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 Et₂Zn 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

Reactions were performed on a mmol scale, and products were purified by column chromatography on silica gel or by crystallization. All new compounds were characterized by their melting point, 1D- and 2D-NMR, elemental analysis, and optical rotation. The enantiomeric 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
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 NaBH₄, 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](image)

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](image)

8: $R^1 = CH_2Ph$, $R^2 = CH_2Ph$; 11: $R^1 = H$, $R^2 = CH(Me)Ph(R)$; 12: $R^1 = H$, $R^2 = CH(Me)Ph(S)$
Furthermore, hydroboration of compound 8 was accomplished by treatment with BH$_3$.Me$_2$S, followed by oxidation of the intermediate with H$_2$O$_2$ to give a 3:1 mixture of two diastereomers. 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](image)

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 diastereomeric mixture of 17 (Scheme 5).

![Scheme 5. Stereoselective reduction and epoxidation](image)

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 $\alpha$ position. Debenzylation by hydrogenolysis of compounds 18–21 over Pd/C in MeOH resulted in primary aminodiol 22 (Scheme 6).
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).

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 \( \Delta E(\text{spiro} \rightarrow \text{oxazine}, \text{spiro}^* \rightarrow \text{oxazine}^*) = 11.8 - 13.8 \text{ kcal/mol} \) 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. **Application 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 \((S)-1\text{-phenyl-1-propanol} [(S)-28] \) and \((R)-1\text{-phenyl-1-propanol} [(R)-28] \) (Scheme 8).

![Scheme 8. Model reaction of enantioselective catalysis](image)

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 \( \alpha \)-methylene-\( \gamma \)-butyrolactones**

The key intermediate (\(+\)-\( \alpha \)-methylene-\( \gamma \)-butyrolactone 31 was prepared from (\(-\)-isopulegol 29) with regioselective hydroxylation, followed by two-step oxidation and ring closure of the obtained \( \gamma \)-hydroxy-substituted \( \alpha,\beta \)-unsaturated carboxylic acid. Diastereomeric (\(-\)-\( \alpha \)-methylene-\( \gamma \)-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).
Synthesis of \((-\)
-isopulegol-based \(\alpha\)-methylene-\(\gamma\)-butyrolactones \(31\) and \(33\)

7. Synthesis of isopulegol-based chiral \(\beta\)-aminolactones

Nucleophilic addition of primary and secondary amines to \(\alpha\)-methylene-\(\gamma\)-butyrolactone \(31\) has proved to be an efficient method for the preparation of a highly diversified library of \(\beta\)-aminolactones (Scheme 10).

The optimized conditions in the case of \(31\) were also applied for the preparation of (+)-neoisopulegol-based \(\beta\)-aminolactones \(42\)–\(47\) starting from \(33\). The reaction of \(33\) with some amino esters was effective at elevated temperature to achieve amino ester-based \(\beta\)-aminolactone derivatives \(48\)–\(49\).
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 \( \alpha \)- and \( \beta \)-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 10. Nucleophilic addition of 31 to amines and aminoesters

\[ \text{R}^1\text{R}^2\text{NH, dry EtOH, 25–70 °C, 20 h} \]

\[ 40 \]

\[ \text{β-Alanine ethyl ester. HCl, Et}_3\text{N, dry EtOH, 25 °C, 20 h, 60\%} \]

\[ \text{L-Alanine ethyl ester. HCl, Et}_3\text{N, dry EtOH, 25 °C, 20 h} \]

\[ 41 \]

\[ 40 \]

\[ 41 \]

\[ \text{COOC}_2\text{H}_5 \]

34: \( R^1 = \text{H}, R^2 = \text{Bn} \)
35: \( R^1 = \text{H}, R^2 = \text{CH(Me)Ph(R)} \)
36: \( R^1 = \text{H}, R^2 = \text{CH(Me)Ph(S)} \)
37: \( R^1 = R^2 = \text{C}_2\text{H}_5 \)
38: \( R^1 = R^2 = -(\text{CH}_2)_5^- \)
39: \( R^1 = \text{Bn}, R^2 = \text{Bn} \)
Scheme 11. Preparation of $\beta$-aminoamides from 31

Scheme 12. Preparation of dipeptides from 31
The preparation of $\beta$-aminoamides 61–63 was achieved by reacting $\beta$-aminolactones 42–44 with primary amines. Acidic hydrolysis of $\beta$-aminoamides 61–63 led to $\beta$-aminolactones 42–44. Debenzylation with appropriate catalysts gave primary $\beta$-aminoamides 64–66 (Scheme 13).

Scheme 13. Preparation of $\beta$-aminoamides from 42–44

9. Antiproliferative activity

Antiproliferative activities of the prepared $\beta$-aminolactone and $\beta$-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 $\beta$-aminolactone-typed monoterpane derivatives proved to be ineffective against the utilized cell lines, the $N$-(S)-$\alpha$-methylbenzyl-substituted $\beta$-aminoamide analogues (52, 63) exhibited modest growth inhibitory activities. The most potent newly-prepared monoterpane 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

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

IF: 5.160

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

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