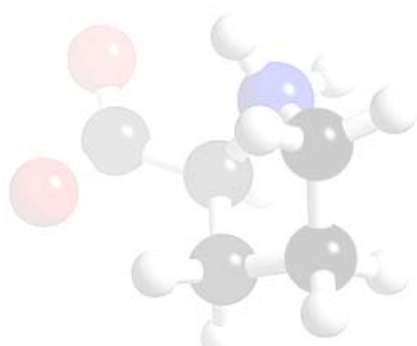


**Stereoselective Approach to New Conformationally
Restricted α -Amino Acids,
Stereoselective Synthesis of α -Trifluoromethylated
 α -Amino Acids**



Dissertation

zur Erlangung des akademischen Grades
des Doktors der Naturwissenschaften
an der Universität Konstanz

vorgelegt von

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ABBREVIATIONS

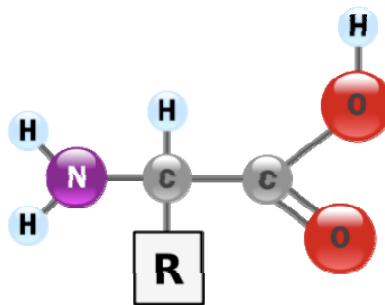
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|--------------|--|
| ATR | Attenuated total reflectance |
| Boc | <i>tert</i> -Butyloxycarbonyl |
| Bn | Benzyl |
| <i>n</i> -Bu | <i>n</i> -Butyl |
| <i>t</i> -Bu | <i>tert</i> -Butyl |
| Bz | Benzoyl |
| Cbz | Carbobenzyloxy |
| CDI | <i>N,N'</i> -Dicyclohexylcarbodiimide |
| DCM | Dichloromethane |
| de | Diastereomeric excess |
| DEAD | Diethyl azodicarboxylate |
| DMF | Dimethylformamide |
| DMI | 1,3-Dimethyl-2-imidazolidinone |
| DMSO | Dimethyl sulfoxide |
| DMPU | 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone |
| EE | Ethyl acetate |
| ee | Enantiomeric excess |
| Et | Ethyl |
| EWG | Electron withdrawing group |
| Fmoc | 9-Fluorenylmethyloxycarbonyl |
| GC-MS | Gas-chromatography with mass selective detector |
| HMBC | Heteronuclear multiple bond correlation |
| HPLC | High pressure liquid chromatography |
| HRMS | High-resolved mass-spectrometry |
| HSQC | Heteronuclear single quantum coherence |
| IR | Infrared |
| LAH | Lithium aluminium hydride |
| LDA | Lithium diisopropylamide |
| LiHMDS | Lithium bis(trimethylsilyl)amide |
| mCPBA | <i>meta</i> -Chloroperoxybenzoic acid |
| MeO | Methoxy |
| MS | Mass-spectrometry |
| NMR | Nuclear magnetic resonance |
| NOESY | Nuclear Overhauser effect spectroscopy |

| | |
|--------------|---|
| Ns | 4-Nitrobenzenesulfonyl |
| PE | Petroleum ether |
| Ph | Phenyl |
| PPTS | Pyridinium <i>p</i> -toluenesulfonate |
| <i>i</i> -Pr | <i>iso</i> -Propyl |
| Py | Pyridine |
| rt | Room temperature |
| TBAF | Tetra- <i>n</i> -butylammonium fluoride |
| TBDMS | <i>tert</i> -Butyldimethylsilyl |
| TFAA | Trifluoroacetic anhydride |
| THF | Tetrahydrofuran |
| TLC | Thin-layer chromatography |
| TMS | Trimethylsilyl |
| Ts | Tosyl, <i>p</i> -methylbenzosulphonyl |

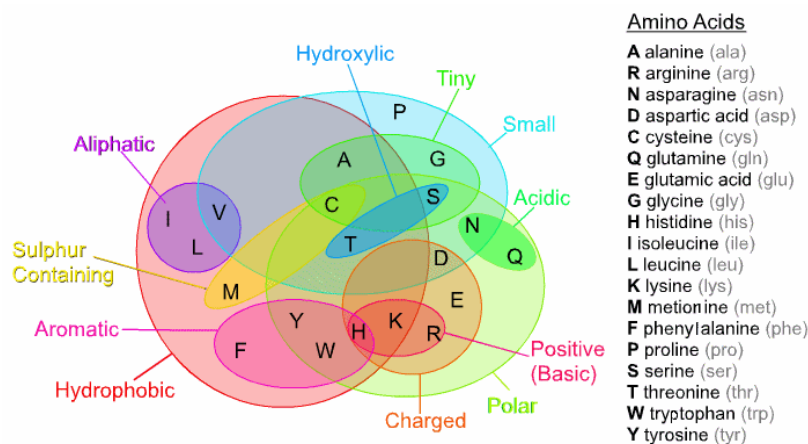
1 INTRODUCTION

What are amino acids (AAs)?

AAs are molecules containing an amine group, a carboxylic acid group and a side chain that varies between different AAs. These molecules contain the key elements of carbon, hydrogen, oxygen, and nitrogen. These molecules are particularly important in biochemistry where this term refers to α -amino acids with the general formula $H_2NCHR\text{COOH}$, where R is an organic substituent.¹



At least 300 AAs were described in nature but only 20 of these are typically found as components in human peptides and proteins.² AAs make up 75% of the human body. They are essential to nearly every bodily function. Every chemical reaction that takes place in a human body depends on AAs and the proteins that they build.



Why unnatural AAs?

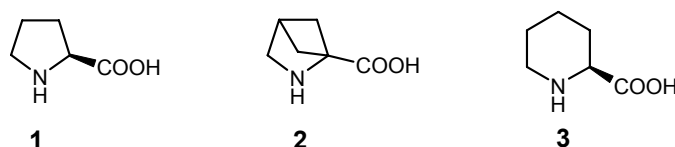
Unnatural AAs, the non-genetically-coded AAs that either occur naturally or are chemically synthesized, are becoming very important tools for modern drug discovery research. Due to their structural diversity and functional versatility, they are widely used as chiral building blocks and molecular scaffolds in constructing combinatorial libraries. Many of these unnatural AAs are important components in pharmaceuticals and developmental drugs.

1.1 CRAAs

1.1.1 PEPTIDES AND PEPTIDOMIMETICS

Peptides occur throughout nature in a wide range of roles essential to virtually every biochemical process. Peptides (from the Greek *πεπτιδία*, "small digestibles") are short polymers formed from the linking, in a defined order, of α -amino acids. The major problem in the area of peptide research is the conformational flexibility of most natural peptides and the high dependence of their conformation on the environment. One very successful approach to overcome these drawbacks is the use of peptidomimetics.

Peptidomimetics are small protein-like molecules designed to mimic natural peptides or proteins. These mimetics should have the ability to bind to their natural targets in the same way as the natural peptide sequences do from which their structure was derived and hence should produce the same biological effects. It is possible to design these molecules in such a way that they show the same biological effects as their peptide role models but with enhanced properties like a higher proteolytic stability, higher bioavailability and also often with improved selectivity or potency. This makes them interesting targets for the discovery of new drug candidates.³ Conformationally restricted and metabolically more stable peptidomimetics are obtained using usually unnatural AAs. In principle, two different starting points exist for the modification of the peptide at the amino acid level. One is the amino acid side chain which can be rigidified for example by the use of sterically demanding groups (for example incorporation of conformationally restricted α -amino acids – CRAAs); the other is the backbone of the peptide. L-Proline **1**, its bicyclic analogue 2,4-methanoproline **2** and pipercolic acid **3** are examples of CRAAs.



From the whole variety of thoroughly investigated amino acids we would like to pay attention to CRAAs, analogues of natural proline and natural non proteinogenic pipercolic acid (the proline homologue).

1.1.2 SECONDARY STRUCTURE OF PEPTIDES

The design of peptidomimetics and peptide models is based on the knowledge of the secondary structure elements of peptides. Conformation of polypeptide chain can be described in terms of the torsion angles φ , ψ and ω whereas the conformation of side chains of amino acids – in terms of torsion angles χ_1 , χ_2 , χ_3 and so on (*Figure 1*).⁴

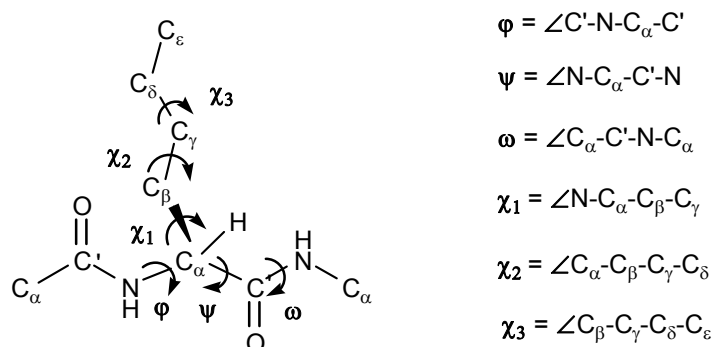


Figure 1. The torsion angles φ , ψ , ω and χ in peptides

The most typical values of the torsion angles for the secondary structure of peptides were determined analyzing experimental structural data and computer simulations. Based on these values it is possible to predict in the first approximation the effects of a replacement of natural AAs by its conformationally restricted analogues. If torsion angles at the peptide bond formed by CRAAs are similar to corresponding torsion angles of a secondary structure element of the native peptide, stabilization of this structure element is expected.

Proline has a special place among the proteinogenic AAs because of its secondary structure inducing and stabilizing properties and hence its influence on the biological behavior of peptides.

It was reported a complete structural analysis of the Pro-Xaa-Val sequence (with Xaa being Gly, Ac_3C (1-aminocyclopropane-1-carboxylic acid) and Ac_5C (1-aminocyclopentane-1-carboxylic amino acid)), using both computer simulation and experimental techniques.⁵

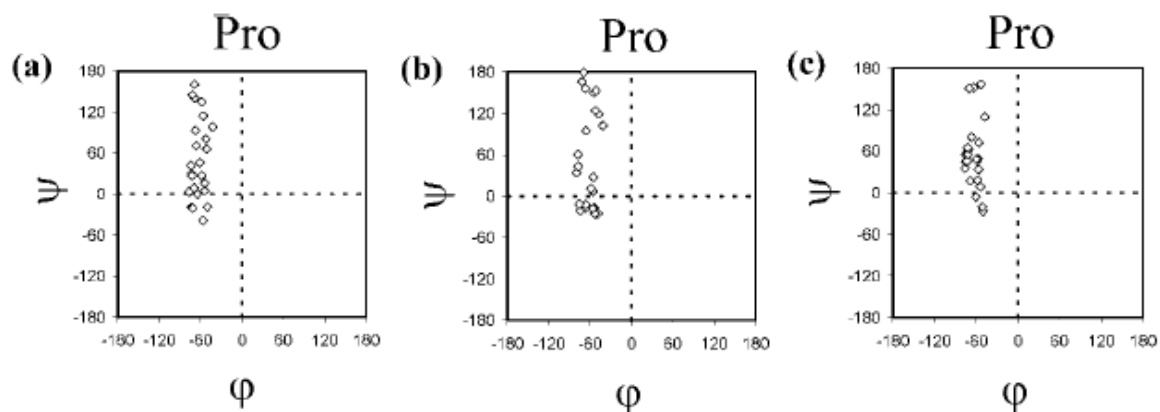
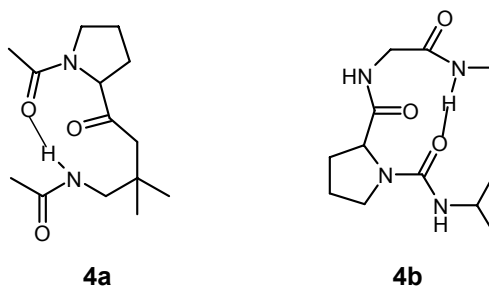


Figure 2. Comparison between the conformational preferences of the Pro residue in (a) Ac-Pro-Gly-Val-NHMe, (b) Ac-Pro-Ac₃C-Val-NHMe, (c) Ac-Pro-Ac₅C-Val-NHMe. The dihedral angles represented in the conformational maps correspond to the minima found by Molecular Dynamics simulated annealing

The ϕ angle of the Pro residues confined to values around -60° , whereas ψ angle varies from $\sim -30^\circ$ to $\sim 165^\circ$ (Figure 2). All the Ac-Pro-Gly-Val-NHMe minima are characterized by a hydrogen bond between the acetyl CO group and the Val NH moiety, which forms the ten-membered cycle typical of a β -turn. This result is in line with the well-known propensity of proline to occupy the $i+1$ position of β -turns.

The crystal structures of **4a** and **4b** show that these molecules can form 10-membered ring C=O - - H-N hydrogen bonds analogues to those commonly observed in β -turns.⁶

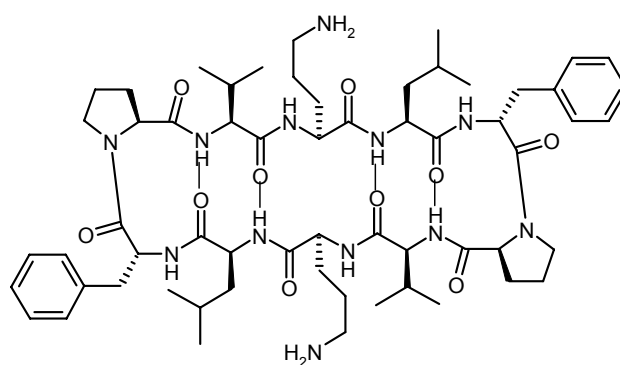


The torsion angle ω is very often disregarded because it does not reflect structural features of the corresponding peptide bond NH-CO in full. In an ideal case this angle is 0° for the *cis*-configuration of the peptide bond and 180° for the *trans*-configuration. The *trans*-isomer of a typical peptide bond is favored greatly over the *cis*-isomer. In contrast, a *trans*-bond involving the nitrogen atom of a proline residue is favored only slightly, and both isomers are common in peptide and folded proteins.^{7, 8} The *cis* - *trans* isomerisation of a peptide bond is closely related to many biologically important processes, primarily, to folding/unfolding.⁹

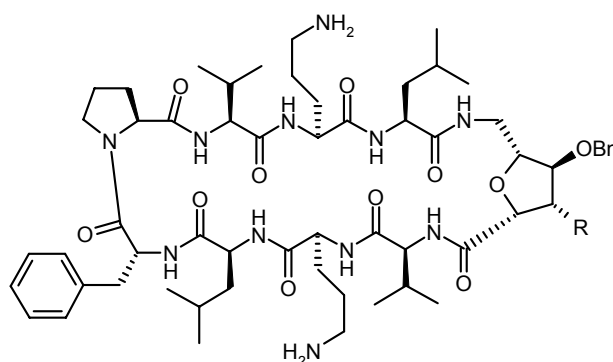
1.1.3 BIOLOGICAL APPLICATION

Proline, pipercolic acid and different CRAAs are included in numerous biologically active compounds. The practice of constraining natural amino acids like their conformationally constrained counterparts was highly successful in the design and synthesis of peptidomimetic molecules.

Gramicidine S (GS) is a cationic antimicrobial peptide which is active against a wide range of bacteria, both Gram-positive and Gram-negative strains, and as such represents an attractive lead compound for the development of new antibiotic strategies. Research on GS analogues with improved medicinal properties is mainly aimed at the development of analogues that have bacterial properties inherent to GS, while not being active against erythrocytes. Some novel dipeptide isosters were used to replace the D-Phe/ Pro turn motif of GS. The biological evaluation revealed that **5a** was similarly active as **5b** and slightly less active compared to GS.¹⁰

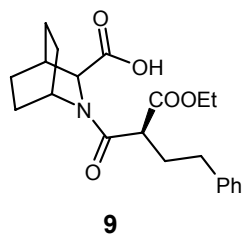


Gramicidin S

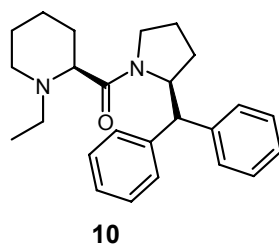


5a (R = H)
5b (R = OBn)

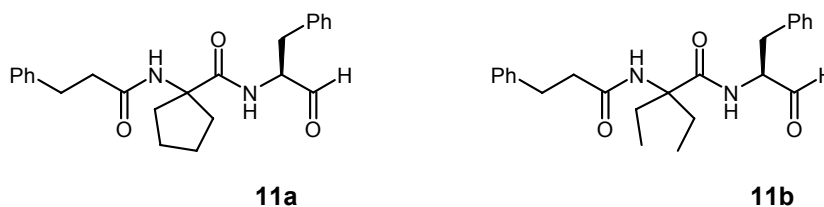
It was found that incorporation of bicycloproline into α -ketoamide such as Hepatitis C virus (HCV) protease inhibitor **6** demonstrated therapeutic potential. Starting from **6** structural modifications at P4 alone or in combination with additional modification at P1' or P1



Pipecolic acid was used in the synthesis of the pharmaceutical **10** with antimicrobial properties.¹⁵

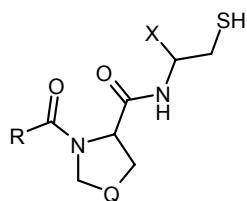


The effect of incorporating α, α' -diethylglycine and α -aminocyclopentane carboxylic acid at the P₂ position of inhibitors on μ -calpain inhibition was studied. Potentially effective and selective inhibitors (**11a**, **11b**) of μ -calpain versus cathepsin B were synthesized.¹⁶



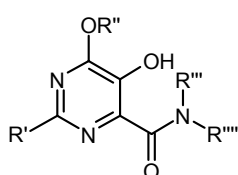
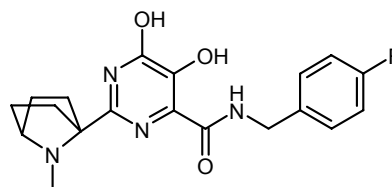
Proline and pipecolic acid as an integral part were used in the synthesis of constrained azacycles – monocyclic, bicyclic and polycyclic amino acid analogues, into which pharmacologically or structurally relevant functional groups were incorporated.¹⁷

Molecules having a residue of a classical non-steroidal anti-inflammatory drug (NSAID) and an antioxidant moiety, both attached through amide bonds to L-proline, *trans*-4-hydroxy-L-proline or DL-pipecolic acid residue.¹⁸ These compounds (some of them are given as **12**) could find useful applications, among others, in slowing the progression or delaying the onset of neurodegenerative diseases.

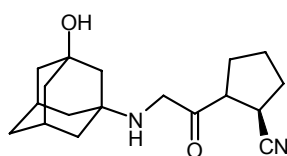
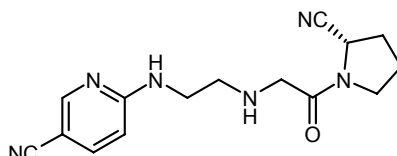
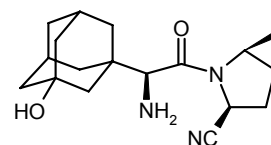


12 Q= CH₂, CH₂CH₂, CHOH
 R= indomethacin residue, naproxen residue
 X= COOC₂H₅, H

4,5-Dyhydroxypyrimidine-6-carboxamides of formula **13** are described as inhibitors of HIV integrase and inhibitors of HIV replication. These compounds are useful in the prevention and treatment of HIV infection and in the prevention, delay in the onset, and treatment of AIDS. The *N*-protected 7-azabicyclo[2.2.1]heptane-1-carboxylic acid was used in the synthesis of HIV inhibitor **13a**.¹⁹

**13****13a**

Another interesting area of the CRAAs usage is DPP-IV inhibitors. Dipeptidylpeptidase IV (DPP-IV) is a drug target for Type II diabetes. It is the primary enzyme responsible for degradation of incretins, such as glucagon-like peptide-1 (GLP-1), which is a hormone responsible for the glucose-dependent stimulation of insulin in the human body.^{20, 21} There are a number of DPP-IV inhibitors, containing proline and 3,5-methanoproline residue, known, such as NVP-LAF237 (vildagliptin) **14**,²² NVP-DPP728 **15**,^{23, 24} saxagliptin **16**.^{25, 26}

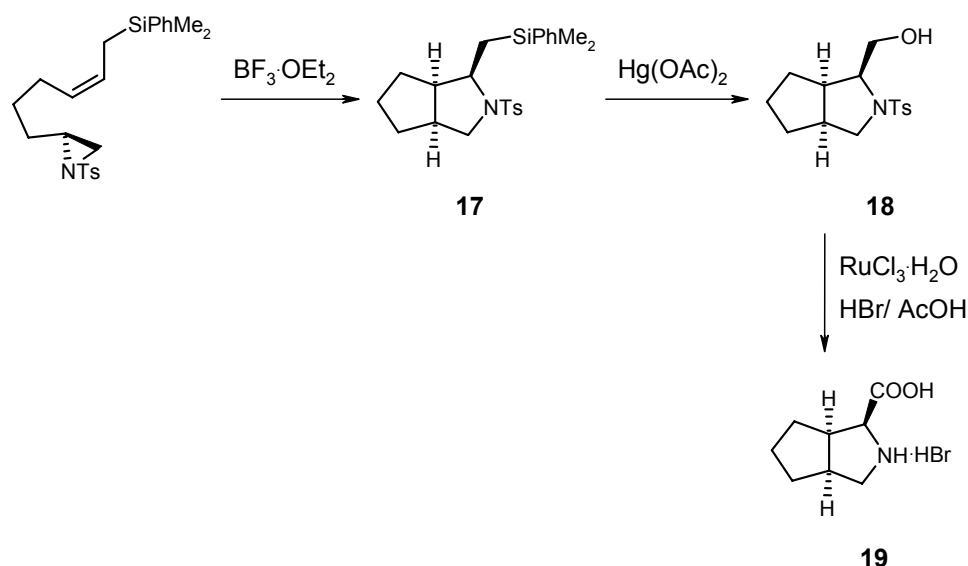
**14****15****16**

Thus, conformationally restricted amino monocyclic and bicyclic natural and unnatural amino acids can be directly incorporated in a potent biologically active molecule as a part of design element.

1.1.4 SYNTHESIS OF CRAAs – PROLINE AND PIPECOLIC ACID ANALOGUES

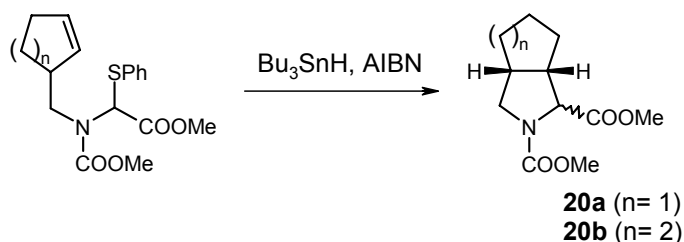
A great number of methods for the preparation of a CRAA and its derivatives have been developed, but almost every CRAA requires an individual approach to its synthesis. Therefore, examples of the synthesis of the known bi- and tricyclic proline and pipercolic acid analogues are given in this part.

The synthesis of bicyclic proline analogues using a formal [3+2] intramolecular aziridine-allylsilane cycloaddition reaction was reported by Bergmeier *et al.*²⁷ The preparation of proline analogues is described in *Scheme 1*. Oxidation of **17** to the alcohol **18** was carried out using mercuric acetate. Oxidation to the corresponding carboxylic acid and the removal of the tosyl group gave the amino acid **19**. This synthesis allows the preparation of both 5-5 and 6-5 fused ring systems.



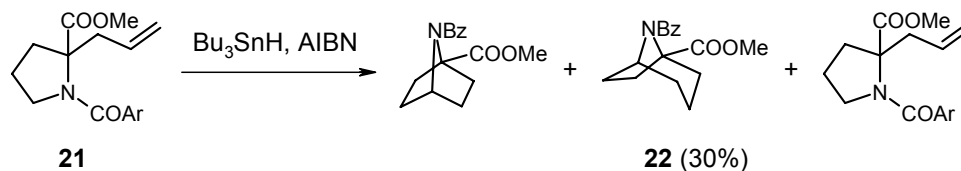
Scheme 1.

Reductive cyclizations of several α -(phenylthio)glycine derivatives with 3-alkenyl substituent at nitrogen were performed by Speckamp and co-workers (*Scheme 2*).²⁸ These reactions proceed *via* 2-aza-5-alken-1-yl radicals as intermediates and lead to bicyclic proline analogues **20a**, **20b**.



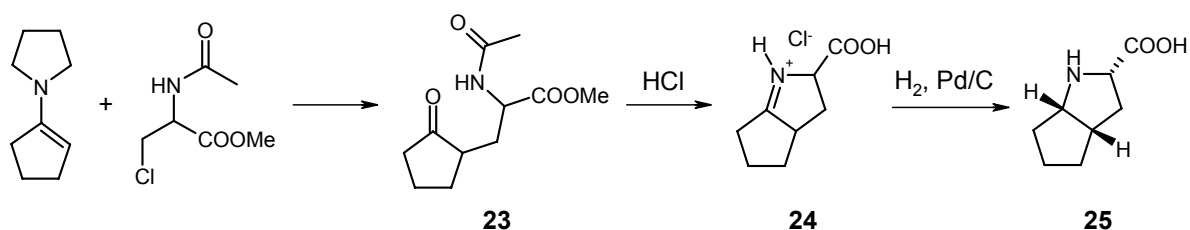
Scheme 2.

Treatment of methyl 1-(*o*-bromobenzoyl)-2-(prop-2-enyl)pyrrolidine-2-carboxylate **21** with Bu_3SnH in the presence of a catalytic amount of AIBN gave three different products, one of them is 8-azabicyclo[3.2.1]octane **22** (Scheme 3).²⁹



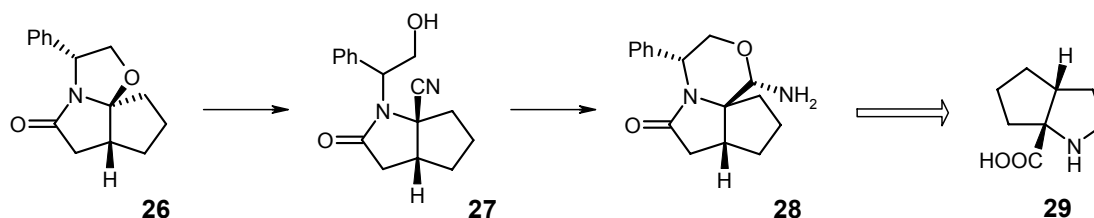
Scheme 3.

The bicyclic amino acid **25** was synthesized *via* enamine reaction.³⁰ Starting from cyclopentanopyrrolidine and the chloroalanine derivative, the intermediate **23** was generated. Cyclization, followed by hydrogenation of **24** with Pd/C led to the racemic mixture of **25** (Scheme 4).



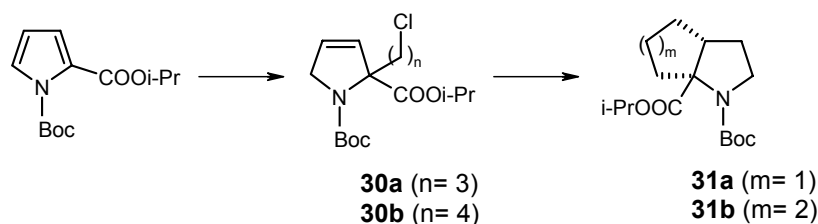
Scheme 4.

Dorsey *et al.* reported a strategy toward CRAA **29**.³¹ Exposure of Meyers' lactam **26** to TMSCN in the presence of a Lewis acid led to *N*-acetyl aminonitrile **27**. In an attempt to reduce its nitrile function selectively the stable *N,O*-acetal **28** was obtained in a good yield as a single diastereomer, from which bicycloproline **29** can be synthesized (Scheme 5).



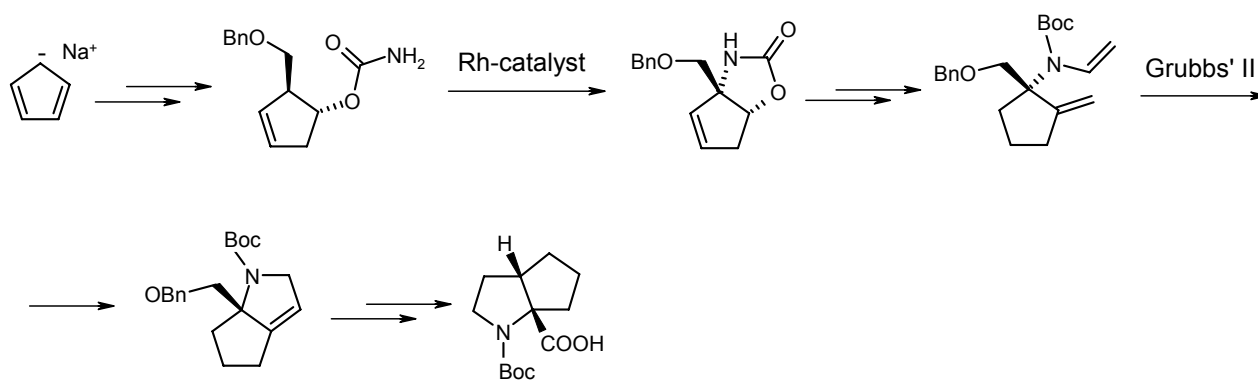
Scheme 5.

Synthesis of racemic *N*-Boc protected *iso*-propyl ester **31** of bicycloproline was also reported.³² Pyrrolines **30a** and **30b** were prepared by the reductive alkylation of electron-deficient pyrrole. These compounds were subjected to radical cyclization and gave *cis*-diastereomers **31a** and **31b** (Scheme 6).



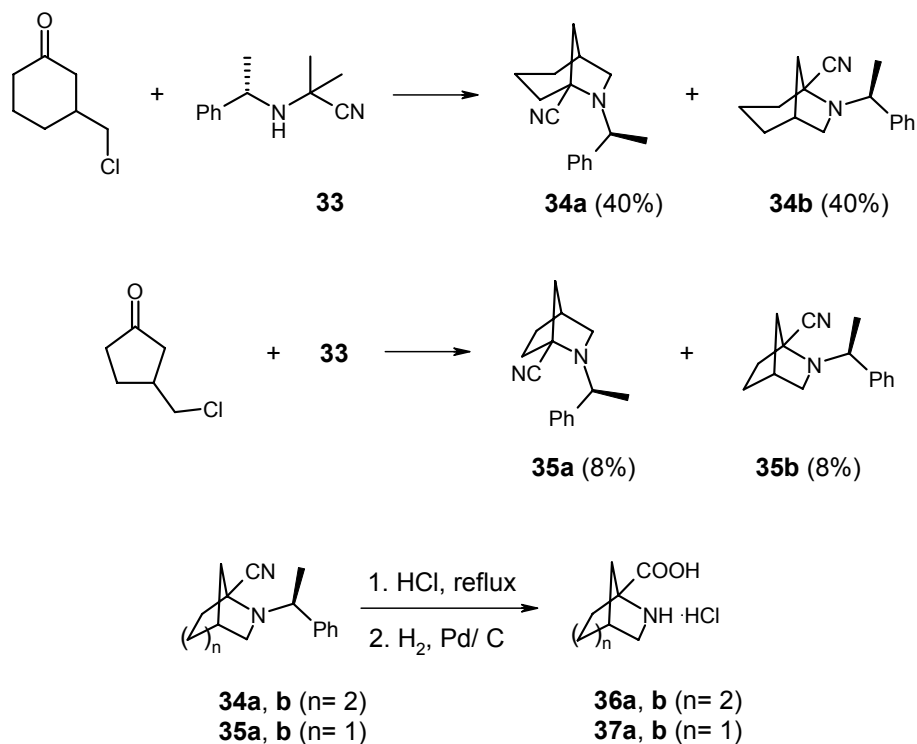
Scheme 6.

(+)-*N*-Boc-bicycloproline **32b** has been recently achieved starting from cyclopentadienylide.³³ Key steps include a rhodium-catalyzed nitrenoid C-H insertion to install the *tert*-alkylamine and a ring-closing metathesis reaction to form the pyrrolidine ring (Scheme 7).



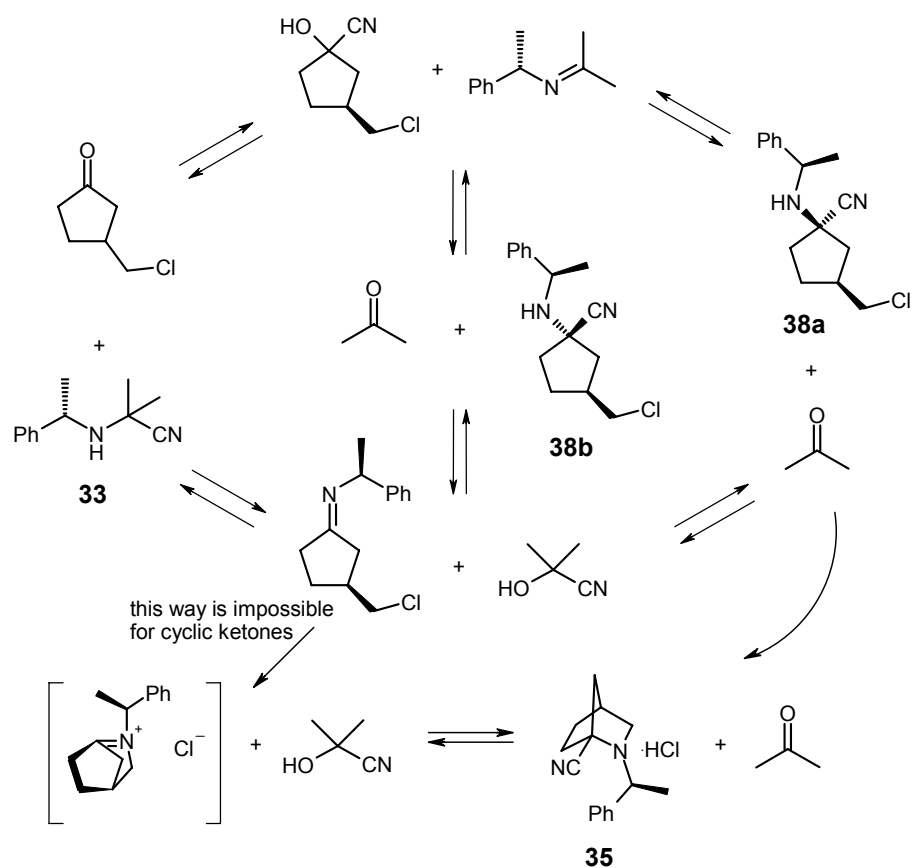
32b
Scheme 7.

2-cyanopyrrolidines are used as building blocks for the synthesis of cage systems, alkaloids and their analogues, amino acids and other biologically active compounds.³⁴⁻³⁶ One of the most interesting applications of 2-cyanopyrrolidines in organic synthesis is their transformation to proline analogues. A reaction of 2-methyl-2-(((1*S*)-1-phenylethyl)amino)propanenitrile **33** with corresponding γ -functionalized carbonyl compounds was used as a key step in the synthesis of 2-azabicyclo[2.2.1]heptane-1-carboxylic acid **37** and 6-azabicyclo[3.2.1]octane-5-carboxylic acid **36**.^{37, 38} Hydrolysis and deprotection by hydrogenolysis of 2-cyanopyrrolidines allowed to obtain new CRAAs **36**, **37** in reasonable yields (Scheme 8).



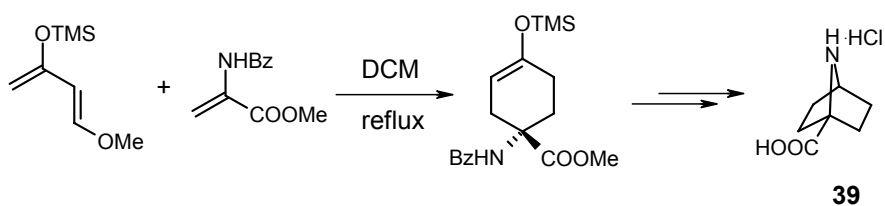
Scheme 8.

The mechanism for cyclization with 2-methyl-2-(((1*S*)-1-phenylethyl)amino)propanenitrile **33** was suggested by Grygorenko *et al.*³⁷ Aminonitrile **38** is a key intermediate. *Scheme 9* illustrates this for the reaction of **33** with one of the enantiomers of 3-chloromethyl-cyclopentanone. In the case of cyclic ketones, only one diastereomer of aminonitrile **38** (namely, **38a**) can undergo the cyclization, while the second, **38b**, has first to be converted to **38a**.



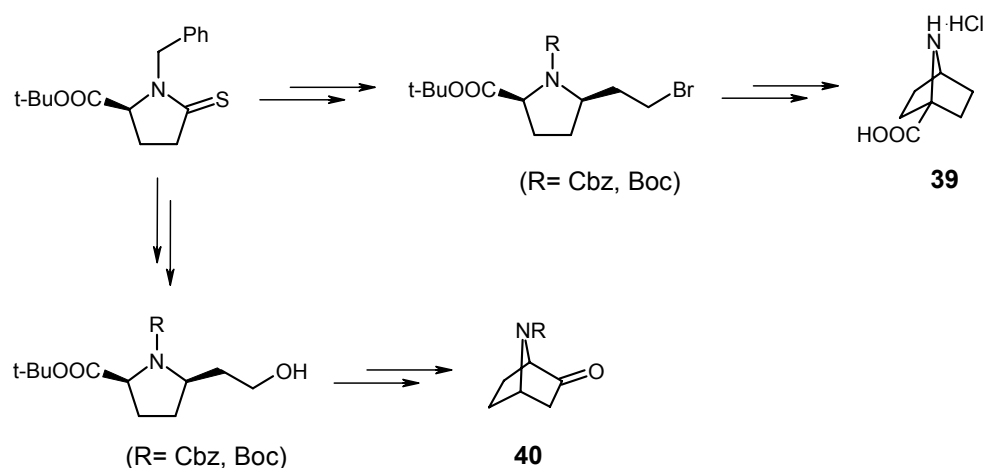
Scheme 9.

Avenoza *et al.* described a new synthetic route to 7-azabicyclo[2.2.1]heptane-1-carboxylic acid **39**, in which the key step is the Diels-Alder reaction using methyl 2-benzamidoacrylate as dienophile (Scheme 10).³⁹ This CRAA was obtained as a mixture of enantiomers from achiral starting material.

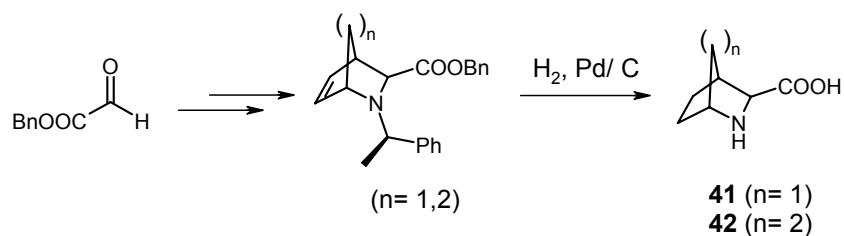


Scheme 10.

This optically pure CRAA **39** was prepared by usage of a thiolactam sulfide contraction and a transannular alkylation sequence as the key C-C bond-forming steps, starting from L-glutamic acid.⁴⁰ Decarboxylation of the C-1 carboxy unit of the latter intermediate also demonstrated the potential applicability of the method for natural product synthesis, with the short chirospesific preparation of the (+)-epibatidine precursor **40**.

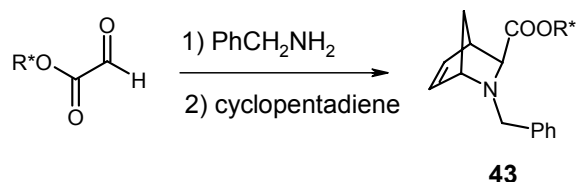


Synthesis of the CRAA – 2-azabicyclo[2.2.1]heptane-3-carboxylic acid **41** – was accomplished following the procedure of Stella *et al.*^{41, 42} Condensation of glyoxalate with (*R*)-phenylethylamine in refluxing benzene yielded the chiral imine that underwent hetero-Diels-Alder reaction with cyclopentadiene to give a mixture of diastereomers that were easily separated by column chromatography. Hydrogenation of the double bond and removal of *N*-methylbenzyl group gave CRAA **41**. The same strategy was used to synthesize CRAA **42** (*Scheme 12*).



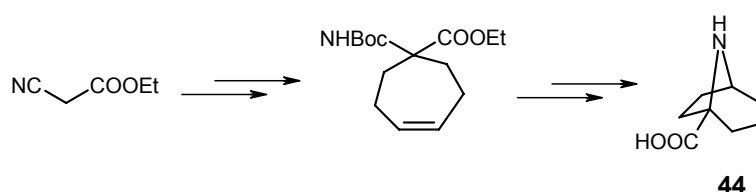
To synthesize CRAA **41** cyano-(toluene-4-sulfonylimino)-acetic acid ethyl ester can be used instead of the chiral imine with (*R*)-phenylethylamine moiety.⁴³

The asymmetric aza-Diels-Alder reaction of the (*1R*)-8-phenylmenthyl or (*1R*)-8-phenylisoneomenthyl glyoxylate-derived *N*-benzylimine with cyclopentadiene resulted in the enantioselective synthesis of the corresponding pure [(*1S*,3-*exo*)-2-benzyl-2-azabicyclo[2.2.1]hept-5-ene]-3-carboxylates **43** (*Scheme 13*).⁴⁴



Scheme 13.

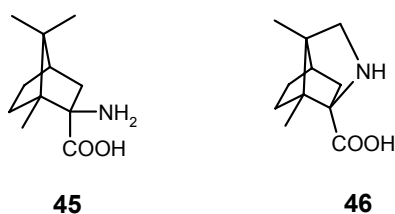
A straightforward synthesis of 8-azabicyclo[3.2.1]octane-1-carboxylic acid **44**, a proline analogue with a bicyclic structure, was described by Casabonaa *et al.*⁴⁵ The procedure makes use of readily available starting materials and involves simple, high-yielding transformations (*Scheme 14*).



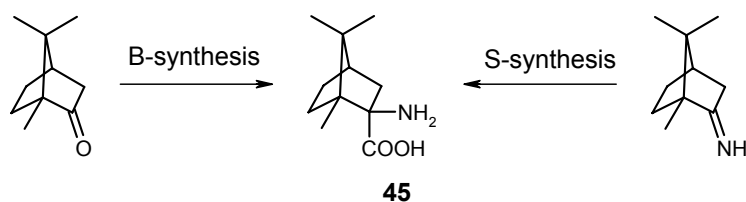
Scheme 14.

Camphor is a naturally occurring terpenoid. The distinctive odor of camphor is familiar to many consumers, as it has been traditionally used in mothballs and some medical preparations to reduce itching, to treat respiratory tract diseases involving mucous membrane inflammation. It is also used in a wide variety of other applications, along with other similar plant derived chemicals, including film manufacture, plastics, lacquers, and some explosives.

Two CRAAs **45** and **46** with a camphor moiety were synthesized till now:

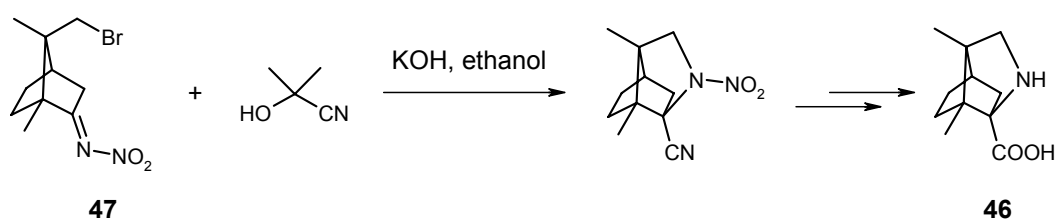


2-aminobornane-2-carboxylic acid **45** was obtained exclusively from D-camphor by both the Strecker and the Bucherer reactions (*Scheme 15*).^{46,47}



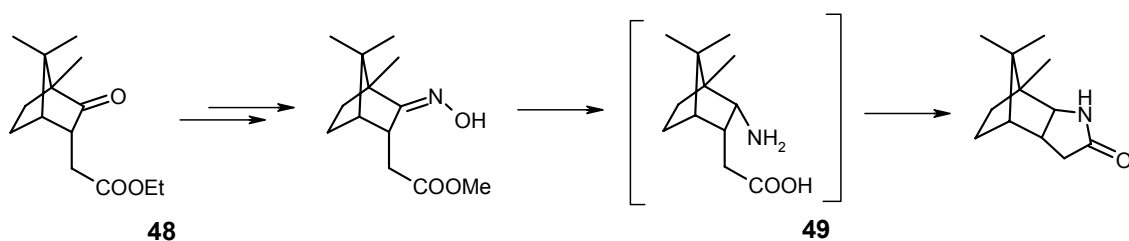
Scheme 15.

A chiral tricyclic proline analogue **46** can be prepared starting from camphor, available in both enantiomeric forms.⁴⁸ The intramolecular ‘domino’-type cyclization of the 8-bromocamphor derivative **47** containing a C=N bond was used as a key step (Scheme 16).



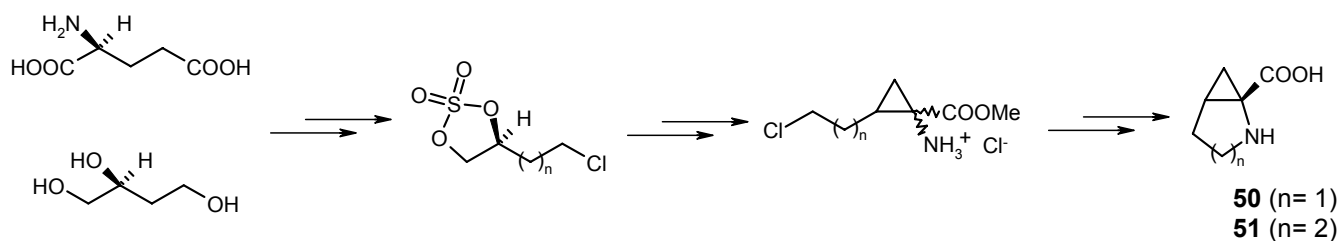
Scheme 16.

Tricyclic lactam – 3-aza-1,10,10-trimethyltricyclo[5.2.1.0^{2,6}]decan-4-one – was formed instead of amino acid **49** starting from the camphor derivative **48**.⁴⁹ Apparently here operates the so called “neighbor group effect” resulting in hydrolysis of the ester and in cyclization of the amino acid **49** (Scheme 17).



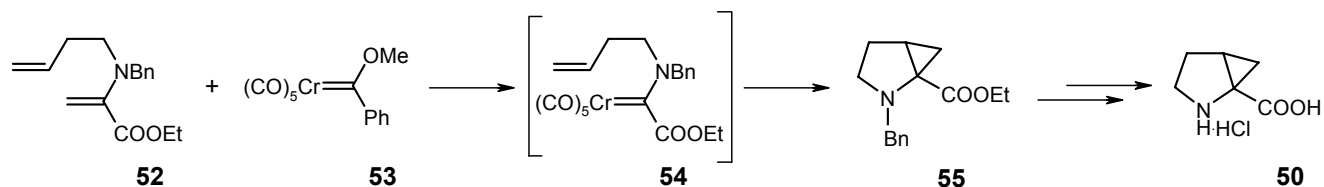
Scheme 17.

2,3-methanoamino acids are of interest due to the biological activities exhibited by these compounds. The potential value of such substances as enzyme inhibitors or in the synthesis of conformationally constrained peptidomimetics was recognized.^{50, 51} The asymmetric synthesis of the optically active 2,3-methano analog of pipercolic acid **51** and 2,3-methanoproline **50**, starting from L-glutamic acid and (S)-(-)-butanetriol respectively, was reported by Hercouet *et al.*⁵²



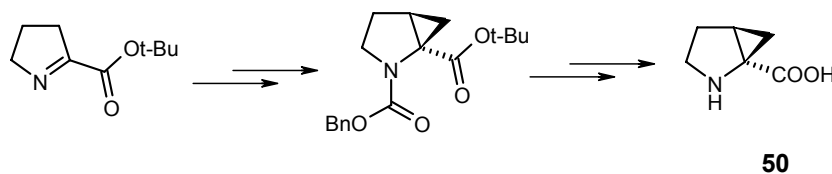
Scheme 18.

Hydrochloride of CRAA **50** can be synthesized in a different way. An attempt to synthesize homoallylaminocarbene **54** by metathesis reaction of dehydroamino acid **52** and carbene complex **53** led to ethyl *N*-benzylhomoprolinate **55**, which probably arises from the intramolecular cyclopropanation of aminocarbene **54** under reaction conditions (Scheme 19).⁵³



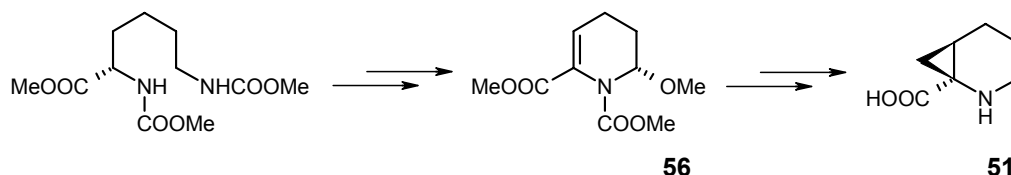
Scheme 19.

2,3-methanoproline **50** was also prepared by treatment of *N*-benzyloxycarbonyl-2,3-dehydroproline *tert*-butyl ester with diazomethane followed by protolysis of the resulting pyrazoline and its deprotection (Scheme 20).⁵⁴ Its *N*-acetyl-*N'*-methylamide derivative, a model peptide, was synthesized and the conformation, namely the values of the torsion angles φ , ψ and ω were determined by X-ray analysis.



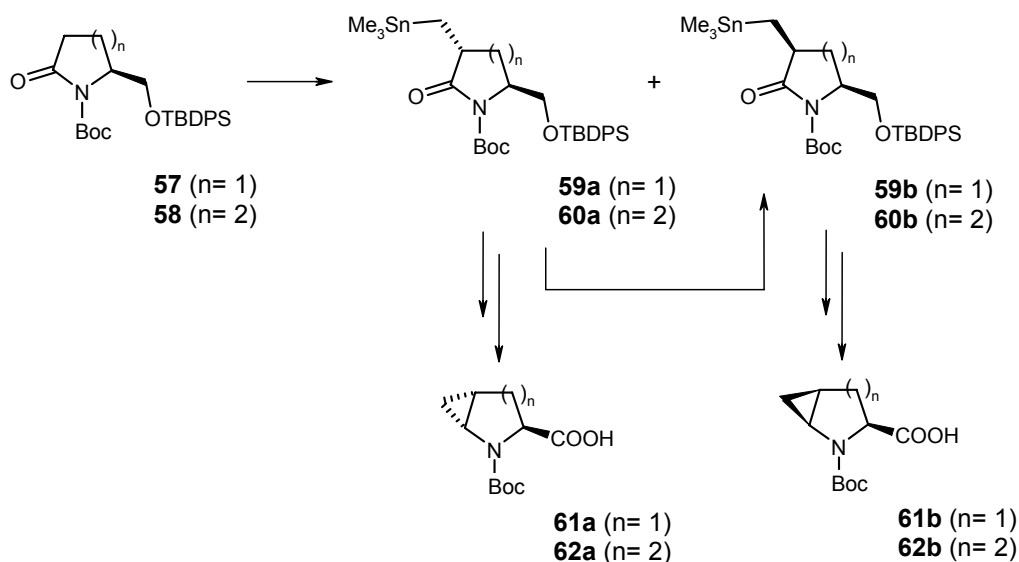
Scheme 20.

2,3-Didehydro-1,2-bis(methoxycarbonyl)-6-methoxypiperidine **56** prepared from L-lysine by using electrochemical oxidation, was cyclopropanated, and then this product was transformed to optically active CRAA **51** (Scheme 21).⁵⁵ It was shown that the 6-methoxy group in **56** was an effective chiral auxiliary.



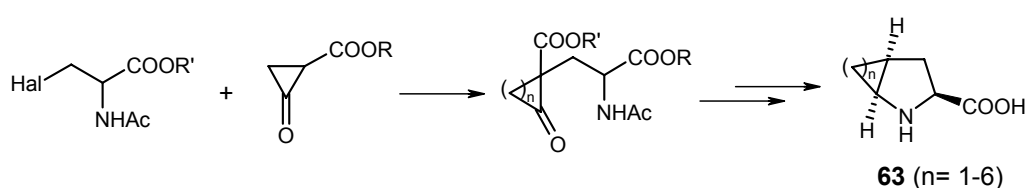
Scheme 21.

The stereocontrolled synthesis of the diastereomeric 4,5-methano-L-prolines and 5,6-methano-L-pipecolic acids by the intramolecular cyclopropanation reaction of iminium ions was performed by Hanessian *et al.*⁵⁶ Treatment of the readily available lactams **57** and **58**⁵⁷ with LiHMDS and MeSnCH₂I gives the alkylated products **59** and **60**. *N*-Boc protected CRAAs **61** and **62** can be obtained from these intermediates in a few steps (Scheme 22).



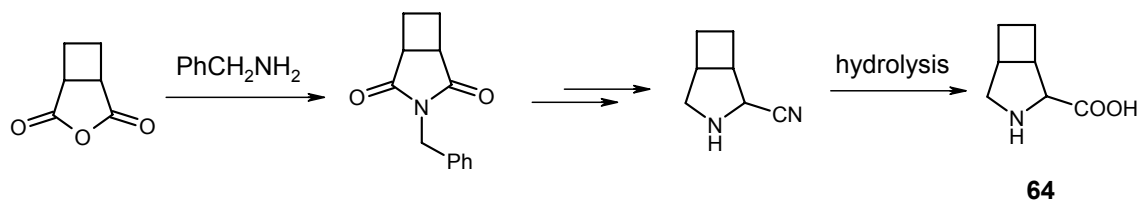
Scheme 22.

Recently, Sarakinos reported the preparation of cycloalkanone β -substituted alanine derivatives and their use in the preparation of enantiomerically enriched α -amino acids **63**, one of them was 4,5-ethanoproline (Scheme 23).⁵⁸ Furthermore, the present invention related to the preparation of pharmaceutically active products such as perindopril and ramipril using the novel cycloalkanone β -substituted alanine derivatives.



Scheme 23.

Preparation of *cis*- and *trans*-2-carboxy-3-azabicyclo[3.2.0]heptanes – 3,4-ethanoprolines **64** – was performed by Haddock starting from *cis*-1,2-cyclobutane carboxylic acid anhydride (Scheme 24).⁵⁹



Scheme 24.

Both non-stereoselective and stereoselective routes to the synthesis of many CRAAs have already been developed. An individual approach to these compounds is required in almost every case.

1.2 α TFM AAs

Fluorine-containing amino acids and molecules containing them have enjoyed widespread bioorganic applications such as biological traces, mechanistic probes, enzyme inhibitors and medical applications including control of blood pressure, allergies and tumor growth. On the other hand, α -amino acids containing the trifluoromethyl group are of particular interest due to the unique characteristics of this group.

Fluorine is one of the most abundant elements on earth, yet it occurs extremely rarely in biological compounds. Due to the specific properties of the fluorine atom, including their small steric size, high electronegativity and carbon-fluorine bond strength and the sensitivity of ^{19}F NMR spectroscopy along with large ^{19}F - ^1H coupling constants etc, the introduction of the fluorine atom into many biologically active molecules can bring about remarkable and profound changes in their physical, chemical and biological properties. Among them, fluorine-containing amino acids and large molecules containing them, α -trifluoromethylated α -amino acids (α Tfm AAs) form a special class of man-made quaternary α,α -disubstituted α -amino acids of considerable interest in modern peptide chemistry. α,α -Dialkylation leads to the stabilization of certain secondary structure motifs while fluorination brings in its unique properties, such as high electronegativity, high lipophilicity, and steric demand that non-linearly increases with the number of fluorine atoms. Incorporation of C^α -fluoroalkyl amino acids into peptides can retard proteolytic degradation and enhance *in vivo* absorption as well as drug permeability through certain body barriers.⁶⁰ Stabilization of secondary structure motifs was also observed. A further advantage of fluoromodification is the enhancement of thermal stability of peptides.⁶¹ Incorporation of trifluoromethyl groups generally increases the chemical stability of molecules due to the high bond strength.

1.2.1 RETROSYNTHETIC APPROACH TO α TFM AAs

There are two main strategies to introduce fluoroalkyl groups into organic molecules: direct fluorination and introduction of fluorine *via* fluorine-containing building blocks. Although the first approach is more straightforward, provided that suitable fluorinating agents are available, control of regio- and stereoselectivity is often difficult to achieve. Besides many of the reagents currently used for direct introduction of fluorine and perfluoroalkyl groups are expensive, toxic, corrosive and can be explosive.

The most commonly used, commercially available fluorinated building blocks that can be used in synthesis of α -fluorinated amino acids are given below.

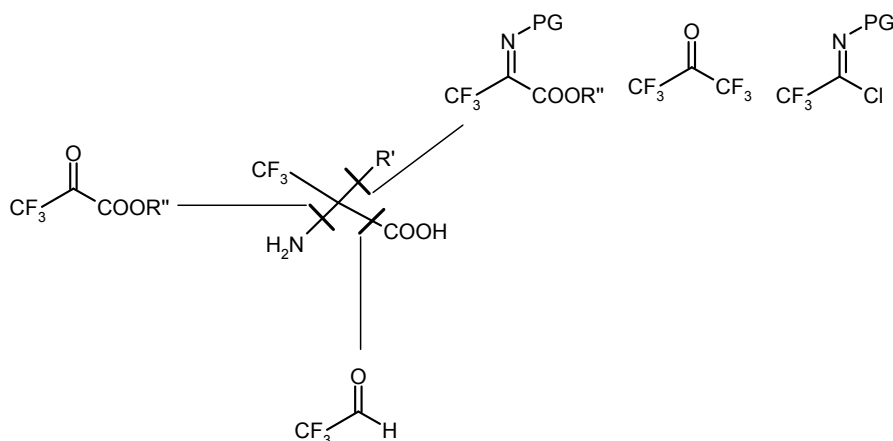
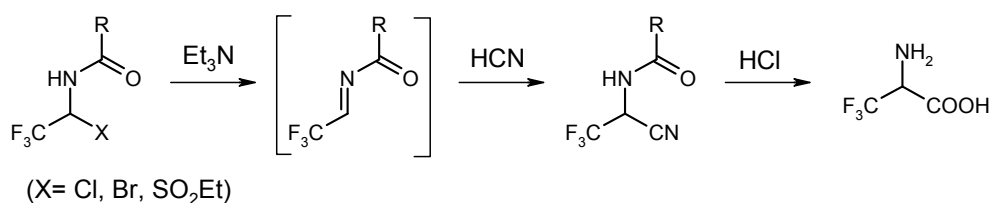


Figure 3. Retrosynthetic approach to fluorinated amino acids

Each retrosynthetic disconnection demonstrates the introduction of the missing substituent and is linked to the starting materials that are used for this transformation. The most straightforward approach to α Tfm AAs uses highly functionalized imines of trifluoropyruvates, delivering structurally diverse target compounds in a few steps.

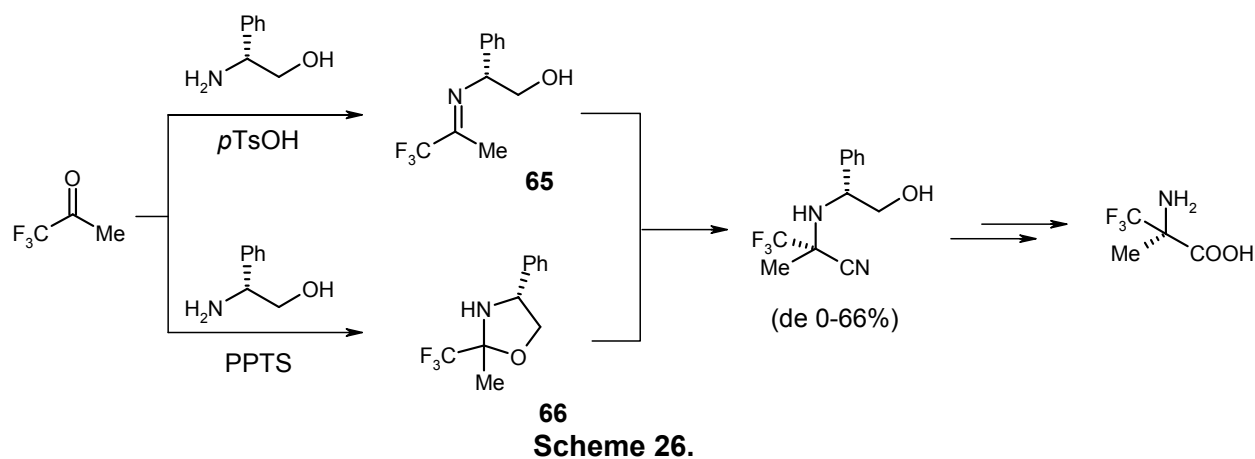
1.2.2 STRECKER REACTION IN THE SYNTHESIS OF α TFM AAs

The Strecker reaction is one of the most versatile methods for preparing α -amino acids. According to this route, aldehydes and ketones react with cyanide in the presence of an amine hydrochloride to form α -aminonitrile that is hydrolyzed to give the corresponding α -amino acid. Modification of this reaction is used to synthesize some α Tfm AAs. Some examples are the synthesis of α TfmAla⁶² and α TfmPhe. Weygand and Steglich reported the synthesis of 3,3,3-trifluoroalanine (α TmfGly) (Scheme 25).^{63, 64}

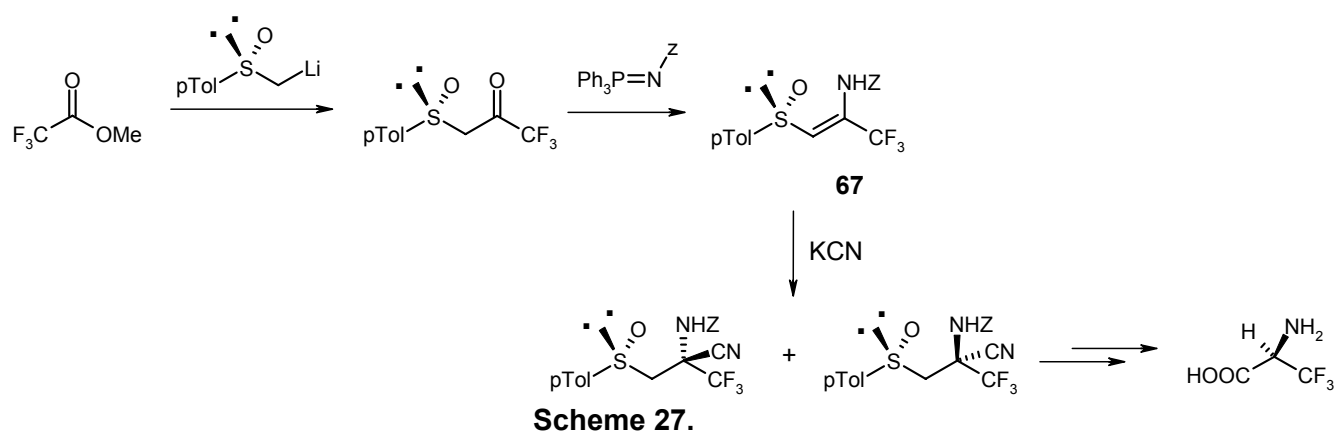


Scheme 25.

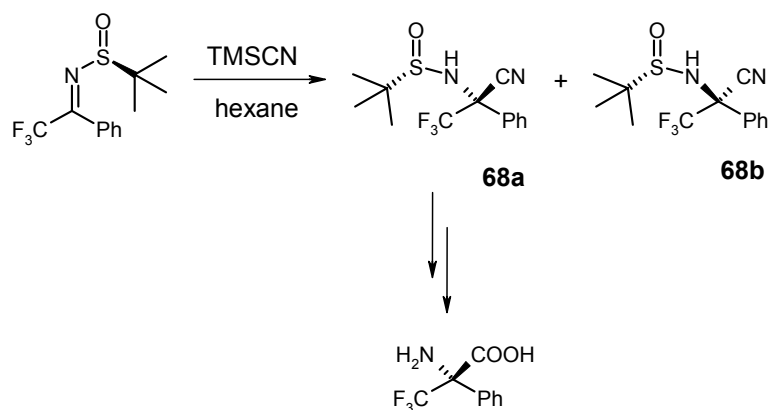
Brigau and co-workers investigated the asymmetric Strecker-type reaction of chiral imines **65** and oxazolidines **66** with TMSCN and different Lewis acids.⁶⁵ (*R*)-phenylglycinol and (*S*)- α -methylbenzylamine⁶⁶ were used as chiral auxiliaries. The synthons afforded amino nitriles generally in high yield although the diastereoselection proved to be low to moderate. This route was used to synthesize α TmfGly and α TmfAla⁶⁶ (Scheme 26).



Efficient synthesis of optically pure α -(fluoroalkyl)- β -sulfinyl enamines was achieved by aza-Wittig (Staudinger) reaction of triphenyliminophosphoranes with the corresponding α -fluorinated- α' -sulfinyl ketones.^{67, 68} Compounds **67** were used further in the asymmetric Strecker reaction. Synthesis of (*R*)-3,3,3-trifluoroalanine as an example of such conversions is given in *Scheme 27*.



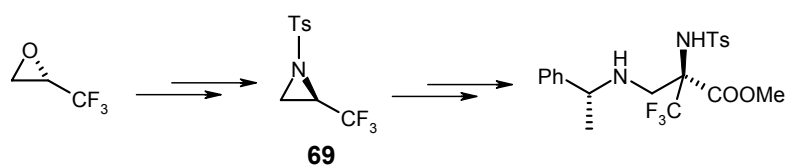
An example of an asymmetric Strecker reaction involving chiral sulfinimines derived from α -trifluoromethyl ketones and (*R*)-*tert*-butylsulfonamide was reported by Lu and co-workers.⁶⁹ The reaction of α Tfm-sulfinimines with TMSCN in the absence of catalysts in different solvents was investigated. Best results were obtained in hexane, furnishing stereoisomer **68a** in 98% de. The optically active (*S*)-2-amino-2-phenyl-1,1,1-trifluoropropanoic acid was synthesized by this method.



Scheme 28.

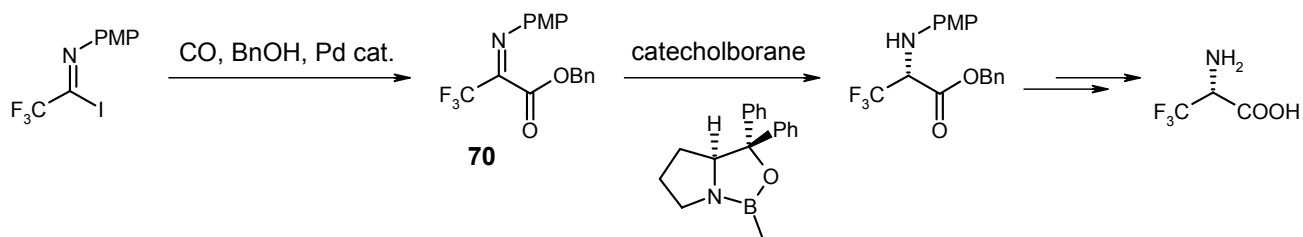
1.2.3 NON-STEREOSELECTIVE AND STEREOSELECTIVE SYNTHESIS OF α Tfm AAs

Uneyama reported a new approach to enantiomerically pure α Tfm α -amino acid, which involves the use of optically pure α -trifluoromethylated aziridines **69** as intermediates (these compounds can be prepared starting from 2,3-epoxy-1,1,1-trifluoropropane (Scheme 29)).^{70, 71}



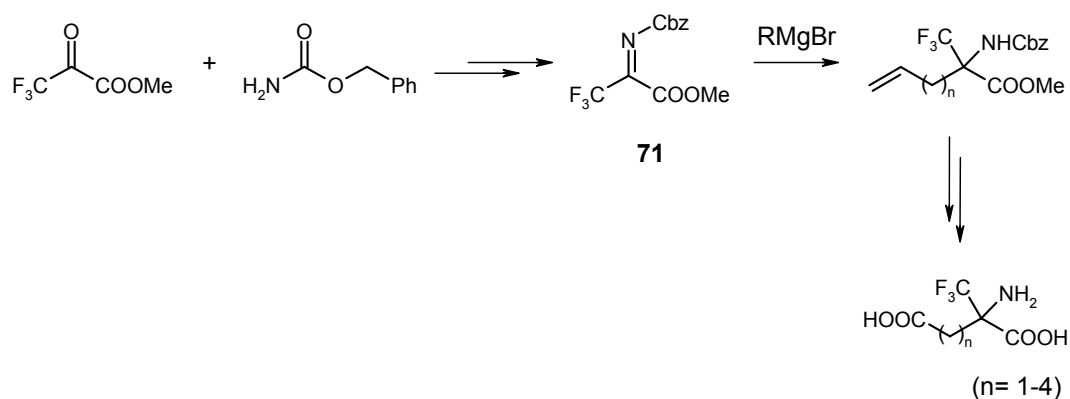
Scheme 29.

Homologation of trifluoroacetimidoyl iodides by palladium-catalyst under CO atmosphere (1 atm) in the presence of alcohols gives α -imino perfluoroalkanoates which are transformed to α Tfm AAs.⁷² The rate and the yield of the reaction were affected by the nature of the *N*-aryl group and the alcohol. Electron donating substituents at the nitrogen atom such as *p*-methoxyphenyl and the use of primary alcohols proved to promote the conversion. Asymmetric hydrogenation of **70** led to α TfmGly with 62% ee.⁷³



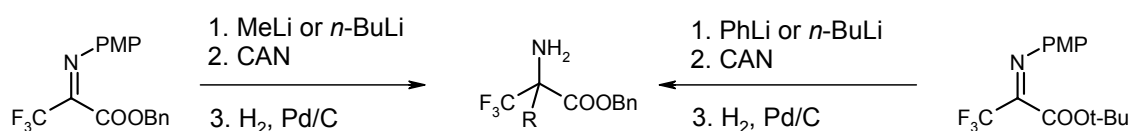
Scheme 30.

The most general approach to $C^{\alpha,\alpha}$ -disubstituted fluorinated AAs is based on the addition of carbon nucleophiles to the $C=N$ bond of *N*-substituted imines of alkyl trifluoropyruvate. Grignard reagents are the nucleophiles of choice because they are tolerated by many functional groups. The introduction of unsaturated alkyl chains into **71** is a valuable method for more complex and functionalized $C^{\alpha,\alpha}$ -disubstituted fluorinated AAs (Scheme 31). This methodology was used to synthesize α TfmAsp, α Tfm-2-aminoheptanedioic acid.⁷⁴



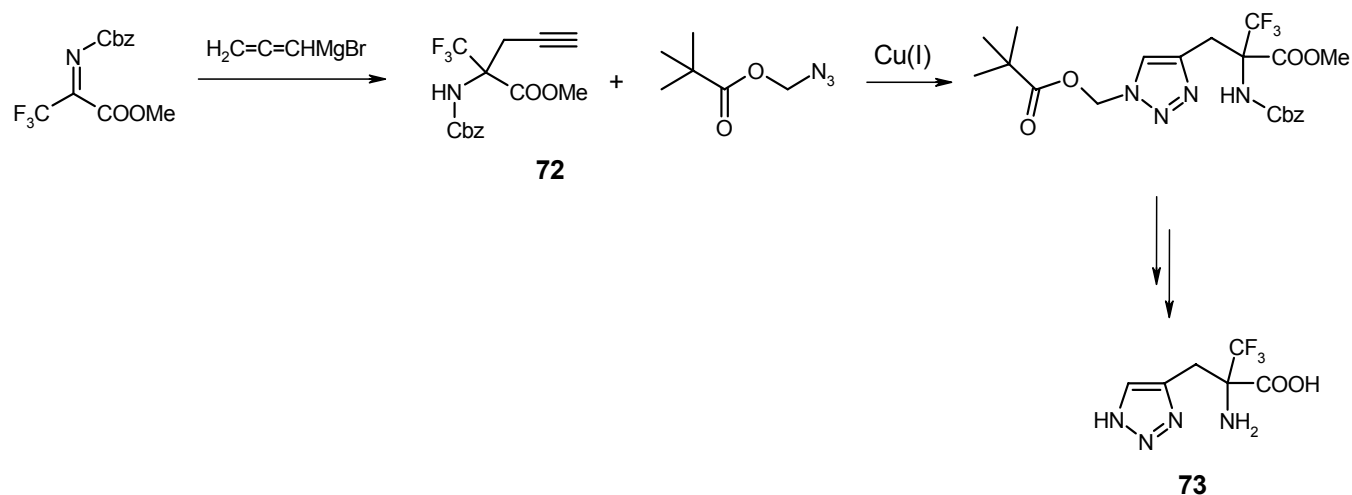
Scheme 31.

N-Protected imines of fluorinated pyruvates have been submitted to alkylation procedure to give α Tfm AAs of high structural diversity (Scheme 32). In this case, organolithium reagents were used as nucleophiles.^{72, 75}



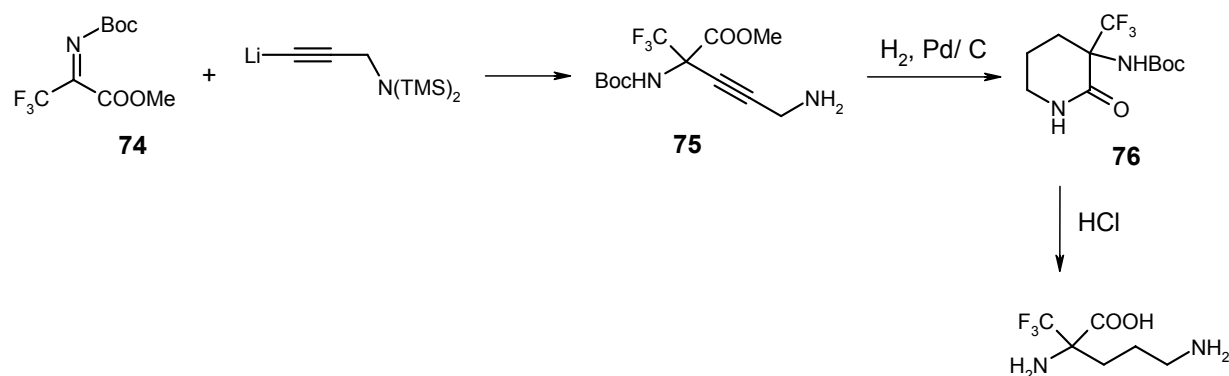
Scheme 32.

An efficient method for the preparation of functionalized α Tfm-substituted azahistidine analogues was developed by Osipov and co-workers.⁷⁶ The method is based on the regioselective addition of allenylmagnesium bromide to highly electrophilic imines of trifluoropyruvates and subsequent 1,3-dipolar Huisgen cycloaddition between **72** and organic azides. An example of the synthesis of free α Tfm azahistidine **73** is given in Scheme 33.



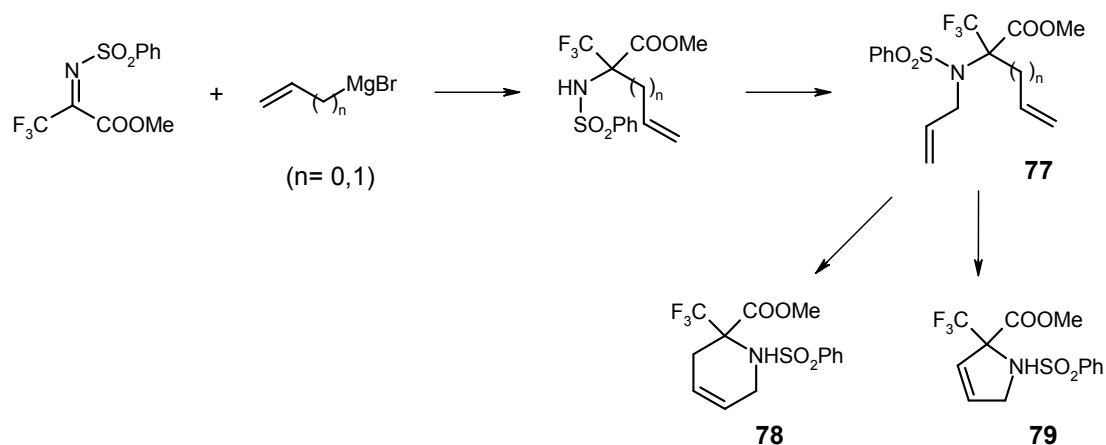
Scheme 33.

A new approach to α Tfm ornithine is based on the addition of an organo-lithiated nucleophile to alkoxy carbonyl imines of trifluoropyruvate.⁷⁷ The adduct **75** generated by reaction of **74** with lithiated *N,N*-bis(trimethylsilyl)aminomethyl acetylide, was cyclized to 2-piperidone derivative **76** via hydrogenation of the triple bond (Scheme 34).



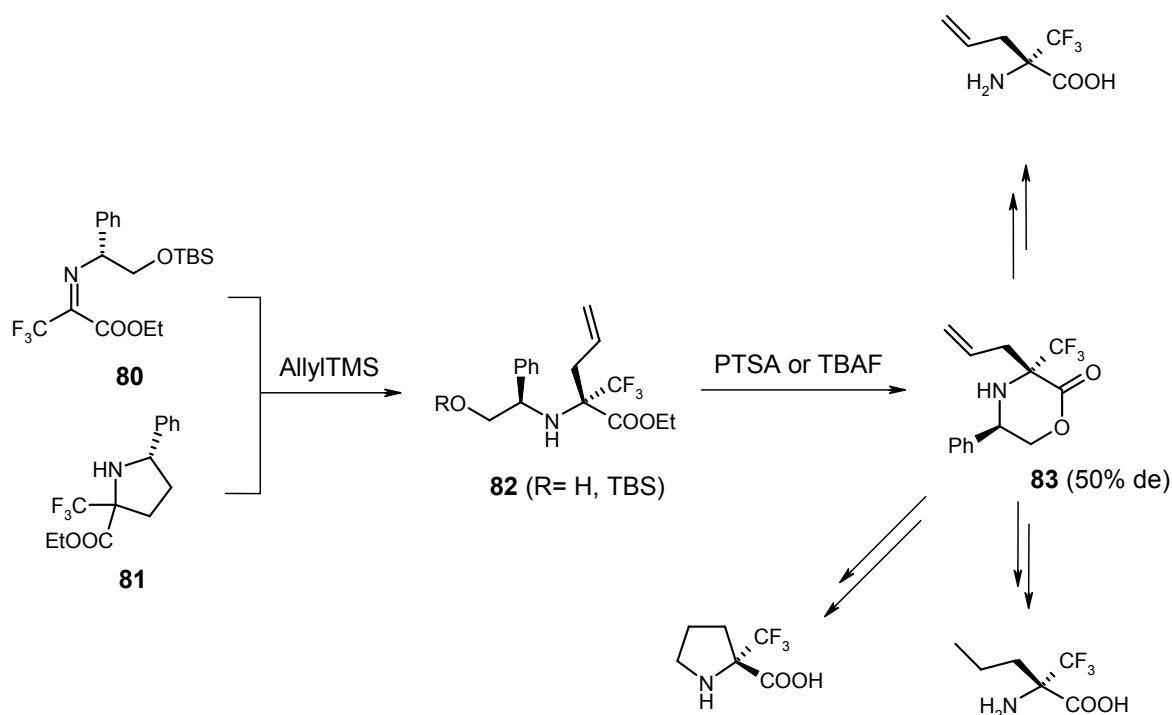
Scheme 34.

The twofold addition of unsaturated side chains to *N*-substituted imines of trifluoropyruvate and subsequent intramolecular ring-closing metathesis (RCM) can be used as a general approach for the preparation of cyclic fluorinated amino acid derivatives. An application of this strategy for the synthesis of α Tfm dehydroprolinate **79** and dehydropipecolate **78** was described by Osipov *et al.*⁷⁸ The preparation of the key compounds **77** with two alkene chains was achieved in two steps: (1) introduction of the vinyl (or allyl) side chain *via* Grignard addition and (2) *N*-allylation with allyl bromide.



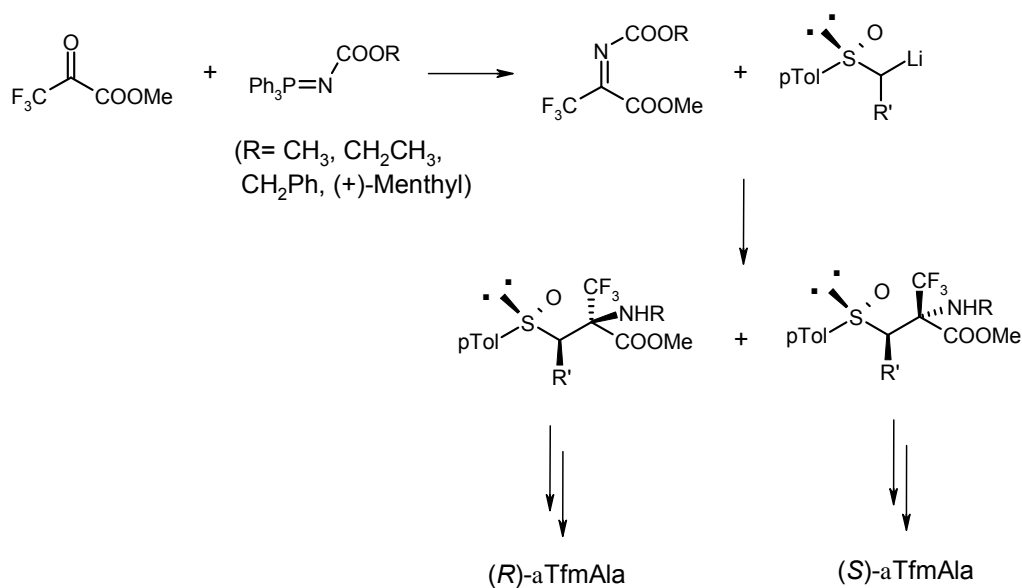
Scheme 35.

Chaume and co-workers reported a concise synthesis of both enantiomers of α Tfm-proline and (*S*)- α Tfm-prolinol from ethyl trifluoropyruvate. The key step of this strategy involves the Lewis acid promoted diastereoselective allylation of chiral α Tfm imines **80** or oxazolidines **81** (Scheme 36).⁷⁹ These synthons can be prepared from trifluoropyruvate by reaction with commercially available (*R*)-phenylglycinol or a protected derivative thereof. The diastereomers formed after cyclization of the allylated intermediates **82** to morpholinone **83** can be separated by flash chromatography. The compound **83** proved to be a valuable intermediate for the synthesis of (*S*)- α Tfm-allylglycine and (*S*)- α Tfm-norvaline.



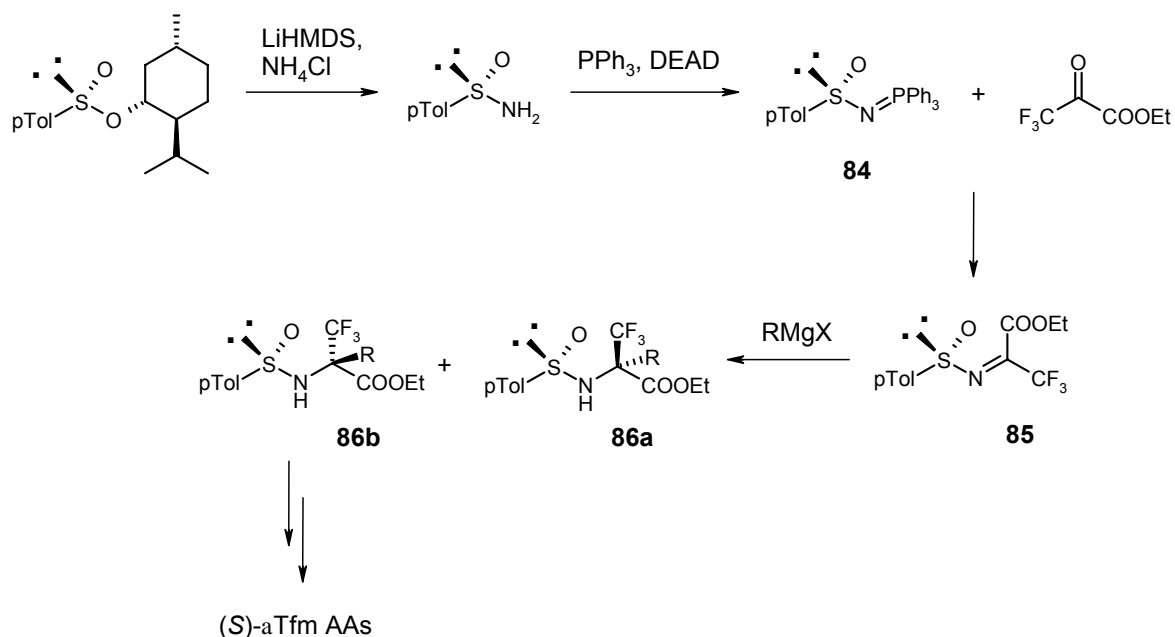
Scheme 36.

Optically pure α Tfm AAs can be prepared by the reaction of *N*-alkoxycarbonyl imines of alkyl trifluoropyruvates with a chiral lithiated sulfoxide.⁸⁰ The reaction takes place with reasonable yields but with low diastereoselectivity. Nevertheless, single diastereomers can be obtained in optically pure form by chromatographic separation. After cleavage of the chiral auxiliary and deprotection optically pure (*S*)- and (*R*)- α TfmAla were released (*Scheme 37*).

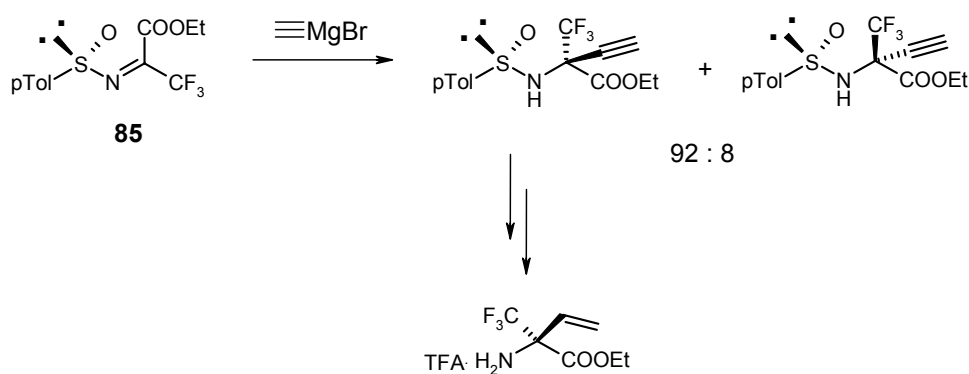


Scheme 37.

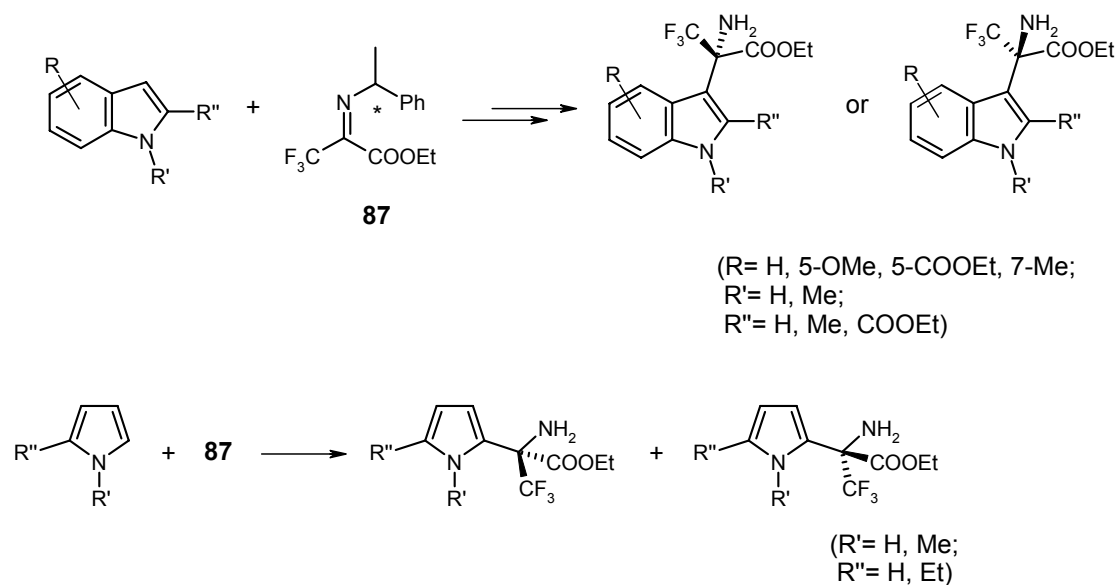
A new preparatively useful method for the synthesis of non-racemic α Tfm AAs was presented by Zanda and co-workers.^{81, 82} The key building block is the sulfinimine **85** prepared *via* Staudinger reaction from trifluoropyruvic esters and the chiral *N*-sulfinyl iminophosphorane **84**. The sulfinimine **85** was reacted with a wide range of Grignard reagents. The diastereoselective outcomes depend on the nature of the Grignard reagent, and normally, sterically hindered nucleophiles gave de up to 76%. The sulfinamides **86** were purified by flash chromatography and were easily converted to the corresponding α Tfm AAs (*Scheme 38*).



Interestingly, the reaction of **85** with vinyl and phenylmagnesium halides resulted in the complete addition of the Grignard reagent to the sulfur atom. Nevertheless, α Tfm- α -vinylglycine could be synthesized by an indirect approach *via* addition of ethynylmagnesium bromide to the sulfinimine **85** and subsequent reduction of the triple bond.⁸³

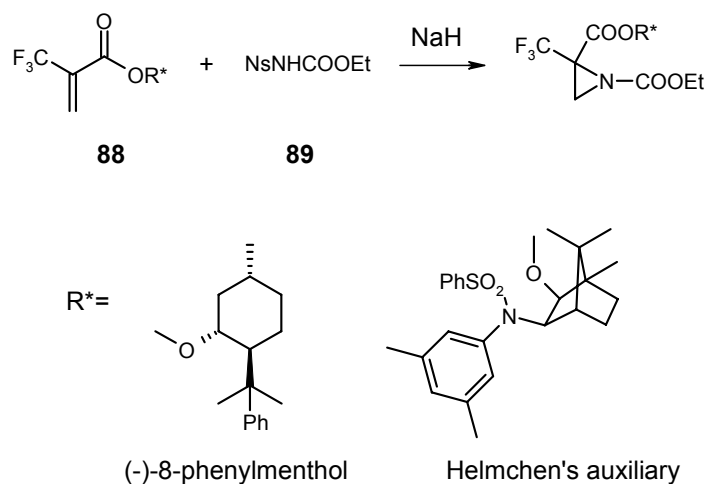


Abid *et al.* developed a new simple synthesis of enantiomerically enriched α Tfm- α -(heteroaryl)-glycine derivatives *via* stereoselective aminoalkylation of indoles and pyrroles.⁸⁴ The triflic acid-catalyzed reaction of **87** with indoles and pyrroles and the subsequent Pd-catalyzed hydrogenolysis of the methylbenzyl group provided the products in high yields and ee up to 98%.



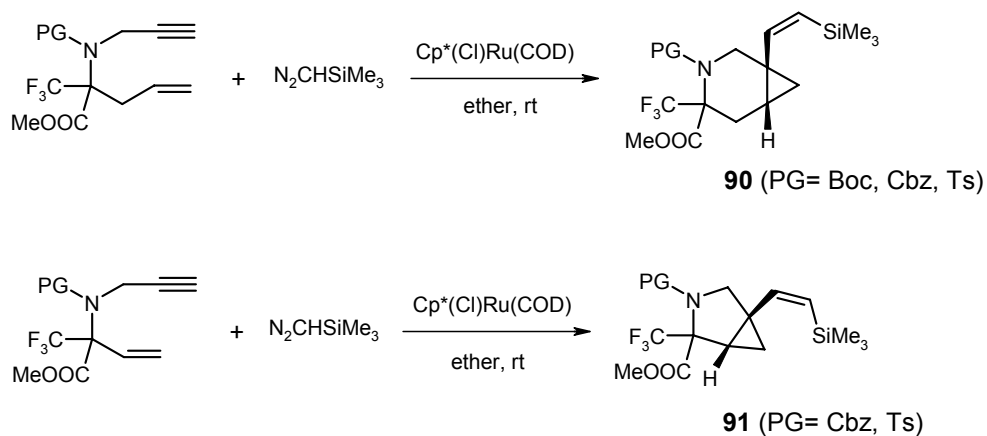
Scheme 40.

The aziridination reaction of 2-(trifluoromethyl)acrylates **88** with nosylcarbamate **89** proceeds in a stepwise manner and it is possible to isolate the aziridination product by changing the reaction conditions (Scheme 41).⁸⁵ The diastereoselective induction depends on the choice of the chiral auxiliary. The use of (-)-8-phenylmenthol induces a low diastereoselectivity, more satisfactory results were obtained by using the bulkier Helmchen's auxiliary.



Scheme 41.

Eckert *et al.* reported a synthesis of fluorinated bicyclo[3.1.0]hexane and [4.1.0]heptane amino esters by ruthenium catalyzed tandem addition of diazoalkane/bicyclization of fluorinated enynes.⁸⁶ Cp*(Cl)Ru(COD) was used as a precatalyst in this reaction. Products **90** and **91** were obtained as a mixture of diastereomers (d.r. ~ 50:50 – 67:33), each diastereomer shows a Z-configuration for the CH=CHSiMe₃ group.

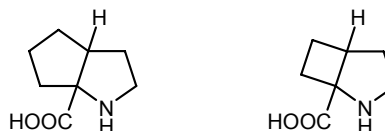
**Scheme 42.**

Many methods of the synthesis of α Tfm AAs are based on the obtaining of racemic products. Due to the route to non-racemic α Tfm AAs the chiral sulphinimines can be used as chiral auxiliaries. (*R*)-phenylglycinol and (*S*)- α -methylbenzylamine are also used as chiral auxiliaries. The stereocontrol in the formation of the stereogenic quaternary centre depends on a chiral substrate and the nature of Grignard reagents (or other nucleophiles).

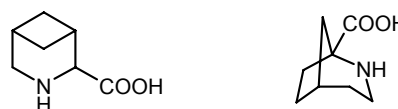
2 OBJECTIVES

- As shown in the introduction, CRAAs are used in the synthesis of peptide models, peptidomimetics and biologically active compounds. We focused on the developing of the approach to new proline and pipercolic acid analogues using a reaction of corresponding γ - and δ -functionalized carbonyl compounds with 2-methyl-2-(((1S)-1-phenylethyl)amino)propanenitrile **33** as a key step.

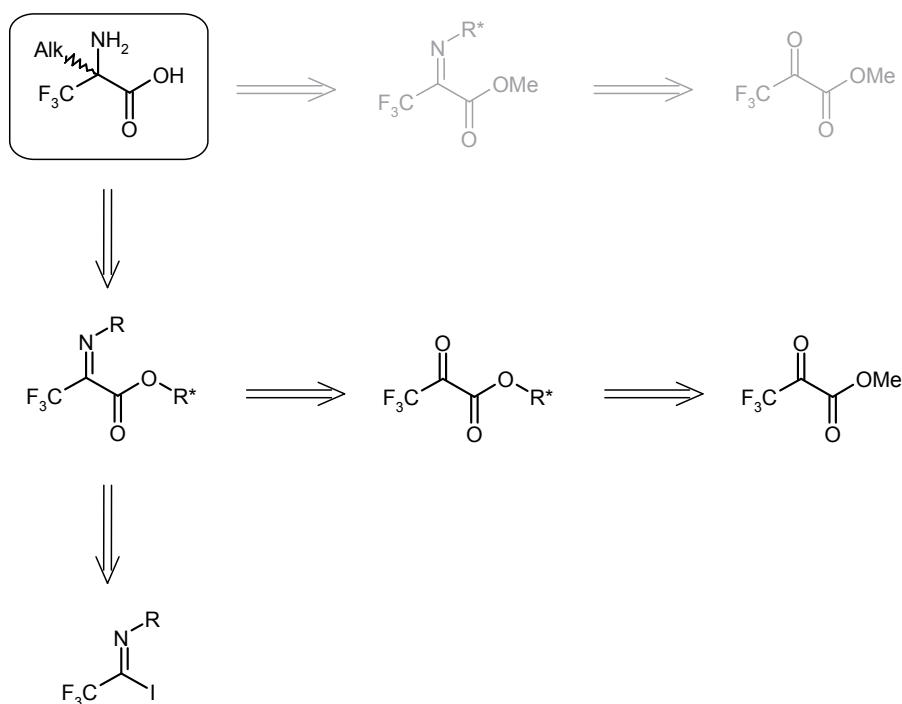
Proline analogues



Pipercolic acid analogues



- Synthesis of α Tfm AAs was described in the introduction. Stereoselective approach in most cases is based on the use of a chiral auxiliary at the nitrogen atom. Sometimes these methods have drawbacks, such as poor stereocontrol or impossibility to separate a mixture of formed enantiomers. We focused on another approach to α Tfm AAs using a chiral auxiliary in the ester moiety of a molecule:



3 RESULTS AND DISCUSSION

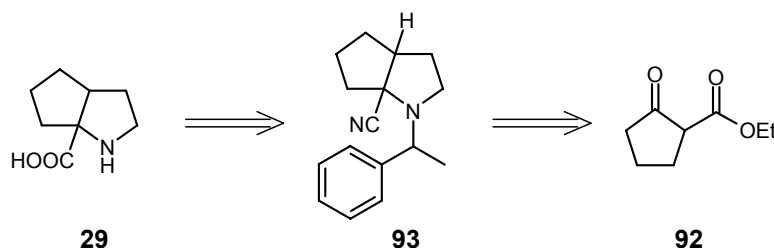
3.1 CRAAs

3.1.1 2,3-PROPANOPROLINE

- *Synthesis of 2,3-propanoprolin*

Almost all AAs are chiral, and many of them have more than one chirality element. Synthetic routes to such molecules are based mostly on the use of asymmetric induction. Several types of induction are known. Asymmetric induction caused by the inherent chirality of the substrate usually makes use of a chiral center in the near vicinity to the reacting fragment. The starting material is often derived from chiral pool. This strategy was used by Del Valle³³ for the synthesis of Boc-protected bicycloproline derivative **32b**. The synthesis was carried out starting from (2*R*,3*S*)-2-benzyloxymethylcyclopent-3-enol. Nevertheless, this route is rather long and led only to one enantiomer. Trauner and co-workers reported a strategy toward bicycloproline starting from Meyer's lactam, providing a potential precursor to **29**.³¹

In catalytic asymmetric induction the chirality is introduced in the substrate by chiral catalysts. Finally, the non-racemic compounds can be synthesized with the help of chiral auxiliary groups or fragments, which are to be removed after the synthesis. We used the latter type of induction in a novel synthesis of bicycloproline **29**. As the chiral auxiliary we chose (1*S*)-(α)-phenylethylamine residue, which was often used in asymmetric synthesis. The presence of this chiral auxiliary in the starting compounds might allow separation of diastereomers and/or chiral induction after their transformations. The chiral auxiliary can be removed by hydrogenolysis of the isolated diastereomeric products. Therefore, the γ -functionalized carbonyl compound **94** modified with (1*S*)-(α)-phenylethylamine auxiliary was used as the key intermediate in our synthesis of bicycloproline **29**. Retrosynthetic approach to the target molecule is given below (*Scheme 43*).

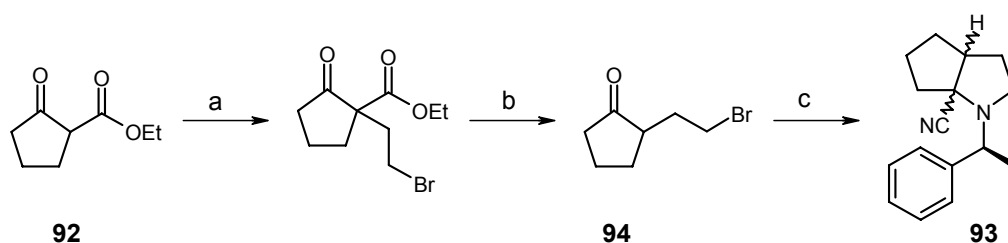


Scheme 43.

Commercially available ethyl 2-oxocyclopentanecarboxylate **92** was used to prepare the starting γ -bromoketone **94**. It was prepared by alkylation of the β -oxoester with 1,2-dibromoethane and potassium carbonate in refluxing acetone, followed by decarboxylation in hydrobromic acid (*Scheme 44*).⁸⁷ The reaction of 1,2-dibromoethane with the β -oxoester can also be carried out in DMF, however, in a lower yield.⁸⁸

The key step of the synthesis of bicycloproline is the reaction of **94** with chiral aminonitrile **33** containing (1*S*)-(α)-phenylethylamine moiety. The compound **33** was synthesized according to the procedure described in the literature.³⁷

The reaction of the γ -bromoketone **94** with **33** led to a mixture of two compounds in a 60% yield. Theoretically the formation of four diastereomers is possible in this case. But signals of only two aminonitriles were present in ¹H and ¹³C NMR spectra of the crude product. After chromatographic purification, the formed diastereomers **93** were obtained in optically and chemically pure form.



Reagents and conditions: (a) 1,2-dibromoethane, K₂CO₃, acetone, Δ 9 h, yield 65%; (b) 48% HBr in H₂O, Δ 2 h, yield 75%; (c) aminonitrile **33**, dry CH₃CN, Δ 48 h, yield 30% for each isomer.

Scheme 44.

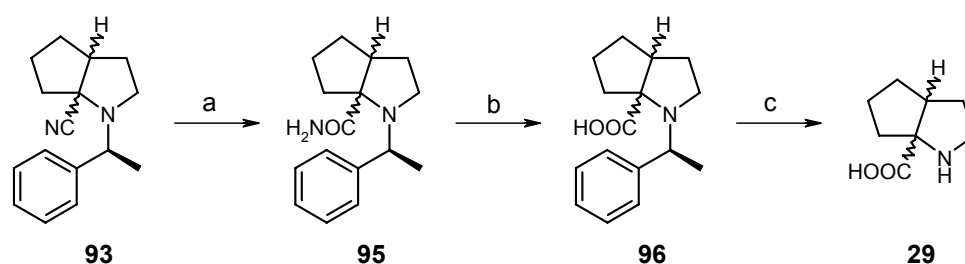
The next step was the synthesis of AAs from the both diastereomers of **93**. Hydrolysis of aminonitriles and deprotection by hydrogenolysis were usually used in similar cases, which is described in the literature.³⁵ However, reflux in aqueous HCl did not lead to the desired AAs, elimination of HCN was observed. Therefore, we tried to optimize the reaction conditions, but with limited success (*Table 1*).

Table 1. Reaction conditions of hydrolysis of 2-cyanopyrrolidines **93**

| | Reaction conditions | Product | Yield |
|---|--------------------------|--------------|----------|
| 1 | 37% HCl in water, reflux | Iminium salt | quantit. |
| 2 | 37% HCl in water, rt | Educt | quantit. |
| 3 | HCl in MeOH, rt | Iminium salt | quantit. |

After the unsuccessful attempts to hydrolyze the CN group we decided to synthesize the AAs **29** stepwise. First, corresponding amides **95** were obtained from 2-cyanopyrrolidines **93** in ~89% yield and then they were hydrolyzed to give the amino acids **96** (*Scheme 45*). Cleavage of the (1*S*)-(α)-phenylethylamine fragment from the both

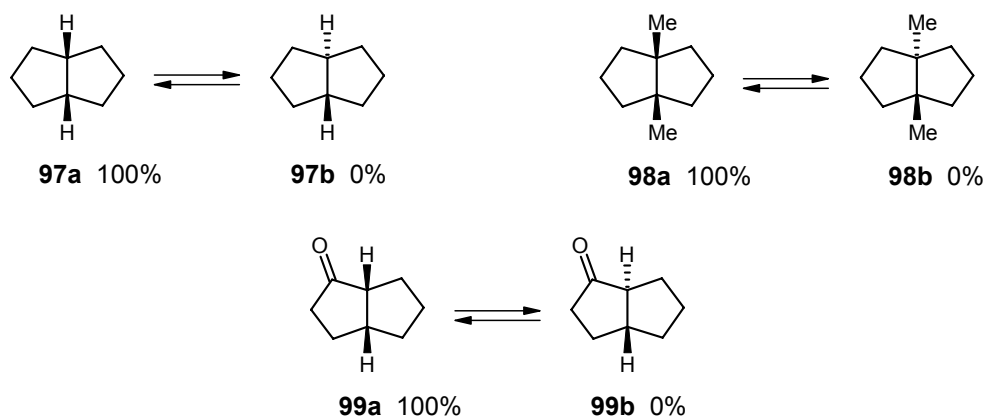
diastereomers of **96** was carried out by hydrogenolysis (over 10% Pd/C). Zwitter-ionic amino acids **29** were obtained after ion-exchange chromatography.



Reagents and conditions: (a) H_2SO_4 conc., hexane, $-10\text{ }^\circ\text{C}$ 3 h, $0\text{ }^\circ\text{C}$ 3 h, rt 48 h, yield 89%; (b) 6 M HCl, Δ 10 h; (c) H_2 – Pd/C, 50 atm, $35\text{ }^\circ\text{C}$ 36 h, yield 68% over two steps.

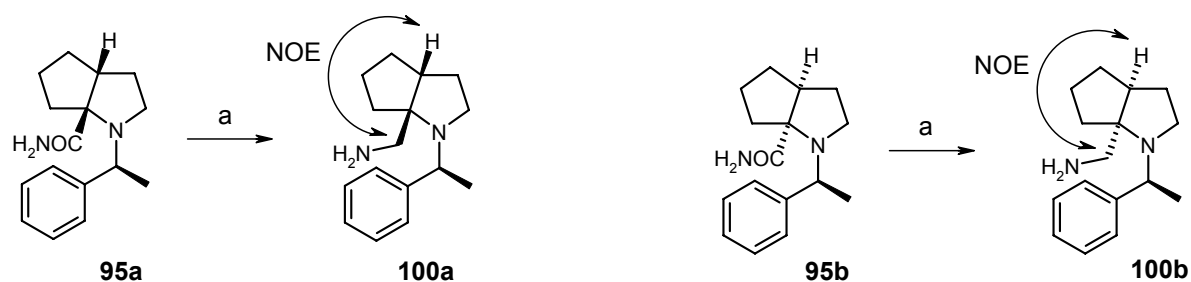
Scheme 45.

The calculated energies and their differences between *cis*- and *trans*-fused bicycles were provided for bicyclo[3.3.0]octanones, bicyclo[4.3.0]nonanones etc. by Hudlicky and co-workers.⁸⁹ In the case of bicyclo[3.3.0]octanones **99** and the corresponding hydrocarbons **97**, **98** it is clear that the *cis*-fused products are appreciably energetically favorable; the average energy differences is 7 – 8 kcal/mol, therefore, it is reasonable to assume that under equilibrium conditions (for example, in the case of **99**) the *trans*-fused compound would equilibrate to the *cis*-isomer.



Scheme 46.

Based on the calculation results mentioned above, and suggesting that the reaction leading to **93** is reversible, we assumed that only *cis*-isomers of bicycloproline **29** were obtained. To prove it experimentally, the corresponding derivatives **100** were synthesized (Scheme 47). The methylene group, which was formed by reduction with LAH, gave the opportunity to measure the NOE for both isomers. The NOE was observed between protons of methyne groups and the methylene groups (CH_2NH_2) for both diastereomers (Figure 4), which is possible only in the case of *cis*-configuration.



Reagents and conditions: (a) LiAlH₄, THF, Δ 3.5 h, yield 79%.

Scheme 47.

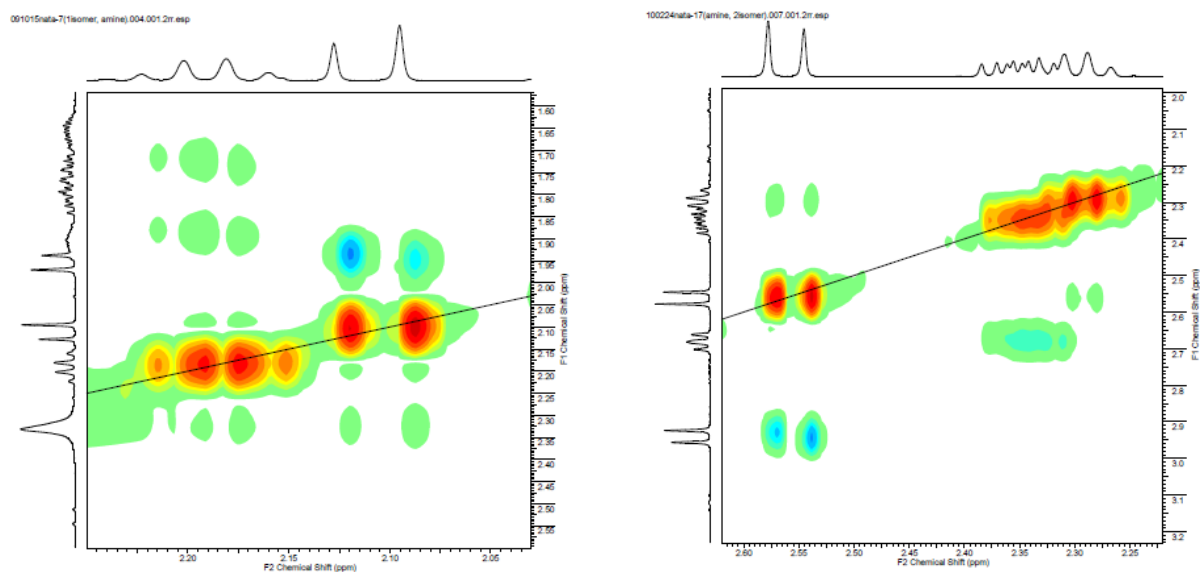
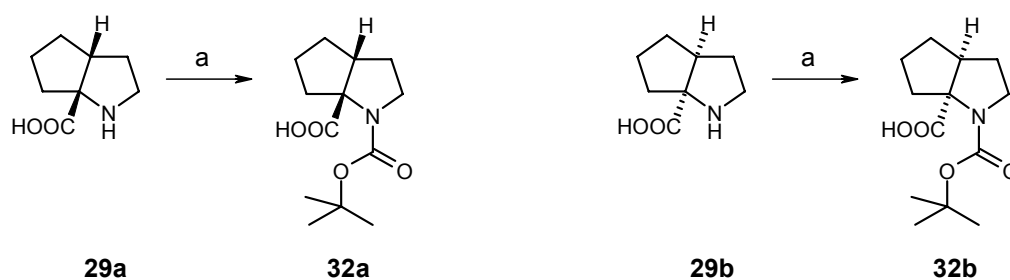


Figure 4. NOESY spectra of compounds **100a** and **100b**

Next, we determined the absolute configuration of stereocenters in **29**. It is usually obtained by X-ray crystallography. An alternative technique is determination of the optical rotation and its comparison with the known value for this compound. The optical rotation angle for *N*-Boc protected amino acid was reported by Del Valle *et al.*³³ Therefore, it was decided to synthesize the corresponding *N*-Boc derivatives **32a**, **32b** from **29** and compare their optical rotation power with the reported data. *N*-Boc protected derivatives **32a**, **32b** of two enantiomers were synthesized according to the standard procedure (*Scheme 48*).



Reagents and conditions: (a) Boc₂O, NaOH (1 M solution), THF, rt 36 h, yield 67%.

Scheme 48.

According to the experimental data, optical rotation ($[\alpha]_D$) for one of the isomers, namely for **32b**, is $+6.8^\circ$ and for the other -6.8° . The comparison with the literature $[\alpha]_D$ helped to assign the absolute configuration of the synthesized isomers.

In summary, short and efficient enantioselective synthesis of *cis*-bicycloproline was elaborated.

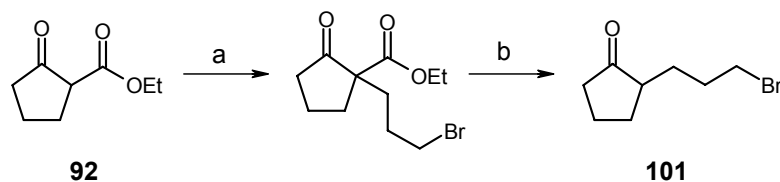
- *Synthesis of the Ac-HKWXWW-NH₂ peptide*

The nucleocapsid (NC) protein of HIV-1 is a very small, basic protein containing two retroviral zinc fingers. NC is initially synthesized as part of the Gag polyprotein. As a domain of Gag NC promotes the packaging of the viral genome, a process that requires the recognition of a specific viral packaging sequence (Ψ element). The NC domain is required for the annealing of the tRNA^{Lys,3} to the primer binding site. When the particle infects a new host cell, NC is a crucial co-factor in reverse transcription and integration. It acts also as a nucleic acid chaperone.⁹⁰ Due to numerous functions of the NC protein in the viral life, it is an attractive target for the development of antiviral agents. Since the recognition of target nucleic acids is required in the initial step of most NC-mediated processes, attempts were made to find small molecules capable of competing with this recognition.^{91, 92} Such Trp-rich hexapeptide as Ac-HKWPWW-NH₂ was studied as a representative of these peptides.⁹²

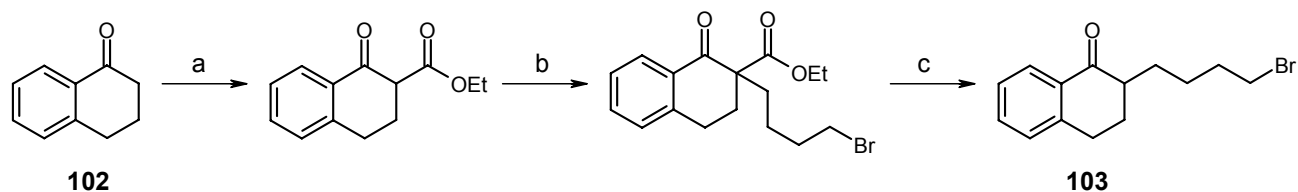
Since the above mentioned peptide had binding properties in order to inhibit NC functions during HIV-1 replication, it was determined to investigate the replacement of proline by its conformationally restricted analogue – 2,3-propanoproline – in the hexapeptide. For this purpose Fmoc-protected derivative of CRAA **29b** was synthesized according to the general procedure. The Ac-HKWXWW-NH₂ (where X – bicycloproline **29b**) peptide was synthesized by solid phase peptide synthesis at the Louis Pasteur University (Strasbourg, France). Its antiviral activity is under investigation.

3.1.2 REACTION OF AMINONITRILE **33** WITH δ - AND ε -BROMOKETONES

To investigate further application of 2-methyl-2-(((1S)-1-phenylethyl)amino)propanenitrile **33** some other functionalized carbonyl compounds were tested as the substrates. Compounds **101** and **103** were prepared according to the standard procedures from commercially available ethyl 2-oxocyclopentanecarboxylate **92** and 1-tetralone **102**, respectively.^{88, 93}



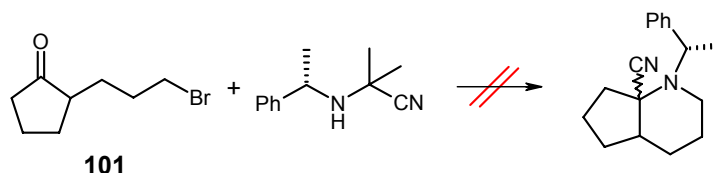
Reagents and conditions: (a) Br(CH₂)₃Br, K₂CO₃, DMF, rt overnight; (b) 48% HBr in H₂O, Δ 2 h.

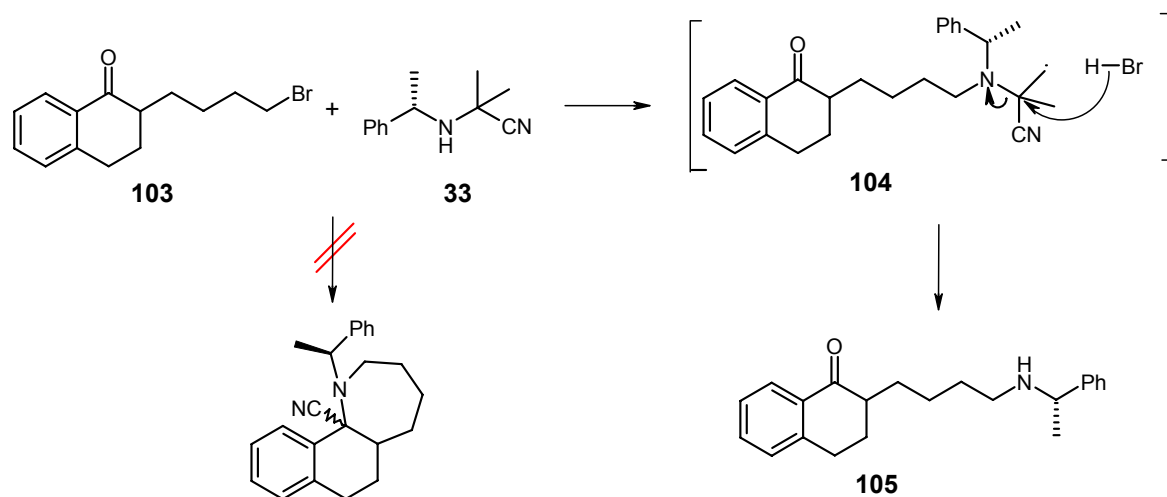


Reagents and conditions: (a) diethyl carbonate, NaH, toluene, 80 °C 3h, yield 69%; (b) 1,4-dibromobutane, NaH, DMPU, dioxane, (c) 48% HBr in H₂O, propionic acid, Δ 4 h, yield 89%.

Scheme 49.

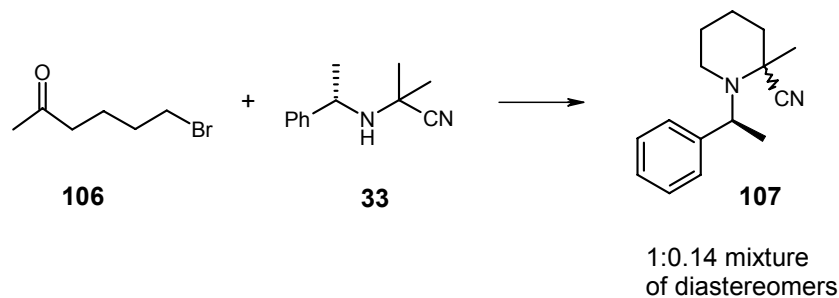
Reaction of **101** with **33** did not lead to the bicyclic aminonitrile as expected; instead, a mixture of unidentified products was formed. In the case of **103**, the corresponding aminonitrile did not form either; compound **105** was formed predominantly. We suppose that the remote position of the halogen substituent and the decreased reactivity of the carbonyl group in **103** makes the cyclization reactions unfavorable. The intermediate **104** was suggested for the reaction (*Scheme 50*).





Scheme 50.

The δ -bromoketone **106** was also tested in the reaction with 2-methyl-2-(((1*S*)-1-phenylethyl)amino)propanenitrile **33**. In this case, 2-cyanopiperidine **107** was obtained as a mixture of two diastereomers in a 45% yield (Scheme 51). The ratio of isomers of 1:0.14 was determined from the ^1H NMR spectrum. Thus, the stereoselectivity of the reaction was higher than that for the formation of **93** (see the previous section).



Reagents and conditions: dry CH_3CN , Δ 72 h, yield 45% of two isomers.

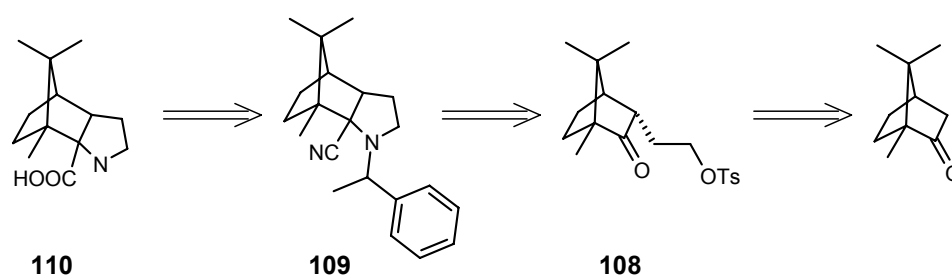
Scheme 51.

3.1.3 SYNTHESIS OF A CAMPHOR-DERIVED 2-CYANOPYRROLIDINE

Camphor is usually used as a starting material for the synthesis of different chiral compounds. This natural terpenoid is available on a large scale from natural sources in both enantiomeric forms; therefore, it is widely used in asymmetric syntheses.

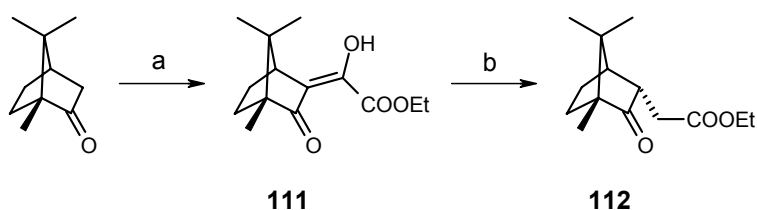
The idea of using the terpenoids in amino acid synthesis is not new. For example, CRAA **45** was synthesized more than 50 years ago.⁴⁶ It was found that **45** inhibits transport of leucine and isoleucine into cells. It should be noted, that camphor-derived amino acids have a large lipophilic skeleton, which increases hydrophobicity of the amino acid residue. Another example of a highly lipophilic CRAAs is 6,7-dimethyl-4-azatricyclo[4.3.0.0^{3,7}]nonane-3-carboxylic acid **46**. Syntheses of **45** and **46** are described in the introduction.

A strategy toward a new amino acid **110** based on the camphor skeleton was developed in this work. Our approach (Scheme 52) was based on the synthesis of the functionalized ketone **108** followed by cyclization with the chiral aminonitrile **33** and further transformation of the formed 2-cyanopyrrolidine **109** into the amino acid **110**.



Scheme 52.

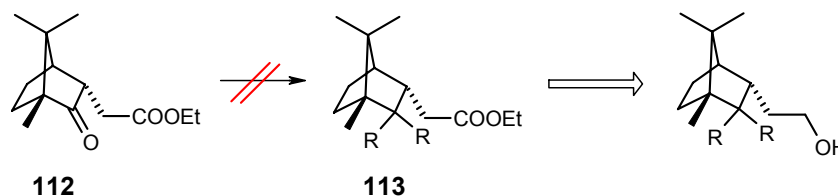
Ethyl camphoroxalate **111** was prepared by the known procedure.⁹⁴ Clemmensen reduction of **111** proceeded under thermodynamic control and led to the product resulting from the attack of the reducing agent from the sterically less hindered side to yield ethyl *endo*-camphoracetate **112**, as to be expected for this type of bornane derivative. The *exo*-diastereomer which formed in minor amounts was removed by recrystallization.



Reagents and conditions: (a) NaH, then diethyl oxalate, xylene, yield 90%;
(b) Zn/HCl, Et₂O, 0 °C 1 h, yield 95%.

Scheme 53.

Protection of the keto group in **112** would enable reducing the ester group with LAH. Different conditions to synthesize the protected derivatives **113** failed (*Table 2*). Only the starting compound was isolated after the reaction in each case by column chromatography.

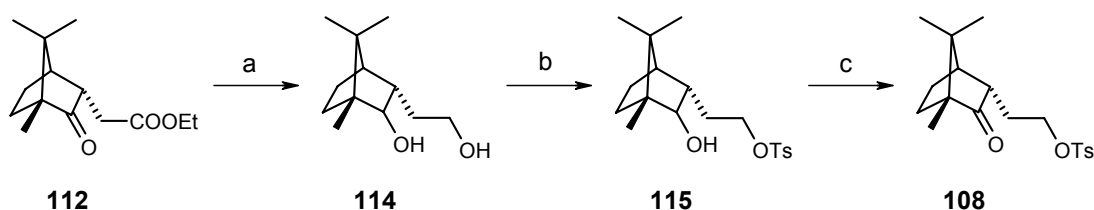


Scheme 54.

Table 2. Protection of the keto group in **112**

| | Reaction conditions | Product |
|---|--|---------|
| 1 | trimethyl orthoformate, MeOH, reflux | Educt |
| 2 | ethylene glycol, <i>p</i> -TsOH, toluene, reflux | Educt |
| 3 | 1,2-ethanedithiol, <i>p</i> -TsOH, toluene, reflux | Educt |

Therefore, we focused on an alternative approach to the functionalized ketone **108**. First, both ester and carbonyl groups were reduced to form the diol **114**. Then the tosylate **115** was prepared leaving the secondary alcohol untouched. The tosylate was stable enough during the next step - oxidation of **115** with sodium dichromate. Thus, the functionalized carbonyl compound **108** was synthesized starting from D-camphor in 5 steps in a good yield (*Scheme 55*).

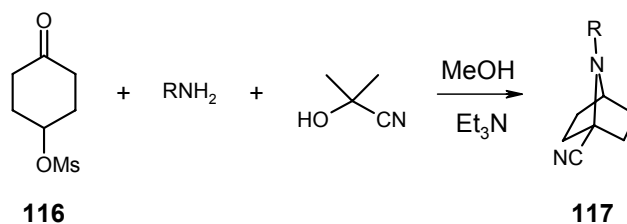


Reagents and conditions: (a) LiAlH₄, Et₂O, Δ 3 h, yield 83%; (b) *p*-TsCl, Et₃N, DCM, 0 °C – rt 12 h, yield 82%; (c) Na₂Cr₂O₇, H₂SO₄, Et₂O/H₂O, 25 °C 2 h, yield 72%.

Scheme 55.

The key step – cyclization of **108** – was carried out under different conditions.

The reaction conditions described by Heugebaert and co-workers allow obtaining aminonitriles **117** with different R (*Scheme 56*).⁹⁵ Cyclization of **116** in the presence of different amines and acetone cyanohydrine proceeded in various yields (*Table 3*).

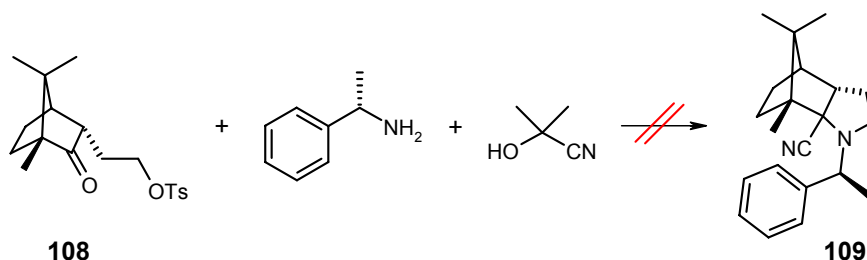


Scheme 56.

Table 3. Cyclization of **116** with different amines

| | Amine | Product, 117 | Yield, % |
|---|-----------------------|---|----------|
| 1 | 4-methoxybenzylamine | 7-(4-methoxybenzyl)-7-azabicyclo[2.2.1]heptane-1-carbonitrile | 97 |
| 2 | benzylamine | 7-benzyl-7-azabicyclo[2.2.1]heptane-1-carbonitrile | 60 |
| 3 | <i>i</i> -propylamine | 7- <i>i</i> -propyl-7-azabicyclo[2.2.1]heptane-1-carbonitrile | 39 |
| 4 | <i>n</i> -propylamine | 7-propyl-7-azabicyclo[2.2.1]heptane-1-carbonitrile | 58 |
| 5 | allylamine | 7-allyl-7-azabicyclo[2.2.1]heptane-1-carbonitrile | 56 |
| 6 | <i>i</i> -butylamine | 7- <i>i</i> -butyl-7-azabicyclo[2.2.1]heptane-1-carbonitrile | 43 |

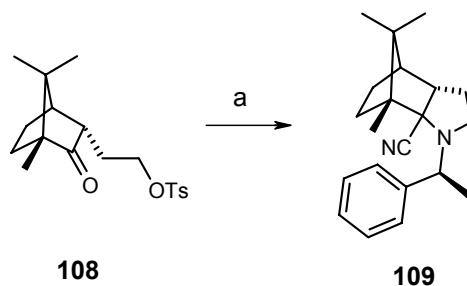
Being aware of these literature results⁹⁵ we decided to apply them to the reaction of **108** with (1*S*)-(α)-phenylethylamine; however, no product was isolated. We suppose that the amine nucleophilicity is one of the dominating factors determining the reaction progress, in addition to the steric factors.



Scheme 57.

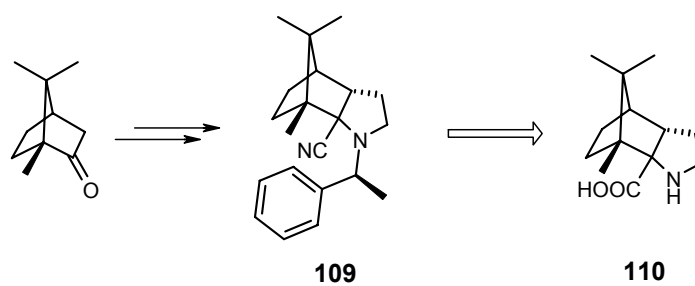
Reflux for 72 h in dry acetonitrile also did not lead to **109**, a mixture of different by-products was detected by GC-MS analysis and TLC. Only when the solvent (acetonitrile)

was allowed to evaporate during the heating, the product **109** was isolated in a 25% yield. One diastereomer was formed predominantly and only trace amounts of the other one were formed during the cyclization.



Reagents and conditions: (a) aminonitrile **33**, dry CH_3CN , $100\text{ }^\circ\text{C}$ 60 h, yield 25%.
Scheme 58.

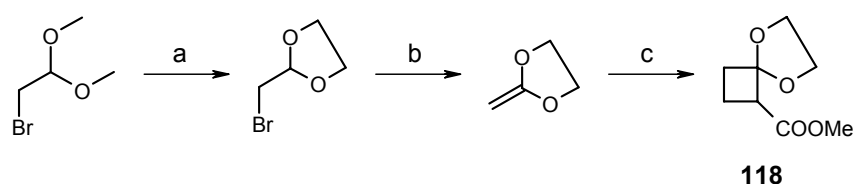
The compound **109** can be applied in further transformation to CRAA **110**.



Scheme 59.

3.1.4 SYNTHESIS OF 2,3-ETHANOPROLINE

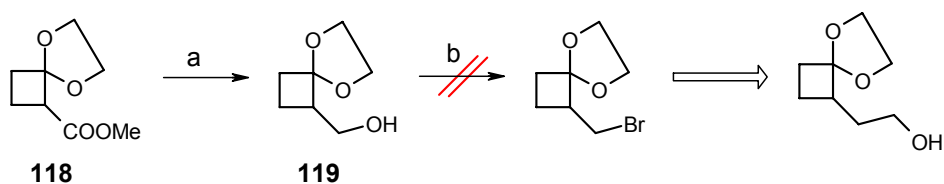
Synthetic approaches to 3,4- and 4,5-ethanoproline, which have been recently developed, were described in the introduction. We developed a route to the previously unknown optically active 2,3-ethanoproline, in which the 2-azabicyclo[3.2.0]heptane skeleton was constructed by the reaction of the corresponding carbonyl compound with 2-methyl-2-(((1S)-1-phenylethyl)amino)propanenitrile **33**. The synthesis commenced from 5,8-dioxaspiro[3,4]octane-1-carboxylic acid methyl ester **118** which we synthesized by [2+2] cycloaddition using the described procedures.⁹⁶



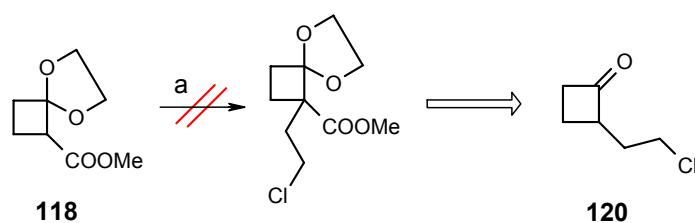
Reagents and conditions: (a) ethylene glycol, *p*-TsOH, Δ 2 h, yield 87%; (b, c) *t*-BuOK then methyl acrylate, Δ 5 days, yield 49%.

Scheme 60.

Different possible synthetic routes to a γ -functionalized carbonyl compound were investigated. According to one of them, the ester group of **118** was reduced to give alcohol **119**, which was subjected to the Appel reaction. A mixture of unidentified products was obtained. Another route shown in *Scheme 61* could allow access to functionalized ketone **120**. However, the attempt to alkylate the lithium enolate formed from the ester **118** was not successful, a mixture of unidentified products was obtained again.



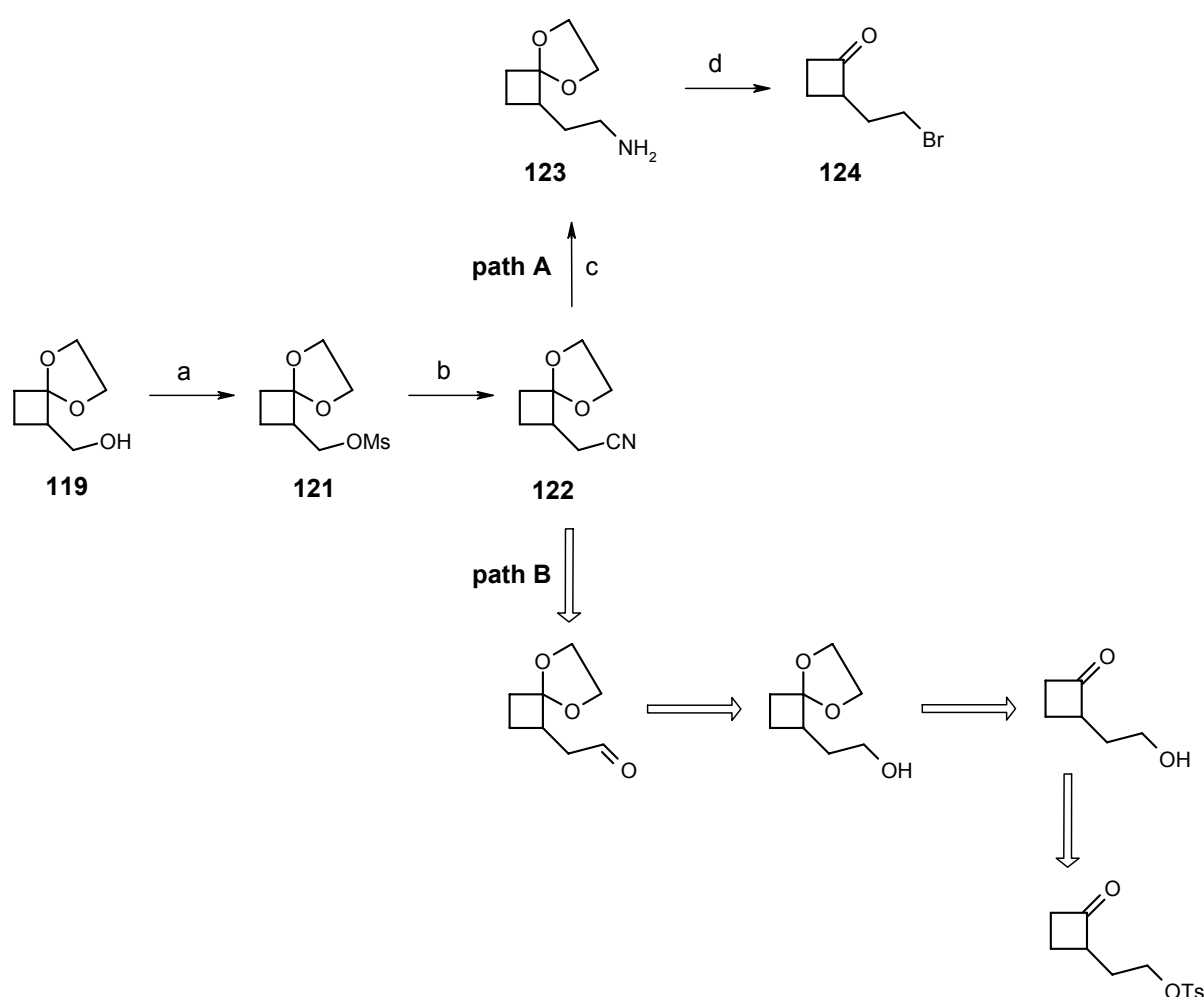
Reagents and conditions: (a) LiAlH₄, Et₂O, Δ 3 h, yield 91%; (b) CBr₄, PPh₃, yield 0%.



Reagents and conditions: (a) ClCH₂CH₂Br, LDA, DMPU, -78 °C \rightarrow rt, THF, yield 0%.

Scheme 61.

We then focused our effort on preparation of the γ -bromoketone **124** (Scheme 62). The alcohol **119** was converted to the mesylate **121** and used in the next step - nucleophilic substitution. It is known that cyanide ion is a strong nucleophile and displaces mesylate at primary carbon and elongate the chain by one carbon atom. Two possible paths were envisaged at this step. The shorter path A was chosen, though it was rather risky. Reduction of the nitrile **122** proceeded in almost quantitative yield. The synthesis of the γ -bromoketone **124** from **123** is a combination of three steps. When the primary amine **123** is treated with nitrous acid, an unstable diazonium salt is formed. This salt loses N_2 to give a planar carbocation, which reacts with the nucleophile (Br^-) in an S_N1 process. At the same time, deprotection of the keto group proceeded yielding **124** in a 43% yield.

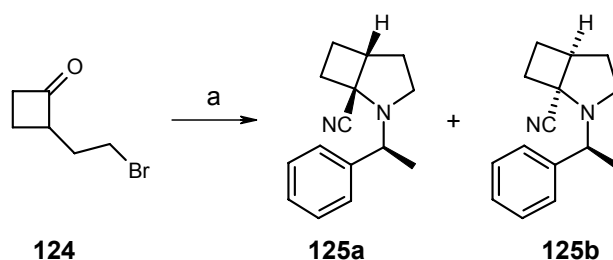


Reagents and conditions: (a) MsCl, Et_3N , DCM, $-30\text{ }^\circ\text{C} \rightarrow \text{rt}$; (b) KCN, DMF, $90\text{ }^\circ\text{C}$ 60 h, yield 63% in two steps; (c) $LiAlH_4$, Et_2O , Δ 3 h, yield 91%; (d) $NaNO_2$, NaBr, HBr, H_2O $0\text{ }^\circ\text{C}$ then rt 5 h, yield 43%.

Scheme 62.

The reaction of the γ -bromoketone **124** with **33** led to a 1:1 mixture of two diastereomers **125** in a 41% yield (Scheme 63). Unfortunately, column chromatography did

not allow the separation of these isomers. Nevertheless, the compounds were successfully separated by means of semi-preparative HPLC.



Reagents and conditions: (a) aminonitrile **33**, dry CH₃CN, Δ 42 h, yield 41% of two isomers.

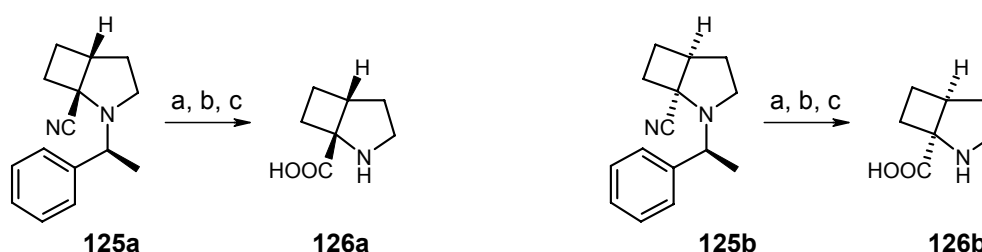
Scheme 63.

J-HMBC is used for measurement of long-range $J(X,H)$ coupling constants. To prove the relative configuration of the synthesized substances long-range $J(C,H)$ coupling constants between the CN-group and proton of the methyne group were measured and compared with those obtained for **93**. As can be seen from the *Table 4*, coupling constants of diastereomers **125** are similar to the coupling constants of aminonitriles **93**. Based on these data we can conclude that the two 2-cyanopyrrolidines have *cis* fusion of the rings.

Table 4. Long-range $J(C,H)$ coupling constants

| | Compound | Long-range $J(C,H)$ coupling constant (Hz) |
|---|-----------------------------|--|
| 1 | 125a and 125b | 9.9 and 8.9 |
| 2 | 93a and 93b | 8.6 and 9.6 |

Hydrolysis of the aminonitriles **125a**, **125b** gave the amino acids which were deprotected by hydrogenolysis under the conditions described for bicycloproline **29** (*Scheme 64*).



Reagents and conditions: (a) H₂SO₄ conc., hexane, -10 °C 3 h, 0 °C 3 h, rt 48 h, yield 78%; (b) 6 M HCl, Δ 10 h; (c) H₂ – Pd/C, 50 atm, 35 °C 36 h, yield 46% over two steps.

Scheme 64.

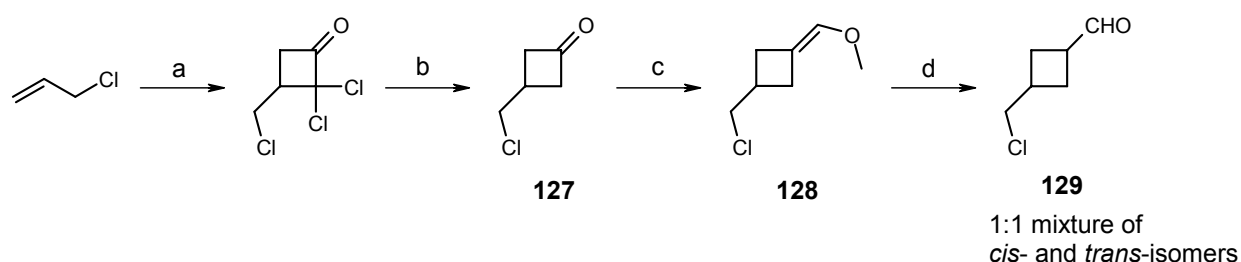
In conclusion, a new optically active CRAA – 2,3-ethanoproline **126** – was synthesized using as a key step the reaction of 2-(2-bromoethyl)-cyclobutanone **124** with 2-methyl-2-(((1S)-1-phenylethyl)amino)propanenitrile **33**.

3.1.5 ROUTE TO PIPECOLIC ACID ANALOGUES

• *Route to 3,5-methanopipelic acid*

L-Pipelic acid is a natural non proteinogenic α -amino acid commonly found in plants. This L-proline homologue is biosynthesized from D-lysine⁹⁷, but its biological role still remains obscure. Although being sometimes incorporated in complex biologically active molecules such as Rapamycin or FK 506, pipelic acid and related compounds most often occur in the free form in biological systems.⁹⁸ Numerous natural or man-made derivatives of this amino acid displayed interesting biological properties, such as anesthetic, NMDA antagonist – a class of anesthetics that work to antagonize, or inhibit the action of the *N*-methyl D-aspartate receptor (NMDAR), anticoagulant or glycosidase inhibition. In addition, L-pipelic acid, as well as other AAs showing a 6-membered ring have been used in peptide chemistry as analogues of L-proline.

We developed a route to a new CRAA – 3,5-methanopipelic acid – an analog of pipelic acid. A building block – 2-cyanopiperidine **131** was synthesized for this purpose. The cyclobutane ring was constructed first by the known reaction – [2+2] cycloaddition of dichloroketene and allyl chloride.⁹⁹ The Wittig reaction represents a valuable method for introducing the carbonyl functionality. Condensation of **127** with triphenyl(methoxymethylene)phosphorane afforded the enol ether in a 40% yield. Acidolysis of **128** with trifluoroacetic acid in DCM yielded the δ -halocarbonyl compound **129** as a mixture of *cis*- and *trans*-isomers (*Scheme 65*). Although they cannot be separated by chromatography, they were easily assigned in the ¹H NMR spectrum, which showed two types of signals characteristic for two geometrical isomers.

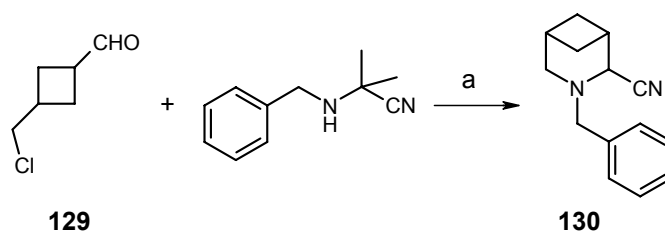


Reagents and conditions: (a) Cl_3CCOCl , POCl_3 , Zn-Cu couple, diethyl ether, Δ 24 h, yield 37%; (b) Zn, HOAc, Δ 4 h, yield 85%; (c) $\text{Ph}_3\text{P}^+\text{CH}_2\text{OMeCl}^-$, *n*-BuLi, THF, 0 °C 10 min, rt 5 h, yield 40%; (d) CF_3COOH , DCM, rt 30 min, yield 84%.

Scheme 65.

First, we carried out the cyclization of **129** with 2-benzylamino-2-methylpropionitrile to see if the key reaction proceeded at all. The reaction of **129** as a mixture of *cis*-/*trans*-

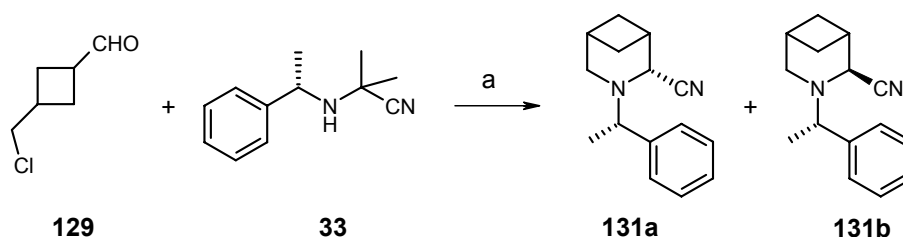
isomers gave 2-cyanopiperidine **130** which was isolated by column chromatography in a 27% yield.



Reagents and conditions: (a) dry CH₃CN, Δ 48 h, yield 27%.

Scheme 66.

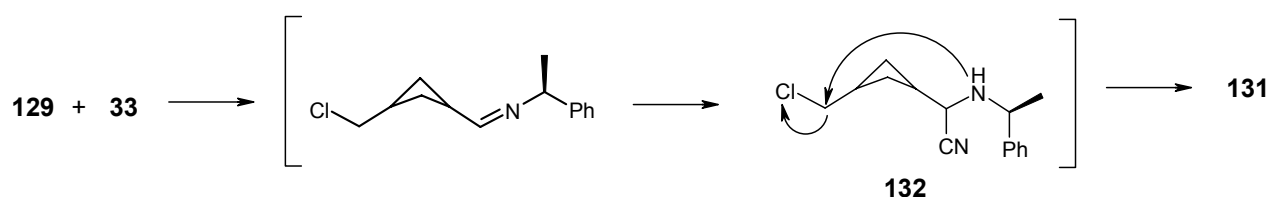
Reaction of the δ -chloroaldehyde **129** with 2-methyl-2-(((1S)-1-phenylethyl)amino)propanenitrile **33** can allow obtaining the desired building block **131** in enantiomerically pure form. Unfortunately, even after prolonged reaction time a mixture of chiral 2-cyanopiperidines **131a**, **131b** was isolated only in a 10% yield. The ratio of diastereomers was determined with the help of the ¹H NMR spectrum and turned out to be 1:0.68.



Reagents and conditions: (a) dry CH₃CN, Δ 120 h, yield 10% of two diastereomers.

Scheme 67.

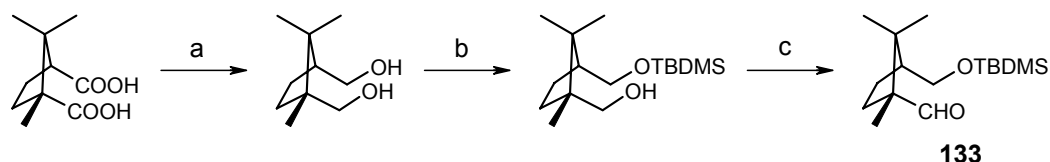
The low reactivity of 3-chloromethyl-cyclobutanecarbaldehyde **129** can be explained by the mechanism in *Scheme 68*. Since the mechanism involves the formation of the intermediates **132**, the geometrical unfavorable position of the nucleophile (NH) has the influence on the intramolecular cyclization and decreases the yield of the 2-cyanopiperidine **131**.



Scheme 68.

- Route to 2-cyanopiperidine based on camphor skeleton

We tried to react **33** with a new δ -functionalized carbonyl compound **133**. This precursor was synthesized starting from D-(+)-camphoric acid. Lanz *et al.* reported the total synthesis of Sarcinaxanthin, where the aldehyde **133** was synthesized as an intermediate.¹⁰⁰ We used this approach to obtain **133** for the subsequent transformation (Scheme 69).

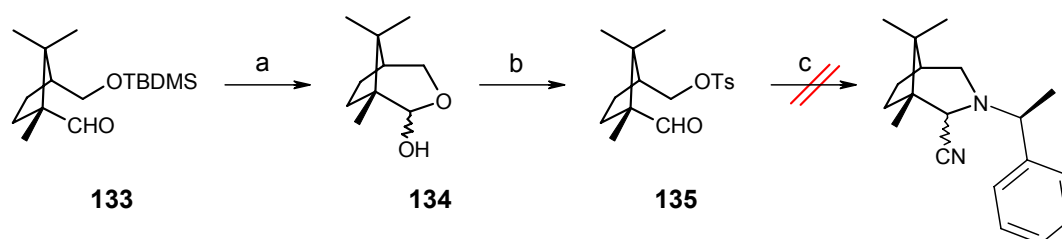


Reagents and conditions: (a) LiAlH_4 , diethyl ether/ THF, Δ 5 h, yield 78%; (b) TBDMSCl, DCM, $0\text{ }^\circ\text{C} \rightarrow \text{rt}$, yield 79%; (c) oxalyl chloride, DMSO, Et_3N , DCM, $-78\text{ }^\circ\text{C} \rightarrow -10\text{ }^\circ\text{C}$, rt 1 h, yield 87%.

Scheme 69.

Deprotection of **133** with TBAF afforded unexpected product **134** instead of the aldehyde in a good yield. Nevertheless, the reaction of **136** with *p*-TsCl allowed obtaining the δ -functionalized aldehyde **135** in a 38% yield.

Since the compound **135** turned out to be less reactive than **129**, no product was observed in the reaction with **33**.

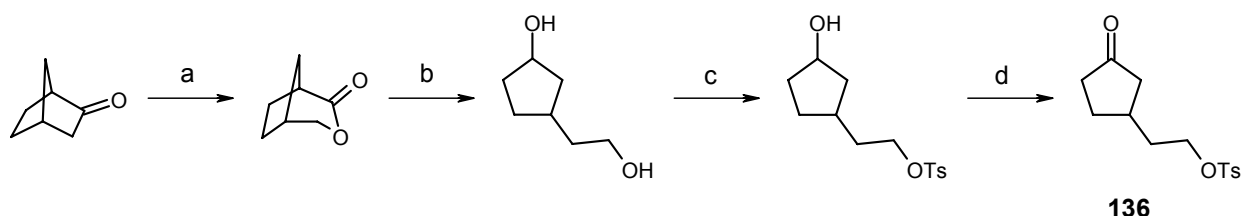


Reagents and conditions: (a) $\text{TBAF} \cdot 3\text{H}_2\text{O}$, THF, rt 48 h, yield 70%; (b) *p*-TsCl, pyridine, $0\text{ }^\circ\text{C}$ 72 h, yield 38%; (c) aminonitrile **33**, dry CH_3CN , Δ 72 h, yield 0%.

Scheme 70.

- *Route to 2-cyanopiperidine with 2-azabicyclo[3.2.1]octane skeleton*

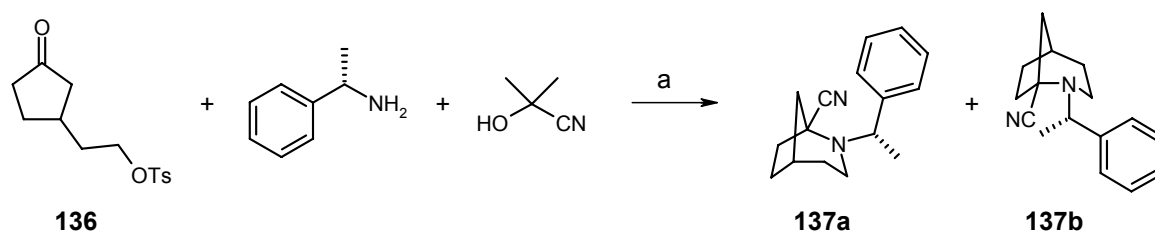
Another δ -functionalized carbonyl compound **136** was synthesized starting from norcamphor (*Scheme 71*).¹⁰¹



Reagents and conditions: (a) mCPBA, DCM, rt overnight, yield 72%; (b) LiAlH₄, diethyl ether, rt 1 h, yield 88%; (c) *p*-TsCl, Et₃N, DCM, rt 48 h, yield 74%; (d) CrO₃, CH₃COOH, acetone, yield 52%.

Scheme 71.

Cyclization of the δ -functionalized carbonyl compound **136** with aminonitrile **33** was carried out under different conditions. The best yield was derived using the methodology which was applied in the synthesis of **110**. Aminonitriles **137a** and **137b** were obtained in a 1:1 ratio. Column chromatography allows the partial separation of the compounds.



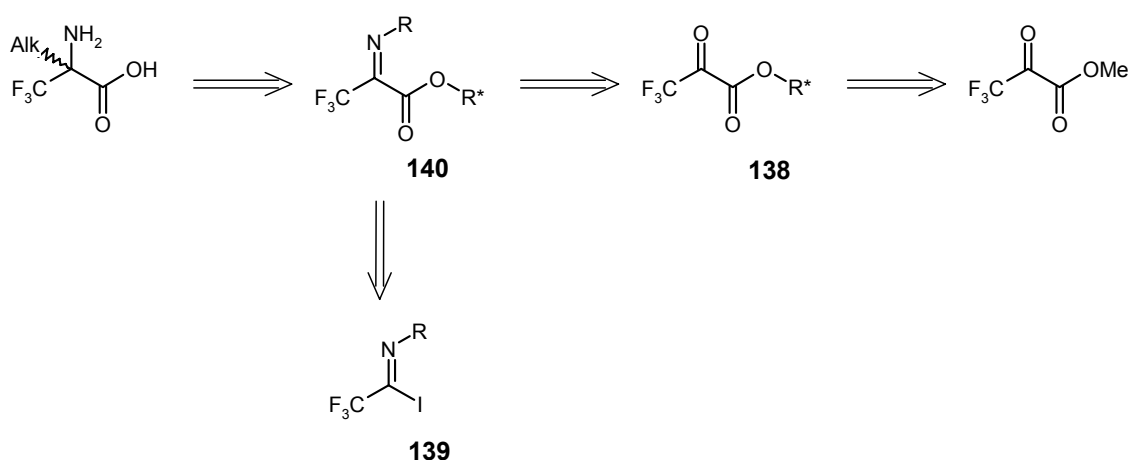
Reagents and conditions: (a) dry CH₃CN, 120 °C 36 h, yield 40% of two diastereomers.

Scheme 72.

2-Cyanopiperidine **137** is an appropriate precursor for the synthesis of new 2-azabicyclo[3.2.1]octane-1-carboxylic acid.

3.2 α TfM AAs

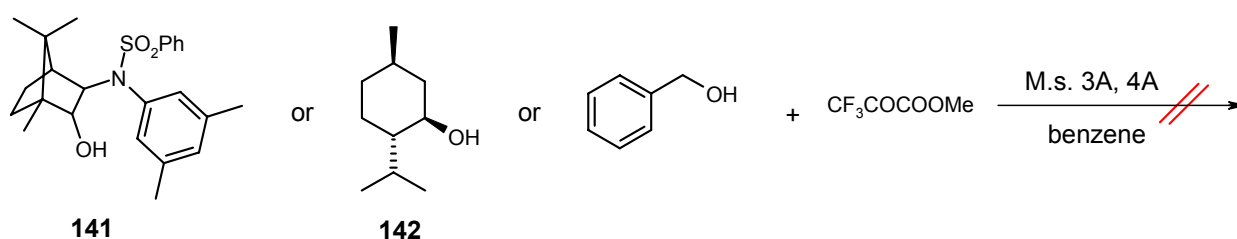
Starting compounds carrying a chiral auxiliary at the nitrogen atom for the synthesis of chiral α Tfm AAs were described in the introduction. In our work we decided to investigate another stereoselective approach to α Tfm AAs. Such chiral auxiliaries as L-menthol **142**, 8-phenylmenthol **148** or Helmchen's alcohol **141** were used successfully in the form of chiral esters. These reagents give a possibility to carry out a reaction with high diastereomeric control or at least to separate formed diastereomers.¹⁰²⁻¹⁰⁵ That's why we applied these alcohols as a chiral auxiliary in the synthesis of chiral imino esters **140**. *Scheme 73* gives an overview about two possible paths to such esters.



Scheme 73.

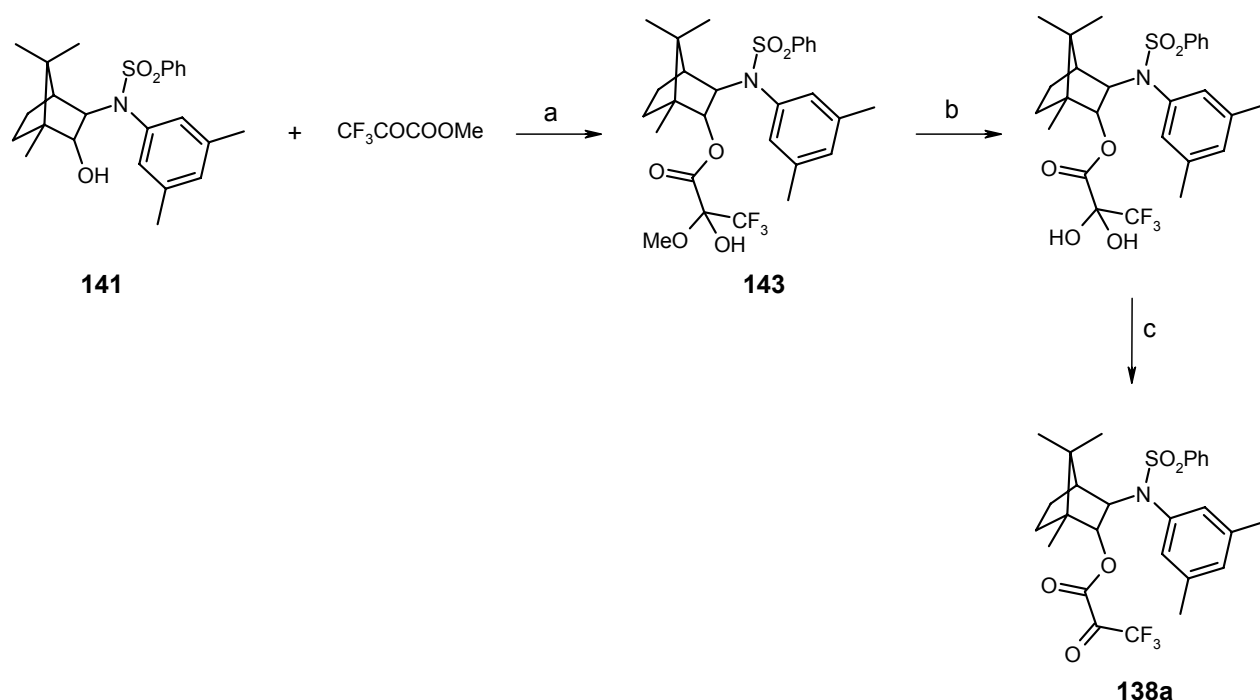
3.2.1 APPROACH TO α TfM AAs USING CHIRAL α -KETO ESTERS

First, we tried to synthesize chiral α -keto esters **138**. For this purpose the transesterification of methyl trifluoropyruvate was chosen as a key step in the synthesis of α Tfm AAs. It was reported that a use of a suitable molecular sieve permitted reaction of any alcohol R'OH with methyl ester RCOOMe.^{106, 107} The attempt to transesterificate using molecular sieve type 3A and 4A didn't lead to the desired product (*Scheme 74*).



Scheme 74.

Cesium fluoride is found to be an efficient catalyst for the transesterification of β -keto esters with various alcohols.¹⁰⁸ We investigated this catalyst in the reaction of methyl trifluoropyruvate with Helmchen's alcohol **141** and L-menthol **142**. In the case of **142**, a mixture of different compounds was obtained. To our surprise Helmchen's alcohol **141** was reacted with methyl trifluoropyruvate to produce a compound **143**. Apparently the reaction proceeds because the equilibrium is pushed towards the ester **143** side by trapping MeOH with trifluoropyruvate. It is known that such hemiacetals with EWG are stable. Hydrolysis of hemiacetal followed by dehydration reaction provided α -keto ester **138a** bearing a chiral auxiliary (Scheme 75).

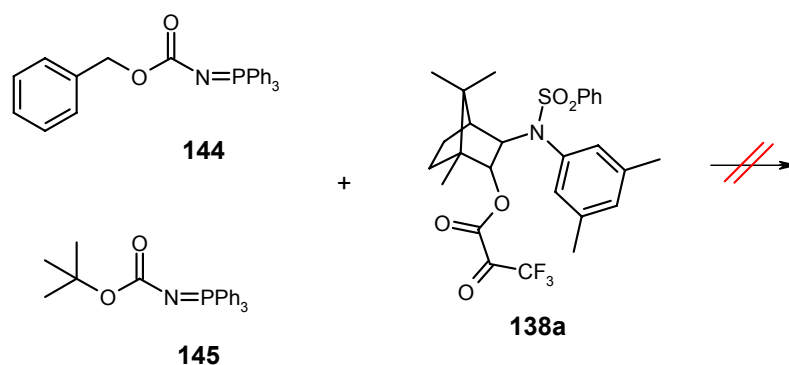


Reagents and conditions: (a) CsF, dry diethyl ether, 76 °C 72 h, yield 51%; (b) sat. NaHCO_3 , CH_3CN , rt 3 h; (c) TFAA, Py, dry diethyl ether, 0 °C 2 h, yield 71% over two steps.

Scheme 75.

In the reaction of **138a** with either benzyl carbamate or *tert*-butyl carbamate no product was detected.

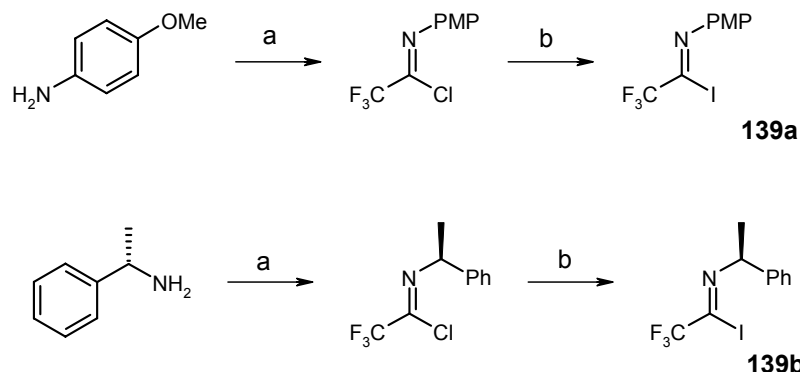
As alternative approach the Staudinger (aza-Wittig) reaction was used to synthesize chiral imines. There are many examples of the usage of phosphinimines in the reactions with carbonyl compounds. For this purpose compounds **144** and **145** were prepared starting from PhCH_2OH and Boc_2O , respectively. It was supposed to apply them for the reaction with the compound **138a** (Scheme 76). But the reaction did not occur; just the starting compounds were isolated.



Scheme 76.

3.2.2 NUCLEOPHILIC REACTIONS OF α -TRIFLUOROMETHYL CARBANIONS

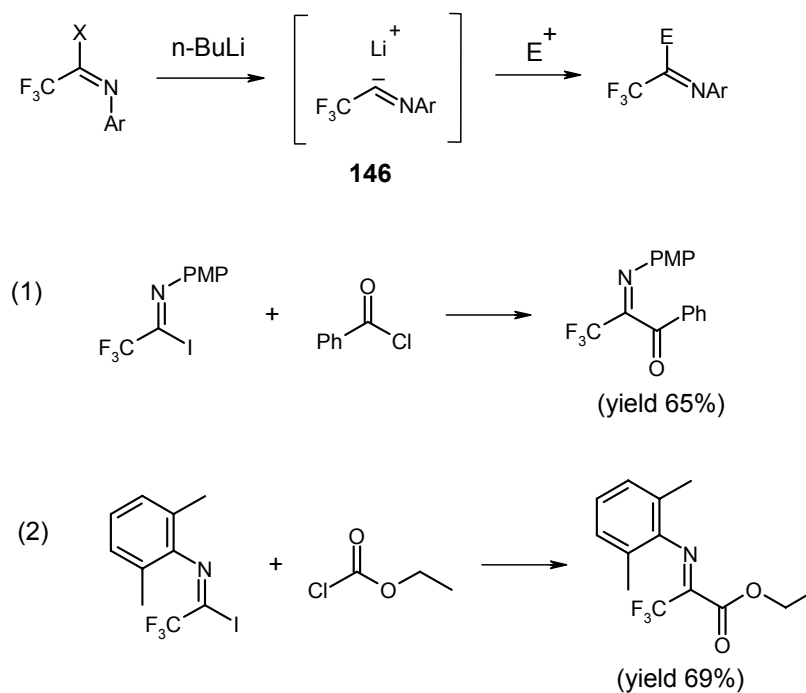
Since the approach using the chiral α -keto ester **138a** in the synthesis of imino esters **140** proved to be unsuccessful, we focused on another methodology starting from iminoamines **139**. Compounds **139a** and **139b** were synthesized according to the literature (Scheme 77).¹⁰⁹ As the substance **139b** was just mentioned in ref¹¹⁰, but neither experimental nor spectroscopic data were given, its synthesis and characterisation are described in the experimental section.



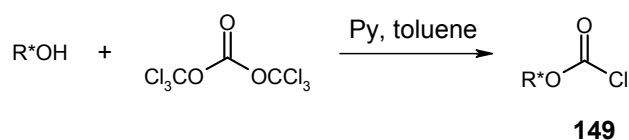
Reagents and conditions: (a) CF_3COOH , PPh_3 , Et_3N , CCl_4 , Δ 3 h, yield 91% (for **139a**) and 85% (for **139b**); (b) NaI , acetone, rt overnight, yield quantit.

Scheme 77.

Generation and nucleophilic reactions of α -trifluoromethyl carbanions would be a promising entry to the synthesis of trifluoromethylated compounds. Uneyama and co-workers performed a generation of trifluoroacetimidoyl lithium **146**, a synthetic equivalent of trifluoroacetyl lithium and its reaction with electrophiles (Scheme 78).^{111, 112}

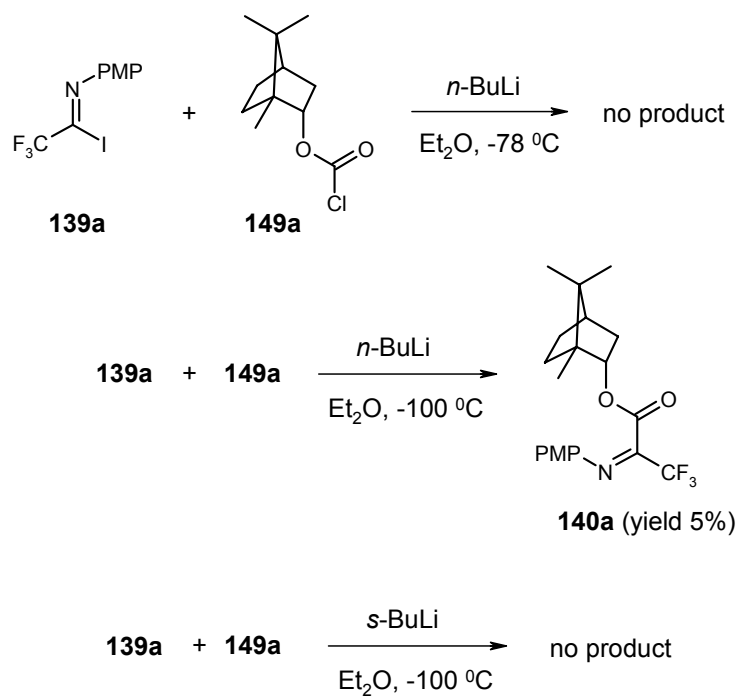
**Scheme 78.**

We decided to apply chiral reagents instead of ethyl chloroformate. For this purpose chloroformates **149a**, **149b**, **149c** were obtained by the reaction with triphosgene in quantitative yields (*Scheme 79*).

**Scheme 79.****Table 5.** Preparation of chloroformates **149**

| | Compd. № | R*OH | Yield (%) |
|---|-------------|-------------------------------|-----------|
| 1 | 149a | L-borneol 147 | 91 |
| 2 | 149b | 8-phenylmenthol 148 | 89 |
| 3 | 149c | Helmchen's alcohol 141 | 94 |

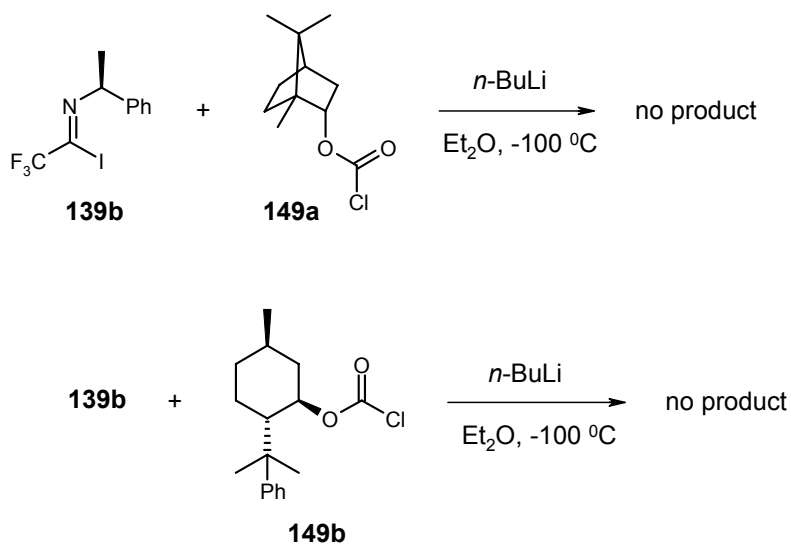
First, we tested the reactivity of **149a** toward trifluoroacetimidoyl iodides **139a** and **139b**. The chiral imine **140a** was isolated in a very low yield according to Uneyama's procedure (*Scheme 80*).



Scheme 80.

Attempts to conduct the reaction of **149b** and **149c** with imidoyl iodide **139a** under above mentioned reaction conditions resulted in no product (Scheme 81).

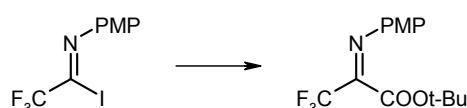
Unfortunately, the other trifluoroacetimidoyl iodide **139b** didn't react with either **149a** or **149b**.



Scheme 81.

3.2.3 PALLADIUM-CATALYZED CARBOALKOXYLATION

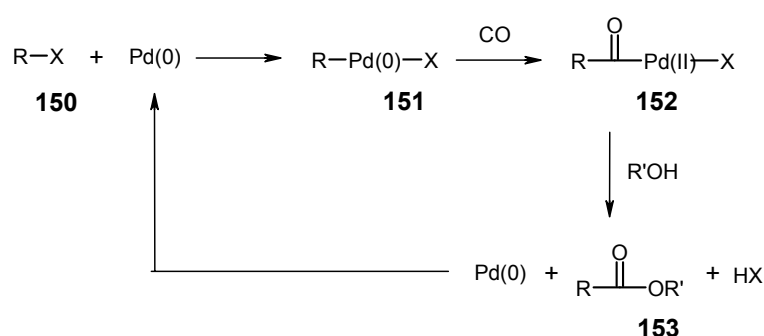
In the introduction the synthesis of α -imino perfluoroalkanoates based on the palladium-catalyzed carbonylation was described.^{72, 75} *tert*-Butanol, *iso*-propanol, L-menthol **142** were used in the reaction with fluorinated imidoyl halides. The rate and the yield of the reaction were affected by the nature of the *N*-aryl group and the alcohol. Electron-donating substituents at nitrogen such as *p*-methoxyphenyl and the use of primary alcohols proved to promote the conversion. Tertiary and secondary alcohols are no good trapping reagents due to their steric hindrance. The use of DMI promoted the *tert*-butoxycarbonylation remarkably.^{72, 75}



Reagents and conditions: Pd₂(dba)₃·CHCl₃, CO (1 atm), *t*-BuOH, K₂CO₃, DMI, rt 4 d, yield 74%.

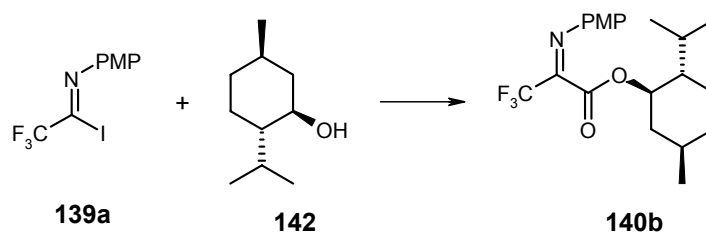
Scheme 82.

Uneyama and co-workers proposed a mechanism for the transition-metal-catalyzed carbonylation (Scheme 83).⁷⁵ The reaction is considered to proceed *via* an palladium (II) intermediate **152** that is formed by oxidative addition of palladium (0) to halides **150**, followed by insertion of carbon monoxide into the palladium-carbon bond of **151**. The subsequent nucleophilic attack of the alcohol at **152** would close the catalytic cycle, affording the ester **153**.



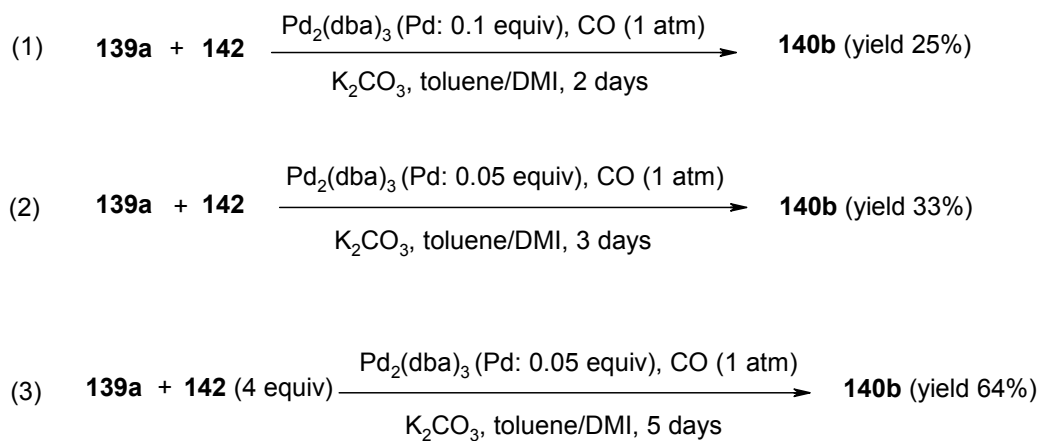
Scheme 83.

First, a reaction with L-menthol **142** was carried out to reproduce the methodology. The Pd-catalyzed carboalkoxylation of acetimidoyl iodide **139a** gave the product **140b** in a 11% yield.



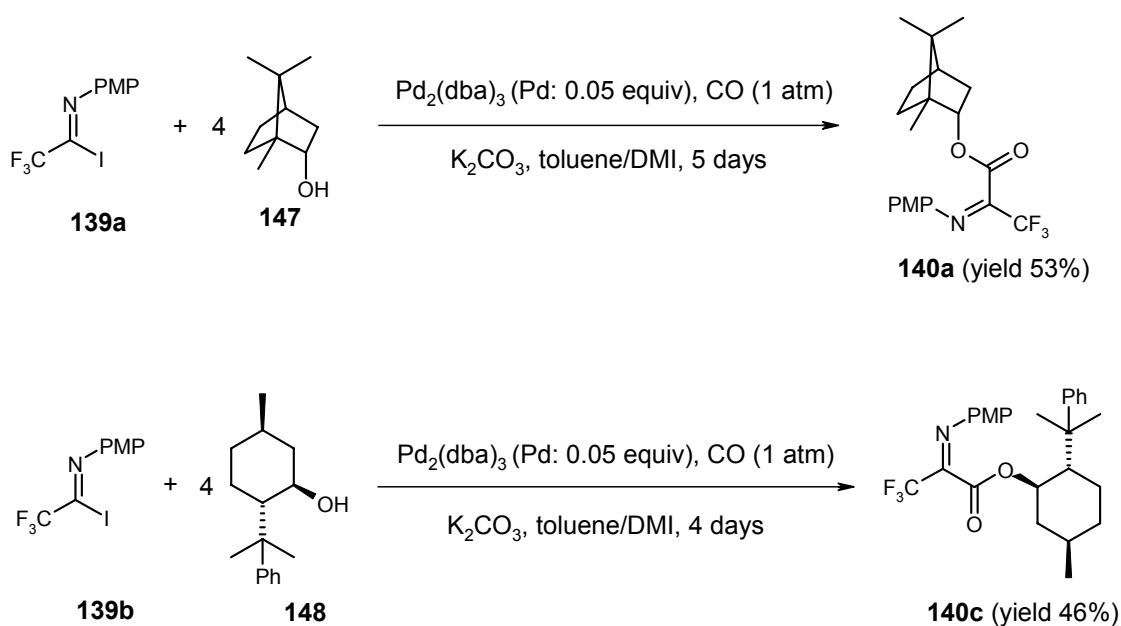
Reagents and conditions: $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (Pd, 0.1 eq), CO (1 atm), K_2CO_3 , toluene/DMI, rt 48 h.
Scheme 84.

Different reaction conditions were explored to optimize the yield of the reaction. The exchange of $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ with the solvent free variant $\text{Pd}_2(\text{dba})_3$ proved favorable. Further optimization regarding reaction time and equivalents of the chiral auxiliary led to the imino ester **140b** in a 64% yield (entry 3, *Scheme 85*).



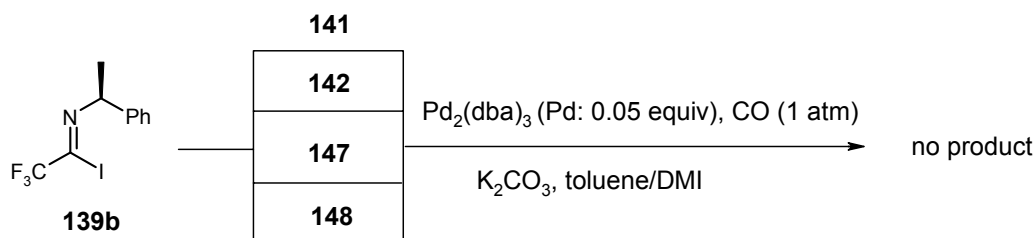
Scheme 85.

The optimized procedure was found to work well with 8-phenylmenthol **148** and L-borneol **147** (*Scheme 86*). Attempts to transform **139a** and **139b** to chiral imines using Helmchen's alcohol **141** weren't of success.



Scheme 86.

Whereas **139a** was reacted with all chiral auxiliaries except Helmchen's alcohol **141**, **139b** didn't react with any of the four auxiliaries; it therefore seems that the sterical demand of **139b** is too high for the successful carboalkoxylation.



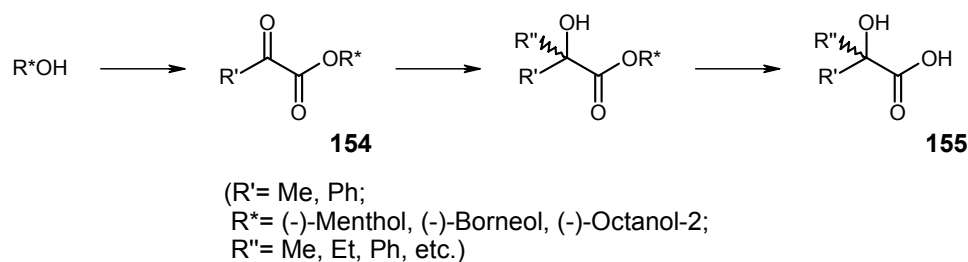
Scheme 87.

3.2.4 NUCLEOPHILIC ALKYLATION OF IMINO ESTERS

Nucleophilic alkylation of the imine moiety for some chiral compounds was shown in the introduction. The use of different nucleophiles induces a different diastereoselectivity. Chiral auxiliaries also proved to have influence on the diastereomeric excess of the reaction.

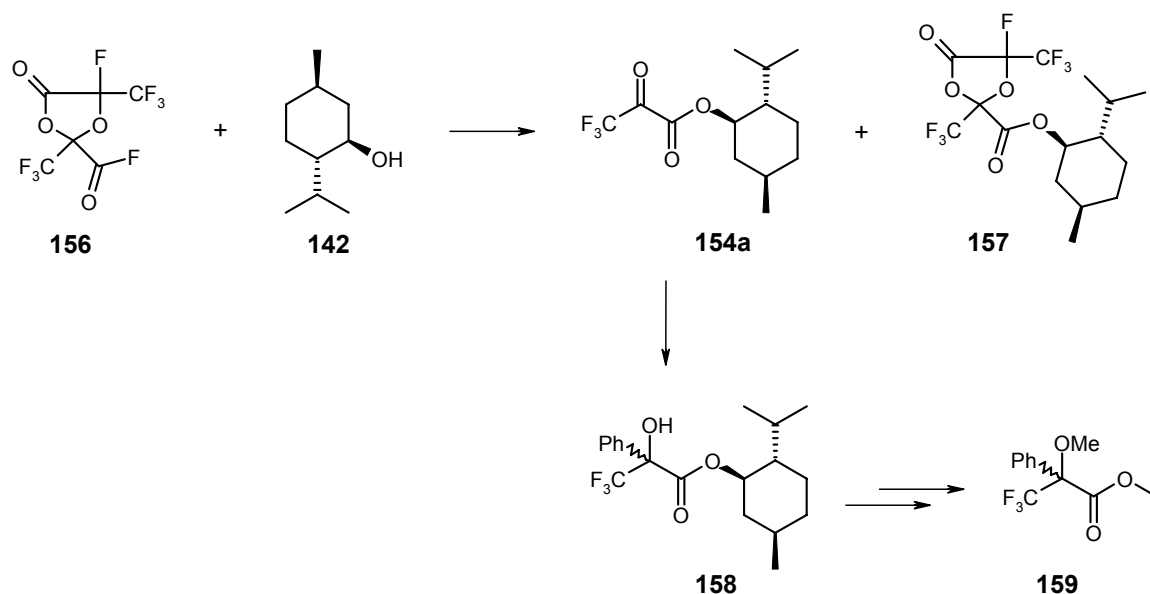
We should dwell on the influence of the chiral moiety on the diastereoselective outcome in the reaction of such molecules like imino esters. Not so many examples are given in the literature; nevertheless some asymmetric syntheses can be taken for comparison. Prelog investigated the asymmetric reaction between α -keto esters **154** bearing a chiral moiety and Grignard reagents.^{113, 114} The addition of a nucleophile followed by hydrolysis furnished the formation of acids **155** in excess of one of two possible enantiomers

(Scheme 88). Stereoisomers of corresponding configuration should predominate regardless the nature of the achiral R' group.



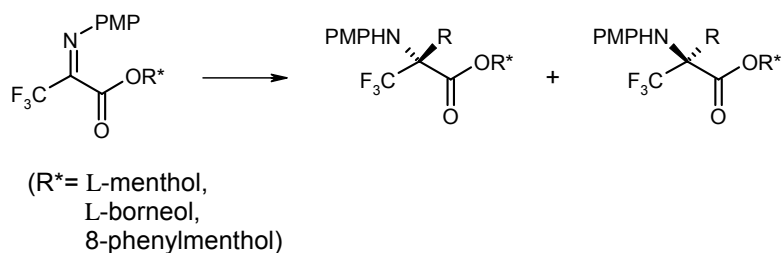
Scheme 88.

To confirm the minor influence of the nature of achiral group R' Mosher investigated the reactions of (-)-menthyl trifluoropyruvate **154a** and (-)-menthyl glyoxylate with Grignard reagents.¹¹⁵ Treatment of (-)-menthyl glyoxylate with phenylmagnesium bromide gave (-)-menthyl mandelate which he showed to have the S-configuration by reduction to the known S-(+)-phenylethylene glycol (19% ee). In an attempt to investigate the influence of the CF₃-group, Mosher prepared menthyl trifluoropyruvate **154a** from the dimer of trifluoropyruvyl fluoride **156**. The dimer **157** was isolated as a second product in this reaction. Treatment of **154a** with PhMgBr gave (-)-menthyl α-trifluoromethyl-α-hydroxyphenylacetate **158**. The measured rotation of its derivative **159** corresponded to 22% excess of the S(-)-enantiomer.



Scheme 89.

Nucleophilic alkylation was investigated for imino esters **140a**, **140b** and **140c**. These compounds were treated with different organometallic compounds (Scheme 90).



Reagents and conditions: RMgX or RLi, diethyl ether, -78 °C → 0 °C then sat. NH₄Cl.

Scheme 90.

As shown in *Table 6*, the reaction of **140b** with Grignard reagent proceeds with low yields. In the case of **140a** and **140c** no product was detected. The use of organolithium reagents as nucleophiles gave better results. The reaction mixture was quenched by adding water, sat. NH₄Cl or 1N HCl (the best procedure turned out to be in the case of ammonium chloride). In each case a mixture of diastereomers was obtained. Two types of signals are observed in ¹H and ¹⁹F NMR spectra of the product, it confirms the formation of two diastereomers.

Table 6. Alkylation of imino esters **140a**, **140b**, **140c**

| | Imino ester | CH ₂ =CHMgBr | <i>n</i> -BuLi | PhLi |
|---|-------------|-------------------------|----------------|------|
| 1 | 140b | 23% | 57% | 39% |
| 2 | 140a | — | 46% | 28% |
| 3 | 140c | — | 31% | — |

Since the signals in ¹H NMR were very close to each other, it was impossible to determine the ratio of the formed products. The alkylated compounds could not also be separated by column chromatography. The analytical HPLC was performed. Unfortunately, the compounds were found to be inseparable (*Figure 5* and *6*), but the ratio of some formed diastereomers could be determined. For instance, the ratio of diastereomers obtained from **140a** and PhLi was 1:0.48.

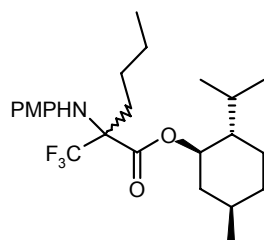
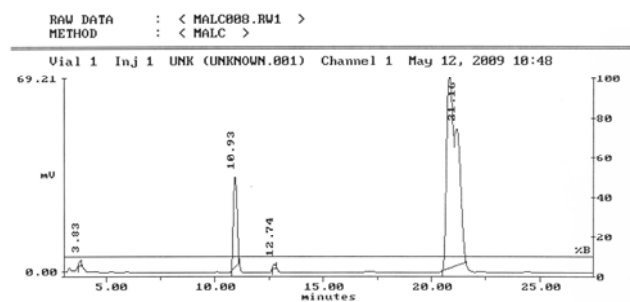


Figure 5.



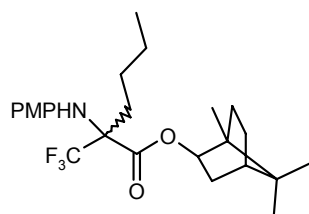
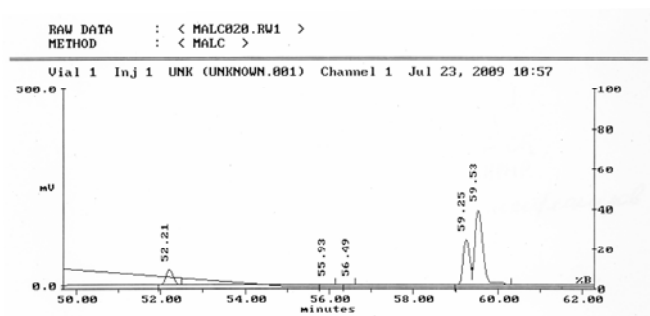
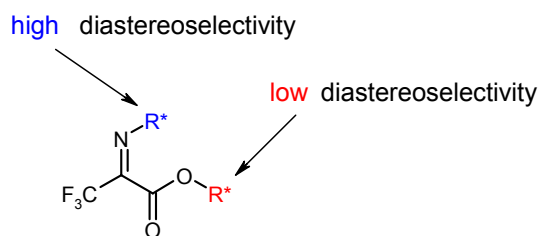


Figure 6.



Based on the obtained results it can be assumed that the low diastereoselectivity depends on the position and nature of a chiral auxiliary in the molecule. Since the stereogenic center in the corresponding imino esters is farther than in compounds bearing a chiral auxiliary at nitrogen, the diastereoselective outcome is definitely lower.

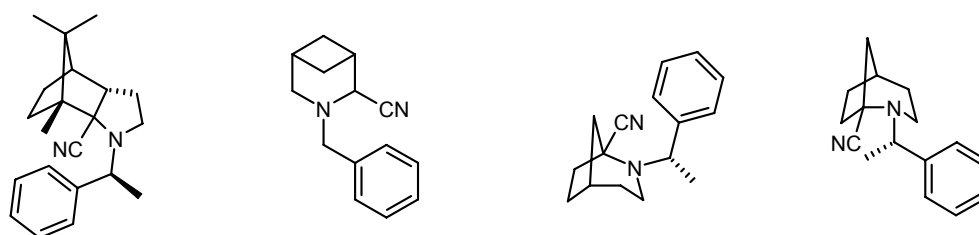


4 SUMMARY

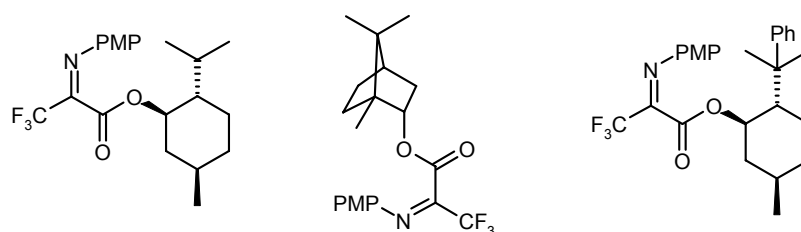
- New optically active free amino acids, namely 2,3-ethano- and 2,3-propanoprolines, were synthesized using a reaction of corresponding γ -functionalized carbonyl compounds with 2-methyl-2-(((1S)-1-phenylethyl)amino)propanenitrile **33** as a key step.



- Ac-HKWXWW-NH₂ peptide (X – 2,3-propanoprolines) was synthesized. Its antiviral activity is currently under investigation at the Louis Pasteur University (Strasbourg, France).
- Approach to a new camphor-derived 2-cyanopyrrolidine and 2-cyanopiperidines was developed.



- Reaction of some δ - and ϵ -functionalized carbonyl compounds with 2-methyl-2-(((1S)-1-phenylethyl)amino)propanenitrile **33** was investigated. It was determined that in this case the reaction isn't as effective as for γ -functionalized carbonyl compounds and depends on the nature of a functionalized carbonyl compound.
- The Pd-catalyzed carboalkoxylation of 2,2,2-trifluoro-*N*-(*p*-anisyl)-acetimidoyl iodide and 2,2,2-trifluoro-*N*-(1-phenylethyl)-acetimidoyl iodide was investigated. The reaction conditions were optimized that gave possibility to obtain the following imino esters:



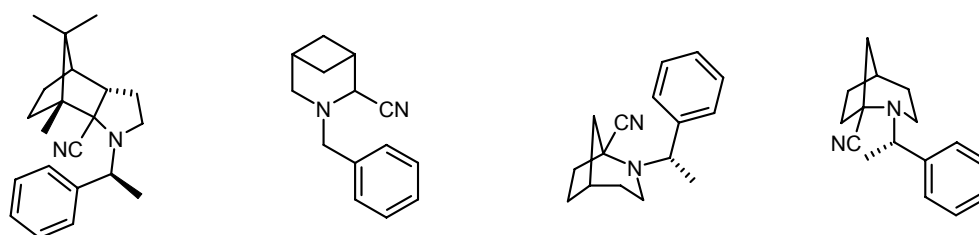
- Nucleophilic alkylation of the above mentioned imino esters was performed. It was shown that the remote position of the chiral auxiliary and the nature of a nucleophile have a drastic effect on the diastereoselectivity of the reaction.

5 ZUSAMMENFASSUNG

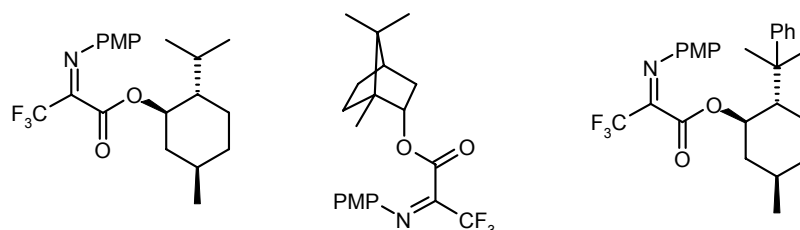
- Neue optisch aktive freie Aminosäuren (2,3-Ethano- und 2,3-Propanoprolin) wurden synthetisiert. Der Schlüsselschritt war die Reaktion von den entsprechenden γ -funktionalisierten Carbonylverbindungen mit 2-Methyl-2-(((1S)-1-phenylethyl)amino)propanonitril **33**.



- Das Ac-HKWXWW-NH₂ Peptid (X – 2,3-Propanoprolin) wurde vor kurzem synthetisiert und die antivirale Aktivität wird zur Zeit an der Louis Pasteur Universität (Strasbourg, Frankreich) untersucht.
- Es wurde ein Zugang zu dem neuen 2-Cyanopyrrolidin mit Campher-Fragment und den neuen 2-Cyanopiperidinen entwickelt.



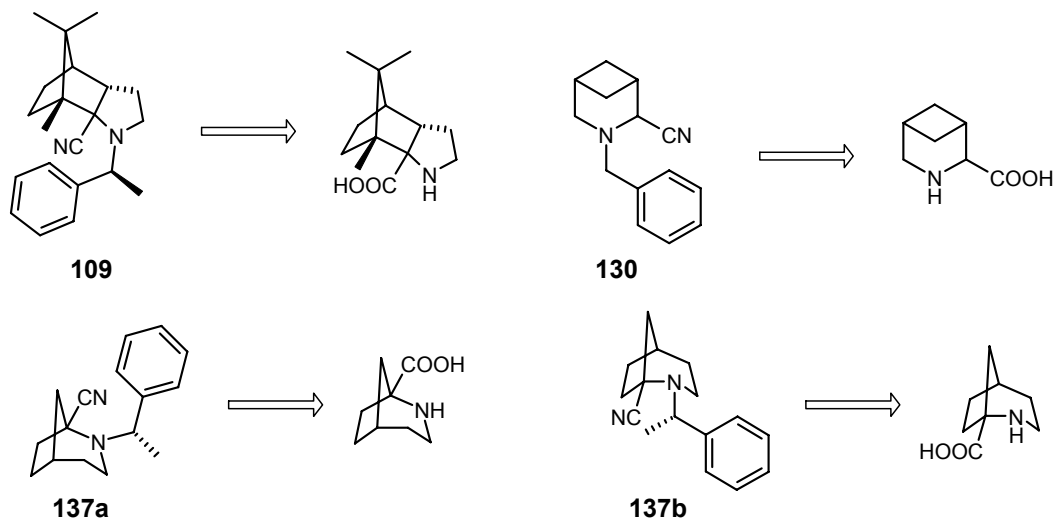
- Die Reaktion von einigen δ - und ε -funktionalisierten Carbonylverbindungen mit 2-Methyl-2-(((1S)-1-phenylethyl)amino)propanonitril **33** wurde untersucht. Es wurde festgestellt, dass die Reaktion nicht so effektiv wie bei γ -funktionalisierten Carbonylverbindungen ist und von der Natur der funktionalisierten Carbonylverbindungen abhängt.
- Die Palladium katalysierte Carboalkoxylierung von 2,2,2-Trifluoro-*N*-(*p*-anisyl)-acetimidoyliodid und 2,2,2-Trifluoro-*N*-(1-phenylethyl)-acetimidoyliodid wurde untersucht und die Reaktionsbedingungen optimiert. So konnten die folgenden Iminoester dargestellt werden.



- Die nucleophile Alkylierung von den obengenannten Iminoestern wurde vorgestellt und gezeigt, dass die entfernte Position von einem chiralen Auxiliar einen drastischen Effekt auf die Diastereoselektivität der Reaktion hat.

6 OUTLOOK

- As shown for 2,3-ethano and 2,3-propanoproline, these optically active CRAAs were achieved in a few steps starting from the corresponding 2-cyanopyrrolidines. In a same way new CRAAs can be synthesized from **109**, **130** and **137**.



- N*-acetyl-*N'*-methylamide derivatives of CRAAs are often used as peptide mimics. Their conformation can give an indication of the conformational behavior of new AAs in peptides. The following dihedral angles φ , ψ and ω – the secondary structure elements of peptides – can be determined by X-ray diffraction studies. *N*-acetyl-*N'*-methylamide derivatives of 2,3-ethano and 2,3-propanoprolines and other CRAAs can be synthesized using the procedure developed before.¹¹⁶
- Synthesis of Ac-HKWXWW-NH₂ peptides, where X is a CRAA (for example 2,3-propanoproline or 2,3-ethanoproline) and study of their antiviral activity is a promising field in development of drug candidates.

7 EXPERIMENTAL SECTION

All operations with air- and moisture-sensitive compounds were performed under nitrogen atmosphere using the Schlenk-and-syringe techniques, or in MBRAUN Labmaster 130 glovebox (filled with nitrogen). The reactions under high pressure were performed in the stainless-steel autoclave from Carl-Roth (50 ml).

The solvents were purified according to standard procedures.

The starting materials were purchased from Acros, Sigma-Aldrich, Fluka, Merck, ABCR, AlfaAesar and used "as is". A part of reagents was taken from the collections of chemicals of AG Groth.

Column chromatography was performed on MN Kieselgel 60 M (silica gel, 40-63 μm 230-400 mesh ASTM, Macherey-Nagel, Düren, Germany) or on neutral or basic alumina from Fluka (0.05-0.15 mm, Brokmann activity I).

TLC was performed on polymeric plates Polygram Sil G/UV₂₅₄ (0.2 mm of silica gel, Macherey-Nagel, Düren, Germany), or on aluminium plates from Merck (silica gel 60 or neutral alumina, F254). The spots were observed under UV-lamp or visualized by phosphor-molybdenic acid pentahydrate (5% solution in EtOH).

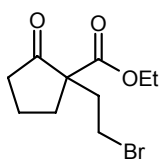
Analytical HPLC was performed on Merck RP-18 column (250 x 4.1 mm) using gradient or isocratic elution by acetonitrile – water mixture (UV detection at 254 nm).

GC-MS was performed on Agilent 7890/5975 GC/MSD System equipped with Phenomenex Zebron ZB-5 column (30m x 0.25mm x 0.25 μm). Helium was used as a carrier gas. Measurement conditions MS: EI, 70 eV. EI-MS and FAB-MS were performed on Finnigan MAT8200 mass spectrometer. ESI-MS was performed on Bruker micrOTOF II in positive mode (Bruker Daltonics).

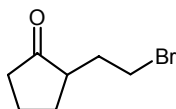
Rotation angles were measured on the Perkin-Elmer 241 polarimeter with 5 sec integration time.

IR-Spectroscopy was performed on Perkin Elmer Spectrum 100 Series FT-IR.

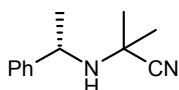
¹H and ¹³C NMR spectra were recorded on Jeol JNM-LA 400 or Bruker Avance 400 at 400 MHz and 100.62 MHz, respectively. CDCl₃ (δ [¹H] = 7.26 ppm, δ [¹³C] = 77.0 ppm) and CD₃OD (δ [¹H] = 3.31 ppm, δ [¹³C] = 49.15 ppm) were used as reference. Spin-spin coupling constants (J) are given in Hertz. Following abbreviations are used for multiplicity: s – singlet, d – doublet, t – triplet, q – quartet, p – pentet, dd - doublet of doublets, dt - doublet of triplets, td – triplet of doublets, qd – quartet of doublets, m – multiplet.

Ethyl 1-(2-bromoethyl)-2-oxocyclopentanecarboxylate

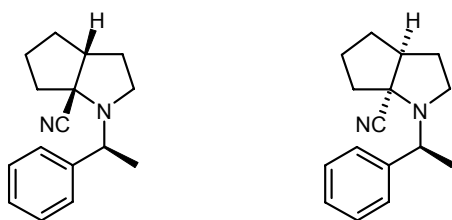
The compound was prepared by a procedure described in the literature.⁸⁷ A mixture of ethyl 2-oxocyclopentanecarboxylate **92** (50 g, 0.321 mol, 1 eq), potassium carbonate (110.6 g, 0.801 mol, 2.5 eq) and 1,2-dibromoethane (138.8 ml, 1.6 mol, 5 eq) was dissolved in 650 ml of dry acetone and heated at reflux for 9 h, and then stirred at rt overnight. The suspension was filtered, the filtrate was concentrated, and excess of 1,2-dibromoethane was distilled off at 10 mbar/ 60 °C. The crude product was used in the next step without further purification.

2-(2-Bromoethyl)-cyclopentanone **94**

The compound **94** was prepared by a procedure described in the literature.⁸⁷ Ethyl 1-(2-bromoethyl)-2-oxocyclopentanecarboxylate (10 g, 0.038 mol) was dissolved in hydrobromic acid (48%, 40 ml) and the solution was heated for 2 h. The solution was cooled to rt, diluted with water (50 ml) and extracted with diethyl ether. The aqueous phase was neutralized with solid sodium hydrogen carbonate and again extracted with diethyl ether. The combined organic phases were washed with a saturated solution of sodium hydrogen carbonate, dried (MgSO₄), filtered and evaporated under reduced pressure. The residue was distilled (99 °C/ 4 Torr) to give 75% (5.45 g, 0.029 mol) of the product. IR, ¹H, ¹³C NMR spectra were identical with those described in ref.⁸⁷

2-Methyl-2-(((1S)-1-phenylethyl)amino)propanenitrile **33**

The compound was prepared by a procedure described in the literature.³⁷ 19.22 ml (0.21 mol, 1.02 eq) of acetone cyanohydrine and 25 g of (1S)-(α)-phenylethylamine (0.207 mol) were mixed in 66 ml of absolute methanol and allowed to stand overnight. Then the mixture was evaporated to dryness to give 38.8 g of the pure product (0.207 mol, 100%). IR, ¹H, ¹³C NMR spectra were identical with those described in ref.³⁷

1-((1S)-1-Phenylethyl)-hexahydrocyclopenta[b]pyrrole-6a-carbonitrile 93

Aminonitrile **33** 12.19 g (0.065 mol, 1.05 eq) was added to a solution of **94** (11.79 g, 0.062 mol, 1 eq) in 200 ml of dry acetonitrile. The mixture was refluxed for 48 h, then poured into excess of 10% sodium hydroxide solution and extracted with DCM. The combined extracts were dried (MgSO_4) and evaporated under reduced pressure. The residue was chromatographed (gradient PE – EE, 20:1 – 10:1 as an eluent) to give 4.44 g of each isomer (0.019 mol, 30%).

93a

^1H NMR (400 MHz, CDCl_3), δ : 7.24 – 7.14 (m, 5H, CH arom), 3.60 (q, $J = 6.5$ Hz, 1H, $\text{CH}(\text{CH}_3)$), 2.97 (m, 1H, CH), 2.59 (dd, $J = 9.5, 6.8$ Hz, 1H, CH_2), 2.24 – 2.15 (m, 2H, CH_2, CH_2), 1.97 – 1.69 (m, 5H, $\text{CH}_2, \text{CH}_2, \text{CH}_2, \text{CH}_2$), 1.45 (m, 1H, CH_2), 1.36 (d, $J = 6.5$ Hz, 3H, $\text{CH}(\text{CH}_3)$), 1.26 (m, 1H, CH_2).

^{13}C NMR (100 MHz, CDCl_3), δ : 145.6, 128.4, 127.0, 126.8, 121.3, 67.9, 62.7, 55.0, 53.9, 41.9, 33.1, 30.5, 26.1, 24.5.

IR (ATR, cm^{-1}): 2218 ($\nu_{\text{C}\equiv\text{N}}$).

MS (m/z): 240 (M^+), 225, 163, 105 ($\text{PhCH}(\text{CH}_3)$).

Anal. calcd. for $\text{C}_{16}\text{H}_{20}\text{N}_2$: C, 79.96; H, 8.39; N, 11.66. Found C, 79.72; H, 8.37; N, 11.70.

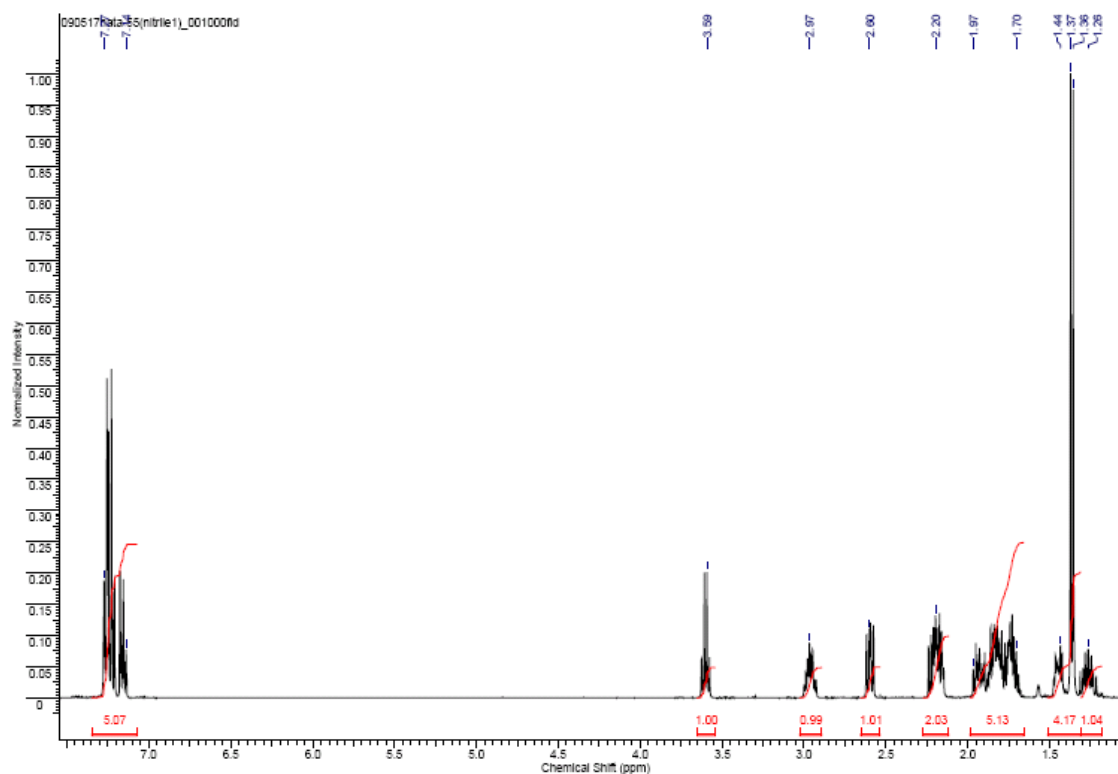


Figure 7. ^1H NMR spectrum of **93a**

93b

^1H NMR (400 MHz, CDCl_3), δ : 7.45 – 7.27 (m, 5H, CH arom), 3.88 (q, $J = 6.5$ Hz, 1H, $\text{CH}(\text{CH}_3)$), 3.06 (m, 1H, CH), 2.89 (m, 1H, CH_2), 2.58 (m, 1H, CH_2), 2.00 (m, 1H, CH_2), 1.76 – 1.54 (m, 2H, CH_2 , CH_2), 1.42 (d, $J = 6.5$ Hz, 3H, $\text{CH}(\text{CH}_3)$), 1.49 – 1.19 (m, 5H, CH_2 , CH_2 , CH_2).

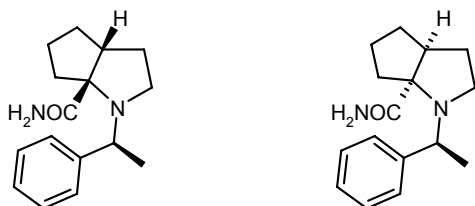
^{13}C NMR (100 MHz, CDCl_3), δ : 144.9, 128.2, 127.4, 127.1, 126.8, 69.4, 59.0, 52.5, 51.0, 38.5, 33.4, 30.7, 25.6, 21.3.

IR (ATR, cm^{-1}): 2217 ($\nu\text{C}\equiv\text{N}$).

MS (m/z): 240 (M^+), 225, 163, 105 ($\text{PhCH}(\text{CH}_3)$).

Anal. calcd. for $\text{C}_{16}\text{H}_{20}\text{N}_2$: C, 79.96; H, 8.39; N, 11.66. Found C, 79.72; H, 8.40; N, 11.62.

1-((1S)-1-Phenylethyl)-hexahydrocyclopenta[b]pyrrole-6a-carboxylic acid amide **95**



To a solution of 2.77 g (0.012 mol) of **93** in hexane at -10°C was slowly added 18.22 ml of concentrated H_2SO_4 . The mixture was stirred 3 h at -10°C , then 3 h at 0°C and

48 h at room temperature. The reaction mixture was poured onto ice and made basic with a saturated aqueous ammonia solution. The product was extracted with diethyl ether. The combined extracts were dried over MgSO_4 and evaporated under reduced pressure to give 2.65 g (0.01 mmol, 89%) of the product.

95a

^1H NMR (400 MHz, CDCl_3), δ : 7.31 – 7.18 (m, 5H, CH arom), 6.86 (s, 1H, NH_2), 5.15 (s, 1H, NH_2), 3.85 (q, $J = 6.8$ Hz, 1H, $\text{CH}(\text{CH}_3)$), 3.20 (dd, $J = 8.8, 7$ Hz, 1H, CH_2), 2.80 (m, 1H, CH_2), 2.53 (q, $J = 8.3$ Hz, 1H, CH), 2.27 (m, 1H, CH_2), 1.99 – 1.90 (m, 2H, CH_2 , CH_2), 1.77 – 1.67 (m, 3H, CH_2 , CH_2), 1.56 (dd, $J = 12.3, 5.3$ Hz, 1H, CH_2), 1.44 (d, $J = 6.8$ Hz, 3H, $\text{CH}(\text{CH}_3)$), 1.22 (m, 1H, CH_2).

^{13}C NMR (100 MHz, CDCl_3), δ : 180.9, 144.9, 128.2, 127.3, 126.9, 78.6, 57.3, 52.5, 47.3, 35.5, 30.9, 30.2, 27.9, 21.4.

IR (ATR, cm^{-1}): 3439 (νNH_2), 3255 (νNH_2), 1674 (Amid I, II).

MS (GC-MS): $m/z = 258$ (M^+), 214, 110, 105 ($\text{PhCH}(\text{CH}_3)$).

Anal. calcd. for $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}$: C, 74.38; H, 8.58; N, 10.84. Found C, 74.65; H, 8.60; N, 10.81.

$[\alpha]_{\text{D}} = -13.9^\circ$ (c 0.33, MeOH).

95b

^1H NMR (400 MHz, CDCl_3), δ : 7.58 (s., 1H, NH_2), 7.35 – 7.24 (m, 5H, CH arom), 5.52 (s, 1H, NH_2), 3.56 (q, $J = 6.5$ Hz, 1H, $\text{CH}(\text{CH}_3)$), 2.61 (m, 2H, CH, CH_2), 2.39 (m, 1H, CH_2), 2.25 (m, 1H, CH_2), 1.97 (m, 1H, CH_2), 1.90 – 1.77 (m, 3H, CH_2 , CH_2), 1.71 (m, 1H, CH_2), 1.39 (dd, $J = 12.6, 5$ Hz, 1H, CH_2), 1.30 (d, $J = 6.8$ Hz, 3H, $\text{CH}(\text{CH}_3)$), 1.16 (m, 1H, CH_2).

^{13}C NMR (100 MHz, CDCl_3), δ : 182.4, 146.0, 128.5, 127.1, 126.8, 77.2, 60.8, 53.9, 51.3, 33.6, 30.2, 28.0, 27.9, 22.8.

IR (ATR, cm^{-1}): 3425 (νNH_2), 3232 (νNH_2), 1628 (Amid I, II).

MS (GC-MS): $m/z = 258$ (M^+), 214, 110, 105 ($\text{PhCH}(\text{CH}_3)$).

Anal. calcd. for $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}$: C, 74.38; H, 8.58; N, 10.84. Found C, 74.51; H, 8.56; N, 10.82.

$[\alpha]_{\text{D}} = -27.6^\circ$ (c 0.53, MeOH).

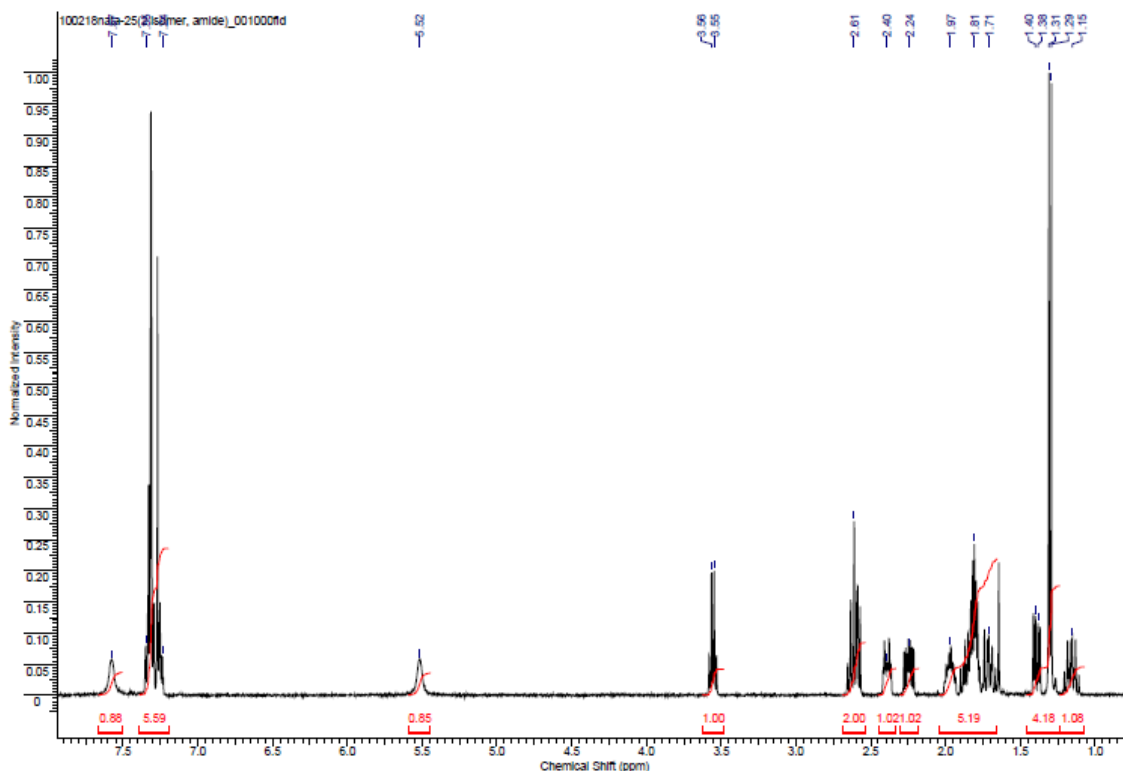
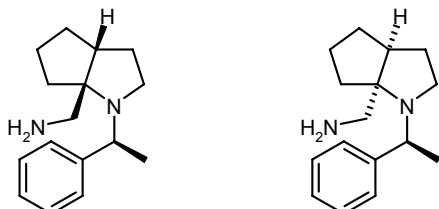


Figure 8. ^1H NMR spectrum of **95b**

[1-((1S)-1-Phenylethyl)-hexahydro-cyclopenta[b]pyrrol-6a-yl]-methylamine 100



To a stirred suspension of LAH (0.059 g, 0.0016 mol) in dry THF was added dropwise a solution of **95** (0.2 g, 0.0008 mol) in dry THF under nitrogen. The reaction mixture was refluxed for 3.5 h then quenched by the addition of distilled water. The insoluble white solid was separated by filtration and the solvent was removed under reduced pressure to afford 0.149 g (0.0006 mol, 79%) of the product.

100a

^1H NMR (400 MHz, CDCl_3), δ : 7.34 – 7.20 (m, 5H, CH arom), 3.81 (q, $J = 6.8$ Hz, 1H $\text{CH}(\text{CH}_3)$), 3.13 (t, $J = 8$ Hz, 1H, CH_2), 2.77 (m, 1H, CH_2), 2.36 (s, 2H, NH_2), 2.22 (m, 1H, CH), 2.12 (d, $J = 13$ Hz, 1H, CH_2), 1.98 (d, $J = 13$ Hz, 1H, CH_2), 1.93 (m, 1H, CH_2), 1.87 – 1.66 (m, 3H, CH_2 , CH_2 , CH_2), 1.42 (d, $J = 6.8$ Hz, 3H, $\text{CH}(\text{CH}_3)$), 1.39 (m, 1H, CH_2), 1.35 (m, 1H, CH_2), 1.24 (m, 2H, CH_2 , CH_2).

^{13}C NMR (100 MHz, CDCl_3), δ : 147.1, 128.1, 126.54, 126.49, 75.8, 56.0, 47.8, 47.3, 46.4, 33.9, 32.8, 30.5, 26.0, 22.4.

MS (GC-MS): $m/z = 242$ (M-2), 214, 110, 79, 51.

100b

^1H NMR (400 MHz, CDCl_3), δ : 7.35 – 7.31 (m, 5H, CH arom), 3.69 (q, $J = 6.5$ Hz, 1H, $\text{CH}(\text{CH}_3)$), 2.94 (d, $J = 13$ Hz, 1H, CH_2), 2.68 (m, 1H, CH_2), 2.56 (d, $J = 13$ Hz, 1H, CH_2), 2.35 (m, 1H, CH_2), 2.30 (m, 1H, CH), 1.87 (m, 1H, CH_2), 1.85 (s, 2H, NH_2), 1.81 – 1.65 (m, 3H, CH_2 , CH_2 , CH_2), 1.40 (m, 1H, CH_2), 1.37 (d, $J = 6.5$ Hz, 3H, $\text{CH}(\text{CH}_3)$), 1.34 (m, 1H, CH_2), 1.27 (dd, $J = 12.1, 5.5$ Hz, 1H, CH_2), 1.15 (m, 1H, CH_2).

^{13}C NMR (100 MHz, CDCl_3), δ : 147.0, 128.2, 127.1, 126.6, 75.1, 59.4, 50.8, 50.1, 48.6, 33.8, 31.7, 30.5, 26.2, 23.5.

MS (GC-MS): $m/z = 242$ (M-2), 214, 110, 79, 51.

Hexahydrocyclopenta[b]pyrrole-6a-carboxylic acid 29

6 M hydrochloric acid was added to **95**. The resulting mixture was refluxed overnight then cooled, filtered and evaporated under reduced pressure. Water was added and subsequently removed by evaporation under reduced pressure. This operation was repeated twice to remove the excess of HCl. To the obtained solid residue, absolute ethanol was added, the resulting mixture was refluxed, then cooled and left in an ice bath for 3 h. Ammonium hydrochloride was filtered off, the filtrate was evaporated to dryness. The solid obtained was dissolved in methanol and hydrogenated (10% Pd/C, 50 atm, 35°C) for 36 h. The catalyst was filtered off, and the solvent was removed by rotary evaporation. The crude product was purified using ion-exchange chromatography (strong cationite, 3.5% aqueous ammonia solution as an eluent). Yield of the product 68%.

^1H NMR (400 MHz, CD_3OD), δ : 3.29 (m, 2H, CH_2), 2.93 (m, 1H, CH), 2.32 (m, 1H, CH_2), 2.20 (m, 1H, CH_2), 2.08 – 1.76 (m, 4H, CH_2 , CH_2 , CH_2), 1.72 (m, 1H, CH_2), 1.60 (m, 1H, CH_2).

^{13}C NMR (100 MHz, CD_3OD), δ : 177.3, 80.8, 50.5, 47.3, 37.4, 33.9, 32.0, 27.1.

MS (m/z): 155 (M^+), 126, 110, 83, 55.

Anal. calcd. for $\text{C}_8\text{H}_{13}\text{NO}_2$: C, 61.91; H, 8.44; N, 9.03. Found C, 62.04; H, 8.43; N, 9.01.

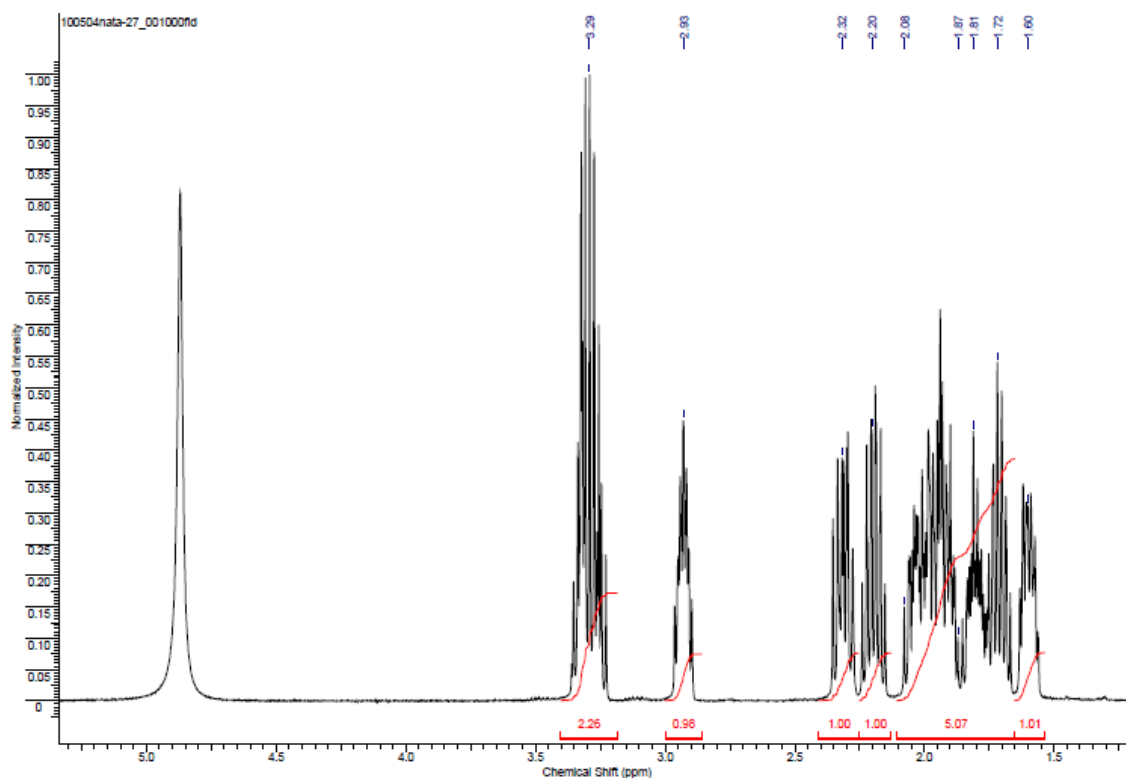
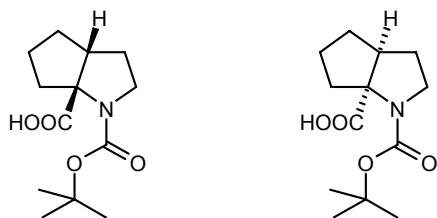


Figure 9. ^1H NMR spectrum of **29**

1-(*tert*-butoxycarbonyl)-octahydrocyclopenta[*b*]pyrrole-6a-carboxylic acid **32**



Di-*tert*-butyl dicarbonate (0.113 g, 0.00052 mol, 1.1 eq) was added to a solution of **29** (0.073 g, 0.00047 mol, 1 eq) in THF and 1 M solution of aqueous sodium hydroxide (0.3 ml). The reaction mixture was stirred 36 h at rt. The THF was then evaporated, and the aqueous phase was acidified to pH ~ 2-3 by addition of an aqueous solution of 1% hydrochloric acid. The white precipitate was filtered and dried *in vacuo* to give 0.08 g of the product (0.00014 mol, 67%). ^1H , ^{13}C NMR spectra were identical with those described in ref.³³

Ac-HKWXWW-NH₂ peptide synthesis (X – 2,3-propanoproline **29b**)

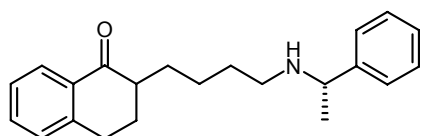
The Ac-HKWXWW-NH₂ peptide was synthesized by solid phase peptide synthesis on a 433A synthesizer (ABI, Foster City, CA). Fmoc-protected amino acids were purchased from ABI. All other reagents for the SPPS and peptide purification were from ABI or Aldrich.

The peptide was synthesized at a 0.1 mmole scale using the standard fluorenylmethoxycarbonyl (Fmoc)-amino acid-coupling protocols starting from 0.6 mmol/g

Rink Amide MBHA resin (100-200 mesh) (Merck/Novabiochem). Coupling was performed by HBTU/HOBt solution (ABI) 10-fold excess of all amino acids except X was used. Fmoc-protective groups were systematically removed by 2x20 min treating with 20% piperidine/1% DBU in NMP; efficiency of the deprotection was controlled by UV-detector of the peptide synthesizer. At least 97% of present Fmoc-groups were removed upon the first piperidine treatment in all the cases. Coupling of all amino acids was followed by residual amino group acylation ($\text{Ac}_2\text{O}/\text{DCC}$) in order to block synthesis of the peptide with missing amino acids and to control efficiency of each coupling. The third amino acid (X) was introduced by double coupling using 2:1 and 1:1 acid:peptide ratio (to decrease using of the acid) therefore the coupling time was extended to 3h and 1h for 1st and 2nd coupling steps, respectively (comparing to ~30min coupling time for standard 10-fold reagent excess conditions). Coupling of this amino acid was at least (95±5)% efficient (determined by the UV absorption after Fmoc-deprotection). Coupling of the next amino acid (W) to the rigid proline derivative in standard conditions shows ~25% efficiency, probably due to the steric hindrance. This amino acid was introduced using double coupling with extended reaction time (2x2 h). Further couplings were efficiently performed using standard protocols. The cleavage and side-chain deprotection was done by TFA containing 5% H_2O and 2.5% TIS (iPr_3SiH), 7 ml, 1.5 h incubation, 10 °C to rt. The solution was filtered and peptide was precipitated by 40 ml of cold (-10 °C) Et_2O with further 15 min incubation at -20 °C.

Peptide was purified by HPLC on a C8 column (uptisphere 300A, 5 μm ; 250X10, Interchim, France) with a linear gradient 10 to 50% B in 30 min and monitored at 280 nm.

2-[4-((1S)-1-Phenylethylamino)butyl]-3,4-dihydro-2H-naphthalen-1-one 105



Aminonitrile **33** 1.2 g (0.064 mol, 1.05 eq) was added to a solution of 1.71 g (0.061 mol, 1 eq) of **103** in dry acetonitrile. The mixture was refluxed for 48 h, the solid product was filtered off and dissolved in excess of 10% sodium hydroxide solution and extracted with DCM. The organic phase was dried (MgSO_4) and evaporated under reduced pressure to give 0.78 g of one of two diastereomers (0.0024 mol, 40%).

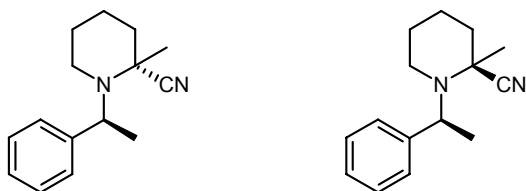
^1H NMR (400 MHz, CDCl_3), δ : 7.92 (d, $J = 7.8$ Hz, 1H, CH arom), 7.34 (td, $J = 7.5$, 1.5 Hz, 1H, CH arom), 7.22 – 7.11 (m, 7H, CH arom), 3.66 (q, $J = 6.5$ Hz, 1H, $\text{CH}(\text{CH}_3)$), 2.87 (m, 2H, CH_2), 2.48 – 2.31 (m, 3H, CH, CH_2), 2.11 (m, 1H, CH_2), 1.87 – 1.72 (m, 2H, CH_2 , CH_2), 1.63 (s, 1H, NH), 1.47 – 1.28 (m, 5H, CH_2 , CH_2 , CH_2), 1.26 (d, $J = 6.5$ Hz, 3H, $\text{CH}(\text{CH}_3)$).

^{13}C NMR (100 MHz, CDCl_3), δ : 200.0, 145.9, 143.8, 132.9, 132.6, 128.5, 128.3, 127.4, 126.7, 126.50, 126.47, 58.4, 53.3, 47.6, 47.4, 30.4, 29.3, 28.3, 24.8, 24.2.

IR (ATR, cm^{-1}): 3325 (νNH), 1679 ($\nu\text{C=O}$).

HRMS (m/z): calcd for $\text{C}_{22}\text{H}_{27}\text{NO}$ ($M+1$) 322.2165. Found 322.2170.

2-Methyl-1-((1S)-1-phenylethyl)-piperidine-2-carbonitrile **107**



Aminonitrile **33** 2.76 g (0.015 mol, 1.05 eq) was added to a solution of 2.5 g (0.014 mol, 1 eq) of **106** in dry acetonitrile. The mixture was refluxed for 48 h, then poured into excess of 10% sodium hydroxide solution and extracted with DCM. The combined extracts were dried (MgSO_4) and evaporated under reduced pressure. The residue was chromatographed (PE – EE, 3:1 as an eluent) to give 1.43 g of a mixture of two isomers (0.006 mol, 45%).

Major isomer.

^1H NMR (400 MHz, CDCl_3), δ : 7.43 – 7.22 (m, 5H, CH arom), 4.45 (q, $J = 7$ Hz, 1H, $\text{CH}(\text{CH}_3)$), 2.57 (m, 2H, CH_2), 1.93 – 1.55 (m, 8H, CH_2 , CH_2 , CH_2 , CH_3), 1.52 (d, $J = 6.8$ Hz, 3H, $\text{CH}(\text{CH}_3)$), 1.33 (m, 1H, CH_2).

^{13}C NMR (100 MHz, CDCl_3), δ : 144.4, 128.0, 127.1, 126.5, 122.0, 55.9, 54.3, 42.5, 40.4, 26.6, 25.6, 22.3, 11.3.

Minor isomer.

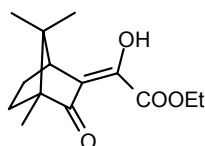
^1H NMR (400 MHz, CDCl_3), δ : 7.43 – 7.22 (m, 5H, CH arom), 4.33 (q, $J = 7$ Hz, $\text{CH}(\text{CH}_3)$), 3.11 (m, 1H, CH_2), 2.38 (td, $J = 11.8, 2.5$ Hz, 1H, CH_2), 1.95 – 1.62 (m, 9H, CH_2 , CH_2 , CH_3), 1.49 (d, $J = 7$ Hz, $\text{CH}(\text{CH}_3)$).

^{13}C NMR (100 MHz, CDCl_3), δ : 139.6, 128.6, 127.9, 127.4, 120.2, 56.8, 56.4, 44.0, 40.8, 26.2, 26.1, 21.9, 20.4.

IR (ATR, cm^{-1}): 2215 ($\nu\text{C}\equiv\text{N}$).

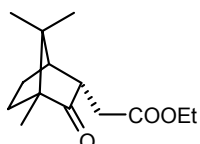
Anal. calcd. for $\text{C}_{15}\text{H}_{20}\text{N}_2$: C, 78.90; H, 8.83; N, 12.27. Found C, 78.95; H, 8.85; N, 12.30.

Hydroxy-(4,7,7-trimethyl-3-oxobicyclo[2.2.1]hept-2-ylidene)-acetic acid ethyl ester **111**



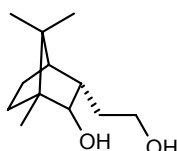
The compound was prepared by a procedure described in the literature.⁹⁴ A solution of 15 g (0.099 mol) of D-camphor in 45 ml of anhydrous xylene was added to the suspension of 8.6 g (60%, 0.215 mol) of sodium hydride suspended in paraffin in 54 ml of anhydrous xylene. The mixture was refluxed for 4 h, cooled to 10 °C, and 29.8 g (0.204 mol) of diethyl oxalate was added as fast as possible with ice cooling, controlling that the reaction temperature did not exceed 50 °C. The mixture was stirred for 12 h at rt and poured into a mixture of 100 g of ice and 100 ml of conc. hydrochloric acid. The phases were separated and the aqueous layer was extracted several times with PE/ diethyl ether (1:1). The combined organic layers were washed with a half-saturated sodium hydrogen carbonate solution, dried (MgSO₄), and the solvent was evaporated to give 22.4 g (0.089 mol, 90%) of the product. ¹H, ¹³C NMR spectra were identical with those described in ref.⁹⁴

Ethyl 4,7,7-trimethyl-3-oxobicyclo[2.2.1]heptane-endo-2-acetate **112**



The compound was prepared by a procedure described in the literature.¹¹⁷ A suspension of 11.6 g (0.177 mol) of zinc dust in 300 ml of 2% hydrochloric acid was stirred for 5 min, filtered off, washed with 300 ml of water, 300 ml of ethanol and 300 ml of diethyl ether, and dried for 15 min at 90 °C *in vacuo*. The activated zinc dust was added in small portions to a solution of 4 g (0.016 mol) of **111** in 130 ml of anhydrous diethyl ether saturated with hydrogen chloride at 0 °C. The mixture was stirred for 1 h, the zinc dust was filtered off and washed with diethyl ether. The combined organic layers were washed with water and a half-saturated sodium hydrogen carbonate solution. The aqueous layer was acidified with conc. hydrochloric acid and extracted several times with diethyl ether. The combined organic layers were dried over MgSO₄, and the solvent was evaporated to give 3.6 g of the product (0.015 mol, 95%), identical with those described in ref.¹¹⁷

3-(2-Hydroxyethyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol **114**



To a stirred suspension of LAH (0.84 g, 0.022 mol, 0.8 eq) in dry diethyl ether (100 ml) was added dropwise a solution of **112** (6.58 g, 0.028 mol, 1 eq) in dry diethyl ether under nitrogen. The reaction mixture was refluxed for 3 h then quenched by the addition of distilled

water. The insoluble white solid was separated by filtration and the solvent was removed under reduced pressure to afford 4.54 g (0.023 mol, 83%) of the product.

^1H NMR (400 MHz, CDCl_3), δ : 3.75 (m, 1H, CH_2), 3.67 (m, 1H, CH_2), 3.16 (d, $J = 4$ Hz, 1H, CH), 3.01 (s, 2H, OH), 2.08 (m, 1H, CH), 1.63 – 1.45 (m, 5H, CH, CH_2 , CH_2), 1.29 (m, 1H, CH_2), 1.03 (s, 3H, CH_3), 0.90 (m, 1H, CH_2), 0.85 (s, 3H, CH_3), 0.83 (s, 3H, CH_3).

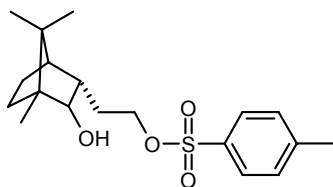
^{13}C NMR (100 MHz, CDCl_3), δ : 86.3, 62.4, 49.5, 49.3, 47.3, 46.1, 34.6, 34.0, 20.6, 20.3, 19.5, 11.4.

IR (ATR, cm^{-1}): 3339 (νOH).

MS (m/z): 198 (M^+), 180, 95, 69, 55.

Anal. calcd. for $\text{C}_{12}\text{H}_{22}\text{O}_2$: C, 72.68; H, 11.18. Found C, 72.45; H, 11.16.

Toluene-4-sulfonic acid 2-(3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl)-ethyl ester 115



To a solution of 1 g (0.005 mol) of **114** and 3.51 ml (0.025 mol, 5 eq) of dry triethylamine in 20 ml of DCM were added at cooling 1.04 g (0.005 mol, 1.08 eq) of *p*-TsCl in one portion. The resulting solution was stirred overnight, then poured into excess of water and extracted with DCM. The combined extracts were dried over MgSO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (PE – EE, 2:1 as an eluent) to give 1.46 g (0.004 mol, 82%) of the product.

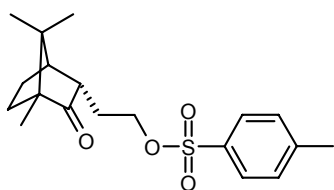
^1H NMR (400 MHz, CDCl_3), δ : 7.78 (d, $J = 8$ Hz, 2H, CH arom), 7.34 (d, $J = 8$ Hz, 2H, CH arom), 4.08 (m, 2H, CH_2OTs), 3.04 (d, $J = 4$ Hz, 1H, CH), 2.44 (s, 3H, $\text{C}_6\text{H}_4\text{CH}_3$), 2.00 (m, 1H, CH), 1.86 (s, 1H, OH), 1.83 (m, 1H, CH_2), 1.67 (m, 1H, CH_2), 1.48 (m, 3H, CH, CH_2), 1.18 (m, 1H, CH_2), 0.99 (s, 3H, CH_3), 0.85 (m, 1H, CH_2), 0.83 (s, 3H, CH_3), 0.80 (s, 3H, CH_3).

^{13}C NMR (100 MHz, CDCl_3), δ : 144.7, 133.0, 129.8, 127.8, 85.9, 70.0, 49.5, 48.1, 47.4, 45.0, 34.2, 30.5, 21.6, 20.6, 20.0, 19.4, 11.3.

IR (ATR, cm^{-1}): 3565 (νOH), 1365, 1173 ($\nu\text{R-SO}_2\text{-OR}'$).

MS (m/z): 352 (M^+), 334, 162, 133, 55.

Anal. calcd. for $\text{C}_{19}\text{H}_{28}\text{O}_4\text{S}$: C, 64.74; H, 8.01. Found C, 64.68; H, 8.02.

Toluene-4-sulfonic acid 2-(4,7,7-trimethyl-3-oxobicyclo[2.2.1]hept-2-yl)-ethyl ester 108

To a solution of 0.65 g (0.0018 mol) of **115** in diethyl ether was added at cooling a solution of $\text{Na}_2\text{Cr}_2\text{O}_7$ (0.68 g) and conc. H_2SO_4 (0.45 ml) in 2 ml of water. The resulting mixture was stirred for 2 hours, and then the organic phase was separated. The aqueous phase was extracted with diethyl ether. The combined extracts were dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (PE – EE, 3:1 as an eluent) to give 0.47 g (0.0013 mol, 72%) of the product.

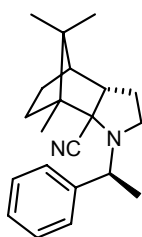
^1H NMR (400 MHz, CDCl_3), δ : 7.79 (d, $J = 8.5$ Hz, 2H, CH arom), 7.35 (d, $J = 8.5$ Hz, 2H, CH arom), 4.14 (td, $J = 6.5, 1.8$ Hz, 2H, CH_2), 2.45 (s, 3H, $\text{C}_6\text{H}_4\text{CH}_3$), 2.38 (m, 1H, CH), 1.99 (m, 2H, CH, CH_2), 1.79 – 1.58 (m, 3H, CH_2 , CH_2 , CH_2), 1.41 (m, 1H, CH_2), 1.24 (m, 1H, CH_2), 0.97 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.82 (s, 3H, CH_3).

^{13}C NMR (100 MHz, CDCl_3), δ : 220.6, 145.0, 133.0, 130.0, 128.0, 69.4, 58.7, 46.4, 46.0, 45.98, 31.1, 26.9, 21.8, 20.3, 19.6, 19.3, 9.6.

IR (ATR, cm^{-1}): 1736 ($\nu\text{C}=\text{O}$), 1358, 1175 ($\nu\text{R}-\text{SO}_2-\text{OR}'$).

MS (m/z): 350 (M^+), 322, 195, 135, 95, 55.

Anal. calcd. for $\text{C}_{19}\text{H}_{26}\text{O}_4\text{S}$: C, 65.11; H, 7.48. Found C, 65.28; H, 7.50.

1,10,10-Trimethyl-3-((1S)-1-phenylethyl)-3-azatricyclo[5.2.1.0^{2,6}]decane-2-carbonitrile 109

Aminonitrile **33** (0.564 g, 0.003 mol, 1.05 eq) was added to a solution of 1 g (0.0029 mol, 1 eq) of **108** in dry acetonitrile. The mixture was heated at 100 °C for 60 h with an air condenser, cooled, poured into excess of 10% sodium hydroxide solution and extracted with DCM. The combined extracts were dried (MgSO_4) and evaporated under reduced pressure. The residue was chromatographed (PE – EE, 20:1 as an eluent) to give 0.22 g of the product (0.0007 mol, 25%).

^1H NMR (400 MHz, CDCl_3), δ : 7.37 – 7.25 (m, 5H, CH arom), 3.76 (q, $J = 7$ Hz, 1H, $\text{CH}(\text{CH}_3)$), 3.29 (m, 1H, CH), 3.09 (m, 1H, CH_2), 2.64 (m, 1H, CH_2), 2.27 (m, 1H, CH_2), 1.67 –

1.57 (m, 5H, CH₂, CH₂, CH), 1.43 (m, 1H, CH₂), 1.41 (d, J = 7 Hz, 3H, CH(CH₃)), 1.23 (s, 3H, CH₃), 1.22 (s, 3H, CH₃), 1.01 (s, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃): δ: 144.1, 128.2, 127.5, 127.0, 120.9, 71.6, 60.2, 55.1, 54.7, 54.0, 53.1, 47.3, 28.6, 24.2, 22.7, 22.4, 20.5, 19.9, 15.0.

IR (ATR, cm⁻¹): 2214 (νC≡N).

MS (*m/z*): 308 (M⁺), 293, 239, 105 (PhCH(CH₃)).

Anal. calcd. for C₂₁H₂₈N₂: C, 81.77; H, 9.15; N, 9.08. Found C, 81.53; H, 9.14; N, 9.11.

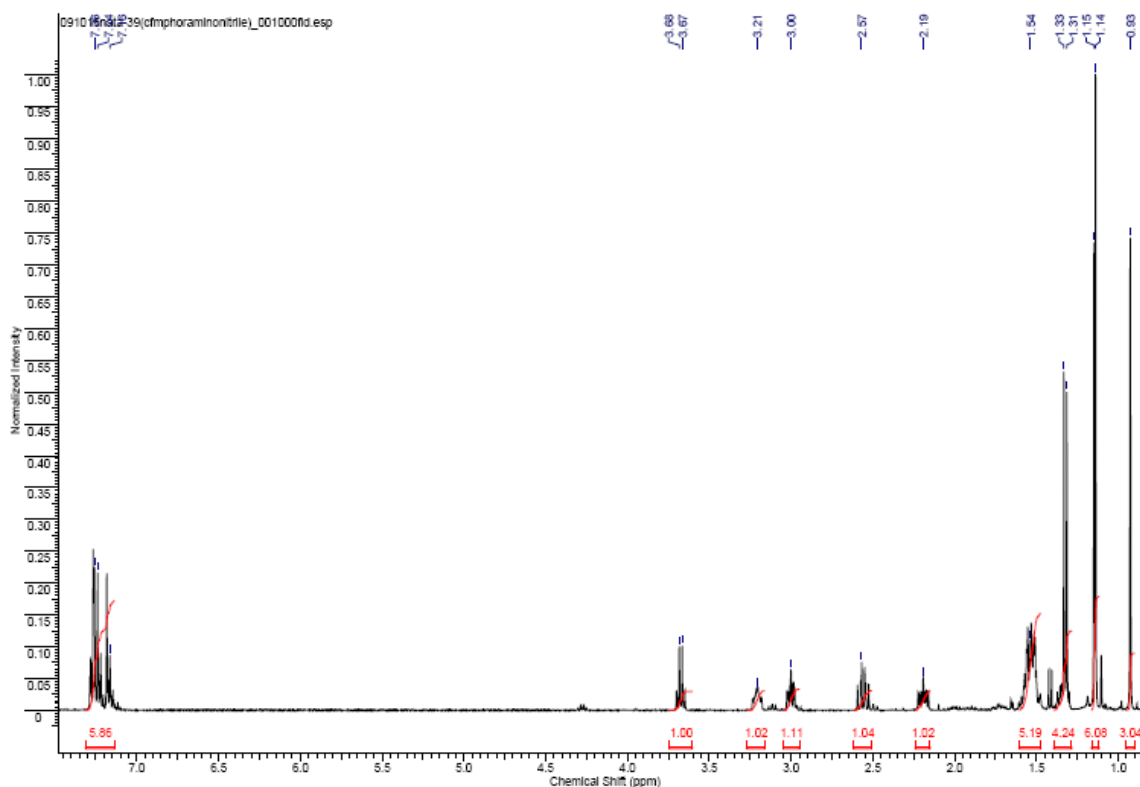
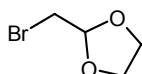
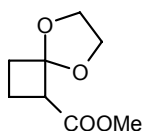


Figure 10. ¹H NMR spectrum of **109**

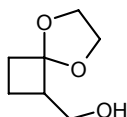
2-(Bromomethyl)-1,3-dioxolane



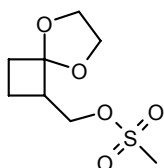
The compound was prepared by a procedure described in the literature.¹¹⁸ To a stirred mixture of bromoacetaldehyde dimethyl acetate 173 g (1.024 mol) and ethylene glycol 63.5 g (1.024 mol) was added *p*-TsOH (2 g). The mixture was heated to 110 °C for 2 h with collection of methanol distillate *via* Vigreux column. Distillation (14 mbar / 67 °C) furnished the 1,3-dioxolane (83%) as a colourless oil. ¹H, ¹³C NMR spectra were identical with those of a commercially available sample.

5,8-Dioxa-spiro[3,4]octane-1-carboxylic acid methyl ester 118

The compound was prepared by a procedure described in the literature.⁹⁶ To a suspension of *t*-BuOK (70.42 g, 0.629 mol, 1.5 eq) in 480 ml of *tert*-butanol was added 2-(bromomethyl)-1,3-dioxolane (70 g, 0.419 mol, 1 eq). The reaction mixture was refluxed for 2 h. The product together with *tert*-butanol was collected at 90 °C under vacuum (till 80 mbar). The distillate and 82.9 ml of methyl acrylate (0.923 mol) were refluxed for 5 days under an inert atmosphere. Distillation (105 °C / 25 mbar) furnished the product (49% over 2 steps) as a colorless oil. ¹H, ¹³C NMR spectra were identical with those described in the literature.⁹⁶

(5,8-Dioxa-spiro[3.4]oct-1-yl)-methanol 119

To a stirred suspension of LAH (1.7 g, 0.045 mol) in dry diethyl ether was added dropwise a solution of **118** (7.7 g, 0.045 mol) in dry diethyl ether under nitrogen. The reaction mixture was refluxed for 3 h then quenched by the addition of distilled water. The insoluble white solid was separated by filtration and the solvent was removed under reduced pressure to afford 5.87 g (0.041 mol, 91%) of the product. ¹H, ¹³C NMR spectra were identical with those described in the literature.⁹⁶

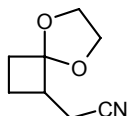
Methanesulfonic acid 5,8-dioxa-spiro[3.4]oct-1-ylmethyl ester 121

A solution of **119** (5.87 g, 0.041 mol, 1 eq) and triethylamine (8.5 ml, 0.061 mol, 1.5 eq) in dichloromethane (100 ml) was cooled to -30 °C and a solution of methanesulfonyl chloride (3.47 ml, 0.045 mol, 1.1 eq) was added dropwise, taking care that the temperature did not exceed -30 °C. The resulting suspension was warmed to +10 °C then poured into water. The organic phase was separated, washed with brine. After drying over MgSO₄, and evaporating the solvent, the residue was passed through a short layer of silica gel (PE – EE, 2:1 as an eluent) to give the product, which was used immediately in the next step.

^1H NMR (400 MHz, CDCl_3), δ : 4.32 (dd, $J = 10, 8.8$ Hz, 1H, CH_2), 4.2 (dd, $J = 9.8, 6$ Hz, 1H, CH_2), 3.89 (m, 4H, $\text{OCH}_2\text{CH}_2\text{O}$), 3.0 (s, 3H, CH_3), 2.91 (m, 1H, CH), 2.38 – 2.23 (m, 2H, CH_2), 1.87 (m, 1H, CH_2), 1.43 (m, 1H, CH_2).

^{13}C NMR (100 MHz, CDCl_3), δ : 108.1, 68.5, 64.7, 64.3, 46.5, 37.2, 33.2, 14.7.

(5,8-Dioxa-spiro[3.4]oct-1-yl)-acetonitrile **122**



To a solution of 9.06 g (0.041 mol, 1 eq) of **121** in DMF (100 ml) was added KCN (5.29 g, 0.082 mol, 2 eq) and the resulting mixture was stirred for 72 h at 90 °C. The reaction mixture was poured into water and extracted with diethyl ether. The organic phase was washed with water, brine, dried over MgSO_4 and evaporated under reduced pressure. The residue was chromatographed (PE – EE, 3:1 as an eluent) to give 4.05 g of the product (0.026 mol, 65% over 2 steps).

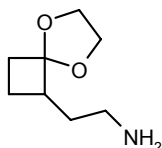
^1H NMR (400 MHz, CDCl_3), δ : 3.95 (m, 4H, $\text{OCH}_2\text{CH}_2\text{O}$), 2.85 (m, 1H, CH), 2.48 (m, 2H, CH_2), 2.29 (m, 1H, CH_2), 1.97 (m, 1H, CH_2), 1.41 (m, 1H, CH_2).

^{13}C NMR (100 MHz, CDCl_3), δ : 118.8, 108.1, 64.9, 64.6, 43.8, 33.4, 17.9, 17.0.

IR (ATR, cm^{-1}): 2248 ($\nu\text{C}\equiv\text{N}$).

MS (m/z): 154 (M+1), 136, 127.

2-(5,8-Dioxa-spiro[3.4]oct-1-yl)-ethylamine **123**



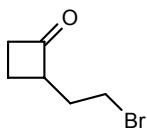
To a stirred suspension of LAH (0.87 g, 0.023 mol) in dry diethyl ether was added dropwise a solution of **122** (3.5 g, 0.023 mol) in dry diethyl ether under nitrogen. The reaction mixture was refluxed for 4 h then quenched by the addition of distilled water. The insoluble white solid was separated by filtration and the solvent was removed under reduced pressure to afford 3.27 g (0.021 mol, 91%).

^1H NMR (400 MHz, CDCl_3), δ : 3.88 (m, 4H, $\text{OCH}_2\text{CH}_2\text{O}$), 2.69 (m, 2H, CH_2), 2.59 (m, 1H, CH), 2.17 (m, 2H, CH_2), 1.83 (m, 1H, CH_2), 1.72 (m, 1H, CH_2), 1.58 (m, 1H, CH_2), 1.33 (m, 1H, CH_2), 1.26 (s, 2H, NH_2).

^{13}C NMR (100MHz, CDCl_3), δ : 109.9, 64.14, 64.07, 45.1, 40.2, 33.5, 33.1, 18.4.

IR (ATR, cm^{-1}): 3372 (νNH_2), 3288 (νNH_2), 2942, 1569.

MS (m/z): 158 (M+1), 127.

2-(2-Bromoethyl)-cyclobutanone 124

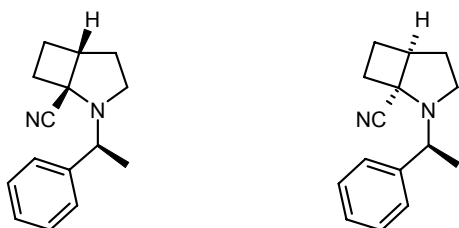
123 (1.5 g, 0.01 mol) was dissolved in 56 ml of water. Hydrobromic acid solution (6.3 ml, 47% aqueous solution) and 6.4 g of sodium bromide were added to the solution which was then cooled to 0 °C. Sodium nitrite (8.7 g) was added to the mixture and it was stirred at rt overnight. The mixture was neutralized by sodium bicarbonate, extracted with DCM. The organic phase was dried over MgSO₄ and evaporated under reduced pressure. The residue was chromatographed (PE – EE, 5:1 as an eluent) to give 0.727 g of the product (0.004 mol, 43% yield).

¹H NMR (400 MHz, CDCl₃), δ : 3.53 (m, 1H, CH), 3.47 (m, 2H, CH₂), 3.12 (m, 1H, CH₂), 2.97 (m, 1H, CH₂), 2.28 (m, 2H, CH₂, CH₂), 2.05 (m, 1H, CH₂), 1.70 (m, 1H, CH₂).

¹³C NMR (100 MHz, CDCl₃), δ : 210.3, 58.6, 44.8, 32.6, 30.7, 16.7.

MS (GC/MS): m/z = 176 and 178 (M⁺), 148 and 150, 93, 55.

Anal. calcd. for C₆H₉BrO: C, 40.71; H, 5.12. Found C, 40.82; H, 5.12.

2-((1S)-1-Phenylethyl)-2-azabicyclo[3.2.0]heptane-1-carbonitrile 125

Aminonitrile **33** (0.77 g, 0.0039 mol, 1.05 eq) was added to a solution of 0.69 g (0.0039 mol, 1 eq) of **124** in 15 ml of dry acetonitrile. The mixture was refluxed for 42 h, then poured into excess of 10% sodium hydroxide solution and extracted with DCM. The combined extracts were dried over MgSO₄ and evaporated under reduced pressure. The residue was chromatographed (PE – EE, 20:1 as an eluent) to give 0.361 g of the mixture of products (0.0016 mol, 41%). Compounds were separated by semi-preparative HPLC to give pure diastereomers (Zorbax SB-C18 semi-preparative column, CH₃CN–H₂O (80 : 20) as an eluent, 25 °C, flow rate – 30 ml/min, retention times 22.5 min (**125a**) and 26.6 min (**125b**)).

125a

¹H NMR (400 MHz, CDCl₃), δ : 7.40 – 7.28 (m, 5H, CH arom), 3.72 (q, J = 6.5 Hz, 1H, CH(CH₃)), 3.26 (m, 1H, CH), 2.83 (m, 1H, CH₂), 2.67 (m, 1H, CH₂), 2.37 (m, 2H, CH₂), 2.31 (m, 1H, CH₂), 1.97 (m, 1H, CH₂), 1.87 (m, 1H, CH₂), 1.65 (m, 1H, CH₂), 1.44 (d, J = 6.5 Hz, 3H, CH(CH₃)).

^{13}C NMR (100 MHz, CDCl_3), δ : 144.5, 128.5, 127.5, 127.2, 119.8, 60.8, 59.0, 53.2, 45.3, 30.7, 27.9, 24.3, 23.4.

IR (ATR, cm^{-1}): 2218 ($\nu\text{C}\equiv\text{N}$).

MS (m/z): 226 (M^+), 105 ($\text{PhCH}(\text{CH}_3)$).

Anal. calcd. for $\text{C}_{15}\text{H}_{18}\text{N}_2$: C, 79.61; H, 8.02; N, 12.38. Found C, 79.55; H, 7.99; N, 12.41.

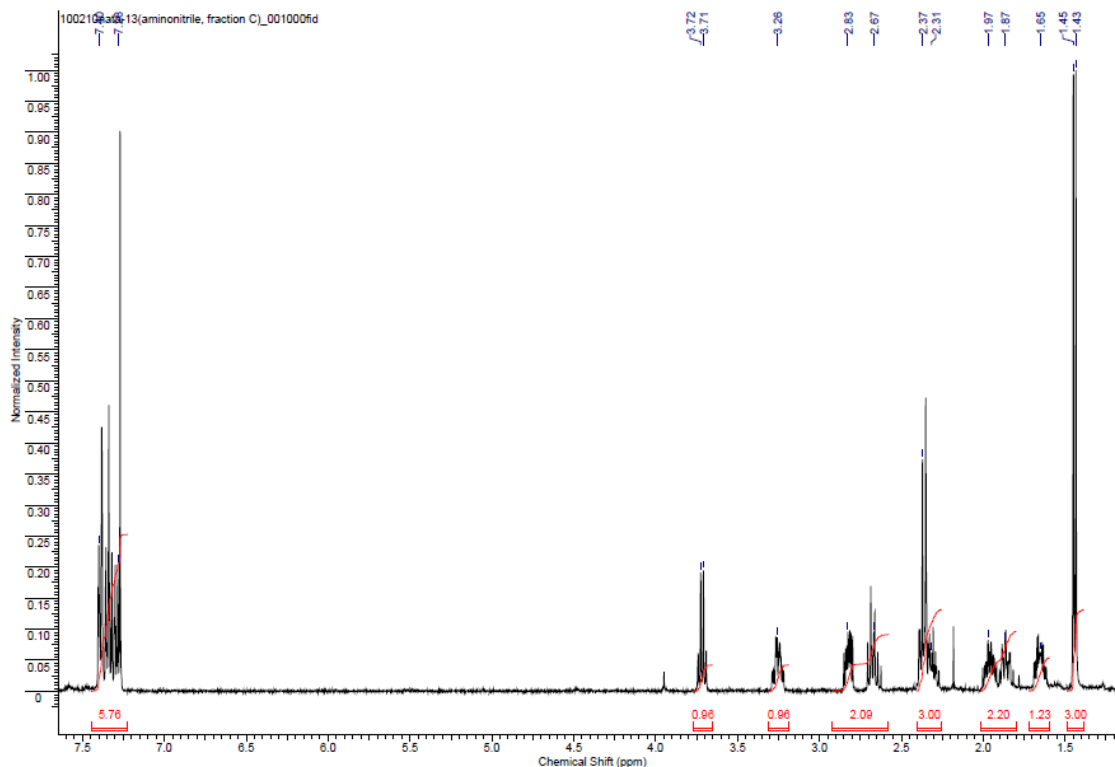


Figure 11. ^1H NMR spectrum of **125a**

125b

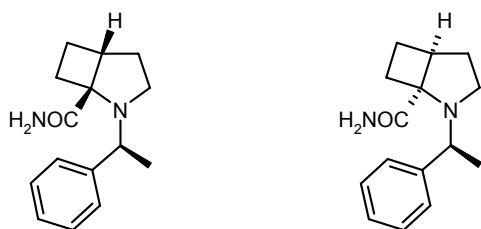
^1H NMR (400 MHz, CDCl_3), δ : 7.42 – 7.25 (m, 5H, CH arom), 3.74 (q, $J = 6.5$ Hz, 1H, $\text{CH}(\text{CH}_3)$), 3.39 (m, 1H, CH), 2.86 (m, 1H, CH_2), 2.73 (m, 1H, CH_2), 2.35 – 2.24 (m, 3H, CH_2 , CH_2), 1.98 (m, 1H, CH_2), 1.59 (m, 1H, CH_2), 1.56 (m, 1H, CH_2), 1.5 (d, $J = 6.8$ Hz, 3H, $\text{CH}(\text{CH}_3)$).

^{13}C NMR (100 MHz, CDCl_3), δ : 144.8, 128.4, 127.3, 127.1, 123.2, 60.5, 57.6, 51.8, 46.0, 30.0, 23.4, 23.3, 21.5.

IR (ATR, cm^{-1}): 2216 ($\nu\text{C}\equiv\text{N}$).

MS (m/z): 226 (M^+), 105 ($\text{PhCH}(\text{CH}_3)$).

Anal. calcd. for $\text{C}_{15}\text{H}_{18}\text{N}_2$: C, 79.61; H, 8.02; N, 12.38. Found C, 79.60; H, 8.04; N, 12.42.

2-((1S)-1-Phenylethyl)-2-azabicyclo[3.2.0]heptane-1-carboxylic acid amide

To a solution of 0.26 g (0.0012 mol) of **125** in hexane at -10°C was slowly added 1.79 ml of concentrated H_2SO_4 . The mixture was stirred 3 h at -10°C , then 3 h at 0°C and 48 h at room temperature. The reaction mixture was poured onto ice and made basic with a saturated aqueous ammonia solution. The product was extracted with diethyl ether. The combined extracts were dried over MgSO_4 and evaporated under reduced pressure to give 0.22 g of the product (0.0009 mol, 78%).

Diastereomer from 125a

^1H NMR (400 MHz, CDCl_3), δ : 7.27 – 7.20 (m, 5H, CH arom), 6.36 (s, 1H, NH_2), 4.62 (s, 1H, NH_2), 3.76 (q, $J = 6.8$ Hz, 1H, $\text{CH}(\text{CH}_3)$), 3.44 (dd, $J = 9, 7$ Hz, 1H, CH_2), 3.04 (m, 1H, CH_2), 2.79 (m, 2H, CH, CH_2), 2.20 – 2.05 (m, 2H, CH_2 , CH_2), 1.92 (m, 1H, CH_2), 1.63 (m, 1H, CH_2), 1.53 (d, $J = 6.8$ Hz, 2H, $\text{CH}(\text{CH}_3)$), 1.44 (m, 1H, CH_2).

^{13}C NMR (100 MHz, CDCl_3), δ : 177.7, 143.6, 128.1, 127.8, 127.4, 71.0, 57.4, 50.2, 45.9, 29.7, 21.2, 20.1, 17.3.

IR (ATR, cm^{-1}): 3423 (νNH_2), 3272 (νNH_2), 1643 (Amid I, II).

MS (GC/MS): $m/z = 244$ (M^+), 216, 105 ($\text{PhCH}(\text{CH}_3)$), 77.

Anal. calcd. for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}$: C, 73.74; H, 8.25; N, 11.46. Found C, 73.92; H, 8.24; N, 11.42.

Diastereomer from 125b

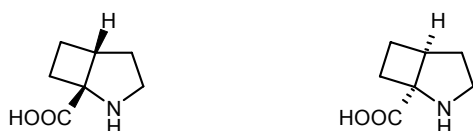
^1H NMR (400 MHz, CDCl_3), δ : 7.35 – 7.25 (m, 5H, CH arom), 7.2 (s, 1H, NH_2), 5.44 (s, 1H, NH_2), 3.59 (q, $J = 6.78$ Hz, 1H, $\text{CH}(\text{CH}_3)$), 2.96 – 2.86 (m, 3H, CH, CH_2 , CH_2), 2.65 (m, 1H, CH_2), 2.17 (m, 1H, CH_2), 2.08 (m, 1H, CH_2), 1.85 (m, 1H, CH_2), 1.51 (m, 1H, CH_2), 1.46 (m, 1H, CH_2), 1.16 (d, $J = 6.78$ Hz, 3H, $\text{CH}(\text{CH}_3)$).

^{13}C NMR (100 MHz, CDCl_3), δ : 179.5, 145.6, 128.5, 127.1, 126.8, 69.5, 61.3, 53.6, 46.1, 29.9, 22.6, 20.03, 14.99.

IR (ATR, cm^{-1}): 3445 (νNH_2), 3260 (νNH_2), 1673 (Amid I, II).

MS (GC/MS): $m/z = 244$ (M^+), 216, 105 ($\text{PhCH}(\text{CH}_3)$), 77.

Anal. calcd. for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}$: C, 73.74; H, 8.25; N, 11.46. Found C, 73.86; H, 8.24; N, 11.48.

2-Azabicyclo[3.2.0]heptane-1-carboxylic acid 126

The compound was prepared following the procedure described for **29**. Yield of the product is 46% over two steps.

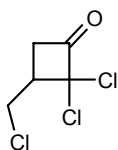
^1H NMR (400 MHz, CD_3OD), δ : 3.72 (m, 2H, CH_2), 3.29 (m, 1H, CH), 2.81 (m, 1H, CH_2), 2.43 (m, 1H, CH_2), 2.30 (m, 1H, CH_2), 2.16 – 1.95 (m, 2H, CH_2), 1.82 (m, 1H, CH_2).

^{13}C NMR (100 MHz, CD_3OD), δ : 172.1, 70.3, 47.2, 42.7, 31.5, 25.9, 21.3.

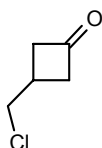
IR (ATR, cm^{-1}): 3358 ($\nu_{\text{as}}(\text{NH}_2^+)$), 3215 ($\nu_{\text{s}}(\text{NH}_2^+)$), 1693, 1614, 1583 ($\delta(\text{NH}_2^+)$, $\nu_{\text{as}}(\text{COO}^-)$ and $\nu_{\text{s}}(\text{COO}^-)$).

MS (m/z): 141, 127, 113, 100, 95, 82, 68, 54.

Anal. calcd. for $\text{C}_7\text{H}_{11}\text{NO}_2$: C, 59.56; H, 7.85; N, 9.92. Found C, 59.42; H, 7.84; N, 9.90.

3-(Chloromethyl)-2,2-dichlorocyclobutanone

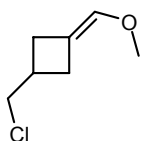
The compound was prepared by a procedure described in the literature.⁹⁹ Trichloroacetyl chloride (19.5 ml) and POCl_3 (25 ml) in 140 ml of dry diethyl ether were added to a solution of 26.7 g (0.349 mol) of allyl chloride and 14 g of a Zn-Cu couple in 180 ml of dry diethyl ether under nitrogen at 0 °C. After the reaction mixture refluxed for 24 h (under nitrogen), the solution was filtered over Celite and washed with diethyl ether. The filtrate was evaporated to 200 ml. This solution was extracted with petroleum ether. The clear yellow upper solution was decanted from the brown residue into a separatory funnel. The organic layer was washed with water and brine, dried (MgSO_4). Evaporation of the solvent lead to 10 g (0.053 mol) of the product. ^1H , ^{13}C NMR spectra were identical with those described in ref.⁹⁹

3-(Chloromethyl)cyclobutanone 127

The compound was prepared by a procedure described in the literature.⁹⁹ A solution of 11.5 g (0.006 mol) of 3-(chloromethyl)-2,2-dichlorocyclobutanone in 10 ml of acetic acid

(glacial) was slowly added to a solution of 26 g zinc in 100 ml of acetic acid. During the addition, the solution started to reflux and refluxing was maintained for an additional 4 h. After cooling, the mixture was filtered over Celite and washed with DCM. The filtrate was poured into a separatory funnel containing 100 ml of DCM. The solution was washed with water and afterward with a saturated NaHCO₃ solution until basic. The organic phase was dried (MgSO₄) and evaporated under reduced pressure. Distillations of the crude product lead to 5.89 g (0.05 mol, 81%) of the product. ¹H, ¹³C NMR spectra were identical with those described in ref.⁹⁹

1-Chloromethyl-3-methoxymethylene-cyclobutane **128**



To a stirred suspension of (methoxymethyl)triphenylphosphonium chloride (18.19 g, 0.053 mol, 1.04 eq) in THF (270 ml) at 0 °C under nitrogen was added a 1.6 M solution of *n*-BuLi (36.7 ml, 0.059 mol, 1.15 eq) in hexane. The resulting deep-red solution was stirred at 0 °C for 10 min, and to it was quickly added a solution of **127** (6.05 g, 0.051 mol) in 50 ml of THF. The reaction mixture was stirred for 5 h then the solvents were evaporated under reduced pressure, the residue was triturated with hexane. The filtrate was separated and evaporated under reduced pressure. The residue was chromatographed (PE – EE, 7:1 as an eluent) to give 2.99 g of the product (0.02 mol, 40%) as a mixture of *cis*-, *trans*-isomers.

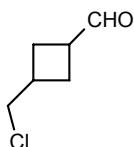
¹H NMR (400 MHz, CDCl₃), δ : 5.83 (m, 1H, CH), 3.60 (d, J = 2.3 Hz, 1H, CH₂), 3.58 (d, J = 2.3 Hz, 1H, CH₂), 3.56 (s, 3H, CH₃), 2.92 – 2.65 (m, 3H, CH₂, CH), 2.49 – 2.36 (m, 2H, CH₂).

¹³C NMR (100 MHz, CDCl₃), δ : 140.3, 111.1, 59.1, 49.3, 33.7, 31.3, 31.0.

IR (ATR, cm⁻¹): 2947, 1710, 1446.

MS (GC-MS): *m/z* = 146 (M⁺), 131, 111, 81, 53.

3-Chloromethyl-cyclobutanecarbaldehyde **129**



To a solution of **128** (2.22 g, 0.015 mol) in 60 ml of DCM at rt were added trifluoroacetic acid (4 ml), and a few drops of water. The solution was stirred for 30 min, and then saturated sodium bicarbonate was added to quench the reaction. The aqueous layer was extracted several times with DCM; the combined organic layers were washed with brine and dried over MgSO₄. The solvents were evaporated under reduced pressure. The residue

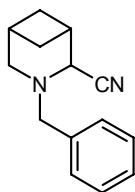
was chromatographed (PE – EE, 5:1 as an eluent) to give 1.69 g of the product (0.013 mol, 84%).

^1H NMR (400 MHz, CDCl_3), δ : 9.80 (d, $J = 1.5$ Hz, 1H, CHO), 9.69 (d, $J = 1.8$ Hz, 1H, CHO), 3.59 (d, $J = 6.8$ Hz, 2H, CH_2Cl), 3.49 (d, $J = 6.8$ Hz, 2H, CH_2Cl), 3.17 – 3.05 (m, 2H, CH (*cis*-), CH (*trans*-)), 2.77 – 2.61 (m, 2H, CH (*cis*-), CH (*trans*-)), 2.47 – 2.40 (m, 2H, CH_2 (*cis*-), CH_2 (*trans*-)), 2.35 – 2.28 (m, 2H, CH_2 (*cis*-), CH_2 (*trans*-)), 2.10 – 2.02 (m, 2H, CH_2 , CH_2 (*cis*-); m, 2H, CH_2 , CH_2 (*trans*-)).

IR (ATR, cm^{-1}): 1717 ($\nu\text{C=O}$).

MS (GC-MS): $m/z = 132$ (M^+), 114, 97, 83, 67, 55.

3-Benzyl-3-aza-bicyclo[3.1.1]heptane-2-carbonitrile 130



2-Benzylamino-2-methyl-propionitrile 1.75 g (0.01 mol, 1.05 eq) was added to a solution of 1.27 g (0.0096 mol, 1 eq) of **129** in dry acetonitrile. The mixture was refluxed for 48 h, then poured into excess of 10% sodium hydroxide solution and extracted with DCM. The combined extracts were dried (MgSO_4) and evaporated under reduced pressure. The residue was chromatographed (PE – EE, 4:1 as an eluent) to give 0.549 g of the product (0.0026 mol, 27%).

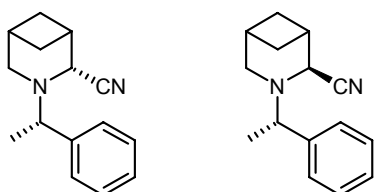
^1H NMR (400 MHz, CDCl_3), δ : 7.41 – 7.28 (m, 5H, CH arom), 4.01 (d, $J = 4.5$ Hz, 1H, CH), 3.93 (d, $J = 13.6$ Hz, 1H, CH_2Ph), 3.82 (d, $J = 13.3$ Hz, 1H, CH_2Ph), 3.08 (dd, $J = 9.8, 4.5$ Hz, 1H, CH_2), 2.85 (d, $J = 10$ Hz, 1H, CH_2), 2.58 (p, $J = 5.5$ Hz, 1H, CH), 2.42 (p, $J = 5.5$ Hz, 1H, CH), 2.21 (m, 1H, CH_2), 2.04 (m, 1H, CH_2), 1.95 (m, 1H, CH_2), 1.72 (m, 1H, CH_2).

^{13}C NMR (100 MHz, CDCl_3), δ : 137.2, 129.0, 128.4, 127.4, 118.1, 57.8, 55.2, 54.2, 36.1, 33.6, 33.1, 28.7.

MS (m/z): 212 (M^+), 202, 186, 161, 147, 121.

Anal. calcd. for $\text{C}_{14}\text{H}_{16}\text{N}_2$: C, 79.21; H, 7.60; N, 13.20. Found C, 79.44; H, 7.62; N, 13.17.

3-((1S)-1-Phenylethyl)-3-azabicyclo[3.1.1]heptane-2-carbonitrile 131



Aminonitrile **33** 1.92 g (0.01 mol, 1.05 eq) was added to a solution of 1.29 g (0.0097 mol, 1 eq) of **129** in dry acetonitrile. The mixture was refluxed for 120 h, then poured into excess of 10% sodium hydroxide solution and extracted with DCM. The combined extracts were dried (MgSO_4) and evaporated under reduced pressure. The residue was chromatographed (PE – EE, 5:1 as an eluent) to give 0.11 g (0.0005 mol, 10%) of a mixture of (2*R*)- and (2*S*)-diastereomers (1:0.68).

Major isomer:

^1H NMR (400 MHz, CDCl_3), δ : 7.41 – 7.28 (m, 5H, CH arom), 3.91 (q, $J = 6.8$ Hz, 1H, $\text{CH}(\text{CH}_3)$), 3.81 (d, $J = 5.3$ Hz, 1H, CH), 3.38 (dd, $J = 10.4$ Hz, 1H, CH_2), 2.84 (d, $J = 10$ Hz, 1H, CH_2), 2.47 (m, 2H, CH, CH), 2.16 (m, 1H, CH_2), 1.96 (m, 2H, CH_2), 1.65 (m, 1H, CH_2), 1.44 (d, $J = 6.5$ Hz, 3H, $\text{CH}(\text{CH}_3)$).

Minor isomer:

^1H NMR (400 MHz, CDCl_3), δ : 7.34 – 7.24 (m, 5H, CH arom), 4.41 (d, $J = 5$ Hz, 1H, CH) 3.83 (q, $J = 6.8$ Hz, 1H, $\text{CH}(\text{CH}_3)$), 2.77 (ddd, $J = 10, 5, 1$ Hz, 1H, CH_2), 2.66 (m, 1H, CH), 2.43 (d, $J = 10$ Hz, 1H, CH_2), 2.27 (m, 1H, CH_2), 2.16 (m, 1H, CH_2), 1.96 (m, 2H, CH_2), 1.65 (m, 1H, CH_2), 1.46 (d, $J = 6.8$ Hz, 3H, $\text{CH}(\text{CH}_3)$).

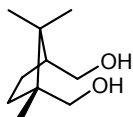
^{13}C NMR (100 MHz, CDCl_3), δ : 143.9 (minor), 143.7 (major), 128.6, 128.5, 127.5, 127.41, 127.37, 127.2, 118.5 (major), 118.3 (minor), 61.2 (minor), 61.1 (major), 54.9 (major), 53.8 (minor), 52.0 (minor), 50.6 (major), 36.2 (minor), 36.0 (major), 34.05, 34.06, 33.1 (major), 33.0 (minor), 28.1, 27.8, 21.6 (major), 20.1 (minor).

MS (m/z): 226 (M^+), 211, 149, 121, 105 ($\text{PhCH}(\text{CH}_3)$), 77.

IR (ATR, cm^{-1}): 2219 ($\nu\text{C}\equiv\text{N}$).

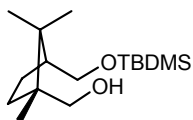
Anal. calcd. for $\text{C}_{15}\text{H}_{18}\text{N}_2$: C, 79.61; H, 8.02; N, 12.38. Found C, 79.45; H, 8.04; N, 12.39.

(1*R*,3*S*)-(3-Hydroxymethyl-1,2,2-trimethyl-cyclopentyl)-methanol

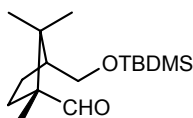


To a stirred suspension of LAH (3.2 g, 0.084 mol) in dry diethyl ether (70 ml) and THF (70 ml) was added dropwise a solution of D-camphoric acid (5.5 g, 0.028 mol) in dry diethyl ether under nitrogen. The reaction mixture was refluxed for 5 h then quenched by the addition of distilled water. The insoluble white solid was separated by filtration and the solvent was removed under reduced pressure to afford 3.67 (0.021 mol, 78%) of the product.

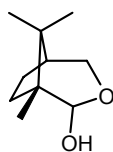
^1H , ^{13}C NMR spectra were identical with those described in ref.¹¹⁹

(1R,3S)-3-(((tert-Butyl)dimethylsilyloxy)methyl)-1,2,2-trimethyl-cyclopentane-1-methanol

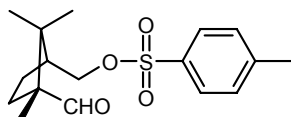
3.67 g (0.021 mol) of (3-hydroxymethyl-1,2,2-trimethyl-cyclopentyl)-methanol was dissolved in DCM (25 ml) and TBDMSCl (3.53 g, 0.023 mol of 50% solution in toluene) in DCM (15 ml) was added dropwise at 0 °C within 30 min. The mixture was stirred overnight, poured into water. The aqueous layer was extracted several times with diethyl ether. The combined organic layers were washed with brine and dried (MgSO₄), the solvents were removed *in vacuo*. The residue was chromatographed (PE – EE, 4:1 as an eluent) to give 4.82 g of the product (0.017 mol, 79%). ¹H, ¹³C NMR spectra were identical with those described in ref.¹⁰⁰

(1R,3S)-3-(((tert-Butyl)dimethylsilyloxy)methyl)-1,2,2-trimethyl-cyclopentane-1-carbaldehyde 133

The compound was prepared by a procedure described in the literature.¹¹⁹ To a solution of oxalyl chloride (2.88 ml, 0.034 mol, 2 eq) in dry DCM (60 ml) at -78 °C was added dropwise DMSO (3.57 ml, 0.05 mol, 3 eq) in dry DCM (6 ml) over a period of 15 min and the mixture was stirred at -78 °C for 15 min. A solution of 3-(((tert-butyl)dimethylsilyloxy)methyl)-1,2,2-trimethyl-cyclopentane-1-methanol (4.8 g, 0.017 mol, 1 eq) in dry DCM (19 ml) was added dropwise at -78 °C over a period of 30 min and the reaction mixture was stirred at -78 °C for 30 min. Triethylamine (11.64 ml, 0.084 mol, 5 eq) was added dropwise at -78 °C over a period of 10 minutes and the reaction mixture was stirred for 1 h. The temperature of the mixture was allowed to rise to -10 °C, and then stirred for additional 1 h at rt. Saturated NH₄Cl solution was added to the mixture, the organic layer was separated, the aqueous layer was extracted with diethyl ether. The combined organic layers were dried (MgSO₄), and then the solvents were removed *in vacuo*. The residue was chromatographed (PE – EE, 7:1 as an eluent) to give 4.14 g of the product (0.015 mol, 87%). ¹H, ¹³C NMR spectra were identical with those described in ref.¹⁰⁰

1,8,8-Trimethyl-3-oxabicyclo[3.2.1]octan-2-ol 134

To a solution of **133** (1.25 g, 0.0044 mol, 1 eq) in THF was added TBAF·3H₂O (1.66 g, 0.0053 mol, 1.2 eq). The mixture was stirred for 48 h at rt. The solvent was removed *in vacuo* and the residue was dissolved in diethyl ether. The organic layer was washed several times with water, dried over MgSO₄ and the solvent was evaporated under reduced pressure. The residue was chromatographed (PE – EE, 10:3 as an eluent) to give 0.523 g (0.0031 mol, 70%) of the product. The mixture of *endo*- and *exo*-isomers in ratio 1:0.22 was obtained. ¹H, ¹³C NMR and GC-MS data were identical with those described in ref.¹²⁰

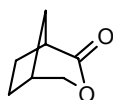
Toluene-4-sulfonic acid 3-formyl-2,2,3-trimethyl-cyclopentylmethyl ester 135

To a solution of 0.84 g (0.0049 mol) of **134** in 3 ml of pyridine at 0 °C was added 1.51 g (0.0079 mol, 1.6 eq) of *p*-toluenesulfonyl chloride. The mixture was stirred at 0 °C for 72 h. The solid material was removed by filtration, water (0.17 ml) was added and the solution was stirred for an additional 5 h. The solution was poured into an ice – 10% hydrochloric acid mixture. The aqueous layer was extracted several times with DCM and diethyl ether; the combined organic layers were dried over MgSO₄. The solvents were evaporated under reduced pressure. The residue was chromatographed (PE – EE, 2.5:1 as an eluent) to give 0.608 g of the product (0.0019 mol, 38%).

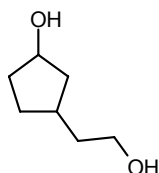
¹H NMR (400 MHz, CDCl₃), δ : 9.60 (s, 1H, CHO), 7.79 (d, J = 8.3 Hz, 2H, CH arom), 7.36 (d, J = 8.5 Hz, 2H, CH arom), 4.06 (dd, J = 9.5, 6.8 Hz, 1H, CH₂), 3.93 (dd, J = 9.5, 7.5 Hz, 1H, CH₂), 2.46 (s, 3H, CH₃), 2.32 (m, 1H, CH₂), 2.25 (m, 1H, CH), 1.94 (m, 1H, CH₂), 1.35 (m, 2H, CH₂, CH₂), 1.05 (s, 3H, CH₃), 1.03 (s, 3H, CH₃), 0.76 (s, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃), δ : 205.7, 144.8, 133.0, 129.9, 127.8, 71.0, 58.8, 46.6, 45.7, 30.0, 25.0, 23.5, 21.7, 19.1, 18.2.

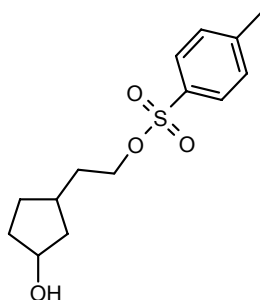
IR (ATR, cm⁻¹): 1724 (ν C=O), 1361, 1174 (ν R-SO₂-OR').

3-Oxabicyclo[3.2.1]octan-2-one

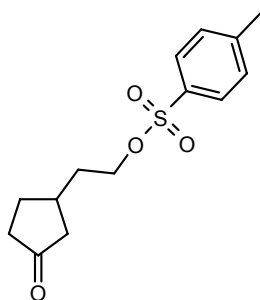
The compound was prepared by a procedure described in the literature in a 72% yield.¹⁰¹ ¹H, ¹³C NMR spectra were identical with those described in ref.¹⁰¹

3-(2-Hydroxyethyl)cyclopentanol

The compound was prepared by a procedure described in the literature in a 88% yield.¹⁰¹ ¹H, ¹³C NMR spectra were identical with those described in ref.¹⁰¹

2-(3-Hydroxycyclopentyl)ethyl 4-methylbenzenesulfonate

To a solution of 3-(2-hydroxyethyl)cyclopentanol (2 g, 0.015 mol, 1 eq) in 33 ml of DCM was added TsCl (3.22 g, 0.017 mol, 1.1 eq) and Et₃N (2.35 ml, 0.017 mol, 1.1 eq) at ambient temperature. After stirring for 48 h, the resulting suspension was concentrated *in vacuo* and the residue was purified by column chromatography (PE – EE, 1:1 as a eluent) to give 3.23 g of the product (0.011 mol, 74%). ¹H, ¹³C NMR spectra were identical with those described in ref.¹⁰¹

2-(3-Oxocyclopentyl)ethyl 4-methylbenzenesulfonate 136

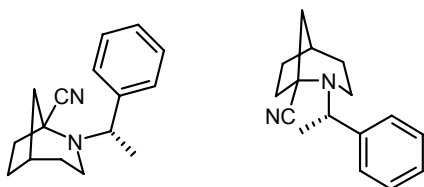
To a solution of 2-(3-hydroxycyclopentyl)ethyl 4-methylbenzenesulfonate (1.94 g, 0.0068 mol) in 2 ml of acetone and 4 ml acetic acid was added slowly CrO₃ in 2 ml of acetic acid and 1 ml of water at 0 °C. The reaction mixture was stirred at rt for 45 minutes and then diluted with 50 ml of diethyl ether. The organic layer was washed with saturated Na₂CO₃ and water, dried over MgSO₄ and evaporated under reduced pressure. The residue was chromatographed (PE – EE, 1:1 as an eluent) to give 1 g of the product (0.0035 mol, 52%).

¹H NMR (400 MHz, CDCl₃), δ : 7.80 (d, J = 8.3 Hz, 2H, CH arom), 7.36 (d, J = 8 Hz, 2H, CH arom), 4.09 (m, 2H, CH₂OTs), 2.46 (s, 3H, CH₃), 2.35 – 2.25 (m, 3H, CH, CH₂, CH₂), 2.14 (m, 2H, CH₂, CH₂), 1.81 (m, 2H, CH₂), 1.74 (m, 1H, CH₂), 1.48 (m, 1H, CH₂).

¹³C NMR (100 MHz, CDCl₃), δ : 218.1, 144.9, 132.9, 129.9, 127.8, 68.7, 44.5, 38.3, 34.5, 33.6, 29.2, 21.6.

IR (ATR, cm⁻¹): 1737 (ν C=O), 1354, 1173 (ν R-SO₂-OR').

2-((1S)-1-Phenylethyl)-2-azabicyclo[3.2.1]octane-1-carbonitrile 137



(1S)-(α)-Phenylethylamine (0.324 g, 0.0027 mol, 1.04 eq) and 0.698 ml of acetone cyanohydrin (0.0077 mol, 3 eq) was added to a solution of 0.72 g (0.0026 mol, 1 eq) of **136** in dry acetonitrile. The mixture was heated at 120 °C for 36 h with an air condenser, cooled, poured into excess of 10% sodium hydroxide solution and extracted with DCM. The combined extracts were dried (MgSO₄) and evaporated under reduced pressure. The residue was chromatographed (PE – EE, 3:1 as an eluent) to give 0.245 g (0.001 mol, 40%) of the product as a 1:1 mixture of two diastereomers. The diastereomers can be partially separated by column chromatography (PE – EE, 3:1 as an eluent).

137a

¹H NMR (400 MHz, CDCl₃), δ : 7.42 – 7.24 (m, 5H, CH arom), 4.64 (q, J = 6.8 Hz, 1H, CH(CH₃)), 2.5 (td, J = 12, 4.3 Hz, CH₂), 2.40 (m, 3H, CH, CH₂, CH₂), 2.14 (td, J = 13, 4.5 Hz, 1H, CH₂), 2.07 (m, 1H, CH₂), 1.98 – 1.88 (m, 2H, CH₂, CH₂), 1.54 (m, 2H, CH₂, CH₂), 1.47 (d, J = 7 Hz, 3H, CH(CH₃)), 1.23 (m, 1H, CH₂).

¹³C NMR (100 MHz, CDCl₃), δ : 143.7, 127.9, 127.7, 126.7, 121.9, 59.0, 47.2, 37.3, 34.8, 34.5, 30.3, 28.5, 13.7.

IR (ATR, cm⁻¹): 2237 (ν C≡N).

MS (*m/z*): 240 (M⁺), 225, 163, 136, 105 (PhCH(CH₃)).

137b

^1H NMR (400 MHz, CDCl_3), δ : 7.39 – 7.26 (m, 5H, CH arom), 4.64 (q, $J = 6.8$ Hz, 1H, $\text{CH}(\text{CH}_3)$), 2.98 (m, 1H, CH_2), 2.32 (m, 1H, CH), 2.29 (m, 1H, CH_2), 2.03 (m, 1H, CH_2), 1.88 (ddd, $J = 10.8, 5, 2.3$ Hz, 1H, CH_2), 1.72 – 1.53 (m, 3H, $\text{CH}_2, \text{CH}_2, \text{CH}_2$), 1.48 (d, $J = 7$ Hz, 3H, $\text{CH}(\text{CH}_3)$), 1.36 – 1.15 (m, 3H, $\text{CH}_2, \text{CH}_2, \text{CH}_2$).

^{13}C NMR (100 MHz, CDCl_3), δ : 139.6, 128.8, 128.1, 127.3, 122.4, 61.8, 60.1, 47.5, 37.7, 34.7, 31.9, 30.5, 28.4, 20.0.

IR (ATR, cm^{-1}): 2237 ($\nu\text{C}\equiv\text{N}$).

MS (m/z): 240 (M^+), 225, 163, 136, 105 ($\text{PhCH}(\text{CH}_3)$).

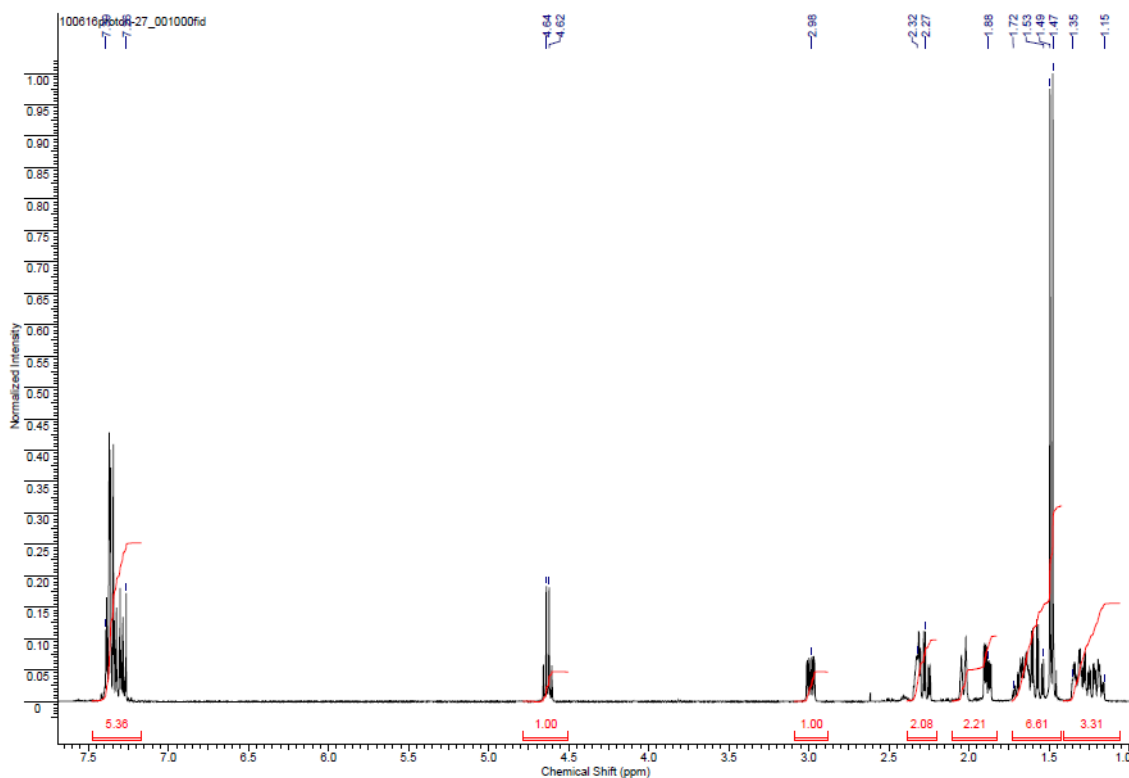
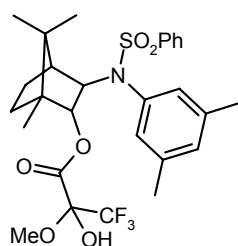


Figure 12. ^1H NMR spectrum of **137b**

3,3,3-Trifluoro-2-hydroxy-2-methoxy-propionic acid 3-[benzenesulfonyl-(3,5-dimethyl-phenyl)-amino]-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl ester **143**



Helmchen's alcohol **141** was added to a solution of 0.71 ml (0.0064 mol) of methyl trifluoropyruvate and 0.197 g of CsF in dry benzene (20 ml) under nitrogen. The reaction mixture was heated at 76 °C for 72 h. The solid material was removed by filtration and

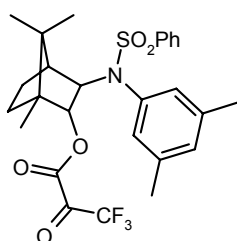
benzene was evaporated under reduced pressure. The residue was recrystallized from diethyl ether to give 1.86 g (0.0033 mol, 51%) of the product.

^1H NMR (400 MHz, CDCl_3), δ : 7.65 (m, 3H, CH arom), 7.51 (m, 2H, CH arom), 7.33 (s, 1H, CH arom), 6.97 (s, 1H, CH arom), 6.41 (s, 1H, OH), 6.00 (s, 1H, CH arom), 4.51 (d, $J = 8.8$ Hz, 1H, CH), 4.34 (dd, $J = 8.8, 3.3$ Hz, 1H, CH), 3.89 (s, 3H, CH_3O), 2.37 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 1.85 – 1.52 (m, 3H), 0.97 (m, 2H), 0.96 (s, 3H, CH_3), 0.77 (s, 3H, CH_3), 0.72 (s, 3H, CH_3).

^{19}F NMR (376 MHz, CDCl_3), δ : -80.88.

IR (ATR, cm^{-1}): 3416 (νOH), 1747 ($\nu\text{C=O}$), 1333, 1153 ($\nu\text{R-SO}_2\text{-NR}_2$).

3,3,3-Trifluoro-2-oxopropionic acid 3-[benzenesulfonyl-(3,5-dimethyl-phenyl)-amino]-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl ester 138a



To a solution of 1.37 g (0.0024 mol) of **143** in acetonitrile a saturated NaHCO_3 solution was added. The reaction was conveniently monitored to completion by ^{19}F NMR, usually within 3 h. Acetonitrile was evaporated under reduced pressure and water was added to the residue. The aqueous solution was extracted with DCM. The organic layer was dried (MgSO_4), concentrated *in vacuo* to give a white powder, which was used in the next step without further purification. Pyridine (0.3 ml, 0.0037 mol, 2 eq) and trifluoroacetic anhydride (0.26 ml, 0.0019 mol, 1 eq) were added to a solution of the hydrate (1.03 g, 0.0019 mol, 1 eq) in dry diethyl ether at 0 °C. The reaction mixture was stirred for 2 h. The solid material was removed by filtration and diethyl ether was evaporated under reduced pressure. The residue was dried *in vacuo* to give 0.917 g of the product (0.0017 mol, 71%).

^1H NMR (400MHz, CDCl_3), δ : 7.52 (m, 1H, CH arom), 7.35 – 7.32 (m, 4H, CH arom), 7.16 (s, 1H, CH arom), 6.85 (s, 1H, CH arom), 5.66 (s, 1H, CH arom), 5.4 (d, $J = 7$ Hz, 1H, CH), 4.04 (d, $J = 7$ Hz, 1H, CH), 2.35 (s, 3H, CH_3), 1.96 (s, 3H, CH_3), 1.8 (d, $J = 4.5$ Hz, 1H), 1.75 (m, 1H), 1.62 (m, 1H), 1.44 (m, 1H), 1.19 (m, 1H), 0.92 (s, 3H, CH_3), 0.88 (s, 3H, CH_3), 0.63 (s, 3H, CH_3).

^{19}F NMR (376 MHz, CDCl_3), δ : -82.41.

IR (ATR, cm^{-1}): 1759 (νCOOR), 1678 ($\nu\text{C=O}$) 1339, 1131 ($\nu\text{R-SO}_2\text{-NR}_2$).

MS (m/z): 537 (M^+), 412, 396, 274, 254, 160, 105.

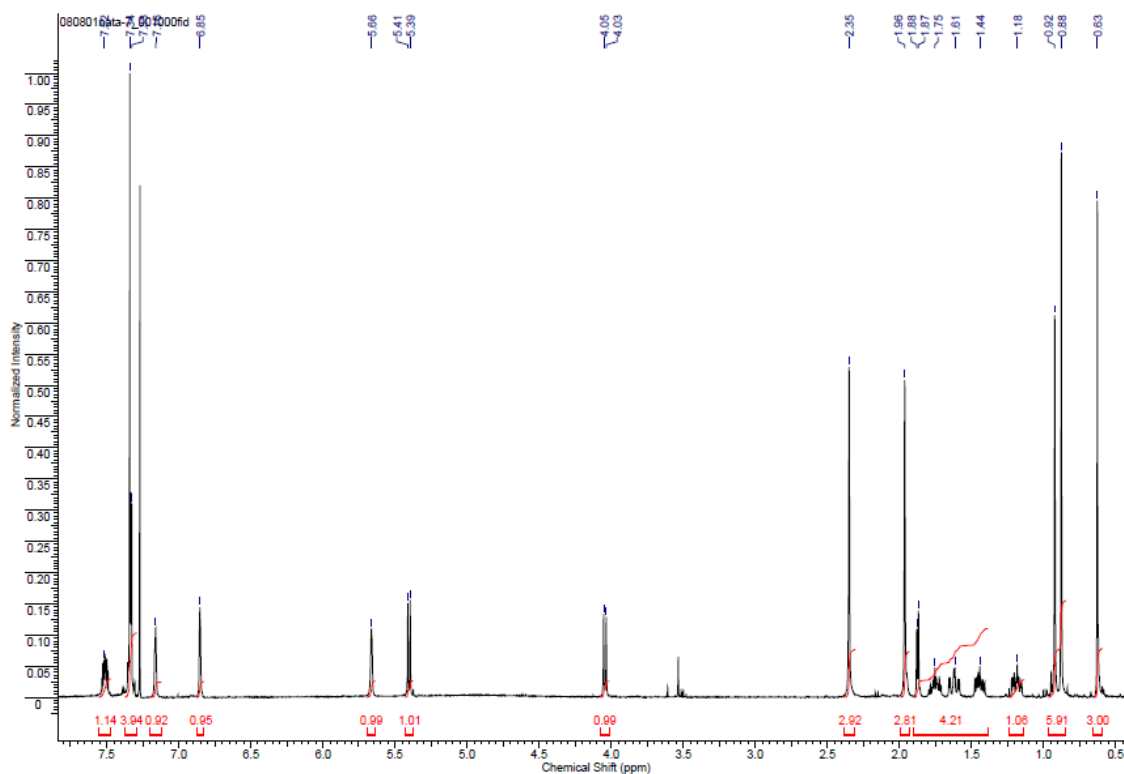
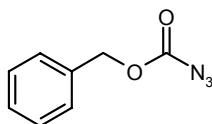


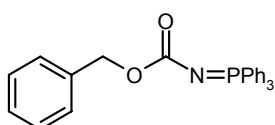
Figure 13. ^1H NMR spectrum of **138a**

Benzyl azidoformate



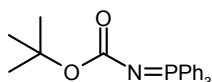
The compound was prepared following the literature procedure.¹²¹ To a stirred solution of benzyl alcohol (1.08 g, 0.01 mol, 1 eq) and sodium azide (1.3 g, 0.02 mol, 2 eq) in acetone was added triethylamine (2.08 ml, 0.015 mol, 1.5 eq) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min and a solution of triphosgen (1.49 g, 0.005 mol, 0.5 eq) in acetone was added dropwise. The reaction mixture was stirred at 0 °C for 1 h and then allowed to warm up to rt. It was stirred for 24 h at rt, the solid material was removed by filtration and the filtrate was diluted with an equal volume of water and extracted with EE. The organic phase was washed with water, brine and dried over MgSO_4 . The solvent was removed *in vacuo* and the residue was chromatographed (PE – EE, 3.5:1 as an eluent) to give 1.36 g of the product (0.0077 mol, 77%). IR and ^1H NMR spectrum were identical with those described in ref.¹²¹

N-Cbz-Triphenyliminophosphate **144**



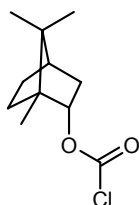
To a solution of benzyl azidoformate (0.51 g, 0.0029 mol, 1 eq) in dry hexane was added slowly triphenyl phosphine (0.755 g, 0.0029 mol, 1 eq) (strong evolution of nitrogen occurred during the addition). The reaction mixture was stirred at rt for 1 h, the solvent was evaporated under reduced pressure to give 0.947 g (0.0023 mol, 80%) of the product. Spectral data were identical with those described in ref.^{122, 123}

***N*-Boc-Triphenyliminophosphane 145**



The compound was prepared following the literature procedure.¹²⁴ To a solution of *tert*-butyl carbazate (1.176 g, 0.0089 mol, 1 eq) in acetic acid and water cooled to 0 °C was added NaNO₂ (0.676 g, 0.0098 mol, 1.1 eq) in portions over 15 min. The solution was stirred for 0.5 h at 0 °C and then extracted with diethyl ether. The combined organic layers were washed with water, saturated NaHCO₃ solution, brine and dried over MgSO₄. This solution was used in the next step. The ether solution was cooled to 0 °C, and PPh₃ (2.33 g, 0.0089 mol, 1 eq) was added while stirring (strong evolution of nitrogen occurred during the addition). Then the reaction mixture was stirred for 0.5 h at rt. The precipitate was filtered, washed with diethyl ether and dried *in vacuo* to give 3.09 g of the product (0.0082 mol, 92%). Spectral data were identical with those described in ref.¹²⁴

1,7,7-Trimethylbicyclo[2.2.1]hept-2-yl chlorocarbonate 149a



The compound was prepared following the procedure described for **149c**.

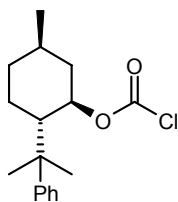
¹H NMR (400 MHz, CDCl₃), δ : 5.00 (ddd, J = 10, 3.3, 2.3 Hz, 1H, CH), 2.41 (m, 1H, CH₂), 1.92 (m, 1H, CH₂), 1.80 (m, 1H, CH₂), 1.74 (m, 1H, CH), 1.41 – 1.27 (m, 2H, CH₂, CH₂), 1.19 (dd, J = 14.3, 3.3 Hz, 1H, CH₂), 0.91 (s, 3H, CH₃), 0.90 (s, 6H, CH₃, CH₃).

¹³C NMR (100 MHz, CDCl₃), δ : 150.7, 89.4, 49.3, 48.1, 44.7, 36.1, 27.8, 26.8, 19.6, 18.7, 13.4.

IR (ATR, cm⁻¹): 2957, 1772 (ν C=O), 1455.

MS (GC-MS): m/z = 216 (M⁺), 201, 136, 121, 95, 81, 55.

Anal. calcd. for C₁₁H₁₇ClO₂: C, 60.97; H, 7.91. Found C, 61.05; H, 7.93.

5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl chlorocarbonate 149b

The compound was prepared following the procedure described for **149c**.

^1H NMR (400 MHz, CDCl_3), δ : 7.35 – 7.17 (m, 5H, CH arom), 4.80 (td, $J = 10.8, 4.5$ Hz, 1H, CH), 2.08 – 1.99 (m, 2H, CH, CH_2), 1.64 (m, 2H, CH_2), 1.44 (m, 1H, CH), 1.39 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.16 (m, 1H, CH_2), 1.07 (m, 1H, CH_2), 0.91 (d, $J = 6.5$ Hz, 3H, CH_3), 0.85 (m, 1H, CH_2).

^{13}C NMR (100 MHz, CDCl_3), δ : 149.9, 149.8, 128.2, 125.6, 125.4, 83.9, 50.6, 41.0, 39.8, 34.1, 31.4, 26.8, 26.7, 26.6, 21.6.

IR (ATR, cm^{-1}): 2956, 1773 ($\nu\text{C}=\text{O}$).

MS (m/z): 294 (M^+), 215, 119, 105, 81.

Anal. calcd. for $\text{C}_{17}\text{H}_{23}\text{ClO}_2$: C, 69.26; H, 7.86. Found C, 69.05; H, 7.89.

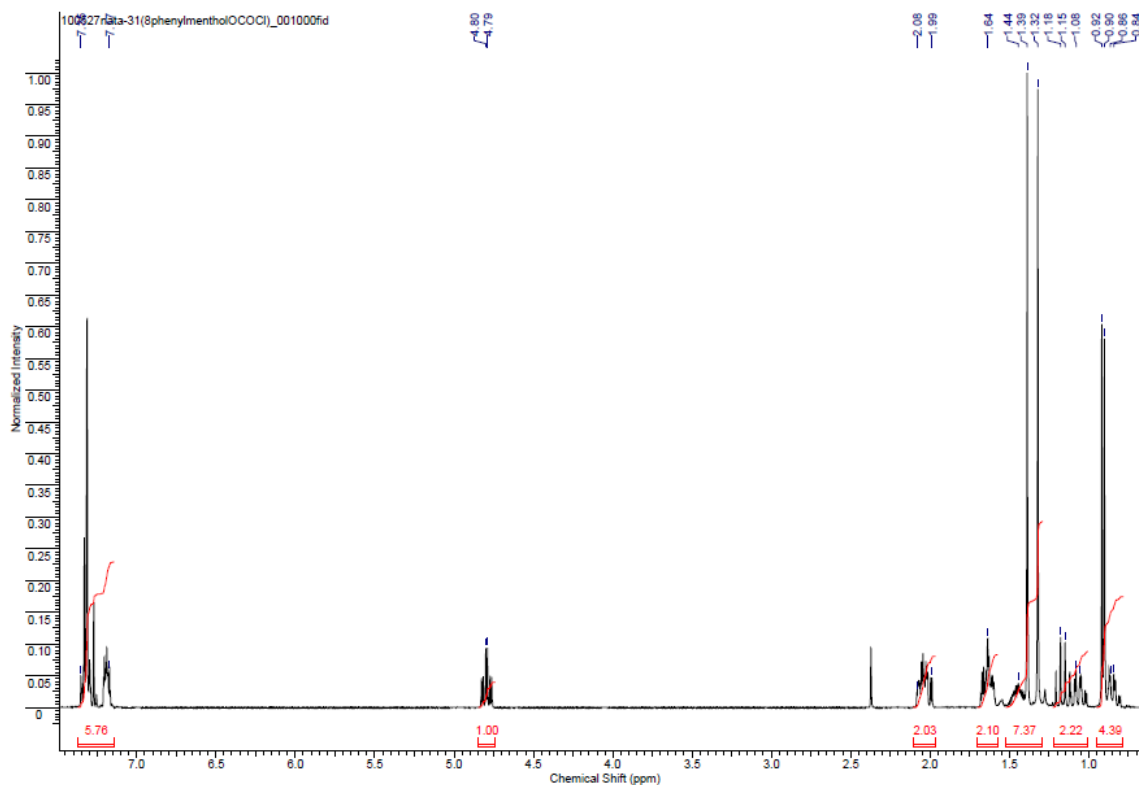
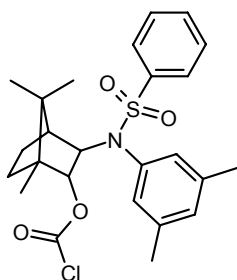


Figure 14. ^1H NMR spectrum of **149b**

3-[*N*-(3,5-Dimethylphenyl)-*N*-phenylsulfonyl-amino]-2-bornanyl chlorocarbonate 149c

The compound was prepared following the literature procedure.¹⁰² To a solution of triphosgene (3.24 g, 0.011 mol, 1.5 eq) in 50 ml of anhydrous toluene Helmchen's alcohol **141** (3 g, 0.0073 mol, 1 eq) and pyridine (0.88 ml, 0.011 mol, 1.5 eq) were added in 1 h at 0 °C. The solution was stirred for 24 h. After filtration, toluene was removed under reduced pressure and the product was obtained as a white solid in quantitative yield after crystallization from pentane.

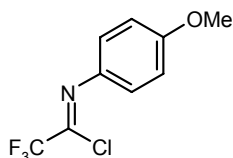
¹H NMR (400 MHz, CDCl₃), δ : 7.58 – 7.40 (m, 5H, CH arom), 6.92 (s, 1H, CH arom), 6.89 (s, 1H, CH arom), 6.20 (s, 1H, CH arom), 5.28 (d, J = 8.3 Hz, 1H, CH), 4.32 (dd, J = 8.5, 3.8 Hz, 1H, CH), 2.28 (s, 3H, CH₃), 2.15 (s, 3H, CH₃), 1.92 (m, 1H, CH), 1.75 (m, 1H, CH₂), 1.35 – 1.20 (m, 3H, CH₂, CH₂), 1.02 (s, 3H, CH₃), 0.91 (s, 3H, CH₃), 0.87 (s, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃), δ : 150.5, 138.7, 138.4, 137.6, 136.9, 132.8, 129.7, 128.8, 128.33, 128.32, 128.2, 85.0, 58.4, 51.4, 49.3, 45.8, 27.0, 21.1, 21.0, 19.5, 19.31, 19.28, 14.1.

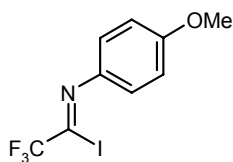
IR (ATR, cm⁻¹): 2956, 1777 (ν C=O), 1349, 1167 (ν R-SO₂-NR₂).

MS (*m/z*): 475 (M⁺), 395, 334, 254, 132.

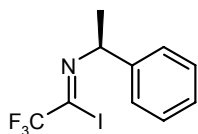
Anal. calcd. for C₂₅H₃₀ClNO₄S: C, 63.08; H, 6.35; N, 2.94. Found C, 63.26; H, 6.33; N, 2.94.

2,2-Trifluoro-*N*-(4-methoxy-phenyl)-acetimidoyl chloride

The compound was prepared following the literature procedure.¹⁰⁹ A solution of PPh₃ (34.5 g, 0.132 mol), Et₃N (7.3 ml, 0.053 mol), CF₃COOH (3.4 ml, 0.044 mol) in 42 ml of CCl₄ was stirred on the ice bath for 10 min. Then *p*-anisidine (6.48 g, 0.053 mol) in 21 ml of CCl₄ was added to a solution. The mixture was refluxed for 3 h, solvents were removed *in vacuo*, and the residue was diluted with hexane and filtered. The filtrate was concentrated under reduced pressure, and the residue distilled to give 9.5 g (0.04 mol, 91%) of the product. Spectral data were identical with those described in ref.¹⁰⁹

2,2,2-Trifluoro-*N*-(4-methoxy-phenyl)-acetimidoyl iodide 139a

The compound was prepared following the literature procedure.¹⁰⁹ A mixture of NaI (12.71 g, 0.085 mol, 3 eq) and 2,2,2-trifluoro-*N*-(4-methoxy-phenyl)-acetimidoyl chloride (6.7 g, 0.028 mol, 1 eq) in acetone was stirred under nitrogen at rt in the dark overnight. The mixture was washed with aqueous Na₂S₂O₃ and extracted with EE. The organic extracts were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (PE – EE, 9:1, as an eluent) to give the product in quantitative yield. Spectral data were identical with those described in ref.¹⁰⁹

2,2,2-Trifluoro-*N*-((1*S*)-1-phenylethyl)-acetimidoyl chloride 139b

2,2,2-Trifluoro-*N*-((1*S*)-1-phenylethyl)-acetimidoyl chloride was prepared following the literature procedure.¹⁰⁹ The product was distilled off at 10 mbar/ 80 °C.

A mixture of NaI (7.83 g, 0.052 mol, 3 eq) and 2,2,2-trifluoro-*N*-(1-phenylethyl)-acetimidoyl chloride (4.1 g, 0.017 mol, 1 eq) in dry acetone was stirred under nitrogen at rt in the dark overnight. The mixture was washed with aqueous Na₂S₂O₃ and extracted with EE. The extracts were washed with brine, dried over MgSO₄, and concentrated *in vacuo* to give the product in quantitative yield.

¹H NMR (400 MHz, CDCl₃), δ : 7.30 – 7.16 (m, 5H, CH arom), 4.31 (q, J = 6.5 Hz, 1H, CH(CH₃)), 1.42 (d, J = 6.8 Hz, 3H, CH(CH₃)).

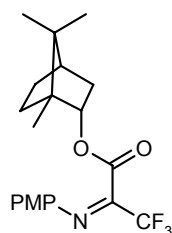
¹³C NMR (100 MHz, CDCl₃), δ : 141.0, 128.8, 127.9, 126.8, 114.7 (q, J_{C-F} = 278 Hz), 74.5, 112.9 (q, J_{C-C-F} = 42.6 Hz), 22.9.

¹⁹F NMR (376 MHz, CDCl₃), δ : -71.52.

IR (ATR, cm⁻¹): 1688 (νC=N).

MS (*m/z*): 327 (M⁺), 199, 165, 127, 105, 77.

Anal. calcd. for C₁₀H₉F₃NI: C, 36.72; H, 2.77; N, 4.28. Found C, 36.78; H, 2.77; N, 4.27.

3,3,3-Trifluoro-2-(4-methoxy-phenylimino)-propionic acid 1,7,7-trimethylbicyclo[2.2.1]hept-2-yl ester 140a

The compound was prepared following the procedure described for **140b**. The reaction mixture was stirred for 120 h to give 53% of the product.

^1H NMR (400 MHz, CDCl_3), δ : 7.01 (d, $J = 9$ Hz, 2H, CH arom), 6.90 (d, $J = 9$ Hz, 2H, CH arom), 4.94 (dd, $J = 9.8, 2.3$ Hz, 1H, CH), 3.82 (s, 3H, OCH_3), 2.30 (m, 1H, CH_2), 1.71 – 1.56 (m, 3H, CH, CH_2 , CH_2), 1.23 (m, 1H, CH_2), 1.02 (m, 1H, CH_2), 0.89 (m, 1H, CH_2), 0.87 (s, 3H, CH_3), 0.84 (s, 3H, CH_3), 0.71 (s, 3H, CH_3).

^{13}C NMR (100 MHz, CDCl_3), δ : 160.6, 159.2, 147.3 (q, $J_{\text{C-C-F}} = 36$ Hz), 139.4, 121.9, 118.6 (q, $J_{\text{C-F}} = 278.8$ Hz), 114.4, 83.5, 55.5, 48.8, 47.8, 44.6, 35.9, 27.7, 26.8, 19.6, 18.7, 13.1.

^{19}F NMR (376 MHz, CDCl_3), δ : -69.6.

IR (ATR, cm^{-1}): 1735 ($\nu_{\text{C=O}}$), 1505.

MS (m/z): 383 (M^+), 247, 202, 137, 81.

Anal. calcd. for $\text{C}_{20}\text{H}_{24}\text{F}_3\text{NO}_3$: C, 62.65; H, 6.31; N, 3.65. Found C, 62.48; H, 6.30; N, 3.64.

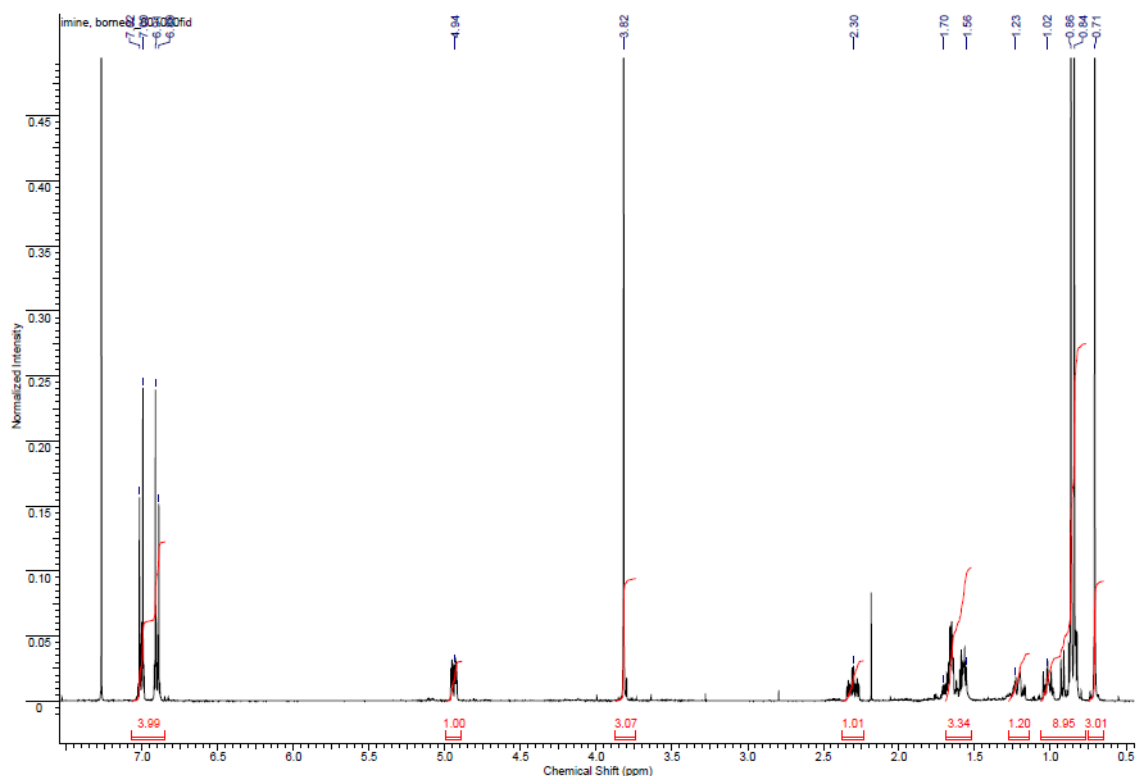
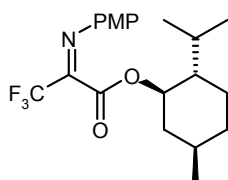


Figure 15. ^1H NMR spectrum of **140a**

3,3-Trifluoro-2-(4-methoxy-phenylimino)-propionic acid 2-isopropyl-5-methyl-cyclohexyl ester **140b**



The compound was prepared following the modified literature procedure.⁷⁵ A flask with a CO (1 atm) balloon attached was charged with $\text{Pd}_2(\text{dba})_3$ (0.076 g) and K_2CO_3 (0.96 g). Then 1.1 g (0.0033 mol) of trifluoroacetimidoyl iodide **139a** in 5 ml of toluene was added to the catalyst mixture. Subsequently 2.06 g (0.0134 mol) of L-menthol **142** in 5 ml of toluene and 1.1 ml of DMI were added. The reaction vessel was wrapped in aluminium foil and the reaction mixture was stirred for 120 h. The resulting suspension was filtered through a short pad of Celite. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (hexane – diethyl ether, 130:3 as an eluent) to give 0.824 g of the product (0.0021 mol, 64%).

^1H NMR (400 MHz, CDCl_3), δ : 7.01 (d, $J = 9$ Hz, 2H, CH arom), 6.89 (d, $J = 9$ Hz, 2H, CH arom), 4.76 (td, $J = 11, 4.5$ Hz, 1H, CH), 3.82 (s, 3H, OCH_3), 1.89 (m, 1H, CH_2), 1.65 (m, 2H, CH_2, CH_2), 1.48 – 1.27 (m, 3H, CH, CH, CH), 1.04 – 0.77 (m, 3H, $\text{CH}_2, \text{CH}_2, \text{CH}_2$), 0.89 (d, $J = 6.5$ Hz, 3H, CH_3), 0.78 (d, $J = 6.8$ Hz, 3H, CH_3), 0.62 (d, $J = 7$ Hz, 3H, CH_3).

^{13}C NMR (100 MHz, CDCl_3), δ : 160.3, 159.2, 147.9 (q, $J_{\text{C-C-F}} = 36.7$ Hz), 139.3, 122.0, 118.4 (q, $J_{\text{C-F}} = 278.8$ Hz), 114.3, 77.8, 55.4, 46.5, 39.9, 33.8, 31.3, 25.4, 22.8, 21.8, 20.7, 15.7.

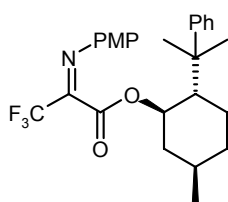
^{19}F NMR (376 MHz, CDCl_3), δ : -69.53.

IR (ATR, cm^{-1}): 1735 ($\nu_{\text{C=O}}$), 1504.

MS (m/z): 385 (M^+), 247, 202, 139, 83, 55.

Anal. calcd. for $\text{C}_{20}\text{H}_{26}\text{F}_3\text{NO}_3$: C, 62.33; H, 6.80; N, 3.63. Found C, 62.17; H, 6.76; N, 3.64.

3,3,3-Trifluoro-2-(4-methoxy-phenylimino)-propionic acid 5-methyl-2-(1-methyl-1-phenylethyl)-cyclohexyl ester **140c**



The compound was prepared following the procedure described for **140b**. The reaction mixture was stirred for 96 h to give 46% of the product.

^1H NMR (400 MHz, CDCl_3), δ : 7.28 – 7.14 (m, 5H, CH arom), 6.86 (m, 4H, CH arom), 4.84 (td, $J = 10.5, 4.3$ Hz, 1H, CH), 3.81 (s, 3H, OCH_3), 1.78 (m, 2H, CH, CH_2), 1.54 – 1.35 (m, 3H, CH_2 , CH_2 , CH), 1.17 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 0.94 (m, 1H, CH_2), 0.81 (d, $J = 6.5$ Hz, 3H, CH_3), 0.71 (qd, $J = 13.1, 3.5$ Hz, 1H, CH_2), 0.51 (q, $J = 11$ Hz, 1H, CH_2).

^{13}C NMR (100 MHz, CDCl_3), δ : 159.5, 159.0, 147.4 (q, $J_{\text{C-C-F}} = 36.7$ Hz), 139.3, 128.0, 125.3, 121.9, 118.4 (q, $J_{\text{C-F}} = 278.8$ Hz), 114.0, 78.7, 55.5, 50.2, 40.4, 39.7, 34.1, 31.2, 27.2, 26.8, 25.4, 21.6.

^{19}F NMR (376 MHz, CDCl_3), δ : -68.7.

IR (ATR, cm^{-1}): 1728 ($\nu_{\text{C=O}}$), 1504.

MS (m/z): 461 (M^+), 247, 201, 105, 55.

Anal. calcd. for $\text{C}_{26}\text{H}_{30}\text{F}_3\text{NO}_3$: C, 67.66; H, 6.55; N, 3.03. Found C, 67.85; H, 6.54; N, 3.03.

General procedure for the nucleophilic alkylation of **140a**, **140b** and **140c**.

To a solution of imino ester (1 eq) in diethyl ether under nitrogen at -78 °C was added RMgX or RLi (1.1 eq) dropwise. The reaction mixture was warmed to 0 °C and quenched with saturated aqueous NH_4Cl . The aqueous layer was extracted with diethyl ether and the combined organic phase was washed with brine and dried over MgSO_4 . The solvent was removed under reduced pressure, the residue was purified by column chromatography (hexane – diethyl ether, 10:1 as a eluent) to give a product (mixture of diastereomers).

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