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Synthesis of the C1–C9 segment of bryostatin †

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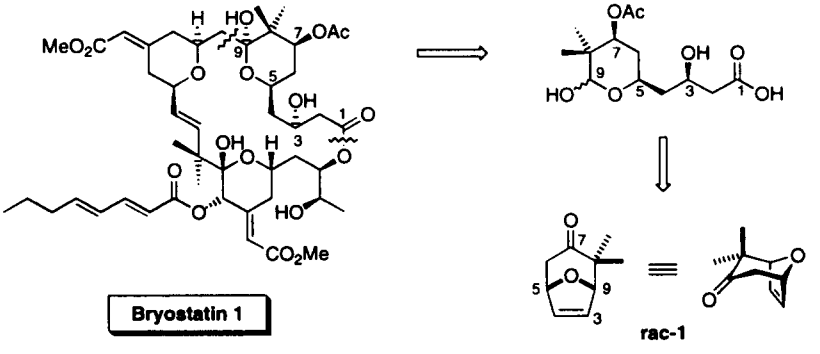
Abstract: The C1–C9 segment of bryostatin has been prepared in 11 steps in 21% overall yield. © 1997 Elsevier Science Ltd. All rights reserved.

The bryostatins are a class of highly oxygenated marine macrolides with a polyacetate backbone. They exhibit exceptional therapeutic antineoplastic activities and feature a variety of structural and stereochemical challenges.[1] Although several synthetic contributions leading to fragments of the bryostatins have been published including the C1–C9 segment,[2] so far only Masamune and his coworkers[3] have achieved a total synthesis of bryostatin 7.

We here report a simple and efficient synthesis of the C1–C9 segment (Scheme 1) starting from the inexpensive and easily accessible (40 g per batch) 2,2-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one **rac-1**.[4] Conversion into the protected *endo*-alcohol **rac-2** (Scheme 2) was carried out under standard conditions. The asymmetric hydroboration of **rac-2** (Scheme 2) followed the pioneering work of Professor H. C. Brown[5] and required careful temperature control (−15°C) as well as little solvent (THF). In this fashion the reaction was completed after 3 days. After this modified kinetic separation of racemic benzyl ether **rac-2**, PCC- and Baeyer–Villiger oxidation afforded lactones **3** and **4** as a 1:1 mixture of structural isomers which could easily be separated[6] by standard flash chromatography. Both lactones **3** and **4** were enantiomerically pure [Eu(hfc)$_2$ shift measurements]. Thus, **rac-1** furnished three of the required four stereocentres in only five steps.



Scheme 1. Retrosynthetic analysis of the C1–C9 fragment of bryostatin 1.

Attempts to open lactone **3** to methyl acetal **5** under basic conditions were not successful.[7] However, refluxing **3** in MeOH and in the presence of catalytic H$^+$ under anhydrous conditions gave methyl acetal **5** in excellent yield.[8] In turn the resulting acetal **5** could be opened with the soft–hard combination ethanedithiol–$BF_3 \cdot OEt_2$.[9] β-Hydroxy ester **6** was protected as TIPS ether and refunctionalized in two steps to aldehyde **7**. The asymmetric aldol reaction of **7** with chiral acetate (*S*)-**9** was carried out by the Braun–Devant procedure[10] to give stereogenic centre C3 with the correct (*R*)-configuration of

† Dedicated to Professor Herbert C. Brown on the occasion of his 85th birthday.

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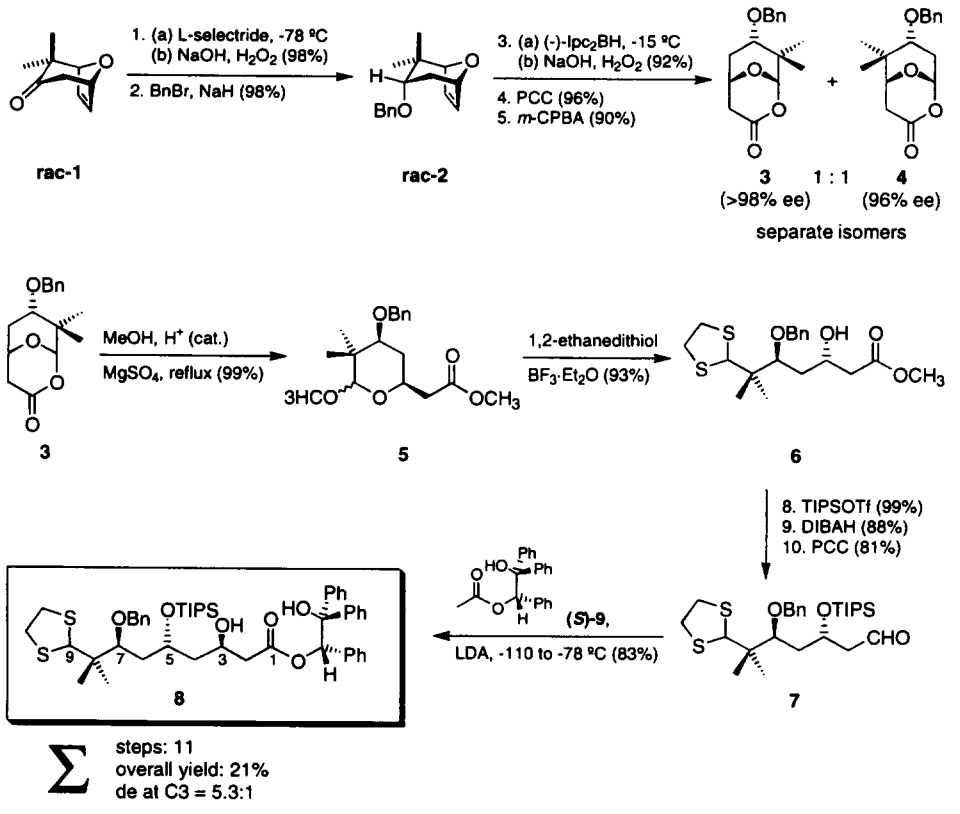

Scheme 2. Synthesis of the C1–C9 segment of bryostatin 1.

bryostatin 1. The absolute configuration of β-hydroxy ester **6** and of aldol adduct **8** was determined via the *O*-methyl mandelate.[11]

Experimental

General

Melting points were determined on a Büchi apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 1710 infrared spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 400 spectrometer in deuterated chloroform unless otherwise stated, with tetramethylsilane as an internal standard. Mass spectra were recorded on a Finnigan MAT 312 (70 eV) or a VG Autospec spectrometer. Microanalyses were performed in the Department of Organic Chemistry of the University of Hannover. Preparative column chromatography was performed on J. T. Baker silica gel (particle size 30–60 μm). Analytical TLC was carried out on aluminum-backed 0.2 mm silica gel 60 F_{254} plates (E. Merck). DMF was dried over BaO, distilled over calcium hydride under reduced pressure and stored over 4 Å molecular sieves. THF was distilled over sodium and benzophenone before use. Diethyl ether (E), cyclohexane (CH) and ethyl acetate (EA) were distilled before use.

endo-*3-Benzyloxy-2,2-dimethyl-8-oxabicyclo[3.2.1]oct-6-ene* **rac-2**

To a solution of **rac-1** (3.00 g, 19.7 mmol) in THF (30 ml) was added L-selectride (21.7 ml, 21.7 mmol, 1.0 M solution in THF) within 1 h (perfusor) at −78°C. The mixture was stirred for 1 h at the same temperature and then allowed to reach 0°C slowly. Water (1 ml) was added followed by NaOH (5.2 g, 130 mmol) in H_2O (5 ml). H_2O_2 (13.4 ml, 130 mmol, 30% solution) was added very slowly

and the resulting mixture was stirred for 1 h at r.t. The aqueous phase was separated, saturated with $MgSO_4$ and extracted with CH_2Cl_2 (10 ml portions), until no product was detectable in the aqueous layer (TLC). The combined organic phase was washed with $NaHSO_3$ (50 ml). The aqueous phase was saturated with $MgSO_4$ and extracted with CH_2Cl_2, until no product was detectable in the aqueous layer (TLC). The combined organic layer was dried ($MgSO_4$), filtered, evaporated and purified by chromatography (CH:EA=4:1) to afford *endo*-2,2-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-ol (3.0 g, 98%), colourless oil, which was crystalline at −20°C. IR ($CHCl_3$) ν 3596, 3000, 2956, 2928, 2872, 1472, 1404, 1384, 1364, 1344, 1292, 1276, 1260, 1240, 1172, 1060, 1024, 1004, 944, 928, 900, 880, 852 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 3H, H-8eq), 1.15 (s, 3H, H-8ax), 1.62 (dm, *J*=15 Hz, 1H, H-4eq), 2.36 (ddd, *J*=15, 6, 4 Hz, 1H, H-4ax), 2.54–3.23 (bs, 1H, RO*H*), 3.45 (dm, *J*=5 Hz, 1H, H-3), 4.18 (m, 1H, H-1), 4.71 (m, 1H, H-5), 6.43 (dd, *J*=6, 2 Hz, 1H, H-6/7), 6.48 (dd, *J*=6, 2 Hz, 1H, H-6/7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0 (C-8eq), 26.7 (C-8ax), 33.2 (C-4), 38.3 (C-2), 73.4 (C-3), 77.8 (C-5), 85.8 (C-1), 134.7 (C-6/7), 136.0 (C-6/7); MS *m/z* 154 (M^+, 1.5) 136 (4), 126 (5), 121 (13), 110 (32), 95 (27), 82 (100), 71 (96); HRMS calcd for $C_9H_{14}O_2$: 154.0994, found 154.0999.

To a solution of the alcohol (10 g, 65 mmol) in THF (100 ml) was added NaH (5.2 g, 130 mmol, 60% dispersion in mineral oil) carefully at 0°C. Benzyl bromide (8.5 ml, 72 mmol) was added and the mixture was heated to reflux for 1 h. The reaction was quenched by careful addition of H_2O (10 ml) at 0°C. The aqueous phase was separated, acidified (2 N HCl) and extracted with E, until no product was detectable in the aqueous layer (TLC). The combined organic layer was dried ($MgSO_4$), the solvent removed and the crude product chromatographed (CH:EA=95:5) to give **rac-2** (15.7 g, 99%), colourless oil. IR ($CHCl_3$) ν 3292, 3088, 3064, 3000, 2984, 2956, 2868, 1712, 1600, 1496, 1472, 1452, 1384, 1364, 1312, 1280, 1256, 1176, 1096, 1072, 1024, 996, 932, 912, 884, 844, 604, 548 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 3H, H-8eq), 1.15 (s, 3H, H-8ax), 1.63 (dm, *J*=15 Hz, 1H, H-4eq), 2.13 (ddd, *J*=15, 6, 4 Hz, 1H, H-4ax), 3.18 (dd, *J*=5, 1 Hz, 1H, H-3), 4.11 (bs, 1H, H-1), 4.27 (d, *J*=12 Hz, 1 H, OC*H*$_2$Ph), 4.46 (d, *J*=12 Hz, 1 H, OC*H*$_2$Ph), 4.65 (m, 1H, H-5), 6.23 (dd, *J*=6, 2 Hz, 1H, H-6/7), 6.30 (dd, *J*=6, 2 Hz, 1H, H-6/7), 7.20–7.35 (m, 5 H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1 (C-8eq), 27.2 (C-8ax), 28.8 (C-4), 38.4 (C-2), 72.0 (C-3), 77.8 (C-5), 80.4 (O*C*H$_2$Ph), 86.0 (C-1), 127.06 (*ortho* Ar–C), 127.1 (*para* Ar–C), 128.1 (*meta* Ar–C), 132.7 (C-6/7), 134.2 (C-6/7), 139.3 (Ar–C); MS *m/z* 244 (M^+, 5), 216 (4), 200 (9), 175 (15), 163 (27), 153 (91), 136 (67), 121 (69), 105 (51), 91 (99), 81 (100); HRMS calcd for $C_{16}H_{20}O_2$: 244.1463, found 244.1457.

(1S,5S,7S)-7-Benzyloxy-8,8-dimethyl-2,9-dioxabicyclo[3.3.1]nonan-3-one **3** *and (1S,5R,7R)-7-benzyloxy-6,6-dimethyl-2,9-dioxabicyclo[3.3.1]nonan-3-one* **4**

In a typical approach, BH_3·DMS (13.9 ml, 146 mmol, ~10.5 M solution in DMS) was added to a solution of (+)-α-pinene (50 g, 365 mmol) (84–92% ee) in E (20 ml). The reaction temperature was kept below bp without external cooling or stirring to afford crystals of (−)-Ipc_2BH as large as possible. After 16 h at r.t. and 2 h at 0°C the supernatant solution was removed by syringe and the big white crystals were washed with ice-cold E (3×15 ml). Then the crystals were pulverized with a glass rod under a stream of N_2. To the (−)-Ipc_2BH was added bicyclo ether (100 mmol) in E (1.5 ml/g) at −78°C. The reaction mixture was kept at −15°C for 7 days and shaken manually twice a day to dissolve the (−)-Ipc_2BH. The reaction was quenched with NaOH (27 g, 675 mmol) in H_2O (135 ml) at 0°C. Then H_2O_2 (75 ml, 675 mmol, 30% solution) was added within 30 min (perfusor). After complete addition the mixture was stirred for 1 h at r.t. and then acidified (conc. HCl) at 0°C. The aqueous phase was separated, saturated with $MgSO_4$ and extracted with CH_2Cl_2, until no product was detectable in the aqueous layer (TLC). The combined organic phase was washed with $NaHSO_3$ (50 ml). The aqueous phase was saturated with $MgSO_4$ and extracted with CH_2Cl_2, until no product was detectable in the aqueous layer (TLC). The combined organic layer was dried ($MgSO_4$), evaporated and chromatographed (CH:EA=9:1) to afford the regioisomeric alcohols.

Rac-2 (20 g, 82 mmol) was allowed to react as described above to afford (1*R*,3*S*,5*R*,7*S*)-3-benzyloxy-2,2-dimethyl-8-oxabicyclo[3.2.1]octan-7-ol and (1*R*,3*R*,5*R*,6*S*)-3-benzyloxy-2,2-dimethyl-

8-oxabicyclo[3.2.1]octan-6-ol (1:1) (19.1 g, 89%), which could not be separated by chromatography. IR ($CHCl_3$) ν 3520, 3336, 3064, 2972, 2932, 2832, 1652, 1616, 1496, 1472, 1452, 1400, 1368, 1328, 1300, 1264, 1228, 1160, 1096, 1068, 1024, 992, 952, 908, 968, 848, 632, 612, 592, 548, 516 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92/1.06/1.08/1.09 (s, je 3H, H-8) 1.54–1.72 (m, 2H, H-6_{endo}), 1.66 (d, *J*=15 Hz, 1H, H-4eq), 1.82 (d, *J*=15 Hz, 1H, H-4eq), 1.95–2.08 (m, 2H, H-4ax), 2.25 (bs, 2H, O*H*), 2.67 (dd, *J*=13, 7 Hz, 1H, H-6_{exo}), 2.99 (dd, *J*=13, 7 Hz, 1H, H-6_{exo}), 3.14 (bs, 2H, H-3), 3.57 (s, 1H, H-1), 3.86 (d, *J*=8 Hz, 1H, H-1), 4.10 (d, *J*=4 Hz, 1H, H-5), 4.26 (d, *J*=4 Hz, 1H, OCH_2Ar), 4.29 (d, *J*=4 Hz, 1H, OCH_2Ar), 4.43–4.57 (m, 4H, H-5/7/ OCH_2Ar), 4.82 (dm, *J*=6 Hz, 1H, H-7), 7.25–7.38 (m, 10H, Ar–*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ {2.28, 22.34} (C-8eq), {26.1, 26.2} (C-8ax), {28.5, 9.9} (C-4), {37.6, 38.0} (C-2), {38.3, 41.7} (C-6), {71.6, 71.9} (OCH_2Ph), {72.7, 74.4, 75.4, 79.67, 79.75, 82.3, 83.1, 91.3} (C-1/3/5/7), {127.0, 127.1, 127.31, 127.33, 128.3} (*ortho/meta/para* Ar–C), 138.7 (Ar–C); MS (60°C) *m/z* 262 (M^+, 5), 193 (35), 176 (11), 175 (53), 172 (24), 171 (100), 170 (17), 156 (56), 155 (61), 154 (80), 153 (36); HRMS calcd for $C_{16}H_{22}O_3$: 262.1569, found 262.1571.

To a solution of the regioisomeric alcohols (20.0 g, 76.3 mmol) in CH_2Cl_2 (200 ml) was added pyridinium chlorochromate (PCC) on silica gel (46 g, 92 mmol, 2 mmol PCC per g) at 0°C. The mixture was stirred for 16 h at r.t. and then filtered through silica gel. The solvent was removed and the crude product purified by chromatography (CH:EA=4:1) to afford the ketones (1*R*,3*S*,5*S*)-3-benzyloxy-2,2-dimethyl-8-oxabicyclo[3.2.1]octan-7-one (**A**) and (1*R*,3*R*,5*R*)-3-benzyloxy-2,2-dimethyl-8-oxabicyclo[3.2.1]octan-6-one (**B**) (1:1) (19.1 g, 96%), colourless oil. IR ($CHCl_3$) ν 3088, 3064, 2988, 2960, 2932, 2872, 1756, 1600, 1496, 1472, 1452, 1404, 1352, 1324, 1272, 1244, 1224, 1156, 1096, 1072, 1048, 1020, 984, 956 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ {0.95, 1.08, 1.15, 1.21} (s, each 3H, H-8), 1.83 [dm, *J*=14 Hz, 1H, H-4eq (**A**)], 2.09 [dm, *J*=14 Hz, 1H, H-4eq (**B**)], 2.18 [ddd, *J*=15, 4, 1 Hz, 1H, H-4ax (**B**)], 2.26 [ddd, *J*=15, 4, 1 Hz, 1H, H-4ax (**A**)], 2.44 [ddd, *J*=17, 8, 2 Hz, 1H, H-6_{exo} (**B**)], 2.4–2.7 [m, 2H, H-6 (**A**)], 2.87 [d, *J*=17 Hz, 1H, H-6_{endo} (**B**)], 3.28 (bs, 2H, H-3), 3.41 [s, 1H, H-1 (**A**)], 3.94 [bs, 1H, H-1 (**B**)], 4.08–4.15 [m, 3H, H-5 (**B**)/2×OCH_2Ar], 4.38 (d, *J*=12 Hz, 1H, OCH_2Ar), 4.55 (d, *J*=12 Hz, 1H, OCH_2Ar), 4.68 [dd, *J*=8, 4 Hz, 1H, H-5 (**A**)], 7.2–7.35 (m, 10H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ {20.9, 22.5} (C-8eq), {24.8, 25.5} (C-8ax), {29.0, 29.3} (C-4), {37.7, 39.9} (C-2), {39.6, 41.7} (C-6), {71.1, 71.5} (OCH_2Ar), {73.4, 75.1, 79.3, 79.5, 82.2, 82.8} (C-1/3/5), {126.8, 127.3, 127.46, 127.54, 128.26, 128.33, 128.7, 129.58, 129.66, 129.7} (*ortho/meta/para* Ar–C), {138.0, 138.2} (Ar–C), {213.0, 215.2} (C-7); MS *m/z* 260 (M^+, 1), 169 (44), 152 (4), 151 (6), 139 (10), 127 (5), 125 (10), 122 (9), 109 (20), 106 (37), 105 (64), 95 (11), 92 (12), 91 (100); HRMS calcd for $C_{16}H_{20}O_3$: 260.1412, found 260.1412.

To a suspension of regioisomeric ketones (10.0 g, 38.4 mmol) and $NaHCO_3$ (6.50 g, 76.8 mmol) in CH_2Cl_2 (200 ml) was added *m*-CPBA (19.0 g, 76.8 mmol, ~70%) and the mixture was stirred for 16 h at r.t. NaOH (6.20 g, 154 mmol) in H_2O (30 ml) was added and the mixture was stirred until it became clear. The aqueous phase was separated, saturated with $MgSO_4$ and extracted with E, until no product was detectable in the aqueous layer (TLC). The combined organic layer was dried ($MgSO_4$), evaporated and chromatographed (CH:EA=9:1) to afford **3** (5.0 g, 47%) and **4** (4.6 g, 43%). Data for **3**, white solid, mp 95–97°C, $[\alpha]_D^{20}=-117.4$ (*c* 0.8, $CHCl_3$). IR ($CHCl_3$) ν 3064, 3000, 2960, 2868, 1740, 1496, 1476, 1452, 1388, 1372, 1348, 1292, 1264, 1232, 1108, 1076, 1016, 1000, 944, 912, 892, 868 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 3H, H-8eq), 1.15 (s, 3H, H-8ax), 1.86 (dm, *J*=15 Hz, 1H, H-4eq), 2.29 (dm, *J*=15 Hz, 1H, H-4ax), 2.48 (d, *J*=18 Hz, 1H, H-6_{endo}), 2.92 (ddm, *J*=18, 8 Hz, 1H, H-6_{exo}), 3.37 (bs, 1H, H-3), 4.39 (m, 1H, H-5), 4.40 (d, *J*=12 Hz, 1H, OCH_2Ar), 4.63 (d, *J*=12 Hz, 1H, OCH_2Ar), 5.15 (s, 1H, H-1), 7.23-7.37 (m, 5H, Ar–*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ d 22.2 (C-8eq), 24.5 (C-8ax), 28.2 (C-4), 35.9 (C-6), 38.7 (C-2), 65.5 (C-5), 72.2 (OCH_2Ar), 77.8 (C-3), 103.5 (C-1), 127.61 (*para* Ar–C), 127.62 (*ortho* Ar–C), 128.3 (*meta* Ar–C), 137.6 (Ar–C), 166.2 (C-7); MS (70°C) *m/z* 276 (M^+, 3), 261 (10), 230 (21), 215 (4), 210 (4), 191 (3), 175 (7), 170 (26), 156 (15), 140 (15), 139 (38), 124 (14), 123 (11), 121 (21), 120 (10), 111 (22), 110 (21), 109 (14), 107 (11), 105 (26), 99 (11), 97 (50), 95 (58), 91 (100); HRMS calcd for $C_{16}H_{20}O_4$: 276.1362, found

276.1357. Data for **4**, mp 73–75°C, $[\alpha]_D^{20}=-109.6$ (*c* 0.115, $CHCl_3$). IR ($CHCl_3$) ν 3064, 2992, 2964, 2940, 2872, 1736, 1600, 1476, 1452, 1388, 1344, 1272, 1236, 1164, 1092, 1040, 1000, 972, 912, 884 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (s, 3H, H-8eq), 1.12 (s, 3H, H-8ax), 2.00 (ddd, *J*=15, 7, 3 Hz, 1H, H-4ax), 2.31 (dm, *J*=15 Hz, 1H, H-4eq), 2.73–2.90 (m, 2H, H-6), 3.36 (bs, 1H, H-3), 3.80 (d, *J*=7 Hz, 1H, H-5), 4.25 (d, *J*=12 Hz, 1H, OCH_2Ar), 4.68 (d, *J*=12 Hz, 1H, OCH_2Ar), 5.70 (m, 1H, H-1), 7.23–7.37 (m, 5H, Ar–*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6 (C-8eq), 26.3 (C-8ax), 28.5 (C-4), 33.1 (C-6), 38.0 (C-2), 71.4 (OCH_2Ar), 75.4 (C-5), 77.6 (C-3), 97.2 (C-1), 128.5 (*para* Ar–C), 128.9 (*ortho* Ar–C), 129.2 (*meta* Ar–C), 138.4 (Ar–C), 167.4 (C-7); MS (70°C) *m/z* 276 (M^+, 0.4), 258 (5), 232 (2), 215 (3), 187 (4), 185 ($M^+-C_7H_7$, 3), 170 (4), 163 (4), 156 (4), 155 (10), 152 (6), 146 (4), 144 (8), 139 (6), 133 (7), 124 (5), 120 (10), 105 (18), 92 (13), 91 (100); HRMS calcd for $C_9H_{13}O_4$ ($M^+-C_7H_7$): 185.0814, found 185.0821.

(2S,4S,6S/R)-4-Benzyloxy-5,5-dimethyl-6-methoxy-tetrahydropyran-2-acetic acid, methyl ester **5**

A mixture of **3** (1.4 g, 5.0 mmol), $MgSO_4$ (4.2 g) and H_2SO_4 (1 drop) in MeOH (25 ml) was heated to reflux for 16 h. H_2O (15 ml) was added and the aqueous layer extracted until no product was detectable in the aqueous layer (TLC). The combined organic phase was dried ($MgSO_4$), filtered and evaporated. Chromatography (CH:EA=4:1) afforded **5** (1.6 g, 99%) as an anomeric mixture [**5**(6*S*)/**5**(6*R*), ~3:1), colourless oil. IR ($CHCl_3$) ν 3428, 3088, 3064, 2992, 2952, 2888, 2832, 1736, 1604, 1496, 1436, 1388, 1360, 1324, 1268, 1192, 1144, 1108, 1052, 1024, 972, 932, 908, 884 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (6*S*) 1.00 (s, 3H, H-8eq), 1.03 (s, 3H, H-8ax), 1.47 (q, *J*=12 Hz, 1H, H-4ax), 1.89 (ddd, *J*=12, 5, 2 Hz, 1H, H-4eq), 2.45 (dd, *J*=16, 5 Hz, 1H, H-6), 2.58 (dd, *J*=16, 9 Hz, 1H, H-6), 3.31 (s, 3H, H-10), 3.64 (dd, *J*=12, 5 Hz, 1H, H-3), 3.69 (s, 3H, H-9), 4.14–4.22 (m, 1H, H-5), 4.19 (s, 1H, H-1), 4.45 (d, *J*=12 Hz, 1H, OCH_2Ar), 4.61 (d, *J*=12 Hz, 1H, OCH_2Ar), 7.23–7.35 (m, 5H, Ar–*H*); NOE (200 MHz, CD_2Cl_2) (6*S*) H-8eq irradiated: H-1 (3.4%); H-8ax irradiated: H-1 (3.1%); H-1 irradiated: H-8eq (24.3%), H-8ax (22.5%); δ(6*R*) 0.92 (s, 3H, H-8eq), 1.02 (s, 3H, H-8ax), 1.42 (m, 1H, H-4ax), 1.92 (ddd, *J*=12, 5, 2 Hz, 1H, H-4eq), 2.49 (dd, *J*=16, 5 Hz, 1H, H-6), 2.70 (dd, *J*=16, 8 Hz, 1H, H-6), 3.15 (dd, *J*=12, 5 Hz, 1H, H-3), 3.43 (s, 3H, H-10), 3.68 (s, 3H, H-9), 3.75–3.83 (m, 1H, H-5), 3.87 (s, 1H, H-1), 4.43 (d, *J*=12 Hz, 1H, OCH_2Ar), 4.63 (d, *J*=12 Hz, 1H, OCH_2Ar), 7.23–7.35 (m, 5H, Ar–*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ(6*S*) 18.7 (C-8eq), 22.8 (C-8ax), 32.6 (C-4), 39.1 (C-2), 40.6 (C-6), 51.6 (C-9), 55.0 (C-10), 64.7 (C-5), 71.4 (OCH_2Ar), 77.8 (C-3), 106.9 (C-1), 127.36 (*ortho* Ar–C), 127.37 (*para* Ar–C), 128.3 (*meta* Ar–C), 139.1 (Ar–C), 171.6 (C-7); δ(6*R*) 12.4 (C-8eq), 21.9 (C-8ax), 32.3 (C-4), 34.7 (C-2), 40.4 (C-6), 51.6 (C-9), 57.2 (C-10), 68.6 (C-5), 71.3 (OCH_2Ar), 81.2 (C-3), 107.8 (C-1), 127.4 (*ortho* Ar–C), 127.5 (*meta* Ar–C), 128.3 (*para* Ar–C), 138.7 (Ar–C), 171.4 (C-7); MS (60°C) *m/z* 322 (M^+, 1), 305 (2), 291 (18), 219 (11), 199 (24), 193 (25), 185 (25), 184 (15), 183 (19), 177 (12), 176 (11), 171 (27), 169 (10), 163 (29), 162 (62), 160 (20), 156 (26), 155 (30), 154 (64), 151 (35), 147 (25), 145 (25), 143 (26), 139 (26), 129 (25), 127 (25), 123 (25), 119 (25), 117 (20), 113 (23), 111 (26), 109 (22), 107 (25), 103 (26), 101 (27), 99 (23), 97 (29), 95 (38), 92 (68), 91 (100); HRMS calcd for $C_{18}H_{26}O_5$: 322.1780, found 322.1780.

(3S,5S)-5-Benzyloxy-6-([1,3]dithiolan-2-yl)-3-hydroxy-6-methyl-heptanoic acid, methyl ester **6**

To a solution of **5** (2.12 g, 6.56 mmol) in CH_2Cl_2 (65 ml) was added 1,2-ethanediol (1.1 ml, 1.24 g, 13.1 mmol) followed by $BF_3 \cdot OEt_2$ (2.48 ml, 2.80 g, 19.7 mmol) and the mixture was stirred at r.t. The reaction was monitored by TLC. After 5 min the mixed thioacetal was formed, which was less polar than **5**. Then the product spot appeared, which was more polar than **5**. After 30 min a further spot appeared below the product spot. At this point the reaction was quenched by addition of sat. aq. $NaHCO_3$ solution (10 ml) at 0°C. The aqueous phase was extracted with E, until no product was detectable in the aqueous layer (TLC). The combined organic layer was dried ($MgSO_4$), evaporated and chromatographed (CH:EA=4:1) to afford **6** (2.37 g, 94%), white solid, mp 65–66°C, $[\alpha]_D^{20}=-0.8$ (*c* 2.14, $CHCl_3$). IR ($CHCl_3$) ν 3548, 3088, 3064, 3008, 2972, 2928, 2876, 1724, 1600, 1496, 1436, 1400, 1384, 1364, 1328, 1276, 1196, 1176, 1096, 1068, 1028, 992, 952 cm^{-1}; ^1H NMR (400 MHz,

$CDCl_3$) δ 1.02 (s, 3H, H-8), 1.10 (s, 3H, H-8), 1.54 (ddd, *J*=14, 10, 2 Hz, 1H, H-4), 1.71 (ddd, *J*=14, 10, 2 Hz, 1H, H-4), 2.43 (dd, *J*=17, 6 Hz, 1H, H-6), 2.51 (dd, *J*=17, 3 Hz, 1H, H-6), 3.16 (m, 4H, H-9), 3.70 (s, 3H, OCH_3), 3.80 (dd, *J*=10, 2 Hz, 1H, H-3), 4.20 (bs, 1H, H-5), 4.76 (s, 2H, OCH_2Ar), 4.89 (s, 1H, H-1), 7.25–7.40 (m, 5H, Ar–*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0 (C-8), 21.0 (C-8), 38.2 (C-4), 38.6 (C-9), 38.8 (C-9), 41.6 (C-6), 44.1 (C-2), 51.7 (OCH_3), 62.6 (C-1), 64.9 (C-5), 75.1 (OCH_2Ar), 81.9 (C-3), 127.39 (*para* Ar–*C*), 127.40 (*ortho* Ar–*C*), 128.3 (*meta* Ar–*C*), 138.9 (Ar–*C*), 173.4 (C-7); MS (140°C) *m/z* 384 (M^+, 0), 276 (24), 174 (9), 173 (20), 159 (8), 147 (23), 129 (11), 107 (7), 105 (70), 92 (9), 91 (100); HRMS calcd for $C_{19}H_{28}O_4S_2$: 384.1429, found 384.1416.

(3S,5S)-5-Benzyloxy-6-([1,3]dithiolan-2-yl)-6-methyl-3-triisopropylsilyloxy-heptanal **7**

A mixture of **6** (2.2 g, 5.7 mmol), imidazole (0.973 g, 42.6 mmol) and triisopropyl triflate (1.85 ml, 2.10 g, 6.90 mmol) in DMF (4.4 ml) was stirred for 16 h at 100°C and then diluted with H_2O (10 ml). The aqueous phase was separated, saturated with $MgSO_4$ and extracted with EA (3×10 ml) until no product was detectable in the aqueous layer (TLC). The combined organic layer was dried ($MgSO_4$), filtered and evaporated. Chromatography (CH:EA=97:3) afforded (3*S*,5*S*)-5-benzyloxy-6-([1,3]dithiolan-2-yl)-6-methyl-3-triisopropylsilyloxy-heptanoic acid, methyl ester (3.05 g, 99%), colourless oil, $[\alpha]_D^{20}$=+2.6 (*c* 0.89, $CHCl_3$). IR ($CHCl_3$) ν 3388, 3368, 2944, 2892, 2868, 1732, 1600, 1496, 1464, 1436, 1384, 1308, 1280, 1228, 1164, 1100, 1012, 944 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ d 1.01 (s, 3H, H-8), 1.05 (s, 3H, H-8), 1.08 (m, 21H, $Si(CH(CH_3)_2)_3$), 1.72–1.86 (m, 2H, H-4), 2.58 (dd, *J*=15, 7 Hz, 1H, H-6), 2.64 (dd, *J*=15, 6 Hz, 1H, H-6), 3.17 (m, 4H, H-9), 3.65 (s, 3H, OCH_3), 3.66 (dd, *J*=16, 6 Hz, 1H, H-3), 4.51 (m, 1H, H-5), 4.68 (d, *J*=11 Hz, 1H, OCH_2Ar), 4.73 (d, *J*=11 Hz, 1H, OCH_2Ar), 4.95 (s, 1H, H-1), 7.23–7.38 (m, 5H, Ar–*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9 ($SiCH(CH_3)_2$), 18.2/18.3 ($SiCH(CH_3)_2$), 19.5 (C-8), 21.1 (C-8), 38.8 (C-9), 40.6 (C-4), 43.9 (C-6), 44.5 (C-2), 51.5 (OCH_3), 62.6 (C-1), 68.6 (C-5), 74.0 (OCH_2Ar), 83.2 (C-3), 127.2 (*ortho* Ar–*C*), 127.3 (*para* Ar–*C*), 128.2 (*meta* Ar–*C*), 138.9 (Ar–*C*), 171.7 (C-7); MS (150°C) *m/z* 540 (M^+, 0), 499 (14), 498 ($M^+-C_3H_7$, 40), 432 (5), 391 (6), 390 (22), 261 (7), 260 (40), 230 (5), 217 (41), 215 (16), 159 (7), 145 (12), 131 (12), 105 (73), 103 (12), 91 (100), 75 (15); HRMS calcd for $C_{25}H_{41}O_4S_2Si$ ($M^+-C_3H_7$): 497.2216, found 497.2120.

To a solution of TIPS-protected **6** (178 mg, 0.33 mmol) in toluene (4 ml) was added DIBAH (0.73 ml, 0.73 mmol, 1 M solution in hexane) at 0°C. After 3 h at r.t. H_2O (10 ml) was added, the aqueous phase separated, saturated with $MgSO_4$ and extracted with EA until no product was detectable in the aqueous layer (TLC). The combined organic layer was dried ($MgSO_4$), filtered and evaporated. Chromatography (CH:EA=9:1) afforded (3*R*,5*S*)-5-benzyloxy-6-([1,3]dithiolan-2-yl)-6-methyl-3-triisopropylsilyloxy-heptan-1-ol (149 mg, 88%), colourless oil, $[\alpha]_D^{20}$=−7.2 (*c* 1.2, $CHCl_3$). IR ($CHCl_3$) ν 3464, 2964, 2944, 2892, 2868, 1672, 1604, 1496, 1464, 1424, 1384, 1304, 1280, 1244, 1096, 1028, 916 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (s, 3H, H-8), 1.08 (s, 3H, H-8), 1.10 (m, 21H, $Si(CH(CH_3)_2)_3$), 1.73–1.92 (m, 4H, H-4, H-6), 2.35 (bs, 1H, O*H*), 3.16 (m, 4H, H-9), 3.64 (m, 2H, H-7), 3.78 (m, 1H, H-3), 4.21 (m, 1H, H-5), 4.65 (d, *J*=11 Hz, 1H, OCH_2Ar), 4.73 (d, *J*=11 Hz, 1H, OCH_2Ar), 4.93 (s, 1H, H-1), 7.23–7.36 (m, 5H, Ar–*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9 ($SiCH(CH_3)_2$), 18.3 ($SiCH(CH_3)_2$), 19.7 (C-8), 21.2 (C-8), {38.77, 38.79} (C-9), {39.4, 39.9} (C-4+6), 44.6 (C-2), 59.7 (C-7), 62.6 (C-1), 70.2 (C-5), 74.4 (OCH_2Ar), 83.8 (C-3), 127.1 (*ortho* Ar–*C*), 127.4 (*para* Ar–*C*), 128.3 (*meta* Ar–*C*), 138.8 (Ar–*C*); MS (170°C) *m/z* 512 (M^+, 0), 469 ($M^+-C_3H_7$, 4), 362 (13), 267 (5), 231 (31), 227 (8), 213 (7), 202 (7), 187 (28), 159 (14), 157 (8), 151 (8), 145 (22), 131 (10), 120 (10), 116 (14), 105 (74), 103 (9), 92 (9), 91 (100), 75 (14); HRMS calcd for $C_{27}H_{48}O_3S_2Si$ ($M^+-C_3H_7$): 469.2266, found 469.2271.

To a solution of the alcohol (390 mg, 0.76 mmol) in CH_2Cl_2 (8 ml) was added PCC on silica gel (460 mg, 0.912 mmol, 2 mmol PCC/g) at 0°C. The mixture was stirred for 2 h and then filtered through silica gel. The solvent was removed and the crude product purified by chromatography (CH:EA=9:1) to yield **7** (314 mg, 81%), colourless oil, $[\alpha]_D^{20}$=−3.5 (*c* 2.0, $CHCl_3$). IR ($CHCl_3$) ν 3064, 2944, 2892, 2868, 2728, 1720, 1600, 1496, 1464, 1420, 1384, 1364, 1280, 1248, 1096, 1012, 908 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (s, 3H, H-8), 1.05 (s, 3H, H-8), 1.08 (m, 21H, Si(C*H*(CH_3)$_2$)$_3$), 1.77 (m, 1H, H-4), 1.89 (ddd, *J*=14, 7, 3 Hz, 1H, H-4), 2.68 (m, 2H, H-6), 3.17 (m, 4H, H-9), 3.65 (dd, *J*=9, 3 Hz, 1H, H-3), 4.51 (m, 1H, H-5), 4.66 (d, *J*=11 Hz, 1H, OCH_2Ar), 4.73 (d, *J*=11 Hz, 1H, OCH_2Ar), 4.92 (s, 1H, H-1), 7.23–7.36 (m, 5H, Ar–*H*), 9.79 (t, *J*=2 Hz, 1H, H-7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8 (Si*C*H(CH_3)$_2$), 18.3 (SiCH(*C*H_3)$_2$), 19.7 (C-8), 21.1 (C-8), {38.80, 38.81} (C-9), 40.8 (C-4), 44.6 (C-2), 52.3 (C-6), 62.5 (C-1), 67.3 (C-5), 74.2 (O*C*H_2Ar), 83.4 (C-3), 127.1 (*ortho* Ar–*C*), 127.4 (*para* Ar–*C*), 128.3 (*meta* Ar–*C*), 138.7 (Ar–*C*), 201.5 (C-7); MS (110°C) *m/z* 510 (M^+, 0), 467 ($M^+-C_3H_7$, 4), 405 (5), 404 (8), 403 (24), 363 (5), 362 (6), 361 (24), 360 (20), 359 (74), 333 (5), 332 (7), 331 (28), 323 (8), 322 (27), 321 (100), 318 (5), 317 (4); HRMS calcd for $C_{24}H_{39}O_3S_2Si$ ($M^+-C_3H_7$): 467.2110, found 467.2105.

(3R,5R,7S)-7-Benzyloxy-8-([1,3]dithiolan-2-yl)-3-hydroxy-8-methyl-5-triisopropylsilyloxy-nonanoic acid, (S)-2-hydroxy-1,2,2-triphenylethyl ester **8**

To a solution of diisopropylamine (0.084 ml, 61.0 mg, 0.601 mmol) in THF (1 ml) was added BuLi (0.462 ml, 0.601 mmol, ~1.3 M solution in hexane) at −78°C. The mixture was stirred for 15 min at 0°C and then recooled to −78°C. This solution was added to a solution of (*S*)-(−)-2-hydroxy-1,2,2-triphenylethyl acetate (91.0 mg, 0.273 mmol) in THF (1 ml) at −78°C. The mixture was stirred for 30 min at 0°C while the deep-yellow dianion of (*S*)-**9** was formed. The mixture was cooled to −110°C and aldehyde **7** (120 mg, 0.250 mmol) in THF (1 ml) was added very slowly. The resulting mixture was stirred for 2 h at −110°C and 1 h at −78°C. Sat. aq. NH_4Cl solution (1 ml) was added, the mixture was allowed to reach r.t. and diluted with H_2O (10 ml). The aqueous phase was separated, saturated with $MgSO_4$ and extracted with EA until no product was detectable in the aqueous layer (TLC). The combined organic layer was dried ($MgSO_4$), filtered and evaporated. Chromatography (CH:EA=95:5) afforded **8** (mixture of diastereomers, 5.3:1, determined by ^{1}H NMR). Yield: 175 mg (86%), colourless oil, $[\alpha]_D^{20}=-123.6$ (*c* 0.475, $CHCl_3$). IR ($CHCl_3$) ν 3444, 3088, 3060, 3028, 2940, 2864, 1732, 1492, 1448, 1380, 1360, 1340, 1276, 1244, 1156, 1096, 1060, 1000, 884 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (major isomer) δ 1.01 (s, 3H, H-8), 1.07 (s, 3H, H-8), 1.08 (m, 21H, Si(C*H*(CH_3)$_2$)$_3$), 1.42–1.82 (m, 4H, H-4+6), 2.14–2.34 (m, 2H, H-10), 2.51 (d, *J*=3 Hz, 1H, H-15), 2.95 (s, 1H, H-14), 3.09 (bm, 1H, H-7), 3.16 (m, 4H, H-9), 3.52 (dd, *J*=8, 4 Hz, 1H, H-3), 4.18 (m, 1H, H-5), 4.58 (d, *J*=11 Hz, 1H, OCH_2Ar), 4.68 (d, *J*=11 Hz, 1H, OCH_2Ar), 4.89 (s, 1H, H-1), 6.68 (s, 1H, H-12), 7.00–7.20 (m, 11H, Ar–*H*), 7.20–7.41 (m, 6H, Ar–*H*), 7.53 (m, 1H, Ar–*H*), 7.70 (m, 2H, Ar–*H*); ^{13}C NMR (100 MHz, $CDCl_3$) (major isomer) δ 12.8 (Si*C*H(CH_3)$_2$), {18.23, 18.25, 18.32} (SiCH(*C*H_3)$_2$), 19.7 (C-8), 21.2 (C-8), {38.68, 38.73, 38.75} (C-4+6+9), 42.4 (C-10), 44.7 (C-2), 62.5 (C-1), 65.0 (C-7), 70.2 (C-5), 74.0 (O*C*H_2Ar), 78.8 (C-12), 80.2 (C-13), 83.9 (C-3), {126.2, 126.25, 126.35, 126.6, 126.99, 127.03, 127.30, 127.38, 127.41, 127.5, 127.6, 127.7, 128.1, 128.24, 128.28, 128.34, 128.36} (*ortho+para+meta* Ar–*C*), {138.8, 142.5, 145.1} (Ar–*C*), 171.1 (C-11); FAB-MS 865 ([M+Na]$^+$, 100), 825 (25).

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