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Terpenoid Amino Alcohols

Stereoselective Synthesis of Limonene-Based Chiral 1,3-Amino Alcohols 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 reaction. The reaction was studied in detail, and was optimised for both compounds. The addition of secondary and primary amines to both keto alkenes followed by in-situ reduction of the resulting aminoketones with sodium borohydride gave new bicyclic terpenoid secondary and tertiary 1,3-amino alcohols and aminodiols with excellent diastereoselectivities. Regioisomeric aminodiols were prepared stereoselectively from the unsaturated 1,3-amino alcohols by hydroboration with $Me_2S{\cdot}BH_3$/H_2O_2.

Introduction

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

Chiral aminodiols, which combine the chemical properties of 1,2- and 1,3-amino alcohols, have also been widely used as chiral auxiliaries in enantioselective synthesis.[11–15] Moreover, they are also excellent building blocks for the synthesis of various heterocyclic compounds, through participation of specific hydroxy groups in ring closure reactions with the amino group. Aminodiols have been shown 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 hydroxy group with 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.); others show significant biological activity (aristeromycin, etc.).[11,17]

Monoterpene-based aminodiols have also been shown to be excellent starting materials for the synthesis of nucleoside analogues with remarkable activity as inhibitors of sodium/calcium exchangers (NCX).[18,19]

In this paper, we report the preparation of limonene-based chiral 1,3-amino alcohols and aminodiols, a new family of bi- and tri-functional terpenoids. The synthesis proceeds through stereoselective transformations, starting from commercially available (–)- and (+)-limonene.

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. Compound (–)-**1** was metallated by treatment with the strong base *n*-butyllithium/TMEDA (tetramethylethylene diamine),[20–22] followed by treatment with trimethoxyborane to produce a boron-substituted limonenyl derivative. The boron was then removed by treatment with hydrogen peroxide as an oxidising agent to produce (*S*)-*p*-mentha-1,8-dien-9-ol [(–)-**2**], with a hydroxy group at the 10-position. This metallation was not selective,[20] and (*S*)-perillyl-alcohol was also formed. Unfortunately, attempts to separate the regioisomeric alcohols were unsuccessful on a gram scale. Consequently, MnO_2 was used to oxidise the mixture of alcohols to (*S*)-perillaldehyde and (*S*)-*p*-mentha-1,8-dien-9-al [(–)-**3**]; these were easily separated by column chromatography. Compound (–)-**3** was then converted into carboxylic acid (–)-**4** by a literature method (Scheme 1).[23–25]

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 reac-

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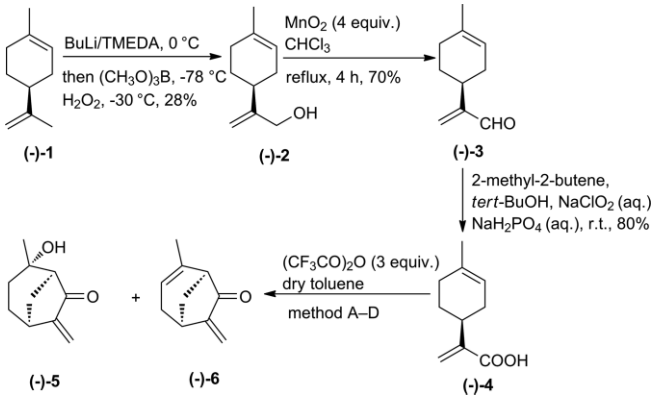


Scheme 1. Synthesis of bicyclic methylene ketones (–)-**5** and (–)-**6**.

tion[23,24] was observed. This gave two products: methylene ketone (–)-**6**, and its hydroxy-substituted analogue (–)-**5** (Scheme 1). It is interesting to note that although both keto alkenes are new compounds, cytotoxic kaurane-type natural diterpenoids have similar structures,[26] and a partially saturated analogue of **6** is 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), compound **5** was formed as the major product under kinetic control, whereas at 25 °C, the products were formed in a 1:1 ratio. In contrast, the thermodynamically preferred product **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, an acid catalyst, or acetic anhydride were tested, the reaction failed.

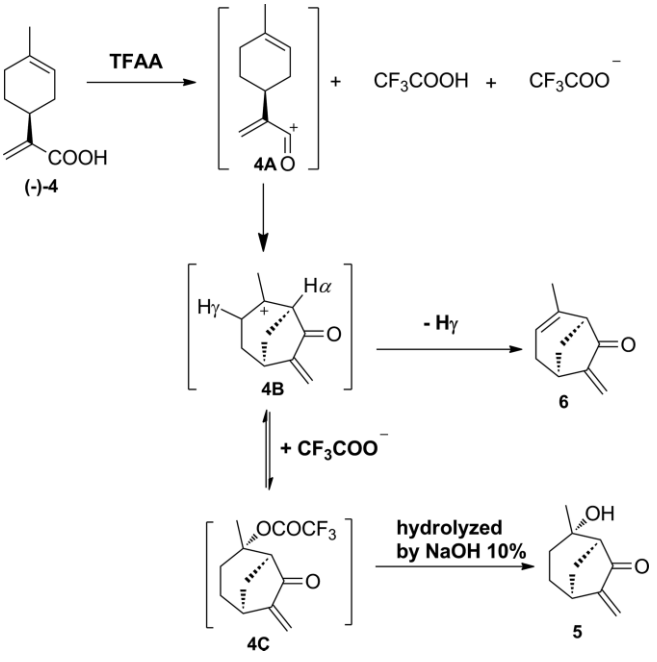
Table 1. Cyclisation reaction of (*S*)-isoperyllic acid (**4**).

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 spectroscopy. [b] Isolated, combined yield of **5** and **6**.

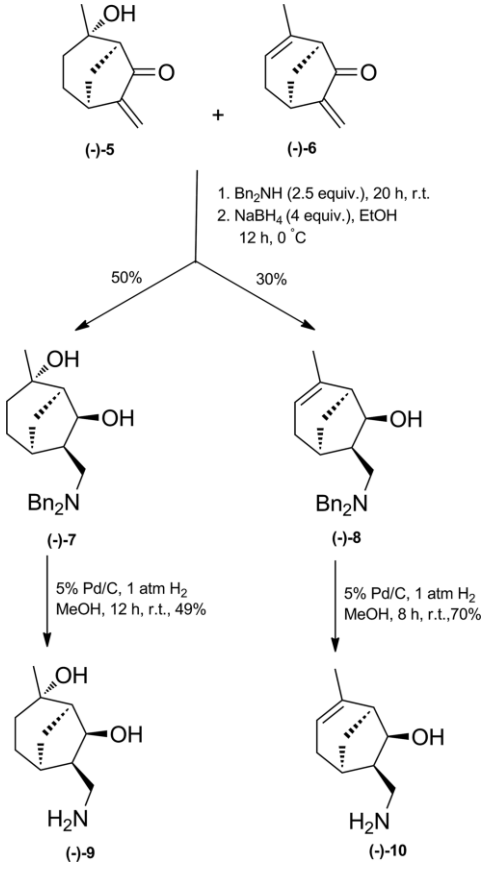
The reaction between the carboxylic acid and the double bond in the presence of TFAA can be interpreted by a mechanism involving a carbocation (Scheme 2).[28,29] In the first step, acylium ion **4A** is formed through attack of TFAA onto the carboxylic acid group. Intramolecular attack onto the olefinic bond then gives carbocation **4B**. This species 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]

The separation of (–)-**5** and (–)-**6** was difficult on a gram scale; therefore, 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 amino-



Scheme 2. Proposed mechanism of the intramolecular acylation reaction.

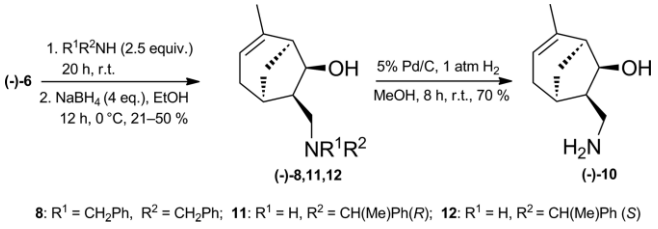
ketones were converted into tertiary aminodiol (–)-**7** and amino alcohol (–)-**8** by in-situ reduction with $NaBH_4$.[30] The two products obtained were easily separated by column chromatogra-



Scheme 3. Stereoselective synthesis of limonene-based amino alcohols and aminodiols.

phy as a result of their different polarities. Hydrogenolysis of these compounds over Pd/C in MeOH gave primary aminodiol (–)-**9** and amino alcohol (–)-**10** in moderate yields (Scheme 3).[23,24]

Subsequently, methylene ketone (–)-**6**, prepared by an optimised cyclisation reaction (Table 1) at 100 °C, was also treated with amines to try to use the presence of the ring system to affect the stereoselectivity of the addition. These reactions were highly stereoselective, and led to the formation of tertiary and secondary amino alcohols (–)-**8**, (–)-**11**, and (–)-**12** (Scheme 4).



8: $R^1 = CH_2Ph$, $R^2 = CH_2Ph$; **11**: $R^1 = H$, $R^2 = CH(Me)Ph(R)$; **12**: $R^1 = H$, $R^2 = CH(Me)Ph(S)$

Scheme 4. Stereoselective synthesis of amino alcohols.

The relative configurations of (–)-**8**, (–)-**11**, and (–)-**12** were determined by NOESY spectroscopic analysis. Clear NOE correlations were observed between 6-H and 8-H, 5-H, and 7-H, and between 1-H and 7-H. Therefore, the structures of **8**, **11**, and **12** were determined to be as shown in Figure 1.

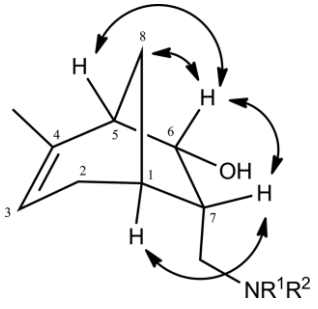


Figure 1. Determination of the configuration (–)-**8**, (–)-**11**, and (–)-**12** by NOESY analysis.

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

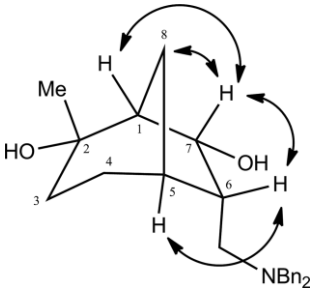
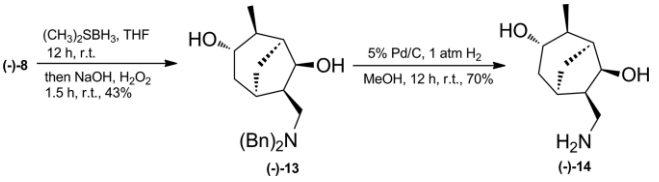


Figure 2. NOESY effects for the determination of the configuration of (–)-**7**.

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 spectroscopic analysis of the crude product). Our efforts failed to isolate the minor product; only the major product (–)-**13** was obtained after column chromatography. The configuration of the new stereogenic centres in (–)-**13** was determined by NMR spectroscopy, using NOESY experiments. Debenzylation with the H_2/Pd/C system and purification of the crude product gave aminodiol (–)-**14** in acceptable yield (Scheme 5).



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

NOESY analysis of (–)-**13** revealed considerable NOE effects between 7-H and 1-H and 6-H, between 6-H and 5-H, 7-H, and 8-H, between 5-H and 4-H, and between H-CH_3 and 3-H (Figure 3).

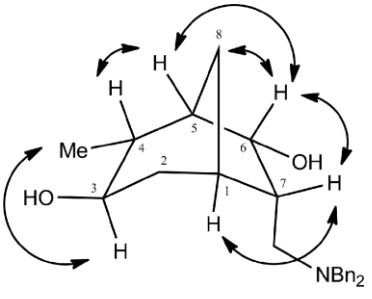


Figure 3. Determination of the structure of aminodiol (–)-**13** by NOESY analysis.

The procedure described above was repeated with (+)-limonene [(+)-**1**] to obtain enantiomeric counterparts (+)-**3**–(+)-**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 attack on the electrophilic acylium ion moiety by the olefinic bond. The cyclisation reaction was optimised for both products. Aza-Michael addition of secondary and primary amines onto methylene ketones resulted in aminodiols and 1,3-amino alcohols in highly stereoselective reactions. These compounds were used to prepare a new family of terpenoid amino alcohols and aminodiols with high diastereoselectivity.

Experimental Section

General Methods: ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance DRX 400 spectrometer [400 MHz (^{1}H) and 100 MHz (^{13}C), δ = 0 ppm (tetramethylsilane)]. Chemical shifts are expressed in ppm (δ) relative to tetramethylsilane, which was used as an internal reference. *J* values are given in Hz. Optical rotations were measured with a Perkin–Elmer 341 polarimeter. Melting points were determined with a Kofler apparatus. Microanalyses were carried out with a Perkin–Elmer 2400 elemental analyser. Chromatographic separations were carried out on Merck Kieselgel 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 [(–)-**1** and (+)-**1**] are available commercially from Merck Co. All chemicals and solvents were used as supplied. THF and toluene were dried with 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 consistent with literature data.[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 a solution of (–)-**3** (5.68 g, 37.8 mmol) and 2-methyl-2-butene (27.0 mL, 255.0 mmol) in *t*BuOH (50.0 mL) at room temperature. The mixture was stirred for 12 h. The solution was then concentrated under reduced pressure, and the residue was made alkaline with NaOH solution (10 % aq.; 200 mL). The mixture was extracted with *n*-hexane (3 × 100 mL). The aqueous phase was acidified with HCl solution (25 % aq.; pH = 3–4), and extracted with Et_2O (3 × 100 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 4:1) followed by recrystallisation (*n*-hexane) to give compound (–)-**4** (5.05 g, 80 %) as white crystals. M.p. 71–73 °C. $[\alpha]_D^{20}$ = –69 (*c* = 0.27, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.49–1.59 (m, 1 H), 1.66 (s, 3 H), 1.82–1.91 (m, 2 H), 1.93–1.98 (m, 1 H), 2.06–2.12 (m, 1 H), 2.22–2.26 (m, 1 H), 2.66–2.73 (m, 1 H), 5.40 (s, 1 H), 5.65 (s, 1 H), 6.34 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 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) ppm. $C_{10}H_{14}O_2$ (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]: Synthesised analogously to (–)-**4** starting from (+)-**3**. $[\alpha]_D^{20}$ = +65 (*c* = 0.27, MeOH). 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 Procedures for Acylation Reactions Between Olefins and Carboxylic Acids, Using TFAA as Catalyst

Method A: TFAA (8.0 mL, 57.5 mmol) was added to a solution of carboxylic acid (–)-**4** (3.1 g, 18.6 mmol) in dry toluene (70 mL) at 0 °C. The resulting solution was stirred for 48 h at 0 °C, and then the mixture was then diluted with toluene (100 mL), extracted with NaOH solution (10 % aq.; 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: TFAA (5.0 mL, 35.97 mmol) was added to a solution of (–)-**4** (2.0 g, 12.0 mmol) in dry toluene (45 mL). The mixture was heated at reflux for 6 h. When the reaction was complete, the mixture was diluted with toluene (70 mL), and extracted with NaOH solution (10 % aq.; 50 mL), then 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) to give 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 = 1.48–1.57 (m, 1 H), 1.64 (s, 3 H), 1.71–1.76 (m, 1 H), 1.83–1.88 (m, 1 H), 1.98–2.07 (m, 2 H), 2.19 (dd, *J* = 5.1, 15.5 Hz, 1 H), 3.13 (s, 1 H), 3.16–3.19 (m, 1 H), 5.37 (s, 1 H), 6.01 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 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) ppm. $C_{10}H_{14}O_2$ (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]: Synthesised analogously to (–)-**5** starting from (+)-**4**. $[\alpha]_D^{20}$ = +55 (*c* = 0.495, MeOH). 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 = 1.75–1.78 (m, 4 H), 1.90–1.95 (m, 1 H), 2.02–2.06 (m, 1 H), 2.55–2.62 (m, 1 H), 2.73 (d, *J* = 4.4 Hz, 1 H), 3.06 (t, *J* = 5.4 Hz, 1 H), 5.36 (br. s, 1 H), 5.47 (s, 1 H), 5.94 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 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) ppm. $C_{10}H_{12}O$ (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]: Synthesised analogously to (–)-**6** starting from (+)-**4**. $[\alpha]_D^{20}$ = +230 (*c* = 0.315, MeOH). 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** formed by method A (2.7 g) was mixed with dibenzylamine (9.0 mL, 46.8 mmol). The mixture was stirred for 20 h at room temperature. When TLC indicated that the reaction was complete, the mixture was dissolved in a mixture of dry EtOH (40 mL) and water (5 mL), and the solution was cooled to 0 °C. Solid $NaBH_4$ (2.7 g, 71.4 mmol) was added to the mixture in small portions, then the mixture was stirred overnight in an ice bath. The mixture was then quenched with water (100 mL), and extracted with CH_2Cl_2 (3 × 100 mL). The organic phase was dried (Na_2SO_4), and the solvents were evaporated in vacuo. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 19:1 to 2:1) to give compound (–)-**7** (2.0 g, 50 %) and compound (–)-**8** (0.58 g, 30 %).

Data for 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 = 1.09 (dd, *J* = 6.6, 14.3 Hz, 1 H), 1.16–1.22 (m, 2 H), 1.26 (s, 3 H), 1.28–1.36 (m, 1 H), 1.57–1.62 (m, 1 H), 1.91 (br. s, 1 H), 2.04–2.08 (m, 2 H), 2.36–2.42 (m, 2 H), 2.95 (t, *J* = 13.8 Hz, 1 H), 3.21 (d, *J* = 13.1 Hz, 2 H), 3.98 (d, *J* = 13.1 Hz, 2 H), 4.47 (dd, *J* = 6.6, 9.4 Hz, 1 H), 7.24–7.34 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 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) ppm. $C_{24}H_{31}NO_2$ (365.51): calcd. C 78.86, H 8.55, N 3.83; found C 78.68, H 8.60, N 3.60.

Data for 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 = 1.51–1.56 (m, 1 H), 1.61–1.64 (m, 4 H), 1.79–1.83 (d, *J* = 17.8 Hz, 1 H), 2.07–2.12 (m, 1 H), 2.20 (q, *J* = 4.7, 6.0 Hz, 1 H), 2.28 (t, *J* = 4.4 Hz, 1 H), 2.36–2.42 (m, 1 H), 2.48 (dd, *J* = 5.2, 11.9 Hz, 1 H), 2.93 (t, *J* = 12.0 Hz, 1 H), 3.42 (d, *J* = 13.6 Hz, 2 H), 3.77 (d, *J* = 13.6 Hz, 2 H), 4.31 (dd, *J* = 5.7, 9.3 Hz, 1 H), 5.02 (s, 1 H), 7.23–7.32 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 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) ppm. $C_{24}H_{29}NO$ (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]: Synthesised analogously to (–)-**7** starting from the mixture of (+)-**5** and (+)-**6**. $[\alpha]_D^{20}$ = +13 (*c* = 0.25, MeOH). 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]: Synthesised analogously to (–)-**8** starting from the mixture of (+)-**5** and (+)-**6**. $[\alpha]_D^{20}$ = +58 (*c* = 0.29, MeOH). 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 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) for 20 h at room temperature. When TLC indicated that the reaction was completed, the mixture was dissolved in a 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 then the mixture was stirred overnight in an ice bath. The mixture was then quenched with water (100 mL), and extracted with CH_2Cl_2 (3 × 100 mL). The organic phases were combined, washed with HCl solution (5 % aq.; 100 mL), and then dried (Na_2SO_4), and the solvents were evaporated in vacuo. The crude product was purified by recrystallisation (*n*-hexane/CH_2Cl_2) to give 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]: White crystals (1.48 g, 30 %). M.p. 108–185 °C. $[\alpha]_D^{20}$ = –71 (*c* = 0.27, MeOH). 1.48–1.64 (m, 4 H), 1.73 (s, 3 H), 1.93 (d, *J* = 6.2 Hz, 3 H), 2.08 (d, *J* = 17.8 Hz, 3 H), 2.30 (br. s, 2 H), 2.67 (br. s, 2 H), 2.97 (q, *J* = 12.0, 21.1 Hz, 1 H), 4.25 (br. s, 1 H), 4.65 (br. s, 1 H), 5.13 (s, 1 H), 7.37–7.45 (m, 3 H), 7.65–7.67 (m, 2 H), 8.64 (br. s, 1 H), 9.79 (br. s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 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) ppm. $C_{18}H_{25}NO$ (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]: Synthesised analogously to (–)-**11**. $[\alpha]_D^{20}$ = +76 (*c* = 0.27, MeOH). 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]: White crystals (1.04 g, 21 %). M.p. 108–184 °C. $[\alpha]_D^{20}$ = –131 (*c* = 0.34, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50–1.55 (m, 1 H), 1.61 (d, *J* = 13.9 Hz, 2 H), 1.63 (s, 3 H), 1.87 (d, *J* = 6.8 Hz, 3 H), 2.07–2.12 (m, 1 H), 2.24–2.31 (m, 2 H), 2.69–2.79 (m, 2 H), 2.98 (q, *J* = 9.8, 20.9 Hz, 1 H), 4.27–4.30 (m, 1 H), 4.57 (dd, *J* = 5.9, 9.2 Hz, 1 H), 5.00 (s, 1 H), 7.35–7.44 (m, 3 H), 7.52–7.55 (m, 2 H), 8.56 (br. s, 1 H), 9.79 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 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) ppm. $C_{18}H_{25}NO$ (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]: Synthesised analogously to (–)-**12**. $[\alpha]_D^{20}$ = +141.7 (*c* = 0.34, MeOH). 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]: $(CH_3)_2S{\cdot}BH_3$ (700 µL) was added to a cooled (0 °C) solution of (–)-**8** (1 g, 2.88 mmmol) in dry THF (30 mL) under an argon atmosphere. The mixture was stirred overnight at room temperature. The resulting solution was then treated with NaOH (3 M aq.; 3 mL) and hydrogen peroxide solution (30 % aq.; 3 mL), and diluted with 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 × 100 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (*n*-hexane/EtOAc, 9:1 to 2:1) to give (–)-**13** (0.45 g, 43 %) as white crystals. M.p. 191–193 °C. $[\alpha]_D^{20}$ = –14 (*c* = 0.26, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10 (d, *J* = 6.9 Hz, 3 H), 1.26–1.46 (m, 5 H), 1.76–1.83 (m, 1 H), 2.00–2.05 (m, 1 H), 2.20–2.23 (m, 1 H), 2.30–2.37 (m, 1 H), 2.41 (dd, *J* = 5.3, 12.4 Hz, 1 H), 3.02 (t, *J* = 12.6 Hz, 1 H), 3.28 (d, *J* = 12.8 Hz, 2 H), 3.44–3.51 (m, 1 H), 3.94 (d, *J* = 13.1 Hz, 2 H), 4.47 (dd, *J* = 6.6, 9.5 Hz), 7.25–7.35 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 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) ppm. $C_{24}H_{31}NO_2$ (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]: Synthesised analogously to (–)-**13**. $[\alpha]_D^{20}$ = +16 (*c* = 0.26, MeOH). 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 and (–)-13: A solution of aminodiol (–)-**7** or (–)-**13** (1.05 g, 2.88 mmol) in MeOH (5 mL) was added to a suspension of Pd/C (5 %; 225 mg) in MeOH (30 mL). The mixture was stirred under a hydrogen atmosphere for 12 h at room temperature. When TLC showed that the reaction was complete, the mixture was filtered through a pad of Celite, and the solvent was removed under reduced pressure. The crude product crystallised from Et_2O to give (–)-**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]: White crystals (0.26 g, 49 %). M.p. 210–220 °C. $[\alpha]_D^{20}$ = –31 (*c* = 0.22, MeOH). ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 1.05–1.10 (m, 1 H), 1.15–1.24 (m, 4 H), 1.34 (d, *J* = 9.3 Hz, 1 H), 1.54–1.62 (m, 2 H), 1.85–1.90 (m, 1 H), 1.96 (s, 1 H), 2.11 (d, *J* = 11.4 Hz, 1 H), 2.13–2.19 (m, 1 H), 2.71 (dd, *J* = 6.4, 12.6 Hz, 1 H), 2.97 (dd, *J* = 8.5, 12.6 Hz, 1 H), 3.20–3.60 (br. s, 4 H), 4.38 (dd, *J* = 6.6, 10.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 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) ppm. $C_{10}H_{19}NO_2$ (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]: Synthesised analogously to (–)-**9** starting from (+)-**7**. $[\alpha]_D^{20}$ = +33 (*c* = 0.22, MeOH). 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]: White crystals (0.37 g, 70 %). M.p. 230–235 °C. $[\alpha]_D^{20}$ = –16 (*c* = 0.25, MeOH). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.10 (d, *J* = 6.9 Hz, 3 H), 1.21–1.44 (m, 4 H), 1.81–1.85 (m, 1 H), 2.03–2.17 (m, 3 H), 2.71–2.76 (m, 1 H), 2.97–3.03 (m, 1 H), 3.59–3.65 (m, 1 H), 4.24 (d, *J* = 5.5 Hz, 1 H), 4.40 (quin, 1 H), 5.00 (d, *J* = 5.5 Hz, 1 H), 7.94 (br. s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 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) ppm. $C_{10}H_{19}NO_2$ (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]: Synthesised analogously to (–)-**14** starting from (+)-**13**. $[\alpha]_D^{20}$ = +19 (*c* = 0.25, MeOH). 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 Compounds (–)-8, (–)-11, and (–)-12: Pd/C (5 %; 225 mg) was suspended in MeOH (30 mL), and tertiary amino alcohol (–)-**8** (1.00, 2.88 mmol) or secondary amino alcohol (–)-**11** or (–)-**12** (0.78, 2.88 mmol) was added. The mixture was stirred under a hydrogen atmosphere at room temperature and atmospheric pressure for 8 h. When the reaction was complete, the mixture was filtered through a Celite pad, and the solvent was evaporated to dryness. The crude product crystallised from Et$_2$O to give 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]: White crystals (0.34 g, 70 %). M.p. 191–193 °C. $[\alpha]_D^{20}$ = –188 (*c* = 0.25, MeOH). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.53–1.61 (m, 2 H), 1.65 (d, *J* = 1.3 Hz, 3 H), 1.87 (d, *J* = 18.2 Hz, 1 H), 2.10–2.17 (m, 2 H), 2.28–2.34 (m, 2 H), 2.70–2.77 (m, 1 H), 2.86–2.95 (m, 1 H), 4.31–4.36 (m, 1 H), 5.10 (d, *J* = 4.8 Hz, 1 H), 5.15 (s, 1 H), 7.74 (br. s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 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$_q$) ppm. $C_{10}H_{17}NO$ (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]: Synthesised analogously to (–)-**10**. $[\alpha]_D^{20}$ = +223 (*c* = 0.25, MeOH). 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: Terpenoids · Stereoselective synthesis · Chiral pool · Cyclization · Amino alcohols · Fused-ring systems

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