

Supporting Information

Enantioselective Total Synthesis of Aspergillide C

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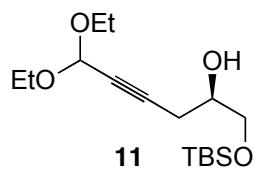
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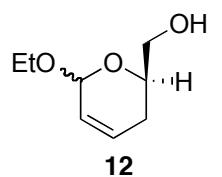
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General Information

IR spectra were recorded by an FT/IR spectrometer using an ATR (ZnSe) attachment. ¹H NMR spectra were recorded at 500 MHz and ¹³C NMR spectra were recorded at 125 MHz with TMS as an internal standard in CDCl₃. Optical rotation values were measured as solutions in CHCl₃ unless otherwise stated. High-resolution MS data were obtained by operating in the EI or FAB mode. Column chromatography was performed using 70–230 mesh silica gel. Solvents for reactions were distilled prior to use: THF from Na and benzophenone; MeOH from Mg and I₂; CH₂Cl₂ from CaH₂. All air- or moisture-sensitive reactions were conducted under a nitrogen atmosphere.

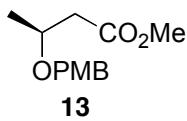


(R)-1-(tert-Butyldimethylsilyloxy)-6,6-diethoxy-4-hexyn-2-ol (11). To a stirred solution of **10** (0.393 g, 3.07 mmol) in THF (6 mL) was added dropwise *n*-BuLi (1.66 M in hexane, 1.85 mL, 3.07 mmol) at -78 °C. After 1h, a solution of **9** (0.386 g, 2.05 mmol) in THF (10 mL) was added, and the resulting mixture was stirred for 15 min. To the mixture was added dropwise BF₃·OEt₂ (0.38 mL, 3.08 mmol), and the mixture was gradually warmed to -30 °C and stirred overnight. The mixture was quenched with satd NaHCO₃ aq and extracted with EtOAc. The extract was successively washed with water and brine, dried (Na₂SO₄), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc = 6:1) to give 0.592 g (91%) of **11** as a pale yellow oil. [α]²⁸_D -10.8 (c 1.58, CHCl₃); IR: ν_{max} 3451 (br m), 2245 (w), 1050 (s), 835 (s); ¹H NMR (500 MHz): δ 0.08 (6H, s), 0.91 (9H, s), 1.23 (6H, t, *J* = 7.1 Hz), 2.43–2.54 (3H, m), 3.54–3.63 (3H, m), 3.69–3.76 (3H, m), 3.79–3.86 (1H, m), 5.26 (1H, s); ¹³C NMR (125 MHz): δ -5.48, -5.45, 15.0 (2C), 18.2, 23.2, 25.8 (3C), 60.7 (2C), 65.6, 70.0, 77.7, 82.2, 91.3; HRMS (FAB): *m/z* calcd for C₁₆H₃₂O₄SiNa, 339.1968; found, 339.1966 ([M+Na]⁺).

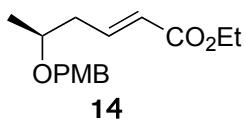


[(2R,6R/S)-6-Ethoxy-3,6-dihydro-2H-pyran-2-yl]methanol (12). A mixture of **11** (298 mg, 0.941 mmol), 5% Pd/BaSO₄ (107 mg) and quinoline (8 μL) in EtOH (4.5 mL) was stirred at rt for 20 min under a hydrogen atmosphere. The hydrogen was replaced with nitrogen gas, and then camphorsulfonic acid (72 mg) was added. The resulting mixture was stirred for 1.5 h, and filtered. The filtrate was diluted with satd NaHCO₃ aq and extracted with CH₂Cl₂. The extract was washed with brine, dried (Na₂SO₄), and concentrated in vacuo. The residue was purified by silica gel column chromatography to give 118 mg (79%) of **12** as a pale yellow oil. [α]²⁵_D +55.3 (c 1.73, CHCl₃) (lit.⁹ [α]²⁰_D -58 (c 0.74, CHCl₃) for the (2S)-enantiomer of **12**); IR: ν_{max} 3452 (br m), 3044 (w), 1658 (w), 1048 (s), 1004 (s); ¹H NMR (500 MHz): δ 1.25 (3H, t, *J* = 7.1 Hz), 1.90 (1H, dm, *J* = 17.6 Hz), 2.02–2.08 (1H, br m, OH), 2.14 (1H, dm, *J* = 17.6 Hz), 3.54 (1H, dq, *J*

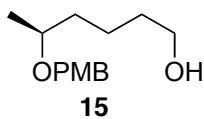
δ = 9.3, 7.1 Hz), 3.61 (1H, dt, J = 11.7, 5.9 Hz), 3.74 (1H, ddd, J = 11.7, 7.1, 2.9 Hz), 3.85 (1H, dq, J = 9.3, 7.1 Hz), 4.02–4.08 (1H, m), 5.02 (1H, br s), 5.76 (1H, dm, J = 9.8 Hz), 6.02 (1H, dd, J = 9.8, 5.9 Hz); ^{13}C NMR (125 MHz): δ 15.3, 25.9, 63.3, 65.2, 66.8, 94.4, 125.4, 128.3; HRMS (EI): m/z calcd for $\text{C}_8\text{H}_{14}\text{O}_3$, 158.0943; found, 158.0952 (M^+).



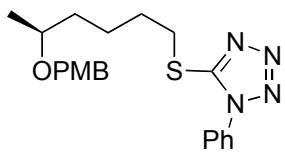
Methyl (S)-3-(4-methoxybenzyloxy)butanoate (13). Compound **13** was prepared from methyl (S)-3-hydroxybutanoate in 95% yield according to the literature [PMBOC(=NH)CCl₃, CSA, CH₂Cl₂, rt, 7 h].^{8a} $[\alpha]^{26}_{\text{D}} +23.0$ (c 1.19, CHCl₃) [lit.^{8c} $[\alpha]_{\text{D}} -22.0$ (c 10.7, CHCl₃) for the (*R*)-enantiomer of **13**]; IR: ν_{max} 1736 (vs), 1613 (m), 1513 (s), 1246 (vs), 1173 (s), 1033 (s); ^1H NMR (500 MHz): δ 1.24 (3H, d, J = 6.3 Hz), 2.42 (1H, dd, J = 15.1, 5.4 Hz), 2.64 (1H, dd, J = 15.1, 7.3 Hz), 3.67 (3H, s), 3.79 (3H, s), 3.95–4.02 (1H, m), 4.43 (1H, d, J = 11.2 Hz), 4.50 (1H, d, J = 11.2 Hz), 6.86 (2H, d, J = 8.5 Hz), 7.24 (2H, d, J = 8.5 Hz); ^{13}C NMR (125 MHz): δ 19.8, 41.8, 51.5, 55.2, 70.5, 71.5, 113.7 (2C), 129.2 (2C), 130.5, 159.1, 171.9; HRMS (EI): m/z calcd for $\text{C}_{13}\text{H}_{18}\text{O}_4$, 238.1205; found, 238.1205 (M^+).



Ethyl (S)-5-(4-Methoxybenzyloxy)-2-hexenoate (14). To a stirred solution of **13** (2.10 g, 8.81 mmol) in CH₂Cl₂ (60 mL) was added dropwise DIBAL (1.03 M in hexane, 10.0 mL, 10.3 mmol) at –78 °C. After 4 h, the mixture was quenched with satd Rochelle's salt aq, and then gradually warmed to rt. The mixture was extracted with EtOAc, and the extract was successively washed with water and brine, dried (MgSO₄), and concentrated in vacuo to give an aldehyde intermediate (1.87 g) as a yellow oil, which was taken up in THF (20 mL). The solution was added dropwise to a solution of Ph₃P=CHCO₂Et (3.89 g, 11.2 mmol) in THF (30 mL) at rt. The mixture was stirred at 65 °C for 2 h, and then at rt overnight before being concentrated in vacuo. The residue was diluted with a mixture of hexane and ether, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to give 2.23 g (91%) of **14** as a pale yellow oil. $[\alpha]^{26}_{\text{D}} +7.03$ (c 1.53, CHCl₃); IR: ν_{max} 1716 (s), 1513 (m), 1246 (s), 1173 (m), 1035 (m); ^1H NMR (500 MHz): δ 1.21 (3H, d, J = 5.9 Hz), 1.23 (3H, t, J = 7.2 Hz), 2.32–2.39 (1H, m), 2.43–2.50 (1H, m), 3.60–3.67 (1H, m), 3.79 (3H, s), 4.19 (2H, q, J = 7.2 Hz), 4.42 (1H, d, J = 11.2 Hz), 4.50 (1H, d, J = 11.2 Hz), 5.87 (1H, d, J = 15.6 Hz), 6.87 (2H, d, J = 8.5 Hz), 6.97 (1H, dt, J = 15.6, 7.6 Hz), 7.25 (2H, d, J = 8.5 Hz); ^{13}C NMR (125 MHz): δ 14.2, 19.6, 39.2, 55.2, 60.1, 70.1, 73.1, 113.7 (2C), 123.3, 129.1 (2C), 130.5, 145.3, 159.1, 166.3; HRMS (EI): m/z calcd for $\text{C}_{16}\text{H}_{22}\text{O}_4$, 278.1518; found, 278.1523 (M^+).

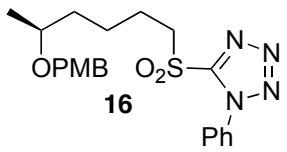


(S)-5-(4-Methoxybenzyloxy)-1-hexanol (15). To a stirred suspension of NiCl_2 (0.858 g, 6.49 mmol) in MeOH (15 mL) was added a solution of **14** (1.77 g, 6.38 mmol) in MeOH (25 mL) at 0 °C. To the mixture was added portionwise NaBH_4 (1.34 g, 34.7 mmol) over 20 min, and the mixture was stirred for 3 h before being filtered. The filtrate was diluted with satd NaHCO_3 aq and concentrated vacuo. The residue was diluted with water and extracted with EtOAc . The extract was successively washed with water and brine, dried (MgSO_4), and concentrated in vacuo to give a saturated ester intermediate as a colorless oil (1.83 g). The ester was dissolved in THF (15 mL) and added dropwise to a stirred suspension of LiAlH_4 (0.318 g, 8.37 mmol) in THF (35 mL) at 0 °C. After being stirred at rt for 6 h, the mixture was quenched by successively adding water (0.3 mL), 10% NaOH aq (0.3 mL), and water (1.0 mL). The mixture was then dried (MgSO_4) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ EtOAc = 2:1) to give 1.48 g (97%) of **15** as a colorless oil. $[\alpha]^{26}_D +28.2$ (*c* 1.16, CHCl_3); IR: ν_{max} 3387 (br m), 1613 (m), 1513 (s), 1245 (s), 1034 (s); ^1H NMR (500 MHz): δ 1.18 (3H, d, *J* = 5.9 Hz), 1.35–1.49 (3H, m), 1.49–1.63 (3H, m), 1.80 (1H, br s, OH), 3.46–3.53 (1H, m), 3.60 (2H, t, *J* = 6.6 Hz), 3.79 (3H, s), 4.37 (1H, d, *J* = 11.7 Hz), 4.50 (1H, d, *J* = 11.7 Hz), 6.87 (2H, d, *J* = 8.5 Hz), 7.26 (2H, d, *J* = 8.5 Hz); ^{13}C NMR (125 MHz): δ 19.5, 21.7, 32.6, 36.3, 55.2, 62.6, 69.9, 74.4, 113.7 (2C), 129.2 (2C), 131.0, 159.0; HRMS (EI): *m/z* calcd for $\text{C}_{14}\text{H}_{22}\text{O}_3$, 238.1569; found, 238.1574 (M^+).

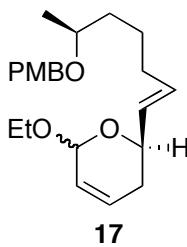


5-[(S)-5-(4-Methoxybenzyloxy)hexylthio]-1-phenyl-1H-tetrazole. To a stirred mixture of 1-phenyl-1*H*-tetrazole-5-thiol (1.41 g, 7.77 mmol) and Ph_3P (2.05 g, 7.81 mmol) in CH_2Cl_2 (15 mL) was successively added a solution of **15** (1.65 g, 6.94 mmol) in CH_2Cl_2 (20 mL) and a solution of DEAD (40 % in toluene, 3.80 mL, 8.34 mmol) at 0 °C. The mixture was at rt for 3.5 h, quenched with satd NaHCO_3 aq., and extracted with CH_2Cl_2 . The extract was washed with brine, dried (MgSO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ EtOAc = 5:1) to give 2.65 g (96%) of the title compound as a colorless oil. $[\alpha]^{26}_D +18.0$ (*c* 1.20, CHCl_3); IR: ν_{max} 1612 (m), 1511 (s), 1499 (s), 1244 (s), 1034 (m); ^1H NMR (500 MHz): δ 1.17 (3H, d, *J* = 5.9 Hz), 1.43–1.52 (2H, m), 1.53–1.63 (2H, m), 1.81 (2H, qui, *J* = 7.3 Hz), 3.80 (2H, t, *J* = 7.3 Hz), 3.49 (1H, sex, *J* = 5.9 Hz), 3.78 (3H, s), 4.35 (1H, d, *J* = 11.2 Hz), 4.50 (1H, d, *J* = 11.2 Hz), 6.86 (2H, d, *J* = 8.5 Hz), 7.25 (2H, d, *J* = 8.5 Hz), 7.51–7.59 (5H, m); ^{13}C NMR (125 MHz): δ 19.5, 24.5, 29.0, 33.2, 36.0, 55.2, 69.9, 73.9, 113.7 (2C), 123.8 (2C), 129.1 (2C), 129.7 (2C), 130.0, 130.9, 133.6, 154.4, 159.0; HRMS (FAB): *m/z* calcd for $\text{C}_{21}\text{H}_{27}\text{O}_2\text{N}_4\text{S}$, 399.1855; found, 399.1859 ($[\text{M}+\text{H}]^+$).

5-[(S)-5-(4-Methoxybenzyloxy)hexane-1-sulfonyl]-1-phenyl-1*H*-tetrazole

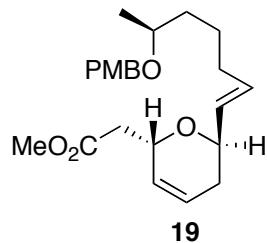


(16). To a stirred solution of **15** (2.61 g, 6.54 mmol) in CH_2Cl_2 (30 mL) was added portionwise MCPBA (5.42 g, 20.4 mmol) at 0 °C. The mixture was gradually warmed to rt and stirred overnight before being quenched with satd $\text{Na}_2\text{S}_2\text{O}_3$ aq at 0 °C. The mixture was diluted with a mixture of CH_2Cl_2 , Et_2O and 5 M NaOH aq, and extracted with Et_2O . The extract was successively washed satd NaHCO_3 aq and brine, dried (MgSO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ EtOAc = 4:1) to give 2.47 g (88%) of **16** as a colorless oil. $[\alpha]^{27}_D +17.5$ (*c* 1.02, CHCl_3); IR: ν_{max} 1513 (m), 1339 (s), 1246 (s), 1149 (s), 1034 (m); ^1H NMR (500 MHz): δ 1.18 (3H, d, *J* = 5.9 Hz), 1.45–1.66 (4H, m), 1.93 (2H, qui, *J* = 7.6 Hz), 3.46–3.53 (1H, m), 3.65–3.76 (2H, m), 3.79 (3H, s), 4.34 (1H, d, *J* = 11.2 Hz), 4.51 (1H, d, *J* = 11.2 Hz), 6.87 (2H, d, *J* = 8.5 Hz), 7.25 (2H, d, *J* = 8.5 Hz), 7.57–7.64 (3H, m), 7.68 (2H, d, *J* = 6.8 Hz); ^{13}C NMR (125 MHz): δ 19.5, 22.0, 24.1, 35.9, 55.2, 55.9, 70.0, 73.6, 113.7 (2C), 125.0 (2C), 129.2 (2C), 129.7 (2C), 130.8, 131.4, 133.0, 153.4, 159.1; HRMS (FAB): *m/z* calcd for $\text{C}_{21}\text{H}_{26}\text{O}_4\text{N}_4\text{SNa}$, 453.1572; found, 453.1576 ($[\text{M}+\text{Na}]^+$).

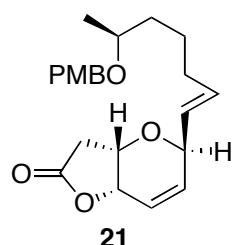


(2*R*,6*R/S*)-6-Ethoxy-2-[(1*E*,6*S*)-6-(4-methoxybenzyloxy)-1-heptenyl]-3,6-dihydro-2*H*-pyran (17). To a stirred solution of $(\text{COCl})_2$ (0.250 mL, 2.90 mmol) in CH_2Cl_2 (5 mL) was added dropwise a solution of DMSO (0.420 mL, 5.91 mmol) in CH_2Cl_2 (13 mL) at -78 °C. After 15 min, a solution of **12** (408 mg, 2.58 mmol) in CH_2Cl_2 (5 mL) was added, and the mixture was stirred for 30 min. Et_3N (1.80 mL, 12.9 mmol) was then added dropwise, and the mixture was gradually warmed to -30 °C over 3 h. The mixture was quenched with satd NaHCO_3 aq and extracted with CH_2Cl_2 . The extract was washed with brine, dried (MgSO_4), and concentrated in vacuo to give **7** (0.506 mg) as an orange oil. To a stirred solution of **16** (1.47 g, 3.41 mmol) in DME (20 mL) was added a solution of KHMDS (0.5 M in toluene, 6.80 mL, 3.40 mmol) at -78 °C. After 20 min, a solution of **7** (0.506 mg) in DME (15 mL) was added, and the mixture was stirred at -78 °C for 1 h, and then gradually warmed to -10 °C. After being stirred overnight at -10 °C, the mixture was quenched with satd NaHCO_3 aq and extracted with EtOAc . The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ EtOAc = 10:1) to give 645 mg (69%) of **17** as a colorless oil. $[\alpha]^{24}_D +46.8$ (*c* 1.18, CHCl_3); IR: ν_{max} 3039 (w), 1613 (m), 1513 (s), 1246 (s), 1039 (s); ^1H NMR (500 MHz): δ 1.17 (3H, d, *J* = 6.3 Hz), 1.24 (3H, t, *J* = 7.3 Hz), 1.37–1.62 (4H, m), 1.95–2.14 (4H, m), 3.49 (1H, sex, *J* = 6.3 Hz), 3.54 (1H, dq, *J* = 9.3, 7.3 Hz), 3.80 (3H, s), 3.84 (1H, dq, *J* = 9.3, 7.3 Hz), 4.32–4.37 (1H, m), 4.38 (1H, d, *J* = 11.2 Hz), 4.49 (1H, d, *J* = 11.2 Hz), 5.01 (1H, br s), 5.52 (1H, dd, *J* =

15.1, 6.3 Hz), 5.72 (1H, dt, J = 15.1, 6.8 Hz), 5.75 (1H, br d, J = 9.8 Hz), 6.01 (1H, dd, J = 9.8, 5.4 Hz), 6.87 (2H, d, J = 8.5 Hz), 7.26 (2H, d, J = 8.5 Hz); ^{13}C NMR (125 MHz): δ 15.4, 19.6, 24.9, 30.6, 32.3, 36.1, 55.2, 63.2, 66.8, 69.9, 74.3, 94.7, 113.7 (2C), 125.6, 128.7, 129.1 (2C), 130.1, 131.1, 132.7, 159.0; HRMS (EI): m/z calcd for $\text{C}_{22}\text{H}_{32}\text{O}_4$, 360.2300; found, 360.2303 (M^+).

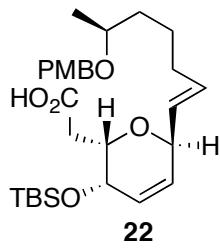


Methyl {(2*S*,6*R*)-6-[(1*E*,6*S*)-6-(4-methoxybenzyloxy)-1-heptenyl]-5,6-dihydro-2*H*-pyran-2-yl}acetate (19). To a stirred solution of **17** (47.4 mg, 0.132 mmol) in CH_3CN (1.0 mL) was successively added **18** (60.0 μL , 0.275 mmol) and $\text{BF}_3\text{:OEt}_2$ (20.0 μL , 0.162 mmol) at -30 $^{\circ}\text{C}$. After 25 min, the mixture was quenched with satd NaHCO_3 aq and extracted with EtOAc . The extract was washed with brine, dried (MgSO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ EtOAc = 10:1) to give 33.1 mg (65%) of **19** and 12.8 mg (25%) of the corresponding *cis*-isomer as pale yellow oils. $[\alpha]^{29}_D$ +60.1 (c 1.56, CHCl_3); IR: ν_{max} 3030 (w), 1738 (vs), 1613 (m), 1513 (s), 1246 (vs); ^1H NMR (500 MHz): δ 1.17 (3H, d, J = 5.9 Hz), 1.36–1.62 (4H, m), 2.00–2.13 (4H, m), 2.52 (1H, dd, J = 15.1, 5.9 Hz), 2.69 (1H, dd, J = 15.1, 8.5 Hz), 3.48 (1H, sex, J = 5.9 Hz), 3.70 (3H, s), 3.80 (3H, s), 4.15 (1H, br q, J = 6.0 Hz), 4.38 (1H, d, J = 11.2 Hz), 4.49 (1H, d, J = 11.2 Hz), 4.65–4.70 (1H, m), 5.51 (1H, dd, J = 15.6, 5.9 Hz), 5.68 (1H, dt, J = 15.6, 7.1 Hz), 5.72 (1H, dm, J = 10.3 Hz), 5.88 (1H, dm, J = 10.3 Hz), 6.87 (2H, d, J = 8.8 Hz), 7.26 (2H, d, J = 8.8 Hz); ^{13}C NMR (125 MHz): δ 19.6, 25.0, 30.1, 32.3, 36.1, 39.5, 51.7, 55.2, 68.8, 69.1, 69.9, 74.3, 113.7 (2C), 125.0, 128.1, 129.1 (2C), 129.9, 131.1, 132.9, 159.0, 171.4; HRMS (FAB): m/z calcd for $\text{C}_{23}\text{H}_{32}\text{O}_5\text{Na}$, 411.2147; found, 411.2145 ($[\text{M}+\text{Na}]^+$).



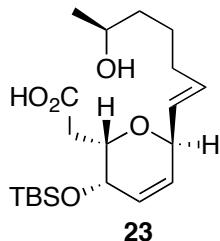
(3*aS*,5*R*,7*aS*)-5-[(1*E*,6*S*)-6-(4-Methoxybenzyloxy)-1-heptenyl]-3,3*a*,5,7*a*-tetrahydrofuro[3,2-*b*]pyran-2-one (21). To a stirred solution of **19** (113.6 mg, 0.292 mmol) in THF (0.6 mL) was added a solution of NaOH (35.0 mg, 0.875 mmol) in water (0.15 mL) at rt. The mixture was stirred at 40 $^{\circ}\text{C}$ for 5 h, and then cooled to rt. To the mixture was successively added a solution of NaHCO_3 (241 mg, 2.87 mmol) in water (1 mL) and a solution of I_2 (102 mg, 0.400 mmol) and KI (269 mg, 1.62 mmol) in water (1 mL). After being stirred overnight in the dark, the mixture was quenched with satd $\text{Na}_2\text{S}_2\text{O}_3$ aq and extracted with CHCl_3 . The extract was washed with brine, dried (MgSO_4), and concentrated in vacuo to give **20** (162 mg) as a yellow oil [^1H NMR (500 MHz): δ 1.18 (3H, d, J = 6.3 Hz, 14-H₃), 1.36–1.62 (4H, m, 11-H₂ and 12-H₂), 2.00–2.08 (2H, m, 10-H₂), 2.09 (1H, ddd, J = 14.3, 12.6, 9.9 Hz, 6*β*-H), 2.46 (1H, ddd, J = 14.3, 5.2, 4.1 Hz, 6*α*-H), 2.70 (2H, d, J = 5.8 Hz, 2-H₂), 3.44–3.54 (1H, m,

13-H), 3.80 (3H, s, O-CH₃), 4.12 (1H, ddd, *J* = 12.6, 8.0, 4.1 Hz, 5-H), 4.27 (1H, ddd, *J* = 9.9, 5.8, 5.2 Hz, 7-H), 4.36 (1H, d, *J* = 11.5 Hz, Ar-CH), 4.51 (1H, d, *J* = 11.5 Hz, Ar-CH), 4.56 (1H, dt, *J* = 5.5, 5.8 Hz, 3-H), 4.78 (1H, dd, *J* = 8.0, 5.5 Hz, 4-H), 5.49 (1H, ddt, *J* = 15.4, 5.8, 1.4 Hz, 8-H), 5.70 (1H, ddt, *J* = 15.4, 1.1, 6.6 Hz, 9-H), 6.87 (2H, dm, *J* = 8.8 Hz, Ar-H₂), 7.26 (2H, dm, *J* = 8.8 Hz, Ar-H₂); aspergillide numbering (see Figure 1)]. To a stirred solution of **20** (162 mg) in THF (3.5 mL) was added DBU (75.0 μ L, 0.502 mmol) at rt. After 12 h, additional DBU (32.5 μ L, 0.217 mmol) was added, and the mixture was stirred overnight. The mixture was concentrated in vacuo, and the residue was purified by silica gel column chromatography to give 49.4 mg (45%) of **21** as a colorless oil. $[\alpha]^{26}_D$ +173 (*c* 0.850, CHCl₃); IR: ν_{max} 1770 (vs), 1612 (m), 1512 (s), 1246 (s), 1036 (s); ¹H NMR (500 MHz): δ 1.18 (3H, d, *J* = 5.9 Hz), 1.36–1.46 (2H, m), 1.46–1.60 (2H, m), 2.06 (1H, q, *J* = 6.8 Hz), 2.59 (1H, d, *J* = 18.1 Hz), 2.80 (1H, dd, *J* = 18.1, 5.4 Hz), 3.49 (1H, sex, *J* = 5.9 Hz), 3.80 (3H, s), 4.36 (1H, d, *J* = 11.2 Hz), 4.44 (1H, dd, *J* = 5.4, 3.4 Hz), 4.48 (1H, dd, *J* = 3.9, 3.4 Hz), 4.50 (1H, d, *J* = 11.2 Hz), 4.66–4.69 (1H, m), 5.52 (1H, dd, *J* = 15.6, 5.4 Hz), 5.63 (1H, dt, *J* = 15.6, 6.8 Hz), 6.10 (1H, dd, *J* = 10.3, 4.4 Hz), 6.23 (1H, dd, *J* = 10.3, 3.9 Hz), 6.87 (2H, d, *J* = 8.5 Hz), 7.26 (2H, d, *J* = 8.5 Hz); ¹³C NMR (125 MHz): δ 19.5, 24.9, 32.4, 36.2, 37.1, 55.2, 66.4, 69.9, 71.7, 72.5, 74.2, 113.7 (2C), 120.2, 126.1, 129.1 (2C), 131.0, 135.5, 136.6, 159.0, 175.2; HRMS (FAB): *m/z* calcd for C₂₂H₂₈O₅Na, 395.1834; found, 395.1834 ([M+Na]⁺).

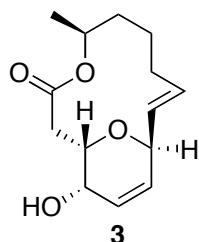


{(2S,3S,6S)-3-(tert-Butyldimethylsilyloxy)-6-[(1E,6S)-6-(4-methoxybenzyloxy)-1-heptenyl]-3,6-dihydro-2H-pyran-2-yl}acetic acid (22). To a stirred solution of **21** (17.4 mg, 46.7 μ mol) in THF (0.15 mL) was added a solution of LiOH·H₂O (2.3 mg, 55 μ mol) in water (30 μ L) at rt. After 2 h, the mixture was concentrated in vacuo to give a lithium carboxylate salt as a yellow solid, which was then taken up in DMF (0.2 mL). To the solution was successively added a solution of imidazole (19.8 mg, 0.291 mmol) and DMAP (4.3 mg, 35 μ mol) in DMF (0.25 mL) and TBSOTf (51 μ L, 0.218 mmol) at rt. After 1.5 h, water (2.0 μ L) was added, and the mixture was stirred for 2 h. The mixture was diluted with water and extracted with CH₂Cl₂. The extract was washed with brine, dried (MgSO₄), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc = 2:1) to give 23.5 mg (quant) of **22** as a pale yellow oil. $[\alpha]^{26}_D$ +160 (*c* 0.39, CHCl₃); IR: ν_{max} ~3000 (br m), 1711 (s), 1513 (s), 1248 (s), 1053 (s); ¹H NMR (500 MHz): δ 0.08 (3H, s), 0.09 (3H, s), 0.90 (9H, s), 1.17 (3H, d, *J* = 6.3 Hz), 1.35–1.45 (2H, m), 1.45–1.53 (1H, m), 1.54–1.62 (1H, m), 1.98–2.10 (2H, m), 2.60 (1H, dd, *J* = 15.6, 4.6 Hz), 2.71 (1H, dd, *J* = 15.6, 8.5 Hz), 3.49 (1H, sex, *J* = 6.3 Hz), 3.80 (3H, s), 3.99–4.02 (1H, m), 4.16–4.21 (1H, m), 4.39 (1H, d, *J* = 11.2 Hz), 4.51 (1H, d, *J* = 11.2 Hz), 4.68 (1H, d, *J* = 5.9 Hz),

5.48 (1H, dd, J = 15.1, 5.9 Hz), 5.67 (1H, dt, J = 15.1, 6.8 Hz), 5.82–5.88 (2H, m), 6.87 (2H, d, J = 8.7 Hz), 7.27 (2H, d, J = 8.7 Hz); ^{13}C NMR (125 MHz): δ –4.7, –4.2, 18.2, 19.5, 24.7, 25.8 (3C), 32.2, 35.6, 36.0, 55.3, 64.2, 69.6, 69.9, 72.5, 74.4, 113.7 (2C), 126.6, 126.9, 129.3 (2C), 130.5, 130.9, 135.4, 159.0, 174.1; HRMS (EI): m/z calcd for $\text{C}_{28}\text{H}_{44}\text{O}_6\text{Si}$, 504.2908; found, 504.2913 (M^+).



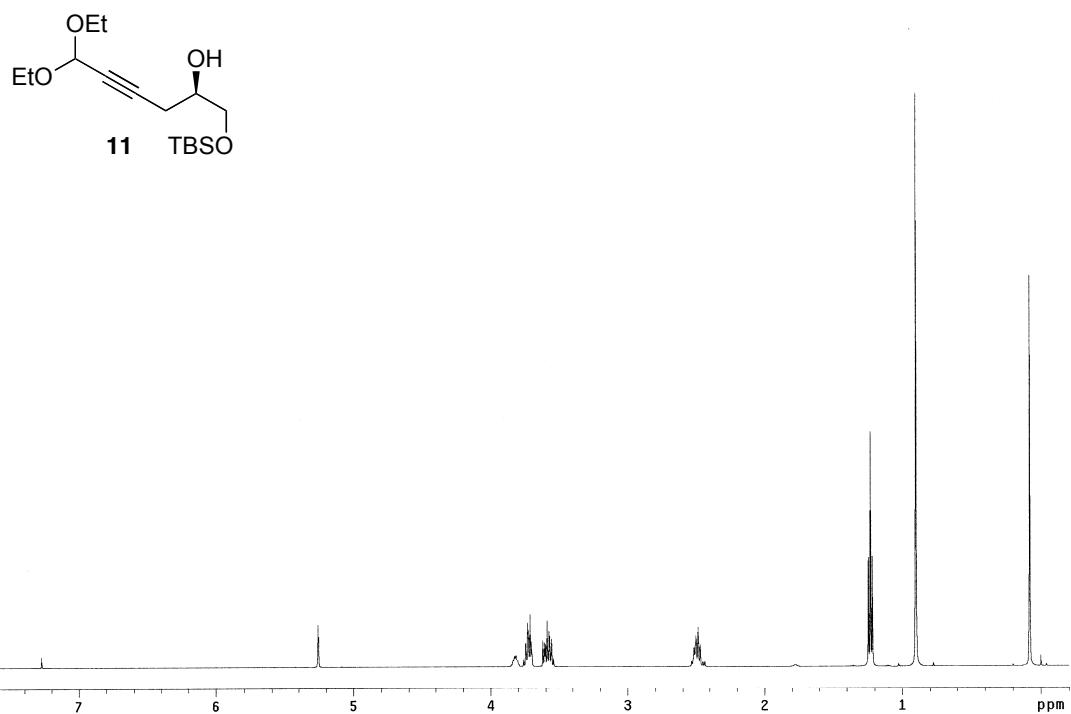
{(2S,3S,6S)-3-(tert-Butyldimethylsilyloxy)-6-[(1E,6S)-6-hydroxy-1-heptenyl]-3,6-dihydro-2H-pyran-2-yl}acetic acid (23). To a stirred mixture of **22** (13.5 mg, 26.7 μmol) in CH_2Cl_2 (0.6 mL)/1M phosphate buffer (pH 7.0, 0.3 mL) was added DDQ (31.0 mg, 133 μmol) at 0 °C. After 3 h, additional DDQ (6.5 mg, 29 μmol) was added, and the mixture was stirred at rt for 8 h. To the mixture was added again DDQ (7.9 mg, 35 μmol), and the mixture was stirred for an additional 8 h. The mixture was extracted with CH_2Cl_2 , and the extract was washed with brine, dried (MgSO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc = 2:1–1:2) to give 6.8 mg (66%) of **23** as a pale yellow oil. $[\alpha]^{25}_D$ +158 (c 0.30, CHCl_3); IR: ν_{max} 3424 (br m), 3035 (w), ~3000 (br m), 1712 (s), 1051 (s), 834 (s); ^1H NMR (500 MHz): δ 0.086 (3H, s), 0.093 (3H, s), 0.90 (9H, s), 1.18 (3H, d, J = 6.3 Hz), 1.25 (1H, s, OH), 1.34–1.52 (3H, m), 1.55–1.63 (1H, m), 2.00–2.08 (1H, m), 2.08–2.16 (1H, m), 2.53 (1H, dd, J = 16.1, 3.9 Hz), 2.72 (1H, dd, J = 16.1, 8.8 Hz), 3.82 (1H, sex, J = 6.3 Hz), 3.93–3.96 (1H, m), 4.18 (1H, dt, J = 8.8, 3.2 Hz), 4.69 (1H, d, J = 5.9 Hz), 5.51 (1H, dd, J = 15.6, 5.9 Hz), 5.66 (1H, dt, J = 15.6, 6.6 Hz), 5.85–5.91 (2H, m); ^{13}C NMR (125 MHz): δ –4.6, –4.1, 18.2, 22.8, 24.4, 25.9 (3C), 31.7, 36.0, 37.7, 64.4, 68.1, 69.5, 72.5, 126.7, 127.5, 130.7, 134.8, 174.9; HRMS (FAB): m/z calcd for $\text{C}_{20}\text{H}_{36}\text{O}_5\text{SiNa}$, 407.2229; found, 407.2237 ($[\text{M}+\text{Na}]^+$).



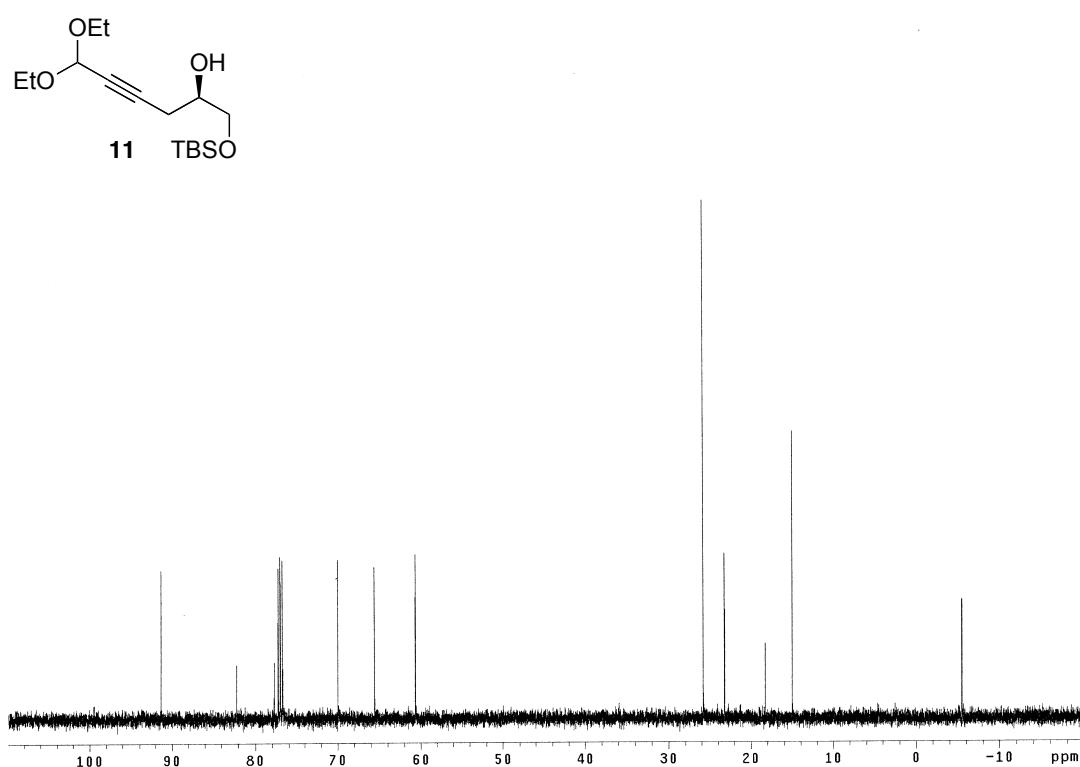
(1S,5S,9E,11S,14S)-14-Hydroxy-5-methyl-4,15-dioxabicyclo[9.3.1]pentadeca-9,12-dien-3-one (3). To a stirred solution of **23** (4.0 mg, 10 μmol) and Et_3N (10 μL , 72 μmol) in THF (0.15 mL) was added 2,4,6-trichlorobenzoyl chloride (9.0 μL , 56 μmol) at 0 °C, and the mixture was stirred at 0 °C for 1 h, and then at rt for 2.5 h. The mixture was diluted with toluene (2 mL) and stirred for an additional 1.5 h. The resulting mixture was added dropwise to a solution of DMAP (32.4 mg, 265 μmol) in toluene (15 mL) at 100 °C over 7 h. After being cooled to rt, the mixture was diluted with EtOAc, and the solution was successively washed with 0.5 M HCl aq, satd NaHCO_3 aq, and brine, dried (MgSO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1) to give a macrolactone intermediate (5.4 mg) as a yellow oil, which was then taken up in THF (0.1 mL). To the solution was added a mixture of TBAF (1M solution in THF) and HF (40% aqueous solution) (25:1, 40

μL) at rt, and the mixture was stirred overnight before being diluted with water. The mixture was diluted with EtOAc and washed with brine, dried (MgSO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography to give 2.0 mg (76%) of **3** as a white solid (mp 115.5–116.0 °C). $[\alpha]^{25}_{\text{D}} +83$ (*c* 0.14, MeOH) (lit.¹ $[\alpha]^{25}_{\text{D}} +66.2$ (*c* 0.19, MeOH); IR: ν_{max} 3268 (br m), 3030 (w), 1720 (s), 1288 (m), 1242 (m), 1180 (m), 1075 (m), 1034 (s); ¹H NMR (500 MHz, C_6D_6): δ 0.99 (3H, d, *J* = 6.8 Hz), 1.12–1.21 (1H, m), 1.25–1.33 (1H, m), 1.31 (1H, d, *J* = 11.2 Hz, OH), 1.37–1.46 (1H, m), 1.54–1.64 (2H, m), 1.92–1.99 (1H, m), 2.25 (1H, dd, *J* = 13.9, 1.7 Hz), 2.87 (1H, dd, *J* = 13.9, 11.2 Hz), 3.23 (1H, dd, *J* = 11.2, 5.4 Hz), 4.04 (1H, br d, *J* = 11.2 Hz), 4.45–4.49 (1H, m), 5.11–5.17 (1H, m), 5.18 (1H, dd, *J* = 15.6, 3.9 Hz), 5.42 (1H, dd, *J* = 9.8, 3.7 Hz), 5.74 (1H, ddd, *J* = 9.8, 5.4, 2.0 Hz), 5.94 (1H, dddd, *J* = 15.6, 9.3, 5.9, 1.5 Hz); ¹³C NMR (125 MHz): δ 18.7, 23.7, 31.0, 32.0, 38.8, 64.5, 69.5, 69.8, 72.0, 126.2, 128.3, 131.8, 135.0, 170.0; HRMS (EI): *m/z* calcd for $\text{C}_{14}\text{H}_{20}\text{O}_4$, 252.1362; found, 252.1362 (M^+).

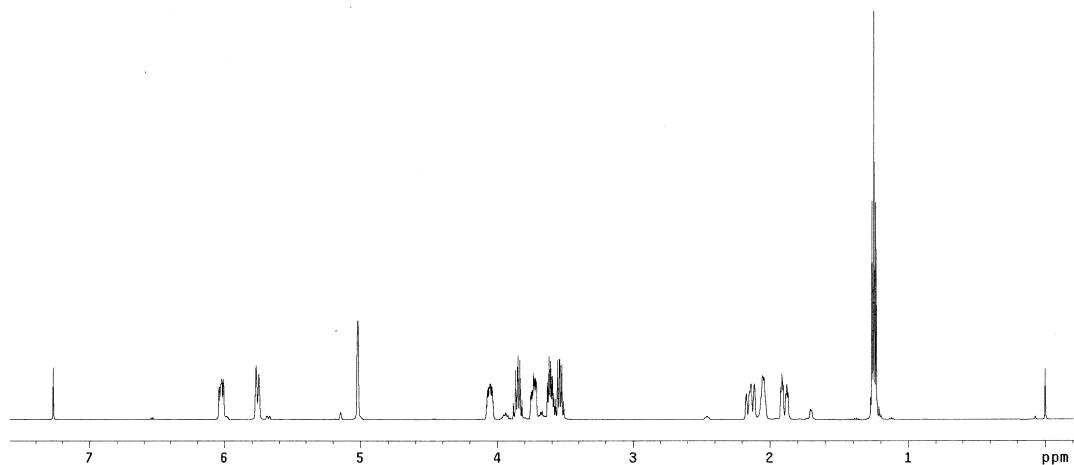
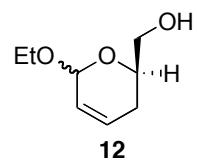
¹H NMR (500 MHz, CDCl₃)



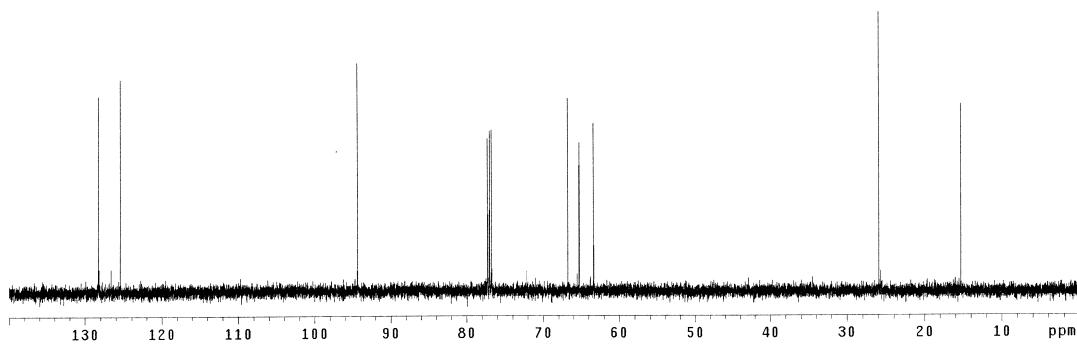
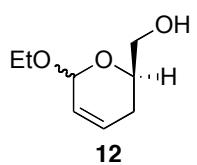
¹³C NMR (125 MHz, CDCl₃)



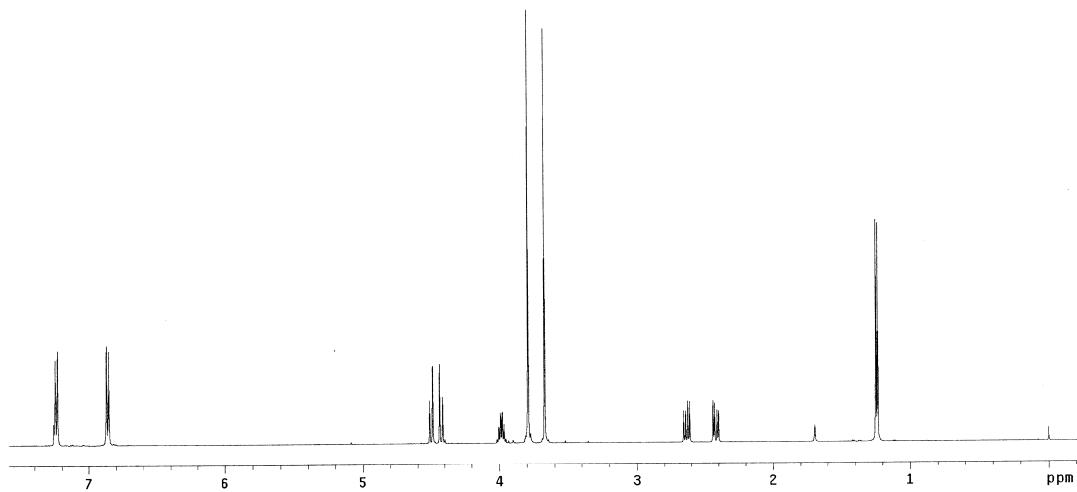
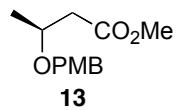
¹H NMR (500 MHz, CDCl₃)



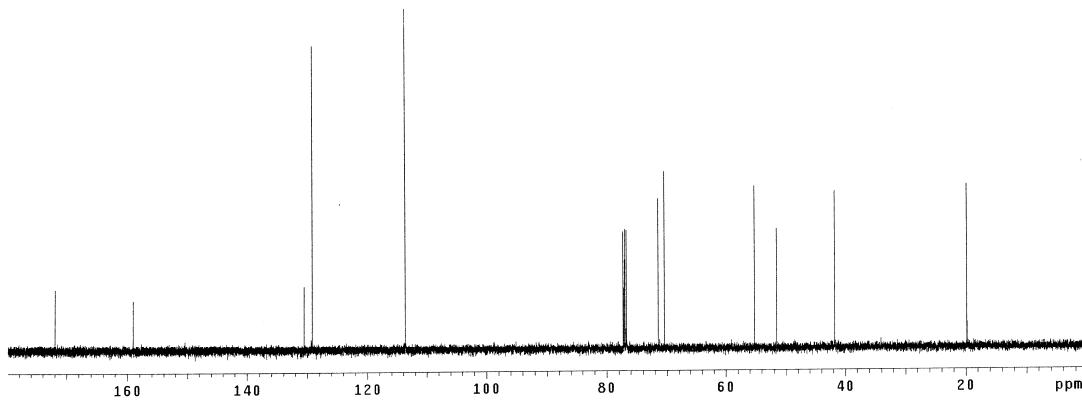
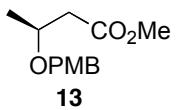
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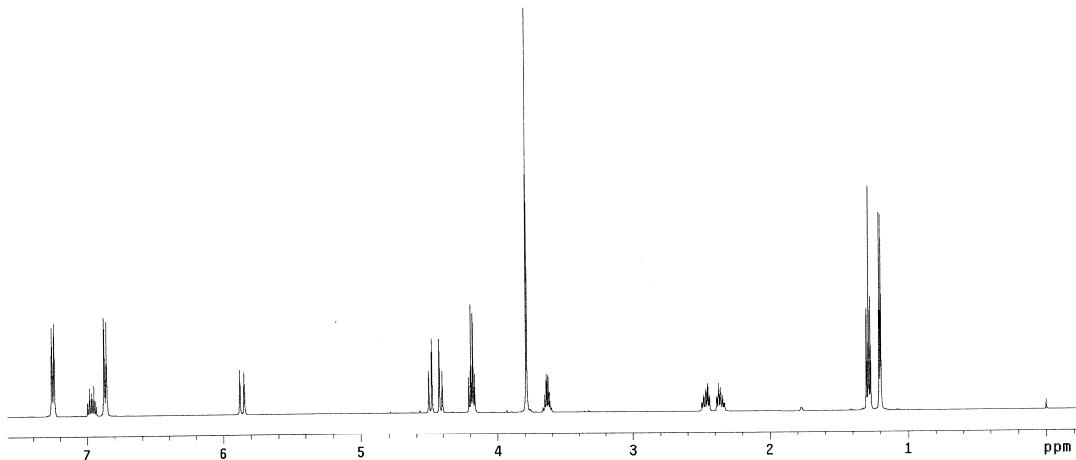
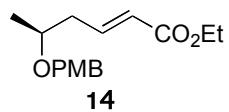
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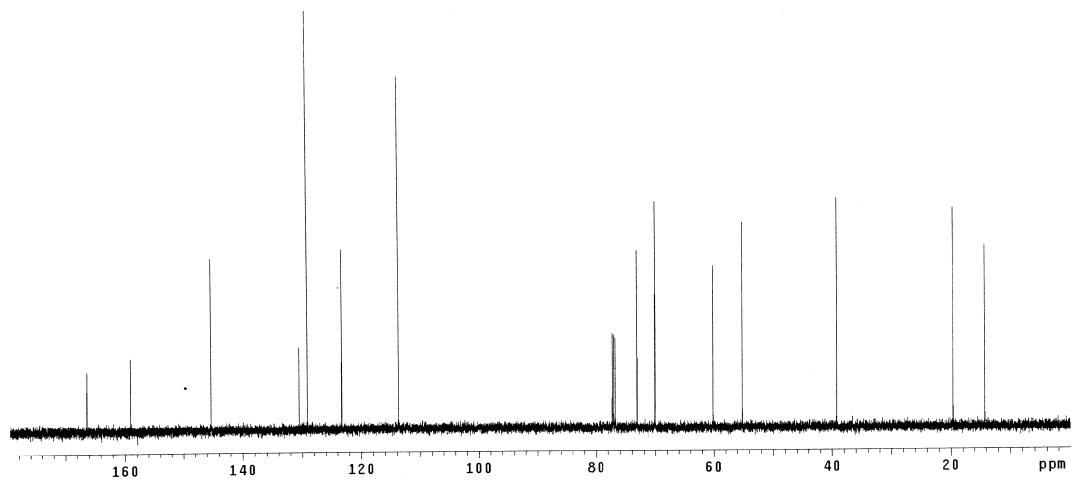
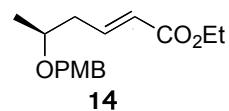
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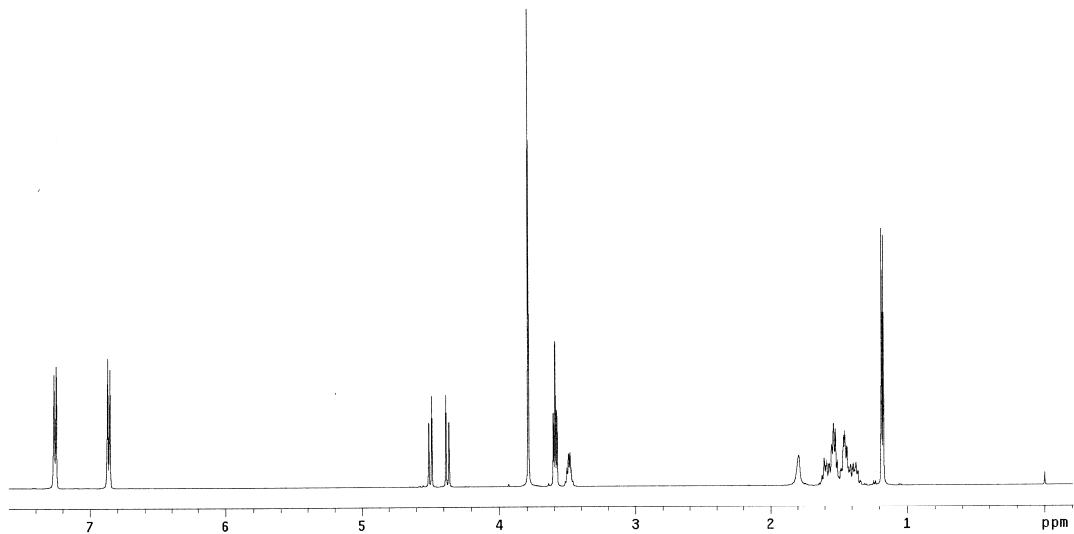
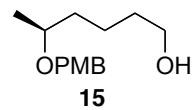
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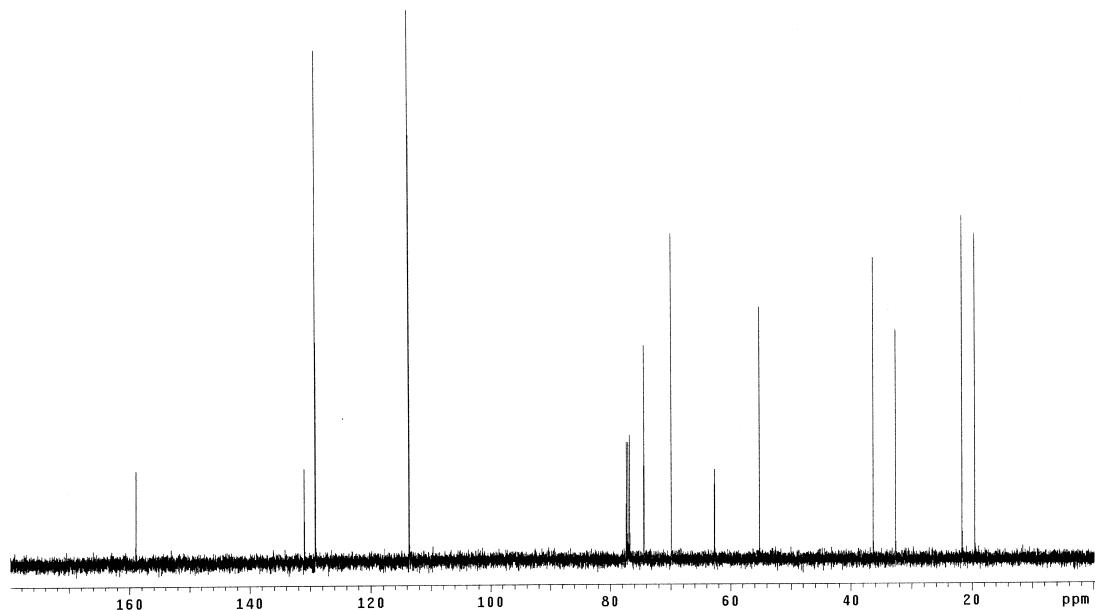
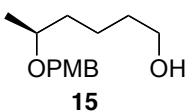
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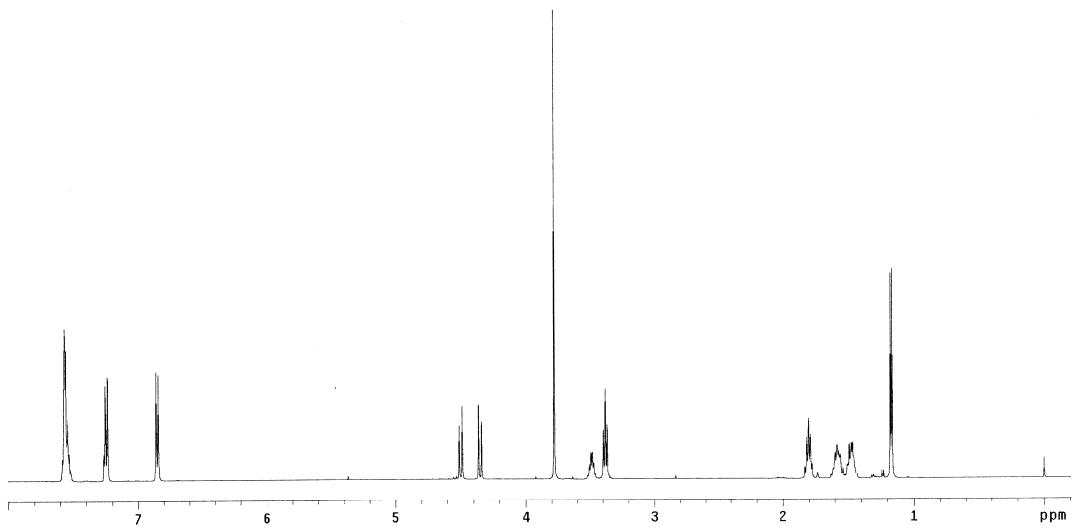
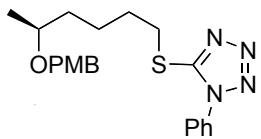
^1H NMR (500 MHz, CDCl_3)



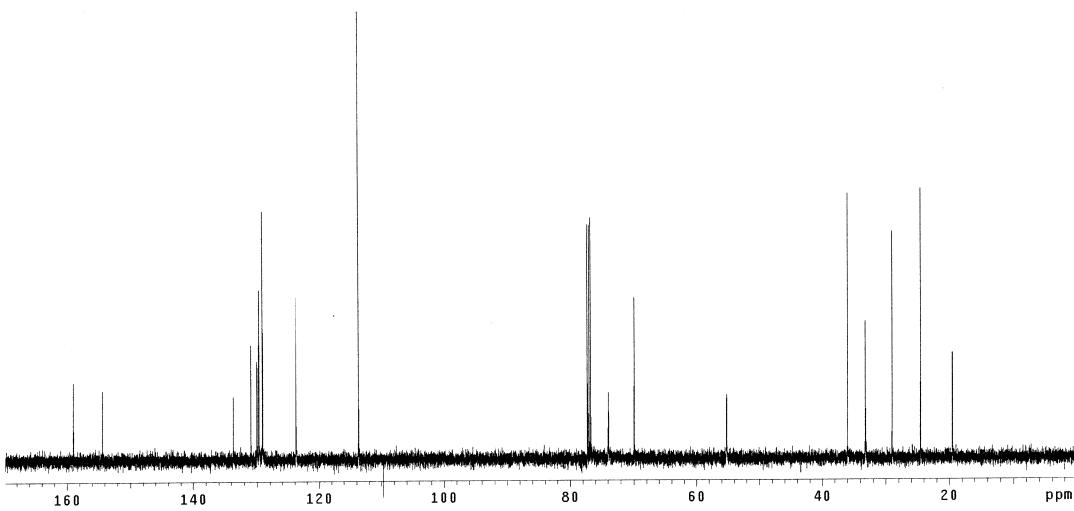
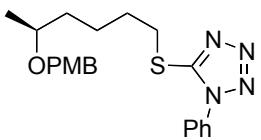
^{13}C NMR (125 MHz, CDCl_3)



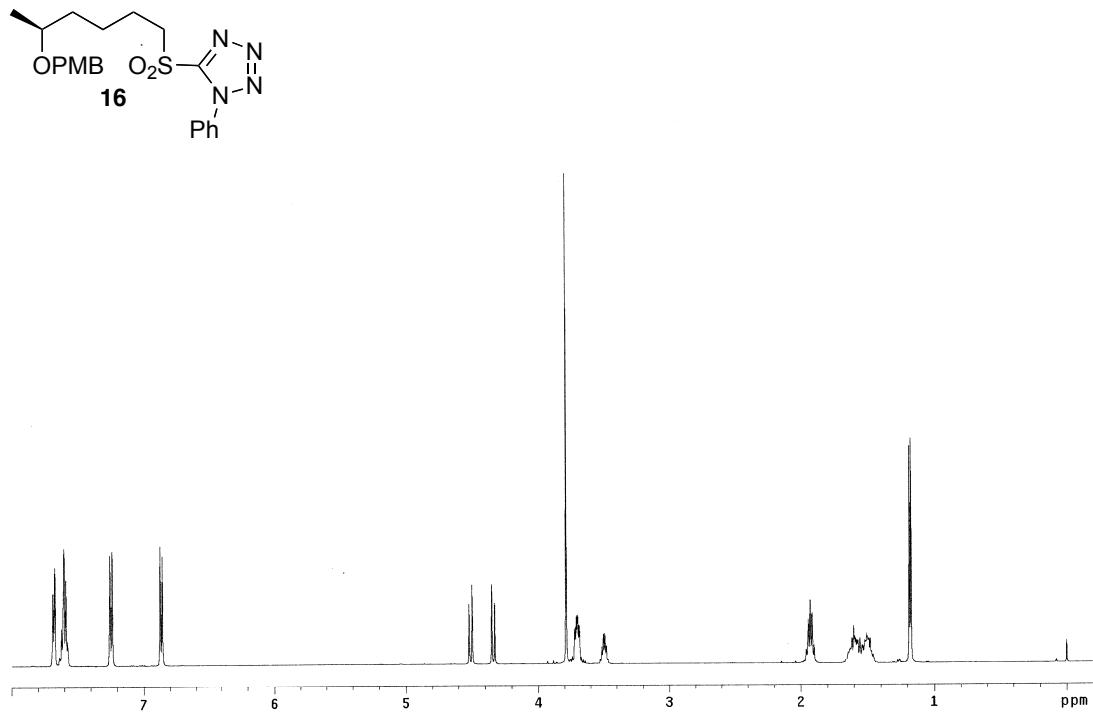
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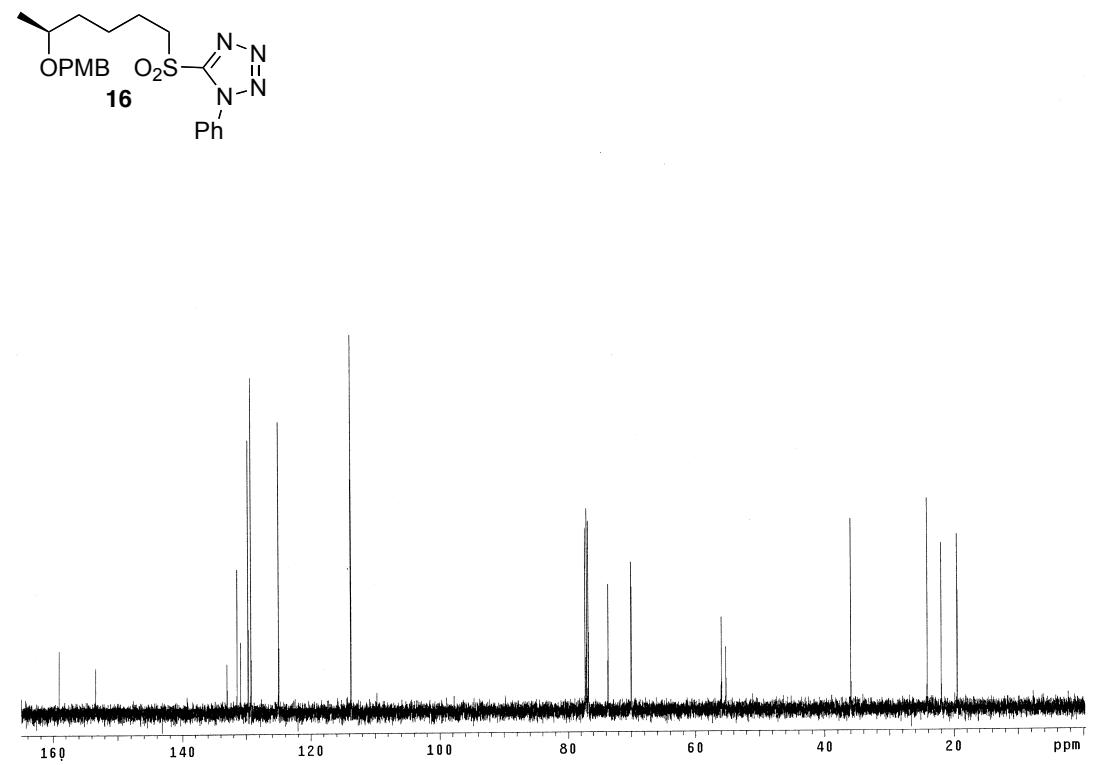
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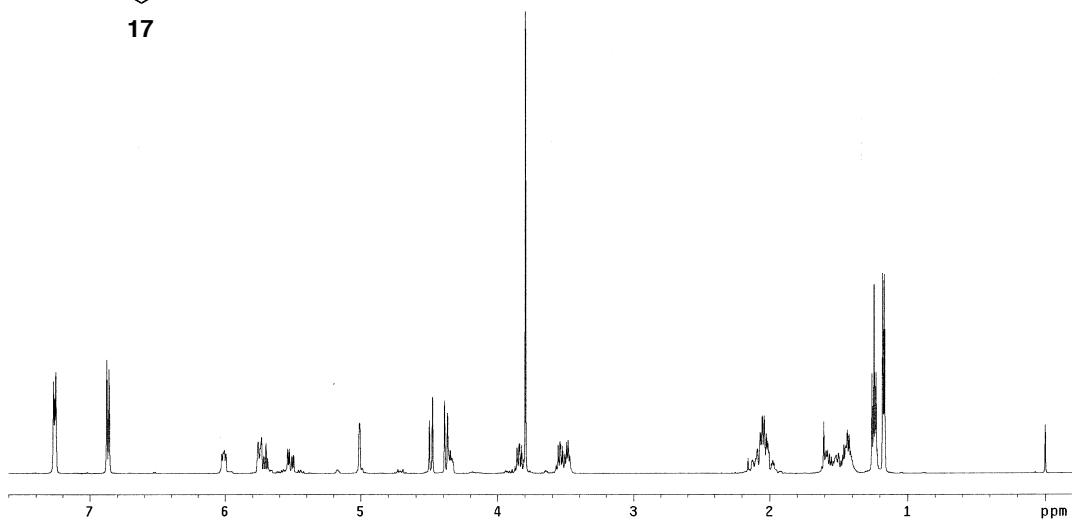
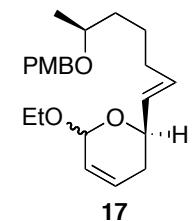
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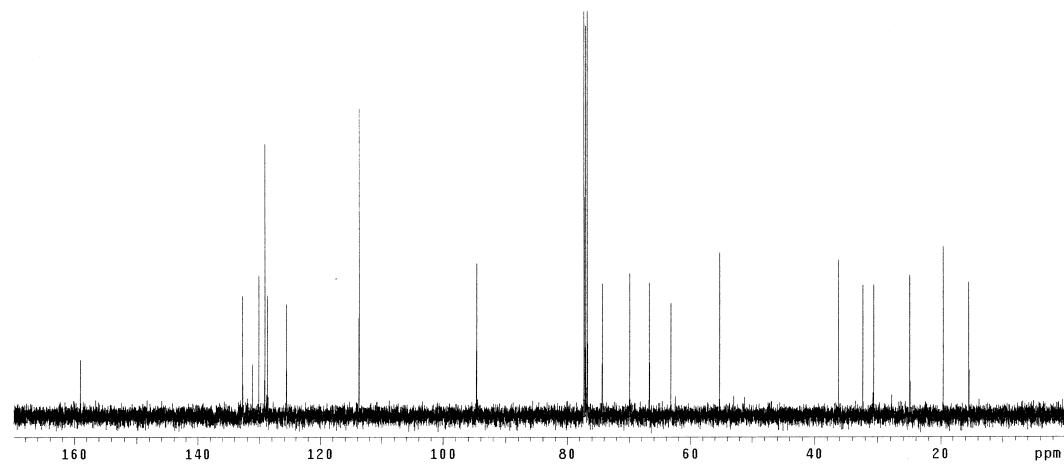
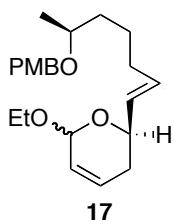
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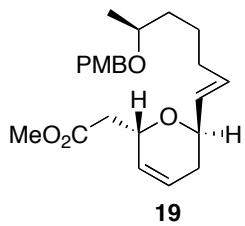
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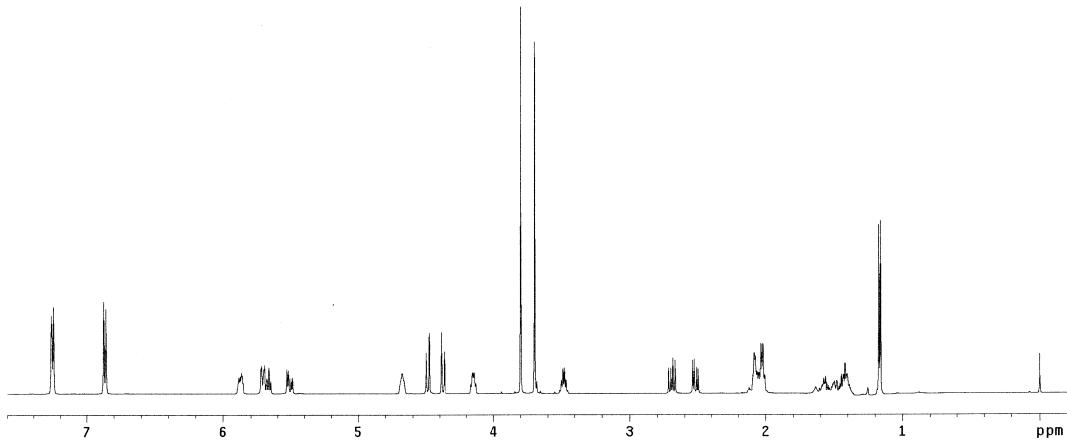
^{13}C NMR (125 MHz, CDCl_3)



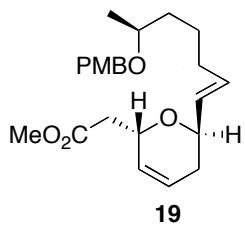
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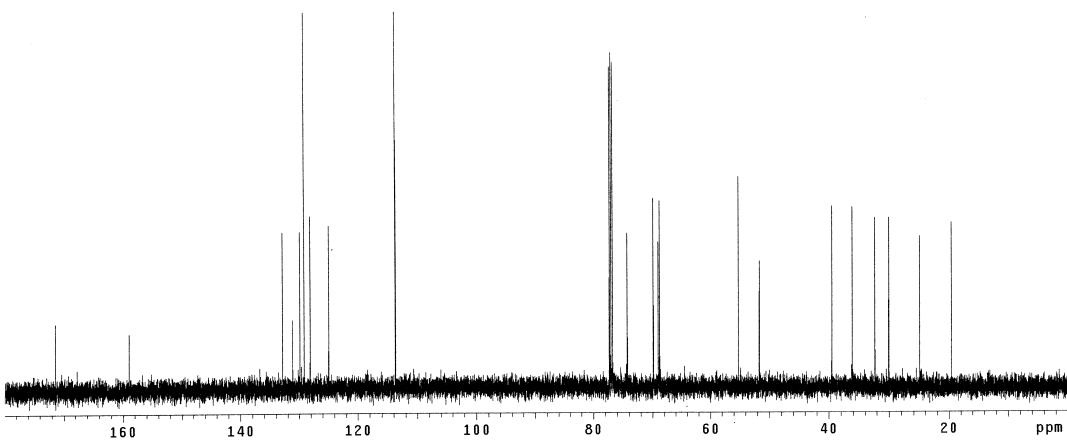
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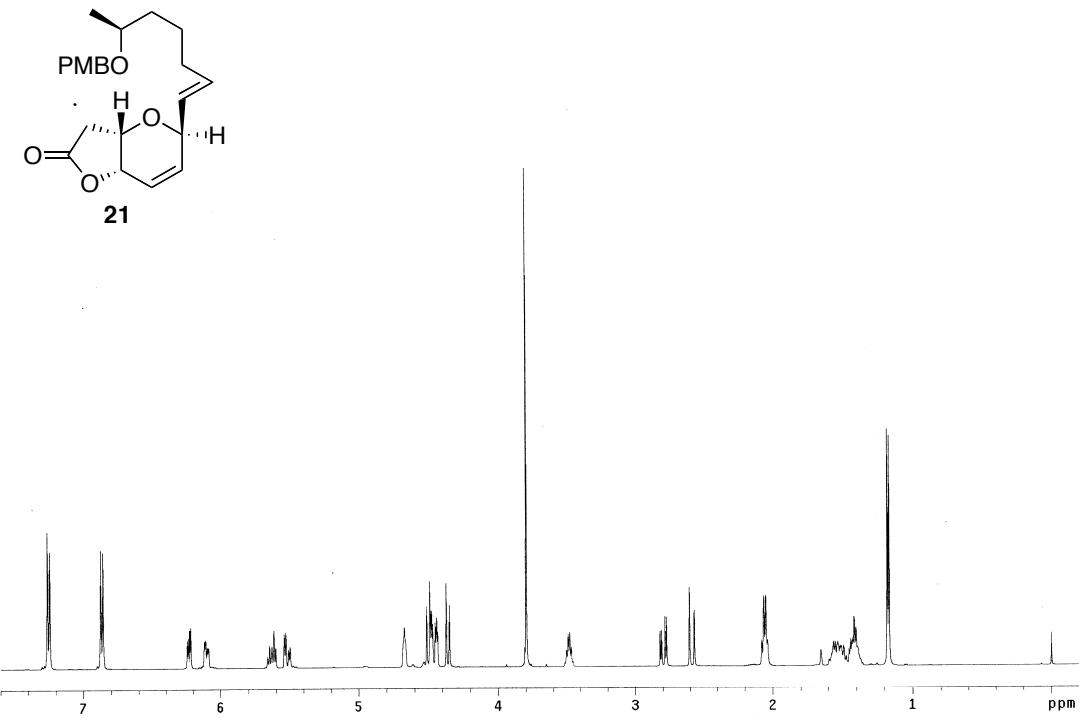
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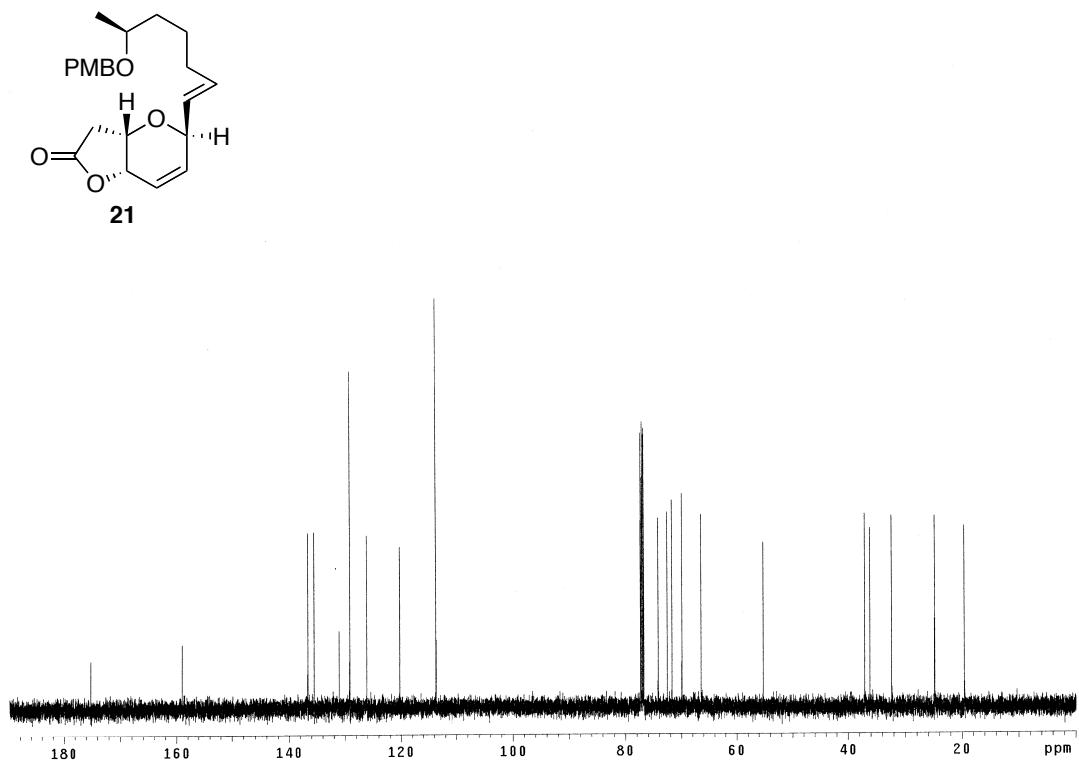
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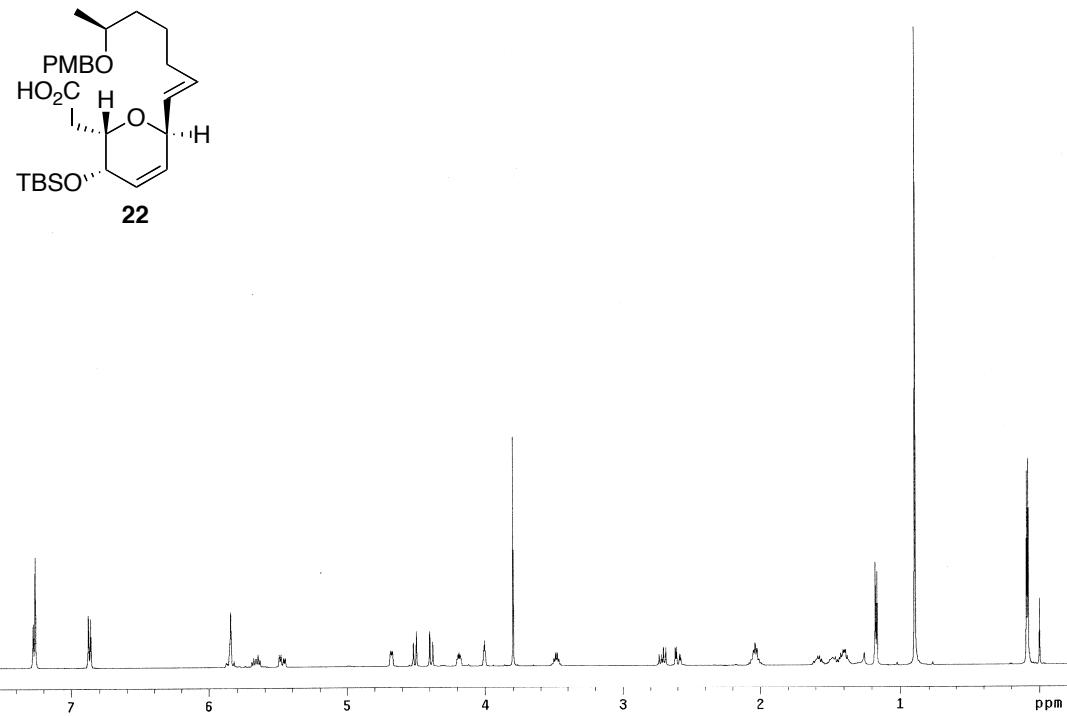
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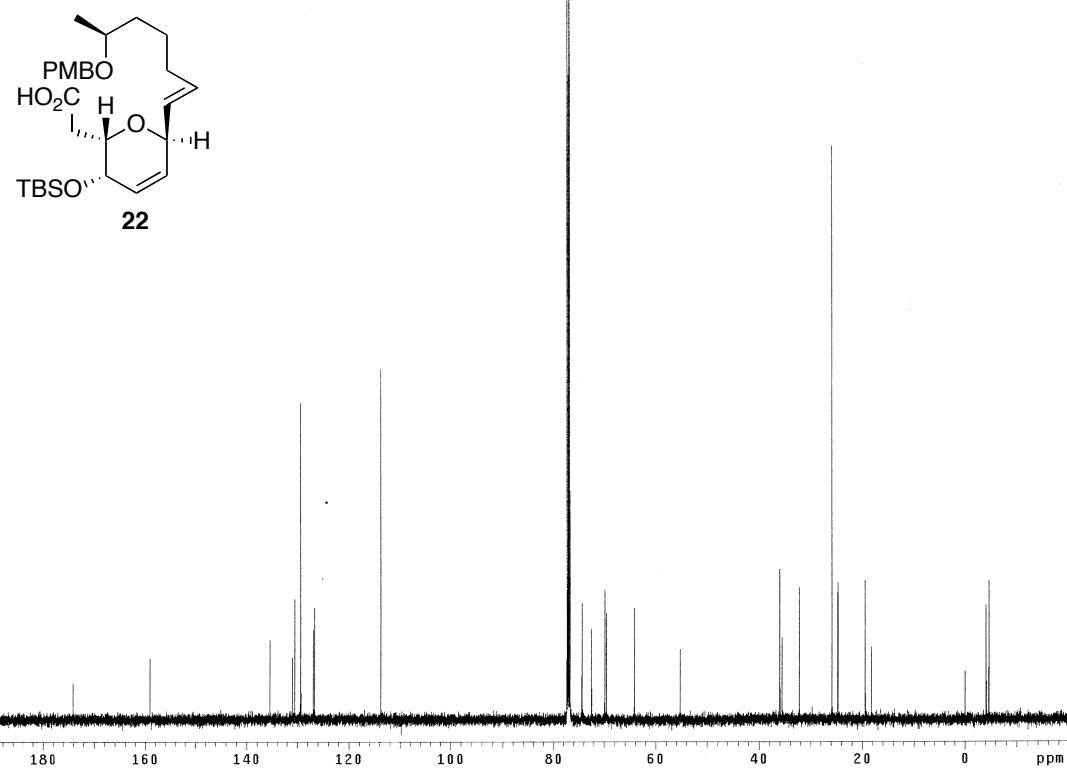
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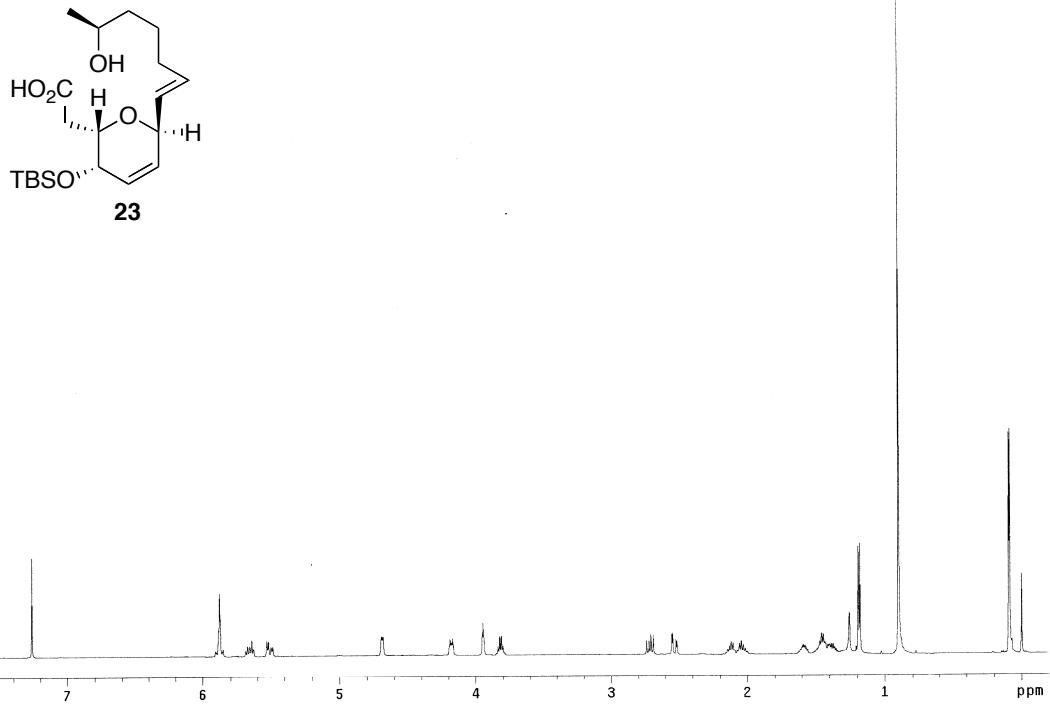
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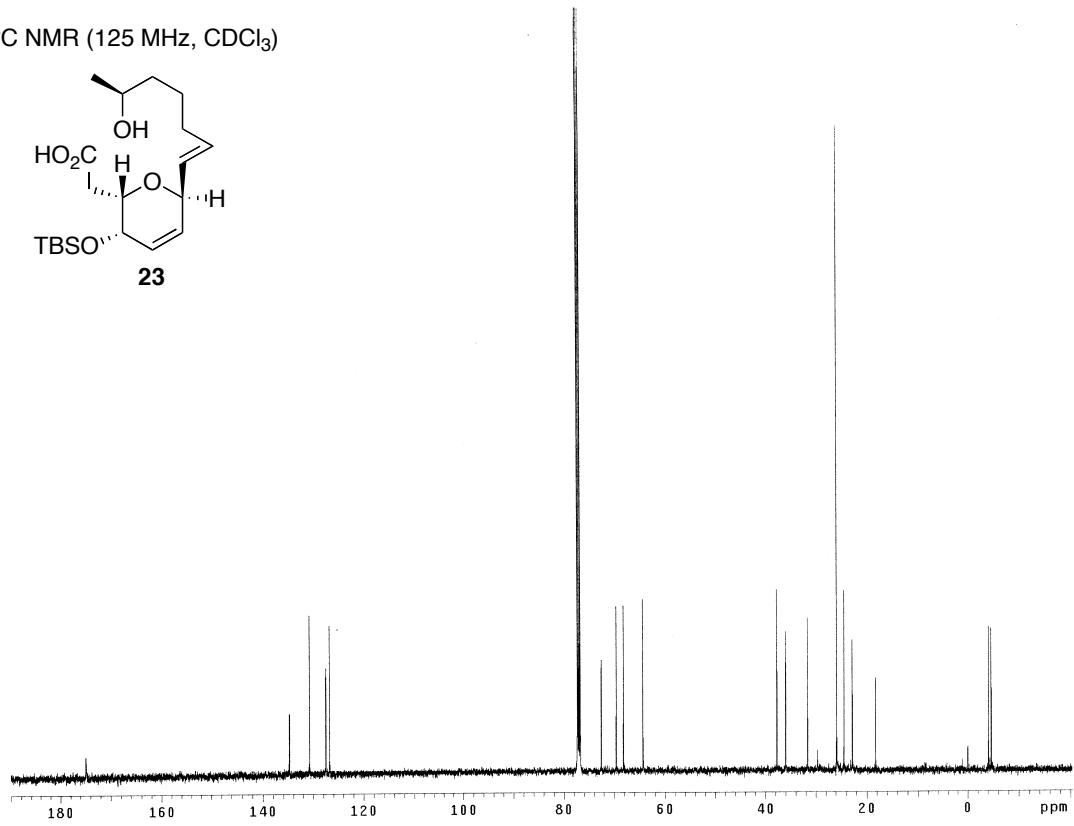
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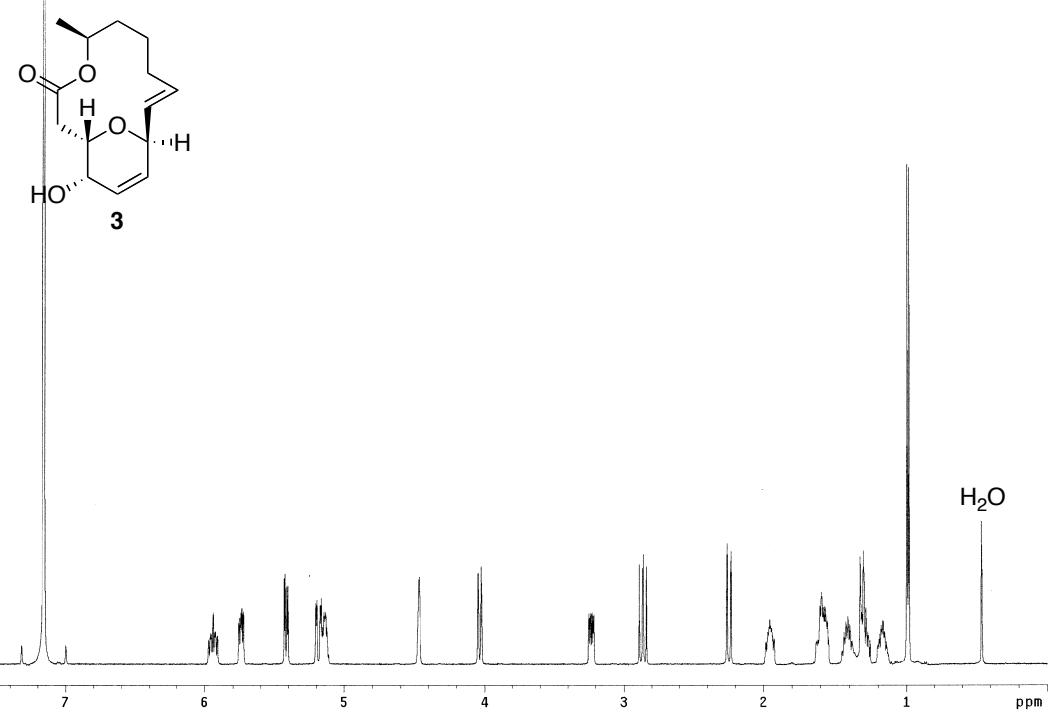
^1H NMR (500 MHz, CDCl_3)



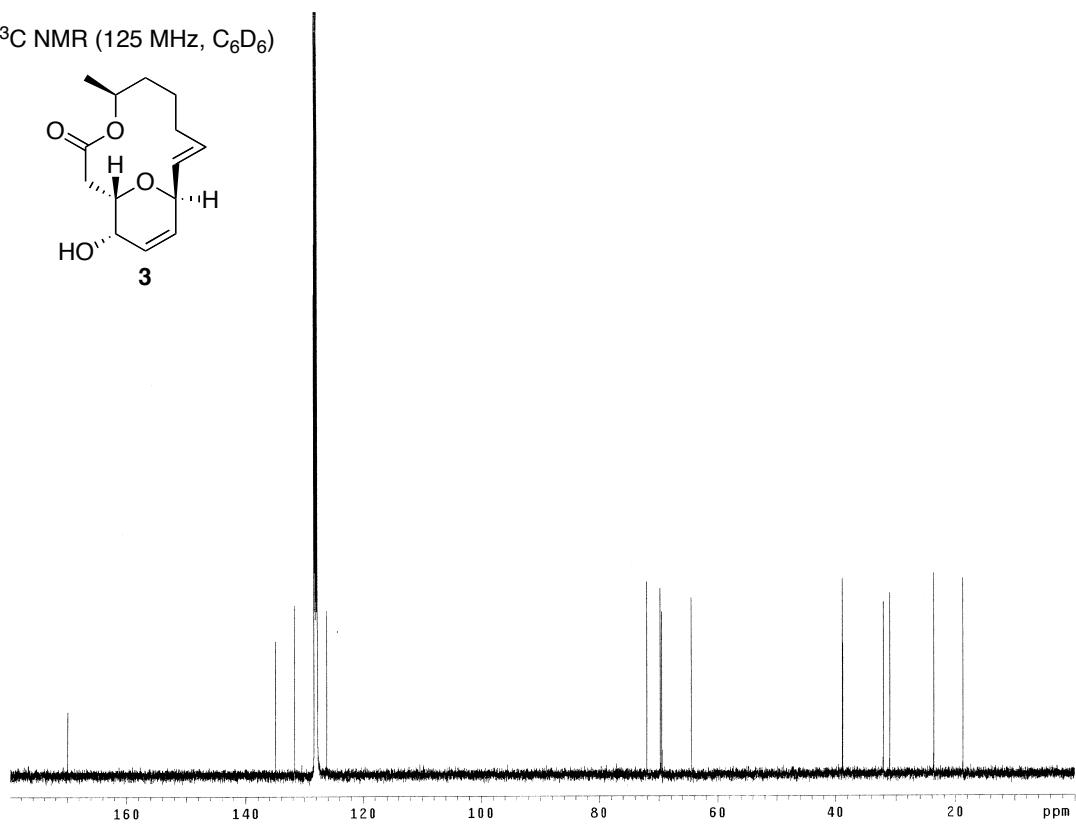
^{13}C NMR (125 MHz, CDCl_3)



¹H NMR (500 MHz, C₆D₆)



¹³C NMR (125 MHz, C₆D₆)



¹H and ¹³C NMR data for aspergillide C (3)

position	δ_{H}		δ_{C}	
	synthetic (500 MHz)	natural (400 MHz) ^{a,b}	synthetic (125 MHz)	natural (100 MHz) ^a
1			170.0	170.0
2	2.87 (dd, 13.9, 11.2) 2.25 (dd, 13.9, 1.7)	2.87 (br dd, 14.0, 11.2) 2.24 (br dd, 14.0, 2.0)	38.8	38.8
3	4.04 (br d, 11.2)	4.04 (ddd, 11.2, 2.0, 1.6)	69.8	69.8
4	3.23 (dd 11.2, 5.4)	3.23 (ddd, 11.2, 2.0, 1.6)	64.5	64.6
5	5.74 (ddd, 9.8, 5.4, 2.0)	5.74 (dddd, 10.4, 5.6, 2.4, 2.0) ^c	128.3 ^d	128.0
6	5.42 (dd, 9.8, 3.7)	5.42 (br dd, 10.4, 3.6)	131.8	131.8
7	4.45–4.49 (m)	4.46 (dddd, 4.0, 3.6, 2.0, 1.6)	72.0	72.0
8	5.18 (dd, 15.6, 3.9)	5.18 (br dd, 15.6, 4.0)	126.2	126.2
9	5.94 (dddd, 15.6, 9.3, 5.9, 1.5)	5.94 (dddd, 15.6, 9.6, 6.0, 1.6)	135.0	135.0
10	1.92–1.99 (m) 1.54–1.64 (m, 2H)	1.96 (dddd, 12.8, 9.6, 6.0, 2.4) 1.61 (dddd, 12.8, 6.0, 2.4, 1.9)	31.0	31.0
11	1.37–1.46 (m) 1.12–1.21 (m)	1.42 (m) 1.17 (m)	23.7	23.7
12	1.54–1.64 (m, 2H) 1.25–1.33 (m)	1.56 (m) 1.28 (m)	32.0	32.1
13	5.11–5.17 (m)	5.14 (m)	69.5	69.5
14	0.99 (d, 6.8)	0.99 (d, 6.8)	18.7	18.7
4-OH	1.31 (d, 11.2)	1.32		

^a Chemical shifts reported by Kusumi et al. for natural aspergillide C (*Org. Lett.* **2008**, *10*, 225–228).

^b Judging from the ¹H NMR spectrum of natural aspergillide C included in the Supporting Information of the above-mentioned report, Kusumi's original chemical shift data were considered to be obtained by regarding the chemical shift for the residual solvent signal ($\text{C}_6\text{D}_5\text{H}$) as δ 7.20. The data listed above were corrected by adjusting the solvent signal to δ 7.16 (original data – 0.04).

^c The coupling constant, J = 2.4, should be a misassignment.

^d The chemical shift, δ 128.3, could be inaccurate because of its overlapping with huge signals of C_6D_6 .

