Supporting Information

Synthesis of 9-substituted tetrahydrodiazepinopurines: Studies toward the total synthesis of asmarines.

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EXPERIMENTAL

General methods. Starting materials, reagents and solvents were purchased from commercial suppliers and were used without further purification. Petroleum ether refers to the fractions with bp 64-68 °C. THF was freshly distilled from sodium metal and benzophenone under an atmosphere of argon before use. Vacuum liquid chromatography (VLC) was performed using silica gel 60 H (Merck, 107736) prewashed with methanol.

Analysis. Melting points were determined on a Electrothermal IA9000 melting point apparatus and are uncorrected. IR spectra were obtained with a Bruker FTIR Vector 22 spectrometer and are reported in cm^{-1} . EIMS, CIMS and FABMS measurements were recorded on a Fisons, Autospec Q instrument. Electrospray MS measurements were performed on an AppliedBiosystems Q-STAR Pulsar instrument. NMR Spectra were recorded at either Bruker ARX-500, Bruker Avance-400 or Bruker Avance-200 spectrometers using standard Bruker pulse sequences. Chemical shifts (δ) are reported in ppm and the residual solvent pick used as internal standard. All NMR spectra were taken in d_6 -DMSO unless otherwise reported. The ^1H - ^{15}N HMBC experiments were optimized for a delay of 55 ms, the ^{15}N chemical shifts are reported with respect to liquid NH_3 as a reference standard.

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1-Bromo-5-phenyl-pentan-3-ol (32). To a stirred solution of phenetylmagnesium bromide prepared from Mg (843 mg, 35 mmol) and phenetylbromide (6.5 g, 35mmol) in dry THF (20 mL) under argon atmosphere, at $-10\text{ }^{\circ}\text{C}$ was added 3-bromo-propanal (10 g, 73 mmol) in dry THF (30 mL) over a period of 1 h. The solution was poured onto saturated aq. NH_4Cl (40 mL) and extracted with ether ($2 \times 50\text{mL}$). The combined organic layer was dried over Na_2SO_4 , and concentrated in vacuo. The residue was purified by VLC (CH_2Cl_2 /petroleum ether, 3:2) affording compound **32** (1.8 g, 21%) as an unstable oil (used readily in the next stage): ^1H NMR (200 MHz,

CDCl₃) δ 7.23-7.34 (m, 5H), 3.87 (m, 1H), 3.60 (t, J = 6.5 Hz, 1H), 2.77 (m, 2H), 2.03 (m, 2H), 1.81 (m, 2H); ¹³C NMR (50 MHz, CDCl₃) δ 141.0, 128.5, 128.4, 125.9, 69.2, 40.0, 39.0, 31.9, 30.5; MS (CI) m/z (rel intensity): 243 (13, MH⁺), 225 (47), 145 (90).

N⁶-Benzyloxy-7-(5-phenyl-pentan-3-ol)-9-diphenyl-methyladeninium bromide (11d). Compound **11d** was prepared from compound **13c** (710 mg, 1.75 mmol) and **32** (1.3 g, 5.5 mmol) in DMF (5 mL) by allowing them to react at 75 °C for 5 days according to a previous published procedure.¹ The residue was purified by VLC (methanol/EtOAc, 1:10) affording compound **11d** (1.0 g, 90%) as an amorphous solid: ¹H NMR (200 MHz) δ 9.14 (s, 1H), 7.81 (s, 1H), 7.12-7.43 (m, 21H), 5.04 (s, 2H), 4.72 (d, J = 5.5 Hz, 1H), 4.44 (m, 1H), 4.34 (m, 1H), 3.36 (m, 1H), 2.62 (m, 1H), 2.53 (m, 1H), 1.90 (m, 1H), 1.81 (m, 1H), 1.60 (m, 2H); ¹³C NMR (125 MHz) δ 148.7, 142.0, 140.9, 137.7, 137.1, 136.6, 136.3, 129.0, 128.8, 128.3, 128.2, 127.8, 125.6, 111.1, 75.7, 67.0, 63.0, 48.0, 38.8, 36.5, 31.2; MS (FAB) m/z (rel intensity): 570 (45, MH⁺), 167 (100); HRMS (FAB): calcd for C₃₆H₃₅N₅O₂ (MH⁺) 570.2869 found 570.2861.

N⁶-Benzyloxy-7-(5-phenyl-pentan-3-ol)adenine (12d). Compound **12d** was prepared from **11d** (300 mg, 0.46 mmol) by reacting it with a mixture of TFA (10 mL) and CH₂Cl₂ (10 mL) at room temperature for 24 h, according to a previous published procedure.¹ The residue was purified by VLC (methanol/EtOAc, 1:20) affording compound **12d** (185 mg, 55%) as an amorphous solid: ¹H NMR (200 MHz) δ 11.23 (br s, 1H), 7.83 (s, 1H), 7.56 (s, 1H), 7.10-7.41 (m, 10H), 4.97 (s, 2H), 4.78 (br d, 1H), 4.21 (m, 2H), 3.30 (br m, 1H), 2.55 (m, 2H), 1.52-1.89 (m, 4H); ¹³C NMR (50 MHz) δ 150.7, 143.4, 142.6, 141.4, 140.2, 138.7, 128.5, 127.9, 125.9, 109.7, 75.3, 66.5, 49.0, 44.5, 38.7, 31.7; MS (CI) *m/z* (rel intensity): 404 (17, M⁺), 107 (100); HRMS (CI): calcd for C₂₃H₂₆N₅O₂ (MH⁺) 404.2086, found 404.2083.

7,8,9,10-Tetrahydro-10-benzyloxy-9-phenethyl-[1,4]diazepino[1,2,3-*g,h*]purine (12e). Compound **12e** was prepared from **12d** (114 mg, 0.28 mmol), triphenylphosphine (237 mg, 0.9 mmol) and diisopropylazodicarboxylate (171 mg, 0.85 mmol) in dry THF (7 mL) under argon atmosphere at 40 °C for 3 h and then at room temperature for 16 h according to a previous published procedure.¹ The residue was purified by VLC (methanol/EtOAc, 1:12) affording compound **12e** (58 mg, 54%) as an amorphous solid: ¹H NMR (500 MHz) δ 8.49 (s, 1H), 8.40 (s, 1H), 7.16-7.40 (m, 10H), 5.07 (d, *J* = 10 Hz, 1H), 4.94 (d, *J* = 10 Hz, 1H), 4.42 (m, 1H), 4.21 (m, 1H), 3.89 (m, 1H), 2.72 (m, 1H), 2.58 (m, 1H), 2.42 (m, 1H), 2.18 (m, 1H), 2.02 (m, 1H), 1.89 (m, 1H); ¹³C NMR (50 MHz) δ 159.4, 152.3, 150.7, 146.2, 141.3, 132.0, 129.6, 128.6, 127.6, 126.2, 109.6, 76.3, 61.4, 41.8, 32.0, 29.3, 28.9; MS (EI) *m/z* (rel

intensity): 385 (7, M^+), 279 (30), 174 (100); HRMS (EI): calcd for $C_{23}H_{23}N_5O$ (M^+) 385.1903, found 385.1909.

7,8,9,10-Tetrahydro-10-hydroxy-9-phenethyl-[1,4]diazepino[1,2,3-*g,h*]purine (5).

Compound **5** was prepared from **12e** (37 mg, 0.1 mmol) in 30% HBr in AcOH (1 ml) at 100 °C for 3.5 h according to previous published procedure.¹ The residue was purified by VLC (methanol/EtOAc, 1:6) affording compound **5** (21 mg, 74%) as an amorphous solid: 1H NMR (400 MHz) δ 8.34 (br s, 1H), 8.33 (br s, 1H), 7.14-7.24 (m, 5H), 4.39 (m, 1H), 4.26 (m, 1H), 3.97 (m, 1H), 2.72 (m, 1H), 2.60 (m, 1H), 2.51 (m, 1H), 2.34 (m, 1H), 2.08 (m, 1H), 1.83 (m, 1H); ^{13}C NMR (125 MHz) δ 158.4, 151.8, 150.6, 141.9, 141.4, 128.3, 125.8, 108.9, 62.7, 41.6, 31.6, 29.8, 28.7; MS (EI) m/z (rel intensity): 295 (10, M^+), 279 (10), 174 (35); HRMS (EI): calcd for $C_{16}H_{17}N_5O$ (M^+) 295.1433, found 295.1435.

¹H NMR spectra of compound 13a (200 MHz, d₆-DMSO).

¹³C NMR spectra of compound 13a (100 MHz, d₆-DMSO).

¹H NMR spectra of compound 13b (200 MHz, d₆-DMSO).

¹³C NMR spectra of compound 13b (50 MHz, d₆-DMSO).

¹H NMR spectra of compound 14a (200 MHz, d₆-DMSO).

¹³C NMR spectra of compound 14a (125 MHz, d₆-DMSO).

^1H NMR spectra of compound 15a (400 MHz, $\text{d}_6\text{-DMSO}$).

^{13}C NMR spectra of compound 15a (100 MHz, $\text{d}_6\text{-DMSO}$).

¹H NMR spectra of compound 17a (200 MHz, d₆-DMSO).

¹H-¹⁵N HMBC spectra of compound 17a (40 MHz, d₆-DMSO).

¹H NMR spectra of compound 18a (200 MHz, d₆-DMSO, 80 °C).

¹³C NMR spectra of compound 18a (125 MHz, d₆-DMSO).

¹H NMR spectra of compound 6 (400 MHz, d₆-DMSO).

¹³C NMR spectra of compound 6 (125 MHz, d₆-DMSO, 60 °C).

^1H - ^{15}N HMBC spectra of compound 6 (40 MHz, d_6 -DMSO, 60 °C).

¹H NMR spectra of compound 7·HBr (200 MHz, d₆-DMSO).

¹³C NMR spectra of compound 7·HBr (125 MHz, d₆-DMSO).

¹H NMR spectra of compound 19 (500 MHz, d₆-DMSO).

¹³C NMR spectra of compound 19 (125 MHz, d₆-DMSO).

¹H NMR spectra of compound 20b (400 MHz, d₆-DMSO).

¹³C NMR spectra of compound 20b (100 MHz, d₆-DMSO).

¹H NMR spectra of compound 8 (500 MHz, d₆-DMSO).

¹H NMR spectra of compound 26 (500 MHz, d₆-DMSO).

¹³C NMR spectra of compound 26 (125 MHz, d₆-DMSO).

¹H NMR spectra of compound 27 (400 MHz, d₆-DMSO).

¹³C NMR spectra of compound 27 (100 MHz, d₆-DMSO).

¹H NMR spectra of compound 9 (400 MHz, d₆-DMSO).

¹³C NMR spectra of compound 9 (100 MHz, d₆-DMSO).

References.

- (1) Pappo, D.; Kashman, Y.; *Tetrahedron* **2003**, 59, 6493-6501.