PhD Thesis

Stereoselective synthesis and application of pinane-based bi- and trifunctional chiral ligands

Mounir RAJI

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Mounir RAJI

Supervisor:

Prof. Dr. Zsolt Szakonyi

Institute of Pharmaceutical Chemistry

Doctoral School of Pharmaceutical Sciences

University of Szeged

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Catalysts, **2020**, 10, 474–491

IF: 4.14

[2] Ákos Bajtel, **Mounir Raji**, Matti Haukka, Ferenc Fülöp, Zsolt Szakonyi

Stereoselective synthesis and transformation of pinane-based 2-amino-1,3-diols

Beilstein Journal of Organic Chemistry, **2021**, 17, 983–990

IF: 2.88

[3] **Mounir Raji**, Tam Minh Le, Antal Csámpai, Viktória Nagy, István Zupkó, Zsolt Szakonyi

Stereoselective synthesis and applications of pinane-based chiral 1,4-aminoalcohol derivatives

Synthesis, **2022**, accepted, DOI: 10.1055/s-0040-1719887

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[4] **Mounir Raji**, Tam Minh Le, Thu Huynh, András Szekeres, Viktória Nagy, István Zupkó, Zsolt Szakonyi

Divergent synthesis, antiproliferative and antimicrobial studies of 1,3-aminoalcohol and 3-amino-1,2-diol based diaminopyrimidines

Chemistry & Biodiversity, **2022**, 19 : 5 Paper: e202200077

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Scientific lectures

Raji Mounir

Synthesis of bi- and trifunctional pinane-based chiral synthons

XLII. Kémiai Előadói Napok

Szeged, 28-30 October 2019, oral presentation

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Synthesis and application of chiral 3-amino-1,2-diols derived from natural (−)-β-pinene

MTA 2019, Szteroid- és Terpenoidkémiai Munkabizottság

Szeged, 20-22 November 2019, oral presentation

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Synthesis and investigation of pinane-based chiral tridentate ligands in the asymmetric catalytic reactions

3rd International Conference on Pharmaceutical and Medical Sciences

Martin, Kraków, Szeged, 24-26th of September 2020, oral presentation

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Synthesis and *in vitro* Antiproliferative Studies of Pinane-Based Pyrimidine Derivatives

XXIX European Colloquium on Heterocyclic Chemistry

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Synthesis and investigation of pinane-type, pyridine-based di- and trifunctional synthons

A Szegedi Ifjú Szerves Kémikusok Támogatásáért Alapítvány 21. tudományos előadóülése

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Stereoselective synthesis and antimicrobial evaluation of monoterpene-based bi-, tri and tetrafunctionalized chiral synthons

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Pharmacological investigation of a newly synthesized monoterpene derivatives on human cancer cell lines in vitro

11th ISCTICO – HUPHAR – IUPHAR – Conference, October 27-30, 2021 - Pécs, Hungary, P84, oral presentation

List of abbreviation

AcOH: Acetic Acid

Boc_2O: Di-*tert*-butyl dicarbonate

t-BuOH: *tert*-Butyl alcohol

CDI: Carbonyldiimidazole

CSI: chlorosulfonyl isocyanate

DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCC: *N*,*N*'-Dicyclohexylcarbodiimide

DCE: 1,2-Dichloroethane

DCM: Dichloromethane

DIBAL: Diisobutylaluminium hydride

DIPEA: *N*,*N*-Diisopropylethylamine

DMAP: 4-Dimethylaminopyridine

DMF: Dimethylformamide

Et_2O: Diethyl ether

Et_2Zn: Diethylzinc

Et_3N: Triethylamine

EtOAc: Ethyl acetate

EtOH: Ethanol

GC: Gas chromatography

HMPTA: Hexamethylphosphoramide

i-PrOH: Isopropyl alcohol

LAH: Lithium aluminium hydride

Li-Nap: Lithium naphthalenide

*m*CPBA: *m*-Chloroperoxybenzoic acid

MeCN: Acetonitrile

MeOH: Methanol

MeONa: Sodium methanolate

MsCl: Methanesulfonyl chloride

MW: Microwave

n-BuLi: *n*-Butyllithium

NMO: *N*-Methylmorpholine *N*-oxide

NOESY: Nuclear Overhauser Effect SpectroscopY

p-TsOH: *p*-Toluenesulfonic acid

rt: Room Temperature

SAR: Specific absorption rate

TBAB: Tetrabutylammonium bromide

TBDPSCl: *t*-Butyl(chloro)diphenylsilane

t-BuOCl: *t*-Butyl hypochlorite

t-BuOOH: *t*-Butyl hydroperoxide

TEA: Triethylamine

TFA: Trifluoroacetic acid

TFAA: Trifluoroacetic anhydride

THF: Tetrahydrofuran

TMEDA: Tetramethylethylenediamine

$Vo(acac)_2$: Vanadium(IV)-oxyacetylacetonate

1. Introduction

The use of chiral synthons in asymmetric heterogeneous and homogeneous catalysis is becoming more common in organic chemistry[1,2]. It has been found that several natural products, in particular, monoterpenes such as camphor[3–5], (+)-pulegone[6], α- and β-pinene[7–10], (–)-myrtenol[11], (+)-3-carene[12], and (–)-isopulegol[13] may serve as excellent sources for producing chiral bi- and trifunctional compounds including aminoalcohols and aminodiols, as well as heterocycles.

Besides their chemical value, aminoalcohols and aminodiols possess significant biological activities, such as cyclin-dependent kinase inhibitor[14], cytokine modulator[15] or even renin inhibitor[16] effects. Aminodiols have also been reported to express biological properties such as a gastro-protective effect[17] or HIV protease[18] inhibition, or even antibiotic[19] and anticancer activity[20]. Furthermore, these moieties have proven to be highly efficient building blocks[21–23], and have been used as starting materials for the stereoselective synthesis of compounds of pharmacological importance. For example, 1,3-oxazines potent anticancer compounds exhibit tumor-selective cytotoxicity[24] and they are also used to prevent Alzheimer's disease[25], while 1,3-thiazines are applied for their analgesic activity[26] or as cannabinoid receptor (CBR) agonists[26]. 2-Iminothiazolidines often bear antifungal and antimicrobial[27] effects and they exhibit BACE1 inhibitor[25], cannabinoid receptor agonist[26,28,29] or neuroprotective[30] activities. In addition to their application in synthetic chemistry, aminodiols may also be used as chiral ligands and auxiliaries in enantioselective reactions[31–33]. As a result, the preparation of new chiral aminodiols has been a topic of increasing interest in recent years. Several chelating ligands have been prepared[34–37], but new types synthesized from inexpensive starting materials are still needed.

Accordingly, monoterpene-based 1,2- and 1,3-aminoalcohols have been demonstrated to be excellent chiral auxiliaries in a variety of stereoselective transformations, notably intramolecular radical cyclizations[38], intramolecular [2+2] photocycloadditions[39], and Grignard addition[40]. Among these, the enantioselective addition of diethylzinc to aldehydes initiated by Oguni and Omi has attracted considerable attention. However, there are only a few examples of 1,4-aminoalcohols, derived from monoterpenes, such as (+)-camphor[35,41–47], (−)-fenchone[35,41,42,44], norbornene[48], and (−)-menthone[49] used successfully as chiral catalysts with high catalytic activity. Furthermore, the 1,4-aminoalcohol moiety has proven to be a privileged structural motif found in a wide range of biologically relevant molecules, including Terfenadine[50] and Ibutilide[51].

Additionally, several aminodiols, including 3-amino-1,2-diols, combine the characteristics of both 1,2- and 1,3-aminoalcohols. They play a crucial role in many areas of human life. A number of these compounds, *e.g.*, aristeromycin[15,19,20,23], have been used as starting materials for the synthesis of compounds with important pharmacological properties. They may also serve as starting materials for the synthesis of a wide range of biologically active compounds (*e.g.* cytoxazone)[15,19]. Second on the list of commonly used aminodiols are derivatives bearing the 2-amino-1,3-diol unit due to its prevalence in human cells in the form of sphingosine, which utilizes sphingolipids as second messengers, and it plays a crucial role in cell growth, differentiation, cell recognition, and apoptosis[52–58]. In addition to their biological importance, these compounds have been successfully used in enantioselective synthesis as chiral ligands[59,60].
On the another hand, natural pyrimidine compounds are known for their biological values and they are present in various natural products, such as thiamine (vitamin B1)[61] or nucleosides[62]. As a class, pyrimidine-related molecules have even greater pharmacological potential. Several amino- or diaminopyrimidines, for instance, are known to possess anti-inflammatory[62], anti-HIV[63], antituberculotic[64], antiproliferative[65], antineoplastic[66], antituberculotic[67], antimalarial[68], as well as anticancer activity[69,70]. Furthermore, in the last few decades, the coupling between aminoalcohols and pyrimidine gained a high interest in medicinal chemistry, thanks to their bioactivities, like aristeromycin[71] and neplanocin A[72] displaying antibiotic and antitumor activity, respectively. Additionally, carbovir and BCA have been identified as inhibitors of the human immunodeficiency virus (HIV) or anticancer agents, for instance, JAK and KDR or ALK inhibitors[73–75].

Considering the advantages of monoterpenes, the aim of my PhD work was to synthesize varied bi- and tri-functionalized pinane building blocks starting from commercially available enantiopure natural monoterpenes (−)-α and β-pinene, (−)-myrtenol, and (−)-apopinene as shown in Figure 1. Additionally, we studied their ring-closure processes with aldehydes and 2-phenylisothiocyanate, and we also performed couplings between pinane-based aminoalcohols with a variety of pyrimidine compounds to obtain pyrimidine derivatives. Aminodiols and their ring-closed derivatives were planned to be applied as chiral catalysts in the enantioselective addition of Et_2Zn to benzaldehyde.

On the other hand, we also planned to combine pinane-based aminoalcohols and a representative aminodiol reported previously with diaminopyrimidine moieties to study the antiproliferative activity of the prepared compounds on multiple human cancer cell lines along with our newly developed pinane-derived 1,4-aminoalcohols. Furthermore, their antimicrobial activity against Gram-negative and Gram-positive bacteria has also become the focus of our interest.

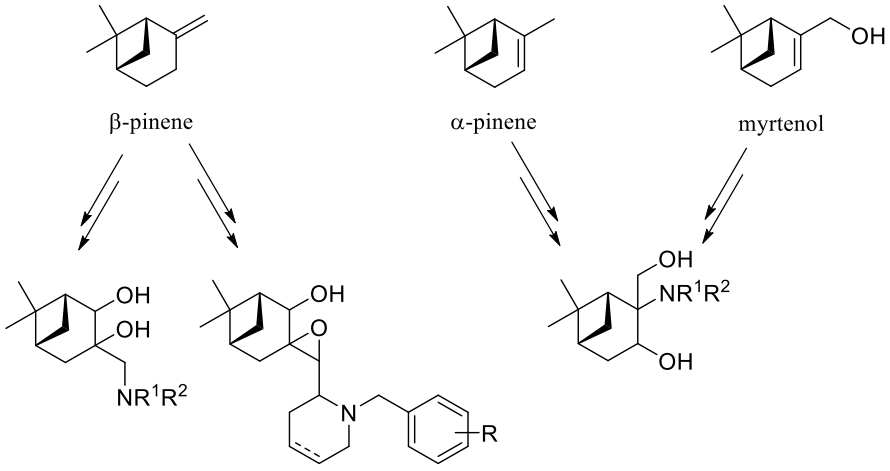


Figure 1

2. Literature survey

2.1 Synthesis and importance of chiral aminoalcohols

2.1.1 Synthesis and application of chiral alicyclic 1,3-aminoalcohols

In recent years, a variety of approaches have been established for the synthesis of the 1,3-aminoalcohol moiety. For instance, the reduction of β-amino acids or esters (**II**) obtained via cycloaddition reaction, followed by solvolysis[76–78], or by aza-Michael-addition of amines carried out with α,β-unsaturated esters[78–80]. Common methods used for the preparation of γ-aminoalcohols are hydrogenolysis and the catalyzed ring opening of β-lactams followed by reduction[79,81,82] **(I)**. However, the most frequently applied approach is the stereoselective Mannich condensation carried out with (**IV)** followed by stereoselective reduction of the formed amino ketones[83,84] (**V**). Furthermore, β-hydroxynitriles (**III**) and dihydrooxazines (**VI**), obtained by 1,3-dipolar cycloaddition, have also proven to be good intermediates for the preparation of alicyclic 1,3-aminoalcohols[85–88]. Figure 2 summarizes the most often used methods for the preparation of γ-aminoalcohols based on the literature.

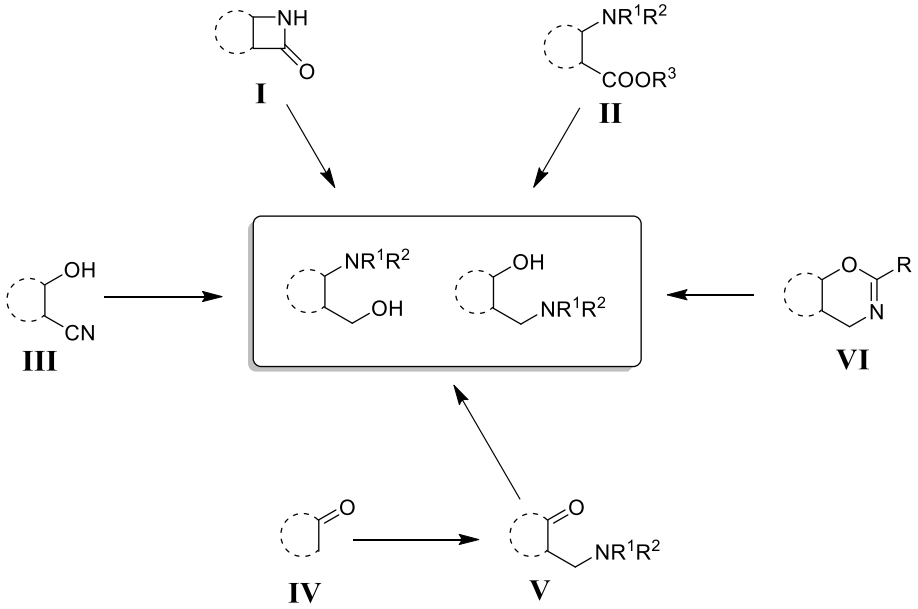


Figure 2

In addition to their biological values, enantiomerically pure aminoalcohol and aminodiol derivatives are applied as chiral auxiliaries or catalysts in enantioselective transformations.

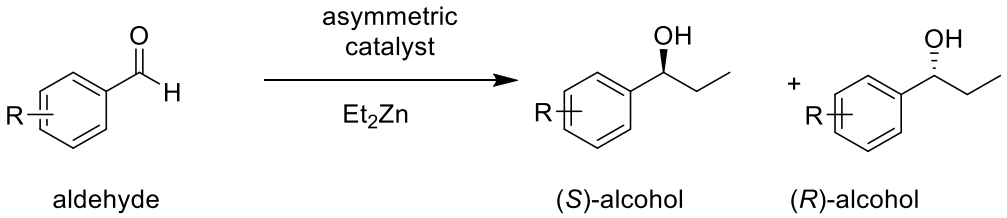
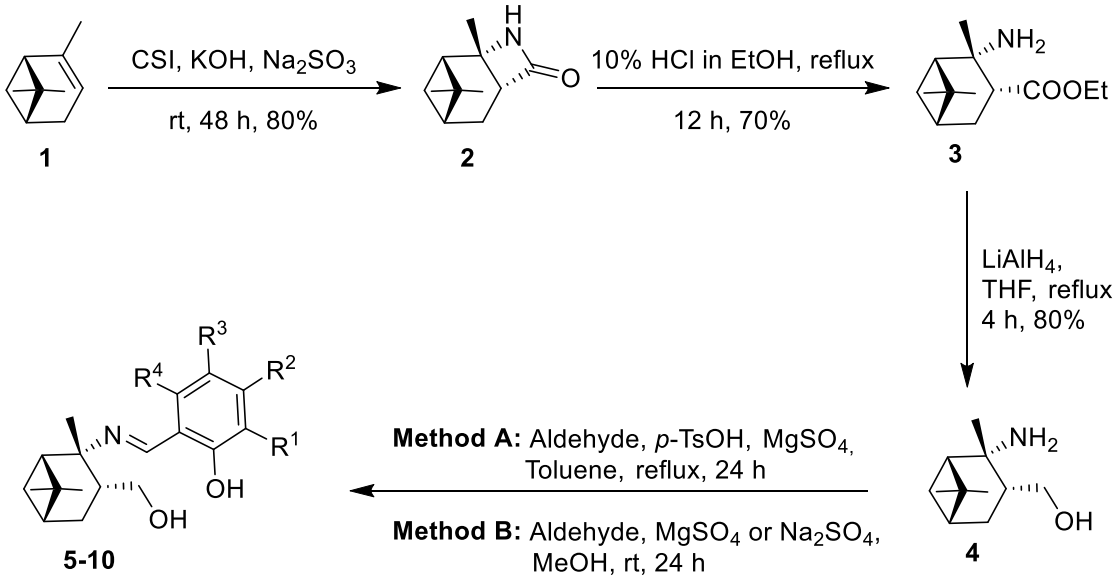


Figure 3

After the breakthrough achieved by Kitamura *et al.*[89] in the asymmetric synthesis, several chiral ligands derived from optically active monoterpenes were developed, such as (+)- and (−)-pinene[7,90,91], (+)-carene[7,11,12], (–)-menthone[37], (–)-fenchone[92], (+)-sabinol[93], (–)-nopinone[94] or (–)-pulegone[6]. Then these were subsequently applied in enantioselective transformations.

In order to prepare 1,3-aminoalcohol **4**, (+)-α-pinene took part in a cycloaddition reaction with CSI, and the obtained β-lactam was then reacted with ethanol containing HCl to give β-aminoester **3**, which was subsequently reduced by LAH to afford the desired 1,3-aminoalcohol[95] **4**. A series of chiral Schiff bases **5–10** were obtained by reacting 1,3-aminoalcohol **4** with different salicylaldehydes (Scheme 1).

At first, Jaworska *et al*. investigated the catalytic value of the synthesized Schiff bases **5–10** in the enantioselective addition of diethylzinc to benzaldehyde but only a moderate *ee* of 36% was observed with (*S*)-selectivity. However, by replacing benzaldehyde with *p*-bromobenzaldehyde, the catalytic value increased to 90% *ee* with the same selectivity. In the next stage, the enantioselective cyanation of aldehydes with benzaldehydes was examined in the presence of 20 mol% of chiral Schiff bases **5–10**, and an *ee* of 60% was achieved. Note, however, that in the case of (*E*)-cinnamaldehyde, the highest *ee* was over 99% with (*R*)-selectivity[96].



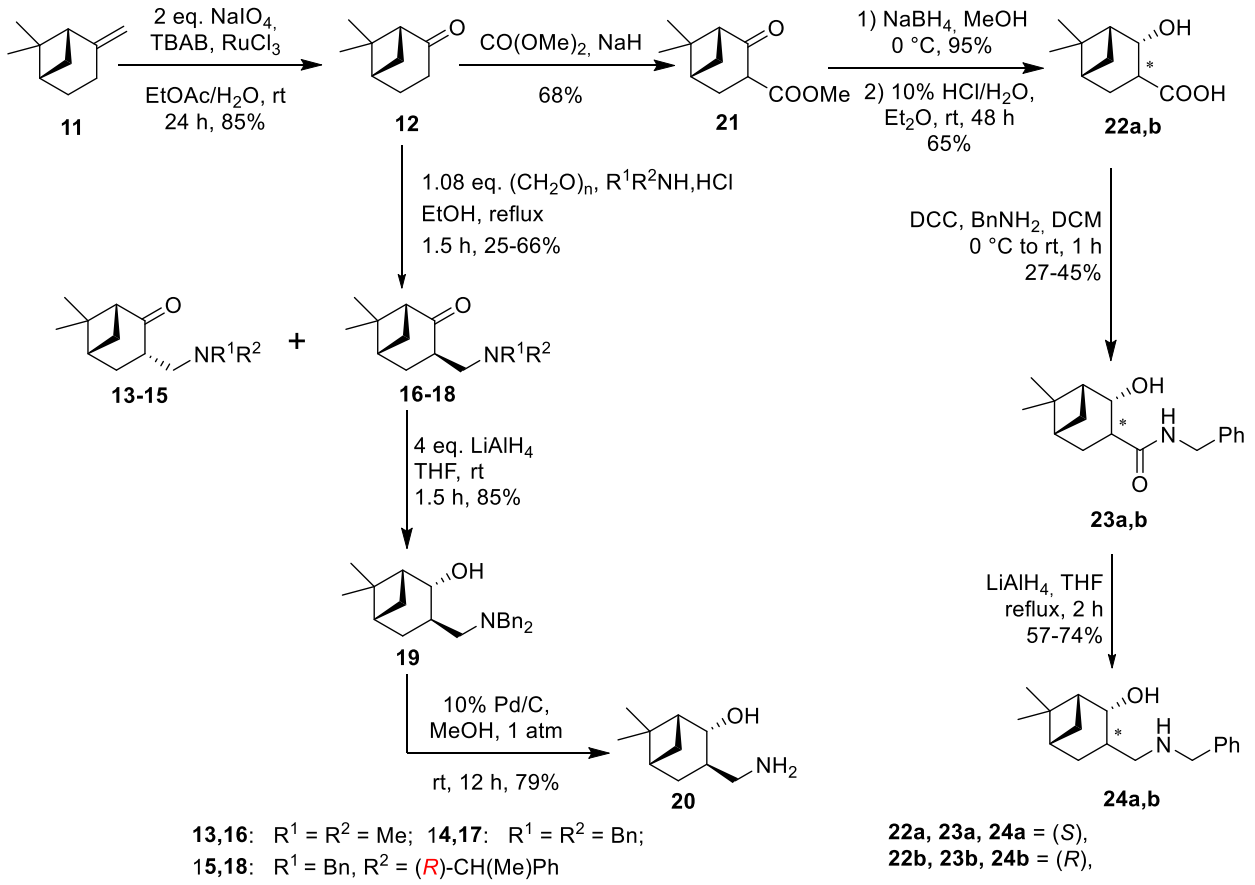
5: $R^1 = R^2 = R^3 = R^4 = H$ (57%)
6: $R^1 = Me$, $R^2 = R^3 = R^4 = H$ (46%)
7: $R^1 = t\text{-Bu}$, $R^2 = R^4 = H$, $R^3 = Me$ (88%)
8: $R^1 = R_3 = t\text{-Bu}$, $R^2 = R^4 = H$ (60%)
9: $R^1 = R^2 = R^4 = H$, $R^3 = Br$ (77%)
10: $R^1 = H$, R^2= *N*,*N*-diethylamino, $R^3 = R^4 = H$ (64%)

Scheme 1

Natural monoterpene-based 1,3-aminoalcohol was prepared by Szakonyi and co-workers starting from (−)-β-pinene **11**. By oxidizing **11**, the key intermediate nopinone **12** was formed, which was converted to Mannich-bases **13–18** in the presence of paraformaldehyde and amine hydrochlorides. The $LiAlH_4$-mediated reduction of **17** proceeded stereoselectively, and the resulting dibenzyl aminoalcohol **19** took part in a catalytic debenzylation in the presence of Pd on carbon leading to the formation of pinane-based primary 1,3-aminoalcohol **20**.

In the same work, another path was developed for the synthesis of 1,3-aminoalcohols starting from nopinone **12**. β-Oxoester **21** was prepared by reacting **12** with dimethyl carbonate under alkaline conditions, followed by stereoselective reduction and hydrolysis of the esters formed. Diastereoisomers **22a** and **22b** were then successfully converted into amides **23a,b** with benzylamine in the presence of DCC. After the reduction of amides with LAH, pinane-based secondary 1,3-aminoalcohols **24a,b** were obtained (Scheme 2). Aminoalcohols **19**, **20**, **23**, and

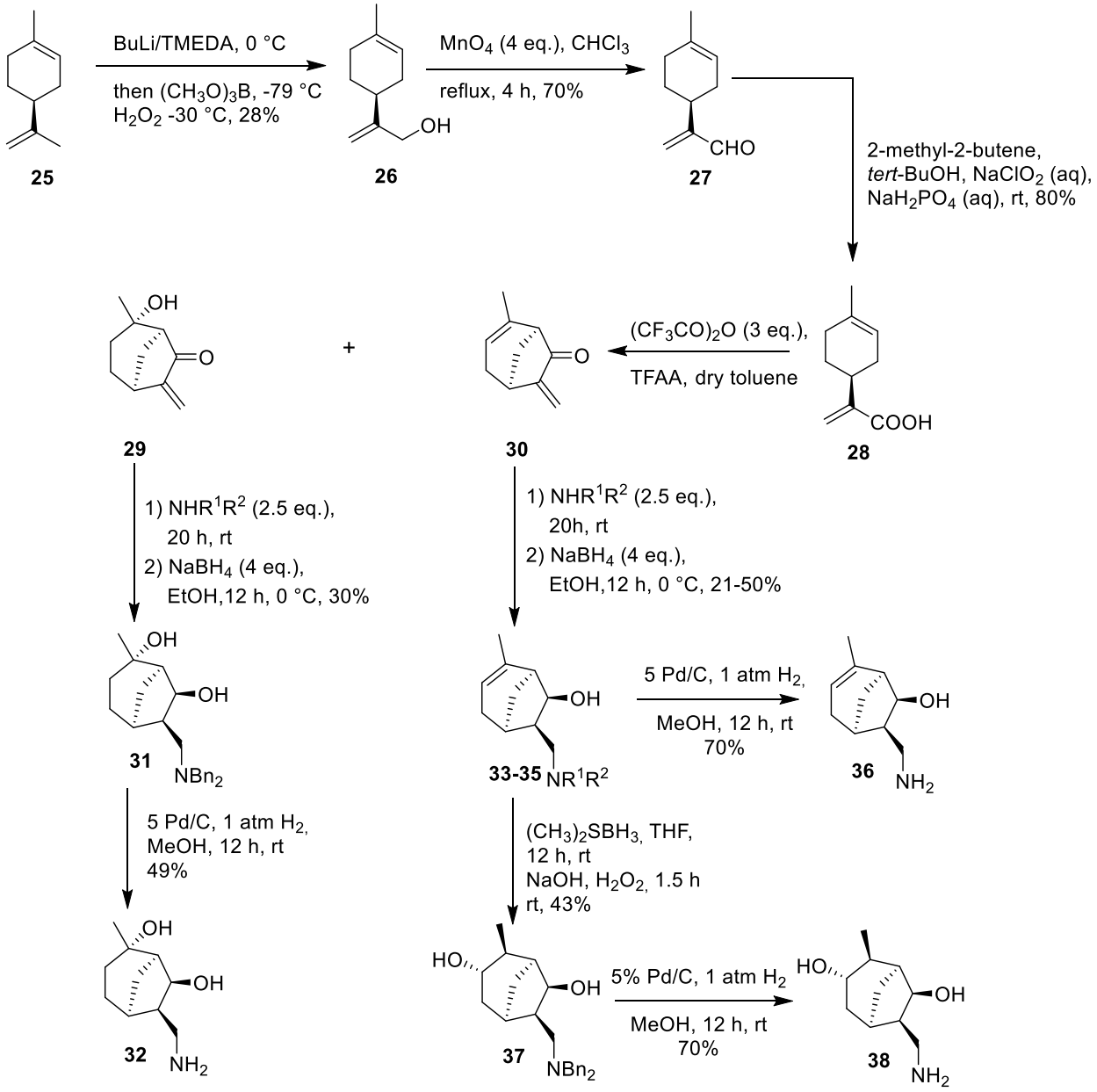
24 (10 mol%) were applied as chiral catalysts in the addition of Et_2Zn to benzaldehyde observing low catalytical activity[94].



Scheme 2

In 2017, a library of chiral 1,3-aminoalcohols was synthesized in several steps starting from (−)-(*S*)-limonene. After an allylic hydroxylation in the presence of a strong base followed by oxidations, the resulting (*S*)-isoperyllic acid **28** took part in an unexpected intramolecular ring closing reaction in the presence of $(CF_3CO)_2O$ (TFAA) and gave two products: hydroxy-substituted analogue **29** and its methylene ketone derivative **30**. Aza-Michael addition of secondary and primary amines on **29** and **30** followed by *in situ* reduction of the ketone function with $NaBH_4$ followed by hydrogenolysis of **31** and **33–35** over Pd/C in MeOH produced primary aminodiol **32** and aminoalcohol **36**.

The synthesis of structural isomer aminodiol **38** was achieved by the hydroboration of compound **33** upon treatment with borane dimethyl sulfide followed by oxidation of the boron intermediate with hydrogen peroxide[97]. (Scheme 3)



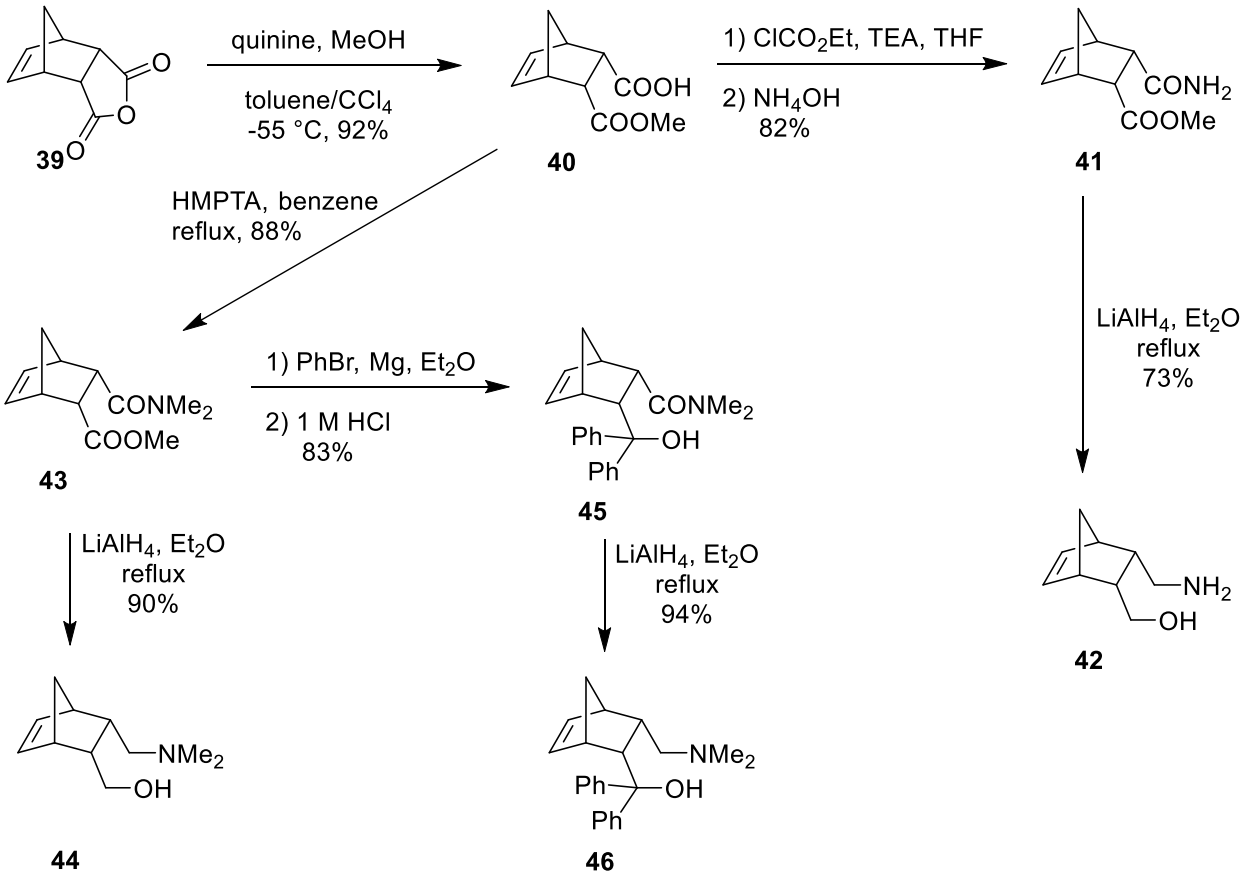
33: $R^1 = R^2 = CH_2Ph$; **34**: $R^1 = H$, $R^2 = CH(Me)Ph$ (*R*); **35**: $R^1 = H$, $R^2 = CH(Me)Ph$ (*S*)

Scheme 3

2.1.2 Synthesis and application of chiral alicyclic 1,4-aminoalcohols

While the synthesis of 1,2- and 1,3-aminoalcohols has undergone noticeable progress in recent years, only a handful of new synthetic approaches to 1,4-aminoalcohols has been reported. These include asymmetric Mannich reactions of α-thio acetaldehydes[98], the use of a Grignard reagent on 2-tosylaminotetrahydrofuran[99], applying silyl enol ethers or 1,3-dicarbonyl derivatives in the Lewis-acid-catalyzed ring opening reaction of semicyclic *N*,*O*-acetals[100,101], addition of amines to 2-sulfinyl dienes[102] or reductive N−O bond cleavage of 1,2-oxazines[103]. In contrast, only a few examples of monoterpene-based 1,4-aminoalcohols, including (+)-camphor[46], (−)-fenchone[35], norbornene[48], and (−)-menthone[49] have been successfully used as chiral catalysts.

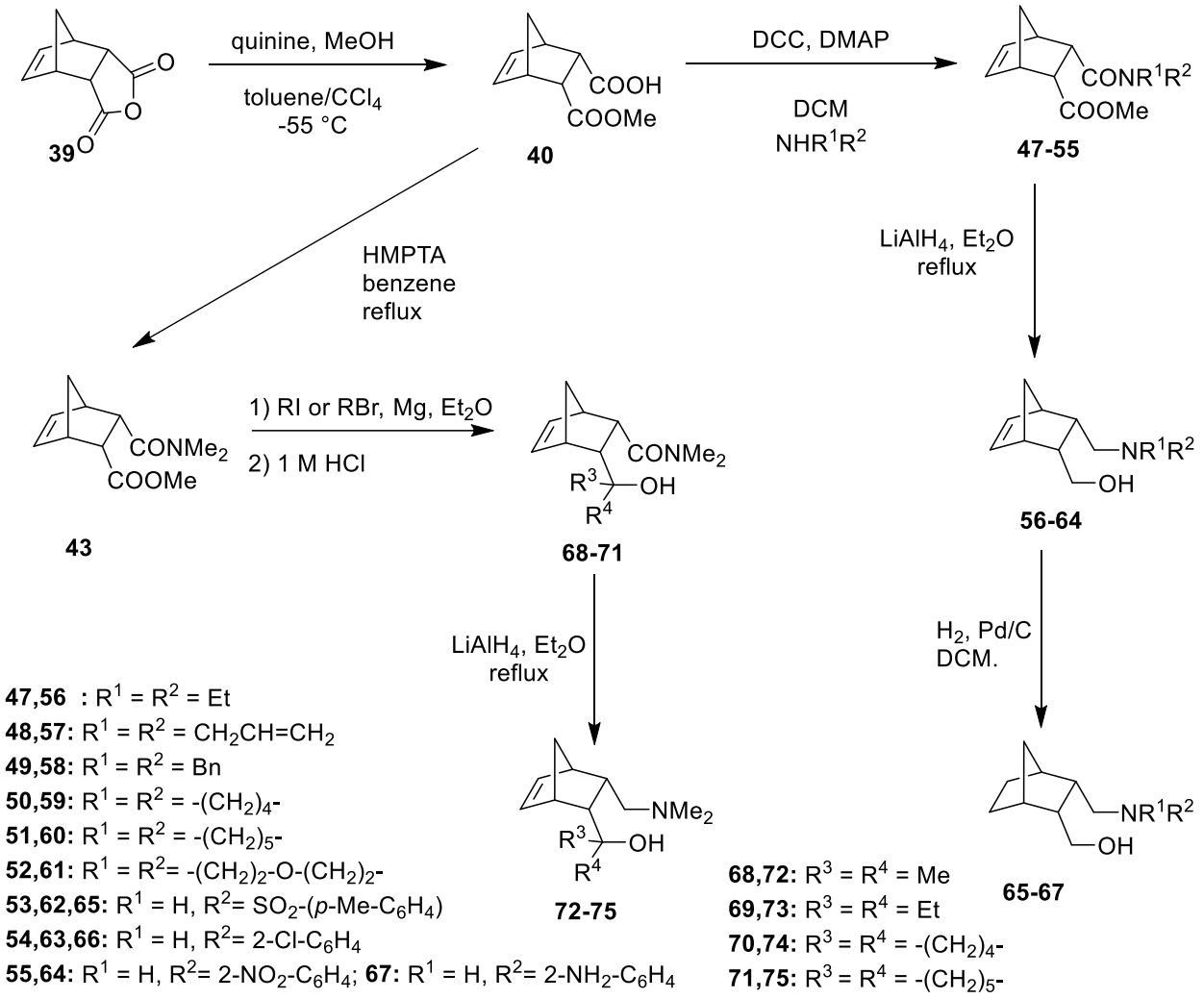
In 2005, a Turkish team succeeded in the development of a library of norbornene-based 1,4-aminoalcohols. The quinine-mediated desymmetrization of anhydride **39** with methanol resulted in *cis*-monoester (−)-**40**. After a chemoselective activation of the carboxylic acid group with ethyl chloroformate, the amide function was built up with NH_4OH, and the resulting compound **41** took part in a subsequent LAH reduction leading to the formation of primary 1,4-aminoalcohol **42**. *N*,*N*-Dimethyl aminoalcohol **44** was formed by treating monoester (−)-**40** with hexamethylphosphoramide followed by LAH reduction of **43** affording *N*,*N*-dimethyl-substituted *cis*-1,4-aminoalcohol **44**. Utilizing the Grignard method, **43** was treated with phenylmagnesium bromide to form diphenyl-substituted derivative **45**. The latter after reduction afforded new tertiary 1,4-aminoalcohol **46** as shown in Scheme 4[104].



Scheme 4

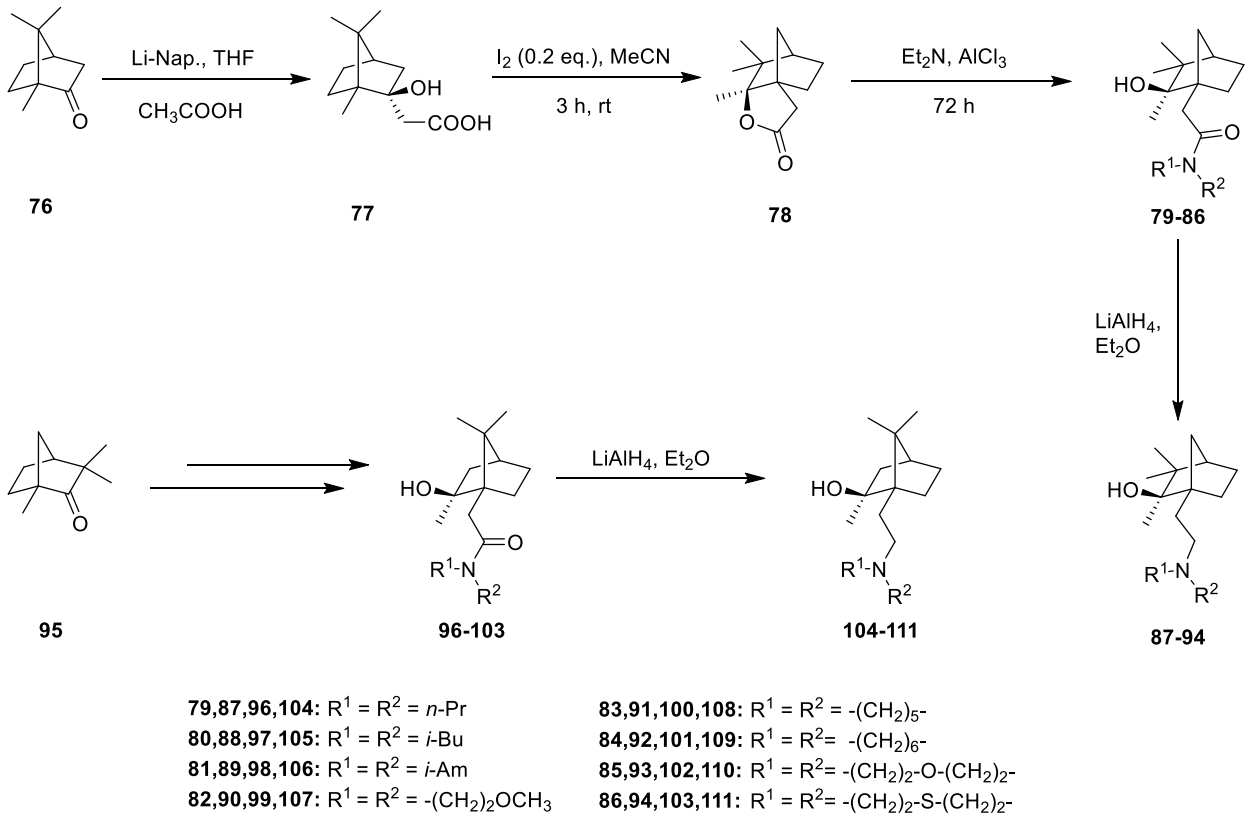
Two years later, another research group decided to pursue the aforementioned work. The *N*-functionalization of key intermediate *cis*-monoester **40** was done by the DCC coupling method leading to the formation of *N*,*N*-disubstituted acyclic and cyclic amides **47–55**. LAH reduction of **9–17** afforded tertiary 1,4-aminoalcohol library **56–64**. In the case of **62–64** the norbornene backbone was subsequently transformed into norbornane derivatives **65–67** via Pd-catalyzed hydrogenation. On the other hand, the functionalization of the ester group of *N*,*N*-dimethyl amide derivative **43** was performed by Grignard addition. Subsequent reduction of **68–71** delivered chiral 1,4-aminoalcohols **72–75**. (Scheme 5)

The obtained aminoalcohol derivatives **56–67** and **72–75** were applied as chiral ligands in the addition of Et_2Zn to benzaldehyde. The best *ee* values were observed for norbornane **65–67** (*ee* > 80%) with the highest value of 97% with (*S*)-selectivity[48].



Scheme 5

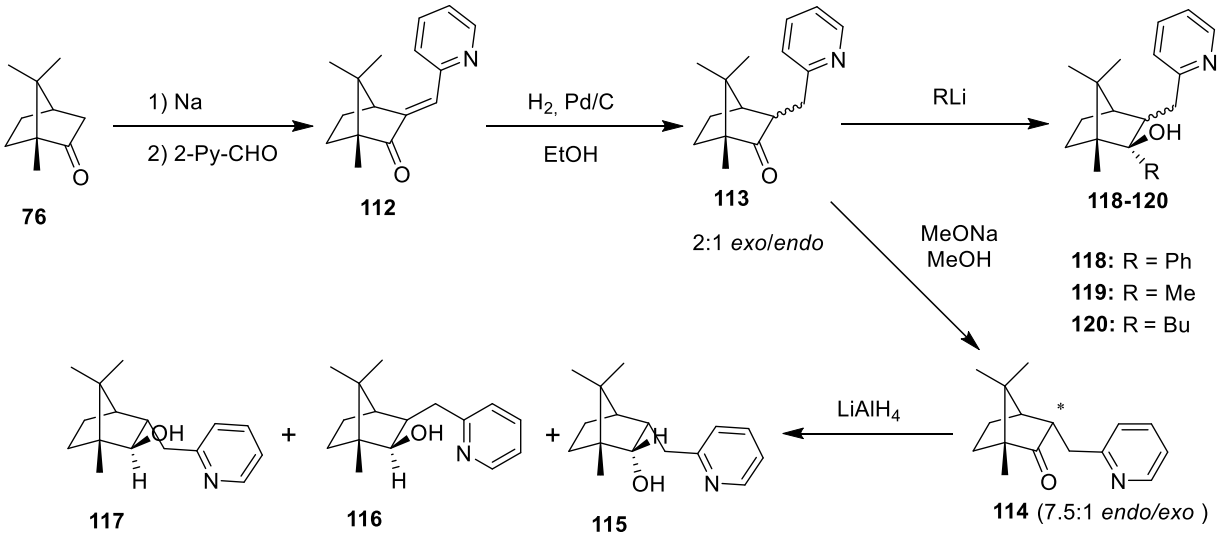
Another synthetic route to obtain monoterpene-based 1,4-aminoalcohols is presented on Scheme **6**. A nucleophilic attack of an *in situ* generated acetic acid dianion on (+)-camphor, followed by a lactonization of **77** in the presence of a catalytic amount of iodine, triggered a Meerwein-type rearrangement[105] to give intermediate **78**. The reaction of lactone **78** with secondary amines in the presence of aluminium chloride resulted in the formation of a variety of hydroxyamides **79–86**, which were easily reduced to generate a library of 1,4-aminoalcohols **87–94**. Likewise, the same protocol was applied for the preparation of the second library of **104–111** starting from (−)-fenchone (**76**) (Scheme 6). Aminolalcohols **87–94** and **104–111** were applied as chiral catalysts (5 mol%) in the enantioselective addition of diethylzinc to aldehydes with good catalytic results (*ee* > 90%) with (*S*)-selectivity[44] observed in several cases.



79,87,96,104: $R^1 = R^2 =$ *n*-Pr
80,88,97,105: $R^1 = R^2 =$ *i*-Bu
81,89,98,106: $R^1 = R^2 =$ *i*-Am
82,90,99,107: $R^1 = R^2 = -(CH_2)_2OCH_3$
83,91,100,108: $R^1 = R^2 = -(CH_2)_5-$
84,92,101,109: $R^1 = R^2 = -(CH_2)_6-$
85,93,102,110: $R^1 = R^2 = -(CH_2)_2-O-(CH_2)_2-$
86,94,103,111: $R^1 = R^2 = -(CH_2)_2-S-(CH_2)_2-$

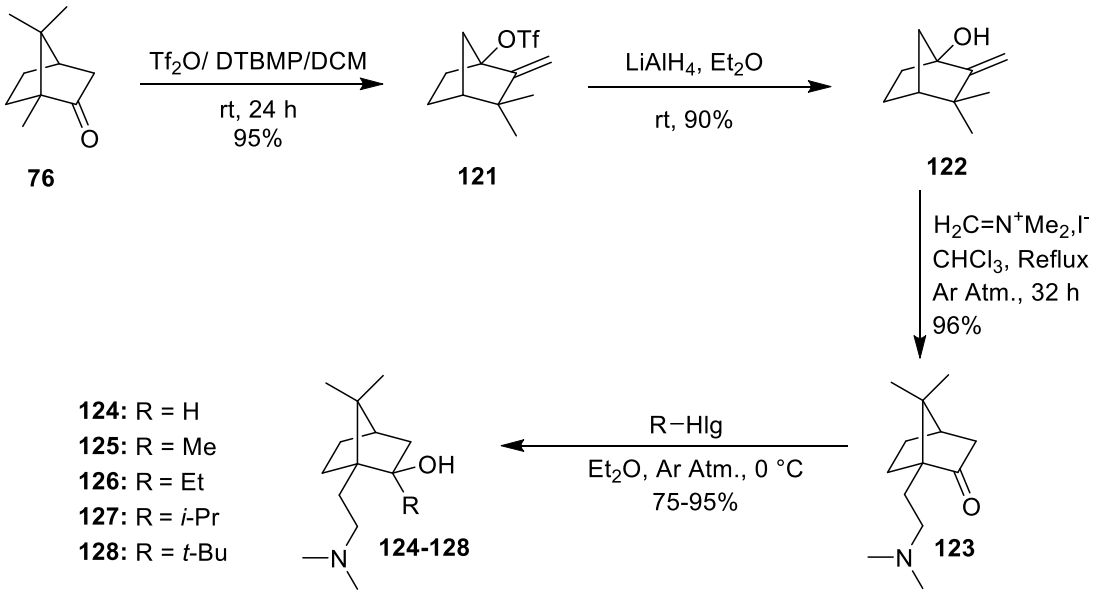
Scheme 6

Nevalainen and his team[46] reported a new method for the preparation of camphor-based 1,4-aminoalcohols by reacting (+)-camphor with picoline aldehyde to give enone **112**. The palladium-catalyzed hydrogenation of this latter compound rendered ketone **113** as a 2:1 *exo*/*endo* mixture of diastereoisomers. After isomerization of the mixture with sodium methoxide in methanol, the *endo* diastereoisomer became the major product with a 7.5:1 *endo*/*exo* ratio. The LAH reduction of this mixture of ketones (**114**) afforded 1,4-aminoalcohols **115–117**. *trans*-**117** (2-*exo*,3-*endo*) and the 3.2:1 mixture of *cis*-**115** and **116** (2-*endo*,3-*endo*/2-*exo*,3-*exo*) have been separated with flash chromatography. The 2:1 *exo*/*endo* mixture **113** took part in an organometallic reaction in a polar solvent and the most favorable approach was an attack from the less hindered *endo* side leading to *cis* (2-*exo*/3-*exo*) products **118–120** (Scheme 7). In a subsequent reaction, ligands **115–120** were used in the catalytic addition of diethylzinc to benzaldehyde (5 mol%) delivering products with moderate to good enantioselectivity (*ee* = 88%) in favor of (*S*) configuration applying **117** (2-*exo*,3-*endo*).



Scheme 7

In 2003, García *et al.*[106] reported a method for the preparation of camphor-based 1,4-aminoalcohols. The enantiospecific Wagner–Meerwein rearrangement was applied on (+)-camphor to prepare 1-norbornyl triflate **121**, followed by a LAH reduction and a second Wagner–Meerwein rearrangement on 2-methylenenorbornan-1-ol **122** to obtain aminoketone **123**. Finally, a highly stereocontrolled addition of different nucleophiles to the carbonyl function resulted in the library of δ-amino isoborneols **124–128**. When **124–128** were tested in diethylzinc addition to benzaldehyde with only a moderate catalytic chiral induction observed. (Scheme 8)



Scheme 8

2.2. Synthesis and importance of chiral aminodiols

2.2.1. Synthesis and application of chiral alicyclic 3-amino-1,2-diols

Since 3-amino-1,2-diols combine the chemical and pharmacological properties of both 1,2- and 1,3-aminoalcohols, the preparation of 3-amino-1,2-diols has gained a high interest in recent decades, and a variety of synthetic methods have been developed to obtain these trifunctional synthons. The most common methods are aminolysis of epoxyalcohols[107] or hydrolysis of epoxyamines[108]. Additional reactions, such as dihydroxylation of protected amino alkenes[109] or nucleophilic substitution of a good leaving group[110], can also be used for the same purpose. The ring opening with nitrogen nucleophiles (ammonia, amines, azides) of epoxyalcohols prepared by Sharpless epoxidation has been frequently applied for the asymmetric synthesis of 3-amino-1,2-diols[111–118].

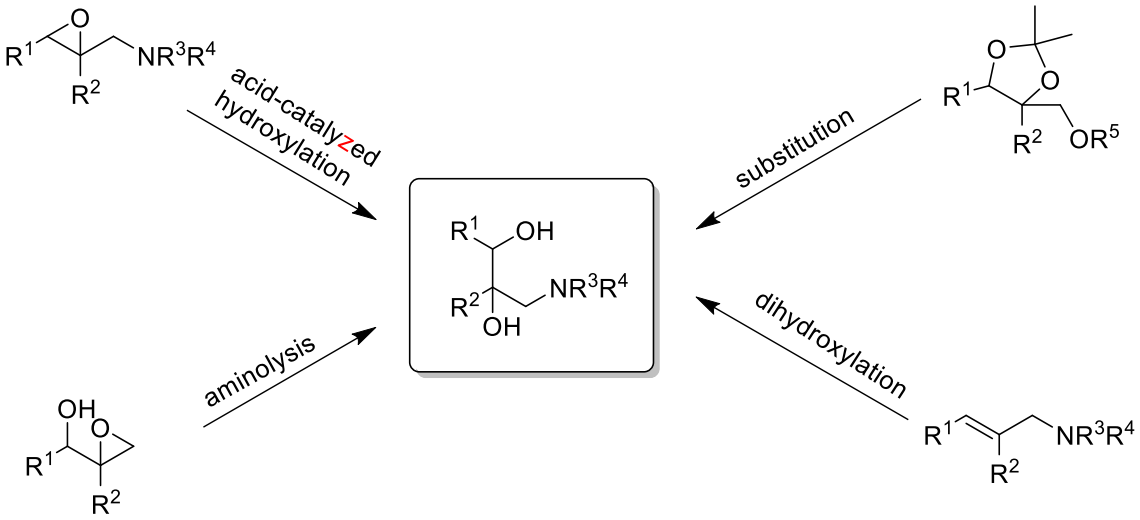
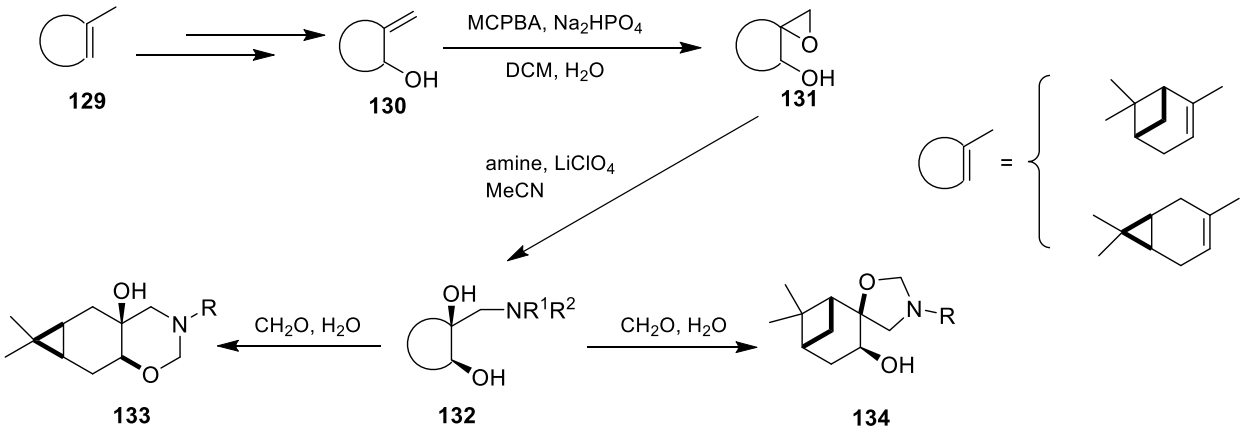


Figure 4

A library of natural monoterpene-based 3-amino-1,2-diols has been developed by Szakonyi *et al.*[10,12,119], starting from commercially available (+)-3-carene and α-pinene enantiomers. The synthesis of monoterpene-based allylalcohols **130** was developed by stereospecific epoxidation followed by a rearrangement, according to literature methods. The formation of the new oxirane ring proceeded stereoselectively in both cases by using *m*CPBA resulting in monoterpene-based epoxyalcohols **131**. Aminodiol libraries **132** with pinane and carane skeleton were prepared by regioselective aminolysis of **131** with primary and secondary amines in the presence of $LiClO_4$.

The ring closure with formaldehyde was also investigated and a regioselective process was observed with different regioselectivity in each case. In the case of carene-based aminodiols, the formation of the condensed 1,3-oxazine ring of **133** was observed. However, in the case of pinane-based aminodiols, the regioselectivity went toward the formation of spiro-oxazolidine ring **134**.

The catalytic value of these monoterpene-based aminodiols and their derivatives has been tested (applying 10 mol% ligand) in the enantioselective addition of Et_2Zn to benzaldehyde (**Scheme 9**). According to the results, carene-based aminodiol and its modified derivatives afforded an *ee* value of 96 %. Considering pinene derivatives, the best result of an *ee* of 84% was observed in favor of (*S*)-1-phenyl-1-propanol selectivity.

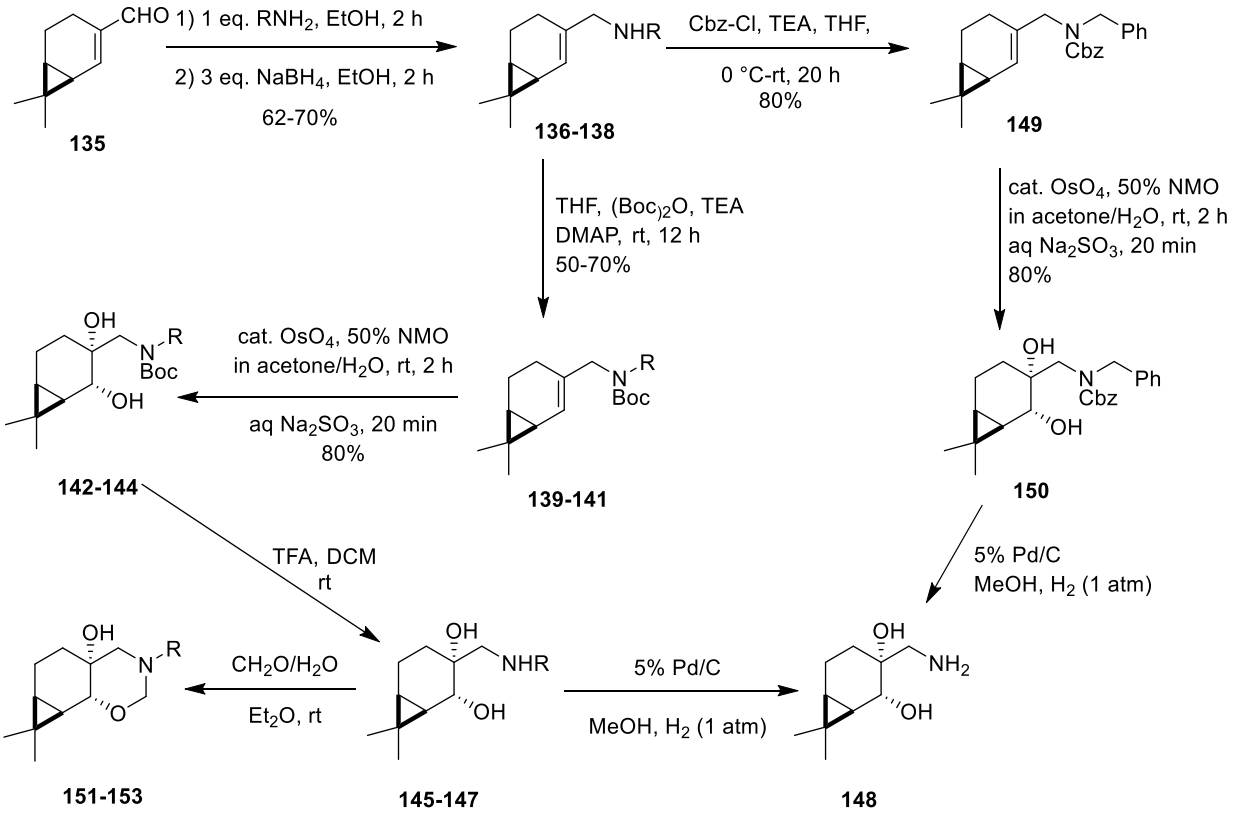


Scheme 9

The second most typical method used for the synthesis of 3-amino-1,2-diols is stereoselective dihydroxylation with the OsO_4–NMO system. A new carene-based library has been prepared starting from allylic aldehyde **135** obtained from natural *S*-(−)-perillaldehyde. The reductive amination of **135** with different primary amines formed allylic secondary amines **136–138**. In order to study the importance of the protection group on the stereoselectivity of the dihydroxylation reaction, the amino function was protected with Boc (**139–141**) as well as with Cbz (**149**). Dihydroxylation of protected allyamines with the OsO_4–NMO system took place in both cases. The stereoselectivity of the reactions proceeded in a similar manner furnishing compounds **142–144** and **150** in good yields. The deprotection of **142–144** led to the formation of secondary aminodiols **145–147**. Finally, primary 3-amino-1,2-diol **148** was obtained by

palladium-catalyzed debenzylation of **145–147** or Cbz-protected **150**. The reaction between aminodiols **145–147** and formaldehyde has been performed and it took place in favor of 1,3-oxazines **151–153**. (Scheme 10)

The obtained aminodiols and 1,3-oxazines were applied in the addition of Et_2Zn to an aldehyde showing enantiomeric excess over 90% with (*S*)-selectivity[120].



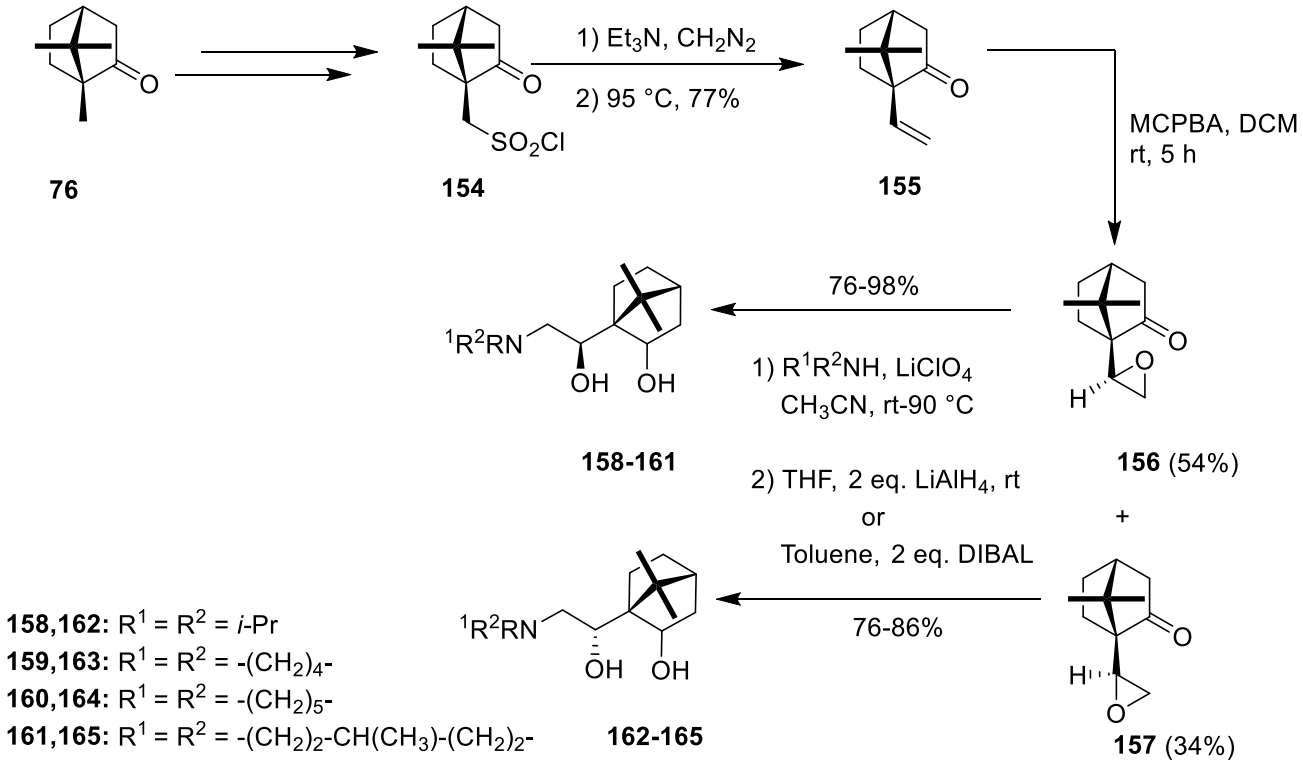
136,139,142,145,151: R = CH_2Ph; **137,140,143,146,152:** R = CH(Me)Ph (*R*);

138,141,144,147,153: R = CH(Me)Ph (*S*);

Scheme 10

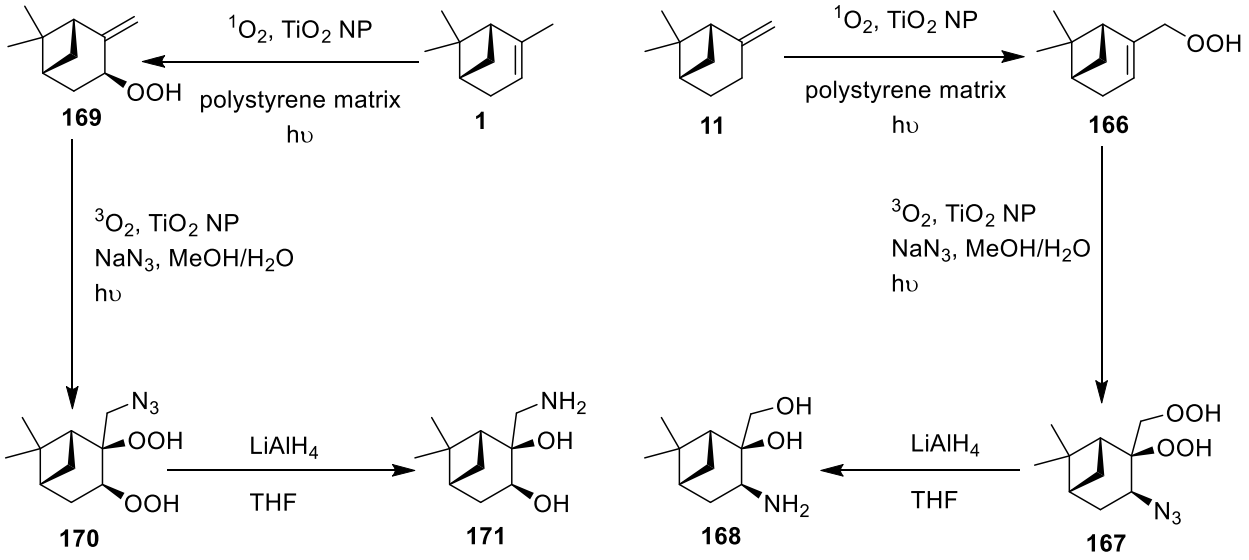
Another method for the synthesis of 3-amino-1,2-diols has been developed by Stoyanova *et al.*[36], starting from the commercially available 10-camphorsulfonyl chloride **154**. (1*S*)-10-Methylenecamphor **155** was obtained by the Fisher–Opitz reaction on **154**. However, in 2002, a Spanish team has reported a ~~5~~ five-step procedure for the formation of **155** starting from natural monoterpene (+)-camphor. The epoxidation reaction of compound **155** led to the formation of diastereomeric epoxyketone **156** and **157**. Their aminolysis in the presence of $LiClO_4$ followed

by subsequent reduction of the carbonyl function gave camphor-based 3-amino-1,2-diols **158–161** and **162–165**. The application of aminodiols (3 mol%) was tested in diethylzinc addition to benzaldehyde, but only moderate asymmetric inductions were observed[121]. (Scheme 11)



Scheme 11

Another method for the synthesis of pinene-based 3-amino-1,2-diols via a photochemical process catalyzed by photoinduced electron transfer (PET) was reported by Griesbeck and co-workers in 2010. Starting from α-pinene **1** and β-pinene **11**, regioisomeric primary aminodiols **168** and **171** have been synthesized in 3 steps, after a photocatalyzed singlet oxygen ene reaction and azidobishydroperoxidation in the presence of titanium dioxide followed by standard LAH reduction[122]. (Scheme 12)

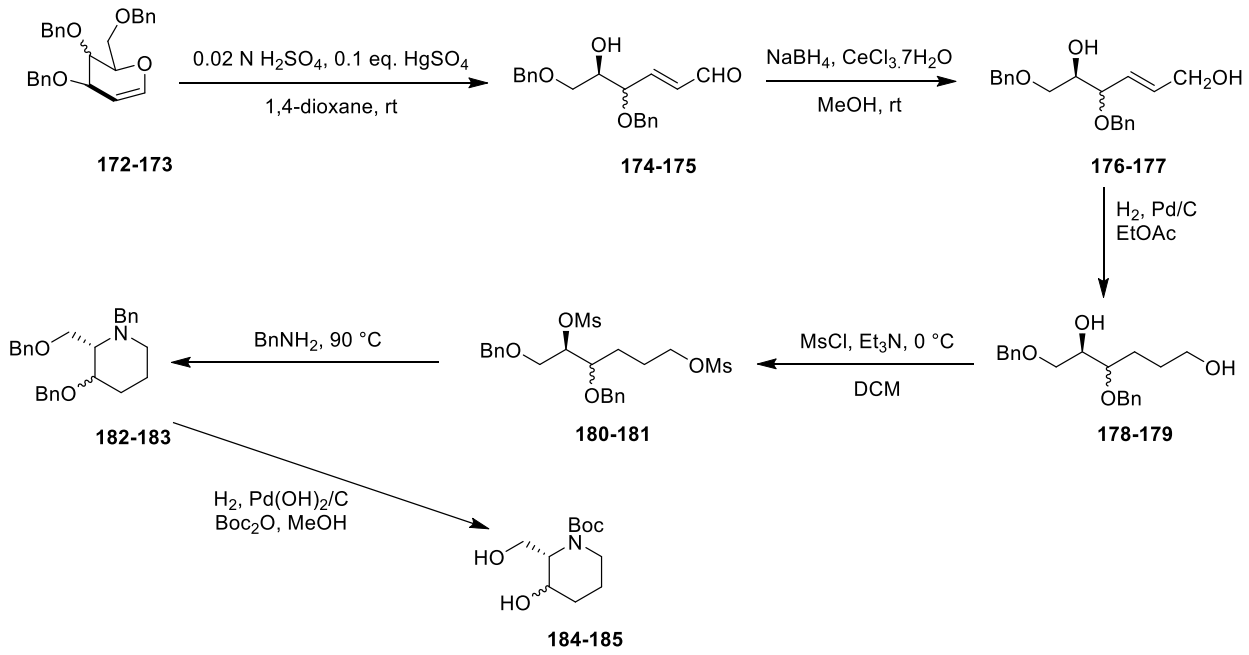


Scheme 12

2.2.2. Synthesis and application of 2-amino-1,3-diols

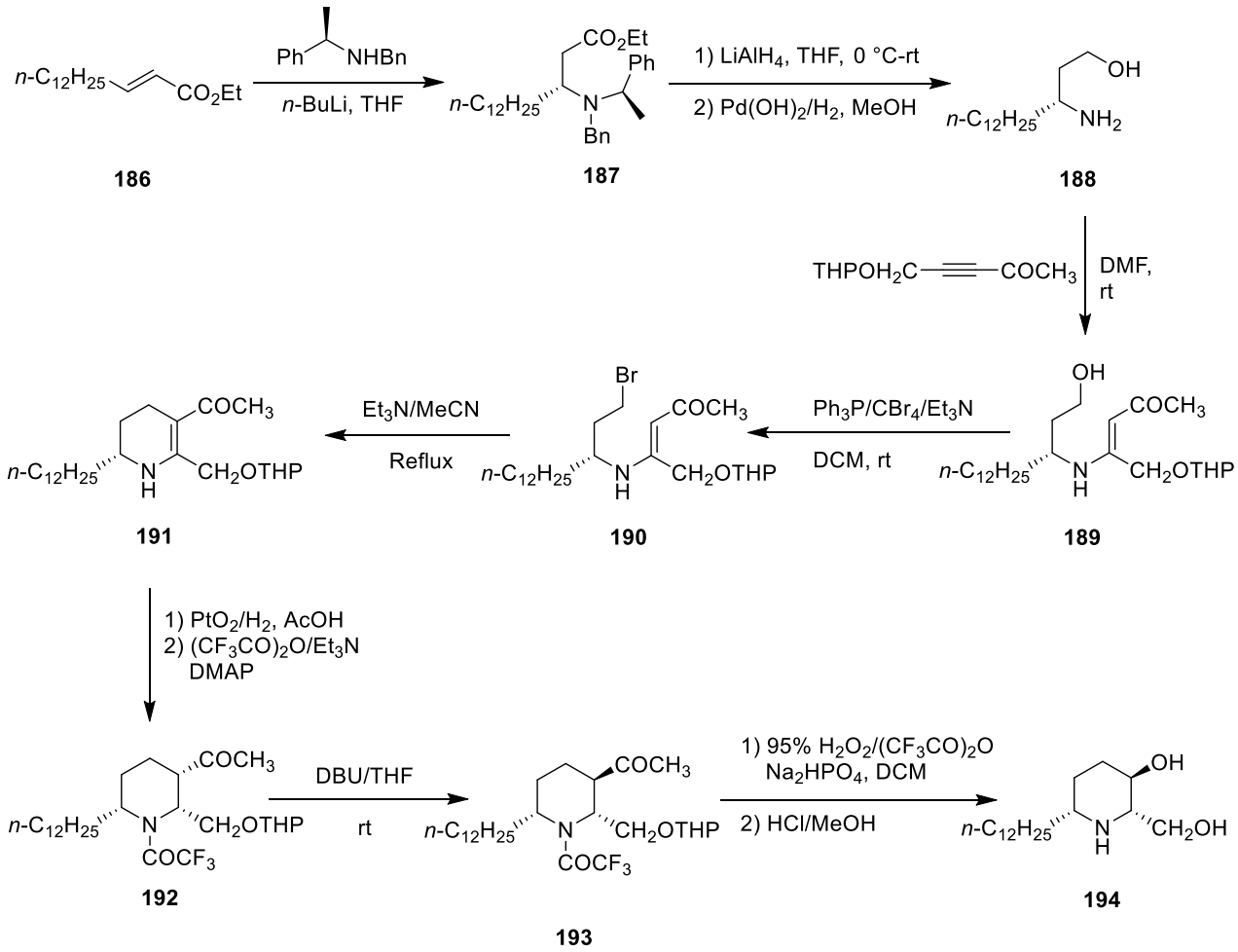
Only a handful of monoterpene-based 2-amino-1,3-diol have been reported. However, several synthetic pathways were developed due to the very attractive biological values of monocyclic or noncyclic analogues in the treatment of Alzheimer's disease[123], cancer[124], multiple sclerosis[125], and inflammation[126].

For instance, deoxoprosophylline isomers **184** and **185** as cyclic 2-amino-1,3-diol target molecules were prepared by Kokatla *et al.*[127] in six steps starting from 3,4,6-tri-*O*-benzylated glycals **172** and **173**, which were subjected to Perlin hydrolysis to **174** and **175** (Scheme 13). Monohydroxy aldehydes took part in a reduction under Luche condition and gave diols **176** and **177**. Chemoselective saturation of the double bonds was successfully performed under H_2 atmosphere catalyzed with Pd/C followed by mesylation of the free hydroxy groups of **178** and **179** by using mesyl chloride resulting in dimesylates **180** and **181**. The dimesylates formed were then subjected to cyclization with benzylamine and, finally, debenzylation and *in situ* Boc protection gave cyclic 2-amino-1,3-diols **184** and **185**.



Scheme 13

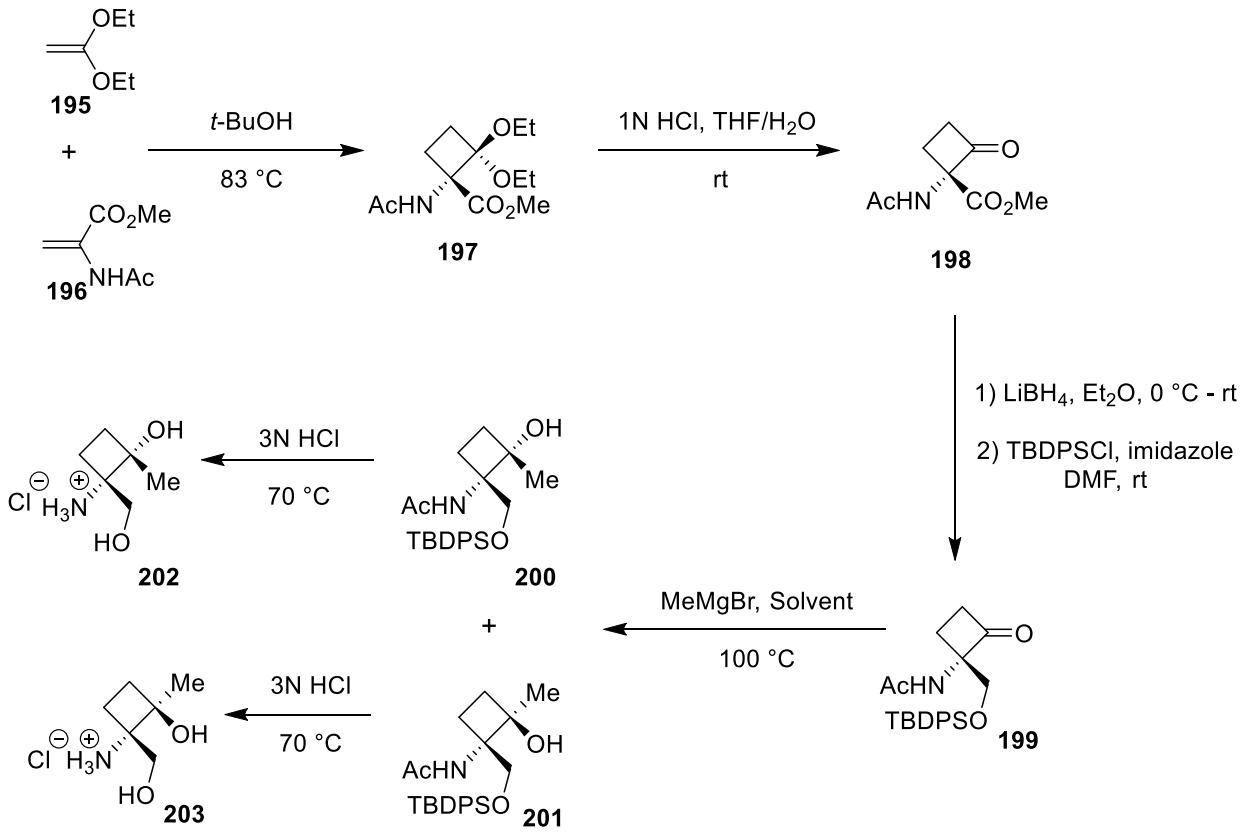
Ma and Ma[128] developed a multiple-step reaction for the preparation of cyclic 2-amino-1,3-diol (–)-deoxoprosophylline **194**, starting from methyl crotonate **186**. Michael addition of α-methylbenzylamine to **186** led to β-amino ester **187**, which underwent LAH reduction followed by hydrogenolysis, providing the desired δ-aminoalcohol **188**. Then this compound was successfully added to the alkynone again through the Michael reaction at room temperature to produce enamine **189**. The **190** bromo derivative obtained by the treatment of **189** with triphenylphosphane and carbon tetrabromide gave **190**. The latter upon heating under basic conditions gave cyclic enamine **191**. The hydrogenation of **191** catalyzed by PtO_2 afforded the corresponding saturated piperidine **192**, which was protected with trifluoroacetic anhydride. Epimerization of the 3-acetyl group of **192** produced **193** as the thermodynamically more stable major isomer. Baeyer–Villiger oxidation of **193** with trifluoroperacetic acid prepared an *in situ* followed by alcohol deprotection with 6 N HCl carried out in methanol afforded (−)-deoxoprosophylline **194**. (Scheme 14)



186 187 188 189 190 191 192 193 194

Scheme 14

Pérez-Fernàndez and co-workers[129] developed 2-amino-1,3-diols containing a cyclobutane substructure. A thermal [2 + 2] cycloaddition was performed between ketene diethyl acetal **195** and 2-acetamidoacrylates **196** followed by hydrolysis of formed **197** with HCl resulting in ketone **198**. (Scheme 15) After chemoselective reduction of the ester function and protection of the obtained alcohol group with *tert*-butyldiphenylsilyl chloride, the stereoselective addition of methylmagnesium bromide to **199** was carried out. The process was found to be solvent dependent. In dimethoxyethane or dioxane, the *trans* stereoisomer **201** was the major compound, while in diethyl ether or hexane, the *cis* stereoisomer **200** was the predominant product. By hydrolyzing both compounds in 3 N HCl aqueous solution, all protecting groups were removed, giving hydrochloride salts of *cis* **202** and *trans* **203** 2-amino-1,3-diols in good yields.



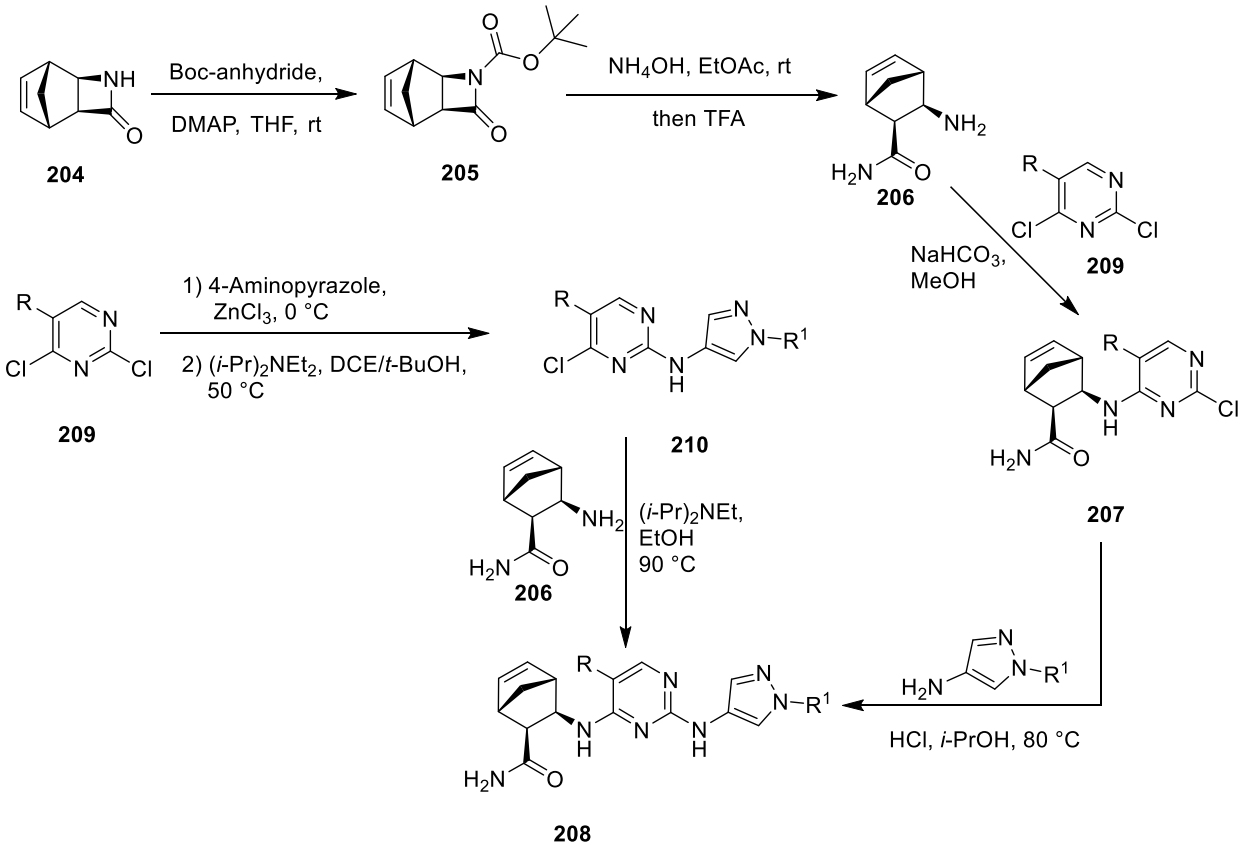
Scheme 15

2.3. Synthesis and importance of pyrimidine compounds

Pyrimidine-related molecules have gained high interest due to diverse pharmacological applications. Amino- and diaminopyrimidines have been shown to exhibit anti-inflammatory[63], tyrosine kinase inhibitor[130], anti-HIV[64], anti-tubercular[65], anticancer as JAK and KDR inhibitor[130,131], antiproliferative activity[66], and even antimalarial actions[68].

The known anticancer properties of these derivatives initiated Curtin and his team to develop pyrazole diaminopyrimidines as dual inhibitors of KDR and Aurora B kinases starting from commercially available lactam **204**. Boc-protection provided protected compound **205**, which took part in ring opening with ammonium hydroxide followed by amine deprotection with TFA resulting in carboxamides **206**. The addition of 2,4-dichloropyrimidines **209** to key intermediate **206** led to product **207**, which took part in a second coupling with a variety of pyrazoles affording the **208** library.

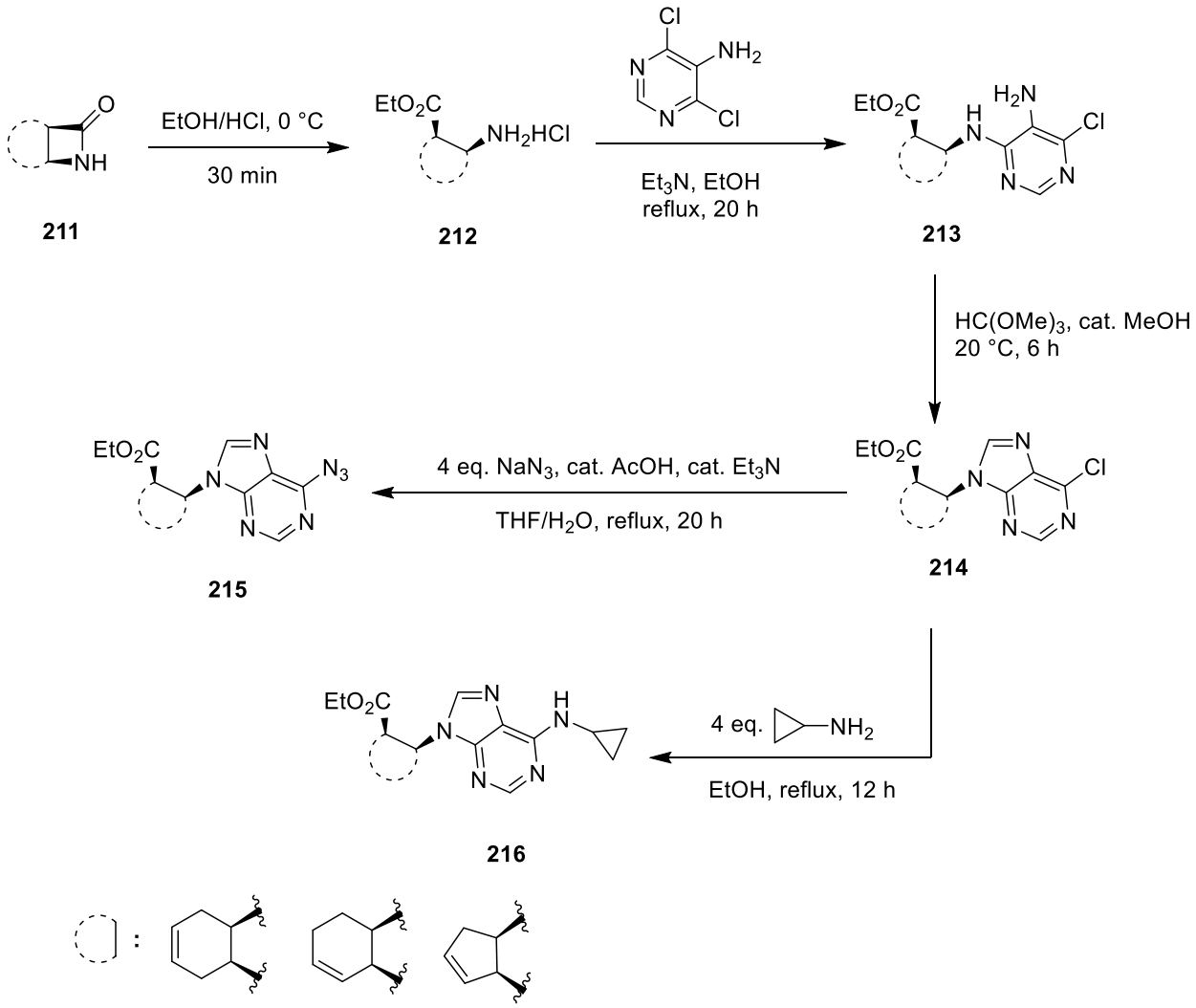
In another method, the regioselective $ZnCl_2$-mediated addition of 4-aminopyrazole derivatives to the 2-positions of pyrimidines **209** provided intermediates **210** in modest yield. When When amino function of carboxamide **206** reacted with chloropyrimidines **210** in the presence of Hunig's base, the desired products **208** were obtained. A SAR approach resulted in analogues showing moderate antitumor activity, significant aqueous solubility, and significant cellular activity. Unfortunately, these compounds were pan-kinase inhibitors with limited therapeutic indices and, consequently, they could not be used against tumors in human therapy[69]. (Scheme 16)



Scheme 16

Due to their wild range of bioactivity, carbocyclic nucleoside analogues gained a high interest. Remete *et al.*[132] have developed some derivatives in a stereocontrolled synthetic pathway. *cis*-Amino ester hydrochloride **212** was obtained from β-lactam **211**. Intermediates **212** were subjected to *N*-arylation with 5-amino-4,6-dichloropyrimidine to furnish pyrimidines **213**. The second heteroring was generated by reacting the pyrimidine intermediate with trimethyl orthoformate serving 6-chloropurines **214** coupled with cycloalkenes. The remaining chlorine

atom of the obtained nucleoside analogue **214** was then replaced with *N*-nucleophiles to obtain nucleoside analogues **215** and **216**, as shown in Scheme 17.



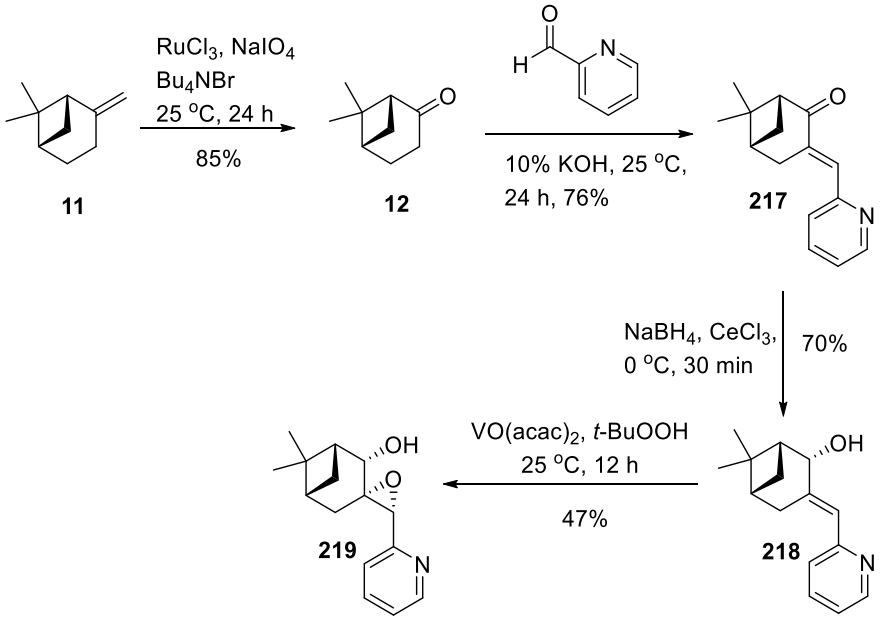
Scheme 17

3. Results and discussion

3.1. Synthesis of pinane-based chiral bi- and trifunctional ligands

3.1.1. Synthesis of pinane-based 1,4-aminoalcohols

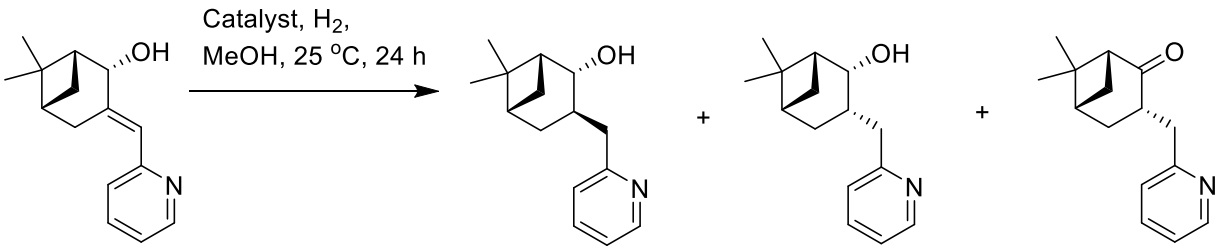
The synthesis of key intermediate (+)-nopinone **12** was accomplished as previously reported starting from (−)-*β*-pinene using $RuCl_3$ and $NaIO_4$[94,133–135]. Diastereoselective aldol condensation of 2-pyridinecarboxaldehyde with **12** under alkaline conditions provided *α,β*-unsaturated ketone **217** in 74% yield. Subsequent reduction of **217** under Luch condition in the presence of $CeCl_3$ as a complexing agent led to the formation of *endo*-compound **218** in high yield and stereoselectivity. Epoxidation of **218** with *t*-BuOOH in dry toluene in the presence of $VO(acac)_2$ as catalyst gave *cis*-epoxide **219** in a stereoselective manner **(**Scheme 18).



Scheme 18

Regioselective catalytic hydrogenation of *α,β*-unsaturated aminoalcohol **218** gave a mixture of **220** and **221** (Scheme 19). Our results demonstrated that reduction of the carbon−carbon double bonds led to *diendo* aminoalcohol **221** as the major product. Obviously, the addition of hydrogens can take place from either the *Re* or the *Si* side. Interestingly, the ratio of **220** and **221** depends on catalysts. In the presence 5% Pt/C as catalyst, **221** was formed as the major product (*d.r.* = 10:1 by NMR determination). In turn, the ratio of the two products was found to be 3:1

when 5% Pd/C was used as a catalyst. Besides the desired products, compound **222** was also isolated as a minor component. The formation of **222** from **218** could be explained by a metal-catalyzed abstraction of hydrogen *gem* to the hydroxy group to afford the corresponding allylic radical. This intermediate would evolve to an enol by isomerization and creation of new carbon-hydrogen bond, followed by an enol–keto tautomerization leading finally to **222**[136].

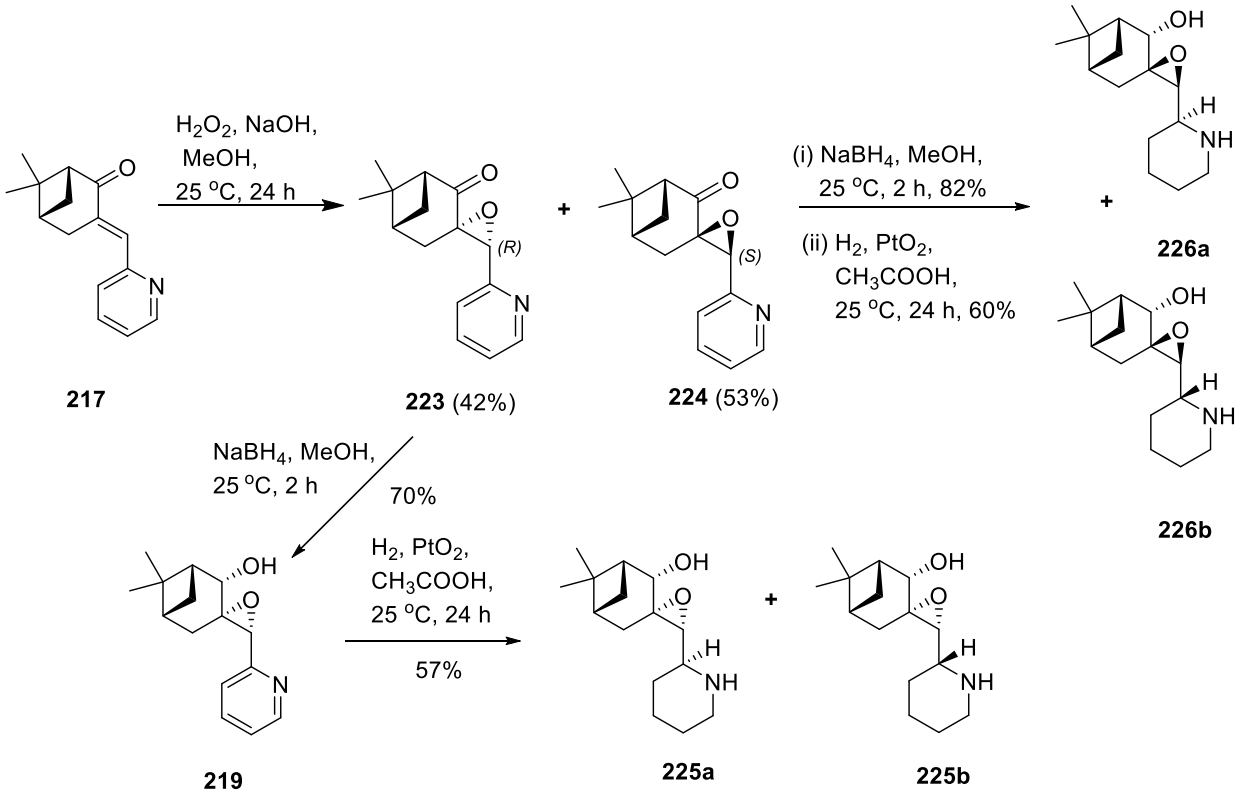


Catalyst	**5% Pt/C**	1	:	10	:	2
	5% Pd/C	1	:	3	:	1

Scheme 19

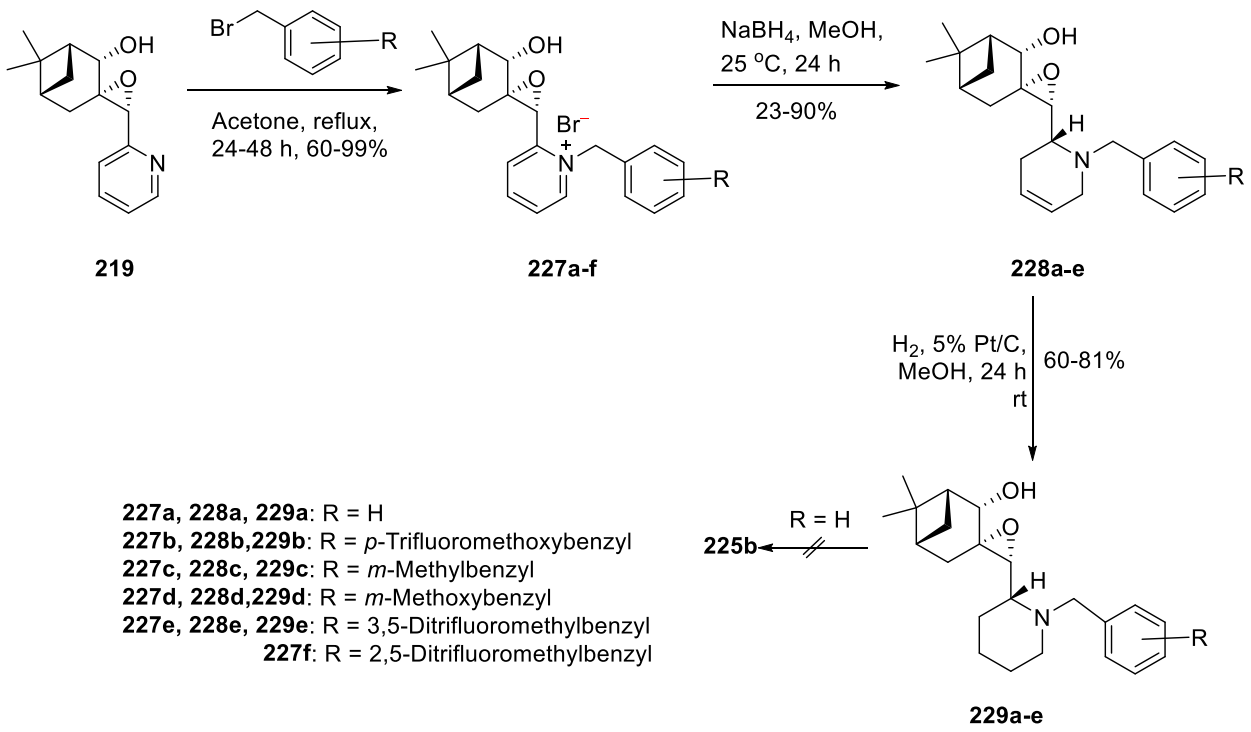
To expand the family of ligands, *α,β*-saturated ketone **217** was first subjected to epoxidation using H_2O_2 in alkaline conditions providing the corresponding epoxides **223** and **224** in excellent yields (Scheme 20). After separation of the diastereoisomers by column chromatography, subsequent hydride reduction of epoxide **223** with $NaBH_4$ in MeOH led to the formation of **219** with high diastereoselectivity. The opening process failed when ring-opening of epoxide **219** was attempted with different reductants such as *L*-selectride and LAH or applying epoxide hydrolysis under acidic or alkaline conditions.

In our next experiment, aminoalcohol **219** was subjected to catalytic hydrogenation using Adam′s catalyst in glacial acetic acid[47]. Both epimers **225a** and **225b** of the expected piperidine product were formed in almost equal amounts (*d.r.* = 1:1). Unfortunately, efforts to separate these diastereomers proved to be unsuccessful. Compound **124** underwent similar reactions providing a mixture of **226a** and **226b.**



Scheme 20

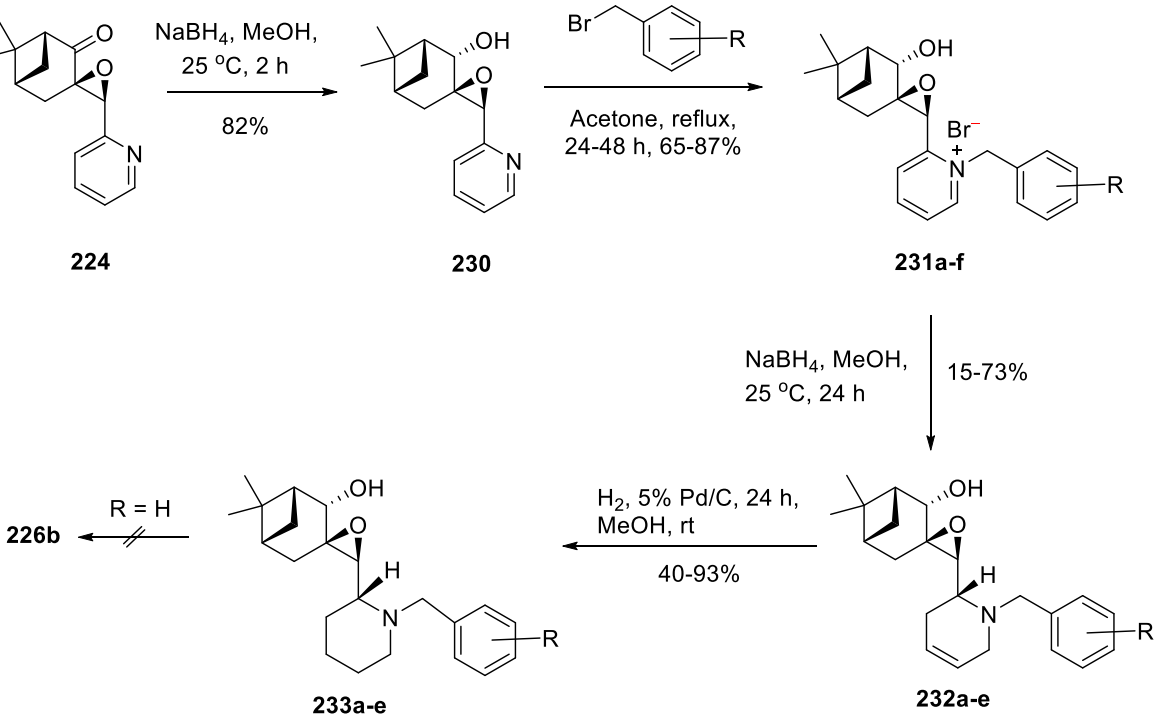
To overcome the obstacles in chromatographic separation, another reductive route to **225b** was adopted (Scheme 21). Namely, quaternary ammonium salts **227a–f** were easily synthesized by heating **219** with benzyl bromide derivatives in acetone at reflux temperature[137]. Then the products (**227a–f**) were subjected to hydride reduction with $NaBH_4$ to obtain **228a–f** in a stereoselective reaction. Subsequent hydrogenation of **228a–f** in methanol, catalyzed by 5% Pd/C afforded **229a–f**. Our attempts failed to convert **229a** to **225b** despite the extended reaction time, increased temperature or pressure. Similar to epoxide **219**, the ring-opening of **229a** with different nucleophiles failed.



Scheme 21

In the same manner, as described above, ketone **224** was reduced to aminoalcohol **230** in good yield. Compound **230** was then transformed into isomers **233a–f**. (Scheme 22)

In order to rationalize the resistance of the epoxide ring during the nucleophile-initiated opening reaction, selected compounds **228a** and **232a** as suitable models were chosen for detailed structural analysis by professor Antal Csámpai. First, with the combined use of high-resolution ^{1}H- and ^{13}C-NMR methods, we determined their relative configuration, which is also influenced by the conformational chirality introduced by the tetrahydropyridine ring.



231a, 232a, 233a: R = H
231b, 232b, 233b: R = *p*-Trifluoromethoxybenzyl
231c, 232c, 233c: R = *m*-Methylbenzyl
231d, 232d, 233d: R = *m*-Methoxybenzyl
231e, 232e, 233e: R = 3,5-Ditrifluoromethylbenzyl
231f: R = 2,5-Ditrifluoromethylbenzyl

Scheme 22

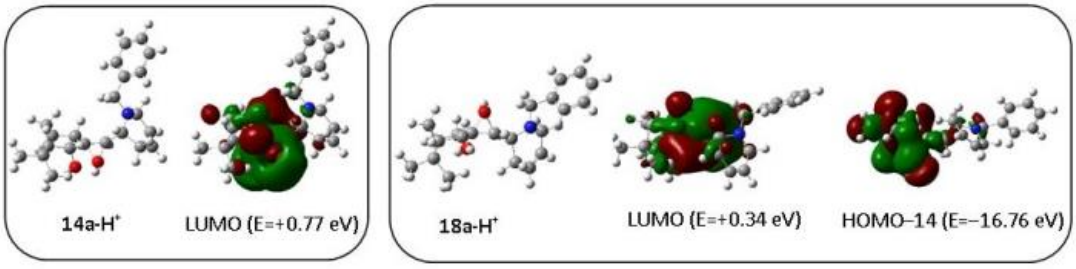
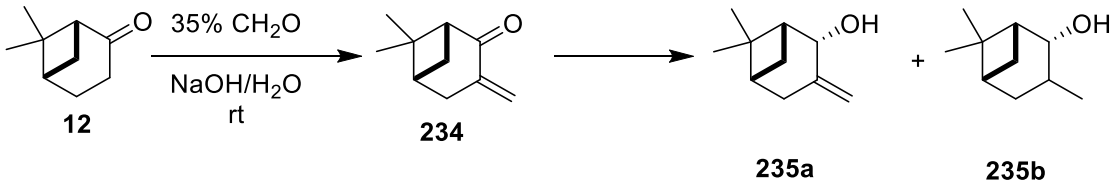


Figure 5: Selected molecular orbitals of *O*-protonated cations **228a** and **232a** (**228a–H**$^+$ and **232a–H**$^+$, resp.) accounting for the resistance of the nucleophile-initiated opening of the epoxide ring.

3.1.2. Synthesis of pinane-based 3-amino-1,2-diol and analogue

Key intermediate 3-methylenenopinone **234** was prepared from (−)-nopinone **12**, which was converted into (−)-3-methylenenopinone **234** by applying formaldehyde in alkaline conditions according to literature methods[138,139]. (Scheme 23) Reduction of **234** with $NaBH_4$ in various solvents gave a mixture of **235a** and **235b**. It is important to note that whereas allylic alcohol **235a** was formed in a highly stereoselective manner, **235b** exists as a 4:1 mixture of two *cis*-diastereomers (*diexo* and *diendo*, based on ^{1}H-NMR measurement and comparison with data in the literature)[140,141].



Scheme 23

Table 1: Stereoselective reduction of **234**.

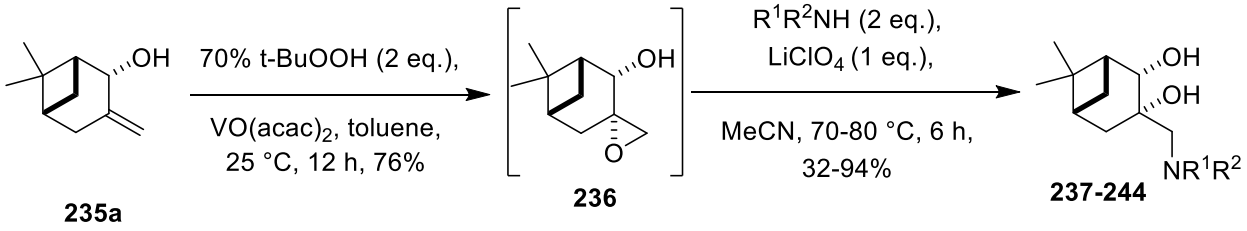
Entry	Reductant	Additive	Solvent	T (°C)	t (h)	Ratio 235a/235b[a]	Yield [b] (%)
1	$NaBH_4$	-	MeOH	-20°C	6	3:1	86
2	$NaBH_4$	-	MeOH	0	1	1:1	86
3	$NaBH_4$	$CeCl_3$	MeOH	0	0.5	100:1	87
4	$NaBH_4$	-	Et_2O	0	3	3:1	76
5	$NaBH_4$	-	EtOH	0	48	1:3	84

[a] Based on ^{1}H-NMR measurements of the crude product. [b] Isolated, combined yield of **235a** and **235b**.

When Et_2O was applied as a solvent, **235a** was formed as the main product (**235a**:**235b** = 3:1), whereas the ratio of the two products in EtOH changed to **235a**:**235b** = 1:3. In contrast, when MeOH was used as a solvent, the two products formed in a 1:1 ratio. In addition, it is interesting to note that the ratio of **235a** and **235b** also depended on temperature. At –20 °C in MeOH, compound **235a** was obtained as the major product, although **235a** and **235b** could not be separated by conventional technics. Applying the condition of Luche reaction, in the presence of $CeCl_3$ as additive, **235a** was obtained as the single product. This procedure not only allowed highly regioselective reduction but also enhanced the reaction rate. The probable reason is the effect of Ce^{3+}, as hard Lewis acid. Despite its weak acidity, it certainly contributes to both the

regioselectivity and the high reaction rate through coordination to the oxygen of the carbonyl function[142].

Epoxidation of **235a** with *t*-BuOOH in the presence of $VO(acac)_2$ as catalyst furnished epoxide **236** as a single product in a stereoselective reaction[142,143]. (Scheme 24) Since purification of epoxide **236** could not be performed in an effective way without its decomposition, the crude product with a purity of approximately 92% (based on ^1H NMR measurement) was treated with various amines to perform the aminolysis of the oxirane ring. Our previous results clearly demonstrated that when aminodiols were applied as catalysts in enantioselective reactions, their *N*-substituents definitely influenced the enantioselectivity of their catalyzed reaction[10,94,111,143]. Consequently, aminodiol library **237–244** was prepared by aminolysis of **236** with secondary and primary amines in the presence of lithium perchlorate as a catalyst.



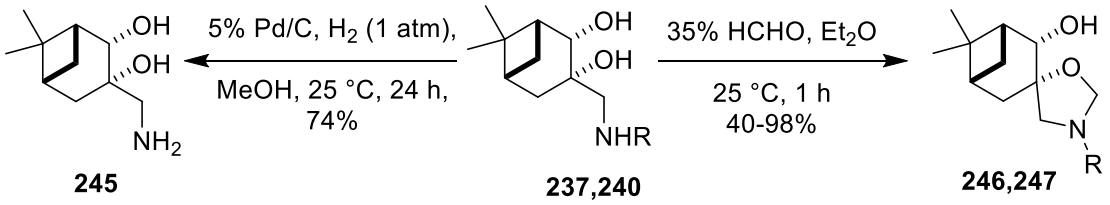
235a **236** **237-244**

237: R^1 = H, R^2 = Bn, **238**: R^1 = H, R^2 = CH(Me)Ph (*R*), **239**: R^1 = H, R^2 = CH(Me)Ph (*S*)
240: R^1 = H, R^2 = $CH(Me)_2$, **241**: R^1 = Bn, R^2 = Bn, **242**: R^1 = Bn, R^2 = CH(Me)Ph (*R*),
243: R^1 = Bn, R^2 = CH(Me)Ph (*S*), **244:** R^1=R^2=-$(CH_2)_2$-CH(Bn)-$(CH_2)_2$-

Scheme 24

Primary aminodiol **245** was obtained in moderate yield by debenzylation of the corresponding *N*-benzyl aminodiol **237** under standard conditions by hydrogenolysis over Pd/C. (Scheme 25)

The ring closure reaction of **237** and **240** with formaldehyde was also investigated to study the regioselectivity of the reaction[6,10,94]. When these aminodiols were treated with formaldehyde under mild conditions, spiro-oxazolidines **246** and **247** were obtained in highly regioselective ring closure, with similar regioselectivity as observed in the case of pinane-based regioisomers. This regioselectivity, however, is opposite to those of the carene-based analogues reported recently[12,120].

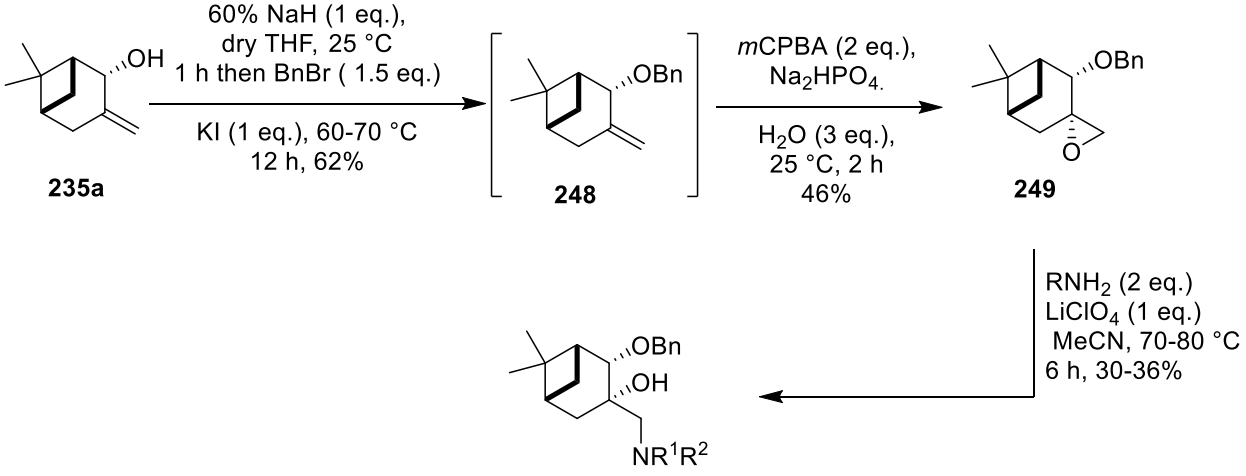


245 **237,240** **246,247**

237,246: R = Bn, **240,247**: R = $CH(Me)_2$

Scheme 25

On the other hand, to assess the importance of the secondary hydroxy group in the catalytic application of our aminodiols, allylic alcohol **235a** was transformed into *O*-benzyl derivative **248**. (Scheme 26) Surprisingly, the separation of **248** and the benzyl bromide reagent was unsuccessful using classical chromatography methods. Therefore, **248** was transformed to epoxide **249** with *m*CPBA, and the latter could be easily purified (in contrast to its epoxyalcohol analogue **236**) on a gram scale by simple column chromatography in good yield[144–147]. The aminolysis of the formed oxirane ring of **249** with different amines afforded *O*-benzyl aminodiols **250–153**[31,111]. The relative configurations of compounds **237–244** together with **250–253** were determined by means of NOESY experiments.



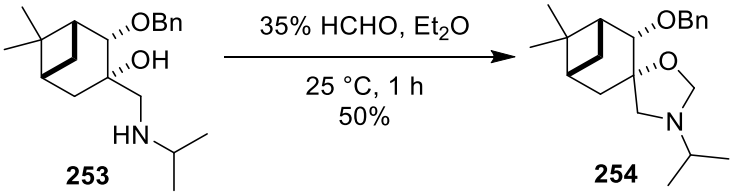
235a **248** **249**

250–253

250: R^1 = H, R^2 = Bn, **251**: R^1 = H, R^2 = CH(Me)Ph (*R*), **252**: R^1 = H, R^2 = CH(Me)Ph (*S*)
253: R^1 = H, R^2 = $CH(Me)_2$

Scheme 26

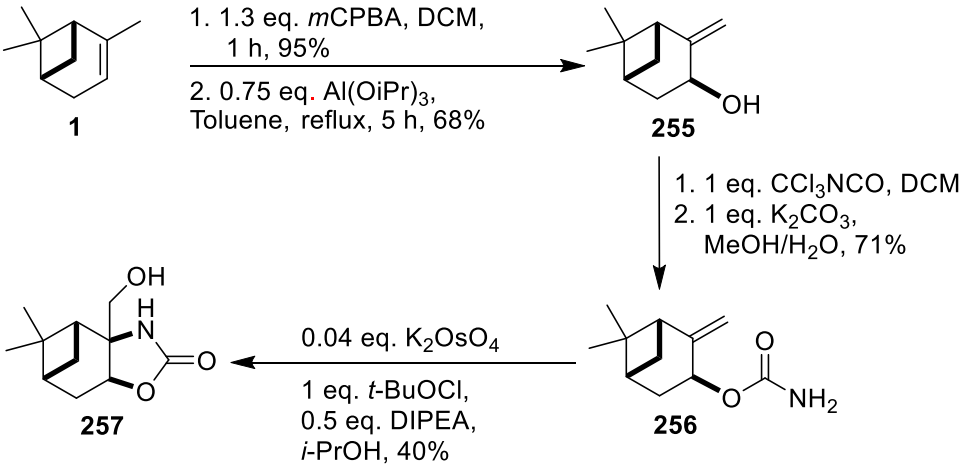
The regioselectivity of the ring closure of **253** with formaldehyde was investigated[6,10,120], which led to the formation of spiro-oxazolidine **254** in 50% yield (Scheme 27).



Scheme 27

3.1.3. Synthesis of pinane-based 2-amino-1,3-diol derivatives

The synthesis of isopinocarveol (**255**), the key intermediate allylic alcohol, was performed according to a literature procedure in good yield[148]. (Scheme 28) The first step was the stereoselective epoxidation of (–)-α-pinene **1**, carried out with *m*CPBA, followed by base-catalyzed allylic rearrangement mediated by aluminium isopropoxide ($Al(OiPr)_3$). The resulting allylic alcohol **255** was reacted with trichloroacetyl isocyanate, followed by alkaline treatment, delivering carbamate **256** in good yield[149–151]. In the next step, the ring closer of **256** was accomplished by using potassium osmate(VI) catalyst and *t*-BuOCl in the presence of DIPEA, affording oxazolidine-2-one **257**[10].



Scheme 28

The absolute configuration of **257** was determined by 2D NMR spectroscopic techniques. Clear NOE signals were observed between the H-7a and Me-10 as well as the H_a-9 and Me-10 protons. Besides NOESY experiments, the structure was also elucidated by X-ray crystallography (Figure 6).

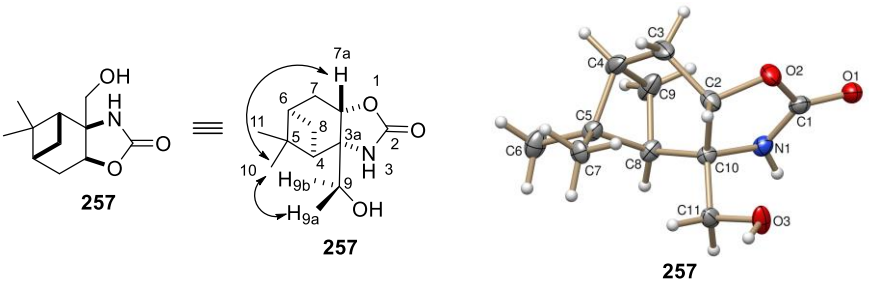
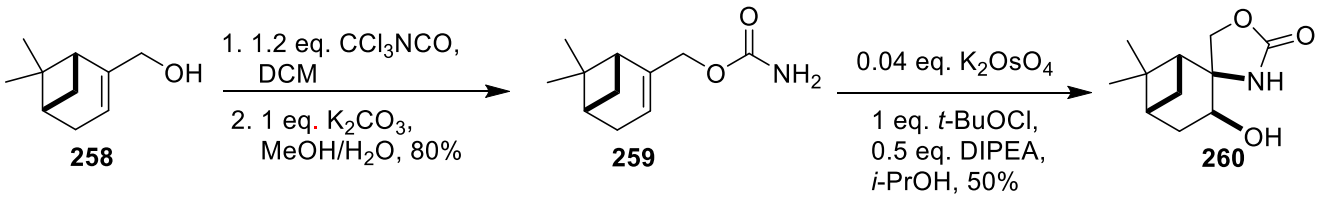


Figure 6: NOESY experiments and X-ray structure elucidation of oxazolidin-2-one **257**.

To synthesize regioisomeric spiro-oxazolidinone derivative **260**, commercially available (1*R*)-(–)-myrtenol (**258**) was chosen as starting material. The synthesis method was similar to that mentioned above for (–)-isopinocarveol. In the first step, carbamate **259** was prepared[152], then aminohydroxylation was carried out with potassium osmate(VI) catalysis, which led to the formation of spiro-oxazolidine-2-one **260** in a highly regio- and stereoselective manner. On the basis of NMR spectroscopic measurements of the crude product, spiro derivative **260** was shown to be formed exclusively with the relative configuration depicted in Scheme 30. Besides 2D NMR spectroscopic studies, the absolute configuration of **260** was determined by the transformation of **260** into the corresponding aminodiols **261** and **262** and comparing products with those obtained from regioisomer **257** (Scheme 29).

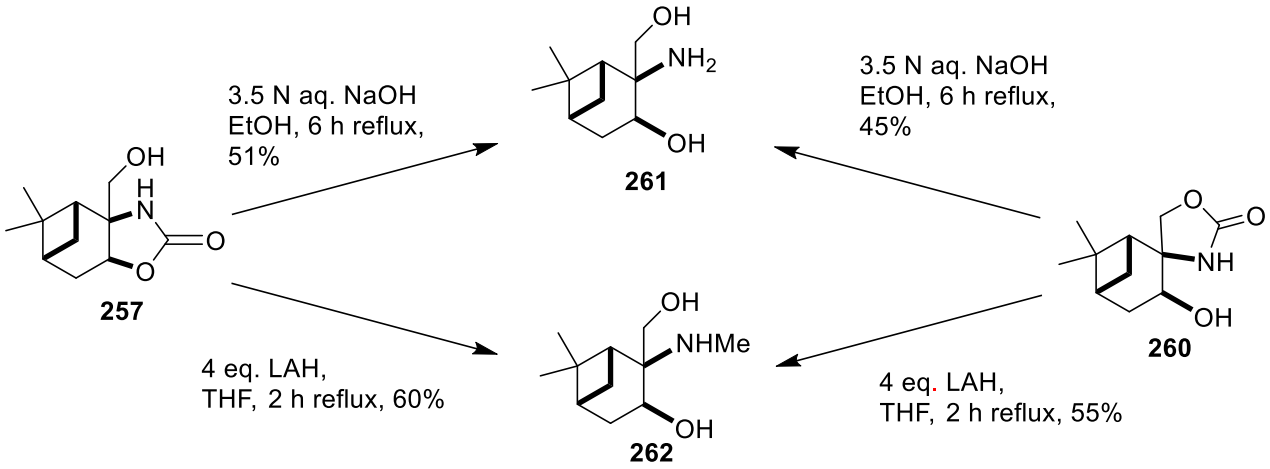


Scheme 29

Synthesis and transformations of pinane-based 2-amino-1,3-diols

To obtain a library of pinane-based 2-amino-1,3-diols, oxazolidine-2-ones **257** and **260** were applied as starting materials. Alkaline hydrolysis of both **257** and **260** resulted in the same

primary aminodiol **261**[153]. (Scheme 30) According to the NMR spectra and other physical and chemical properties, there was no difference between the products of the two reactions. Since the relative configuration of compound **257** was clarified by NMR spectroscopy and X-ray crystallographic results, we were able to assign the stereochemistry of spiro derivate **260**, too. In a similar manner, LAH reduction of both **257** and **260** gave the same *N*-methylaminodiol **262** with modest yield.

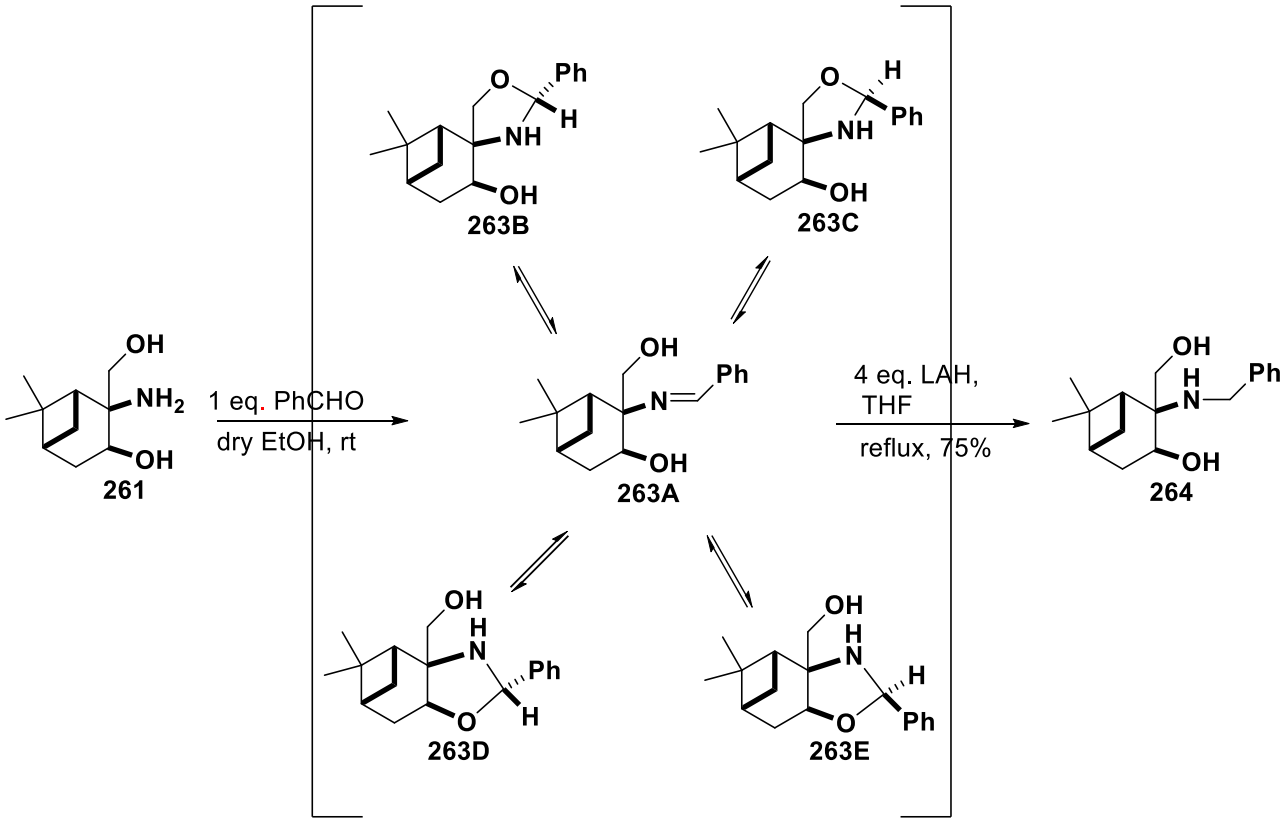


Scheme 30

Subsequently, **261** was reacted with benzaldehyde generating Schiff base **263A** *in situ*. (Scheme 31) Our efforts to reduce it with sodium borohydride to *N*-benzylaminodiol either at room temperature or under reflux conditions failed. ^{1}H-NMR spectroscopic measurements in $CDCl_3$ clearly showed that the crude product was a five-component tautomeric mixture containing condensed oxazolidine **263E** as the main component. Additional minor components included the other condensed oxazolidine (**263D**), spiro compounds **263B** and **263C** as well as Schiff-base **263A** existing in a ratio of **263A**:**263B**:**263C**:**263D**:**263E** = 4:<1:4:12:79[154,155]. The structure of the five components **263A–E** was determined by 2D NMR spectroscopic techniques (NOESY and HMBC). Since this finding is quite unusual in the case of Schiff bases, we decided to study the ring/chain tautomeric mixture (**263A–E**) in the reaction of **261** with benzaldehyde by ^{1}H-NMR spectroscopy. When a time-dependent ^{1}H-NMR spectroscopic measurement was accomplished, we observed that the equilibrium composition was established rapidly, without any significant change in the ratio of the tautomers. The equilibrium shifting strongly to product **263E** and steric hindrance of the β- hydroxy groups at both sides can account for the difficulty of

the reduction process and the necessity to use a stronger reducing agent and more severe conditions.

The reduction step, therefore, was performed by applying LAH and longer refluxing time, resulting in the expected **264** product.

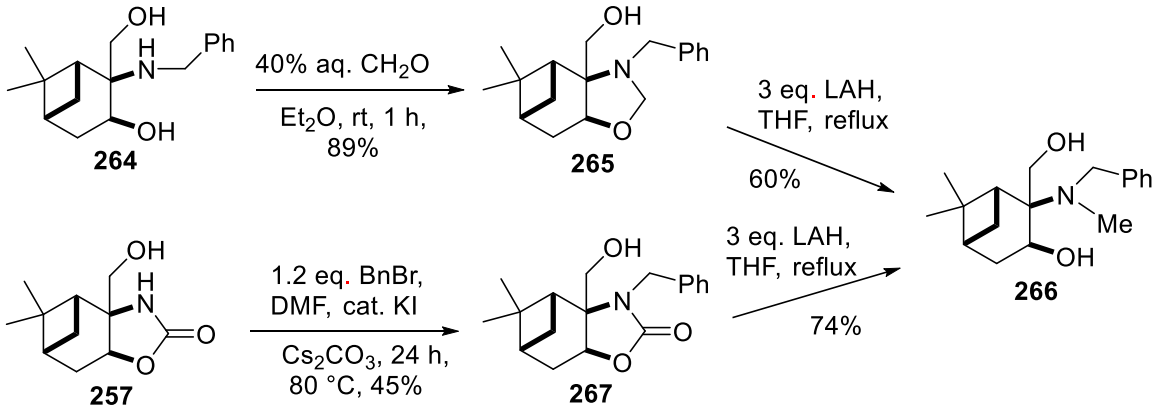


263A:**263B**:**263C**:**263D**:**263E** = 4: <1: 4:12:79

Scheme 31

When **264** was treated with formaldehyde at room temperature, pinane-fused oxazolidine **265** was obtained regioselectively (Scheme 32). This was indicated by clear HMBC correlations between CH_2 of the oxazolidine ring and the anellation carbons. It is in contrast to the results observed in the case of regioisomeric 3-amino-1,2-diols, where spiro-oxazolidines formed exclusively[156]. The structure of **265** and, therefore, the regioselectivity of the reaction were determined by 2D NMR and X-ray techniques. Clear NOE signals were observed between the H-7a and Me-10 as well as the H_a-9 and Me-10 protons. In addition to NOESY experiments, the structure was also elucidated by X-ray crystallography (Figure 7).

LAH reduction of oxazolidine **265** gave *N*-benzyl,*N*-methyl analogue **266** which, alternatively, was prepared directly from 2-oxazolidinone **267** via *N*-benzylation followed by LAH reduction in two steps.



Scheme 32

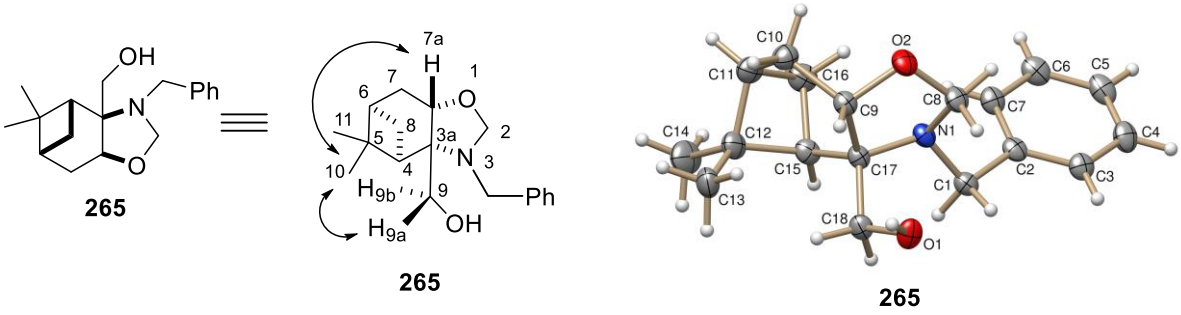
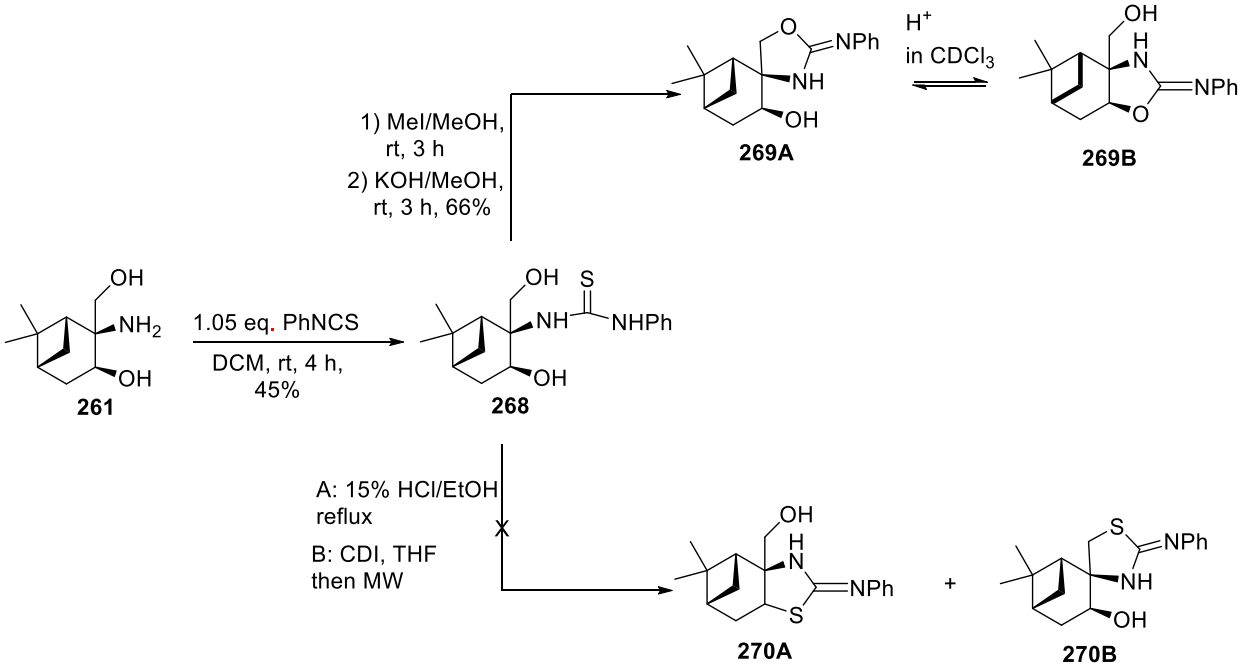


Figure 7: NOESY experiments and X-ray structure proof/verification of the structure of oxazolidine **265**.

When **261** was reacted with phenylisothiocyanate, thiourea **268** was obtained, which underwent regioselective ring closure resulting in **269A**. (Scheme 33) It is important to note that this regioselectivity is the opposite to that observed in the reaction of aminodiols **261** and **264** with aldehydes, but it is similar to that found in our earlier study with pinane-based 3-amino-1,2-diols[156]. During the NMR spectroscopic study of **269A** in $CDCl_3$ for 30 days, an unknown slow ring–ring tautomerization was observed, leading to a 1:1 mixture of two regioisomers **269A** and

269B. Compound **269B** could be isolated from the mixture by column chromatography in pure form.

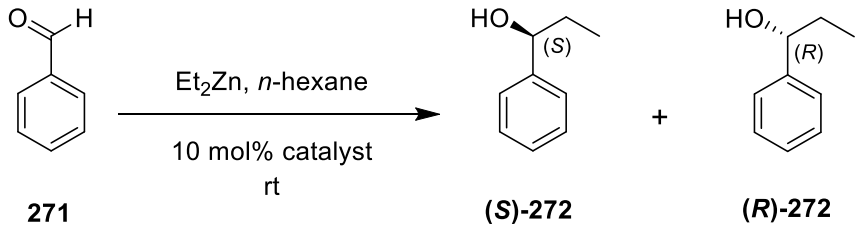


Scheme 33

The synthesis of heteroanalogue 2-phenyliminothiazolidines **270A** and **270B** failed, even when the reaction was attempted under acid catalysis or via the formation of carbonyl imidazole intermediate by methods we applied successively earlier in the synthesis of monoterpene-fused 2-imino-1,3-thiazines[77,157].

3.1.4. Application of aminodiols as chiral ligands for catalytic addition of diethylzinc to aldehydes

Applying aminodiols **237–247** and **250–254** as chiral catalysts in the addition of diethylzinc to benzaldehyde (**271**), formation of an enantiomeric mixture of (*S*)- and (*R*)-1-phenyl-1-propanol **272** was obtained. (Scheme 34)



Scheme 34

Our results are presented in Table 2. The enantiomeric excess of 1-phenyl-1-propanols (*S*)-**272** and/or (*R*)-**272** was determined by chiral GC (CHIRASIL-DEX CB column) according to literature methods[158,159]. Low to good enantioselectivities were observed. The results clearly show that all aminodiols favored the formation of the *(R)*-enantiomer of **272**. In contrast, applying **251** led to (*S*)-enantiomer **272** as the main product. Aminodiol **241** and **252** afforded the best *ee* value (*ee* = 80%) with an (*R*)-selectivity, whereas **251** showed the best *ee* value (*ee* = 74%) with an (*S*)-selectivity. Moreover, enantioselectivities were also observed in the addition of diethylzinc to aminodiols **237–239** catalyzed by benzaldehyde. In crontrast, lower, but still good selectivities were obtained with the use of *O*-benzyl aminodiol derivatives **250–253**. We suppose that the highly rigid structure of these derivatives in the transition states leads to better selectivities when compared to flexible moieties. Furthermore, our results clearly indicate that the spiro-oxazolidine ring (ligand **247** and **254**) has weaker catalytic performance compared with fused 1,3-oxazine systems[12,120]. These results show good accordance with those observed with sabinane- or pinane-based spiro-oxazolidines reported in our earlier studies[10,93].

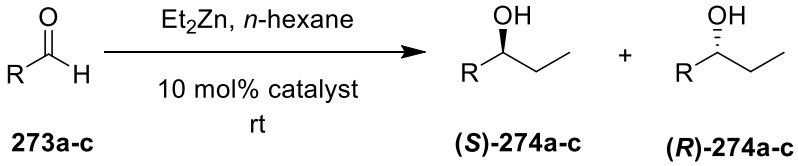
Table 2: Addition of diethylzinc to benzaldehyde, catalyzed by aminoalcohol/ aminodiol derivatives.

Entry	Ligand [a]	Yield [b] (%)	*ee* [c] (%)	Configuration [d]
1	**237**	83	5	*(R)*
2	**238**	92	23	*(R)*
3	**239**	80	31	*(R)*
4	**240**	85	4	*(R)*
5	**121**	85	80	*(R)*
6	**242**	90	3	*(R)*
7	**243**	95	16	*(R)*
8	**244**	80	60	*(R)*
9	**245**	83	-	-
10	**246**	83	26	*(R)*

11	**247**	85	35	*(R)*
12	**250**	95	73	*(R)*
13	**251**	87	74	*(S)*
14	**252**	83	80	*(R)*
15	**253**	80	40	*(R)*
16	**254**	93	10	*(R)*

[a] 10 mol%. [b] Data given after silica column chromatography. [c] Determined by measuring the *ee* of the crude product by GC (Chirasil-DEX CB column). [d] Determined by comparing optical rotations and the t_R of GC analysis with literature data[158,159].

With best catalysts **251** and **252**, the diethylzinc addition reaction was extended to other aromatic and aliphatic aldehydes. (Scheme 35) The enantiomeric purities of the 1-aryl- and 1-alkyl-1-propanols obtained were determined by GC on a CHIRASIL-DEX CB column or by chiral HPLC analysis on a Chiralcel OD-H column, according to the literature methods[12].



Scheme 35

Table 3: Addition of diethylzinc to aldehydes, catalyzed by 10 mol% **251** or **252**.

Entry	**Catalyst**	**R**	**Yield [a] (%)**	***ee* [b] (%)**	**Configuration [c]**
1	**251**	(4-MeO)C_6H_4	80	92	*(S)*
2	**251**	(3-MeO)C_6H_4	78	84	*(S)*
3	**251**	(3-Me)C_6H_4	75	78	*(S)*
4	**252**	(4-MeO)C_6H_4	83	85	*(R)*
5	**252**	(3-MeO)C_6H_4	92	87	*(R)*
6	**252**	(3-Me)C_6H_4	80	84	*(R)*
7	**252**	cyclohexyl	85	48	*(R)*
8	**252**	*n*-butyl	80	45	*(R)*

[a] Data given after silica column chromatography. [b] Determined on the crude product by HPLC (Chiracel OD-H) or GC (Chirasil-DEX CB column). [c] Determined by comparing the t_R of the HPLC analysis and the optical rotation with the literature data[12].

3.1.5. Antiproliferative activity of the prepared compounds

Since the epoxide moieties are able to form covalent bonds between the putative target proteins and the inhibitor, irreversible inhibition of the molecular target took place and, consequently, antiproliferative activity was examined[160]. The *in vitro* cytotoxic activities of the prepared 4-amino-2,3-epoxide-1-ol analogues were also investigated by Prof. Zupko and his group at the Department of Pharmacodynamics and Biopharmacy against a panel of human malignant cell lines isolated from cervical (SiHA and HeLa), breast (MCF7 and MDA-MB-231), and ovary (A2780) cancers.

Concerning the pharmacological activities of the tested pinane analogues, compounds containing the heteroaromatic pyridine ring (**219**, **227a**, and **231a**) exhibited no considerable antiproliferative action against the utilized human cancer cell lines. Full saturation of the pyridine ring (**229a**, **229d**, **233a**, and **233d**) resulted in similar negligible or modest activities eliciting 30–50% cell growth inhibition at higher concentration (30 μM). Partial saturation, on the other hand, led to molecules eliciting substantial activities, which were comparable to those obtained by the reference agent cisplatin. The *trans* orientation of the epoxy function seems to be preferred, especially in the case of **228c** and **232c**. Substituents of the benzyl ring on the tetrahydropyridine function do not seem to determine the activity of the obtained analogue, but non-substituted compounds elicited relatively low activity against the ovarian cancer cell line with the exception of **232a**.

Table 4: Antiproliferative properties of selected pinane analogues

		Growth Inhibition (%) ± SEM				
Compound	**Conc. (μM)**	**HeLa**	**SiHa**	**MDA-MB-231**	**MCF-7**	**A2780**
228a	10	<20	<20	28.16 ± 0.43	<20	<20
	30	33.85 ± 2.00	77.01 ± 1.65	41.10 ± 3.07	<20	47.73 ± 1.52
228b	10	<20	40.56 ± 1.64	55.68 ± 1.28	44.74 ± 1.50	39.31 ± 3.16
	30	95.59 ± 0.74	75.21 ± 0.64	90.09 ± 0.81	84.97 ± 3.05	95.45 ± 1.16
228c	10	<20	<20	<20	<20	<20
	30	24.25 ± 1.32	<20	37.22 ± 1.22	33.41 ± 1.74	64.09 ± 1.77

228d	10	<20	54.15 ± 2.35	71.67 ± 2.17	48.99 ± 2.71	90.38 ± 0.89
	30	85.79 ± 0.26	92.76 ± 0.58	89.93 ± 0.86	97.97 ± 1.46	95.99 ± 1.56
232a	10	<20	28.96 ± 3.12	<20	21.50 ± 2.28	91.37 ± 1.51
	30	76.19 ± 2.61	88.38 ± 0.71	43.86 ± 0.65	86.14 ± 2.84	98.18 ± 0.47
232b	10	25.63 ± 1.32	38.97 ± 2.73	58.49 ± 2.78	29.26 ± 3.00	33.46 ± 1.93
	30	83.98 ± 1.63	85.38 ± 1.54	93.95 ± 0.75	98.26 ± 2.28	99.07 ± 0.46
232c	10	<20	47.99 ± 3.03	69.33 ± 1.95	56.93 ± 2.35	88.65 ± 0.58
	30	87.67 ± 2.24	93.03 ± 1.72	94.80 ± 0.14	96.07 ± 1.47	97.45 ± 0.41
232d	10	<20	23.09 ± 2.86	44.44 ± 1.21	62.03 ± 2.17	77.22 ± 2.85
	30	66.61 ± 1.54	92.58 ± 1.91	89.26 ± 0.88	97.45 ± 1.35	99.37 ± 1.19
233a	10	<20	<20	<20	<20	<20
	30	51.48 ± 0.32	35.17 ± 0.78	36.42 ± 0.59	21.15 ± 2.55	<20
233d	10	<20	<20	27.30 ± 1.74	<20	<20
	30	24.25 ± 2.76	<20	40.40 ± 2.85	20.90 ± 1.69	26.22 ± 2.42
Cisplatin	10	42.61 ± 2.33	60.98 ± 0.92	67.51 ± 1.01	53.03 ± 2.29	83.57 ± 2.21
	30	99.93 ± 0.26	88.95 ± 0.53	87.75 ± 1.10	86.90 ± 1.24	95.02 ± 0.28

*Cancer cell growth inhibition values less than 20% were considered insignificant and are not given numerically

3.2. Synthesis and biological activities of pinane-based diaminopyrimidines

3.2.1. Synthesis of pinane-based diaminopyrimidines

As a part of starting material synthesis, pinane-based chiral 1,3-aminoalcohols **20**, **275**, and **276** were prepared in several steps from commercially available monoterpenes (−)-apopinene (**275** and **276**)[7,161] and (−)-*β*-pinene (**20**)[94], respectively, following literature methods. (Figure 8) In the same way, 3-amino-1,2-diol **168** was also synthesized from (1*R*)-myrtenol[11].

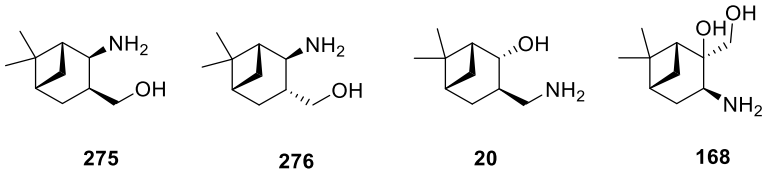
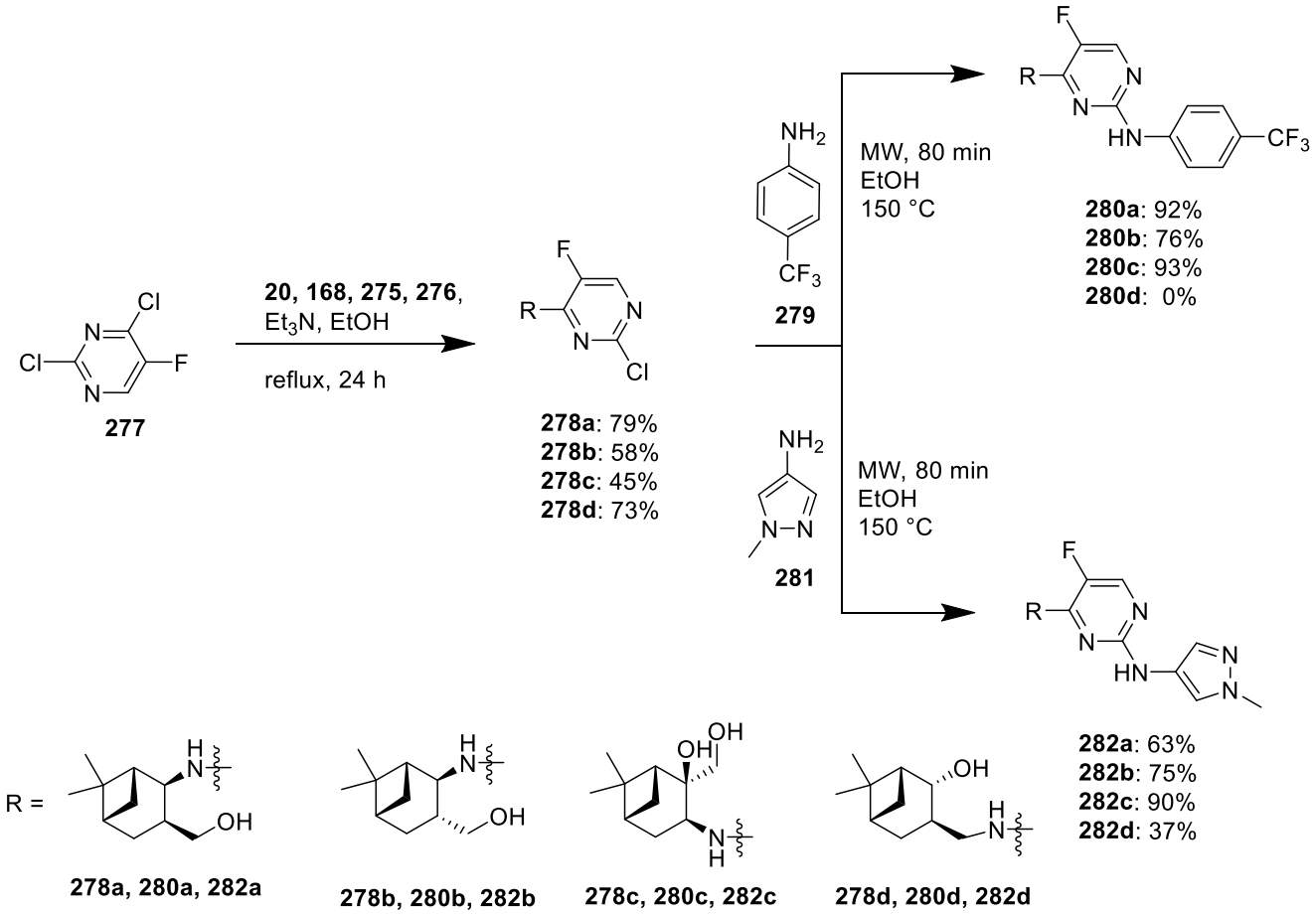


Figure 8

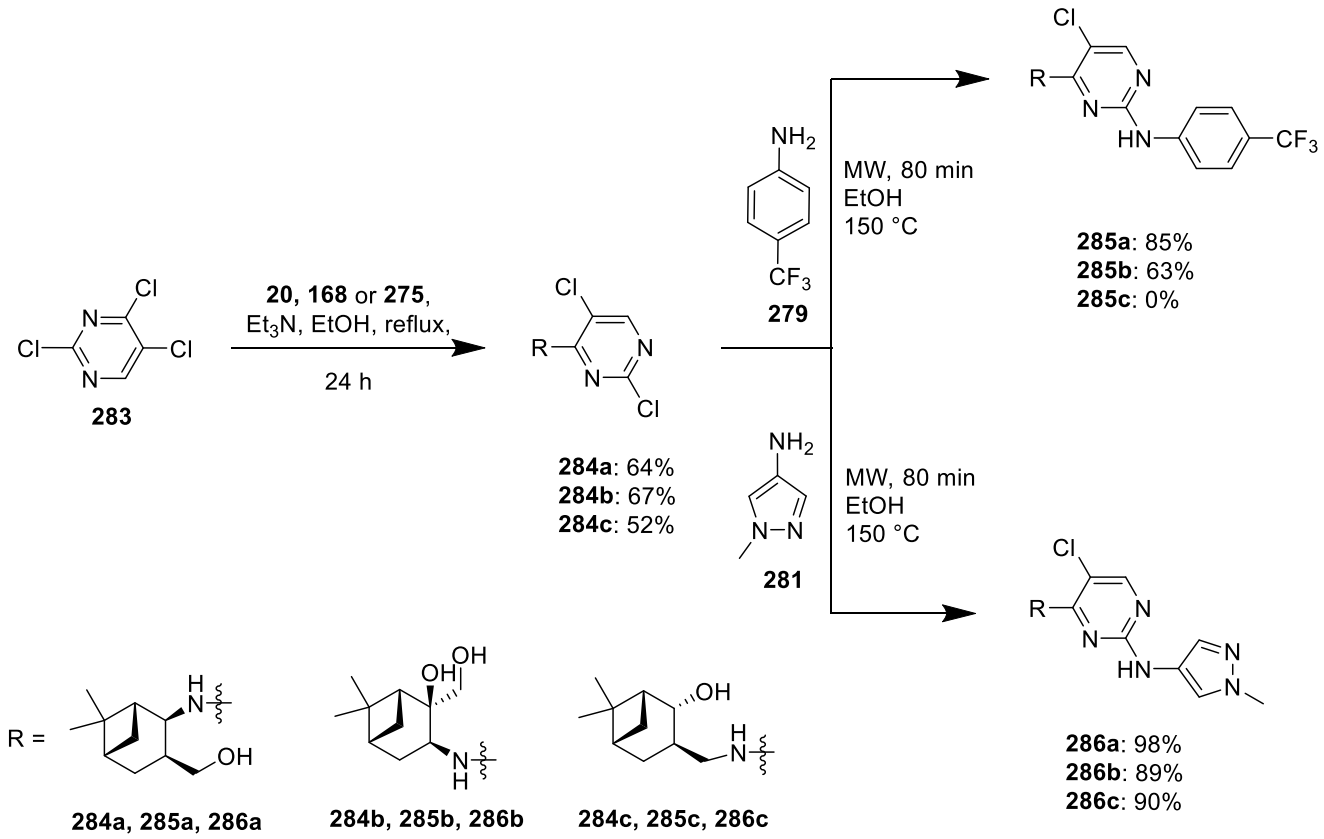
Key intermediates **278a–d**, prepared by condensation of aminoalcohols **20**, **275**, and **276** and aminodiol **168** with 2,4-dichloro-5-fluoropyrimidine (**277**) in the presence of Et_3N in EtOH[132], could be easily isolated by simple column chromatography with high (**278a** and **278d**) or moderate yields (**278b** and **278c**). (Scheme 36) In the next step, a microwave-assisted S_NAr coupling reaction of **278a–c** with 4-aminobenzotrifluoride (**279**) in EtOH at 150 °C yielded

derivatives **280a–c** as solid precipitates in good yields (over 76%)[162], while the coupling reaction of **278d** led only to slow degradation of the reactant during the process. Following the procedure mentioned above, pyrazole pyrimidines **282a–d** were obtained by coupling reactions between **278a–d** with 4-amino-1-methylpyrazole (**281**) in good (**282a–c)** or moderate yields (**282d**).



Scheme 36

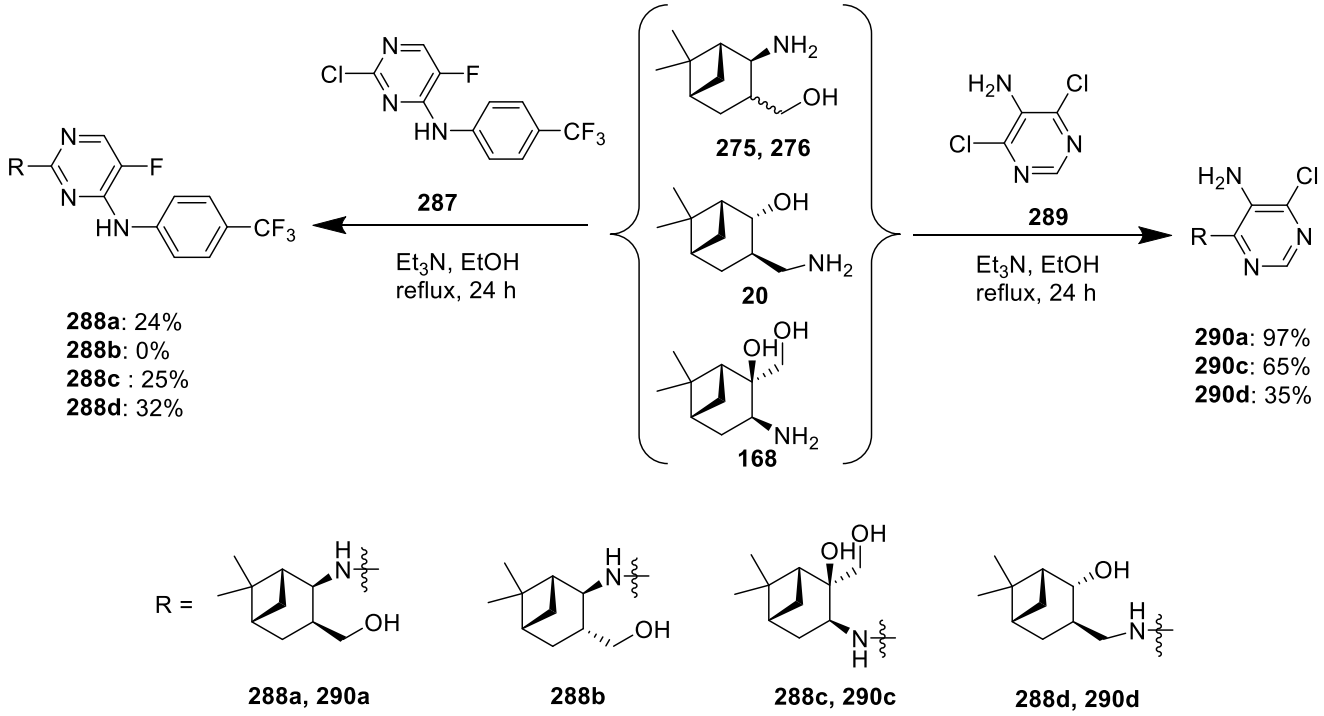
In a manner, similar to that shown in Scheme 36, the preparation of 5-chloro analogues **285a–c** and **286a–c** was carried out by coupling **20, 168**, and **275** with 2,4,5-trichloropyrimidine (**283**) followed by reaction of intermediates **284a–c** with 4-aminobenzotrifluoride or 4-amino-1-methylpyrazole. It must be noted that compounds **284a–b** were smoothly transferred to **285a–b** in good to excellent yields. In contrast, the coupling of **284c** with 4-aminobenzotrifluoride did not provide any trace of desired product **285c** (Scheme 37).



Scheme 37

The preparation of regioisomeric 4-aniline-substituted pyrimidines was accomplished *via* an alternative pathway, presented in Scheme 38. In the first step, 2-chloro-5-fluoro-6-(4-(trifluoromethyl)phenylamino)pyrimidine **287** was synthesized according to a literature procedure[163]. S_NAr-type coupling reaction of **287** with aminoalcohols **275** and **20** and aminodiol **168** resulted in **288a**, **288c**, and **288d** with low yields, while the coupling reaction with **276** was ineffective in obtaining **288b**. It may be due to the low reactivity of chlorine in position 2 of the pyrimidine moiety.

Likewise, further coupling reactions were accomplished by utilizing 5-amino-4,6-dichloropyrimidine as a coupling agent. Pinane-based pyrimidines **290a** and **290c–d** were formed in good (**290a** and **c**) to moderate yields (**290d**). Unfortunately, the next coupling reactions at the remaining chlorine at position 6 were unsuccessful either under standard heating or microwave-assisted conditions.



Scheme 38

3.2.2. Biological properties of pinane-based diaminopyrimidines

3.2.2.1 Antiproliferative activity

The antiproliferative properties of the prepared monoterpene-based diaminopyrimidines were determined *in vitro* by Prof. Zupko and his group on a panel of human adherent cancer lines, including cells from cervical (HeLa, SiHa), breast (MDA-MB-231, MCF7), and ovary cancers (A2780) using MTT assay. Based on the obtained activities concerning the structure–activity relationships, some conclusions could be arrived at. Compounds with primary amino function on the pyrimidine ring or monoamino-substituted pyrimidines are either ineffective (**284b**, **290c**, and **290d**) or exert modest activities (*i.e.* less than 60% even at 30 μM; **278a–d**, **284a**, **284b**, **290c**, and **290d**). Compound **290a** seems to be an exception resulting in more than 95% growth inhibition against HeLa cells in a selective manner. Comparing the effect of *p*-CF_3-phenyl and 4-pyrazolyl substituents at the 2-amino function, the *p*-CF_3-phenyl substituent renders better activities than the 4-pyrazolyl substituent in the case of the 6-F analogues (**280a/282a**, **280c/282c**, and **285b/286b**). However, concerning 6-chloro-substituted diaminopyrimidines

(**17a/286a**), an opposite relationship was found. Although the stereochemistry of the 1,3-aminoalcohol function at the pinane system has no remarkable influence on the antiproliferative activity, the *cis* configuration of the 1,3-aminoalcohol moiety is somewhat preferred (**278a/278b**, **280a/280b**), albeit with only a modest difference (**282a/282b**). Further observations also confirmed that the position of the monoterpene component in the diaminopyrimidine ring does not seem relevant; both positions 2 (**280c/20c**) and 4 (**280a/288a**) have promoting effects. Interestingly, chloro substitution at the diaminopyrimidine skeleton displayed a more pronounced effect on the growth of cancer cells than the corresponding fluoro derivatives (**282a/286a**).

Analogue **286a** exerted higher cell growth inhibition than reference agent cisplatin against all cell lines, while **290a** proved to be selective for one of the cervical cell lines. Both molecules can be considered promising prototypes of novel anticancer agents, and they are worth further investigation to explore the mechanism of the action.

Table 5: Antiproliferative properties of selected pinane-based pyrimidine analogues

		Growth Inhibition (%) ± SEM				
Comp.	**Conc. (μM)**	**Hela**	**SiHa**	**MBA-MB-231**	**MCF7**	**A2780**
278a	10	36.67 ± 1.41	–*	–	–	–
	30	57.49 ± 0.73	22.37 ± 1.32	–	43.58 ± 1.35	30.38 ± 1.51
280a	10	43.44 ± 0.58	27.96 ± 1.12	–	–	23.62 ± 3.32
	30	98.69 ± 0.22	95.07 ± 0.99	98.51 ± 0.21	98.30 ± 0.25	99.05 ± 0.33
280b	10	–	–	–	–	–
	30	76.92 ± 0.30	50.99 ± 1.73	27.12 ± 1.31	65.79 ± 0.26	62.41 ± 2.13
280c	10	39.66 ± 1.40	–	41.87 ± 0.66	–	–
	30	76.21 ± 0.81	72.46 ± 1.91	68.83 ± 1.38	56.85 ± 2.56	66.22 ± 1.20
282a	10	29.79 ± 3.82	–	37.75 ± 1.99	25.47 ± 1.91	62.17 ± 0.23
	30	49.39 ± 1.92	53.95 ± 1.78	61.97 ± 1.11	75.99 ± 2.31	91.11 ± 0.12
282b	10	42.07 ± 2.44	24.67 ± 1.73	–	35.79 ± 2.41	–
	30	74.39 ± 1.00	47.04 ± 1.46	48.28 ± 1.71	69.19 ± 1.63	74.74 ± 1.09
282c	10	29.09 ± 0.88	33.77 ± 2.88	–	32.37 ± 3.38	–
	30	51.39 ± 1.15	38.49 ± 1.65	–	45.18 ± 1.12	–
282d	10	24.12 ± 1.89	30.58 ± 1.68	–	25.63 ± 0.71	64.95 ± 2.94
	30	52.81 ± 0.72	57.85 ± 1.08	25.81 ± 0.72	54.94 ± 0.69	80.19 ± 0.49
285a	10	39.89 ± 2.83	–	27.65 ± 2.22	34.83 ± 2.85	79.14 ± 1.91
	30	98.99 ± 0.25	96.59 ± 0.65	96.65 ± 0.30	94.70 ± 0.33	98.28 ± 0.24
285b	10	60.29 ± 1.51	40.49 ± 2.10	-	53.41 ± 0.44	42.58 ± 1.04
	30	97.89 ± 0.14	95.45 ± 0.49	94.97 ± 0.19	90.84 ± 0.46	96.97 ± 0.16
286a	10	99.13 ± 0.19	93.06 ± 0.65	72.79 ± 1.09	84.74 ± 0.32	95.17 ± 0.99

	30	100.20 ± 0.11	94.31 ± 0.68	86.75 ± 0.92	90.75 ± 0.54	97.06 ± 0.20
286b	10	–	24.07 ± 1.38	-	33.75 ± 2.41	34.81 ± 2.94
	30	63.50 ± 1.64	57.89 ± 1.07	20.18 ± 2.70	66.07 ± 1.30	80.61 ± 0.92
286c	10	45.07 ± 2.92	33.07 ± 1.54	23.28 ± 1.75	46.35 ± 2.67	84.72 ± 0.62
	30	67.74 ± 1.33	68.87 ± 1.23	50.51 ± 1.90	75.95 ± 0.92	93.28 ± 0.40
288a	10	–	–	–	–	29.81 ± 1.66
	30	29.62 ± 2.13	–	39.11 ± 3.06	30.24 ± 0.64	60.64 ± 0.46
288c	10	–	–	–	27.80 ± 1.85	30.59 ± 1.59
	30	97.72 ± 0.42	100.45 ± 1.39	99.17 ± 0.54	96.12 ± 0.84	100.00 ± 0.44
288d	10	29.02 ± 2.26	–	27.15 ± 1.34	–	26.19 ± 1.88
	30	95.06 ± 0.47	90.39 ± 0.57	93.88 ± 0.53	90.52 ± 1.03	91.75 ± 3.12
290a	10	95.92 ± 0.39	-	-	37.88 ± 2.62	48.96 ± 2.03
	30	97.96 ± 0.25	26.42 ± 2.67	-	39.68 ± 2.22	55.91 ± 1.16
Cispl.	10	42.61 ± 2.33	60.98 ± 0.92	67.51 ± 1.01	53.03 ± 2.29	83.57 ± 2.21
	30	99.93 ± 0.26	88.95 ± 0.53	87.75 ± 1.10	86.90 ± 1.24	95.02 ± 0.28

* Cancer cell growth inhibition values less than 20% were considered negligible and are not given numerically.

3.2.2.2 Antimicrobial activity

The *in vitro* antimicrobial activities of the synthesized compounds were studied by Dr. András Szekeres and his team from the Department of Microbiology. Activties against four strains of bacteria and two of fungi were determined. The complete biological screening data are summarized in Table 6. 2,4-Diaminopyrimidine scaffolds (**280a–b**, **284a–c**, **285a**, **288a**) yielded a significant effect on Gram-positive bacteria, while 4,5-diaminopyrimidines (**290a–d**) are potent derivatives against *P. aeruginosa*. None of the synthesized compounds had any reliable activity against fungi.

The *in vitro* Gram-positive inhibitory activity of 2,4-diaminopyrimidine derivatives allowed to draw a preliminary structure–activity relationship. Specifically, compound **285a** displayed excellent potency against *B. substilis* and *S. aureus* at low concentrations (10 μg/mL). In particular, the introduction of the pyrazole group at position 2 of the pyrimidine ring (**286a**) resulted in a substantial loss of activity, while the chloro substituent at C-2 (**284a**) exhibited favourable selectivity over *B. substilis*. Introducing the fluoro group at position C-5 of the pyrimidine ring (**280a**) led to decreasing antibacterial activity.

Table 6: Antimicrobial properties of selected pinane-based pyrimidine analogues

		Inhibitory effect (%) ± RSD (%)					
		Gram-positive		Gram-negative		Yeast	
Comp.	Conc. (μg/mL)	*B. subtilis* SZMC0209	*S. aureus* SZMC14611	*E. coli* SZMC6271	*P. aeruginosa* SZMC23290	*C. albicans* SZMC1533	*C. krusei* SZMC1352
Amp	100	94.30 ± 1.01	90.34 ± 2.49	96.13 ± 3.21	49.44 ± 9.43	-	-
	10	88.85 ± 2.34	79.54 ± 3.88	92.28 ± 6.26	10.70 ± 15.29	-	-
Nys	100	-	-	-	-	91.55 ± 9.11	95.52 ± 15.52
	10	-	-	-	-	89.96 ± 5.05	-
278d	100	57.82 ± 11.82	10.43 ± 5.46	1.79 ± 0.46	-	1.96 ± 6.09	-
	10	12.01 ± 10.19	5.36 ± 2.00	2.16 ± 0.89	-	-	-
280a	100	86.26 ± 2.35	70.00 ± 12.30	-	7.32 ± 6.35	4.20 ± 6.37	-
	10	-	-	-	-	-	-
280b	100	93.08 ± 7.02	81.97 ± 2.37	4.73 ± 2.72	45.93 ± 5.51	-	-
	10	86.23 ± 1.00	76.37 ± 1.73	-	35.63 ± 2.94	-	-
284a	100	74.18 ± 16.82	15.39 ± 5.08	10.84 ± 2.09	8.67 ± 23.86	1.87 ± 6.50	-
	10	44.84 ± 6.78	14.17 ± 2.83	-	-	3.14 ± 5.94	-
284b	100	-	39.34 ± 2.84	4.05 ± 2.13	16.02 ± 2.82	-	-
	10	2.12 ± 5.57	30.82 ± 5.85	2.62 ± 2.19	2.34 ± 17.25	1.27 ± 15.76	-
284c	100	64.81 ± 6.76	16.40 ± 5.26	9.59 ± 3.44	-	-	-
	10	58.64 ± 8.82	7.02 ± 5.30	3.25 ± 1.38	6.17 ± 14.45	-	-
285a	100	100.00 ± 15.40	100.00 ± 2.56	11.80 ± 6.56	9.93 ± 11.61	17.64 ± 5.31	7.75 ± 8.59
	10	95.66 ± 2.44	84.86 ± 9.16	7.90 ± 4.58	-	-	2.84 ± 3.45
288a	100	83.46 ± 5.14	18.11 ± 5.06	-	34.83 ± 5.58	-	-
	10	-	-	4.81 ± 7.67	-	-	-
290d	100	2.01 ± 23.40	55.46 ± 3.59	17.31 ± 0.87	44.97 ± 12.13	17.71 ± 8.23	-
	10	-	32.85 ± 1.98	1.20 ± 1.00	36.32 ± 10.04	1.82 ± 7.45	-

To confirm and extend our observations regarding the critical role of the 1,3-aminodiol moiety at C-4 on both potency and selectivity, analogues of **280a** and **284a**, where the 1,3-aminoalcohol was systematically modified, were prepared and tested. Alternate inhibitors associated with the 3-amino-1,2-diol motif (**280c**, **284b**) demonstrated the complete disappearance of antibacterial activity. Interestingly, 1,3-aminoalcohol **280b**, the epimer of **280a**, showed significant growth inhibition on Gram-positive bacteria at low concentration (10 μM) and it was found to be an active inhibitor against *P. aeruginosa*, while analogue **284c** displayed equipotent activity relative to its regioisomer (**284a**).

Finally, introduction of both the 1,3-aminoalcohol moiety into the C-2 position and substituted aniline at C-4 (**288a**) enhanced the selectivity over *B. Subtilis.*

4. Summary

As part of my thesis work, I synthesized and studied new monoterpene-based chiral aminoalcohols as well as aminodiols derived from natural monoterpenes such as (1*R*)-(−)-myrtenol, (–)-*α*- and *β*-pinene. In addition, preparation of pinane-based pyrimidine derivatives was also accomplished.

Starting from commercially available (–)-*β*-pinene, nopinone was prepared and it was reacted in an aldol condensation with picoline aldehyde. The reduction of bicyclic amino ketone **217** under Luch condition followed by epoxidation gave key epoxy alcohol intermediate **219**. However, the direct epoxydation of the α,β-unsaturated ketone proved to be non-stereoselective, and subsequent reduction of the resulting epoxyketones led to the formation of epoxyalcohols **219** and **230**. After quaternization of the pyridine amine with a variety of benzyl bromides, the reduction of the pyridine ring to piperidine was therefore successful and stereoselective.

The resistance of the oxirane ring during the nucleophile-initiated opening reaction was interpreted by a systematic series of comparative Hartree–Fock modeling study using the 6-31+G(d,p) basis set.

Starting from nopinone, a library of 3-amino-1,2-diols was prepared by aldolization with formaldehyde. Subsequent reduction of the ketone followed by epoxidation led to epoxyalcohol **236** in a stereospecific manner. Ring opening of the oxirane ring with primary and secondary amines afforded the required aminodiols **237–244** as well as *O*-benzyl derivatives **250–253**. Ring closure with formaldehyde was also investigated with the exclusive formation of spirooxazolidines **246**, **247**, and **253**.

A small library of pinane-based 2-amino-1,3-diols was synthesized in a stereoselective manner starting from (1*R*)-(−)-myrtenol and isopinocarveol prepared from *α*-pinene. Pinane-condensed or spiro-oxazolidin-2-ones **257** and **260** were formed in three steps by a stereoselective hydroxyamination process. The resulting primary and secondary 2-amino-1,3-diols underwent a regioselective ring closure with formaldehyde and benzaldehyde producing pinane-condensed

oxazolidines. In the case of 2-phenyliminooxazolidine, an interesting ring–ring tautomerism was observed in $CDCl_3$.

The catalytic value of the aminoalcohols, aminodiols, and their ring-closed derivatives was tested in the enantioselective addition of diethylzinc to aldehydes. Aminodiol **241** and **252** afforded the best value *ee* = 80% with an (*R*)-selectivity with benzaldehyde, whereas *O*-benzyl aminodiol **251** afforded (*S)*-selectivity up to *ee* = 92% when used with 4-methoxybenzaldehyde. However, pinane-based 1,4-aminoalcohols showed poor selectivity with the best, but still with a moderate *ee* value of 33%.

Antiproliferative activities of the pinane-based 1,4-aminoalcohol library were explored and the structure–activity relationships were studied. The resulting 4-tetrahydropyridine 2,3-epoxy-1-ols exert marked antiproliferative action on a panel of human cancer cell lines. The *in vitro* pharmacological studies have clearly shown that the 1,4-aminoalcohol function together with the oxirane and tetrahydropyridine ring systems seem to be essential for reliable antiproliferative activity. However, the stereochemistry of the oxirane ring and the *N*-substituents on the tetrahydropyridine function have no influence on the antiproliferative effect.

Pinane-based aminoalcohols **20**, **275**, and **276** and aminodiol **168** were prepared according to literature methods, and were condensed with 2,4-dichloro-5-fluoropyrimidine, 2,4,5-trichloropyrimidine, or 5-amino-4,6-dichloropyrimidine followed by coupling with 4-trifluoromethylaniline or 4-amino-1-methylpyrazole, resulting in a new library of chiral, pinane-based 2,4- or 3,4-diaminopyrimidines. Cytotoxic activity of compounds against human tumor cell lines (A2780, SiHa, HeLa, MCF-7, and MDA-MB-231) was investigated. In our preliminary study, the 2,4-diaminopyrimidine and 1-methylpyrazol moieties seemed to be essential for reliable antiproliferative activity. The antimicrobial activity of the prepared compounds against different bacterial and fungal strains was also evaluated. The 2,4-diaminopyrimidine moiety appeared to be essential, but effect of its aromatic or heteroaromatic substitution is opposite to that found in antiproliferative activity. Finally, the *N*-4-trifluorophenyl substitution showed a clear advantage over 1-methylpyrazol. The stereochemistry of the pinane ring system had a weak influence on the cytotoxic or antibacterial activity.

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