Synthesis of 4-(1-Propynyl)-1-(5-hexene-1,3-diynyl)-1,3-cyclohexadiene and 4-(1-Propynyl)-1-(4-(trimethylsilyl)-1,3-butadiynyl)-1,3-cyclohexadiene

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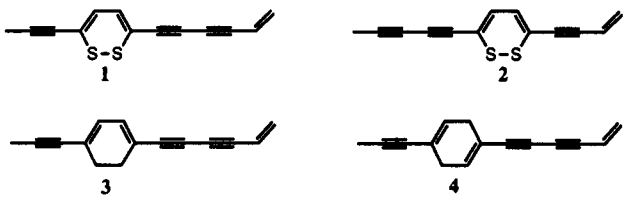
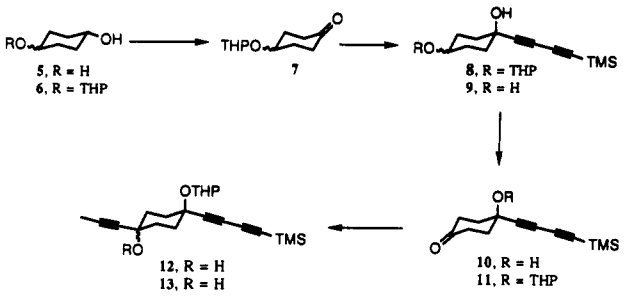
Thiarubrine A (1), thiarubrine B (2), and other 1,2-dithiins show significant bioactivity.[1-12] In order to evaluate the influence of the 1,2-dithiin ring system in structure activity relationship (SAR) studies, we needed to prepare and evaluate the carbon analogue (3) of thiarubrine A (1) and similar structures.

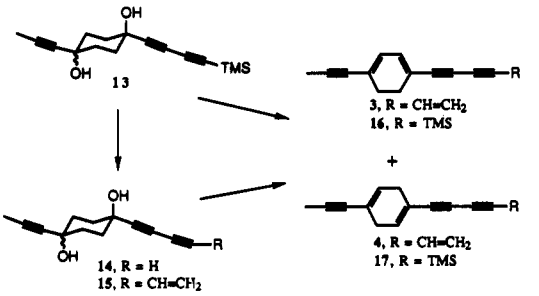


An 11-step synthesis of the 1,3-cyclohexadiene 3 and the isomeric 1,4-cyclohexadiene (4) from 1,4-cyclohexanediol (5) is shown in Schemes I and II. 1,4-Cyclohexanediol (5) was monoprotected (92%) with 3,4-dihydro-2*H*-pyran (DHP),[13] and the THP ether 6 was oxidized by dimethyl sulfoxide–oxalyl chloride[14] to the ketone 7 (87%). The ketone 7 was reacted with freshly generated lithium (trimethylsilyl)-1,3-butadiynylide[15] to yield the acetylenic alcohol 8 (93%) which was detetrahydropyranylated with pyridinium *p*-toluenesulfonate (PPTS)[13] to give diol 9 (97%). The diol 9 was oxidized by dimethyl sulfoxide–oxalyl chloride[14] to the ketone 10 (91%) which was protected with DHP (11, 98%). The THP ether 11 was reacted with lithium propynylide to afford the diacetylenic diols **12a** and **12b** as a diastereomeric mixture (95%). Deprotection of the respective diacetylenic diols 12 with PPTS[13] gave the diastereomeric diols **13a** and **13b** (98%). The trimethylsilyl protecting group on 13 was removed with tetrabutylammonium fluoride[16] to give the terminal alkyne 14 (96%) which was coupled with bromoethene/Pd(0)/CuI to yield the diol (15, 92%, Scheme II).[17] Treatment of the diol 15 with methanesulfonyl chloride and triethylamine[18] gave a 3:1 mixture (88%) of the cyclohexadienes 3 and 4 which was separated on HPLC. The diol 13 reacted with methanesulfonyl chloride to give a 4:1 mixture (87%) of cyclohexadienes 16 and 17 (Scheme II).[18,19]

Scheme I



Scheme II



Experimental Section

HRMS were obtained at 70 eV. CIMS (2-methylpropane) and EIMS were obtained at an ionization potential of 70 or 100 eV. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ unless specified otherwise at 300 and 125 MHz, respectively.

Analytical TLC was performed on Analtech Uniplate 10- × 20-cm (250-μm thick) silica gel GF prescored glass plates, which were developed with 1:1, 2:1, or 10:1 hexanes/ethyl acetate. The plates were visualized by UV or I_2. Flash column chromatography was performed on 230–400-mesh silica gel.

4-(2-Tetrahydropyranyloxy)-1-cyclohexanol (6). To a solution of 1,4-cyclohexanediol (5) (10 g, 86 mM) in dry THF (50 mL) was added DHP (2 g, 2.17 mL, 23.8 mM) and PPTS (20 mg, 0.08 mM).[13] The solution was stirred at rt for 6 h, the solvent was evaporated in vacuo, and the residue was chromatographed (4:1 hexanes/ethyl acetate) to afford the monoprotected alcohol 6 (4.4 g, 22 mmol, 93%): IR (neat, cm^{-1}) 3383, 2939, 2861, 1454, 1366, 1074, 1032; ^1H NMR δ 1.17–1.98 (m, 14 H), 2.75 (s, 1 H), 3.38–3.43 (m, 1 H), 3.51–3.54 (m, 2 H), 3.77–3.84 (m, 1 H), 4.00

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(19) The 4:1 ratio was obtained by comparing the ratio of the vinyl protons of **16** (two doublets at 6.148 and 6.387 ppm) and of **17** (two triplets at 5.911 and 6.211 ppm).

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(t, 1 H, J = 3.5 Hz); ^{13}C NMR δ 19.02, 19.12, 24.79, 24.88, 26.19, 28.46, 29.55, 29.89, 30.34, 30.49, 31.95, 32.26, 61.73, 61.88, 67.00, 68.43, 70.51, 73.25, 95.74, 96.19; HREIMS m/z 200.1408 (calcd for $C_{11}H_{20}O_3$ 200.1412).

4-(2-Tetrahydropyranyloxy)-1-cyclohexanone (7). General Procedure for the Dimethyl Sulfoxide–Oxalyl Chloride Oxidation of Alcohols.[14] A solution of THF (50 mL) and oxalyl chloride (2 mL, 2.80 g, 22 mM) was stirred magnetically as DMSO (3.4 mL, 44 mM) was added at −50 to −60 °C. The reaction was stirred for 2 min, and 4-(2-tetrahydropyranyloxy)-1-cyclohexanol (**6**, 4 g, 20 mM in 20 mL of THF) was added by cannula during 5 min. The reaction mixture was stirred for 15 min, triethylamine (14.0 mL, 15 g, 100 mM) was added, and stirring was continued for 5 min. The reaction mixture was allowed to warm to rt, diethyl ether (100 mL) was added, and the triethylamine hydrochloride was removed by filtration. The organic solution was washed successively with H_2O (5 × 100 mL) and saturated NaCl solution (100 mL), dried ($MgSO_4$), and filtered. The filtrate was concentrated in vacuo, and the residue was chromatographed (10:1 hexanes/ethyl acetate) to give 4-(2-tetrahydropyranyloxy)-1-cyclohexanone (**7**) (clear oil, 3.44 g, 17.4 mmol, 87%): IR (neat, cm^{-1}) 2956, 2870, 1702; ^{1}H NMR δ 1.52–2.18 (m, 10 H), 2.23–2.35 (m, 2 H), 2.51–2.70 (m, 2 H), 3.45–3.75 (m, 1 H), 3.89–3.96 (m, 1 H), 4.07–4.13 (m, 1 H), 4.77 (t, 1 H, J = 2.68 Hz); ^{13}C NMR δ 19.65, 25.23, 30.00, 31.04, 37.15, 37.51, 62.70, 63.74, 96.95, 211.20; HRCIMS $m+1/z$ 199.1336 (calcd for $C_{11}H_{18}O_3$ 198.1256 + 1.0078).

4-(2-Tetrahydropyranyloxy)-1-(4-(trimethylsilyl)-1,3-butadiynyl)cyclohexanol (8). To a solution of 1,4-bis(trimethylsilyl)-1,3-butadiyne[15] (3.89 g, 20 mM) in dry THF (50 mL) in a flask at 0 °C was added CH_3·LiBr (1.5 M in diethyl ether, 14.67 mL, 1.1 equiv)[15] dropwise under N_2. The solution was stirred at rt for 4 h, and the ketone **7** (3.96 g, 20 mM) in THF (10 mL) was added dropwise at rt. The mixture was stirred at rt for 7 h, diluted with 100 mL of a 1:1 diethyl ether/ethyl acetate solution, washed with H_2O (5 × 200 mL), dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo. The residue was chromatographed (6:1 hexanes/ethyl acetate) to afford the alcohol **8** (5.95 g, 18.6 mmol, 93%): IR (neat, cm^{-1}) 3384, 3306, 2946, 2862, 1441, 1355, 1251; ^{1}H NMR δ 0.08 (s, 9 H), 1.43–1.89 (m, 14 H), 3.35–3.41 (m, 2 H), 3.53 (s, 1 H), 3.66 (m, 1 H), 3.75–3.81 (m, 1 H), 4.61 (m, 1 H); ^{13}C NMR δ −0.64, 14.96, 19.21, 25.28, 26.42, 28.65, 30.87, 34.89, 35.25, 61.36, 65.54, 67.40, 68.09, 70.10, 81.33, 86.60, 87.35, 96.06; HRCIMS $m+1/z$ 321.1875 (calcd for $C_{18}H_{28}O_3Si$ 320.1807 + 1.0078).

4-Hydroxy-1-(4-(trimethylsilyl)-1,3-butadiynyl)cyclohexanol (9). To a solution of the alcohol **8** (5.5 g, 17.2 mM) in ethanol (50 mL) was added PPTS (20 mg, 0.08 mM) in one portion. The mixture was refluxed for 3 h, cooled to rt, diluted with 100 mL of a 1:1 diethyl ether/ethyl acetate solution, washed with H_2O (3 × 200 mL), dried ($MgSO_4$), and filtered, the solvent was removed in vacuo, and the residue was chromatographed (5:1 hexanes/ethyl acetate) to afford the diol **9** (3.94 g, 16.7 mM, 97%): IR (KBr, cm^{-1}) 3332, 2956, 2091, 1252, 1066, 845; ^{1}H NMR (acetone-d_6) δ 0.16 (s, 9 H), 1.52–1.57 (m, 6 H), 1.73–1.81 (m, 2 H), 3.52–3.53 (m, 1 H), 4.45 (d, 1 H, J = 3.78 Hz), 5.5 (s, 1 H); ^{13}C NMR (actone-d_6) δ −0.56, 30.01, 35.21, 65.28, 65.79, 66.57, 84.28, 86.54, 87.95; HRCIMS $m+1/z$ 237.1321 (calcd for $C_{13}H_{20}O_2Si$ 236.1232 + 1.0078).

4-Hydroxy-4-(4-(trimethylsilyl)-1,3-butadiynyl)-1-cyclohexanone (10). The diol **9** (3.9 g, 16.53 mM) was oxidized[14] to give the cyclohexanone **10** (3.55 g, 15 mM, 91%): mp 151–152 °C; IR (KBr, cm^{-1}) 3294, 2956, 2226, 2104, 1690, 1443, 1253; ^{1}H NMR (acetone-d_6) δ 0.18 (s, 9 H), 2.13–2.18 (t, 4 H, J = 6.67 Hz), 2.25–2.35 (m, 2 H), 2.45–2.55 (m, 2 H), 5.06 (s, 1 H); ^{13}C NMR (acetone-d_6) δ −0.55, 37.31, 38.97, 66.43, 68.69, 82.08, 87.72, 88.13, 208.33; HRCIMS $m+1/z$ 235.1181 (calcd for $C_{13}H_{18}O_2Si$ 234.1076 + 1.0078).

4-(2-Tetrahydropyranyloxy)-4-(4-(trimethylsilyl)-1,3-butadiynyl)-1-cyclohexanone (11). The alcohol **10** (1.7 g, 7.26 mM) in CH_2Cl_2 (25 mL) was added to DHP (3 mL, 36 mM) and PPTS (20 mg, 0.08 mM), the reaction mixture was stirred at rt for 4 h,[13] diluted with diethyl ether (100 mL), washed with H_2O (4 × 200 mL), dried ($MgSO_4$), and filtered, the solvent was evaporated in vacuo, and the residue was chromatographed (20:1 hexanes/ethyl acetate) to afford the THP ether **11** (2.2 g, 7.12 mmol, 98%): IR (neat, cm^{-1}) 2942, 2868, 2226, 2103, 1720, 1441, 1251; ^{1}H NMR δ 0.11 (s, 9 H), 1.41–2.51 (m, 10 H), 3.37–3.48 (m, 2 H), 3.73–3.85 (m, 2 H), 4.83–5.05 (m, 1 H); ^{13}C NMR δ −0.89, 19.31, 19.91, 24.88, 25.13, 30.26, 31.39, 36.56, 36.83, 37.78, 62.29, 63.29, 65.27, 68.21, 70.81, 76.73, 78.86, 86.57, 87.63, 93.95, 96.27, 208.82; HRCIMS $m+1/z$ 319.1733 (calcd for $C_{18}H_{26}O_3Si$ 318.1651 + 1.0078).

1-(1-Propynyl)-4-(2-tetrahydropyranyl)-4-(4-(trimethylsilyl)-1,3-butadiynyl)-1-cyclohexanol (12). To a solution of propyne (400 mg, 10 mM) in THF (25 mL) at −78 °C was added butyllithium (1 M in THF, 7.61 mL, 7.61 mM). The mixture was stirred at −78 °C for 30 min and then rt for 3 h. To the freshly generated lithium propynylide in THF at 0 °C was added the cyclohexanone **11** (2.2 g, 6.92 mM) in THF (10 mL) dropwise. The mixture was stirred at 0 °C for 30 min and at rt for 7 h, diluted with 100 mL of a 1:1 diethyl ether/ethyl acetate solution, washed with H_2O (4 × 200 mL), dried ($MgSO_4$), and filtered, the solvent was removed in vacuo., and residue was chromatographed (10:1 hexanes/ethyl acetate) to give the alcohols **12a** and **12b** as a mixture of diastereomers. **Diastereomer 12a**: 1.76 g, 4.92 mM, 71%; mp 47–48 °C; IR (KBr, cm^{-1}) 3394, 2951, 2852, 2100, 1439, 1388, 1252; ^{1}H NMR δ 0.19 (s, 9 H), 1.50–2.20 (m, 17 H), 3.49–3.55 (m, 1 H), 3.91–3.95 (m, 1 H), 5.07 (m, 1 H); ^{13}C NMR δ −0.57, 3.45, 19.64, 25.23, 31.62, 33.97, 34.68, 35.49, 35.63, 62.90, 66.65, 69.87, 72.95, 79.03, 79.68, 82.54, 86.98, 87.29, 95.51; HRCIMS $m+1/z$ 257.1369 (MH − $C_5H_{10}O_2$ (THPOH)) (calcd for $C_{21}H_{30}SiO_3$ 358.1964 + 1.0078). **Diastereomer 12b**: 0.59 g, 1.65 mM, 24%.

4-(1-Propynyl)-1-(4-(trimethylsilyl)-1,3-butadiynyl)-1,4-cyclohexanediol (13a). To a solution of the THP ether **12a** (1 g, 2.8 mmol) in absolute ethanol (50 mL) was added PPTS (20 mg, 0.08 mM) in one portion. The mixture was refluxed for 7 h, cooled to rt, and diluted with 100 mL of a 1:1 diethyl ether/ethyl acetate solution, washed with H_2O (3 × 200 mL), dried ($MgSO_4$), and filtered, the solvent was evaporated in vacuo, and the residue was chromatographed (2:1 hexanes/ethyl acetate) to give the diol **13a** (758 mg, 2.76 mM, 99%): IR (KBr, cm^{-1}) 3350, 2957, 2859, 2217, 2103, 1438, 1348, 1290, 1252, 1072; ^{1}H NMR (acetone-d_6) δ 0.15 (s, 9 H), 1.65–1.94 (m, 11 H), 4.33 (s, 1 H), 4.74 (s, 1 H); ^{13}C NMR (acetone-d_6) δ −0.49, 3.20, 36.37, 36.72, 66.84, 67.62, 68.44, 79.34, 83.06, 83.80, 86.83, 88.40; HRCIMS $m+1/z$ 275.1473 (calcd for $C_{16}H_{22}O_2Si$ 274.1389 + 1.0078).

4-(1-Propynyl)-1-(4-(trimethylsilyl)-1,3-butadiynyl)-1,4-cyclohexanediol (13b) was prepared from the THP ether **12b** (500 mg, 1.40 mM) using the procedure described above for the preparation of compound **13a**. The residue was chromatographed (2:1 hexanes/ethyl acetate) to give diol **13b** (371 mg, 1.35 mM, 97%): IR (KBr, cm^{-1}) 3464, 2965, 2224, 2103, 1636, 1441, 1252, 1066, 968, 845; ^{1}H NMR (acetone-d_6) δ 0.18 (s, 9 H), 1.63–1.93 (m, 8 H), 2.08 (s, 3 H), 4.19 (s, 1 H), 4.61 (s, 1 H); ^{13}C NMR (acetone-d_6) δ −0.49, 3.18, 36.29, 36.67, 66.28, 67.21, 68.16, 78.98, 83.64, 84.23, 87.08, 88.56; HRCIMS $m+1/z$ 275.1473 (calcd for $C_{16}H_{22}O_2Si$ 274.1389 + 1.0078).

4-(1-Propynyl)-1-(1,3-butadiynyl)-1,4-cyclohexanediol (14a). To a solution of the alcohol **13a** (300 mg, 1.1 mM) in THF (10 mL) was added tetrabutylammonium fluoride (1 M in THF, 5 mL) and the resulting mixture stirred at rt for 3 h.[16] The mixture was diluted with 50 mL of a 1:1 diethyl ether/ethyl acetate solution, washed with H_2O (3 × 100 mL), dried ($MgSO_4$), and filtered, the solvent was evaporated in vacuo, and the residue was chromatographed (2:1 hexanes/ethyl acetate) to afford the deprotected alcohol **14a** (212 mg, 1.05 mM, 95%): IR (KBr, cm^{-1}) 3310, 2944, 2856, 2240, 1637, 1435; ^{1}H NMR (acetone-d_6) δ 1.69–1.95 (m, 11 H), 2.95 (s, 1 H), 4.29 (s, 1 H), 4.74 (s, 1 H); ^{13}C NMR (acetone-d_6) δ 3.16, 36.47, 36.86, 66.86, 67.60, 67.77, 68.08, 70.29, 79.40, 81.47, 84.09; HRCIMS $m+1/z$ − $2H_2O$ 185.0957 (calcd for $C_{13}H_{14}O_2$ 202.0994 + 1.0078).

4-(1-Propynyl)-1-(1,3-butadiynyl)-1,4-cyclohexanediol (14b) was prepared from the alcohol **13b** (200 mg, 0.73 mM) using the procedure described above for compound **14a**. The residue was chromatographed (2:1 hexanes/ethyl acetate) to afford the deprotected alcohol **14b** (143 mg, 0.71 mM, 97%): IR (KBr, cm^{-1}) 3396, 3266, 2994, 2932, 2248, 1436, 1418; ^{1}H NMR (acetone-d_6) δ 1.74–1.93 (m, 11 H), 2.99 (s, 1 H), 4.20 (s, 1 H), 4.66 (s, 1 H); ^{13}C NMR (acetone-d_6) δ 3.15, 36.15, 36.48, 66.30, 66.98, 67.40, 68.05, 70.29, 79.05, 81.55, 84.04; HRCIMS $m+1/z$ − $2H_2O$ 185.0957 (calcd for $C_{13}H_{14}O_2$ 202.0994 + 1.0078).

4-(1-Propynyl)-1-(5-hexene-1,3-diynyl)-1,4-cyclohexanediol (15). To a solution of bromoethene (300 mg, 2.88 mM) in dry toluene (5 mL) under N_2 was added palladium(0) tetrakistriphenylphosphine (60 mg, 0.052 mM) and the resulting mixture stirred for 30 min at rt. Under N_2 propylamine (0.12 mL, 1.46 mM), CuI (12 mg, 0.06 mM), and the deprotected alcohol **14a** (250 mg, 1.24 mM) were added to the stirring reaction mixture.[17] The reaction mixture was stirred at rt for 4 h, diluted with 50 mL of a 1:1 diethyl ether/ethyl acetate solution, washed with H_2O (4 × 100 mL), dried ($MgSO_4$), and filtered, the solvent was evaporated in vacuo, and the residue was chromatographed (4:1 hexanes/ethyl acetate) to give the diol **15** (260 mg, 1.14 mM, 92%): IR (KBr, cm^{-1}) 2929, 2853, 2238, 1700, 1654, 1637, 1436, 1345, 1080, 989, 948; ^1H NMR (acetone-d_6) δ 1.15–1.95 (m, 11 H), 4.34 (s, 1 H), 4.77 (s, 1 H), 5.65–5.96 (m, 3 H); ^{13}C NMR (acetone-d_6) δ 3.15, 36.53, 36.87, 66.91, 67.89, 74.54, 77.45, 79.41, 83.99, 88.01, 116.61, 131.01; HRCIMS $m+1/z$ 229.1229 (calcd for $C_{15}H_{16}O_2$ 228.1150 (+1.0078)).

4-(1-Propynyl)-1-(5-hexene-1,3-diynyl)-1,3-cyclohexadiene (3) and 4-(1-Propynyl)-1-(5-hexene-1,3-diynyl)-1,4-cyclohexadiene (4). To a solution of the diol **15** (114 mg, 0.5 mM) in dry CH_2Cl_2 (15 mL) at 0 °C under N_2 were added dropwise triethylamine (152 mg, 0.11 mL, 1.50 mM, 3 equiv) and methanesulfonyl chloride (125 mg, 0.086 mL, 1.10 mM, 2.2 equiv).[18] The reaction mixture was stirred at 0 °C under N_2 for 1 h, diluted with diethyl ether (50 mL), washed with H_2O (3 × 50 mL), dried ($MgSO_4$), and filtered, the solvent was evaporated in vacuo, and the residue was chromatographed (40:1 hexanes/ethyl acetate) to afford **3** and **4** (84 mg, 0.44 mmol, 88%): IR (KBr, cm^{-1}) 2995, 2186, 1637, 1420, 966, 920, 844; ^1H NMR δ 1.99 (s, 3 H), 2.31 (s, 4 H), 5.58–6.34 (m, 5 H); ^{13}C NMR δ 4.03, 4.60, 26.15, 26.32, 27.15, 29.95, 31.06, 72.36, 74.48, 74.73, 76.57, 77.21, 77.42, 79.73, 79.89, 81.17, 82.15, 82.32, 83.13, 84.52, 91.55, 116.16, 116.24, 117.27, 122.50, 128.22, 128.39, 129.73, 129.83, 133.35, 134.31; HREIMS m/z 192.0933 (calcd for $C_{15}H_{12}$ 192.0938).

Compounds **3** and **4** were separated, for bioactivity studies, on an Altech Econosphere C18 5-μm 250- × 4.6-mm column with an 85% CH_3CN–15% H_2O solvent system. Both compounds were stored at low temperature under N_2.

4-(1-Propynyl)-1-(4-(trimethylsilyl)-1,3-butadiynyl)-1,3-cyclohexadiene (16) and 4-(1-Propynyl)-1-(4-(trimethylsilyl)-1,3-butadiynyl)-1,4-cyclohexadiene (17). To a solution of the diol **13a** (100 mg, 0.36 mM) in dry CH_2Cl_2 (15 mL) at 0 °C under N_2 was added triethylamine (110 mg, 0.08 mL, 1.08 mmol, 3 equiv) and methanesulfonyl chloride (90 mg, 0.062 mL, 0.79 mmol, 2.2 equiv) dropwise.[18] The reaction mixture was stirred at 0 °C under N_2 for 1 h, diluted with diethyl ether (50 mL), washed with H_2O (3 × 50 mL), dried ($MgSO_4$), and filtered, the solvent was evaporated in vacuo, and the residue was chromatographed (40:1 hexanes/ethyl acetate) to afford a 4:1 mixture[19] of **16** and **17** (75 mg, 0.32 mmol, 87%): IR (KBr, cm^{-1}) 2952, 2178, 2092, 1637, 1248, 843. **Isomer 16:** ^1H NMR δ 0.20 (s, 9 H), 2.00 (s, 3 H), 2.29 (s, 4 H), 6.15 (d, 2 H, J = 5.88 Hz), 6.38 (d, 2 H, J = 5.57 Hz); ^{13}C NMR δ −0.44, 4.66, 25.99, 27.09, 77.79, 78.36, 81.13, 87.97, 91.70, 92.58, 116.93, 122.65, 128.38, 133.88. **Isomer 17:** ^1H NMR δ 0.20 (s, 9 H), 1.92 (s, 3 H), 2.82 (s, 4 H), 5.91 (t, 1 H), 6.21 (t, 1 H, J = 1.66 Hz); ^{13}C NMR δ −0.44, 4.11, 29.84, 31.05, 72.79, 77.38, 79.87, 84.58, 87.80, 89.87, 115.99, 117.21, 128.21, 134.88; HRCIMS $m+1/z$ 239.1221 (calcd for $C_{16}H_{18}Si$ 238.1178 + 1.0078); HREIMS m/z 238.1160 (calcd for $C_{16}H_{18}S$ 238.1178).

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Supplementary Material Available: ^{13}C NMR spectra and ^1H NMR spectra of **3, 4, 6–10,** and **13–17** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.