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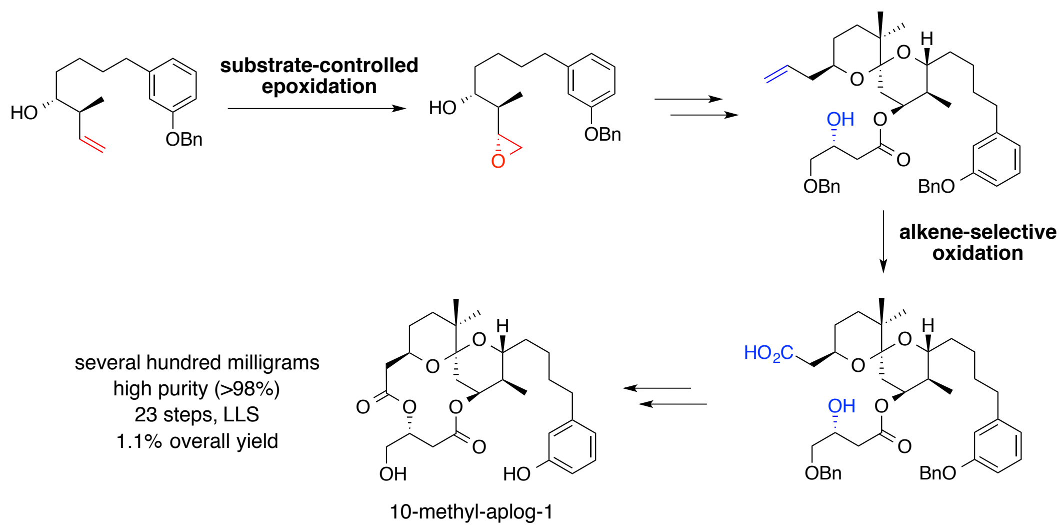
Graphical Abstract



Improved and Large-Scale Synthesis of 10-Methyl-Aplog-1, a Potential Lead for an Anticancer Drug

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Abstract

10-Methyl-aplog-1 (**1**), a simplified analog of tumor-promoting aplysiatoxin, is a potential lead for cancer therapy that exhibits marked and selective growth inhibitory effects against several human cancer cell lines and negligible tumor-promoting activity *in vivo*. However, more detailed evaluations of its toxicity and anticancer activity *in vivo* are hampered by supply problems associated with a non-optimal synthetic method. We here addressed this issue through a more practical and reliable synthetic method that afforded several hundred milligrams of **1** with high purity (>98%) in 23 steps from commercially available *m*-hydroxycinnamic acid with an overall yield of 1.1%. The utilization of two key reactions, substrate-controlled epoxidation and the oxidative cleavage of alkene with a free hydroxyl group, successfully reduced the existing five synthetic steps and markedly improved the handling of large amounts of intermediates. We also demonstrated for the first time that such an analog was synthetically accessible in reliable quantities and also that this large supply could advance *in vivo* trials for the treatment of cancer.

Keywords: anticancer, aplysiatoxin, phorbol ester, protein kinase C, simplified analog

1. Introduction

The family of enzymes known as protein kinase C (PKC) has been widely recognized as an attractive target for treating intractable diseases such as cancer[1], Alzheimer's disease (AD)[2], and acquired immune deficiency syndrome (AIDS)[3] because of its pivotal role in many cellular

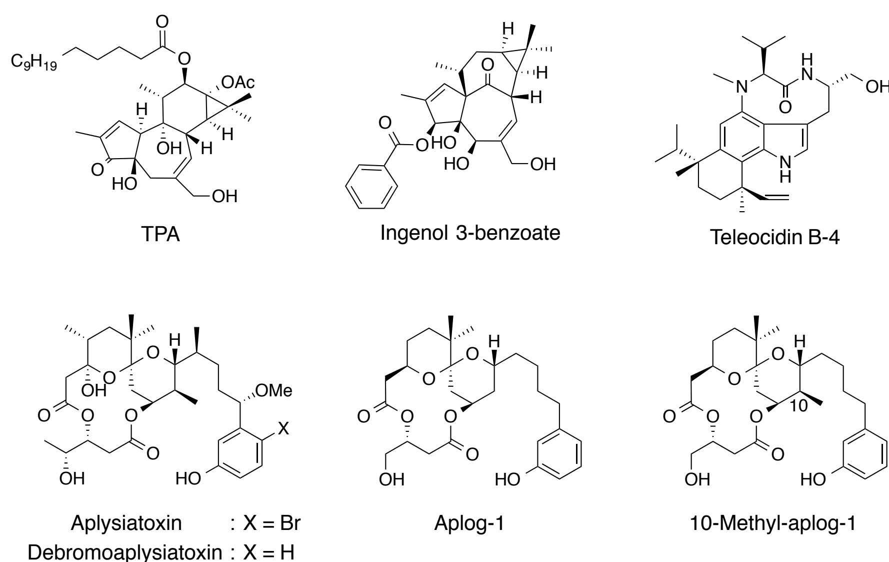


Fig. 1.

Structures of naturally occurring tumor promoters and simplified analogs of aplysiatoxin.

events including differentiation, proliferation, and apoptosis. Thus, natural PKC activators such as phorbol esters, ingenol esters, teleocidins, and aplysiatoxins may serve as therapeutic leads (Fig. 1). Although 12-*O*-tetradecanoylphorbol 13-acetate (TPA) and ingenol 3-angelate have already been evaluated in clinical trials for several cancers,[4,5] their therapeutic use has been impeded by low natural abundance, structural complexity, difficulties associated with their synthesis and modification, as well as their undesired side effects such as tumor-promoting and severe inflammatory activities.

Bryostatin 1 (bryo-1), a lead member of this family, is a fascinating and mysterious PKC activator without tumor-promoting activity *in vivo*. Bryo-1 has been investigated for anticancer activity in at least 43 phase I and phase II clinical trials,[6,7] where it demonstrated an ability to enhance the effects of some anticancer drugs at remarkably low doses (~50 μg/m^2, or ~1–1.5 mg per 8-week treatment cycle). Moreover, bryo-1 improved learning and memory in animal models,[8] and its therapeutic potential for Alzheimer's disease and other neurodegenerative disorders attracted much attention. Despite the promising biological properties of bryo-1, further studies on its unique mode of action and the clinical development have been hampered by its limited availability. Recently, function oriented synthesis of the simplified analogs of bryo-1 have been carried out to address these problems.[9,10]

As an alternative approach, we developed 10-methyl-aplog-1 (**1**, Scheme 1), a simplified analog of aplysiatoxin that exhibits significant anti-proliferative activity against several human

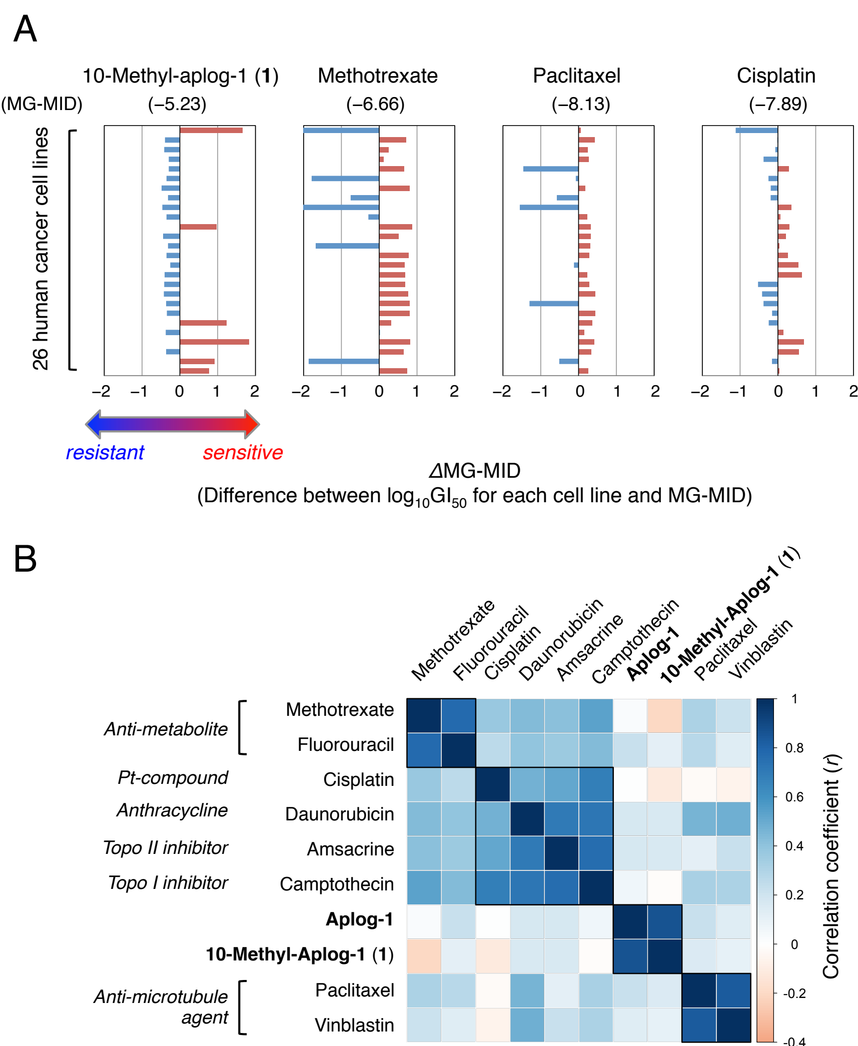


Fig. 2. Efficacy profiles of aplog-1, 10-methyl-aplog-1 (**1**), and several anti-cancer drugs. Data for these anti-cancer drugs were retrieved from the NCI/NIH public database (http://dtp.nci.nih.gov/). A) "Fingerprints" against 26 human cancer cell lines. Data for the following cell lines are listed in top-to-bottom order: Breast (MDA-MB-231/ATCC, MCF7); Prostate (DU-145, PC-3); Renal (ACHN); Ovarian (SK-OV-3, OVCAR-8, OVCAR-5, OVCAR-4, OVCAR-3); Melanoma (LOX IMVI); Central nervous system (U251, SNB-75, SF-539, SF-295, SF-268); Colon (KM12, HT29, HCT-15, HCT-116, HCC-2998); Non-small cell lung (NCI-H522, NCI-H460, NCI-H23, NCI-H226, A549/HTCC). MG-MID, log GI_{50} (log M, 50% cell growth inhibition) mean-graph midpoint. B) A correlation matrix plot based on Pearson correlation coefficients between log GI_{50} values of aplogs and anti-cancer drugs against 26 human cancer cell lines, followed by hierarchical clustering using the complete linkage method.

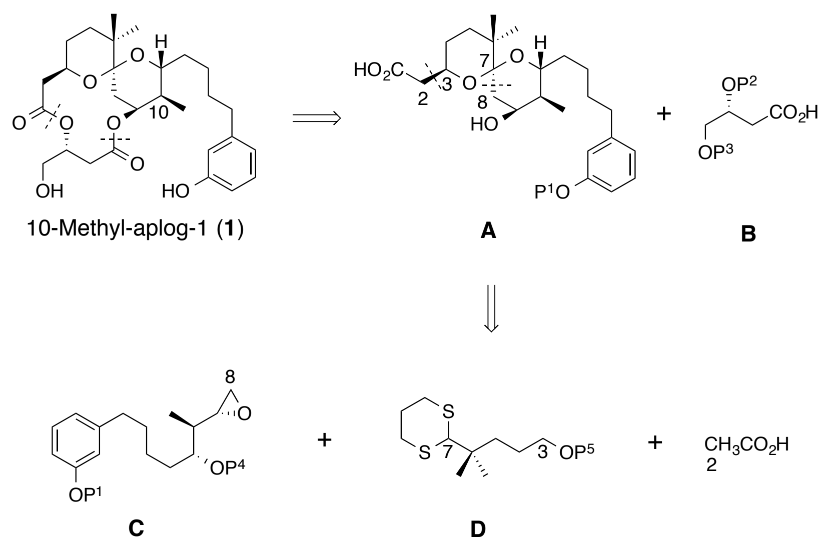
cancer cell lines and negligible tumor-promoting activity in mouse skin.[11] Extensive growth inhibitory assays against 39 human cancer cell lines revealed that its anti-proliferative activity was cell line selective and also that its efficacy profile (fingerprint) was completely different from that of any type of anticancer agent available today, thereby supporting its unique mode of action and a new aspect of anticancer drug development (Fig. 2).

The analog **1** lacked the chiral methyl groups at positions 4, 12, and 30, the methoxy group at position 15 as well as the bromine atom at position 21 to decrease hydrophobicity, and replaced the labile hemiacetal hydroxyl group at position 3 with a hydrogen atom to increase chemical stability. This structural simplification successfully eliminated over 20 synthetic steps and reduced barriers against its practical synthesis without attenuating its marked anti-proliferative activities and ability to activate PKCs.[12] Despite these prospective features as a future therapeutic candidate, the inefficiency of our first-generation synthesis of **1** prevented further experiments on animals and structural optimization for clinical use. To satisfy these needs, we attempted to develop a more practical synthetic method for **1** for the preparation of sufficient amounts of the sample in order to examine its toxicity and anticancer effects in an animal model.

2. Results and discussion

From a synthetic perspective, we maintained the triply convergent route applied in our first-generation synthesis, dissecting **1** at two ester linkages to generate subunits A and B. The further division of fragment A provided two subunits, C and D (Scheme 1). Our previous attempt to construct an anti, anti-stereotriad in subunit C using Smith's iodocarbonate cyclization strategy[13] required three steps from a homoallyl alcohol (**5**) and also gave unsatisfactory results with poor stereoselectivity and a low yield. Moreover, subsequent methanolysis of the carbonate moiety required careful control of the reaction temperature in order to prevent opening of the epoxide ring.[11] This inefficient and complicated process severely disturbed the large-scale preparation of **1**; thus, its improvement was inevitable. We decided to utilize the one-step hydroxyl-directed epoxidation of **5**. Such an approach could facilitate the handling of large-scale intermediates.

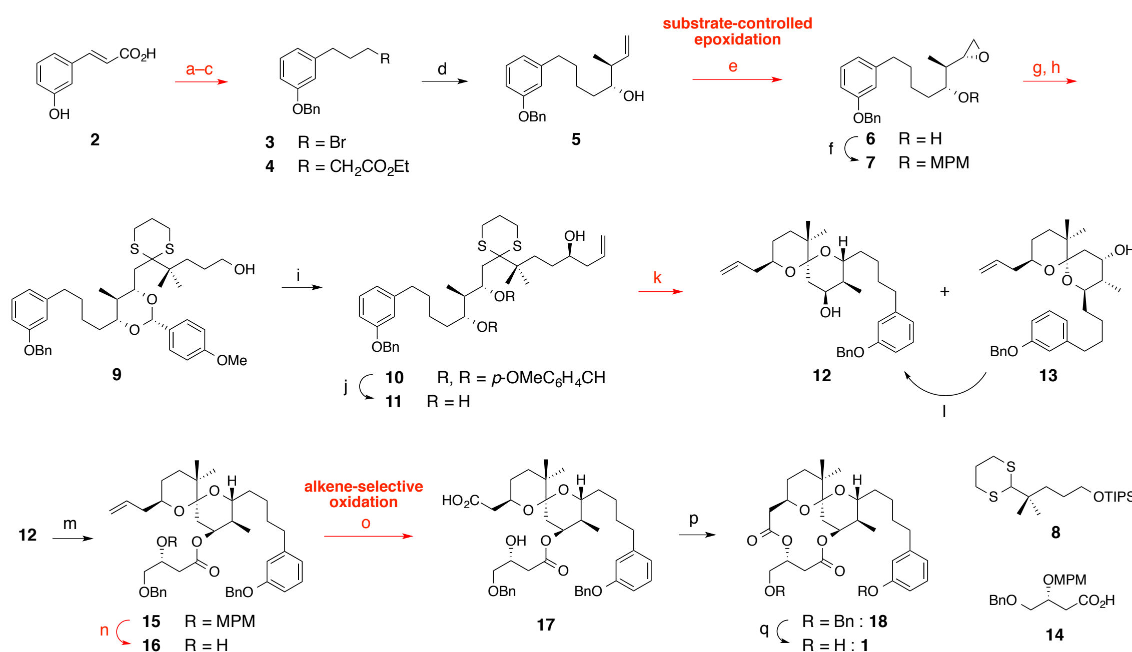
The synthesis of **1** started with the hydrogenation of *m*-hydroxycinnamic acid (**2**), followed by esterification, protection of the phenol group as a benzyl ether, reduction, and bromination to provide a known bromide (**3**) in 91% yield from **2**. In practice, the first four intermediates of this sequence could be carried forward without purification, and the bromide



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

was purified by column chromatography before the next step. This procedure could be performed routinely on a 20-g scale. The substitution of the known bromide with diethyl malonate gave a diester, which was decarbalkoxylated without purification to produce an ester (**4**) in 62 % yield. Partial reduction of **4** to an aldehyde was accomplished on a 5-g scale, and the aldehyde was immediately used for asymmetric Brown crotylation[14] to furnish a homoallyl alcohol (**5**) in 56–84% yield from **4**. The vanadium-catalyzed epoxidation[15] of **5** generated a diastereomeric mixture of epoxyalcohols (anti, anti : syn, anti = 3:1). Although it was difficult to completely separate them, a sufficient amount of pure desired epoxyalcohol (**6**) with an anti, anti-stereotriad was obtained by careful and repeated normal phase chromatography. Therefore, **6** was obtained in 57% yield from **5**. The secondary hydroxyl group of **6** was protected as a *p*-methoxyphenylmethyl (MPM) ether (71%). A total of 9.6 g of subunit C (**7**) was obtained in 11 steps with an overall yield of 17% from **2**.

We previously reported that successful coupling of the epoxide (**7**) with the known dithiane (**8**)[16] required strict dry conditions. Normal vacuum drying was inappropriate for dehydrating large amounts of the compound, and the amount was limited to approximately 70 mg. The azeotropic dehydration of large-scale materials using toluene also appeared to be inapplicable because the benzyl site in the resulting toluene could be lithiated by *n*-butyl lithium to react with electrophiles. To overcome this problem, 200 mg of **7** and 245 mg of **8** were charged in 10-mL flasks separately, spread on the inside walls of the flasks, dried in a vacuum over 2 hours, and the reaction was performed several times. Although our previous method



Scheme 2. Synthesis of **1**. *Reagents and conditions*: (a) (1) 10% Pd/C, H_2, MeOH; (2) $SOCl_2$, MeOH; (3) BnBr, K_2CO_3, Acetone; (b) (1) $LiAlH_4$, THF; (2) CBr_4, PPh_3, CH_2Cl_2; 91% from **2** in five steps. (c) (1) Diethyl malonate, NaH, DMF; (2) LiCl, DMSO, H_2O; 62% in two steps. (d) (1) DIBAL, Toluene; (2) *trans*-2-Butene, KO*t*-Bu, *n*-BuLi, (–)-Ipc_2BOMe, $BF_3{\cdot}OEt_2$, THF; 74% in two steps. (e) $VO(acac)_2$, *t*-BuOOH, CH_2Cl_2, 57%. (f) MPM-Cl, NaH, DMF, THF, 71%. (g) **8**, *n*-BuLi, THF, 94%. (h) (1) DDQ, CH_2Cl_2; (2) $TBAF{\cdot}3H_2O$, THF; 93% in two steps. (i) (1) $SO_3{\cdot}Pyr$, DMSO, Et_3N, CH_2Cl_2; (2) $TiCl_4$, Ti(O*i*-Pr)$_4$, Ag_2O, (*S*)-BINOL, Allyl-$SnBu_3$, CH_2Cl_2; 60% in two steps. (j) TFA, H_2O, THF, 48%. (k) Selectfluor®, MeCN, H_2O; **12**, 56%; **13**, 22%. (l) PPTS, MeCN, CH_2Cl_2; **12**, 73%; **13**, 24%. (m) **14**, TCB-Cl, Et_3N, DMAP, Toluene, 93%. (n) DDQ, pH 7 buffer, CH_2Cl_2, 87%. (o) $KMnO_4$, $NaIO_4$, *t*-BuOH, pH 7 buffer, 71%. (p) TCB-Cl, Et_3N, DMAP, Toluene, 82%. (q) 10% Pd/C, H_2, EtOH, 83%. Improved steps are highlighted in red.

utilized a 2.0 equivalent of **8**, a 1.5 equivalent was sufficient to consume all of **7** without a prolonged reaction time. The application of this method succeeded in producing the coupling product at an excellent yield (94%).

Oxidation of the coupling product at the benzyl site of the MPM ether by treating 1 equivalent of DDQ formed anisylidene acetal to protect the secondary hydroxyl group. We found that the addition of 4 Å molecular sieves to maintain the dehydrated condition was not required for intramolecular acetalization and also simplified the handling of this reaction. Desilylation followed by the Parikh-Doering oxidation[17] of the alcohol (**9**) provided an aldehyde. Maruoka's asymmetric allylation[18] of the aldehyde on a 3-g scale and simple purification by normal phase column chromatography provided a homoallyl alcohol (**10**) in 50–66% yield, as well as a mixture of (*S*)-BINOL and the recovered aldehyde. The mixture was further purified by reverse phase column chromatography to give pure aldehyde, which was again used for asymmetric allylation. Collectively, 60% of the total aldehyde was converted to **10**.

Deprotection of the anisylidene acetal was challenging because of the high stability of the acetal moiety. Our screening for an optimal method for the detachment of the anisylidene acetal suggested that acid-catalyzed hydrolysis using the TFA/H_2O/THF condition was the best because this condition made the purification of the product simpler than previous method. The application of this condition on a 2-g scale provided a triol (**11**) in 41–59% yield and recovered the acetal (**10**) in 34–45%. Collectively, 3.18 g (5.30 mmol) of **11** was obtained in 48% yield from 7.89 g (11.0 mmol) of initial **10**. We found that a careful and accurate workup to neutralize the reaction mixture was essential because severe decomposition of the substrate and product occurred during concentration under acidic condition.

The use of selectflour®[19], an electrophilic fluorinating reagent, more efficiently achieved the simultaneous cleavage of 1,3-dithiane and spiroketalization than the conventional method using hazardous mercury (II). The desired spiroketal (**12**) and undesired one (**13**) were obtained in 51–60% and 22–25% yields, respectively. Treatment of **13** with PPTS produced a 3:1 mixture of **12** and **13**, and this equilibrium reaction was repeated again. Collectively, 1.89 g of **12** was obtained in 73% yield from the triol (**11**). A total of 737 mg of **12** was carried forward to the next steps.

Condensation of the spiroketal (**12**) with the known carboxylic acid (**14**) was achieved using Yamaguchi's method[20]. Detachment of the MPM group using the DDQ/CH_2Cl_2/H_2O condition on a several hundred milligram scale resulted in the unexpected isomerization of at least 30% of the spiroketal, presumably because the prolonged reaction time led to the

decomposition of DDQ to acidify the reaction mixture. Attempts to maintain neutral conditions by employing a phosphate buffer (pH 7.4) instead of distilled water successfully prevented this severe isomerization.

Although our previous experiment suggested that switching of the protecting group from a MPM group to a triethylsilyl group was successful for providing the corresponding carboxylic acid, oxidative cleavage of the olefin group in the corresponding silyl ether resulted in a low yield (22%), presumably because of its poor solubility in the solvent (*t*-BuOH/pH 7 phosphate buffer = 1:1). The utilization of a more hydrophilic olefin (**16**) with a free hydroxyl group produced a carboxylic acid (**17**) in good yield (71%), and oxidation of the free secondary hydroxyl group did not proceed under this condition. This OH-free method omitted the protection/deprotection steps, and markedly improved the efficiency of the oxidative cleavage step.

Yamaguchi's macrolactonization[20] of the *seco*-acid (**17**) was performed at 2 mM to efficiently produce a lactone (**18**) (82%), and the production of a dimer was not confirmed. We also showed that a prolonged time for adding a solution of a mixed anhydride into a solution of DMAP was not needed for the desired intramolecular reaction; that is, the total time for the reagent adding could be shortened to only 15 minutes from 5 hours. Finally, removal of two benzyl groups, and purification by convenient normal phase column chromatography provided 287 mg of 10-methyl-aplog-1 (**1**) in 23 steps from *m*-hydroxycinnamic acid with an overall yield of 1.1%. An additional 500 mg of **1** could be obtained by treating the other 1.15 g of **12** in a similar manner. ^{1}H, ^{13}C NMR, specific optical rotation, and FAB-MS data coincided with previous findings.[11] Its purity was confirmed to be more than 98% by ^{1}H, ^{13}C NMR data and HPLC analysis (Supporting Information). ^{1}H NMR data of **3**, **4**, **7**, **10**, **12**, and **15** also agreed with previous findings.[11]

In summary, we developed a reliable method for synthesizing 10-methyl-aplog-1 (**1**) that could be applied to the production of several hundred milligrams of this potential medicinal lead. Notable features of this synthetic method include one-step hydroxyl-directed epoxidation of the homoallyl alcohol (**5**) and chemoselective oxidation of alkene (**16**) with a free secondary hydroxyl group. An *in vivo* evaluation of the anticancer activity of **1** is currently in progress and will be reported in due course.

3. Experimental section

3.1. General remarks

The following spectroscopic and analytical instruments were used: Digital Polarimeter, P-2200 (Jasco, Tokyo, Japan); ^{1}H, ^{13}C NMR, Avance III 400 and Avance III 500 (Bruker, Germany); HPLC, Waters Model 600E with a Model 2487 UV detector; FAB-MS and HR-FAB-MS, JMS-600H and JMS-700 (JEOL, Tokyo, Japan); IR, FT/IR-470 Plus (Jasco, Tokyo, Japan). HR-ESI-TOF-MS, Xevo G2-S QTof (Waters, MS, USA). HPLC was carried out on YMC packed SIL SL12S05-1006WT, SIL SL12S05-2510WT, ODS-A AA12S05-1006WT (Yamamura Chemical Laboratory, Kyoto, Japan), and CHIRAL CEL OJ-RH (Daicel Corporation, Osaka, Japan). Wakogel C-200 (silica gel, Wako Pure Chemical Industries, Osaka, Japan) and YMC A60-350/250 gel (ODS, Yamamura Chemical Laboratory, Kyoto, Japan) were used for column chromatography. All other chemicals and reagents were purchased from chemical companies and used without further purification. Compounds **8** and **14** were synthesized as reported previously.[16]

3.2. Synthesis of 1-(benzyloxy)-3-(3-bromopropyl)benzene (3).

m-Hydroxycinnamic acid (**2**) (20.0 g, 122 mmol) was treated in a manner similar to the method reported previously[16] to afford the bromide (**3**) (33.8 g, 111 mmol, 91%) as a clear oil.

3.3. Synthesis of ethyl 5-(3-(benzyloxy)phenyl)pentanoate (4).

The bromide (**3**) (33.8 g, 111 mmol) was treated in a manner similar to the method reported previously[16] to afford the ester (**4**) (21.5 g, 68.8 mmol, 62%) as a clear oil.

3.4. Synthesis of (3*S*,4*R*)-8-(3-(benzyloxy)phenyl)-3-methyloct-1-en-4-ol (5).

The ester (**4**) (21.5 g, 68.8 mmol) was subjected to partial reduction[16] followed by Brown's asymmetric crotylation[11,14] as reported previously. Four installments afforded homoallyl alcohol as a clear oil (**5**) (16.6 g, 51.2 mmol) in 74% yield.

3.5. Synthesis of (2*R*,3*R*)-7-(3-(benzyloxy)phenyl)-2-((*R*)-oxiran-2-yl)heptan-3-ol (6).

The typical procedure used for the substrate-controlled epoxidation of the homoallyl alcohol (**5**) was as follows. To a solution of **5** (3.63 g, 11.2 mmol) in CH_2Cl_2 (110 mL) were added vanadyl acetylacetonate (60 mg, 0.224 mmol) and 5.5 M *t*-BuOOH in decane (3.1 mL,

16.8 mmol) at rt. While stirring for 7 h, additional VO $(acac)_2$ (90 mg, 0.37 mmol) and 5.5 M *t*-BuOOH in decane (1.0 mL, 5.50 mmol) were added in two portions. The reaction was quenched with 10% aq. $Na_2S_2O_3$ (100 mL) and the mixture were extracted three times with EtOAc (200 mL x 1, 100 mL x 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, 10% → 20% EtOAc/hexane) to afford an epoxyalcohol as a clear oil (**6**) (2.18 g, 6.41 mmol) and mixture (1.14 g) of the epoxyalcohol (**6**) and byproduct. This procedure was repeated four times to afford 8.78 g of the epoxyalcohol (**6**) and 4.74 g of the mixture of epoxyalcohol (**6**) and byproduct. The combined latter mixture was once again purified by column chromatography (silica gel, 10% → 20% EtOAc/hexane) to afford the epoxyalcohol (**6**) (1.21 g). Finally, 10.0 g (29.4 mmol) of the epoxyalcohol (**6**) was obtained in 57% yield from 16.6 g (51.2 mmol) of the homoallyl alcohol (**5**). ^{1}H NMR (400 MHz, 297.7 K, $CDCl_3$, 0.047 M) δ 0.96 (3H, d, *J* = 7.1 Hz), 1.30 (1H, m), 1.43–1.68 (6H, m), 2.14 (1H, d, *J* = 3.6 Hz), 2.47 (1H, dd, *J* = 4.9, 2.8 Hz), 2.61 (2H, t, *J* = 7.6 Hz), 2.76 (1H, dd, *J* = 4.9, 4.1 Hz), 2.91 (1H, ddd, *J* = 8.1, 4.1, 2.8 Hz), 3.65 (1H, m), 5.05 (2H, s), 6.78–6.82 (3H, m), 7.19 (1H, t, *J* = 7.8 Hz), 7.32–7.45 (5H, m) ppm. ^{13}C NMR (100 MHz, 298.0 K, $CDCl_3$, 0.047 M) δ 12.9, 25.1, 31.4, 34.3, 36.0, 42.2, 45.3, 54.7, 69.9, 75.1, 111.8, 115.1, 121.2, 127.5 (2C), 127.9, 128.6 (2C), 129.2, 137.2, 144.4, 158.9 ppm. IR (KBr) cm^{-1}: 3461, 3033, 2934, 2862, 1582, 1487, 1454, 1258, 1155, 1027, 756, 697. HR-FAB-MS (matrix, *m*-nitrobenzyl alcohol) *m/z*: 340.2039 ($[M]^+$, calcd for $C_{22}H_{28}O_3$ 340.2039). $[\alpha]^{16.8}_D$ +10.8° (*c* = 0.53, $CHCl_3$).

3.6. Synthesis of (*R*)-2-((2*R*,3*R*)-7-(3-(benzyloxy)phenyl)-3-((4-methoxybenzyl)oxy)heptan-2-yl)oxirane (7).

The hydroxyl group of **6** (10.0 g, 29.4 mmol) was protected as the MPM ether, as reported previously[11], in two trials to afford the MPM ether as a clear oil (**7**) (9.6 g, 20.9 mmol) in 71% yield.

3.7. Synthesis of 4-(2-(((2*R*,4*S*,5*R*,6*R*)-6-(4-(3-(benzyloxy)phenyl)butyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)methyl)-1,3-dithian-2-yl)-4-methylpentan-1-ol (9).

Coupling of the epoxide (**7**) (9.6 g, 20.9 mmol) with the dithiane (**8**) (11.8 g, 31.4 mmol) was performed on a several hundred milligram scale by a previously reported method to afford a coupling product (16.4 g, 19.6 mmol) in 94% yield. DDQ-mediated oxidative acetalization,

followed by desilylation using a previously reported method,[11,21] gave the alcohol as a clear oil (**9**) (12.3 g, 18.2 mmol) in 93% yield. ^{1}H NMR: (500 MHz, 295.3 K, $CDCl_3$, 0.017 M) δ 0.93 (3H, d, J = 6.7 Hz), 1.18 (3H, s), 1.19 (3H, s), 1.44–1.78 (11H, m), 1.85 (1H, m), 1.94 (1H, m), 2.38 (1H, dd, J = 16.2, 7.2 Hz), 2.46 (1H, d, J = 16.1 Hz), 2.60 (2H, m), 2.67–2.79 (2H, m), 2.83–2.93 (2H, m), 3.46 (1H, m), 3.55 (2H, br.s), 3.79 (3H, s), 3.93 (1H, dd, J = 9.9, 7.1 Hz), 5.04 (2H, s), 5.45 (1H, s), 6.75–6.82 (3H, m), 6.86 (2H, m), 7.19 (1H, t, J = 7.8 Hz), 7.32 (1H, m), 7.36–7.47 (6H, m) ppm. ^{13}C NMR (125 MHz, 296.2 K, $CDCl_3$, 0.017 M) δ 13.2, 22.5 (br), 23.0 (br), 24.4, 24.9, 26.7, 27.6, 28.3, 31.4, 32.6, 32.9, 36.0, 38.9, 41.5, 44.5, 55.3, 63.7, 63.8, 70.0, 80.3, 82.0, 99.5, 111.9, 113.4 (2C), 115.2, 121.2, 127.3 (2C), 127.5 (2C), 127.9, 128.6 (2C), 129.2, 131.6, 137.3, 144.5, 158.9, 159.7 ppm. IR (KBr) cm^{-1}: 3421, 3032, 2936, 2860, 1614, 1583, 1518, 1250, 1030, 755, 696. HR-FAB-MS (matrix, *m*-nitrobenzyl alcohol): *m/z*: 701.3335 ($[M+Na]^+$, calcd for $C_{40}H_{54}O_5S_2Na$ 701.3310). $[\alpha]^{18.8}_D$ –3.4° (c = 0.58, $CHCl_3$).

3.8. Synthesis of (*R*)-7-(2-(((2*R*,4*S*,5*R*,6*R*)-6-(4-(3-(benzyloxy)phenyl)butyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)methyl)-1,3-dithian-2-yl)-7-methyloct-1-en-4-ol (10).

The alcohol (**9**) (12.3 g, 18.2 mmol) was subjected to Parikh-Doering oxidation, followed by Maruoka's asymmetric allylation on a 3-g scale, as reported previously,[11,16] to afford the homoallyl alcohol as a clear oil (**10**) (7.89 g, 11.0 mmol) in 60% yield.

3.9. Synthesis of (2*S*,3*R*,4*R*)-8-(3-(benzyloxy)phenyl)-1-(2-((*R*)-5-hydroxy-2-methyloct-7-en-2-yl)-1,3-dithian-2-yl)-3-methyloctane-2,4-diol (11).

The typical procedure used for acid hydrolysis of the anisylidene acetal (**10**) was as follows. To a solution of the acetal (**10**) (2.20 g, 3.06 mmol) in THF (120 mL) and H_2O (12 mL) was added TFA (6 mL) at 4 °C. The mixture was heated at 50 °C for 23 h and then cooled to 4 °C. The reaction was quenched with saturated aq. $NaHCO_3$ (100 mL). The mixture was extracted with EtOAc (100 mL x 3). 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, 5% → 20% → 50% EtOAc/hexane) to afford the triol as a clear oil (**11**) (760 mg, 1.27 mmol, 41%) and recovered acetal (**10**) (990 mg, 1.38 mmol, 45%). An additional 5.69 g of **10** was treated similarly in two portions. Finally, 3.18 g (5.30 mmol) of the triol (**11**) was obtained from 7.89 g (11.0 mmol) of the acetal (**10**) in 48% yield. ^{1}H

NMR (500 MHz, 296.3 K, $CDCl_3$, 0.012 M) δ 0.84 (3H, d, J = 6.9 Hz), 1.14 (6H, s), 1.38–1.50 (4H, m), 1.52–1.68 (6H, m), 1.67 (1H, d, J = 3.9 Hz, OH), 1.80 (1H, m), 1.90–2.01 (2H, m), 2.13-2.20 (3H, m), 2.32 (1H, m), 2.60 (2H, m), 2.82–2.89 (2H, m), 2.93-3.01 (2H, m), 3.59–3.61 (2H, m), 3.75 (1H, d, J = 2.5 Hz, OH), 4.30 (1H, m), 4.52 (1H, s, OH), 5.05 (2H, s), 5.13–5.17 (2H, m), 5.82 (1H, m), 6.78–6.83 (3H, m), 7.18 (1H, t, J = 7.8 Hz), 7.31–7.47 (5H, m) ppm. ^{13}C NMR (125 MHz, 296.9 K, $CDCl_3$, 0.012 M) δ 12.9, 22.4, 22.9 (br), 23.0, 25.0, 27.4, 27.5, 31.6, 32.0, 32.7, 34.5, 36.1, 42.1, 42.3, 44.8, 45.6, 63.3, 70.0, 71.3, 73.9, 74.3, 111.9, 115.2, 118.3, 121.2, 127.5 (2C), 127.9, 128.6 (2C), 129.2, 134.7, 137.3, 144.6, 158.9 ppm. IR (KBr) cm^{-1}: 3409, 3065, 3032, 2933, 2859, 1541, 1507, 1457, 1260, 1154, 1038, 695. HR-FAB-MS (matrix, *m*-nitrobenzyl alcohol): *m/z*: 601.3356 ($[MH]^+$, calcd for $C_{35}H_{53}O_4S_2$ 601.3385). $[\alpha]^{19.3}_{D}$ +2.0° (*c* = 0.38, $CHCl_3$).

3.10. Synthesis of (2*R*,3*S*,4*S*,6*R*,8*R*)-8-allyl-2-(4-(3-(benzyloxy)phenyl)butyl)-3,11,11-trimethyl-1,7-dioxaspiro[5.5]undecan-4-ol (12).

The typical procedure used for spiroketalization was as follows. To a solution of a dithiane (**11**) (712 mg, 1.19 mmol) in MeCN (36 mL) and H_2O (1.8 mL) was added Selectfluor® (1.05 g, 2.97 mmol) at 4 °C. After stirring for 30 min at the same temperature, the reaction was quenched with saturated aq. $NaHCO_3$ (40 mL). The mixture was extracted with EtOAc (50 mL x 3), and 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, 5% → 15% EtOAc/hexane) to afford the desired spiroketal as a clear oil (**12**) (317 mg, 0.644 mmol, 54%) and undesired spiroketal as a clear oil (**13**) (131 mg, 0.266 mmol, 22%). An additional 2.47 g of **11** was treated on a several hundred milligram scale in a similar manner to that described above. A total of 1.47 g (2.99 mmol, 56%) of **12** and 577 mg (1.17 mmol, 22%) of **13** were obtained from 3.18 g (5.30 mmol) of **11**. Compound **13**: ^{1}H NMR (500 MHz, 295.0 K, $CDCl_3$, 0.012 M) δ 0.90 (3H, s), 0.95 (3H, s), 0.95 (3H, d, J = 7.0 Hz), 1.14 (1H, dt, J = 13.0 Hz, 3.1 Hz), 1.31 (1H, d, J = 4.9 Hz, OH), 1.34–1.46 (4H, m), 1.58–1.74 (4H, m), 1.69 (1H, dd, J = 13.0, 10.1 Hz), 1.80 (1H, dd, J = 13.2, 5.7 Hz), 1.88 (1H, td, J = 13.0, 5.2 Hz), 1.96 (1H, m), 2.11 (1H, m), 2.16 (1H, m), 2.59 (2H, t, J = 7.4 Hz), 3.62 (1H, m), 3.78 (1H, m), 4.22 (1H, m), 4.98–5.04 (2H, m), 5.05 (2H, s), 5.79 (1H, m), 6.78–6.81 (3H, m), 7.19 (1H, t, J = 7.8 Hz), 7.30–7.45 (5H, m) ppm. ^{13}C NMR (125 MHz, 296.0 K, $CDCl_3$, 0.012 M) δ 11.6, 22.9, 25.8, 26.7, 27.3, 31.3, 33.6, 33.9, 34.1, 36.0, 36.2, 36.8, 40.8, 64.4, 68.8, 70.0, 79.0, 102.6,

111.8, 115.3, 116.4, 121.2, 127.5 (2C), 127.9, 128.6 (2C), 129.2, 135.4, 137.2, 144.3, 158.9 ppm. IR (KBr) cm^{-1}: 3384, 3067, 3033, 2934, 2858, 1584, 1456, 1259, 1155, 985, 917, 758, 740, 695. HR-ESI-TOF-MS (matrix, 50% MeOH/H_2O containing 0.1% formic acid): *m/z*: 515.3124 ($[M+Na]^+$, calcd for $C_{32}H_{45}O_4Na$ 515.3137). $[\alpha]^{26.2}_D$ −9.6° (*c* = 0.36, $CHCl_3$).

The undesired spiroketal (**13**) was subjected to the following acid catalyzed equilibrium reaction. To a solution of **13** (577 mg, 1.17 mmol) in MeCN (20 mL) and CH_2Cl_2 (20 mL) was added PPTS (29.3 mg, 0.117 mmol) at rt. After stirring for 30 min, the reaction was quenched with saturated aq. $NaHCO_3$ (20 mL). After the organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (40 mL x 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, 5% → 10% → 20% EtOAc/hexane) to afford the desired spiroketal (**12**) (420 mg, 0.854 mmol, 73%) and undesired spiroketal (**13**) (137 mg, 0.278 mmol, 24%).

3.11. Synthesis of (2*R*,3*R*,4*S*,6*R*,8*R*)-8-allyl-2-(4-(3-(benzyloxy)phenyl)butyl)-3,11,11-trimethyl-1,7-dioxaspiro[5.5]undecan-4-yl (*R*)-4-(benzyloxy)-3-((4-methoxybenzyl)oxy)butanoate (15).

Condensation of the spiroketal (**12**) (737 mg, 1.50 mmol) with the acid (**14**) (544 mg, 1.65 mmol) was performed in three portions by a previously reported method[6] to afford the ester as a clear oil (**15**) (1.13 g, 1.40 mmol) in 93% yield.

3.12. Synthesis of (2*R*,3*R*,4*S*,6*R*,8*R*)-8-allyl-2-(4-(3-(benzyloxy)phenyl)butyl)-3,11,11-trimethyl-1,7-dioxaspiro[5.5]undecan-4-yl (*R*)-4-(benzyloxy)-3-hydroxybutanoate (16).

The typical procedure used was as follows. To a vigorously stirred solution of the MPM ether (**15**) (514 mg, 0.639 mmol) in CH_2Cl_2 (30 mL) and pH 7.2 phosphate buffer (10 mL) was added DDQ (290 mg, 1.28 mmol) at rt. After 1 h of stirring at rt, the mixture was poured into saturated aq. $NaHCO_3$ (50 mL) and EtOAc (100 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (50 mL x 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, 10% → 20% EtOAc/hexane) to afford an alcohol (**16**) (401 mg, 0.586 mmol, 92%) as a clear oil. An additional 616 mg (0.766 mmol) of **15** was treated in a manner similar to that described above. Finally, 832 mg (1.22 mmol) of

the alcohol (**16**) was obtained from 1.13 g (1.40 mmol) of the MPM ether (**15**) in 87% yield. ^{1}H NMR (500 MHz, 295.8 K, $CDCl_3$, 0.017 M) δ 0.80 (3H, d, *J* = 6.90 Hz), 0.89 (3H, s), 0.93 (3H, s), 1.25 (1H, m), 1.35–1.70 (10H, m), 1.70 (1H, dd, *J* = 15.2, 3.9 Hz), 2.12 (1H, dd, *J* = 15.2, 2.7 Hz), 2.42 (2H, m), 2.54 (1H, dd, *J* = 16.3, 9.3 Hz), 2.59 (1H, t, *J* = 7.5 Hz), 2.62 (1H, dd, *J* = 16.3, 3.6 Hz), 3.46 (1H, dd, *J* = 9.6, 5.2 Hz), 3.51 (1H, dd, *J* = 9.6, 5.8 Hz), 3.62 (1H, m), 3.88 (1H, d, *J* = 3.70 Hz, OH), 3.95 (1H, m), 4.25 (1H, m), 4.56 (2H, s), 4.97–5.01 (2H, m), 5.05 (2H, s), 5.09 (1H, m), 5.75 (1H, m), 6.78–6.84 (3H, m), 7.19 (1H, t, *J* = 7.9 Hz), 7.27–7.47 (10H, m) ppm. ^{13}C NMR (125 MHz, 296.2 K, $CDCl_3$, 0.017 M) δ 13.2, 23.6, 23.8, 24.5, 24.6, 29.9, 31.4, 31.8, 32.4, 36.1, 36.2, 36.8, 39.4, 40.4, 67.0, 68.8, 70.0, 71.8, 72.0, 73.2, 73.5, 100.2, 111.8, 115.2, 116.8, 121.2, 127.5 (2C), 127.7 (3C), 127.9, 128.4 (2C), 128.6 (2C), 129.2, 135.6, 137.3, 138.1, 144.6, 158.9, 171.8 ppm. IR (KBr) cm^{-1}: 3473, 3065, 3032, 2935, 2859, 1732, 1717, 1583, 1456, 1258, 1155, 915, 875, 739, 696. HR-FAB-MS (matrix, *m*-nitrobenzyl alcohol): *m*/*z*: 684.4001 ($[M]^+$, calcd for $C_{43}H_{56}O_7$ 684.4026). $[\alpha]^{29.1}_D$ +47.2° (*c* = 0.57, $CHCl_3$).

3.13. Synthesis of 2-((2*R*,6*R*,8*R*,9*R*,10*S*)-10-(((*R*)-4-(benzyloxy)-3-hydroxybutanoyl)oxy)-8-(4-(3-(benzyloxy)phenyl)butyl)-5,5,9-trimethyl-1,7-dioxaspiro[5.5]undecan-2-yl)acetic acid (17).

The typical procedure used was as follows. To a suspension of $NaIO_4$ (1.0 g, 4.69 mmol) in pH 7.2 phosphate buffer (40 mL) was added $KMnO_4$ (92.6 mg, 0.586 mmol) in one portion. After 15 min of stirring at rt under an Ar atmosphere, the mixture was added to a solution of the alkene (**16**) (401 mg, 0.586 mmol) in *t*-BuOH (40 mL). The reaction mixture was stirred at rt for 45 min, and the reaction was quenched with $Na_2S_2O_3$ (278 mg, 1.76 mmol). The resulting mixture was poured into EtOAc (100 mL) and H_2O (100 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (80 mL x 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, 20% → 40% EtOAc/hexane containing 0.1% AcOH) to afford a *seco*-acid (**17**) (322 mg, 0.459 mmol, 78%) as a clear oil. An additional 431 mg (0.630 mmol) of **16** was treated in a manner similar to that described above. Finally, 609 mg (0.867 mmol) of **17** was obtained from 832 mg (1.22 mmol) of **16** in 71% yield. ^{1}H NMR (400 MHz, 297.3 K, $CDCl_3$, 0.032 M) δ 0.80 (3H, d, *J* = 8.9 Hz), 0.91 (3H, s), 0.94 (3H, s), 1.30 (1H, m), 1.40–1.70 (9H, m), 1.75 (1H, m), 1.75 (1H, dd, *J* = 15.2, 3.9 Hz), 2.10 (1H, dd, *J* = 15.2, 2.7 Hz), 2.47–2.53 (3H, m), 2.57–2.62 (2H, m), 2.72 (1H, dd, *J* =

15.0, 8.0 Hz), 3.48 (1H, dd, J = 9.6, 4.5 Hz), 3.50 (1H, dd, J = 9.6, 6.4 Hz), 3.95 (1H, m), 4.11 (1H, m), 4.30 (1H, m), 4.57 (2H, s), 5.05 (2H, s), 5.12 (1H, m), 6.78–6.87 (3H, m), 7.19 (1H, t, J = 7.8 Hz), 7.28–7.45 (10H, m) ppm. ^{13}C NMR (100 MHz, 297.5 K, $CDCl_3$, 0.032 M) δ 13.2, 23.7, 23.8, 24.4, 26.0, 30.1, 31.4, 31.5, 32.4, 36.0, 36.1, 36.9, 39.1, 41.2, 67.0, 69.3, 69.5, 69.9, 71.2, 73.4, 73.6, 101.2, 111.8, 115.2, 121.2, 127.5 (2C), 127.9, 127.9, 128.0 (2C), 128.5 (2C), 128.6 (2C), 129.2, 137.2, 137.5, 144.5, 158.9, 171.5, 173.0 ppm. IR (KBr) cm^{-1}: 3033, 2935, 2861, 1733, 1717, 1685, 1577, 1457, 1258, 1058, 740, 696. HR-FAB-MS (matrix, *m*-nitrobenzyl alcohol): *m/z*: 703.3876 ($[MH]^+$, calcd for $C_{42}H_{55}O_9$ 703.3846). $[\alpha]^{30.8}_{D}$ +38.8° (c = 0.37, $CHCl_3$).

3.14. Synthesis of (1*R*,3*R*,4*R*,5*S*,9*R*,13*R*)-9-((benzyloxy)methyl)-3-(4-(3-(benzyloxy)phenyl)butyl)-4,16,16-trimethyl-2,6,10,17-tetraoxatricyclo[11.3.1.1^{1,5}]octadecane-7,11-dione (18).

The typical procedure used was as follows. To a solution of the *seco*-acid (**17**) (322 mg, 0.459 mmol) and Et_3N (191 μL, 1.38 mmol) in toluene (23 mL), was added 2,4,6-trichlorobenzoyl chloride (108 μL, 0.689 mmol) at rt. The mixture was stirred at rt for 1 h, and then diluted with toluene (100 mL). The mixture was added dropwise to a solution of DMAP (840 mg, 6.89 mmol) in toluene (100 mL) over 15 min. The anhydride flask was rinsed twice with toluene (5 mL) (each rinse was added in one portion to the reaction mixture). After an additional 2 h of stirring at rt, saturated aq. $NaHCO_3$ (30 mL) was added and the organic layer was separated. The aqueous layer was extracted with EtOAc (50 mL x 2), and 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, 5% → 10% EtOAc/hexane) to afford a lactone (**18**) (243 mg, 0.355 mmol, 77%) as a clear oil. An additional 287 mg (0.408 mmol) of **17** was treated in a manner similar to that described above. Finally, 489 mg (0.714 mmol) of **18** was obtained from 609 mg (0.867 mmol) of **17** in 82% yield. ^{1}H NMR (500 MHz, 295.0 K, $CDCl_3$, 0.029 M) δ 0.77 (3H, d, J = 6.9 Hz), 0.85 (3H, s), 0.96 (3H, s), 1.26–1.57 (10H, m), 1.68 (1H, m), 1.69 (1H, dd, J = 15.4, 4.0 Hz), 2.34 (1H, dd, J = 12.7, 10.9 Hz), 2.45–2.51 (2H, m), 2.60 (2H, t, J = 7.7 Hz), 2.78 (1H, dd, J = 17.1, 3.1 Hz), 2.91 (1H, dd, J = 17.1, 11.5 Hz), 3.58 (1H, dd, J = 10.1, 5.5 Hz), 3.64 (1H, dd, J = 10.1, 3.6 Hz), 3.84 (1H, m), 3.93 (1H, m), 4.49 (1H, d, J = 12.0 Hz), 4.57 (1H, d, J = 12.0 Hz), 5.03 (1H, br.s), 5.05 (2H, s), 5.20 (1H, m), 6.79 (1H, dd, J = 8.2, 2.4 Hz), 6.82 (1H, d, J = 7.5 Hz), 6.86 (1H, br.s), 7.18 (1H, t, J = 7.9 Hz), 7.27–7.45 (10H, m) ppm. ^{13}C NMR (125 MHz, 295.2 K, $CDCl_3$,

0.029 M) δ 13.1, 21.4, 24.3, 26.0, 26.6, 27.3, 31.1, 32.3, 34.7, 36.1, 36.9, 36.9, 37.2, 42.7, 68.3, 68.9, 69.9, 70.2, 70.6, 72.6, 73.5, 99.8, 111.8, 115.2, 121.3, 127.5 (2C), 127.7 (2C), 127.8 (2C), 128.5 (4C), 129.1, 137.4, 137.8, 144.8, 158.9, 170.2 (2C) ppm. IR (KBr) cm^{-1}: 3032, 2935, 2860, 1748, 1733, 1716, 1577, 1457, 1271, 1060, 753, 697. HR-FAB-MS (matrix, *m*-nitrobenzyl alcohol): *m/z*: 685.3734 ($[MH]^+$, calcd for $C_{42}H_{53}O_8$ 685.3740). $[\alpha]^{30.1}_D$ +48.7° (c = 1.00, $CHCl_3$).

3.15. Synthesis of (1*R*,3*R*,4*R*,5*S*,9*R*,13*R*)-9-(hydroxymethyl)-3-(4-(3-hydroxyphenyl)butyl)-4,16,16-trimethyl-2,6,10,17-tetraoxatricyclo[$11.3.1.1^{1,5}$]octadecane-7,11-dione (1).

The removal of the two benzyl groups of the lactone (**18**) (489 mg, 0.714 mmol) was performed in three portions by a method reported previously[6] to afford a crude **1** (357 mg), which was purified by column chromatography (silica gel, 25% → 50% EtOAc/hexane) to afford **1** (287 mg, 0.596 mmol, 83%) as a clear oil. The purity of **1** was more than 98%, which was confirmed by two diverse HPLC systems: YMC packed SIL SL12S05-1006WT using *i*-PrOH:$CHCl_3$:hexane = 5:15:80 (flow rate of 1.0 mL/min; retention time of 11.0 min); YMC packed ODA-A AA12S05-1006WT using MeOH:H_2O = 75:25 (flow rate of 1.0 mL/min; retention time of 13.8 min). IR (KBr) cm^{-1}: 3423, 3021, 2938, 2860, 1717, 1588, 1457, 1297, 1276, 1060, 756, 696. FAB-MS (matrix, *m*-nitrobenzyl alcohol): m/z 505 ($[MH]^+$). ^{1}H NMR and ^{13}C NMR data coincided with those reported previously.[11] A portion of **1** from above (10 mg) was further purified by HPLC (column, YMC-Pack SIL SL12S05-2510WT; solvent, *i*-PrOH:$CHCl_3$:hexane = 5:15:80; flow rate, 3.0 mL/min; pressure, 570 psi; retention time, 24.3 min) to afford the material for confirmation of optical purity by measurement of specific optical rotation and chiral HPLC analysis. $[\alpha]^{25.8}_D$ +67.6° (c 0.505, $CHCl_3$: lit[11], +76.2°). Only one peak was detected by two diverse HPLC systems on CHIRAL CEL OJ-RH using MeOH:H_2O = 80:20 (flow rate of 0.5 mL/min; retention time of 19.2 min) and MeCN:H_2O = 40:60 (flow rate of 0.5 mL/min; retention time of 26.2 min).

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Supporting information

HPLC analysis and NMR spectra of **1**. This material is available via the Internet at http://dx.doi.org/10,1016/j.tet.2014.11.026.

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