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Supporting information

for

Synthesis of Novel Tetranorlabdane Derivatives with Unprecedented Carbon Skeleton

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1. General experimental procedures

Melting points (mp) were determined in capillary tubes and on a Boetius (VEB Analytik, DDR) hot stage. IR spectra were obtained on the Bio-Rad-Win-IR and Perkin-Elmer Models spectrometer in CCl₄ and Nujol. ¹H and ¹³C NMR spectra were recorded in CDCl₃ on a Bruker
Avance DRX 400 (400.13 and 100.61 MHz) spectrometer. Chemical shifts are given in parts per million values in the $\delta$ scale with CHCl$_3$ as reference (set $\delta_H$ at 7.26 ppm and $\delta_C$ 77.00 ppm) and coupling constants $J$ in Hertz. Carbon substitution degrees were established by the DEPT pulse sequence. H,H-COSY, H,C-HSQC and H,C-HMBC experiments were recorded using standard pulse sequences, in the version with z-gradients, as delivered by Bruker. Mass spectra (MS) were run on a Bruker Esquire 3000 spectrometer (EI, 70 eV). Optical rotations ([α]$_D$) were determined on a Jasco DIP 370 polarimeter (Rudolph Research Analytical, Hackettsstown, NJ, USA) with a 1 dm microcell, using CHCl$_3$ as solvent. For analytical TLC, Merck silica gel 60 G in 0.25 mm layers was used. Chromatographic column separations were carried out on Merck silica gel 60 (70-230 mesh) using petroleum ether (PE, bp 40-60 °C) and mixtures of petroleum ether with EtOAc of increasing polarity. All solvents were purified and dried by standard techniques just before use. Usual work-up means that water was added to the reaction mixture, which was then extracted with ether, the combined organic layers were washed with brine, dried over Na$_2$SO$_4$ or MgSO$_4$ and the solvent evaporated under reduced pressure.

**Methyl 2-((3S,4aS,8aS)-3-hydroxy-2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)acetate 12.**

A solution of ketoester 6 (500 mg, 1.80 mmol) in MeOH (10 ml) was added to a stirred solution of CeCl$_3$·7H$_2$O (671 mg, 1.80 mmol) in MeOH (5 mL) at 18°C. After 3 min NaBH$_4$ (68 mg, 1.80 mmol) was added and the mixture was stirred at the same temperature for 0.5 h (TLC control). The reaction mixture was treated with cold 5% HCl solution (5 mL), and after dissolution of the precipitate it was extracted with diethyl ether (3 x 25 mL). The extract was washed with water (2 x 15 mL) and dried. After removal of the solvent the crude product (510 mg) was purified by column chromatography on silica gel (25 g, eluent: PE/EtOAc 85:15), to give hydroxy ester 12 (492 mg, 98%), as white crystals, mp 106°-107°C (PE); [α]$_D^{20}$ +50.8 (c 0.03, CHCl$_3$); IR $\nu_{\text{max}}$ (CCl$_4$): 3492, 2948, 1730, 1467, 1440, 1328, 1159, 1016 cm$^{-1}$; $^1$H NMR (400.13 MHz) $\delta$=4.15 (1H, dd, $J$ 15.6, 7.2 Hz, $H$-7), 3.67 (3H, s, CO$_2$CH$_3$), 3.40 (1H, d, $J$ 17.2 Hz, $H$-11), 2.98 (1H, d, $J$ 17.2 Hz, $H$-11), 2.12 (2H, dd, $J$ 11.6, 7.2 Hz, $H$-6), 1.71 (3H, s, $H$-17), 1.25 (1H, m, $H$-5), 1.00 (3H, s, $H$-20), 0.89 (3H, s, $H$-18), 0.85 (3H, s, $H$-19); $^{13}$C NMR (100.61 MHz) $\delta$=172.8 (C-12), 137.8 (C-9), 132.7 (C-8), 72.9 (C-7), 51.8 (CO$_2$CH$_3$), 49.5 (C-5), 41.2 (C-3), 39.4 (C-10), 35.9 (C-1), 33.0 (C-11), 32.9 (C-19), 32.8 (C-4), 29.7 (C-6), 21.5 (C-18), 19.7 (C-20), 18.7 (C-2), 15.5 (C-17); m/z 280 [(M$^+$, 14)], 221 (5), 207 (25), 191 (8), 173 (9), 157 (25), 135 (11), 124 (100), 109 (65), 96 (29), 81 (14), 69 (24), 55 (31), 41 (40); HRMS (EI): (M$^+$ 14) found 280.20344. C$_{17}$H$_{28}$O$_3$ requires 280.20384.
Methyl 2-((4aS,8aS)-2,5,5,8a-tetramethyl-4a,5,6,7,8,8a-hexahydonaphthalen-1-yl)acetate 13

A solution of concentrated H₂SO₄ (0.16 mL) in THF (0.84 mL) was added to a solution of alcohol 12 (250 mg, 0.89 mmol) in THF (4 mL) and the obtained mixture was stirred for 24 h at room temperature, diluted with water (10 mL) and extracted with ether (3 x 15 mL). The organic layer was washed with water (2 x 20 mL) and dried. The removal of the solvent afforded a yellow oil (247 mg), which was purified by column chromatography on silica gel (5 g, eluent: PE/EtOAc 95:5), to give diene 13 (208 mg, 89%), as white crystals, mp 55-56°C (PE); [α]₀ D₂₂ +67.8 (c 1.17, CHCl₃); IR ν max (film): 2860, 1746, 1467, 1377, 1155, 1120, 750 cm⁻¹; ¹H NMR (400.13 MHz) δ=5.87 (1H, dd, J 9.6, 2.8 Hz, H-7), 5.79 (1H, dd, J 9.6, 2.8 Hz, H-6), 3.68 (3H, s, CO₂CH₃), 3.16 (1H, d, J 16.0 Hz, H-11), 3.04 (1H, d, J 16.0 Hz, H-11), 2.06 (1H, t, J 2.8 Hz, H-5), 1.74 (3H, s, H-17), 0.96 (3H, s, H-20), 0.94 (3H, s, H-18), 0.81 (3H, s, H-19); ¹³C NMR (100.61 MHz) δ=172.9 (C-12), 136.2 (C-9), 129.1 (C-6), 128.4 (C-8), 127.8 (C-7), 52.4 (CO₂CH₃), 51.8 (C-5), 40.8 (C-3), 38.7 (C-10), 35.2 (C-1), 32.9 (C-4), 32.5 (C-11), 32.4 (C-19), 22.7 (C-18), 18.9 (C-2), 18.2 (C-20), 14.9 (C-17); m/z 262 (M⁺, 27), 203 (7), 191 (13), 173 (63), 159 (10), 145 (19), 133 (36), 119 (100), 105 (16), 91 (20), 83 (13), 69 (10), 55 (26), 41 (35); HRMS (EI): M⁺, found 262.19356. C₁₇H₂₆O₂ requires 262.19328.

Methyl 3-(2,6,6,11-tetramethyl-9,10 dioxatricyclo[6.2.2.0²,7]dodec-11-en-1-yl) propanoate 14, methyl 3-(2b,4b,8,8-tetramethylperhydro[1,2]dioxeto[3',4':3,4]naphtha [1,2-c][1,2]dioxet-4-yl)propanoate 15 and (R)-methyl 2-(2,5,5,8a-tetramethyl-3-oxo-3,5,6,7,8,8a-hexahydonaphthalen-1-yl)acetate 16.

2 mg of meso-tetraphenylporphyrin (TPP) were added to a stirred solution of diene 13 (240 mg, 0.92 mmol) in CH₂Cl₂ (25 mL). The resulting mixture was irradiated with two bulb lumps (100 W each) while oxygen was passed through solution, in which the mixture was stirred for 5 h at 5°C. Evaporation of the solvent at the reduced pressure and chromatography of the residue (311 mg) on SiO₂ (16 g, eluent: PE/EtOAc 9:1) gave endoperoxide 14 (57 mg, 21%), as white crystals, mp 68-69°C (from EP/EtOAc 9:1); [α]₀ D₂₃ +11.95 (c 0.21, CHCl₃); IR ν max (film): 2924, 1730, 1356, 1198, 1167, 1107 cm⁻¹; ¹H NMR (400.13 MHz) δ=6.36 (1H, d, J 6.0 Hz, H-7), 4.52 (1H, d, J 6.0 Hz, H-6), 3.68 (3H, s, CO₂CH₃), 2.84 (1H, d, J 16.0 Hz, H-11), 2.62 (1H, d, J 16.0 Hz, H-11), 2.06 (1H, m, H-5), 2.02 (3H, s, H-17), 1.60 (3H, s, H-20), 0.92 (3H, s, H-18), 0.79 (3H, s, H-19); ¹³C NMR (100.61 MHz) δ=169.9 (C-12), 141.8 (C-8), 125.7 (C-7), 86.3 (C-9), 72.3 (C-6), 51.9 (C-5), 51.7 (CO₂CH₃), 45.3 (C-10), 38.8 (C-3), 32.2 (C-4), 31.8 (C-19), 32.0 (C-11), 30.5 (C-1), 24.3 (C-18), 21.3 (C-17), 20.1 (C-20), 18.6 (C-2); m/z 262 [(M⁺ - 32) 10], 205 (3), 193 (18), 187 (19), 173 (29), 151 (10), 133 (20), 119 (44), 109 (95), 95 (57), 81
The next compound eluted with the same system was the known dioxine 15 (19 mg, 7%), as oil; [α]_D \text{27} = -15.49 (c 0.4, CHCl_3); IR ν_{\text{max}} (film): 2951, 1738, 1672, 1436, 1335, 1262, 1172, 1155, 1025, 905 cm\(^{-1}\); \(^1\)H NMR (400.13 MHz) δ=3.67 (3H, s, CO\(\text{2CH}_3\)), 3.15 (1H, d, J 4.0 Hz, H-6), 2.85 (1H, d, J 4.0 Hz, H-7), 2.83 (1H, d, J 16.0 Hz, H-11), 2.56 (1H, d, J 16.0 Hz, H-11), 1.49 (1H, d, J 4.0 Hz, H-5), 1.62 (3H, s, H-17), 1.03 (3H, s, H-19), 1.01 (3H, s, H-18), 0.97 (3H, s, H-20); \(^13\)C NMR (100.61 MHz) δ=170.8 (C-12), 68.4 (C-9), 58.5 (C-8), 52.9 (CO\(\text{2CH}_3\)), 49.1 (C-7), 45.5 (C-5), 40.5 (C-3), 39.7 (C-10), 33.9 (C-1), 33.2 (C-11), 32.7 (C-4), 32.6 (C-19), 22.1 (C-18), 19.3 (C-17), 18.5 (C-2), 17.9 (C-20); m/z 293 [(M+ -33) 18), 194 (5), 167 (10), 159 (8), 133 (20), 124 (6), 109 (24), 85 (22), 81 (16), 69 (43), 55 (35), 41 (48); HRMS (EI): (M+ -32) found 293.17408. C\(_{17}\)H\(_{26}\)O\(_6\) requires 326.19248.

The next compound eluted with the same system was the known dienone 16 (137 mg, 54%), as white crystals, mp 111-112°C (from hexane); [α]_D \text{20} +50.80 (c 6.31, CHCl_3); IR ν_{\text{max}} (nujol): 1715, 1637, 1614, 1371, 1350, 1167 cm\(^{-1}\); \(^1\)H NMR (400.13 MHz) δ=6.31 (1H, s, H-6), 3.68 (3H, s, CO\(\text{2CH}_3\)), 3.43 (1H, d, J 16.9 Hz, H-11), 3.31 (1H, d, J 16.9 Hz, H-11), 1.84 (3H, s, H-17), 1.28 (3H, s, H-20), 1.27 (3H, s, H-18), 1.20 (3H, s, H-19); \(^13\)C NMR (100.61 MHz) δ=186.5 (C-7), 171.9 (C-5), 170.3 (C-12), 154.8 (C-9), 133.3 (C-8), 123.7 (C-6), 52.1 (CO\(\text{2CH}_3\)), 43.6 (C-10), 40.1 (C-3), 37.2 (C-4), 34.9 (C-11), 34.3 (C-1), 32.3 (C-19), 28.5 (C-18), 25.2 (C-20), 18.1 (C-2), 11.6 (C-17); m/z 276 (M+ , 100), 261 (22), 244 (17), 233 (53), 220 (26), 203 (89), 189 (30), 174 (61), 159 (69), 147 (33), 133 (20), 119 (44), 105 (33), 91 (42), 81 (18), 69 (48), 55 (46), 41 (78); HRMS (EI): M+ found 276.17209. C\(_{17}\)H\(_{24}\)O\(_3\) requires 276.17254.

Methyl-2-((1R,4S,4aS,8aS)-1,4-dihydroxy-2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl) acetate 17.

A solution of thiourea (29 mg, 0.37 mmol) in MeOH (1 mL) was added to a solution of endoperoxide 14 (55 mg, 0.19 mmol) in MeOH (1.5 mL) for 10 min. at room temperature. The reaction mixture was stirred at room temperature for 3 h, then diluted with water and extracted with diethyl ether (3 x 25 mL). After drying and solvent removal, the crude product (58 mg) was subjected to column chromatography on silica gel (5 g, eluent: PE/EtOAc 8:2) to give diol 17 (55 mg, 96%) as oil; [α]_D \text{23}^2+24.94 (c 0.19, CHCl_3); IR ν_{\text{max}} (film): 3420, 2930, 1710, 1440, 1380, 1205, 1160, 1067, 1032, 910, 804, 733 cm\(^{-1}\); \(^1\)H NMR (400.13 MHz) δ=5.48 (1H, m H-7), 4.04 (1H, dd, J 10.0, 2.0 Hz, H-6), 3.69 (3H, s, CO\(\text{2CH}_3\)), 2.54 (1H, d, J 16.0 Hz, H-11), 2.46 (1H, d, J 16.0 Hz, H-11), 1.81 (1H, d, J 10.0 Hz, H-5), 1.68 (3H, dd, J 2.0, 1.4 Hz, H-17), 1.14 (3H, s, H-19), 1.04 (3H, s, H-18), 0.88 (3H, s, H-20); \(^13\)C NMR (100.61 MHz) δ=175.4 (C-12), 135.8
Methyl 2-(((1R,4S,4aS,8aS)-4-acetoxy-1-hydroxy-2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)acetate \textit{18}.

Acetic anhydride (2.8 mL) was added to a solution of diol \textit{17} (115 mg, 0.39 mmol) in dry pyridine (4 mL). The mixture was stirred for 2.5 hours at room temperature, then diluted with water (15 mL) and extracted with diethyl ether (3 x 15 mL). The organic solution was washed with (15 mL) 5% solution of sulfuric acid, the saturated solution of sodium bicarbonate (15 mL), water (3 x 15 mL) and dried. After removal of the solvent the crude product (135 mg) was purified by column chromatography on silica gel (7 g, eluent: EP/ EtOAc 85:15) to afford acetate \textit{18} (123 mg, 94%) as oil; \([\alpha]_D^{25} +78.0 \text{ (c 0.8, CHCl}_3\); IR \(\nu_{\text{max}}\) (Nujol): 3580, 3080, 1785, 1510, 1440, 1410, 1315, 1273, 1240, 1140, 1105, 1025, 983 cm\(^{-1}\); \(^1\)H NMR (400.13 MHz) \(\delta=5.37 \text{ (1H, m, H-7)}, 5.33 \text{ (1H, m, H-6)}, 3.71 \text{ (3H, s, CO}_2\text{CH}_3), 2.57 \text{ (1H, d, J 16.0 Hz, H-11)}, 2.47 \text{ (1H, d, J 16.0 Hz, H-11)}, 2.26 \text{ (1H, d, J 10.2 Hz, H-5)}, 2.02 \text{ (3H, s, OAc)}, 1.68 \text{ (3H, s, H-17)}, 0.97 \text{ (3H, s, H-19)}, 0.95 \text{ (3H, s, H-18)}, 0.93 \text{ (3H, s, H-20)}; ^{13}\text{C NMR (100.61 MHz)} \delta=175.4 \text{ (C-12)}, 170.8 \text{ (OAc), 138.2 (C-8), 125.6 (C-7), 75.6 (C-9), 71.2 (C-6), 52.0 (CO}_2\text{CH}_3), 44.6 \text{ (C-5), 43.8 (C-10), 42.3 (C-3), 35.3 (C-19), 34.3 (C-11), 32.9 (C-1), 32.8 (C-4), 22.8 (C-18), 21.6 \text{ (OAc), 19.1 (C-17), 18.4 (C-2), 17.7 (C-20); m/z 338 (M^+ \text{, 4)}, 278 (99), 263 (10), 245 (8), 214 (54), 207 (41), 187 (18), 172 (70), 167 (55), 154 (95), 149 (33), 135 (46), 121 (28), 109 (36), 95 (41), 81 (20), 69 (47), 55 (38), 43 (100); HRMS (EI): found 388.20920. C\(_{19}\)H\(_{30}\)O\(_5\) requires 388.20932.

Methyl 2-(((1S,4S,4aS,8aS)-4-acetoxy-2-(bromomethyl)-1-hydroxy-5,5,8a-trimethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)acetate \textit{19}.

NBS (116 mg, 0.65 mmol) was added to a solution of acetate \textit{18} (110 mg, 0.33 mmol) in dry CCl\(_4\) (5 mL) and the mixture was refluxed for 3 h. Then the solution was filtered and the solvent removed under reduced pressure. The product (170 mg) was purified by column chromatography on silica gel (7 g, eluent: PE/ EtOAc 96:4) to give bromide \textit{19} (103 mg, 76%) as oil; \([\alpha]_D^{20} -10.8^\circ \text{ (c 1.4, CHCl}_3\); IR \(\nu_{\text{max}}\) (film): 3440, 2940, 1730, 1438, 1370, 1247, 1117, 960, 918 cm\(^{-1}\); \(^1\)H NMR (400.13 MHz) \(\delta=5.86 \text{ (1H, d, J 2.75 Hz, H-7)}, 5.41 \text{ (1H, dd, J 2.75 Hz, H-6)}, 4.07 \text{ (2H, brd, J 1.62 Hz, H-17)}, 3.72 \text{ (3H, s, CO}_2\text{CH}_3), 2.86 \text{ (1H, d, J 16.5 Hz, H-11)}, 2.79 (1H,
Methyl 2-((1S,4S,4aS,8aS)-4-acetox y-2-(acetoxymethyl)-1-hydroxy-5,5,8a-trimethyl-1,4,4a,5,6,-7,8,8a-octahydronaphthalen-1-yl)acetate 20.

The mixture of bromide 19 (60 mg, 0.14 mmol) and KOAc (28 mg, 0.28 mmol) in DMSO (1 mL) was stirred for 2h at room temperature, then diluted with water and extracted with diethyl ether. The organic extract was washed with water and dried. The removal of the solvent gave a crude product (65 mg) which was purified by column chromatography on silica gel (1 g, eluent: PE/ EtOAc 95:5) to afford diacetate 20 (50 mg, 88%), as oil; [α]D 20 + 87.94° (c 0.01, CHCl3); IR νmax (film): 3480, 2960, 1740, 1450, 1380, 1250, 1185, 1035, 970, 923 cm⁻¹; 1H NMR (400.13 MHz) δ=5.72 (1H, d, J 2.0 Hz, H-7), 5.44 (1H, dd, J 10.8, 2.0 Hz, H-6), 4.59 (1H, d, J 12.8 Hz, H-17), 4.53 (1H, d, J 12.8 Hz, H-17), 3.71 (3H, s, CO₂CH₃), 2.68 (1H, d, J 16.4 Hz, H-11), 2.59 (1H, d, J 16.4 Hz, H-11), 2.33 (1H, d, J 10.8 Hz, H-5), 2.06 (3H, s, OAc), 2.03 (3H, s, OAc), 0.99 (3H, s, H-19), 0.98 (3H, s, H-18), 0.97 (3H, s, H-20); 13C NMR (100.61 MHz) δ=174.9 (C-12), 170.8 (OAc), 170.5 (OAc), 136.8 (C-8), 131.4 (C-7), 75.2 (C-9), 70.7 (C-6), 65.3 (C-17), 52.2 (CO₂CH₃), 44.8 (C-5), 44.3 (C-10), 42.4 (C-3), 35.5 (C-19), 34.4 (C-1), 32.9 (C-11), 32.8 (C-4), 22.9 (C-18), 21.8 (OAc), 20.9 (OAc), 18.6 (C-2), 17.8 (C-20); m/z 336 [(M⁺-58, 7)], 276 (19), 261 (23), 225 (12), 212 (13), 203 (30), 187 (19), 170 (69), 152 (77), 133 (19), 109 (23), 91 (13), 81 (13), 69 (32), 55 (20), 43 (100); HRMS (EI): found 336.19364.

C₂₁H₃₀O₇ requires 394.46038.

Methyl 2-((8aS)-2-(bromomethyl)-5,5,8a-trimethyl-3-oxo-3,4,5,6,7,8,8a-octahy dronaphthalen-1-yl)acetate 21 and methyl 2-((1R,2R,8aS)-2-bromo-2,5,5,8a-tetramethyl-3-oxodecahydronaphthalen-1-yl)acetate 22.

NBS (0.819 g, 5.38 mmol) was added to a solution of keto ester 6 (1.0 g, 3.59 mmol) in dry CCl₄ (27 mL) and it was refluxed for 2 h. After cooling, the reaction mixture was filtered and the solvent removed under reduced pressure. The resulted crude reaction product (1.4 g) was purified by column chromatography on silica gel (7 g, eluent: PE/EtOAc 95.5:0.5), to give bromide 22 (130 mg, 10%), as white crystals, mp 101-102 ºC (from PE); [found: C, 56.97; H, 7.62; Br, 22.13. C₁₉H₂₅O₃Br requires C, 56.82; H, 7.57; Br, 22.24%]; [α]D 20 -123.1 (c 1.9,
CHCl₃); IR νₓ (CCl₄): 2949, 2928, 2870, 2849, 1738, 1714, 1460, 1436, 1391, 1373, 1230, 1260, 1193, 1171, 1115, 1097, 1066, 1035, 992, 880, 833, 792, 772, 626, 527, 480 cm⁻¹; ¹H NMR (400.13 MHz) δ=3.71 (3H, s, CO₂CH₃), 3.03 (1H, dd, J 16.0, 4.0 Hz, H-11), 2.60 (1H, d, J 16.0 Hz, H-6), 2.46 (1H, dd, J 16.0, 4.0 Hz, H-11), 2.05 (1H, d, J 4.0 Hz, H-9), 1.70 (3H, s, H-17), 1.28 (1H, dd, J 16.0 Hz, 4.0 Hz, H-5), 1.17 (3H, s, H-19), 0.90 (3H, s, H-18), 0.87 (3H, s, H-20); ¹³C NMR (100.61 MHz) δ=202.8 (C-7), 173.8 (C-12), 69.5 (C-8), 56.4 (C-9), 52.1 (CO₂Me), 41.4 (C-3), 39.1 (C-1), 38.9 (C-10), 34.5 (C-11), 33.7 (C-4), 33.1 (C-6), 32.7 (C-19), 27.3 (C-17), 21.1 (C-18), 17.7 (C-2), 14.4 (C-20).

Next, with the same solvent, bromide 21 (1.15 g, 90%), was eluted as white crystals, mp 107-108 °C (from PE); [found: C, 57.17; H, 6.91; Br, 22.21. C₁₇H₂₅O₃Br requires C, 57.14; H, 7.05; Br, 22.37%]; [α]D²⁰ +30.5 (c 6.2, CHCl₃); IR νₓ (CCl₄): 2933, 2867, 2855, 1771, 1741, 1668, 1614, 1457, 1443, 1434, 1389, 1377, 1366, 1339, 1330, 1323, 1257, 1214, 1199, 1168, 1158, 1168, 1038, 1014, 982, 929, 886, 863, 786, 759, 737, 704, 688 cm⁻¹; ¹H NMR (400.13 MHz) δ=4.41 (1H, d, J 9.6 Hz, H-17), 3.95 (1H, d, J 9.6 Hz, H-17), 3.74 (3H, s, CO₂Me), 3.54 (1H, s, H-11), 2.59 (1H, d, J 16.4 Hz, H-11), 2.43 (1H, dd, J 17.6, 14.4 Hz, H-6), 1.78 (1H, d, J 3.2 Hz, H-5), 1.19 (3H, s, H-19), 1.09 (3H, s, H-18), 0.93 (3H, s, H-20); ¹³C NMR (100.61 MHz) δ=196.9 (C-7), 169.8 (C-12), 164.1 (C-9), 134.0 (C-8), 52.6 (CO₂Me), 49.5 (C-5), 41.1 (C-10), 40.8 (C-3), 35.1 (C-1), 34.9 (C-6), 34.1 (C-11), 33.2 (C-4), 32.3 (C-19), 24.6 (C-17), 21.3 (C-18), 18.4 (C-2), 17.5 (C-20).

Dimethyl[4,8,15,19,19-hexamethyl-11,22-dioxoheptacyclo[10.10.2.0¹,14.0³,12.0³,14.0⁴,9.0¹⁵,20]tetra-cosane]-2,13-dicarboxylate 23 and methyl 2-((8aS)-2-(acetoxymethyl)-5,5,8a-trimethyl-3-oxo-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)acetate 24.

KOAc (0.64 mg, 6.44 mmol) was added to a solution of bromide 21 (1.15 g, 3.22 mmol) in dry DMSO (23 mL) and the reaction mixture was stirred overnight at room temperature. Then it was diluted with water (50 mL) and extracted with Et₂O (3x20 mL). An organic layer was washed with water (3 x 30 mL) and dried. After the solvent removal in vacuo, the crude reaction product (1.2 g) was subjected to column chromatography on silica gel (36 g, eluent: PE/EtOAC 95:5), to give dimer 23 (1.54 g, 86%), as white crystals, mp 223-224 °C (from PE). [α]D²⁰ -26.8 (c 18.4, CHCl₃); IR νₓ (CCl₄): 3435, 2958, 2300, 1728,1704, 1618, 1458, 1433, 1381, 1368, 1255, 1192, 1159, 1069, 1043, 1024, 839, 799 cm⁻¹; ¹H NMR (400.13 MHz): Unit A δ=3.58 (3H, s, CO₂Me), 3.23 (1H, s, H-11), 1.20-2.80 (11H, overlapped signals, H-1, H-3, H-5, H-6, H-17), 0.95 (6H, s, H-18 and H-19), 0.78 (3H, s, H-20); Unit B δ=3.80 (1H, s, H-11’), 3.57 (3H, s, CO₂Me), 1.20-2.80 (11H, overlapped signals, H-1’, H-3’, H-5’, H-6’, H-17’), 1.01 (3H, s, H-19’), 0.95 (3H, s, H-18’), 0.92 (3H, s, H-20’). ¹³C NMR (100.61 MHz): Unit A δ=210.7 (C-7),
172.3 (C-12), 69.9 (C-9), 57.6 (C-8), 53.4 (C-11), 51.9 (CO₂Me), 44.6 (C-5), 40.6 (C-3), 40.4 (C-10), 36.6 (C-6), 34.6 (C-1), 34.2 (C-4), 33.2 (C-18), 21.5 (C-18), 20.6 (C-17), 18.4 (C-2), 15.8 (C-20). Unit B δ=213.9 (C-7'), 169.9 (C-12'), 72.3 (C-9'), 51.9 (CO₂Me), 51.8 (C-8'), 45.9 (C-11'), 41.8 (C-5'), 39.1 (C-10'), 39.1 (C-6'), 38.2 (C-1'), 33.0 (C-19'), 30.0 (C-4'), 27.1 (C-17'), 22.6 (C-18'), 20.4 (C-20'), 18.6 (C-2').

The next compound eluted from the chromatographic column with the same eluent was acetate 24 (140 mg, 14%), as yellow oil; [found: C, 64.13; H, 8.40. C₁₈H₂₈O₅ requires C, 64.26; H, 8.38%]; [α]D²⁴ +31.9 (c 0.2, CHCl₃); IR νmax (film): 3457, 2954, 1930, 1870, 1739, 1673, 1613, 1461, 1434, 1380, 1365, 1335, 1234, 1199, 1163, 1072, 1024, 963, 830, 786, 745, 624, 421 cm⁻¹; ¹H NMR (400.13 MHz) δ=4.83 (1H, d, J 12.0 Hz, H-17), 4.79 (1H, d, J 12.0 Hz, H-17), 3.71 (3H, s, CO₂Me), 3.55 (1H, d, J 16.0 Hz, H-11), 3.37 (1H, d, J 16.0 Hz, H-11), 2.58 (1H, dd, J 17.6, 3.6 Hz, H-6), 2.42 (1H, dd, J 17.6, 14.4 Hz, H-6), 2.02 (3H, s, OAc), 1.79 (1H, m, H-5), 1.12 (s, 3H, H-19), 0.93 (3H, s, H-18), 0.91 (3H, H-20); ¹³C NMR (100.61 MHz) δ=198.4 (C-7), 171.0 (OAc), 170.4 (C-12), 165.3 (C-9), 131.9 (C-8), 58.0 (C-17), 52.5 (CO₂Me), 49.6 (C-5), 41.0 (C-10), 40.9 (C-3), 35.2 (C-1), 34.9 (C-6), 33.9 (C-11), 33.2 (C-4), 32.3 (C-19), 21.3 (C-18), 20.9 (OAc), 18.4 (C-2), 18.1 (C-20).

Syntheses of terpeno-heterocycle 30 and dimer 27.

K₂CO₃ (0.042 g, 0.3 mmol) was added to a solution of 3(2H)-piridazinone 28 or 4,5-dihydro-3(2H)-piridazinone 29 (0.02 g, 0.1 mmol) in dry DMAA (3 mL). A solution of bromide 21 (0.072 g, 0.2 mmol) in dry DMAA (1 mL) was added dropwise (30 min, stirring), to the resulted mixture. The mixture was stirred at room temperature for 48 h, then filtered and the residue was washed with Et₂O (2 x 10 mL). After solvents removal under reduced pressure, crude reaction products were re-dissolved in small volumes of acetone, adsorbed on SiO₂ and eluted with mixture of PE/EtOAc (1:1) to give N-substituted terpeno-pyridazinone derivative 30 (0.07 g, 75% yield) and dimer 27 (0.078 g, 70%).

For 30: as oil. [α]D²⁴ +145.9 (c 0.4, CHCl₃); IR νmax (film): 2949, 2930, 1736, 1662, 1590, 1254, 1198, 1160, 1115, 818 cm⁻¹; ¹H NMR (400.13 MHz) δ=7.61 (1H, d, J 10.0 Hz, H-4'), 7.56 (2H, d, J 10.0 Hz, H-2" and H-6"), 7.21 (2H, d, J 10.0 Hz, H-3" and H-5"), 6.96 (1H, d, J 10.0 Hz, H-3'), 5.22 (1H, d, J 15.0 Hz, H-17), 4.95 (1H, d, J 15.0 Hz, H-17), 3.66 (1H, d, J 20.0 Hz, H-11), 3.58 (3H, s, CO₂Me), 3.39 (1H, d, J 20.0 Hz, H-11), 2.63 (1H, dd, J 25.0, 5.0 Hz, H-6), 2.46 (1H, dd, J 25.0, 15.0 Hz, H-6), 2.38 (3H, s, H-7"), 1.91 (1H, dd, J 15.0, 5.0 Hz, H-5), 1.14 (3H, s, H-
19), 0.92 (6H, both s, H-18 and H-20); $^{13}$C NMR (100.61 MHz) δ =198.3 (C-7), 170.3 (C-12), 164.0 (C-9), 159.7 (C-2'), 143.9 (C-5'), 139.3 (C-4''), 132.3 (C-8), 132.1 (C-1''), 129.6 (C-3', C-3'' and 5''), 129.5 (C-4''), 125.5 (C-2'' and 6''), 52.4 (CO$_2$Me), 49.5 (C-5), 45.9 (C-17), 41.1 (C-10), 40.9 (C-3), 35.2 (C-6), 35.1 (C-1), 34.7 (C-4), 32.4 (C-19), 21.3 (C-7''), 18.4 (C-18), 18.2 (C-20); m/z 462 [(M +, 7)], 276 (55), 261 (34), 245 (4), 173 (12), 151 (9), 139 (8), 118 (4), 102 (4), 95 (6), 93 (7), 79 (9), 69 (17), 57 (8), 53 (9), 41 (33); HRMS (EI): found 337.20026. C$_{28}$H$_{35}$O$_4$N$_2$ requires 462.5876.

For 27: as white crystals, mp 147-148 ºC (from PE). [α]$_D^{25}$ -63.5 (c 0.5, CHCl$_3$); IR $\nu_{\text{max}}$ (CCl$_4$): 2950, 2928, 1725, 1710, 1662, 1606, 1158, 1148, 1066, 1026, 980 cm$^{-1}$; $^1$H NMR (400.13 MHz): Unit A δ =4.23 (2H, d, J 1.4 Hz, H-11), 3.59 (3H, s, CO$_2$Me), 2.15 (1H, t, J 9.0 Hz, H-5), 1.20-2.80 (10H, overlapped signals, H-1, H-2, H-3, H-6, H-17), 1.15 (3H, s, H-20), 0.95 (3H, s, H-18), 0.92 (3H, s, H-19); Unit B δ =6.0 (1H, s, H-11''), 3.65 (3H, s, CO$_2$Me), 2.05 (2H, m, H-17'), 1.82 (1H, dd, J 13.3, 6.0 Hz, H-5'), 1.20-2.80 (10H, overlapped signals, H-1', H-2', H-3', H-6', H-17'), 1.06 (3H, s, H-20'), 0.92 (3H, s, H-18'), 0.90 (3H, s, H-19'). $^{13}$C NMR (100.61 MHz): Unit A δ =200.8 (C-7), 172.9 (C-12), 161.0 (C-9), 132.7 (C-8), 53.2 (C-11), 52.0 (CO$_2$Me), 49.6 (C-5), 41.0 (C-3), 40.5 (C-10), 35.7 (C-6), 34.4 (C-1), 33.3 (C-4), 32.9 (C-19), 21.8 (C-18), 20.6 (C-17), 20.1 (C-20), 18.5 (C-2). Unit B δ =209.9 (C-7'), 175.8 (C-9'), 166.5 (C-12), 114.5 (C-11'), 56.6 (C-8'), 51.4 (CO$_2$Me), 44.3 (C-5'), 42.8 (C-10'), 41.2 (C-3'), 40.3 (C-1'), 37.6 (C-6'), 33.9 (C-4'), 32.2 (C-19'), 31.3 (C-17'), 22.1 (C-20'), 21.9 (C-18'), 19.0 (C-2'), m/z 552 [(M$^+$, 5)], 261 (11), 205 (11), 189 (5), 165 (7), 152 (12), 149 (20), 137 (11), 125 (13), 109 (28), 97 (37), 82 (14), 79 (13), 59 (11), 56 (19), 44 (31); HRMS (EI): (M$^+$ -30) found 552.34571. C$_{34}$H$_{48}$O$_6$ requires 552.7496.

2. Crystal structure determination

Crystallographic measurements for compounds 14, 21, 23 and 27, were carried out with an Oxford-Diffraction XCALIBUR E CCD diffractometer equipped with a graphite-monochromated Mo-$K_\alpha$ radiation. The crystals were placed at 40 mm from the CCD detector. The unit cell determination and data integration were carried out using the CrysAlis package of Oxford Diffraction [CrysAlis RED, Oxford Diffraction Ltd., Version 1.171.34.76, 2003]. All structures were solved by direct methods using SHELXS-97 [Sheldrick, G.M. A short history of SHELX. Acta Crystallogr. 2008, A64, 112-122] and refined by the full-matrix least-squares on F$_0^2$ with SHELXL-97 with anisotropic displacement parameters for non-hydrogen atoms. All H atoms attached to carbon were introduced in idealized positions (d$_{\text{CH}}$ = 0.96 Å), using the riding model, with their isotropic displacement parameters fixed at 120% of their riding atoms. The
refinement of the Flack parameter for structure 21 has demonstrated the presence of an enantiopure compound. In the absence of significant anomalous scattering, the absolute configuration for 14, 23 and 27 could not be reliably determined, so that the Friedel pairs were merged and any reference to the Flack parameter was removed.

Crystal data for 14. C_{17}H_{26}O_{4} (M_r = 294.38 g·mol⁻¹), monoclinic, a = 10.6035(15) Å, b = 7.5859(5) Å, c = 11.1502(11) Å, β = 117.136(15) °, V = 798.16(15) Å³, T = 200 K, space group P2₁, Z = 2, 5960 coll. refl., 3133 indep. (R_int = 0.0221), Gof = 1.027, R₁ = 0.0457, wR(F²) = 0.1025.

Crystal data for 21. C_{17}H_{25}O_{3}Br (M_r = 357.28 g·mol⁻¹), orthorhombic, a = 11.3834(3) Å, b = 11.8943(3) Å, c = 12.2322(3) Å, V = 1656.22(7) Å³, T = 150 K, space group P2₁2₁2₁, Z = 4, 13965 coll. refl., 2929 indep. (R_int = 0.0357), Gof = 1.078, R₁ = 0.0236, wR(F²) = 0.0556, Flack parameter 0.003(8).

Crystal data for 23. C_{34}H_{48}O_{6} (M_r = 552.72 g·mol⁻¹), orthorhombic, a = 9.9354(9) Å, b = 12.0058(5) Å, c = 24.7267(12) Å, V = 2949.5(3) Å³, T = 200 K, space group P2₁2₁2₁, Z = 4, 14676 coll. refl., 3270 indep. (R_int = 0.0566), Gof = 1.033, R₁ = 0.0473, wR(F²) = 0.0921.

Crystal data for 27. C_{34}H_{48}O_{6} (M_r = 552.72 g·mol⁻¹), orthorhombic, a = 10.3273(12) Å, b = 15.7273(14) Å, c = 18.7880(14) Å, V = 3051.6(5) Å³, T = 200 K, space group P2₁2₁2₁, Z = 4, 11342 coll. refl., 4371 indep. (R_int = 0.0713), Gof = 1.061, R₁ = 0.0975, wR(F²) = 0.2496.

Crystallographic data for 14, 21, 23 and 27 have been deposited at the Cambridge Crystallographic Data Centre as Supplementary Publications No. CCDC-1015229, CCDC-905898, CCDC-895912 and CCDC 1472747, respectively. Copies of the data can be obtained free of charge from CCDC (12 Union Road, Cambridge CB2 1EZ, UK; Tel.: + 44 1223 336 408; fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk; www:http://ccdc.cam.ac.uk).

3. Antimicrobial and antifungal activity assessment

Fungi: Aspergillus niger ATCC 53346, Penicillium frequentans ATCC 10110, and Alternaria alternata ATCC 8741, and Gram-negative bacteria Pseudomonas aeruginosa ATCC 27813 and Gram-positive Bacillus polymyxa ATCC 15970 were provided by the American Type Culture Collection (ATCC, USA).
Sample solutions of 0.5%, 1%, and 2% concentrations were obtained by dissolution of appropriate amounts of tested compounds 6, 16, 20, 21, 22, 23, 27, and 30 in fixed volumes of dimethyl sulfoxide (DMSO).

It must be mentioned that for fungi a Sabouraud type agar medium was used supplemented with dextrose (4%, SDA) and for bacteria - a Standard I nutrient agar medium.

Microorganisms suspensions were prepared using the method of successive agar dilutions according to the standard Minimum Inhibitory Concentration (MIC) [Microbiology Guide to Interpreting Minimum Inhibitory Concentration © 2013 Laboratories, Inc. • UK206-0613 / UK-MAR-EXT-338] and their cultivation was carried out according to standard procedures (SR-EN 1275:2006 and NCCLS guidelines) [National Committee on Clinical Laboratory Standards (NCCLS) Antimicrobial Susceptibility Standards (ATS) 2003, for M7 (CMI) and M100]. The final charge-stock inoculum was prepared as 1 x 10^{-4} mg/mL concentration and inoculated plates were incubated at 30 °C for 7 days.

First observations were made after 48 hours and those final after 7 days of incubation, using visual, microscopy and photography MIC analyses that resulted in the establishment of densities of viable present microorganisms. Assessments were made against the control plate for each type of microorganisms.