Supporting Information

A Versatile Enantioselective Synthesis of Barrenazines

Miguel Peña-López, M. Montserrat Martínez, Luis A. Sarandeses,* and José Pérez Sestelo*

Departamento de Química Fundamental, Universidade da Coruña, E-15071 A Coruña, Spain

sestelo@udc.es; qfsarand@udc.es

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General methods. Unless otherwise is stated, all reactions were conducted in flame dried glassware under a positive pressure of argon. Reaction temperatures refer to external bath temperatures. Anhydrous solvents were obtained by distillation from CaH₂ (CH₂Cl₂ and pyridine) or from the sodium/benzophenone (THF and Et₂O). All other commercially available reagents were used as received. Organic extracts were dried over anhydrous MgSO₄, filtered, and concentrated by using a rotary evaporator at aspirator pressure (20–30 mmHg). TLC was effected on silica gel 60 F₂₅₄ (layer thickness 0.2 mm) and components were located by observation under UV light and/or by treating the plates with a phosphomolybdic acid, or *p*-anisaldehyde reagent followed by heating. Column chromatography was performed on silica gel (230–400 mesh).¹ NMR spectra were performed in a Bruker Avance 300 or Bruker Avance 500 spectrometers in CDCl₃ using the residual solvent signal at δ = 7.26 ppm (¹H) or δ = 77.0 ppm (¹³C) as internal standard. DEPT was used to assign carbon types. The low resolution electron-impact mass spectra were measured on a Thermo Finnigan Trace MS spectrometer at 70 eV. The high resolution mass spectra were measured on a Thermo Finnigan MAT 95XP spectrometer. Infrared spectra were taken with a Bruker Vector 22. Optical rotation values were determined at room temperature in a JASCO DIP-1000 Digital polarimeter. IR spectra were taken with ATR (“attenuated total reflectance”). Melting points are uncorrected.

17

4-(*tert*-Butyldimethylsilyloxy)butan-1-ol (17).² To a cold solution of 1,4-butanediol (4.0 mL, 45.14 mmol) in THF (50 mL) at 0 °C, a solution of *n*-BuLi (19.3 mL, 2.34 M in hexanes, 45.14 mmol) was slowly added. After 30 min, a solution of TBSCl (6.18 g, 41.04 mmol) in THF (20 mL) was added dropwise via cannula and the reaction was allowed to reach room temperature overnight. The solvent was evaporated under reduced pressure and the residue was partitioned between water (50 mL) and CH₂Cl₂ (50 mL). The aqueous phase was extracted with CH₂Cl₂ (2 × 25 mL) and the combined organic extracts were washed with brine (40 mL), dried, filtered and concentrated in vacuo. The residue was purified by column chromatography (30% EtOAc/hexanes) to give **17** (8.54 g, 41.78 mmol, 93%) as a yellow oil. ¹H NMR (300 MHz, CDCl₃, 25 °C) δ 0.06 (s, 6 H), 0.89 (s, 9 H), 1.60–1.67 (m, 4 H), 2.70 (t, *J* = 5.8 Hz, 1 H), 3.60–3.68 (m, 4 H); ¹³C NMR (75 MHz, CDCl₃, 25 °C) δ –5.4 (2 × CH₃), 18.3 (C), 25.9 (3 × CH₃), 29.8 (CH₂), 30.1 (CH₂), 62.7 (CH₂), 63.3 (CH₂) ppm; IR (ATR) 3344, 2951, 2929, 2885, 2857, 2359, 2341 cm^{–1}; MS (ESITOF) *m/z* (%) 205 (M⁺ + H, 100),

(1) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

(2) Keck, G. E.; Welch, D. S. *Org. Lett.* **2002**, *4*, 3687–3690.

187 (2), 133 ($M^+ - C_4H_9SiO$, 8); HRMS (ESITOF) calcd for $C_{10}H_{25}O_2Si$ 205.1618 ($M^+ + H$), found 205.1619.

6

4-(tert-Butyldimethylsilyloxy)butanal (6).³ To a $-78\text{ }^\circ\text{C}$ solution of oxalyl chloride (5.4 mL, 61.87 mmol) in CH_2Cl_2 (50 mL) was added DMSO (9.4 mL, 132.00 mmol) dropwise via syringe. After 30 min, a solution of **17** (8.43 g, 41.25 mmol) in CH_2Cl_2 (20 mL) was added via cannula. Following an additional 1 h, the cloudy suspension was treated with Et_3N (28.7 mL, 206.25 mmol) to produce a homogeneous solution. Upon warming to $0\text{ }^\circ\text{C}$ overnight, the yellow suspension formed was quenched with saturated $NaHCO_3$ (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3x40 mL) and the combined organic extracts were washed with additional saturated $NaHCO_3$ (40 mL) and concentrated in vacuo to $\sim 1/2$ volume. The remaining aqueous layers were washed with Et_2O (3x20 mL), and the combined organic layers were washed with saturated $NaHCO_3$ (50 mL), brine (50 mL), dried, filtered and concentrated under reduced pressure. Purification by flash chromatography (30% EtOAc/hexanes) afforded 7.70 g of **6** (38.05 mmol, 92%) as a yellow oil. 1H NMR (300 MHz, $CDCl_3$, $25\text{ }^\circ\text{C}$) δ 0.03 (s, 6 H), 0.88 (s, 9 H), 1.81–1.89 (q, $J = 6.0$ Hz, 2 H), 2.47–2.52 (dt, $J = 7.1, 1.6$ Hz, 2 H), 3.64 (t, $J = 6.0$ Hz, 2 H), 9.78 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, $25\text{ }^\circ\text{C}$) δ -5.4 ($2 \times CH_3$), 18.2 (C), 25.5 (CH_2), 25.9 ($3 \times CH_3$), 40.7 (CH_2), 62.0 (CH_2), 202.6 (C); IR (ATR) 2953, 2928, 2886, 2856, 2714, 2360, 1726 cm^{-1} ; MS (ESITOF) m/z (%) 203 ($M^+ + H$, 38), 187 (6); HRMS (ESITOF) calcd for $C_{10}H_{23}O_2Si$ 203.1461 ($M^+ + H$), found: 203.1460.

7

(S)-7-(tert-Butyldimethylsilyloxy)-1-hepten-4-ol (7).⁴ To a solution of (+)-Ipc₂BOMe (18.22 g, 57.59 mmol) in Et_2O (80 mL) at $0\text{ }^\circ\text{C}$ was added dropwise a solution of allylmagnesium bromide in Et_2O (53.7 mL, 1 M, 53.70 mmol). After 5 min, the reaction mixture was allowed to reach rt and was stirred 45 min to give a white suspension. The suspension was cooled to $0\text{ }^\circ\text{C}$, allowed to settle for 20 min, and the supernatant filtered under Ar. The filtrate was cooled

(3) Taillier, C.; Gille, B.; Bellosta, V.; Cossy, J. *J. Org. Chem.* **2005**, *70*, 2097-2108.

(4) Rauniyar, V.; Zhai, H.; Hall, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 8481-8490.

to $-100\text{ }^{\circ}\text{C}$ and a solution of aldehyde **6** (7.15 g, 35.33 mmol) in Et_2O (20 mL) was added dropwise over 1 h. After stirring at the same temperature for 3 h, the reaction was quenched with 2 M aqueous NaOH (50 mL) and 30 wt% aqueous H_2O_2 (20 mL). The resulting mixture was stirred at room temperature overnight, the layers were separated, and the aqueous phase was extracted with Et_2O (3 $\times$ 50 mL). The combined organic extracts were washed with brine (50 mL), dried, filtered and concentrated in vacuo. The residue was purified by column chromatography (15% EtOAc/hexanes) to give alcohol **7** (7.26 g, 29.70 mmol, 84%) as a colorless oil. $[\alpha]_{\text{D}}^{25} -5.6$ (c 0.5, CHCl_3); ^1H NMR (300 MHz, CDCl_3 , $25\text{ }^{\circ}\text{C}$) δ 0.07 (s, 6 H), 0.91 (s, 9 H), 1.59–1.71 (m, 4 H), 2.16–2.33 (m, 2 H), 2.59 (d, $J = 3.6\text{ Hz}$, 1 H), 3.65–3.69 (m, 3 H), 5.09–5.16 (m, 2 H), 5.78–5.92 (m, 1 H); ^{13}C NMR (75 MHz, CDCl_3 , $25\text{ }^{\circ}\text{C}$) δ -5.4 ($2 \times \text{CH}_3$), 18.3 (C), 25.9 ($3 \times \text{CH}_3$), 29.1 (CH_2), 33.9 (CH_2), 41.9 (CH_2), 63.4 (CH_2), 70.6 (CH), 117.5 (CH_2), 135.1 (CH); IR (ATR) 3361, 3077, 2951, 2928, 2856, 2360, 2338 cm^{-1} ; MS (ESITOF) m/z (%) 245 ($\text{M}^+ + \text{H}$, 100), 227 (8), 203 ($\text{M}^+ - \text{C}_3\text{H}_5$, 10); HRMS (ESITOF) calcd for $\text{C}_{13}\text{H}_{29}\text{O}_2\text{Si}$ 245.1931 ($\text{M}^+ + \text{H}$), found 245.1939.

The enantiomeric ratio of the compound was determined by formation of diastereomeric esters with (*S*)-(+)-2-methoxy-2-trifluoro-2-phenylacetyl chloride ((*S*)-MTPACl, 1.5 equiv), DMAP (1.0 equiv), Et_3N (5.0 equiv) and **7** (1.0 equiv). The crude was partitioned between saturated NaHCO_3 (5 mL) and Et_2O (5 mL). The aqueous phase was extracted with Et_2O (2 $\times$ 5 mL), and the organic extracts washed with brine (10 mL), dried, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (10% EtOAc/hexanes). ^{19}F NMR analysis of the Mosher esters revealed a 92% *ee* in the allylation reaction. ^1H NMR (500 MHz, CDCl_3 , $25\text{ }^{\circ}\text{C}$) δ 0.03 (s, 6 H), 0.88 (s, 9 H), 1.48–1.62 (m, 2 H), 1.66–1.88 (m, 2 H), 2.36 (t, $J = 6.3\text{ Hz}$, 2 H), 3.54 (s, 3 H), 3.58–3.62 (dt, $J = 6.2, 2.6\text{ Hz}$, 2 H), 5.00–5.04 (m, 2 H), 5.15–5.20 (q, $J = 6.0\text{ Hz}$, 1 H), 5.59–5.68 (m, 1 H), 7.37–7.41 (m, 3 H), 7.53–7.56 (m, 2 H); ^{13}C NMR (125 MHz, CDCl_3 , $25\text{ }^{\circ}\text{C}$) δ -5.3 ($2 \times \text{CH}_3$), 18.3 (C), 25.9 ($3 \times \text{CH}_3$), 28.4 (CH_2), 29.8 (CH_2), 38.0 (CH_2), 55.4 (CH), 62.5 (CH_2), 76.4 (CH_3), 118.4 (CH_2), 121.4 (C), 125.3 (C), 127.4 (CH), 128.3 (CH), 129.5 (CH), 132.3 (C), 132.7 (CH), 166.2 (C); ^{19}F NMR (470 MHz, CDCl_3 , $25\text{ }^{\circ}\text{C}$) δ -71.57 , -71.65 .

8

(*R*)-(4-Azidohept-6-enyloxy)(*tert*-butyl)dimethylsilane (8**).** Diphenylphosphoryl azide (0.87 mL, 4.04 mmol) was added to a solution of alcohol **7** (98 mg, 0.40 mmol), PPh_3 (211 mg, 0.81 mmol) and DEAD (0.37 mL, 40% in toluene, 0.81 mmol) in THF (5 mL) and the

reaction was stirred at room temperature for 24 h. Concentration in vacuo and purification by column chromatography (10% Et₂O/hexanes) gave azide **8** (108 mg, 0.40 mmol, 99%) as a colorless oil. $[\alpha]_D^{25} +16.8$ (*c* 0.20, CHCl₃); ¹H NMR (300 MHz, CDCl₃, 25 °C) δ 0.05 (s, 6 H), 0.89 (s, 9 H), 1.26–1.70 (m, 4 H), 2.31 (t, *J* = 6.8 Hz, 2 H), 3.35–3.38 (m, 1 H), 3.61–3.65 (m, 2 H), 5.11–5.18 (m, 2 H), 5.75–5.88 (m, 1 H); ¹³C NMR (75 MHz, CDCl₃, 25 °C) δ –5.3 (2 × CH₃), 18.3 (C), 25.9 (3 × CH₃), 29.2 (CH₂), 30.3 (CH₂), 38.8 (CH₂), 62.1 (CH), 62.6 (CH₂), 118.1 (CH₂), 133.9 (CH); IR (ATR) 2952, 2927, 2856, 2099, 1643, 1471 cm^{–1}; MS (ESITOF) *m/z* (%) 270 (M⁺ + H, 14), 226 (M⁺ – N₃, 18), 110 (43); HRMS (ESITOF) calcd for C₁₃H₂₈ON₃Si 270.1996 (M⁺ + H), found 270.2004.

(R)-7-(tert-Butyldimethylsilyloxy)-1-hepten-4-amine (9). A mixture of azide **8** (5.28 g, 19.59 mmol) and PPh₃ (7.81 g, 29.78 mmol) in H₂O (3 mL) and THF (18 mL) was stirred at room temperature overnight. Evaporation of solvents and purification of the residue by column chromatography (20% MeOH/CH₂Cl₂) gave **9** (3.30 g, 13.55 mmol, 69%) as a colorless oil. $[\alpha]_D^{25} +4.3$ (*c* 0.17, CHCl₃); ¹H NMR (300 MHz, CDCl₃, 25 °C) δ 0.04 (s, 6 H), 0.89 (s, 9 H), 1.25–1.67 (m, 4 H), 1.94–2.04 (m, 1 H), 2.20–2.28 (m, 1 H), 2.76–2.84 (m, 1 H), 3.62 (t, *J* = 6.2 Hz, 2 H), 5.06–5.11 (m, 2 H), 5.72–5.86 (m, 1 H); ¹³C NMR (75 MHz, CDCl₃, 25 °C) δ –5.3 (2 × CH₃), 18.3 (C), 25.9 (3 × CH₃), 29.5 (CH₂), 33.9 (CH₂), 42.5 (CH₂), 50.5 (CH), 63.2 (CH₂), 117.3 (CH₂), 135.8 (CH); IR (ATR) 3076, 2952, 2927, 2855, 2359, 1828 cm^{–1}; MS (ESITOF) *m/z* (%) 244 (M⁺ + H, 100), 112 (3); HRMS (ESITOF) calcd for C₁₃H₃₀ONSi 244.2091 (M⁺ + H), found 244.2103.

Benzyl (R)-7-(tert-Butyldimethylsilyloxy)-1-hepten-4-ylcarbamate (18). To a solution of **9** (580 mg, 2.39 mmol) and Et₃N (0.80 mL, 5.98 mmol) in THF (7 mL), at 0 °C, was added CbzCl (0.51 mL, 3.59 mmol) via syringe, and the mixture was stirred at room temperature overnight. The reaction was quenched with H₂O (30 mL) and the aqueous phase was extracted with EtOAc (3 × 20 mL). The organic extracts were washed with brine (40 mL), dried, filtered and concentrated under reduced pressure. The residue was purified by column

chromatography (20% EtOAc/hexanes) to afford **18** (760 mg, 2.02 mmol, 85%) as a yellow oil. $[\alpha]_D^{25} +16.3$ (c 0.16, CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25 °C) δ 0.04 + 0.05 (2 s, 6 H), 0.90 (s, 9H), 1.34–1.67 (m, 4 H), 2.14–2.41 (m, 2 H), 3.62 (t, J = 5.5 Hz, 2 H), 3.74 (m, 1 H), 5.03–5.14 (m, 4 H), 5.71–5.86 (m, 1 H), 7.31–7.38 (m, 5 H); ^{13}C NMR (75 MHz, CDCl_3 , 25 °C) δ –5.3, 18.3, 25.9, 29.0, 29.2, 30.8, 31.2, 39.5, 39.9, 49.5, 50.5, 62.8, 62.9, 66.5, 69.7, 117.6, 117.9, 128.0, 128.5, 134.2, 134.7, 136.7, 155.9, 157.3; IR (ATR) 3322, 3073, 2951, 2925, 2854, 2361, 2340 cm^{-1} ; MS (ESITOF) m/z (%) 378 ($\text{M}^+ + \text{H}$, 100), 214 (34); HRMS (ESITOF) calcd for $\text{C}_{21}\text{H}_{36}\text{O}_3\text{NSi}$ 378.2458 ($\text{M}^+ + \text{H}$), found 378.2477.

Benzyl (*R*)-Allyl[7-(*tert*-butyldimethylsilyloxy)-1-hepten-4-yl]carbamate (5**).** A solution of (*R*)-7-(*t*-butyldimethylsilyloxy)-1-hepten-4-ylcarbamate (1.34 g, 3.55 mmol) in a mixture of THF/DMF (24 mL, 3:1) was cooled at 0 °C, and KHMDS (14.2 mL, 0.5 M in toluene, 7.09 mmol) was added dropwise. The mixture was stirred for 30 min at 0 °C, and allyl bromide (0.92 mL, 10.64 mmol) was added via syringe. After 1 h at room temperature, the reaction was quenched by addition of aq 1 M HCl (5 mL) and diluted with H_2O (25 mL). The aqueous phase was extracted with EtOAc (3 $\times$ 25 mL), and the combined organic extracts washed with brine (40 mL), dried, filtered and concentrated in vacuo. The crude was purified by column chromatography (10% Et_2O /hexanes) to afford **5** (996 mg, 2.38 mmol, 67%) as a pale yellow oil. $[\alpha]_D^{25} +11.7$ (c 0.25, CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25 °C) δ 0.04 (s, 6 H), 0.89 (s, 9 H), 1.41–1.64 (m, 4 H), 2.14–2.43 (m, 2 H), 3.48–3.66 (m, 2 H), 3.70–3.84 (m, 2 H), 3.99–4.23 (m, 1 H), 4.94–5.22 (m, 6 H), 5.60–5.97 (m, 2 H), 7.30–7.38 (m, 5 H); ^{13}C NMR (75 MHz, CDCl_3 , 25 °C) δ –5.3, 18.3, 25.9, 28.8, 29.2, 29.7, 38.1, 38.4, 45.7, 46.4, 56.4, 62.6, 62.7, 66.9, 67.1, 116.2, 116.5, 116.9, 117.0, 117.1, 127.6, 127.8, 127.9, 128.4, 135.2, 135.4, 135.8, 136.9, 156.5; IR (ATR) 3347, 3080, 2927, 2855, 2165, 2053, 1982 cm^{-1} ; MS (ESITOF) m/z (%) 418 ($\text{M}^+ + \text{H}$, 100), 374 (2); HRMS (ESITOF) calcd for $\text{C}_{24}\text{H}_{40}\text{O}_3\text{NSi}$ 418.2771 ($\text{M}^+ + \text{H}$), found 418.2788.

4

Benzyl **(R)-6-[3-(tert-Butyldimethylsilyloxy)propyl]-5,6-dihydro-1(2H)-pyridinecarboxylate (4).** To a solution of **5** (4.04 g, 9.67 mmol) in CH₂Cl₂ (25 mL) at room temperature was added Cl₂(Cy₃P)₂RuCHPh (398 mg, 0.484 mmol, 5% mol), and the solution was stirred for 2 h. The solvent was evaporated and the residue purified by flash chromatography (10% EtOAc/hexanes) to give **4** (3.17 g, 8.14 mmol, 84%) as a pale yellow oil. $[\alpha]_D^{25} +13.2$ (*c* 0.29, CHCl₃); ¹H NMR (300 MHz, CDCl₃, 25 °C) δ 0.03 (s, 6 H), 0.88 (s, 9 H), 1.91–1.96 (m, 1 H), 2.42–2.48 (m, 1 H), 3.52 (m, 3 H), 4.22–4.54 (m, 2 H), 5.16 (s, 2 H), 5.62–5.75 (m, 2 H), 7.28–7.37 (m, 5 H); ¹³C NMR (75 MHz, CDCl₃, 25 °C) δ –5.3 (2 × CH₃), 18.3 (C), 25.9 (3 × CH₃), 27.6 (CH₂), 29.0 (CH₂), 29.6 (CH₂), 39.8 (CH₂), 48.1 (CH), 62.7 (CH₂), 67.0 (CH₂), 122.8 (CH), 123.3 (CH), 127.8 (CH), 127.9 (CH), 128.4 (CH), 136.9 (C), 155.6 (C); IR (ATR) 3035, 2926, 2854, 2361, 1951, 1698 cm^{–1}; MS (ESITOF) *m/z* (%) 390 (M⁺ + H, 100), 297 (5); HRMS (ESITOF) calcd for C₂₂H₃₆O₃NSi 390.2458 (M⁺ + H), found 390.2469.

10

Benzyl **(1S,4R,6R)-4-[3-(tert-Butyldimethylsilyloxy)propyl]-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (10).** To a solution of **4** (392 mg, 1.00 mmol) in CH₃CN (15 mL), at 0 °C, was added an aqueous solution of Na₂EDTA (0.2 mL, 0.1 M, 0.02 mmol) and trifluoroacetone (1 mL) via a precooled syringe. To this solution was added a mixture of sodium bicarbonate (592 mg, 7.04 mmol) and Oxone[®] (3.09 g, 5.03 mmol) all at once. The reaction was allowed to reach room temperature overnight and quenched with H₂O (10 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 20 mL), and the combined organic extracts washed with brine (30 mL), dried, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (30% EtOAc/hexanes) to give **10** (338 mg, 0.83 mmol, 83%, *dr* = 96:4) as a colorless oil. $[\alpha]_D^{25} -4.9$ (*c* 0.37, CHCl₃); ¹H NMR (300 MHz, CDCl₃, 25 °C) δ 0.04 (s, 6 H), 0.89 (s, 9 H), 1.36–1.54 (m, 3 H), 1.64–1.77 (m, 2 H), 2.09–2.22 (m, 1 H), 3.13 (m, 1 H), 3.22–3.27 (m, 2 H), 3.59 (m, 2 H), 4.07–4.29 (m, 1 H), 4.32–4.57 (m, 1 H), 5.13 (s, 2 H), 7.29–7.39 (m, 5 H); ¹³C NMR (75 MHz, CDCl₃, 25 °C) δ –5.3 (2 × CH₃), 18.3 (C), 25.9 (3 × CH₃), 27.1 (CH₂), 28.4 (CH₂), 29.1 (CH₂), 37.7

(CH₂), 46.3 (CH), 48.3 (CH), 49.1 (CH), 62.3 (CH₂), 67.2 (CH₂), 127.8 (CH), 127.9 (CH), 128.5 (CH), 136.7 (C), 156.1 (C); IR (ATR) 3442, 2951, 2927, 2855, 2360, 2341, 2107, 1697 cm⁻¹; MS (ESITOF) *m/z* (%) 406 (M⁺ + H, 100), 362 (11); HRMS (ESITOF) calcd for C₂₂H₃₆O₄NSi 406.2408 (M⁺ + H), found 406.2419.

Benzyl (2*R*,4*R*,5*R*)-4-Azido-2-(3-(*tert*-butyldimethylsilyloxy)propyl)-5-hydroxypiperidine-1-carboxylate (11). A mixture of **10** (338 mg, 0.833 mmol), NaN₃ (975 mg, 15.00 mmol) and NH₄Cl (802 mg, 15.00 mmol) in MeOH/H₂O (9 mL, 8:1) was warmed at 65 °C overnight. The reaction mixture was cooled, diluted with saturated NaHCO₃ (20 mL) and extracted with CH₂Cl₂ (3 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried, filtered and concentrated in vacuo. The crude was purified by column chromatography (40% EtOAc/hexanes) to yield **11** as a yellow oil (291 mg, 0.648 mmol, 78%). [α]_D²⁵ +12.7 (*c* 0.40, CHCl₃); ¹H NMR (300 MHz, CDCl₃, 25 °C) δ 0.04 (s, 6 H), 0.89 (s, 9 H), 1.43–1.53 (m, 2 H), 1.57–1.68 (m, 2 H), 1.89–2.02 (m, 1 H), 2.18–2.26 (m, 1 H), 2.55 (br s, 1 H), 3.25–3.30 (d, *J* = 14.5 Hz, 1 H), 3.60 (t, *J* = 6.0 Hz, 2 H), 3.74 (br s, 2 H), 4.00–4.05 (d, *J* = 14.5 Hz, 1 H), 4.21–4.30 (m, 1 H), 5.12–5.15 (d, *J* = 6.8 Hz, 2 H), 7.30–7.39 (m, 5 H); ¹³C NMR (75 MHz, CDCl₃, 25 °C) δ –5.3 (2 × CH₃), 18.3 (C), 25.9 (3 × CH₃), 27.2 (CH₂), 28.1 (CH₂), 29.8 (CH₂), 41.1 (CH₂), 50.1 (CH), 59.2 (CH), 62.6 (CH₂), 67.3 (CH), 67.4 (CH₂), 127.8 (CH), 128.1 (CH), 128.5 (CH), 136.5 (C), 156.7 (C); IR (ATR) 3423, 2954, 2922, 2852, 2360, 2341, 2102, 1698, 1677 cm⁻¹; MS (ESITOF) *m/z* (%) 449 (M⁺ + H, 100), 405 (2); HRMS (ESITOF) calcd for C₂₂H₃₇O₄N₄Si 449.2578 (M⁺ + H), found 449.2585.

Stereochemical assignment for 11: The regiochemistry of the epoxide-opening reaction, predicted by the Fürst-Platter rule, was assigned based in the ¹H-¹³C correlation observed in the HMBC experiment between the H-2 (4.21-4.30 ppm) and the C-4 (59.2 ppm). The stereochemistry of the azide and the hydroxyl groups, both in axial disposition, was assigned based in the low coupling constant between H4-H5 and H5-H6 observed in the ¹H NMR.

12

Dibenzyl (3R,8R)-3,8-Di[3-(*tert*-butyldimethylsilyloxy)propyl]-1,3,4,6,8,9-hexahydrodipyrido(3,4-*b*:3',4'-*e*)-pyrazine-2,7-dicarboxylate (12). To a stirred solution of the azido alcohol **11** (275 mg, 0.613 mmol) in CH₂Cl₂ (5 mL) at room temperature was added Dess-Martin periodinane (312 mg, 0.735 mmol). After an additional 1 h, the reaction mixture was partitioned between CH₂Cl₂ (10 mL) and a 1:1 mixture of saturated aq Na₂S₂O₃ (10 mL) and saturated aq NaHCO₃ (10 mL). The organic extract was dried, filtered and concentrated under reduced pressure. The crude was used in the next step without purification.

Sodium hydrogen telluride was prepared by heating powdered tellurium (195 mg, 1.53 mmol) and NaBH₄ (138 mg, 3.65 mmol) at 75 °C in ethanol (7 mL) for 1 h and cooling to rt. To the resulting dark red solution a solution of the previously obtained azido ketone in ethanol (3 mL) was added. The mixture turned to black and was further stirred open to the air overnight. The mixture was filtered through celite and the organic extract concentrated in vacuo. The crude was purified by column chromatography (20% EtOAc/hexanes) to afford **12** as a pale yellow oil (211 mg, 0.262 mmol, 86% overall yield). [α]_D²⁵ +57.4 (*c* 0.34, CHCl₃); ¹H NMR (300 MHz, CDCl₃, 25 °C) δ -0.01 (s, 12 H), 0.84 (s, 18 H), 1.51 (m, 8 H), 2.78–2.83 (m, 2 H), 3.23–3.27 (m, 2 H), 3.58 (m, 4 H), 4.28–4.33 (m, 2 H), 4.71–4.80 (m, 2 H), 5.07–5.26 (m, 6 H), 7.32–7.38 (m, 10 H); ¹³C NMR (75 MHz, CDCl₃, 25 °C) δ -5.4 (4 $\times$ CH₃), 18.2 (2 $\times$ C), 25.9 (6 $\times$ CH₃), 27.7 (2 $\times$ CH₂), 29.2 (2 $\times$ CH₂), 35.3 (2 $\times$ CH₂), 43.8 (2 $\times$ CH₂), 49.0 (2 $\times$ CH), 62.2 (2 $\times$ CH₂), 67.6 (2 $\times$ CH₂), 128.0 (2 $\times$ CH), 128.1 (2 $\times$ CH), 128.5 (2 $\times$ CH), 136.3 (2 $\times$ C), 146.1 (4 $\times$ C), 155.4 (2 $\times$ C); IR (ATR) 2925, 2853, 2361, 1701, 1497, 1454, 1423 cm⁻¹; MS (ESITOF) *m/z* (%) 803 (M⁺ + H, 100), 381 (7), 338 (6); HRMS (ESITOF) calcd for C₄₄H₆₇O₆N₄Si₂ 803.4593 (M⁺ + H), found 803.4598.

13

Dibenzyl (3R,8R)-3,8-Di(3-hydroxypropyl)-1,3,4,6,8,9-hexahydrodipyrido(3,4-*b*:3',4'-*e*)-pyrazine-2,7-dicarboxylate (13). To a solution of **12** (44.6 mg, 0.055 mmol) in THF (3 mL) at 0 °C was added a solution of TBAF (0.22 mL, 1 M in THF, 0.222 mmol) and the resulting mixture was stirred at room temperature for 4 h. The solvent was removed under reduced pressure and the residual oil was purified by column chromatography (100% EtOAc) to yield

13 (31.6 mg, 0.054 mmol, 99%) as a colorless oil. $[\alpha]_D^{25} +70.1$ (c 0.25, CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25 °C) δ 1.55 (m, 8 H), 2.06 (m, 2 H), 2.78–2.84 (m, 2 H), 3.20–3.27 (m, 2 H), 3.60 (m, 4 H), 4.28–4.34 (m, 2 H), 4.73–4.81 (m, 2 H), 5.05–5.17 (m, 6 H), 7.31–7.35 (m, 10 H); ^{13}C NMR (75 MHz, CDCl_3 , 25 °C) δ 28.0 ($2 \times \text{CH}_2$), 29.0 ($2 \times \text{CH}_2$), 35.1 ($2 \times \text{CH}_2$), 43.8 ($2 \times \text{CH}_2$), 49.1 ($2 \times \text{CH}$), 62.1 ($2 \times \text{CH}_2$), 67.7 ($2 \times \text{CH}_2$), 128.0 ($2 \times \text{CH}$), 128.2 ($2 \times \text{CH}$), 128.5 ($2 \times \text{CH}$), 136.2 ($2 \times \text{C}$), 146.4 ($4 \times \text{C}$), 155.5 ($2 \times \text{C}$); IR (ATR) 3399, 2923, 2853, 2360, 2340, 1694, 1497 cm^{-1} ; MS (ESITOF) m/z (%) 575 ($\text{M}^+ + \text{H}$, 100), 531 (9), 142 (13); HRMS (ESITOF) calcd for $\text{C}_{32}\text{H}_{39}\text{O}_6\text{N}_4$ 575.2864 ($\text{M}^+ + \text{H}$), found 575.2859.

14

Dibenzyl (3R,8R)-3,8-Di(3-iodopropyl)-1,3,4,6,8,9-hexahydrodipyrido(3,4-*b*:3',4'-*e*)-pyrazine-2,7-dicarboxylate (14). To a solution of **13** (25.5 mg, 0.044 mmol) in CH_2Cl_2 (3 mL) at room temperature, Ph_3P (35 mg, 0.133 mmol), imidazole (12.1 mg, 0.177 mmol) and I_2 (33.8 mg, 0.133 mmol) were successively added. After 45 min, the reaction mixture was poured in a separatory funnel with saturated $\text{Na}_2\text{S}_2\text{O}_3$ (15 mL), and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with brine (20 mL), dried, filtered and concentrated to give a residue which was purified by column chromatography (100% Et_2O), to afford **14** (33 mg, 0.041 mmol, 94%) as a colorless oil. $[\alpha]_D^{25} +55.8$ (c 0.32, CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25 °C) δ 1.54–1.65 (m, 4 H), 1.83 (m, 4 H), 2.78–2.84 (m, 2 H), 3.18–3.29 (m, 6 H), 4.29–4.34 (m, 2 H), 4.74–4.83 (m, 2 H), 5.09–5.19 (m, 6 H), 7.33–7.38 (m, 10 H); ^{13}C NMR (75 MHz, CDCl_3 , 25 °C) δ 6.0 ($2 \times \text{CH}_2$), 29.8 ($2 \times \text{CH}_2$), 32.3 ($2 \times \text{CH}_2$), 35.3 ($2 \times \text{CH}_2$), 43.8 ($2 \times \text{CH}_2$), 48.3 ($2 \times \text{CH}$), 67.8 ($2 \times \text{CH}_2$), 128.1 ($2 \times \text{CH}$), 128.3 ($2 \times \text{CH}$), 128.6 ($2 \times \text{CH}$), 136.2 ($2 \times \text{C}$), 146.2 ($4 \times \text{C}$), 155.3 ($2 \times \text{C}$); IR (ATR) 2925, 2852, 2360, 1695, 1497, 1422, 1398, 1338 cm^{-1} ; MS (ESITOF) m/z (%) 795 ($\text{M}^+ + \text{H}$, 18), 186 (100); HRMS (ESITOF) calcd for $\text{C}_{32}\text{H}_{37}\text{O}_4\text{N}_2\text{I}_2$ 795.0898 ($\text{M}^+ + \text{H}$), found 795.0897.

15

Dibenzy (3*R*,8*R*)-3,8-Diheptyl-1,3,4,6,8,9-hexahydrodipyrido(3,4-*b*:3',4'-*e*)-pyrazine-2,7-dicarboxylate (15). To a solution of CuBr•SMe₂ (3.7 mg, 0.018 mmol) and **14** (28.7 mg, 0.036 mmol) in THF (4 mL) at −78 °C, was added a solution of butylmagnesium bromide in THF (0.47 mL, 0.61 M, 0.289 mmol). The reaction was allowed to reach 0 °C overnight and quenched with saturated NH₄Cl (5 mL). The mixture was filtered through celite, washing with Et₂O, and the organic extract was washed with saturated NH₄Cl (10 mL), brine (10 mL), dried, filtered and concentrated in vacuo. The residue was purified by column chromatography (20% EtOAc/hexanes) to yield **15** (20.7 mg, 0.032 mmol, 88%) as a colorless oil. [α]_D²⁵ +67.1 (*c* 0.30, CHCl₃); ¹H NMR (300 MHz, CDCl₃, 25 °C) δ 0.87 (t, *J* = 6.7 Hz, 6 H), 1.23–1.53 (m, 24 H), 2.77–2.83 (m, 2 H), 3.20–3.27 (m, 2 H), 4.26–4.32 (m, 2 H), 4.63–4.87 (m, 2 H), 5.08–5.19 (m, 6 H), 7.32–7.38 (m, 10 H); ¹³C NMR (75 MHz, CDCl₃, 25 °C) δ 14.0 (2 × CH₃), 22.6 (4 × CH₂), 26.1 (2 × CH₂), 29.1 (2 × CH₂), 29.2 (2 × CH₂), 31.5 (2 × CH₂), 31.7 (2 × CH₂), 43.8 (2 × CH₂), 49.3 (2 × CH), 67.5 (2 × CH₂), 128.0 (2 × CH), 128.1 (2 × CH), 128.5 (2 × CH), 136.4 (2 × C), 146.1 (2 × C), 146.3 (2 × C), 155.4 (2 × C); IR (ATR) 2922, 2852, 2358, 2051, 1701, 1497 cm^{−1}; MS (ESITOF) *m/z* (%) 655 (M⁺ + H, 100), 381 (44); HRMS (ESITOF) calcd for C₄₀H₅₅O₄N₄ 655.4217 (M⁺ + H), found 655.4210.

16

Dibenzy (3*R*,8*R*)-3,8-(Dihept-6-en-1-yl)-1,3,4,6,8,9-hexahydrodipyrido(3,4-*b*:3',4'-*e*)-pyrazine-2,7-dicarboxylate (16). To a solution of CuBr•SMe₂ (3.4 mg, 0.016 mmol) and **14** (26 mg, 0.033 mmol) in THF (4 mL) at −78 °C, was added a solution of 3-butenylmagnesium bromide in THF (0.75 mL, 0.35 M, 0.263 mmol). The reaction was allowed to reach 0 °C overnight and quenched with saturated NH₄Cl (5 mL). The mixture was filtered through celite, washing with Et₂O, and the organic extract was washed with saturated NH₄Cl (10 mL), brine (10 mL), dried, filtered and concentrated in vacuo. The residue was purified by column chromatography (15% EtOAc/hexanes) to yield **16** (18.6 mg, 0.028 mmol, 87%) as a colorless oil. [α]_D²⁵ +83.1 (*c* 0.25, CHCl₃); ¹H NMR (300 MHz, CDCl₃, 25 °C) δ 1.19–1.52 (m, 16 H), 2.00 (m, 4 H), 2.77–2.83 (m, 2 H), 3.20–3.27 (m, 2 H), 4.25–4.31 (m, 2 H), 4.63–4.86 (m, 2 H), 4.91–5.00 (m, 4 H), 5.05–5.28 (m, 6 H), 5.70–5.84 (m, 2 H), 7.32–7.38 (m, 10

H); ^{13}C NMR (75 MHz, CDCl_3 , 25 °C) δ 25.9 (2 $\times$ CH_2), 28.7 (2 $\times$ CH_2), 31.5 (2 $\times$ CH_2), 33.6 (2 $\times$ CH_2), 35.0 (2 $\times$ CH_2), 35.6 (2 $\times$ CH_2), 43.8 (2 $\times$ CH_2), 49.4 (2 $\times$ CH), 67.5 (2 $\times$ CH_2), 114.3 (2 $\times$ CH_2), 128.0 (2 $\times$ CH), 128.1 (2 $\times$ CH), 128.5 (2 $\times$ CH), 136.4 (2 $\times$ C), 138.8 (2 $\times$ CH), 146.4 (4 $\times$ C), 155.4 (2 $\times$ C); IR (ATR) 2924, 2853, 2360, 1699, 1639, 1497, 1452 cm^{-1} ; MS (ESITOF) m/z (%) 651 ($\text{M}^+ + \text{H}$, 100), 381 (4); HRMS (ESITOF) calcd for $\text{C}_{40}\text{H}_{51}\text{O}_4\text{N}_4$ 651.3904 ($\text{M}^+ + \text{H}$), found 651.3921.

Barrenazine A (1).⁵ To a solution of **15** (14.3 mg, 0.022 mmol) in CH_2Cl_2 (1 mL) at 0 °C, was added Me_3SiI (3 $\times$ 25 μL , 0.525 mmol) at 30 min intervals. Then, the bath was removed and the mixture was stirred overnight at room temperature. The reaction was quenched with MeOH (1 mL), the solvent was removed under reduced pressure, and the residue was purified by column chromatography (10% MeOH/ CH_2Cl_2) to afford **1** (6.7 mg, 0.017 mmol, 80%) as a white solid. Mp 93–94 °C; $[\alpha]_{\text{D}}^{25}$ -54.9 (c 0.33, MeOH); ^1H NMR (500 MHz, CD_3OD , 25 °C) δ 0.92–0.95 (t, J = 6.9 Hz, 6 H), 1.31–1.76 (m, 24 H), 2.64–2.69 (m, 2 H), 2.94–3.05 (m, 4 H), 4.05 (s, 4 H); ^{13}C NMR (125 MHz, CD_3OD , 25 °C) δ 14.5 (2 $\times$ CH_3), 23.8 (2 $\times$ CH_2), 26.9 (2 $\times$ CH_2), 30.4 (2 $\times$ CH_2), 30.9 (2 $\times$ CH_2), 33.0 (2 $\times$ CH_2), 37.0 (2 $\times$ CH_2), 38.0 (2 $\times$ CH_2), 50.1 (2 $\times$ CH_2), 54.7 (2 $\times$ CH), 149.2 (2 $\times$ C), 149.8 (2 $\times$ C); IR (ATR): 3383, 2956, 2918, 2850, 2361, 1716 cm^{-1} ; MS (ESITOF) m/z (%) 387 ($\text{M}^+ + \text{H}$, 100), 194 (20); HRMS (ESITOF) calcd for $\text{C}_{24}\text{H}_{43}\text{N}_4$ 387.3482 ($\text{M}^+ + \text{H}$), found 387.3492.

Barrenazine B (2).⁵ To a solution of **16** (9.4 mg, 0.014 mmol) in CH_2Cl_2 (1 mL) at 0 °C, was added Me_3SiI (3 $\times$ 20 μL , 0.432 mmol) at 30 min intervals. Then, the bath was removed and the mixture was stirred overnight at room temperature. The reaction was quenched with MeOH (1 mL), the solvent was removed under reduced pressure, and the residue was purified by column chromatography (10% MeOH/ CH_2Cl_2) to afford **2** (4.1 mg, 0.011 mmol, 74%) as a

(5) (a) Focken, T.; Charette, A. B. *Org. Lett.* **2006**, 8, 2985–2988. (b) Martínez, M. M.; Sarandeses, L. A.; Pérez Sestelo, J. *Tetrahedron Lett.* **2007**, 48, 8536–8539.

white solid. Mp 75-76 °C; $[\alpha]_D^{25}$ -74.0 (*c* 0.25, MeOH); ^1H NMR (500 MHz, CD_3OD , 25 °C) δ 1.30–1.69 (m, 16 H), 2.04–2.17 (m, 4 H), 2.63–2.69 (m, 2 H), 2.94–3.04 (m, 4 H), 4.04 (s, 4 H), 4.93–4.96 (ddt, J = 10.1, 2.2, 1.2 Hz, 2 H), 4.99–5.04 (ddt, J = 17.0, 3.6, 1.4 Hz, 2 H), 5.80–5.93 (ddt, J = 17.0, 10.2, 6.6 Hz, 2 H); ^{13}C NMR (125 MHz, CD_3OD , 25 °C) δ 26.7 (2 $\times$ CH_2), 29.9 (2 $\times$ CH_2), 30.3 (2 $\times$ CH_2), 34.8 (2 $\times$ CH_2), 36.9 (2 $\times$ CH_2), 37.9 (2 $\times$ CH_2), 50.1 (2 $\times$ CH_2), 54.6 (2 $\times$ CH), 114.8 (2 $\times$ CH_2), 140.0 (2 $\times$ CH), 149.2 (2 $\times$ C), 149.8 (2 $\times$ C); IR (ATR) 3291, 3075, 2924, 2854, 2174, 2111, 2049, 2011 cm^{-1} ; MS (ESITOF) m/z (%) 383 ($\text{M}^+ + \text{H}$, 100); HRMS (ESITOF) calcd for $\text{C}_{24}\text{H}_{39}\text{N}_4$ 383.3169 ($\text{M}^+ + \text{H}$), found 383.3179.