Synthesis and Biological Evaluation of 10,11-Dihydrodictyostatin, a Potent Analogue of the Marine Anticancer Agent Dictyostatin[§]

Ian Paterson,*[,†] Nicola M. Gardner,[†] Karine G. Poullennec,[†] and Amy E. Wright[‡]

University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, U.K., and Harbor Branch Oceanographic Institution, 5600 US 1 North, Ft. Pierce, Florida 34946

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By employing a diverted total synthesis strategy with late-stage intermediates, 10,11-dihydrodictyostatin (**5**) was prepared and evaluated *in vitro* for growth inhibition against a range of human cancer cell lines, including the NCI/ADR Taxol-resistant cell line. This novel dictyostatin analogue was found to retain potent antimitotic activity, with a comparable profile to discodermolide and Taxol, functioning by microtubule stabilization and G2/M arrest. These SAR studies provide further insight into the interaction between dictyostatin (**1**) and its tubulin target.

In 1994, Pettit *et al*. reported the isolation of the novel 22-membered macrolide dictyostatin (**1**, Figure 1) from a marine sponge of the genus *Spongia* collected in the Republic of Maldives, which also proved to be an important natural source of the spongistatins.[1a] Initial biological evaluation of dictyostatin revealed it to be a potent antimitotic agent, but a more in-depth study was impeded by the low isolation yield (1.35 mg from ca. 400 kg of sponges). At the time, a complete assignment of stereochemistry was not achieved,[1b] thwarting further development for almost a decade until its reisolation by Wright and co-workers[2] from a deep-sea sponge of the family *Corallistidae*, collected off the coast of Jamaica. With this newly available sample, a conclusive stereochemical assignment for dictyostatin was disclosed by us in 2004, based on extensive NMR experiments using Murata's *J*-based configuration analysis and molecular modeling.[3] This structure was confirmed soon after through two concurrent total syntheses, reported independently by ourselves[4a] and the Curran group,[4b,c] and more recently by Phillips[4d] and Ramachandran.[4e] There has been an upsurge in biological interest in dictyostatin with its identification as a microtubule-stabilizing agent,[2,5] promoting it into the elite ranks of Taxol (**2**), epothilone B (**3**), and discodermolide (**4**), along with several other natural products.[6] Dictyostatin potently inhibits cancer cell growth *in vitro* at low nanomolar concentrations, which is maintained against Taxol-resistant cell lines, and is generally more active than discodermolide and also binds to the taxoid binding site on β-tubulin.[2,5] Efforts continue toward the goal of developing a scalable synthesis to provide the larger quantities of dictyostatin required for preclinical evaluation of this promising anticancer agent, as well as analogue studies, pursued by the Curran group and ourselves,[7] to help define the minimum pharmacophore and enable structural simplification.

The macrocyclic polyketide dictyostatin shows close structural and stereochemical homology, having the same configuration at 10 out of its 11 stereocenters, with the open-chain discodermolide (**4**), an extensively studied anticancer agent,[8] isolated initially from another Caribbean sponge (*Discodermia dissoluta*), that was advanced into clinical trials.[9] These similarities are underscored by the convincing overlay of their preferred solution conformations (Figure 1)[4a] and permit the pre-existing library of discodermolide analogues,[7,8] together with the recently determined bioactive conformation of discodermolide,[10] to be used as tools in the design

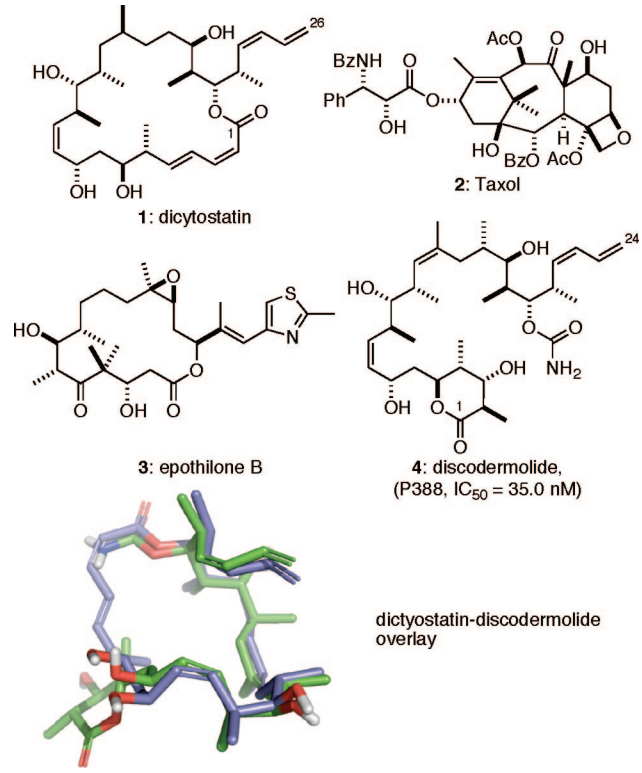

Figure 1. Structures of dictyostatin, Taxol, epothilone B, and discodermolide and overlay of global minima structures of dictyostatin and discodermolide.

of novel dictyostatin congeners. Herein, we report the synthesis of 10,11-dihydrodictyostatin (**5**, Figure 2) and provide preliminary biological data, including growth inhibition against human cancer cell lines, indicating that it represents a potent new analogue of dictyostatin.

Results and Discussion

Our initial premise for targeting the 10,11-dihydro analogue of dictyostatin was the availability of SAR data for a series of reduced derivatives **6**, **7**, and **8** of discodermolide obtained semisynthetically by catalytic hydrogenation, as reported by Gunasekera et al. (Figure 2).[8a] Although not prepared directly, the retention of biological activity in the corresponding 8,9-dihydro analogue of discodermolide was presumed from consideration of the available IC_{50} data (P-388 leukemia cell line) reported for these saturated derivatives.

[§] Dedicated to Dr. G. Robert Pettit of Arizona State University for his pioneering work on bioactive natural products.

* To whom correspondence should be addressed. Tel: +44-1223-336407. Fax: +44-1223-336362. E-mail: ip100@cam.ac.uk.

[†] University Chemical Laboratory.

[‡] Harbor Branch Oceanographic Institution.

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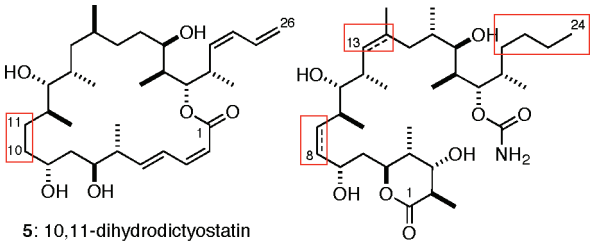
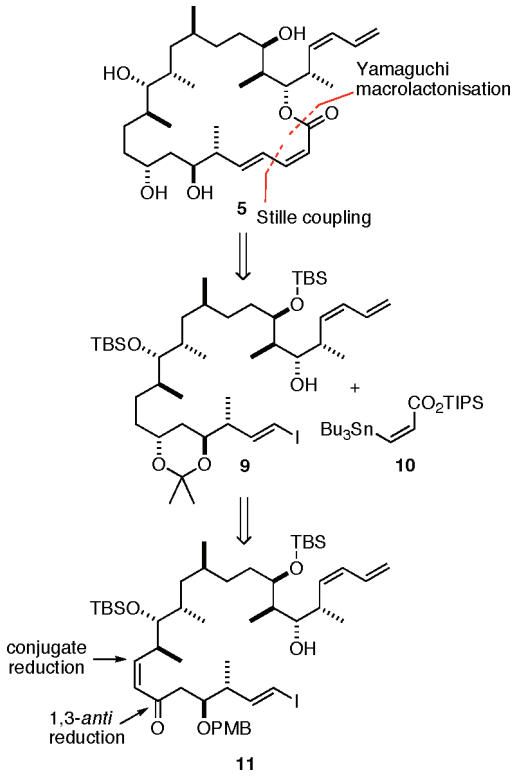


Figure 2. Structures of 10,11-dihydrodictyostatin and related hydrogenated derivatives **6**, **7**, and **8** of discodermolide.

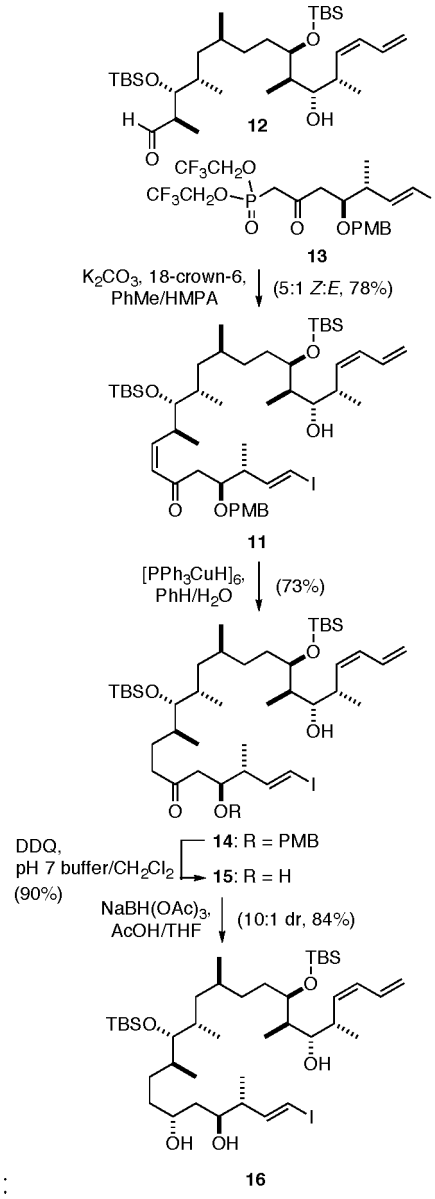
Scheme 1. Retrosynthetic Analysis of 10,11-Dihydrodictyostatin



Notably, the presence of the C13−C14 alkene, but not the C8−C9 alkene or terminal 1,3-diene, appears to be critical for maintaining biological activity in discodermolide. In the dictyostatin structure, this *Z*-trisubstituted alkene is not present and instead there is a methyl-bearing stereocenter at C16 that is considered important for retaining antiproliferative activity against Taxol-resistant cell lines.[7a] This led us to propose that saturation solely of the C10−C11 (*Z*)-alkene in dictyostatin might lead to a useful structural simplification without adversely affecting the cytotoxicity profile. From a pragmatic standpoint, it was attractive to employ a diverted total synthesis strategy[11] to access this novel analogue by suitable manipulation of advanced intermediates employed previously.[4a,7a] As outlined retrosynthetically in Scheme 1, conjugate reduction of the highly functionalized enone **11** and subsequent 1,3-*anti* reduction of the derived *β*-hydroxy ketone might provide ready access to a pivotal 10,11-dihydro intermediate, **9**, thus enabling completion of the desired analogue **5** by Stille coupling with the vinyl stannane **10** and macrolactonization, as employed in our earlier dictyostatin total synthesis.[4a]

Preparation of the advanced C16−C26 enone **11** (Scheme 2) was first achieved by an HWE fragment coupling, based on extension of the Still−Gennari variant[12a] used in our discodermolide work,[12b]

Scheme 2. Preparation of C4−C26 Advanced Intermediate



between the known C11−C26 aldehyde **12**[4a] and the C10−C16 phosphonate **13**[7a] to afford the (*Z*)-enone **11** predominantly (78%, 5:1 *Z*:*E*). As anticipated, conjugate reduction of both the (*E*) and (*Z*)-enones proceeded smoothly using freshly prepared Stryker's reagent[13] ($[Ph_3PCuH]_6$) and gave the desired ketone **14** (68%). Subsequent oxidative PMB ether cleavage of **14** with DDQ was followed by an Evans−Saksena reduction[14] of the resulting *β*-hydroxy ketone **15** with $NaBH(OAc)_3$ to provide 1,3-*anti* diol **16**, with a useful level of control over the C9 configuration (84%, 10:1 dr). Interestingly, the diastereoselectivity of this transformation is increased relative to the same reaction carried out on the corresponding *β*-hydroxy (*Z*)-enone derived from **11** (3:1 dr).

At this stage, we now needed to complete the 26-carbon dictyostatin backbone and perform the macrocyclization (Scheme 3). First, treatment of 1,3-diol **16** with $(MeO)_2CMe_2$ in the presence of catalytic PPTS gave the acetonide **9** (90%). A Stille coupling using copper(I) thiophene-2-carboxylate[15] (CuTC) of the vinyl iodide **9** with the stannane **10** and *in situ* TIPS cleavage (KF) then gave the corresponding acid **17** (73%) in readiness for macrolactonization. Using the previously employed Yamaguchi protocol,[4a,7a] the macrolactone **18** was isolated (without any apparent *Z* to *E* isomerization of the dienoate) in 60% yield and submitted to global deprotection using HF•pyridine to generate the targeted 10,11-

Scheme 3. Completion of the Synthesis of 10,11-Dihydrodictyostatin

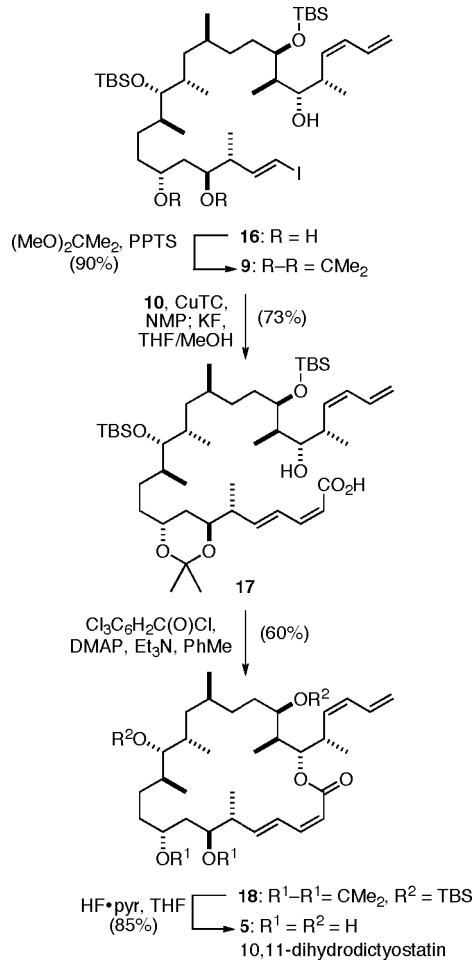


Table 1. Cytotoxicity of Dictyostatin (**1**), Taxol (**2**), Discodermolide (**4**), and 10,11-Dihydrodictyostatin (**5**) in Cultured Human Cancer Cell Lines as Determined by MTT Metabolism Following 72 h Exposure to the Test Agent

	IC_{50}/nM[a]			
compound	AsPC-1 (pancreatic)	DLD-1 (colon)	PANC-1 (pancreatic)	NCI/ADR (Taxol-resistant)
1	9.0 (±5.6)	0.8 (±3.8)	3.4 (±0.2)	9.8 (±1.5)
2	20 (±23)	11 (±1)	7 (±2)	1000 (±140)
4	98 (±34)	29 (±8)	59 (±34)	160 (±34)
5	43 (±9.4)	10 (±1.5)	18 (±0.7)	300 (±190)

[a] Values are ± standard deviation (in parentheses) from a minimum of four separate experiments.

dihydrodictyostatin (**5**) in 85% yield, purified by HPLC prior to biological evaluation.

Biological Evaluation. The cell growth inhibitory activity of 10,11-dihydrodictyostatin was evaluated *in vitro* and measured relative to dictyostatin itself, Taxol and discodermolide against four human cancer cell lines: AsPC-1 (pancreatic), DLD-1 (colon), PANC-1 (pancreatic), and NCI-ADR (Taxol-resistant) (Table 1). Across the range of Taxol-sensitive cancer cell lines (ASP-1, DLD-1, PANC-1), the synthesized dictyostatin analogue **5** displayed a low nanomolar level of cytotoxicity similar to that of Taxol and was found to be 2–3 times more active than discodermolide, with a corresponding 5–12-fold drop in activity relative to dictyostatin itself. In common with discodermolide, however, 10,11-dihydrodictyostatin's activity was significantly reduced upon a switch to the Taxol-resistant NCI/ADR line. In a separate series of incubatory experiments performed on the PANC-1 cell line, the dihydro compound **5** was shown to act in an analogous fashion to dictyostatin, through a mechanism of microtubule stabilization, causing both an accumulation of cells at the G2/M phase (Figure 3a) and formation of characteristic dense intracellular microtubule bundles (Figure 3b).

From these results, we conclude that the *Z*-configured C10−C11 olefin does not contribute significantly to the cytotoxicity of dictyostatin and hence to maintaining the bioactive conformation of the 22-membered macrolide. However, in the NCI/ADR cell line, where the overexpression of a P-glycoprotein efflux pump in the cell membrane gives rise to its observed resistance to Taxol, the 10*Z*-unsaturation must play an important role in maintaining the mechanism through which dictyostatin can bypass the pump. These results are consistent with the conclusions made from the corresponding set of saturated discodermolide analogues[9] and further reinforce the similarities observed between these two microtubule-stabilizing agents.

In conclusion, we have designed and accessed by total synthesis the novel dictyostatin analogue **5** with a cytotoxicity profile comparable to that of discodermolide and Taxol. Taken together with information gained from other analogue studies,[7] this further increases our understanding of the SAR of dictyostatin with its tubulin target and represents further progress toward the goal of synthesizing a simplified analogue with a cytotoxicity profile comparable to that of the parent natural product.

Experimental Section

Biological Assays. Cytotoxicity assays were conducted using a standard MTT-based protocol as described previously.[16] Cell cycle and immunofluorescence imaging of PANC-1 cells were conducted as per protocols described previously.[2]

General Experimental Procedures. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or C_6D_6 on a Bruker Avance TXI 700, BB-ATM, TCI-ATM, and DRX-400. IR spectra were measured on a Perkin-Elmer Spectrum One (FT-IR) spectrophotometer. HRMS were obtained from the EPSRC Mass Spectrometry Service (Swansea, UK) using a Micromass Q-TOF or Bruker Bioapex FT-ICR spectrometer. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter, and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1} at a concentration *c* (g/100 mL). Preparative HPLC on a Daicel CHIRALCEL OD HPLC column (250 mm, 10 Å, flow 1 mL/min) used IPA/hexane (gradients) as solvent, with UV absorption detetction at 254 nm. Analytical TLC was carried out on Merck Kieselgel 60 F_{254} plates with visualization using UV (254 nm), potassium permanganate, and/or PMA/Ce$(SO_4)_2$ dip. Flash column chromatography was carried out on Merck Kieselgel 60 (230–440 mesh) under a positive pressure. Solvents were redistilled prior to use. Reagents were used as received unless stated otherwise.

(4*E*,6*R*,7*S*,10*Z*,12*S*,13*R*,14*S*,16*S*,19*R*,20*R*,21*S*,22*S*,20*Z*)-13,19-Bis-(*tert*-butyldimethylsilyloxy)-21-hydroxy-4-iodo-7-(*p*-methoxybenzyloxy)-6,12,14,16,20,22-hexamethyltricosa-4,10,23,25-tetraen-9-one (11).

To a mixture of 18-crown-6 (908 mg, 3.43 mmol) and K_2CO_3 (142 mg, 1.03 mmol) in toluene (16 mL) and HMPA (1.6 mL) at 0 °C was added via cannula a solution of aldehyde **12**[4a] (200 mg, 0.343 mmol) and phosphonate **13**[7a] (326 mg, 0.515 mmol) in toluene (16 mL) and HMPA (1.6 mL). After 5 days stirring at 0 °C, the reaction was quenched by the addition of saturated aqueous NH_4Cl (20 mL), and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (5% EtOAc/hexane) afforded (*Z*)-enone **11** (212 mg, 65%) and its isomeric (*E*)-enone (26 mg, 13%) as yellow oils: $[\alpha]^{20}_D$ −23.8 (*c* 0.21, $CHCl_3$); IR (liquid film)/cm^{-1} 2956, 2929, 2856, 1690, 1610, 1514, 1461; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.21 (2H, d, *J* = 8.5 Hz, H-Ar), 6.84 (2H, d, *J* = 8.4 Hz, H-Ar), 6.62 (1H, app dt, *J* = 10.8, 16.6 Hz, H-25), 6.49 (1H, dd, *J* = 8.7, 14.5 Hz, H-11), 6.32 (1H, dd, *J* = 9.9, 11.4 Hz, H-5), 6.10−6.06 (2H, m, H-4, H-24), 6.02 (1H, d, *J* = 14.5 Hz, H-10), 5.40 (1H, app t, *J* = 10.3 Hz, H-23), 5.20 (1H, dd, *J* = 1.6, 16.9 Hz, H-26a), 5.11 (1H, d, *J* = 10.1 Hz, H-26b), 4.50 and 4.38 (2H, AB system, *J* = 11.0 Hz, OCH_2Ar), 3.88 (1H, app dt, *J* = 4.9, 6.6 Hz, H-7), 3.78 (3H, s, $ArOCH_3$), 3.76−3.70 (2H, m, H-6, H-13), 3.48 (1H, app t, *J* = 3.2 Hz, H-19), 3.45 (1H, dd, *J* = 2.3, 7.3 Hz, H-21), 2.78 (1H, app qnd, *J* = 6.5, 9.8 Hz, H-22), 2.70 (1H, dd, *J* = 6.9 Hz, 16.6 Hz, H-8a), 2.51 (1H, dd, *J* = 5.2, 16.5 Hz, H-8b),

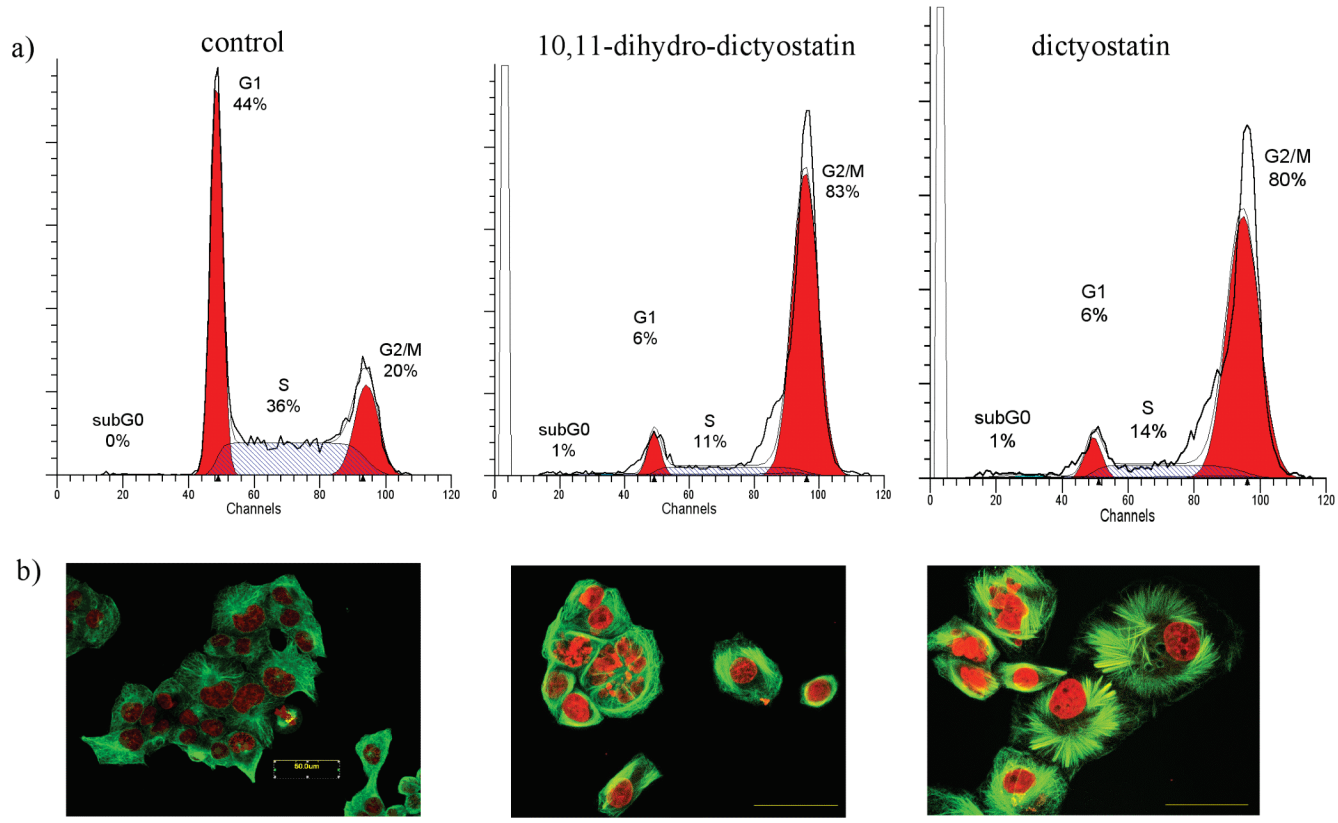


Figure 3. (a) Cell cycle analysis by flow cytometry of PANC-1 cells incubated for 24 h with 0.05% methanol (vehicle control), 100 nM 10,11-dihydrodictyostatin, or 100 nM dictyostatin. Histograms represent samples of approximately 1×10^4 cells per test and are plotted as cell number (*y*-axis) vs fluorescence intensity (*x*-axis). Both 10,11-dihydrodictyostatin and 100 nM dictyostatin show an accumulation of cells at the G2/M phase. (b) Immunofluorescence images of PANC-1 cells stained with anti-a-tubulin (green) and propidium iodide (red) and observed by confocal microscopy. Cells were exposed to 0.05% methanol (vehicle control), 100 nM 10,11-dihydrodictyostatin, or 100 nM dictyostatin. Both 10,11-dihydrodictyostatin and 100 nM dictyostatin show dense microtubule bundles characteristic of microtubule-polymerizing and -stabilizing agents.

2.45–2.38 (1H, m, H-12), 2.32 (1H, br s, OH), 1.70–1.65 (1H, m, H-20), 1.65–1.52 (3H, m, H-14, H-15a, H-18a), 1.41–1.20 (5H, m, H-15b, H-16, H_2-17, H-18b), 1.03 (3H, d, J = 6.9 Hz, CH_3-12), 1.00 (3H, d, J = 7.0 Hz, CH_3-6), 0.94 (3H, d, J = 6.6 Hz, CH_3-22), 0.91–0.86 (21H, m, $SiC(CH_3)_3 \times 2$, CH_3-20), 0.82 (6H, app t, J = 6.6 Hz, CH_3-14, CH_3-16), 0.07 (3H, s, $Si(CH_3)$), 0.06 (6H, s, $Si(CH_3)$ v 2), 0.05 (3H, s, $Si(CH_3)$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 199.3, 159.2, 152.5, 147.8, 135.4, 132.3, 130.5, 129.9, 129.4, 125.2, 117.7, 113.7, 79.8, 76.8, 75.8, 72.2, 55.3, 46.7, 44.6, 41.3, 41.0, 37.6, 36.4, 36.1, 35.9, 32.1, 31.31, 31.29, 30.6, 26.2, 26.0, 20.5, 19.1, 18.4, 18.1, 17.7, 15.8, 15.6, 6.8, −3.6, −3.7, −4.2, −4.4; HRMS (ES^+) calcd for $C_{49}H_{85}IO_6Si_2Na$ $[M + Na]^+$ 975.4832, found 975.4833; R_f 0.46 (10% EtOAc/hexane).

(4*E*,6*R*,7*S*,12*S*,13*S*,14*S*,16*S*,19*R*,20*R*,21*S*,22*S*,23*Z*)-13,19-Bis(*tert*-butyldimethylsilyloxy)-21-hydroxy-4-iodo-7-(*p*-methoxybenzyloxy)-6,12,14,16,20,22-hexamethyltricosa-4,23,25-trien-9-one (14). To a solution of enone **11** (73 mg, 0.077 mmol) at rt in deoxygenated toluene (2 mL) and water (5 μL) was added $[Ph_3PCuH]_6$ (45 mg, 0.031 mmol). After stirring for 2 h, the reaction mixture was concentrated *in vacuo*, and flash chromatography (7% EtOAc/hexane) afforded ketone **14** (54 mg, 73%) as a colorless oil: $[\alpha]^{20}_D$ +11.7 (*c* 0.99, $CHCl_3$); IR (liquid film)/cm^{-1} 2956, 2929, 2857, 1713, 1612, 1514, 1462; ^{1}H NMR (500 MHz, C_6D_6) δ_H 7.21 (2H, d, J = 8.7 Hz, H-Ar), 6.80 (2H, d, J = 8.6 Hz, H-Ar), 6.72 (1H, app dt, J = 10.6, 17.3 Hz, H-25), 6.49 (1H, dd, J = 8.4, 14.5 Hz, H-5), 6.09 (1H, app t, J = 11.0 Hz, H-24), 5.79 (1H, dd, J = 0.9, 14.5 Hz, H-4), 5.45 (1H, app t, J = 10.6 Hz, H-23), 5.15 (1H, dd, J = 1.8, 17.0 Hz, H-26a), 5.06 (1H, d, J = 10.1 Hz, H-26b), 4.39 and 4.29 (2H, AB system, J = 11.0 Hz, OCH_2Ar), 3.90 (1H, app q, J = 5.1 Hz, H-19), 3.87 (1H, app sep, J = 3.7 Hz, H-7), 3.54 (1H, dd, J = 4.1, 6.5 Hz, H-21), 3.40 (1H, dd, J = 2.3, 5.6 Hz, H-13), 3.31 (3H, s, $ArOCH_3$), 2.89 (1H, app qnd, J = 6.7, 10.1 Hz, H-22), 2.42 (1H, dd, J = 7.7, 16.4 Hz, H-8a), 2.25–2.12 (2H, m, H-6, H-10a), 2.08 (1H, dd, J = 4.6, 16.6 Hz, H-8b), 2.04–1.95 (1H, m, H-10b), 1.88–1.71 (3H, m, H-14, H-18a, H-20), 1.71–1.62 (1H, m, H-18b), 1.61–1.41 (5H, m, H-11a, H-12, H-16, H_2-17), 1.39–1.27 (2H, m, H-11b, H-15a), 1.20–1.13 (1H, m, H-15b), 1.11 (3H, d, J = 6.6 Hz, CH_3-14), 1.05 (9H, s, $SiC(CH_3)_3$), 1.02 (9H, s, $SiC(CH_3)_3$), 0.99 (9H, app d, J = 6.9 Hz, CH_3-16, CH_3-20, CH_3-22), 0.85 (3H, d, J = 6.9 Hz, CH_3-12), 0.83 (3H, d, J = 6.9 Hz, CH_3-6), 0.18 (3H, s, $Si(CH_3)$), 0.16 (6H, s, $Si(CH_3) \times 2$), 0.13 (3H, s, $Si(CH_3)$); ^{13}C NMR (125 MHz, C_6D_6) δ_C 207.8, 159.7, 148.1, 135.1, 132.8, 131.1, 130.6, 129.6, 117.9, 114.0, 79.9, 77.8, 76.1, 76.0, 75.6, 72.5, 54.7, 45.0, 44.6, 43.8, 42.4, 39.5, 38.1, 36.6, 33.3, 32.3, 32.2, 30.9, 27.1, 26.5, 26.2, 20.5, 18.8, 18.3, 17.9, 16.5, 15.4, 15.1, 8.6, −3.40, −3.44, −3.6, −4.3; HRMS (ES^+) calcd for $C_{49}H_{91}IO_6Si_2N$ $[M + NH_4]^+$ 972.5424, found 972.5426; R_f 0.26 (15% EtOAc/hexane).

(4*E*,6*R*,7*S*,12*S*,13*S*,14*S*,16*S*,19*R*,20*R*,21*S*,22*S*,23*Z*)-13,19-Bis(*tert*-butyldimethylsilyloxy)-7,21-dihydroxy-4-iodo-6,12,14,16,20,22-hexamethyltricosa-4,23,25-trien-9-one (15). To a solution of PMB ether **14** (50 mg, 0.052 mmol) in CH_2Cl_2 (1.6 mL) and pH 7 buffer (160 μL) at 0 °C was added DDQ (142 mg, 0.624 mmol). After 30 min, the reaction mixture was diluted with pH 7 buffer (5 mL) and CH_2Cl_2 (5 mL) and warmed to rt, and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 4 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (15% EtOAc/hexane) afforded alcohol **15** (40 mg, 90%) as a colorless oil: $[\alpha]^{20}_D$ −18.7(*c* 0.65, $CHCl_3$); IR (liquid film)/cm^{-1} 3464, 2956, 2929, 2857, 1709, 1602, 1461; ^{1}H NMR (500 MHz, C_6D_6) δ_H 6.72 (1H, app dt, J = 11.4, 17.1 Hz, H-25), 6.54 (1H, dd, J = 8.6, 14.6 Hz, H-5), 6.10 (1H, app t, J = 11.1 Hz, H-24), 5.76 (1H, dd, J = 0.9, 14.6 Hz, H-4), 5.45 (1H, app t, J = 10.5 Hz, H-23), 5.16 (1H, dd, J = 1.8, 16.8 Hz, H-26a), 5.06 (1H, d, J = 10.0 Hz, H-26b), 3.89 (1H, app q, J = 5.9 Hz, H-19), 3.72 (1H, br d, J = 9.8 Hz, H-7), 3.54 (1H, br t, J = 5.5 Hz, H-21), 3.37 (1H, dd, J = 3.2, 5.6 Hz, H-13), 2.93–2.85 (2H, m, H-22, OH), 2.14 (1H, dd, J = 10.0, 17.2 Hz, H-8a), 2.09–2.01 (1H, m, H-10a), 1.97–1.89 (2H, m, H-10b, H-15a), 1.87–1.73 (5H, m, H-6, H-8b, H-14, H-18a,

H-20), 1.71–1.62 (1H, m, H-18b), 1.61–1.50 (4H, m, H-11a, H-12, H-16, H-17a), 1.49–1.42 (1H, m, H-17b), 1.29–1.21 (1H, m, H-11b), 1.19–1.14 (1H, m, H-15b), 1.11 (3H, d, J = 6.9 Hz, CH_3-14), 1.06 (9H, s, $SiC(CH_3)_3$), 1.01 (9H, s, $SiC(CH_3)_3$), 1.02–0.98 (9H, m, CH_3-16, CH_3-20, CH_3-22), 0.85 (3H, d, J = 6.9 Hz, CH_3-12), 0.83 (3H, d, J = 6.9 Hz, CH_3-6), 0.17 (3H, s, $Si(CH_3)$), 0.16 (6H, s, $Si(CH_3)$ × 2), 0.13 (3H, s, $Si(CH_3)$); ^{13}C NMR (125 MHz, C_6D_6) δ_C 210.6, 147.9, 135.0, 132.7, 130.6, 117.9, 80.1, 76.0, 75.9, 75.6, 70.1, 46.6, 46.1, 43.6, 41.7, 39.5, 37.7, 36.5, 33.4, 32.2, 32.1, 30.9, 26.7, 26.5, 26.2, 20.6, 18.8, 18.3, 17.9, 16.6, 15.8, 15.5, 8.7, −3.4, −3.6, −4.3; HRMS (ESI^+) calcd for $C_{41}H_{80}IO_5Si_2$ $[M + H]^+$ 835.4583, found 835.4591; R_f 0.62 (20% EtOAc/hexane).

(4*E*,6*R*,7*S*,9*R*,12*S*,13*S*,14*S*,16*S*,19*R*,20*R*,21*S*,22*S*,23*Z*)-13,19-Bis(*tert*-butyldimethylsilyloxy)-4-iodo-6,12,14,16,20,22-hexamethyltricosa-4,23,25-triene-7,9,21-triol (16). To a solution of $NaBH(OAc)_3$ (16 mg, 0.078 mmol) in THF (750 μL) at 0 °C was added via cannula a solution of alcohol **15** (13 mg, 0.016 mmol) in THF (750 μL) and AcOH (30 μL). After warming to rt, the reaction mixture was stirred for 3 h before quenching with saturated aqueous $NaHCO_3$ (1 mL) and Na^+/K^+ tartrate solution (2 mL). This biphasic mixture was stirred vigorously for 1 h before the phase separation and extraction of the aqueous phase with CH_2Cl_2 (3 × 4 mL). The combined organic extracts were dried (Na_2SO_4), concentrated *in vacuo*, and purified using flash chromatography (10% EtOAc/hexane) to afford *anti*-alcohol **16** (9.5 mg, 74%) and its isomeric *syn*-alcohol (1.3 mg, 10%) as colorless oils: $[\alpha]^{20}_D$ −10.9 (*c* 0.48, $CHCl_3$); IR (liquid film)/cm^{-1} 3407, 2956, 2929, 2857, 1468, 1378; ^{1}H NMR (500 MHz, C_6D_6) δ_H 6.72 (1H, app dt, J = 10.5, 17.1 Hz, H-25), 6.46 (1H, dd, J = 8.7, 14.5 Hz, H-5), 6.10 (1H, app t, J = 11.1 Hz, H-24), 5.77 (1H, dd, J = 0.7, 14.4 Hz, H-4), 5.44 (1H, app t, J = 10.5 Hz, H-23), 5.16 (1H, dd, J = 1.8, 16.8 Hz, H-26a), 5.07 (1H, d, J = 10.4 Hz, H-26b), 3.91–3.86 (1H, m, H-19), 3.73–3.67 (1H, m, H-9), 3.56–3.52 (1H, m, H-21), 3.51–3.48 (1H, m, H-7), 3.43 (1H, dd, J = 2.9, 5.5 Hz, H-13), 3.39–3.35 (1H, m, OH), 2.89 (1H, app qnd, J = 6.7, 9.9 Hz, H-22), 2.01–1.14 (17H, m, H-6, H_2-8, H_2-10, H_2-11, H-12, H-14, H_2-15, H-16, H_2-17, H_2-18, H-20), 1.11 (3H, d, J = 7.0 Hz, CH_3-20), 1.07 (9H, s, $Si(CH_3)_3$), 1.03 (3H, d, J = 6.7 Hz, CH_3-6), 1.02 (9H, s, $Si(CH_3)_3$), 1.01–0.96 (9H, m, CH_3-12, CH_3-16, CH_3-22), 0.77 (3H, d, J = 7.0 Hz, CH_3-14), 0.17 (3H, s, $Si(CH_3)$), 0.16 (6H, s, $Si(CH_3)$ × 2), 0.13 (3H, s, $Si(CH_3)$); ^{13}C NMR (125 MHz, C_6D_6) δ_C 148.4, 135.1, 132.7, 130.6, 118.0, 80.1, 76.06, 76.02, 75.5, 71.3, 69.7, 47.1, 43.9, 40.3, 39.6, 39.0, 36.5, 36.0, 33.2, 32.2, 32.1, 30.9, 29.8, 26.5, 26.2, 26.1, 20.6, 18.8, 18.3, 17.9, 16.8, 15.7, 8.7, −3.37, −3.43, −3.6, −4.3; HRMS (ESI^+) calcd for $C_{41}H_{82}IO_5Si_2$ $[M + H]^+$ 837.4740, found 837.4745; R_f 0.46 (30% EtOAc/hexane).

(4*E*,6*S*,7*S*,9*R*,12*R*,13*S*,14*S*,16*S*,19*S*,20*S*,21*S*,22*S*,23*Z*)-13,19-Bis(*tert*-butyldimethylsilyloxy)-(2,2-dimethyl)-7,9-dioxan-4-iodo-6,12,14,16,20,22-hexamethyltricosa-4,23,25-triene-21-ol (9). To a solution of triol **16** (21.8 mg, 0.026 mmol) in 2,2-dimethoxypropane (3 mL) was added a crystal of PPTS. After 2 h, the reaction mixture was concentrated *in vacuo*, and flash chromatography (15% EtOAc/hexane) afforded acetonide **9** (20.5 mg, 90%) as a colorless oil: $[\alpha]^{20}_D$ −26.1 (*c* 0.39, $CHCl_3$); IR (liquid film)/cm^{-1} 2955, 2930, 2857, 1462, 1379; ^{1}H NMR (500 MHz, C_6D_6) δ_H 6.72 (1H, app dt, J = 11.0, 17.1 Hz, H-25), 6.63 (1H, dd, J = 8.1, 14.4 Hz, H-5), 6.08 (1H, app t, J = 11.0 Hz, H-24), 5.81 (1H, d, J = 14.6 Hz, H-4), 5.42 (1H, app t, J = 10.4 Hz, H-23), 5.15 (1H, d, J = 16.9 Hz, H-26a), 5.05 (1H, d, J = 10.3 Hz, H-26b), 3.92–3.88 (1H, m, H-19), 3.67–3.60 (1H, m, H-9), 3.54–3.47 (2H, m, H-7, H-21), 3.40 (1H, dd, J = 2.1, 6.0 Hz, H-13), 2.88 (1H, app qnd, J = 6.7, 10.2 Hz, H-22), 2.01–1.93 (1H, m, H-6), 1.91–1.14 (16H, m, H_2-8, H_2-10, H_2-11, H-12, H-14, H_2-15, H-16, H_2-17, H_2-18, H-20), 1.33 (3H, s, $OC(CH_3)$), 1.31 (3H, s, $OC(CH_3)$), 1.11 (3H, d, J = 7.1 Hz, CH_3-20), 1.07 (9H, s, $SiC(CH_3)_3$), 1.02 (9H, s, $SiC(CH_3)_3$), 1.02 (6H, m, CH_3-14, CH_3-16), 0.98 (3H, d, J = 7.0 Hz, CH_3-22), 0.96 (3H, d, J = 7.0 Hz, CH_3-12), 0.80 (3H, d, J = 7.0 Hz, CH_3-6), 0.162 (3H, s, $Si(CH_3)$), 0.157 (3H, s, $Si(CH_3)$), 0.15 (3H, s, $Si(CH_3)$), 0.14 (3H, s, $Si(CH_3)$); ^{13}C NMR (125 MHz, C_6D_6) δ_C 148.5, 135.1, 132.7, 130.7, 118.0, 100.4, 79.8, 76.1, 75.7, 75.6, 69.4, 67.4, 45.2, 43.9, 39.3, 38.8, 36.63, 36.56, 34.8, 33.0, 32.32, 32.26, 30.9, 29.8, 26.5, 26.2, 24.7, 24.6, 20.3, 18.8, 18.3, 17.8, 16.6, 15.3, 15.2, 8.5, −3.3, −3.4, −3.6, −4.3; HRMS (ESI^+) calcd for $C_{44}H_{89}IO_5Si_2N$ $[M + NH_4]^+$ 894.5318, found 894.5313; R_f 0.84 (30% EtOAc/hexane).

(2*Z*,4*E*,6*S*,7*S*,9*R*,12*R*,13*S*,14*S*,16*S*,19*S*,20*S*,21*S*,22*S*,23*Z*)-13,19-Bis(*tert*-butyldimethylsilyloxy)-(2,2-dimethyl)-7,9-dioxan-21-hydroxy-6,12,14,16,20,22-hexamethyl-23,25-dienyl-2,4-dienoic acid (17). To a deoxygenated solution (freeze–thaw) of iodide **9** (7.8 mg, 8.9 μmol) and stannane **10** (18 mg, 36 μmol) in NMP (450 μL) at rt was added CuTC (17 mg, 89 μmol). After stirring for 16 h, the reaction was quenched by the addition of NH_4Cl (1 mL). The phases were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was redissolved in THF (300 μL) and MeOH (150 μL), and to it at rt was added KF (10 mg, 176 μmol). The reaction mixture was stirred for 4 h, before quenching with saturated aqueous NH_4Cl (1 mL). Again, the phases were separated, the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (5% EtOAc/hexane → 20% EtOAc/hexane) afforded acid **17** (5.3 mg, 73%) as a colorless oil: $[\alpha]^{20}_D$ −33.2 (*c* 0.27, $CHCl_3$); IR (liquid film)/cm^{-1} 2956, 2928, 2856, 1692, 1636, 1601, 1461, 1378; ^{1}H NMR (500 MHz, C_6D_6) δ_H 7.72 (1H, dd, J = 11.9, 15.4 Hz, H-4), 6.72 (1H, app dt, J = 10.6, 17.2 Hz, H-25), 6.31 (1H, app t, J = 11.4 Hz, H-3), 6.09 (1H, app t, J = 11.3 Hz, H-24), 6.05 (1H, dd, J = 8.0, 15.0 Hz, H-5), 5.54 (1H, d, J = 11.1 Hz, H-2), 5.44 (1H, app t, J = 10.3 Hz, H-23), 5.15 (1H, d, J = 16.9 Hz, H-26a), 5.06 (1H, d, J = 9.9 Hz, H-26b), 3.92–3.87 (1H, m, H-19), 3.73–3.66 (1H, m, H-9), 3.66–3.60 (1H, m, H-7), 3.57–3.52 (1H, m, H-21), 3.41 (1H, dd, J = 2.3, 6.2 Hz, H-13), 2.89 (1H, app qnd, J = 7.0, 10.0 Hz, H-22), 2.24–2.17 (1H, m, H-6), 1.96–1.12 (16H, m, H_2-8, H_2-10, H_2-11, H-12, H-14, H_2-15, H-16, H_2-17, H_2-18, H-20), 1.41 (3H, s, $OC(CH_3)$), 1.37 (3H, s, $OC(CH_3)$), 1.11 (3H, d, J = 6.7 Hz, CH_3-20), 1.07 (9H, s, $SiC(CH_3)_3$), 1.02 (9H, s, $SiC(CH_3)_3$), 1.02–0.95 (15H, m, CH_3-6, CH_3-12, CH_3-14, CH_3-16, CH_3-22), 0.16 (6H, s, $Si(CH_3)$ × 2), 0.16 (3H, s, $Si(CH_3)$), 0.14 (3H, s, $Si(CH_3)$); ^{13}C NMR (125 MHz, C_6D_6) δ_C 148.1, 147.4, 135.0, 132.7, 130.7, 118.0, 100.4, 79.7, 76.2, 75.7, 70.1, 67.4, 43.9, 42.0, 39.4, 38.8, 37.0, 36.5, 34.8, 33.0, 32.32, 32.26, 30.8, 30.2, 29.8, 28.3, 27.4, 26.5, 26.2, 20.3, 18.8, 18.3, 17.9, 16.6, 16.2, 15.3, 14.3, 13.9, 8.5, 1.4, −3.37, −3.40, −3.6, −4.3; HRMS (ESI^+) calcd for $C_{47}H_{89}O_7Si_2$ $[M + H]^+$ 821.6141, found 821.6139; R_f 0.67 (20% EtOAc/hexane).

Protected Macrolactone 18. To a solution of acid **17** (2.7 mg, 3.3 μmol) in toluene (250 μL) at rt was added Et_3N (10 μL of a 0.88 M solution in toluene, 8.6 μmol), then 2,4,6-trichlorobenzoyl chloride (10 μL of a 0.87 M solution in toluene, 5.9 μmol). After 3 h, with observation of complete mixed anhydride formation (R_f = 0.34, 15% EtOAc/hexane), the reaction mixture was diluted with toluene (5 mL) and DMAP (39 μL, 0.082 M solution in toluene, 3.3 μmol) was added. After stirring for 36 h, the reaction mixture was filtered through a plug of silica, eluting with Et_2O, and concentrated *in vacuo*. Flash chromatography (100% hexane to 5% EtOAc) afforded macrolactone **18** (1.6 mg, 60%) as a colorless oil: $[\alpha]^{20}_D$ −3.0 (*c* 0.29, $CHCl_3$); IR (liquid film)/cm^{-1} 2956, 2930, 2857, 1707, 1640, 1462, 1379; ^{1}H NMR (500 MHz, C_6D_6) δ_H 7.53 (1H, dd, J = 11.1, 15.3 Hz, H-4), 6.73 (1H, app dt, J = 10.6, 16.6 Hz, H-25), 6.25 (1H, app t, J = 11.3 Hz, H-3), 6.15 (1H, app t, J = 11.0 Hz, H-24), 5.80 (1H, dd, J = 7.1, 15.5 Hz, H-5), 6.57 (1H, d, J = 11.4 Hz, H-2), 5.67–5.61 (1H, m, H-23), 5.59 (1H, app t, J = 5.8 Hz, H-21), 5.19 (1H, d, J = 16.4 Hz, H-26a), 5.09 (1H, d, J = 10.0 Hz, H-26b), 3.90 (1H, ddd, J = 2.8, 6.0, 9.2 Hz, H-7), 3.82–3.76 (1H, m, H-9), 3.76–3.71 (1H, m, H-19), 3.47 (1H, app t, J = 3.2 Hz, H-13), 3.21–3.13 (1H, m, H–22), 2.42–2.34 (1H, m, H-6), 2.04–1.97 (1H, m, H-20), 1.83–1.67 (5H, m, H-8a, H-10a, H-12, H-14, H-18a), 1.65–1.49 (3H, m, H-8b, H-10b, H-16), 1.45–1.23 (12H, m, H_2-11, H_2-15, H_2-17, $OC(CH_3)$ × 2), 1.14 (3H, d, J = 6.9 Hz, CH_3-6), 1.11 (3H, d, J = 6.9 Hz, CH_3-20), 1.09 (3H, d, J = 6.7 Hz, CH_3-22), 1.07 (3H, d, J = 6.9 Hz, CH_3-12 or 14), 1.05 (9H, s, $SiC(CH_3)_3$), 1.04 (9H, s, $SiC(CH_3)_3$), 1.00 (3H, d, J = 6.6 Hz, CH_3-12 or 14), 0.95 (3H, d, J = 6.6 Hz, CH_3-16), 0.151 (3H, s, $Si(CH_3)$), 0.148 (3H, s, $Si(CH_3)$), 0.13 (3H, s, $Si(CH_3)$), 0.12 (3H, s, $Si(CH_3)$); ^{13}C NMR (C_6D_6, 125 MHz) δ_C 171.4, 165.9, 144.7, 134.0, 132.4, 130.4, 127.5, 118.3, 118.2, 100.3, 79.7, 74.3, 69.0, 68.0, 66.8, 44.9, 41.2, 40.2, 39.4, 34.5, 34.1, 32.1, 30.9, 30.4, 28.1, 26.3, 26.24, 26.15, 25.1, 25.0, 20.4, 18.6, 18.4, 18.1, 16.3, 16.2, 10.3, −3.6, −3.7, −4.0, −4.2; HRMS (ES^+) calcd for $C_{47}H_{86}O_6Si_2Na$ $[M + Na]^+$ 825.5828, found 825.5866; R_f 0.29 (4% EtOAc/hexane).

10,11-Dihydrodictyostatin (5). To a solution of macrolactone **18** (3.2 mg, 4.0 μmol) in THF (408 μL) at 0 °C was added HF·pyridine (87 μL). After slow warming to rt, the reaction mixture was stirred for 48 h. The reaction was diluted with EtOAc (1 mL) and subsequently quenched by the addition of saturated $NaHCO_3$ (1 mL) after cooling to 0 °C. The phases were then separated, the aqueous phase was extracted with EtOAc (3 × 3 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Initial flash chromatography (100% EtOAc) afforded 10,11-dihydrodictyostatin **5** (1.8 mg,

85%) as a white solid, which was further subject to HPLC (10% IPA/hexane) purification: $[\alpha]^{20}_{D}$ +5.6 (*c* 0.16, $CHCl_3$); IR (liquid film)/cm^{-1} 3370, 2924, 2853, 1684, 1637, 1601, 1455; ^{1}H NMR (500 MHz, C_6D_6) δ_H 7.50 (1H, dd, J = 11.0, 15.8 Hz, H-4), 6.58 (1H, app dt, J = 10.5, 16.9 Hz, H-25), 6.20 (1H, app t, J = 11.1 Hz, H-3), 5.97 (1H, app t, J = 10.9 Hz, H-24), 5.78 (1H, dd, J = 7.3, 15.7 Hz, H-5), 5.57 (1H, d, J = 11.5 Hz, H-2), 5.39 (1H, app t, J = 10.5 Hz, H-23), 5.23 (1H, dd, J = 4.4, 7.2 Hz, H-21), 5.10 (1H, dd, J = 1.2, 16.3 Hz, H-26a), 5.01 (1H, br d, J = 10.2 Hz, H-26b), 3.93 (1H, app q, J = 5.6 Hz, H-7), 3.76 (1H, app qn, J = 6.2 Hz, H-9), 3.56–3.52 (1H, m, H-19), 3.23 (1H, dd, J = 3.7, 7.1 Hz, H-13), 2.99 (1H, app qnd, J = 6.7, 10.2 Hz, H-22), 2.37–2.30 (1H, m, H-6), 2.28–2.21 (1H, br s, OH), 2.17–2.09 (2H, m, OH × 2), 1.83–1.67 (4H, m, H-12, H-14, H-20, OH), 1.66–1.52 (6H, m, H_2-8, H-10a, H-15a, H-16, H-18a), 1.45–1.18 (7H, m, H-10b, H_2-11, H-15b, H_2-17, H-18b), 1.03 (3H, d, J = 7.1 Hz, CH_3-20), 1.01 (3H, d, J = 7.0 Hz, CH_3-6), 0.99 (3H, d, J = 6.4 Hz, CH_3-14), 0.91 (3H, d, J = 6.5 Hz, CH_3-16), 0.88 (3H, d, J = 6.7 Hz, CH_3-22), 0.85 (3H, d, J = 6.7 Hz, CH_3-12); ^{13}C NMR (125 MHz, C_6D_6) δ_C 166.8 (C, C-1), 146.7 (CH, C-5), 144.7 (CH, C-3), 134.1 (CH, C-23), 132.5 (CH, C-25), 130.4 (CH, C-24), 127.6 (CH, C-4), 118.0 (CH_2, C-26), 117.1 (CH, C-2), 78.1 (CH, C-21), 76.5 (CH, C-13), 72.8 (CH, C-19), 71.6 (CH, C-7), 70.2 (CH, C-9), 42.9 (CH, C-6), 40.6 (CH, C-20), 38.5 (CH_2, C-8), 35.4 (CH, C-12), 35.3 (CH, C-22), 33.8 (CH_2, C-10), 32.8 (CH_2, C-11), 32.7 (CH_2, C-18), 32.4 (CH, C-14), 29.5 (CH, C-16), 27.6 (CH_2, C-17), 25.4 (CH_2, C-15), 21.3 (CH_3, C-16), 17.6 (CH_3, C-22), 16.6 (CH_3, C-12), 15.8 (CH_3, C-6), 15.1 (CH_3, C-14), 9.3 (CH_3, C-20); HRMS (ES^+) calcd for $C_{32}H_{54}O_6Na$ $[M + Na]^+$ 557.3813, found 557.3818; R_f 0.52 (100% EtOAc); t_R 18 min (10% IPA/hexane).

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Supporting Information Available: Copies of NMR spectra for new compounds reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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