

Silenes in Organic Synthesis: A Concise Synthesis of (±)-Epipicropodophyllin.

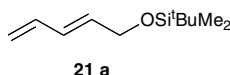
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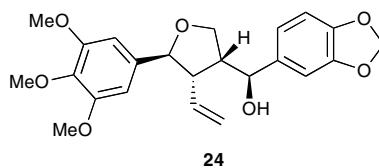
For standard experimental procedures see full text article

(E)-1-tert-Butyldimethylsilyloxy-2,4-pentadiene **21a**



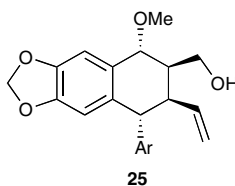
^tButyldimethylsilylchloride (2.69 g, 17.83 mmol) in DMF (15 ml) was added to a stirred solution of alcohol **21b** (1.00 g, 11.89 mmol) and imidazole (2.60 g, 29.73 mmol) in DMF (15 ml) at room temperature and stirred for 18 h. The reaction was quenched with water (30 ml) and washed with saturated brine solution. The aqueous layer separated and extracted with diethyl ether. The combined organic extracts were dried over MgSO₄, filtered and concentrated *in vacuo* to afford a yellow oil. Flash column chromatography (petroleum ether, petroleum ether/diethyl ether [4:1]) afforded **21a** as a colourless oil (2.26 g, 96 %); R_f: 0.4 (pet. ether/ether 9:1); ν_{max} (ATR) 2956, 2929, 2857, 1620, 1463, 1362, 1254, 1124, 1103, 1002, 934, 900, 833, 774, 670 cm⁻¹; δ_H (500 MHz, CDCl₃) 6.35 (1H, dt, *J* 16.8, 10.1 4-*H*), 6.24 (1H, dd, *J* 15.0, 10.1 3-*H*) 5.78 (1H, dt *J* 15.0, 5.0, 2-*H*), 5.18 (1H, bd, *J* 16.8, 5-*HH*), 5.05 (1H, bd, *J* 10.1, 5-*HH*), 4.22 (2H, d, *J* 5.0, 1-*H*), 0.92 (9H, s, -SiC(CH₃)₃), 0.08 (6H, s, -Si(CH₃)₂); δ_C (126 MHz) 136.5 (C-4), 133.2 (C-2), 130.3 (C-3), 116.6 (C-5), 63.3 (C-1), 25.9 (-SiC(CH₃)₃), 18.4 (-SiC(CH₃)₃), -5.2 (-Si(CH₃)₂); δ_{Si} (99 MHz) -20.4 (-SiMe₂^tBu); *m/z* (EI) 198 (M⁺, 1 %), 183 (M⁺ - CH₃, 2), 141 (M⁺ - ^tBu, 90), 75 (M⁺ - 5 CH₃); HRMS (ES⁺) Found MNa⁺, 221.1332, C₁₁H₂₂ONaSi requires M⁺ 221.1332.

(3*RS*,4*SR*,5*SR*) 3-Ethenyl-4-[(*SR*) hydroxy-(3'',4''-methylenedioxyphenyl)methyl)]-2-(3',4',5'-trimethoxyphenyl)tetrahydrofuran **24**



Following the same procedure as described for compound **14** hydroxymethyl silacycle **15** (0.1g, 0.3mmol) was combined with 3,4,5-trimethoxybenzaldehyde dimethylacetal to give, without purification of the intermediate fluorosilane, the title compound **24** as a white solid (0.02g, 20%); R_f 0.2 (pet. ether/ether 1:1); m.p. 140-142; ν_{\max} (thin film) 3500-3184 (broad-OH), 3006, 2983, 2884, 2361, 2245, 1592, 1504, 1488, 1418, 1357, 1247, 1129, 1041, 1001 cm^{-1} ; δ_H (500 MHz, CDCl_3) 6.89 (1H, s, Ar-H), 6.77 (2H, s, Ar-H), 6.48 (2H, s, Ar-H), 5.97 (2H, s, $-\text{OCH}_2\text{O}-$), 5.69 (1H, ddd, J 17, 10, 10, 3-CH=), 5.11-5.06 (3H, m, $=\text{CH}_2$, 2-H), 4.47 (1H, dd, J 10, 2, 4-CH), 3.84 (6H, s, Ar- OCH_3), 3.82 (3H, s, Ar- OCH_3), 3.63 (2H, m, 5-H), 3.21 (1H, m, 3-H), 3.00 (1H, m, 4-H), 2.10 (1H, d, J 2, OH); δ_C (126 MHz, CDCl_3) 153.0 (Ar-C), 147.7 (Ar-C), 136.9 (Ar-C), 135.1 (Ar-C), 134.6 (Ar-C), 133.4 (3-CH=), 128.2 (Ar-C), 120.0 (Ar-C), 119.1 ($=\text{CH}_2$), 108.5 (Ar-C), 106.9 (Ar-C), 103.1 (Ar-C), 101.4 (OCH_2O), 84.7 (C-1), 73.7 (4-CH), 68.5 (C-5), 61.1 (Ar- OCH_3), 56.3 (Ar- OCH_3), 52.5 (C-4), 51.8 (C-3); m/z (ES^+) 437 (MNa^+), 851 (2MNa^+); HRMS (ES^+) Found MNa^+ , 437.1573, $\text{C}_{23}\text{H}_{26}\text{O}_7\text{Na}$ requires M^+ 437.1571.

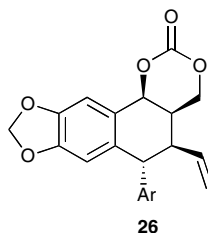
(1*SR*,2*SR*,3*RS*,4*SR*) 3-Ethenyl-2-(hydroxymethyl)-6,7-methylenedioxy-1-methoxy-4-(3',4',5'-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene **25**



A solution of tetralol **14** (50 mg, 0.1mmol) in acetone (2ml) was treated with *p*-toluenesulfonic acid (2 mg, 0.01mmol) and molecular sieves at room temperature. The solution was then treated with 2,2-dimethoxypropane (0.1ml, 1mmol) and reacted for 1 h. The reaction mixture was then poured into H_2O and extracted with Et_2O (3 x 10ml). The combined organic layers were dried over MgSO_4 , filtered, concentrated and dried *in vacuo*. Flash chromatography (pet. ether/ether [3:2], [1:1], [1:2], [2:3], [1:4], ether) afforded the title compound **25** as a colourless oil (11 mg, 20%); R_f 0.8 (ether); ν_{\max} (thin film) 3420 (broad-OH), 3082, 3010, 2935, 2836, 1718,

1590, 1504, 1483, 1419, 1329, 1234, 1129, 1041 cm^{-1} ; δ_{H} (500 MHz, CDCl_3) 6.87 (1H, s, Ar-H), 6.39 (1H, s, Ar-H), 6.27 (2H, s, Ar-H), 5.94 (1H, d, J 1.5, OCHHO), 5.93 (1H, d, J 1.5, OCH₂O), 5.80 (1H, ddd, J 17, 10, 8, 3-CH=), 5.11 (1H, bd, J 17, =CHH), 5.06 (1H, bd, J 10, =CHH), 4.48 (1H, d, J 7, 1-H), 3.82 (3H, s, 4'-OCH₃), 3.78-3.73 (9H, s, 2-CHH, OH, 4-H, 3'-OCH₃), 3.64 (1H, m, 2-CHH), 3.40 (3H, s, 1-OCH₃), 2.97 (1H, m, 3-H), 2.44 (1H, m, 2-H); δ_{C} (126 MHz, CDCl_3) 153.2 (Ar-C), 147.9 (Ar-C), 146.9 (Ar-C), 141.1 (Ar-C), 138.7 (3-CH=), 136.7 (Ar-C), 132.6 (Ar-C), 128.3 (Ar-C), 117.2 (=CH₂), 110.1 (Ar-C), 108.6 (Ar-C), 106.4 (Ar-C), 101.3 (OCH₂O), 78.6 (C-1), 63.1 (2-CH₂), 61.1 (1-OCH₃), 56.3 (Ar-OCH₃), 54.5 (Ar-OCH₃), 49.5 (C-4), 45.9 (C-3), 40.3 (C-2); m/z (ES^+) 451 (MNa^+), 879 (2MNa^+); HRMS (ES^+) Found MNa^+ , 451.1731, $\text{C}_{24}\text{H}_{28}\text{O}_7\text{Na}$ requires M^+ 451.1727.

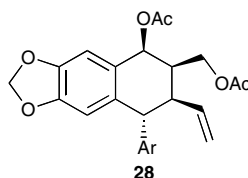
(4a*SR*,5*RS*,6*SR*,10*bRS*) 5-ethenyl-8,9-methylenedioxy-6-(3',4',5'-trimethoxyphenyl)-4a,5,6,10b-tetrahydro-4H-naphtho[1,2-d][1,3]dioxin-2-one **26**



A solution of naphthalene diol (20 mg, 0.05mmol) in dichloromethane (2ml) was treated consecutively with carbonyldiimidazole (0.008g, 0.05mmol) and a catalytic amount of DMAP. The reaction was stirred at room temperature for 2 h after which time aq. NH_4Cl (10ml) was added. The aqueous layer was separated and extracted with dichloromethane (3 x 20ml). The combined organic layers were dried over MgSO_4 , filtered, concentrated and dried *in vacuo*. Flash chromatography (ether) afforded the title compound as a cream gum (17 mg, 80%); R_f 0.4 (ether); ν_{max} (thin film) 2966, 2934, 2246, 1748 (C=O), 1591, 1505, 1485, 1464, 1421, 1242, 1129, 1041 cm^{-1} ; δ_{H} (500 MHz, CDCl_3) 7.06 (1H, s, Ar-H), 6.36 (1H, s, Ar-H), 6.16 (2H, s, Ar-H), 5.97 (1H, s, -OCHHO-), 5.95 (1H, s, -OCHHO-), 5.78 (1H, m, 5-CH=), 5.65 (1H, d, J 5, 10b-H), 5.14 (2H, m, =CH₂), 4.55 (1H, dd, J 11, 5, 4-HH), 4.33 (1H, d, J 11, 5, 4-CHH), 3.84-3.82 (1H, m, 6-H), 3.82 (3H, s, Ar-OCH₃), 3.77 (6H, s, Ar-OCH₃), 2.82 (1H, m, 5-H), 2.77 (1H, m, 4a-H); δ_{C} (126 MHz, CDCl_3) 153.3 (Ar-C), 148.6 (Ar-C), 148.4 (C=O), 147.4 (Ar-C), 139.0 (5-CH=), 136.9 (Ar-C), 136.9 (Ar-C), 130.5 (Ar-C), 125.5 (Ar-C), 118.1 (=CH₂), 109.5 (Ar-C), 107.7 (Ar-C), 105.9 (Ar-C), 101.4 (OCH₂O), 77.0 (C-10b), 67.4 (4a-CH₂), 60.8 (Ar-OCH₃), 56.2 (Ar-OCH₃), 48.8

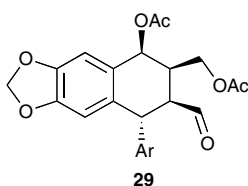
(C-6), 46.8 (C-5), 32.5 (C-4a); m/z (ES^+) 504 ($[M+MeCN]Na^+$), 903 ($2MNa^+$); HRMS (ES^+) Found $[M+MeCN]Na^+$, 504.1632, $C_{26}H_{27}O_8NNa$ requires M^+ 504.1629.

(1*RS*,2*SR*,3*RS*,4*SR*)-1-Acetoxy-2-acetoxymethyl-3-ethenyl-6,7-methylenedioxy-4-(3',4',5'-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene **28**



A solution of diol **14** (50 mg, 0.1mmol) in dichloromethane (2ml) was treated consecutively with DIPEA (0.08ml, 0.5mmol), acetic anhydride (0.03ml, 0.3mmol) and a catalytic amount of DMAP. The reaction was stirred at room temperature for 10min after which time aq. NH_4Cl (10ml) was added. The aqueous layer was separated and extracted with dichloromethane (3 x 20ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pet. ether/ether [3:7], [2:3], [1:4]) afforded the title compound as a colourless oil (50 mg, 82%); R_f 0.5 (pet. ether/ether 2:3); ν_{max} (thin film) 3074, 2960, 2890, 1731 (C=O), 1590, 1504, 1485, 1418, 1369, 1239, 1129, 1041 cm^{-1} ; δ_H (500 MHz, $CDCl_3$) 6.88 (1H, s, Ar-*H*), 6.41 (1H, s, Ar-*H*), 6.24 (1H, d, J 5, 1-*H*), 6.13 (2H, s, Ar-*H*), 6.00 (1H, m, 3-CH=), 5.95 (1H, d, J 1.3, OCHHO), 5.93 (1H, d, J 1.3, OCHHO), 5.07 (2H, m, =CH₂), 4.20 (1H, dd, J 11, 9, 2-CHHOAc), 4.00 (1H, d, J 4, 4-*H*), 3.91 (1H, d, J 11, 9, 2-CHHOAc), 3.82 (3H, s, 4'-OCH₃), 3.76 (6H, s, Ar-OCH₃), 2.66-2.55 (2H, m, 2-*H*, 3-*H*), 2.08 (3H, s, CH₃CO), 2.00 (3H, s, 1-CH₃CO₂); δ_C (126 MHz, $CDCl_3$) 171.2 (C=O), 171.1 (C=O), 153.3 (Ar-C), 148.3 (Ar-C), 147.2 (Ar-C), 140.6 (Ar-C), 138.8 (3-CH=), 136.9 (Ar-C), 130.9 (Ar-C), 128.2 (Ar-C), 116.5 (=CH₂), 110.1 (Ar-C), 108.5 (Ar-C), 106.1 (Ar-C), 101.6 (OCH₂O), 68.4 (C-1), 63.2 (2-CH₂), 61.1 (Ar-OCH₃), 56.4 (Ar-OCH₃), 50.7 (C-4), 47.5 (C-3), 36.2 (C-2), 21.4 (CH₃CO), 21.1 (1-CH₃CO₂); m/z (ES^+) 521 (MNa^+), 1018 ($2MNa^+$); HRMS (ES^+) Found MNa^+ , 521.1785, $C_{27}H_{30}O_9Na$ requires M^+ 521.1782.

(1*RS*,2*SR*,3*RS*,4*SR*)-1-acetoxy-2-acetoxymethyl-3-ethenyl-6,7-methylenedioxy-4-(3',4',5'-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene-3-carboxaldehyde **29**



A solution of diacetate **28** (30 mg, 0.06mmol) in THF:H₂O (1:1, 3ml) was treated with 2,6-lutidine (0.01ml, 0.1mmol), osmium tetroxide (1 mg, 0.006mmol) and sodium periodate (50 mg, 0.3mmol) at room temperature. The solution was stirred for 3 h then poured into H₂O and extracted with DCM (3 x 10ml). The combined organic layers were dried over MgSO₄, filtered, concentrated and dried *in vacuo*. Flash column chromatography (pet. ether/ether [3:7], [2:3], [1:4]) afforded the title compound as a white gum (12 mg, 39%); R_f 0.3 (pet. ether/ether 3:7); ν_{\max} (thin film) 2962, 2938, 1736 (C=O), 1591, 1505, 1485, 1419, 1371, 1238, 1130, 1041 cm⁻¹; δ_{H} (500 MHz, CDCl₃) 9.83 (1H, s, 3-CHO), 6.87 (1H, s, Ar-H), 6.48 (1H, s, Ar-H), 6.21 (1H, d, J 4, 1-H), 6.17 (2H, s, Ar-H), 5.98 (1H, d, J 1.2 OCHHO), 5.95 (1H, d J 1.2 OCHHO), 4.64 (1H, d, J 5, 4-H), 4.41 (1H, d, J 11, 8, 2-CHHOAc), 4.10 (1H, d, J 11, 8, 2-CHHOAc), 3.82 (3H, s, Ar-OCH₃), 3.77 (6H, s, Ar-OCH₃), 2.92 (1H, m, 2-H), 2.79 (1H, m, 3-H), 2.08 (3H, s, CH₃CO), 2.03 (3H, s, 1-CH₃CO₂); δ_{C} (126 MHz, CDCl₃) 200.8 (CHO), 170.9 (C=O), 170.5 (C=O), 153.6 (Ar-C), 148.7 (Ar-C), 147.4 (Ar-C), 139.8 (Ar-C), 137.2 (Ar-C), 130.5 (Ar-C), 127.6 (Ar-C), 110.1 (Ar-C), 108.5 (Ar-C), 106.1 (Ar-C), 101.6 (OCH₂O), 68.7 (C-1), 61.8 (2-CH₂), 61.0 (Ar-OCH₃), 56.5 (Ar-OCH₃), 54.7 (C-3), 43.2 (C-4), 36.3 (C-2), 21.3 (CH₃CO), 21.0 (1-CH₃CO₂); *m/z* (ES⁺) 523 (MNa⁺); HRMS (ES⁺) Found MNa⁺, 523.1580, C₂₆H₂₈O₁₀Na requires *M*⁺ 523.1575.