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Highly Stereoselective Total Synthesis of (+)-9-*epi*-Dictyostatin and (–)-12,13-Bis-*epi*-dictyostatin

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The total syntheses of (+)-9-*epi*-dictyostatin (**1a**) and (–)-12,13-bis-*epi*-dictyostatin (**1b**), diastereomers of the antimitotic marine sponge-derived macrolide (–)-dictyostatin (**1**), were achieved by creating 11 stereogenic centers and 4 stereogenic double bonds with a high level of stereocontrol. The yield for the 29-step longest linear sequence from Roche ester was 1.53 and 1.52%, respectively. The final key steps to these unnatural products were the addition of vinylzincates C10-C26 to aldehyde C1–C9 (leading surprisingly to complete stereoselectivity for the 9*R*-configuration in **28a** and for the 9*S*-configuration in 12,13-bis-epimeric **28b**), followed by Yamaguchi macrolactonization and global deprotection. (–)-12,13-Bis-*epi*-dictyostatin (**1b**) displayed a dramatic decrease of cytotoxicity and of the affinity toward the paclitaxel binding site of microtubules.

Introduction

The sponge-derived macrolide (–)-dictyostatin (**1**, Scheme 1) has been reported to be a potent, paclitaxel-like inducer of tubulin polymerization and to inhibit human cancer cell proliferation at low nanomolar concentrations, with activity somewhat superior to the already very active discodermolide.[1] With the recent withdrawal of discodermolide from clinical development[2] the importance of dictyostatin further increases. Moreover, (–)-dictyostatin is also extremely potent against paclitaxel-resistant human cancer cell lines over-expressing the P-glycoprotein efflux pump.[1] The structure of (–)-dictyostatin (**1**) with full stereochemical assignments was established by Paterson and coworkers in 2004,[3] and four total syntheses were completed in the period 2004–2007.[4] A growing number of research groups have recently been involved in targeting this interesting natural product, and the syntheses of several analogs (e.g., desmethyldictyostatins, *epi*-dictyostatins, bis-*epi*-dictyostatins, hydrodictyostatins, methoxy-dictyostatins),[5] discodermolide/dictyostatin hybrids,[6] and various fragments and synthetic intermediates[7] have been described. The development of dictyostatin analogs is an appealing goal from a pharmaceutical perspective, and provides interesting opportunities for structural simplification whilst maintaining biological potency, and for better understanding the structure-activity-relationships of this class of antitumor agents. Although much work has been carried out in this area, syntheses of dictyostatin analogs modified at C12 and/or C13 were never reported. In this full paper, we describe a highly stereoselective total synthesis of two non-natural analogs of (–)-dictyostatin: (+)-9-*epi*-dictyostatin (**1a**) and (–)-12,13-bis-*epi*-dictyostatin (**1b**), building on our previous work in this field.[5j,7j–7k] Our retrosynthetic approach, shown in Scheme 1 and common to the two target molecules, disconnects the macrolide ring into two key intermediates: C1–C9 aldehyde **2**, prepared from the corresponding alcohol,[7k] and C10–C26 vinyl iodides **3a** and **3b**, prepared by taking advantage of a synthetic route partially described in two communications from our group.[5j,7j]

Results and Discussion

The synthesis of fragments C10-C26 is based on the disconnection of the target compounds into four key intermediates, as shown in Scheme 2.

The synthesis of alkyne **4** (Scheme 3) started from commercially available (*S*)-3-hydroxy-2-methylpropionate [(*S*)-Roche ester, **8**] which was converted into its PMB ether **9** [PMBOC(=NH)CCl_3, PPTS, DCM/Cy, 92%]. $LiAlH_4$ reduction (**10**, 87%)[8] followed by iodination (I_2, PPh_3, imidazole) provided compound **11** in high yield (95%). Myers' alkylation[9] gave amide **12** in 92% yield and with a > 98:2 diastereomeric ratio (*dr*) in favor of the desired diastereomer. Reduction with the borane–ammonia complex

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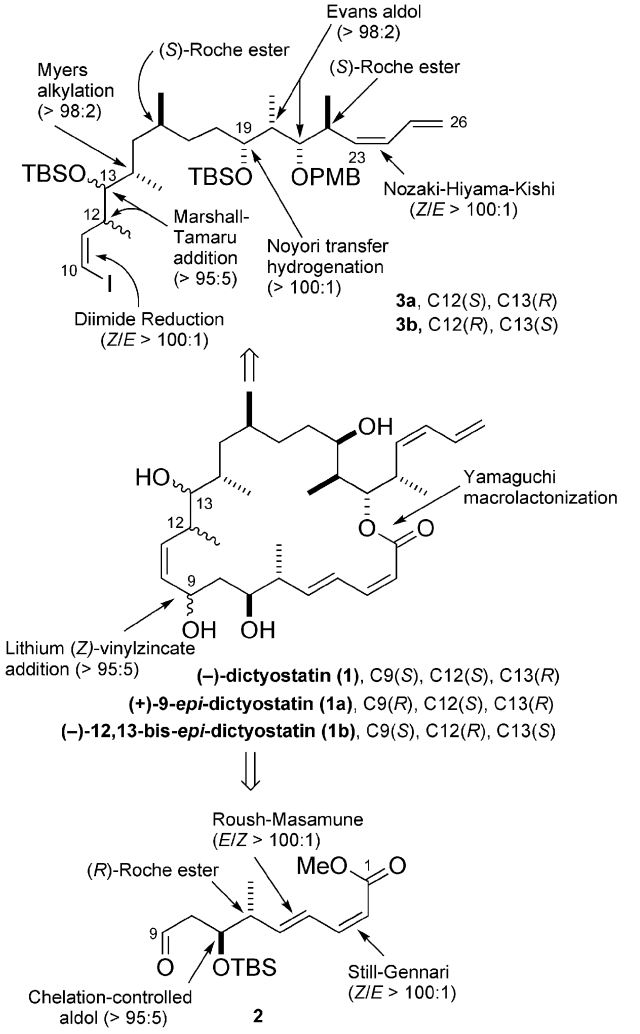
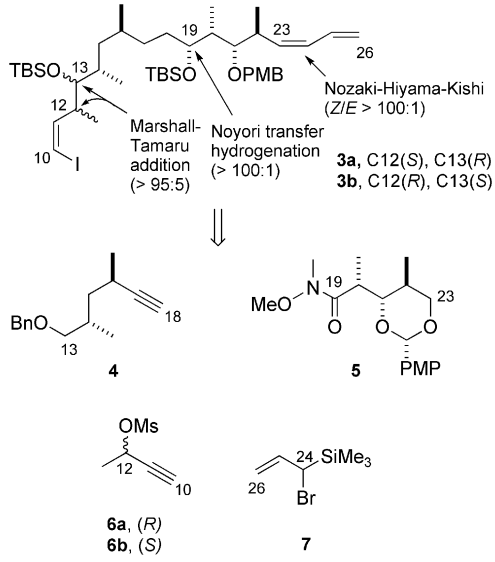


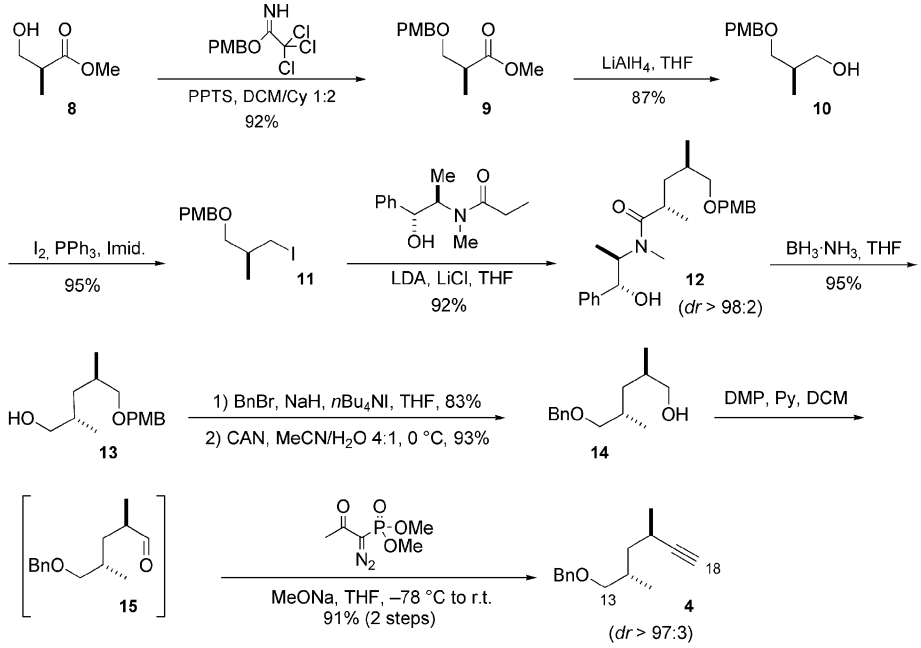
Scheme 1. Retrosynthetic approach to (+)-9-*epi*-dictyostatin (**1a**) and 12,13-bis-*epi*-dictyostatin (**1b**), with key reactions involved and associated diastereomeric ratios.



Scheme 2. Retrosynthetic approach to C10-C26 fragments **3a** and **3b** (dictyostatin numbering).

afforded alcohol **13** in 95% yield. Benzyl protection (NaH, BnBr, nBu$_4$NI, 83%), followed by selective removal of the PMB group over the benzyl group [ceric ammonium nitrate (CAN), CH_3CN/H_2O (4:1)], delivered alcohol **14** in 93% yield. Dess–Martin oxidation furnished aldehyde **15**, which was not isolated, but directly homologated to alkyne **4**.

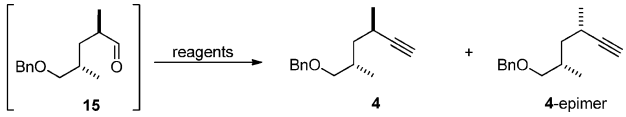
For the latter step, different methods were investigated with the twofold aim of obtaining a high yield and avoiding epimerization at the α-stereocenter (Table 1). Shioiri's lithiodiazomethane protocol, which takes advantage of the Colvin rearrangement [Table 1, entry 1; Me_3SiCHN_2, LDA, THF],[10] provided the desired alkyne **4** in good yield (61%) as a single diastereomer.[7j] Unfortunately, the yield could



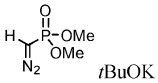
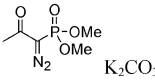
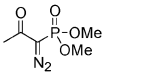
Scheme 3. Synthesis of alkyne **4** (dictyostatin numbering).

not be reproduced during the scale-up (from 0.1 to 1.0 gram scale). Corey–Fuchs dibromo-olefination (Table 1, entry 2; CBr_4, PPh_3, Zn, DCM), followed by *n*BuLi-promoted elimination,[11] caused no epimerization but the yield could not be improved above a modest 35%. The Seiferth-Gilbert procedure [Table 1, entry 3; $HC(N_2)PO(OMe)_2$, *t*BuOK, THF][12] gave a reasonable yield (59%) accompanied by 10% epimerization. Finally, the Ohira-Bestmann protocol was explored: under the original conditions [Table 1, entry 4; $CH_3COC(N_2)PO(OMe)_2$, K_2CO_3, MeOH, room temp.][13] a good yield (88%) was obtained, but with extensive epimerization of the α stereocenter (*dr* = 75:25). After a thorough investigation, we found that the epimerization could be suppressed by avoiding the protic solvent and decreasing the temperature. Eventually, optimal conditions [Table 1, entry 5; $CH_3COC(N_2)PO(OMe)_2$ (4 equiv.), MeONa (4 equiv.), THF, –78 °C to room temp.][14] were identified which allowed the synthesis of alkyne **4** in excellent yield (91%) and diastereomeric ratio (*dr* > 97:3).

Table 1. Different methodologies for the alkynylation of aldehyde **15**.



15 **4** **4**-epimer

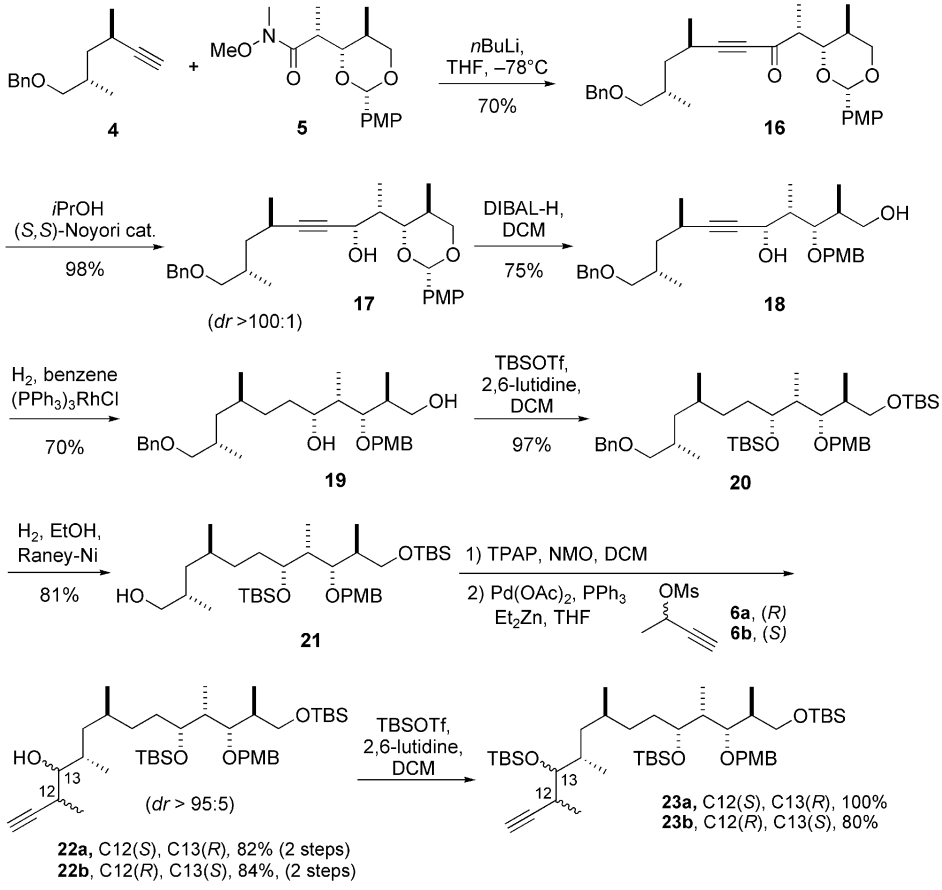
Entry	Reagents	Solvent and conditions	Yield %	**4**/**4**-epimer ratio
1	Me_3SiCHN_2, LDA	THF, −78 °C to r.t.	61	> 97:3
2	i) CBr_4, PPh_3, Zn ii) *n*BuLi	CH_2Cl_2 THF, −78 °C to r.t.	35	> 97:3
3	 *t*BuOK	THF, −78 °C	59	90:10
4	 K_2CO_3	MeOH, r.t.	88	75:25
5	 (4 equiv.) MeONa (4 equiv.)	THF, −78 °C to r.t.	91	> 97:3

The second key intermediate, Weinreb amide **5**, was prepared according to Smith III and co-workers.[8] In our first approach,[7j] Weinreb amide **5** was reduced to the corresponding aldehyde, which was then coupled to alkyne **4** via the Carreira asymmetric alkynylation protocol [(–)-(1*R*,2*S*)-*N*-methylephedrine, $Zn(OTf)_2$, Et_3N, toluene, 67%][15] to give alcohol **17**. However, this reaction proved capricious and poorly reproducible during the scale-up. We thus opted for the direct addition of alkyne **4** to Weinreb amide **5** (Scheme 4; *n*BuLi, THF, 70%) to form ynone **16**, which was then subjected to a Noyori asymmetric transfer hydrogenation [(*S*,*S*)-Noyori catalyst, *i*PrOH][16] to give the desired alcohol **17** in excellent yield (98%) with a > 100:1 diastereomeric ratio. Acetal **17** was cleaved with DIBAL-H to generate diol **18** in 75% yield. Hydrogenation (under 4 bar H_2 pressure) of the propargylic alcohol **18**, in the presence of 10 mol-% Wilkinson's catalyst, afforded the desired saturated compound **19** (70%), which was then silylated to give the fully protected tetraol **20** in 97% yield. Selective removal of the benzyl group over the PMB group (H_2, Raney-Ni, EtOH)[17] furnished primary alcohol **21** in 81% yield, which was oxidized (TPAP/NMO)[18] to the corresponding aldehyde. Subsequent Marshall–Tamaru palladium-catalyzed allenylzinc addition[19] with the mesylate of (*R*)-3-butyn-2-ol (**6a**) gave alcohol **22a** (82% over two steps) with a high level of diastereoselectivity (*dr* > 98:2) in favor of the desired *anti*,*syn* adduct. Using the enantiomeric mesylate **6b**, derived from (*S*)-3-butyn-2-ol, the diastereomeric alcohol **22b** was prepared (84% over two steps) with a ≥ 95:5 *anti*,*anti*/*anti*,*syn* ratio, which was used to access 12,13-bis-*epi*-dictyostatin. From this point, we carried forward two parallel syntheses, denoted **a** [C12(*S*), C13(*R*)] and **b** [C12(*R*), C13(*S*)] (dictyostatin numbering).

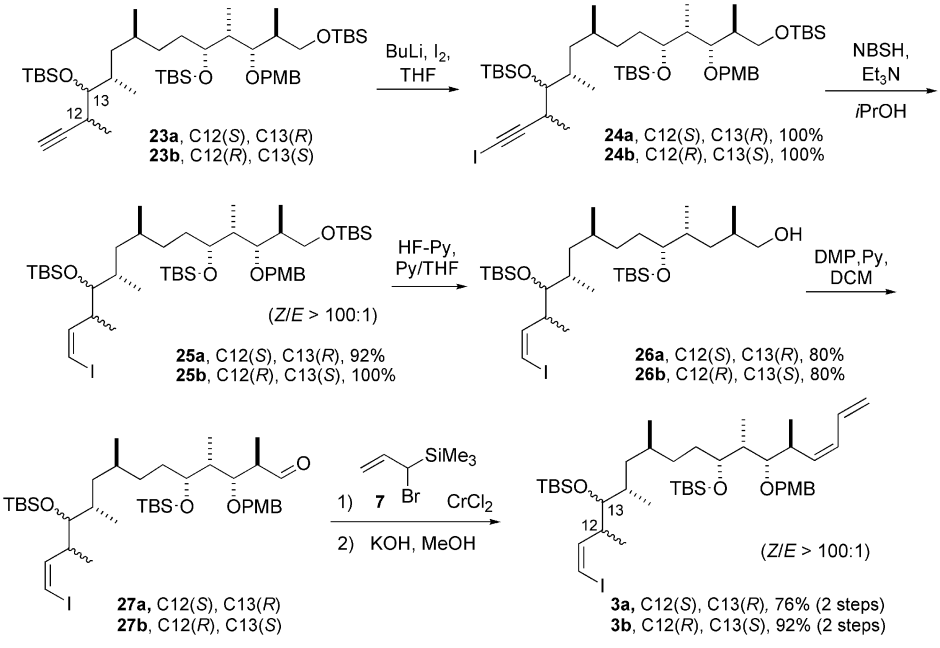
TBS protection of alcohols **22a**–**b** afforded alkynes **23a**–**b**, which were then lithiated with *n*BuLi and converted into the corresponding alkynyl iodides **24a**–**b** in quantitative yield (Scheme 5). Reduction of compounds **24** with diimide[5d,20] provided (*Z*)-vinyl iodides **25a**–**b** as single diastereoisomers (*Z*/*E* > 100:1) in excellent yield (92–100%). The primary *tert*-butyldimethylsilyl ether of **25a**–**b** was selectively cleaved (HF·Py, THF/Py, 80%) to give compounds **26a**–**b**, which were converted into aldehydes **27a**–**b** by oxidation with Dess–Martin periodinane. The latter compounds were treated with (1-bromoallyl)trimethylsilane **7** under Nozaki–Hiyama–Kishi coupling conditions ($CrCl_2$),[21] followed by Peterson elimination (KOH, MeOH) to give the C10-C26 fragments **3a** and **3b** in good yield and excellent diastereoselectivity (*Z*/*E* > 100:1).[22]

Following Ramachandran's lead,[4d] lithiation of (*Z*)-vinyl iodides **3a** and **3b** (*t*BuLi) and subsequent treatment with dimethylzinc provided the corresponding lithium (*Z*)-vinylzincates,[23] which were added to β-silyloxy aldehyde **2** to give the coupling products **28a** and **28b** in moderate yield (40%) and excellent diastereomeric ratio (> 95:5) (Scheme 6).

On the basis of the structural assignment of the final product **1a** (vide infra) the stereochemistry of the newly created stereogenic center in compound **28a** turned out to be 9*R*. We found this outcome quite surprising, as the addition of the same (*Z*)-vinylzincate to a very similar aldehyde (**2** with the ethyl ester instead of the methyl ester) was reported to give an excellent ratio in favor of the 9*S* stereoisomer.[4d] Unexpectedly, however, the addition of the **3b**-derived lithium (*Z*)-vinylzincate to aldehyde **2** gave the desired 9*S* isomer **28b**. The C9 configuration for compound **28b** was assigned according to the Rychnovsky's NMR method.[24] For this purpose, a small amount of **28b** was totally deprotected (HF·Py, THF, 76%) and quantitatively converted into the corresponding 7,9-acetonide (**28b**-acetonide) using 2,2-dimethoxypropane and PPTS (Scheme 7). Following the Rychnovsky's rule, the stereochemistry of 1,3-diol aceton-

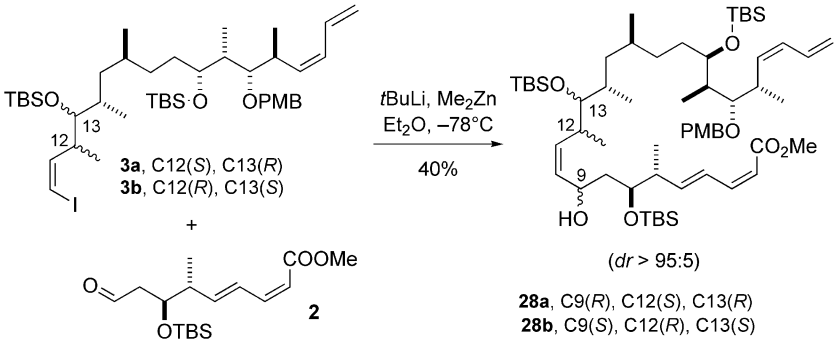


Scheme 4. Synthesis of C10-C23 fragments **23a** and **23b** (dictyostatin numbering).

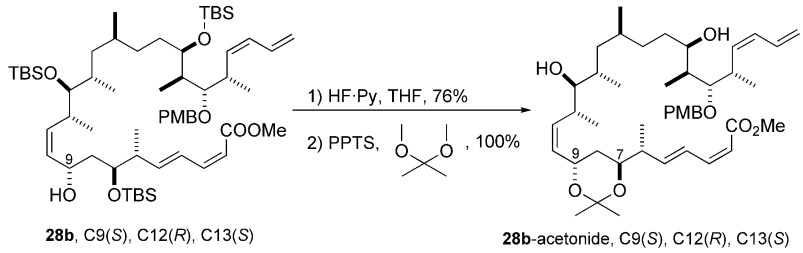


Scheme 5. Synthesis of C10-C26 fragments **3a** and **3b** (dictyostatin numbering).

ides can be assigned on the basis of the relevant ^{13}C NMR chemical shifts: the quaternary C atom of the acetonide was observed at δ = 100.7 ppm, and the methyl-C signals were observed at δ = 24.4 and 25.2 ppm (Figure 1), clearly pointing to an *anti*-1,3-diol relationship and therefore to 9*S* stereochemistry.



Scheme 6. (*Z*)-vinylzincate coupling reactions.



Scheme 7. Synthesis of 7,9-acetonide **28b**-acetonide.

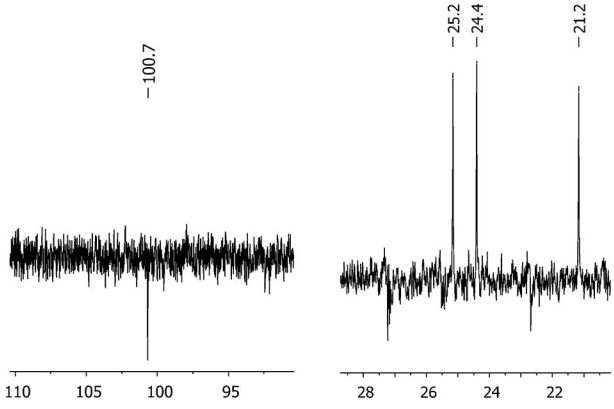
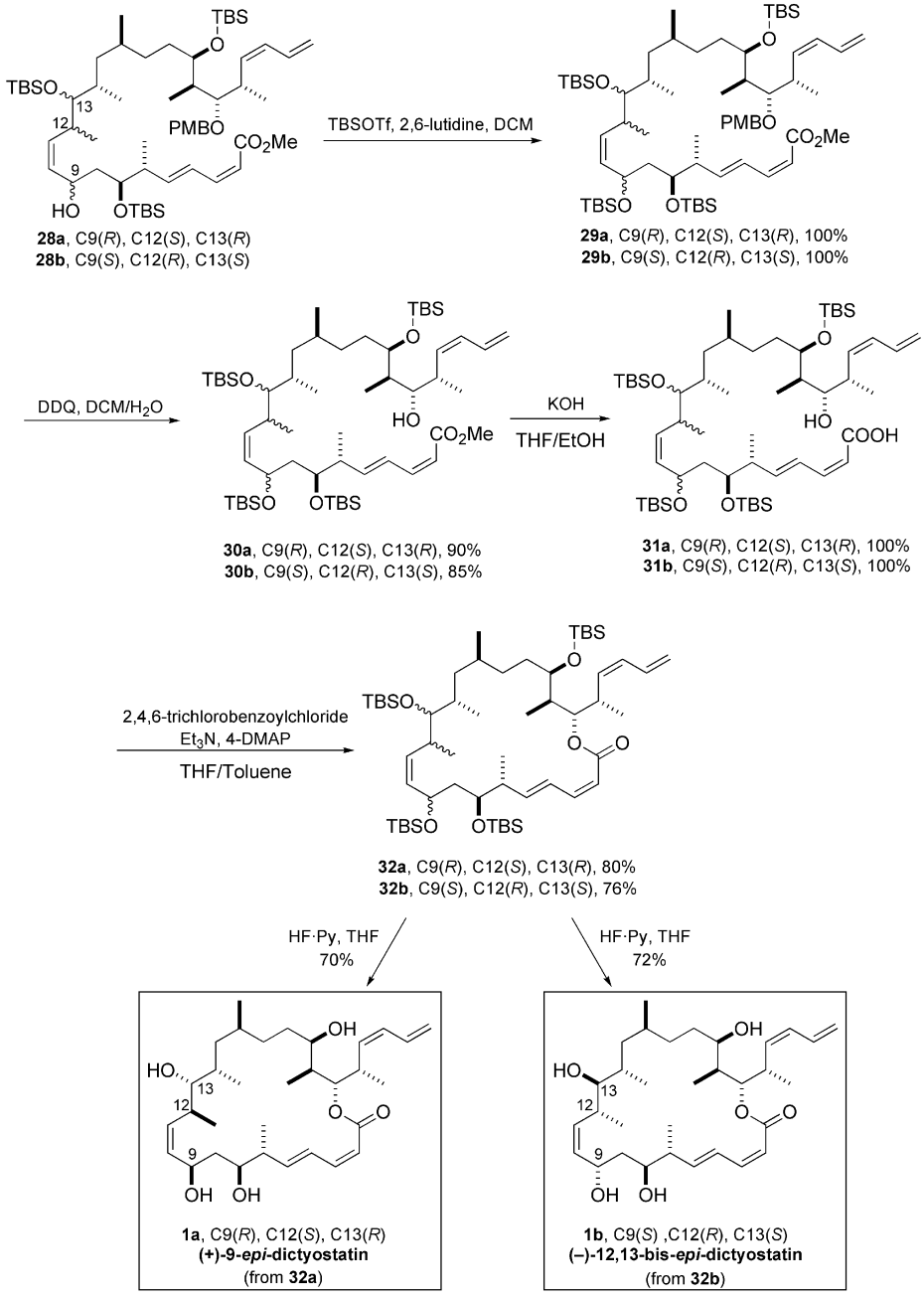


Figure 1. Relevant peaks in the ^{13}C NMR spectrum of **28b**-acetonide.

The secondary alcohol of compounds **28a**–**b** was subsequently silylated with TBSOTf to give the fully protected intermediates **29a**–**b** (100%, Scheme 8). Selective PMB removal with DDQ provided compounds **30a**–**b** (85–90%), which were then saponified under basic conditions (KOH) to provide *seco*-acids **31a**–**b** (100%). Yamaguchi macrolactonization[25] of *seco*-acids **31** gave macrolides **32a**–**b** in good yield (76–80%), together with a small amount (5–10%) of the (2*E*,4*E*)-dienoates ($J_{H2\text{-}H3}$ = 15.2 Hz for the **a** series and $J_{H2\text{-}H3}$ = 15.3 Hz for the **b** series), probably formed via a reversible Michael addition of DMAP to the (2*Z*,4*E*)-dienoates,[4e] which could be separated by flash chromatography. Global deprotection of the TBS groups of **32a** with 3 N HCl/MeOH in THF (2.2:1 volume ratio)[4d] caused extensive degradation of the product, while the use of HF·Py in THF[4c,4e] cleanly converted **32a** into (+)-9-*epi*-dictyostatin (**1a**, 70%) and **32b** into (–)-12,13-bis-*epi*-dictyostatin (**1b**, 72%).

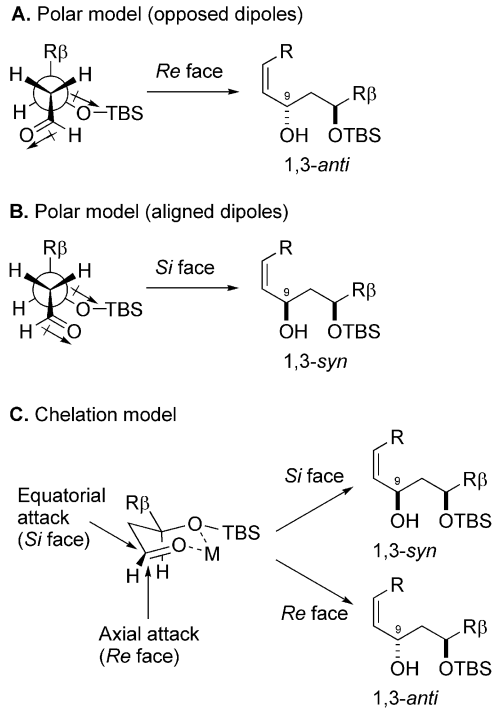
Our synthetic compound **1a** produced analytical data (^1H NMR in CD_3OD, $[\alpha]_D$) in disagreement with those recorded from an authentic sample of (–)-dictyostatin (**1**) kindly provided by Prof. Ian Paterson (University of Cambridge, UK), but proved to be identical (^1H NMR and ^{13}C NMR in [D$_6$]benzene, $[\alpha]_D$, HRMS, IR, R_f) to the compounds described by Paterson[5c] and Curran[5i] as (+)-9-*epi*-dictyostatin. In principle, compound **28a** could be easily conveyed into the total synthesis of (–)-dictyostatin (**1**) by oxidation of the 9*R*-allylic alcohol to the corresponding 9-ketone, completion of the synthetic sequence (as outlined in Scheme 8) and reduction of the enone to the 9*S*-allylic alcohol ($NaBH_4$, $CeCl_3{\cdot}7H_2O$, EtOH, –30 °C)[4a] immediately before final deprotection. The synthetic compound **1b** is a novel (–)-dictyostatin analog and was fully characterized (^1H NMR and ^{13}C NMR in [D$_6$]benzene, $[\alpha]_D$, HRMS, IR, R_f) by us for the first time.

In order to find a rationale for the observed stereochemical outcome of the lithium (*Z*)-vinylzincate coupling reactions (Scheme 6), we searched for literature precedents. According to the 1,3-asymmetric induction models thoroughly investigated by Evans,[26] steric interactions in the aldehyde conformations are minimized when the β-alkyl substituent (*R*β) is oriented *anti* to the C*α*-C=O bond as in structures **A** and **B** shown in Scheme 9. Usually, β-OTBS substituted aldehydes afford preferentially the 1,3-*anti* diastereomer via the polar model **A**, where dipoles are opposed.[26] When aluminum Lewis acids (Me_2AlCl or $MeAlCl_2$) are used, exceptional chelation control reinforces the 1,3-*anti* stereochemical outcome (model **C**, axial attack).[27] In the case of



Scheme 8. Completion of the total syntheses.

α-OTBS substituted aldehydes, addition reactions of (*Z*)-disubstituted vinylzinc reagents, in the presence of added RZnX (1.5 equiv.), have been shown to proceed via a Cram-chelation mechanism.[28] Recently, Curran and co-workers studied the addition of a (*Z*)-vinyllithium compound to aldehyde **2**, and reported a ca. 2:1 1,3-*anti*/1,3-*syn* diastereomeric ratio.[5i] Addition of other (*Z*)-vinyllithium compounds to similar aldehydes gave 1,3-*anti*/1,3-*syn* ratios ranging from 1.5:1 to 1:1.9.[5d,5i,29] These results suggest that also models **B** and/or **C** (equatorial attack), leading to the 1,3-*syn* diastereomer, can make a substantial impact in these addition reactions. In summary, it appears that for this particular type of (*Z*)-vinylmetal addition reactions the 1,3-asymmetric induction models have no predictive value, as the stereochemical outcome is mainly dependent on the induction of the chiral (*Z*)-vinylmetal reagent rather than on the preference of the β-OTBS substituted aldehyde. Indeed, using the same β-OTBS substituted aldehyde **2** and the two bis-epimeric lithium (*Z*)-dimethylalkenylzincates derived from **3a** and **3b**, we observed the opposite stereochemical outcome at C9: 9*R* in **28a** (1,3-*syn*) and 9*S* in **28b** (1,3-*anti*).



Scheme 9. 1,3-Asymmetric induction models.

Biological Evaluation

The cell growth inhibitory activity of (+)-9-*epi*-dictyostatin (**1a**) and (–)-12,13-bis-*epi*-dictyostatin (**1b**), as compared to that of (–)-dictyostatin (**1**), were determined against two ovarian carcinoma cell lines (Table 2). As already reported with other cell lines,[5c,5i] the 9-*epi* diastereomer (**1a**) showed an IC_{50} a hundred times higher than that of dictyostatin (**1**) both in cells sensitive to chemotherapy and in cells resistant to chemotherapy by P-glycoprotein overexpression, maintaining approximately the same relative resistance ratio of dictyostatin [(*R*)/(*S*) = 0.95 vs. 1.12, see Table 2]. The 12,13-bis-*epi* diastereomer (**1b**) displayed a total loss of activity ($IC_{50} > 20$ μM).

Both compounds were evaluated for their ability to inhibit the binding of the fluorescent taxoid Flutax-2 to the paclitaxel binding site of microtubules.[30] The binding constants were calculated from the Flutax-2 displacement isotherms at 35 °C (see the Supporting Information).[30] Dictyostatin (**1**, $K_{app} = 16.7 \times 10^7$ M^{-1}) is roughly 4 times more powerful than docetaxel ($K_{app} = 3.9 \times 10^7$ M^{-1}), 9-*epi*-dictyostatin (**1a**, $K_{app} = 2.6 \times 10^6$ M^{-1}) is more than 10 times less powerful and 12,13-bis-*epi*-dictyostatin (**1b**, $K_{app} < 10^5$ M^{-1}) is at least 400 times less powerful. Therefore, while dictyostatin (**1**) strongly inhibits Flutax-2 as described, (+)-9-*epi*-dictyostatin (**1a**) is a weaker inhibitor and 12,13-bis-*epi*-dictyostatin (**1b**) fails to significantly displace the fluorescent taxane from its binding site, indicating that the lack of cytotoxicity arises from the reduced affinity for the paclitaxel binding site of microtubules. The above data indicate that stereocenters in 12,13 are very relevant for the biological activity. This can be either due to a local steric effect

Table 2. Cytotoxicity of (–)-dictyostatin (**1**), (+)-9-*epi*-dictyostatin (**1a**) and (–)-12,13-bis-*epi*-dictyostatin (**1b**) in ovarian carcinoma cell lines sensitive to chemotherapy (A2780) and resistant to chemotherapy by P-glycoprotein overexpression (A2780AD).[a]

Compound	IC_{50}/nM[b]		*R*/*S*[c]
	A2780	A2780AD	
(–)-Dictyostatin (**1**)	2.86 ± 0.9	3.2 ± 0.6	1.12
(+)-9-*epi*-Dictyostatin (**1a**)	241 ± 93	228 ± 53	0.95
(–)-12,13-Bis-*epi*-dictyostatin (**1b**)	> 20000	>20000	–

[a] IC_{50} (50% inhibition of cell proliferation) of the compounds in ovarian carcinomas determined with the MTT assay modified as referenced in the Exp. Section (Biological assays). [b] IC_{50} values [nM] are the mean ± standard error values for three independent experiments. [c] The relative resistance of A2780AD cell line, obtained dividing the IC_{50} of the resistant cell line by the IC_{50} of the parental A2780 cell line.

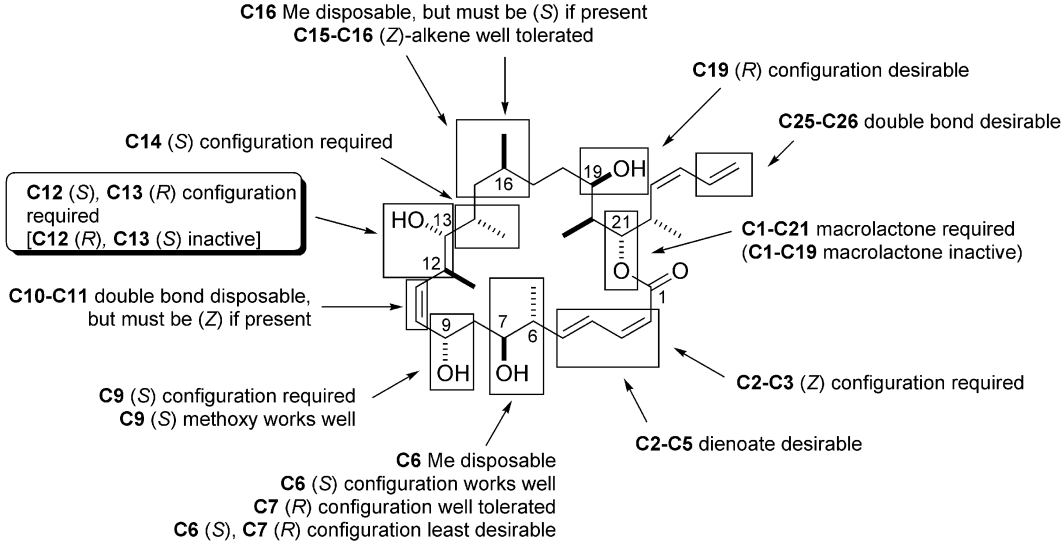


Figure 2. Qualitative structure-activity relationships in dictyostatins.

or to a global effect altering the entire macrocyclic conformation. In fact, a NOESY experiment in CD_3OD showed a substantially different pattern of NOE correlations compared to dictyostatin (see the Supporting Information),[3] witnessing a different macrocyclic conformation induced by the inversion of the C12,C13 stereocenters.

Conclusions

A highly stereoselective total synthesis of (+)-9-*epi*-dictyostatin (**1a**) was carried out in 1.53% overall yield (calculated over 29 steps, longest linear sequence from the Roche ester). Unfortunately, unnatural configuration at C9 is known to cause a substantial drop in cytotoxicity relative to dictyostatin (**1**).[5c,5i] However, the new synthetic route is flexible enough to allow for inversion at C9 by oxidation–reduction,[4a,4e] thus providing potential access to the natural product. Through a simple adjustment in the synthetic sequence, i.e. by using the mesylate of (*S*)-3-butyn-2-ol in the Marshall–Tamaru palladium-catalyzed allenylzinc addition, we also synthesized (–)-12,13-bis-*epi*-dictyostatin (**1b**) in 1.52% overall yield. This novel non-natural analog of dictyostatin displayed a dramatic decrease of cytotoxicity and of affinity for the paclitaxel binding site of microtubules, due to a different macrocyclic conformation induced by the inversion of the C12,C13 stereocenters.

These biological results add a piece of information to the structure-activity relationships based on dictyostatin analogs developed by the Paterson and Curran research groups (Figure 2).

Experimental Section

General: ^1H (400.13 MHz) and ^{13}C (100.58 MHz) NMR spectra were recorded on a Bruker Avance-400 spectrometer. ^1H NMR chemical shifts are reported relative to TMS, and the solvent resonance was employed as the internal standard ($CDCl_3$, δ = 7.26; C_6D_6, δ = 7.16 ppm). The following abbreviations are used to describe spin multiplicity: s singlet, d doublet, t triplet, q quartet, m multiplet, dd doublet-doublet, td triplet-doublet, dt doublet-triplet, br. broad signal. ^{13}C NMR spectra were recorded with complete proton decoupling, and the chemical shifts are reported relative to TMS with the solvent resonance as the internal standard ($CDCl_3$, δ = 77.0; C_6D_6, δ = 128.06 ppm). Infrared spectra were recorded on a standard FT/IR spectrophotometer. Optical rotation values were measured on an automatic polarimeter with a 1-dm cell at the sodium D line. High resolution mass spectra (HRMS) were performed on a Fourier Transform Ion Cyclotron Resonance (FT-ICR) Mass Spectrometer APEX II & Xmass software (Bruker Daltonics) – 4.7 T Magnet (Magnex) equipped with ESI source, available at C.I.G.A. (Centro Interdipartimentale Grandi Apparecchiature dell'Università degli Studi di Milano). All reactions were carried out in oven- or flame-dried glassware under nitrogen atmosphere, unless stated otherwise. All commercially available reagents were used as received. All solvents were dried by standard procedures before use. Organic extracts were dried with anhydrous Na_2SO_4. Reactions were magnetically stirred and monitored by TLC on silica gel (60 F254 pre-coated glass plates, 0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with a ceric ammonium molybdate or $KMnO_4$ solution. Flash chromatography was performed on silica gel (60 Å, particle size 0.040–0.062 mm) according to the procedure of Still and co-workers.[31] Yields refer to chromatographically and spectroscopically pure compounds, unless stated otherwise.

Methyl (2*Z*,4*E*,6*R*,7*S*)-7-(*tert*-Butyldimethylsilyloxy)-6-methyl-9-oxonona-2,4-dienoate (2): A solution of methyl (2*Z*,4*E*,6*R*,7*S*)-7-(*tert*-butyldimethylsilyloxy)-9-hydroxy-6-methylnona-2,4-dienoate[7k] (140 mg, 0.42 mmol, 1 equiv.) in DCM (2.5 mL) was treated at 0 °C with pyridine (86 μL, 1.04 mmol, 2.5 equiv.) and DMP (214 mg, 0.50 mmol, 1.2 equiv.). The reaction mixture was warmed to room temperature and stirred for 1 h. After completion of the reaction, satd. aq. $NaHCO_3$ (7 mL) and $Na_2S_2O_3$ (760 mg, 3.06 mmol) were added. The mixture was stirred for 30 min, then the phases were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried with Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash chromatography (8:2 hexane/EtOAc) to give aldehyde **2** (135 mg, 100% yield) as a yellow oil; R_f = = 0.37 (8:2 hexane/EtOAc). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 3 H), 0.11 (s, 3 H), 0.90 (s, 9 H), 1.12 (d, J = 6.8 Hz, 3 H), 2.45–2.61 (m, 3 H), 3.75 (s, 3 H), 4.24 (m, 1 H), 5.65 (d, J = 11.3 Hz, 1 H), 6.00 (dd, J = 7.9, 15.5 Hz, 1 H), 6.58 (t, J = 11.3 Hz, 1 H), 7.40 (dd, J = 11.2, 15.4 Hz, 1 H), 9.80 (dd, J = 1.9, 2.3 Hz, 1 H) ppm.

(*R*)-But-3-yn-2-yl Methanesulfonate (6a) and (*S*)-But-3-yn-2-yl Methanesulfonate (6b): TEA (5.31 mL, 38.1 mmol, 4 equiv.) and methanesulfonyl chloride (2.21 mL, 28.6 mmol, 3 equiv.) were added to a solution of (*R*)-but-3-yn-2-ol or (*S*)-but-3-yn-2-ol (0.75 mL, 9.52 mmol, 1 equiv.) in DCM (7.5 mL) at –78 °C. The reaction mixture was stirred for 40 min and then quenched with satd. aq. $NaHCO_3$ (8 mL). Phases were separated and the aqueous layer was washed with DCM (2 × 10 mL). The combined organic extracts were washed with brine, dried and concentrated under reduced pressure (800 mbar). The residue was purified by flash column chromatography (6:3 pentane/Et_2O) to afford the desired product **6a** or **6b** (1.39 g, 100% yield) as a colorless liquid; R_f = 0.65 (8:2 DCM/EtOAc). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.58 (d, J = 6.8 Hz, 3 H), 2.74 (d, J = 2.4 Hz, 1 H) 3.06 (s, 3 H), 5.20 (m, 1 H) ppm.

(1-Bromoallyl)trimethylsilane (7): *n*BuLi (1.6 M in hexane, 15 mL, 24 mmol, 1.2 equiv.) was added to a stirred solution of *i*Pr$_2$NH (3.64 mL, 26 mmol, 1.3 equiv.) in THF (6 mL) at –78 °C. After stirring at 0 °C for 30 min, the solution was added to a flask containing allyl bromide (2.08 mL, 24 mmol, 1.2 equiv.) and chlorotrimethylsilane (2.52 mL, 20 mmol, 1 equiv.) in THF (5 mL) at –78 °C. After stirring for 1 h, the reaction was quenched by adding satd. aq. NH_4Cl (12 mL). Phases were separated and the aqueous phase was extracted with pentane (3 × 10 mL). The combined organic extracts were dried and concentrated under reduced pressure. The residue was purified by flash chromatography (9:1 pentane/Et_2O) to give the desired product **7** (2.83 g, 73% yield) as a colorless liquid; R_f = 0.77 (95:5 hexane/EtOAc). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.16 (s, 9 H), 3.82 (d, J = 9.6 Hz, 1 H), 5.06 (d, J = 10.0 Hz, 1 H), 5.19 (d, J = 16.8 Hz, 1 H), 5.95 (m, 1 H) ppm.

({[(2*S*,4*R*)-2,4-Dimethylhex-5-yn-1-yl]oxy}methyl)benzene (4). Shioiri Alkynylation: A solution of *n*BuLi in hexane (1.6 M, 1.17 mL, 1.87 mmol, 1.4 equiv.) was added to a solution of DIPA (262 μL, 1.87 mmol, 1.4 equiv.) in THF (10 mL) at 0 °C. After 30 min at 0 °C, the mixture was cooled to –78 °C, and trimethylsilyldiazomethane in Et_2O (2.0 M, 935 μL, 1.87 mmol, 1.4 equiv.) was added. After 30 min, a solution of aldehyde **15**[7j] (295 mg,

1.34 mmol, 1 equiv.) in THF (3.5 mL) was slowly added, and the mixture was stirred for 1 h at –78 °C. Temperature was raised to room temperature, and stirring was maintained overnight. The mixture was then poured into ice-cooled water, and extracted with Et_2O. The combined organic extracts were dried and concentrated under reduced pressure. The residue was purified by flash chromatography (10:1 hexane/EtOAc) to afford the alkyne **4** as a yellow oil (176.9 mg, 61% yield over two steps).

Bestmann–Ohira Alkynylation: A solution of dimethyl (1-diazo-2-oxopropyl)phosphonate (3.73 g, 19.4 mmol, 4 equiv.) in THF (37 mL) was slowly added to a cooled (–78 °C) solution of MeONa (1.05 g, 19.4 mmol, 4 equiv.) in THF (84 mL). After 15 min, a solution of aldehyde **15**[7j] (1.07 g, 4.85 mmol, 1 equiv.) in THF (25 mL) was added. The resulting mixture was stirred at –78 °C for 30 min, allowed to reach room temperature over 1.5 h, quenched with satd. aq. NH_4Cl (15 mL) and diluted with water (40 mL). Phases were separated and the aqueous layer extracted with Et_2O (3 × 40 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography (100:1 hexane/EtOAc) to afford product **4** (0.95 g, 91% yield over two steps) as a yellow oil; R_f = 0.87 (10:1 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (d, J = 6.8 Hz, 3 H), 1.17–1.22 (m, 1 H), 1.23 (d, J = 6.8 Hz, 3 H), 1.58–1.68 (m, 1 H), 2.05 (d, J = 2.4 Hz, 1 H), 2.08–2.20 (m, 1 H), 2.50–2.62 (m, 1 H), 3.30–3.39 (m, 2 H), 4.50 (s, 2 H), 7.26–7.37 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.9 (CH_3), 22.0 (CH_3), 23.8 (CH), 32.0 (CH), 41.2 (CH_2), 68.8 (CH), 73.3 (CH_2), 76.5 (CH_2), 89.4 (C_0), 127.8 (CH), 127.9 (CH), 128.7 (CH), 139.2 (C_0) ppm. HRMS (ESI): calcd. for $C_{15}H_{20}NaO$: 239.14064 [M + Na]$^+$; found 239.14059.

(2*R*,6*R*,8*S*)-9-(Benzyloxy)-2-[(4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl]-6,8-dimethylnon-4-yn-3-one (16): Alkyne **4** (969 mg, 4.48 mmol, 1 equiv.) was dissolved in THF (45 mL), cooled to –78 °C and treated with *n*BuLi (1.6 M in hexane, 2.8 mL, 1 equiv.). After 5 min, the mixture was warmed to 0 °C and stirred for 30 min. The solution was then recooled to –78 °C and Weinreb amide **5**[8] (1.64 g, 5.06 mmol, 1.1 equiv.) in THF (2.8 mL) was added slowly. After 5 min the solution was warmed to 0 °C and stirred for 1 h. The reaction was quenched with a satd. aq. NH_4Cl (2.8 mL). The aqueous phase was extracted with Et_2O and the combined organic extracts were washed with brine and dried with Na_2SO_4. Filtration and concentration under reduced pressure, followed by flash chromatography (9:1 hexane/EtOAc) afforded the ynone **16** (1.5 g, 70% yield) as a pale yellow oil; R_f = 0.53 (8:2 hexane/EtOAc). $[\alpha]_D^{22}$ = +46.4 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81 (d, J = 6.7 Hz, 3 H), 0.97 (d, J = 6.7 Hz, 3 H), 1.26–1.29 (m, 1 H), 1.27 (d, J = 6.6 Hz, 3 H), 1.27 (d, J = 7.2 Hz, 3 H), 1.74 (ddd, J = 4.2, 10.5, 14.4 Hz, 1 H), 2.00–2.11 (m, 2 H), 2.76 (m, 2 H), 3.31 (d, J = 6.2 Hz, 2 H) 3.55 (t, J = 11.1 Hz, 1 H), 3.80 (s, 3 H), 4.15 (dd, J = 6.4, 13.3 Hz, 1 H), 4.23 (dd, J = 2.8, 10.1 Hz, 1 H), 4.50 (s, 2 H), 5.48 (s, 1 H), 6.86 (d, J = 8.7 Hz, 2 H), 7.33 (m, 7 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.3 (CH_3), 11.8 (CH_3), 16.5 (CH_3), 20.8 (CH_3), 24.0 (CH), 30.9 (CH), 32.0 (CH), 40.2 (CH_2), 49.4 (CH), 55.1 (CH_3), 72.8 (CH_2), 72.9 (CH_2), 75.8 (CH_2), 80.4 (C_0), 82.8 (CH), 98.1 (C_0), 100.9 (CH), 113.3 (CH), 127.3 (CH), 127.4 (CH), 128.3 (CH), 131.2 (C_0), 138.8 (C_0), 159.8 (C_0), 188.7 (C_0) ppm. IR (neat): $\tilde{\nu}$ = 699, 737, 829, 1034, 1078, 1127, 1249, 1303, 1372, 1392, 1456, 1518, 1615, 1678, 1737, 2207, 2850, 2874, 2933, 2968 cm^{-1}. HRMS (ESI): calcd. for $C_{30}H_{38}O_5Na$: 501.26115 [M + Na]$^+$; found 501,26102.

(2*S*,3*S*,6*R*,8*S*)-9-(Benzyloxy)-2-[(4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl]-6,8-dimethylnon-4-yn-3-ol (17): (*S*,*S*)-Noyori catalyst (156 mg, 0.246 mmol, 0.2 equiv.)[16] was added to a solution of ynone **16** (588 mg, 1.23 mmol, 1 equiv.) in *i*PrOH (12 mL). After stirring for 5 h at room temperature, the solvent was removed under vacuum and the residue purified by flash column chromatography (9:1 hexane/EtOAc), affording the propargylic alcohol **17** (580 mg, 98% yield) as a colorless oil; R_f = 0.37 (8:2 hexane/EtOAc). $[\alpha]_D^{20}$ = +35.9 (c = 1.03, $CHCl_3$). ^{1}H NMR (400 MHz, C_6D_6): δ = 0.45 (d, J = 6.8 Hz, 3 H), 1.07 (d, J = 6.8 Hz, 3 H), 1.12–1.22 (m, 1 H), 1.25 (d, J = 6.8 Hz, 3 H), 1.38 (d, J = 6.8 Hz, 3 H), 1.77–1.84 (m, 1 H), 1.97–2.05 (m, 2 H), 2.25 (br. s, 1 H), 2.38–2.43 (m, 1 H), 2.62–2.69 (m, 1 H), 3.16–3.31 (m, 2 H), 3.34 (s, 3 H), 3.34–3.43 (m, 1 H), 3.87 (dd, J = 2.0, 10.0 Hz, 1 H), 4.02 (dd, J = 4.8, 11.2 Hz, 1 H), 4.46 (s, 2 H), 4.75 (d, J = 5.6 Hz, 1 H), 5.61 (s, 1 H), 6.89 (d, J = 8.6 Hz, 2 H), 7.18–7.43 (m, 5 H), 7.68 (d, J = 8.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 9.2 (CH_3), 12.1 (CH_3), 17.1 (CH_3), 22.6 (CH_3), 24.5 (CH), 31.2 (CH), 32.8 (CH), 41.7 (CH), 41.8 (CH_2), 55.2 (CH_3), 67.0 (CH), 73.6 (CH_2), 76.7 (CH_2), 76.8 (CH_2), 82.7 (C_0), 85.8 (CH), 89.7 (C_0), 102.0 (CH), 114.3 (CH), 129.0 (CH), 132.4 (C_0), 136.7 (C_0), 161.2 (C_0) ppm. IR (neat): $\tilde{\nu}$ = 1462, 1518, 1615, 1732, 2851, 2874, 2933, 2969, 3024, 3040, 3501 cm^{-1}. HRMS (ESI): calcd. for $C_{30}H_{40}O_5Na$: 503.27680 [M + Na]$^+$; found 503.27575.

(3*S*,4*R*,5*S*,7*S*,10*R*,11*R*,12*S*,13*S*)-10,14-Bis(*tert*-butyldimethylsilanyloxy)-12-(4-methoxybenzyloxy)-3,5,7,11,13-pentamethyltetradec-1-yn-4-ol (22a): Triphenylphosphane (recrystallized from ethanol prior to use, 4.6 mg, 0.0175 mmol, 0.05 equiv.), the crude aldehyde obtained from alcohol **21**[7j] (220 mg, 0.35 mmol, 1 equiv.) and (*R*)-mesylbutynol **6a** (78 mg, 0.53 mmol, 1.5 equiv.) were sequentially added to a cooled (–78 °C) solution of $Pd(OAc)_2$ (3.9 mg, 0.0175 mmol, 0.05 equiv.) in THF (3.5 mL). Diethylzinc (1.0 M in hexane, 1.05 mL, 1.05 mmol, 3 equiv.) was added over 15 min. After 10 min, the temperature was raised to –20 °C, and the reaction mixture was stirred overnight at –20 °C. The mixture was quenched with satd. aq. NH_4Cl and extracted with Et_2O. The Et_2O layer was washed with brine, dried and concentrated under vacuum. The residue was purified by flash column chromatography (95:5 hexane/EtOAc) to afford product **22a** (196 mg, 82% yield over two steps) as a yellow oil with very high diastereoselectivity (dr > 98:2); R_f = 0.49 (8:2 hexane/EtOAc). $[\alpha]_D^{22}$ = –4.5 (c = 0.61, $CHCl_3$). ^{1}H NMR (400 MHz, C_6D_6): δ = 0.20 (s, 6 H), 0.27 (s, 6 H), 1.04 (d, J = 6.8 Hz, 3 H), 1.06 (d, J = 6.8 Hz, 3 H), 1.13 (s, 9 H), 1.17 (d, J = 6.8 Hz, 3 H), 1.18 (s, 9 H), 1.22 (d, J = 6.9 Hz, 3 H), 1.31 (d, J = 6.9 Hz, 3 H), 1.62–1.95 (m, 9 H), 2.11–2.19 (m, 2 H), 2.62–2.67 (m, 1 H), 3.28 (dd, J = 6.0, 10.8 Hz, 1 H), 3.43 (s, 3 H), 3.80–3.87 (m, 2 H), 3.92–4.00 (m, 2 H), 4.77 (d, J_{AB} = 10.8 Hz, 1 H, upfield part of an AB system), 4.83 (d, J_{AB} = 10.8 Hz, 1 H, downfield part of an AB system), 6.97 (d, J = 8.8 Hz, 2 H), 7.49 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = –4.7 (CH_3), –3.6 (CH_3), –3.4 (CH_3), 11.1 (CH_3), 14.5 (CH_3), 16.0 (CH_3), 18.0 (CH_3), 18.9 (C_0), 21.2 (CH_3), 26.7 (CH_3), 26.8 (CH_3), 31.0 (CH), 31.7 (CH), 32.1 (CH_2), 32.7 (CH_2), 33.6 (CH), 39.9 (CH), 40.7 (CH), 42.1 (CH_2), 55.2 (CH_3), 65.5 (CH_2), 71.7 (CH), 74.6 (CH_2), 75.5 (CH), 77.5 (CH), 81.4 (CH), 86.6 (C_0), 114.5 (CH), 129.5 (CH), 132.6 (C_0), 160.0 (C_0) ppm. IR (neat): $\tilde{\nu}$ = 1255, 1301, 1386, 1462, 1470, 1514, 1613, 1727, 2655, 2663, 2857, 2882, 2930, 2956, 3306 cm^{-1}. HRMS (ESI): calcd. for $C_{39}H_{72}O_5Si_2Na$: 699.48105 [M + Na]$^+$; found 699.48154.

(5*R*,6*S*,8*S*,11*R*,12*R*,13*S*,14*S*)-5-[(*S*)-But-3-yn-2-yl]-11-[(*tert*-butyldimethylsilyl)oxy]-13-[(4-methoxybenzyl)oxy]-2,2,3,3,6,8,12,14,17,17,18,18-dodecamethyl-4,16-dioxa-3,17-disilanonadecane (23a): Freshly distilled 2,6-lutidine (0.13 mL, 1.16 mmol, 4 equiv.) and TBSOTf (0.1 mL, 0.43 mmol, 1.5 equiv.) were added to a stirred solution of compound **22a** (196 mg, 0.29 mmol, 1 equiv.) in DCM

(7 mL) at –20 °C. On completion of the reaction (approximately 2 h), the mixture was quenched with satd. aq. NH_4Cl (3 mL). The organic phase was separated and the aqueous layer extracted with DCM. The combined organic extracts were washed with brine, dried with Na_2SO_4 and the solvents evaporated. Purification of the crude product by flash chromatography (7:3 hexane/EtOAc) afforded compound **23a** (229 mg, 100% yield) as a colorless oil; R_f = 0.80 (8:2 hexane/EtOAc). $[a]_D^{22}$ = –3.1 (c = 0.51, $CHCl_3$). ^1H NMR (400 MHz, C_6D_6): δ = 0.21 (s, 6 H), 0.25 (s, 3 H), 0.26 (s, 3 H), 0.27 (s, 3 H), 0.28 (s, 3 H), 1.10 (d, J = 7.2 Hz, 3 H), 1.12 (d, J = 6.8 Hz, 3 H), 1.13 (s, 9 H), 1.16 (s, 9 H), 1.19 (s, 9 H), 1.23 (d, J = 7.2 Hz, 3 H), 1.30 (d, J = 6.8 Hz, 3 H), 1.31 (d, J = 6.4 Hz, 3 H), 1.32–1.13 (m, 2 H), 1.81–1.64 (m, 4 H), 2.01–1.96 (m, 1 H), 2.02 (d, J = 2.4 Hz, 1 H), 2.17–2.13 (m, 3 H), 2.79–2.71 (m, 1 H), 3.43 (s, 3 H), 4.01–3.69 (m, 5 H), 4.77 (d, J_{AB} = 10.8 Hz, 1 H, upfield part of an AB system), 4.83 (d, J_{AB} = 10.8 Hz, 1 H, downfield part of an AB system), 6.97 (d, J = 8.4 Hz, 2 H), 7.49 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = –4.7 (CH_3), –3.6 (CH_3), –3.3 (CH_3), –3.2 (CH_3), –3.1 (CH_3), 11.0 (CH_3), 15.9 (CH_3), 16.0 (CH_3), 18.0 (CH_3), 18.9 (C_0), 19.1 (C_0) 20.9 (CH_3), 26.6 (CH_3), 26.7 (CH_3), 26.8 (CH_3), 31.4 (CH), 32.4 (CH_2), 32.7 (CH_2), 32.9 (CH), 34.1 (CH), 39.9 (CH), 40.7 (CH), 43.7 (CH_2), 55.2 (CH_3), 65.6 (CH_2), 71.2 (CH), 74.7 (CH_2), 75.4 (CH), 78.5 (CH), 81.5 (CH), 87.9 (C_0), 114.5 (CH), 129.5 (CH), 132.6 (C_0), 160.0 (C_0) ppm. IR (neat): $\tilde{\nu}$ = 1256, 1471, 1514, 1587, 1614, 2856, 2884, 2904, 2929, 2957, 3312 cm^{-1}. HRMS (ESI): calcd. for $C_{45}H_{86}O_5Si_3Na$: 813.56753 [M + Na]$^+$; found 813.56718.

(5*R*,6*S*,8*S*,11*R*,12*R*,13*S*,14*S*)-11-(*tert*-Butyldimethylsilyloxy)-5-[(*S*)-4-iodobut-3-yn-2-yl]-13-(4-methoxybenzyloxy)-2,2,3,3,6,8,12,14,17,17,18,18-dodecamethyl-4,16-dioxa-3,17-disilanonadecane (24a): A 1.6 M solution of *n*BuLi in hexane (0.22 mL, 0.35 mmol, 1.2 equiv.) was added dropwise over 5 min to a solution of alkyne **23a** (229 mg, 0.29 mmol, 1 equiv.) in THF (1.5 mL) at –50 °C. After 1 h, a solution of iodine (125 mg, 0.50 mmol, 1.7 equiv.) in THF (0.10 mL) was added. The mixture was stirred at –50 °C for 30 min, then warmed to a room temperature over 30 min. After quenching by the addition of satd. aq. $Na_2S_2O_3$ solution (0.8 mL) and brine (0.8 mL), the mixture was extracted with EtOAc (3 × 3 mL) and the combined organic layers were washed with brine (2 × 4 mL). The organic phase was dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (9.5:0.5 hexane/EtOAc) to give the desired product **24a** (266 mg, 100% yield) as a colorless oil; R_f = 0.40 (9.5:0.5 hexane/EtOAc). $[a]_D^{19}$ = –24.0 (c = 0.4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 9 H), 0.10 (s, 6 H), 0.11 (s, 3 H), 0.85 (d, J = 6.7 Hz, 3 H), 0.88 (d, J = 6.5 Hz, 3 H), 0.93 (s, 9 H), 0.93 (s, 9 H), 0.94 (s, 9 H), 0.94 (d, J = 6.7 Hz, 3 H), 1.00 (d, J = 6.8 Hz, 3 H), 0.98–1.05 (m, 2 H), 1.18 (d, J = 7.1 Hz, 3 H), 1.27–1.50 (m, 4 H), 1.63 (m, 1 H), 1.81 (m, 2 H), 1.91 (m, 1 H), 2.76 (m, 1 H), 3.48 (dd, J = 4.3, 6.7 Hz, 1 H), 3.52 (dd, J = 2.5, 5.7 Hz, 1 H), 3.69 (m, 3 H), 3.83 (s, 3 H), 4.50 (d, J_{AB} = 10.9 Hz, 1 H, upfield part of an AB system), 4.57 (d, J_{AB} = 10.9 Hz, 1 H, downfield part of an AB system), 6.89 (d, J = 8.6 Hz, 2 H), 7.27 (d, J = 8.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –3.7 (CH_3), –3.6 (CH_3), –3.3 (CH_3), –3.2 (CH_3), –3.1 (CH_3), 10.8 (CH_3), 15.4 (CH_3), 16.0 (CH_3), 18.0 (CH_3), 18.9 (C_0), 19.0 (C_0), 19.6 (C_0), 20.7 (CH_3), 26.7 (CH_3), 26.8 (CH_3), 30.4 (CH_2), 31.1 (CH), 32.3 (CH_2), 32.5 (CH_2), 33.7 (CH), 35.1 (CH), 39.5 (CH), 40.3 (CH), 43.5 (CH_2), 56.0 (CH_3), 65.3 (CH_2), 74.7 (CH_2), 74.9 (CH), 78.3 (CH), 81.7 (CH), 114.4 (CH), 129.6 (CH), 132.4 (C_0), 159.6 (C_0) ppm. IR (neat): $\tilde{\nu}$ = 670, 773, 835, 939, 1078, 1171, 1250, 1301, 1361, 1387, 1462, 1514, 1613, 2856, 2928 cm^{-1}. HRMS (ESI): calcd. for $C_{45}H_{85}IO_5Si_3Na$: 939.46417 [M + Na]$^+$; found 939.46033.

(5*R*,6*S*,8*S*,11*R*,12*R*,13*S*,14*S*)-11-(*tert*-Butyldimethylsilyloxy)-5-[(*S*,*Z*)-4-iodobut-3-en-2-yl]-13-(4-methoxybenzyloxy)-2,2,3,3,6,8,12,14,17,17,18,18-dodecamethyl-4,16-dioxa-3,17-disilanonadecane (25a): A solution of iodoalkyne **24a** (266 mg, 0.29 mmol, 1 equiv.) in THF (0.7 mL) and *i*PrOH (0.7 mL) at room temperature was treated with TEA (53 μL, 0.377 mmol, 1.3 equiv.) and NBSH (74.0 mg, 0.34 mmol, 1.1 equiv.). After 12 h, additional TEA (24 μL, 0.174 mmol, 0.6 equiv.) and NBSH (33.0 mg, 0.15 mmol, 0.5 equiv.) were added, and the mixture was stirred for 12 h. The reaction was quenched by adding water (1.7 mL) and the mixture was extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with brine (2 × 3 mL), dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (9.5:0.5 hexane/EtOAc) to give the desired product **25a** (245 mg, 92% yield) as a colorless oil; R_f = 0.85 (8:2 hexane/EtOAc). $[a]_D^{23}$ = +2.9 (c = 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 6 H), 0.08 (s, 3 H), 0.09 (s, 3 H), 0.10 (s, 6 H), 0.86 (d, J = 7.2 Hz, 3 H), 0.90 (d, J = 8.0 Hz, 3 H), 0.93 (s, 30 H), 0.99 (d, J = 6.8 Hz, 3 H), 1.00 (d, J = 7.0 Hz, 3 H), 1.28–1.47 (m, 6 H), 1.60–1.71 (m, 2 H), 1.80 (m, 1 H), 1.90 (m, 1 H), 2.71 (m, 1 H), 3.48 (m, 2 H), 3.68 (m, 3 H), 3.82 (s, 3 H), 4.49 (d, J_{AB} = 10.9 Hz, 1 H, upfield part of an AB system), 4.57 (d, J_{AB} = 10.9 Hz, 1 H, downfield part of an AB system), 6.14 (d, J = 7.3 Hz, 1 H), 6.29 (dd, J = 7.3, 8.8 Hz, 1 H), 6.89 (d, J = 8.7 Hz, 2 H), 7.28 (d, J = 8.7 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 (CH_3), –5.2 (CH_3), –4.3 (CH_3), –4.0 (CH_3), –3.7 (CH_3), –3.6 (CH_3), 10.1 (CH_3), 15.2 (CH_3), 15.8 (CH_3), 17.7 (CH_3), 18.1 (C_0), 18.3 (C_0), 18.4 (C_0), 20.5 (CH_3), 26.0 (CH_3), 26.1 (CH_3), 26.2 (CH_3), 29.7 (CH_2), 30.8 (CH), 31.1 (CH_2), 31.6 (CH_2), 35.3 (CH), 38.9 (CH), 39.6 (CH), 41.5 (CH_2), 43.5 (CH), 55.2 (CH_3), 64.6 (CH_2), 74.0 (CH_2), 74.2 (CH), 79.1 (CH), 81.1 (CH), 81.2 (CH), 113.7 (CH), 128.9 (CH), 131.6 (C_0), 144.2 (CH), 158.9 (C_0) ppm. IR (neat): $\tilde{\nu}$ = 773, 805, 835, 1079, 1256, 1377, 1462, 1514, 1611, 2855, 2927, 2956 cm^{-1}. HRMS (ESI): calcd. for $C_{45}H_{87}IO_5Si_3Na$: 941.47982 [M + Na]$^+$; found 941.47749.

(2*S*,3*S*,4*R*,5*R*,8*S*,10*S*,11*R*,12*S*,*Z*)-5,11-Bis(*tert*-butyldimethylsilyloxy)-14-iodo-3-(4-methoxybenzyloxy)-2,4,8,10,12-pentamethyltetradec-13-en-1-ol (26a): A solution of compound **25a** (680 mg, 0.74 mmol, 1 equiv.) in THF (3.8 mL) at 0 °C was treated with a solution of HF·Py in THF/pyridine [16.5 mL, prepared by slow addition of commercially available 70% HF in pyridine (1.3 mL) to a mixture of pyridine (5.0 mL) and THF (10.2 mL)]. The reaction mixture was warmed to room temperature and stirred for 3 h. After quenching the reaction by the addition of satd. aq. $NaHCO_3$ (30 mL), the mixture was extracted with EtOAc (4 × 20 mL). The combined organic extracts were washed with satd. aq. $CuSO_4$ (3 × 15 mL) and brine (2 × 40 mL), dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (9:1 hexane/EtOAc) to give the desired product **26a** (477 mg, 80% yield) as a colorless oil; R_f = 0.29 (8:2 hexane/EtOAc). $[a]_D^{16}$ = +9.6 (c = 0.9, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 3 H), 0.08 (s, 3 H), 0.09 (s, 3 H), 0.10 (s, 3 H), 0.88 (d, J = 6.5 Hz, 3 H), 0.89 (d, J = 6.8 Hz, 3 H), 0.86–0.91 (m, 2 H), 0.94 (s, 18 H), 1.01 (d, J = 7.0 Hz, 3 H), 1.02 (d, J = 6.8 Hz, 3 H), 1.13 (d, J = 7.1 Hz, 3 H), 1.28–1.47 (m, 4 H), 1.60–1.71 (m, 2 H), 1.90 (m, 1 H), 1.96 (m, 1 H), 2.71 (m, 1 H), 2.87 (br. s, 1 H), 3.48 (m, 2 H), 3.61 (m, 2 H), 3.83 (s, 3 H), 3.84 (m, 1 H), 4.55 (s, 2 H), 6.13 (d, J = 7.3 Hz, 1 H), 6.30 (t, J = 7.3 Hz, 1 H), 6.89 (d, J = 8.6 Hz, 2 H), 7.28 (d, J = 8.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –3.7 (CH_3), –3.1 (CH_3), –2.9 (CH_3), 10.7 (CH_3), 16.5 (CH_3), 16.7 (CH_3), 18.5 (CH_3), 18.8 (C_0), 19.1 (C_0), 21.2 (CH_3), 26.7 (CH_3), 26.9 (CH_3), 31.5 (CH), 32.3 (CH_2), 32.8 (CH_2), 36.2 (CH), 37.6 (CH), 41.2 (CH), 42.1 (CH_2), 44.0 (CH),

56.0 (CH_3), 65.9 (CH_2), 74.3 (CH), 76.0 (CH_2), 79.8 (CH), 81.9 (CH), 86.7 (CH), 114.6 (CH), 130.0 (CH), 131.2 (C_0), 144.8 (CH), 159.9 (C_0) ppm. IR (neat): $\tilde{\nu}$ = 773, 805, 1028, 1255, 1377, 1461, 1514, 1614, 2067, 2959, 3448 cm^{-1}. HRMS (ESI): calcd. for $C_{39}H_{73}IO_5Si_2Na$ [M + Na]$^+$: 827.39334; found 827.39126.

(2*R*,3*R*,4*R*,5*R*,8*S*,10*S*,11*R*,12*S*,*Z*)-5,11-Bis(*tert*-butyldimethylsilyloxy)-14-iodo-3-(4-methoxybenzyloxy)-2,4,8,10,12-pentamethyltetradec-13-enal (27a): A solution of alcohol **26a** (394 mg, 0.49 mmol 1 equiv.) in DCM (3.1 mL) was treated at 0 °C with pyridine (0.10 mL, 1.2 mmol, 2.5 equiv.) and DMP (250 mg, 0.59 mmol, 1.2 equiv.). The reaction mixture was warmed to room temperature and stirred for 1 h. After completion of the reaction, satd. aq. $NaHCO_3$ (8.0 mL) and $Na_2S_2O_3$ (888 mg, 3.6 mmol) were added. The resulting mixture was stirred for 30 min, then the phases were separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried (Na_2SO_4) and evaporated under reduced pressure, providing the crude aldehyde **27a**, which was used without further purification; R_f = 0.60 (8:2 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 3 H), 0.08 (s, 3 H), 0.09 (s, 3 H), 0.10 (s, 3 H), 0.84–0.94 (m, 2 H), 0.88 (d, J = 6.3 Hz, 3 H), 0.89 (d, J = 6.7 Hz, 3 H), 0.93 (s, 9 H), 0.94 (s, 9 H), 1.01 (d, J = 6.4 Hz, 3 H), 1.02 (d, J = 6.6 Hz, 3 H), 1.17 (d, J = 6.9 Hz, 3 H), 1.28–1.49 (m, 4 H), 1.58–1.73 (m, 2 H), 1.90 (m, 1 H), 2.71 (m, 1 H), 2.80 (m, 1 H), 3.49 (m, 1 H), 3.68 (m, 2 H), 3.83 (s, 3 H), 4.52 (s, 2 H), 6.13 (d, J = 7.3 Hz, 1 H), 6.30 (t, J = 7.3 Hz, 1 H), 6.89 (d, J = 8.6 Hz, 2 H), 7.27 (d, J = 8.6 Hz, 2 H), 9.83 (d, J = 2.2 Hz, 1 H) ppm.

(5*R*,6*S*,8*S*,11*R*)-5-[(*S*,*Z*)-4-Iodobut-3-en-2-yl]-11-[(2*R*,3*S*,4*S*,*Z*)-3-(4-methoxybenzyloxy)-4-methylocta-5,7-dien-2-yl]-2,2,3,3,6,8,13,13,14,14-decamethyl-4,12-dioxa-3,13-disilapentadecane (3a): To a slurry of $CrCl_2$ (301 mg, 2.45 mmol, 5 equiv.) in THF (4.9 mL), obtained by sonication and cooled to 0 °C, freshly prepared aldehyde **27a** (394 mg, 0.49 mmol, 1 equiv.) in THF (1.7 mL) and (1-bromoallyl)trimethylsilane (**7**, 530 mg, 2.74 mmol, 5.6 equiv.) were added. The resulting mixture was stirred for 3 h at room temperature before being re-cooled to 0 °C and quenched by the addition of MeOH (2.1 mL) and 6 N aqueous KOH (4.2 mL). After stirring for 20 h at room temperature, the phases were separated and the aqueous layer was extracted with DCM (4 × 5 mL). The combined organic extracts were washed with brine (2 × 15 mL), dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (100:0.5 hexane/EtOAc) to give the desired product **3a** (308 mg, 76% yield over two steps) as a colorless oil; R_f = 0.45 (10:0.5 hexane/EtOAc). $[\alpha]_D^{22}$ = +22.4 (c = 0.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04–0.11 (m, 12 H), 0.77–1.01 (m, 14 H), 0.94 (s, 9 H), 0.95 (s, 9 H), 1.12 (d, J = 6.9 Hz, 3 H), 1.25–1.38 (m, 4 H), 1.59–1.70 (m, 3 H), 2.70 (m, 1 H), 3.00 (m, 1 H), 3.35 (dd, J = 2.9, 7.9 Hz, 1 H), 3.47 (m, 1 H), 3.63 (m, 1 H), 3.83 (s, 3 H), 4.56 (d, J_{AB} = 10.6 Hz, 1 H, upfield part of an AB system), 4.52 (d, J_{AB} = 10.5 Hz, 1 H, downfield part of an AB system), 5.12 (d, J = 10.1 Hz, 1 H), 5.20 (d, J = 16.8 Hz, 1 H), 5.60 (t, J = 10.6 Hz, 1 H), 6.03 (t, J = 11.1 Hz, 1 H), 6.13 (d, J = 7.3 Hz, 1 H), 6.28 (t, J = 7.4 Hz, 1 H), 6.60 (ddd, J = 10.7, 10.7, 16.9 Hz, 1 H), 6.89 (d, J = 8.4 Hz, 2 H), 7.31 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –3.8 (CH_3), –3.2 (CH_3), –3.0 (CH_3), –2.9 (CH_3), 9.9 (CH_3), 16.5 (CH_3), 18.4 (CH_3), 18.9 (C_0), 19.1 (C_0), 19.5 (CH_3), 21.1 (CH_3), 26.7 (CH_3), 26.9 (CH_3), 31.3 (CH), 31.9 (CH_2), 33.1 (CH_2), 35.9 (CH), 36.0 (CH), 41.2 (CH), 42.1 (CH_2), 44.0 (CH), 56.0 (CH_3), 73.4 (CH), 75.8 (CH_2), 79.9 (CH), 81.9 (CH), 85.2 (CH), 114.4 (CH), 117.9 (CH_2), 129.6 (CH), 129.8 (CH), 132.1 (C_0), 133.0 (CH), 135.3 (CH), 144.9 (CH), 159.7 (C_0) ppm. IR (neat): $\tilde{\nu}$ = 772, 835, 1039, 1172, 1251, 1376, 1462, 1514, 1613, 1735, 2855, 2927 cm^{-1}. HRMS (ESI): calcd. for $C_{42}H_{75}IO_4Si_2Na$: 849.41408 [M + Na]$^+$; found 849.41248.

Methyl (2*Z*,4*E*,6*R*,7*S*,9*R*,10*Z*,12*S*,13*R*,14*S*,16*S*,19*R*,20*R*,21*S*,22*S*,23*Z*)-7,13,19-Tris(*tert*-butyldimethylsilyloxy)-9-hydroxy-21-(4-methoxybenzyloxy)-6,12,14,16,20,22-hexamethylhexacosa-2,4,10,23,25-pentaenoate (28a): To a solution of *t*BuLi (1.7 M in pentane, 0.17 mL, 0.29 mmol, 2.2 equiv.) in Et_2O (0.2 mL) kept at –78 °C under argon atmosphere, a solution of vinyl iodide **3a** (110 mg, 0.13 mmol, 1 equiv.) in Et_2O (0.4 mL) was added. After stirring for 30 min, dimethylzinc (2.0 M in toluene, 0.11 mL, 0.21 mmol, 1.6 equiv.) was added dropwise and the reaction mixture was further stirred at –78 °C for 15 min. A solution of aldehyde **2** (64 mg, 0.20 mmol, 1.5 eq, azeotropically dried with toluene), in Et_2O (0.6 mL) was added dropwise, and the mixture was stirred for 1 h at –78 °C. The reaction was quenched with water (2.2 mL), warmed to room temperature and diluted with Et_2O (3.6 mL). Phases were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with brine (2 × 5 mL), dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (10:0.5 hexane/EtOAc) and the following compounds were isolated (the reported R_f values were obtained using 8:2 hexane/EtOAc as the eluent): (i) de-iodinated alkene C10-C26 (R_f = = 0.67, 49 mg); (ii) 9*R* addition product **28a** (R_f = 0.55, 53 mg, 40% yield, light yellow oil); (iii) unknown product lacking C23-C26 diene portion (R_f = 0.50, <5% compared to the 9*R* addition product, MS-ESI$^+$ 782.5); (iv) unreacted aldehyde C1-C9 **2** (R_f = 0.37, 32 mg); (v) mixture of unreacted aldehyde and unknown product – possibly, the 9*S* addition product (R_f = 0.31, < 5% compared to the 9*R* addition product); R_f = 0.55 (8:2 hexane/EtOAc). $[\alpha]_D^{19}$ = +2.6 (c = 1.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 3 H), 0.06 (s, 3 H), 0.10 (s, 3 H), 0.11 (s, 9 H), 0.80–0.82 (m, 1 H), 0.83 (d, J = 6.5 Hz, 3 H), 0.87 (d, J = 6.8 Hz, 3 H), 0.90 (d, J = 7.0 Hz, 3 H), 0.92 (s, 9 H), 0.93 (s, 9 H), 0.95 (s, 9 H), 0.97 (d, J = 6.8 Hz, 3 H), 1.06–1.07 (m, 1 H), 1.12 (d, J = 6.8 Hz, 6 H), 1.17–1.42 (m, 4 H), 1.44–1.62 (m, 2 H), 1.65–1.79 (m, 3 H), 2.38 (br. s, 1 H), 2.63 (m, 1 H), 2.71 (m, 1 H), 3.01 (m, 1 H), 3.34 (m, 2 H), 3.64 (m, 1 H), 3.74 (s, 3 H), 3.82 (s, 3 H), 3.88 (m, 1 H), 4.49 (m, 1 H), 4.51 (d, J_{AB} = 10.6 Hz, 1 H, upfield part of an AB system), 4.58 (d, J_{AB} = 10.6 Hz, 1 H, downfield part of an AB system), 5.12 (d, J = 10.2 Hz, 1 H), 5.20 (dd, J = 1.8, 16.8 Hz, 1 H), 5.40 (m, 2 H), 5.61 (t, J = 11.4 Hz, 1 H), 5.62 (d, J = 11.4 Hz, 1 H), 6.00–6.09 (m, 2 H), 6.58 (t, J = 11.3 Hz, 1 H), 6.62 (t, J = 10.7 Hz, 1 H), 6.89 (d, J = 8.6 Hz, 2 H), 7.30 (d, J = 8.6 Hz, 2 H), 7.41 (dd, J = 11.3, 15.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4 (CH_3), –4.4 (CH_3), –4.3 (CH_3), –3.8 (CH_3), –3.5 (CH_3), –2.7 (CH_3), 9.2 (CH_3), 14.7 (CH_3), 15.4 (CH_3), 18.1 (C_0), 18.2 (C_0), 18.6 (C_0), 18.8 (CH_3), 19.0 (CH_3), 20.2 (CH_3), 25.9 (CH_3), 26.0 (CH_3), 26.4 (CH_3), 30.3 (CH), 31.5 (CH_2), 32.4 (CH_2), 34.0 (CH), 35.2 (CH), 36.8 (CH), 40.5 (CH), 41.4 (CH_2), 42.4 (CH_2), 42.5 (CH), 51.1 (CH_3), 55.3 (CH_3), 65.3 (CH), 72.8 (CH), 73.6 (CH), 75.1 (CH_2), 79.6 (CH), 84.4 (CH), 113.7 (CH), 115.6 (CH), 117.2 (CH_2), 127.1 (CH), 128.9 (CH), 129.1 (CH), 131.4 (C_0), 132.4 (CH), 132.6 (CH), 134.6 (CH), 136.2 (CH), 145.5 (CH), 147.0 (CH), 159.0 (C_0), 166.8 (C_0) ppm. IR (neat): $\tilde{\nu}$ = 773, 836, 1075, 1174, 1251, 1377, 1462, 1514, 1613, 1637, 1720, 2855, 2926, 3503 cm^{-1}. HRMS (ESI): calcd. for $C_{59}H_{106}O_8Si_3Na$: 1049.70877 [M + Na]$^+$; found 1049.70940.

Methyl (2*Z*,4*E*,6*R*,7*S*,9*R*,10*Z*,12*S*,13*R*,14*S*,16*S*,19*R*,20*R*,21*S*,22*S*,23*Z*)-7,9,13,19-Tetrakis(*tert*-butyldimethylsilyloxy)-21-(4-methoxybenzyloxy)-6,12,14,16,20,22-hexamethylhexacosa-2,4,10,23,25-pentaenoate (29a): 2,6-Lutidine (18 μL, 0.156 mmol, 4 equiv.) and TBSOTf (18 μL, 0.078 mmol, 2 equiv.) were added dropwise to a stirred solution of **28a** (40 mg, 0.039 mmol, 1 equiv.)

in DCM (0.3 mL) cooled to –78 °C. After stirring at –78 °C for 1 h, the reaction was quenched by adding satd. aq. $NaHCO_3$ (1.7 mL) dropwise, then it was warmed to room temperature. The mixture was diluted with DCM (11 mL), layers were separated and the aqueous phase was extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine (2 × 5 mL), dried with Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash chromatography (10:0.5 hexane/EtOAc) to give the desired product **29a** (45 mg, 100% yield) as a pale yellow oil; R_f = 0.80 (8:2 hexane/EtOAc). $[\alpha]_D^{24}$ = +7.3 (*c* = 0.4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 3 H), 0.06 (s, 3 H), 0.06 (s, 3 H), 0.08 (s, 3 H), 0.10 (s, 9 H), 0.10 (s, 3 H), 0.80–0.82 (m, 1 H), 0.82 (d, *J* = 6.1 Hz, 3 H), 0.83 (d, *J* = 6.9 Hz, 3 H), 0.86 (d, *J* = 6.8 Hz, 3 H), 0.91 (s, 9 H), 0.92 (s, 9 H), 0.92 (s, 9 H), 0.94 (s, 9 H), 0.97 (d, *J* = 6.8 Hz, 3 H), 1.01 (m, 1 H), 1.12 (d, *J* = 6.8 Hz, 3 H), 1.12 (d, *J* = 6.8 Hz, 3 H), 1.27–1.42 (m, 4 H), 1.46 (m, 1 H), 1.62–1.72 (m, 4 H), 2.49 (m, 1 H), 2.59 (m, 1 H), 3.00 (m, 1 H), 3.34 (dd, *J* = 3.1, 8.0 Hz, 1 H), 3.41 (m, 1 H), 3.64 (m, 1 H), 3.72 (s, 3 H), 3.82 (s, 3 H), 3.93 (m, 1 H), 4.43 (br. t, *J* = 8.4 Hz, 1 H), 4.52 (d, J_{AB} = 10.6 Hz, 1 H, upfield part of an AB system), 4.57 (d, J_{AB} = 10.6 Hz, 1 H, downfield part of an AB system), 5.11 (d, *J* = 10.2 Hz, 1 H), 5.20 (dd, *J* = 1.7, 16.9 Hz, 1 H), 5.25 (dd, *J* = 8.2, 11.4 Hz, 1 H), 5.47 (t, *J* = 10.5 Hz, 1 H), 5.58–5.63 (m, 2 H), 6.02 (t, *J* = 11.0 Hz, 1 H), 6.20 (dd, *J* = 8.9, 15.5 Hz, 1 H), 6.55–6.65 (m, 2 H), 6.89 (d, *J* = 8.7 Hz, 2 H), 7.30 (d, *J* = 8.7 Hz, 2 H), 7.43 (dd, *J* = 11.2, 15.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.8 (CH_3), –4.7 (CH_3), –4.3 (CH_3), –4.5 (CH_3), –4.1 (CH_3), –3.8 (CH_3), –3.5 (CH_3), 9.1 (CH_3), 14.1 (CH_3), 15.6 (CH_3), 18.0 (C_0), 18.1 (C_0), 18.2 (C_0), 18.5 (CH_3), 18.9 (CH_3), 20.5 (CH_3), 25.8 (CH_3), 26.0 (CH_3), 26.0 (CH_3), 26.2 (CH_3), 30.5 (CH), 31.7 (CH_2), 32.6 (CH_2), 35.1 (CH), 35.2 (CH), 36.5 (CH), 40.4 (CH), 40.9 (CH), 41.5 (CH_2), 44.8 (CH_2), 50.9 (CH_3), 55.3 (CH_3), 66.4 (CH), 72.4 (CH), 72.6 (CH), 75.1 (CH_2), 79.1 (CH), 84.5 (CH), 113.7 (CH), 115.0 (CH), 117.2 (CH_2), 127.4 (CH), 128.9 (CH), 129.1 (CH), 131.4 (C_0), 131.6 (CH), 132.4 (CH), 132.6 (CH), 134.6 (CH), 146.0 (CH), 147.2 (CH), 159.0 (C_0), 166.8 (C_0) ppm. IR (neat): $\tilde{\nu}$ = 669, 802, 865, 1078, 1257, 1361, 1412, 1461, 1514, 1637, (a719), 2856, 2928, 2961 cm^{-1}. HRMS (ESI): calcd. for $C_{65}H_{120}O_8Si_4Na$: 1163.79525 [*M* + Na]$^+$; found 1163.79601.

Methyl (2*Z*,4*E*,6*R*,7*S*,9*R*,10*Z*,12*S*,13*R*,14*S*,16*S*,19*R*,20*R*,21*S*,22*S*,23*Z*)-7,9,13,19-Tetrakis(*tert*-butyldimethylsilyloxy)-21-hydroxy-6,12,14,16,20,22-hexamethylhexacosa-2,4,10,23,25-pentaenoate (30a): DDQ (11.6 mg, 0.051 mmol, 1.3 equiv.) was added to a solution of the PMB ether **29a** (44.0 mg, 0.039 mmol, 1 equiv.) in DCM (1.2 mL) stirred at 0 °C in the presence of 0.12 mL of a KH_2PO_4/K_2HPO_4 buffer solution (pH = 7). The reaction was stirred at 0 °C for 1 h before being quenched by dropwise addition of satd. aq. $NaHCO_3$ (19 mL). After diluting with DCM (37 mL), layers were separated and the aqueous phase was extracted with DCM (3 × 30 mL). The combined organic extracts were washed with brine (2 × 30 mL), dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (95:5 hexane/EtOAc) to give the desired product **30a** (35.9 mg, 90% yield) as a colorless oil; R_f = 0.35 (9:1 hexane/EtOAc). $[\alpha]_D^{18}$ = –4.1 (*c* = 0.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 3 H), 0.07 (s, 3 H), 0.08 (s, 3 H), 0.10 (s, 12 H), 0.11 (s, 3 H), 0.85 (d, *J* = 6.9 Hz, 3 H), 0.89–0.90 (m, 6 H), 0.90 (m, 1 H), 0.92–0.95 (m, 39 H), 0.99 (d, *J* = 6.9 Hz, 3 H), 1.01–1.08 (m, 1 H), 1.13 (d, *J* = 6.8 Hz, 3 H), 1.18–1.50 (m, 5 H), 1.58–1.79 (m, 4 H), 2.51 (m, 1 H), 2.59 (m, 1 H), 2.83 (m, 1 H), 3.44 (m, 1 H), 3.50 (dd, *J* = 2.1, 7.3 Hz, 1 H), 3.73 (s, 3 H), 3.78 (m, 1 H), 3.95 (m, 1 H), 4.45 (t, *J* = 8.4 Hz, 1 H), 5.14 (d, *J* = 10.3 Hz, 1 H), 5.21–5.29 (m, 2 H), 5.48 (m, 2 H), 5.60 (d, *J* = 11.3 Hz, 1 H); 6.12 (t, *J* = 11.0 Hz, 1 H); 6.20 (dd, *J* = 8.9, 15.5 Hz, 1 H), 6.60 (t, *J* = 11.3 Hz, 1 H), 6.62–6.71 (m, 1 H), 7.43 (dd, *J* = 11.3, 15.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.8 (CH_3), –4.7 (CH_3), –4.4 (CH_3), –4.1 (CH_3), –3.9 (CH_3), –3.8 (CH_3), –3.7 (CH_3), –3.5 (CH_3), 6.8 (CH_3), 15.7 (CH_3), 17.8 (CH_3), 18.0 (C_0), 18.1 (C_0), 18.1 (C_0), 18.5 (CH_3), 20.2 (CH_3), 20.6 (CH_3), 25.8 (CH_3), 25.9 (CH_3), 25.9 (CH_3), 26.2 (CH_3), 30.7 (CH), 31.7 (CH_2), 32.4 (CH_2), 35.5 (CH), 36.1 (CH), 36.5 (CH), 37.7 (CH), 40.9 (CH), 41.6 (CH_2), 44.8 (CH_2), 50.9 (CH_3), 66.5 (CH), 72.4 (CH), 76.8 (CH), 77.8 (CH), 79.2 (CH), 115.0 (CH), 117.2 (CH_2), 127.3 (CH), 129.9 (CH), 131.4 (CH), 132.3 (CH), 132.7 (CH), 135.4 (CH), 145.9 (CH), 147.1 (CH), 166.6 (C_0) ppm. IR (neat): $\tilde{\nu}$ = 799, 1020, 1093, 1260, 1412, 1461, 1601, 1637, 1720, 2855, 2927, 2961, 3447 cm^{-1}. HRMS (ESI): calcd. for $C_{57}H_{112}O_7Si_4Na$: 1043.73773 [*M* + Na]$^+$; found 1043.73670.

(2*Z*,4*E*,6*R*,7*S*,9*R*,10*Z*,12*S*,13*R*,14*S*,16*S*,19*R*,20*R*,21*S*,22*S*,23*Z*)-7,9,13,19-Tetrakis(*tert*-butyldimethylsilyloxy)-21-hydroxy-6,12,14,16,20,22-hexamethylhexacosa-2,4,10,23,25-pentaenoic Acid (31a): To a stirred solution of the ester **30a** (35.0 mg, 0.034 mmol, 1 equiv.) in THF (1.8 mL) and EtOH (4.1 mL), KOH (1 N solution in water, 0.33 mL) was added, and the reaction was refluxed (bath temperature: 52 °C) for 5 h. The solvent was removed in vacuo. The residue was diluted with Et_2O (26 mL) and satd. aq. NH_4Cl solution (8 mL); layers were separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated under reduced pressure. The product was purified by flash chromatography (9:1 hexane/EtOAc) to afford the *seco*-acid **31a** (34.3 mg, 100% yield) as a colorless oil; R_f = 0.26 (8:2 hexane/EtOAc). $[\alpha]_D^{32}$ = +3.4 (*c* = 0.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 6 H), 0.04 (s, 3 H), 0.05 (s, 3 H), 0.06 (s, 3 H), 0.07 (s, 6 H), 0.08 (s, 3 H), 0.82 (d, *J* = 7.0 Hz, 3 H), 0.85 (d, *J* = 6.9 Hz, 3 H), 0.86 (d, *J* = 6.2 Hz, 3 H), 0.88 (s, 9 H), 0.89 (s, 9 H), 0.89–0.92 (m, 1 H), 0.90 (s, 18 H), 0.92 (d, *J* = 7.1 Hz, 3 H), 0.96 (d, *J* = 6.8 Hz, 3 H), 0.99–1.05 (m, 1 H), 1.09 (d, *J* = 6.7 Hz, 3 H), 1.22–1.46 (m, 5 H), 1.60–1.66 (m, 3 H), 1.73–1.76 (m, 1 H), 2.43 (m, 1 H), 2.56 (m, 1 H), 2.78 (m, 1 H), 3.41 (m, 1 H), 3.53 (dd, *J* = 2.7, 7.6 Hz, 1 H), 3.75 (m, 1 H), 3.91 (m, 1 H), 4.40 (br. t, *J* = 8.6 Hz, 1 H), 5.11 (d, *J* = 10.2 Hz, 1 H), 5.19–5.27 (m, 2 H), 5.38–5.48 (m, 2 H), 5.57 (d, *J* = 11.4 Hz, 1 H), 6.10 (t, *J* = 11.0 Hz, 1 H), 6.22 (dd, *J* = 9.0, 15.5 Hz, 1 H), 6.58–6.67 (m, 2 H), 7.36 (dd, *J* = 11.4, 15.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.8 (CH_3), –4.7 (CH_3), –4.4 (CH_3), –4.1 (CH_3), –3.8 (CH_3), –3.7 (CH_3), –3.5 (CH_3), 7.4 (CH_3), 15.6 (CH_3), 17.7 (CH_3), 18.0 (C_0), 18.1 (C_0), 18.5 (C_0), 18.7 (CH_3), 20.3 (CH_3), 20.5 (CH_3), 25.8 (CH_3), 25.9 (CH_3), 26.0 (CH_3), 26.2 (CH_3), 30.7 (CH), 31.9 (CH_2), 32.0 (CH_2), 35.5 (CH), 36.2 (CH), 37.1 (CH), 38.1 (CH), 41.0 (CH), 42.3 (CH_2), 45.0 (CH_2), 66.5 (CH), 72.4 (CH), 76.5 (CH), 77.3 (CH), 79.3 (CH), 114.6 (CH), 117.8 (CH_2), 127.4 (CH), 130.1 (CH), 131.5 (CH), 132.2 (CH), 132.7 (CH), 135.1 (CH), 147.3 (CH), 147.9 (CH), 169.2 (C_0) ppm. IR (neat): $\tilde{\nu}$ = 774, 836, 1005, 1027, 1081, 1255, 1377, 1461, 1600, 1636, 1686, 2855, 2927, 2955, 3417 cm^{-1}. HRMS (ESI): calcd. for $C_{56}H_{109}O_7Si_4$: 1005.72559 [*M* – H]$^-$; found 1005.72635.

(3*Z*,5*E*,7*R*,8*S*,10*R*,11*Z*,13*S*,14*R*,15*S*,17*S*,20*R*,21*R*,22*S*)-8,10,14,20-Tetrakis(*tert*-butyldimethylsilyloxy)-22-[(*S*,*Z*)-hexa-3,5-dien-2-yl]-7,13,15,17,21-pentamethyloxacyclodocosa-3,5,11-trien-2-one (32a): To a solution of the *seco*-acid **31a** (18.0 mg, 0.018 mmol, 1 equiv.) in THF (2.2 mL) cooled to 0 °C, Et_3N (15 μL, 0.108 mmol, 6 equiv.) and 2,4,6-trichlorobenzoyl chloride (14 μL, 0.09 mmol, 5 equiv.) were added. The reaction was stirred at 0 °C for 1 h and monitored by TLC (90:10 hexane/EtOAc; R_f(anhydride) = 0.4) before being added to a 4-DMAP (22.0 mg, 0.18 mmol, 10 equiv.) solution in toluene (8.9 mL) at room temperature. The mixture was

stirred at room temperature for 24 h (TLC: 97:3 hexane/EtOAc; R_f(macrolactone) = 0.31) and the solvent was removed in vacuo. The residue was diluted with Et_2O (22 mL) and water (16 mL), layers were separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (2 × 15 mL), dried with Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash chromatography (9:1 hexane/DCM; R_f(macrolactone) = 0.13) to give macrolactone **32a** (14.0 mg, 80% yield) as a pale yellow oil; R_f = 0.31 (97:3 hexane/EtOAc). $[\alpha]_D^{21}$ = –19.6 (c = 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 6 H), 0.05 (s, 3 H), 0.06 (s, 9 H), 0.07 (s, 6 H), 0.84–0.85 (m, 6 H), 0.86–0.89 (m, 6 H), 0.89–0.90 (br. s, 27 H), 0.92 (s, 9 H), 1.01 (d, J = 6.8 Hz, 3 H), 1.10 (d, J = 7.0 Hz, 3 H), 1.11 (m, 2 H), 1.15–1.32 (m, 4 H), 1.38–1.55 (m, 3 H), 1.62 (m, 1 H), 1.78–1.86 (m, 1 H), 2.41–2.47 (m, 1 H), 2.47–2.54 (m, 1 H), 3.05 (m, 1 H), 3.41 (d, J = 2.8 Hz, 1 H), 3.56 (m, 1 H), 3.94 (m, 1 H), 4.41 (t, J = 8.8 Hz, 1 H), 5.12–5.28 (m, 4 H), 5.43 (t, J = 10.4 Hz, 1 H), 5.50–5.54 (m, 2 H), 6.05 (t, J = 11.0 Hz, 1 H), 6.16 (dd, J = 9.1, 15.5 Hz, 1 H), 6.53 (t, J = 11.5 Hz, 1 H), 6.61 (dt, J = 10.6, 16.8 Hz, 1 H), 7.17 (dd, J = 11.2, J = 15.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.0 (CH_3), –4.8 (CH_3), –4.4 (CH_3), –4.1 (CH_3), –3.8 (CH_3), –3.7 (CH_3), –3.3 (CH_3), 10.7 (CH_3), 14.1 (CH_3), 14.3 (CH_3), 18.0 (C_0), 18.1 (CH_3), 18.1 (C_0), 18.7 (C_0), 18.7 (CH_3), 21.2 (CH_3), 25.8 (CH_3), 25.9 (CH_3), 26.3 (CH_3), 29.5 (CH_2), 29.7 (CH_2), 30.2 (CH), 34.5 (CH), 37.9 (CH), 39.3 (CH), 40.0 (CH), 41.1 (CH), 43.8 (CH_2), 44.8 (CH_2), 66.5 (CH), 72.4 (CH), 73.1 (CH), 77.3 (CH), 81.8 (CH), 116.7 (CH), 118.1 (CH_2), 127.6 (CH), 130.0 (CH), 131.5 (CH), 132.1 (CH), 132.4 (CH), 133.4 (CH), 143.7 (CH), 146.2 (CH), 166.4 (C_0) ppm. IR (neat): $\tilde{\nu}$ = 662, 743, 799, 1020, 1260, 1413, 1462, 1637, 1709, 2854, 2927, 2961 cm^{-1}. HRMS (ESI): calcd. for $C_{56}H_{108}O_6Si_4Na$: 1011.71152 [M + Na]$^+$; found 1011.71340.

(3*Z*,5*E*,7*R*,8*S*,10*R*,11*Z*,13*S*,14*R*,15*S*,17*S*,20*R*,21*S*,22*S*)-22-[(*S*,*Z*)-Hexa-3,5-dien-2-yl]-8,10,14,20-tetrahydroxy-7,13,15,17,21-pentamethyloxacyclodocosa-3,5,11-trien-2-one (1a): To a solution of macrolactone **32a** (10.0 mg, 10.2 μmol, 1 equiv.) in THF (1.34 mL) kept at 0 °C in a plastic vial, HF·Py (0.34 mL) was added dropwise over 2 min, and the solution was allowed to slowly warm to room temperature. The reaction was stirred for 20 h, then it was cooled to 0 °C, diluted with EtOAc (7.0 mL) and quenched with a satd. aq. $NaHCO_3$ solution (7.0 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash chromatography (3:7 hexane/EtOAc) to give (+)-9-*epi*-dictyostatin (**1a**) (3.8 mg, 70% yield) as a white powder; R_f = 0.54 (100% EtOAc). $[\alpha]_D^{31}$ = +43.4 (c = 0.17, $CHCl_3$). ^{1}H NMR (400 MHz, C_6D_6): δ = 0.85 (d, J = 6.7 Hz, 3 H), 0.92 (d, J = 6.5 Hz, 3 H), 0.93 (d, J = 6.5 Hz, 3 H), 0.99 (d, J = 6.6 Hz, 6 H), 1.03 (d, J = 7.0 Hz, 3 H), 1.24–1.58 (m, 7 H), 1.69–1.84 (m, 3 H), 1.83–1.94 (m, 2 H), 2.19–2.28 (m, 1 H), 2.81–2.96 (m, 2 H), 3.18–3.22 (m, 1 H), 3.26–3.35 (m, 1 H), 3.41–3.53 (m, 2 H), 3.90–3.96 (m, 1 H), 4.21 (br. s, 1 H), 4.60 (br. s, 1 H), 4.98–5.02 (m, 2 H), 5.09 (t, J = 16.7 Hz, 1 H), 5.27–5.38 (m, 2 H), 5.44 (dd, J = 4.4, 11.6 Hz, 1 H), 5.56 (d, J = 11.3 Hz, 1 H), 5.74 (dd, J = 6.2, 15.8 Hz, 1 H), 5.98 (t, J = 11.0 Hz, 1 H), 6.25 (t, J = 11.3 Hz, 1 H), 6.58 (dt, J = 10.6, 16.7 Hz, 1 H), 7.89 (dd, J = 11.3, 15.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 9.4 (CH_3), 14.9 (CH_3), 16.7 (CH_3), 17.6 (CH_3), 18.5 (CH_3), 21.9 (CH_3), 30.3 (CH), 32.9 (CH_2), 33.5 (CH_2), 33.6 (CH), 35.1 (CH), 35.9 (CH), 40.7 (CH), 41.6 (CH_2), 41.7 (CH_2), 42.2 (CH), 71.1 (CH), 73.8 (CH), 74.2 (CH), 76.6 (CH), 77.7 (CH), 116.3 (CH), 118.0 (CH_2), 127.5 (CH), 130.5 (CH), 132.5 (CH), 133.1 (CH), 133.8 (CH), 133.9 (CH), 146.2 (CH), 146.9 (CH), 167.2 (C_0) ppm. IR (neat): $\tilde{\nu}$ = 665, 740, 804, 1019, 1380, 1415, 1460, 1602, 1637, 1685, 1709, 2927, 2961, 3380 cm^{-1}. HRMS (ESI): calcd. for $C_{32}H_{52}O_6Na$: 555.36561 [M + Na]$^+$; found 555.36537.

(3*R*,4*S*,5*S*,7*S*,10*R*,11*R*,12*S*,13*S*)-10,14-Bis(*tert*-butyldimethylsilanyloxy)-12-(4-methoxy-benzyloxy)-3,5,7,11,13-pentamethyltetradec-1-yn-4-ol (22b): Triphenylphosphane (recrystallized from ethanol prior to use, 5.8 mg, 22 μmol, 0.05 equiv.), the crude aldehyde obtained from alcohol **21**[7j] (276 mg, 0.44 mmol, 1 equiv.) and (*S*)-mesylbutynol **6b** (98 mg, 0.66 mmol, 1.5 equiv.) were sequentially added to a cooled (–78 °C) solution of $Pd(OAc)_2$ (5 mg, 22 μmol, 0.05 equiv.) in THF (4.5 mL). Diethylzinc (1.0 M in hexane, 1.35 mL, 1.35 mmol, 3 equiv.) was added over 15 min. After 10 min, the temperature was raised to –20 °C and the reaction mixture was stirred overnight. The mixture was then quenched with satd. aq. NH_4Cl/Et_2O, 1:1. The Et_2O layer was washed with brine, dried and concentrated in vacuo. The residue was purified by flash column chromatography (95:5 hexane/EtOAc) to afford the product **22b** (252 mg, 84% over two steps) as a yellow oil with high diastereoselectivity (dr > 95:5); R_f = 0.39 (8:2 hexane/EtOAc). $[\alpha]_D^{23}$ = –4.6 (c = 0.51, $CHCl_3$). ^{1}H NMR (400 MHz, C_6D_6): δ = 0.20 (s, 6 H), 0.26 (s, 6 H), 1.00 (d, J = 6.4 Hz, 3 H), 1.10 (d, J = 6.8 Hz, 3 H), 1.03–1.15 (m, 1 H), 1.13 (s, 9 H), 1.18 (s, 9 H), 1.22 (d, J = 6.8 Hz, 3 H), 1.26 (d, J = 6.8 Hz, 3 H), 1.30 (d, J = 7.2 Hz, 3 H), 1.46–1.95 (m, 7 H), 2.06–2.20 (m, 3 H), 2.68 (m, 1 H), 3.05 (m, 1 H), 3.43 (s, 3 H), 3.79–4.00 (m, 4 H), 4.76 (d, J_{AB} = 11.2 Hz, 1 H, upfield part of an AB system), 4.82 (d, J_{AB} = 11.2 Hz, 1 H, downfield part of an AB system), 6.96 (d, J = 8.4 Hz, 2 H), 7.48 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = –4.7 (CH_3), –3.6 (CH_3), –3.4 (CH_3), 11.1 (CH_3), 16.0 (CH_3), 17.3 (CH_3), 18.8 (CH_3), 18.9 (C_0), 19.0 (C_0), 21.9 (CH_3), 26.3 (CH_3), 26.4 (CH_3), 31.0 (CH), 31.5 (CH), 32.0 (CH_2), 35.7 (CH), 39.9 (CH), 40.6 (CH_2), 40.8 (CH), 55.2 (CH_3), 65.6 (CH_2), 71.8 (CH), 74.6 (CH_2), 75.6 (CH), 79.6 (CH), 81.4 (CH), 114.5 (CH), 129.5 (CH), 132.6 (C_0), 160.0 (C_0) ppm. IR (neat): $\tilde{\nu}$ = 3309, 2960, 2933, 2850, 2663, 2655, 1727, 1613, 1514, 1470, 1462, 1386, 1360, 1301, 1255 cm^{-1}. HRMS (ESI): calcd. for $C_{39}H_{72}O_5Si_2Na$: 699.48105 [M + Na]$^+$; found 699.47937.

(5*S*,6*S*,8*S*,11*R*,12*R*,13*S*,14*S*)-5-[(*R*)-But-3-yn-2-yl]-11-[(*tert*-butyldimethylsilyl)oxy]-13-[(4-methoxybenzyl)oxy]-2,2,3,3,6,8,12,14,17,17,18,18-dodecamethyl-4,16-dioxa-3,17-disilanonadecane (23b): 2,6-Lutidine (0.22 mL, 1.85 mmol, 5 equiv.) and TBSOTf (0.26 mL, 1.11 mmol, 3 equiv.) were added dropwise to a stirred solution of **22b** (252 mg, 0.37 mmol, 1 equiv.) in DCM (9.3 mL) cooled to 0 °C. After stirring at 0 °C for 1.5 h, the reaction was quenched by adding satd. aq. NH_4Cl (3.5 mL) dropwise, then it was warmed to room temperature. Layers were separated and the aqueous phase was extracted with DCM (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried with Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash chromatography (98:2 hexane/EtOAc) to give the desired product **23b** (234 mg, 80% yield) as a colorless oil; R_f = 0.62 (85:15 hexane/EtOAc). $[\alpha]_D^{22}$ = –4.8 (c = 0.3, $CHCl_3$). ^{1}H NMR (400 MHz, C_6D_6): δ = 0.09 (s, 6 H), 0.11 (s, 3 H), 0.12 (s, 3 H), 0.14 (s, 3 H), 0.15 (s, 3 H),0.99 (d, J = 6.1 Hz, 3 H), 1.01 (s, 9 H), 1.05 (s, 9 H), 1.06 (s, 9 H), 1.11 (d, J = 7.1 Hz, 3 H), 1.13 (d, J = 7.1 Hz, 3 H), 1.19 (d, J = 6.9 Hz, 3 H), 1.23 (d, J = 7.1 Hz, 3 H), 1.28–1.35 (m, 2 H), 1.50–1.58 (m, 2 H), 1.59–1.70 (m, 2 H), 1.79–1.86 (m, 1 H), 1.90 (d, J = 2.5 Hz, 1 H), 2.02 (m, 3 H), 2.65 (m, 1 H), 3.31 (s, 3 H), 3.42 (dd, J = 3.9, 4.9 Hz, 1 H), 3.69 (dd, J = 3.9, 6.9 Hz, 1 H), 3.73 (dd, J = 3.4, 9.7 Hz, 1 H), 3.81 (m, 1 H), 3.87 (m, 1 H), 4.64 (d, J_{AB} = 11.1 Hz, 1 H, upfield part of an AB system), 4.71 (d, J_{AB} = 11.1 Hz, 1 H, downfield part of an AB

system), 6.84 (d, J = 8.6 Hz, 2 H), 7.36 (d, J = 8.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 (CH_3), –5.2 (CH_3), –4.3 (CH_3), –4.1 (CH_3), –4.0 (CH_3), –3.9 (CH_3), 10.1 (CH_3), 15.3 (CH_3), 16.7 (CH_3), 18.1 (C_0), 18.2 (CH_3), 18.3 (C_0), 18.4 (C_0), 20.9 (CH_3), 25.9 (CH_3), 26.0 (CH_3), 26.1 (CH_3), 30.2 (CH), 30.5 (CH), 31.0 (CH_2), 31.4 (CH_2), 35.1 (CH), 38.8 (CH), 39.7 (CH), 40.3 (CH_2), 55.3 (CH_3), 64.6 (CH_2), 69.9 (CH), 73.9 (CH_2), 74.3 (CH), 78.8 (CH), 80.9 (CH), 87.3 (C_0), 113.7 (CH), 128.9 (CH), 131.6 (C_0), 158.9 (C_0) ppm. IR (neat): $\tilde{\nu}$ = 625, 669, 774, 836, 939, 1040, 1079, 1172, 1251, 1302, 1361, 1387, 1463, 1514, 1614, 2856, 2929 cm^{-1}. HRMS (ESI): calcd. for $C_{45}H_{86}O_5Si_3Na$: 813.56753 [M + Na]$^+$; found 813.56975.

(5*S*,6*S*,8*S*,11*R*,12*R*,13S,14*S*)-11-[(*tert*-Butyldimethylsilyl)oxy]-5-[(*R*)-4-iodobut-3-yn-2-yl]-13-[(4-methoxybenzyl)oxy]-2,2,3,3,6,8,12,14,17,17,18,18-dodecamethyl-4,16-dioxa-3,17-disilanonadecane (24b): A 1.6 M solution of *n*BuLi in hexane (0.22 mL, 0.35 mmol, 1.2 equiv.) was added dropwise over 5 min to a solution of alkyne **23b** (231 mg, 0.29 mmol, 1 equiv.) in THF (1.5 mL) at –50 °C. After 1 h, a solution of iodine (125 mg, 0.50 mmol, 1.7 equiv.) in THF (0.1 mL) was added. The mixture was stirred at –50 °C for 30 min, then warmed to room temperature over 30 min. After quenching by the addition of a satd. aq. $Na_2S_2O_3$ solution (0.8 mL) and brine (0.8 mL), the mixture was extracted with EtOAc (3 × 3 mL) and the combined organic layers were washed with brine (2 × 4 mL). The organic phase was dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (95:5 hexane/EtOAc) to give the desired product **24b** (268 mg, 100% yield) as a colorless oil; R_f = 0.41 (95:5 hexane/EtOAc). $[\alpha]_D^{28}$ = –0.9 (c = 0.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 9 H), 0.06 (s, 3 H), 0.07 (s, 3 H), 0.09 (s, 3 H), 0.89 (d, J = 7.0 Hz, 3 H), 0.92 (s, 9 H), 0.92 (s, 9 H), 0.93 (s, 9 H), 0.94 (d, J = 7.0 Hz, 3 H), 0.95 (d, J = 7.0 Hz, 3 H), 0.98 (d, J = 6.9 Hz, 3 H), 1.17 (d, J = 7.1 Hz, 3 H), 1.28–1.33 (m, 3 H), 1.35–1.44 (m, 3 H), 1.58–1.62 (m, 1 H), 1.73–1.82 (m, 2 H), 1.89 (m, 1 H), 2.76 (m, 1 H), 3.40 (t, J = 4.4 Hz, 1 H), 3.48 (dd, J = 4.2, 6.9 Hz, 1 H), 3.61–3.70 (m, 3 H), 3.80 (s, 3 H), 4.48 (d, J_{AB} = 10.9 Hz, 1 H, upfield part of an AB system), 4.56 (d, J_{AB} = 10.9 Hz, 1 H, downfield part of an AB system), 6.87 (d, J = 8.7 Hz, 2 H), 7.26 (d, J = 8.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4 (CH_3), –5.3 (C_0), –5.2 (CH_3), –4.2 (CH_3), –4.1 (CH_3), –4.0 (CH_3), –3.9 (CH_3), 10.1 (CH_3), 15.3 (CH_3), 16.7 (CH_3), 18.1 (C_0), 18.2 (CH_3), 18.3 (C_0), 18.3 (C_0), 20.8 (CH_3), 25.9 (CH_3), 26.0 (CH_3), 26.1 (CH_3), 30.5 (CH), 31.1 (CH_2), 31.4 (CH_2), 32.5 (CH), 35.0 (CH), 38.9 (CH), 39.7 (CH), 39.9 (CH_2), 55.3 (CH_3), 64.7 (CH_2), 73.9 (CH_2), 74.4 (CH), 79.0 (CH), 80.9 (CH), 97.6 (C_0), 113.7 (CH), 128.9 (CH), 131.7 (C_0), 158.9 (C_0) ppm. IR (neat): $\tilde{\nu}$ = 670, 773, 836, 1038, 1078, 1172, 1250, 1302, 1361, 1387, 1462, 1514, 1614, 1677, 2208, 2855, 2928, 2954 cm^{-1}. HRMS (ESI): calcd. for $C_{45}H_{85}IO_5Si_3Na$: 939.46417 [M + Na]$^+$; found 939.46313.

(5*S*,6*S*,8*S*,11*R*,12*R*,13*S*,14*S*)-11-[(*tert*-Butyldimethylsilyl)oxy]-5-[(*R*,*Z*)-4-iodobut-3-en-2-yl]-13-[(4-methoxybenzyl)oxy]-2,2,3,3,6,8,12,14,17,17,18,18-dodecamethyl-4,16-dioxa-3,17-disilanonadecane (25b): A solution of iodoalkyne **24b** (147 mg, 0.16 mmol, 1 equiv.) in THF (0.4 mL) and *i*PrOH (0.4 mL) at room temperature was treated with TEA (30 μL, 0.21 mmol, 1.3 equiv.) and NBSH (38.0 mg, 0.18 mmol, 1.1 equiv.). After 12 h, additional TEA (10 μL, 0.10 mmol, 0.6 equiv.) and NBSH (17.0 mg, 0.08 mmol, 0.5 equiv.) were added, and the mixture was stirred for 12 h. The reaction was quenched by adding water (1.0 mL) and the mixture was extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with brine (2 × 3 mL), dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (95:5 hexane/EtOAc) to give the desired product **25b** (147 mg, 100% yield) as a colorless oil; R_f = 0.85 (8:2 hexane/EtOAc). $[\alpha]_D^{24}$ = –14.3 (c = 0.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 6 H), 0.05 (s, 3 H), 0.06 (s, 3 H), 0.07 (s, 3 H), 0.08 (s, 3 H), 0.81 (d, J = 6.9 Hz, 3 H), 0.90 (d, J = 7.1 Hz, 3 H), 0.91 (s, 12 H), 0.92 (s, 9 H), 0.93 (s, 9 H), 0.97 (d, J = 6.8 Hz, 3 H), 0.98 (d, J = 6.8 Hz, 3 H), 0.99–1.02 (m, 1 H), 1.22–1.32 (m, 2 H), 1.36–1.49 (m, 3 H), 1.58–1.62 (m, 1 H), 1.66–1.73 (m, 1 H), 1.78 (m, 1 H), 1.88 (m, 1 H), 2.68 (m, 1 H), 3.46 (dd, J = 4.1, 6.9 Hz, 1 H), 3.49 (dd, J = 1.8, 5.1 Hz, 1 H), 3.62–3.69 (m, 3 H), 3.80 (s, 3 H), 4.47 (d, J_{AB} = 10.9 Hz, 1 H, upfield part of an AB system), 4.55 (d, J_{AB} = 10.9 Hz, 1 H, downfield part of an AB system), 6.06 (d, J = 7.3 Hz, 1 H), 6.38 (dd, J = 7.3, 8.8 Hz, 1 H), 6.86 (d, J = 8.7 Hz, 2 H), 7.25 (d, J = 8.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 (CH_3), –5.2 (CH_3), –4.2 (CH_3), –3.9 (CH_3), –3.7 (CH_3), 10.2 (CH_3), 15.3 (CH_3), 15.5 (CH_3), 18.2 (C_0), 18.3 (C_0), 18.8 (CH_3), 20.6 (CH_3), 26.8 (CH_3), 29.7 (CH_2), 30.5 (CH), 31.5 (CH_2), 36.5 (CH), 39.0 (CH), 39.8 (CH), 41.2 (CH_2), 41.6 (CH), 55.3 (CH_3), 64.7 (CH_2), 74.0 (CH_2), 74.3 (CH), 79.0 (CH), 80.4 (CH), 81.0 (CH), 113.7 (CH), 128.9 (CH), 131.7 (C_0), 144.2 (CH), 159.0 (C_0) ppm. IR (neat): $\tilde{\nu}$ = 773, 836, 1038, 1078, 1171, 1249, 1301, 1360, 1387, 1461, 1514, 1614, 1677, 2855, 2928, 2954 cm^{-1}. HRMS (ESI): calcd. for $C_{45}H_{87}IO_5Si_3Na$: 941.47982 [M + Na]$^+$; found 941.47890.

(2*S*,3*S*,4*R*,5*R*,8*S*,10*S*,11*S*,12*R*,*Z*)-5,11-Bis[(*tert*-butyldimethylsilyl)oxy]-14-iodo-3-[(4-methoxybenzyl)oxy]-2,4,8,10,12-pentamethyltetradec-13-en-1-ol (26b): A solution of compound **25b** (147 mg, 0.16 mmol, 1 equiv.) in THF (0.8 mL) at 0 °C was treated with a solution of HF·Py in THF/pyridine [3.6 mL, prepared by slow addition of commercially available 70% HF in pyridine (0.31 mL) to a mixture of pyridine (1.1 mL) and THF (2.2 mL)]. The reaction mixture was warmed to room temperature and stirred for 4 h. After quenching the reaction by the addition of satd. aq. $NaHCO_3$ (6 mL), the mixture was extracted with EtOAc (4 × 10 mL). The combined organic extracts were washed with satd. aq. $CuSO_4$ (3 × 10 mL) and brine (2 × 10 mL), dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (9:1 hexane/EtOAc) to give the desired product **26b** (102 mg, 80% yield) as a colorless oil; R_f = 0.29 (8:2 hexane/EtOAc). $[\alpha]_D^{25}$ = –9.0 (c = 0.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 3 H), 0.06 (s, 3 H), 0.07 (s, 3 H), 0.08 (s, 3 H), 0.82 (d, J = 6.9 Hz, 3 H), 0.89 (d, J = 6.8 Hz, 3 H), 0.91 (s, 9 H), 0.92 (s, 9 H), 0.98 (d, J = 7.1 Hz, 3 H), 1.01 (d, J = 6.9 Hz, 3 H), 1.11 (d, J = 7.0 Hz, 3 H), 1.20–1.70 (m, 8 H), 1.88 (m, 1 H), 1.95 (m, 1 H), 2.68 (m, 1 H), 3.44–3.49 (m, 2 H), 3.56–3.64 (m, 2 H), 3.78–3.82 (m, 1 H), 3.80 (s, 3 H), 4.53 (s, 2 H), 6.06 (d, J = 7.3 Hz, 1 H), 6.38 (dd, J = 7.4, 8.8 Hz, 1 H), 6.87 (d, J = 8.6 Hz, 2 H), 7.26 (d, J = 8.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4 (CH_3), –4.2 (CH_3), –3.8 (CH_3), –3.7 (CH_3), 10.1 (CH_3), 15.5 (CH_3), 15.8 (CH_3), 18.2 (C_0), 18.3 (C_0), 18.8 (CH_3), 20.5 (CH_3), 26.0 (CH_3), 26.1 (CH_3), 30.5 (CH), 31.8 (CH_2), 31.9 (CH_2), 36.6 (CH), 37.0 (CH), 40.7 (CH), 41.1 (CH_2), 41.6 (CH), 55.3 (CH_3), 65.2 (CH_2), 73.8 (CH), 75.2 (CH_2), 79.0 (CH), 80.4 (CH), 85.9 (CH), 113.9 (CH), 129.3 (CH), 130.6 (C_0), 144.2 (CH), 159.3 (C_0) ppm. IR (neat): $\tilde{\nu}$ = 772, 806, 835, 1037, 1077, 1251, 1302, 1378, 1462, 1514, 1612, 2852, 2925, 2955, 3447 cm^{-1}. HRMS (ESI): calcd. for $C_{39}H_{73}IO_5Si_2Na$ [M + Na]$^+$: 827.39334; found 827.39306.

(2*R*,3*R*,4*R*,5*R*,8*S*,10*S*,11*S*,12*R*,*Z*)-5,11-Bis[(*tert*-butyldimethylsilyl)oxy]-14-iodo-3-[(4-methoxybenzyl)oxy]-2,4,8,10,12-pentamethyltetradec-13-enal (27b): A solution of alcohol **26b** (91 mg, 0.11 mmol 1 equiv.) in DCM (0.6 mL) was treated at 0 °C with pyridine (23 μL, 0.28 mmol, 2.5 equiv.) and DMP (58 mg, 0.14 mmol, 1.2 equiv.). The reaction mixture was warmed to room temperature and stirred for 1 h. After completion of the reaction, satd. aq.

$NaHCO_3$ (2.0 mL) and $Na_2S_2O_3$ (205 mg, 0.82 mmol) were added. The resulting mixture was stirred for 30 min, then the phases were separated and the aqueous phase was extracted with Et_2O (3 × 4 mL). The combined organic extracts were washed with brine (2 × 5 mL), dried (Na_2SO_4) and evaporated under reduced pressure, providing the crude aldehyde **27b**, which was used without further purification; R_f = 0.60 (8:2 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 3 H), 0.05 (s, 3 H), 0.06 (s, 3 H), 0.07 (s, 3 H), 0.82 (d, J = 6.9 Hz, 3 H), 0.88 (d, J = 6.4 Hz, 3 H), 0.90 (s, 9 H), 0.92 (s, 9 H), 0.98 (d, J = 7.0 Hz, 3 H), 1.00 (d, J = 6.9 Hz, 3 H), 1.15 (d, J = 7.0 Hz, 3 H), 1.27–1.36 (m, 3 H), 1.38–1.43 (m, 2 H), 1.53–1.69 (m, 3 H), 1.87 (m, 1 H), 2.67 (m, 1 H), 2.78 (m, 1 H), 3.48 (dd, J = 1.9, 5.1 Hz 1 H), 3.67 (m, 2 H), 3.80 (s, 3 H), 4.49 (s, 2 H), 6.06 (d, J = 7.3 Hz, 1 H), 6.37 (dd, J = 7.3, 8.8 Hz, 1 H), 6.86 (d, J = 8.7 Hz, 2 H), 7.23 (d, J = 8.6 Hz, 2 H), 9.80 (d, J = 2.3 Hz, 1 H) ppm.

(5*S*,6*S*,8*S*,11*R*)-5-[(*R*,*Z*)-4-Iodobut-3-en-2-yl]-11-{(2*R*,3*S*,4*S*,*Z*)-3-[(4-methoxybenzyl)oxy]-4-methylocta-5,7-dien-2-yl}-2,2,3,3,6,8,13,13,14,14-decamethyl-4,12-dioxa-3,13-disilapentadecane (3b): To a slurry of $CrCl_2$ (69 mg, 0.57 mmol, 5 equiv.) in THF (1.1 mL), obtained by sonication and cooled to 0 °C, freshly prepared aldehyde **27b** (0.11 mmol, 1 equiv.) in THF (0.4 mL) and (1-bromoallyl)trimethylsilane (**7**, 122 mg, 0.63 mmol, 5.6 equiv.) were added. The resulting mixture was stirred for 3 h at room temperature before being re-cooled to 0 °C and quenched by the addition of MeOH (0.5 mL) and 6 N aqueous KOH (1.0 mL). After stirring for 20 h at room temperature, the phases were separated and the aqueous layer was extracted with DCM (4 × 5 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (100:0.5 hexane/EtOAc) to give the desired product **3b** (86 mg, 92% yield over two steps) as a colorless oil; R_f = 0.50 (95:5 hexane/EtOAc). $[\alpha]_D^{22}$ = –0.6 (c = 0.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 3 H), 0.06 (s, 3 H), 0.07 (s, 3 H), 0.08 (s, 3 H), 0.79 (d, J = 6.9 Hz, 3 H), 0.84 (d, J = 6.3 Hz, 3 H), 0.85–0.97 (m, 2 H), 0.92 (s, 9 H), 0.93 (s, 9 H), 0.95 (d, J = 7.4 Hz, 3 H), 0.97 (d, J = 7.3 Hz, 3 H), 1.10 (d, J = 6.9 Hz, 3 H), 1.18–1.37 (m, 4 H), 1.48–1.54 (m, 1 H), 1.57–1.67 (m, 2 H), 2.67 (m, 1 H), 2.98 (m, 1 H), 3.33 (dd, J = 3.3, 7.8 Hz, 1 H), 3.46 (dd, J = 1.9, 5.1 Hz, 1 H), 3.61 (m, 1 H), 3.80 (s, 3 H), 4.49 (d, J_{AB} = 10.6 Hz, 1 H, upfield part of an AB system), 4.56 (d, J_{AB} = 10.6 Hz, 1 H, downfield part of an AB system), 5.10 (d, J = 10.1 Hz, 1 H), 5.18 (dd, J = 1.8, 16.8 Hz, 1 H), 5.58 (t, J = 10.6 Hz, 1 H), 6.01 (t, J = 11.1 Hz, 1 H), 6.06 (d, J = 7.3 Hz, 1 H), 6.37 (dd, J = 7.3, 8.8 Hz, 1 H), 6.58 (td, J = 10.7, 16.8 Hz, 1 H), 6.87 (d, J = 8.7 Hz, 2 H), 7.28 (d, J = 8.7 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4 (CH_3), –4.2 (CH_3), –3.7 (CH_3), –3.5 (CH_3), 9.3 (CH_3), 15.5 (CH_3), 18.2 (C_0), 18.3 (C_0), 18.7 (CH_3), 18.8 (CH_3), 20.5 (CH_3), 26.0 (CH_3), 26.1 (CH_3), 30.2 (CH), 31.6 (CH_2), 32.2 (CH_2), 35.3 (CH), 36.4 (CH), 40.6 (CH), 41.1 (CH2), 41.6 (CH), 55.3 (CH_3), 72.8 (CH), 75.0 (CH_2), 79.1 (CH), 80.4 (CH), 84.4 (CH), 113.7 (CH), 117.2 (CH_2), 128.9 (CH), 129.1 (CH), 131.4 (C_0), 132.4 (CH), 134.6 (CH), 144.2 (CH), 159.0 (C_0) ppm. IR (neat): $\tilde{\nu}$ = 772, 804, 835, 868, 1039, 1179, 1257, 1361, 1377, 1462, 1514, 1613, 2854, 2925, 2956 cm^{-1}. HRMS (ESI): calcd. for $C_{42}H_{75}IO_4Si_2Na$: 849.41408 [M + Na]$^+$; found 849.41270.

Methyl (2*Z*,4*E*,6*R*,7*S*,9*S*,10*Z*,12*R*,13*S*,14*S*,16*S*,19*R*,20*R*,21*S*,22*S*,23*Z*)-7,13,19-Tris[(*tert*-butyldimethylsilyl)oxy]-9-hydroxy-21-[(4-methoxybenzyl)oxy]-6,12,14,16,20,22-hexamethylhexacosa-2,4,10,23,25-pentaenoate (28b): To a solution of *t*BuLi (1.7 M in pentane, 0.15 mL, 0.23 mmol, 2.2 equiv.) in Et_2O (0.2 mL) kept at –78 °C under argon atmosphere, a solution of vinyl iodide **3b** (86 mg, 0.104 mmol, 1 equiv.) in Et_2O (0.4 mL) was added. After stirring for 30 min, dimethylzinc (2.0 M in toluene, 0.08 mL, 0.17 mmol, 1.6 equiv.) was added dropwise and the reaction mixture was further stirred at –78 °C for 15 min. A solution of aldehyde **2** (51 mg, 0.16 mmol, 1.5 eq, azeotropically dried with toluene) in Et_2O (0.5 mL) was added dropwise, and the mixture was stirred for 1 h at –78 °C. The reaction was quenched with water (2.0 mL), warmed to room temperature and diluted with Et_2O (3.0 mL). Phases were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with brine (2 × 5 mL), dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (10:0.3 hexane/EtOAc) and the following compounds were isolated (the reported R_f values were obtained using 8:2 hexane/EtOAc as the eluent): (i) de-iodinated alkene C10-C26 (R_f = 0.67, 36 mg); (ii) mixture of unknown products (R_f = 0.45–0.48, <5% compared to the 9*S* addition product); (iii) 9*S* addition product **28b** (R_f = 0.41, 42 mg, 40% yield, light yellow oil); (iv) unreacted aldehyde C1-C9 **2** (R_f = 0.37, 29 mg); (v) unknown product (R_f = 0.29, < 5% compared to the 9*S* addition product); R_f = 0.41 (8:2 hexane/EtOAc). $[\alpha]_D^{29}$ = –10.6 (c = 0.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 6 H), 0.07 (s, 3 H), 0.08 (s, 6 H), 0.13 (s, 3 H), 0.72–0.78 (m, 1 H), 0.83 (d, J = 6.4 Hz, 3 H), 0.84 (d, J = 6.9 Hz, 3 H), 0.88–0.91 (m, 5 H), 0.90 (s, 9 H), 0.91 (s, 9 H), 0.92 (s, 9 H), 0.95 (d, J = 6.8 Hz, 3 H), 1.07 (d, J = 6.9 Hz, 3 H), 1.10 (d, J = 6.9 Hz, 3 H), 1.17–1.41 (m, 6 H), 1.45–1.55 (m, 1 H), 1.61–1.68 (m, 1 H), 2.01 (br. s, 1 H), 2.55 (m, 1 H), 2.69 (m, 1 H), 2.98 (m, 1 H), 3.30–3.34 (m, 2 H), 3.61 (m, 1 H), 3.72 (s, 3 H), 3.80 (s, 3 H), 3.95 (m, 1 H), 4.49 (d, J_{AB} = 10.6 Hz, 1 H, upfield part of an AB system), 4.54–4.59 (m, 1 H), 4.55 (d, J_{AB} = 10.8 Hz, 1 H, downfield part of an AB system), 5.09 (d, J = 10.1 Hz, 1 H), 5.17 (dd, J = 1.7, 16.8 Hz, 1 H), 5.33 (dd, J = 8.8, 10.8 Hz, 1 H), 5.51–5.58 (m, 2 H), 5.59 (d, J = 11.5 Hz, 1 H), 5.96–6.06 (m, 2 H), 6.53–6.62 (m, 2 H), 6.86 (d, J = 8.7 Hz, 2 H), 7.28 (d, J = 8.8 Hz, 2 H), 7.37 (dd, J = 11.3, 15.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.5 (CH_3), –4.4 (CH_3), –4.3 (CH_3), –3.7 (CH_3), –3.6 (CH_3), –3.5 (CH_3), 9.3 (CH_3), 14.5 (CH_3), 16.0 (CH_3), 18.1 (C_0), 18.2 (C_0), 18.4 (C_0), 18.8 (CH_3), 20.1 (CH_3), 20.8 (CH_3), 25.9 (CH_3), 26.0 (CH_3), 26.2 (CH_3), 30.3 (CH), 31.0 (CH_2), 32.2 (CH_2), 35.0 (CH), 35.2 (CH), 35.7 (CH), 40.4 (CH_2), 40.6 (CH), 41.0 (CH_2), 43.1 (CH), 51.0 (CH_3), 55.3 (CH_3), 64.2 (CH), 72.3 (CH), 72.8 (CH), 75.0 (CH_2), 80.5 (CH), 84.4 (CH), 113.7 (CH), 115.6 (CH), 117.2 (CH_2), 126.8 (CH), 128.9 (CH), 129.1 (CH), 131.4 (CH), 131.4 (C_0), 132.4 (CH), 134.6 (CH), 135.0 (CH), 145.5 (CH), 147.2 (CH), 159.0 (C_0), 166.9 (C_0) ppm. IR (neat): $\tilde{\nu}$ = 773, 806, 836, 1039, 1080, 1174, 1252, 1377, 1462, 1514, 1602, 1638, 1721, 2855, 2926, 2955, 3427 cm^{-1}. HRMS (ESI): calcd. for $C_{59}H_{106}O_8Si_3Na$: 1049.70877 [M + Na]$^+$; found 1049.70714.

Methyl (2*Z*,4*E*,6*R*,7*S*,9*S*,10*Z*,12*R*,13*S*,14*S*,16*S*,19*R*,20*S*,21*S*,22*S*,23*Z*)-7,9,13,19-Tetrahydroxy-21-[(4-methoxybenzyl)oxy]-6,12,14,16,20,22-hexamethylhexacosa-2,4,10,23,25-pentaenoate (28b-acetonide precursor): To a solution of **28b** (12.0 mg, 11.6 μmol, 1 equiv.) in THF (1.5 mL) kept at 0 °C in a plastic vial, HF·Py (0.35 mL) was added dropwise over 2 min, and the solution was allowed to slowly warm to room temperature. The reaction mixture was stirred for 24 h, then it was cooled to 0 °C, diluted with EtOAc (8 mL) and quenched with a satd. aq. $NaHCO_3$ solution (8 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash chromatography (1:1 hexane/EtOAc) to give the desired de-silylated product (6.0 mg, 76% yield) as a white powder; R_f = 0.15 (1:1 hexane/EtOAc). ^{1}H NMR (400 MHz, C_6D_6): δ = 0.84 (d, J = 5.4 Hz, 3 H), 0.95 (d, J = 6.9 Hz, 3 H), 0.97 (d, J =

7.7 Hz, 3 H), 0.99 (d, J = 7.5 Hz, 3 H), 1.04 (d, J = 6.8 Hz, 3 H), 1.07 (d, J = 6.5 Hz, 3 H), 1.24–1.36 (m, 4 H), 1.52–1.71 (m, 7 H), 2.24 (m, 1 H), 2.82–2.89 (m, 2 H), 3.06 (m, 1 H), 3.30 (s, 3 H), 3.31 (m, 1 H), 3.38 (s, 3 H), 3.75 (s, 1 H), 3.93 (m, 1 H), 4.34 (d, J_{AB} = 10.2 Hz, 1 H, upfield part of an AB system), 4.60 (d, J_{AB} = 10.2 Hz, 1 H, downfield part of an AB system), 4.83 (m, 1 H), 5.08 (d, J = 10.0 Hz, 1 H), 5.14–5.24 (m, 2 H), 5.49 (t, J = 10.2 Hz, 1 H), 5.60 (d, J = 11.3 Hz, 1 H), 5.67 (t, J = 9.3 Hz, 1 H), 6.02–6.13 (m, 2 H), 6.31 (t, J = 11.2 Hz, 1 H), 6.71 (dt, J = 10.6, 16.8 Hz, 1 H), 6.81 (d, J = 7.7 Hz, 2 H), 7.29 (d, J = 7.7 Hz, 2 H), 7.84 (m, 1 H) ppm. HRMS (ESI): calcd. for $C_{41}H_{64}O_8Na$: 707.44934 [M + Na]$^+$; found 707.44853.

(*R*,2*Z*,4*E*)-Methyl 6-((4*S*,6*S*)-6-{(1*Z*,3*R*,4*S*,5*S*,7*S*,10*R*,11*S*,12*S*,13*S*,14*Z*)-4,10-Dihydroxy-12-[(4-methoxybenzyl)oxy]-3,5,7,11,13-pentamethylheptadeca-1,14,16-trien-1-yl}-2,2-dimethyl-1,3-dioxan-4-yl)hepta-2,4-dienoate (28b-acetonide): A small crystal of PPTS was added to a solution of **28b**-acetonide precursor (6.0 mg, 8.8 μmol) in 2,2-dimethoxypropane (0.45 mL) and DCM (0.1 mL). The reaction mixture was stirred at room temperature for 2 h, then quenched with satd. aq. $NaHCO_3$ (5 mL). Phases were separated and the aqueous layer was extracted with DCM (3 × 5 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (8:2 hexane/EtOAc) to give **28b**-acetonide (6.3 mg, 100% yield) as a colorless oil; R_f = 0.59 (1:1 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87–0.91 (m, 7 H), 0.94 (d, J = 6.8 Hz, 3 H), 0.96 (d, J = 7.0 Hz, 3 H), 1.03 (d, J = 6.8 Hz, 3 H), 1.08 (d, J = 6.9 Hz, 3 H), 1.11–1.15 (m, 1 H), 1.24–1.29 (m, 2 H), 1.33 (s, 3 H), 1.38 (s, 3 H), 1.42–1.50 (m, 3 H), 1.64–1.77 (m, 4 H), 2.63 (dd, J = 7.4 Hz, 16.3, 1 H), 2.70 (br. s, 1 H), 3.04–3.10 (m, 2 H), 3.41 (m, 1 H), 3.65–3.76 (m, 2 H), 3.72 (s, 3 H), 3.79 (s, 3 H), 4.41 (d, J_{AB} = 10.3 Hz, 1 H, upfield part of an AB system), 4.54 (dd, J = 6.5, 15.6, Hz, 1 H), 4.68 (d, J_{AB} = 10.3 Hz, 1 H, downfield part of an AB system), 5.13 (d, J = 10.2 Hz, 1 H), 5.22 (d, J = 16.8 Hz, 1 H), 5.35 (m, 1 H), 5.46 (m, 2 H), 5.61 (d, J = 11.3 Hz, 1 H), 6.08 (m, 2 H), 6.58 (t, J = 11.3 Hz, 1 H), 6.66 (m, 1 H), 6.84 (d, J = 8.6 Hz, 2 H), 7.24 (m, 2 H), 7.39 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 6.7 (CH_3), 14.1 (CH_3), 15.6 (CH_3), 17.3 (CH_3), 18.2 (CH_3), 21.2 (CH_3), 24.4 (CH_3), 25.2 (CH_3), 30.2 (CH), 31.7 (CH_2), 32.4 (CH_2), 32.5 (CH), 35.5 (CH), 35.9 (CH), 36.6 (CH_2), 37.6 (CH_2), 39.0 (CH), 41.6 (CH), 51.1 (CH_3), 55.3 (CH_3), 63.0 (CH), 69.7 (CH), 74.1 (CH_2), 75.2 (CH), 79.1 (CH), 87.6 (CH), 100.7 (C_0), 113.8 (CH), 115.7 (CH), 117.8 (CH_2), 120.3 (CH), 127.0 (CH), 129.5 (CH), 130.3 (CH), 130.9 (C_0), 132.4 (CH), 135.3 (CH), 136.6 (CH), 145.5 (CH), 146.9 (CH), 159.3 (C_0), 166.9 (C_0) ppm. HRMS (ESI): calcd. for $C_{44}H_{68}O_8Na$: 747.48064 [M + Na]$^+$; found 747.48058.

Methyl (2*Z*,4*E*,6*R*,7*S*,9*S*,10*Z*,12*R*,13*S*,14*S*,16*S*,19*R*,20*R*,21*S*,22*S*,23*Z*)-7,9,13,19-Tetrakis[(*tert*-butyldimethylsilyl)oxy]-21-[(4-methoxybenzyl)oxy]-6,12,14,16,20,22-hexamethylhexacosa-2,4,10,23,25-pentaenoate (29b): 2,6-Lutidine (9 μL, 78 μmol, 4 equiv.) and TBSOTf (9 μL, 39 μmol, 2 equiv.) were added dropwise to a stirred solution of **28b** (20.0 mg, 19.5 μmol, 1 equiv.) in DCM (0.2 mL) cooled to –78 °C. After stirring at –78 °C for 2 h, the reaction was quenched by adding satd. aq. $NaHCO_3$ (1.5 mL) dropwise, then it was warmed to room temperature. The mixture was diluted with DCM (5 mL), layers were separated and the aqueous phase was extracted with DCM (3 × 5 mL). The combined organic extracts were washed with brine (2 × 5 mL), dried with Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash chromatography (95:5 hexane/EtOAc) to give the desired product **29b** (22.2 mg, 100% yield) as a pale yellow oil; R_f = 0.80 (8:2 hexane/EtOAc). $[\alpha]_D^{29}$ = –14.7 (c = 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 3 H), 0.04 (s, 6 H), 0.07 (s, 6 H), 0.08 (s, 6 H), 0.10 (s, 3 H), 0.83 (d, J = 6.8 Hz, 6 H), 0.82–0.95 (m, 8 H), 0.84 (s, 9 H), 0.90 (s, 9 H), 0.91 (s, 9 H), 0.92 (s, 9 H), 1.04 (d, J = 6.8 Hz, 3 H), 1.10 (d, J = 6.9 Hz, 3 H), 1.20–1.39 (m, 5 H), 1.47–1.55 (m, 2 H), 1.59–1.67 (m, 2 H), 2.53 (m, 1 H), 2.62 (m, 1 H), 2.97 (m, 1 H), 3.31–3.35 (m, 2 H), 3.61 (m, 1 H), 3.72 (s, 3 H), 3.80 (s, 3 H), 3.92 (m, 1 H), 4.49–4.57 (m, 1 H), 4.50 (d, J_{AB} = 10.6 Hz, 1 H, upfield part of an AB system), 4.54 (d, J_{AB} = 10.6 Hz, 1 H, downfield part of an AB system), 5.09 (d, J = 10.6 Hz, 1 H), 5.17 (d, J = 16.8 Hz, 1 H), 5.26 (dd, J = 9.3, 10.9 Hz, 1 H), 5.55–5.62 (m, 2 H), 5.59 (d, J = 11.1 Hz, 1 H), 5.97–6.02 (m, 2 H), 6.52–6.62 (m, 2 H), 6.86 (d, J = 8.6 Hz, 2 H), 7.27 (d, J = 8.8 Hz, 2 H), 7.36 (dd, J = 11.3, 15.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.5 (CH_3), –4.3 (CH_3), –4.2 (CH_3), –4.1 (CH_3), –4.0 (CH_3), –3.7 (CH_3), –3.5 (CH_3), –2.9 (CH_3), 9.2 (CH_3), 13.5 (CH_3), 16.7 (CH_3), 18.1 (C_0), 18.2 (C_0), 18.4 (C_0), 18.9 (CH_3), 20.9 (CH_3), 20.6 (CH_3), 25.8 (CH_3), 25.9 (CH_3), 26.0 (CH_3), 26.2 (CH_3), 29.7 (CH_2), 30.1 (CH), 31.6 (CH_2), 34.3 (CH), 35.1 (CH), 36.1 (CH), 40.5 (CH), 41.0 (CH_2), 43.4 (CH_2), 43.5 (CH), 51.0 (CH_3), 55.3 (CH_3), 66.7 (CH), 72.2 (CH), 72.7 (CH), 75.1 (CH_2), 80.3 (CH), 84.4 (CH), 113.6 (CH), 115.4 (CH), 117.2 (CH_2), 126.8 (CH), 128.9 (CH), 129.0 (CH), 131.3 (CH), 131.4 (C_0), 132.3 (CH), 132.4 (CH), 134.5 (CH), 145.6 (CH), 147.3 (CH), 158.9 (C_0), 166.9 (C_0) ppm. IR (neat): $\tilde{\nu}$ = 773, 802, 836, 1005, 1040, 1082, 1174, 1251, 1462, 1514, 1602, 1638, 1721, 2855, 2927, 2955 cm^{-1}. HRMS (ESI): calcd. for $C_{65}H_{120}O_8Si_4Na$: 1163.79525 [M + Na]$^+$; found 1163.79475.

Methyl (2*Z*,4*E*,6*R*,7*S*,9*S*,10*Z*,12*R*,13*S*,14*S*,16*S*,19*R*,20*R*,21*S*,22*S*,23*Z*)-7,9,13,19-Tetrakis[(*tert*-butyldimethylsilyl)oxy]-21-hydroxy-6,12,14,16,20,22-hexamethylhexacosa-2,4,10,23,25-pentaenoate (30b): DDQ (5.7 mg, 25 μmol, 1.3 equiv.) was added to a solution of the PMB ether **29b** (22.2 mg, 19.5 μmol, 1 equiv.) in DCM (0.6 mL) stirred at 0 °C in the presence of 7 μL of a KH_2PO_4/K_2HPO_4 buffer solution (pH = 7). The reaction was stirred at 0 °C for 1 h before being quenched by dropwise addition of satd. aq. $NaHCO_3$ (8 mL). After diluting with DCM (18 mL), layers were separated and the aqueous phase was extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (6:4 hexane/DCM) to give the desired product **30b** (17.0 mg, 85% yield) as a colorless oil; R_f = 0.38 (95:5 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 3 H), 0.05 (s, 9 H), 0.07 (s, 3 H), 0.09 (s, 6 H), 0.11 (s, 3 H), 0.87–0.94 (m, 11 H), 0.89 (s, 9 H), 0.90 (s, 9 H), 0.91 (s, 9 H), 0.92 (s, 9 H), 0.95 (d, J = 6.7 Hz, 6 H), 1.04 (d, J = 6.8 Hz, 3 H), 1.25–1.34 (m, 3 H), 1.38–1.44 (m, 2 H), 1.50–1.71 (m, 4 H), 2.35 (br. s, 1 H), 2.53 (m, 1 H), 2.63 (m, 1 H), 2.80 (m, 1 H), 3.35 (m, 1 H), 3.48 (dd, J = 2.2, 7.6 Hz, 1 H), 3.73 (s, 3 H), 3.74–3.78 (m, 1 H), 3.93 (m, 1 H), 4.54 (t, J = 8.8 Hz, 1 H), 5.12 (d, J = 10.3 Hz, 1 H), 5.21 (d, J = 16.9 Hz, 1 H), 5.22–5.28 (m, 1 H), 5.42 (t, J = 10.5 Hz, 1 H), 5.56–5.63 (m, 1 H), 5.59 (d, J = 11.0 Hz, 1 H), 5.99 (dd, J = 7.1, 15.5 Hz, 1 H), 6.09 (t, J = 11.1 Hz, 1 H), 6.55 (t, J = 11.4 Hz, 1 H), 6.63 (td, J = 10.8, 17.1 Hz, 1 H), 7.36 (dd, J = 11.3, 15.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4 (CH_3), –4.3 (CH_3), –4.2 (CH_3), –4.1 (CH_3), –4.0 (CH_3), –3.8 (CH_3), –3.7 (CH_3), –2.9 (CH_3), 6.7 (CH_3), 14.1 (CH_3), 15.6 (CH_3), 17.7 (CH_3), 18.0 (C_0), 18.1 (C_0), 18.4 (C_0), 20.7 (CH_3), 21.0 (CH_3), 25.8 (CH_3), 25.9 (CH_3), 26.0 (CH_3), 26.1 (CH_3), 30.9 (CH), 31.0 (CH_2), 31.6 (CH_2), 34.2 (CH), 36.0 (CH), 36.2 (CH), 37.5 (CH), 41.1 (CH_2), 43.4 (CH_2), 43.5 (CH), 51.1 (CH_3), 66.7 (CH), 72.2 (CH), 77.3 (CH), 77.9 (CH), 80.2 (CH), 115.4 (CH), 117.7 (CH_2), 126.8 (CH), 129.8 (CH), 131.2 (CH), 132.3 (CH), 132.5 (CH), 135.4 (CH), 145.6 (CH), 147.3

(CH), 166.9 (C_0) ppm. HRMS (ESI): calcd. for $C_{57}H_{112}O_7Si_4Na$: 1043.73773 [M + Na]$^+$; found 1043.73677.

(2*Z*,4*E*,6*R*,7*S*,9*S*,10*Z*,12*R*,13*S*,14*S*,16*S*,19*R*,20*R*,21*S*,22*S*,23*Z*)-7,9,13,19-Tetrakis[(*tert*-butyldimethylsilyl)oxy]-21-hydroxy-6,12,14,16,20,22-hexamethylhexacosa-2,4,10,23,25-pentaenoic Acid (31b): To a stirred solution of the ester **30b** (17.0 mg, 16.6 μmol, 1 equiv.) in THF (0.8 mL) and EtOH (2.1 mL), KOH (1 N solution in water, 0.17 mL) was added, and the reaction was refluxed (bath temperature: 52 °C) for 24 h. The mixture was diluted with Et_2O (8 mL) and satd. aq. NH_4Cl (3.5 mL); layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated under reduced pressure. The product was purified by flash chromatography (9:1 hexane/EtOAc) to afford the *seco*-acid **31b** (16.7 mg, 100% yield) as a colorless oil; R_f = 0.22 (8:2 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 3 H), 0.04 (s, 3 H), 0.05 (s, 3 H), 0.06 (s, 3 H), 0.07 (s, 3 H), 0.09 (s, 6 H), 0.11 (s, 3 H), 0.86 (s, 9 H), 0.86–0.92 (m, 11 H), 0.89 (s, 9 H), 0.91 (s, 9 H), 0.92 (s, 9 H), 0.95 (d, J = 6.7 Hz, 6 H), 1.04 (d, J = 6.8 Hz, 3 H), 1.28–1.44 (m, 4 H), 1.51–1.61 (m, 2 H), 1.63–1.72 (m, 3 H), 2.53 (m, 1 H), 2.63 (m, 1 H), 2.80 (m, 1 H), 3.35 (m, 1 H), 3.48 (dd, J = 2.6 Hz, 7.5, 1 H), 3.76 (m, 1 H), 3.90 (m, 1 H), 4.53 (t, J = 8.9 Hz, 1 H), 5.12 (d, J = 10.3 Hz, 1 H), 5.21 (d, J = 16.8 Hz, 1 H), 5.27 (m, 1 H), 5.42 (t, J = 10.4 Hz, 1 H), 5.60 (m, 2 H), 6.02–6.11 (m, 2 H), 6.58–6.68 (m, 2 H), 7.34 (dd, J = 11.4 Hz, 15.3, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4 (CH_3), –4.3 (CH_3), –4.2 (CH_3), –4.0 (CH_3), –3.8 (CH_3), –3.7 (CH_3), –3.0 (CH_3), 6.8 (CH_3), 14.0 (CH_3), 15.8 (CH_3), 17.7 (CH_3), 18.1 (C_0), 18.4 (C_0), 20.6 (CH_3), 20.9 (CH_3), 25.8 (CH_3), 25.9 (CH_3), 26.0 (CH_3), 26.1 (CH_3), 30.3 (CH), 31.0 (CH_2), 31.6 (CH_2), 34.2 (CH), 36.1 (CH), 36.2 (CH), 37.7 (CH), 41.1 (CH_2), 43.5 (CH), 43.7 (CH_2), 66.7 (CH), 72.3 (CH), 76.8 (CH), 77.8 (CH), 80.1 (CH), 114.8 (CH), 117.7 (CH_2), 127.0 (CH), 130.0 (CH), 131.4 (CH), 132.3 (CH), 132.4 (CH), 135.3 (CH), 147.4 (CH), 148.2 (CH), 169.9 (C_0) ppm. HRMS (ESI): calcd. for $C_{56}H_{109}O_7Si_4$: 1005.72559 [M – H]$^-$; found 1005.72430.

(3*Z*,5*E*,7*R*,8*S*,10*S*,11*Z*,13*S*,14*R*,15*S*,17*S*,20*R*,21*R*,22*S*)-8,10,14,20-Tetrakis(*tert*-butyldimethylsilyloxy)-22-[(*S*,*Z*)-hexa-3,5-dien-2-yl]-7,13,15,17,21-pentamethyloxacyclododecosa-3,5,11-trien-2-one (32b): To a solution of the *seco*-acid **31b** (16.7 mg, 16.6 μmol, 1 equiv.) in THF (2 mL) cooled to 0 °C, Et_3N (1 μL, 0.099 mmol, 6 equiv.) and 2,4,6-trichlorobenzoyl chloride (13 μL, 0.083 mmol, 5 equiv.) were added. The reaction was stirred at 0 °C for 1 h and monitored by TLC (9:1 hexane/EtOAc; R_f(anhydride) = 0.33) before adding a 4-DMAP (18.5 mg, 0.165 mmol, 10 equiv.) solution in toluene (8 mL) at room temperature. The mixture was stirred at room temperature for 24 h (TLC: 97:3 hexane/EtOAc; R_f(macrolactone) = 0.31) and the solvent was removed in vacuo. The residue was diluted with Et_2O (20 mL) and water (14 mL), layers were separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (2 × 15 mL), dried with Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash chromatography (9:1 hexane/DCM; R_f(macrolactone) = 0.13) to give macrolactone **32b** (12.5 mg, 76% yield) as a colorless oil; R_f = 0.31 (97:3 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 3 H), 0.02 (s, 3 H), 0.05 (s, 3 H), 0.07 (s, 3 H), 0.08 (s, 3 H), 0.09 (s, 3 H), 0.10 (s, 3 H), 0.12 (s, 3 H), 0.82–0.88 (m, 10 H), 0.90 (s, 9 H), 0.91 (s, 18 H), 0.92 (s, 9 H), 0.97 (d, J = 6.7 Hz, 6 H), 1.02–1.06 (m, 1 H), 1.05 (d, J = 6.9 Hz, 3 H), 1.17–1.43 (m, 4 H), 1.49–1.61 (m, 2 H), 1.68–1-72 (m, 2 H), 1.81 (m, 1 H), 2.31 (m, 1 H), 2.57 (dt, J = 7.0 Hz, 10.8, 1 H), 3.14 (m, 1 H), 3.41–3.47 (m, 2 H), 3.80 (m, 1 H), 4.33 (br. t, 1 H), 5.14–5.24 (m, 4 H), 5.51–5.59 (m, 3 H), 6.03 (t, J = 11.0 Hz, 1 H), 6.17 (dd, J = 9.5 Hz, 15.4, 1 H), 6.58–6.68 (m, 2 H), 7.26 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.7 (CH_3), –4.5 (CH_3), –4.0 (CH_3), –3.9 (CH_3), –3.8 (CH_3), –3.5 (CH_3), –3.2 (CH_3), 9.5 (CH_3), 14.1 (CH_3), 18.0 (C_0), 18.1 (C_0), 18.3 (CH_3), 19.5 (CH_3), 19.8 (CH_3), 20.6 (CH_3), 25.9 (CH_3), 26.2 (CH_3), 31.8 (CH_2), 32.8 (CH), 33.5 (CH), 34.8 (CH), 35.0 (CH), 37.4 (CH_2), 39.0 (CH), 41.2 (CH_2), 42.4 (CH), 45.4 (CH_2), 65.0 (CH), 70.9 (CH), 72.5 (CH), 79.4 (CH), 79.7 (CH), 117.5 (CH), 118.1 (CH_2), 128.9 (CH), 129.6 (CH), 130.0 (CH), 132.0 (CH), 132.1 (CH), 135.6 (CH), 143.1 (CH), 144.7 (CH), 166.5 (C_0) ppm. HRMS (ESI): calcd. for $C_{56}H_{108}O_6Si_4Na$: 1011.71152 [M + Na]$^+$; found 1011.71116.

(3*Z*,5*E*,7*R*,8*S*,10*S*,11*Z*,13*S*,14*R*,15*S*,17*S*,20*R*,21*S*,22*S*)-22-[(*S*,*Z*)-Hexa-3,5-dien-2-yl]-8,10,14,20-tetrahydroxy-7,13,15,17,21-pentamethyloxacyclododecosa-3,5,11-trien-2-one (1b): To a solution of macrolactone **32b** (12.5 mg, 12.7 μmol, 1 equiv.) in THF (1.7 mL) kept at 0 °C in a plastic vial, HF·Py (0.43 mL) was added dropwise over 2 min, and the solution was allowed to slowly warm to room temperature. The reaction mixture was stirred for 24 h, then it was cooled to 0 °C, diluted with EtOAc (9 mL) and quenched with a satd. aq. $NaHCO_3$ solution (9 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash chromatography (2:8 hexane/EtOAc) to give **1b** (4.8 mg, 72% yield) as a white powder; R_f = 0.30 (100% EtOAc). $[a]_D^{15}$ = –8.4 (c = 0.08, $CHCl_3$). ^{1}H NMR (400 MHz, C_6D_6): δ = 0.84 (d, J = 6.5 Hz, 3 H), 0.94 (d, J = 6.8 Hz, 3 H), 0.93–0.97 (m, 1 H), 0.95 (d, J = 6.2 Hz, 3 H), 0.98 (d, J = 6.8 Hz, 3 H), 1.02 (d, J = 6.9 Hz, 3 H), 1.09 (t, J = 8.1 Hz, 3 H), 1.13–1.18 (m, 2 H), 1.38–1.49 (m, 3 H), 1.53–1.60 (m, 1 H), 1.63–1.66 (m, 1 H), 1.71–1.85 (m, 3 H), 2.10 (br. s, 1 H), 2.24 (m, 1 H), 2.38 (br. s, 1 H), 2.78 (m, 1 H), 2.96 (dd, J = 1.7, 9.0 Hz, 1 H), 3.13 (dt, J = 6.4, 17.2 Hz, 1 H), 3.51–3.55 (m, 1 H), 3.65–3.70 (m, 1 H), 4.79 (dd, J = 11.5, 7.2 Hz, 1 H), 5.00 (d, J = 10.4 Hz, 1 H), 5.08 (d, J = 16.8 Hz, 1 H), 5.16 (t, J = 10.5 Hz, 1 H), 5.38 (t, J = 5.7 Hz, 1 H), 5.49–5.69 (m, 4 H), 5.99 (t, J = 11.0 Hz, 1 H), 6.23 (t, J = 11.3 Hz, 1 H), 6.61 (dt, J = 10.6, 16.8 Hz, 1 H), 7.45 (dd, J = 11.0, 15.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 9.0 (CH_3), 16.4 (CH_3), 17.8 (CH_3), 17.9 (CH_3), 20.1 (CH_3), 20.9 (CH_3), 31.7 (CH_2), 31.9 (CH), 33.0 (CH_2), 33.3 (CH), 34.4 (CH), 36.1 (CH), 36.8 (CH_2), 40.1 (CH), 41.4 (CH_2), 43.6 (CH), 65.6 (CH), 71.4 (CH), 72.3 (CH), 78.7 (CH), 79.7 (CH), 117.8 (CH_2), 118.2 (CH), 128.7 (CH), 130.1 (CH), 132.3 (CH), 133.7 (CH), 134.5 (CH), 134.6 (CH), 142.6 (CH), 145.0 (CH), 166.4 (C_0) ppm. IR (neat): $\tilde{\nu}$ = 665, 741, 807, 1018, 1380, 1415, 1461, 1600, 1637, 1685, 1709, 2926, 2961, 3380 cm^{-1}. HRMS (ESI): calcd. for $C_{32}H_{52}O_6Na$: 555.36561 [M + Na]$^+$; found 555.36660.

Biological Assays: The binding of the ligands to the Paclitaxel binding site was measured as described previously.[32] Binding constants for compounds reversibly displacing Flutax-2 were calculated using Equigra v5.[33] Ovarian carcinoma cells A2780 and P-glycoprotein-overexpressing ovarian carcinoma cells A2780AD were cultured as described previously.[34] Cytotoxicity experiments were performed with the MTT assay modified as described previously.[35]

Supporting Information (see footnote on the first page of this article): Copies of the NMR spectra (^{1}H, ^{13}C) for all new compounds described in this paper; NOESY experiment on (–)-12,13-bis-*epi*-dictyostatin (**1b**); competition experiments between Flutax-2 and several ligands for the paclitaxel binding site.

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