Synthesis of Antineoplastic Analogs of Aplysiatoxin with Various Side Chain Structures

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ABSTRACT

We have recently developed a simplified analog of aplysiatoxin with anti-proliferative activity (**1**). To investigate the structure–activity relationship of its side chain, an alternative synthetic route of **1** has been established. Via the key intermediate **6**, *p*-hydroxyl or *o*,*m*-dihydroxyl derivatives (**4** and **5**) as well as **1** were synthesized and their biological activities were evaluated. Although the position of the hydroxyl group in the benzene ring did not change the affinity for protein kinase C isozymes or the ability to induce the Epstein-Barr virus early antigen, anti-proliferative activities against several human cancer cell lines of **1** were superior to those of **4**.

INTRODUCTION

Protein kinase C (PKC) is a family of serine/threonine kinases that play a pivotal role in cell proliferation, differentiation, and apoptosis.[1,2] Eleven PKC isozymes are classified into three groups: conventional (α, βI, βII, γ), novel (δ, ε, η, θ), and atypical (ζ, λ/ι).[3] Naturally-occurring tumor promoters such as 12-*O*-tetradecanoylphorbol 13-acetate (TPA), teleocidin B-4, and aplysiatoxin (ATX) bind to tandem C1 domains (C1A, C1B) in the regulatory regions of conventional and novel PKC isozymes, inducing their translocation to the cellular membrane, driven by an affinity for anionic phospholipids, resulting in the abnormal activation of PKC.[4]

Bryostatin 1 (bryo-1)[5] is also a potent activator of PKC isolated from the marine bryozoan *Bugula neritina*. Although bryo-1, like tumor promoters, binds to the C1 domains of PKC isozymes and activates them, it exhibits little tumor-promoting activity.[6] Bryo-1 has anticancer activity and is currently undergoing clinical trials for the treatment of solid tumors, leukemia, and lymphoma.[7] Bryo-1 is also considered to have therapeutic potential for Alzheimer's disease[8] (AD) and AIDS[9] where PKC isozymes are involved. However, the yield of bryo-1 isolated from natural sources is quite low.[10] Recently, efficient means of producing bryo-related compounds have been reported,[11–13] but it remains difficult to obtain a sufficient amount of bryos for clinical use.

While other natural and synthetic PKC activators such as TPA and teleocidin analogs also have potential for the treatment of cancer[14] and AD,[15] serious adverse effects such as gross hematuria, a grand mal seizure, syncope, and hypotension were encountered during a phase I clinical trial.[14] Pleiotropic effects including tumor-promoting activity of these compounds would thus be of particular concern. Since hydrophobicity of PKC activators generally correlates with their tumor-promoting ability,[16,17] prostratin (12-deoxyphorbol 13-acetate), a less hydrophobic phorbol ester without tumor-promoting activity, is promising in the anti-HIV therapy.[18] However, isolation yield of prostratin from natural sources was poor like bryo-1, and its binding potency for PKC isozymes was very weak.

To solve these problems, we have developed simplified analogs of ATX (**1** and **2**)[19] with less hydrophobicity. Compound **1**, synthesized in only 22 steps, behaved like bryo-1 in the translocation of PKCδ, a PKC isozyme involved in anti-tumor promotion and anti-proliferative effects in several cancer cell lines,[20,21] and in the induction of the Epstein–Barr virus early antigen (EBV-EA). The anti-proliferative activity of **1** against many human cancer cell lines was comparable to that of bryo-1.[19] In the EBV-EA induction test, **1** showed weak EA induction and suppressed the induction by the tumor promoter TPA, suggesting **1** as well as bryo-1 to be an anti-tumor promoter rather than tumor promoter.[19]

We have recently synthesized a dehydroxyl derivative of **1** (**3**), similar in affinity for PKCδ to **1**.[22] While the anti-proliferative activities of **3** against 39 human cancer cell lines were almost equivalent to those of **1**, effects on some cell lines, *e.g.*, LOX-IMVI melanoma and St-4 stomach cancer cell lines, were different from those of **1**.[22] The anti-tumor-promoting activity of **3** estimated by the EBV-EA induction test was weaker than that of **1**,18 indicating the phenolic hydroxyl group of **1** to be important for the activity. Therefore, it is necessary to investigate the influence of this group on various biological activities for the development of analogs with less adverse effects. Although the synthesis of **1** was established,[19] it is not easy to modify its side chain. Notably, derivatives with an *o*- or *p*-hydroxyl group on the benzene ring cannot be synthesized by the previous route[19] because of the oxidation at the benzyl position in the last stages of the synthesis. In this paper, we describe an alternative route for producing **1** *via* a key intermediate (**6**) with a primary hydroxyl group in the side chain. New analogs of **1** with *p*-hydroxyl (**4**) or *o*,*m*-dihydroxyl groups (**5**) were synthesized using the key intermediate, and their biological activities were evaluated.

RESULTS AND DISCUSSION

To elucidate the effects of a phenolic hydroxyl group in the benzene ring on biological activities, we planned the synthesis of **4** and **5** as shown in Scheme 1. The production of **4** and **5** could be quite difficult through

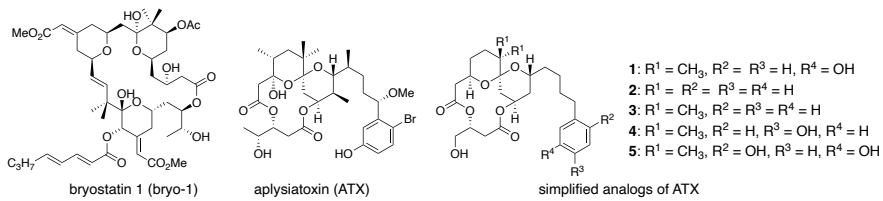
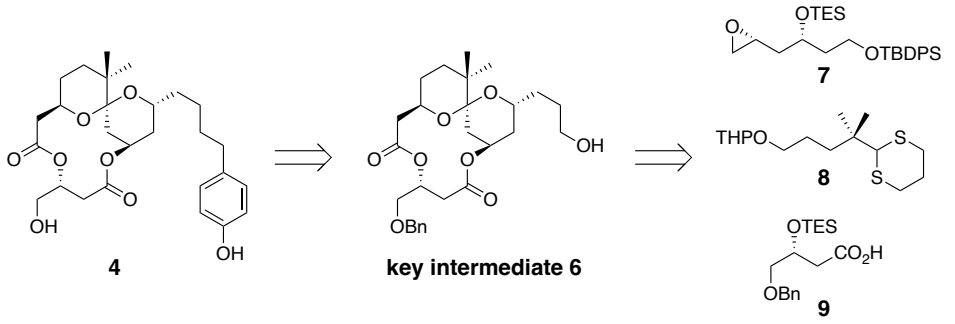


Figure 1: Structure of bryostatin 1 (bryo-1), aplysiatoxin (ATX), and simplified analogs of ATX (**1** – **5**).

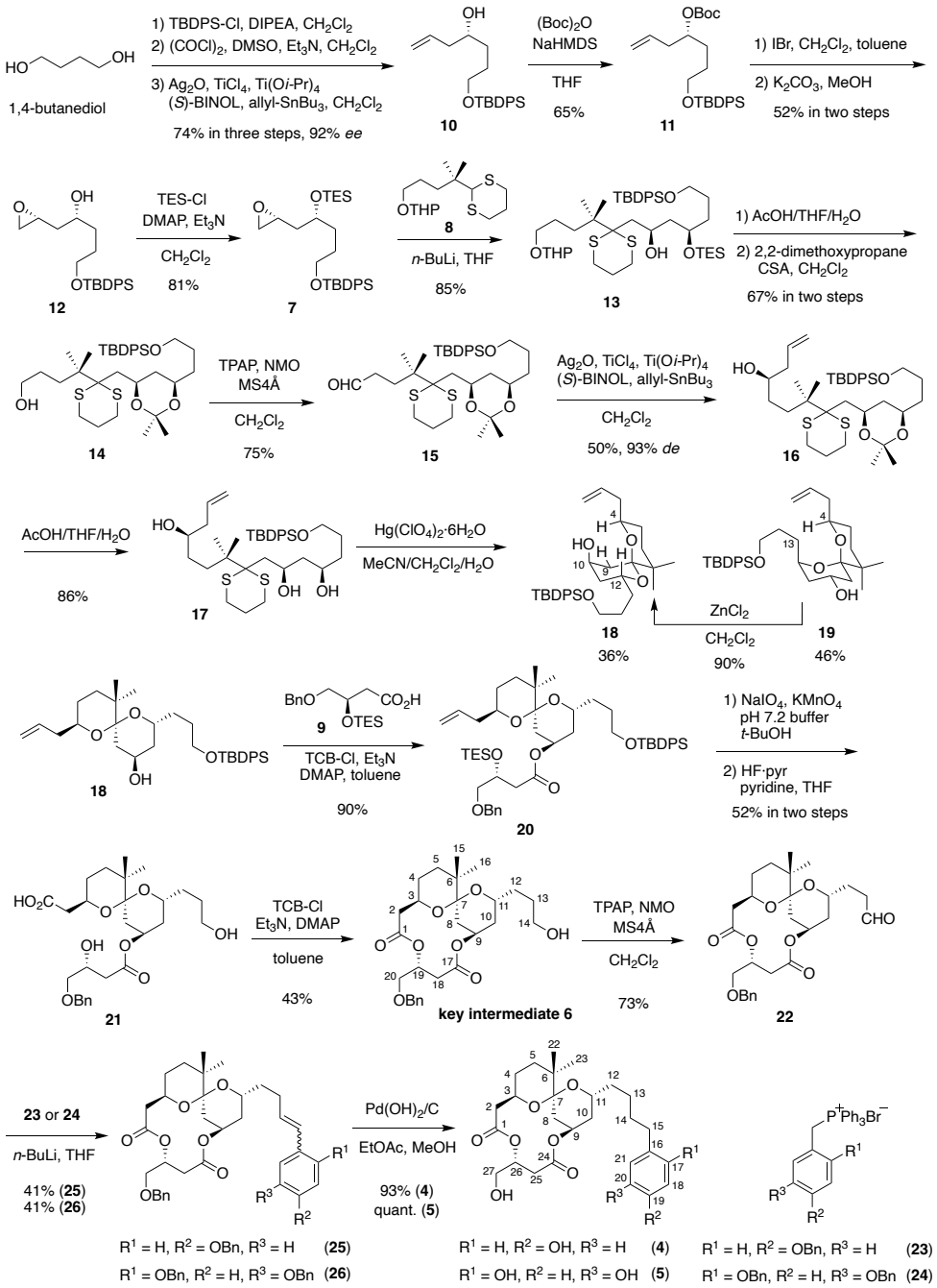


Scheme 1. Retrosynthetic analysis of **4**.

the previous route[19] where oxidative cleavage of the double bond with $KMnO_4$ was employed before final cyclization of the diolide ring. A benzyloxy group at the *o*- or *p*-position of the alkyl benzene would activate the aromatic ring to induce a side reaction (*e.g.*, oxidation at the benzyl position). Based on this, we planned an alternative route via the key intermediate **6**. This intermediate has a common structure of each derivative (**4** and **5**), and each side chain can be inserted in the final stages of the synthesis. This route also enables us to synthesize derivatives of **1** with various substituents more easily.

Synthesis of the key intermediate (**6**) was carried out by referring to our previous synthetic scheme for **1**[19] with appropriate modifications (Scheme 2). Synthesis of **6** began with the preparation of known (4*R*)-1-(*tert*-butyldiphenylsilyloxy)hept-6-en-4-ol[23] (**10**, 92% *ee*) from 1,4-butanediol in three steps including protection of one hydroxyl group with tert-butyldiphenylsilyl (TBDPS) ether, Swern oxidation, and asymmetric Maruoka's allylation.[24] Protection of the alcohol (**10**) with *tert*-butyl carbonate provided **11**. Stereoselective iodocarbonate cyclization by Duan and Smith[25] followed by treatment with K_2CO_3 in MeOH gave an epoxide (**12**). The hydroxyl group of **12** was protected with triethylsilyl (TES) ether to yield the epoxide unit (**7**).

The epoxide (**7**) was coupled with **8**, which was prepared from [(4-(1,3-dithian-2-yl)-4-methylpentyl)oxy]-triisopropylsilane,[19] to yield **13**. Selective deprotection of 2-tetrahydropyranyl (THP) and TES groups of **13**, followed by protection of a resulting diol with 2,2-dimethoxypropane afforded **14**. After several trials, it was found that THP is most appropriate to protect the hydroxyl group of **8**. Compound **14** was converted into an aldehyde (**15**) by Ley oxidation[26] followed by Maruoka's asymmetric allylation[24] to give **16** (93% *de*). Deprotection of the isopropylidene group of **16** afforded a diol (**17**). Subsequent cleavage of the dithiane gave a mixture of spiroketals (**18** and **19**) at a ratio of 1:1.3. Their configurations were determined by NOESY experiments; NOE cross-peaks were observed between H-12 and C10-OH, and between H-4 and H-$9_{eq.}$ in **18**, and between H-4 and H-13 in **19**. The undesired isomer (**19**) was converted into the



Scheme 2. Synthesis of **4** and **5**.

desired one (**18**) by chelation with zinc chloride.[27]

The carboxylic acid unit (**9**) was synthesized from (*R*)-1-(benzyloxy)-3-(1,3-dithian-2-yl)-propan-2-ol[28] prepared from (*R*)-(−)-glycidyl ether, by protection of a hydroxyl group with TES ether, cleavage of dithiane, and Pinnick oxidation.[29] Compound **18** was condensed with **9** by the method of Yamaguchi and co-workers.[30] The resultant **20** was converted to a carboxylic acid (**21**) by oxidative cleavage of the olefin followed by deprotection of TES and TBDPS. Further Yamaguchi's macrolactonization[30] afforded the key intermediate **6** in 18 steps from 1,4-butanediol with an overall yield of 0.6%. Although **21** had two hydroxyl groups, only the desired one reacted with the carboxyl group to close the ring because of the long distance between another hydroxyl group and the carboxyl group.

The synthesis of **4** and **5** was completed via the key intermediate **6**, which was converted to an aldehyde (**22**). The side chain units (**23** and **24**) were prepared by conventional methods, bromination and heating with triphenylphosphine. Wittig reactions of **22** with each side chain unit provided **25** and **26** as 2:1 and 4:5 *E*/*Z* mixtures, respectively. Finally, catalytic hydrogenation of **25** and **26** provided **4** and **5**, respectively. Compound **1** was also obtained similarly from **22** (see experimental section).

Table 1: K_i values for the inhibition of [^{3}H]PDBu binding by **1**–**5** and ATX.

PKC C1 peptide	K_i (nM)					
	1[a]	**2**[a]	**3**[b]	**4**	**5**	ATX[b]
α-C1A	63	2400	120	58 (6)[c]	180 (30)	0.40
δ-C1A	140	6800	130	170 (30)	1400 (400)	12
δ-C1B	7.4	170	9.8	6.6 (1.0)	44 (8)	0.41

[a] Cited from Nakagawa (2009).[19] [b] Cited from Yanagtia (2010).[22] [c] Standard deviation from triplicate experiments.

Table 2: Log GI_{50} Values for **1**, **3**, **4**, and Bryo-1 against Several Human Cancer Cell Lines.

Cancer type	Cell Line	Log GI_{50}			
		1[a]	**3**[b]	**4**	Bryo-1[c]
Breast	HBC-4	−6.33	−6.28	−6.32	NR[d]
	MDA-MB-231	−5.61	−5.67	−5.16	−5.20
Colon	HCC2998	−5.43	−5.53	−5.26	−5.30
Lung	NCI-H460	−5.60	−5.83	−5.81	−5.60
	A549	−5.32	−5.49	−5.12	−5.20
Melanoma	LOX-IMVI	−5.74	−5.17	−4.97	NR[d]
Stomach	St-4	−5.55	−6.05	−5.12	NR[d]
	MKN45	−5.33	−6.09	−5.14	NR[d]

[a] Cited from Nakagawa (2009).[19] [b] Cited from Yanagtia (2010).[22] [c] Cited from Wender (2002).[31] [d] Not reported.

Compounds **4** and **5** were initially evaluated for their affinity for the synthetic C1 domains of PKCα and δ by inhibition of the specific binding of [^{3}H]phorbol 12,13-dibutylate (PDBu) as reported previously.[32–34] α-C1A, the major PDBu-binding site of PKCα,[33,34] was selected as representative of conventional PKC isozymes. Both the C1A and C1B domains of PKCδ were employed since binding to these domains could be important for bryo-1-like activities.[35] The affinity of **4** for these peptides was almost

equal to that of **1** (Table 1). This suggests that the position of the phenolic hydroxyl group at the side chain might not affect the binding to PKCα and δ-C1 peptides. The side chain of **1** would interact with membrane phospholipids nonspecifically in the PKC–ligand–phospholipid ternary complex, as that of ATX.[36] In contrast, the affinity of **5** with two phenolic hydroxyl groups for PKCα and δ-C1 peptides decreased, possibly because of decreased hydrophobicity. The affinity of **5** was stronger than that of **2** lacking the dimethyl group at the spiroketal moiety, though **5** is slightly more hydrophilic than **2** (Clog P of **2**: 1.9, that of **5**: 1.6). Although the side chain of **5** appears to interact non-specifically with membrane phospholipids, the affinity of **5** for PKC isozymes might remain to some extent.

Anti-proliferative activity of **4** against a panel of 39 human cancer cell lines was evaluated as described previously.[37] Since compounds with weak affinity for PKCδ were deduced to show low anti-proliferative activity as observed in **2**,[19] only **4** was subjected to evaluation. The growth inhibitory activity was expressed as the GI_{50} (M), the concentration required to inhibit cell growth by 50% compared to an untreated control. The average of the log GI_{50} values of each 39 human cancer cell line was expressed as MG-MID.

Compound **4** showed anti-proliferative activity comparable to **1** and **3**; the MG-MID of **4** was –4.97, almost equal to those of **1** and **3** (–4.98 and –5.09, respectively). The cell lines with log GI_{50} values less than –5.00 are listed in Table 2. Compound **4** showed anti-proliferative activity comparable to **1** and **3**; the MG-MID of **4** was –4.97, almost equal to those of **1** and **3** (–4.98 and –5.09, respectively). The cell lines with log GI_{50} values less than –5.00 are listed in Table 2. Slightly stronger activity of **3** without phenolic hydroxyl group might be ascribable to its increasing membrane permeating ability.[22] While PKC binding ability of **1** and **4** were almost equal to each other, **1** showed stronger anti-proliferative activity against several of the cell lines in Table 2, especially MDA-MB-231, LOX-IMVI, and St-4 cells, than **4**. Compound **1** also showed stronger activity against LOX-IMVI than **3**. These results suggest that there might be targets other than PKC isozymes that the phenolic hydroxyl group at *meta*-position interacts with.

The most likely adverse effects of **1** and its derivatives would be tumor-promotion because these compounds possess the skeleton of tumor-promoting ATX. Hence, possible tumor-promoting activity was estimated by the Epstein–Barr virus early antigen (EBV-EA) induction test as described previously.[38] EBVs, strictly controlled by host human lymphoblastoid Raji cells, are activated by tumor promoters to produce early antigen.[39] As shown in Figure 2a, TPA, a potent tumor promoter, strongly induced EBV-EA production at 100 nM. On the other hand, **4** and **5** as well as **1** showed weak EA induction even at 1000 nM (Figure 2a), with **5** slightly weaker than **1** and **4**. Compound **1** exhibited not only weak EA-induction but also an inhibitory effect on the EA-production induced by TPA.[19] Similarly, 100 nM of **4** and **5** both significantly suppressed the EA induction by TPA (32 nM) (Figure 2b). These results suggest that anti-tumor-promoting activity might not correlate with the affinity for PKC isozymes and that the existence of a phenolic hydroxyl group would be important for inhibitory activity against tumor promoters as reported previously.[22]

In summary, we developed an alternative synthetic route for **1** to modify its side chain. Using this route via the key intermediate (**6**), new derivatives with hydroxyl groups at the *p*- or *o*,*m*-positions of the benzene ring (**4** and **5**) as well as **1** were synthesized. Many derivatives of **1** with various side chain structures would be available by this route. The affinity for PKCα and δ-C1 peptides and anti-tumor-promoting activity of **4** were almost the same as those of **1**. However, the anti-proliferative activity of **4** against several cancer cell lines was slightly different from that of **1**. Further study on the structure–activity relationship of the side chain of **1** is necessary for its structural optimization as a therapeutic lead.

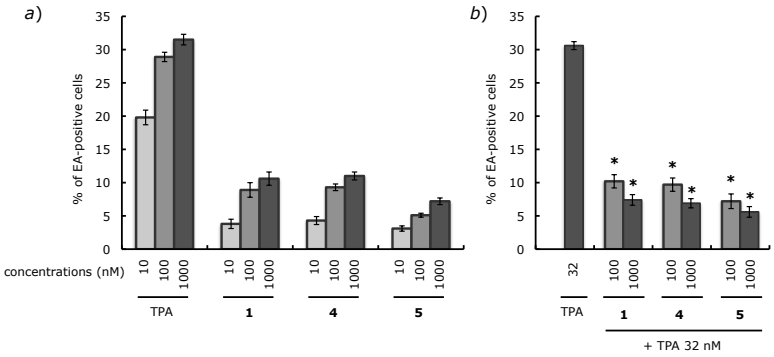


Figure 2: Epstein–Barr virus early antigen (EBV-EA)-induction test for **1**, **4**, and **5**. a) EA-inducing ability of TPA, **1**, **4**, and **5**. Percentages of EA-positive cells are shown. Error bars represent the standard error of the mean (SEM, $n = 3$). b) Inhibitory effects of **1**, **4**, and **5** on EBV-EA production induced by 32 nM of TPA. Percentages of EA-positive cells are shown. Error bars represent SEM ($n = 3$). *P<0.01 vs. TPA 32 nM (t-test).

EXPERIMENTAL

General remarks

Digital Polarimeter, Jasco P-2200; ^{1}H, ^{13}C, and 2-D NMR, AVANCE III 400 and AVANCE III 500 (Bruker, Germany, ref. TMS, 296 K); HPLC, Waters Model 600E with a Model 2487 UV detector; HR-FAB-MS and HR-EI-MS, JMS-600H and JMS-700 (JEOL, Tokyo, Japan); HPLC was carried out on an SL12S05-2510WT (silica gel, 10 mm i.d. × 250 mm) column (Yamamura Chemical Laboratory, Japan). Wako gel^{TM} C-200 (silica gel, Wako Pure Chemical Industries, Japan) and YMC A60-350/250 gel (ODS, Yamamura Chemical Laboratory) were used for column chromatography. [^{3}H]PDBu (19.6 Ci/mmol) was purchased from PerkinElmer Japan, Yokohama. All other chemicals and reagents were purchased from chemical companies and used without further purification.

Synthesis of the epoxide unit 7.

To a solution of (4*R*)-1-(*tert*-butyldiphenylsilyloxy)hept-6-en-4-ol (**10**) (1.77 g, 4.80 mmol) in THF (25 mL) was added dropwise 1 M NaHMDS in THF (6.0 mL, 6.0 mmol, 1.25 equiv.) at 4 °C. After 30 min of stirring, $(Boc)_2O$ (1.40 g, 6.42 mmol, 1.33 equiv.) was added, and the reaction mixture was stirred for 6 h at rt. The reaction was quenched with brine (30 mL) and water (10 mL), and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 1% EtOAc/hexane) to afford **11** (1.46 g, 3.12 mmol, 65%) as clear oil. Compound **11**: $[\alpha]_D$ +6.5° (c 1.28, $CHCl_3$, 20.8 °C); ^{1}H NMR δ (400 MHz, $CDCl_3$, 0.038 M) ppm: 1.04 (9H, s), 1.47 (9H, s), 1.59–1.78 (4H, m), 2.34 (2H, t, J = 7.1 Hz), 3.66 (2H, m), 4.69 (1H, m), 5.05–5.12 (2H, m), 5.76 (1H, m), 7.36–7.40 (6H, m), 7.65 (4H, m); ^{13}C NMR δ (125 MHz, $CDCl_3$, 0.107 M) ppm: 19.21, 26.85 (3C), 27.81 (3C), 28.33, 30.04, 38.71, 63.50, 76.42, 81.67, 117.80, 127.61 (4C), 129.55 (2C), 133.56 (2C), 133.93, 135.56 (4C), 153.37; HR-FAB-MS (matrix: 3-nitrobenzyl alcohol): m/z 469.2761 (MH^+, calcd for $C_{28}H_{41}O_4Si$, 469.2774).

To a solution of **11** (6.84 g, 14.6 mmol) in toluene (77 mL) was added IBr (4.50 g, 21.8 mmol, 1.5 equiv.) in CH_2Cl_2 (30 mL) dropwise at −78 °C under an Ar atmosphere. After 2 h of stirring at the same temperature, the reaction was quenched with a 1:1 mixture of 10% aq. $Na_2S_2O_3$ and saturated aq. $NaHCO_3$ (200 mL), and the reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 15% EtOAc/hexane) to afford an iodide. To a solution of the iodide in anhydrous MeOH (70 mL) was added K_2CO_3 (7.46 g, 54.0 mmol, 5 equiv.). After 3 h of stirring at rt, the reaction was quenched with H_2O (120 mL), and the reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 20% EtOAc/hexane) to yield **12** (2.88 g, 7.50 mmol, 52% in 2 steps) as clear oil. Compound **12**: $[\alpha]_D$ +7.6° (*c* 0.45, $CHCl_3$, 18.2 °C); ^{1}H NMR δ (400 MHz, $CDCl_3$, 0.038 M) ppm: 1.05 (9H, s), 1.58–1.70 (5H, m), 1.80 (1H, dt, *J* = 14.3, 4.2 Hz), 2.51 (1H, dd, *J* = 5.0, 2.7 Hz), 2.69 (1H, d, *J* = 3.5 Hz, OH), 2.78 (1H, dd, *J* = 5.0, 4.1 Hz), 3.09 (1H, m), 3.70 (2H, t, *J* = 5.7 Hz), 3.90 (1H, m), 7.36–7.43 (6H, m), 7.67 (4H, m); ^{13}C NMR δ (125 MHz, $CDCl_3$, 0.107 M) ppm: 19.21, 26.85 (3C), 28.17, 30.46, 37.11, 46.40, 48.93, 54.71, 63.33, 127.64 (4C), 129.60 (2C), 133.82 (2C), 135.56 (4C); HR-FAB-MS (matrix: 3-nitrobenzyl alcohol): *m/z* 385.2199 (MH^+, calcd for $C_{23}H_{33}O_3Si$, 385.2199).

To a solution of **12** (2.88 g, 7.50 mmol) in CH_2Cl_2 (60 mL) was added DMAP (3.70 g, 30.1 mmol, 4 equiv.) and Et_3N (5.20 mL, 37.7 mmol, 5 equiv.). To this solution was added TES-Cl (1.90 mL, 11.3 mmol, 1.5 equiv.) dropwise at 4 °C under an Ar atmosphere. After 10 min of stirring at the same temperature, the reaction mixture was stirred at rt for an additional 1.5 h. The reaction was quenched with saturated aq. $NaHCO_3$ (100 mL), and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 2% EtOAc/hexane) to yield **7** (3.0 g, 6.0 mmol, 81%) as clear oil. Compound **7**: $[\alpha]_D$ +2.3° (*c* 0.52, $CHCl_3$, 21.6 °C); ^{1}H NMR δ (400 MHz, $CDCl_3$, 0.024 M) ppm: 0.59 (6H, q, *J* = 7.9 Hz), 0.95 (9H, t, *J* = 7.9 Hz), 1.04 (9H, s) 1.58–1.63 (5H, m), 1.75 (1H, dt, *J* = 14.0, 5.9 Hz) 2.44 (1H, dd, *J* = 5.1, 2.7 Hz), 2.74 (1H, t, *J* = 4.5 Hz), 3.00 (1H, m), 3.67 (2H, m), 3.88 (1H, t, *J* = 5.4 Hz), 7.37–7.42 (6H, m), 7.66 (4H, m); ^{13}C NMR δ (125 MHz, $CDCl_3$, 0.107 M) ppm: 5.00 (3C), 6.91 (3C), 19.21, 26.85 (3C), 28.46, 33.57, 40.17, 46.92, 49.57, 63.94, 70.16, 127.60 (4C), 129.53 (2C), 134.01 (2C), 135.56 (4C); HR-FAB-MS (matrix: 3-nitrobenzyl alcohol): *m/z* 499.3057 (MH^+, calcd for $C_{29}H_{47}O_3Si_2$, 499.3064).

Synthesis of 8.

To a solution of [(4-(1,3-dithian-2-yl)-4-methylpentyl)oxy]triisopropylsilane15 (2.59 g, 7.06 mmol) in THF (20 mL) was added 1 M tetrabutylammonium fluoride in THF (9.2 mL, 9.2 mmol, 1.5 equiv.) at 4 °C. After 1.5 h of stirring at rt, the reaction was quenched with saturated aq. $NaHCO_3$ (80 mL), and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 30% EtOAc/hexane) to afford an alcohol. To a solution of the alcohol in CH_2Cl_2 (15 mL) were added PPTS (357 mg, 1.42 mmol, 0.2 equiv.) and dihydropyran (0.72 mL, 8.0 mmol, 1.25 equiv.). After 40 h of stirring at rt, the reaction was quenched with saturated aq. $NaHCO_3$ (30 mL), and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 4% EtOAc/hexane) to yield **8** (1.76 g, 5.79 mmol, 82% in 2 steps) as clear oil. Compound **8** (a racemic mixture): ^{1}H NMR δ (400 MHz, $CDCl_3$, 0.071 M) ppm: 1.09 (6H, s), 1.47-1.63 (8H, m), 1.69–1.85 (3H, m), 2.05–2.09 (1H, m), 2.88 (4H, dd, *J* = 7.9, 3.3 Hz), 3.38 (1H, dt, *J* = 9.4, 6.9 Hz), 3.50 (1H, m), 3.72 (1H, dt, *J* = 9.4, 7.0 Hz), 3.88 (1H, m), 4.03 (1H, s), 4.58 (1H, dd, *J* = 4.4, 2.7 Hz); ^{13}C NMR δ (125 MHz, $CDCl_3$, 0.141 M) ppm: 19.76, 24.21, 25.40 (2C), 25.50, 26.18, 30.78, 31.45 (2C), 36.57, 37.96, 60.68, 62.49, 68.06, 98.89;

HR-EI-MS: m/z 304.1537 (M^+, calcd for $C_{15}H_{28}O_2S_2$, 304.1531).

Synthesis of the carboxylic acid unit 9.

To a solution of (*R*)-1-(benzyloxy)-3-(1,3-dithian- 2-yl)propan-2-ol[28] (560 mg, 1.97 mmol) in THF (15 mL) were added imidazole (400 mg, 5.88 mmol, 3.0 equiv.) and TES-Cl (0.50 mL, 3.0 mmol, 1.5 equiv.) at rt. After 1.5 h of stirring at rt under an Ar atmosphere, the reaction was quenched with brine (25 mL), and the reaction mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 5% EtOAc/hexane) to afford a dithiane. To a solution of the dithiane in MeCN (16 mL) and H_2O (4.0 mL) were added $NaHCO_3$ (440 mg, 5.2 mmol, 2.9 equiv.) and methyl iodide (4.39 mL, 70.4 mmol, 39 equiv.). After 18 h of stirring at rt, the reaction was poured into H_2O (40 mL), and the mixture was extracted with EtOAc. The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 3% EtOAc/hexane) to afford an aldehyde (475 mg). To a solution of the aldehyde (20.0 mg, 0.065 mmol) in *t*-BuOH (0.5 mL) was added 2-methyl-2-butene (0.33 mL, 0.066 mmol, 10 equiv.), and then cooled at 4 °C. To the reaction mixture, a solution of $NaClO_4$ (9.5 mg, 0.091 mmol, 1.4 equiv.) in saturated aq. NaH_2PO_4 (0.5 mL) was added, and the mixture was stirred for 30 min at 4 °C. After being stirred for 1.5 h at rt, the mixture was poured into H_2O (8 mL), and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 15% EtOAc/hexane) to yield **9** (18.5 mg, 0.0571 mmol, 73%) as yellow oil. Since **9** was slightly labile at rt, it was prepared just before use and stored at –78 °C. Compound **9**: $[\alpha]_D$ +16.9° (*c* 1.00, $CHCl_3$, 8.9 °C); ^{1}H NMR δ (400 MHz, $CDCl_3$, 0.12 M) ppm: 0.60 (6H, q, J = 7.9 Hz), 0.93 (9H, t, J = 7.9 Hz), 2.52 (1H, dd, J = 15.4, 7.0 Hz), 2.69 (1H, dd, J = 15.4, 5.0 Hz), 3.40 (1H, dd, J = 9.6, 6.2 Hz), 3.49 (1H, dd, J = 9.6, 5.1 Hz), 4.29 (1H, m), 4.53 (2H, s), 7.32 (5H, m); ^{13}C NMR δ (125 MHz, $CDCl_3$, 0.099 M) ppm: 4.82 (3C), 6.69 (3C), 39.97, 68.24, 73.44, 73.77, 127.67 (2C), 127.69, 128.39 (2C), 138.00, 176.12; HR-FAB-MS (matrix: glycerol): m/z 325.1827 (MH^+, calcd for $C_{17}H_{29}O_4Si$, 325.1835).

Synthesis of the key intermediate 6.

To a solution of **8** (45 mg, 0.15 mmol, 1.9 equiv.) in THF (0.3 mL) was added 1.6 M *n*-BuLi in hexane (110 μL, 0.176 mmol, 2.2 equiv.) under an Ar atmosphere. After 1 h of stirring at rt, the reaction was cooled at 4 °C. A solution of 7 (40 mg, 0.08 mmol) in THF (0.25 mL) was then added, and the reaction mixture was stirred for 3 h at 4 °C. The reaction was quenched with saturated aq. NH_4Cl (2.5 mL), and the reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 4.5% EtOAc/hexane) to yield **13** (55 mg, 0.068 mmol, 85%) as clear oil. This procedure was repeated 47 times to give 2.46 g of **13**. Compound **13** (a diastereomeric mixture); ^{1}H NMR δ (500 MHz, $CDCl_3$, 0.030 M) ppm: 0.61 (6H, q, J = 8.2 Hz), 0.96 (9H, t, J = 8.0 Hz), 1.04 (9H, s), 1.11 (3H, s), 1.13 (3H, s), 1.53–1.72 (15H, m), 1.82–1.91 (3H, m), 2.02 (1H, dd, J = 15.6, 1.5 Hz), 2.12 (1H, dd, J = 15.6, 8.0 Hz), 2.76–2.98 (4H, m), 3.38 (1H, m), 3.50 (1H, m), 3.67 (2H, t, J = 6.0 Hz), 3.73 (1H, m), 3.87 (1H, m), 3.96 (1H, m), 4.11 (1H, s, OH), 4.33 (1H, br.t, J = 6.6 Hz), 4.58 (1H, t, J = 3.6 Hz), 7.36–7.43 (6H, m), 7.67 (4H, m); ^{13}C NMR δ (125 MHz, $CDCl_3$, 0.030 M) ppm: 5.18 (3C), 6.96 (3C), 19.25, 19.70, 22.30, 22.43, 23.14, 25.34, 25.54, 26.90 (3C), 27.17, 27.42, 28.30, 30.80, 33.04, 33.30, 45.53, 45.63, 45.68, 62.38, 63.63, 64.18, 67.81, 68.32, 70.37, 98.86, 127.60 (4C), 129.51 (2C), 134.14 (2C), 135.60 (4C); Some of the ^{13}C NMR signals were doubled according to the THP diastereomers (δ45.53 and 98.86); HR-FAB-MS (matrix: 3-nitrobenzyl alcohol): m/z 825.4410 (MNa^+, calcd for $C_{44}H_{74}O_5S_2Si_2Na$, 825.4414).

Compound **13** (2.46 g, 3.07 mmol) dissolved in AcOH, THF and H_2O (6:2:1 v/v, 63 mL) was stirred for 1.5 h at 55 °C. The solution was concentrated *in vacuo* with toluene (15 mL). The residue was diluted

with EtOAc (15 mL) and quenched with saturated aq. $NaHCO_3$ (25 mL), and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 50% EtOAc/hexane) to yield a triol. To a solution of the triol in CH_2Cl_2 (23 mL) were added 2,2-dimethoxypropane (3.50 mL, 28.8 mmol, 12 equiv.) and 10-camphorsulfonic acid (CSA, 55.3 mg, 0.238 mmol, 0.1 equiv.) at rt. The reaction mixture was stirred at rt for 2 h, and quenched with saturated aq. $NaHCO_3$ (50 mL). The resultant mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (25 mL), and silica gel (Wakogel^{TM} C-200, 1.5 g, 1 equiv. *v*/*v*) was added to the solution. The mixture was stirred at rt for 2.5 h, and then filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 25% EtOAc/hexane) to yield **14** (1.33 g, 2.07 mmol, 67% in 2 steps) as clear oil. Compound **14**: $[\alpha]_D$ +1.5° (*c* 0.26, $CHCl_3$, 14.0 °C); ^{1}H NMR δ (400 MHz, $CDCl_3$, 0.014 M) ppm: 1.05 (9H, s), 1.13 (6H, s), 1.34 (3H, s), 1.38 (3H, s), 1.52–1.72 (10H, m), 1.82 (1H, m), 2.02 (1H, m), 2.21 (1H, dd, *J* = 16.3, 2.2 Hz), 2.35 (1H, dd, *J* = 16.3, 5.3 Hz), 2.68 (2H, m), 2.84 (1H, m), 3.08 (1H, m), 3.62-3.68 (4H, dt, *J* = 12.4, 6.2 Hz), 3.81 (1H, m), 4.23 (1H, dt, *J* = 11.7, 2.5 Hz), 7.35–7.42 (6H, m), 7.66 (4H, m); ^{13}C NMR δ (100 MHz, $CDCl_3$, 0.062 M) ppm: 19.23, 19.60, 22.47, 22.62, 24.84, 26.89 (4C), 27.00, 28.01, 28.24, 30.30, 32.67, 32.93, 38.60, 43.40, 43.52, 63.44, 63.81 (2C), 68.04, 68.90, 98.52, 127.61 (4C), 129.54 (2C), 134.01, 134.04, 135.57 (4C); HR-FAB-MS (matrix: 3-nitrobenzyl alcohol): *m*/*z* 667.3302 (MNa^+, calcd for $C_{36}H_{56}O_4S_2SiNa$, 667.3287).

To a solution of **14** (480 mg, 0.745 mmol) in CH_2Cl_2 (16 mL) were added *N*-methylmorpholine *N*-oxide (131 mg, 1.12 mmol, 1.5 equiv.) and molecular sieve 4Å (MS4Å, 480 mg, 1.0 equiv. *w*/*w*). Tetrapropylammonium perruthenate (TPAP, 12.2 mg, 0.0347 mmol, 4.69 mol%) was then added, and the reaction mixture was stirred for 30 min at rt. The mixture was concentrated *in vacuo*, and the residue was purified by column chromatography (silica gel, 10% EtOAc/hexane) to yield **15** (360 mg, 0.56 mmol, 75%) as clear oil. Compound **15**: $[\alpha]_D$ +2.9° (*c* 0.56, $CHCl_3$, 23.3 °C); ^{1}H NMR δ (400 MHz, $CDCl_3$, 0.050 M) ppm: 1.05 (9H, s), 1.12 (6H, s), 1.34 (3H, s), 1.37 (3H, s), 1.51–1.72 (6H, m), 1.83 (1H, m), 2.05 (3H, m), 2.23 (1H, dd, *J* = 16.3, 2.0 Hz), 2.34 (1H, dd, *J* = 16.3, 5.4 Hz), 2.43 (2H, m), 2.70 (2H, m), 2.83 (1H, m), 3.07 (1H, m), 3.67 (2H, t, *J* = 6.3 Hz), 3.82 (1H, m), 4.23 (1H, dt, *J* = 11.7, 2.6 Hz), 7.35–7.42 (6H, m), 7.66 (4H, m), 9.78 (1H, t, *J* = 1.9 Hz); ^{13}C NMR δ (100 MHz, $CDCl_3$, 0.050 M) ppm: 19.23, 19.58, 22.61 (2C), 24.74, 26.84, 26.89 (3C), 27.04, 28.02, 29.34, 30.28, 32.69, 38.63, 40.09, 43.16, 43.65, 63.08, 63.80, 67.85, 68.85, 98.54, 127.60 (4C), 129.54 (2C), 134.01, 134.04, 135.57 (4C), 202.75; HR-FAB-MS (matrix: 3-nitrobenzyl alcohol): *m*/*z* 643.3340 (MH^+, calcd for $C_{36}H_{55}O_4S_2Si$, 643.3311).

1 M $TiCl_4$ in CH_2Cl_2 (0.37 mL, 0.37mmol, 0.32 equiv.) was diluted with CH_2Cl_2 (3.7 mL) at 4 °C under an Ar atmosphere. Ti(O*i*-Pr)$_4$ (0.34 mL, 1.2 mmol, 1.0 equiv.) was added, and the solution was stirred for 1 h at rt. Ag_2O (232 mg, 1.00 mmol, 0.83 equiv.) was added, and the solution was stirred for 5 h at rt in the dark. (*S*)-(−)-1,1'-bi-2-naphthol (430 mg, 1.5 mmol, 1.3 equiv.) was added after the solution was diluted with CH_2Cl_2 (7.4 mL). Following 2 h of stirring at rt, the dark red mixture was added to a solution of **15** (742 mg, 1.15 mmol) in Et_2O (11.1 mL) at −15 °C. Allyl – $SnBu_3$ (10.4 mL, 33.6mmol, 30 equiv.) was added, and the mixture was stirred for 1 h at the same temperature. The resulting reaction mixture was kept in a freezer at −20 °C for 18 h without stirring, and then stirred for 2 h at 4 °C. The reaction was quenched with saturated aq. NH_4Cl (25 mL), and the mixture was extracted with EtOAc. The combined organic layers were filtered and washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 6% EtOAc/hexane; ODS, 95% MeOH) to yield **16** (390 mg, 0.57 mmol, 50%, 93% de) as clear oil. Diastereomeric excess was determined by the modified Mosher's method.[40] Compound **16**: $[\alpha]_D$ +3.6° (*c* 0.80, $CHCl_3$, 15.3 °C); ^{1}H NMR δ (400 MHz, $CDCl_3$, 0.018 M) ppm: 1.05 (9H, s), 1.12 (3H, s), 1.13 (3H, s), 1.34 (3H, s), 1.38 (3H, s), 1.44–1.69 (9H, m), 1.84 (2H, m), 1.98 (1H, m), 2.15 (1H, m), 2.22 (1H, dd, *J* = 16.3, 2.2 Hz), 2.35 (2H, m), 2.68 (2H, tt, *J* = 13.6, 4.4 Hz), 2.84 (1H, m), 3.08 (1H, m), 3.60 (1H, m), 3.67 (2H, t, *J* = 6.3 Hz), 3.80 (1H, m), 4.23 (1H, dt, *J* = 9.0, 2.5 Hz), 5.13 (1H, s), 5.16 (1H, m), 5.83 (1H, m), 7.36–7.44 (6H, m), 7.66 (4H,

m); ^{13}C NMR δ (100 MHz, $CDCl_3$, 0.018 M) ppm: 19.25, 19.61, 22.48, 22.72, 24.86, 26.92 (3C), 26.96, 27.05, 28.06, 30.33, 32.06, 32.73, 32.95, 38.65, 41.87, 43.54, 43.64, 63.52, 63.86, 68.08, 68.93, 71.42, 98.55, 118.18, 127.61 (4C), 129.54 (2C), 134.08, 134.81, 135.01, 135.59 (4C); HR-FAB-MS (matrix: 3-nitrobenzyl alcohol): *m/z* 707.3589 (MNa^+, calcd for $C_{39}H_{60}O_4S_2SiNa$, 707.3600).

Compound **16** (495 mg, 0.724 mmol) was dissolved in AcOH, THF, and H_2O (4:2:1 *v/v*, 8 mL). The mixture was stirred for 50 min at 55 °C. The reaction was concentrated *in vacuo* with toluene. The residue was diluted with EtOAc (10 mL) and quenched with saturataed aq. $NaHCO_3$ (20 mL), and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 30 % EtOAc/hexane) to afford **17** (350 mg, 0.54 mmol, 75%) as a clear oil. Compound **17**: $[\alpha]_D$ +3.6° (*c* 1.32, $CHCl_3$, 12.2 °C); ^{1}H NMR δ (500 MHz, $CDCl_3$, 0.011 M) ppm: 1.04 (9H, s), 1.13 (3H, s), 1.13 (3H, s), 1.44–1.73 (9H, m), 1.80 (1H, m), 1.93–2.00 (3H, m), 2.18 (2H, m), 2.33 (1H, m), 2.83–3.01 (4H, m), 3.62 (1H, m), 3.69 (2H, t, *J* = 6.2 Hz), 3.89 (1H, m), 4.04 (1H, br.s, OH), 4.52 (1H, m, OH), 4.56 (1H, br.s), 5.15 (2H, m), 5.83 (1H, m), 7.35–7.44 (6H, m), 7.67 (4H, m); ^{13}C NMR δ (125 MHz, $CDCl_3$, 0.011 M) ppm: 19.24, 22.39, 22.63, 23.07, 26.92 (3C), 27.36, 27.54, 28.61, 32.06, 32.75, 34.30, 42.09, 44.48, 45.12, 45.59, 63.21, 64.17, 71.10, 71.29, 71.54, 118.33, 127.63 (4C), 129.55 (2C), 134.04 (2C), 134.67, 135.62 (4C); HR-FAB-MS (matrix: 3-nitrobenzyl alcohol): *m/z* 645.3498 (MH^+, calcd for $C_{36}H_{57}O_4S_2Si$, 645.3468).

To a solution of **17** (350 mg, 0.54 mmol) in MeCN (2.0 mL), CH_2Cl_2 (2.0 mL), and H_2O (2.0 mL) was added $Hg(ClO_4)_2 \cdot 6\,H_2O$ (545 mg, 1.08 mmol, 2.0 equiv.) at 4 °C. After 45 min of stirring at the same temperature, the reaction mixture was poured into EtOAc (15 mL) and saturated aq. $Na_2S_2O_3$ (25 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (5% → 10% EtOAc/hexane) to afford **18** (104 mg, 0.194 mmol, 36%) and **19** (133 mg, 0.248 mmol, 46%).

To a solution of **19** (148 mg, 0.276 mmol) in CH_2Cl_2 (6.0 mL) was added $ZnCl_2$ (112 mg, 0.824 mmol, 3.0 equiv.) at rt. After 30 min of stirring at rt, the reaction was quenched with saturated aq. $NaHCO_3$ (20 mL), and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 10 % EtOAc/hexane) to afford **18** (134 mg, 0.250 mmol, 90%) as clear oil. Compound **18**: $[\alpha]_D$ +33.1° (*c* 0.735, $CHCl_3$, 28.7 °C); ^{1}H NMR δ (500 MHz, $CDCl_3$, 0.056 M) ppm: 0.88 (3H, s), 0.95 (3H, s), 1.05 (9H, s), 1.34 (1H, m), 1.42–1.74 (10H, m), 2.20 (1H, m), 2.29 (2H, m), 3.69 (2H, t, *J* = 6.4 Hz), 3.78 (1H, t, *J* = 6.5 Hz), 3.81 (1H, d, *J* = 11.0 Hz, OH), 4.07 (1H, dt, *J* = 11.0, 3.1 Hz), 4.15 (1H, m), 5.09 (2H, m), 5.80 (1H, ddt, *J* = 17.2, 10.1, 7.2 Hz), 7.36–7.43 (6H, m), 7.67 (4H, m); ^{13}C NMR δ (125 MHz, $CDCl_3$, 0.060 M) ppm: 19.26, 22.46, 25.50, 26.37, 26.92 (3C), 28.42, 29.29, 32.26, 33.29, 36.76, 37.98, 40.87, 63.72, 64.08, 65.59, 72.59, 102.76, 117.88, 127.59 (4C), 129.50 (2C), 134.23 (2C), 134.81, 135.60 (4C); HR-FAB-MS (matrix: 3-nitrobenzyl alcohol): *m/z* 559.3204 (MNa^+, calcd for $C_{33}H_{48}O_4SiNa$, 559.3220). Compound **19**: $[\alpha]_D$ −5.2° (*c* 1.14, $CHCl_3$, 32.9 °C); ^{1}H NMR δ (500 MHz, $CDCl_3$, 0.048 M) ppm: 0.85 (3H, s), 0.96 (3H, s), 1.05 (9H, s), 1.12 (1H, dt, *J* = 12.9, 3.3 Hz), 1.32-1.72 (8H, m), 1.89 (1H, td, *J* = 13.0, 5.0 Hz), 1.98 (1H, m), 2.05–2.20 (3H, m), 3.67 (2H, m), 3.79 (1H, m), 3.89 (1H, m), 4.22 (1H, m), 4.97 (2H, m), 5.75 (1H, ddt, *J* = 17.2, 10.1, 7.2 Hz), 7.35–7.47 (6H, m), 7.67 (4H, m); ^{13}C NMR δ (125 MHz, $CDCl_3$, 0.071 M) ppm: 19.23, 22.96, 25.70, 26.90 (3C), 27.47, 29.55, 32.07, 33.63, 36.21, 36.46, 38.02, 40.70, 62.42, 63.92, 68.68, 71.33, 102.29, 116.18, 127.61 (4C), 129.54 (2C), 134.12 (2C), 135.56, 135.59 (4C); HR-FAB-MS (matrix: 3-nitrobenzyl alcohol): *m/z* 559.3222 (MNa^+, calcd for $C_{33}H_{48}O_4SiNa$, 559.3220).

To a solution of **9** (260 mg, 0.80 mmol, 1.7 equiv.) in toluene (12.5 mL) were added Et_3N (0.14 mL, 1.3 mmol, 2.8 equiv.) and 2,4,6-trichlorobenzoyl chloride (0.14 mL, 0.87 mmol, 1.9 equiv.). After 2 h of stirring at rt, the mixture was added to a solution of **18** (243 mg, 0.453 mmol) and DMAP (166 mg, 1.36 mmol, 3 equiv.) in toluene (12.5 mL) at rt. The mixture was heated to 50 °C and stirred for 1.5 h at the

same temperature. The reaction mixture was poured into H_2O (30 mL), and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 3% EtOAc/hexane) to afford **20** (343 mg, 0.407 mmol, 90%) as clear oil. Compound **20**: $[\alpha]_D$ +22.3° (*c* 0.360, $CHCl_3$, 14.7 °C); ^{1}H NMR δ (400 MHz, $CDCl_3$, 0.078 M) ppm: 0.59 (6H, q, *J* = 7.8 Hz), 0.84 (3H, s), 0.92 (9H, t, *J* = 7.8 Hz), 0.95 (3H, s), 1.05 (9H, s), 1.35–1.51 (7H, m), 1.64 (4H, m), 2.26 (3H, m), 2.49 (1H, dd, *J* = 15.3, 8.0 Hz), 2.60 (1H, dd, *J* = 15.3, 4.6 Hz), 3.37 (1H, dd, *J* = 9.5, 6.1 Hz), 3.46 (1H, br.s), 3.47 (1H, dd, *J* = 9.5, 5.3 Hz), 3.68 (2H, m), 4.23 (1H, m), 4.34 (1H, m), 4.52 (2H, d, *J* = 2.1 Hz), 4.96 (1H, d, *J* = 8.3 Hz), 5.00 (1H, d, *J* = 11.9 Hz), 5.09 (1H, t, *J* = 3.3 Hz), 5.82 (1H, ddt, *J* = 17.3, 10.2, 7.1 Hz), 7.27–7.43 (11H, m), 7.67 (4H, m); ^{13}C NMR δ (125 MHz, $CDCl_3$, 0.009 M) ppm: 4.92 (3C), 6.79 (3C), 19.26, 21.53, 25.55, 26.50, 26.59, 26.93 (3C), 28.31, 32.15, 34.24, 34.61, 36.88, 40.74, 41.06, 63.91, 64.14, 68.11, 68.44, 71.68, 73.33, 74.27, 100.07, 116.56, 127.58 (4C), 127.59 (3C), 128.33 (2C), 129.46 (2C), 134.30 (2C), 135.21, 135.60 (4C), 138.27, 171.68; HR-FAB-MS (matrix: 3-nitrobenzyl alcohol): *m*/*z* 865.4910 (MNa^+, calcd for $C_{50}H_{74}O_7Si_2Na$, 865.4871).

To a suspension of $NaIO_4$ (21.0 mg, 0.0981 mmol, 8.0 equiv.) in pH 7.2 buffer (1.0 mL) was $KMnO_4$ (1.93 mg, 0.0122 mmol, 1.0 equiv.) and stirred for 10 min at rt. The mixture was added to a solution of **20** (10.3 mg, 0.0122 mmol) in *t*-BuOH (1.0 mL). After 1 h of stirring at rt, the reaction was quenched with $Na_2S_2O_3$ (5.9 mg). The resulting mixture was poured into EtOAc (8 mL) and H_2O (8 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 10% EtOAc/hexane containing 0.5% AcOH) to afford a carboxylic acid (6.9 mg). To a solution of the carboxylic acid (35.8 mg, 0.0416 mmol) in THF (2.0 mL) was added a mixture of HF·pyridine, pyridine, and THF (1:2:8 *v*/*v*, 1.7 mL). After 11.5 h of stirring at 4 °C, the reaction was diluted with H_2O (5 mL) and warmed to rt. The mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 70% EtOAc/hexane containing 0.5% AcOH) to afford **21** (16.4 mg, 0.032 mmol, 52% in 2 steps) as clear oil. Compound **21**: $[\alpha]_D$ +25.0° (*c* 0.90, $CHCl_3$, 29.0 °C); ^{1}H NMR δ (500 MHz, $CDCl_3$, 0.065 M) ppm: 0.92 (3H, s), 0.99 (3H, s), 1.39–1.77 (11H, m), 2.09 (1H, br.d, *J* = 15.3 Hz), 2.47 (1H, dd, *J* = 14.4, 4.5 Hz), 2.56 (2H, m), 2.71 (1H, dd, *J* = 14.4, 8.2 Hz), 3.52 (2H, dd, *J* = 5.2, 1.0 Hz), 3.66 (2H, dd, *J* = 6.0, 4.4 Hz), 4.14 (1H, br.s), 4.27 (2H, m), 4.58 (2H, s), 5.18 (1H, s), 7.27–7.37 (5H, m); ^{13}C NMR δ (125 MHz, $CDCl_3$, 0.065 M) ppm: 22.95, 24.75, 26.47, 28.14, 28.36, 32.23 (2C), 34.09, 36.85, 39.20, 41.63, 62.65, 64.24, 67.48, 67.57, 69.64, 73.57 (2C), 101.35, 127.92 (2C), 127.93, 128.50 (2C), 137.58, 171.52, 173.38; HR-FAB-MS (matrix: glycerol): *m*/*z* 509.2743 (MH^+, calcd for $C_{27}H_{41}O_9$, 509.2751).

To a solution of **21** (17.0 mg, 0.0335 mmol) in toluene (5.5 mL) were added Et_3N (20 mL, 0.2 mmol, 6.0 equiv.) and 2,4,6-trichlorobenzoyl chloride (5.8 μL, 0.037 mmol, 1.1 equiv.). After 3 h of stirring at rt, the mixture was diluted with toluene (16.5 mL). It was then added dropwise to a solution of DMAP (61.2 mg, 0.05 mmol, 15 equiv.) in toluene (45 mL) at 4 °C over 4.5 h. The resulting mixture was stirred at rt for an additional 30 min, and poured into water (40 mL). The mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 40 % EtOAc/hexane) to afford **6** (7.0 mg, 0.014 mmol, 43%) as clear oil. Compound **6**: $[\alpha]_D$ +63.3° (*c* 0.41, $CHCl_3$, 28.3 °C); ^{1}H NMR δ (500 MHz, $CDCl_3$, 0.017 M) ppm: 0.87 (3H, s, H_3-15 or 16), 1.01 (3H, s, H_3-15 or 16), 1.35–1.55 (7H, m, H_2-4, H-5a, H_2-10, H_2-12), 1.59–1.73 (4H, m, H-5b, H-8a, H_2-13), 1.84 (1H, br.s, OH), 2.34 (1H, dd, *J* = 12.7, 10.9 Hz, H-2a), 2.46 (1H, br.d, *J* = 15.6 Hz, H-8b), 2.52 (1H, dd, *J* = 12.7, 2.8 Hz, H-2b), 2.76 (1H, dd, *J* = 16.9, 3.0 Hz, H-18a), 2.89 (1H, dd, *J* = 16.9, 11.6 Hz, H-18b), 3.56 (1H, dd, *J* = 10.1, 5.5 Hz, H-20a), 3.63 (1H, dd, *J* = 10.1, 3.7 Hz, H-20b), 3.70 (2H, m, H_2-14), 3.87 (1H, tt, *J* = 10.9, 2.9 Hz, H-3), 4.26 (1H, m, H-11), 4.50 (1H, d, *J* = 12.0 Hz, Bn), 4.57 (1H, d, *J* = 12.0 Hz, Bn), 5.20 (1H, br.s, H-9), 5.25 (1H, m, H-19), 7.33 (5H, m, Bn); ^{13}C NMR δ (125 MHz, $CDCl_3$, 0.017 M) ppm: 21.27 (C-15

or 16), 25.31 (C-8), 25.89 (C-15 or 16), 27.25 (C-4), 28.24 (C-13), 31.84 (C-12), 34.73 (C-5), 34.83 (C-10), 36.92 (C-6), 37.48 (C-18), 42.75 (C-2), 62.43 (C-14), 63.58 (C-11), 68.46 (C-9), 68.99 (C-19), 70.32 (C-20), 70.74 (C-3), 73.51 (Bn), 100.51 (C-7), 127.71 (2C, Bn), 127.85 (Bn), 128.47 (2C, Bn), 137.78 (Bn), 169.96 (C-17), 170.31 (C-1). These NMR signals were assigned by ^{1}H-^{1}H COSY, HMQC, and HMBC. HR-FAB-MS (matrix: 3-nitrobenzyl alcohol): *m/z* 491.2643 (MH^+, calcd for $C_{27}H_{39}O_8$, 491.2645).

Synthesis of the side chain unit 24.

To a solution of 2,5-dibenzyloxybenzyl bromide (68 mg, 0.18 mmol) in toluene (4 mL) was added PPh_3 (65 mg, 0.25 mmol, 1.4 equiv.) and the mixture was heated to 80 °C. After 20 h of stirring at the same temperature, a brown precipitate formed. Toluene was removed by decantation and the residue was triturated with ether. The white solid was separated by filtration and washed well with hexane to yield a hydroscopic salt (**24**) (65.4 mg, 0.101 mmol, 56%). Compound **24**: mp. 85–100 °C ; ^{1}H NMR δ (500 MHz, $CDCl_3$, 0.27 M) ppm: 4.42 (2H, s), 4.89 (2H, s), 5.22 (2H, br.d, *J* = 13.6 Hz), 6.58 (1H, d, *J* = 8.8 Hz), 6.83 (1H, dt, *J* = 9.0, 2.9 Hz), 7.13 (3H, m), 7.23 (2H, m), 7.32–7.38 (6H, m), 7.50 (12H, m), 7.72 (3H, m); HR-FAB-MS (matrix: 3-nitrobenzyl alcohol): *m/z* 565.2297 ($[M–Br]^+$, calcd for $C_{39}H_{34}O_2P$, 565.2296).

Synthesis of 4 and 5.

To a solution of **6** (3.6 mg, 7.3 μmol) in CH_2Cl_2 (0.8 mL) were added *N*-methylmorpholine-*N*-oxide (1.3 mg, 0.013 mmol, 1.8 equiv.) and MS4Å (4.0 mg, 1.1 equiv. *w/w*). Tetrapropylammonium perruthenate (0.13 mg, 0.373 μmol, 5 mol%) was then added, and the reaction mixture was stirred for 40 min at rt. The resultant mixture, loaded directly onto a silica gel column, was purified by column chromatography (silica gel, 40% EtOAc/hexane) to afford **22** (2.6 mg, 5.3 μmol, 73%) as clear oil. Compound **22**: $[\alpha]_D$ +55.1° (*c* 0.20, $CHCl_3$, 29.1 °C); ^{1}H NMR δ (500 MHz, $CDCl_3$, 0.019 M) ppm: 0.85 (3H, s), 0.98 (3H, s), 1.34–1.72 (8H, m), 1.81 (1H, m), 2.33 (1H, dd, *J* = 12.7, 10.9 Hz), 2.49 (3H, m), 2.62 (1H, m), 2.76 (1H, dd, *J* = 16.9, 3.0 Hz), 2.89 (1H, dd, *J* = 16.9, 11.4 Hz), 3.56 (1H, dd, *J* = 10.1, 5.5 Hz), 3.64 (1H, dd, *J* = 10.1, 3.8 Hz), 3.86 (1H, tt, *J* = 11.0, 3.0 Hz), 4.20 (1H, m), 4.50 (1H, d, *J* = 12.0 Hz), 4.57 (1H, d, *J* = 12.0 Hz), 5.20 (2H, m), 7.27–7.36 (5H, m), 9.79 (1H, t, *J* = 1.5 Hz); ^{13}C NMR δ (125 MHz, $CDCl_3$, 0.012 M) ppm: 21.33, 25.22, 25.84, 27.24, 28.14, 34.56, 34.69, 36.90, 37.44, 40.12, 42.71, 63.51, 68.17, 68.97, 70.30, 70.76, 73.50, 100.39, 127.71 (2C), 127.85, 128.47 (2C), 137.77, 169.94, 170.27, 202.83; HR-FAB-MS (matrix: 3-nitrobenzyl alcohol): *m/z* 489.2480 (MH^+, calcd for $C_{27}H_{37}O_8$, 489.2488).

To a solution of the phosphonium bromide **23**[41] (21.5 mg, 0.04 mmol, 5.1 equiv.) in THF (0.4 mL) was added 1.6 M *n*-BuLi (20 μL, 0.032 mmol, 4.1 equiv.) at 4 °C. After 20 min of stirring at the same temperature, the solution of **22** (3.0 mg, 6.2 μmol) in THF (0.25 mL) was added to the mixture at −78 °C. The reaction mixture was stirred for 3 h at the same temperature and warmed to 4 °C. After stirring for 30 min at 4 °C, the mixture was diluted with EtOAc (1.0 mL) and the reaction was quenched with saturated aq. NH_4Cl (2.5 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 15% EtOAc/hexane) to afford **25** (1.7 mg, 2.5 μmol, 41%) as clear oil. Compound **25**: *E*-Alkene, ^{1}H NMR δ (400 MHz, $CDCl_3$, 0.004 M) ppm: 0.88 (3H, s), 1.02 (3H, s), 1.25–1.68 (10H, m), 2.31 (2H, m), 2.49 (2H, m), 2.76 (1H, dd, *J* = 12.3, 3.1 Hz), 2.88 (1H, dd, *J* = 16.9, 11.5Hz), 3.60 (2H, m), 3.87 (1H, m), 4.23 (1H, m), 4.48 (1H, d, *J* = 12.0 Hz), 4.57 (1H, d, *J* = 12.0 Hz), 5.04 (2H, s), 5.20 (2H, m), 6.14 (1H, dt, *J* = 15.8, 7.0 Hz), 6.33 (1H, d, *J* = 15.8 Hz), 6.90 (2H, d, *J* = 8.7 Hz), 7.24–7.44 (12H, m); *Z*-Alkene, ^{1}H NMR δ (400 MHz, $CDCl_3$, 0.004 M) ppm: 0.86 (3H, s), 0.95 (3H, s), 1.25-1.68 (10H, m), 2.31 (2H, m), 2.49 (2H, m), 2.72 (1H, dd, *J* = 12.3, 3.0 Hz), 2.88 (1H, dd, *J* = 16.8, 11.2Hz), 3.60 (2H, m), 3.87 (1H, m), 4.23 (1H, m), 4.50 (1H, d, *J* = 12.0 Hz), 4.57 (1H, d, *J* = 12.0 Hz), 5.06 (2H, s), 5.20 (2H, m), 5.60 (1H, dt, *J* = 11.6, 7.6 Hz), 6.35

(1H, d, J = 11.8 Hz), 6.93 (2H, d, J = 8.8 Hz), 7.24-7.44 (12H, m); HR-FAB-MS (matrix: 3-nitrobenzyl alcohol): m/z 669.3423 (MH^+, calcd for $C_{41}H_{49}O_8$, 669.3427).

To a solution of **25** (4.7 mg, 7.0 μmol) in EtOAc (0.7 mL) and MeOH (0.7 mL) was added $Pd(OH)_2/C$ (1.3 mg, 30% w/w). The mixture was vigorously stirred under an H_2 atmosphere for 4.5 h. The reaction mixture was filtered and concentrated *in vacuo*. The residue was purified by HPLC (column: SL12S05-2510WT; solvent: *i*-PrOH : $CHCl_3$: hexane = 8:12:80; flow rate: 3.0 mL/min; pressure: 510 psi; UV detector: 254 nm; retention time: 22.0 min) to afford **4** (3.2 mg, 6.5 μmol, 93%) as clear oil. Compound **4**; $[\alpha]_D$ +40.7° (c 0.42, $CHCl_3$, 29.3 °C); ^{1}H NMR δ (500 MHz, $CDCl_3$, 0.017 M) ppm: 0.86 (3H, s, H_3-22 or 23), 0.98 (3H, s, H_3-22 or 23), 1.34–1.49 (8H, m, H_2-4, H_2-5, H_2-10, H_2-13), 1.51–1.66 (5H, m, H-8a, H_2-12, H_2-14), 2.35 (1H, br.t, J = 5.6 Hz, OH), 2.40 (1H, dd, J = 12.9, 10.9 Hz, H-2a), 2.49 (1H, br.d, J = 15.6 Hz, H-8b), 2.54 (3H, m, H-2b, H_2-15), 2.71 (1H, dd, J = 16.6, 3.3 Hz, H-25a), 2.79 (1H, dd, J = 16.6, 11.2 Hz, H-25b), 3.75 (2H, m, H_2-27), 3.88 (1H, tt, J = 8.1, 2.8 Hz, H-3), 4.15 (1H, m, H-11), 5.01 (1H, br.s, Ph-OH), 5.18–5.22 (2H, m, H-9, H-26), 6.75 (2H, d, J = 8.5 Hz, H-18, H-20), 7.06 (2H, d, J = 8.4 Hz, H-17, H-21); ^{13}C NMR δ (500 MHz, $CDCl_3$, 0.017 M) ppm: 21.20 (C-22 or 23), 24.62 (C-13), 25.18 (C-8), 25.93 (C-22 or 23), 27.29 (C-4), 31.43 (C-14), 34.58 (C-12), 34.75 (C-15), 34.96 (C-10), 35.48 (C-5), 36.90 (C-25), 37.03 (C-6), 42.73 (C-2), 63.77 (C-11), 64.44 (C-27), 68.81 (C-9), 70.58 (C-3), 71.80 (C-26), 100.26 (C-7), 115.06 (2C, C-18, C-20), 129.49 (2C, C-17, C-21), 135.10 (C-16), 153.51 (C-19), 169.63 (C-24), 171.57 (C-1). These NMR signals were assigned by ^{1}H-^{1}H COSY, HSQC, and HMBC. HR-FAB-MS (matrix: 3-nitrobenzyl alcohol): m/z 491.2649 (MH^+, calcd for $C_{27}H_{39}O_8$, 491.2645).

To a solution of the phosphonium bromide **24** (27.0 mg, 0.042 mmol, 11.0 equiv.) in THF (0.5 mL) was added 1.6 M *n*-BuLi in hexane (20 μL, 0.032 mmol, 8.4 equiv.) at 4 °C. After stirring for 30 min at the same temperature, a portion of the mixture (0.25 mL) was added to a solution of the aldehyde **22** (1.7 mg, 3.5 μmol) in THF (0.15 mL) at −78 °C. The mixture was stirred for 1.5 h at the same temperature, and warmed at −10 °C. After 1.5 h of stirring at −10 °C, the mixture was diluted with EtOAc (1.0 mL), and the reaction was quenched with saturated aq. NH_4Cl (2.5 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 20% EtOAc/hexane) to afford **26** (1.1 mg, 1.4 μmol, 41%) as clear oil. Compound **26**: *E*-Alkene, ^{1}H NMR δ (400 MHz, $CDCl_3$, 0.004 M) ppm: 0.88 (3H, s), 1.02 (3H, s), 1.33–1.68 (9H, m), 2.25–2.52 (5H, m), 2.70 (1H, dd, J = 6.5, 3.0 Hz), 2.86 (1H, dd, J = 11.4, 3.5 Hz), 3.56 (2H, m), 3.85 (1H, m), 4.22 (1H, m), 4.44 (1H, d, J = 12.0 Hz), 4.53 (1H, d, J = 12.0 Hz), 5.02 (4H, s), 5.20 (2H, m), 6.27 (1H, dt, J = 15.9, 7.0 Hz), 6.72–6.86 (3H, m), 6.94–7.44 (16H, m); *Z*-Alkene, ^{1}H NMR δ (400 MHz, $CDCl_3$, 0.004 M) ppm: 0.82 (3H, s), 0.95 (3H, s), 1.33-1.68 (9H, m), 2.25-2.52 (5H, m), 2.74 (1H, dd, J = 6.5, 3.0 Hz), 2.90 (1H, dd, J = 11.4, 3.5 Hz), 3.56 (2H, m), 3.85 (1H, m), 4.22 (1H, m), 4.48 (1H, d, J = 12.0 Hz), 4.56 (1H, d, J = 12.0 Hz), 5.02 (2H, s), 5.04 (2H, s), 5.20 (2H, m), 5.75 (1H, dt, J = 11.8, 7.3 Hz), 6.57 (1H, J = 11.8 Hz), 6.72-6.86 (2H, m), 6.94-7.44 (16H, m); HR-FAB-MS (matrix: 3-nitrobenzyl alcohol): m/z 774.3740 (M^+, calcd for $C_{48}H_{54}O_9$, 774.3768).

To a solution of **26** (2.5 mg, 3.2 μmol) in EtOAc (0.45 mL) and MeOH (0.45 mL) was added $Pd(OH)_2/C$ (1.0 mg, 40% w/w). The mixture was vigorously stirred under an H_2 atmosphere for 2.5 h. The reaction mixture was filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 70% EtOAc/hexane) to afford **5** (1.6 mg, 3.2 μmol, quant.) as clear oil. Compound **5**: $[\alpha]_D$ +53.7° (c 0.14, $CHCl_3$, 12.4 °C); ^{1}H NMR δ (400 MHz, $CDCl_3$, 0.006 M) ppm: 0.87 (3H, s, H_3-22 or 23), 0.94 (3H, s, H_3-22 or 23), 1.41 (7H, m, H_2-4, H_2-5, H-10a, H-12a, H-13a), 1.50–1.76 (6H, m, H-8a, H-10b, H-12b, H-13b, H_2-14), 2.31 (1H, t, J = 6.0 Hz, 27-OH), 2.39–2.64 (5H, m, H_2-2, H-8b, H2-15), 2.78 (2H, m, H_2-25), 3.77 (2H, m, H_2-27), 3.91 (1H, tt, J = 10.7, 3.1 Hz, H-3), 4.27 (1H, m, H-11), 4.89 (1H, s, 17-OH), 5.20 (2H, m, H-9, H-26), 5.75 (1H, s, 20-OH), 6.57 (1H, dd, J = 8.5, 3.0 Hz, H-19), 6.69 (1H, d, J = 8.5 Hz, H-18), 6.76 (1H, d, J = 2.9 Hz, H-21); ^{13}C NMR δ (125 MHz, $CDCl_3$, 0.006 M) ppm: 21.16 (C-22 or 23), 24.13 (C-13), 25.25 (C-8), 25.91 (C-22 or 23), 27.25 (C-4), 27.72 (C-14), 29.20 (C-15),

34.28 (C-12), 34.55 (C-5), 35.04 (C-10), 36.95 (C-6), 37.07 (C-25), 42.88 (C-2), 62.63 (C-11), 64.17 (C-27), 68.93 (C-9), 70.63 (C-3), 72.49 (C-26), 100.44 (C-7), 113.12 (C-19), 116.42 (C-21), 116.63 (C-18), 130.29 (C-16), 147.19 (C-17), 150.52 (C-20), 169.42 (C-24), 172.99 (C-1). These NMR signals were assigned by ^{1}H-^{1}H COSY, HSQC, and HMBC. HR-FAB-MS (matrix: glycerol): m/z 506.2508 (M^+, calcd for $C_{27}H_{38}O_9$, 506.2516).

Synthesis of 1.

To a solution of 2-benzyloxybenzyl bromide (163 mg, 0.588 mmol) in toluene (8.5 mL) was added PPh_3 (216 mg, 0.824 mmol, 1.4 equiv.) and heated to 110 °C. After 12.5 h of stirring at the same temperature, the reaction mixture was kept in a freezer at –20 °C for 1 h. The mixture was filtered and washed well with hexane to yield (3-benzyloxybenzyl)triphenylphosphonium bromide (310 mg, 0.59 mmol, quant.) as a white solid. (3-Benzyloxybenzyl)triphenylphosphonium bromide: mp. 228–233 °C; ^{1}H NMR δ (500 MHz, $CDCl_3$, 0.33 M) ppm: 4.78 (2H, s), 5.37 (2H, d, J = 14.4 Hz), 6.66 (1H, d, J = 7.5 Hz), 6.85 (2H, m), 7.02 (1H, t, J = 7.9 Hz), 7.33 (5H, m), 7.60 (6H, m), 7.75 (9H, m); HR-FAB-MS (matrix: 3-nitrobenzyl alcohol): m/z 459.1881 ($[M–Br]^+$, calcd for $C_{32}H_{28}OP$, 459.1878).

To a solution of the phosphonium bromide (19.0 mg, 0.035 mmol, 5.7 equiv.) in THF (9 mL) was added 1.6 M *n*-BuLi in hexane (20 μL, 0.035 mmol, 5.2 equiv.) at 4 °C. After 30 min of stirring at the same temperature, a portion of the mixture (0.52 mL) was added to the aldehyde **22** (3.0 mg, 6.2 μmol) at –78 °C. The mixture was stirred for 2 h at the same temperature and warmed at 4 °C. After 4 h of stirring at 4 °C, the reaction mixture was diluted with EtOAc (1.0 mL) and the reaction was quenched with saturated aq. NH_4Cl (2.5 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 25% EtOAc/hexane) to afford a mixture of alkenes (1.0 mg, 1.5 μmol). To a solution of the alkenes (2.0 mg, 3.0 μmol) in EtOAc (0.5 mL) and MeOH (0.5 mL) was added $Pd(OH)_2$/C (1.0 mg, 0.5 equiv. w/w). The mixture was vigorously stirred under an H_2 atmosphere for 6 h. The reaction mixture was filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 40% EtOAc/hexane) to afford **1** (1.5 mg, 3.1 μmol, 25% in 2 steps) as clear oil. Compound **1**: $[\alpha]_D$ +43.6° (c 0.15, $CHCl_3$, 15.7 °C: lit,[19] +47°); ^{1}H NMR and FAB-MS data coincided with those reported previously.[19]

Inhibition of Specific Binding of [^{3}H]PDBu to PKC C1 Peptides.

The binding of [^{3}H]PDBu to the PKC C1 peptides (α-C1A, δ-C1A, and δ-C1B) was evaluated by the procedure of Sharkey and Blumberg[32] with slight modifications as reported previously[33,34] with 50 mM Tris-maleate buffer (pH 7.4 at 4 °C), 10 – 40 nM each PKC C1 peptide, 20 nM [^{3}H]PDBu (19.6 Ci/mmol), 50 μg/mL 1,2-dioleoyl-*sn*-glycero-3-phospho-L-serine (Sigma), 3 mg/mL bovine γ-globulin (Sigma), and various concentrations of inhibitors. Binding affinity was evaluated on the basis of the concentration required to cause 50% inhibition of the specific binding of [^{3}H]PDBu, IC_{50}, which was calculated with Microsoft Excel. The inhibition constant, K_i, was calculated by the method of Sharkey and Blumberg.[32]

Anti-proliferative activity against a Panel of 39 Human Cancer Cell Lines.

A panel of 39 human cancer cell lines established by Yamori and coworkers[37] according to the NCI method with modifications was employed, and cell growth inhibitory activity was measured as reported previously.[37] In brief, the cells were plated in 96-well plates in RPMI 1640 medium supplemented with 5% fetal bovine serum and allowed to attach overnight. The cells were incubated with each test compound for 48 h. Cell growth was estimated by the sulforhodamine B assay. The 50% growth inhibition (GI_{50}) parameter was calculated as reported previously.[37] Absorbance for the control well (C) and the test well

(T) were measured at 525 nm along with that for the test well at time 0 (T_0). Cell growth inhibition (% growth) by each concentration of drug (10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}, and 10^{-4} M) was calculated as $100[(T - T_0)/(C - T_0)]$ using the average of duplicate points. By processing these values, each GI_{50} value, defined as $100[(T - T_0)/(C - T_0)] = 50$, was determined.

EBV-EA Induction Test.

Human B-lymphoblastoid Raji cells (5×10^5 / mL) were incubated at 37 °C under a 5% CO_2 atmosphere in 1 mL of RPMI 1640 medium (supplemented with 10% fetal bovine serum) with 4 mM sodium *n*-butyrate (a synergist) and 10, 100, or 1000 nM of each test compound for the induction test, or 100 nM of each test compound in the presence of 32 nM of TPA for the inhibition test. In the induction test, each test compound was added as 2 μL of a DMSO solution (5, 50, and 500 μM stock solution) along with 2 μL DMSO; the final DMSO concentration was 0.4%. In the inhibition test, TPA was added as 2 μL of a DMSO solution (16 μM stock solution), 10 min after the addition of each test compound (2 μL of a DMSO solution: 50 μM). After incubation for 48 h, smears were made from the cell suspension, and the EBV-EA-expressing cells were stained by a conventional indirect immunofluorescence technique with an NPC patient's serum (a gift from Kobe University) and FITC-labeled anti-human IgG (DAKO, Glostrup, Denmark) as reported previously.[38,39] In each assay, at least 500 cells were counted and the proportion of the EA-positive cells was recorded. Cell viability exceeded 60% in each experiment.

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References

[1] Yasutomi Nishizuka. The role of protein kinase C in cell surface signal transduction and tumour promotion. *Nature*, 308:693–698, 1984.

[2] Yasutomi Nishizuka. Protein kinase C and lipid signaling for sustained cellular responses. *The FASEB Journal*, 9(7):484–496, 1995.

[3] Alexandra C. Newton. Protein kinase C: Structural and spatial regulation by phosphorylation, cofactors, and macromolecular interactions. *Chemical Reviews*, 101(8):2353–2364, 2001.

[4] Yoshito Kishi and Robert R. Rando. Structural Basis of Protein Kinase C Activation by Tumor Promoters. *Accounts of Chemical Research*, 31(4):163–172, apr 1998.

[5] George R. Pettit, Cherry L. Herald, Dennis L. Doubek, Delbert L. Herald, Edward Arnold, and Jon Clardy. Isolation and structure of bryostatin 1. *Journal of the American Chemical Society*, 104(24):6846–6848, dec 1982.

[6] M. Gschwendt, G. Fürstenberger, S. Rose-John, M. Rogers, W. Kittstein, G. R. Pettit, C. L. Herald, and F. Marks. Bryostatin 1, an activator of protein kinase C, mimics as well as inhibits biological effects of the phorbol ester TPA in vivo and in vitro. *Carcinogenesis*, 9(4):555–562, 1988.

[7] Jerome D Winegarden, Ann M Mauer, Thomas F Gajewski, Philip C Hoffman, Stuart Krauss, Charles M Rudin, and Everett E Vokes. A phase II study of bryostatin-1 and paclitaxel in patients with advanced non-small cell lung cancer. *Lung cancer (Amsterdam, Netherlands)*, 39(2):191–6, feb 2003.

[8] T. J. Nelson and D. L. Alkon. Neuroprotective versus tumorigenic protein kinase C activators. *Trends in Biochemical Sciences*, 34(3):136–145, 2009.

[9] Rajeev Mehla, Shalmali Bivalkar-Mehla, Ruonan Zhang, Indhira Handy, Helmut Albrecht, Shailendra Giri, Prakash Nagarkatti, Mitzi Nagarkatti, and Ashok Chauhan. Bryostatin Modulates Latent HIV-1 Infection via PKC and AMPK Signaling but Inhibits Acute Infection in a Receptor Independent Manner. *PLoS ONE*, 5(6):e11160, jun 2010.

[10] Roger Mutter and Martin Wills. Chemistry and clinical biology of the bryostatins. *Bioorganic and Medicinal Chemistry*, 8(8):1841–1860, 2000.

[11] Barry M. Trost and Guangbin Dong. Total synthesis of bryostatin 16 using atom-economical and chemoselective approaches. *Nature*, 456(7221):485–488, nov 2008.

[12] Gary E. Keck, Yam B. Poudel, Thomas J. Cummins, Arnab Rudra, and Jonathan A. Covel. Total Synthesis of Bryostatin 1. *Journal of the American Chemical Society*, 133(4):744–747, feb 2011.

[13] Paul A. Wender and Adam J. Schrier. Total Synthesis of Bryostatin 9. *Journal of the American Chemical Society*, 133(24):9228–9231, jun 2011.

[14] Dale Schaar, Lauri Goodell, Joseph Aisner, Xiao Xing Cui, Zheng Tao Han, Richard Chang, John Martin, Stephanie Grospe, Liesel Dudek, Joan Riley, Jacqueline Manago, Yong Lin, Eric H. Rubin, Allan Conney, and Roger K. Strair. A phase I clinical trial of 12-*O*-tetradecanoylphorbol-13-acetate for patients with relapsed/refractory malignancies. *Cancer Chemotherapy and Pharmacology*, 57(6):789–795, jun 2006.

[15] Alan P. Kozikowski, Yihua Chen, Tapadar Subhasish, Nancy E. Lewin, Peter M. Blumberg, Zhenyu Zhong, Melissa A. D'Annibale, Weng-Long Wang, Yong Shen, and Brett Langley. Searching for Disease Modifiers—PKC Activation and HDAC Inhibition—A Dual Drug Approach to Alzheimer's Disease that Decreases Aβ Production while Blocking Oxidative Stress. *ChemMedChem*, 4(7):1095–1105, jul 2009.

[16] S. Zayed, B. Sorg, and E. Hecker. Structure Activity Relations of Polyfunctional Diterpenes of the Tigliane Type, VI 1. *Planta Medica*, 50(01):65–69, feb 1984.

[17] Z Szallasi, L Krsmanovic, and P M Blumberg. Nonpromoting 12-deoxyphorbol 13-esters inhibit phorbol 12-myristate 13-acetate induced tumor promotion in CD-1 mouse skin. *Cancer research*, 53(11):2507–12, jun 1993.

[18] Kirk R. Gustafson, John H. Cardellina, James B. McMahon, Robert J. Gulakowski, Junichi Ishitoya, Zoltan Szallasi, Nancy E. Lewin, Peter M. Blumberg, and Owen S. Weislow. A nonpromoting phorbol from the Samoan medicinal plant Homalanthus nutans inhibits cell killing by HIV-1. *Journal of Medicinal Chemistry*, 35(11):1978–1986, may 1992.

[19] Yu Nakagawa, Ryo C. Yanagita, Naoko Hamada, Akira Murakami, Hideyuki Takahashi, Naoaki Saito, Hiroshi Nagai, and Kazuhiro Irie. A simple analogue of tumor-promoting aplysiatoxin is an antineoplastic agent rather than a tumor promoter: Development of a synthetically accessible protein kinase C activator with bryostatin-like activity. *Journal of the American Chemical Society*, 131(22):7573–7579, 2009.

[20] Peter J. Reddig, Nancy E. Dreckschimdt, Helga Ahrens, Robita Simsiman, Ching Ping Tseng, Jun Zou, Terry D. Oberley, and Ajit K. Verma. Transgenic mice overexpressing protein kinase Cδ in the epidermis are resistant to skin tumor promotion by 12-*O*-tetradecanoylphorbol-13-acetate. *Cancer Research*, 59(22):5710–5718, 1999.

[21] Zhimin Lu, Armand Hornia, You-Wei Jiang, Qun Zang, Shigeo Ohno, and David A. Foster. Tumor Promotion by Depleting Cells of Protein Kinase Cδ. *Molecular and Cellular Biology*, 17(6):3418–3428, jun 1997.

[22] Ryo C. Yanagita, Hiroaki Kamachi, Keisuke Tanaka, Akira Murakami, Yu Nakagawa, Harukuni Tokuda, Hiroshi Nagai, and Kazuhiro Irie. Role of the phenolic hydroxyl group in the biological activities of simplified analogue of aplysiatoxin with antiproliferative activity. *Bioorganic and Medicinal Chemistry Letters*, 20(20):6064–6066, 2010.

[23] Gangguo Zhu and Ei-ichi Negishi. Fully Reagent-Controlled Asymmetric Synthesis of (−)-Spongidepsin via the Zr-Catalyzed Asymmetric Carboalumination of Alkenes (ZACA Reaction). *Organic Letters*, 9(15):2771–2774, jul 2007.

[24] Hideo Hanawa, Daisuke Uraguchi, Shunsuke Konishi, Takuya Hashimoto, and Keiji Maruoka. Catalytic Asymmetric Allylation of Aldehydes and Related Reactions with Bis(((*S*)-binaphthoxy)(isopropoxy)titanium) Oxide as a μ-Oxo-Type Chiral Lewis Acid. *Chemistry – A European Journal*, 9(18):4405–4413, sep 2003.

[25] James J. W. Duan and Amos B. Smith. Iodine monobromide (IBr) at low temperature: enhanced diastereoselectivity in electrophilic cyclizations of homoallylic carbonates. *The Journal of Organic Chemistry*, 58(14):3703–3711, jul 1993.

[26] Steven V. Ley, Joanne Norman, William P. Griffith, and Stephen P. Marsden. Tetrapropylammonium Perruthenate, $Pr_4N^+RuO_4^-$, TPAP: A Catalytic Oxidant for Organic Synthesis. *Synthesis*, 1994(07):639–666, 1994.

[27] David A. Evans, B.Wesley Trotter, Paul J. Coleman, Bernard Côté, Luiz Carlos Dias, Hemaka A. Rajapakse, and Andrew N. Tyler. Enantioselective total synthesis of altohyrtin C (spongistatin 2). *Tetrahedron*, 55(29):8671–8726, jul 1999.

[28] Guy Solladie and Jean Hutt. Asymmetric synthesis of polyhydroxylated natural products II. The C-1/C-12 unit of amphotericin B. *Tetrahedron Letters*, 28(7):797–800, jan 1987.

[29] Balkrishna S. Bal, Wayne E. Childers, and Harold W. Pinnick. Oxidation of α,β-un saturated aldehydes. *Tetrahedron*, 37(11):2091–2096, jan 1981.

[30] Junji Inanaga, Kuniko Hirata, Hiroko Saeki, Tsutomu Katsuki, and Masaru Yamaguchi. A rapid esterification by means of mixed anhydride and its application to large-ring lactonization. *Bulletin of the Chemical Society of Japan*, 52(7):1989–1993, 1979.

[31] Paul A Wender, Jeremy L Baryza, Chad E Bennett, F Christopher Bi, Stacey E Brenner, Michael O Clarke, Joshua C Horan, Cindy Kan, Emmanuel Lacôte, Blaise Lippa, Peter G Nell, and Tim M Turner. The practical synthesis of a novel and highly potent analogue of bryostatin. *Journal of the American Chemical Society*, 124(46):13648–9, nov 2002.

[32] Nancy A. Sharkey and Peter M. Blumberg. Highly lipophilic phorbol esters as inhibitors of specific [^{3}H]phorbol 12,13-dibutyrate binding. *Cancer Research*, 45:19–24, 1985.

[33] Kazuhiro Irie, Kentaro Oie, Akifumi Nakahara, Yoshiaki Yanai, Hajime Ohigashi, Paul A. Wender, Hiroyuki Fukuda, Hiroaki Konishi, and Ushio Kikkawa. Molecular basis for protein kinase C isozyme-selective binding: The synthesis, folding, and phorbol ester binding of the cysteine-rich domains of all protein kinase C isozymes. *Journal of the American Chemical Society*, 120(36):9159–9167, 1998.

[34] Mayumi Shindo, Kazuhiro Irie, Akifumi Nakahara, Hajime Ohigashi, Hiroaki Konishi, Ushio Kikkawa, Hiroyuki Fukuda, and Paul A. Wender. Toward the identification of selective modulators of protein kinase C (PKC) isozymes: Establishment of a binding assay for PKC isozymes using synthetic C1 peptide receptors and identification of the critical residues involved in the phorbol ester binding. *Bioorganic and Medicinal Chemistry*, 9(8):2073–2081, 2001.

[35] Krisztina Bögi, Patricia S. Lorenzo, Zoltán Szállási, Péter Ács, Gerhardt S. Wagner, and Peter M. Blumberg. Differential selectivity of ligands for the C1a and C1b phorbol ester binding domains of protein kinase Cδ: Possible correlation with tumor- promoting activity. *Cancer Research*, 58(7):1423–1428, 1998.

[36] A. M. Jeffrey and R. M. Liskamp. Computer-assisted molecular modeling of tumor promoters: rationale for the activity of phorbol esters, teleocidin B, and aplysiatoxin. *Proceedings of the National Academy of Sciences*, 83(2):241–245, jan 1986.

[37] Takao Yamori, Akio Matsunaga, Shigeo Sato, Kanami Yamazaki, Akiko Komi, Kazuhiro Ishizu, Izumi Mita, Hajime Edatsugi, Yasuhiro Matsuba, Kimiko Takezawa, Osamu Nakanishi, Hiroshi Kohno, Yuki Nakajima, Hironori Komatsu, Toshio Andoh, and Takashi Tsuruo. Potent antitumor activity of MS-247, a novel DNA minor groove binder, evaluated by an *in vitro* and *in vivo* human cancer cell line panel. *Cancer Research*, 59(16):4042–4049, 1999.

[38] Yohei Ito, Sugio Yanase, Jun Fujita, Takashi Harayama, Matao Takashima, and Hiroshi Imanaka. A short-term in vitro assay for promoter substances using human lymphoblastoid cells latently infected with Epstein-Barr virus. *Cancer Letters*, 13(1):29–37, jun 1981.

[39] Harald zur Hausen, Georg W. Bornkamm, Rainer Schmidt, and Erich Hecker. Tumor initiators and promoters in the induction of Epstein–Barr virus. *Proceedings of the National Academy of Sciences*, 76(2):782–785, feb 1979.

[40] Ikuko Ohtani, Takenori Kusumi, Yoel Kashman, and Hiroshi Kakisawa. High-field FT NMR application of Mosher's method. The absolute configurations of marine terpenoids. *Journal of the American Chemical Society*, 113(11):4092–4096, may 1991.

[41] M. Carmen Carreño, Renaud Des Mazery, Antonio Urbano, Françoise Colobert, and Guy Solladié. Reductive Cyclizations of Hydroxysulfinyl Ketones: Enantioselective Access to Tetrahydropyran and Tetrahydrofuran Derivatives. *The Journal of Organic Chemistry*, 68(20):7779–7787, oct 2003.