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Application of 2-Azabicyclo[2.2.1]Hept-5-En-3-One (Vince Lactam) in Synthetic Organic and Medicinal Chemistry

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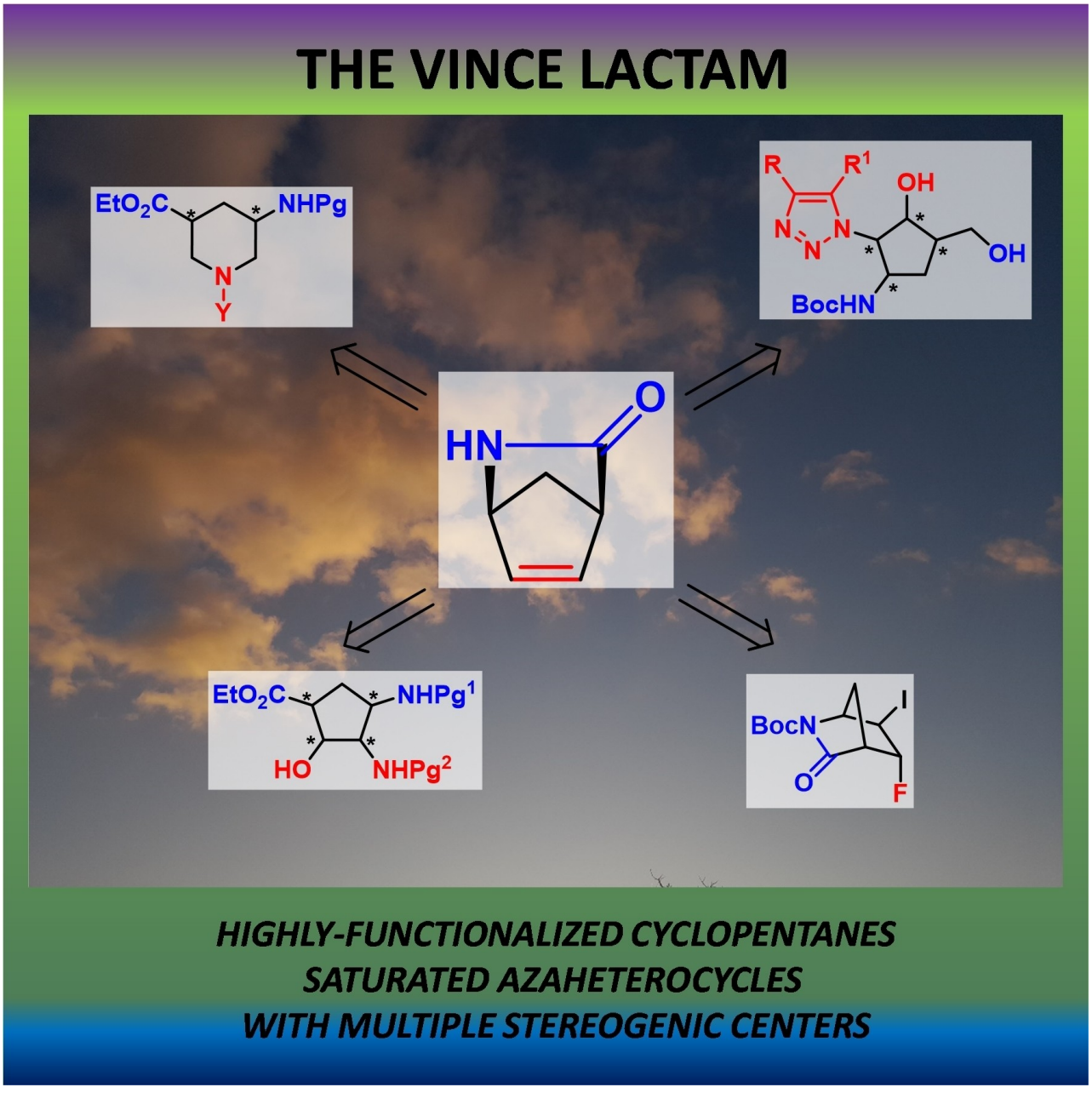

Abstract: 2-Azabicyclo[2.2.1]hept-5-en-3-one (Vince lactam) is known to be a valuable building block in synthetic organic chemistry and drug research. It is an important precursor to access of some blockbuster antiviral drugs such as Carbovir or Abacavir as well as other carbocyclic neuraminidase inhibitors as antiviral agents. The ring C=C bond of the Vince lactam allows versatile chemical manipulations to create not only functionalized γ-lactams, but also γ-amino acid derivatives with a cyclopentane framework. The aim of the current account is to summarize the chemistry of Vince lactam, its synthetic utility and application in organic and medicinal chemistry over the last decade.

Keywords: amino acid, functionalization, lactam, selectivity, stereocontrol

1. Introduction

As a consequence of its chemical and functional diversity, within a 3-dimentional architecture, the two enantiomeric forms of Vince lactam (2-azabicyclo[2.2.1]hept-5-en-3-one), are widely utilized building units in synthetic organic and medicinal chemistry.[1] Its synthetic utility benefits from a constrained bicyclic scaffold possessing two stereogenic carbon atoms, an electrophilic carbonyl group susceptible to lactam ring opening, and an endocyclic double bond that can be functionalized in a variety of ways. Furthermore, 4-amino-cyclopent-2-ene-1-carboxylic acid, the lactam opening product, also readily available in two enantiomeric forms, is a versatile carbocyclic compound that has been used in a variety of contexts as an unnatural carbocyclic ß-amino acid in synthetic and medicinal chemistry (Figure 1).

Vince lactam (2-azabicyclo[2.2.1]hept-5-en-3-one), known as an important precursor to several biologically active compounds or blockbuster drugs, was used for the synthesis of carbocyclic nucleosides such as the antiviral *Carbovir*, *Abacavir* or *Entecavir* (Figure 2), and to access some bioactive natural analogues such as *Aristeromycin* or *Neplanocin A* (Figure 3).[1a]

Vince lactam is a useful synthon for versatile syntheses to form other bioactive compounds or commercial drugs (*e.g.*, carbocyclic *Ribavirin* analogs with antiviral properties, or the antiviral drug *Peramivir*, Figure 4), as well as of various highly functionalized cyclopentanes (amino acid derivatives, amino ketones, amino alcohols, etc.).[1]

The aim of the current paper is to provide current insights into the most important applications of the two enantiomeric forms of Vince lactam in synthetic and medicinal chemistry. We summarize the results of new reports utilizing Vince lactam as a centerpiece for chemical functionalization expanding on the comprehensive and excellent review published in 2012 by Robert Vince.[1a] The focus of the current review is on the synthetic transformations of Vince lactam, demonstrating its importance as a versatile chiral building block to access highly functionalized enantiomerically pure amino carbocyclic molecules with many applications in organic and medicinal chemistry.

1.1. Synthesis of 2-Azabicyclo[2.2.1]Hept-5-En-3-One (Vince Lactam)

The most often used preparation technique for the synthesis of racemic Vince lactam (**1**) is different variations of Diels–Alder cycloadditions, such as the cycloaddition reaction of tosyl cyanide with cyclopentadiene. Tosyl cyanide, serving as dienophile in the reaction, was prepared in almost quantitative yield via the bubbling of cyanogen chloride through the aqueous solution of sodium 4-methylbenzenesulfinate. Next, freshly synthesized cyclopentadiene (prepared by thermolysis of commercially available dicyclopentadiene) was reacted with the dienophile and the desired Vince lactam was isolated in 72% yield. (Scheme 1).[1a]

Several research groups were interested to investigate Diels–Alder cycloaddition between chlorosulfonyl isocyanate and 1,3-cyclodienes (such as cyclopentadiene).[2] Apart from the formation of the β-lactam, the thermodynamically more stable 1,4-addition product was also detected. Malpass and his research group investigated the mechanism of the rearrangement of the 1,2-cycloaddition product into the 1,4-cycloaddition derivative.[2d] They successfully prepared *N*-chlorosulfonyl β-lactam (1,2-cycloaddition product), which was subjected immediately to hydrolysis with aqueous solution of

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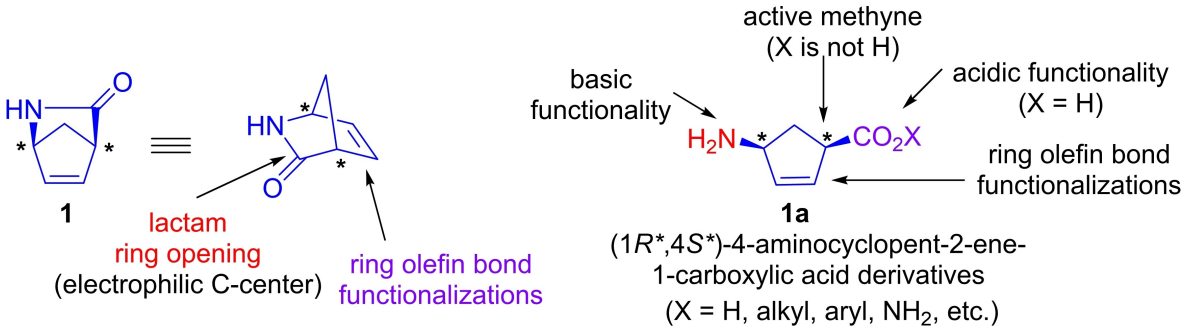


Figure 1. The structure of (1*S**,4*R**)-2-azabicyclo[2.2.1]hept-5-en-3-one (Vince lactam, **1**) and (1*R**,4*S**)-4-aminocyclopent-2-ene-1-carboxylic acid derivatives (**1a**).

Loránd Kiss completed his Ph.D. in 2002 in the Department of Organic Chemistry at the Faculty of Sciences, Debrecen University (Debrecen, Hungary) under the supervision of Prof. Sándor Antus. In 2003, he joined the research group of Prof. Ferenc Fülöp at the Institute of Pharmaceutical Chemistry, University of Szeged (Szeged, Hungary), where he started working in chemistry of cyclic β-amino acid chemistry. He followed post-doctoral research in the laboratories of Prof. Norbert De Kimpe at Ghent University (Ghent, Belgium), and Prof. Santos Fustero, University of Valencia. He is currently director of the Institute of Organic Chemistry, Research Center for Natural Sciences (Budapest) and head of the Stereochemistry Research Group. His scientific interest is directed towards the selective functionalization of unnatural amino acid derivatives, and on the synthesis of highly functionalized fluorine-containing small molecules.

Melinda Nonn graduated as chemist in 2007 from Babes-Bolyai University, Faculty of Chemistry and Chemical Engineering (Cluj-Napoca, Kolozsvár, Romania). She received her PhD degree at the Institute of Pharmaceutical Chemistry, University of Szeged (Hungary) under the supervision of Prof. Ferenc Fülöp in 2013. Since 2022 she has been working at the Institute of Materials and Environmental Chemistry, Research Center for Natural Sciences (Budapest). Her research interest includes synthesis of highly functionalized cyclic amino acid derivatives, development of asymmetric synthetic methods toward the preparation of this class of derivatives and organofluorine chemistry.

Santos Fustero studied chemistry at the University of Zaragoza, where he obtained his bachelor's degree in 1972. He received his Ph.D. in organic chemistry in1975 from the same university under the supervision of Profs. Barluenga and Gotor. He carried out postdoctoral studies for two years at Prof. Lehmkuhl's group at the Max-Planck-Institut für Kohlenforschung in Mülheim/Ruhr, Germany. In 1983, he became an associate professor at the University of Oviedo, and in 1990, he was promoted to a full professor at the University of Valencia. His research interests include organofluorine and medicinal chemistry, organocatalysis, heterocyclic chemistry and new reaction methodologies.

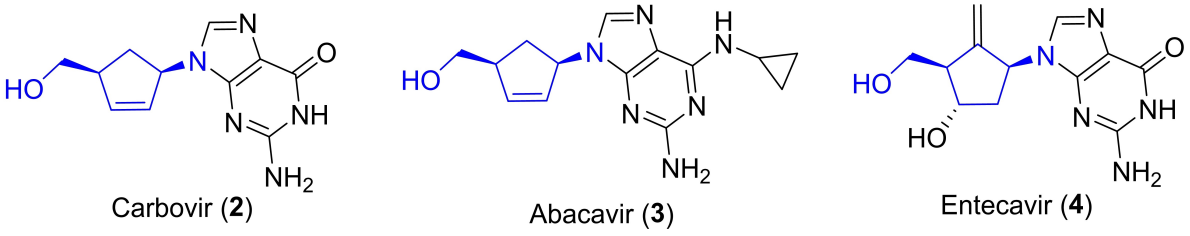


Figure 2. Some synthetic carbocyclic nucleosides with antiviral properties.

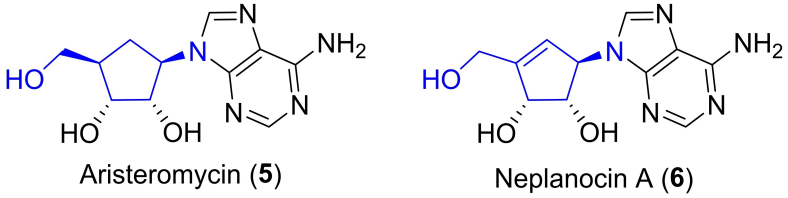


Figure 3. Bioactive natural carbocyclic nucleosides.

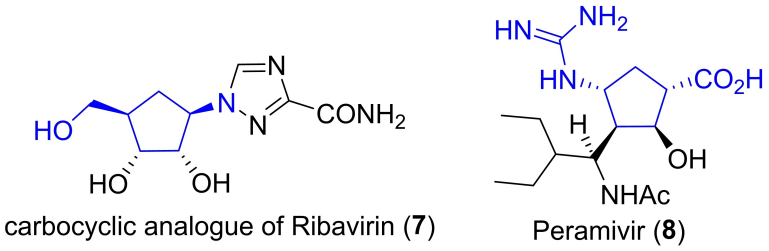
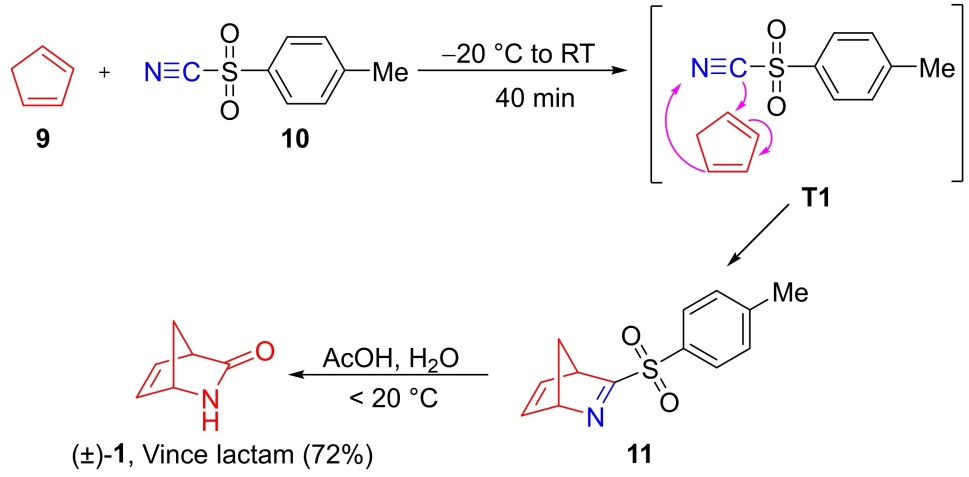
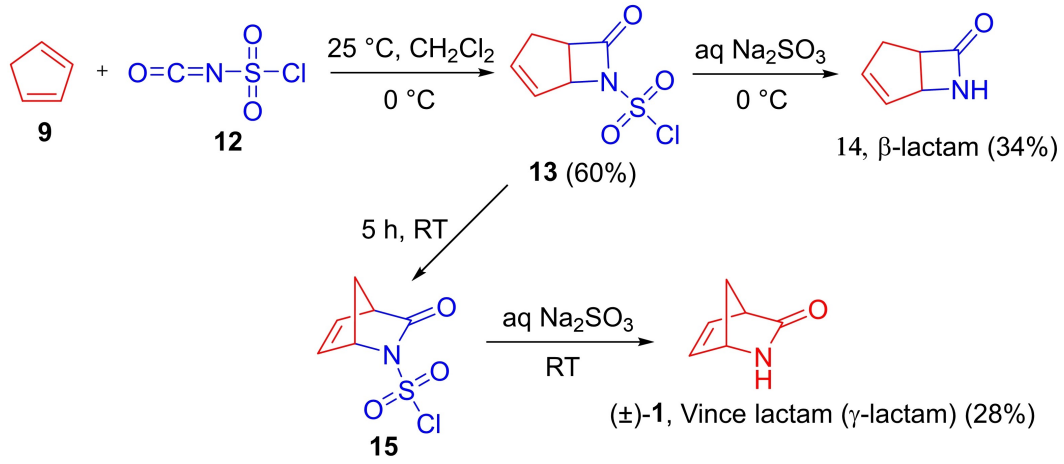


Figure 4. Structures of the antiviral Peramivir and the carbocyclic analogue of antiviral Ribavirin.

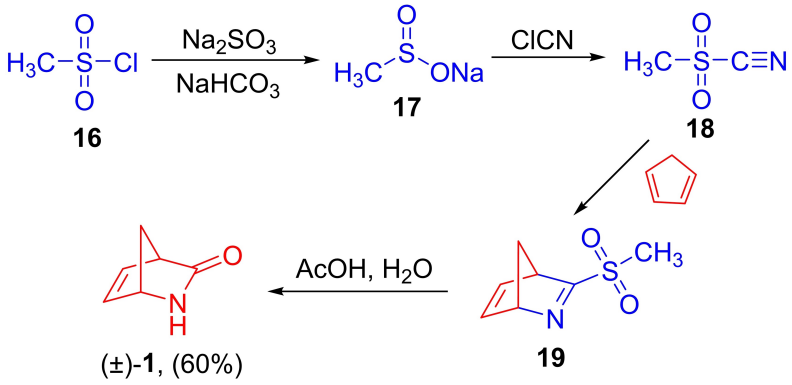


Scheme 1. Synthesis of racemic Vince lactam via one-pot Diels–Alder cycloaddition.

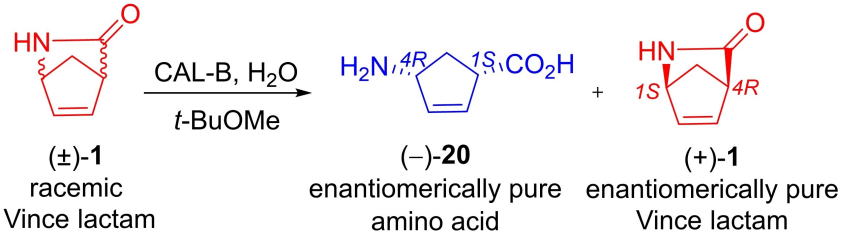
sodium sulfite leading to the corresponding β-lactam isolated in 34% yield. When the reaction mixture of the unstable *N*-chlorosulfonyl β-lactam was stirred at room temperature, it led to rearrangement into γ-lactam, which was transformed to racemic Vince lactam in 28% yield upon treatment with aqueous sulfite solution (Scheme 2).



Scheme 2. Synthesis of racemic Vince lactam with chlorosulfonyl isocyanate (CSI) cycloaddition to cyclopentadiene.



Scheme 3. Synthesis of racemic Vince lactam in an industrial scale.

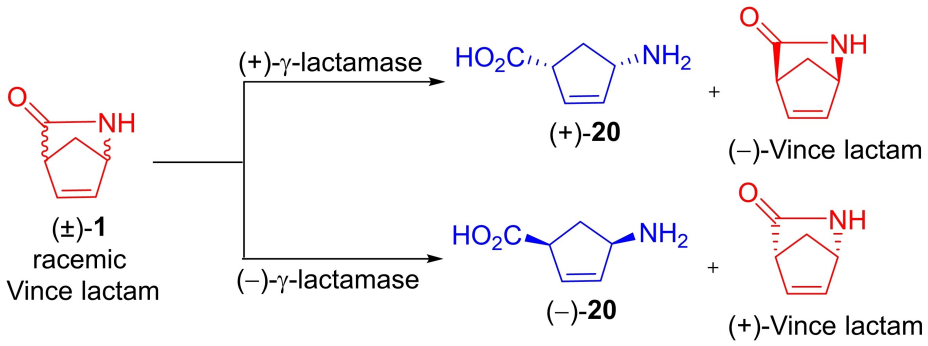


Scheme 4. Synthesis of Vince lactam in enantiomerically pure form and of γ-amino cyclopentenecarboxylate (γ-ACPC).

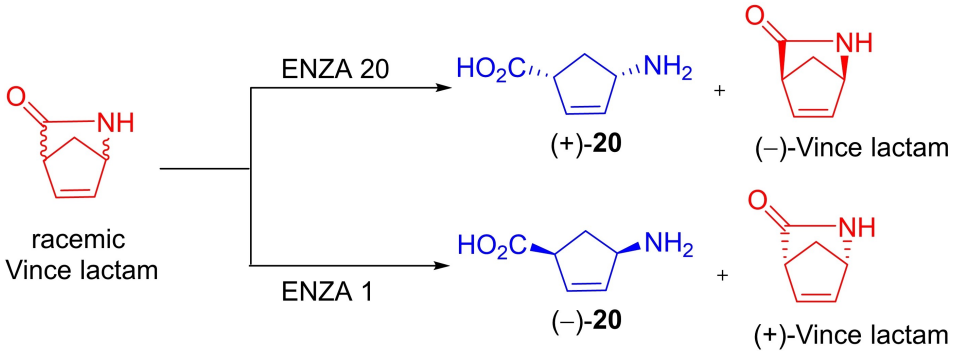
In a more user-friendly protocol for the synthesis of Vince lactam methanesulfonyl cyanide as a dienophile was used instead of tosyl cyanide. The dienophile, prepared from the methanesulfonyl chloride, was transformed to the corresponding methanesulfinate, followed by the addition of cyanogen chloride. In the next step, the cycloaddition between the dienophile and cyclopentadiene was performed. Using controlled amount of glacial acetic acid in the last step, the desired Vince lactam was prepared in good yield (Scheme 3).[3,1a]

1.2. Synthesis of Enantiomerically Pure Vince-Lactam

The synthetic procedures presented in the previous section provided the Vince lactam in racemic form. Several methods



Scheme 5. Preparation of Vince lactam enantiomers.



Scheme 6. Bioenzymatic resolution of racemic Vince lactam.

to prepare the enantiomerically pure counterparts are also known in the literature.

An efficient method to synthesize the enantiomer form of Vince lactam is based on the kinetic enzymatic resolution of its racemic form. The enantioselective hydrolysis of racemic Vince lactam ((±)-**1**) by CAL-B (lipase B from *Candida antarctica*, produced by submerged fermentation of genetically modified *Aspergillus oryzae* and adsorbed on a macroporous resin) in *t*-BuOMe afforded enantiomerically pure amino acid (−)-**20** (γ-ACPC) (ee > 99 %) and the dextrorotatory enantiomer of the lactam ((+)-**1**; ee > 99 %, Scheme 4).[4a]

The same research group described another efficient resolution methodology performing CAL-B-mediated hydrolysis of *N*-hydroxymethylated Vince lactam providing optically pure lactam and the corresponding γ-amino acid enantiomer with a cyclopentene framework.[4b]

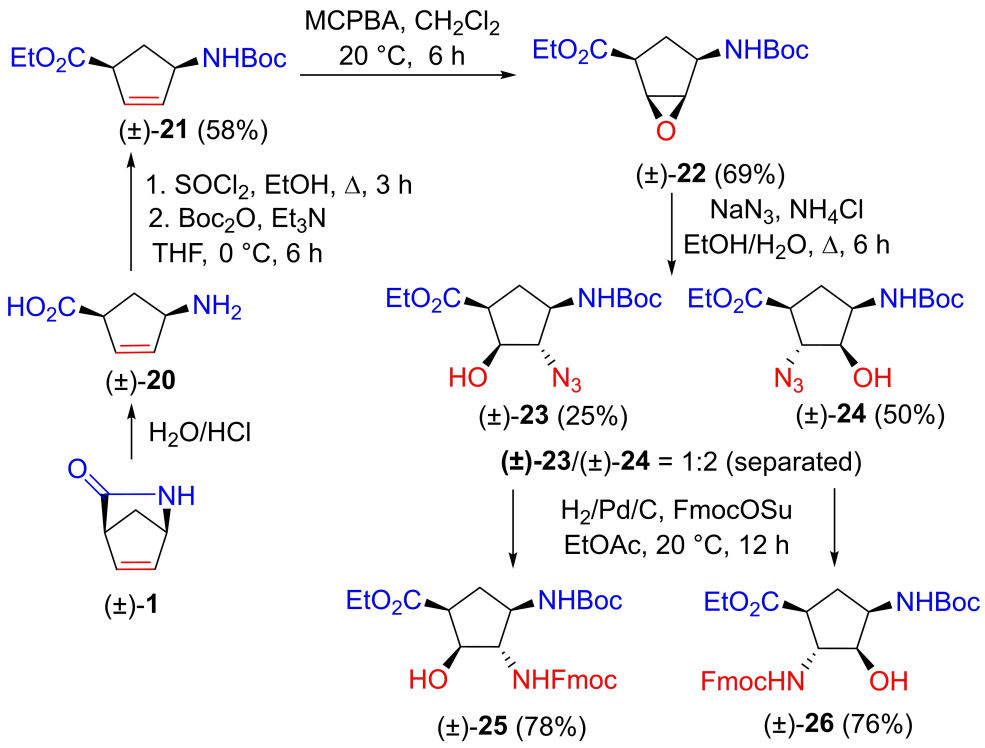
Another enzymatic route for the preparation of both enantiomers of Vince lactam was described by Zheng and co-authors in 2014. Both (+)-γ-lactamase and (−)-γ-lactamase (derived from *Bradyrhizobium japonicum* USDA 6) could be used easily to prepare the Vince lactam enantiomers in this biocatalytic pathway in 99 % ee in a selective manner (Scheme 5).[5]

Enzymes ENZA 20 and ENZA 1 specifically furnished the levo- and dextrorotatory enantiomers, respectively, from racemic Vince lactam (Scheme 6).[1a]

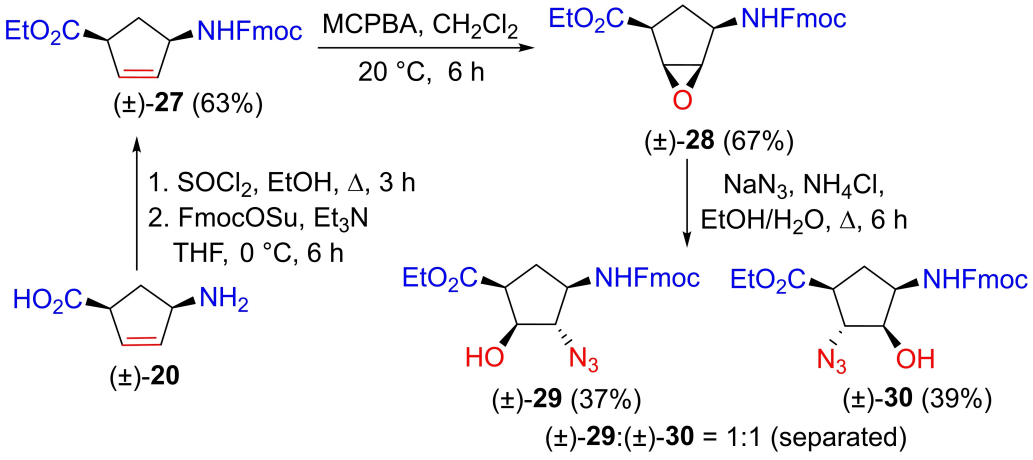
It is important to note that all three approaches depicted above afford both the desired Vince lactam enantiomers and the corresponding cyclopentene γ-amino acid enantiomers.

2. Transformation of Vince Lactam through its Ring Olefin Bond Functionalizations

As mentioned in the Introduction, an important feature of Vince lactam is its endocyclic ring double bond, which is subject to versatile chemical functionalizations. In this section various functionalization strategies of olefin bond in Vince lactam will be briefly summarized and discussed.



Scheme 7. Synthesis of orthogonally protected diaminocyclopentanecarboxylates (±)-**25** and (±)-**26** from Vince lactam (±)-**1**.



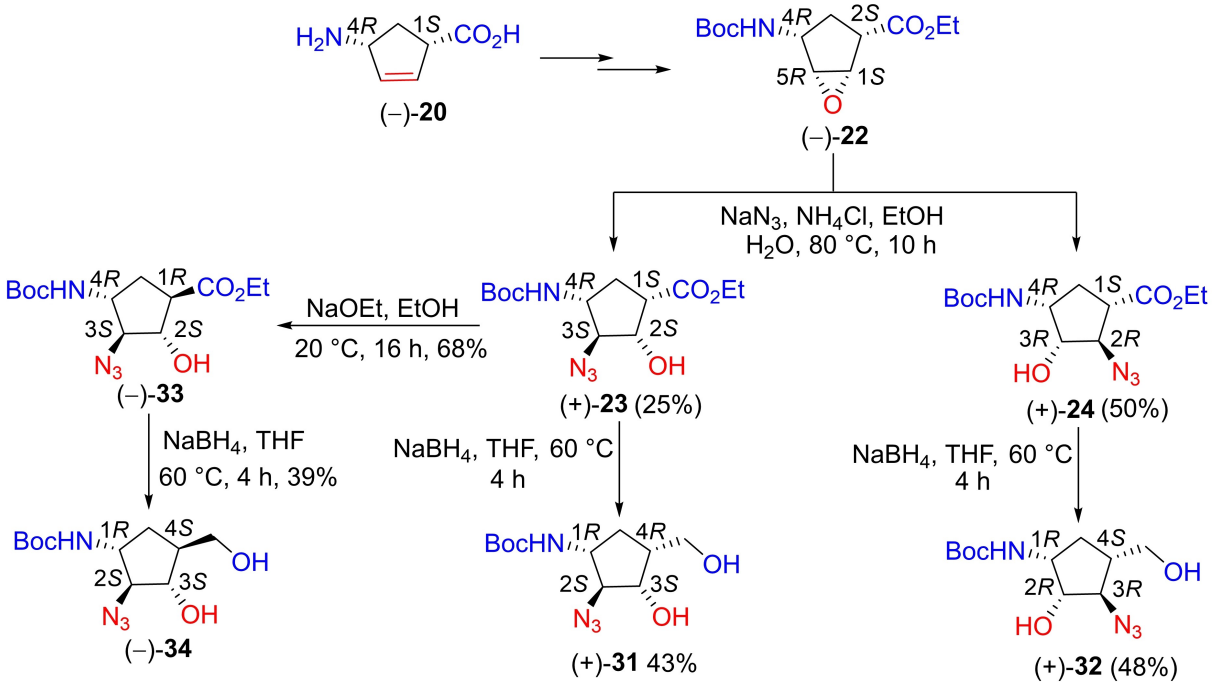
Scheme 8. Synthesis of functionalized aminocyclopentanecarboxylates (±)-**29** and (±)-**30** from racemic Vince lactam **1**.

2.1. Ring Olefin Bond Functionalization with Oxirane Formation/Oxirane Opening Strategy

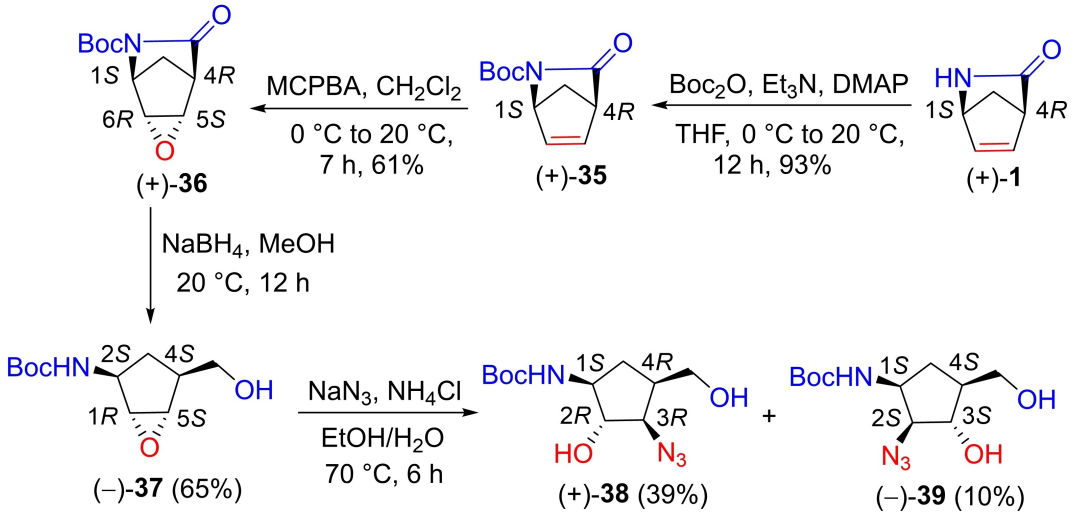
2.1.1. Synthesis of Orthogonally Protected Diamino Carboxylic Acids

Olefin bond epoxidation is a widely used methodology for the incorporation of versatile functional groups into the structure of an organic molecule. Epoxidation and oxirane ring opening with various nucleophiles – besides the formation of a hydroxy group – allows the creation of a series of moieties, such as amino, sulfanyl, thioalkoxy, alkoxy, nitrile, alkyl, alkynyl, aryl, halogen etc..[6]

Some orthogonally protected diamino cyclopentanecarboxylate isomers could be easily accessed through epoxidation/oxirane opening of the ring C=C bond of Vince lactam. An illustrative example is depicted on Scheme 7. Racemic lactam

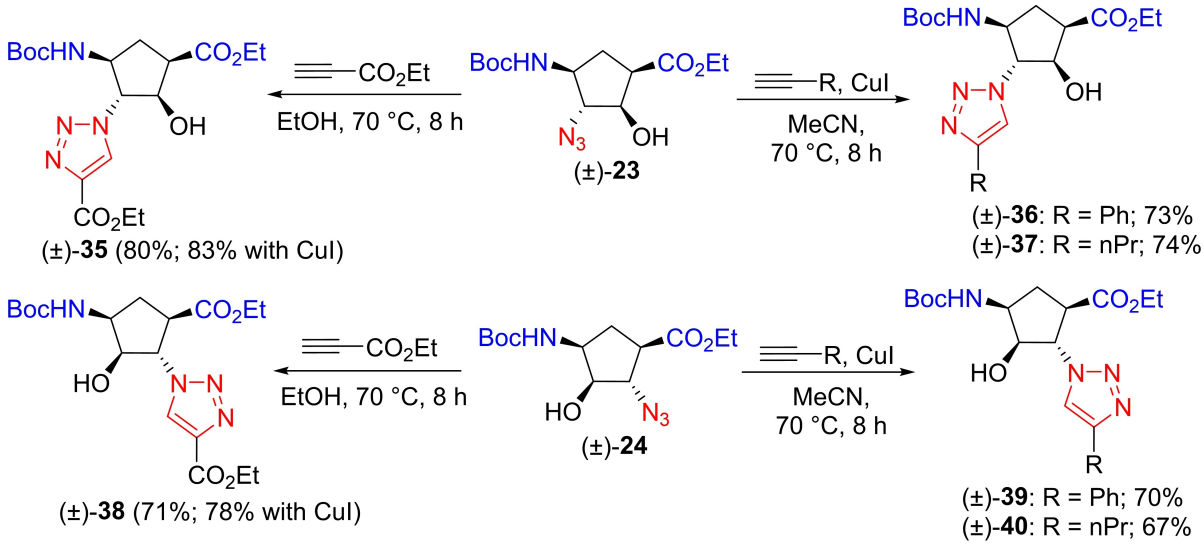


Scheme 9. Synthesis of azido alcohol stereoisomers (+)-**31**, (+)-**32** and (−)-**34** from amino acid (−)-**20** through epoxy amino ester (−)-**22**.



Scheme 10. Synthesis of azido alcohol stereoisomers (+)-**38** and (−)-**39** from lactam (+)-**1** through epoxy lactam (+)-**36**.

(±)-**1** underwent ring opening with hydrolysis to give amino acid (±)-**20**, which in turn led to amino ester (±)-**21** after amino Boc-protection. Next, epoxidation of the ring olefin bond in compound (±)-**21**, due to the H-bonding directing effect[1,6,7] of the carbamate, proceeded in a *cis*-diastereoselective manner yielding *"all-cis"* epoxy amino ester derivative (±)-**22**. Azidolysis with oxirane opening in ester (±)-**22** afforded regioisomeric products (±)-**23** and (±)-**24** in 1 : 2 ratio. The major compound possesses the azido function closest to the ester group ((±)-**24**). The reason for regioselectivity was interpreted based on electronic effects. However, further extension and additional studies might be beneficial to better understand these phenomena. After separation, both isomers were effectively converted by azido group reduction/amino group Fmoc-protection to the corresponding orthogonally



Scheme 11. Synthesis of 1,2,3-triazolo-γ-amino esters (±)-**35**–(±)-**40**.

Boc/Fmoc protected cyclic diamino esters (±)-**25** and (±)-**26** (Scheme 7).[8]

Further manipulation of the amino protecting groups were described as when *N*-Fmoc-protected amino ester (±)-**27**, subjected to olefin bond epoxidation followed by azidolysis, gave two azido ester regioisomers (±)-**29** and (±)-**30** in a 1 : 1 ratio, which in turn were separated and isolated (Scheme 8).[8]

2.1.2. Synthesis of Amino Cyclopentanols

As presented in Section 1.2, enzymatic resolution with *CAL-B* of racemic Vince lactam provided optically pure lactam and cyclopentene γ-amino acid. Synthetic manipulations with both enantiomerically pure substances allowed the synthesis of some highly functionalized cyclopentanes in enantiomerically pure form. After transformation into the corresponding epoxy amino esters, followed by azidolysis and ester group reduction, amino acid enantiomer (−)-**20** provided azido alcohol isomers (+)-**31** and (+)-**32**. The number of azido alcohol stereoisomers could be increased when ester (+)-**23** under epimerization mediated by NaOEt (through its active methine at C-1) across amino ester (−)-**33** resulted in azide (−)-**34**, a stereoisomer of compounds (+)-**31** and (+)-**32** (Scheme 9).[4a]

While epoxidation of amino ester (±)-**21** proceeded diastereoselectively due to H-bonding directing effect, the epoxidation of lactam (+)-**35**, because of steric effect, took place with "opposite/trans" diastereoselectivity and resulted in epoxy lactam (+)-**36**. In this case the manipulation sequence first followed a lactam opening with hydride and then azidolysis of (−)-**37** furnished the corresponding separable amino-azido alcohols (+)-**38** and (−)-**39** (Scheme 10).[4a]

2.1.3. Synthesis of 1,2,3-Triazole-Containing Amino Esters and Amino Alcohols

The 1,2,4-triazole skeleton is a key component of the antiviral agent Ribavirin and its analogs (see Figure 4), while the 1,2,3-triazole skeleton is present in various triazole-modified nucleoside analogs.[9] Azido ester derivatives prepared earlier were used in alkyne–azide dipolar click reaction. Thus, azido amino ester isomers (±)-**23** and (±)-**24** were subjected to thermal azide–alkyne dipolar cycloaddition with ethyl propiolate (activated acetylenes with an EWG ester group) furnishing the corresponding 1.2.3-triazole-substituted amino esters (±)-**35** and (±)-**38** in a regioselective manner (Scheme 11).[9a] The same azido esters ((±)-**23** and (±)-**24**) could be converted to other triazole-substituted derivatives by reacting them with phenylacetylene or but-1-yne. However, in these cases, the thermal cycloaddition did not function. Instead, the transformation giving selectively the 1,4-disubstutied 1,2,3-triazole derivatives (±)-**36**, (±)-**37**, (±)-**39** and (±)-**40** (Scheme 11) could be accomplished only in the presence of CuI as catalyst.[9a]

The high diversity of the synthetic protocol was demonstrated by synthesizing other isomeric triazole derivatives (Figure 5),[9a] and some triazole-substituted, highly functionalized cyclopentanols in enantiomerically pure form as well (Figure 6).[10]

It should be noted that the copper-catalyzed azide–alkyne 1,3-dipolar cycloaddition was efficiently carried out. In addition to the synthesis of amino acid derivatives, the substrate scope was extended by using flow methodologies.[9b]

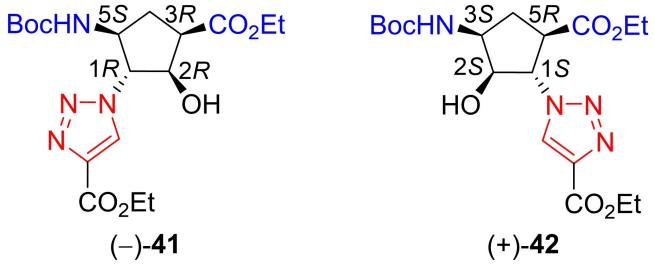


Figure 5. Structures of triazole-substituted amino ester enantiomers (±)-**41** and (±)-**42**.

2.1.4. Synthesis of Fluorine-Containing Derivatives

Over the past two decades organofluorine chemistry has become a highly expanding research area in organic chemistry and drug design. The relevance of organofluorine drugs has increased considerably (around 30% of drugs introduced on the market contain at least one fluorine atom), and they have become an important compound class in medicinal chemistry and drug discovery.[11] As a result of its high prevalence of organofluorine molecules in pharmaceutical research, an increasing interest has been exerted to incorporate a fluorine atom into the structure of an organic molecule.[12]

Among the various methods for the controlled (regio- and stereoselective) introduction of a fluorine atom into organic scaffolds, oxirane formation/oxirane opening followed by hydroxy–fluorine exchange constitutes a common and convenient method in this purpose.[6a,12d,e,13] The functionalization strategy based on olefin bond epoxidation/oxirane opening/HO-F exchange was efficiently applied for the fluorination of Vince lactam and the synthesis of 2-fluoro-3-aminocyclopentanecarboxylic acid. This compound, in turn, was considered to be an interesting monomer in foldamer chemistry. Thus, racemic Vince lactam after *N*-*p*-methyoxybenzyl (PMB) protection was submitted to diastereoselective epoxidation providing compound (+)-**47**. On treatment with HBr and then with trimethylsilyl triflate (TMSOTf) through a ring rearrangement process, epoxide (+)-**47** afforded derivatives (+)-**48** or (+)-**49**. Next, radical debromination and silyl group cleavage resulted in a derivative containing a hydroxy group. Subsequent treatment with diethylaminosulfur trifluoride through a HO-F exchange with retention of configuration led to fluorine-containing lactam (+)-**51**. Finally, PMB group removal, lactam rig opening under acid mediated hydrolysis, and amino-Boc protection furnished the desired fluorine-containing γ-amino acid (+)-**52** with the fluorine in a *trans* relative stereochemistry to the amino and carboxylic groups (Scheme 12).[14]

A fluorine-containing cyclopentene γ-amino acid (**61**) as a new and highly efficient GABA aminotransferase (GABA-AT) inactivator was identified by the Silverman group.[15] The key steps for the incorporation of the fluorine atom into the skeleton of the cyclic GABA analog were based on the Vince lactam ring olefin bond epoxidation, followed by oxirane opening with ring rearrangement, and the by HO-F exchange. The levorotatory (−)-**1** enantiomer of Vince lactam after *N*-PMB protection underwent epoxidation and led, through compound **53**, to the desired oxirane derivative **47**. Next, BF_3OEt_2-mediated epoxide opening in AcOH suffered skeletal rearrangement (similar to **48**→**50**, Scheme 12). Then, hydroxy MOM protection gave through compound **54** γ-lactam derivative **55** with two orthogonally protected hydroxy groups, MOM and Ac respectively (for the mechanism see also Scheme 25). Base-mediated deacetylation of **55** provided **56** with a hydroxy group suitable for HO-F exchange. Nucleophilic fluorination of compound **56** with DAST proceeded with retention of configuration and yielded fluorinated lactam **57**. Full retention of relative configuration results from the anchimeric assistance of the lactam *N*-atom through the formation of a transient aziridinium intermediate. Derivative **57** after MOM deprotection, OH-tosylation, and *N*-deprotection afforded lactam derivative **59**, which in turn by *N*-Boc protection, lactam opening via methanolysis and, finally, *N*-deprotection gave the desired fluorinated amino acid **61** (Scheme 13) (for the mechanism see also Scheme 25)..[15]

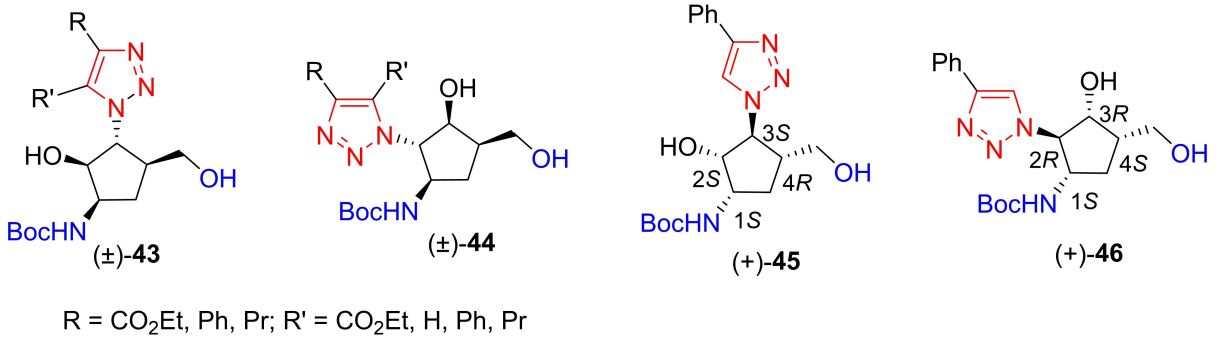
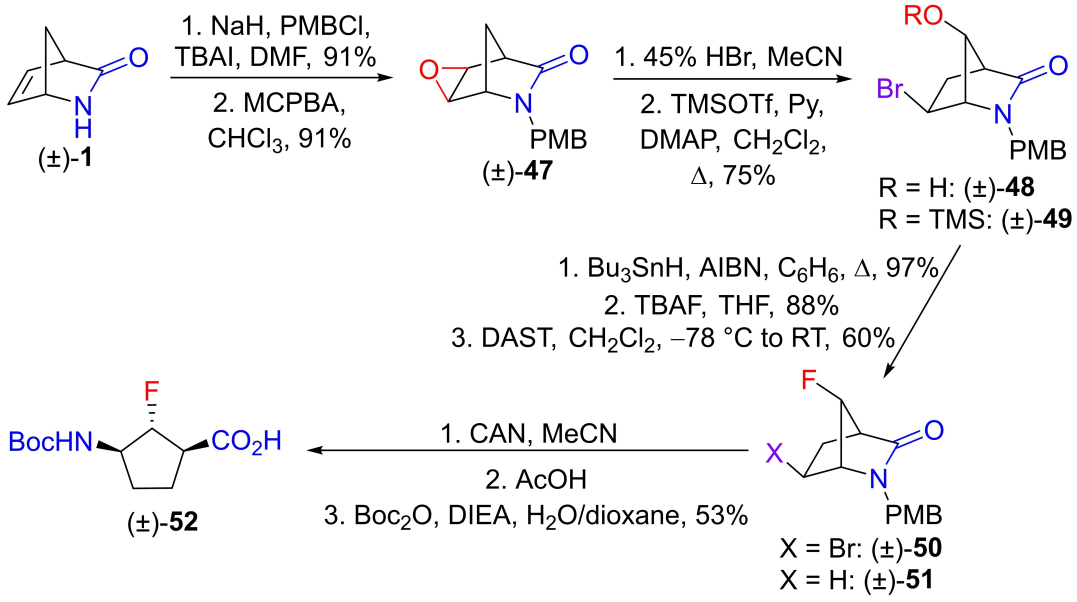
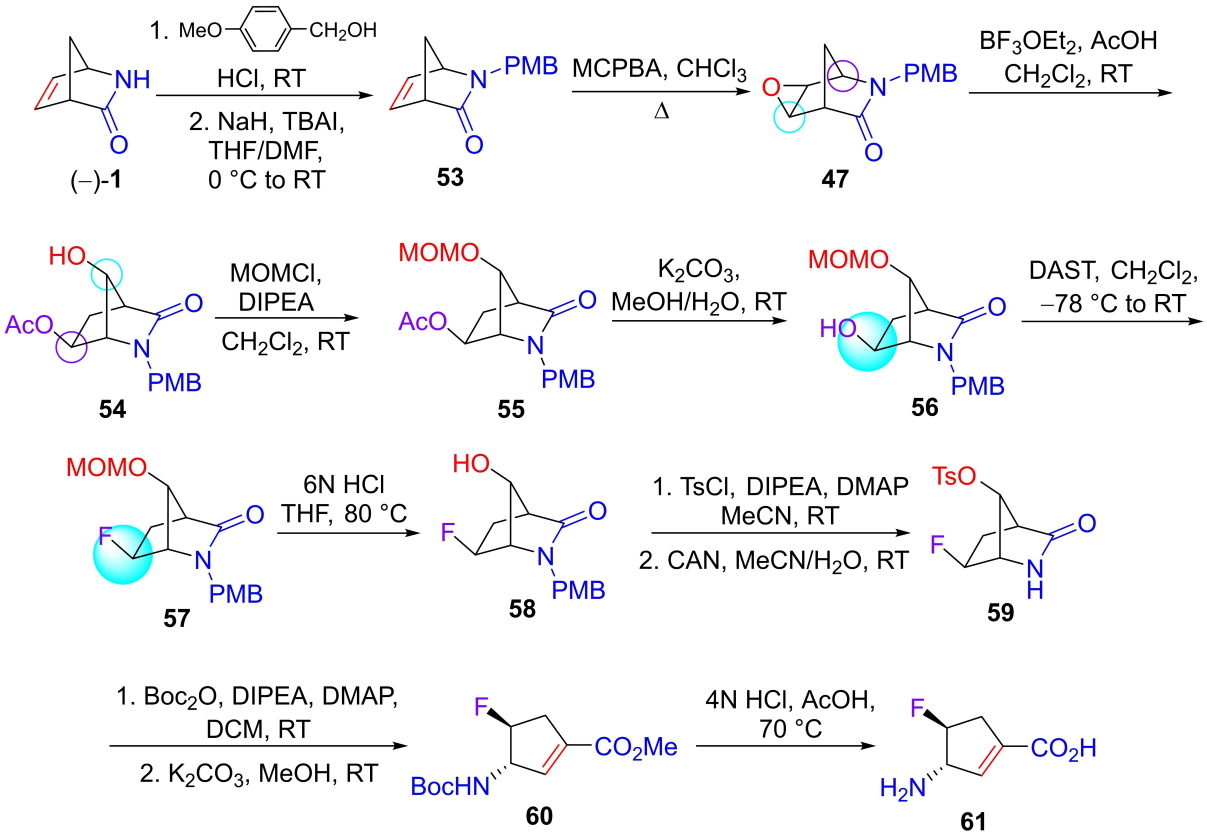


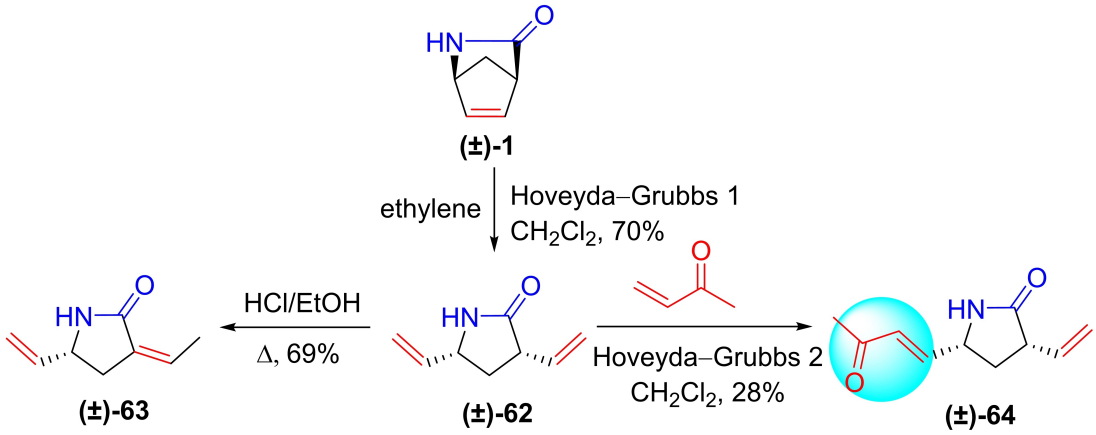
Figure 6. Structures of triazole-substituted amino alcohols (±)-**43**, (±)-**44**, (+)-**45**, and (+)-**46**.



Scheme 12. Synthesis of fluorine-containing γ-ACPC.



Scheme 13. Synthesis of inactivator of GABA aminotransferase for normal functioning of the central nervous system (antiepileptic).



Scheme 14. Transformation of lactam (±)-**1** with metathesis.

2.2. Transformation of 2-Azabicyclo[2.2.1]Hept-5-En-3-One through Metathesis

Olefin metathesis is a powerful tool in synthetic organic chemistry to access various types of sophisticated molecular entities, across double-bond manipulations. Variations of this methodology, such as ring-opening metathesis (ROM), ring-closing metathesis (RCM), cross-metathesis (CM), cross enyne metathesis (CEYM), ring-closing enyne metathesis (RCEYM), and ring-rearrangement metathesis (RRM), are widely applied for the synthesis of bioactive derivatives, natural products, and other highly functionalized unsaturated molecules including the industry.[16]

Racemic Vince lactam (±)-**1**, thanks to its ring olefin bond, could be functionalized by means of metathesis protocols. Thus (±)-**1** underwent ring opening metathesis by ethenolysis in the presence of the Ru-based Hoveyda–Grubbs 1 catalyst and afforded divinylated pyrrolidinone (±)-**62**. Interestingly, when divinylated lactam (±)-**62** was submitted to cross-metathesis with methyl vinyl ketone, chemodifferentiation of the olefin bonds in (±)-**62** was observed leading to monocoupled product (±)-**64** (Scheme 14). This selectivity in CM was explained by the coordinating ability of the lactam heteroatom with the Ru atom of the catalyst. Since chelation with the amide *O*-atom is more favored, the process leads to CM closest to the *N*-atom. Acid-mediated isomerization of (±)-**62** readily gave novel unsaturated lactam (±)-**63** (Scheme 14).[17]

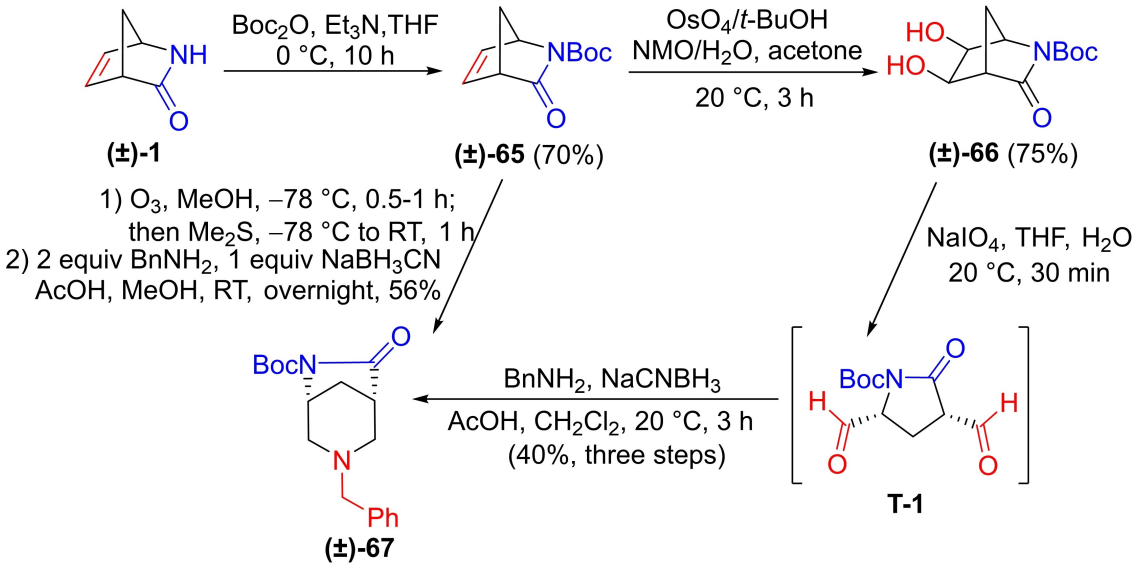
2.3. Oxidative Ring Opening/Ring Closure with Reductive Amination

2.3.1. Synthesis of Functionalized Azaheterocycles

Oxidative ring cleavage of cycloalkane scaffolds across their ring olefin bond, followed by cyclization with primary amines under reductive amination is an elegant, mild, and efficient approach towards the construction of various azaheterocyclic systems.[18] Vince lactam as starting compound was conveniently applied using oxidative ring opening/ring closure with reductive amination methodology for the synthesis of several functionalized piperidine scaffolds.

N-Boc-protected Vince lactam ((±)-**65**) was subjected to oxidative ring opening/cyclization with reductive amination in two alternative routes. One approach was based on OsO_4-catalyzed *cis*-dihydroxylation of the ring olefin bond with *N*-methylmorpholine *N*-oxide (NMO), which afforded diol derivative (±)-**66**. The $NaIO_4$-mediated oxidative vicinal diol cleavage, across the unstable dialdehyde intermediate **T-1**, in reaction with benzylamine in the presence of $NaCNBH_3$, through cyclization, furnished bicyclic lactam (±)-**67** (Scheme 15). A shorter, one-pot route involved the ozonolysis of (±)-**65** and the reductive amination step, and it afforded the desired bicyclic lactam (±)-**67** in a slightly higher overall yield (Scheme 15).[19]

In view of the high relevance of organofluorine compounds in drug research,[11,12] some fluorine-containing γ-lactam derivatives were readily synthesized from *N*-Boc-protected Vince lactam (±)-**65**, by using the ozonolysis-promoted ring-opening/ring-closing method presented above. Dialdehyde **T-1** (formed after ozonolysis of (±)-**65**) on treatment with various fluorine-containing primary amines in the presence of $NaCNBH_3$ and $NaHCO_3$, resulted in the corresponding di- or trifluorinated bicyclic scaffolds (±)-**68**–(±)-**70**. It was observed, however, that with an excess of amine, formation of

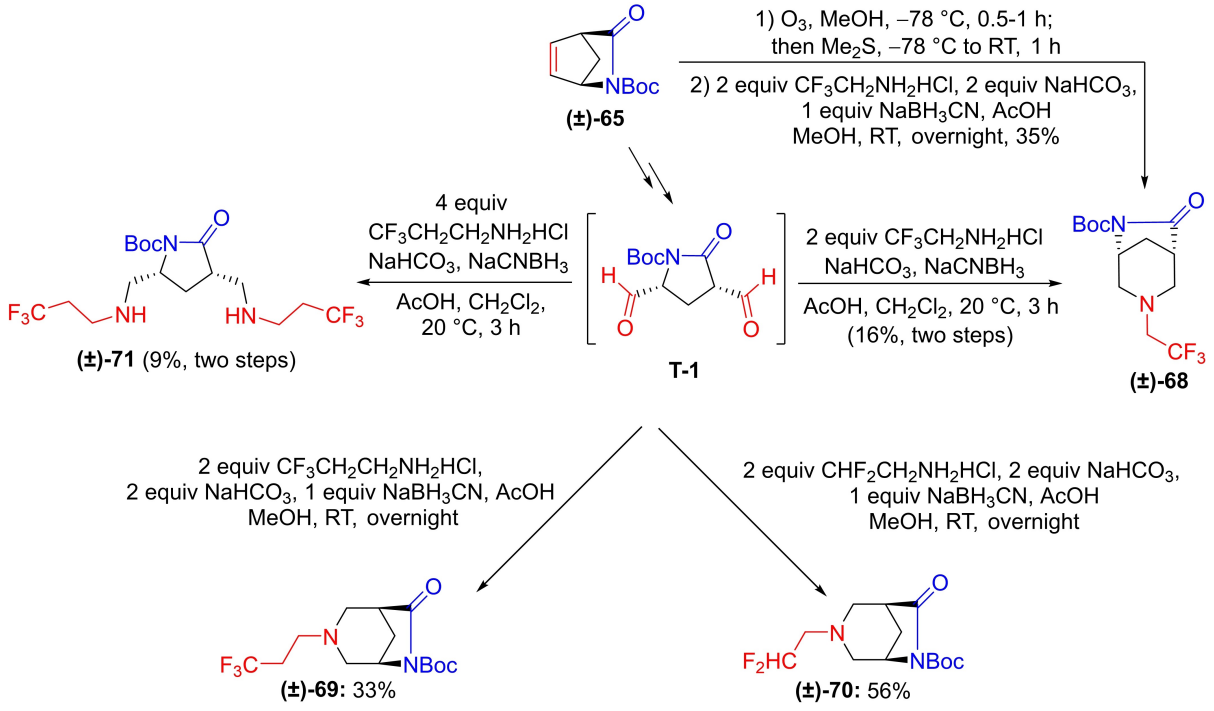


Scheme 15. Synthesis of bicyclic γ-lactam derivative (±)-**67**.

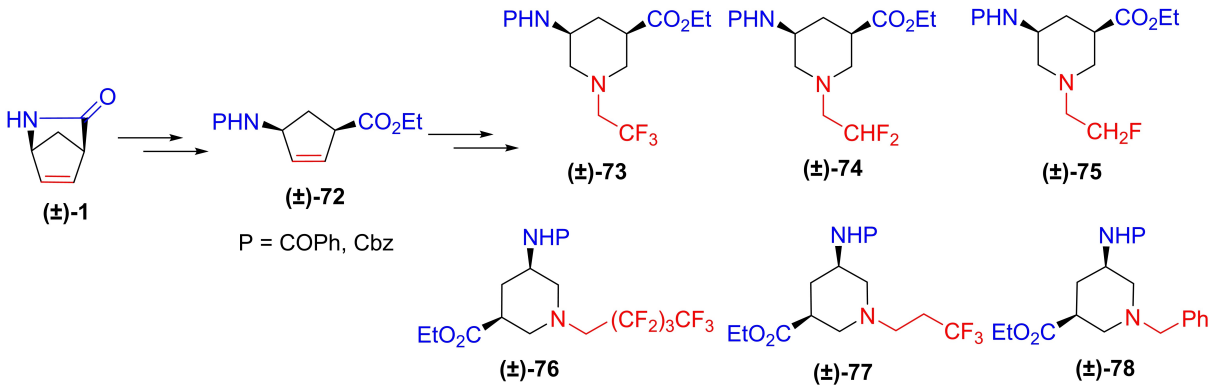
(±)-**71** took place instead of cyclization/deamination (Scheme 16).[20]

Stereocontrolled transformation of Vince lactam ((±)-**1**) through the corresponding cyclopentene γ-amino esters (±)-**72** involving oxidative ring cleavage/cyclization could also be extended to the access of some novel γ-amino esters with a piperidine framework ((±)-**73**-(±)–**78**) (Scheme 17).[19]

It is important to address the stereocontrolled character of the transformations. Note, that the dialdehyde intermediate (**T-2**) possesses active hydrogens in the α position relative to



Scheme 16. Synthesis of fluorine-containing γ-lactam derivatives (±)-**68**-(±)-**71**.



Scheme 17. Synthesis of fluorine-containing γ-amino ester derivatives (±)-**73**–(±)-**78**.

the formyl moieties. Nevertheless, the possible enolization, which would lead through the cyclization process with inversion of configuration of the piperidine ring containing the ester and protected amino groups in *trans* relationship, did not take place. The preferred diequatorial arrangement of both the ester and the amino groups may be responsible for the conservation of the configuration of the stereocenters and relative stereochemistry. Accordingly, the products were formed across **T-3** and **T-4**, bearing the two groups in *cis* relative arrangement (Scheme 18).[19]

2.4. Ring olefin Bond Functionalization with Aziridine Formation/Aziridine Opening; Synthesis of Fluorine-Containing, Functionalized Azaheterocycles

Olefin bond aziridination followed by aziridine ring opening is a prevalent difunctionalization strategy to create versatile functionalities such as amines, amino alcohols, amino nitriles, haloamines, alkylamines etc. selectively, with stereocontrol.[21] Fluorinative transformations of aziridine-containing molecules, through the opening of the aziridine ring with fluoride are known in the literature furnishing novel fluorine-containing scaffolds with a β-fluorinated amino unit in their structure.[22]

γ-Amino ester (±)-**21** (derived from Vince lactam), when subjected to aziridination with Chloramine-T in the presence of phenyl-trimethylammomium tribromide (PTAB), resulted in the formation of aziridine derivative (±)-**79** in 58% yield with *cis*-diastereoselectivity (Scheme 19).[23]

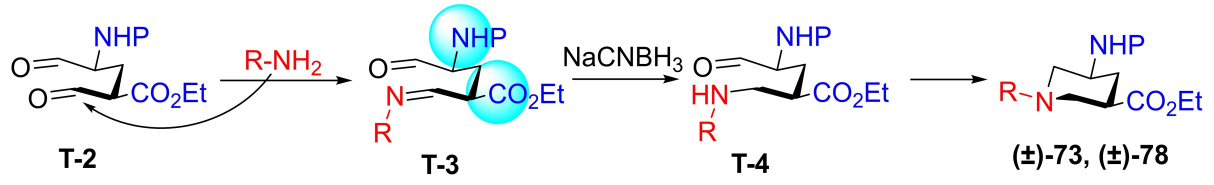
Next, aziridine (±)-**79** was submitted to a fluorination. On treatment with XtalFluor-M, aziridine ring opening proceeded to give fluorine-containing imidazolone derivative (±)-**80**. The route to the formation of cyclized compound (±)-**80** is represented on Scheme 20.

2.5. Transformation of 2-Azabicyclo[2.2.1]Hept-5-En-3-One through Halonium Activation

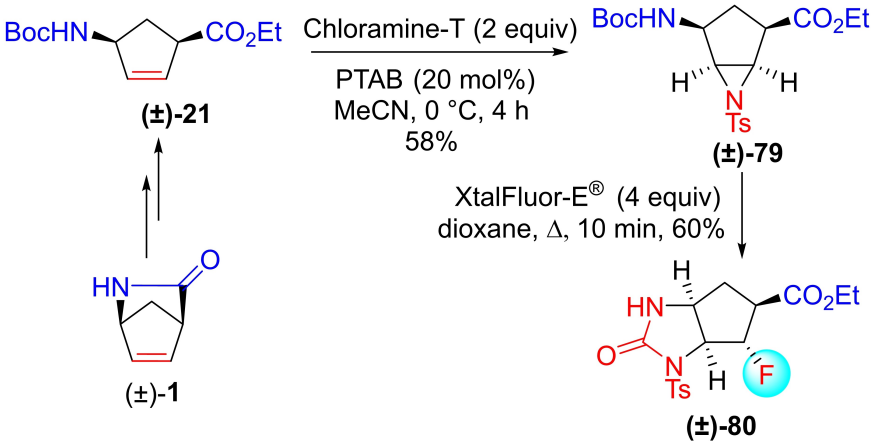
Activation with halonium ion (by using common reagents, such as *N*-halogenosuccinimides (NXS), phenyl-trimethylammonium tribromide (PTAB), or other *N*-halogen compounds such as 1,3-dibromo-5,5-dimethylhydantoin (DBH) followed by versatile further transformations, is a convenient method for the functionalization of a certain organic molecule across its olefin bond.[24]

Halonium ion activation of Vince lactam is the first step for the synthesis of antiepileptic agent OV329 (**81**) (Figure 7).[25]

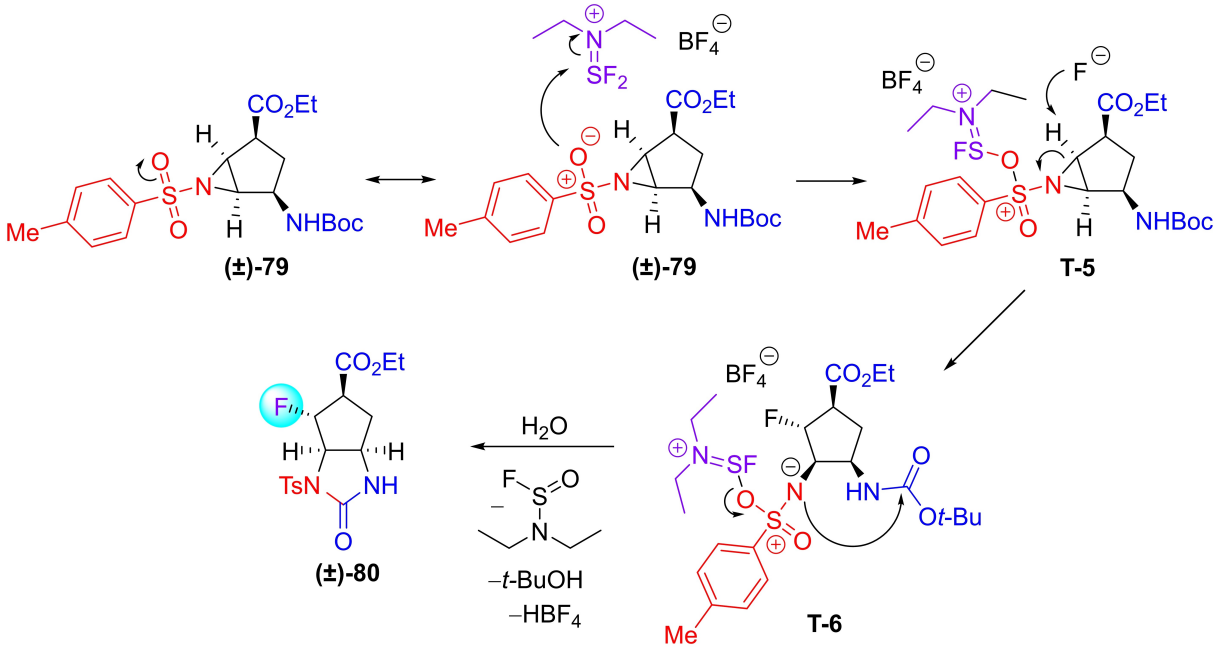
The key molecular entities towards the access of compound **81** were the difluoromethylene unit containing brominated γ-amino ester **83** (in which the difluoromethylene unit was installed with Hu's reagent) or phenylselenyl analogue **82** (in which the fluorinated element was installed by the Wittig



Scheme 18. Formation of piperidine cis γ-amino ester derivatives (±)-**73** and (±)-**78** (the blue circles refers to the conservation of the configuration of the chiral centers).



Scheme 19. Synthesis of fluorine-containing ester derivative (±)-**80**.



Scheme 20. Formation of fluorine-containing ester derivative (±)-**80**.

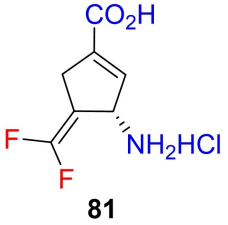
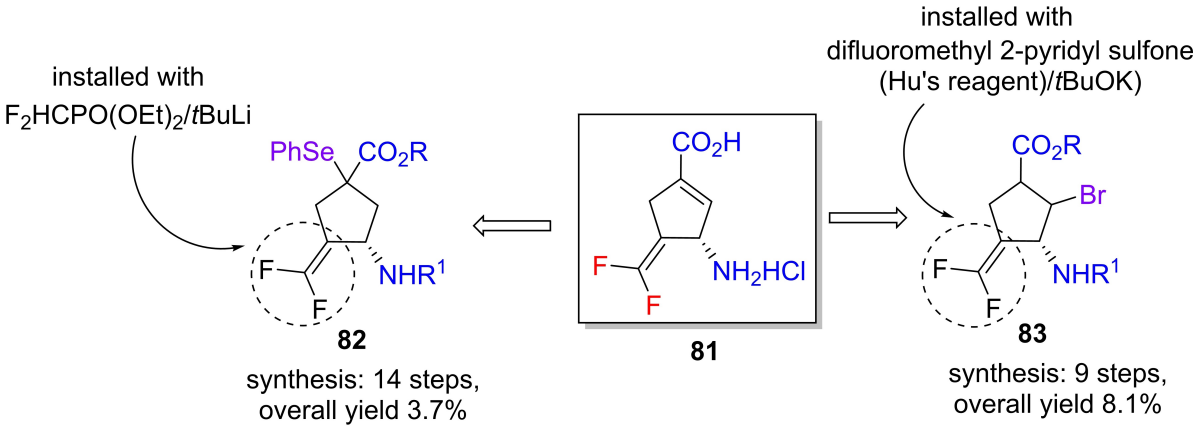


Figure 7. Structure of antiepileptic agent OV329 [(*S*)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid, **81**)].

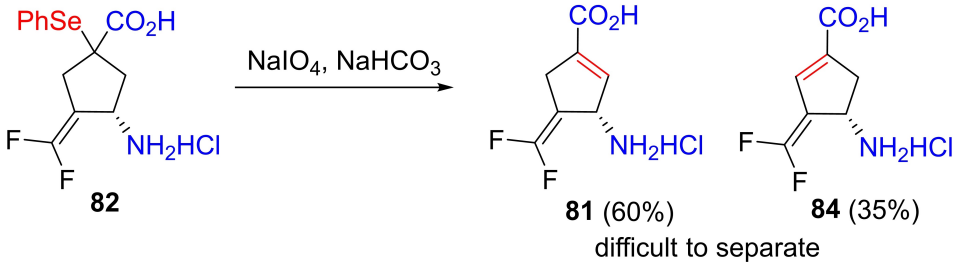
reaction) (Scheme 21). The overall yield of the latter procedure was lower (3.7 % versus 8.1 %).[25]

The major reason for the inferiority of the latter method (transformation of scaffold **82** containing the phenlyselenyl group) was shown to be the oxidative elimination step, which provided two products (**81** and **84**), whose separation was difficult to achieve (Scheme 22).

In contrast to the above-mentioned pathway, HBr elimination from **83** was expected to furnish a single elimination product (**81**). The related retrosynthetic pathway starting from



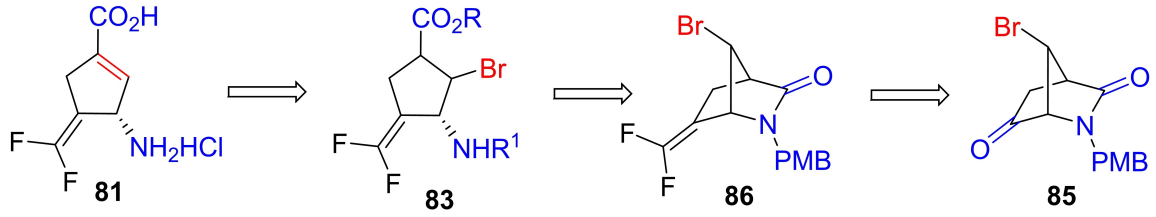
Scheme 21. Retrosynthesis of OV329 (**81**).



Scheme 22. Transformation of **82** into OV329.

a brominated γ-lactam structure (**85**) is depicted on Scheme 23.

Thus, the synthetic protocol started from Vince lactam (**1**) which, after protection with *p*-methoxybenzyl alcohol (PMBOH), involved olefin bond functionalization with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) (Figure 8) in Ac_2O led to lactam derivative **87** by skeletal rearrangement (Scheme 24). This skeletal reorganization might be easily interpreted by halonium activation, subsequent intramolecular reorganization with the nucleophilic involvement of the lactam *N*-atom, followed by nucleophilic attack of the acetoxy group as depicted in Scheme 25.



Scheme 23. Detailed retrosynthesis of OV329.

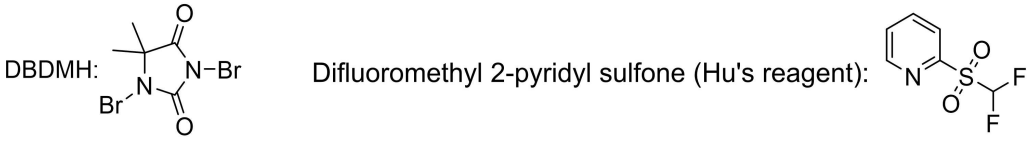
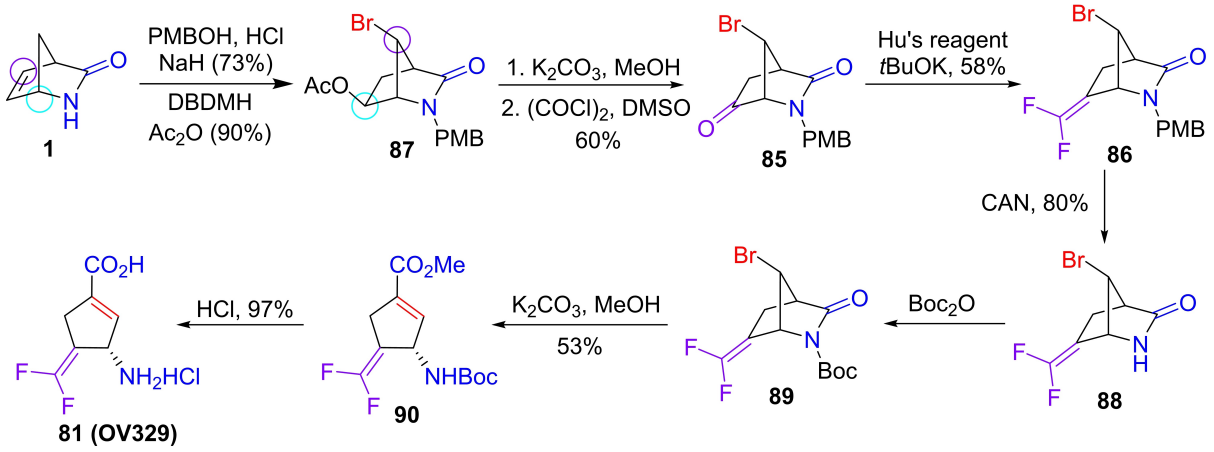
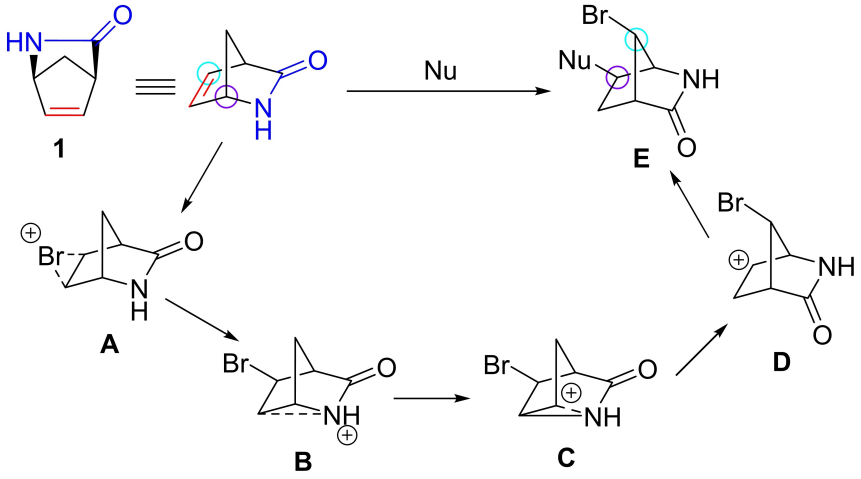


Figure 8. Structures of 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) and difluoromethyl 2-pyridyl sulfone (Hu's reagent).



Scheme 24. Synthesis of OV329.



Scheme 25. Halonium-activated rearrangement of Vince lactam into structure E (Nu = AcO).[26]

Compound **87** underwent deacetylation followed by Swern oxidation and it gave product **85**, which in turn, on treatment with Hu's reagent afforded lactam **86** possessing the difluoromethylene unit in its structure. Next, PMB removal, *N*-Boc protection, lactam methanolysis, and *N*-deprotection pathway resulted in the desired compound **81** (Scheme 24).[25]

The synthesis of another biologically interesting cyclopentane γ-amino acid derivative (**95**) started with lactam **91**. It was reacted with trifluorinated methyl propanoate in the presence of $TiCl_4$ through its keto functionality giving compounds **92** and **93**. After chromatographic separation, compound **92** furnished target amino acid derivative **95** by ceric ammonium nitrate treatment (PMB deprotection) and lactam hydrolysis (Scheme 26).[27]

Several other fluorine-containing cyclopentane γ-amino acid derivatives, having structural similarities to compound **95**, were reported to have an enhanced potency toward GABA-AT, and they also exhibited inhibitory activity toward hOAT (human ornithine aminotransferase) inhibitors, but with a relatively lower efficiency (Figure 9).[28]

The syntheses of additional structural motifs as hOAT inhibitors possessing a geminal difluoro element in their

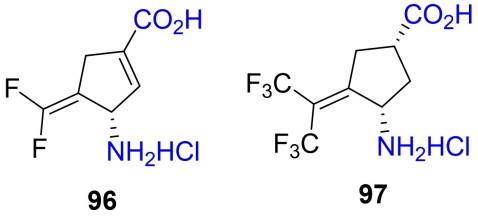
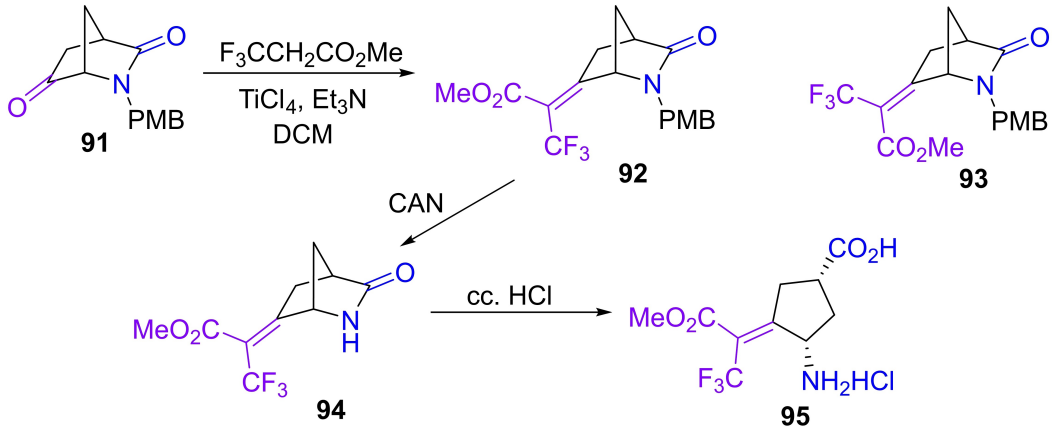


Figure 9. Some hOAT inhibitors.

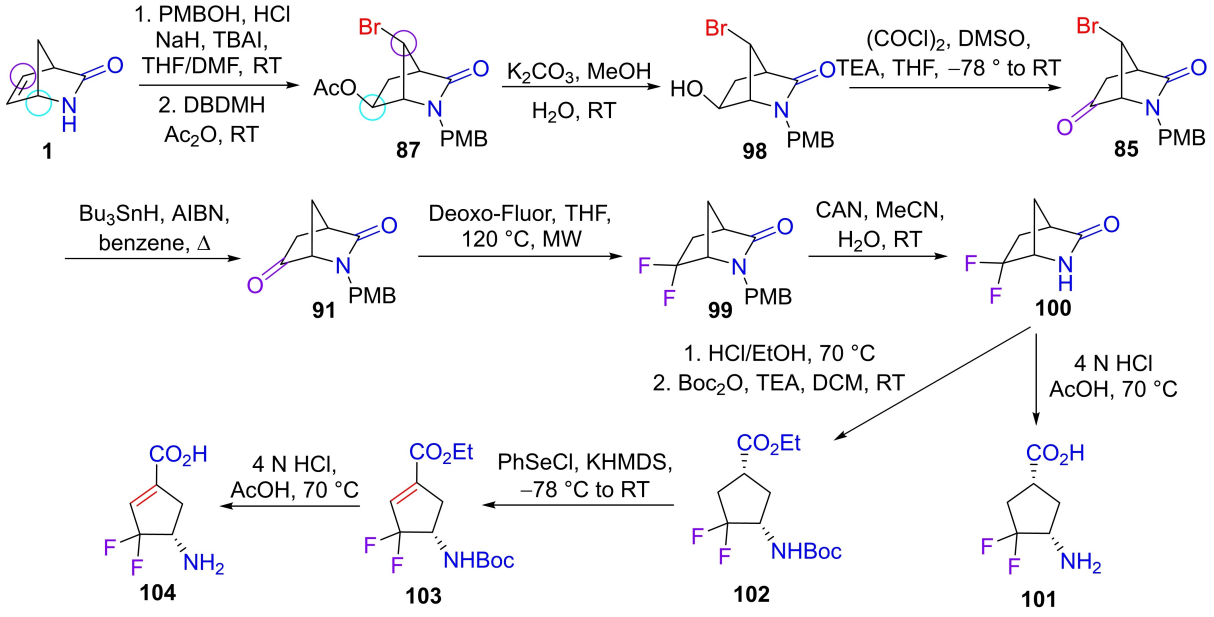


Scheme 26. Synthesis of inactivator of human OAT (treatment for hepatocellular carcinoma).

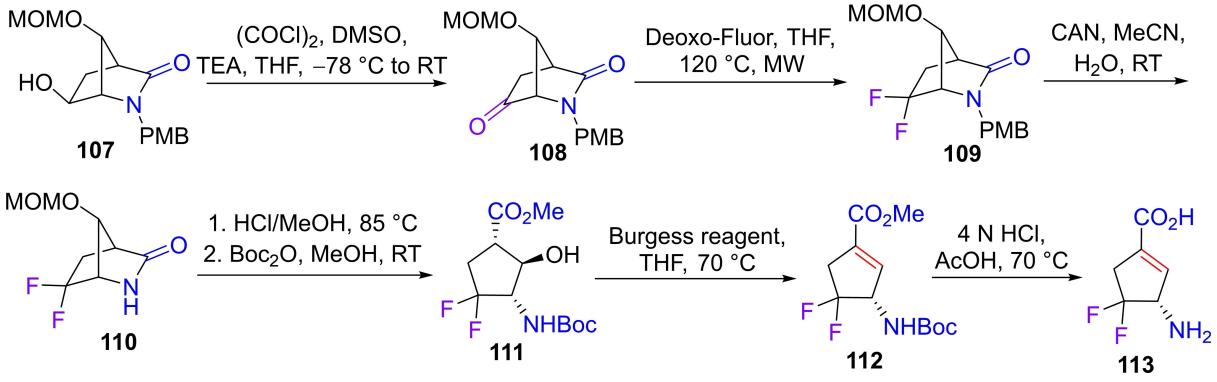
structure, were reported recently by Silverman's team. The procedure started from Vince lactam, whose *N*-PMB protection and treatment with DBDMH in Ac_2O provided compounds **87** across halogenative rearrangement (see also Scheme 25). Desacetylation of lactam **87** followed by alcoholic hydroxy group oxidation led to **85**, which in turn was submitted to reductive debromination on treatment with Bu_3SnH in the presence of azobisisobutyronitrile (AIBN) leading to compound **91**. Next, compound **91** was subjected to oxo–difluorine exchange with Deoxo-Fluor furnishing **99** which, after PMB-deprotection and lactam ring opening, led to amino acid **101** (by hydrolysis) and **102** (by ethanolysis and *N*-Boc-protection). The latter compound provided the corresponding fluorinated amino acid **104** across oxidative selenylation and acidic hydrolysis (Scheme 27).[29]

Figure 10 shows the structure of a difluorinated cyclopentene γ.amino acid **105** as well as its six-membered analog **106** as hOAT inhibitors.[29]

A novel isomer of *gem*-difluoro γ-aminocyclopentenecarboxylic acid **104** with the ring double bond located between C1-C2 (**113**) could be accessed from lactam **107** in six steps. First, the oxidation of the alcoholic hydroxy group gave **108** which, after deoxidative fluorination and PMB removal, afforded difluorinated lactam **110** (Scheme 28). Next, **110**



Scheme 27. Synthesis of inactivator of human OAT **101** and **104**.



Scheme 28. Synthesis of inactivator of human OAT (human ornithine aminotransferase).

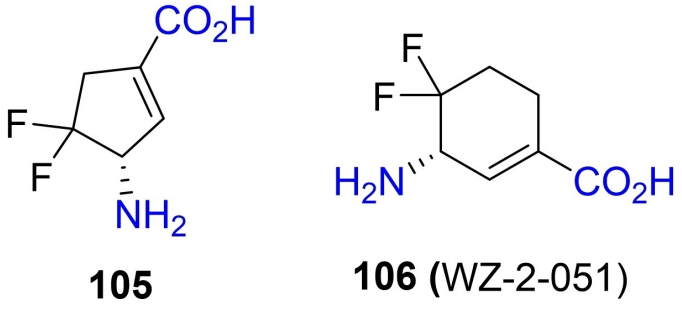
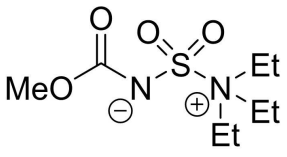


Figure 10. Structures of some inactivator of human OAT (human ornithine aminotransferase).

underwent acidic methanolysis, MOM-deprotection, and then *N*-Boc protection to yield hydroxylated amino ester **111**. Finally, water elimination with Burgess reagent (Figure 11) and acidic treatment of **112** furnished target derivative **113** (Scheme 28).[29]



methyl *N*-(triethylammoniumsulfonyl)carbamate

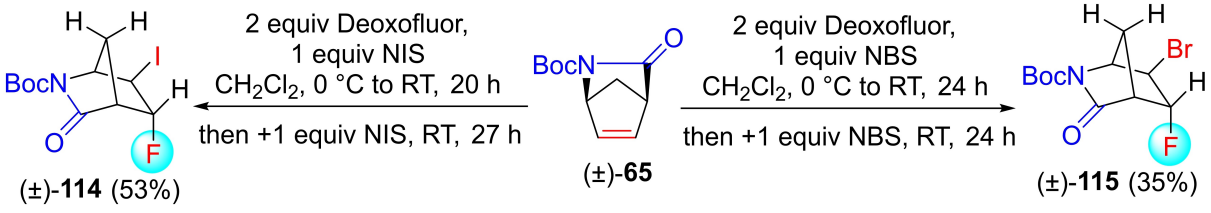
Figure 11. The structure of Burgess reagent.

2.5.1. Transformation of Vince Lactam through Halofluorination; Synthesis of Fluorine-Containing Molecules

Halofluorination is a simple, effective method for the incorporation of a fluorine atom into the structure of a certain organic molecule across its olefin bond.[30] An interesting halofluorination of the Vince lactam by using Deoxofluor and *N*-halosuccinimide was described (Scheme 29). Although the yields of the formed halofluorinated products (**114** and **115**) were modest, the halofluorination of Vince lactam proceeded selectively leading to a single product in each case.

2.6. Functionalizations Across Nitrile–Oxide Dipolar Cycloadditions

The 1,3-dipolar cycloaddition of nitrile oxides to olefins is a widely used method for the functionalization of an olefin bond and for the preparation of various isoxazoline scaffolds. Furthermore, the isoxazoline framework might be readily converted into various functional elements in a certain organic molecule including 1,3-amino alcohols, amino ketones, β-hydroxy esters, imino alcohols, β-hydroxy nitriles, β-hydroxy ketones or α,β-unsaturated ketones.[31]



Scheme 29. Transformation of lactam (±)-**65** across halofluorination.

2.6.1. Synthesis of Peramivir

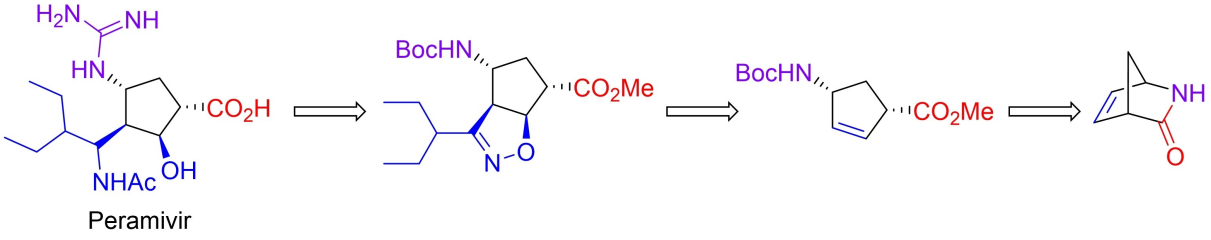
Neuraminidase inhibitors were recommended as first-line drugs in the treatment of influenza. A relevant neuraminidase inhibitor is the drug Peramivir [trade name Rapivab, or Rapiacta (Japan), or PeramiFlu (Korea)] (**8**, Scheme 30). FDA issued and emergency use authorization for Peramivir in 2009, while it was approved for the treatment of influenza in 2014.[32]

Vince lactam served as precursor for the synthesis of Peramivir and several synthetic methods for its preparation were published during the last two decades. A common feature of all methods involved in the synthesis of Peramivir was dipolar cycloaddition of nitrile oxide to the ring olefin bond of cyclopentene γ-amino ester derived from Vince lactam. The general retrosynthetic concept toward Peramivir is depicted on Scheme 30. The key step of the process is the stereo- and regioselective 1,3-dipolar nitrile oxide cycloaddition to the olefin bond.

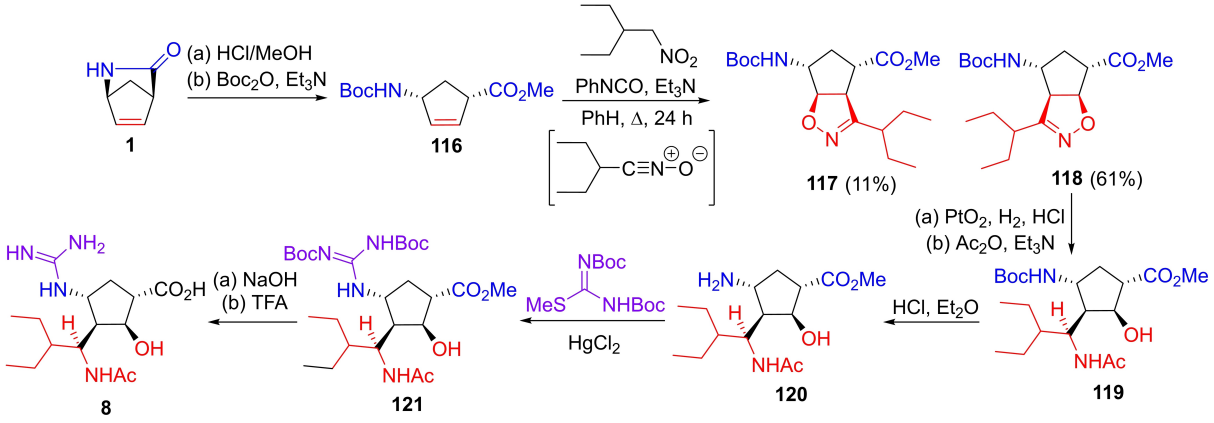
Nitrile oxides, in general, are unstable dipoles and, therefore, they must be generated in situ in the reaction mixture. Two methods for their generation are known in the literature: a base-induced dehydrohalogenation of hydroximoyl chlorides (Huisgen method) and dehydration of primary nitroalkane derivatives (Mukaiyama method).[33]

A synthetic approach to Peramivir, an extension of the method by Chand et al. published earlier[34a] involving nitrile oxide generation according to the Mukaiyama method, was investigated by Fand and co-authors. The substituent effect and studies on reagent formation and experimental conditions were described.[34b] Nitrile oxide used in the reaction was generated thermally from 2-ethyl-1-nitrobutane *in situ* with phenyl isocyanate in the presence of triethylamine as base and it was reacted with amino ester **116** (derived from Vince lactam). This 1,3-dipolar cycloaddition proceeded diastereoselectively and led to two isoxazoline regioisomers **117** (minor) and **118** (major) in approximately a ratio of 1:6. After separation of the two isoxazoline-fused derivatives, major product **118** was subjected to reductive heteroring opening, which in turn gave compound **119** in a selective manner with the generation of a novel chiral center. Next, cyclopentane amino ester **120**, generated by Boc deprotection of **119**, was treated with 1,3-*bis*(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea in the presence of $HgCl_2$ to furnish compound **121**. Finally, base-catalyzed ester hydrolysis and Boc deprotection with trifluoroacetic acid (TFA) of **121** afforded Peramivir (**8**) (Scheme 31).[34b]

The same research group applied the Huisgen method as well in order to carry out nitrile oxide generation and 1,3-dipolar cycloaddition. Thus, the desired nitrile oxide for the



Scheme 30. Retrosynthesis of the antiviral drug Peramivir.



Scheme 31. Synthesis of the antiviral drug Peramivir (**8**).

cycloaddition reaction, generated from ethyl-*N*-hydroxybutanimidoyl chloride in the presence of Et_3N at room temperature, was reacted with amino ester **116**. In comparison with the Mukayama method described above (see Scheme 31), cycloaddition under Huisgen conditions led to the formation of two isoxazoline isomers **118** and **117** with a higher regioselectivity (91 : 9) (Scheme 32).

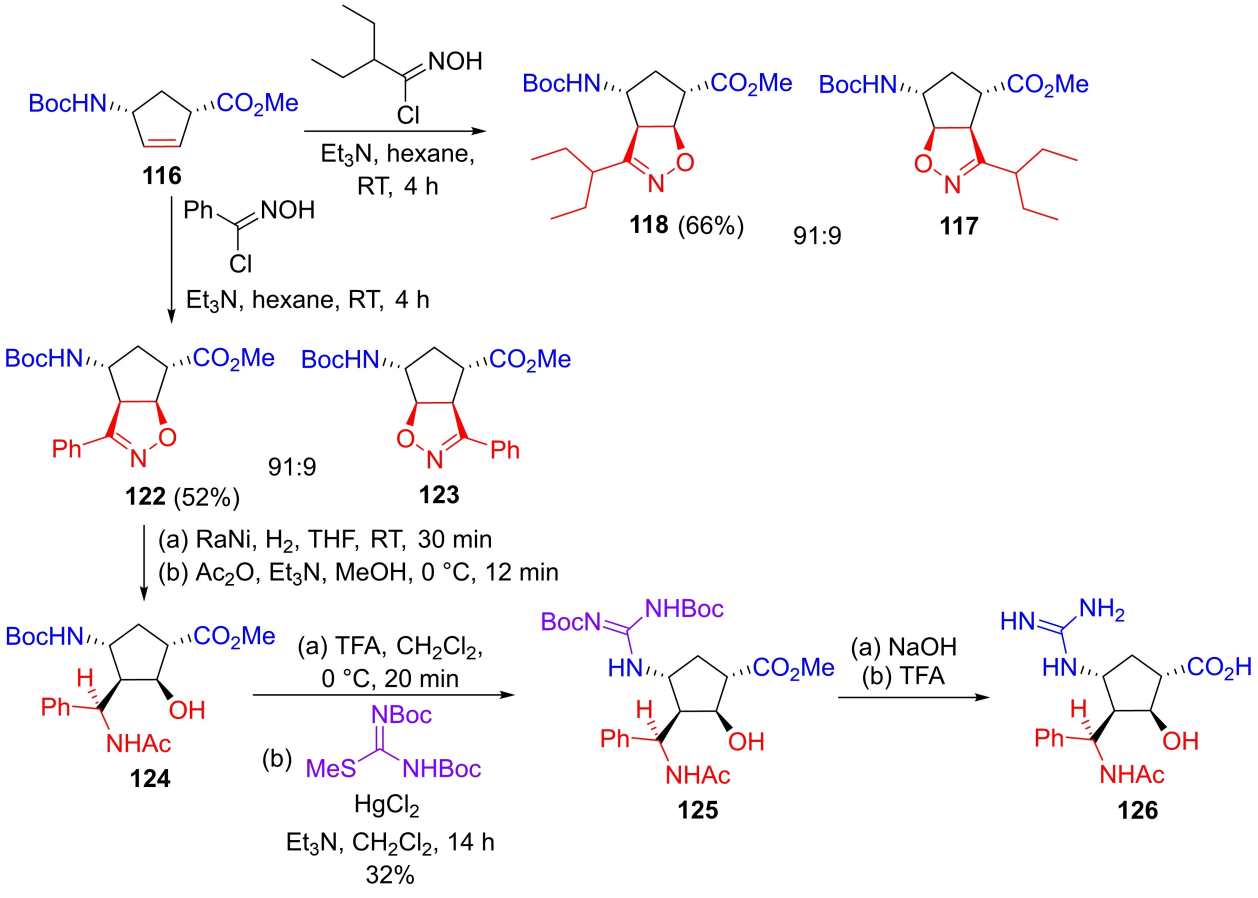
Peramivir analogs were also prepared by the same group with an illustrative example depicted on Scheme 32.[34b] Nitrile oxide, *in situ* generated from *N*-hydroxybenzimidoyl chloride and Et_3N in reaction with γ-amino ester **116**, provided two isoxazoline-anulated regioisomers **122** and **123** in a diastereoselective manner (approximate ratio 10 : 1). After separation, major isomer **122** gave highly functionalized cyclopentane derivative **124** across heterocyclic ring opening under reductive conditions. Subsequent *N*-acetylation, *N*-Boc deprotection, *N*-guanidinylation, ester hydrolysis, and Boc deprotection yielded Peramivir analog **126** (Scheme 32).

An alternative synthetic protocol to Peramivir was reported by Chen and co-authors.[35] In this work nitrile oxide was generated *in situ* from 2-ethylbutanal oxime and NaOCl affording isoxazoline-fused derivative **118**, as the sole product, although only in a 68 % yield.

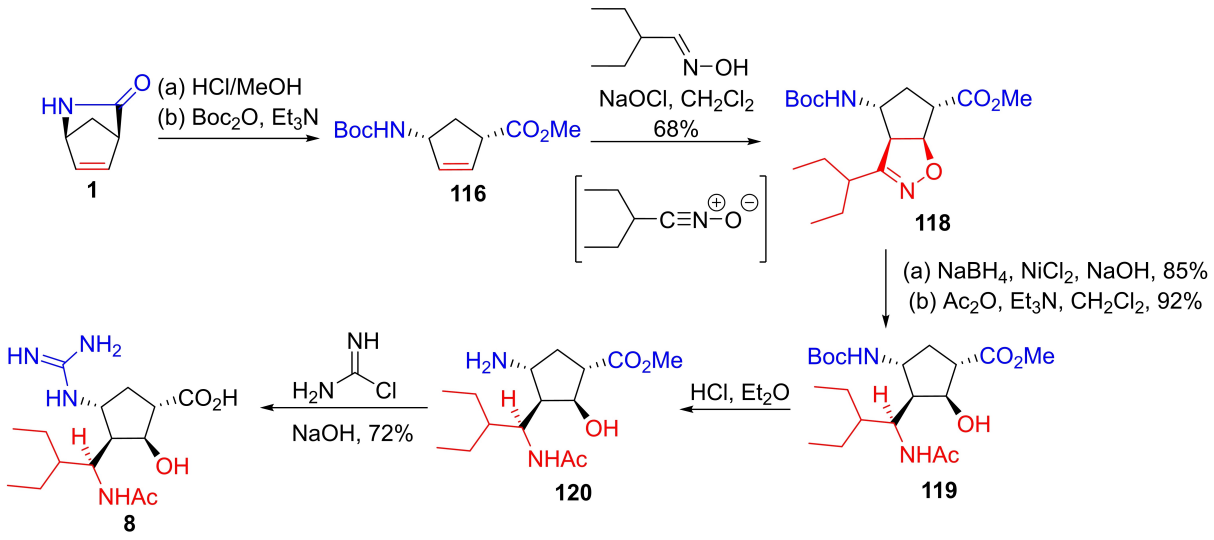
The reductive ring opening in **118** was achieved with $NaBH_4$ in the presence of $NiCl_2$ and it proceeded diastereoselectively furnishing compound **120** after amino group acetylation and *N*-Boc deprotection. The guanidine moiety was introduced onto **120** by using chloroformamidine under basic conditions affording Peramivir in 72 % (Scheme 33).[35]

Peramivir phosphonate derivatives as phosphorous analogs of Peramivir were synthesized and investigated as neuraminidase inhibitors in a work by Wong and co-authors.[36] The retrosynthesis of the phosphonate analog involved key steps of nitrile oxide cycloaddition, isoxazoline opening, iododecarboxylation, and oxirane formation/oxirane opening with phosphite as depicted on Scheme 34.

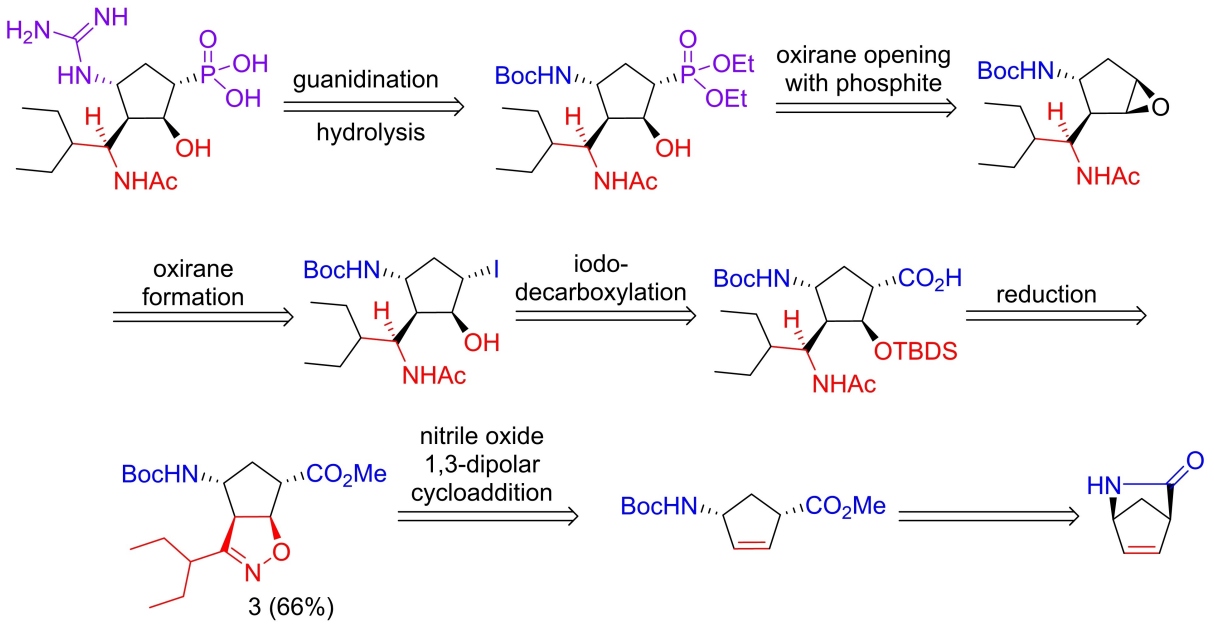
The procedure started with the transformation of amino ester **119** synthesized earlier into *O*-*t*butylsilyl-protected analog **127**. A iododecarboxylation was accomplished with diacetoxy iodobenzene and I_2 forming compound **12**. TBS group cleavage and intramolecular iodine displacement led to oxirane **129**, which in turn after exploring suitable experimental



Scheme 32. Synthesis of Peramivir analog **126**.



Scheme 33. An alternative synthesis of the antiviral drug Peramivir.

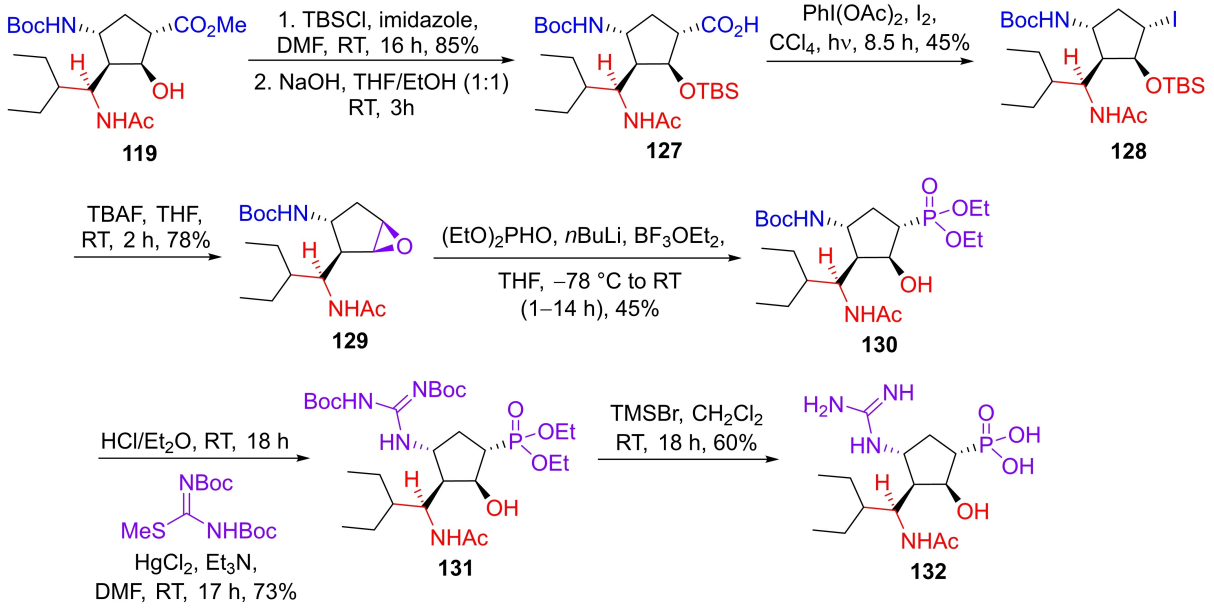


Scheme 34. Retrosynthesis of a Peramivir phosphonate.

conditions, was reacted with diethyl phosphite in the presence of boron trifluoride etherate to give compound **130** regioselectively, across oxirane opening. In the final step, *N*-Boc deprotection, guanidinylation, and Boc deprotection afforded target derivative **130** (Scheme 35).[36]

The synthesis of other Peramivir phosphonate analogs[36] as well as analogs bearing hydrophilic side chains[37] was also reported. The latter anti-influenza agents were investigated and described to exhibit high activity against the H275Y mutant (Figure 12).

An extension of the studies of Peramivir analogs was described by Fang and co-authors. Thus, a Peramivir conjugate as orally available agents against influenza H275Y mutant was synthesized by transformation of compound **138** involving its hydroxy group activation and coupling with caffeic acid derivative **141** leading to Peramivir analogs **140** (Scheme 36).[38]



Scheme 35. Synthesis of Peramivir phosphonate analog **132**.

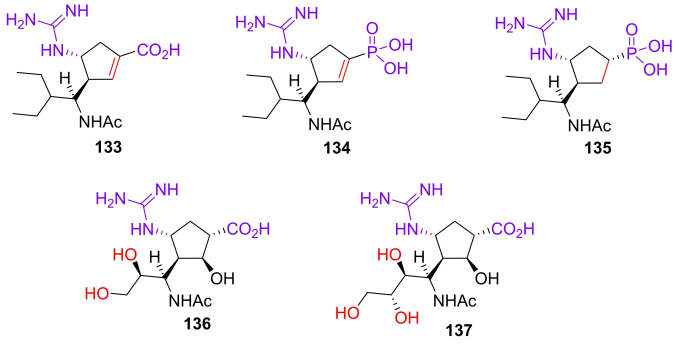
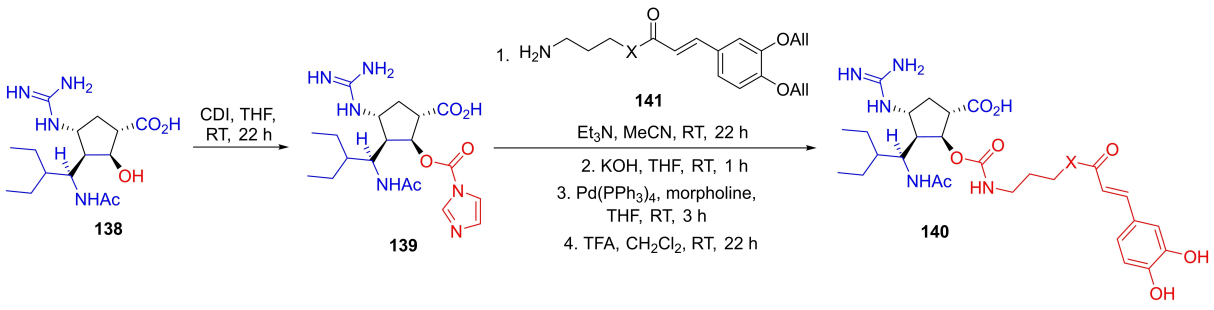


Figure 12. Structures of some Peramivir analogs.

2.6.2. Other Cycloadditions

Cyclopentene-based amino ester 1**42**, with an acrylate unit in its structure, was designated as an intermediate for the synthesis of a number of bioactive nucleosides. Cycloadditions to *N*-Boc-protected methyl cyclopentenecarboxylates (**142** or **143**) of (2-(methoxymethyl)allyl)trimethylsilane (**144**) or *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (**145**) gave stereoselectively some cyclopentane- or pyrrolidine-fused amino ester scaffolds. The reaction procedure started from Vince lactam (**1**), which was converted via common steps (lactam opening under methanolysis/*N*-Boc protection) to amino ester **116**. In the next step compound **116**, underwent double bond isomerization in the presence of DBU providing amino ester **142**. Reaction of **142** with (2-(methoxymethyl)allyl)trimethylsilane in the presence of $Pd(OAc)_2$ and $P(OiPr)_3$ with the generation of a trimethylenemethane species



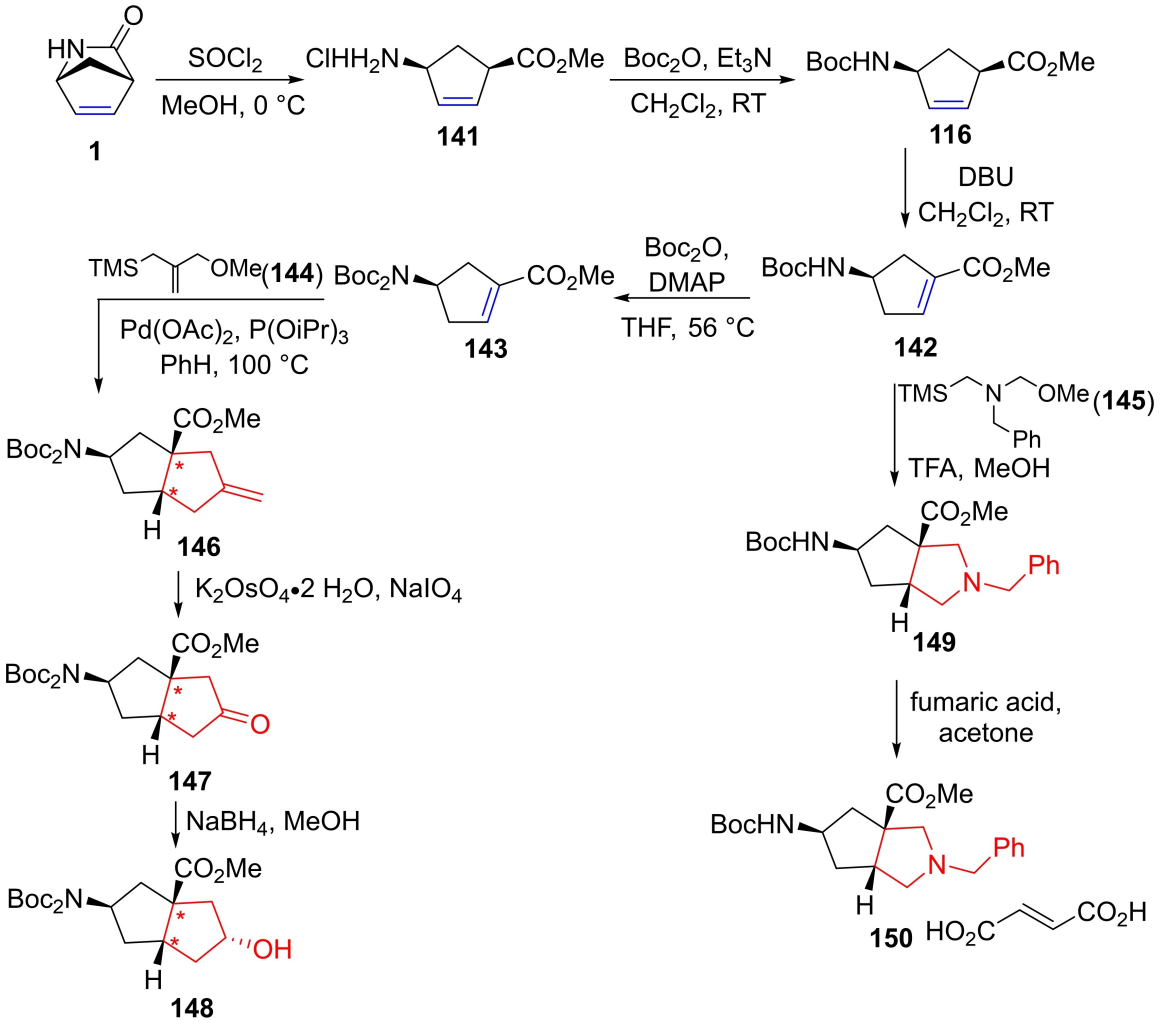
Scheme 36. Synthesis of Peramivir analog **140** (X = O, NH).

failed to afford the desired cyclopentane-fused derivative. The most probable reason is the competing reaction of the electrophilic reagent with the NHBoc group. Therefore, double *N*-Boc protection was accomplished to yield ester **5**, which in turn gave in a similar reaction the desired annulated compound **146** as a mixture of two stereoisomers in a ratio of 6:1. Furthermore, osmylation of **146** to the diol and oxidative cleavage led to the ketone **147** which was stereoselectively reduced the corresponding hydroxyl derivative **148** (Scheme 37).

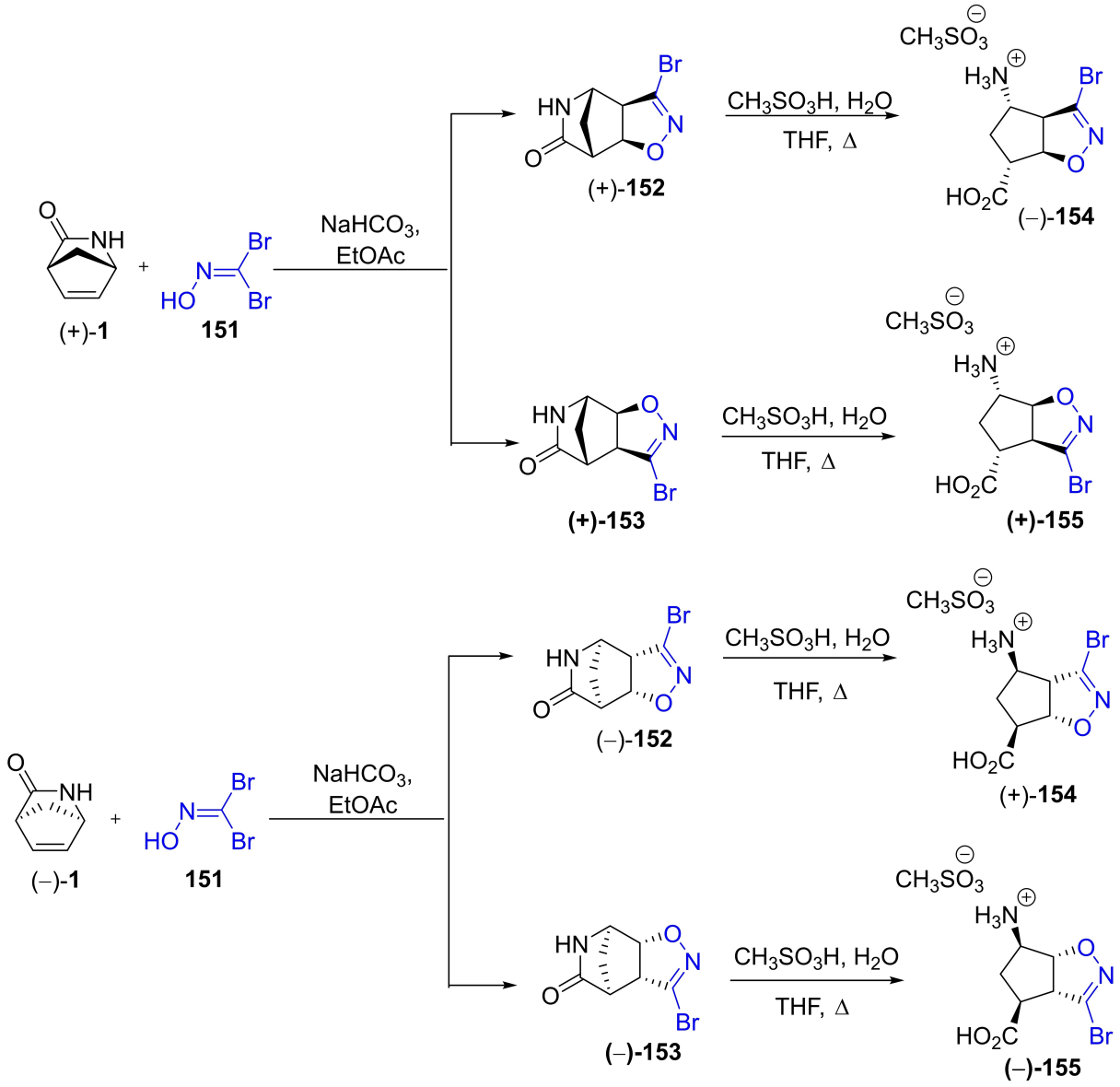
Contrary to the cycloaddition with **144**, azomethine ylide cycloaddition of *N*-Boc-monoprotected ester **142**, involving *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (**145**), proceeded smoothly and, due to steric factors (*N*-benzyl, NHBoc), led stereoselectively to the desired pyrrolidine-fused scaffold **149**, which was isolated as its fumarate salt **150** (Scheme 37).[39]

Some isoxazoline-fused bicyclic γ-amino acid derivatives have been synthesized and reported as inhibitors of γ-aminobutyrate aminotransferase (GABA-AT). The dextrorotatory enantiomer of Vince lactam ((+)-**1**) was subjected to 1,3-dipolar cycloaddition of bromonitrile oxide, generated *in situ* by dehydrohalogenation of dibromoformaldoxime (**151**) in the presence of $NaHCO_3$ yielding regioisomer isoxazolines (+)-**152** and (+)-**153**. Both adducts, after separation on treatment with H_2O in the presence of methansulfonic acid, afforded the corresponding optically pure isoxazoline-fused cyclopentane γ-amino acids (−)-**154** and (+)-**155**. A similar pathway using levorotatory Vince lactam gave enantiomers (+)-**154** and (−)-**155** (Scheme 38).

All four stereoisomers [(−)-**154**, (+)-**155**, (+)-**154** and (−)-**155**] were tested in vitro for their ability to inactivate mammalian GABA-AT. The presence of bromine on the



Scheme 37. Cycloaddition reaction to amino esters **142** and **143**.



Scheme 38. Cycloaddition reaction of γ-lactam enantiomers (+)-**1** and (−)-**1** with dibromoformaldoxime under basic conditions.

isooxazoline ring may also offer the possibility for further functionalizations in forthcoming investigations.[40]

2.7. Arylation Methods of Vince Lactam

It is well-known that the aromatic–aromatic (π–π) and CH–π interactions in and between various helix-type structures may exert significant influence on the secondary or tertiary arrangements of oligopeptides. Accordingly, amino acids possessing an aryl structural unit have received high significance in peptide research.[41]

Since Vince lactam is a direct precursor of cyclopentene γ-amino acid, its arylation might be considered of importance according to the reasons described above. The first description of Vince lactam hydroarylation was based on the Pd-catalyzed modified Heck reaction with various iodoarenes studying the effect of electron-donating or electron-withdrawing substituents. The reaction was highly efficient in view of the formation of the arylated scaffolds (82–99%) and it was found to be highly dependent on reaction conditions. In particular, the solvent had a strong effect on the outcome of the reaction. Thus, benzene, EtOAc or THF favored the formation of the regioisomer in which the aryl group is attached to the ring

further from the ring *N*-atom (2). In contrast, in DMF or MeCN the formation of the other regioisomer was favored, in which the aryl group is connected to the ring carbon closest to the *N*-atom (3) (Scheme 39).[42]

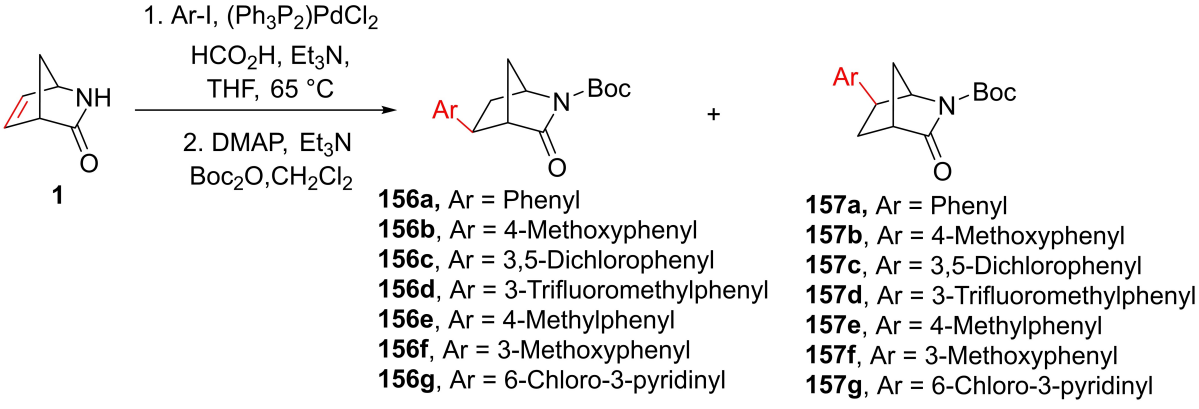
It is known, that γ-aminocyclopentanecarboxylic acid can mimic not only γ-aminobutanoic acid (GABA), but as a conformationally rigid scaffold, it is considered to be an interesting building element in the field of peptidomimetics and foldamers, which may influence the secondary structure of oligopetides. A regioselective and stereoselective hydroarylation protocol was described by Kamelet and co-authors, which was based on Rh-catalyzed coupling with arylboronic acids in the presence of phosphine-based ligands. The procedure was extended to several arylboronic acids with versatile substitution patterns. Boronic acids with formyl or protic functionality failed to yield arylated substances. It was an interesting finding that Vince lactam itself gave exclusively the C-6-substituted product. In turn, in the case of lactams with *N*-Bn, PMB, 2-NAP, Me or Ph substituents, a mixture of two arylated regioismers was formed with the major isomer being the C-5-substituted derivative (Scheme 40, Table 1). The arylated Vince lactams could be transformed by acid-catalyzed lactam ring opening followed by Fmoc protection into the corresponding amino acids for peptide design.[43a]

Recently, Hanessian and co-authors have published a similar arylation protocol of the *N*-benzylated Vince lactam. Application of the BnO-substituted boronic acid furnished the corresponding arylated Vince lactam regioisomers in 7 : 1 ratio[43b] (compare with entry 15, Table 1).

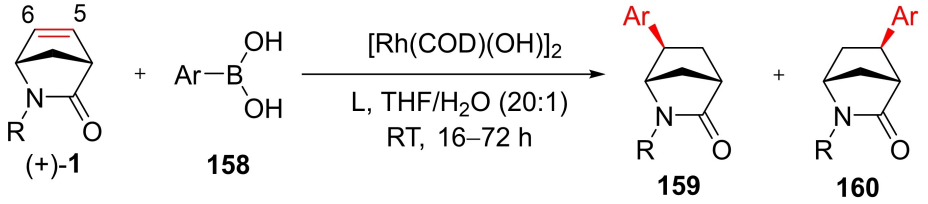
A Cu(II)-mediated oxidative *N*-arylation pathway of Vince lactam with arylboronic acids was carried under various conditions under microwave irradiation. Several aromatic or heteroaromatic boronic acid derivatives were applied in this procedure giving the desired *N*-aryl-substituted lactams in moderate or good yields (Scheme 41, Table 2).[44]

The same research group investigated the Rh-catalyzed *C*-arylation with arylboronic acids under microwave irradiation. All reactions furnished a mixture of two regioisomers in various ratios. Better yields were attained with arylboronic acids possessing electron-donating groups, while transformations with heteroaromatic boronic acids either failed or gave only moderate yields, although the highest selectivity was observed in the case of thiophenylboronic acid (Scheme 42, Table 3).[44]

Interestingly, a simultaneous/one-pot *N*- and *C*-arylation could be performed when Vince lactam was reacted with arylboronic acids in the presence of $Cu(OAc)_2$ and a Rh complex under microwave conditions. The main products were identified to be diarylated products **164** and **165** with small quantities of *C*-arylated derivatives (Scheme 43, Table 4). The major regioisomer was identified with the aryl group being attached to C-6 of the Vince lactam.[44]

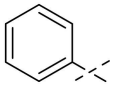
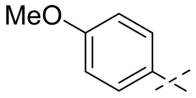
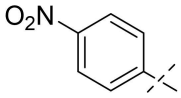
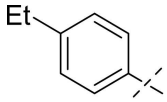
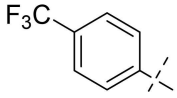
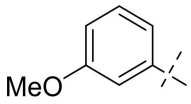
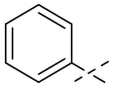
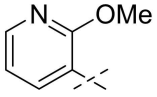
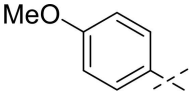
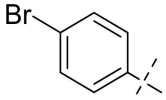
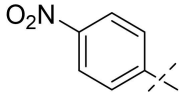
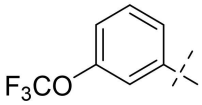
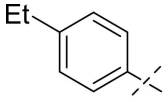
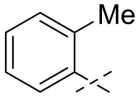
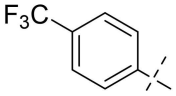
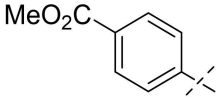
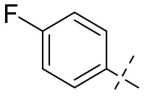
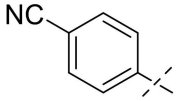
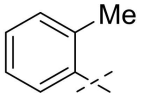
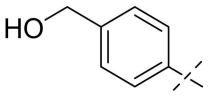
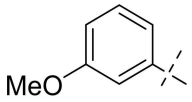
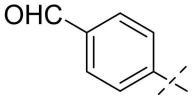
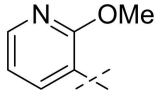
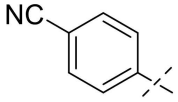


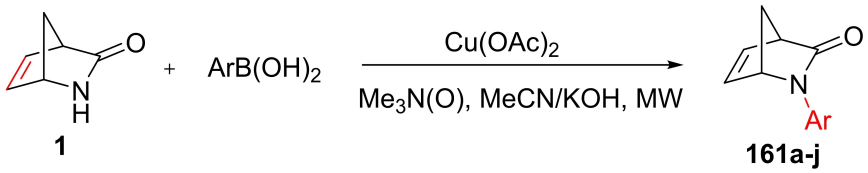
Scheme 39. Hydroarylation of 2-azabicyclo[2.2.1]hept-5-en-3-one with several aryl iodides.



Scheme 40. Hydroarylation of (+)-Vince lactam; L = (*R*)-1-[(S_p)-2-(diphenylphosphino)ferrocenyl]ethyldi-*tert*-butylphosphine [(*R*,*S*)-*t*Bu-Josiphos] or (*R*)-1-[(S_p)-2-(diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine [(*R*,*S*)-Josiphos]; NAP = naphthyl; PMB = *p*-methoxybenzyl.

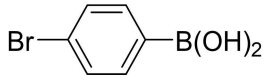
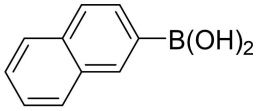
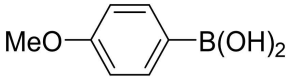
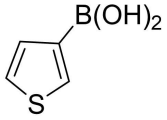
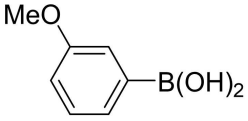
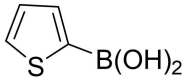
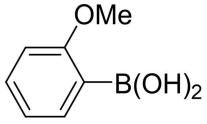
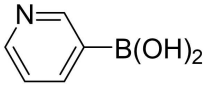
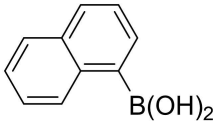
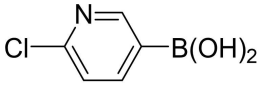
Table 1. Hydroarylation of Vince lactam.

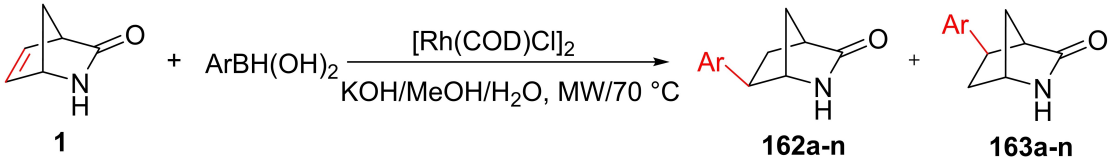
Entry	Ar	R	Yield (%) Ratio of **159:160**	Entry	Ar	R	Yield (%) Ratio of **159:160**
1		H	76 (only **159**)	17	Ph	3,4-DMB	1:6
2		H	75(only **159**)	18	Ph	DPM	1:5
3		H	80 (only **159**)	19	Ph	2-NAP	1:7
4		H	76 (only **159**)	20	Ph	Me	1:5
5		H	83 (only **159**)	21	Ph	Ph	1:2
6		H	86 (only **159**)	22		PMB	68 (**160**) (1:7)
7		H	82 (only **159**)	23		PMB	74 (**160**) (1:6)
8		H	83 (only **159**)	24		PMB	81 (**160**) (1:33)
9		H	78 (only **159**)	25		PMB	73 (**160**) (1:6)
10		H	87 (only **159**)	26		PMB	81 (**160**) (1:13)
11		H	89 (only **159**)	27		PMB	70 (**160**) (1:7)
12		H	76 (only **159**)	28		PMB	77 (only **160**)
13		H	0	29		PMB	71 (**160**) (1:7)
14		H	0	30		PMB	70 (only **160**)
15	Ph	Bn	1:7	31		PMB	76 (**160**) (1:27)



Scheme 41. Cu-Catalyzed *N*-arylation of Vince lactam.

Table 2. N-Arylation of Vince lactam.

Entry	Ar	Yield (%)	Entry	Ar	Yield (%)
1		69 (**161 a**)	6		54 (**161 f**)
2		72 (**161 b**)	7		76 (**161 g**)
3		83 (**161 c**)	8		59 (**161 h**)
4		58 (**161 d**)	9		85 (**161 i**)
5		70 (**161 e**)	10		80 (**161 j**)

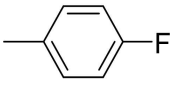
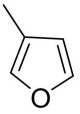
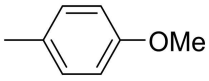
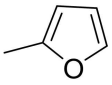
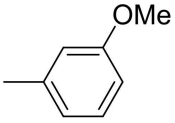
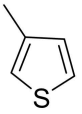
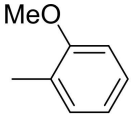
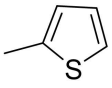
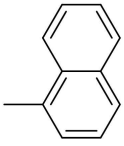
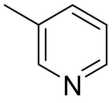
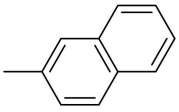
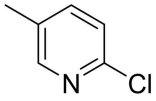


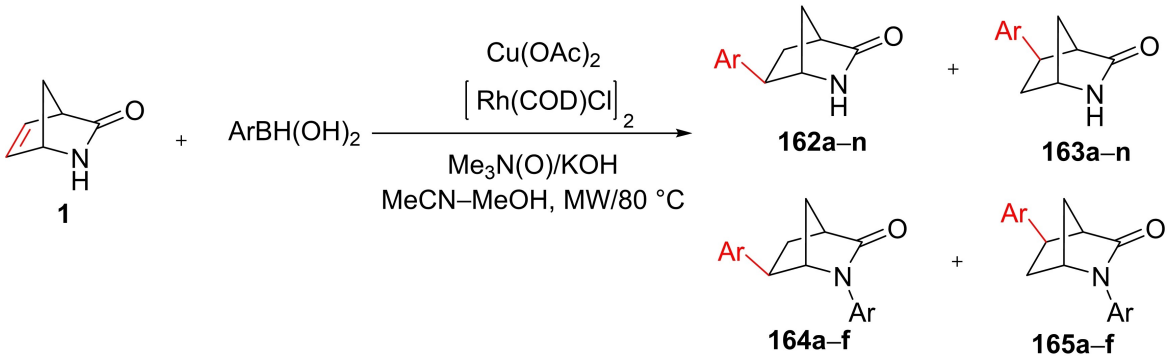
Scheme 42. Rhodium-catalyzed *C*-arylation of Vince lactam.

2.8. Alkylation of Vince Lactam

The Karlsson group described a synthetic strategy for the preparation of 1,2,4-trisubstituted cyclopentanes **169** starting from the commercially available homochiral Vince lactam **1** (Scheme 44). The key step of the method is the diastereoselective 1,4-conjugate addition of alkyl cuprates to α,β-unsaturated endocyclic ester **167**. The research group developed a three-step telescoped sequence (esterification, Boc-protection, and isomerization of the double bond) for the preparation of compound **167** to avoid the time-consuming isolation of all intermediates. The overall yield of 84% from **166** to **167** (three steps) indicates the success of the method. For the synthesis of compound **168 a** a known method was used. Starting from the commercially available benzylmagnesium chloride in the presence of CuI and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) the corresponding cuprate was obtained. It was followed by the addition of TMSCl (an additive, which enhanced reactivity of a weakly reactive α,β-unsaturated ester) and compound **167** prepared earlier. According to the NMR spectra, a mixture of diastereoisomers was detected with the kinetically favored *1S,2R,4R* isomer of

Table 3. C-Arylation of Vince lactam.

Entry	Ar	Yield (%) (ratio of **162:163**)	Entry	Ar	Yield (%) ratio of **162:163**
1		77 (70:30)	7		*no isolable product*
2		84 (80:20)	8		*no isolable product*
3		84 (74:26)	9		41 (98:2)
4		70 (77:23)	10		52 (98:2)
5		48 (74:26)	11		*no isolable product*
6		53 (85:15)	12		65 (75:25)

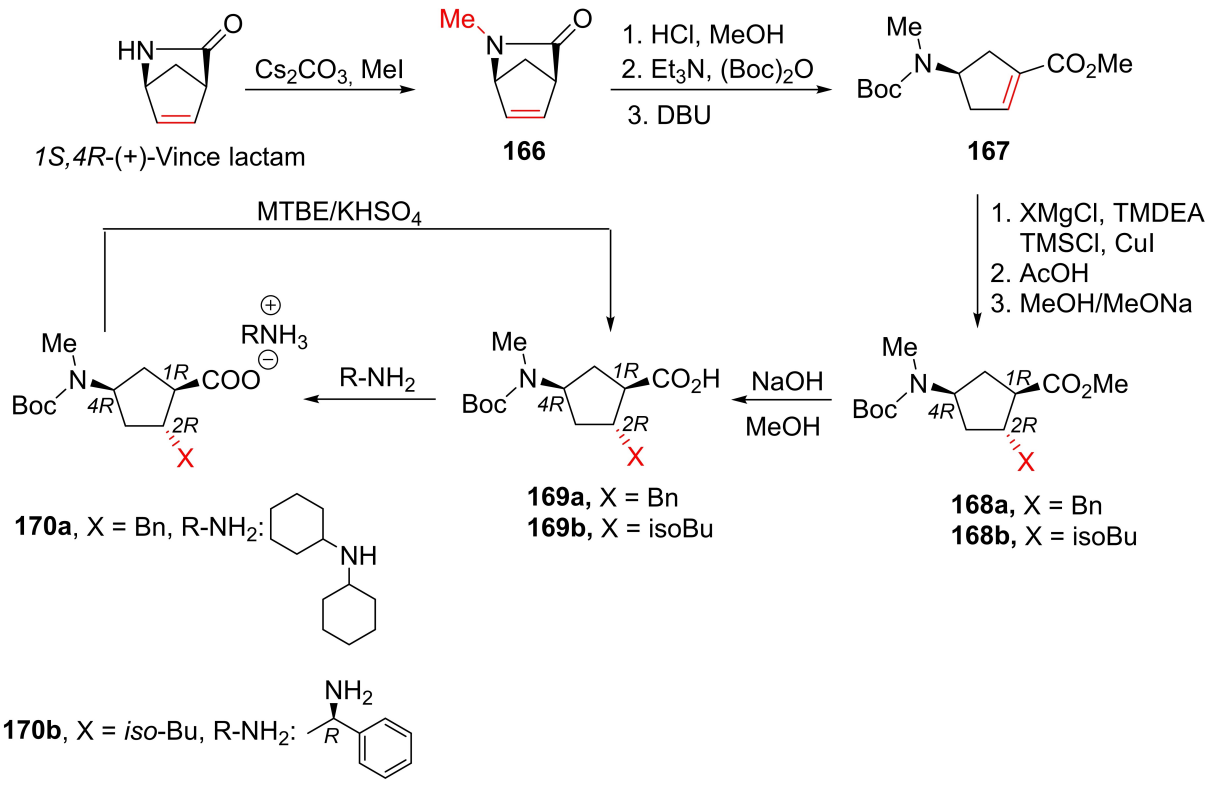


Scheme 43. One-pot reactions between Vince lactam and some arylboronic acids; simultaneous *N*-and *C*-arylations of Vince lactam.

Table 4. C- and N-Arylation of Vince lactam.

Entry	Ar	Yield (%) (ratio of **164:165**)
1	4-bromophenyl	40 (5a:6a 7:3)
2	2-bromophenyl	–
3	4-methoxyphenyl	36 (7:3)
4	2-methoxyphenyl	31 (7:3)
5	3-methoxyphenyl	45 (7:3)
6	6-chloropyridin-3-yl	–

168a as the main product. The other two products were the (*1S,2S,4R*) and (*1R,2S,4R*) isomers of **168a**. To obtain the thermodynamically stable *1R,2R,4R* product **168a**, the epimerization of the tentative *1S,2R,4R* isomer of **168a** was performed in MeOH by treating the crude mixture of **168a** in the presence of a catalytic amount of NaOMe. After several hours, the *1S,2R,4R* isomer was transformed to the desired *1R2R,4R* isomer in a ratio of 95:5. Crystallization of ester **168a** was unsuccessful. For the crystallization of carboxylic acid **169a** another possibility was chosen. Salt formation of



Scheme 44. Alkylation of Vince lactam.

compound **169a** with dicyclohexylamine (DCHA) in isopropyl acetate furnished the stereoisomerically pure salt **170a**, and an acidic extraction afforded the desired compound **169a** (Scheme 44).

A similar synthetic strategy was used for the preparation of compound **169b** with only a lower overall yield compared with the yield obtained for the analogous compound **169a**. The difference is mainly explained by the lower π-facial selectivity in the cuprate addition and a less efficient crystallization.[45]

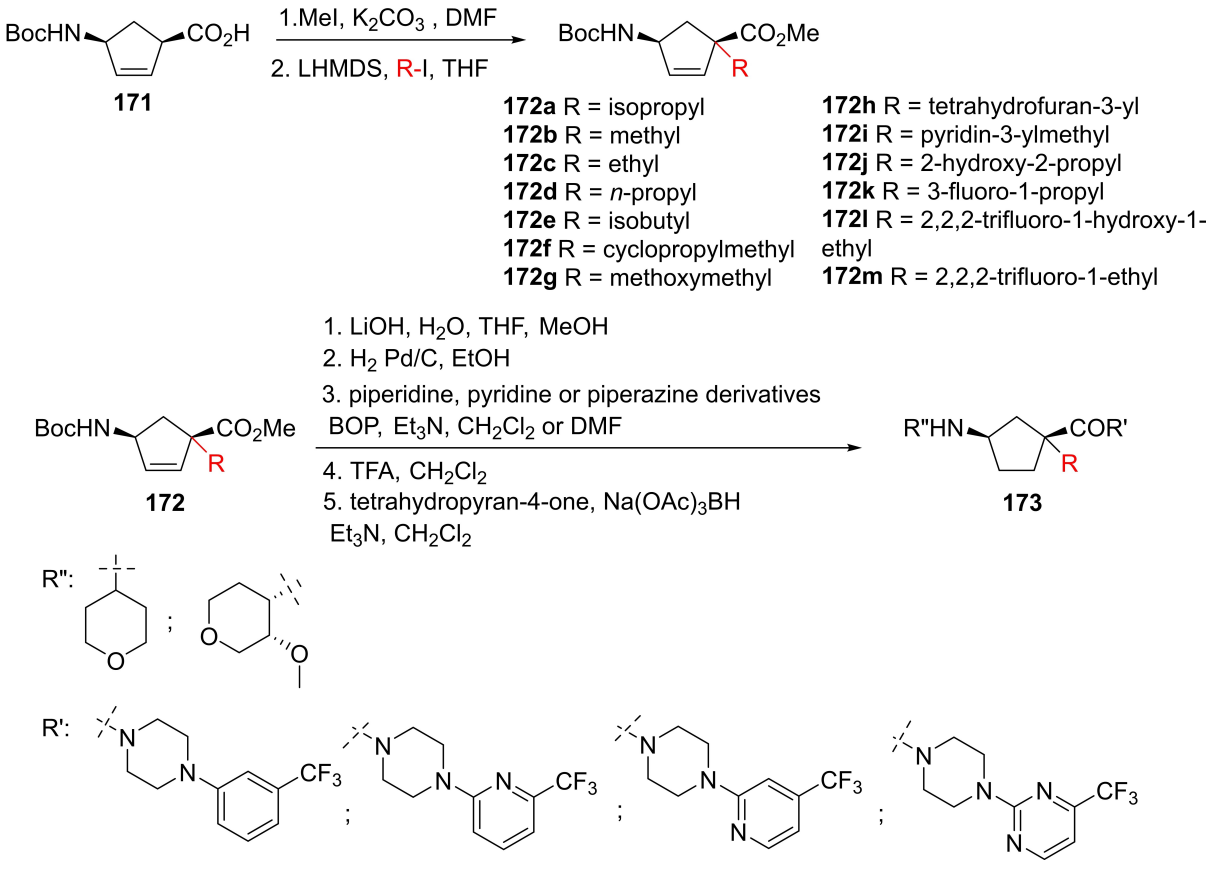
Zheng et al. described the synthesis and investigation of some selective C–C chemokine receptor type 2 antagonist CCR2. It is a member of the family of G-protein-coupled receptors (GPCRs), which contains in their structure a γ-aminocyclopentane carboxylate element.[46] Both the carboxylic and the amino groups of the cyclopentane γ-amino acid were functionalized, namely with substituted piperazines (carboxylic) and tetrahydropyran-2*H*-4-yl (amino) frameworks. First, enantiopure amino acid **171** was converted into the corresponding methyl ester, followed by alkylation with various iodoalkanes in the presence of lithium hexamethyldisilazide (LHMDS) affording compounds **172a–m**. The minor *trans* isomer was removed by crystallization and the *cis* compound was subjected to hydrogenation giving the corresponding cyclopentane amino acid. Next, the latter was coupled with a series of piperidine, piperazine, and tetrahydropyridine derivatives in the presence of (benzotriazol-1-yloxy)*tris*(dimethylamino)phosphonium hexafluorophosphate (BOP). Selected structures are shown on Scheme 45. Finally, after the removal of the Boc group, reductive amination with tetrahydropyran-4-one gave the desired compounds (**173**) (Scheme 45).[46]

2.9. Retroaldol-Aldol Reaction of Vince Lactam Derivatives

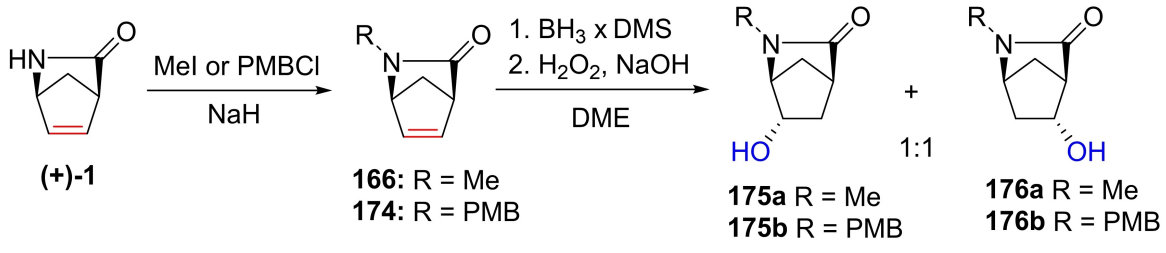
An unexpected retroaldol–aldol reaction of a hydroxylated Vince lactam was published by Brönalt and co-workers.[47] Starting from Vince lactam (+)-**1**, *N*-alkylated derivatives **166** and **174** have been prepared using MeI or *p*-methoxybenzyl chloride (PMBCl). Next, the hydroboration/oxidation reactions gave regioisomers **175** and **176** in a ratio of 1:1 (Scheme 46). The isomers were separated by column chromatography.

A temperature dependent equilibrium process was observed when compounds **175** and **176** were treated with a base (NaH) in THF at 0 °C (Scheme 47).

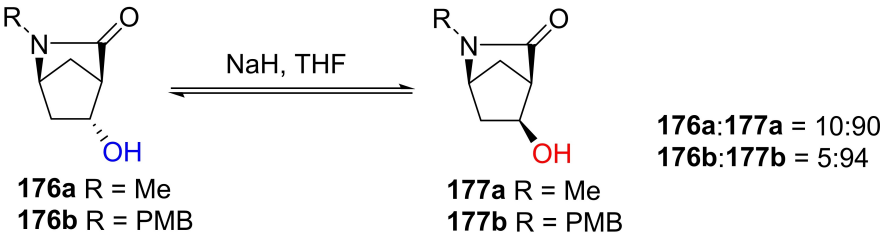
On the basis of this information, the research group investigated the retroaldol–aldol reaction. The concentration was found to have a minor effect on the outcome of the



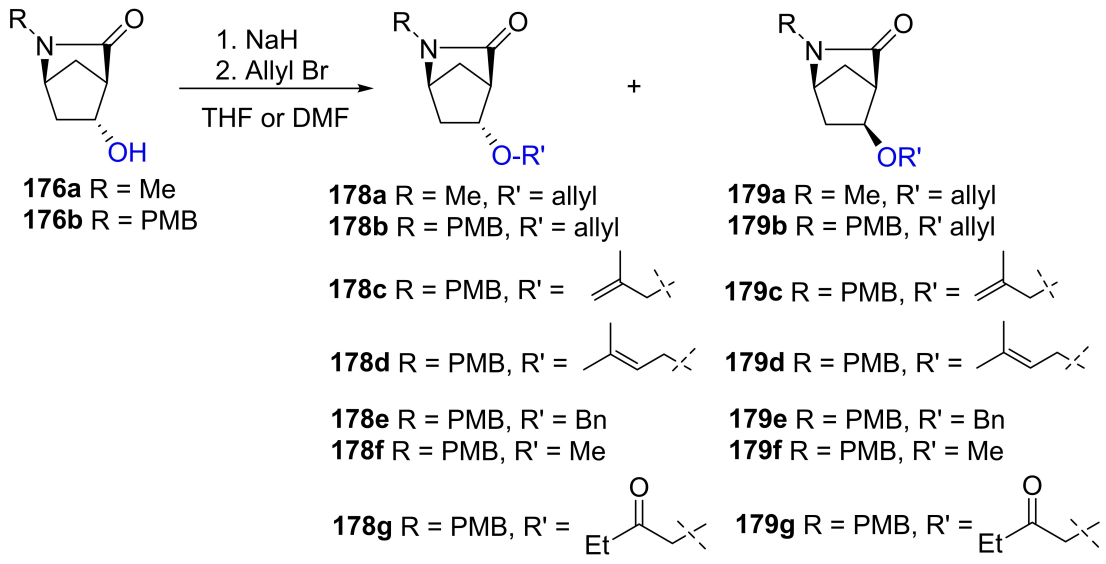
Scheme 45. Alkylation of cyclopentene γ-amino acid and functionalizations of the amino and carboxylic moieties.



Scheme 46. *N*-Alkylation and hydroboration of Vince lactam.



Scheme 47. Isomerization of hydroxylated Vince lactam.



Scheme 48. Alkylation reactions of compound **176**.

reaction. In contrast, they observed a strong solvent effect. Namely, *O*-alkylation in DMF was faster than retroaldol–aldol rearrangement giving only products with retention of configuration (**178**). In THF, in turn, *O*-alkylation was slower than rearrangement, giving products selectively with inversion of stereochemistry (**179**) (Scheme 48).

In DMSO, an irreversible retroaldol reaction of **176b** took place followed by a fast intramolecular proton transfer giving ring-opened aldehyde **180** (Scheme 49).[47]

3. Miscellaneous

In this section we give a brief overview about the syntheses and transformations of γ-aminocyclopentenecarboxylic acid and Vince lactam, other than ring olefin bond functionalization.

3.1. Synthesis of Conformationally Restricted GABA Analogs

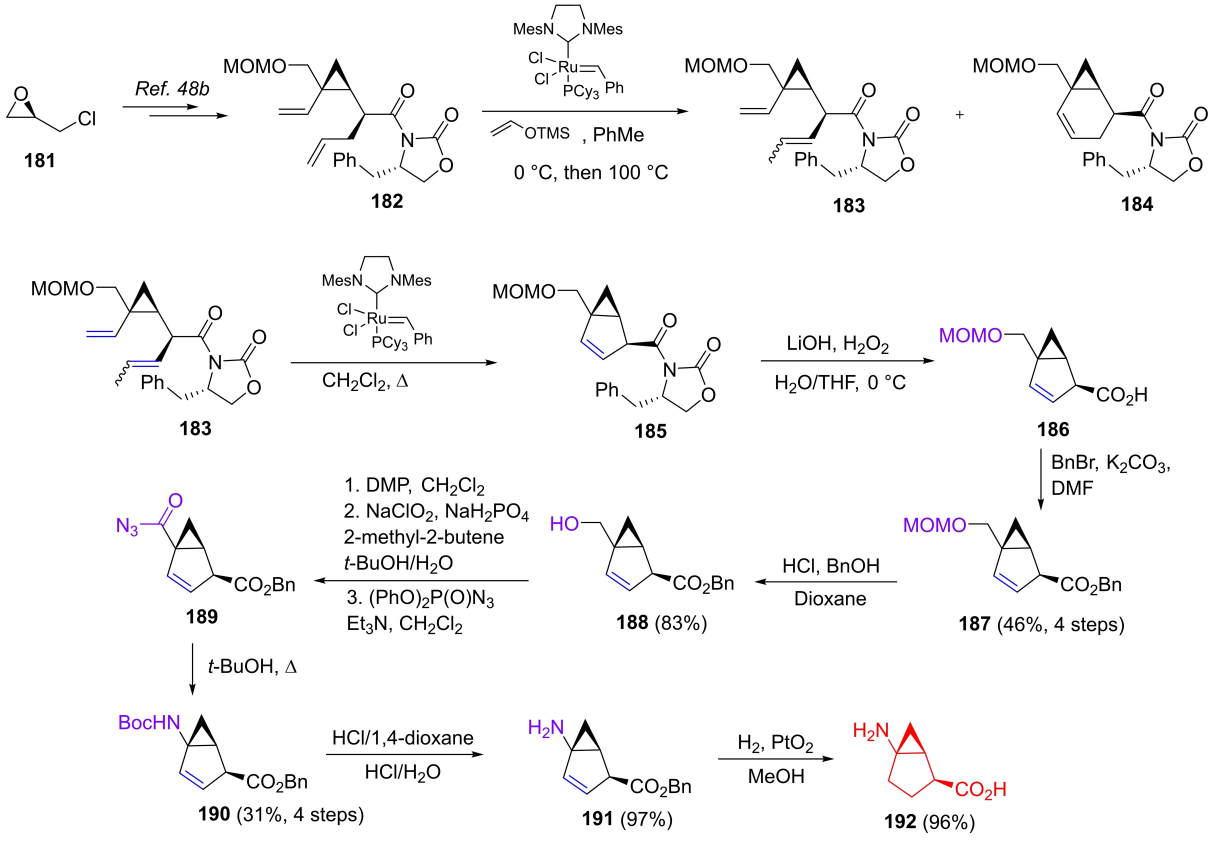
Some γ-amino acid derivatives as conformationally constrained five- and six-membered GABA analogs were recently synthesized by Shuto and co-workers.[48a] The key step of the procedure was the transformation of diolefinated compound **182** (derived from *R*-epichlorohydrin[48b]) with metathesis.

Scheme 49. Retroaldol reaction in DMSO.

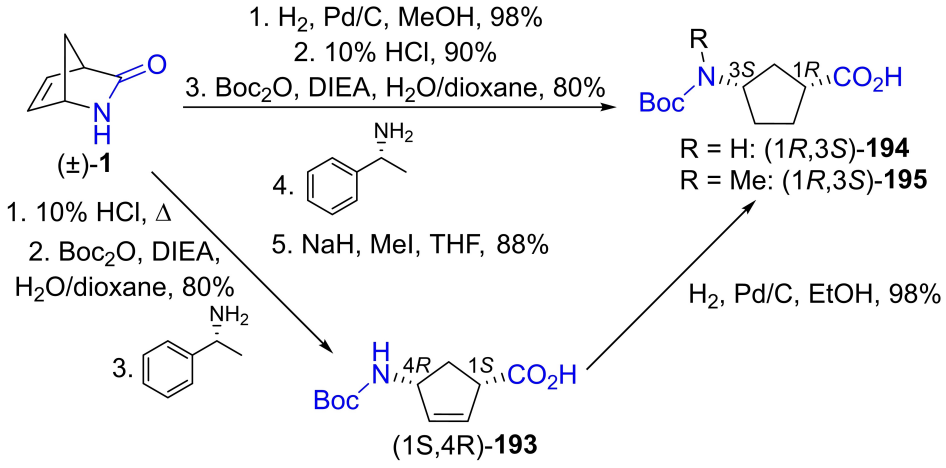
Thus, compound **182** in the presence of Grubbs 2nd generation catalyst was reacted with trimethylsilyl vinyl ether to form six-membered ring-closing metathesis (RCM) product **184** as well as **183** the isomerization product of the terminal olefin moiety. Next, compound **183**, when submitted to RCM, provided **185** containing the desired five-membered ring. Oxazolidinone removal followed by carboxyl group protection across benzylation furnished **187**, which, after hydroxy group deprotection, oxidation, and Curtius rearrangement, resulted in amino ester **190**. Finally, removal of the amino and carboxylic protective groups afforded the desired target molecule **192** (Scheme 50).[48a]

Functionalization of the amino group allowed the access to some novel GABA analogs. Granja and co-authors transformed racemic Vince lactam on treatment with enantiopure α-methylbenzylamine to optically active γ-amino acid **193**, which after *N*-methylation led to amino acid **195**. An alternative route to **195** consisted of olefin bond saturation, lactam ring opening, *N*-Boc protection, resolution, and *N*-methylation with MeI (Scheme 51).[14]

Other novel conformationally constrained GABA analogs with the location of the ring olefin bond between C1-C2 were prepared by Allan's group.[49] The key step of the transformations was the DBU-mediated olefin bond isomerization, across its active hydrogen atom at C1 of amino ester **116** into product **196**, which was readily converted by common



Scheme 50. Synthesis of conformationally restricted GABA analogues.

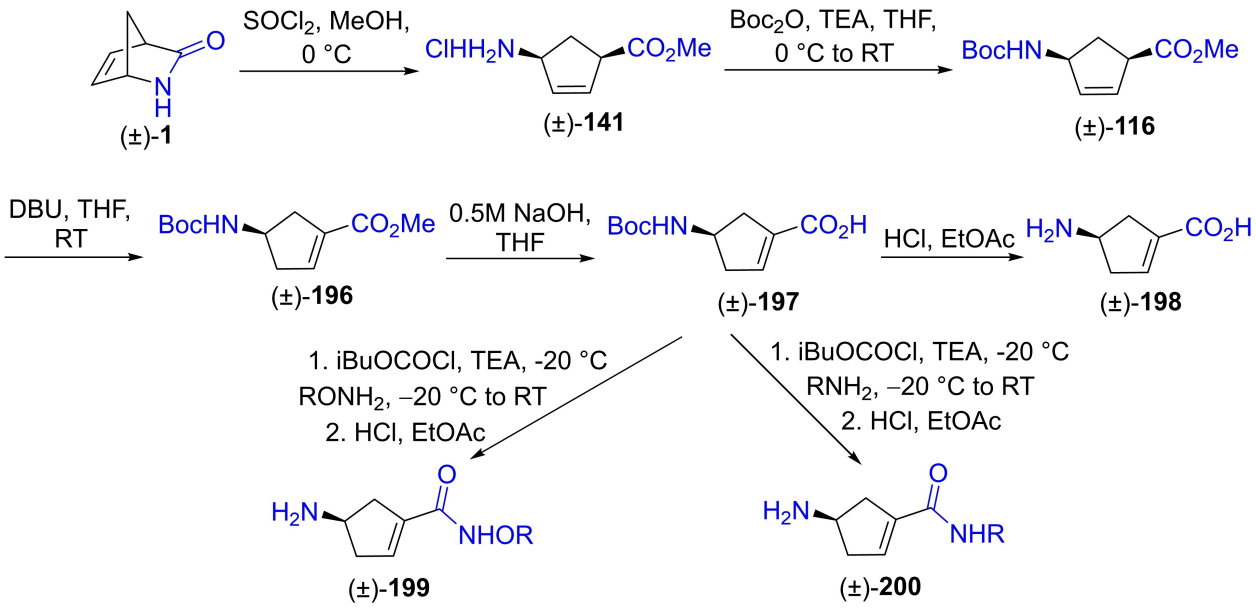


Scheme 51. Synthesis of enantiomerically pure γ-aminocyclopentanecarboxylic acids.

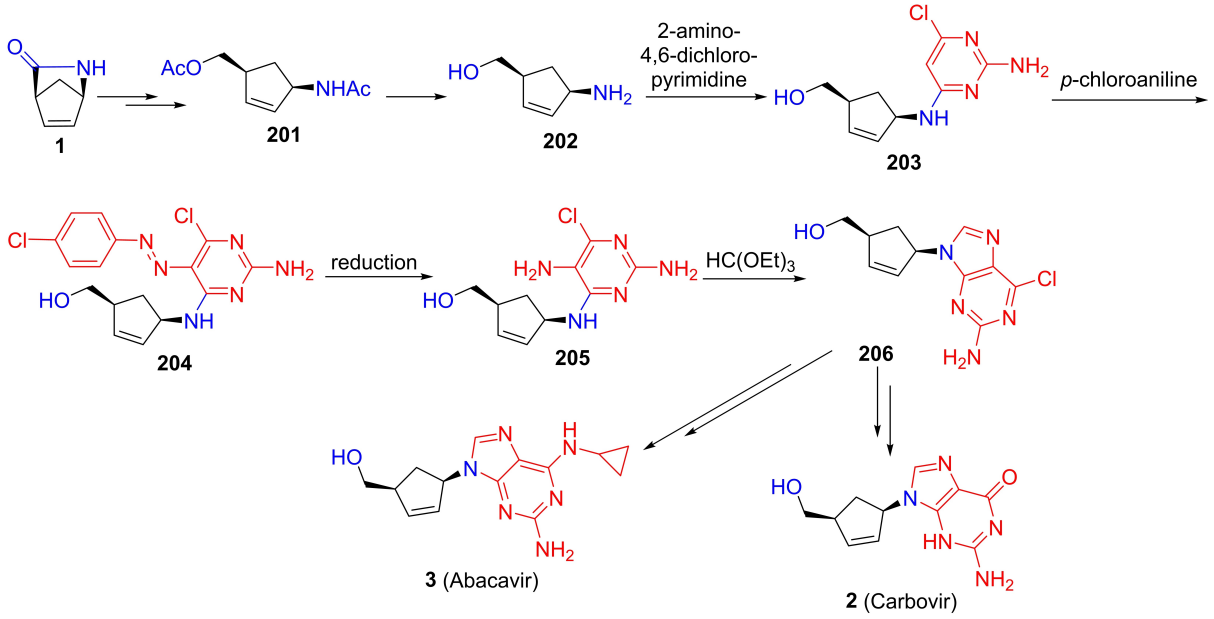
procedures into its amino acid, amide, and carbamate derivatives (**198**–**200**) (Scheme 52).[49]

3.2. Transformation of Vince Lactam into Carbanucleoside Analogs

Vince lactam is a precursor to the synthesis of carbocyclic nucleosides. Scheme 53 describes the schematic synthesis of



Scheme 52. Synthesis of 4-aminocyclopent-1-enecarboxylic acid, amides and hydroxamates.



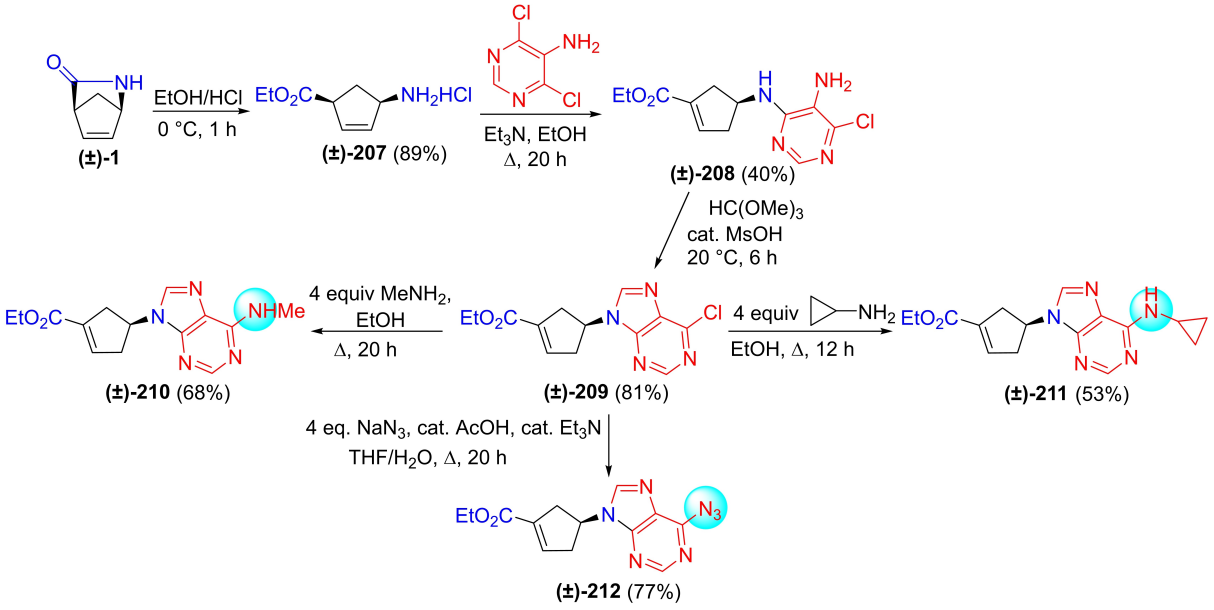
Scheme 53. Synthesis of the antiviral agents Abacavir and Carbovir.

synthetic blockbuster antiviral drugs Carbovir (**2**) and Abacavir (**3**). The key steps of the synthetic route were lactam ring opening, introduction of the pyrimidine ring, and construction of the purine skeleton.[1a]

A similar synthetic protocol allowed the preparation of some carbanucleoside analogs (**209**–**212**) with various substituents (azido, cyclopropylamino, methylamino) on the purine framework (Scheme 54).[50]

4. Conclusions and Outlook

The current review is intended to provide an insight into some synthetically useful applications of Vince lactam (2-



Scheme 54. Transformation of Vince lactam into some carbanucleoside analogs.

azabicyclo[2.2.1]hept-5-en-3-one) useful in organic and medicinal chemistry. Vince lactam, as an interesting small molecular scaffold with high chemical and structural diversity offers the opportunity to carry out versatile transformations to form a series of highly functionalized molecular elements. Moreover, this valuable molecule is utile for the synthesis of not only some conformationally rigid GABA analogs, but it serves as precursor for some antiviral drugs such as *Carbovir*, *Abacavir* or *Peramivir*. Taking into consideration the increasing importance to develop anti-influenza agents and other antiviral products, Vince lactam may function, either in its racemic or optically pure form, as a useful starting compound to access these types of products and other related derivatives with biological potential.

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