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First Total Synthesis of Gliomasolide C and Formal Total Synthesis of Sch-725674

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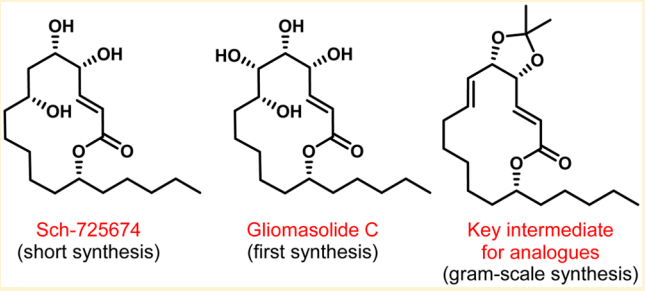
Supporting Information

ABSTRACT: Syntheses of two 14-membered macrolides Sch-725674 and Gliomasolide C are described here. The first total synthesis of Gliomasolide C, the short synthesis of Sch-725674, and regioselective Wacker oxidation of internal olefin are the highlights of this disclosure. In addition, a key macrocycle with orthogonal functionalities was designed and synthesized on a gram scale for the generation of analogues.



The family of 14-membered macrolides has a special attraction in the literature as they possess excellent biological properties.[1] Macrolides such as erythromycin, rustmicin, migrastatin, clonostachydiol, and sekothrixide are some of the biologically important examples of this family.[1] Erythromycin[2] and clarithromycin[3] are the examples of U.S. FDA approved drugs for the treatment of bacterial infections. Therefore, a lot of interest in 14-membered macrocylic lactones was generated among the chemists as part of their medicinal chemistry and total synthesis programs.[4] Along these lines, Sch-725674 (**1**) and very recently isolated gliomasolides caught our attention to start a program toward the total synthesis and screening of their various analogues. Sch-725674, isolated by Yang and co-workers from a culture of *Aspergillus sp*., showed antifungal properties, and it became a popular target for total synthesis.[5] The first total synthesis of Sch-725674 and its analogues with all possible stereoisomers has been accomplished by the Curran's group using fluorous chemistry.[6] Following Curran's synthesis, two elegant total syntheses of Sch-725674 by the Prasad[7] and Kaliappan[8] groups appeared. Very recently, five related gliomasolides (A–E, **2**–**6**) were isolated by Xu and co-workers from a sponge-derived fungus *Gliomastix sp*. ZSDS1-F7-2 (Figure 1).[9] In a limited biological screening, gliomasolide A displayed anticancer activity against HeLa (human epithelial carcinoma cell line) cells. However, so far, no synthetic efforts were documented on gliomasolides. Our efforts toward the syntheses of this group of natural products (Figure 1) are discussed here.

Retrosynthetically, the target molecules are envisioned from the acyclic *E*-olefin intermediates which, in turn, could be prepared from the known building blocks **7**, **8**, and **9** using cross-metathesis reaction (Scheme 1). To begin with, compound **7**[10] prepared from (*R*)-2-pentyloxirane opening with 5-hexenyl Grignard reagent, was subjected to cross-metathesis[11] using Grubbs' second-generation catalyst (G-II) with another olefinic partner **8**[12] constructed from ribose using

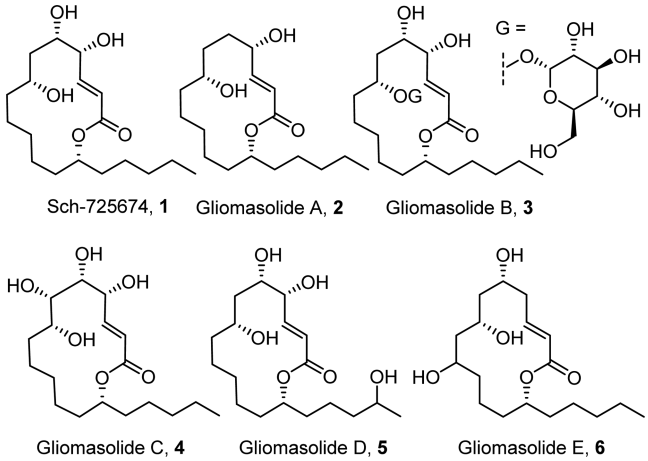


Figure 1. Structures of Sch-725674 and gliomasolides.

known chemistry. The outcome from this metathesis reaction was isolation of the intermediate **10** in 82% yield with an excellent *E*-selectivity. After having compound **10** in hand, our next task was a regioselective oxidation of the internal olefin to introduce an oxygen functionality away from chiral centers present in the molecule.

After a few failed attempts, Wacker oxidation[13] under high oxygen pressure (200 psi O_2, 0.5 equiv of $PdCl_2$, 70 °C in DMA:H_2O for 14 h) afforded desired ketone **11** in a highly regioselective manner. It is worth mentioning that, in a very few occasions, these kinds of transformations were documented in the literature.[14] In going forward, a seemingly simple ester hydrolysis step proved to be difficult in our hands under various basic conditions. However, the use of bis(tributyltin)oxide in

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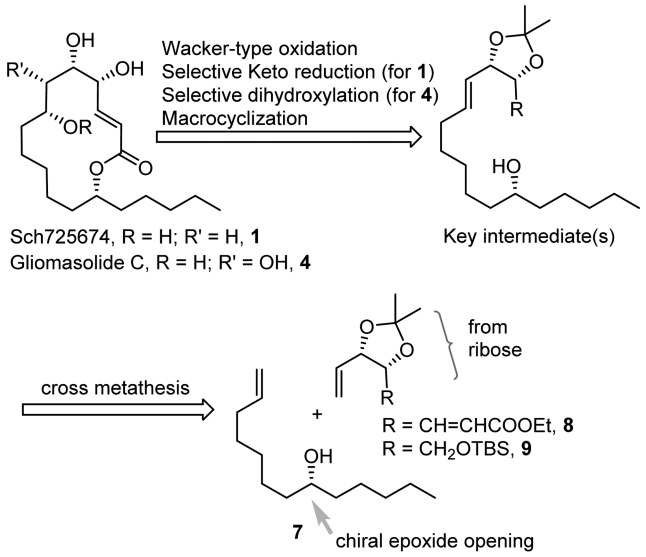
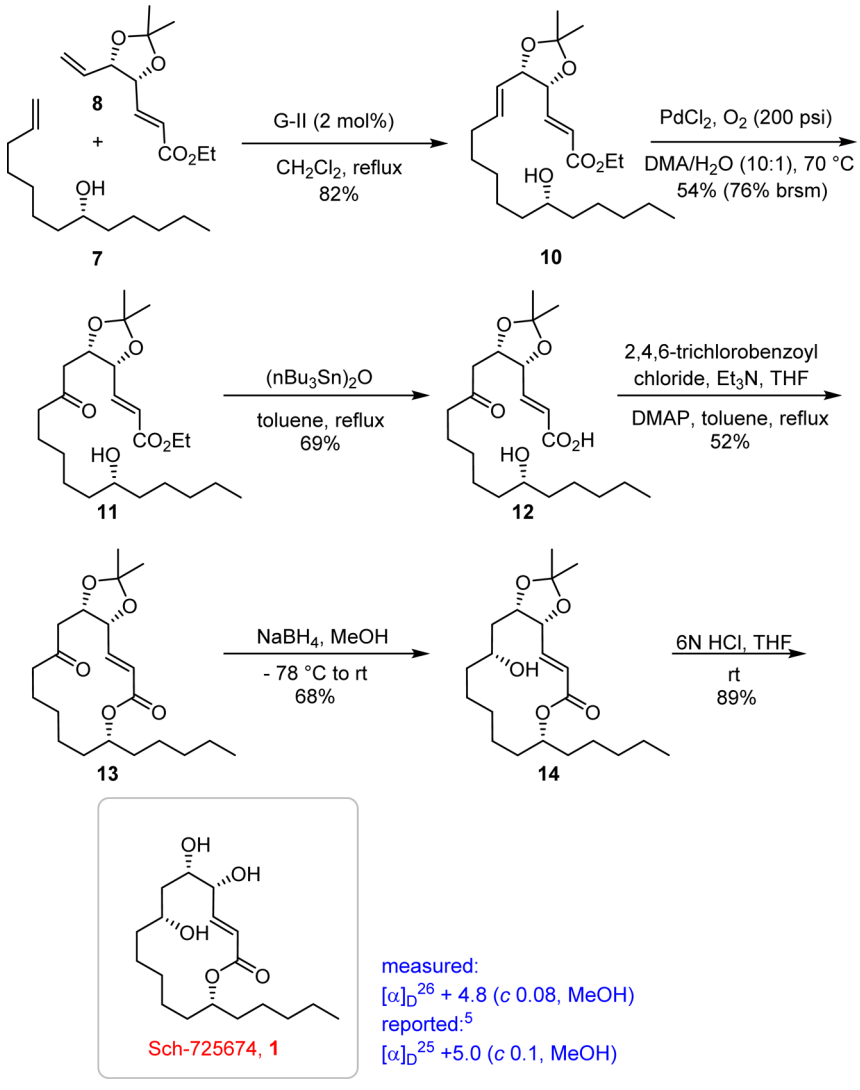
Scheme 1. Retrosynthetic Analysis of the Target NPs



refluxing toluene resulted in the formation of seco-acid **12** in 69% yield.[15] Compound **12** was subjected to Yamaguchi macrolactonization[16] using 2,4,6-trichloro benzoyl chloride and DMAP under refluxing conditions in toluene to afford known macrolactone **13**[8] in 52% yield. All the spectral data of **13** were compared and found to be identical. Stereoselective reduction of the carbonyl functionality to afford the desired compound **14** was achieved with $NaBH_4$/MeOH in 68% yield. As it was mentioned in Kaliappan's synthesis, the high stereoselectivity may be explained by the substrate control.[8] The deprotection of vicinal hydroxyl groups by exposing it to 6 N HCl in THF furnished the natural product Sch-725674 in 89% yield (Scheme 2). The spectral data of synthesized and natural compounds were compared and found to be identical in all respects.[17] It is worth highlighting that compound **14**, in which the free hydroxyl group can be glycosylated, followed by release of remaining hydroxyl groups, is an interesting intermediate for the synthesis of gliomasolide B, which is part of future work from this group.

Next, we diverted our efforts toward gliomasolide C, a structurally unique natural macrolide with four consecutive hydroxyl groups on the macrolide backbone. Cross-metathesis reaction between the intermediates **7** and **9**[18] using 2 mol % of

Scheme 2. Total Synthesis of Sch-725674



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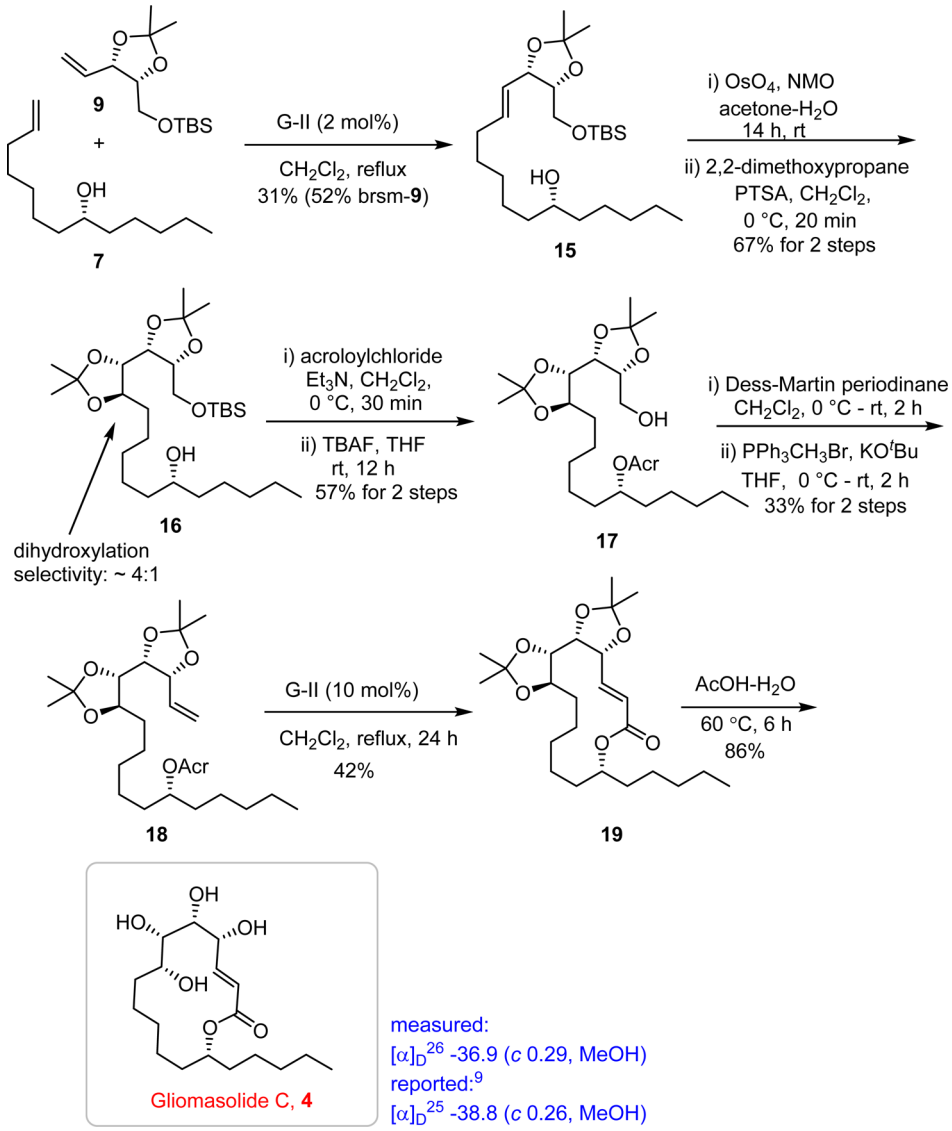
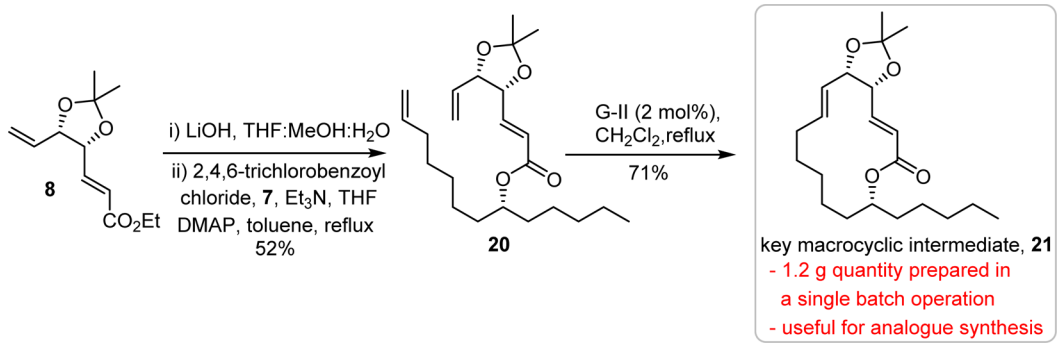
J. Org. Chem. 2016, 81, 290−296

Scheme 3. Total Synthesis of Gliomasolide C



Scheme 4. Gram-Scale Synthesis of Key Macrocycle



G-II resulted in compound **15** possessing the desired olefin with *E*-geometry. The substrate controlled dihydroxylation using OsO_4/NMO in acetone:H_2O mixture, followed by protection of the resulting hydroxyl groups, produced compound **16** in 67% isolated yield (after two steps) with ~4:1 (dr) selectivity, as determined by NMR (only the required diastereomer is shown in Scheme 3).[19] The mixture of isomers was transformed to compound **17** by treating with acrolyl chloride/Et_3N in DCM, followed by deprotection of the TBS group with TBAF in THF. At this stage, the major compound was cleanly separated and characterized completely. Oxidation of the primary alcohol **17** with Dess−Martin periodinane, followed by Wittig reaction, afforded diene **18** in moderate yields. We could not purify the compound **18**

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completely. At this stage, the diene **18** was subjected to ring-closing metathesis (RCM)[20] using 10 mol % G-II, generating macrocycle **19** in 42% yield. Finally, both the acetonide protecting groups were removed using aqueous acetic acid to afford the gliomasolide C in 86% yield (Scheme 3). All the spectral data of synthesized gliomasolide C were identical to those of the natural product.[9] Previously, the structure of gliomasolide C was determined by single X-ray analysis by Xu and co-workers.[9]

After the successful syntheses of the two natural products, we have planned to generate a focused library of compounds around this scaffold by considering the importance of 14-membered macrolides. Toward this goal, the known ester **8** was hydrolyzed and re-esterified with compound **7** under Yamaguchi conditions to provide compound **20**, which, in turn, was subjected to RCM to afford key macrocylic intermediate **21**, and it was completely characterized using various spectral methods (Scheme 4). All the three reactions described in Scheme 4 were carried out on a gram-scale level, and 1.2 g of the macrocycle **21** was prepared in a single batch operation. It is interesting to note that the macrocycle **21** contains (i) two chemically distinct olefins which can be selectively functionalized and (ii) a fused dioxolane moiety on the macrocycle that can be used to induce stereoselectivity for preparing various analogues. However, our attempts to synthesize Sch-725674 (**1**) and gliomasolide C (**4**) from macrocycle (**21**) were unsuccessful (see the Supporting Information for details).

Thus, we have achieved (1) the formal total synthesis of Sch-725674, a popular synthetic target using a short sequence of reactions, (2) the first total synthesis of gliomasolide C, a functionally embellished macrocycle among the family of gliomasolides, and (3) gram-scale synthesis of a macrocyclic diene (**21**) with appropriate functionalities suitable for selective modifications, which can be utilized for the generation of the analogues. The chemistry described here can be applied to the synthesis of other members of the group.

EXPERIMENTAL SECTION

General. All reagents, starting materials, and solvents (including dry solvents) were obtained from commercial suppliers and used as such without further purification. Reactions were carried out in oven-dried glassware under a positive pressure of argon unless otherwise mentioned. Air-sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus via rubber septa. Reactions were monitored by thin-layer chromatography (TLC) with 0.25 mm precoated silica gel plates (60 F254). Visualization was accomplished with either UV light, iodine adsorbed on silica gel, or by immersion in an ethanolic solution of phosphomolybdic acid (PMA), *p*-anisaldehyde, or $KMnO_4$, followed by heating with a heat gun for ~15 s. Column chromatography was performed on silica gel (100–200 or 230–400 mesh size). Deuterated solvents for NMR spectroscopic analyses were used as received. All ^1H NMR and ^{13}C NMR spectra were obtained using a 200, 400, or 500 MHz spectrometer. Coupling constants were measured in hertz. All chemical shifts were quoted in ppm, relative to TMS, using the residual solvent peak as a reference standard. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. HRMS (ESI) were recorded on an ORBITRAP mass analyzer. Infrared (IR) spectra were recorded on an FT-IR spectrometer as thin films using NaCl plates. Optical rotations were recorded on a polarimeter at 589 nm. Chemical nomenclature was generated using Chem Bio Draw Ultra 14.0; melting points were recorded on a melting point apparatus.

Ethyl(*E*)-3-((4*R*,5*S*)-5-((*R*,*E*)-8-hydroxytridec-1-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (10). Grubbs second-generation catalyst (G-II) (18 mg, 0.02 mmol) was added to a solution of alcohol **7** (130 mg, 0.66 mmol), ester **8** (100 mg, 0.44 mmol) in dry degassed CH_2Cl_2 (5.0 mL), and the resulting solution was stirred under reflux for 6 h, rm was concentrated *in vacuo*. The crude product was purified by flash chromatography over 200–400 mesh silica gel (15% EtOAc/Petroleum ether) to afford hydroxyl ester **10** (145 mg, 82%) as a light yellow oil. $[\alpha]_D^{26}$ +27.54 (*c* 0.16, $CHCl_3$); IR υ_{max} (film): 3450, 3015, 1708, 1371, 1257 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.79 (dd, *J* = 15.6, 5.4 Hz, 1H), 6.05 (dd, *J* = 15.6, 1.5 Hz, 1H), 5.78 (td, *J* = 15.3, 6.8 Hz, 1H), 5.36–5.26 (m, 1H), 4.73–4.65 (m, 2H), 4.00 (q, *J* = 7.1 Hz, 2H), 3.64–3.52 (m, 1H), 2.11–2.01 (m, 2H), 1.53 (s, 3H), 1.37 (s, 3H, merged with multiplet), 1.43–1.24 (m, 19H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 144.2, 137.0, 125.0, 122.4, 109.2, 79.7, 77.6, 71.9, 60.5, 37.4, 37.3, 32.1, 31.9, 29.0, 28.7, 27.8, 25.3 (3C), 22.6, 14.2, 14.0; HRMS (ESI): *m*/*z* calculated for $C_{23}H_{40}O_5Na$ $[M + Na]^+$ 419.2768, found 419.2761.

Ethyl(*E*)-3-((4*R*,5*S*)-5-((*R*)-8-hydroxy-2-oxotridecyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (11). $PdCl_2$ (24 mg, 0.13 mmol) was added to a solution of dimethylacetamide (20 mL), H_2O (2.0 mL) in a 100 mL Parr steel reactor, and the resulting solution was stirred under 200 psi O_2 pressure for 1 h at rt. Compound **10** (100 mg, 0.25 mmol) in DMA (3.0 mL) was added, and the mixture was heated at 70 °C under 200 psi O_2 pressure for 14 h. The rm was cooled, H_2O (50 mL) was added, and extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography over 200–400 mesh silica gel (20% EtOAc/Petroleum ether) to afford keto alcohol **11** (56 mg, 54%, 76%, based on recovery of starting material) as a light yellow oil. $[\alpha]_D^{25}$ +6.68 (*c* 0.86, $CHCl_3$); IR υ_{max} (film): 3420, 2930, 1715, 1654, 1217 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.70 (dd, *J* = 15.4, 5.8 Hz, 1H), 6.05 (dd, *J* = 15.6, 1.2 Hz, 1H), 4.83–4.79 (m, 1H), 4.70 (q, *J* = 6.8 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.57–3.54 (m, 1H), 2.75 (dd, *J* = 17.4, 6.4 Hz, 1H), 2.48 (dd, *J* = 17.2, 7.2 Hz, 1H), 2.43–2.33 (m, 2H), 1.60–1.50 (m, 2H), 1.49 (s, 3H), 1.44–1.37 (m, 5H), 1.36 (s, 3H), 1.35–1.19 (m, 12H), 0.88 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.3, 165.9, 142.9, 123.4, 108.9, 76.6, 73.9, 71.8, 60.6, 43.8, 43.3, 37.5, 37.1, 31.9, 29.1, 27.7, 25.3 (2C), 25.2, 23.4, 22.6, 14.2, 14.0; HRMS (ESI): *m*/*z* calculated for $C_{23}H_{40}O_6Na$ $[M + Na]^+$ 435.2717, found 435.2714.

(*E*)-3-((4*R*,5*S*)-5-((*R*)-8-Hydroxy-2-oxotridecyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylic Acid (12). To a solution of ethyl ester **11** (170 mg, 0.41 mmol) in toluene (5.0 mL) was added bis(tributyltin)-oxide (1.2 g, 2.06 mmol), and the resulting solution was stirred under reflux for 24 h, rm was cooled, and evaporated. The resulting crude was dissolved in EtOAc (10 mL) and washed with 1 N HCl (2 × 10 mL), and the organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography over 200–400 mesh silica gel (50% EtOAc/Petroleum ether) to afford seco-acid **12** (110 mg, 69%) as a light yellow oil. $[\alpha]_D^{28}$ +3.70 (*c* 0.4, $CHCl_3$); IR υ_{max} (film): 3426, 3020, 1709, 1528, 1382, 1216 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.77 (dd, *J* = 15.6, 5.9 Hz, 1H), 6.07 (d, *J* = 15.6, 1.7 Hz, 1H), 4.89–4.85 (m, 1H), 4.77–4.73 (m, 1H), 3.64–3.61 (m, 1H), 2.76 (dd, *J* = 18.1, 5.6 Hz, 1H), 2.60 (dd, *J* = 17.8, 8.8 Hz, 1H), 2.45–2.30 (m, 2H), 1.66–1.52 (m, 2H), 1.50 (s, 3H), 1.47–1.40 (m, 5H), 1.38 (s, 3H), 1.37–1.21 (m, 9H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.6, 168.8, 144.8, 122.8, 108.8, 76.4, 73.9, 72.1, 43.9, 43.2, 37.2, 36.6, 31.8, 28.9, 27.6, 25.3, 25.1, 24.9, 23.8, 22.6, 14.0; HRMS (ESI): *m*/*z* calculated for $C_{21}H_{35}O_6$ $[M - H]^+$ 383.2428, found 383.2429.

(3a*R*,8*R*,15a*S*,*E*)-2,2-Dimethyl-8-pentyl-8,9,10,11,12,13,15,15a-octahydro-6*H*-[1,3]dioxolo[4,5-*e*][1]-oxacyclotetradecine-6,14(3a*H*)-dione (13). 2,4,6-Trichlorobenzoyl chloride (90 μL, 0.58 mmol) was added to a solution of seco-acid **12** (220 mg, 0.57 mmol), triethylamine (160 μL, 1.14 mmol) at 0 °C, and the resulting solution was stirred at rt for 8 h, diluted with dry toluene

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J. Org. Chem. 2016, 81, 290–296

(20 mL), and added dropwise to a refluxing solution of DMAP (349 mg, 2.86 mmol) in toluene (150 mL) over a period of 24 h. The resulting rm was further stirred under reflux for 24 h, and rm was cooled evaporated, dissolved in EtOAc (10 mL), washed with aqueous saturated $NaHCO_3$ (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography over 200−400 mesh silica gel (5% EtOAc/Petroleum ether) to afford compound **13** (110 mg, 52%) as a light yellow oil. $[\alpha]_D^{26}$ −23.5 (*c* 0.31, $CHCl_3$); IR υ_{max} (film): 2931, 1712, 1643, 1271 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.61 (dd, *J* = 15.6, 6.6 Hz, 1H), 6.08 (dd, *J* = 15.6, 1.0 Hz, 1H), 5.01−4.95 (m, 1H), 4.83 (td, *J* = 6.8, 1.0 Hz, 1H), 4.78−4.73 (m, 1H), 2.86 (dd, *J* = 19.1, 11.0 Hz, 1H), 2.68 (dd, *J* = 18.8, 2.7 Hz, 1H), 2.49−2.42 (m, 1H), 2.20−2.14 (m, 1H), 1.72−1.53 (m, 4H), 1.49 (s, 3H), 1.46−1.39 (m, 2H), 1.37 (s, 3H), 1.34−1.16 (m, 10H), 0.87 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.0, 165.9, 140.7, 125.1, 108.9, 76.7, 75.9, 74.3, 45.9, 41.8, 34.5, 32.0, 31.8, 28.9, 28.0, 25.5, 25.4, 24.6, 24.2, 22.7, 14.0; HRMS (ESI): *m*/*z* calculated for $C_{21}H_{34}O_5Na$ $[M + Na]^+$ 389.2298, found 389.2298. All the data were compared and found to be identical to data reported by Kaliappan's group.[8]

(3a*R*,8*R*,14*R*,15a*S*,*E*)-14-Hydroxy-2,2-dimethyl-8-pentyl-3a,8,9,10,11,12,13,14,15,15a-decahydro-6*H*-[1,3]dioxolo[4,5-*e*][1]oxacyclotetradecin-6-one (14).[8] $NaBH_4$ (20 mg, 0.52 mmol) was added to a solution of compound **13** (75 mg, 0.20 mmol) in anhydrous MeOH (4.0 mL) at −78 °C, and the resulting solution was allowed to warm to rt for 3 h. The rm was quenched with saturated aqueous NH_4Cl (5.0 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography over 200−400 mesh silica gel (15−20% EtOAc/Petroleum ether) to afford alcohol **14** (51 mg, 68%) as a light yellow oil. $[\alpha]_D^{28}$ −28.05 (*c* 1.12, $CHCl_3$); IR υ_{max} (film): 3423, 2928, 1712, 1644, 1217 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.81 (dd, *J* = 15.9, 7.1 Hz, 1H), 6.04 (dd, *J* = 15.9, 1.2 Hz, 1H), 5.11−5.04 (m, 1H), 4.83 (t, *J* = 7.6 Hz, 1H), 4.67 (t, *J* = 6.9 Hz, 1H), 3.88−3.82 (m, 1H), 3.35 (bs, 1H), 1.87−1.75 (m, 2H), 1.70 (d, *J* = 15.4 Hz, 2H), 1.61 (s, 3H), 1.53−1.45 (m, 4H), 1.39 (s, 3H), 1.36−1.19 (m, 10H), 1.18−1.05 (m, 2H), 0.87 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 143.4, 124.0, 109.0, 77.7, 77.2, 76.3, 67.3, 36.2, 35.6, 34.7, 32.5, 31.7, 29.0, 26.7, 25.1, 24.9, 24.5, 23.6, 22.5, 14.0; HRMS (ESI): *m*/*z* calculated for $C_{21}H_{36}O_5Na$ $[M + Na]^+$ 391.2455, found 391.2444.

(5*R*,6*S*,8*R*,14*R*,*E*)-5,6,8-Trihydroxy-14-pentyloxacyclotetradec-3-en-2-one (1). 6 N aqueous HCl (44 μL, 0.27 mmol) was added to a solution of hydroxyl compound **14** (10 mg, 0.027 mmol), and the resulting solution was stirred at rt for 4 h. The rm was concentrated *in vacuo*. The crude product was purified by flash chromatography over 200−400 mesh silica gel (45% EtOAc/Petroleum ether) to afford Sch-725674 (8.0 mg, 89%) as a white solid. m.p: 182−184 °C; $[\alpha]_D^{26}$ +4.8 (*c* 0.08, MeOH); IR υ_{max} (film): 3423, 2929, 2858, 1712, 1424, 1216, 1095 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 6.87 (dd, *J* = 15.8, 6.1 Hz, 1H), 6.08 (dd, *J* = 15.8, 1.5 Hz, 1H), 4.98−4.92 (m, 1H), 4.50−4.47 (m, 1H), 3.99 (quin, *J* = 6.3 Hz, 1H), 3.87−3.84 (m, 1H), 1.84 (dt, *J* = 14.7, 6.1 Hz, 1H), 1.74−1.50 (m, 5H), 1.45−1.25 (m, 11H), 1.23−1.12 (m, 3H), 0.91 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 168.4, 149.3, 123.1, 77.6, 76.0, 72.9, 69.5, 38.3, 36.8, 36.5, 34.1, 33.0, 29.5, 27.0, 26.4, 25.8, 23.8, 14.5; HRMS (ESI): *m*/*z* calculated for $C_{18}H_{33}O_5[M + H]^+$ 329.2323, found 329.2320.

(*R*,*E*)-13-((4*S*,5*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)tridec-12-en-6-ol (15). G-II (31 mg, 0.04 mmol) was added to a degassed solution of TBS compound **9** (500 mg, 1.84 mmol), compound **7** (545 mg, 2.75 mmol) in CH_2Cl_2 (5.0 mL), and the resulting solution was stirred under reflux for 18 h. The rm was concentrated *in vacuo*. The crude product was purified by flash chromatography over 200−400 mesh silica gel (10−15% EtOAc/Petroleum ether) to afford alcohol **15** (250 mg, 31%, 52% brsm) as a light yellow oil. $[\alpha]_D^{29}$ +2.25 (*c* 1.4, $CHCl_3$); IR υ_{max} (film): 3474, 3015, 2990, 1463, 1381, 1254, 1166 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.79−5.72 (m, 1H), 5.49 (dd, *J* = 15.4, 8.1 Hz, 1H), 4.57 (t, *J* = 7.2 Hz, 1H), 4.13 (q, *J* = 6.0 Hz, 1H), 3.65−3.56 (m, 3H), 2.05 (q, *J* = 6.8 Hz, 2H), 1.46 (s, 3H), 1.45−1.37 (m, 8H), 1.35 (s, 3H), 1.34−1.19 (m, 8H), 0.88 (s, 9H, merged with triplet of $-CH_3$), 0.88 (t, *J* = 6.7 Hz, 3H, merged with −OTBS singlet), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 125.1, 108.2, 78.7, 78.7, 72.0, 62.5, 37.5, 37.4, 32.3, 31.9, 29.3, 29.0, 27.9, 25.9, 25.5, 25.4, 25.3, 22.6, 18.3, 14.0, −5.4; HRMS (ESI): *m*/*z* calculated for $C_{25}H_{50}O_4SiNa$ $[M + Na]^+$ 465.3371, found 465.3367.

(*R*)-1-((4*S*,4′*R*,5*R*,5′*R*)-5′-(((*tert*-Butyldimethylsilyl)oxy)-methyl)-2,2,2′,2′-tetramethyl-[4,4′-bi(1,3-dioxolan)]-5-yl)-undecan-6-ol (16). OsO_4 (2.5 wt % in ^tBuOH, 220 μL, 0.025 mmol) was added to a solution of compound **15** (280 mg, 0.63 mmol), *N*-methylmorphiline-*N*-oxide (486 mg, 1.9 mmol) in 2:1 acetone:H_2O (6.0 mL) at rt, and the resulting solution was stirred for 12 h. The rm was quenched with solid Na_2SO_3 and stirred for 30 min, and the rm was extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was carried to the next step without further purification.

PTSA (11 mg, 0.063 mmol) was added to a solution of dihydroxy compound (0.63 mmol) and 2,2-dimethoxypropane (0.4 mL, 3.17 mmol) in CH_2Cl_2 (5.0 mL) at 0 °C, and the mixture was stirred for 30 min at same temperature. The rm was quenched with saturated aqueous $NaHCO_3$ (5.0 mL), and the rm was extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography over 200−400 mesh silica gel (8−10% EtOAc/Petroleum ether) to afford alcohol **16** (220 mg, ∼4:1 selectivity, 67% over 2 steps) as a light yellow oil. IR υ_{max} (film): 3423, 2928, 1644, 1217 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.24−4.21 (m, 1H), 4.00 (dd, *J* = 9.2, 6.2 Hz, 1H), 3.96−3.88 (m, 2H), 3.89 (br. s., 1H), 3.74 (dd, *J* = 11.5, 6.4 Hz, 1H), 3.68 (dd, *J* = 8.8, 7.5 Hz, 1H), 3.57 (bs, 1H), 1.79−1.74 (m, 1H), 1.55−1.50 (m, 1H), 1.42 (s, 3H), 1.35 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H), 1.44−1.24 (m, 16H), 0.90 (s, 9H), 0.88 (t, *J* = 6.4 Hz, 3H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 108.7, 108.7, 81.3, 79.1, 78.6, 77.4, 71.9, 62.3, 37.4, 37.4, 33.6, 31.9, 29.6, 27.7, 27.4, 27.1, 26.0, 25.9, 25.5, 25.4, 25.3, 22.6, 18.4, 14.0, −5.3; HRMS (ESI): *m*/*z* calculated for $C_{28}H_{56}O_6SiNa$ $[M + Na]^+$ 539.3728, found 539.3722.

(*R*)-1-((4*S*,4′*R*,5*R*,5′*R*)-5′-(Hydroxymethyl)-2,2,2′,2′-tetramethyl-[4,4′-bi(1,3-dioxolan)]-5-yl)undecan-6-yl Acrylate (17). Acryloyl chloride (0.11 mL, 1.44 mmol) was added to a solution of compound **16** (190 mg, 0.36 mmol), Et_3N (1.0 mL, 7.22 mmol) in CH_2Cl_2 (3.0 mL) at 0 °C, and the resulting solution was stirred for 30 min at the same temperature. The rm was quenched with saturated aqueous $NaHCO_3$ (5.0 mL), and the rm was extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude was used for the next transformation without further purification.

TBAF (1.0 M in THF, 0.54 mL, 0.54 mmol) was added to a solution of the above obtained compound in THF (3.0 mL), and the mixture was stirred at rt for 14 h. The rm was concentrated *in vacuo*. The crude product was purified by flash chromatography over 200−400 mesh silica gel (15−20% EtOAc/Petroleum ether) to afford compound **17** (95 mg, 57% over 2 steps) as a light yellow oil. $[\alpha]_D^{25}$ +1.50 (*c* 0.67, $CHCl_3$); IR υ_{max} (film): 3420, 2933, 1710, 1634, 1217 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.38 (dd, *J* = 17.4, 1.7 Hz, 1H), 6.10 (dd, *J* = 17.4, 10.5 Hz, 1H), 5.80 (dd, *J* = 10.4, 1.6 Hz, 1H), 4.98−4.92 (m, 1H), 4.36 (td, *J* = 7.6, 5.6, Hz, 1H), 4.09 (dd, *J* = 9.7, 6.0 Hz, 1 H), 4.01−3.91 (m, 1H), 3.89−3.73 (m, 2H), 3.67 (dd, *J* = 9.7, 7.5 Hz, 1H), 2.89 (dd, *J* = 8.9, 5.5 Hz, 1H), 1.78−1.74 (m, 1H), 1.55−1.44 (m, 5H), 1.41 (s, 3H), 1.40 (s, 3H), 1.36 (s, 3H), 1.35 (s, 3H) 1.43−1.21 (m, 12H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 130.1, 129.0, 109.2, 108.9, 81.4, 78.9, 77.7, 77.2, 74.6, 60.6, 34.1 (2C), 33.6, 31.7, 29.5, 27.7, 27.4, 26.9, 25.9, 25.2, 25.2, 24.9, 22.5, 14.0; HRMS (ESI): *m*/*z* calculated for $C_{25}H_{44}O_7Na$ $[M + Na]^+$ 479.2979, found 479.2967.

(*R*)-1-((4*S*,4′*R*,5*R*,5′*R*)-2,2,2′,2′-Tetramethyl-5′-vinyl-[4,4′-bi-(1,3-dioxolan)]-5-yl)undecan-6-yl Acrylate (18). Dess−Martin

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periodinane (185 mg, 0.44 mmol) was added to a solution of compound **17** (100 mg, 0.22 mmol) in CH_2Cl_2 (3.0 mL) at 0 °C, and the resulting solution was stirred for 1 h at rt. The rm was quenched with saturated aqueous $NaHCO_3$ (5.0 mL), and the rm was extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude was used for the next transformation without further purification.

The above obtained aldehyde in THF (2.0 mL) was added to a yellow suspension of single carbon ylide generated from PPh_3CH_3Br (234 mg, 0.65 mmol), KO^{t}Bu (61 mg, 0.55 mmol) in THF (3.0 mL), at 0 °C, and the resulting solution was stirred for 30 min at the same temperature. The rm was quenched with saturated aqueous NH_4Cl (5.0 mL), and the rm was extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography over 200−400 mesh silica gel (5% EtOAc/Petroleum ether) to afford diene **18** (33 mg, 33% over 2 steps) as a light yellow oil. (observed a very close UV active impurity at product *rf* on TLC, which we are unable to separate in column). IR υ_{max} (film): 3020, 2930, 2861, 1712, 1651, 1453, 1220 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.38 (dd, J = 17.2, 1.2 Hz, 1H), 6.10 (dd, J = 17.2, 10.2 Hz, 1H), 5.96 (ddd, J = 16.9, 10.5, 6.1 Hz, 1H), 5.80 (dd, J = 10.4, 1.2 Hz, 1H), 5.46−5.32 (m, 1H), 5.28−5.18 (m, 1H), 4.98−4.90 (m, 1H), 4.73−4.67 (m, 1H), 4.05 (dd, J = 9.3, 6.3 Hz, 1H), 3.97−3.89 (m, 1H), 3.56 (dd, J = 9.2,7.3 Hz, 1H), 1.55−1.53 (m, 4H), 1.46 (s, 3 H), 1.36 (s, 3H), 1.35 (s, 6H), 1.33−1.26 (m, 14H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 133.6, 130.2, 129.0, 117.4, 109.0, 108.7, 80.8, 79.5, 78.8, 77.8, 74.6, 34.1, 33.7, 31.7, 29.7, 29.6, 27.7, 27.4, 27.1, 26.0, 25.4, 25.2, 24.9, 22.5, 14.0 HRMS (ESI): m/z calculated for $C_{26}H_{44}O_6Na$ $[M + Na]^+$ 475.3030, found 475.3022.

(3a*R*,8*R*,13a*R*,16a*S*,16b*R*,*E*)-2,2,15,15-Tetramethyl-8-pentyl-3a,8,9,10,11,12,13,13a,16a,16b-decahydro-6*H*-bis([1,3]-dioxolo)[4,5-*e*:4′,5′-*g*][1]oxacyclotetradecin-6-one (19). G-II (6 mg, 7.3 μmol) was added to degassed solution of diene **18** (33 mg, 73 μmol) in CH_2Cl_2 (15 mL), and the resulting solution was stirred under reflux for 18 h. The rm was concentrated *in vacuo*. The crude product was purified by flash chromatography over 200−400 mesh silica gel (5−8% EtOAc/Petroleum ether) to afford macrocycle **19** (13 mg, 42%) as a light yellow oil. IR υ_{max} (film): 2931, 1712, 1643, 1271 cm^{-1}; $[\alpha]_D^{26}$ +2.75 (c 0.09, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.62 (dd, J = 15.8, 7.6 Hz, 1H), 6.03 (dd, J = 15.8, 1.2 Hz, 1H), 5.04 (ddt, J = 8.2, 5.5, 2.4 Hz, 1H), 4.78 (dt, J = 7.6, 1.1 Hz, 1H), 4.57 (dd, J = 7.6, 1.5 Hz, 1H), 4.26−4.19 (m, 1H), 3.86 (dd, J = 5.3, 1.7 Hz, 1H), 1.76−1.70 (m, 1H), 1.66−1.62 (m, 1H), 1.56 (s, 3H), 1.54−1.45 (m, 2H), 1.43 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H), 1.39−1.18 (m, 14H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 143.0, 124.5, 109.5, 109.4, 79.9, 78.8, 76.1, 76.1, 75.7, 34.0, 32.2, 31.7, 31.2, 28.3, 27.8, 27.2, 27.1, 25.2, 24.7, 22.6, 22.5, 22.0, 14.0; HRMS (ESI): m/z calculated for $C_{24}H_{40}O_6Na$ $[M + Na]^+$ 447.2717, found 447.2729.

(5*R*,6*R*,7*S*,8*R*,14*R*,*E*)-5,6,7,8-Tetrahydroxy-14-pentyl-oxacyclotetradec-3-en-2-one (4). 4:1 AcOH−H_2O (0.75 mL) was added to compound **19** (10 mg, 0.235 mmol), and the resulting solution was stirred at 60 °C for 6 h. The rm was concentrated *in vacuo*. The crude product was purified by flash chromatography over 100−200 mesh silica gel (5% MeOH/CH_2Cl_2) to furnish gliomasolide C (**4**) (8.0 mg, 86%) as a white solid. m.p: 172−174 °C; $[\alpha]_D^{26}$ −36.9 (c 0.29, MeOH); IR υ_{max} (film): 3385, 3020, 2927, 1715, 1602, 1424, 1215 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 6.94 (dd, J = 15.6, 4.6 Hz, 1H), 6.18 (dd, J = 15.6, 1.9 Hz, 1H), 5.05−4.99 (m, 1H), 4.60−4.58 (m, 1H), 4.09 (ddd, J = 7.8, 5.4, 1.7 Hz, 1H), 3.99 (t, J = 3.4 Hz, 1H), 3.37−3.36 (m, 1H), 1.77−1.71 (m, 1H), 1.70−1.62 (m, 1H), 1.61−1.54 (m, 2H), 1.52−1.42 (m, 3H), 1.39−1.29 (m, 8H), 1.17−1.07 (m, 3H), 0.91 (t, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 168.4, 147.5, 123.2, 77.9, 77.3, 73.6, 71.2, 71.2, 36.2, 34.5, 32.8, 32.8, 30.3, 27.6, 26.3, 26.3, 23.6, 14.3; HRMS (ESI): m/z calculated for $C_{18}H_{32}O_6Na$ $[M + Na]^+$ 367.2091, found 367.2083.

(*R*)-Tridec-12-en-6-yl (*E*)-3-((4*R*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)acrylate (20). Lithium hydroxide monohydrate (1.2 g, 28.5 mmol) was added to a solution of ester **8** (2.50 g, 11.1 mmol) in THF:MeOH:H_2O (3:2:1) 60 mL at 0 °C, and the resulting solution was stirred at rt for 3 h. The rm was evaporatd *in vacuo*, and H_2O (25 mL) was added. The rm was washed with diethyl ether (3 × 10 mL) and neutralized with 10% citric acid up to pH 6. The rm was extracted with EtOAc (3 × 15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude was used for the next transformation without further purification.

2,4,6-Trichlorobenzoyl chloride (1.6 mL, 10.1 mmol) was added to a solution of the above obtained acid (2.0 g, 10.1 mmol), alcohol (2.3 g, 12.1 mmol), Et_3N (1.7 mL, 12.1 mmol), DMAP (1.4 g, 12.1 mmol) in dry toluene (50 mL), and the resulting solution was stirred at rt for 14 h. The rm was concentrated *in vacuo*. The crude product was purified by flash chromatography over 200−400 mesh silica gel (6% EtOAc/Petroleum ether) to afford diene **20** (2.0 g, 52%) as a light yellow oil. $[\alpha]_D^{25}$ +42.40 (c 0.23, $CHCl_3$); IR υ_{max} (film): 3020, 2859, 1731, 1375, 1216 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.75 (dd, J = 15.6, 5.9 Hz, 1H), 6.05 (dd, J = 15.4, 1.5 Hz, 1H), 5.84−5.78 (m, 1H), 5.69 (ddd, J = 17.3,10.1, 7.6 Hz, 1H), 5.35 (td, J = 17.0,1.3 Hz, 1H), 5.25 (dd, J = 10.3, 1.0 Hz, 2H), 5.02−4.94 (m, 1H), 4.94−4.88 (m, 1H), 4.80−4.73 (m, 1H), 4.73−4.68 (m, 1H), 2.07−2.00 (m, 2H), 1.55 (s, 3H), 1.55−1.51 (m, 4H), 1.41 (s, 3H), 1.380−1.22 (m, 12H), 0.86 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 143.1, 139.0, 133.5, 123.2, 119.2, 114.2, 109.5, 79.8, 77.5, 74.6, 34.0 (2C), 33.6, 31.7, 29.0, 28.7, 27.7, 25.3, 25.1, 24.9, 22.5, 14.0; HRMS (ESI): m/z calculated for $C_{23}H_{38}O_4Na$ $[M + Na]^+$ 401.2662, found 401.2666.

(3a*R*,4*E*,8*R*,14*E*,15a*S*)-2,2-Dimethyl-8-pentyl-3a,8,9,10,11,12,13,15a-octahydro-6*H*-[1,3]dioxolo[4,5-*e*][1]-oxacyclotetradecin-6-one (21). G-II (90 mg, 0.1 mmol) was added to degassed solution of diene **20** (2.0 g, 5.29 mmol) in CH_2Cl_2 (2.0 L), and the resulting solution was stirred under reflux for 18 h. The rm was concentrated *in vacuo*. The crude product was purified by flash chromatography over 200−400 mesh silica gel (6% EtOAc/Petroleum ether) to afford macrocycle **21** (1.29 g, 71%) as a light yellow oil. $[\alpha]_D^{26}$ +8.77 (c 0.40, $CHCl_3$); IR υ_{max} (film): 2930, 2861, 1712, 1651, 1220 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.66 (dd, J = 15.9, 8.8 Hz, 1H), 5.88 (d, J = 15.9 Hz, 1H), 5.55−5.45 (m, 1H), 5.32 (dd, J = 15.9, 7.6 Hz, 1H), 5.00−4.94 (m, 1H), 4.73−4.66 (m, 1H), 4.63−4.59 (m, 1H), 2.17−2.13 (m, 1H), 1.98−1.94 (m, 1H), 1.78−1.71 (m, 1H), 1.57 (s, 3H), 1.55−1.45 (m, 3H), 1.40 (s, 3H), 1.33−1.10 (m, 12H), 0.87 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 143.9, 133.7, 127.8, 124.3, 110.0, 80.3, 78.1, 76.6, 34.6, 32.6, 32.4, 31.7, 29.9, 28.4, 28.1, 26.2, 25.6, 25.0, 22.5, 14.0; HRMS (ESI): m/z calculated for $C_{21}H_{34}O_4Na$ $[M + Na]^+$ 373.2349, found 373.2346.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02318.

NMR comparison tables of the natural vs synthetic target compounds, experimental results of attempted syntheses of the target natural products (**1** and **4**) from macrocycle (**21**), and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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DEDICATION

This work is dedicated to Professor S. Chandrasekaran, Indian Institute of Science, Bangalore, on the occasion of his 70th birthday.

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