RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2020, **10**, 38468

Stereoselective synthesis and application of isopulegol-based bi- and trifunctional chiral compounds†

Tam Minh Le,[ab] Thu Huynh,[c] Gábor Endre,[c] András Szekeres,[c] Ferenc Fülöp[ab] and Zsolt Szakonyi[*ad]

A new family of isopulegol-based bi- and trifunctional chiral ligands was developed from commercially available (−)-isopulegol. Nucleophilic addition of primary amines towards (+)-α-methylene-γ-butyrolactone was accomplished, followed by reduction of the obtained β-aminolactones to provide aminodiols in highly stereoselective reactions. Epoxidation of (−)-isopulegol and subsequent oxirane ring opening with primary amines resulted in *N*-substituted aminodiols. The regioselective ring closure of these aminodiols with formaldehyde was also investigated. Benzylation of isopulegol furnished *O*-benzyl-protected isopulegol, which was transformed into aminoalcohols *via* epoxidation and ring opening of the corresponding epoxides. First benzyl-protected isopulegol was subjected to hydroxylation and epoxidation, then aminolysis of the served oxiranes delivered aminodiols. On the other hand, (−)-isopulegol was oxidised to diol, which was again converted into both dibenzyl- and monobenzyl-protected diol derivatives. The products were transformed into aminoalcohols and aminodiols, respectively, by aminolysis of their epoxides. The ring opening of epoxides, derived from diols with primary amines was also performed producing aminotriols. Dihydroxylation of (−)-isopulegol or derivatives with OsO_4/NMO gave isopulegol-based di-, tri- and tetraols. The antimicrobial activity and antioxidant property, measuring DPPH$^{\bullet}$ free radical scavenging activity of aminodiol and aminotriol derivatives as well as di-, tri- and tetraols were also explored. In addition, structure–activity relationships were examined from the aspects of substituent effects and stereochemistry on the aminodiol and aminotriol systems.

Received 9th September 2020
Accepted 10th October 2020

DOI: 10.1039/d0ra07739a

rsc.li/rsc-advances

Introduction

Monoterpenes constitute an interesting group of plant secondary metabolites.[1,2] They are readily available, relatively nontoxic and inexpensive constituents. Moreover, monoterpenes possess many important pharmacological activities.[3] For example, limonene and perillyl alcohol have chemopreventive activity against cancer,[4–6] whereas linalool and eucalyptol exert synergistic antiproliferative and anticholinesterase effects.[7,8] In addition, some of these compounds, such as 1,8-cineole, geraniol, linalool,[9] thymol[10] along with limonene, α-pinene, β-pinene, γ-terpinene and linalyl acetate,[8] as well as santolina alcohol, borneol, sabinol, *trans*-sabinyl acetate and α-thujone,[10] have been found to be relatively potent DPPH$^{\bullet}$ radical scavengers. This property is directly related to their structures.[11] It is worth pointing out that essential oils also display excellent antimicrobial activity.[12–14] For instance, linalool and α-terpineol exhibited strong activity against periodontopathic and cariogenic bacteria,[15] while citral, linalool and β-pinene had an effect on *Saccharomyces cerevisiae*.[16] Furthermore, linalyl acetate, (+)-menthol and thymol were found to be efficient against *Staphylococcus aureus* and *Escherichia coli*,[17] while thymol, carvacrol, *p*-cymene and γ-terpinene showed inhibitory activity towards *S. aureus* and *E. coli*.[18] Apart from proven properties, many monoterpenes exert antibiotic,[19,20] nematicidal,[21] anti-inflammatory[22,23] and analgesic[24] influences. Some monoterpenes are used as important flavour agents in foods, drinks, perfumes, cosmetics and tobacco,[25] while others such as 1,8-cineole[26] and pinene[27] have been considered as important biopesticides. Monoterpenes, therefore, are widely used in medicine, industry and agriculture.[28–30]

[a]*Institute of Pharmaceutical Chemistry, University of Szeged, Interdisciplinary Excellence Centre, Eötvös utca 6, H-6720 Szeged, Hungary. E-mail: leminhtam@pharm.u-szeged.hu; fulop@pharm.u-szeged.hu; szakonyi@pharm.u-szeged.hu; Fax: +36-62-545705; Tel: +36-62-546809*

[b]*Stereochemistry Research Group of the Hungarian Academy of Sciences, Eötvös utca 6, H-6720 Szeged, Hungary*

[c]*Department of Microbiology, University of Szeged, Közép fasor 52, 6726 Szeged, Hungary. E-mail: huynh_thu@hcmut.edu.vn; egabcy@gmail.com; andras.j.szekeres@gmail.com*

[d]*Interdisciplinary Centre of Natural Products, University of Szeged, Eötvös utca 6, H-6720 Szeged, Hungary*

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0ra07739a

We have planned to combine aminodiol moieties of cardiovascular, cytostatic and antiviral effectiveness with monoterpenic skeletons.[31–33] Aristeromycin analogues, for example, are widely used as effective agents against a range of viruses, including the human immunodeficiency, hepatitis B, herpes simplex, varicella-zoster, influenza and hepatitis C viruses.[34–36] The Abbott aminodiol, found to be a useful building block for the preparation of potent renin inhibitors Zankiren® and Enalkiren®, was introduced into the therapy of hypertension.[37,38] Aminodiols can also exert antidepressive activity. For instance, (*S*,*S*)-reboxetine is a selective norepinephrine reuptake inhibitor for the treatment of unipolar depression,[39] while others such as (2*R*,3*R*,7*Z*)-2-aminotetradec-7-ene-1,3-diol are potent antimicrobial metabolites.[40] Besides their varied, well-known influences, aminodiols may serve as starting materials for the synthesis of biologically active natural compounds, *e.g.* cytoxazone, a selective modulator of the secretion of T_H2 cytokine.[41,42] Apart from their biological interest, monoterpene-based aminodiols have been demonstrated to be excellent chiral auxiliaries in a wide range of stereoselective transformations including intramolecular radical cyclisation,[43] intramolecular [2 + 2] photocycloaddition[44] and Grignard addition.[45,46]

In order to combine the properties of monoterpenes and aminodiols as well as to develop new, efficient and commercially available chiral ligands, naturally occurring chiral monoterpenes such as (+)- and (−)-α-pinene,[47–49] (+)-carene,[50,51] (+)-camphor,[52,53] (−)-fenchone,[54] (−)-menthone,[55] (−)-myrtenol,[56,57] (+)-neoisopulegol,[58,59] (*S*)-perillyl alcohol,[60] (−)-pulegone,[61] or (+)-sabinol[62] have been widely used as key intermediates for the synthesis of aminodiols.

Monoterpene-based diols also possess marked biological properties, *e.g.* antiparkinsonian activity[63] and skin microcirculatory improvement,[64,65] whereas monoterpene-based triols have been utilised as cytotoxic[66,67] and anti-inflammatory agents.[68]

Therefore, our primary objective of the present research was to prepare a new library of isopulegol-based bi-, tri- or even tetrafunctionalised chiral synthons, such as aminodiols and aminotriols as well as di-, tri- and tetraols, starting from commercially available natural (−)-isopulegol and to evaluate the influence of these new isopulegol derivatives on antimicrobial attributes on multiple bacterial and yeast strains and their DPPH˙ free-radical scavenging activity.

Results and discussion

The key intermediate (+)-α-methylene-γ-butyrolactone **4** was prepared from commercially available (−)-isopulegol **1**. Acetylation of alcohol **1** to its acetate **2**, followed by regioselective oxidation of **2** gave diol **3**, which was transformed to lactone **4** by two-step oxidation and ring closure of obtained γ-hydroxy-substituted α,β-unsaturated carboxylic acid applying literature methods (Fig. 1).[69–74]

Nucleophilic addition of primary amines to α-methylene-γ-butyrolactone **4** has proved to be an efficient method for the preparation of a highly diversified library of β-aminolactones **5–8**.[58,75] Treatment of β-aminolactones with $LiAlH_4$ resulted in secondary aminodiols **9–12**. Debenzylation *via* hydrogenolysis of aminodiols **9–11** over Pd/C in MeOH gave primary aminodiol **13** in moderate yields. In order to study the regioselectivity of ring closure of the aminodiol function, we attempted to incorporate one of the hydroxy groups of aminodiols into 1,3-oxazinane or 1,3-oxazepinane ring.[51,61,76] When aminodiols **9–12** were reacted with HCHO under mild conditions, 1,3-oxazinane were obtained in highly regioselective ring closure. Since either the hydrogenolysis of *N*-benzyl analogues **9–11** or the formation of the oxazine ring system (**14–17**) had no effect on the absolute configuration, the relative configuration of the chiral centres of **13–17** is known to be the same as that of **9–12** (Scheme 1).[51,76]

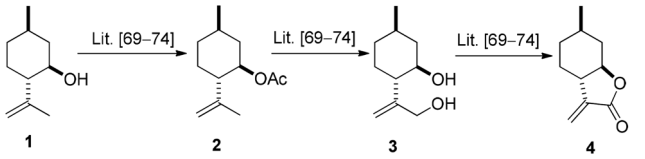
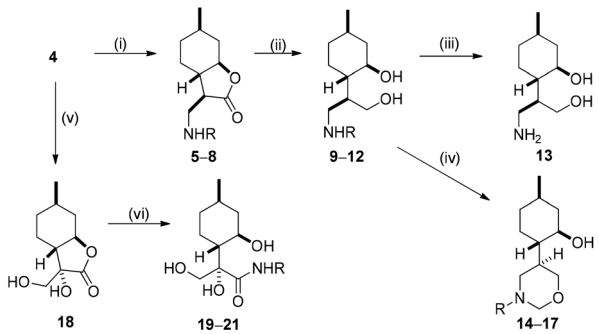


Fig. 1 Synthesis of (−)-isopulegol-based (+)-α-methylene-γ-butyrolactone.

Dihydroxylation of **4** with the OsO_4/NMO system furnished **18** in low yield.[51,61] The ring opening of α,β-dihydroxylactone **18** was performed by using 4 equivalents of primary amines under reflux conditions in anhydrous THF to form α,β-dihydroxyamides **19–21**. It is important to mention that the ring opening of lactones with (*R*)- and (*S*)-α-methylbenzylamine required longer reactions than utilizing benzylamine. This is probably due to steric hindrance exerted by the α-methyl group (Scheme 1). Note that the acylation of diols bearing an adjacent amide function forms an important structural moiety with potential biological applications.[77] For example, asterobactin and vioprolide A have been identified as a new antibiotic and a new antifungal peptolide, respectively.[78,79]

The relative configuration of compound **18** was determined by means of NOESY experiments: clear NOE signals were



5, 9, 14, 19: R = CH_2Ph; **6, 10, 15, 20**: R = CH(Me)Ph (*R*); **7, 11, 16, 21**: R = CH(Me)Ph (*S*); **8, 12, 17**: R = $CH(Me)_2$

Scheme 1 Synthesis of (−)-isopulegol-based aminodiols. Reaction conditions: (i) RNH_2 (1 equiv.), dry EtOH, 25 °C, 20 h, 65–75%; (ii) $LiAlH_4$ (2 equiv.), dry Et_2O, 25 °C, 4 h, 50–70%; (iii) 5% Pd/C, H_2 (1 atm), MeOH, 25 °C, 24 h, 50–67%; (iv) 35% HCHO, Et_2O, 25 °C, 1 h, 64–74%; (v) 2% OsO_4/*t*-BuOH, 50% NMO/H_2O, acetone, 25 °C, 24 h, 28%; (vi) RNH_2 (4 equiv.), dry THF, 60 °C, 24–72 h, 35–56%.

observed between the OH-8 and H-3 as well as OH-9 and H-4 protons (Fig. 2).

Homoallylic epoxidation of (−)-isopulegol **1** with *m*-CPBA provided a 1 : 1 mixture of epoxides **23a** and **23b** in good yield.[80] The two epoxides were separated by column chromatography to give more polar isomer **23a** and less polar isomer **23b**. The ring opening of epoxide **23a** with different primary amines in the presence of $LiClO_4$ as catalyst delivered aminodiols **24a–27a**.[81,82] Debenzylation of **24a–26a** by hydrogenolysis over Pd/C in MeOH resulted in aminodiol **28a** in excellent yields. When aminodiols **24a–27a** were treated with HCHO at room temperature, oxazolidines **29a–32a** were obtained *via* highly regioselective ring closures, similar to the regioisomeric 1,3-oxazinane analogues. The other epoxide **23b** underwent similar reactions to afford **24b–32b** in excellent yields. Dihydroxylation of (−)-isopulegol **1** was performed with OsO_4 in the presence of a stoichiometric amount of co-oxidant NMO to afford a diastereoisomeric mixture of **22a** and **22b** in a ratio of 1 : 1.[83] The epimeric mixture was purified by column chromatography followed by recrystallisation to provide **22b** in crystalline form and **22a** as a colourless oil (Scheme 2).

Gram-scale separation of **23a** and **23b** turned out to be difficult. In order to enhance the resolution by column chromatography, benzyl-protected isopulegol **33** was prepared.[84,85] Epoxidation of **33** with *m*CPBA furnished a 1 : 1 mixture of epoxides **34a** and **34b**. After separation by column chromatography, they were subjected to aminolysis with primary amines. Interestingly, epoxide **34b** upon aminolysis was transformed preferentially, while **34a** did not react. This is probably due to steric hindrance exerted by either the benzyl or the methyl group at the α position in epoxide **34a**. Consequently, the mixture of **34a** and **34b** was used for the ring-opening reaction. The resulting aminoalcohols (**35b–38b**) could be easily separated from **34a** on a gram scale by simple column chromatography with good yields. The synthesis of primary aminodiol **28b** was accomplished by hydrogenolysis of **35b–37b** over Pd/C in high yields, while debenzylation of **34a** provided **23a** in a moderate yield of 53% (Scheme 3).

syn-Selective dihydroxylation of compound **33** with OsO_4 in the presence of a stoichiometric amount of co-oxidant NMO produced a 1 : 1.7 epimeric mixture of **39a** and **39b** in a favourable yield. Our effort to separate the mixture failed. Fortunately, their carbonates, obtained from the diols with triphosgene, could be easily isolated. It is well known that this carbonation reaction maintains the stereochemical configuration of the original diol.[86,87] Accordingly, the reactions of **39a** and **39b** with triphosgene successfully afforded **40a** and **40b**, respectively. After purification, carbonates **40a** and **40b** were reduced by $LiAlH_4$ (LAH). The reaction proceeded smoothly giving the corresponding diols **39a** and **39b** in good yields. It has been reported that reduction with LAH gives the corresponding diol with the same stereochemical configuration of the carbon atoms as of the original moiety.[88,89] Debenzylation

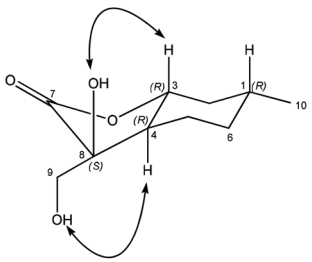
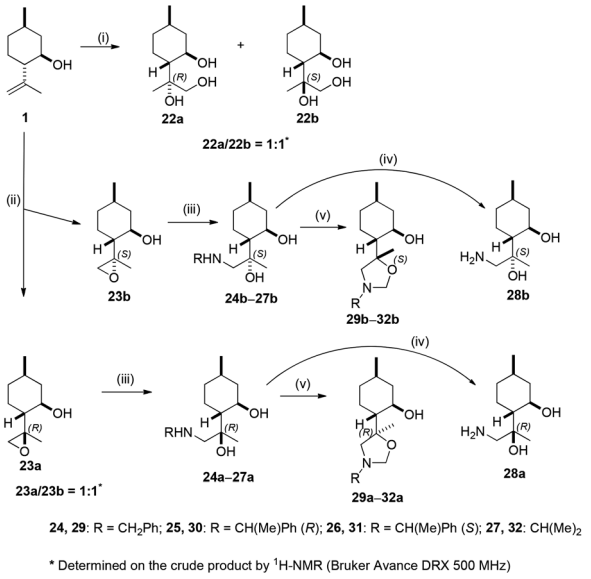
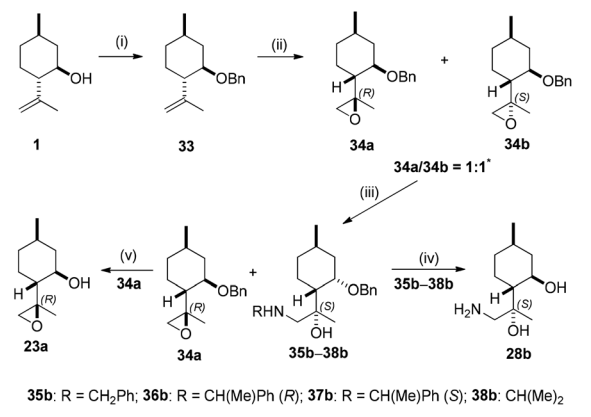


Fig. 2 Determination of the structure of diol **18** by NOESY.



Scheme 2 Synthesis of (−)-isopulegol-based aminodiols. Reaction conditions: (i) 2% OsO_4/*t*-BuOH, 50% NMO/H_2O, acetone, 25 °C, 24 h, 33% (**22a**), 33% (**22b**); (ii) *m*CPBA (2 equiv.), $Na_2HPO_4{\cdot}12H_2O$ (3 equiv.), CH_2Cl_2, 25 °C, 2 h, 29% (**23a**), 43% (**23b**); (iii) RNH_2 (2 equiv.), $LiClO_4$ (1 equiv.), MeCN, 70–80 °C, 8 h, 75–95% (**23a**), 50–90% (**23b**); (iv) 5% Pd/C, H_2 (1 atm), MeOH, 25 °C, 24 h, 87–95% (**28a**), 85–90% (**28b**); (v) 35% HCHO, Et_2O, 25 °C, 1 h, 89–97% (**29a–32a**), 85–90% (**29b–32b**).



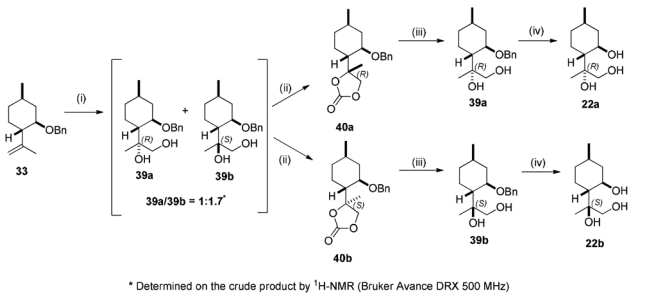
Scheme 3 Synthesis of (−)-isopulegol-based aminodiol derivatives. Reaction conditions: (i) NaH (1.5 equiv.), BnBr (1.5 equiv.), KI (1.5 equiv.), dry THF, 60 °C, 12 h, 70%; (ii) *m*CPBA (2 equiv.), $Na_2HPO_4{\cdot}12H_2O$ (3 equiv.), CH_2Cl_2, 25 °C, 2 h, 43% (**34a**), 25% (**34b**); (iii) RNH_2 (2 equiv.), $LiClO_4$ (1 equiv.), MeCN, 70–80 °C, 20 h, 31–45%; (iv) 5% Pd/C, H_2 (1 atm), MeOH, 25 °C, 24 h, 65–70%; (v) 5% Pd/C, H_2 (1 atm), *n*-hexane : EtOAc = 9 : 1, 25 °C, 24 h, 53%.

of **39a** and **39b** by hydrogenolysis over Pd/C resulted in triols **22a** and **22b**, respectively, with excellent yields (Scheme 4).

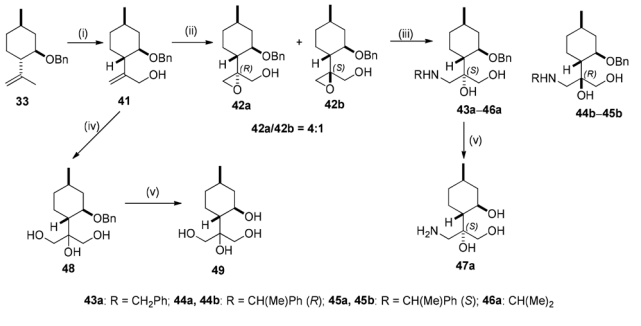
To extend the investigation of the substituent effects in the ring opening of epoxide, **33** was oxidised to **41**. The epoxidation of **41** with *m*CPBA delivered a 4 : 1 mixture of epoxides **42a** and **42b**. The separation of **42a** and **42b** was not satisfactory on a gram scale; therefore, the mixture was treated with different primary amines in the presence of $LiClO_4$ resulting in a library of aminodiols. In our delight, aminodiols were well-separated when chiral amines (*R*)- and (*S*)-methylbenzylamines were applied, while in the case of benzylamine and isopropylamine, only the major products were isolated. The debenzylation of **43a–45a** by hydrogenolysis over Pd/C gave aminodiol **47a** with satisfactory yields. Tetraol **49** was prepared by dihydroxylation of **41** with the OsO_4/NMO system, followed by hydrogenolysis of **48** over Pd/C (Scheme 5).

During our attempt to improve the resolution of aminodiols **43b–46b**, we realised that *O*-benzylation of **41** could serve this purpose; however, the synthesis of **50b** starting from **41** failed. Fortunately, it was achieved by reacting **3** with benzyl bromide under reflux condition in dry THF. Besides expected product **50b**, **50a** also formed as a side product. Epoxidation of **50b** with *m*CPBA produced a 1 : 1 mixture of epoxides **51a** and **51b**. The ring opening of the oxirane mixture was accomplished with different primary amines resulting in a library of aminoalcohols **52a–55a** and **52b–55b**, respectively. The debenzylation of **52a–54a** and **52b–54b** by hydrogenolysis over Pd/C gave, respectively, aminotriols **47a** and **47b** with exceptional yields. Compound **50b** was treated with the OsO_4/NMO system providing a 3 : 1 mixture of diols **56a** and **56b**. Removal of the protecting group of **56a** gave tetraol **49** with good yield (Scheme 6).

The epoxidation of **50a** with *m*CPBA gave a 2 : 1 mixture of epoxides **57a** and **57b**. The ring opening of this epoxide mixture was carried out with different primary amines to form a library of aminodiols **58a–61a** and **58b–61b**, respectively. Primary aminotriols **47a** and **47b** were prepared *via* the usual way by hydrogenolysis of aminodiols **58a–60a** and **58b–60b** over Pd/C. Dihydroxylation of **50b** with the OsO_4/NMO system provided triols **62a** and **62b** in a 2 : 1 ratio with an excellent yield of 90%.



Scheme 4 Synthesis of (−)-isopulegol-based diols. Reaction conditions: (i) 2% OsO_4/*t*-BuOH, 50% NMO/H_2O, acetone, 25 °C, 24 h, 88%; (ii) triphosgene (0.5 equiv.), pyridine (4 equiv.), dry CH_2Cl_2, 25 °C, 2 h, 36% (**40a**), 36% (**40b**); (iii) $LiAlH_4$ (2 equiv.), dry Et_2O, 0 °C, 4 h, 95% (**39a**), 56% (**39b**); (iv) 5% Pd/C, H_2 (1 atm), MeOH, 25 °C, 24 h, 95% (**39a**), 91% (**39b**).

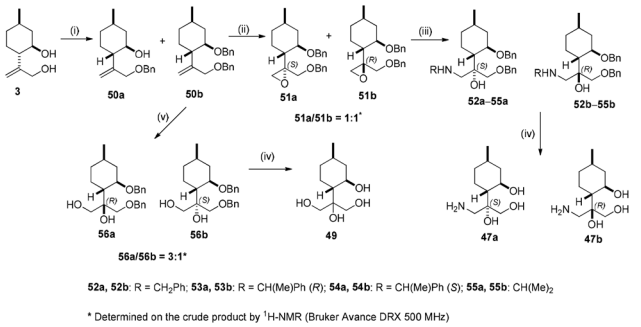


Scheme 5 Synthesis of (−)-isopulegol-based aminotriol derivatives. Reaction conditions: (i) SeO_2 (0.24 equiv.), 70% *t*-BuOOH (4 equiv.), $CHCl_3$, 60 °C, 20 h, then $LiAlH_4$ (3 equiv.), dry Et_2O, 0 °C, 6 h, 60%; (ii) *m*CPBA (2 equiv.), $Na_2HPO_4 \cdot 12H_2O$ (3 equiv.), CH_2Cl_2, 25 °C, 2 h, 64% (**42a**), 15% (**42b**); (iii) RNH_2 (2 equiv.), $LiClO_4$ (1 equiv.), MeCN, 70–80 °C, 6 h, 46–58% (**42a**), 14% (**42b**); (iv) NMO/H_2O, 2% OsO_4/*t*-BuOH, acetone, 25 °C, 24 h, 60%; (v) 5% Pd/C, H_2 (1 atm), MeOH, 25 °C, 24 h, 87–95% (**47a**), 86% (**48**).

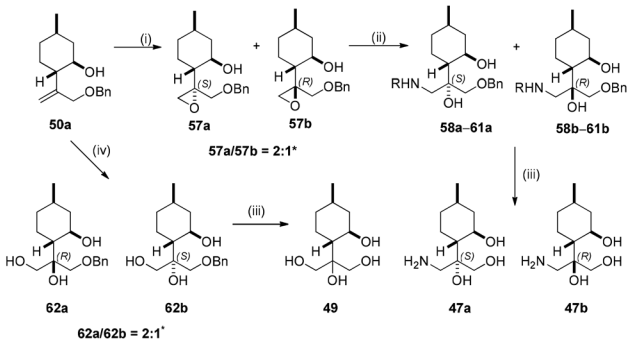
Debenzylation of **62a–b** by hydrogenolysis over Pd/C resulted in tetraol **49** with excellent yields (Scheme 7).

On the other hand, epoxidation of allylic diol **3** with *m*CPBA was successfully applied to form the mixture of epoxy diols **63a** and **63b** in a 3.5 : 1 ratio. After separation by chromatography, the oxirane ring of **63a** was opened with primary amines and $LiClO_4$ as catalyst to deliver aminotriol library **64a–67a**. Primary aminotriol **47a** was obtained by debenzylation of the corresponding aminotriols **64a–66a** under standard conditions by hydrogenation in the presence of a Pd/C catalyst. Diastereoisomeric aminotriols **65b–66b** were prepared by ring opening of **63b** with chiral amines (*R*)- and (*S*)-methylbenzylamine. The synthesis of tetraol **49** was effectively performed by selective dihydroxylation of **3** with the OsO_4/NMO system (Scheme 8).

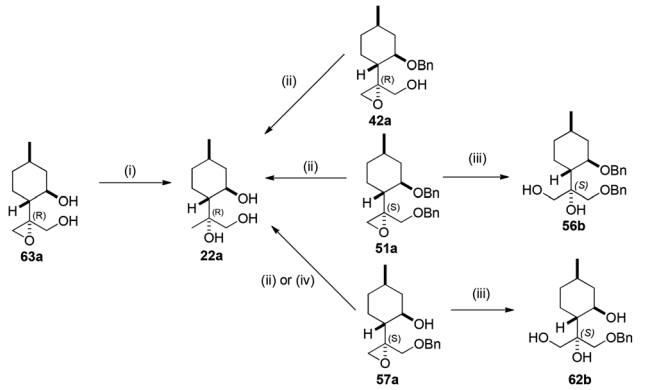
The relative configuration of primary aminotriol **47a** was determined through epoxide **63a**. To this aim, epoxide **63a** was reduced with $LiAlH_4$ (LAH) to the corresponding triol **22a** (see



Scheme 6 Synthesis of (−)-isopulegol-based aminotriol derivatives. Reaction conditions: (i) NaH (1.5 equiv.), BnBr (3.0 equiv.), KI (1.5 equiv.), dry THF, 60 °C, 12 h, 40% (**50b**), 19% (**50a**); (ii) *m*CPBA (2 equiv.), $Na_2HPO_4 \cdot 12H_2O$ (3 equiv.), CH_2Cl_2, 25 °C, 2 h, 38% (**51a**), 28% (**51b**); (iii) RNH_2 (2 equiv.), $LiClO_4$ (1 equiv.), MeCN, 70–80 °C, 6 h, 25–40% (**51a**), 29–42% (**51b**); (iv) NMO/H_2O, 2% OsO_4/*t*-BuOH, acetone, 25 °C, 24 h, 50% (**56a**), 15% (**56b**); (v) 5% Pd/C, H_2 (1 atm), MeOH, 25 °C, 24 h, 95–98% (**47a–b**), 83% (**56a**).



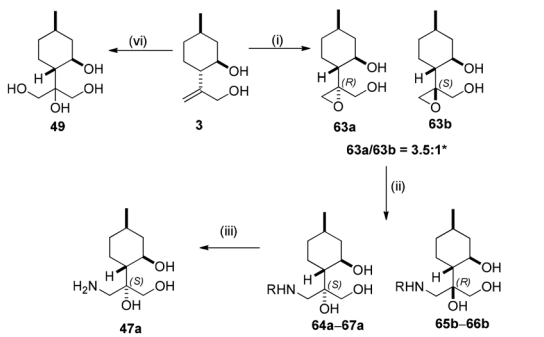
Scheme 7 Synthesis of (−)-isopulegol-based aminotriol derivatives. Reaction conditions: (i) *m*CPBA (2 equiv.), $Na_2HPO_4 \cdot 12H_2O$ (3 equiv.), CH_2Cl_2, 25 °C, 2 h, 38% (**57a**), 15% (**57b**); (ii) RNH_2 (2 equiv.), $LiClO_4$ (1 equiv.), MeCN, 70–80 °C, 6 h, 39–50% (**57a**), 16–21% (**57b**); (iii) 5% Pd/C, H_2 (1 atm), MeOH, 25 °C, 24 h, 90–93% (**47a–b**), 97% (**62a**), 95% (**62b**); (iv) NMO/H_2O, 2% OsO_4/*t*-BuOH, acetone, 25 °C, 24 h, 59% (**62a**), 29% (**62b**).



Scheme 9 Determination of the structure of (−)-isopulegol-based aminotriol as well as triol derivatives. Reaction conditions: $LiAlH_4$ (2 equiv.), dry THF, 25 °C, 6 h, 70%; (ii) 5% Pd/C, H_2 (1 atm), *n*-hexane : EtOAc = 9 : 1, 25 °C, 24 h, 90% (**42a**), 78% (**51a**), 90% (**57a**); (iii) 3 M NaOH, DMSO, 25 °C, 2–24 h, 33% (**56b**), 57% (**62b**); (iv) $LiAlH_4$ (2 equiv.), dry THF, 25 °C, 6 h then 5% Pd/C, H_2 (1 atm), *n*-hexane : EtOAc = 9 : 1, 25 °C, 24 h, 87%.

configurations in Scheme 9). It has been reported that reduction with LAH gives the corresponding triol with the same stereochemical configuration at the carbon atoms as of the original moiety.[88,89] The stereochemical structures of triol **22a** is well-known in the literature;[83] therefore, the absolute configuration of epoxide **63a** could also be determined.

The absolute configuration of **42a**, **51a** and **57a** was confirmed by debenzylation *via* hydrogenolysis over Pd/C to provide triol **22a** with stereochemical retention. To prove that the stereochemical configuration of the epoxide was maintained during reaction, **57a** was reduced with $LiAlH_4$ then debenzylated applying the 5% Pd/C/H_2 system to give **22a** in good yield. The stereostructure of **56b** and **62b** were assigned by treatment of **51a** and **57a** with NaOH taking place with retention of stereochemistry (Scheme 9).[90]



Scheme 8 Synthesis of (−)-isopulegol-based aminotriols. Reaction conditions: (i) *m*CPBA (2 equiv.), $Na_2HPO_4 \cdot 12H_2O$ (3 equiv.), CH_2Cl_2, 25 °C, 2 h, 33% (**63a**), 7% (**63b**); (ii) RNH_2 (2 equiv.), $LiClO_4$ (1 equiv.), MeCN, 70–80 °C, 6 h, 62–77% (**63a**), 87–93% (**63b**); (iii) 5% Pd/C, H_2 (1 atm), MeOH, 25 °C, 24 h, 67–75%; (iv) NMO/H_2O, 2% OsO_4/*t*-BuOH, acetone, 25 °C, 24 h, 53%.

Since several aminodiols as well as aminotriols exerted antimicrobial activities on various microorganisms,[91] antimicrobial activities of the prepared aminodiol and aminotriol analogues were also explored against two yeasts as well as two Gram-positive and two Gram-negative bacteria (Table 1, only the best results are shown).

Our tests revealed that di-*O*-benzyl aminotriol derivatives (**52a–b**) possess potential antimicrobial properties over 80% against both the two Gram-positive and the yeast species. In the case of *B. subtilis*, these compounds proved to be the most effective agents even at a low concentration of 10 μg mL^{-1}, while other derivatives (**45a–b** and **58a–b**) showed lower activities. Removal of one of the two benzyl protecting groups in aminotriol derivatives (**45a–b** and **58a–b**) led to improved selective inhibition on *B. subtilis*. The almost complete loss of antibacterial activity resulting from the replacement of all *O*-benzyloxy groups with hydroxyl group as demonstrated with aminotriol derivatives **66a–b** suggests that the benzyl moiety is a key element to have satisfactory antimicrobial activity in the case of aminotriols.

Among aminodiol derivatives, only *O*-benzyl aminodiol **35b** presented activity against *B. subtilis*, whereas debenzylated derivative **9** had no effect. This result indicates that the *O*-benzyloxy group attached to the cyclohexyl ring is responsible for activity of the studied antibacterial agents.

The available data demonstrated that the *O*-benzyloxy group on the cyclohexyl ring (**41** and **50b**) is much more effective to induce antimicrobial activity than the 1-BnO-propen-2-yl group (**50a**).

In comparison, α-methylene-γ-butyrolactone **4**, the most effective compound against *C. albicans* and *C. krusei*, was found to possess highly selective effectiveness on the yeast species.

The synthetic aminodiol and aminotriol derivatives were also evaluated for their antioxidant activity using DPPH assays (Table 2, only the detected activities are shown).

In the DPPH study, aminodiol **9** displayed a potential antioxidant effect, while the aminotriol derivatives (**58a–b**) had only moderate effects. The results of this survey, namely improvement of antioxidant activity alongside with the

Table 1 Antimicrobial activity of derivatives expressed in *I*% values

		Inhibitory effect[a] (%) ± RSD (%)					
		Gram positive		Gram negative		Yeast	
Anal	Conc. (μg mL^{-1})	*B. subtilis*	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
4	100	31.51 ± 4.58	—	—	—	94.30 ± 5.46	88.22 ± 5.36
	10	—	—	—	—	—	—
30a	100	46.53 ± 2.55	—	—	—	—	—
	10	34.92 ± 6.84	—	—	—	—	—
30b	100	52.97 ± 8.35	—	—	23.00 ± 9.26	—	—
	10	41.69 ± 10.35	—	—	—	—	—
35b	100	92.04 ± 1.18	—	—	—	25.86 ± 1.43	—
	10	57.37 ± 6.13	—	—	—	—	—
41	100	76.58 ± 11.68	—	—	—	23.49 ± 7.28	—
	10	25.17 ± 6.00	—	—	—	—	—
43a	100	91.72 ± 3.98	—	—	30.58 ± 1.51	22.64 ± 6.99	—
	10	—	—	—	—	—	—
45a	100	91.29 ± 1.86	—	—	23.37 ± 2.81	—	—
	10	—	—	—	—	—	—
45b	100	77.98 ± 6.27	—	—	—	—	—
	10	1.53 ± 2.93	—	—	—	—	—
50b	100	76.30 ± 16.90	—	—	—	—	—
	10	45.25 ± 11.25	—	—	—	—	—
52a	100	77.67 ± 3.81	73.44 ± 1.78	—	—	86.64 ± 2.54	84.92 ± 4.20
	10	93.88 ± 1.77	—	—	—	—	—
52b	100	87.23 ± 4.17	68.03 ± 4.74	—	—	81.47 ± 5.04	81.00 ± 4.03
	10	94.63 ± 1.01	—	—	—	41.25 ± 9.35	—
56a	100	78.20 ± 7.98	—	—	—	—	—
	10	—	—	—	—	—	—
58a	100	60.52 ± 2.49	—	—	26.09 ± 4.61	—	—
	10	—	—	—	—	—	—
58b	100	68.93 ± 6.85	—	—	—	—	—
	10	34.63 ± 7.99	—	—	—	—	—
66a	100	31.48 ± 11.69	—	—	—	—	39.76 ± 3.24
	10	—	—	—	—	—	—

[a] Inhibitory effect values less than 20% are considered negligible and not presented numerically. Compounds **1**, **3**, **9**, **13**, **14**, **18**, **19**, **22a–b**, **24a–b**, **28a–b**, **30a**, **33**, **39a–b**, **47a–b**, **48**, **49**, **50a**, **56b**, **62a–b**, **64a** and **66b** were also examined but did not elicit 20% inhibitory effect even at 100 μg mL^{-1}.

replacement of the *O*-benzyloxy moiety with a hydroxyl group, show that efficiency depends on the hydroxyl function of the cyclohexyl ring more significantly than on the 1-hydroxypropen-2-yl group.

The hydroxyl group of molecules play remarkable role in their antioxidant property.[92] Recently, there are two proposed mechanisms by which antioxidants containing hydroxyl group can act protectively. In the first mechanism, the free radical (*e.g.* DPPH) removes a hydrogen atom from the hydroxyl group that itself becomes a radical, in this way the functional group donates a proton to the free radicals and neutralise it (*e.g.* DPPH-H). In the second mechanism, called as one-electron transfer, the hydroxyl group can give an electron to the free radical becoming itself a radical cation.[93]

Table 2 Antioxidant effects of active synthetic derivatives expressed in IC_{50} values

Compound	DPPH antioxidant activity (μmol mL^{-1}) ± SD
9	8.47 ± 0.56
24b	75.63 ± 0.01
28a	204.77 ± 9.1
30a	72.76 ± 0.03
45a	87.61 ± 0.14
58a	33.74 ± 3.74
58b	56.63 ± 0.01
Gallic acid	0.16 ± 0.01

Although aminotriol **58a** was less active than aminodiols, its antioxidant property is still considered to be notable compared with aminotriol **45a**. This result again demonstrates that the hydroxyl group on the cyclohexyl ring is necessary for antioxidant property.

Conclusion

A new library of isopulegol-based chiral aminodiols and aminotriols was developed from commercially available (−)-isopulegol. The isopulegol-based chiral di-, tri- and tetraols are promising substrates for the preparation of chiral crown ethers. α,β-Dihydroxyamides, accessed through the ring opening of α,β-

dihydroxylactones, are widely applicable in the synthesis of natural products and in saccharide chemistry.

Our result proved again that steric hindrance exerted by both benzyl and methyl groups at the α position in epoxide **34a** makes its conformationally constrained structure to restrict the approach of nucleophiles in aminolysis.

O-Benzyl aminotriol and aminodiol derivatives exert markedly selective antibacterial action on *B. subtilis*, while di-*O*-benzyl aminotriols have also shown significant effectiveness not only against Gram-positive bacteria strains but also against yeast species. Moreover, our result also indicated the potential antifungal activity of α-methylene-γ-butyrolactones.

In addition, aminodiol and aminotriol derivatives were applied as antioxidant agents in DPPH assay. *N*-Benzyl aminodiols are still considered to exert notable antioxidant property.

Finally, *in vitro* studies have clearly shown that the *O*-benzyl substituent on the cyclohexyl ring in aminodiol and aminotriol derivatives is essential to have antimicrobial effect, whereas the hydroxyl group on this ring is crucial on the antioxidant property. The stereochemistry of the aminotriol and aminotriol derivatives has no influence on either effect.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

We are grateful for financial supports from the EU-funded Hungarian grant GINOP-2.3.2-15-2016-00012, Ministry of Human Capacities, Hungary grant 20391-3/2018/FEKUSTRAT, Hungarian Research Foundation (OTKA No. K 115731), University of Szeged Open Access Fund (grant No. 4969) and Tamás Szilasi for his experimental assistance.

References

1 L. M. Ciesla, K. A. Wojtunik-Kulesza, A. Oniszczuk and M. Waksmundzka-Hajnos, Antioxidant synergism and antagonism between selected monoterpenes using the 2,2-diphenyl-1-picrylhydrazyl method: Antioxidant synergism and antagonism between selected monoterpenes, *Flavour Fragrance J.*, 2016, **31**, 412–419.

2 Y. Wen Xu, Effects of salicylic acid on monoterpene production and antioxidant systems in Houttuynia cordata, *Afr. J. Biotechnol.*, 2012, **11**, 1364–1372.

3 F. Bakkali, S. Averbeck, D. Averbeck and M. Idaomar, Biological effects of essential oils – A review, *Food Chem. Toxicol.*, 2008, **46**, 446–475.

4 N. L. S. Chan, H. Wang, Y. Wang, H. Y. Leung and L. K. Leung, Polycyclic aromatic hydrocarbon-induced CYP1B1 activity is suppressed by perillyl alcohol in MCF-7 cells, *Toxicol. Appl. Pharmacol.*, 2006, **213**, 98–104.

5 P. L. Crowell, Monoterpenes in breast cancer chemoprevention, *Breast Cancer Res. Treat.*, 1997, **46**, 191–197.

6 M. N. Gould, Prevention and therapy of mammary cancer by monoterpenes, *J. Cell. Biochem.*, 1995, **59**, 139–144.

7 B. Rodenak Kladniew, M. Polo, S. Montero Villegas, M. Galle, R. Crespo and M. García de Bravo, Synergistic antiproliferative and anticholesterogenic effects of linalool, 1,8-cineole, and simvastatin on human cell lines, *Chem.-Biol. Interact.*, 2014, **214**, 57–68.

8 R. Tundis, M. R. Loizzo, M. Bonesi, F. Menichini, V. Mastellone, C. Colica and F. Menichini, Comparative study on the antioxidant capacity and Cholinesterase inhibitory activity of Citrus aurantifolia Swingle, C. aurantium L., and C. bergamia Risso and Poit. Peel Essential Oils, *J. Food Sci.*, 2012, **77**, H40–H46.

9 G. Ruberto and M. T. Baratta, Antioxidant activity of selected essential oil components in two lipid model systems, *Food Chem.*, 2000, **69**, 167–174.

10 M. Nikolić, J. Glamočlija, I. C. F. R. Ferreira, R. C. Calhelha, Â. Fernandes, T. Marković, D. Marković, A. Giweli and M. Soković, Chemical composition, antimicrobial, antioxidant and antitumor activity of Thymus serpyllum L., Thymus algeriensis Boiss. and Reut and Thymus vulgaris L. essential oils, *Ind. Crops Prod.*, 2014, **52**, 183–190.

11 K. A. Wojtunik, L. M. Ciesla and M. Waksmundzka-Hajnos, Model studies on the antioxidant activity of common terpenoid constituents of essential oils by means of the 2,2-diphenyl-1-picrylhydrazyl method, *J. Agric. Food Chem.*, 2014, **62**, 9088–9094.

12 A. Ahmad, S. van Vuuren and A. Viljoen, Unravelling the complex antimicrobial interactions of essential oils -The case of Thymus vulgaris (Thyme), *Molecules*, 2014, **19**, 2896–2910.

13 A. C. R. da Silva, P. M. Lopes, M. M. B. de Azevedo, D. C. M. Costa, C. S. Alviano and D. S. Alviano, Biological activities of α-Pinene and β-Pinene enantiomers, *Molecules*, 2012, **17**, 6305–6316.

14 J. Nguefack, O. Tamgue, J. B. L. Dongmo, C. D. Dakole, V. Leth, H. F. Vismer, P. H. Amvam Zollo and A. E. Nkengfack, Synergistic action between fractions of essential oils from Cymbopogon citratus, Ocimum gratissimum and Thymus vulgaris against Penicillium expansum, *Food Control*, 2012, **23**, 377–383.

15 S.-N. Park, Y. K. Lim, M. O. Freire, E. Cho, D. Jin and J.-K. Kook, Antimicrobial effect of linalool and α-terpineol against periodontopathic and cariogenic bacteria, *Anaerobe*, 2012, **18**, 369–372.

16 N. Belletti, S. S. Kamdem, G. Tabanelli, R. Lanciotti and F. Gardini, Modeling of combined effects of citral, linalool and β-pinene used against Saccharomyces cerevisiae in citrus-based beverages subjected to a mild heat treatment, *Int. J. Food Microbiol.*, 2010, **136**, 283–289.

17 D. Trombetta, F. Castelli, M. G. Sarpietro, V. Venuti, M. Cristani, C. Daniele, A. Saija, G. Mazzanti and G. Bisignano, Mechanisms of antibacterial action of three monoterpenes, *Antimicrob. Agents Chemother.*, 2005, **49**, 2474–2478.

18 M. Cristani, M. D'Arrigo, G. Mandalari, F. Castelli, M. G. Sarpietro, D. Micieli, V. Venuti, G. Bisignano, A. Saija

and D. Trombetta, Interaction of four monoterpenes contained in essential oils with model membranes: implications for their antibacterial activity, *J. Agric. Food Chem.*, 2007, **55**, 6300–6308.

19 W. T. Langeveld, E. J. A. Veldhuizen and S. A. Burt, Synergy between essential oil components and antibiotics: a review, *Crit. Rev. Microbiol.*, 2014, **40**, 76–94.

20 V. Pereira, C. Dias, M. C. Vasconcelos, E. Rosa and M. J. Saavedra, Antibacterial activity and synergistic effects between Eucalyptus globulus leaf residues (essential oils and extracts) and antibiotics against several isolates of respiratory tract infections (Pseudomonas aeruginosa), *Ind. Crops Prod.*, 2014, **52**, 1–7.

21 N. G. Ntalli, F. Ferrari, I. Giannakou and U. Menkissoglu-Spiroudi, Synergistic and antagonistic interactions of terpenes against Meloidogyne incognita and the nematicidal activity of essential oils from seven plants indigenous to Greece, *Pest Manag. Sci.*, 2011, **67**, 341–351.

22 K. R. Riella, R. R. Marinho, J. S. Santos, R. N. Pereira-Filho, J. C. Cardoso, R. L. C. Albuquerque-Junior and S. M. Thomazzi, Anti-inflammatory and cicatrizing activities of thymol, a monoterpene of the essential oil from Lippia gracilis, in rodents, *J. Ethnopharmacol.*, 2012, **143**, 656–663.

23 A. Djouahri, B. Saka, L. Boudarene, F. Benseradj, S. Aberrane, S. Aitmoussa, C. Chelghoum, L. Lamari, N. Sabaou and A. Baaliouamer, In vitro synergistic/antagonistic antibacterial and anti-inflammatory effect of various extracts/essential oil from cones of Tetraclinis articulata (Vahl) Masters with antibiotic and anti-inflammatory agents, *Ind. Crops Prod.*, 2014, **56**, 60–66.

24 A. G. Guimarães, J. S. S. Quintans and L. J. Quintans-Júnior, Monoterpenes with analgesic activity-A systematic review, *Phytother. Res.*, 2013, **27**, 1–15.

25 A. Aharoni, M. Jongsma and H. Bouwmeester, Volatile science? Metabolic engineering of terpenoids in plants, *Trends Plant Sci.*, 2005, **10**, 594–602.

26 H. T. Prates, J. P. Santos, J. M. Waquil, J. D. Fabris, A. B. Oliveira and J. E. Foster, Insecticidal activity of monoterpenes against Rhyzopertha dominica (F.) and Tribolium castaneum (Herbst), *J. Stored Prod. Res.*, 1998, **34**, 243–249.

27 W.-S. Choi, B.-S. Park, Y.-H. Lee, D. Y. Jang, H. Y. Yoon and S.-E. Lee, Fumigant toxicities of essential oils and monoterpenes against Lycoriella mali adults, *Crop Prot.*, 2006, **25**, 398–401.

28 B. A. Leita, A. C. Warden, N. Burke, M. S. O'Shea and D. Trimm, Production of p-Cymene and hydrogen from a bio-renewable feedstock–1,8-cineole (Eucalyptus oil), *Green Chem.*, 2010, **12**, 70–76.

29 W. Chen and A. M. Viljoen, Geraniol — A review of a commercially important fragrance material, *South Afr. J. Bot.*, 2010, **76**, 643–651.

30 G. P. P. Kamatou, I. Vermaak, A. M. Viljoen and B. M. Lawrence, Menthol: A simple monoterpene with remarkable biological properties, *Phytochemistry*, 2013, **96**, 15–25.

31 A. E. Wróblewski, I. E. Głowacka and D. G. Piotrowska, 1′-Homonucleosides and their structural analogues: A review, *Eur. J. Med. Chem.*, 2016, **118**, 121–142.

32 J. M. Sadler, S. L. Mosley, K. M. Dorgan, Z. S. Zhou and K. L. Seley-Radtke, Synthetic strategies toward carbocyclic purine–pyrimidine hybrid nucleosides, *Bioorg. Med. Chem.*, 2009, **17**, 5520–5525.

33 K. A. Jacobson, D. K. Tosh, K. S. Toti and A. Ciancetta, Polypharmacology of conformationally locked methanocarba nucleosides, *Drug Discovery Today*, 2017, **22**, 1782–1791.

34 A. C. Allepuz, R. Badorrey, M. D. Díaz-de-Villegas and J. A. Gálvez, Diastereoselective reduction of ketimines derived from (R)-3,4-dihydroxybutan-2-one: an alternative route to key intermediates for the synthesis of anticancer agent ES-285, *Tetrahedron: Asymmetry*, 2010, **21**, 503–506.

35 R. K. Mishra, C. M. Coates, K. D. Revell and E. Turos, Synthesis of 2-Oxazolidinones from β-Lactams: stereospecific total synthesis of (−)-Cytoxazone and all of Its stereoisomers, *Org. Lett.*, 2007, **9**, 575–578.

36 A. Grajewska and M. D. Rozwadowska, Stereoselective synthesis of cytoxazone and its analogues, *Tetrahedron: Asymmetry*, 2007, **18**, 803–813.

37 H. Kleinert, S. Rosenberg, W. Baker, H. Stein, V. Klinghofer, J. Barlow, K. Spina, J. Polakowski, P. Kovar, J. Cohen, *et al.*, Discovery of a peptide-based renin inhibitor with oral bioavailability and efficacy, *Science*, 1992, **257**, 1940–1943.

38 S. Chandrasekhar, S. Mohapatra and J. S. Yadav, Practical synthesis of Abbott aminodiol: A core unit of the potent renin inhibitor Zankiren, *Tetrahedron*, 1999, **55**, 4763–4768.

39 K. Toribatake, S. Miyata, Y. Naganawa and H. Nishiyama, Asymmetric synthesis of optically active 3-amino-1,2-diols from N-acyl-protected allylamines *via* catalytic diboration with Rh[bis(oxazolinyl)phenyl] catalysts, *Tetrahedron*, 2015, **71**, 3203–3208.

40 E. Richelle-Maurer, J.-C. Braekman, M. Kluijver, R. Gomez, G. de Vyver, R. Soest and C. Devijver, Cellular location of (2R,3R,7Z)-2-aminotetradec-7-ene-1, 3-diol, a potent antimicrobial metabolite produced by the Caribbean sponge Haliclona vansoesti, *Cell Tissue Res.*, 2001, **306**, 157–165.

41 H. Kakeya, M. Morishita, H. Koshino, T. Morita, K. Kobayashi and H. Osada, Cytoxazone: A novel Cytokine modulator containing a 2-Oxazolidinone ring produced by Streptomyces sp., *J. Org. Chem.*, 1999, **64**, 1052–1053.

42 A. S. Paraskar and A. Sudalai, Enantioselective synthesis of (−)-Cytoxazone and (+)-epi-Cytoxazone, novel cytokine modulators *via* Sharpless asymmetric epoxidation and l-proline catalyzed Mannich reaction, *Tetrahedron*, 2006, **62**, 5756–5762.

43 R. Pedrosa, C. Andrés, J. P. Duque-Soladana and C. D. Rosón, Regio- and stereoselective 6- exo - trig radical cyclisations onto chiral perhydro-1,3-benzoxazines: synthesis of enantiopure 3-alkylpiperidines, *Tetrahedron: Asymmetry*, 2000, **11**, 2809–2821.

44 R. Pedrosa, C. Andrés, J. Nieto and S. del Pozo, Synthesis of enantiopure 3-Azabicyclo[3.2.0]heptanes by

diastereoselective intramolecular [2+2] photocycloaddition reactions on chiral perhydro-1,3-benzoxazines, *J. Org. Chem.*, 2003, **68**, 4923–4931.

45 C. Andrés, J. Nieto, R. Pedrosa and N. Villamañán, Synthesis of enantiopure primary amines by stereoselective ring opening of chiral Octahydro-1,3-benzoxazines by Grignard and Organoaluminum reagents, *J. Org. Chem.*, 1996, **61**, 4130–4135.

46 A. Alberola, C. Andrés and R. Pedrosa, Diastereoselective ring opening of 2-substituted N-Benzyl-4,4, 7α-trimethyl-trans-octahydro-1,3-benzoxazines by Grignard reagents. Highly enantioselective synthesis of primary amines, *Synlett*, 1990, **1990**, 763–765.

47 Y.-J. Cherng, J.-M. Fang and T.-J. Lu, Pinane-type tridentate reagents for enantioselective reactions: reduction of ketones and addition of Diethylzinc to aldehydes, *J. Org. Chem.*, 1999, **64**, 3207–3212.

48 Y.-J. Cherng, J.-M. Fang and T.-J. Lu, A new pinane-type tridentate modifier for asymmetric reduction of ketones with lithium aluminum hydride, *Tetrahedron: Asymmetry*, 1995, **6**, 89–92.

49 Z. Szakonyi, A. Hetényi and F. Fülöp, Synthesis of enantiomeric spirooxazolines and spirooxazolidines by the regioselective ring closure of (–)-α-pinene-based aminodiols, *Arkivoc*, 2007, **2008**, 33.

50 Z. Szakonyi, K. Csillag and F. Fülöp, Stereoselective synthesis of carane-based aminodiols as chiral ligands for the catalytic addition of diethylzinc to aldehydes, *Tetrahedron: Asymmetry*, 2011, **22**, 1021–1027.

51 Z. Szakonyi, Á. Csőr, A. Csámpai and F. Fülöp, Stereoselective synthesis and modelling-driven optimisation of Carane-based aminodiols and 1,3-Oxazines as catalysts for the enantioselective addition of diethylzinc to benzaldehyde, *Chem.–Eur. J.*, 2016, **22**, 7163–7173.

52 M. P. Stoyanova, B. L. Shivachev, R. P. Nikolova and V. Dimitrov, Highly efficient synthesis of chiral aminoalcohols and aminodiols with camphane skeleton, *Tetrahedron: Asymmetry*, 2013, **24**, 1426–1434.

53 D.-S. Lee, S.-M. Chang, C.-Y. Ho and T.-J. Lu, Enantioselective addition of diethylzinc to aldehydes catalyzed by chiral O, N, O-tridentate phenol ligands derived from camphor, *Chirality*, 2016, **28**, 65–71.

54 I. Philipova, V. Dimitrov and S. Simova, Synthesis of new enantiopure aminodiols and their use as ligands for the addition of diethylzinc to benzaldehyde, *Tetrahedron: Asymmetry*, 1999, **10**, 1381–1391.

55 S. Panev, A. Linden and V. Dimitrov, Chiral aminoalcohols with a menthane skeleton as catalysts for the enantioselective addition of diethylzinc to benzaldehyde, *Tetrahedron: Asymmetry*, 2001, **12**, 1313–1321.

56 K. Csillag, L. Németh, T. A. Martinek, Z. Szakonyi and F. Fülöp, Stereoselective synthesis of pinane-type tridentate aminodiols and their application in the enantioselective addition of diethylzinc to benzaldehyde, *Tetrahedron: Asymmetry*, 2012, **23**, 144–150.

57 Y.-J. Cherng, J.-M. Fang and T.-J. Lu, Pinane-type tridentate reagents for enantioselective reactions: reduction of ketones and addition of diethylzinc to aldehydes, *J. Org. Chem.*, 1999, **64**, 3207–3212.

58 T. Le, P. Bérdi, I. Zupkó, F. Fülöp and Z. Szakonyi, Synthesis and transformation of (-)-Isopulegol-based chiral β-aminolactones and β-aminoamides, *Int. J. Mol. Sci.*, 2018, **19**, 3522.

59 F. Z. Bamou, T. M. Le, B. Volford, A. Szekeres and Z. Szakonyi, Synthesis and application of 1,2-aminoalcohols with neoisopulegol-based octahydrobenzofuran core, *Molecules*, 2019, **25**, 21.

60 R. Outouch, S. Oubaassine, M. Ait Ali, L. El Firdoussi and A. Spannenberg, Crystal structure of (1S ,2R,4 S)-1-[(morpholin-4-yl)methyl]-4-(prop-1-en-2-yl)cyclohexane-1,2-diol, *Acta Crystallogr., Sect. E: Crystallogr. Commun.*, 2015, **71**, 79–81.

61 T. Gonda, Z. Szakonyi, A. Csámpai, M. Haukka and F. Fülöp, Stereoselective synthesis and application of tridentate aminodiols derived from (+)-pulegone, *Tetrahedron: Asymmetry*, 2016, **27**, 480–486.

62 Y. Tashenov, M. Daniels, K. Robeyns, L. Van Meervelt, W. Dehaen, Y. Suleimen and Z. Szakonyi, Stereoselective syntheses and application of chiral bi- and tridentate ligands derived from (+)-Sabinol, *Molecules*, 2018, **23**, 771.

63 O. V. Ardashov, A. V. Pavlova, I. V. Il'ina, E. A. Morozova, D. V. Korchagina, E. V. Karpova, K. P. Volcho, T. G. Tolstikova and N. F. Salakhutdinov, Highly Potent Activity of (1R,2R,6S)-3-Methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol in animal models of Parkinson's disease, *J. Med. Chem.*, 2011, **54**, 3866–3874.

64 D. A. Brown, M. T. Canning, S. L. Nay, A. V. Pena and D. B. Yarosh, Bicyclic monoterpene diols stimulate release of nitric oxide from skin cells, increase microcirculation, and elevate skin temperature, *Nitric Oxide*, 2006, **15**, 70–76.

65 D. A. Brown, K. Lesiak, W.-Y. Ren, K. L. Strzelecki and A. A. Khorlin, Bicyclic monoterpene diols induce differentiation of S91 melanoma and PC 12 pheochromocytoma cells by a cyclic Guanosine-monophosphate-dependent pathway, *Pigm. Cell Res.*, 1999, **12**, 36–47.

66 S. Hammami, A. I. Elshamy, R. E. Mokni, A. Snene, K. Iseki, H. Dhaouadi, Y. Okamoto, M. Suenaga, M. Noji, A. Umeyama and Y. Asakawa, Chemical Constituents of the Aerial Parts of Daucus carota subsp. hispidus growing in Tunisia, *Nat. Prod. Commun.*, 2019, **14**, 1934578X1986351.

67 P. L. Crowell, Z. Ren, S. Lin, E. Vedejs and M. N. Gould, Structure-activity relationships among monoterpene inhibitors of protein isoprenylation and cell proliferation, *Biochem. Pharmacol.*, 1994, **47**, 1405–1415.

68 A. E.-H. H. Mohamed, N. S. Mohamed, A. R. Hamed and M.-E. F. Hegazy, Anti-inflammatory activity of highly oxygenated terpenoids from Achillea biebersteinii Afan, *Z. Naturforsch. C Biosci.*, 2016, **71**, 429–432.

69 T. J. Brocksom, R. B. dos Santos, N. A. Varanda and U. Brocksom, An efficient synthesis of monoterpene α-methylene-γ-butyrolactones, *Synth. Commun.*, 1988, **18**, 1403–1410.

70 T. J. Brocksom, J. Tercio and B. Ferreira, A biomimetic synthesis of α-methylene-γ-butyrolactones, *Synth. Commun.*, 1981, **11**, 105–119.
71 M. Carda and J. A. Marco, Total synthesis of the monoterpenes (−)-mintlactone and (+)-isomintlactone, *Tetrahedron*, 1992, **48**, 9789–9800.
72 D. Friedrich and F. Bohlmann, Total synthesis of various elemanolides, *Tetrahedron*, 1988, **44**, 1369–1392.
73 M. Schlosser and M. Kotthaus, Isopulegol as a model compound: metalation and substitution of an allylic position in the presence of an unprotected hydroxy function, *Eur. J. Org. Chem.*, 1999, **1999**, 459–462.
74 S. Serra and C. Fuganti, Enzyme-mediated preparation of enantiomerically pure p-Menthan- 3,9-diols and their use for the synthesis of natural p-menthane lactones and ethers, *Helv. Chim. Acta*, 2002, **85**, 2489–2502.
75 N. J. Lawrence, A. T. McGown, J. Nduka, J. A. Hadfield and R. G. Pritchard, Cytotoxic michael-type amine adducts of α-methylene lactones alantolactone and isoalantolactone, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 429–431.
76 Z. Szakonyi, A. Hetényi and F. Fülöp, Synthesis and application of monoterpene-based chiral aminodiols, *Tetrahedron*, 2008, **64**, 1034–1039.
77 D. Wu, J. Li and W. Wang, Selective formation of monoacylated diols through a mild Passerini reaction: selective formation of monoacylated diols through a mild Passerini reaction, *Eur. J. Org. Chem.*, 2018, **2018**, 3022–3030.
78 A. Nemoto, Y. Hoshino, K. Yazawa, A. Ando, Y. Mikami, H. Komaki, Y. Tanaka and U. Gräfe, Asterobactin, a new Siderophore group antibiotic from Nocardia asteroides, *J. Antibiot.*, 2002, **55**, 593–597.
79 D. Schummer, G. Höfle, E. Forche, H. Reichenbach, V. Wray and T. Domke, Antibiotics from Gliding bacteria, LXXVI. Vioprolides: new antifungal and cytotoxic peptolides from Cystobacter violaceus, *Liebigs Ann.*, 2006, **1996**, 971–978.
80 J. H. Kim, H. J. Lim and S. H. Cheon, A facile synthesis of (6S,1′S)-(+)-hernandulcin and (6S,1′R)-(+)-epihernandulcin, *Tetrahedron*, 2003, **59**, 7501–7507.
81 B. P. Shivani and A. K. Chakraborti, Zinc(II) perchlorate hexahydrate catalyzed opening of epoxide ring by amines: applications to synthesis of (RS)/(R)-Propranolols and (RS)/(R)/(S)-Naftopidils, *J. Org. Chem.*, 2007, **72**, 3713–3722.
82 S. C. Bergmeier, The Synthesis of vicinal amino alcohols, *Tetrahedron*, 2000, **56**, 2561–2576.
83 Y. Yuasa and Y. Yuasa, Synthesis and absolute configuration at C(8) of 'p-Menthane-3,8,9-triol' derived from (-)-Isopulegol, *Helv. Chim. Acta*, 2004, **87**, 2602–2607.
84 B. R. Travis, R. S. Narayan and B. Borhan, Osmium tetroxide-promoted catalytic oxidative cleavage of olefins: An organometallic ozonolysis, *J. Am. Chem. Soc.*, 2002, **124**, 3824–3825.
85 G. N. Costa, R. M. B. Carrilho, L. D. Dias, J. C. Viana, G. L. B. Aquino, M. Pineiro and M. M. Pereira, Highly efficient Rh(I)/tris-binaphthyl monophosphite catalysts for hydroformylation of sterically hindered alkyl olefins, *J. Mol. Catal. A: Chem.*, 2016, **416**, 73–80.
86 I. Paterson, E. A. Anderson, S. M. Dalby, J. H. Lim and P. Maltas, The stereocontrolled total synthesis of spirastrellolide A methyl ester. Fragment coupling studies and completion of the synthesis, *Org. Biomol. Chem.*, 2012, **10**, 5873–5886.
87 S. Superchi, M. I. Donnoli, G. Proni, G. P. Spada and C. Rosini, Induction of cholesteric mesophases by simple cyclic derivatives of p,p′-disubstituted 1,2-Diphenylethane-1,2-diols: importance of shape and polarizability effects, *J. Org. Chem.*, 1999, **64**, 4762–4767.
88 I. S. Marcos, L. Castañeda, P. Basabe, D. Díez and J. G. Urones, Synthesis of sibiricinone A, sibiricinone B and leoheterin, *Tetrahedron*, 2008, **64**, 10860–10866.
89 P. A. Wender, N. Buschmann, N. B. Cardin, L. R. Jones, C. Kan, J.-M. Kee, J. A. Kowalski and K. E. Longcore, Gateway synthesis of daphnane congeners and their protein kinase C affinities and cell-growth activities, *Nat. Chem.*, 2011, **3**, 615–619.
90 K. Chen and P. S. Baran, Total synthesis of eudesmane terpenes by site-selective C–H oxidations, *Nature*, 2009, **459**, 824–828.
91 T. M. Le, T. Szilasi, B. Volford, A. Szekeres, F. Fülöp and Z. Szakonyi, Stereoselective synthesis and investigation of Isopulegol-based chiral ligands, *Int. J. Mol. Sci.*, 2019, **20**, 4050.
92 W. Brand-Williams, M. E. Cuvelier and C. Berset, Use of a free radical method to evaluate antioxidant activity, *LWT–Food Sci. Technol.*, 1995, **28**, 25–30.
93 E. Bendary, R. R. Francis, H. M. G. Ali, M. I. Sarwat and S. El Hady, Antioxidant and structure–activity relationships (SARs) of some phenolic and anilines compounds, *Ann. Agric. Sci.*, 2013, **58**, 173–181.