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Stereoselective synthesis of new monoterpene β-amino alcohols

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ABSTRACT

The regio- and stereoselective osmium-catalysed aminohydroxylation of (+)-2-carene (99% ee), and (+)-3-carene (99% ee), (−)-β-pinene (99% ee) and (−)-camphene (75% ee) with chloramine-T is described. The products β-hydroxy-*p*-toluenesulfonamides were reduced with sodium in liquid ammonia to give the corresponding β-amino alcohols with 48–83% yields. The methylation-reduction of β-hydroxy-*p*-toluenesulfonamides gave β-methylamino alcohols with 33–55% yields.

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1. Introduction

β-Amino alcohols are important physiologically active compounds,[1] for example, β-blockers,[2] selective HIV protease inhibitors[3] and antibiotics.[4] They are also used as chiral auxiliaries and ligands in asymmetric synthesis.[5–14] Several synthetic methods leading to β-amino alcohols are known, for example, the reaction of aziridines with oxygen nucleophiles,[15] and epoxides with nitrogen nucleophiles,[16] the reduction and addition of organometallics to α-amino acids,[1] and aminohydroxylation of olefins.[17–24]

β-Amino alcohols derived from (−)-α-pinene, and camphor-derived DAIB are chiral auxiliaries and ligands.[25] Recently, amino alcohols prepared from (−)-α-pinene and (−)-β-pinene were employed in a highly enantioselective reduction of ketones,[5,26] and the addition of diethylzinc to benzaldehyde.[27] Herein we undertook the synthesis of new β-amino alcohols and β-methylamino alcohols from (+)-2- and (+)-3-carene, (−)-β-pinene, and (−)-camphene by aminohydroxylation.

Recently, Pinheiro[28] reported the reaction of (−)-camphene, (−)-α- and (−)-β-pinene with a stoichiometric amount of the imido-osmium compound *t*-BuN=OsO_3, and with chloramine-T trihydrate in the presence of osmium tetroxide. However, the products β-hydroxy-*p*-toluenesulfonamides, obtained with high regio- and stereoselectivity, were not transformed into the corresponding β-amino alcohols.

2. Results and discussion

(+)-3-Carene **1**, 99% ee; (+)-2-carene **2**, 99% ee; (−)-β-pinene **3**, 99% ee and (−)-camphene **4**, 75% ee were used for the study. (−)-β-Pinene, 99% ee, was prepared from commercial (−)-α-pinene, 99% ee, by a literature procedure.[29] First, the aminohydroxylation of 1-methylcyclohexene, reported earlier by Sharpless,[19] was tested as a model reaction to determine the best reaction conditions. Changing the solvent, temperature, time and catalyst loading, we found that the reaction of 1-methylcyclohexene with chloramine-T in *tert*-butanol–water, 5:1 in the presence of 0.4 mol % of osmium tetroxide, after 18 h at reflux, gave the product in 78% yield. The yield was slightly lower when compared to the reported 82% yield obtained in *tert*-butanol after much longer time (96 h) and higher catalyst loading.[19] Considering our reaction conditions appropriate for the aminohydroxylation of the selected terpenes, their reactivity was examined and the following order was found: 2-carene < 3-carene < 1-methylcyclohexene. Consequently, in the aminohydroxylation reactions of carenes the catalyst loading was increased to 1 mol %.

The aminohydroxylation of (+)-3-carene **1** with chloramine-T under the conditions described above produced β-hydroxy-*p*-toluenesulfonamide **5** in 68% yield. Its reduction with sodium in liquid ammonia gave β-amino alcohol **6** in 72% yield. The reaction of **5** with methyl iodide in the presence of potassium carbonate in *N*,*N*-dimethylformamide gave **7** in 89% yield. The *N*-methylated-*p*-toluenesulfonamide group was reduced with sodium in liquid ammonia and *N*-methyl-β-amino alcohol **8** was obtained in 67% yield (Scheme 1). The β-hydroxy-*p*-toluenesulfonamides **5**, **7** and *cis*-β-amino alcohols **6**, **8** were easily isolated by column chromatography. Their structures were confirmed by ^{1}H, ^{13}C, HETCOR and COSY NMR analysis. A monocrystal of **7** was obtained and its X-ray analysis showed the *cis*-position of the hydroxyl and *N*-methyl-*p*-toluenesulfonamido group (Fig. 1).[30] The spectroscopic data and specific rotation of **6** were identical with an authentic sample, prepared by an independent much longer procedure.[31]

The same methodology was applied to (+)-2-carene **2** (99% ee), which was transformed into the corresponding β-hydroxy-*p*-toluenesulfonamide **9** in 48%. The lower yield when compared to the reaction of (+)-3-carene is probably due to higher steric hindrance of the double bond adjacent to the *gem*-dimethyl substituted cyclopropane ring. β-Hydroxy-*p*-toluenesulfonamide **9** was transformed into *cis*-β-amino alcohol **10**, 48% yield, and its *N*-methyl

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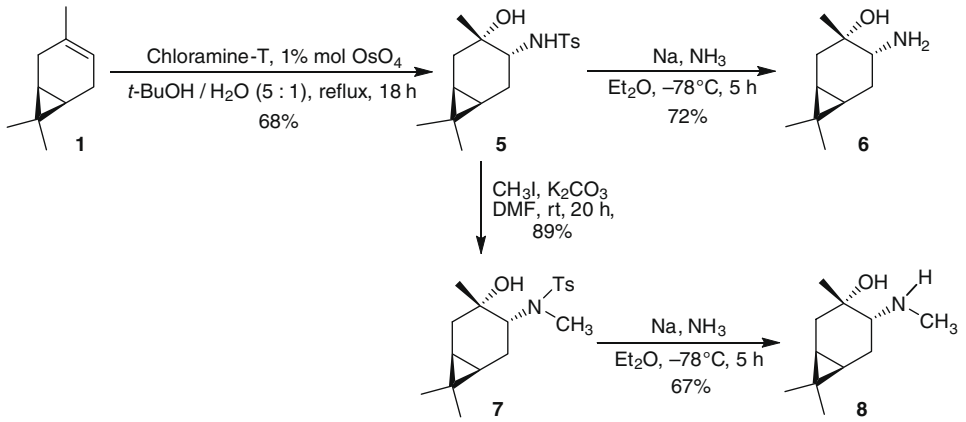


Scheme 1. Stereoselective osmium-catalysed aminohydroxylation of (+)-3-carene.

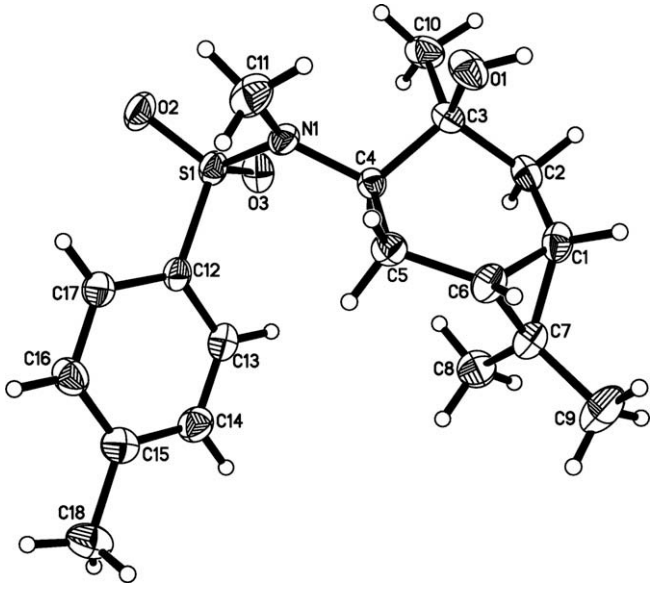


Figure 1. X-ray crystal structure of **7**.

derivative **12**, 55% yield, by the reduction and methylation-reduction, respectively, following the same procedures as described for **6** and **8** (Table 1). The structure of β-hydroxy-*N*-methyl-*p*-toluenesulfonamide **11** was established by X-ray analysis (Fig. 2).[32]

Aminohydroxylation of (−)-β-pinene **3** produced the corresponding β-hydroxy-*p*-toluenesulfonamide **13** in 73% yield, higher compared to the carenes. The product was transformed with β-amino alcohol **14** in 58% yield. Methylation of **13** produced the *N*-methyl derivative **15** in a quantitative yield. Removal of the tosyl group gave β-methylamino alcohol **16** in 37% yield. (Table 1) The structure of **13**, as established by X-ray analysis[33] (Fig. 3), enables the same structural assignment of its derivatives **14**–**16**.

The aminohydroxylation of (−)-camphene **4** (75% ee), carried out in the same manner as described above, produced the corresponding β-hydroxy-*p*-toluenesulfonamide **17** in 60% yield. The product was further transformed into the corresponding β-amino alcohol **18** and its *N*-methyl derivative **20** (Table 1). Crystals of **17** could not be obtained, and its structure is based on ^{1}H, ^{13}C and HETCOR NMR analysis. All β-hydroxy-*p*-toluenesulfonamides and β-amino alcohols could be easily isolated by column chromatography.

3. Conclusions

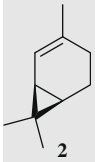
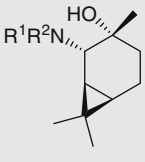
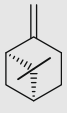
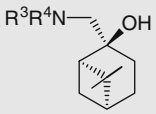
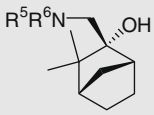
A convenient stereoselective synthesis of β-amino alcohols and β-methylamino alcohols of high enantiomeric purity by osmium-catalysed aminohydroxylation of (+)-3-carene, (+)-2-carene and (−)-β-pinene has been developed. (−)-Camphene (75% ee) has also been transformed into the corresponding β-amino alcohols. The following reactivity order of trisubstituted double bonds in this reaction was observed: 2-carene < 3-carene < 1-methylcyclohexane.

4. Experimental

4.1. General

All experiments were carried out under an air atmosphere. Reagents were generally of the best quality commercial grade

Table 1
Stereoselective osmium-catalysed aminohydroxylation of **2–4**

Olefin	Product, yield (%)	Olefin	Product, yield (%)	Olefin	Product, yield (%)
 **2**		 **3**		 **4**	
	9: R^1 = H, R^2 = Ts,48% **10**: R^1 = H, R^2 = H, 48% **11**: R^1 = Me, R^2 = Ts, 42% **12**: R^1 = Me, R^2 = H, 55%		**13**: R^3 = H, R^4 = Ts, 73% **14**: R^3 = H, R^4 = H, 58% **15**: R^3 = Me, R^4 = Ts, 99% **16**: R^3 = Me, R^4 = H, 37%		**17**: R^5 = H, R^6 = Ts, 60% **18**: R^5 = H, R^6 = H, 83% **19**: R^5 = Me, R^6 = Ts, 99% **20**: R^5 = Me, R^6 = H, 33%

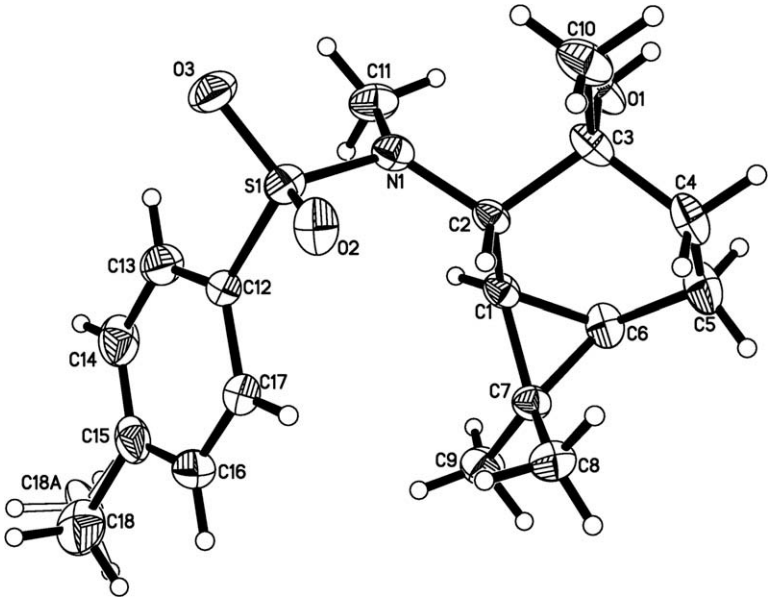


Figure 2. X-ray crystal structure of **11**.

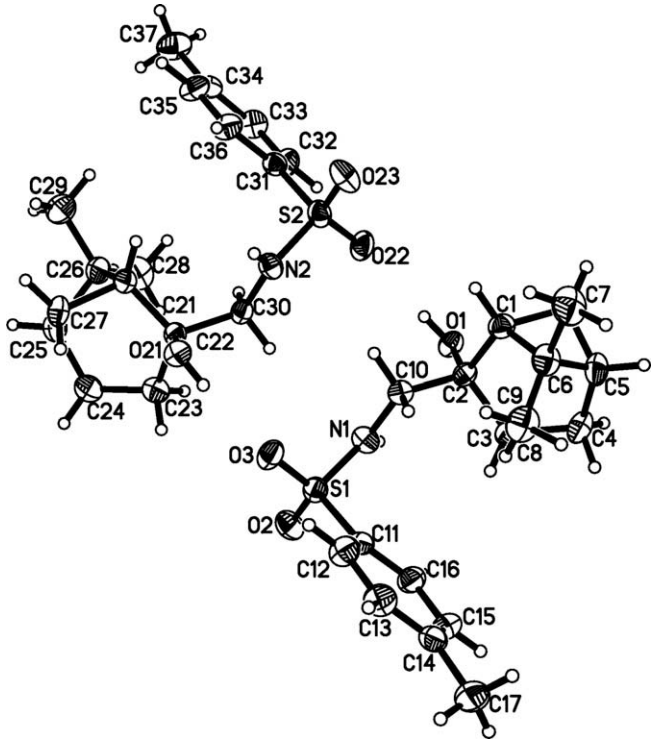


Figure 3. X-ray crystal structure of **13**.

and used without further purification. ^{1}H, ^{13}C, HETCOR and COSY NMR spectra were recorded on a Varian Gemini 200 multinuclear instrument and on a Bruker AMX 300 MHz instrument. MS spectra were recorded on an AMD 604 spectrometer. Optical rotations were measured on a PolAAr 3000 automatic polarimeter. GC analyses were performed on a Perkin-Elmer AutoSystem XL chromatograph. Melting points were determined in open glass capillaries and are uncorrected. Elemental analyses and HRMS were performed by Microanalysis Laboratory, Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw. The X-ray data were collected at 293(2) K with the Oxford Sapphire CCD diffractometer, graphite monochromator, Mo Kα radiation (λ = 0.71073 Å). The structure was solved by direct methods and refined with the full-matrix least-squares on F^2 with the use of SHELX-97.[34] Non-hydrogen atoms were refined anisotropically, while hydrogen atoms were constrained as riding atoms. The numerical absorption correction was applied.[35] The absolute configuration was determined by the Flack method.[36]

4.2. Materials

Silica Gel 60, E. Merck 230–400 mesh, was used for preparative column chromatography. Analytical TLC was performed using Macherey-Nagel Polygram Sil G/UV_{254} 0.2 mm plates. (1*S*,6*R*)-(+)-3-Carene (99% ee), (1*S*,6*R*)-(+)-2-carene (99% ee), (1*S*,5*S*)-(−)-α-pinene (99% ee), (1*S*,4*S*)-(−)-camphene (75% ee), chloramine-T trihydrate, osmium tetroxide were commercial materials. (−)-β-Pinene (99% ee) was prepared according to the literature.[29]

4.3. *N*-((1*R*,3*R*,4*S*,6*S*)-4-Hydroxy-4,7,7-trimethylbicyclo[4.1.0]heptan-3-yl)-4-methylbenzene-sulfonamide 5. Typical procedure

Chloramine-T trihydrate (8.50 g, 31.3 mmol) and osmium tetroxide catalyst (2.5 ml, 0.25 mmol, 0.1 M solution in *tert*-butyl alcohol) were added to a stirred solution of (+)-3-carene **2** (3.41 g, 25 mmol) in *tert*-butyl alcohol (25 ml) and water (5 ml), and then the reaction mixture was stirred at reflux for 18 h. The reaction mixture was cooled to room temperature and sodium borohydride (0.40 g) was added, and the resulting solution was stirred for 1 h at room temperature. Solvents were removed in vacuo and the oily residue was extracted with ethyl acetate (3 × 70 ml), washed with a 1% solution of sodium hydroxide in brine (50 ml) and with brine (2 × 50 ml), dried over anhydrous magnesium sulfate and concentrated. The crude product was purified on silica gel column chromatography (230–400 mesh) using (*n*-hexan/ethyl acetate, 3:2): 5.47 g, 68%; mp 45–48 °C, $[\alpha]_D^{20} = +34.5$ (*c* 1.5, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 0.59 (td, *J* = 4.5 Hz, *J* = 9.0 Hz, 1H, CH), 0.68 (td, *J* = 1.2 Hz, *J* = 9.0 Hz, 1H, CH), 0.85 (s, 3H, CH_3), 0.94 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.27 (dd, *J* = 4,5 Hz, *J* = 15.6 Hz, 1H, CH_2), 1.50–1.69 (m, 2H, CH_2), 1.87 (s, 1H, OH), 2.05 (dd, *J* = 9.6 Hz, *J* = 15.6 Hz, 1H, CH_2),

2.42 (s, 3H, CH_3), 2.82 (td, J = 7.8 Hz, J = 9.9 Hz, 1H, CH), 4.84 (d, J = 9.6 Hz, 1H, NH), 7.28 (m, 2H, CH), 7.73 (m, 2H, CH); ^{13}C NMR (200 MHz, $CDCl_3$) δ (ppm): 14.91 (CH_3), 15.84 (CH_3), 21.46 (CH_3), 28.44 (CH_3), 25.61 (CH_2), 34.14 (CH_2), 20.46 (CH), 25.99 (CH), 56.95 (CH), 126.73 (2CH), 129.55 (2CH), 17.40 (C), 69.68 (C), 138.77 (C), 143.00 (C). Anal. Calcd for $C_{17}H_{25}NO_3S$: C, 63.13; H, 7.79; N, 4.33; S, 9.91. Found: C, 63.05; H, 7.72; N, 4.41; S, 9.82.

4.4. (1*S*,3*S*,4*R*,6*R*)-4-Amino-3,7,7-trimethylbicyclo[4.1.0]heptan-3-ol 6. Typical procedure

A solution of **5** (3.45 g, 10 mmol) in dry ethyl ether (50 ml) was added to liquid ammonia (250 ml) at −78 °C after which sodium (3.00 g) was added in portions. The reaction mixture was stirred for 5 h at −78 °C and then was left overnight. The residue was quenched with water (100 ml) and methanol (50 ml), extracted with ethyl ether (4 × 100 ml), dried over anhydrous magnesium sulfate and concentrated. The crude product was purified on silica gel column chromatography (230–400 mesh) using (dichloromethane/methanol, 1:1, 2.5% triethylamine): 1.30 g, 72%; mp 65–69 °C, $[\alpha]_D^{20} = +12.5$ (c 3.2, $CHCl_3$). ^{1}H, ^{1}H × ^{1}H COSY NMR (300 MHz, $CDCl_3$) δ (ppm) (subscript c or t means, that proton is *cis* or *trans* to the dimethyl bridge): 0.56 (td, J = 4.5 Hz, J = 9.1 Hz, 1H, CH_{6t}), 0.68 (t, J = 8.7 Hz, 1H, CH_{1t}), 0.83 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.08 (dd, J = 4.5 Hz, J = 15.6 Hz, 1H, CH_2, H_{5c}), 1.45 (ddd, J = 8.7 Hz, J = 10.5 Hz, J = 14.7 Hz, 1H, CH_2, H_{2c}), 1.80 (dd, J = 6.9 Hz, J = 14.7 Hz, 1H, CH_2, H_{2t}), 1.99 (dd, J = 9.3 Hz, J = 15.6 Hz, 1H, CH_2, H_{5t}), 2.08 (br s, 3H, OH, NH_2), 2.24 (dd, J = 6.9 Hz, J = 10.5 Hz, 1H, CH, H_{3c}); ^{13}C NMR (200 MHz, $CDCl_3$) δ (ppm): 15.05 (CH_3), 25.85 (CH_3), 28.59 (CH_3), 26.23 (CH_2), 32.92 (CH_2), 16.53 (CH), 20.39 (CH), 53.37 (CHN), 17.06 (C), 69.17 (C); HETCOR ^{1}H × ^{13}C NMR cross peaks: 0.56 (td)—16.53 (CH), 0,68 (t)—20.39 (CH), 0.83 (s)—15.05 (CH_3), 0.92 (s)—28.59 (CH_3), 1.05 (s)—25.85 (CH_3), 1.08 (dd)—32.92 (CH_2), 1.45 (ddd)—26.23 (CH_2), 1.80 (dd)—26.23 (CH_2), 1.99 (dd)—32.92 (CH_2), 2.24 (dd)—53.37 (CHN). MS: EI 70 eV, *m/z* 124 (52.89), 111 (37.34), 96 (38.72), 84 (30.90), 73 (100.00), 44 (48.36), 41 (39.91); HRMS (EI) calcd for $C_{10}H_{19}NO$: 169.14666, found 169.14640.

4.5. *N*-((1*R*,3*R*,4*S*,6*S*)-4-Hydroxy-4,7,7-trimethylbicyclo[4.1.0]heptan-3-yl)-*N*-4-dimethylbenzene-sulfonamide 7. Typical procedure

Methyl iodide (1.60 g, 1.2 mmol) and potassium carbonate (2.20 g, 13.9 mmol) were added to the solution of **5** (3.00 g, 9.3 mmol) in dry *N*,*N*-dimethylformamide (30 ml). The reaction mixture was stirred for 20 h at room temperature and then filtered through Celite pad and concentrated to dryness. To the crude product water (50 ml) was added. Then the product was extracted with ethyl acetate (2 × 50 ml), dried over anhydrous magnesium sulfate and concentrated. The crude product was purified on silica gel column chromatography (230–400 mesh) using (*n*-hexane/ethyl acetate, 3:2): 2.77 g, 89%; mp 153–155 °C, $[\alpha]_D^{20} = +64.5$ (c 2.0, $CHCl_3$). Crystals of this product could be obtained by slow evaporation of *n*-pentane/diethyl ether solution. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 0.58 (td, J = 4.4 Hz, J = 9.2 Hz, 1H, CH), 0.72 (t, J = 8.8 Hz, 1H, CH), 0.96 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.20 (dd, J = 7.0 Hz, J = 14.2 Hz, 1H, CH_2), 1.35 (dd, J = 4.6 Hz, J = 15.2 Hz, 1H, CH_2), 1.82 (s, 1H, OH), 1.84 (ddd, J = 7.6 Hz, J = 12.0 Hz, J = 14.2 Hz, 1H, CH_2), 1.98 (dd, J = 9.4 Hz, J = 15.6 Hz, 1H, CH_2), 2.41 (s, 3H, CH_3), 2.89 (s, 3H, CH_3), 3.48 (dd, J = 7.0 Hz, J = 12.2 Hz, 1H, CH), 7.27 (m, 2H, CH), 7.33 (m, 2H, CH); ^{13}C NMR (200 MHz, $CDCl_3$) δ (ppm): 14.85 (CH_3), 21.44 (CH_3), 25.67 (CH_3), 28.85 (CH_3), 29.72 (CH_3), 18.54 (CH_2), 36.28 (CH_2), 16.56 (CH), 20.64 (CH), 59.18 (CH), 126.91 (2CH), 129.52 (2CH), 17.98 (C), 71.08 (C), 137.25 (C), 142.90 (C). Anal. Calcd for $C_{18}H_{27}NO_3S$: C, 64.06; H, 8.06; N, 4.15; S, 9.50. Found: C, 64.15; H, 8.01; N, 4.31; S, 9.38.

4.6. (1*S*,3*S*,4*R*,6*R*)-3,7,7-Trimethyl-4-(methylamino)bicycl [4.1.0] heptan-3-ol 8

This compound was prepared from **7** as described above: 1.37 g, 67%; mp 69–71 °C, $[\alpha]_D^{20} = -29.9$ (c 2.5, $CHCl_3$). ^{1}H, ^{1}H × ^{1}H COSY NMR (300 MHz, $CDCl_3$) δ (ppm) (subscript c or t means, that proton is *cis* or *trans* to the dimethyl bridge): 0.63 (td, J = 4.5 Hz, J = 9.3 Hz, 1H, CH, H_{6t}), 0.71 (td, J = 1.5 Hz, J = 9.3 Hz, 1H, CH, H_{1t}), 0.88 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 1.11 (dd, J = 4.5 Hz, J = 15.3 Hz, 1H, CH_2, H_{5c}), 1.13 (s, 3H, CH_3), 1.53 (ddd, J = 7.8 Hz, J = 9.6 Hz, J = 14.1 Hz, 1H, CH_2, H_{2c}), 1.84 (ddd, J = 1.5 Hz, J = 6.6 Hz, J = 14.1 Hz, 1H, CH_2, H_{2t}), 1.96–2.04 (m, 4H, CH, CH_2, NH, OH, H_{5t}, H_{3c}), 2.38 (s, 3H, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 15.22 (CH_3), 27.46 (CH_3), 28.62 (CH_3), 34.92 (CH_3), 23.96 (CH_2), 33.12 (CH_2), 16.82 (CH), 19.93 (CH), 61.86 (CHN), 17.21 (C), 69.42 (C); HETCOR ^{1}H × ^{13}C NMR cross peaks: 0.63 (td)—16.82 (CH), 0.71 (td)—19.93 (CH), 0.88 (s)—15.22 (CH_3), 0.97 (s)—28.62 (CH_3), 1.11 (dd)—33.12 (CH_2), 1.13 (s)—27.46 (CH_3), 1.53 (ddd)—23.96 (CH_2), 1.84 (ddd)—23.96 (CH_2), 1.96–2.04 (m)—33.12 (CH_2), 61.86 (CHN), 2.38 (s)—34.92 (CH_3); MS: EI 70 eV, *m/z* 138 (71.76), 125 (46.31), 124 (47.44), 110 (49.07), 87 (100.00), 57 (31.35), 44 (80.65), 43 (37.54), 41 (30.19). HRMS (EI) calcd for $C_{11}H_{21}NO$: 183.16231, found 183.16298.

4.7. *N*-((1*S*,2*S*,3*R*,6*R*)-3-Hydroxy-3,7,7-trimethylbicyclo[4.1.0] heptan-2-yl)-4-methylbenzene-sulfonamide 9

This compound was prepared from **2** as described above: 48%; mp 157–160 °C, $[\alpha]_D^{20} = +48.7$ (c 1.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.10 (dd, J = 3.6 Hz, J = 9.3 Hz, 1H, CH), 0.56 (s, 3H, CH_3), 0.59 (t, J = 8.1 Hz, 1H, CH), 0.80 (s, 3H, CH_3), 1.11 (ddd, J = 7.8 Hz, J = 12.3 Hz, J = 14.7 Hz, 1H, CH_2), 1.26 (s, 3H, CH_3), 1.50–1.64 (m, 2H, CH_2), 1.74 (s, 1H, OH), 1.78–1.92 (m, 1H, CH_2), 2.40 (s, 3H, CH_3), 2.80 (dd, J = 3.6 Hz, J = 10.2 Hz, 1H, CH), 5.13 (d, J = 11,1 Hz, 1H, NH), 7.30 (m, 2H, CH), 7.77 (m, 2H, CH); ^{13}C NMR (200 MHz, $CDCl_3$) δ (ppm): 14.61 (CH_3), 21.38 (CH_3), 26.18 (CH_3), 28.17 (CH_3), 14.72 (CH_2), 35.23 (CH_2), 19.66 (CH), 26.08 (CH), 54.70 (CH), 127.10 (2CH), 129.52 (2CH), 17.15 (C), 70.03 (C), 138.86 (C), 142.97 (C). Anal. Calcd for $C_{17}H_{25}NO_3S$: C, 63.13; H, 7.79; N, 4.33; S, 9.91. Found: C, 63.02; H, 7.74; N, 4.45; S, 9.87.

4.8. (1*S*,2*S*,3*R*,6*R*)-2-Amino-3,7,7-trimethylbicyclo[4.1.0]heptan-3-ol 10

This compound was prepared from **9** as described above: 48%; mp 58–60 °C, $[\alpha]_D^{20} = -8.4$ (c 2.7, $CHCl_3$). ^{1}H, ^{1}H × ^{1}H COSY NMR (300 MHz, $CDCl_3$) δ (ppm) (subscript c or t means, that proton is *cis* or *trans* to the dimethyl bridge): 0.24 (dd, J = 9.3 Hz, J = 3.6 Hz, 1H, CH, H_{1t}), 0.69 (t, J = 9.0 Hz, 1H, CH, H_{6t}), 0.92 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 0.95–1.07 (m, 1H, CH_2, H_{4c}), 1.10 (s, 3H, CH_3), 1.51 (ddt, J = 1.2 Hz, J = 7.5 Hz, J = 14.7 Hz, 1H, CH_2, H_{5c}), 1.58 (ddd, J = 1.5 Hz, J = 8.1 Hz, J = 14.1 Hz, 1H, CH_2, H_{4t}), 1.83–1.98 (m, 1H, CH_2, H_{5t}), 2.12 (br s, 3H, OH, NH_2), 2.35 (d, J = 3.6 Hz, 1H, CH); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 15.11 (CH_3), 26.29 (CH_3), 29.16 (CH_3), 15.09 (CH_2), 34.38 (CH_2), 19.88 (CH), 26.57 (CH), 51.69 (CHN), 16.83 (C), 68.88 (C); HETCOR ^{1}H × ^{13}C NMR cross peaks: 0.24 (dd)—26.57 (CH), 0.69 (t)—19.88 (CH), 0.92 (s)—15.11 (CH_3), 1.01 (s)—29.16 (CH_3), 0.95–1.07 (m)—34.38 (CH_2), 1.10 (s)—26.29 (CH_3), 1.51 (ddt)—15.09 (CH_2), 1.58 (ddd)—34.38 (CH_2), 1.83–1.98 (m)—15.09 (CH_2), 2.35 (d)—51.69 (CHN); MS: EI 70 eV, *m/z* 96 (100.00), 84 (32.73), 83 (31.20); HRMS (EI) calcd for $C_{10}H_{19}NO$ ($M+H^+$) 170.15394, found 170.15473.

4.9. *N*-((1*S*,2*S*,3*R*,6*R*)-3-Hydroxy-3,7,7-trimethylbicyclo[4.1.0]heptan-2-yl)-*N*,4-dimethylbenzene-sulfonamide 11

This compound was prepared from **9** as described above: 42%; mp 140–142 °C, $[\alpha]_D^{20} = -51.0$ (*c* 1.45, $CHCl_3$). Crystals of this product could be obtained by slow evaporation of *n*-pentane/diethyl ether solution. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.34 (dd, *J* = 4.8 Hz, *J* = 9.0 Hz, 1H, CH), 0.70 (t, *J* = 8.4 Hz, 1H, CH), 0.74 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.14 (ddd, *J* = 7.8 Hz, *J* = 12.3 Hz, *J* = 13.2 Hz, 1H, CH_2), 1.32 (s, 3H, CH_3), 1.53–1.63 (m, 3H, CH_2, OH), 1.79–1.94 (m, 1H, CH_2), 2.41 (s, 3H, CH_3), 3.05 (s, 3H, CH_3), 3.46 (d, *J* = 4.8 Hz, 1H, CH), 7.30 (m, 2H, CH), 7.68 (m, 2H, CH); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 14.80 (CH_3), 21.44 (CH_3), 25.92 (CH_3), 28.32 (CH_3), 31.39 (CH_3), 14.78 (CH_2), 36.89 (CH_2), 19.41 (CH), 20.05 (CH), 57.60 (CH), 127.11 (2CH), 129.42 (2CH), 17.22 (C), 71.91 (C), 137.00 (C), 142.78 (C). Anal. Calcd for $C_{18}H_{27}NO_3S$: C, 64.06; H, 8.06; N, 4.15; S, 9.50. Found: C, 64.21; H, 8.10; N, 4.27; S, 9.32.

4.10. (1*S*,2*S*,3*R*,6*R*)-3,7,7-Trimethyl-2-(methylamino)bicyclo[4.1.0]heptan-3-ol 12

This compound was prepared from **11** as described above: 55%; oil, $[\alpha]_D^{20} = +36.4$ (*c* 2.15, $CHCl_3$). ^{1}H, ^{1}H × ^{1}H COSY NMR (300 MHz, $CDCl_3$) δ (ppm) (subscript *c* or *t* means, that proton is *cis* or *trans* to the dimethyl bridge): 0.35 (dd, *J* = 3.9 Hz, *J* = 9.3 Hz, 1H, CH, H_{1t}), 0.69 (td, *J* = 1.8 Hz, *J* = 8.7 Hz, 1H, CH, H_{6t}), 0.93 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.12 (ddd, *J* = 7.5 Hz, *J* = 11.1 Hz, *J* = 14.4 Hz, 1H, CH_2, H_{4c}), 1.22 (s, 3H, CH_3), 1.47 (ddt, *J* = 2.2 Hz, *J* = 7.5 Hz, *J* = 14.7 Hz, 1H, CH_2, H_{5c}), 1.60 (ddd, *J* = 2.5 Hz, *J* = 8.1 Hz, *J* = 14.4 Hz, 1H, CH_2, H_{4t}), 1.85–1.96 (m, 1H, CH_2, H_{5c}), 1.97 (d, *J* = 4.2 Hz, 1H, CH, H_{2c}), 2.20–2.40 (br s, 2H, OH, NH), 2.49 (s, 3H, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 15.31 (CH_3), 26.93 (CH_3), 28.59 (CH_3), 34.32 (CH_3), 15.11 (CH_2), 35.73 (CH_2), 19.94 (CH), 24.88 (CH), 60.72 (CHN), 16.85 (C), 69.58 (C); HETCOR ^{1}H × ^{13}C NMR cross peaks: 0.35 (dd)—24.88 (CH), 0.69 (td)—19.94 (CH), 0.93 (s)—15.31 (CH_3), 1.05 (s)—28.59 (CH_3), 1.12 (ddd)—35.73 (CH_2), 1.22 (s)—26.93 (CH_3), 1.47 (ddt)—15.11 (CH_2), 1.60 (ddd)—35.73 (CH_2), 1.85–1.96 (m)—15.11 (CH_2), 1.97 (d)—60.72 (CHN), 2.49 (s)—34.32 (CH_3); MS: EI 70 eV, *m/z* 110 (100.00), 98 (30.23), 97 (35.22), 57 (49.93), 36 (31.46); HRMS (EI) calcd for $C_{11}H_{21}NO$: 183.16231, found 183.16184.

4.11. *N*-(((1*R*,2*S*,5*S*)-2-Hydroxy-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methyl)-4-methylbenzene-sulfonamide 13

This compound was prepared from **3** as described above: 73%; mp 130–133 °C, $[\alpha]_D^{20} = -19.0$ (*c* 1.5, $CHCl_3$), lit.[28] t.t. 123–125 °C, $[\alpha]_D^{20} = -3.0$ (*c* 1.3, $CHCl_3$). Crystals of this product could be obtained by slow evaporation of diethyl ether solution. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.88 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.33 (d, *J* = 10.2 Hz, 1H, CH_2), 1.64–1.96 (m, 6H, CH, $2CH_2$, OH), 2.01 (t, *J* = 5.0 Hz, 1H, CH), 2.22 (m, 1H, CH_2), 2.43 (s, 3H, CH_3), 2.91 (dd, *J* = 12.3 Hz, *J* = 6.3 Hz, 1H, CH_2), 3.03 (dd, *J* = 12.3 Hz, *J* = 6.3 Hz, 1H, CH_2), 4.83 (t, *J* = 6.3 Hz, 1H, NH), 7.31 (m, 2H, CH), 7.73 (m, 2H, CH); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 21.45 (CH_3), 23.02 (CH_3), 27.17 (CH_3), 24.53 (CH_2), 26.70 (CH_2), 28.64 (CH_2), 52.56 (CH_2), 40.90 (CH), 49.56 (CH), 127.01 (2CH), 129.64 (2CH), 38.15 (C), 76.08 (C), 136.93 (C), 143.26 (C). Anal. Calcd for $C_{17}H_{25}NO_3S$: C, 63.13; H, 7.79; N, 4.33; S, 9.91. Found: C, 63.22; H, 7.81; N, 4.40; S, 9.75.

4.12. (1*R*,2*S*,5*S*)-2-(Aminomethyl)-6,6-dimethylbicyclo[3.1.1]heptan-2-ol 14

This compound was prepared from **13** as described above: 58%; mp 45–47 °C, $[\alpha]_D^{20} = -51.3$ (*c* 2.6, $CHCl_3$). ^{1}H, ^{1}H × ^{1}H COSY NMR (300 MHz, $CDCl_3$) δ (ppm): 0.89 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.50 (d, *J* = 9.9 Hz, 1H, CH_2), 1.66–1.81 (m, 3H, CH_2), 1.87–2.20 (m, 6H, 2CH, $0.5CH_2$, OH, NH_2), 2.16–2.23 (m, 1H, CH_2), 2.60 (d, *J* = 12.6 Hz, 1H, CH_2, H_{10}), 2.72 (d, *J* = 12.6 Hz, 1H, CH_2, H_{10}); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 23.49 (CH_3), 27.58 (CH_3), 24.86 (CH_2), 27.13 (CH_2), 28.68 (CH_2), 51.31 (CH_2), 41.00 (CH), 49.48 (CH), 38.11 (C), 75.46 (C); HETCOR ^{1}H × ^{13}C NMR cross peaks: 0.89 (s)—23.49 (CH_3), 1.20 (s)—27.58 (CH_3), 1.50 (d)—27.13 (CH_2), 1.66–1.81 (m)—28.68 (CH_2), 1.87–2.20 (m)—24.86 (CH_2), 41.00 (CH), 49.48 (CH), 2.16–2.23 (m)—27.13 (CH_2), 2.60 (d)—51.31 (CH_2), 2.72 (d)—51.31 (CH_2); MS: EI 70 eV, *m/z* 139 (92.50), 121 (36.83), 83 (78.78), 69 (100.00), 41 (57.27); HRMS (EI) calcd for $C_{10}H_{19}NO$ ($M+H^+$) 170.15394, found 170.15323. Anal. Calcd for $C_{10}H_{19}NO$: C, 70.86; H, 11.35; N, 8.15. Found: C, 70.96; H, 11.31; N, 8.28.

4.13. *N*-(((1*R*,2*S*,5*S*)-2-Hydroxy-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methyl)-*N*-4-dimethylbenzene-sulfonamide 15

This compound was prepared from **13** as described above: 99%; $[\alpha]_D^{20} = -16.5$ (*c* 3.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.00 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.48 (d, *J* = 7.2 Hz, 1H, CH_2), 1.70–2.04 (m, 5H, CH, $1.5CH_2$, OH), 2.12 (t, *J* = 5.5 Hz, 1H, CH), 2.18–2.25 (m, 2H, CH_2), 2.43 (s, 3H, CH_3), 2.85 (d, *J* = 15.9 Hz, 1H, CH_2), 2.87 (s, 3H, CH_3), 3.16 (d, *J* = 14.4 Hz, 1H, CH_2), 7.32 (m, 2H, CH), 7.66 (m, 2H, CH); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 21.48 (CH_3), 23.18 (CH_3), 27.28 (CH_3), 39.18 (CH_3), 24.83 (CH_2), 27.02 (CH_2), 28.19 (CH_2), 59.79 (CH_2), 40.98 (CH), 50.09 (CH), 127.52 (2CH), 129.69 (2CH), 38.28 (C), 76.89 (C), 134.17 (C), 143.45 (C). Anal. Calcd for $C_{18}H_{27}NO_3S$: C, 64.06; H, 8.06; N, 4.15; S, 9.50. Found: C, 64.02; H, 8.12; N, 4.38; S, 9.53.

4.14. (1*R*,2*S*,5*S*)-6,6-Dimethyl-2-((methylamino)methyl)bicyclo[3.1.1]heptan-2-ol 16

This compound was prepared from **15** as described above: 37%; mp 38–40 °C, $[\alpha]_D^{20} = -60.0$ (*c* 1.15, $CHCl_3$). ^{1}H, ^{1}H × ^{1}H COSY NMR (300 MHz, $CDCl_3$) δ (ppm): 0.92 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 1.51 (d, *J* = 9.9 Hz, 1H, CH_2), 1.71–1.84 (m, 3H, CH_2), 1.87–1.99 (m, 3H, 2CH, $0.5CH_2$), 2.13–2.21 (m, 1H, CH_2), 2.44 (s, 3H, CH_3), 2.53 (d, *J* = 12.0 Hz, 1H, CH_2, H_{10}), 2.67 (d, *J* = 12.0 Hz, 1H, CH_2, H_{10}), 2.61–2.83 (br s, 2H, OH, NH); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 23.57 (CH_3), 27.56 (CH_3), 37.16 (CH_3), 24.91 (CH_2), 27.15 (CH_2), 29.15 (CH_2), 61.93 (CH_2), 40.91 (CH), 50.35 (CH), 38.11 (C), 75.00 (C); HETCOR ^{1}H × ^{13}C NMR cross peaks: 0.92 (s)—23.57 (CH_3), 1.21 (s)—27.56 (CH_3), 1.51 (d)—27.15 (CH_2), 1.71–1.84 (m)—24.91 (CH_2), 29.15 (CH_2), 1.87–1.99 (m)—24.91 (CH_2), 40.91 (CH), 50.35 (CH), 2.13–2.21 (m)—27.15 (CH_2), 2.44 (s)—37.16 (CH_3), 2.53 (d)—61.93 (CH_2), 2.67 (d)—61.93 (CH_2); MS: EI 70 eV, *m/z* 45 (67.17), 44 (100.00); HRMS (EI) calcd for $C_{11}H_{21}NO$: 183.16231, found 183.16291.

4.15. *N*-(((1*R*,2*R*,4*S*)-2-Hydroxy-3,3-dimethylbicyclo[2.2.1]heptan-2-yl)methyl)-4-methylbenzene-sulfonamide 17

This compound was prepared from **4** as described above: 60%; mp 116–118 °C, $[\alpha]_D^{20} = +14.2$ (*c* 1.25, $CHCl_3$), lit.[28] mp 126–128 °C, $[\alpha]_D^{20} = +14.1$ (*c* 1.84, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 0.89 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 1.00–1.20 (m, 1H, CH_2), 1.20–1.60 (m, 3H, CH_2, OH), 1.60–1.80 (m, 3H, CH_2), 1.80–1.90 (m, 1H, CH), 2.10 (m, 1H, CH), 2.43 (s, 3H, CH_3), 2.83 (dd, *J* = 4.4 Hz, *J* = 12.2 Hz, 1H, CH_2), 3.13 (dd, *J* = 7.8 Hz, *J* = 12.0 Hz, 1H, CH_2), 4.86 (m, 1H, NH), 7.33 (m, 2H, CH), 7.74 (m, 2H, CH); ^{13}C NMR (200 MHz, $CDCl_3$) δ (ppm): 21.51 (CH_3), 21.89 (CH_3), 24.88 (CH_3), 22.78 (CH_2), 23.40 (CH_2), 34.19 (CH_2), 46.17 (CH_2), 47.85 (CH), 49.65 (CH), 127.11 (2CH), 129.71 (2CH), 44.03 (C), 81.37 (C), 136.55 (C), 143.33 (C). Anal. Calcd for $C_{17}H_{25}NO_3S$: C, 63.13; H, 7.79; N, 4.33; S, 9.91. Found: C, 63.01; H, 7.84; N, 4.55; S 9.82.

4.16. (1*R*,2*R*,4*S*)-2-(Aminomethyl)-3,3-dimethylbicyclo[2.2.1] heptan-2-ol 18

This compound was prepared from **17** as described above: 83%; mp 89–91 °C, $[\alpha]_D^{20} = +18.7$ (*c* 1.1, DMSO). ^{1}H, ^{1}H × ^{1}H COSY NMR (300 MHz, C_5D_5N) δ (ppm): 0.90 (s, 3H, CH_3), 1.07 (m, 1H, CH_2), 1.20 (s, 3H, CH_3), 1.20–1.44 (m, 2H, CH_2), 1.47–1.57 (m, 1H, CH_2), 1.70 (m, 2H, CH), 2.33 (m, 2H, CH_2), 2.89 (d, *J* = 12.9 Hz, 1H, CH_2, H_{10}), 3.07 (d, *J* = 12.9 Hz, 1H, CH_2, H_{10}), 4.42 (br s, 3H, OH, NH_2); ^{13}C NMR (300 MHz, C_5D_5N) δ (ppm): 22.19 (CH_3), 26.30 (CH_3), 23.15 (CH_2), 24.29 (CH_2), 34.93 (CH_2), 44.36 (CH_2), 47.88 (CH), 50.20 (CH), 43.20 (C), 80.54 (C); HETCOR ^{1}H × ^{13}C NMR cross peaks: 0.90 (s)—22.19 (CH_3), 1.07 (m)—34.93 (CH_2), 1.20 (s)—26.30 (CH_3), 1.20–1.44 (m)—23.15 (CH_2), 24.29 (CH_2), 1.47–1.57 (m)—24.29 (CH_2), 1.70 (m)—50.20 (CH), 2.33 (m)—34.93 (CH_2), 47.88 (CH), 2.89 (d)—44.36 (CH_2), 3.07 (d)—44.36 (CH_2); MS: EI 70 eV, *m/z* 169 (32.30), 139 (64.58), 138 (36.21), 109 (36.16), 100 (62.86), 95 (54.35), 72 (37.11), 69 (54.64), 67 (58.78), 43 (100.00), 41 (63.63); HRMS (EI) calcd for $C_{10}H_{19}NO$: 169.14666, found 169.14583.

4.17. *N*-(((1*R*,2*R*,4*S*)-2-Hydroxy-3,3-dimethylbicyclo[2.2.1] heptan-2-yl)methyl)-*N*-4-dimethylbenzene-sulfonamide 19

This compound was prepared from **17** as described above: 99%; mp >200 °C, $[\alpha]_D^{20} = +1.4$ (*c* 2.2, DMSO). ^{1}H NMR (200 MHz, DMSO-d_6) δ (ppm): 0.80 (s, 3H, CH_3), 0.85 (s, 3H, CH_3), 0.97 (d, *J* = 9.6 Hz, 1H, CH), 1.10–1.50 (m, 3H, CH_2, OH), 1.62 (m, 2H, CH_2), 1.97 (d, *J* = 11.4 Hz, 1H, CH_2), 2.07 (d, *J* = 3.0 Hz, 1H, CH), 2.38 (s, 3H, CH_3), 2.41 (m, 1H, CH_2), 2.73 (s, 3H, CH_3), 3.13 (br s, 1H, CH_2), 3.54 (d, *J* = 13.6 Hz, 1H, CH_2), 7.43 (m, 2H, CH), 7.61 (m, 2H, CH); ^{13}C NMR (200 MHz, DMSO-d_6) δ (ppm): 20.94 (CH_3), 21.98 (CH_3), 25.54 (CH_3), 37.23 (CH_3), 22.19 (CH_2), 23.47 (CH_2), 33.89 (CH_2), 52.31 (CH_2), 46.80 (CH), 49.07 (CH), 127.22 (2CH), 129.76 (2CH), 44.44 (C), 80.69 (C), 133.25 (C), 143.12 (C). Anal. Calcd for $C_{18}H_{27}NO_3S$: C, 64.06; H, 8.06; N, 4.15; S, 9.50. Found: C, 63.98; H, 7.96; N, 4.46; S, 9.64.

4.18. (1*R*,2*R*,4*S*)-3,3-Dimethyl-2-((methylamino)methyl)bicyclo [2.2.1]heptan-2-ol 20

This compound was prepared from **19** as described above: 33%; $[\alpha]_D^{20} = +18.2$ (*c* 1.35, MeOH). ^{1}H, ^{1}H × ^{1}H COSY NMR (300 MHz, C_5D_5N) δ (ppm): 0.93 (s, 3H, CH_3), 1.06 (d, *J* = 11.1 Hz, 1H, CH_2), 1.20 (s, 3H, CH_3), 1.19–1.22 (m, 1H, CH_2), 1.30–1.44 (m, 2H, CH_2), 1.47–1.58 (m, 1H, CH_2), 1.69 (m, 1H, CH), 2.30–2.37 (m, 2H, CH, CH_2), 2.48 (s, 3H, CH_3), 2.69 (d, *J* = 12.0 Hz, 1H, CH_2, H_{10}), 2.94 (d, *J* = 12.0 Hz, 1H, CH_2, H_{10}), 4.80 (br s, 2H, OH, NH); ^{13}C NMR (300 MHz, C_5D_5N) δ (ppm): 22.25 (CH_3), 26.18 (CH_3), 36.83 (CH_3), 23.38 (CH_2), 24.37 (CH_2), 35.05 (CH_2), 54.71 (CH_2), 48.68 (CH), 50.02 (CH), 44.06 (C), 80.11 (C); HETCOR ^{1}H × ^{13}C NMR cross peaks: 0.93 (s)—22.25 (CH_3), 1.06 (d)—35.05 (CH_2), 1.20 (s)—26.18 (CH_3), 1.19–1.22 (m)—24.37 (CH_2), 1.30–1.44 (m)—23.38 (CH_2), 1.47–1.58 (m)—24.37 (CH_2), 1.69 (m)—50.02 (CH), 2.30–2.37 (m)—35.05 (CH_2), 48.68 (CH), 2.48 (s)—36.83 (CH_3), 2.69 (d)—54.71 (CH_2), 2.94 (d)—54.71 (CH_2); MS: EI 70 eV, *m/z* 45 (64.93), 44 (100.00); HRMS (EI) calcd for $C_{11}H_{21}NO$: 183.16231, found 183.16196.

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30. Crystallographic data for the structures in this letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk). Colourless 0.36 × 0.27 × 0.22 mm crystals of **7** were obtained from *n*-pentane/diethyl ether solution. The compound crystallised in the orthorhombic space group $P2_12_12_1$. Cell parameters $a = 7.9054(4)$, $b = 13.0108(7)$, $c = 17.472(1)$ Å, $V = 1797.1(2)$ Å^3, D_{calcd} 1.247 Mg/m^3, $Z = 4$, $F(0\,0\,0) = 728$, $\mu = 0.194$ mm^{-1}. The maximum and minimum transmissions of 0.9576 and 0.9330. $R_1 = 0.0527$, $wR_2 = 0.0898$ for reflections $I > 2\sigma(I)$. Absolute structure was determined by the Flack method, $x = 0.05(7)$. The structural data for **7** have been deposited at the Cambridge Crystallographic Data Centre: (CCDC No. 719487).
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32. Colourless 0.36 × 0.19 × 0.12 mm crystals of **11** were obtained from *n*-pentane/diethyl ether solution. The compound crystallised in the orthorhombic space group $P2_12_12_1$. Cell parameters $a = 6.1766(4)$, $b = 11.3964(7)$, $c = 25.951(2)$ Å, $V = 1826.7(2)$ Å^3, D_{calcd} 1.227 Mg/m^3, $Z = 4$, $F(0\,0\,0) = 728$, $\mu = 0.191$ mm^{-1}. The maximum and minimum transmissions of 0.9774 and 0.9347. $R_1 = 0.0659$, $wR_2 = 0.1069$ for reflections $I > 2\sigma(I)$. The absolute structure was determined by the Flack method, $x = -0.01(8)$. Non-hydrogen atoms were refined anisotropically, hydrogen atoms were constrained as riding atoms. The structural data for **11** have been deposited at the Cambridge Crystallographic Data Centre: (CCDC No. 719488).
33. Colourless 0.54 × 0.24 × 0.1 mm crystals of **13** were obtained from diethyl ether solution. The compound crystallised in the monoclinic space group $P2_1$. Cell parameters $a = 11.8432(8)$, $b = 6.6168(4)$, $c = 21.884(1)$ Å, $\beta = 96.386(5)°$, $V = 1704.3(2)$ Å^3, D_{calcd} 1.261 Mg/m^3, $Z = 4$, $F(0\,0\,0) = 696$, $\mu = 0.202$ mm^{-1}. The maximum and minimum transmissions of 0.9673 and 0.9316. $R_1 = 0.0514$, $wR_2 = 0.1063$ for reflections $I > 2\sigma(I)$. Absolute structure was determined by the Flack method, $x = 0.08(7)$. The structural data for **13** have been deposited at the Cambridge Crystallographic Data Centre: (CCDC No. 719486).
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