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Note

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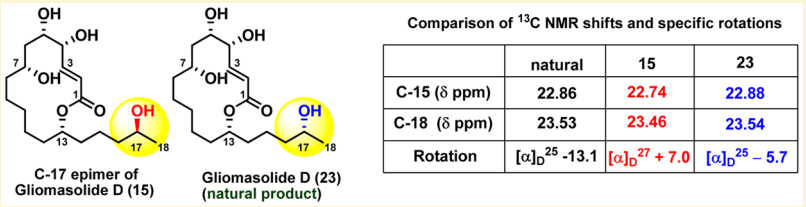
Determination of the Absolute Configuration of Gliomasolide D through Total Syntheses of the C-17 Epimers

B. Seetharamsingh,[†,‡] Routholla Ganesh,[†] and D. Srinivasa Reddy*[,†,‡]

[†]CSIR−National Chemical Laboratory, Division of Organic Chemistry, Dr. Homi Bhabha Road, Pune, 411008, India

[‡]Academy of Scientific and Innovative Research (AcSIR), New Delhi, 110025, India

Supporting Information



ABSTRACT: The absolute configuration at C-17, the carbon bearing the distal hydroxy group of the 14-membered natural product gliomasolide D, was assigned as *R* by comparison of ^{13}C NMR shifts and specific rotation values of the epimers at C-17. The first total synthesis of gliomasolide D along with its C-17 epimer, regioselective macrocyclization (18 membered vs 14 membered), and regioselective Wacker oxidation are highlights of the present work.

Gliomasolides A−E (**1**−**5**) (Figure 1) are 14-membered macrolides isolated from the sponge-derived fungus

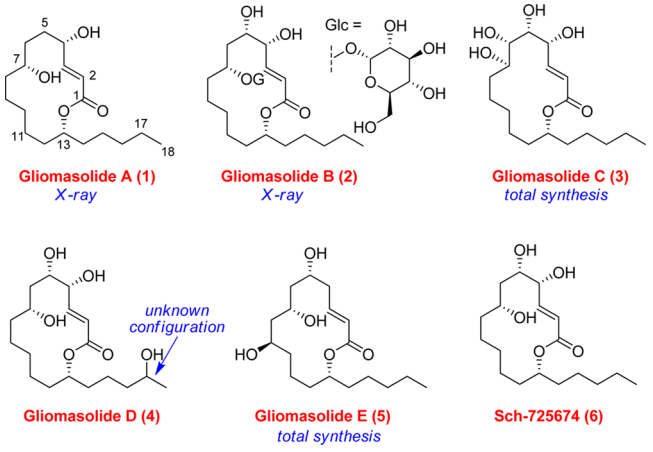


Figure 1. Structures of gliomasolides A−E and Sch-725674.

Gliomastix sp. ZSDS1-F7-2, collected from the South China Sea by the research groups of Liu and Xu.[1] The structure and stereochemical configuration of gliomasolide A (**1**) and gliomasolide B (**2**) were determined by extensive 2D NMR analysis followed by single-crystal X-ray analysis. The structure of gliomasolide C (**3**) was determined by 2D NMR analysis and was later confirmed by its total synthesis by our group.[2] However, the configurations at C-17 in gliomasolide D (**4**) and at C-9 in gliomasolide E (**5**) were not established by the Liu and Xu groups because of the limited quantities of the isolated natural products.[1] Very recently the absolute configuration of gliomasolide E (**5**) was established by Mohapatra's group with the help of ^{13}C NMR and specific rotation comparison of both possible configurations at C-9.[3] The structures of these natural products are close to the structure of previously isolated and well-known natural product Sch-725674 (**6**).[4] From a biological activity point of view, Sch-725674 has shown good antifungal activity, but the biological activities of gliomasolides A−E were not fully evaluated. However, gliomasolide A (**1**) showed moderate cytotoxic activity against HeLa (human epithelial carcinoma cell line) cells.[1] Because of the interesting structure and biological activity, the natural product Sch-725674 has been a popular target for synthesis and has attracted the attention of many researchers[5] including our group.[2] Considering structural similarities between compound **6** and the new gliomasolide family, we became interested in this class of compounds. Determination of the correct absolute configuration of gliomasolide D (**4**) would be more challenging due to the placement of the hydroxy group at C-17 in the side chain, which is quite distant from the other stereocenters. Having synthesized one member of this family (gliomasolide C, **3**)[2] and the challenge associated with the assignment of the configuration at a remote stereocenter in gliomasolide D (**4**) prompted us to focus on the synthesis of two possible stereoisomers of **4**, epimeric at the C-17 position. This exercise will help in determining the actual structure of gliomasolide D and also will provide sufficient quantities of materials for biological evaluation. With this background, we initiated our efforts, and the details are presented in this Note.

The key disconnections and sources of chirality for the planned synthesis are shown in Figure 2. As per the plan, our

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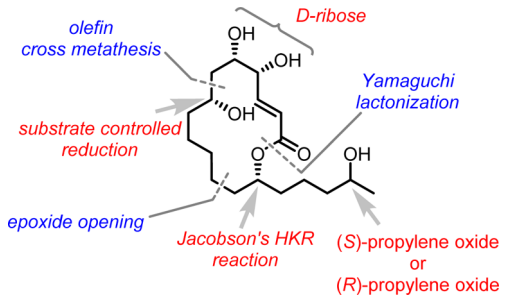


Figure 2. Sources of chirality and key disconnections to access both C-17 stereoisomers of gliomasolide D.

synthesis started with commercially available (*S*)-propylene oxide **7**, which on treatment with 3-butenylmagnesium bromide followed by protection of the resulting alcohol with *tert*-butyldimethylsilyl chloride (TBSCl) afforded TBS ether **8**.[6] Compound **8** was converted to the diasteromeric mixture of epoxide **9** using oxone, which was then subjected to hydrolytic kinetic resolution[7] with (*R*,*R*)-salen Co(III)-OAc (prepared from commercially available precatalyst using AcOH)[7] to afford pure epoxide **10**. The epoxide was regioselectively opened with 5-hexenylmagnesium bromide followed by a cross metathesis[8] between the resulting olefin and intermediate **11** (a known compound prepared from D-ribose)[9] in the presence of Grubbs' second-generation catalyst, affording the key intermediate **12**, in which most of the desired functional groups are in place.

The ester group present in **12** was hydrolyzed with LiOH to give the corresponding carboxylic acid, which upon Wacker-type oxidation[10] ($PdCl_2$ in DMA/H_2O, 200 psi of O_2, 70 °C) produced the desired carbonyl compound **13** in a highly regioselective manner. To our delight, the TBS group was also removed under these reaction conditions. This result also prompted us to test selective macrocyclization between two possibilities (14-membered vs 18-membered macrocycles) because of two free hydroxy groups present in **13**. The seco acid was subjected to Yamaguchi conditions,[11] yielding macrocycle **14** in 47% isolated yield. Considering the two possible modes of cyclization, we wanted to confirm the structure of the macrocycle. For that purpose, we have recorded the HMBC spectrum of **14** and confirmed the structure (Figure 3). In the HMBC spectrum, we found that H-13 (δ_H 4.82) has a correlation to the ester carbonyl carbon C-1 (δ_C 165.7), which clearly confirms the 14-membered ring. Compound **14**, on substrate-controlled reduction using $NaBH_4$,[5d,2] followed by deprotection of the acetonide resulted in the desired macrocycle **15** (*S*-configuration at C-17 of gliomasolide D) (Scheme 1).

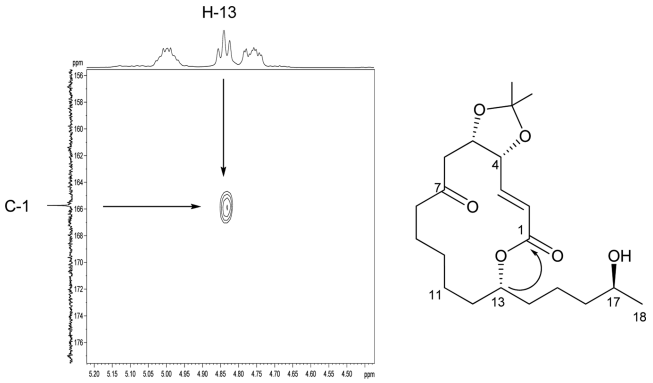
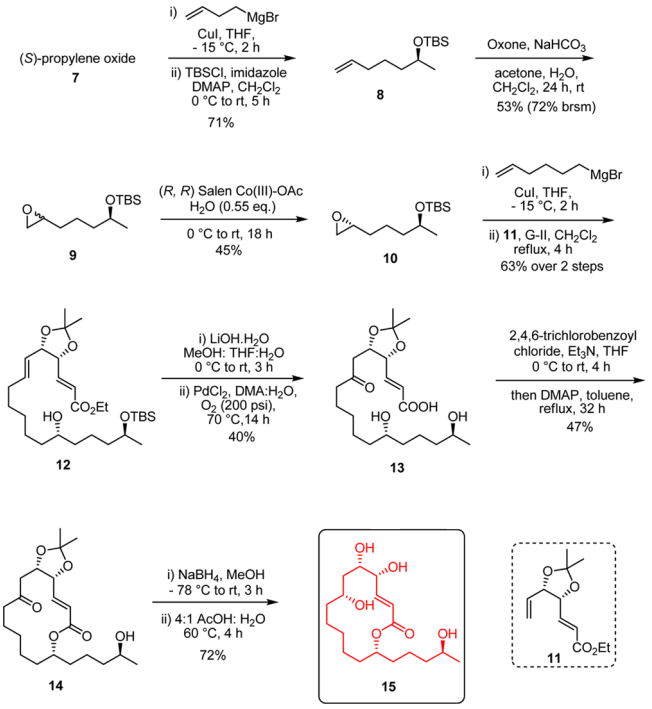


Figure 3. HMBC correlation of H-13 to ester carbonyl C-1 of compound **14**.

Scheme 1. Synthesis of Gliomasolide D (15, with *S*-Configuration at C-17)



The ^{1}H NMR spectra of both natural product **4** and synthetic compound **15** were compared and were found to be very similar. However, careful comparison of the ^{13}C NMR spectra revealed minor discrepancies at two positions (C-18: δ_C 23.53 vs 23.46 ppm and C-15: δ_C 22.86 vs 22.74). We also measured the optical rotation of **15** and found a significant difference with respect to that of natural gliomasolide D including the sign of rotation (Table 1). Although the ^{13}C NMR shift differences are minor, the difference in the specific rotations clearly suggests that C-17 of the natural gliomasolide D has the *R*-configuration and not the *S*-configuration as present in compound **15**. To prove this aspect, we have synthesized compound **23** (Scheme S1) through the intermediacy of **17** to **22** starting from commercially available (*R*)-propylene oxide **16** using a similar reaction sequence to that described in Scheme 1. (Compounds **16**–**22** are either the enantiomers or epimers of compounds **7**–**14**.) After the successful synthesis of macrocycle **23** with the C-17 *R*-configuration, the ^{13}C NMR spectra were compared. To our delight, the ^{13}C NMR spectra of **23** and natural gliomasolide were a better match than the NMR data of **15** (Table 1). Also, compound **23** has the same sign of the specific rotation as the natural product. However, the magnitude of specific rotation of **23** ($[\alpha]^{25}_D$ −5.7, *c* 0.15, MeOH) is significantly lower than the specific rotation reported for gliomasolide D (−13.1) (Table 1).[12] We believe, based on this evidence, the absolute configuration at C-17 of natural gliomasolide D can be assigned as the *R*-configuration.

Thus, we have assigned the absolute configuration at C-17 of gliomasolide D as the *R*-configuration by synthesizing both the C-17 epimers and comparing ^{13}C NMR shifts and specific

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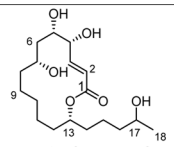
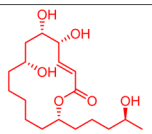
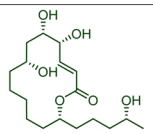
Table 1. ^{13}C NMR and Specific Rotation Comparisons of Natural Gliomasolide D (75 MHz),[1,a] Compounds 15 (100 MHz), and 23 (100 MHz) in CD_3OD

Carbon	 natural compound	 compound 15	 compound 23
1	168.26	168.21	168.22
2	122.91	122.95	122.94
3	149.22	149.20	149.20
4	75.87	75.88	75.88
5	72.72	72.74	72.75
6	38.14	38.17	38.17
7	69.31	69.31	69.31
8	36.64	36.69	36.68
9	25.59	25.62	25.62
10	29.34	29.38	29.38
11	26.79	26.81	26.82
12	33.88	33.86	33.92
13	77.42	77.42	77.37
14	36.39	36.40	36.41
15	22.86	22.74	22.88
16	39.87	39.91	39.91
17	68.42	68.36	68.42
18	23.53	23.46	23.54
Specific rotation	$[\alpha]_D^{25}$ −13.1 (*c* 0.35, MeOH)	$[\alpha]_D^{27}$ + 7.0 (*c* 0.8, MeOH)	$[\alpha]_D^{25}$ −5.7 (*c* 0.15, MeOH)

[a]The NMR shifts for natural gliomasolide D were extracted from the ^{13}C NMR spectrum in the Supporting Information of ref 1 (reported as 0.01 ppm).

rotation values. The small chemical shift differences between the diastereomers, coupled with a comparison of the specific rotations, helped us to determine the C-17 absolute configuration of the natural product. The first total synthesis of gliomasolide D and regioselective macrocyclization (18-membered vs 14-membered) are highlights of the present synthesis.

EXPERIMENTAL SECTION

General Experimental Procedures. 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 with 0.25 mm precoated silica gel plates (60 F_{254}). Visualization was accomplished with either UV light, iodine adsorbed on silica gel, or immersion in an ethanolic solution of phosphomolybdic acid, *p*-anisaldehyde, or $KMnO_4$ followed by heating with a heat gun for ∼15 s. Optical rotations were recorded on a JASCO P-2000 polarimeter at 589 nm. Infrared spectra were recorded on a Bruker Alpha FT-IR spectrometer as thin films in chloroform using NaCl plates. All ^1H NMR and ^{13}C NMR spectra were obtained using a 200, 400, or 500 MHz Bruker spectrometer. Coupling constants were measured in hertz. All chemical shifts are quoted in ppm using the residual solvent peak as a reference standard. Column chromatography was performed on silica gel (100−200 or 230−400 mesh size). HRMS (ESI) spectra were recorded on a Thermo Scientific Q Exactive ORBITRAP mass analyzer. Chemical nomenclature was generated using Chem Bio Draw Ultra 14.0.

(*S*)-*tert*-Butyl(hept-6-en-2-yloxy)dimethylsilane (8).[5] 3-Butenylmagnesium bromide (freshly prepared from 3-butenyl bromide, 12.5 mL, 123.9 mmol, Mg 2.97 g, 123.9 mmol in 250 mL of anhydrous tetrahydrofuran (THF)) was added dropwise to a suspension of (*S*)-propylene oxide (5.4 mL, 77.4 mmol) and CuI (1.5 g, 7.44 mmol) in anhydrous THF (80 mL) at −15 °C and stirred at the same temperature for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with Et_2O (3 × 50 mL), and the combined organic layers were washed with brine (50 mL). The Et_2O solution was dried over anhydrous Na_2SO_4 and then evaporated under reduced pressure.

Imidazole (11.7 g, 172 mmol), TBSCl (14.2 g, 94.7 mmol), and N,N-dimethylaminopyridine (DMAP) (1.05 g, 8.6 mmol) were added to the crude compound obtained above in CH_2Cl_2 (200 mL) at 0 °C. The resulting mixture was stirred at room temperature (rt) for 5 h, quenched with saturated aqueous $NaHCO_3$ (50 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash chromatography over 200−400 mesh silica gel (0−5% CH_2Cl_2/petroleum ether) to afford compound **8** (12.5 g, 71%) as a light yellow liquid: $[\alpha]^{25}_D$ +11.2 (*c* 3.7, $CHCl_3$); IR ν_{max} (film) 3015, 1371, 1257, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ_H 5.82 (m, 1H), 4.95 (m, 2H), 3.78 (m, 1H), 2.04 (q, *J* = 6.5 Hz, 2H), 1.43 (m, 4H), 1.12 (d, *J* = 6.1 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ_C 139.0, 114.3, 68.5, 39.2, 33.8, 25.9 (3C), 25.1, 23.8, 18.1, −4.4, −4.7.

***tert*-Butyldimethyl(((2*S*)-5-(oxiran-2-yl)pentan-2-yl)oxy)-silane (9).** Oxone (37 g, 246 mmol) was added portionwise to a solution of compound **8** (7.0 g, 30.7 mmol) and $NaHCO_3$ (26 g, 300 mmol) in CH_2Cl_2 (200 mL) and H_2O (150 mL) at 0 °C, followed by acetone (44 mL, 614 mmol), and the mixture was stirred at rt for 24 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography over 200−400 mesh silica gel (0−5% EtOAc/petroleum ether) to afford compound **9** (4.0 g, 53%, 72% based on recovery of starting material) as a light yellow liquid: IR ν_{max} (film) 2955, 1463, 1255, 1216, 896 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 3.76 (m, 1H), 2.87 (m, 1H), 2.71 (t, *J* = 4.3 Hz, 1H), 2.42 (m, 1H), 1.44 (m, 6H), 1.10 (d, *J* = 6.1 Hz, 3H), 0.86 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 68.3, 68.3, 52.2, 52.2, 46.9, 39.4, 39.3, 32.5, 32.4, 25.8 (3C), 23.7, 22.2, 22.1, 18.1, −4.4, −4.8; HRESIMS *m*/*z* 245.1934 $[M + H]^+$ (calcd for $C_{13}H_{29}O_2Si$, 245.1931).

***tert*-Butyldimethyl(((*S*)-5-((*R*)-oxiran-2-yl)pentan-2-yl)oxy)-silane (10).** (*R*,*R*)-Salen Co(III)-OAc (25 mg, 0.041 mmol) catalyst was added to neat epoxide **9** (2.0 g, 8.2 mmol) at 0 °C, and H_2O (88 μL, 4.92 mmol) was added dropwise over 10 min, followed by THF (3.0 mL). The resulting reaction mixture was allowed to warm to rt and stirred for 18 h. The solvent was evaporated, and the mixture was purified by column chromatography over 200−400 mesh silica gel (0−5% EtOAc/petroleum ether) to afford compound **10** (900 mg, 45%) as a light yellow liquid: $[\alpha]^{25}_D$ +14.6 (*c* 0.98, $CHCl_3$); IR ν_{max} (film) 3019, 2955, 1464, 1255, 1216, 896 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 3.77 (m, 1H), 2.89 (m, 1H), 2.73 (t, *J* = 4.6 Hz, 1H), 2.45 (dd, *J* = 4.9, 2.4 Hz, 1H), 1.58−1.36 (m, 6H), 1.11 (d, *J* = 5.9 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 68.4, 52.3, 47.0, 39.4, 32.5, 25.9 (3C), 23.8, 22.2, 18.1, −4.4, −4.8; HRESIMS *m*/*z* 245.1935 $[M + H]^+$ (calcd for $C_{13}H_{29}O_2Si$, 245.1931).

Ethyl (*E*)-3-((4*R*,5*S*)-5-((8*S*,12*S*,*E*)-12-((*tert*-Butyldimethylsilyl)oxy)-8-hydroxytridec-1-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (12). 5-Hexenylmagnesium bromide (0.5 M, 18.04 mL, 9.02 mmol) was added dropwise to a suspension of epoxide **10** (1.1 g, 4.5 mmol) and CuI (88 mg, 0.45 mmol) in THF (50 mL) at −15 °C. The suspension was stirred at the

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same temperature for 2 h, then quenched with saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous Na_2SO_4, and the solvent was evaporated. The product was purified by short-column chromatography over 100−200 mesh silica gel (5−10% EtOAc/petroleum ether) to afford an olefinic intermediate (1.1 g, 73%), which was used in the next step without further purification.

Grubbs' second-generation catalyst (G-II) (62 mg, 0.073 mmol) was added to a solution of the above obtained olefin (3.65 mmol) and ester **11** (550 mg, 2.43 mmol) in dry degassed CH_2Cl_2 (10 mL), and the resulting solution was stirred under reflux for 4 h. The mixture was concentrated *in vacuo*, and the crude product was purified by flash chromatography over 200−400 mesh silica gel (20−25% EtOAc/petroleum ether) to afford hydroxy ester **12** (810 mg, 63%) as a light yellow oil: $[\alpha]^{25}_D$ +37.7 (*c* 1.8, $CHCl_3$); IR ν_{max} (film) 3350, 3020, 2400, 1720, 1215 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 6.79 (dd, *J* = 15.6, 5.4 Hz, 1H), 6.05 (d, *J* = 15.6 Hz, 1H), 5.77 (m, 1H), 5.31 (dd, *J* = 7.8, 15.2 Hz, 1H), 4.69 (m, 2H), 4.19 (q, *J* = 7.3 Hz, 2H), 3.77 (m, 1H), 3.57 (m, 1H), 2.05 (m, 2H), 1.53 (s, 3H), 1.36 (m, 14H), 1.39 (s, 3H), 1.28 (t, *J* = 6.8 Hz, 3H), 1.11 (d, *J* = 5.9 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 166.0, 144.2, 136.9, 125.0, 122.4, 109.2, 79.7, 77.6, 71.8, 68.6, 60.5, 39.7, 37.5, 37.3, 32.1, 29.0, 28.7, 27.8, 25.9 (3C), 25.3, 25.3, 23.8, 21.9, 18.1, 14.2, −4.4, −4.7; HRESIMS *m/z* 549.3587 $[M + Na]^+$ (calcd for $C_{29}H_{54}O_6SiNa$, 549.3582).

(3a*R*,8*S*,15a*S*,*E*)-8-((*S*)-4-Hydroxypentyl)-2,2-dimethyl-8,9,10,11,12,13,15,15a-octahydro-6*H*-[1,3]dioxolo[4,5-*e*][1]-oxacyclotetradecine-6,14(3a*H*)-dione (14). To a solution of **12** (500 mg, 0.95 mmol) in 10 mL of MeOH/THF/H_2O (1:1:1) at 0 °C was added LiOH·H_2O (120 mg, 2.85 mmol). The mixture was allowed to warm to rt and was stirred for 3 h. The organic solvent was evaporated, and the aqueous solution was neutralized with 10% aqueous citric acid (5 mL) at 0 °C, then extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated, and the crude product was used in the next step without further purification.

$PdCl_2$ (52 mg, 0.3 mmol) was added to a solution of dimethylacetamide (DMA, 20 mL) and H_2O (2.0 mL) in a 100 mL Parr steel reactor, then stirred under 200 psi O_2 pressure for 1 h at rt. The above obtained compound (0.95 mmol) in DMA (3.0 mL) was added and heated at 70 °C under 200 psi O_2 pressure for 14 h. The mixture was cooled to rt, and the solvents were evaporated under reduced pressure. The residue was dissolved in EtOAc (20 mL) and washed with H_2O (3 × 5 mL), and the combined organic extracts were 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 (5−10% MeOH/EtOAc) to afford seco acid **13** (160 mg, 40%) as a light yellow oil: HRESIMS *m/z* 423.2342 $[M + Na]^+$ (calcd for $C_{21}H_{36}O_7Na$, 423.2353).

2,4,6-Trichlorobenzoyl chloride (83 μL, 0.54 mmol) was added to a solution of the seco-acid **13** (200 mg, 0.5 mmol) and Et_3N (140 μL, 1.0 mmol) in THF (2.0 mL) at 0 °C and was stirred at rt for 6 h. After dilution with dry toluene (20 mL) the mixture was added dropwise to a refluxing solution of DMAP (610 mg, 5.0 mmol) in toluene (150 mL) over a period of 18 h. The resulting reaction mixture was further stirred under reflux for 24 h. After cooling, the solvents were evaporated, and the crude product was 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 (45−50% EtOAc/petroleum ether) to afford compound **14** (85 mg, 47%) as a light yellow oil: $[\alpha]^{25}_D$ −16.5 (*c* 2.7, $CHCl_3$); IR ν_{max} (film) 3440, 2935, 1717, 1650, 1217 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 6.61 (dd, *J* = 15.6, 6.8 Hz, 1H), 6.07 (d, *J* = 15.6 Hz, 1H), 4.97 (m, 1H), 4.82 (m, 1H), 4.74 (m, 1H), 3.75 (m, 1H), 2.87 (dd, *J* = 18.6, 10.7 Hz, 1H), 2.70 (dd, *J* = 18.6, 2.5 Hz, 1H), 2.45 (m, 1H), 2.15 (m, 1H), 1.63 (m, 6H), 1.50 (m, 3H), 1.37 (m, 8H), 1.38 (s, 3H), 1.16 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 208.7, 165.7, 140.6, 124.8, 108.7, 76.5, 75.5, 74.1, 67.9, 45.8, 41.5, 39.0, 34.4, 31.8, 28.6, 27.8, 25.3, 24.4, 24.0, 23.5, 21.7; HRESIMS *m/z* 405.2252 $[M + Na]^+$ (calcd for $C_{21}H_{34}O_6Na$, 405.2248).

(5*R*,6*S*,8*R*,14*S*,*E*)-5,6,8-Trihydroxy-14-((*S*)-4-hydroxypentyl)-oxacyclotetradec-3-en-2-one (15). To a solution of compound **14** (25 mg, 0.07 mmol) in MeOH (3.0 mL) was added $NaBH_4$ (5.4 mg, 0.14 mmol) at −78 °C, and the mixture was allowed to warm to rt for 3 h. The reaction mixture was diluted with EtOAc (10 mL) and washed with saturated $NaHCO_3$ (5.0 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The product obtained was dissolved in 4:1 AcOH/H_2O (3.0 mL) and stirred at 60 °C for 4 h. After evaporation of solvent the crude product was purified by flash chromatography over 200−400 mesh silica gel (0−5% MeOH/CH_2Cl_2) to afford compound **15** (16 mg, 72%) as a white, amorphous solid: $[\alpha]^{27}_D$ +7.0 (*c* 0.8, MeOH); IR ν_{max} (film) 3330, 3020, 2400, 1715, 1210 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ_H 6.87 (dd, *J* = 15.9, 6.1 Hz, 1H), 6.06 (s, 1H), 4.96 (m, 1H), 4.48 (m, 1H), 3.97 (m, 1H), 3.84 (m, 1H), 3.69 (m, 1H), 1.83 (m, 1H), 1.68 (m, 3H), 1.56 (m, 3H), 1.33 (m, 11H), 1.14 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR data, Table 1; HRESIMS *m/z* 367.2094 $[M + Na]^+$ (calcd for $C_{18}H_{32}O_6Na$, 367.2091).

(5*R*,6*S*,8*R*,14*S*,*E*)-5,6,8-Trihydroxy-14-((*R*)-4-hydroxypentyl)-oxacyclotetradec-3-en-2-one (23). To a solution of compound **22** (12 mg, 0.03 mmol) in MeOH (3.0 mL) was added $NaBH_4$ (2.2 mg, 0.06 mmol) at −78 °C, and the mixture was allowed to warm to rt for 3 h. The reaction mixture was diluted with EtOAc (10 mL) and washed with saturated $NaHCO_3$ (5.0 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The product obtained was dissolved in 4:1 AcOH/H_2O (3.0 mL) and stirred at 60 °C for 4 h. After evaporation of solvent the crude product was purified by flash chromatography over 200−400 mesh silica gel (0−5% MeOH/CH_2Cl_2) to afford compound **23** (7.8 mg, 75%) as a white, amorphous solid: $[\alpha]^{25}_D$ −5.7 (*c* 0.15, MeOH); IR ν_{max} (film) 3450, 2935, 1717, 1650, 1217 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ_H 6.87 (dd, *J* = 15.9, 6.1 Hz, 1H), 6.08 (d, *J* = 15.9 Hz, 1H), 4.97 (m, 1H), 4.48 (m, 1H), 3.99 (m, 1H), 3.85 (m, 1H), 3.69 (m, 1H), 1.82 (m, 1H), 1.65 (m, 6H), 1.40 (m, 9H), 1.20 (m, 2H), 1.14 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR data, Table 1; HRESIMS *m/z* 367.2093 $[M + Na]^+$ (calcd for $C_{18}H_{32}O_6Na$, 367.2091).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.6b00926.

Copies of ^1H NMR, ^{13}C NMR, and 2D NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ds.reddy@ncl.res.in.

ORCID

D. Srinivasa Reddy: 0000-0003-3270-315X

Notes

The authors declare no competing financial interest.

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