Ring Opening Of Epoxides By Chelated Amino Acid Ester Enolates

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My Grandfather (Late) and my parents!

Acknowledgement

In the name of Allah, the most Beneficent, the most Merciful, the most Gracious. I would have been nothing without His grace. My faith remains incomplete without the respect for Holy Prophet Muhammad (PBUH), the great Messenger, Who conveyed the message of Truth and showed us the right way to live.

These are moments of great pleasure and satisfaction for me while I am finishing my Ph.D thesis…….a dream soon coming true. When I look back on my academic journey, time seizes and mind wanders through various corridors of memories of life reminding me of the best days of my life spent with my class fellows, friends and my family. Starting from Prep. class to the highest level of education was a long journey and at each step I was fortunate to have nice, sincere people who made this journey easier and easier as the time went on. In my success, many people around me have a great role who I would like to thank.

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I am grateful to Higher Education Commission Pakistan and DAAD (Germany) for giving me a PhD scholarship.

Last but not the least, I thank my family for supporting throughout my life. Without their love and support, I would not have been able to get to the place where I stand today.

Ameer Fawad Zahoor

Abstract

Epoxides are very versatile building blocks in organic synthesis. High ring strain in epoxides (greater than 20 kcal/mol) ensures their synthetic utility for nucleophilic ring opening reactions. Until now different methodologies have been developed for the ring opening of epoxides but use of chelated amino acid ester and dipeptide enolates has not been reported so far for such reactions.

This thesis deals with the ring opening of epoxides with chelated amino acid ester enolates. Different epoxides (aryl and alkyl substituted) were used for regioselective ring opening reactions. Depending on the substitution pattern, the reaction proceeds either in a S_N1-type (aryl epoxides) or a S_N2-type (alkyl epoxides) fashion, giving rise to γ-hydroxy α-amino acids. The products of ring opening reactions were successfully subjected to further synthetic applications. Ring opening products of aryl epoxides were used in synthesis of a wide range of modified β-substituted phenylalanine derivatives. On the other hand, ring opening products of alkyl epoxides were oxidized and the ketones obtained were successfully subjected to various carbonyl additions e.g., Passerini and Reformatsky reactions as well as to allylations and methylations. Moreover, the methodology was also successfully applied to peptide modifications.

Kurzfassung

Epoxide sind sehr vielseitige Synthesebausteine in der organischen Chemie. Die große Ringspannung der Epoxide (>20 kcal/mol) ist verantwortlich für ihre gute Reaktivität gegenüber Nukleophilen (Ringöffnung). Zwar wurden bis heute zahlreiche Methoden entwickelt, um Epoxide zu öffnen, aber die Verwendung von chelatisierten Aminosäureester- und Dipeptidenolaten ist bis dato nicht beschrieben.

Diese Arbeit befasst sich mit der regioselektiven Ringöffnung unterschiedlich substituierter Epoxide durch chelatisierte Aminosäureesterenolate. Abhängig vom Substitutionsmuster kann die Ringöffnung sowohl nach einem S_N1-Mechanismus (Arylepoxide) als auch nach einem S_N2-Mechanismus (Alkylepoxide) ablaufen. Die so erhaltenen γ-Hydroxy- α-aminosäuren wurden in zahlreichen synthetischen Anwendungen eingesetzt. So konnten die bei der Verwendung von Arylepoxiden erhaltenen Produkte zu β-modifizierten Phenylalaninderivaten umgesetzt werden. Die Produkte der Alkylepoxide wiederum wurden oxidiert und die erhaltene ketone anschließend erfolgreich in verschiedenen Carbonylreaktionen (z.B.: Passerini, Reformatsky) eingesetzt. Außerdem wurde diese Methode erfolgreich bei Peptidmodifizierung verwendet.

Contents

Abbreviations

abs.	absolute
Ac	Acetyl, [CH_3–CO]
AIBN	Azo-bis-(isobutyronitril), [NC–$(CH_3)_2$C–N=N–C$(CH_3)_2$–CN]
Ar	Aromatic
Bn	Benzyl, [C_6H_5–CH_2]
Boc	*tert*-Butyloxycarbonyl, [$(CH_3)_3$C–O–CO]
Bu	*n*-Butyl, [CH_3–$(CH_2)_2$–CH_2]
*t*Bu	*tert*-Butyl, [$(CH_3)_3$C]
*n*BuLi	*n*-Butyllithium, [$H_9C_4^+$ Li^-]
CI	Chemical Ionization
Cy	Cyclohexyl, [C_6H_{11}]
dba	Dibenzylidenacetone, [$(H_5C_6$–CH=CH$)_2$CO]
d^{t}bpe	1,2-Bis-(di-*tert*-butylphosphino)-ethan, [^{t}Bu$_2$P–CH_2–CH_2–P^{t}Bu$_2$]
DBPO	Dibenzoylperoxid, [$(C_6H_5$–COO$)_2$]
DIAD	Diisopropylazodicarboxylate, [$(CH_3)_2$CH–O–CO$)_2N_2$]
DMSO	Dimthylsulfoxide
dr	Diastereomeric ratio
ds	Diastereoselectivity
EA	Ethyl acetate, [CH_3–COO–CH_2–CH_3]
Et	Ethyl, [C_2H_5]
fac	facial Configuration
g	Gram
GC	Gaschromatography
h	hour
Hex	Hexyl, [C_6H_{13}]
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
HSQC	Heteronuclear Single Quantum Coherence
J	Coupling constant
LHMDS	Lithiumhexamethylsisilazane, [Li^+ $((CH_3)_3Si)_2N^-$]
*m*CPBA	*meta*-Chloroperbenzoic acid, [*m*-Cl–C_6H_4–CO–OOH]
M.Pt.	Melting point
Me	Methyl, [CH_3]
MHz	Megahertz
min	Minute
mg	Milligram
mmol	Millimole

mol%	Mole percent
N	Normality of solution
NMR	Nuclear Magnetic Resonance
Ph	Phenyl, [C_6H_5]
ppm	Parts per million
*i*Pr	Isopropyl, [$(CH_3)_2CH$]
R_f	Retention factor
r.t.	Room temperature
t	Reaction time
T	Temperature (in °C)
TBAF	N,N,N,N-Tetra-*n*-butylammoniumfluorid, [$(H_9C_4)_4N^+ F^-$)]
TBDMS	*tert*-Butyl-dimethylsilyl, [$((CH_3)_3C)(CH_3)_2Si$]
TBDPS	*tert*-Butyl-diphenylsilyl, [$((CH_3)_3C)(C_5H_6)_2Si$]
TFA	Trifluoracetyl, [$F_3C–CO$]
THF	Tetrahydrofuran, [C_4H_8O]
THP	Tetrahydropyranyl, [C_5H_9O]
TMS	Trimethylsilyl, [$(CH_3)_3Si$]
Tos	*para*-Toluenesulfonyl, [$CH_3–C_6H_5–SO_2$]

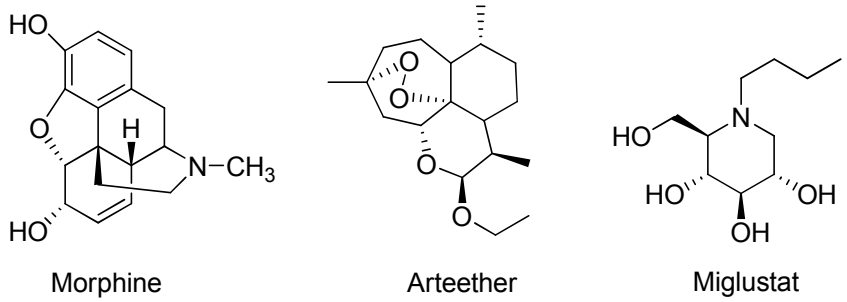
1 Preface

The advent of the fact that organic compounds could be synthesized in the laboratory brought a tremendous change in scientific research. Friedrich Wöhler[1], was the first organic chemist to synthesize an organic compound (urea) in 1828 from inorganic material (ammonium cyanate), undermined the *Vital Force Theory*. Soon after this discovery, acetic acid[2] and '*Mauveine*'[3] were synthesized. In 1853 Charles Frederic Gerhardt synthesized aspirin[4]. All of these efforts and investigations by chemists resulted in the beginning of pharmaceutical industry in the late 19th century when aspirin was manufactured by the german company Bayer.

In contrast to discoveries ealier which were rather accidental in nature, a new trend was observed in organic chemistry in late 19th century when more systematic and well-planned approaches were applied. R. B. Woodword and E. J. Corey gave organic synthesis a status of fine art. Some of most spectacular achievements of R. B. Woodward are quinine[5], patulin[6], cholestrol and cortisone[7], lancosterol[8], lysergic acid[9], strychnine[10], chlorophyll *a*[11], cephalosporin[12] and prostaglandin $F_{2\alpha}$[13]. A new turnaround in history of organic chemistry was observed when E. J. Corey introduced the concept of retrosynthetic analyis. E. J. Corey was awarded nobel prize for his contributions towards organic chemistry.

As the investigations went on, many new methodologies were developed for homo/cross-coupling reactions. Wurtz[14], Kolbe[15], Grignard[16], Ulman[17], Kumada[18], Corriu[19], Kochi[20], Mizoroki[21], Heck[22], Negishi[23], Stille[24], Suzuki[25], Hiyama[26], Buchwald[27], Hartwig[28] and many others paved the way to solve those synthetic challenges in organic synthesis which otherwise would have been very improbable to solve. These coupling reactions cover a wide range of different substrates and allow them to couple, giving rise to new *C-C*, *C-N* or *C-O* linkages.

In parallel to the developments in new synhetic approaches, discoveries of natural products also went forward and remarkable milestones have been achieved in this arena. The first isolation and purification of morphine (Figure 1.1) from opium by Sertürner[29] laid the foundation of pharmacology as an independent discipline. Since then hundreds of new natural products have been isolated and purified.



Morphine Arteether Miglustat

Figure 1.1: Structures of morphine, arteether and miglustat (natural products).

An important class of natural products are amino acids which are present in living organisms as structural units. In 1806, the first amino acid asparginine was discovered and isolated from asparagus.[30] The twenty proteinogenic amino acids are a special category since they are fundamental as building blocks for the proteins in all life forms. These amino acids are joined together to short polymer chains called peptides or long polymer chains called polypeptides or proteins. The human body contains over 50,000 different forms of proteins. In principle, amino acids are classified into proteinogenic (found in proteins) and nonproteinogenic amino acids (not present in proteins). In general, approximately 1,000 naturally occuring amino acids are known and scientists in various disciplines of science like chemists, pharmacists and biologists are engaged in studying their properties for more than 200 years. The basic framework of an amino acid is shown in figure 1.2.

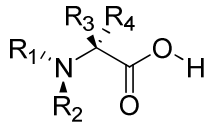
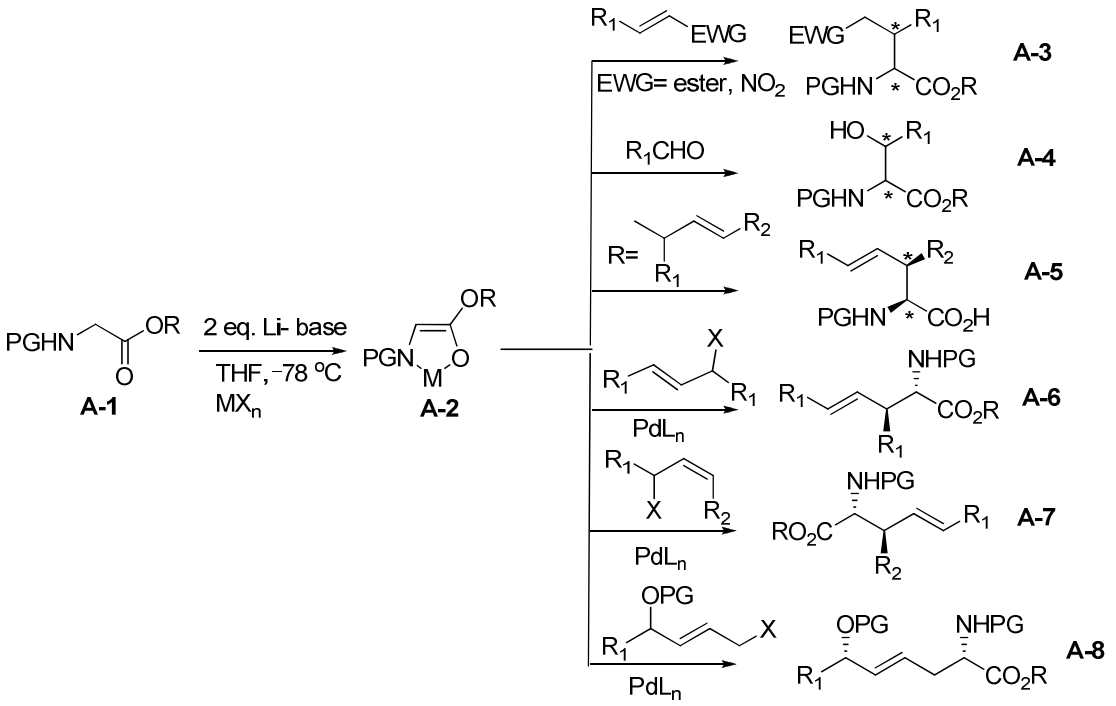


Figure 1.2: Basic framework of amino acids.

Among others, non-proteinogenic amino acids are of considerable interest because of their enzyme inhibitory activity, their protease resistence, and their influence on the conformation of peptides. Many of the pharmaceutical drugs and biologically active compounds are comprised of unnatural amino acids. Unnatural amino acids have also become important starting materials for drug-like molecules, and unnatural amino acids with diverse physiochemical and biological properties can be encoded in mamalian cells.[31] As a result of such synthetic utilities many new methodologies for the synthesis of unnatural amino acids have emerged.

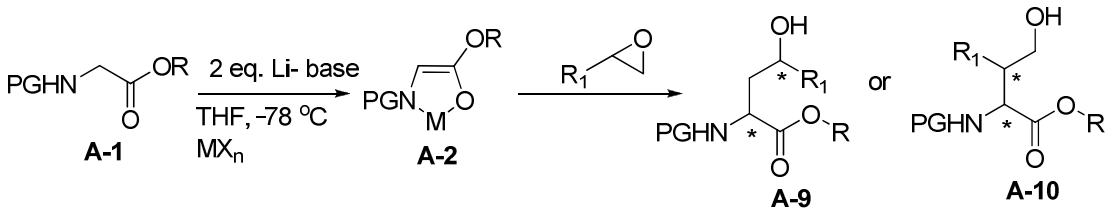
Prof. Dr. Uli Kazmaier's research group is actively involved since years in developing new synthetic methodologies and their applications in synthesis of natural products. The group has developed new methodologies for the stereoselective syntheses of amino acids. Chelated enolates of *N*-protected glycine esters have been allowed to react with various electrophiles and in general new *C*-*C* bonds are formed in a highly stereoselective fashion. Many complex and highly functionalized amino acids have been synthesized so far (Scheme 1.1).



Scheme 1.1: Reactions of chelated glycine ester enolate by Kazmaier's research group.

Moreover peptide modifications are also under investigation and this methodology has been employed in various synthetic applications.[32]

Since glycine ester enolates have proved to be very effective nucleophiles in various reactions, we were interested to figure out if the ring opening of epoxides could also be carried out with glycine ester enolates. Because epoxide openings are popular reactions, various groups have reported the ring opening of epoxides with a variety of nucleophiles which will be discussed in chapter 2, but so far ring opening reactions of epoxides with chelated amino acid ester enolates is not yet described. This work will investigate the ring opening of epoxides with glycine ester enolates and will cover the effect of various factors such as the effect of chelating metal salts, the protective groups, and the substituents on the epoxide ring, etc. After optimization of the reaction conditions, synthetic utility of the methodology will be investigated (Scheme 1.2).



Scheme 1.2: Ring opening of epoxides with chelated glycine ester enolates.

2 Introduction

Epoxides are versatile synthetic intermediates and considered as 'spring-loaded' rings for further synthetic applications.[33] High ring strain in epoxides (greater than 20 kcal/mol) ensures their synthetic utility for nucleophilic ring opening reactions. The reactivity of epoxides is further enhanced with the use of Lewis acids.[34] Generally, epoxides are easily prepared by the oxidation of the corresponding alkenes.[35] The nucleophilic ring-opening of epoxides provides an excellent synthetic strategic for the formation of new *C*-*C* bond formation in a stereo-defined fashion.[36]

Nucleophilic ring opening of epoxides has been used as key step in the syntheses of a number of natural products and drugs, and is therefore of considerable interest for synthetic organic and medicinal chemists. Until now different methodologies have been developed for the ring opening of epoxides. This chapter will cover selected methodologies for epoxide synthesis and the ring opening of epoxides with various nucleophiles (amines, imines, cyanide, azides, alcohols, carbon-based nucleophiles) recently reported by different research groups.

2.1 Synthesis of epoxides

Generally, epoxides can be prepared by a variety of methods. Most common starting materials for the synthesis of epoxides are olefins. Many reactions like Prilezhaev reaction, Davis oxaziridine oxidation, Shi asymmetric epoxidation, Jacobsen-Katsuki epoxidation, Weitz-Scheffer epoxidation, Sharpless epoxidation, etc. employ the use of alkenes as starting materials. Whereas α-halo esters are the starting materials for Darzens glycidic ester condensation reaction, Corey-Chaykovsky epoxidation reaction involves the reaction between sulphur ylides and aldehydes or ketones. In this part we will focus on Darzens glycidic ester condensation and Corey-Chaykovsky epoxidation.

2.1.1 Darzens glycidic ester condensation

The synthesis of α, β-epoxy esters (glycidic esters) from aldehydes and ketones and α-halo esters under basic condition is known as Darzens glycidic ester condensation. This method was first reported by Erlenmeyer who investigated the condensation of benzaldehyde with ethylchloroacetate in the presence of sodium metal.[37] Darzens modified and developed the method further and reported that NaOEt could be used as base, whereas other bases like sodium amide, *N*-ethyl-*N*-(tributylstannyl)carbamate could also be used for this transformation.[38] The mechanism of this reaction proceeds through two steps. First step is the deprotonation of α-halo ester and is the rate determining step. The resulting enolate

attacks the carbonyl group of an aldehyde or ketone. The intermediate formed undergoes S_Ni reaction in a second step to form the epoxide ring (Figure 2.1).

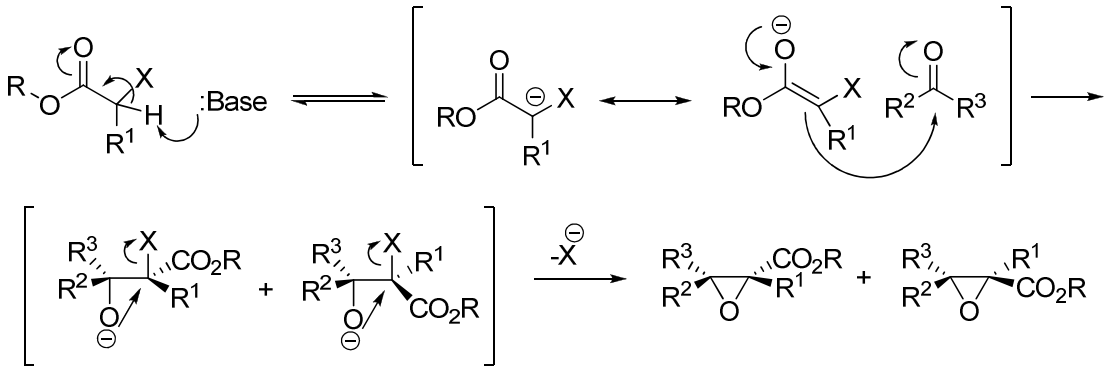
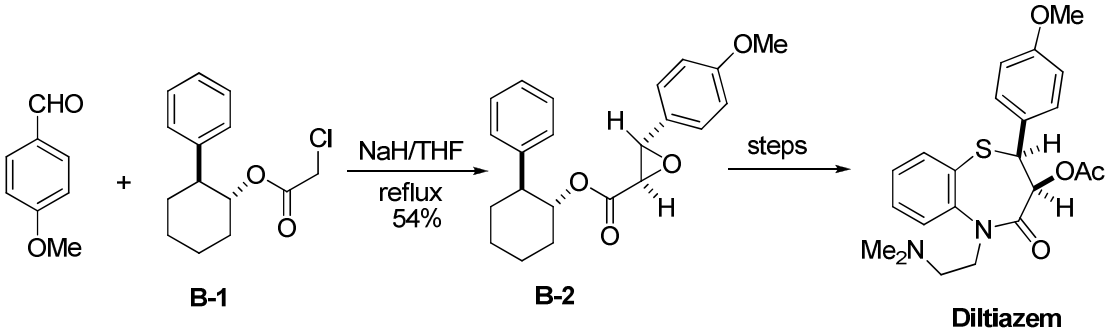


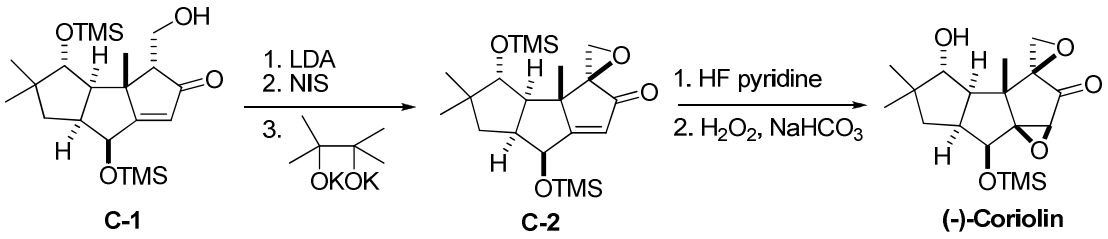
Figure 2.1: Mechanism of Darzens glycidic ester condensation.

Schwartz *et al* synthesized many calcium channel blockers of the diltiazem group enantioselectively by an auxiliary-induced asymmetric version of this reaction.[39] They condensed *p*-anisaldehyde with enantiomerically pure α-chloro acetate **B-1** which gave rise to a pair of diastereomeric glycidic esters which could be separated by crystallisation (Scheme 2.1).



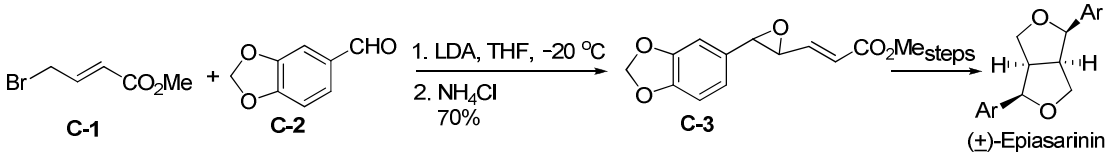
Scheme 2.2: Synthesis of epoxides **B-2** by Schwartz *et al*. [39]

Kuwajima *et al* used Darzens type reaction during synthesis of (-)-coriolin, whereby a spiro epoxide moiety was constructed on the triquinane skeleton (Scheme 2.2).[40]



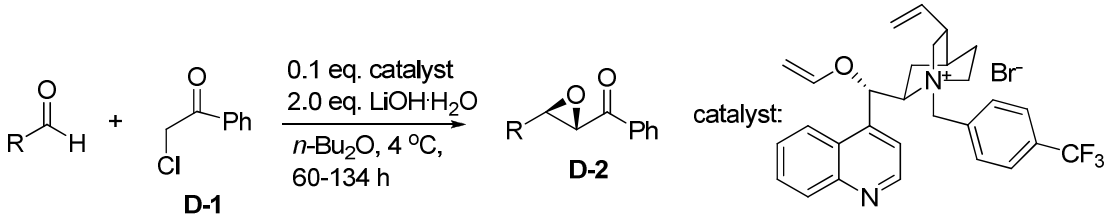
Scheme 2.2: Synthesis of epoxide **C-2** by Kuwajima *et al* using a Darzens type reaction. [40]

Steel *et al* used a Darzens condensation in their five step synthesis of (±)-epiasarinin from piperonal.[41] The vinyl epoxide **C-3** was prepared by treating a solution of (*E*)-methyl-4-bromocrotonate and piperonal with LDA, and subsequent quenching the reaction mixture with NH_4Cl (Scheme 2.3).



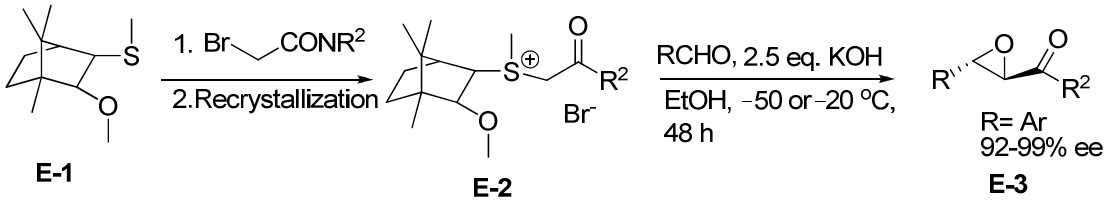
Scheme 2.3: Synthesis of epoxide **C-3** by Steel *et al* using a Darzens type reaction.[41]

Arai *et al* reported a phase transfer catalyzed asymmetric Darzens reaction. They used a chiral ammonium salt derived from cinchonine as phase transfer catalyst and the Darzens products were obtained in moderate to high yields (Scheme 2.4).[42]



Scheme 2.4: Asymmetric synthesis of epoxide **D-2** by using phase tranfer catalyst by Arai *et al*.[42]

Aggarwal *et al* modified the Darzens reaction and reported the use of camphor-derived sulfonium salts for the highly enantioselective synthesis of glycidic amides (Scheme 2.5).[43]



Scheme 2.5: Asymmetric synthesis of epoxy amides by Aggarwal *et al*.[43]

2.1.2 Corey-Chaykovsky epoxidation

The synthesis of epoxides by the reaction of aldehydes and ketones with sulphur ylides is known as Corey-Chaykovsky reaction. E. J. Corey and M. Chaykovsky reported the synthesis of epoxides from sulphur ylides for the first time in 1962.[44] When aldehydes and ketones are allowed to react with dimethyl sulfoxonium methylide or dimethyl sulfonium methylide, epoxides are produced. The sulphur ylides are generated *in situ* by deprotonation of the sulfonium salts using strong bases (Figure 2.2).

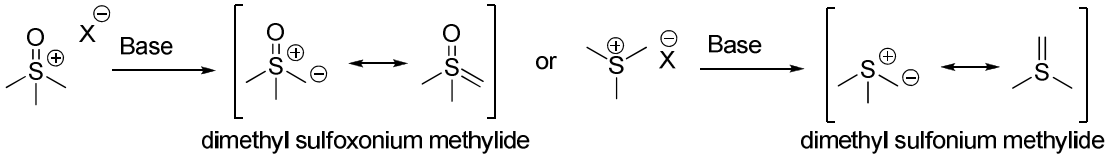


Figure 2.2: *In situ* generation of sulfur ylides.

The ylide acts as nucleophile and attacks the carbonyl group of an aldehyde or ketone. The resulting oxygen anion acts as an intramolecular nucleophile and attacks electrophilic ylide carbon which bears sulfonium cation as good leaving group (Figure 2.3).

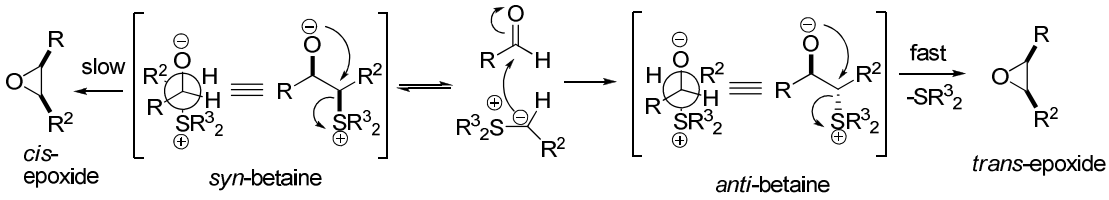
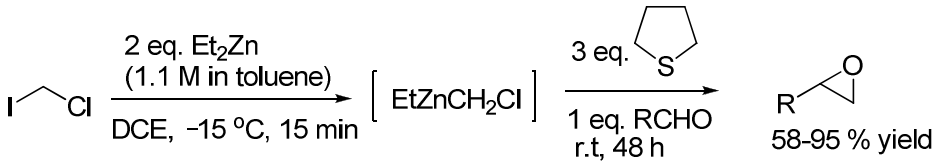


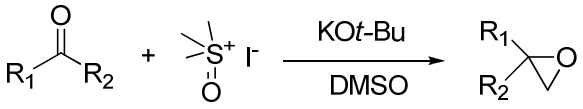
Figure 2.3: Mechanism of Corey-Chaykovsky epoxidation.

Aggarwal *et al* developed a new application of organozinc reagents for the epoxidation of carbonyl compounds using sulphur ylides.[45] The methodology resulted in moderate to high yields (58-95 %) (Scheme 2.6).



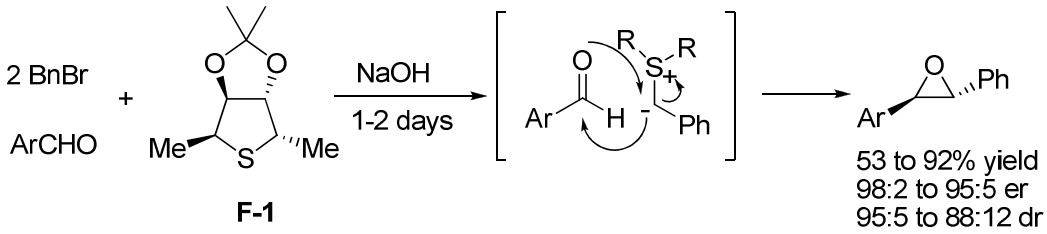
Scheme 2.6: Application of Simmons-Smith reagent towards epoxidation according to Aggarwal *et al*.[45]

Ng modified the methodology and reported the use of potassium *tert*-butoxide as base instead of sodium hydride.[46] This method could also be used for large scale epoxide preparations (Scheme 2.7).



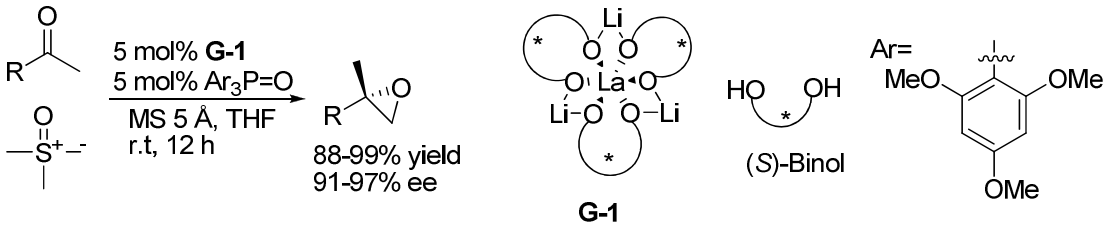
Scheme 2.7: Modification of Corey-Chaykovsky epoxidation acording to Ng.[46]

Metzner *et al* reported new 2,5-dimethylthiolanes as promoters with locked conformation which facilitated the asymmetric addition of chiral sulfonium ylides to aldehydes.[47] They could synthesize *trans*-stilbene oxide derivatives with enantiomeric ratios (er) ranging from 95:5 to 98:2 (Scheme 2.8).



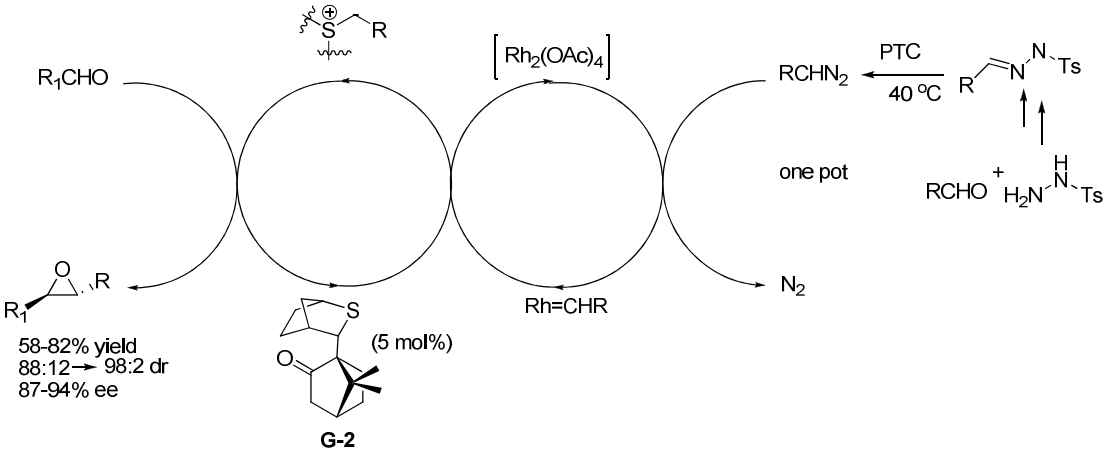
Scheme 2.8: Use of 2,5-dimethylthiolanes as promoters towards epoxidation according to Metzner *et al.*[47]

Shibasaki *et al* developed the methodology to synthesize chiral 2,2-disubstituted terminal epoxides.[48] A La-Li_3-tris(binaphthoxide) (**G-1**) complex with 2,4,6-trimethoxyphenyl phosphine oxide was used to promote the addition of dimethyloxosulfonium methylide to ketones. As a result, 2,2-disubstituted epoxides were obtained in high yields and high enantioselectivities (Scheme 2.9).



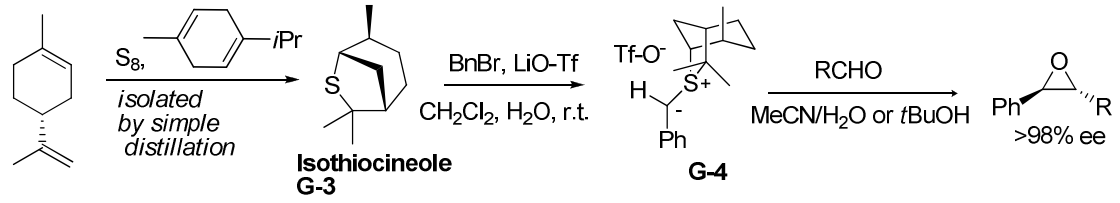
Scheme 2.9: Synthesis of chiral 2,2-disubstituted terminal epoxides according to Shibasaki *et al.*[48]

Aggarwal *et al* developed a new class of sulfides which could affectively convert carbonyl compounds directly into epoxides.[49] The methodology resulted in moderate to high yields with control of the absolute and relative stereochemistry by generating diazo compound as reactive intermediate *in situ* from tosyl hydrazone salts (Scheme 2.10).



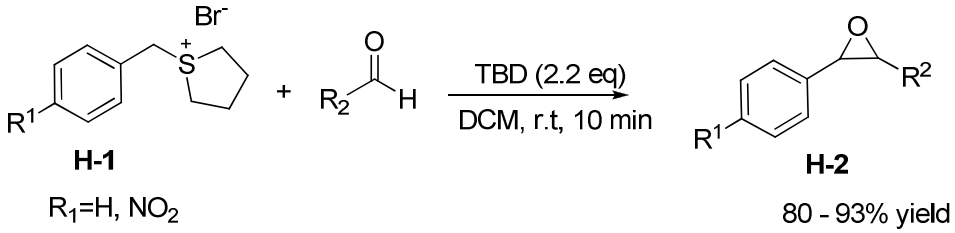
Scheme 2.10: Synthesis of chiral epoxides by Aggarwal *et al.* [49]

The same group later on reported the synthesis of chiral 1,2-arylalkyl and α-β-unsaturated epoxides by using a new chiral sulphide **G-3**. They used this methodology in the convergent and stereoselective synthesis of quinine and quinidine (Scheme 2.11).[50]



Scheme 2.11: Synthesis of chiral epoxides by Aggarwal *et al* using isothiocineole.[50]

Philips and Graham reported the use of guanidine bases in the Corey-Chaykovsky epoxidation.[51] The protocol employs guanidine bases such as 1,5,7-triaza-bicyclo[4.4.0]dec-1-ene (TBD) or 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-1-ene (MTBD) for the *in situ* generation of sulfonium ylides from sulfonium salts. The reaction is fast and the corresponding epoxides are produced in excellent yields and high selectivity for *trans* products. The methodology is also useful for both enolizable and nonenolizable, as well as and α-β-unsaturated aldehydes. Moreover the method allows the use of an oxidant such as manganese dioxide, for the development of an oxidation-epoxidation protocol (Scheme 2.12).



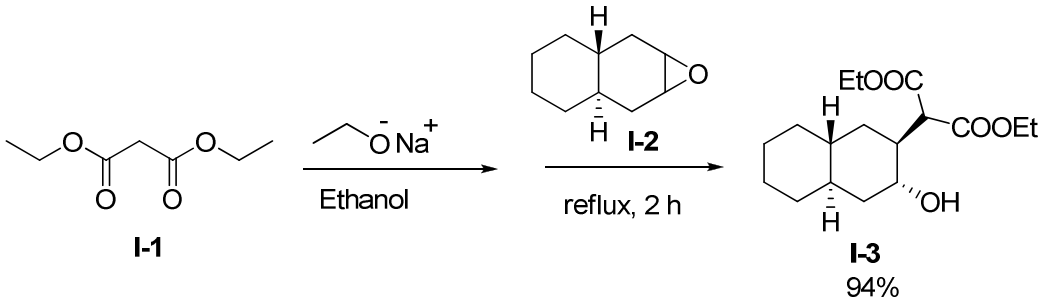
Scheme 2.12: Use of guanidine bases in epoxide synthesis by Philips and Graham.[51]

2.2 Ring opening of epoxides by nucleophiles

2.2.1 Carbon nucleophiles

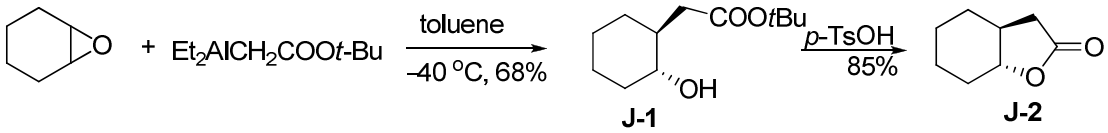
2.2.1.1 Ester enolates as nucleophiles

Generally malonic ester enolates have been used as nucleophiles for epoxide ring opening reactions which proceed through inversion of configuration, hence *trans* fused γ-lactones can be obtained. This was demonstrated elegantly by Johnson *et al*[52] during their study on the conformational analysis of cyclohexanes. In this study they opened the ring of epoxide **I-2** using diethyl malonic ester enolate and obtained **I-3** in 94% yield (Scheme 2.13).



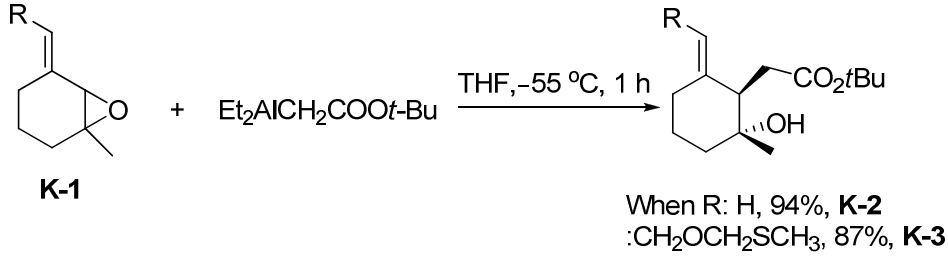
Scheme 2.13: Ring opening of epoxide **I-2** with diethyl malonic ester enolate.[52]

Danishefsky *et al* converted epoxides to *trans*-fused γ-lactones.[53] They treated the aluminium enolate of *tert*-butylacetate with cyclohexene oxide in toluene and the resulting hydroxy ester **J-1** was cyclized to lactone **J-2** using *p*-toluenesulfonic acid as shown in Scheme 2.14.



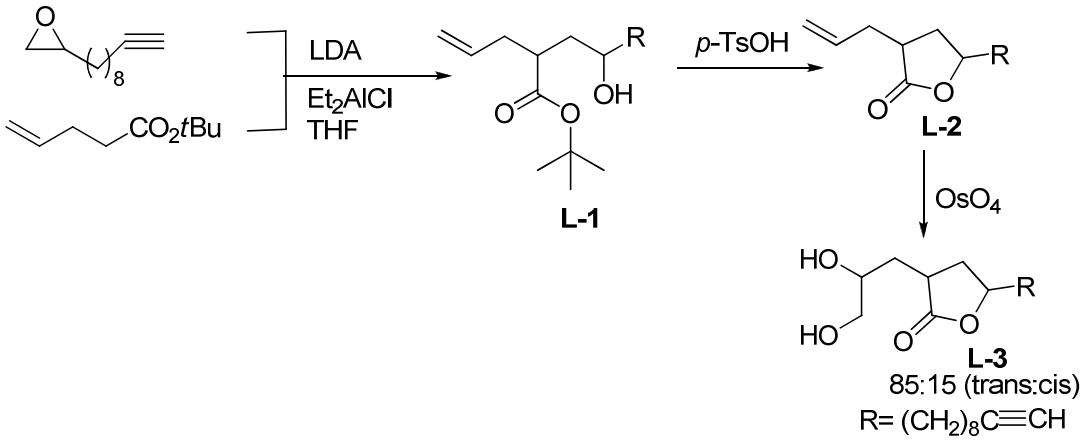
Scheme 2.14: Ring opening of epoxide **J-1** and application towards γ-lactone **J-2** according to Danishefsky *et al.* [53]

Battiste *et al* used substituted analogs of cyclohexene oxide and treated them with same enolate as Danishefsky *et al* did.[54] With this study they could demonstrate that the methodology could also tolerate different functional groups (Scheme 2.15).



Scheme 2.15: Ring opening of epoxides according to Battiste *et al.*[54]

The ring opening reactions with aluminium enolates do not necessarily result in high yields, but side products are generally minimal or even absent upon workup. The methodology was applied in the first synthesis of (±)-rubrynolide by Taylor *et al*.[55] The epoxide of 1-dodecen-11-yne was treated with the *t*-butyl ester of 4-pentenoic acid to give hydroxy ester **L-1** which was then cyclized and osmylated to yield rubrynolide (Scheme 2.16).



Scheme 2.16: Synthesis of rubrynolide according to Taylor *et al*.[55]

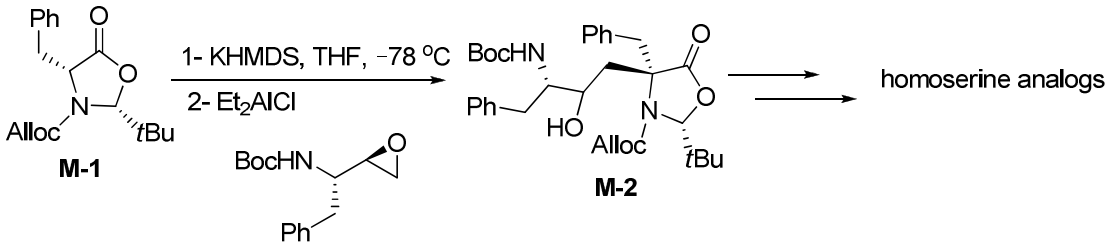
The same group also reported stereoselective reactions of ester enolates with epoxides. They allowed lithium enolate of *tert*-butyl acetate (generated from LDA) to react with propylene oxide, but even after 24 h <1% of product was produced. However, with the addition of Et_2AlCl the desired product was obtained in reasonable yield. It could be assumed that Li-enolates of *tert*-butyl acetate was not reactive enough to open epoxide ring but Al-enolates could open the epoxide ring (Table 2.1).[56]

Table 2.1: Ring opening of epoxides Taylor *et al*.[56]

Entry	R	Base	R’	Yield,[a] %	syn:anti
1	Me	LDA	Me	56 [a](70)	84:16
2	Me	LDA	Et	43 [a]	84:16
3	Me	LDA	*i*-Pr	56 [a]	88:12
4	Me	LDA	*t*-Bu	38 [a]	95:5

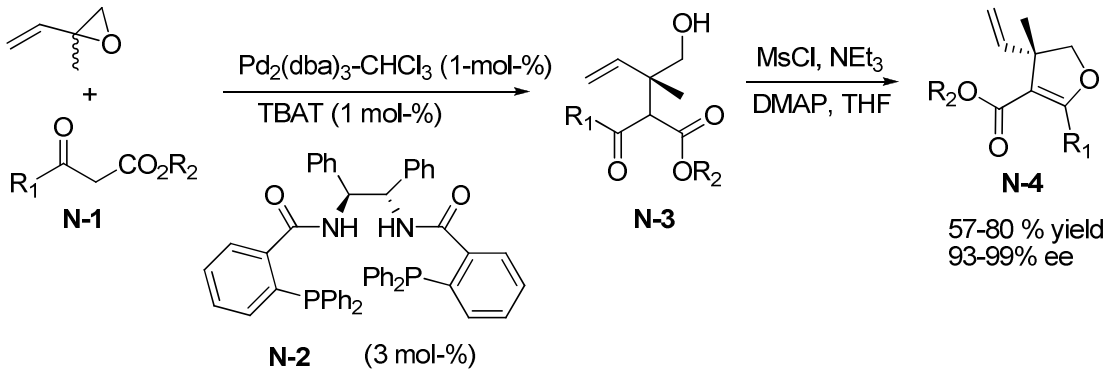
[a] Distilled yield.

Hirschman *et al* used the Karady/Seebach oxazolidinone for alkylation with epoxides and got the products in moderate to good yields with high diastereoselectivity.[57] They generated aluminium enolate of oxazolidinone **M-1** which was allowed to react with several epoxides. The methodology is effective as it proves to be a nice approach for the synthesis of uncoded homoserine analogs (Scheme 2.17).



Scheme 2.17: Synthesis of homoserine analogs according to Hirschman *et al*.[57]

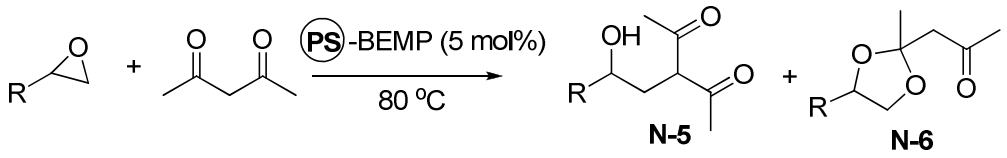
Trost and Jiang used ethyl acetoacetate for asymmetric addition to isoprene monoepoxide.[58] The reaction was catalysed by 1 mol % of $[Pd_2(dba)_3]CHCl_3$ and 3 mol % of chiral ligand **N-2**. The regio- as well as enantioselectivity could be controlled by the use of chiral ligand **N-2**. Products **N-3** were obtained as mixture of diastereomers which were converted to dihydrofurans **N-4.** Good yields of the desired 1,2-adducts were obtained with a variety of β-ketoesters with 57-80% yield and 93-99% ee (Scheme 2.18).



Scheme 2.18: Regio- and enantioselective ring opening of isoprene monoepoxide with β-keto esters according to Trost and Jiang. [58]

Pizzo *et al* developed a catalytic method for ring opening of epoxides by activated methylenes promoted by a polymer-supported base.[59] The reaction was carried out under solvent-free conditions and best results could be achieved by polystyrene-supported bases such as 5 mol % of PS-BEMP or PS-DMAP (Table 2.2).

Table 2.2: Ring opening of epoxides according to Pizzo *et al.* [59]



Entry	Epoxide	Time (h)	Yield[a] (%)	**N-5**/**N-6**[b]
1	Phenyl glycidyl ether	18	92	71/29
2	Allyl glycidyl ether	24	72	72/28
3	Benzyl glycidyl ether	48	80	66/34

[a] Overall isolation yield. [b] Measured by NMR.

The formation of **N-6** could be explained by a mechanism shown in figure 2.4.

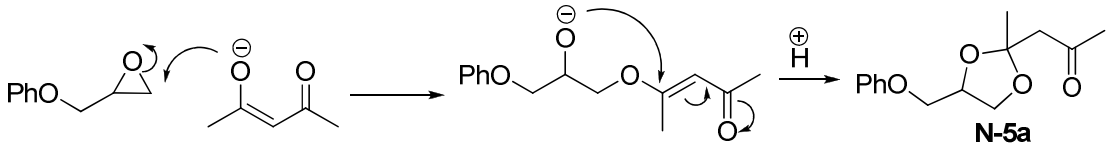
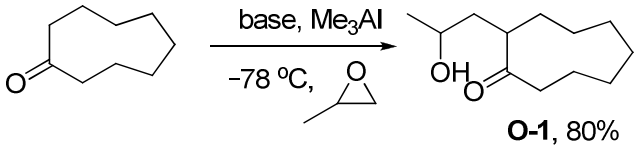


Figure 2.4: Formation of dioxane **N-5a**.

2.2.1.2 Ketone enolates as nucleophiles

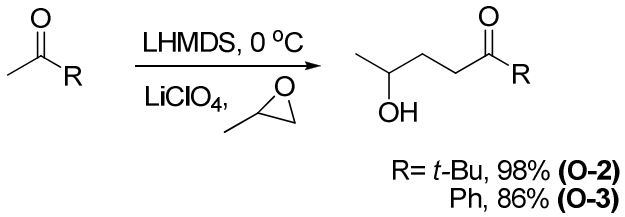
Initially, lithium enolates of ketones did not react with epoxides. Taylor *et al* attempted to react the enolates of acetophenone, 3-pentanone and cyclohexanone with epoxides but no product was obtained (even after the treatment of the epoxides with 3-pentanone for several hours at r.t.).[60] Attempts were also made to react aluminium enolates of ketones but no significant yields of desired products were obtained.

Schreiber found that the alkylation of lithium enolate of cyclononanone with propylene oxide could be performed cleanly in 80% yield when 2.4 eq. of Me_3Al was added.[61] This work was reported in connection with the synthesis of (±)-recifeiolide (Scheme 2.19).



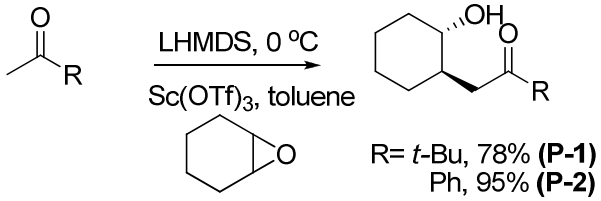
Scheme 2.19: Alkylation of cyclononanone enolate with propylene oxide according to Screiber.[61]

Crotti *et al* reported the use of $LiClO_4$ as Lewis acid and found the desired products in high yields, but still this methodology suffered from some limitations: a) in certain cases elevated temperatures were used (50 °C), b) large amount of promoting salt had to be used (1.5:1 ratio to the epoxide), and c) in certain cases long reaction times are necessary (Scheme 2.20).[62]



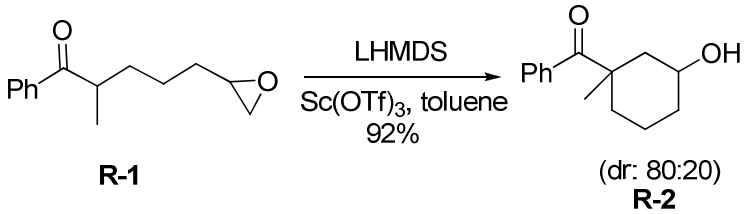
Scheme 2.20: Epoxide opening by ketone enolates according to Crotti *et al*. [62]

Crotti's group then tried to remove the shortcomings in their methodology by the use of lanthanum triflates. They tested many metal salts and found $Sc(OTf)_3$ to be the best one which could open epoxide ring at lower temperature, with shorter reaction time and high yield (Scheme 2.21).



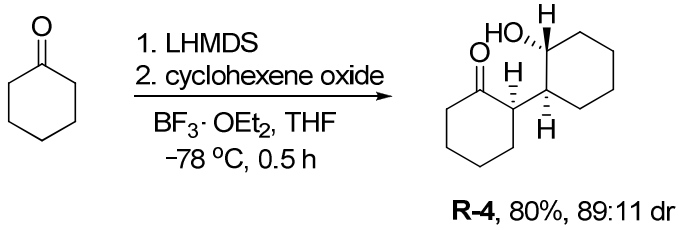
Scheme 2.21: $Sc(OTf)_3$ assisted ring opening of cyclohexene oxide according to Crotti *et al*.[62]

This methodology was then applied to intramolecular ring opening reaction and 3-, 5- and 7-membered rings. For example, epoxide **R-1** was subjected to intramolecular ring opening reaction and γ-hydroxy ketone **R-2** was obtained in 92% yield with a diastereoselectivity of 80% (Scheme 2.22).



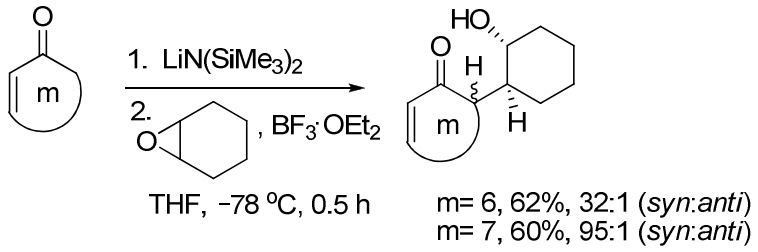
Scheme 2.22: Intramolecular ring opening of epoxides according to Crotti *et al*.[62]

Posner *et al* reported the ring opening of epoxides with several enolates of five- to seven-membered cycloalkanones.[63] The ring opening reaction resulted in 57-76% yields and proceeded with 4-8:1 diastereoselectivity. For example ring opening of cyclohexene oxide with cyclohexanone afforded **R-4** in 80% yield with a diastereomeric ratio of 89:11 (Scheme 2.23).



Scheme 2.23: Ring opening of epoxides according to Posner *et al*.[63]

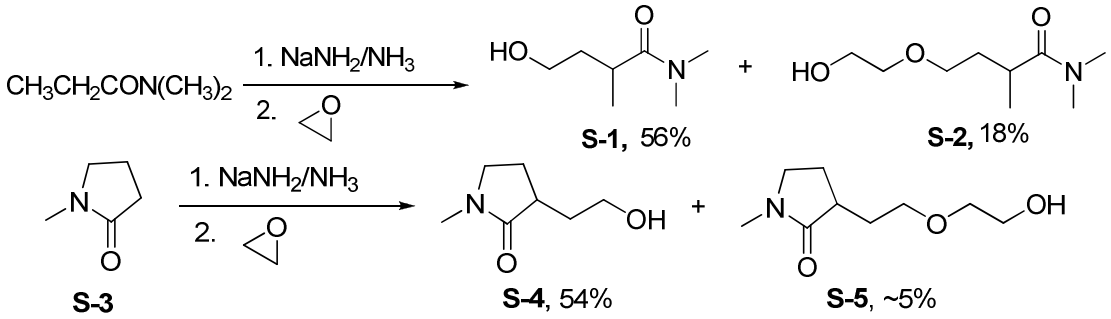
The same group later on reported the ring opening of cyclohexene oxide with the enolates of 2-cyclohexenone and 2-cycloheptenone in 60-62% yields with 32-95:1 diastereoselectivity (Scheme 2.24).[64]



Scheme 2.24: Ring opening of epoxides according to Posner *et al*.[64]

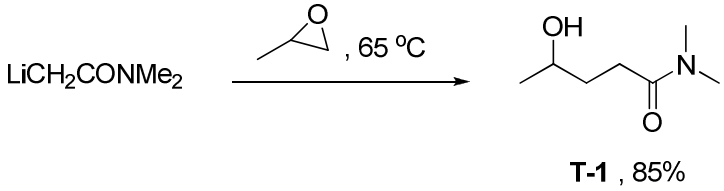
2.2.1.3 Amide enolates as nucleophiles

Tertiary amide enolates react with epoxides and several reports have been published on this topic. Sucrow *et al* produced enolates of tertiary amides with $NaNH_2$ but the reaction resulted in low yield.[65] It was observed that besides the desired products **S-1**and **S-4**, minor-products **S-2** and **S-5** were also formed (Scheme 2.25).



Scheme 2.25: Ring opening of epoxides with amide enolates according to Sucrow *et al*.[65]

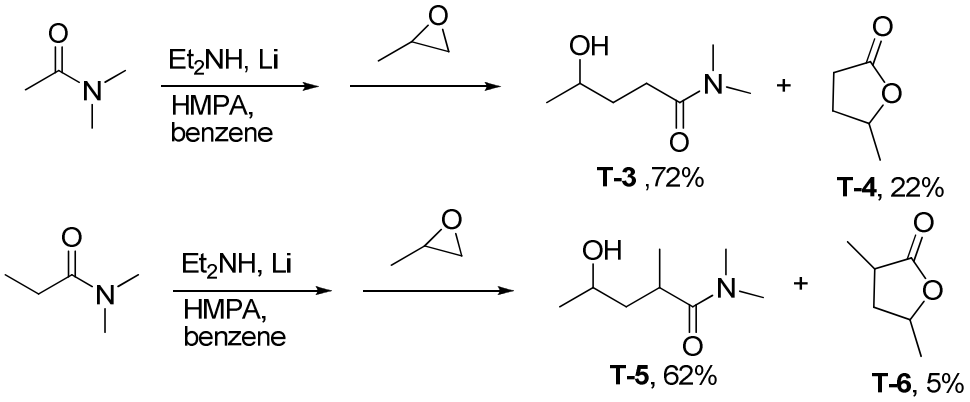
Woodbury and Rathke produced the lithium enolate of *N,N*-dimethylacetamide by using LDA and treated it with propylene oxide.[66] The resulting hydroxyamide was obtained in 85% yield (Scheme 2.26).



Scheme 2.26: Ring opening of epoxides with amide enolates according to Woodward and Rathke.[66]

Normant *et al* treated lithium dialkylamide enolates with the same epoxide. The 'activated' lithium dialkylamide enolates were produced with Li, Et_2NH and HMPA in benzene (Scheme 2.27). They observed formation of some lactone when the workup was done under neutral conditions. Upon treatment with 4M HCl the crude or pure

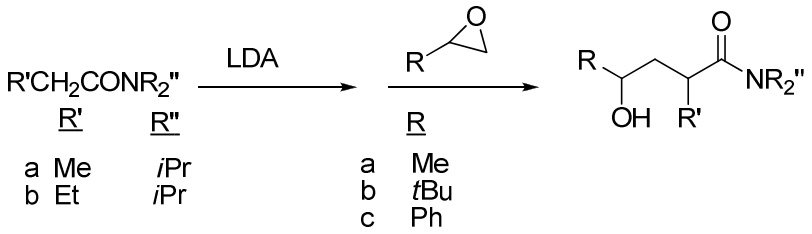
hydroxyamide products yielded the corresponding lactones after 24 h treatment, thus it proved to be a good alternative method for synthesis of lactones.[67]



Scheme 2.27: Ring opening of epoxides with amide enolates according to Normant *et al.*[67]

Sauriol-Lord and Grindley generated enolates of amides using LDA as base in THF or ether at 0 °C. In certain cases they removed the initial solvent in vacuum before the reaction solvent was added. They observed significant diastereoselectivities when the substituents on the nitrogen were large (Table 2.3).[68]

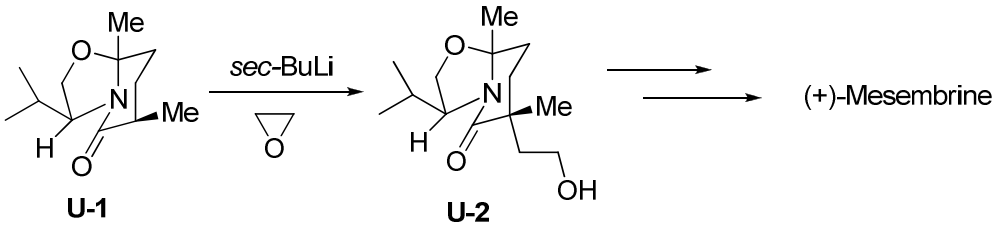
Table 2.3: Ring opening of epoxides according to Sauriol-Lord and Grindley.[68]



Entry	Amide	Epoxide	Solvent	Temperature (°C)[a]	% Conversion	*syn:anti*
1	b	a	Ether	−78	1-2	>95:5
2	b	c	Ether	0	48	90:10
3	b	d	Ether	0	78	90:10

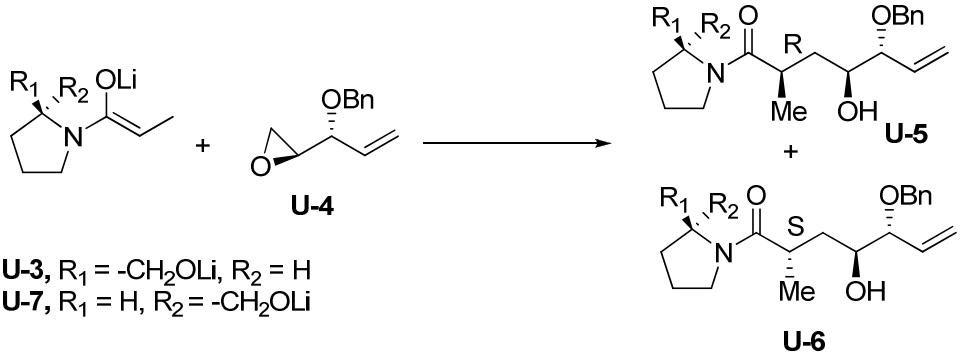
[a] Reaction times 5-6 h. [b] 2 h. [c] 24 h reaction time.

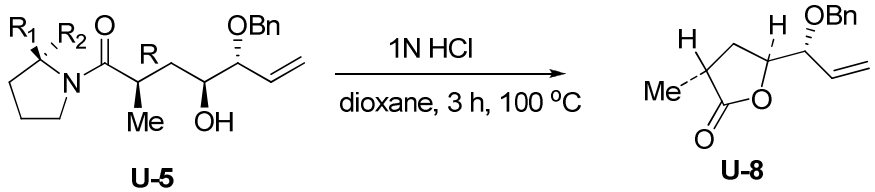
Although the diastereoselectivity was not high in most cases, this methodology was applied in asymmetric synthesis. Meyers *et al* used this protocol for the asymmetric synthesis of (+)-Mesembrine.[69] They treated enolate of bicyclic lactam **U-1** with ethylene oxide and converted the products into 4-substituted-cyclopentenes and cyclohexenes in high enantiomeric excess (Scheme 2.28).

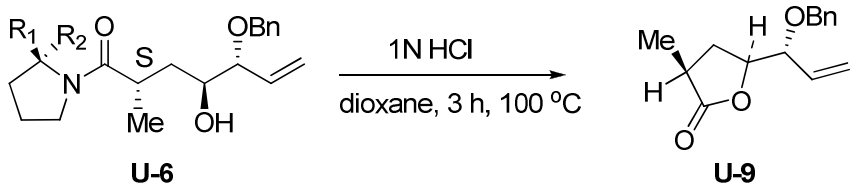


Scheme 2.28: Ring opening of ethylene oxide with amide enolate (**U-1**) according to Meyers *et al.*[69]

Askin *et al* worked on the synthesis of immunosuppressant FK-506.[70] During their studies they alkylated chiral prolinol propionamide enolates with epoxides and interestingly a reversal of facial selectivity was observed. The prolinol amide was treated with LDA to produce the enolate **U-3** and with a 5-fold excess of this enolate the epoxide **U-4** was opened up giving rise to the γ-hydroxy amides **U-5** and **U-6**. Generally, one would expect the attack of **U-3** on the epoxide **U-4** to give rise to **U-5** for steric reasons but the ratio of **U-5:U-6** was 13:87. Similarly, when they treated enolate **U-7** with epoxide **U-4**, the reaction was almost selective to give exclusively **U-5**. A possible explanation for this stereochemical outcome might be the coordination of the epoxide towards the Li-alkoxide, directing the electrophile to the sterically more hindered face of the enolate. They treated the compounds **U-5** and **U-6** with 1N HCl in dioxane at 100 °C for 3 h to yield optically active lactones **U-8** and **U-9** (Scheme 2.29).



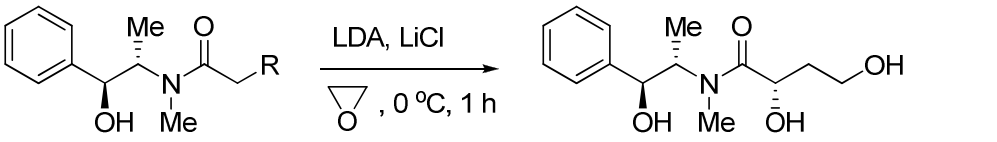




U-6 **U-9**

Scheme 2.29: Ring opening of epoxide (**U-4**) with amide enolates (**U-3, U-7**) according to Askin *et al.*[70]

Myers and McKinstry synthesized enantiomerically enriched γ-lactones and γ-hydroxy ketones by ring opening of epoxides by pseudoephedrine amide enolates.[71] They extensively studied the methodology and investigated the stereochemical outcome of the reaction. The enolate of (*S,S*)-pseudoephedrine or pseudoephedrine hydrocinnamide (R= CH_3 and CH_2Ph respectively) was generated by treatment with 2.1 eq. of LDA and it was allowed to react with 5 eq. of the epoxide in the presence of LiCl. The ring opening reaction proceeded in high yields but low diastereoselectivity (Scheme 2.30).



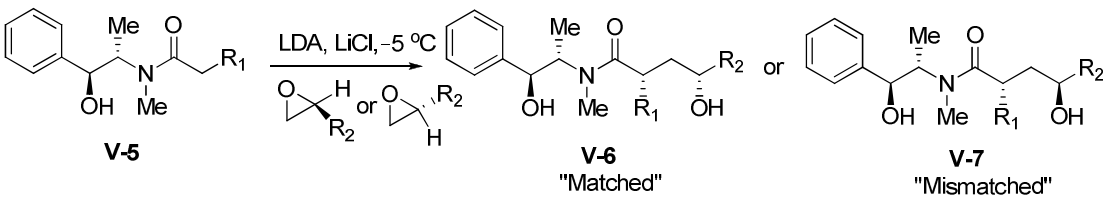
V-1, R = CH_3
V-2, R = CH_2Ph

V-3, R = CH_3, 96% (49% de)
V-4, R = CH_2Ph, 96% (59% de)

Scheme 2.30: Ring opening of ethylene oxide with amide enolates (**V-1, V-2**) according to Myers and McKinstry.[71]

When chiral and monosubstituted enantiomerically enriched (□ 89% ee) epoxides were treated with pseudoephedrine enolate they observed that the inherent π-facial selectivity of pseudoephedrine amide enolate determined the stereochemical outcome of the reaction. Moreover the alkylation was also influenced by the stereochemistry of epoxide. They observed that 1,3-*syn* product was obtained in case of matched combination, whereas in case of mismatched combination the 1,3-*anti* products were formed (Table 2.4).

Table 2.4: Ring opening reaction with ‘‘Matched’’ and ‘‘Mismatched’’ epoxides according to Myers and McKinstry [a].[71]



V-5

V-6
"Matched"

V-7
"Mismatched"

Entry	R_1	R_2	time (h)	Yield %	de	Product
1	CH_3	CH_3	4	88	93	''Matched''
2	Bn	CH_3	9	86	≥99	''Matched''
3	CH_3	CH_3	6	86	73	''Mismatched''
4	Bn	CH_3	10	79	45	''Mismatched''

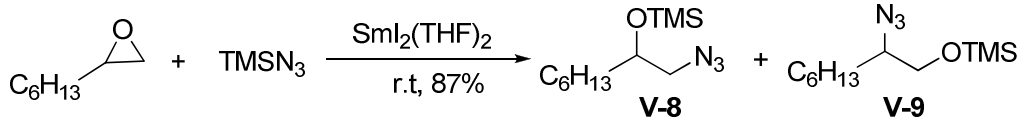
[a] 2 eq. of epoxide was used in each experiment.

2.2.2 Nitrogen containing nucleophiles

2.2.2.1 Amines, azide and aminocid esters as nucleophiles

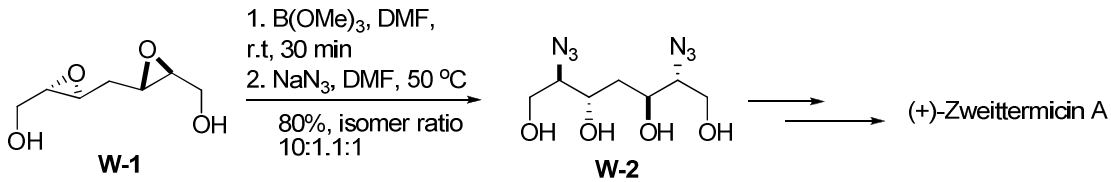
β-Amino alcohols are considered important organic compounds because of their chemical and biological applications and generally they are easily synthesized by ring opening of epoxides by amines. Various chemists have worked on this topic and as a result, a variety of catalysts have been developed, such as trimethylsilyl azide. The development of such catalysts avoids the use of elevated temperatures, excess of amine and long reaction times. A variety of lanthanide derivatives have proved to be efficient catalyst for such ring opening reactions.[72]

Ring opening of epoxides assisted by samarium diiodide was first investigated when trimethylsilyl azide was used as nucleophile.[73] For example ring opening of octene oxide with trimethylsilyl azide resulted in 87% overall yield with a ratio (**V-8:V-9**) of 90:10 (Scheme 2.31).



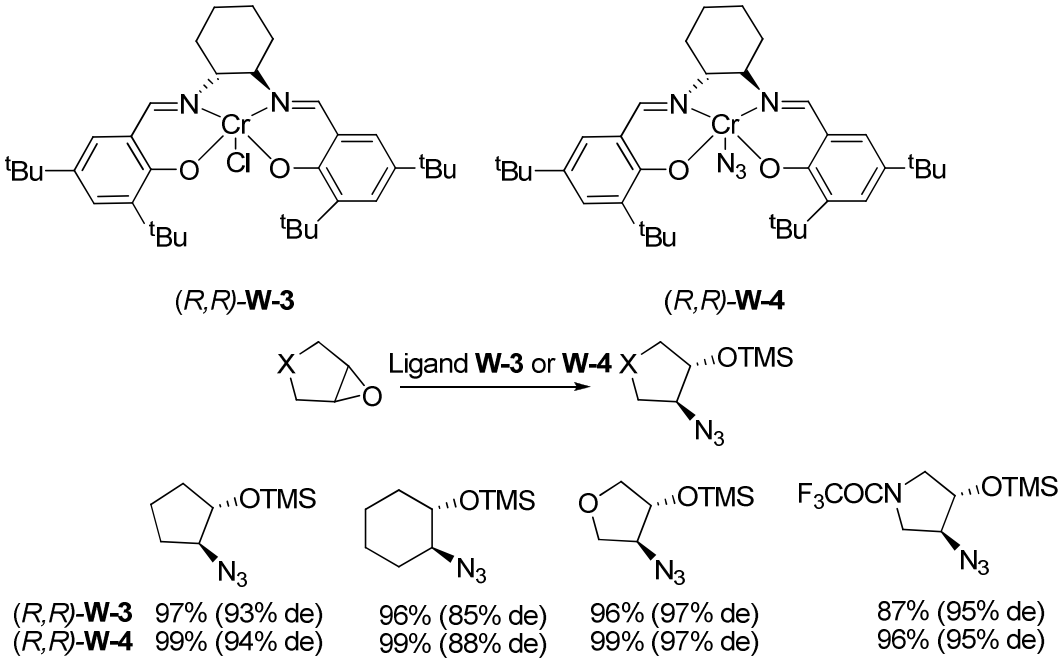
Scheme 2.31: Ring opening of octene oxide with trimethylsilyl azide.

Molinski *et al* applied the methodology of ring opening of epoxide by sodium azide during their formal total synthesis of (+)-Zwittermicin A (Scheme 2.32).[74]



Scheme 2.32: Ring opening with NaN_3 assisted by $B(OMe)_3$ according to Molinski *et al.*[74]

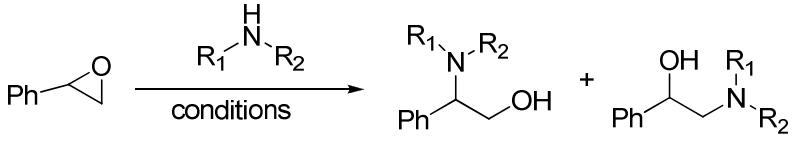
Jacobsen *et al* used trimethylsilyl azide as nucleophile and obtained 1, 2-azido silylether with good to high enantioselectivity (over 94% ee for cyclopentene derivatives).[75] They employed the catalysts **W-3** and **W-4** which could be reused for 10 times without significant loss of activity (Scheme 2.33).



Scheme 2.33: Ring opening with NaN_3 assisted by catalysts **W-3** and **W-4** according to Jacobsen *et al*.[75]

Ethanol amines are produced when epoxide rings are opened by amines. The reaction takes place under a variety of conditions and different catalysts have been employed for this purpose. At elevated temperatures ring opening of styrene oxide occurs in the absence of any catalyst. As a result amino alcohol is produced and attack is observed at more substituted α-position (Table 2.5, entry 1). With the use of catalyst and microwave irradiation, the reaction time could be reduced (Table 2.5, entry 2) and when LiBr was used, the reaction temperature could also be lowered as well (Table 2.5, entries 3 and 4). Interestingly the mode of attack depended upon the type of nucleophile.[76] (Table 2.5)

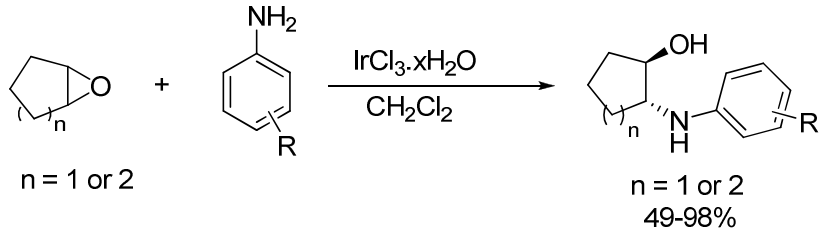
Table 2.5: Ring opening of epoxides with amines.[76]



Entry	Amine	R_1	R_2	catalyst	temp	Time	Yield(%)
1	Ethanolamine	HOEt	H	none	90°C*	3 h	99[a]
2	p-bromoaniline	(*p*-Br)Ph	H	$Bi(TFA)_3$	MW	40 s	90[b]
3	p-chloroaniline	(*p*-Cl)Ph	H	LiBr (5mol%)	RT	5 h	100[a]
4	Piperidine	$(CH_2)_5$	$(CH_2)_5$	LiBr (5mol%)	RT	5 h	98[a]

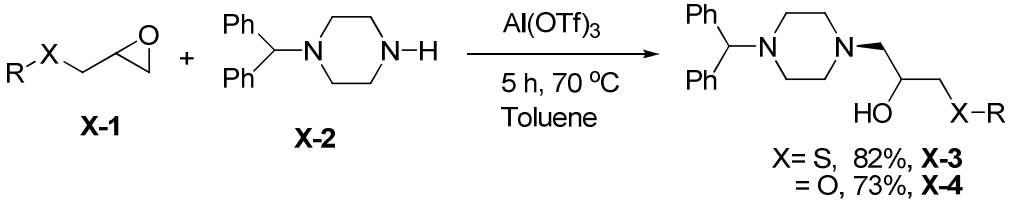
[a] neat. [b] MeCN. * sealed tube.

Peddinti *et al* performed aminolysis of epoxides using iridium trichloride as a catalyst and good results were obtained. They opened cyclohexene oxide and cyclopentene oxide with a variety of substituted anilines and significant results were obtained (Scheme 2.33).[77] Similarly they used aliphatic amines a well and yields in range of 79-87% had been obtained.



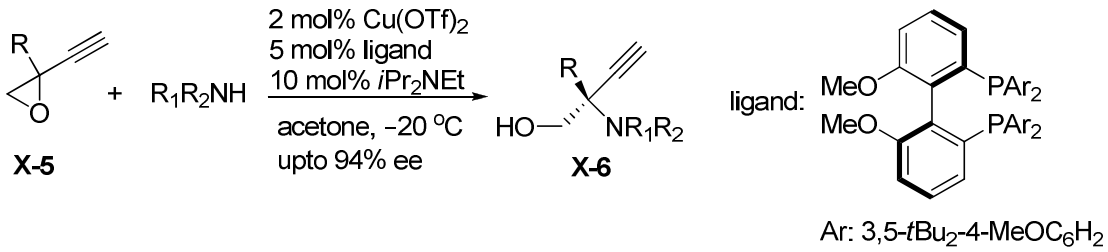
Scheme 2.33: Ring opening of epoxides with amines according to Peddinti *et al*.[77]

Williams and Cullen reported $Al(OTf)_3$-mediated ring opening of epoxides and they applied the methodology in the synthesis of piperazine derived physiologically active products (Scheme 2.34).[78]



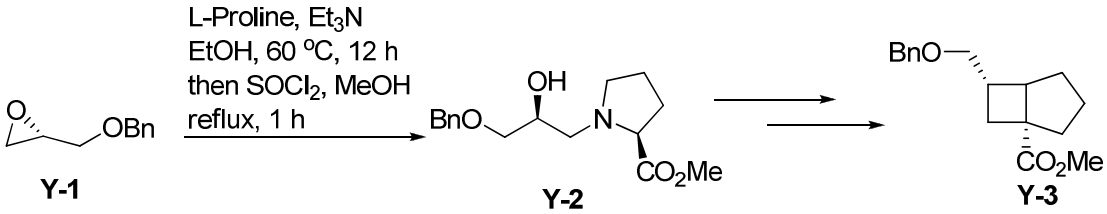
Scheme 2.34: Ring opening of epoxides with amines assisted by $Al(OTf)_3$ according to Williams and Cullen.[78]

Nishibayashi *et al* reported enantioselective copper catalysed ring-opening reactions of ethynyl epoxides with amines using (*R*)-DTMB-MeO-BIPHEP as chiral ligand.[79] The methodology resulted in high yields and provided selectivities up to 94% ee (Scheme 2.35).



Scheme 2.35: Ring opening of ethynyl epoxides with amines assisted by $Cu(OTf)_2$ according to Nishibayashi *et al.*[79]

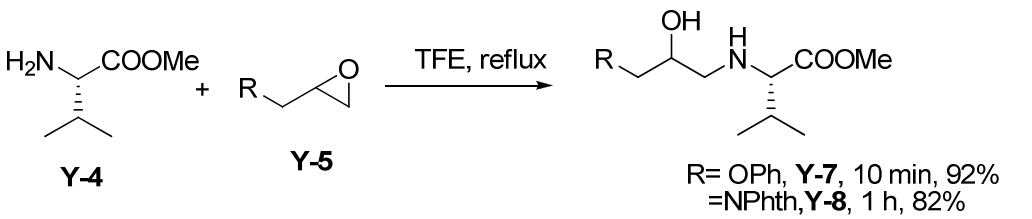
Couty *et al* used L-proline for the ring opening of (*R*)-*O*-benzyl glycidol (98% ee) in basic medium and the product was used for the synthesis of azabicyclo[3.2.0]heptane derivatives (Scheme 2.36).[80]

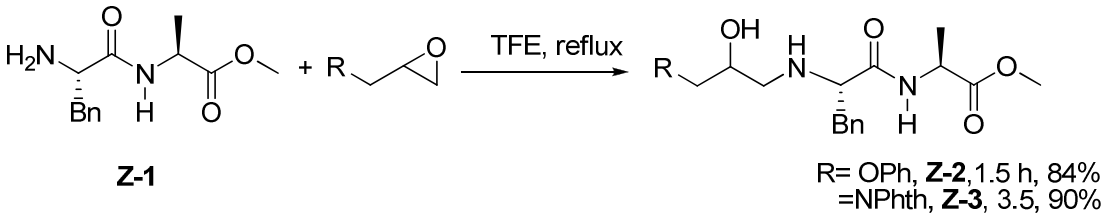


Scheme 2.36: Synthesis of bicyclic azetidines by ring opening of epoxide with L-proline according to Couty *et al.*[80]

They also used β-cyclodextrin to assist the ring opening of (*S*)-*O*-benzyl glycidol (98% ee) and used it for the synthesis of other isomer of azabicyclo[3.2.0]heptane derivatives.

Crousse *et al* reported the ring opening of epoxides by amino acid esters in refluxing trifluoroethanol (TFE) without any catalyst.[81] The methodology involved short reaction times and yields obtained were high. They used a variety of amino acid esters and different epoxides. Similarly they used dipeptide **Z-1** for ring opening reaction and corresponding β-peptidyl alcohol derivate was obtained in good yields and in reasonable reaction time (Scheme 2.37).





Scheme 2.37: Ring opening of epoxides with amino acid esters and dipeptides according to Crousse *et al.*[81]

3 Results and Discussion

3.1 Aim of thesis

In recent years much work has been investigated in the field of epoxide ring opening methodologies. This work has been discussed in relatively detail in chapter 2. Many nucleophiles have been used for the epoxide ring opening reactions e.g. ester enolates, ketone enolates, amide enolates, amines, azide, alcohols, etc. Similarly, many investigations have been reported on the asymmetric ring opening of epoxides and many chiral ligands and metal salt complexes have been synthesized and utilized in this protocol. In spite of all the advances in this area, the nucleophilic ring opening of epoxides with aminoacid ester enolates remains unexplored.

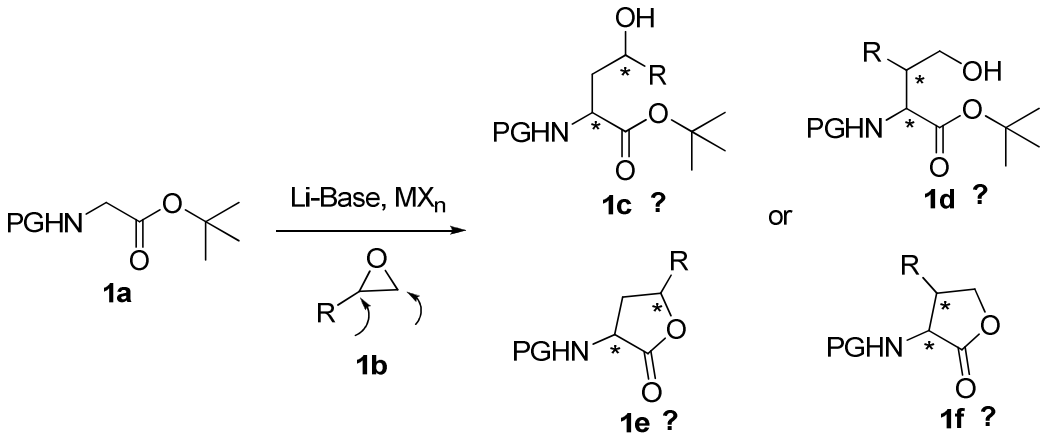
Since the last two decades our group has been working since years on the synthesis of unnatural amino acids. Many unnatural and functionalized amino acids and dipeptides have been synthesized. In all reactions investigated, the double deprotonated *N*-protected glycine ester is transmetallated with $ZnCl_2$, and the resulting chelated amino acid ester enolate (with fixed geometry) is allowed to react with various electrophiles at relatively low temperature. These enolates are thermally more stable compared to non-chelated enolates and show higher selectivity in wide range of reactions such as aldol[82] and Michael additions[83], as well as transition metal catalyzed allylic alkylations[84] (Scheme 1.1). Similarly, this methodology has been applied to peptides modifications and the stereochemical outcome of the reaction could be controlled by stereogenic centers in the peptide chain. [85]

Encouraged by these results, we decided to investigate the ring opening reactions of epoxides with amino acid ester enolates to find the answers to following questions:

1- Can chelated amino acid ester enolates be used for epoxide opening reactions?
2- If the reactions work, would they be diastereo and regioselective?
3- What could be the best conditions of these reactions?
4- What could be synthetic applications of this methodology?

In principle, four different products (**1c**, **1d**, **1e** and **1f**) or mixture of them can be obtained (Scheme 3.1). If the enolate of **1a** attacks the epoxide **1b** at the less substituted carbon of epoxide ring, it should give rise to product **1c** in an S_N2 fashion. In this case the *in situ* generated alkoxide could attack the *tert*-butyl ester group to form lactone **1e**. Whereas, if the enolate of **1a** attacks at the higher substituted carbon of the epoxide ring it should give rise to **1d**, possibly *via* a S_N1-type

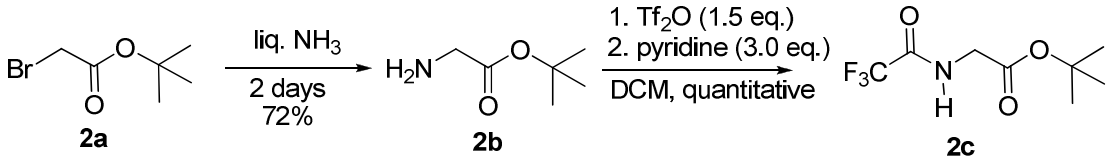
mechanism, which can form the lactone **1f** if the alkoxide attacks the ester functionality.



Scheme 3.1: Generalized form of ring opening of epoxides by amino acid ester enolates.

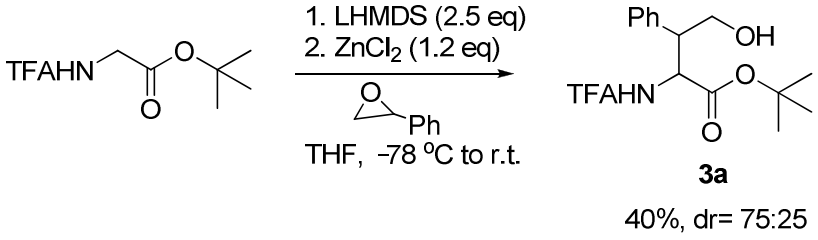
3.2 First attempt for ring opening of epoxides:

Firstly, TFA-protected *t*-butylglycinate **2c** was synthesized by ammonolysis of commercially available t-butyl bromoacetate in liquid ammonia for 2 days to get *tert*-butyl glycinate **2b** in 72% yield which was then protected with trifluoroacetic anhydride quantitatively to get **2c** (Scheme 3.2).



Scheme 3.2: Synthesis of TFA-protected *t*-butylglycinate **2c**.

The enolate of **2c** was then allowed to react with styrene oxide at –78 °C and the reaction mixture was slowly warmed up to room temperature overnight (Scheme 3.3).



Scheme 3.3: Ring opening reaction of styrene oxide.

The reaction was found to be highly regioselective in nature, giving rise to a single regioisomer only. Compound **3a** was obtained in 40% yield and with a diastereomeric ratio of 75:25. The formation of product **3a** could be explained by an S_N1-type mechanism as described in figure 3.1. The epoxide oxygen probably

coordinates to the Lewis acid and opens up to form a stable carbenium ion **A** which is further attacked by enolate **B** giving rise to intermediate **C**. Acidic hydrolysis leads to the formation of the observed product **3a**.

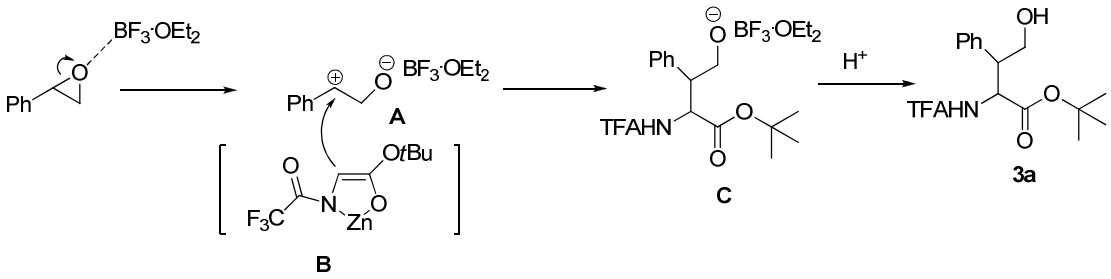


Figure 3.1: Formation of **3a** by a proposed S_N1 mechanism.

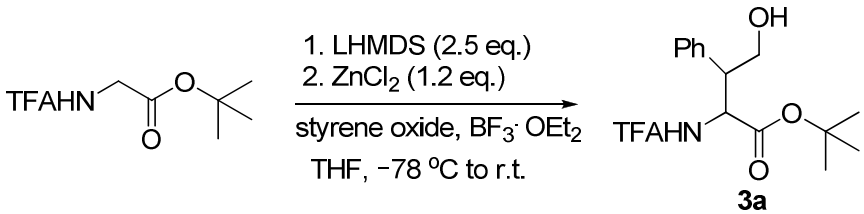
Since the yield and diastereoselectivity of the reaction was not up to the expectation, we carried out further work to optimize reaction conditions by changing different parameters such as temperature, electrophile equivalents, *N*-protecting group, metal salts and substituents on the epoxide ring.

3.3 Optimization of reaction parameters:

3.3.1 Screening of electrophile equivalents:

In order to optimise the reaction parameters, initial screening was done by changing the equivalents of the epoxide. We were interested to see if increase in electrophile equivalents had any influence on the yield and diastereoselectivities. Therefore, the amount of styrene oxide was increased up to 5 equivalents, but unfortunately it was observed that this didn't result in better diastereoselectivity. However, significant changes were observed on the yield of product **3a**. Further variation was made by the using $BF_3 \cdot OEt_2$ as Lewis acid (LA). The results obtained are as shown in table 3.1.

Table 3.1: Screening of Electrophile Equivalents



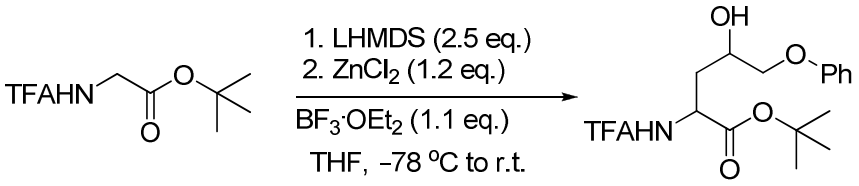
Entry	Epoxide (eq.)	$BF_3 \cdot OEt_2$ (eq.)	Yield (%)	dr
1	1.0	---	40	75:25
2	1.0	1.1	60	75:25
3	1.5	1.1	67	76:24
4	2.0	1.1	70	76:24

5	3.0	1.1	62	76:24
6	4.0	1.1	55	76:24
7	5.0	1.1	45	76:24

In the absence of the Lewis acid ($BF_3 \cdot OEt_2$) and with one equivalent of epoxide only 40% yield of compound **3a** could be achieved (entry 1). The addition of 1.1 equivalents of Lewis acid increased the yield of the product up to 60% (entry 2). Increasing the amount of epoxide up to 2 equivalents improved the yield to 70% (entry 3). However, a further increase in the epoxide equivalents resulted in a drop in the yield (entries 5 to 7). It was observed that the best yield could be obtained when 2 eq. of epoxide were used in combination with 1.1 eq. of $BF_3 \cdot OEt_2$, but it had no significant influence on diastereoselectivity (entry 4).

In order to confirm the results, the same conditions were applied to phenyl glycidyl ether and similar results were obtained (Table 3.2).

Table 3.2: Screening of electrophile equivalents using phenyl glycidyl ether.



8a

Entry	Epoxide	Epoxide (eq.)	Yield (%)	dr
1	Phenyl glycidyl ether	1.0	63	58:42
2	Phenyl glycidyl ether	1.5	86	56:44
3	Phenyl glycidyl ether	2.0	88	56:44

Here also, it was observed that the increase in eq. of epoxide from 1 eq. to 1.5 eq. resulted in increase of yield up to 86% but an effect on the diastereoselectivity was not observed (entries 1 and 2). A further increase in epoxide eq. could improve the yield slightly (88%, entry 3). The yields in case of ring opening of phenyl glycidyl ether were higher (88%) compared to those obtained in ring opening of styrene oxide (70%). However, the diastereoselectivity in case of styrene oxide was slightly better (75%) compared to that obtained in case of phenyl glycidyl ether (56%).

Interestingly, the ring opening of phenyl glycidyl ether resulted in the formation of the other regioisomer **4a**, probably *via* S_N2 mechanism as shown in figure 3.2. The enolate **B** attacks at the less hindered carbon of epoxide **A** giving rise to intermediate **C**, which on acidic hydrolysis of intermediate **C** provides compound **4a**.

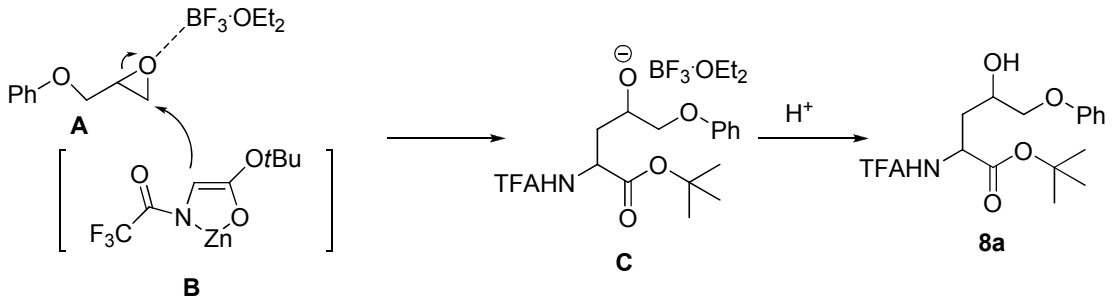
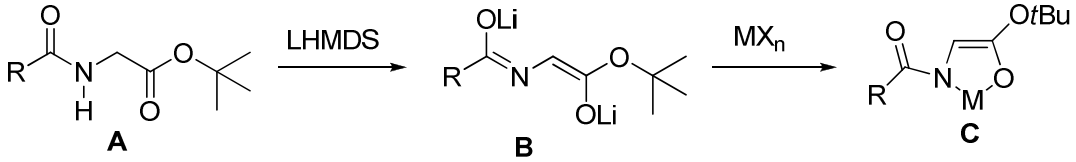


Figure 3.2: Formation of **4a** by a proposed S_N2 mechanism.

3.3.2 Screening of Metal salts:

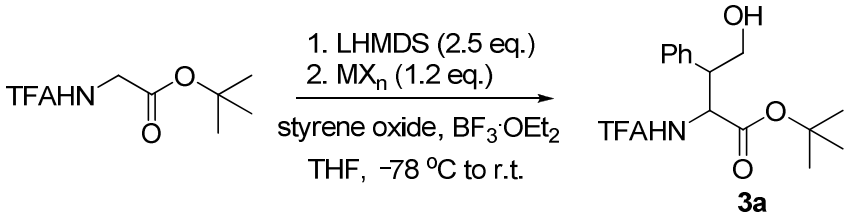
The choice of the metal salt plays a very important role in the stereochemical outcome of enolate reactions.[86] The doubly deprotonated aminoacid ester enolate **B**, obtained *via* deprotonation with strong Li-bases such as LDA or LHMDS can be transmetallated with an appropriate metal salt to generate a geometrically fixed metal-enolate complex **C** (Scheme 3.4).



Scheme 3.4: Transmetallation and formation of chelated amino acid ester enolate.

The fixed geometry of this enolate **C** in some cases results in products with high stereoselectivities. As the stability of enolate geometry probably depends on the chelating metal salt used, further optimization was made by using different metal salts (Table 3.3).

Table 3.3: Screening of Metal salts.



Entry	MX_n	$BF_3{\cdot}OEt_2$ (eq.)	Yield (%)	dr
1	$ZnCl_2$	1.1	70	75:25
2	$Ti(O\ iPr)_4$	---	22	78:22
3	$Ti(O\ iPr)_4$	1.1	60	78:22
4	$Ti(O\ iPr)_3Cl$	---	15	72:28

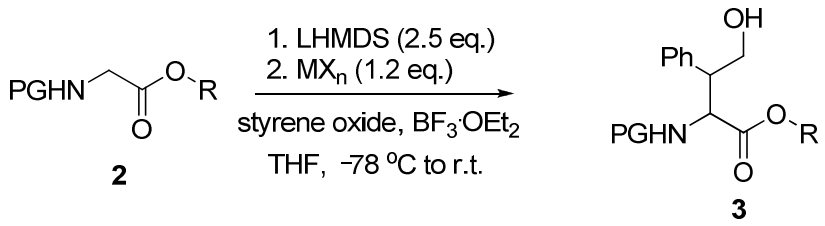
5	$Ti(O\ iPr)_3Cl$	1.1	62	72:28
6	$AlEt_2Cl$	---	14	69:31
7	$AlEt_2Cl$	1.1	69	69:31
8	$MnCl_2$	1.1	63	72:28
9	$MgCl_2$	1.1	60	65:35
10	$NiCl_2$	1.1	67	63:37
11	$CuCl_2$	1.1	--	--
12	LiCl	1.1	70	64:36

It was observed that the reaction proceeded smoothly with all metal salts except $CuCl_2$ (entry 11) and moderate to high yields were obtained, but the effect on the diastereoselectivity was not significant. In cases when $Ti(OiPr)_4$ was used as chelating metal salt in the presence of Lewis acid, the diastereoselectivity improved slightly (78%) but the yield was only moderate (60%) and without Lewis acid the yield dropped dramatically to only 22% (entries 2 and 3). The same observation was made when $Ti(OiPr)_3Cl$ was used. The diastereoselectivity was moderate (72%) but without the Lewis acid the yield dropped to 15% (entries 4 and 5). The use of other metal salts $AlEt_2Cl$, $MnCl_2$, $MgCl_2$, $NiCl_2$, $CuCl_2$ and LiCl also didn't help to increase diastereoselectivity (entries 6 to 12). From the results obtained in table 3.3 we could conclude that $ZnCl_2$ probably is the best choice compared to the other metal salts, both in terms of yields and selectivity.

3.3.3 Effect of protecting groups:

After screening the electrophile equivalents and the chelating metal salts, we were interested to observe the influence of the *N*-protecting group (PG) on the yield and diastereoselectivity, since the *N*-protecting group plays an important role in building a fixed, double co-ordinated amino acid ester enolate. Therefore, different *N*-protected glycine esters were synthesized and allowed to react with styrene oxide. The results are summarized in table 3.4.

Table 3.4: Effect of protecting groups (PG & R) on the yield and diastereoselectivity.



Entry	Nucleophile	MX_n	PG	R	Product	Yield (%)	dr
1	**2c**	$ZnCl_2$	TFA	*t*-Bu	**3a**	70	75:25
2	**2d**	$ZnCl_2$	Tos	*t*-Bu	**3b**	traces	75:25
3	**2e**	$ZnCl_2$	TFA	Me	**3c**	65	70:30
4	**2f**	$ZnCl_2$	Z	*t*-Bu	**3d**	traces	75:25
5	**2g**	$ZnCl_2$	Bz	*t*-Bu	**3e**	71	68:32
6	**2h**	$ZnCl_2$	Tos	Me	**3f**	traces	75:25
7	**2i**	$Ti(OiPr)_4$	Tos	Me	**3g**	traces	n.d[a]
8	**2j**	$Ti(OiPr)_4$	Tos	*t*-Bu	**3h**	traces	n.d[a]
9	**2k**	$Ti(OiPr)_4$	Z	*t*-Bu	**3i**	25	52:48

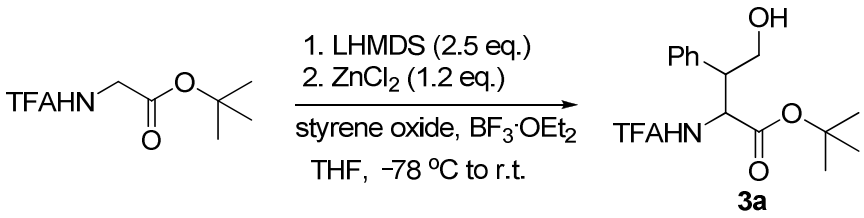
[a] Not determined.

It was found that the reactions of Ts and Z protected glycine ester enolates with epoxide resulted in significant drop of the yield and still moderate diastereoselectivities were obtained (entries 2, 4 and 6). The result didn't improve much when $Ti(OiPr)_4$ was used as chelating metal salt (entries 7 to 9). However, when TFA protected methyl glycinate was used as nucleophile, product **3c** was obtained in 65% yield with a diastereoselectivity of 70% (entry 3). In case of entry 5 where Bz protected glycine ester was used, it resulted in the desired product **3d** in 71% yield with comparable diastereoselectivity (68%). Based on these results obtained, it could be easily concluded that the combination of the TFA- and *tert*-butyl group gave better results compared to other protecting groups.

3.3.4 Effect of temperature:

We have observed that the enolate reactions begin at –78 °C. Taking this into consideration our next aim was to find out if the temperature has any influence on the diastereoselectivity. We carried out the reaction at –78 °C and warmed the reaction mixture quickly to room temperature. The samples were taken out in intervals of 15–20 °C during warm up and checked by GC (Table 3.5).

Table 3.5: Effect of temperature on diastereoselectivity.



3a

Entry	Temperature (°C)	dr
1	–78	75:25
2	–65	73:27
3	–45	76:24
4	–10	76:24
5	rt	76:24

It was found that the reaction begins at –78 °C and significant amount of product had been formed just after 5 min. The results obtained at various temperatures showed that there was no effect of the reaction temperature on the diastereoselectivity which was constantly at 75±2 %.

After screening all the reaction parameters, we could clearly increase the yield of the product from 40% to 70% which is quite significant, but the diastereoselectivity of the epoxide ring opening couldn't be improved. Therefore, we fixed our optimized reaction conditions for epoxide opening reaction as:

- TFA-protected *t*-butyl glycine ester as nucleophile.
- $ZnCl_2$ as chelating metal salt.
- 2.5 eq. LHMDS as base.
- $BF_3 \cdot OEt_2$ as Lewis acid.
- 1.5 eq. of epoxide.

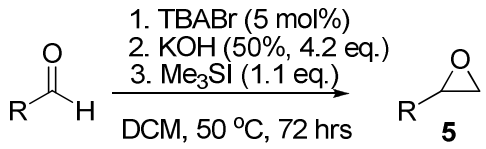
3.4 Synthesis of substrates:

After optimizing the reaction conditions, we were interested to apply this methodology also to other epoxides. Therefore, we synthesized several aromatic epoxides (with aromatic substituents on the epoxide ring) as well as aryl glycidyl ethers.

3.4.1 Synthesis of aromatic epoxides:

A variety of different aromatic epoxides were synthesized by using the method described by Märkl *et al*[87]. The results obtained are summarized in table 3.6.

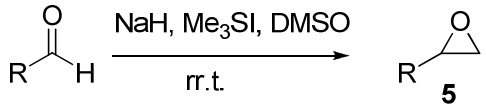
Table 3.6: Synthesis of epoxides from aldehydes.



Entry	Aldehyde	Epoxide	Conversion (%)
1	2-methoxy benzaldehyde	**5a**	85
2	4-methoxy benzaldehyde	**5b**	No conversion
3	2,4,6-trimethoxy benzaldehyde	**5c**	No conversion
4	4-bromo benzaldehyde	**5d**	99
5	2-bromobenzaldehyde	**5e**	85
6	4-tolyl aldehyde	**5f**	91
7	1-naphthaldehyde	**5g**	No conversion

The conversion of aldehydes to epoxides was observed to be substrate depended. In case of 2-methoxy, 4-bromo, 2-bromo and 4-methyl benzaldehydes considerable conversion was observed (entries 1, 4, 5, and 6) but with of 4-methoxy benzaldehyde, 2, 4, 6-trimethoxy benzaldehyde and 1-naphthaldehyde only starting materials were recovered even after stirring the reaction at 50 °C for 72 h (entries 2, 3 and 7). Since it was not possible to isolate the epoxides from the unreacted aldehydes, we used another method for the synthesis of epoxides reported by Archelas *et al*[88] using NaH as base and DMSO as solvent (Table 3.7).

Table 3.7: Synthesis of epoxides using NaH as base and DMSO as solvent.

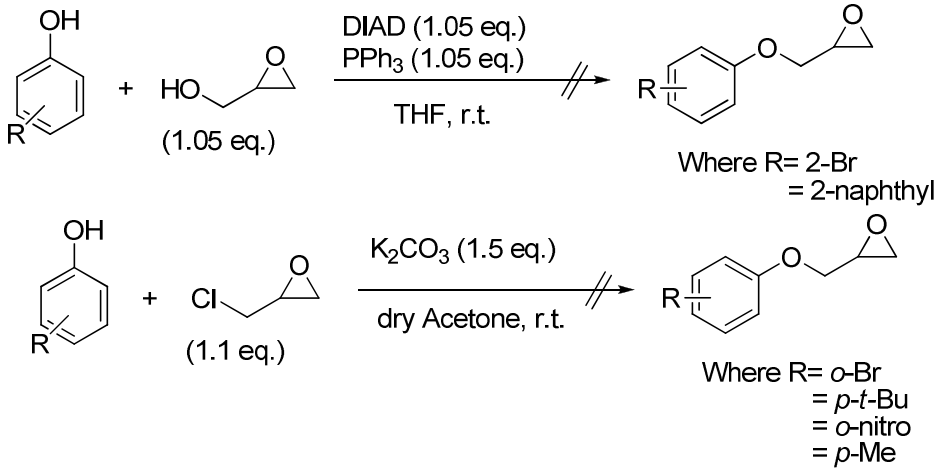


Entry	Aldehyde	Epoxide	Yield (%)	Conversion (%)
1	2-methoxy benzaldehyde	**5a**	90	100
2	4-methoxy benzaldehyde	**5b**	84	100
3	4-bromo benzaldehyde	**5d**	78	100
5	4-tolyl aldehyde	**5f**	76	100
6	1-naphthaldehyde	**5g**	86	100
7	2-chloro benzaldehyde	**5j**	80	100
8	4-chloro benzaldehyde	**5k**	88	100
9	2-tolyl aldehyde	**5l**	84	100
10	3,4-dichloro benzaldehyde	**5m**	86	100
11	2-nitro benzaldehyde	**5n**	80	100

The results obtained showed complete conversion of the aldehydes to epoxides under these conditions. The conversion was checked by ^{1}HNMR of crude reaction mixture. The presence of different substituents on the aromatic ring didn't affect the outcome of the reaction. The reaction time was also significantly shorter (3 h) and high isolated yields were obtained (76–90%).

3.4.2 Synthesis of aryl glycidyl ethers:

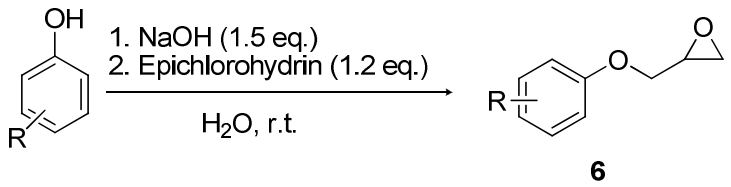
After synthesizing the aromatic epoxides, we attempted to synthesize aryl glycidyl ethers by Mitsunobu reaction as described by Lepore and He[89], but the desired products could not be obtained. Further attempts were made to synthesize aryl glycidyl ethers by using anhydrous K_2CO_3 as base and acetone as solvent. But under these conditions also very low conversions were observed and starting materials (phenols) were recovered (Scheme 3.5).



Scheme 3.5: Attempt to synthesize aryl glycidyl ethers.

As these protocols were not successful, we changed the method again and used NaOH as a base and water as solvent, according to literature[90]. The results obtained by this method are summarized in table 3.8. This method resulted in higher yields (73–95%). The products could be purified by column chromatography. Different aryl glycidyl ethers were synthesized by this methodology and subjected to ring opening reactions.

Table 3.8: Synthesis of aryl glycidyl ethers by method **A** and **B**.



6

Entry	R	Epoxide	Yield

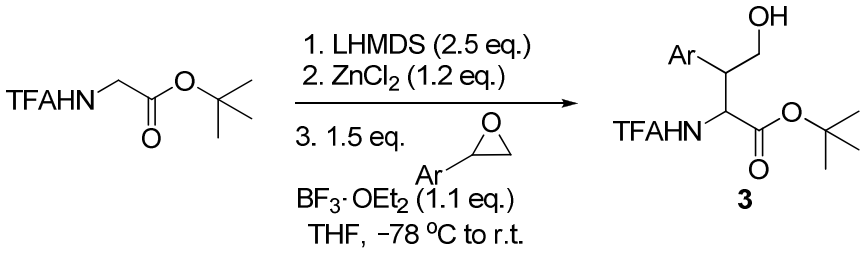
			(%)
1	4-NO_2	**6b**	75
2	2-Br-4-Me	**6c**	75
3	4-*t*-Bu	**6d**	80
4	4-Me	**6e**	88
5	4-OMe	**6f**	90
6	4-Cl	**6g**	81
7	2-NO_2	**6h**	73
8	2-CN	**6i**	95

3.5 Ring opening reactions of epoxides:

3.5.1 Ring opening of aromatic epoxides with amino acid ester enolates:

After synthesizing all the required epoxides, we treated these epoxides with the enolate of TFA protected *tert*-butyl glycinate. The results obtained are summarized in table 3.9.

Table 3.9: Ring opening of aromatic epoxides.



Entry	Epoxide	Ar	Product	Yield (%)	ds (*syn*) (%)
1	**5b**	4-$MeOC_6H_4$	**3J**	71	67
2	**5a**	2-$MeOC_6H_4$	**3k**	60	70
3	**5k**	4-ClC_6H_4	**3l**	79	73
4	**5j**	2-ClC_6H_4	**3m**	72	75
5	**5d**	4-BrC_6H_4	**3n**	71	85
6	**5m**	3,4-$Cl_2C_6H_4$	**3o**	82	71
7	**5g**	1-naphthyl	**3p**	79	76
8	**5l**	2-$CH_3C_6H_4$	**3q**	71	72
9	**5f**	4-$CH_3C_6H_4$	**3r**	70	77
10	**5n**	2-$NO_2C_6H_4$	**3s**	No reaction	---

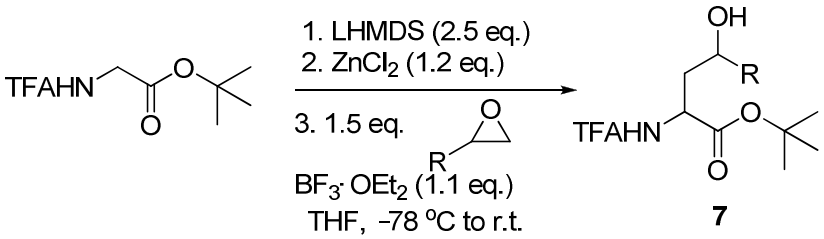
These reactions were highly regiospecific. In all cases exclusively S_N1-products were obtained with significant yields and moderate diastereoselectivities. The attack

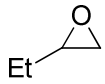
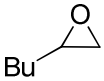
of the enolate at the benzylic carbon of the epoxide was observed, so it was obvious that the nucleophilic attack on the *in situ* formed benzilic carbenium ion is significantly faster than the S_N2 attack. The effect of substituents on the aromatic ring had no significant influence on the diastereoselectivity. For example when *para* - and *ortho*- substituted styrene oxides were subjected to ring opening reaction, products **3b** and **3c** were obtained with diastereoselectivities of 67 and 70% which are comparable (entries 2, 3). Similarly, the effect of *p*- and *o*-chloro substituent on phenyl ring was also not significant (entries 4, 5). The same was true for compounds **3g**, **3h**, **3i** and **3j** (entries 7-10). In the case of entry 11 where an *o*-NO_2 derivative was used, no ring opening product was observed and the epoxide **5n** was recovered. However, in terms of diastereoselectivity, best results were obtained with *p*-bromo derivative which gave rise to product **3f** with a diastereoselectivity of 85% (entry 6).

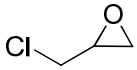
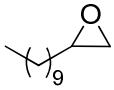
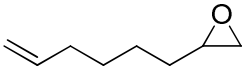
3.5.2 Ring opening of aliphatic epoxides:

In the next step, we subjected aliphatic epoxides for the ring opening reactions. Here the ring opening of aliphatic epoxides resulted in higher yields but unfortunately the diastereoselectivities of the products **7** were even lower as compared to those obtained in ring opening of aromatic epoxides. Interestingly, in comparison with aromatic epoxides the attack of the nucleophile was observed at the sterically less hindered carbon which depicts an S_N2 mechanism. In all cases the obtained yields were quite high ranging from 82 to 92%, whereas diastereoselectivities ranged from 56 to 68%. The results obtained from ring opening of aliphatic epoxides are summarized in table 3.10.

Table 3.10: Ring opening of aliphatic epoxides.



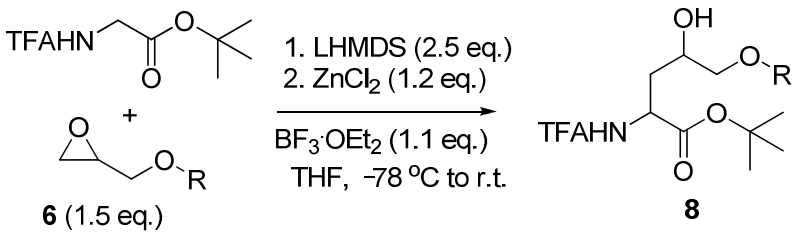
Entry	Epoxide	Product	Yield (%)	ds (%)
1		**7a**	92	68
2		**7b**	88	68
3		**7c**	86	66

4		**7d**	82	56
5		**7e**	85	65
6		**7f**	87	65

3.5.3 Ring opening of aryl glycidyl ethers:

After ring opening reactions of aromatic and aliphatic epoxides, we subjected a variety of aryl glycidyl ethers to ring opening and the results obtained were quite similar to those of aliphatic epoxides both in terms of yield and selectivity (Table 3.11). Exclusive formation of S_N2 products was observed. The effect of substituents on the diastereoselectivity was not significant. Different electron donating substituents (entries 2, 3, 4, 5 and 6) and electron withdrawing substituents (7, 8 and 9) on the aryl group were used but it didn't result in better diastereoselectivities but excellent yields (72–88%) were obtained. The results were quite similar to those obtained in ring opening reaction of aliphatic epoxides (Table 3.10).

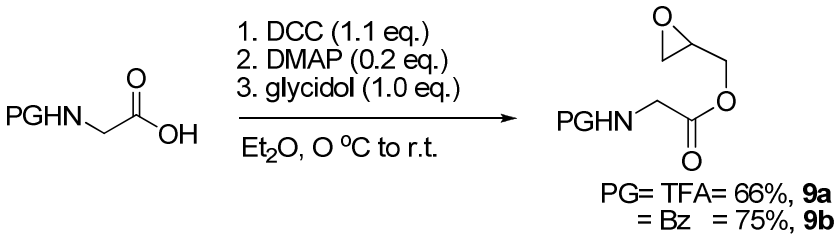
Table 3.11: Ring opening of aryl glycidyl ethers.



Entry	Epoxide	Product	Yield (%)	ds (%)
1	Phenyl	**8a**	86	56
2	2-Br-4-CH_3-C_6H_3	**8b**	72	58
3	*p*-*t*-ButylC_6H_4	**8c**	79	57
4	*p*-MeC_6H_4	**8d**	81	55
5	*p*-OMeC_6H_4	**8e**	85	60
6	*p*-ClC_6H_4	**8f**	88	51
7	*p*-$NO_2C_6H_4$	**8g**	83	56
8	*o*-$NO_2C_6H_4$	**8h**	84	66
9	*o*-CNC_6H_4	**8i**	85	57

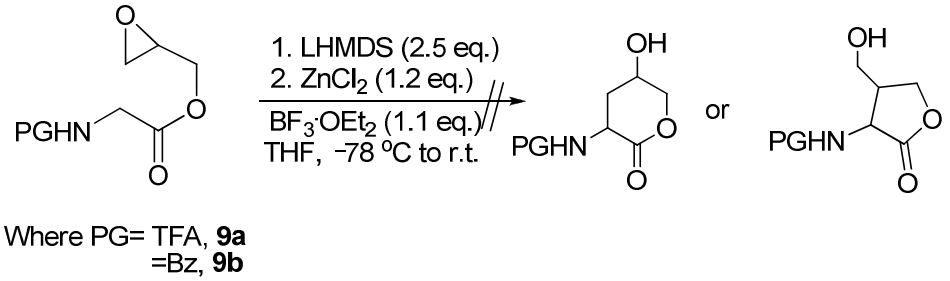
3.5.4 Intramolecular ring opening of epoxides:

Encouraged by the results obtained with various aliphatic and aromatic epoxides, we were interested to see if this methodology could also be applied to the intramolecular ring opening of epoxides. To investigate this issue, we synthesized substrates **9a** and **9b** as shown in Scheme 3.6.



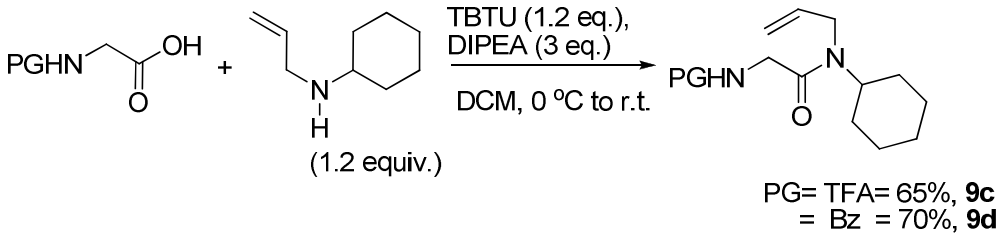
Scheme 3.6: Synthesis of substrates **9a** and **9b**.

N-benzoyl and *N*-TFA glycine were allowed to couple with glycidol in diethyl ether in the presence of DCC and DMAP as catalyst. The products **9a** and **9b** were obtained in 75 and 66% yields respectively. The substrates **9a** and **9b** were then subjected to intramolecular ring opening reaction (Scheme 3.7). In both cases no desired product was obtained. Instead, giving out an unidentified rubber like polymeric substance was formed which might be the outcome of an intermolecular reaction rather than an intramolecular reaction.



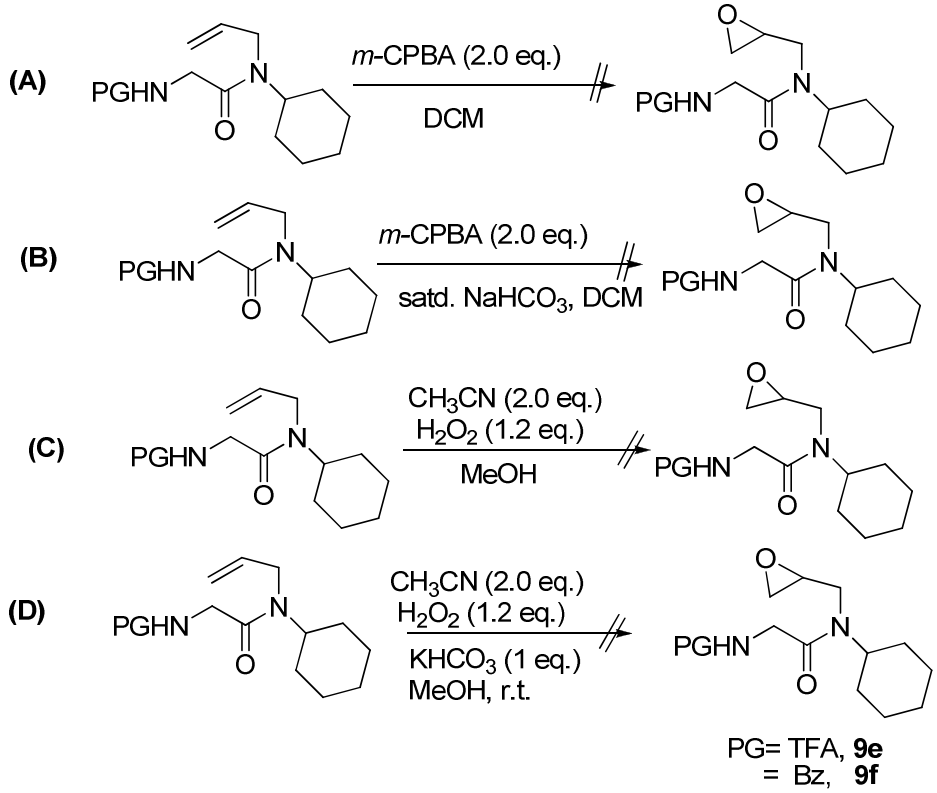
Scheme 3.7: Intramolecular ring opening of substrates **9a** and **9b**.

Further attempts were made to use epoxy amides **9e** and **9f** for intramolecular ring opening reaction of epoxide. By incorporation of a secondary amine bond we hoped that *via* the free rotation around the amide bond, the epoxide might come in suitable orientation (*cis* amide bond) for intramolecular opening, while the corresponding ester functionality prefers the *trans*-conformation. To proceed with this idea we synthesized **9c** and **9d** by coupling of *N*-protected glycine with allyl cyclohexyl amine in presence of TBTU and DIPEA in DCM at 0 °C (Scheme 3.8).



Scheme 3.8: Synthesis of substrates for intramolecular ring opening reaction.

The amides **9c** and **9d** were then subjected to epoxidation by different methods but, unfortunately none of them resulted in desired product (Scheme 3.9).

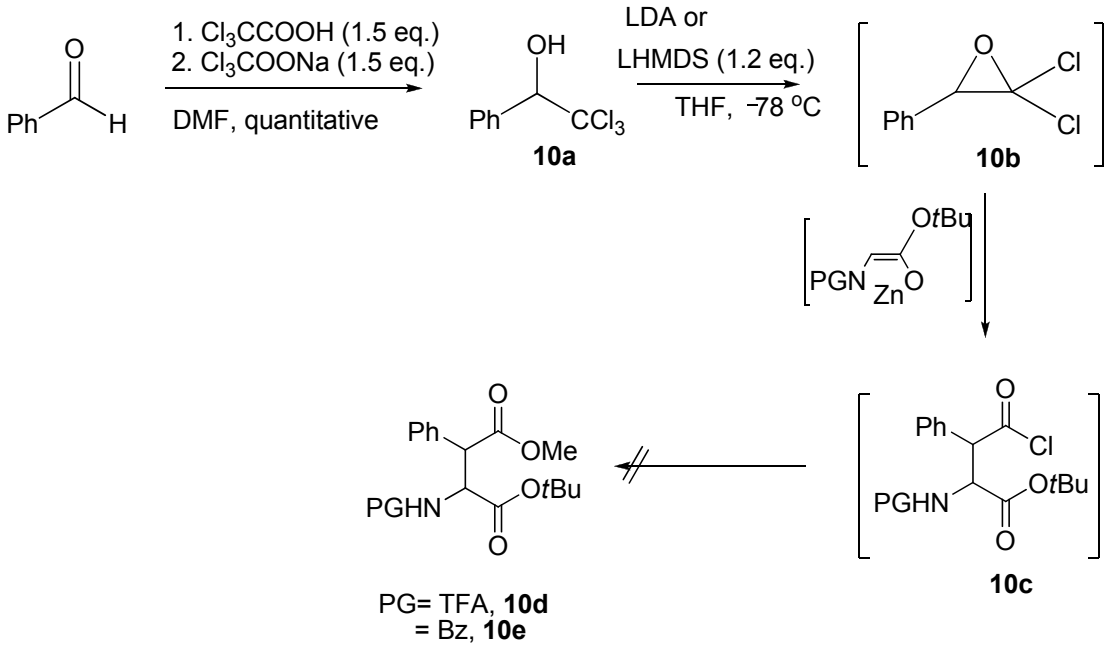


Scheme 3.9: Attempts to synthesize **9e** and **9f**.

In reaction **A** the standard conditions of the Prilezhaev epoxidation were applied to achieve epoxidation products **9e** and **9f** but it resulted in only the recovery of the starting material, and the desired product was not obtained. Therefore, we slightly modified the procedure and used satd. $NaHCO_3$ as a base which also didn't give rise to the desired products.[91] Furthermore, we decided to change the epoxidation conditions and used a combination of CH_3CN and H_2O_2, with and without base, as described by Schuh e*t al*[92], but in all cases a complete recovery of starting material was observed.

3.5.5 Ring opening of *gem*-dichloro styrene oxide:

After we had obtained good results in the case of aromatic epoxides we attempted to use functionalized styrene oxides e.g., *gem*-dicloro styrene oxide **10b**. For this purpose, we synthesized alcohol **10a** which was used for *in situ* generation of epoxide **10b**. The alcohol **10a** was treated with LHMDS at –78 °C to generate **10b** which was then transferred to the enolates of *N*-benzoyl and *N*-TFA *t*-butyl glycinate. These reactions also didn't give any desired product and we could only isolate the starting material **10a** quantitatively. Obviously, under these conditions the epoxide **10b** was not formed and therefore, so we changed the base and used LDA for the *in situ* generation of epoxide **10b**. But also in this case the alcohol **10a** was recovered (Scheme 3.10).



Scheme 3.10: Attempt of ring opening of *gem*-dichloro styrene oxide **10b**.

3.6 Synthetic applications:

After the ring opening of epoxides was successfully performed, the products were subjected to various synthetic applications. These γ-hydroxy amino acid esters **7** and **8** should be easily oxidized to γ-keto amino acid esters **11** (Figure 3.3). The γ-keto amino acid esters **11** should be good substrates for all kinds of carbonyl additions such as Passerini, Reformatsky and Ugi reactions as well as allylations, methylations, or Grignard additions, etc. Figure 3.3 gives an overview on the reactions planned.

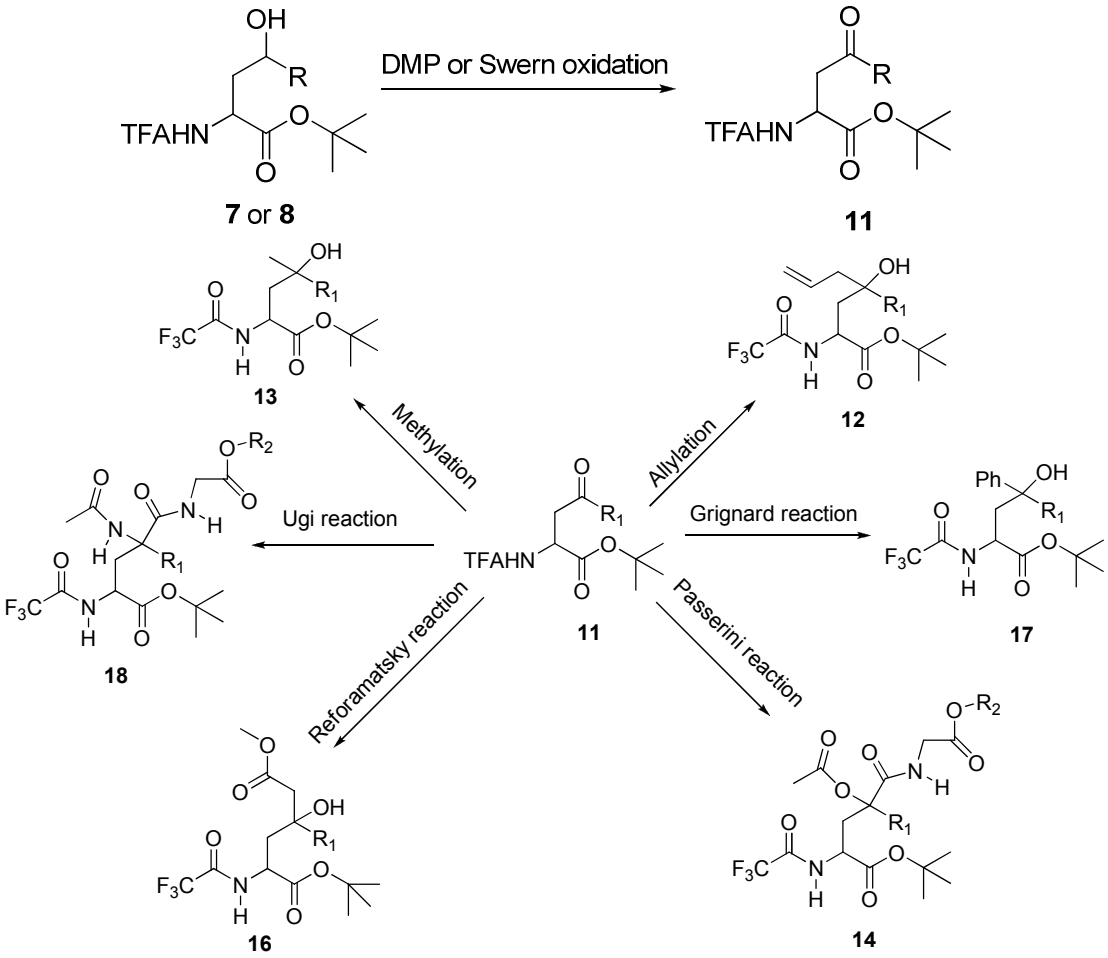
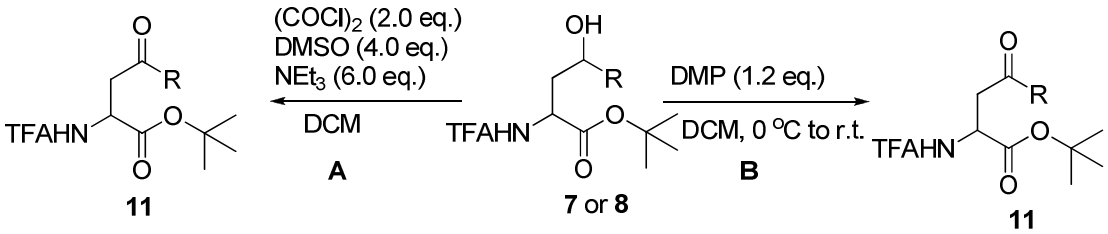


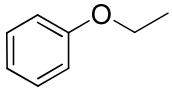
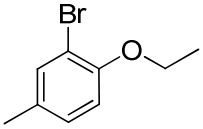
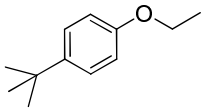
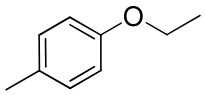
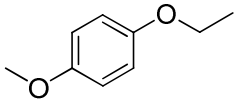
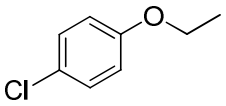
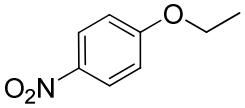
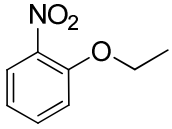
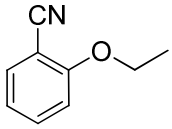
Figure 3.3: Plan of synthetic applications of compounds **11**.

3.6.1 Synthesis of γ-keto aminoacid esters:

In order to synthesize γ-keto aminoacid esters, the compounds **7** and **8** were subjected to Swern and Dess-Martin oxidation reactions. The results obtained in both the reactions are summarized in table 3.12.

Table 3.12: Synthesis of γ-keto amino acids esters.



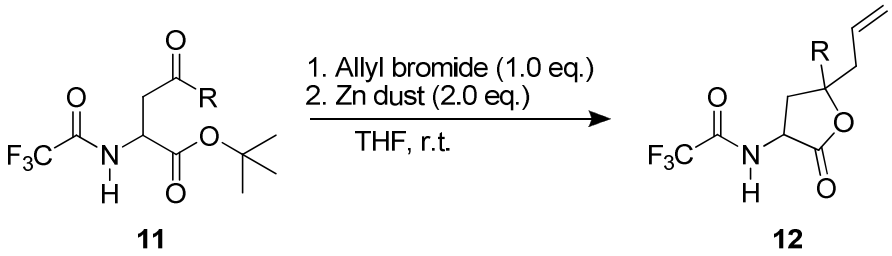
Entry	R	Compound	Yield **A** (%)	Yield **B** (%)
1	Me	**11a**	78	91
2	Et	**11b**	79	92
3	*n*-Bu	**11c**	81	89
4	Chloromethyl	**11d**	75	90
5	1-hexenyl	**11e**	76	88
6		**11f**	76	93
7		**11g**	68	91
8		**11h**	72	90
9		**11i**	74	88
10		**11j**	75	85
11		**11k**	72	82
12		**11l**	74	84
13		**11m**	75	87
14		**11n**	76	84
15	*n*-decyl	**11o**	72	81

It was found that the yields of the Dess-Martin oxidation were clearly better than those obtained from Swern oxidations. In case of Dess-Martin oxidation the obtained yields were in range of 82–92% whereas in case of Swern oxidation the yields were comparatively low (68–81%). Moreover, it was observed that the oxidation reaction in both cases was independent of the substituent pattern of amino acids.

3.6.2 Allylation of γ-keto aminoacid esters 11:

In the next step different γ-keto amino acid esters **11** were subjected to allylation using allyl bromide and Zn dust. Interestingly, it was observed that instead of the expected allylic alcohols, the corresponding lactones were formed. The formation of lactones is reasonable since the *in situ* formed $ZnBr_2$ is strong lewis acid enough to catalyze the elimination of ester functionality. As a result, lactones **12** are obtained in moderate yields (60–70%). The results are summarized in table 3.13

Table 3.13: Allylation of γ-keto amino acids esters **11**.



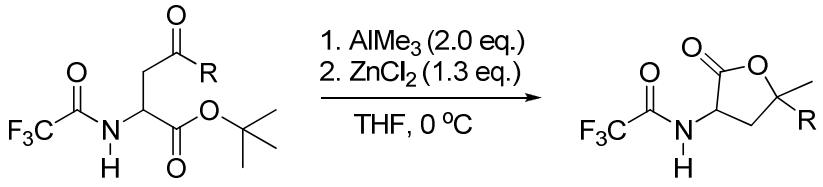
11 **12**

Entry	Ketone	R	Prouct	Yield (%)
1	**11f**	$PhOCH_2$	**12a**	60
2	**11k**	*p*-$ClPhOCH_2$	**12b**	66
3	**11n**	*o*-$CNPhOCH_2$	**12c**	62
4	**11a**	Me	**12d**	70
5	**11c**	*n*-Bu	**12e**	65
6	**11d**	CH_2Cl	**12f**	64
7	**11e**	1-hexenyl	**12g**	62
8	**11o**	*n*-decyl	**12h**	61

3.6.3 Methylation of γ-keto aminoacid esters 11:

After having the nice results for the formation of lactones (table 3.13), we wanted to apply same methodology for methylation reactions. To begin with, we selected $AlMe_3$ as methylating reagent. The strong Lewis acidic nature of $AlMe_3$ and $ZnCl_2$ should also give rise to lactones **14**. The results obtained from this reaction are summarized in table 3.14.

Table 3.14: Methylation of γ-keto amino acids esters **11**.



11 **14**

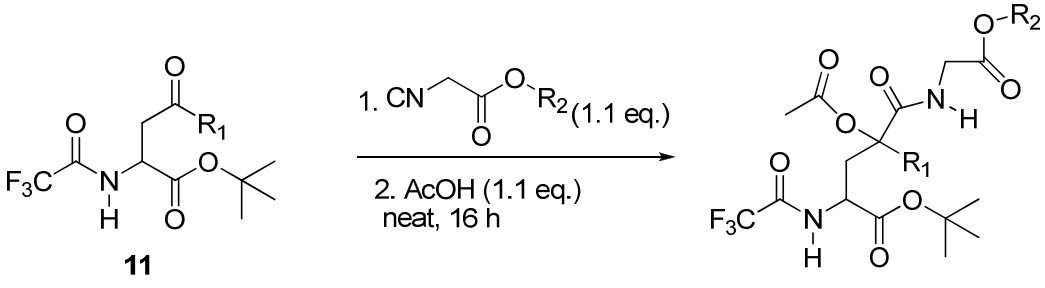
Entry	Ketone	R	Product	Yield (%)
1	**11f**	$PhOCH_2$	**14a**	60
2	**11k**	*p*-$ClPhOCH_2$	**14b**	58
3	**11n**	*o*-$CNPhOCH_2$	**14c**	66
4	**11a**	Me	**14d**	60
5	**11d**	CH_2Cl	**14e**	66

Generally a solution of the γ-keto amino acids esters **11** was stirred in DCM in the presence of $ZnCl_2$ at 0 ^oC which results in the *in situ* formation of γ-keto amino acids esters-$ZnCl_2$ complex. This mixture is then transferred to 2 M solution of $AlMe_3$ at 0 ^oC in hexane for methylation. The effect of the substituents was not significant and the reaction proceeded smoothly providing lactones **14** in good yields (58–66%).

3.6.4 Passerini and Ugi reactions of γ-keto aminoacid esters 11.

Next, we wanted to see if γ-keto amino acids esters **11** are also suitable candidates for Passerini reaction. Different γ-keto amino acids esters were subjected to this three component reaction and the results obtained are summarized in table 3.15.

Table 3.15: Passerini reaction of γ-keto amino acids esters.

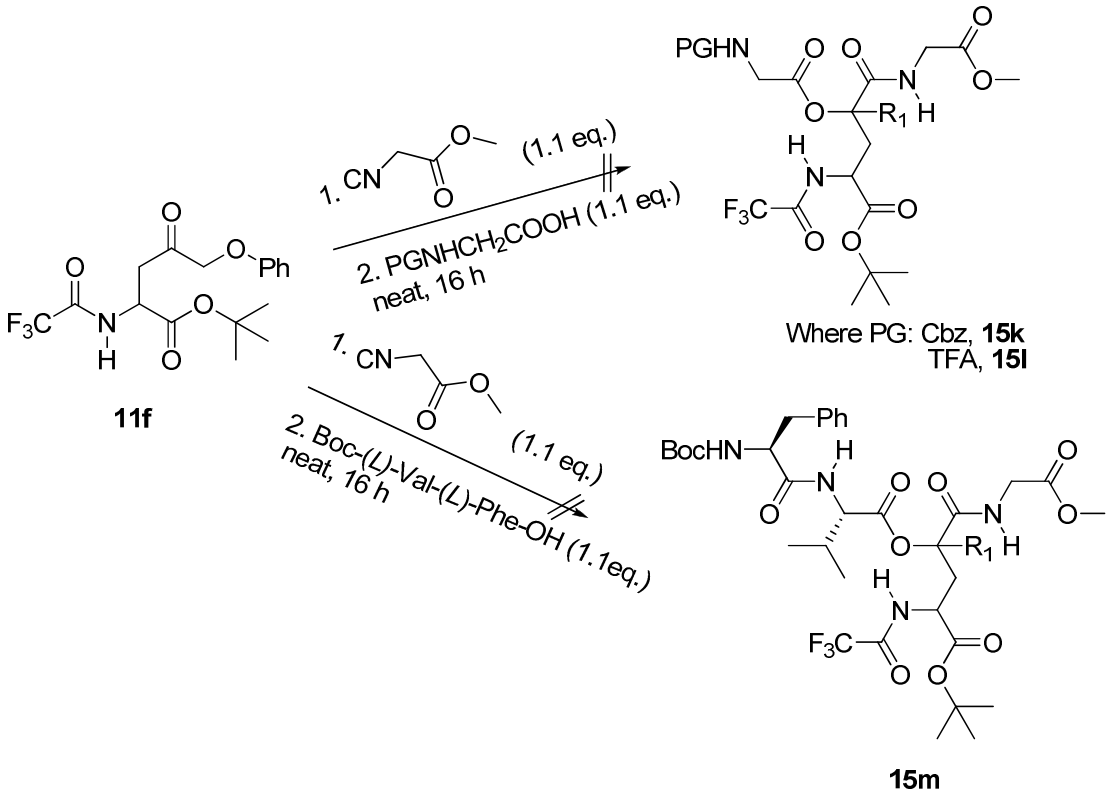


11 **15**

Entry	Ketone	R_1	R	Product	Yield (%)
1	**11f**	$PhOCH_2$	Me	**15a**	53
2	**11m**	*o*-NO_2PhOCH_2	Me	**15b**	58
3	**11k**	*p*-$ClPhOCH_2$	Me	**15c**	65
4	**11f**	$PhOCH_2$	Et	**15d**	57
5	**11k**	*p*-$ClPhOCH_2$	Et	**15e**	64
6	**11l**	*p*-NO_2PhOCH_2	Et	**15f**	59
7	**11a**	Me	Me	**15g**	No reaction
8	**11d**	CH_2Cl	Me	**15h**	61
9	**11c**	*n*-Bu	Me	**15i**	No reaction

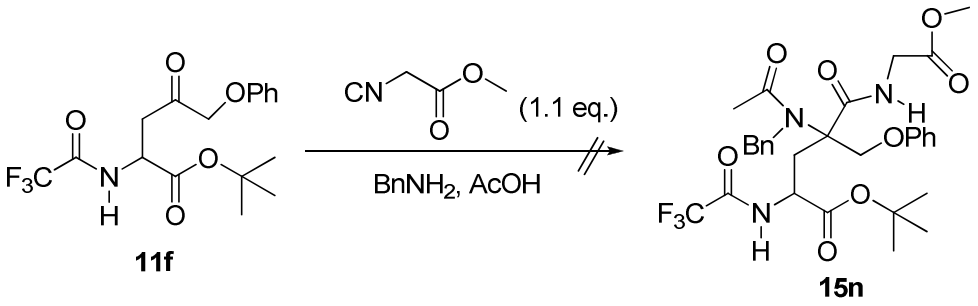
Promising results were obtained and generally all examples gave rise to the desired products **15** in acceptable yields (53–65%). Surprisingly, no reaction was observed with the alkyl substituted ketones **11a** and **11c** (entries 8 and 10), and starting material was recovered in these cases. From this observation, we could conclude that only functionalized and activated ketones can undergo Passerini reactions. Obviously, the electron withdrawing effect of the phenoxy- or chloro-substituents is strong enough for activation.

Encouraged by the results obtained with Passerini reaction we wanted to develop further applications of this reaction by using amino acids and dipeptides instead of the simple acetic acid. For this purpose we carried out few reactions with **11f** using Cbz- and TFA- protected glycine as an acid component whereas Boc-*L*-Val-*L*-Phe-OH was used a dipeptide (Scheme 3.11). Unfortunately, these reactions didn't form any desired product and only starting material was recovered. It was observed that during the reaction after all the reagents had been added, a homogenous mixture was not formed, which could be a reason for failure of this reaction. This problem was solved by adding a few drops of trifluoroethanol (TFE) just enough to homogenize the reaction mixture, but still we could not obtain that desired product and also here starting material **11f** was recovered. A possible reason could be the bulkiness of the amino acids and the dipeptide, since acetic acid is a small molecule compared to those.



Scheme 3.11: Passerini reaction of **11f** using amino acids and dipeptide.

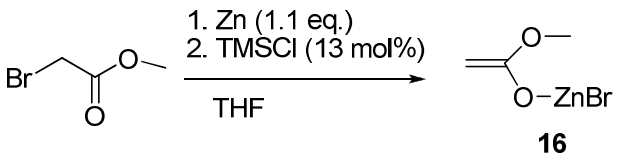
Then we tried to figure out if Ugi reactions can be carried out with these γ-keto amino acids esters **11**. Compound **11f** was subjected to Ugi reaction following scheme 3.12 but again reaction didn't yield in desired product. Instead the starting material was recovered. Interestingly, the Passerini product was also not observed probably due to the presence of benzyl amine acting as a base and suppressing the formation of Passerini product.



Scheme 3.12: Ugi reaction of **11f**.

3.6.5 Reformatsky reactions of γ-keto aminoacid esters 11:

We had already observed that γ-keto amino acids esters **11** proved to be good substrates for Zn-mediated allylation reactions, and therefore, we also tried Reformatsky reactions with these substrates and obtained good results (Table 3.16). The Reformatsky reagent was prepared by treating methyl bromo acetate with Zn according to scheme 3.13.

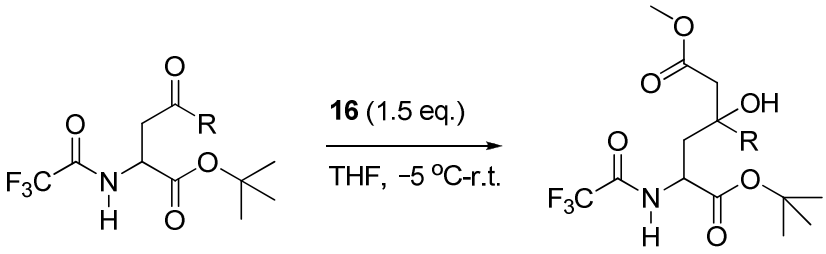


16

Scheme 3.13: Preparation of Reformatsky reagent **15**.

The Reformatsky reagent **16** was obtained in approximately 1.6 M concentration and allowed to react with γ-keto amino acids esters **11**. The results are summarized in table 3.16.

Table 3.16: Reformatsky reaction of γ-keto amino acids esters **11**.



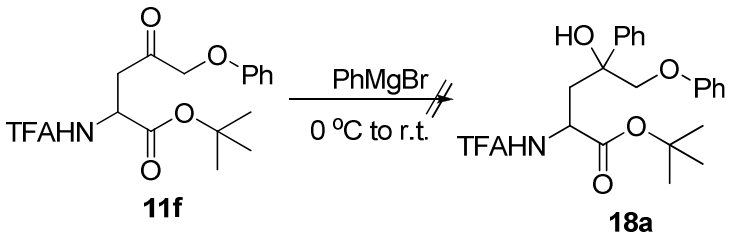
11 **17**

Entry	Ketone	R	Compound	Yield (%)
1	**11k**	*p*-ClPhOCH$_2$	**17a**	90
2	**11d**	ClCH$_2$	**17b**	85

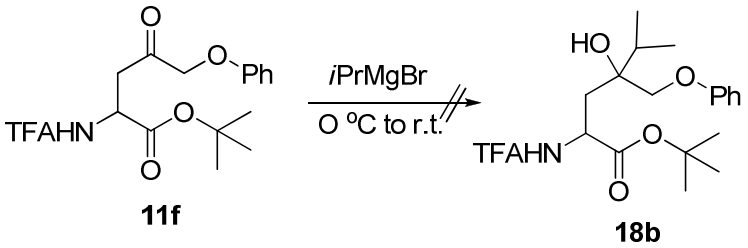
Generally, a solution of **16** was added to γ-keto amino acids esters **11** at –5 °C and the reaction mixture stirred over night. The reaction proceeded smoothly and high yields were obtained. Compound **17a** and **17b** were isolated in 90 and 85% yields respectively.

3.6.6 Grignard reactions of γ-keto aminoacid esters 11:.

Since organo-metallic reagents resulted in good yields, therefore, we subjected γ-keto amino acids esters **11** also to Grignard reaction as shown in scheme 3.14.



11f **18a**



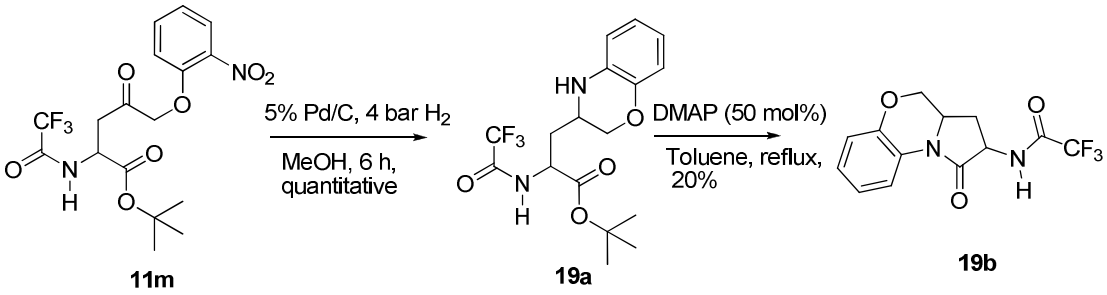
11f **18b**

Scheme 3.14: Grignard reaction of γ-keto aminoacid ester **11f**.

Compound **11f** was allowed to react with Grignard reagent at 0 °C but in both cases complete decomposition of compound **11f** was observed. The presence of ester and amide groups in compound **11f** could also be potential electrophilic centers for the attack of the Grignard reagent. Thus, the reaction resulted in the formation of many unidentified side products.

3.6.7 Synthesis of heterocyclic compounds based on amino acid esters.

In the next step, we were interested to see if the methodology can be applied for the synthesis of heterocyclic compounds, based on amino acid esters. For example we targeted to synthesize benzomorpholine based TFA *tert*-butyl glycinate **19a**. For this purpose we subjected **11m** to one pot reduction reductive amination according to scheme 3.15.

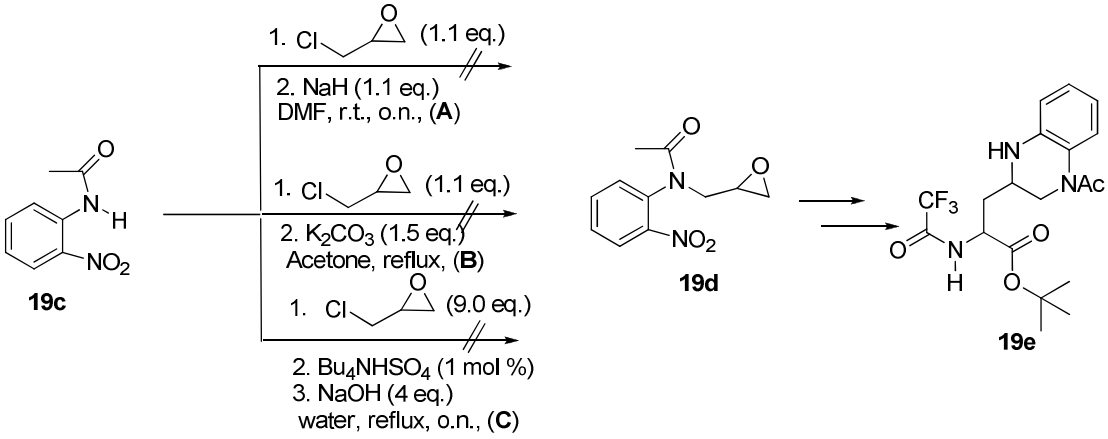


11m **19a** **19b**

Scheme 3.15: Synthesis of compounds **19a** and **19b**.

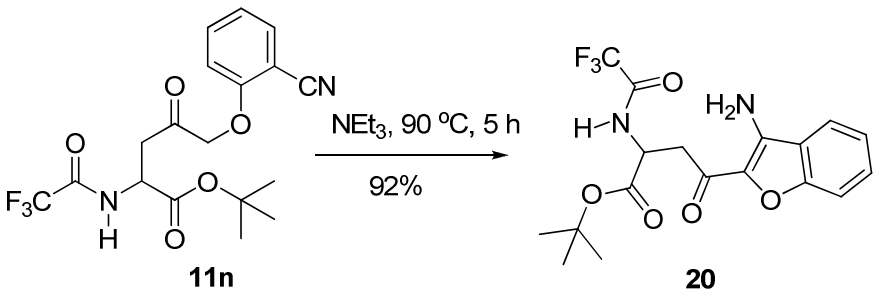
In the first step, the reduction of nitro group to an amino group takes place under H_2 pressure (4 bar) which attacks the carbonyl group in a reductive amination process to yield compound **19a**. The reaction proceeded smoothly and compound **19a** was isolated quantitatively. Then we tried to cyclize **19a** and we refluxed it in toluene in the presence of 50 mol% DMAP. Fortunately, we could cyclize it to make another heterocyclic compound **19b** in 20% yield. Based on this reaction we tried to synthesize benzopiperazine based TFA *ter*-butyl glycinate **19e** and for this we attempted to synthesize epoxide **19d**. Different methods were applied by using different reaction conditions but unfortunately none of them proved to be successful. In reaction **A** we used NaH as base and DMF as solvent and the reaction mixture was stirred at room temperature over night, but it didn't result in epoxide

formation and starting material **19c** was recovered. In cases of reactions **B** and **C** we used K_2CO_3 and NaOH as bases and we refluxed the reaction mixtures in acetone and water respectively, but this resulted in a cleavage of the amide group without the formation of epoxide **19d** (Scheme 3.16).



Scheme 3.16: Attempts to synthesize epoxide **19d**.

A further attempt was made to synthesize functionalized benzofuran based TFA *ter*-butyl glycinate **20**. The reaction was performed by refluxing **11n** at 90 ^{o}C for 5 h. Complete conversion was observed after that time (as monitored by TLC) giving rise to functionalized benzofuran based TFA *ter*-butyl glycinate **20** in 92% yield (Scheme 3.17).

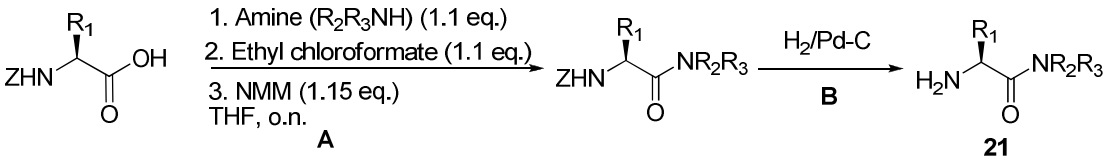


Scheme 3.17: Synthesis of benzofuran based TFA ter-butyl glycinate **20**.

3.6.8 Synthesis of constrained peptides.

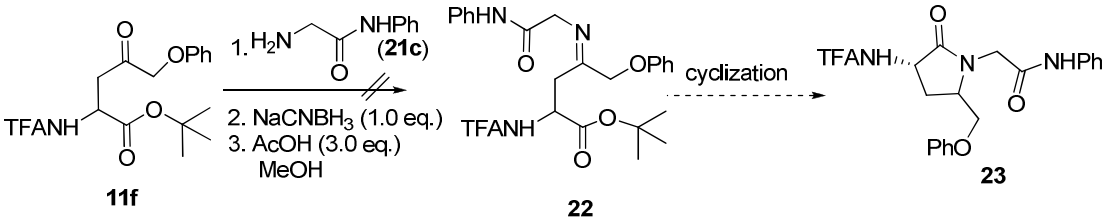
Due to the synthetic utility of constrained peptides in peptide based drugs, we were interested to apply our methodology to the synthesis of constrained peptides. For this purpose we considered different amides **21** which were synthesized by coupling of amino acids with amines in the presence of ethyl chloroformate and *N*-methyl morpholine. The results are summarized in table 3.17.

Table 3.17: Synthesis of substrates **21** for reductive amination.



Entry	Amino acid	Amine	Yield **A** (%)	Yield **B** (%)	Product
1	Z-Phenylalanine	Aniline	92	quantitative	**21a**
2	Z-Phenylalanine	pyrrolidine	90	quantitative	**21b**
3	Z-glycine	Aniline	88	quantitative	**21c**
4	Z-glycine	pyrrolidine	92	quantitative	**21d**

The coupling reaction worked in high yields (88–92%) and the resulting amides were then subjected to deprotection by hydrogenation under 1 bar H_2 in the presence of Pd/C. The reaction proceeded smoothly and compounds **21** were isolated in quantitative yields. The products **21** were then used in reductive amination reactions following scheme 3.18.

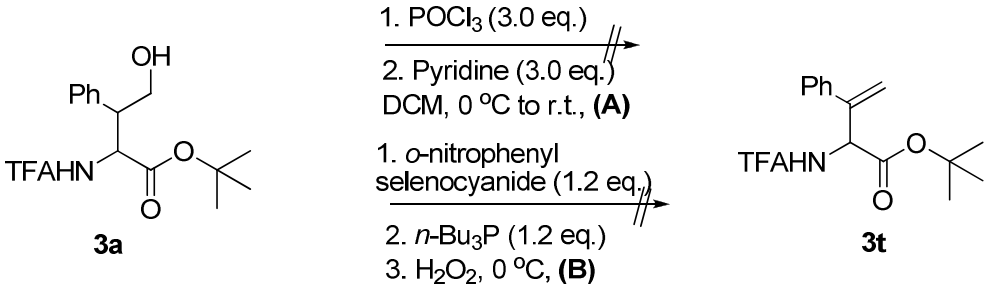


Scheme 3.18: Attempt to synthesize constrained peptide **23**.

Compound **11f** was allowed to react with **21c** under reductive amination conditions, but the desired product **22** was not obtained. Instead, a reduction of the keto group in **11f** to alcohol was observed.

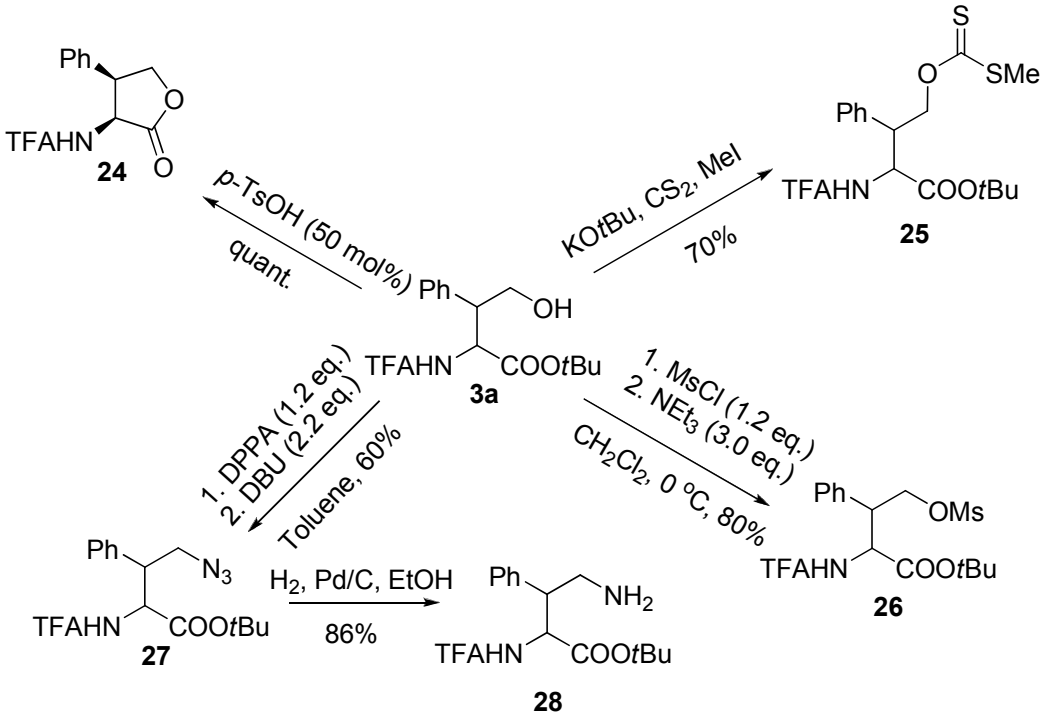
3.6.9 Synthesis of β-substituted phenylalanine derivatives:

Next we were interested to see if β-γ-unsaturated amino acid ester **3a-1** could be synthesized from derivative **3a**. For this purpose compound **3a** was subjected to two alternative elimination conditions but unfortunately the desired product could not be isolated in either case. In case of reaction **A** compound **3a** was allowed to react with $POCl_3$ and pyridine but it didn't result in desired product. Similarly compound **3a** was subjected to oxidative elimination by using *o*-nitrophenyl selenocyanate and hydrogen per oxide but no product could be isolated. In both the cases only decomposition of the starting material **3a** was observed (Scheme 3.19).



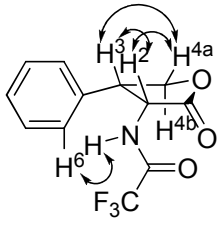
Scheme 3.19: Attempt to synthesize β-γ-unsaurated amino acid ester **3t**.

Since β-branched amino acids are important building blocks of biologically active peptides, we subjected the products **3** of the ring opening reaction of aromatic epoxides to further transformations. As an example compound **3a** was subjected to several modifications as described in scheme 3.20.



Scheme 3.20: Synthesis of β-substituted phenylalanine derivatives from **3a**.

It was observed that **3a** could be transformed into a variety of derivatives. Lactonization of **3a** could be performed easily using *p*-toluenesulfonic acid, and lactone **24** was achieved quantitatively. To determine the configuration of our phenylalanine derivatives we subjected the major diastereomer of **1a** to acid catalyzed lactonization (Scheme 3.20) which gave rise to lactone **24** (Figure 3.5). The *syn*-configuration of lactone **24** was identified by NOE measurement. A notable NOE difference (~6%) was observed between H^3 and H^2/H^{4a} and between H^2 and H^{4a}. Similarly an NOE correlation between N-H and H^6 was also observed.



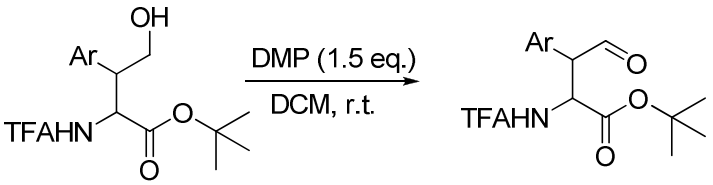
24

Figure 3.5: NOE measurement of lactone **24**.

The compound **3a** was allowed to react with MsCl at 0 ^{o}C to obtain mesylate **26**, a good substrate for nucleophilic substitution reactions. Xanthate **25** was synthesized in 70% yield by treating compound **3a** under chugaev conditions and should be a good precursor for radical reactions. Moreover **3a** was allowed to react with DPPA (diphenylphosphoryl azide) and DBU in toluene to yield azide **27** in 60% yield which is a suitable candidate for 'click chemistry'. The azide **27** was further hydrogenated to yield amine **28** in 86 % yield.

Further work was carried out by subjecting the compounds **3** to oxidation under Dess-Martin conditions to give aldehydes **29**. It was observed that even after using 1.5 equivalents of Dess-Martin reagent the oxidations of compounds **3** were in complete. However the yields of the oxidation reaction were in a good range (65–72%). The results obtained from oxidation reaction are summarized in table 3.18.

Table 3.18: Synthesis of aldehydes **29**.

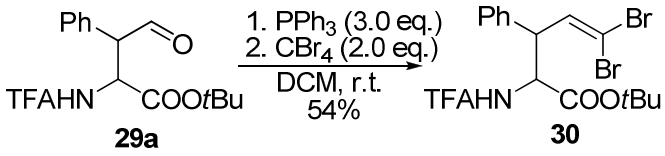


3 **29**

Entry	Ar	Compound	Yield (%)
1	Ph	**29a**	71
2	*p*-tolyl	**29b**	78
3	*o*-tolyl	**29c**	74
4	*p*-ClPh	**29d**	75
5	*o*-ClPh	**29e**	73

These aldehydes can be good substrates for carbonyl additions. As an example compound **29a** was allowed to react with CBr_4 in the presence of PPh_3 at 0 ^{o}C and

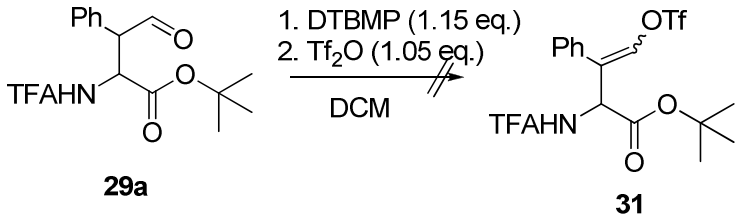
dibromo alkene was obtained in 54% yield *via* Corey-Fuchs reaction (Scheme 3.21). This substrate should be a good candidate for regioselective cross coupling reactions.



29a **30**

Scheme 3.21: Synthesis of Corey-Fuchs intermediate **30**.

Further attempts were made to synthesize triflate **31** which could be useful substrate for cross coupling reactions. For this purpose we subjected **29a** to react with triflic anhydride in the presence of DTBMP (di-*t*-butyl methyl pyridine) but unfortunately the desired product was not obtained, only decomposition of **29a** was observed (Scheme 3.22).

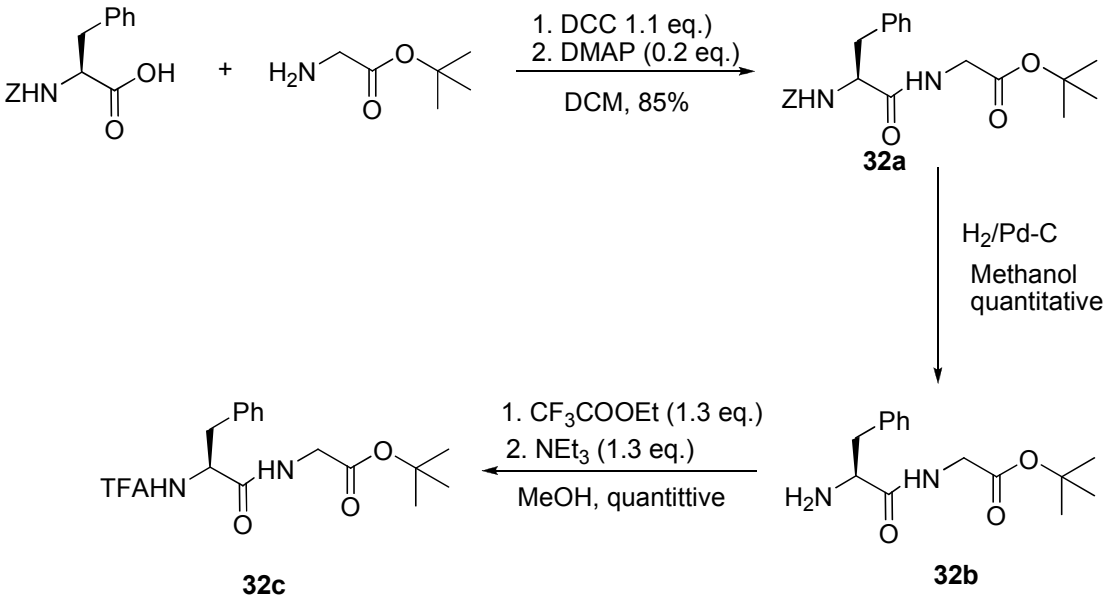


29a **31**

Scheme 3.22: Attempt to synthesize triflate **31**.

3.6.10 Application to peptide modifications:

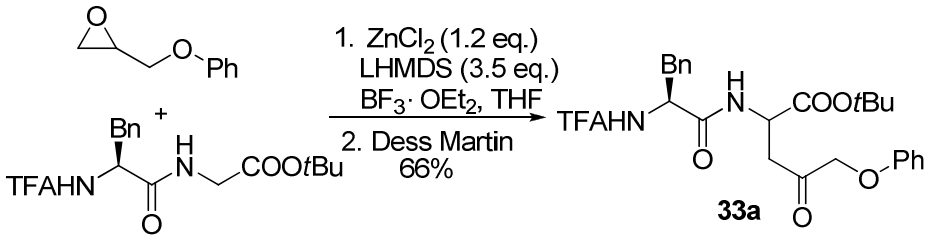
Since the results obtained in ring opening reactions were encouraging so we decided to see if the same methodology could be useful for the modification of peptides. For this purpose we synthesized a phenylalanine dipeptide as a nucleophile following scheme 3.23.



Scheme 3.23: Synthesis of dipeptide **32c**.

The Z-phenylalanine was allowed to couple with *tert*-butyl glycinate by the DCC-coupling method which gave compound **32a** in 85% yield. This was further subjected to deprotection of Z-group under H_2 pressure (1 bar) in the presence of Pd/C which yielded **32b** quantitatively. Compound **32b** was then protected by using ethyl trifluoroacetate to achieve dipeptide **32c** which was isolated quantitatively.

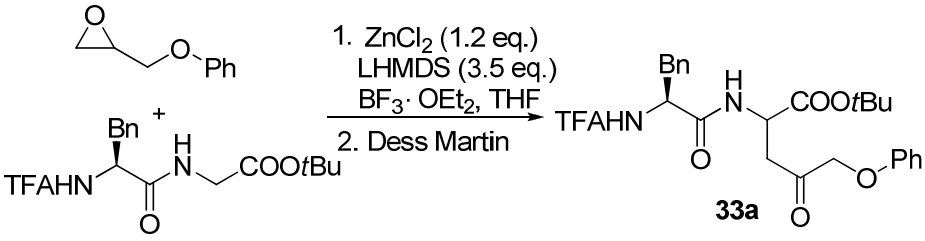
The dipeptide **32c** was then subjected to analogous reaction conditions as used for ring opening by TFA *ter*-butyl glycinate. Only the amount of base (LHMDS) was increased to 3.5 equivalents. The ring opening products were directly oxidized to corresponding ketones (Scheme 3.24).



Scheme 3.24: Ring opening of phenyl glycidyl ether with dipeptide enolate.

We were encouraged to see that the desired product **33a** was obtained in 66% yield over two steps. To see if the amount of epoxide and Lewis acid could affect the reaction outcome, we performed few reactions using different epoxide equivalents with and without Lewis acid and the observations are shown in table 3.19.

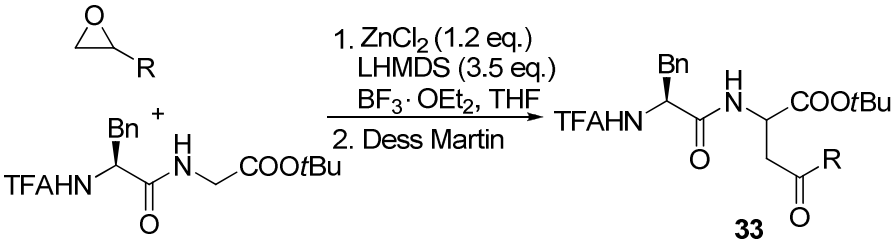
Table 3.19: Effect of epoxide equivalents and $BF_3{\cdot}OEt_2$.



Entry	$BF_3{\cdot}OEt_2$ (eq.)	Epoxide (eq.)	Yield (%)	dr
1	-----	1.0	42	70:30
2	1.1	1.0	50	72:28
3	----	1.2	54	65:35
4	1.1	1.2	65	73:27
5	----	1.5	55	69:31
6	1.1	1.5	68	72:28

It was observed that in the absence of Lewis acid and with one equivalent of the epoxide, the product **33a** could be obtained in 40% yield (entry 1). However with the use of Lewis acid the yield increased to 50% (entry 2). 1.5 equivalents of phenyl glycidyl ether could result in higher yield whereas the presence of Lewis acid results in significant increase of product (entry 6). The yield increased to 54% when epoxide equivalents were increased to 1.2 and when Lewis acid was added the yield increased to 65% (entries 3 and 4). A further increase in epoxide equivalents increased the yield slightly (entries 5 and 6). The same trend was observed during optimization of conditions when TFA *ter*-butyl glycinate was used as nucleophile. Then we subjected various aliphatic epoxides and aryl glycidyl ethers for ring opening reaction. The results obtained are summarized in table 3.20.

Table 3.20: Examples of peptide modification reaction.



Entry	R	Compound	Yield (%)	ds(%)
1	$PhOCH_2$	**33a**	66	70
2	*p*-$ClPhOCH_2$	**33b**	68	64
3	*p*-NO_2PhOCH_2	**33c**	72	68
4	*o*- NO_2PhOCH_2	**33d**	65	70
5	Me	**33e**	64	68
6	$ClCH_2$	**33f**	66	67
7	Et	**33g**	68	68

The reactions proceeded smoothly in all cases. The effect of substituents on the epoxide ring was not significant on the diastereoselectivity. Ring opening of aliphatic epoxides was achieved in moderate yields (64–68%) and the diastereoselectivities were around 67% (entries 5 to 7). Same was true for ring opening of aryl glycidyl ethers which resulted in 65 to 72% yields and diastereoselectivities ranging from 64 to 70% (entries 1 to 4).

4 Experimental Section

4.1 General Information

All reactions were carried out in oven-dried glassware (100 ^{o}C) under nitrogen unless otherwise stated. Septa, disposable syringes and needles were used for the transfer of reagents and other liquid chemicals. For drying of organic phases water-free sodium sulphate was used.

^{1}H-NMR-spectra were measured on a 400 MHz nuclear magnetic resonance spectrometer (model *AV-400*). $CDCl_3$ was used as solvent. The solvent peak was calibrated at 7.26 ppm. The analysis of spectra was done with *PC-software MestRe-C*. The abbreviations used for interpretation of nmr spectra are: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet or br = broad. Chemical shifts were δ-values and were measured in ppm.

^{13}C-NMR-spectra were also measured on a frequency of 100 MHz on a nuclear magnetic resonance spectrometer (model *AV-400*). $CDCl_3$ was used as solvent. The solvent peak was calibrated at 77.0 ppm. The analysis of spectra was done with *PC-software MestRe-C*. The abbreviations used for analysis are: s = singlet, d = doublet, t = triplet, q = quartet. Chemical shifts were δ-values and were measured in ppm.

Preparative flash column chromatography was performed using columns packed with silica gel grade 60 (35-70μm) purchased from *Macherey-Nagel.*

Melting points were measured in open glass capillaries on apparatus *MEL-TEMP II* purchased from *Laboratory Devices* and are uncorrected.

Thin-layer chromatography was done using commercially available precoated Polygram® SIL-G/UV 254 plates purchased from the company *Fluka.* The detection of spots was done under UV-light, I_2-vapours or $KMnO_4$ solution.

High Pressure liquid chromatography was performed on the instrument purchased from company *Shimadzu* (model *10A VP*). As an achiral column *LiChrosorb Si-60* (250 4, diameter 5 m) was used purchased from the company *Phenomenex.* The evaluation was done with *Class VP-Software* (*Schimadzu*).

Elemental analyses was performed at the Institute for Organic Chemistry, University of Saarland by Miss Heike Roeser on the instrument *Leco* (model *CHN900*).

High resolution mass spectrometry (HRMS) was performed at the Institute for Organic Chemistry, University of Saarland by Mr. Rudi Thomas on the instrument *MAT 95Q* purchased from the company *Finnigan*. The fragmentation was carried out through chemical ionization (CI) or electron ionization (EI).

Solvents were dried by refluxing the corresponding solvent over suitable drying agent. Tetrahydrofuran (THF) was dried over lithium aluminium hydride (LAH), dichloromethane (DCM) was dried over powdered CaH_2. Commercial grade solvents like ethyl acetate, hexane, diethyl ether were distilled prior to use.

4.2 General Experimental Procedures (GPs)

GP 1: Synthesis of aromatic epoxides

To a solution of Me_3SI (1.8 g, 8.8 mmol) in dry DMSO (8 ml) NaH (400 mg, 8.8 mmol) was added at room temperature and the reaction mixture was allowed to stir under nitrogen. After 20 min, a solution of the corresponding aldehyde (7.3 mmol) in dry DMSO (8 ml) was added dropwise within 20 min. After stirring for another 3 h, the reaction mixture was poured into cold water (40 ml) and extracted thrice with ethyl acetate. The collected organic phases were dried over Na_2SO_4 and the solvent was removed under vacuum. The crude epoxide was purified by bulb-to-bulb distillation under reduced pressure.

GP 2: Synthesis of aryl glycidyl ethers

To a solution of NaOH (0.66 g, 16.5 mmol) in water (5.5 ml) the corresponding phenol (11.0 mmol) was added, and the reaction mixture was stirred for 30 min. After the addition of epichlorohydrin (1.2 g, 12.9 mmol), the reaction was stirred at room temperature for 8 h and extracted with dichloromethane. The crude epoxide was purified by column chromatography (silica gel, DCM/hexane).

GP 3: Ring opening reactions of epoxides

In a Schlenk tube hexamethyldisilazane (497 mg, 3.08 mmol) was dissolved in dry THF (5.0 ml). After the solution had been cooled to –78 °C, a 1.6 M solution of *n*-BuLi (1.72 ml, 2.75 mmol) was added slowly. The solution was stirred for 10 min before the cooling bath was removed and the solution was stirred for a further 10 min. In a second Schlenk flask $ZnCl_2$ (180 mg, 1.32 mmol) was dried with a heat gun under vacuum and dissolved in THF (5.0 ml). After the solution had been cooled to room temperature, the Tfa-Gly-O*t*Bu (250 mg, 1.1 mmol) was added and cooled to –78° C before the LHMDS solution was added slowly. The resulting solution was stirred for 30 min at –78 °C. Then the corresponding epoxide (1.65 mmol) was added followed by the addition of $BF_3 \cdot OEt_2$ (78.1 mg, 0.55 mmol). The reaction mixture was allowed to warm to r.t. over night before it was hydrolyzed with 1M HCl and extracted thrice with ethyl acetate. The combined organic layers were dried (Na_2SO_4), the solvent was evaporated in vacuo, and the crude product was purified by flash chromatography (silica gel, hexanes/EtOAc).

GP 4: Dess-Martin oxidation

To a solution of the corresponding γ-hydroxy amino acid ester **7** or **8** (1.32 mmol) in dry dichloromethane Dess-Martin periodinane (721 mg, 1.7 mmol) was added at 0 ^{o}C under nitrogen and the mixture was allowed to stir at room temperature for 3 h. After the reaction was quenched with a saturated solution of $NaHCO_3$ containing $Na_2S_2O_3$, the mixture was extracted in dichloromethane. The organic layers were washed with a saturated solution of NaCl, dried over Na_2SO_4 and the solvent removed in vacuo. The corresponding γ-keto amino acid ester **11** was obtained after column chromatography (silica gel, EtOAc/hexane).

GP 5: Swern oxidation

To a solution of oxalyl chloride (67 mg, 0.52 mmol) in dry dichloromethane (0.5 ml) at –78 ^{o}C DMSO (82.8 mg, 1.06 mmol) was added and the solution was allowed to stir for 10 min before a solution of corresponding γ-hydroxy amino acid ester **7** or **8** (0.26 mmol) was added dropwise. The reaction mixture was allowed to stir at the same temperature for another 1 h before triethylamine (134 mg, 1.32 mmol) was added. The cooling bath was removed after 15 min, and the reaction mixture was allowed to warm to room temperature. Water (5 ml) was added and the reaction mixture was stirred for additional 10 min. The reaction mixture was extracted with dichloromethane, the organic layers were washed with 1 N HCl, saturated NaCl soln., dried over Na_2SO_4 and the solvent was removed in vacuo. The corresponding γ-keto amino acid ester **11** was obtained after column chromatography (silica gel, EtOAc/hexane).

GP 6: Allylation of γ-keto amino acid ester 11[93]

To a suspension of Zn dust (19.1 mg, 0.29 mmol) in dry THF (0.5 ml) at room temperature allyl bromide (18 mg, 0.15 mmol) was added. After stirring for 30 min, a solution of corresponding γ-keto amino acid ester **11** (0.15 mmol) in THF (0.15 ml) was added dropwise and stirring was continued for 1 h. The reaction was quenched with NH_4Cl, extracted with dichloromethane, dried over Na_2SO_4 and the solvent was removed under vacuo. The crude product was purified by column chromatography (silica gel, ethyl acetate/hexane).

GP 7: Methylation of γ-keto amino acid ester 11[94]

To a solution of $ZnCl_2$ (34 mg, 0.25 mmol) in dry THF (3.0 ml) a solution of corresponding γ-keto amino acid ester **11** (0.19 mmol) was added at room temperature and the mixture was allowed to stir for 30 min. The resulting solution was transferred into a 2 M solution of $AlMe_3$ (27.8 mg, 0.38 mmol) at 0 °C and warmed up to room temperature. The reaction mixture was decomposed with MeOH at 0 °C. The solvent was removed and diluted with 5 % aqueous sulphuric acid solution. The aqueous layer was extracted with dichloromethane, dried over Na_2SO_4 and the crude product was purified by column chromatography (silica gel, EtOAc/hexane).

GP 8: Passerini reaction of γ-keto amino acid ester 11[95]

To a sample of pure γ-keto amino acid ester **11** (0.27 mmol) under N_2 in a 5 ml round bottom flask was added acetic acid (17.6 mg, 0.29 mmol) and the corresponding isonitrile (0.29 mmol) was added. The resulting homogeneous solution was stirred at r.t. under nitrogen for 20 h. The crude product was purified by column chromatography (silica gel, EtOAc/hexane).

GP 9: Reformatsky reaction of γ-keto amino acid ester 11[96]

To a solution of the corresponding γ-keto amino acid ester **11** (0.15 mmol) in dry THF (0.5 ml) a 1.6 M solution of Zn-bromo-ester (0.22 mmol) was added at –5 °C and allowed to warm to room temperature over night. The reaction was quenched with 1 M HCl solution and extracted in ethyl acetate. The organic layers were washed with a saturated solution of NaCl, dried over Na_2SO_4 and the solvent removed in vacuo. The product was obtained after column chromatography (silica gel, EtOAc/hexane).

GP 10: Peptide modifications

In an oven-dried Schlenk tube hexamethyldisilazane (411 mg, 2.54 mmol) was dissolved in dry THF (5.0 ml). After the solution was cooled to –78 °C, a 1.6 M solution of *n*-BuLi (1.5 ml, 2.34 mmol) was added slowly. The solution was stirred for 10 min before the cooling bath was removed and the solution was stirred for a further 10 min. In a second Schlenk flask $ZnCl_2$ (109 mg, 0.80 mmol) was dried with a heat gun under vacuum and dissolved in THF (2.0 ml). The corresponding dipeptide (250 mg, 0.67 mmol) was added and the solution was cooled to –78 °C before the

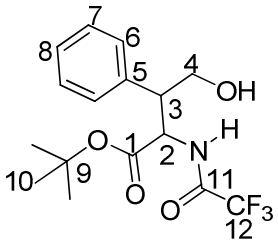
LHMDS solution was added slowly *via* syringe. The resulting solution was stirred for 60 min at –78 °C. Then the corresponding epoxide (1.0 mmol) was added directly to the enolate at –78 °C, followed by $BF_3 \cdot OEt_2$ (47.4 mg, 0.34 mmol). The reaction mixture was allowed to warm to r.t. over night before it was hydrolyzed with 1M HCl and extracted three times with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in vacuo. The crude product was re-dissolved in 10 ml dry dichloromethane and Dess-Martin periodinane (1.0 mmol) was added in one portion at 0 ^{o}C. After the oxidation was complete, the reaction was quenched by saturated aqueous solution of $NaHCO_3$ containing $Na_2S_2O_3$ and extracted three times in ethyl acetate. The combined organic layers were dried (Na_2SO_4), the solvent was removed in vacuo, and the crude product was purified by flash chromatography (silica gel, hexanes/EtOAc).

4.3 Syntheses of Compounds

tert-Butyl-4-hydroxy-3-phenyl-2-(2,2,2-trifluoroacetamido) butanoate (3a)

According to the general procedure **GP-3**, TFA-Gly-OtBu (250 mg, 1.1 mmol), styrene oxide (264 mg, 2.2 mmol), hexamethyldisilazane (497 mg, 3.08 mmol), *n*-BuLi (1.72 ml, 2.75 mmol) and $BF_3 \cdot OEt_2$ (172 mg, 1.2 mmol) were allowed to react to give **3a** after flash chromatography (silica, hexanes/EtOAc 8:2) in 70% yield (268 mg, 0.77 mmol) as a colorless oil.

[TLC: Hex/EA 8:2, R_f = 0.41]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, $^3J_{NH,2}$ = 7.5 Hz, 1 H, N-H), 7.22–7.31 (m, 5 H, 6-H, 7-H, 8-H), 4.79 (dd, $^3J_{2,NH}$ = $^3J_{2,3}$ = 7.7 Hz, 1 H, 2-H), 3.91–3.99 (m, 2 H, 4-H), 3.19 (dt, $^3J_{3,2}$ = 7.6 Hz, $^3J_{3,4}$ = 5.3 Hz, 1 H, 3-H), 2.66 (bs, 1 H, O-H), 1.24 (s, 9 H, 10-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 157.1 (q, *J* = 37.4 Hz), 137.1, 128.6, 128.5, 127.8, 115.6 (q, *J* = 285.8 Hz), 83.3, 63.7, 55.8, 49.3, 27.5.

Minor diastereomer (selected signals)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.33 (m, 3 H, 7-H, 8-H), 7.07–7.06 (m, 2 H, 6-H), 7.03 (d, $^3J_{NH,2}$ = 7.2 Hz, 1 H, N-H), 5.03 (dd, $^3J_{2,NH}$ = 7.9 Hz, $^3J_{2,3}$ = 3.4 Hz, 1 H, 2-H), 3.73–3.83 (m, 2 H, 4-H), 1.41 (s, 9 H, 10-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 135.3, 128.8, 128.4, 128.3, 84.1, 62.1, 53.5, 50.3, 27.9.

HRMS (CI):	Calculated	Found
$C_{12}H_{11}F_3NO_4$ $[M\text{-}C_4H_9]^+$	290.0640	290.0612

Elemental Analysis:

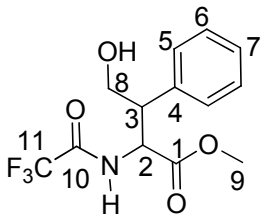
$C_{16}H_{20}F_3NO_4$	Calculated	C 55.33	H 5.80	N 4.03
(347.33):	Found:	C 54.99	H 5.81	N 4.29

Methyl 4-hydroxy-3-phenyl-2-(2,2,2-trifluoroacetamido) butanoate (3c)

According to the general procedure **GP-3**, TFA-Gly-OMe (204 mg, 1.1 mmol), styrene oxide (264 mg, 2.2 mmol), hexamethyldisilazane (497 mg, 3.08 mmol), *n*-BuLi

(1.72 ml, 2.75 mmol) and $BF_3 \cdot OEt_2$ (172 mg, 1.2 mmol) were allowed to react to give **3c** after flash chromatography (silica, hexanes/EtOAc 8:2) in 70% yield (219 mg, 0.74 mmol) as white solid with a melting point of 46 °C.

[TLC: Hex/EA 8:2, R_f = 0.48]



Major diastereomer:

^{1}H NMR (400 MHz, CDCl3**):** δ = 7.09–7.39 (m, 5 H, 5-H, 6-H, 7-H), 6.36 (bs, 1 H, N-H), 4.95–5.03 (m, 1 H, 2-H), 4.00–4.15 (m, 2 H, 8-H), 3.64 (s, 3 H, 9-H), 3.37 (dd, $^3J_{3,2}$ = 11.2 Hz, $^3J_{3,2}$ = 6.0 Hz, 1 H, 3-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2, 157.1 (q, *J* = 37.4 Hz), 136.9, 129.4, 128.8, 128.0, 115.6 (q, *J* = 285.8 Hz), 63.5, 55.6, 52.6, 44.2.

Minor diastereomer (selected signals)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (bs, 1 H, N-H), (m, 5 H, 5-H, 6-H, 7-H), 7.09-7.39 (m, 5 H, 5-H, 6-H, 7-H), 4.01-4.14 (m, 2 H, 8-H), 3.64 (s, 3 H, 9-H).

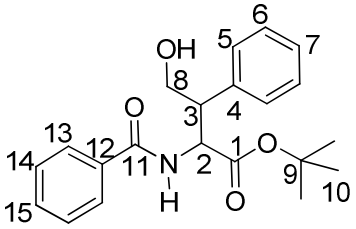
^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 136.8, 129.3, 128.8, 128.0, 63.5, 55.6, 52.6, 44.2.

HRMS (CI):	Calculated	Found
$C_{13}H_{14}F_3NO_4$[M]+:	305.0875	305.0899

***tert*-Butyl 2-benzamido-4-hydroxy-3-phenylbutanoate (3e)**

According to the general procedure **GP-3**, Bz-Gly-OMe (259 mg, 1.1 mmol), styrene oxide (264 mg, 2.2 mmol), hexamethyldisilazane (497 mg, 3.08 mmol), *n*-BuLi (1.72 ml, 2.75 mmol) and $BF_3 \cdot OEt_2$ (172 mg, 1.2 mmol) were allowed to react to give **3e** after flash chromatography (silica, hexanes/EtOAc 8:2) in 71% yield (278 mg, 0.78 mmol) as white solid with a melting point of 52 °C.

[TLC: Hex/EA 8:2, R_f = 0.30]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82–7.84 (m, 2 H, 7-H, 15-H), 7.27–7.56 (m, 8 H, 5-H, 6-H, 13-H, 14-H), 7.05 (d, $^3J_{NH,2}$ = 8.0 Hz, 1 H, N-H), 5.08 (dd, $^3J_{2,3}$ = 9.7 Hz, $^3J_{2,NH}$ = 8.2 Hz, 1 H, 2-H), 4.01 (dd, $^2J_{8a,8b}$ = 11.9 Hz, $^3J_{8a,3}$ = 4.3 Hz, 1 H, 8a-H), 3.83 (dd, $^2J_{8b,8a}$ = 11.9 Hz, $^3J_{8b,3}$ = 3.3 Hz, 1 H, 8b-H), 2.97 (td, $^3J_{3,2}$ = 9.7, $^3J_{3,8}$ = 3.8 Hz, 1 H, 3-H), 1.53 (s, 9 H, 10-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 167.9, 138.7, 133.3, 132.1, 129.1, 128.7, 128.3, 127.3, 127.1, 82.6, 63.5, 54.8, 52.0, 27.4.

Minor diastereomer (selected signals)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.55 (m, 8 H, 5-H, 6-H, 13-H, 14-H), 6.98 (bs, 1 H, N-H), 5.21 (dd, $^3J_{2,3}$ = 7.6 Hz, $^3J_{2,NH}$ = 3.4 Hz, 1 H, 2-H), 1.40 (s, 9 H, 10-H).

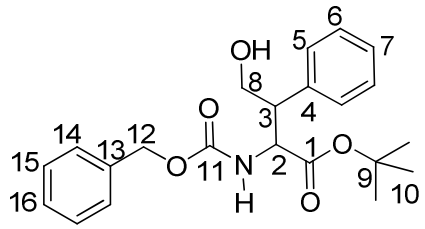
^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 167.9, 138.7, 133.3, 132.1, 129.1, 128.7, 128.3, 82.6, 63.5, 54.8, 52.0, 27.4.

HRMS (CI):	Calculated	Found
$C_{21}H_{25}NO_4[M+1]^+$:	356.1817	356.1896

***tert*-Butyl 2-(benzyloxycarbonylamino)-4-hydroxy-3-phenylbutanoate (3i)**

According to the general procedure **GP-3**, Z-Gly-OMe (241 mg, 1.1 mmol), styrene oxide (264 mg, 2.2 mmol), hexamethyldisilazane (497 mg, 3.08 mmol), *n*-BuLi (1.72 ml, 2.75 mmol) and $BF_3 \cdot OEt_2$ (172 mg, 1.2 mmol) were allowed to react to give **3i** after flash chromatography (silica, hexanes/EtOAc 8:2) in 71% yield (106 mg, 0.28 mmol) as a colorless solid with a melting point of 59 °C.

[TLC: Hex/EA 8:2, R_f = 0.25]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.37 (m, 5 H, 14-H, 15-H, 16-H), 5.60 (d, $^3J_{NH,2}$ = 8.5 Hz, 1 H, N-H), 5.16 (d, $^2J_{12a,12b}$ = 12.2 Hz, 1 H, 12a-H), 5.12 (d, $^2J_{12b,12a}$ = 12.2 Hz, 1 H, 12b-H), 4.65 (dd, $^3J_{2,NH}$ = $^3J_{2,3}$ = 8.8 Hz, 1 H, 2-H), 3.98 (dd, $^2J_{8a,8b}$ = 11.7 Hz, $^3J_{8a,3}$ = 4.9 Hz, 1 H, 8a-H), 3.82–3.84 (m, 1 H, 8b-H), 2.94–2.96 (m, 1 H, 3-H), 1.16 (s, 9 H, 10-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 156.5, 136.0, 129.0, 128.5, 128.4, 128.3, 128.2, 128.1, 127.4, 82.3, 67.3, 63.4, 55.9, 51.7, 27.4.

Minor diastereomer (selected signals)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.35 (m, 5 H, 14-H, 15-H, 16-H), 5.30 (d, $^{3}J_{NH,2}$ = 8.0 Hz, 1 H, N-H), 5.10 (s, 2 H, 12-H), 4.65 (dd, $^{3}J_{2,NH}$ = 8.4 Hz, $^{3}J_{2,3}$ = 3.9 Hz, 1 H, 2-H), 3.56–3.68 (m, 2 H, 8-H), 1.45 (s, 9 H, 10-H).

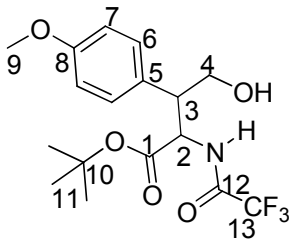
^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 156.5, 136.0, 129.0, 128.3, 128.2, 128.1, 127.4, 82.3, 67.3, 63.4, 55.9, 51.7, 27.4.

HRMS (CI):	Calculated	Found
$C_{22}H_{27}NO_5$ $[M+1]^+$:	385.1889	385.1879

***tert*-Butyl 4-hydroxy-3-(4-methoxyphenyl)-2-(2,2,2-trifluoroacetamido) butanoate (3j)**

According to the general procedure **GP-3** TFA-Gly-O*t*Bu (250 mg, 1.1 mmol), 4-methoxy styrene oxide (330 mg, 2.2 mmol), hexamethyldisilazane (497 mg, 3.08 mmol, 2.8 equiv), *n*-BuLi (1.72 ml, 2.75 mmol) and $BF_3 \cdot OEt_2$ (172 mg, 1.2 mmol, 0.5 eq.) were allowed to react give **3j** after flash chromatography (silica, hexanes/EtOAc 8:2) in 71% yield (295 mg, 0.78 mmol) as a colorless oil.

[TLC: Hex/EA 8:2, R_f = 0.32]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, $^{3}J_{NH,2}$ = 8.1 Hz, 1 H, N-H), 6.85–6.95 (m, 4 H, 6-H, 7-H), 4.90 (dd, $^{3}J_{2,NH}$ = $^{3}J_{2,3}$ = 6.8 Hz, 1 H, 2-H) , 4.10 (dd, $^{2}J_{4a,4b}$ = 11.2 Hz, $^{3}J_{4a,3}$ = 6.4 Hz, 1 H, 4a-H), 4.00 (dd, $^{2}J_{4b,4a}$ = 11.1 Hz, $^{3}J_{4b,3}$ = 5.4 Hz, 1 H, 4b-H), 3.83 (s, 3 H, 9-H), 3.19 (dt, $^{3}J_{3,2}$ = 7.6 Hz, $^{3}J_{3,4}$ = 5.3 Hz, 1 H, 3-H), 1.32 (s, 9 H, 11-H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 157.2 (q, *J* = 37.4 Hz), 156.9, 135.6, 121.1, 115.6 (q, *J* = 285.8 Hz), 114.6, 82.8, 63.2, 55.3, 55.2, 43.0, 27.7.

Minor diastereomer (selected signals)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, $^3J_{NH,2}$ = 5.9 Hz, 1 H, N-H), 7.23–7.29 (m, 4 H, 6-H, 7-H), 4.95 (dd, $^3J_{2,NH}$ = 8.2 Hz, $^3J_{2,3}$ = 5.0 Hz, 1 H, 2-H), 4.00 (dd, $^2J_{4a,4b}$ = 11.1 Hz, $^3J_{4a,3}$ = 5.4 Hz, 1 H, 4a-H), 3.84 (s, 3 H, 9-H), 1.28 (s, 9 H, 11-H).

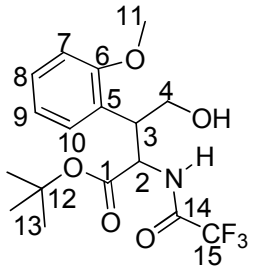
^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 156.5, 136.1, 114.9, 83.2, 63.2, 55.2, 45.5, 27.7.

HRMS (CI):	Calculated	Found
$C_{17}H_{22}F_3NO_5$ $[M+1]^+$:	378.1484	378.1499

***tert*-Butyl 4-hydroxy-3-(2-methoxyphenyl)-2-(2,2,2-trifluoro-acetamido) butanoate (3k)**

According to the general procedure **GP-3**, TFA-Gly-O*t*Bu (250 mg, 1.1 mmol), 2-methoxy styrene oxide (330 mg, 2.2 mmol), hexamethyldisilazane (497 mg, 3.08 mmol), *n*-BuLi (1.72 ml, 2.75 mmol, 2.5 eq.) and $BF_3 \cdot OEt_2$ (172 mg, 1.2 mmol) were allowed to react to give **3k** after flash chromatography (silica, hexanes/EtOAc 8:2) in 60% yield (249 mg, 0.66 mmol) as a colorless oil.

[TLC: Hex/EA 8:2, R_f = 0.33]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, $^3J_{NH,2}$ = 5.9 Hz, 1 H, N-H), 7.23–7.32 (m, 4 H, 7-H, 8-H, 9-H, 10-H), 4.90 (dd, $^3J_{2,NH}$ = $^3J_{2,3}$ = 6.9 Hz, 1 H, 2-H), 4.10 (dd, $^2J_{4a,4b}$ = 11.2 Hz, $^3J_{4a,3}$ = 6.4 Hz, 1 H, 4a-H), 3.99 (dd, $^2J_{4b,4a}$ = 11.1 Hz, $^3J_{4b,3}$ = 5.4 Hz, 1 H, 4b-H), 2.94-2.96 (m, 1 H, 3-H), 3.84 (s, 3 H, 11-H), 1.28 (s, 9 H, 13-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 157.2 (q, *J* = 37.3 Hz), 156.5, 142.5, 130.5, 129.2, 128.9, 126.8, 115.5 (q, *J* = 285.5 Hz), 82.8, 63.2, 55.3, 55.2, 43.0, 27.7.

Minor diastereomer (selected signals)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, $^3J_{NH,2}$ = 8.0 Hz, 1 H, N-H), 6.85–6.95 (m, 4 H, 7-H, 8-H, 9-H, 10-H), 4.95 (dd, $^3J_{2,NH}$ = 8.2 Hz, $^3J_{2,3}$ = 5.0 Hz, 1 H, 2-H), 3.83 (s, 3 H, 11-H), 1.32 (s, 9 H, 13-H).

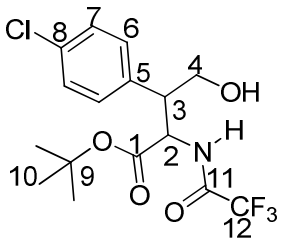
^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 129.2, 128.9, 126.8, 82.8, 63.2, 55.3, 55.2, 43.0, 27.7.

HRMS (CI):	Calculated	Found
$C_{17}H_{22}F_3NO_5$ $[M+1]^+$:	378.1484	378.1499

***tert*-Butyl 3-(4-chlorophenyl)-4-hydroxy-2-(2,2,2-trifluoroacetamido) butanoate (3l)**

According to the general procedure **GP-3**, TFA-Gly-O*t*Bu (250 mg, 1.1 mmol), *p*-chloro styrene oxide (340 mg, 2.2 mmol), hexamethyldisilazane (497 mg, 3.08 mmol), *n*-BuLi (1.72 ml, 2.75 mmol) and $BF_3 \cdot OEt_2$ (172 mg, 1.2 mmol) were allowed to react to give **3l** after flash chromatography (silica, hexanes/EtOAc 8:2) in 79% yield (332 mg, 0.87 mmol) as a colorless oil.

[TLC: Hex/EA 8:2, R_f = 0.32]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, $^3J_{NH,2}$ = 7.5 Hz, 1 H, N-H), 7.30–7.32 (m, 2 H, 6-H), 7.23–7.26 (m, 2 H, 7-H), 4.83 (dd, $^3J_{2,NH}$ = $^3J_{2,3}$ = 7.8 Hz, 1 H, 2-H), 3.98 (dd, $^3J_{4a,3}$ = 4.8 Hz, $^2J_{4a,4b}$ = 1.9 Hz, 1 H), 3.94 (dd, $^3J_{3,4a}$ = 4.8 Hz, $^2J_{4a,4b}$ = 1.9 Hz, 1 H, 4b-H), 3.19 (dt, $^3J_{3,2}$ = 7.6 Hz, $^3J_{3,4}$ = 4.8 Hz, 1 H, 3-H), 1.30 (s, 9 H, 10-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 157.4 (q, *J* = 37.4 Hz), 139.9, 135.9, 128.8, 127.6, 115.6 (q, *J* = 285.8 Hz), 83.7, 63.4, 55.5, 48.9, 27.6.

Minor diastereomer (selected signals)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, $^3J_{NH,2}$ = 7.8 Hz, 1 H, N-H), 5.02 (dd, $^3J_{2,NH}$ = 7.8 Hz, $^3J_{2,3}$ = 3.4 Hz, 1 H, 2-H), 3.71–3.76 (m, 2 H, 4-H), 3.55 (ddd, $^3J_{3,4a}$ = 9.6 Hz, $^3J_{3,4a}$ = 5.6 Hz, $^3J_{3,2}$ = 3.4 Hz, 1 H, 3-H), 3.45 (bs, 1 H, O-H), 1.45 (s, 9 H, 10-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4, 129.6, 129.0, 84.4, 62.0, 53.4, 49.7, 28.0.

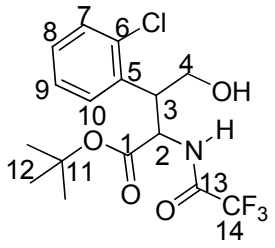
HRMS (CI):	Calculated	Found
$C_{16}H_{19}ClF_3NO_4$ $[M-C_4H_9]^+$:	324.0250	324.0274

***tert*-Butyl 3-(2-chlorophenyl)-4-hydroxy-2-(2,2,2-trifluoroacetamido) butanoate (3m)**

According to the general procedure **GP-3**, TFA-Gly-O*t*Bu (250 mg, 1.1 mmol), 2-chloro styrene oxide (340 mg, 2.2 mmol), hexamethyldisilazane (497 mg, 3.08 mmol), *n*-BuLi (1.72 ml, 2.75 mmol, 2.5 eq.) and $BF_3 \cdot OEt_2$ (172 mg, 1.2 mmol) were

allowed to react to give **3m** after flash chromatography (silica, hexanes/EtOAc 8:2) in 72% yield (302 mg, 0.79 mmol) as a colorless oil.

[TLC: Hex/EA 8:2, R_f = 0.33]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, $^3J_{NH,2}$ = 7.5 Hz, 1 H, N-H), 7.30–7.32 (m, 2 H, 7-H, 10-H), 7.23–7.26 (m, 2 H, 8-H, 9-H), 4.83 (dd, $^3J_{2,NH}$ = $^3J_{2,3}$ = 7.8 Hz, 1 H, 2-H), 3.98 (dd, $^3J_{4a,3}$ = 4.8 Hz, $^2J_{4a,4b}$ = 1.9 Hz, 1 H, 4a-H), 3.94 (dd, $^3J_{4b,3}$ = 4.8 Hz, $^2J_{4b,4a}$ = 1.9 Hz, 1 H, 4b-H), 3.19 (dt, $^3J_{3,2}$ = 7.6 Hz, $^3J_{3,4}$ = 4.8 Hz, 1 H, 3-H), 1.30 (s, 9 H, 12-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 157.4 (q, *J* = 37.4 Hz), 135.9, 133.8, 129.9, 129.7, 127.5, 126.2, 115.6 (q, *J* = 285.8 Hz), 83.7, 63.4, 55.5, 48.9, 27.6.

Minor diastereomer (selected signals)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, $^3J_{NH,2}$ = 7.8 Hz, 1 H, N-H), 5.02 (dd, $^3J_{2,NH}$ = 7.8 Hz, $^3J_{2,3}$ = 3.4 Hz, 1 H, 2-H), 3.71–3.76 (m, 2 H, 4-H), 3.55 (ddd, $^3J_{3,4a}$ = 9.6 Hz, $^3J_{3,4b}$ = 5.6 Hz, $^3J_{3,2}$ = 3.4 Hz, 1 H, 3-H), 3.45 (bs, 1 H, O-H), 1.45 (s, 9 H, 12-H).

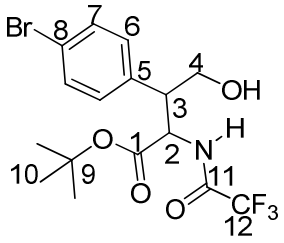
^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4, 129.6, 129.0, 84.4, 62.0, 53.4, 49.7, 28.0.

HRMS (CI):	Calculated	Found
$C_{16}H_{19}ClF_3NO_4$ $[M\text{-}C_4H_9]^+$:	324.0250	324.0274

***tert*-Butyl 3-(4-bromophenyl)-4-hydroxy-2-(2,2,2-trifluoroacet-amido) butanoate (3n)**

According to the general procedure **GP-3**, TFA-Gly-O*t*Bu (250 mg, 1.1 mmol), 4-bromo styrene oxide (438 mg, 2.2 mmol), hexamethyldisilazane (497 mg, 3.08 mmol, 2.8 equiv), *n*-BuLi (1.72 ml, 2.75 mmol, 2.5 eq.) and $BF_3 \cdot OEt_2$ (172 mg, 1.2 mmol) were allowed to react to give **3n** after flash chromatography (silica, hexanes/EtOAc 8:2) in 79% yield (371 mg, 0.87 mmol) as a colorless oil.

[TLC: Hex/EA 8:2, R_f = 0.33]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (d, $^{3}J_{NH,2}$ = 7.4 Hz, 1 H, N-H), 7.43–7.46 (m, 2 H, 7-H), 7.15-7.18 (m, 2 H, 6-H), 4.80 (dd, $^{3}J_{2,NH}$ = $^{3}J_{2,3}$ = 7.8 Hz, 1 H, 2-H), 3.94 (d, $^{3}J_{4,3}$ = 4.9 Hz, 2 H, 4-H), 3.17 (dt, $^{3}J_{3,2}$ = 7.6 Hz, $^{3}J_{3,4}$ = 4.8 Hz, 1 H, 3-H), 1.29 (s, 9 H, 10-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 157.3 (q, *J* = 37.3 Hz), 136.5, 131.7, 130.3, 121.8, 115.6 (q, *J* = 285.8 Hz), 83.7, 63.3, 55.5, 48.8, 27.6.

Minor diastereomer (selected signals)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.05 (d, $^{3}J_{NH,2}$ = 6.7 Hz, 1 H), 5.03 (dd, $^{3}J_{2,NH}$ = 7.8 Hz, $^{3}J_{2,3}$ = 3.4 Hz, 1 H, 2-H), 3.71–3.80 (m, 2 H, 4-H), 3.54 (ddd, $^{3}J_{3,4a}$ = 9.4 Hz, $^{3}J_{3,4b}$ = 5.8 Hz, $^{3}J_{3,2}$ = 3.4 Hz, 1 H, 3-H), 1.45 (s, 9 H, 10-H).

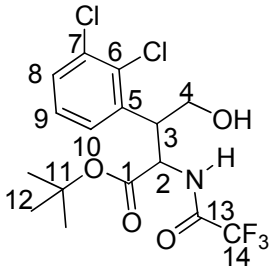
^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4, 134.4, 132.0, 129.9, 122.4, 84.4, 62.0, 53.4, 49.8, 28.0.

HRMS (CI):	Calculated	Found
$C_{16}H_{19}BrF_3NO_4$ $[M+1]^+$:	427.0429	427.0444

***tert*-Butyl 3-(3,4-dichlorophenyl)-4-hydroxy-2-(2,2,2-trifluoroacetamido) butanoate (3o)**

According to the general procedure **GP-3**, TFA-Gly-O*t*Bu (250 mg, 1.1 mmol), 3, 4-dicloro styrene oxide (416 mg, 2.2 mmol), hexamethyldisilazane (497 mg, 3.08 mmol, 2.8 equiv), n-BuLi (1.72 ml, 2.75 mmol, 2.5 eq.) and $BF_3 \cdot OEt_2$ (172 mg, 1.2 mmol) were allowed to react to give **3o** after flash chromatography (silica, hexanes/EtOAc 8:2) in 82% yield (376 mg, 0.90 mmol) as a colorless oil.

[TLC: Hex/EA 8:2, R_f = 0.33]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.43 (m, 3 H, 8-H, 10-H, N-H), 7.16 (dd, $^3J_{9,10}$ = 8.3 Hz, $^3J_{9,8}$ = 2.1 Hz, 1 H, 9-H), 4.82 (dd, $^3J_{2,3}$ = $^3J_{2,NH}$ = 7.9 Hz, 1 H, 2-H), 3.89–3.99 (m, 2 H, 4-H), 3.14 (dt, $^3J_{3,2}$ = 7.8 Hz, $^3J_{3,4}$ = 4.5 Hz, 1 H, 3-H), 2.48 (dd, $^3J_{OH,4a}$ = $^3J_{OH,4b}$ = 5.2 Hz, 1 H, O-H), 1.31 (s, 9 H, 12-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6, 157.4 (q, *J* = 37.7 Hz), 137.8, 132.7, 132.0, 130.6, 130.5, 128.1, 115.6 (q, *J* = 285.7 Hz), 84.1, 63.1, 55.2, 48.8, 27.6.

Minor diastereomer (selected signals)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, $^3J_{8,9}$ = 8.3 Hz, 1 H, 8-H), 7.20 (d, $^3J_{10,9}$ = 2.1 Hz, 1 H, 10-H), 7.03 (d, $^3J_{NH,2}$ = 7.2 Hz, 1 H, N-H), 6.92 (dd, $^3J_{9,8}$ = 8.3 Hz, $^3J_{9,10}$ = 2.1 Hz, 1 H, 9-H), 5.00 (dd, $^3J_{2,NH}$ = 7.7 Hz, $^3J_{2,3}$ = 3.3 Hz, 1 H, 2-H), 3.70–3.77 (m, 2 H, 4-H), 3.51 (ddd, $^3J_{3,4b}$ = 9.4 Hz, $^3J_{3,4a}$ = 6.3 Hz, $^3J_{3,2}$ = 3.2 Hz, 1 H, 3-H), 1.45 (s, 9 H, 12-H).

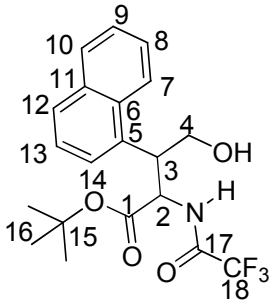
^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.2, 135.7, 133.0, 132.6, 130.8, 130.8, 127.2, 84.5, 61.8, 53.4, 49.5, 28.0.

HRMS (CI):	Calculated	Found
$C_{16}H_{18}Cl_2F_3NO_4$ $[M+1]^+$:	417.0535	417.0595

***tert*-Butyl 4-hydroxy-3-(naphthalen-1-yl)-2-(2,2,2-trifluoroacetamido) butanoate (3p)**

According to the general procedure **GP-3**, TFA-Gly-O*t*Bu (250 mg, 1.1 mmol), 1-naphthyl oxirane (374 mg, 2.2 mmol), hexamethyldisilazane (497 mg, 3.08 mmol), *n*-BuLi (1.72 ml, 2.75 mmol) and $BF_3 \cdot OEt_2$ (172 mg, 1.2 mmol) were allowed to react to give **3p** after flash chromatography (silica, hexanes/EtOAc 8:2) in 71% yield (310 mg, 0.78 mmol) as a colorless oil.

[TLC: Hex/EA 8:2, R_f = 0.34]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (dd, $^3J_{13,14}$ = $^3J_{13,12}$ = 7.8 Hz, 1 H, 13-H), 7.80 (d, $^3J_{14,13}$ = 8.0 Hz, 1 H, 14-H), 7.68 (d, $^3J_{NH,2}$ = 7.6 Hz, 1 H, N-H), 7.43–7.59 (m, 5 H, 7-H, 8-

H, 9-H, 10-H, 12-H), 4.99 (dd, $^3J_{2,NH} = {}^3J_{2,3}$ = 7.3 Hz, 1 H), 4.23 (ddd, $^3J_{3,4a} = {}^3J_{3,4b} = {}^3J_{3,2}$ = 5.4 Hz, 1 H, 3-H), 4.09–4.15 (m, 2 H, 4-H), 1.18 (s, 9 H, 16-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 157.2 (q, *J* = 37.4 Hz), 133.9, 133.5, 131.6, 129.2, 128.3, 126.6, 125.7, 125.4, 125.2, 122.3, 115.6 (q, *J* = 285.8 Hz), 83.3, 63.9, 56.2, 43.0, 27.4.

Minor diastereomer (selected signals)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, $^3J_{NH,2}$ = 8.5 Hz, 1 H, N-H), 5.16 (dd, $^3J_{2,NH}$ = 7.7 Hz, $^3J_{2,3}$ = 4.1 Hz, 1 H, 2-H), 4.54 (dt, $^3J_{3,4}$ = 9.5 Hz, $^3J_{3,2}$ = 4.5 Hz, 1 H, 3-H), 3.80–3.93 (m, 2 H, 4-H), 1.09 (s, 9 H, 16-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 129.1, 128.5, 126.5, 125.9, 125.0, 123.2, 84.2, 63.1, 53.9, 27.4.

HRMS (CI):	Calculated	Found
$C_{20}H_{22}F_3NO_4$ $[M]^+$:	397.1501	397.1507

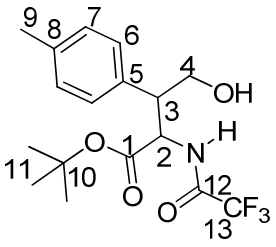
Elemental Analysis:

$C_{20}H_{22}F_3NO_4$	Calculated	C 60.45	H 5.58	N 3.52
(397.38):	Found:	C 60.11	H 5.91	N 3.65

***tert*-Butyl-4-hydroxy-3-*p*-tolyl-2-(2,2,2-trifluoroacetamido) butanoate (3q)**

According to the general procedure **GP-3**, TFA-Gly-O*t*Bu (250 mg, 1.1 mmol), *p*-methyl styrene oxide (295 mg, 2.2 mmol), hexamethyldisilazane (497 mg, 3.08 mmol), *n*-BuLi (1.72 ml, 2.75 mmol) and $BF_3 \cdot OEt_2$ (172 mg, 1.2 mmol) reacted to give **3q** after flash chromatography (silica, hexanes/EtOAc 8:2) in 70% yield (278 mg, 0.77 mmol) as a colorless oil.

[TLC: Hex/EA 8:2, R_f = 0.36]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (d, $^3J_{NH,2}$ = 6.4 Hz, 1 H, N-H), 7.14 (bs, 4 H, 6-H, 7-H), 4.82 (dd, $^3J_{2,NH} = {}^3J_{2,3}$ = 7.5 Hz, 1 H, 2-H), 3.98 (dd, $^3J_{4,3}$ = 5.5 Hz, $^2J_{4a,4b} = {}^2J_{4b,4a}$ = 1.8 Hz, 2 H, 4-H), 3.21 (dt, $^3J_{3,2}$ = 7.2 Hz, $^3J_{3,2}$ = 5.5 Hz, 1 H, 3-H), 2.33 (s, 3 H, 9-H), 1.31 (s, 9 H, 11-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 157.1 (q, *J* = 37.4 Hz), 137.6, 133.9, 129.4, 128.4, 115.6 (q, *J* = 285.8 Hz), 83.4, 63.8, 55.7, 49.1, 27.6, 21.0.

Minor diastereomer (selected signals)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, $^3J_{NH,2}$ = 6.7 Hz, 1 H, N-H), 7.12–7.17 (m, 4 H, 6-H, 7-H), 4.59 (dd, $^3J_{2,NH}$ = 7.5 Hz, $^3J_{2,3}$ = 2.8 Hz, 1 H, 2-H), 4.15–4.21 (m, 1 H, 3-H), 2.85-2.96 (m, 2 H, 4-H), 2.35 (s, 3 H, 9-H), 1.57 (s, 9 H, 11-H).

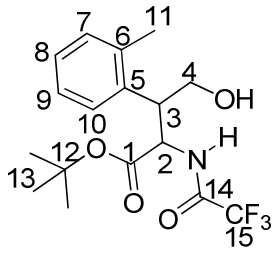
^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.3, 157.2 (q, *J* = 37.1 Hz), 136.7, 133.6, 129.5, 129.2, 115.7 (q, *J* = 285.7 Hz), 84.1, 73.7, 57.4, 39.7, 28.1, 20.9.

HRMS (CI):	Calculated	Found
$C_{17}H_{22}F_3NO_4$ $[M+1]^+$:	362.1534	362.1549

***tert*-Butyl-4-hydroxy-3-*o*-tolyl-2-(2,2,2-trifluoroacetamido) butanoate (3r)**

According to the general procedure, TFA-Gly-O*t*Bu (250 mg, 1.1 mmol), *o*-methyl styrene oxide (295 mg, 2.2 mmol), hexamethyldisilazane (497 mg, 3.08 mmol), *n*-BuLi (1.72 ml, 2.75 mmol) and $BF_3 \cdot OEt_2$ (172 mg, 1.2 mmol) reacted to give **3r** after flash chromatography (silica, hexanes/EtOAc 8:2) in 70% yield (282 mg, 0.77 mmol) as a colorless oil.

[TLC: Hex/EA 8:2, R_f = 0.35]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, $^3J_{NH,2}$ = 6.7 Hz, 1 H, N-H), 7.34–7.37 (m, 1 H, 7-H), 7.15–7.19 (m, 3 H, 8-H, 9-H, 10-H), 4.79 (dd, $^3J_{2,NH}$ = $^3J_{2,3}$ = 8.1 Hz, 1 H, 2-H), 3.93 (d, $^3J_{4,3}$ = 5.4 Hz, 2 H, 4-H), 3.55 (dt, $^3J_{3,2}$ = 8.3 Hz, $^3J_{3,4}$ = 5.4 Hz, 1 H, 3-H), 2.33 (s, 3 H, 11-H), 1.23 (s, 9 H, 13-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 157.2 (q, *J* = 37.4 Hz), 139.9, 135.6, 130.7, 129.8, 127.8, 126.2, 115.5 (q, *J* = 285.5 Hz), 83.1, 63.9, 55.7, 44.7, 27.4, 19.7.

Minor diastereomer (selected signals)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.99 (dd, $^3J_{2,NH}$ =7.7 Hz, $^3J_{2,3}$ = 4.4 Hz, 1 H, 2-H), 3.81–3.87 (m, 1 H, 3-H), 2.39, (s, 3 H, 11-H), 1.31 (s, 9 H, 13-H).

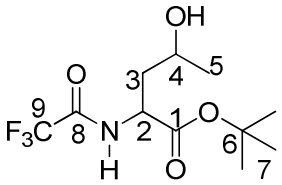
^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 136.7, 134.4, 131.1, 126.2, 84.2, 62.9, 53.8, 44.9, 27.6, 19.9.

HRMS (CI):	Calculated	Found
$C_{17}H_{22}F_3NO_4$ $[M+1]^+$:	362.1534	362.1566

***tert*-Butyl 4-hydroxy-2-(2,2,2-trifluoroacetamido) pentanoate (7a)**

According to the general procedure **GP-3**, TFA-Gly-O*t*Bu (250 mg, 1.1 mmol), propylene oxide (128 mg, 2.2 mmol), hexamethyldisilazane (497 mg, 3.08 mmol, 2.8 equiv), *n*-BuLi (1.72 ml, 2.75 mmol, 2.5 eq.) and $BF_3 \cdot OEt_2$ (172 mg, 1.2 mmol) were allowed to react to give **7a** after flash chromatography (silica, hexanes/EtOAc 8:2) in 92% yield (289 mg, 1.01 mmol) as a colorless oil.

[TLC: DCM/Hex 95:5, R_f = 0.28]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (bs, 1 H, N-H), 4.59 (dt, $^3J_{2,3}$ = 8.1 Hz, $^3J_{2,NH}$ = 3.6 Hz, 1 H, 2-H), 3.86–3.89 (m, 1 H, 4-H), 2.74 (d, $^3J_{OH,4}$ = 3.2 Hz, 1 H, O-H), 1.92 (ddd, $^2J_{3a,3b}$ = 14.2 Hz, $^3J_{3a,4}$ = 10.4 Hz, $^3J_{3a,2}$ = 3.7 Hz, 1 H, 3a-H), 1.82 (ddd, $^2J_{3b,3a}$ = 14.3 Hz, $^3J_{3b,4}$ = 8.5 Hz, $^3J_{3b,4}$ = 2.6 Hz, 1 H, 3b-H), 1.48 (s, 9 H, 7-H), 1.26 (d, $^3J_{5,4}$ = 6.2 Hz, 3 H, 5-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7, 157.4 (q, *J* = 37.2 Hz), 115.7 (q, *J* = 285.6 Hz), 83.2, 64.8, 51.5, 39.9, 27.8, 23.5.

Minor diastereomer (selected signals):

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (bs, 1 H ,N-H), 4.42 (ddd, $^3J_{2,3}$ = $^3J_{2,H}$ = 6.2 Hz, 1 H, 2-H), 3.92–3.99 (m, 1 H, 4-H), 2.03 (ddd, $^2J_{3a,3b}$ = 14.5 Hz, $^3J_{3a,2}$ = 5.7 Hz, $^3J_{3a,4}$ = 3.2 Hz, 1 H, 3a-H), 1.96 (s, 1 H, O-H), 1.89 (ddd, $^2J_{3b,3a}$ = 14.5 Hz, $^3J_{3b,2}$ = 9.3 Hz, $^3J_{3b,4}$ = 6.5 Hz, 1 H, 3b-H), 1.45 (s, 9 H, 7-H), 1.23 (d, $^3J_{5,4}$ = 6.2 Hz, 3 H, 5-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 156.8, (q, *J* = 37.3 Hz), 115.6 (q, *J* = 285.8 Hz), 83.1, 65.5, 52.1, 39.4, 27.8, 24.1.

HRMS (CI):	Calculated	Found
$C_{11}H_{18}F_3NO_4$ $[M+1]^+$:	286.1221	286.1273

Elemental Analysis:

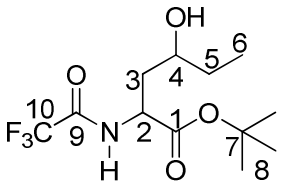
$C_{11}H_{18}F_3NO_4$	Calculated	C 46.31	H 6.36	N 4.91
(285.26):	Found	C 46.46	H 6.21	N 5.18

***tert*-Butyl 4-hydroxy-2-(2,2,2-trifluoroacetamido) hexanoate (7b)**

According to the general procedure **GP-3**, TFA-Gly-O*t*Bu (250 mg, 1.1 mmol), butene oxide (158 mg, 2.2 mmol), hexamethyldisilazane (497 mg, 3.08 mmol, 2.8

equiv), *n*-BuLi (1.72 ml, 2.75 mmol, 2.5 eq.) and $BF_3 \cdot OEt_2$ (172 mg, 1.2 mmol) were allowed to react to give **7b** after flash chromatography (silica, hexanes/EtOAc 8:2) in 88% yield (290 mg, 0.97 mmol) as a colorless oil.

[TLC: DCM/Hex 95:5, R_f = 0.30]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, $^3J_{NH,2}$ = 6.3 Hz, 1 H, N-H), 4.64–4.69 (m, 1 H, 2-H), 3.55–3.62 (m, 1 H, 4-H), 2.68 (bs, 1 H, O-H), 1.87–1.93 (m, 2 H, 3-H), 1.51–1.54 (m, 2 H, 5-H), 1.49 (s, 9 H, 8-H), 0.95 (t, $^3J_{6,5}$ = 7.5 Hz, 3 H, 6-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7, 157.4 (q, *J* = 37.2 Hz), 115.7 (q, *J* = 285.6 Hz), 83.2, 70.1, 52.4, 38.2, 30.4, 27.9, 9.8.

Minor diastereomer (selected signals):

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (bs, 1 H ,N-H), 4.42 (ddd, $^3J_{2,3}$ = $^3J_{2,H}$ = 6.1 Hz, 1 H, 2-H), 3.67–3.73 (m, 1 H, 4-H), 2.11 (ddd, $^2J_{3a,3b}$ = 14.5 Hz, $^3J_{3a,2}$ = 5.8 Hz, $^3J_{3a,4}$ = 2.7 Hz, 1 H, 3a-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 156.8, (q, *J* = 37.3 Hz), 115.6 (q, *J* = 285.8 Hz), 83.1, 70.6, 52.1, 37.1, 30.7, 27.8, 9.5.

HRMS (CI):	Calculated	Found
$C_{12}H_{20}F_3NO_4$ $[M]^+$:	299.1344	299.1329

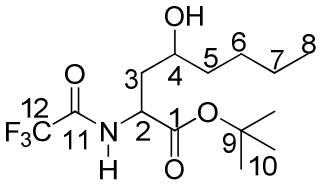
Elemental Analysis:

$C_{12}H_{20}F_3NO_4$ $[M]^+$:	Calculated	C 48.16	H 6.74	N 4.68
(299.13):	Found	C 48.08	H 6.47	N 4.64

***tert*-Butyl 4-hydroxy-2-(2,2,2-trifluoroacetamido) octanoate (7c)**

According to the general procedure **GP-3**, TFA-Gly-O*t*Bu (250 mg, 1.1 mmol), 1-hexene oxide (220 mg, 2.2 mmol), hexamethyldisilazane (497 mg, 3.08 mmol, 2.8 equiv), *n*-BuLi (1.72 ml, 2.75 mmol, 2.5 eq.) and $BF_3 \cdot OEt_2$ (172 mg, 1.2 mmol) were allowed to react to give **7c** after flash chromatography (silica, hexanes/EtOAc 8:2) in 86% yield (309 mg, 0.95 mmol) as a colorless oil.

[TLC: DCM/Hex 95:5, R_f = 0.29]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, $^{3}J_{NH,2}$ = 6.3 Hz, 1 H, N-H), 4.61–4.65 (m, 1 H, 2-H), 3.61–3.66 (m, 1 H, 4-H), 2.83 (bs, 1 H, O-H), 1.85–1.88 (m, 2 H, 3-H), 1.47 (s, 9 H, 8-H), 1.23–1.37 (m, 6 H, 5-H, 6-H, 7-H), 0.88 (t, $^{3}J_{6,5}$ = 6.9 Hz, 3 H, 8-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7, 157.4 (q, *J* = 37.2 Hz), 115.7 (q, *J* = 285.6 Hz), 83.1, 68.8, 51.5, 37.7, 37.2, 27.8, 27.6, 22.4, 13.9.

Minor diastereomer (selected signals):

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (bs, 1 H, N-H), 4.43 (ddd, $^{3}J_{2,3}$ = $^{3}J_{2,H}$ = 6.1 Hz, 1 H, 2-H), 3.69–3.71 (m, 1 H, 4-H), 2.07 (ddd, $^{2}J_{3a,3b}$ = 14.5 Hz, $^{3}J_{3a,2}$ = 5.8 Hz, $^{3}J_{3a,4}$ = 2.6 Hz, 1 H, 3a-H), 1.48 (s, 9 H, 10-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 156.8, (q, *J* = 37.3 Hz), 115.6 (q, *J* = 285.8 Hz), 83.0, 69.3, 52.2, 38.4, 37.7, 27.8, 27.4.

HRMS (CI):	Calculated	Found
$C_{14}H_{24}F_3NO_4$ $[M\text{-}C_4H_9]^+$:	270.0953	270.0942

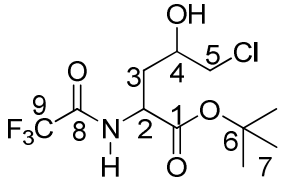
Elemental Analysis:

$C_{14}H_{24}F_3NO_4$	Calculated	C 51.37	H 7.39	N 4.28
(327.33):	Found	C 51.41	H 7.38	N 3.80

***tert*-Butyl 5-chloro-4-hydroxy-2-(2,2,2-trifluoroacetamido) pentanoate (7d)**

According to the general procedure **GP-3**, TFA-Gly-O*t*Bu (250 mg, 1.1 mmol), epichlorohydrin (204 mg, 2.2 mmol), hexamethyldisilazane (497 mg, 3.08 mmol, 2.8 equiv), *n*-BuLi (1.72 ml, 2.75 mmol, 2.5 eq.) and $BF_3 \cdot OEt_2$ (172 mg, 1.2 mmol) were allowed to react to give **7d** after flash chromatography (silica, hexanes/EtOAc 8:2) in 82% yield (288 mg, 0.90 mmol) as a colorless oil.

[TLC: DCM/Hex 95:5, R_f = 0.28]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, $^{3}J_{2,3}$ = 7.3 Hz, 1 H, N-H), 4.68 (dt, $^{3}J_{2,NH}$ = 7.7 Hz, $^{3}J_{2,3}$ = 3.8 Hz, 1 H, 2-H), 3.83–3.90 (m, 1 H, 4-H), 3.53 (dd, $^{2}J_{5a,5b}$ = 10.0 Hz, $^{3}J_{5a,4}$ = 4.0

Hz, 1 H, 5a-H), 3.49 (dd, $^{2}J_{5b,5a}$ = 10.0 Hz, $^{3}J_{5b,4}$ = 5.2 Hz, 1 H, 5b-H), 3.35 (d, $^{3}J_{OH,4}$ = 3.9 Hz, 1 H, O-H), 1.94–2.08 (m, 2 H, 3-H), 1.47 (s, 9 H, 7-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 157.4 (q, *J* = 37.2 Hz), 115.7 (q, *J* = 285.6 Hz), 83.7, 66.7, 51.1, 48.7, 35.5, 27.8.

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, $^{3}J_{2,3}$ = 6.0 Hz, 1 H, N-H), 4.50 (ddd, $^{3}J_{2,3}$ = $^{3}J_{2,H}$ = 5.9 Hz, 1 H, 2-H), 3.91–3.98 (m, 1 H, 4-H), 3.57 (dd, $^{2}J_{5a,5b}$ = 11.2 Hz, $^{3}J_{5a,4}$ = 4.1 Hz, 1 H, 5a-H), 3.49 (dd, $^{2}J_{5b,5a}$ = 11.2 Hz, $^{3}J_{5b,4}$ = 6.6 Hz, 1 H, 5b-H), 2.72 (d, $^{3}J_{OH,4}$ = 5.1 Hz, 1 H, O-H), 2.20 (ddd, $^{2}J_{3a,3b}$ = 14.5 Hz, $^{3}J_{3a,2}$ = 5.9 Hz, $^{3}J_{3a,4}$ = 2.9 Hz, 1 H, 3a-H), 1.98–2.06 (m, 1 H, 3b-H), 1.47 (s, 9 H, 7-H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4, 157.4 (q, *J* = 37.2 Hz), 115.7 (q, *J* = 285.6 Hz), 83.6, 68.4, 51.3, 49.3, 35.0, 27.7.

HRMS (CI):	Calculated	Found
$C_{11}H_{17}ClF_3NO_4$ $[M+1]^+$:	321.0769	321.0795

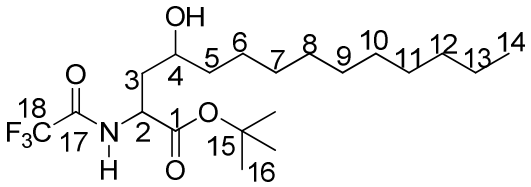
Elemental Analysis:

$C_{11}H_{17}ClF_3NO_4$	Calculated	C 41.32	H 5.36	N 4.38
(319.07):	Found	C 41.43	H 5.08	N 4.54

***tert*-Butyl 4-hydroxy-2-(2,2,2-trifluoroacetamido) tetradecanoate (7e)**

According to the general procedure **GP-3**, TFA-Gly-O*t*Bu (250 mg, 1.1 mmol), 1, 2 epoxy dodecane (405 mg, 2.2 mmol), hexamethyldisilazane (497 mg, 3.08 mmol, 2.8 equiv), *n*-BuLi (1.72 ml, 2.75 mmol, 2.5 eq.) and $BF_3 \cdot OEt_2$ (172 mg, 1.2 mmol) were allowed to react to give **7e** after flash chromatography (silica, hexanes/EtOAc 8:2) in 85% yield (385 mg, 0.94 mmol) as a colorless oil.

[TLC: DCM/Hex 95:5, R_f = 0.33]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, $^{3}J_{NH,2}$ = 7.5 Hz, 1 H, N-H), 4.62–4.67 (m, 1 H, 2-H), 3.60–3.68 (m, 1 H, 4-H), 2.63 (d, $^{3}J_{OH,4}$ = 4.0 Hz, 1 H, O-H), 1.85–1.88 (m, 2 H, 3-H), 1.48 (s, 9 H, 16-H), 1.25 (bs, 18 H, 5-H, 6-H, 7-H, 8-H, 9-H, 10-H, 11-H, 12-H, 13-H), 0.87 (t, $^{3}J_{14,13}$ = 6.9 Hz, 9 H, 14-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 157.4 (q, *J* = 37.2 Hz), 115.7 (q, *J* = 285.6 Hz), 83.1, 69.3, 60.4, 52.1, 37.9, 37.8, 31.8, 29.6, 29.5, 29.4, 29.3, 27.8, 25.3, 22.6, 21.0, 14.2, 14.1.

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (d, $^{3}J_{NH,2}$ = 5.7 Hz, 1 H, N-H), 4.45 (ddd, $^{3}J_{2,3a}$ = $^{3}J_{2,3b}$ = $^{3}J_{2,H}$ = 6.0 Hz, 1 H, 2-H), 3.71–3.79 (m, 1 H, 4-H), 2.09 (ddd, $^{2}J_{3a,3b}$ = 14.5 Hz, $^{3}J_{3a,2}$ = 5.4 Hz, $^{3}J_{3a,4}$ = 2.6 Hz, 1 H, 3a-H), 2.04 (bs, 3 H, 5-H, O-H), 1.85–1.93 (m, 1 H, 3b-H), 1.48 (s, 9 H, 16-H), 1.23–1.27 (m, 19 H, 6-H, 7-H, 8-H, 9-H, 10-H, 11-H, 12-H, 13-H, 14-H).

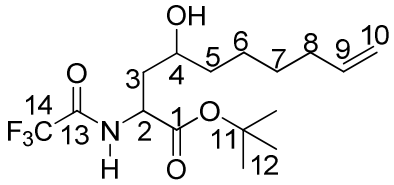
^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 157.6 (q, *J* = 37.2 Hz), 115.7 (q, *J* = 285.6 Hz), 83.1, 69.3, 60.4, 52.1, 37.9, 37.8, 31.8, 29.6, 29.5, 29.4, 29.3, 27.8, 25.3, 22.6, 21.0, 14.1, 14.2.

HRMS (CI):	Calculated	Found
$C_{20}H_{36}F_3NO_4[M]^+$:	411.2596	411.2593

***tert*-Butyl 4-hydroxy-2-(2,2,2-trifluoroacetamido) dec-9-enoate (7f)**

According to the general procedure **GP-3**, TFA-Gly-O*t*Bu (250 mg, 1.1 mmol), 1, 2-epoxy-7-octene (278 mg, 2.2 mmol), hexamethyldisilazane (497 mg, 3.08 mmol, 2.8 equiv), *n*-BuLi (1.72 ml, 2.75 mmol, 2.5 eq.) and $BF_3 \cdot OEt_2$ (172 mg, 1.2 mmol) were allowed to react to give **7f** after flash chromatography (silica, hexanes/EtOAc 8:2) in 87% yield (338 mg, 0.96 mmol) as a colorless oil.

[TLC: DCM/Hex 95:5, R_f = 0.30]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, $^{3}J_{NH,2}$ = 7.3 Hz, 1 H, N-H), 5.73–5.83 (m, 1 H, 9 H), 4.93–5.02 (m, 2 H, 10-H), 4.65 (dt, $^{3}J_{2,NH}$ = 7.7 Hz, $^{3}J_{2,3}$ = 4.3 Hz, 1 H, 2-H), 3.59–3.66 (m, 1 H, 4-H), 2.72 (bs, 1 H, O-H), 2.03–2.08 (m, 2 H, 3-H), 1.81–1.92 (m, 4 H, 5-H, 6-H), 1.48 (s, 9 H, 12-H), 1.25–1.42 (m, 4 H, 7-H, 8-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 136.6, 114.5, 157.4 (q, *J* = 37.2 Hz), 115.7 (q, *J* = 285.6 Hz), 83.3, 68.6, 51.4, 38.8, 37.3, 33.5, 28.6, 27.9, 24.9.

Minor diastereomer:

δ = **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.51 (bs, 1 H, N-H), 5.72–5.82 (m, 1 H, 9-H), 4.93–5.01 (m, 2 H, 10-H), 4.64 (ddd, $^{3}J_{2,NH} = {}^{3}J_{2,3a} = {}^{3}J_{2,3b}$ = 6.0 Hz, 1 H, 2-H), 3.75 (bs, 1 H, 4-H), 2.02–2.10 (m, 3 H, 3-H, O-H), 1.85–1.92 (m, 2 H, 5-H), 1.47 (s, 9 H, 12-H), 1.28–1.41 (m, 4 H, 7-H, 8-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 157.6 (q, *J* = 37.2 Hz), 138.5, 115.7 (q, *J* = 285.6 Hz), 114.5, 83.1, 69.2, 52.1, 37.8, 37.7, 33.5, 28.6, 27.8, 24.7.

HRMS (CI):	Calculated	Found
$C_{16}H_{26}F_3NO_4$ $[M+1]^+$:	354.1847	354.1879

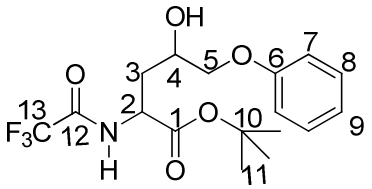
Elemental Analysis:

$C_{16}H_{26}F_3NO_4$	Calculated	C 54.38	H 7.42	N 3.96
(353.37):	Found:	C 54.40	H 7.10	N 4.42

***tert*-Butyl 4-hydroxy-5-phenoxy-2-(2,2,2-trifluoroacetamido) pentanoate (8a)**

According to the general procedure **GP-3**, TFA-Gly-O*t*Bu (250 mg, 1.1 mmol), phenyl glycidyl ether (330 mg, 2.2 mmol), hexamethyldisilazane (497 mg, 3.08 mmol, 2.8 equiv), *n*-BuLi (1.72 ml, 2.75 mmol, 2.5 eq.) and $BF_3 \cdot OEt_2$ (172 mg, 1.2 mmol) were allowed to react to give **8a** after flash chromatography (silica, hexanes/EtOAc 8:2) in 86% yield (357 mg, 0.95 mmol) as a colorless oil.

[TLC: DCM/Hex 95:5, R_f = 0.34]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, $^{3}J_{NH,2}$ = 7.8 Hz, 1 H, N-H), 7.23–7.29 (m, 2 H, 7-H), 6.95 (dd, $^{3}J_{9,8}$ = 7.4 Hz, 1 H, 9-H), 6.85–6.87 (m, 2 H, 8-H), 4.71 (dt, $^{3}J_{2,NH}$ = 7.5 Hz, $^{3}J_{2,3}$ = 4.4 Hz, 1 H, 2-H), 4.01–4.11 (m, 1 H, 4-H), 3.91 (dd, $^{2}J_{5a,5b}$ = 7.9 Hz, $^{3}J_{5a,4}$ = 3.1 Hz, 1 H, 5a-H), 3.88 (dd, $^{2}J_{5b,5a}$ = 7.8 Hz, $^{3}J_{5b,4}$ = 5.2 Hz, 1 H, 5b-H), 3.83 (d, $^{3}J_{OH,4}$ = 3.3 Hz, 1 H, O-H), 1.98–2.09 (m, 2 H, 3-H), 1.47 (s, 9 H, 11-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 158.1, 157.4 (q, *J* = 37.4 Hz), 129.5, 121.4, 115.7 (q, *J* = 285.6 Hz), 114.4, 83.4, 71.3, 67.4, 51.2, 34.5, 27.9.

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (bs, 1 H, N-H), 7.23–7.28 (m, 2 H, 7-H), 6.96 (dd, $^{3}J_{9,8}$ = 7.4 Hz, 1 H, 9-H), 6.85–6.87 (m, 2 H, 8-H), 4.51 (ddd, $^{3}J_{2,NH} = {}^{3}J_{2,3a} = {}^{3}J_{2,3b}$ = 5.9

Hz, 1 H, 2-H), 4.09–4.16 (m, 1 H, 4-H), 3.94 (dd, $^{2}J_{5a,5b}$ = 9.4 Hz, $^{3}J_{5a,4}$ = 3.5 Hz, 1 H, 5a-H), 3.88 (dd, $^{2}J_{5b,5a}$ = 9.3 Hz, $^{3}J_{5b,4}$ = 7.1 Hz, 1 H, 5b-H), 2.52 (d, $^{3}J_{OH,4}$ = 4.3 Hz, 1 H, O-H), 2.05–2.24 (m, 1 H, 3-H), 1.47 (s, 9 H, 11-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4, 158.1, 157.4 (q, *J* = 37.4 Hz), 129.6, 121.4, 115.7 (q, *J* = 285.6 Hz), 114.5, 83.4, 71.4, 67.4, 51.7, 33.8, 27.8.

HRMS (CI):	Calculated	Found
$C_{17}H_{22}F_3NO_5$ $[M]^+$:	377.1450	377.1447

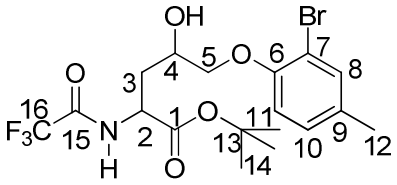
Elemental Analysis:

$C_{17}H_{22}F_3NO_5$	Calculated	C 54.11	H 5.88	N 3.71
(377.35):	Found	C 54.64	H 5.62	N 3.95

tert-Butyl 5-(2-bromo-4-methylphenoxy)-4-hydroxy-2-(2,2,2-trifluoroacetamido) pentanoate (8b)

According to the general procedure **GP-3**, TFA-Gly-O*t*Bu (250 mg, 1.1 mmol), 2-Br-4-methyl phenyl glycidyl ether (535 mg, 2.2 mmol), hexamethyldisilazane (497 mg, 3.08 mmol, 2.8 equiv), *n*-BuLi (1.72 ml, 2.75 mmol, 2.5 eq.) and $BF_3 \cdot OEt_2$ (172 mg, 1.2 mmol) were allowed to react to give **8b** after flash chromatography (silica, hexanes/EtOAc 8:2) in 72% yield (372 mg, 0.79 mmol) as a colorless oil.

[TLC: DCM/Hex 95:5, R_f = 0.34]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, $^{3}J_{NH,2}$ = 7.8 Hz, 1 H, N-H), 7.37 (s, 1 H, 8-H), 7.06 (d, $^{3}J_{11,10}$ = 8.0 Hz, 1 H, 11-H), 6.79 (d, $^{3}J_{10,11}$ = 8.2 Hz, 1 H, 10-H), 4.74 (dt, $^{3}J_{2,NH}$ = 7.3 Hz, $^{3}J_{2,3}$ = 3.9 Hz, 1 H, 2-H), 4.12–4.17 (m, 1 H, 4-H), 3.87–4.02 (m, 2 H, 5-H), 3.25 (d, $^{3}J_{OH,4}$ = 2.0 Hz, 1 H, O-H), 2.28 (s, 3 H, 12-H), 2.04–2.20 (m, 2 H, 3-H), 1.50 (s, 9 H, 14-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.1, 152.4, 157.4 (q, *J* = 37.4 Hz), 133.7, 132.7, 129.0, 115.7 (q, *J* = 285.6 Hz), 114.0, 112.2, 83.4, 73.2, 67.5, 51.2, 34.2, 27.9, 20.1.

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (bs, 1 H, N-H), 7.36 (s, 1 H, 8-H), 4.55 (ddd, $^{3}J_{2,NH}$ = $^{3}J_{2,3a}$ = $^{3}J_{2,3b}$ = 5.8 Hz, 1 H, 2-H), 1.50 (s, 9 H, 14-H).

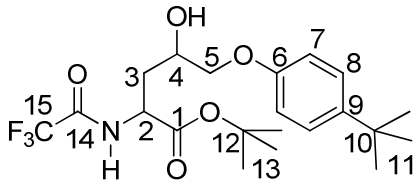
^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5, 157.4 (q, *J* = 37.4 Hz), 152.1, 133.7, 132.6, 129.6, 115.7 (q, *J* = 285.6 Hz), 113.0, 112.1, 73.0, 67.1, 51.5, 33.7, 27.8.

HRMS (CI):	Calculated	Found
$C_{18}H_{23}BrF_3NO_5[M+1]^+$:	471.0691	471.0677

tert-Butyl 5-(4-tert-butylphenoxy)-4-hydroxy-2-(2,2,2-trifluoroacetamido) pentanoate (8c)

According to the general procedure **GP-3**, TFA-Gly-O*t*Bu (250 mg, 1.1 mmol), 4-*tert*-butyl phenyl glycidyl ether (454 mg, 2.2 mmol), hexamethyldisilazane (497 mg, 3.08 mmol, 2.8 equiv), *n*-BuLi (1.72 ml, 2.75 mmol, 2.5 eq.) and $BF_3 \cdot OEt_2$ (172 mg, 1.2 mmol) were allowed to react to give **8c** after flash chromatography (silica, hexanes/EtOAc 8:2) in 79% yield (377 mg, 0.87 mmol) as a colorless oil.

[TLC: DCM/Hex 95:5, R_f = 0.35]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, $^3J_{NH,2}$ = 7.8 Hz, 1 H, N-H), 7.28–7.32 (m, 2 H, 7-H), 6.81–6.85 (m, 2 H, 8-H), 4.73 (dt, $^3J_{2,NH}$ = 7.4 Hz, $^3J_{2,3}$ = 4.1 Hz, 1 H, 2-H), 4.07–4.13 (m, 1 H, 4-H), 3.87–3.94 (m, 2 H, 5-H), 3.13 (d, $^3J_{OH,4}$ = 3.0 Hz, 1 H, O-H), 1.99–2.12 (m, 2 H, 3-H), 1.48 (s, 9 H, 13-H), 1.27 (s, 9 H, 11-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 157.4 (q, $J_{9,F}$ = 37.4 Hz), 155.8, 126.3, 115.7 (q, $J_{8,F}$ = 285.6 Hz), 113.9, 83.4, 71.4, 67.5, 51.2, 34.5, 34.0, 31.1, 27.9.

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, $^3J_{NH,2}$ = 5.3 Hz, 1 H, N-H), 7.28–7.32 (m, 2 H, 7-H), 6.80–6.84 (m, 2 H, 8-H), 4.53 (ddd, $^3J_{2,NH}$ = $^3J_{2,3a}$ = $^3J_{2,3b}$ = 5.9 Hz, 1 H, 2-H), 4.11–4.14 (m, 1 H, 4-H), 3.95 (dd, $^2J_{5a,5b}$ = 9.4 Hz, $^3J_{5a,4}$ = 3.5 Hz, 1 H, 5a-H), 3.86 (dd, $^2J_{5b,5a}$ = 9.4 Hz, $^3J_{5b,4}$ = 7.0 Hz, 1 H, 5b-H), 2.57 (bs, 1 H, O-H), 2.23 (dd, $^2J_{3a,3b}$ = 14.5 Hz, $^3J_{3a,2}$ = 5.7 Hz, $^3J_{3a,4}$ = 3.0 Hz, 1 H, 3a-H), 2.10 (dd, $^2J_{3b,3a}$ = 14.5 Hz, $^3J_{3b,4}$ = 9.8 Hz, $^3J_{3b,2}$ = 5.9 Hz, 1 H, 3b-H), 1.49 (s, 9 H, 13-H), 1.29 (s, 9 H, 11-H).

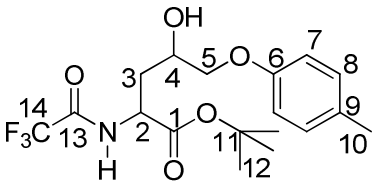
^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5, 157.4 (q, *J* = 37.4 Hz), 155.8, 144.2, 126.3, 115.7 (q, *J* = 285.6 Hz), 114.0, 83.3, 71.5, 67.4, 51.7, 34.0, 33.8, 31.4, 27.8.

HRMS (CI):	Calculated	Found
$C_{21}H_{30}F_3NO_5$ $[M]^+$:	433.2076	433.2075

tert-Butyl 4-hydroxy-5-(_p_-tolyloxy)-2-(2,2,2-trifluoroacetamido) pentanoate (8d)

According to the general procedure **GP-3**, TFA-Gly-O*t*Bu (250 mg, 1.1 mmol), 4-methyl phenyl glycidyl ether (361 mg, 2.2 mmol), hexamethyldisilazane (497 mg, 3.08 mmol, 2.8 equiv), *n*-BuLi (1.72 ml, 2.75 mmol, 2.5 eq.) and $BF_3 \cdot OEt_2$ (172 mg, 1.2 mmol) were allowed to react to give **8d** after flash chromatography (silica, hexanes/EtOAc 8:2) in 81% yield (349 mg, 0.89 mmol) as a colorless oil.

[TLC: DCM/Hex 95:5, R_f = 0.33]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, $^3J_{NH,2}$ = 7.5 Hz, 1 H, N-H), 7.08 (d, $^3J_{2,3}$ = 8.3 Hz, 2 H, 7-H), 6.77–6.80 (m, 2 H, 8-H), 4.73 (dt, $^3J_{2,NH}$ = 7.4 Hz, $^3J_{2,3}$ = 4.2 Hz, 1 H, 2-H), 4.06–4.16 (m, 1 H, 4-H), 3.81–3.97 (m, 2 H, 5-H), 2.29 (s, 3 H, 10-H), 2.03–2.13 (m, 2 H, 3-H), 1.49 (s, 9 H, 12-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 157.4 (q, *J* = 37.4 Hz), 156.0, 130.0, 129.0, 115.7 (q, *J* = 285.6 Hz), 114.3, 83.4, 71.6, 67.5, 51.2, 34.5, 27.9, 20.4.

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, $^3J_{NH,2}$ = 5.5 Hz, 1 H, N-H), 4.53 (ddd, $^3J_{2,NH}$ = $^3J_{2,3a}$ = $^3J_{2,3b}$ = 5.9 Hz, 1 H, 2-H), 2.28 (s, 3 H, 10-H), 2.03–2.13 (m, 2 H, 3-H), 1.49 (s, 9 H, 12-H).

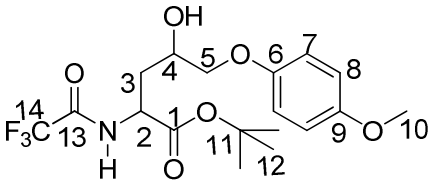
^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 155.8, 130.7, 83.3, 71.6, 67.4, 51.6, 33.8, 27.8.

HRMS (CI):	Calculated	Found
$C_{18}H_{24}F_3NO_5[M]^+$:	391.1607	391.1616

tert-Butyl 4-hydroxy-5-(4-methoxyphenoxy)-2-(2,2,2-trifluoroacetamido) pentanoate (8e)

According to the general procedure **GP-3**, TFA-Gly-O*t*Bu (250 mg, 1.1 mmol), 4-methoxy phenyl glycidyl ether (396 mg, 2.2 mmol), hexamethyldisilazane (497 mg, 3.08 mmol, 2.8 equiv), *n*-BuLi (1.72 ml, 2.75 mmol, 2.5 eq.) and $BF_3 \cdot OEt_2$ (172 mg, 1.2 mmol) were allowed to react to give **8e** after flash chromatography (silica, hexanes/EtOAc 8:2) in 85% yield (381 mg, 0.93 mmol) as a colorless oil.

[TLC: DCM/Hex 95:5, R_f = 0.32]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, $^{3}J_{NH,2}$ = 7.0 Hz, 1 H, N-H), 6.83–6.85 (m, 4 H, 7-H, 8-H), 4.73 (dt, $^{3}J_{2,NH}$ = 7.4 Hz, $^{3}J_{2,3}$ = 4.5 Hz, 1 H, 2-H), 4.06–4.14 (m, 1 H, 4-H), 3.79–3.93 (m, 2 H, 5-H), 3.77 (s, 3 H, 10-H), 3.11 (d, $^{3}J_{OH,4}$ = 3.3 Hz, 1 H, O-H), 2.03–2.13 (m, 2 H, 3-H), 1.49 (s, 9 H, 12-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 157.4 (q, *J* = 37.4 Hz), 152.2, 130.0, 129.0, 115.7 (q, *J* = 285.6 Hz), 115.4, 83.4, 72.6, 65.5, 55.8, 51.2, 36.5, 27.9.

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (s, 1 H, N-H), 4.53 (ddd, $^{3}J_{2,NH}$ = $^{3}J_{2,3a}$ = $^{3}J_{2,3b}$ = 5.9 Hz, 1 H, 2-H), 4.07–4.13 (m, 1 H, 4-H), 3.77 (s, 3 H, 10-H), 2.19–2.25 (m, 1 H, 3a-H), 1.49 (s, 9 H, 12-H).

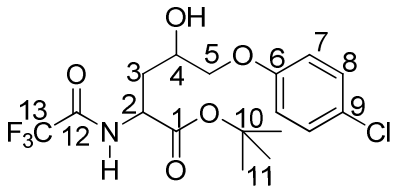
^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3, 152.1, 129.9, 129.0, 115.5, 83.4, 72.6, 65.5, 55.6, 51.2, 36.9, 27.8.

HRMS (CI):	Calculated	Found
$C_{18}H_{24}F_3NO_6[M]^+$:	407.1556	407.1550

***tert*-Butyl 5-(4-chlorophenoxy)-4-hydroxy-2-(2,2,2-trifluoroacetamido) pentanoate (8f)**

According to the general procedure **GP-3**, TFA-Gly-O*t*Bu (250 mg, 1.1 mmol), 4-methoxy phenyl glycidyl ether (407 mg, 2.2 mmol), hexamethyldisilazane (497 mg, 3.08 mmol, 2.8 equiv), *n*-BuLi (1.72 ml, 2.75 mmol, 2.5 eq.) and $BF_3 \cdot OEt_2$ (172 mg, 1.2 mmol) were allowed to react to give **8f** after flash chromatography (silica, hexanes/EtOAc 8:2) in 88% yield (399 mg, 0.97 mmol) as a colorless oil.

[TLC: DCM/Hex 95:5, R_f = 0.32]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, $^3J_{NH,2}$ = 7.0 Hz, 1 H ,N-H), 6.83-6.85 (m, 4 H, 7-H, 8-H), 4.73 (dt, $^3J_{2,NH}$ = 7.4 Hz, $^3J_{2,3}$ = 4.5 Hz, 1 H, 2-H), 4.06-4.14 (m, 1 H, 4-H), 3.79-3.93 (m, 2 H, 5-H), 3.11 (d, $^3J_{OH,4}$ = 3.3 Hz, 1 H, O-H), 2.03-2.13 (m, 2 H, 3-H), 1.49 (s, 9 H, 11-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 157.4 (q, *J* = 37.4 Hz), 152.2, 130.0, 129.0, 115.7 (q, *J* = 285.6 Hz), 115.4, 114.9, 83.4, 72.6, 65.5, 55.8, 51.2, 27.9.

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (s, 1 H, N-H), 4.53 (ddd, $^3J_{2,NH}$ = $^3J_{2,3a}$ = $^3J_{2,3b}$ = 5.9 Hz, 1 H, 2-H), 4.07-4.13 (m, 1 H, 4-H), 3.77 (s, 3 H, 10-H), 2.19-2.25 (m, 1 H, 3a-H), 1.49 (s, 9 H, 12-H).

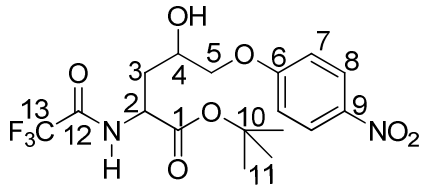
^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3, 152.1, 129.9, 129.0, 115.5, 114.7, 83.4, 72.6, 65.5, 55.6, 51.2, 27.8.

HRMS (CI):	Calculated	Found
$C_{17}H_{21}ClF_3NO_5$ $[M]^+$:	411.1060	411.1075

***tert*-Butyl 4-hydroxy-5-(4-nitrophenoxy)-2-(2,2,2-trifluoroacetamido) pentanoate (8g)**

According to the general procedure **GP-3**, TFA-Gly-O*t*Bu (250 mg, 1.1 mmol), 4-nitro phenyl glycidyl ether (429 mg, 2.2 mmol), hexamethyldisilazane (497 mg, 3.08 mmol, 2.8 equiv), *n*-BuLi (1.72 ml, 2.75 mmol, 2.5 eq.) and $BF_3 \cdot OEt_2$ (172 mg, 1.2 mmol) were allowed to react to give **8g** after flash chromatography (silica, hexanes/EtOAc 8:2) in 83% yield (386 mg, 0.91 mmol) as a colorless oil.

[TLC: DCM/Hex 95:5, R_f = 0.31]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, $^3J_{NH,2}$ = 7.5 Hz, 1 H, N-H), 7.08 (d, $^3J_{2,3}$ = 8.3 Hz, 2 H, 7-H), 6.77–6.80 (m, 2 H, 8-H), 4.73 (dt, $^3J_{2,NH}$ = 7.4 Hz, $^3J_{2,3}$ = 4.2 Hz, 1 H, 2-H), 4.06-4.16 (m, 1 H, 4-H), 3.81–3.97 (m, 2 H, 5-H), 2.03–2.13 (m, 2 H, 3-H), 1.49 (s, 9 H, 12-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 157.4 (q, *J* = 37.4 Hz), 156.0, 130.0, 129.0, 115.7 (q, *J* = 285.6 Hz), 114.3, 113.9, 83.4, 71.6, 67.5, 51.2, 34.5, 27.9.

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, $^{3}J_{NH,2}$ = 5.5 Hz, 1 H, N-H), 4.54 (ddd, $^{3}J_{2,NH}$ = $^{3}J_{2,3a}$ = $^{3}J_{2,3b}$ = 5.9 Hz, 1 H, 2-H), 2.03–2.13 (m, 2 H, 3-H), 1.49 (s, 9 H, 12-H).

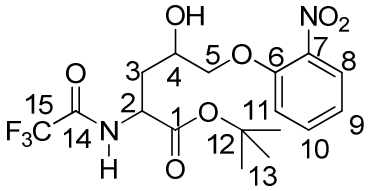
^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 155.8, 130.7, 83.3, 71.6, 67.4, 51.6, 33.8, 27.8.

HRMS (CI):	Calculated	Found
$C_{17}H_{21}F_3N_2O_7$ $[M]^+$:	423.1334	423.1416

***tert*-Butyl 4-hydroxy-5-(2-nitrophenoxy)-2-(2,2,2-trifluoroacetamido) pentanoate (8h)**

According to the general procedure **GP-3**, TFA-Gly-O*t*Bu (250 mg, 1.1 mmol), 2-nitro phenyl glycidyl ether (429 mg, 2.2 mmol), hexamethyldisilazane (497 mg, 3.08 mmol, 2.8 equiv), *n*-BuLi (1.72 ml, 2.75 mmol, 2.5 eq.) and $BF_3 \cdot OEt_2$ (172 mg, 1.2 mmol) were allowed to react to give **8h** after flash chromatography (silica, hexanes/EtOAc 8:2) in 84% yield (390 mg, 0.92 mmol) as a colorless oil.

[TLC: DCM/Hex 95:5, R_f = 0.31]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (dd, $^{3}J_{8,9}$ = 8.5 Hz, $^{3}J_{8,10}$ = 1.7 Hz, 1 H, 8-H), 7.81 (d, $^{3}J_{NH,2}$ = 7.5 Hz, 1 H, N-H), 7.52–7.57 (m, 1 H, 11-H), 7.01–7.06 (m, 2 H, 9-H, 10-H), 4.53 (ddd, $^{3}J_{2,NH}$ = $^{3}J_{2,3}$ = 5.7 Hz, 1 H, 2-H), 4.13–4.18 (m, 2 H, 5-H), 4.01–4.05 (m, 1 H, 4-H), 2.91 (d, $^{3}J_{OH,4}$ = 4.9 Hz, 1 H, O-H), 2.04–2.16 (m, 2 H, 3-H), 1.49 (s, 9 H, 13-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.1, 157.4 (q, *J* = 37.4 Hz), 151.8, 139.8, 134.4, 125.9, 121.3, 115.7 (q, *J* = 285.6 Hz), 115.1, 83.5, 73.2, 67.1, 51.1, 34.2, 27.8.

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (dd, $^{3}J_{8,9}$ = 8.1 Hz, $^{3}J_{8,10}$ = 1.7 Hz, 1 H, 8-H), 7.53–7.57 (m, 1 H, 11-H), 7.81 (d, $^{3}J_{NH,2}$ = 7.3 Hz, 1 H, N-H), 7.05–7.11 (m, 2 H, 9-H, 10-H), 4.72 (dt, $^{3}J_{2,NH}$ = 7.4 Hz, $^{3}J_{2,3}$ = 4.2 Hz, 1 H, 2-H), 4.11–4.18 (m, 2 H, 5-H), 4.00–4.05 (m, 1 H, 4-H), 3.52 (d, $^{3}J_{OH,4}$ = 2.5 Hz, 1 H, O-H), 2.30 (ddd, $^{2}J_{3a,3b}$ = 14.5 Hz, $^{3}J_{3a,2}$ = 5.6 Hz, $^{3}J_{3a,4}$ = 2.9 Hz, 1 H, 3a-H), 2.10 (ddd, $^{2}J_{3b,3a}$ = 14.6 Hz, $^{3}J_{3b,4}$ = 9.6 Hz, $^{3}J_{3b,2}$ = 5.4 Hz, 1 H, 3b-H), 1.51 (s, 9 H, 13-H).

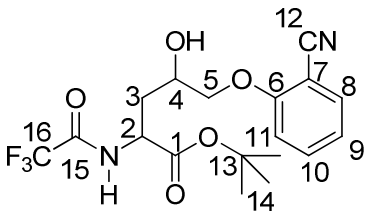
^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.3, 151.9, 134.5, 126.0, 121.3, 115.0, 83.6, 73.2, 66.7, 51.4, 33.6, 27.8.

HRMS (CI):	Calculated	Found
$C_{17}H_{21}F_3N_2O_7$ $[M]^+$:	423.1334	423.1413

***tert*-Butyl 5-(2-cyanophenoxy)-4-hydroxy-2-(2,2,2-trifluoroacetamido) pentanoate (8i)**

According to the general procedure **GP-3**, TFA-Gly-O*t*Bu (250 mg, 1.1 mmol), 2-cyano phenyl glycidyl ether (385 mg, 2.2 mmol), hexamethyldisilazane (497 mg, 3.08 mmol, 2.8 equiv), *n*-BuLi (1.72 ml, 2.75 mmol, 2.5 eq.) and $BF_3 \cdot OEt_2$ (172 mg, 1.2 mmol) were allowed to react to give **8i** after flash chromatography (silica, hexanes/EtOAc 8:2) in 85% yield (376 mg, 0.94 mmol) as a colorless oil.

[TLC: DCM/Hex 95:5, R_f = 0.31]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, $^3J_{NH,2}$ = 7.5 Hz, 1 H, N-H), 7.52–7.58 (m, 2 H, 8-H, 11-H), 7.05 (t, $^3J_{9,10}$ = 7.5 Hz, 1 H, 9-H), 6.94–6.99 (m, 1 H, 10-H), 4.71–4.76 (m, 1 H, 2-H), 4.18–4.24 (m, 2 H, 5-H), 3.89–4.09 (m, 1 H, 4-H), 3.34 (d, $^3J_{OH,4}$ = 4.0 Hz, 1 H, O-H), 2.08–2.13 (m, 2 H, 3-H), 1.50 (s, 9 H, 14-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0, 157.2 (q, *J* = 37.4 Hz), 134.4, 134.1, 122.2, 115.5 (q, *J* = 285.8 Hz), 114.8, 112.1, 102.6, 83.9, 72.7, 48.8, 40.3, 27.7.

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (d, $^3J_{NH,2}$ = 5.8 Hz, 1 H, N-H), 4.55 (dt, $^3J_{2,NH}$ = $^3J_{2,3}$ = 5.7 Hz, 1 H, 2-H) 4.21–4.18 (m, 2 H, 4-H), 2.66 (d, $^3J_{OH,4}$ = 4.5 Hz, 1 H, O-H), 2.32 (ddd, $^2J_{3a,3b}$ = 14.5 Hz, $^3J_{3a,2}$ = 5.7 Hz, $^3J_{3a,4}$ = 3.2 Hz, 1 H, 3a-H), 2.15–2.20 (m, 1 H, 3b-H), 1.50 (s, 9 H, 14-H),

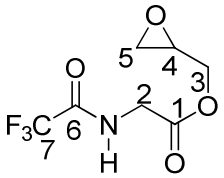
^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 122.2, 114.8, 112.1, 102.6, 83.6, 72.7, 48.8, 40.4, 27.8.

HRMS (CI):	Calculated	Found
$C_{18}H_{21}F_3N_2O_5$ $[M+1]^+$:	403.1436	403.1482

Oxiran-2-ylmethyl 2-(2,2,2-trifluoroacetamido) acetate (9a)

To a solution of glycidol (2.5 g, 34 mmol) in dichloromethane (150 ml) was added TFA-Gly-OH (6.65 g, 37 mmol) and DMAP (0.82 g, 6.7 mmol) at room temperature. The reaction mixture was converted to 0 °C and DCC (7.65 g, 37 mmol) was added. The mixture was allowed to warm to room temperature over night and filtered over celite. The solvent was removed under vacuum and the crude product was purified by flash column chromatography to give **9a** in 66% yield (5.1 g, 22 mmol) as a colorless solid with a melting point of 60 °C.

[TLC: Hex/EA 2:8, R_f = 0.58]



^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.98 (bs, 1 H, N-H), 4.54 (dd, $^2J_{3a,3b}$ = 12.2 Hz, $^3J_{3a,4}$ = 2.9 Hz, 1 H, 3a-H) , 4.18 (d, $^3J_{2,NH}$ = 5.3 Hz, 2 H, 2-H), 4.03 (dd, $^2J_{3b,3a}$ = 12.2 Hz, $^3J_{3b,4}$ = 6.5 Hz, 1 H, 3b-H), 3.20–3.24 (m, 1 H, 4-H), 2.87 (dd, $^2J_{5a,5b}$ = $^3J_{5a,5b}$ = 4.4 Hz, 1 H, 5a-H), 2.66 (dd, $^2J_{5b,5a}$ = 4.7 Hz, $^3J_{5b,4}$ = 2.6 Hz, 1 H, 5b-H).

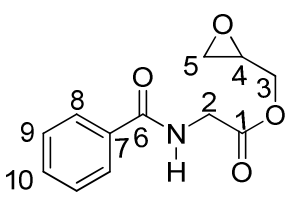
^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9, 157.2 (q, *J* = 37.4 Hz), 115.5 (q, *J* = 287.4 Hz), 66.3, 48.8, 44.5, 41.1.

HRMS (CI):	Calculated	Found
$C_7H_8F_3NO_4$ $[M+1]^+$:	228.0439	228.0447

Oxiran-2-ylmethyl 2-benzamidoacetate (9b)

To a solution of glycidol (2.5 g, 34 mmol) in dichloromethane (150 ml) was added Bz-Gly-OH (6.65 g, 37 mmol) and DMAP (0.82 g, 6.7 mmol) at room temperature. The reaction mixture was converted to 0 °C and DCC (7.65 g, 37 mmol) was added. The mixture was allowed to warm to room temperature over night and filtered over celite. The solvent was removed under vacuum and the crude product was purified by flash column chromatography to give **9b** in 75% yield (5.9 g, 25 mmol) as a colorless solid with a melting point of 63 °C.

[TLC: Hex/EA 2:8, R_f = 0.59]



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79–7.82 (m, 2 H, 8-H), 7.49–7.53 (m, 1 H, 10-H), 7.41–7.45 (m, 2 H, 9-H, 10-H), 6.71 (bs, 1 H, N-H), 4.51 (dd, $^{2}J_{3a,3b}$ = 12.2 Hz, $^{3}J_{3a,4}$ = 3.5 Hz, 1 H, 3a-H) , 4.28 (d, $^{3}J_{2,NH}$ = 4.5 Hz, 2 H, 2-H), 4.04 (dd, $^{2}J_{3b,3a}$ = 12.2 Hz, $^{3}J_{3b,4}$ = 6.3 Hz, 1 H, 3b-H), 3.21–3.25 (m, 1 H, 4-H), 2.87 (dd, $^{2}J_{5a,5b}$ = $^{3}J_{5a,5b}$ = 4.4 Hz, 1 H, 5a-H), 2.66 (dd, $^{2}J_{5b,5a}$ = 4.8 Hz, $^{3}J_{5b,4}$ = 2.6 Hz, 1 H, 5b-H).

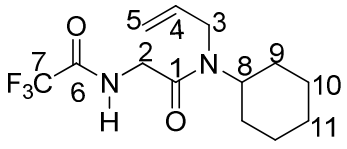
^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 167.4, 133.6, 131.8, 128.6, 127.0, 65.8, 49.0, 44.6, 41.6.

HRMS (CI):	Calculated	Found
$C_{12}H_{13}NO_4$ $[M+1]^+$:	235.0845	235.0828

***N*-(2-(Allyl(cyclohexyl)amino)-2-oxoethyl)-2,2,2-trifluoroacetamide (9c)**

To a solution of TFA-Gly-OH (1.4 g, 8.7 mmol) in dichloromethane (100 ml) was added TBTU (6.65 g, 37 mmol) and DIPEA (3.2 g, 9.7 mmol) at 0 °C. After 15 min allyl cyclohexyl amine (1.4 g, 10 mmol) was added. The mixture was allowed to stir for 10 min before cooling bath was removed and the reaction was stirred over night. The reaction was quenched with water, washed with 1N $KHSO_4$, satd. $NaHCO_3$, water, and with brine. The organic layer was dried over Na_2SO_4 and solvent was removed in vacuo. The crude product was purified by flash column chromatography to give 9c in 65% yield (1.6 g, 9.6 mmol) as yellow oil.

[TLC: Hex/EA 7:3, R_f = 0.50]



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (bs, 1 H, N-H), 5.71–5.83 (m, 1 H, 4-H), 5.12–5.26 (m, 2 H, 5-H), 4.07–4.16 (m, 2 H, 2-H), 3.95 (d, $^{3}J_{3a,4}$ = 5.7 Hz, 1 H, 3a-H), 3.82–3.84 (m, 2 H, 11-H, 3b-H), 1.25–1.88 (m, 10 H, 9-H, 10-H, 11-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4, 165.2, 157.2 (q, *J* = 37.4 Hz), 131.8, 115.5 (q, *J* = 287.4 Hz), 117.4, 61.7, 44.2, 29.7, 25.7, 25.2.

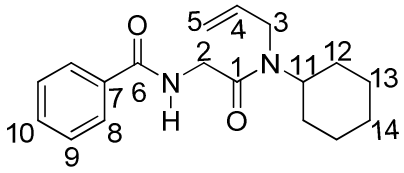
HRMS (CI):	Calculated	Found
$C_{13}H_{19}F_3N_2O_2$ $[M]^+$:	292.1399	292.1406

***N*-(2-(Allyl (cyclohexyl) amino)-2-oxoethyl) benzamide (9d)**

To a solution of Bz-Gly-OH (1.5 g, 8.4 mmol) in dichloromethane (100 ml) was added TBTU (6.65 g, 37 mmol) and DIPEA (3.2 g, 9.7 mmol) at 0 °C. After 15 min allyl cyclohexyl amine (1.4 g, 10 mmol) was added. The mixture was allowed to stir for 10

min before cooling bath was removed and the reaction was stirred over night. The reaction was quenched with water, washed with 1N $KHSO_4$, satd. $NaHCO_3$, water, and with brine. The organic layer was dried over Na_2SO_4 and solvent was removed in vacuo. The crude product was purified by flash column chromatography to give **9c** in 65% yield (3.6 g, 12 mmol) as yellow oil.

[TLC: Hex/EA 7:3, R_f = 0.50]



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80–7.85 (m, 3 H, 10-H, N-H), 7.41–7.52 (m, 2 H, 8-H, 9-H), 5.75–5.87 (m, 1 H, 4-H), 5.12–5.28 (m, 2 H, 5-H), 4.30 (d, $^2J_{2a,2b}$ = 3.8 Hz, 1 H, 2a-H), 4.22 (d, $^2J_{2b,2a}$ = 3.9 Hz, 1 H, 2b-H), 3.97 (d, $^3J_{3a,4}$ = 5.6 Hz, 1 H, 3a-H), 3.88–3.90 (m, 2 H, 11-H, 3b-H), 1.23–1.87 (m, 10 H, 12-H, 13-H, 14-H).

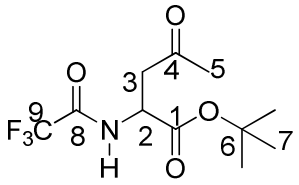
^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 164.2, 134.2, 132.1, 131.8, 127.5, 128.8, 117.4, 61.7, 44.2, 29.7, 25.7, 25.1.

HRMS (CI):	Calculated	Found
$C_{18}H_{24}N_2O_2$ $[M]^+$:	300.1838	300.1876

***tert*-Butyl 4-oxo-2-(2,2,2-trifluoroacetamido) pentanoate (11a)**

According to the general procedure for Dess-Martin oxidation **GP-4**, alcohol **7a** (377 mg, 1.32 mmol), Dess-Martin periodinane (721 mg, 1.7 mmol) reacted to give **7c** after flash chromatography (silica, hexanes/EtOAc 8:2) in 91% yield (340 mg, 1.20 mmol) as a colorless oil.

[TLC: Hex/EA 75:25, R_f = 0.53]



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (bs, 1 H ,N-H), 4.59 (td, $^3J_{2,NH}$ = 7.8 Hz, $^3J_{2,3}$ = 3.8 Hz, 1 H, 2-H), 3.22 (dd, $^2J_{3a,3b}$ = 18.6 Hz, $^3J_{3a,2}$ = 4.0 Hz, 1 H, 3a-H) , 3.97 (dd, $^2J_{3b,3a}$ = 18.6 Hz, $^3J_{3b,2}$ = 4.0 Hz, 1 H, 3b-H), 2.10 (s, 3 H, 5-H), 1.43 (s, 9 H, 7-H).

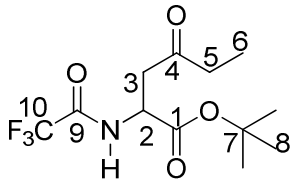
^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.1, 168.0, 156.8 (q, *J* = 37.4Hz), 115.5 (q, *J* = 285.6 Hz), 83.4, 49.0, 43.5, 29.7, 27.6.

HRMS (CI)	Calculated	Found
$C_{11}H_{16}F_3NO_4$ $[M+1]^+$	284.1065	284.1080

***tert*-Butyl 4-oxo-2-(2,2,2-trifluoroacetamido) hexanoate (11b)**

According to the general procedure for Dess-Martin oxidation **GP-4**, alcohol **7b** (395 mg, 1.32 mmol), Dess-Martin periodinane (721 mg, 1.7 mmol) reacted to give **11b** after flash chromatography (silica, hexanes/EtOAc 8:2) in 92% yield (363 mg, 1.22 mmol) as a colorless oil.

[TLC: Hex/EA 75:25, R_f = 0.53]



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.39 (bs, 1 H, N-H), 4.61 (td, $^3J_{2,N\text{-}H}$ = 8.0 Hz, $^3J_{2,3}$ = 4.0 Hz, 1 H, 2-H), 3.21 (dd, $^2J_{3b,3a}$ = 18.4 Hz, $^3J_{3b,2}$ = 4.0 Hz, 1 H, 3b-H), 2.93 (dd, $^2J_{3a,3b}$ = 18.4 Hz, $^3J_{3a,2}$ = 4.0 Hz ,1 H, 3a-H), 2.41–2.47 (m, 2 H, 5-H), 1.05 (t, $^3J_{6,5}$ = 7.3 Hz, 3 H, 6-H), 1.43 (s, 9 H, 8-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 209.1, 168.1, 156.8 (q, *J* = 37.4 Hz), 115.5 (q, *J* = 285.7 Hz), 83.3, 49.1, 42.5, 35.8, 27.6, 7.9.

HRMS (CI)	Calculated	Found
$C_{12}H_{18}F_3NO_4$ $[M+1]^+$	298.1221	298.1253

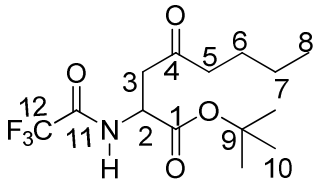
Elemental Analysis:

$C_{12}H_{18}F_3NO_4$	Theoret.	C 48.48	H 6.10	N 4.71
(297.27):	Found	C 48.48	H 6.03	N 4.96

***tert*-Butyl 4-oxo-2-(2,2,2-trifluoroacetamido) octanoate (11c)**

According to the general procedure for Dess-Martin oxidation **GP-4**, alcohol **7d** (432 mg, 1.32 mmol), Dess-Martin periodinane (721 mg, 1.7 mmol) reacted to give **11c** after flash chromatography (silica, hexanes/EtOAc 8:2) in 89% yield (382 mg, 1.17 mmol) as colorless oil.

[TLC: Hex/EA 75:25, R_f = 0.53]



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.38 (bs, 1 H, N-H), 4.61 (td, $^3J_{2,N\text{-}H}$ = 7.9 Hz, $^3J_{2,3}$ = 3.9 Hz, 1 H, 2-H), 3.22 (dd, $^2J_{3b,3a}$ = 18.4 Hz, $^3J_{3b,2}$ = 3.9 Hz ,1 H, 3b-H), 2.94 (dd, $^2J_{3a,3b}$ = 18.4 Hz, $^3J_{3a,2}$ = 3.9 Hz ,1 H, 3a-H), 2.41 (dt, $^2J_{5a,5b}$ = $^2J_{5b,5a}$ = 7.4 Hz, $^3J_{5,6}$ = 2.6 Hz, 2 H, 5-

H), 1.50–1.58 (m, 2 H, 6-H), 1.43 (s, 9 H, 10-H), 1.29 (sextet, $^{3}J_{7,8}$ = 7.3 Hz, $^{3}J_{7,6}$ = 14.9 Hz, 2 H, 7-H), 0.89 (t, $^{3}J_{8,7}$ = 7.3 Hz, 3 H, 8-H).

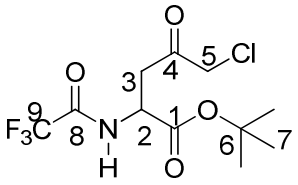
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 208.9, 168.1, 156.8 (q, *J* = 37.4 Hz), 115.6 (q, *J* = 285.6 Hz), 83.3, 49.1, 42.9, 42.3, 27.7, 25.6, 22.1, 13.8.

HRMS (CI):	Calculated	Found
$C_{14}H_{22}F_3NO_4$ $[M+1]^+$	325.1501	325.1512

***tert*-Butyl 5-chloro-4-oxo-2-(2,2,2-trifluoroacetamido) pentanoate (11d)**

According to the general procedure for Dess-Martin oxidation **GP-4**, alcohol **7d** (422 mg, 1.32 mmol), Dess-Martin periodinane (721 mg, 1.7 mmol) reacted to give **11d** after flash chromatography (silica, hexanes/EtOAc 8:2) in 90% yield (377 mg, 1.18 mmol) as colorless solid with a melting point of 51 °C.

[TLC: Hex/EA 75:25, R_f = 0.50]



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.29 (bs, 1 H, N-H), 4.69 (td, $^{3}J_{2,N\text{-}H}$ = 8.0 Hz, $^{3}J_{2,3}$ = 4.2 Hz, 1 H, 2-H), 3.24 (dd, $^{2}J_{3b,3a}$ = 18.6 Hz, $^{3}J_{3b,2}$ = 4.2 Hz, 1 H, 3b-H), 3.19 (dd, $^{2}J_{3a,3b}$ = 18.8 Hz, $^{3}J_{3a,2}$ = 4.4 Hz, 1 H, 3a-H), 2.17 (d, $^{2}J_{5a,5b}$ = $^{2}J_{5b,5a}$ = 2.8 Hz, 2 H, 5-H), 1.45 (s, 9 H, 7-H).

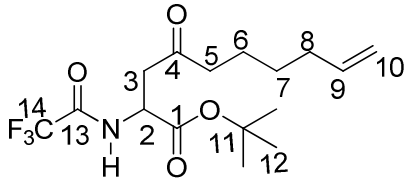
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 200.7, 167.7, 157.1 (q, *J* = 37.7 Hz), 118.3 (q, *J* = 285.8 Hz), 84.0, 49.0, 47.4, 40.5, 27.7.

HRMS (CI):	Calculated	Found
$C_{11}H_{15}ClF_3NO_4$ $[M]^+$	317.0642	317.0764

***tert*-Butyl 4-oxo-2-(2,2,2-trifluoroacetamido) dec-9-enoate (11e)**

According to the general procedure for Dess-Martin oxidation **GP-4**, alcohol **7f** (466 mg, 1.32 mmol), Dess-Martin periodinane (721 mg, 1.7 mmol) reacted to give **11e** after flash chromatography (silica, hexanes/EtOAc 8:2) in 88% yield (408 mg, 1.16 mmol) as colorless solid with a melting point of 54 °C.

[TLC: Hex/EA 75:25, R_f = 0.50]



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.38 (bs, 1 H, N-H), 4.61 (td, $^{3}J_{2,NH}$ = 7.90 Hz, $^{3}J_{2,3}$ = 3.9 Hz, 1 H, 2-H), 3.22 (dd, $^{2}J_{3b,3a}$ = 18.4 Hz, $^{3}J_{3b,2}$ = 3.9 Hz, 1 H, 3b-H), 2.94 (dd, $^{2}J_{3a,3b}$ = 18.4 Hz, $^{3}J_{3a,2}$ = 3.9 Hz ,1 H, 3a-H), 2.03 (dt, $^{2}J_{5a,5b}$ = $^{2}J_{5b,5a}$ = 7.42 Hz, $^{3}J_{5,6}$ = 2.6 Hz, 2 H, 5-H), 1.51–1.63 (m, 2 H, 6-H), 1.32–1.40 (m, 2 H, 7-H).

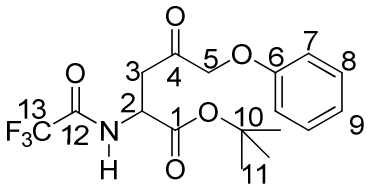
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 208.9, 168.1, 156.8 (q, *J* = 37.4 Hz), 115.6 (q, *J* = 285.6 Hz), 83.3, 49.1, 42.9, 42.3, 27.7, 25.6, 22.1, 13.8.

HRMS (CI):	Calculated	Found
$C_{16}H_{24}F_3NO_4$ $[M]^+$	352.1691	352.1712

***tert*-Butyl 4-oxo-5-phenoxy-2-(2,2,2-trifluoroacetamido) pentanoate (11f)**

According to the general procedure for Dess-Martin oxidation **GP-4**, alcohol **8a** (498 mg, 1.32 mmol), Dess-Martin periodinane (721 mg, 1.7 mmol) reacted to give **11f** after flash chromatography (silica, hexanes/EtOAc 8:2) in 93% yield (461 mg, 1.23 mmol) as colorless solid with a melting point of 58 °C.

[TLC: Hex/EA 7:3, R_f = 0.55]



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.29–7.33 (m, 2 H, 8-H), 7.02 (dd, $^{3}J_{9,8a}$ = $^{3}J_{9,8b}$ = 7.6 Hz, 1 H, 9-H), 6.86–6.88 (m, 2 H, 7-H), 4.73 (td, $^{3}J_{2,N-H}$ = 7.6 Hz, $^{3}J_{2,3}$ = 4.3 Hz, 1 H, 2-H), 4.57 (d, $^{2}J_{5a,5b}$ = $^{2}J_{5b,5a}$ = 1.2 Hz, 2 H, 5-H), 3.21 (dd, $^{2}J_{3a,3b}$ = 18.8 Hz, $^{3}J_{3a,2}$ = 4.4 Hz 1 H, 3a-H), 3.42 (dd, $^{2}J_{3b,3a}$ = 18.8 Hz, $^{3}J_{3b,2}$ = 4.4 Hz, 1 H, 3b-H), 1.45 (s, 9 H, 11-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 205.9, 168.0, 157.3 157.2 (q, *J* = 37.4 Hz), 129.7, 122.1, 115.5 (q, *J* = 289.0 Hz), 114.4, 83.7, 72.5, 48.7, 40.4, 27.7.

HRMS (CI)	Calculated	Found
$C_{17}H_{20}F_3NO_5[M]^+$	375.1294	375.1289

Elemental Analysis:

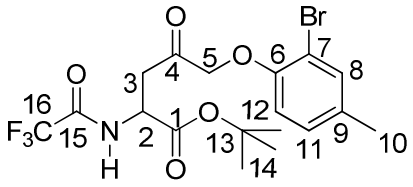
$C_{17}H_{20}F_3NO_5$	Theoret.	C 54.40	H 5.37	N 3.73
(375.34):	Found	C 54.73	H 5.75	N 3.79

***tert*-Butyl 5-(2-bromo-4-methylphenoxy)-4-oxo-2-(2,2,2-trifluoroacetamido) pentanoate (11g)**

According to the general procedure for Dess-Martin oxidation **GP-4**, alcohol **8b** (621 mg, 1.32 mmol), Dess-Martin periodinane (721 mg, 1.7 mmol) reacted to give

11g after flash chromatography (silica, hexanes/EtOAc 8:2) in 91% yield (563 mg, 1.20 mmol) as colorless solid with a melting point of 95 °C.

[TLC: Hex/EA 7:3, R_f = 0.55]



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, $^3J_{12,11}$ = 1.5 Hz, 1 H, 12-H), 7.28 (d, $^3J_{NH,2}$ = 7.3 Hz, 1 H, N-H), 7.04 (dd, $^3J_{11,12}$ = 1.5 Hz, $^3J_{11,8}$ = 8.3 Hz, 1 H, 11-H), 7.40 (d, $^3J_{8,11}$ = 8.0 Hz, 1 H, 8-H), 4.77 (td, $^3J_{2,N\text{-}H}$ = 8.1 Hz, $^3J_{2,3}$ = 4.2 Hz, 1 H, 2-H), 4.55 (d, $^2J_{5a,5b}$ = $^2J_{5b,5a}$ = 1.8 Hz, 2 H, 5-H), 3.53 (dd, $^2J_{3a,3b}$ = 19.0 Hz, $^3J_{3a,2}$ = 4.4 Hz, 1 H, 3a-H), 3.32 (dd, $^2J_{3b,3a}$ = 19.0 Hz, $^3J_{3b,2}$ = 4.1 Hz, 1 H, 3b-H), 2.28 (s, 3 H, 10-H), 1.45 (s, 9 H, 14-H).

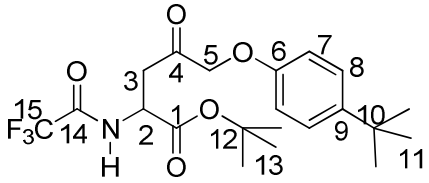
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 205.7, 168.0, 157.2 (q, *J* = 37.4 Hz), 151.7, 134.2, 133.2, 129.0, 113.2, 111.9, 115.5 (q, *J* = 289.0 Hz), 83.7, 73.5, 48.7, 40.7, 27.7, 20.2.

HRMS (CI):	Calculated	Found
$C_{18}H_{21}BrF_3NO_5[M]^+$	467.0555	467.0586

***tert*-Butyl 5-(4-tert-butylphenoxy)-4-oxo-2-(2,2,2-trifluoroacetamido) pentanoate (11h)**

According to the general procedure for Dess-Martin oxidation **GP-4**, alcohol **8c** (522 mg, 1.32 mmol), Dess-Martin periodinane (721 mg, 1.7 mmol) reacted to give **11h** after flash chromatography (silica, hexanes/EtOAc 8:2) in 90% yield (513 mg, 1.20 mmol) as colorless solid with a melting point of 60 °C.

[TLC: Hex/EA 7:3, R_f = 0.56]



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.29–7.33 (m, 3 H, 7-H, N-H), 6.68–6.90 (m, 2 H, 8-H), 4.72 (td, $^3J_{2,N\text{-}H}$ = 8.0 Hz, $^3J_{2,3}$ = 4.2 Hz, 1 H, 2-H), 4.54 (s, 2 H, 5-H), 3.41 (dd, $^2J_{3a,3b}$ = 18.9 Hz, $^3J_{3a,2}$ = 4.2 Hz 1 H, 3a-H), 3.21 (dd, $^2J_{3b,3a}$ = 18.9 Hz, $^3J_{3b,2}$ = 4.2 Hz ,1 H, 3b-H), 1.44 (s, 9 H, 11-H), 1.29 (s, 9 H, 13-H).

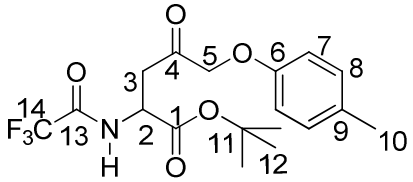
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 206.2, 168.0, 157.2 (q, *J* = 37.6 Hz), 155.2, 144.8, 126.6, 115.5 (q, *J* = 285.8 Hz), 113.8, 83.7, 72.6, 48.7, 40.3, 34.1, 31.4, 27.7.

HRMS (CI):	Calculated	Found
$C_{21}H_{28}F_3NO_5[M]^+$	431.1920	431.1935

***tert*-Butyl 4-oxo-5-(*p*-tolyloxy)-2-(2,2,2-trifluoroacetamido) pentanoate (11i)**

According to the general procedure for Dess-Martin oxidation **GP-4**, alcohol **8d** (517 mg, 1.32 mmol), Dess-Martin periodinane (721 mg, 1.7 mmol) reacted to give **11i** after flash chromatography (silica, hexanes/EtOAc 8:2) in 88% yield (452 mg, 1.16 mmol) as colorless solid with a melting point of 95 °C.

[TLC: Hex/EA 7:3, R_f = 0.55]



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.31 (d, $^3J_{NH,2}$ = 7.1 Hz, 1 H, N-H), 7.09 (d, $^3J_{7,8}$ = 7.1 Hz, 2 H, 7-H), 6.72–6.80 (m, 2 H, 8-H), 4.72 (td, $^3J_{2,NH}$ = 8.3 Hz, $^3J_{2,3}$ = 4.3 Hz, 1 H, 2-H), 4.53 (s, 2 H, 5-H), 3.40 (dd, $^2J_{3a,3b}$ = 18.8 Hz, $^3J_{3a,2}$ = 4.2 Hz, 1 H, 3a-H), 3.21 (dd, $^2J_{3b,3a}$ = 18.8 Hz, $^3J_{3b,2}$ = 4.2 Hz, 1 H, 3b-H), 2.29 (s, 9 H, 10-H), 1.45 (s, 9 H, 12-H).

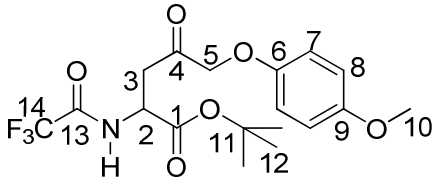
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 206.2, 168.0, 157.2 (q, *J* = 37.6 Hz), 155.3, 131.4, 130.2, 115.5 (q, *J* = 285.8 Hz), 114.2, 83.7, 72.7, 48.7, 40.3, 27.7, 20.4.

HRMS (CI):	Calculated	Found
$C_{18}H_{22}F_3NO_5[M]^+$	389.1450	389.1423

***tert*-Butyl 5-(4-methoxyphenoxy)-4-oxo-2-(2,2,2-trifluoroacetamido) pentanoate (11 j)**

According to the general procedure for Dess-Martin oxidation **GP-4**, alcohol **8e** (538 mg, 1.32 mmol), Dess-Martin periodinane (721 mg, 1.7 mmol) reacted to give **11j** after flash chromatography (silica, hexanes/EtOAc 8:2) in 85% yield (455 mg, 1.12 mmol) as colorless solid with a melting point of 92 °C.

[TLC: Hex/EA 7:3, R_f = 0.50]



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, $^3J_{N\text{-}H,2}$ = 7.4 Hz, 1 H, N-H), 6.79–6.84 (m, 4 H, 7-H, 8-H), 4.72 (td, $^3J_{2,N\text{-}H}$ = 8.0 Hz, $^3J_{2,3}$ = 4.2 Hz, 1 H, 2-H), 4.51 (s, 2 H, 5-H), 3.76 (s, 3

H, 10-H), 3.39 (dd, $^{2}J_{3a,3b}$ = 18.8 Hz, $^{3}J_{3a,2}$ = 4.2 Hz, 1 H, 3a-H), 3.21 (dd, $^{2}J_{3b,3a}$ = 18.8 Hz, $^{3}J_{3b,2}$ = 4.2 Hz, 1 H, 3b-H), 1.44 (s, 9 H, 12-H).

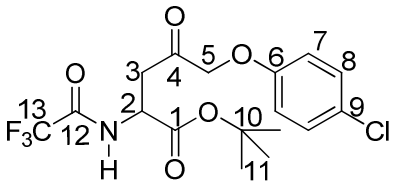
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 206.2, 168.0, 157.2 (q, *J* = 37.4 Hz), 154.7, 151.5, 115.5 (q, *J* = 285.8 Hz), 115.4, 114.8, 83.7, 73.2, 55.6, 48.7, 40.3, 27.7.

HRMS (CI):	Calculated	Found
$C_{18}H_{22}F_3NO_6[M]^+$	405.1399	405.1406

***tert*-Butyl 5-(4-chlorophenoxy)-4-oxo-2-(2,2,2-trifluoroacetamido) pentanoate (11k)**

According to the general procedure for Dess-Martin oxidation **GP-4**, alcohol **8f** (544 mg, 1.32 mmol), Dess-Martin periodinane (721 mg, 1.7 mmol) reacted to give **11k** after flash chromatography (silica, hexanes/EtOAc 8:2) in 85% yield (444 mg, 1.08 mmol) as colorless oil.

[TLC: Hex/EA 7:3, R_f = 0.51]



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.32 (d, $^{3}J_{NH,2}$ = 7.3 Hz, 1 H, N-H), 7.22–7.25 (m, 2 H, 7-H), 6.77–6.81 (m, 2 H, 8-H), 4.71 (td, $^{3}J_{2,NH}$ = 8.0 Hz, $^{3}J_{2,3}$ = 4.2 Hz, 1 H, 2-H), 4.53 (d, $^{2}J_{5a,5b}$ = $^{2}J_{5b,5a}$ = 1.3 Hz, 2 H, 5-H), 3.36 (dd, $^{2}J_{3a,3b}$ = 18.8 Hz, $^{3}J_{3a,2}$ = 4.2 Hz, 1 H, 3a-H), 3.19 (dd, $^{2}J_{3b,3a}$ = 18.8 Hz, $^{3}J_{3b,2}$ = 4.2 Hz, 1 H, 3b-H), 1.43 (s, 9 H, 12-H).

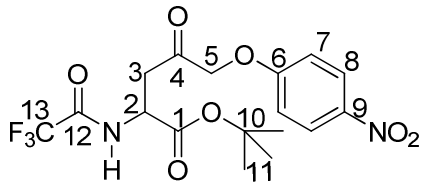
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 205.1, 167.9, 157.2 (q, *J* = 37.4 Hz), 155.9, 129.6, 127.0, 115.7, 115.5 (q, *J* = 285.8 Hz), 114.0, 83.8, 72.6, 48.7, 40.3, 27.7.

HRMS (CI):	Calculated	Found
$C_{17}H_{19}ClF_3NO_5[M]^+$	409.0904	409.0883

***tert*-Butyl 5-(4-nitrophenoxy)-4-oxo-2-(2,2,2-trifluoroacetamido) pentanoate (11l)**

According to the general procedure for Dess-Martin oxidation **GP-4**, alcohol **8g** (558 mg, 1.32 mmol), Dess-Martin periodinane (721 mg, 1.7 mmol) reacted to give **11l** after flash chromatography (silica, hexanes/EtOAc 8:2) in 84% yield (466 mg, 1.11 mmol) as white solid with a melting point of 90 °C.

[TLC: Hex/EA 7:3, R_f = 0.49]



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.21–8.27 (m, 2 H, 8-H), 7.53–7.57 (m, 1 H, 9-H), 7.35 (td, $^{3}J_{NH,2}$ = 6.5 Hz, 1 H, N-H), 6.95–6.99 (m, 2 H, 7-H), 4.75 (td, $^{3}J_{2,NH}$ = 7.3 Hz, $^{3}J_{2,3}$ = 4.5 Hz, 1 H, 2-H), 4.72 (d, $^{2}J_{5a,5b}$ = $^{2}J_{5b,5a}$ = 1.7 Hz, 2 H, 5-H), 3.37 (dd, $^{2}J_{3a,3b}$ = 18.5 Hz, $^{3}J_{3a,2}$ = 4.3 Hz, 1 H, 3a-H), 3.32 (dd, $^{2}J_{3b,3a}$ = 18.5 Hz, $^{3}J_{3b,2}$ = 4.4 Hz, 1 H, 3b-H), 1.47 (s, 9 H, 12-H).

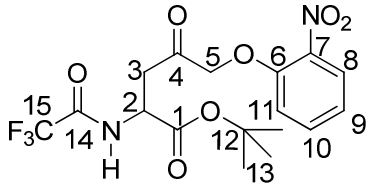
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 205.1, 167.9, 157.2 (q, *J* = 37.4 Hz), 155.9, 129.6, 127.0, 115.7, 115.5 (q, *J* = 285.8 Hz), 114.0, 83.8, 72.6, 48.7, 40.3, 27.7.

HRMS (CI):	Calculated	Found
$C_{17}H_{19}F_3N_2O_7[M]^+$	420.1144	420.1171

***tert*-Butyl 5-(2-nitrophenoxy)-4-oxo-2-(2,2,2-trifluoroacetamido) pentanoate (11m)**

According to the general procedure for Dess-Martin oxidation **GP-4**, alcohol **8h** (558 mg, 1.32 mmol), Dess-Martin periodinane (721 mg, 1.7 mmol) reacted to give **11k** after flash chromatography (silica, hexanes/EtOAc 8:2) in 87% yield (483 mg, 1.15 mmol) as white solid with a melting point of 91 °C.

[TLC: Hex/EA 8:2, R_f = 0.48]



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.93 (dd, $^{3}J_{8,9}$ = 8.1 Hz, $^{3}J_{8,10}$ = 1.7 Hz, 1 H, 8-H), 7.53–7.57 (m, 1 H, 9-H), 7.28 (bs, 1 H, N-H), 7.12–7.16 (m, 1 H, 10-H), 6.96 (dd, $^{3}J_{11,10}$ = 8.5 Hz, $^{3}J_{11,9}$ = 1.0 Hz, 1 H, 11-H), 4.79 (td, $^{3}J_{2,NH}$ = 7.8 Hz, $^{3}J_{2,3}$ = 4.3 Hz, 1 H, 2-H), 4.72 (d, $^{2}J_{5a,5b}$ = $^{2}J_{5b,5a}$ = 5.0 Hz, 2 H, 5-H), 3.50 (dd, $^{2}J_{3a,3b}$ = 18.8 Hz, $^{3}J_{3a,2}$ = 4.5 Hz, 1 H, 3a-H), 3.32 (dd, $^{2}J_{3b,3a}$ = 18.8 Hz, $^{3}J_{3b,2}$ = 4.2 Hz, 1 H, 3b-H), 1.46 (s, 9 H, 12-H).

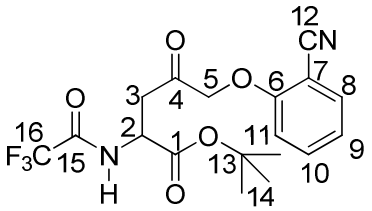
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 204.2, 168.0, 157.2 (q, *J* = 37.4 Hz), 150.7, 134.4, 126.2, 122.0, 115.5 (q, *J* = 285.8 Hz), 114.6, 83.9, 73.3, 48.8, 40.6, 27.7.

HRMS (CI):	Calculated	Found
$C_{17}H_{19}F_3N_2O_7[M]^+$	420.1144	420.1156

***tert*-Butyl 5-(2-cyanophenoxy)-4-oxo-2-(2,2,2-trifluoroacetamido) pentanoate (11n)**

According to the general procedure for Dess-Martin oxidation **GP-4**, alcohol **8h** (531 mg, 1.32 mmol), Dess-Martin periodinane (721 mg, 1.7 mmol) reacted to give **11k** after flash chromatography (silica, hexanes/EtOAc 8:2) in 84% yield (444 mg, 1.11 mmol) as white solid with a melting point of 72 °C.

[TLC: Hex/EA 7:3, R_f = 0.49]



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.51–7.64 (m, 2 H, 8-H, 9-H), 7.28 (d, $^3J_{NH,2}$ = 6.8 Hz, 1 H, N-H), 7.10 (dd, $^3J_{10,11}$ = $^3J_{10,9}$ = 7.2 Hz, 1 H, 10-H), 6.82 (d, $^3J_{11,10}$ = 8.4 Hz, 1 H, 11-H), 4.78 (td, $^3J_{2,NH}$ = 7.6 Hz, $^3J_{2,3}$ = 4.4 Hz, 1 H, 2-H), 4.69 (d, $^2J_{5a,5b}$ = $^2J_{5b,5a}$ = 3.7 Hz, 2 H, 5-H), 3.48 (dd, $^2J_{3a,3b}$ = 18.8 Hz, $^3J_{3a,2}$ = 4.4 Hz, 1 H, 3a-H), 3.28 (dd, $^2J_{3b,3a}$ = 18.8 Hz, $^3J_{3b,2}$ = 4.3 Hz, 1 H, 3b-H), 1.43 (s, 9 H, 12-H).

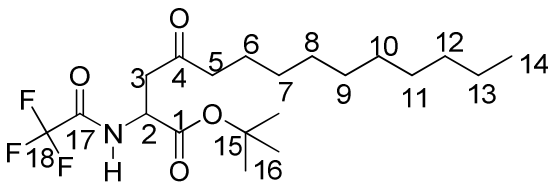
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 204.1, 168.0, 157.2 (q, *J* = 37.4 Hz), 134.4, 134.1, 122.2, 115.5 (q, *J* = 285.8 Hz), 112.1, 102.6, 83.9, 72.7, 48.8, 40.3, 27.7.

HRMS (CI):	Calculated	Found
$C_{18}H_{19}F_3N_2O_5[M+1]^+$	401.1280	401.1334

***tert*-Butyl 4-oxo-2-(2,2,2-trifluoroacetamido) tetradecanoate (11o)**

According to the general procedure for Dess-Martin oxidation GP-4, alcohol **7e** (531 mg, 1.32 mmol), Dess-Martin periodinane (721 mg, 1.7 mmol) reacted to give **11o** after flash chromatography (silica, hexanes/EtOAc 8:2) in 84% yield (444 mg, 1.11 mmol) as white solid with a melting point of 55 °C.

[TLC: Hex/EA 95:5, R_f = 0.52]



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.37 (bs, 1 H, N-H), 4.61 (td, $^3J_{2,NH}$ = 7.86 Hz, $^3J_{2,3}$ = 3.8 Hz, 1 H, 2-H), 3.22 (dd, $^2J_{3b,3a}$ = 18.4 Hz, $^3J_{3b,2}$ = 3.8 Hz ,1 H, 3b-H), 2.94 (dd, $^2J_{3a,3b}$ = 18.4 Hz, $^3J_{3a,2}$ = 3.9 Hz, 1 H, 3a-H), 1.50–1.62 (m, 2 H, 6-H), 2.34–2.46 (m, 2 H, 5-H),

1.20–1.34 (m, 14 H, 6-H, 7-H, 8-H, 9-H, 10-H, 11-H, 12-H, 13-H, 14-H), 0.86 (t, $^{3}J_{14,13}$ = 6.72 Hz, 3 H, 14-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 208.9, 168.1, 156.8 (q, *J* = 37.4Hz), 115.6 (q, *J* = 285.7 Hz), 83.3, 49.1, 42.9, 42.6, 31.8, 29.4, 29.3, 29.2, 29.2, 29.0, 27.7, 23.6, 22.6, 14.1.

HRMS (CI):	Calculated	Found
$C_{20}H_{34}F_3NO_4$ $[M+1]^+$	410.2473	410.2521

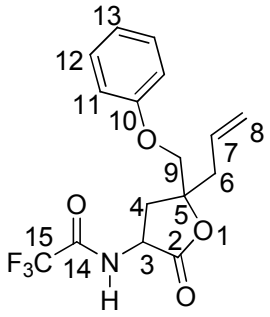
Elemental Analysis:

$C_{20}H_{34}F_3NO_4$	Theoret.	C 58.66	H 8.37	N 3.42
(409.48):	Found	C 58.86	H 7.91	N 3.48

***N*-(5-Allyl-2-oxo-5-(phenoxymethyl)tetrahydrofuran-3-yl)-2,2,2-trifluoroacetamide (12a)**

According to the general procedure for allylation **GP-6**, ketone **11f** (56 mg, 0.15 mmol), Zn dust (19.1 mg, 0.29 mmol) and allyl bromide (18 mg, 0.15 mmol) reacted to give **12a** after flash chromatography (silica, hexanes/EtOAc 8:2) in 60% yield (31 mg, 0.09 mmol) as colorless solid with a melting point of 87 °C.

[TLC: Hex/EA 7:3, Rf = 0.54]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.32 (m, 3 H, 11-H, N-H), 6.86–6.90 (m, 2 H, 12-H), 5.76–5.86 (m, 1 H, 7-H), 5.21–5.31 (m, 2 H, 8-H), 4.81 (dt, $^{3}J_{3,4}$ = 10.0 Hz, $^{3}J_{3,NH}$ = 6.5 Hz, 1 H, 3-H), 4.09 (d, $^{2}J_{9a,9b}$ = 10.0 Hz, 1 H, 9a-H), 4.00 (d, $^{2}J_{9b,9a}$ = 10.1 Hz, 1 H, 9b-H), 2.95 (dd, $^{2}J_{6a,6b}$ = 12.9 Hz, $^{3}J_{6a,7}$ = 9.6 Hz, 1 H, 6a-H), 2.56–2.65 (m, 2 H, 4-H), 2.32 (dd, $^{2}J_{6b,6a}$ = 13.7 Hz, $^{3}J_{6b,7}$ = 8.1 Hz, 1 H, 6b-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 157.6 (q, *J* = 37.4Hz), 157.5, 129.9, 129.7, 129.7, 122.0, 121.1, 115.6 (q, *J* = 285.7 Hz), 114.6, 84.8, 72.5, 50.8, 41.5, 36.0.

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.97–7.04 (m, 2 H, 12-H), 5.77–5.86 (m, 1 H, 7-H), 5.22–5.28 (m, 2 H, 8-H), 4.84–4.91 (m, 1 H, 3-H), 4.09 (d, $^{2}J_{9a,9b}$ = 10.7 Hz, 1 H, 9a-H),

3.98 (d, $^{2}J_{9b,9a}$ = 10.3 Hz, 1 H, 9b-H), 2.77 (dd, $^{2}J_{6a,6b}$ = 13.0 Hz, $^{3}J_{6a,7}$ = 10.3 Hz, 1 H, 6a-H), 2.55–2.66 (m, 2 H, 4-H), 2.22 (dd, $^{2}J_{6b,6a}$ = 12.9 Hz, $^{3}J_{6b,7}$ = 10.8 Hz, 1 H, 6b-H).

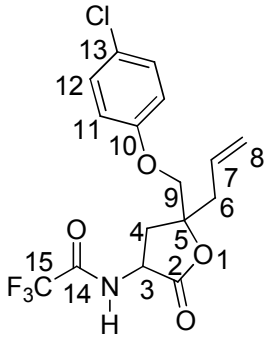
^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5, 156.8, 130.0, 129.8, 129.6, 122.2, 121.1, 114.8, 85.0, 72.2, 49.4, 40.6, 34.4.

HRMS (CI):	Calculated	Found
$C_{16}H_{16}F_3NO_4$ $[M]^+$	343.1031	343.1068

_N_-(5-Allyl-5-((4-chlorophenoxy)methyl)-2-oxotetrahydrofuran-3-yl)-2,2,2-trifluoroacetamide (12b)

According to the general procedure for allylation **GP-6**, ketone **11k** (61 mg, 0.15 mmol), Zn dust (19.1 mg, 0.29 mmol) and allyl bromide (18 mg, 0.15 mmol) reacted to give **12b** after flash chromatography (silica, hexanes/EtOAc 8:2) in 66% yield (37 mg, 0.10 mmol) as colorless solid with a melting point of 90 °C.

[TLC: Hex/EA 8:2, R_f = 0.53]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.27 (m, 2 H, 11-H), 6.96 (d, $^{3}J_{NH,3}$ = 5.0 Hz, 1 H, N-H), 6.80–6.84 (m, 2 H, 12-H), 5.75–5.85 (m, 1 H, 7-H), 5.27–5.32 (m, 2 H, 8-H), 4.81 (ddd, $^{3}J_{3,NH}$ = $^{3}J_{3,4}$ = 8.8 Hz, 1 H, 3-H), 4.06 (d, $^{2}J_{9a,9b}$ = 10.1 Hz, 1 H, 9a-H), 3.96 (d, $^{2}J_{9b,9a}$ = 10.1 Hz, 1 H, 9b-H), 2.79 (dd, $^{2}J_{6a,6b}$ = 13.6 Hz, $^{3}J_{6a,7}$ = 10.2 Hz, 1 H, 6a-H), 2.53-2.63 (m, 2 H, 4-H), 2.79 (dd, $^{2}J_{6b,6a}$ = 13.6 Hz, $^{3}J_{6b,7}$ = 8.6 Hz, 1 H, 6b-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2, 156.8 (q, *J* = 37.4Hz), 156.3, 129.7, 129.6, 127.2, 122.0, 116.8, 116.2, 115.6 (q, *J* = 285.7 Hz), 84.9, 72.5, 49.6, 40.6, 34.3.

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.27 (m, 2 H, 11-H), 6.79–6.85 (m, 3 H, 12-H, N-H), 5.76–5.86 (m, 1 H, 7-H), 5.23–5.33 (m, 2 H, 8-H), 5.02 (dt, $^{3}J_{3,4}$ = 10.2 Hz, $^{3}J_{3,NH}$ = 5.8 Hz, 1 H, 3-H), 4.08 (d, $^{2}J_{9a,9b}$ = 10.0 Hz, 1 H, 9a-H), 3.98 (d, $^{2}J_{9b,9a}$ = 10.0 Hz, 1 H, 9b-H), 2.99 (dd, $^{2}J_{6a,6b}$ = 13.0 Hz, $^{3}J_{6a,7}$ = 9.5 Hz, 1 H, 6a-H), 2.55–2.66 (m, 2 H, 4-H), 2.21 (dd, $^{2}J_{6b,6a}$ = 13.0 Hz, $^{3}J_{6b,7}$ = 10.7 Hz, 1 H, 6b-H).

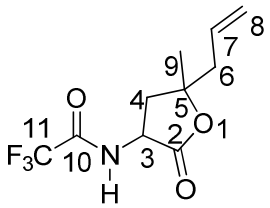
^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7, 156.2, 129.7, 129.6, 121.4, 116.0, 84.7, 72.9, 50.8, 41.6, 36.1.

HRMS (CI):	Calculated	Found
$C_{16}H_{15}ClF_3NO_4$ $[M]^+$	377.0642	377.0635

***N*-(5-Allyl-5-methyl-2-oxotetrahydrofuran-3-yl)-2,2,2-trifluoroacetamide (12d)**

According to the general procedure for allylation **GP-6**, ketone **11a** (42 mg, 0.15 mmol), Zn dust (19.1 mg, 0.29 mmol) and allyl bromide (18 mg, 0.15 mmol) reacted to give **12d** after flash chromatography (silica, hexanes/EtOAc 8:2) in 70% yield (26 mg, 0.11 mmol) as colorless solid with a melting point of 82 °C.

[TLC: Hex/EA 7:3, R_f = 0.44]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.80 (bs, 1 H, N-H), 5.70–5.80 (m, 1 H, 7-H), 5.17–5.27 (m, 2 H, 8-H), 4.81 (ddd, $^3J_{3,4a}$ = 11.6 Hz, $^3J_{3,4b}$ = 8.7 Hz, $^3J_{3,NH}$ = 5.7 Hz, 1 H, 3-H), 2.69 (dd, $^2J_{4a,4b}$ = 12.7 Hz, $^3J_{4a,3}$ = 8.8 Hz, 1 H, 4a-H), 2.43–2.57 (m, 2 H, 6-H), 2.06 (dd, $^2J_{4a,4b}$ = $^3J_{4a,3}$ = 12.7 Hz, 1 H, 4b-H), 1.46 (s, 3 H, 9-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5, 157.6 (q, *J* = 37.4 Hz), 130.8, 120.7, 115.6 (q, *J* = 285.7 Hz), 84.8, 50.1, 45.6, 39.1.

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.97 (bs, 1 H, N-H), 5.73–5.83 (m, 1 H, 7-H), 5.22–5.27 (m, 2 H, 8-H), 4.71 (ddd, $^3J_{3,4a}$ = 11.1 Hz, $^3J_{3,4b}$ = 9.4 Hz, $^3J_{3,NH}$ = 6.1 Hz, 1 H, 3-H), 2.86 (dd, $^2J_{4a,4b}$ = 13.0 Hz, $^3J_{4a,3}$ = 9.3 Hz, 1 H, 4a-H), 2.43–2.44 (m, 2 H, 6-H), 2.06 (dd, $^2J_{4a,4b}$ = 13.0 Hz, $^3J_{4a,3}$ = 11.3 Hz, 1 H, 4b-H), 1.51 (s, 3 H, 9-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 131.0, 121.0, 85.2, 50.5, 44.4, 39.0.

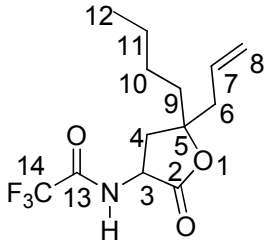
HRMS (CI):	Calculated	Found
$C_{10}H_{12}F_3NO_3$ $[M]^+$	251.0769	251.0789

***N*-(5-Allyl-5-butyl-2-oxotetrahydrofuran-3-yl)-2,2,2-trifluoroacetamide (12e)**

According to the general procedure for allylation **GP-6**, ketone **11c** (48 mg, 0.15 mmol), Zn dust (19.1 mg, 0.29 mmol) and allyl bromide (18 mg, 0.15 mmol) reacted

to give **12e** after flash chromatography (silica, hexanes/EtOAc 8:2) in 65% yield (29 mg, 0.09 mmol) as colorless solid with a melting point of 80 °C.

[TLC: Hex/EA 8:2, R_f = 0.45]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.90 (bs, 1 H, N-H), 5.72–5.82 (m, 1 H, 7-H), 5.19–5.30 (m, 2 H, 8-H), 4.65–4.72 (m, 1 H, 3-H), 2.76–2.82 (m, 1 H, 4a-H), 2.44 (d, $^3J_{6,7}$ = 7.0 Hz, 2 H, 6-H), 1.99 (dd, $^2J_{4b,4a}$ = 12.9 Hz, $^3J_{4b,3}$ = 11.3 Hz, 1 H, 4b-H), 1.69–1.78 (m, 2 H, 9-H), 1.30–1.38 (m, 4 H, 10-H, 11-H), 0.89–0.94 (m, 3 H, 12-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 157.6 (q, *J* = 37.4 Hz), 130.8, 121.0, 115.6 (q, *J* = 285.7 Hz), 87.5, 50.5, 42.3, 39.6, 37.5, 25.1, 22.7, 13.8.

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95 (bs, 1 H, N-H), 5.67–5.77 (m, 1 H, 7-H), 5.16–5.29 (m, 2 H, 8-H), 4.72 (dt, $^3J_{3,4}$ = 10.0 Hz, $^3J_{3,NH}$ = 6.0 Hz, 1 H, 3-H), 2.70 (dd, $^2J_{4a,4b}$ = 12.8 Hz, $^3J_{4b,3}$ = 9.5 Hz, 1 H, 4a-H), 2.03 (dd, $^2J_{4b,4a}$ = 13.0 Hz, $^3J_{4b,3}$ = 11.3 Hz, 1 H, 4b-H), 1.66–1.73 (m, 2 H, 9-H).

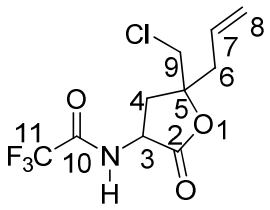
^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 130.8, 120.6, 87.3, 50.1, 43.2, 38.0, 37.3, 25.6, 22.7, 13.8.

HRMS (CI):	Calculated	Found
$C_{13}H_{18}F_3NO_3$ $[M+1]^+$	294.1272	294.1292

***N*-(5-Allyl-5-(chloromethyl)-2-oxotetrahydrofuran-3-yl)-2,2,2-trifluoroacetamide (12f)**

According to the general procedure for allylation **GP-6**, ketone **11d** (48 mg, 0.15 mmol), Zn dust (19.1 mg, 0.29 mmol) and allyl bromide (18 mg, 0.15 mmol) reacted to give **12f** after flash chromatography (silica, hexanes/EtOAc 8:2) in 64% yield (27 mg, 0.09 mmol) as colorless solid with a melting point of 82 °C.

[TLC: Hex/EA 7:3, R_f = 0.52]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (bs, 1 H, N-H), 5.70–5.82 (m, 1 H, 7-H), 5.21–5.33 (m, 2 H, 8-H), 4.81 (dt, $^{3}J_{3,4}$ = 10.2 Hz, $^{3}J_{3,NH}$ = 6.6 Hz, 1 H, 3-H), 3.61–3.74 (m, 2 H, 4-H), 2.88 (dd, $^{2}J_{6a,6b}$ = $^{2}J_{6b,7}$ = 11.8 Hz, 1 H, 6a-H), 2.63 (d, $^{2}J_{9a,9b}$ = $^{2}J_{9b,9a}$ = 7.3 Hz, 2 H, 9-H), 2.29 (dd, $^{2}J_{6b,6a}$ = 13.5 Hz, $^{3}J_{6b,7}$ = 10.5 Hz, 1 H, 6b-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5, 157.6 (q, *J* = 37.4 Hz), 129.7, 122.3, 115.6 (q, *J* = 285.7 Hz), 85.0, 50.4, 49.4, 42.9, 35.4.

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (bs, 1 H, N-H), 5.73–5.83 (m, 1 H, 7-H), 5.22–5.27 (m, 2 H, 8-H), 4.71 (dt, $^{3}J_{3,4}$ = 10.2 Hz, $^{3}J_{3,NH}$ = 6.8 Hz, 1 H, 3-H), 2.74 (dd, $^{2}J_{6a,6b}$ = 13.2 Hz, $^{2}J_{6a,7}$ = 10.2 Hz, 1 H, 6a-H), 2.58 (d, $^{2}J_{9a,9b}$ = $^{2}J_{9b,9a}$ = 7.3 Hz, 2 H, 9-H), 2.21 (dd, $^{2}J_{6b,6a}$ = 14.5 Hz, $^{3}J_{6b,7}$ = 4.2 Hz, 1 H, 6b-H).

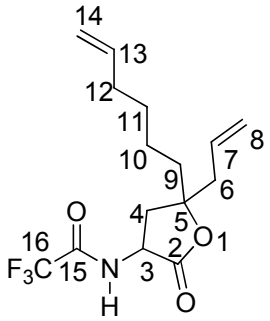
^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1, 157.6 (q, *J* = 37.4 Hz), 129.5, 121.6, 84.7, 49.8, 49.2, 40.9, 34.9.

HRMS (CI):	Calculated	Found
$C_{10}H_{11}ClF_3NO_3$ $[M+1]^+$	285.0380	285.0395

***N*-(5-Allyl-5-(hex-5-enyl)-2-oxotetrahydrofuran-3-yl)-2,2,2-trifluoroacetamide (12g)**

According to the general procedure for allylation **GP-6**, ketone **11e** (53 mg, 0.15 mmol), Zn dust (19.1 mg, 0.29 mmol) and allyl bromide (18 mg, 0.15 mmol) reacted to give **12g** after flash chromatography (silica, hexanes/EtOAc 8:2) in 62% yield (30 mg, 0.09 mmol) as colorless solid with a melting point of 96 °C.

[TLC: Hex/EA 7:3, R_f = 0.53]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.93 (bs, 1 H, N-H), 5.71–5.83 (m, 2 H, 7-H, 13-H), 5.22–5.30 (m, 2 H, 8-H), 4.94–5.03 (m, 2 H, 14-H), 4.65–4.72 (m, 1 H, 3-H), 2.78 (dd, $^{2}J_{4a,4b}$ = 13.0 Hz, $^{3}J_{4b,3}$ = 9.4 Hz, 1 H, 4a-H), 2.44 (d, $^{2}J_{6,7}$ = 7.3 Hz, 2 H, 6-H), 1.69–1.75 (m, 2 H, 12-H), 1.98 (dd, $^{2}J_{4b,4a}$ = 13.0 Hz, $^{3}J_{4b,3}$ = 11.3 Hz, 1 H, 4b-H), 1.69–1.78 (m, 2 H, 9-H), 1.32–1.46 (m, 4 H, 10-H, 11-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 157.6 (q, *J* = 37.4 Hz), 138.2, 130.8, 121.1, 115.6 (q, *J* = 285.7 Hz), 114.8, 87.4, 50.4, 42.2, 39.7, 37.5, 33.3, 28.7, 22.4.

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.93 (bs, 1 H, N-H), 5.71–5.83 (m, 2 H, 7-H, 13-H), 5.22–5.30 (m, 2 H, 8-H), 4.94–5.03 (m, 2 H, 14-H), 4.68 (dt, $^{3}J_{3,4}$ = 10.8 Hz, $^{3}J_{3,NH}$ = 5.7 Hz, 1 H, 3-H), 2.80 (dd, $^{2}J_{4a,4b}$ = 13.0 Hz, $^{3}J_{4b,3}$ = 9.4 Hz, 1 H, 4a-H), 2.72 (dd, $^{2}J_{4b,4a}$ = 13.0 Hz, $^{3}J_{4b,3}$ = 9.3 Hz, 1 H, 4b-H), 1.69–1.78 (m, 2 H, 9-H), 1.32–1.46 (m, 4 H, 10-H, 11-H).

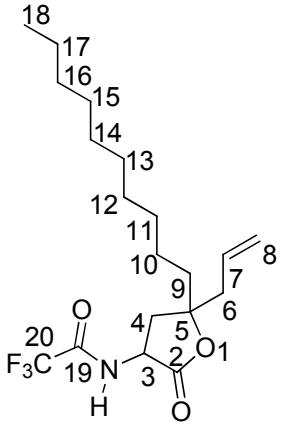
^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 138.2, 130.8, 121.1, 114.8, 87.4, 50.4, 42.2, 39.7, 37.5, 33.3, 28.7, 22.4.

HRMS (CI):	Calculated	Found
$C_{15}H_{20}F_3NO_3$ $[M+1]^+$	319.1395	319.1406

***N*-(5-Allyl-5-decyl-2-oxotetrahydrofuran-3-yl)-2,2,2-trifluoroacetamide (12h)**

According to the general procedure for allylation **GP-6**, ketone **11o** (61 mg, 0.15 mmol), Zn dust (19.1 mg, 0.29 mmol) and allyl bromide (18 mg, 0.15 mmol) reacted to give **12h** after flash chromatography (silica, hexanes/EtOAc 8:2) in 61% yield (35 mg, 0.09 mmol) as colorless solid with a melting point of 100 °C.

[TLC: Hex/EA 7:3, R_f = 0.55]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.99 (d, $^{3}J_{NH,3}$ = 4.8 Hz, 1 H, N-H), 5.67–5.82 (m, 1 H, 7-H), 5.16–5.29 (m, 2 H, 8-H), 4.67–4.74 (m, 1 H, 3-H), 2.77 (dd, $^{2}J_{4a,4b}$ = 13.0 Hz, $^{3}J_{4b,3}$ = 9.4 Hz, 1 H, 4a-H), 2.44 (d, $^{3}J_{6,7}$ = 7.3 Hz, 2 H, 6-H), 1.98 (dd, $^{2}J_{4b,4a}$ = 13.0 Hz, $^{3}J_{4b,3}$ = 11.3 Hz, 1 H, 4b-H), 1.69–1.75 (m, 2 H, 9-H), 1.25 (bs, 16 H, 10-H, 11-H, 12-H, 13-H, 14-H, 15-H, 16-H, 17-H), 0.87 (t, $^{3}J_{18,17}$ = 6.8 Hz, 3 H, 18-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 157.6 (q, *J* = 37.4 Hz), 130.8, 121.0, 115.6 (q, *J* = 285.7 Hz), 87.5, 50.4, 42.2, 39.8, 37.4, 31.8, 29.6, 29.5, 29.4, 29.3, 29.2, 23.0, 22.6, 14.0.

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.84 (d, $^{3}J_{NH,3}$ = 5.3 Hz, 1 H, N-H), 5.71–5.82 (m, 1 H, 7-H), 5.22–5.30 (m, 2 H, 8-H), 4.68 (ddd, $^{3}J_{3,4b}$ = 11.1 Hz, $^{3}J_{3,4a}$ = 9.5 Hz, $^{3}J_{3,NH}$ = 5.6 Hz, 1 H, 3-H), 2.79 (dd, $^{2}J_{4a,4b}$ = 13.0 Hz, $^{3}J_{4b,3}$ = 9.4 Hz, 1 H, 4a-H), 2.44 (d, $^{2}J_{6,7}$ = 7.3 Hz, 2 H, 6-H), 1.97 (dd, $^{2}J_{4b,4a}$ = 13.0 Hz, $^{3}J_{4b,3}$ = 11.3 Hz, 1 H, 4b-H), 1.70–1.76 (m, 2 H, 9-H), 1.25 (bs, 16 H, 10-H, 11-H, 12-H, 13-H, 14-H, 15-H, 16-H, 17-H), 0.87 (t, $^{3}J_{18,17}$ = 6.8 Hz, 3 H, 18-H).

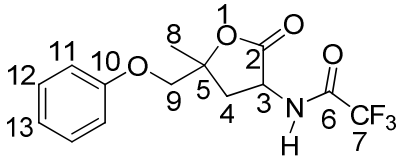
^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 130.9, 121.0, 87.5, 50.5, 42.3, 39.9, 37.5, 31.8, 29.6, 29.5, 29.4, 29.3, 29.2, 23.0, 22.6, 14.0.

HRMS (CI):	Calculated	Found
$C_{19}H_{30}F_3NO_3$ $[M+1]^+$	378.2211	378.2238

2,2,2-Trifluoro-N-(5-methyl-2-oxo-5-(phenoxymethyl)tetrahydrofuran-3-yl) acetamide (14a)

According to the general procedure **GP-7**, ketone **11f** (71 mg, 0.19 mmol), $ZnCl_2$ (34 mg, 0.25 mmol) and $AlMe_3$ (27.8 mg, 0.38 mmol) reacted to give **14a** after flash chromatography (silica, hexanes/EtOAc 8:2) in 60% yield (36 mg, 0.11 mmol) as white solid with a melting point of 108 °C.

[TLC: Hex/EA 75:25, R_f = 0.28]



Major diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.28–7.33 (m, 4 H, 11-H, 12-H), 7.08 (d, $^{3}J_{NH,3}$ = 5.0 Hz, 1 H, N-H), 7.01–7.05 (m, 1 H, 13-H), 4.78 (td, $^{3}J_{3,4a}$ = 9.6 Hz, $^{3}J_{3,NH}$ = 7.0 Hz, 1 H, 3-H),

4.10 (d, $^{2}J_{9a,9b}$ = 10.1 Hz, 1 H, 9a-H), 3.98 (d, $^{2}J_{9b,9a}$ = 10.1 Hz, 1 H, 9b-H), 2.71 (dd, $^{2}J_{4a,4b}$ = 13.5 Hz, $^{3}J_{4a,3}$ = 9.9 Hz, 1 H, 4a-H), 2.40 (dd, $^{2}J_{4a,4b}$ = 13.5 Hz, $^{3}J_{4a,3}$ = 8.2 Hz, 1 H, 4b-H), 1.58 (s, 3 H, 8-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.3, 157.6, 157.2 (q, *J* = 38.8 Hz), 129.8, 122.3, 115.5 (q, *J* = 285.8 Hz), 114.8, 83.5, 73.1, 49.5, 36.9, 23.2.

Minor diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.03–5.10 (m, 1 H, 3-H), 4.09 (d, $^{2}J_{9a,9b}$ = 10.1 Hz, 1 H, 9a-H), 3.96 (d, $^{2}J_{9b,9a}$ = 10.1 Hz, 1 H, 9b-H), 3.11 (dd, $^{2}J_{4a,4b}$ = 13.0 Hz, $^{3}J_{4a,3}$ = 9.5 Hz, 1 H, 4a-H), 2.40 (dd, $^{2}J_{4a,4b}$ = 13.0 Hz, $^{3}J_{4a,3}$ = 10.7 Hz, 1 H, 4b-H), 1.54 (s, 3 H, 8-H), 1.55 (s, 3 H, 8-H).

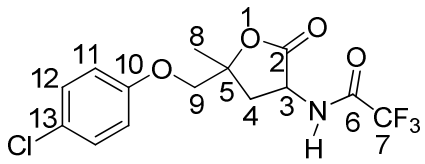
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 173.0, 129.7, 122.0, 114.6, 83.5, 73.1, 51.3, 38.5, 24.1.

HRMS (CI):	Calculated	Found
$C_{14}H_{14}F_3NO_4$ $[M+1]^+$	317.0875	317.0870

_N_-(5-((4-Chlorophenoxy)methyl)-5-methyl-2-oxotetrahydrofuran-3-yl)-2,2,2-trifluoroacetamide (14b)

According to the general procedure **GP-7**, ketone **11k** (78 mg, 0.19 mmol), $ZnCl_2$ (34 mg, 0.25 mmol) and $AlMe_3$ (27.8 mg, 0.38 mmol) reacted to give **14b** after flash chromatography (silica, hexanes/EtOAc 8:2) in 58% yield (39 mg, 0.11 mmol) as white solid with a melting point of 112 °C.

[TLC: Hex/EA 75:25, R_f = 0.29]



Major diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.23–7.28 (m, 2 H, 11-H), 6.90 (d, $^{3}J_{NH,3}$ = 5.0 Hz, 1 H, N-H), 6.79–6.85 (m, 2 H, 12-H), 5.03 (dt, $^{3}J_{3,4a}$ = 10.1 Hz, $^{3}J_{3,NH}$ = 6.0 Hz, 1 H, 3-H), 4.06 (d, $^{2}J_{9a,9b}$ = 10.1 Hz, 1 H, 9a-H), 3.94 (d, $^{2}J_{9b,9a}$ = 10.1 Hz, 1 H, 9b-H), 3.09 (dd, $^{2}J_{4a,4b}$ = 13.1 Hz, $^{3}J_{4a,3}$ = 9.5 Hz, 1 H, 4a-H), 2.40 (dd, $^{2}J_{4a,4b}$ = 13.0 Hz, $^{3}J_{4a,3}$ = 10.8 Hz, 1 H, 4b-H), 1.58 (s, 3 H, 8-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.2, 157.2 (q, *J* = 38.8 Hz), 156.3, 129.6, 127.2, 116.1, 115.5 (q, *J* = 285.8 Hz), 83.3, 73.9, 51.2, 38.4, 24.1.

Minor diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$ δ = 7.23–7.28 (m, 2 H, 11-H), 7.01 (bs, 1 H, N-H), 6.79–6.85 (m, 2 H, 12-H), 5.03 (dt, $^{3}J_{3,4a}$ = 9.4 Hz, $^{3}J_{3,NH}$ = 7.0 Hz, 1 H, 3-H), 4.06 (d, $^{2}J_{9a,9b}$ = 10.0 Hz, 1 H, 9a-H), 3.95 (d, $^{2}J_{9b,9a}$ = 10.1 Hz, 1 H, 9b-H), 2.72 (dd, $^{2}J_{4a,4b}$ = 13.3 Hz, $^{3}J_{4a,3}$ = 9.7 Hz, 1 H, 4a-H), 2.40 (dd, $^{2}J_{4a,4b}$ = 13.0 Hz, $^{3}J_{4a,3}$ = 9.1 Hz, 1 H, 4b-H), 1.58 (s, 3 H, 8-H).

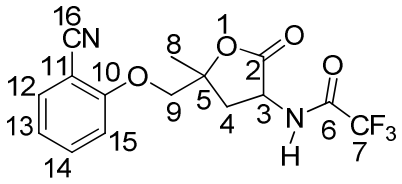
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.1, 129.6, 127.1, 115.5, 83.4, 73.2, 49.5, 38.6, 23.1.

HRMS (CI):	Calculated	Found
$C_{14}H_{13}ClF_3NO_4$ $[M+1]^+$	353.0456	353.0419

***N*-(5-((2-Cyanophenoxy)methyl)-5-methyl-2-oxotetrahydrofuran-3-yl)-2,2,2-trifluoroacetamide (14c)**

According to the general procedure **GP-7**, ketone **11n** (76 mg, 0.19 mmol), $ZnCl_2$ (34 mg, 0.25 mmol) and $AlMe_3$ (27.8 mg, 0.38 mmol) reacted to give **14c** after flash chromatography (silica, hexanes/EtOAc 8:2) in 66% yield (43 mg, 0.13 mmol) as white solid with a melting point of 110 °C.

[TLC: Hex/EA 8:2, R_f = 0.26]



Major diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, $^{3}J_{NH,3}$ = 7.3 Hz, 1 H, N-H), 7.53–7.58 (m, 2 H, 14-H, 15-H), 7.08 (dd, $^{3}J_{13,12}$ = $^{3}J_{13,14}$ = 7.6 Hz, 1 H, 13-H), 6.96 (d, $^{3}J_{12,13}$ = 8.2 Hz, 1 H, 12-H), 5.09 (dt, $^{3}J_{3,4a}$ = 10.3 Hz, $^{3}J_{3,NH}$ = 7.9 Hz, 1 H, 3-H), 4.27 (d, $^{2}J_{9a,9b}$ = 10.3 Hz, 1 H, 9a-H), 4.04 (d, $^{2}J_{9b,9a}$ = 10.3 Hz, 1 H, 9b-H), 2.67 (d, $^{2}J_{4,3}$ = 10.5 Hz, 1 H, 4-H), 1.57 (s, 3 H, 8-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.9, 160.1, 157.2 (q, *J* = 38.8 Hz), 134.8, 133.0, 122.1, 115.5 (q, *J* = 285.8 Hz), 113.2, 102.4, 82.6, 73.2, 35.1, 23.2.

Minor diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.53–7.58 (m, 2 H, 14-H, 15-H), 7.47 (bs, 1 H, N-H), 4.22 (d, $^{2}J_{9a,9b}$ = 9.7 Hz, 1 H, 9a-H), 3.99 (d, $^{2}J_{9b,9a}$ = 9.7 Hz, 1 H, 9b-H), 2.98 (dd, $^{2}J_{4a,4b}$ =

12.9 Hz, $^{3}J_{4a,3}$ = 10.1 Hz, 1 H, 4a-H), 2.41 (dd, $^{2}J_{4a,4b}$ = 13.0 Hz, $^{3}J_{4a,3}$ = 10.3 Hz, 1 H, 4b-H), 1.63 (s, 3 H, 8-H).

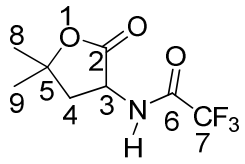
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.9, 159.6, 133.6, 117.0, 113.2, 112.1, 101.9, 82.2, 74.1, 51.5, 36.2, 23.9.

HRMS (CI):	Calculated	Found
$C_{15}H_{13}F_3N_2O_4$ $[M]^+$	342.0827	342.0867

***N*-(5,5-Dimethyl-2-oxotetrahydrofuran-3-yl)-2,2,2-trifluoroacetamide (14d)**

According to the general procedure **GP-7**, ketone **11a** (54 mg, 0.19 mmol), $ZnCl_2$ (34 mg, 0.25 mmol) and $AlMe_3$ (27.8 mg, 0.38 mmol) reacted to give **14d** after flash chromatography (silica, hexanes/EtOAc 8:2) in 60% yield (26 mg, 0.11 mmol) as white solid with a melting point of 89 °C.

[TLC: Hex/EA 8:2, R_f = 0.26]



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.00 (bs, 1 H, N-H), 4.78 (ddd, $^{3}J_{3,4a}$ = 11.8 Hz, $^{3}J_{3,NH}$ = 8.7 Hz, $^{3}J_{3,4b}$ = 6.1 Hz, 1 H, 3-H), 2.79 (dd, $^{2}J_{4b,4a}$ = 12.6 Hz, $^{3}J_{4b,3}$ = 8.7 Hz, 1 H, 4b-H), 2.79 (dd, $^{2}J_{4b,4a} \approx {}^{3}J_{4b,3}$ = 12.2 Hz, 1 H, 4a-H), 1.54 (s, 3 H, 8-H), 1.48 (s, 3 H, 9-H).

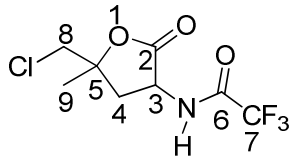
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.2, 157.2 (q, *J* = 38.8 Hz), 115.5 (q, *J* = 285.8 Hz), 83.6, 50.5, 41.5, 28.8, 26.8.

HRMS (CI):	Calculated	Found
$C_8H_{10}F_3NO_3$ $[M+1]^+$	226.0646	226.0673

***N*-(5-(Chloromethyl)-5-methyl-2-oxotetrahydrofuran-3-yl)-2,2,2-trifluoroacetamide (14e)**

According to the general procedure for methylation **GP-7**, ketone **11d** (60 mg, 0.19 mmol), $ZnCl_2$ (34 mg, 0.25 mmol) and $AlMe_3$ (27.8 mg, 0.38 mmol) reacted to give **14f** after flash chromatography (silica, hexanes/EtOAc 8:2) in 66% yield (33 mg, 0.13 mmol) as white solid with a melting point of 95 °C.

[TLC: Hex/EA 75:25, R_f = 0.28]



Major diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.87 (bs, 1 H, N-H), 4.77–4.84 (m, 1 H, 3-H), 3.73 (d, $^{2}J_{8a,8b}$ = 11.8 Hz, 1 H, 8a-H), 3.62 (d, $^{2}J_{8b,8a}$ = 11.8 Hz, 1 H, 8b-H), 4.04 (d, $^{2}J_{9b,9a}$ = 10.3 Hz, 1 H, 9b-H), 2.75 (dd, $^{2}J_{4a,4b}$ = 13.0 Hz, $^{3}J_{4a,3}$ = 9.0 Hz, 1 H, 4a-H), 2.31 (dd, $^{2}J_{4b,4a}$ = 13.0 Hz, $^{3}J_{4b,3}$ = 11.1 Hz, 1 H, 4b-H), 1.59 (s, 3 H, 8-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.2, 157.2 (q, *J* = 38.8 Hz), 115.5 (q, *J* = 285.8 Hz), 83.6, 50.5, 50.3, 37.7, 24.1.

Major diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.86 (bs, 1 H, N-H), 4.75–4.85 (m, 1 H, 3-H), 3.00 (dd, $^{2}J_{4a,4b}$ = 13.5 Hz, $^{3}J_{4a,3}$ = 10.0 Hz, 1 H, 4a-H), 2.31 (dd, $^{2}J_{4b,4a}$ = 13.5 Hz, $^{3}J_{4b,3}$ = 10.3 Hz, 1 H, 4b-H), 1.59 (s, 3 H, 8-H).

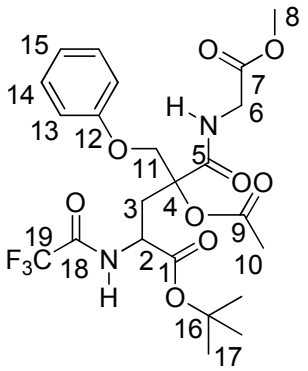
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.2, 83.6, 50.5, 50.3, 37.7, 24.1.

HRMS (CI):	Calculated	Found
$C_8H_9ClF_3NO_3$ $[M]^+$	259.0223	259.0182

***tert*-Butyl 4-acetoxy-5-(2-methoxy-2-oxoethylamino)-5-oxo-4-(phenoxymethyl)-2-(2,2,2-trifluoroacetamido) pentanoate (15a)**

According to the general procedure for Passerini reaction **GP-8**, ketone **11f** (101 mg, 0.27 mmol), acetic acid (17.6 mg, 0.29 mmol) and methyl 2-isocyanoacetate (29 mg, 0.29 mmol) reacted to give **15a** after flash chromatography (silica, hexanes/EtOAc 8:2) in 53% yield (82 mg, 0.13 mmol) as white solid with a melting point of 109 °C.

[TLC: Hex/EA 7:3, R_f =0.35]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, $^3J_{NHTFA,2}$ = 8.0 Hz, 1 H, N_{TFA}-H), 7.44 (t, $^3J_{NH,6}$ = 5.4 Hz, 1 H, N-H), 7.24–7.33 (m, 5 H, 13-H, 14-H, 15-H), 4.73 (d, $^2J_{11a,11b}$ = 9.8 Hz, 1 H, 11a-H), 4.54–4.59 (m, 1 H, 2-H), 4.43 (d, $^2J_{11b,11a}$ = 9.8 Hz, 1 H, 11b-H), 4.17–4.29 (m, 2 H, 6-H), 3.80 (s, 3 H, 8-H), 2.93 (dd, $^2J_{3a,3b}$ = 15.2 Hz, $^3J_{3a,2}$ = 9.9 Hz, 1 H, 3a-H), 2.65 (dd, $^2J_{3b,3a}$ = 14.7 Hz, $^3J_{3b,2}$ = 11.0 Hz, 1 H, 3b-H), 2.08 (s, 3 H, 10-H), 1.48 (s, 9 H, 17-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 169.7, 169.1, 168.5, 156.7, 129.5, 121.8, 115.0, 114.9, 114.7, 83.5, 83.1, 68.5, 52.3, 50.1, 41.2, 34.2, 27.8, 21.5.

Minor diastereomer (selected signals)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.98–7.02 (m, 2 H, N-H, 15-H), 6.89–6.93 (m, 5 H, 13-H, 14-H, N_{TFA}-H), 4.88 (d, $^2J_{11a,11b}$ = 9.9 Hz, 1 H, 11a-H), 4.69–4.74 (m, 1 H, 2-H), 4.22 (d, $^2J_{11b,11a}$ = 9.7 Hz, 1 H, 11b-H), 3.92–4.04 (m, 2 H, 6-H), 3.79 (s, 3 H, 8-H), 2.53 2.65 (dd, $^2J_{3b,3a}$ = 15.2 Hz, $^3J_{3b,2}$ = 3.2 Hz, 1 H, 3b-H), 2.19 (s, 3 H, 10-H), 1.48 (s, 9 H, 17-H).

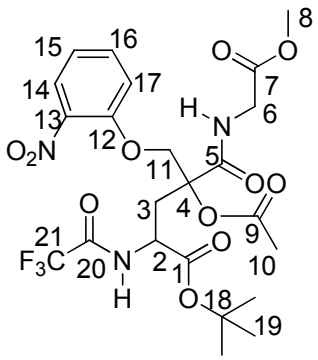
^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 169.5, 169.1, 168.4, 129.5, 83.4, 83.0, 68.3, 48.9, 33.0, 27.8, 21.3.

HRMS (CI):	Calculated	Found
$C_{23}H_{29}F_3N_2O_9$ $[M\text{-}C_4H_9]^+$	477.1121	477.1175

***tert*-Butyl 4-acetoxy-5-(2-methoxy-2-oxoethylamino)-4-((2-nitrophenoxy)methyl)-5-oxo-2-(2,2,2-trifluoroacetamido) pentanoate (15b)**

According to the general procedure **GP-8**, ketone **11m** (113 mg, 0.27 mmol), acetic acid (17.6 mg, 0.29 mmol) and methyl 2-isocyanoacetate (29 mg, 0.29 mmol) reacted to give **15b** after flash chromatography (silica, hexanes/EtOAc 8:2) in 58% yield (97 mg, 0.17 mmol) as white solid with a melting point of 105 °C.

[TLC: Hex/EA 7:3, R_f =0.33]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84–7.88 (m, 1 H, 14-H), 7.78 (d, $^3J_{NHTFA,2}$ = 8.0 Hz, 1 H, N_{TFA}-H), 7.45 (t, $^3J_{NH,6}$ = 5.8 Hz, 1 H, N-H), 7.51–7.55 (m, 1 H, 17-H), 6.99–7.09 (m, 2

H, 15-H, 16-H), 4.93 (d, $^{2}J_{11a,11b}$ = 9.3 Hz, 1 H, 11a-H), 4.57–4.73 (m, 1 H, 2-H), 4.53 (d, $^{2}J_{11b,11a}$ = 9.3 Hz, 1 H, 11b-H), 4.28 (dd, $^{2}J_{6a,6b}$ = 17.9 Hz, $^{3}J_{6a,NH}$ = 6.7 Hz, 1 H, 6a-H), 3.29 (dd, $^{2}J_{6b,6a}$ = 17.9 Hz, $^{3}J_{6b,NH}$ = 5.1 Hz, 1 H, 6b-H), 3.76 (s, 3 H, 8-H), 2.65 (dd, $^{2}J_{3a,3b}$ = 14.7 Hz, $^{3}J_{3a,2}$ = 11.0 Hz, 1 H, 3a-H), 2.55 (dd, $^{2}J_{3b,3a}$ = 15.0 Hz, $^{3}J_{3b,2}$ = 3.5 Hz, 1 H, 3b-H), 2.10 (s, 3 H, 10-H), 1.45 (s, 9 H, 19-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2, 169.6, 169.4, 168.3, 151.0, 139.5, 134.5, 125.9, 121.3, 117.0, 114.6, 83.4, 82.6, 69.4, 52.5, 50.2, 48.8, 41.3, 33.2, 27.7, 21.3.

Minor diastereomer (selected signals)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (t, $^{3}J_{NH,6}$ = 5.4 Hz, 1 H, N-H), 6.99-7.09 (m, 2 H, 15-H, 16-H), 5.08 (d, $^{2}J_{11a,11b}$ = 9.3 Hz, 1 H, 11a-H), 4.50–4.56 (m, 1 H, 2-H), 4.36 (d, $^{2}J_{11b,11a}$ = 9.3 Hz, 1 H, 11b-H), 4.01–4.03 (m, 2 H, 6-H), 3.72 (s, 3 H, 8-H), 2.96-3.02 (m, 2 H, 3-H), 2.23 (s, 3 H, 10-H), 1.45 (s, 9 H, 19-H).

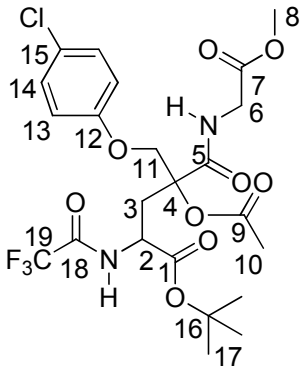
^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7, 169.5, 169.3, 168.2, 151.1, 139.4, 125.6, 121.3, 114.4, 82.4, 69.5, 52.4, 41.2, 32.5, 21.5.

HRMS (CI):	Calculated	Found
$C_{23}H_{28}F_3N_3O_{11}$ $[M+1]^+$	580.1709	580.1798

***tert*-Butyl 4-acetoxy-4-((4-chlorophenoxy)methyl)-5-(2-methoxy-2-oxoethylamino)-5-oxo-2-(2,2,2-trifluoroacetamido)pentanoate (15c)**

According to the general procedure **GP-8**, ketone **11k** (111 mg, 0.27 mmol), acetic acid (17.6 mg, 0.29 mmol) and methyl 2-isocyanoacetate (29 mg, 0.29 mmol) reacted to give **15c** after flash chromatography (silica, hexanes/EtOAc 8:2) in 65% yield (107 mg, 0.19 mmol) as white solid with a melting point of 102 °C.

[TLC: Hex/EA 7:3, R_f =0.33]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (d, $^{3}J_{NHTFA,2}$ = 8.2 Hz, 1 H, N_{TFA}-H), 7.41 (t, $^{3}J_{NH,6}$ = 5.5 Hz, 1 H, N-H), 7.20–7.23 (m, 2 H, 14-H), 6.79–6.83 (m, 2 H, 13-H), 4.83 (d, $^{2}J_{11a,11b}$

= 9.8 Hz, 1 H, 11a-H), 4.50–4.53 (m, 1 H, 2-H), 4.41 (d, $^{2}J_{11b,11a}$ = 9.8 Hz, 1 H, 11b-H), 4.10–4.28 (m, 2 H, 6-H), 3.77 (s, 3 H, 8-H), 2.84 (dd, $^{2}J_{3a,3b}$ = 15.0 Hz, $^{3}J_{3a,2}$ = 10.0 Hz, 1 H, 3a-H), 2.60 (dd, $^{2}J_{3b,3a}$ = 14.7 Hz, $^{3}J_{3b,2}$ = 11.0 Hz, 1 H, 3b-H), 2.18 (s, 3 H, 10-H), 1.46 (s, 9 H, 17-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 169.5, 169.1, 168.5, 156.4, 129.5, 129.4, 126.7, 116.2, 116.0, 83.6, 83.1, 68.9, 52.5, 50.0, 41.2, 34.1, 27.8, 21.6.

Minor diastereomer (selected signals)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.23 (m, 3 H, 14-H, N-H), 6.93 (d, $^{3}J_{NHTFA,2}$ = 9.0 Hz, 1 H, N_{TFA}-H), 6.80–6.83 (m, 2 H, 13-H), 4.66 (d, $^{2}J_{11a,11b}$ = 9.8 Hz, 1 H, 11a-H), 4.66–4.72 (m, 1 H, 2-H), 4.17 (d, $^{2}J_{11b,11a}$ = 9.8 Hz, 1 H, 11b-H), 3.87–4.00 (m, 2 H, 6-H), 3.77 (s, 3 H, 8-H), 2.97 (dd, $^{2}J_{3a,3b}$ = 14.7 Hz, $^{3}J_{3a,2}$ = 3.3 Hz, 1 H, 3a-H), 2.50 (dd, $^{2}J_{3b,3a}$ = 15.0 Hz, $^{3}J_{3b,2}$ = 3.2 Hz, 1 H, 3b-H), 2.06 (s, 3 H, 10-H), 1.45 (s, 9 H, 17-H).

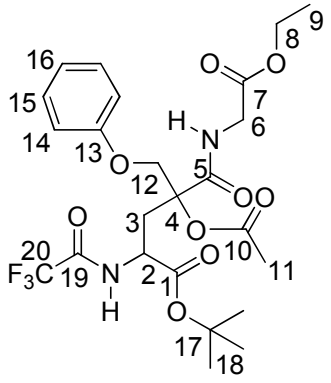
^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0, 169.5, 168.4, 129.4, 116.2, 83.5, 83.1, 68.6, 48.8, 41.1, 32.9, 27.8, 21.3.

HRMS (CI):	Calculated	Found
$C_{23}H_{28}ClF_3N_2O_9$ $[M+1]^+$	570.1406	570.1473

***tert*-Butyl 4-acetoxy-5-(2-ethoxy-2-oxoethylamino)-5-oxo-4-(phenoxymethyl)-2-(2,2,2-trifluoroacetamido)pentanoate (15d)**

According to the general procedure **GP-8**, ketone **11f** (101 mg, 0.27 mmol), acetic acid (17.6 mg, 0.29 mmol) and ethyl 2-isocyanoacetate (33 mg, 0.29 mmol) reacted to give **15d** after flash chromatography (silica, hexanes/EtOAc 8:2) in 58% yield (91 mg, 0.17 mmol) as white solid with a melting point of 109 °C.

[TLC: Hex/EA 7:3, R_f = 0.32]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, $^{3}J_{NHTFA,2}$ = 8.0 Hz, 1 H, N_{TFA}-H), 7.39 (t, $^{3}J_{NH,6}$ = 5.4 Hz, 1 H, N-H), 7.24–7.28 (m, 3 H, 15-H, 16-H), 6.95–6.99 (m, 2 H, 14-H), 4.86 (d, $^{2}J_{11a,11b}$ = 9.9 Hz, 1 H, 11a-H), 4.51–4.57 (m, 1 H, 2-H), 4.40 (d, $^{2}J_{11b,11a}$ = 9.8 Hz, 1 H,

11b-H), 4.18–4.26 (m, 4 H, 6-H, 8-H), 2.92 (dd, $^{2}J_{3a,3b}$ = 14.5 Hz, $^{3}J_{3a,2}$ = 9.1 Hz, 1 H, 3a-H), 2.63 (dd, $^{2}J_{3b,3a}$ = 14.7 Hz, $^{3}J_{3b,2}$ = 11.0 Hz, 1 H, 3b-H), 2.16 (s, 3 H, 11-H), 1.46 (s, 9 H, 18-H), 1.28 (t, $^{3}J_{9,8}$ = 7.2 Hz, 3 H, 9-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0, 169.6, 169.1, 168.5, 157.7, 156.7, 129.5, 126.2, 121.8, 115.0, 83.4, 83.1, 68.5, 61.7, 50.1, 41.4, 34.1, 27.8, 21.5, 14.0.

Minor diastereomer (selected signals)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.28 (m, 3 H, 15-H, N_{TFA}-H), 6.96–6.99 (m, 2 H, 16-H, N-H), 4.71 (d, $^{2}J_{11a,11b}$ = 9.8 Hz, 1 H, 11a-H), 4.64–4.69 (m, 1 H, 2-H), 3.89–4.12 (m, 4 H, 6-H, 8-H), 2.97 (dd, $^{2}J_{3a,3b}$ = 13.7 Hz, $^{3}J_{3a,2}$ = 2.5 Hz, 1 H, 3a-H), 2.06 (s, 3 H, 11-H), 1.28 (t, $^{3}J_{9,8}$ = 7.2 Hz, 3 H, 9-H).

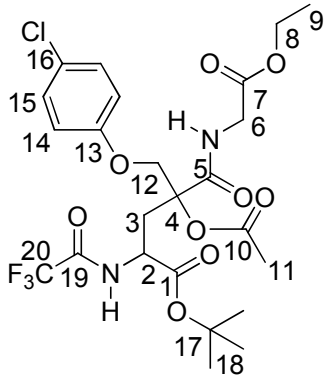
^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7, 169.1, 168.5, 129.5, 114.9, 83.4, 83.0, 68.0, 49.9, 33.0, 21.3.

HRMS (CI):	Calculated	Found
$C_{24}H_{31}F_3N_2O_9$ $[M+1]^+$	549.2015	549.2045

***tert*-Butyl 4-acetoxy-4-((4-chlorophenoxy)methyl)-5-(2-ethoxy-2-oxoethylamino)-5-oxo-2-(2,2,2-trifluoroacetamido) pentanoate (15e)**

According to the general procedure **GP-8**, ketone **11k** (111 mg, 0.27 mmol), acetic acid (17.6 mg, 0.29 mmol) and ethyl 2-isocyanoacetate (33 mg, 0.29 mmol) reacted to give **15e** after flash chromatography (silica, hexanes/EtOAc 8:2) in 64% yield (108 mg, 0.19 mmol) as white solid with a melting point of 107 °C.

[TLC: Hex/EA 7:3, R_f = 0.33]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, $^{3}J_{NHTFA,2}$ = 8.0 Hz, 1 H, N_{TFA}-H), 7.38 (t, $^{3}J_{NH,6}$ = 5.5 Hz, 1 H, N-H), 7.18–7.23 (m, 2 H, 15-H), 6.78–6.82 (m, 2 H, 14-H), 4.83 (d, $^{2}J_{11a,11b}$ = 9.9 Hz, 1 H, 11a-H), 4.50–4.55 (m, 1 H, 2-H), 4.40 (d, $^{2}J_{11b,11a}$ = 9.8 Hz, 1 H, 11b-H), 4.16–4.26 (m, 4 H, 6-H, 8-H), 2.90 (dd, $^{2}J_{3a,3b}$ = 15.0 Hz, $^{3}J_{3a,2}$ = 10.0 Hz, 1 H, 3a-H),

2.60 (dd, $^{2}J_{3b,3a}$ = 14.7 Hz, $^{3}J_{3b,2}$ = 11.2 Hz, 1 H, 3b-H), 2.18 (s, 3 H, 11-H), 1.45 (s, 9 H, 18-H), 1.28 (t, $^{3}J_{9,8}$ = 7.2 Hz, 3 H, 9-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 169.5, 169.1, 168.5, 156.7, 156.4, 129.4, 126.7, 116.3, 115.5, 83.5, 83.1, 68.9, 61.8, 50.1, 41.3, 33.9, 27.8, 21.6, 14.0.

Minor diastereomer (selected signals)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.23 (m, 3 H, N-H, 15-H), 7.02 (d, $^{3}J_{NHTFA,2}$ = 8.9 Hz, 1 H, N_{TFA}-H), 6.79–6.83 (m, 2 H, 14-H), 4.67 (d, $^{2}J_{11a,11b}$ = 9.8 Hz, 1 H, 11a-H), 4.64–4.67 (m, 1 H, 2-H), 2.97 (dd, $^{2}J_{3a,3b}$ = 14.7 Hz, $^{3}J_{3a,2}$ = 3.3 Hz, 1 H, 3a-H), 2.50 (dd, $^{2}J_{3b,3a}$ = 15.0 Hz, $^{3}J_{3b,2}$ = 3.3 Hz, 1 H, 3b-H), 2.06 (s, 3 H, 11-H), 1.45 (s, 9 H, 18-H), 1.28 (t, $^{3}J_{9,8}$ = 7.2 Hz, 3 H, 9-H).

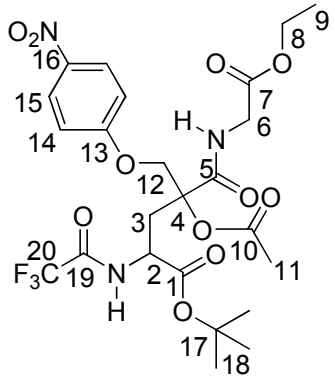
^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7, 169.1, 169.1, 168.4, 116.3, 83.4, 83.1, 68.6, 48.8, 41.3, 32.8, 21.3.

HRMS (CI):	Calculated	Found
$C_{24}H_{30}ClF_3N_2O_9$ $[M]^+$	582.1592	582.1563

***tert*-Butyl 4-acetoxy-5-(2-ethoxy-2-oxoethylamino)-4-((4-nitrophenoxy)methyl)-5-oxo-2-(2,2,2-trifluoroacetamido) pentanoate (15f)**

According to the general procedure **GP-8**, ketone **11l** (111 mg, 0.27 mmol), acetic acid (17.6 mg, 0.29 mmol) and ethyl 2-isocyanoacetate (33 mg, 0.29 mmol) reacted to give **15f** after flash chromatography (silica, hexanes/EtOAc 8:2) in 59% yield (108 mg, 0.19 mmol) as white solid with a melting point of 108 °C.

[TLC: Hex/EA 7:3, R_f = 0.34]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, $^{3}J_{NHTFA,2}$ = 8.0 Hz, 1 H, N_{TFA}-H), 7.39 (t, $^{3}J_{NH,6}$ = 5.4 Hz, 1 H, N-H), 7.18–7.23 (m, 2 H, 15-H), 6.78–6.82 (m, 2 H, 14-H), 4.83 (d, $^{2}J_{11a,11b}$ = 9.9 Hz, 1 H, 11a-H), 4.50–4.55 (m, 1 H, 2-H), 4.40 (d, $^{2}J_{11b,11a}$ = 9.8 Hz, 1 H, 11b-H), 4.16–4.26 (m, 4 H, 6-H, 8-H), 2.90 (dd, $^{2}J_{3a,3b}$ = 15.0 Hz, $^{3}J_{3a,2}$ = 10.0 Hz, 1 H, 3a-H),

2.60 (dd, $^{2}J_{3b,3a}$ = 14.7 Hz, $^{3}J_{3b,2}$ = 11.2 Hz, 1 H, 3b-H), 2.18 (s, 3 H, 11-H), 1.45 (s, 9 H, 18-H), 1.28 (t, $^{3}J_{9,8}$ = 7.2 Hz, 3 H, 9-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 169.5, 169.1, 168.5, 156.7, 156.4, 129.4, 126.7, 116.3, 115.5, 83.5, 83.1, 68.9, 61.8, 50.1, 41.3, 33.9, 27.8, 21.6, 14.0.

Minor diastereomer (selected signals)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02 (d, $^{3}J_{NHTFA,2}$ = 8.9 Hz, 1 H, N_{TFA}-H), 6.79–6.83 (m, 2 H, 14-H), 4.67 (d, $^{2}J_{11a,11b}$ = 9.8 Hz, 1 H, 11a-H), 4.64–4.67 (m, 1 H, 2-H), 2.97 (dd, $^{2}J_{3a,3b}$ = 14.7 Hz, $^{3}J_{3a,2}$ = 3.3 Hz, 1 H, 3a-H), 2.50 (dd, $^{2}J_{3b,3a}$ = 15.0 Hz, $^{3}J_{3b,2}$ = 3.3 Hz, 1 H, 3b-H), 2.06 (s, 3 H, 11-H), 1.45 (s, 9 H, 18-H), 1.28 (t, $^{3}J_{9,8}$ = 7.2 Hz, 3 H, 9-H).

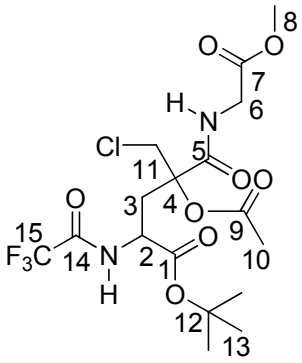
^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7, 169.1, 169.1, 168.4, 116.3, 83.4, 83.1, 68.6, 48.8, 41.3, 32.8, 21.3.

HRMS (CI):	Calculated	Found
$C_{24}H_{30}F_3N_3O_{11}$ $[M+1]^+$	594.1866	594.1933

***tert*-Butyl 4-acetoxy-4-(chloromethyl)-5-(2-methoxy-2-oxoethylamino)-5-oxo-2-(2,2,2-trifluoroacetamido)pentanoate (15h)**

According to the general procedure **GP-8**, ketone **11d** (86 mg, 0.27 mmol), acetic acid (17.6 mg, 0.29 mmol) and ethyl 2-isocyanoacetate (33 mg, 0.29 mmol) reacted to give **15h** after flash chromatography (silica, hexanes/EtOAc 8:2) in 59% yield (84 mg, 0.18 mmol) as white solid with a melting point of 93 °C.

[TLC: Hex/EA 7:3, R_f = 0.34]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, $^{3}J_{NHTFA,2}$ = 8.2 Hz, 1 H, N_{TFA}-H), 7.40 (t, $^{3}J_{NH,6}$ = 5.5 Hz, 1 H, N-H), 4.64–4.69 (m, 1 H, 2-H), 4.44 (d, $^{2}J_{11a,11b}$ = 11.6 Hz, 1 H, 11a-H), 4.31 (d, $^{2}J_{11b,11a}$ = 9.8 Hz, 1 H, 11b-H), 4.08 (dd, $^{2}J_{6a,6b}$ = 18.3 Hz, $^{3}J_{6a,2}$ = 5.27 Hz, 1 H, 6a-H), 3.92–3.98 (m, 1 H, 6b-H), 3.78 (s, 3 H, 8-H), 2.90 (dd, $^{2}J_{3a,3b}$ = 15.0 Hz, $^{3}J_{3a,2}$ = 10.4 Hz, 1 H, 3a-H), 2.53 (dd, $^{2}J_{3b,3a}$ = 14.7 Hz, $^{3}J_{3b,2}$ = 11.1 Hz, 1 H, 3b-H), 2.27 (s, 3 H, 10-H), 1.44 (s, 9 H, 13-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 169.3, 168.8, 168.3, 157.0, 117.1, 83.9, 83.6, 52.6, 50.2, 45.7, 41.2, 34.8, 27.7, 21.6.

Minor diastereomer (selected signals)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (t, $^{3}J_{NH,6}$ = 4.8 Hz, 1 H, N-H), 6.91 (d, $^{3}J_{NHTFA,2}$ = 8.7 Hz, 1 H, N_{TFA}-H), 4.44–4.50 (m, 1 H, 2-H), 4.16 (d, $^{2}J_{11a,11b}$ = 11.7 Hz, 1 H, 11a-H), 3.89–3.98 (m, 2 H, 6-H), 3.78 (s, 3 H, 8-H), 3.01 (dd, $^{2}J_{3a,3b}$ = 14.7 Hz, $^{3}J_{3a,2}$ = 3.3 Hz, 1 H, 3a-H), 2.43 (dd, $^{2}J_{3b,3a}$ = 15.0 Hz, $^{3}J_{3b,2}$ = 3.1 Hz, 1 H, 3b-H), 1.44 (s, 9 H, 13-H)

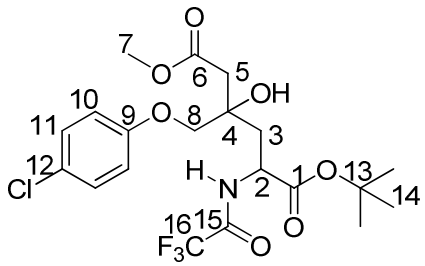
^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4, 168.9, 168.8, 168.1, 83.8, 83.5, 49.1, 34.3, 21.3.

HRMS (CI):	Calculated	Found
$C_{17}H_{24}ClF_3N_2O_8$ $[M+1]^+$	477.1252	477.1209

1-*tert*-Butyl 6-methyl 4-((4-chlorophenoxy)methyl)-4-hydroxy-2-(2,2,2-trifluoro-acetamido) hexanedioate (17a)

According to the general procedure for Reformatsky reaction **GP-9**, ketone **11k** (61 mg, 0.15 mmol) and 1.6 M solution of Zn-bromo-ester (48 mg, 0.22 mmol) reacted to give **17a** after flash chromatography (silica, hexanes/EtOAc 8:2) in 90% yield (65 mg, 0.14 mmol) as white solid with a melting point of 70 °C.

[TLC: DCM/Hex 95:5, R_f = 0.25]



Major diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, $^{3}J_{NH,2}$ = 5.8 Hz, 1 H, N-H), 7.22–7.25 (m, 2 H, 14-H), 6.78–6.82 (m, 2 H, 15-H), 4.50 (ddd, $^{3}J_{2,3b}$ = 8.6 Hz, $^{3}J_{2,3a}$ = 6.4 Hz, $^{3}J_{2,NH}$ = 4.4 Hz, 1 H, 2-H), 3.92 (d, $^{2}J_{8a,8b}$ = 9.2 Hz, 1 H, 8a-H), 3.88 (d, $^{2}J_{8b,8a}$ = 9.2 Hz, 1 H, 8b-H), 3.70 (s, 3 H, 7-H), 2.80 (d, $^{2}J_{5a,5b}$ = 16.2 Hz, 1 H, 5a-H), 2.67 (d, $^{2}J_{5b,5a}$ = 9.2 Hz, 1 H, 5b-H), 2.25–2.29 (m, 1 H, 3a-H), 2.17 (dd, $^{2}J_{3b,3a}$ = 14.9 Hz, $^{3}J_{3b,2}$ = 8.6 Hz, 1 H, 3b-H), 1.44 (s, 9 H, 14-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.5, 169.1, 157.2 (q, *J* = 38.8 Hz), 156.5, 129.4, 126.6, 115.8, 115.5 (q, *J* = 285.8 Hz), 83.1, 72.5, 72.4, 52.1, 50.9, 39.4, 37.2, 27.7.

Minor diastereomer (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, $^3J_{NH,2}$ = 5.8 Hz, 1 H, N-H), 4.50 (ddd, $^3J_{2,3b}$ = 8.6 Hz, $^3J_{2,3a}$ = 6.4 Hz, $^3J_{2,NH}$ = 4.4 Hz, 1 H, 2-H), 3.92 (d, $^2J_{8a,8b}$ = 9.2 Hz, 1 H, 8a-H), 3.88 (d, $^2J_{8b,8a}$ = 9.2 Hz, 1 H, 8b-H), 3.70 (s, 3 H, 7-H), 2.80 (d, $^2J_{5a,5b}$ = 16.2 Hz, 1 H, 5a-H), 2.67 (d, $^2J_{5b,5a}$ = 9.2 Hz, 1 H, 5b-H), 2.25–2.29 (m, 1 H, 3a-H), 2.17 (dd, $^2J_{3b,3a}$ = 14.9 Hz, $^3J_{3b,2}$ = 8.6 Hz, 1 H, 3b-H), 1.44 (s, 9 H, 14-H).

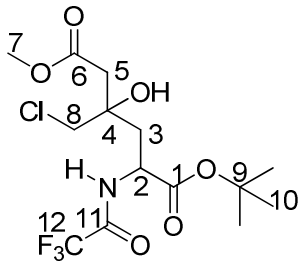
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.5, 169.1, 129.4, 126.6, 115.8, 83.1, 72.5, 72.4, 52.1, 50.9, 39.4, 37.2, 27.7.

HRMS (CI):	Calculated	Found
$C_{20}H_{25}ClF_3NO_7$ $[M+1]^+$	485.1242	485.1234

***tert*-Butyl 6-methyl 4-(chloromethyl)-4-hydroxy-2-(2,2,2-trifluoroacetamido) hexanedioate**

According to the general procedure for Reformatsky reaction **GP-9**, ketone **11d** (61 mg, 0.15 mmol) and 1.6 M solution of Zn-bromo-ester (48 mg, 0.22 mmol) reacted to give **17b** after flash chromatography (silica, hexanes/EtOAc 8:2) in 90% yield (65 mg, 0.14 mmol) as white solid with a melting point of 63 °C.

[TLC: DCM/Hex 95:5, R_f = 0.46]



Major diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, $^3J_{NH,2}$ = 6.0 Hz, 1 H, N-H), 4.69 (dt, $^3J_{2,3}$ = 8.6 Hz, $^3J_{2,NH}$ = 4.1 Hz, 1 H, 2-H), 3.92 (d, $^2J_{8a,8b}$ = 15.3 Hz, 1 H, 8a-H), 3.88 (d, $^2J_{8b,8a}$ = 15.3 Hz, 1 H, 8b-H), 3.70 (s, 3 H, 7-H), 2.80 (d, $^2J_{5a,5b}$ = 16.2 Hz, 1 H, 5a-H), 2.67 (d, $^2J_{5b,5a}$ = 9.2 Hz, 1 H, 5b-H), 2.25–2.29 (m, 1 H, 3a-H), 2.17 (dd, $^2J_{3b,3a}$ = 14.9 Hz, $^3J_{3b,2}$ = 8.6 Hz, 1 H, 3b-H), 1.44 (s, 9 H, 14-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.5, 169.1, 157.2 (q, *J* = 38.8 Hz), 115.5 (q, *J* = 285.8 Hz), 83.1, 72.5, 72.4, 52.1, 50.9, 39.4, 37.2, 27.7.

Minor diastereomer (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.92 (d, $^2J_{8a,8b}$ = 15.3 Hz, 1 H, 8a-H), 3.88 (d, $^2J_{8b,8a}$ = 15.3 Hz, 1 H, 8b-H), 3.70 (s, 3 H, 7-H), 2.80 (d, $^2J_{5a,5b}$ = 16.2 Hz, 1 H, 5a-H), 2.67 (d,

$^{2}J_{5b,5a}$ = 9.2 Hz, 1 H, 5b-H), 2.25–2.29 (m, 1 H, 3a-H), 2.17 (dd, $^{2}J_{3b,3a}$ = 14.9 Hz, $^{3}J_{3b,2}$ = 8.6 Hz, 1 H, 3b-H), 1.44 (s, 9 H, 14-H).

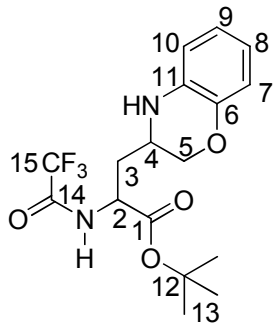
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.5, 169.1, 15783.1, 72.5, 72.4, 52.1, 50.9, 39.4, 37.2, 27.7.

HRMS (CI):	Calculated	Found
$C_{14}H_{21}ClF_3NO_6$ $[M+1]^+$	392.1088	392.1071

***tert*-Butyl 3-(3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)-2-(2,2,2-trifluoroacet-amido) propanoate (19a)**

To a solution of ketone **11m** (50 mg, 0.12 mmol) in methanol (15 ml) was added 5% Pd-C (12.5 mg) and the solution was allowed to stir under H_2 pressure (4 bar). After stirring for 6 h the solution was filtered over celite and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica, hexanes/EtOAc 8:2) to yield **19a** in 100% yield (45 mg, 0.12 mmol) as a colorless solid with a melting point of 64 °C.

[TLC: Hex/EA 7:3, R_f = 0.46]



Major diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, $^{3}J_{NHTFA,2}$ = 7.3 Hz, 1 H, N_{TFA}-H), 6.79–6.84 (m, 2 H, 7-H, 10-H), 6.65–6.69 (m, 2 H, 8-H, 9-H), 4.69 (ddd, $^{3}J_{2,3a}$ = 10.4 Hz, $^{3}J_{2,3b}$ = 8.0 Hz, $^{3}J_{2,NHTFA}$ = 3.5 Hz, 1 H, 2-H), 4.07 (dd, $^{2}J_{5a,5b}$ = 10.7 Hz, $^{3}J_{5a,4}$ = 2.8 Hz, 1 H, 5a-H), 3.98 (dd, $^{2}J_{5b,5a}$ = 10.7 Hz, $^{3}J_{5b,4}$ = 4.1 Hz, 1 H, 5b-H), 3.40–3.45 (m, 1 H, 4-H), 2.19 (ddd, $^{2}J_{3a,3b}$ = 14.3 Hz, $^{3}J_{3a,2}$ = 10.9 Hz, $^{3}J_{3a,4}$ = 3.5 Hz, 1 H, 3a-H), 2.19 (ddd, $^{2}J_{3a,3b}$ = 14.0 Hz, $^{3}J_{3b,2}$ = 10.3 Hz, $^{3}J_{3b,4}$ = 3.0 Hz, 1 H, 3b-H), 1.48 (s, 9 H, 13-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.0, 157.2 (q, *J* = 38.8 Hz), 143.5, 132.0, 122.0, 118.8, 116.7, 116.1, 115.5 (q, *J* = 285.8 Hz), 84.1, 68.2, 50.7, 46.7, 35.7, 27.9.

Minor diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.12 (d, $^3J_{NHTFA,2}$ = 6.3 Hz, 1 H, N_{TFA}-H), 6.76–6.82 (m, 2 H, 7-H, 10-H), 6.57–6.70 (m, 2 H, 8-H, 9-H), 4.69 (ddd, $^3J_{2,3a}$ = $^3J_{2,3b}$ = $^3J_{2,NHTFA}$ = 6.4 Hz, 1 H, 2-H), 4.09 (dd, $^3J_{5a,5b}$ = 10.7 Hz, $^3J_{5a,4}$ = 2.7 Hz, 1 H, 5a-H), 4.00 (dd, $^3J_{5b,5a}$ = 10.7 Hz, $^3J_{5b,4}$ = 4.9 Hz, 1 H, 5b-H), 3.55–3.60 (m, 1 H, 4-H), 2.13 (ddd, $^2J_{3a,3b}$ = 14.3 Hz, $^3J_{3a,2}$ = 6.1 Hz, $^3J_{3a,4}$ = 4.7 Hz, 1 H, 3a-H), 1.97–2.04 (m, 1 H, 3b-H), 1.45 (s, 9 H, 13-H).

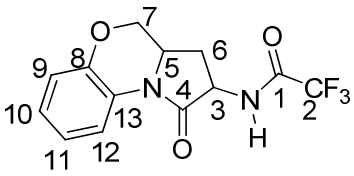
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.7, 143.5, 131.8, 121.8, 119.1, 116.8, 116.1, 84.1, 68.0, 51.3, 47.4, 34.7, 27.8.

HRMS (CI):	Calculated	Found
$C_{17}H_{21}F_3N_2O_4$ $[M]^+$	374.1453	374.1479

2,2,2-Trifluoro-N-(1-oxo-2,3,3a,4-tetrahydro-1H-benzo[b]pyrrolo[1,2-d][1,4]oxazin-2-yl) acetamide (19b)

A solution of **19a** (50 mg, 0.13 mmol) in dry toluene (2.2 ml) and DMAP (8 mg, 50 mol%) was refluxed for 4 h under nitrogen before it was cooled to r.t and diluted with DCM. The mixture was washed with 1N HCl, water and brine. The organic layer was dried over Na_2SO_4, removed in vacuo and purified by column chromatography (silica, hexanes/EtOAc 8:2) to yield **19b** in 20% yield (8.0 mg, 0.12 mmol) as a colorless solid with a melting point of 58 °C.

[TLC: Hex/EA 7:3, R_f = 0.50]



Major diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.37 (dd, $^3J_{10,9}$ = 8.2 Hz, $^3J_{10,11}$ = 1.5 Hz, 1 H, 10-H), 7.32 (bs, 1 H, N-$_{TFA}$H), 6.94–7.11 (m, 3 H, 9-H, 11-H, 12-H), 4.66 (ddd, $^3J_{3,6a}$ = 11.4 Hz, $^3J_{3,6b}$ = 8.0 Hz, $^3J_{3,NHTFA}$ = 5.4 Hz, 1 H, 3-H), 4.45 (dd, $^2J_{7a,7b}$ = 11.0 Hz, $^3J_{7a,5}$ = 3.2 Hz, 1 H, 7a-H), 3.90–4.03 (m, 1 H, 5-H), 3.54 (dd, $^2J_{7b,7a}$ = $^3J_{7b,5}$ = 10.5 Hz, 1 H, 7b-H), 3.04 (ddd, $^2J_{6a,6b}$ = 12.4 Hz, $^3J_{6a,3}$ = 8.0 Hz, $^3J_{6a,5}$ = 5.8 Hz, 1 H, 6a-H), 1.53–1.61 (m, 1 H, 6b-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 167.6, 157.2 (q, *J* = 38.8 Hz), 144.8, 125.8, 123.5, 121.7, 119.1, 117.3, 115.5 (q, *J* = 285.8 Hz), 68.6, 51.2, 50.7, 29.9.

Minor diastereomer (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.93–7.09 (m, 3 H, 9-H, 11-H, 12-H), 4.66 (ddd, $^3J_{3,6a}$ = 11.3 Hz, $^3J_{3,6b}$ = 7.9 Hz, $^3J_{3,NHTFA}$ = 4.4 Hz, 1 H, 3-H), 4.45 (dd, $^2J_{7a,7b}$ = 10.9 Hz, $^3J_{7a,5}$ = 3.6 Hz, 1 H, 7a-H), 3.90-4.03 (m, 1 H, 5-H).

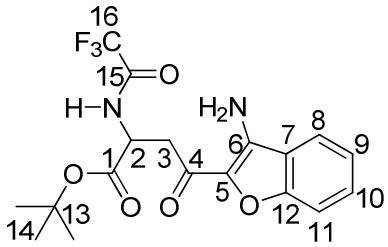
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 167.6, 125.8, 123.5, 121.7, 119.1, 117.3, 68.6, 51.2, 50.7, 29.9.

HRMS (CI):	Calculated	Found
$C_{13}H_{11}F_3N_2O_3$ $[M]^+$	300.0722	300.0727

***tert*-Butyl 4-(3-aminobenzofuran-2-yl)-4-oxo-2-(2,2,2-trifluoroacetamido) butanoate (20)**

Ketone **11n** (90 mg, 0.22 mmol) was refluxed in dry triethylamine (2.5 ml) under nitrogen. After the reaction was complete, triethylamine was removed in vacuo and the crude product was purified by column chromatography (silica, hexanes/EtOAc 8:2) to yield **20** in 100% yield (90 mg, 0.22 mmol) as colorless oil.

[TLC: Hex/EA 7:3, R_f = 0.28]



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, $^3J_{NHTFA,2}$ = 7.8 Hz, 1 H, N_{TFA}-H), 7.50–7.59 (m, 2 H, 8-H, 11-H), 7.39–7.41 (m, 1 H, 9-H), 7.23–7.27 (m, 1 H, 10-H), 5.69 (bs, 2 H, N-H), 4.85 (td, $^3J_{2,3}$ = 8.3 Hz, $^3J_{2,NHTFA}$ = 4.2 Hz, 1 H, 2-H), 3.68 (dd, $^2J_{3a,3b}$ = 17.6 Hz, $^3J_{3a,2}$ = 4.3 Hz, 1 H, 3a-H), 3.68 (dd, $^2J_{3b,3a}$ = 17.6 Hz, $^3J_{3b,2}$ = 4.3 Hz, 1 H, 3b-H), 1.49 (s, 9 H, 13-H).

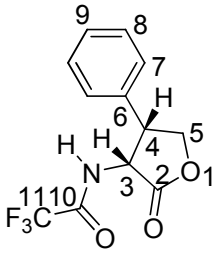
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 187.4, 168.6, 157.2 (q, *J* = 38.8 Hz), 154.4, 140.0, 134.2, 130.2, 122.5, 120.7, 120.3, 115.5 (q, *J* = 285.8 Hz), 112.7, 83.0, 49.3, 38.6, 27.7.

HRMS (CI):	Calculated	Found
$C_{18}H_{19}F_3N_2O_5[M]^+$:	400.1246	400.1269

2,2,2-Trifluoro-N-((3*R*,4*S*)-2-oxo-4-phenyltetrahydrofuran-3-yl) acetamide (24)

To a solution of **3a** (100 mg, 0.29 mmol) in dichloromethane was added *p*-toluenesulfonic acid (25 mg, 0.15 mmol) at room temperature and allowed to stir over night. After the reaction was complete, the solvent was removed in vacuo and crude product was purified by chromatography to give lactone **24** after flash chromatography (silica, hexanes/EtOAc 8:2) in 98% yield (78 mg, 0.28 mmol) as a colorless solid with a melting point of 45 °C.

[TLC: DCM/Hex 95:5, R_f = 0.48]



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.39 (m, 3 H, 8-H, 9-H), 7.09–7.13 (m, 2 H, 7-H), 6.25 (bs, 1 H, N-H), 5.00 (dd, $^3J_{3,NH}$ = 8.1 Hz, $^3J_{3,4}$ = 6.7 Hz, 1 H, 3-H), 4.80 (dd, $^2J_{5a,5b}$ = 9.9 Hz, $^3J_{5a,4}$ = 5.0 Hz, 1 H, 5a-H), 4.76 (dd, $^2J_{5b,5a}$ = 9.9 Hz, $^3J_{5b,4}$ = 1.2 Hz, 1 H, 5b-H), 4.14 (dd, $^2J_{4,5}$ = 8.2 Hz, $^2J_{4,3}$ = 7.4 Hz, 1 H, 4-H).

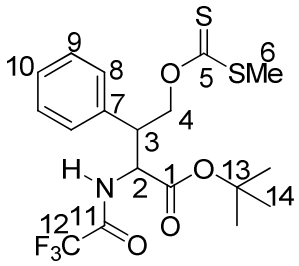
^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7, 157.3 (q, *J* = 38.2 Hz), 134.9, 129.4, 128.6, 127.1, 116.6 (q, *J* = 285.4 Hz), 71.9, 53.6, 44.2.

HRMS (CI):	Calculated	Found
$C_{12}H_{10}F_3NO_3$ $[M+1]^+$:	274.0646	274.0651

***tert*-Butyl 4-(methylthiocarbonothioyloxy)-3-phenyl-2-(2,2,2-trifluoroacetamido) butanoate (25)**

To a solution of **3a** (100 mg, 0.28 mmol) in THF (30 ml) was added KO*t*Bu (32.3 mg, 0.28 mmol) at 0 °C. The mixture was stirred for 2 h, followed by the addition of CS_2 (33 mg, 0.43 mmol), and the reaction mixture was stirred for another 1.5 h before MeI (123 mg, 0.86 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. Then ether was added, followed by ice-water. The aqueous layer was extracted with ether three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent removed in vacuo. The crude product was purified by flash chromatography (silica, hexanes/EtOAc 8:2) to give **25** in 70% yield (88 mg, 0.20 mmol) as a yellow oil.

[TLC: DCM/Hex 95:5, R_f = 0.35]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.36 (m, 3 H, 9-H, 10-H), 7.16–7.19 (m, 2 H, 8-H), 6.89 (d, $^3J_{NH,2}$ = 7.8 Hz, 1 H, N-H), 5.07 (dd, $^2J_{4a,4b}$ = 11.3 Hz, $^3J_{4a,3}$ = 7.4 Hz, 1 H, 4a-H), 4.92 (dd, $^3J_{2,3}$ = $^3J_{2,NH}$ = 6.7 Hz, 1 H, 2-H), 4.90 (dd, $^2J_{4b,4a}$ = 11.2 Hz, $^3J_{4b,3}$ = 6.6 Hz, 1 H, 4b-H), 3.71 (ddd, $^3J_{3,4}$ = $^3J_{3,2}$ = 6.7 Hz, 1 H, 3-H), 2.53 (s, 3 H, 6-H), 1.37 (s, 9 H, 14-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 215.4, 167.8, 156.6 (q, *J* = 37.4 Hz), 135.2, 128.9, 128.7, 128.4, 115.6 (q, *J* = 286.1 Hz), 84.2, 73.1, 54.8, 46.5, 27.8, 19.0.

Minor diastereomer (selected signals)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.88 (d, $^{3}J_{NH,2}$ = 7.9 Hz, 1 H, N-H), 5.16 (dd, $^{3}J_{4a,4b}$ = 8.4 Hz, $^{3}J_{4a,3}$ = 6.8 Hz, 1 H, 4a-H), 4.68 (dd, $^{2}J_{4b,4a}$ = 11.3 Hz, $^{3}J_{4b,3}$ = 6.2 Hz, 1 H, 2-H), 2.47 (s, 3 H, 6-H), 1.19 (s, 3 H, 14-H).

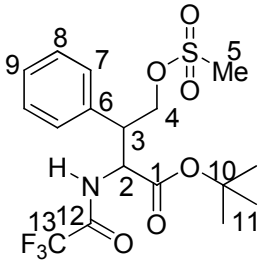
^{13}C NMR (100 MHz, $CDCl_3$): δ = 215.4, 166.7, 137.3, 128.7, 128.6, 127.8, 82.7, 73.9, 52.2, 43.3, 27.5.

HRMS (CI):	Calculated	Found
$C_{18}H_{22}F_3NO_4S_2$ $[M+1]^+$:	438.0976	438.0990

***tert*-Butyl 4-(methylsulfonyloxy)-3-phenyl-2-(2,2,2-trifluoro-acetamido) butanoate (26)**

To a solution of **3a** (60 mg, 0.17 mmol) in dichloromethane (1 ml) at 0 °C triethyl amine (52 mg, 0.51 mmol) was added and the solution was stirred for 30 min. After 30 min, MsCl (24 mg, 0.21 mmol) was added and the solution was allowed to stir for 18 h before it was quenched with water. The aqueous phase was extracted with dichloromethane. The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent removed in vacuo. The crude product was purified by flash chromatography (silica, hexanes/EtOAc 8:2) to give mesylate **26** in 80% yield (59 mg, 0.12 mmol) as a colorless oil.

[TLC: DCM/Hex 95:5, R_f = 0.22]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.36 (m, 3 H, 9-H, 8-H), 7.16–7.18 (m, 2 H, 7-H), 7.01 (d, $^{3}J_{NH,2}$ = 8.0 Hz, 1 H, N-H), 4.91 (dd, $^{3}J_{2,3}$ = $^{3}J_{2,NH}$ = 6.4 Hz, 1 H, 2-H), 4.67 (dd, $^{2}J_{4a,4b}$ = 10.4 Hz, $^{3}J_{4a,3}$ = 7.7 Hz, 1 H), 4.53 (dd, $^{2}J_{4b,4a}$ = 10.4 Hz, $^{3}J_{4b,3}$ = 6.5 Hz, 1 H,), 3.56 (ddd, $^{3}J_{3,4a}$ = $^{3}J_{3,4b}$ = $^{3}J_{3,2}$ = 6.8 Hz, 1 H, 3-H), 2.94 (s, 3 H, 5-H), 1.34 (s, 9 H, 11-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 156.7 (q, *J* = 37.6 Hz), 134.6, 129.0, 128.6, 128.3, 115.5 (q, *J* = 285.9 Hz), 83.4, 68.7, 54.4, 47.2, 37.5, 27.6.

Minor diastereomer (selected signals)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.36 (m, 3 H, 9-H, 8-H), 7.09–7.11 (m, 2 H, 7-H), 6.63 (d, $^3J_{NH,2}$ = 8.4 Hz, 1 H, N-H), 5.00 (dd, $^3J_{2,3}$ = 8.6 Hz, $^3J_{2,NH}$ = 3.3 Hz, 1 H, 2-H), 4.42–4.50 (m, 2 H, 4-H), 3.79 (ddd, $^3J_{3,2}$ = 9.2 Hz, $^3J_{3,4a}$ = 6.2 Hz, $^3J_{3,4b}$ = 3.4 Hz, 1 H), 3.03 (s, 3 H, 5-H), 1.46 (s, 9 H, 11-H).

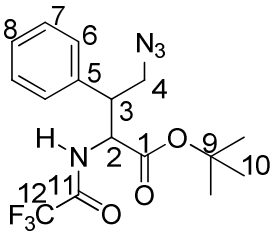
^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 133.6, 129.1, 128.8, 128.2, 84.5, 68.5, 53.3, 47.1, 37.5, 27.9.

HRMS (CI):	Calculated	Found
$C_{17}H_{22}F_3NO_6S$ $[M+1]^+$:	426.1153	426.1170

***tert*-Butyl 4-azido-3-phenyl-2-(2,2,2-trifluoroacetamido) butanoate (27)**

To a solution of **3a** (200 mg, 0.58 mmol) in toluene (4 ml) at 0 °C was added DBU (193 mg, 1.27 mmol) and DPPA (191 mg, 0.69) and the solution was allowed to warm to room temperature over night. The reaction was quenched with NH_4Cl and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent removed in vacuo. The crude product was purified by flash chromatography (silica, hexanes/EtOAc 8:2) to give azide **27** in 60% yield (129 mg, 0.35 mmol) as a colorless oil.

[TLC: DCM/Hex 95:5, R_f = 0.52]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.39 (m, 4 H, N-H, 7-H, 8-H), 7.19–7.21 (m, 2 H, 6-H), 4.47 (dd, $^2J_{4a,4b}$ = 11.1 Hz, $^3J_{4a,2}$ = 4.6 Hz, 1 H, 4a-H), 4.26–4.32 (m, 2 H, 4b-H, 2-H), 3.23–3.27 (m, 1 H, 3-H), 1.25 (s, 9 H, 10-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 156.7 (q, *J* = 37.6 Hz), 136.3, 129.0, 128.1, 127.9, 115.5 (q, *J* = 285.9 Hz), 82.1, 68.9, 60.9, 40.0, 27.6.

Minor diastereomer (selected signals)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.48 (dd, $^2J_{4a,4b}$ = 11.0 Hz, $^3J_{4a,2}$ = 4.7 Hz, 1 H, 4a-H), 4.25–4.31 (m, 2 H, 4b-H, 2-H), 3.22–3.26 (m, 1 H, 3-H), 1.29 (s, 9 H, 10-H).

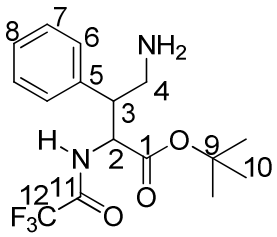
^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.0, 136.3, 129.1, 128.1, 128.0, 82.1, 69.0, 60.9, 40.0, 27.6.

HRMS (CI):	Calculated	Found
$C_{16}H_{19}F_3N_4O_3$ $[M+1]^+$:	373.1443	373.1469

***tert*-Butyl 4-amino-3-phenyl-2-(2,2,2-trifluoroacetamido) butanoate (28)**

To a solution of **3a** (108 mg, 0.29 mmol) in methanol (10 ml) was added acetic acid (17.4 mg, 0.29 mmol) and 5 % palladium on carbon (10 mg) and the solution was hydrogenated at ambient pressure for 1 h. After the reaction was complete, the solution was filtered over celite to remove the catalyst. The solution was diluted with ether and satd. K_2CO_3 solution. The aqueous layer was extracted in ether. The combined organic layers were dried over Na_2SO_4 and the solvent removed in vacuo. The crude product was purified by flash chromatography (silica, hexanes/EtOAc 8:2) to give amine **28** quantitatively (100 mg, 0.29 mmol) as a white solid with a melting point of 70 °C.

[TLC: DCM/Hex 95:5, R_f = 0.20]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.36 (m, 3 H, 8-H, 6-H), 7.16–7.18 (m, 2 H, 7-H), 7.01 (d, $^3J_{NHTFA,2}$ = 8.0 Hz, 1 H, N_{TFA}-H), 5.11 (bs, 2 H, N-H), 4.91 (dd, $^3J_{2,3}$ = $^3J_{2,NHTFA}$ = 6.4 Hz, 1 H, 2-H), 4.67 (dd, $^2J_{4a,4b}$ = 10.4 Hz, $^3J_{4a,3}$ = 7.7 Hz, 1 H), 4.53 (dd, $^2J_{4b,4a}$ = 10.4 Hz, $^3J_{4b,3}$ = 6.5 Hz, 1 H,), 3.56 (ddd, $^3J_{3,4a}$ = $^3J_{3,4b}$ = $^3J_{3,2}$ = 6.8 Hz, 1 H, 3-H), 1.34 (s, 9 H, 11-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 156.7 (q, *J* = 37.6 Hz), 134.6, 129.0, 128.6, 128.3, 115.5 (q, *J* = 285.9 Hz), 83.4, 54.4, 32.2, 37.5, 27.6.

Minor diastereomer (selected signals)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.36 (m, 3 H, 9-H, 8-H), 7.09–7.11 (m, 2 H, 7-H), 6.63 (d, $^3J_{NH,2}$ = 8.4 Hz, 1 H, N-H), 5.00 (dd, $^3J_{2,3}$ = 8.6 Hz, $^3J_{2,NH}$ = 3.3 Hz, 1 H, 2-H), 4.42–4.50 (m, 2 H, 4-H), 3.79 (ddd, $^3J_{3,2}$ = 9.2 Hz, $^3J_{3,4a}$ = 6.2 Hz, $^3J_{3,4b}$ = 3.4 Hz, 1 H), 1.46 (s, 9 H, 11-H).

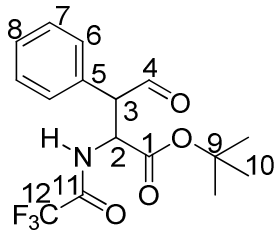
^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 133.6, 129.1, 128.8, 128.2, 84.5, 53.3, 47.1, 37.5, 27.9.

HRMS (CI):	Calculated	Found
$C_{16}H_{21}F_3N_2O_3$ $[M+1]^+$:	347.1538	347.1568

***tert*-Butyl 4-oxo-3-phenyl-2-(2,2,2-trifluoroacetamido) butanoate (29a)**

According to the general procedure for Dess-Martin oxidation, derivative **3a** (347 mg, 1.0 mmol), Dess-Martin periodinane (636 mg, 1.5 mmol) reacted to give **29a** after flash chromatography (silica, hexanes/EtOAc 8:2) in 66% yield (228 mg, 0.66 mmol) as a colorless oil.

[TLC: Hex/EA 8:2, R_f = 0.44]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.76 (s, 1 H, 4-H), 7.38–7.45 (m, 5 H, 6-H, 7-H, 8-H), 7.10 (d, $^3J_{NH,2}$ = 8.3 Hz, 1 H, N-H), 4.98 (dd, $^3J_{2,3}$ = 9.2 Hz, $^3J_{2,3}$ = 4.3 Hz, 1 H, 2-H), 4.52 (d, $^3J_{3,2}$ = 4.4 Hz, 1 H, 3-H), 1.47 (s, 9 H, 10-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.7, 167.5, 156.9 (q, *J* = 37.5 Hz), 130.9, 129.5, 129.3, 128.8, 115.6 (q, *J* = 285.6 Hz), 84.0, 59.1, 53.0, 27.7.

Minor diastereomer (selected signals)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.85 (s, 1 H, 4-H), 7.15–7.22 (m, 5 H, 5 H, 6-H, 7-H, 8-H), 6.70 (d, $^3J_{NH,2}$ = 7.5 Hz, 1 H, N-H), 5.14 (dd, $^3J_{2,3}$ = 8.3, $^3J_{2,3}$ = 5.5 Hz, 1 H, 2-H), 4.30 (d, $^3J_{3,2}$ = 5.4 Hz, 1 H, 3-H), 1.48 (s, 9 H, 10-H).

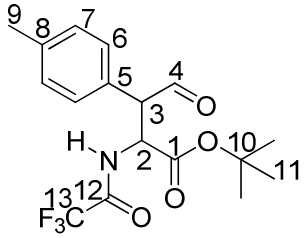
^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.7, 168.7, 167.6, 131.1, 129.6, 129.3, 128.3, 84.3, 59.4, 53.6, 27.8.

HRMS (CI):	Calculated	Found
$C_{16}H_{18}F_3NO_4$ $[M+1]^+$:	346.1221	346.1253

***tert*-Butyl 4-oxo-3-*p*-tolyl-2-(2,2,2-trifluoroacetamido) butanoate (29b)**

According to the general procedure for Dess-Martin oxidation, derivative **3q** (347 mg, 1.0 mmol), Dess-Martin periodinane (636 mg, 1.5 mmol) reacted to give **29b** after flash chromatography (silica, hexanes/EtOAc 8:2) in 74% yield (266 mg, 0.74 mmol) as a colorless oil.

[TLC: Hex/EA 8:2, R_f = 0.45]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.71 (s, 1 H, 4-H), 7.05–7.16 (m, 5 H, 6-H, 7-H, N-H), 4.95 (dd, $^3J_{2,NH}$ = 9.0, $^3J_{2,3}$ = 4.3 Hz, 1 H, 2-H), 4.80 (d, $^3J_{3,2}$ = 4.0 Hz, 1 H, 3-H), 2.48 (s, 3 H, 9-H), 1.48 (s, 9 H, 11-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.5, 167.7, 156.9 (q, *J* = 37.5 Hz), 131.6, 128.9, 128.7, 126.4, 115.5 (q, *J* = 285.5 Hz), 83.7, 55.8, 52.0, 27.6, 19.3.

Minor diastereomer (selected signals)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.80 (s, 1 H, 4-H), 7.36–7.39 (m, 4 H, 6-H, 7-H), 6.80 (d, $^3J_{NH,2}$ = 7.4 Hz, 1 H, N-H), 5.09 (dd, $^3J_{2,NH}$ = 8.4 Hz, $^3J_{2,3}$ = 6.4 Hz, 1 H, 2-H), 4.47 (d, $^3J_{3,2}$ = 6.6 Hz, 1 H, 3-H), 2.45 (s, 3 H, 9-H), 1.44 (s, 9 H, 11-H).

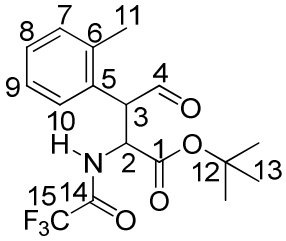
^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.9, 167.8, 137.9, 131.5, 129.6, 129.4, 128.7, 84.1, 56.2, 52.2, 27.7, 19.7.

HRMS (CI):	Calculated	Found
$C_{17}H_{20}F_3NO_4$ $[M+1]^+$:	360.1378	360.1394

***tert*-Butyl 4-oxo-3-*o*-tolyl-2-(2,2,2-trifluoroacetamido) butanoate (29c)**

According to the general procedure for Dess-Martin oxidation, derivative **3r** (361 mg, 1.0 mmol), Dess-Martin periodinane (636 mg, 1.5 mmol) reacted to give **29c** after flash chromatography (silica, hexanes/EtOAc 8:2) in 75% yield (271 mg, 0.75 mmol) as a colorless oil.

[TLC: Hex/EA 8:2, R_f = 0.45]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.68 (s, 1 H, 4-H), 7.27–7.33 (m, 4 H, 7-H, 8-H, 9-H, 10-H), 6.78 (d, $^3J_{NH,2}$ = 7.4 Hz, 1 H, N-H), 4.88 (dd, $^3J_{2,NH}$ = 7.5 Hz, $^3J_{2,3}$ = 3.9 Hz, 1 H, 2-H), 4.80 (d, $^3J_{3,2}$ = 4.0 Hz, 1 H, 3-H), 2.48 (s, 3 H, 11-H), 1.48 (s, 9 H, 13-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.5, 167.7, 156.9 (q, *J* = 37.5 Hz), 138.9, 131.6, 128.9, 128.7, 127.2, 126.4, 115.5 (q, *J* = 285.9 Hz), 83.7, 55.8, 52.0, 27.6, 19.3.

Minor diastereomer (selected signals)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.75 (s, 1 H, 4-H), 6.87 (d, $^{3}J_{NH,2}$ = 7.9 Hz, 1 H, N-H), 5.09 (dd, $^{3}J_{2,NH}$ = 8.4 Hz, $^{3}J_{2,3}$ = 6.4 Hz, 1 H, 2-H), 4.47 (d, $^{3}J_{3,2}$ = 6.6 Hz, 1 H, 3-H), 2.45 (s, 3 H, 11-H), 1.44 (s, 9 H, 13-H).

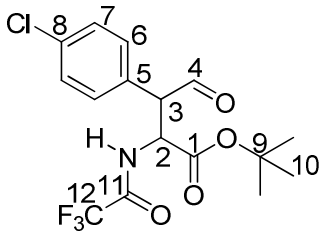
^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.9, 167.8, 137.9, 131.5, 129.6, 129.4, 128.7, 84.1, 56.2, 52.2, 27.7, 19.7.

HRMS (CI):	Calculated	Found
$C_{17}H_{20}F_3NO_4$ $[M+1]^+$:	360.1378	360.1392

***tert*-Butyl 3-(4-chlorophenyl)-4-oxo-2-(2,2,2-trifluoroacet-amido) butanoate 29d**

According to the general procedure for Dess-Martin oxidation, derivative **3l** (382 mg, 1.0 mmol), Dess-Martin periodinane (636 mg, 1.5 mmol) reacted to give **29d** after flash chromatography (silica, hexanes/EtOAc 8:2) in 65% yield (248 mg, 0.65 mmol) as a colorless oil.

[TLC: Hex/EA 8:2, R_f = 0.41]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.71 (s, 1 H, 4-H), 6.78 (d, $^{3}J_{NH,2}$ = 8.7 Hz, 1 H, N-H), 7.05–7.16 (m, 4 H, 6-H, 7-H), 4.95 (dd, $^{3}J_{2,NH}$ = 9.0 Hz, $^{3}J_{2,3}$ = 4.3 Hz, 1 H, 2-H), 4.48 (d, $^{3}J_{3,2}$ = 4.3 Hz, 1 H, 3-H), 1.45 (s, 9 H, 10-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.3, 167.4, 156.7 (q, *J* = 37.6 Hz), 135.0, 130.9, 129.7, 129.4, 115.5 (q, *J* = 285.9 Hz), 84.6, 58.9, 53.2, 27.8.

Minor diastereomer (selected signals)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.80 (s, 1 H, 4-H), 7.36–7.39 (m, 4 H, 6-H, 7-H), 6.80 (d, $^{3}J_{NH,2}$ = 7.4 Hz, 1 H, N-H), 5.05 (dd, $^{3}J_{2,NH}$ = 7.9 Hz, $^{3}J_{2,3}$ = 5.4 Hz, 1 H, 2-H), 4.23 (d, $^{3}J_{3,2}$ = 5.4 Hz, 1 H, 3-H), 1.45 (s, 9 H, 10-H).

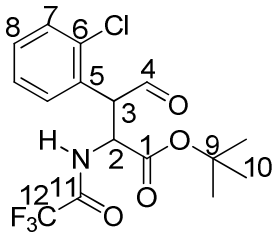
^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.1, 167.1, 135.2, 130.8, 129.6, 84.4, 58.3, 53.4, 27.7.

HRMS (CI):	Calculated	Found
$C_{16}H_{17}ClF_3NO_4$ $[M\text{-}C_4H_9]^+$:	322.0094	322.0079

***tert*-Butyl 3-(2-chlorophenyl)-4-oxo-2-(2,2,2-trifluoroacetamido) butanoate (29e)**

According to the general procedure for Dess-Martin oxidation, derivative **3m** (382 mg, 1.0 mmol), Dess-Martin periodinane (636 mg, 1.5 mmol) reacted to give **29e** after flash chromatography (silica, hexanes/EtOAc 8:2) in 73% yield (277 mg, 0.73 mmol) as a colorless oil.

[TLC: Hex/EA 8:2, R_f = 0.44]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.68 (s, 1 H, 4-H), 7.27–7.33 (m, 4 H, 7-H, 8-H, 9-H, 10-H), 6.78 (d, $^3J_{NH,2}$ = 7.4 Hz, 1 H, N-H), 4.88 (dd, $^3J_{2,NH}$ = 7.5 Hz, $^3J_{2,3}$ = 3.9 Hz, 1 H, 2-H), 4.80 (d, $^3J_{3,2}$ = 4.0 Hz, 1 H, 3-H), 1.48 (s, 9 H, 13-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.5, 167.7, 156.9 (q, *J* = 37.5 Hz), 138.9, 131.6, 128.9, 128.7, 127.2, 126.4, 115.5 (q, *J* = 285.9 Hz), 83.7, 55.8, 52.0, 27.6.

Minor diastereomer (selected signals)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.75 (s, 1 H, 4-H), 6.87 (d, $^3J_{NH,2}$ = 7.9 Hz, 1 H, N-H), 5.09 (dd, $^3J_{2,NH}$ = 8.4 Hz, $^3J_{2,3}$ = 6.4 Hz, 1 H, 2-H), 4.47 (d, $^3J_{3,2}$ = 6.6 Hz, 1 H, 3-H), 1.44 (s, 9 H, 13-H).

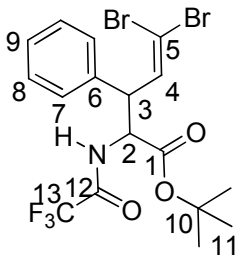
^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.9, 167.8, 137.9, 131.5, 129.6, 129.4, 128.7, 84.1, 56.2, 52.2, 27.7.

HRMS (CI):	Calculated	Found
$C_{16}H_{17}ClF_3NO_4$ $[M]^+$:	379.0798	379.0786

***tert*-Butyl 5,5-dibromo-3-phenyl-2-(2,2,2-trifluoroacetamido) pent-4-enoate (30)**

A solution of CBr_4 (115 mg, 0.35 mmol) and PPh_3 (182 mg, 0.69 mmol) in dichloromethane (1 ml) was stirred at 0 °C for 30 min. The solution was, then, cooled to –78 °C and a solution of **3a** (60 mg, 0.17 mmol) in dichloromethane (1.5 ml) was added. The reaction was warmed to 0 °C and the mixture was allowed to stir for 1.5 h. The reaction was quenched with ether and the contents were filtered over Celite. The solvent was removed in vacuo and the crude product was purified by flash

chromatography (silica, hexanes/EtOAc 8:2) to give **30** in 54% yield (46 mg, 0.09 mmol) as colorless oil.



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.45 (m, 5 H, 7-H, 8-H, 9-H), 7.23 (d, $^{3}J_{4,3}$ = 9.0 Hz, 1 H, 4-H), 7.10 (d, $^{3}J_{NH,2}$ = 8.3 Hz, 1 H, N-H), 4.98 (dd, $^{3}J_{2,3}$ = 9.2 Hz, $^{3}J_{2,3}$ = 4.3 Hz, 1 H, 2-H), 4.52 (dd, $^{3}J_{3,2}$ = 8.9 Hz, $^{3}J_{3,2}$ = 4.4 Hz, 1 H, 3-H), 1.47 (s, 9 H, 10-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.5, 156.9 (q, *J* = 37.5 Hz), 135.9, 131.3, 129.5, 129.3, 128.8, 115.6 (q, *J* = 285.6 Hz), 95.4, 84.0, 59.1, 31.2, 27.7.

Minor diastereomer (selected signals)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, $^{3}J_{4,3}$ = 9.0 Hz, 1 H, 4-H), 7.10 (d, $^{3}J_{NH,2}$ = 8.3 Hz, 1 H, N-H), 4.98 (dd, $^{3}J_{2,3}$ = 9.2 Hz, $^{3}J_{2,3}$ = 4.3 Hz, 1 H, 2-H), 4.52 (dd, $^{3}J_{3,2}$ = 8.9 Hz, $^{3}J_{3,2}$ = 4.4 Hz, 1 H, 3-H), 1.47 (s, 9 H, 10-H).

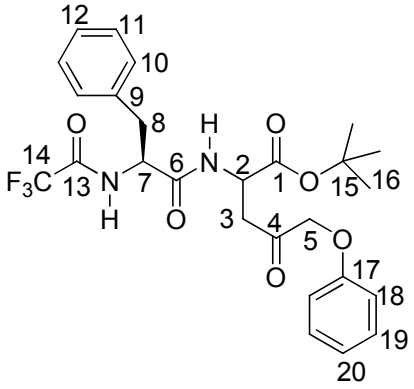
^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 131.3, 129.5, 129.3, 128.8, 95.4, 84.0, 59.1, 31.2, 27.7.

HRMS (CI):	Calculated	Found
$C_{17}H_{18}Br_2F_3NO_3$ $[M\text{-}C_4H_9]^+$:	441.8901	441.8921

***tert*-Butyl 4-oxo-5-phenoxy-2-((*S*)-3-phenyl-2-(2,2,2-trifluoroacetamido) propanamido) pentanoate (33a)**

According to the general procedure **GP-10**, TFA-Phe-Ala-Gly-O*t*Bu (250 mg, 0.67 mmol), phenyl glycidyl ether (150.1 mg, 1.0 mmol), hexamethyldisilazane (411 mg, 2.54 mmol), *n*-BuLi (1.5 ml, 2.34 mmol) and $BF_3 \cdot OEt_2$ (47.4 mg, 0.34 mmol) were allowed to react to give **33a** after flash chromatography (silica, hexanes/EtOAc 8:2) in 66% yield (231 mg, 0.44 mmol) as a white solid with a melting point of 106 °C.

[TLC: Hex/EA 8:2, R_f = 0.30]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13–7.33 (m, 9 H, 10-H, 11-H, 18-H, 19-H, 12 or 20-H), 7.00–7.03 (m, 1 H, 12-H or 20-H), 6.85 (bs, 2 H, N_{TFA}-H), 6.44 (d, $^{3}J_{NH,2}$ = 8.4 Hz, 1 H, N-H), 4.63–4.70 (m, 2 H, 7-H, 2-H), 4.41 (s, 2 H, 5-H), 3.11–3.20 (m, 2 H, 3-H), 2.98 (dd, $^{2}J_{8a,8b}$ = 13.5 Hz, $^{3}J_{8a,7}$ = 8.8 Hz, 1 H, 8a-H), 2.80 (dd, $^{2}J_{8b,8a}$ = 18.8 Hz, $^{3}J_{8b,7}$ = 4.3 Hz, 1 H, 8b-H), 1.36 (s, 9 H, 16-H).

^{13}C NMR (100 MHz, $CDCl_3$) (from mixture): δ = 205.7, 168.8, 168.7, 157.4, 156.5 (q, *J* = 37.3 Hz), 135.3, 129.7, 129.2, 128.7, 127.2, 121.9, 114.4, 115.6 (q, *J* = 285.9 Hz), 82.9, 72.3, 54.6, 48.1, 41.0, 38.5, 27.7.

Minor diastereomer (selected signals):

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.58 (d, $^{3}J_{NH,2}$ = 7.6 Hz, 1 H, N-H), 4.66–4.71 (m, 1 H, 7-H), 4.62 (q, $^{3}J_{2,3}$ = 6.7 Hz, 1 H, 2-H), 4.53 (d, $^{2}J_{3a,3b}$ = $^{2}J_{3b,3a}$ = 0.8 Hz, 2 H, 3-H), 3.28 (dd, $^{2}J_{8b,8a}$ = 18.6 Hz, $^{3}J_{8b,7}$ = 4.4 Hz, 1 H, 8b-H), 1.44 (s, 9 H, 16-H).

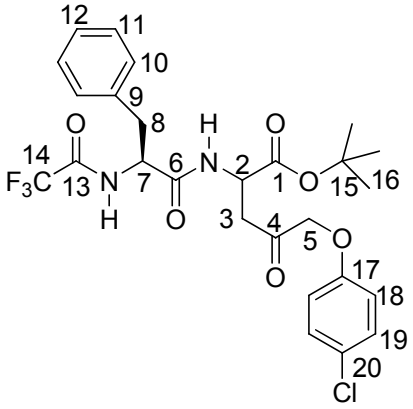
^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.9, 169.0, 168.9, 134.9, 129.6, 129.2, 128.6, 127.3, 121.8, 115.5 (q, *J* = 285.5 Hz), 82.9, 72.4, 54.3, 48.6, 41.0, 38.2, 27.7.

HRMS (CI):	Calculated	Found
$C_{26}H_{29}F_3N_2O_6$ $[M]^+$:	522.1978	522.1953

tert-Butyl 5-(4-chlorophenoxy)-4-oxo-2-((*S*)-3-phenyl-2-(2,2,2-trifluoroacetamido) propanamido) pentanoate (33b)

According to the general procedure **GP-10**, TFA-Phe-Ala-Gly-O*t*Bu (250 mg, 0.67 mmol), 4-chloro phenyl glycidyl ether (184.6 mg, 1.0 mmol), hexamethyldisilazane (411 mg, 2.54 mmol), *n*-BuLi (1.5 ml, 2.34 mmol) and $BF_3 \cdot OEt_2$ (47.4 mg, 0.34 mmol) were allowed to react to give **33b** after flash chromatography (silica, hexanes/EtOAc 8:2) in 68% yield (254 mg, 0.46 mmol) as a white solid with a melting point of 106 °C.

[TLC: Hex/EA 8:2, R_f = 0.29]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.31 (m, 6 H, 10-H, 11-H, 12-H, N-H), 7.00 (d, $^{3}J_{NH,2}$ = 7.3 Hz, 1 H, N-H), 6.76–6.83 (m, 4 H, 18-H, 19-H), 6.53 (d, $^{3}J_{NH,2}$ = 7.8 Hz, 1 H, N-H), 4.65–4.71 (m, 1 H, 7-H), 4.61 (td, $^{3}J_{2,3}$ = 13.4 Hz, $^{3}J_{2,NH}$ = 6.6 Hz, 1 H, 2-H), 4.49 (d, $^{2}J_{5a,5b}$ = 16.8 Hz, 1 H, 5b-H), 3.27 (dd, $^{2}J_{8a,8b}$ = 18.5 Hz, $^{3}J_{8a,2}$ = 4.3 Hz, 1 H, 8a-H), 3.18 (dd, $^{2}J_{3a,3b}$ = 13.9 Hz, $^{3}J_{8a,2}$ = 6.7 Hz, 1 H, 3a-H), 3.07–3.14 (m, 2 H, 3b-H, 8b-H), 1.44 (s, 9 H, 16-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.9, 168.8, 168.4, 156.9 (q, *J* = 37.5 Hz), 154.7, 151.6, 135.2, 129.3, 128.8, 127.3, 115.6 (q, *J* = 285.6 Hz), 115.4, 83.0, 73.2, 55.6, 54.7, 48.1, 40.9, 38.6, 27.7.

Minor diastereomer, selected signals:

^{1}H NMR (400 MHz, $CDCl_3$): 7.16–7.31 (m, 6 H, 10-H, 11-H, 12-H, N_{TFA}-H), 6.82–6.87 (m, 4 H, 18-H, 19-H), 6.40 (d, $^{3}J_{NH,2}$ = 8.0 Hz, 1 H, N-H), 4.63–4.71 (m, 2 H, 2-H, 7-H), 4.37 (s, 2 H, 5-H), 3.12–3.21 (m, 2 H, 3a-H, 8a-H), 2.99 (dd, $^{2}J_{3b,3a}$ = 13.9 Hz, $^{3}J_{3b,2}$ = 8.8 Hz, 1 H, 3b-H), 2.99 (dd, $^{2}J_{8b,8a}$ = 18.7 Hz, $^{3}J_{3b,2}$ = 4.3 Hz, 1 H, 3b-H), 1.38 (s, 9 H, 16-H).

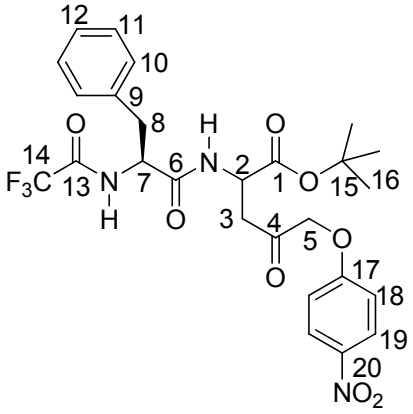
^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.2, 168.8, 168.6, 154.6, 129.3, 128.8, 127.5, 115.5, 115.0, 114.8, 83.1, 73.3, 55.6, 54.3, 48.6, 41.0, 38.2, 27.8.

HRMS (CI):	Calculated	Found
$C_{26}H_{28}ClF_3N_2O_6$ $[M+1]^+$:	558.1558.	558.1575

tert-Butyl 5-(4-nitrophenoxy)-4-oxo-2-((*S*)-3-phenyl-2-(2,2,2-trifluoroacetamido) propanamido) pentanoate (33c)

According to the general procedure **GP-10**, TFA-Phe-Ala-Gly-O*t*Bu (250 mg, 0.67 mmol), 4-nitro phenyl glycidyl ether (180.2 mg, 1.0 mmol), hexamethyldisilazane (411 mg, 2.54 mmol), *n*-BuLi (1.5 ml, 2.34 mmol) and $BF_3 \cdot OEt_2$ (47.4 mg, 0.34 mmol) were allowed to react to give **33c** after flash chromatography (silica, hexanes/EtOAc 8:2) in 72% yield (273 mg, 0.48 mmol) as a white solid with a melting point of 105 °C.

[TLC: Hex/EA 8:2, R_f = 0.28]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13–7.31 (m, 6 H, 10-H, 11-H, 12-H, N_{TFA}-H), 6.78–6.88 (m, 4 H, 18-H, 19-H), 6.31 (d, $^3J_{NH,2}$ = 7.3 Hz, 1 H, N-H), 4.63–4.71 (m, 2 H, 7-H, 2-H), 4.49 (d, $^2J_{5a,5b}$ = 16.8 Hz, 1 H, 5a-H), 4.45 (d, $^2J_{5b,5a}$ = 16.9 Hz, 1 H, 5b-H), 3.27 (dd, $^2J_{8a,8b}$ = 18.5 Hz, $^3J_{8a,2}$ = 4.4 Hz, 1 H, 8a-H), 3.19 (dd, $^2J_{3a,3b}$ = 13.9 Hz, $^3J_{3a,2}$ = 6.5 Hz, 1 H, 3a-H), 3.09 (dd, $^2J_{3b,3a}$ = 13.8 Hz, $^3J_{3b,2}$ = 6.2 Hz, 1 H, 3b-H), 3.10–3.15 (m, 1 H, 8b-H), 1.43 (s, 9 H, 16-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.9, 168.8, 168.4, 156.9 (q, *J* = 37.5 Hz), 154.7, 151.6, 135.2, 129.3, 128.8, 127.3, 115.6 (q, *J* = 285.6 Hz), 115.4, 83.0, 73.2, 55.6, 54.7, 48.1, 40.9, 38.6, 27.7.

Minor diastereomer, selected signals:

^{1}H NMR (400 MHz, $CDCl_3$): 7.14–7.29 (m, 6 H, 10-H, 11-H, 12-H, N_{TFA}-H), 6.81–6.87 (m, 4 H, 18-H, 19-H), 6.40 (d, $^3J_{NH,2}$ = 8.0 Hz, 1 H, N-H), 4.63–4.71 (m, 2 H, 2-H, 7-H), 4.37 (s, 2 H, 5-H), 3.12–3.21 (m, 2 H, 3a-H, 8a-H), 2.99 (dd, $^2J_{3b,3a}$ = 13.9 Hz, $^3J_{3b,2}$ = 8.8 Hz, 1 H, 3b-H), 2.99 (dd, $^2J_{8b,8a}$ = 18.7 Hz, $^3J_{3b,2}$ = 4.3 Hz, 1 H, 3b-H), 1.38 (s, 9 H, 16-H).

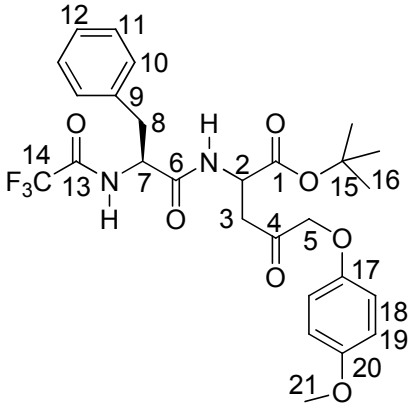
^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.2, 168.8, 168.6, 154.6, 129.3, 128.8, 127.5, 115.5, 115.0, 114.8, 83.1, 73.3, 55.6, 54.3, 48.6, 41.0, 38.2, 27.8.

HRMS (CI):	Calculated	Found
$C_{26}H_{28}F_3N_3O_8$ $[M+1]^+$:	568.1862.	568.1878

tert-Butyl 5-(4-methoxyphenoxy)-4-oxo-2-((*S*)-3-phenyl-2-(2,2,2-trifluoroacetamido) propanamido) pentanoate (33d)

According to the general procedure **GP-10**, TFA-Phe-Ala-Gly-O*t*Bu (250 mg, 0.67 mmol), 4-methoxy phenyl glycidyl ether (180.2 mg, 1.0 mmol), hexamethyldisilazane (411 mg, 2.54 mmol), *n*-BuLi (1.5 ml, 2.34 mmol) and $BF_3 \cdot OEt_2$ (47.4 mg, 0.34 mmol) were allowed to react to give **33d** after flash chromatography (silica, hexanes/EtOAc 8:2) in 65% yield (241 mg, 0.44 mmol) as a white solid with a melting point of 108 °C.

[TLC: Hex/EA 8:2, R_f = 0.29]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17–7.31 (m, 5 H, 10-H, 11-H, 12-H, N-H), 7.01 (d, $^{3}J_{NH,2}$ = 7.3 Hz, 1 H, N-H), 6.79–6.84 (m, 4 H, 18-H, 19-H), 6.53 (d, $^{3}J_{NH,2}$ = 7.8 Hz, 1 H, N-H), 4.66–4.70 (m, 1 H, 7-H), 4.61 (td, $^{3}J_{2,3}$ = 13.4, $^{3}J_{2,NH}$ = 6.6 Hz, 1 H, 2-H), 4.49 (d, $^{2}J_{5a,5b}$ = 16.8 Hz, 1 H, 5b-H), 3.76 (s, 3 H, 21-H), 3.27 (dd, $^{2}J_{8a,8b}$ = 18.5 Hz, $^{3}J_{8a,2}$ = 4.3 Hz, 1 H, 8a-H), 3.18 (dd, $^{2}J_{3a,3b}$ = 13.9 Hz, $^{3}J_{3a,2}$ = 6.7 Hz, 1 H, 3a-H), 3.07–3.14 (m, 2 H, 3b-H, 8b-H), 1.44 (s, 9 H, 16-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.9, 168.8, 168.4, 156.9 (q, *J* = 37.5 Hz), 154.7, 151.6, 135.2, 129.2, 128.8, 127.4, 115.6 (q, *J* = 285.6 Hz), 115.5, 114.9, 83.0, 73.2, 55.7, 54.7, 48.2, 40.9, 38.6, 27.7.

Minor diastereomer (selected signals):

^{1}H NMR (400 MHz, $CDCl_3$): 7.14–7.30 (m, 6 H, 10-H, 11-H, 12-H, N_{TFA}-H), 6.81–6.87 (m, 4 H, 18-H, 19-H), 6.31 (d, $^{3}J_{NH,2}$ = 7.8 Hz, 1 H, N-H), 4.60–4.69 (m, 2 H, 7-H, 2-H), 4.37 (s, 2 H, 5-H), 3.77 (s, 3 H, 21-H), 3.13–3.21 (m, 2 H, 3a-H, 8a-H), 2.97 (dd, $^{2}J_{3a,3b}$ = 13.8 Hz, $^{3}J_{3a,2}$ = 8.8 Hz, 1 H, 3a-H), 2.79 (dd, $^{2}J_{8a,8b}$ = 18.7 Hz, $^{3}J_{8a,2}$ = 4.3 Hz, 1 H, 8a-H), 1.38 (s, 9 H, 16-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.2, 168.8, 168.6, 156.9 (q, *J* = 37.5 Hz), 154.6, 129.3, 128.8, 127.5, 115.6 (q, *J* = 285.6 Hz), 115.5, 115.0, 114.8, 83.1, 73.3, 55.6, 54.3, 48.6, 41.0, 38.2, 27.8.

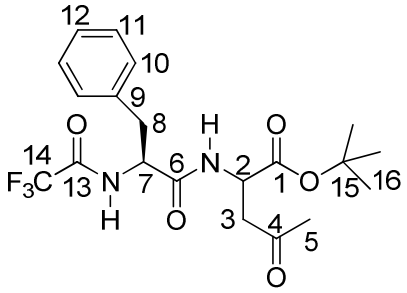
HRMS (CI):	Calculated	Found
$C_{27}H_{31}F_3N_2O_7$ $[M]^+$:	552.2083.	552.2076

tert-Butyl 4-oxo-2-((*S*)-3-phenyl-2-(2,2,2-trifluoroacetamido) propanamido) pentanoate (33e)

According to the general procedure **GP-10**, TFA-Phe-Ala-Gly-O*t*Bu (250 mg, 0.67 mmol), propylene oxide (58.1 mg, 1.0 mmol), hexamethyldisilazane (411 mg, 2.54 mmol), *n*-BuLi (1.5 ml, 2.34 mmol) and $BF_3 \cdot OEt_2$ (47.4 mg, 0.34 mmol) were allowed

to react to give **33e** after flash chromatography (silica, hexanes/EtOAc 8:2) in 64% yield (185 mg, 0.43 mmol) as a white solid with a melting point of 96 °C.

[TLC: Hex/EA 8:2, R_f = 0.30]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.34 (m, 4 H, 10-H, 11-H), 7.17–7.19 (m, 1 H, 12-H), 7.13 (d, $^3J_{NH,2}$ = 7.8 Hz, 1 H, N-H), 6.68 (d, $^3J_{NHTFA,2}$ = 7.5 Hz, 1 H, N_{TFA}-H), 4.63–4.68 (m, 1 H, 7-H), 4.60 (td, $^3J_{2,NH}$ = 8.2 Hz, $^3J_{2,3}$ = 4.2 Hz, 1 H, 2-H), 3.21 (dd, $^2J_{3a,3b}$ = 13.9 Hz, $^3J_{3a,2}$ = 6.4 Hz, 1 H, 3a-H), 3.07–3.17 (m, 2 H, 3a-H, 8a-H), 2.90 (dd, $^2J_{8a,8b}$ = 18.3 Hz, $^3J_{8a,2}$ = 9.0 Hz, 1 H, 8a-H), 2.14 (s, 3 H, 5-H), 1.44 (s, 9 H, 16-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.3, 168.9, 168.6, 156.9 (q, *J* = 37.5 Hz), 134.8, 129.3, 128.7, 127.4, 115.6 (q, *J* = 285.6 Hz), 82.8, 54.2, 48.9, 44.7, 38.3, 29.8, 27.8.

Minor diastereomer (selected signals):

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (bs, 1 H, N_{TFA}-H), 7.45 (bs, 1 H, N-H), 7.14–7.27 (m, 5 H, 10-H, 11-H, 12-H), 4.74 (bs, 2 H, 2-H, 7-H), 3.20 (dd, $^2J_{3a,3b}$ = 13.9 Hz, $^3J_{3a,2}$ = 6.1 Hz, 1 H, 3a-H), 2.91 (dd, $^2J_{8a,8b}$ = 18.3 Hz, $^3J_{8a,2}$ = 4.2 Hz, 1 H, 8a-H), 2.12 (s, 3 H, 5-H), 1.37 (s, 9 H, 16-H).

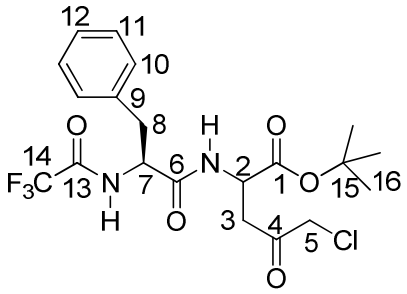
^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.2, 168.7, 168.4, 134.8, 129.3, 128.7, 127.4, 82.8, 54.2, 48.9, 44.5, 38.3, 29.8, 27.7.

HRMS (CI):	Calculated	Found
$C_{20}H_{25}F_3N_2O_5$ $[M+1]^+$:	431.1749.	431.1794.

***tert*-Butyl 5-chloro-4-oxo-2-((*S*)-3-phenyl-2-(2,2,2-trifluoroacetamido) propanamido) pentanoate (33f)**

According to the general procedure **GP-10**, TFA-Phe-Ala-Gly-O*t*Bu (250 mg, 0.67 mmol), epichlorohydrin (92.5 mg, 1.0 mmol), hexamethyldisilazane (411 mg, 2.54 mmol), *n*-BuLi (1.5 ml, 2.34 mmol) and $BF_3 \cdot OEt_2$ (47.4 mg, 0.34 mmol) were allowed to react to give **33f** after flash chromatography (silica, hexanes/EtOAc 8:2) in 66% yield (205 mg, 0.44 mmol) as a white solid with a melting point of 99 °C.

[TLC: Hex/EA 8:2, R_f = 0.30]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16–7.31 (m, 6 H, 10-H, 11-H, 12-H, N-H), 6.82 (d, $^3J_{NHTFA,2}$ = 7.5 Hz, 1 H, N_{TFA}-H), 4.69–4.74 (m, 1 H, 7-H), 4.60 (td, $^3J_{2,NH}$ = 7.8 Hz, $^3J_{2,NH}$ = 4.3 Hz, 1 H, 2-H), 4.07 (d, $^2J_{5a,5b}$ = 15.5 Hz, 1 H, 5a-H), 4.02 (d, $^2J_{5b,5a}$ = 15.4 Hz, 1 H, 8b-H), 3.06–3.29 (m, 4 H, 3-H, 8-H), 1.44 (s, 9 H, 16-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.7, 169.1, 168.6, 156.9 (q, *J* = 37.5 Hz), 134.9, 129.2, 128.7, 127.4, 115.6 (q, *J* = 285.6 Hz), 83.2, 54.4, 48.9, 47.6, 41.3, 38.2, 27.7.

Minor diastereomer (selected signals):

^{1}H NMR (400 MHz, $CDCl_3$): 6.81 (d, $^3J_{NHTFA,2}$ = 7.5 Hz, 1 H, N_{TFA}-H), 4.69–4.74 (m, 2 H, 7-H, 2-H), 4.07 (d, $^2J_{5a,5b}$ = 15.5 Hz, 1 H, 5a-H), 4.02 (d, $^2J_{5b,5a}$ = 15.4 Hz, 1 H, 8b-H), 3.06–3.29 (m, 4 H, 3-H, 8-H), 1.45 (s, 9 H, 16-H).

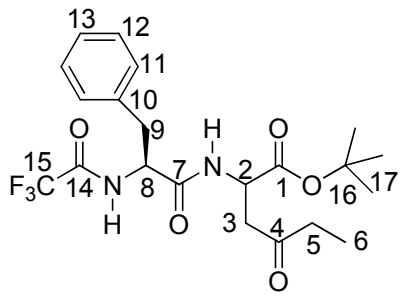
^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.7, 169.1, 168.6, 129.2, 128.7, 127.4, 115, 83.2, 54.4, 48.9, 47.6, 41.3, 38.2, 27.7.

HRMS (CI):	Calculated	Found
$C_{20}H_{24}ClF_3N_2O_5$ $[M]^+$:	464.1326.	464.1326

***tert*-Butyl 4-oxo-2-((*S*)-3-phenyl-2-(2,2,2-trifluoroacetamido) propanamido) hexanoate (33g)**

According to the general procedure **GP-10**, TFA-Phe-Ala-Gly-O*t*Bu (250 mg, 0.67 mmol), 1, 2-butene oxide (72.1 mg, 1.0 mmol), hexamethyldisilazane (411 mg, 2.54 mmol), *n*-BuLi (1.5 ml, 2.34 mmol) and $BF_3 \cdot OEt_2$ (47.4 mg, 0.34 mmol) were allowed to react to give **33g** after flash chromatography (silica, hexanes/EtOAc 8:2) in 68% yield (201 mg, 0.45 mmol) as a white solid with a melting point of 102 °C.

[TLC: Hex/EA 8:2, R_f = 0.30]



Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16–7.31 (m, 5 H, 10-H, 11-H, 12-H), 7.14 (bs, 1 H, N_{TFA}-H), 6.82 (d, $^{3}J_{NH,2}$ = 7.5 Hz, 1 H, N-H), 4.69–4.74 (m, 1 H, 7-H), 4.60 (td, $^{3}J_{2,NH}$ = 7.8 Hz, $^{3}J_{2,NH}$ = 4.3 Hz, 1 H, 2-H), 3.06–3.29 (m, 4 H, 3-H, 8-H), 2.41–2.47 (m, 2 H, 5-H), 1.44 (s, 9 H, 16-H), 1.05 (t, $^{3}J_{6,5}$ = 7.34 Hz, 3 H, 6-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.7, 169.1, 168.6, 156.9 (q, *J* = 37.5 Hz), 134.9, 129.2, 128.7, 127.4, 115.6 (q, *J* = 285.6 Hz), 83.2, 54.4, 48.9, 41.3, 35.6, 38.2, 27.6, 7.9.

Minor diastereomer (selected signals):

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14–7.31 (m, 6 H, 10-H, 11-H, 12-H, N_{TFA}-H), 6.82 (d, $^{3}J_{NH,2}$ = 7.6 Hz, 1 H, N-H), 4.69–4.74 (m, 1 H, 7-H), 4.60 (td, $^{3}J_{2,NH}$ = 7.9 Hz, $^{3}J_{2,NH}$ = 4.3 Hz, 1 H, 2-H), 3.06–3.29 (m, 4 H, 3-H, 8-H), 2.41–2.47 (m, 2 H, 5-H), 1.44 (s, 9 H, 16-H), 1.06 (t, $^{3}J_{6,5}$ = 7.3 Hz, 3 H, 6-H).

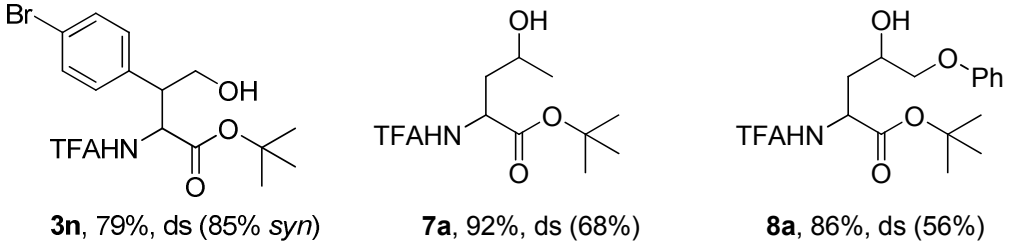
^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.7, 169.1, 168.6, 134.9, 129.2, 128.7, 127.4, 83.2, 54.4, 47.6, 41.3, 38.2, 27.7, 8.0.

HRMS (CI):	Calculated	Found
$C_{21}H_{27}F_3N_2O_5$ $[M+1]^+$:	445.1908	445.1906

5 Summary

The aim of this work was to investigate if the chelated amino acid ester enolates are suitable nucleophiles for the regioselective ring opening of epoxides and if these nucleophiles can transfer chirality in the products. For this purpose, a variety of epoxides (aromatic, aliphatic and aryl glycidyl ethers) were synthesized and subjected to ring opening reactions.

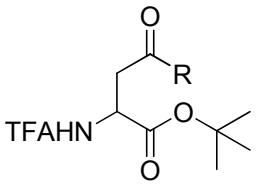
The ring opening of aryl epoxides proceeded smoothly and the products **3** were obtained in good yields (70–82%) but with moderate diastereoselectivities (67–81%). In all cases, the reaction was observed to be regioselective and the products were obtained *via* a S_N1-type mechanism. In case of alkyl substituted epoxides, the attack on the less hindered carbon was observed, probably due to a S_N2-type mechanism. As a result, products **7** and **8** were obtained in high yields (72–92%) also with relatively lower diastereoselectivities (51–68%) (Figure 5.1).



3n, 79%, ds (85% *syn*) **7a**, 92%, ds (68%) **8a**, 86%, ds (56%)

Figure 5.1: Ring opening products of alkyl and aryl epoxides.

After successful regioselective ring opening of epoxides, these products were subjected to various synthetic applications. The alcohols **7** and **8** were oxidized and δ-keto amino acid esters **11** were obtained in excellent yields (82–93%) (Figure 5.2).



11, 82−93%

Figure 5.2: δ-keto amino acid esters **11**.

These δ-keto amino acid esters **11** were allowed to undergo carbonyl additions like Passerini, Reformatsky reactions as well as allylations, methylations. In the case of allylations, the corresponding lactones **12** were formed in good yields (60–70%). The same trend was observed when ketones **11** were subjected to methylation reactions. Formation of lactones **14** was observed in moderate yields (58–66%) (Figure 5.3).

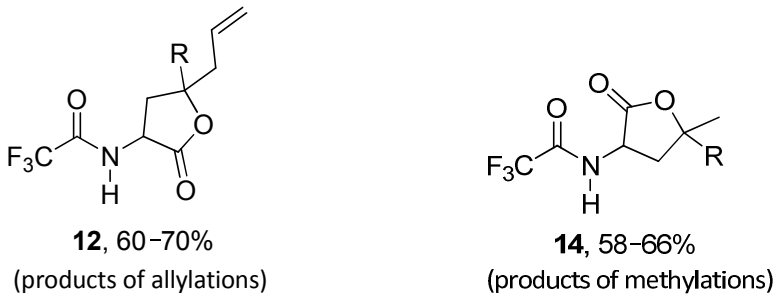


FIgure 5.3: Allylation and methylation products of ketones **11**.

Next, we subjected δ-keto amino acid esters **11** to Passerini and Reformatsky reactions. In case of Passerini reaction, the products **15** were obtained in acceptable yields (53–61%). Similarly, Reformatsky reaction proceeded smoothly, and the desired products **17** were obtained in 85–90% yield (Figure 5.4).

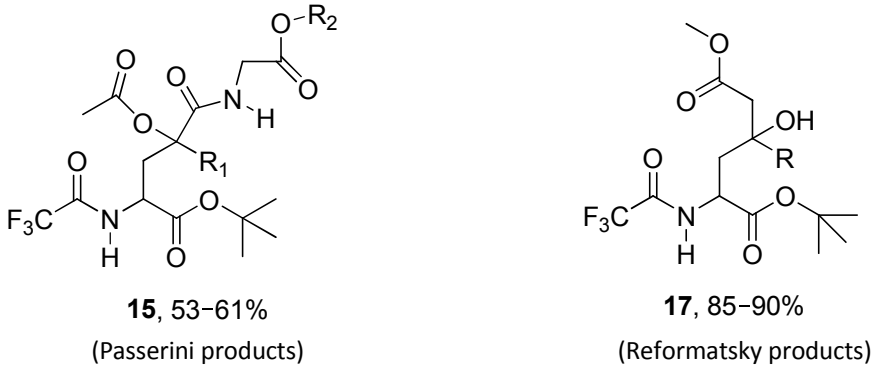


FIgure 5.4: Passerini reaction of ketones **11**.

The methodology was also applied to synthesize heterocyclic compounds based on amino acid esters, and Benzomorpholine based glycine ester **19a**, Benzomorpholine derivative **19b** and Benzofuran based glycine ester **20** were synthesized successfully (Figure 5.5).

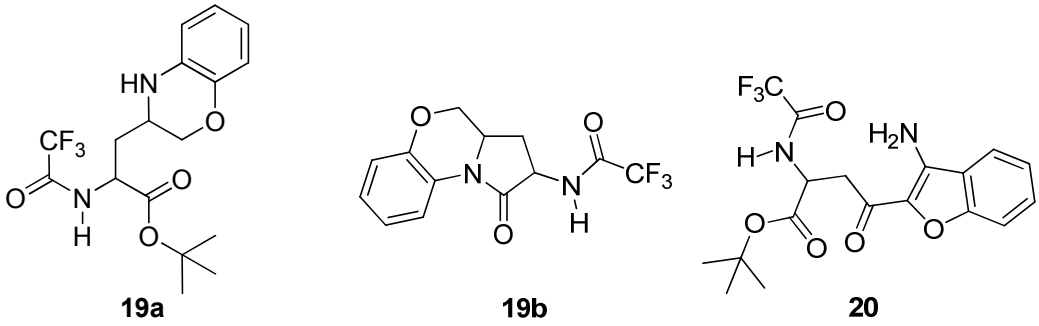


Figure 5.5: Synthesis of heterocyclic compounds **19a** and **19b**.

Next, we used aryl derivatives **3** for further modifications and variety of different β-substituted phenylalanine derivatives (**25**–**28**) were synthesized. Moreover, the derivatives **3** were oxidized and the corresponding aldehydes **29** were obtained in good yields (71–78%). These aldehydes can be good substrates for carbonyl

additions. As an example, aldehyde **29a** was converted to dibromo alkene **30** *via* Corey-Fuchs reaction, a substrate for regioselective cross-coupling reaction (Figure 5.6).

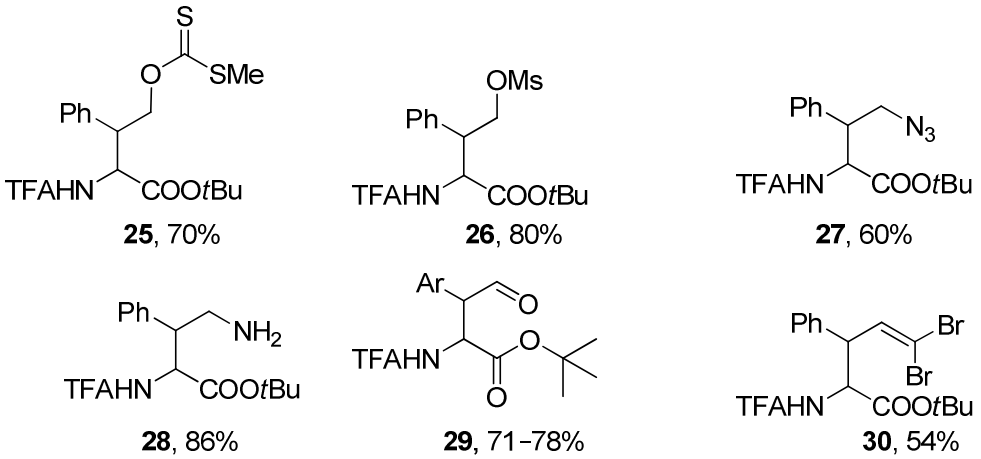
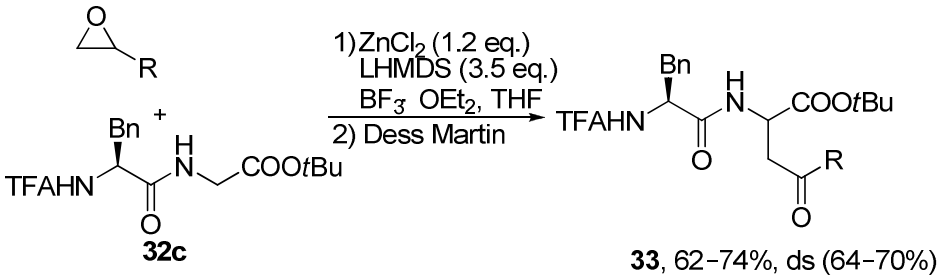


Figure 5.6: β-substituted phenylalanine derivatives.

In the final stage of the work, the methodology was applied to peptide modification reactions. As nucleophile, TFA-phenylalanine dipeptide **32c** was selected and subjected to ring opening of different epoxides. The ring opening products were directly oxidized and the corresponding ketones **33** were obtained in acceptable yields (64–72%) with diastereoselectivities ranging from 64–70% (Scheme 5.1).



Scheme 5.1: Peptide modifications through epoxide ring openings.

In conclusion, we could show that chelated enolates of α-amino acid esters and peptides are suitable nucleophiles for the regioselective ring opening of epoxides. Depending on the substitution pattern, the reaction proceeds either in a S_N1-type (aryl epoxides) or a S_N2-type (alkyl epoxides) fashion. Ring opening of aryl epoxides with chelated enolates as nucleophiles gives direct access to a wide range of modified phenylalanine derivatives in only a few steps. Whereas, products of alkyl epoxides have been successfully used in a variety of synthetic applications such as Passerini, Reformatsky reactions as well as allylations, methylations, and for the synthesis of heterocyclic compounds based on amino acid esters. Furthermore, the protocol has been successfully applied to peptide modifications.

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