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ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 5873–5878

Synthesis of the C15–C23 fragment of dictyostatin using a highly stereoselective Carreira alkynylation

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Received 1 December 2006; revised 29 January 2007; accepted 30 January 2007
Available online 2 February 2007

Abstract—A straightforward synthesis of the C15–C23 fragment of dictyostatin has been achieved by a highly stereoselective Carreira alkynylation between alkyne **1** and aldehyde **2**, followed by three chemoselective reductions.

1. Introduction

The sponge-derived macrolide dictyostatin (Fig. 1) has been reported to exhibit paclitaxel-like effects on cellular microtubules and to inhibit human cancer cell proliferation at low nanomolar concentrations and with activity superior to discodermolide (ED_{50} 0.38 nM, P338 leukemia cells).[1] The structure of dictyostatin with full stereochemical assignments was recently established,[2] and four total syntheses were completed by Paterson and co-workers (2004),[3] Curran and co-workers (2004),[4] and more recently by Phillips and O'Neil (2006),[5] and Ramachandran and co-workers (2007).[6] Curran and co-workers published a fluorous mixture synthesis of (−)-dictyostatin and three of its diastereomers,[7] a synthesis of (−)-16-normethyldictyostatin,[8] while syntheses of discodermolide–dictyostatin hybrids were reported by both the Curran[9] and the Paterson groups.[10] The syntheses of various fragments (typically the C1–C9, the C11–C23, and the C10–C23 segments) have also been described,[11] and a growing number of research groups has been recently involved in targeting this interesting natural product.[12]

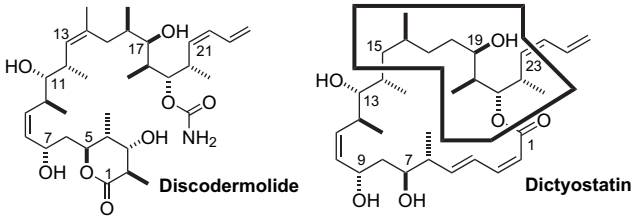

Figure 1. Marine cytotoxic agents discodermolide and dictyostatin.

The development of a practical and flexible synthesis of dictyostatin is still an important goal, particularly as the natural supply is extremely scarce. With the recent withdrawal of discodermolide from clinical development,[13] the importance of dictyostatin increases further.

2. Results and discussion

Our synthetic efforts toward dictyostatin were initially focused on the preparation of the C15–C23 fragment of the macrolide, containing five of its eleven stereocenters (Fig. 1).

Alkyne **1** was prepared from methyl (*R*)-3-benzyloxy-2-methylpropionate following a procedure described by Trost and Papillon in 2004 (Scheme 1).[14] DIBAL-H reduction in dichloromethane gave an aldehyde, which was not isolated but treated sequentially in situ with methanol (to quench the excess DIBAL-H), the Bestmann–Ohira reagent,[15,16] and sodium methoxide in THF,[17] to afford alkyne **1** in 78% isolated yield.

Alkyne **1** was treated with *n*-BuLi in THF at −78 °C and then with aldehyde **2** (prepared according to Smith III and coworkers, Scheme 1)[18] to afford a mixture of the two diastereomeric propargylic alcohols **3** and **4** in a 6:4 ratio (49% yield, Scheme 2). Alternatively, a Carreira asymmetric alkynylation ($Zn(OTf)_2$, Et_3N, toluene, RT)[19] was carried out with either of the two enantiomers of *N*-methyl-ephedrine: the reaction with (+)-(1*S*,2*R*)-*N*-methyl-ephedrine (mismatched pair) gave the addition product in 33% yield, with a diastereomeric ratio of 9:1 in favor of the undesired *R*-alcohol **4**. On the contrary, the Carreira coupling with (−)-(1*R*,2*S*)-*N*-methyl-ephedrine (matched pair)[20] gave the desired *S*-alcohol **3** in 96% yield as a single diastereomer (Scheme 2).

Keywords: Alkynylation; Antitumor agents; Dictyostatin; Stereocontrol.
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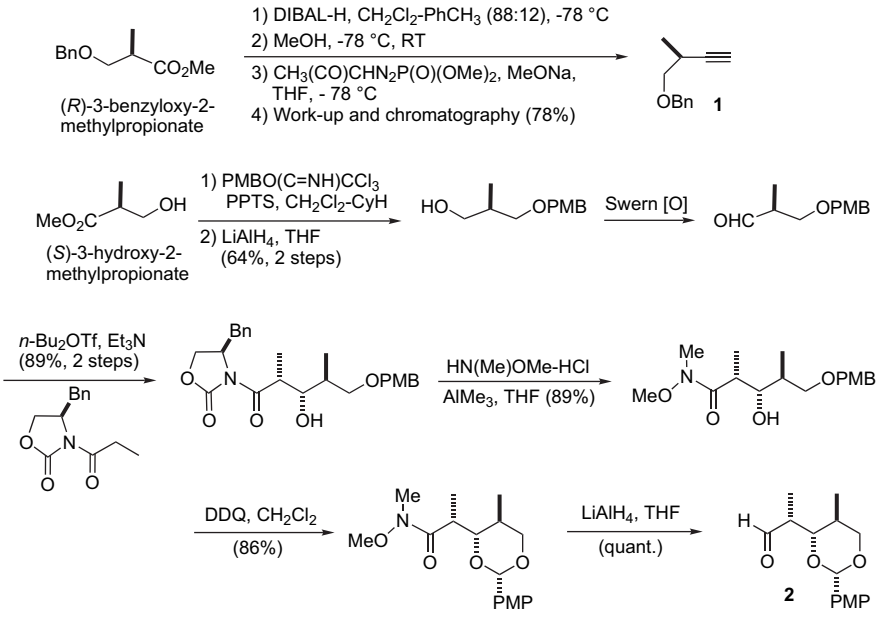
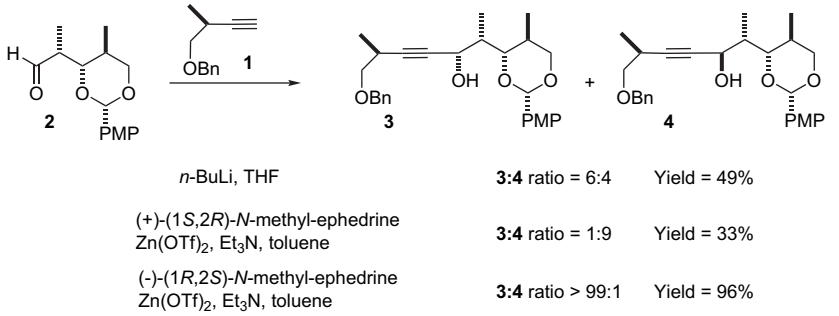
doi:10.1016/j.tet.2007.01.067

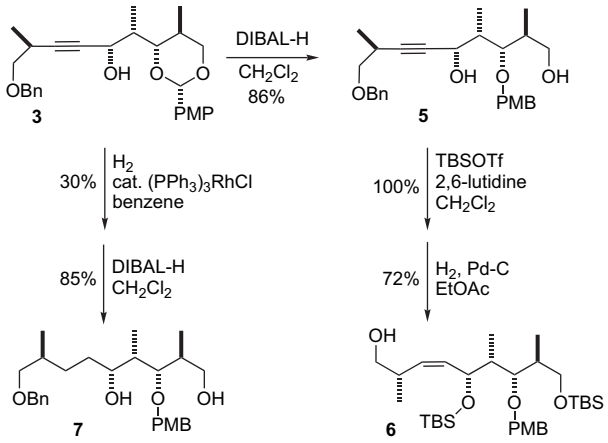


Scheme 1. Synthesis of alkyne **1** and aldehyde **2**.



Scheme 2. Stereoselective Carreira alkynylation.

Hydrogenation of alcohol **3** in the presence of a catalytic amount (10%) of Wilkinson's catalyst[21] in benzene, gave the desired saturated compound in a low yield (30%), which was then cleaved with DIBAL-H in dichloromethane[18] to give diol **7** (85%) (Scheme 3). Alternatively, acetal **3** was cleaved with DIBAL-H to generate diol **5** in 86% yield.

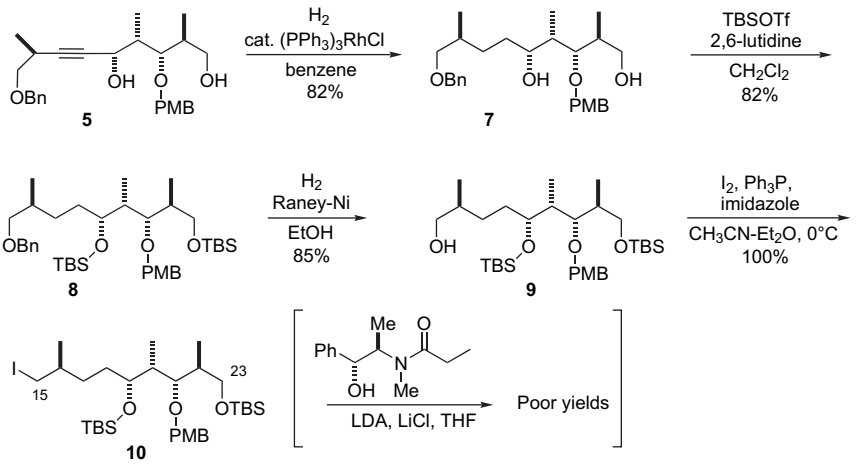


Scheme 3. Problematic routes to the C15–C23 fragment.

When diol **5** was first silylated (TBSOTf, 2,6-lutidine, CH_2Cl_2) and then reduced (H_2, Pd/C, EtOAc), *Z*-alkene **6** was obtained cleanly, with concomitant benzyl removal, but could not be further reduced to the corresponding alkane (Scheme 3). Hydrogenation of propargylic alcohol **5** with Wilkinson's catalyst[21] gave the saturated compound **7** in a much improved 82% yield (Scheme 4).

Double protection of diol **7**, by reaction with TBSOTf in the presence of 2,6-lutidine, gave compound **8** in 82% yield. Selective removal of the benzyl group over the PMB group (H_2, Raney-Ni, EtOH),[22] gave alcohol **9** in 85% yield. Finally, alcohol **9** was treated with I_2, PPh_3, imidazole[23] to give iodide **10** (C15–C23) in a quantitative yield, ready for further elongation of the carbon chain.

Preliminary experiments with the Myers' alkylation[24] revealed a very poor reactivity of iodide **10**; long reaction times and forcing reaction conditions (elevated temperatures, huge excess of the enolate and use of DMPU as co-solvent) did not help so far. These problems might be due to the bulky (although remote!) protective groups, as recently discussed by Crimmins and Slade.[25] Further studies are currently in progress.



Scheme 4. Synthesis of the C15–C23 fragment of dictyostatin.

3. Experimental

3.1. General procedures

All reactions were carried out in flame-dried glassware under argon atmosphere. All commercially available reagents were used as received. The solvents were dried by distillation over the following drying agents and were transferred under nitrogen: CH_3CN (CaH_2), CH_2Cl_2 (CaH_2), $(CH_2Cl)_2$ (CaH_2), MeOH (CaH_2), Et_3N (CaH_2), *i*-Pr_2EtN (CaH_2), $HN(TMS)_2$ (CaH_2), THF (Na), Et_2O (Na), benzene (Na), toluene (Na), *n*-hexane (Na). Organic extracts were dried over anhydrous Na_2SO_4. Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} precoated glass plates (0.25 mm thickness) or basic alumina supported on aluminum foils. TLC R_f values are reported. Visualization was accomplished by irradiation with a UV lamp and/or staining with ceric ammonium molybdate (CAM) solution. Flash column chromatography was performed using silica gel 60 Å, particle size 40–64 μm, following the procedure by Still and co-workers.[26] Proton NMR spectra were recorded on 400, 300, or 200 MHz spectrometers. Proton chemical shifts are reported in parts per million (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$, δ 7.26 ppm; DMSO-d_6, δ 2.50 ppm). The following abbreviations are used to describe spin multiplicity: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad signal, dd=doublet of doublet, dt=doublet of triplet, ddd=doublet of doublet of doublet. Carbon NMR spectra were recorded on 400 (100 MHz), 300 (75 MHz) or 200 (50 MHz) spectrometers with complete proton decoupling. Carbon chemical shifts are reported in parts per million (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ 77.0 ppm). Infrared spectra were recorded on a standard infrared spectrophotometer; peaks are reported in cm^{-1}. Optical rotation values were measured on an automatic polarimeter at the sodium D line. High resolution mass spectra (HRMS) were performed on a hybrid quadrupole time-of-flight mass spectrometer equipped with an ESI ion source. A reserpine solution 100 pg/μl (about 100 count/s), 0.1% $HCOOH/CH_3CN$ 1:1, was used as reference compound (Lock Mass).

3.1.1. ((*S*)-2-Methyl-but-3-ynyloxymethyl)-benzene (1). A solution of DIBAL-H (1.5 M in toluene, 3.52 mL, 5.28 mmol) was added dropwise (over 30 min) to a cold (−78 °C), stirred solution of methyl (*R*)-3-benzyloxy-2-methyl-propionate (957 mg, 4.60 mmol) in CH_2Cl_2 (25.0 mL). After 30 min, methanol (0.25 mL, 6.21 mmol) was added. The cooling bath was removed and the mixture [containing (*R*)-3-benzyloxy-2-methyl-propionaldehyde] was allowed to warm to room temperature. A solution of sodium methoxide (25 wt % in methanol, 3.0 mL, 13.10 mmol) in THF (9.0 mL) was added dropwise (over 15 min) to a stirred solution of (1-diazo-2-oxo-propyl)-phosphonic acid dimethyl ester[15–17] $CH_3(CO)CHN_2P(O)(OMe)_2$ (2.5 g, 13.10 mmol) in THF (45.0 mL) at −78 °C, followed by cannulation of the aldehyde solution over 5 min. The cooling bath was removed and after 30 min a saturated aqueous solution of Rochelle's salt (90.0 mL) was added. The mixture was vigorously stirred for a further 30 min and the two phases were separated; the aqueous phase was extracted twice with diethyl ether and the combined organic phases were dried over Na_2SO_4. Purification of the crude product by flash chromatography (*n*-hexane/EtOAc, 9.5:0.5) afforded alkyne **1** (625 mg, 78%) as a colorless oil. R_f=0.25 (*n*-hexane/EtOAc, 9.5:0.5); $[\alpha]_D^{20}$ −5.1 (*c* 1, in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ=7.36 (br s, 5H), 4.61 (s, 2H), 3.58 (dd, ^1J=9.0 Hz, ^2J=6.3 Hz, 1H), 3.43 (dd, ^1J=9.0 Hz, ^2J=7.3 Hz, 1H), 2.78–2.75 (m, 1H), 2.12 (d, J=2 Hz, 1H), 1.27 ppm (d, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=138.9, 129.1, 128.3, 87.1, 74.5, 73.8, 69.7, 27.3, 18.3 ppm; FTIR (CCl_4): ν=3313, 3030, 2963, 1548, 1261, 1217 cm^{-1}; HRMS (ESI): calcd for $C_{12}H_{14}NaO$: 197.09369 $[M+Na]^+$; found: 197.09361 (resolution 46,900).

3.1.2. (2*S*,3*S*,6*S*)-7-Benzyloxy-2-[(2*S*,4*S*,5*S*)-2-(4-methoxy-phenyl)-5-methyl-[1,3]dioxan-4-yl]-6-methyl-hept-4-yn-3-ol (3). Zinc triflate (1.42 g, 3.91 mmol) was dried in a two-necked flask while heating under vacuum. (−)-*N*-Methylephedrine (532 mg, 2.97 mmol) was then added, and the vessel was purged with argon for 15 min. Toluene (3.0 mL) was added, followed by triethylamine (0.41 mL, 2.97 mmol) and the mixture was stirred at room temperature for 2 h. The mixture was then treated with a solution of alkyne **1** (518 mg, 2.97 mmol) in dry toluene (0.9 mL),

stirred for a further 15 min, and then with a solution of aldehyde **2**[18] (246 mg, 0.93 mmol) in toluene (1.2 mL). The reaction progress was monitored by TLC. After 24 h the reaction mixture was diluted with diethyl ether and quenched with a saturated NH_4Cl solution (15.0 mL). The organic phase was separated and the aqueous layer was extracted with ether (3×20 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4. Purification of the crude product by flash chromatography (*n*-hexane/EtOAc, 8:2) afforded diastereoisomerically pure propargylic alcohol **3** (392 mg, 96%) as a colorless oil. R_f=0.21 (*n*-hexane/EtOAc, 8:2); $[\alpha]_D^{20}$ +34.6 (*c* 1, in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.39–7.28 (m, 7H), 6.89 (d, *J*=8.4 Hz, 2H), 5.47 (s, 1H), 4.59–4.57 (m, 3H), 4.12 (dd, ^1J=11.2 Hz, ^2J=4.8 Hz, 1H), 3.82 (d, *J*=4.4 Hz, 1H), 3.81 (s, 3H), 3.55 (dd, ^1J=9.2 Hz, ^2J=6.0 Hz, 2H), 3.50 (t, *J*=10.8 Hz, 1H), 3.40 (dd, ^1J=8.8 Hz, ^2J=7.2 Hz, 1H), 2.85–2.78 (m, 1H), 2.71 (br s, 1H), 2.11–2.07 (m, 1H), 2.00–1.98 (m, 1H), 1.24 (d, *J*=7.2 Hz, 3H), 1.19 (d, *J*=6.8 Hz, 3H), 0.77 ppm (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=160.5, 138.8, 131.5, 129.0, 128.7, 128.2, 127.8, 114.2, 101.6, 87.9, 86.4, 81.7, 74.6, 73.7, 67.4, 55.9, 41.0, 31.1, 27.3, 18.5, 8.5 ppm; FTIR (CCl_4): ν=3619, 3540, 3065, 3030, 2973, 2931, 2842, 2228, 1623, 1519, 1465, 1369, 1303, 1254, 1169, 1123 cm^{-1}; HRMS (ESI): calcd for $C_{27}H_{34}NaO_5$: 461.22985 $[M+Na]^+$; found: 461.22909 (resolution 25,200).

3.1.3. (2*S*,3*R*,6*S*)-7-Benzyloxy-2-[(2*S*,4*S*,5*S*)-2-(4-methoxy-phenyl)-5-methyl-[1,3]dioxan-4-yl]-6-methyl-hept-4-yn-3-ol (4). Zinc triflate (153 mg, 0.42 mmol) was dried in a two-necked flask while heating under vacuum. (+)-*N*-Methylephedrine (57 mg, 0.32 mmol) was then added and the vessel was purged with argon for 15 min. Toluene (1.0 mL) was added, followed by triethylamine (0.045 mL, 0.32 mmol) and the mixture was stirred at room temperature for 2 h. The mixture was then treated with a solution of alkyne **1** (56 mg, 0.32 mmol) in dry toluene (0.2 mL), stirred for a further 15 min, and then with a solution of aldehyde **2**[18] (26.4 mg, 0.10 mmol) in toluene (0.2 mL). The reaction progress was monitored by TLC. After 48 h the reaction mixture was diluted with diethyl ether and quenched with a saturated NH_4Cl solution (3 mL). The organic phase was separated and the aqueous layer was extracted with ether (3×5 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4. Purification of the crude product by flash chromatography (*n*-hexane/EtOAc, 8:2) afforded a mixture of diastereomeric propargylic alcohols **3** and **4** in a 1:9 ratio (14.5 mg, 33%) as a colorless oil. The diastereomeric ratio was determined by NMR. *Data for **4***: R_f= 0.21 (*n*-hexane/EtOAc, 8:2); $[\alpha]_D^{20}$ −18.6 (*c* 1, in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.38–7.28 (m, 7H), 6.88 (d, *J*=7.5 Hz, 2H), 5.48 (s, 1H), 4.59–4.57 (m, 3H), 4.11 (dd, ^1J=10.5 Hz, ^2J=4.6 Hz, 1H), 3.82 (d, *J*=4.4 Hz, 1H), 3.81 (s, 3H), 3.57–3.50 (m, 3H), 3.40 (dd, ^1J=9.1 Hz, ^2J=6.8 Hz, 1H), 2.86–2.80 (m, 1H), 2.68 (br s, 1H), 2.11–2.07 (m, 1H), 2.00–1.98 (m, 1H), 1.25 (d, *J*=7.1 Hz, 3H), 1.15 (d, *J*=7.2 Hz, 3H), 0.75 ppm (d, *J*=7.2 Hz, 3H).

3.1.4. (2*S*,3*S*,6*S*)-7-Benzyloxy-2-[(2*S*,4*S*,5*S*)-2-(4-methoxy-phenyl)-5-methyl-[1,3]dioxan-4-yl]-6-methyl-hept-4-yn-3-ol (3) and (2*S*,3*R*,6*S*)-7-benzyloxy-2-[(2*S*,4*S*,5*S*)-2-(4-methoxy-phenyl)-5-methyl-[1,3]dioxan-4-yl]-6-methyl-hept-4-yn-3-ol (4). *n*-BuLi (1.6 M solution in hexane, 0.094 mL, 0.15 mmol) was added slowly to a stirred solution of alkyne **1** (21 mg, 0.12 mmol) in THF (2.0 mL) at −78 °C. The yellowish solution was stirred for 90 min at −78 °C. A solution of aldehyde **2**[18] (26.4 mg, 0.10 mmol) in THF (0.5 mL) was added dropwise and the solution became colorless. The reaction was stirred overnight at −78 °C. A saturated NH_4Cl aqueous solution was then added, the layers were separated, and the aqueous phase extracted with ether (3×4 mL). The combined organic extracts were dried over Na_2SO_4. Purification of the crude product by flash chromatography (*n*-hexane/EtOAc, 8:2) afforded a mixture of diastereomeric propargylic alcohols **3** and **4** in a 6:4 ratio (21.5 mg, 49%) as a colorless oil. The diastereomeric ratio was determined by NMR. R_f=0.21 (*n*-hexane/EtOAc, 8:2).

3.1.5. (2*S*,3*S*,4*S*,5*S*,8*S*)-9-Benzyloxy-3-(4-methoxy-benzyloxy)-2,4,8-trimethyl-non-6-yne-1,5-diol (5). A solution of DIBAL-H (1.5 M in toluene, 2.28 mL, 3.42 mmol) was added to a solution of acetal **3** (298 mg, 0.68 mmol) in CH_2Cl_2 (10 mL) at −78 °C. After stirring for 20 min at −78 °C, for 1 h at 0 °C, and for 30 min at room temperature, the reaction mixture was quenched with methanol (5 mL) at −78 °C. The mixture was filtered through a pad of Celite, rinsed with CH_2Cl_2 (3×50 mL), and the resulting solution evaporated to give a yellowish solid. Purification of the crude product by flash chromatography (*n*-hexane/EtOAc, 6:4) afforded diol **5** (258 mg, 86%) as a colorless oil. R_f=0.23 (*n*-hexane/EtOAc, 6:4); $[\alpha]_D^{20}$ +14.7 (*c* 1, in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.36–7.27 (m, 7H), 6.88 (d, *J*=8.5 Hz, 2H), 4.56 (m, 4H), 4.41 (d, *J*=6.6 Hz, 1H), 3.82 (s, 3H), 3.72 (dd, ^1J=7.5 Hz, ^2J=3.1 Hz, 1H), 3.65 (d, *J*=5.2 Hz, 2H), 3.53 (dd, ^1J=9 Hz, ^2J=6.3 Hz, 1H), 3.40 (dd, ^1J=8.7 Hz, ^2J=7.1 Hz, 1H), 2.80–2.90 (m, 1H), 2.64 (br s, 1H), 2.52 (br s, 1H), 2.01–1.99 (m, *J*=9 Hz, 1H), 1.95–1.85 (m, 1H), 1.24 (d, *J*=6.9 Hz, 3H), 1.12 (d, *J*=6.9 Hz, 3H), 0.94 ppm (d, *J*=7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=160.0, 138.8, 131.1, 130.1, 129.1, 128.4, 128.3, 114.6, 89.3, 85.2, 82.1, 75.1, 74.7, 73.7, 71.9, 66.7, 66.4, 55.9, 43.6, 38.9, 27.5, 18.4, 15.4, 10.7 ppm; FTIR (CCl_4): ν=3619, 3520, 3065, 3030, 2966, 2936, 2877, 2238, 1619, 1521, 1461, 1254, 1100, 1051 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{36}NaO_5$: 463.24550 $[M+Na]^+$; found: 463.24487 (resolution 25,500).

3.1.6. (2*S*,3*S*,4*S*,5*R*,8*S*)-9-Benzyloxy-3-(4-methoxy-benzyloxy)-2,4,8-trimethyl-nonane-1,5-diol (7). A solution of propargylic diol **5** (198 mg, 0.45 mmol) in dry benzene (12 mL) was added to a dried two-necked flask. One neck was sealed and the other was fitted with a three-way stopcock connected to an atmospheric pressure hydrogenation apparatus and a vacuum pump. The solution was accurately degassed and purged with hydrogen, then Wilkinson's catalyst $Rh(PPh_3)_3Cl$ (42 mg, 0.045 mmol) was added and the mixture was stirred overnight. Silica gel was added and the solvent was evaporated. Purification of the crude product by flash chromatography (*n*-hexane/EtOAc, from 9:1 to 8:2) afforded diol **7** (164 mg, 82%) as a yellowish oil. R_f=0.23 (*n*-hexane/EtOAc, 85:15); $[\alpha]_D^{20}$ +11.1 (*c* 1, in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.37–7.29 (m, 7H), 6.89 (d, *J*=8.6 Hz, 2H), 4.61 (A part of an AB system, *J*=10.5 Hz, 1H), 4.57 (B part of an AB system, *J*=10.5 Hz,

1H), 4.52 (s, 2H), 3.81 (s, 3H), 3.76–3.66 (m, 5H), 3.56 (dd, ^1J=6.9 Hz, ^2J=3.9 Hz, 1H), 3.38–3.28 (m, 2H), 2.52 (br s, 2H), 2.06 (m, 1H), 1.81–1.78 (m, 2H), 1.55–1.49 (m, 2H), 1.01–0.96 ppm (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=160.1, 139.4, 130.8, 130.3, 129.5, 129.0, 128.2, 128.1, 114.6, 87.4, 76.5, 75.6, 74.9, 73.7, 66.2, 55.9, 40.2, 38.4, 34.2, 33.2, 30.8, 17.9, 15.5, 8.1 ppm; FTIR (CCl_4): ν=3640, 3526, 2934, 2875, 1613, 1515, 1455, 1362, 1250, 1216, 1174, 817 cm^{-1}; HRMS (ESI): calcd for $C_{27}H_{40}NaO_5$: 467.27680 [M+Na]$^+$; found: 467.27637 (resolution 24,900).

3.1.7. 1-{(1*S*,2*R*,3*R*,6*S*)-7-Benzyloxy-3-(*tert*-butyl-dimethyl-silanyloxy)-1-[(*S*)-2-(*tert*-butyl-dimethyl-silanyloxy)-1-methyl-ethyl]-2,6-dimethyl-heptyloxymethyl}-4-methoxy-benzene (8). Freshly distilled 2,6-lutidine (0.10 mL, 0.86 mmol) and TBSOTf (169 mg, 0.64 mmol) were added to a stirred solution of diol **7** (93.4 mg, 0.21 mmol) in CH_2Cl_2 (3.0 mL) at −78 °C. The reaction mixture was stirred for 30 min at −78 °C and then quenched with a saturated NH_4Cl aqueous solution. The organic phase was separated and the aqueous layer extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated. Purification of the crude product by flash chromatography (*n*-hexane/EtOAc, 95:5) afforded compound **8** (116 mg, 82%) as a colorless oil. R_f=0.19 (*n*-hexane/EtOAc, 95:5); $[\alpha]_D^{20}$ +2.3 (*c* 1, in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.35 (br s, 5H), 7.29 (d, *J*=8.4 Hz, 2H), 6.91 (d, *J*=8.4 Hz, 2H), 4.57–4.46 (m, 4H), 3.82 (s, 3H), 3.69–3.50 (m, 3H), 3.50 (dd, ^1J=6.7 Hz, ^2J=4.2 Hz, 1H), 3.33 (dd, ^1J=9.0 Hz, ^2J=6.0 Hz, 1H), 3.23 (dd, ^1J=7.0 Hz, ^2J=9.0 Hz, 1H), 1.92–1.89 (m, 1H), 1.83–1.80 (m, 1H), 1.74–1.71 (m, 1H), 1.14–1.12 (m, 1H), 0.99 (d, *J*=6.8 Hz, 3H), 0.95–0.93 (m, 27H), 0.10–0.05 ppm (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.6, 139.5, 132.4, 129.6, 129.0, 128.1, 128.0, 114.4, 81.7, 78.0, 77.7, 77.4, 76.7, 74.9, 74.6, 73.7, 65.4, 40.3, 39.6, 34.6, 32.2, 29.7, 26.7, 17.9, 15.9, 10.8, −3.5, −3.9 ppm; FTIR (CCl_4): ν=3066, 3032, 1613, 1586, 1549, 1388, 1302, 1181, 1172, 939 cm^{-1}; HRMS (ESI): calcd for $C_{39}H_{68}NaO_5Si_2$: 695.44975 [M+Na]$^+$; found: 695.44742 (resolution 20,000).

3.1.8. (2*S*,5*R*,6*R*,7*S*,8*S*)-5,9-Bis-(*tert*-butyl-dimethyl-silanyloxy)-7-(4-methoxy-benzyloxy)-2,6,8-trimethyl-nonan-1-ol (9). Raney-nickel was washed with water until the washings were pH neutral and then rinsed five times with absolute EtOH. A solution of compound **8** (100 mg, 0.149 mmol) in absolute EtOH (10 mL) was added, the mixture was accurately degassed, and then purged three times with hydrogen. After stirring for 24 h, the Raney-nickel was removed by filtration and the filtrate purified by flash chromatography (*n*-hexane/EtOAc, 92:8) to afford alcohol **9** (74 mg, 85%) as a colorless oil. R_f=0.14 (*n*-hexane/EtOAc, 92:8); $[\alpha]_D^{20}$ −3.3 (*c* 1, in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.27 (d, *J*=8.6 Hz, 2H), 6.89 (d, *J*=8.6 Hz, 2H), 4.57 (A part of an AB system, *J*=11.0 Hz, 1H), 4.49 (B part of an AB system, *J*=11.0 Hz, 1H), 3.82 (s, 3H), 3.73–3.65 (m, 3H), 3.49 (dd, ^1J=7.5 Hz, ^2J=3.0 Hz, 2H), 3.39 (dd, ^1J=6.7 Hz, ^2J=3.5 Hz, 1H), 1.90–1.81 (m, 2H), 1.58–1.28 (m, 3H), 1.13–1.09 (m, 1H), 0.98 (d, *J*=6.9 Hz, 3H), 0.96–0.89 (m, 27H), 0.10–0.07 ppm (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.6, 132.3, 129.6, 114.4, 81.5, 74.7, 74.6, 68.9, 65.3, 56.0, 40.1, 39.5, 36.8, 32.1, 29.0, 26.7, 26.7, 18.8, 17.4, 10.8, −3.4, −3.6 ppm; HRMS (ESI): calcd for $C_{32}H_{62}NaO_5Si_2$: 605.40280 [M+Na]$^+$; found: 605.39994 (resolution 23,100).

3.1.9. 1-{(1*S*,2*R*,3*R*,6*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-1-[(*S*)-2-(*tert*-butyl-dimethyl-silanyloxy)-1-methyl-ethyl]-7-iodo-2,6-dimethyl-heptyloxymethyl}-4-methoxy-benzene (10). Imidazole (46 mg, 0.67 mmol), triphenylphosphine (176 mg, 0.67 mmol), and iodine (140 mg, 0.55 mmol) were added sequentially to a solution of alcohol **9** (100 mg, 0.172 mmol) in a mixture of diethyl ether/acetonitrile 2:1 (4.5 mL). The reaction mixture was stirred for 1.5 h at room temperature and then quenched with an aqueous solution of sodium thiosulfate. The organic phase was separated and the aqueous layer extracted with ether (3×20 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4. Purification of the crude product by flash chromatography (*n*-hexane/EtOAc, 99:1) afforded iodide **10** (119 mg, 100%) as a colorless oil. R_f=0.21 (*n*-hexane/EtOAc, 99:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.23 (d, *J*=11 Hz, 2H), 6.85 (d, *J*=11 Hz, 2H), 4.56 (A part of an AB system, *J*=14.7 Hz, 1H), 4.45 (B part of an AB system, *J*=14.7 Hz, 1H), 3.79 (s, 3H), 3.68–3.61 (m, 3H), 3.48–3.46 (m, 2H), 3.16–3.08 (m, 2H), 1.87–1.76 (m, 2H), 1.45–1.20 (m, 3H), 0.97–0.67 (m, 27H), 0.125–0.00 ppm (m, 13H); HRMS (ESI): calcd for $C_{32}H_{61}NaIO_4Si_2$: 715.30453 [M+Na]$^+$; found: 715.30311 (resolution 16,000).

Acknowledgements

We thank the European Commission for financial support (IHP Network grant 'Design and synthesis of microtubule stabilizing anticancer agents' HPRN-CT-2000-00018) and for a postdoctoral fellowship to O.S. ('Marie Curie' MEIF-CT-2003-500880). We also gratefully acknowledge Merck Research Laboratories (Merck's Academic Development Program Award to C.G.), Ministero dell'Università e della Ricerca (PRIN prot. 2006030449), and Università degli Studi di Milano for financial support and for a postdoctoral fellowship (Assegno di ricerca) to C.M.

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