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SYNTHESIS OF AMINOALKYLATED AZIRIDINES FROM (+)-3-CARENE

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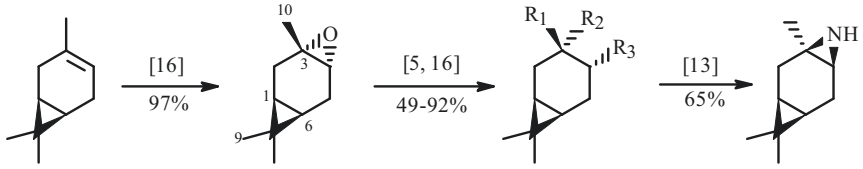
Aminoalkylated carane-type aziridines were synthesized via epoxidation of (+)-3-carene by H_2O_2 solution (7%) in EtOAc catalyzed by α-Al_2O_3 nanoparticles, opening of the epoxide by NaN_3, and cyclization of the azidoalcohol by Ph_3P followed by condensation of the resulting aziridines with formalin and secondary amines. The cytotoxicity of the aminoalkylated aziridines with heteroorganic substituents increased on going from a five-membered pyrrolidine ring substituent to a six-membered piperidine ring and decreased sharply upon replacing a piperidine by a morpholine ring or increased on going to a piperazine ring. The structures of products were established using IR and NMR spectroscopy and an X-ray crystal structure analysis.

Keywords: (+)-3-carene, aziridines, aminoalkylation, cytotoxicity.

(+)-3-Carene (**1**) fostered a positive outcome on osteoporosis due to increased mineralization of bone tissue [1]. Also, acetylcholine esterase inhibitor and monoterpene **1** was proposed for treating Alzheimer's disease [2, 3]. Transformation of plant metabolites to enhance or diminish their native properties is a promising direction for designing active ingredients of medicinal formulations [4–7]. Transformations of bicyclic olefine **1** into optically active compounds are also known [8–11]. Several carane-type aziridines were reported [12–15], although their aminoalkylated derivatives were not synthesized for biological studies.

This issue was resolved by selecting aziridine **2** [13], which was synthesized according to Scheme 1, including initial preparation of epoxide **3** using H_2O_2 solution (7%) in EtOAc in the presence of α-Al_2O_3 nanoparticles [16].



Scheme 1

Known methods for preparing azides **4a**,**b** include opening of epoxide **3** by NaN_3 in the presence of NH_4Cl in refluxing alcohols or stirring with NaN_3 in aqueous AcOH at 30°C [13, 14]. The researchers noted that, in the first instance, an equal mixture of azides **4a**,**b** (49% overall yield) formed whereas, in the second, compound **4a** (65% yield) formed regiospecifically. This contradicted the literature [15] reporting a mixture of isomeric (86:14) **4a**,**b** in 92% overall yield.

Under these conditions, we isolated predominantly (74% yield) **4a** with mp 32°C instead of a product with mp 35°C [15].

The sample PMR spectrum (ppm) featured 3H singlets for *gem*-dimethyls (0.97 and 1.02) and 10-Me (1.35) and four 1H doublets of doublets for H-2 and H-5 (1.3, 2.11 and 1.7, 2.09, respectively). A doublet for the OH proton appeared at medium field (1.96 ppm). Resonances of H-1, H-4, and H-6 differed from those in the literature [15].

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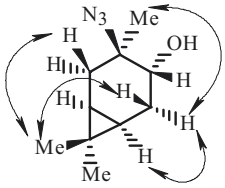


4a

Fig. 1. NOESY correlations in **4a**.

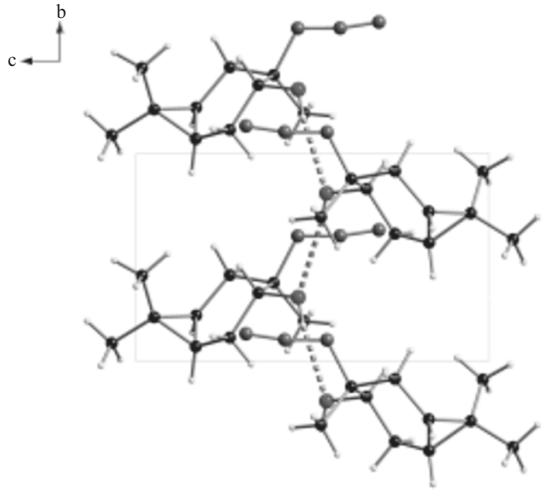


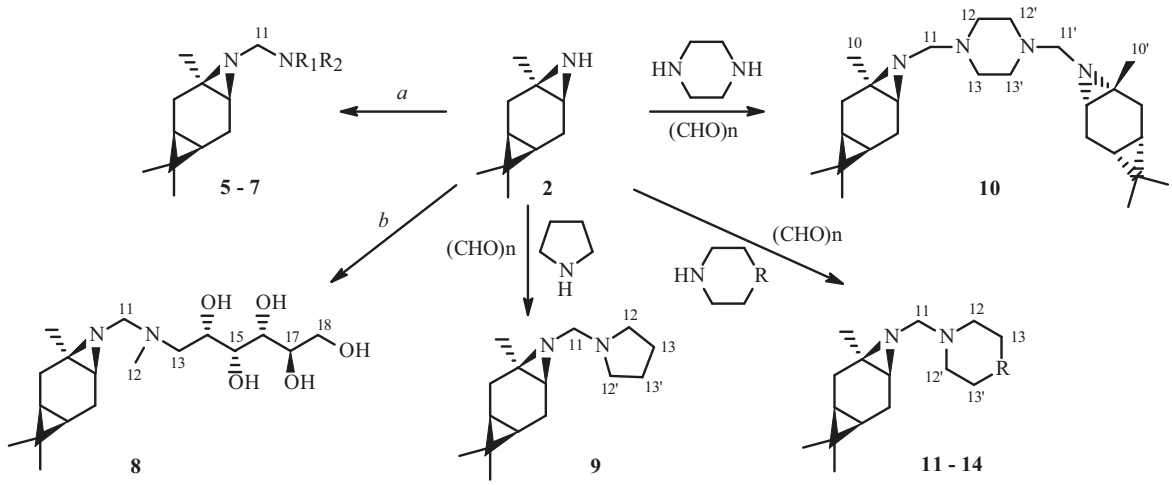
Fig. 2. Homomolecular structure of azidoalcohol **4a**.

Protons H-1 and H-6 were attributed before to a multiplet at 0.69–0.80 ppm whereas they resonated in the studied sample as two separate resonances, i.e., a triplet of doublets at 0.74 ppm and a triplet at 0.78 ppm. Also, the multiplicities of H-4 differed. In our instance, it was found as a doublet of doublets of doublets. A NOESY correlation was observed between H-5α and H-6 and the 10-Me group. The Me-8 protons coupled with H-2α, H-4, and H-5β, respectively (Fig. 1). The IR spectrum of **4a** had azide bands at 2099 cm^{-1} and characteristic OH bands at 3440 cm^{-1}. Also, a maximum at 1381 cm^{-1} confirmed that the *gem*-dimethyl group was present. The structure of **4a** was confirmed by an X-ray crystal structure analysis (XSA).

A crystal of $C_{10}H_{17}ON_3$ was monoclinic with homomolecular contacts in a structure stabilized by H-bonds (Fig. 2).

Aziridine **2** that was required for studying aminoalkylation was prepared by reacting azidoalcohol **4a** with Ph_3P (65% yield). However, azidoalcohol **4b** did not give the corresponding aziridine [13].

Next, the course of the Mannich reaction was studied as a function of the secondary amine using Scheme 2.



5: $R_1 = R_2 = Et$; **6:** $R_1 = Ph$, $R_2 = Et$; **7:** $R_1 = R_2 = CH_2CH_2OH$; **11:** R = N-Me; **12:** R = N-Ph; **13:** R = CH_2; **14:** R = O

a. HN-R_1R_2, $(CHO)_n$; *b*. *N*-methyl-D-glucamine, $(CHO)_n$

Scheme 2

Reaction of amine **2** with formalin and diethylamine formed **5** in 87% yield. Its PMR spectrum (ppm) contained two 3H singlets for the *gem*-dimethyl group (at 0.87 and 0.98), a 6H triplet for two methyls at 1.06, a 4H quartet for ethyl methylenes at 2.54–2.66, and two doublets (3.03, 3.53) for protons of the methylene linking the diethylamino and aziridine fragments, in contrast with the spectrum of aziridine **2**.

The yield of phenylethylamine **6** decreased by 10% as compared with diethylamine derivative **5**. The yield increased insignificantly to 89% for diethanolamine derivative **7**.

Aminosugar derivative **8** was prepared by reacting aziridine **2** with formaldehyde and *N*-methyl-D-glucamine. The reaction with pyrrolidine proceeded in high yield to give diamine **9**. The reaction of piperazine with two equivalents of aziridine **2** and formaldehyde produced symmetric *bis*-amine **10** (95% yield); with *N*-methylpiperazine, phenylpiperazine, and piperidine, high yields of corresponding products **11**–**13**, respectively. The reaction of aziridine **2** and formaldehyde with morpholine gave the best aminoalkylation yield to form **14**.

The synthesized compounds were tested for inhibition of HIV-1 (strain III_B) and HIV-2 (strain ROD) replication in acutely infected MT-4 cells with parallel determination of their cytotoxicity in these same cells. None of the tested compounds affected replication of the viruses at concentrations lower than the cytotoxic ones (CC_{50} from 0.04 to 0.74 mM). Thus, regioisomers **4a** and **4b** exhibited different cytotoxicities with CC_{50} values of 0.56 ± 0.05 and 0.36 mM, respectively. Aziridine **2** was prepared from azide **4a** and showed the lowest cytotoxicity of all studied compounds with CC_{50} = 0.74 ± 0.06 mM. The cytotoxicity of diethylamino derivative **5** was 2.5 times greater than that of starting **2**. Replacing ethyl by phenyl increased the cytotoxicity even more for **6**, i.e., ~15 times greater than that of **2**.

Compound **7** had cytotoxicity that was comparable with that of **6**, was a diethanolamine derivative, and had the highest cytotoxicity (CC_{50} = 0.04 ± 0.01 mM) of the whole spectrum of compounds analyzed by us. Adding a pyrrolidine substituent in **9** produced cytotoxicity comparable to that of **5**. Piperazine derivatives **10**, **11**, and **12** had cytotoxicities inferior to and significantly less than that of the pyrrolidine derivative. The toxicity of piperidine derivative **13** was comparable to that of **10**. The cytotoxicity of morpholine derivative **14** was only slightly greater than that of **2** and comparable to that of azide **4a**. Thus, the cytotoxicity of the aminoalkylated aziridines derived from (+)-3-carene with heteroorganic substituents increased on going from a five-membered pyrrolidine ring to a six-membered piperidine ring and decreased sharply on replacing piperidine by morpholine and increased on going to piperazine. Starting aziridine **2** and azide **4a** had the lowest cytotoxicities.

EXPERIMENTAL

IR spectra were recorded on a PerkinElmer Spectrum 100 FTIR spectrometer. PMR and ^{13}C NMR spectra were taken from solutions (2–3%) with TMS internal standard on a Bruker Avance III spectrometer (400.13 and 100.61 MHz). Specific rotation was measured on a Jacso-2000 automated polarimeter. Elemental analyses of the synthesized compounds were recorded on an Elementar Vario LIII instrument. Column chromatography used silica gel (SiO_2, 40/63 μ, Fluka); preparative TLC, Silpearl silica gel with UV indicator UV-254; and TLC, Silica gel F_{254} plates (Merck). Compounds were detected by aqueous $Ce_3[P(Mo_{12}O_{40})]_4$ solution (5%).

Preparative TLC used Silpearl silica gel with UV indicator UV-254.

(+)-3-Carene (**1**), $[\alpha]_D^{20}$ +17.0° (neat); *N*-methyl-D-glucamine, $[\alpha]_D^{20}$ –16.5° (*c* 2, H_2O); and α-Al_2O_3 (4–5 nm) were purchased (Aldrich). Petroleum ether fraction 35–45°C was used.

XSA. Crystallographic structural data and experimental conditions given in the work were deposited in the Cambridge Crystallographic Database (deposit@ccdc.cam.ac.uk) as a supplement (CCDC-1861493). The XSA was performed at 296 K on a Stoe IPDS II diffractometer with monochromatic MoKα-radiation. The structure was solved by direct methods and refined by anisotropic full-matrix least squares methods using the SHELXL-2014/6 program.

(1*S*,3*R*,5*S*,7*R*)-3,8,8-Trimethyl-4-azatricyclo[5.1.0^{3,5}]octane (2) was synthesized in 65% yield by the literature method [13].

(1*S*,3*S*,5*R*,7*R*)-3,8,8-Trimethyl-4-oxatricyclo[5.1.0^{3,5}]octane (3) was synthesized in 97% yield by the literature method [16].

(1*R*,3*R*,4*R*,6*S*)-4-Azido-4,7,7-trimethylbicyclo[4.1.0]heptan-3-ol (4a) was synthesized in 74% yield by the literature methods [15, 16].

(1*S*,3*S*,4*S*,6*R*)-4-Azido-3,7,7-trimethylbicyclo[4.1.0]heptan-3-ol (4b) was synthesized in 30% yield by the literature method [15].

General Aminoalkylation Method. A mixture of aziridine **2** (1.51 g, 10 mmol) in aqueous formalin (40%, 750 mg, 10 mmol) was stirred at room temperature, treated with secondary amine, stirred for 8 h, treated with benzene (50 mL), and evaporated. The procedure was repeated four times. The resulting precipitate with R_f 0.3–0.4 (CH_2Cl_2–MeOH, 9:1) was chromatographed on a flat glass plate (20 × 30 cm) with unattached Silpearl sorbent (2-mm layer) using various solvents as mobile phases. The plate was eluted twice with CH_2Cl_2–MeOH (9:1). The sample was extracted by placing scraped sorbent into a Schott glass filter, treating with MeOH, and removing the solvent to afford the sample for the studies.

***N*-Ethyl-*N*-{[(1*S*,3*R*,5*S*,7*R*)-3,8,8-trimethyl-4-azatricyclo[5.1.0.0^{3,5}]octan-4-yl]methyl}ethaneamine (5).** Yield 87%, yellow oil, $[\alpha]_D^{20}$ –7.80° (*c* 0.01, MeOH). IR spectrum (ν, cm^{-1}): 1065, 1100, 1207 (C-N), 1379 (Me_2C), 2928 (N-CH_2-N). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.48–0.72 (2H, m, H-1, 6), 0.56 (2H, m, Hα-2, Hβ-5), 0.87 (3H, s, H-8), 0.98 (3H, s, H-9), 1.06 (6H, t, J = 7.0, H-13, 13′), 1.21 (3H, s, H-10), 1.29–1.35 (1H, m, H-4), 1.87 (1H, dd, J = 15.3, 9.0, Hα-5), 2.6 (4H, m, H-12, 12′), 2.65–2.75 (1H, m, Hβ-2), 3.03 (1H, d, J = 11.7, H-11), 3.53 (1H, d, J = 11.7, H-11). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 70.5 (CH_2, C-11), 45.7 (CH_2, C-12, 12′), 44.8 (CH, C-4), 37.4 (C, C-3), 28.8 (CH_3, C-9), 28.2 (CH_2, C-2), 20.0 (CH_2, C-5), 19.7 (CH, C-1), 19.4 (CH, C-6), 18.7 (C, C-7), 18.5 (CH_3, C-10), 15.0 (CH_3, C-8), 12.6 (2 CH_3, C-13, 13′). $C_{15}H_{28}N_2$.

***N*-Ethyl-*N*-{[(1*S*,3*R*,5*S*,7*R*)-3,8,8-trimethyl-4-azatricyclo[5.1.0.0^{3,5}]octan-4-yl]methyl}aniline (6).** Yield 78%, yellow oil, $[\alpha]_D^{20}$ +5.42° (*c* 0.01, MeOH). IR spectrum (ν, cm^{-1}): 1193, 1255 (C-N), 1374 (Me_2C), 1504, 1598 (arom), 2928, 2926 (N-CH_2-N). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.58 (2H, m, H-1, 6), 0.72 (2H, m, Hα-2, Hβ-5), 0.82 (3H, s, H-8), 0.97 (3H, s, H-9), 1.01 (3H, s, H-10), 1.16 (3H, t, J = 7.0, H-13), 1.91 (1H, dd, J = 15.0, 8.5, Hα-5), 2.19–2.37 (1H, m, Hβ-2), 3.16 (2H, q, J = 7.1, H-12), 3.73 (1H, d, J = 12.5, H-11), 4.07 (1H, d, J = 12.5, H-11), 6.60 (2H, d, J = 7.8, H-15, 15′), 6.69 (1H, t, J = 7.3, H-17), 6.87 (2H, m, H-16, 16′). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 148.4 (C, C-14), 129.2 (CH, C-16, 16′), 129.2 (CH, C-16,16′, 128.4 (CH, C-17), 112.8 (CH, C-15, 15′), 77.2 (CH_2, C-11), 44.7 (CH, C-4), 44.3 (CH_2, C-12), 38.4 (C, C-3), 28.7 (CH_2, C-2), 20.4 (CH_2, C-5), 20.1 (CH, C-6), 19.9 (CH, C-1), 19.1 (C, C-7), 18.4 (CH_3, C-10), 14.9 (CH_3, C-8), 12.7 (CH_3, C-13). $C_{19}H_{28}N_2$.

2,2′-{[(1*S*,3*R*,5*S*,7*R*)-3,8,8-Trimethyl-4-azatricyclo[5.1.0.0^{3,5}]octan-4-yl]methyl}azanediyl)di(ethan-1-ol) (7). Yield 89%, yellow oil, $[\alpha]_D^{20}$ –7.58° (*c* 0.01, MeOH). IR spectrum (ν, cm^{-1}): 1042, 1160 (C-N), 1376 (Me_2C), 2933 (N-CH_2-N), 3363 (OH). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.62 (2H, m, H-1, 6), 0.74 (2H, m, Hβ-2, 5), 0.84 (3H, s, H-8), 0.99 (3H, s, H-9), 1.32 (3H, s, H-10), 1.94 (1H, dd, J = 7.7, 4.5, H-4), 2.01 (1H, dd, J = 14.7, 7.6, Hα-5), 2.30 (1H, dt, J = 18.3, 9.1, Hα-2), 2.69–2.75 (2H, m, H-12, 12′), 2.98 (2H, dt, J = 6.8, 1.2, H-12, 12′), 3.59–3.65 (2H, m, H-13, 13′), 3.76 (2H, dt, J = 6.5, 0.6, H-13, 13′), 4.30 (2H, m, H-11). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 86.9 (CH_2, C-11), 63.2 (CH_2, C-12), 60.5 (CH_2, C-13′), 56.3 (CH_2, C-13), 52.1 (CH_2, C-12′), 38.0 (CH, C-4), 35.7 (C, C-3), 28.5 (CH_3, C-9), 27.1 (CH_2, C-2), 26.4 (CH_3, C-10), 21.7 (CH_2, C-5), 21.2 (CH, C-6), 20.9 (CH, C-1), 19.8 (C, C-7), 14.7 (CH_3, C-8). $C_{15}H_{28}N_2O_2$.

***N*-Methyl-*N*-(1*S*,3*R*,5*S*,7*R*)-3,8,8-trimethyl-4-{[(2*S*,3*R*,4*R*,5*R*)-aminoheptane-1,2,3,4,5-pentaol] methyl}azatricyclo [5.1.0.0^{3,5}]octane (8)**. Yield 74%, yellow oil, $[\alpha]_D^{20}$ +2.93° (*c* 0.01, MeOH). IR spectrum (ν, cm^{-1}): 1076, 1145,1197 (C-N), 1378 (Me_2C), 2926 (N-CH_2-N), 3354 (OH). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.46–0.73 (2H, m, H-1, 6), 0.82 (3H, s, H-8), 0.96 (3H, s, H-9), 1.06–1.24 (2H, m, Hβ-2, 5), 1.28 (3H, s, H-10), 1.52 (1H, dd, J = 7.7, 4.3, H-4), 2.24 (3H, s, H-12), 2.27 (1H, d, J = 12.0, Hα-5), 2.34–2.48 (1H, m, Hα-2), 2.96 (1H, d, J = 12.0, H-11), 3.47–4.07 (8H, m, H-13, 14, 15, 16, 17, 18), 4.13–4.67 (6H, m, H-11, 5-OH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 86.5 (CH_2, C-11), 77.2 (CH, C-17), 73.4 (CH, C-16), 70.7 (CH, C-15), 67.1 (CH, C-14), 63.3 (CH_2, C-18), 59.2 (CH_2, C-13), 40.4 (CH_3, C-12), 38.2 (CH, C-4), 35.9 (C, C-3), 28.5 (CH_3, C-9), 27.0 (CH_3, C-10), 26.2 (CH_2, C-2), 21.6 (CH_2, C-5), 21.2 (CH, C-6), 20.9 (CH, C-1), 20.0, 19.9 (C, C-7), 14.5 (CH_3, C-8). $C_{18}H_{34}N_2O_5$.

(1*S*,3*R*,5*S*,7*R*)-3,8,8-Trimethyl-4-[(pyrrolidin-1-yl)methyl]-4-azatricyclo[5.1.0.0^{3,5}]octane (9). Yield 92%, yellow oil, $[\alpha]_D^{20}$ –16.50° (*c* 0.01, MeOH). IR spectrum (ν, cm^{-1}): (1098, 1145 (C-N), 1374 ($C(Me)_2$), 2927 (N-CH_2-N). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.54 (2H, m, H-1, 6), 0.83 (3H, s, H-8), 0.84 (2H, m, Hβ-2, 5), 0.95 (3H, s, H-9), 1.21 (3H, s, H-10), 1.34 (1H, dd, J = 7.6, 4.3, H-4), 1.69–1.78 (4H, m, H-13, 13′), 1.87 (1H, dd, J = 15.0, 8.5, Hα-2), 2.21 (1H, dt, J = 7.9, 5.0, Hα-5), 2.51–2.69 (4H, m, H-12, 12′), 2.91, 3.51 (1H each, d, J = 10.0, H-11). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 73.2 (CH_2, C-11), 51.1 (2 CH_2, C-12, 12′), 45.0 (CH, C-4), 38.4 (C, C-3), 28.9 (CH_2, C-2), 28.7 (CH_3, C-9), 23.5 (2CH_2, C-13, 13′), 20.4 (CH_2, C-5), 20.0 (CH, C-6), 19.9 (CH, C-1), 19.1 (C, C-7), 18.1 (CH_3, C-10), 15.0 (CH_3, C-8). $C_{15}H_{26}N_2$.

1,4-*Bis*{[(1*S*,3*R*,5*S*,7*R*)-3,8,8-trimethyl-4-azatricyclo[5.1.0^{3,5}]octan-4-yl]methyl}piperazine (10). Yield 95%, whitish-yellow powder, mp 83–84°C (hexane–Et_2O), $[\alpha]_D^{20}$ –12.71° (*c* 0.01, MeOH). IR spectrum (ν, cm^{-1}): 1096, 1153, 1164 (C-N), 1375 (Me_2C), 2926 (N-CH_2-N). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.55 (4H, m, H-1, 6, 1′, 6′), 0.78 (4H, m, Hβ-2, 5, 2′, 5′), 0.83 (6H, s, H-8, 8′), 0.96 (6H, s, H-9, 9′), 1.21 (6H, s, H-10, 10′), 1.34 (2H, dd, J = 7.6, 4.4, H-4, 4′), 1.87 (2H, dd, J = 15.0, 8.4, Hα-2, 2′), 2.22 (2H, dt, J = 16.9, 8.1, Hα-5, 5′), 2.55 (8H, m, H-12, 12′, 13, 13′), 2.85 (2H, d, J = 10.6, H-11, 11′), 3.42 (2H, d, J = 10.5, H-11, 11′). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 76.5 (2 CH_2, C-11, 11′), 50.9 (4 CH_2, C-12, 12′, 13, 13′), 45.4 (2CH, C-4, 4′), 38.4 (2 C, C-3, 3′), 29.0 (2 CH_2, C-2, 2′), 28.6 (2 CH_3, C-9, 9′), 20.5 (2 CH_2, C-5, 5′), 20.1 (2 CH, C-6, 6′), 20.0 (2CH, C-1, 1′), 19.2 (2 C, C-7, 7′), 18.0 (2 CH_3, C-10, 10′), 15.0 (2 CH_3, C-8, 8′). $C_{26}H_{44}N_4$.

(1*S*,3*R*,5*S*,7*R*)-3,8,8-Trimethyl-4-[(4-methylpiperazin-1-yl)methyl]-4-azatricyclo[5.1.0.0^{3,5}]octane (11). Yield 88%, yellow oil, $[\alpha]_D^{20}$ –9.96° (*c* 0.02, MeOH). IR spectrum (ν, cm^{-1}): 1099, 1157, 1170 (C-N), 1375 (Me_2C), 2926 (N-CH_2-N). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.52 (2H, m, H-1, 6), 0.76 (2H, m, H*β*-2, 5), 0.78 (3H, s, H-8), 0.91 (3H, s, H-9), 1.16 (3H, s, H-10), 1.27 (1H, dd, J = 7.6, 4.2, H-4), 1.82 (1H, dd, J = 15.1, 8.5, H*α*-2), 2.15 (1H, dd, J = 15.3, 8.1, H*α*-5), 2.22 (3H, s, Me-14), 2.37 (4H, m, H-13, 13′), 2.56 (4H, m, H-12, 12′), 2.82, 3.37 (1H each, d, J = 10.5, H-11). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 76.26 (CH_2, C-11), 54.96 (2 CH_2, C-12, 12′), 50.43 (2 CH_2, C-13, 13′), 46.02 (CH_3, C-14), 45.29 (CH_2, C-4), 38.25 (C, C-3), 28.91 (CH_2, C-2), 28.62 (CH_3, C-9), 20.37 (CH_2, C-5), 20.01 (CH, C-6), 19.96 (CH, C-1), 19.12 (C, C-7), 18.02 (CH_3, C-10), 14.94 (CH_3, C-8). $C_{16}H_{29}N_3$.

(1*S*,3*R*,5*S*,7*R*)-3,8,8-Trimethyl-4-[(4-phenylpiperazin-1-yl)methyl]-4-azatricyclo[5.1.0.0^{3,5}]octane (12). Yield 86%, yellow oil, $[\alpha]_D^{20}$ –10.83° (*c* 0.01, MeOH). IR spectrum (ν, cm^{-1}): 1128, 1141, 1234 (C-N), 1379 (Me_2C), 1452, 1509, 1600 (arom.), 2922 (N-CH_2-N). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.50–0.73 (2H, m, H-1, 6), 0.87 (3H, s, H-8), 0.88 (2H, m, H*β*-2, 5), 0.99 (3H, s, H-9), 1.26 (3H, s, H-10), 1.40 (1H, dd, J = 7.6, 4.4, H-4), 1.92 (1H, dd, J = 15.0, 8.5, H*α*-2), 2.25 (1H, dt, J = 15.9, 8.0, H*α*-5), 2.65–2.82 (4H, m, H-13, 13′), 2.95 (1H, d, J = 10.6, H-11), 3.23 (4H, m, H-12, 12′), 3.49 (1H, d, J = 10.6, H-11), 6.84 (1H, t, J = 7.2, H-17), 6.94 (2H, d, J = 8.2, H-15, 15′), 7.26 (2H, t, J = 7.2, H-16, 16′). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 151.5 (C, C-14), 129.0 (2 CH, C-15, 15′), 119.4 (CH, C-17), 116.0 (2 CH, C-16, 16′), 76.4 (CH_2, C-11), 50.7 (2 CH, C-13, 13′), 49.1 (2 CH_2, C-12, 12′), 45.3 (CH, C-4), 38.4 (C, C-3), 28.9 (CH_2, C-2), 28.7 (CH_3, C-9), 20.4 (CH_2, C-5), 20.0 (CH, C-6), 19.9 (CH, C-1), 19.1 (C, C-7), 18.1 (CH_3, C-10), 15.0 (CH_3, C-8). $C_{21}H_{31}N_3$.

(1*S*,3*R*,5*S*,7*R*)-3,8,8-Trimethyl-4-[(piperidin-1-yl)methyl]-4-azatricyclo[5.1.0.0^{3,5}]octane (13). Yield 91%, yellow oil, $[\alpha]_D^{20}$ –8.60° (*c* 0.01, MeOH). IR spectrum (ν, cm^{-1}): 1093, 1120 (C-N), 1377 (Me_2C), 2929 (N-CH_2-N). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.6 (2H, m, H-1, 6), 0.84 (3H, s, H-8), 0.85 (2H, m, H*β*-2, 5), 0.95 (3H, s, H-9), 1.17 (3H, s, H-10), 1.38 (2H, m, H-4, 14), 1.55 (4H, m, H-13, 13′), 1.84 (1H, dd, J = 15.0, 8.5, H*α*-2), 2.18 (1H, td, J = 12.4, 9.9, H*α*-5), 2.40–2.58 (4H, m, H-12, 12′), 2.82, 3.38 (1H each, d, J = 10.8, H-11). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 77.0 (CH_2, C-11), 51.8 (2 CH_2, C-12, 12′), 45.3 (CH, C-4), 38.0 (C, C-3), 28.7 (CH_2, C-2), 28.5 (CH_3, C-9), 25.8 (2 CH_2, C-13, 13′), 24.3 (CH_2, C-5), 20.3 (CH_2, C-14), 19.8 (CH, C-6), 19.9 (CH, C-1), 19.1 (C, C-7), 15.0 (CH_3, C-8). $C_{16}H_{28}N_2$.

(1*S*,3*R*,5*S*,7*R*)-3,8,8-Trimethyl-4-[(morpholin-1-yl)methyl]-4-azatricyclo[5.1.0.0^{3,5}]octane (14). Yield 94%, yellow oil, $[\alpha]_D^{20}$ –8.46° (*c* 0.01, MeOH). IR spectrum (ν, cm^{-1}): 1071, 1115 (C-N), 1375 (Me_2C), 2926 (N-CH_2-N). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.44–0.68 (2H, m, H-1, 6), 0.82 (3H, s, H-8), 0.84 (2H, m, H*β*-2, 5), 0.96 (3H, s, H-9), 1.19 (3H, s, H-10), 1.34 (1H, dd, J = 7.5, 4.1, H-4), 1.86 (1H, dd, J = 15.0, 8.5, H*α*-2), 2.20 (1H, dt, J = 15.8, 7.9, H*α*-5), 2.41–2.63 (4H, m, H-12, 12′), 2.83, 3.37 (1H each, d, J = 10.3, H-11), 3.69 (4H, t, J = 4.6, H-13, 13′). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 76.7 (CH_2, C-11), 66.9 (2 CH_2, C-13, 13′), 51.1 (CH_2, C-12, 12′), 45.3 (CH, C-4), 38.3 (C, C-3), 28.8 (CH_2, C-2), 28.6 (CH_3, C-9), 20.3 (CH_2, C-5), 19.9 (CH, C-1), 19.9 (CH, C-6), 19.1 (C, C-7), 15.0 (CH_3, C-8). $C_{15}H_{26}N_2O$.

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