FULL PAPER

Stereoselective Synthesis of Limonene-based Chiral 1,3-Aminoalcohols and Aminodiols

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Abstract: An unexpected ring-closing reaction of an α,β-unsaturated carboxylic acid, derived from (*R*)- and -(*S*)-limonene**,** in the presence of trifluoroacetic anhydride (TFAA) resulted in bicyclic *α*-methylene ketones and their hydroxylated analogues in a stereoselective intramolecular acylation. The reaction was studied in detail and optimized for both compounds. Addition of secondary and primary amines to both keto alkenes followed by *in situ* reduction of formed aminoketones with sodium borohydride gave new bicyclic terpenoid secondary and tertiary 1,3-aminoalcohols and aminodiols with excellent diastereoselectivity. Regioisomeric aminodiols were prepared stereoselectively from the unsaturated 1,3-aminoalcohols via hydroboration reaction with Me_2S. BH_3/H_2O_2 system.

Introduction

Cyclic chiral aminoalcohols have many important applications in chiral catalysis[1-8] and in the synthesis of biologically active compounds as building blocks.[9,10] Many monoterpenes, such as (+)-pulegone,[1] (+)- and (-)-3-carane,[2,3] as well as (+)- and (-)-*α*-pinene,[4] have been widely used as starting materials for the synthesis of various aminoalcohols, which are applied as chiral additives and catalysts in several chemical transformations.[1-3,9] Monoterpene-based 1,2- and 1,3-aminoalcohols, prepared stereoselectively from commercially available monoterpenes, have proven to be excellent catalysts in a wide range of stereoselective reactions including catalytic asymmetric carbon-carbon bond formation, dialkylzinc addition to aldehydes, and asymmetric allylic alkylation.[5-8,10]

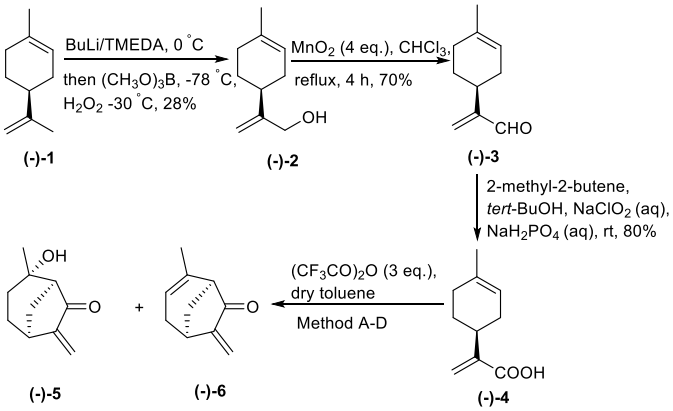
Chiral aminodiols, which combine the chemical properties of 1,2- and 1,3-aminoalcohols, have also been widely used as chiral auxiliaries in enantioselective syntheses.[11-15] Moreover, they are excellent building blocks for the synthesis of versatile heterocyclic compounds depending upon the participation of specific hydroxyl groups in ring closure with the amino group. Aminodiols proved to be excellent starting materials for the synthesis of both 1,3-oxazines and spiro 1,3-heterocycles.[1,12,16] Since the resulting heterocycles contain a free hydroxyl group having coordinating ability, this may give rise to greater rigidity within a transition state, and hence to higher enantioselective induction in asymmetric transformations.[3] Aminodiols also serve as substrates for the synthesis of biologically active natural compounds (cytoxazone, etc.), while others exhibit significant biological activities (aristeromycin, etc.).[11,17]

Monoterpene-based aminodiols were also found to be excellent starting materials for the synthesis of nucleoside analogues with remarkable sodium/calcium exchanger (NCX) inhibitor activity.[18,19]

In our present work we report the preparation of limonene-based chiral 1,3-aminoalcohols and aminodiols, a new family of bi- and tri-functional terpenoids starting from commercially available (-)- and (+)-limonene via stereoselective transformations.

Results and Discussion

Starting from commercially available (-)-(*S*)-limonene **1**, key intermediate bicyclic methylene ketones (-)-**5** and (-)-**6** were prepared in a four-step synthesis. (-)-**1** was metalated by treatment with the strong base *n*-butyllithium/TMEDA,[20-22] followed by trimethoxyborane treatment to produce a boron-substituted limonenyl derivative. Then boron was removed by hydrogen peroxide as oxidizing agent to produce (*S*)-*p*-mentha-1,8-dien-9-ol (-)-**2** bearing a hydroxyl group at position 10. Metalation is not selective,[20] resulting in (*S*)-perillylalcohol as well. Unfortunately, separation of the regioisomeric alcohols was unsuccessfull in a gram scale. Consequently, MnO_2 was used to oxidize the mixture of alcohols to (*S*)-perillaldehyde and (*S*)-*p*-mentha-1,8-dien-9-al (-)-**3**, which were easily separated by column chromatography. (-)-**3** was then converted to carboxylic acid (-)-**4** using a literature method (Scheme 1).[23-25]



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

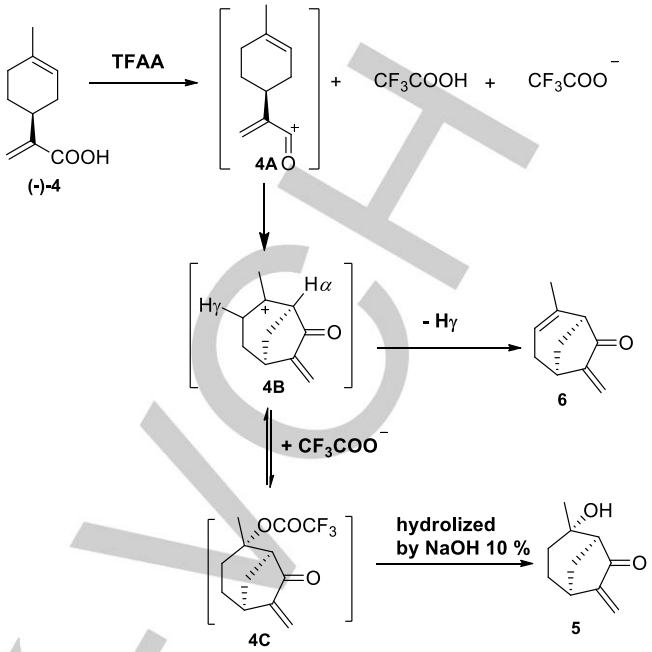
When (*S*)-isoperyllic acid (-)-**4** was then treated with $(CF_3CO)_2O$ (TFAA) in dry toluene to prepare the corresponding *tert*-butyl ester, an unexpected intramolecular ring closing reaction[23,24] was observed resulting in two products: methylene ketone (-)-**6** and its hydroxyl-substituted analogue (-)-**5** (Scheme 1). It is interesting to note, that although both keto alkenes are new compounds, similar structures can be found in the structure of cytotoxic kaurane-type natural diterpenoids[26] and a partially saturated analogue of **6** is also known to be a natural component of *Japanese* sour citrus fruits.[27] The temperature strongly affected the yield and the ratio of the two products. At low temperature (0 °C), formation of the kinetically controlled **5** was observed as the main product, whereas at 25 °C the products were formed in a ratio of 1:1. In contrast, the thermodynamically preferred **6** was obtained as a single product at 100 °C. [28] At lower temperature, the yield of the reaction dropped dramatically without any remarkable changes in the **5**:**6** ratio (Table 1). When other solvents, acid catalyst or acetic anhydride was applied, the reaction failed.

Table 1. Cyclisation reaction of (*S*)-isoperyllic acid (**4**).

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

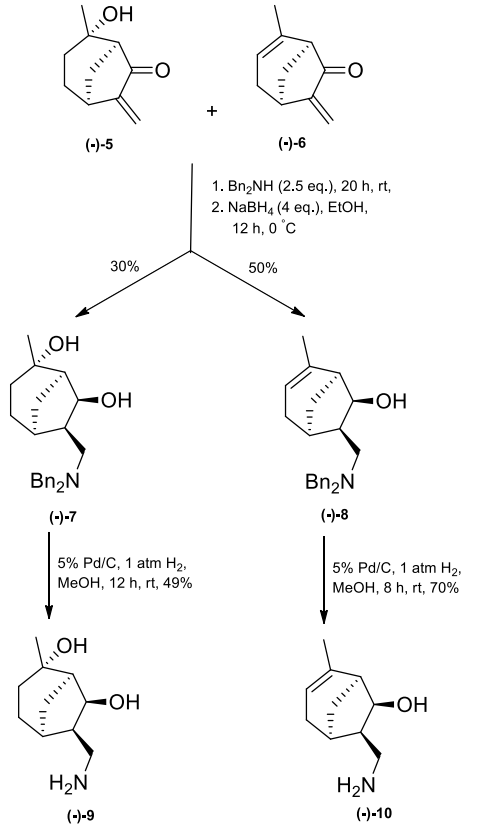
[a] Based on ^{1}H-NMR measurements. [b] Isolated, combined yield of **5** and **6**.

The reaction between the carboxylic acid and the double bond in the presence of TFAA can be interpreted by a carbonium ion mechanism (Scheme 2).[28,29] In the first step, acylium ion **4A** is formed upon the attack of TFAA to the carboxylic acid group followed by an intramolecular attack on the olefinic bond to yield carbonium ion **4B**. The latter loses the *γ*-proton to form ketone **6** or reacts with the trifluoroacetate anion to yield ester **4C**, which undergoes hydrolysis under work-up conditions to deliver **5**.[28]



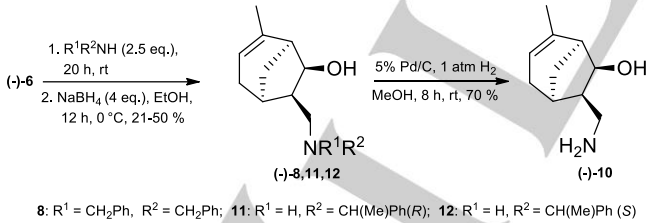
Scheme 2. Proposed pathway of the intramolecular acylation reaction.

The separation of (-)-**5** and (-)-**6** was difficult in a gram scale; therefore, the mixture of (-)-**5** and (-)-**6** was reacted with dibenzylamine in aza-Michael addition. Since the addition of the amine was found to be reversible, intermediate aminoketones were converted into tertiary aminodiol (-)-**7** and aminoalcohol (-)-**8** by *in situ* reduction with $NaBH_4$.[30] The two products obtained could easily be separated by column chromatography based on their different polarity. Hydrogenolysis of these compounds over Pd/C in MeOH afforded primary aminodiol (-)-**9** and aminoalcohol (-)-**10** in moderate yields (Scheme 3).[23,24]



Scheme 3. Stereoselective synthesis of limonene-based aminoalcohols and aminodiols.

Subsequently, methylene ketone (-)-**6**, prepared in an optimized cyclisation reaction (Table 1) at 100 °C, was also reacted with amines to exploit the effect of ring system on the stereoselectivity of the addition obtaining tertiary and secondary aminoalcohols (-)-**8**, (-)-**11** and (-)-**12** in highly stereoselective reactions (Scheme 4).



Scheme 4. Stereoselective synthesis of aminoalcohols.

The relative configuration of (-)-**8**, (-)-**11** and (-)-**12** was determined by NOESY spectral analysis. Clear NOE correlations were observed between H-6 and H-8, H-5, H-7, and between H-1 and H-7. Therefore, the structure of **8**, **11** and **12** was determined as presented in Figure 1.

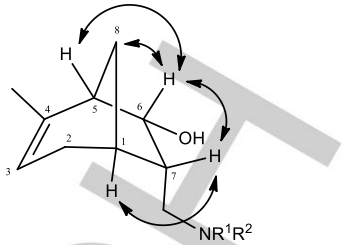


Figure 1. Determination of configuration (-)-**8**,**11**,**12** by NOESY.

The configurations of new stereogenic centers of (-)-**7** were determined by NOESY, where noteworthy NOE effects were also observed between H-7 and H-8, H-1, H-6, as well as between H-5 and H-6. The structure of (-)-**7** was determined as shown in Figure 2.

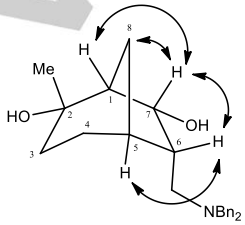
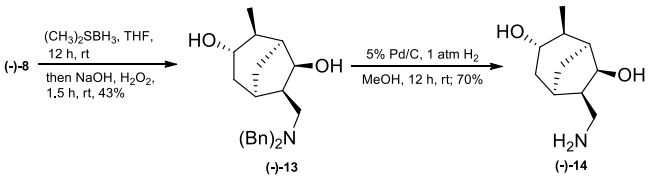


Figure 2. NOESY effects of the configuration of (-)-**7**.

The synthesis of structural isomeric aminodiol (-)-**13** was accomplished by hydroboration of compound (-)-**8** by treatment with borane dimethyl sulfide followed by oxidation of the boron intermediate with hydrogen peroxide (Scheme 5). Note, that the addition resulted in two diastereoisomers of (-)-**13** with a ratio of 3:1 (based on NMR measurement of the crude product). Our efforts failed to isolate the minor compound, and only major product (-)-**13** could be obtained after column chromatography. The configuration of the new stereogenic centers in (-)-**13** was determined by NMR with NOESY experiments. Debenzylation with the H_2/Pd/C system and purification of the crude product provided aminodiol (-)-**14** in acceptable yield (Scheme 5).



Scheme 5. Synthesis of 6-amino-1,4-diols.

The NOESY experiments of (-)-**13**, where considerable NOE effects were observed between H-7 and H-1, H-6, between H-6 and H-5, H-7, H-8, between H-5 and H-4, and between H-CH_3 and H-3 (Figure 3).

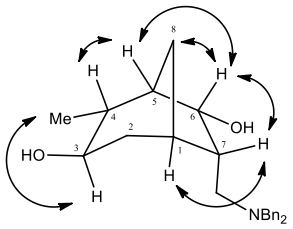


Figure 3. Determination of the structure of aminodiol (-)-**13** by NOESY.

The procedure described above was repeated with (+)-limonene (+)-**1** to obtain enantiomeric counterparts (+)-**3** to (+)-**14**.

Conclusions

Starting from natural (+)- and (-)-limonene, new terpenoid bicyclic methylene ketones were obtained through an unexpected intramolecular acylation. The reaction pathway involves the formation of an acylium ion in the reaction of the carboxylic acid group with TFAA, followed by the attack of the electrophilic acylium ion moiety on the olefinic bond. The cyclisation was optimized for both products. Aza-Michael addition of secondary and primary amines on methylene ketones resulted in aminodiols and 1,3-aminoalcohols in highly stereoselective reactions. These compounds were used to prepare a new family of terpenoid aminoalcohols and aminodiols with high diastereoselectivity.

Experimental Section

General methods: ^{1}H- and ^{13}C-NMR were recorded on Bruker Avance DRX 400 spectrometer [400 MHz (^{1}H) and 100 MHz (^{13}C), δ = 0 (TMS)]. Chemical shifts are expressed in ppm (δ) relative to TMS as the internal reference. *J* values are given in Hz. Optical rotations were obtained with a Perkin-Elmer 341 polarimeter. Melting points were determined on a Kofler apparatus and are uncorrected. Microanalyses were performed on a Perkin-Elmer 2400 elemental analyser. Chromatographic separations were carried out on Merck Kiesegel 60 (230-400 mesh ASTM). Reactions were monitored with Merck Kieselgel 60 F_{254}-precoated TLC plates (0.25 mm thickness).

Starting materials: (*S*)- and (*R*)-limonene [(-)- and (+)-**1**] are available commercially from Merck Co. All chemicals and solvents were used as supplied. THF and toluene were dried over Na wire. (*S*)- and (*R*)-isoperillyl alcohol [(-)-**2** and (+)-**2**)] and (*S*)-and (*R*)-*p*-mentha-1,8-dien-9-al [(-)-**3** and (+)-**3**] were prepared according to literature procedures, and all their spectroscopic data were similar as described.[20]

(-)-(*S*)-*p*-Mentha-1,8-dien-9-oic acid ((-)-**4**): A solution of $NaClO_2$ (5.6 g, 61.9 mmol) and NaH_2PO_4 (6.8 g, 56.7 mmol) in water (40 mL) was added to the solution of (-)-**3** (5.68 g, 37.8 mmol) and 2-methyl-2-butene (27.0 mL, 255.0 mmol) in *tert*-BuOH (50.0 mL) at room temperature and the mixture was stirred for 12 h. The solution was then concentrated under reduced pressure and the residue was made alkaline with 10% aqueous NaOH solution (200 mL) and extracted with *n*-hexane (3 x 100 mL). The aqueous phase was acidified with 25% aqueous HCl solution (pH = 3-4) and extracted with Et_2O (3 x 100 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified with column chromatography on silica gel, eluting with *n*-hexane : EtOAc (4:1) followed by recrystallisation (*n*-hexane) affording 5.05 g (80%) compound (-)-**4** as white crystals; m.p. 71-73 °C; $[\alpha]_D^{20}$ = - 69 (*c* 0.27 MeOH); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.49-1.59 (m, 1H), 1.66 (s, 3H), 1.82-1.91 (m, 2H), 1.93-1.98 (m, 1H), 2.06-2.12 (m, 1H), 2.22-2.26 (1H, m), 2.66-2.73 (1H, m), 5.40 (1H, s), 5.65 (s, 1H), 6.34 (s, 1H), ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 23.5 (CH_3), 28.4 (CH_2), 30.4 (CH_2), 31.4 (CH_2), 34.7 (CH), 120.3 (CH), 125.3 (CH_2), 133.9 (C_q), 144.9 (C_q), 173.2 (C=O). $C_{10}H_{14}O_2$ (166.22): calcd. C 72.26, H 8.49; found C 72.30, H 8.25 .

(+)-(*R*)-*p*-Mentha-1,8-dien-9-oic acid ((+)-**4**): synthesized analogously to (-)-**4** from (+)-**3**; $[\alpha]_D^{20}$ = + 65 (*c* 0.27 MeOH). All spectroscopic data were similar to those of (-)-**4**. $C_{10}H_{14}O_2$ (166.22): calcd. C 72.26, H 8.49; found C 72.34, H 8.32.

General procedure for acetylation between olefin with carboxylic acid, using TFAA as catalyst. **Method A**: To solution of carboxylic acid (-)-**4** (3.1 g, 18.6 mmol) in dry toluene (70 mL) TFAA (8.0 mL, 57.5 mmol) was added at 0 °C. The resulting solution was stirred for 48 h at 0 °C, and the mixture was then diluted with toluene (100 mL), extracted with 10% aqueous NaOH solution (70 mL), and then with water (70 mL) and brine (70 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The crude product was subjected to column chromatography on silica gel (*n*-hexane/EtOAc = 19:1) to give a 67:33 mixture of (-)-**5** and (-)-**6** (2.37 g, 80%).

Method B: To solution of (-)-**4** (2.0 g, 12.0 mmol) in dry toluene (45 mL) TFAA (5.0 mL, 35.97 mmol) was added. The mixture was refluxed for 6 h. When completed, the reaction mixture was diluted with toluene (70 mL) and extracted with 10% aqueous NaOH solution (50 mL), next with water (50 mL), and with brine (50 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The crude product was subjected to column chromatography on silica gel (*n*-hexane/EtOAc = 19:1), resulting in compound (-)-**6** (2.0 g, 56%).

(-)-(1*S*,4*S*,5*S*)-4-Hydroxy-4-methyl-7-methylenebicyclo[3.2.1]octan-6-one ((-)-**5**): yellow oil; $[\alpha]_D^{20}$ = - 48 (*c* 0.495 MeOH); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 1.48-1.57 (m, 1H), 1.64 (s, 3H), 1.71-1.76 (m, 1H), 1.83-1.88 (m, 1H), 1.98-2.07 (m, 2H), 2.19 (dd, *J* = 5.1, 15.5 Hz, 1H), 3.13 (s, 1H), 3.16-3.19 (m, 1H), 5.37 (s, 1H), 6.01 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 23.4 (CH_3), 29.3 (CH_2), 30.2 (CH_2), 31.5 (CH_2), 38.5 (CH), 54.3 (CH), 87.9 (C_q), 116.4 (CH_2), 147.9 (C_q), 203.5 (C=O). $C_{10}H_{14}O_2$(166.22): calcd. C 72.26; H 8.49; found C 72.35, H 8.30.

(+)-(1*R*,4*R*,5*R*)-4-Hydroxy-4-methyl-7-methylenebicyclo[3.2.1]octan-6-one ((+)-**5**): synthesized analogously to (-)-**5** from (+)-**4**; $[\alpha]_D^{20}$ = + 55 (*c* 0.495 MeOH). All spectroscopic data were similar to those of (-)-**5**. $C_{10}H_{14}O_2$ (166.22): calcd. C 72.26; H 8.49; found C 72.40, H 8.32.

(-)-(1*S*,5*S*)-4-Methyl-7-methylenebicyclo[3.2.1]oct-3-en-6-one ((-)-**6**): yellow oil; $[\alpha]_D^{20}$ = - 215 (*c* 0.315 MeOH); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.75-1.78 (m, 4H), 1.90-1.95 (m, 1H), 2.02-2.06 (m, 1H), 2.55-2.62 (m, 1H), 2.73 (d, *J* = 4.4 Hz, 1H), 3.06 (t, *J* = 5.4 Hz 1H), 5.36 (brs, 1H), 5.47 (s, 1H), 5.94 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 22.6 (CH_3), 30.7 (CH_2), 35.5 (CH_2), 37.5 (CH), 51.8 (CH), 116.1 (CH_2), 121.6 (CH), 134.6 (C_q), 150.9 (C_q). $C_{10}H_{12}O$ (148.20): calcd. C 81.04, H 8.16; found C 81.00, H 8.20.

(+)-(1*R*,5*R*)-4-Methyl-7-methylenebicyclo[3.2.1]oct-3-en-6-one ((+)-**6**): synthesized analogously to (-)-**6** from (+)-**4**; $[\alpha]_D^{20}$ = + 230 (*c* 0.315 MeOH). All spectroscopic data were similar to those of (-)-**6**. $C_{10}H_{12}O$ (148.20): calcd. C 81.04, H 8.16, found C 81.11, H 8.23.

(-)-(1*R*,2*S*,5*S*,6*R*,7*S*)-6-((Dibenzylamino)methyl)-2-methylbicyclo[3.2.1]octane-2,7-diol ((-)-**7**) and **(-)-(1*S*,5*S*,6*R*,7*R*)-7-((Dibenzylamino)methyl)-4-methylbicyclo[3.2.1]oct-3-en-6-ol** ((-)-**8**): A mixture of acylation products (-)-**5** and (-)-**6** based on **Method A** (2.7 g) was mixed with dibenzylamine (9.0 mL, 46.8 mmol) in neat. The mixture was stirred for 20 h at room temperature. When completed (indicated by TLC), the mixture was dissolved in the mixture of dry EtOH (40 mL) and water (5 mL) and cooled to 0 °C. Solid $NaBH_4$ (2.7 g, 71.4 mmol) was added to the mixture in small portions followed by stirring overnight in ice bath. The mixture was then quenched with water (100 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The organic phase was dried (Na_2SO_4) and evaporated in vacuo. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 19:1 to 2:1), resulting in 2.0 g (50 %) of compound (-)-**7** and 0.58 g (30 %) of compound (-)-**8**. Compound (-)-**7**: white crystals; m.p. 108-183 °C; $[\alpha]_D^{20}$ = - 14 (*c* 0.25 MeOH); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 1.09 (dd, *J* = 6.6, 14.3 Hz, 1H), 1.16-1.22 (m, 2H), 1.26 (s, 3H), 1.28-1.36 (m, 1H), 1.57-1.62 (m, 1H), 1.91 (brs, 1H), 2.04-2.08 (m, 2H), 2.36-2.42 (m, 2H), 2.95 (t, 13.8 Hz, 1H), 3.21 (d, *J* = 13.1 Hz, 2H), 3.98 (d, *J* = 13.1 Hz, 2H), 4.47 (dd, *J* = 6.6, 9.4 Hz, 1H), 7.24-7.34 (m, 10H) ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 24.2 (CH_2), 31.0 (CH_3), 31.9 (CH_2), 32.5 (CH_2), 36.3 (CH), 39.0 (CH), 50.7 (CH), 52.3 (CH_2), 58.6 (CH_2) 72.7 (C_q), 73.7 (C_q), 127.3 (CH), 128.6 (CH), 129.5 (CH), 138.0 (C_q). $C_{24}H_{31}NO_2$ (365.51): calcd. C 78.86, H 8.55, N 3.83; found C 78.68, H 8.60, N 3.60. Compound (-)-**8**: white crystals; m.p. 165-169 °C; $[\alpha]_D^{20}$ = -63 (*c* 0.29 MeOH); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 1.51-1.56 (m, 1H), 1.61-1.64 (m, 4H), 1.79-1.83 (d, *J* = 17.8 Hz, 1H), 2.07-2.12 (m, 1H), 2.20 (q, *J* = 4.7, 6.0 Hz, 1H), 2.28 (t, *J* = 4.4 Hz, 1H), 2.36-2.42 (m, 1H), 2.48 (dd, *J* = 5.2, 11.9 Hz, 1H), 2.93 (t, *J* = 12.0 Hz, 1H), 3.42 (d, *J* = 13.6 Hz, 2H), 3.77 (d, *J* = 13.6 Hz, 2H), 4.31 (dd, *J* = 5.7, 9.3 Hz, 1H), 5.02 (s, 1H), 7.23-7.32 (m, 10H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 25.1 (CH_3), 29.8 (CH_2), 32.5 (CH_2), 36.2 (CH), 38.9 (CH), 45.4 (CH), 54.6 (CH_2), 58.0 (CH_2), 78.3 (CH), 117.8 (CH), 127.3 (CH), 128.4 (CH), 129.6 (CH), 137.8 (C_q), 140.3 (C_q). $C_{24}H_{29}NO$ (347.49): calcd. C 82.95, H 8.41, N 4.03; found C 82.75, H 8.22, N 4.05.

(+)-(1*S*,2*R*,5*R*,6*S*,7*R*)-6-((Dibenzylamino)methyl)-2-methylbicyclo[3.2.1]octane-2,7-diol ((+)-**7**): synthesized analogously to (-)-**7** from the mixture of (+)-**5** and (+)-**6**; $[\alpha]_D^{20}$ = + 13 (*c* 0.25 MeOH). All spectroscopic data were similar to those of (-)-**7**. $C_{24}H_{31}NO_2$ (365.51): calcd. C 78.86, H 8.55, N 3.83; found C 78.70, H 8.68, N 3.73.

(+)-(1*R*,5*R*,6*S*,7*S*)-7-((Dibenzylamino)methyl)-4-methylbicyclo[3.2.1]oct-3-en-6-ol ((+)-**8**): synthesized analogously to (-)-**8** from the mixture of (+)-**5** and (+)-**6**; $[\alpha]_D^{20}$ = + 58 (*c* 0.29 MeOH). All spectroscopic data were similar to those of (+)-**8**. $C_{24}H_{29}NO$ (347.49): calcd. C 82.95, H 8.41, N 4.03; found C 82.78, H 8.49, N 3.98.

General procedure for preparation of conjugate addition with primary amines: Compound (-)-**6** obtained by method **B** (2.7 g, 18.2 mmol) was stirred with (*R*)-methylbenzylamine or (*S*)-methylbenzylamine (6.0 mL, 46.8 mmol) in neat for 20 h at room temperature. When the reaction was completed (indicated by TLC), the mixture was dissolved in the mixture of dry EtOH (40 mL) and water (5 mL) and cooled to 0 °C. Solid $NaBH_4$ (2.7 g, 71.4 mmol) was added to the mixture in small portions and stirred overnight in an ice bath. The mixture was then quenched with water (100 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The organic phases were combined and washed with 5% aqueous HCl solution (100 mL), then dried (Na_2SO_4) and evaporated in vacuo. The crude product was purified by recrystallisation (*n*-hexane/CH_2Cl_2), resulting in compounds (-)-**11** and (-)-**12**, respectively.

(-)-(1*S*,5*S*,6*R*,7*R*)-4-Methyl-7-((((*R*)-1-phenylethyl)amino)methyl)bicyclo[3.2.1]oct-3-en-6-ol ((-)-**11**): 1.48 g (30%); white crystals; m.p. 108-185 °C; $[\alpha]_D^{20}$ = - 71 (*c* 0.27 MeOH); 1.48-1.64 (m, 4H), 1.73 (s, 3H), 1.93 (d, *J* = 6.2 Hz, 3H), 2.08 (d, *J* = 17.8 Hz, 3H), 2.30 (br s, 2H), 2.67 (br s, 2H), 2.97 (q, 1H), 4.25 (br s, 1H), 4.65 (br s, 1H), 5.13 (s, 1H), 7.37-7.45 (m, 3H), 7.65-7.67 (m, 2H), 8.64 (br s, 1H), 9.79 (br s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 23.9 (CH_3), 25.3 (CH_3), 29.9 (CH_2), 32.6 (CH_2), 36.0 (CH), 43.7 (CH), 45.0 (CH), 47.2 (CH_2), 58.8 (CH), 77.7 (CH), 118.4 (CH), 126.5 (CH), 127.3 (CH), 128.7 (CH), 139.8 (C_q), 144.9 (C_q). $C_{18}H_{25}NO$ (271.40): calcd. C 79.66, H 9.28, N 5.16; found C 79.60, H 9.12, N 5.03.

(+)-(1*R*,5*R*,6*S*,7*S*)-4-Methyl-7-((((*S*)-1-phenylethyl)amino)methyl)bicyclo[3.2.1]oct-3-en-6-ol ((+)-**11**) synthesized analogously to (-)-**11**; $[\alpha]_D^{20}$ = + 76 (*c* 0.27 MeOH). All spectroscopic data were similar to those of (-)-**11**. $C_{18}H_{25}NO$ (271.40): calcd. C 79.66, H 9.28, N 5.16; found C 79.73, H 9.38, N 4.91.

(-)-(1*S*,5*S*,6*R*,7*R*)-4-Methyl-7-((((*S*)-1-phenylethyl)amino)methyl)bicyclo[3.2.1]oct-3-en-6-ol ((-)-**12**): 1.04 g (21%); white crystals; m.p. 108-184 °C; $[\alpha]_D^{20}$ = -131 (*c* 0.34 MeOH); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 1.50-1.55 (m, 1H), 1.61 (d, *J* = 13.9 Hz, 2H), 1.63 (s, 3H), 1.87 (d, *J* = 6.8 Hz, 3H), 2.07-2.12 (m, 1H), 2.24-2.31 (m, 2H), 2.69-2.79 (m, 2H), 2.98 (q, 1H), 4.27-4.30 (m, 1H), 4.57 (dd, *J* = 5.9, 9.2 Hz, 1H), 5.00 (s, 1H), 7.35-7.44 (m, 3H), 7.52-7.55 (m, 2H), 8.56 (br s, 1H), 9.79 (br s, 1H) ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 20.1 (CH_3), 24.9 (CH_3), 29.5 (CH_2), 32.5 (CH_2), 36.2 (CH), 40.0 (CH), 44.8 (CH), 45.2 (CH_2), 49.2 (CH), 75.0 (CH), 117.4 (CH), 127.9 (CH), 129.2 (CH), 129.3 (CH), 135.9 (C_q), 139.9 (C_q). $C_{18}H_{25}NO$ (271.40): calcd C 79.66, H 9.28, N 5.16; found C 79.52, H 9.13, N 5.02.

(+)-(1*R*,5*R*,6*S*,7*S*)-4-Methyl-7-((((*R*)-1-phenylethyl)amino)methyl)bicyclo[3.2.1]oct-3-en-6-ol ((+)-**12**): synthesized analogously to (-)-**12**; $[\alpha]_D^{20}$ = + 141.7 (*c* 0.34 MeOH). All spectroscopic data were similar to those of (-)-**12**. $C_{18}H_{25}NO$ (271.40): calcd. C 79.66, H 9.28, N 5.16; found C 79.73, H 9.31, N 4.93.

(-)-(1*R*,3*S*,4*S*,5*S*,6*R*,7*R*)-7-((Dibenzylamino)methyl)-4-methylbicyclo[3.2.1]octane-3,6-diol ((-)-**13**): To the cooled (0 °C) solution of (-)-**8** (1 g, 2.88 mmmol) in dry THF (30 mL) was added $(CH_3)_2S.BH_3$ (700 µL) under the argon atmosphere. The mixture was stirred overnight at room temperature. The resulting solution then was treated with 3M aqueous NaOH (3 mL) and 30% aqueous hydrogen peroxide solution (3 mL) diluted in dry EtOH (10 mL). The mixture was stirred for 1.5 h at room temperature and then it was diluted with EtOAc (100 mL) and extracted with water (3 x 100 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated under reduce pressure. The crude product obtained was purified by chromatography on silica gel (*n*-hexane/EtOAc = 9:1 to 2: 1 as eluent), resulting in 0.45 g (43%) of (-)-**13** as white crystals; m.p. 191-193 °C; $[\alpha]_D^{20}$ = -14 (*c* 0.26 MeOH); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 1.10 (d, *J* = 6.9 Hz, 3H), 1.26-1.46 (m, 5H), 1.76-1.83 (m, 1H), 2.00-2.05 (m, 1H), 2.20-2.23 (m, 1H), 2.30-2.37 (m, 1H), 2.41 (dd, *J* = 5.3, 12.4 Hz, 1H), 3.02 (t, *J* = 12.6 Hz, 1H), 3.28 (d, *J* = 12.8 Hz, 2H), 3.44-3.51 (m, 1H), 3.94 (d, *J* = 13.1 Hz, 2H), 4.47 (dd, *J* = 6.6, 9.5 Hz), 7.25-7.35 (m, 10H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) : 17.8 (CH_3), 37.1 (CH_2), 38.0 (CH), 38.5 (CH_2), 40.2 (CH), 45.5 (C_q), 45.7 (CH), 51.1 (CH_2), 58.5 (CH_2), 70.9 (CH), 75.6 (CH), 127.6 (CH), 128.6 (CH), 129.6 (CH). $C_{24}H_{31}NO_2$ (365.51): calcd. C 77.86, H 8.55, N 3.83; found C 77.70, H 8.50, N 3.62.

(+)-(1*S*,3*R*,4*R*,5*S*,6*S*,7*S*)-7-((Dibenzylamino)methyl)-4-methylbicyclo[3.2.1]octane-3,6-diol ((+)-**13**): synthesized analogously to (-)-**13**; $[\alpha]_D^{20}$ = + 16 (*c* 0.26 MeOH). All spectroscopic data were similar to those of (-)-**13**. $C_{24}H_{31}NO_2$ (365.51): calcd. C 77.86, H 8.55, N 3.83; found C 77.93, H 8.62, N 3.87.

General procedure for debenzylation and crystallisation of aminodiols (-)-**7 or** (-)-**13**: A solution of aminodiols (-)-**7** or (-)-**13** (1.05 g, 2.88 mmol) in MeOH (5 mL) was added to a suspension of 5% Pd/C (225 mg) in MeOH (30 mL). The mixture was stirred under H_2 atmosphere for 12 h at room temperature. After the reaction was completed (monitored by means of TLC), the mixture filtered through a pad of Celite and the solvent was removed by reduced pressure. The crude product crystallized in Et_2O, resulting (-)-**9** or (-)-**14** as white crystals.

(-)-(1*S*,2*R*,5*R*,6*S*,7*R*)-6-(Aminomethyl)-2-methylbicyclo[3.2.1]octane-2,7-diol ((-)-**9**): 0.26 g (49%) ; white crystals; m.p. 210-220 °C; $[\alpha]_D^{20}$ = -31 (*c* 0.22 MeOH); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) 1.05-1.10 (m, 1H), 1.15-1.24 (m, 4H), 1.34 (d, *J* = 9.3 Hz, 1H), 1.54-1.62 (m, 2H), 1.85-1.90 (m, 1H), 1.96 (s, 1H), 2.11 (d, *J* = 11.4 Hz, 1H), 2.13-2.19 (m, 1H), 2.71 (dd, *J* = 6.4, 12.6 Hz, 1H), 2.97 (dd, *J* = 8.5, 12.6 Hz, 1H), 3.20-3.60 (brs, 4H), 4.38 (dd, *J* = 6.6, 10.4 Hz, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 23.4 (CH_2), 30.9 (CH_3), 31.0 (CH_2), 32.7 (CH_2), 35.1 (CH), 36.9 (CH_2), 42.0 (CH), 50.0 (CH), 70.3 (C_q), 70.5 (CH). $C_{10}H_{19}NO_2$ (185.26): calcd. C 64.83, H 10.34, N 7.56; found C 64.85, H 10.30, N 7.47.

(+)-(1*R*,2*S*,5*S*,6*R*,7*S*)-6-(Aminomethyl)-2-methylbicyclo[3.2.1]octane-2,7-diol ((+)-**9**): synthesized analogously to (-)-**9** from (+)-**7**; $[\alpha]_D^{20}$ = + 33 (*c* 0.22 MeOH). All spectroscopic data were similar to those of (-)-**9**. $C_{10}H_{19}NO_2$ (185.26): calcd. C 64.83, H 10.34, N 7.56; found C 64.89, H 10.38, N 7.39.

(-)-(1*R*,3*S*,4*S*,5*S*,6*R*,7*R*)-7-(Aminomethyl)-4-methylbicyclo[3.2.1]octane-3,6-diol ((-)-**14**): 0.37 g (70%); white crystals; m.p. 230-235 °C; $[\alpha]_D^{20}$ = -16 (*c* 0.25 MeOH); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) 1.10 (d, *J* = 6.9 Hz, 3H), 1.21-1.44 (m, 4H), 1.81-1.85 (m, 1H), 2.03-2.17 (m, 3H), 2.71-2.76 (m, 1H), 2.97-3.03 (m, 1H), 3.59-3.65 (m, 1H), 4.24 (d, *J* = 5.5 Hz, 1H), 4.40 (quin, 1H), 5.00 (d, *J* = 5.5 Hz, 1H), 7.94 (br s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 17.9 (CH_3), 35.8 (CH_2), 36.8 (CH), 37.1 (CH_2), 37.7 (CH_2), 42.3 (CH), 44.5 (CH), 45.3 (CH), 68.6 (CH), 72.1 (CH). $C_{10}H_{19}NO_2$ (185.26): calcd. C 64.83, H 10.34, N 7.56; found C 64.63, H 10.20, N 7.66.

(+)-(1*S*,3*R*,4*R*,5*R*,6*S*,7*S*)-7-(Aminomethyl)-4-methylbicyclo[3.2.1]octane-3,6-diol ((+)-**14**): synthesized analogously to (-)-**14** from (+)-**13**; $[\alpha]_D^{20}$ = + 19 (*c* 0.25 MeOH). All the spectroscopic data were similar to those of (-)-**14**. $C_{10}H_{19}NO_2$ (185.26): calcd. C 64.83, H 10.34, N 7.56; found: C 64.75, H 10.23, N 7.69.

Procedure for the debenzylation and crystallisation of compound (-)-**8**, (-)-**11** or (-)-**12**: To a suspension of palladium-on-carbon (5% Pd/C, 225 mg) in MeOH (30 mL), the tertiary aminoalcohol (-)-**8** (1.00, 2.88 mmol) or secondary aminoalcohol (-)-**11** or (-)-**12** (0.78, 2.88 mmol) was added, and the mixture was stirred under a H_2 atmosphere at room temperature and normal pressure for 8 h. When the reaction completed, the mixture was filtered through a Celite pad and the solution was evaporated to dryness. The crude product crystallized in Et_2O, resulting in the formation of compound (-)-**10** (0.34 g, 70%).

(-)-(1*S*,5*S*,6*R*,7*R*)-7-(Aminomethyl)-4-methylbicyclo[3.2.1]oct-3-en-6-ol ((-)-**10**): 0.34 g (70%) ; white crystals; m.p. 191-193 °C; $[\alpha]_D^{20}$ = -188 (*c* 0.25 MeOH); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm) 1.53-1.61 (m, 2H), 1.65 (d, *J* = 1.3 Hz, 3H), 1.87 (d, *J* = 18.2 Hz, 1H), 2.10-2.17 (m, 2H), 2.28-2.34 (m, 2H), 2.70-2.77 (m, 1H), 2.86-2.95 (m, 1H), 4.31-4.36 (m, 1H), 5.10 (d, *J* = 4.8 Hz, 1H), 5.15 (s, 1H), 7.74 (br s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 24.9 (CH_3), 29.1 (CH_2), 31.6 (CH_2), 34.6 (CH), 37.9 (CH_2), 40.9 (CH), 44.6 (CH), 75.3 (CH), 117.3 (CH), 139.3 (C_q). $C_{10}H_{17}NO$ (167.25): calcd. C 71.81, H 10.25, N 8.37; found C 71.63, H 10.20, N 8.15.

(+)-(1*R*,5*R*,6*S*,7*S*)-7-(Aminomethyl)-4-methylbicyclo[3.2.1]oct-3-en-6-ol ((+)-**10**): synthesized analogously to (-)-**10** ; $[\alpha]_D^{20}$ = + 223 (*c* 0.25 MeOH). All the spectroscopic data were similar to those of (-)-**10**. $C_{10}H_{17}NO$ (167.25): calcd. C 71.81, H 10.25, N 8.37; found C 71.89, H 10.36, N 8.21.

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Keywords: limonene • stereoselective •intramolecular cyclisation • 1,3-aminoalcohol • aminodiol

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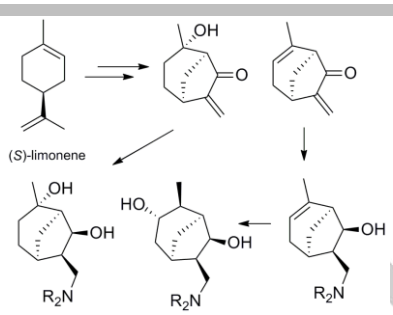
Entry for the Table of Contents

FULL PAPER

New bicyclic terpenoid tertiary, secondary and primary 1,3-aminoalcohols and aminodiols were prepared starting from (*S*)- and (*R*)-limonene. Intramolecular acylation of isoperillic acid resulted in methylene ketones which were converted to aminoalcohols and aminodiols via addition of amines, followed by stereoselective reduction of the *in situ* formed aminoketones.



Stereoselective synthesis of terpenoid aminoalcohols*

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

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