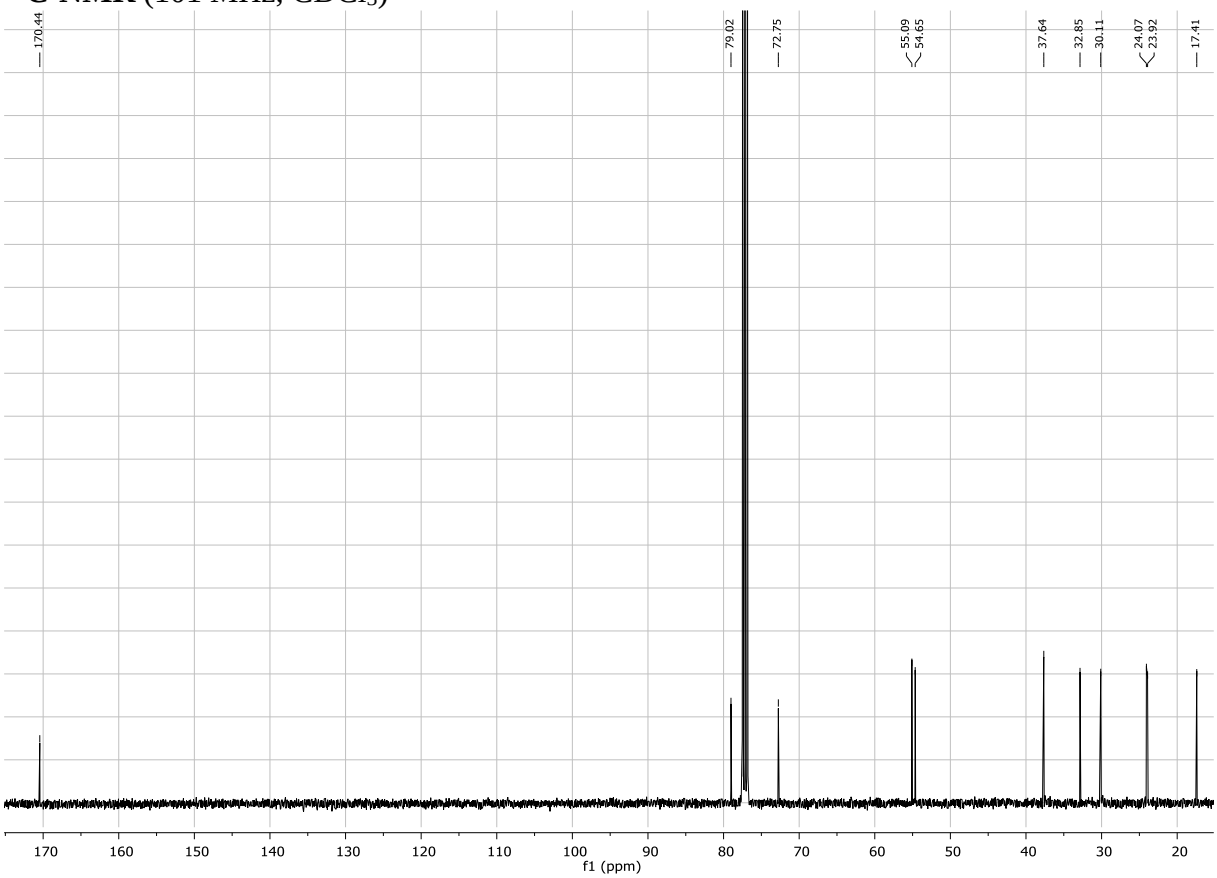
[30] Minimal traces of *m*CBA present in the spectrum.

***trans*-2-Hydroxycyclohexyl (3-methyl-2-oxiranyl)acetate 24a: (DS1)**

^{1}H-NMR (400 MHz, $CDCl_3$)

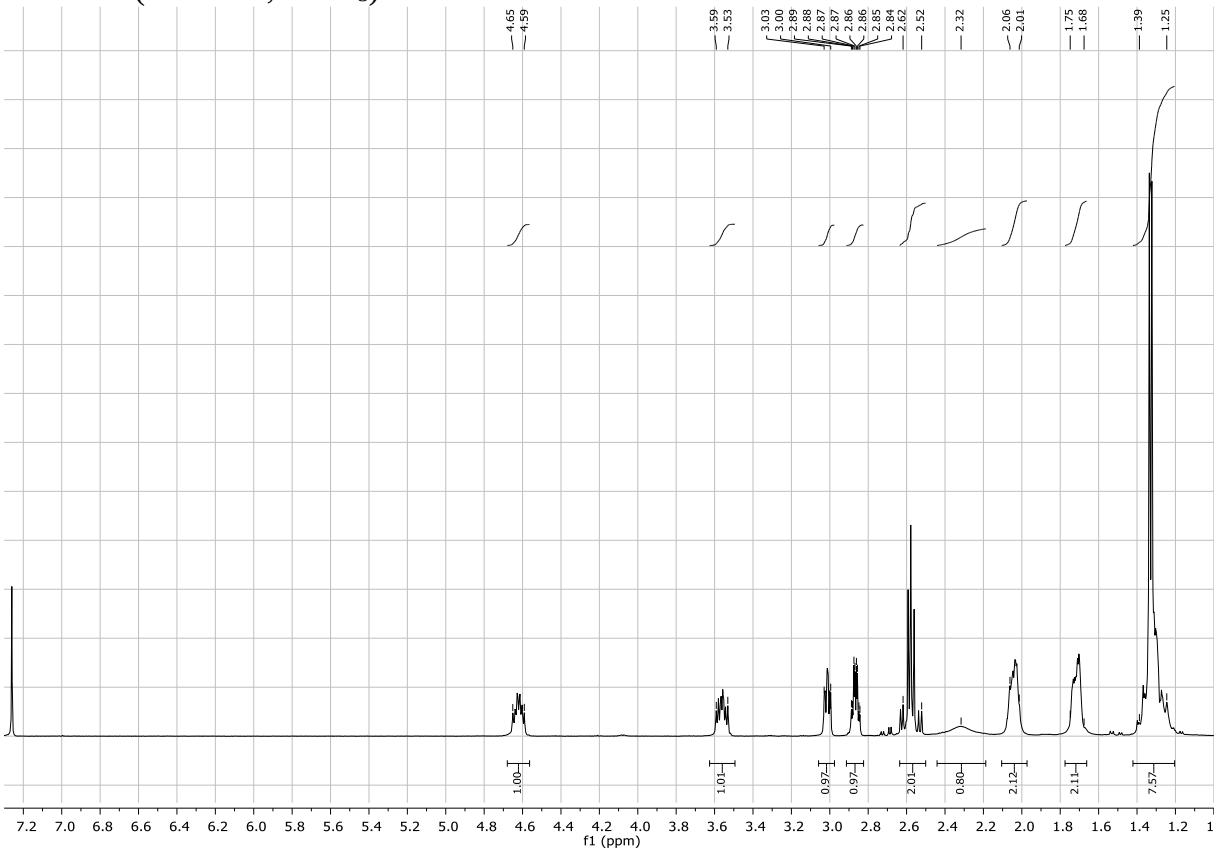


^{13}C-NMR (101 MHz, $CDCl_3$)

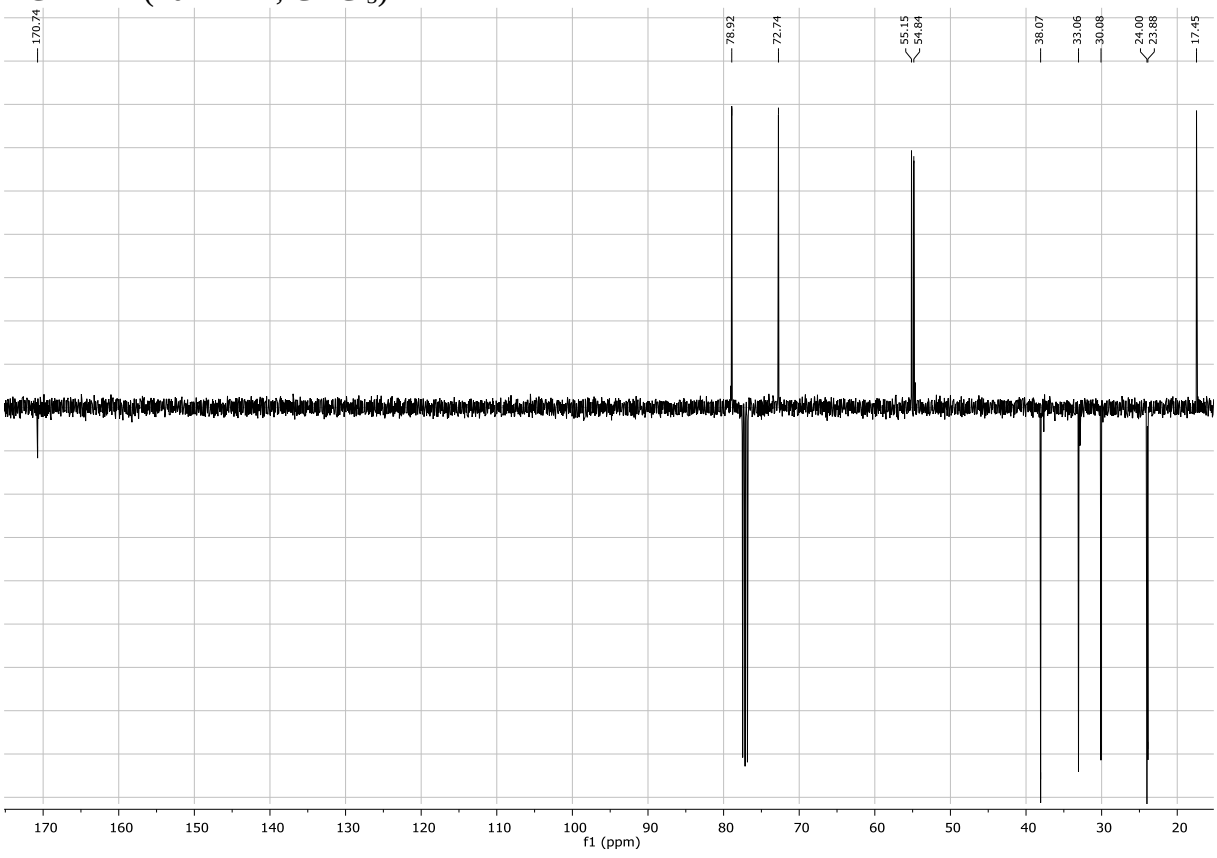


***trans*-2-Hydroxycyclohexyl (3-methyl-2-oxiranyl)acetate 24a: (DS2)**

^{1}H-NMR (400 MHz, $CDCl_3$)

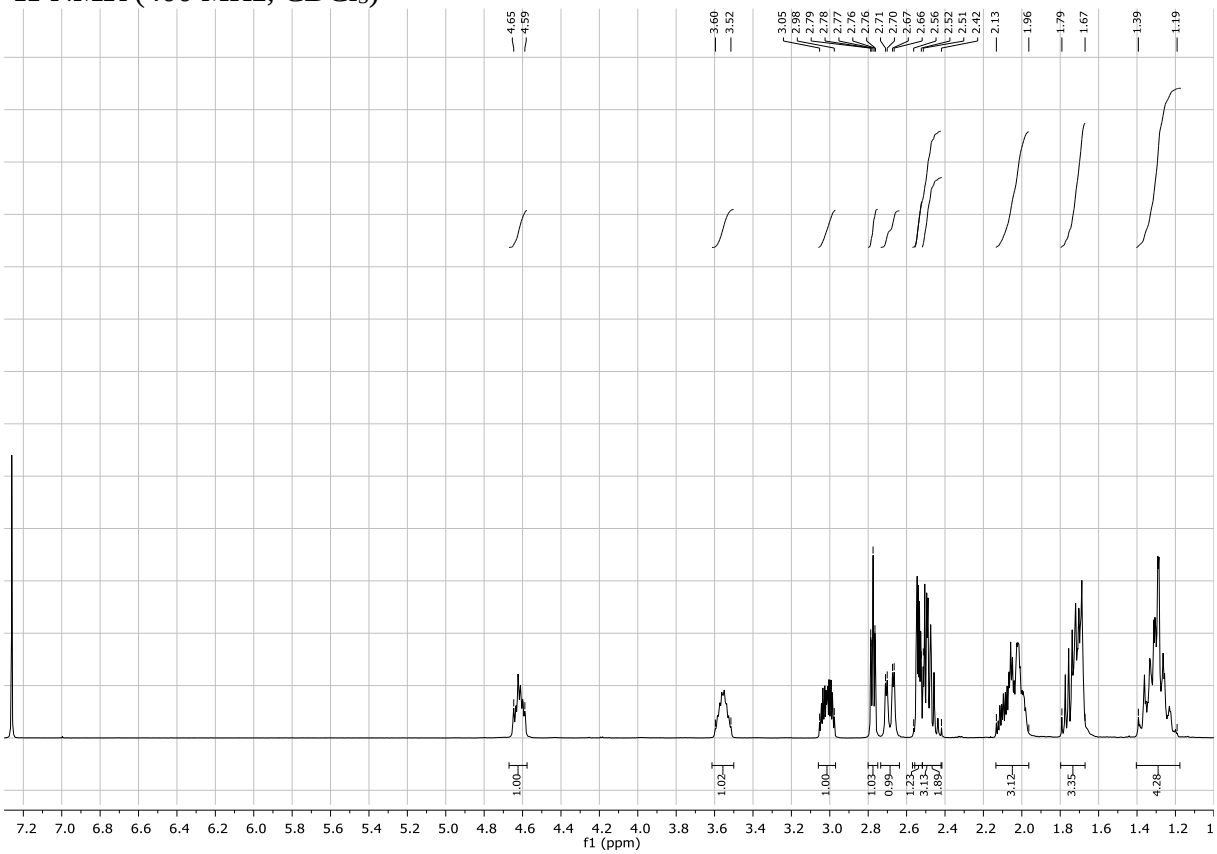


^{13}C-NMR (101 MHz, $CDCl_3$)

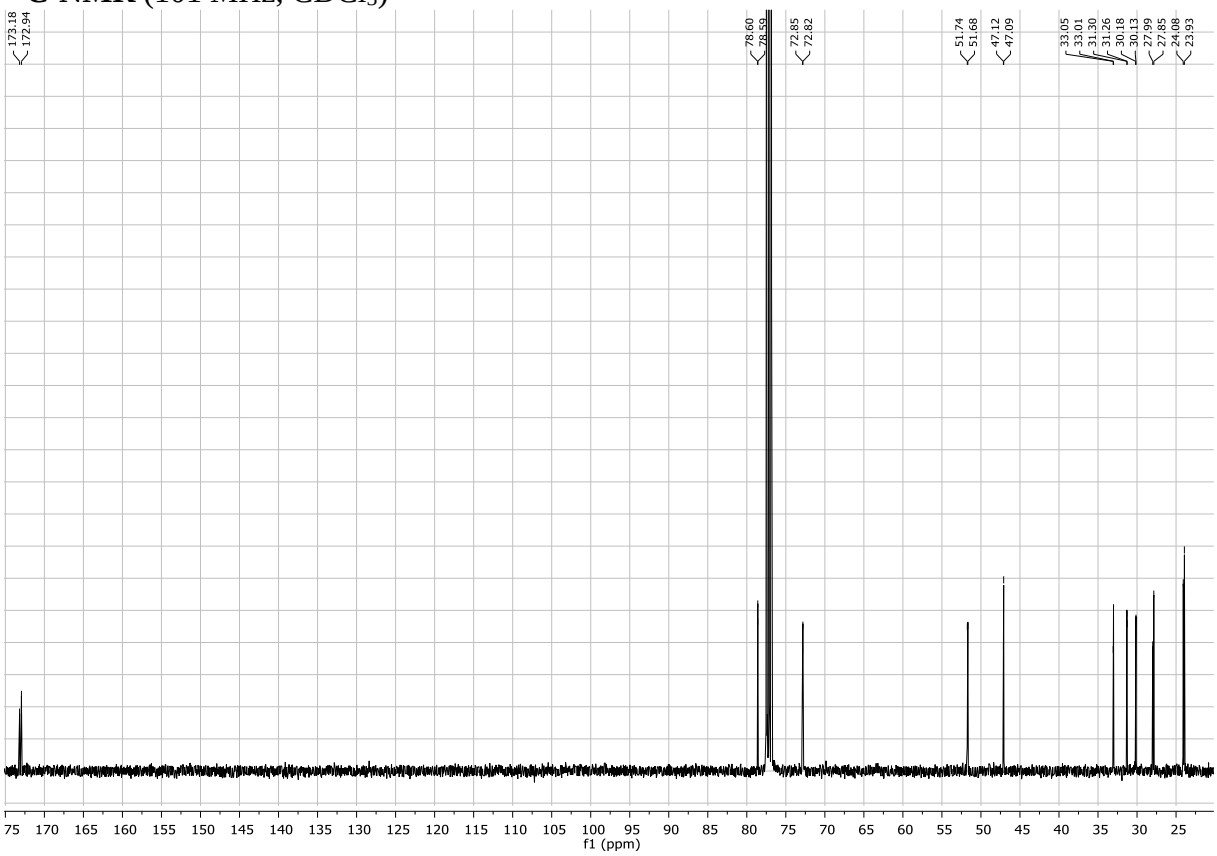


***trans*-2-Hydroxycyclohexyl 3-(2-oxiranyl)propionate 24b:**

^{1}H-NMR (400 MHz, $CDCl_3$)

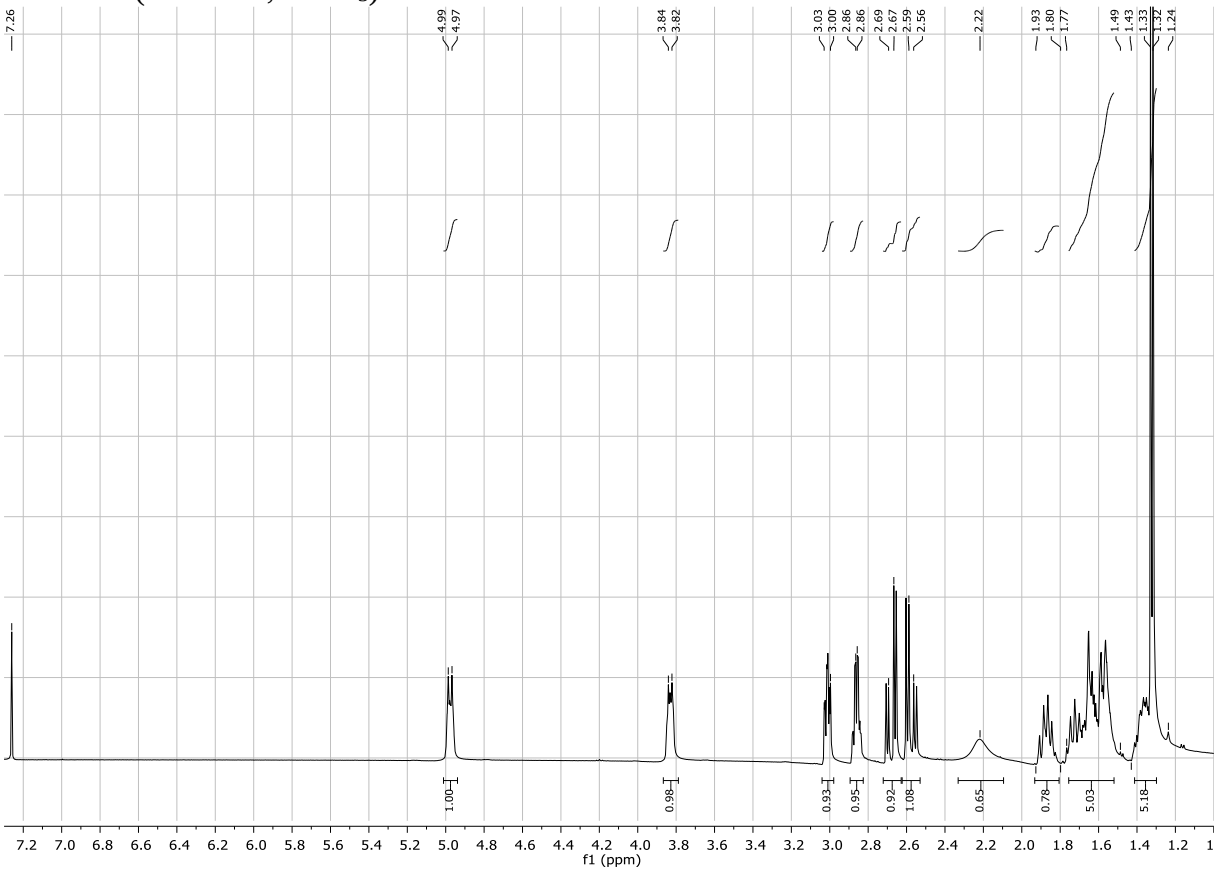


^{13}C-NMR (101 MHz, $CDCl_3$)

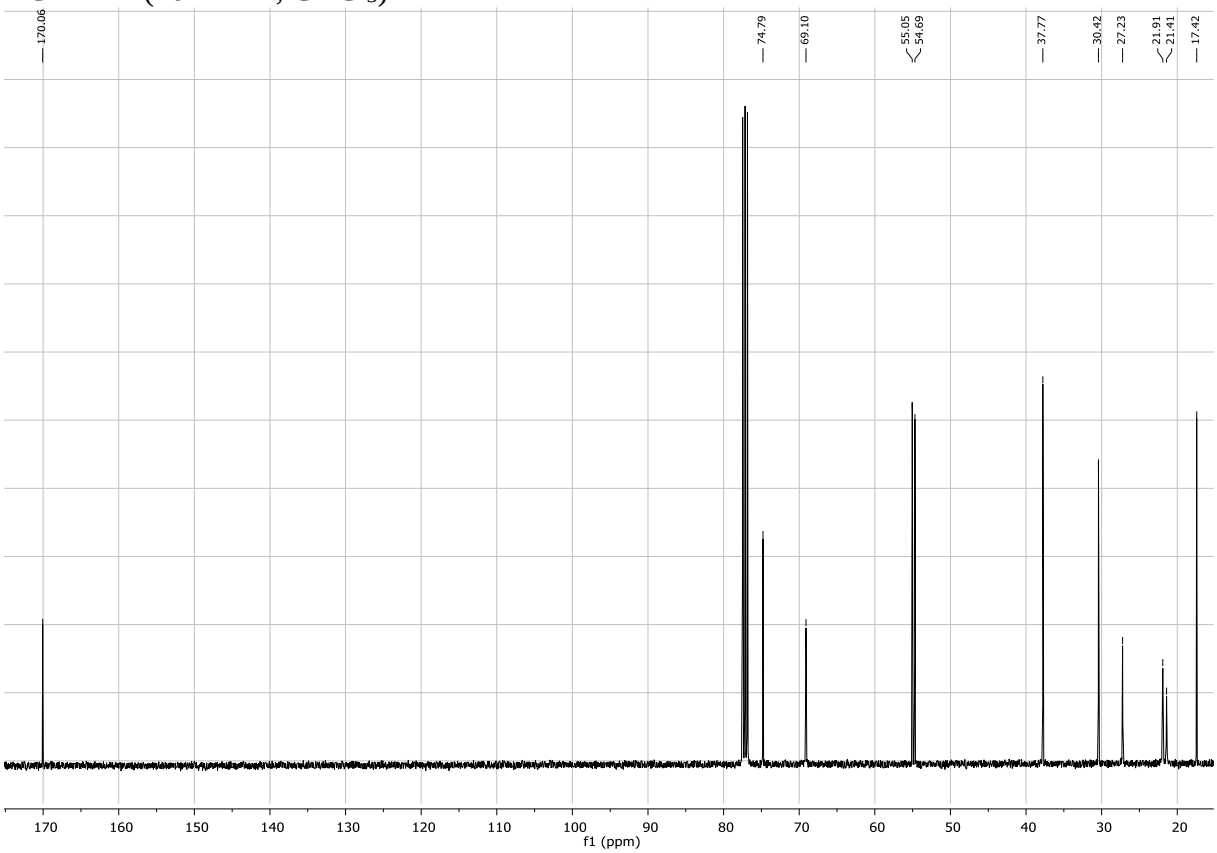


***cis*-2-Hydroxycyclohexyl (3-methyl-2-oxiranyl)acetate 25a: (DS1)**

^{1}H-NMR (400 MHz, $CDCl_3$)

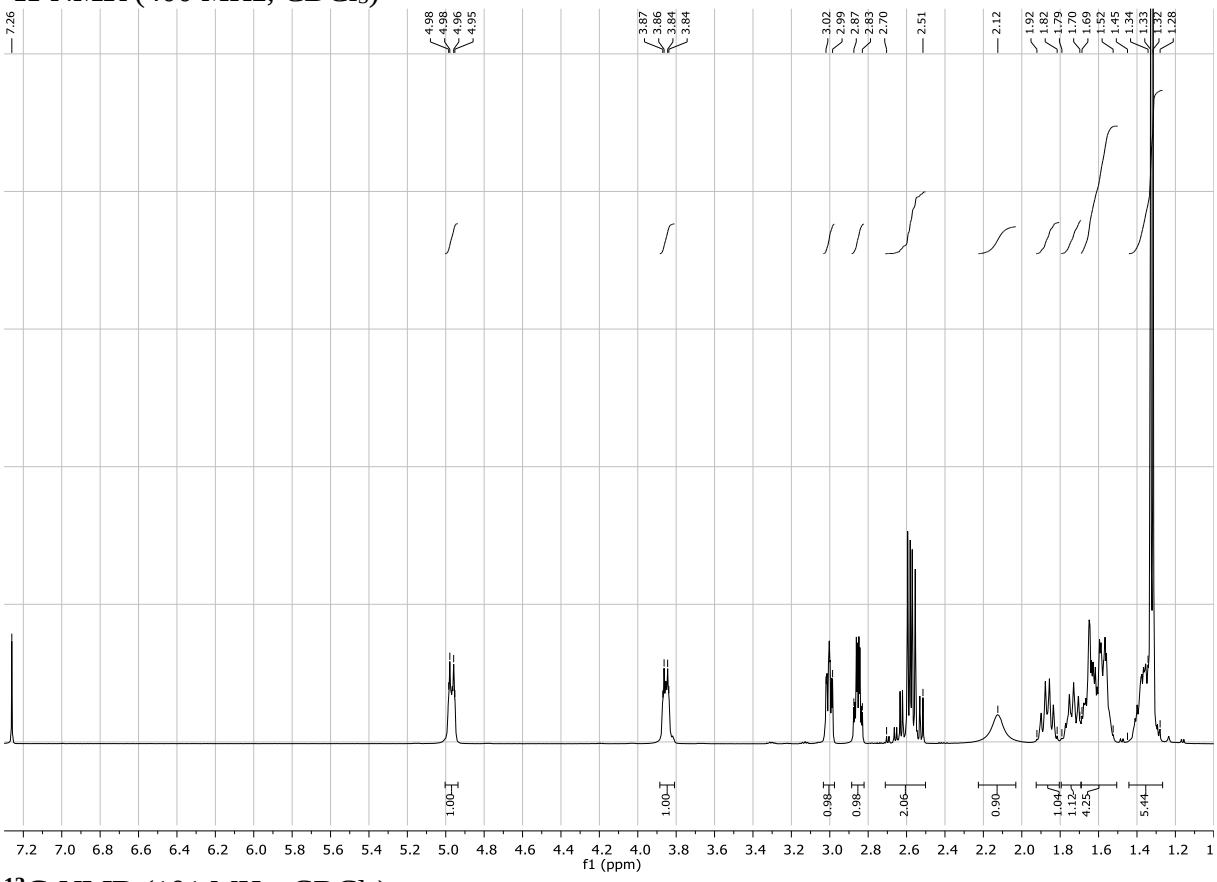


^{13}C-NMR (101 MHz, $CDCl_3$)

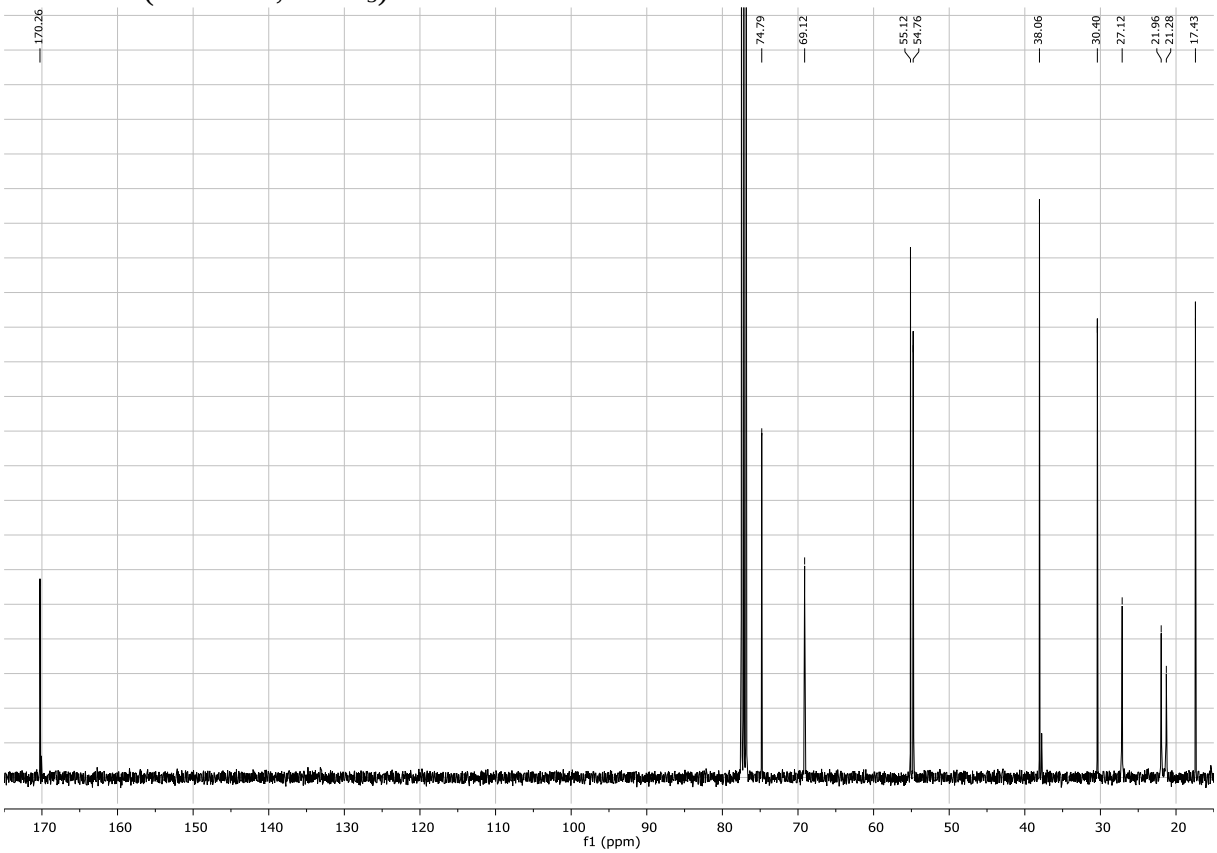


***cis*-2-Hydroxycyclohexyl (3-methyl-2-oxiranyl)acetate 25a: (DS2)**

^{1}H-NMR (400 MHz, $CDCl_3$)

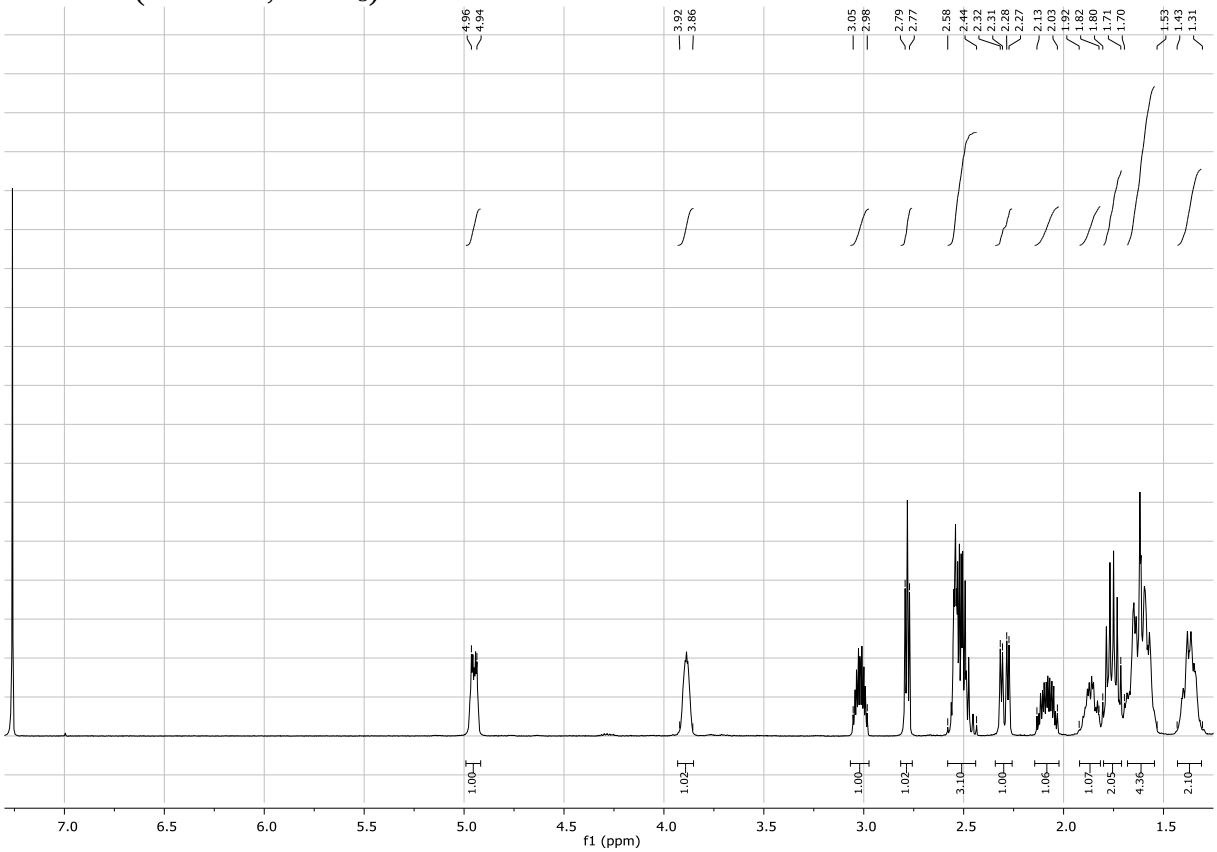


^{13}C-NMR (101 MHz, $CDCl_3$)

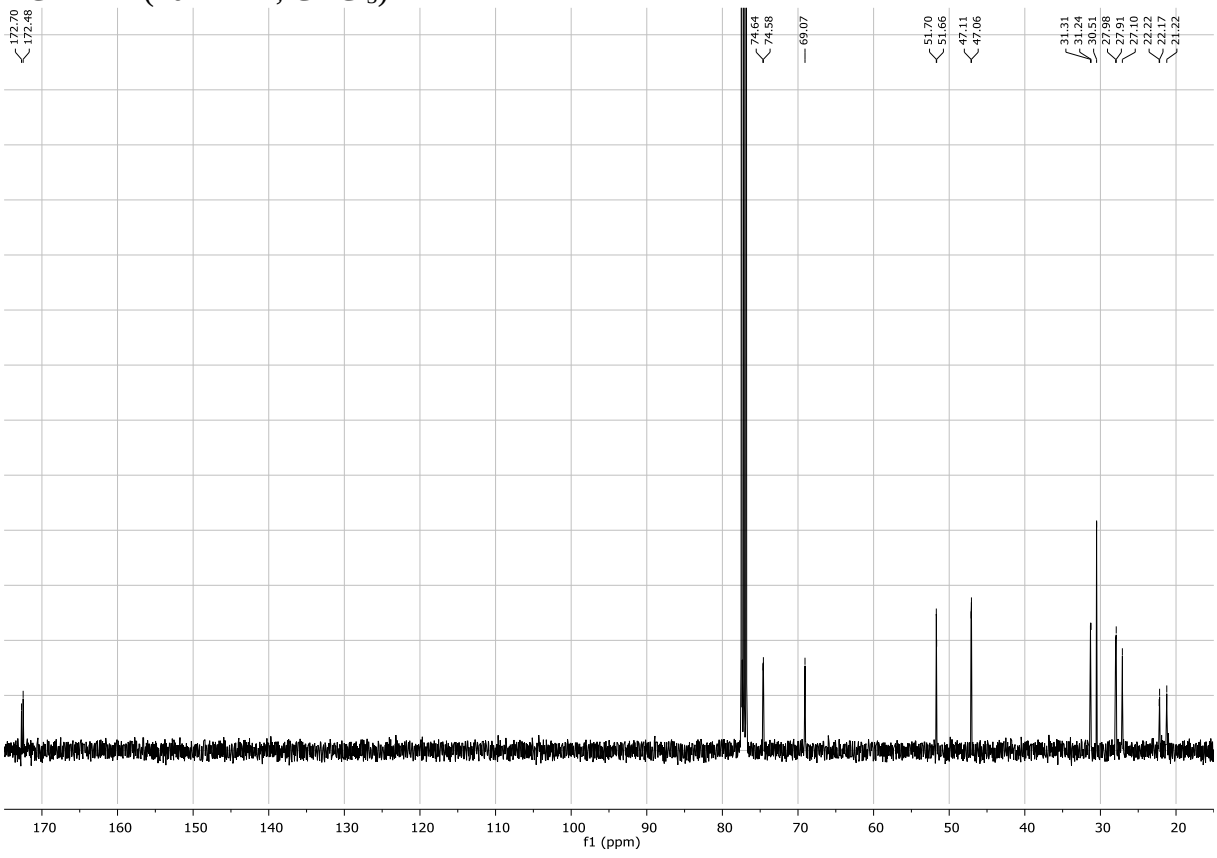


***cis*-2-Hydroxycyclohexyl 3-(2-oxiranyl)propionate 25b:**

^{1}H-NMR (400 MHz, $CDCl_3$)

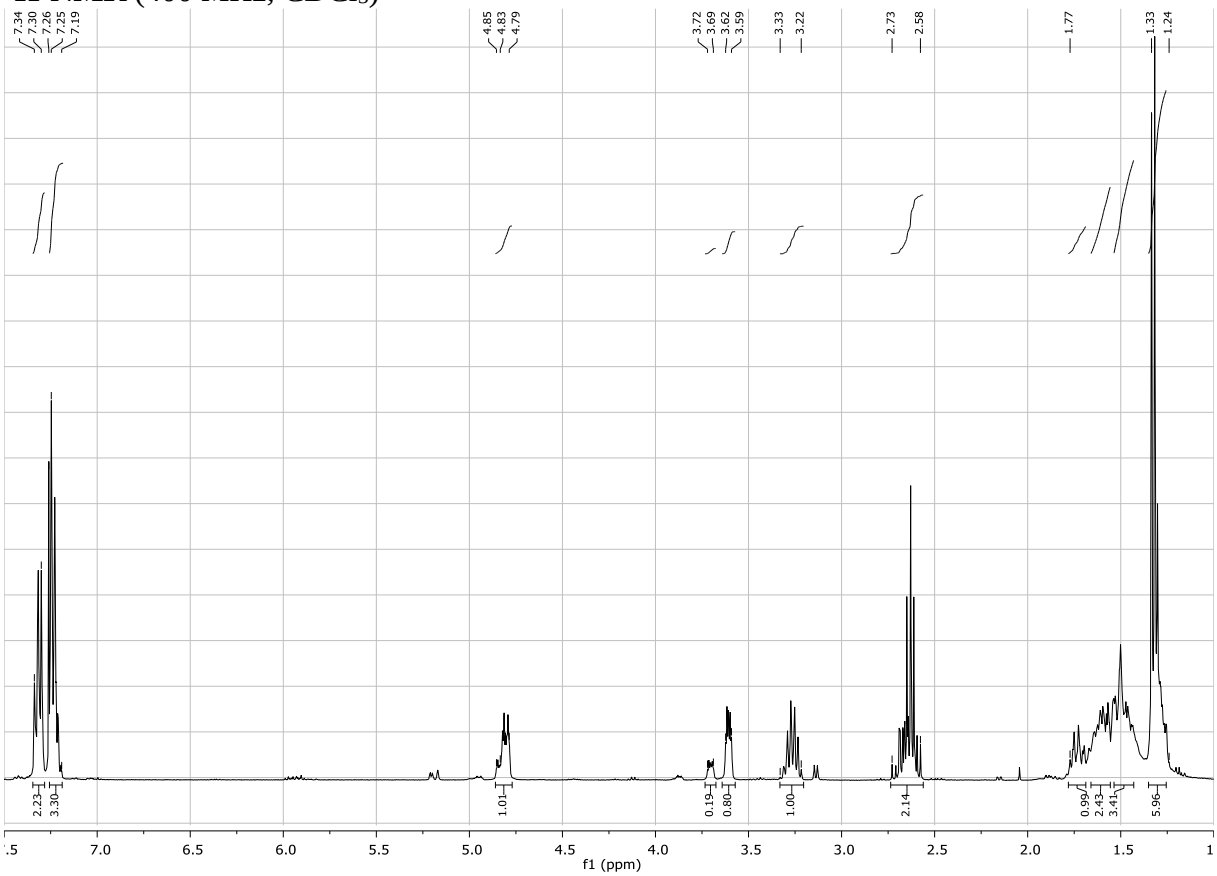


^{13}C-NMR (101 MHz, $CDCl_3$)

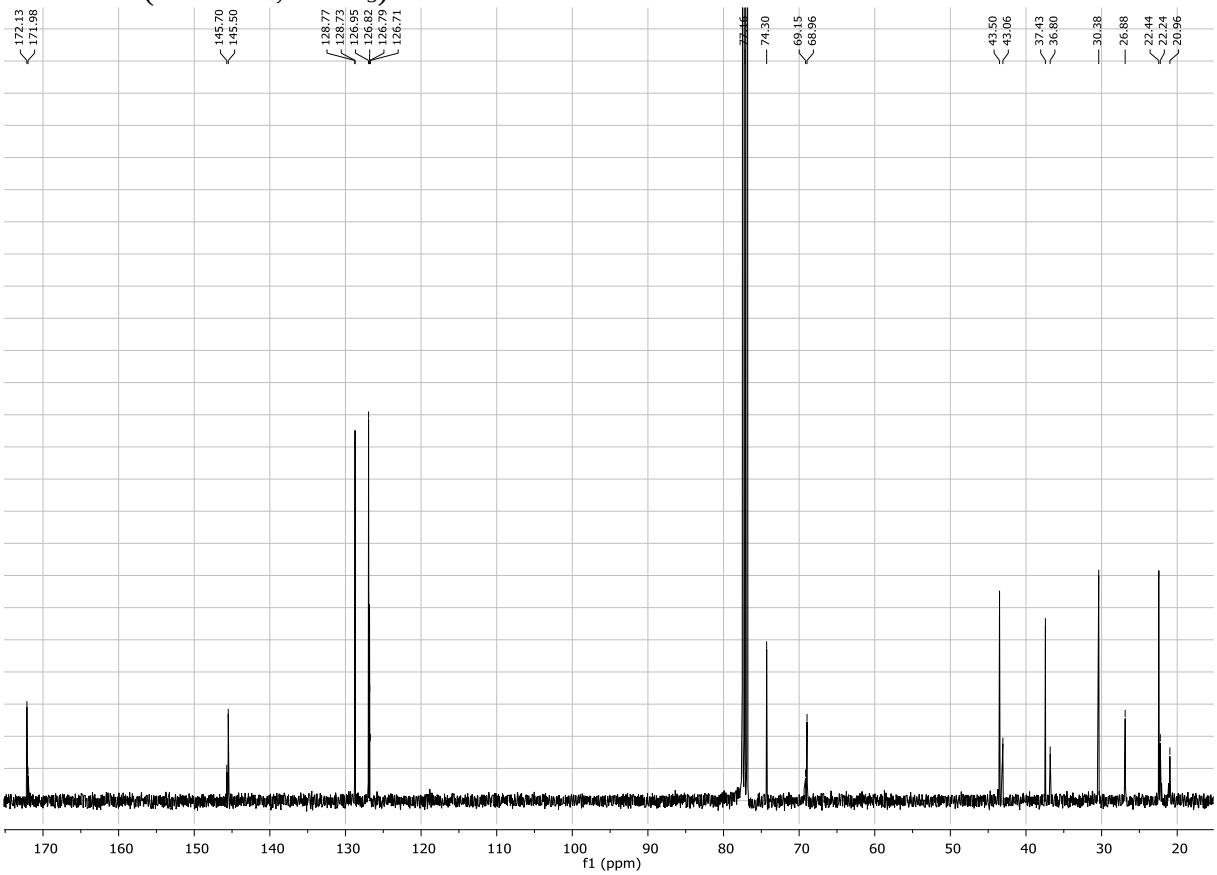


***cis*-2-Hydroxycyclohexyl 3-phenylbutyrate 27:**

^{1}H-NMR (400 MHz, $CDCl_3$)

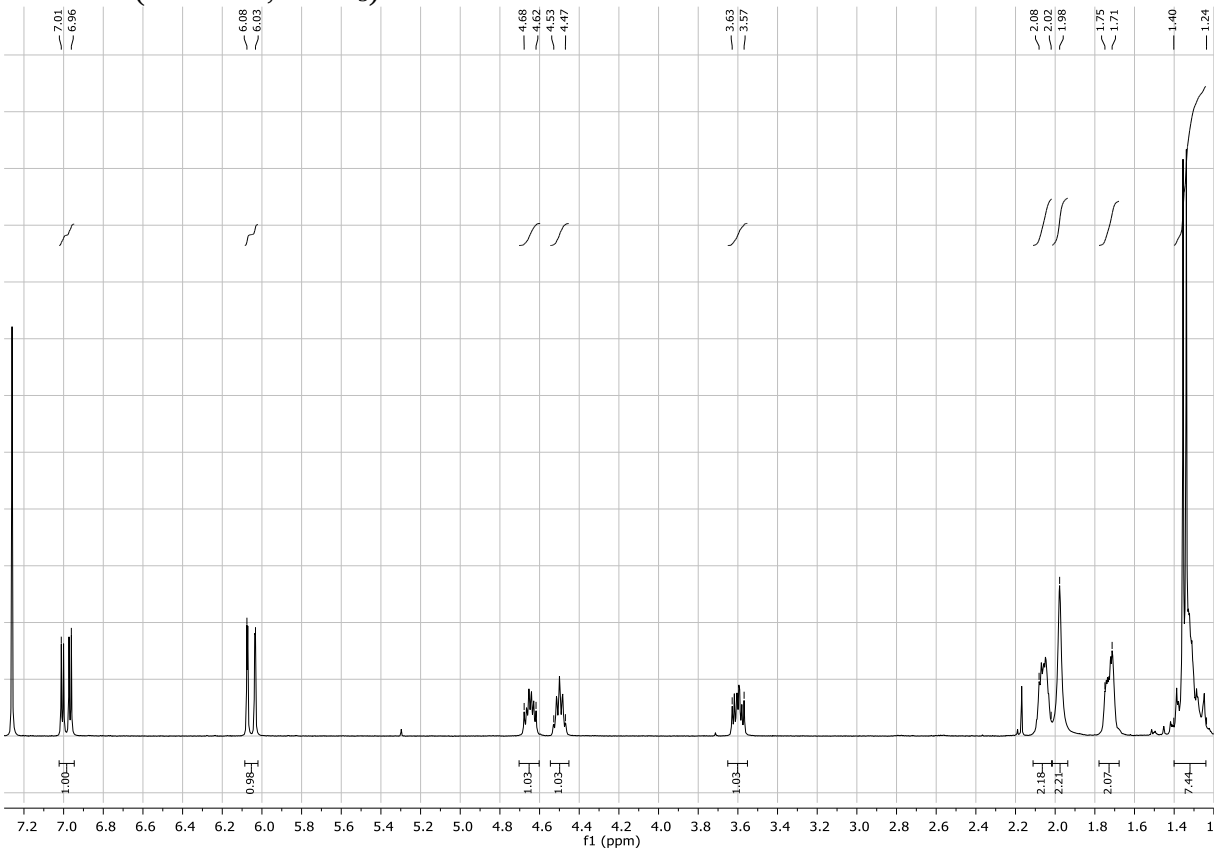


^{13}C-NMR (101 MHz, $CDCl_3$)

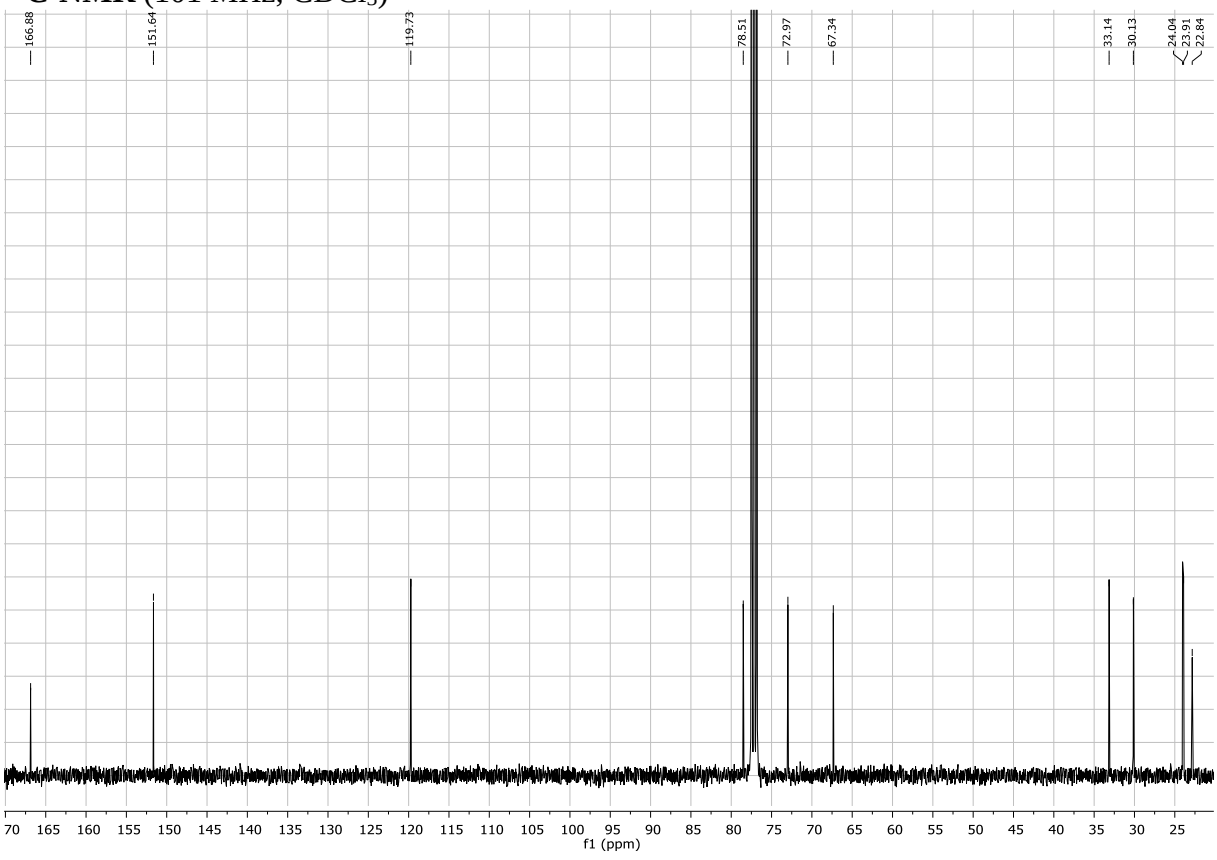


***trans*-2-Hydroxycyclohexyl (*E*)-4-hydroxy-2-pentenoate 31:**

^{1}H-NMR (400 MHz, $CDCl_3$)

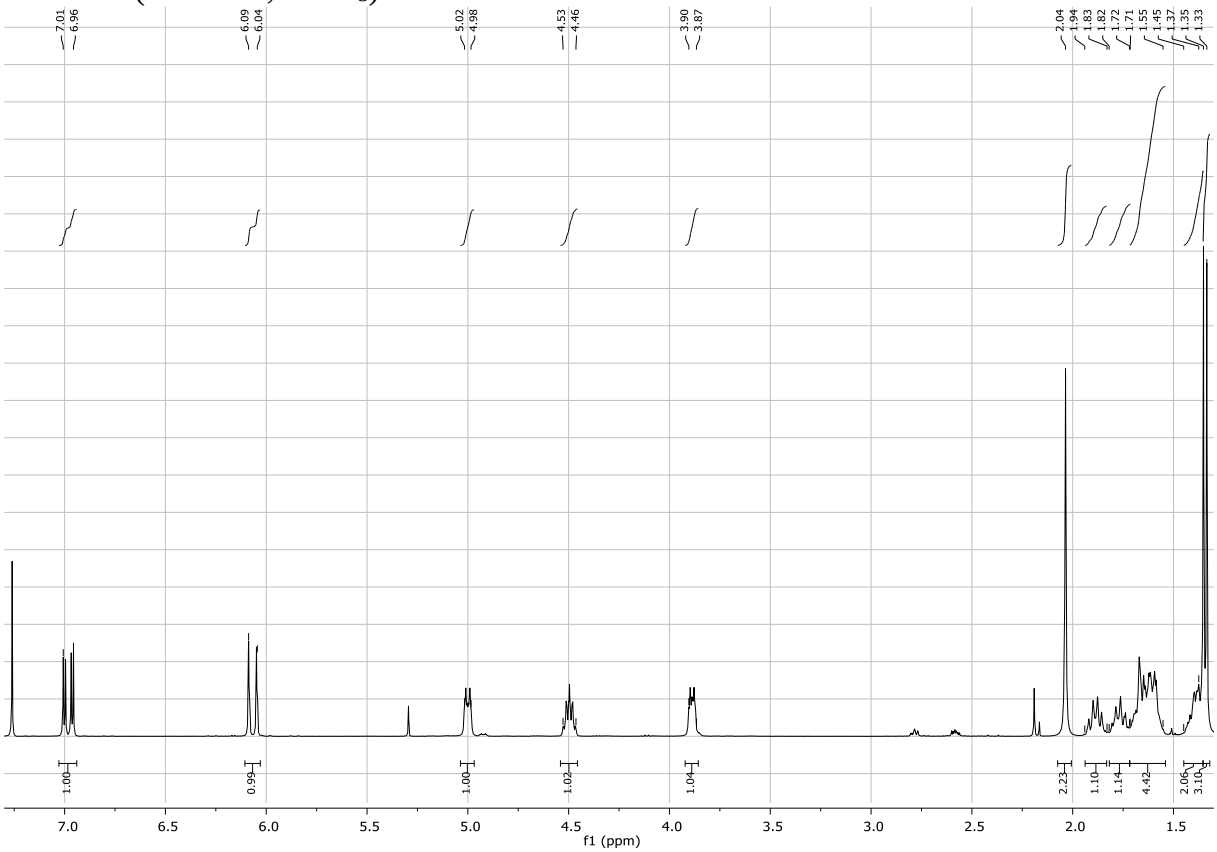


^{13}C-NMR (101 MHz, $CDCl_3$)

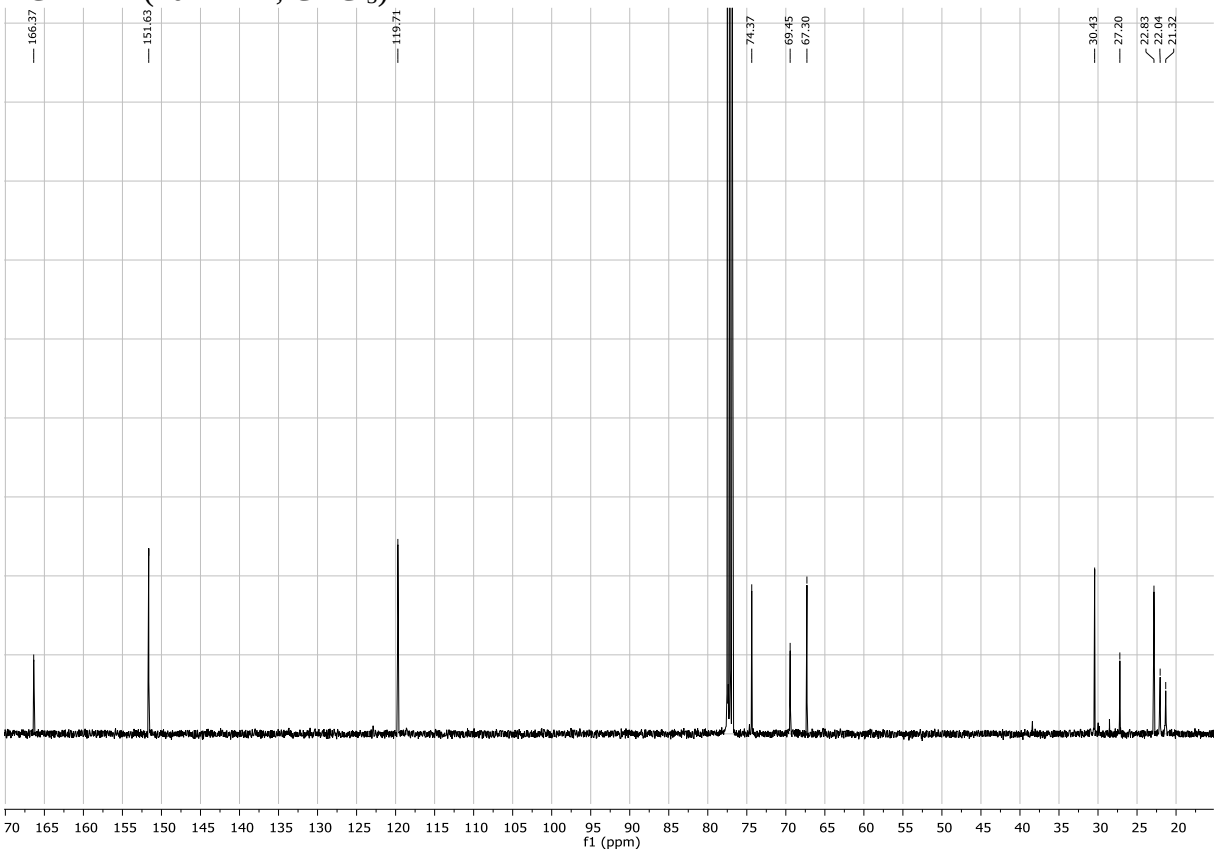


***cis*-2-Hydroxycyclohexyl (*E*)-4-hydroxy-2-pentenoate 32:**

^{1}H-NMR (400 MHz, $CDCl_3$)

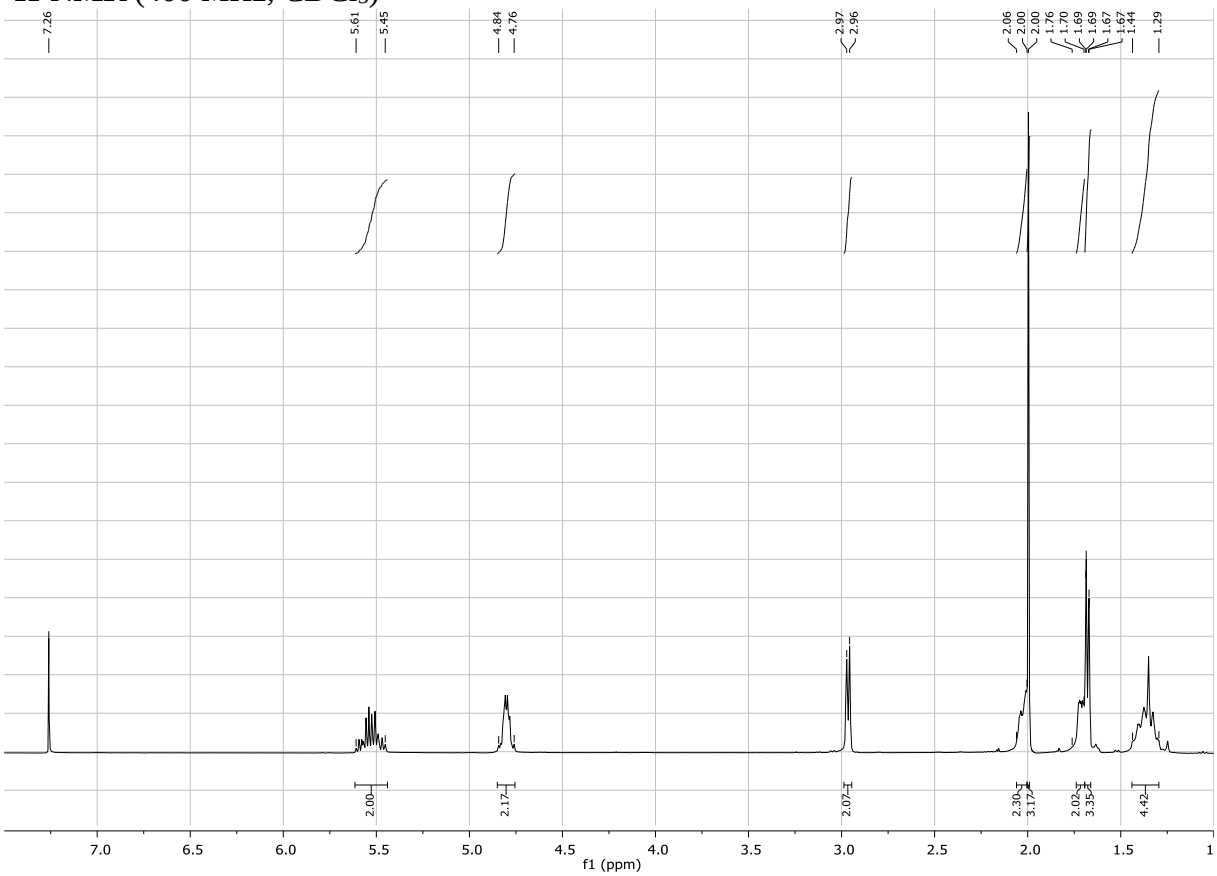


^{13}C-NMR (101 MHz, $CDCl_3$)

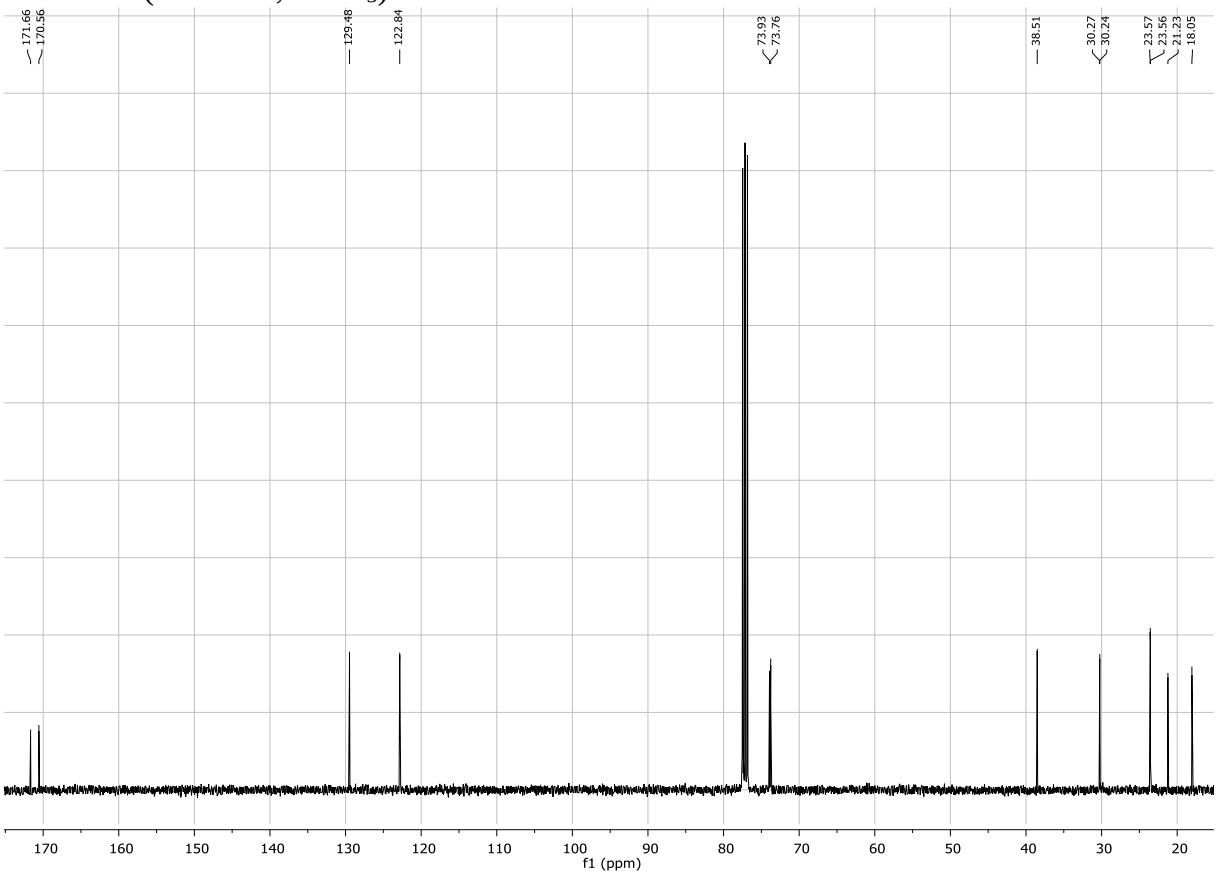


***trans*-2-Acetoxycyclohexyl (*E*)-3-pentenoate 33:**

^{1}H-NMR (400 MHz, $CDCl_3$)

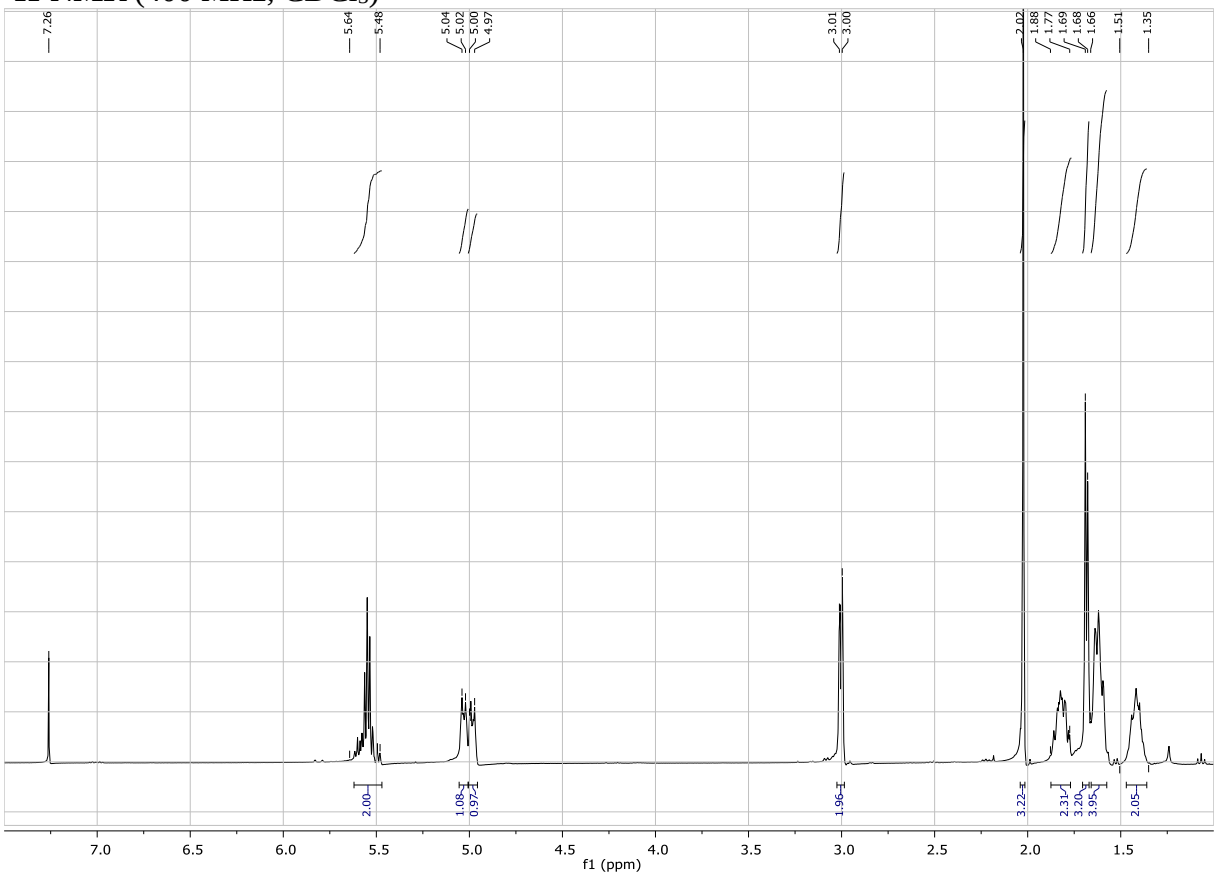


^{13}C-NMR (101 MHz, $CDCl_3$)

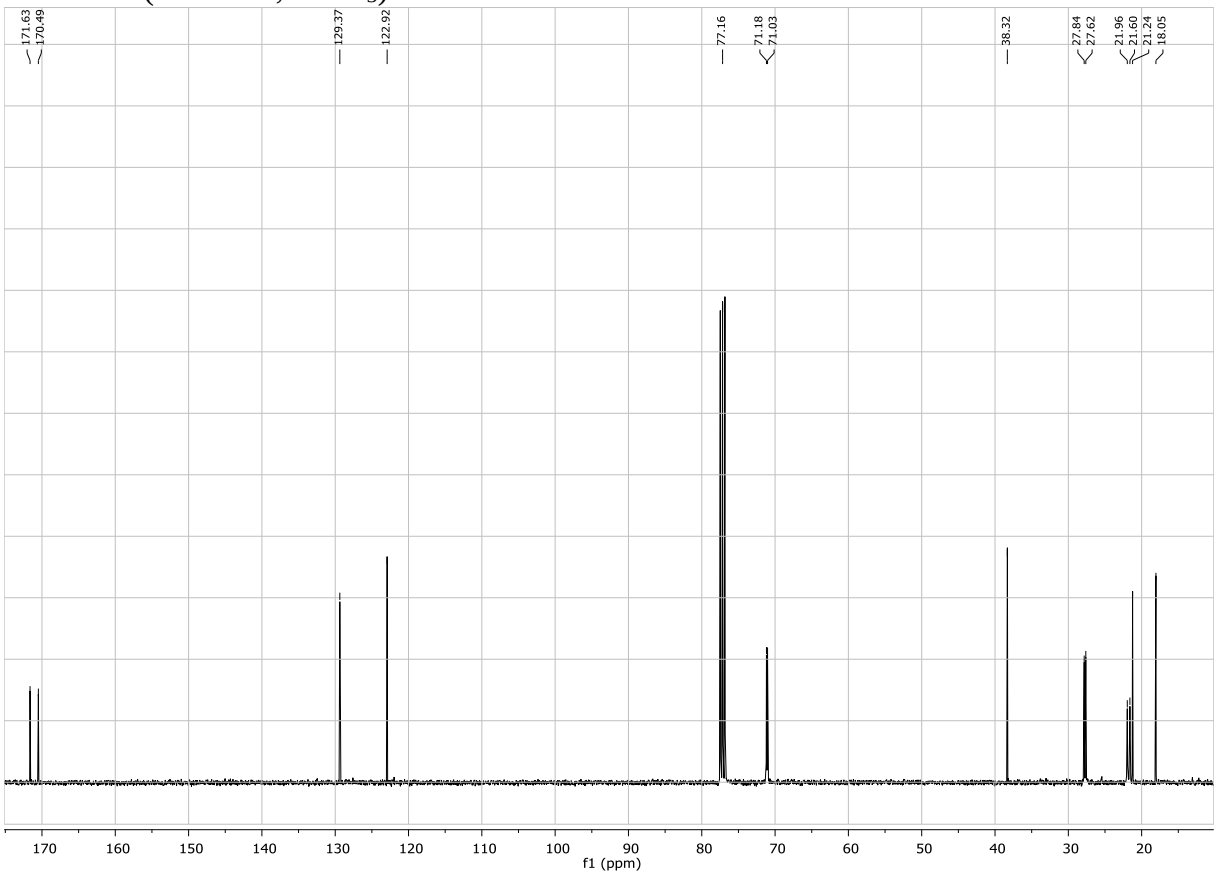


***cis*-2-Acetoxycyclohexyl (*E*)-3-pentenoate 34:**

^{1}H-NMR (400 MHz, $CDCl_3$)

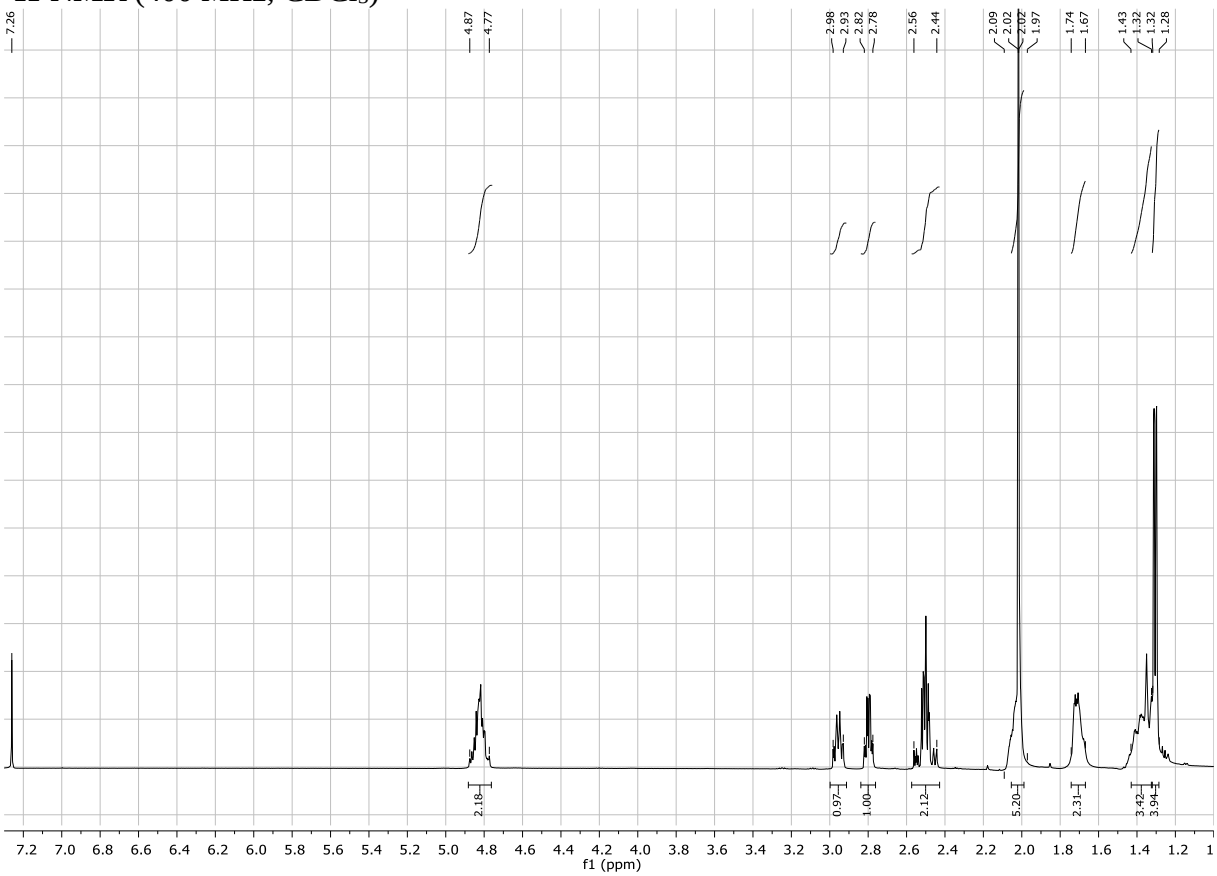


^{13}C-NMR (101 MHz, $CDCl_3$)

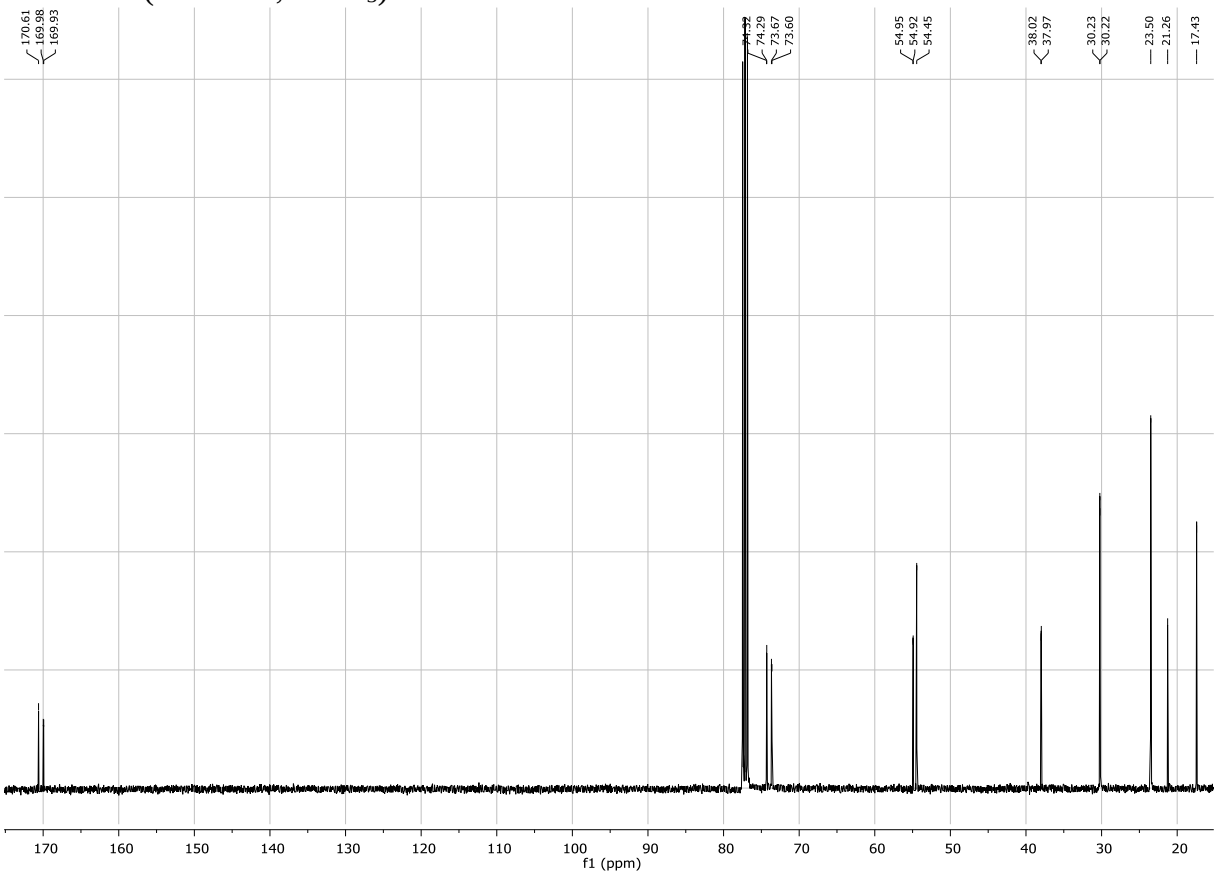


***trans*-2-Acetoxycyclohexyl (3-methyl-2-oxiranyl)acetate 35:**

^{1}H-NMR (400 MHz, $CDCl_3$)

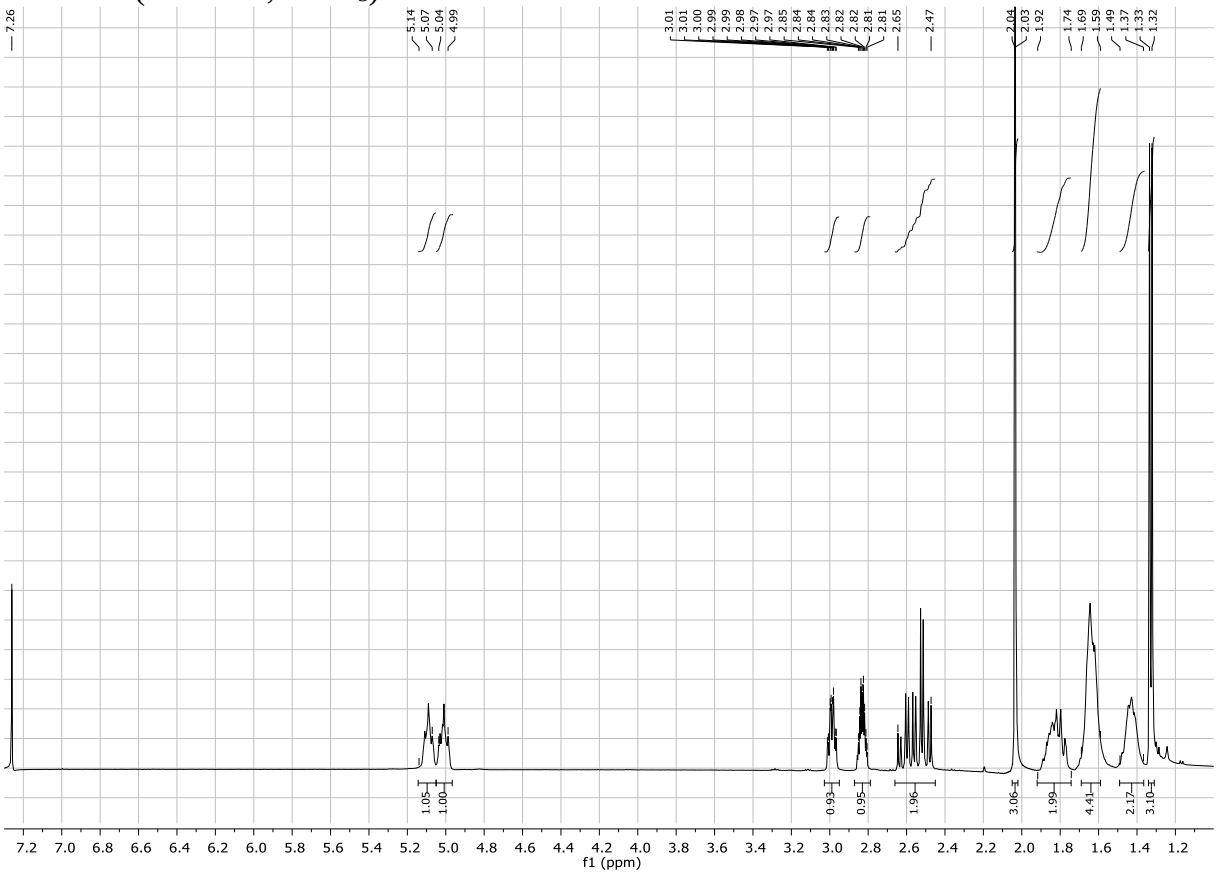


^{13}C-NMR (101 MHz, $CDCl_3$)

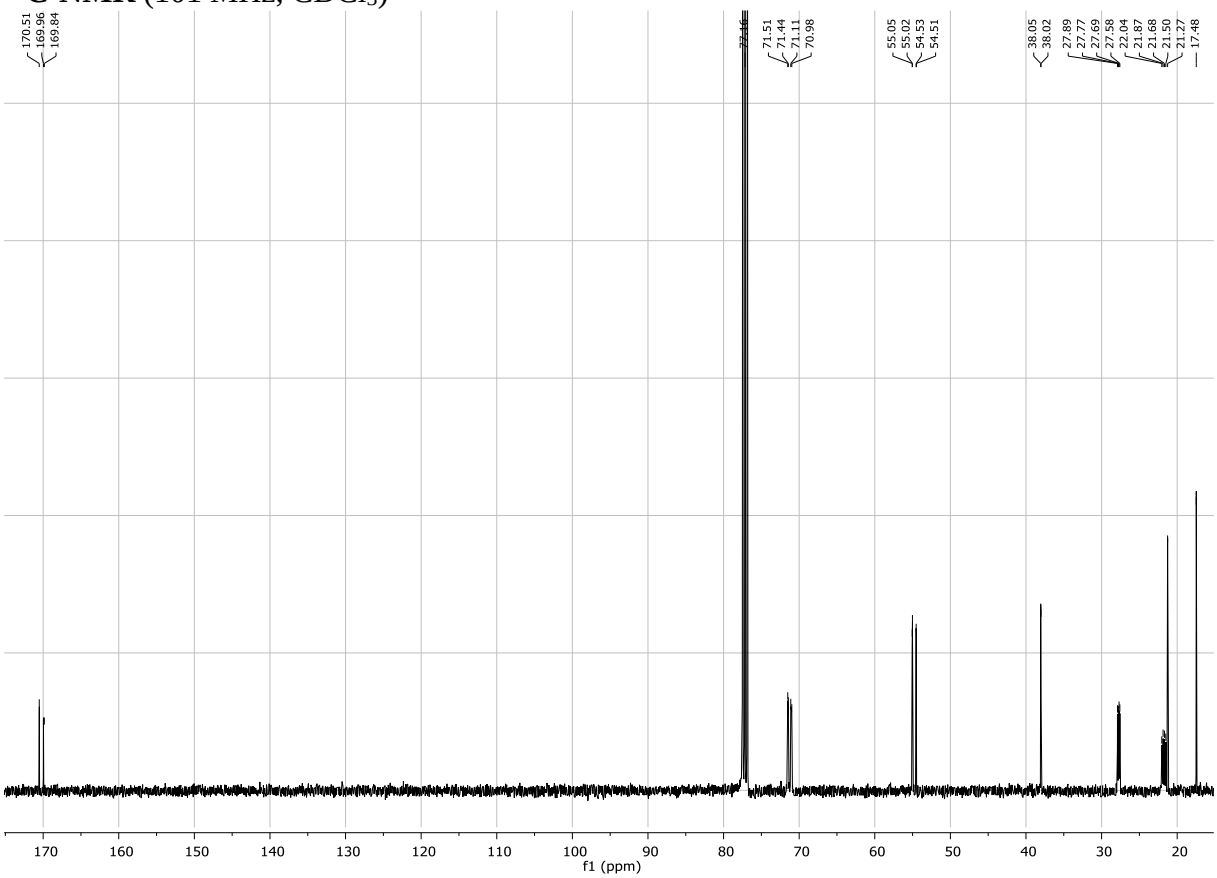


***cis*-2-Acetoxycyclohexyl (3-methyl-2-oxiranyl)acetate 36:**

^{1}H-NMR (400 MHz, $CDCl_3$)

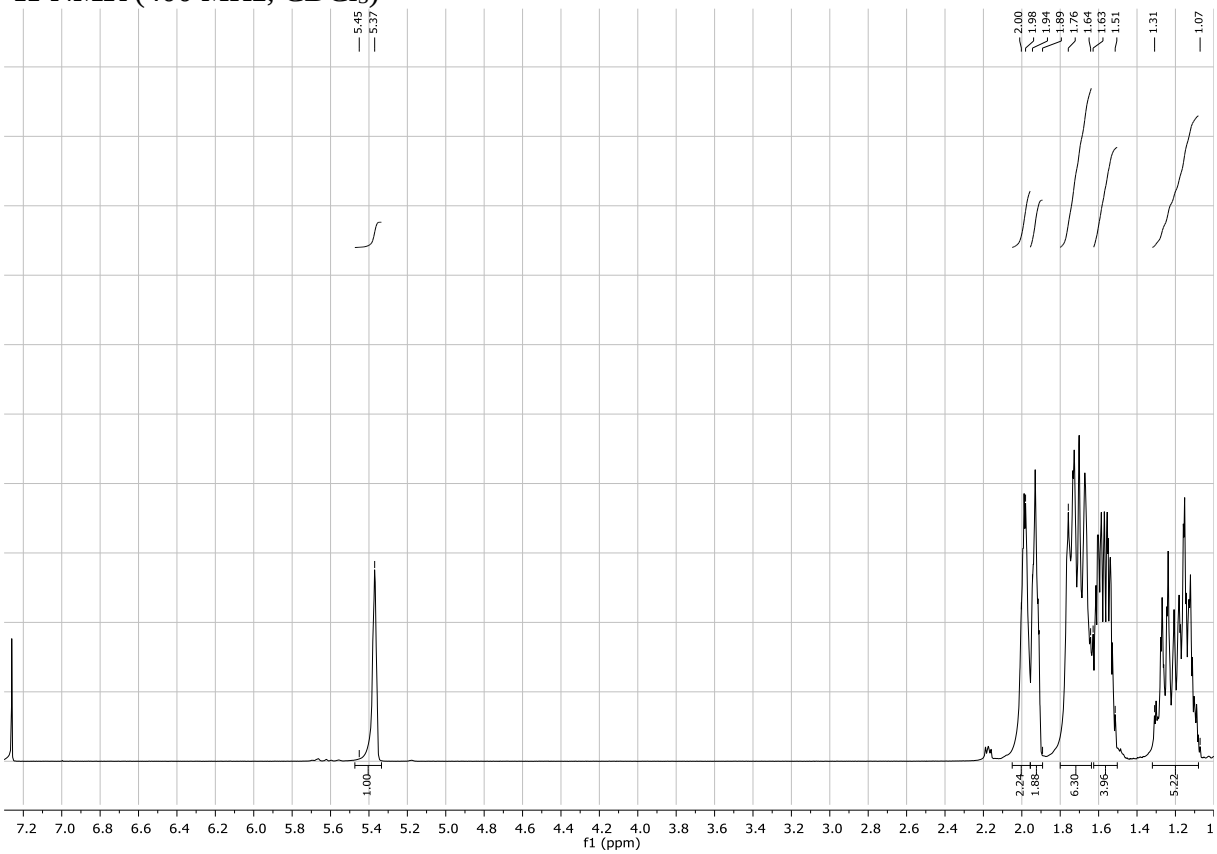


^{13}C-NMR (101 MHz, $CDCl_3$)

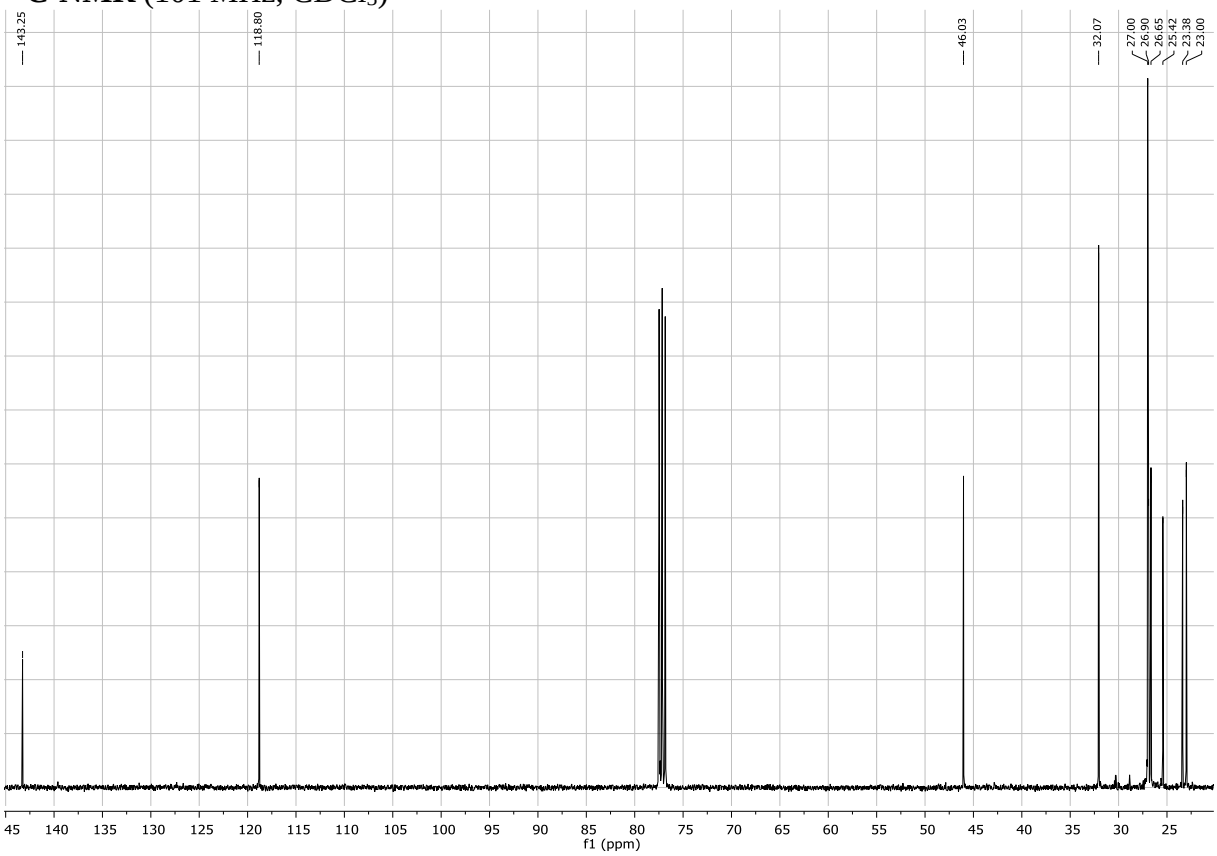


1-Cyclohexylcyclohexene 40:

^{1}H-NMR (400 MHz, $CDCl_3$)

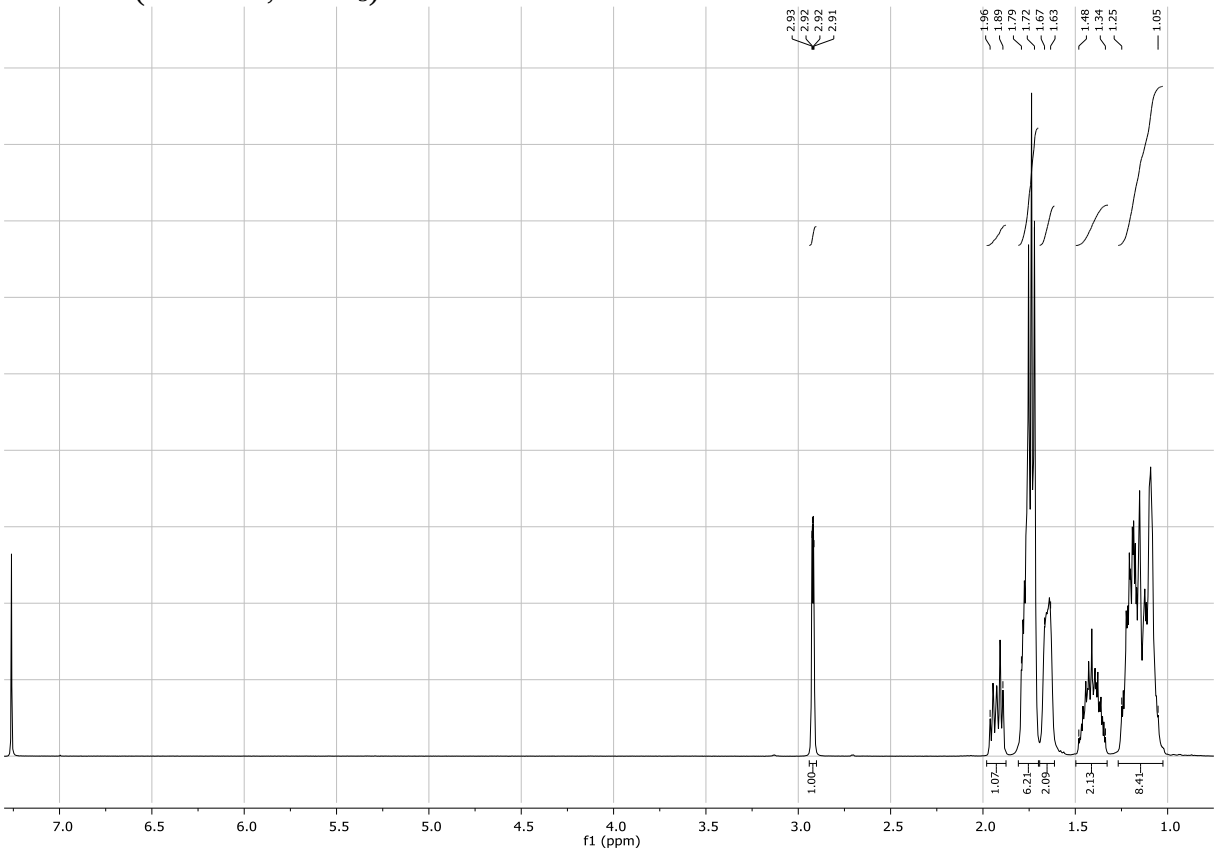


^{13}C-NMR (101 MHz, $CDCl_3$)

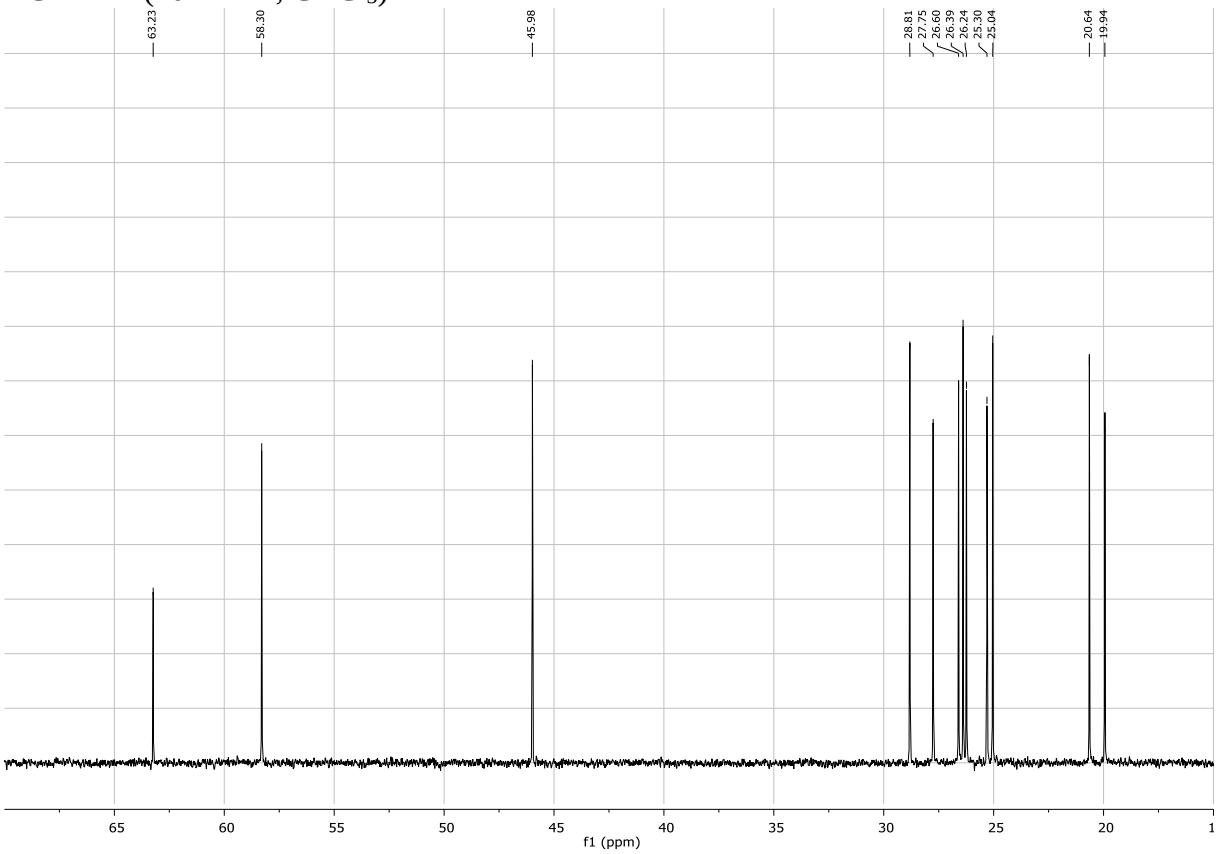


1-Cyclohexyl-7-oxabicyclo[4.1.0]heptane 41:

^{1}H-NMR (400 MHz, $CDCl_3$)

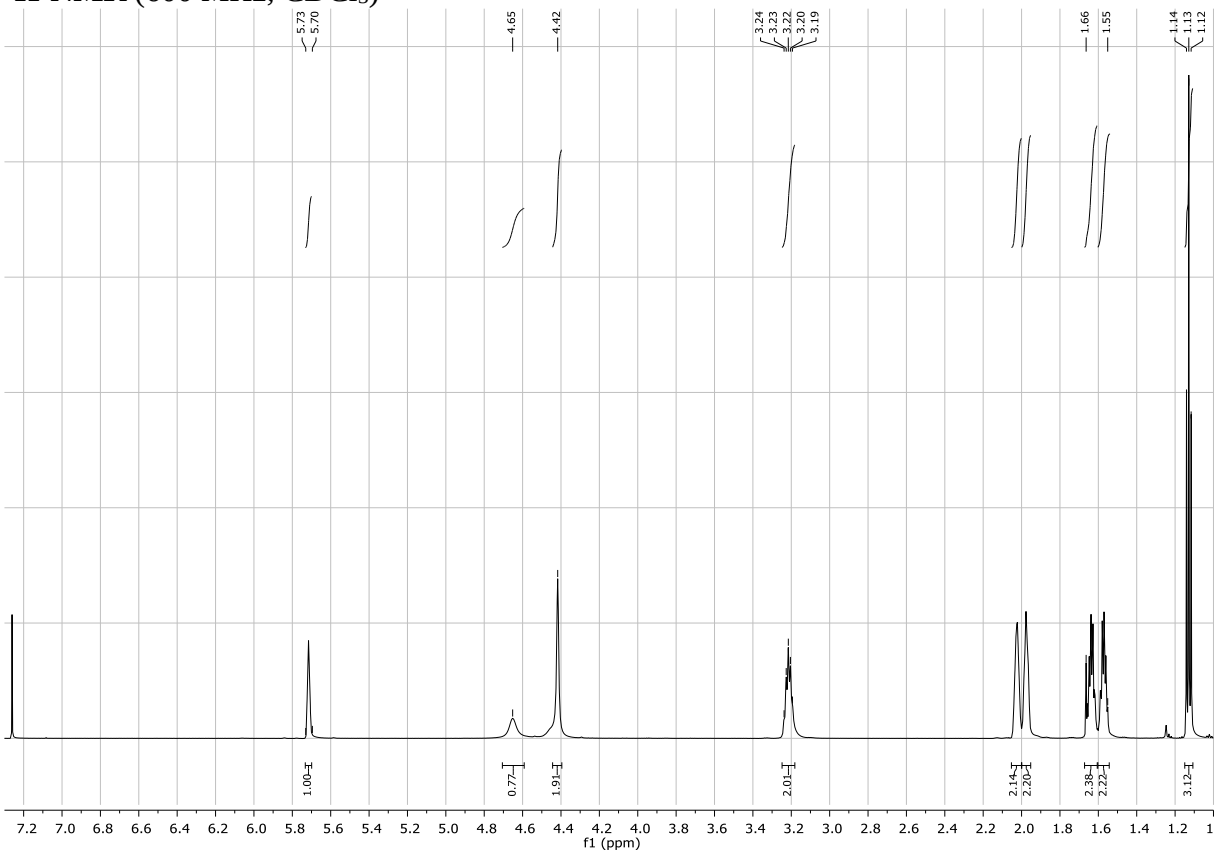


^{13}C-NMR (101 MHz, $CDCl_3$)

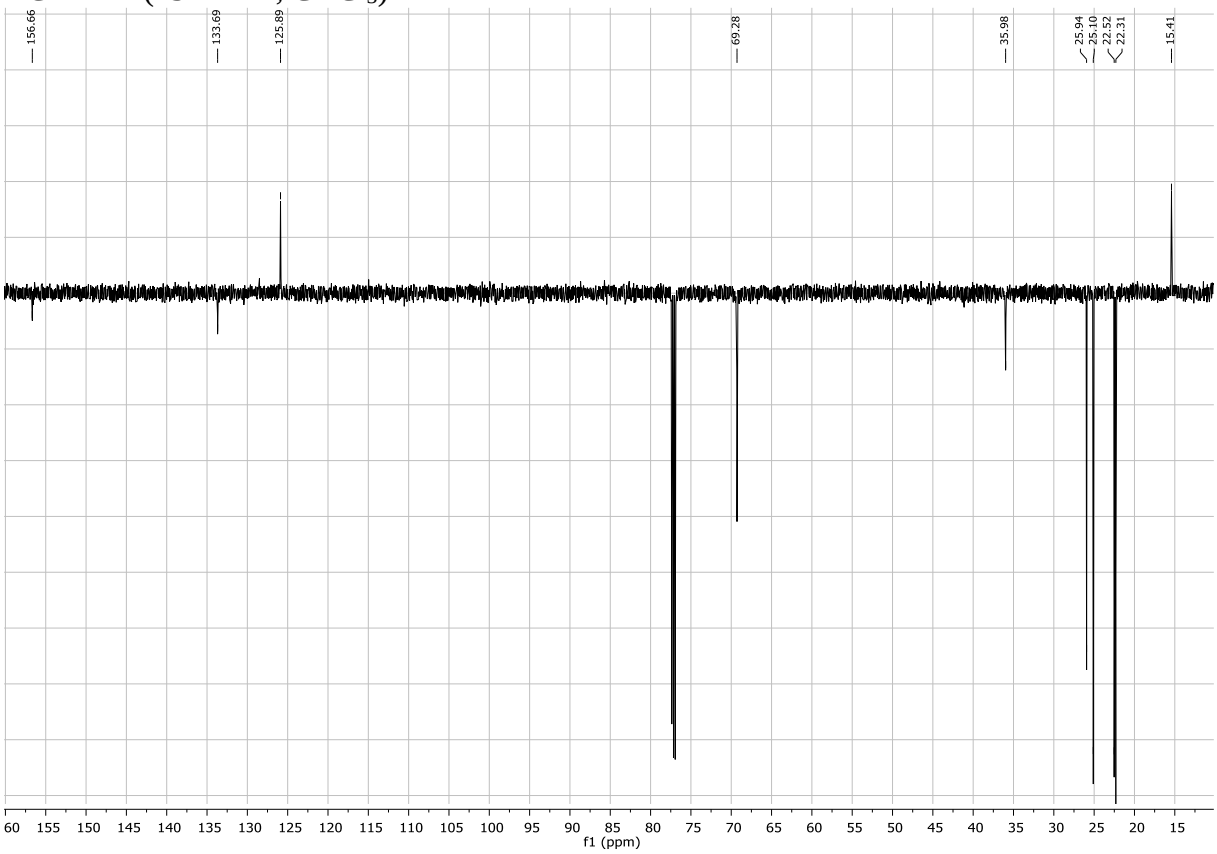


Cyclohex-1-en-1-ylmethyl ethylcarbamate 52c:

^{1}H-NMR (600 MHz, $CDCl_3$)

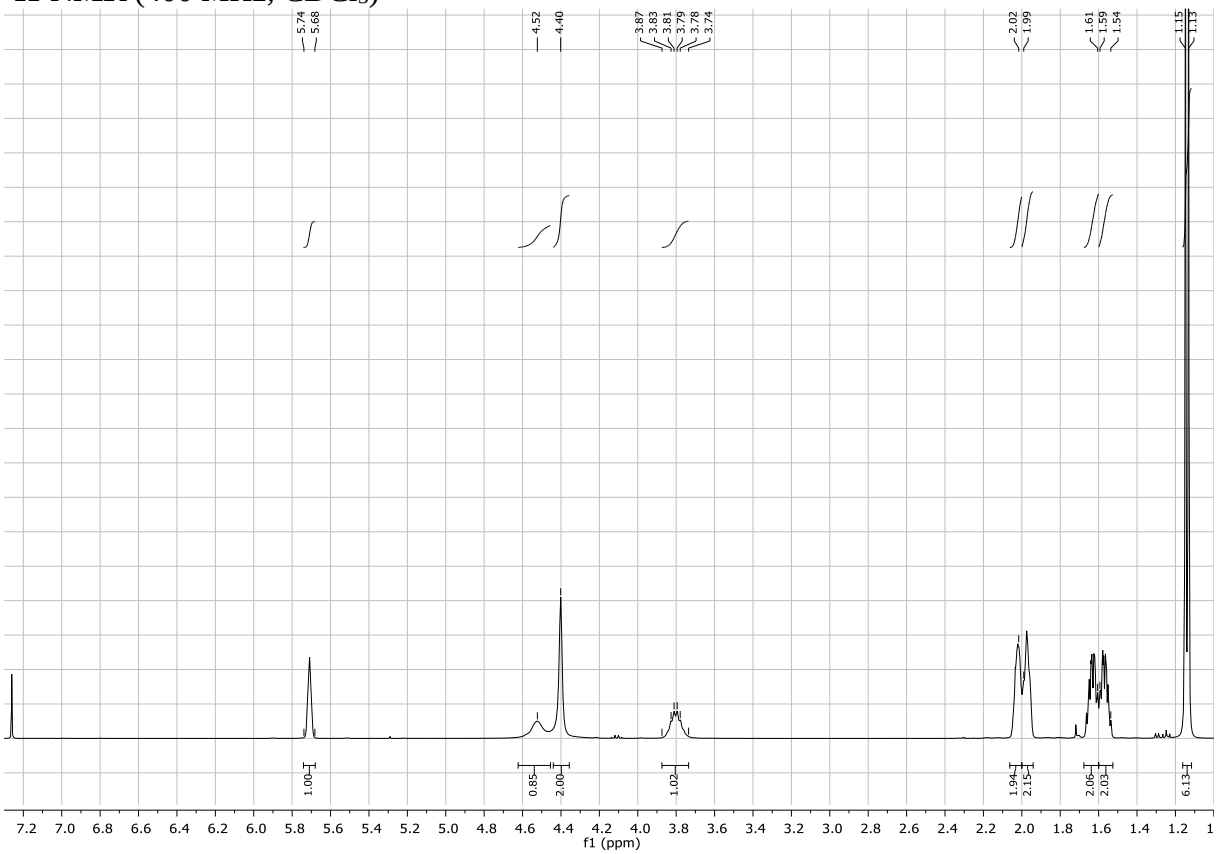


^{13}C-NMR (151 MHz, $CDCl_3$)

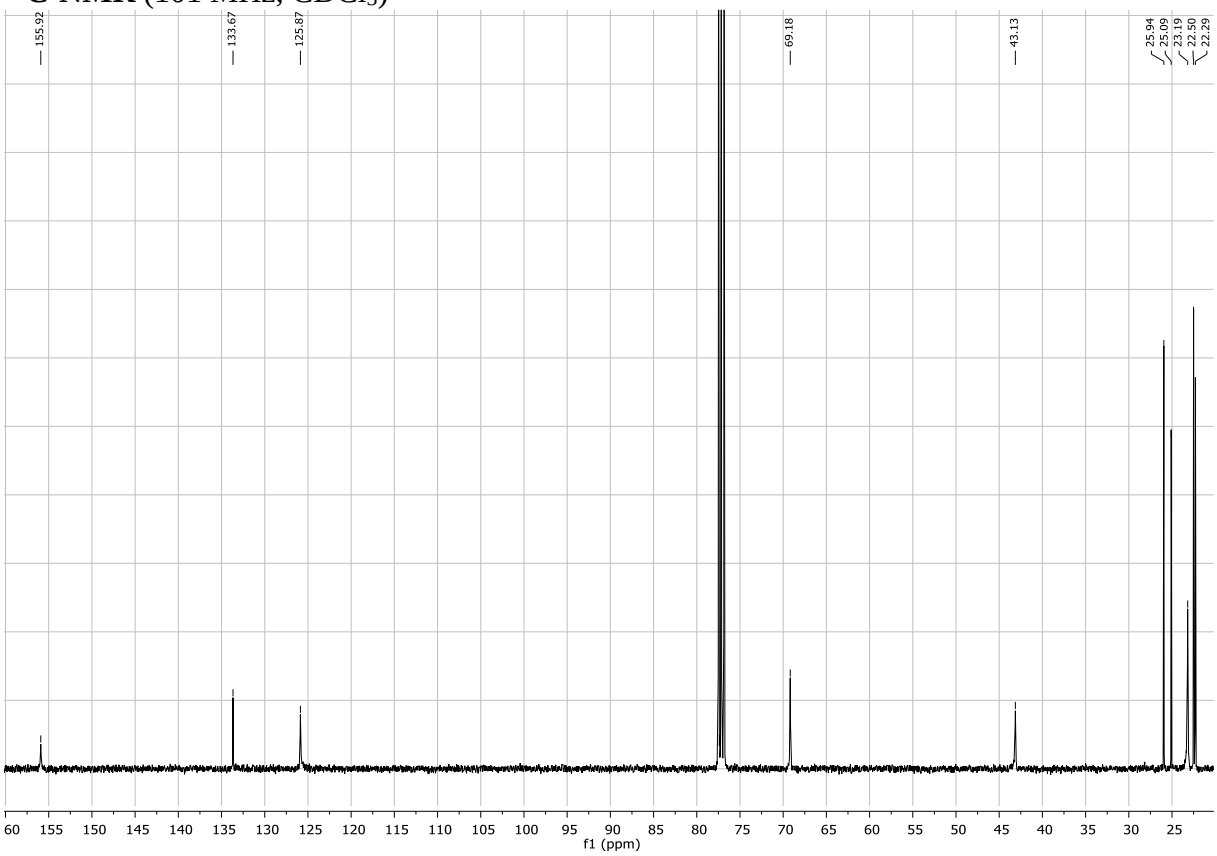


Cyclohex-1-en-1-ylmethyl isopropylcarbamate 52d:

^{1}H-NMR (400 MHz, $CDCl_3$)

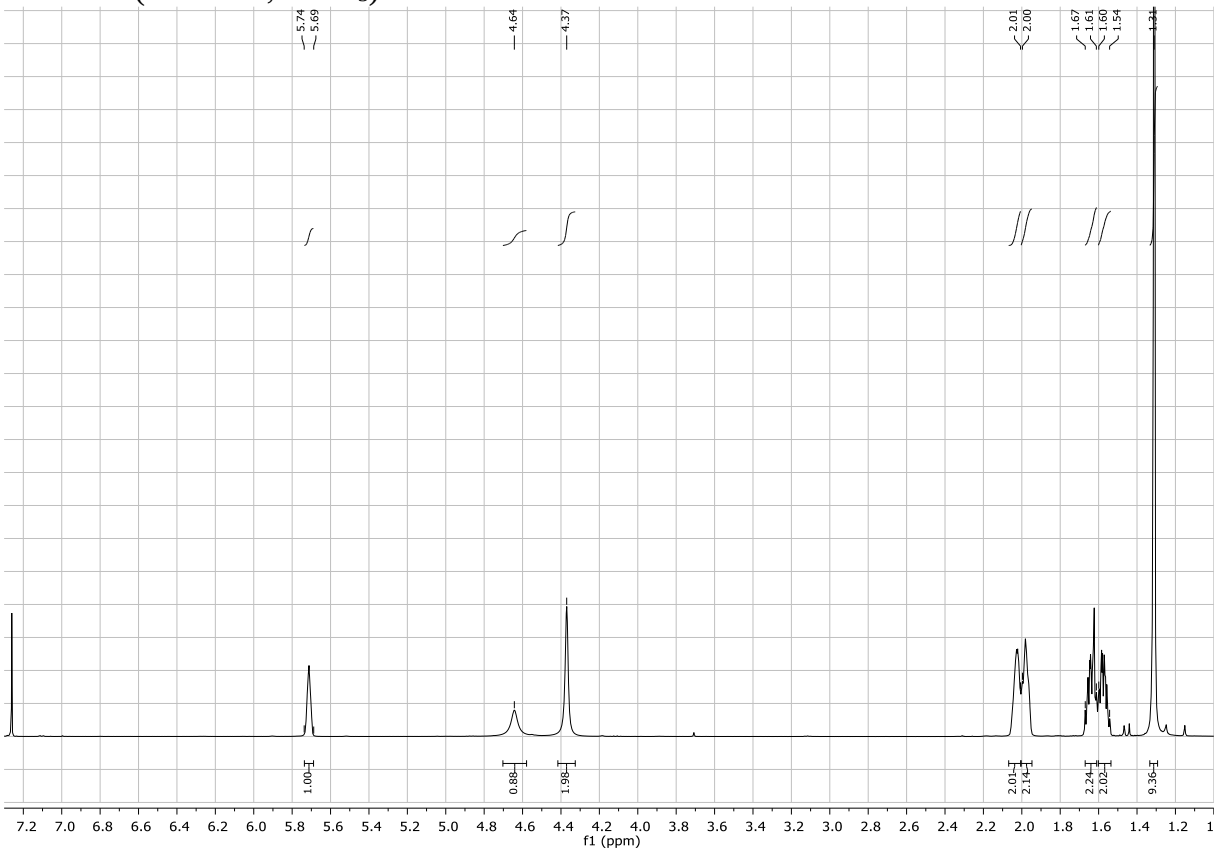


^{13}C-NMR (101 MHz, $CDCl_3$)

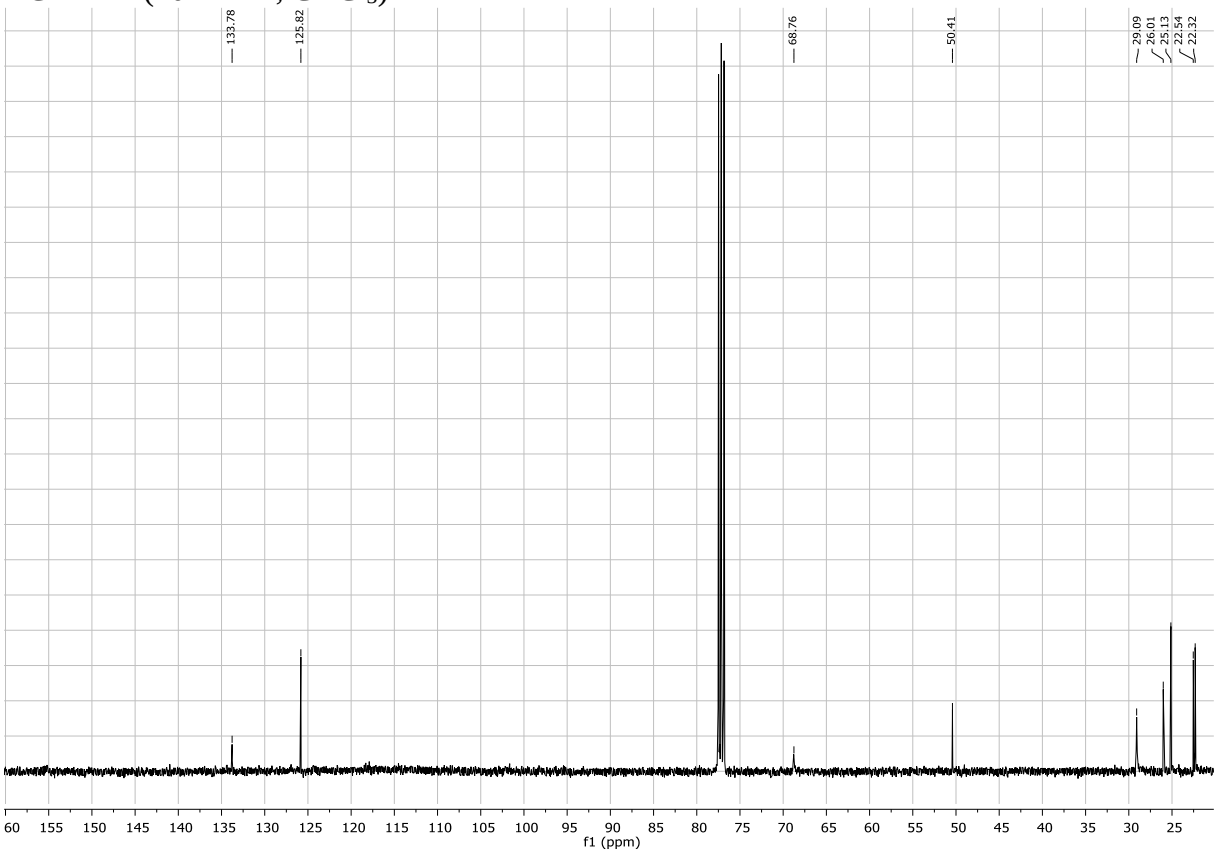


Cyclohex-1-en-1-ylmethyl *tert*-butylcarbamate 52e:

^{1}H-NMR (400 MHz, $CDCl_3$)

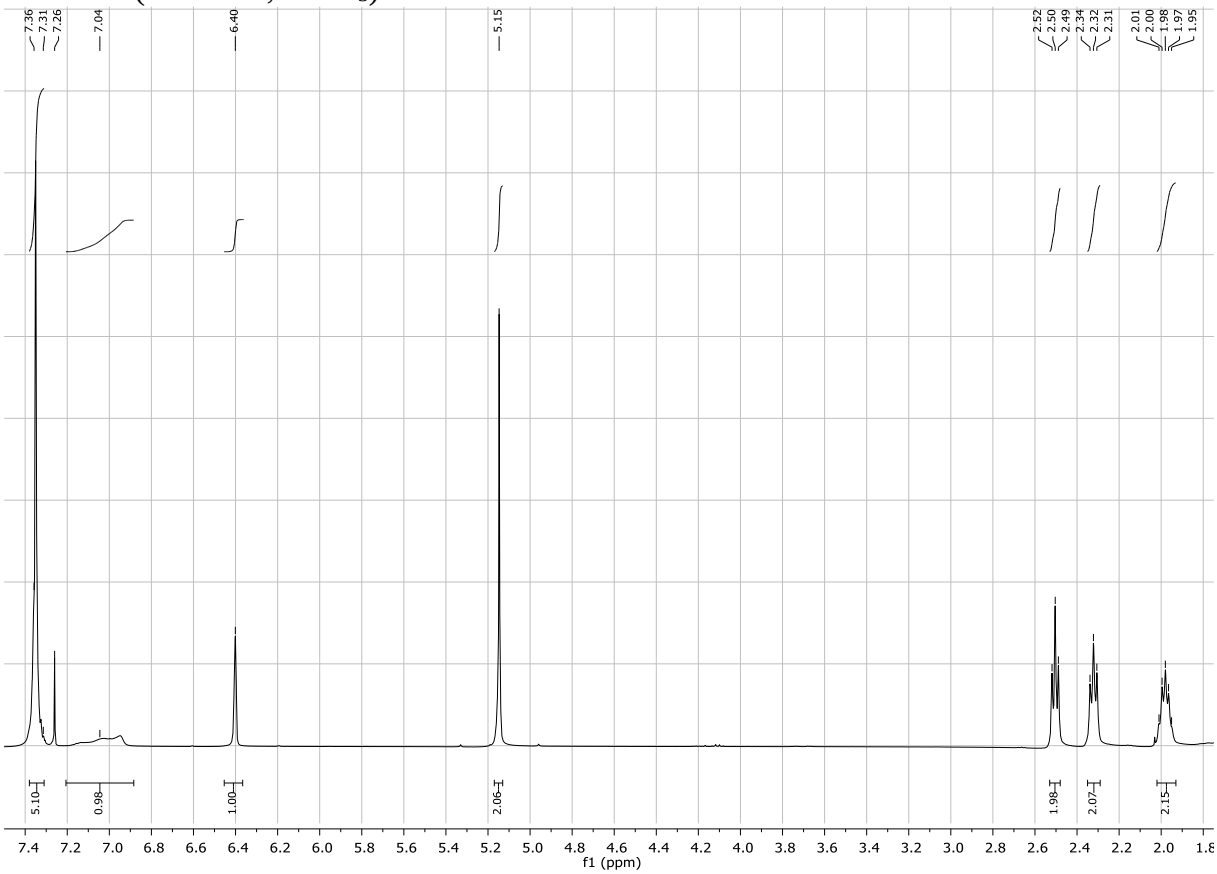


^{13}C-NMR (101 MHz, $CDCl_3$)

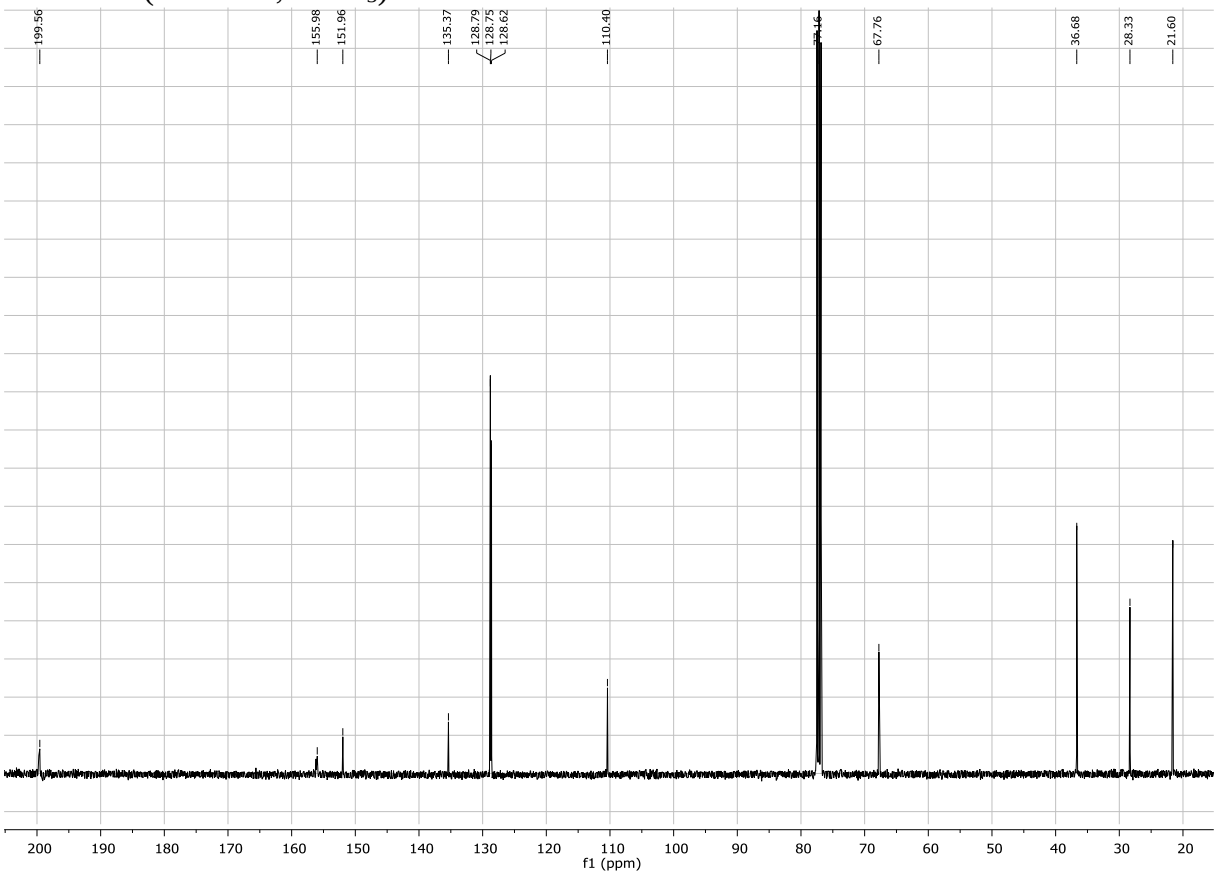


1-(Benzyloxycarbonylamino)-1-cyclohexen-3-one 66:

^{1}H-NMR (400 MHz, $CDCl_3$)

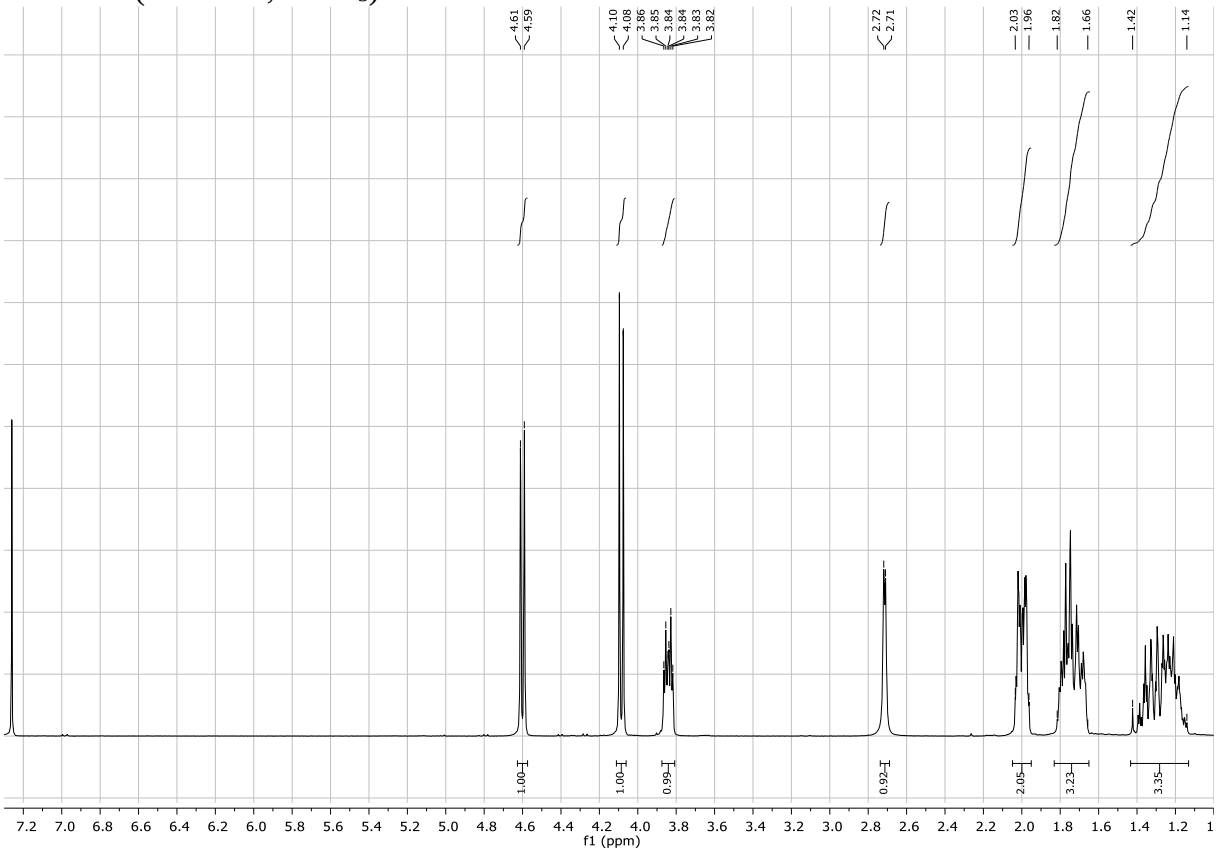


^{13}C-NMR (101 MHz, $CDCl_3$)

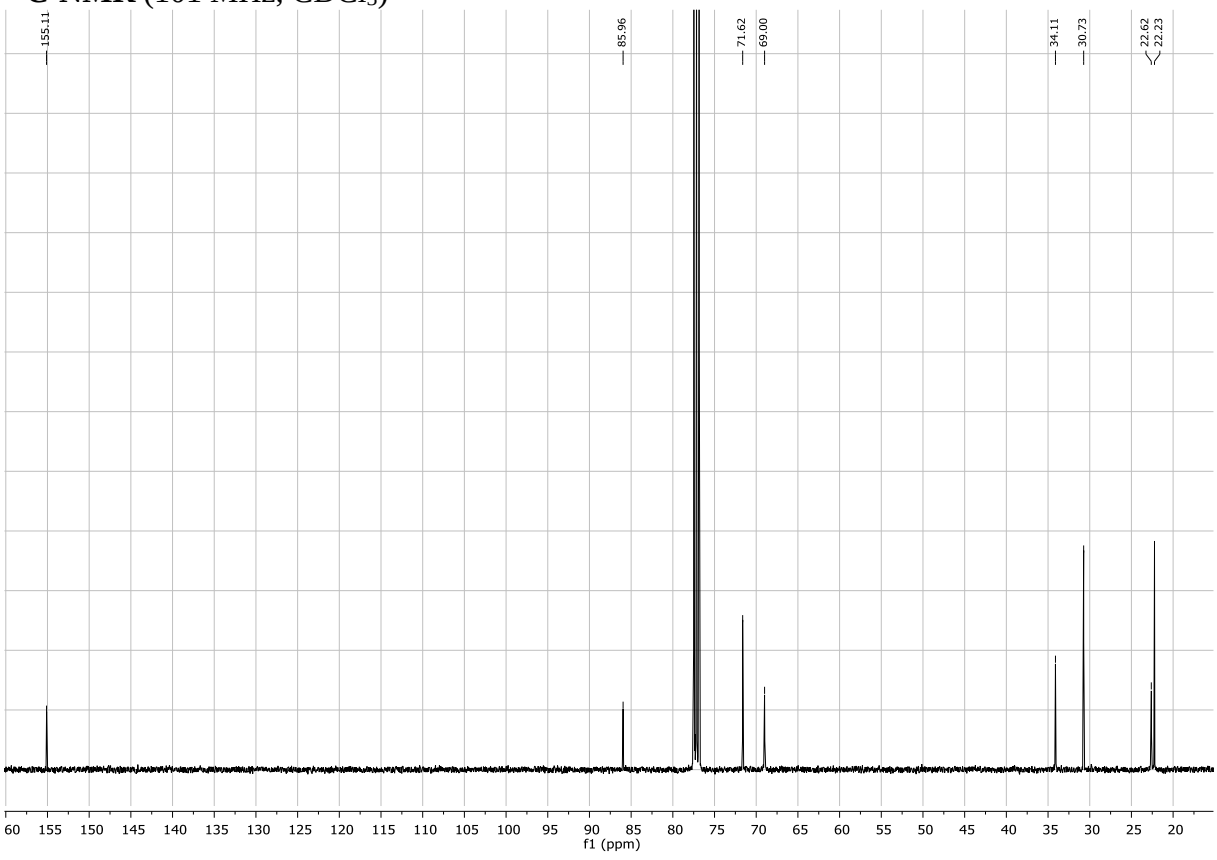


6-Hydroxy-1,3-dioxaspiro[4.5]decan-2-one 75:

^{1}H-NMR (400 MHz, $CDCl_3$)

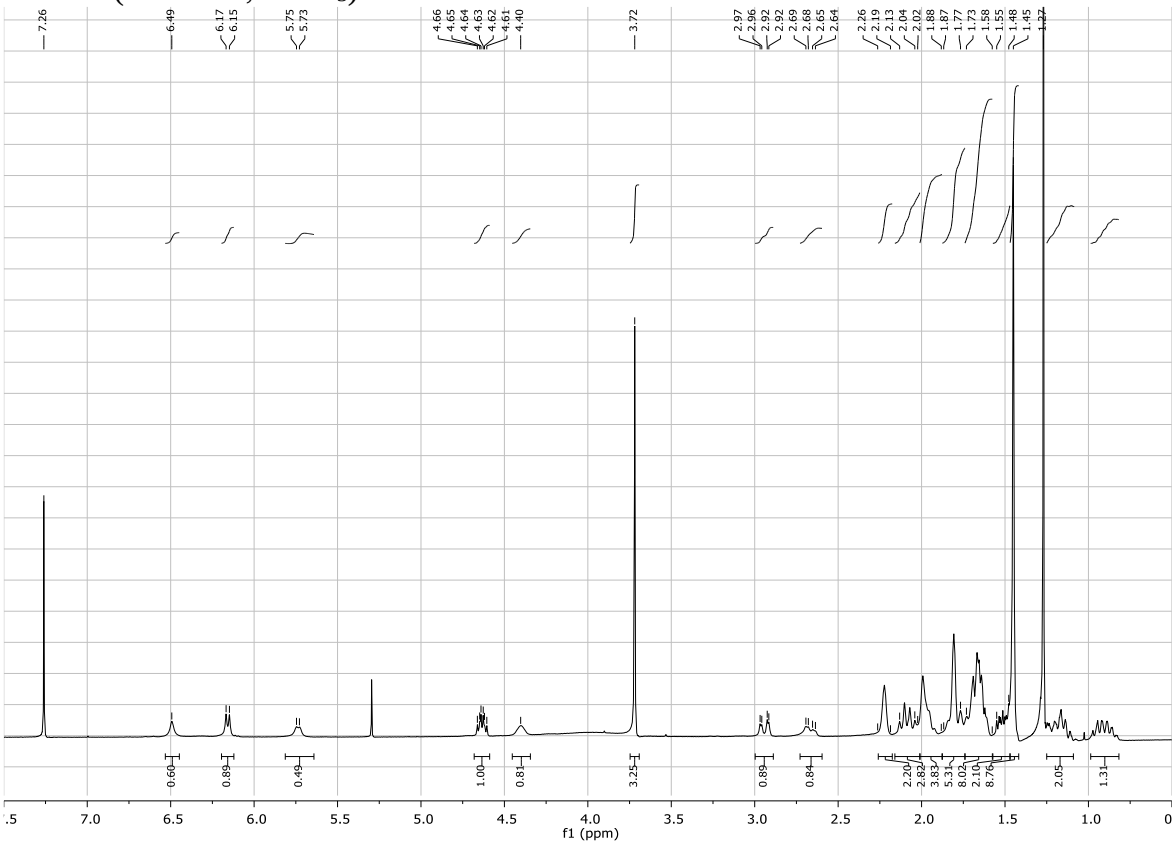


^{13}C-NMR (101 MHz, $CDCl_3$)

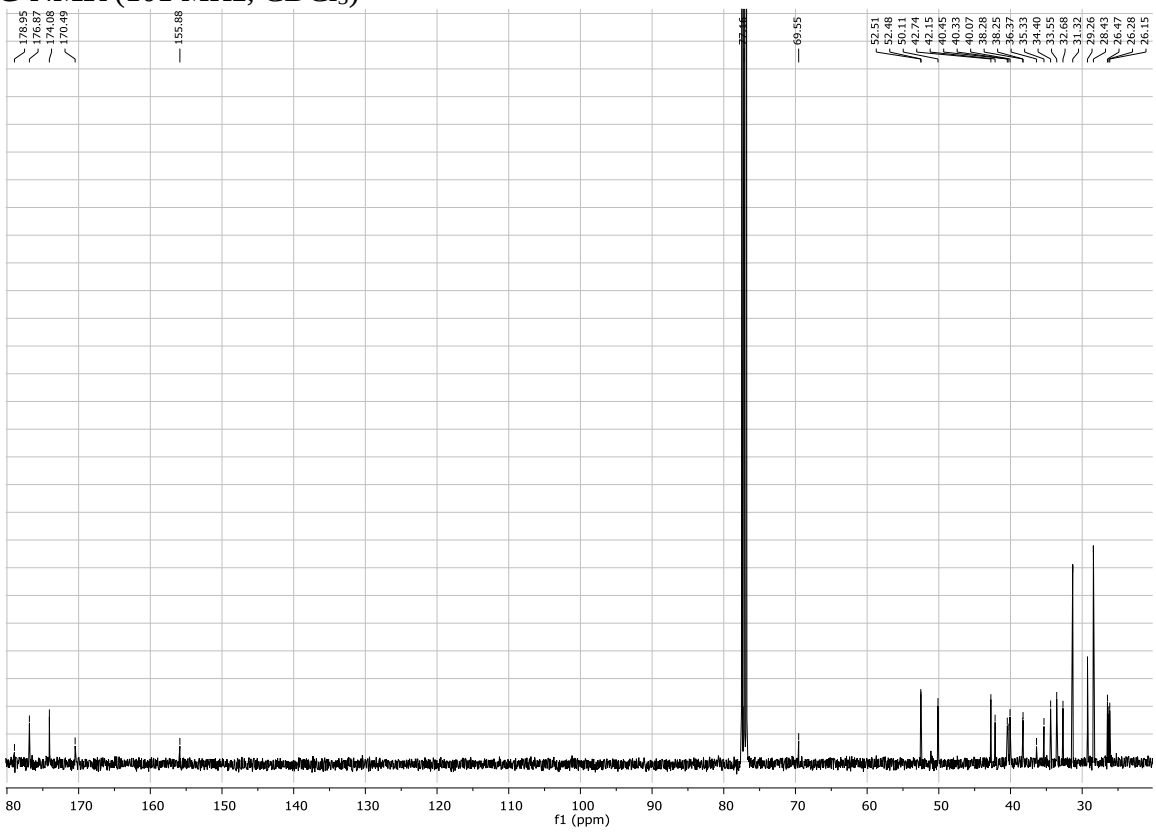


Boc-Asp(OH)-AdGly-Cha-OMe 96:[31]

^{1}H-NMR (400 MHz, $CDCl_3$)



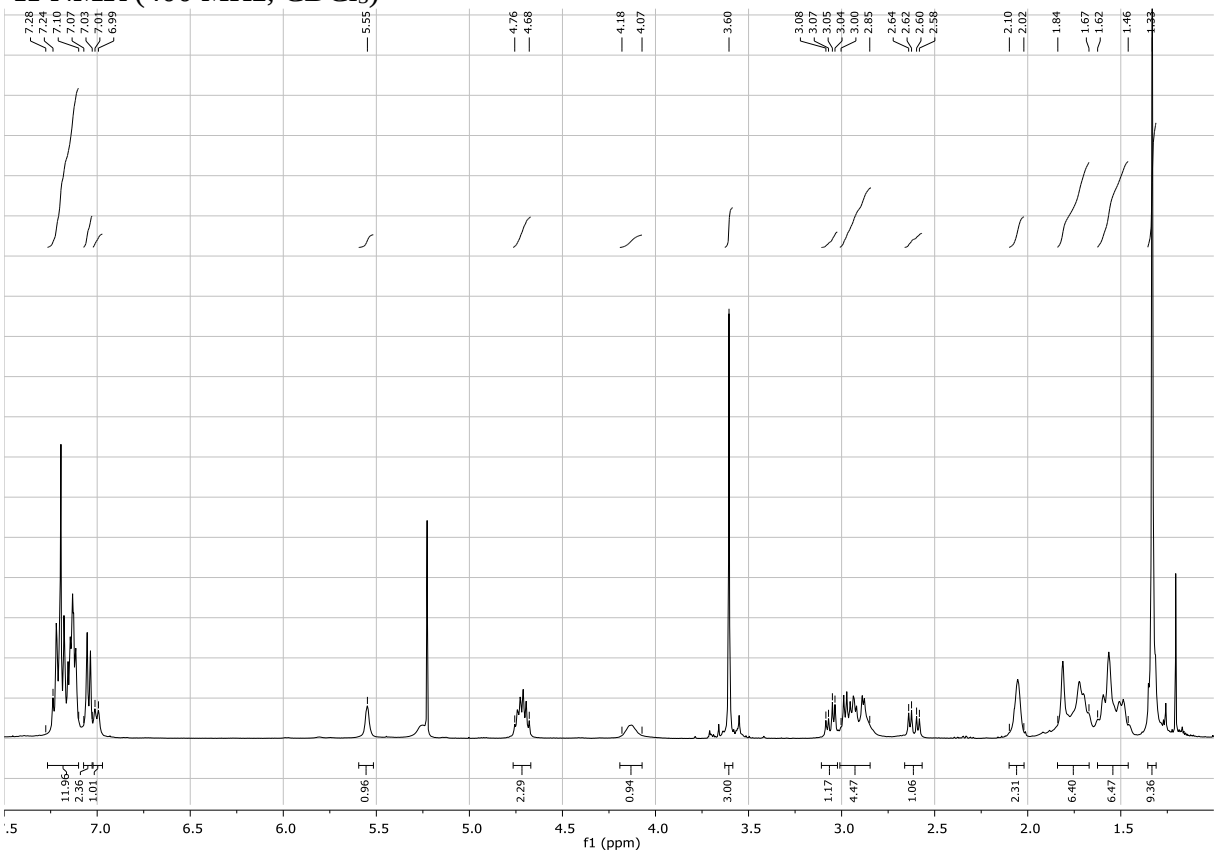
^{13}C-NMR (101 MHz, $CDCl_3$)



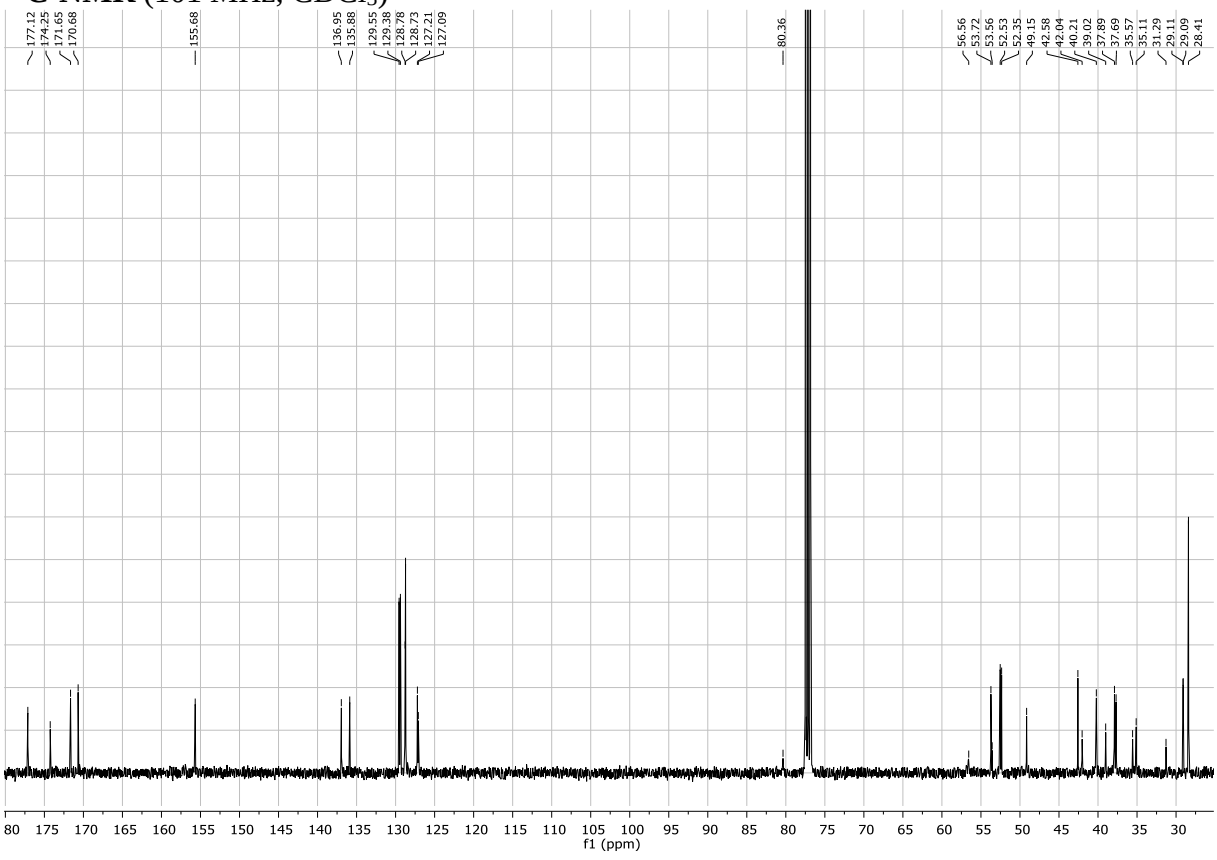
[31] Spektrum contains ^{t}BuOH (1.27 ppm)

Boc-Phe-AdGly-Asp(OH)-Phe-OMe 100:

^{1}H-NMR (400 MHz, $CDCl_3$)

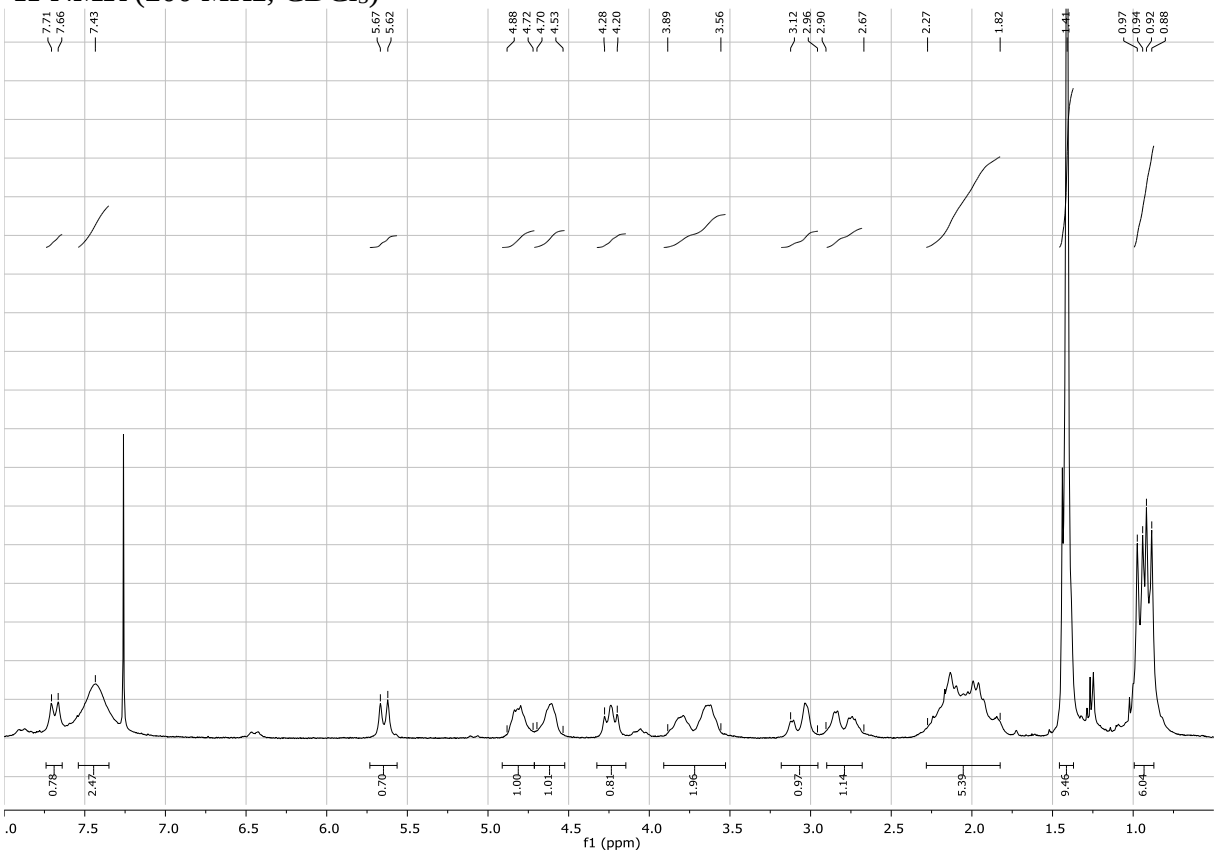


^{13}C-NMR (101 MHz, $CDCl_3$)

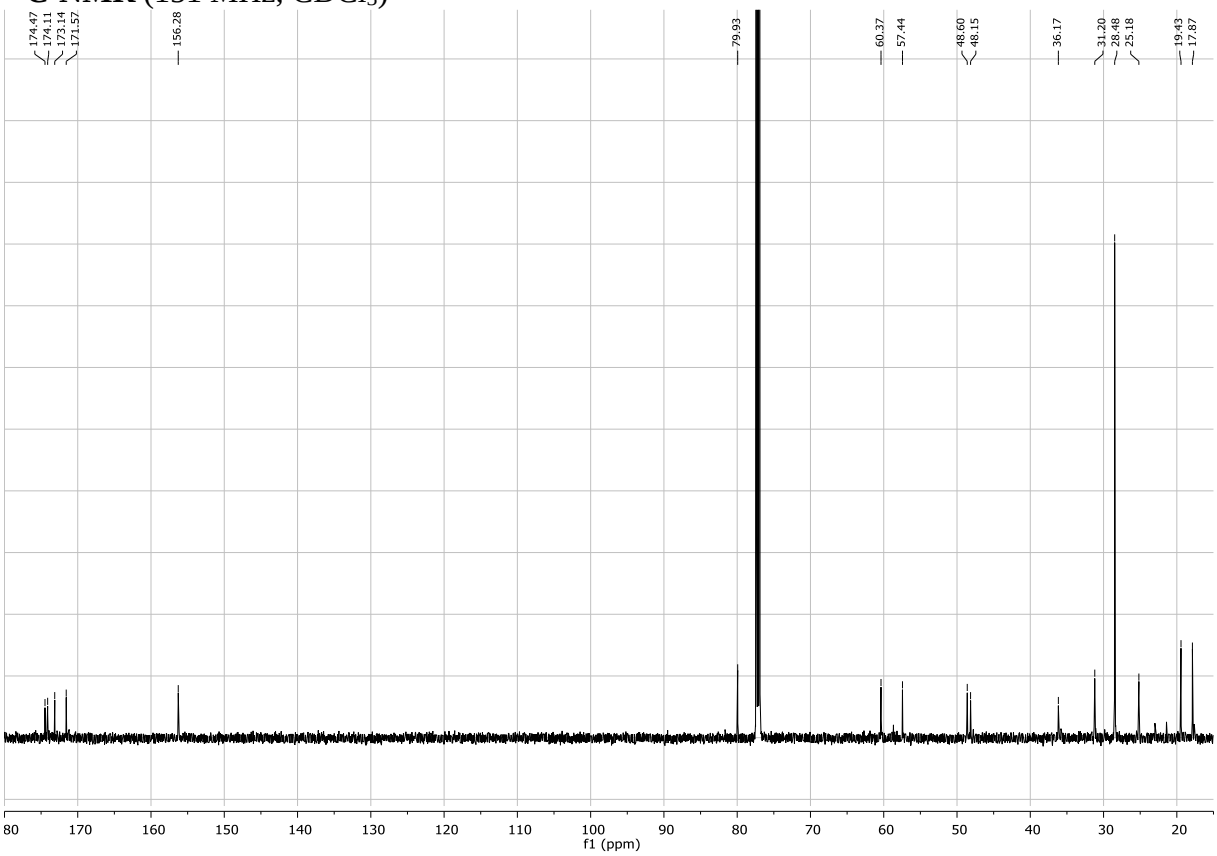


Boc-Val-Pro-Asp(OH)-OH 102:

^{1}H-NMR (200 MHz, $CDCl_3$)

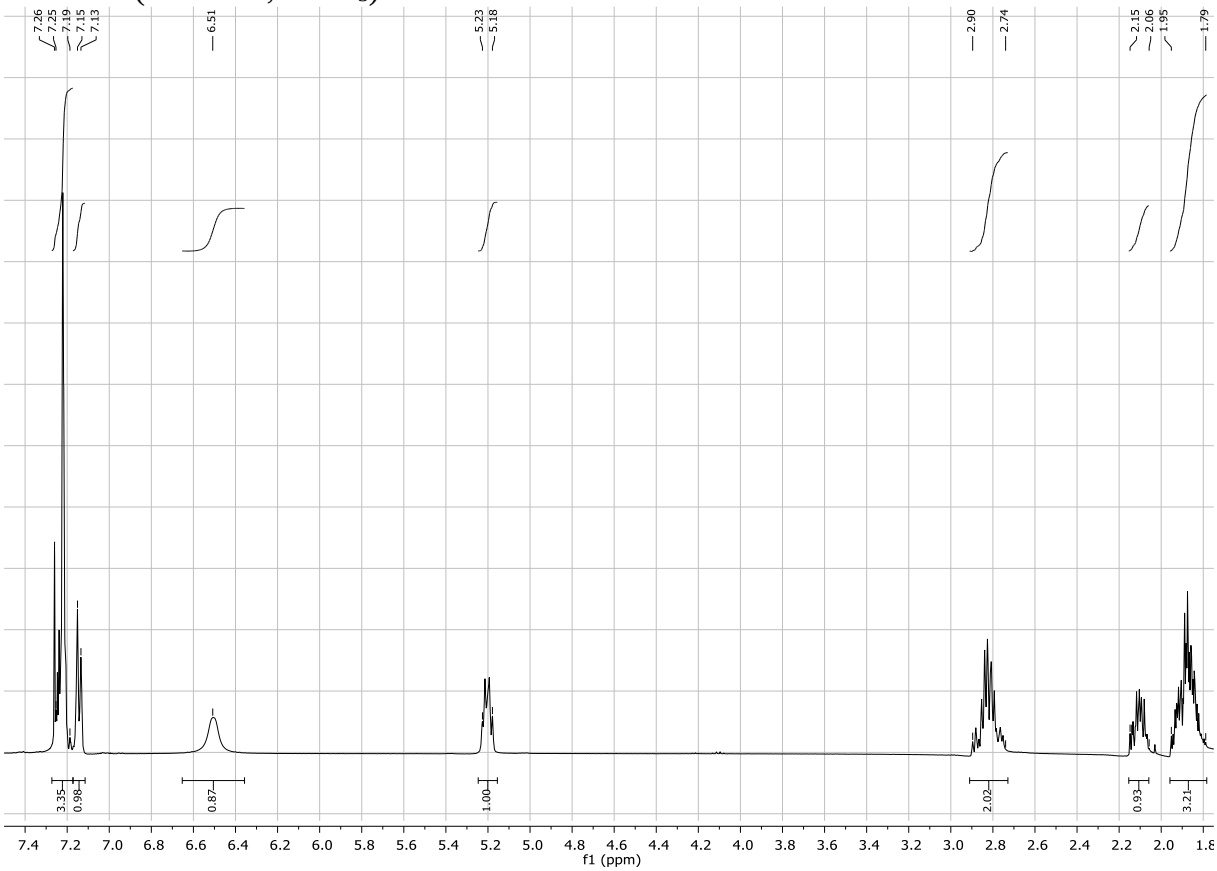


^{13}C-NMR (151 MHz, $CDCl_3$)

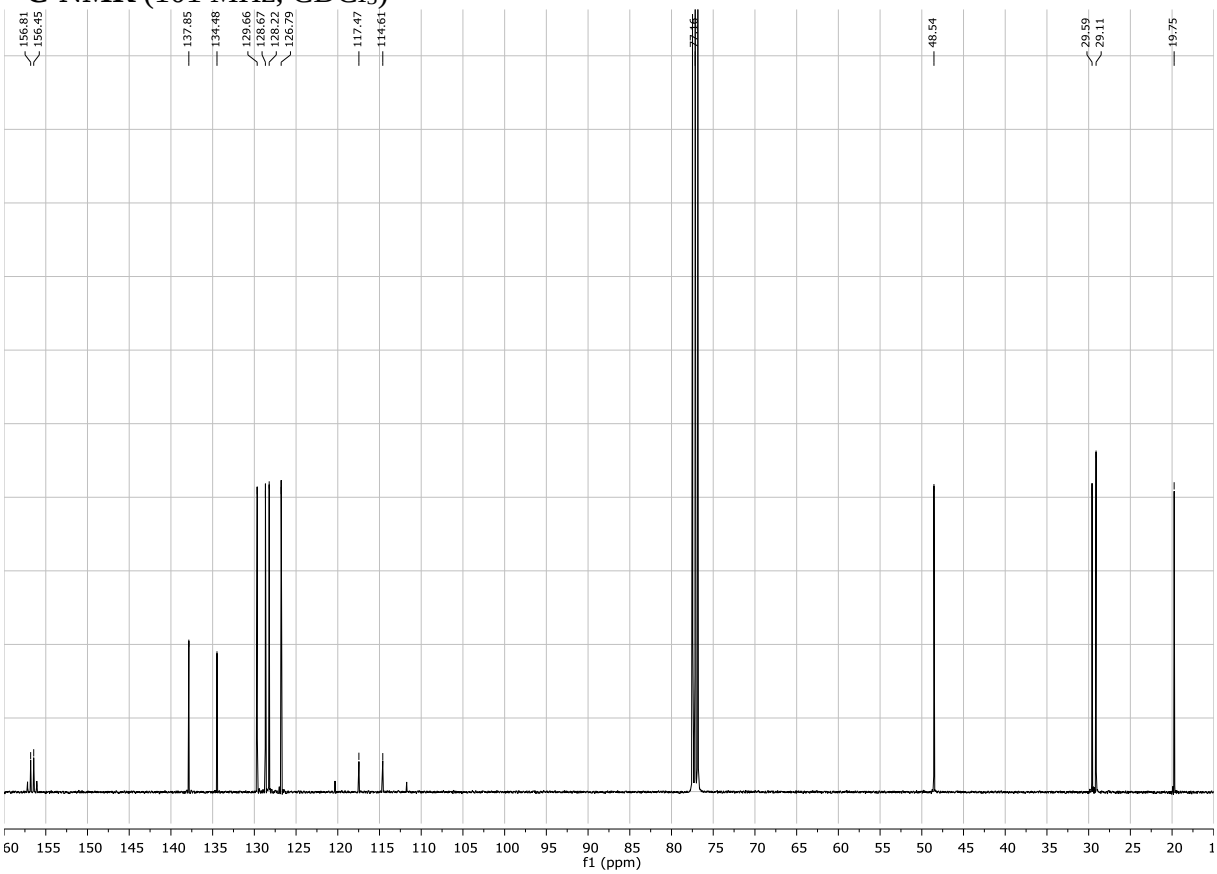


2,2,2-Trifluoro-1-(1,2,3,4-tetrahydronaphth-1-ylamino)-1-ethanone 114:

^{1}H-NMR (400 MHz, $CDCl_3$)

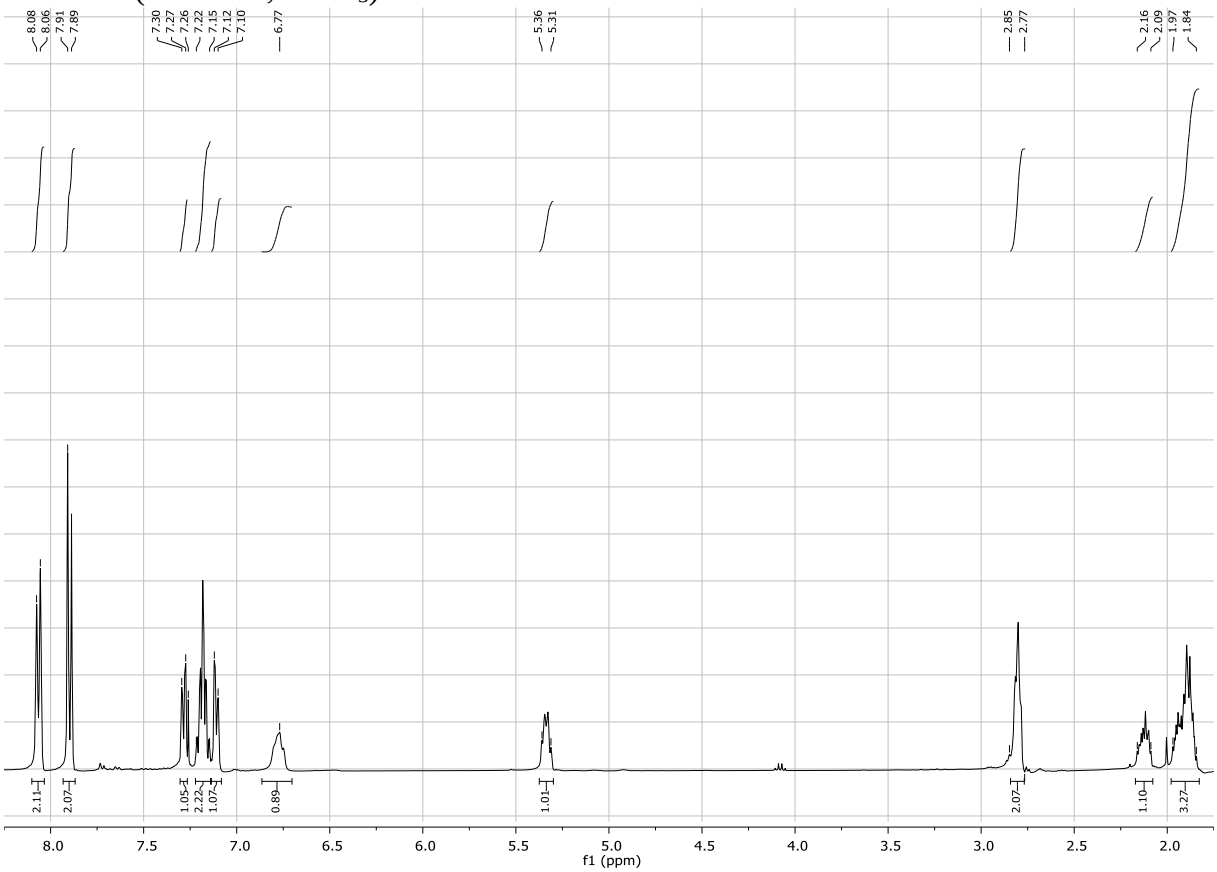


^{13}C-NMR (101 MHz, $CDCl_3$)

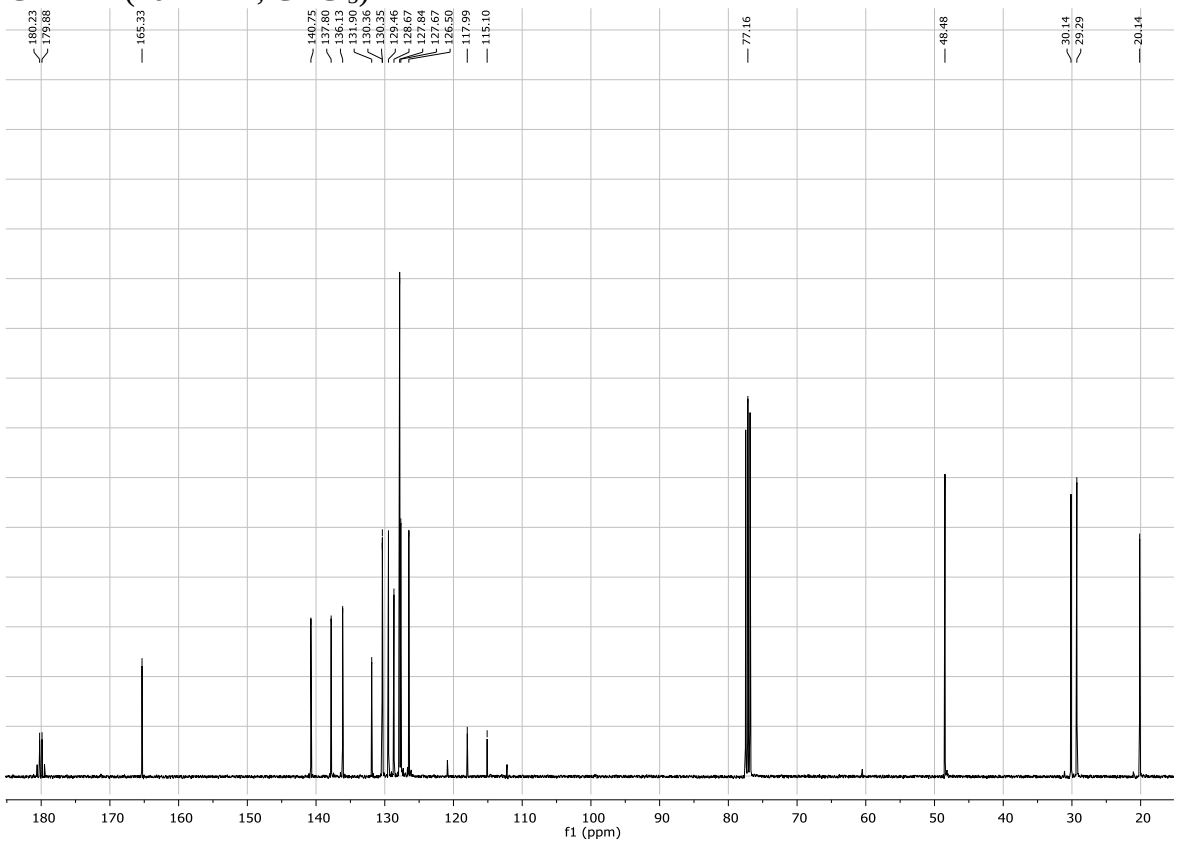


2,2,2-Trifluoro-1-(*p*-((1,2,3,4-tetrahydronaphth-1-ylamino)carbonyl)phenyl)-1-ethanone 115:

^{1}H-NMR (400 MHz, $CDCl_3$)

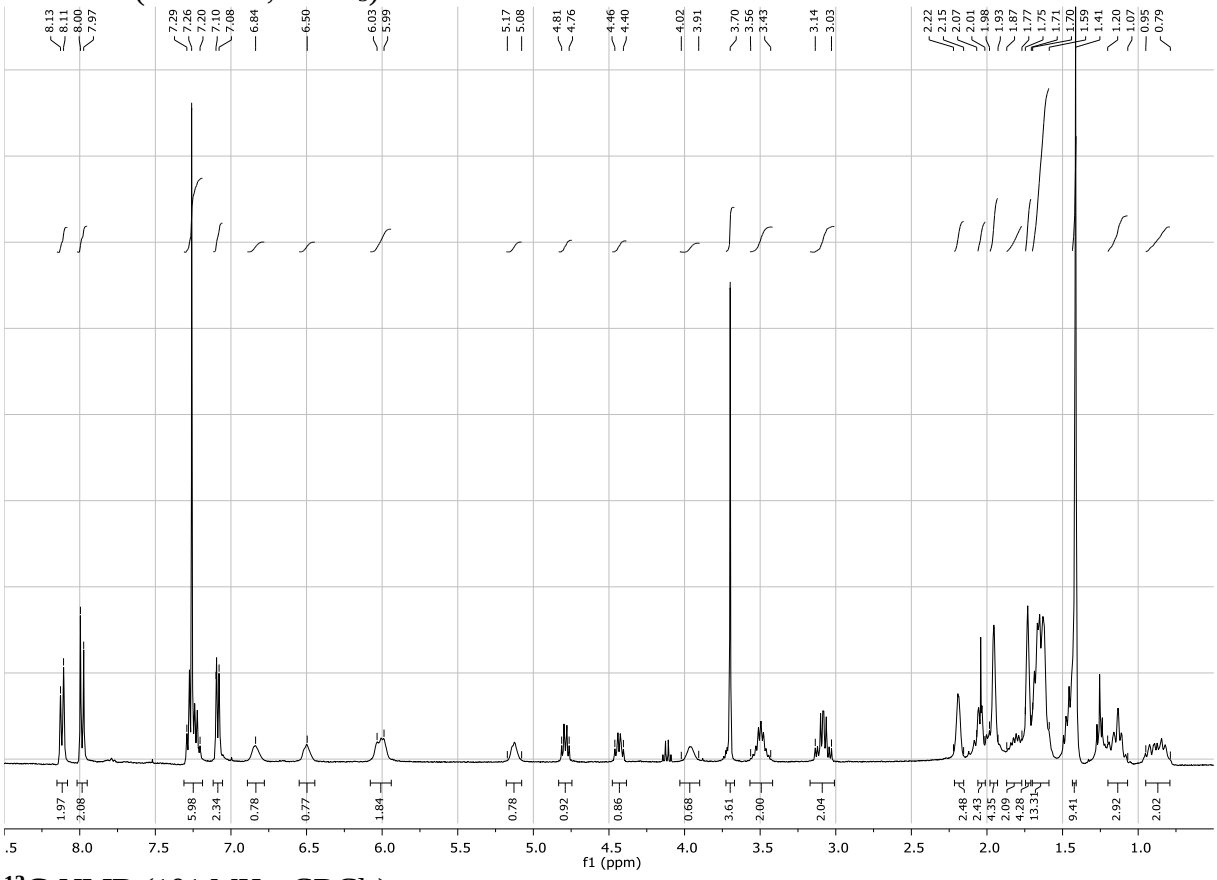


^{13}C-NMR (101 MHz, $CDCl_3$)

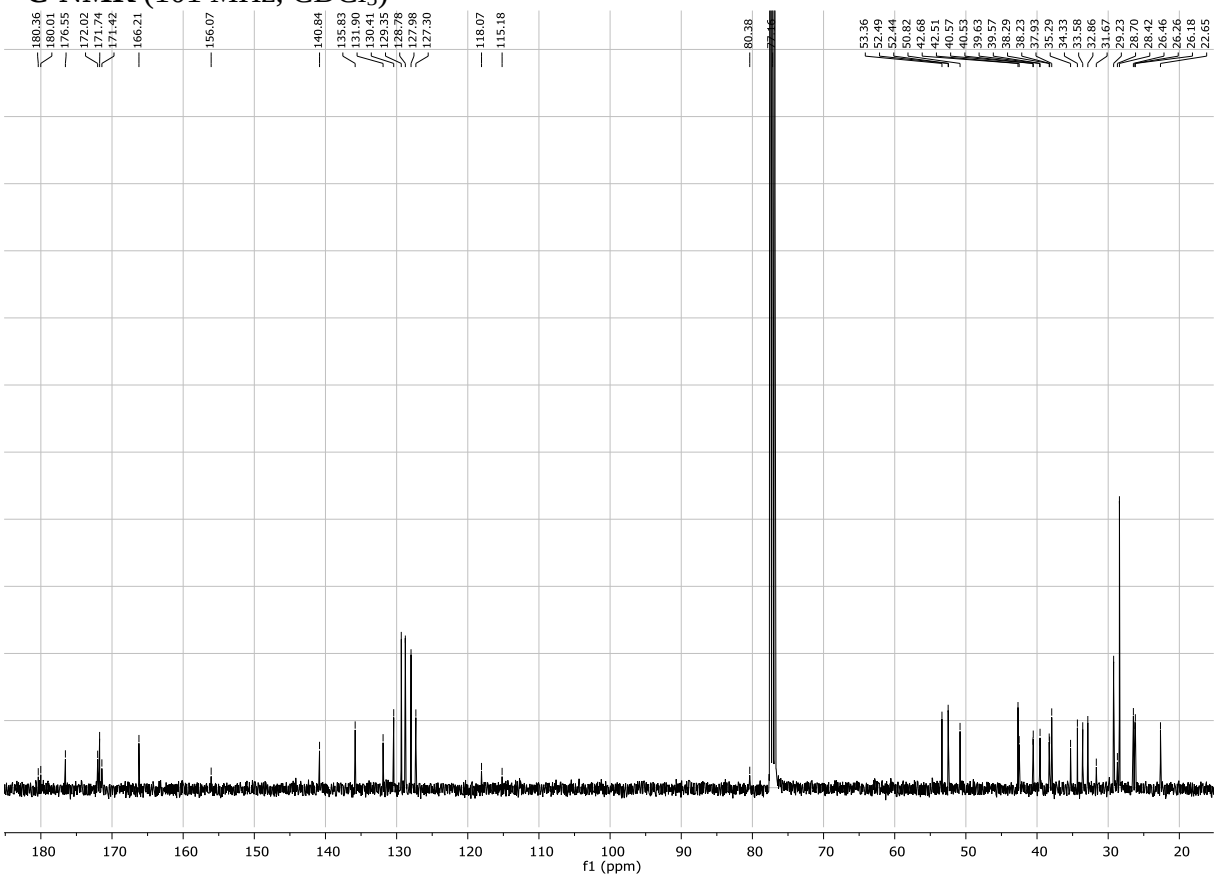


Boc-Lys(CM)-AdGly-Cha-Phe-OMe 122:

^{1}H-NMR (400 MHz, $CDCl_3$)

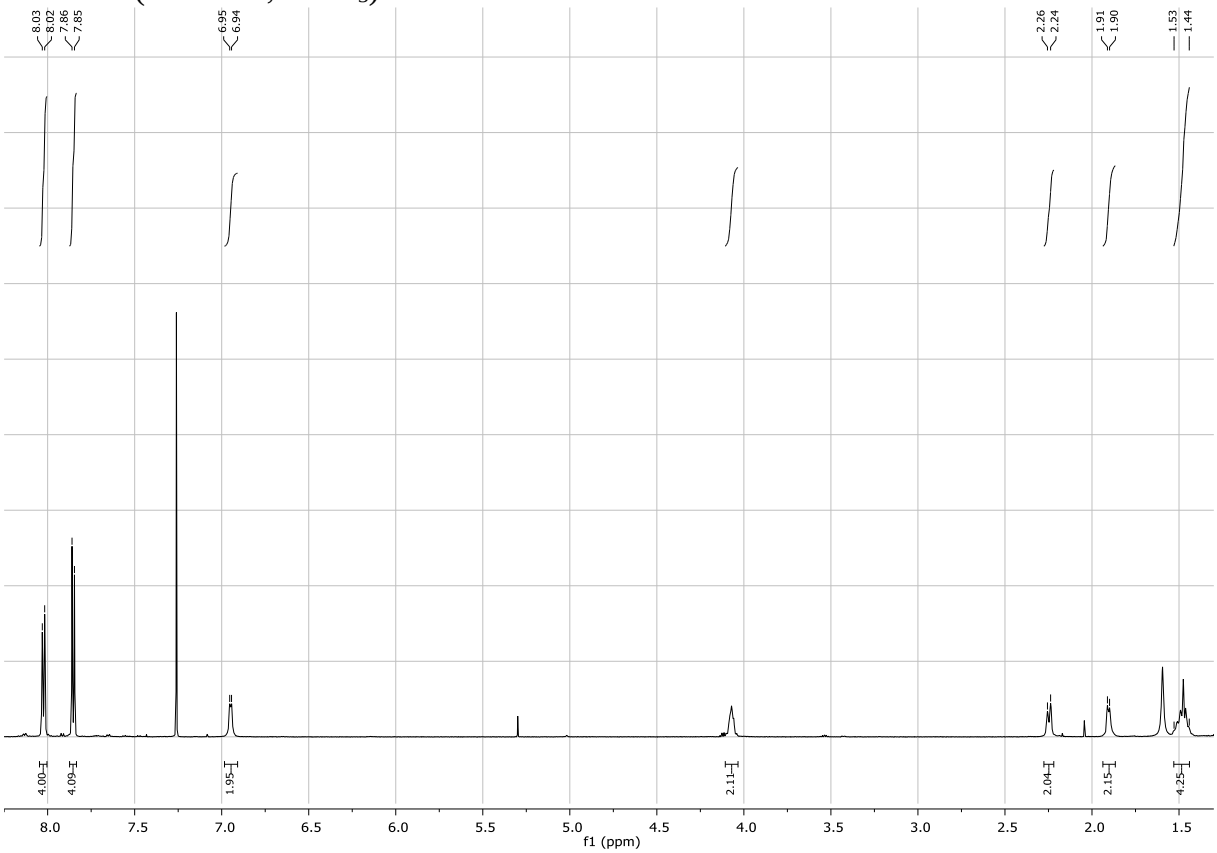


^{13}C-NMR (101 MHz, $CDCl_3$)

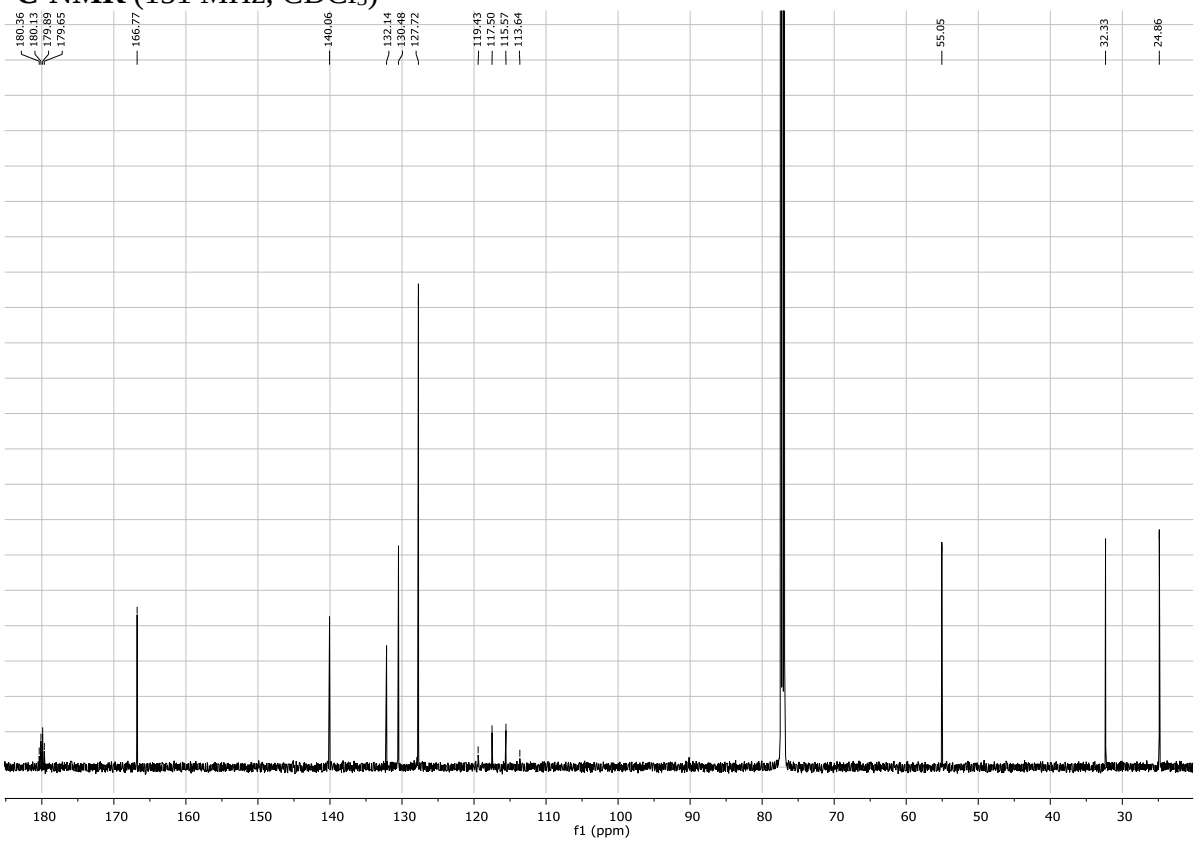


1-(*p*-(((1*S*,2*S*)-2-(*p*-(2,2,2-Trifluoroacetyl)benzoylamino)cyclohexylamino) carbonyl)phenyl)-2,2,2-trifluoro-1-ethanone 128:

^{1}H-NMR (600 MHz, $CDCl_3$)

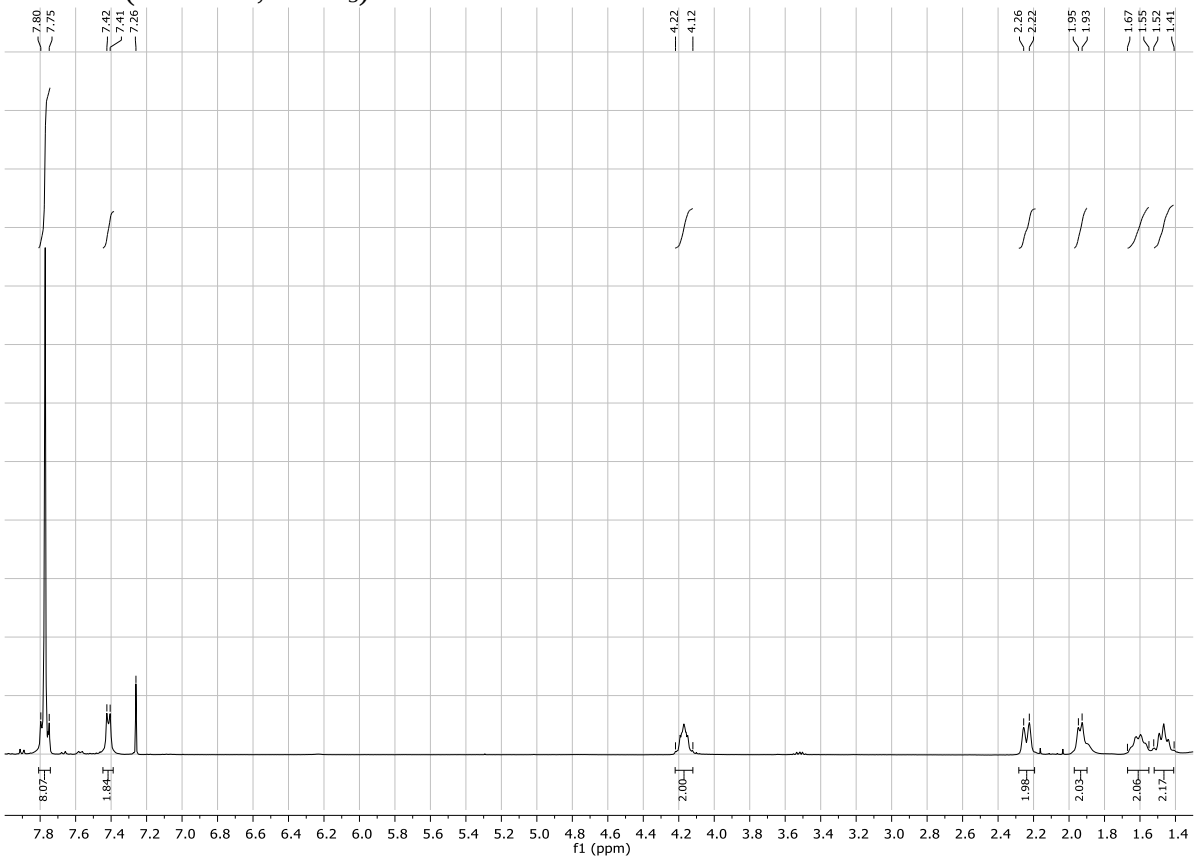


^{13}C-NMR (151 MHz, $CDCl_3$)

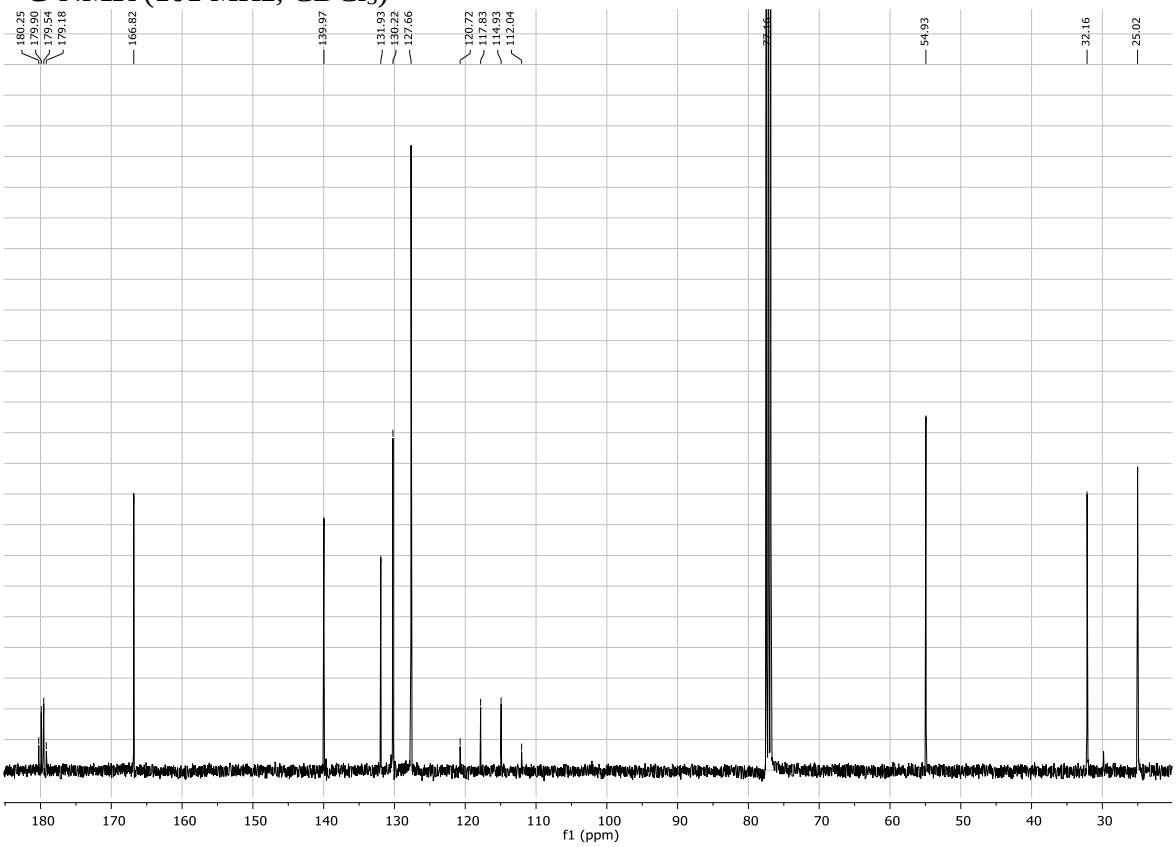


1-(*p*-(((1*R*,2*R*)-2-(*p*-(2,2,2-Trifluoroacetyl)benzoylamino)cyclohexylamino)carbonyl) phenyl)-2,2,2-trifluoro-1-ethanone 129:

^{1}H-NMR (400 MHz, $CDCl_3$)

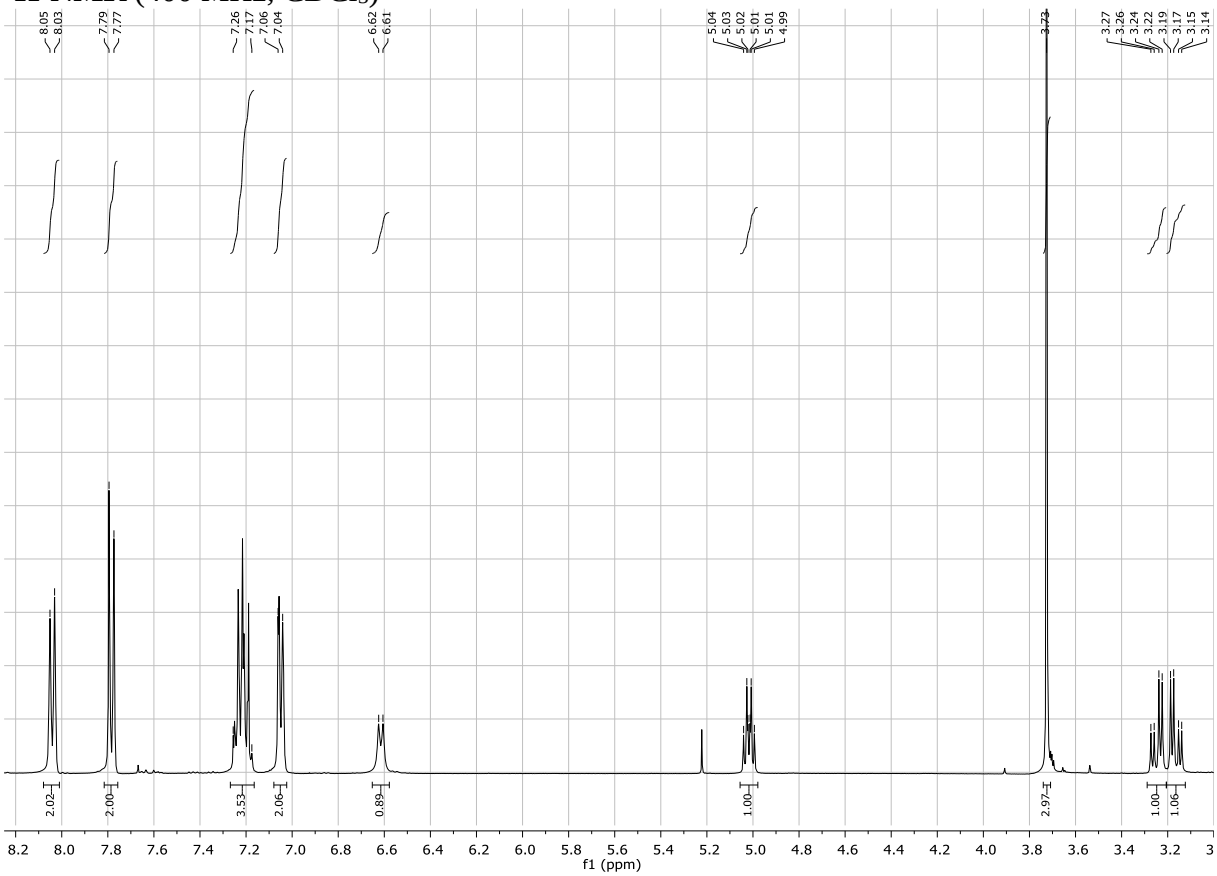


^{13}C-NMR (101 MHz, $CDCl_3$)

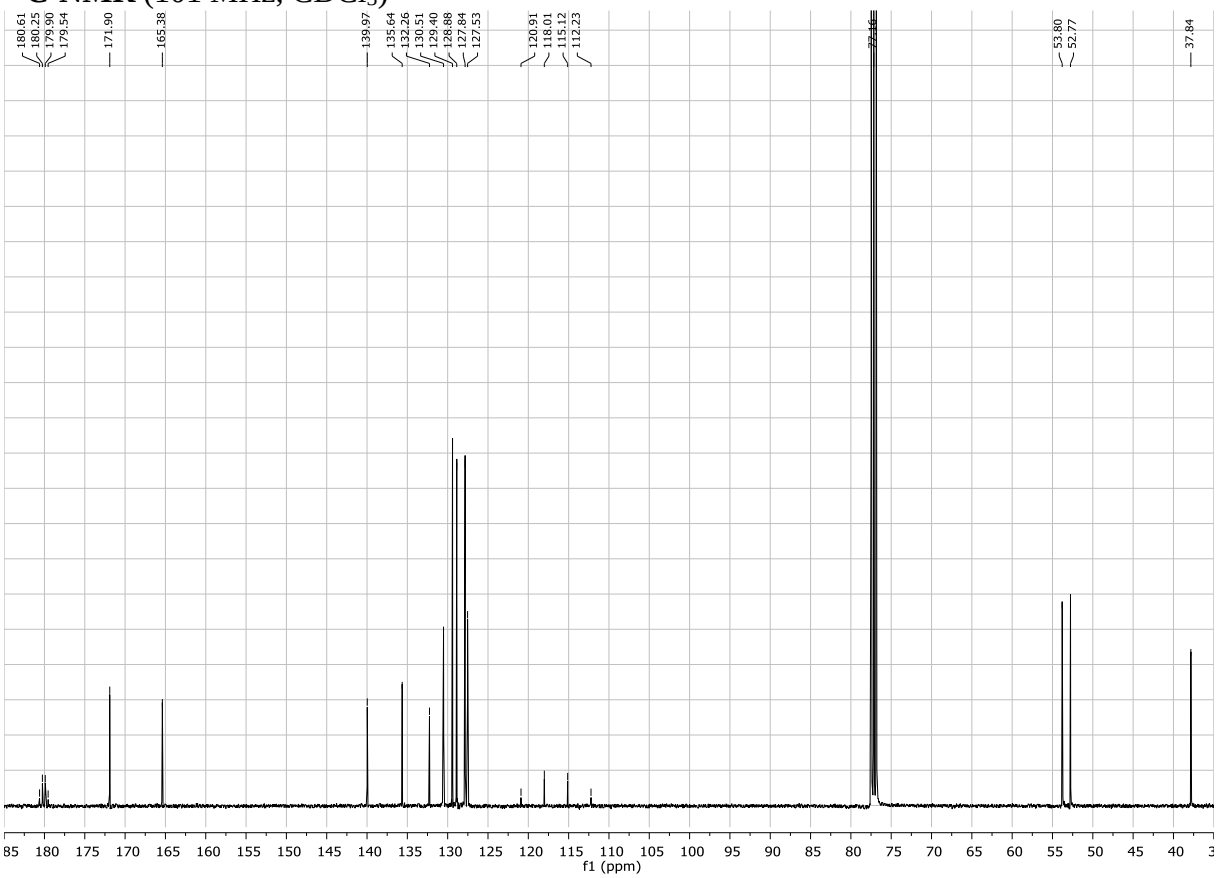


Methyl (2*S*)-3-phenyl-2-(*p*-(2,2,2-trifluoroacetyl)benzoylamino)propionate 131:

^{1}H-NMR (400 MHz, $CDCl_3$)

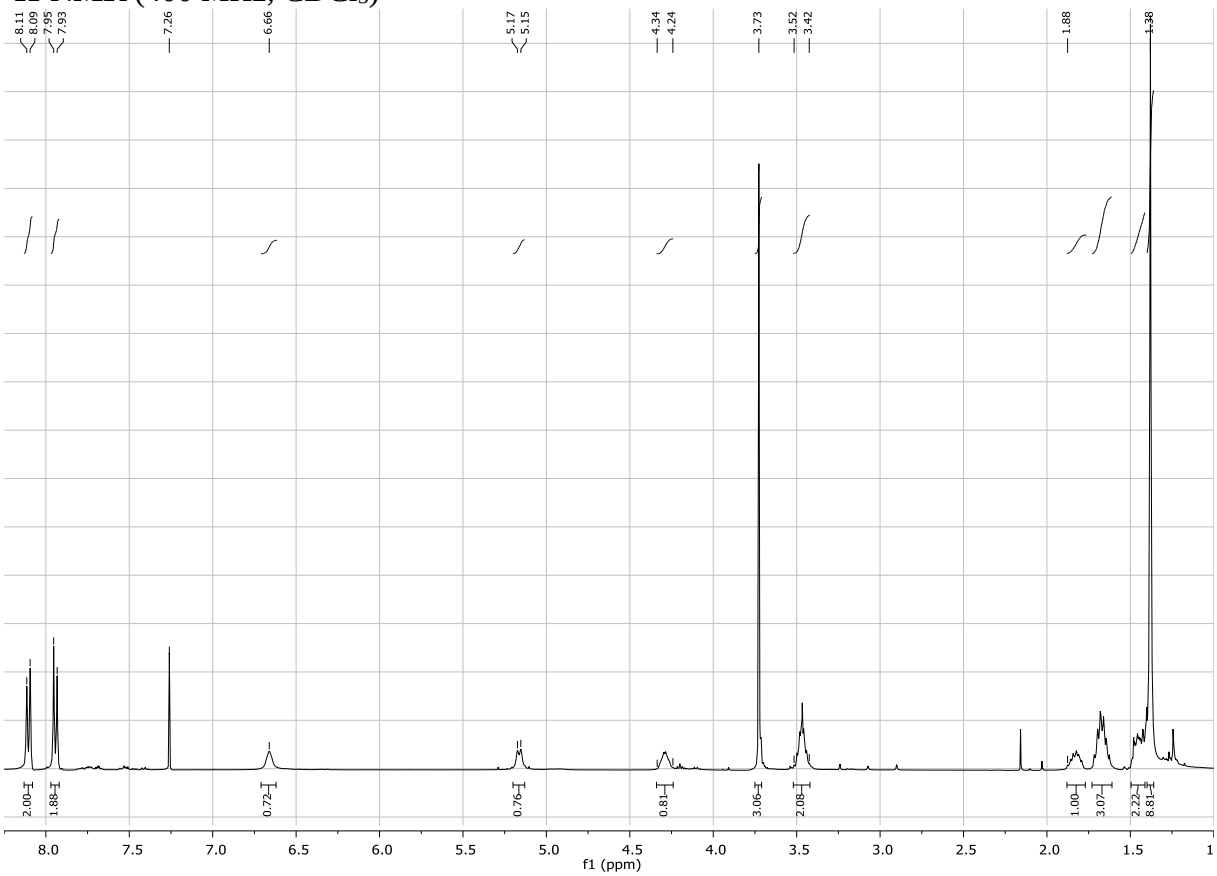


^{13}C-NMR (101 MHz, $CDCl_3$)

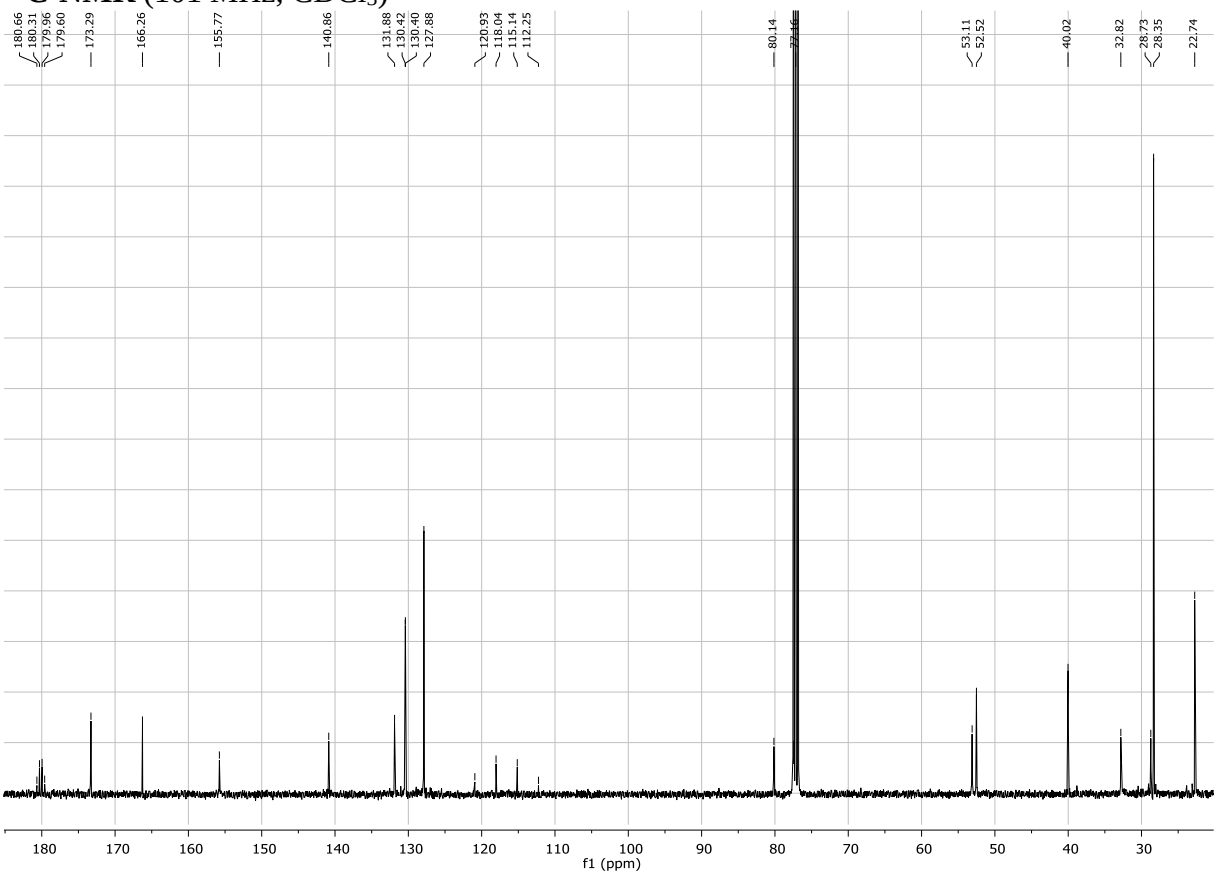


Boc-Lys(CM)-OMe 137:

^{1}H-NMR (400 MHz, $CDCl_3$)

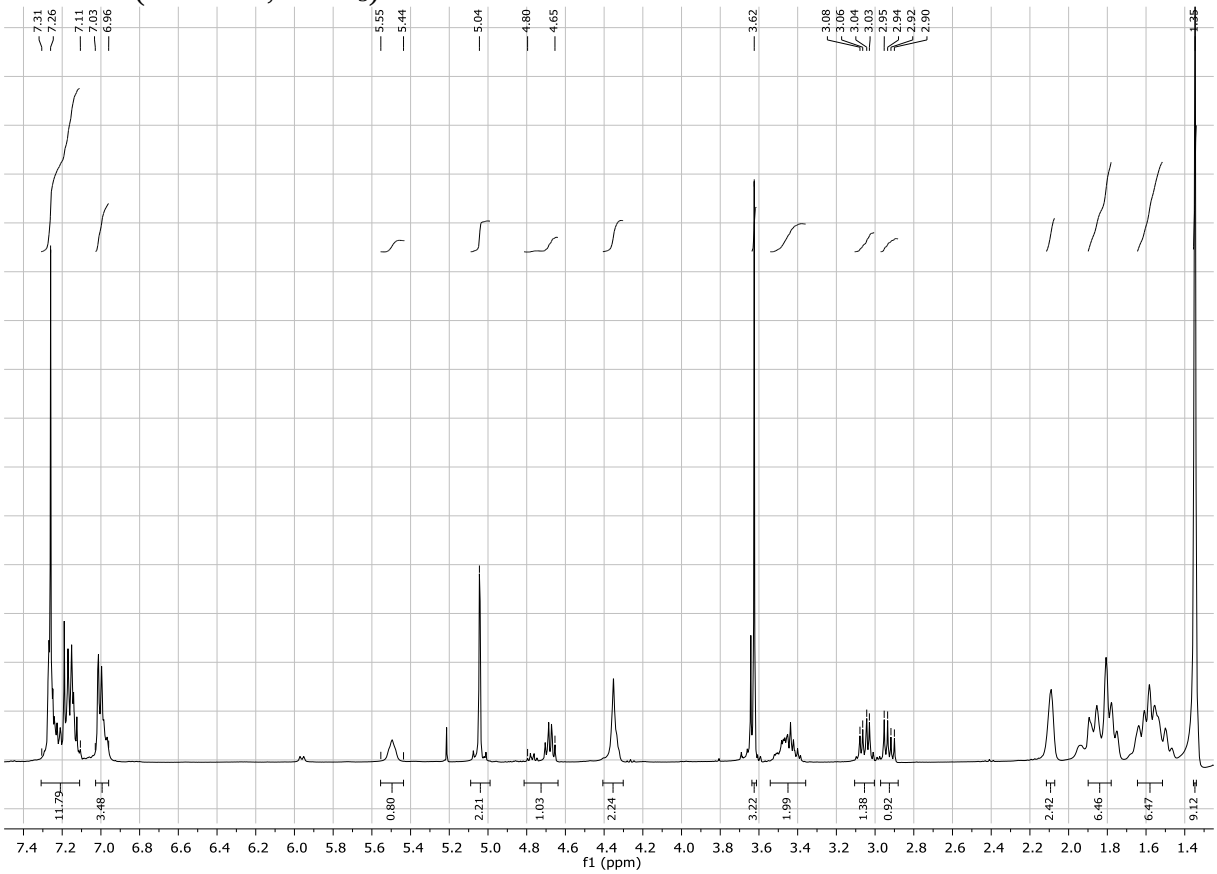


^{13}C-NMR (101 MHz, $CDCl_3$)

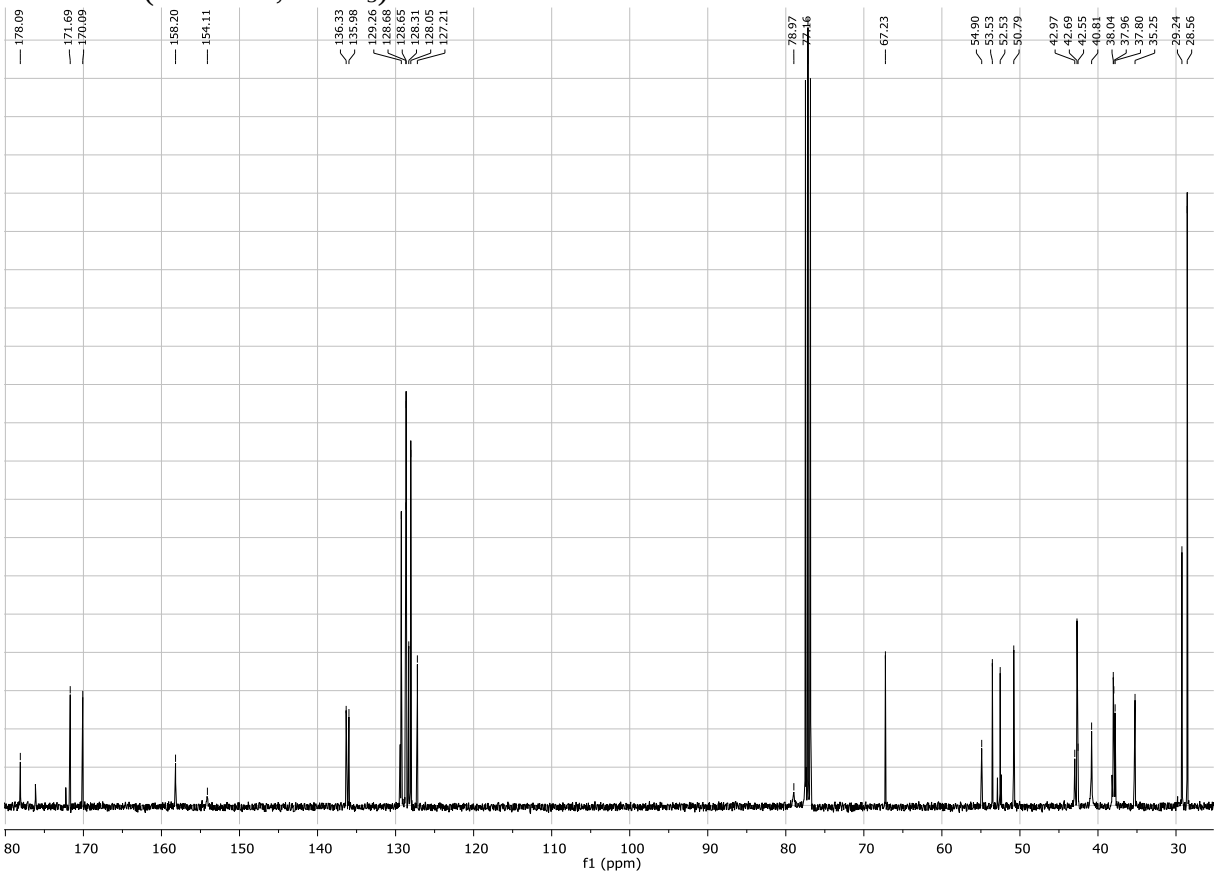


Boc-AdGly-Dap(Cbz)-Phe-OMe 142:

^{1}H-NMR (400 MHz, $CDCl_3$)

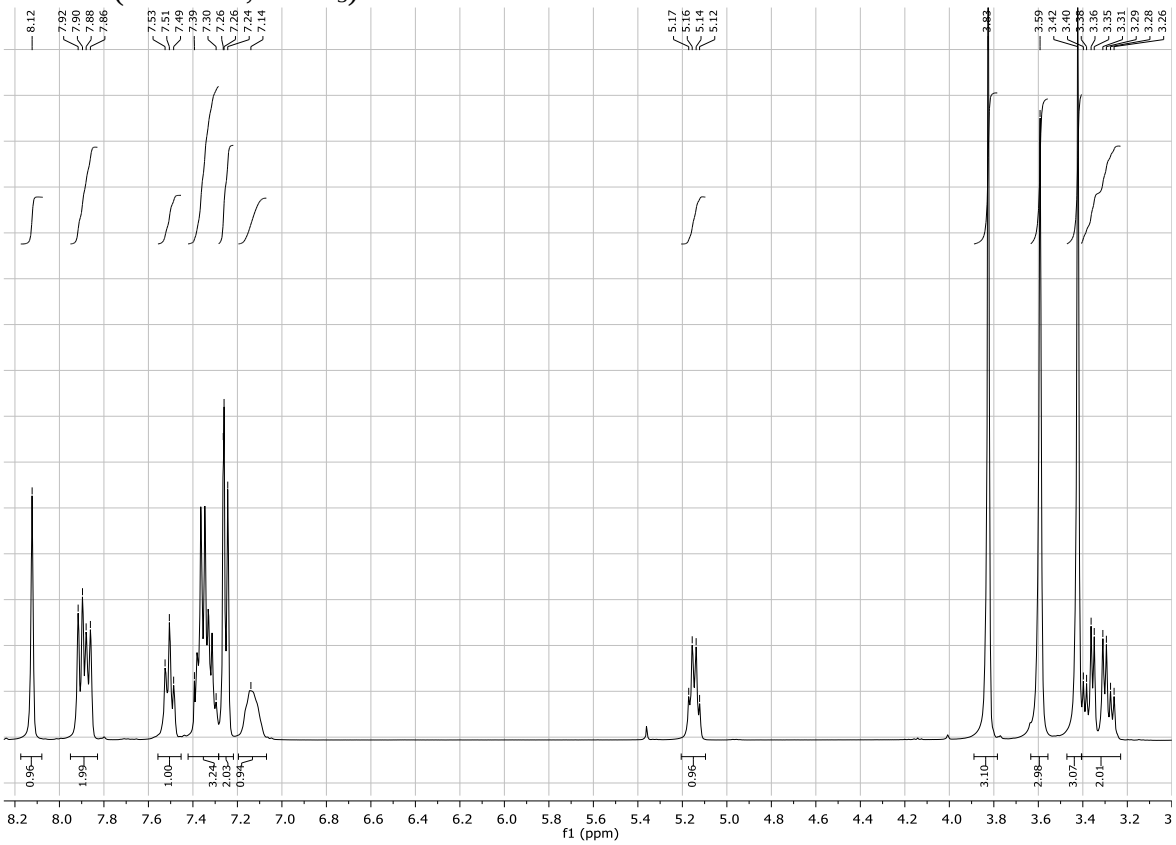


^{13}C-NMR (101 MHz, $CDCl_3$)

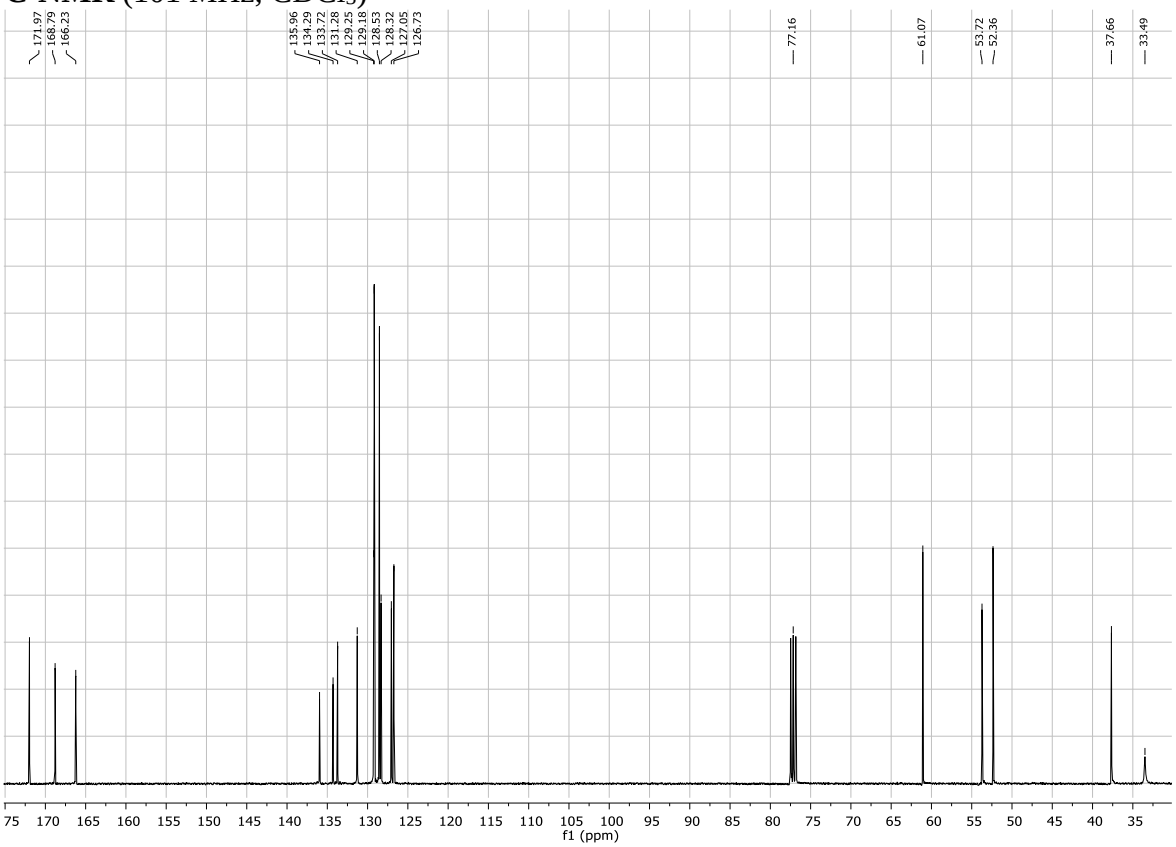


Methyl (2*S*)-2-(*m*-((*N*-methylmethoxyamino)carbonyl)benzoylamino)-3-phenyl-propionate 149:

^{1}H-NMR (400 MHz, $CDCl_3$)

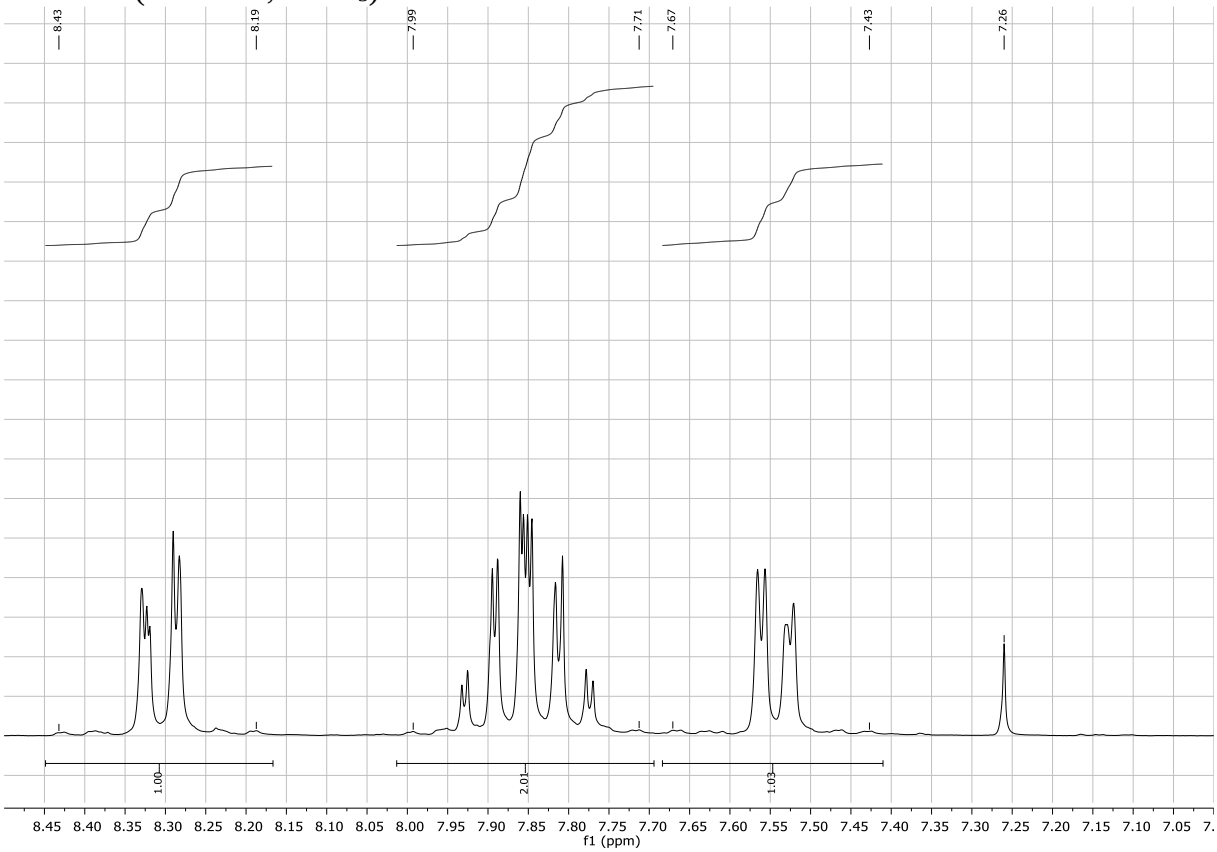


^{13}C-NMR (101 MHz, $CDCl_3$)

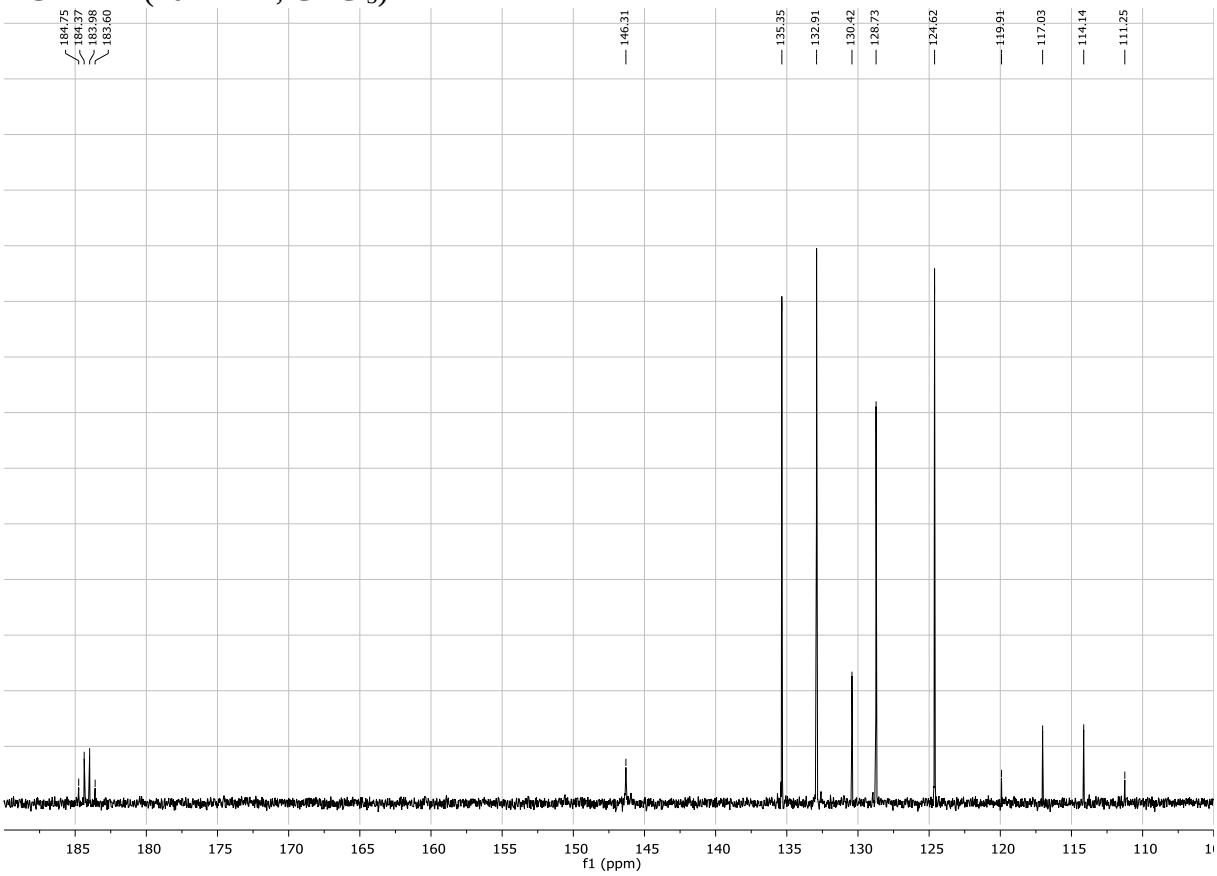


2,2,2-Trifluoro-1-(*o*-nitrophenyl)-1-ethanone *ortho*-154:

^{1}H-NMR (200 MHz, $CDCl_3$)

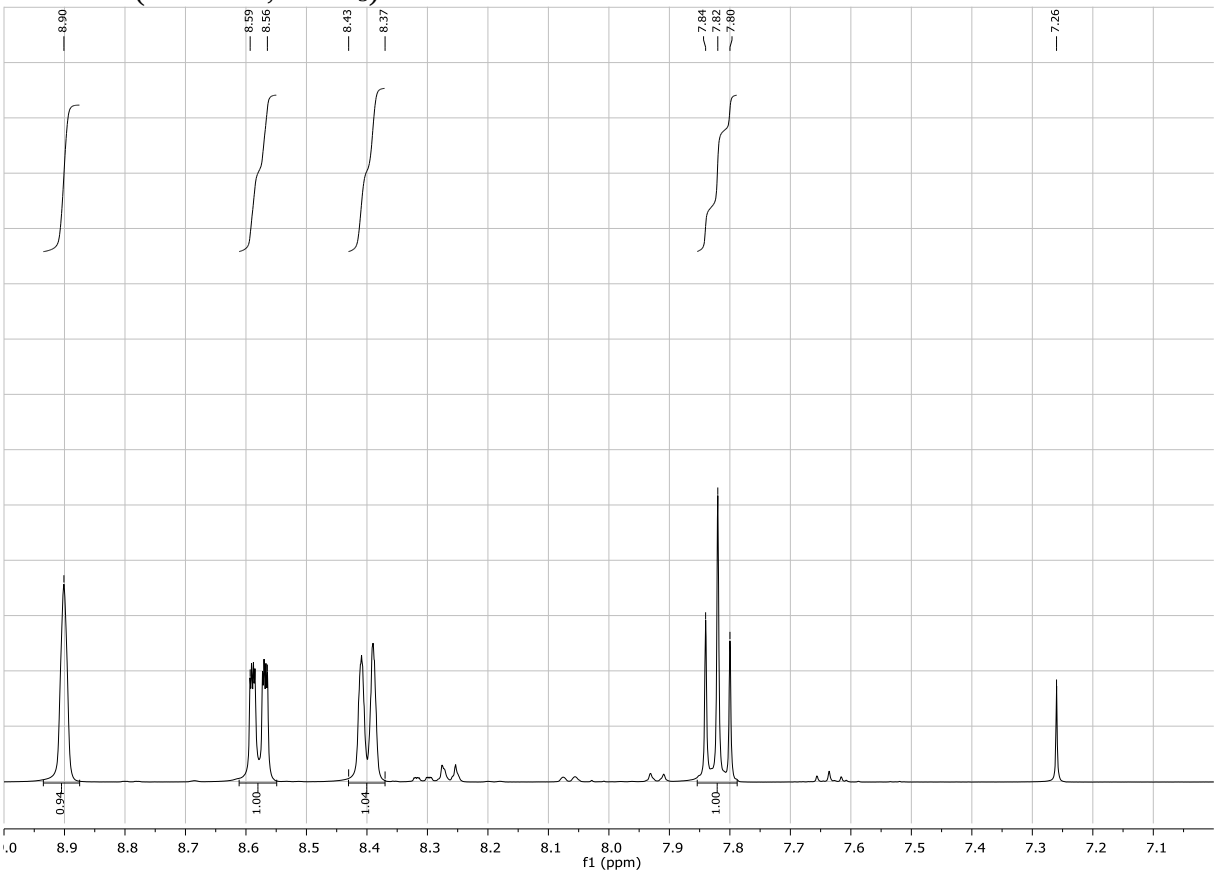


^{13}C-NMR (101 MHz, $CDCl_3$)

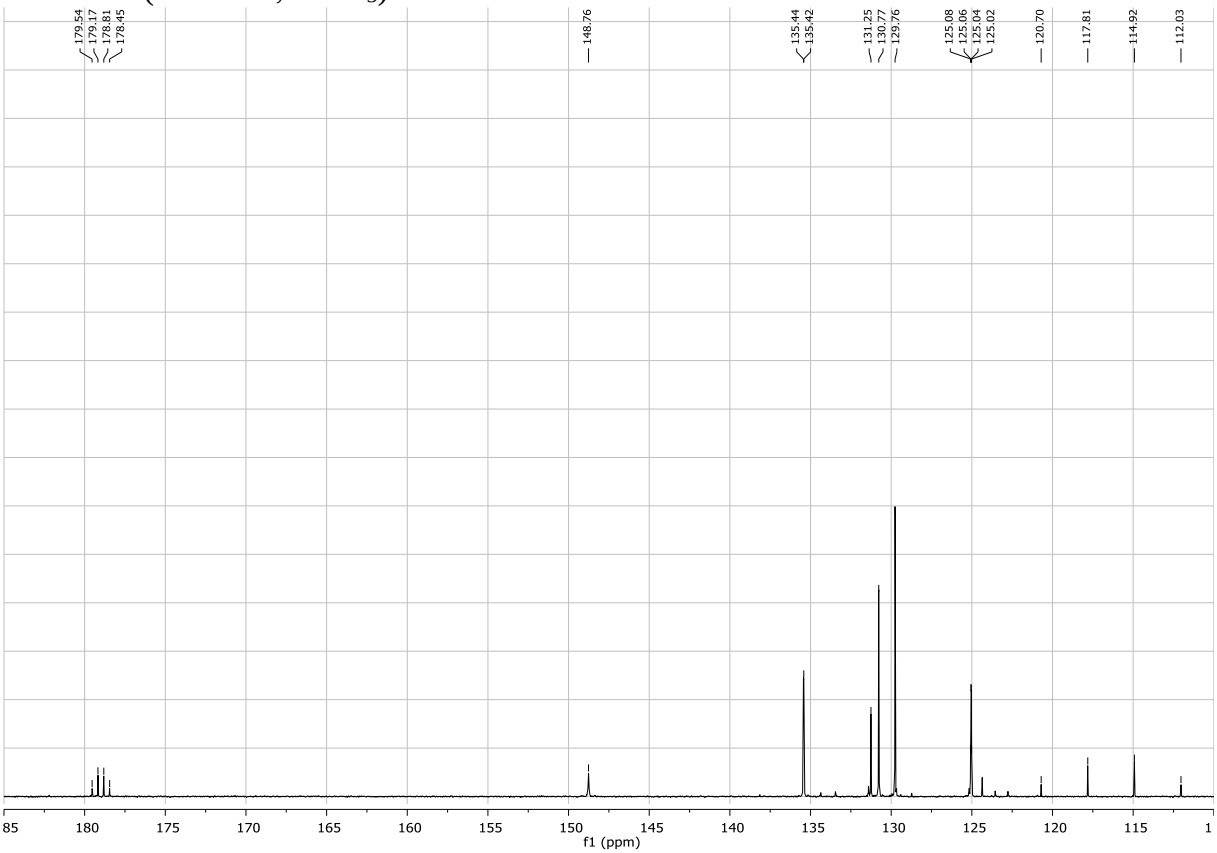


2,2,2-Trifluoro-1-(*m*-nitrophenyl)-1-ethanone *meta*-154:

^{1}H-NMR (400 MHz, $CDCl_3$)

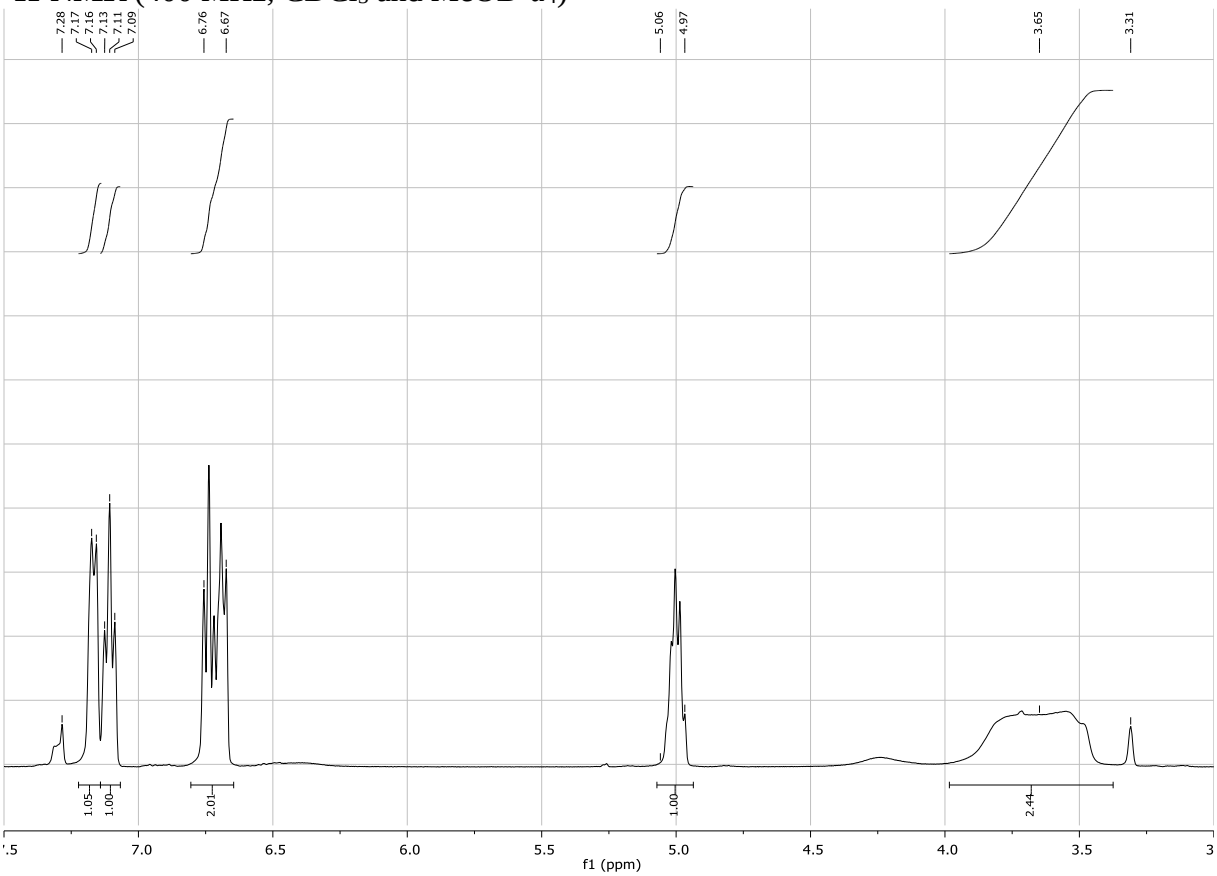


^{13}C-NMR (101 MHz, $CDCl_3$)

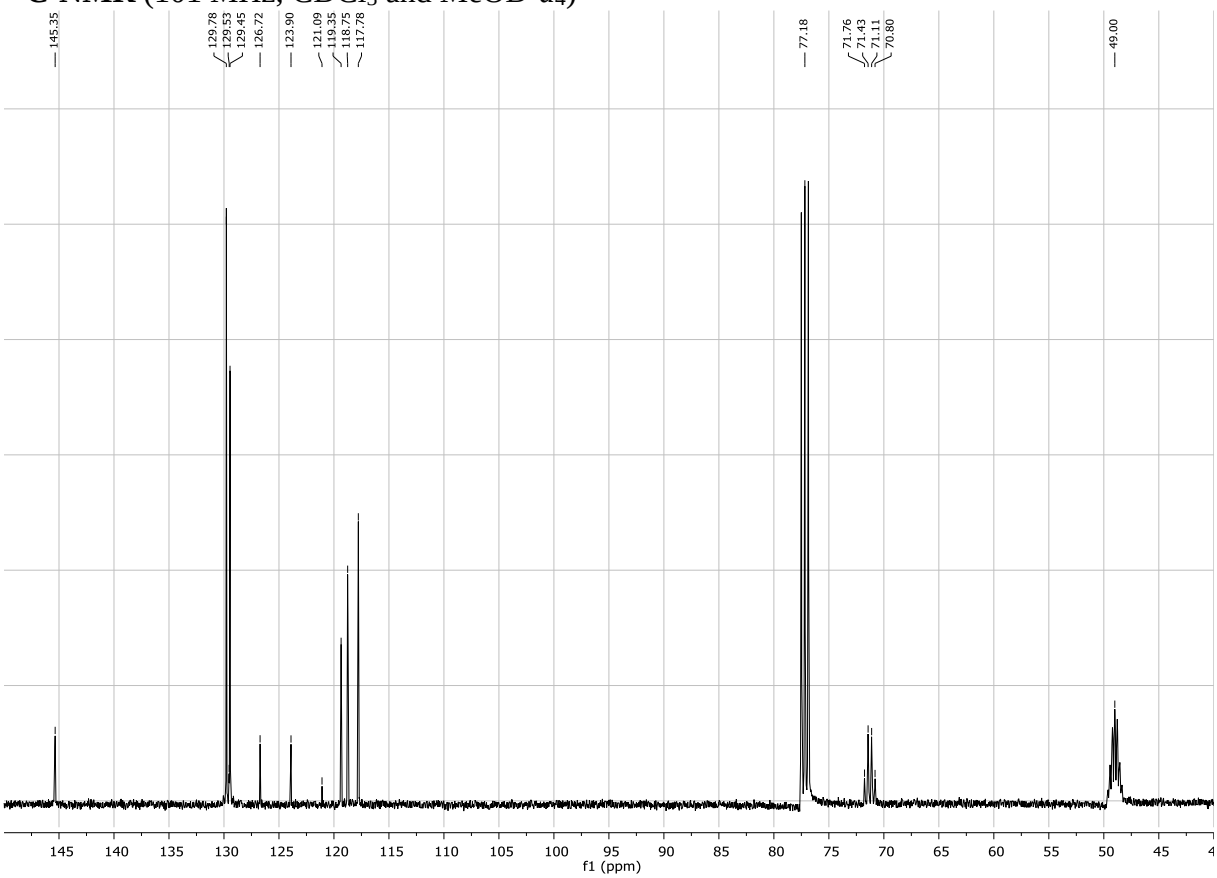


1-(*o*-Aminophenyl)-2,2,2-trifluoro-1-ethanol *ortho*-155:

^{1}H-NMR (400 MHz, $CDCl_3$ and MeOD-d_4)

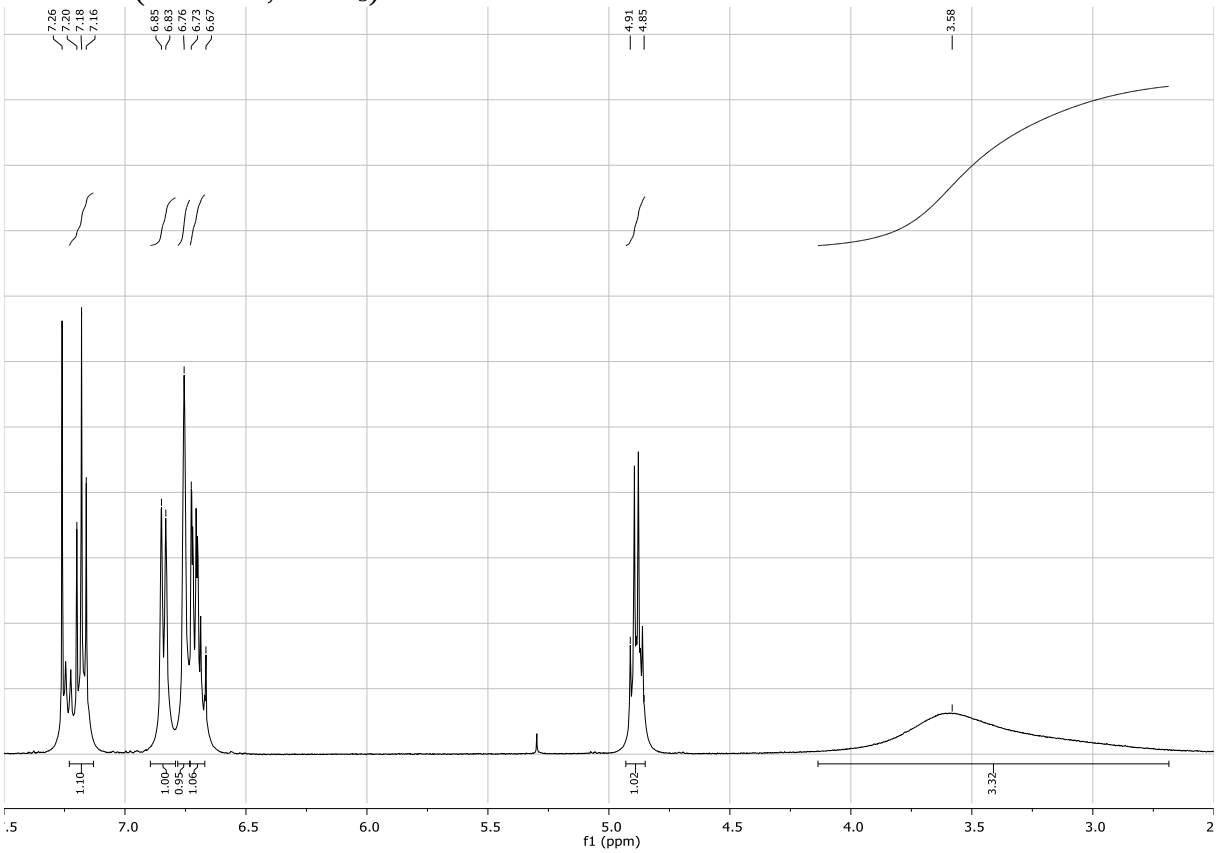


^{13}C-NMR (101 MHz, $CDCl_3$ and MeOD-d_4)

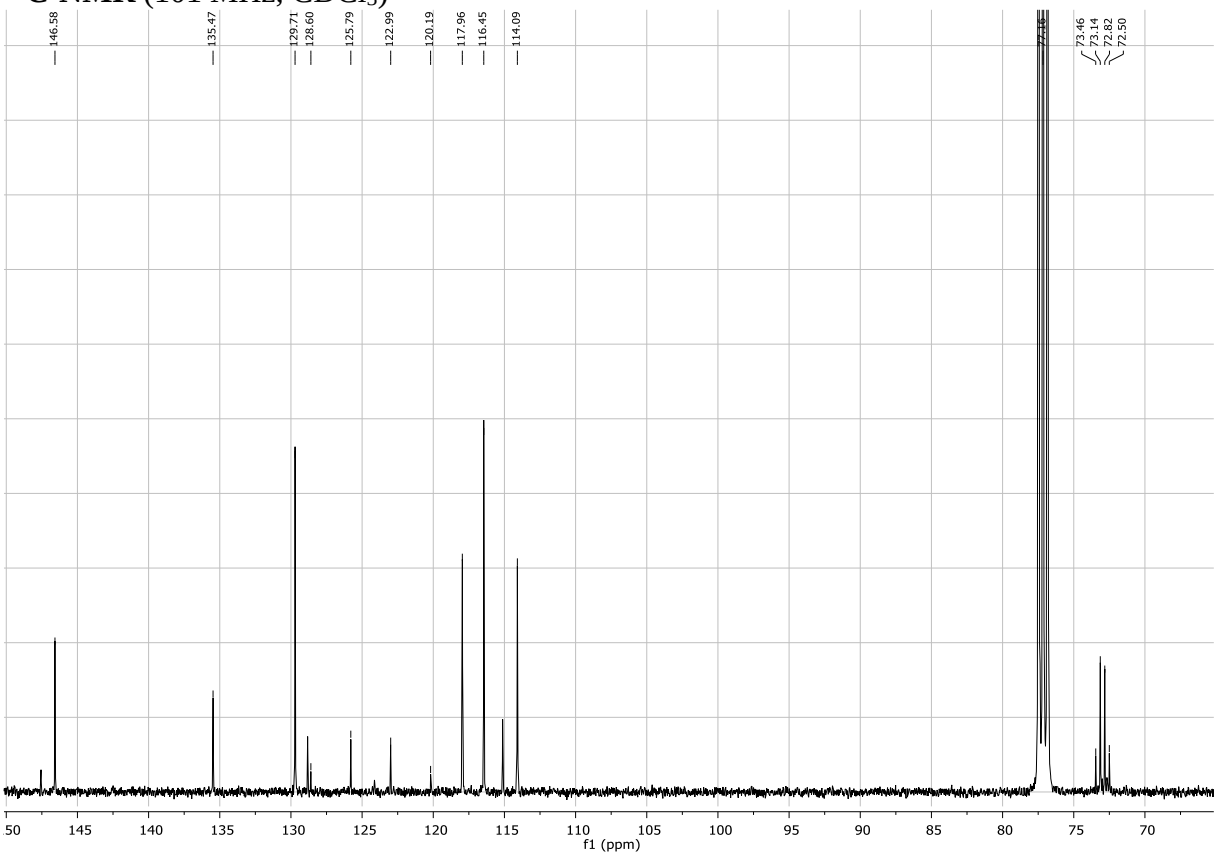


1-(*m*-Aminophenyl)-2,2,2-trifluoro-1-ethanol *meta*-155:

^{1}H-NMR (400 MHz, $CDCl_3$)

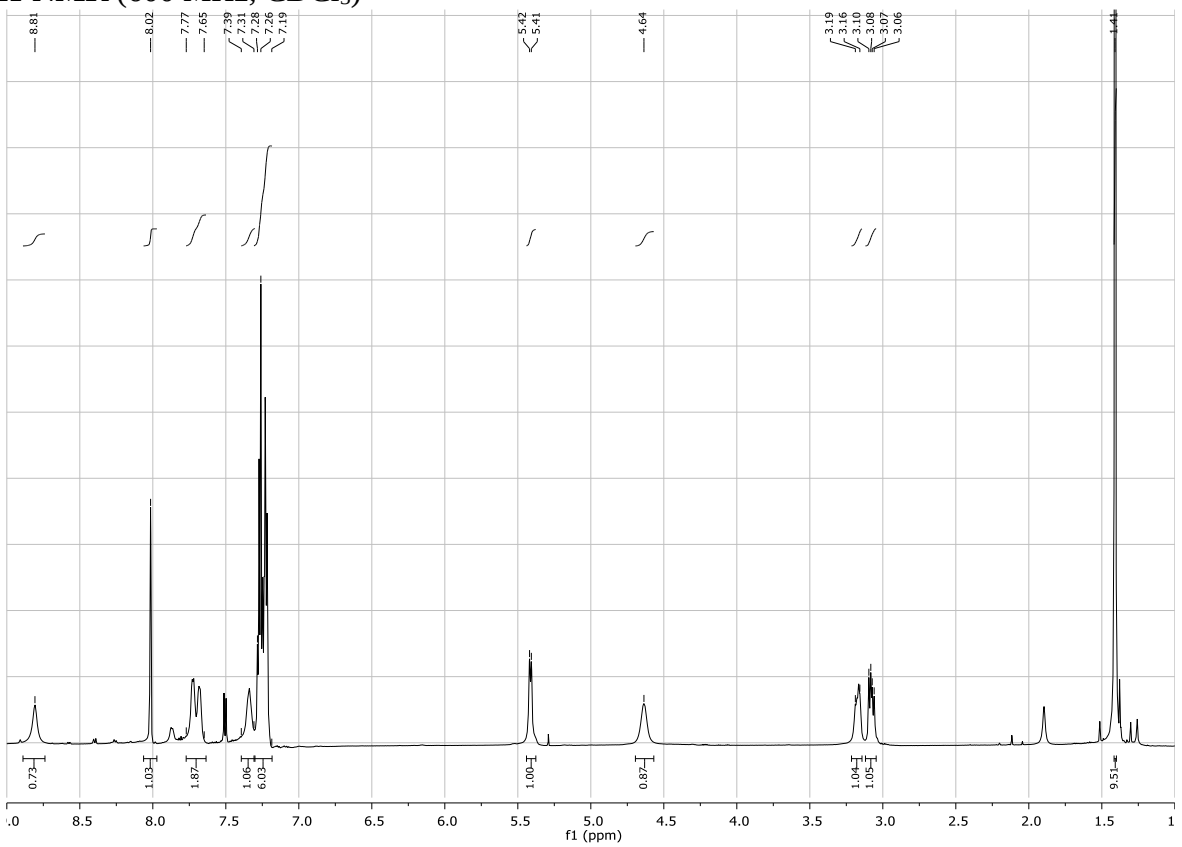


^{13}C-NMR (101 MHz, $CDCl_3$)

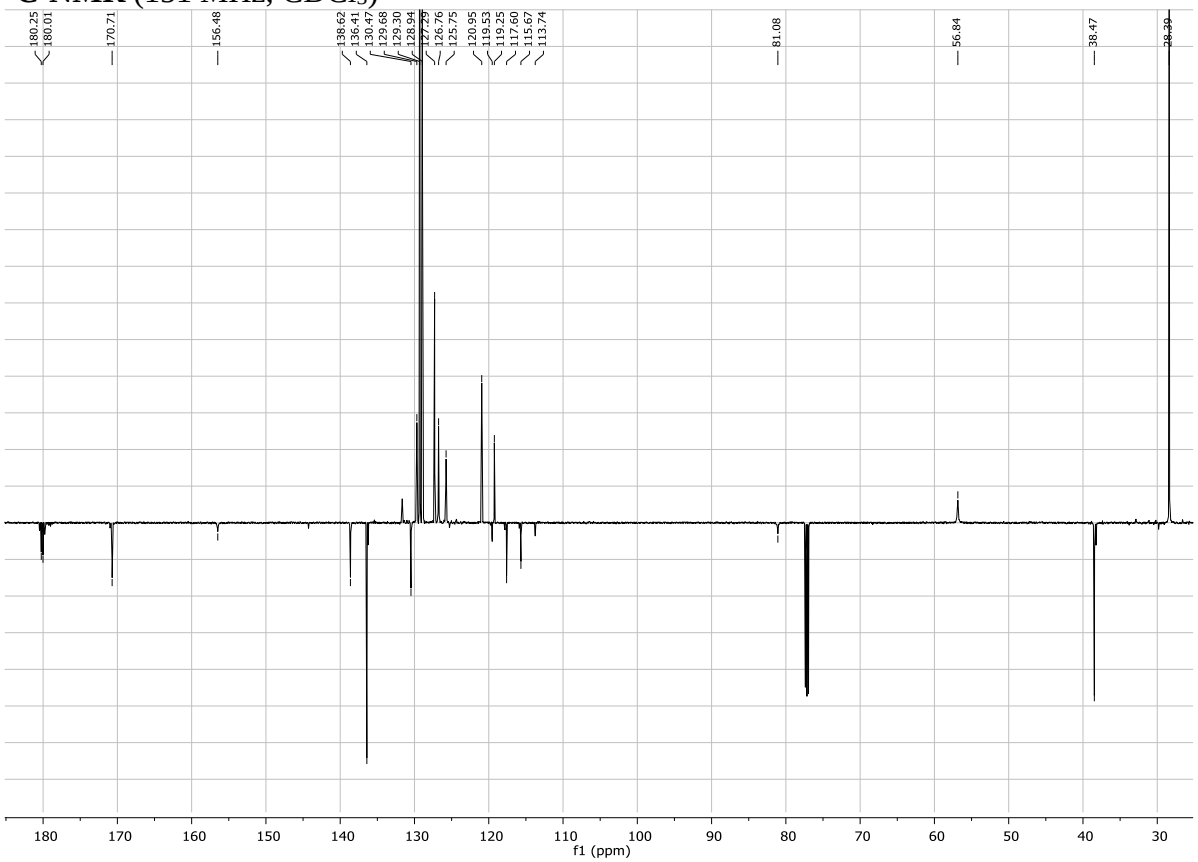


(1*S*)-1-Benzyl-2-oxo-2-(*m*-(2,2,2-trifluoroacetyl)phenylamino)ethylamino 2,2-dimethylpropionate *meta*-161:

^{1}H-NMR (600 MHz, $CDCl_3$)

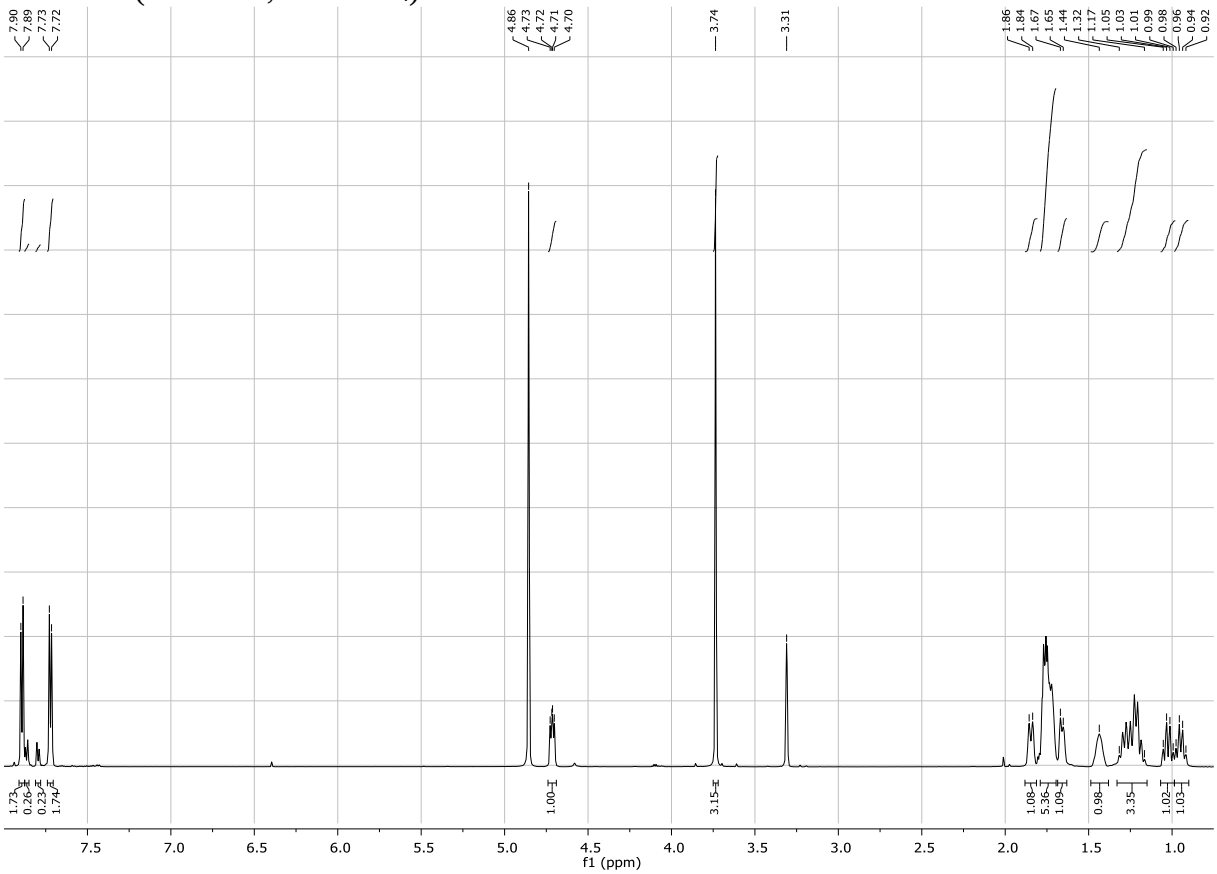


^{13}C-NMR (151 MHz, $CDCl_3$)

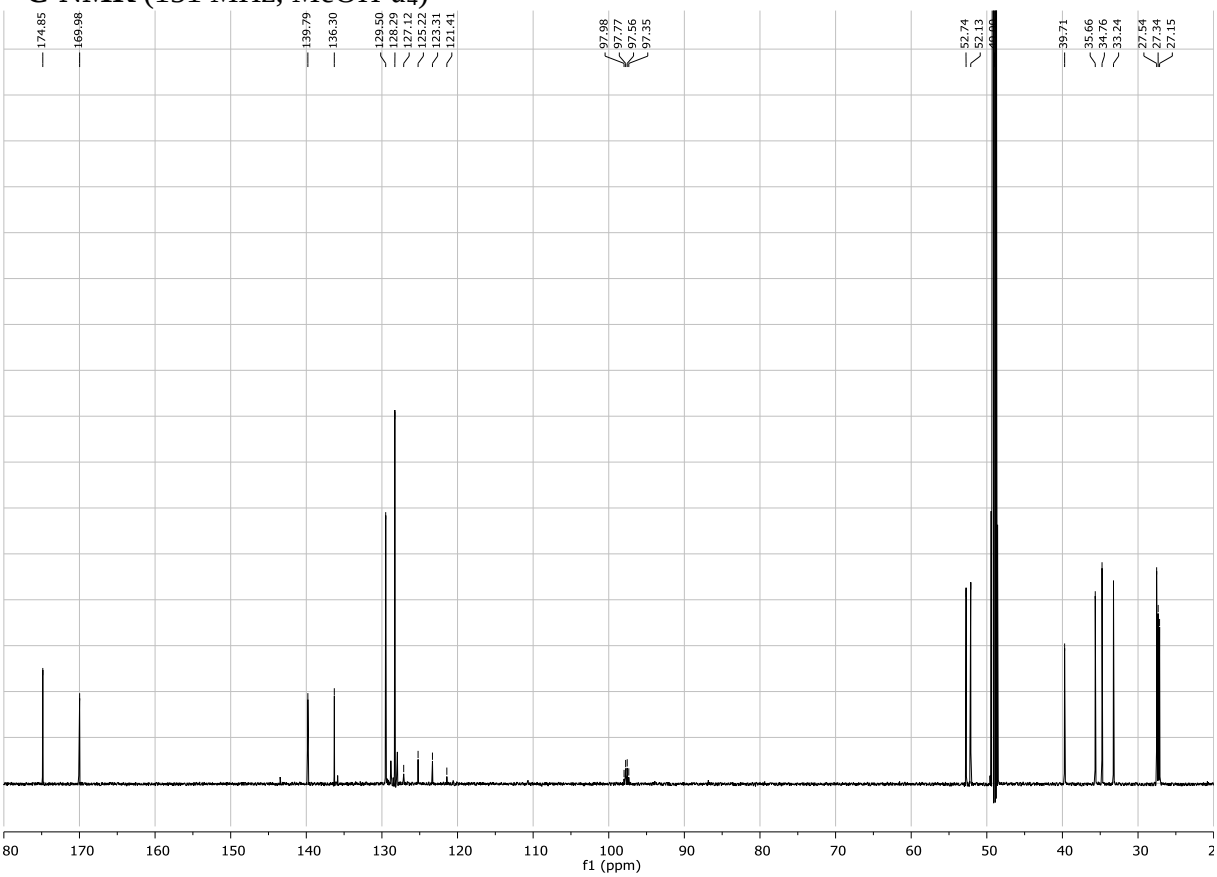


Methyl (2*S*)-3-cyclohexyl-2-(*p*-(2,2,2-trifluoroacetyl)benzoylamino)propionate 166:

^{1}H-NMR (600 MHz, MeOH-d_4)

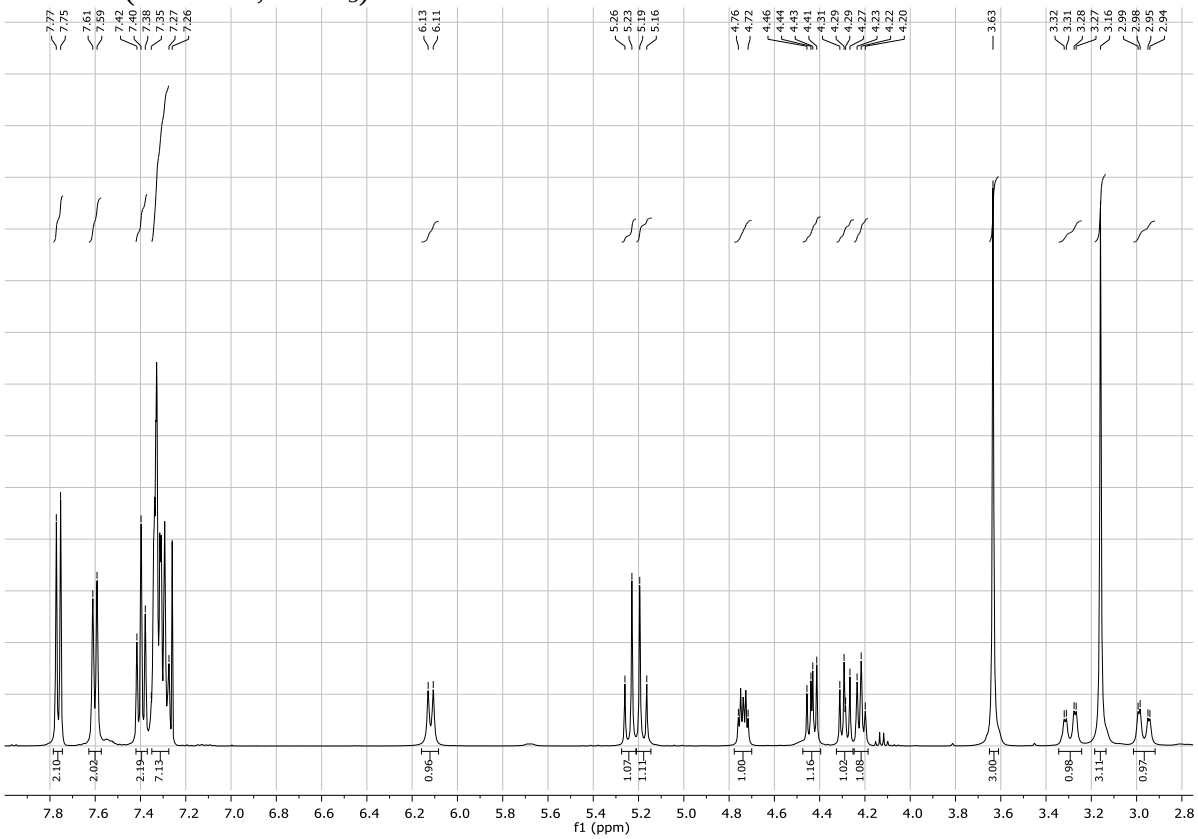


^{13}C-NMR (151 MHz, MeOH-d_4)

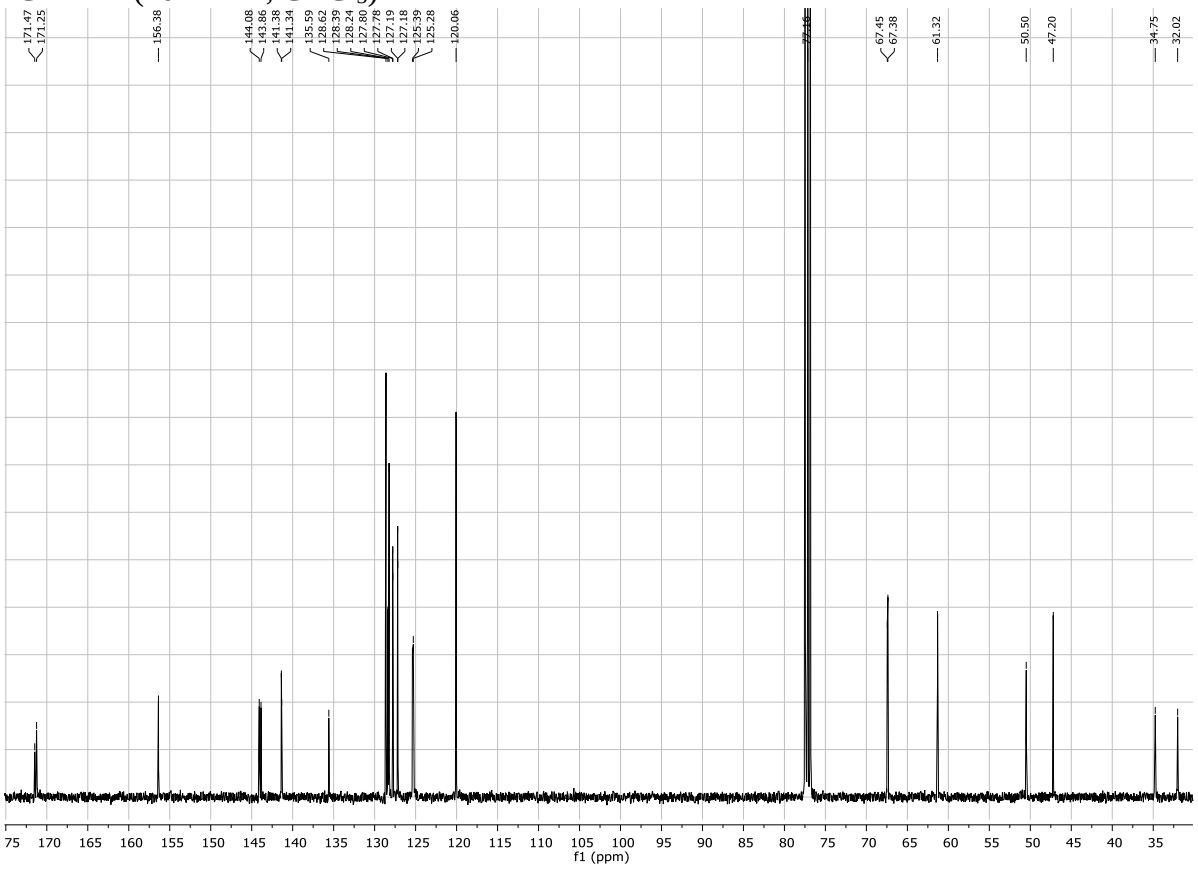


Benzyl (2*S*)-4-(*N*-methylmethoxyamino)-2-((9*H*-fluoren-9-yl)methoxycarbonylamino)-4-oxo-butyrate 168:

^{1}H-NMR (400 MHz, $CDCl_3$)

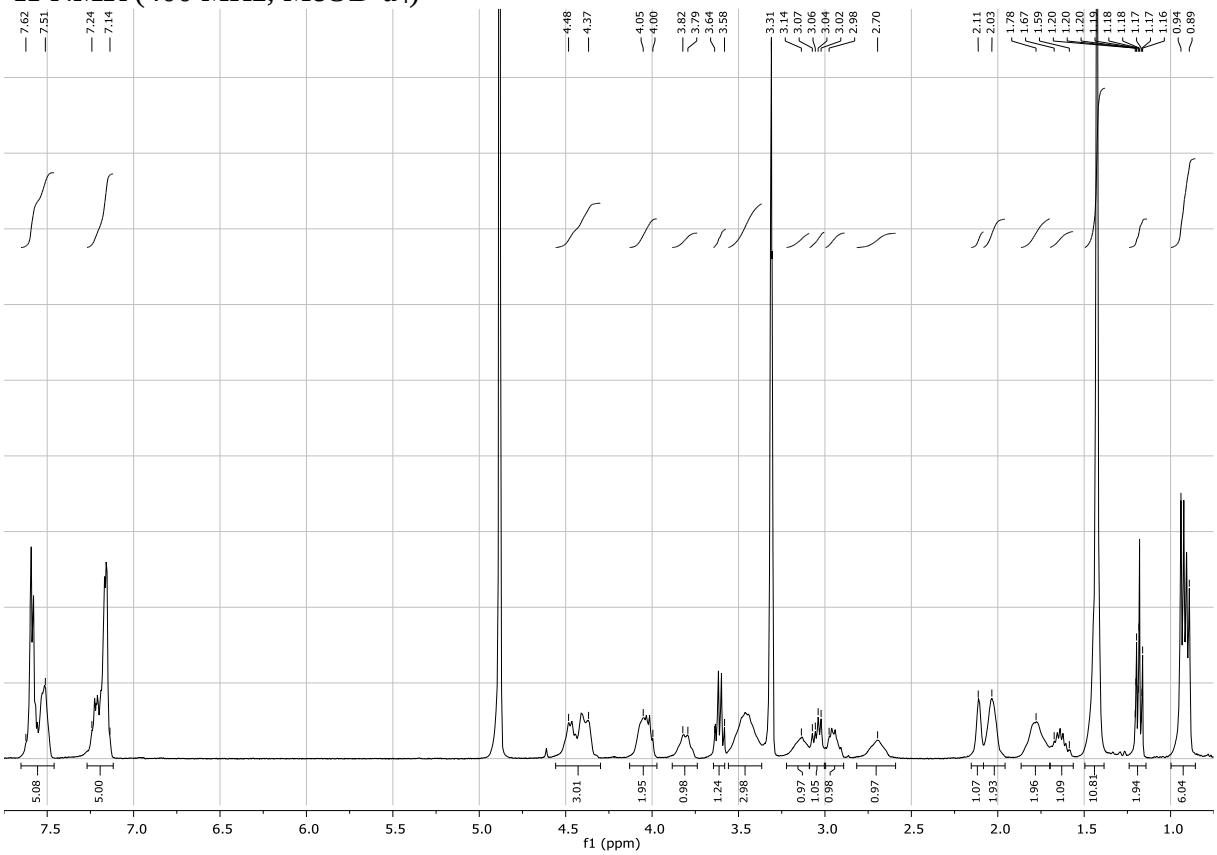


^{13}C-NMR (101 MHz, $CDCl_3$)

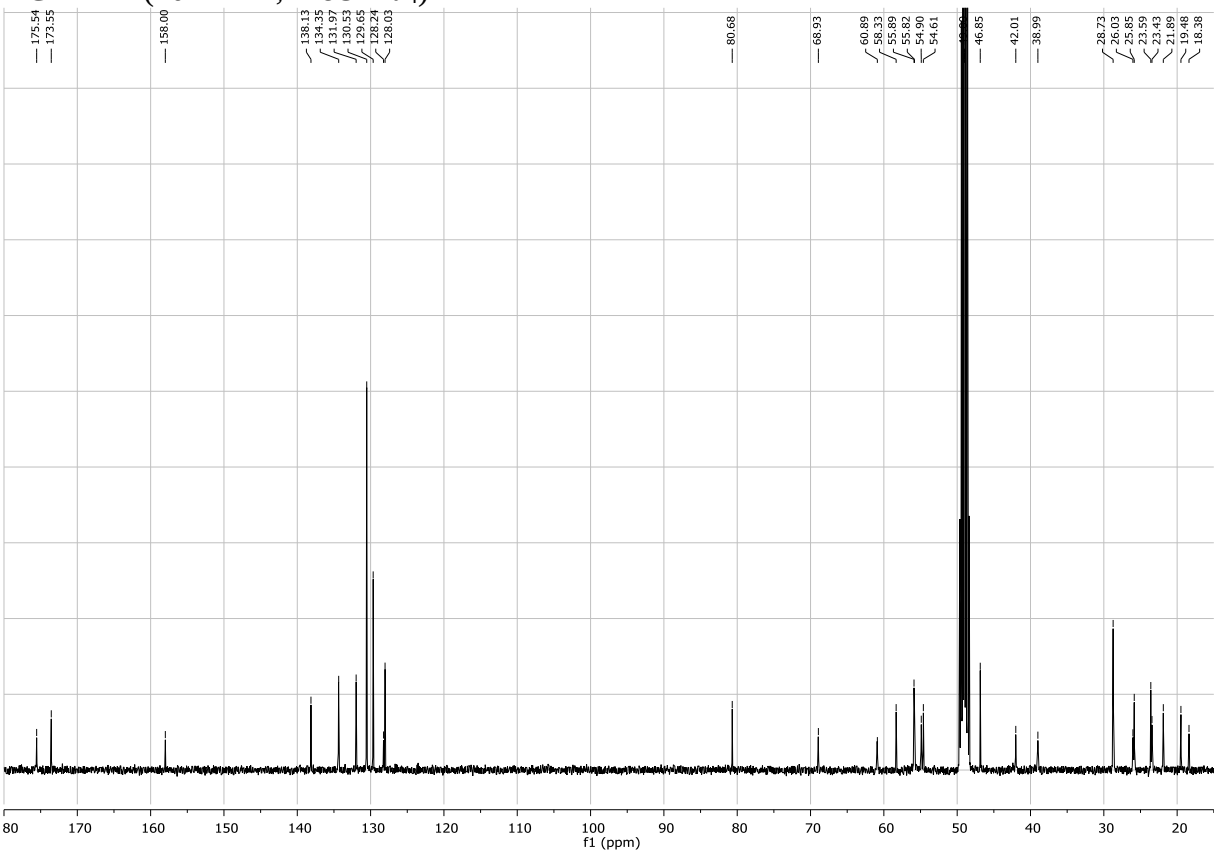


Boc-Leu-Phe-((3*S*)-*N*-benzylquinuclidinium) bromide 182:

^{1}H-NMR (400 MHz, MeOD-d_4)

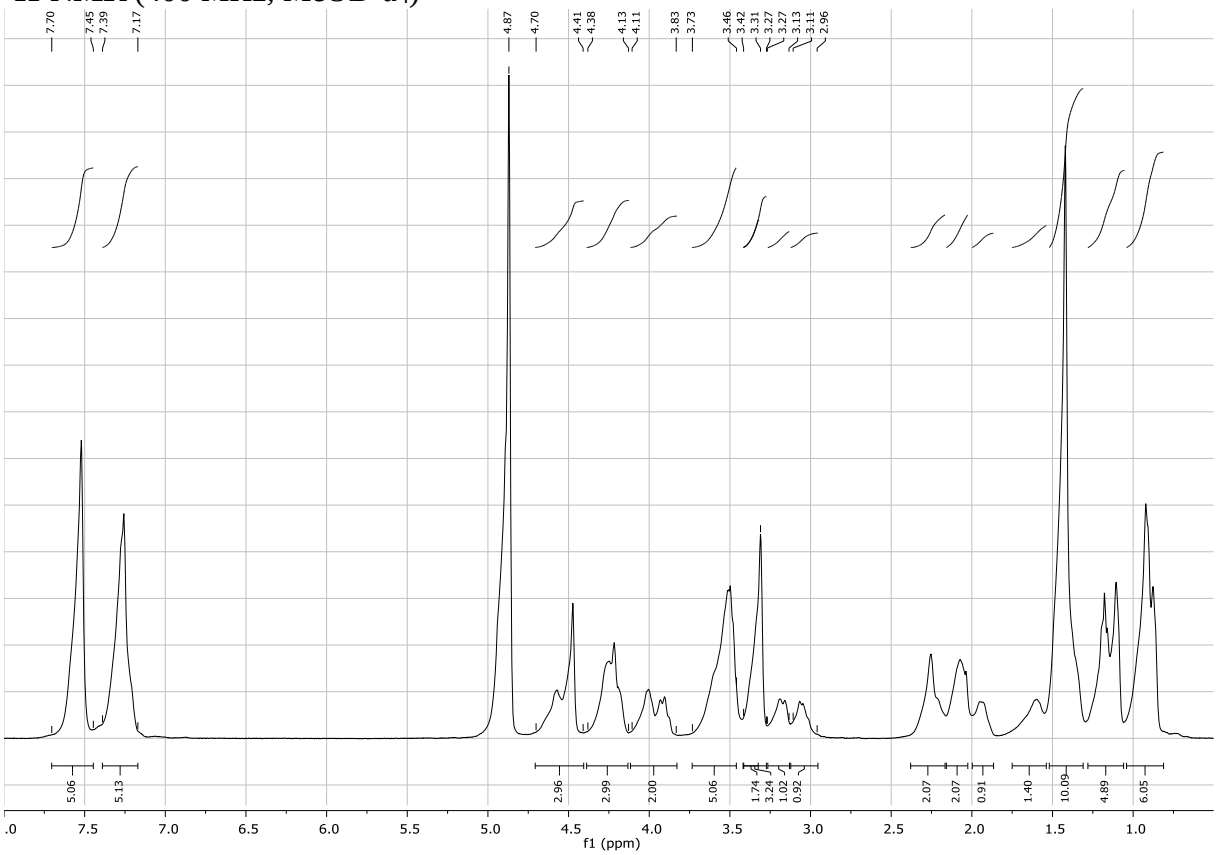


^{13}C-NMR (101 MHz, MeOD-d_4)

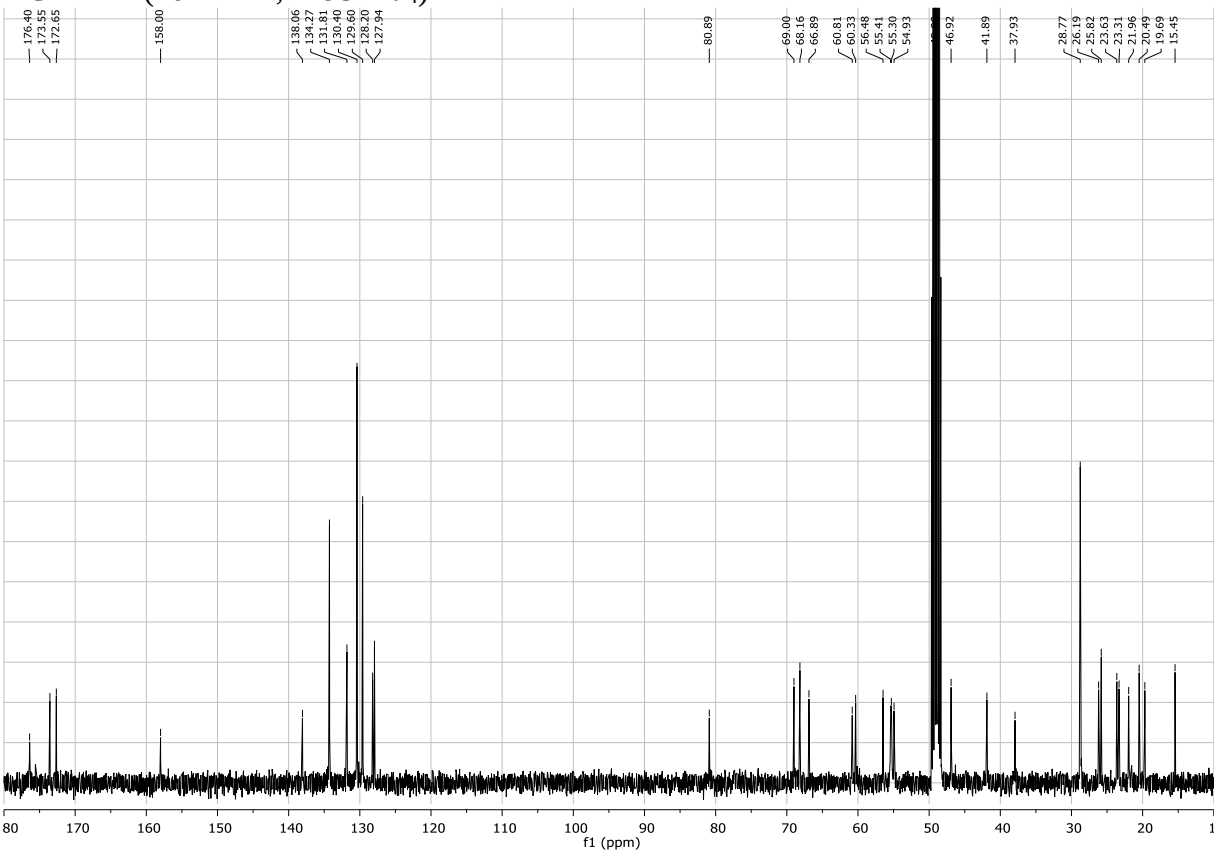


Boc-Leu-Phe-Thr-((3*S*)-*N*-benzylquinuclidinium) bromide 185:

^{1}H-NMR (400 MHz, MeOD-d_4)

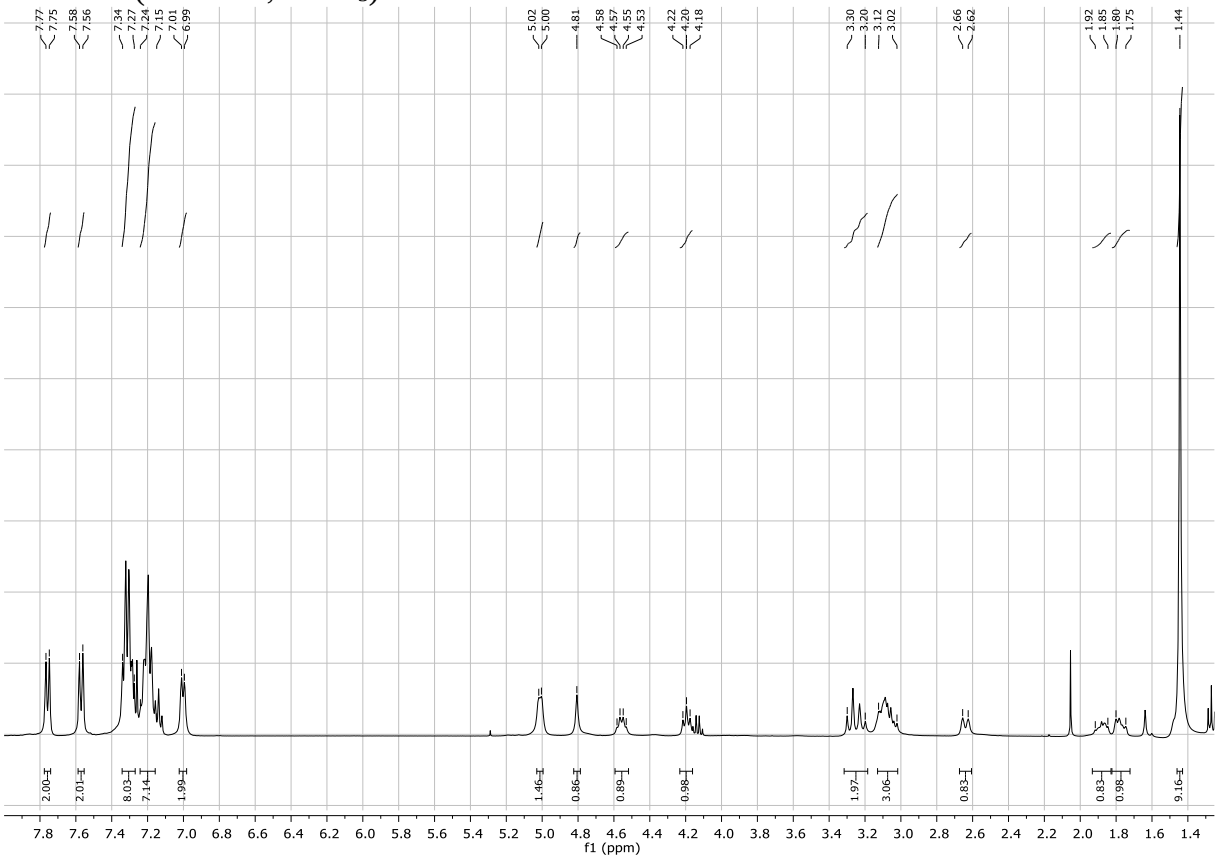


^{13}C-NMR (101 MHz, MeOD-d_4)

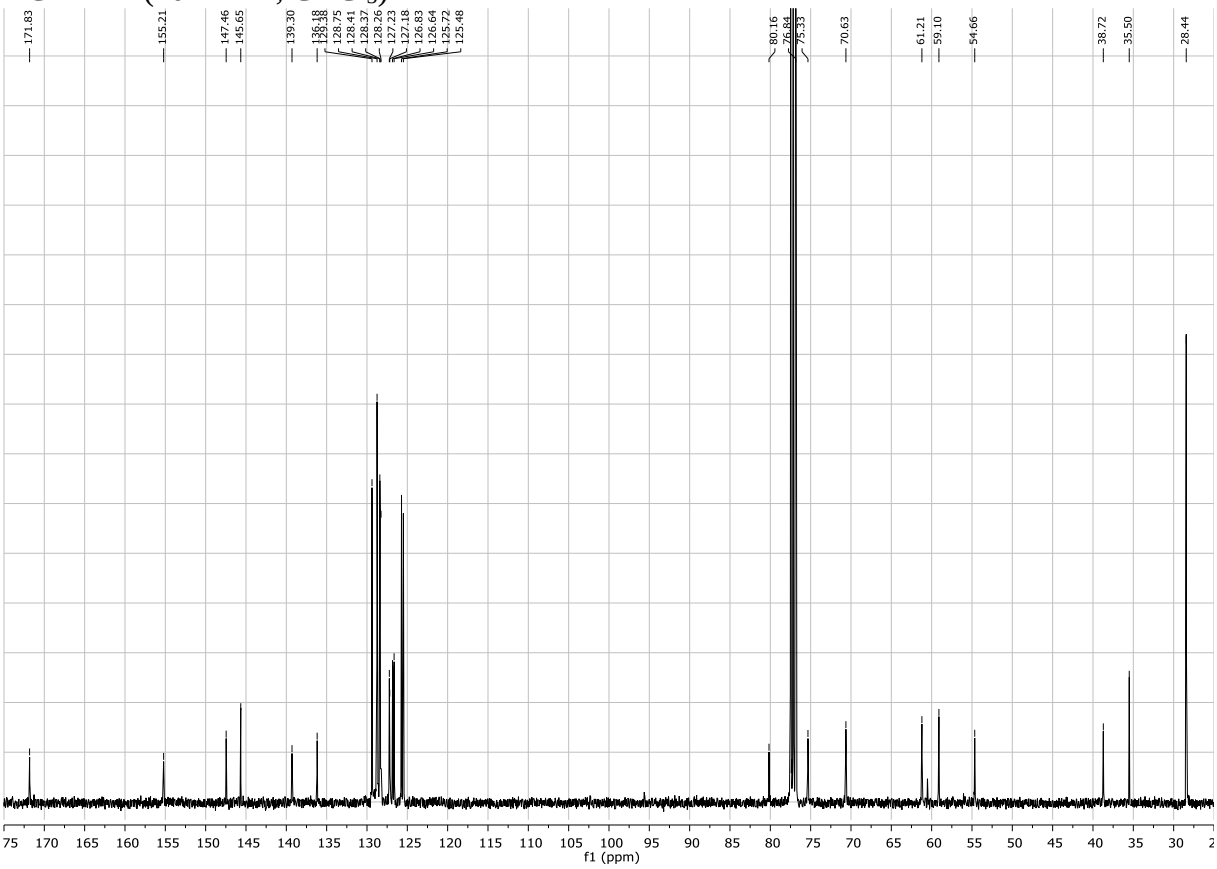


Boc-Phe-((2*S*,4*R*)-4-oxy-2-pyrrolidinyl)diphenylmethanol 189:

^{1}H-NMR (400 MHz, $CDCl_3$)

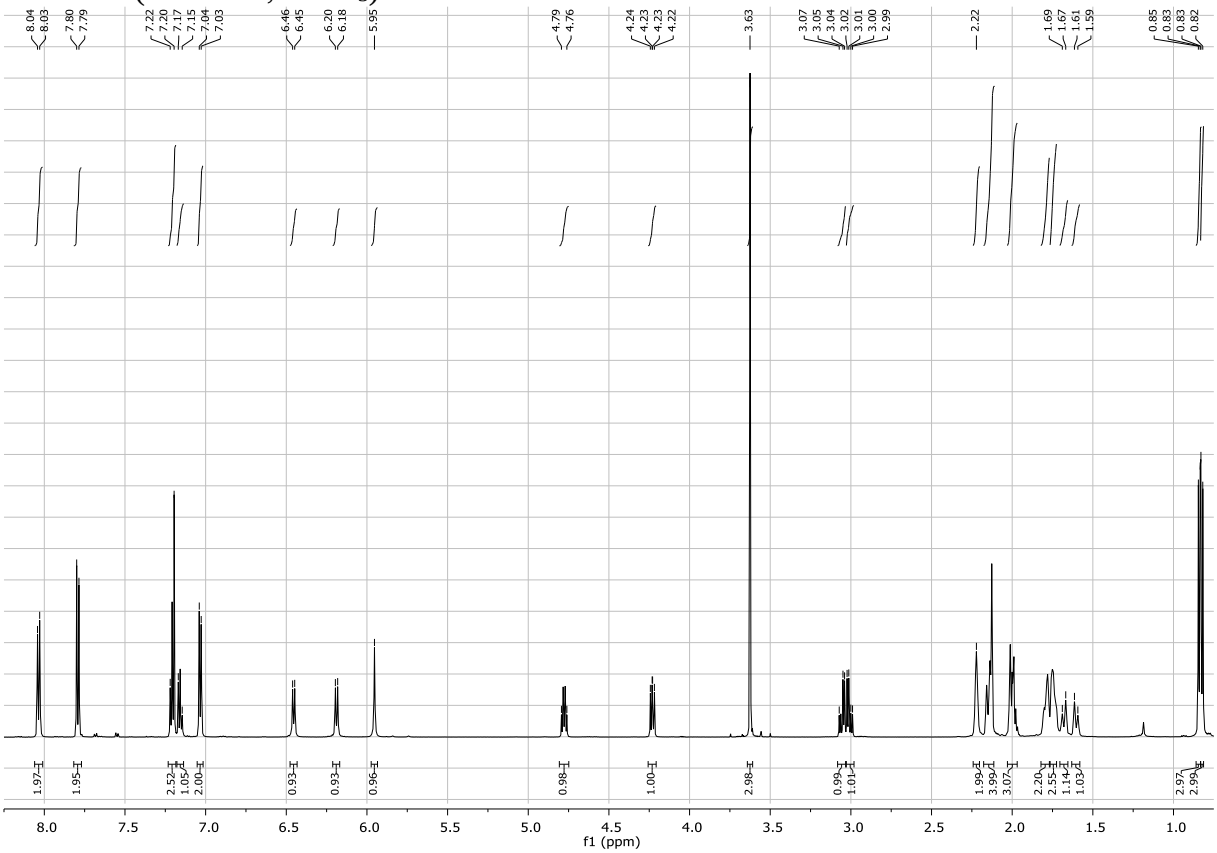


^{13}C-NMR (101 MHz, $CDCl_3$)

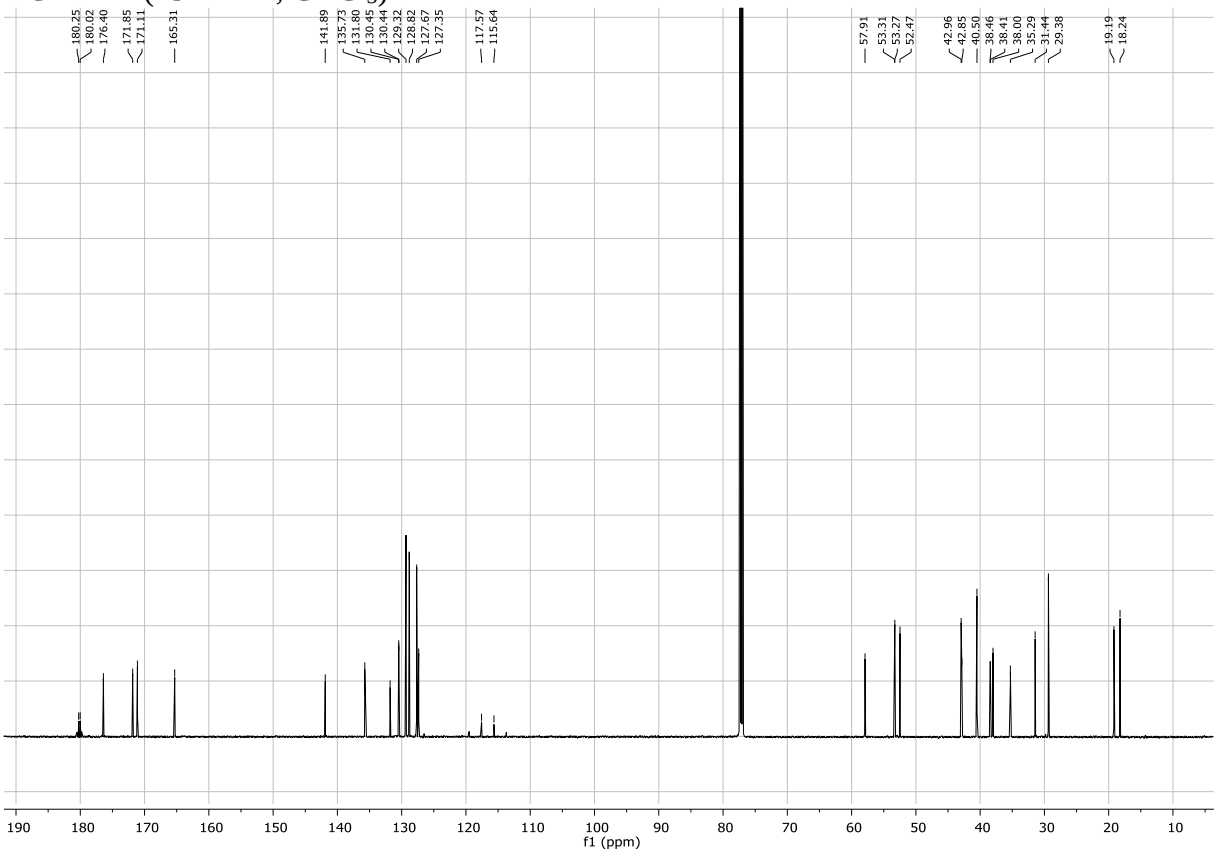


CM-AdGly-Val-Phe-OMe 214:

^{1}H-NMR (600 MHz, $CDCl_3$)

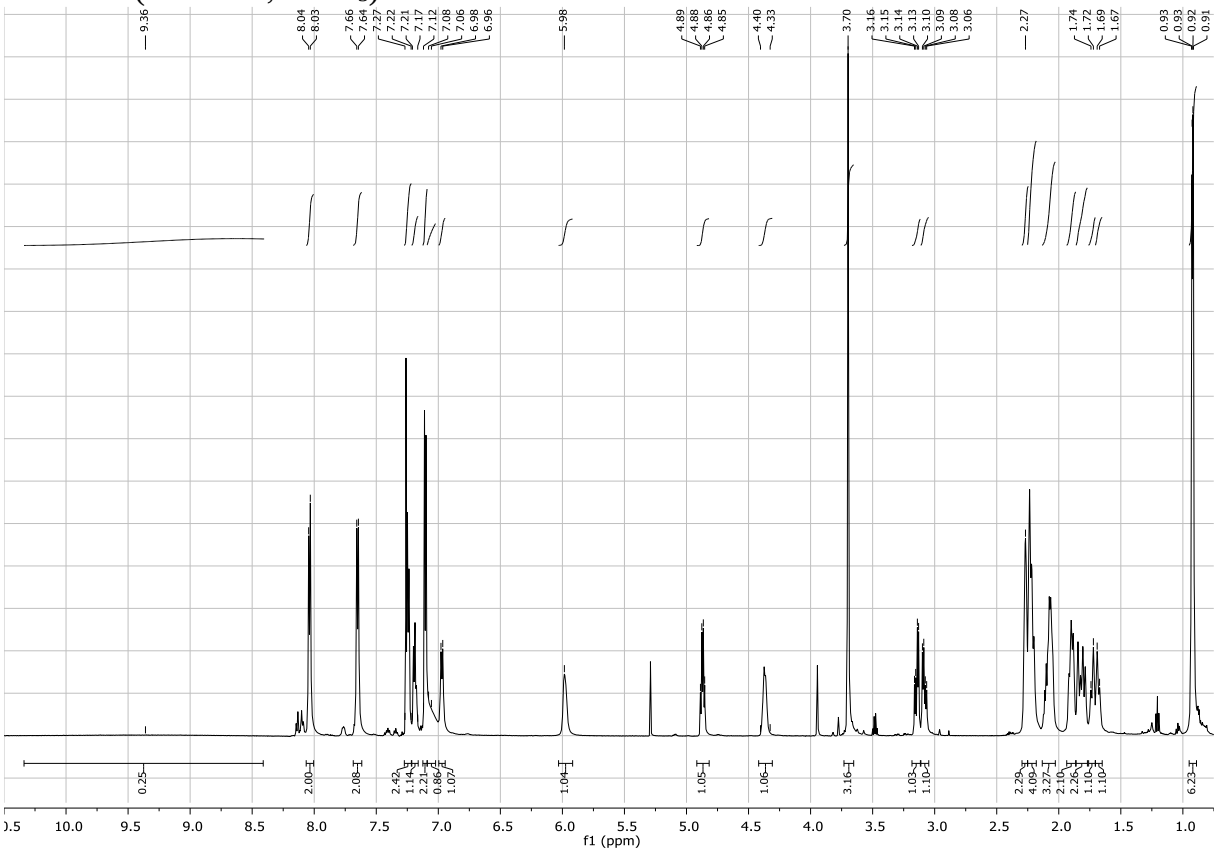


^{13}C-NMR (151 MHz, $CDCl_3$)

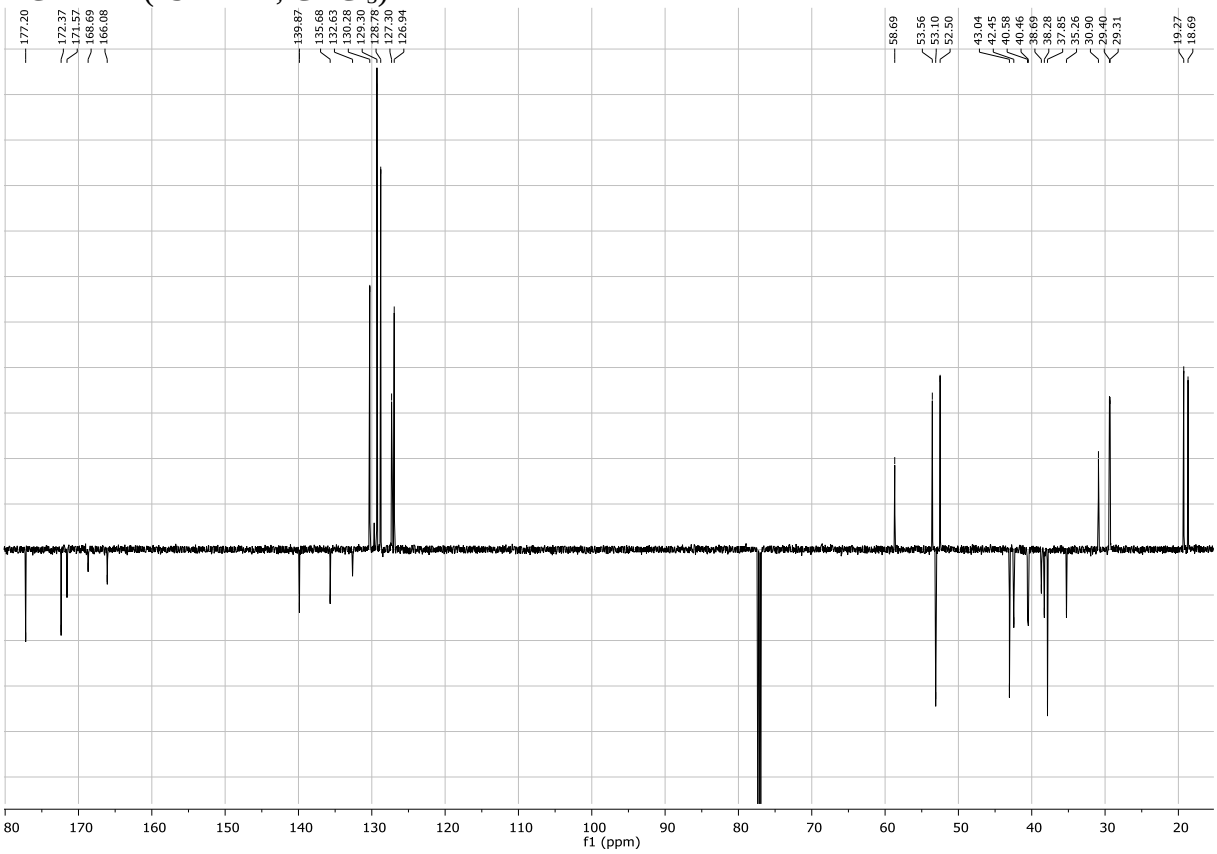


Terephthalic acid-AdGly-Val-Phe-OMe 215:

^{1}H-NMR (600 MHz, $CDCl_3$)



^{13}C-NMR (151 MHz, $CDCl_3$)



11.Crystal Structures

Cyclohex-1-en-1-ylmethyl *tert*-butylcarbamate 52e:

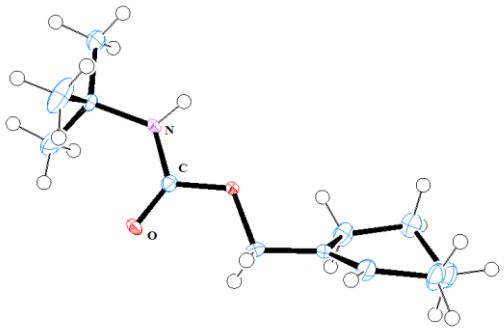


Table 48: Crystal data and structure refinement for mo_schr15036_0m_a.

Identification code	mo_schr15036_0m_a	
Empirical formula	C12 H21 N O2	
Formula weight	211.30	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 9.6757(4) Å	α= 90°.
	b = 11.4499(5) Å	β= 90°.
	c = 22.0810(10) Å	γ = 90°.
Volume	2446.26(18) $Å^3$	
Z	8	
Density (calculated)	1.147 Mg/m^3	
Absorption coefficient	0.077 mm^{-1}	
F(000)	928	
Crystal size	0.282 x 0.079 x 0.064 mm^3	
Theta range for data collection	2.799 to 25.076°.	
Index ranges	-11<=h<=11, -13<=k<=13, -26<=l<=26	
Reflections collected	22049	
Independent reflections	2166 [R(int) = 0.0635]	
Completeness to theta = 25.242°	98.1 %	
Absorption correction	Semi-empirical from equivalents	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2166 / 0 / 140	
Goodness-of-fit on F^2	1.447	
Final R indices [I>2sigma(I)]	R1 = 0.1093, wR2 = 0.2796	
R indices (all data)	R1 = 0.1223, wR2 = 0.2931	
Extinction coefficient	0.109(12)	
Largest diff. peak and hole	0.652 and -0.663 $e.Å^{-3}$	

Table 49: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for mo_schr15036_0m_a. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	Y	z	U(eq)
O(001)	868(3)	4463(3)	7301(1)	20(1)
O(002)	2863(3)	3953(3)	6846(1)	16(1)
N(003)	2950(4)	5186(3)	7612(2)	17(1)
C(004)	2113(4)	4539(4)	7268(2)	13(1)
C(005)	2980(4)	2835(4)	5934(2)	15(1)
C(006)	3101(5)	1705(4)	5805(2)	19(1)
C(007)	3696(5)	3758(4)	5568(2)	22(1)
C(008)	4807(5)	3277(4)	5152(2)	22(1)
C(009)	2514(5)	5836(4)	8159(2)	17(1)
C(00A)	2061(5)	3232(4)	6439(2)	20(1)
C(00B)	3917(6)	1243(4)	5280(2)	29(1)
C(00C)	1324(6)	6664(5)	8017(2)	32(1)
C(00D)	4291(6)	2201(5)	4829(2)	28(1)
C(00E)	3765(6)	6571(6)	8345(3)	39(2)
C(00F)	2110(7)	4974(5)	8649(2)	40(2)

Table 50: Bond lengths [Å] and angles [°] for mo_schr15036_0m_a.

O(001)-C(004)	1.210(5)	C(009)-C(00C)	1.524(7)
O(002)-C(004)	1.358(5)	C(009)-C(00E)	1.531(7)
O(002)-C(00A)	1.446(5)	C(00A)-H(00E)	0.9900
N(003)-C(004)	1.335(5)	C(00A)-H(00F)	0.9900
N(003)-C(009)	1.480(5)	C(00B)-C(00D)	1.524(7)
N(003)-H(003)	0.8800	C(00B)-H(00G)	0.9900
C(005)-C(006)	1.330(7)	C(00B)-H(00H)	0.9900
C(005)-C(00A)	1.498(6)	C(00C)-H(00I)	0.9800
C(005)-C(007)	1.499(6)	C(00C)-H(00J)	0.9800
C(006)-C(00B)	1.498(6)	C(00C)-H(00K)	0.9800
C(006)-H(006)	0.9500	C(00D)-H(00L)	0.9900
C(007)-C(008)	1.517(7)	C(00D)-H(00M)	0.9900
C(007)-H(00A)	0.9900	C(00E)-H(00N)	0.9800
C(007)-H(00B)	0.9900	C(00E)-H(00O)	0.9800
C(008)-C(00D)	1.509(7)	C(00E)-H(00P)	0.9800
C(008)-H(00C)	0.9900	C(00F)-H(00Q)	0.9800
C(008)-H(00D)	0.9900	C(00F)-H(00R)	0.9800
C(009)-C(00F)	1.517(7)	C(00F)-H(00S)	0.9800

C(004)-O(002)-C(00A)	114.9(3)	O(002)-C(00A)-H(00F)	110.0
C(004)-N(003)-C(009)	124.7(4)	C(005)-C(00A)-H(00F)	110.0
C(004)-N(003)-H(003)	117.6	H(00E)-C(00A)-H(00F)	108.4
C(009)-N(003)-H(003)	117.6	C(006)-C(00B)-C(00D)	112.1(4)
O(001)-C(004)-N(003)	127.6(4)	C(006)-C(00B)-H(00G)	109.2

O(001)-C(004)-O(002)	122.5(4)	C(00D)-C(00B)-H(00G)	109.2
N(003)-C(004)-O(002)	109.9(3)	C(006)-C(00B)-H(00H)	109.2
C(006)-C(005)-C(00A)	120.5(4)	C(00D)-C(00B)-H(00H)	109.2
C(006)-C(005)-C(007)	122.0(4)	H(00G)-C(00B)-H(00H)	107.9
C(00A)-C(005)-C(007)	117.5(4)	C(009)-C(00C)-H(00I)	109.5
C(005)-C(006)-C(00B)	123.7(4)	C(009)-C(00C)-H(00J)	109.5
C(005)-C(006)-H(006)	118.1	H(00I)-C(00C)-H(00J)	109.5
C(00B)-C(006)-H(006)	118.1	C(009)-C(00C)-H(00K)	109.5
C(005)-C(007)-C(008)	113.4(4)	H(00I)-C(00C)-H(00K)	109.5
C(005)-C(007)-H(00A)	108.9	H(00J)-C(00C)-H(00K)	109.5
C(008)-C(007)-H(00A)	108.9	C(008)-C(00D)-C(00B)	111.0(4)
C(005)-C(007)-H(00B)	108.9	C(008)-C(00D)-H(00L)	109.4
C(008)-C(007)-H(00B)	108.9	C(00B)-C(00D)-H(00L)	109.4
H(00A)-C(007)-H(00B)	107.7	C(008)-C(00D)-H(00M)	109.4
C(00D)-C(008)-C(007)	110.4(4)	C(00B)-C(00D)-H(00M)	109.4
C(00D)-C(008)-H(00C)	109.6	H(00L)-C(00D)-H(00M)	108.0
C(007)-C(008)-H(00C)	109.6	C(009)-C(00E)-H(00N)	109.5
C(00D)-C(008)-H(00D)	109.6	C(009)-C(00E)-H(00O)	109.5
C(007)-C(008)-H(00D)	109.6	H(00N)-C(00E)-H(00O)	109.5
H(00C)-C(008)-H(00D)	108.1	C(009)-C(00E)-H(00P)	109.5
N(003)-C(009)-C(00F)	109.2(4)	H(00N)-C(00E)-H(00P)	109.5
N(003)-C(009)-C(00C)	111.2(4)	H(00O)-C(00E)-H(00P)	109.5
C(00F)-C(009)-C(00C)	110.9(4)	C(009)-C(00F)-H(00Q)	109.5
N(003)-C(009)-C(00E)	105.7(4)	C(009)-C(00F)-H(00R)	109.5
C(00F)-C(009)-C(00E)	111.6(5)	H(00Q)-C(00F)-H(00R)	109.5
C(00C)-C(009)-C(00E)	108.1(4)	C(009)-C(00F)-H(00S)	109.5
O(002)-C(00A)-C(005)	108.6(4)	H(00Q)-C(00F)-H(00S)	109.5
O(002)-C(00A)-H(00E)	110.0	H(00R)-C(00F)-H(00S)	109.5
C(005)-C(00A)-H(00E)	110.0		

Table 51: Anisotropic displacement parameters ($Å^2$x 10^3) for mo_schr15036_0m_a. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(001)	7(2)	26(2)	26(2)	-12(1)	1(1)	0(1)
O(002)	7(2)	24(2)	17(2)	-11(1)	0(1)	-1(1)
N(003)	7(2)	25(2)	19(2)	-10(2)	1(1)	1(2)
C(004)	15(2)	12(2)	12(2)	-1(2)	-1(2)	2(2)
C(005)	10(2)	20(2)	13(2)	-3(2)	-3(2)	1(2)
C(006)	20(2)	18(2)	20(2)	-3(2)	6(2)	-7(2)
C(007)	32(3)	14(2)	20(2)	0(2)	0(2)	4(2)
C(008)	30(3)	18(2)	19(2)	3(2)	6(2)	-2(2)
C(009)	15(2)	19(2)	16(2)	-9(2)	0(2)	1(2)
C(00A)	16(2)	25(3)	20(2)	-11(2)	-4(2)	-3(2)
C(00B)	33(3)	20(3)	33(3)	-14(2)	10(2)	-6(2)
C(00C)	37(3)	28(3)	29(3)	-15(2)	-7(2)	10(2)

C(00D)	31(3)	32(3)	20(2)	-6(2)	10(2)	-5(2)
C(00E)	22(3)	54(4)	42(3)	-36(3)	-2(2)	2(3)
C(00F)	76(5)	29(3)	16(2)	-1(2)	5(3)	3(3)

Table 52: Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for mo_schr15036_0m_a.

	x	Y	z	U(eq)
H(003)	3826	5229	7506	20
H(006)	2645	1159	6060	23
H(00A)	4120	4331	5847	27
H(00B)	3000	4176	5321	27
H(00C)	5068	3879	4851	27
H(00D)	5639	3080	5392	27
H(00E)	1274	3684	6275	24
H(00F)	1689	2548	6659	24
H(00G)	3371	634	5070	34
H(00H)	4775	876	5432	34
H(00I)	1561	7141	7663	48
H(00J)	1159	7175	8366	48
H(00K)	488	6211	7931	48
H(00L)	5016	1912	4551	33
H(00M)	3468	2403	4585	33
H(00N)	4558	6057	8417	59
H(00O)	3549	7001	8717	59
H(00P)	3988	7124	8021	59
H(00Q)	1332	4498	8508	60
H(00R)	1839	5401	9015	60
H(00S)	2898	4467	8741	60

1-(Benzyloxycarbonylamino)-1-cyclohexen-3-one 66:

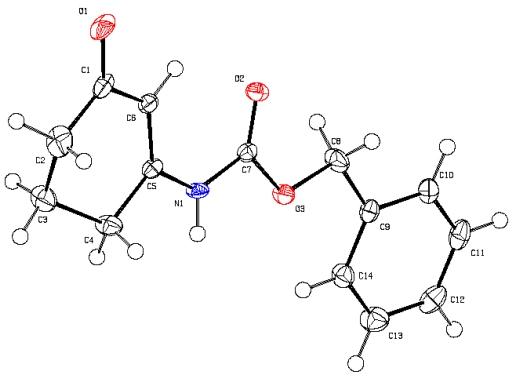


Table 53: Crystal data and structure refinement for schr15033.

Identification code	schr15033
Empirical formula	C14 H15 N O3

Formula weight	245.27	
Temperature	99(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 7.1379(4) Å	α = 90°.
	b = 17.4393(10) Å	β = 106.555(2)°.
	c = 10.4161(5) Å	γ = 90°.
Volume	1242.85(12) $Å^3$	
Z	4	
Density (calculated)	1.311 Mg/m^3	
Absorption coefficient	0.093 mm^{-1}	
F(000)	520	
Crystal size	0.559 x 0.325 x 0.198 mm^3	
Theta range for data collection	3.093 to 25.064°.	
Index ranges	-8<=h<=8, -20<=k<=20, -12<=l<=12	
Reflections collected	32806	
Independent reflections	2214 [R(int) = 0.0908]	
Completeness to theta = 25.064°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7425 and 0.7053	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2214 / 0 / 167	
Goodness-of-fit on F^2	1.090	
Final R indices [I>2sigma(I)]	R1 = 0.0398, wR2 = 0.0922	
R indices (all data)	R1 = 0.0501, wR2 = 0.0963	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.171 and -0.281 $e.Å^{-3}$	

Table 54: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å2x 103) for schr15033. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	11408(2)	7265(1)	3786(1)	31(1)
N(1)	6956(2)	7104(1)	6402(1)	16(1)
C(1)	10798(2)	7518(1)	4704(2)	22(1)
O(2)	5988(2)	6116(1)	4888(1)	22(1)
C(2)	11852(3)	8160(1)	5588(2)	31(1)
C(3)	10514(2)	8612(1)	6216(2)	27(1)
O(3)	4662(2)	6303(1)	6595(1)	18(1)
C(4)	9434(2)	8076(1)	6906(2)	22(1)
C(5)	8473(2)	7427(1)	6017(1)	15(1)
C(6)	9100(2)	7186(1)	4973(1)	17(1)
C(7)	5882(2)	6469(1)	5860(1)	15(1)
C(9)	1990(2)	5575(1)	6938(1)	17(1)
C(8)	3384(2)	5658(1)	6108(2)	25(1)
C(10)	815(2)	4921(1)	6751(2)	21(1)

C(11)	-539(2)	4823(1)	7458(2)	26(1)
C(12)	-744(2)	5373(1)	8366(2)	27(1)
C(13)	419(2)	6021(1)	8555(2)	29(1)
C(14)	1776(2)	6122(1)	7847(2)	22(1)

Table 55: Bond lengths [Å] and angles [°] for schr15033.

O(1)-C(1)	1.2389(18)	C(3)-C(4)	1.517(2)	C(9)-C(14)	1.383(2)	C(12)-H(12)	0.9500
N(1)-C(7)	1.3725(19)	C(3)-H(3A)	0.9900	C(9)-C(10)	1.395(2)	C(13)-C(14)	1.386(2)
N(1)-C(5)	1.3784(18)	C(3)-H(3B)	0.9900	C(9)-C(8)	1.500(2)	C(13)-H(13)	0.9500
N(1)-H(1)	0.862(18)	O(3)-C(7)	1.3454(17)	C(8)-H(8A)	0.9900	C(14)-H(14)	0.9500
C(1)-C(6)	1.440(2)	O(3)-C(8)	1.4461(17)	C(8)-H(8B)	0.9900		
C(1)-C(2)	1.508(2)	C(4)-C(5)	1.499(2)	C(10)-C(11)	1.383(2)		
O(2)-C(7)	1.2056(17)	C(4)-H(4A)	0.9900	C(10)-H(10)	0.9500		
C(2)-C(3)	1.522(2)	C(4)-H(4B)	0.9900	C(11)-C(12)	1.384(2)		
C(2)-H(2A)	0.9900	C(5)-C(6)	1.3550(19)	C(11)-H(11)	0.9500		
C(2)-H(2B)	0.9900	C(6)-H(6)	0.9500	C(12)-C(13)	1.383(2)		

C(7)-N(1)-C(5)	127.08(12)	C(5)-C(4)-H(4A)	109.2	O(3)-C(8)-H(8B)	109.8
C(7)-N(1)-H(1)	115.7(12)	C(3)-C(4)-H(4A)	109.2	C(9)-C(8)-H(8B)	109.8
C(5)-N(1)-H(1)	116.8(12)	C(5)-C(4)-H(4B)	109.2	H(8A)-C(8)-H(8B)	108.3
O(1)-C(1)-C(6)	120.46(15)	C(3)-C(4)-H(4B)	109.2	C(11)-C(10)-C(9)	120.67(15)
O(1)-C(1)-C(2)	120.80(15)	H(4A)-C(4)-H(4B)	107.9	C(11)-C(10)-H(10)	119.7
C(6)-C(1)-C(2)	118.71(13)	C(6)-C(5)-N(1)	124.99(14)	C(9)-C(10)-H(10)	119.7
C(1)-C(2)-C(3)	112.46(13)	C(6)-C(5)-C(4)	122.15(13)	C(10)-C(11)-C(12)	120.26(15)
C(1)-C(2)-H(2A)	109.1	N(1)-C(5)-C(4)	112.84(12)	C(10)-C(11)-H(11)	119.9
C(3)-C(2)-H(2A)	109.1	C(5)-C(6)-C(1)	121.35(14)	C(12)-C(11)-H(11)	119.9
C(1)-C(2)-H(2B)	109.1	C(5)-C(6)-H(6)	119.3	C(13)-C(12)-C(11)	119.25(15)
C(3)-C(2)-H(2B)	109.1	C(1)-C(6)-H(6)	119.3	C(13)-C(12)-H(12)	120.4
H(2A)-C(2)-H(2B)	107.8	O(2)-C(7)-O(3)	124.98(13)	C(11)-C(12)-H(12)	120.4
C(4)-C(3)-C(2)	110.50(13)	O(2)-C(7)-N(1)	126.63(13)	C(12)-C(13)-C(14)	120.65(16)
C(4)-C(3)-H(3A)	109.6	O(3)-C(7)-N(1)	108.39(11)	C(12)-C(13)-H(13)	119.7
C(2)-C(3)-H(3A)	109.6	C(14)-C(9)-C(10)	118.69(14)	C(14)-C(13)-H(13)	119.7
C(4)-C(3)-H(3B)	109.6	C(14)-C(9)-C(8)	123.29(13)	C(9)-C(14)-C(13)	120.48(14)
C(2)-C(3)-H(3B)	109.6	C(10)-C(9)-C(8)	118.00(13)	C(9)-C(14)-H(14)	119.8
H(3A)-C(3)-H(3B)	108.1	O(3)-C(8)-C(9)	109.19(12)	C(13)-C(14)-H(14)	119.8
C(7)-O(3)-C(8)	114.44(11)	O(3)-C(8)-H(8A)	109.8		
C(5)-C(4)-C(3)	112.16(12)	C(9)-C(8)-H(8A)	109.8		

Table 56: Anisotropic displacement parameters (Å2x 103) for schr15033. The anisotropic displacement factor exponent takes the form: -2p2[h2 a*2U11 + ... + 2 h k a* b* U12]

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	44(1)	30(1)	32(1)	9(1)	31(1)	12(1)
N(1)	17(1)	21(1)	14(1)	-5(1)	9(1)	-4(1)
C(1)	27(1)	22(1)	24(1)	10(1)	16(1)	10(1)
O(2)	30(1)	20(1)	18(1)	-5(1)	11(1)	-5(1)

C(2)	25(1)	32(1)	46(1)	2(1)	24(1)	-6(1)
C(3)	26(1)	25(1)	35(1)	-7(1)	16(1)	-9(1)
O(3)	17(1)	20(1)	20(1)	-5(1)	9(1)	-7(1)
C(4)	18(1)	28(1)	23(1)	-8(1)	12(1)	-6(1)
C(5)	12(1)	19(1)	15(1)	2(1)	6(1)	2(1)
C(6)	20(1)	17(1)	15(1)	2(1)	8(1)	2(1)
C(7)	15(1)	16(1)	14(1)	1(1)	4(1)	2(1)
C(9)	15(1)	18(1)	18(1)	4(1)	3(1)	1(1)
C(8)	27(1)	22(1)	30(1)	-9(1)	14(1)	-11(1)
C(10)	21(1)	18(1)	22(1)	3(1)	4(1)	-2(1)
C(11)	21(1)	26(1)	28(1)	9(1)	3(1)	-8(1)
C(12)	19(1)	39(1)	25(1)	8(1)	10(1)	-2(1)
C(13)	27(1)	34(1)	29(1)	-4(1)	14(1)	-3(1)
C(14)	21(1)	21(1)	26(1)	-2(1)	9(1)	-4(1)

Table 57: Hydrogen coordinates (x 104) and isotropic displacement parameters (Å2x 10 3) for schr15033.

	x	y	z	U(eq)
H(1)	6730(30)	7286(10)	7114(17)	24(4)
H(2A)	12415	8512	5051	38
H(2B)	12944	7943	6308	38
H(3A)	11298	8981	6875	33
H(3B)	9559	8906	5512	33
H(4A)	10367	7865	7723	26
H(4B)	8427	8370	7183	26
H(6)	8406	6791	4407	20
H(8A)	4166	5184	6166	30
H(8B)	2647	5741	5158	30
H(10)	947	4540	6131	25
H(11)	-1332	4376	7320	31
H(12)	-1673	5307	8853	33
H(13)	286	6401	9177	34
H(14)	2564	6570	7987	26

6-Hydroxy-1,3-dioxaspiro[4.5]decan-2-one 75:

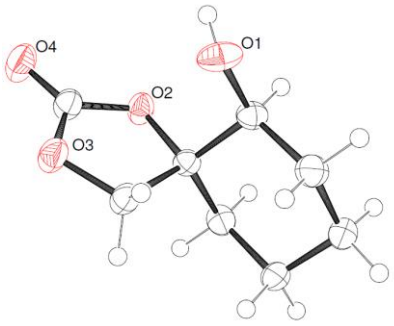


Table 58: Crystal data and structure refinement for schreiner14003.

Identification code	schreiner14003	
Empirical formula	C8 H12 O4	
Formula weight	172.18	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 7.4670(15) Å	α= 90°.
	b = 5.4625(11) Å	β= 95.16(3)°.
	c = 19.454(4) Å	γ = 90°.
Volume	790.3(3) $Å^3$	
Z	4	
Density (calculated)	1.447 Mg/m^3	
Absorption coefficient	0.116 mm^{-1}	
F(000)	368	
Crystal size	0.380 x 0.290 x 0.200 mm^3	
Theta range for data collection	2.102 to 27.510°.	
Index ranges	-8<=h<=9, -7<=k<=6, -24<=l<=24	
Reflections collected	9267	
Independent reflections	1792 [R(int) = 0.1243]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	Empirical	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1792 / 0 / 110	
Goodness-of-fit on F^2	0.933	
Final R indices [I>2sigma(I)]	R1 = 0.0455, wR2 = 0.0927	
R indices (all data)	R1 = 0.0913, wR2 = 0.1073	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.202 and -0.261 $e.Å^{-3}$	

Table 59: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for schreiner14003. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	2056(2)	6825(3)	3839(1)	22(1)
O(1)	589(2)	7330(2)	2681(1)	38(1)
C(2)	2290(2)	7134(3)	3076(1)	26(1)
O(2)	1093(2)	4529(2)	3914(1)	28(1)
C(3)	3391(3)	9407(3)	2955(1)	32(1)
O(3)	-776(2)	7307(2)	4262(1)	36(1)
C(4)	5194(3)	9392(4)	3385(1)	33(1)
O(4)	-1626(2)	3394(2)	4207(1)	42(1)
C(5)	4938(3)	9033(4)	4142(1)	31(1)
C(6)	3864(2)	6711(3)	4254(1)	28(1)

C(7)	772(2)	8698(3)	4113(1)	29(1)
C(8)	-532(3)	4945(3)	4132(1)	29(1)

Table 60: Bond lengths [Å] and angles [°] for schreiner14003.

C(1)-O(2)	1.460(2)	C(3)-C(4)	1.520(3)
C(1)-C(6)	1.510(3)	O(3)-C(8)	1.330(2)
C(1)-C(2)	1.520(3)	O(3)-C(7)	1.434(2)
C(1)-C(7)	1.531(2)	C(4)-C(5)	1.514(3)
O(1)-C(2)	1.428(2)	O(4)-C(8)	1.195(2)
C(2)-C(3)	1.519(3)	C(5)-C(6)	1.527(3)
O(2)-C(8)	1.340(2)		

O(2)-C(1)-C(6)	109.62(14)	O(1)-C(2)-C(1)	110.99(15)	C(4)-C(5)-C(6)	111.10(17)
O(2)-C(1)-C(2)	107.15(15)	C(3)-C(2)-C(1)	110.68(16)	C(1)-C(6)-C(5)	110.22(16)
C(6)-C(1)-C(2)	110.52(15)	C(8)-O(2)-C(1)	110.76(13)	O(3)-C(7)-C(1)	104.92(13)
O(2)-C(1)-C(7)	102.10(13)	C(2)-C(3)-C(4)	112.04(17)	O(4)-C(8)-O(3)	123.92(16)
C(6)-C(1)-C(7)	113.52(16)	C(8)-O(3)-C(7)	110.44(13)	O(4)-C(8)-O(2)	124.51(16)
C(2)-C(1)-C(7)	113.38(16)	C(5)-C(4)-C(3)	110.64(15)	O(3)-C(8)-O(2)	111.56(15)
O(1)-C(2)-C(3)	108.86(16)				

Table 61: Anisotropic displacement parameters ($Å^2 x\ 10^3$) for schreiner14003. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(1)	24(1)	19(1)	25(1)	0(1)	2(1)	0(1)
O(1)	42(1)	33(1)	36(1)	2(1)	-16(1)	-5(1)
C(2)	28(1)	26(1)	24(1)	1(1)	-1(1)	0(1)
O(2)	26(1)	21(1)	37(1)	1(1)	10(1)	-1(1)
C(3)	40(1)	31(1)	27(1)	2(1)	4(1)	-6(1)
O(3)	25(1)	28(1)	56(1)	-9(1)	12(1)	-2(1)
C(4)	30(1)	34(1)	37(1)	-6(1)	10(1)	-7(1)
O(4)	31(1)	35(1)	61(1)	-2(1)	14(1)	-6(1)
C(5)	21(1)	39(1)	33(1)	-8(1)	2(1)	-3(1)
C(6)	25(1)	34(1)	24(1)	2(1)	0(1)	5(1)
C(7)	23(1)	25(1)	40(1)	-3(1)	5(1)	-1(1)
C(8)	24(1)	29(1)	34(1)	0(1)	4(1)	0(1)

Table 62: Hydrogen coordinates ($x\ 10^4$) and isotropic displacement parameters ($Å^2 x\ 10^3$) for schreiner14003.

	x	y	z	U(eq)
H(1)	195	5924	2580	46
H(2)	2937	5671	2913	31
H(3A)	2705	10877	3073	39
H(3B)	3595	9509	2460	39
H(4A)	5951	8054	3226	40
H(4B)	5823	10961	3323	40
H(5A)	4298	10465	4313	37

H(5B)	6128	8922	4409	37
H(6A)	4538	5265	4111	34
H(6B)	3690	6536	4750	34
H(7A)	1331	9501	4536	35
H(7B)	439	9970	3762	35

2,2,2-Trifluoro-1-(*m*-nitrophenyl)-1-ethanone *meta*-154:

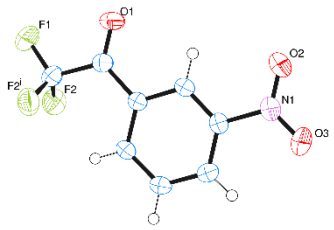


Table 63: Crystal data and structure refinement for schreiner12022.

Identification code	schreiner12022	
Empirical formula	C8 H4 F3 N O3	
Formula weight	219.12	
Temperature	190(2) K	
Wavelength	0.71073 A	
Crystal system	Orthorombic	
Space group	Pnma	
Unit cell dimensions	a = 11.804(2) Å	α= 90°.
	b = 6.7160(13) Å	β= 90°.
	c = 10.677(2) Å	γ = 90°.
Volume	846.4(3) Å^3	
Z	4	
Density (calculated)	1.720 Mg/m^3	
Absorption coefficient	0.173 mm^{-1}	
F(000)	440	
Crystal size	0.85 x 0.40 x 0.05 mm^3	
Theta range for data collection	2.57 to 27.51°.	
Index ranges	-12<=h<=15, -8<=k<=8, -13<=l<=13	
Reflections collected	5643	
Independent reflections	1057 [R(int) = 0.0495]	
Completeness to theta = 27.51°	99.6 %	
Absorption correction	Empirical	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1057 / 0 / 100	
Goodness-of-fit on F^2	1.047	
Final R indices [I>2sigma(I)]	R1 = 0.0382, wR2 = 0.1029	
R indices (all data)	R1 = 0.0534, wR2 = 0.1118	
Largest diff. peak and hole	0.243 and -0.240 e.Å^{-3}	

Table 64: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for schreiner12022. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1)	-9072(1)	2500	4794(1)	64(1)
F(2)	-10215(1)	4096(1)	3598(1)	53(1)
O(1)	-7671(1)	2500	2965(2)	65(1)
O(2)	-6602(2)	2500	-1446(2)	66(1)
O(3)	-7869(2)	2500	-2873(2)	85(1)
N(1)	-7584(2)	2500	-1787(2)	47(1)
C(1)	-9010(2)	2500	1318(2)	31(1)
C(2)	-10143(2)	2500	952(2)	31(1)
C(3)	-10430(2)	2500	-306(2)	33(1)
C(4)	-9596(2)	2500	-1209(2)	33(1)
C(5)	-8477(2)	2500	-825(2)	34(1)
C(6)	-8157(2)	2500	411(2)	34(1)
C(7)	-8647(2)	2500	2643(2)	38(1)
C(8)	-9548(2)	2500	3683(2)	41(1)

Table 65: Bond lengths [Å] and angles [°] for schreiner12022.

O(2)-N(1)	1.214(3)	C(4)-C(5)	1.383(3)
O(3)-N(1)	1.208(3)	C(4)-H(7)	0.91(2)
N(1)-C(5)	1.472(3)	C(5)-C(6)	1.372(3)
C(1)-C(2)	1.394(3)	C(6)-H(8)	0.96(2)
C(1)-C(6)	1.397(3)	C(7)-C(8)	1.539(3)
C(1)-C(7)	1.478(3)	C(8)-F(2)#1	1.3330(15)
C(2)-C(3)	1.386(3)		

O(3)-N(1)-O(2)	123.65(19)	C(4)-C(3)-H(6)	117.8(12)	C(1)-C(6)-H(8)	119.6(13)
O(3)-N(1)-C(5)	118.07(19)	C(2)-C(3)-H(6)	122.0(12)	O(1)-C(7)-C(1)	123.48(19)
O(2)-N(1)-C(5)	118.29(18)	C(3)-C(4)-C(5)	118.38(18)	O(1)-C(7)-C(8)	117.15(19)
C(2)-C(1)-C(6)	119.85(18)	C(3)-C(4)-H(7)	121.9(15)	C(1)-C(7)-C(8)	119.37(17)
C(2)-C(1)-C(7)	123.12(17)	C(5)-C(4)-H(7)	119.7(15)	F(1)-C(8)-F(2)	108.35(11)
C(6)-C(1)-C(7)	117.03(17)	C(6)-C(5)-C(4)	123.21(17)	F(1)-C(8)-F(2)#1	108.35(11)
C(3)-C(2)-C(1)	120.40(17)	C(6)-C(5)-N(1)	118.30(17)	F(2)-C(8)-F(2)#1	107.05(17)
C(3)-C(2)-H(5)	120.2(13)	C(4)-C(5)-N(1)	118.49(17)	F(1)-C(8)-C(7)	110.84(18)
C(1)-C(2)-H(5)	119.4(13)	C(5)-C(6)-C(1)	117.91(18)	F(2)-C(8)-C(7)	111.06(11)
C(4)-C(3)-C(2)	120.24(18)	C(5)-C(6)-H(8)	122.5(13)	F(2)#1-C(8)-C(7)	111.06(11)

Table 66: Anisotropic displacement parameters ($Å^2$x 10^3) for schreiner12022. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U11	U22	U33	U23	U13	U12
F(1)	65(1)	98(1)	28(1)	0	-5(1)	0
F(2)	55(1)	55(1)	48(1)	-7(1)	9(1)	10(1)
O(1)	31(1)	123(2)	42(1)	0	-10(1)	0
O(2)	34(1)	115(2)	49(1)	0	10(1)	0

O(3)	59(1)	166(2)	31(1)	0	9(1)	0
N(1)	39(1)	62(1)	38(1)	0	7(1)	0
C(1)	26(1)	35(1)	32(1)	0	0(1)	0
C(2)	24(1)	34(1)	35(1)	0	2(1)	0
C(3)	26(1)	34(1)	39(1)	0	-5(1)	0
C(4)	34(1)	34(1)	32(1)	0	-6(1)	0
C(5)	30(1)	39(1)	31(1)	0	4(1)	0
C(6)	24(1)	43(1)	34(1)	0	0(1)	0
C(7)	31(1)	50(1)	34(1)	0	-3(1)	0
C(8)	41(1)	53(1)	30(1)	0	-2(1)	0

Table 67: Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for schreiner12022.

	x	y	z	U(eq)
H(5)	-10709(19)	2500	1560(20)	32(5)
H(6)	-11202(19)	2500	-581(19)	33(5)
H(7)	-9760(20)	2500	-2040(20)	44(6)
H(8)	-7381(19)	2500	670(20)	38(6)

Table 68: Torsion angles [°] for schreiner12022.

C(6)-C(1)-C(2)-C(3)	0.0	O(3)-N(1)-C(5)-C(4)	0.0	C(2)-C(1)-C(7)-C(8)	0.0
C(7)-C(1)-C(2)-C(3)	180.0	O(2)-N(1)-C(5)-C(4)	180.0	C(6)-C(1)-C(7)-C(8)	180.0
C(1)-C(2)-C(3)-C(4)	0.0	C(4)-C(5)-C(6)-C(1)	0.0	O(1)-C(7)-C(8)-F(1)	0.0
C(2)-C(3)-C(4)-C(5)	0.0	N(1)-C(5)-C(6)-C(1)	180.0	C(1)-C(7)-C(8)-F(1)	180.0
C(3)-C(4)-C(5)-C(6)	0.0	C(2)-C(1)-C(6)-C(5)	0.0	O(1)-C(7)-C(8)-F(2)	120.50(12)
C(3)-C(4)-C(5)-N(1)	180.0	C(7)-C(1)-C(6)-C(5)	180.0	C(1)-C(7)-C(8)-F(2)	-59.50(12)
O(3)-N(1)-C(5)-C(6)	180.0	C(2)-C(1)-C(7)-O(1)	180.0	O(1)-C(7)-C(8)-F(2)#1	-120.50(12)
O(2)-N(1)-C(5)-C(6)	0.0	C(6)-C(1)-C(7)-O(1)	0.0	C(1)-C(7)-C(8)-F(2)#1	59.50(12)

12.Literature

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