SUPPORTING INFORMATION

Carbocyclic Ribosyl Amines: Synthesis of 5-Substituted Carbocyclic ß-Ribofuranosylamines

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General Methods. The starting materials, solvents, and reagents were obtained commercially and were used without further purification unless otherwise mentioned. When anhydrous solvents were needed, the commercial reagent grade was stirred for 18 h over calcium hydride and distilled. Silica gel (35–70 μ) was used for flash column chromatography and silica gel (100–200 mesh) was used for open-column chromatography. ^{1}H-NMR spectra were referenced to internal TMS, and ^{13}C-NMR spectra were recorded at 75 mHz and referenced to internal TMS. Melting points are reported uncorrected. Preparative HPLC using silica gel was performed using a Dynamax–60 Å column.

(±)-*N*-*tert*-Butyloxycarbonyl-2-azabicyclo[2.2.1]hept-5-en-3-one (4a): DMAP (0.6 g, 4.92 mmol) was added to a solution of 2-azabicyclo[2.2.1]hept-5-en-3-one (0.5 g, 4.6 mmol) in methylene chloride (10 mL) followed by addition of a solution of di-*tert*-butyl dicarbonate (2.5 g, 11.5 mmol) in methylene chloride (10 mL). The solution was stirred at room temperature overnight and the solvent evaporated in vacuo. The residue was purified by flash column chromatography on silica gel using hexanes-ethyl acetate as the eluent to give a white solid (0.92 g, 96%): mp 85.2–85.4 °C, reported mp[1] 84-86 °C; TLC R_f 0.31 (silica gel, hexanes-ethyl acetate, 80:20), R_f 0.52 (silica gel, hexane-ethyl acetate, 50:50); ^{1}H-NMR ($CDCl_3$) δ 1.50 (s, 9H), 2.14 (d, J = 8.5 Hz, 1H), 2.35 (d, J = 8.5 Hz, 1H), 3.39 (s, 1H), 4.95 (s, 1H), 6.65 (m, 1H), 6.90 (dd, J = 5.3 Hz, 2.2 Hz, 1H); ^{13}C-NMR ($CDCl_3$): δ 28.0, 54.4, 54.9, 62.4, 82.6, 138.2, 140.0, 150.4, 176.2. Anal. Calcd. for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.42; H, 7.33; N, 6.51.

Bromination of (±)-*N*-*tert*-butyloxycarbonyl-2-azabicyclo[2.2.1]hept-5-en-3-one (4a).[2] To a solution of *N*-*tert*-butyloxycarbonyl-2-azabicyclo[2.2.1]hept-5-en-3-one (0.5 g, 2.4 mmol) in methylene chloride (20 mL) was added a solution of bromine (0.42 g, 2.64 mmol)

in methylene chloride (10 mL), drop wise over a period of 45 min, and the mixture was stirred for 4 h at room temperature. Another equivalent of bromine (0.42 g, 2.64 mmol) was added and stirring continued for another 6 h. The volatiles were evaporated *in vacuo* and the residue was purified by flash column chromatography on silica gel using hexanes-ethyl acetate (80:20) as the eluent. Further purification by preparative HPLC on a silica gel column afforded 4 products as white solids.

Product-1: mp 160.1-160.4 °C; ^{1}H-NMR ($CDCl_3$) δ 1.53 (s, 9H), 2.17 (dt, J = 11 Hz, 1.85 Hz, 1H), 2.48 (dt, J = 11 Hz, 1.85 Hz, 1H), 3.15 (d, J = 1.9 Hz, 1H), 4.42 (dd, J = 6.7 Hz, 1.9 Hz, 1H), 4.55 (dd, J = 6.7 Hz, 1.85 Hz, 1H), 4.65 (d, J = 1.65 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 28.0, 33.6, 47.9, 51.0, 57.2, 65.5, 84.3, 148.5, 170.2. Anal. Calcd. for $C_{11}H_{15}Br_2NO_3$: C, 35.80; H, 4.10; N, 3.80. Found: C, 35.91; H, 4.08; N, 3.83.

Product-2 (**5a**): mp 159.7-160.2 °C; ^{1}H-NMR ($CDCl_3$) δ 1.53 (s, 9H), 2.70 (m, 2H), 3.02 (d, J = 1.3 Hz, 1H), 4.06 (m, 1H), 4.34 (t, J = 1.3 Hz, 1H), 4.73 (t, J = 1.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 27.9, 33.5, 40.4, 45.7, 53.7, 66.4, 84.8, 147.4, 169.2. Anal. Calcd. for $C_{11}H_{15}Br_2NO_3$: C, 35.80; H, 4.10; N, 3.80. Found: C, 35.92; H, 4.05; N, 3.77.

Product-3: mp 179.5-179.9 °C; ^{1}H-NMR ($CDCl_3$) δ 1.54 (s, 9H), 2.32 (s, 2H), 3.11 (s, 1H), 4.20 (s, 1H), 4.53 (t, J = 2.5 Hz, 1H), 4.76 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ 27.9, 36.7, 50.2, 56.8, 56.9, 63.5, 83.8, 148.8, 169.7. Anal. Calcd. for $C_{11}H_{15}Br_2NO_3$: C, 35.80; H, 4.10; N, 3.80. Found: C, 35.95; H, 4.03; N, 3.92.

Product-4: mp 95.7-96.4 °C; ^{1}H-NMR ($CDCl_3$) δ 1.54 (s, 9H), 2.23 (dm, J = 11 Hz, 1H), 2.35 (dm, J = 11 Hz, 1H), 3.11 (m, 1H), 4.25 (m, 1H), 4.51 (m, 1H), 4.58 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ 28.0, 35.2, 49.5, 52.5, 54.4, 63.9, 84.2, 148.7, 169.0. Anal. Calcd. for $C_{11}H_{15}Br_2NO_3$: C, 35.80; H, 4.10; N, 3.80. Found: C, 36.01; H, 4.02; N, 3.71.

(±)-*N*-[(4,4'-Dimethoxydiphenyl)methyl]-2-azabicyclo[2.2.1]hept-7-*anti*-bromo-5-en-3-one (6c): This compound was synthesized in three steps and 30% overall yield starting from lactam **3** by N-protection, bromination, and dehydrobromination. To a solution of the lactam **3** [(1*S*)-(+)-2-azabicyclo[2.2.1]hept-5en-3one] (0.5 g, 4.6 mmol) in CH_2Cl_2 (30 mL) was added finely powdered sodium hydroxide (0.7 g) and potassium carbonate (1 g) followed by benzyl tributyl ammonium bromide (0.2 g). The mixture was stirred with a magnetic stirring bar and 4,4'-dimethoxydiphenyl methyl chloride (1.2 g, 4.6 mmol) was added as a solution in methylene chloride (20 mL), drop wise. The mixture was stirred at room temperature for 12 hrs. The mixture was diluted with methylene chloride (50 mL), extracted with water, dil. HCl, saturated brine, dried (Na_2SO_4) and purified by flash column chromatography on silica gel using hexanes-ethyl acetate as the eluent to give (±)-*N*-[(4,4'-dimethoxydiphenyl)methyl]-2-azabicyclo[2.2.1]hept-5-en-3-one (**4c**) as colorless oil (1 g, 66%): TLC R_f 0.19 (silica gel, hexanes-ethyl acetate, 70:30), R_f 0.43 (silica gel, hexane-ethyl acetate, 50:50); ^{1}H-NMR ($CDCl_3$) δ 2.06 (d, J = 7.6 Hz, 1H), 2.44 (d, J = 7.6 Hz, 1H), 3.41 (s, 1H), 3.80 (s, 3H), 3.81 (s, 3H), 4.14 (s, 1H), 5.88 (dd, J = 5 Hz, 2 Hz, 1H), 6.21 (s, 1H), 6.29 (d, J = 5 Hz, 1H), 6.82 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 6.97 (d, J = 8.5 Hz, 2H), 7.12 (d, J = 8.5 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ 53.7, 55.2, 55.2, 57.6, 57.7, 61.1, 113.6, 128.2, 130.2, 130.9, 132.4, 134.9, 140.0, 158.5, 159.1, 178.6; MS *m/z* 335 (M^+, EI).

To a solution of *N*-[(4,4'-dimethoxydiphenyl)methyl]-2-azabicyclo[2.2.1]hept-5-en-3-one (**4c**) (2 g, 6 mmol) in methylene chloride (30 mL) was added a solution of bromine (0.96 g, 6 mmol) in methylene chloride (20 mL), drop wise over a period of 20 min and the mixture was stirred at room temperature for 18 h. The mixture was evaporated in vacuo and the residue was purified by flash column chromatography on silica gel using hexanes-ethyl

acetate as the eluent to give (±)-*N*-[(4,4'-dimethoxydiphenyl)methyl]-2-azabicyclo[2.2.1]heptan-6,7-dibromo-3-one (**5c**) as white solid (1.53 g, 51.8%): mp 207.3-207.4 °C; TLC R_f 0.36 (silica gel, hexanes-ethyl acetate, 70:30), R_f 0.63 (silica gel, hexane-ethyl acetate, 50:50); ^{1}H-NMR ($CDCl_3$) δ 2.40 (dd, J = 14 Hz, 8.4 Hz, 1H), 2.57 (dt, J = 14 Hz, 4.4 Hz, 1H), 3.02 (s, 1H), 3.18 (m, 1H), 3.82 (s, 3H), 3.84 (s, 3H), 4.14 (s, 1H), 4.51 (s, 1H), 6.36 (s, 1H), 6.91 (m, 4H), 7.04 (d, J = 8.5 Hz, 2H), 7.18 (d, J = 8.5 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ 33.6, 41.4, 48.4, 53.1, 55.4, 56.8, 66.0, 114.1, 114.6, 128.2, 130.2, 130.8, 159.0, 159.8, 171.6; MS: *m/z* 493, 495, 497 (M^+, Br_2 isotope pattern, EI).

A mixture of *N*-[(4,4'-dimethoxydiphenyl)methyl]-2-azabicyclo[2.2.1]heptan-6,7-dibromo-3-one (**5c**) (0.32 g, 0.65 mmol) and DBU (3 mL) was heated at 120 °C in an oil bath for 12 h. Upon cooling, the reaction mixture was diluted with methylene chloride (50 mL) and extracted with dilute HCl solution, washed with water, saturated brine and dried (Na_2SO_4). The solvent was evaporated in vacuo and the residue purified by flash column chromatography on silica gel using hexanes:ethyl acetate as the eluent to give pure **6c** as a white solid (0.24 g, 89%); mp 123.6-123.9 °C; TLC R_f 0.36 (silica gel, hexanes-ethyl acetate, 70:30), R_f 0.63 (silica gel, hexane-ethyl acetate, 50:50); ^{1}H-NMR ($CDCl_3$) δ 3.56 (s, 1H), 3.81 (s, 3H), 3.82 (s, 3H), 4.21 (s, 1H), 4.80 (s, 1H), 5.98 (dd, J = 5.0 Hz, 1.8 Hz, 1H), 6.25 (s, 1H), 6.28 (m, 1H), 6.84 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.5 Hz, 2H), 6.97 (d, J = 8.5 Hz, 2H), 7.10 (d, J = 8.5 Hz, 2H; ^{13}C-NMR ($CDCl_3$) δ 55.3, 57.8, 60.1, 66.1, 66.2, 114.0, 128.3, 129.6, 130.6, 131.4, 132.4, 138.0, 158.9, 159.4, 173.7; MS: *m/z* 414, 416 (MH^+, Br isotope pattern, FAB). Anal. Calcd. for $C_{21}H_{20}BrNO_3$: C, 60.88; H, 4.86; N, 3.38. Found: C, 61.03; H, 4.99; N, 3.40.

(±)-*N*-[(4,4'-Dimethoxydiphenyl)methyl]-2-azabicyclo[2.2.1]hept-7-bromo-5,6-diol-3-one (7c & 8c): The olefin, *N*-[(4,4'-dimethoxydiphenyl)methyl]-2-azabicyclo[2.2.1]hept-7-bromo-5-en-3-one (**6c**, 1 g, 2.42 mmol), was suspended in a mixture of acetone (25 mL) and water (20 mL). *tert*-butanol (10 mL) was then added to give a clear solution. *N*-methylmorpholine-*N*-oxide (0.95 g, 7.05 mmol) was then added with stirring followed by a solution of osmium tetroxide (41 mg, 0.16 mmol) in *tert*-butanol (1 mL) and the mixture was heated at reflux for 30 h. The mixture was allowed to cool to room temperature and quenched with a slurry of sodium sulfite (0.5 g) and florisil (2 g) in water (20 mL) and filtered. Solvent was removed form the filtrate under reduced pressure and the residue was partitioned between water (20 mL) and chloroform (20 mL) and the layers separated. The aqueous layer was extracted 4 times with chloroform (20 mL), the combined organic layers washed with saturated brine and evaporated in vacuo to give a cream colored solid, which was purified by flash column chromatography on silica gel using hexanes-ethyl acetate as the eluent to give two pure compounds as white solids.

Product-1 (**8c**): mp 187.4-187.9 °C; TLC R_f 0.56 (silica gel, hexanes-ethyl acetate, 30:70), R_f 0.40 (silica gel, hexane-ethyl acetate, 50:50); ^{1}H-NMR ($CDCl_3$) δ 2.73 (d, J = 7.6 Hz, 1H), 2.76 (d, J = 7.6 Hz, 1H), 3.24 (s, 1H), 3.44 (dd, J = 7.6 Hz, 6.4 Hz, 1H), 3.82 (s, 6H), 4.08 (s, 1H), 4.24 (dd, J = 7.6 Hz, 6.4 Hz, 1H), 4.47 (s, 1H), 6.32 (s, 1H), 6.90 (m, 4H), 7.03 (d, J = 8.5 Hz, 2H), 7.16 (d, J = 8.5 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ 47.0, 55.3, 57.1, 57.8, 64.4, 70.4, 72.7, 114.1, 114.4, 128.2, 129.8, 130.4, 130.7, 159.0, 159.6, 169.9; MS *m/z* 448, 450 (MH^+, Br isotope pattern, FAB). Anal. Calcd. for $C_{21}H_{22}BrNO_5$: C, 56.26; H, 4.94; N, 3.12. Found: C, 56.23; H, 5.13; N, 3.04.

Product-2 (**7c**): mp 95.3 - 96.1 °C; TLC R_f 0.45 (silica gel, hexanes-ethyl acetate, 30:70), R_f 0.29 (silica gel, hexane-ethyl acetate, 50:50); ^{1}H-NMR ($CDCl_3$) δ 2.15 (d, J = 7.6 Hz, 1H), 2.90 (d, J = 4 Hz, 1H), 3.23 (s, 1H), 3.80 (s, 6H), 4.03 (s, 1H), 4.27 (s, 1H), 4.65 (m, 2H), 6.20 (s, 1H), 6.88 (m, 4H), 7.15 (d, J = 8.5 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ 46.6, 55.3, 57.3, 60.5, 65.2, 66.6, 68.9, 114.0, 114.1, 129.0, 130.4, 131.2, 131.5, 158.9, 159.3, 170.7; MS: *m/z* 448, 450 (MH^+, Br isotope pattern, FAB). Anal. Calcd. for $C_{21}H_{22}BrNO_5$: C, 56.26; H, 4.94; N, 3.12. Found: C, 56.32; H, 5.04; N, 3.05.

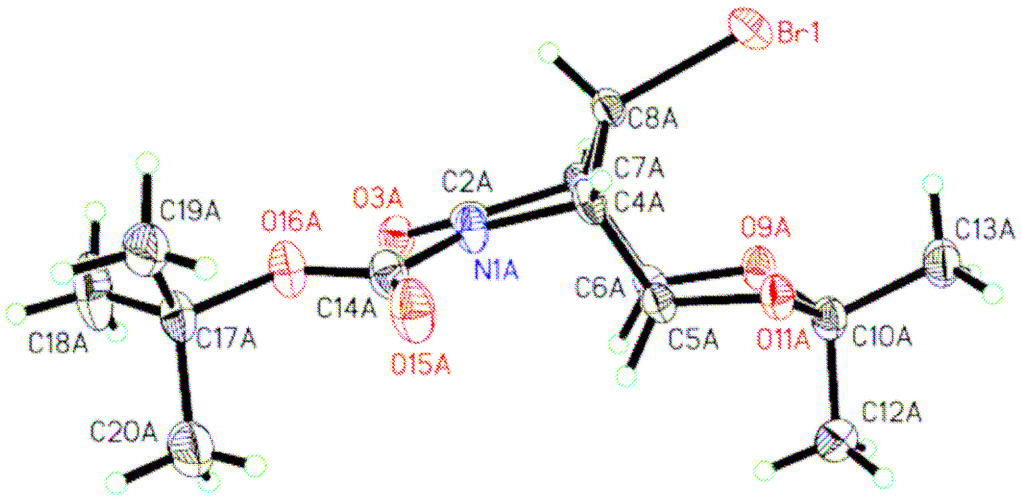

Figure 1. An Ortep diagram of one molecule of **10** from single crystal X-ray diffraction analysis confirms structural assignment as the *exo*-diol. The atoms are represented as 50% thermal ellipsoids. Unit cell crystal packing, details of data collection, structure refinement, and tables of atomic coordinates etc. are included as part of the crystallographic information file.

Table 1. Crystal data and structure refinement for **10**.

Identification code	**10**
Empirical formula	$C_{14}H_{20}BrN_5$
Formula weight	362.22
Temperature	173(2) K
Wavelength	0.71073 A
Crystal system, space group	hexagonal, P3(2)
Unit cell dimensions	a = 12.7298(2) A alpha = 90 deg. b = 12.7298(2) A beta = 90 deg. c = 33.4904(8) A gamma = 120 deg.
Volume	4699.96(15) A^3
Z, Calculated density	12, 1.536 Mg/m^3
Absorption coefficient	2.644 mm^-1
F(000)	2232
Crystal size	0.44 x 0.38 x 0.32 mm
Theta range for data collection	1.85 to 29.14 deg.
Limiting indices	-16<=h<=17, -17<=k<=17, -44<=l<=26
Reflections collected / unique	32390 / 12069 [R(int) = 0.0277]
Completeness to theta = 29.14	92.7 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	12069 / 1 / 758
Goodness-of-fit on F^2	0.939
Final R indices [I>2sigma(I)]	R1 = 0.0257, wR2 = 0.0476
R indices (all data)	R1 = 0.0356, wR2 = 0.0494
Absolute structure parameter	-0.003(3)
Extinction coefficient	0.00069(6)
Largest diff. peak and hole	0.391 and -0.338 e.A^-3

References

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(2) Evans, C.; McCague, R.; Roberts, S. M.; Sutherland, A. G. *Journal of the Chemical Society. Perkin Transactions I* **1991**, 656-657.