Synthesis of Tetrahydrocannabinols based on an Indirect 1,4-Addition Strategy

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General Methods. Infrared (IR) spectra are reported in wave numbers (cm^{-1}). The ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured in CDCl_3 using SiMe_4 ($\delta = 0$ ppm) and the center line of CDCl_3 triplet ($\delta = 77.1$ ppm) as internal standards, respectively. Signal patterns are indicated as br s, broad singlet; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants (J) are given in hertz (Hz). The coupling constants between ^{13}C and ^{31}P of the enol phosphates are given in the ^{13}C NMR spectral data. Some of the signals in the ^{13}C NMR spectra appearing as broad singlets with low intensity, probably owing to the restriction of free rotation of the aromatic ring are represented as br s.

3-[(2,6-Dimethoxy-4-pentyl)phenyl]-2-iodo-4-[(1-methyl-1-triethylsilyloxy)ethyl]-1-cyclohexanone (23c). According to the procedure for synthesis of **23b**, cuprate **10c** was prepared from the bis methyl ether of olivetol (300 mg, 1.44 mmol) in Et_2O (5 mL), $n\text{-BuLi}$ (0.61 mL, 2.75 M in hexane, 1.68 mmol), CuCN (64 mg, 0.716 mmol) in Et_2O (5 mL), and submitted to reaction with a solution of enone **22a** (190 mg, 0.482 mmol) and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.060 mL, 0.478 mmol) in Et_2O (5 mL) to afford the title compound **23c** (193 mg, 67% yield) after purification by chromatography (hexane/ EtOAc): IR (neat) 1726, 1610, 1581, 1458 cm^{-1} ; ^1H NMR δ 0.54–0.66 (m, 6 H), 0.87 (t, $J = 7$ Hz, 3 H), 0.97 (t, $J = 8$ Hz, 9 H), 1.22 (s, 3 H), 1.30 (s, 3 H), 1.18–1.39 (m, 4 H), 1.52–1.73 (m, 2 H), 1.96–2.26 (m, 3 H), 2.47–2.62 (m, 3 H), 2.66–2.80 (m, 1 H), 3.55 (s, 3 H), 3.81 (s, 3 H), 4.45 (dd, $J = 9, 5$ Hz, 1 H), 5.63 (d, $J = 9$ Hz, 1 H), 6.28 (d, $J = 1$ Hz, 1 H), 6.33 (d, $J = 1$ Hz, 1 H); ^{13}C NMR δ 6.9, 7.3, 14.2, 22.7, 22.9, 28.4, 29.9, 31.1, 31.8, 36.5, 38.6, 40.2, 43.9, 50.5, 53.6, 55.6, 76.5, 104.0, 104.3, 118.8, 143.3, 157.3, 157.5, 202.2. Anal. Calcd for $\text{C}_{28}\text{H}_{47}\text{IO}_4\text{Si}$: C, 55.80; H, 7.86. Found: C, 56.14; H, 8.01.

3-(1,3-Dimethoxynaphthalene-2-yl)-2-iodo-4-[(1-methyl-1-triethylsilyloxy)ethyl]-1-cyclohexanone (23e). According to the procedure for

synthesis of **23b**, cuprate **10e** was prepared from the bis methyl ether of 1,3-dimethoxynaphthalene (569 mg, 3.02 mmol) in Et₂O (5 mL), *n*-BuLi (1.34 mL, 2.40 M in hexane, 3.22 mmol), and CuCN (135 mg, 1.51 mmol) in Et₂O (5 mL), and submitted to reaction with a solution of enone **22a** (398 mg, 1.01 mmol) and BF₃·Et₂O (0.152 mL, 1.21 mmol) in Et₂O (5 mL) at -78 °C to afford **23e** (434 mg, 74% yield) after purification by chromatography (hexane/EtOAc): IR (neat) 1715, 1724, 1626, 1598, 1574 cm⁻¹; ¹H NMR δ 0.56–0.72 (m, 6 H), 0.99 (t, *J* = 8 Hz, 9 H), 1.26 (s, 3 H), 1.48 (s, 3 H), 1.84–1.97 (m, 1 H), 2.01–2.24 (m, 2 H), 2.48–2.65 (m, 1 H), 2.76–2.95 (m, 1 H), 3.68 (s, 3 H), 4.09 (s, 3 H), 4.67 (dd, *J* = 9, 4 Hz, 1 H), 5.88 (d, *J* = 9 Hz, 1 H), 6.92 (s, 1 H), 7.31–7.48 (m, 2 H), 7.71 (d, *J* = 8 Hz, 1 H), 7.97 (d, *J* = 8 Hz, 1 H); ¹³C NMR δ 6.9, 7.3, 23.1, 28.9, 30.0, 36.6, 42.9, 43.2, 51.6, 53.5, 62.0, 76.8, 102.5, 122.6, 123.2, 123.7, 126.4, 126.78, 126.85, 134.2, 154.0, 155.8, 201.4. HRMS (CI) *m/z* calcd for C₂₇H₃₉IO₄Si (M⁺) 582.1662, found: 582.1654.

3-[(2,6-Bis(methoxymethoxy)-4-pentyl)phenyl]-4-[(1,1-dimethyl)ethyl]-2-iodo-1-cyclohexanone (23f). According to the procedure for synthesis of **23b**, cuprate **10b** was prepared from the bis MOM ether of olivetol (722 mg, 2.69 mmol) in Et₂O (5 mL), *n*-BuLi (1.57 mL, 2.01 M in hexane, 3.16 mmol), and CuCN (120 mg, 1.34 mmol) in Et₂O (5 mL), and submitted to reaction with a solution of enone **22b** (250 mg, 0.899 mmol) and BF₃·Et₂O (0.135 mL, 1.07 mmol) in Et₂O (5 mL) at -78 °C to afford **23f** (330 mg, 67% yield) after purification by chromatography (hexane/EtOAc): IR (neat) 1725, 1610, 1584 cm⁻¹; ¹H NMR δ 0.83–0.91 (m, 12 H), 1.20–1.36 (m, 5 H), 1.48–1.65 (m, 2 H), 1.72–1.96 (m, 1 H), 2.00–2.11 (m, 1 H), 2.18–2.32 (m, 1 H), 2.44–2.74 (m, 3 H), 3.41 (s, 3 H), 3.52 (s, 3 H), 4.21 (dd, *J* = 10, 7 Hz, 1 H), 4.78 (d, *J* = 7 Hz, 1 H), 5.00 (d, *J* = 7 Hz, 1 H), 5.19 (s, 2 H), 5.42 (d, *J* = 10 Hz, 1 H), 6.57 (d, *J* = 1 Hz, 1 H), 6.59 (d, *J* = 1 Hz, 1 H); ¹³C NMR 14.2, 22.6, 23.5, 27.8, 30.9, 31.7, 34.2, 36.4, 36.8, 38.4, 46.0, 49.4, 56.2, 56.4, 94.0, 95.1, 107.5, 107.6, 120.8, 143.9, 155.4, 155.5, 202.7. HRMS (CI) *m/z* calcd for C₂₅H₃₉IO₅ (M⁺) 546.1842, found: 546.1842.

3-[(2,6-Dimethoxy-4-pentyl)phenyl]-2-iodo-1-cyclohexanone (23g).

According to the procedure for synthesis of **23b**, cuprate **10c** was prepared from the bis methyl ether of olivetol (562 mg, 2.70 mmol) in Et₂O (5 mL), *n*-BuLi (1.32 mL, 2.40 M in hexane, 3.14 mmol), and CuCN (120 mg, 1.35 mmol) in Et₂O (5 mL), and submitted to reaction with a solution of enone **22c** (200 mg, 0.900 mmol) and BF₃·Et₂O (0.135 mL, 1.08 mmol) in Et₂O (5 mL) at -78 °C to afford **23g** (232 mg, 60% yield) after purification by chromatography (hexane/EtOAc): IR (neat) 1711, 1609, 1580, 1456

cm⁻¹; ¹H NMR δ 0.91 (t, J = 7 Hz, 3 H), 1.26–1.47 (m, 5 H), 1.54–1.83 (m, 3 H), 1.94–2.07 (m, 2 H), 2.29–2.44 (m, 2 H), 2.57 (t, J = 8 Hz, 2 H), 3.05 (ddd, J = 16, 8, 5 Hz, 1 H), 3.73 (s, 6 H), 5.00 (dd, J = 5, 1 Hz, 1 H), 6.36 (s, 2 H); ¹³C NMR δ 14.2, 22.7, 24.5, 29.9, 31.1, 31.8, 36.6, 37.8, 41.2, 42.1, 55.1, 104.4, 114.8, 143.6, 158.0, 202.6. Anal. Calcd for C₁₉H₂₇IO₃: C, 53.03; H, 6.32. Found C, 53.11; H, 6.33.

3-(1,3-Dimethoxynaphthalene-2-yl)-2-iodo-1-cyclohexanone (23h).

According to the procedure for synthesis of **23b**, cuprate **10e** was prepared from the bis methyl ether of 1,3-dimethoxynaphthalene (254 mg, 1.35 mmol) in Et₂O (5 mL), *n*-BuLi (0.66 mL, 2.40 M in hexane, 1.58 mmol), and CuCN (60 mg, 0.67 mmol) in Et₂O (5 mL), and submitted to reaction with a solution of enone **22c** (100 mg, 0.450 mmol) and BF₃·Et₂O (0.070 mL, 0.56 mmol) in Et₂O (5 mL) at –78 °C to afford **23h** (124 mg, 68% yield) after purification by chromatography (hexane/EtOAc): IR (neat) 1713, 1458, 1335 cm⁻¹; ¹H NMR δ 1.70–2.65 (m, 6 H), 3.00 (dt, J = 16, 6 Hz, 1 H), 3.76 (s, 3 H), 4.00 (s, 3 H), 5.18 (d, J = 6 Hz, 1 H), 6.94 (s, 1 H), 7.32–7.50 (m, 2 H), 7.53 (d, J = 8 Hz, 1 H), 8.0 (d, J = 8 Hz, 1 H). HRMS (CI) m/z calcd for C₁₈H₁₉IO₃ (M⁺) 410.0379, found: 410.0345.

Phosphate 12c. By using the procedure for synthesis of **12b**, iodoketone **23c** (140 mg, 0.232 mmol) in THF (5 mL), EtMgBr (0.35 mL, 1.0 M in THF, 0.35 mmol), and CIP(O)(OEt)₂ (0.083 mL, 0.58 mmol) afforded the title product **12c** (99 mg, 70% yield) after purification by chromatography: IR (neat) 1607, 1579, 1458 cm⁻¹; ¹H NMR δ 0.45–0.55 (m, 6 H), 0.86–0.96 (m, 15 H), 1.06 (s, 3 H), 1.24–1.36 (m, 13 H), 1.53–1.68 (m, 3 H), 2.14–2.28 (m, 2 H), 2.30–2.44 (m, 2 H), 2.53 (t, J = 8 Hz, 2 H), 3.75 (s, 6 H), 4.01–4.15 (m, 5 H), 5.04 (dt, J = 3, 2.5 Hz, 1 H), 6.33 (br s, 2 H); ¹³C NMR δ 6.9, 7.3, 14.3, 16.2 (d, J = 7 Hz), 22.7, 25.4, 26.4, 28.2 (d, J = 3 Hz), 30.1, 31.3, 31.8, 32.3, 36.6, 46.7, 55.5, 63.9 (d, J = 6 Hz), 76.2, 103.0 (br s), 104.6 (br s), 115.1 (d, J = 6 Hz), 119.4, 142.1, 147.0 (d, J = 9 Hz), 157.1 (br s), 158.8 (br s). Anal. Calcd for C₃₂H₅₇O₇PSi: C, 62.71; H, 9.37. Found: C, 62.62; H, 9.43.

Phosphate 12e. By using the procedure for synthesis of **12b**, iodoketone **23e** (430 mg, 0.738 mmol) in THF (5 mL), EtMgBr (1.11 mL, 1.0 M in THF, 1.11 mmol), and CIP(O)(OEt)₂ (0.27 mL, 1.85 mmol) afforded the title product **12e** (262 mg, 60% yield) after purification by chromatography: IR (neat) 1687, 1625, 1597, 1458 cm⁻¹; ¹H NMR δ 0.41–0.53 (m, 6 H), 0.75–1.17 (m, 15 H), 1.20–1.38 (m, 6 H), 1.58–1.80 (m, 1 H), 2.18–2.63 (m, 4 H), 3.89 (s, 3 H), 3.90 (s, 3 H), 4.01–4.29 (m, 5 H), 5.18 (br s, 1

H), 6.91 (s, 1 H), 7.30–7.47 (m, 2 H), 7.69 (d, $J = 8$ Hz, 1 H), 7.95 (d, $J = 8$ Hz, 1 H).
HRMS (CI) m/z calcd for $C_{31}H_{49}O_7PSi$ (M^+) 592.2985; found: 592.2983.

Phosphate 12f. By using the procedure for synthesis of **12b**, iodoketone **23f** (210 mg, 0.384 mmol) in THF (5 mL), EtMgBr (0.58 mL, 1.0 M in THF, 0.58 mmol), and $ClP(O)(OEt)_2$ (0.14 mL, 0.97 mmol) afforded the title product **12f** (135 mg, 63% yield) after purification by chromatography: IR (neat) 1692, 1608, 1580 cm^{-1} ; 1H NMR 0.78 (br s, 9 H), 0.89 (t, $J = 7$ Hz, 3 H), 1.21–1.37 (m, 10 H), 1.43–1.63 (m, 3 H), 1.92–2.07 (m, 1 H), 2.19–2.32 (m, 2 H), 2.34–2.46 (m, 1 H), 2.51 (t, $J = 8$ Hz, 2 H), 3.49 (br s, 6 H), 4.03–4.15 (m, 5 H), 5.08 (q, $J = 3$ Hz, 1 H), 5.15 (s, 4 H), 6.56 (s, 2 H); ^{13}C NMR δ 14.0, 15.9 (d, $J = 7$ Hz), 22.4, 25.8, 28.3, 28.4, 30.9, 31.5, 32.9, 33.6, 36.1, 44.7, 56.1, 63.9 (d, $J = 6$ Hz), 94.8, 108.5, 115.4 (d, $J = 6$ Hz), 121.6, 142.7, 147.1 (d, $J = 9$ Hz), 155 (br s), 157 (br s). Anal. Calcd for $C_{29}H_{49}O_8P$: C, 62.57; H, 8.87. Found: C, 62.48; H, 8.87.

Phosphate 12g. By using the procedure for synthesis of **12b**, iodoketone **23g** (150 mg, 0.348 mmol) in THF (5 mL), EtMgBr (0.52 mL, 1.0 M in THF, 0.52 mmol), and $ClP(O)(OEt)_2$ (0.13 mL, 0.89 mmol) afforded the title product **12g** (89 mg, 58% yield) after purification by chromatography: IR (neat) 1683, 1607, 1580 cm^{-1} ; 1H NMR δ 0.90 (t, $J = 7$ Hz, 3 H), 1.24–1.44 (m, 10 H), 1.53–1.95 (m, 6 H), 2.11–2.44 (m, 2 H), 2.54 (t, $J = 8$ Hz, 2 H), 3.76 (s, 6 H), 4.00–4.22 (m, 5 H), 5.39 (d, $J = 2$ Hz, 1 H), 6.35 (s, 2 H); ^{13}C NMR δ 14.1, 16.2 (d, $J = 7$ Hz), 22.6, 23.4, 27.0, 27.5 (d, $J = 3$ Hz), 31.2 (d, $J = 7$ Hz), 31.7, 36.5, 55.7, 63.8 (d, $J = 6$ Hz), 104.3, 116.4 (d, $J = 4$ Hz), 118.0, 142.3, 145.3 (d, $J = 9$ Hz), 158.2. Anal. Calcd for $C_{23}H_{37}O_6P$: C, 62.71; H, 8.47. Found: C, 62.69; H, 8.26.

Phosphate 12h. By using the procedure for synthesis of **12b**, iodoketone **23h** (120 mg, 0.292 mmol) in THF (5 mL), EtMgBr (0.44 mL, 1.0 M in THF, 0.44 mmol), and $ClP(O)(OEt)_2$ (0.11 mL, 0.75 mmol) afforded the title product **12h** (76 mg, 62% yield) after purification by chromatography: IR (neat) 1625, 1597 cm^{-1} ; 1H NMR δ 1.34 (t, $J = 7$ Hz, 6 H), 1.74–2.60 (m, 6 H), 3.89 (s, 3 H), 3.91 (s, 3 H), 4.05–4.35 (m, 5 H), 5.48 (br s, 1 H), 6.93 (s, 1 H), 7.30–7.47 (m, 2 H), 7.70 (d, $J = 8$ Hz, 1 H), 7.98 (d, $J = 8$ Hz, 1 H); ^{13}C NMR δ 16.3 (d, $J = 7$ Hz, 1 H), 23.4, 27.6 (d, $J = 3$ Hz), 33.0, 55.5, 63.0, 64.0 (d, $J = 6$ Hz), 102.2, 115.5 (d, $J = 6$ Hz), 122.2, 123.5, 125.8, 126.2, 126.5, 133.8, 146.2 (d, $J = 9$ Hz), 154.5, 157.3. Anal. Calcd for $C_{22}H_{29}O_6P$: C, 62.85; H, 6.95. Found: C, 62.79; H, 7.38.

3-[(2,6-Dimethoxy-4-pentyl)phenyl]-1-methyl-4-[(1-methyl-1-triethylsilyloxy)ethyl]-1-cyclohexene (31c). According to the procedure for synthesis of **31b**, methylation of enol phosphate **12c** (250 mg, 0.41 mmol) in THF (5 mL) was carried out with MeMgCl (0.36 mL, 2.80 M in THF, 1.01 mmol) and Ni(acac)₂ (10 mg, 0.039 mmol) in THF (5 mL) to afford **31c** (174 mg, 90% yield): IR (neat) 1607, 1578 cm⁻¹; ¹H NMR δ 0.51 (q, *J* = 8 Hz, 6 H), 0.84–0.98 (m, 15 H), 1.06 (s, 3 H), 1.63 (s, 3 H), 1.2–1.7 (m, 7 H), 1.84–1.96 (m, 1 H), 2.01–2.19 (m, 2 H), 2.32–2.44 (m, 1 H), 2.54 (t, *J* = 8 Hz, 2 H), 3.75 (br s, 6 H), 3.90 (d, *J* = 9 Hz, 1 H), 4.95 (br s, 1 H), 6.33 (s, 2 H); ¹³C NMR δ 7.0, 7.4, 14.3, 22.8, 23.5, 25.4, 26.5, 30.1, 30.7, 31.3, 31.9, 34.0, 36.6, 47.1, 55.8, 76.6, 104.2 (br s), 105.6 (br s), 121.7, 125.4, 132.3, 141.6, 157.0 (br s), 159.0 (br s). Anal. Calcd for C₂₉H₅₀O₃Si: C, 73.36; H, 10.61. Found C, 73.22; H, 10.37.

3-[(2,6-Bis-(2-trimethylsilylethyloxymethoxy)-4-pentyl)phenyl]-1-methyl-4-[(1-methyl-1-triethylsilyloxy)ethyl]-1-cyclohexene (31d). According to the procedure for synthesis of **31b**, methylation of enol phosphate **12d** (200 mg, 0.236 mmol) in THF (5 mL) was carried out with MeMgCl (0.21 mL, 2.80 M in THF, 0.588 mmol) and Ni(acac)₂ (6 mg, 0.023 mmol) in THF (5 mL) to afford **31d** (156 mg, 93% yield): IR (neat) 1607, 1579 cm⁻¹; ¹H NMR δ 0.01 (br s, 18 H), 0.51 (q, *J* = 8 Hz, 6 H), 0.85–1.00 (m, 19 H), 1.10 (s, 3 H), 1.22–1.46 (m, 6 H), 1.52–1.60 (m, 1 H), 1.61 (s, 3 H), 1.85–2.23 (m, 3 H), 2.34–2.45 (m, 1 H), 2.50 (t, *J* = 8 Hz, 2 H), 3.73 (t, *J* = 8 Hz, 4 H), 3.89 (d, *J* = 10 Hz, 1 H), 4.90–5.25 (m, 5 H), 6.59 (s, 2 H); ¹³C NMR δ –1.1, 7.0, 7.4, 14.3, 18.3, 22.8, 23.5, 25.3, 26.3, 30.3, 30.8, 31.2, 31.9, 34.6, 36.4, 47.3, 66.0, 66.2, 76.6, 93.1, 93.5, 108.4, 109.1, 122.7, 125.7, 132.1, 141.8, 155.0, 156.9. HRMS (EI) *m/z* calcd for C₃₉H₇₄O₅Si₃ ((M+H)⁺) 707.4922, found: 707.4925.

3-(1,3-Dimethoxynaphthalene-2-yl)-1-methyl-4-[(1-methyl-1-triethylsilyloxy)ethyl]-1-cyclohexene (31e). According to the procedure for synthesis of **31b**, methylation of enol phosphate **12e** (180 mg, 0.304 mmol) in THF (5 mL) was carried out with MeMgCl (0.27 mL, 2.80 M in THF, 0.76 mmol) and Ni(acac)₂ (8 mg, 0.03 mmol) in THF (5 mL) to afford **31e** (136 mg, 99% yield): IR (neat) 1625, 1596, 1573, 1456 cm⁻¹; ¹H NMR δ 0.39 (q, *J* = 8 Hz, 6 H), 0.76–1.08 (m, 15 H), 1.60 (s, 3 H), 1.35–1.70 (m, 2 H), 1.85–2.20 (m, 3 H), 2.30–2.65 (m, 1 H), 3.60–4.20 (m, 7 H), 4.99 (s, 1 H), 6.84 (s, 1 H), 7.27–7.36 (m, 2 H), 7.61 (d, *J* = 8 Hz, 1 H), 7.88 (d, *J* = 6 Hz, 1 H). HRMS (CI) *m/z* calcd for C₂₈H₄₂O₃Si (M⁺) 454.2903, found: 454.2904.