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Total Synthesis of (+)-Aspicilin by an Alkyne-Based Approach and Its Biological Evaluation

Chada Raji Reddy,*[a] Nagavaram Narsimha Rao,[a] Pombala Sujitha,[b] and Chityal Ganesh Kumar[b]

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The stereoselective total synthesis of (+)-aspicilin is described. The pivotal step in this approach is the generation of an enyne intermediate by the coupling of an alkyne with vinyl iodide, which constructed the C6–C7 bond. Conversion of the enyne to the desired macrolide was achieved through Sharpless asymmetric dihydroxylation and Yamaguchi macrolactonization as the key steps. Additionally, the biological activity of (+)-aspicilin was evaluated on A549, HeLa, and MCF7 cancer cell lines.

Introduction

The 18-membered macrocyclic lactone (+)-aspicilin (**1**, Figure 1) was initially isolated in 1900 from a lichen of the *Lecanoraceae* family,[1] and its basic structure was elucidated in 1973.[2] The determination of both relative and absolute configurations was attained in 1985 by NMR spectroscopy, single-crystal X-ray analysis, and the degradation and synthesis of a fragment.[3] With four stereocenters, which include one contiguous *syn–anti* triol skeleton, **1** has fascinated synthetic organic chemists.[4] The first synthesis of **1** was accomplished in 1988 with photolactonization as the key step.[4q] Subsequently, various strategies have been developed for the total synthesis of **1** [4a–4n] and its isomers.[4o–4q] The design and execution of a new synthetic route that enables easy access to substrates, which proceeds with high selectivity, in good yield, and requires mild reaction conditions, is still important. To date, the biological activity of **1** has not been investigated. Hence, our work to explore alkyne-based approaches to macrolides[5] prompted us to develop a new strategy for the total synthesis of **1** and evaluate its biological activity.

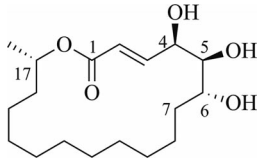

Figure 1. Structure of **1**.

[a] Division of Natural Products Chemistry, CSIR – Indian Institute of Chemical Technology,
Hyderabad 500007, India
Fax: +91-40-2716-0512
E-mail: rajireddy@iict.res.in
[b] Chemical Biology Laboratory, CSIR – Indian Institute of Chemical Technology,
Hyderabad 500007, India

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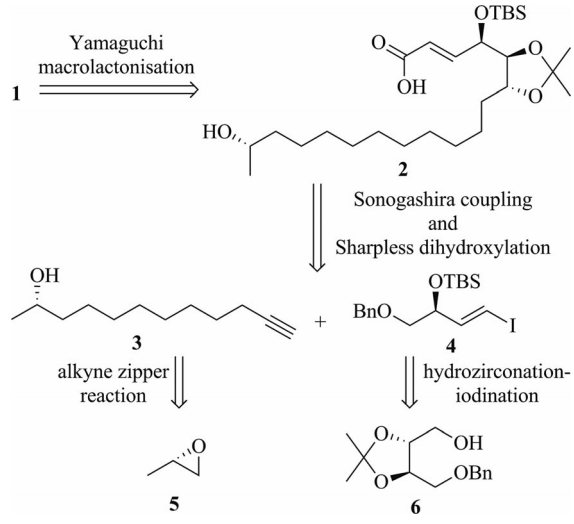
Results and Discussion

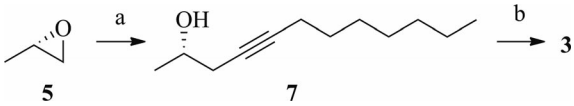
In this synthesis, we aimed to use alkyne chemistry, which has various advantages such as the easy accessibility of the desired alkyne fragments in high yields, the assembly of the two subunits can be accomplished under mild reaction conditions, and the generation of the desired stereocenters using alkyne functionality. Thus, total synthesis of **1** is envisaged by Yamaguchi macrolactonization of *seco*-acid **2**, which was delivered from two key fragments **3** and **4** using Sonogashira coupling and Sharpless asymmetric dihydroxylation as the key reactions. Subunit **3** was obtained from



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

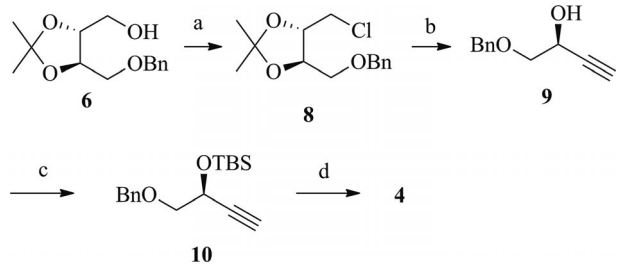
oxirane **5** by an alkyne-zipper reaction, and **4** was achieved from hydrozirconation–iodination of the known precursor **6** (Scheme 1).

Firstly, **3** was obtained from (*S*)-propylene oxide **5** (Scheme 2). Epoxide **5** was opened with 1-nonyne with *n*BuLi/hexamethylphosphoramide (HMPA) in tetrahydrofuran (THF) to provide homopropargylic alcohol **7** in 86% yield. The internal alkyne of **7** was transformed to terminal alkyne **3** through a zipper reaction using KH and 1,3-diaminopropane.[6]



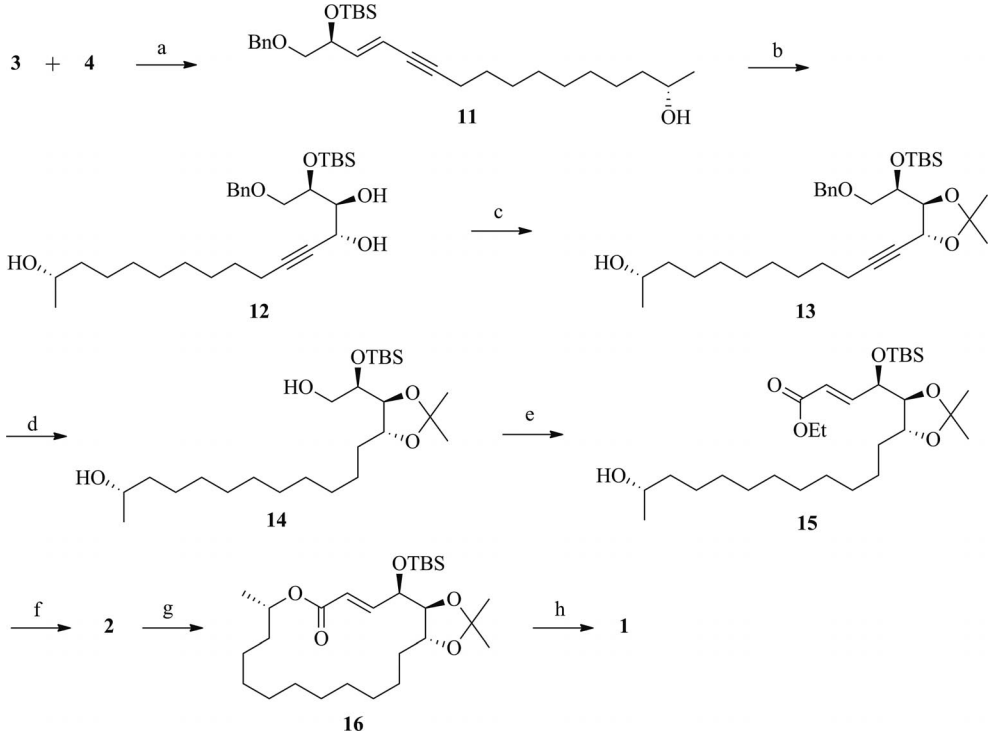
Scheme 2. Synthesis of **3**. Reagents and conditions: (a) 1-nonyne, *n*BuLi, THF, HMPA, –40 to 0 to –20 °C to room temp., 14 h, 86%; (b) KH, 1,3-diaminopropane, 40 °C to room temp., 16 h, 83%.

The synthesis of Sonogashira coupling precursor **4** began with the known alcohol **6**, derived from (–)-2,3-*O*-isopropylidene-D-threitol.[7] The chlorination of **6** using Ph_3P/CCl_4 gave **8** in 95% yield, which was subjected to an elimination reaction with *n*BuLi/HMPA in THF to afford the propargylic alcohol **9** in 96% yield.[8] The protection of **9** [*tert*-butyldimethylsilyl chloride (TBSCl)/imidazole] to give TBS-ether **10** proceeded in 96% yield. Hydrozirconation–iodination of **10** using Cp_2ZrCl_2/super hydride/I_2 reaction conditions[9] provided **4** (76% yield) ready for the coupling (Scheme 3).



Scheme 3. Synthesis of **4**. Reagents and conditions: (a) PPh_3, CCl_4, 80 °C, 12 h, 95%; (b) *n*BuLi, THF, HMPA, –30 °C, 1 h, 96%; (c) TBSCl, imidazole, *N*,*N*-dimethylformamide (DMF), 0 °C to room temp., 12 h, 96%; (d) Cp_2ZrCl_2, super hydride, I_2, room temp., 2 h, 76%.

Sonogashira coupling[10] between **3** and **4** was particularly effective to form the key C6–C7 bond and provide enyne **11** in good yield. Compound **11** with the unprotected hydroxy group was further transformed to **1**. The key Sharpless asymmetric dihydroxylation[11] of **11** was accomplished using AD-mix-β/$MeSO_2NH_2$, *t*BuOH/H_2O to obtain polyol **12** in 72% yield as a separable 9:1 diastereomeric mixture. Protection of the newly generated 1,2-diol as acetonide **13** followed by hydrogenation using 10% Pd/C in EtOH in the presence of hydrogen (one-pot debenzylation and alkyne reduction) afforded the diol **14**. Selective oxidation of the primary alcohol in **14** was attained with 2,2,6,6-tetramethylpiperidine-1-oxy radical (TEMPO)/bis-(acetoxy)iodobenzene (BAIB) in CH_2Cl_2 to aldehyde, which



Scheme 4. Synthesis of **1**. Reagents and conditions: (a) CuI, $PdCl_2(PPh_3)_2$, Et_3N, 0 °C to room temp., 3 h, 84%; (b) AD-mix-β, $MeSO_2NH_2$, *t*BuOH/H_2O, 0 °C, 72 h, 72%; (c) 2,2-dimethoxypropane, camphorsulfonic acid (CSA, 20 mg), CH_2Cl_2, 0 °C to room temp., 1 h, 88%; (d) H_2/PdC (10%), EtOH, room temp., 12 h, 82%; (e) i) TEMPO, BAIB, CH_2Cl_2, room temp., 2 h; ii) PPh_3=$CHCO_2Et$, CH_2Cl_2, 0 °C to room temp., 2 h, 78%; (f) LiOH, THF/MeOH/H_2O (8:1:1), room temp., 8 h (g) 2,4,6-trichlorobenzoyl chloride, Et_3N, 0 °C, 4 h, DMAP, toluene, 100 °C, 10 h, 68% over two steps; (h) 2 M HCl in MeOH, 0 °C, 5 h, 86%.

was subsequently exposed to a one-pot two-carbon Wittig olefination (PPh_3=CHCOOEt) to obtain α,β-unsaturated ester **15** (*E*/*Z* ratio 40:1 by ^{1}H NMR) in 78% yield.[12] The hydrolysis of **15** by LiOH in THF/MeOH/H_2O gave *seco*-acid **2** for the macrolactonization reaction. The hydroxy acid **2** was exposed to Yamaguchi reaction conditions [2,4,6-trichlorobenzoyl chloride/Et_3N/4-(dimethylamino)-pyridine (DMAP), 100 °C][13] to provide the protected macrolide **16**. Treatment of **16** with 2 M HCl in MeOH afforded **1** [m.p. 153–155 °C. $[\alpha]_D^{20}$ = +37.9 (*c* = 0.64, $CHCl_3$)] in 86% yield (Scheme 4). The characterization of our synthetic sample was identical to literature data (^{1}H and ^{13}C NMR spectroscopy and optical rotation).

Compound **1** was tested against various cancer cell lines using an MTT assay [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide].[14] It showed promising inhibitory activity on the proliferation of A549 (IC_{50} = 14.7 μM over 24 h), HeLa (IC_{50} = 17.9 μM over 24 h), and MCF7 (IC_{50} = 12.0 μM over 24 h) cancer cell lines. It did not exhibit any cytotoxicity towards Neuro2a or MDA-MB-231 cancer cell lines. Furthermore, antibacterial and antifungal activities were also evaluated and showed no potential activity.[15]

Conclusions

An efficient strategy has been developed for the total synthesis of (+)-aspicilin (**1**) in 12 linear steps in 13.2% overall yield from the known alcohol **6**. The characteristic features of this alkyne-based approach included: (i) synthesis of the desired fragments by alkyne chemistry, (ii) assembly of the two subunits by Sonogashira coupling, (iii) generation of the required stereocenters by Sharpless asymmetric dihydroxylation, and (iv) Yamaguchi macrolatonization to construct the 18-membered macrolactone ring. The cytotoxic actitivity towards A549, HeLa, and MCF7 cancer cells has also been disclosed.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with 300, 400, 500, or 75 MHz spectrometers at ambient temperature. FTIR spectra were recorded as KBr discs or neat. Optical rotations were measured with a digital polarimeter using a 2 mL cell with a 1 dm path length. All the reagents and solvents were reagent grade and used without purification unless specified otherwise. Technical grade ethyl acetate and hexanes used for column chromatography were distilled prior to use. When used as a reaction solvent, THF was freshly distilled from sodium benzophenone ketyl. Column chromatography was carried out using silica gel (60–120 mesh and 100–200 mesh) packed in glass columns. All the reactions were performed under an atmosphere of nitrogen in flame-dried or oven-dried glassware with magnetic stirring.

(*S*)-Dodec-4-yn-2-ol (7): To a stirred solution of 1-nonyne (8.5 mL, 51.7 mmol) in dry THF (30 mL) at –40 °C was added *n*BuLi (1.6 M in hexane, 21.5 mL, 34.5 mmol) dropwise. The reaction mixture was warmed to 0 °C over 30 min and then recooled to –20 °C. To this was added dry HMPA (8 mL) followed by (*S*)propylene oxide (**5**, 2.4 mL, 34.5 mmol) in HMPA (8 mL) over 15 min. The reaction mixture was stirred at –20 °C for 30 min, warmed to room temperature over 4 h, and stirred for 12 h at room temperature. The reaction mixture was poured into iced water (50 mL) and extracted with diethyl ether (4 × 50 mL). The combined organic layer was washed with brine (50 mL), dried with Na_2SO_4, concentrated, and purified by column chromatography (hexanes/diethyl ether, 80:20) to provide **7** (5.4 g, 86%) as a yellow liquid. $[\alpha]_D^{20}$ = +11.7 (*c* = 1.12, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3383, 2927, 2857, 1459, 1114, 1082, 938 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.8 (sext, *J* = 5.7 Hz, 1 H), 2.37–2.29 (m, 1 H), 2.27–2.19 (m, 1 H), 2.17–2.12 (m, 2 H), 1.86 (br. s, OH), 1.54–1.44 (m, 2 H), 1.41–1.24 (m, 8 H), 1.22 (d, *J* = 5.4 Hz, 3 H), 0.89 (t, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 82.7, 76.0, 66.4, 31.5, 29.1, 28.8, 28.7, 28.6, 22.4, 21.9, 18.5, 13.8 ppm.

(*S*)-Dodec-11-yn-2-ol (3): Potassium hydride (35% suspension in mineral oil, 2.05 g, 15.4 mmol) was weighed in an oven-dried round-bottomed flask and washed with diethyl ether (3 × 5 mL) under nitrogen. To the oil-free potassium hydride was added 1,3-diaminopropane (15 mL) at room temperature, and the mixture was heated for 1 h at 40 °C. The reaction mixture was cooled to 0 °C, and **7** (700 mg, 3.85 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 15 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to 0 °C and quenched with ice. The aqueous layer was extracted with diethyl ether (2 × 25 mL). The combined organic layer was washed with 2 M HCl (25 mL) and water (25 mL) and dried with Na_2SO_4. The organic solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (hexanes/diethyl ether, 80:20) to give **3** (581 mg, 83%) as a colorless oil. $[\alpha]_D^{20}$ = +7.3 (*c* = 1.20, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3309, 2929, 2856, 2116, 1461, 1373, 1125, 629 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.79–3.72 (m, 1 H), 2.15 (td, *J* = 7.0, 2.0 Hz, 2 H), 1.84 (t, *J* = 2.0 Hz, 1 H), 1.55–1.48 (m, 2 H), 1.46–1.26 (m, 12 H), 1.17 (d, *J* = 6.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 84.4, 67.9, 67.6, 39.0, 29.4, 29.2, 28.8, 28.5, 28.2, 25.5, 23.1, 18.1 ppm.

(4*R*,5*S*)-4-(Benzyloxymethyl)-5-(chloromethyl)-2,2-dimethyl-1,3-dioxolane (8): To a stirred solution of **6** (5.0 g, 19.8 mmol) in CCl_4 (100 mL) was added triphenyl phosphane (10 g, 39.6 mmol) at room temperature, and the mixture was heated to reflux for 12 h. The reaction mixture was cooled to 0 °C, diluted with hexanes (100 mL), and stirred for 30 min. The precipitate was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (hexanes/EtOAc, 97:3) to give **8** (5.07 g, 95%) as a colorless oil. $[\alpha]_D^{20}$ = –2.6 (*c* = 1.00, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 2988, 2864, 1373, 1245, 1216, 1085, 741, 698 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.21 (m, 5 H), 4.57 (s, 2 H), 4.11–3.99 (m, 2 H), 3.68–3.54 (m, 4 H), 1.41 (s, 3 H), 1.40 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.6, 128.3, 127.7, 127.5, 109.9, 78.0, 77.8, 73.5, 70.4, 44.4, 27.0, 26.9 ppm. HRMS (ESI): calcd. for $C_{14}H_{19}ClO_3Na$ $[M + Na]^+$ 293.0915; found 293.0929.

(*S*)-1-(Benzyloxy)but-3-yn-2-ol (9): To a solution of HMPA (5.14 mL, 29.6 mmol) in THF (30 mL) was added *n*BuLi (2.5 M in hexanes, 10.3 mL, 25.9 mmol) at –30 °C under a nitrogen atmosphere. To this mixture was added **8** (1.0 g, 3.7 mmol) in THF (5 mL) dropwise. The reaction mixture was stirred for 1 h at –30 °C. After the completion of the reaction (monitored by TLC), the mixture was treated with a saturated aqueous solution of NH_4Cl (25 mL) and extracted with diethyl ether (2 × 25 mL). The combined organic layer was washed with brine (20 mL), dried with

Na_2SO_4, and the organic solvents were evaporated under reduced pressure. The residue was purified by flash column chromatography (hexanes/EtOAc, 80:20) to give **9** (625 mg, 96%) as a colorless oil. $[\alpha]_D^{20}$ = +7.7 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3290, 2917, 2865, 2117, 1452, 1112, 743, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.22 (m, 5 H), 4.59 (s, 2 H), 4.53–4.45 (m, 1 H), 3.62 (dd, *J* = 9.6, 3.3 Hz, 1 H), 3.57–3.49 (m, 1 H), 2.47 (br. s, OH), 2.37 (d, *J* = 1.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.4, 128.3, 127.7, 127.6, 81.7, 73.5, 73.3, 73.2, 61.2 ppm.

(*S*)-[1-(Benzyloxy)but-3-yn-2-yloxy](*tert*-butyl)dimethylsilane (10): To a stirred solution of **9** (575 mg, 3.26 mmol) in DMF (5 mL) was added imidazole (776 mg, 11.4 mmol) followed by *tert*-butyldimethylsilyl chloride (740 mg, 4.9 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 12 h. After completion of the reaction, the mixture was diluted by saturated aqueous $NaHCO_3$ solution (20 mL), and the aqueous phase was extracted with diethyl ether (2 × 20 mL). The combined organic layer was washed with brine (20 mL), dried with Na_2SO_4, and evaporated under reduced pressure. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 95:5) to give **10** (907 mg, 96%) as a colorless oil. $[\alpha]_D^{20}$ = +23.3 (*c* = 1.20, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 2932, 2858, 1462, 1253, 1101, 836, 778 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.27 (m, 5 H), 4.58 (s, 2 H), 4.51 (ddd, *J* = 6.7, 5.2, 2.2 Hz, 1 H), 3.59–3.49 (m, 2 H), 2.33 (d, *J* = 2.2 Hz, 1 H), 0.91 (s, 9 H), 0.13 (s, 3 H), 0.11 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.5, 128.3, 127.5, 83.1, 74.4, 73.4, 72.9, 62.8, 25.7, 18.2, –4.7, –4.9 ppm. HRMS (ESI): calcd. for $C_{17}H_{26}O_2NaSi$ $[M + Na]^+$ 313.15943; found 313.15894.

(*S*,*E*)-[1-(Benzyloxy)-4-iodobut-3-en-2-yloxy](*tert*-butyl)dimethylsilane (4): To a solution of $[Cp_2ZrCl_2]$ (2.32 g, 7.93 mmol) in THF (32 mL) was added $LiEt_3BH$ (7.93 mL, 1 M in THF, 7.93 mmol) at room temperature over 20 min. The reaction mixture was stirred for 1 h before **10** (1.15 g, 3.97 mmol) in THF (16 mL) was added dropwise. The mixture was stirred for 30 min before the addition of I_2 (1.5 g, 5.96 mmol) at 0 °C, and stirring continued for 30 min. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution (30 mL). The aqueous phase was extracted with diethyl ether (2 × 25 mL). The combined organic layer was washed with brine (20 mL), dried with Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (hexanes/EtOAc, 97:3) to give **4** (1.26 g, 76%) as a colorless liquid. $[\alpha]_D^{20}$ = +3.2 (*c* = 1.30, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 2954, 2930, 2891, 2856, 1464, 1362, 1253, 1096, 835, 777 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.20 (m, 5 H), 6.57 (dd, *J* = 14.3, 5.1 Hz, 1 H), 6.32 (dd, *J* = 14.3, 1.3 Hz, 1 H), 4.50 (s, 2 H), 4.29–4.21 (m, 1 H), 3.38–3.32 (m, 2 H), 0.89 (s, 9 H), 0.05 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146, 138, 128.2, 127.5, 77.1, 74.1, 73.8, 73.3, 25.7, 18.2, –4.8 ppm. HRMS (ESI): calcd. for $C_{17}H_{27}O_2INaSi$ $[M + Na]^+$ 441.07172; found 441.07239.

(2*S*,15*S*,*E*)-16-(Benzyloxy)-15-(*tert*-butyldimethylsilyloxy)hexadec-13-en-11-yn-2-ol (11): To a solution of **4** (450 mg, 1.08 mmol) and **3** (196 mg, 1.08 mmol) in triethylamine (10 mL) was added bis(triphenylphosphane)palladium(II) dichloride (76 mg, 0.11 mmol) at 0 °C. The mixture was stirred for 15 min at 0 °C before copper(I) iodide (41.1 mg, 0.21 mmol) was added. After stirring for 10 min at 0 °C, the reaction mixture was warmed to room temperature and stirred for another 2.5 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (hexanes/EtOAc, 90:10) to afford **11** (428 mg, 84%) as a light yellow oil. $[\alpha]_D^{20}$ = +1.2 (*c* = 1.00, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3429, 2929, 2856, 1719, 1271, 1118, 836, 779, 714 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.22 (m, 5 H), 6.00 (dd, *J* = 15.7, 5.5 Hz, 1 H), 5.69 (dt, *J* = 15.7, 1.8 Hz, 1 H), 4.51 (s, 2 H), 4.36–4.30 (m, 1 H), 3.79–3.70 (m, 1 H), 3.35 (d, *J* = 6.4 Hz, 2 H), 2.27 (td, *J* = 6.4, 1.8 Hz, 2 H), 1.56–1.47 (m, 2 H), 1.47–1.24 (m, 12 H), 1.17 (d, *J* = 5.5 Hz, 3 H), 0.90 (s, 9 H), 0.05 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.4, 138.1, 128.1, 127.5, 127.4, 110.4, 91.0, 78.5, 74.5, 73.2, 71.7, 67.8, 39.2, 29.4, 29.3, 28.9, 28.7, 28.6, 25.7, 25.6, 23.3, 19.3, 18.1, –4.8 ppm. HRMS (ESI): calcd. for $C_{29}H_{48}O_3NaSi$ $[M + Na]^+$ 495.32649; found 495.32566.

(2*S*,13*R*,14*S*,15*R*)-16-(Benzyloxy)-15-(*tert*-butyldimethylsilyloxy)-hexadec-11-yne-2,13,14-triol (12): Compound **11** (600 mg, 1.27 mmol) was dissolved in a mixture of *tert*-butyl alcohol (6.4 mL) and water (6.4 mL) and cooled to 0 °C. To this was added methane sulfonamide (121 mg, 1.27 mmol) followed by AD-mix-β (1.8 g), and the mixture was stirred for 72 h at 0 °C. After completion of the reaction (monitored by TLC), the reaction mixture was quenched by adding solid sodium sulfite (2 g) and stirred for 1 h. The mixture was diluted with water (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layer was dried with Na_2SO_4, and the solvents evaporated to dryness under reduced pressure. The residue was purified by column chromatography (hexanes/EtOAc, 85:15) to give **12** (462 mg, 72%) as a separable diastereomeric mixture (9:1). Major isomer: $[\alpha]_D^{20}$ = –3.2 (*c* = 1.44, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3446, 2927, 2855, 1631, 1458, 1251, 1092, 836, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.29 (m, 5 H), 4.54 (s, 2 H), 4.57–4.52 (m, 1 H), 4.01 (q, *J* = 5.3 Hz, 1 H), 3.84–3.74 (m, 1 H), 3.71 (dd, *J* = 6.0, 3.0 Hz, 1 H), 3.61 (d, *J* = 5.3 Hz, 1 H), 2.21 (td, *J* = 6.8, 2.2 Hz, 2 H), 1.54–1.24 (m, 14 H), 1.18 (d, *J* = 6.8 Hz, 3 H), 0.89 (s, 9 H), 0.11 (s, 3 H), 0.07 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.5, 128.3, 127.7, 127.6, 86.3, 78.6, 76.2, 73.5, 72.3, 71.1, 68.1, 62.6, 39.2, 29.4, 29.3, 28.9, 28.7, 28.5, 25.7, 25.6, 23.4, 18.7, 18.0, –4.5, –5.0 ppm. HRMS (ESI): calcd. for $C_{29}H_{50}O_5NaSi$ $[M + Na]^+$ 529.33197; found 529.33079. Minor isomer: $[\alpha]_D^{20}$ = –3.8 (*c* = 0.60, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 5 H), 4.54 (s, 2 H), 4.32 (d, *J* = 7.2 Hz, 1 H), 4.16 (t, *J* = 7.2 Hz, 1 H), 3.81–3.75 (m, 1 H), 3.61 (d, *J* = 7.2 Hz, 1 H), 3.57 (dd, *J* = 9.7, 6.4 Hz, 1 H), 3.50 (dd, *J* = 9.7, 5.6 Hz, 1 H), 2.22 (td, *J* = 7.2, 1.6 Hz, 2 H), 1.54–1.47 (m, 2 H), 1.46–1.24 (m, 12 H), 1.18 (d, *J* = 6.6 Hz, 3 H), 0.89 (s, 9 H), 0.11 (s, 3 H), 0.07 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.8, 128.3, 127.7, 127.6, 87.6, 77.2, 75.4, 73.4, 71.6, 70.2, 68.1, 64.3, 39.3, 29.5, 29.4, 28.9, 28.8, 28.4, 25.8, 25.6, 23.4, 18.7, 18.0, –4.3, –5.0 ppm.

(*S*)-12-[(4*R*,5*S*)-5-{(*R*)-2-(Benzyloxy)-1-(*tert*-butyldimethylsilyloxy)-ethyl}-2,2-dimethyl-1,3-dioxolan-4-yl]dodec-11-yn-2-ol (13): To **12** (440 mg, 0.87 mmol) in CH_2Cl_2 (5 mL) was added CSA (20 mg, 0.087 mmol) followed by 2,2-dimethoxypropane (0.32 mL, 2.6 mmol). The mixture was stirred for 1 h at room temperature. After completion of the reaction (monitored by TLC), saturated $NaHCO_3$ solution (15 mL) was added to the reaction mixture and it was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layer was dried with Na_2SO_4, and the solvents evaporated to dryness under reduced pressure. The residue was purified by column chromatography (hexanes/EtOAc, 90:10) to give **13** (420 mg, 88%) as a colorless oil. $[\alpha]_D^{20}$ = +12.2 (*c* = 1.00, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3447, 2929, 2856, 1461, 1372, 1252, 1152, 1064, 835, 777 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.25 (m, 5 H), 4.68 (d, *J* = 7.0 Hz, 1 H), 4.52 (s, 2 H), 4.14 (dd, *J* = 7.0, 3.0 Hz, 1 H), 4.07–4.02 (m, 1 H), 3.82–3.74 (m, 1 H), 3.57 (dd, *J* = 10.0, 6.0 Hz, 1 H), 3.48 (dd, *J* = 10.0, 6.0 Hz, 1 H), 2.18 (t, *J* = 7.0 Hz, 2 H), 1.52–1.21 (m, 14 H), 1.47 (s, 3 H), 1.40 (s, 3 H), 1.18 (d, *J* = 6.0 Hz, 3 H), 0.90 (s, 9 H), 0.09 (s, 3 H), 0.07 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.1, 128.2, 127.5, 109.6, 86.9, 82.4, 78.2,

73.3, 72.2, 70.8, 68.1, 66.3, 39.3, 29.5, 29.4, 29.0, 28.8, 28.4, 26.7, 26.0, 25.8, 25.7, 23.4, 18.8, 18.1, –4.5, –4.7 ppm. MS (ESI): *m*/*z* = 569.3588 $[M + Na]^+$.

(*S*)-12-[(4*R*,5*S*)-5-{(*R*)-1-(*tert*-Butyldimethylsilyloxy)-2-hydroxyethyl}-2,2-dimethyl-1,3-dioxolan-4-yl]dodecan-2-ol (14): Palladium on carbon (100 mg, 10% w/w) was added to a solution of **13** (250 mg, 0.46 mmol) in EtOH (5 mL), and the heterogeneous mixture was stirred overnight under a hydrogen atmosphere. After the completion of the reaction, the mixture was filtered through a small pad of Celite, and the resulting filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexanes/EtOAc, 80:20) to give **14** (172 mg, 82%) as a colorless liquid. $[\alpha]_D^{20}$ = +8.5 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3428, 2927, 2856, 1463, 1372, 1251, 1066, 835, 775 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.90–3.91 (m, 1 H), 3.80–3.73 (m, 1 H), 3.71–3.60 (m, 4 H), 2.07 (br. s, OH), 1.73–1.23 (m, 20 H), 1.37 (s, 3 H), 1.34 (s, 3 H), 1.17 (d, *J* = 5.5 Hz, 3 H), 0.90 (s, 9 H), 0.12 (s, 3 H), 0.10 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 108.7, 81.3, 80.4, 74.0, 68.0, 65.0, 39.3, 34.6, 29.7, 29.5, 29.4, 27.3, 27.1, 26.2, 25.7, 23.4, 17.9, –4.4, –4.5 ppm. HRMS (ESI): calcd. for $C_{25}H_{52}O_5SiNa$ $[M + Na]^+$ 483.3476; found 483.3432.

(*R*,*E*)-Ethyl 4-(*tert*-Butyldimethylsilyloxy)-4-[(4*S*,5*R*)-5-{(*S*)-11-hydroxydodecyl}-2,2-dimethyl-1,3-dioxolan-4-yl]but-2-enoate (15): To **14** (220 mg, 0.48 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added BAIB (178 mg, 0.55 mmol) and TEMPO (7.1 mg, 0.05 mmol). The mixture was stirred for 2 h at room temperature, cooled to 0 °C, and (ethocycarbonlymethylene)triphenylphosphorane (216 mg, 0.62 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 2 h. After completion of the reaction, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography (hexanes/EtOAc, 90:10) to afford **15** (197 mg, 78%) as a colorless liquid. $[\alpha]_D^{20}$ = +10.0 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3446, 2928, 2856, 1721, 1352, 1463, 1372, 1257, 1166, 1072, 838, 777 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.96 (dd, *J* = 15.0, 5.0 Hz, 1 H), 6.03 (d, *J* = 15.0 Hz, 1 H), 4.34 (t, *J* = 5.0 Hz, 1 H), 4.24–4.16 (m, 2 H), 3.96 (td, *J* = 9.0, 4.0 Hz, 1 H), 3.82–3.76 (m, 1 H), 3.58 (t, *J* = 7.0 Hz, 1 H), 1.78–1.55 (m, 2 H), 1.52–1.22 (m, 18 H), 1.38 (s, 6 H), 1.19 (d, *J* = 6.0 Hz, 3 H), 0.92 (s, 9 H), 0.09 (s, 3 H), 0.04 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2, 147.8, 121.6, 108.7, 82.8, 78.6, 72.8, 68.1, 60.4, 39.3, 34.4, 29.6, 29.6, 29.5, 29.4, 27.4, 27.1, 26.1, 25.8, 25.7, 23.4, 18.1, 14.2, –4.5, –4.6 ppm. HRMS (ESI): calcd. for $C_{29}H_{56}O_6SiNa$ $[M + Na]^+$ 551.3738; found 551.3717.

(*R*,*E*)-4-(*tert*-Butyldimethylsilyloxy)-4-[(4*S*,5*R*)-5-{(*S*)-11-hydroxydodecyl}-2,2-dimethyl-1,3-dioxolan-4-yl]but-2-enoic Acid (2): To a solution of **15** (190 mg, 0.36 mmol) in THF/MeOH/H_2O (8:1:1, 5 mL) was added LiOH (151 mg, 3.6 mmol). The reaction mixture was stirred at room temperature for 8 h. The residue was diluted with H_2O (5 mL), and the resulting solution was acidified to about pH 7 with 2 N HCl and extracted with EtOAc (2 × 25 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated in vacuo, and the resulting crude *seco*-acid **2** (180 mg, quantitative) was used in the next step without further purification. $[\alpha]_D^{20}$ = +9.5 (*c* = 1.08, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3446, 2928, 2856, 1704, 1376 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.06 (dd, *J* = 15.0, 4.6 Hz, 1 H), 6.05 (d, *J* = 15.0 Hz, 1 H), 4.40 (t, *J* = 4.6 Hz, 1 H), 4.00–3.94 (m, 1 H), 3.85–3.78 (m, 1 H), 3.60 (t, *J* = 6.9 Hz, 1 H), 1.62–1.22 (m, 20 H), 1.38 (s, 6 H), 1.19 (d, *J* = 5.7 Hz, 3 H), 0.93 (s, 9 H), 0.10 (s, 3 H), 0.05 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1, 150.0, 121.0, 108.7, 82.7, 78.3, 72.6, 68.3, 39.1, 34.3, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 27.4, 27.1, 26.0, 25.8, 25.5, 23.3, 18.1, –4.5, –4.6 ppm. MS (ESI): 523.3207 $[M + Na]^+$.

Macrolactone 16: To a solution of **2** (180 mg, 0.36 mmol) in THF (10 mL) at 0 °C were added Et_3N (0.3 mL, 2.16 mmol) and 2,4,6-$Cl_3C_6H_2COCl$ (0.28 mL, 1.8 mmol). After stirring at room temperature for 4 h, the reaction mixture was diluted with toluene (10 mL) and added dropwise to a solution of DMAP (1.3 g, 10.8 mmol) in toluene (200 mL) at 100 °C over 10 h. After cooling to room temperature, the mixture was concentrated to about 20 mL, diluted with EtOAc (25 mL), and the solution was successively washed with 0.5 M aqueous HCl (10 mL), saturated aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (hexanes/EtOAc, 98:2) to provide **16** (118 mg, 68%) as a colorless oil. $[\alpha]_D^{20}$ = +19.5 (*c* = 0.64, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 2929, 2858, 1718, 1457, 1372, 1255, 1115, 976, 835 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.82 (dd, *J* = 14.8, 4.9 Hz, 1 H), 6.01 (d, *J* = 14.8 Hz, 1 H), 5.08–4.99 (m, 1 H), 4.66–4.60 (m, 1 H), 4.05 (t, *J* = 5.9 Hz, 1 H), 3.72 (d, *J* = 7.9 Hz, 1 H), 1.62–1.22 (m, 20 H), 1.40 (s, 3 H), 1.38 (s, 3 H), 1.25 (d, *J* = 5.9 Hz, 3 H), 0.94 (s, 9 H), 0.11 (s, 3 H), 0.07 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.3, 146.1, 122.3, 108.0, 82.3, 74.5, 70.8, 70.3, 35.8, 32.8, 27.8, 27.3, 27.0, 26.9, 26.8, 25.9, 25.8, 24.4, 24.2, 20.5, 18.2, –4.5, –4.8 ppm. HRMS (ESI): calcd. for $C_{27}H_{50}O_5SiNa$ $[M + Na]^+$ 505.3320; found 505.3338.

(+)-Aspicilin (1): To a solution of **16** (90 mg, 0.18 mmol) in MeOH (1 mL) at 0 °C was added 2 M HCl in MeOH (3 mL). The mixture was stirred for 5 h at 0 °C. After completion of the reaction (monitored by TLC), the solvent was evaporated under reduced pressure, and the residue was purified by flash column chromatography (hexanes/EtOAc, 30:70) to give **1** (52 mg, 86%) as a colorless solid. M.p. 153–155 °C. $[\alpha]_D^{20}$ = +37.9 (*c* = 0.64, $CHCl_3$) {ref.[4g]: $[\alpha]_D^{22}$ = +37.5 (*c* = 0.55, $CHCl_3$), ref.[4i]: $[\alpha]_D^{23}$ = +38.5 (*c* = 0.22, $CHCl_3$)}. IR (KBr): $\tilde{\nu}_{max}$ = 3449, 3289, 2926, 2855, 1718, 1662, 1459, 1370, 1245, 1179, 1075 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.91 (dd, *J* = 16.3, 5.4 Hz, 1 H), 6.13 (d, *J* = 16.3 Hz, 1 H), 5.05 (sext, *J* = 6.2 Hz, 1 H), 4.62–4.55 (m, 1 H), 3.77 (td, *J* = 7.0, 2.3 Hz, 1 H), 3.66 (br. s, 1 H), 3.62–3.55 (m, 1 H), 3.36 (br. s, 1 H), 2.83 (br. s, 1 H), 1.56 (q, *J* = 6.2 Hz, 4 H), 1.47–1.15 (m, 16 H), 1.25 (d, *J* = 6.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 144.6, 123.0, 74.7, 73.3, 71.1, 69.9, 35.6, 32.0, 28.2, 27.7, 27.5, 27.2, 27.1, 26.3, 24.2, 23.6, 20.4 ppm. HRMS (ESI): calcd. for $C_{18}H_{32}O_5Na$ $[M + Na]^+$ 328.2142; found 328.2134.

Supporting Information (see footnote on the first page of this article): Copies of ^1H and ^{13}C NMR spectra for all compounds.

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