

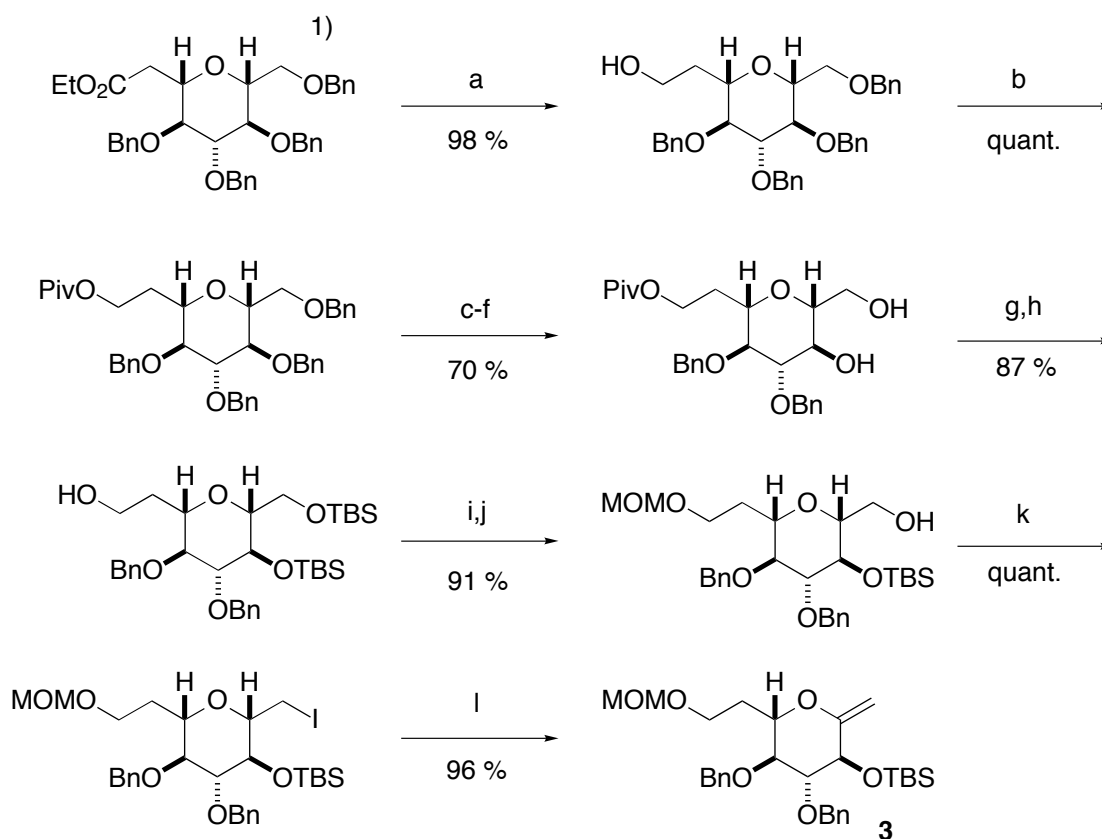
Supporting Information

A General Method for Convergent Synthesis of Polycyclic Ethers Based on Suzuki Cross-Coupling: Concise Synthesis of the ABCD Ring System of Ciguatoxin

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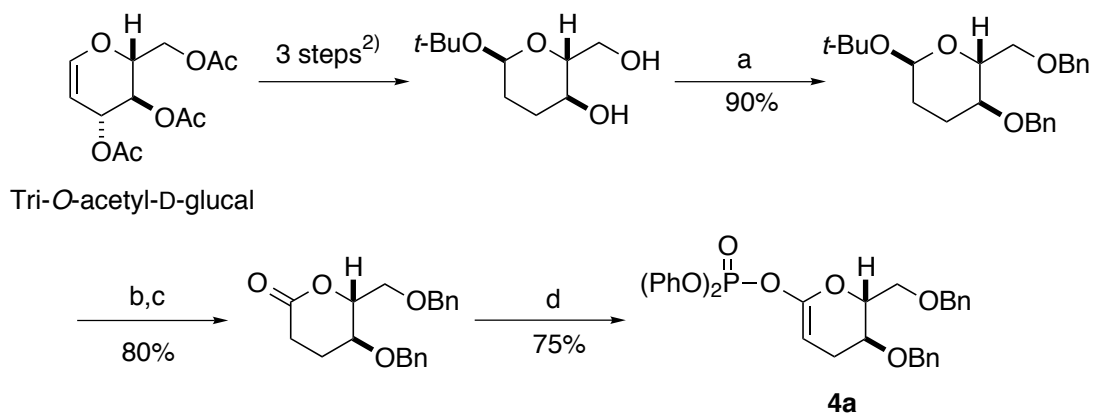
Synthetic Scheme for Compound 3



^aReagents and conditions : (a) DIBAL, CH₂Cl₂, -78 °C; (b) PivCl, Et₃N, DMAP, CH₂Cl₂, r.t.; (c) H₂, Pd(OH)₂/C, EtOAc-MeOH, r.t.; (d) CSA, Me₂C(OMe)₂, DMF-CH₂Cl₂, r.t.; (e) NaHMDS, BnBr, Bu₄NI, DMF, 0 °C; (f) CSA, MeOH-CH₂Cl₂, r.t.; (g) TBSOTf, 2,6-lutidine, CH₂Cl₂, 0 °C; (h) DIBAL, CH₂Cl₂, -78 °C; (i) MOMCl, *i*-Pr₂NEt, Bu₄NI, CH₂Cl₂, 0 °C; (j) CSA, MeOH-CH₂Cl₂, 0 °C; (k) I₂, imidazole, PPh₃, benzene, r.t.; (l) *t*-BuOK, THF, 0 °C.

1) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976.

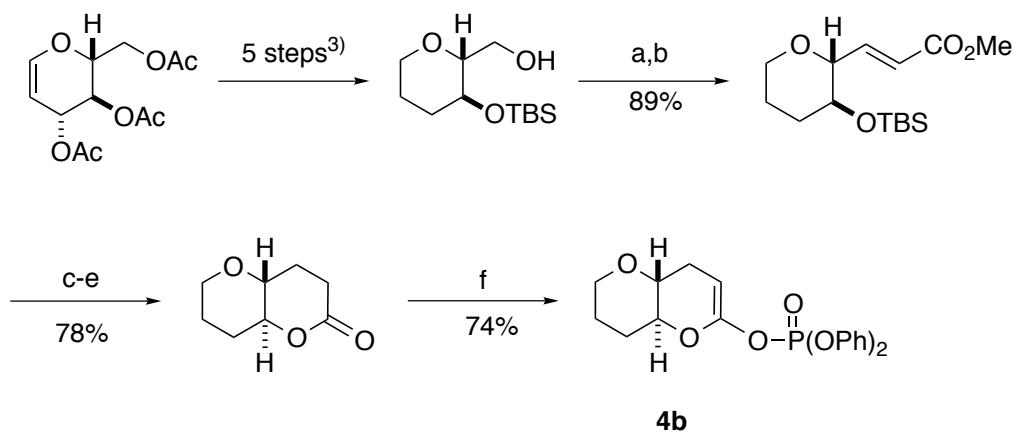
Synthetic Scheme for Compound 4a



^a**Reagents and conditions** : (a) NaH, BnBr, *n*-Bu₄NI, DMF, 0 °C to r.t.; (b) 1M HCl, 80% AcOH, 60 °C; (c) TPAP, NMO, molecular sieve 4Å, CH₂Cl₂, r.t.; (d) KHMDS, (PhO)₂P(O)Cl, THF-HMPA, -78 °C.

2) Isobe, M.; Ichikawa, Y.; Funabashi, Y.; Mio, S.; Goto, T. *Tetrahedron* **1986**, *42*, 2863.

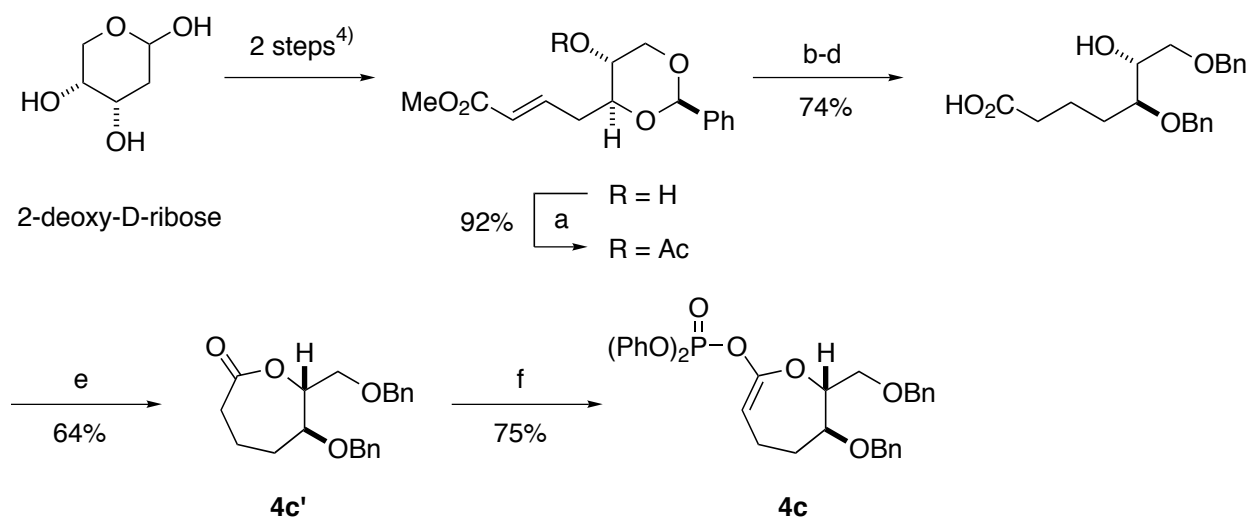
Synthetic Scheme for Compound 4b



^a**Reagents and conditions** : (a) SO₃·Pyr, Et₃N, CH₂Cl₂-DMSO (4:1), 0 °C; (b) Ph₃P=CHCO₂Me, benzene, r.t.; (c) H₂, Pd(OH)₂/C, EtOAc, r.t.; (d) CSA, MeOH, reflux; (e) CSA, benzene, reflux; (f) KHMDS, (PhO)₂P(O)Cl, THF-HMPA, -78 °C.

3) Nicolaou, K. C.; DeFrees, S. A.; Hwang, C.-K.; Stylianides, N.; Carroll, P. J.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 3029.

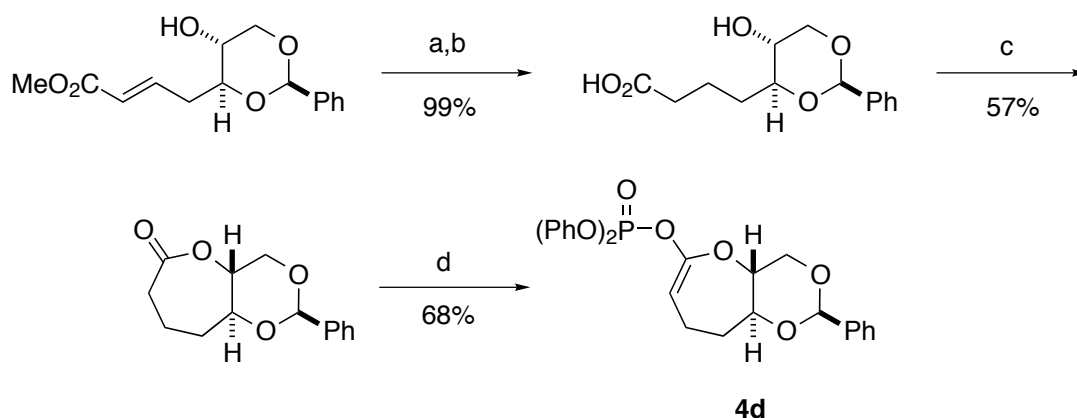
Synthetic Scheme for Compound 4c



^a**Reagents and conditions** : (a) Ac_2O , DMAP, Et_3N , CH_2Cl_2 , r.t.; (b) H_2 , $\text{Pd}(\text{OH})_2/\text{C}$, EtOAc , r.t.; (c) $\text{BnOC}(=\text{NH})\text{CCl}_3$, cat. TfOH , CH_2Cl_2 -hexane, r.t.; (d) aq. NaOH , THF - MeOH , r.t.; (e) 2,4,6-trichlorobenzoylchloride, Et_3N , THF , r.t.; DMAP, benzene, reflux; (f) KHMDs , $(\text{PhO})_2\text{P}(\text{O})\text{Cl}$, THF - HMPA , -78°C .

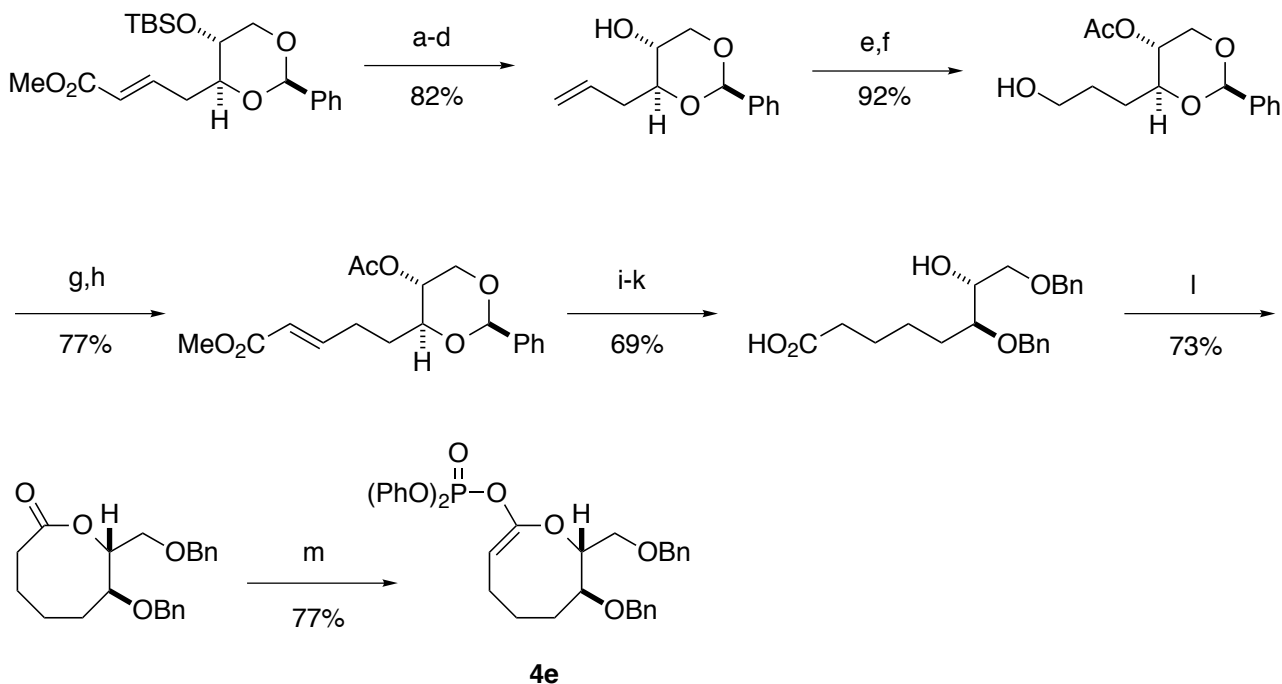
4) (a) Nicolaou, K. C.; Veal, C. A.; Hwang, C.-K.; Hutcinson, J.; Prasad, C. V. C.; Oglivie, W. W. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 299. (b) Nicolaou, K. C.; Wallace, P. A.; Shi, S.; Ouellette, M. A.; Bunnage, M. E.; Gunzner, J. L.; Agrios, K. A.; Shi, G.-q.; Gärtner, P.; Yang, Z. *Chem. Eur. J.* **1999**, *5*, 618.

Synthetic Scheme for Compound 4d



^a**Reagents and conditions** : (a) H_2 , Pd/C , EtOAc , r.t.; (b) KOH , THF - MeOH - H_2O (1:1:1), 50°C ; (c) 2,4,6-trichlorobenzoylchloride, Et_3N , THF , r.t.; DMAP, toluene, r.t.; (d) KHMDs , $(\text{PhO})_2\text{P}(\text{O})\text{Cl}$, THF - HMPA , -78°C .

Synthetic Scheme for Compound 4e



^a**Reagents and conditions** : (a) OsO₄, NMO, THF-H₂O (1:1), r.t.; (b) NaIO₄, THF-H₂O (1:1), r.t.; (c) Ph₃P⁺CH₃Br⁻, NaHMDS, THF, 0 °C; (d) *n*-Bu₄NF, THF, r.t.; (e) Ac₂O, DMAP, Et₃N, CH₂Cl₂, r.t.; (f) 9-BBN, THF, r.t.; then aq. NaHCO₃, H₂O₂, 0 °C; (g) SO₃·Pyr, Et₃N, CH₂Cl₂-DMSO (2:1), 0 °C; (h) Ph₃P=CHCO₂Me, toluene, 80 °C; (i) H₂, Pd(OH)₂/C, EtOAc, r.t.; (j) BnOC(=NH)CCl₃, cat. TfOH, CH₂Cl₂, r.t.; (k) NaOH, THF-MeOH-H₂O (1:1:1), 60 °C; (l) 2,4,6-trichlorobenzoylchloride, Et₃N, THF, r.t.; then DMAP, benzene, 80 °C; (m) KHMDS, (PhO)₂P(O)Cl, THF-HMPA, -78 °C.

Typical Experimental Procedure for Synthesis of Cyclic Ketene Acetal Phosphate 4

To a solution of seven-membered lactone **4c'** (288.1 mg, 0.847 mmol) in THF (15 mL) and HMPA (0.44 mL, 2.53 mmol) was added diphenylphosphoryl chloride (0.44 mL, 2.11 mmol). The solution was cooled to -78 °C and treated with potassium bis(trimethylsilylamide) (KHMDS, 0.5 M in toluene, 3.38 mL, 1.69 mmol). After stirring for 1 h, the reaction mixture was diluted with ether (20 mL) and 3% aqueous ammonia solution (20 mL), and the resultant mixture was vigorously stirred at room temperature for 30 min. The organic phase was separated, washed with brine (20 mL), dried (Na₂SO₄), filtered, and evaporated. Flash chromatography on silica gel (0-20% ethyl acetate-hexane containing 2% triethylamine) afforded ketene acetal phosphate **4c** (364.0 mg, 75%).

Typical Experimental Procedure for Suzuki Cross-Coupling Reaction

exo-Olefin **3** (155.5 mg, 0.2945 mmol) was treated with 9-BBN (0.5 M in THF, 1.53 mL, 0.765 mmol) and the resultant solution was stirred at room temperature for 1 h and then at 60 °C for 2 h. The reaction mixture was cooled to room temperature and treated with 1M aqueous NaHCO₃ (0.88 mL, 0.88 mmol). After stirring for 15 min, Pd(PPh₃)₄ (34.1 mg, 0.0295 mmol) followed by a solution of enol phosphate **4c** (337.6 mg, 0.5902 mmol) in DMF (3.5 mL) were successively added, and the resulting mixture was stirred at 50 °C for 20 h. After cooling, the reaction mixture was diluted with ether (40 mL), washed with brine (20 mL), dried (Na₂SO₄), filtered and evaporated. The residue was dissolved in THF (5 mL), cooled to 0 °C, and treated with 3M NaOH (0.5 mL) followed by 30% H₂O₂ (0.2 mL). The resulting mixture was stirred at room temperature for 30 min, diluted with ethyl acetate (40 mL), washed with saturated aqueous Na₂SO₃ and brine, dried (Na₂SO₄), filtered, and evaporated. Flash chromatography on silica gel (8% ethyl acetate-hexane containing Et₃N) gave coupling product **5c** (243.1 mg, 97%) as a colorless oil.

Spectroscopic Data for Compounds 5a-f

Compound 5a: $[\alpha]_D^{31} = +53.7^\circ (c = 0.55, C_6H_6)$; IR (film) $\nu_{max} = 3032, 2925, 1684, 1458, 1360, 1308, 1254, 1105, 847, 739, 694\text{ cm}^{-1}$; ¹H NMR (500 MHz, CDCl₃) δ 7.24-7.11 (m, 20H), 4.83 (d, $J = 11.9\text{ Hz}$, 1H), 4.71 (d, $J = 11.6\text{ Hz}$, 1H), 4.63 (d, $J = 10.7\text{ Hz}$, 1H), 4.52 (d, $J = 11.9\text{ Hz}$, 1H), 4.49-4.42 (m, 5H), 4.40 (s, 2H), 4.38 (m, 1H), 3.85 (m, 1H), 3.68-3.62 (m, 3H), 3.54 (m, 1H), 3.41 (m, 1H), 3.33 (m, 1H), 3.24 (m, 1H), 3.20-3.16 (m, 4H), 3.13 (dd, $J = 9.2, 8.9\text{ Hz}$, 1H), 2.47 (dd, $J = 14.7, <1\text{ Hz}$, 1H), 2.22 (m, 1H), 2.04-1.95 (m, 2H), 1.82 (dd, $J = 14.7, 9.8\text{ Hz}$, 1H), 1.52 (m, 1H), 0.82 (s, 9H), -0.05 (s, 3H), -0.13 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 150.6, 143.3, 139.0, 138.5, 138.1, 130.5, 129.0, 128.4, 128.3, 128.1, 127.9, 127.7, 127.6, 127.55, 127.49, 127.0, 126.7, 125.4, 96.5, 94.0, 87.0, 83.5, 77.8, 76.9, 76.0, 75.2, 75.1, 75.0, 73.3, 71.1, 70.6, 69.3, 64.5, 55.0, 41.9, 36.6, 32.4, 27.2, 26.8, 26.0, 25.7, 24.7, 18.0, -3.6, -4.1; HRMS (FAB) calcd for C₅₀H₆₆O₉SiNa [(M+Na)⁺] 861.4374, found 861.4402.

Compound 5b: $[\alpha]_D^{31} = +6.55^\circ (c = 0.50, C_6H_6)$; IR (film) $\nu_{max} = 3033, 2937, 2860, 1678, 1460, 1363, 1257, 1151, 1105, 1057, 847, 775, 739, 694\text{ cm}^{-1}$; ¹H NMR (500 MHz, CDCl₃) δ 7.36-7.14 (m, 10H), 4.93 (d, $J = 11.9\text{ Hz}$, 1H), 4.80 (d, $J = 11.9\text{ Hz}$, 1H), 4.72 (d, $J = 10.7\text{ Hz}$, 1H), 4.60-4.55 (m, 3H), 4.49 (m, 1H), 3.91 (m, 1H), 3.68 (ddd, $J = 9.5, 7.6, 4.3\text{ Hz}$, 1H), 3.61 (m, 1H), 3.47-3.28 (m, 9H), 3.24 (dd, $J = 9.2, 9.2\text{ Hz}$, 1H), 2.56 (dd, $J = 14.3, <1\text{ Hz}$, 1H), 2.23 (ddd, $J = 16.2, 5.2, 4.9\text{ Hz}$, 1H), 2.17-2.10 (m, 2H), 2.02 (m, 1H), 1.88 (dd, $J = 14.3, 9.8\text{ Hz}$, 1H), 1.78-1.67 (m, 2H), 1.65-1.50 (m, 2H), 0.87 (s, 9H), 0.05 (s, 3H), -0.03 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 151.2, 138.9, 138.0, 128.3, 128.1, 127.9, 127.7, 127.0, 126.7, 96.5, 95.0, 87.0, 83.4, 78.3, 76.0, 75.2, 75.1, 75.1, 75.0, 74.8, 67.7, 64.4, 55.1, 36.6, 32.3, 29.2, 27.8, 26.0, 25.4, 18.0, -3.6, -4.2; HRMS (FAB) calcd for C₃₈H₅₆O₈SiNa [(M+Na)⁺] 691.3642, found 691.3627.

Compound 5c: $[\alpha]_D^{31} = +64.3^\circ (c = 0.47, C_6H_6)$; IR (film) 3033, 2927, 1680, 1458, 1363, 1254, 1103, 847, 739, 696 cm^{-1} ; 1H NMR (500 MHz, C_6D_6) δ 7.39-7.02 (m, 20H), 5.08 (d, $J = 12.2$ Hz, 1H), 4.85-4.80 (m, 2H), 4.64-4.58 (m, 2H), 4.54 (d, $J = 12.5$ Hz, 1H), 4.50 (d, $J = 10.7$ Hz, 1H), 4.48 (d, $J = 12.4$, 1H), 4.35 (d, $J = 11.9$ Hz, 1H), 4.34 (m, 1H), 3.96 (d, $J = 11.6$ Hz, 1H), 3.89-3.82 (m, 2H), 3.75 (m, 1H), 3.70 (d, $J = 4.3$ Hz, 1H), 3.68 (s, 2H), 3.67 (m, 1H), 3.57 (ddd, $J = 9.8, 9.8, 2.1$ Hz, 1H), 3.53-3.50 (m, 2H), 3.28 (dd, $J = 9.8, 8.9$ Hz, 1H), 3.23 (s, 3H), 2.90 (dd, $J = 14.3, <1$ Hz, 1H), 2.61 (m, 1H), 2.32 (m, 1H), 2.22 (dd, $J = 14.3, 10.1$ Hz, 1H), 2.19 (m, 1H), 1.92-1.89 (m, 2H), 1.71 (m, 1H), 0.98 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 157.1, 139.8, 139.4, 139.2, 138.9, 128.5, 128.43, 128.36, 128.3, 128.0, 127.8, 127.74, 127.66, 127.54, 127.51, 127.17, 126.7, 106.3, 96.9, 87.4, 84.1, 83.9, 77.74, 77.66, 76.1, 75.8, 75.1, 75.0, 73.2, 71.4, 70.9, 64.6, 54.9, 38.9, 33.0, 29.0, 26.3, 20.9, 18.3, -3.3, -4.0; HRMS (FAB) calcd for $C_{51}H_{68}O_9SiNa [(M+Na)^+]$ 875.4530, found 875.4506.

Compound 5d: $[\alpha]_D^{31} = +47.3^\circ (c = 0.25, C_6H_6)$; IR (film) $\nu_{max} = 3033, 2933, 2867, 1685, 1460, 1367, 1107, 1067, 847, 744, 694$ cm^{-1} ; 1H NMR (500 MHz, C_6D_6) δ 7.66-7.64 (m, 3H), 7.38-7.36 (m, 2H), 7.22-7.02 (m, 10H), 5.38 (s, 1H), 5.03-4.95 (m, 2H), 4.79 (d, $J = 11.9$ Hz, 1H), 4.70 (d, $J = 11.0$ Hz, 1H), 4.62 (d, $J = 10.0$ Hz, 1H), 4.60 (d, $J = 10.0$ Hz, 1H), 4.51 (d, $J = 11.0$ Hz, 1H), 4.42 (m, 1H), 3.85 (ddd, $J = 9.5, 9.2, 5.5$ Hz, 1H), 3.78 (ddd, $J = 9.5, 6.7, 4.3$ Hz, 1H), 3.67 (m, 1H), 3.64-3.58 (m, 2H), 3.57-3.42 (m, 4H), 3.27 (dd, $J = 9.2, 8.9$ Hz, 1H), 3.24 (s, 3H), 2.73 (dd, $J = 14.0, <1$ Hz, 1H), 2.29 (m, 1H), 2.15 (m, 1H), 2.08 (dd, $J = 14.0, 10.0$ Hz, 1H), 2.03 (m, 1H), 1.94 (m, 1H), 1.67 (m, 1H), 1.60 (m, 1H), 0.96 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 156.9, 139.7, 138.8, 138.8, 128.8, 128.53, 128.46, 128.4, 128.3, 127.9, 127.7, 127.2, 126.8, 126.7, 110.4, 101.1, 96.8, 87.3, 83.8, 83.0, 78.1, 76.0, 75.7, 75.2, 75.1, 75.0, 69.5, 64.2, 54.9, 38.8, 32.9, 32.5, 26.1, 21.3, 18.3, -3.3, -4.2; HRMS (FAB) calcd for $C_{44}H_{60}O_9SiNa [(M+Na)^+]$ 783.3904, found 783.3895.

Compound 5e: $[\alpha]_D^{31} = +47.5^\circ (c = 0.90, C_6H_6)$; IR (film) $\nu_{max} = 3030, 2931, 2867, 1662, 1458, 1363, 1254, 1105, 847, 739, 696$ cm^{-1} ; 1H NMR (500 MHz, C_6D_6) δ 7.39-7.04 (m, 20H), 5.01 (d, $J = 12.0$ Hz, 1H), 4.82 (d, $J = 12.2$ Hz, 1H), 4.76 (dd, $J = 8.9, 6.7$ Hz, 1H), 4.71 (d, $J = 11.0$ Hz, 1H), 4.63-4.58 (m, 3H), 4.53-4.48 (m, 2H), 4.46 (d, $J = 11.6$ Hz, 1H), 4.15 (d, $J = 11.6$ Hz, 1H), 3.89 (m, 1H), 3.82 (m, 1H), 3.75 (dd, $J = 10.5, 2.3$ Hz, 1H), 3.72-3.61 (m, 3H), 3.55-3.43 (m, 3H), 3.27 (dd, $J = 9.0, 9.0$ Hz, 1H), 3.22 (s, 3H), 2.99 (dd, $J = 13.9, <1$ Hz, 1H), 2.56 (m, 1H), 2.33 (m, 1H), 2.18-2.08 (m, 2H), 2.02-1.93 (m, 2H), 1.86 (m, 1H), 1.79 (m, 1H), 1.67 (m, 1H), 0.97 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 153.7, 139.8, 139.4, 139.2, 138.9, 128.7, 128.6, 128.5, 128.5, 128.4, 128.3, 128.0, 128.0, 127.8, 127.7, 127.6, 127.5, 127.2, 126.8, 103.5, 96.8, 87.4, 84.0, 80.2, 78.7, 77.8, 76.3, 75.8, 75.1, 75.0, 73.5, 72.4, 70.9, 64.9, 54.9, 39.2, 33.1, 26.3, 25.8, 24.4, 24.0, 18.3, -3.3, -4.0; HRMS (FAB) calcd for $C_{52}H_{70}O_9SiNa [(M+Na)^+]$ 889.4687, found 889.4709.

Compound 5f: $[\alpha]_D^{31} = +31.8^\circ (c = 0.47, C_6H_6)$; IR (film) $\nu_{max} = 3027, 2933, 2860, 1743, 1668, 1458, 1392, 1363, 1298, 1254, 1209, 1103, 847, 769, 742, 694\text{ cm}^{-1}$; $^1\text{H NMR}$ (500 MHz, C_6D_6) δ 7.64-7.62 (m, 3H), 7.38-7.36 (m, 2H), 7.22-7.02 (m, 10H), 5.80-5.70 (m, 2H), 5.35 (s, 1H), 5.07 (dd, $J = 7.9, 7.3\text{ Hz}$, 1H), 5.03 (d, $J = 11.9\text{ Hz}$, 1H), 4.82 (d, $J = 11.9\text{ Hz}$, 1H), 4.70 (d, $J = 11.0\text{ Hz}$, 1H), 4.66 (d, $J = 6.4\text{ Hz}$, 1H), 4.63 (d, $J = 6.4\text{ Hz}$, 1H), 4.56 (dd, $J = 10.4, 4.9\text{ Hz}$, 1H), 4.50 (d, $J = 11.0\text{ Hz}$, 1H), 3.94 (ddd, $J = 10.4, 10.4, 4.9\text{ Hz}$, 1H), 3.87-3.74 (m, 3H), 3.68 (dd, $J = 10.4, 10.4\text{ Hz}$, 1H), 3.57 (ddd, $J = 9.8, 9.8, 2.1\text{ Hz}$, 1H), 3.54-3.37 (m, 4H), 3.32-3.22 (m, 5H), 2.72 (dd, $J = 14.7, <1\text{ Hz}$, 1H), 2.38-2.26 (m, 2H), 2.03 (dd, $J = 14.7, 10.7\text{ Hz}$, 1H), 1.64 (m, 1H), 0.96 (s, 9H), 0.10 (s, 3H), 0.03 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, C_6D_6) δ 156.5, 139.6, 138.8, 138.7, 131.9, 129.0, 128.9, 128.5, 128.5, 128.4, 128.3, 128.2, 128.0, 127.8, 127.3, 126.8, 126.7, 124.4, 113.4, 101.7, 97.0, 87.4, 84.0, 81.2, 77.5, 76.1, 75.8, 75.8, 75.2, 75.1, 71.0, 64.4, 55.0, 39.6, 33.0, 29.7, 26.2, 23.5, 18.2, -3.5, -3.7; HRMS (FAB) calcd for $C_{46}H_{62}O_9SiNa [(M+Na)^+]$ 809.4061, found 809.4037.

Synthetic Procedures and Spectroscopic Data for Compounds 6-12

Alcohol 6. To a solution of 2,3-dimethyl-2-butene (0.062 mL, 0.522 mmol) in THF (0.3 mL) at 0 °C was added $BH_3 \cdot THF$ (0.98 M in THF, 0.535 mL, 0.524 mmol). After 1 h, the thexylborane solution was added to a solution of enol ether **5c** (111.6 mg, 0.131 mmol) in THF (0.7 mL) at -20 °C. The resultant solution was stirred at -20 °C for 6 h and then at 0 °C for 17 h. The reaction mixture was quenched with H_2O (1 mL), and treated with 3M NaOH (1 mL) followed by 30% H_2O_2 (0.5 mL). After stirring for 2 h, the reaction mixture was diluted with ethyl acetate (20 mL), washed with aqueous saturated Na_2SO_3 and brine, dried (Na_2SO_4), filtered, and evaporated. Flash chromatography on silica gel (20-30% ethyl acetate-hexane) afforded alcohol **6** (83.4 mg, 73%) as a colorless oil, along with the recovered **5c** (16.9 mg, 15%). **6:** $[\alpha]_D^{31} = +30.3^\circ (c = 0.47, CHCl_3)$; IR (film) 3471, 3043, 2929, 1749, 1458, 1362, 1254, 1101, 847, 739, 696 cm^{-1} ; $^1\text{H NMR}$ (500 MHz, $CDCl_3$) δ 7.36-7.14 (m, 20H), 4.95 (d, $J = 11.9\text{ Hz}$, 1H), 4.82 (d, $J = 11.9\text{ Hz}$, 1H), 4.75 (d, $J = 10.8\text{ Hz}$, 1H), 4.60-4.46 (m, 4H), 4.59 (s, 2H), 4.35 (d, $J = 11.6\text{ Hz}$, 1H), 3.74 (m, 1H), 3.68 (ddd, $J = 5.1, 4.9, 4.7\text{ Hz}$, 1H), 3.64-3.56 (m, 3H), 3.53-3.50 (m, 2H), 3.47-3.43 (m, 3H), 3.40-3.32 (m, 2H), 3.32 (s, 3H), 3.23 (dd, $J = 9.3, 9.3\text{ Hz}$, 1H), 2.16-2.10 (m, 2H), 1.97 (m, 1H), 1.86-1.79 (m, 2H), 1.76-1.66 (m, 2H), 1.63-1.55 (m, 1H), 0.87 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, $CDCl_3$) δ 139.0, 138.6, 138.5, 138.0, 128.3, 128.1, 127.8, 127.7, 127.6, 127.5, 127.0, 126.6, 125.7, 96.4, 86.9, 83.1, 82.7, 82.2, 78.5, 76.6, 76.2, 75.0, 74.9, 74.8, 73.3, 73.2, 71.4, 70.7, 64.1, 55.3, 35.5, 31.9, 28.3, 26.0, 23.6, 18.1, -3.4, -4.1; HRMS (FAB) calcd for $C_{51}H_{70}O_{10}SiNa [(M+Na)^+]$ 893.4636, found 893.4620.

Hydroxy Methyl Acetal 7. To a solution of $(COCl)_2$ (0.025 mL, 0.287 mmol) in CH_2Cl_2 (1 mL) at -78 °C was dropwise added DMSO (0.027 mL, 0.380 mmol). After 10 min, a solution of **6** (81.2 mg, 0.0933 mmol) in CH_2Cl_2 (1 mL) was added to the mixture and the resulting solution was stirred

at -78 °C for 40 min. The mixture was treated with Et₃N (0.104 mL, 0.747 mmol), and stirred at -78 °C for 10 min and then allowed to warm to 0 °C over 1 h. The resultant mixture was diluted with ethyl acetate, washed with 1N HCl, saturated aqueous NaHCO₃, H₂O and brine, dried (Na₂SO₄), filtered and evaporated to give the crude ketone, which was used in the next reaction without further purification.

A solution of the above ketone in MeOH-CH₂Cl₂ (4:1, 1 mL) was treated with *p*-TsOH·H₂O (35.5 mg, 0.187 mmol). The resultant mixture was stirred at room temperature for 18 h and then at 55 °C for 4 h. After cooling, the reaction mixture was quenched with aqueous saturated NaHCO₃. The solution was diluted with ethyl acetate, washed with aqueous saturated NaHCO₃ and brine, dried (Na₂SO₄), filtered, and evaporated. Flash chromatography on silica gel (30-40% ethyl acetate-hexane) afforded hydroxy methyl acetal **7** (55.4 mg, 82%) as a colorless oil: $[\alpha]_D^{31} = -47.4^\circ$ ($c = 0.23$, CHCl₃); IR (film) 3495, 3030, 2905, 1496, 1453, 1364, 1219, 1088, 737, 698 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.38-7.22 (m, 20H), 4.96 (d, $J = 11.1$ Hz, 1H), 4.90 (d, $J = 10.9$ Hz, 1H), 4.75 (d, $J = 11.1$ Hz, 1H), 4.58 (d, $J = 10.9$ Hz, 1H), 4.54-4.48 (m, 3H), 4.37 (d, $J = 11.9$ Hz, 1H), 3.81 (ddd, $J = 5.9, 5.9, 3.6$ Hz, 1H), 3.73-3.70 (m, 3H), 3.57 (dd, $J = 9.0, 8.9$ Hz, 1H), 3.51-3.44 (m, 3H), 3.39-3.35 (m, 2H), 3.26 (m, 1H), 3.26 (s, 3H), 3.12 (ddd, $J = 11.4, 9.6, 4.4$ Hz, 1H), 2.07-1.85 (m, 6H), 1.77-1.65 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 138.8, 138.4, 138.3, 138.1, 128.4, 128.3, 128.03, 128.00, 127.8, 127.7, 126.7, 99.2, 84.6, 83.7, 81.6, 80.5, 79.9, 78.7, 75.4, 75.1, 74.3, 74.2, 73.3, 71.5, 70.7, 61.2, 47.1, 34.2, 32.0, 25.9, 21.6; HRMS calcd for C₄₄H₅₂O₉Na [(M+Na)⁺] 747.3509, found 747.3502.

Olefin 8. A solution of hydroxy methyl acetal **7** (49.8 mg, 68.8 μmol) and Et₃N (0.05 mL, 0.358 mmol) in CH₂Cl₂-DMSO (4:1, 1 mL) was cooled to 0 °C and treated with SO₃·pyridine complex (43.8 mg, 0.275 mmol). The resulting mixture was stirred at 0 °C for 1.4 h and then at room temperature for 2 h. The reaction mixture was diluted with ethyl acetate, washed with 1N HCl, aqueous saturated NaHCO₃ and brine, dried (Na₂SO₄), filtered, and evaporated to give the crude aldehyde, which was used in the next reaction without further purification.

To a suspension of methyltriphenylphosphonium bromide (73.7 mg, 0.206 mmol) in THF (1 mL) at 0 °C was added NaHMDS (1M in THF, 0.193 mL, 0.193 mmol). After stirring for 30 min, a solution of the above aldehyde in THF-CH₂Cl₂ (5:7, 1.2 mL) was added to the ylide solution and the resultant mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched with aqueous saturated NH₄Cl, diluted with ethyl acetate, washed with H₂O and brine, dried (Na₂SO₄), filtered, and evaporated. Flash chromatography on silica gel (10-20% ethyl acetate-hexane) afforded olefin

8 (39.3 mg, 79%) as a colorless oil: $[\alpha]_D^{31} = -23.4^\circ$ ($c = 0.69$, CHCl_3); IR (film) 3024, 2902, 1637, 1495, 1454, 1363, 1215, 1080, 912, 741, 698 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.35-7.23 (m, 20H), 5.88 (ddt, $J = 17.2, 10.2, 6.6$ Hz, 1H), 5.08-5.03 (m, 2H), 4.96 (d, $J = 11.1$ Hz, 1H), 4.90 (d, $J = 10.8$ Hz, 1H), 4.75 (d, $J = 11.1$ Hz, 1H), 4.59 (d, $J = 10.8$ Hz, 1H), 4.55-4.47 (m, 3H), 4.38 (d, $J = 11.8$ Hz, 1H), 3.82 (ddd, $J = 6.0, 5.9, 3.8$ Hz, 1H), 3.69 (m, 1H), 3.54 (dd, $J = 6.7, 6.5$ Hz, 1H), 3.49 (dd, $J = 10.2, 6.0$ Hz, 1H), 3.48 (dd, $J = 12.1, 4.5$ Hz, 1H), 3.39 (dd, $J = 10.2, 5.9$ Hz, 1H), 3.38-3.31 (m, 2H), 3.28 (m, 1H), 3.27 (s, 3H), 3.08 (ddd, $J = 11.3, 9.7, 4.3$ Hz, 1H), 2.55 (m, 1H), 2.26 (m, 1H), 2.08 (ddd, $J = 11.0, 4.5, 4.3$ Hz, 1H), 2.01-1.85 (m, 4H), 1.75 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 138.9, 138.5, 138.42, 138.36, 134.7, 128.4, 128.3, 128.0, 127.9, 127.64, 127.60, 127.5, 116.9, 99.1, 84.7, 84.0, 81.3, 80.8, 79.1, 78.7, 75.2, 75.1, 74.5, 74.1, 73.3, 71.6, 70.6, 47.1, 36.1, 32.0, 26.1, 21.6; HRMS (FAB) calcd for $\text{C}_{44}\text{H}_{52}\text{O}_8\text{Na}$ $[(\text{M}+\text{Na})^+]$ 743.3560, found 743.3558.

Tricyclic Ether 9. To a solution of olefin **8** (29.1 mg, 40.4 μmol) in $\text{CH}_3\text{CN}-\text{CH}_2\text{Cl}_2$ (5:3, 0.8 mL) at 0 $^\circ\text{C}$ were added Et_3SiH (0.052 mL, 0.326 mmol) followed by $\text{BF}_3\cdot\text{OEt}_2$ (0.015 mL, 0.118 mmol). After stirring for 1.5 h, the reaction mixture was quenched with aqueous saturated with NaHCO_3 . The solution was diluted with ethyl acetate, washed with aqueous saturated with NaHCO_3 and brine, dried (Na_2SO_4), filtered, and evaporated. Flash chromatography on silica gel (15-20% ethyl acetate-hexane) afforded tricyclic ether **9** (24.1 mg, 86%) as a white solid: $[\alpha]_D^{31} = +4.65^\circ$ ($c = 0.97$, CHCl_3); IR (film) 3030, 2866, 1954, 1732, 1643, 1495, 1452, 1363, 1211, 1072, 910, 741, 698 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.36-7.26 (m, 20H), 5.87 (ddt, $J = 17.2, 10.1, 6.6$ Hz, 1H), 5.09-5.04 (m, 2H), 4.97 (d, $J = 11.2$ Hz, 1H), 4.93 (d, $J = 10.8$ Hz, 1H), 4.75 (d, $J = 11.2$ Hz, 1H), 4.61 (d, $J = 10.9$ Hz, 1H), 4.54 (d, $J = 12.6$ Hz, 1H), 4.53 (s, 2H), 4.33 (d, $J = 11.8$ Hz, 1H), 3.77 (ddd, $J = 4.9, 4.9, 4.9$ Hz, 1H), 3.70 (m, 1H), 3.59 (dd, $J = 8.6, 8.6$ Hz, 1H), 3.47-3.44 (m, 2H), 3.37-3.26 (m, 3H), 3.15-3.07 (m, 3H), 2.57 (m, 1H), 2.37 (ddd, $J = 11.5, 4.3, 4.3$ Hz, 1H), 2.25 (m, 1H), 2.05 (m, 1H), 1.91-1.89 (m, 2H), 1.67 (m, 1H), 1.55 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 139.0, 138.5, 138.4, 138.3, 134.7, 128.35, 128.32, 128.27, 128.0, 127.9, 127.62, 127.59, 127.53, 127.45, 116.9, 84.2, 83.7, 82.4, 81.9, 81.0, 79.7, 79.0, 78.3, 75.1, 74.9, 74.0, 73.2, 71.6, 70.7, 37.1, 36.1, 26.4, 23.7; HRMS (FAB) calcd for $\text{C}_{44}\text{H}_{50}\text{O}_7\text{Na}$ $[(\text{M}+\text{Na})^+]$ 713.3454, found

713.3450.

Alcohol 10. A solution of tricyclic ether 9 (24.5 mg, 35.5 μ mol) in CH₂Cl₂ (1 mL) was cooled to 0 °C and treated with iodine (90.1 mg, 0.355 mmol). The resultant solution was allowed to warm to room temperature and stirred at room temperature for 6 h. After cooling to 0 °C, the reaction was quenched with saturated aqueous Na₂SO₃. The mixture was diluted with ethyl acetate, washed with brine, dried (Na₂SO₄), filtered, and evaporated. Flash chromatography on silica gel (5-20% ethyl acetate-hexane) afforded cyclic iodoether (22.3 mg, 87%) as a white solid.

To a solution of the above iodoether (22.3 mg, 30.7 μ mol) in ether-MeOH (2:1, 1.5 mL) were sequentially added zinc powder (18.1 mg, 0.277 mmol) and acetic acid (3 μ L, 52 μ mol). The resulting suspension was stirred at room temperature overnight and filtered through a pad of celite. Evaporation of the solvent and flash chromatography on silica gel (5-20% ethyl acetate-hexane) afforded alcohol 10 (17.7 mg, 96%) as a white solid, which was used without further purification.

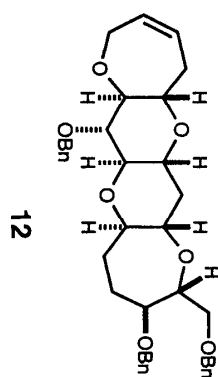
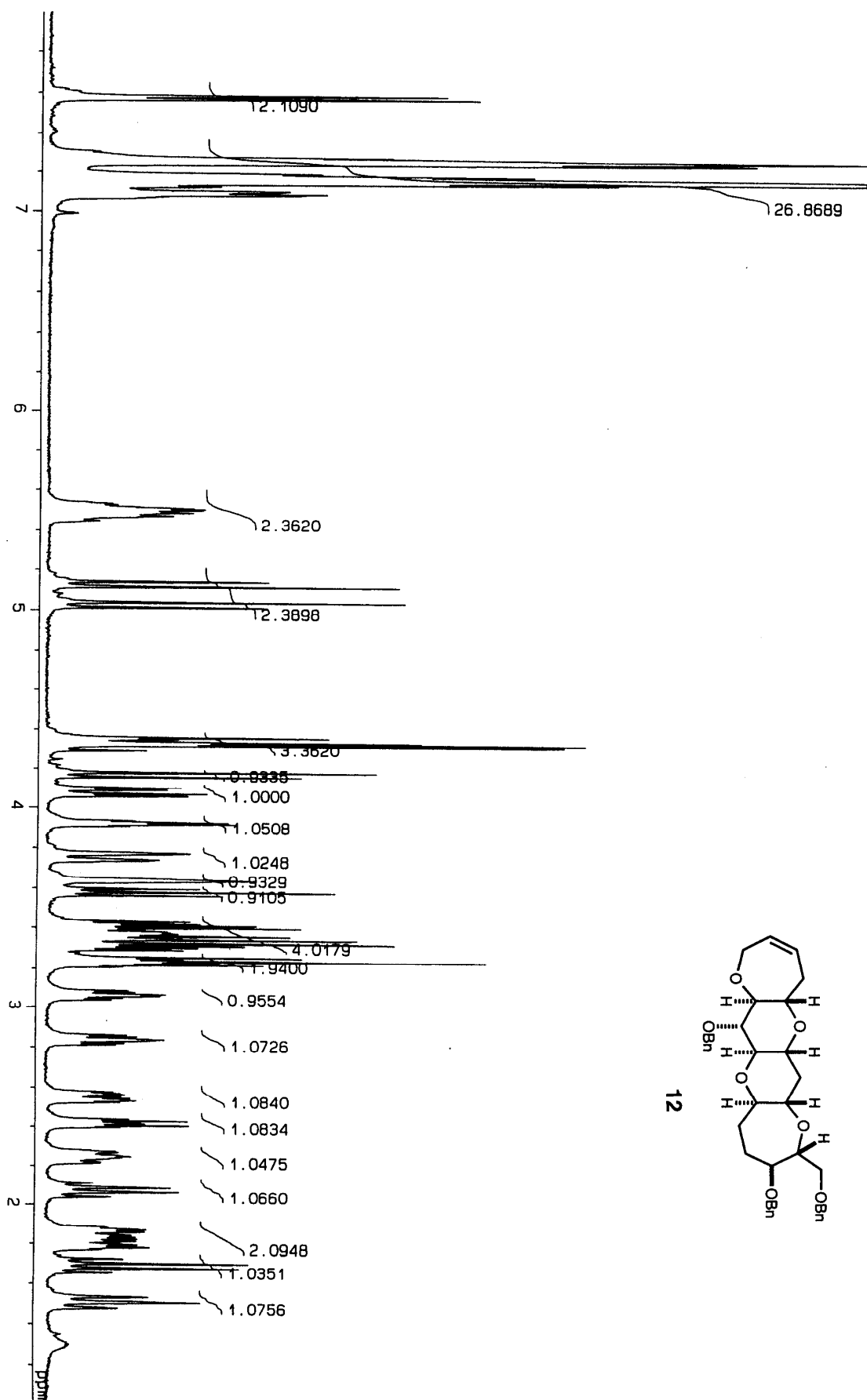
Bisolefin 11. To a solution of alcohol 10 (17.7 mg, 29.5 μ mol) in DMF (0.5 mL) at 0 °C was added NaHMDS (1M in THF, 0.12 mL, 0.12 mmol). After stirring for 1 h, allyl bromide (8 mL, 0.09 mmol) was added to the solution. The resultant mixture was stirred at 0 °C for 4 h and then allowed to warm to room temperature overnight. The reaction was quenched with aqueous saturated NH₄Cl at 0 °C. The mixture was diluted with ethyl acetate, washed with H₂O and brine, dried (Na₂SO₄), filtered, and evaporated. Flash chromatography on silica gel (10% ethyl acetate-hexane) afforded bisolefin **11** (14.7 mg, 78%) as a white solid: $[\alpha]_D^{31} = -5.38^\circ$ ($c = 0.22$, CHCl₃); IR (film) 3028, 2864, 1643, 1452, 1362, 1074, 914, 741, 696 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.37-7.24 (m, 15H), 5.93-5.82 (m, 2H), 5.22 (dd, $J = 17.0, 2.0$ Hz, 1H), 5.14-5.02 (m, 3H), 4.91 (d, $J = 11.0$ Hz, 1H), 4.71 (d, $J = 11.0$ Hz, 1H), 4.53 (d, $J = 13.0$ Hz, 1H), 4.52 (s, 2H), 4.36 (dddd, $J = 12.0, 5.8, 1.3, 1.3$ Hz, 1H), 4.31 (d, $J = 11.5$ Hz, 1H), 4.09 (dddd, $J = 12.0, 5.8, 1.3, 1.3$ Hz, 1H), 3.74 (m, 1H), 3.67 (m, 1H), 3.48 (dd, $J = 8.8, 8.8$ Hz, 1H), 3.46-3.39 (m, 2H), 3.33-3.26 (m, 2H), 3.13-3.01 (m, 4H), 2.54 (m, 1H), 2.34 (m, 1H), 2.23 (ddd, $J = 7.3, 7.3, 7.3$ Hz, 1H), 1.91-1.84 (m, 2H), 1.64 (m, 1H), 1.54 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 139.0, 138.4, 138.3, 135.0, 134.7,

128.3, 128.26, 127.9, 127.63, 127.60, 127.55, 127.46, 116.9, 84.0, 83.7, 82.2, 81.8, 81.0, 79.8, 79.0, 78.2, 74.9, 74.2, 74.0, 73.2, 71.5, 70.6, 37.1, 36.1, 26.3, 23.6; HRMS (FAB) calcd for C₄₀H₄₈O₇Na [(M+Na)⁺] 663.3298, found 663.3290.

Tetracyclic Ether 12. To a solution of diene **11** (8.2 mg, 13 μmol) in CH₂Cl₂ (2 mL) was added a solution of Grubbs' catalyst (2.1 mg, 5.2 μmol) in CH₂Cl₂ (0.5 mL). The resultant solution was stirred at room temperature for 2.5 h. Evaporation of the solvent and flash chromatography on silica gel (20% ethyl acetate-hexane) afforded tetracyclic ether **12** (10.2 mg, quant.) as a white solid: [α]_D²⁵ = -0.12° (*c* = 0.41, CHCl₃); IR (film) 3028, 2865, 1739, 1450, 1365, 1086, 741, 698 cm⁻¹; ¹H NMR (500 MHz, C₆D₆) δ 7.40-7.15 (m, 15H), 5.63-5.53 (m, 2H), 5.23- 5.10 (m, 2H), 4.45-4.38 (m, 3H), 4.25 (d, *J* = 11.9 Hz, 1H), 4.16 (dd, *J* = 15.6, 5.3 Hz, 1H), 4.01 (m, 1H), 3.84 (dd, *J* = 15.6, 2.4 Hz, 1H), 3.73 (m, 1H), 3.67 (dd, *J* = 8.9, 8.6 Hz, 1H), 3.52-3.38 (m, 3H), 3.35-3.29 (m, 2H), 3.15 (ddd, *J* = 10.7, 9.2, 4.3 Hz, 1H), 2.93 (ddd, *J* = 11.6, 9.5, 4.3 Hz, 1H), 2.64 (ddd, *J* = 16.2, 7.6, 4.0 Hz, 1H), 2.51 (ddd, *J* = 11.6, 4.6, 4.3 Hz, 1H), 2.33 (m, 1H), 2.16 (dddd, *J* = 11.9, 11.9, 11.9, <1 Hz, 1H), 1.97-1.86 (m, 2H), 1.78 (ddd, *J* = 11.6, 11.3, 11.3 Hz, 1H), 1.60 (dddd, *J* = 14.3, 13.4, <1, <1 Hz, 1H); ¹³C NMR (125 MHz, C₆D₆) δ 140.6, 139.11, 139.10, 131.7, 128.6, 128.4, 128.3, 127.91, 127.89, 127.8, 127.7, 127.4, 126.5, 87.9, 83.8, 82.7, 82.2, 82.1, 79.4, 78.8, 77.2, 75.2, 73.8, 73.3, 72.0, 70.8, 68.5, 38.0, 35.2, 26.7, 23.5; HRMS (FAB) calcd for C₃₈H₄₄O₇Na [(M+Na)⁺] 635.2985, found 635.2977.

¹H NMR Spectrum for Compound **12** (500 MHz, C₆D₆)

MI-I-182/C606/2-18-1999



¹³C NMR Spectrum for Compound **12** (125 MHz, C₆D₆)

