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Enantioselective synthesis of aurisides A and B, cytotoxic macrolide glycosides of marine origin

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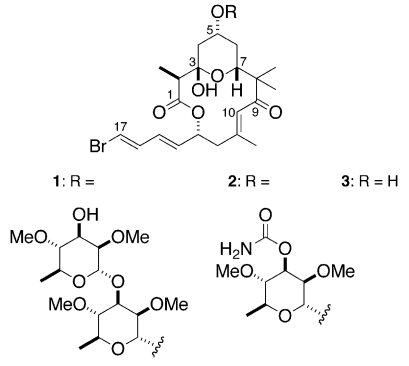
Abstract—The enantioselective synthesis of aurisides A and B, macrolide glycosides of marine origin, was achieved by a convergent approach. The C1–C9 segment **4** was prepared from (*R*)-pantolactone, and the C10–C17 segment **14** was synthesized from (*R*)-glycidyl trityl ether. The Nozaki–Hiyama–Kishi reaction between **4** and **14** and subsequent reactions gave seco acid **10**, which was converted into the aglycon (**3**) of aurisides by construction of the 14-membered lactone and bromine-substituted conjugated diene. The glycosylation reaction of the aglycon provided aurisides A and B.

1. Introduction

The sea hare *Dolabella auricularia* (Aplysiidae) is known to be a rich source of cytotoxic and/or antitumor peptides and other unique metabolites.[1,2] Aurisides A (**1**) and B (**2**) are macrolide glycosides isolated from Japanese sea hare *D. auricularia*, which exhibit cytotoxicity against HeLa S_3 cells with IC_{50} values of 0.17 and 1.2 μg mL^{-1}, respectively.[3] The main structural features of aurisides are a bromine-substituted conjugated diene, a 14-membered lactone, and a cyclic hemiacetal. The biological activity and structural novelty of aurisides prompted us to initiate the investigation toward the synthesis of **1** and **2**. We had achieved the synthesis of aglycon (**3**) of aurisides,[4] and synthetic studies of aurisides have been carried out by a few groups.[5] Recently, total synthesis of **1** and **2** were achieved by Paterson and co-workers.[6] Several natural products structurally related to **1** and **2** have been isolated,[7] and studies have been made on synthesis of these compounds.[8] We describe herein enantioselective synthesis of aurisides A (**1**) and B (**2**) according to a convergent synthetic methodology with some improvement of our previous synthesis of their aglycon (**3**).[4]



2. Results and discussions

The outline of our previous synthesis of the aglycon of aurisides is shown in Scheme 1. There are some serious problems in this route: (1) the macrolactonization of seco acid **5** required vigorous conditions because of steric hindrance of trityl group and led to elimination of methanol to give lactones **6a** and **6b**; (2) re-formation of the cyclic hemiacetal and construction of the bromine-substituted conjugated diene proceeded only in poor yields. Therefore, we began reinvestigating more efficient routes. The second-generation strategy is illustrated in Scheme 2. We planned to construct the cyclic structure of aurisides by the macrolactonization of seco acid **11** or **12**. We expected that macrolactonization of **11** or **12** provided lactone **9** or **10** without elimination of methanol under milder conditions than the previous synthesis, because the steric hindrance around 13-hydroxyl group

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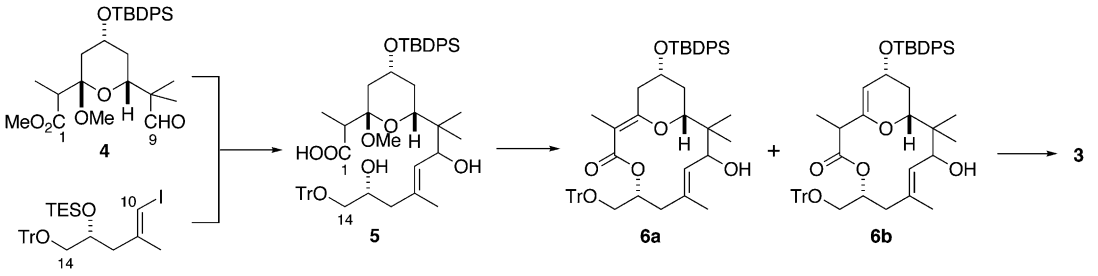
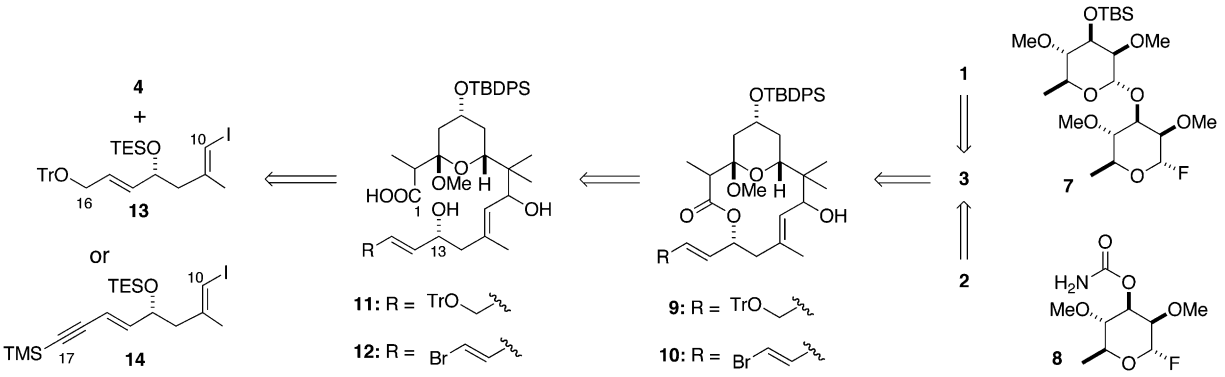


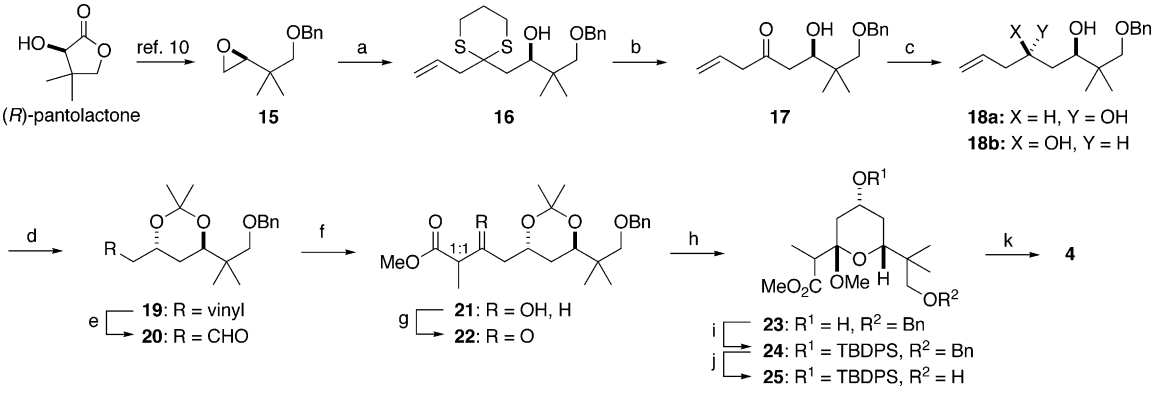
Scheme 1. Outline of the previous synthesis of aglycon (**3**) of aurisides.



Scheme 2. The second generation strategy for synthesis of aurisides A (**1**) and B (**2**).

in **11** and **12** are much smaller than that in **5**. The seco acid **11** could be synthesized from C1–C9 segment **4** and C10–C16 segment **13** by Nozaki–Hiyama–Kishi reaction as a key step. The seco acid **12** might be obtained from **4** and C10–C17 segment **14**, which possesses a conjugated enyne group, a precursor of the bromine-substituted conjugated diene. The glycosylation of **3** with fluorosugars **7** and **8** under the Mukaiyama protocol[9] could provide aurisides A (**1**) and B (**2**), respectively, in the same way as Paterson and co-workers.[6]

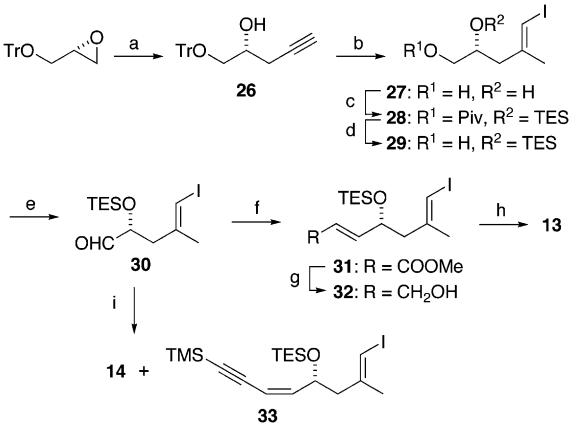
The synthesis of C1–C9 segment **4** started from commercially available (*R*)-pantolactone (Scheme 3). (*R*)-Pantolactone was converted into epoxide **15** by a four-step sequence of reactions.[10] Alkylation of the carbanion generated from 2-allyldithiane with **15** afforded alcohol **16** (92%). Careful deprotection[11] of the dithioacetal moiety in **16** gave ketone **17** (77%). Stereoselective reduction of **17** with tetramethylammonium triacetoxyborohydride[12] afforded *anti*-1,3-diol **18a** (86%) along with *syn*-1,3-diol **18b** (7%). *anti*-1,3-Diol **18a** was transformed into acetonide **19** (97%), the stereochemistry of which was confirmed to be *anti* by the ^{13}C chemical shifts of two acetonide methyls (δ_C 24.6 and 24.2).[13] Oxidative cleavage of the vinyl group in **19** gave aldehyde **20** (96%), rhodium-catalyzed Reformatsky-type reaction[14] of which with methyl 2-bromopropionate provided a diastereomeric mixture of β-hydroxy esters **21** (88%).[15] Swern oxidation of **21** afforded β-keto ester **22** as an inseparable 1:1 mixture of diastereomers concerning the secondary methyl group (88%). Acid treatment of **22** in methanol led to cyclic methyl acetal **23** (96%), the secondary hydroxyl



Scheme 3. (a) 2-Allyldithiane, BuLi, THF–hexane, −78 °C→−30 °C, 92%; (b) $(CF_3CO_2)_2IPh$, MeOH, 0 °C; H_2O, AcOH, THF, rt, 77%; (c) $Me_4NBH(OAc)_3$, AcOH, MeCN, −30 °C, 86%; (d) $(MeO)_2CMe_2$, CSA, acetone, rt, 97%; (e) OsO_4, NMO, acetone–^{t}BuOH, rt; $NaIO_4$, H_2O, rt, 96%; (f) methyl 2-bromopropionate, Et_2Zn, $RhCl(PPh_3)_3$, THF, 0 °C, 88%; (g) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C; Et_3N, −78 °C→0 °C, 88%; (h) $CH(OMe)_3$, PPTS, MeOH, 50 °C, 96%; (i) TBDPSCl, imidazole, 0 °C, 100%; (j) H_2, 20% $Pd(OH)_2$–C, dioxane, rt, 96%; (k) DMSO, SO_3·pyridine, Et_3N, rt, 95%.

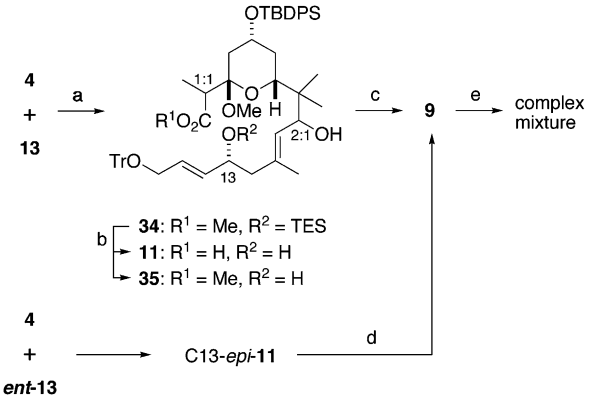
group of which was silylated to give silyl ether **24** (100%). Cleavage of the benzyl group in **24** afforded alcohol **25** (96%), which was oxidized to provide C1–C9 segment **4** (95%).

The synthesis of C10–C16 and C10–C17 segments, **13** and **14**, began with an alkylation reaction of lithium acetylide with (*R*)-glycidyl trityl ether to afford acetylene **26** in 97% yield (Scheme 4). Carbometallation of **26** followed by treatment with iodine gave vinyl iodide **27**,[16] accompanied by cleavage of the trityl group (50%). Protection of the primary hydroxyl group in **27** followed by silylation of the secondary hydroxyl group afforded silyl ether **28** (92%), which was converted into primary alcohol **29** (99%). Oxidation of **29** gave aldehyde **30** (95%), the Wittig reaction of which with $MeO_2CCH{=}PBu_3$[17] provided conjugated ester **31** as a sole product (92%). Reduction of **31** afforded alcohol **32** (86%), the hydroxyl group of which was tritylated to give C10–C16 segment **13** (89%). Wittig olefination reaction of aldehyde **30** with TMS–C≡CCH_2PPh_3Br and BuLi provided C10–C17 segment **14** (57%) along with *cis*-isomer **33** (9%).



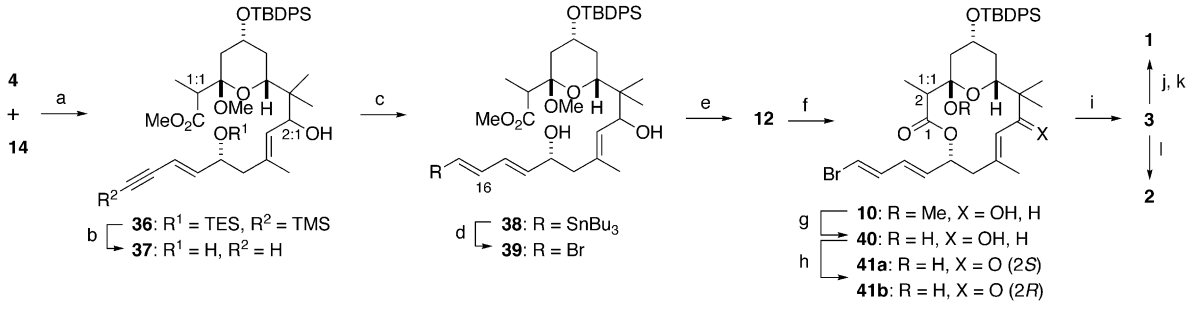
Scheme 4. (a) $LiC{\equiv}CH{\cdot}NH_2(CH_2)_2NH_2$, THF–DMSO, rt, 97%; (b) Cp_2ZrCl_2, Me_3Al, CH_2Cl_2, rt; I_2, THF, rt, 50%; (c) PivCl, pyridine, 0 °C→rt; TESCl, rt, 92%; (d) DIBAL, CH_2Cl_2, −78 °C, 99%; (e) Dess–Martin periodinane, CH_2Cl_2, pyridine, rt, 95%; (f) $MeO_2CCH{=}PBu_3$, benzoic acid, toluene, 90 °C, 92%; (g) DIBAL, THF–hexane, −78 °C, 86%; (h) TrCl, Et_3N, DMAP, CH_2Cl_2, rt, 89%; (i) TMS–C≡CCH_2PPh_3Br, BuLi, THF, (**14**) 57%, (**33**) 9%.

Coupling reaction between C1–C9 segment **4** and C10–C16 segment **13** was effected by means of Nozaki–Hiyama–Kishi reaction[18] to give alcohol **34** in 90% yield as a 2:1 mixture of diastereomers concerning the allylic hydroxyl group (Scheme 5). Hydrolysis of the methyl ester and silyl groups in **34** afforded seco acid **11** (69%) along with ester **35** (19%). The macrolactonization of **11** was accomplished by the Yamaguchi method[19] to give lactone **9** (29%) without elimination of methanol in contrast to that of **5**. To improve the yield of macrolactonization, we tried macrolactonization by an alternative method. Coupling reaction between C1–C9 segment **4** and *ent*-**13**, prepared from (*S*)-trityl glycidyl ether, gave seco acid C13-*epi*-**11**. Macrolactonization of C13-*epi*-**11** under Mitsunobu condition[20] provided lactone **9**, however, the yield was not improved (<30%). Treatment of **9** with formic acid in ether to remove the trityl group afforded not desired alcohol but a complex mixture. Therefore, another synthetic route was investigated.



Scheme 5. (a) 0.6% $NiCl_2$–$CrCl_2$, DMSO, rt, 90%; (b) LiOH, H_2O, MeOH, THF, (**11**) 69%, (**35**) 19%; (c) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, rt; DMAP, toluene, 80 °C, 29%; (d) $^{i}PrO_2CN{=}NCO_2{}^{i}Pr$, PPh_3, toluene, 0 °C→rt, <30%; (e) HCO_2H, ether, rt.

Coupling reaction between C1–C9 segment **4** and C10–C17 segment **14** gave a diastereomeric mixture of alcohol **36** in 81% yield (Scheme 6). The trimethylsilyl and triethylsilyl groups in **36** were removed to give acetylene **37** (98%), hydrostannation of which afforded vinylstannane **38** (81%),[21] which was contaminated by (16*Z*)-isomer. The minor (16*Z*)-isomer could be separated by HPLC at a later stage in the synthesis. Treatment of **38** with NBS gave bromodiene **39** (98%), which was hydrolyzed under basic conditions to provide seco acid **12** (63%). The macrolactonization of **12** under Yamaguchi condition afforded lactone **10** (57%), which was treated with aqueous acid to give hemiacetal **40**



Scheme 6. (a) 0.5% $NiCl_2$–$CrCl_2$, DMSO, rt, 81%; (b) Bu_4NF, AcOH, THF, 0 °C, 98%; (c) Bu_3SnH, AIBN, THF, 70 °C, 81%; (d) NBS, THF, 0 °C, 98%; (e) NaOH, H_2O, MeOH, THF, 63%; (f) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, rt; DMAP, toluene, reflux, 57%; (g) H_2O, AcOH, acetone, rt, 86%; (h) Dess–Martin periodinane, CH_2Cl_2, pyridine, rt, (**41a**) 27%, (**41b**) 21%; (i) Bu_4NF, AcOH, THF, rt, 90% from **41a**, 96% from **41b**; (j) **7**, $SnCl_2$, $AgClO_4$, MS 4Å, Et_2O, 0 °C→rt; (k) HF·pyridine, THF, 0 °C→rt, 42% in two steps; (l) **8**, $SnCl_2$, $AgClO_4$, MS 4Å, Et_2O, 0 °C→rt, 68%.

(86%). The oxidation of allylic hydroxyl group in **40** gave a separable 1:1 mixture of conjugated enones, which was separated by HPLC to afford pure **41a** and **41b**. The minor (16*Z*)-isomer could be completely removed at this stage. The stereochemistry of **41a** and **41b** was determined by NOESY. Removal of the silyl group in **41a** gave the aglycon (**3**) of aurisides A and B (90%). Under the same condition, enone **41b** was converted into **3** with epimerization at C2 (96%). The glycosylation reaction of **3** with fluorosugar **7** followed by desilylation afforded auriside A (**1**) (42%).[6] Similarly, the reaction between **3** and **8** gave auriside B (**2**) (68%).[6] Synthetic aurisides A (**1**) and B (**2**) were found to be identical to natural **1** and **2** in all respects, respectively, including the spectroscopic (UV, IR, ^{1}H NMR, MS, and $[\alpha]_D$) and chromatographic properties.

3. Conclusion

In conclusion, enantioselective synthesis of aurisides A (**1**) and B (**2**) was achieved from (*R*)-pantolactone in 26 steps (1.4% overall yield) and 25 steps (2.3% overall yield), respectively. In comparison with the previous synthesis of the aglycon **3** of aurisides A (**1**) and B (**2**) reported as a communication[4] in 1998 (0.021% overall yield), the synthetic procedures of **3** have been much improved as regards overall yield (3.3%).

4. Experimental

4.1. General

Optical rotations were measured with a JASCO DIP-370 polarimeter or a JASCO DIP-1000 polarimeter. ^{1}H NMR spectra were recorded on a JEOL JNM-EX270 (270 MHz), a Bruker AVANCE-400M (400 MHz), or a Bruker AVANCE 500 (500 MHz) instrument. Chemical shifts are reported in parts per million from internal standards [tetramethylsilane (0.00 ppm) for $CDCl_3$ and C_6D_5H (7.16 ppm) for C_6D_6] and *J* values are in hertz. ^{13}C NMR spectra were recorded on a JEOL JNM-EX270 (67.8 MHz) or a Bruker AVANCE 500 (125 MHz) instrument. Chemical shifts are reported in parts per million from the solvent peak (77.0 ppm for $CDCl_3$, 128.0 ppm for C_6D_6). IR spectra were recorded on a JASCO FT/IR-300 instrument. FAB mass spectra were recorded on a JEOL SX-102 instrument. ESI mass spectra were recorded on a QStar/Pulsar *i* spectrometer (Applied Biosystems). Both TLC analysis and preparative TLC were conducted on E. Merck precoated silica gel 60 F_{254} (0.25 mm layer thickness). Fuji Silysia silica gel BW-820 MH and FL-60D were used for column chromatography unless otherwise noted. Organic solvents for moisture-sensitive reactions were distilled from the following drying agents: THF and ether (Na–benzophenone ketyl), benzene and toluene (Na), acetonitrile and triethylamine (calcium hydride), DMSO (calcium hydride under reduced pressure), CH_2Cl_2 (P_2O_5), acetone (anhydrous K_2CO_3), and MeOH (Mg). All moisture-sensitive reactions were performed under an atmosphere of nitrogen, and the starting materials were azeotropically dried with benzene before use. All new compounds were determined to be >95% pure by ^{1}H NMR unless otherwise noted.

4.1.1. Alcohol 16. To a stirred solution of 2-allyldithiane (5.03 g, 31.4 mmol) in dry THF (50 mL) cooled at −78 °C was added a 1.6 M solution of *n*-BuLi in hexane (18.4 mL, 29.5 mmol) dropwise. The reaction mixture was stirred at −20 °C for 1.5 h. After cooling to −78 °C, a solution of epoxide **15** (4.05 g, 19.6 mmol) in THF (3 mL, 2×2 mL rinse) was added dropwise, and the mixture was kept at −30 °C for 2 h. The reaction was quenched with water (100 mL), and the mixture was extracted with Et_2O (2×100 mL). The combined extracts were washed with brine (100 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (200 g, hexane–ether 5:1) to give **16** (6.60 g, 92%) as a colorless oil: TLC, R_f 0.39 (hexane–ether 2:1); $[\alpha]_D^{25}$ +25.9 (*c* 1.02, $CHCl_3$); IR (neat) 3490, 2960, 2860, 1640, 1100 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.36–7.26 (m, 5H), 5.94 (m, 1H), 5.15 (d, *J*=17.0 Hz, 1H), 5.14 (d, *J*=10.3 Hz, 1H), 4.53 (d, *J*=12.2 Hz, 1H), 4.51 (d, *J*=12.2 Hz, 1H), 3.89 (dd, *J*=6.9, 3.6 Hz, 1H), 3.39 (d, *J*=8.9 Hz, 1H), 3.30 (d, *J*=8.9 Hz, 1H), 2.95–2.70 (m, 6H), 2.08 (m, 2H), 2.04–1.88 (m, 2H), 1.60 (br s, 1H), 0.96 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 138.0, 133.0, 128.2, 127.4, 127.3, 118.3, 78.4, 74.1, 73.4, 51.9, 43.6, 40.3, 39.0, 26.4, 26.1, 24.9, 22.6, 20.1; HRMS (ESI) calcd for $C_{20}H_{30}NaO_2S_2$ $(M+Na)^+$ 389.1585, found 389.1604.

4.1.2. Ketone 17. To a stirred solution of alcohol **16** (2.80 g, 7.64 mmol) in MeOH cooled at 0 °C was added [bis(trifluoroacetoxy)iodo]benzene (3.33 g, 7.74 mmol). The reaction mixture was stirred at 0 °C for 45 min and diluted with ether (100 mL), saturated aqueous $NaHCO_3$ (60 mL), and 5% aqueous $Na_2S_2O_3$ (60 mL). The organic layer was separated, and the aqueous layer was extracted with ether (100 mL, 50 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (70 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated. The residual oil was dissolved in THF (15 mL), H_2O (5 mL), and acetic acid (15 mL), and the solution was stirred at room temperature for 15 min. The reaction mixture was cooled at 0 °C, neutralized with saturated aqueous $NaHCO_3$ (225 mL), and extracted with ether (2×200 mL, 100 mL). The combined extracts were washed with H_2O (100 mL) and brine (100 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (200 g, hexane–ether 10:1→5:1) to give **17** (1.63 g, 77%) as a colorless oil: TLC, R_f 0.36 (hexane–ether 1:1); $[\alpha]_D^{23}$ +45.5 (*c* 0.98, $CHCl_3$); IR (neat) 3480, 3030, 2960, 2870, 1710, 1640, 1100 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 5.92 (ddt, *J*=17.0, 10.3, 6.9 Hz, 1H), 5.17 (d, *J*=10.3 Hz, 1H), 5.13 (d, *J*=17.0 Hz, 1H), 4.52 (d, *J*=12.5 Hz, 1H), 4.48 (d, *J*=12.5 Hz, 1H), 4.02 (dd, *J*=8.6, 4.0 Hz, 1H), 3.35 (d, *J*=8.9 Hz, 1H), 3.30 (d, *J*=8.9 Hz, 1H), 3.23 (d, *J*=6.9 Hz, 2H), 2.57 (dd, *J*=16.0, 8.6 Hz, 1H), 2.50 (dd, *J*=16.0, 4.0 Hz, 1H), 1.64 (br s, 1H), 0.93 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 209.1, 137.8, 130.2, 128.2, 127.6, 127.5, 118.8, 78.5, 73.6, 73.4, 48.5, 44.3, 38.1, 22.2, 19.9; HRMS (ESI) calcd for $C_{17}H_{24}NaO_3$ $(M+Na)^+$ 299.1623, found 299.1650.

4.1.3. *anti*-1,3-Diol 18a and *syn*-1,3-diol 18b. To a stirred solution of tetramethylammonium triacetoxyborohydride (3.14 g, 11.9 mmol) in acetonitrile (10 mL) and acetic acid (10 mL) cooled at −40 °C was added a solution of ketone

17 (745 mg, 2.70 mmol) in acetonitrile (1.5 mL, 3×0.4 mL rinse). The reaction mixture was stirred at −40 °C, kept at −30 °C for 12 h, diluted with saturated aqueous Na/K tartrate (35 mL), stirred at room temperature for 50 min, and extracted with CH_2Cl_2 (3×60 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (70 mL), and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 100 g, hexane–EtOAc 4:1) to give **18a** (644 mg, 86%) and *syn*-1,3-diol **18b** (56 mg, 7%) as a colorless oil. Compound **18a**: TLC, R_f 0.39 (hexane–EtOAc 2:1); $[\alpha]_D^{23}$ +26.5 (*c* 1.32, $CHCl_3$); IR (neat) 3430, 3030, 2960, 2870, 1640, 1100 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 5.83 (ddt, *J*=17.0, 10.3, 6.8 Hz, 1H), 5.12 (d, *J*=17.0 Hz, 1H), 5.10 (d, *J*=10.3 Hz, 1H), 4.54 (d, *J*=12.0 Hz, 1H), 4.48 (d, *J*=12.0 Hz, 1H), 3.98 (m, 1H), 3.83 (ddd, *J*=9.1, 3.8, 3.8 Hz, 1H), 3.60 (d, *J*=3.8 Hz, 1H), 3.40 (d, *J*=8.9 Hz, 1H), 3.33 (d, *J*=8.9 Hz, 1H), 2.60 (d, *J*=5.1 Hz, 1H), 2.30 (dd, *J*=6.8, 6.8 Hz, 2H), 1.62–1.48 (m, 2H), 0.92 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 137.5, 135.0, 128.1, 127.4, 127.2, 117.0, 79.5, 74.6, 73.4, 67.9, 41.8, 38.0, 36.9, 22.5, 19.6; HRMS (ESI) calcd for $C_{17}H_{26}NaO_3$ $(M+Na)^+$ 301.1780, found 301.1782. Compound **18b**: R_f 0.48 (hexane–EtOAc 2:1); ^1H NMR (270 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 5.85 (ddt, *J*=17.0, 10.3, 6.9 Hz, 1H), 5.10 (d, *J*=17.0 Hz, 1H), 5.08 (d, *J*=10.3 Hz, 1H), 4.53 (d, *J*=13.5 Hz, 1H), 4.48 (d, *J*=13.5 Hz, 1H), 4.12 (br s, 1H), 4.07–3.85 (m, 2H), 3.72 (br s, 1H), 3.39 (d, *J*=8.9 Hz, 1H), 3.29 (d, *J*=8.9 Hz, 1H), 2.25 (m, 2H), 1.60 (m, 1H), 1.41 (m, 1H), 0.91 (s, 3H), 0.90 (s, 3H).

4.1.4. Acetonide 19. To a stirred solution of *anti*-1,3-diol **18a** (482 mg, 1.73 mmol) in acetone (6 mL) were added 2,2-dimetoxypropane (2.9 mL, 24 mmol) and (±)-camphorsulfonic acid (23.4 mg, 0.101 mmol). The reaction mixture was stirred at room temperature for 19 h, diluted with saturated aqueous $NaHCO_3$ (10 mL), and extracted with ether (3×25 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (26 g, hexane–ether 25:1→10:1→2:1→1:2) to give **19** (540 mg, 97%) as a colorless oil: TLC, R_f 0.82 (hexane–EtOAc 5:1); $[\alpha]_D^{24}$ +29.8 (*c* 0.97, $CHCl_3$); IR (neat) 2980, 2880, 1220, 1100 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.36–7.28 (m, 5H), 5.80 (ddt, *J*=17.0, 10.3, 6.8 Hz, 1H), 5.09 (d, *J*=17.0 Hz, 1H), 5.03 (d, *J*=10.3 Hz, 1H), 4.51 (d, *J*=12.2 Hz, 1H), 4.45 (d, *J*=12.2 Hz, 1H), 3.79 (dd, *J*=10.3, 6.2 Hz, 1H), 3.75 (m, 1H), 3.29 (d, *J*=8.4 Hz, 1H), 3.17 (d, *J*=8.4 Hz, 1H), 2.30 (ddd, *J*=14.3, 6.8, 6.8 Hz, 1H), 2.18 (ddd, *J*=14.3, 6.8, 6.8 Hz, 1H), 1.77 (ddd, *J*=12.3, 10.3, 5.9 Hz, 1H), 1.40 (ddd, *J*=12.3, 9.7, 6.2 Hz, 1H), 1.30 (s, 6H), 0.90 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 138.9, 134.7, 128.2, 127.3, 127.2, 116.5, 100.2, 76.5, 73.2, 69.4, 66.7, 40.2, 37.6, 32.6, 24.6, 24.2, 20.5, 19.7; HRMS (ESI) calcd for $C_{20}H_{30}NaO_3$ $(M+Na)^+$ 341.2093, found 341.2081.

4.1.5. Aldehyde 20. To a stirred solution of acetonide **19** (1.58 g, 4.97 mmol) in acetone (48 mL) and H_2O (16 mL) were added *N*-methylmorpholine-*N*-oxide (1.02 g, 8.70 mmol) and a 0.078 M solution of osmium tetroxide in *tert*-butyl alcohol (2.8 mL, 0.22 mmol). After being stirred at room temperature for 2 h, a 0.4 M aqueous sodium periodate (34 mL, 13 mmol) was added. The reaction mixture was stirred at room temperature for 30 min and extracted with EtOAc (3×50 mL). The combined extracts were washed with saturated aqueous $Na_2S_2O_3$ (50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (50 g, hexane–EtOAc 5:1) to give **20** (1.53 g, 96%) as a colorless oil: TLC, R_f 0.71 (hexane–EtOAc 2:1); $[\alpha]_D^{22}$ +24.2 (*c* 1.03, $CHCl_3$); IR (neat) 2980, 2870, 1730, 1380, 1220, 1100 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.75 (dd, *J*=2.6, 1.7 Hz, 1H), 7.35–7.26 (m, 5H), 4.51 (d, *J*=12.2 Hz, 1H), 4.44 (d, *J*=12.2 Hz, 1H), 4.25 (dddd, *J*=9.9, 8.3, 5.9, 4.6 Hz, 1H), 3.83 (dd, *J*=9.9, 6.6 Hz, 1H), 3.30 (d, *J*=8.6 Hz, 1H), 3.16 (d, *J*=8.6 Hz, 1H), 2.60 (ddd, *J*=16.5, 8.3, 2.6 Hz, 1H), 2.46 (ddd, *J*=16.5, 4.6, 1.7 Hz, 1H), 1.89 (ddd, *J*=12.5, 9.9, 5.9 Hz, 1H), 1.42 (ddd, *J*=12.5, 9.9, 6.6 Hz, 1H), 1.32 (s, 3H), 1.29 (s, 3H), 0.91 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 200.9, 138.7, 128.9, 128.1, 127.2, 100.6, 76.3, 73.2, 69.2, 62.6, 49.2, 37.7, 32.8, 24.7, 24.0, 20.6, 19.8; HRMS (FAB) calcd for $C_{19}H_{28}NaO_4$ $(M+Na)^+$ 343.1886, found 343.1857.

4.1.6. β-Hydroxy ester 21. To a stirred solution of $RhCl(PPh_3)_3$ (15.0 mg, 0.0160 mmol) in THF (4 mL) at 0 °C were added methyl 2-bromopropionate (0.045 mL, 0.40 mmol), a solution of aldehyde **20** (99.1 mg, 0.310 mmol) in THF (1.0 mL, 3×0.3 mL rinse), and a 1.0 M hexane solution of Et_2Zn (0.91 mL). The mixture was stirred at 0 °C for 20 min, and 2-bromopropionate (0.020 mL, 0.18 mmol) was added to the mixture. After being stirred at 0 °C for 15 min, saturated aqueous $NaHCO_3$ (10 mL) was added. The reaction mixture was filtered through Florisil, and the filtrate was extracted with EtOAc (20 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (7 g, hexane–EtOAc 3:1) to give **21** (107 mg, 88%) as a colorless oil: TLC, R_f 0.47 (hexane–EtOAc 3:1); IR (neat) 3500, 2990, 2860, 1740, 1220, 1100 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5H), 4.50 (d, *J*=12.3 Hz, 1H), 4.44 (d, *J*=12.3 Hz, 1H), 4.22–3.90 (m, 2H), 3.85–3.75 (m, 1H), 3.71 (s, 1.5H), 3.67 (s, 1.5H), 3.29 (d, *J*=8.6 Hz, 0.5H), 3.28 (d, *J*=8.6 Hz, 0.5H), 3.15 (d, *J*=8.6 Hz, 0.5H), 3.14 (d, *J*=8.6 Hz, 0.5H), 3.13 (d, *J*=6.2 Hz, 0.5H), 3.06 (d, *J*=4.3 Hz, 0.5H), 2.60–2.48 (m, 1H), 1.88–1.35 (m, 4H), 1.34 (s, 1.5H), 1.32 (s, 1.5H), 1.29 (s, 3H), 1.21 (d, *J*=7.1 Hz, 1.5H), 1.19 (d, *J*=7.1 Hz, 0.75H), 1.15 (d, *J*=7.1 Hz, 0.75H), 0.89 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 176.1, 176.0, 175.4, 175.3, 138.73, 138.67, 128.9, 128.09, 128.07, 128.05, 127.19, 127.17, 127.14, 125.1, 100.6, 100.41, 100.37, 76.4, 76.3, 73.2, 70.3, 69.4, 69.2, 68.7, 68.19, 68.12, 64.5, 64.3, 51.72, 51.67, 45.7, 45.5, 39.8, 39.5, 39.14, 39.09, 37.7, 37.6, 33.30, 33.23, 32.77, 32.72, 24.9, 24.7, 24.14, 24.09, 20.62, 20.59, 20.56, 19.7, 13.1, 12.1, 11.6; HRMS (ESI) calcd for $C_{23}H_{36}NaO_6$ $(M+Na)^+$ 431.2410, found 431.2396.

4.1.7. β-Keto ester 22. To a stirred solution of oxalyl chloride (0.047 mL, 0.54 mmol) in CH_2Cl_2 (1.5 mL) cooled at −78 °C was added a 3.6 M solution of DMSO in CH_2Cl_2 (0.35 mL, 1.3 mmol) dropwise. The resulting solution was

stirred at −78 °C for 5 min, and a solution of β-hydroxy ester **21** (198 mg, 0.485 mmol) in CH_2Cl_2 (1 mL, 0.5 mL rinse) was added dropwise. The mixture was stirred at −78 °C for 15 min, and triethylamine (0.20 mL, 1.43 mmol) was added. The resulting mixture was stirred at −78 °C for 5 min, warmed to 0 °C, and stirred for 10 min. The mixture was diluted with H_2O (3 mL) and extracted with ether (3×10 mL). The combined extracts were washed with brine (3 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (4 g, hexane–EtOAc 20:1→10:1→5:1) to give **22** (173 mg, 88%) as a colorless oil: TLC, R_f 0.57 (hexane–EtOAc 3:1); IR (neat) 2990, 2860, 1750, 1720, 1220, 1100 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.33–7.26 (m, 5H), 4.50 (d, J=12.3 Hz, 1H), 4.44 (d, J=12.3 Hz, 1H), 4.19 (m, 1H), 3.83–3.76 (m, 1H), 3.72 (s, 3H), 3.59 (q, J=7.1 Hz, 0.5H), 3.58 (q, J=7.1 Hz, 0.5H), 3.29 (d, J=8.6 Hz, 1H), 3.15 (d, J=8.6 Hz, 1H), 2.80 (dd, J=16.2, 7.9 Hz, 1H), 2.57 (dd, J=16.2, 5.1 Hz, 1H), 1.89 (m, 1H), 1.41–1.31 (m, 1H), 1.34 (d, J=7.1 Hz, 1.5H), 1.32 (d, J=7.1 Hz, 1.5H), 1.28 (s, 1.5H), 1.27 (s, 1.5H), 1.26 (s, 3H), 0.89 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 203.7, 170.8, 138.8, 128.14, 128.12, 127.25, 127.21, 127.20, 100.6, 100.4, 76.4, 73.2, 69.3, 69.2, 63.8, 63.6, 53.3, 53.1, 52.4, 47.7, 47.3, 37.7, 32.8, 24.6, 24.1, 20.6, 19.75, 19.72, 12.7, 12.5; HRMS (ESI) calcd for $C_{23}H_{34}NaO_6$ $(M+Na)^+$ 429.2253, found 429.2262.

4.1.8. Cyclic methyl acetal 23. To a stirred solution of β-keto ester **22** (1.20 g, 10.3 mmol) in methanol (30 mL) were added trimethyl orthoformate (4.7 mL, 43 mmol) and pyridinium *p*-toluenesulfonate (71.6 mg, 0.29 mmol). The mixture was stirred at room temperature for 1 h, diluted with saturated aqueous $NaHCO_3$ (35 mL), and extracted with ether (4×50 mL). The combined extracts were washed with H_2O and brine (30 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (40 g, hexane–EtOAc 3:1→2:1→1:1) to give **23** (785 mg, 96%) as a colorless oil: TLC, R_f 0.24 (hexane–EtOAc 2:1); IR (neat) 3450, 2950, 2870, 1740, 1100, 1030 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.39–7.26 (m, 5H), 4.51 (d, J=12.2 Hz, 0.5H), 4.50 (d, J=12.2 Hz, 0.5H), 4.43 (d, J=12.2 Hz, 0.5H), 4.42 (d, J=12.2 Hz, 0.5H), 4.08 (m, 1H), 3.67 (s, 1.5H), 3.63 (s, 1.5H), 3.58 (dd, J=11.9, 1.6 Hz, 0.5H), 3.57 (dd, J=11.9, 1.6 Hz, 0.5H), 3.49 (s, 1.5H), 3.40 (d, J=8.6 Hz, 0.5H), 3.38 (d, J=8.6 Hz, 0.5H), 3.17 (d, J=8.6 Hz, 0.5H), 3.14 (d, J=8.6 Hz, 0.5H), 3.10 (s, 1.5H), 3.07 (q, J=7.2 Hz, 0.5H), 3.02 (q, J=6.9 Hz, 0.5H), 2.10 (ddd, J=12.2, 4.6, 1.6 Hz, 0.5H), 2.00 (ddd, J=12.2, 4.8, 1.6 Hz, 0.5H), 1.94–1.81 (m, 1H), 1.74 (dd, J=12.2, 11.2 Hz, 0.5H), 1.40 (dd, J=12.2, 10.8 Hz, 0.5H), 1.27–1.06 (m, 1H), 1.21 (d, J=6.9 Hz, 1.5H), 1.11 (d, J=7.2 Hz, 1.5H), 0.95 (s, 1.5H), 0.93 (s, 1.5H), 0.89 (s, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 174.0, 173.2, 138.54, 138.47, 128.1, 127.2, 127.1, 101.3, 101.2, 73.1, 73.0, 72.5, 72.1, 65.4, 65.1, 51.7, 51.5, 47.3, 47.0, 44.8, 43.4, 38.3, 38.1, 38.0, 37.4, 34.0, 33.9, 21.4, 21.2, 20.4, 20.2, 13.2, 11.6; HRMS (ESI) calcd for $C_{21}H_{32}NaO_6$ $(M+Na)^+$ 403.2097, found 403.2118.

4.1.9. Silyl ether 24. To a stirred solution of cyclic methyl acetal **23** (445 mg, 1.17 mmol) and imidazole (263 mg, 3.86 mmol) in DMF (2.5 mL) was added *tert*-butyldiphenylsilyl chloride (0.46 mL, 1.8 mmol). The mixture was stirred at 0 °C for 2 h, diluted with 5% aqueous $NaHCO_3$ (30 mL), and extracted with EtOAc (3×20 mL). The combined extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (46 g, hexane–EtOAc 8:1) to give **24** (739 mg, 100%) as a colorless oil: TLC, R_f 0.64 (hexane–EtOAc 3:1); IR (neat) 2960, 2860, 1740, 1110, 700 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.74–7.60 (m, 4H), 7.43–7.21 (m, 11H), 4.40 (d, J=12.4 Hz, 1H), 4.35 (d, J=12.4 Hz, 1H), 4.22–4.05 (m, 1H), 3.63 (s, 1.5H), 3.62 (s, 1.5H), 3.49 (s, 1.5H), 3.33–3.25 (m, 2H), 3.06–3.00 (m, 1H), 2.97 (s, 1.5H), 2.93 (q, J=7.3 Hz, 1H), 2.13–1.09 (m, 4H), 1.16 (d, J=7.3 Hz, 1.5H), 1.05 (s, 9H), 1.01 (d, J=7.3 Hz, 1.5H), 0.79 (s, 1.5H), 0.77 (s, 1.5H), 0.74 (s, 1.5H), 0.73 (s, 1.5H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 174.1, 173.2, 138.64, 138.56, 135.7, 134.7, 134.4, 134.3, 129.3, 128.1, 127.6, 127.37, 127.35, 127.2, 127.1, 101.3, 101.2, 77.2, 73.1, 72.3, 71.9, 67.2, 51.6, 51.4, 47.2, 46.9, 44.9, 43.4, 38.1, 38.0, 37.5, 34.5, 34.4, 27.09, 27.08, 26.6, 21.3, 21.1, 20.5, 20.2, 19.2, 14.3, 13.2, 11.6; HRMS (ESI) calcd for $C_{37}H_{50}NaO_6Si$ $(M+Na)^+$ 641.3274, found 641.3250.

4.1.10. Alcohol 25. A mixture of silyl ether **24** (66 mg, 0.13 mmol) and 20% $Pd(OH)_2$ on carbon (26 mg) in dioxane (3 mL) was stirred under a hydrogen atmosphere at room temperature for 2 h. The mixture was filtered through a pad of Celite, and the residue was washed with EtOAc. The filtrate and the washings were combined and concentrated. The residual oil was purified by column chromatography on silica gel (4 g, hexane–EtOAc 5:1→3:1) to give **25** (52 mg, 96%) as a colorless oil: TLC, R_f 0.57 (hexane–EtOAc 2:1); IR (neat) 3540, 2960, 2860, 1740, 1110, 1040, 700 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.68–7.64 (m, 4H), 7.42–7.33 (m, 6H), 4.07 (m, 1H), 3.69 (s, 1.5H), 3.65 (s, 1.5H), 3.44–3.18 (m, 3H), 3.09 (s, 1.5H), 3.03 (s, 1.5H), 2.95 (q, J=7.3 Hz, 1H), 2.08–1.86 (m, 1H), 1.72–0.80 (m, 3H), 1.17 (d, J=7.3 Hz, 1.5H), 1.06 (s, 9H), 1.03 (d, J=7.3 Hz, 1.5H), 0.79 (s, 1.5H), 0.76 (s, 1.5H), 0.74 (s, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 174.0, 173.3, 136.1, 135.0, 134.9, 134.6, 129.9, 127.9, 102.3, 102.0, 78.3, 76.5, 72.1, 71.5, 67.2, 67.1, 52.3, 52.2, 48.2, 47.6, 45.6, 43.9, 39.0, 38.4, 38.1, 38.0, 35.4, 35.3, 27.51, 27.49, 23.1, 22.5, 20.0, 19.7, 19.6, 13.4, 11.8; HRMS (ESI) calcd for $C_{30}H_{44}NaO_6Si$ $(M+Na)^+$ 551.2805, found 551.2822.

4.1.11. C1–C9 segment 4. To a stirred solution of alcohol **25** (79 mg, 0.11 mmol) in DMSO (4.3 mL) were added triethylamine (0.42 mL, 3.0 mmol) and sulfur trioxide pyridine complex (153 mg, 0.961 mmol). The mixture was stirred at room temperature for 1 h, diluted with saturated aqueous $NaHCO_3$ (15 mL), and extracted with EtOAc (3×15 mL). The combined extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (4 g, hexane–EtOAc 9:1) to give **4** (75 mg, 95%) as a colorless oil: TLC, R_f 0.63 (hexane–EtOAc 3:1); IR (neat) 2950, 2860, 1740, 1110, 700 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.49 (s, 0.5H), 9.47 (s, 0.5H), 7.68–7.64 (m, 4H), 7.42–7.33 (m, 6H), 4.09 (m, 1H), 3.65 (s, 1.5H), 3.63 (s, 1.5H), 3.44 (dd, J=12.4, 2.1 Hz, 0.5H), 3.39 (dd, J=12.2, 2.1 Hz,

0.5H), 3.07 (s, 1.5H), 2.97 (s, 1.5H), 2.95 (q, J=7.6 Hz, 0.5H), 2.90 (q, J=7.6 Hz, 0.5H), 2.05–1.12 (m, 4H), 1.15 (d, J=7.6 Hz, 1.5H), 1.05 (s, 9H), 1.01 (d, J=7.6 Hz, 1.5H), 0.99 (s, 1.5H), 0.94 (s, 1.5H), 0.87 (s, 1.5H), 0.85 (s, 1.5H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 205.3, 205.0, 173.8, 172.8, 135.62, 135.61, 134.39, 134.36, 134.1, 134.0, 129.51, 129.49, 129.48, 127.4, 101.7, 101.6, 73.1, 72.5, 66.49, 66.42, 51.7, 51.6, 48.9, 48.7, 47.5, 47.2, 44.6, 43.1, 38.1, 37.4, 34.35, 34.32, 27.0, 19.2, 19.0, 18.9, 16.65, 16.60, 13.1, 11.5; HRMS (ESI) calcd for $C_{37}H_{50}NaO_6Si$ $(M+Na)^+$ 549.2648, found 549.2648.

4.1.12. Acetylene 26. To a stirred solution of 90% lithium acetylide ethylenediamine complex (16.2 g, 158 mmol) in DMSO (90 mL) kept at 20 °C was added a solution of (*R*)-glycidyl trityl ether (25.0 g, 79.0 mmol) in THF (25 mL, 3 mL rinse) over 30 min. The mixture was stirred at room temperature for 30 min, cooled to 0 °C, diluted with saturated aqueous NH_4Cl (50 mL) and H_2O (20 mL), and extracted with ether (3×70 mL). The combined extracts were washed with brine (70 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (100 g, hexane–EtOAc 8:1) to give **26** (26.2 g, 97%) as a colorless oil: TLC, R_f 0.49 (hexane–EtOAc 3:1); $[\alpha]_D^{24}$ −3.1 (*c* 1.11, $CHCl_3$); IR (neat) 3300, 3060, 2920, 1490, 1450, 1070, 760, 710 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.48–7.20 (m, 15H), 3.92 (m, 1H), 3.27 (dd, J=9.2, 4.6 Hz, 1H), 3.22 (dd, J=9.2, 5.9 Hz, 1H), 2.49 (ddd, J=11.9, 5.9, 2.6 Hz, 1H), 2.43 (ddd, J=11.9, 5.9, 2.3 Hz, 1H), 2.36 (d, J=5.3 Hz, 1H), 1.96 (dd, J=2.6, 2.3 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 143.5, 128.5, 127.7, 126.9, 86.7, 80.3, 70.5, 69.1, 66.0, 23.9; HRMS (ESI) calcd for $C_{24}H_{22}NaO_2$ $(M+Na)^+$ 365.1517, found 365.1494.

4.1.13. Vinyl iodide 27. A 2.0 M solution of trimethylaluminum in toluene (0.50 mL, 1.0 mmol) was added to a stirred suspension of zirconocene dichloride (57 mg, 0.19 mmol) in CH_2Cl_2 (1.0 mL). After being stirred at room temperature for 15 min, a solution of acetylene **26** (99 mg, 0.29 mmol) in CH_2Cl_2 (0.5 mL, 0.3 mL rinse) was added, and the resulting mixture was stirred at room temperature for 24 h. A solution of iodine (104 mg, 0.41 mmol) in THF (0.4 mL) was added, and the mixture was stirred at room temperature for 50 min. After the mixture was cooled to 0 °C, the reaction was quenched by addition of sodium fluoride (0.2 g) and THF–H_2O (5:1, 6 mL), and the mixture was stirred at room temperature for 15 min. After addition of magnesium sulfate (0.5 g), the mixture was further stirred for 15 min and filtered through a pad of Celite, and the residue was washed with EtOAc. The filtrate and the washings were combined and concentrated. The residual oil was dissolved in ether (10 mL), and the solution was washed with saturated aqueous $Na_2S_2O_3$ (3 mL). The aqueous layer was extracted with EtOAc (3×5 mL). The organic layers were combined, washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 8 g, benzene–acetonitrile 4:1 → 3:1) to give **27** (35 mg, 50%) as a colorless oil: TLC, R_f 0.55 (benzene–acetonitrile 1:1); $[\alpha]_D^{26}$ +8.7 (*c* 0.96, $CHCl_3$); IR (neat) 3370, 2930, 1270, 1090, 1040 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.06 (m, 1H), 3.87 (m, 1H), 3.67 (ddd, J=11.1, 6.4, 3.4 Hz, 1H), 3.47 (ddd, J=11.1, 6.4, 5.4 Hz, 1H), 2.42 (ddd, J=13.8, 7.9, 1.1 Hz, 1H), 2.35 (ddd, J=13.8, 5.9, 1.1 Hz, 1H), 2.02 (d, J=3.4 Hz, 1H), 1.90 (d, J=1.3 Hz, 3H), 1.86 (t, J=6.4 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 143.9, 77.7, 69.6, 66.0, 42.9, 24.2; HRMS (ESI) calcd for $C_6H_{11}INaO_2$ $(M+Na)^+$ 264.9701, found 264.9696.

4.1.14. Silyl ether 28. To a stirred solution of vinyl iodide **27** (5.05 g, 20.9 mmol) in pyridine (42 mL) cooled at 0 °C was added pivaloyl chloride (2.59 mL, 21.1 mmol). The mixture was stirred at 0 °C for 30 min, and triethylsilyl chloride (3.6 mL, 22 mmol) was added. The mixture was stirred at room temperature for 30 min, diluted with H_2O (50 mL), and extracted with hexane (3×50 mL). The combined extracts were washed with brine (30 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (50 g, hexane–ether 50:1 → 10:1) to give **28** (8.44 g, 92%) as a colorless oil: TLC, R_f 0.65 (hexane–ether 9:1); $[\alpha]_D^{26}$ +9.1 (*c* 0.88, $CHCl_3$); IR (neat) 2960, 2870, 1730, 1460, 1280, 1150, 1000, 740 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.97 (s, 1H), 4.01–3.86 (m, 3H), 2.43 (dd, J=13.8, 5.1 Hz, 1H), 2.36 (dd, J=13.8, 5.9 Hz, 1H), 1.86 (s, 3H), 1.20 (s, 9H), 0.95 (t, J=7.6 Hz, 9H), 0.56 (q, J=7.6 Hz, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 178.1, 143.8, 77.9, 68.2, 67.4, 44.8, 38.8, 27.3, 24.5, 6.9, 5.0; HRMS (ESI) calcd for $C_{17}H_{33}INaO_3Si$ $(M+Na)^+$ 463.1141, found 463.1116.

4.1.15. Alcohol 29. To a stirred solution of silyl ether **28** (540 mg, 1.23 mmol) in CH_2Cl_2 (5 mL) cooled at −78 °C was added a 0.95 M solution of diisobutylaluminum hydride (2.9 mL, 2.7 mmol). The mixture was stirred at −78 °C for 1 h, and the reaction was quenched by addition of methanol (1 mL). The mixture was warmed to room temperature, diluted with saturated aqueous Na/K tartrate (40 mL), and stirred for 15 min. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3×20 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (20 g, hexane–EtOAc 9:1) to give **29** (433 mg, 99%) as a colorless oil: TLC, R_f 0.45 (benzene–acetonitrile 9:1); $[\alpha]_D^{22}$ −0.47 (*c* 1.14, $CHCl_3$); IR (neat) 3450, 2950, 2870, 1240, 1110, 1000, 740 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.98 (m, 1H), 3.86 (m, 1H), 3.54 (dd, J=11.1, 3.8 Hz, 1H), 3.42 (dd, J=11.1, 3.8 Hz, 1H), 2.45 (ddd, J=12.7, 6.5, 1.1 Hz, 1H), 2.38 (ddd, J=12.7, 5.8, 1.1 Hz, 1H), 1.86 (d, J=1.1 Hz, 3H), 1.76 (br s, 1H), 0.96 (t, J=7.6 Hz, 9H), 0.61 (q, J=7.6 Hz, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 144.0, 77.9, 70.6, 65.9, 44.0, 24.5, 6.9, 5.1; HRMS (ESI) calcd for $C_{12}H_{25}INaO_2Si$ $(M+Na)^+$ 379.0566, found 379.0578.

4.1.16. Aldehyde 30. To a stirred solution of alcohol **29** (1.45 g, 4.07 mmol) in CH_2Cl_2 (41 mL) were added pyridine (4.5 mL, 57 mmol) and Dess–Martin periodinane (5.17 g, 12.2 mmol). The mixture was stirred at room temperature for 1.5 h, diluted with saturated aqueous $Na_2S_2O_3$ (50 mL) and saturated aqueous $NaHCO_3$ (50 mL), and stirred for 15 min. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3×70 mL). The organic layers were combined, washed with brine (50 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (30 g, hexane–EtOAc 9:1) to give **30** (1.37 g, 95%) as a colorless oil: TLC, R_f 0.48 (hexane–ether 3:1); $[\alpha]_D^{22}$ +45.6 (*c* 1.01,

$CHCl_3$); IR (neat) 2950, 2870, 1730, 1120, 1010, 740 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.60 (d, J=1.8 Hz, 1H), 6.03 (m, 1H), 4.05 (ddd, J=7.6, 4.9, 1.8 Hz, 1H), 2.53 (ddd, J=13.8, 4.9, 0.8 Hz, 1H), 2.47 (ddd, J=13.8, 7.6, 0.8 Hz, 1H), 1.87 (d, J=1.1 Hz, 3H), 0.95 (t, J=7.6 Hz, 9H), 0.60 (q, J=7.6 Hz, 6H); HRMS (ESI) calcd for $C_{12}H_{23}INaO_2Si$ $(M+Na)^+$ 377.0410, found 377.0381.

4.1.17. C10–C17 segment 14. To a stirred solution of (3-trimethylsilyl-2-propynyl)triphenylphosphonium bromide (228 mg, 0.50 mmol) in THF (2.5 mL) cooled at −78 °C was added a 1.6 M solution of BuLi in hexane (0.28 mL, 0.45 mmol). After being stirred at −78 °C for 30 min, a solution of aldehyde **30** (148 mg, 0.42 mmol) in THF (3 mL, 2×1 mL rinse) was added. The mixture was stirred at −78 °C for 3 h, warmed to room temperature, diluted with H_2O, and extracted with hexane (3×5 mL). The combined extracts were washed with brine (7 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 8 g, hexane–benzene 15:1) to give **14** (105 mg, 57%) and its *cis*-isomer **33** (17 mg, 9%) as a colorless oil. Compound **14**: TLC, R_f 0.45 (hexane–benzene 5:1); $[\alpha]_D^{20}$ +13.2 (c 0.33, $CHCl_3$); IR (neat) 2960, 2880, 2150, 1250, 1080, 1010, 840, 740 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.13 (dd, J=15.7, 5.4 Hz, 1H), 5.97 (s, 1H), 5.70 (dd, J=15.7, 1.6 Hz, 1H), 4.26 (m, 1H), 2.49 (dd, J=13.5, 6.8 Hz, 1H), 2.32 (dd, J=13.5, 5.4 Hz, 1H), 1.85 (s, 3H), 0.94 (t, J=7.6 Hz, 9H), 0.57 (q, J=7.6 Hz, 6H), 0.19 (s, 9H); HRMS (ESI) calcd for $C_{18}H_{33}INaOSi_2$ $(M+Na)^+$ 471.1013, found 471.1012. Compound **33**: TLC, R_f 0.40 (hexane–benzene 5:1); ^1H NMR (270 MHz, $CDCl_3$) δ 5.94 (s, 1H), 5.86 (dd, J=10.8, 8.6 Hz, 1H), 5.47 (dd, J=10.8, 0.8 Hz, 1H), 4.80 (m, 1H), 2.46 (dd, J=13.5, 7.3 Hz, 1H), 2.33 (dd, J=13.5, 4.3 Hz, 1H), 1.89 (s, 3H), 0.94 (t, J=7.6 Hz, 9H), 0.57 (q, J=7.6 Hz, 6H), 0.20 (s, 9H).

4.1.18. Conjugated ester 31. To a stirred solution of aldehyde **30** (129 mg, 0.364 mmol) in toluene (4.5 mL) heated at 90 °C were added benzoic acid (8.6 mg, 0.069 mmol) and 1 M solution of (methoxycarbonylmethylene)tributylphosphorane in toluene (0.70 mL, 0.70 mmol). The mixture was stirred at 90 °C for 15 min, diluted with saturated aqueous NH_4Cl (4 mL), and extracted with ether (3×4 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (4 mL) and brine (4 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (5 g, hexane–ether 50:1 → 15:1) to give **31** (138 mg, 92%) as a colorless oil: TLC, R_f 0.51 (hexane–ether 3:1); $[\alpha]_D^{22}$ +12.0 (c 1.05, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 6.89 (dd, J=15.7, 4.9 Hz, 1H), 6.00 (dd, J=15.7, 1.6 Hz, 1H), 5.98 (m, 1H), 4.40 (dddd, J=7.6, 4.9, 4.9, 1.6 Hz, 1H), 3.75 (s, 3H), 2.44 (ddd, J=13.8, 7.6, 1.1 Hz, 1H), 2.38 (ddd, J=13.8, 4.9, 0.8 Hz, 1H), 1.87 (d, J=1.4 Hz, 3H), 0.94 (t, J=7.6 Hz, 9H), 0.58 (q, J=7.6 Hz, 6H).

4.1.19. Alcohol 32. To a stirred solution of conjugated ester **31** (80 mg, 0.20 mmol) in THF (3 mL) cooled at −78 °C was added 0.93 M solution of diisobutylaluminum hydride in hexane (0.86 mL, 0.80 mmol). The mixture was stirred at −78 °C for 25 min, and the reaction was quenched by addition of methanol (0.1 mL). The mixture was warmed to room temperature, diluted with ether (3 mL) and saturated aqueous Na/K tartrate (5 mL), and stirred for 15 min. The organic layer was separated, and the aqueous layer was extracted with ether (3×5 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (4 g, hexane–EtOAc 20:1 → 10:1 → 7:1) to give **32** (66 mg, 86%) as a colorless oil: TLC, R_f 0.37 (hexane–EtOAc 3:1); $[\alpha]_D^{22}$ +6.5 (c 1.07, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 5.93 (q, J=0.8 Hz, 1H), 5.78 (ddt, J=15.6, 0.7, 5.1 Hz, 1H), 5.65 (ddt, J=15.6, 5.7, 0.8 Hz, 1H), 4.24 (m, 1H), 4.13 (dd, J=5.1, 0.8 Hz, 2H), 2.43 (dd, J=13.2, 7.3 Hz, 1H), 2.33 (dd, J=13.2, 5.4 Hz, 1H), 1.85 (d, J=0.8 Hz, 3H), 1.40 (br s, 1H), 0.94 (t, J=7.6 Hz, 9H), 0.57 (q, J=7.6 Hz, 6H).

4.1.20. C10–C16 segment 13. To a stirred solution of alcohol **32** (55 mg, 0.14 mmol) in CH_2Cl_2 (0.5 mL) were added triethylamine (0.06 mL, 0.4 mmol), 4-(dimethylamino)pyridine (3.3 mg, 0.027 mmol), and trityl chloride (69.7 mg, 0.250 mmol), and the mixture was stirred at room temperature for 16 h. The mixture was diluted with saturated aqueous $NaHCO_3$ (1 mL) and extracted with ether (3×1 mL). The combined extracts were washed with brine (1 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (4 g, hexane–EtOAc 50:1) to give **13** (80 mg, 89%) as a colorless oil: TLC, R_f 0.73 (hexane–EtOAc 3:1); $[\alpha]_D^{22}$ +9.7 (c 1.08, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 7.48–7.20 (m, 15H), 5.95 (s, 1H), 5.83 (dd, J=15.7, 5.9 Hz, 1H), 5.69 (dt, J=15.7, 4.6 Hz, 1H), 4.26 (m, 1H), 3.57 (d, J=4.6 Hz, 2H), 2.45 (dd, J=13.2, 7.3 Hz, 1H), 2.36 (dd, J=13.2, 5.1 Hz, 1H), 1.88 (s, 3H), 0.96 (t, J=7.6 Hz, 9H), 0.60 (q, J=7.6 Hz, 6H).

4.1.21. Alcohol 34. To a stirred solution of C1–C9 segment **4** (43 mg, 0.082 mmol) and C10–C16 segment **13** (225 mg, 0.36 mmol) in DMSO (1.5 mL) were added nickel chloride (0.6 mg, 0.0047 mmol) and chromium(II) chloride (203 mg, 1.65 mmol). The mixture was stirred at room temperature for 4 days, diluted with saturated aqueous NH_4Cl (4 mL), and extracted with ether (3×7 mL). The organic layers were combined, washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (8 g, hexane–EtOAc 50:1 → 10:1 → 6:1) to give a diastereomeric mixture of **34** (77 mg, 90%) as a colorless oil: TLC, R_f 0.50 (hexane–EtOAc 3:1); ^1H NMR (270 MHz, $CDCl_3$) δ 7.68–7.64 (m, 4H), 7.42–7.16 (m, 21H), 5.80 (dd, J=15.4, 5.9 Hz, 1H), 5.65 (dt, J=15.4, 4.9 Hz, 1H), 5.21 (m, 1H), 4.36–4.20 (m, 1.5H), 4.15–4.00 (m, 1.5H), 3.64 (s, 3H), 3.60–3.50 (m, 2H), 3.30 (m, 1H), 3.11 (s, 0.5H), 3.09 (s, 1H), 3.06 (s, 0.5H), 3.03 (s, 1H), 2.94 (m, 1H), 2.40–1.10 (m, 6H), 1.68 (s, 2H), 1.62 (s, 1H), 1.17 (m, 1.5H), 1.06 (s, 9H), 1.05–0.93 (m, 10.5H), 0.76 (s, 3H), 0.67–0.56 (m, 9H). A signal due to one proton (OH) was not observed.

4.1.22. Seco acid 11. To a stirred solution of alcohol **34** (27 mg, 0.026 mmol) in THF (0.6 mL) and MeOH (0.3 mL) was added a 2 M aqueous NaOH (0.1 mL). The mixture was stirred at 40 °C for 29 h, acidified with 1 M aqueous HCl, and extracted with ether (4×5 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give a oil, which was purified by column chromatography on silica gel (FL-60D, 3 g, hexane–EtOAc 3:1 → 2:1 → 1:1) to

give **11** (16 mg, 69%) and ester **35** (5 mg, 19%) as a colorless oil. Compound **11**: TLC, R_f 0.17–0.39 (hexane–EtOAc 1:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.68–7.64 (m, 4H), 7.46–7.19 (m, 21H), 5.88–5.73 (m, 2H), 5.32 (m, 1H), 4.41 (m, 1H), 4.25 (m, 1H), 4.12 (m, 1H), 3.67–3.56 (m, 2H), 3.35 (m, 1H), 3.04 (s, 3H), 2.91 (m, 1H), 2.30–1.10 (m, 6H), 1.72 (s, 2H), 1.67 (s, 1H), 1.17 (m, 1.5H), 1.06 (s, 9H), 0.96–0.81 (m, 4.5H), 0.67 (s, 0.5H), 0.60 (s, 1.5H), 0.55 (s, 1H). Signals due to three protons (COOH, OH) were not observed; MS (FAB) *m/z* 942 $(M+2Na-H)^+$. Compound **35**: TLC, R_f 0.55–0.71 (hexane–EtOAc 1:1); 7.70–7.64 (m, 4H), 7.46–7.19 (m, 21H), 5.88–5.73 (m, 2H), 5.21 (m, 1H), 4.40–4.20 (m, 2H), 4.09 (m, 1H), 3.66 (s, 3H), 3.67–3.56 (m, 2H), 3.33 (m, 1H), 3.08 (s, 1H), 3.04 (s, 2H), 2.95 (m, 1H), 2.35–1.12 (m, 6H), 1.71 (s, 3H), 1.20 (m, 1.5H), 1.06 (s, 9H), 1.04 (m, 1.5H), 0.96 (m, 3H), 0.63 (m, 3H). A signal due to one proton (OH) was not observed.

4.1.23. Lactone 9. A solution of triethylamine and 2,4,6-trichlorobenzoyl chloride in THF (0.25 mL, 0.054 mmol for Et_3N and 0.016 mmol for 2,4,6-$Cl_3C_6H_2COCl$), prepared from triethylamine (0.18 mL), 2,4,6-trichlorobenzoyl chloride (0.06 mL), and THF (6 mL), was added to seco acid **11** (11 mg, 0.012 mmol). The mixture was stirred at room temperature for 2.5 h and diluted with toluene (22 mL) to give a solution of mixed anhydride, which was added to a solution of 4-(dimethylamino)pyridine (14 mg, 0.12 mmol) in toluene (1.5 mL) warmed at 80 °C over 1 h. The mixture was stirred at 80 °C for 30 min, cooled to room temperature, and washed with brine (10 mL). The aqueous layer was extracted with ether (2×5 mL), and the organic layers were combined, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (0.3 g, hexane–EtOAc 10:1→7:1→5:1) to give **9** (3.1 mg, 29%) as a colorless oil: TLC, R_f 0.50, 0.57, 0.64 (hexane–EtOAc 3:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.68–7.64 (m, 4H), 7.46–7.19 (m, 21H), 5.86–5.73 (m, 2H), 5.67–5.25 (m, 2H), 4.44–4.04 (m, 2H), 3.61 (m, 2H), 3.04 (s, 1.5H), 3.01 (m, 1H), 2.85 (s, 1.5H), 2.72 (m, 1H), 2.30–1.10 (m, 6H), 1.72 (m, 3H), 1.17 (m, 3H), 1.06 (s, 9H), 0.90–0.75 (m, 6H). A signal due to one proton (OH) was not observed; MS (FAB) *m/z* 901 $(M+Na)^+$.

4.1.24. *C*13-*epi*-Seco acid 11. TLC, R_f 0.17–0.39 (hexane–EtOAc 1:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.68–7.64 (m, 4H), 7.46–7.19 (m, 21H), 5.88–5.73 (m, 2H), 5.33 (m, 1H), 4.43 (m, 1H), 4.26 (m, 1H), 4.08 (m, 1H), 3.60 (m, 2H), 3.30 (m, 1H), 3.04 (m, 3H), 2.91 (m, 1H), 2.30–1.10 (m, 6H), 1.73 (s, 2H), 1.70 (s, 1H), 1.15 (m, 1.5H), 1.06 (s, 9H), 1.04 (m, 1.5H), 0.90 (m, 3H), 0.58 (m, 3H). Signals due to three protons (COOH, OH) were not observed; MS (FAB) *m/z* 942 $(M+2Na-H)^+$.

4.1.25. Alcohol 36. To a stirred solution of C1–C9 segment **4** (71.3 mg, 0.135 mmol) and C10–C17 segment **14** (519 mg, 1.16 mmol) in DMSO (2.7 mL) were added nickel chloride (1.7 mg, 0.013 mmol) and chromium(II) chloride (314 mg, 2.55 mmol). The mixture was stirred at room temperature for 5 days, diluted with saturated aqueous NH_4Cl (10 mL), and extracted with EtOAc (3×10 mL). The organic layers were combined, washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (10 g, hexane–EtOAc 18:1→7:1) to give a diastereomeric mixture of **36** (92.2 mg, 81%) as a colorless oil: TLC, R_f 0.60 (hexane–EtOAc 3:1); IR (neat) 3520, 2960, 2880, 2140, 1740, 1250, 1080, 840, 740, 700 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.69–7.62 (m, 4H), 7.45–7.32 (m, 6H), 6.14 (dd, *J*=15.9, 5.4 Hz, 1H), 5.63 (d, *J*=15.9 Hz, 1H), 5.20 (m, 1H), 4.36–4.02 (m, 3H), 3.69 (s, 1.5H), 3.65 (s, 1.5H), 3.45–3.31 (m, 1H), 3.10 (s, 1.5H), 3.05 (s, 1.5H), 2.95 (m, 1H), 2.35–1.12 (m, 6H), 1.67 (s, 3H), 1.17 (m, 1.5H), 1.06 (s, 9H), 1.02–0.80 (m, 13.5H), 0.63–0.53 (m, 9H), 0.18 (s, 9H). A signal due to one proton (OH) was not observed; HRMS (ESI) calcd for $C_{48}H_{76}NaO_7Si_3$ $(M+Na)^+$ 871.4797, found 874.4799.

4.1.26. Acetylene 37. To a stirred solution of alcohol **36** (70.0 mg, 0.824 mmol) in THF (2.7 mL) cooled at 0 °C was added a solution of tetrabutylammonium fluoride (Bu_4NF) and acetic acid (0.70 mL, 0.7 mmol for Bu_4NF and 0.6 mmol for acetic acid) prepared from a 1.0 M solution of Bu_4NF in THF (0.90 mL) and acetic acid (0.050 mL). The mixture was stirred at 0 °C for 4 h, diluted with brine (15 mL), and extracted with EtOAc (3×15 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (2 g, hexane–EtOAc 2:1) to give **37** (53.4 mg, 98%) as a colorless oil: TLC, R_f 0.45 (hexane–benzene 5:1); IR (neat) 3300, 2960, 2860, 1740, 1210, 1110, 1040, 760, 700 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.69–7.64 (m, 4H), 7.46–7.31 (m, 6H), 6.23 (dd, *J*=15.9, 5.1 Hz, 1H), 5.73 (d, *J*=15.9 Hz, 1H), 5.31 (d, *J*=9.2 Hz, 1H), 4.38–4.03 (m, 3H), 3.68 (s, 1.5H), 3.66 (s, 1.5H), 3.40–3.31 (m, 1H), 3.08 (s, 1.5H), 3.04 (s, 1.5H), 2.95 (m, 1H), 2.86 (s, 1H), 2.35–1.12 (m, 6H), 1.69 (s, 3H), 1.17 (m, 1.5H), 1.06 (s, 9H), 1.02–0.80 (m, 4.5H), 0.65 (s, 1.5H), 0.62 (s, 1.5H). Signals due to two protons (OH) were not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 173.5, 145.9, 135.7, 134.7, 134.6, 134.1, 133.5, 129.49, 129.47, 127.43, 127.41, 102.2, 79.0, 77.2, 76.2, 75.6, 69.9, 66.5, 65.9, 61.1, 51.8, 47.3, 40.5, 30.4, 29.8, 29.1, 27.3, 27.0, 21.7, 19.19, 19.17, 17.2, 15.4, 13.8, 11.5, 11.3, 9.6; HRMS (ESI) calcd for $C_{39}H_{54}NaO_7Si$ $(M+Na)^+$ 685.3536, found 685.3547.

4.1.27. Vinylstannane 38. To a stirred solution of acetylene **37** (193 mg, 0.291 mmol) in THF (9.7 mL) were added tributyltin hydride (0.094 mL, 0.035 mmol) and 2,2′-azobisisobutyronitrile (10.6 mg, 0.0646 mmol). The mixture was stirred at 70 °C for 2 h, cooled to room temperature, and concentrated. The residual oil was purified by column chromatography on silica gel (5 g, hexane–EtOAc 5:1→2:1) to give **38** (225 mg, 81%) as a colorless oil: TLC, R_f 0.50 (hexane–EtOAc 2:1); IR (neat) 3460, 2930, 2860, 1740, 1200, 1110, 1040, 700 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.69–7.64 (m, 4H), 7.46–7.21 (m, 6H), 6.49 (dd, *J*=18.6, 10.0 Hz, 1H), 6.23 (d, *J*=18.6 Hz, 1H), 6.18 (dd, *J*=15.1, 10.0 Hz, 1H), 5.64 (dd, *J*=15.1, 6.2 Hz, 1H), 5.31 (d, *J*=9.2 Hz, 1H), 4.38–4.03 (m, 3H), 3.68 (s, 1.5H), 3.65 (s, 1.5H), 3.39–3.26 (m, 1H), 3.08 (s, 1.5H), 3.04 (s, 1.5H), 2.95 (m, 1H), 2.35–1.80 (m, 4H), 1.72–0.80 (m, 38H), 1.06 (s, 9H), 0.64 (s, 1.5H), 0.61 (s, 1.5H). Signals due to two protons (OH) were not observed; HRMS (ESI) calcd for $C_{51}H_{82}NaO_7Si^{120}Sn$ $(M+Na)^+$ 977.4761, found 977.4725.

4.1.28. Bromodiene 39. To a stirred solution of vinylstannane **38** (128 mg, 0.134 mmol) in THF (4.5 mL) cooled

at 0 °C was added *N*-bromosuccinimide (34.0 mg, 0.197 mmol). The mixture was stirred at 0 °C for 30 min, diluted with 10% aqueous $Na_2S_2O_3$ (10 mL), and extracted with EtOAc (3×10 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (3 g, hexane–EtOAc 3:2) to give **39** (97.7 mg, 98%) as a colorless oil: TLC, R_f 0.50 (hexane–EtOAc 1:1); IR (neat) 3460, 2930, 2860, 1740, 1210, 1110, 1040, 760, 700 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.68–7.64 (m, 4H), 7.45–7.31 (m, 6H), 6.69 (dd, *J*=13.5, 10.3 Hz, 1H), 6.31 (d, *J*=13.5 Hz, 1H), 6.18 (dd, *J*=15.1, 10.3 Hz, 1H), 5.73 (dd, *J*=15.1, 5.4 Hz, 1H), 5.31 (d, *J*=8.9 Hz, 1H), 4.38–4.03 (m, 3H), 3.69 (s, 1.5H), 3.65 (s, 1.5H), 3.39–3.30 (m, 1H), 3.08 (s, 1.5H), 3.04 (s, 1.5H), 2.95 (m, 1H), 2.31–1.12 (m, 6H), 1.70 (s, 3H), 1.17 (m, 1.5H), 1.06 (s, 9H), 1.02–0.80 (m, 4.5H), 0.64 (s, 1.5H), 0.61 (s, 1.5H). Signals due to two protons (OH) were not observed; HRMS (ESI) calcd for $C_{39}H_{55}{}^{79}BrNaO_7Si$ $(M+Na)^+$ 765.2798, found 765.2793.

4.1.29. Seco acid 12. To a stirred solution of bromodiene **39** (66.2 mg, 0.089 mmol) in THF (1.2 mL) and MeOH (0.6 mL) was added a 2 M aqueous NaOH (0.2 mL). The mixture was stirred at 40 °C for 23 h, acidified with 1 M aqueous HCl, and extracted with EtOAc (4×5 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give a oil, which was purified by column chromatography on silica gel (FL-60D, 2 g, hexane–EtOAc 5:1→3:1→1:1) to give **12** (40.8 mg, 63%) as a colorless oil: TLC, R_f 0.08–0.39 (hexane–EtOAc 1:1); IR (neat) 3440, 2930, 2860, 1710, 1220, 1110, 1040, 980, 760, 700 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.68–7.64 (m, 4H), 7.45–7.31 (m, 6H), 6.69 (dd, *J*=13.5, 10.3 Hz, 1H), 6.30 (d, *J*=13.5 Hz, 1H), 6.18 (dd, *J*=15.1, 10.3 Hz, 1H), 5.73 (dd, *J*=15.1, 5.7 Hz, 1H), 5.31 (d, *J*=8.6 Hz, 1H), 4.48–4.03 (m, 3H), 3.49–3.30 (m, 1H), 3.06 (s, 1.5H), 3.04 (s, 1.5H), 2.95 (m, 1H), 2.31–1.12 (m, 6H), 1.70 (s, 3H), 1.17 (m, 1.5H), 1.06 (s, 9H), 1.02–0.80 (m, 4.5H), 0.67 (s, 1.5H), 0.58 (s, 1.5H). Signals due to three protons (COOH, OH) were not observed; HRMS (ESI) calcd for $C_{38}H_{53}{}^{79}BrNaO_7Si$ $(M+Na)^+$ 751.2642, found 751.2612.

4.1.30. Lactone 10. A solution of triethylamine and 2,4,6-trichlorobenzoyl chloride in THF (0.47 mL, 0.082 mmol for Et_3N and 0.023 mmol for 2,4,6-$Cl_3C_6H_2COCl$), prepared from triethylamine (0.15 mL), 2,4,6-trichlorobenzoyl chloride (0.05 mL), and THF (6 mL), was added to seco acid **12** (15.3 mg, 0.0210 mmol). The mixture was stirred at room temperature for 2 h and diluted with toluene (35 mL) to give a solution of mixed anhydride, which was added to a solution of 4-(dimethylamino)pyridine (26.0 mg, 0.210 mmol) in refluxing toluene (7 mL) over 2 h. The mixture was heated at reflux for 30 min, cooled to room temperature, and washed with brine (10 mL). The aqueous layer was extracted with EtOAc (2×15 mL), and the organic layers were combined, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 1 g, hexane–EtOAc 8:1) to give **10** (8.5 mg, 57%) as a colorless oil: TLC, R_f 0.34, 0.40, 0.50 (hexane–EtOAc 3:1); IR (neat) 3510, 2930, 2860, 1730, 1180, 1110, 1040, 760, 700 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.68–7.64 (m, 4H), 7.45–7.31 (m, 6H), 6.70 (dd, *J*=13.5, 10.0 Hz, 1H), 6.34 (d, *J*=13.5 Hz, 0.5H), 6.33 (d, *J*=13.5 Hz, 0.5H), 6.09 (m, 1H), 5.80–5.58 (m, 2H), 5.43 (m, 1H), 4.05–3.85 (m, 2H), 3.09 (m, 1.5H), 3.01 (m, 1H), 2.86 (m, 1.5H), 2.74 (m, 1H), 2.17–1.00 (m, 6H), 1.65 (m, 3H), 1.26 (m, 3H), 1.05 (s, 9H), 0.93–0.80 (m, 6H). A signal due to one proton (OH) was not observed; HRMS (ESI) calcd for $C_{38}H_{51}{}^{79}BrNaO_6Si$ $(M+Na)^+$ 733.2536, found 733.2544.

4.1.31. Hemiacetal 40. A solution of lactone **10** (22.4 mg, 0.0315 mmol) in acetone (0.4 mL), H_2O (0.2 mL), and acetic acid (0.8 mL) was stirred at room temperature for 30 min. The mixture was concentrated and purified by column chromatography on silica gel (FL-60D, 1 g, hexane–EtOAc 7:1) to give **40** (19.0 mg, 86%) as a colorless oil: TLC, R_f 0.34, 0.44 (hexane–EtOAc 3:1); IR (neat) 3440, 2960, 2860, 1700, 1190, 1110, 1040, 980, 760, 700 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.68–7.64 (m, 4H), 7.45–7.31 (m, 6H), 6.69 (dd, *J*=13.5, 10.8 Hz, 1H), 6.37 (d, *J*=13.5 Hz, 1H), 6.15 (dd, *J*=14.9, 10.8 Hz, 1H), 5.78–5.29 (m, 3H), 5.41 (d, *J*=2.2 Hz, 0.5H), 4.30–4.15 (m, 1.5H), 4.23 (d, *J*=2.2 Hz, 0.5H), 3.86 (m, 0.5H), 3.75 (d, *J*=8.9 Hz, 0.5H), 3.36 (d, *J*=8.9 Hz, 0.5H), 2.51 (m, 1H), 2.30–1.00 (m, 6H), 1.69 (s, 1.5H), 1.68 (s, 1.5H), 1.26 (m, 3H), 1.06 (s, 9H), 0.87 (m, 3H), 0.76 (m, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 174.4, 173.7, 141.8, 136.9, 136.6, 136.3, 135.7, 134.5, 134.3, 134.0, 133.5, 133.3, 132.7, 132.6, 131.8, 130.0, 129.6, 128.9, 128.6, 128.5, 128.0, 127.5, 110.3, 110.2, 98.2, 97.71, 97.66, 94.7, 74.3, 73.9, 72.0, 71.9, 71.60, 71.55, 71.4, 71.1, 67.2, 67.1, 67.0, 50.1, 48.7, 48.1, 47.5, 47.4, 46.4, 41.3, 41.2, 41.0, 40.8, 40.4, 40.0, 38.9, 38.8, 35.3, 34.9, 34.8, 34.4, 29.7, 27.0, 25.2, 25.0, 24.4, 24.1, 22.7, 22.5, 19.3, 19.1, 15.7, 14.1, 13.6, 12.6, 11.5, 11.2, 11.1; HRMS (ESI) calcd for $C_{37}H_{49}{}^{79}BrNaO_6Si$ $(M+Na)^+$ 719.2379, found 719.2370.

4.1.32. Enones 41a and 41b. To a stirred solution of hemiacetal **40** (19.0 mg, 0.027 mmol) in CH_2Cl_2 (0.6 mL) were added pyridine (0.05 mL) and Dess–Martin periodinane (38.3 mg, 0.090 mmol). The mixture was stirred at room temperature for 1 h, diluted with saturated aqueous $Na_2S_2O_3$ (5 mL), stirred for 15 min, and extracted with ether (3×5 mL). The combined organic layers were washed with brine (3 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 1 g, hexane–EtOAc 9:1) to give a mixture of enones **41a** and **41b** (17.4 mg, 92%). The mixture of enones (43.9 mg) were purified by HPLC [Develosil ODS-HG-5 (ϕ 4.6× 250 mm), 95% MeOH, flow rate 5 mL min^{-1}, detection at 254 nm] to give crude enone **41a** (17.8 mg, t_R=47 min) and pure **41b** (13.0 mg, t_R=38 min, 27%) as a colorless oil. The crude enone **41a** was further purified by PLC (200×200×0.25 mm, two plates, hexane–ether 3:1) to give pure enone **41a** (10.2 mg, 21%) as a colorless oil. Compound **41a**: TLC, R_f 0.33 (hexane–ether 3:1); $[\alpha]_D^{20}$ +18.6 (*c* 0.196, $CHCl_3$); IR (neat) 3448, 1705, 1682, 1423, 1176, 1110, 980 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.68–7.63 (m, 4H), 7.45–7.33 (m, 6H), 6.70 (dd, *J*=13.5, 10.8 Hz, 1H), 6.40 (d, *J*=13.5 Hz, 1H), 6.23 (s, 1H), 6.18 (dd, *J*=15.0, 10.8 Hz, 1H), 5.72 (dd, *J*=15.0, 6.5 Hz, 1H), 5.66 (m, 1H), 4.32 (d, *J*=2.7 Hz, 1H), 4.17 (m, 1H), 3.45 (dd, *J*=11.9, 2.2 Hz, 1H), 2.56 (q, *J*=7.2 Hz, 1H), 2.30–2.23 (m, 2H), 2.06 (s, 3H), 2.03 (dd, *J*=11.9, 3.2 Hz, 1H), 1.30–1.15 (m, 3H), 1.19 (s, 3H), 1.07 (d, *J*=7.2 Hz, 3H), 1.07 (s, 9H),

0.80 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 204.6, 175.9, 147.7, 136.0, 135.6, 134.2, 134.1, 131.3, 129.6, 129.1, 127.5, 126.1, 110.6, 98.2, 74.1, 71.0, 66.7, 49.0, 47.9, 47.6, 41.3, 34.6, 27.1, 21.2, 19.3, 19.2, 18.7, 12.5; HRMS (FAB) calcd for $C_{37}H_{47}{}^{79}BrNaO_6Si$ $(M+Na)^+$ 717.2223, found 717.2234. Compound **41b**: TLC, R_f 0.28 (hexane–ether 3:1); $[\alpha]_D^{21}$ +11.4 (*c* 0.214, $CHCl_3$); IR (neat) 3437, 1697, 1427, 1261, 1169, 1107, 980 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.69–7.63 (m, 4H), 7.46–7.33 (m, 6H), 6.70 (dd, *J*=13.5, 10.8 Hz, 1H), 6.40 (d, *J*=13.5 Hz, 1H), 6.21 (s, 1H), 6.18 (dd, *J*=14.0, 10.8 Hz, 1H), 5.78–5.67 (m, 2H), 5.11 (d, *J*=2.7 Hz, 1H), 4.28 (m, 1H), 3.44 (dd, *J*=11.9, 2.2 Hz, 1H), 2.56 (q, *J*=7.0 Hz, 1H), 2.31–2.24 (m, 2H), 2.05 (s, 3H), 1.86 (dd, *J*=11.6, 3.0 Hz, 1H), 1.64–1.50 (m, 2H), 1.27 (m, 1H), 1.25 (d, *J*=7.0 Hz, 3H), 1.20 (s, 3H), 1.07 (s, 9H), 0.79 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 204.9, 173.3, 147.3, 136.0, 135.6, 135.6, 134.3, 134.1, 131.3, 129.6, 129.6, 129.1, 127.5, 126.3, 110.1, 98.4, 73.8, 71.2, 66.8, 49.3, 48.6, 47.3, 40.8, 34.3, 27.1, 21.1, 19.2, 18.4, 11.4; HRMS (FAB) calcd for $C_{37}H_{47}{}^{79}BrNaO_6Si$ $(M+Na)^+$ 717.2223, found 717.2200.

4.1.33. Aglycon 3. To a stirred solution of a diastereomeric mixture of enone **41a** (2.2 mg, 0.0032 mmol) in THF (0.5 mL) was added a solution of tetrabutylammonium fluoride (Bu_4NF) and acetic acid (0.19 mL, 0.18 mmol for Bu_4NF and 0.19 mmol for acetic acid) prepared from a 1.0 M solution of Bu_4NF in THF (0.85 mL) and acetic acid (0.050 mL). The mixture was stirred at room temperature for 20 h, diluted with brine (5 mL), and extracted with ether (3×4 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 0.3 g, toluene–acetone 9:1) to give **3** (1.3 mg, 90%) as a colorless oil. Using the same procedure as described above, **3** (1.7 mg, 96%) was obtained from **41b** (2.7 mg, 0.022 mmol). Compound **3**: TLC, R_f 0.35 (benzene–acetone 5:1), 0.37 (hexane–EtOAc 3:1); $[\alpha]_D^{31}$ +6.7 (*c* 0.045, MeOH); IR (neat) 3450, 2970, 2860, 1710, 1680, 1610, 1200, 1180, 980, 760 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 6.40 (dd, *J*=13.7, 10.8 Hz, 1H), 6.32 (d, *J*=1.0 Hz, 1H), 5.91 (d, *J*=13.7 Hz, 1H), 5.65 (dd, *J*=15.1, 10.8 Hz, 1H), 5.57 (m, 1H), 5.19 (dd, *J*=15.1, 6.3 Hz, 1H), 4.82 (d, *J*=3.0 Hz, 1H), 3.94 (m, 1H), 3.87 (dd, *J*=11.8, 2.0 Hz, 1H), 2.47 (q, *J*=7.3 Hz, 1H), 2.29 (d, *J*=1.0 Hz, 1H), 1.99 (m, 1H), 1.97 (dd, *J*=13.2, 11.7 Hz, 1H), 1.82 (dd, *J*=13.2, 2.5 Hz, 1H), 1.53 (m, 1H), 1.14 (s, 3H), 1.08 (s, 3H), 1.07 (m, 1H), 0.98 (d, *J*=7.3 Hz, 3H), 0.81 (dt, *J*=3.0, 11.2 Hz, 1H). A signal due to one proton (5-OH) was not observed; ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7, 176.1, 148.2, 136.1, 131.3, 129.3, 126.1, 110.8, 98.3, 74.3, 71.1, 64.9, 49.1, 47.8, 47.6, 41.1, 34.3, 21.3, 19.3, 18.6, 12.5; HRMS (ESI) calcd for $C_{21}H_{29}{}^{79}BrNaO_6$ $(M+Na)^+$ 479.1045, found 479.1041.

4.1.34. Auriside A (1). To a stirred suspension of stannous chloride (3.1 mg, 0.017 mmol), silver perchlorate (3.3 mg, 0.016 mmol), and MS 4Å (43 mg) in ether (0.2 mL) at 0 °C was added a solution of aglycon **3** (2.2 mg, 0.0048 mmol) and fluorosugar **7** (9.9 mg, 0.021 mmol) in ether (0.1 mL, 3×0.05 mL rinse). The mixture was stirred at room temperature for 24 h, diluted with saturated aqueous $NaHCO_3$ (3 mL), and extracted with EtOAc (3×10 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 2 g, hexane–EtOAc 5:1) to give TBS ether of auriside A (1.9 mg) as a colorless oil.

To a stirred solution of TBS ether of auriside A (0.9 mg) in THF (0.06 mL) cooled at 0 °C was added HF·pyridine complex (0.013 mL). The mixture was stirred at room temperature for 18 h, diluted with saturated aqueous $NaHCO_3$ (2 mL), and extracted with EtOAc (3×10 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 1 g, hexane–EtOAc 1:3) followed by HPLC [Develosil ODS-HG-5 (ϕ 4.6×250 mm), 75% MeOH, flow rate 5 mL min^{-1}, detection at 215 nm] to give auriside A (**1**) (0.8 mg, 42% in two steps) as a colorless oil: TLC, R_f 0.20 (hexane–EtOAc 1:4); $[\alpha]_D^{23}$ −31 (*c* 0.040, MeOH); ^{1}H NMR (500 MHz, C_6D_6) δ 6.40 (dd, *J*=13.5, 10.9 Hz, 1H), 6.35 (s, 1H), 5.91 (d, *J*=13.5 Hz, 1H), 5.63 (dd, *J*=15.4, 10.9 Hz, 1H), 5.56 (m, 1H), 5.34 (d, *J*=1.5 Hz, 1H), 5.18 (dd, *J*=15.4, 6.5 Hz, 1H), 5.04 (d, *J*=2.0 Hz, 1H), 4.93 (d, *J*=2.5 Hz, 1H), 4.30 (dd, *J*=9.5, 3.1 Hz, 1H), 4.26 (m, 1H), 4.24 (dd, *J*=9.5, 3.7 Hz, 1H), 4.09 (dq, *J*=9.5, 6.2 Hz, 1H), 3.94 (dd, *J*=11.8, 2.0 Hz, 1H), 3.90 (dq, *J*=9.5, 6.2 Hz, 1H), 3.68 (dd, *J*=3.1, 2.0 Hz, 1H), 3.56 (dd, *J*=3.7, 1.5 Hz, 1H), 3.49 (s, 3H), 3.46 (t, *J*=9.5 Hz, 1H), 3.31 (s, 3H), 3.26 (s, 3H), 3.16 (t, *J*=9.5 Hz, 1H), 3.07 (s, 3H), 2.48 (q, *J*=7.2 Hz, 1H), 2.33 (dd, *J*=11.8, 4.4 Hz, 1H), 2.30 (s, 3H), 2.18 (m, 1H), 1.97 (t, *J*=12.1 Hz, 1H), 1.82 (m, 1H), 1.81 (m, 1H), 1.43 (d, *J*=6.2 Hz, 1H), 1.35 (d, *J*=6.2 Hz, 1H), 1.24 (q, *J*=11.8 Hz, 1H), 1.14 (s, 3H), 1.05 (s, 3H), 1.03 (td, *J*=11.8, 2.5 Hz, 1H), 0.97 (d, *J*=7.2 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 203.3, 176.4, 147.5, 136.5, 131.7, 129.2, 126.4, 110.8, 98.6, 98.5, 96.3, 84.4, 83.3, 81.6, 81.5, 79.5, 74.6, 72.1, 71.3, 71.1, 69.1, 68.3, 60.8, 60.7, 58.8, 57.9, 49.3, 48.1, 47.5, 39.8, 31.5, 21.6, 19.5, 18.6, 18.4, 18.1, 12.4; MS (FAB) *m/z* 827 $(M+Na)^+$.

4.1.35. Auriside B (2). To a stirred suspension of stannous chloride (3.1 mg, 0.017 mmol), silver perchlorate (3.4 mg, 0.017 mmol), and MS 4Å (45 mg) in ether (0.2 mL) at 0 °C was added a solution of aglycon **3** (2.3 mg, 0.0050 mmol) and fluorosugar **8** (5.4 mg, 0.023 mmol) in ether (0.9 mL, 2×0.05 mL rinse). The mixture was stirred at room temperature for 2 h, diluted with saturated aqueous $NaHCO_3$ (5 mL), and extracted with EtOAc (3×15 mL). The combined extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 1 g, hexane–EtOAc 1:2) followed by HPLC [Develosil ODS-HG-5 (ϕ 4.6×250 mm), 55% MeCN, flow rate 5 mL min^{-1}, detection at 215 nm] to give auriside B (**2**) (2.3 mg, 68%) as a colorless oil: R_f 0.30 (hexane–EtOAc 1:2); $[\alpha]_D^{19}$ −27 (*c* 0.080, MeOH); ^{1}H NMR (500 MHz, C_6D_6) δ 6.40 (dd, *J*=13.5, 10.8 Hz, 1H), 6.35 (s, 1H), 5.91 (d, *J*=13.5 Hz, 1H), 5.63 (dd, *J*=15.3, 10.8 Hz, 1H), 5.57 (m, 1H), 5.54 (dd, *J*=9.5, 3.2 Hz, 1H), 5.20 (dd, *J*=15.3, 6.6 Hz, 1H), 5.04 (d, *J*=2.0 Hz, 1H), 4.94 (d, *J*=1.9 Hz, 1H), 4.25 (m, 1H), 3.99 (dq, *J*=9.5, 6.2 Hz, 1H), 3.94 (dd, *J*=11.8, 1.9 Hz, 1H), 3.82 (dd, *J*=3.2, 2.0 Hz, 1H), 3.73 (br s, 2H), 3.52 (t, *J*=9.5 Hz, 1H), 3.36 (s, 3H), 3.22 (s, 3H), 2.49 (q, *J*=7.2 Hz, 1H), 2.30 (s, 3H), 2.27 (dd, *J*=11.8, 4.4 Hz,

1H), 1.97 (t, J=12.2 Hz, 1H), 1.80 (m, 1H), 1.80 (m, 1H), 1.37 (d, J=6.2 Hz, 1H), 1.23 (q, J=11.8 Hz, 1H), 1.16 (s, 3H), 1.06 (s, 3H), 0.97 (d, J=7.2 Hz, 1H),0.96 (dt, J=11.8, 1.9 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 203.5, 176.5, 155.7, 147.4, 136.5, 131.7, 129.2, 126.4, 110.8, 98.5, 96.3, 81.4, 79.9, 75.0, 74.6, 71.3, 68.6, 60.4, 58.7, 49.3, 48.0, 47.4, 39.6, 31.4, 21.6, 19.4, 18.6, 18.1, 12.4; MS (FAB) m/z 696 $(M+Na)^+$.

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