TOTAL SYNTHESIS OF THE POLYENE-POLYOL MACROLIDE RK-397, FEATURING CROSS-COUPPLINGS OF ALKYNYLEPOXIDE MODULES

Svetlana A. Burova and Frank E. McDonald*

Department of Chemistry, Emory University, 1515 Pierce Drive, Atlanta, GA 30322

SUPPORTING INFORMATION

Complete experimental details and compound characterizations, crystallographic data for a derivative of compound **23**, discussion of attempted hydration from iodocyclization of the *tert*-butylcarbonate derivative of **38**, and comparison of spectral data of synthetic and natural RK-397 (**4**) and tetraacetone derivative **52**.

General: ^1H NMR and ^{13}C NMR spectra were measured in CDCl_3 on INOVA 400 or INOVA 600 NMR spectrometers. All proton NMR spectra were recorded at 400 or 600 MHz and were referenced with residual chloroform (7.27 ppm) or residual methanol (4.87 ppm). All carbon NMR spectra were measured at 100 or 150 MHz and were referenced with 77.2 ppm resonance of residual chloroform. Infrared spectra were recorded on sodium chloride discs on Mattson Genesis II FT-IR. High - resolution FAB mass spectra were collected on JEOL SX102 at 6kV-Xe using 3-nitrobenzyl alcohol, in some cases with addition of Lil as a matrix. MALDI mass spectra were collected on Voyager-STR MALDI time-of flight mass spectrometer using 2, 5-dihydroxybenzoic acid. Elemental analyses were performed by Atlantic Microlab, Inc in Norcross, GA. Optical rotations were measured using a 10 cm cell with Perkin-Elmer Polarimeter 241 MC. All reactions were conducted in oven-dried (125°C) glassware under an atmosphere of dry argon. All common reagents and solvents were obtained from commercial suppliers and used without further purification unless otherwise indicated. Solvents were dried by standard methods. Flash chromatography was carried out on standard grade silica gel 60Å, 32-63 μ .

(3S,4S)-2,4-Dimethyl-3-(*p*-methoxybenzyloxy)-5-hexene (16): (3S,4S)-2,4-Dimethylhex-5-en-3-ol¹ (**15**, 5.0 g, 75% pure, 29.3 mmol) and freshly prepared 4-methoxybenzyltrichloroacetimidate² were dissolved in CH₂Cl₂ (40 mL), and 10-camphorsulfonic acid (930 mg, 3.98 mmol) was added. The mixture was stirred for 16 h, diluted with water and extracted with ether. The organic fractions were dried with MgSO₄, filtered, concentrated and chromatographed with pentane – ether (98 : 2). PMBn ether **16** was isolated in 67% yield (4.9 g).

¹H NMR (CDCl₃, 600 MHz): δ 7.29 (d, 2H, *J*= 8.4 Hz), 6.88 (d, 2H, *J*= 8.4 Hz), 5.85 (m, 1H), 5.06 (d, 1H, *J*= 17.4 Hz), 4.98 (d, 1H, *J*= 9.0 Hz), 4.54 (d, 1H, *J*= 10.2 Hz), 4.49 (d, 1H, *J*=10.2 Hz), 3.81 (s, 3H), 3.01 (t, 1H, *J*= 5.4 Hz), 2.45 (m, 1H), 1.87 (m, 1H), 1.08 (d, 3H, *J*= 6.6 Hz), 0.96 (m, 6H). ¹³C NMR (CDCl₃, 150 MHz): δ 159.2, 142.9, 131.5, 129.4, 113.9, 113.8, 88.6, 75.0, 55.5, 41.3, 31.2, 20.6, 17.7, 15.6. HRMS (FAB+): Calcd. for C₁₆H₂₄O₂Li ([M+Li]⁺), 255.1936. Found, 255.1937.

(4S,5S)-4,6-Dimethyl-5-(*p*-methoxybenzyloxy)-*trans*-hept-2-enoate, methyl ester (18). *p*-Methoxybenzyl ether **16** (4.7 g, 19 mmol) and methyl acrylate (5.1 mL, 57 mmol) were dissolved in CH₂Cl₂ (15 mL), and (4,5-dihydroIMes)Cl₂Ru=CH-(*o*-O*i*Pr)C₆H₄ (**25**, 250 mg, 42 μmol) was added as a solid in one portion. The reaction was refluxed for 5 h then stirred for 2 days at ambient temperature and concentrated. The residue was chromatographed with pentane - ether (92.5 : 7.5) producing 58% yield (3.4 g) of **18**.

¹H NMR (CDCl₃, 600 MHz): δ 7.27 (d, 2H, *J*= 7.8 Hz), 7.01 (dd, 1H, *J*= 15.6; 5.4 Hz), 6.78 (d, 2H, *J*= 7.8 Hz), 5.86 (d, 1H, *J*= 15.6 Hz), 4.48 (s, 2H), 3.81 (s, 3H), 3.75 (s, 3H), 3.08 (t, 1H, *J*= 5.4Hz), 2.62 (m, 1H), 1.82 (m, 1H), 1.12 (d, 3H, *J*= 6.6 Hz), 0.96 (m, 6H).

1. (a) Dreher, S. D.; Leighton, J. L. *J. Am. Chem. Soc.* **2001**, 123, 341. (b) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, 108, 5919. (c) For *ent*-**15**, see: Ghosh, A. K.; Liu, W. *J. Org. Chem.* **1997**, 62, 7908.

2. Preparation of 4-methoxybenzyltrichloroacetimidate: 4-methoxybenzyl alcohol (5.0 mL, 40 mmol) was dissolved in ether (15 mL), and NaH (60% in mineral oil, 400 mg, ca. 10.0 mmol) was added. The reaction was stirred for 30 min then cooled to 0°C, and Cl₃CCN (4.0 mL, 40 mmol) was slowly added. The mixture was slowly warmed to room temperature and stirred for 1.5 h, then diluted with saturated NaHCO₃ and extracted with ether. The organic fractions were dried with MgSO₄, filtered and concentrated producing crude 4-methoxybenzyltrichloroacetimidate (ca. 39 mmol).

^{13}C NMR (CDCl_3 , 150 MHz): δ 167.4, 159.3, 152.9, 131.0, 129.5, 120.2, 113.9, 87.6, 75.0, 55.5, 51.7, 40.0, 31.5, 20.5, 17.7, 14.9. IR (neat, cm^{-1}): 2960 (s, br), 2870 (s, br), 1725 (s), 1655 (s), 1630 (s), 1515 (s), 1465 (s), 1435 (s), 1300 (s), 1250 (s, br), 1175 (s, br), 1060 (s), 990 (s). HRMS (FAB $^{+}$): Calcd. for $\text{C}_{18}\text{H}_{26}\text{O}_4$ ($[\text{M}]^{+}$), 306.1831. Found, 306.1856. Anal. Calcd. for $\text{C}_{18}\text{H}_{26}\text{O}_4$: C, 70.56; H, 8.55. Found: C, 70.26, H, 8.66. $[\alpha]_{\text{D}}^{+15}$ (c 0.990, CHCl_3).

(4S,5S)-4,6-Dimethyl-5-(*p*-methoxybenzyloxy)-*trans*-hept-2-enal (20): 1M solution of DIBAL-H in CH_2Cl_2 (32.4 mL, 32.4 mmol) was added dropwise to a solution of methyl ester **18** (3.3 g, 10.8 mmol) in CH_2Cl_2 (50 mL) at -78°C . The mixture was stirred at -78°C for 30 min, then quenched with anhydrous EtOAc (35 mL). After additional stirring at -78°C for 30 min, the reaction mixture was poured into saturated aqueous solution of sodium- potassium tartrate and stirred 16 h at room temperature. The layers were separated aqueous fractions were extracted with ether and ethyl acetate. Combined organic fractions were dried with MgSO_4 , filtered, concentrated and chromatographed with pentane – ether (8 : 2) to yield (4S,5S)-4,6-dimethyl-5-(*p*-methoxybenzyloxy)-*trans*-hept-2-en-1-ol (2.73 g, 91% yield).

^1H NMR (CDCl_3 , 600 MHz): δ 7.28 (d, 2H, J = 8.4 Hz), 6.88 (d, 2H, J = 8.4 Hz), 5.78 (m, 2H), 4.51 (s, 2H), 4.10 (d, 2H, J = 4.8 Hz), 3.81 (s, 3H), 2.99 (t, 1H, J = 6.0 Hz), 2.47 (m, 1H), 1.85 (m, 1H), 1.07 (d, 3H, J = 6.6 Hz), 0.96 (m, 6H). ^{13}C NMR (CDCl_3 , 150 MHz): δ 159.2, 136.8, 131.4, 129.4, 128.3, 113.8, 88.5, 75.0, 64.0, 55.5, 39.8, 31.2, 20.6, 17.7, 15.9. IR (neat, cm^{-1}): 3390 (m, br), 2960 (s, br), 2870 (s, br), 1610 (s), 1510 (s), 1465 (m), 1380 (m), 1300 (m), 1250 (s), 1170 (m), 1080 (s, br), 1040 (s, br), 955 (m), 820 (m). HRMS (FAB $^{+}$): Calcd. for $\text{C}_{17}\text{H}_{26}\text{O}_3\text{Li}$ ($[\text{M}+\text{Li}]^{+}$), 285.2042. Found, 285.2029. Anal. Calcd. for $\text{C}_{17}\text{H}_{26}\text{O}_3$: C, 73.34; H, 9.41. Found: C, 73.24, H, 9.53. $[\alpha]_{\text{D}}^{+8}$ (c 1.000, CHCl_3).

(4S,5S)-4,6-Dimethyl-5-(*p*-methoxybenzyloxy)-*trans*-hept-2-en-1-ol (2.67 g, 9.63 mmol) and Et_3N (8.75 mL) were dissolved in CH_2Cl_2 (40 mL) and cooled to 0°C . A solution of SO_3 -pyridine complex (4.6 g, 28.9 mmol) in DMSO (20 mL) was added slowly at 0°C . After addition, the reaction was stirred at ambient temperature for 4 h, then diluted with

saturated aqueous NaHCO₃ and extracted with CH₂Cl₂ and Et₂O. The organic fractions were dried with MgSO₄, filtered and concentrated. Aldehyde **20** (2.37 g, 89% yield) was purified by flash chromatography with a mixture of pentane – ether (8 : 2).

¹H NMR (CDCl₃, 600 MHz): δ 9.47 (d, 1H, *J* = 7.8 Hz), 7.26 (d, 2H, *J* = 8.4 Hz), 6.88 (d, 2H, *J* = 8.4 Hz), 6.84 (dd, 1H, *J* = 16.2; 7.8 Hz), 6.12 (dd, 1H, *J* = 16.2; 8.4 Hz), 4.54 (d, 1H, *J* = 10.8 Hz), 4.46 (d, 1H, *J* = 10.8 Hz), 3.81 (s, 3H), 3.14 (t, 1H, *J* = 5.4 Hz), 2.75 (m, 1H), 1.85 (m, 1H), 1.16 (d, 3H, *J* = 6.6 Hz), 0.98 (m, 6H). ¹³C NMR (CDCl₃, 150 MHz): δ 194.4, 162.2, 159.4, 132.0, 130.8, 129.5, 113.9, 87.3, 74.9, 55.4, 40.2, 31.5, 20.4, 18.1, 14.4. IR (neat, cm⁻¹): 2960 (s, br), 2875 (s, br), 2730 (w), 1690 (s), 1630 (m), 1610 (s), 1515 (s), 1465 (s), 1380 (w), 1300 (m), 1250 (s), 1175 (s), 1110-1035 (s, br), 980 (m), 825 (s). HRMS (FAB+): Calcd. for C₁₇H₂₄O₃Li ([M+Li]⁺), 283.1885. Found, 283.1894. Anal. Calcd. for C₁₇H₂₄O₃: C, 73.88; H, 8.75. Found: C, 73.97, H, 8.87. [α]_D +14 (c 1.040, CHCl₃).

Diol (22). Et₃N (3.4 mL, 24.7 mmol) and Et₂O (30 mL) were added to a 1M hexane solution of freshly prepared (-)-lpc₂BOTf³ (25 mL, 25 mmol). The mixture was cooled to -78°C and a solution of 4-(trimethylsilyl)-3-butyne-2-one (3.37 mL, 20.5 mmol) in Et₂O (6 mL) was slowly injected over 5 min. After additional stirring for 3 h at -78°C, a solution of aldehyde **20** (2.27 g, 8.22 mmol) in Et₂O (6 mL) was added via cannula to the freshly formed solution of enol borinate **21**. The reaction was slowly warmed to -30°C and stirred for 17 h, then it was cooled to -70°C and solid NaBH₄ (3.1 g, 82.2 mmol) was added in one portion followed by dropwise addition of methanol (15 mL). After 10 h at -70°C, the reaction was diluted with AcOH (9 mL) and left stirring overnight at room temperature. H₂O₂ (15 mL) and 3N NaOH were slowly (Caution! Exothermic reaction!) and simultaneously added to the reaction from two different syringes at 0°C. After addition, the mixture was left for 10-20 min at 0°C, then for 5 h at room temperature. The reaction was quenched with a saturated aqueous solution of Na₂SO₃ at 0°C (Caution! Exothermic reaction!), then was extracted with ether, dried with Na₂SO₄. The

3. (a) Paterson, I.; Goodman, J. M. *Tetrahedron Lett.* **1989**, 30, 997. (b) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, 46, 4663.

reaction was filtered, concentrated and chromatographed with mixture of pentane – ether (75 : 25 → 70 : 30) to yield diol **22** (3.3 g, 97% yield).

^1H NMR (CDCl_3 , 600 MHz): δ 7.28 (d, 2H, J = 8.4 Hz), 6.88 (d, 2H, J = 8.4 Hz), 5.69 (dd, 1H, J = 7.8 Hz), 5.51 (dd, 1H, J = 15.0, 6.6 Hz), 4.60 (dd, 1H, J = 8.4, 4.2 Hz), 4.50 (s, 2H), 4.35 (m, 1H), 3.81 (s, 3H), 2.98 (t, 1H, J = 5.4 Hz), 2.44 (m, 1H), 1.97 (m, 1H), 1.88 (m, 1H), 1.84 (m, 1H), 1.07 (d, 3H, J = 7.2 Hz), 0.95 (t, 6H, J = 7.2 Hz). ^{13}C NMR (CDCl_3 , 150 MHz): δ 159.2, 136.0, 131.4, 131.2, 129.4, 113.9, 106.1, 89.9, 88.5, 75.0, 72.3, 62.3, 55.5, 44.4, 39.8, 31.2, 20.6, 17.8, 15.9, 0.0. IR (neat, cm^{-1}): 3390 (s, br), 2960 (s, br), 2900 (s), 2870 (s), 2170 (m), 1615 (s), 1515 (s), 1465 (s), 1380 (m), 1300 (m), 1250 (s), 1170 (m), 1065 (s, br), 980 (m), 845 (s), 760 (m). HRMS (FAB+): Calcd. for $\text{C}_{17}\text{H}_{24}\text{O}_4\text{SiLi}$ ($[\text{M}+\text{Li}]^+$), 425.2699. Found, 425.2701. Anal. Calcd. for $\text{C}_{24}\text{H}_{38}\text{O}_4\text{Si}$: C, 68.86; H, 9.15. Found: C, 68.33; H, 9.22. $[\alpha]_{\text{D}}^{+10}$ (c 0.885, CHCl_3).

Monoacetone 23. Diol **22** (3.2 g, 7.66 mmol) was dissolved in methanol (15 mL), and K_2CO_3 (560 mg, 4.0 mmol) was added, in order to remove the alkynyl trimethylsilyl group. The reaction was stirred at ambient temperature for 3 h, then diluted with water and extracted with ether. The organic fractions were dried with Na_2SO_4 , filtered and concentrated to give a crude sample of the terminal alkyne. This material was dissolved in 2,2-dimethoxypropane (15 mL), $\text{TsOH}\cdot\text{H}_2\text{O}$ (250 mg) and 3 Å molecular sieves (300 mg) were added. The mixture was stirred at room temperature for 17 h, then diluted with Et_3N (1 mL), filtered and concentrated. The residue was chromatographed with pentane–ether (85:15 → 8:2) to produce two fractions of diol **23**: first fraction: dr, 1 : 1.4 (desired diastereomer as a minor compound) (360 mg, 12%) and a more polar second fraction: dr, 6.25 : 1 (desired diastereomer as a major compound) (2.22 g, 75%).

^1H NMR (CDCl_3 , 600 MHz): δ 7.29 (d, 2H, J = 8.4 Hz), 6.88 (d, 2H, J = 8.4 Hz), 5.69 (dd, 1H, J = 15.6, 7.8 Hz), 5.46 (dd, 1H, J = 15.6, 6.6 Hz), 4.69 (m, 1H), 4.49 (s, 2H), 4.31 (m, 1H), 3.81 (s, 3H), 2.97 (t, 1H, J = 6.0 Hz), 2.48 (s, 1H), 2.45 (m, 1H), 1.83 (m, 1H), 1.73 (m, 2H), 1.49 (s, 3H), 1.48 (s, 3H), 1.07 (d, 3H, J = 6.6 Hz), 0.95 (d, 6H, J = 6.6 Hz). ^{13}C NMR (CDCl_3 , 150 MHz): δ 159.2, 136.8, 131.3, 129.5, 129.0, 113.8, 99.6, 88.5, 82.6, 75.0, 73.0, 69.8, 60.2, 55.4, 39.7, 37.5, 31.2, 30.3, 20.5, 19.6, 17.9, 15.4. IR (neat, cm^{-1}): 3285 (m), 2960 (s), 2935 (s), 2870 (s), 1615 (s), 1515 (s), 1465 (s), 1380 (s),

1300 (s), 1250 (s), 1200 (s), 1700 (s), 1085 (s), 970 (s), 920 (m), 875 (m), 825 (s). HRMS (FAB⁺): Calcd. for C₂₄H₃₄O₄Li ([M+Li]⁺), 393.2617. Found, 393.2625. Anal. Calcd. for C₂₄H₃₄O₄: C, 74.58; H, 8.87. Found: C, 74.46; H, 8.97. [α]_D +36 (c 0.740, CHCl₃).

Structure determination by crystallography: **Compound 23** was subjected to standard oxidative deprotection of the PMBn ether with DDQ in wet CH₂Cl₂. A suitable crystal of the C31-alcohol corresponding to deprotection of **23** was coated with Paratone N oil, suspended in small fiber loop and placed in a coated nitrogen stream at 173 K on a Bruker D8 SMART 1000 CCD sealed tube diffractometer with graphite monochromated CuK α (1.54178 Å) radiation. Data were measured using series of combination of phi and omega scans with 10 seconds frame exposures. There were two unique molecules in the asymmetric unit of the cell that were the same in chemical composition, but different in their orientation of the terminal chain group, the CH(OH)-CH(CH₃)₂ end groups were rotated by 120°C about C(7)- C(8) bond in the two different conformers.

Thermal ellipsoid diagram:

Table 1. Crystal data and structure refinement.

Empirical formula	C ₁₆ H ₂₆ O ₃	
Formula weight	266.37	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	C2	
Unit cell dimensions	a = 40.5363(8) Å b = 7.6077(1) Å c = 10.7656(2) Å	$\alpha = 90^\circ$. $\beta = 96.553(2)^\circ$. $\gamma = 90^\circ$.
Volume	3298.29(10) Å ³	
Z	8	
Density (calculated)	1.073 Mg/m ³	
Absorption coefficient	0.574 mm ⁻¹	
F(000)	1168	
Crystal size	0.19 x 0.17 x 0.13 mm ³	
Theta range for data collection	4.13 to 66.60°	
Index ranges	-43 ≤ h ≤ 48, -8 ≤ k ≤ 8, -11 ≤ l ≤ 11	
Reflections collected	7922	
Independent reflections	4569 [R(int) = 0.0306]	
Completeness to theta = 66.60°	93.4 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	4569 / 1 / 551	
Goodness-of-fit on F ²	1.063	
Final R indices [I > 2σ(I)]	R1 = 0.0301, wR2 = 0.0655	
R indices (all data)	R1 = 0.0355, wR2 = 0.0698	
Absolute structure parameter	-0.12(15)	
Largest diff. peak and hole	0.138 and -0.168 e.Å ⁻³	

Table 2. Atomic coordinates (× 10⁴) and equivalent isotropic displacement parameters (Å² × 10³). U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
C(1A)	1867(1)	8635(3)	5067(2)	39(1)
C(2A)	1903(1)	6379(3)	6650(2)	32(1)
C(3A)	1696(1)	5169(3)	5740(2)	32(1)
C(4A)	1469(1)	6257(3)	4808(2)	31(1)
C(5A)	1300(1)	5072(3)	3821(2)	33(1)
C(6A)	979(1)	4742(3)	3671(2)	32(1)
C(7A)	812(1)	3351(3)	2831(2)	32(1)
C(8A)	664(1)	1958(3)	3651(2)	29(1)

C(9A)	531(1)	295(3)	2979(2)	34(1)
C(10A)	1659(1)	9914(3)	5725(2)	50(1)
C(11A)	2099(1)	9540(4)	4279(3)	60(1)
C(12A)	2147(1)	5375(3)	7472(2)	39(1)
C(13A)	2331(1)	4485(3)	8112(2)	52(1)
C(14A)	554(1)	4126(3)	1843(2)	44(1)
C(15A)	791(1)	-563(3)	2265(2)	46(1)
C(16A)	415(1)	-988(3)	3913(3)	51(1)
O(1A)	1661(1)	7523(2)	4228(1)	36(1)
O(2A)	2077(1)	7601(2)	5947(1)	37(1)
O(3A)	417(1)	2772(2)	4310(1)	39(1)
C(1B)	8237(1)	9060(3)	9(2)	33(1)
C(2B)	8189(1)	6484(3)	-1290(2)	31(1)
C(3B)	8426(1)	5500(3)	-335(2)	32(1)
C(4B)	8661(1)	6812(3)	387(2)	29(1)
C(5B)	8865(1)	5969(3)	1478(2)	33(1)
C(6B)	9187(1)	5722(2)	1584(2)	30(1)
C(7B)	9391(1)	4879(3)	2678(2)	31(1)
C(8B)	9567(1)	3220(3)	2288(2)	29(1)
C(9B)	9338(1)	1824(3)	1632(2)	36(1)
C(10B)	8413(1)	10210(3)	-869(2)	42(1)
C(11B)	8022(1)	10132(4)	770(2)	48(1)
C(12B)	7937(1)	5309(3)	-1934(2)	39(1)
C(13B)	7747(1)	4342(3)	-2467(2)	55(1)
C(14B)	9645(1)	6202(3)	3280(3)	49(1)
C(15B)	9094(1)	1092(4)	2473(3)	53(1)
C(16B)	9542(1)	358(3)	1138(2)	53(1)
O(1B)	8470(1)	8170(2)	891(1)	33(1)
O(2B)	8021(1)	7827(2)	-671(1)	33(1)
O(3B)	9768(1)	2462(2)	3334(1)	39(1)

Table 3. Bond lengths [Å] and angles [°]

C(1A)-O(1A)	1.433(2)	C(4A)-O(1A)	1.428(2)
C(1A)-O(2A)	1.433(2)	C(4A)-C(5A)	1.498(2)
C(1A)-C(11A)	1.503(3)	C(5A)-C(6A)	1.316(2)
C(1A)-C(10A)	1.517(3)	C(6A)-C(7A)	1.502(2)
C(2A)-O(2A)	1.433(2)	C(7A)-C(14A)	1.524(3)
C(2A)-C(12A)	1.465(3)	C(7A)-C(8A)	1.543(3)
C(2A)-C(3A)	1.525(3)	C(8A)-O(3A)	1.435(2)
C(3A)-C(4A)	1.525(3)	C(8A)-C(9A)	1.525(3)

C(9A)-C(16A)	1.515(3)	C(6A)-C(7A)-C(8A)	108.48(15)
C(9A)-C(15A)	1.518(3)	C(14A)-C(7A)-C(8A)	112.61(16)
C(12A)-C(13A)	1.171(3)	O(3A)-C(8A)-C(9A)	111.28(15)
C(1B)-O(2B)	1.428(2)	O(3A)-C(8A)-C(7A)	108.96(15)
C(1B)-O(1B)	1.429(2)	C(9A)-C(8A)-C(7A)	115.97(16)
C(1B)-C(11B)	1.505(3)	C(16A)-C(9A)-C(15A)	110.2(2)
C(1B)-C(10B)	1.523(3)	C(16A)-C(9A)-C(8A)	109.82(17)
C(2B)-O(2B)	1.433(2)	C(15A)-C(9A)-C(8A)	111.61(17)
C(2B)-C(12B)	1.470(3)	C(13A)-C(12A)-C(2A)	176.0(2)
C(2B)-C(3B)	1.522(3)	C(4A)-O(1A)-C(1A)	115.48(13)
C(3B)-C(4B)	1.529(3)	C(2A)-O(2A)-C(1A)	114.55(13)
C(4B)-O(1B)	1.435(2)	O(2B)-C(1B)-O(1B)	110.38(15)
C(4B)-C(5B)	1.501(2)	O(2B)-C(1B)-C(11B)	105.90(17)
C(5B)-C(6B)	1.311(2)	O(1B)-C(1B)-C(11B)	105.93(15)
C(6B)-C(7B)	1.503(2)	O(2B)-C(1B)-C(10B)	111.28(15)
C(7B)-C(14B)	1.530(3)	O(1B)-C(1B)-C(10B)	111.44(16)
C(7B)-C(8B)	1.531(3)	C(11B)-C(1B)-C(10B)	111.64(19)
C(8B)-O(3B)	1.434(2)	O(2B)-C(2B)-C(12B)	108.21(15)
C(8B)-C(9B)	1.530(3)	O(2B)-C(2B)-C(3B)	109.46(15)
C(9B)-C(16B)	1.520(3)	C(12B)-C(2B)-C(3B)	111.75(17)
C(9B)-C(15B)	1.520(3)	C(2B)-C(3B)-C(4B)	109.33(16)
C(12B)-C(13B)	1.169(3)	O(1B)-C(4B)-C(5B)	106.59(14)
O(1A)-C(1A)-O(2A)	110.57(16)	O(1B)-C(4B)-C(3B)	109.25(14)
O(1A)-C(1A)-C(11A)	105.71(16)	C(5B)-C(4B)-C(3B)	111.97(16)
O(2A)-C(1A)-C(11A)	105.25(18)	C(6B)-C(5B)-C(4B)	125.69(18)
O(1A)-C(1A)-C(10A)	110.97(17)	C(5B)-C(6B)-C(7B)	125.58(18)
O(2A)-C(1A)-C(10A)	111.28(17)	C(6B)-C(7B)-C(14B)	109.55(17)
C(11A)-C(1A)-C(10A)	112.8(2)	C(6B)-C(7B)-C(8B)	111.61(15)
O(2A)-C(2A)-C(12A)	108.58(15)	C(14B)-C(7B)-C(8B)	110.30(16)
O(2A)-C(2A)-C(3A)	108.71(15)	O(3B)-C(8B)-C(9B)	110.11(16)
C(12A)-C(2A)-C(3A)	111.02(17)	O(3B)-C(8B)-C(7B)	110.93(15)
C(2A)-C(3A)-C(4A)	110.00(17)	C(9B)-C(8B)-C(7B)	114.99(15)
O(1A)-C(4A)-C(5A)	108.98(15)	C(16B)-C(9B)-C(15B)	110.9(2)
O(1A)-C(4A)-C(3A)	109.63(14)	C(16B)-C(9B)-C(8B)	110.20(18)
C(5A)-C(4A)-C(3A)	109.46(17)	C(15B)-C(9B)-C(8B)	112.38(18)
C(6A)-C(5A)-C(4A)	124.62(19)	C(13B)-C(12B)-C(2B)	177.4(2)
C(5A)-C(6A)-C(7A)	125.36(19)	C(1B)-O(1B)-C(4B)	115.70(13)
C(6A)-C(7A)-C(14A)	111.95(17)	C(1B)-O(2B)-C(2B)	114.26(13)

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
C(1A)	43(1)	38(1)	33(1)	3(1)	-9(1)	-14(1)
C(2A)	29(1)	36(1)	31(1)	2(1)	2(1)	-2(1)
C(3A)	32(1)	31(1)	34(1)	0(1)	5(1)	-3(1)
C(4A)	29(1)	32(1)	33(1)	-3(1)	3(1)	-5(1)
C(5A)	34(1)	32(1)	32(1)	-3(1)	4(1)	-6(1)
C(6A)	32(1)	32(1)	32(1)	-1(1)	2(1)	-2(1)
C(7A)	32(1)	33(1)	29(1)	-5(1)	4(1)	-5(1)
C(8A)	25(1)	32(1)	30(1)	-1(1)	3(1)	-1(1)
C(9A)	30(1)	33(1)	39(1)	-3(1)	2(1)	-2(1)
C(10A)	65(2)	32(1)	50(2)	-3(1)	-10(1)	-2(1)
C(11A)	68(2)	65(2)	45(2)	10(1)	-3(1)	-37(2)
C(12A)	29(1)	45(1)	40(1)	-2(1)	0(1)	0(1)
C(13A)	39(1)	61(2)	53(2)	5(1)	-4(1)	5(1)
C(14A)	54(2)	41(1)	33(1)	2(1)	-8(1)	-10(1)
C(15A)	54(2)	37(1)	49(2)	-8(1)	12(1)	1(1)
C(16A)	52(2)	36(2)	67(2)	-2(1)	19(1)	-12(1)
O(1A)	40(1)	38(1)	30(1)	3(1)	0(1)	-15(1)
O(2A)	32(1)	43(1)	36(1)	1(1)	0(1)	-11(1)
O(3A)	31(1)	47(1)	41(1)	-11(1)	8(1)	-4(1)
C(1B)	33(1)	32(1)	31(1)	-2(1)	-7(1)	8(1)
C(2B)	26(1)	33(1)	33(1)	-2(1)	0(1)	1(1)
C(3B)	29(1)	31(1)	36(1)	0(1)	2(1)	5(1)
C(4B)	26(1)	33(1)	29(1)	2(1)	0(1)	6(1)
C(5B)	33(1)	35(1)	30(1)	4(1)	1(1)	7(1)
C(6B)	33(1)	29(1)	27(1)	-1(1)	0(1)	3(1)
C(7B)	31(1)	32(1)	27(1)	-2(1)	-3(1)	5(1)
C(8B)	27(1)	33(1)	26(1)	2(1)	-2(1)	3(1)
C(9B)	42(1)	30(1)	33(1)	1(1)	-8(1)	-1(1)
C(10B)	48(1)	34(1)	43(1)	4(1)	-2(1)	-3(1)
C(11B)	49(1)	53(2)	41(1)	-7(1)	-4(1)	20(1)
C(12B)	34(1)	43(1)	39(1)	-2(1)	-3(1)	1(1)
C(13B)	41(1)	61(2)	61(2)	-12(1)	-3(1)	-10(1)
C(14B)	60(2)	33(1)	46(2)	-9(1)	-21(1)	5(1)
C(15B)	45(2)	47(2)	66(2)	-2(1)	-4(1)	-14(1)
C(16B)	77(2)	32(1)	46(2)	-6(1)	-7(1)	6(1)
O(1B)	33(1)	35(1)	29(1)	-1(1)	-4(1)	9(1)
O(2B)	26(1)	38(1)	35(1)	-3(1)	-2(1)	7(1)
O(3B)	39(1)	43(1)	32(1)	-1(1)	-7(1)	12(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^{-3}$).

	x	y	z	U(eq)
H(2A)	1753(4)	7020(30)	7164(17)	34(5)
H(3A1)	1563(5)	4320(30)	6218(17)	44(6)
H(3A2)	1845(4)	4460(30)	5283(16)	29(5)
H(4A)	1305(5)	6890(30)	5260(17)	35(5)
H(5A)	1447(4)	4390(30)	3320(16)	33(5)
H(6A)	825(4)	5370(20)	4156(16)	24(4)
H(7A)	988(4)	2730(30)	2382(16)	35(5)
H(8A)	843(4)	1560(20)	4311(16)	28(5)
H(9A)	342(4)	660(20)	2380(16)	28(5)
H(10A)	1495(5)	9390(30)	6270(20)	59(7)
H(10B)	1514(6)	10600(30)	5100(20)	67(8)
H(10C)	1802(6)	10710(30)	6200(20)	63(7)
H(11A)	2247(6)	10380(30)	4810(20)	66(7)
H(11B)	2233(6)	8610(40)	3860(20)	77(9)
H(11C)	1975(6)	10270(40)	3680(20)	80(9)
H(13A)	2478(6)	3790(40)	8610(20)	79(9)
H(14A)	448(5)	3190(30)	1275(19)	50(6)
H(14B)	361(5)	4760(30)	2223(19)	47(6)
H(14C)	645(5)	5000(30)	1283(19)	56(7)
H(15A)	849(5)	210(30)	1530(20)	50(6)
H(15B)	710(5)	-1710(30)	1870(20)	62(7)
H(15C)	999(5)	-880(30)	2820(20)	61(7)
H(16A)	328(6)	-2070(40)	3480(20)	73(8)
H(16B)	244(6)	-480(30)	4360(20)	63(7)
H(16C)	596(6)	-1330(30)	4520(20)	71(9)
H(30A)	251(6)	2710(40)	3890(20)	65(9)
H(2B)	8318(4)	7030(20)	-1929(16)	27(5)
H(3B1)	8298(4)	4900(30)	269(16)	30(5)
H(3B2)	8555(4)	4620(20)	-751(15)	24(5)
H(4B)	8813(4)	7350(30)	-197(16)	30(5)
H(5B)	8735(5)	5470(30)	2131(18)	45(6)
H(6B)	9313(4)	6110(20)	906(16)	26(5)
H(7B)	9240(4)	4520(30)	3318(17)	35(5)
H(8B)	9729(4)	3610(20)	1684(15)	29(5)
H(9B)	9198(4)	2430(30)	907(17)	40(5)
H(10D)	8546(5)	9510(30)	-1430(18)	44(6)
H(10E)	8575(5)	11050(30)	-337(19)	43(6)
H(10F)	8253(5)	11060(30)	-1340(20)	60(7)
H(11D)	7851(5)	10810(30)	208(19)	53(6)
H(11E)	7906(5)	9370(30)	1300(20)	58(7)
H(11F)	8165(5)	11010(30)	1300(20)	53(6)

H(13B)	7602(6)	3640(30)	-2840(20)	65(8)
H(14D)	9820(6)	6520(40)	2660(20)	81(9)
H(14E)	9757(5)	5680(30)	4040(20)	60(7)
H(14F)	9527(5)	7280(30)	3503(19)	57(7)
H(15D)	8955(5)	220(30)	2073(19)	54(7)
H(15E)	8931(6)	2030(40)	2680(20)	70(8)
H(15F)	9215(6)	570(30)	3270(20)	62(7)
H(16D)	9675(5)	-250(30)	1810(20)	52(6)
H(16E)	9401(6)	-530(40)	720(20)	59(7)
H(16F)	9708(6)	850(40)	580(20)	74(8)
H(3OB)	9663(5)	2450(40)	3900(20)	53(8)

Table 6. Torsion angles [°].

O(2A)-C(2A)-C(3A)-C(4A)	-54.7(2)
C(12A)-C(2A)-C(3A)-C(4A)	-174.09(16)
C(2A)-C(3A)-C(4A)-O(1A)	53.2(2)
C(2A)-C(3A)-C(4A)-C(5A)	172.68(16)
O(1A)-C(4A)-C(5A)-C(6A)	-127.3(2)
C(3A)-C(4A)-C(5A)-C(6A)	112.8(2)
C(4A)-C(5A)-C(6A)-C(7A)	-169.69(18)
C(5A)-C(6A)-C(7A)-C(14A)	-120.7(2)
C(5A)-C(6A)-C(7A)-C(8A)	114.4(2)
C(6A)-C(7A)-C(8A)-O(3A)	62.60(19)
C(14A)-C(7A)-C(8A)-O(3A)	-61.9(2)
C(6A)-C(7A)-C(8A)-C(9A)	-170.95(16)
C(14A)-C(7A)-C(8A)-C(9A)	64.6(2)
O(3A)-C(8A)-C(9A)-C(16A)	-58.2(2)
C(7A)-C(8A)-C(9A)-C(16A)	176.50(18)
O(3A)-C(8A)-C(9A)-C(15A)	179.30(18)
C(7A)-C(8A)-C(9A)-C(15A)	54.0(2)
O(2A)-C(2A)-C(12A)-C(13A)	-139(3)
C(3A)-C(2A)-C(12A)-C(13A)	-20(3)
C(5A)-C(4A)-O(1A)-C(1A)	-173.53(16)
C(3A)-C(4A)-O(1A)-C(1A)	-53.7(2)
O(2A)-C(1A)-O(1A)-C(4A)	53.8(2)
C(11A)-C(1A)-O(1A)-C(4A)	167.3(2)
C(10A)-C(1A)-O(1A)-C(4A)	-70.1(2)
C(12A)-C(2A)-O(2A)-C(1A)	177.94(16)
C(3A)-C(2A)-O(2A)-C(1A)	57.0(2)
O(1A)-C(1A)-O(2A)-C(2A)	-55.6(2)
C(11A)-C(1A)-O(2A)-C(2A)	-169.28(19)
C(10A)-C(1A)-O(2A)-C(2A)	68.2(2)
O(2B)-C(2B)-C(3B)-C(4B)	-54.9(2)

C(12B)-C(2B)-C(3B)-C(4B)	-174.78(16)
C(2B)-C(3B)-C(4B)-O(1B)	53.1(2)
C(2B)-C(3B)-C(4B)-C(5B)	170.92(16)
O(1B)-C(4B)-C(5B)-C(6B)	-128.1(2)
C(3B)-C(4B)-C(5B)-C(6B)	112.5(2)
C(4B)-C(5B)-C(6B)-C(7B)	179.93(18)
C(5B)-C(6B)-C(7B)-C(14B)	-118.3(2)
C(5B)-C(6B)-C(7B)-C(8B)	119.3(2)
C(6B)-C(7B)-C(8B)-O(3B)	178.25(16)
C(14B)-C(7B)-C(8B)-O(3B)	56.2(2)
C(6B)-C(7B)-C(8B)-C(9B)	-56.0(2)
C(14B)-C(7B)-C(8B)-C(9B)	-178.01(18)
O(3B)-C(8B)-C(9B)-C(16B)	-61.3(2)
C(7B)-C(8B)-C(9B)-C(16B)	172.49(18)
O(3B)-C(8B)-C(9B)-C(15B)	62.9(2)
C(7B)-C(8B)-C(9B)-C(15B)	-63.3(2)
O(2B)-C(2B)-C(12B)-C(13B)	172(5)
C(3B)-C(2B)-C(12B)-C(13B)	-67(5)
O(2B)-C(1B)-O(1B)-C(4B)	54.48(19)
C(11B)-C(1B)-O(1B)-C(4B)	168.69(18)
C(10B)-C(1B)-O(1B)-C(4B)	-69.7(2)
C(5B)-C(4B)-O(1B)-C(1B)	-175.53(15)
C(3B)-C(4B)-O(1B)-C(1B)	-54.4(2)
O(1B)-C(1B)-O(2B)-C(2B)	-55.55(19)
C(11B)-C(1B)-O(2B)-C(2B)	-169.77(17)
C(10B)-C(1B)-O(2B)-C(2B)	68.7(2)
C(12B)-C(2B)-O(2B)-C(1B)	179.36(15)
C(3B)-C(2B)-O(2B)-C(1B)	57.3(2)

Table 7. Hydrogen bonds for **23** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(3A)-H(3OA)...O(3B)#10.77(2)	1.99(2)	2.729(2)	161(3)	
O(3B)-H(3OB)...O(3A)#20.78(2)	2.01(2)	2.735(2)	156(2)	

Symmetry transformations used to generate equivalent atoms: #1 x-1, y, z #2 -x+1, y, -z+1

4-Methoxybenzyl ether (S)-28. 4-Methoxybenzyltrichloroacetimidate² (freshly prepared from 4-methoxybenzyl alcohol, 6.3 mL, 51 mmol) was combined with alkynyl alcohol (S)-**26** (5.6 g, 33.3 mmol), CH₂Cl₂ (10 mL), and 10-camphorsulfonic acid (500 mg, 2.2 mmol). The reaction was stirred for 4 days, diluted with water and extracted with ether. Organic fractions were dried with MgSO₄, filtered, concentrated and chromatographed with pentane – ether (95 : 5 → 8: 2). The PMB ether (S)-**28** was isolated in 74% yield (7.08 g).

¹H NMR (CDCl₃, 400 MHz): δ 7.30 (d, 2H, *J* = 8.4 Hz), 6.89 (d, 2H, *J* = 8.4 Hz), 5.88 (m, 1H), 5.12 (m, 2H), 4.74 (d, 1H, *J* = 11.2 Hz), 4.48 (d, 1H, *J* = 11.6 Hz), 4.09 (t, 1H, *J* = 6.4 Hz), 3.82 (s, 3H), 2.49 (m, 2H), 0.22 (s, 9H). ¹³C NMR (CDCl₃, 100 MHz): δ 159.4, 133.8, 130.1, 129.9, 117.7, 113.9, 104.4, 91.3, 70.2, 68.4, 55.4, 40.2, 0.13. IR (neat, cm⁻¹): 2960 (s), 2900 (s), 2860 (s), 2835 (s), 2170 (m), 1640 (m), 1610 (s), 1590 (m), 1510 (s), 1465 (m), 1330 (s), 1250 (s), 1170 (s), 1080 (s), 1040 (s), 845 (s), 760 (s). HRMS (FAB+): Calcd. for C₁₇H₂₄O₂Si ([M]⁺), 288.1546. Found, 288.1550. Anal. Calcd. for C₁₇H₂₄O₂Si: C, 70.78; H, 8.39. Found: C, 70.30; H, 8.49. [α]_D -108 (c 0.900, CHCl₃).

Epoxide 30. *m*-Chloroperbenzoic acid (12.9 g, 73.8 mmol) was added in one portion to a solution of PMB ether (S)-**28** (7.08 g, 24.6 mmol) in CH₂Cl₂ (50 mL). The reaction mixture was stirred at room temperature for 6 h, then diluted with saturated aqueous Na₂SO₃ at 0°C, stirred for 30 min, neutralized with saturated NaHCO₃ and extracted with CH₂Cl₂ and ether. Organic fractions were dried with MgSO₄, filtered, concentrated and chromatographed with pentane: ether (8: 2) to yield 435 mg (6%) of starting (S)-**28** and 5.9 g (79% yield) of the epoxide as an approximately 1: 1 mixture of diastereomers. ¹H NMR (CDCl₃, 400 MHz): δ 7.29 (m, 4H), 7.89 (m, 4H), 4.75 (m, 2H), 4.47 (m, 2H), 4.26 (m, 2H), 3.81 (s, 6H), 3.14 (m, 2H), 2.79 (m, 2H), 2.54 (m, 2H), 1.95 (m, 4H), 0.22 (s, 9H), 0.21 (s, 9H). ¹³C NMR (CDCl₃, 100 MHz): δ 159.5, 129.9, 129.1, 113.9, 104.1, 103.8, 91.9, 91.4, 70.5, 70.3, 66.4, 66.3, 55.4, 49.4, 49.3, 47.6, 47.2, 39.3, 39.9, 0.04. IR (neat, cm⁻¹): 3000 (m), 2960 (s), 2865 (m), 2170 (m), 1725 (m), 1615 (s), 1585 (m), 1515 (s), 1465 (m), 1300 (s), 1250 (s), 1175 (s), 1075 (br, s), 1035 (s), 845 (br, s), 760 (s). [α]_D -102 (c 0.865, CHCl₃).

A solution of this epoxide diastereomer mixture (3.1 g, 10.2 mmol) and (S, S)-salen Co(III) OAc polymer-supported cobalt catalyst⁴ (500 mg) in THF (8 mL) was stirred at room temperature for 5 min, and then distilled water (750 μ L, 41.7 mmol) was added. After stirring for 22 h, the reaction was poured into a separatory funnel, and the layers were separated. The organic layer was dried with Na₂SO₄, filtered, concentrated. After chromatography of the residue with pentane – ether (8 : 2), 1.3 g (42% yield) of the epoxide **30** was obtained as a single diastereomer. Continued chromatography with hexane - ethyl acetate (1 : 1) yielded 1.78 g (54% yield) of the diol **32** as a 4 : 1 mixture of diastereomers.

Epoxide 30: ¹H NMR (CDCl₃, 400 MHz): δ 7.30 (d, 2H, *J* = 8.4 Hz), 6.89 (d, 2H, *J* = 8.4 Hz), 4.76 (d, 1H, *J* = 11.2 Hz), 4.48 (d, 1H, *J* = 11.2 Hz), 4.27 (m, 1H), 3.81 (s, 3H), 3.15 (m, 1H), 2.81 (m, 1H), 2.55 (m, 1H), 1.98 (m, 1H), 1.91 (m, 1H), 0.21 (s, 9H). ¹³C NMR (CDCl₃, 100 MHz): δ 159.5, 130.0, 129.8, 114.0, 104.0, 91.5, 70.5, 66.3, 55.4, 49.3, 47.6, 39.3, 0.1. IR (neat, cm⁻¹): 3000 (m), 2960 (s), 2865 (m), 2170 (m), 1720 (m), 1610 (s), 1585 (m), 1515 (s), 1465 (m), 1300 (m), 1250 (s), 1175 (m), 1090 (s, br), 1035 (s), 845 (s, br), 760 (s). HRMS (FAB⁺): Calcd. for C₁₇H₂₄O₃SiLi ([M+Li]⁺), 311.1655. Found, 311.1669. Anal. Calcd. for C₁₇H₂₄O₃Si: C, 67.07; H, 7.95. Found: C, 66.91; H, 8.01. [α]_D⁻⁹⁴ (c 0.795, CHCl₃).

Diol 32: ¹H NMR (CDCl₃, 400 MHz): δ 7.21 (d, 2H, *J* = 8.4 Hz), 6.83 (d, 2H, *J* = 8.8 Hz), 4.70 (d, 1H, *J* = 11.2 Hz), 4.40 (d, 1H, *J* = 11.2 Hz), 4.24 (m, 1H), 3.86 (m, 1H), 3.75 (s, 3H), 3.52 (m, 1H), 3.42 (m, 1H), 3.30 (s, br, 1H, -OH), 2.51 (s, br, 1H, -OH), 1.91 (m, 1H), 1.80 (m, 1H), 0.15 (s, 9H). ¹³C NMR (CDCl₃, 100 MHz): δ 159.6, 130.0, 129.4, 114.0, 103.6, 91.9, 70.8, 70.5, 67.65, 66.54, 55.4, 39.0, 0.0. IR (KBr, cm⁻¹): 3200 (br, m), 2955 (m), 2850 (m), 2170 (w), 1615 (m), 1515 (s), 1405 (m), 1250 (s), 1175 (m), 1095 (s), 1025 (s), 890 (m), 840 (s), 760 (m). HRMS (FAB⁺): Calcd. for C₁₇H₂₆O₄SiLi ([M+Li]⁺), 329.1760. Found, 329.1774. Anal. Calcd. for C₁₇H₂₆O₄Si: C, 63.32; H, 8.13. Found: C, 63.34; H, 8.15. [α]_D⁻¹¹⁴ (c 0.860, CHCl₃, dr, 4:1).

4. Annis, D. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 4147.

(R)-Epoxide 33. A suspension of CuBr (1.56g, 10.8 mmol) in Et₂O (100 mL) was cooled to –70°C, and 1M THF solution of vinylmagnesium bromide (52 mL, 52.0 mmol), followed by addition of (*R*)-(-)-epichlorohydrin (5 g, 54.0 mmol). The reaction was slowly warmed to –40°C and stirred for 2 days, then poured into water, filtered through Celite and extracted with ether. Organic fractions were dried with MgSO₄ and filtered. Solvent was distilled off at normal pressure and the residue was distilled in vacuum producing corresponding chlorohydrin in 84% yield (5.47 g, bp 55-59°C / 15 torr). ¹H and ¹³C NMR were identical to corresponding racemic compound⁵, [α]^{RT}_D -5 (c 1.400, CHCl₃).

KOH (2.9 g) was combined with freshly prepared chlorohydrin (5.4 g, 44.8 mmol) in a reaction flask fitted with a distillation head. Wet epoxide **33** was distilled at atmospheric pressure (bp 80-85°C), then dried with MgSO₄ and decanted producing clean **33** (3.0 g, 81% yield). ¹H and ¹³C NMR were identical to the corresponding racemic compound⁵, [α]^{RT}_D 0 (c 1.575, CHCl₃).

(4R)-7-(trimethylsilyl)-1-hepten-6-yne-4-ol (34). A solution of (trimethylsilyl)acetylene (10.3 mL, 71 mmol) in THF (220 mL) was cooled to –78°C, and 2.5 M THF solution of *n*-BuLi (30 mL, 75 mmol) was added. After addition, the reaction was warmed to ambient temperature and stirred for 1.5 h, then BF₃·Et₂O (9.3 mL, 78.5 mmol) was added at –78°C producing the alkynylboron nucleophile. After 20 min, a solution of epoxide **33** (3.0 g, 35.7 mmol) was added via cannula to the reaction. The mixture was stirred at –78°C for 1 h, then diluted with saturated aqueous NaCl and extracted with ether. Organic fractions were dried with MgSO₄, filtered and concentrated. The residue was vacuum distilled to yield a fraction with bp. ca. 160°C/ 0.4 torr, which was additionally purified by flash chromatography with pentane – ether (85 : 15) yielding 4.89 g (75%) of alcohol **34**.

¹H NMR (CDCl₃, 600 MHz): δ 5.84 (m, 1H), 5.15 (m, 2H), 3.81 (m, 1H), 2.44 (m, 2H), 2.38 (m, 1H), 2.30 (m, 1H), 0.17 (s, 9H). ¹³C NMR (CDCl₃, 150 MHz): δ 134.3, 118.5, 103.1, 87.9, 69.2, 40.8, 28.2, 0.2. IR (neat, cm⁻¹): 3400 (m, br), 2960 (m), 2915 (m), 2175 (m), 1640 (w), 1420 (w, br), 1250 (m), 1080 (m), 1020 (m), 920 (m), 840 (s), 760 (m). HRMS (FAB+): Calcd. for C₁₀H₁₈OSiLi ([M+Li]⁺), 189.1287. Found, 189.1281. Anal. Calcd. for C₁₀H₁₈OSi: C, 65.87; H, 9.95. Found: C, 64.26; H, 9.74. [α]_D +0.6 (c 0.630, CHCl₃).

5. (a) Schuda, A.; Mazzocchi, P. H.; Fritz, G.; Morgan, T. *Synthesis* **1986**, 309. (b) Zemribo, R.;

Preparation of 35:

Epoxidation of hydroxyalkene **34**: Epoxidation of **34** was performed in analogy to epoxidation of (S)-**28**. The above epoxyalcohol was obtained in 77% yield with dr, 1.2:1: ^1H NMR (CDCl_3 , 600 MHz): δ 4.00 (m, 2.2H), 3.16 (m, 1H), 3.11 (m, 1.2H), 2.84 (t, 1H, $J = 4.8$ Hz), 2.80 (t, 1.2H, $J = 4.8$ Hz), 2.60 (m, 1.2H), 2.54 (m, 1H), 2.49 (m, 3.4H), 2.44 (m, 1H), 2.41 (s, br, 2.2H, -OH), 0.16 (s, 19.8H). ^{13}C NMR (CDCl_3 , 150 MHz): δ 102.7, 88.1, 68.6, 67.8, 50.3, 50.0, 47.1, 46.8, 38.7, 38.4, 29.1, 28.9, 0.21.

Protection of the C4-alcohol: The epoxyalcohol (1.68g, 8.5 mmol) from the previous experiment was dissolved in DMF (14 mL), and NaH (60% in mineral oil, 510 mg, 12.7 mmol) was added in one portion (Caution! Gas evolution!). The reaction was stirred for 10 min and 4-methoxybenzylchloride (3.45 mL, 25.5 mmol) was slowly added at 0°C , followed by addition of crystalline Bu_4NI (4.7 g, 12.7 mmol). The mixture was warmed to ambient temperature and stirred for 25 h, then diluted with water and extracted with ether. Combined organic fractions were dried with MgSO_4 , filtered, concentrated and chromatographed with pentane – ether (7 : 3) producing the PMB-protected epoxyalcohol in 73% yield (1.54 g, dr, 1.2: 1), with loss of the alkynyl TMS substituent.

^1H NMR (CDCl_3 , 600 MHz): δ 7.29 (m, 4.4H), 6.89 (m, 4.4H), 4.62 (m, 2.2H), 4.49 (m, 2.2H), 3.81 (m, 6.6H), 3.73 (m, 2.2H), 3.09 (m, 1H), 3.06 (m, 1.2H), 2.81 (t, 1H, $J = 4.2$ Hz), 2.74 (t, 1.2H, $J = 4.2$ Hz), 2.58- 2.48 (m, 6.6H), 2.03 (m, 2.2H), 1.99- 1.89 (m, 4.4H). ^{13}C NMR (CDCl_3 , 150 MHz): δ 159.4 (2C), 130.35, 130.32, 129.59, 129.54, 114.0 (2C), 80.80, 80.71, 74.83, 74.75, 71.6, 71.1, 70.6 (2C), 55.4 (2C), 49.60, 49.56, 47.7, 46.8, 37.6, 36.8, 24.3, 23.9. IR (neat, cm^{-1}): 3290 (m), 2995 (m), 2915 (m), 2870 (m), 1610 (m), 1510 (s), 1465 (m), 1350 (m), 1300 (m), 1250 (s), 1175 (m), 1095 (s), 1035 (s), 820 (s). HRMS (FAB+): Calcd. for $\text{C}_{15}\text{H}_{18}\text{O}_3\text{SiLi}$ ($[\text{M}+\text{Li}]^+$), 253.1416. Found, 253.1422. Anal. Calcd. for $\text{C}_{15}\text{H}_{18}\text{O}_3$: C, 73.15; H, 7.37. Found: C, 72.90; H, 7.42. $[\alpha]_D +46$ (c 0.690, CHCl_3).

Replacement of the alkynyl-TMS substituent: PMB-protected epoxyalcohol (610 mg, 2.48 mmol) from previous experiment was dissolved in THF (15 mL). To this solution, 2.5M THF solution of *n*-BuLi (1.1mL, 2.75 mmol) was added at -55°C . The reaction

was stirred for 10 min at -50°C and TMSCl was slowly added. The mixture was stirred for 0.5 h at -40°C , diluted with saturated aqueous NaCl and extracted with ether. The organic fractions were dried with MgSO_4 , filtered and concentrated. The residue was chromatographed with pentane – ether (7 : 3) producing (4*R*)-**35** in 55% yield (434 mg, dr, 1.2: 1).

^1H NMR (CDCl_3 , 600 MHz): δ 7.30 (d, 4.4H, J = 8.4 Hz), 6.89 (d, 4.4H, J = 8.4 Hz), 4.65 (d, 1H, J = 11.4 Hz), 4.62 (d, 1.2H, J = 11.4 Hz), 4.52 (d, 1H, J = 11.4 Hz), 4.49 (d, 1.2H, J = 11.4 Hz), 3.81 (s, br, 6.6H), 3.10 (m, 1H), 3.06 (m, 1.2H), 2.81 (t, 1H, J = 4.2 Hz), 2.74 (t, 1.2H, J = 4.2 Hz), 2.65-2.57 (m, 2.2H), 2.55-2.48 (m, 6.6H), 1.96- 1.75 (m, 4.4H), 0.16 (s, 19.8H). ^{13}C NMR (CDCl_3 , 150 MHz): δ 159.4 (2C), 130.52, 130.47, 129.58, 129.54, 114.0 (2C), 103.56, 103.51, 87.0 (2C), 75.2 (2C), 71.7 (2C), 71.2 (2C), 55.5 (2C), 49.7, 49.6, 47.8, 47.0, 37.7, 37.2, 25.9, 25.6, 0.2. IR (neat, cm^{-1}): 2995 (m), 2955 (s), 2915 (s), 2860 (m), 2175 (s), 1610 (s), 1510 (s), 1465 (m), 1345 (m), 1300 (m), 1250 (s), 1175 (s), 1095 (s), 1035 (s), 845 (s), 760 (s). $[\alpha]_{\text{D}}^{25} +26$ (c 0.195, CHCl_3).

Hydrolytic kinetic resolution of epoxide (4*R*)-35** with Jacobsen cobalt catalyst.** A solution of epoxide (4*R*)-**35** (765 mg, 2.4 mmol) and (S, S)-salenCo(III)OAc (160 mg, 0.24 mmol) in THF (1 mL) was stirred at room temperature for 5 min, and then distilled water (200 μL , 11.1 mmol) was added. After stirring for 1 h, the reaction was dried with Na_2SO_4 , filtered, concentrated. After chromatography of the residue with pentane- ether (85: 15), 247 mg (32% yield) of epoxide (2*S*, 4*R*)-**36** was obtained as a single diastereomer. Continued chromatography with ether (100%) yields 378 mg (47% yield) of diol (2*R*, 4*R*)-**37** as a single diastereomer.

(2*S*, 4*R*)-**36**. ^1H NMR (CDCl_3 , 600 MHz): δ 7.29 (d, 2H, J = 9.0 Hz), 6.88 (d, 2H, J = 9.0 Hz), 4.62 (d, 1H, J = 11.4 Hz), 4.49 (d, 1H, J = 11.4 Hz), 3.81 (s, 3H), 3.06 (m, 1H), 2.74 (t, 1H, J = 4.8 Hz), 2.63 (dd, 1H, J = 17.4, 6.0 Hz), 2.49 (m, 3H), 1.92 (m, 1H), 1.85 (m, 1H), 0.16 (s, 9H). ^{13}C NMR (CDCl_3 , 400 MHz): δ 159.4, 130.5, 129.5, 113.9, 103.5, 87.0, 75.2, 71.1, 55.5, 49.7, 47.0, 37.2, 25.6, 0.2. IR (neat, cm^{-1}): 2955 (m), 2916 (s), 2850 (m), 2175 (m), 1610 (m), 1515 (s), 1465 (m), 1250 (s), 1095 (m, br), 1035 (m), 845 (s, br), 760 (m). HRMS (FAB $^{+}$): Calcd. for $\text{C}_{18}\text{H}_{26}\text{O}_3\text{SiLi}$ ($[\text{M}+\text{Li}]^{+}$), 325.1811. Found, 325.1823. $[\alpha]_{\text{D}}^{25} +24$ (c 0.155, CHCl_3).

Attempted hydration from iodocyclization of the *tert*-butyl carbonate derivative of **38:** In our original approach⁶ we could selectively convert the internal alkyne of diyne **7** into hydroxyketone **8** (figure 4 of main text) through iodocyclization of a carbonate derivative of the homopropargylic alcohol, followed by deiodination under radical conditions. Therefore, the alkynyl alcohol **38** was converted to the corresponding *tert*-butylcarbonate ester followed by cyclization with IBr to cleanly produce light-sensitive cyclic iodocarbonate **i**. However radical deiodination of **i** with Bu₃SnH did not produce desired enol carbonate, but instead resulted in loss of olefin at C28-C29 and loss of *p*-methoxybenzyl ether to give a compound tentatively assigned as structure **ii** (scheme i). Indeed, generation of free radical **iii** at C24 five atoms away from the C28-C29 unsaturation most likely resulted in radical cyclization to produce a five-membered ring. The newly formed radical at C29 can then abstract a benzylic hydrogen from the PMB ether, resulting in deprotection of the C31-alcohol via proposed intermediate **iv**.

Scheme i. Radical cyclization side-reaction upon deiodination

(a) Boc₂O, Et₃N, cat. DMAP, CH₂Cl₂ (77%). (b) IBr, CH₂Cl₂ / toluene, 0°C. (c) Bu₃SnH, cat. Et₃N, hexane, 0° to 20°C

6. Burova, S. A.; McDonald, F. E. *J. Am. Chem. Soc.* **2002**, *124*, 8188.

Compound **ii** was partially characterized by ^1H NMR spectroscopy: (CDCl_3 , 600 MHz): δ 4.81 (m, 1H), 4.67 (dm, 1H, J = 11.4 Hz), 4.46 (dd, 1H, J = 10.8, 3.6 Hz), 3.89 (m, 1H), 3.26 (dd, 1H, J = 9.0, 5.4 Hz), 2.60 (dd, 2H, J = 5.4, 1.8 Hz), 2.23 (m, 1H), 2.10- 2.01 (m, 3H), 1.72 (m, 2H), 1.47 (s, 6H), 1.00 (d, 3H, J = 6.0 Hz), 0.93 (m, 6H), 0.91 (s, 9H), 0.16 (s, 9H), 0.14 (s, 3H), 0.09 (s, 3H).

Alkynyl alcohol 39. A solution of alkyne **23** (288 mg, 0.75 mmol) in THF (5 mL) was cooled to -50°C , and a solution of $n\text{-BuLi}$ (0.33mL, 0.82 mmol) in hexane was added. The reaction was stirred 2.5 h at -60 to -40°C and $\text{BF}_3\cdot\text{OEt}_2$ (100 μL , 0.86 mmol) was added at -78°C . The mixture was stirred 15 min at -78°C and a solution of epoxide **30** (520 mg, 1.7 mmol) in THF (2 mL) was added via cannula. The mixture was stirred at -78°C for 1.5 h, then diluted with saturated aqueous NaCl and extracted with ether. Organic fractions were dried with MgSO_4 , filtered and concentrated. After chromatography of the residue with pentane - ether (6: 4) 328 mg of a mixture of starting epoxide **30** and alkyne **23** was isolated, along with 425 mg (82% yield) of alkynyl alcohol **39**. A larger quantity of alkynyl alcohol **39** (1.57 g) was prepared in similar unoptimized protocol from **23** and **30** in 44% yield.

^1H NMR (CDCl_3 , 600 MHz): δ 7.28 (m, 4H), 6.87 (m, 4H), 5.68 (dd, 1H, J = 15.6, 7.8 Hz), 5.45 (dd, 1H, J = 15.6, 6.0 Hz), 4.74 (d, 1H, J = 11.4 Hz), 4.69 (m, 1H), 4.48 (s, 2H), 4.43 (d, 1H, J = 11.4 Hz), 4.36 (m, 1H), 4.29 (m, 1H), 4.14 (m, 1H), 3.81(s, 3H), 3.80 (s, 3H), 2.96 (t, 1H, J = 6.0 Hz), 2.54 (q, 1H), 2.42 (m, 3H), 1.98 (m, 1H), 1.92 (m, 1H), 1.82 (m, 1H), 1.69 (m, 1H), 1.48 (s, 3H), 1.47 (s, 3H), 1.07 (d, 3H, J = 6.6 Hz), 0.95 (d, 6H, J = 6.6 Hz). ^{13}C NMR (CDCl_3 , 150 MHz): δ 159.6, 159.2, 136.7, 131.3, 129.9, 129.5, 129.2, 114.0, 113.8, 103.8, 99.4, 91.9, 88.6, 81.2, 75.0, 70.6, 70.0, 67.2, 66.8, 60.5, 55.4, 46.4, 41.4, 39.8, 38.0, 31.1, 30.3, 20.5, 19.6, 17.8, 15.5. IR (neat, cm^{-1}): 3450 (m, br), 2960 (s), 2935 (s), 2870 (s), 2170 (w), 1615 (s), 1590 (m), 1515 (s), 1465 (m), 1380 (s), 1300 (m), 1250 (s), 1200 (s), 1170 (s), 1080 (s, br), 1035 (s), 970 (m), 950 (m), 845 (s), 760 (m). HRMS (FAB $^+$): Calcd. for $\text{C}_{41}\text{H}_{58}\text{O}_7\text{SiLi}$ ($[\text{M}+\text{Li}]^+$), 697.4112. Found, 697.4147. Anal. Calcd. for $\text{C}_{41}\text{H}_{58}\text{O}_7\text{Si}$: C, 71.27; H, 8.46. Found: C, 71.02; H, 8.45. $[\alpha]_{\text{D}}^{-18}$ (c 0.480, CHCl_3).

Hydromethylsilylether 40. Alkynyl alcohol **39** (1.49 g, 2.17 mmol) was dissolved in (Me₂SiH)NH (2.3 mL, 13.0 mmol) and heated at 100°C for 15 h, then the reaction was connected to the vacuum for 4 h, producing crude **40** which was taken to the next step without purification.

¹H NMR (CDCl₃, 600 MHz): δ 7.28 (m, 4H), 6.88 (m, 4H), 5.67 (dd, 1H, *J* = 15.6, 8.4 Hz), 5.45 (dd, 1H, *J* = 15.6, 6.6 Hz), 4.73 (d, 1H, *J* = 10.8 Hz), 4.65 (m, 2H), 4.48 (s, 2H), 4.39 (d, 1H, *J* = 10.8 Hz), 4.26 (m, 2H), 4.06 (m, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 2.96 (t, 1H, *J* = 6.0 Hz), 2.42 (m, 3H), 2.10 (m, 1H), 1.83 (m, 2H), 1.67 (m, 2H), 1.48 (s, 3H), 1.46 (s, 3H), 1.07 (d, 3H, *J* = 6.6 Hz), 0.95 (d, 6H, *J* = 6.6 Hz), 0.20 (s, 9H), 0.19 (d, 3H, *J* = 1.8 Hz), 0.16 (d, 3H, *J* = 1.8 Hz). ¹³C NMR (CDCl₃, 150 MHz): δ 159.4, 159.2, 136.7, 131.4, 130.2, 129.9, 129.5, 129.3, 113.9, 113.8, 105.0, 99.4, 90.7, 88.6, 82.0, 80.9, 75.1, 70.4, 68.7, 65.6, 60.6, 55.5, 43.4, 39.8, 37.9, 31.2, 30.4, 28.1, 20.6, 19.6, 17.8, 15.6, 0.1, -0.7, -0.9. IR (neat, cm⁻¹): 2960 (s, br), 2935 (s, br), 2870 (s), 2170 (m), 2115 (m, br), 1610 (s), 1515 (s), 1465 (m), 1380 (m), 1300 (m), 1250 (s), 1170 (s), 1080 (s, br), 1040 (m), 905 (s), 845 (s), 760 (m). HRMS (FAB⁺): Calcd. for C₄₃H₆₄O₇Si₂Li ([M+Li]⁺), 755.4351. Found, 755.4382.

β-hydroxyketone 42 and 43. To a solution of crude hydrodimethylsilyl ether **40** (ca. 2.17 mmol) in THF (10 mL), a solution of platinum(0)-1, 3-divinyl-1, 1, 3, 3-tetramethyldisiloxane complex in xylenes (70 μL) was added. The reaction was stirred at ambient temperature for 21 h, producing THF solution of cyclic siloxane **41** (an aliquot of this solution was concentrated and spectroscopic characteristics were recorded). A THF solution of the siloxane was diluted with methanol (15 mL); KHCO₃ (650 mg, 6.61 mmol) and KF (380 mg, 6.51 mmol) were added followed by slow addition of 30% aqueous H₂O₂ (12.5 mL, 108 mmol). After stirring at room temperature for 23 h, the reaction was poured into cooled saturated Na₂SO₃(aq), vigorously stirred for 2- 3 h and extracted with ether. Organic fractions were dried with Na₂SO₄, filtered, concentrated and chromatographed with pentane – ether (1 : 1) producing TMS unprotected alkynyl β-hydroxyketone **43** (207 mg, 13% yield) and β-hydroxyketone **42** (600 mg, 43% yield).

Cyclic siloxane (**41**): ¹H NMR (CDCl₃, 600 MHz): δ 7.29 (d, 4H, *J* = 7.8 Hz), 6.86 (d, 4H, *J* = 7.8 Hz), 5.76 (m, 1H), 5.70 (dd, 1H, *J* = 15.6, 8.4 Hz), 5.48 (dd, 1H, *J* = 15.6, 6.6 Hz),

4.73 (d, 1H, J = 10.8 Hz), 4.59 (m, 1H), 4.49 (d, 2H, J = 4.8 Hz), 4.45 (d, 1H, J = 10.8 Hz), 4.35 (m, 2H), 4.24 (m, 1H), 3.80 (s, 6H), 2.98 (t, 1H, J = 6.0 Hz), 2.63 (m, 1H), 2.44 (m, 1H), 2.22 (m, 1H), 1.96 (m, 1H), 1.86 (m, 2H), 1.52 (s, 3H), 1.46 (s, 3H), 1.08 (d, 3H, J = 6.6 Hz), 0.94 (d, 6H, J = 7.2 Hz). ^{13}C NMR (CDCl_3 , 150 MHz): δ 159.3, 159.2, 141.5, 137.7, 136.2, 131.4, 130.4, 129.8, 129.7, 129.4, 113.8, 105.3, 98.9, 90.3, 88.6, 75.0, 73.0, 70.7, 69.9, 68.3, 66.0, 55.4, 44.8, 39.8, 37.6, 36.4, 31.1, 30.5, 20.5, 20.0, 17.8, 15.5, 1.0, 0.1, -0.2. IR (neat, cm^{-1}): 2960 (s, br), 2870 (s, br), 2170 (w), 1615 (m), 1515 (s), 1465 (m), 1380 (m), 1250 (s), 1170 (m), 1070 (s, br), 1040 (s), 845 (s, br), 785 (m). HRMS (FAB⁺): Calcd. for $\text{C}_{43}\text{H}_{64}\text{O}_7\text{Si}_2\text{Li}$ ($[\text{M}+\text{Li}]^+$), 755.4351. Found, 755.4333.

42: ^1H NMR (CDCl_3 , 600 MHz): δ 7.28 (d, 4H), 6.88 (m, 4H), 5.66 (dd, 1H, J = 15.6, 7.8 Hz), 5.44 (dd, 1H, J = 15.6, 6.6 Hz), 4.73 (d, 1H, J = 10.8 Hz), 4.48 (s, 2H), 4.43 (d, 1H, J = 10.8 Hz), 4.40-4.30 (m, 4H), 3.80 (s, br, 6H), 3.20 (s, br, 1H, -OH), 2.96 (t, 1H, J = 5.4 Hz), 2.69 (dd, 1H, J = 15.6, 7.8 Hz), 2.58 (m, 2H), 2.42 (m, 3H), 1.85 (m, 2H), 1.82 (m, 2H), 1.46 (s, 3H), 1.38 (s, 3H), 1.07 (d, 3H, J = 7.2 Hz), 0.94 (m, 6H). ^{13}C NMR (CDCl_3 , 150 MHz): δ 209.3, 159.5, 159.2, 136.3, 131.4, 130.0, 129.6, 129.5, 113.9, 113.8, 104.4, 99.0, 91.4, 88.6, 75.0, 70.7, 70.1, 66.0, 65.8, 64.6, 55.4, 50.9, 49.8, 42.2, 39.8, 37.0, 31.1, 30.2, 20.6, 19.9, 17.8, 15.6, 0.1. IR (neat, cm^{-1}): 3420 (s, br), 2960 (s), 2915 (s), 2875 (s), 2170 (w), 1710 (m), 1610 (s), 1515 (s), 1460 (m), 1380 (s), 1300 (m), 1250 (s), 1179 (s), 1090 (s), 8445 (m). HRMS (FAB⁺): Calcd. for $\text{C}_{41}\text{H}_{60}\text{O}_8\text{SiLi}$ ($[\text{M}+\text{Li}]^+$), 715.4218. Found, 715. 4210. Anal. Calcd. for $\text{C}_{41}\text{H}_{60}\text{O}_8\text{Si}$: C, 69.48; H, 8.53. Found: C, 68.99; H, 8.53. $[\alpha]_{\text{D}}^{-28}$ (c 0.580, CHCl_3)

43: ^1H NMR (CDCl_3 , 600 MHz): δ 7.28 (m, 4H), 6.88 (m, 4H), 5.66 (dd, 1H, J = 15.6, 8.4 Hz), 5.44 (dd, 1H, J = 15.6, 6.6 Hz), 4.76 (d, 1H, J = 10.8 Hz), 4.48 (s, 2H), 4.43 (d, 1H, J = 10.8 Hz), 4.37 (m, 4H), 3.806 (s, 3H), 3.802 (s, 3H), 3.21 (s, br, 1H, -OH), 2.96 (t, 1H, J = 6.0 Hz), 2.70 (dd, 1H, J = 15.6, 7.2 Hz), 2.58 (m, 2H), 2.51 (d, 1H, J = 2.4 Hz), 2.42 (m, 2H), 1.87 (m, 3H), 1.83 (m, 2H), 1.47 (s, 3H), 1.38 (s, 3H), 1.07 (d, 3H, J = 6.6 Hz), 0.94 (m, 6H). ^{13}C NMR (CDCl_3 , 150 MHz): δ 209.3, 159.6, 159.2, 136.3, 131.4, 130.0, 129.6, 129.5, 114.0, 113.8, 99.0, 88.6, 82.6, 75.0, 74.4, 70.8, 70.1, 65.8, 65.4, 64.4, 55.4, 50.8, 49.7, 42.1, 39.7, 37.0, 31.1, 30.2, 20.5, 19.9, 17.8, 15.5. IR (neat, cm^{-1}): 3450 (s, br), 3290 (s, br), 2960 (s, br), 2870 (s, br), 1710 (s), 1610 (s), 1515 (s), 1465

(s), 1380 (s), 1300 (s), 1250 (s, br), 1175 (s), 1085 (s, br), 1040 (s, br), 975 (s), 825 (s). HRMS (FAB+): Calcd. for $C_{38}H_{52}O_8Li$ ($[M+Li]^+$), 643.3822. Found, 643.3846. Anal. Calcd. for $C_{38}H_{52}O_8$: C, 71.67; H, 8.23. Found: C, 70.87; H, 8.32. $[\alpha]_D^{25}$ -13 (c 0.590, $CHCl_3$).

Diacetonide 44. To a solution of a mixture of β -hydroxyketones **42** (193 mg, 0.27 mmol) and **43** (588 mg, 0.92 mmol) in THF (15 mL), methanol (770 μ L) was added at $-78^\circ C$ followed by 1M solution of Et_2BOMe in THF (1.3 mL, 1.31 mmol). After 3.5 h of stirring, solid $NaBH_4$ (90 mg, 2.38 mmol) was added. The reaction was stirred for 11.5 h at $-78^\circ C$, and then 30 % aqueous H_2O_2 (10 mL) was added. The reaction was allowed to warm to room temperature, stirred for 3h and quenched with saturated aqueous Na_2SO_3 at $0^\circ C$. The reaction was stirred for 1h at room temperatures and extracted with ether. Organic fractions were dried with Na_2SO_4 , filtered, and concentrated to give the crude diol. For removal of the alkynylsilyl group, the residue was dissolved in methanol (5 mL) and treated with K_2CO_3 (90 mg, 0.65 mmol). In 2 h, additional K_2CO_3 (90 mg, 0.65 mmol) was added. The reaction was vigorously stirred for 20 h at room temperature, then diluted with water and extracted with ether. Organic fractions were dried with Na_2SO_4 , filtered and concentrated yielding the crude terminal alkynyl diol. To a solution of this intermediate (ca. 1.19 mmol) in 2, 2-dimethoxypropane (5 mL), $TsOH \cdot H_2O$ (30 mg, 0.16 mmol) and 3Å molecular sieves (300 mg) were added. The reaction was stirred at room temperature for 21 h, diluted with Et_3N , filtered and concentrated. The residue was chromatographed on silica gel pretreated with 2.5 vol % of Et_3N with pentane – ether (75 : 25). Diacetonide **44** was obtained in 67% yield (545 mg, three steps starting from the mixture of **42** and **43**).

1H NMR ($CDCl_3$, 600 MHz): δ 7.28 (d, br, 4H), 6.88 (m, 4H), 5.65 (dd, 1H, J = 15.6, 8.4 Hz), 5.46 (dd, 1H, J = 15.6, 6.0 Hz), 4.72 (d, 1H, J = 11.4 Hz), 4.48 (s, 2H), 4.43 (d, 1H, J = 11.4 Hz), 4.30 (m, 2H), 4.08 (m, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 2.96 (t, 1H, J = 5.4 Hz), 2.44 (s, 1H), 2.43 (m, 1H), 1.88 (m, 1H), 1.82 (m, 2H), 1.48 (m, 3H), 1.45 (s, 3H), 1.43 (m, 3H), 1.41 (s, 3H), 1.36 (s, 3H), 1.32 (s, 3H), 1.07 (d, 3H, J = 6.6 Hz), 0.94 (d, 6H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 159.5, 159.2, 136.0, 131.4, 130.1, 129.9, 129.5, 113.9, 113.8, 98.74, 98.74, 98.70, 88.7, 83.3, 75.0, 73.5, 70.6, 65.0, 64.9, 64.8,

63.9, 55.5, 43.1, 42.9, 39.7, 37.8, 37.6, 31.1, 30.5, 30.4, 20.5, 20.1, 17.9, 15.5. IR (neat, cm^{-1}): 3290 (m, br), 2955 (s, br), 2870 (s), 1610 (s), 1585 (m), 1515 (s), 1465 (s), 1380 (s), 1300 (m), 1250 (s), 1200 (s), 1170 (s), 1105 (s), 1075 (s), 1035 (s), 975 (m), 938 (s), 820 (s).

Alkynyl alcohol 45. To a solution of alkyne **44** (175 mg, 0.176 mmol) in THF (4 mL) a solution of *n*-BuLi (330 μL , 0.85 mmol) in hexane was added at -78°C . The reaction was stirred 2.5 h at $-78 \rightarrow -40^\circ\text{C}$, then $\text{BF}_3 \cdot \text{OEt}_2$ (40 μL , 0.86 mmol) was added at -78°C . The reaction was stirred 10 min at -78°C and a solution of epoxide **36** (126 mg, 0.39 mmol) in THF (2 mL) was added via cannula. The mixture was stirred at -78°C for 3 h, then diluted with saturated aqueous NaCl and extracted with ether. Organic fractions were dried with MgSO_4 , filtered and concentrated. After chromatography of the residue with pentane – ether (1 : 1) 143 mg of a mixture of starting epoxide **36** and alkyne **44** was isolated along with 178 mg (59% yield) of alkynyl alcohol **45**.

^1H NMR (CDCl_3 , 600 MHz): δ 7.27 (m, 6H), 6.88 (m, 6H), 5.65 (dd, 1H, $J = 15.6, 7.8$ Hz), 5.46 (dd, 1H, $J = 15.6, 6.0$ Hz), 4.71 (d, 1H, $J = 10.8$ Hz), 4.68 (d, 1H, $J = 10.8$ Hz), 4.48 (s, 2H), 4.46 (d, 1H, $J = 10.8$ Hz), 4.39 (d, 1H, $J = 10.8$ Hz), 4.30 (m, 2H), 4.07 (m, 3H), 3.93 (m, 1H), 3.809 (s, 3H), 3.805 (s, 6H), 3.73 (m, 1H), 2.96 (t, 1H, $J = 5.4$ Hz), 2.61 (dd, 1H, $J = 16.8, 4.8$ Hz), 2.49 (dd, 1H, $J = 16.8, 6.6$ Hz), 2.43 (m, 3H), 1.99 (m, 1H), 1.86-1.75 (m, 4H), 1.48 (m, 3H), 1.44 (s, 3H), 1.42 (m, 3H), 1.41 (s, 3H), 1.35 (s, 3H), 1.31 (s, 3H), 1.07 (d, 3H, $J = 7.2$ Hz), 0.94 (d, 6H, $J = 6.6$ Hz), 0.16 (s, 9H). ^{13}C NMR (CDCl_3 , 150 MHz): δ 159.6, 159.4, 159.2, 136.0, 131.4, 130.3, 130.1, 129.9, 129.8, 129.5, 114.1, 113.9, 113.8, 103.2, 98.8, 98.7, 88.7, 87.5, 82.2, 81.7, 75.0, 71.2, 70.6, 70.5, 69.8, 65.14, 65.07, 64.8, 64.4, 58.6, 55.5, 43.4, 43.2, 40.4, 39.7, 37.8, 37.7, 31.2, 30.5, 30.4, 27.7, 25.7, 20.5, 20.1, 18.6, 17.9, 15.5, 0.3. IR (neat, cm^{-1}): 3475 (m, br), 2955 (s, br), 2870 (s), 2175 (m), 1610 (s), 1580 (m), 1515 (s), 1465 (m), 1380 (s), 1300 (m), 1250 (s), 1170 (s), 1085 (s, br), 1035 (s), 975 (m), 940 (m), 845 (s). HRMS (FAB $^+$): Calcd. for $\text{C}_{59}\text{H}_{84}\text{O}_{11}\text{SiLi}$ ($[\text{M}+\text{Li}]^+$), 1003.5943. Found, 1003.5900. Anal. Calcd. for $\text{C}_{59}\text{H}_{84}\text{O}_{11}\text{Si}$: C, 71.05; H, 8.49. Found: C, 70.83; H, 8.76. $[\alpha]_{\text{D}}^{-5}$ (c 0.815, CHCl_3).

Hydrodimethylsilylether of 45. The above hydrodimethylsilyl ether was prepared from alkynyl alcohol **45** in analogy with the preparation of **40** from **39**.

^1H NMR (CDCl_3 , 600 MHz): δ 7.24 (m, 6H), 6.83 (m, 6H), 5.62 (dd, 1H, J = 15.6, 7.8 Hz), 5.43 (dd, J = 15.6, 6.6 Hz), 4.66 (d, 1H, J = 10.8 Hz), 4.55 (d, 1H, J = 10.8 Hz), 4.45 (s, 2H), 4.4 (d, 1H, J = 10.8 Hz), 4.37 (d, 1H, J = 11.4 Hz), 4.26 (m, 2H), 4.04 (m, 4H), 3.96 (m, 1H), 3.77 (s, br, 6H), 3.76 (s, 3H), 3.64 (m, 1H), 2.93 (t, 1H, J = 4.8 Hz), 2.53-2.32 (m, 6H), 1.88 (m, 2H), 1.78 (m, 2H), 1.44 (m, 3H), 1.41 (s, 3H), 1.39 (m, 3H), 1.37 (s, 3H), 1.31 (s, 3H), 1.28 (s, 3H), 1.03 (d, 3H, J = 6.6 Hz), 0.90 (d, 6H, J = 6.6 Hz). ^{13}C NMR (CDCl_3 , 150 MHz): δ 159.4, 159.3, 159.2, 136.0, 131.4, 130.7, 130.4, 130.1, 129.9, 129.52, 129.48, 113.94, 113.89, 113.86, 104.0, 98.8, 98.7, 88.7, 88.0, 86.7, 82.8, 75.0, 74.1, 70.9, 70.6, 70.4, 70.1, 65.1, 64.7, 64.3, 55.5, 43.4, 43.2, 41.2, 39.7, 37.8, 37.7, 31.1, 30.5, 30.4, 27.5, 25.8, 20.5, 20.1, 17.9, 15.5, 0.3, -0.6, -0.7.

β -hydroxyketone 46. The β -hydroxyketone was prepared from the above hydrodimethylsilyl ether in 65% yield (two steps), in analogy with **42**.

^1H NMR (CDCl_3 , 600 MHz): δ 7.27 (m, 4H), 7.21 (d, 2H, J = 7.2 Hz), 6.86 (m, 6H), 5.65 (dd, 1H, J = 15.6, 8.4 Hz), 5.46 (dd, 1H, J = 15.6, 6.0 Hz), 4.65 (d, 1H, J = 10.8 Hz), 4.48 (m, 3H), 4.43 (d, 2H, J = 10.8 Hz), 4.31 (d, 2H, J = 10.8 Hz), 4.23 (m, 1H), 4.15 (m, 1H), 4.12- 4.03 (m, 3H), 3.80 (s, 3H), 3.79 (s, 6H), 3.72 (m, 1H), 3.56 (s, br, 1H, -OH), 2.96 (t, 1H, J = 4.8 Hz), 2.71 (dd, 1H, J = 15.6, 7.2 Hz), 2.61- 2.53 (m, 3H), 2.47- 2.40 (m, 3H), 1.81 (m, 1H), 1.76 (m, 2H), 1.63 (m, 2H), 1.53 (m, 2H), 1.48 (m, 2H), 1.45 (s, 3H), 1.43 (m, 2H), 1.41 (s, 3H), 1.39 (s, 3H), 1.36 (s, 3H), 1.06 (d, 3H, J = 6.6 Hz), 0.93 (d, 6H, J = 6.6 Hz), 0.16 (s, 9H). ^{13}C NMR (CDCl_3 , 150 MHz): δ 209.4, 159.5, 159.4, 159.2, 136.0, 131.4, 130.7, 130.1, 130.0, 129.7, 129.6, 129.5, 114.1, 114.0, 113.8, 103.4, 98.8, 98.7, 88.7, 87.3, 76.5, 75.0, 72.3, 71.8, 71.1, 70.6, 66.8, 65.8, 64.7, 55.4, 50.8, 49.7, 43.2, 42.7, 40.9, 39.7, 38.0, 37.8, 31.1, 30.5, 25.5, 20.5, 20.15, 20.09, 17.9, 15.5, 0.21. IR (neat, cm^{-1}): 3490 (m, br), 2960 (s), 2915 (s), 2850 (s), 2175 (m), 1710 (m), 1610 (m), 1580 (m), 1515 (m), 1460 (m), 1380 (m), 1260 (m), 1100 (s, br). HRMS (FAB $^+$): Calcd. for $\text{C}_{59}\text{H}_{86}\text{O}_{12}\text{SiLi}$ ($[\text{M}+\text{Li}]^+$), 1021.6049. Found, 1021.6061. Anal. Calcd. for $\text{C}_{59}\text{H}_{86}\text{O}_{12}\text{Si}$: C, 69.79; H, 8.54. Found: C, 70.13; H, 8.73. $[\alpha]_{\text{D}}^{25} +28$ (c 0.305, CHCl_3).

Triacetone 47 was prepared in 80% yield (three steps) from **46**, by a reaction sequence similar to that reported for the conversion of **42** to **44**.

^1H NMR (CDCl_3 , 600 MHz): δ 7.29- 7.26 (m, 6H), 6.90- 6.86 (m, 6H), 5.66 (dd, 1H, J = 15.6, 7.8 Hz), 5.47 (dd, 1H, J = 15.6, 6.6 Hz), 4.57 (d, 1H, J = 11.4 Hz), 4.48 (m, 4H), 4.42 (d, 1H, J = 11.4 Hz), 4.32 (m, 1H), 4.13- 4.08 (m, 3H), 4.01 (m, 2H), 3.84 (m, 1H), 3.812 (s, 3H), 3.808 (s, 3H), 3.78 (s, 3H), 3.67 (m, 1H), 2.97 (t, 1H, J = 5.4 Hz), 2.48- 2.43 (m, 3H), 2.02 (m, 1H), 1.91 (m, 1H), 1.82 (m, 1H), 1.71 (m, 1H), 1.59 (m, 2H), 1.56- 1.49 (m, 4H), 1.46 (s, 3H), 1.42 (s, br, 9H), 1.39 (s, 3H), 1.38 (s, 3H), 1.30- 1.26 (m, 4H), 1.13 (m, 2H), 1.07 (d, 3H, J = 6.6 Hz), 0.95 (d, 6H, J = 6.6 Hz). ^{13}C NMR (CDCl_3 , 150 MHz): δ 159.4, 159.3, 159.2, 136.0, 131.4, 131.2, 130.5, 130.1, 129.7, 129.48, 129.43, 114.0, 113.9, 113.8, 98.74, 98.66, 98.59, 88.7, 81.2, 75.0, 72.9, 72.3, 70.8, 70.6, 70.4, 66.2, 65.9, 65.6, 65.0, 64.8, 55.4, 43.2, 40.6, 39.7, 38.1, 37.8, 37.4, 31.1, 30.5, 23.9, 20.5, 20.21, 20.16, 20.09, 17.9, 15.5. IR (neat, cm^{-1}): 3290 (w), 2990 (s), 2940 (s), 2915 (s), 2870 (s), 1610 (m), 1510 (s), 1465 (m), 1380 (s), 1300 (m), 1250 (s), 1200 (s), 1170 (s), 1105 (s), 1036 (s), 940 (m), 820 (m). HRMS (MALDI- DHB): m/z 1007.8 ($[\text{M}+\text{Na}]^+$), 967.8 ($[\text{M}+\text{Na}-\text{C}_3\text{H}_4]^+$), 927.8 ($[\text{M}+\text{Na}-2(\text{C}_3\text{H}_4)]^+$), 887.8 ($[\text{M}+\text{Na}-3(\text{C}_3\text{H}_4)]^+$). $[\alpha]_{\text{D}}^{25} +28$ (c 0.320, CHCl_3).

Vinyl iodide 48. Attention! Preparation of $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ from Cp_2ZrCl_2 and LiHBEt_3 yields unreproducible results on a small scale (starting from less than 60 mg of Cp_2ZrCl_2). Additionally, this reduction works well only with a new bottle of Super-Hydride®. To a solution of Cp_2ZrCl_2 (100 mg, 0.34 mmol) in THF (1.0 mL), 1M THF solution of Super-Hydride® (340 μL , 0.34 mmol, freshly opened bottle) was added. The reaction was wrapped in aluminum foil and stirred at ambient temperature for 10 min. After that, vigorous stirring was continued and an aliquot (800 μL) of white suspension of $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ in THF was removed via syringe and disregarded. To the residual $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ (ca. 140.0 μmol) in THF (ca. 540 μL), a solution of alkyne **47** (40 mg, 40.0 μmol) was injected. After 1.5 h of stirring at ambient temperature, 1.5 M THF solution of I_2 was added dropwise until brown- red color persisted. The reaction was stirred additional 15 min, quenched with saturated aqueous Na_2SO_3 (color disappear) and extracted with ether. Combined organic fractions were dried with Na_2SO_4 , filtered and

concentrated. Vinyl iodide **48** was isolated in 90% yield (40 mg) after flash chromatography on silica gel pretreated with 2.5 volume% of Et₃N with pentane – ether (6 : 4).

¹H NMR (CDCl₃, 600 MHz): δ 7.29- 7.24 (m, 6H), 6.90- 6.87 (m, 6H), 6.54 (m, 1H), 6.07 (d, 1H, *J*= 14.4 Hz), 5.66 (dd, 1H, *J*= 15.6, 7.8 Hz), 5.47 (dd, 1H, *J*= 15.6, 6.6 Hz), 4.51 - 4.45 (m, 5H), 4.39 (d, 1H, *J*= 11.4 Hz), 4.32 (m, 1H), 4.08 (m, 4H), 4.00 (m, 1H), 3.96 (m, 1H), 3.811 (s, 3H), 3.809 (s, 3H), 3.79 (s, 3H), 3.56 (m, 1H), 2.97 (t, 1H, *J*= 6.0 Hz), 2.42 (m, 1H), 2.35 (m, 1H), 2.27 (m, 1H), 1.83 (m, 3H), 1.58 (m, 4H), 1.56- 1.48 (m, 7H), 1.46 (s, 6H), 1.42 (s, 9H), 1.393 (s, 3H), 1.388 (s, 3H), 1.07 (d, 3H, *J*= 6.6 Hz), 0.94 (d, 6H, *J*= 6.6 Hz). ¹³C NMR (CDCl₃, 150 MHz): δ 159.4, 159.3, 159.2, 142.7, 136.0, 131.4, 131.2, 130.6, 130.1, 129.7, 129.5, 129.4, 114.04, 113.99, 113.8, 98.76, 98.66, 98.60, 88.7, 75.0, 73.5, 72.4, 71.3, 70.6, 66.1, 65.8, 65.6, 64.9, 64.7, 55.4, 43.2, 40.5, 40.4, 39.7, 38.1, 37.8, 37.5, 31.1, 30.5 (br), 20.5, 20.2, 20.1, 17.9, 15.5. IR (neat, cm⁻¹): 2990 (s), 2940 (s), 2915 (s), 2870 (s), 1610 (s), 1510 (s), 1465 (s), 1380 (s), 1300 (s), 1250 (s), 1200 (s), 1170 (s), 1110 (s), 1040 (s), 940 (s), 820 (s). HRMS (FAB⁺): Calcd. for C₅₉H₈₅IO₁₂Na ([M+Na]⁺), 1135.4983. Found, 1135.4999. [α]_D +23 (c 0.165, CHCl₃).

Triol 49. The PMBn triether **48** (24 mg, 21.8 μmol) was dissolved in CH₂Cl₂ (6 mL), and DDQ (25 mg, 109.0 μmol) was added in one portion. The reaction was shielded from light and stirred at room temperature for 45 min, and then more DDQ (10 mg, 44.0 μmol) was added. After 3 h, the reaction was concentrated and chromatographed on silica gel pretreated with 2.5 volume% of Et₃N with pentane – ether (25 : 75) producing triol **49** (10 mg, 61% yield).

¹H NMR (CDCl₃, 600 MHz): δ 6.57 (m, 1H), 6.11 (d, 1H, *J*= 14.4 Hz), 5.63 (dd, 1H, *J*= 15.6, 7.2 Hz), 5.50 (dd, 1H, *J*= 15.6, 7.2 Hz), 4.34 (m, 1H), 4.20- 4.09 (m, 6H), 3.89 (m, 1H), 3.56 (s, 1H, -OH), 3.29 (t, br, 1H, -OH), 3.16 (t, br, 1H, -OH), 2.35 (m, 1H), 2.26- 2.17 (m, 2H), 1.72 (m, 1H), 1.62 (m, 4H), 1.57 (m, 4H), 1.56- 1.48 (m, 6H), 1.450 (s, 3H), 1.444 (s, 3H), 1.439 (s, 3H), 1.40 (s, 3H), 1.389 (s, 3H), 1.385 (s, 3H), 1.03 (d, 3H, *J*= 6.6 Hz), 0.92 (dd, 6H, *J*= 12.6, 6.6 Hz). ¹³C NMR (CDCl₃, 150 MHz): δ 142.8, 135.0, 131.2, 99.1, 98.9, 98.81, 98.77, 98.74, 79.9, 70.6 (2C), 70.5, 67.5, 66.7, 65.3, 65.0, 64.7, 43.9, 43.3, 43.1, 42.7, 42.2, 39.4, 37.9, 37.4, 37.1, 30.7, 30.5 (2C), 30.3, 20.1, 20.0, 19.9, 19.8, 17.3, 13.9. [α]_D +6 (c 0.501, CDCl₃).

Tetracetone 50. To a solution of triol **49** (10 mg, 13.3 μ mol) in 2, 2-dimethoxypropane (2 mL), a solution of TsOH-H₂O (2 mg, 11.0 μ mol) in water (20 μ L) was added. The reaction was shielded from light and stirred at room temperature for 3 days, then diluted with Et₃N (0.1 mL), concentrated and chromatographed on silica gel pretreated with 2.5 volume% of Et₃N with pentane – ether (1 : 1) yielding tetracetone **50** (9.3 mg, 86% yield).

¹H NMR (CDCl₃, 600 MHz): δ 6.53 (m, 1H), 6.09 (d, 1H, J = 14.4 Hz), 5.63 (dd, 1H, J = 15.6, 6.6 Hz), 5.49 (dd, 1H, J = 15.6, 6.6 Hz), 4.34 (m, 1H), 4.06 (m, 4H), 3.96 (m, 2H), 3.87 (m, 1H), 3.16 (t, br, -OH), 2.35 (m, 1H), 2.26 (m, 1H), 2.16 (m, 1H), 1.82 (m, 1H), 1.72 (m, 1H), 1.57 (m, 3H), 1.49 (m, 7H), 1.46 (m, 3H), 1.44 (s, 3H), 1.41 (s, 3H), 1.40 (s, br, 6H), 1.370 (s, 3H), 1.365 (s, 3H), 1.341 (s, 3H), 1.325 (s, 3H), 1.02 (d, 3H, J = 6.6 Hz), 0.92 (dd, 6H, J = 13.2, 7.2 Hz). ¹³C NMR (CDCl₃, 150 MHz): δ 142.1, 135.0, 131.2, 100.5, 98.8 (3C), 98.7, 79.9, 70.5, 67.9, 65.6, 65.4, 65.2, 64.8, 63.1, 62.5, 43.2, 42.8, 42.4, 42.2, 39.4, 38.8, 38.0, 37.9, 36.0, 30.7, 30.4, 30.50, 30.46, 30.28, 24.8, 24.7, 20.0 (2C), 19.9, 19.8, 17.3, 13.9. $[\alpha]_D^{+11}$ (c 0.465, CDCl₃).

Phosphonate ester of 50. To a solution of alcohol **50** (9.3 mg, 11.7 μ mol) in CH₂Cl₂ (0.5 mL), DMAP (6.2 mg, 51.0 μ mol), BOPPF₆ (21.3 mg, 41.0 μ mol) and diethylphosphonoacetic acid (6.9 mg, 35.0 μ mol) were added. The reaction was stirred at room temperature for 22 h and concentrated. The phosphonate ester was isolated in 91% yield (10 mg) after chromatography on silica gel pretreated with 2.5 volume% of Et₃N with pentane – ether (3 : 7).

¹H NMR (CDCl₃, 600 MHz): δ 6.53 (m, 1H), 6.09 (d, 1H, J = 14.4 Hz), 5.49 (m, 2H), 4.71 (m, 1H), 4.30 (m, 1H), 4.17 (m, 4H), 4.06 (m, 4H), 3.96 (m, 2H), 3.87 (m, 1H), 2.97 (d, 1H $^2J_{P-H}$ = 22.2 Hz), 2.45 (m, 1H), 2.26 (m, 1H), 2.16 (m, 1H), 1.89- 1.80 (m, 2H), 1.57 (m, 4H), 1.52- 1.46 (m, 9H), 1.43 (s, 3H), 1.41 (s, 3H), 1.40 (s, 6H), 1.39 (s, 3H), 1.34 (t, 6H, J = 7.2 Hz), 1.33 (s, 3H), 1.32 (s, 3H), 1.00 (d, 3H, J = 6.6 Hz), 0.88 (d, 6H, J = 6.6 Hz). ¹³C NMR (CDCl₃, 150 MHz): δ 165.8 (d, $^2J_{P-C}$ = 25 Hz), 142.1, 133.4, 131.7, 100.6, 98.77 (2C), 98.75, 98.68, 82.5, 70.5, 67.9, 65.7, 65.4, 65.2, 64.8, 63.2, 62.7 (2C), 62.5, 43.2, 42.8, 42.4, 42.2, 38.8, 38.7, 38.0, 37.7, 36.0, 34.3 (d, $^1J_{P-C}$ = 536 Hz), 30.5, 30.3, 29.7, 24.7, 20.0 (2C), 19.9, 19.8, 16.5 (2C), 16.4, 15.8. IR (neat, cm⁻¹): 2990 (s), 2940

(s), 2915 (s), 1730 (s), 1460 (w), 1380 (s), 1265 (s), 1225 (s), 1200 (s), 1170 (s), 1110 (s), 1050 (s), 1025 (s), 970 (s), 940 (s). $[\alpha]_D^{+13}$ (c 0.525, CDCl_3).

All-*trans*-7-(tributylstannyl)-hepta-2,4,6-trienoic acid, ethyl ester. To a solution of all-*trans*-5-(tributylstannyl)-2,4-pentadien-1-ol⁷ (200 mg, 0.54 mmol) and Et_3N (0.4 mL) in CH_2Cl_2 (3 mL), a solution of SO_3 ·pyridine complex (260 mg, 1.62 mmol) in DMSO (1.2 mL) was added slowly at 0°C. After addition, the reaction was stirred at ambient temperatures for 3 h and concentrated. The corresponding conjugated aldehyde (173 mg, 86% yield) was purified by flash chromatography on silica gel pretreated with 2.5 volume% of Et_3N with mixture of pentane – ether (95 : 5). Spectroscopic characteristics were identical to previously reported.⁷

This aldehyde (160 mg, 0.43 mmol) was dissolved in CH_2Cl_2 (5 mL) and (carbethoxymethylene)triphenylphosphorane (450 mg, 1.29 mmol) was added. The reaction was stirred for 2 days, then concentrated and chromatographed on silica gel pretreated with 2.5 volume% of Et_3N with pentane – ether (95 : 5) yielding above ethyl ester in 95% (184 mg).

Ethyl ester. ¹H NMR (CDCl_3 , 600 MHz): δ 7.31 (dd, 1H, J = 15.6, 11.4 Hz), 6.63 (m, 2H), 6.51 (dd, 1H, J = 15.0, 11.4 Hz), 6.25 (dd, 1H, J = 14.4, 11.4 Hz), 5.90 (d, 1H, J = 15.0 Hz), 4.21 (q, 2H, J = 7.8 Hz), 1.51 (m, 6H), 1.31 (m, 12H), 0.94 (t, 3H, J = 7.8 Hz), 0.90 (t, 9H, J = 7.2 Hz). ¹³C NMR (CDCl_3 , 150 MHz): δ 167.2, 146.0, 144.9, 143.1, 142.3, 128.8, 121.4, 60.4, 29.2, 27.4, 14.5, 13.9, 9.8. IR (neat, cm^{-1}): 2955 (s), 2920 (s), 2850 (m), 1715 (s), 1620 (s), 1460 (m), 1365 (m), 1325 (m), 1240 (m), 1200 (m), 1540 (m), 1130 (s), 1010 (m), 845 (w). HRMS (FAB+): Calcd. for $\text{C}_{21}\text{H}_{39}\text{O}_2\text{Sn}^{120}$ ($[\text{M}+\text{H}]^+$), 443.1972. Found, 443.1960.

All-*trans*-7-(tributylstannyl)-2,4,6-heptatrien-1-ol. To a solution of all-*trans*-7-(tributylstannyl)-hepta-2,4,6-trienoic acid, ethyl ester (90 mg, 0.2 mmol) in CH_2Cl_2 (2 mL), 1M solution of DIBAL-H in CH_2Cl_2 (600 μL , 0.6 mmol) was added at –78°C. The reaction was stirred for 50 min at –78°C then diluted with AcOEt (2 mL) and allowed to

7. Dominguez, B.; Iglesias, B.; Lera, A. R. *Tetrahedron* **1999**, 55, 15071.

warm to room temperature. The mixture was poured into saturated aqueous potassium sodium tartrate and extracted with CH_2Cl_2 . Organic fractions were dried with MgSO_4 , filtered and concentrated. The labile triene-alcohol was isolated in 75% yield (60 mg) after flash chromatography on silica gel pretreated with 2.5 volume% of Et_3N with mixture of pentane – ether (7 : 3). This compound was protected from light, stored in a refrigerator and used in following reactions within two weeks.

^1H NMR (CDCl_3 , 600 MHz): δ 6.57 (dd, 1H, J = 18.0, 9.6 Hz), 6.33 - 6.27 (m, 2H), 6.22 - 6.19 (m, 2H), 5.88 (m, 1H), 4.22 (t, 2H, J = 5.4 Hz), 1.51 (m, 6H), 1.32 (m, 6H), 0.92 - 0.88 (m, 15H). ^{13}C NMR (CDCl_3 , 150 MHz): δ 146.7, 136.3, 136.0, 132.6, 131.8, 130.8, 63.7, 29.3, 27.5, 13.9, 9.7. IR (neat, cm^{-1}): 3305 (m, br), 2955 (s), 2920 (s), 2852 (s), 1605 (w), 1550 (w), 1460 (m), 1375 (m), 1290 (w), 1180 (w), 1080 (m), 1000 (s), 870 (w). HRMS (FAB+): Calcd. for $\text{C}_{19}\text{H}_{36}\text{OSn}^{120}\text{Li}$ ($[\text{M}+\text{Li}]^+$), 407.1948. Found, 407.1961.

Polyene 51. All-*trans*-7-(tributylstannyl)-2,4,6-heptatrien-1-ol (16.1 mg, 40.0 μmol), *i*- Pr_2NEt (7 μL , 40.0 μmol) and Ph_3As (6.5 mg, 20.0 μmol) were dissolved in THF (250 μL). The reaction flask was wrapped in aluminum foil, and a solution of iodide **50** (10.0 mg, 10.0 μmol) in THF (250 μL) and a solution of $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ (2.0 mg, 2.0 μmol) in THF (250 μL) were added simultaneously over 2 h. The reaction was stirred at ambient temperature for 20 h, then concentrated and chromatographed on silica gel pretreated with 2.5 volume% of Et_3N with mixture of pentane – ether (1 : 1 $\rightarrow$ 3 : 7) and then with straight ether. 2.7 mg (27%) of starting iodide **50** was recovered along with 3.1 mg (32%) of desired polyene alcohol **56**.

^1H NMR (CDCl_3 , 600 MHz): δ 6.32- 6.27 (m, 2H), 6.25- 6.11 (m, 4H), 5.85 (m, 1H), 5.71 (m, 1H), 5.50 (m, 2H), 4.72 (dd, 1H, J = 7.8, 4.8 Hz), 4.30 (m, 1H), 4.21 (m, 2H), 4.18 (m, 4H), 4.11- 4.03 (m, 4H), 3.96 (m, 2H), 3.86 (m, 1H), 2.98 (dd, 2H, $^3J_{\text{H-H}}$ = 1.2 Hz, $^2J_{\text{P-H}}$ = 21 Hz), 2.46 (m, 1H), 2.35 (m, 1H), 2.25- 2.18 (m, 2H), 1.89- 1.80 (m, 3H), 1.58 (m, 5H), 1.52- 1.47 (m, 6H), 1.44 (s, 6H), 1.42 (s, 3H), 1.401 (s, 3H), 1.395 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H), 1.35 (s, 3H), 1.32 (s, br, 3H), 1.00 (d, 3H, J = 6.6 Hz), 0.89 (d, 6H, 6.6 Hz).

Macrolactone 52. To a solution of alcohol **51** (3.0 mg, 3.0 μmol) in CH_2Cl_2 (250 μL), crystalline NaHCO_3 (6.3 mg, 75.0 μmol) was added, followed by addition of Dess-Martin periodinane (2.6 mg, 6.0 μmol). The reaction was protected from light and stirred for 2.5 h, then diluted with mixture of saturated $\text{NaHCO}_3(\text{aq})$ and water (3: 1, 0.2 mL) and extracted with ether. Organic fractions were dried with Na_2SO_4 , decanted and concentrated yielding crude aldehyde as 1: 1 mixture of two isomers.

^1H NMR (CDCl_3 , 600 MHz): δ 9.58 (d, 0.5H, J = 8.4 Hz), 9.57 (d, 0.5H, J = 8.4 Hz), 7.24-7.12 (m, 2H), 6.74- 6.67 (m, 1H), 6.52- 6.39 (m, 2H), 6.28- 6.14 (m, 2H), 5.90 (m, 1H), 5.50 (m, 2H), 4.72 (m, 1H, J = 7.2, 4.8 Hz), 4.30 (m, 1H), 4.18 (p, 4H, J = 6.6 Hz), 4.10-4.02 (m, 4H), 3.97 (m, 2H), 3.91 (m, 1H), 2.98 (d, 2H, $^2J_{\text{P-H}}$ = 21.6 Hz), 2.55 (dd, 1H, J = 14.4, 5.4 Hz), 2.46 (m, 1H), 2.38 (m, 1H), 2.28 (m, 1H), 1.90- 1.81 (m, 3H), 1.59 (m, 5H), 1.49 (m, 6H), 1.44 (s, 6H), 1.43 (s, 3H), 1.403 (s, 3H), 1.396 (s, 3H), 1.387 (s, 3H), 1.36 (s, 3H), 1.35 (s, 3H), 1.32 (s, br, 3H), 1.26 (s, br, 3H), 1.00 (d, 3H, J = 7.2 Hz), 0.89 (d, 6H, J = 6.6 Hz).

LiCl (3.1 mg, 75.0 μmol) was dried under vacuum at 145 $^\circ\text{C}$ for several hours, then cooled to room temperature and combined with an acetonitrile (2.4 mL) solution of crude aldehyde obtained by oxidation of **51** (ca. 3.0 μmol). The reaction was shielded from light and stirred for 30 min, then DBU (23 μL , 150.0 μmol) was added. The mixture was stirred for 2 days, diluted with pH 7 phosphate buffer (1 mL) and extracted with ether. Organic fractions were dried with Na_2SO_4 , decanted, concentrated and chromatographed on silica gel pretreated with 2.5volume% of Et_3N with mixture of pentane – ether (6 : 4). 0.7 mg (29% from alcohol **51**) of macrocyclic tetracetone **52** was isolated (R_f , 0.33, pentane - ether, 6 : 4).

^1H NMR (CDCl_3 , 600 MHz): δ 3.35 (dd, 1H, J = 15.6, 12.0 Hz), 6.58 (dd, 1H, J = 14.4, 10.8 Hz), 6.39- 6.35 (m, 2H), 6.32- 6.23 (m, 3H), 6.17- 6.13 (m, 1H), 5.81 (d, 1H, J = 15.6 Hz), 5.65- 5.59 (m, 2H), 5.41 (dd, 1H, J = 15.6, 4.2 Hz), 4.83 (dd, 1H, J = 9.6, 3.0 Hz), 4.30 (m, 1H), 4.04 (m, 1H), 3.97 (m, 3H), 3.90 (m, 1H), 3.84 (m, 1H), 3.77 (m, 1H), 2.62- 2.56 (m, 4H), 1.92- 1.89 (m, 3H), 1.56 (m, 5H), 1.48 (m, 6H), 1.45 (s, 3H), 1.40 (s, 3H), 1.39 (s, 3H), 1.38 (s, 6H), 1.35 (s, 3H), 1.29 (s, 3H), 1.18 (s, 3H), 1.03 (d, 3H, J = 6.6 Hz), 0.94 (d, 3H, J = 7.2 Hz), 0.90 (d, 3H, J = 6.6 Hz).

Synthetic RK-397 (4). To a solution of macrocyclic tetracetone **52** (0.7 mg, 0.86 μ mol) in methanol (200 μ L) Dowex®50Wx2 acidic resin (2 mg) was added. The reaction was vigorously stirred for a day, then decanted concentrated and chromatographed on silica gel pretreated with 2.5 volume% of Et₃N with mixture of methanol – ethylacetate (2 : 8) producing ca. 0.4 mg (ca. 73% yield) of synthetic RK-397 (**4**).

¹H NMR (CDCl₃, 600 MHz): δ 7.30 (dd, 1H, J = 15.0, 11.4 Hz), 6.69 (dd, 1H, J = 14.4, 10.8 Hz), 6.53- 6.35 (m, 4H), 6.31- 6.20 (m, 2H), 5.89 (d, 1H, J = 15.6 Hz), 5.85 (m, 1H), 5.64 (dd, 1H, J = 15.6, 4.8 Hz), 5.52 (dd, 1H, J = 15.6, 4.8 Hz), 4.21 (m, 1H), 4.05 (m, 2H), 3.95- 3.90 (m, 4H), 3.81 (m, 2H), 2.64 (m, 2H), 2.14 (t, 1H, J = 6.6 Hz), 1.92 (m, 1H), 1.64 (m, 2H), 1.45 (m, 2H), 1.39 (m, 1H), 1.35 (s, br, 3H), 1.31 (s, br, 3H), 1.28 (s, br, 3H), 1.06 (d, 3H, J = 6.6 Hz), 0.97 (d, 3H, J = 6.6 Hz), 0.88 (d, 3H, J = 6.6 Hz).

Circular dichroism in MeOH: synthetic RK-397 showed a negative Cotton effect (λ_{max} , 210 nm; λ_{min} , 260 nm). UV (MeOH, λ_{max}): 360 nm. HRMS (MALDI- DHB): m/z 659.38 ([M+Na]⁺).

Figure i. ^1H NMR spectra comparison for synthetic and natural RK-397.

Figure ii. ^1H NMR spectra comparison for synthetic and natural RK-397:
7.8- 5.2 ppm and 4.4-3.4 ppm regions.

Figure iii. ^1H NMR spectra comparison for synthetic and natural RK-397:
3.0-0.8 ppm region.

Figure iv. Circular dichroism spectra of synthetic RK-397 (**4**) in methanol.

Figure v. ¹H NMR spectra comparison for natural and synthetic RK-397 tetracetone **52**.