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

PhD thesis

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Summary of PhD thesis

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Introduction and aims

In asymmetric synthesis, it is necessary for the development of new chiral ligands to obtain enatiopure catalysts. One of the ways to achieve this purpose is the exertion of chiral monoterpenes as starting materials in stereoselective synthesis. The most frequently applied approach to optically active monoterpene derivatives is the transformation of the ring C–C double bond. This general approach 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 important starting materials in synthesis, *β*-aminolactones are used to retain cytotoxicity. Furthermore, the ring-opening of *β*-aminolactones with various amines may provide *β*-aminoamides, which are well-known antibiotics, tyrosine kinase inhibitors, KDR and Aurora B kinase inhibitors, antidiabetes, antitumor and HIV protease and renin inhibitors. Besides interests in the synthesis of *β*-aminoamides, the opening of *β*-aminolactones with *β*-aminoesters is a useful method for the synthesis of dipeptides containing *β*–alanine moiety.

Monoterpene-based 1,2- and 1,3-amino alcohols have been demonstrated to be excellent chiral auxiliaries in a wide range of stereoselective transformations. Moreover, aminodiols, combining the chemical properties of 1,2- and 1,3-amino alcohols are excellent starting materials and catalysts in stereoselective synthesis as well as useful building blocks for the synthesis of 1,3-cyclic heterocycles such as 1,3-oxazines and oxazolidines.

The aim of my thesis work was to synthesize monoterpene-based 2- and 3-functionalized building blocks, such as *β*-amino acid derivatives and aminodiols, starting from (−)-limonene and (−)-isopulegol. Furthermore, the substituent-dependent ring closure of these monoterpene derivatives with formaldehyde is also presented. The aminodiols and their ring-closed derivatives were applied as chiral catalysts in the enantioselective addition of Et_2Zn to benzaldehyde. On the other hand, the antiproliferative activity of *β*-amino acid derivatives, such as *β*-aminolactones and *β*-aminoamides was also studied on multiple cancer cell lines. Finally, the synthesis of dipeptides, which might serve as promising chiral substrates for the preparation of chiral foldamers was also reported.

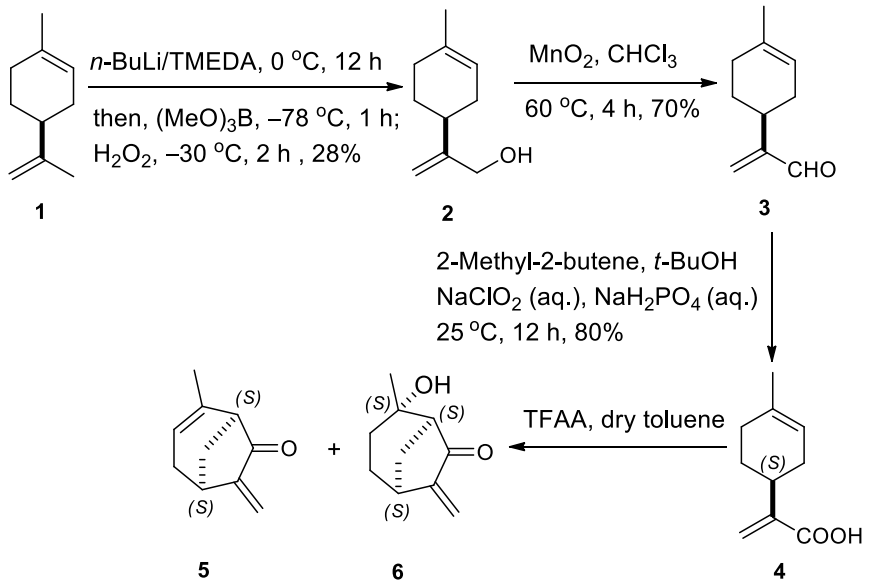
Methods

Reations were perfomed on a mmol scale, and products were purified by column chromatography on silica gel or by crystallization. All new compounds were charaterized by their melting point, 1D- and 2D-NMR, elemental analysis, and optical rotation. The enatiomeric excess of 1-phenyl-1-propanols was checked by chiral GC. The antiproliferative properties were determined by microplate reader (Awareness Technology, Palm City, FL, USA). Calculations were performed by means of the GraphPad Prism 5.01 software (GraphPad Software Inc., San Diego, CA, USA).

Results and discussion

1. Synthesis of limonene-based chiral methylene ketones and analogue

The key bicyclic methylene ketone intermediates were prepared from (–)-limonene **1** with regioselective hydroxylation affording allylic alcohol **2**, which was oxidized to carboxylic acid **4** *via* aldehyde **3**. Intramolecular acylation of **4** gave methylene ketone **5** and its hydroxy-substituted analogue **6** (Scheme 1).

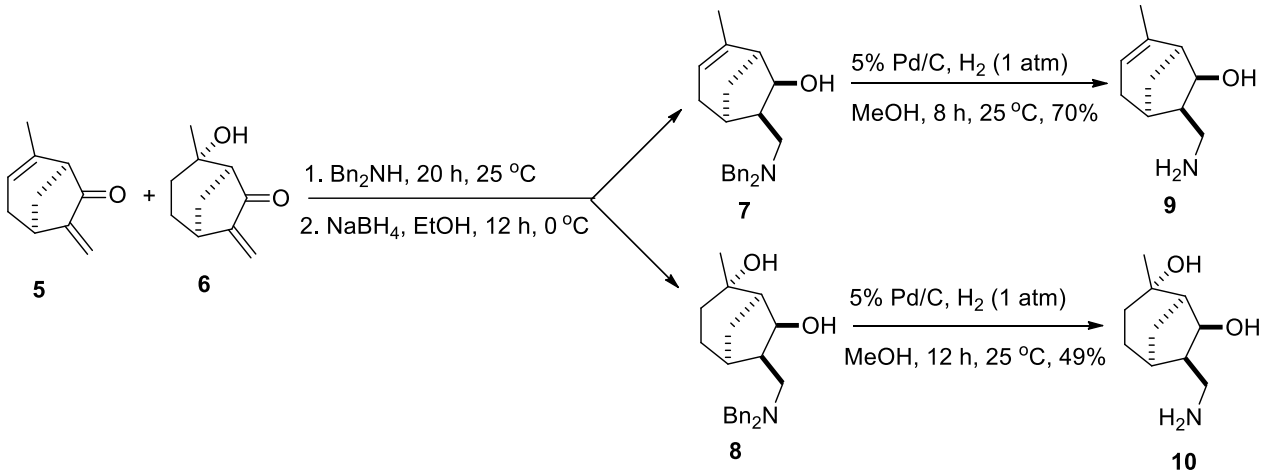


Scheme 1. Synthesis of bicyclic methylene ketones **5** and **6**

The reaction between the carboxylic acid and the double bond in the presence of TFAA was interpreted by a carbocationic mechanism.

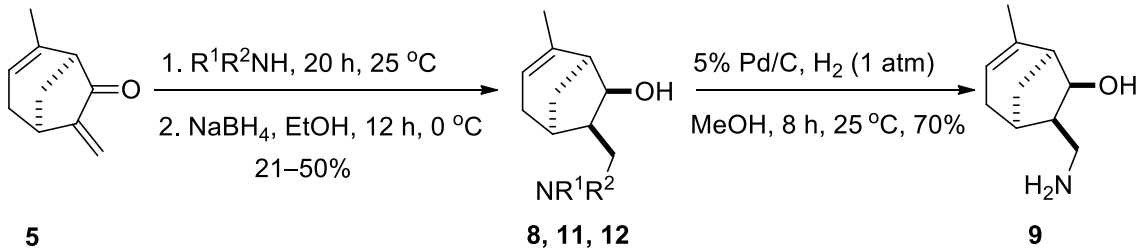
2. Synthesis of limonene-based chiral 1,3-amino alcohols and aminodiols

The mixture of **5** and **6** 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 **7** and aminodiol **8** by *in-situ* reduction of the ketone function with $NaBH_4$, followed by hydrogenolysis of the resulting compounds over Pd/C in MeOH providing primary amino alcohol **9** and aminodiol **10** in moderate yields (Scheme 2).



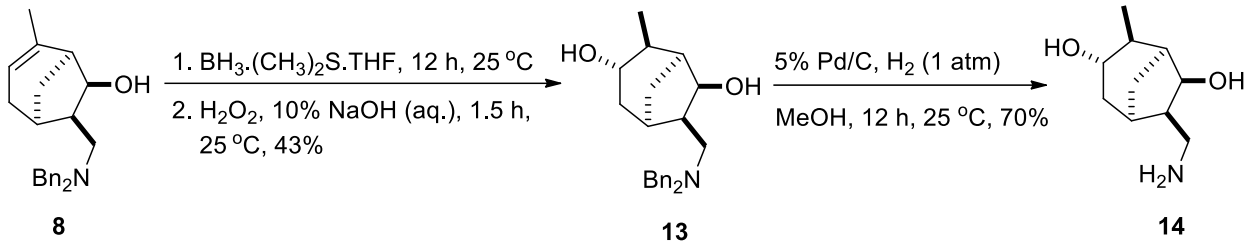
Scheme 2. Stereoselective synthesis of limonene-based amino alcohols and aminodiols

Methylene ketone **5**, prepared by an optimized cyclization reaction at 100 °C, was also treated with different amines to form tertiary and secondary amino alcohols **8**, **11**, and **12** with high stereoselectivity (Scheme 3).



Scheme 3. Stereoselective synthesis of amino alcohols

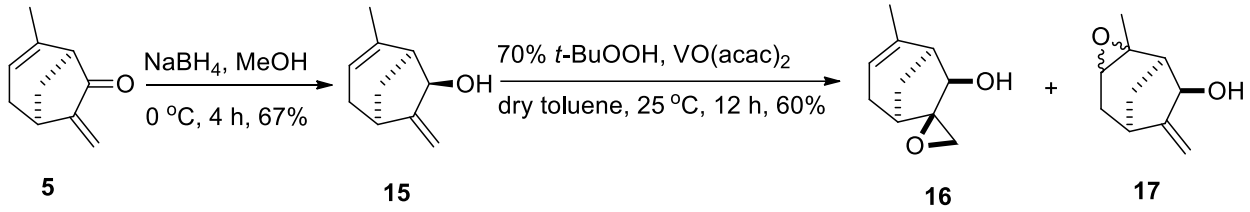
Futhermore, hydroboration of compound **8** was accomplished by treatment with $BH_3.Me_2S$, followed by oxidation of the intermediate with H_2O_2 to give a 3:1 mixture of two diastereomers. **13** However, only the major product **13** could be isolated. Debenzylation with the H_2/Pd/C system gave aminodiol **14** (Scheme 4).



Scheme 4. Synthesis of 6-amino-1,4-diols **13** and **14**

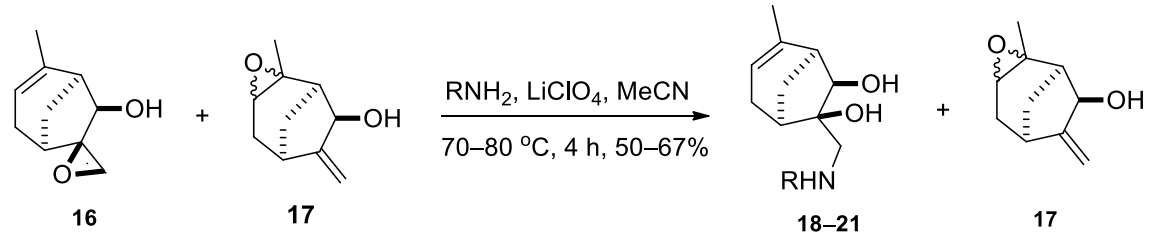
3. Synthesis of limonene-based chiral 3-amino-1,2-diols

Stereoselective reduction of **5** gave allylic alcohol **15**. Epoxidation of **15** in dry toluene in the presence of vanadyl acetylacetonate [$VO(acac)_2$] as the catalyst gave a mixture of **16** and a 4:1 diasteromeric mixture of **17** (Scheme 5).



Scheme 5. Stereoselective reduction and epoxidation

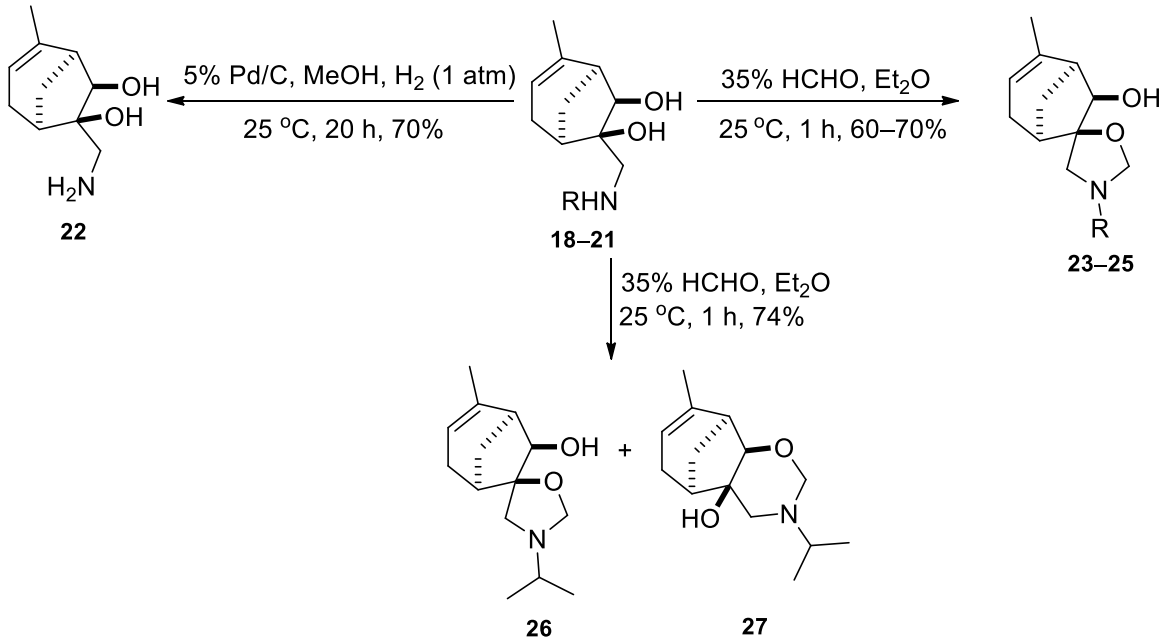
Aminodiol library **18**–**21** was prepared by aminolysis of epoxide **16** with primary amines in the presence of $LiClO_4$ as the catalyst. We observed that during aminolysis with primary amines under the applied conditions, epoxide **16** was transformed preferentially, whereas **17** did not react with the applied nucleophiles. This was probably due to steric hindrance exerted by the methyl group of **17** at the α position. Debenzylation by hydrogenolysis of compounds **18**–**21** over Pd/C in MeOH resulted in primary aminodiol **22** (Scheme 6).



18: R = CH_2Ph; **19**: R = CH(Me)Ph (*S*); **20**: R = CH(Me)Ph (*R*); **21**: R = $CH(Me)_2$

Scheme 6. Ring opening of epoxide **16**

Treatment of aminodiols **18**–**20** with formaldehyde at room temperature afforded spirooxazolidines **23**–**25** through a highly regioselective ring-closing reaction. In contrast, aminodiol **21** afforded a 2:1 mixture of spirooxazolidine **26** and 1,3-oxazine **27** (Scheme 7).



R = CH_2Ph, CH(Me)Ph (*S*), CH(Me)Ph (*R*), $CHMe_2$

Scheme 7. Debenzylation and ring closure reaction

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

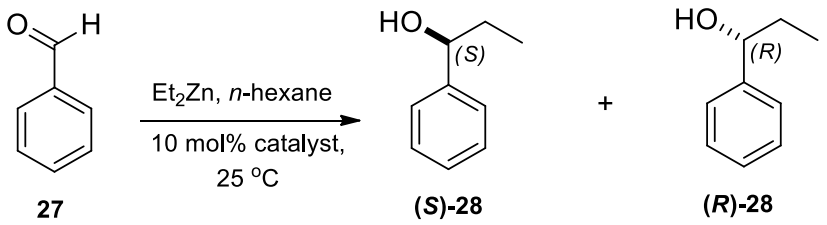
We were interested to get insight into the experienced substrate dependence of the acid-catalyzed, formaldehyde-mediated cyclization reactions of the studied aminodiols. Therefore, all resulting spirocyclic oxazolidines **23–25** and isomeric compound **26** fused with perhydro-1,3-

oxazine along with the possible iminium intermediates were analyzed by a systematic series of comparative DFT modelling carried out at the B3LYP/6-31+G(d,p) level of theory.

The calculated relative energetics of the optimized structures of spirocyclic products and their oxazine-fused counterparts [ΔE(**spiro→oxazine**, **spiro*→oxazine***)=11.8–13.8 kcal/mol] are obviously in line with experimental findings disclosing highly preferential formation of the spirocyclic isomers. The slightly enhanced tendency of isopropyl-substituted model **21** to afford fused oxazine product **26** might be due to acid-catalyzed formation of the iminium cation.

5. Appilcation of limonene-based chiral aminodiols as chiral catalysts

Aminodiol derivatives **18**–**26** were applied as chiral catalysts in the enantioselective addition of diethylzinc to benzaldehyde **27** to form (*S*)-1-phenyl-1-propanol [(*S*)-**28**] and (*R*)-1-phenyl-1-propanol [(*R*)-**28**] (Scheme 8).

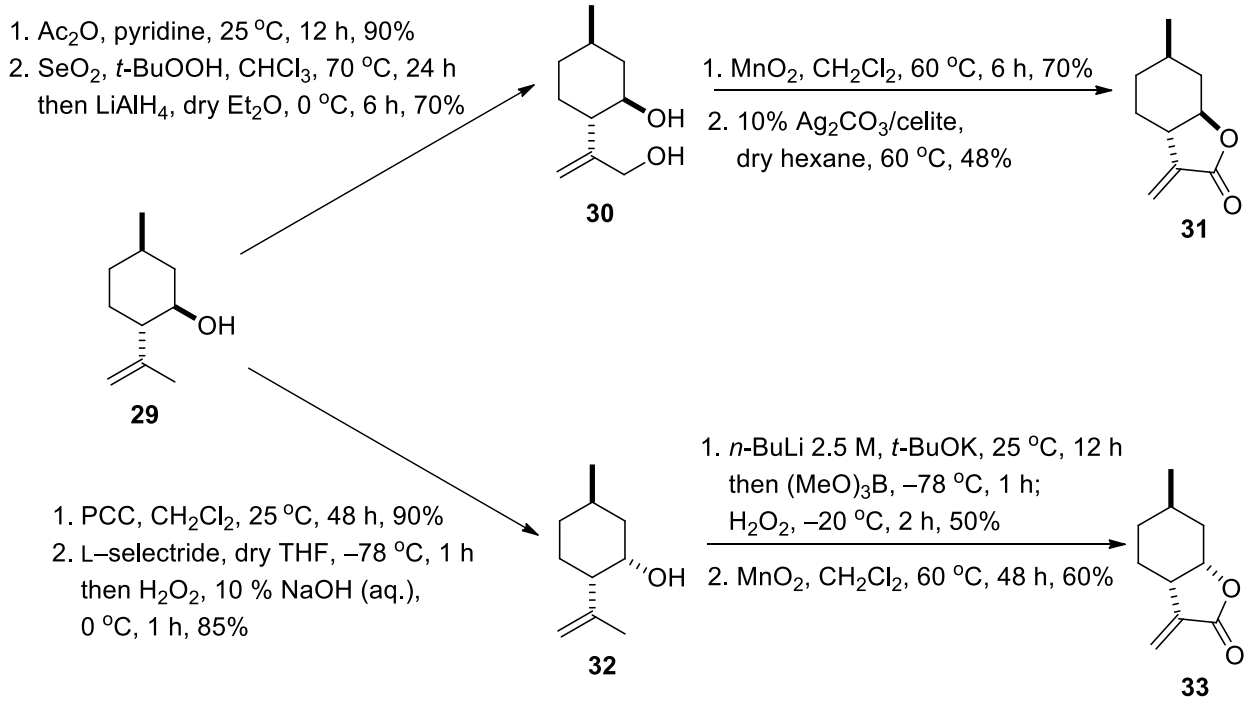


Scheme 8. Model reaction of enantioselective catalysis

Aminodiol **21** afforded the best *ee* value (*ee* = 55%) with *R* selectivity, whereas a 2:1 mixture of **25**/**26** showed the best *ee* value (*ee* = 80%) with *S* selectivity. The results obtained clearly show that the spirooxazolidine ring has poorer catalytic performance than the 1,3-oxazine ring system.

6. Synthesis of isopulegol-based chiral α-methylene-γ-butyrolactones

The key intermediate (+)-α-methylene-γ-butyrolactone **31** was prepared from (–)-isopulegol **29** with regioselective hydroxylation, followed by two-step oxidation and ring closure of the obtained γ-hydroxy-substituted α,β-unsaturated carboxylic acid. Diastereomeric (–)-α-methylene-γ-butyrolactone **33** was prepared in a similar way starting similarly from (–)-isopulegol **29**. In the first step, the hydroxy group of **29** was oxidized followed by stereoselective reduction of the resulting carbonyl group providing (+)-neoisopulegol **32** (Scheme 9).

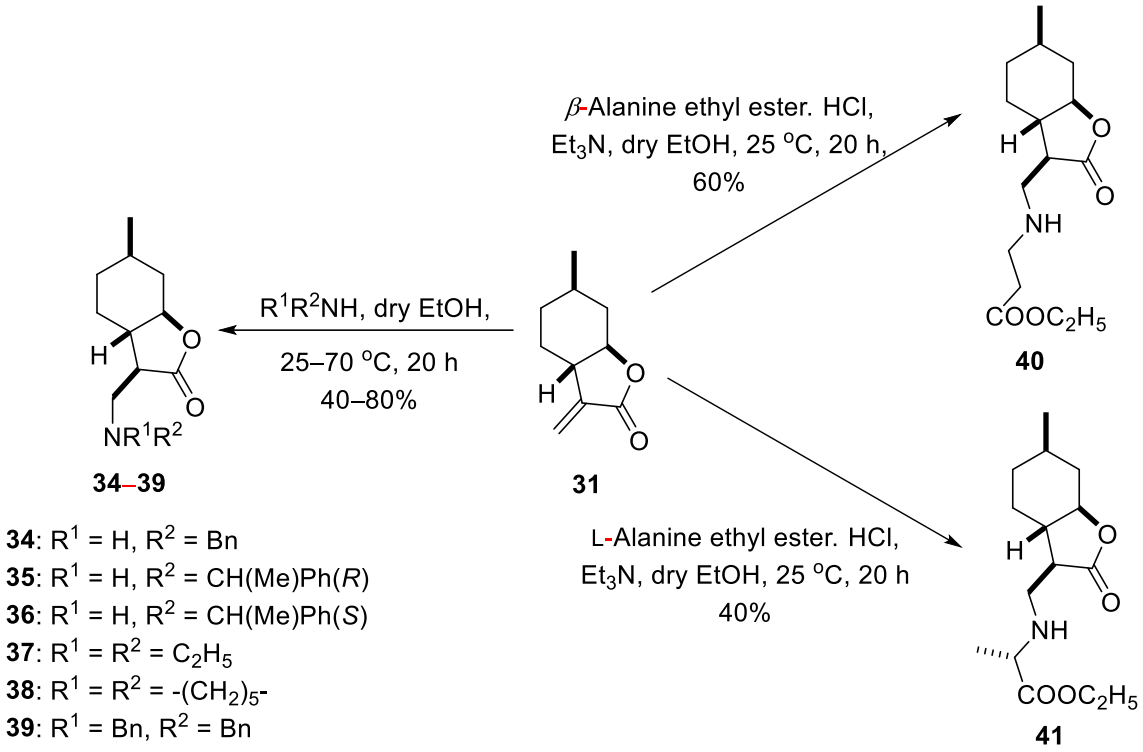


Scheme 9. Synthesis of (–)-isopulegol-based α-methylene-γ-butyrolactones **31** and **33**

7. Synthesis of isopulegol-based chiral β-aminolactones

Nucleophilic addition of primary and secondary amines to α-methylene-γ-butyrolactone **31** has proved to be an efficient method for the preparation of a highly diversified library of β-aminolactones (Scheme 10).

The optimized conditions in the case of **31** were also applied for the preparation of (+)-neoisopulegol-based β-aminolactones **42–47** starting from **33**. The reaction of **33** with some amino esters was effective at elevated temperature to achieve amino ester-based β-aminolactone derivatives **48**–**49**.

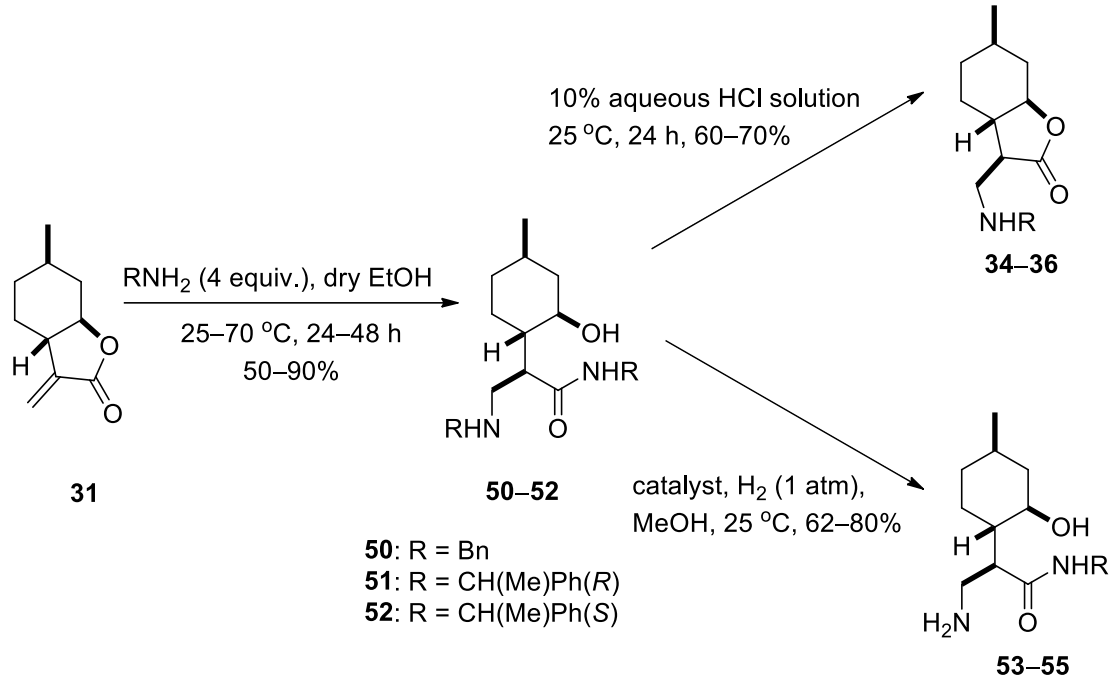


Scheme 10. Nucleophilic addition of **31** to amines and aminoesters

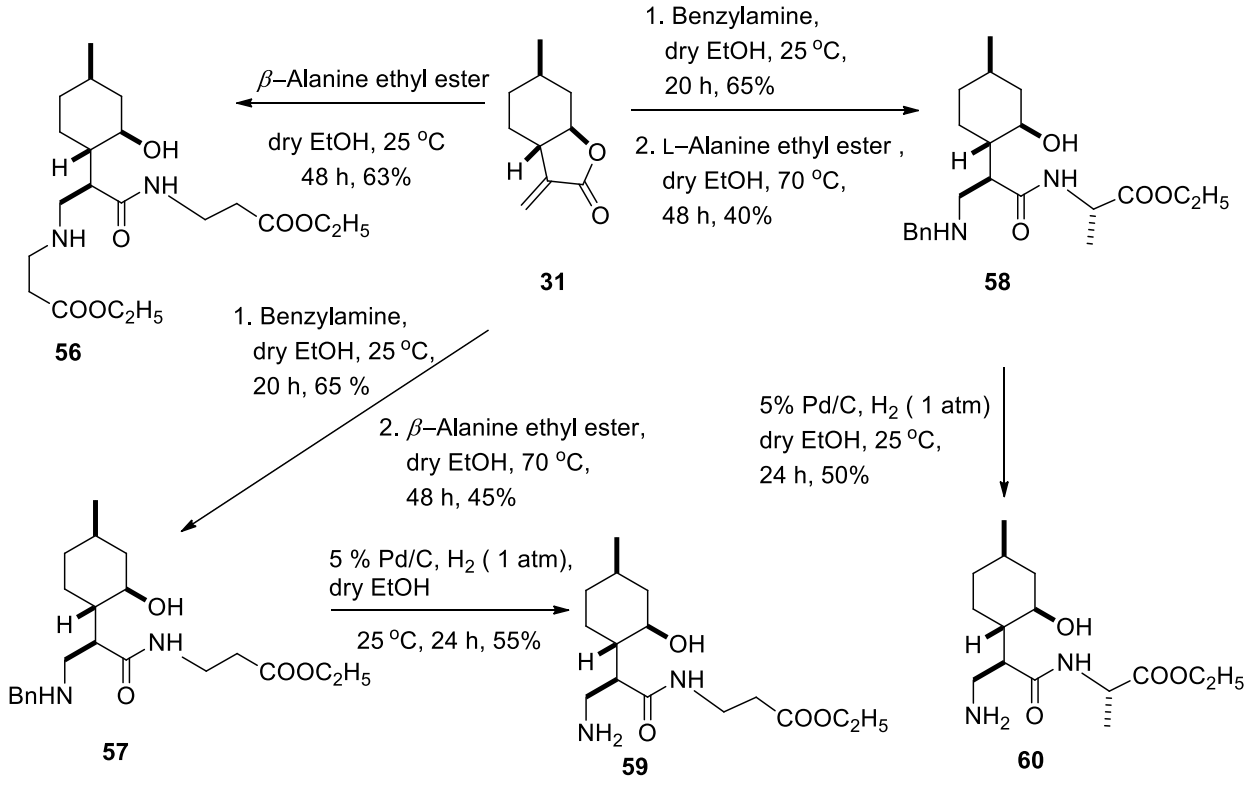
8. Synthesis of *β*-aminoamides and dipeptides

Nucleophilic addition and ring opening of lactones were simultaneously performed from **31** using excess amines to form *β*-aminoamides **50–52**. Hydrolysis of *β*-aminoamides under acidic conditions resulted in the original starting material *β*-aminolactones **34–36**. Debenzylation via hydrogenolysis of compounds **50–52** over appropriate catalysts in MeOH gave primary aminoamides **53–55** (Scheme 11).

In further studies, addition and ring-opening reaction of **31** with *β*-amino ester successfully gave dipeptide **56**. In addition, the opening of *N*-benzyl aminolactone **34** with both the *α*– and *β*–amino ester proceeded smoothly to give *N*-benzyl dipeptides **57**–**58**. Debenzylation through hydrogenolysis over Pd/C and purification of the crude products gave dipeptides **59** and **60** (Scheme 12).

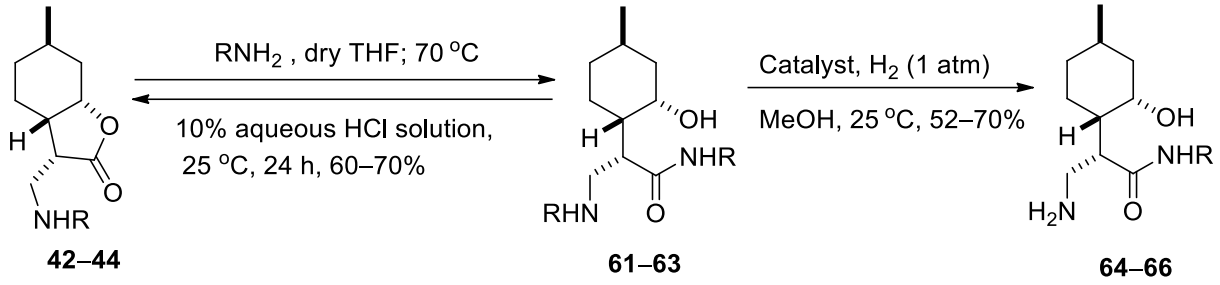


Scheme 11. Preparation of β-aminoamides from **31**



Scheme 12. Preparation of dipeptides from **31**

The preparation of *β*-aminoamides **61–63** was achieved by reacting *β*-aminolactones **42–44** with primary amines. Acidic hydrolysis of *β*-aminoamides **61–63** led to *β*-aminolactones **42–44**. Debenzylation with appropriate catalysts gave primary *β*-aminoamides **64–66** (Scheme 13).



Scheme 13. Preparation of *β*-aminoamides from **42–44**

9. Antiproliferative activity

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. 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 (**52**, **63**) exhibited modest growth inhibitory activities. The most potent newly-prepared monoterpene analogue was compound **52** exerting antiproliferative activity comparable to those of reference agent cisplatin.

Publication related to the thesis

[1] **Tam Le Minh**, Ferenc Fülöp, and Zsolt Szakonyi

Stereoselective synthesis of limonene-based chiral 1,3-amino alcohols and aminodiols

European Journal of Organic Chemistry, **2017**, 45, 6708–6713

IF: 2.882

[2] **Tam Minh Le**, Antal Csampai, Ferenc Fülöp, and Zsolt Szakonyi

Regio- and stereoselective synthesis of bicyclic limonene-based chiral aminodiols and spirooxazolidines

Chemistry: A European Journal, **2018**, 24, 13607–13615

IF: 5.160

[3] **Tam Minh Le**, Péter Bérdi, Zupkó István, Ferenc Fülöp, Zsolt Szakonyi

Synthesis and transformation of (–)-isopulegol-based chiral β-aminolactones and β-aminoamides

International Journal of Molecular Sciences, **2018**, 19, 3522

IF: 3.687

Other publication

[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

Biomedical Chromatography, **2019**, 33. e4517

IF: 1.688

Scientific lectures

Le Minh Tam

Stereoselective synthesis of limonene-based 1,3-amino alcohols and aminodiols

XXXVIII. Kémiai Előadói Napok

Szeged, 17th–19th October, 2016, oral presentation

Le Minh Tam

Synthesis of limonene-based chiral aminodiols

XL. Kémiai Előadói Napok

Szeged, 16th–18th October, 2017, oral presentation

Tam Le Minh, Zsolt Szakonyi, Ferenc Fülöp

Synthesis of limonene-based chiral amino alcohols and aminodiols

17th Blue Danube Symposium on Heterocyclic Chemistry

Linz, Austria, 30th August–2nd September, 2017, poster presentation PO75

Le Minh Tam, Fülöp Ferenc, Szakonyi Zsolt

Synthesis of limonene-based chiral amino alcohols and aminodiols

MTA Heterociklusos és Elemorganikus Kémiai Munkabizottság Ülése

Balatonszemes, May, 2017, oral presentation

Le Minh Tam, Fülöp Ferenc, Szakonyi Zsolt

Synthesis and transformation of isopulegol-based chiral trifunctional synthons

MTA Heterociklusos és Elemorganikus Kémiai Munkabizottság Ülése

Balatonszemes, May, 2018, oral presentation

Szilasi Tamás János, **Le Minh Tam**, Szakonyi Zsolt

(+)-Neoizopulegol alapú királis szintonok szintézise és alkalmazása

MTA Szteroid- és Terpenoidkémiai Munkabizottság,

Szeged, November, 2018, oral presentation