Phenyldimethylsilyl as an Alcohol Surrogate in Intramolecular Diels–Alder Cycloaddition: Synthesis of α-Dictyopterol

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α-Dictyopterol (**1a**), a sesquiterpene isolated from the essential oil of *Dicytopteris divaricata*, has been synthesized from bicyclic ketone **2**, obtained by thermal cyclization of triene intermediate **11**. The key observation is that the phenyldimethylsilyl group, a surrogate for hydroxyl, does not interfere with the internal Diels–Alder cycloaddition.

The sesquiterpene dictyopterol (**1**) was isolated from the essential oil of *Dicytopteris divaricata* as a mixture of α (**1a**) and β (**1b**) isomers.[1] Such C-1 hydroxylated eudesmanes are widely distributed in nature,[2] yet no general route for their synthesis has been reported. We envisioned a synthesis of **1a** via an intramolecular Diels-Alder approach, as outlined retrosynthetically, in which the alkenyl silane **3** serves as a vinyl alcohol surrogate.[3] We now report that the vinyl silane does indeed participate smoothly in the internal Diels-Alder cycloaddition.

The requisite intermediate for the synthesis of **3** was the iodide **4**. Bis(phenyldimethylsilyl) cuprate **7** was added to the protected alkyne **6**, and the intermediate vinyl cuprate was alkylated with iodomethane to give THP ether **8**, according to a procedure established by Fleming (Scheme 1).[4] Deprotection of **8** to alcohol **9** and reaction of the derived tosylate **10** with sodium iodide in acetone[5] afforded vinyl silane **4**.

Dienyl nitrile **5**[6–8] was alkylated smoothly with silane **4** to produce the triene nitrile **3** (Scheme 2). The triene ketone **11** was expeditiously obtained by addition of methyllithium in diethyl ether to **3** at ambient temperature, with subsequent acid hydrolysis.

With ketone **11** in hand, we were prepared to investigate thermal conditons for the critical Diels–Alder step. To our knowledge, the vinyl silane intramolecular Diels–Alder reaction has not previously been reported.[9] After several initial failures, triene **11** was found to cyclize smoothly to *trans-fused* bicyclic ketone **2** in *N,N*-diethylaniline (DEAN) as a solvent at 250 °C in a sealed tube, with 2,5-di-*tert*-butylhydroquinone (DTBH) as a radical inhibitor, following the procedure developed by Parker.[10] Methylenation of **2** under Wittig conditions then gave diene **12**.

The final step involves conversion of the phenyldimethylsilyl group to the hydroxyl group. Fleming has developed methods for this transformation but the reagents

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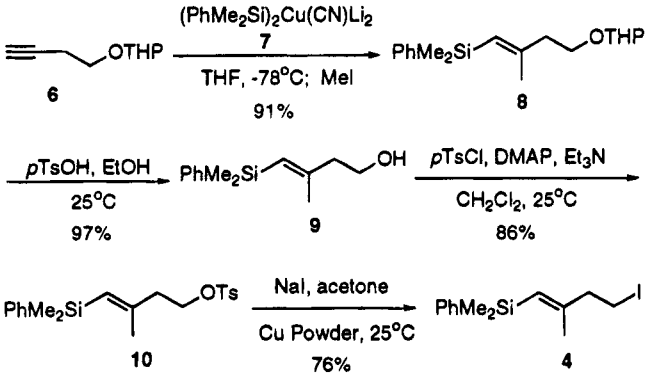
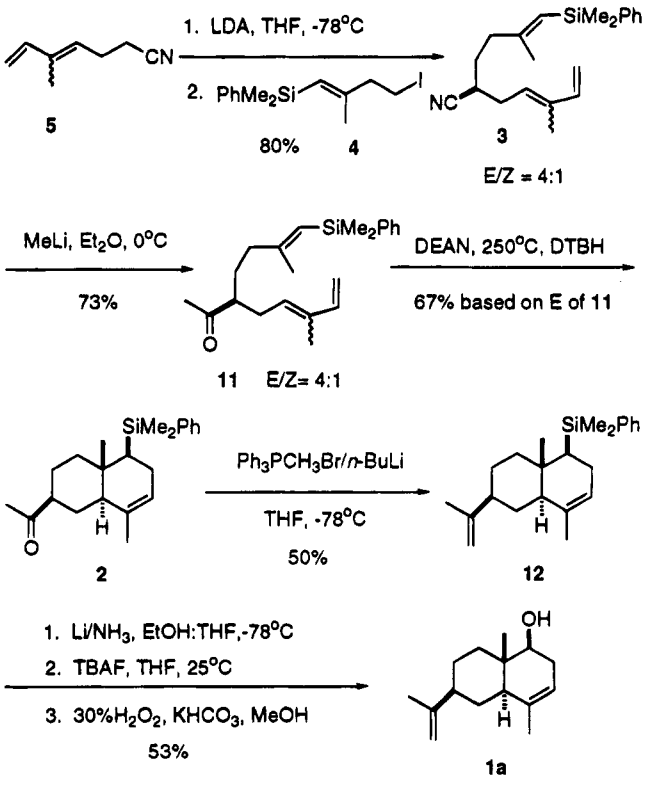
Scheme 1



Scheme 2



employed were incompatible with the carbon–carbon double bond.[11,12] We have recently published a solution to this long-standing problem.[13] Thus, lithium/ammonia reduction of the phenyldimethylsilyl group of **12**, cleavage of the intermediate dihydroaromatic silane with tetrabutylammonium fluoride (TBAF), and aqueous hydrogen peroxide oxidation of the derived silyl fluoride without purification of the intermediates provided α-dictyopterol (**1a**).

Many terpene-derived natural products are hydroxylated at the C-1 position (dictyopterol numbering). The vinyl silane intramolecular Diels–Alder approach outlined here offers a general route to this substitution pattern.

Experimental Section[14]

(*E*)-2-Methyl-1-(phenyldimethylsilyl)-4-(tetrahydropyranyloxy)-1-butene (8). Lithium metal (1.22 g, 1.76 mmol) was added in small pieces to a solution of phenyldimethylchlorosilane (10.0 g, 58.5 mmol) in THF (60 mL) at −10 °C. The burgundy solution was stirred for 4 h and then added dropwise to a suspension of CuCN (2.35 g, 26.3 mmol) in THF (40 mL) at 0 °C. After 20 min, the mixture was cooled to −78 °C, and a solution of THP ether **6** (3.60 g, 23.4 mmol) in THF (30 mL) was added. The mixture was stirred 1 h, and then iodomethane (20.1 g, 146 mmol) was added. The mixture was then stirred and allowed to warm to rt over 4 h. The reaction mixture was partitioned between water (200 mL) and EtOAc (2 × 150 mL). The organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give the THP ether **8** (6.5 g, 91% yield) as a pale yellow oil: TLC R_f (15% EtOAc/petroleum ether) = 0.66; ^{1}H NMR ($CDCl_3$) δ 0.41 (s,6H), 1.54–1.85 (m, 6H), 1.66 (s, 3H), 2.46 (t, J = 7.2 Hz, 2H), 3.50–3.62 (m, 2H), 3.87–3.94 (m, 2H), 4.60–4.66 (m, 1H), 5.47 (s, 1H), 7.33–7.41 (m, 3H), 7.55–7.60 (m, 2H); ^{13}C NMR ($CDCl_3$) δ up: 19.4, 25.5, 30.7, 42.6, 62.0, 66.2, 140.0, 154.2; down: −0.94, 22.5, 98.6, 122.8, 127.7, 128.6, 133.7, 134.2; IR (cm^{-1}) 3150, 2942, 1615, 1428, 1200, 1118, 1062, 1033, 832, 815, 729, 690; MS (m/z, %) 340 (M^+, 3), 269 (25), 255 (12), 197 (48), 135 (100), 105 (20), 85 (42). HRMS calcd for $C_{18}H_{28}O_2Si$ 340.1859; found 340.1861.

(*E*)-2-Methyl-1-(phenyldimethylsilyl)-1-buten-4-ol (9). A mixture of THP ether **8** (2.0 g, 6.57 mmol) and *p*-toluenesulfonic acid monohydrate (1.25 g, 6.57 mmol) in ethanol (100 mL) was stirred for 2 h at room temperature. The mixture was partitioned between water (100 mL) and EtOAc (2 × 100 mL), and the organic extract was dried (Na_2SO_4), concentrated, and chromatographed to afford alcohol **9** (1.40 g, 97% yield) as a colorless oil: TLC R_f (10% EtOAc/petroleum ether) = 0.24; ^{1}H NMR ($CDCl_3$) δ 0.38 (s, 6H), 1.74 (s, 3H), 2.39 (t, J = 6.4 Hz, 2H), 3.73 (t, J = 6.4 Hz, 2H), 5.46 (s, 1H), 7.33–7.36 (m, 3H), 7.51–7.56 (m, 2H); ^{13}C NMR ($CDCl_3$) δ up: 45.6, 60.4, 139.7, 153.3; down: −0.98, 21.9, 123.9, 127.6, 128.6, 133.6; IR (cm^{-1}) 3378, 3068, 2955, 1616, 1427, 1375, 1248, 1046, 909, 834, 783, 731; MS (m/z, %) 219 (M^+ − H,1), 205 (17), 159 (18), 137 (73), 105 (27), 75 (100); HRMS calcd for $C_{13}H_{20}OSi$ 220.1283; found 220.1264.

(*E*)-2-Methyl-1-(phenyldimethylsilyl)-4-[(*p*-toluenesulfonyl)oxy]-1-butene (10). A solution of alcohol **9** (1.10 g, 5.0 mmol), *p*-toluenesulfonyl chloride (1.3 g, 6.9 mmol), and 4-(dimethylamino)pyridine (122 mg, 1.0 mmol) in Et_3N (50 mL) and CH_2Cl_2 (50 mL) was stirred 12 h at room temperature. The reaction mixture was partitioned between water (150 mL) and EtOAc (2 × 100 mL). The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to afford tosylate **10** (1.6 g, 86% yield) as a colorless oil: TLC R_f (20% EtOAc/petroleum ether) = 0.58; ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 6H), 1.64 (s, 3H), 2.40–2.44 (m, 5H), 4.16 (t, J = 6.9 Hz, 2H), 5.34 (s, 1H), 7.29–7.35 (m, 5H), 7.48–7.51 (m, 2H), 7.78 (d, J = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ up: 41.0, 68.4, 139.2, 144.6, 150.7; down: −1.2, 21.4, 21.8, 124.6, 126.86, 127.7, 128.7, 129.4, 129.7, 133.1; IR (cm^{-1}) 3067, 2955, 1617, 1598, 1362, 1248, 1189, 1097, 1020, 964, 907; MS (m/z, %) 365 (1), 291 (100), 229 (71), 149 (32), 135 (17), 91 (97).

(*E*)-4-Iodo-2-methyl-1-(phenyldimethylsilyl)-1-butene (4). A suspension of tosylate **10** (1.5 g, 4.0 mmol) and sodium iodide (6.0 g, 40 mmol) in acetone (20 mL) was stirred 18 h at room temperature over Cu powder (spatula tip). The salt was vacuum-filtered with acetone (20 mL), and the filtrate was concentrated to a yellow oil which was chromatographed to give iodide **4** (1.0 g, 76% yield) as a colorless oil: TLC R_f (petroleum ether) = 0.58; ^{1}H NMR ($CDCl_3$) δ 0.39 (s, 6H), 1.72

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(s, 3H), 2.68 (t, J = 7.5 Hz, 2H), 3.29 (t, J = 6.1 Hz, 2H), 5.45 (s, 1H), 7.35–7.39 (m, 3H), 7.56–7.60 (m,2 H); ^{13}C NMR ($CDCl_3$) δ up: 3.6, 46.1, 139.3, 154.4; down: −1.0, 21.3, 123.3, 127.6, 128.8, 134.0; IR (cm^{-1}) 3066, 2955, 1617, 1426, 1247, 1112, 834; MS (m/z, %) 315 ($M^+ - CH_3$, 8), 275 (3), 247 (56), 185 (41), 175 (37), 145 (100), 105 (52), 59 (44); HRMS calcd for $C_{13}H_{19}ISi$ 330.0301; found 330.0370.

(1*E*,5*S*,7*E*)-5-Cyano-2,8-dimethyl-1-(phenyldimethylsilyl)-1,7,9-decatriene (3). *n*-Butyllithium (0.32 mL, 0.723 mmol, 2.25 M in hexane) was added to a solution of diisopropylamine (70 mg, 0.693 mmol) in THF (2.0 mL) at −78 °C. After 5 min, a solution of dienyl nitrile **5** (73 mg, 0.603 mmol) in THF (2.0 mL) was added, and the bright yellow solution was stirred for 20 min. A solution of iodosilane **4** (240 mg, 0.723 mmol) in THF (2.0 mL) was then added all at once, and the reaction mixture was stirred with warming to rt over 1 h. The mixture was partitioned between water (20 mL) and ether (3 × 10 mL), dried (Na_2SO_4), and chromatographed to afford the triene nitrile **3** (155 mg, 80% yield) as a pale yellow oil: TLC R_f (2% EtOAc/petroleum ether) = 0.58; ^{1}H NMR ($CDCl_3$) δ 0.38 (s, 6H), 1.72 (s, 3H), 1.79 (s, 3H), 2.04–2.62 (m, 7H), 5.05 (d, J = 10.6 Hz, 1H), 5.18 (d, J = 13.6 Hz, 1H), 5.44–5.55 (m, 2H), 6.40 (dd, J = 6.8, 10.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ up: 29.9, 30.7, 39.6, 112.5, 115.4, 137.4, 139.6, 154.4; down: −1.1, 11.9, 21.8, 31.1, 122.6, 126.4, 127.7, 128.7, 132.7, 133.6, 140.6; IR (cm^{-1}) 3160, 2954, 2238, 1617, 1427, 1379, 1247, 1143, 1112, 989, 899, 839, 807, 783, 730, 700; MS (m/z, %) 323 (M^+, 1), 308 (16), 266 (4), 255 (4), 180 (3), 159 (23), 135 (100), 107 (32), 79 (32); HRMS calcd for $C_{21}H_{29}NSi$ 323.2069; found 323.2049. Anal. Calcd for $C_{21}H_{29}NSi$: C, 77.96; H, 9.03. Found: C, 78.19; H, 8.64.

(1*E*,5*S*,7*E*)-5-Acetyl-2,8-dimethyl-1-(phenyldimethylsilyl)-1,7,9-decatriene (11). MeLi (1.08 mL, 1.41 mmol, 1.31 M in ether) was added quickly to a solution of triene nitrile **3** (163 mg, 0.504 mmol) in ether (5.0 mL) at 0 °C. After 0.5 h, acetone (2.0 mL) was added, and the mixture was stirred an additional 10 min and then was quenched by addition of 1% aqueous HCl (1.0 mL). The mixture was partitioned between water (10 mL) and ether (2 × 10 mL). The combined organic extract was dried (Na_2SO_4), concentrated and chromatographed to yield triene ketone **11** (126 mg, 73% yield) as a colorless oil: TLC R_f (2% EtOAc/petroleum ether) = 0.60; ^{1}H NMR ($CDCl_3$) δ 0.34 (s, 6H), 1.66 (s, 3H), 1.72 (s, 3H), 1.76–1.84 (m, 2H), 2.02–2.08 (m, 2H), 2.11 (s, 3H), 2.16–2.57 (m, 3H), 4.94 (d, J = 10.7 Hz, 1H), 5.09 (d, J = 17.3 Hz, 1H), 5.26–5.40 (m, 2H), 6.32 (dd, J = 6.7, 10.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ up: 29.2, 40.1, 111.5, 135.8, 156.2, 211.9; down: −0.96, 11.8, 21.9, 29.5, 52.4, 121.6, 127.1, 127.7, 128.7, 129.2, 133.7, 141.1; IR (cm^{-1}) 3155, 2955, 1711, 1614, 1427, 1353, 1247, 1158, 1112, 989, 834, 728, 699; MS (m/z, %) 325 ($M^+ - CH_3$, 1), 271 (2), 219 (1), 173 (6), 135 (100), 105 (20), 81 (30); HRMS calcd for $C_{22}H_{32}OSi$ 340.2222; found 340.2220. Anal. Calcd for $C_{22}H_{32}OSi$: C, 77.58; H, 9.47. Found: C, 77.64; H, 9.32.

Bicyclic Ketone 2. A mixture of triene ketone **11** (280 mg, 0.822 mmol, *E*/*Z* ratio = 4:1) and 2,5-di-*tert*-butylhydroquinone (spatula tip) in *N*,*N*-diethylaniline (7.0 mL) was heated in a sealed tube at 250 °C for 24 h. The reaction mixture was diluted with ether (20 mL) and poured into 6 N HCl (20 mL). The mixture was stirred for 30 min, and then the layers were separated. The aqueous layer was extracted with ether (2 × 10 mL), and the combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give the bicyclic ketone **2** (140 mg, 67% yield based on *E* component of triene ketone **11**) as a pale yellow oil: TLC R_f (2% EtOAc/petroleum ether) = 0.31; ^{1}H NMR ($CDCl_3$) δ 0.34 (s, 3H), 0.37 (s, 3H), 0.71 (s, 3H), 1.07–1.25 (m, 2H), 1.60–1.73 (m, 4H), 1.83–1.92 (m, 3H), 2.11 (s, 3H), 2.15–2.33 (m, 2H), 5.33 (s, 1H), 7.30–7.33 (m, 3H), 7.46–7.50 (m, 2H); ^{13}C NMR ($CDCl_3$) δ up: 24.0, 25.7, 25.8, 35.8, 40.4, 134.3, 140.3, 211.8; down: −1.8, −1.2, 13.7, 21.2, 27.8, 35.7, 49.2, 51.9, 122.3, 127.6, 128.6, 133.7; IR (cm^{-1}) 3066, 2956, 1708, 1617, 1589, 1427, 1248, 1112; MS (m/z, %) 325 ($M^+ - CH_3$, 1), 262 (1), 219 (1), 179 (1), 135 (100), 105 (16), 75 (14); HRMS calcd for $C_{22}H_{32}OSi$ 340.2222; found 340.2224.

Bicyclic Diene 12. To a suspension of methyltriphenylphosphonium bromide (136 mg, 0.382 mmol) in THF (3.0 mL) at −78 °C was added via syringe *n*-butyllithium (0.16 mL, 0.344 mmol, 2.16 M in hexane). After 0.5 h, a solution of bicyclic ketone **2** (26 mg, 0.0764 mmol) in THF (2.0 mL) was added to the bright yellow suspension. The mixture was allowed to warm to rt over 2 h. The reaction mixture was partitioned between water (5.0 mL) and ether (3 × 5.0 mL). The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to yield the bicyclic diene **12** (13 mg, 50% yield) as a colorless oil: TLC R_f (2% EtOAc/petroleum ether) = 0.86; ^{1}H NMR ($CDCl_3$) δ 0.34 (s, 3H), 0.37 (s, 3H), 0.73 (s, 3H), 1.03–1.17 (m, 4H), 1.38–1.56 (m, 3H), 1.59 (s, 3H), 1.73 (s, 3H), 1.76–2.07 (m, 4H), 4.69 (s, 2H), 5.34 (s, 1H), 7.33-7.37 (m, 3H), 7.50–7.55 (m, 2H); ^{13}C NMR ($CDCl_3$) δ up: 26.1, 27.1, 29.1, 35.9, 40.8, 108.2, 135.1, 140.6, 150.9; down: −1.8, -1.0, 13.9, 20.9, 21.3, 35.8, 46.1, 49.1, 121.8, 127.6, 128.5, 133.8; IR (cm^{-1}) 3066, 2932, 1646, 1558, 1456, 1428, 1374, 1248, 1177, 1112; MS (m/z, %) 337 ($M^+ - 1$, 1), 269 (1), 192 (4), 135 (100), 91 (31), 57 (11); HRMS calcd for $C_{23}H_{34}Si$ 338.2430; found 338.2430.

α-Dictyopterol (1a). To a solution of bicyclic diene **12** (33 mg, 0.0975 mmol) in dry THF:EtOH (10 mL, 1:1 v/v) and condensed ammonia (15 mL) at −78 °C was added lithium metal (30 mg, 4.33 mmol) until the solution was blue with blue foam. The mixture was warmed to room temperature to evaporate the ammonia. The residue was partitioned between water (10 mL) and EtOAc (5 × 2.0 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to a colorless oil. This was taken up in THF (1.0 mL), and tetrabutylammonium fluoride (0.20 mL, 0.20 mmol, 1.0 M in THF) was added. After stirring for 1 h, methanol (0.5 mL), $KHCO_3$ (15 mg, 0.146 mmol), and 30% H_2O_2 (0.11 mL, 0.975 mmol) were added and stirring was continued for 12 h. The mixture was partitioned between water (5.0 mL) and EtOAc (5 × 2.0 mL). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo* to a colorless oil that was chromatographed to afford **1a** (11 mg, 53% yield) as a viscous colorless oil: TLC R_f (15% EtOAc/petroleum ether) = 0.25; ^{1}H NMR ($CDCl_3$) δ 0.76 (s, 3H), 1.0–1.38 (m, 3H), 1.45–1.55 (m, 2H), 1.58 (s, 3H), 1.73 (s, 3H), 1.84–1.92 (m, 5H), 2.15–2.32 (m, 1H), 3.49–3.56 (m, 1H), 4.71 (s, 2H), 5.26 (s, 1H); ^{13}C NMR ($CDCl_3$) δ up: 26.7, 28.8, 32.7, 35.4, 108.9, 135.8, 151.3; down: 9.9, 21.3, 46.3, 47.0, 76.8, 119.8; MS (m/z, %) 220 (M^+, 8), 187 (8), 159 (18), 145 (19), 121 (39), 95 (57), 81 (95), 55 (100).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for **1a**, **2**–**4**, and **8**–**12** (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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