Stereoselective syntheses and application of limonene- and isopulegol-based bi- and trifunctional chiral ligands

PhD thesis

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[1] **Tam Le Minh**, Ferenc Fülöp, Zsolt Szakonyi
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[2] **Tam Minh Le**, Antal Csampai, Ferenc Fülöp, Zsolt Szakonyi
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[4] Tímea Orosz, Attila Bajtai, **Tam Minh Le**, Dániel Tanács, Zsolt Szakonyi, Ferenc Fülöp**,** Antal Péter, István Ilisz

Chiral high-performance liquid and supercritical fluid chromatographic enantioseparations of limonene-based bicyclic amino alcohols and aminodiols on polysaccharide-based chiral stationary phases

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Scientific lectures

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XXXVIII. Kémiai Előadói Napok
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Synthesis and transformation of isopulegol-based chiral trifunctional synthons
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(+)-Neoizopulegol alapú királis szintonok szintézise és alkalmazása
MTA Szteroid- és Terpenoidkémiai Munkabizottság,
Szeged, November, 2018, oral presentation

List of abbreviation

Ac_2O: Acetic anhydride
AcOH: Acetic acid
Ar: Aryl
Bn: Benzyl
Boc: *tert*-Butoxycarbonyl
BOP: Benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate
Cbz: Benzyloxycarbonyl
CNS: Central Nervous System
DBU: 1,8-Diazabicyclo[5.4.1]undec-7-ene
DCE: 1,2-Dichloroethane
DCM: Dichloromethane
DIPEA: Diisopropylethylamine
DMAP: 4-Dimethylaminopyridine
DMF: Dimethyl formamide
DPP-4: Dipeptidyl peptidase IV
Et_2O: Diethyl ether
EtOH: Ethanol
Et_2Zn: Diethylzinc
GC: Gas chromatography
i-PrOH: Isopropyl alcohol
LAH: Lithium aluminium hydride
mCPBA: *m*-Chloroperoxybenzoic acid
MeCN: Acetonitrile
MeOH: Methanol
MsCl: Methanesulfonyl chloride
n-BuLi: *n*-Butyllithium
NMO: *N*-Methylmorpholine *N*-oxide
NOESY: Nuclear Overhauser Effect SpecroscopY
PCC: Pyridinium chlorochromate

rt: Room temperature

t-BuOK: Potassium *tert*-butoxide

TFA: Trifluoroacetic acid

TFAA: Trifluoroacetic anhydride

THF: Tetrahydrofuran

TMEDA: Tetramethylethylenediamine

$VO(acac)_2$: Vanadyl acetylacetonate

1. Introduction and aims

Chiral synthons, applied successfully in asymmetric homogenous and heterogeneous catalysis, are of increasing importance in organic chemistry.[1–3] A large number of natural products such as *α*- and *β*-pinene,[4–6] 2- and 3-carene,[7,8] and (+)-pulegole[9,10] serve as important starting materials for the synthesis of bi- and trifunctional chiral compounds and heterocycles. The most frequently applied approach to optically active monoterpene derivatives is the transformation of the ring C–C double bond.[4,7,8,11] This general method provides an opportunity to access *β*-amino acid derivatives, such as *β*-aminolactones and *β*-aminoamides, as valuable precursors for 1,3-amino alcohols, aminodiols, and diamines.

Besides being important starting materials in the synthesis, *β*-aminolactones possess significant biological activities such as increasing the proportion of cells in the G2/M and S phase[12] and serving as water-soluble derivatives that might retain cytotoxicity through a prodrug mechanism.[13] In addition, ring opening of *β*-aminolactones with different amines may provide *β*-aminoamides, which are well-known subunits of biologically important compounds such as bestatin, a potent aminopeptidase B. Its usefulness in the treatment of cancer through its ability to enhance the cytotoxic activity of known antitumor agents is well-known.[14,15] *β*-Aminoamides exhibit other biological activities as well such as antidiabetic,[16] HIV-protease or renin inhibitor effect.[17] Besides interests in the synthesis of *β*-aminoamides, the opening of *β*-aminolactones with *β*–amino esters is a useful method for the synthesis of dipeptides containing *β*–alanine moiety. *β*–Alanine is a precursor of the antioxidant dipeptide carnosine (*β*–alanine-L–histidine), which is claimed to increase cell viability via an anti-senescence mechanism.[18] *β*–Ala-Gln has been applied in medical fields as a component of patient infusions.[19] Furthermore, *β*–alanine transporters were found to be highly upregulated in antibody-producing cell lines indicating the cell's requirement for this amino acid.[18]

Monoterpene-based 1,2- and 1,3-amino alcohols have been demonstrated to be excellent chiral auxiliaries in a wide range of stereoselective transformations including intramolecular radical cyclizations,[20] intramolecular [2+2] photocycloaddition,[21] and Grignard addition.[22,23] Besides their value in enantioselective catalysis, 1,2- and 1,3-amino alcohols are also excellent building blocks for the synthesis of various heterocyclic ring systems, such as 1,3-oxazines, 1,3-thiazines or 1,4-oxazepams.[24,25] 2-Imino-1,3-thiazines and 2-iminothiazolidines can be found as structural units in biologically relevant compounds, including antifungal and antimicrobial agents,[26] BACE1 inhibitors,[27] or cannabinoid receptor agonists.[28–30]

Moreover, aminodiols, combining the chemical properties of 1,2- and 1,3-amino alcohols derived from naturally occurring terpenes, are excellent starting materials and catalysts in stereoselective synthesis[31–36] and useful building blocks for the synthesis of 1,3-heterocycles such as 1,3-oxazines and oxazolidines. Depending upon the hydroxy group involved in ring closure with the amino group, five- and six-membered rings may be formed stereoselectively. The resulting bicyclic heterocycles bearing a free hydroxy group can contribute to high enantioselective inductions in asymmetric addition reactions.[37–40]

Besides their chemical interests, some natural aminodiols exhibit marked biological activity. For example, aristeromycin, first isolated from *Streptomyces citricolor* and its modified derivatives belong to an important group of carbocyclic nucleosides that exhibit a wide range of pharmacological properties such as antiviral, anticancer, and antitoxoplasma activities. Aristeromycin analogues, in particular, are widely used as antiviral agents against a range of viruses, including human immunodeficiency, hepatitis B, herpes simplex, varicella-zoster, influenza, and hepatitis C virus.[41–43] Other aminodiols may serve as starting materials for the synthesis of biologically active natural compounds. For example, cytoxazone, isolated from *Streptomyces* species, is a selective modulator of the secretion of T_H2 cytokine.[42,43]

In view of the advantages of monoterpenes, our aim was to synthesize monoterpene-based 2- and 3-functionalized building blocks such as β-amino acid derivatives and aminodiols, starting from commercially available enantiopure natural monoterpenes, such as (–)-limonene and (–)-isopulegol.

Futhermore, we also present the substituent-dependent ring closure of these monoterpene derivatives, such as aminodiols, with formaldehyde. Competitive ring-closure processes can provide both spirooxazolidine ring systems and condensed 1,3-oxazines. The results of experimental and theoretical studies of these synthons may expand our knowledge about these trifunctional building blocks in the design and construction of 3D small molecules. Aminodiols and their ring-closed derivatives will be applied as chiral catalysts in the enantioselective addition of Et_2Zn to benzaldehyde.

On the other hand, we also intended to study antiproliferative activity of β-amino acid derivatives, such as β-aminolactones and β-aminoamides on multiple cancer cell lines. Moreover, our goal was to report the synthesis of dipeptides, which might serve as promising chiral substrates for the preparation of foldamers.

2. Literature survey

2.1. Pharmacological importance of chiral aminodiols

Aminodiols have significant biological activity such as chloramphenicol, one of the earliest used antibiotics. Moreover, many molecules containing an aminodiol moiety have proved to be potential HIV protease inhibitors[44] and displayed renin-inhibitory activity.[45] In addition, aristeromycin,[46] a natural carbocyclic nucleoside, is known for its antibiotic and antitumor activities, while 1,2-deoxy azasugars from the fagomine family[47] and aminocarbosugars such as valiolamine and their analogues[48] represent important classes of glycosidase inhibitors (Figure 1). Besides interests in pharmacological activities, aminodiols can serves as starting materials for the preparation of biologically active compounds, such as Taxotere, a chemotherapeutic agent.[49]

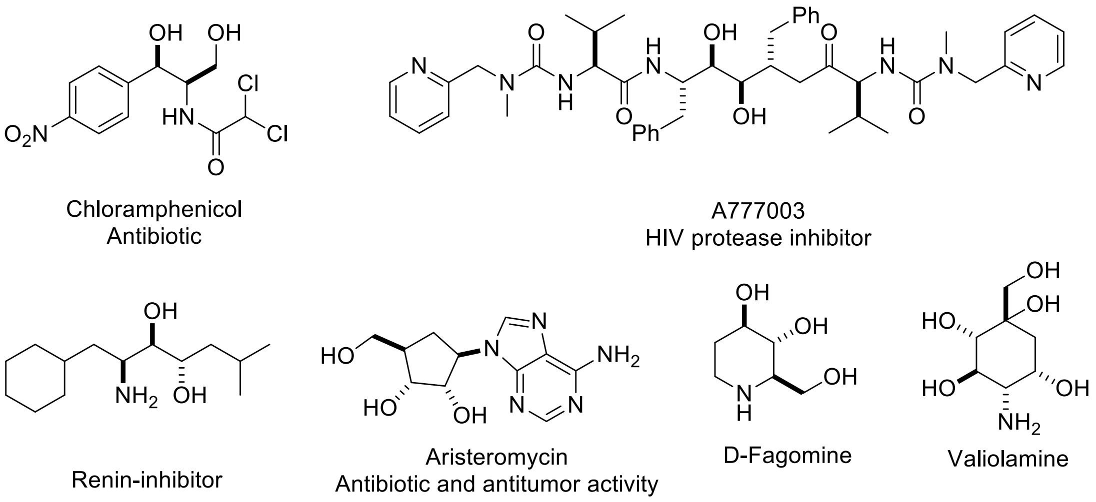
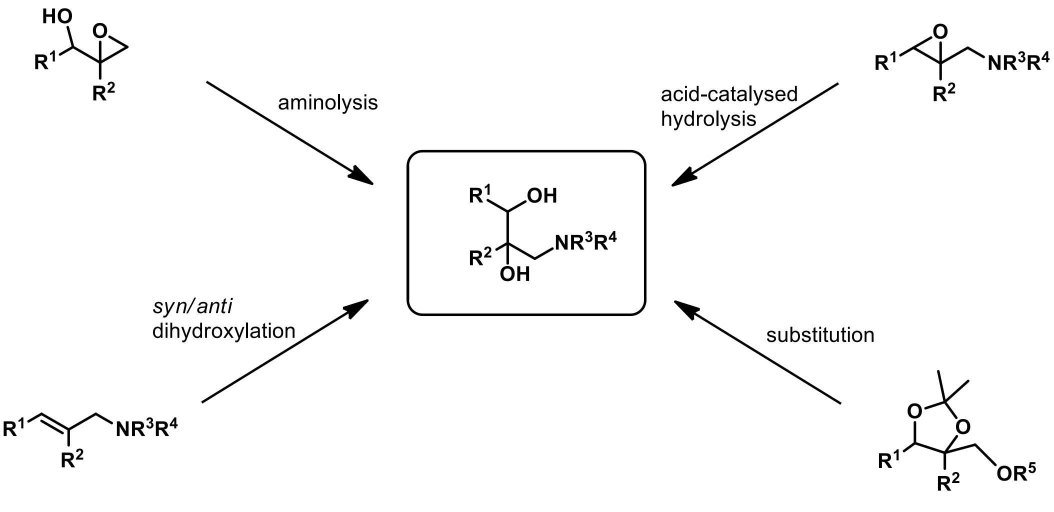


Figure 1. Phamalogical importance of aminodiols

2.2. Synthesis and application of aminodiols

Aminodiols can be prepared by various methods such as aminolysis of epoxyalcohols,[50] dihydroxylation of amino alkenes,[51] hydrolysis of epoxy amines,[52] and nucleophilic substitution of a good leaving group[53] (Scheme 1). For the asymmetric synthesis, Sharpless epoxidation of allylic alcohols, followed by ring opening with nitrogen nucleophiles (ammonia, amines, azides) is frequently applied for preparation of aminodiols.[54–62]



Scheme 1. Methods for preparation of aminodiols

Enantiomerically pure aminodiols and their derivatives are applied as chiral auxiliaries or catalysts in enantioselective transformations (Figure 2).

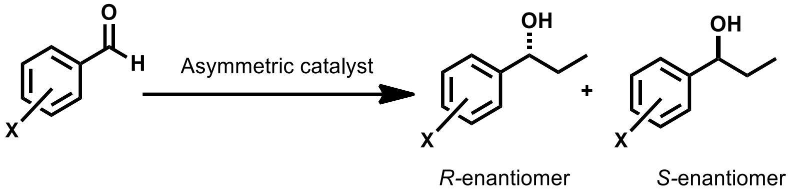
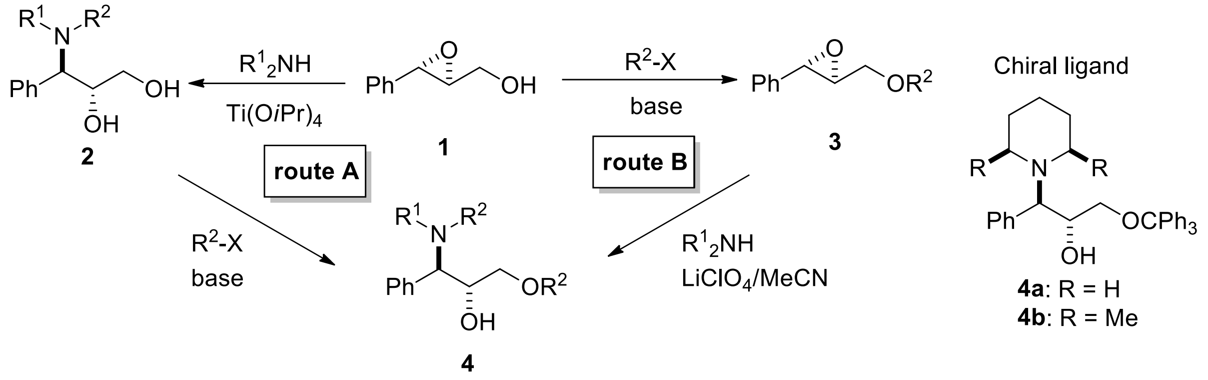


Figure 2. Model reaction for enantioselective catalysis

2.2.1. Synthesis of chiral aminodiols

A library of enantiomerically pure (1*R*,2*R*)-1-dialkylamino-1-phenyl-3-alkoxy-2-propanols **4** was prepared from non-natural chiral compound **1** by Vidal-Ferran *et. al.*[63,64] Aminodiols with general structure **4** were synthesized through two alternative synthetic routes from epoxycinnamyl alcohol **1** by Sharpless epoxidation (Scheme 2). In route *A*, epoxy alcohol **1** was first submitted to a regioselective ring opening by secondary amines, then the resulting amino diols **2** were protected by means of an appropriate R^2-X reagent. In route *B*, the primary hydroxy group in the starting epoxy alcohol **1** was initially protected, and the resulting epoxy ethers **3** were subjected to regioselective ring opening by different secondary amines. Derivatives of **4** were tested (6 mol% ligand) in the enantioselective addition of Et_2Zn to benzaldehyde (Figure 2). According to results, compound **4a** and its modified derivative **4b** afforded the best *ee* values (*ee* = 91% with **4a** and *ee* = 95% with **4b**) with (*S*)-1-phenyl-1-propanol selectivity.

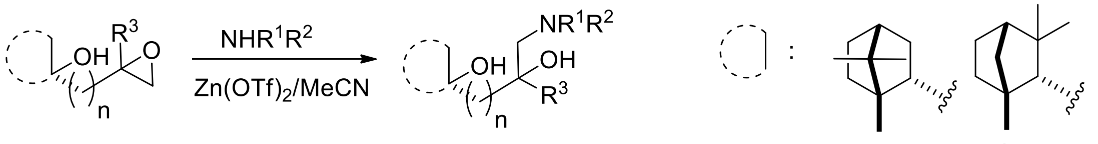


R^1 = -$(CH_2)_4$-; 1'-(*R*)-CH_2OMe-$(CH_2)_4$-; 1'-(*S*)-CH_2OMe-$(CH_2)_4$-; -$(CH_2)_5$-; -$(CH_2)_6$-; -$(CH_2)_2O(CH_2)_2$-; (*i*-Pr)$_2$; Bu$_2$
R^2 = H; CH_3; $PhCH_2$; $PhCH_2$; Ph_2CH; Ph_3C; $^tBuMe_2Si$; X = Cl, Br, I

Scheme 2. Preparation of 3-amino-1,2-diols

Following the breakthrough in asymmetric synthesis achieved by Noyori *et. al.,*[65] several chiral ligands derived from available optically active monoterpenes such as (+)- and (–)-α-pinene,[4,6,66] (+)-carene,[7,8,67,68] (–)-menthone,[69] (–)-fenchone,[70] (+)-sabinol,[71] (–)-nopinone[72] or (–)-pulegone[9,10] were applied in enantioselective transformations.

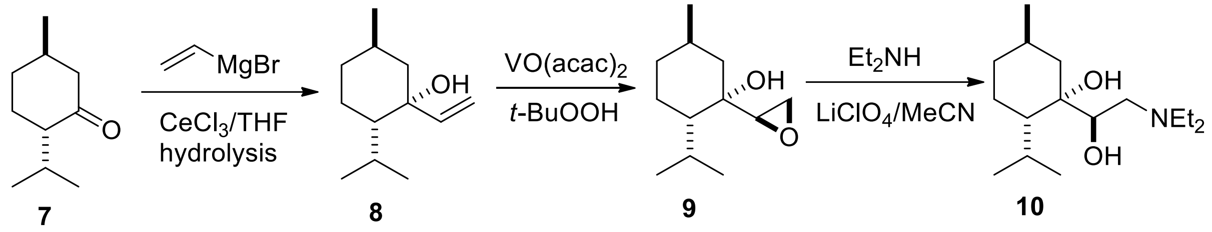
Philipova *et. al.* built an aminodiol moiety by the nucleophilic ring opening of epoxy alcohols derived from (+)-camphor and (–)-fenchone.[73] The aminolysis of epoxy alcohols **5** proceeded with excellent regioselectivity and retention of the configuration resulting in various aminodiols **6** (Scheme 3). The aminodiols (3 mol%) were applied as chiral catalyst in the addition of Et_2Zn and benzaldehyde (Figure 2). The best *ee* value (*ee* = 80%) was achieved by camphor derivative chiral ligand **6a** (n = 0, $R^1 = R^2$ = Et, R^3 = H) with (*S*)-selectivity.



n = 0, 1; $R^1 = R^2$ = Et; R^3 = H, Me: (*R*) or (*S*)

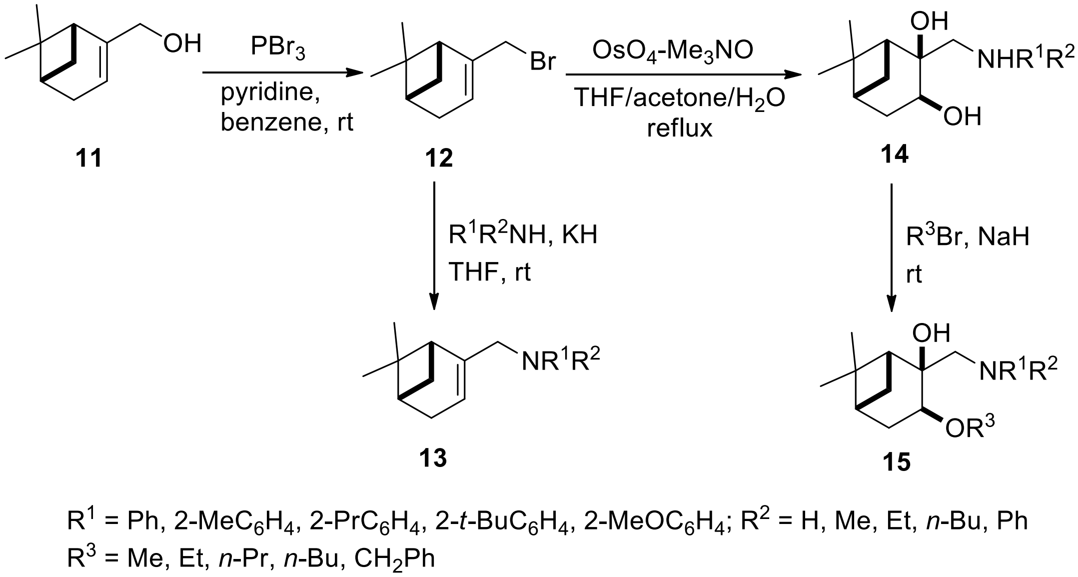
Scheme 3. Preparation of (–)-fenchone-based chiral aminodiols

Optically active aminodiols and amino alcohols based on (–)-menthone were synthesized by Dimitrov *et. al.*[69] As an example, the preparation of aminodiol **10** is illustrated in Scheme 4. Allylic alcohol **8** was obtained as a single diastereomer by the addition of vinyl Grignard reagent to **7**. Aminodiol **10** was achieved by the epoxidation of **8** with *t*-BuOOH and VO(acac)$_2$ as catalyst resulting in **9** with good diastereoselectivity (*de* = 98%), followed by ring opening with secondary amine in the presence of $LiClO_4$. When aminodiol **10** (3 mol%) was applied in the addition of Et_2Zn to benzaldehyde (Figure 2), only a moderate *ee* was observed (*ee* = 40%) with (*S*)-selectivity.



Scheme 4. Preparation of (–)-menthone-based chiral aminodiols

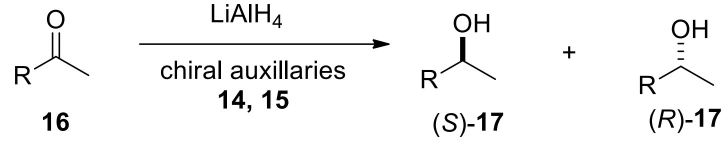
Lu and co-workers found that pinane-type tridentate chiral ligands were excellent catalysts in enantioselective reactions.[31,32] Pinane-based chiral *N*-arylaminodiols, derived from (1*R*)-myrtenol **11**, were prepared by the reaction of **11** with PBr_3, followed by substitution of the bromo function of **12** with different amines to afford allylic amines **13**. The products were converted to aniline-type aminodiols (**14** and **15**) by stereoselective dihydroxylation of the alkene function with the OsO_4-Me_3NO system (Scheme 5).



Scheme 5. Pinane-based chiral aminodiols

Aminodiols **14** and **15** (2 mol%) were also applied as chiral auxiliaries in the asymmetric reduction of various ketones and in the asymmetric alkylation of aldehydes with Et_2Zn. The results showed that the reduction of ketones was best promoted by ligands **14** with (*R*)-**17**

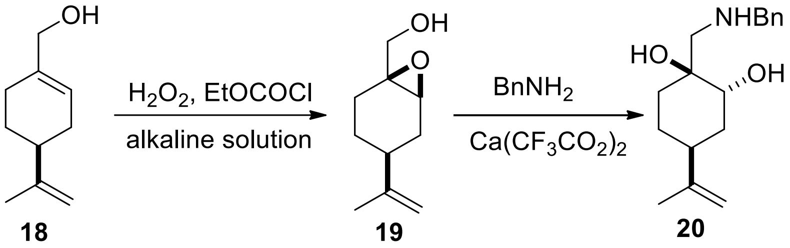
(Scheme 6), while derivatives **15** containing an alkoxy substituent at C-3 exhibited better catalytic activity in the addition of Et_2Zn to aldehydes with (*S*) selectivity.



R = Ph, 2-MeC_6H_4, 2-BrC_6H_4, 2-ClC_6H_4, 2-$MeOC_6H_4$, 2-$NO_2C_6H_4$, 2,4-$(MeO)_2C_6H_3$, 2,5-$(MeO)_2C_6H_3$, 1-naphthyl, 2-furyl, 2-thienyl, PhCH=CH, 1-cyclohexenyl

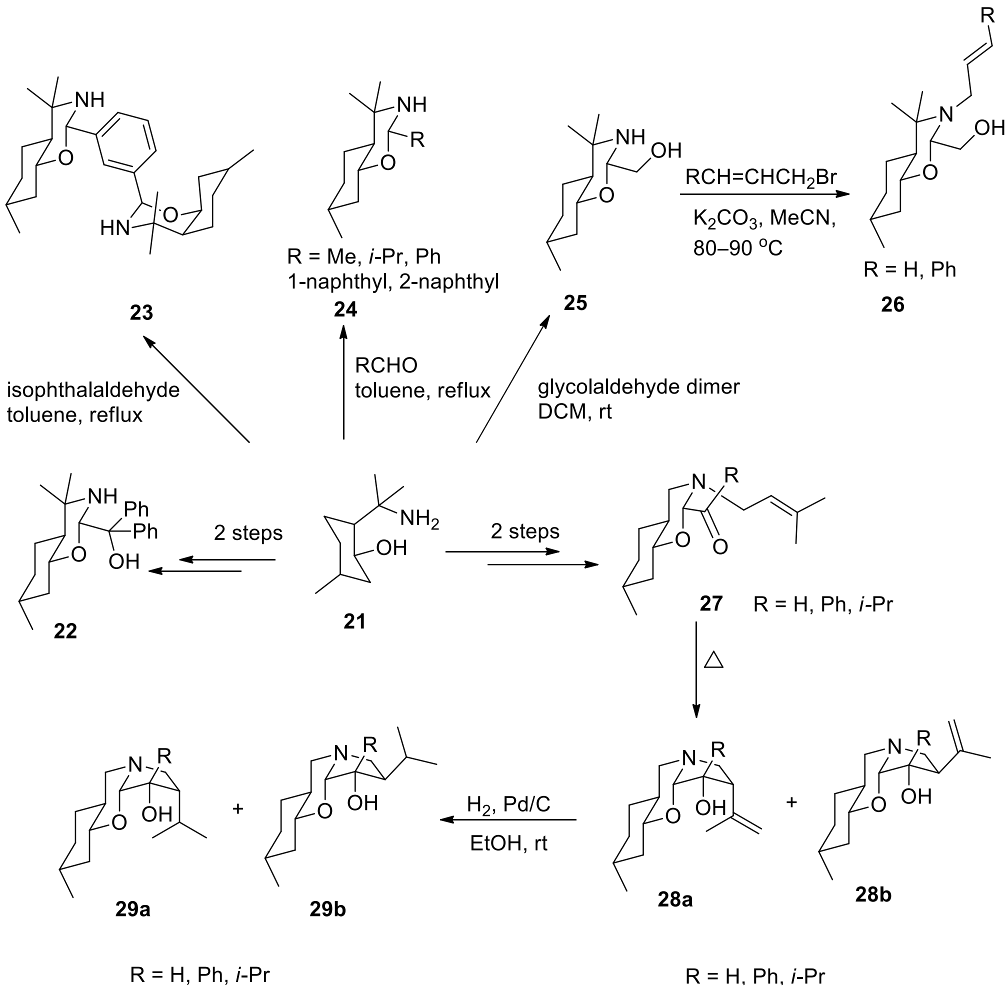
Scheme 6. Model reaction of asymmetric reduction of ketones

Moreover, aminodiol **20** was prepared from (*S*)-perillyl alcohol by Outouch *et. al.*[74] Chiral aminodiol **20** was synthesized by epoxidation of (*S*)-perillyl alcohol **18** followed by oxirane ring opening by benzylamine using [$Ca(CF_3COO)_2$] as catalyst under solvent-free conditions (Scheme 7).



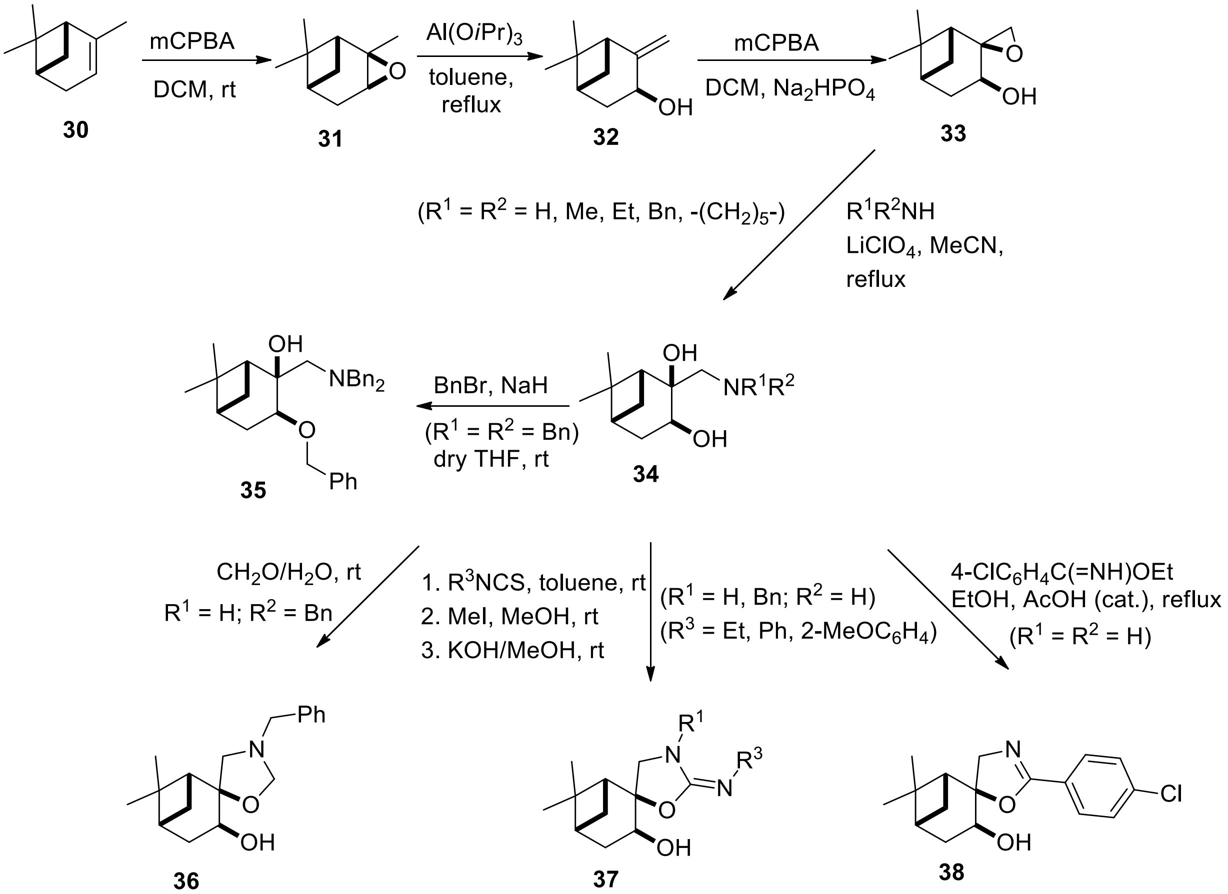
Scheme 7. Chiral aminodiols based on (*S*)-perillyl alcohol

Besides the synthetic importance, aminodiols are valuable precursors for the preparation of cycloalkane-fused five- and six-membered heterocycles. Both oxazolidines[75,76] and 1,3-oxazines[35,77–79] are widely used chiral catalysts in enantioselective synthesis. Based on literature data, Andres and co-workers examined the catalytic effect of 1,3-oxazines prepared from (–)-8-aminomenthol (**21**).[80] Structural diversity was obtained through relatively simple reaction steps (Scheme 8). Then condensation of **21** with different aldehydes provided chiral perhydro-1,3-benzoxazines **22**–**25** as single diastereomers in excellent yields. *N*-Substituted ligands **26**, obtained by alkylation of **25** with allyl and cinnamyl bromides, resulted in improvement in the enantioselectivity of the reaction. Ligands **27** were prepared by the condensation of **21** with phenylglyoxal, followed by *N*-alkylation of the intermediates with prenyl bromide. The cyclization reaction of ketones **27** gave a mixture of two *cis*-3-hydroxy-3,4-disubstituted pyrrolidines (**28a** and **28b**) fused with a perhydro-1,3-benzoxazine structure. Both diastereomers could be obtained as major products depending on the reaction conditions. In order to increase the steric volume in the vicinity of the hydroxyl group, catalytic hydrogenation of the prenyl group to an isopropyl group resulted in **29**. Examination of the catalytic potency, followed by optimization of chiral ligands **22**–**29** (10 mol%), was performed in the reaction of Et_2Zn and 2-naphthaldehyde (Figure 2). Ligand **29b** (R = Ph) improved the ethylation of 2-naphthaldehyde (*ee* = 97%) with (*R*)-selectivity. This ligand also proved to be efficient catalyst in the addition of Me_2Zn to various aldehydes,[81] while ligand **28b** (R = *i*-Pr) was the most efficient catalyst in the asymmetric methylation of α-ketoesters with *ee* = 96%.[82] The studies revealed the importance of the oxazine ring moiety of the ligands to improve enantioselectivity.



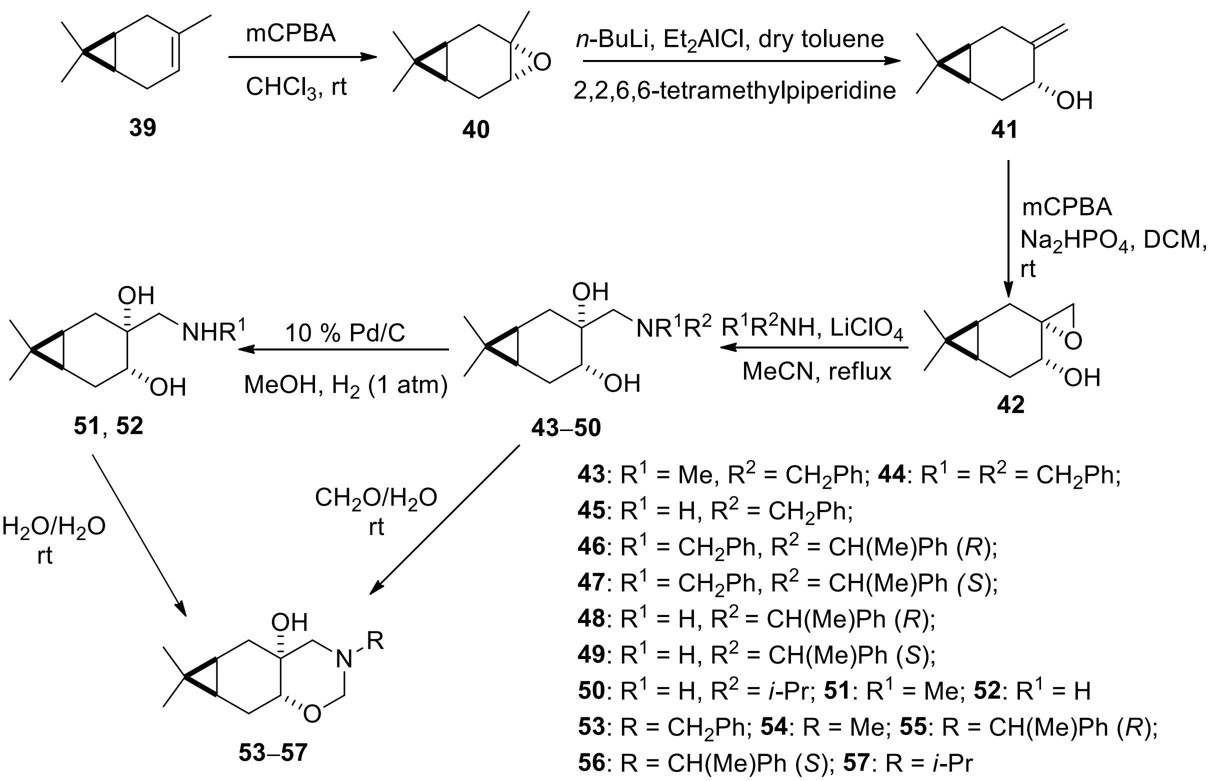
Scheme 8. Chiral perhydro-1,3-benzoxazin derivatives from (–)-8-aminomenthol

Other pinane-based derivatives, derived from (–)-α-pinene, were also prepared.[83] The transformation of **30** to key intermediate epoxy alcohol **33** was accomplished via stereospecific epoxidation and rearrangement followed by stereospecific oxirane ring formation. The aminolysis of **33** led to pinane-based aminodiols **34** when various secondary amines were applied in the presence of $LiClO_4$ as catalyst. The structural diversity of aminodiols **34** offered an opportunity to examine the influence of the *N*-substituents on the enantioselectivity in the reaction of Et_2Zn to benzaldehyde (Figure 2). Increasing enantioselectivity was observed in the sequence NH_2<NHR<NR^1R^2. *O*-Benzyl derivative **35** was applied by regioselective alkylation with benzyl bromide. In order to study the tendency of aminodiols **34** to furnish either spirooxazolidine or 1,3-oxazine, derivatives **36**–**38** were prepared. In each case, formation of the spirooxazolidine derivatives was preferred. (Scheme 9).



Scheme 9. Pinane-based derivatives from (–)-α-pinene

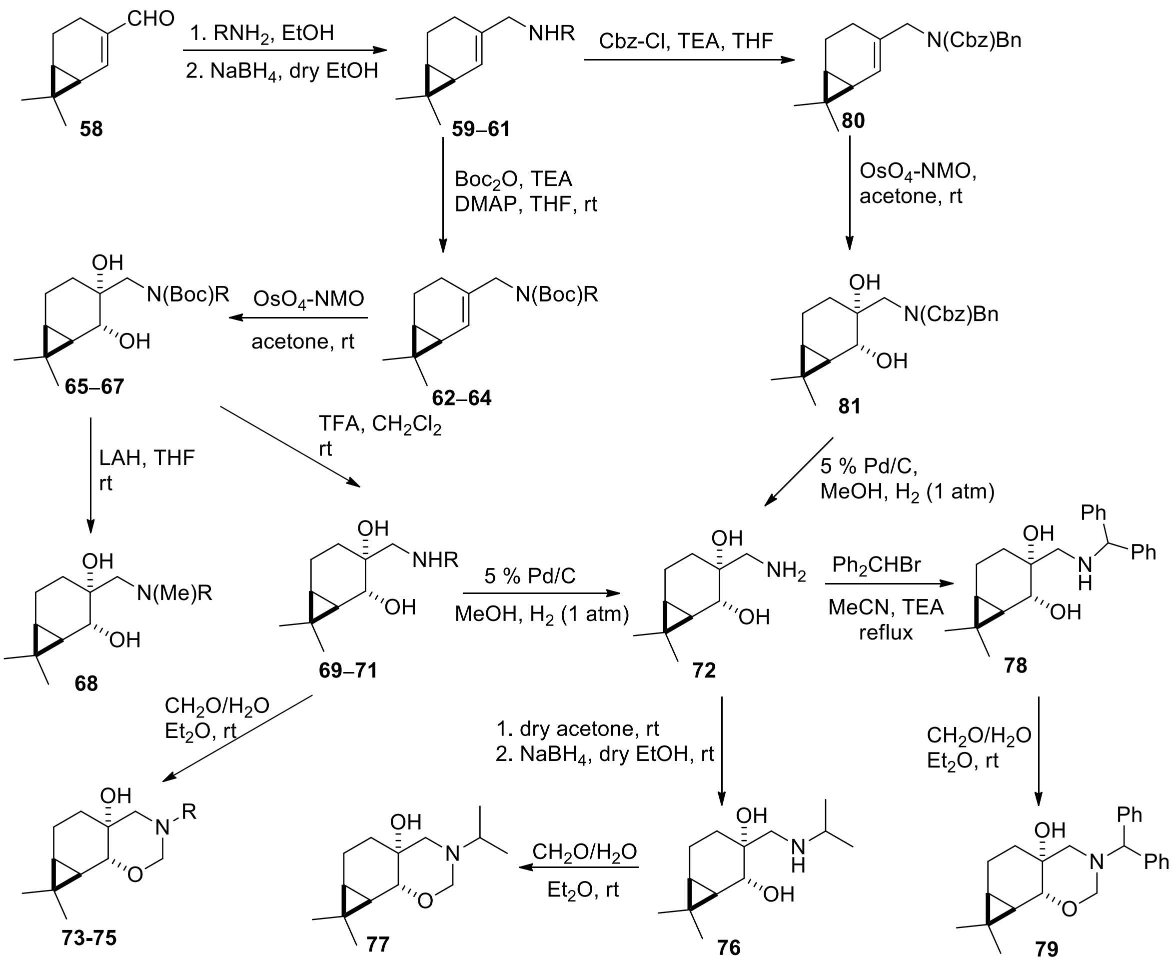
Furthermore, natural monoterpene-based aminodiols, derived from (+)-carene, could be prepared.[7] Epoxidation of **39** with *m*CPBA furnished epoxide **40**, which underwent rearrangement to allyl alcohol **41**. Epoxidation of allylic alcohol **41** with *m*CPBA resulted in epoxy alcohol **42**. Aminodiol library **43**–**50** was prepared by aminolysis of **42** with secondary and primary amines with $LiClO_4$ as catalyst. *N*-Methyl derivative **51** and primary aminodiol **52** were synthesized by debenzylation of **43** and **44** (Scheme 10). Aminodiol derivatives **43**–**52** were used as chiral catalysts in the enantioselective addition of diethylzinc to benzaldehyde (Figure 2). The best, but still moderate, result was obtained with *N*-(*S*)-1-phenylethyl-substituted aminodiol **49**. Aminodiols **45** and **48**–**51** were reacted with CH_2O furnishing 1,3-oxazines **53**–**57** obtained in highly regioselective ring closures. When oxazines **53**–**57** were applied as catalysts in the addition of diethylzinc, the best result (*ee* = 96%) was obtained with the use of *N*-(*R*)-1-phenylethyl-substituted 1,3-oxazine **55**.



43: R^1 = Me, R^2 = CH_2Ph; **44**: R^1 = R^2 = CH_2Ph;
45: R^1 = H, R^2 = CH_2Ph;
46: R^1 = CH_2Ph, R^2 = CH(Me)Ph (*R*);
47: R^1 = CH_2Ph, R^2 = CH(Me)Ph (*S*);
48: R^1 = H, R^2 = CH(Me)Ph (*R*);
49: R^1 = H, R^2 = CH(Me)Ph (*S*);
50: R^1 = H, R^2 = *i*-Pr; **51**: R^1 = Me; **52**: R^1 = H
53: R = CH_2Ph; **54**: R = Me; **55**: R = CH(Me)Ph (*R*);
56: R = CH(Me)Ph (*S*); **57**: R = *i*-Pr

Scheme 10. Preparation of aminodiols from (+)-3-carene

Another synthetic route leading to aminodiols based on carene is presented in Scheme 11.[8] Reductive amination of **58** with various primary amines followed by Boc protection gave protected allylic amines **62**–**64**. Dihydroxylation with OsO_4-NMO system furnished compounds **65**–**67**. The effect of the protecting group on the stereoselectivity of dihydroxylation was examined by applying the Cbz group to **80**. The synthesis of **81** proceeded similarly with excellent stereoselectivity. LAH-mediated reduction of **65** led to **68**. Deprotection of **65**–**67** with TFA resulted in the formation of *N*-benzyl aminodiols **69**–**71**. Primary aminodiol **72** was obtained by catalytic debenzylation of **69**–**71** or Cbz-protected **81**. When aminodiols **69**–**71** were reacted with CH_2O, 1,3-oxazines **73**–**75** were obtained. Aminodiol derivatives **68**–**79** were applied as chiral catalysts in the enantioselective addition of diethylzinc to benzaldehyde (Figure 2). Based on experimental results and DFT modelling, *N*-isopropyl- and *N*-benzhydryl-substituted 1,3-oxazines **77** and **79** were also prepared and provided high enantiomeric excess values (*ee* = 95% for compound **79** and 98% for compound **77** with *S*-selectivity) in the model reactions. It is interesting to mention that both aminodiols and 1,3-oxazines proved to be excellent catalysts in the additions of diethylzinc to either aromatic or aliphatic aldehydes with opposite stereoselectivity.

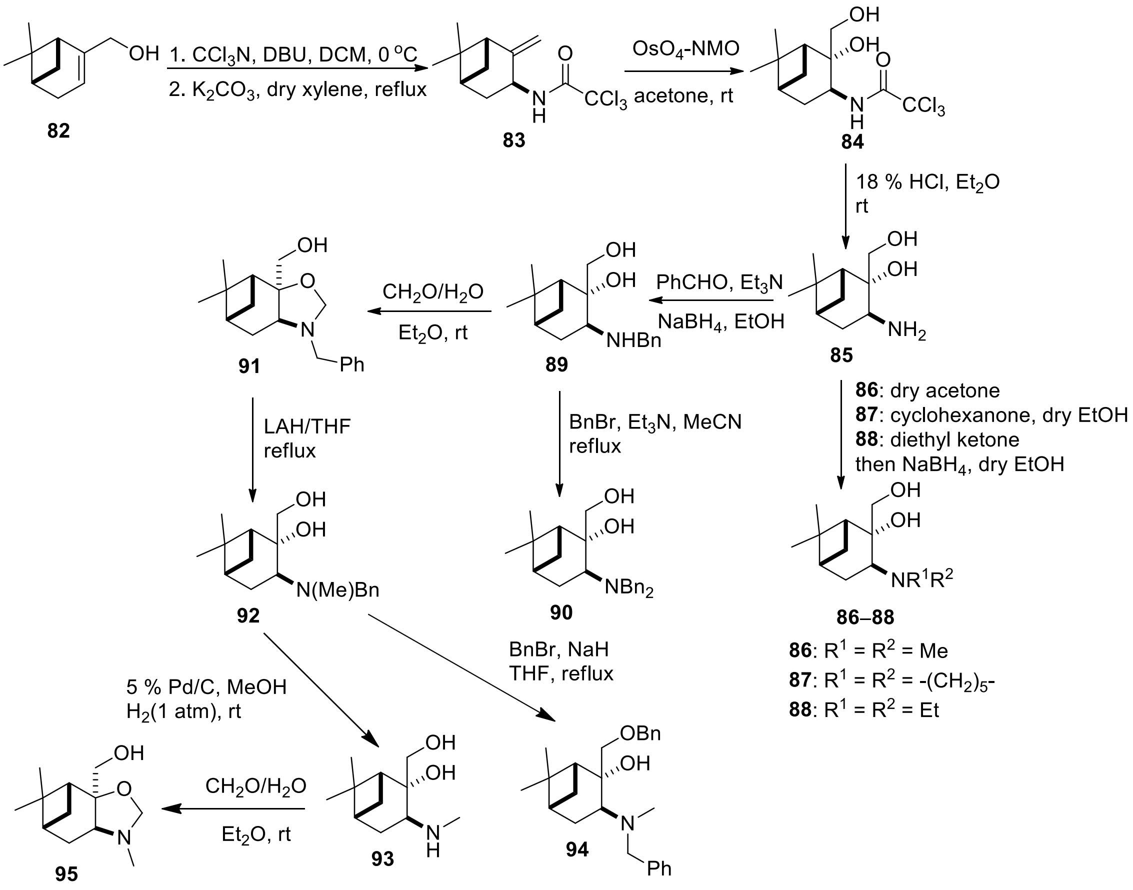


59, **62, 65, 69, 73**: R = Bn; **60**, **63, 66, 70, 74**: R = CH(Me)Ph(*R*); **61**, **64**, **67, 71, 75**: R = CH(Me)Ph(*S*)

Scheme 11. Synthesis of carene-based aminodiols

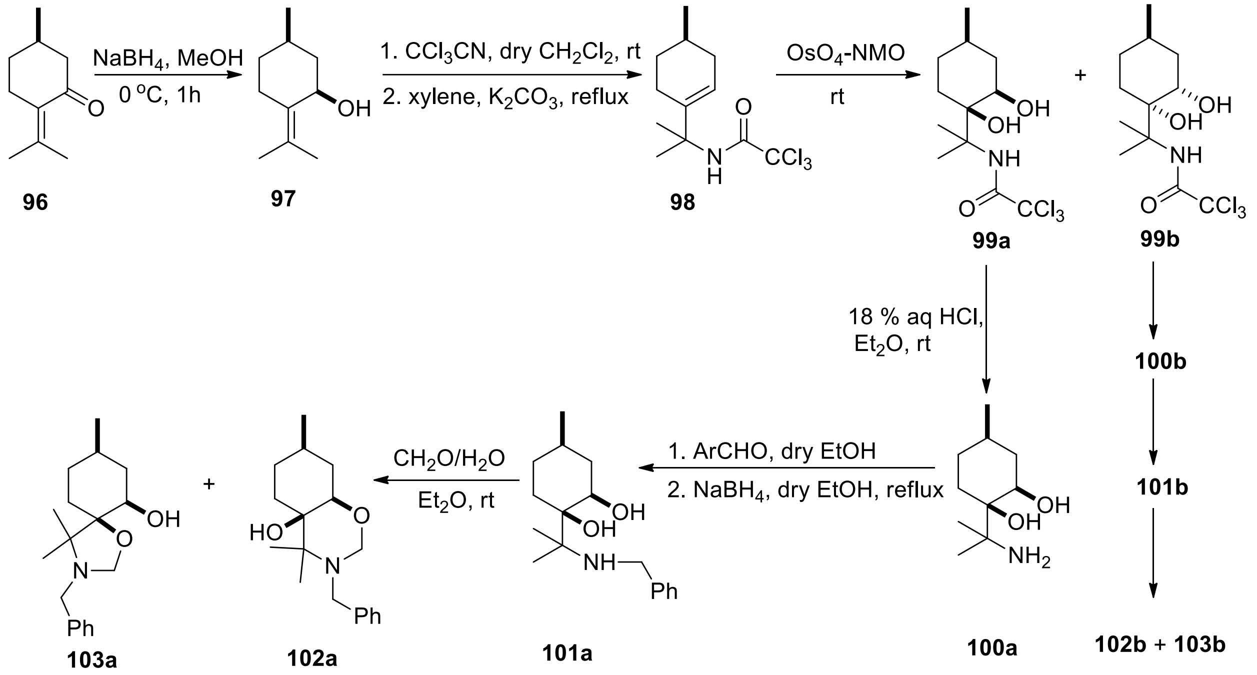
Transformation of (1*R*)-(–)-myrtenol to aminodiols was also reported (Scheme 12).[68] (1*R*)-Myrtenol **82** was transformed into **83** via Overman rearrangement. Dihydroxylation of **83** with

OsO_4-NMO resulted in aminodiol derivative **84**. Primary aminodiol **85** was transformed into secondary derivatives **86**–**88** by reductive amination followed by reduction with $NaBH_4$. A bulky group was conveniently introduced into the amino moiety by the reaction of **85** with benzaldehyde in the presence of Et_3N and $NaBH_4$. In order to increase the steric hindrance on the nitrogen, an additional benzyl group was introduced by the *N*-benzylation of **89** using benzyl bromide in MeCN in the presence of Et_3N. When compound **89** was stirred with aqueous formaldehyde, product **91** with a condensed oxazolidine ring was isolated. The transformation of **91** into *N*-methyl-*N*-benzyl aminodiol **92** was accomplished with $LiAlH_4$ in a treatment at reflux temperature. Debenzylation of **92** gave *N*-methyl aminodiol **93**. The ring closure of **93** displayed the same regioselectivity furnishing oxazolidine **95**. Aminodiols and their ring-closed derivatives **85**–**95** were applied as chiral ligands in the addition of Et_2Zn to benzaldehyde (Figure 2). The best *ee* value (61%) with (*R*)-selectivity was obtained when *N*-benzyl derivative **89** was applied.



Scheme 12. Chiral pinane-based aminodiols from (1*R*)-(–)-myrtenol

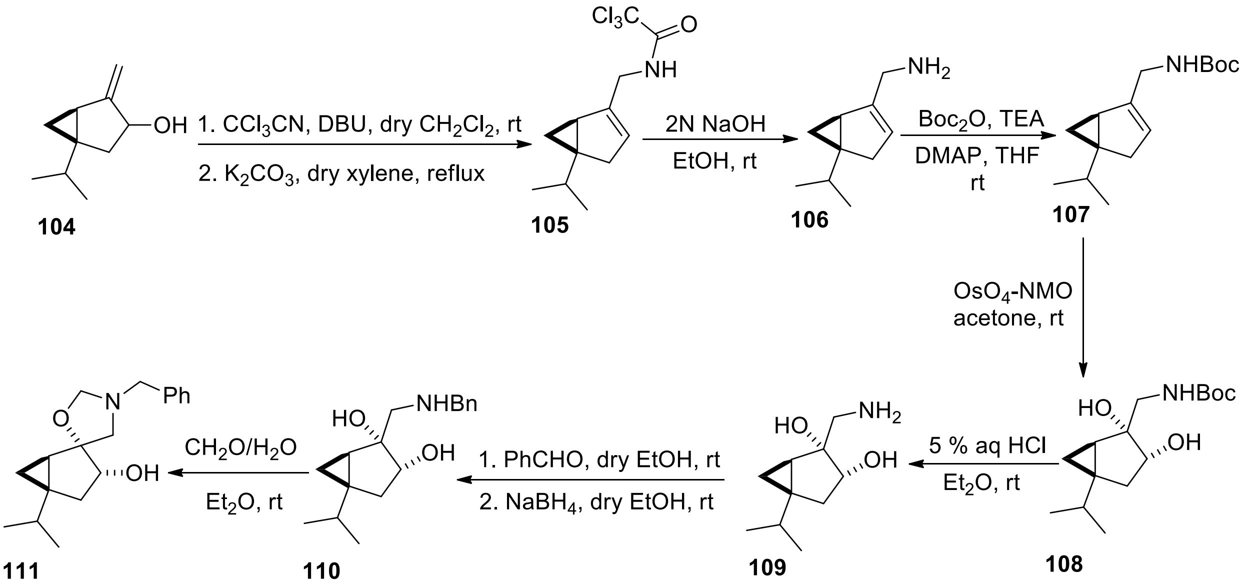
A library of aminodiols, derived from (+)-pulegone, was also reported recently (Scheme 13).[10] (+)-Pulegone **96** was stereoselectively reduced to pulegol **97**, which was then transformed into allyl trichloroacetamide **98**. Dihydroxylation of **98** with the OsO_4-NMO system furnished **99a** and **99b**. After removing the trichloroacetyl group of **99a**, the obtained primary aminodiol **100a** was transformed by reductive alkylation with benzaldehyde into secondary amine **101a**. Stirring **101a** with CH_2O furnished a mixture of 1,3-oxazine **102a** and oxazolidine **103a** in a 1:2 ratio. The transformations discussed above were repeated for diastereomeric aminodiol **100b** obtained from **99b** with similar results. The aminodiol derivatives were used as chiral catalysts in the enantioselective addition of diethylzinc to benzaldehyde (Figure 2). The best *ee* value (*ee* = 90%) with an (*S*)-selectivity was obtained when **103a** was applied.



Scheme 13. Preparation of (+)-pulegone-based chiral aminodiols

Furthermore, (+)-sabinol, a natural compound isolated from the essential oil of *Juniperus sabina* L. (*ee* = 98%), was used to prepare a new family of monoterpene-based chiral aminodiols.[71] Sabinol **104** was transformed into allylamine **106** via the Overmann rearrangement, followed by protecting group exchange resulting in **107**. Stereospecific dihydroxylation of **107**, applying OsO_4 as the catalyst and NMO as the oxidant, produced protected aminodiol **108** as a single diastereomer. Acid-catalyzed removal of the protecting group resulted in primary aminodiol hydrochloride **109**. Aminodiol **109** was transformed to *N*-benzyl derivative **110**, followed by ring closure with CH_2O resulting in spirooxazolidine **111** as the single product (Scheme 14). Application of aminodiols **109**–**111** (10 mol%) was tested in the ethylation of benzaldehyde

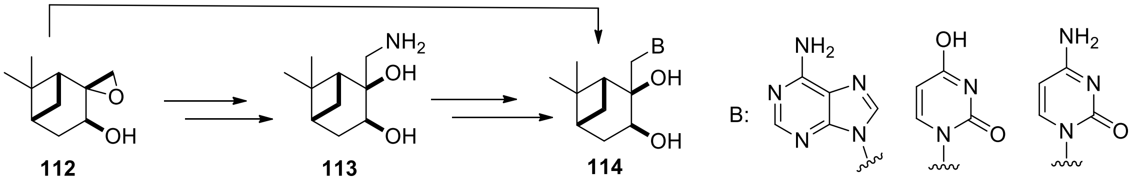
(Figure 2). Only moderate asymmetric induction was observed with the predominant formation of the (*S*)-enantiomer in all cases.



Scheme 14. Preparation of (+)-sabinol-based chiral aminodiols

2.2.2. Application of chiral aminodiols

Besides their value in enantioselective catalysis, aminodiols such as (+)- and (–)-*α*-pinene were also used as building blocks in the synthesis of carbocyclic nucleoside analogs (Scheme 15). The carbocyclic nucleosides, similar to the adenosine analogue natural aristeomycin and neplanocin A, containing a cyclopentane or cyclopentene ring and two or three hydroxy groups on the ring, possessed potent antiviral and antitumour activity. In addition, some of these compounds, such as the antiviral North-methanocarbathymidine (N-MCT) or the species-independent A3 receptor-selective agonist (*N*)-methanocarba-adenosine 5′-uronamides 6, exhibited noteworthy pharmacological activity.[84]



Scheme 15. Carbocyclic nucleosides from α-pinane-based aminodiols

2.3. Pharmacological importance and application of *β*-amino acid derivatives

Several *β*-amino acids, found in natural products, such as cispentacin, icofungipen, and BAY Y9379, possess noteworthy antifungal or antibacterial activities, while tilidin, a phenyl-substituted cyclohexene amino ester, is an analgesic. In addition, *β*-amino acids are considered to be important precursors for pharmacologically interesting *β*-lactams and *β*-aminoamides. Moreover, amino acids may be applied as building blocks in peptide synthesis. The incorporation of novel conformationally restricted *β*-amino acids into peptides and especially to foldamers has attracted considerable interest from the aspect of the preparation of peptide-based drug molecules with high biological potential.[85,86]

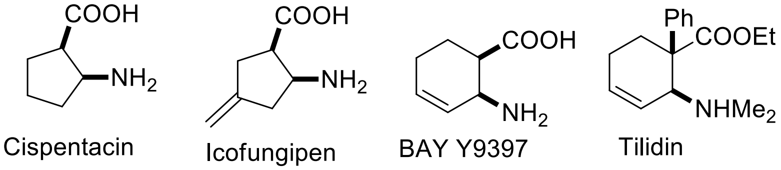


Figure 3. *β*-Amino acid derivatives as drugs

Some *β*-amino acid derivatives such as *β*-aminoamides and *β*-aminolactones have pharmacological importance. Monoterpene-based *β*-aminoamides have been reported to be antibiotics,[85,86] tyrosine kinase inhibitors,[85,86] KDR and Aurora B kinase inhibitors,[87] antidiabetes.[16] They also possess antitumor,[14] HIV protease and renin inhibitor activities,[17] while *β*-aminolactones are well-known as significant cytotoxic agents.[12,13]

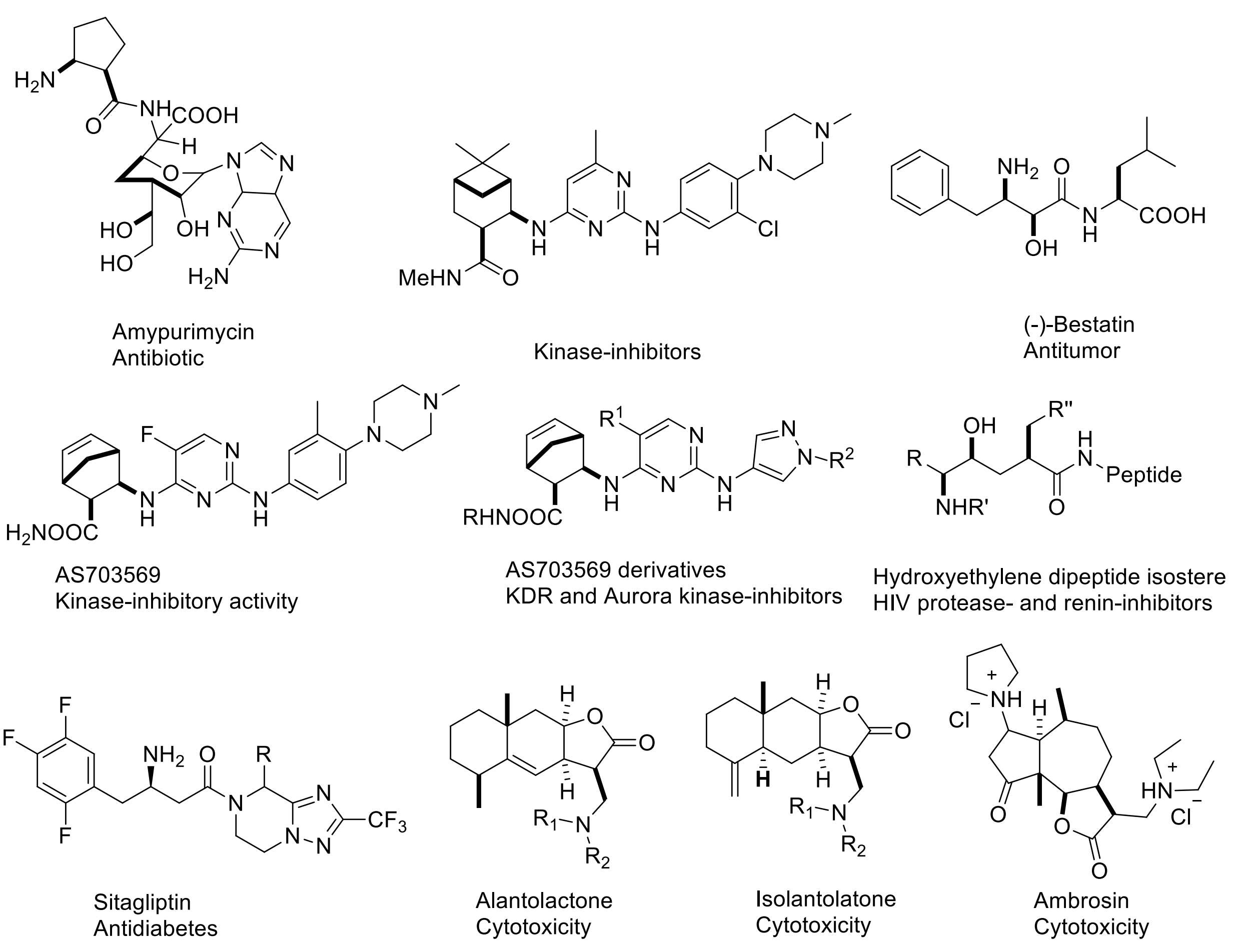


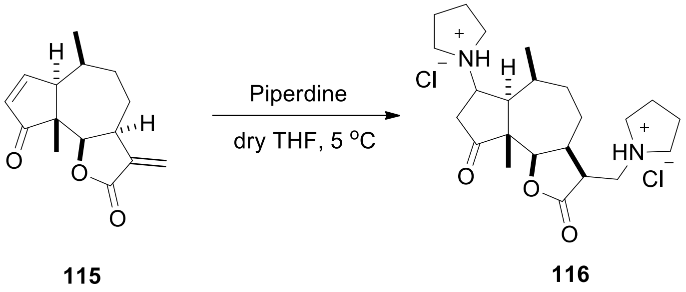
Figure 4. Biological activities of *β*-amino acid derivatives

2.4. Synthesis and application of chiral *β*-aminolactones and *β*-aminoamides

The discovery of the pharmacological importance of cyclic *β*-amino acid derivatives increased the demand for the asymmetric synthesis of these versatile building blocks.[85,88] Reported studies have revealed selective synthesis of cyclic amino acid derivatives such as *β*-aminolactones and *β*-aminoamides and their biological importance.

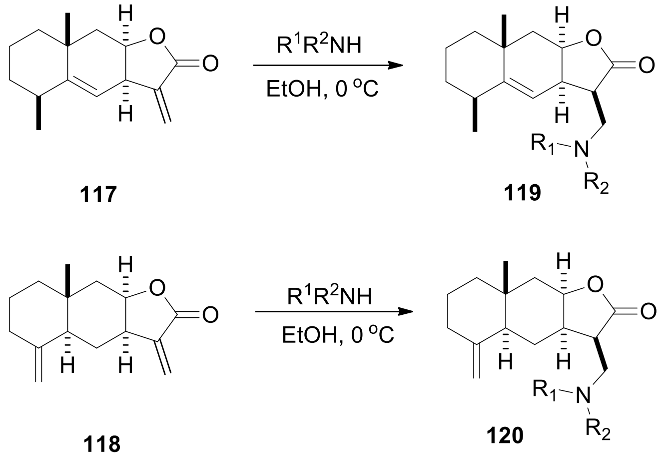
2.4.1. Cyclic *β*-aminolactones with cytotoxic properties

Ambrosin **115**, a naturally occurring pseudoguaianolide sesquiterpene lactone first isolated from *Ambrosia maritima* L., is a clinically useful anticancer agent but has a limited applicability because of its aqueous insolubility. A water-soluble ambrosin derivative was therefore prepared for potential use as prodrug. Michael addition of secondary amines to both *α,β*-unsaturated ketone and *α*-methylene-*γ*-butyrolactone moieties of ambrosin afforded tertiary amine diadducts, that were converted to water-soluble hydrochloride salts (Scheme 16). The salt of the bis-piperidine adduct **116** proved to be the most potent derivative. Its cytotoxic activity only slightly less potent than that of ambrosin itself in a variety of human cancer cell cultures such as human leukemia, non-small-cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, and breast cancer cell lines (GC_{50} = 1–22 μM). This derivative appears to be a promising candidate for further development as a water-soluble ambrosin prodrug.[13]



Scheme 16. Preparation of a water-soluble ambrosin prodrug

Two series of cytotoxic (IC_{50} = 1–24 μM in K562 cell line) *α*-aminomethyl-substituted lactones **119** and **120** were prepared by stereoselective Michael-type addition of amines to alantolactone **117** and isoalantolactone **118**, isolated from the dried roots of *Inula helenium* L. (Scheme 17). The lactones and their amine adducts induce apoptosis and act as alkylating agents.[12]

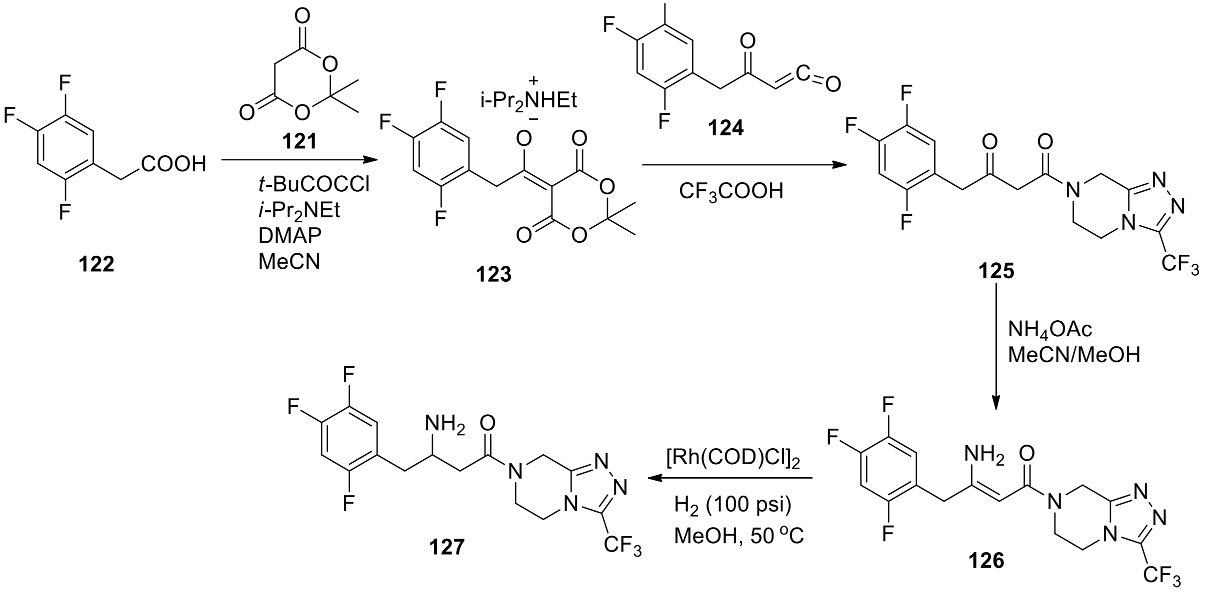


R^1 =Et, Me,-CHMeCHOHPh, $(CH_2)_2OH$, $(CH_2)_2Me$, $(CH_2)_3NMe_2$, CH_2Ph, Me
R^2 = Et, Me, $(CH_2)_2Me$, H
R^1= R^2 = $(-CH_2)_5$-, $(CH_2)_4$-, $-(CH_2)_2NCHO(CH_2)_2$-

Scheme 17. Preparation of *α*-aminomethyl-substituted lactones

2.4.2. *β*-Aminoamides with antidiabetic properties

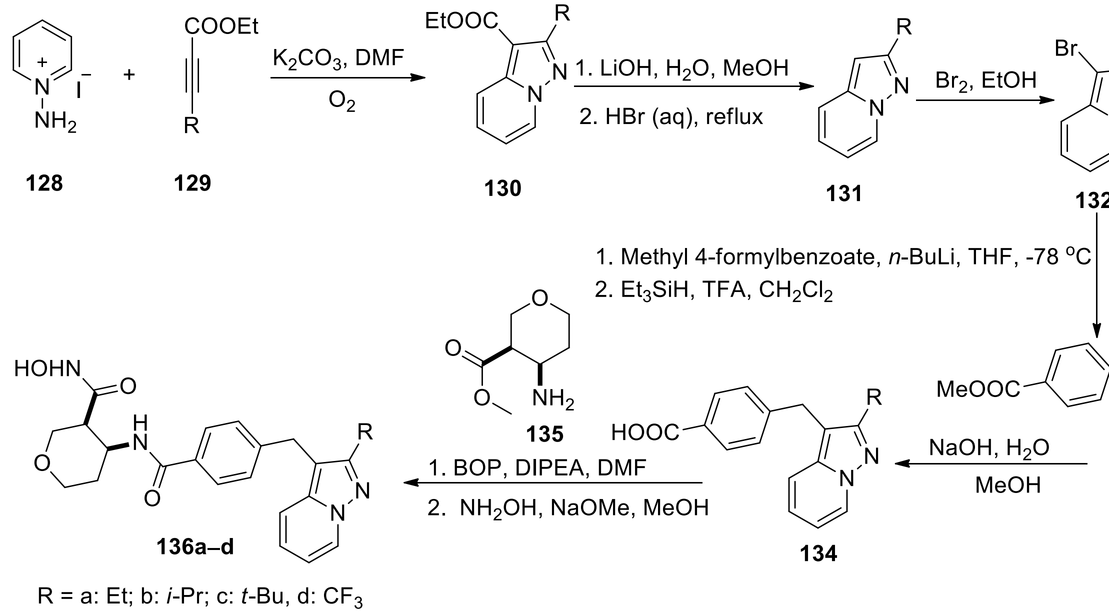
Sitagliptin a selective, potent DPP-4 inhibitor recently received approval for the treatment of type 2 diabetes.[89,90] 2,3,5-Trifluorophenylacetic acid **122** was activated by the formation of a mixed anhydride with pivaloyl chloride, in the presences of **121**, *i*-Pr_2NEt, and a catalytic amount of DMAP in acetonitrile to form Meldrum's adduct **123**. Treatment of **123** with **124** results in the formation of *β*-keto amide **125**. Formation of **127** could be achieved cleanly by mixing **125** with NH_4OAc along with MeOH, then hydrogenation of free enamine **126** in the presence of $[Rh(COD)Cl]_2$ (Scheme 18).[91]



Scheme 18. Preparation of sitagliptin

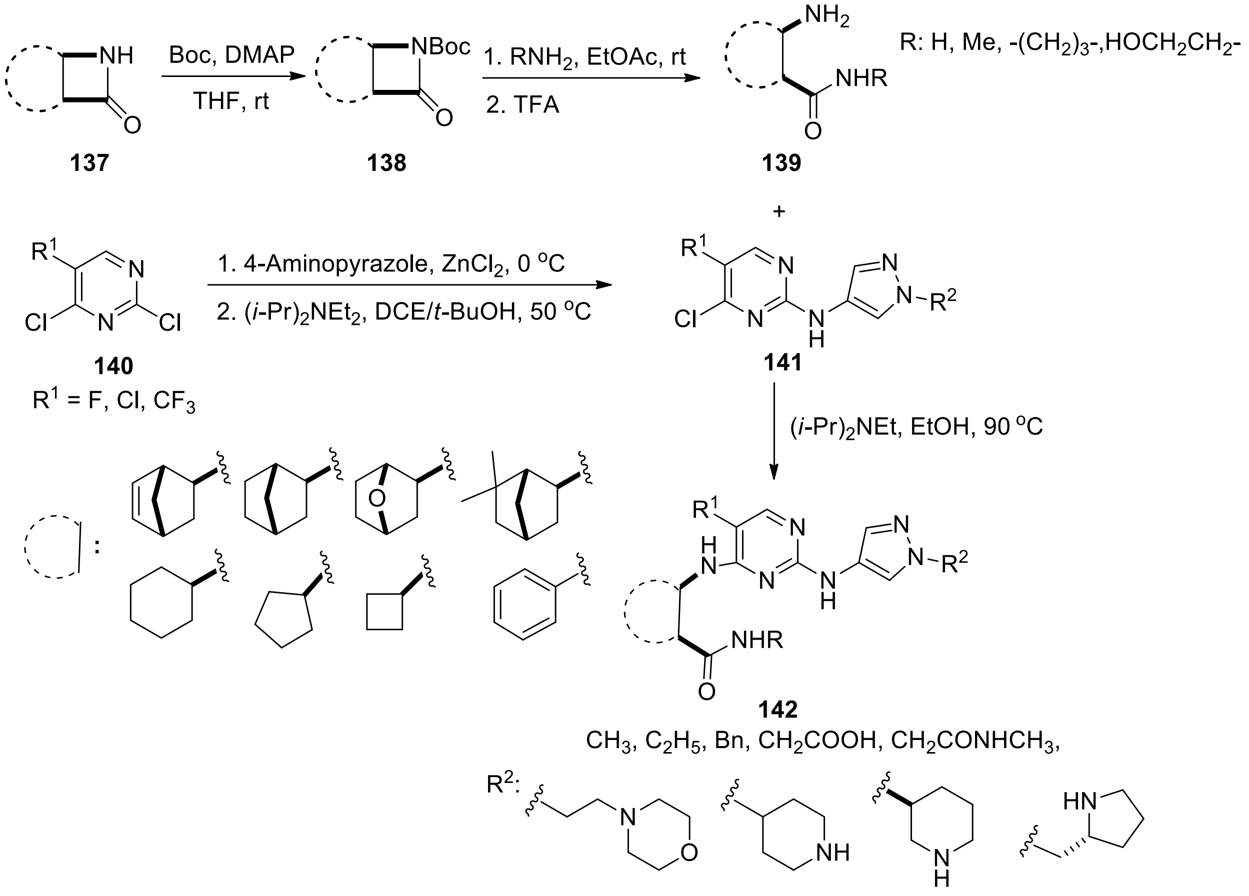
2.4.3. Cyclic *β*-aminoamides with antitumoral properties

Potent and selective inhibitors of tumor necrosis factor - *α* converting enzyme (TACE) were discovered with several new heterocyclic P1′ groups in conjunction with cyclic *β*-amino hydroxamic acid scaffolds. Among them, pyrazolopyridine provided the best overall profile when combined with tetrahydropyran *β*-amino hydroxamic acid scaffold.[92–94] The synthesis of pyrazolopyridine P1′ acid is outlined in Scheme 19. 1-Aminopyridinium iodide **128** was reacted with **129** via [3+2] cycloaddition followed by air oxidation to provide pyrazolopyridine **130**. Saponification and decarboxylation of **130** provided compounds **131**, which was brominated to yield **132**. After treatment with *n*-BuLi, the lithiated pyrazolopyridine intermediate was reacted with methyl 4-formylbenzoate to give an intermediate alcohol that was reduced with triethylsilane and trifluoroacetic acid to provide **133**. Hydrolysis with NaOH completed the synthesis of acids **134**. After hydrolysis of the ester, the resultant acids **134** was coupled with amine **135** using BOP reagent followed by hydroxamic acid formation to yield compounds **136**. Inhibitor **136d** showed IC_{50} value of 1 nM against porcine TACE and 170 nM in the suppression of LPS-induced TNF-α of human whole blood.[93]



Scheme 19. Preparation of pyrazolopyridine P10 acid

Aurora B kinases are a family of serine/threonine-kinases that play a key role in mitosis and are overexpressed in multiple human tumor types. There has been considerable interest in developing Aurora B kinase inhibitors as antitumor agents while KDR is a regulator of vascular permeability and an inducer of endothelial cell proliferation, migration, and survival. Therefore, interruption of the KDR-mediated signaling cascade can provide therapeutic benefit in human cancers. In an effort to identify kinase inhibitors with dual KDR/Aurora B activity and improved aqueous solubility compared to the Abbott dual inhibitor, a series of novel pyrazole pyrimidines were prepared (Scheme 20).[87] Boc-protection of commercially available lactams **137** provided carbamates **138** which were ring-opened with amines to give, after amine deprotection with TFA, carboxamides **139** in high yield. On the other hand, a $ZnCl_2$-mediated, highly regioselective addition of 4-aminopyrazole derivatives to the 2-position of pyrimidines **140** gave intermediates **141** in modest yield. Addition of amines **139** to chloropyrimidines **141** in the presence of Hunig's base at 90 °C gave desired products **142** in high yield. SAR work provided analogs with significant cellular activity, measureable aqueous solubility, and moderate antitumor activity in a mouse tumor model after weekly IP dosing. Unfortunately, these compounds were pan-kinase inhibitors suffering from narrow therapeutic indices, which prohibited their use as antitumor agents.

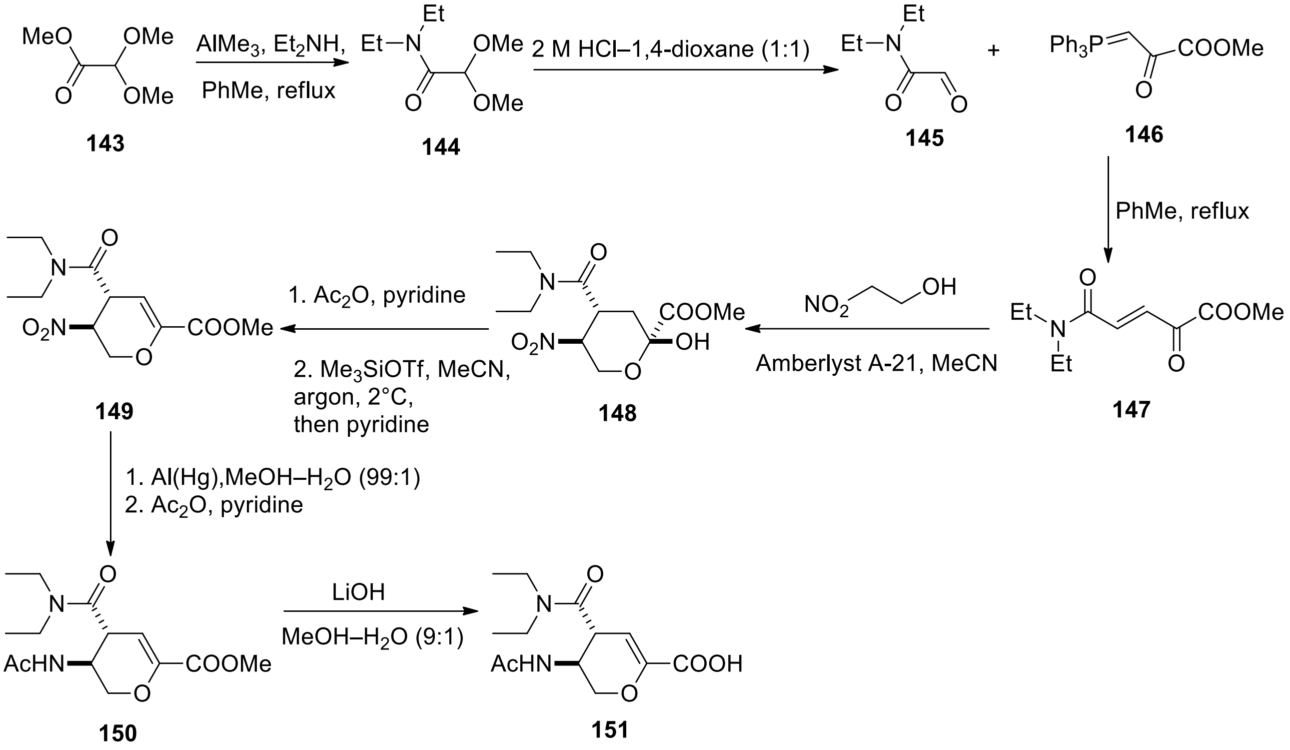


Scheme 20. Preparation of pyrazole pyrimidine derivatives

2.4.4. Cyclic *β*-aminoamides with antiviral properties

Sialidases play a crucial role in the life cycle of the influenza virus. Accordingly, inhibitors of the enzymes are of interest as potential anti-influenza agents.[95–97] (4*R**,5*S**)-5-Acetylamino-4-diethylcarbamoyl-5,6-dihydro-4*H*-pyran-2-carboxylic acid has been synthesized as shown in Scheme 21. Commercially available ester **143** was converted into amide **144**, which afforded aldehyde **145** under acidic conditions. A Wittig condensation of **145** with phosphorane **146** provided enone **147**. In the presence of methanolic sodium methoxide, enone **147** and 2-

nitroethanol reacted to give adduct **148**. The two-step acetylation–elimination sequence of Claesson and Luthman affored **149**. When **149** was treated with aluminum amalgam in moist methanol followed by acetylation, the desired acetamide **150** was isolated. Saponification of ester **150** provided the target acid **151**. It is a moderately active inhibitor of influenza A sialidase (IC_{50} = 1.5 μM).[97]

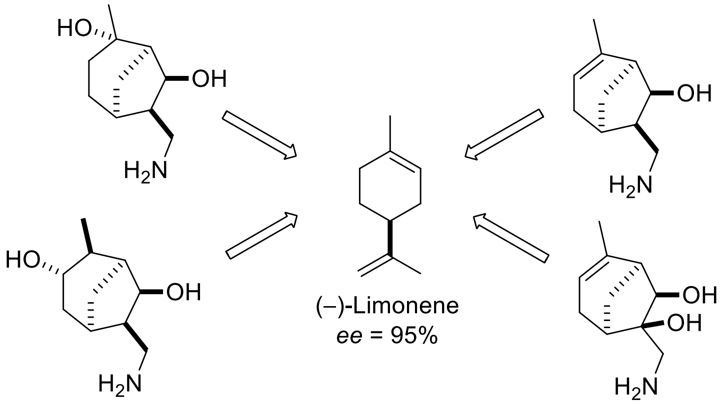


Scheme 21. Synthesis of (4*R**,5*S**)-5-acetylamino-4-diethylcarbamoyl-5,6-dihydro-4*H*-pyran-2-carboxylic acid

3. Results and discussion

3.1. Synthesis of limonene-based chiral bi- and tri-functional ligands

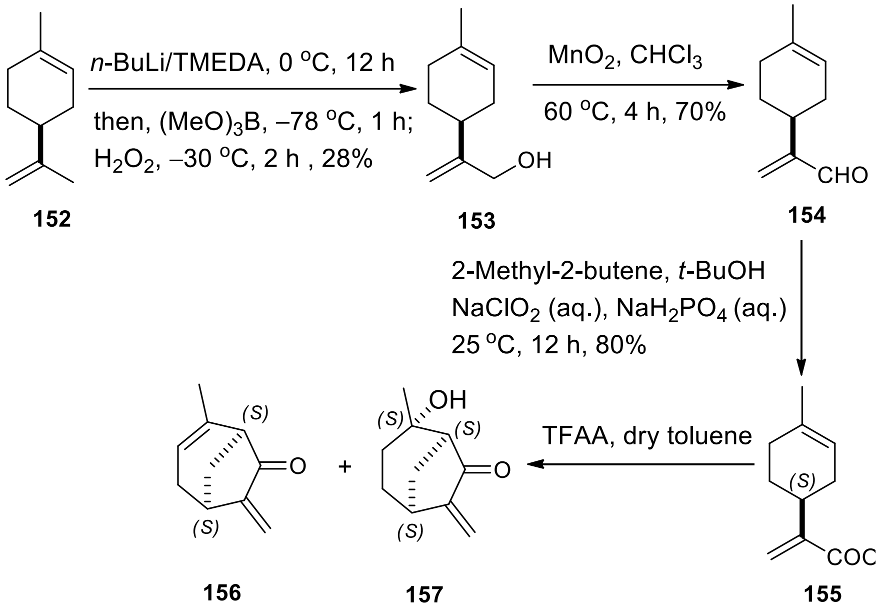
As concerns the synthetic strategy for the preparation of limonene-based chiral bi- and tri-functional ligands demonstrated on Scheme 22, commercially available (–)-limonene (*ee* = 95%) was applied as starting material. Since the chiral centers, in even non-enantiomeric selective cases, can lead to the formation of diastereomers, the optical purity of the products remained the same as the enantiomeric purity of the starting material.



Scheme 22. Stereoselective synthesis of limonene-based chiral amino alcohols and aminodiols

3.1.1. Synthesis of limonene-based chiral methylene ketone and analogue

The key intermediates bicyclic methylene ketones were prepared from (–)-limonene **152** starting with regioselective hydroxylation to afford allylic alcohol **153** according to literature processes.[98,99] The resulting **153** was oxidized to aldehyde **154**,[98] which was converted to carboxylic acid **155**.[100] Intramolecular acylation of **155** gave methylene ketone **156** and its hydroxy-substituted analogue **157** (Scheme 23).



Scheme 23. Synthesis of bicyclic methylene ketones **156** and **157**

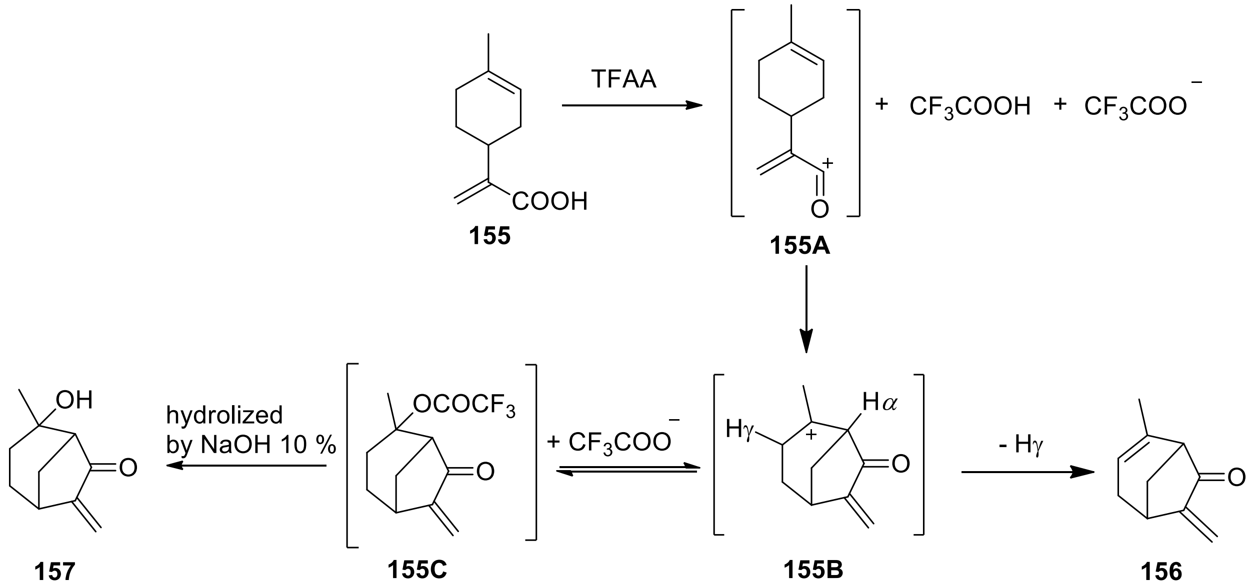
The temperature strongly affected the yield and the ratio of the two products. At 0 °C, compound **157** was formed as the major product under kinetic control, whereas at 25 °C, the products were formed in a 1:1 ratio. In contrast, the thermodynamically preferred product **156** was obtained as a single product at 100 °C. At lower temperature, the yield of the reaction dropped dramatically without any remarkable changes in the **156**/**157** ratio. When other solvents, an acid catalyst or acetic anhydride were tested, the reaction failed (Table 1).

Table 1. Cyclization reaction of (*S*)-isoperyllic acid **155**

Entry	Solvent	Additive	T [°C]	t [h]	Ratio of **156**/**157** (%)[a]	Yield [%][b]
1	Toluene	TFAA	25	12	45:55	91
2	Toluene	Ac_2O	25	48	-	-
3	MeCN	TFAA	25	48	-	-
4	AcOH	-	25	48	-	-
5	Toluene	TFAA	0	48	33:67	80
6	Toluene	TFAA	-20	>48	33:67	40
7	Toluene	TFAA	100	6	>99:<1	56

[a] Based on ^{1}H NMR spectroscopy. [b] Isolated, combined yield of **156** and **157**.

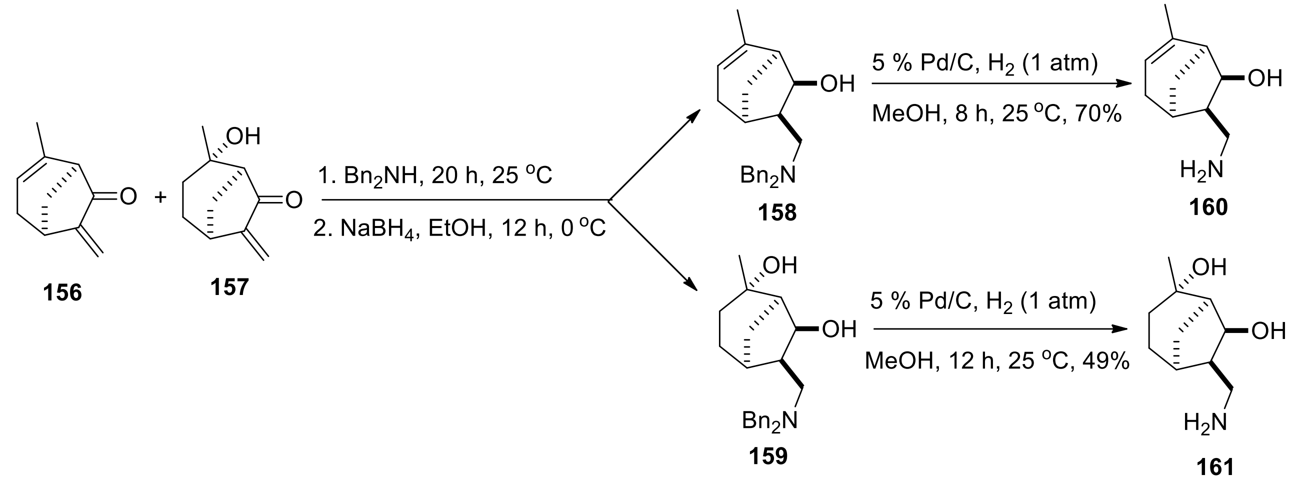
The reaction between the carboxylic acid and the double bond in the presence of TFAA can be interpreted by a mechanism involving a carbocation.[101,102] In the first step, acylium ion **155A** is formed through the attack of TFAA onto the carboxylic acid group. Intramolecular attack onto the olefinic bond then gives carbocation **155B**. This species loses the γ-proton to form ketone **156** or reacts with the trifluoroacetate anion to yield ester **155C**, which undergoes hydrolysis under work-up conditions to deliver **157** (Scheme 24).[101]



Scheme 24. Proposed mechanism of the intramolecular acylation reaction

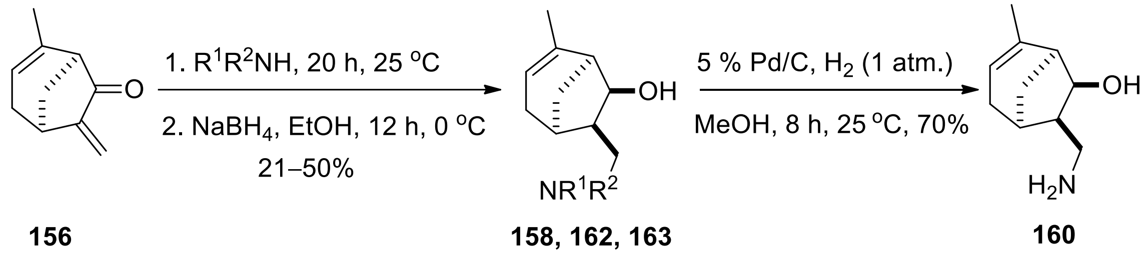
3.1.2. Synthesis of limonene-based chiral 1,3-amino alcohols and aminodiols

The separation of **156** and **157** was difficult on a gram scale; therefore, the mixture of **156** and **157** was treated with dibenzylamine for an aza-Michael addition. Since the addition of the amine was found to be reversible, intermediate aminoketones were converted into tertiary amino alcohol **158** and aminodiol **159** by in-situ reduction of the ketone function with $NaBH_4$, followed by separation of **158** and **159** on column chromatography.[103] Hydrogenolysis of these compounds over Pd/C in MeOH gave primary amino alcohol **160** and aminodiol **161** in moderate yields (Scheme 25). The relative configurations of **158** and **159** were determined by NOESY spectroscopic analysis.



Scheme 25. Stereoselective synthesis of limonene-based amino alcohols and aminodiols

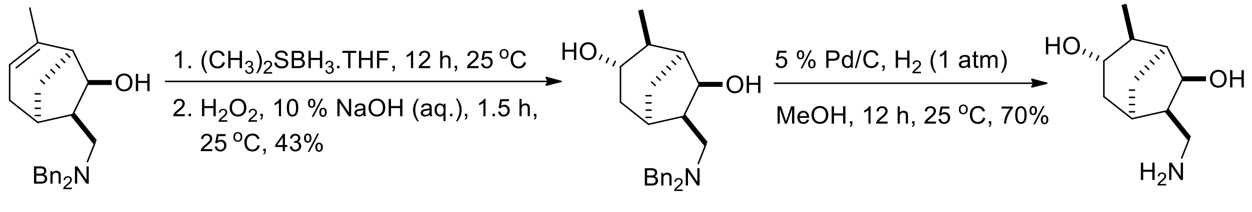
Subsequently, methylene ketone **156**, prepared by an optimized cyclization reaction at 100 °C, was also treated with amines to try to utilize the presence of the ring system to affect the stereoselectivity of the addition. Indeed, the reactions were highly stereoselective and led to the formation of tertiary and secondary amino alcohols **158**, **162**, and **163** (Scheme 26). The configurations of the new stereogenic centers of **162** and **163** were determined by NOESY.



158: R^1 = CH_2Ph, R^2 = CH_2Ph; **162**: R^1 = H, R^2 = CH(Me)Ph(*R*), **163**: R^1 = H, R^2 = CH(Me)Ph(*S*)

Scheme 26. Stereoselective synthesis of amino alcohols

Furthermore, hydroboration of compound **158** was accomplished by treatment with $BH_3·Me_2S$ followed by oxidation of the boron intermediate with H_2O_2. Note that the addition resulted in two diastereomers of **164** with a ratio of 3:1 (based on NMR spectroscopic analysis of the crude product). Our efforts failed to isolate the minor product, only the major product **164** was obtained after column chromatography. Debenzylation with the H_2/Pd/C system gave aminodiol **165** in acceptable yield (Scheme 27). The structure of **164** was also determined by NOESY analysis.

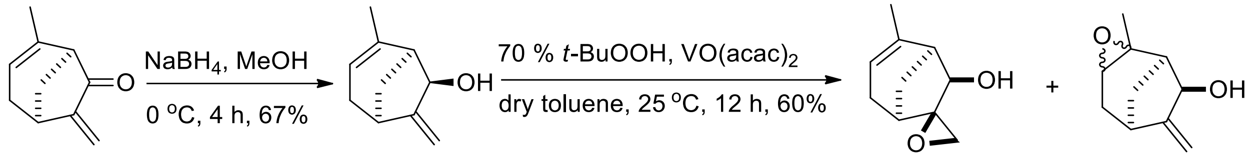


158 **164** **165**

Scheme 27. Synthesis of 6-amino-1,4-diols

3.1.3. Synthesis of limonene-based chiral 3-amino-1,2-diols

Stereoselective reduction of **156** gave allylic alcohol **166**.[10] Epoxidation of **166** in dry toluene in the presence of vanadyl acetylacetonate [VO(acac)$_2$] as the catalyst gave a mixture of **167** and **168**.[104–106] Note, that **168** existed as a 4:1 mixture of two diastereomers. In addition, it is interesting that the ratio of **167** and **168** was dependent on the temperature (Scheme 28).



156 **166** **167** **168**

Scheme 28. Stereoselective reduction and epoxidation

Whereas **167** was formed as the main product at 25 °C, the ratio of the two products was found to be 1:1 at 100 °C. At lower temperatures, the yield dropped dramatically despite the elongated reaction time without any significant change in the **167** to **168** ratio. The yield of **167** could not be increased by changing the ratio of **166** and the oxidizing agent or the temperature (Table 2). The separation of epoxides **167** and **168** could not be effectively performed without product decomposition.

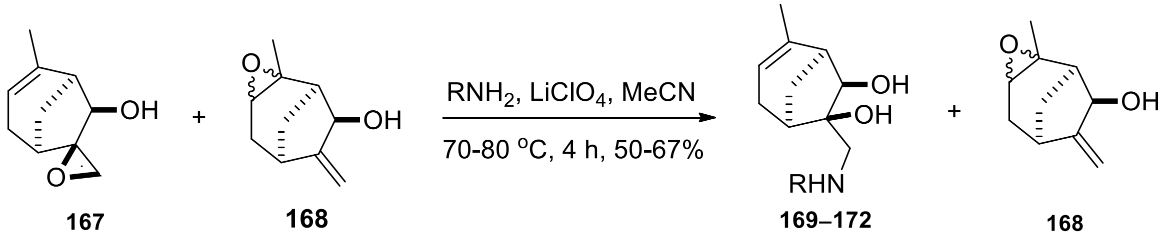
Table 2. Epoxidation of **166**

Entry	166 (mol)	*t*-BuOOH (mol)	T [°C]	t [h]	Ratio of **167**/**168** [a]	Yield [%][b]
1	1	1.5	0	> 96	4:1	40
2	1	1.5	25	12	3:1	60
3	1	1.5	100	4	1:1	70
4	1	3.0	0	48	1:1	60
5	1	3.0	25	6	1:1	65

[a] Based on ^{1}H-NMR measurements of the crude product. [b] Isolated, combined yield of **167** and **168**.

Given that we clearly demonstrated previously that substituents on the nitrogen atom of aminodiols did influence the efficiency of their catalytic activity,[4,11] aminodiol library **169–172** was prepared by aminolysis of epoxide **167** with primary amines in the presence of $LiClO_4$ as the catalyst.[7,11,33,62] However, our efforts in the opening of the epoxide ring with secondary amines were also unsuccessful.

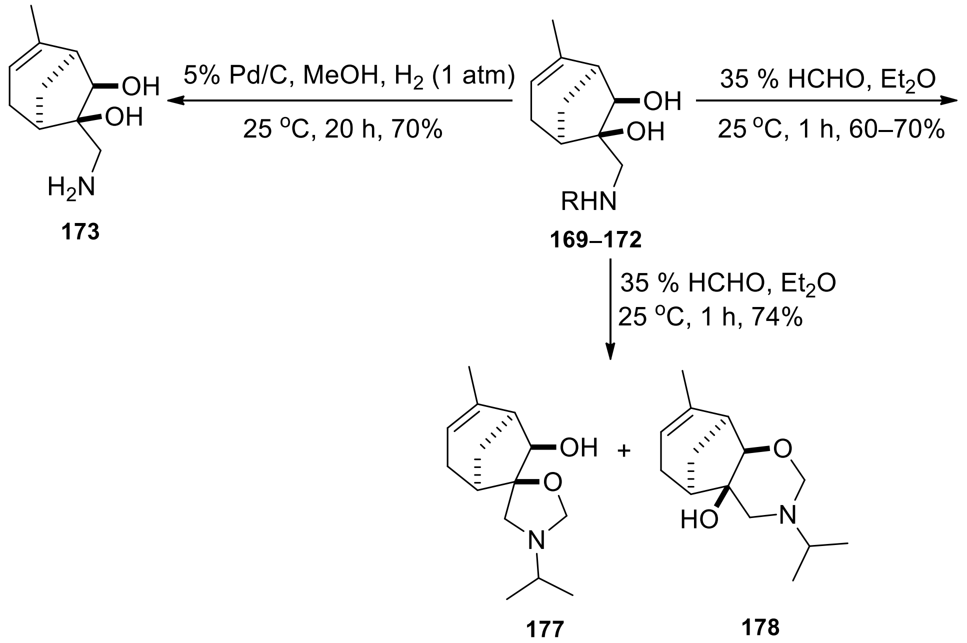
Interestingly, during aminolysis with primary amines under the applied conditions, epoxide **167** was transformed preferentially, whereas **168** did not react. This was probably due to steric hindrance exerted by the methyl group of **168** at the α position. Therefore, aminodiols **169–172** could be easily separated from **168** on a gram scale by simple column chromatography in good yields (Scheme 29). The relative configurations of compounds **169–172** were determined by means of NOESY experiments. Debenzylation by hydrogenolysis of compounds **169–171** over Pd/C in MeOH resulted in primary aminodiol **173** in a moderate yield (Scheme 30).



169: R = CH_2Ph; **170**: R = CH(Me)Ph (*S*); **171**: R = CH(Me)Ph (*R*); **172**: R = $CH(Me)_2$

Scheme 29. Ring opening of epoxide **167**

As the ring closure of monoterpene-based aminodiols with rigid structures enhances their catalytic potential,[7,8] treatment of aminodiols **169**–**171** with formaldehyde at room temperature afforded spirooxazolidines **174**–**176** through a highly regioselective ring-closing reaction. In contrast, aminodiol **172** yielded a mixture of spirooxazolidine **177** and 1,3-oxazine **178**. The temperature strongly affected the ratio of the two products. At 0 °C, exclusive formation of compound **177** was observed, whereas a mixture of **177** and **178** was formed in a ratio of 2:1 at 25 °C. At a higher temperature, no significant changes in the **177**/**178** ratio could be achieved. Upon applying *p*-toluenesulfonic acid (TsOH) as an additive to decrease the pH to 1–2, the ratio of **177** and **178** did not change significantly (**177**/**178** = 1.7:1) and, at the same time, the product yield dropped to 40% (Scheme 30).

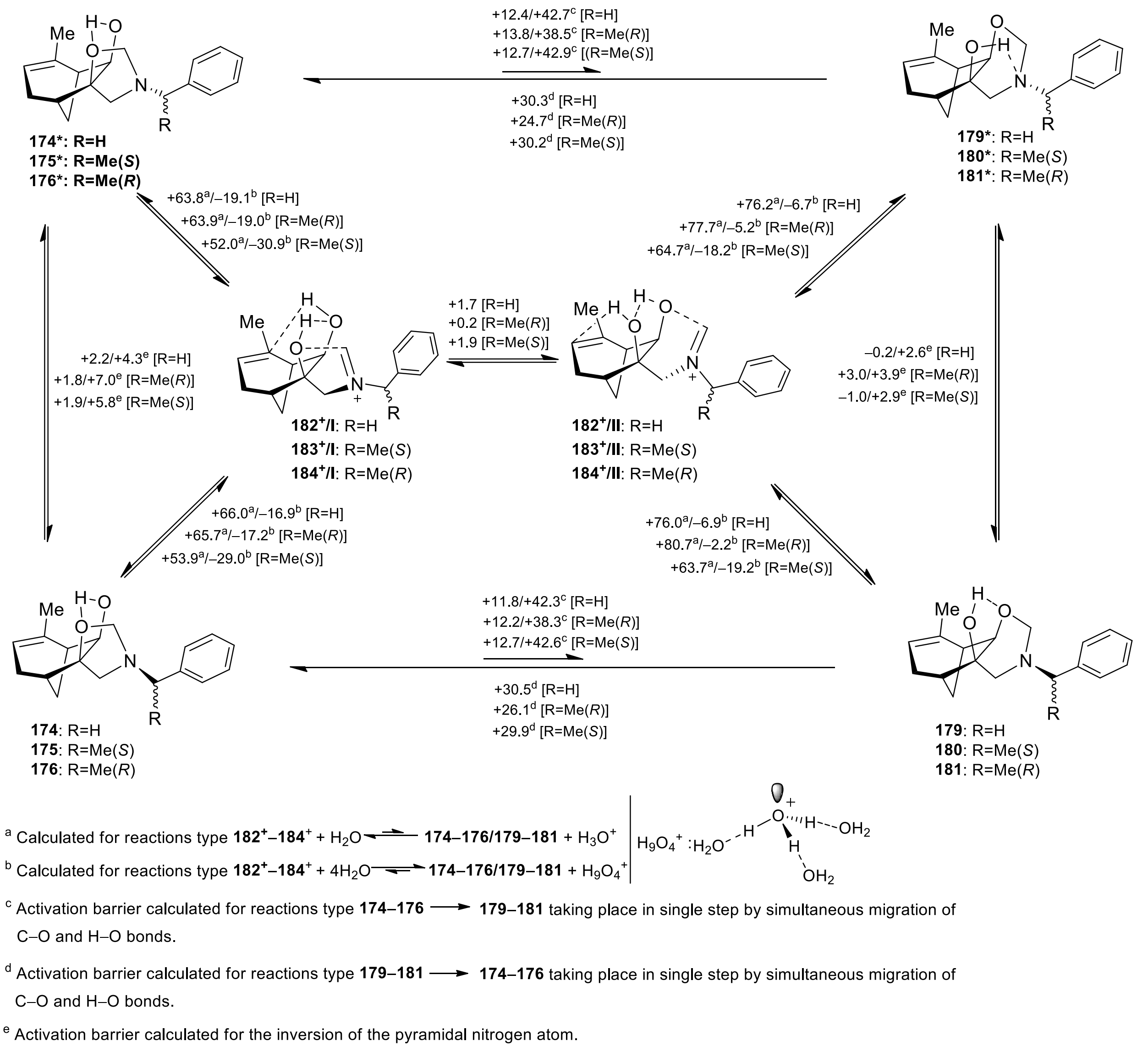


R = CH$_2$Ph, CH(Me)Ph (*S*), CH(Me)Ph (*R*), CHMe$_2$

Scheme 30. Debenzylation and ring closure reaction

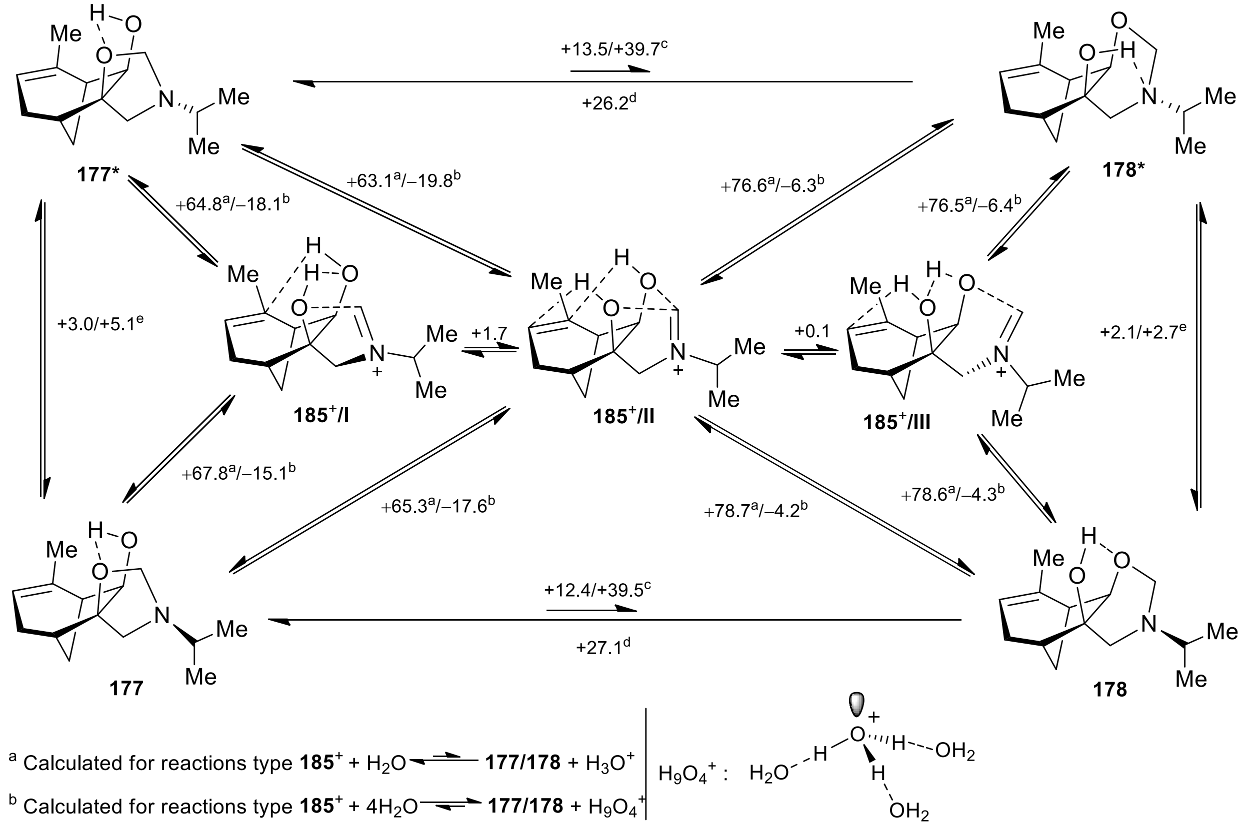
3.1.4. Investigation of ring-closure abilities of limonene-based aminodiols

We were interested to get insight into the experienced substrate dependence of the acid-catalyzed, formaldehyde-mediated cyclization reactions of the studied aminodiols. Therefore, all resulting spirocyclic oxazolidines **174**–**177** and isomeric compound **178** fused with perhydro-1,3-oxazine along with the possible iminium intermediates (Schemes 31 and 32) were analyzed by a systematic series of comparative DFT modelling carried out at B3LYP/6-31+G(d,p) level of theory.[107,108]



Scheme 31. Pathways, energetic, and activation barriers (kcal/mol) calculated for the interconversion of **174**–**176, 179**–**181** and the relevant iminium cationic intermediates involving the inversion of the nitrogen stereogenic center present in the neutral molecules.

The slightly enhanced tendency of isopropyl-substituted model **172** to afford fused oxazine product **178** might be due to acid-catalyzed formation of iminium cation **185$^+$/II**. This unique intermediate is preformed in alternative modes of cyclization, in concentration comparable to those of its rotamers **185$^+$/I** and **185$^+$/III** preformed to single modes of ring closure (Scheme 32).



[a] Calculated for reactions type $\mathbf{185^+} + H_2O \rightleftharpoons$ **177/178** $+ H_3O^+$

[b] Calculated for reactions type $\mathbf{185^+} + 4H_2O \rightleftharpoons$ **177/178** $+ H_9O_4^+$

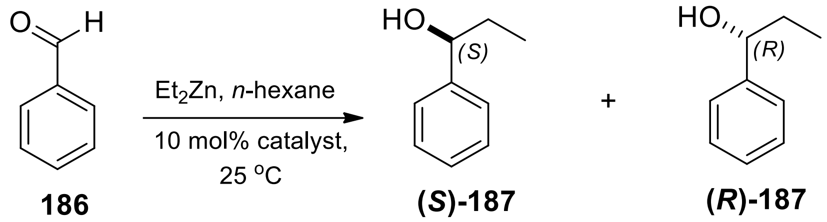
[c] Activation barrier calculated for reactions type **177**⟶**178** taking place in single step by simultaneous migration of C–O and H–O bonds.

[d] Activation barrier calculated for reactions type **178**⟶**177** taking place in single step by simultaneous migration of C–O and H–O bonds.

Scheme 32. Pathways, energetics, and activation barriers (kcal/mol) calculated for the interconversion of **177**, **178** and the relevant iminium cationic intermediates involving the inversions of the nitrogen stereogenic center present in the neutral molecules.

3.1.5. Application of limonene-based chiral aminodiols as chiral catalyst in the model reaction

Aminodiol derivatives **169**–**178** were applied as chiral catalysts in the enantioselective addition of diethylzinc to benzaldehyde **186** to form (*S*)-1-phenyl-1-propanol [(*S*)-**187**] and (*R*)-1-phenyl-1-propanol [(*R*)-**187**] (Scheme 33).



Scheme 33. Model reaction of enantioselective catalysis

The results are presented in Table 3. The enantiomeric purities of propanols (*S*)-**187** and (*R*)-**187** were determined by GC on a CHIRASIL-DEX CB column by using literature methods.[7,11,109,110] Low-to-good enantioselectivities were observed. Aminodiol **172** afforded the best *ee* value (*ee* = 55%) with *R* selectivity (Table 3, entry 4), whereas a 2:1 mixture of **177**/**178** showed the best *ee* value (*ee* = 80%) with *S* selectivity (Table 3, entry 10). The results obtained clearly show that the spirooxazolidine ring has poorer catalytic performance than the 1,3-oxazine ring system. These results correlate well with those observed with pinane- and sabinane-based spirooxazolidines and carane-fused 1,3-oxazines in our earlier studies.[8,11,71]

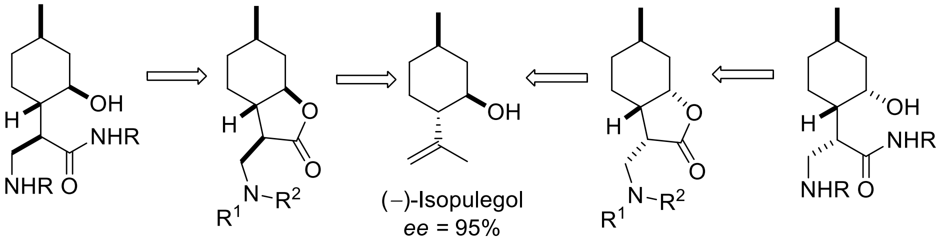
Table 3. Addition of diethylzinc to benzaldehyde catalyzed by aminodiols, oxazolidines, and 1,3-oxazines

Entry	Ligand[a]	Yield[b] (%)	*ee*[c] (%)	Configuration[d]
1	**169**	80	16	(*R*)
2	**170**	85	24	(*R*)
3	**171**	87	40	(*R*)
4	**172**	89	55	(*R*)
5	**173**	87	35	(*R*)
6	**174**	85	30	(*R*)
7	**175**	88	6	(*R*)
8	**176**	83	0	-
9	**177**	90	6	(*R*)
10	**177/178** (2:1)	87	80	(*S*)

[a] 10 mol%. [b]After silica column chromatography. [c] Determined on the crude product by GC (Chirasil-DEX CB column). [d] Determined by comparing the t_R of GC analysis and optical rotations with literature data.

3.2. Synthesis of isopulegol-based bi- and tri-functional ligands

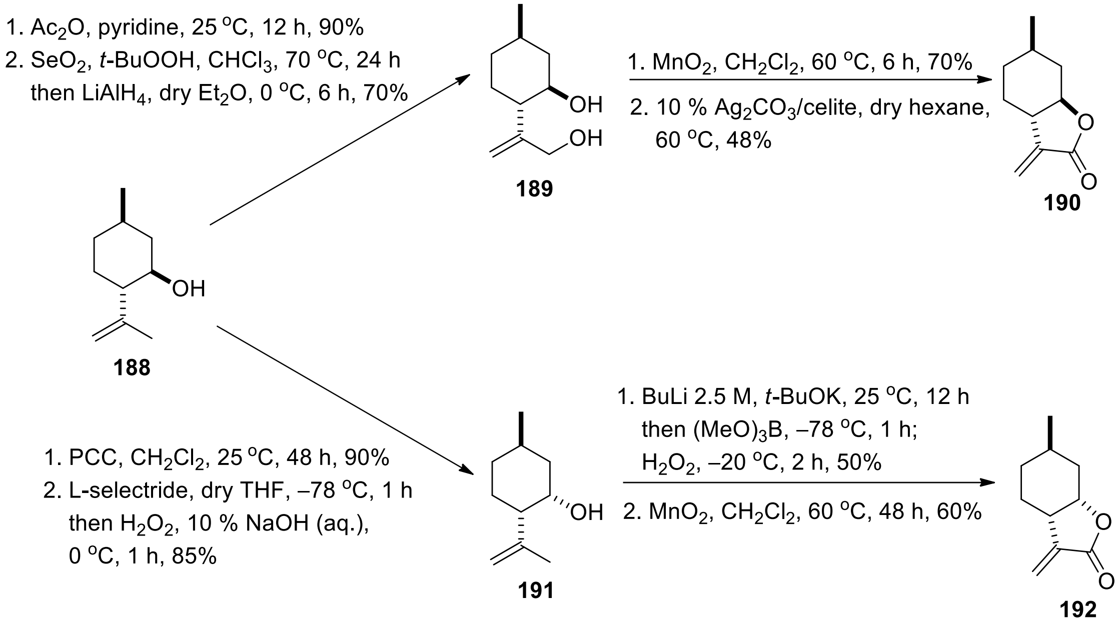
The synthetic strategy for the preparation of monoterpene-based *β*-aminolactones and *β*-aminoamides is demonstrated on Scheme 34 with commercially available natural (–)-isopulegol (*ee* = 95%) as an inexpensive chiral source applied as starting material. Since configuration of chiral centers led, in even non-enantiomeric selective case, to the formation of diastereomers, the optical purity of the products remained identical to the enantiomeric purity of the starting material.



Scheme 34. Synthesis of isopulegol-based chiral *β*-aminolactones and *β*-aminoamides

3.2.1. Synthesis of isopulegol-based chiral *α*-methylene-*γ*-butyrolactone

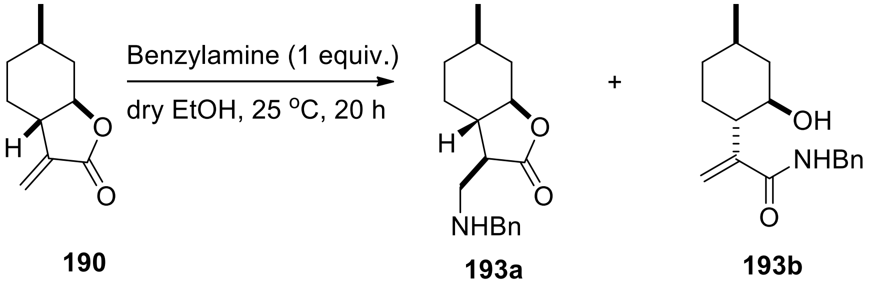
The key intermediate (+)-*α*-methylene-*γ*-butyrolactone **190** was prepared from commercially available (–)-isopulegol **188** with regioselective hydroxylation, followed by two-step oxidation and ring closure of the obtained γ-hydroxy-substituted *α*,*β*-unsaturated carboxylic acid applying literature methods.[111–116] Diastereomeric (–)-*α*-methylene-*γ*-butyrolactone **192** was prepared in a similar way starting from (–)-isopulegol **188**. In the first step, the hydroxy group of **188** was oxidized followed by stereoselective reduction of the resulting carbonyl group providing (+)-neoisopulegol **191** (Scheme 35).[111–117]



Scheme 35. Synthesis of (–)-isopulegol-based α-methylene-γ-butyrolactone **190** and **192**

3.2.2. Synthesis of isopulegol-based chiral β-aminolactones

Nucleophilic addition of primary and secondary amines to α-methylene-γ-butyrolactone **190** and **192** has proved to be an efficient method for the preparation of a highly diversified library of β-aminolactones.[12,118] When the addition of one equivalent of benzylamine to **190** was performed as model reaction, formation of *N*-benzyl aminolactone **193a** and *N*-benzyl methyleneamide **193b** was observed. The effect of the solvent was also studied and it was found that the applied solvent strongly affected both the yield of **193a** and the ratio of the two products (Scheme 36).



Scheme 36. Nucleophilic addition of α-methylene-γ-butyrolactone to benzylamine

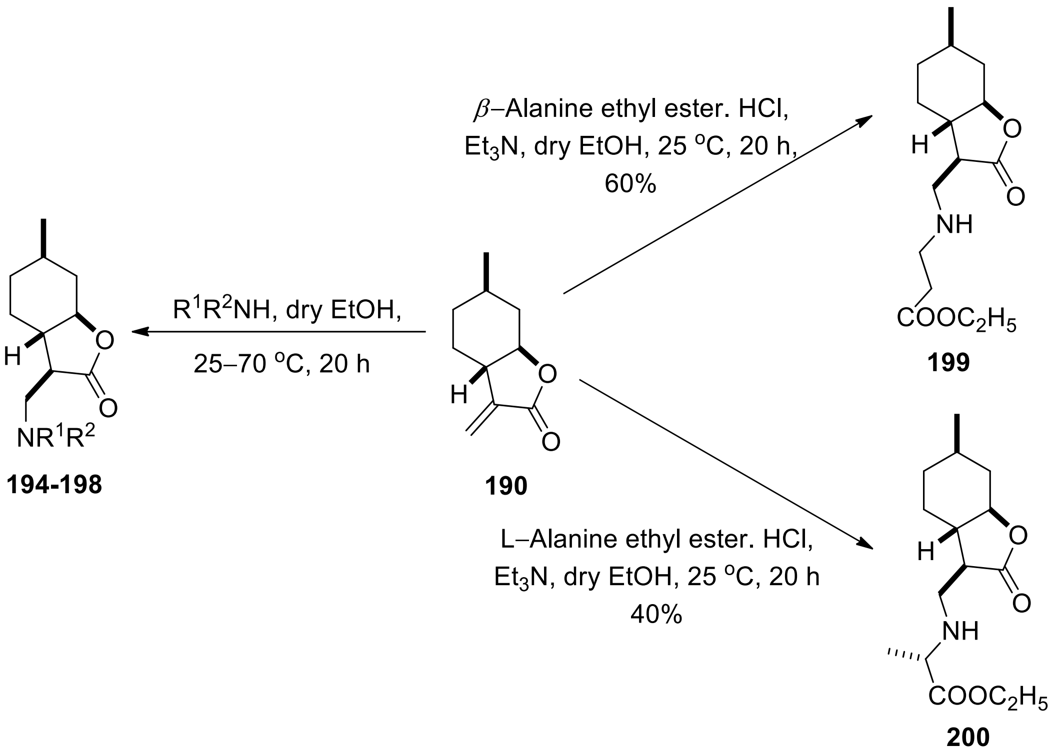
When alcohols as protic solvents were used, formation of **193a** was observed as the main product. Among of three protic solvents applied, EtOH gave target **193a** with the best chemoselectivity. Besides, the ratio of **193a** and **193b** also depended on temperature. In alcohols, in turn, product ratios were similar at 0 °C and 25 °C but the latter provided higher yield. At higher temperature, the yield of **193a** dropped and the products were formed in a ratio of 4:1 even with decreasing reaction times (Table 4).

Table 4. Nucleophilic addition reaction of **190** with benzylamine

Entry	Solvent	Temperature (°C)	Reaction time (h)	Product ratios[a] (%)		Yield of **193a**[b] (%)
				193a	**193b**	
1	DCM	0	20	44	56	10
2	-	0	20	50	50	30
3	DMF	0	20	67	33	44
4	MeOH	0	20	92	8	30
5	*i*-PrOH	0	20	94	6	55
6	EtOH	0	20	94	6	60
7	EtOH	25	20	94	6	65
8	EtOH	40	15	80	20	55
9	EtOH	50	10	80	20	55
10	EtOH	60	7	80	20	50
11	EtOH	70	5	80	20	45

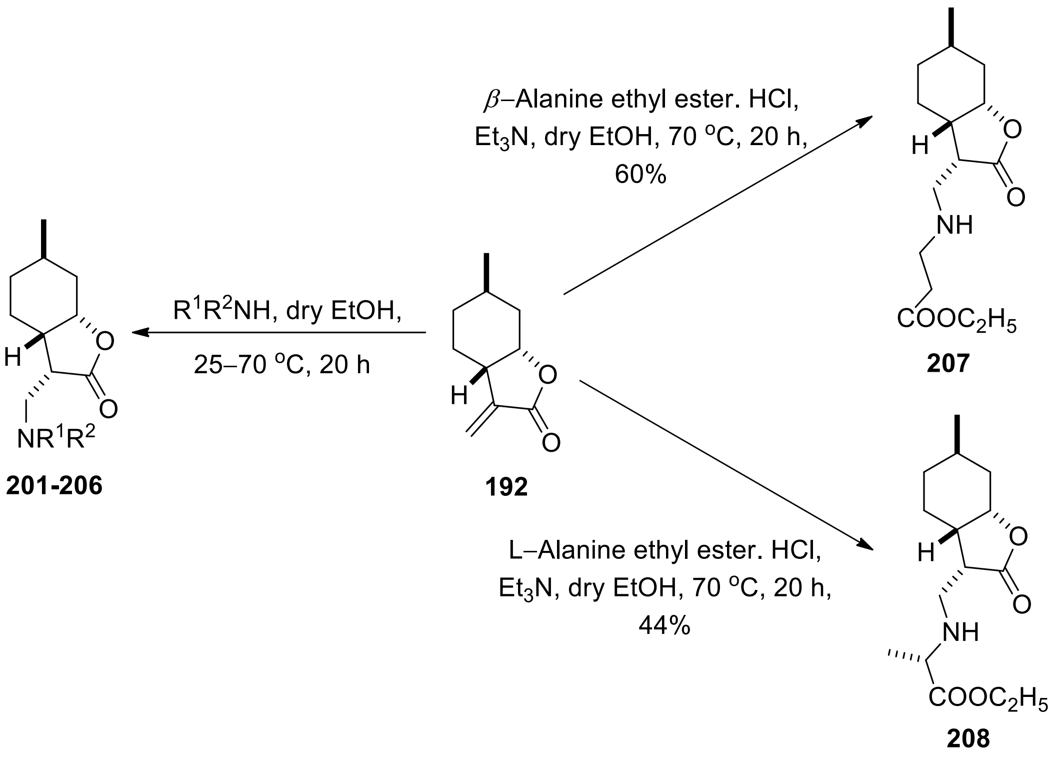
[a] Based on ^{1}H-NMR measurements of the crude product. [b] Isolated yield of **193a**.

After optimizing the conditions for nucleophilic addition with benzylamine, amine adducts **194**–**198** were synthesized from **190** under these conditions (one equivalent of appropriate amine, EtOH, 25 °C) (Scheme 37). Surprisingly, when (*R*)- and (*S*)-*α*-methylbenzylamine and secondary amines were applied, only the formation of aminolactones was observed (Table 5). It is probably due to the steric hindrance of these amines. Besides amines, the best conditions were also successful for the addition of L– or *β*–amino esters as amine sources to prepare some *β*-aminolactones containing amino ester moieties (**199** and **200**, Table 5).



Scheme 37. Nucleophilic addition of **190** to amines and amino esters

The optimized conditions were also applied for the preparation of (+)-neoisopulegol-based *β*-aminolactones **201**–**206** starting from **192** (Scheme 38). Interestingly, under the applied conditions, exclusive formation of the amine adducts was observed. This may be due to the *cis* configuration of **192**, which makes the lactone more hindered for nucleophilic attack (Table 6). The reaction of **192** with some amino esters was effective at elevated temperature to achieve amino ester-based *β*-aminolactone derivatives **207** and **208** (Table 6).



Scheme 38. Nucleophilic addition of **192** to amines

Table 5. Nucleophilic addition reaction of amines with **190**

Entry	Compound	R^1	R^2	Temperature (°C)	Yield (%)
1	**194**	H	(*R*)-α-Methylbenzyl	25	75
2	**195**	H	(*S*)-α-Methylbenzyl	25	71
3	**196**	C_2H_5	C_2H_5	25	50
4	**197**		-$(CH_2)_5$-	25	47
5	**198**	Benzyl	Benzyl	70	59
6	**199**	H	β–Alanine ethyl ester	25	60
7	**200**	H	L–Alanine ethyl ester	25	40

The relative configuration of compounds **194**–**200** and **201**–**208** was determined by means of NOESY experiments.

Table 6. Nucleophilic addition of amines with **192**

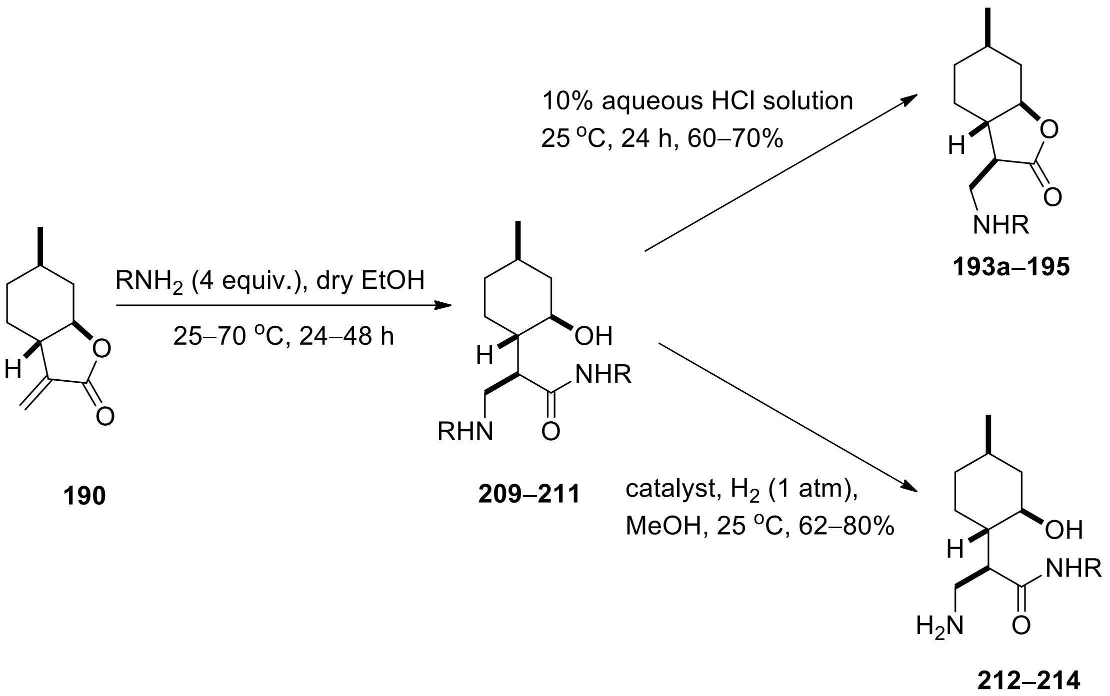
Entry	Compound	R^1	R^2	Temperature (°C)	Yield (%)
1	**201**	H	Benzyl	25	60
2	**202**	H	(*R*)-α-Methylbenzyl	25	65
3	**203**	H	(*S*)-α-Methylbenzyl	25	70
4	**204**	C_2H_5	C_2H_5	25	50
5	**205**		$-(CH_2)_5-$	25	53
6	**206**	Benzyl	Benzyl	70	50
7	**207**	H	β–Alanine ethyl ester	70	60
8	**208**	H	L–Alanine ethyl ester	70	44

3.2.3. Synthesis of β-aminoamides and dipeptides

Nucleophilic addition and ring opening of lactones were simultaneously performed from **190** using excess amines to form β-aminoamides **209**–**211** in one step (Scheme 39). It is interesting that benzylamine recated at room temperature, while (*R*)- and (*S*)-α-methylbenzylamines required higher temperature and longer reactions (Table 7). This is probably due to steric hindrance exerted by the α-methyl group. Our efforts in the opening of lactones with secondary amines failed. Hydrolysis of β-aminoamides under acidic conditions resulted in the original starting material β-aminolactones **193a**–**195** (Scheme 39).

Table 7. Preparation of β-aminoamides from **190** and **201**–**203**

Entry	Compound	R	Temperature (°C)	Reaction time (h)	Yield (%)
1	**209**	Benzyl	25	20	90
2	**210**	(*R*)-α-Methylbenzyl	70	48	58
3	**211**	(*S*)-α-Methylbenzyl	70	48	54
4	**220**	Benzyl	70	24	70
5	**221**	(*R*)-α-Methylbenzyl	70	72	42
6	**222**	(*S*)-α-Methylbenzyl	70	72	45



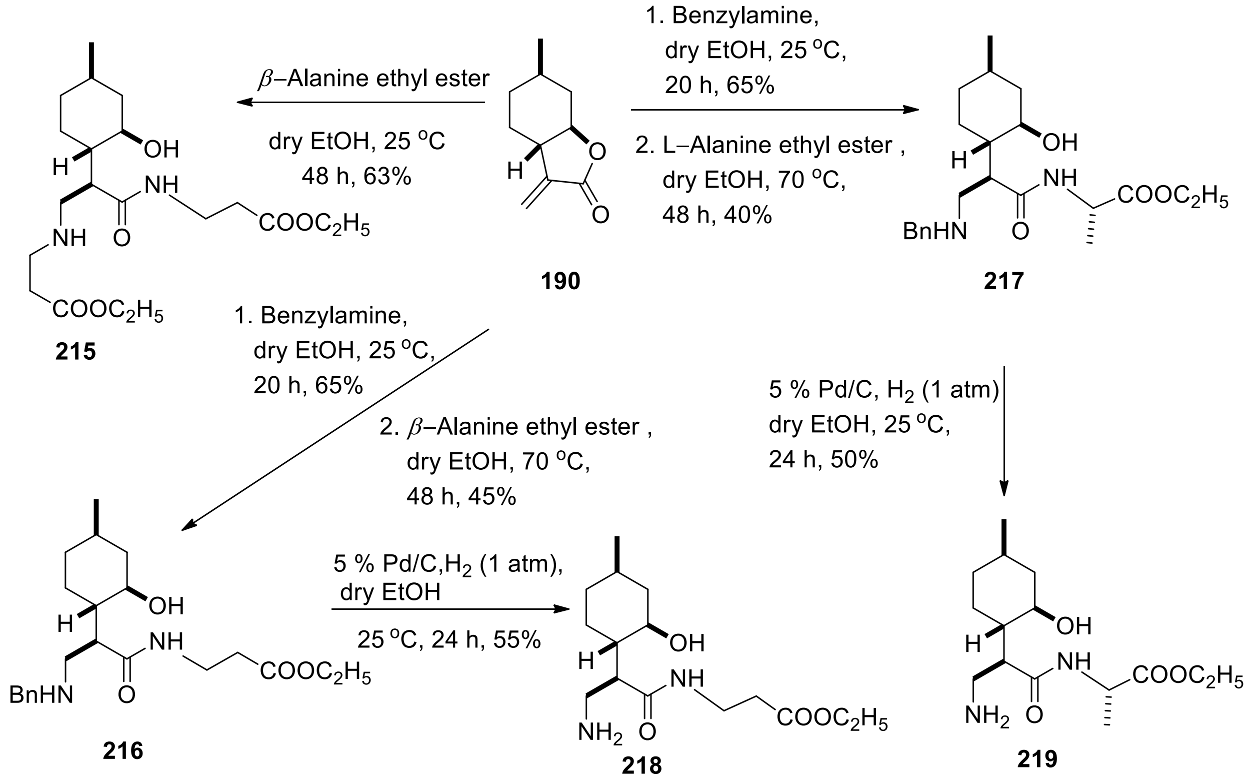
Scheme 39. Preparation of β-aminoamides from **190**

Debenzylation via hydrogenolysis of compounds **209**–**211** over appropriate catalysts in MeOH gave primary aminoamides **212**–**214** in moderate yields (Table 8).

Table 8. Debenzylation of aminoamides **209–211** and **220–222**

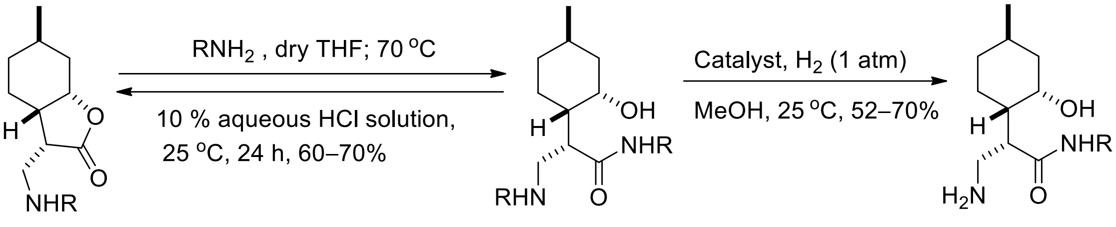
Entry	Compound	R	Catalyst	Reaction time (h)	Yield (%)
1	**212**	Benzyl	5% Pd/C	96	80
2	**213**	(*R*)-α-Methylbenzyl	5% Pd/C	168	62
3	**214**	(*S*)-α-Methylbenzyl	Pd(OH)$_2$/C	200	65
4	**223**	Benzyl	5% Pd/C	96	70
5	**224**	(*R*)-α-Methylbenzyl	5% Pd/C	240	70
6	**225**	(*S*)-α-Methylbenzyl	Pd(OH)$_2$/C	300	52

In further studies, addition and ring-opening reaction of **190** with β–amino ester successfully gave dipeptide **215**. The application of α–amino esters failed despite using long reaction time and elevated temperature. The probable reason is steric hindrance exerted by the α-methyl group of the amino esters. In addition, the opening of *N*-benzyl aminolactone **193a** with both the *α*– and *β*–amino ester proceeded smoothly to give *N*-benzyl dipeptides **216** and **217**. Debenzylation through hydrogenolysis over Pd/C and purification of the crude products gave dipeptides **218** and **219**, suitable starting compounds for peptide synthesis (Scheme 40).



Scheme 40. Preparation of dipeptides from **190**

Our effort to prepare *β*-aminoamides **220**–**222** starting from **192** failed. Fortunately, the synthesis was achieved by reacting *β*-aminolactones **201**–**203** with primary amines under reflux conditions in anhydrous THF[119] (Table 7). However, longer reaction times were needed and lower reaction yields could be observed than in the case of **209**–**211** due to the *cis* configuration of **192**, which makes the lactone more hindered for nucleophilic attack. Similar to **190**, opening of the lactone ring with secondary amines was unsuccessful. Acidic hydrolysis of *β*-aminoamides **220**–**222** led to the original starting material *β*-aminolactones **201**–**203** instead of the expected *β*-amino acids (Scheme 41). Debenzylation with appropriate catalysts gave primary *β*-aminoamides **223**–**225** in moderate yields (Table 8). Note that debenzylation of **211** and **222** could not be performed effectively over Pd/C; instead, $Pd(OH)_2/C$ was the best catalyst applied in this case. The attempted nucleophilic addition and ring opening of **192** with *α*- or *β*-amino esters failed.



201–203 **220–222** **223–225**

Scheme 41. Preparation of *β*-aminoamides from **220**–**222**

3.2.4. Antiproliferative activity

Since several sesquiterpene-based *α*-methylene-*γ*-lactones as well as their derivatives containing the *β*-aminolactone moiety exerted antiproliferative action on adherent human cancer cell lines[12,118], antiproliferative activities of the prepared *β*-aminolactone and *β*-aminoamide analogues were also tested against a panel of human malignant cell lines isolated from cervical (HeLa) and breast (MCF7 and MDA-MB-231) cancers (Table 9). While the *β*-aminolactone-typed monoterpene derivatives proved to be ineffective against the utilized cell lines, the *N*-(*S*)-*α*-methylbenzyl-substituted *β*-aminoamide analogues (**211**, **222**) exhibited modest growth inhibitory activities. The most potent newly-prepared monoterpene analogue was compound **211** exerting antiproliferative activity comparable to those of reference agent cisplatin.

Table 9. Antiproliferative activities of monoterpene analogs

		Growth inhibition (%) ± SEM		
Analog	**Conc. (µM)**	**HeLa**	**MCF7**	**MDA-MB-231**
190	10	–	–	–
	30	–	18.33 ± 2.90	–
192	10	–	–	–
	30	21.10 ± 2.44	–	–
193a	10	16.90 ± 2.60	18.76 ± 2.50	–
	30	28.74 ± 2.30	31.25 ± 3.01	–
195	10	–	–	–
	30	–	17.29 ± 2.90	–

209	10			
	30	31.79 1.95	24.36 2.42	22.75 1.84
237	10	–	–	–
	30	27.09 ± 1.66	–	–
210	10	41.25 ± 2.60	33.96 ± 1.84	24.71 ± 1.86
	30	94.83 ± 0.73	87.93 ± 1.47	70.56 ± 3.51
217	10	–	17.00 ± 2.51	–
	30	–	36.45 ± 1.00	23.43 ± 2.03
220	10	24.36 ± 2.70	17.06 ± 1.46	–
	30	32.43 ± 0.52	40.40 ± 2.88	–
222	10	–	22.70 ± 1.82	19.51 ± 2.35
	30	36.04 ± 0.51	45.41 ± 2.92	34.61 ± 2.22
cisplatin	10	42.61 ± 2.33	53.03 ± 2.29	67.51 ± 1.01
	30	99.93 ± 0.26	86.90 ± 1.24	87.75 ± 1.10

* Growth inhibition values less than 15% are considered negligible and not given numerically. Compounds **194**, **196**, **198**, **201**, and **214** were also examined but did not elicit 15% growth inhibition even at 30 μM.

α-Methylene-γ-lactones are generally believed to be pharmacophores acting as alkylating agents on DNA and proteins.[120] In the present set of (–)-isopulegol analogs, the γ-lactone-type derivatives (**190**, **192**, **193a**, and **195**) exerted weak antiproliferative activities, while the most active member of the presented library (**211**) is not a typical sesquiterpene lactone, but a β-aminoamide. Based on our results, the stereochemistry of the *N*-substituent on amide function [(*S*)-α-methylbenzyl substituent], the *trans* position of the bulky β-aminoamide substituent, and the hydroxyl group on the cyclohexane ring are proposed as a crucial condition of the activity.

Besides interests in biological activities, the reduction of pure β-aminolactones **193a**–**195** together with **201**–**203** to their derivatives, such as 1,3-amino alcohols, proved to be useful chiral auxiliaries in enantioselective synthesis. Besides their value in enantioselective catalysis, 1,3-amino alcohols are good starting materials for the synthesis of various heterocyclic ring systems, such as 1,3-oxazines, 1,3-thiazines or 1,4-oxazepams. Futhermore, epoxidation of (–)-isopulegol **188** and its epimer **191** followed by opening of the oxirane ring with different amines induced by lithium perchlorate affords the corresponding aminodiols. They can also be applied as chiral catalysts, while dihydroxylation of **188** and **199** is useful for the preparation of polyols, which can exert antibacterial activity. On the other hand, diamino alcohols produced by the reduction of

β-aminoamides **209**–**211** as well as **220**–**222** can serve as HIV-protease inhibitors, *Chemokin receptor 2* antagonists, *Cathepsin D* with inhibitor activity or as antitubercular agents.

4. Summary

In my thesis work, systematic synthesis and the study of new monoterpene-based chiral amino alcohols, aminodiols, and *β*-amino acid derivatives derived from natural monoterpenes such as limonene and isopulegol were performed.

Starting from natural (–)-limonene, new terpenoid bicyclic methylene ketones **156**, **157** were obtained through an unexpected intramolecular acylation. Aza-Michael addition of secondary and primary amines onto methylene ketones followed by *in situ* reduction of the resulting aminoketones with sodium borohydride gave new bicyclic terpenoid secondary and tertiary 1,3-amino alcohols **158**, **160**, **162**, **163** and aminodiols **159**, **161** with excellent diastereoselectivities. Regioisomeric aminodiols **164**, **165** were prepared stereoselectively from the unsaturated 1,3-amino alcohols by hydroboration with the $Me_2S{\cdot}BH_3/H_2O_2$ system.

The reduction of bicyclic methylene ketone **156** followed by epoxidation gave a key epoxy alcohol intermediate. Ring opening of the oxirane ring with primary amines induced by lithium perchlorate afforded the required aminodiols **169**–**172**. Substituent-dependent ring closure of the secondary aminodiols with formaldehyde resulted in both spirooxazolidines **174**–**177** and fused 1,3-oxazine **178**.

Cyclization reactions of aminodiols **169**–**172**, resulting in spirocyclic oxazolidines **174**–**177** and an isomeric perhydro-1,3-oxazine-fused compound **178** along with the possible iminium intermediates, were analyzed by a systematic series of comparative DFT models performed at the B3LYP/6-31 + G(d,p) level of theory.

Aminodiols **169**–**172** and their ring-closed derivatives **174**–**178** were applied as chiral catalysts in the enantioselective addition of diethylzinc to benzaldehyde. 1,3-Oxazine **178** proved to be a good catalyst affording *S* selectivities up to *ee* = 80% in the addition of diethylzinc to benzaldehyde.

The synthesis of isopulegol-based *β*-amino acid derivatives has been developed from commercially available (–)-isopulegol. Michael addition of primary and secondary amines towards *α,β*-unsaturated γ-lactones **190**, **192** was accomplished resulting in *β*-aminolactones **193a**–**208** in highly stereoselective reactions. Ring opening of *α,β*-unsaturated γ-lactones **190** as well as β-aminolactones **201**–**203** with different amines furnished β-aminoamides **209**–**211** and **220**–**222** in excellent yields, respectively.

The applicability of aminolactone **193a** in peptide synthesis was examined by opening the lactone ring with α- and β-amino esters providing dipeptides **216**–**219** as promising chiral substrates for the synthesis of foldamers.

The antiproliferative activities of β-aminolactones and β-aminoamides were explored and the structure–activity relationships were studied from the aspects of stereochemistry of the monoterpene ring and the substituent effects on the β-aminoamide ring system. The resulting β-aminoamides **211**, **222** exert marked antiproliferative action on a panel of human cancer cell lines. The *in vitro* pharmacological studies have clearly shown that the *N*-(*S*)-α-methylbenzyl substituent on the β-aminoamide function is essential. The stereochemistry of the β-aminoamides has no influence on the antiproliferative effect.

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