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Total synthesis of attenols A and B

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Abstract—The enantioselective synthesis of attenols A and B, cyclic polyethers of marine origin, was accomplished on a semigram scale by using diastereoselective hydroboration, coupling with lithium acetylide, Lindlar reduction and acid-catalyzed acetal formation. The configuration of the remaining undetermined spiro acetal carbon was unambiguously determined to be 11*S* using this ample supply of attenol A. The antitumor activities of synthetic attenol A were also examined.

1. Introduction

Marine bivalves are rich sources of various unique bioactive compounds. Shellfish of the genus *Pinna* live mainly in shallow areas of the temperate and tropical zones of the Indian and Pacific oceans. The adductor muscle of this bivalve is eaten in Japan and China, and food poisoning frequently occurs from its ingestion. In our continuing search for toxic compounds, we have reported the isolation and structural determination of toxic compounds, pinnatoxins (**3**),[1] and an alkaloidal marine toxin, pinnamine (**4**),[2] from the Okinawan bivalve *Pinna muricata* (Fig. 1). Pinnatoxins are amphoteric carbocyclic compounds which contain 6,7-spiro, 5,6-bicyclo and 6,5,6-trispiro ketal rings. Pinnatoxin A (**3a**)[1a] is the major toxic component in *Pinna* sp. and a Ca^{2+} channel activator. The absolute stereostructure was confirmed by its total synthesis by Kishi and co-workers.[3] Pinnatoxins B (**3b**) and C (**3c**), extremely minor components (1:1 ratio) from *Pinna* sp., are the most potent toxic components in the pinnatoxin series, and their isolation and structural determination were reported by our laboratory.[1d] We achieved the total synthesis of pinnamine (**4**), an alkaloid that contains a dihydropyrone ring and which induces characteristic toxic symptoms, such as scurrying around.[4] We also isolated pinnaic acid (**5**), which has $cPLA_2$ inhibitory activity, from the same Okinawan bivalve *P. muricata*.[5] Furthermore, we have isolated toxic compounds, pteriatoxins (**6**),[6] from another bivalve, *Pteria penguin*, and their structures are similar to those of pinnatoxins. Although pteriatoxin A (20 μg) and pteriatoxins B and C in a 1:1 mixture (8 μg) exist as minute components in viscera (82 kg) of *P. penguin*, these toxins showed significant acute toxicity against mice, with LD_{99}s of 100 and 8 μg/kg, respectively.

In the course of extensive studies on shellfish poisons, we observed that the CH_2Cl_2-soluble fraction of the EtOH extract of the Chinese bivalve *Pinna attenuata* exhibited moderate cytotoxicity against P388 cells, and isolated attenols A (**1**) and B (**2**), cyclic polyethers that exhibit cytotoxicity against P388 cells with IC_{50} values of 24 and 12 μg/mL, respectively.[7] The absolute stereostructures of these attenols were determined by NMR analysis and a modified Mosher's method. The main structural features of attenol A (**1**) are a spiro acetal ring, three contiguous stereocenters and *Z*-disubstituted and terminal olefins. Attenol B (**2**) was determined to be an isomeric polyether of attenol A (**1**) with a 6,8-dioxabicyclo[3.2.1]octane ring. However, their natural scarcity has prevented further biological studies. Recently, we achieved the total synthesis of attenols A (**1**) and B (**2**) to confirm their absolute stereostructures and to evaluate their biological activities.[8] In this paper, we describe an enantioselective and practical synthesis of attenols A (**1**) and B (**2**) and biological studies on attenol A (**1**) based on a good supply of synthetic material. We were able to unambiguously confirm the configuration of the remaining undetermined spiro acetal carbon.

2. Results and discussion

2.1. Synthetic plan

Scheme 1 outlines our strategy for synthesizing attenols A (**1**) and B (**2**).

Since acid treatment of attenol A (**1**) gave a mixture of **1** and **2** (3:1), **1** and **2** were synthesized simultaneously by acetal ring formation of a ketone (**7**) in the final step. Ketone (**7**) was constructed by a Julia coupling reaction[9] between the C1–C11 segment (**8**) and the C12–C21 segment (**9**). The

Keywords: enantioselective synthesis; semigram scale; diastereoselective hydroboration; stereochemistry of spiro acetal ring; biological studies.

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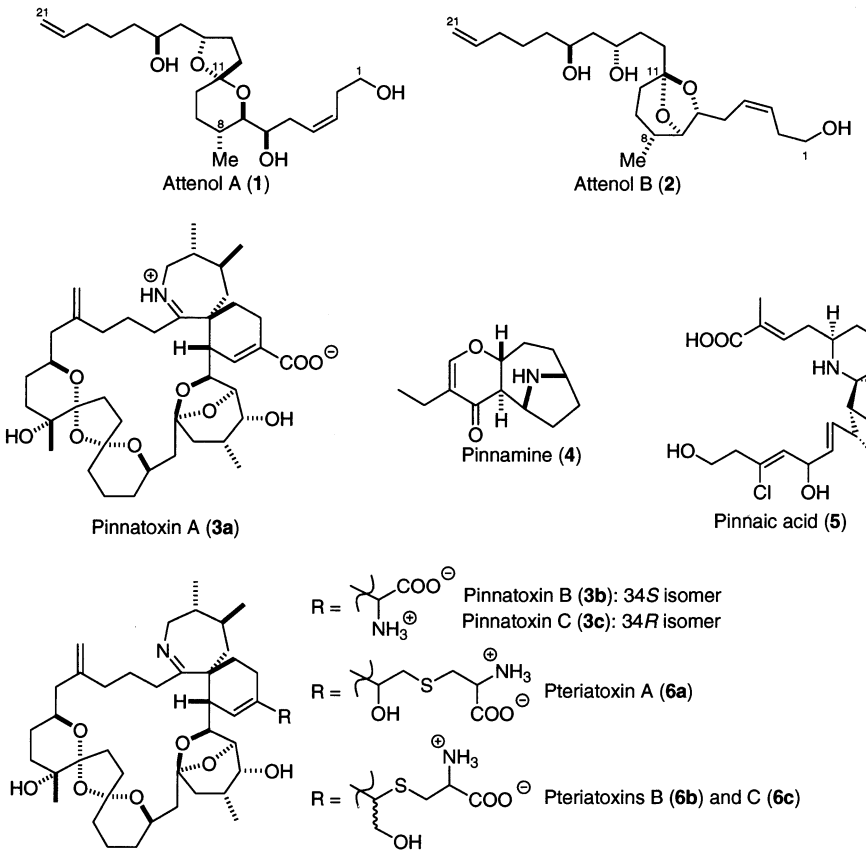
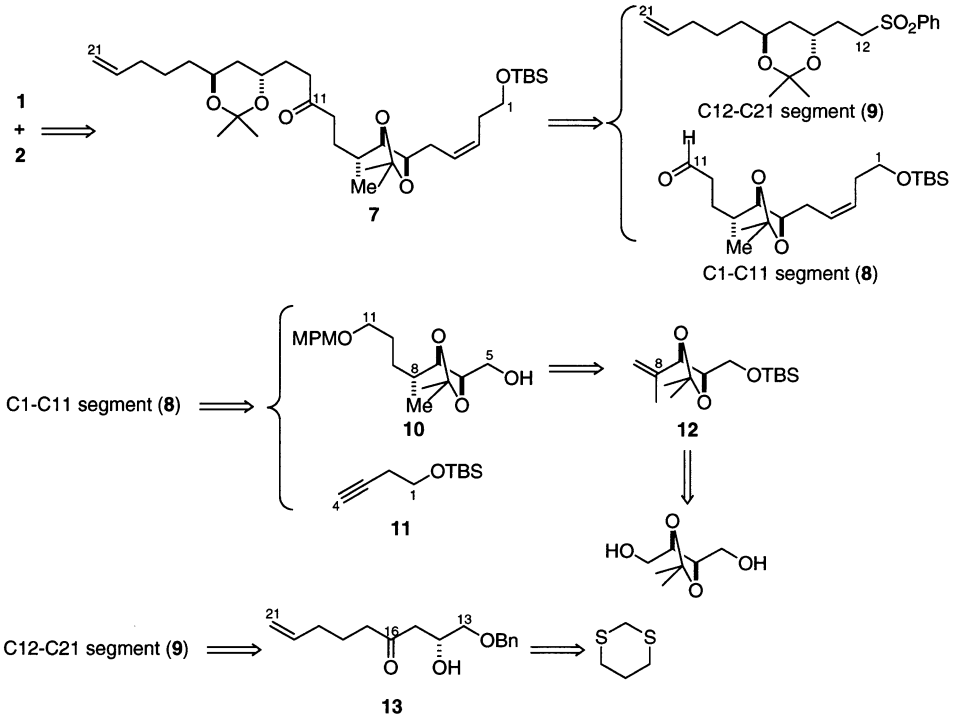


Figure 1. Bioactive compounds isolated from the bivalve *Pinna* sp. and *Pteria penguin*.



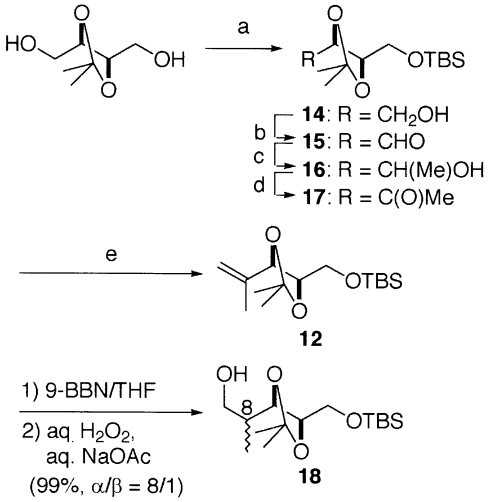
Scheme 1. Retrosynthesis of attenols A and B.

Z-disubstituted olefin was introduced by Lindlar reduction of the disubstituted acetylene, which was prepared from alcohol (**10**) and 4-*tert*-butyldimethylsilyloxy-1-butyne (**11**).[10] The stereochemistry of the C8 methyl group on attenols was introduced by diastereoselective hydroboration of the olefin (**12**). The olefin (**12**) was prepared using 2,3-*O*-isopropylidene-D-threitol as a starting material. The C12–C21 segment (**9**) was derived from *anti*-1,3-diol, which was used to introduce the stereochemistry of the C16 hydroxy group on attenols by stereoselective reduction of β-hydroxy ketone (**13**). The β-hydroxy ketone (**13**) was prepared using 1,3-dithiane as a starting material.

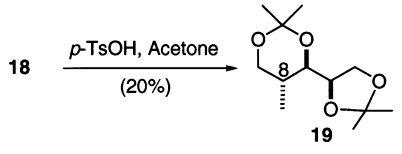
2.2. Synthesis of the C1–C11 segment

Synthesis of the C1–C11 segment **8** began with monosilylation of 2,3-*O*-isopropylidene-D-threitol to give silyl ether **14** (97%) (Scheme 2), Swern oxidation[11] of which afforded aldehyde **15** (91%). Addition of Me_2CuLi to aldehyde **15** gave a diastereomeric mixture of secondary alcohol **16** (90%), which was oxidized to methyl ketone **17** (96%). Wittig reaction of **17** with the phosphorus ylide derived from methyltriphenylphosphonium bromide and *n*-butyllithium afforded olefin **12** in 95% yield. Diastereoselective hydroboration of olefin **12** with 9-BBN followed by oxidation with H_2O_2 provided alcohol **18** (99%, α/β=8/1). Since it was difficult to separate the diastereomers at this stage, the stereoselectivity was determined by ^1H NMR (800 MHz).

The minor β-isomer could be separated by chromatography at a later stage in the synthesis. To determine the stereochemistry of the C8 methyl group, alcohol **18** was transformed into acetonide **19** (Scheme 3). The stereochemistry



Scheme 2. Synthesis of C1–C11 segment—1. (a) TBSCl, NaH, DME, 0°C→rt; (b) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, then Et_3N, −78°C→0°C; (c) MeLi, CuI, Et_2O, −78°C→0°C; (d) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, then Et_3N, −78°C→0°C; (e) Ph_3PCH_3Br, *n*-BuLi, −40°C→0°C.



Scheme 3. Transformation to **19** to determine the stereochemistry of the C8 methyl group.

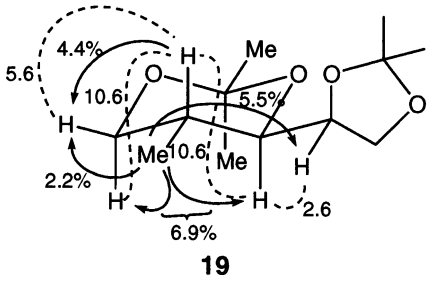


Figure 2. Observed NOE (arrow) and coupling constants (dashed line, in Hz) of **19**.

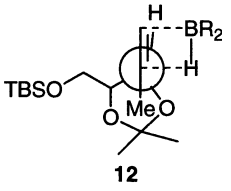


Figure 3. Preferential orientation in diastereoselective hydroboration governed predominantly by steric effects.

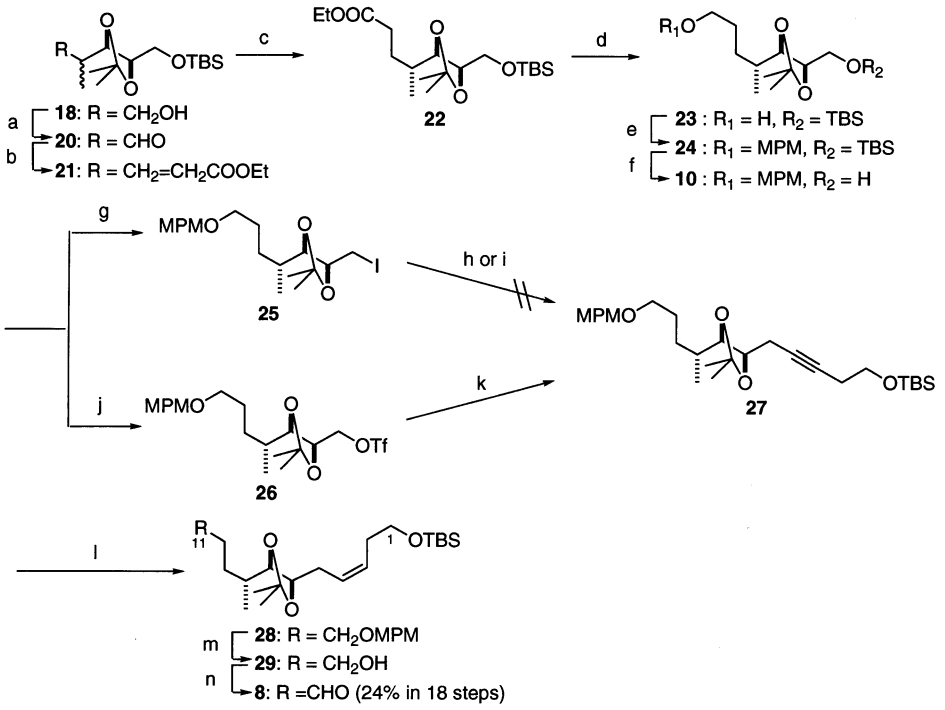
of C8 was determined to be *R* based on coupling constants and NOE experiments for the derived acetonide **19** (Fig. 2).

The stereoselectivity of hydroboration can be explained by considering that 9-BBN approached the less-hindered side of olefin **12**, which adopted the conformation shown in Fig. 3 to minimize allylic strain.[12]

Oxidation of alcohol **18** with Dess–Martin periodinane[13] gave aldehyde **20** (81%) (Scheme 4), which in the Horner–Emmons reaction with $(EtO)_2P(O)CH_2COOEt$ and *t*-BuOK afforded conjugated ester **21** (84%). Hydrogenation of **21** gave ester **22** (87%) and the minor diastereomer regarding C8, which was separated by chromatography at this stage. Reduction of **22** with DIBAL–H and then $NaBH_4$ afforded alcohol **23** (90% in 2 steps). The one-step reduction of **22** to **23** with DIBAL–H or $LiAlH_4$ at a higher temperature led to cleavage of the TBS ether. Protection of the hydroxyl group in **23** as a *p*-methoxybenzyl (MPM) ether group (**24**, 82%) followed by desilylation with *n*-Bu_4NF gave alcohol **10** (99%). Although we initially attempted a coupling reaction of iodide **25** prepared from alcohol **10**, with acetylene **11**, an elimination product was mainly obtained. Using EtMgBr as a base, the same result was observed. Coupling reaction using trifluoromethanesulfonate **26** gave disubstituted acetylene **27** in good yield (82% in 2 steps).[14] Lindlar reduction of **27** afforded *Z*-olefin **28** quantitatively. The *Z*-stereochemistry of the C3–C4 double-bond in **28** was confirmed by the coupling constant (10.9 Hz) between H3 and H4 in ^1H NMR (270 MHz). The MPM group on **28** was removed with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) to give alcohol **29** (96%), oxidation of which with Dess–Martin periodinane provided C1–C11 segment **8** (99%). The overall yield of the C1–C11 segment **8** was 24% in 18 steps.

2.3. Synthesis of the C12–C21 segment

Synthesis of the C12–C21 segment **9** began with alkylation

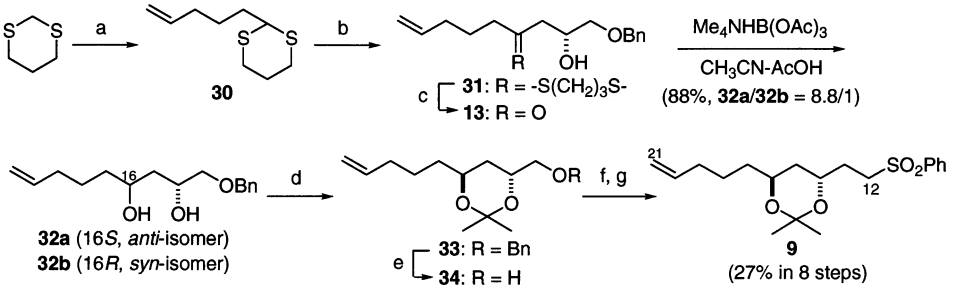


Scheme 4. Synthesis of C1–C11 segment—2. (a) Dess–Martin periodinane, CH_2Cl_2, rt; (b) $(EtO)_2P(O)CH_2COOEt$, *tert*-BuOK, THF, −78°C→0°C; (c) H_2, 5% Rh-Al_2O_3, EtOAc, rt; (d) (i) DIBAL–H, CH_2Cl_2, −78°C, (ii) $NaBH_4$, EtOH, 0°C; (e) MPMCl, NaH, DMF, −20°C; (f) *n*-Bu_4NF, THF, rt; (g) I_2, PPh_3, imidazole, toluene, rt; (h) 4-*tert*-butyldimethylsilyloxy-1-butyne (**11**), *n*-BuLi, HMPA, THF, −78°C, then iodide (**25**), 0°C→10°C; (i) **11**, *n*-BuLi, HMPA, THF, −78°C, then **25**, −35°C→0°C→rt; (j) Tf_2O, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, −20°C; (k) **11**, EtMgBr, THF, −78°C, then **26**, −35°C→rt; (l) H_2, Lindlar catalyst, MeOH, rt; (m) DDQ, CH_2Cl_2-*tert*-BuOH-phosphate buffer (pH 6); (n) Dess–Martin periodinane, CH_2Cl_2, rt.

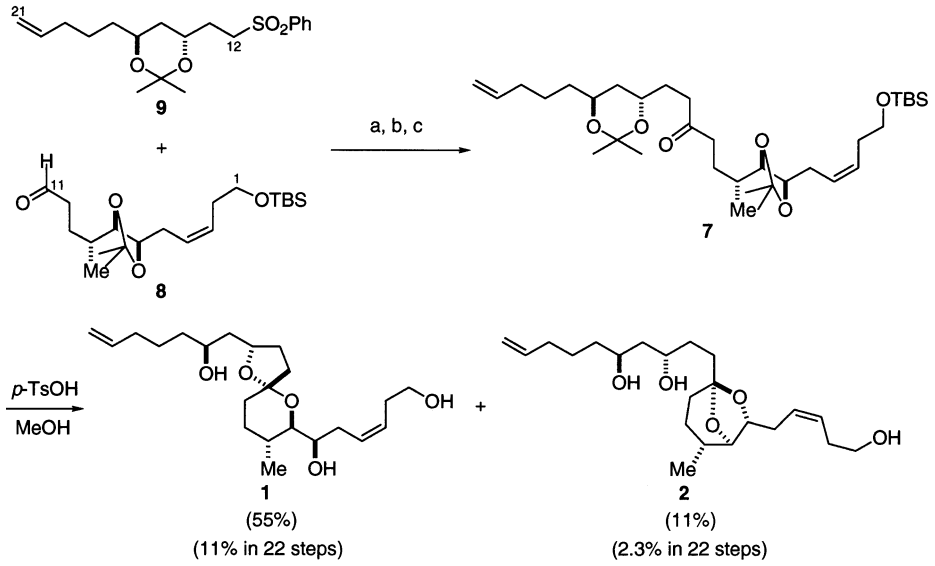
of 1,3-dithiane with 5-bromo-1-pentene to afford olefin **30** (98%) (Scheme 5). Further alkylation of **30** with (*R*)-benzyl glycidyl ether provided alcohol **31** (80%), the dithiane group of which was hydrolyzed[15] to give β-hydroxy ketone **13** (86%). Stereoselective reduction of β-hydroxy ketone **13** with tetramethylammonium triacetoxyborohydride[16] afforded *anti*-1,3-diol **32a** (88%, **32a/32b**=8.8/1), the stereochemistry of which was determined as follows. Two hydroxyl groups of **32a** were protected as an acetonide (100%), the ^{13}C NMR chemical shifts of which revealed that the stereochemistry at C16 was *S*.[17] The benzyl group of **33** was removed with sodium in liquid ammonia to give alcohol **34** (99%). The corresponding tosylate derived from **34** was coupled with the carbanion of methyl phenyl sulfone to give C12–C21 segment **9** (86% in 2 steps). The overall yield of the C12–C21 segment **9** was 27% in 8 steps.

2.4. Synthesis of attenols A and B

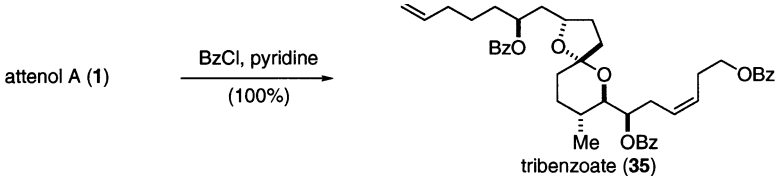
The Julia coupling reaction between C1–C11 segment **8** and the carbanion generated from C12–C21 segment **9** (*n*-BuLi, THF, −78°C) gave a diastereomeric mixture of hydroxy sulfones, which was oxidized (Dess–Martin periodinane, pyridine, CH_2Cl_2, rt) and subsequently reduced with sodium amalgam (5% Na–Hg, Na_2HPO_4, MeOH, 0°C) to afford ketone **7** (85% from **8**) (Scheme 6). Finally, removal of the protecting groups and acetal formation with *p*-TsOH in MeOH at room temperature gave attenols A (**1**, 55%) and B (**2**, 11%). We synthesized 180 mg of attenol A to evaluate its biological activity. Synthetic attenols A (**1**) and B (**2**) were identical to natural **1** and **2** in all respects, including spectral data (IR, ^1H and ^{13}C NMR, HRMS, thin-layer chromatography (TLC), $[\alpha]_D$).



Scheme 5. Synthesis of C12–C21 segment. (a) (i) *n*-BuLi, (ii) 5-bromo-1-pentene, THF, −78°C→rt; (b) (i) *n*-BuLi, (ii) (*R*)-benzyl glycidyl ether, THF, −78°C→rt; (c) $CuCl_2$, CuO, acetone/H_2O, rt; (d) $Me_2C(OMe)_2$, CSA, acetone, rt; (e) Na, Liq. NH_3/THF, −78°C; (f) *p*-TsCl, pyridine, 0°C; (g) $MeSO_2Ph$, *n*-BuLi, THF, reflux.



Scheme 6. Synthesis of attenols A and B. (a) **9**, *n*-BuLi, THF, −78°C, then **8**, −78°C; (b) Dess–Martin periodinane, pyridine, CH_2Cl_2, rt; (c) 5% Na–Hg, Na_2HPO_4, MeOH, 0°C.



Scheme 7. Synthesis of tribenzoate (**35**).

2.5. Determination of the stereochemistry at the spiro acetal carbon (C11)

Since the stereochemistry of the spiro acetal carbon (C11) of natural attenol A (**1**) could not be determined by NOE experiments due to overlap of the ^{1}H NMR signals, the stereochemistry of C11 was deduced as shown in Fig. 1 based on an empirical consideration of the anomeric effect. A sufficient amount of synthetic attenol A (**1**) enabled us to synthesize derivatives, which resolved the configuration of C11 as follows. Tribenzoate (**35**) derived from synthetic attenol A (**1**) solved the problem of the overlap of the ^{1}H NMR signals (Scheme 7). In NOE experiments (600 MHz) on tribenzoate (**35**), irradiation of the signals at H15b (δ_H 2.11) enhanced the signals for H7 (δ_H 3.80, 1.3%) and H16 (δ_H 5.55, 5.7%). Irradiation of the signals at H16 (δ_H 5.55) enhanced the signals for H7 (δ_H 3.80, 0.8%) and H14 (δ_H 4.13, 2.9%). Irradiation of the signals at H7 (δ_H 3.80) enhanced the signals for H22 (δ_H 0.87, 2.8%). Irradiation of the signals at H22 (δ_H 0.87) enhanced the signals for H9a (δ_H 1.48, 2.7%). The NOESY correlations H7/H9b, H8/22 and H9b/22 were observed. A detailed analysis of cross-peaks revealed the stereochemistry of the spiro acetal moiety as shown in Fig. 4, which is based on a reasonable anomeric effect on both the five-membered ring and the six-membered ring.

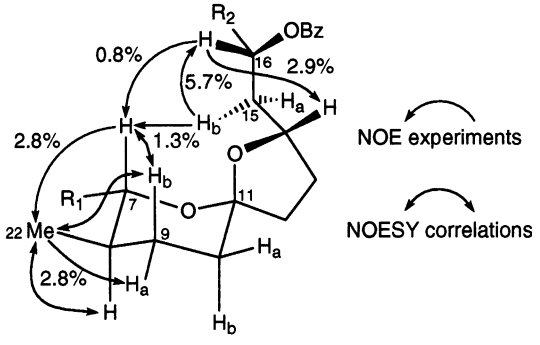


Figure 4. Determination of stereochemistry at the spiro acetal carbon (C11), based on NOE and NOESY correlations.

2.6. Examination of the biological activities of synthetic attenol A

We screened the antitumor activity of synthetic attenol A. Although attenol A exhibited inhibitory activity against P388 cells, it did not appear to inhibit polymerization of tubulin or enzymatic degradation in metastasis. In addition, attenol A did not exhibit antibacterial activity against Gram-negative bacterium. Further biological studies are currently in progress.

3. Conclusion

In conclusion, the enantioselective synthesis of attenols A (**1**) and B (**2**) was achieved with overall yields of 11% and 2.3% in 22 steps, respectively. The C8-stereochemistry was introduced by diastereoselective hydroboration. Finally,

acid-catalyzed spiroketalization gave attenols A and B simultaneously. The spectral data (^{1}H and ^{13}C NMR, $[\alpha]_D$, IR, HRFAB, TLC) of the synthetic attenols were identical to those of the natural products. The stereochemistry of the spiro acetal moiety was unambiguously determined by NOE experiments with tribenzoate (**35**), which was derived from synthetic attenol A (**1**). We synthesized 180 mg of attenol A to evaluate its biological activity. Further biological studies on attenols are currently in progress.

4. Experimental

4.1. General

Unless otherwise noted, materials were obtained from commercial sources and used without further purification. All solvents were purified by standard procedures before use. The starting materials were azeotropically dried with benzene before use. *p*-Toluenesulfonyl chloride,[18] Dess–Martin periodinane,[13,19] and copper(I) iodide[20] were prepared according to procedures in the literature. All reactions involving organometallic reagents were conducted under a nitrogen atmosphere. Fuji Silysia silica gel BW-820 MH, Fuji Silysia silica gel FL-60D and Nacalai Tesque Cosmosil 75C_{18}-OPN were used for column chromatography unless otherwise noted. Merck precoated silica gel 60 F_{254} plates were used for TLC. Visualization was accomplished with UV light, phosphomolybdic acid, or *p*-anisaldehyde solution followed by heating. Optical rotations were measured with a JASCO DIP-1000 polarimeter. IR spectra were recorded on a JASCO FT/IR-230 spectrometer in chloroform. ^{1}H NMR spectra were recorded on a JEOL JNM-EX270 (270 MHz), JEOL JNM-A400 (400 MHz), JEOL JNM-A600 (600 MHz) or JEOL JNM-ECP800 (800 MHz) instrument. Chemical shifts are reported in ppm from internal standards [tetramethylsilane (0.00 ppm) for deuteriochloroform ($CDCl_3$)] and *J* values are in Hertz. ^{13}C NMR spectra were recorded on a JEOL JNM-EX270 (67.8 MHz), a JEOL JNM-A400 (100 MHz), a JEOL JNM-A600 (150 MHz) or a JEOL JNM-ECP800 (201 MHz) instrument using deuteriochloroform ($CDCl_3$) or benzene-d_6 (C_6D_6) as a solvent. Chemical shifts are reported in ppm from the central peak of deuteriochloroform (77.0 ppm) or benzene-d_6 (128.0 ppm). Mass spectra (FABMS, GCEI) were recorded on a JEOL JMS LG2000 spectrometer. The matrix used in FABMS analysis was *m*-nitrobenzyl alcohol. Elemental analyses were performed with a LECO CHN-900 elemental analyzer.

4.1.1. Silyl ether 14. To a stirred solution of 2,3-*O*-isopropylidene-D-threitol (5.00 g, 30.8 mmol) in dry DME (50 mL) cooled to 0°C was added NaH (1.23 g of 60% dispersion in mineral oil, 30.8 mmol). The mixture was stirred at 0°C for 30 min. *tert*-Butyldimethylsilylchloride (4.74 g, 30.5 mmol) was added, and the mixture was stirred at 0°C for 30 min and at room temperature for 3 h. The reaction was quenched by adding water (50 mL) and Et_2O (50 mL). The mixture was extracted with Et_2O (3×100 mL). The combined extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (100 g, hexane/EtOAc, 5:1→0:1) to give **14** (8.25 g, 97%) as a colorless oil: TLC, R_f 0.38 (hexane/EtOAc, 4:1); $[\alpha]^{27}_D$=−5.4 (*c* 0.67, $CHCl_3$); IR ($CHCl_3$) 3600, 3560–3280 (br), 1260, 1078, 840 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.98 (dt, *J*=7.9, 4.6 Hz, 1H), 3.91–3.84 (m, 2H), 3.80–3.63 (m, 3H), 2.36 (dd, *J*=7.9, 4.6 Hz, 1H), 1.41 (s, 3H), 1.40 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 109.1, 80.2, 78.1, 63.7, 62.7, 27.0, 26.9, 25.8 (3C), 18.3, −5.5 (2C); MS (FAB) *m/z* 299 $(M+Na)^+$; HRMS (FAB) calcd for $C_{13}H_{28}O_4SiNa$ $(M+Na)^+$ 299.1654, found 299.1654.

4.1.2. Aldehyde 15. To a solution of oxalyl chloride (4.90 mL, 56.1 mmol) in dry CH_2Cl_2 (40 mL) cooled to −78°C was added a solution of DMSO (8.00 mL, 112 mmol) in CH_2Cl_2 (40 mL) dropwise. The reaction mixture was stirred at −78°C for 15 min. A solution of silyl ether **14** (7.78 g, 28.1 mmol) in CH_2Cl_2 (40 mL) was added dropwise and the mixture was stirred at −78°C for an additional 15 min. Triethylamine (23.6 mL, 169 mmol) was added, and the mixture was stirred at −78°C for 15 min and at 0°C for 30 min. The reaction was quenched with water (50 mL) and extracted with a 3:1 mixture of benzene and ether (400 mL+2×100 mL). The combined extracts were washed with saturated aqueous NH_4Cl (150 mL) and brine (150 mL), dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (200 g, benzene/acetone, 64:1→4:1) to give **15** (7.38 g, 91%) as a colorless oil: TLC, R_f 0.25–0.43 (hexane/EtOAc, 4:1); $[\alpha]^{30}_D$=+10 (*c* 0.35, $CHCl_3$); IR ($CHCl_3$) 2715, 1735, 1258, 1078, 838 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.77 (d, *J*=1.7 Hz, 1H), 4.33 (dd, *J*=7.3, 1.7 Hz, 1H), 4.12 (dt, *J*=7.3, 4.3 Hz, 1H), 3.80 (d, *J*=4.3 Hz, 2H), 1.47 (s, 3H), 1.39 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR: (67.8 MHz, $CDCl_3$) δ 200.8, 111.4, 82.0, 77.6, 62.9, 26.8, 26.3, 25.8 (3C), 18.4, −5.5 (2C); MS (FAB) *m/z* 297 $(M+Na)^+$; HRMS (FAB) calcd for $C_{13}H_{27}O_4Si$ $(M+H)^+$ 275.1679, found 275.1666.

4.1.3. Secondary alcohols 16. To a suspension of copper(I) iodide (4.88 g, 25.6 mmol) in dry Et_2O (50 mL) cooled to −23°C was added a 1.06 M solution of MeLi in Et_2O (50 mL, 53 mmol) dropwise. The mixture was stirred at −23°C for 30 min and cooled to −78°C, and then a solution of aldehyde **15** (3.13 g, 11.4 mmol) in Et_2O (20 mL) was added dropwise. The mixture was stirred at −78°C for 1 h and at 0°C for 30 min. The reaction was quenched by adding a 2:1 mixture of saturated aqueous NH_4Cl and concentrated aqueous NH_3 (90 mL). The resulting mixture was warmed to room temperature, stirred for 1 h, and extracted with Et_2O (3×90 mL). The combined extracts were washed with water (90 mL) and brine (90 mL), dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (80 g, benzene/acetone, 32:1→8:1→0:1) to give a diastereomeric mixture of secondary alcohols **16** (2.97 g, 90%) as a colorless oil, which was used in the next experiment without separation of the diastereomers: TLC, R_f 0.55 (major), 0.61 (minor) (hexane/EtOAc, 2:1); IR ($CHCl_3$) 3600–3280 (br), 1258, 1080, 838 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) [noted only the signal of the major diastereomer] δ 3.96–3.64 (m, 5H), 2.35 (d, *J*=6.6 Hz, 1H), 1.42 (s, 3H), 1.40 (s, 3H), 1.23 (d, *J*=6.3 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) [noted only the signal of the major

diastereomer] δ 108.8, 82.7, 80.5, 66.9, 64.3, 27.1 (2C), 25.9 (3C), 18.4, −5.4, −5.5; MS (GCEI) *m/z* 275 (M^+-CH_3, 17), 233 ($M^+-C_4H_9$, 16), 175 ($M^+-C_6H_{15}Si$, 38), 131 (100); HRMS (FAB) calcd for $C_{14}H_{30}O_4SiNa$ $(M+Na)^+$ 327.1968, found 327.1951.

4.1.4. Methyl ketone 17. To a solution of oxalyl chloride (1.78 mL, 20.4 mmol) in dry CH_2Cl_2 (14 mL) cooled to −78°C was added a solution of DMSO (2.89 mL, 40.8 mmol) in CH_2Cl_2 (14 mL) dropwise. The reaction mixture was stirred at −78°C for 15 min. A solution of secondary alcohols **16** (2.96 g, 10.2 mmol) in CH_2Cl_2 (14 mL) was added dropwise and the mixture was stirred at −78°C for an additional 15 min. Triethylamine (8.59 mL, 61.1 mmol) was added, and the mixture was then stirred at −78°C for 15 min and at 0°C for 30 min. The reaction was quenched with water (30 mL) and extracted with a 3:1 mixture of benzene and ether (28 mL). The combined extracts were washed with water (2×60 mL) and brine (60 mL), dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (30 g, hexane/Et_2O, 16:1→8:1→4:1→0:1) to give **17** (2.83 g, 96%) as a colorless oil: TLC, R_f 0.68 (hexane/EtOAc, 4:1); $[\alpha]^{31}_D$=−18 (*c* 0.31, $CHCl_3$); IR ($CHCl_3$) 1718, 1258, 1220, 1190, 910, 840, 480 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.31 (d, *J*=7.6 Hz, 1H), 4.05 (ddd, *J*=8.1, 7.6, 7.3 Hz, 1H), 3.87 (dd, *J*=11.3, 8.1 Hz, 1H), 3.75 (dd, *J*=11.3, 7.3 Hz, 1H), 2.28 (s, 3H), 1.45 (s, 3H), 1.42 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 208.5, 110.7, 81.5, 78.8, 63.0, 26.9, 26.5, 26.4, 25.9 (3C), 18.4, −5.3, −5.4; MS (GCEI) *m/z* 273 (M^+-CH_3, 4), 231 ($M^+-C_4H_9$, 18), 173 ($M^+-C_6H_{15}Si$, 46), 117 (100); HRMS (FAB) calcd for $C_{14}H_{29}O_4Si$ $(M+H)^+$ 289.1835, found 289.1834.

4.1.5. Olefin 12. To a stirred solution of methyltriphenylphosphonium bromide (7.49 g, 21.0 mmol) in dry THF (45 mL) cooled to −40°C was added dropwise a 1.49 M solution of *n*-BuLi in hexane (13.8 mL, 20.5 mmol) to give a yellow solution. After 1 h, a solution of methylketone **17** (2.82 g, 9.78 mmol) in THF (20 mL) was added. The reaction mixture was stirred at −40°C for 30 min and at room temperature for 12 h and then diluted with ether (65 mL). The solution was washed with 5% aqueous NH_4Cl (65 mL), water (2×50 mL) and brine (50 mL), dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (80 g, hexane/Et_2O, 16:1→8:1→4:1) to give **12** (2.66 g, 95%) as a colorless oil: TLC, R_f 0.64 (hexane/Et_2O, 6:1); $[\alpha]^{32}_D$=0.94 (*c* 0.021, $CHCl_3$); IR ($CHCl_3$) 1220, 1205, 790, 723, 670 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.05 (br s, 1H), 4.95 (br s, 1H), 4.36 (d, *J*=8.3 Hz, 1H), 3.85–3.66 (m, 3H), 1.78 (s, 3H), 1.44 (s, 3H), 1.42 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 142.0, 114.0, 108.9, 81.1, 80.0, 62.8, 27.1 (2C), 25.9 (3C), 18.4, 17.4, −5.3, −5.4; MS (FAB) *m/z* 309 $(M+Na)^+$; HRMS (FAB) calcd for $C_{15}H_{31}O_3Si$ $(M+H)^+$ 287.2042, found 287.2051.

4.1.6. Alcohol 18. To a stirred solution of olefin **12** (2.44 g, 8.53 mmol) in dry THF (54 mL) cooled to 0°C was added a 0.5 M solution of 9-BBN in THF (68 mL, 34 mmol). The reaction mixture was stirred at 0°C for 1 h and at room temperature for 15 h. After the solution was re-cooled to 0°C, 10 mL of ethanol, 34 mL of saturated aqueous sodium acetate and 11 mL of 30% hydrogen peroxide were added in that order. The mixture was stirred at 0°C for 1 h and at room temperature for 5 h, and then the solution was diluted with Et_2O (300 mL), washed with water (2×150 mL), saturated aqueous sodium bicarbonate (150 mL), and saturated aqueous NH_4Cl (150 mL), dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel [(200 g, $CHCl_3$/EtOAc, 32:1→16:1→8:1→4:1→0:1) and (100 g, hexane/$CHCl_3$/EtOAc, 20:1:1→20:2:1→0:0:1)] to give **18** (2.57 g, 99%) as a colorless oil: TLC, R_f 0.16 (hexane/EtOAc, 6:1); IR ($CHCl_3$) 3600–3280 (br), 1258, 1080, 838 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) [noted only the signal of the major diastereomer] δ 3.96–3.64 (m, 2H), 3.93–3.87 (m, 2H), 3.74 (d, *J*=4.0 Hz, 2H), 2.82 (dd, *J*=6.6, 5.0 Hz, 1H), 1.94 (m, 1H), 1.42 (s, 3H), 1.38 (s, 3H), 0.94 (d, *J*=6.9 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) [noted only the signal of the major diastereomer] δ 108.8, 82.7, 80.5, 66.9, 64.3, 38.5, 27.4, 27.1, 25.9 (3C), 18.4, 13.3, −5.4, −5.5; MS (FAB) *m/z* 327 $(M+Na)^+$. HRMS (FAB) calcd for $C_{15}H_{32}O_4SiNa$ $(M+Na)^+$ 327.1951, found 327.1951.

4.1.7. Acetonide 19. To a stirred solution of alcohol **18** (97.2 mg, 319 μmol) in dry acetone (10 mL) was added *p*-toluenesulfonic acid (1.2 mg, 6.39 μmol). The mixture was stirred at room temperature for 22 h. Saturated aqueous $NaHCO_3$ (2 mL) was added and the resulting mixture was extracted with EtOAc (3×10 mL). The combined extracts were washed with water (10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (5 g, hexane/EtOAc, 6:1→5:1→4:1→0:1) to give **19** (14.5 mg, 20%) as a colorless oil: TLC, R_f 0.65 (hexane/EtOAc, 2:1); $[\alpha]^{31}_D$=−82 (*c* 0.15, $CHCl_3$); IR ($CHCl_3$) 1460, 1380, 1370, 1230, 1160, 1060 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.26 (dt, *J*=6.9, 2.6 Hz, 1H), 3.99 (dd, *J*=12.2, 6.9 Hz, 1H), 3.94 (dd, *J*=12.2, 6.9 Hz, 1H), 3.72 (dd, *J*=10.6, 5.3 Hz, 1H), 3.49 (t, *J*=10.6 Hz, 1H), 3.44 (dd, *J*=10.6, 2.6 Hz, 1H), 2.05 (tqd, *J*=10.6, 6.6, 5.3 Hz, 2H), 1.42 (s, 3H), 1.40 (s, 3H), 1.39 (s, 3H), 1.37 (s, 3H), 0.83 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 109.3, 98.3, 75.3, 73.9, 65.9, 64.9, 30.3, 29.3, 25.9, 25.8, 19.2, 12.7; MS (FAB) *m/z* 253 $(M+Na)^+$; HRMS (FAB) calcd for $C_{12}H_{22}O_4Na$ $(M+Na)^+$ 253.1416, found 253.1434.

4.1.8. Aldehyde 20. To a stirred solution of alcohol **18** (2.43 g, 7.99 mmol) in dry CH_2Cl_2 (70 mL) was added Dess–Martin periodinane (4.04 g, 9.53 mmol) at room temperature. The mixture was stirred at room temperature for 1.5 h, and the reaction was quenched by adding saturated aqueous $Na_2S_2O_3$ (50 mL), saturated aqueous $NaHCO_3$ (50 mL), water (50 mL) and Et_2O (290 mL). The resulting mixture was stirred at room temperature for 1 h and extracted with Et_2O (3×100 mL). The combined extracts were washed with water (100 mL) and brine (100 mL), dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (100 g, hexane/Et_2O, 16:1→12:1→8:1) to give **20** (1.95 g, 81%) as a colorless oil: TLC, R_f 0.56 (hexane/Et_2O, 3:1); IR ($CHCl_3$) 2730, 1725, 1255, 1210, 1085, 840 cm^{-1}; ^1H

NMR (270 MHz, $CDCl_3$) [noted only the signal of the major diastereomer] δ 9.78 (d, J=2.3 Hz, 1H), 4.14 (dd, J=7.3, 6.3 Hz, 1H), 4.00–3.68 (m, 3H), 2.62 (m, 1H), 1.39 (s, 6H), 1.16 (d, J=6.9 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) [noted only the signal of the major diastereomer] δ 203.3, 109.3, 79.5, 79.2, 63.8, 48.9, 27.2, 27.0, 25.9 (3C), 18.3, 10.9, −5.4, −5.5; MS (FAB) *m/z* 325 $(M+Na)^+$; HRMS (FAB) calcd for $C_{15}H_{30}O_4SiNa$ $(M+Na)^+$ 325.1811, found 325.1815.

4.1.9. Conjugated ester 21. To a stirred solution of diethyl-(ethoxycarbonyl)methylphosphonate (1.50 g, 6.69 mmol) in THF (10 mL) cooled to 0°C was added potassium *tert*-butoxide (746 mg, 6.64 mmol), and the resulting solution was stirred at room temperature for 1 h. The solution was cooled to −78°C, and a solution of aldehyde **20** (498 mg, 1.65 mmol) in THF (6.0 mL) was added. After the reaction mixture was stirred at −78°C for 1 h and at 0°C for 2 h, ether (15 mL) and saturated aqueous NH_4Cl (15 mL) were added. The resulting mixture was extracted with Et_2O (3×15 mL) and the combined extracts were washed with water (15 mL) and brine (15 mL), dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (35 g, hexane/Et_2O, 20:1→10:1→5:1→0:1) to give **21** (513 mg, 84%) as a colorless oil: TLC, R_f 0.41 (hexane/Et_2O, 3:1); IR ($CHCl_3$) 1715, 1255, 1085, 840 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.01 (dd, J=15.8, 7.9 Hz, 0.87H), 6.91 (dd, J=15.8, 7.9 Hz, 0.13H), 5.87 (dd, J=15.8, 1.0 Hz, 0.13H), 5.84 (d, J=15.8, 1.0 Hz, 0.87H), 4.19 (q, J=6.9 Hz, 2H), 3.94–3.62 (m, 4H), 2.61 (m, 1H), 1.379 (s, 3H), 1.377 (s, 3H), 1.29 (t, J=6.9 Hz, 3H), 1.15 (d, J=6.9 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) [noted only the signal of the major diastereomer] δ 166.4, 149.6, 122.1, 108.9, 81.4, 79.1, 64.0, 60.2, 39.2, 27.2 (2C), 25.9 (3C), 18.3, 16.6, 14.3, −5.4, −5.5; MS (FAB) *m/z* 395 $(M+Na)^+$; HRMS (FAB) calcd for $C_{19}H_{36}O_5SiNa$ $(M+Na)^+$ 395.2229, found 395.2231.

4.1.10. Ester 22. A mixture of conjugated ester **21** (642 mg, 1.72 mmol) and 5% Rh on alumina (66 mg) in EtOAc (17 mL) was stirred under a hydrogen atmosphere at room temperature for 4 h. The reaction mixture was filtered through a pad of Celite, and the residue was washed with EtOAc (50 mL). The filtrate and the washings were combined and concentrated. The residual oil was purified by column chromatography on silica gel [(80 g, hexane/Et_2O, 32:1→16:1→12:1→8:1→0:1) and (FL-60D, 30 g, hexane/Et_2O, 32:1→16:1→8:1)] to give **22** (561 mg, 87%) as a colorless oil: TLC, R_f 0.58 (hexane/Et_2O, 2:1); $[\alpha]^{31}_D$=+11 (*c* 0.28, $CHCl_3$); IR ($CHCl_3$) 1725, 1255, 1110, 840 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.12 (q, J=6.9 Hz, 2H), 3.86 (ddd, J=6.9, 4.0, 4.0 Hz, 1H), 3.76 (t, J=6.9 Hz, 1H), 3.73 (dd, J=10.9, 4.0 Hz, 1H), 3.67 (dd, J=10.9, 4.0 Hz, 1H), 2.43–2.28 (m, 2H), 1.96 (m, 1H), 1.72 (m, 1H), 1.48 (m, 1H), 1.39 (s, 3H), 1.37 (s, 3H), 1.25 (t, J=6.9 Hz, 3H), 0.93 (d, J=6.9 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 173.7, 108.5, 82.0, 79.8, 64.5, 60.2, 35.8, 32.1, 28.0, 27.4, 27.3, 25.9 (3C), 18.4, 15.7, 14.2, −5.3, −5.4; MS (FAB) *m/z* 375 $(M+H)^+$; HRMS (FAB) calcd for $C_{19}H_{38}O_5SiNa$ $(M+Na)^+$ 397.2386, found 397.2392.

4.1.11. Alcohol 23. To a stirred solution of ester **22** (360 mg, 961 μmol) in CH_2Cl_2 (7.0 mL) cooled to −78°C was added a 0.95 M solution of diisobutylaluminum hydride in hexane (5.5 mL, 5.23 mmol) dropwise. The mixture was stirred at −78°C for 3 h and the reaction was quenched by adding MeOH (1.0 mL). The resulting mixture was warmed to room temperature. Ether (120 mL), brine (2.0 mL), and $MgSO_4$ (5.0 g) were added, and the mixture was stirred at room temperature for 2 h. The mixture was filtered through a pad of Celite, and the residue was washed with Et_2O (70 mL). The filtrate and the washings were combined and concentrated to give an aldehyde (318 mg) as a colorless oil, which was used in the next experiment without purification. To a stirred solution of the aldehyde (318 mg) in EtOH (5.0 mL) cooled to 0°C was added sodium borohydride (44 mg, 1.15 mmol). The mixture was stirred at 0°C for 30 min. The reaction was quenched by adding acetone (1.0 mL), and the resulting mixture was stirred at room temperature for 20 min. Saturated aqueous NH_4Cl (3.0 mL) was added, and the mixture was extracted with Et_2O (5.0 mL). The combined extracts were washed with water (15 mL) and brine (15 mL), dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (4 g, hexane/EtOAc, 2:1→0:1) to give **23** (287 mg, 90%) as a colorless oil: TLC, R_f 0.42 (hexane/EtOAc, 2:1); $[\alpha]^{32}_D$=+11 (*c* 0.27, $CHCl_3$); IR ($CHCl_3$) 3620, 3580–3280 (br), 1250, 1050, 840 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.85 (dt, J=6.9, 4.3 Hz, 1H), 3.78–3.68 (m, 5H), 1.78–1.48 (m, 5H), 1.39 (s, 3H), 1.37 (s, 3H), 1.24 (m, 1H), 0.94 (d, J=6.9 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 108.4, 82.1, 79.9, 64.6, 63.2, 36.1, 30.1, 28.7, 27.5, 27.3, 25.9 (3C), 18.4, 15.8, −5.3, −5.4; MS (FAB) *m/z* 355 $(M+Na)^+$; HRMS (FAB) calcd for $C_{17}H_{36}O_4SiNa$ $(M+Na)^+$ 355.2264, found 355.2264.

4.1.12. *p*-Methoxybenzyl ether 24. To a stirred solution of alcohol **23** (799 mg, 2.40 mmol) in dry DMF (1.2 mL) cooled to −20°C were added *p*-methoxybenzyl chloride (0.39 ml, 2.88 mmol) and NaH (106 mg of 60% dispersion in mineral oil, 2.65 mmol). The mixture was stirred at −20°C for 4 days, and the reaction was quenched by adding saturated aqueous NH_4Cl (10 mL). The mixture was extracted with EtOAc (3×30 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 (90 g, hexane/EtOAc, 16:1→8:1→2:1→0:1) to give **24** (894 mg, 82%) as a colorless oil: TLC, R_f 0.58 (hexane/Et_2O, 2:1); $[\alpha]^{31}_D$=+21 (*c* 0.29, $CHCl_3$); IR ($CHCl_3$) 1615, 1515, 1250, 1210, 1085, 840 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.26 (br d, J=8.6 Hz, 2H), 6.87 (br d, J=8.6 Hz, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.85–3.41 (m, 6H), 1.80–1.51 (m, 4H), 1.38 (s, 3H), 1.37 (s, 3H), 1.21 (m, 1H), 0.92 (d, J=6.9 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 159.1, 130.8, 129.2 (2C), 113.8 (2C), 108.3, 82.0, 79.7, 72.6, 70.4, 64.7, 55.3, 36.1, 29.0, 27.5, 27.3, 25.9 (3C), 18.4, 15.7, 14.2, −5.3, −5.4; MS (FAB) *m/z* 475 $(M+Na)^+$; HRMS (FAB) calcd for $C_{25}H_{44}O_5SiNa$ $(M+Na)^+$ 475.2856, found 475.2831.

4.1.13. Alcohol 10. To a stirred solution of *p*-methoxybenzyl ether **24** (1.17 g, 2.59 mmol) in dry THF (6.25 mL)

was added a 1.0 M solution of tetrabutylammonium fluoride (5.07 mL, 5.07 mmol) in THF at room temperature. The mixture was stirred at room temperature for 1 h. Ether (25 mL) and saturated aqueous NH_4Cl (6.5 mL) were added, and the mixture was extracted with EtOAc (3×35 mL). The combined extracts were washed with brine (35 mL), dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (150 g, benzene/acetone, 20:1) to give **10** (869 mg, 99%) as a colorless oil: TLC, R_f 0.41 (hexane/EtOAc, 1:1); $[\alpha]^{32}_D$=+0.44 (*c* 0.20, $CHCl_3$); IR ($CHCl_3$) 3590, 3000, 1610, 1515, 1250, 1215, 1095, 1035 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.26 (br d, *J*=8.6 Hz, 2H), 6.87 (br d, *J*=8.6 Hz, 2H), 4.43 (s, 2H), 3.90 (ddd, *J*=7.6, 5.3, 3.0 Hz, 1H), 3.80 (s, 3H), 3.78 (ddd, *J*=11.9, 6.3, 3.0 Hz, 1H), 3.68 (t, *J*=7.6, 7.6 Hz, 1H), 3.58 (ddd, *J*=11.9, 6.3, 5.3 Hz, 1H), 3.44 (t, *J*=6.3 Hz, 2H), 1.92 (t, *J*=6.3 Hz, 1H), 1.78–1.51 (m, 5H), 1.40 (s, 6H), 1.22 (m, 1H), 0.91 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 159.1, 130.7, 129.3 (2C), 113.8 (2C), 108.5, 80.9, 79.6, 72.6, 70.3, 63.6, 55.3, 36.2, 29.4, 27.3, 27.23, 27.16, 15.3; MS (FAB) *m/z* 361 $(M+Na)^+$; HRMS (FAB) calcd for $C_{19}H_{30}O_5Na$ $(M+Na)^+$ 361.1991, found 361.1995.

4.1.14. Acetylene 27. To a solution of alcohol **10** (15.4 mg, 45.5 μmol) and 2,6-di-*tert*-butyl-4-methylpyridine (40.6 mg, 198 μmol) in dry CH_2Cl_2 (0.70 mL) cooled to −30°C was added trifluoromethanesulfonic anhydride (20 μL, 118 μmol). The reaction mixture was warmed to −10°C, stirred at −10°C for 40 min, and then concentrated in vacuo to give the desired triflate **26** as a clear oil. To a solution of 4-*tert*-butyldimethylsilyloxy-1-butyne (103 mg, 559 μmol) in dry THF (3.5 mL) cooled to −78°C were added HMPA (80 μL, 1.04 mmol) and a 1.56 M solution of *n*-BuLi (0.30 mL, 468 μmol) in hexane. The mixture was stirred at −78°C for 30 min, warmed to −35°C, and kept at this temperature for 10 min. In the meantime, the triflate **26** described above was dissolved in dry THF (0.8 mL), and the resulting solution was added dropwise to the acetylide solution at −35°C. This solution was allowed to warm to room temperature over 5 h. The reaction was quenched with 1:1 saturated aqueous NH_4Cl/water (3.0 mL) and extracted with EtOAc (3×5 mL). The combined extracts were washed with water (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (14 g, hexane/EtOAc, 12:1→8:1→1:1→0:1) to give **27** (18.8 mg, 82%) as a colorless oil; TLC, R_f 0.39 (hexane/EtOAc, 5:1); $[\alpha]^{28}_D$=+14 (*c* 0.21, $CHCl_3$); IR ($CHCl_3$) 1610, 1515, 1250,1090, 840, 730 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.26 (br d, *J*=8.6 Hz, 2H), 6.87 (br d, *J*=8.6 Hz, 2H), 4.43 (s, 2H), 3.88 (dt, *J*=6.6, 5.3 Hz, 1H), 3.80 (s, 3H), 3.69 (t, *J*=6.6 Hz, 1H), 3.69 (t, *J*=7.3 Hz, 2H), 3.44 (t, *J*=6.6 Hz, 2H), 2.58–2.33 (m, 4H), 1.80–1.46 (m, 4H), 1.40 (s, 3H), 1.38 (s, 3H), 1.20 (m, 1H), 0.94 (d, *J*=6.6 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 159.1, 150.2, 130.7, 129.2 (2C), 113.8 (2C), 108.4, 84.3, 79.2, 77.1, 72.6, 70.3, 62.2, 55.3, 35.7, 28.9, 27.5, 27.4, 27.3, 25.9 (3C), 24.4, 23.2, 18.3, 15.8, −5.3 (2C); MS (FAB) *m/z* 527 $(M+Na)^+$; HRMS (FAB) calcd for $C_{29}H_{48}O_5SiNa$ $(M+Na)^+$ 527.3169, found 527.3170.

4.1.15. *Z*-Olefin 28. A mixture of acetylene **27** (3.6 mg, 7.13 μmol) and Lindlar cat. (0.3 mg) in MeOH (0.20 mL) was stirred under a hydrogen atmosphere at room temperature for 6 h. The reaction mixture was filtered through a pad of Celite, and the residue was washed with EtOAc (5.0 mL). The filtrate and the washings were combined and concentrated. The residual oil was purified by column chromatography on silica gel (500 mg, hexane/Et_2O, 8:1→5:1) to give **28** (3.6 mg, 100%) as a colorless oil: TLC, R_f 0.47 (hexane/EtOAc, 5:1); $[\alpha]^{27}_D$=+17 (*c* 0.20, $CHCl_3$); IR ($CHCl_3$) 1610, 1515, 1250, 1220, 1090, 840, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (br d, *J*=8.6 Hz, 2H), 6.87 (br d, *J*=8.6 Hz, 2H), 5.57 (m, 1H), 5.51 (m, 1H), 4.43 (s, 2H), 3.83 (ddd, *J*=7.1, 7.1, 4.2 Hz, 1H), 3.80 (s, 3H), 3.61 (t, *J*=7.1 Hz, 2H), 3.51 (dd, *J*=7.1, 7.1 Hz, 1H), 3.44 (t, *J*=6.6 Hz, 2H), 2.42–2.22 (m, 4H), 1.78–1.42 (m, 4H), 1.38 (s, 3H), 1.36 (s, 3H), 1.22 (m, 1H), 0.92 (d, *J*=6.8 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 159.1, 130.7, 129.2 (2C), 128.0, 126.8, 113.8 (2C), 107.9, 84.7, 78.7, 72.6, 70.4, 62.8, 55.3, 36.0, 32.3, 31.4, 29.1, 27.4, 27.3 (2C), 26.0 (3C), 18.4, 15.8, −5.3 (2C); MS (FAB) *m/z* 529 $(M+Na)^+$; HRMS (FAB) calcd for $C_{29}H_{50}O_5SiNa$ $(M+Na)^+$ 529.3325, found 529.3331.

4.1.16. Alcohol 29. To a stirred solution of *Z*-olefin **28** (105 mg, 207 μmol) in dry CH_2Cl_2 (32 mL), *tert*-butyl alcohol (3.2 mL), and 1 M phosphate buffer (pH 6, 3.2 mL) cooled to 0°C was added 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) (219 mg, 869 μmol). The mixture was warmed to room temperature, and stirring was continued for 1.5 h. The reaction was quenched by adding saturated aqueous $NaHCO_3$ (18 mL), and the resulting mixture was stirred at room temperature for 10 min. The mixture was extracted with $CHCl_3$ (3×40 mL), and the combined extracts were washed with brine (40 mL), dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (7 g, hexane/EtOAc, 5:1→4:1→1:1) to give **29** (76.6 mg, 96%) as a colorless oil: TLC, R_f 0.13 (hexane/EtOAc, 4:1); $[\alpha]^{29}_D$=+20 (*c* 0.20, $CHCl_3$); IR ($CHCl_3$) 3615, 1460, 1380, 1255, 1090, 1050, 840, 660 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.61–5.49 (m, 2H), 3.84 (dt, *J*=4.2, 7.3 Hz, 1H), 3.64–3.50 (m, 3H), 3.62 (t, *J*=7.1 Hz, 1H), 3.52 (t, *J*=7.1 Hz, 1H), 2.42–2.22 (m, 4H), 1.76–1.49 (m, 4H), 1.46 (br s, 1H), 1.38 (s, 3H), 1.37 (s, 3H), 1.22 (m, 1H), 0.93 (d, *J*=6.9 Hz, 3H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 128.1, 126.7, 108.0, 84.7, 78.9, 63.1, 62.8, 36.0, 32.3, 31.4, 30.1, 28.8, 27.4, 27.3, 26.0 (3C), 18.4, 16.0, −5.3 (2C); MS (FAB) *m/z* 409 $(M+Na)^+$; HRMS (FAB) calcd for $C_{21}H_{42}O_4SiNa$ $(M+Na)^+$ 409.2750, found 409.2768.

4.1.17. C1–C11 segment 8. To a stirred solution of alcohol **29** (18.0 mg, 46.6 μmol) in dry CH_2Cl_2 (1.0 mL) and dry pyridine (0.40 mL) was added Dess–Martin periodinane (47.2 mg, 111 μmol) at room temperature. The mixture was stirred at room temperature for 1 h, and the reaction was quenched by adding saturated aqueous $Na_2S_2O_3$ (1.0 mL), saturated aqueous $NaHCO_3$ (1.0 mL) and Et_2O (5.0 mL). The resulting mixture was stirred at room temperature for 30 min and extracted with Et_2O (3×15 mL). The combined extracts were washed with a 1:1 mixture of water and saturated aqueous $NaHCO_3$

(10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (2 g, hexane/EtOAc, 10:1→4:1→2:1→0:1) to give **8** (17.8 mg, 99%) as a colorless oil: TLC, R_f 0.74 (hexane/EtOAc, 2:1); $[\alpha]^{27}_D$=+16 (*c* 0.20, $CHCl_3$); IR ($CHCl_3$) 2740, 1720, 1460, 1380, 1260, 1090, 1060, 840 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.78 (t, *J*=2.0 Hz, 1H), 5.63–5.47 (m, 2H), 3.85 (dt, *J*=4.6, 7.3 Hz, 1H), 3.62 (t, *J*=7.3 Hz, 2H), 3.49 (t, *J*=7.3 Hz, 1H), 2.62–2.24 (m, 4H), 2.05–1.83 (m, 2H), 1.72–1.48 (m, 2H), 1.40 (s, 3H), 1.38 (s, 3H), 1.26 (m, 1H), 0.92 (d, *J*=6.6 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 202.5, 128.2, 126.5, 108.2, 84.5, 79.1, 62.7, 41.5, 35.9, 32.3 (2C), 31.4, 27.34, 27.27, 26.0 (3C), 25.3, 16.1, −5.3 (2C); MS (FAB) *m/z* 407 $(M+Na)^+$; HRMS (FAB) calcd for $C_{21}H_{40}O_4SiNa$ $(M+Na)^+$ 407.2593, found 407.2620.

4.1.18. Olefin 30. To a stirred solution of 1,3-dithiane (5.00 g, 41.6 mmol) in dry THF (125 mL) cooled to −20°C was added a 1.64 M solution of *n*-BuLi in hexane (26.5 mL, 43.5 mmol). The reaction mixture was stirred at −20°C for 1 h. After cooling to −78°C, a solution of 5-bromo-1-pentene (5.07 mL, 42.8 mmol) was added dropwise over 5 min, and the mixture was warmed to room temperature over 3 h. The reaction was quenched with water (30 mL) and extracted with Et_2O (3×50 mL). The combined extracts were washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (150 g, hexane/benzene, 10:1→5:1→1:1) to give **30** (7.66 g, 98%) as a colorless oil: TLC, R_f 0.57 (hexane/Et_2O, 4:1); IR ($CHCl_3$) 1640, 1425, 1270, 1215, 1175, 990, 920 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.79 (ddt, *J*=16.8, 11.2, 6.6 Hz, 1H), 5.02 (br d, *J*=16.8 Hz, 1H), 4.95 (br d, *J*=11.2 Hz, 1H), 4.05 (t, *J*=6.9 Hz, 1H), 2.94–2.78 (m, 4H), 2.17–2.04 (m, 3H), 1.94–1.71 (m, 3H), 1.68–1.58 (m, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 138.1, 115.0, 47.5, 34.8, 33.2, 30.4 (2C), 26.0, 25.8; MS (GCEI) *m/z* 188 $(M)^+$; HRMS (GCEI) calcd for $C_9H_{16}S_2$ $(M)^+$ 188.0694, found 188.0702.

4.1.19. Alcohol 31. To a stirred solution of olefin **30** (7.54 g, 40.0 mmol) in dry THF (60 mL) cooled to −20°C was added a 1.64 M solution of *n*-BuLi in hexane (25 mL, 41.0 mmol). The reaction mixture was cooled to −78°C. A solution of (*R*)-(−)-benzyl glycidyl ether (6.84 g, 41.7 mmol) in dry THF (40 mL) was added and the mixture was warmed to room temperature over 5 h. The reaction was quenched with saturated aqueous NH_4Cl (60 mL) and extracted with Et_2O (3×150 mL). The combined extracts were washed with brine (150 mL), dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel [(100 g, hexane/EtOAc, 20:1→10:1→8:1→4:1→0:1) and (100 g, hexane/EtOAc, 20:1→8:1→4:1)] to give **31** (12.5 g, 80%) as a colorless oil: TLC, R_f 0.10 (hexane/EtOAc, 10:1); $[\alpha]^{27}_D$=+17 (*c* 0.39, $CHCl_3$); IR ($CHCl_3$) 3590, 1640, 1600, 1490, 1360, 1275, 1240, 1100, 990, 915 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.38–7.26 (m, 5H), 5.79 (ddt, *J*=16.8, 11.2, 6.6 Hz, 1H), 5.02 (br d, *J*=16.8 Hz, 1H), 4.97 (br d, *J*=11.2 Hz, 1H), 4.58 (s, 2H), 4.15 (m, 1H), 3.45 (d, *J*=5.6 Hz, 2H), 3.17 (d, *J*=2.6 Hz, 1H), 3.01–2.72 (m, 4H), 2.25 (dd, *J*=15.2, 8.3 Hz, 1H), 2.15–1.84 (m, 7H), 1.72–1.48 (m, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 138.2, 137.8, 128.4 (2C), 127.7 (3C), 115.0, 74.4, 73.3, 67.6, 52.1, 41.3, 39.0, 33.7, 26.3, 26.0, 25.0, 23.2; MS (FAB) *m/z* 375 $(M+Na)^+$; HRMS (FAB) calcd for $C_{19}H_{28}O_2NaS_2$ $(M+Na)^+$ 375.1429, found 375.1399.

4.1.20. Ketone 13. To a solution of alcohol **31** (50.3 mg, 143 μmol) in 99% aqueous acetone (1.5 mL) were added $CuCl_2$ (38.1 mg, 283 μmol) and CuO (45.5 mg, 572 μmol). The mixture was stirred at room temperature for 1 h. The reaction mixture was filtered through a Celite pad and the Celite was washed with Et_2O. The combined filtrate and washings were concentrated under reduced pressure and the residue was diluted again with acetone (50 mL). The solution was concentrated and diluted with EtOAc (15 mL) and 5% aqueous $NaHCO_3$ solution (15 mL). The aqueous layer was 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, 5:1→2:1→0:1) to give **13** (32.4 mg, 86%) as a colorless oil: TLC, R_f 0.34 (hexane/EtOAc, 2:1); $[\alpha]^{28}_D$=+15 (*c* 0.41, $CHCl_3$); IR ($CHCl_3$) 3580, 3520–3200 (br.), 1715, 1640, 1455, 1360, 1125, 1090, 990, 915 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.39–7.26 (m, 5H), 5.75 (ddt, *J*=16.8, 11.2, 6.6 Hz, 1H), 5.05–4.95 (m, 2H), 4.55 (s, 2H), 4.26 (m, 1H), 3.49 (dd, *J*=9.6, 4.6 Hz, 1H), 3.44 (dd, *J*=9.6, 5.9 Hz, 1H), 2.99 (d, *J*=4.3 Hz, 1H), 2.66 (dd, *J*=16.8, 6.9 Hz, 1H), 2.58 (dd, *J*=16.8, 5.0 Hz, 1H), 2.45 (t, *J*=7.3 Hz, 2H), 2.05 (br q, *J*=6.6 Hz, 2H), 1.73–1.62 (m, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 210.7, 137.9, 137.8, 128.4 (2C), 127.7 (3C), 115.3, 73.4, 73.3, 66.9, 45.7, 42.8, 33.0, 22.5; MS (FAB) *m/z* 285 $(M+Na)^+$; HRMS (FAB) calcd for $C_{16}H_{22}O_3Na$ $(M+Na)^+$ 285.1665, found 285.1665.

4.1.21. *anti*-1,3-Diol 32a. To a stirred solution of tetramethylammonium triacetoxyborohydride (2.32 g, 8.82 mmol) in dry acetonitrile (3.0 mL) and acetic acid (3.0 mL) cooled to −40°C was added alcohol **13** (323 mg, 1.23 mmol). The mixture was stirred at −40°C for 1 h, warmed to −30°C, and kept at this temperature for 20 h. The reaction was quenched by adding 1 M aqueous potassium sodium tartrate (25 mL), and the mixture was extracted with EtOAc (3×50 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (50 mL), dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel [(FL-60D, 15 g, benzene/acetone, 10:1→9:1→2:1), (FL-60D, 15 g, benzene/acetone, 10:1→9:1→2:1), and (FL-60D, 7 g, benzene/acetone, 10:1→9:1→2:1)] to give *anti*-isomer **32a** (282 mg, 88%) and *syn*-isomer **32b** (35.3 mg, 11%) as a colorless oil: **32a**; TLC, R_f 0.14 (hexane/EtOAc, 2:1); $[\alpha]^{31}_D$=+3.5 (*c* 0.27, $CHCl_3$); IR ($CHCl_3$) 3590–3240 (br), 1640, 1495, 1455, 1365, 1090, 995, 915 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.26 (m, 5H), 5.80 (ddt, *J*=13.5, 10.2, 6.6 Hz, 1H), 5.00 (br d, *J*=13.5 Hz, 1H), 4.95 (br d, *J*=10.2 Hz, 1H), 4.56 (s, 2H), 4.30 (m, 1H), 3.90 (m, 1H), 3.50 (dd, *J*=9.2, 3.6 Hz, 1H), 3.43 (dd, *J*=9.2, 7.6 Hz, 1H), 2.73 (d, *J*=4.0 Hz, 1H), 2.43 (d, *J*=4.6 Hz, 1H), 2.07 (br q, *J*=6.6 Hz, 2H), 1.70–1.37 (m, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 138.6, 137.8, 128.5 (2C), 127.9, 127.8 (2C), 114.6, 74.4, 73.4, 68.8, 68.1, 39.0, 37.0, 33.6,

25.0; MS (FAB) *m/z* 287 $(M+Na)^+$; HRMS (FAB) calcd for $C_{16}H_{24}O_3Na$ $(M+Na)^+$ 287.1623, found 287.1629. **32b**; TLC, R_f 0.16 (hexane/EtOAc, 2:1); $[\alpha]^{31}_D=+14$ (*c* 0.15, $CHCl_3$); IR ($CHCl_3$) 3590–3440 (br), 1640, 1495, 1455, 1380, 1200, 1170, 1110, 995, 915 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.25 (m, 5H), 5.80 (ddt, *J*=17.1, 10.2, 6.8 Hz, 1H), 4.99 (br d, *J*=17.1 Hz, 1H), 4.94 (br d, *J*=10.2 Hz, 1H), 4.60 (br d, *J*=12.2 Hz, 1H), 4.54 (br d, *J*=12.2 Hz, 1H), 4.08 (m, 1H), 3.83 (m, 1H), 3.51 (dd, *J*=10.0, 5.9 Hz, 1H), 3.37 (dd, *J*=10.0, 5.1 Hz, 1H), 2.05 (br q, *J*=6.8 Hz, 2H), 1.54–1.13 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 137.3, 128.4 (2C), 127.8 (2C), 127.6, 114.5, 73.7, 73.5, 68.6, 68.5, 35.9, 33.6, 30.2, 24.3; MS (FAB) *m/z* 287 $(M+Na)^+$; HRMS (FAB) calcd for $C_{16}H_{24}O_3Na$ $(M+Na)^+$ 287.1623, found 287.1622.

4.1.22. Acetal 33. To a stirred solution of *anti*-1,3-diol **32a** (3.07 g, 11.6 mmol) in dry acetone (1.0 mL) were added 2,2-dimethoxypropane (28.5 mL, 232 mmol) and D-10-camphorsulfonic acid (136 mg, 585 μmol). The mixture was stirred at room temperature for 2 days. EtOAc (26 mL) and saturated aqueous $NaHCO_3$ (26 mL) were added and the mixture was extracted with EtOAc (3×60 mL). The combined extracts were washed with brine (60 mL), dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (150 g, hexane/EtOAc, 20:1→10:1→0:1) to give **33** (3.52 g, 100%) as a colorless oil: TLC, R_f 0.73 (hexane/EtOAc, 2:1); $[\alpha]^{27}_D=+3.7$ (*c* 0.43, $CHCl_3$); IR ($CHCl_3$) 1640, 1600, 1495, 1455, 1380, 1220, 1170, 1090, 915 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.35–7.26 (m, 5H), 5.80 (ddt, *J*=13.5, 10.2, 6.6 Hz, 1H), 5.02 (br d, *J*=13.5 Hz, 1H), 4.94 (br d, *J*=10.2 Hz, 1H), 4.62 (d, *J*=12.2 Hz, 1H), 4.55 (d, *J*=12.2 Hz, 1H), 3.77 (m, 1H), 3.50 (dd, *J*=10.6, 4.3 Hz, 2H), 3.43 (dd, *J*=10.6, 6.6 Hz, 1H), 2.06 (br q, *J*=6.6 Hz, 2H), 1.71–1.34 (m, 6H), 1.38 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 138.7, 138.3, 128.4 (2C), 127.7 (2C), 127.6, 114.5, 100.3, 73.3, 72.7, 66.4, 66.3, 35.3, 34.8, 33.6, 24.8 (2C), 24.7; MS (FAB) *m/z* 305 $(M+H)^+$; HRMS (FAB) calcd for $C_{19}H_{28}O_3Na$ $(M+Na)^+$ 327.1936, found 327.1917.

4.1.23. Alcohol 34. Sodium (0.79 g, 34.4 mmol) was added to a stirred solution of acetal **33** (251 mg, 824 μmol) in THF (4 mL) and liquid NH_3 (30 mL) cooled to −78°C. After the mixture was stirred at −78°C for 30 min, NH_4Cl (10 g) was added. The mixture was allowed to warm to room temperature and then stirred for 1 h. EtOAc (30 mL) and water (50 mL) were added, and the mixture was extracted with EtOAc (3×80 mL). The combined extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (14 g, hexane/EtOAc, 10:1→2:1→1:1→0:1) to give **34** (174 mg, 99%) as a colorless oil: TLC, R_f 0.27 (hexane/EtOAc, 2:1); $[\alpha]^{32}_D=+30$ (*c* 0.34, $CHCl_3$); IR ($CHCl_3$) 3590, 3570–3250 (br), 1640, 1460, 1380, 1220, 1170, 1080, 1010, 915 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.80 (ddt, *J*=17.1, 10.5, 6.6 Hz, 1H), 5.00 (br d, *J*=17.1 Hz, 1H), 4.95 (br d, *J*=10.5 Hz, 1H), 3.95 (m, 1H), 3.76 (m, 1H), 3.62 (ddd, *J*=11.6, 7.8, 3.6 Hz, 1H), 3.51 (ddd, *J*=11.6, 7.8, 3.8 Hz, 1H), 2.06 (br q, *J*, 2H), 1.95 (br s, 1H), 1.65 (ddd, *J*=12.3, 9.3, 5.6 Hz, 1H), 1.56–1.40 (m, 5H), 1.38 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 138.6, 114.6, 100.4, 92.5, 67.5, 66.6, 65.5, 35.3, 33.8, 33.6, 24.9, 24.7; MS (FAB) *m/z* 237 $(M+Na)^+$; HRMS (FAB) calcd for $C_{12}H_{22}O_3Na$ $(M+Na)^+$ 237.1467, found 237.1459.

4.1.24. C12–C21 segment 9. To a stirred solution of alcohol **34** (45.0 mg, 210 μmol) in pyridine (1.0 mL) cooled to 0°C was added *p*-toluenesulfonyl chloride (87.6 mg, 460 μmol). The mixture was stirred at 0°C for 3.5 h, and the reaction was quenched by adding water (2.0 mL). The resulting mixture was extracted with Et_2O (5.0 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give tosylate (80.5 mg) as a colorless oil, which was used in the next experiment without purification. To a stirred solution of methyl phenyl sulfone (163 mg, 853 μmol) in dry THF (7.0 mL) and cooled to −30°C was added a 1.56 M solution of *n*-BuLi in hexane (0.50 mL, 780 μmol). The mixture was warmed to room temperature and kept at this temperature for 40 min. After adding a solution of tosylate (80.5 mg) in THF (1.0 mL), the mixture was stirred at reflux temperature for 22 h. The reaction was quenched by adding saturated aqueous NH_4Cl (2.0 mL), and the mixture was extracted with Et_2O (3×15 mL). The combined extracts were washed with water (10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel [(4 g, hexane/EtOAc, 8:1→6:1→4:1→0:1) and (2 g, hexane/EtOAc, 7:1→6:1→5:1→2:1)] to give **9** (63.6 mg, 86%) as a colorless oil: TLC, R_f 0.48 (hexane/EtOAc, 2:1); $[\alpha]^{28}_D=+17$ (*c* 0.36, $CHCl_3$); IR ($CHCl_3$) 1710, 1640, 1585, 1445, 1380, 1310, 1225, 1150, 1085, 1000, 915, 820 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.94–7.90 (m, 2H), 7.70–7.54 (m, 3H), 5.79 (ddt, *J*=17.2, 10.2, 6.6 Hz, 1H), 4.99 (m, 1H), 4.94 (m, 1H), 4.14–3.69 (m, 2H), 3.31 (ddd, *J*=14.2, 10.6, 5.3 Hz, 1H), 3.09 (ddd, *J*=14.2, 10.2, 5.3 Hz, 1H), 2.10–2.00 (m, 2H), 2.00–1.79 (m, 2H), 1.64–1.22 (m, 6H), 1.28 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 139.2, 138.6, 133.7, 129.3, 128.1, 114.6, 100.4, 66.4, 65.0, 53.1, 38.3, 35.2, 33.6, 28.8, 24.7 (2C), 24.5; MS (FAB) *m/z* 353 $(M+H)^+$; HRMS (FAB) calcd for $C_{19}H_{28}O_4SNa$ $(M+Na)^+$ 375.1606, found 375.1607.

4.1.25. Hydroxy sulfones. To a stirred solution of the C12–C21 segment **9** (67.0 mg, 190 μmol) in THF (0.60 mL) cooled to −78°C was added a 1.56 M solution of *n*-BuLi in hexane (0.10 mL, 156 μmol) dropwise. The mixture was stirred at −78°C for 30 min, and a solution of the C1–C11 segment **8** (14.0 mg, 36.4 μmol) in THF (0.50 mL) was added dropwise. The resulting mixture was stirred at −78°C for 2 h. The reaction was quenched by adding saturated aqueous NH_4Cl (1.0 mL) and EtOAc (5.0 mL), and the mixture was extracted with EtOAc (3×5.0 mL). The combined extracts were washed with water (5.0 mL) and brine (5.0 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→6:1→5:1→4:1) and by ODS column chromatography (3.5 g, MeOH/H_2O, 1:1→2:1→3:1→5:1→7:1→11:1→1:0) to give a diastereomeric mixture of hydroxy sulfones (31.0 mg) as a colorless oil. The hydroxy sulfones were used in the next experiment without separation of the diastereomers.

4.1.26. Keto sulfones. To a stirred solution of hydroxy sulfones (31.0 mg) in dry CH_2Cl_2 (1.0 mL) and dry pyridine (0.4 mL) was added Dess–Martin periodinane (35.2 mg, 83.0 μmol) at room temperature. The mixture was stirred at room temperature for 2 h, and the reaction was quenched by adding saturated aqueous $Na_2S_2O_3$ (15 mL), saturated aqueous $NaHCO_3$ (1.5 mL) and EtOAc (7.0 mL). The resulting mixture was stirred at room temperature for 50 min and extracted with EtOAc (3×15 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated. The combined residual oil was purified by column chromatography on silica gel [(4 g, hexane/EtOAc, 8:1→7:1→6:1→0:1) and (500 mg, hexane/EtOAc, 16:1→12:1→10:1→6:1)] to give keto sulfones (23.8 mg, 89% from **8**) as a colorless oil. The keto sulfones were used in the next experiment without separation of the diastereomers.

4.1.27. Ketone 7. To a stirred solution of the diastereomeric mixture of keto sulfones (1.8 mg, 2.45 μmol) in MeOH (0.20 mL) cooled to 0°C were added Na_2HPO_4 (51.0 mg, 359 μmol) and 5% sodium amalgam (56.7 mg), and the mixture was stirred at 0°C for 2.5 h. The mixture was diluted with saturated aqueous NH_4Cl (1.0 mL) and EtOAc (2.5 mL), stirred at room temperature for 1 h, and extracted with EtOAc (3×5.0 mL). The combined extracts were washed with brine (5.0 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (500 mg, hexane/EtOAc, 8:1→4:1→2:1→0:1) to give **7** (1.4 mg, 96%) as a colorless oil: TLC, R_f 0.46 (hexane/EtOAc, 4:1); $[\alpha]^{29}_D$=+20 (*c* 0.20, $CHCl_3$); IR ($CHCl_3$) 1710, 1640, 1460, 1380, 1225, 1090, 1005, 915, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.80 (ddt, *J*=17.1, 10.3, 6.8 Hz, 1H), 5.59–5.49 (m, 2H), 5.00 (br d, *J*=17.1 Hz, 1H), 4.94 (br d, *J*=10.3 Hz, 1H), 3.84 (dt, *J*=4.2, 7.3 Hz, 1H), 3.79–3.69 (m, 2H), 3.61 (t, *J*=7.1 Hz, 2H), 3.48 (t, *J*=7.1 Hz, 1H), 2.59–2.25 (m, 8H), 2.05 (br. q, *J*=6.8 Hz, 2H), 1.92–1.25 (m, 11H), 1.37 (s, 3H), 1.36 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H), 0.90 (d, *J*=4.9 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 210.6, 152.2, 138.7, 128.1, 126.6, 114.5, 108.1, 100.2, 84.6, 78.9, 77.2, 66.5, 66.0, 62.7, 40.3, 38.8, 38.7, 35.8, 35.3, 33.6, 32.3, 31.4, 29.7, 27.4, 27.3, 26.9, 25.9 (3C), 24.8, 18.3, 16.0, −5.3 (2C); MS (FAB) *m/z* 617 $(M+Na)^+$; HRMS (FAB) calcd for $C_{34}H_{62}O_6SiNa$ $(M+Na)^+$ 617.4213, found 617.4229.

4.1.28. Attenol A (1) and attenol B (2). To a stirred solution of ketone **7** (284 mg, 477 μmol) in MeOH (15 mL) was added *p*-toluenesulfonic acid (21.0 mg, 122 μmol), and the mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with pyridine (23 mL) and toluene (5 mL) and concentrated. This procedure was performed again using the ketone (240 mg, 404 μmol), *p*-toluenesulfonic acid (14.0 mg, 69.7 μmol), MeOH (13 mL), pyridine (18 mL) and toluene (5 mL). The combined crude product was purified by column chromatography on silica gel (FL-60D, 40 g, benzene/acetone, 4:1→3:1→5:2) to give attenol A (**1**) (187 mg, 55%) and attenol B (**2**) (34.9 mg, 11%) as a colorless oil: **1**; TLC, R_f 0.24 (benzene/acetone, 3:1); $[\alpha]^{28}_D$=−9.7 (*c* 0.35, $CHCl_3$) [natural attenol A: $[\alpha]^{28}_D$=−8.0 (*c* 0.38, $CHCl_3$)]; IR ($CHCl_3$) 3460, 1460, 1440 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddt, *J*=17.0, 10.2, 6.0 Hz, 1H), 5.69 (m, 1H), 5.54 (m, 1H), 5.01 (br. d, *J*=17.0 Hz, 1H), 4.96 (br. d, *J*=10.2 Hz, 1H), 4.32 (m, 1H), 3.83 (m, 1H), 3.72 (br. s, 1H), 3.72–3.68 (m, 2H), 3.65 (m, 1H), 3.32 (dd, *J*=10.1, 1.5 Hz, 1H), 2.58 (br. s, 1H), 2.52 (br. dt, *J*=14.3, 8.8 Hz, 1H), 2.42 (m, 1H), 2.29 (m, 1H), 2.14–2.08 (m, 3H), 2.04–1.99 (m, 2H), 1.84 (m, 1H), 1.77–1.70 (m, 5H), 1.66–1.64 (m, 2H), 1.60–1.42 (m, 6H), 0.88 (d, *J*=6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 129.6, 128.0, 114.6, 106.4, 78.04, 77.98, 70.1, 69.6, 62.0, 43.6, 38.5, 36.6, 33.9, 33.7, 33.0, 30.9, 30.8, 30.4, 29.0, 25.1, 17.3; MS (FAB) *m/z* 405 $(M+Na)^+$; HRMS (FAB) calcd for $C_{22}H_{38}O_5Na$ $(M+Na)^+$ 405.2617, found 405.2635; Anal. calcd for $C_{22}H_{38}O_5·H_2O$: C, 65.97; H, 10.07. Found: C, 65.98; H, 9.694. **2**; TLC, R_f 0.14 (benzene/acetone, 3:1); $[\alpha]^{29}_D$=+34 (*c* 0.073, $CHCl_3$) [natural attenol B: $[\alpha]^{28}_D$=31 (*c* 0.065, $CHCl_3$)]; IR ($CHCl_3$) 3400, 1460, 1440 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.81 (ddt, *J*=17.2, 10.2, 6.8 Hz, 1H), 5.56–5.49 (m, 2H), 5.02 (br. d, *J*=17.2 Hz, 1H), 4.95 (br. d, *J*=10.2 Hz, 1H), 4.09 (t, *J*=6.8 Hz, 1H), 4.04 (br. s, 1H), 4.00–3.83 (m, 2H), 3.93 (s, 1H), 3.63–3.59 (m, 2H), 3.39 (br. s, 1H), 2.62 (br. s, 1H), 2.44–2.35 (m, 2H), 2.35–2.24 (m, 2H), 2.10–2.04 (m, 2H), 2.02 (m, 1H), 1.94–1.75 (m, 3H), 1.75–1.48 (m, 8H), 1.48–1.40 (m, 2H), 1.34 (dd, *J*=15.2, 5.7 Hz, 1H), 1.11 (d, *J*=7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.8, 128.5, 127.8, 114.5, 109.6, 83.1, 80.1, 70.2, 69.2, 61.9, 42.5, 36.9, 34.5, 33.74, 33.69, 31.3, 31.2, 30.3 (2C), 25.0, 23.1, 16.9; MS (FAB) *m/z* 405 $(M+Na)^+$; HRMS (FAB) calcd for $C_{22}H_{38}O_5Na$ $(M+Na)^+$ 405.2617, found 405.2636; Anal. calcd for $C_{22}H_{38}O_5·H_2O$: C, 65.97; H, 10.07. Found: C, 65.61; H, 9.628.

4.1.29. Tribenzoate 35. To a stirred solution of attenol A (**1**) (7.2 mg, 18.8 μmol) in pyridine (0.3 mL) cooled to 0°C was added benzoyl chloride (0.1 mL, 861 μmol), and the mixture was stirred at 0°C for 1 h and at room temperature for 34 h. The reaction mixture was diluted with toluene (1.0 mL) and concentrated in vacuo. The residual oil was purified by column chromatography on silica gel (2 g, hexane/EtOAc, 10:1→10:1→8:1) to give **35** (13.1 mg, 100%) as a colorless oil: $[\alpha]^{29}_D$=+21 (*c* 0.42, $CHCl_3$); IR ($CHCl_3$) 1708, 1600, 1450, 1120 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 8.28 (br. d, *J*=8.2 Hz, 2H), 8.22 (br. d, *J*=8.2 Hz, 2H), 8.14 (br. d, *J*=8.2 Hz, 2H), 7.12–7.02 (m, 9H), 5.72 (m, 1H), 5.71 (m, 1H), 5.70 (m, 1H), 5.55 (m, 1H), 5.45 (br. dt, *J*=10.8, 7.3 Hz, 1H), 5.00 (br. d, *J*=9.4 Hz, 1H), 4.95 (br. d, *J*=18.2 Hz, 1H), 4.21 (dt, *J*=10.8, 6.8 Hz, 1H), 4.15 (dt, *J*=10.8, 6.8 Hz, 1H), 4.14 (m, 1H), 3.80 (dd, *J*=9.5, 1.6 Hz, 1H), 3.00 (br. dt, *J*=14.6, 7.3 Hz, 1H), 2.61 (br. dt, *J*=14.6, 7.3 Hz, 1H), 2.52 (br. dq, *J*=13.6, 6.8 Hz, 1H), 2.44 (br. dq, 1H), 2.11 (ddd, *J*=14.3, 8.2, 4.6 Hz, 1H), 2.03 (dd, *J*=12.3, 7.0 Hz, 1H), 1.99 (q, *J*=7.1 Hz, 2H), 1.94 (ddd, *J*=14.3, 7.7, 4.4 Hz, 1H), 1.88 (m, 1H), 1.79 (m, 1H), 1.76 (m, 1H), 1.71 (m, 1H), 1.60 (m, 1H), 1.58 (m, 1H), 1.57 (m, 1H), 1.52 (m, 1H), 1.48 (m, 1H), 1.45 (m, 1H), 1.41 (m, 1H), 1.40 (m, 1H), 0.87 (d, *J*=6.1 Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 166.2, 166.1, 166.0, 138.6, 132.9, 132.8, 132.7, 129.9 (6C), 128.6, 128.5, 128.5, 128.3 (6C), 128.2, 127.7, 115.0, 106.2, 77.8, 76.5, 73.5, 73.3, 64.2, 42.7, 39.0, 34.44, 34.37, 31.5, 31.1, 30.0, 29.4, 27.4, 25.0, 17.3; MS (FAB) *m/z* 717 $(M+Na)^+$;

HRMS (FAB) calcd for $C_{22}H_{38}O_5Na$ $(M+Na)^+$ 717.3403, found 717.3403.

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