A Facile Method for the Solution and Solid Phase Synthesis of Substituted [3.3.1] Bicycles.

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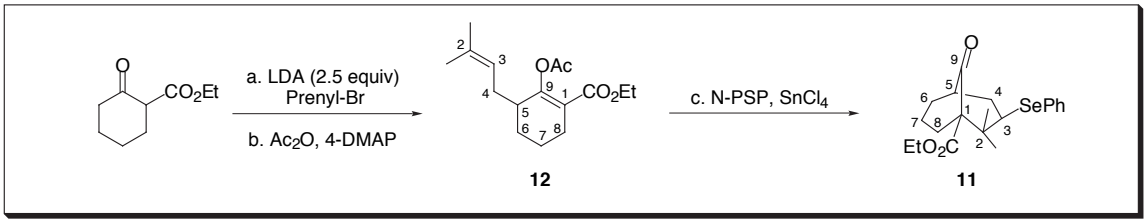
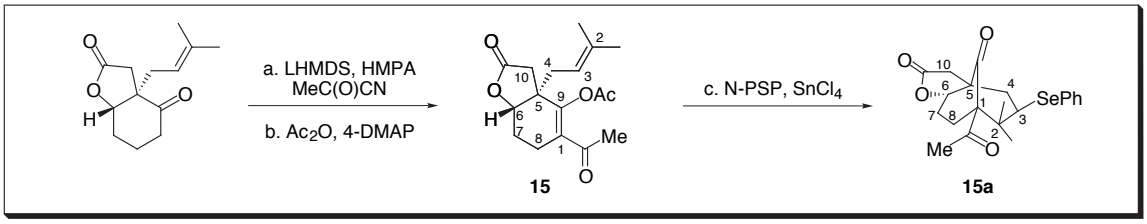
Supporting Information



Preparation and cyclization of enol acetate **12**: To a solution of ethyl 2-cyclohexanonecarboxylate (2.00 g, 11.75 mmol, 1.0 equiv) in THF (25 mL) at -78 °C was added LDA (29.4 mL of 1.0 M solution in THF, 29.4 mmol, 2.5 equiv), and after stirring at -78 °C for 5 min, the solution was warmed to 0 °C and stirred for an additional 30 min followed by addition of 4-bromo-2-methyl-2-butene (1.35 mL, 11.75 mmol, 1.0 equiv). The reaction mixture was then stirred at 0 °C for an additional 30 min and quenched by addition of saturated NH_4Cl solution. After extraction with Et_2O (3 x 100 mL), the combined extracts were dried over $MgSO_4$ and concentrated. The crude product (as a tautomeric mixture) was purified over a short silica column (10% EtOAc in hexanes) and, without further purification, was dissolved in Ac_2O (15 mL). A portion of 4-DMAP (143 mg, 1.18 mmol, 0.1 equiv) was then added and the solution was heated to 80 °C for 30 min. After cooling, the reaction mixture was poured into saturated $NaHCO_3$ and extracted with Et_2O (3 x 100 mL). The combined extracts were dried and concentrated, and the crude residue was purified by column chromatography (silica, 5% EtOAc in hexanes) to yield enol acetate **12** (2.13 g, 64% over two steps). FT-IR (neat) ν_{max} 2936, 2860, 1766, 1714, 1651, 1453, 1367, 1238, 1121, 848 cm^{-1}; ^1H NMR (numbering as shown) (500 MHz, $CDCl_3$) δ 5.02-4.99 (m, 1 H, C-3), 4.07 (q, J = 7.5 Hz, 2 H, Et), 2.41-2.28 (m, 4 H), 2.12 (s, 3 H, Ac), 2.11-2.01 (m, 1 H), 1.78-1.49 (m, 4 H), 1.65 (s, 3 H, Me), 1.55 (s, 3 H, Me), 1.21 (t, J = 8.1 Hz, 3 H, Et); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 165.7, 157.4, 133.2, 122.0, 118.1, 60.2, 50.4, 38.9, 30.0, 26.8, 25.7, 22.0, 19.1, 17.7, 14.1; HRMS calcd for $C_{16}H_{24}O_4$ $[M + H^+]$ 281.1753, found 281.1748.

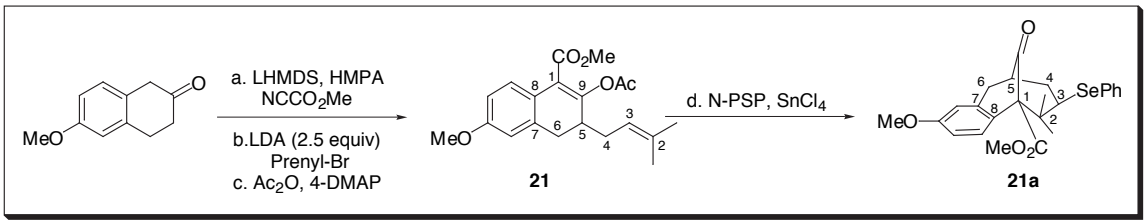
To a solution of **12** (1.00 g, 3.56 mmol, 1.0 equiv) in CH_2Cl_2 at 25 °C was added *N*-(phenylseleno)phthalimide (1.19 g, 3.92 mmol, 1.1 equiv) and after cooling -78 °C, a solution of $SnCl_4$ (3.56 mL of 1.0 M solution in CH_2Cl_2, 3.56 mmol, 1.0 equiv) was added, and the reaction mixture was stirred at -78 °C for 5 min followed by quenching with saturated $NaHCO_3$ solution at -78 °C. After warming to 25 °C, the reaction mixture was extracted with CH_2Cl_2, and the combined extracts were washed with $NaHCO_3$ (50 mL) and brine (50 mL) before being dried over $MgSO_4$. After concentration, the crude product was purified by column chromatography to afford bicycle **11** (1.32 g, 94%). FT-IR (neat) ν_{max} 2936, 2860, 1734(br), 1384, 1121, 912, 738 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.60-7.58 (m, 2 H, Ph), 7.30-7.25 (m, 3 H, Ph), 4.19-4.15 (m, 2 H, Et), 3.88 (dd, *J* = 13.4, 5.3 Hz, 1 H, C-3), 2.57-2.53 (m, 1 H, C-5), 2.49-2.25 (m, 2 H, C-4, C-8), 2.22-2.18 (m, 1 H, C-4), 2.12-2.08 (m, 1 H, C-7), 1.84-1.78 (m, 2 H, C-6, C-7), 1.63-1.58 (m, 2 H, C-6), 1.35 (s, 3 H, Me), 1.26 (t, *J* = 6.9 Hz, 3 H, Et), 1.22 (s, 3 H, Me); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.1, 170.9, 134.5, 130.2, 129.3, 127.7, 65.4, 60.7, 52.7, 47.1, 47.1, 40.0, 33.4, 32.9, 24.5, 21.2, 20.4, 14.1; HRMS calcd for $C_{20}H_{26}O_3Se$ [M + Na^+] 417.0945, found 417.0929.



Preparation and cyclization of enol acetate **15**: To a solution of ketone[a] (2.00 g, 9.00 mmol, 1.0 equiv) and HMPA (1.58 mL, 9.00 mmol, 1.0 equiv) in THF (25 mL) at -78 °C was added LHMDS (10.8 mL of 1.0 M solution in THF, 10.8 mmol, 1.2 equiv), and after stirring at –78 °C for 30 min pyruvonitrile (957 μL, 13.5 mmol, 1.5 equiv) was added. The resulting solution was stirred at -78 °C for 15 min and at 0 °C for an additional 15 min followed by quenching with saturated NH_4Cl and extraction with EtOAc (3 x 150 mL). The combined extracts were dried over $MgSO_4$, concentrated and passed through a short silica column (10% EtOAc in hexanes). To this tautomeric mixture was added Ac_2O (15 mL) and 4-DMAP (110 mg, 0.90 mmol, 0.1 equiv), and the reaction mixture was heated to 80 °C for 30 min. After cooling, the mixture was poured into saturated $NaHCO_3$ and extracted with Et_2O (3 x 100 mL). The combined extracts were dried and concentrated, and the crude residue was purified by column chromatography (silica, 10% EtOAc in hexanes) to yield enol acetate **15** (2.07 g, 75% over two steps). FT-IR (neat) ν_{max} 2968, 2918, 1790, 1760, 1704, 1372, 1193, 1168, 1019, 1019, 927, 878 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.81-4.77 (m, 1 H, C-3), 4.21 (dd, *J* = 13.0, 4.3 Hz, 1 H, C-6), 2.82-2.75 (m, 1 H, C-4), 2.68 (dd, *J* = 17.0, 1.9 Hz, 1 H, C-10), 2.48 (d, *J* = 17.0 Hz, 1 H, C-10), 2.34 (dd, *J* = 14.9, 7.4 Hz, 1 H, C-4), 2.27-2.18 (m, 3 H), 2.18 (s, 3 H, Ac), 2.07 (s, 3 H, Ac), 2.16-2.05 (m, 1 H), 1.64 (s, 3 H, Me), 1.53 (s, 3 H, Me); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 174.9, 167.4, 156.0, 137.3, 122.7, 115.9, 80.9, 57.7, 35.4, 27.6, 25.9, 21.7, 21.1, 20.8, 18.7, 17.8; HRMS calcd for $C_{17}H_{22}O_5$ [M + Na^+] 329.1365, found 329.1362.

[a] Nicolaou, K. C.; Pfefferkorn, J. A.; Kim, S.; Wei, H. X. *J. Am. Chem. Soc.* **1999**, *121*, 4724-4725.

Substrate **15** (300 mg, 0.98 mmol, 1.0 equiv) was cyclized (-23 °C , 5 min) according to the procedure previously described for substrate **12** to afford bicycle **15a** (382 mg, 93%). FT-IR (neat) ν_{max} 2968, 1789, 1722, 1476, 1436, 1242, 1184, 1064, 971, 737 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.52 (m, 2 H, Ph), 7.37-7.28 (m, 3 H, Ph), 4.11 (dd, *J* = 12.5, 5.0 Hz, 1 H, C-6), 3.66 (dd, *J* = 12.8, 10.6 Hz, 1 H, C-3), 3.08 (d, *J* = 17.1 Hz, 1 H, C-10), 2.74 (dd, *J* = 15.1, 10.6 Hz, C-4), 2.46-2.43 (m, 1 H), 2.34-2.31 (m, 1 H), 2.21 (s, 3 H, Me), 2.13 (d, *J* = 17.1 Hz, C-10), 2.13-2.09 (m, 2 H), 1.39 (s, 3 H, Me), 1.15 (s, 3 H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 206.9, 205.2, 173.9, 134.7, 129.6, 128.3, 83.8, 69.4, 57.8, 54.9, 47.8, 39.2, 37.4, 30.9, 25.9, 25.8, 24.2, 21.3; HRMS calcd for $C_{21}H_{24}O_4Se$ $[M + Na^+]$ 443.0737, found 443.0726.

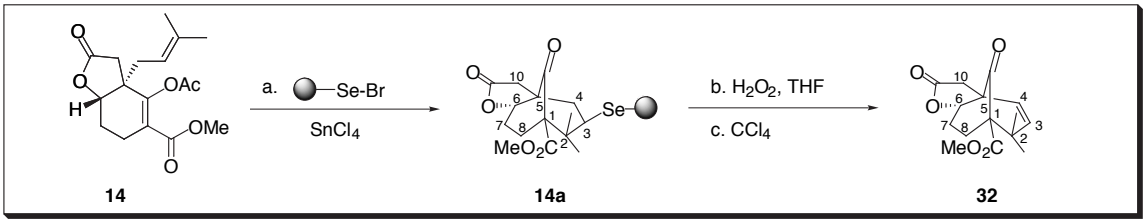


Preparation and cyclization of enol acetate **22**: To a solution of 6-methoxy-2-tetralone[b] (2.00 g, 11.4 mmol, 1.0 equiv) and HMPA (2.08 mL, 11.4 mmol, 1.0 equiv) in THF (40 mL) at -78 °C was added LHMDS (13.7 mL of 1.0 M solution in THF, 13.7 mmol, 1.2 equiv), and after stirring at -78 °C for 30 min methyl cyanoformate (1.36 mL, 17.1 mmol, 1.5 equiv) was added. The resulting solution was stirred at -78 °C for 15 min and then at 0 °C for 15 min followed by quenching with saturated NH_4Cl and extraction with EtOAc (3 x 150 mL). The combined extracts were dried over $MgSO_4$, concentrated and purified by column chromatography (silica, 10% EtOAc in hexanes) to afford the corresponding β-ketoster (2.54 g, 95%). To a solution of this β-ketoster (2.54 g, 10.8 mmol, 1.0 equiv) in THF (25 mL) at -78 °C was added LDA (27.0 mL of 1.0 M solution in THF, 27.0 mmol, 2.5 equiv) and after stirring at -78 °C for 5 min the solution was warmed to 0 °C and stirred for an additional 30 min followed by addition of 4-bromo-2-methyl-2-butene (1.24 mL, 10.8 mmol, 1.0 equiv). The reaction mixture was then stirred at 0 °C for an additional 30 min, and then quenched by the addition of saturated NH_4Cl solution. After extraction with Et_2O (3 x 100 mL), the combined extracts were dried over $MgSO_4$ and concentrated. The crude product (as a mixture of tautomers) was purified over a short silica column (5% EtOAc in hexanes) and subjected directly to acetylation. To this mixture of tautomers was added Ac_2O (15 mL) and 4-DMAP (132 mg, 1.08 mmol, 0.1 equiv), and the resulting solution was heated to 80 °C for 30 min. After cooling, the reaction mixture was poured into saturated $NaHCO_3$ and extracted with Et_2O (3 x 100 mL). The combined extracts were dried and concentrated, and the crude oil was purified by column chromatography (silica, 10% EtOAc in hexanes) to yield enol acetate **22** (2.90

[b] Copinga, S.; Tepper, P. G.; Grol, C. J.; Horn, A. J. *J. Med. Chem.* **1993**, *36*, 2891-2898.

g, 78% over two steps). FT-IR (neat) ν_{max} 2951, 1764, 1726, 1610, 1501, 1433, 1368, 1226, 1013, 871, 821, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.2 Hz, 1 H, Ph), 6.67-6.48 (m, 2 H, Ph), 5.04-4.99 (m, 1 H, C-3), 3.79 (s, 3 H, OMe), 3.73 (s, 3 H, OMe), 3.06 (dd, *J* = 15.6, 6.6 Hz, 1 H, C-6), 2.67 (dd, *J* = 15.7, 5.2 Hz, 1 H, C-6), 2.52-2.47 (m, 1 H, C-5), 2.16 (s, 3 H, Ac), 2.16-1.98 (m, 2 H, C-4), 1.65 (s, 3 H, Me), 1.46 (s, 3 H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 168.7, 166.4, 159.0, 153.8, 134.6, 126.2, 122.7, 121.1, 119.5, 114.5, 111.2, 55.2, 51.9, 37.6, 32.9, 28.1, 25.8, 22.1, 20.7, 18.0; HRMS calcd for $C_{20}H_{24}O_5$ $[M + Na^+]$ 367.1521, found 367.1537.

Substrate **22** (500 mg, 1.45 mmol, 1.0 equiv) was cyclized (-23 °C, 15 min) according to the procedure previously described to afford bicycle **22a** (590 mg, 89%). FT-IR (neat) ν_{max} 2946, 2838, 1728, 1610, 1501, 1451, 1384, 1226, 1121, 1039, 912, 738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.58 (m, 1 H, Ph), 7.32-7.14 (m, 5 H, Ph), 6.76-6.62 (m, 2 H), 3.78 (s, 3 H, OMe), 3.65 (s, 3 H, OMe), 3.41 (dd, *J* = 17.5, 6.5 Hz, 1 H, C-10), 3.18 (dd. *J* = 13.5, 4.9 Hz, 1 H, C-3), 2.99 (d, *J* = 17.5 Hz, 1 H, C-10), 2.79-2.76 (m, 1 H, C-4), 2.46-2.38 (1 H, C-5), 2.22-2.17 (m, 1 H, C-4), 1.35 (s, 3 H, Me), 1.33 (s, 3 H Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 208.8, 171.0, 158.3, 138.3, 136.5, 133.9, 131.7, 129.0, 128.7, 127.4, 112.4, 111.6, 69.9, 55.3, 51.94, 50.4, 47.8, 46.1, 40.8, 38.4, 24.8, 18.6; HRMS calcd for $C_{24}H_{26}O_4Se$ $[M + Na^+]$ 481.0893, found 481.0903.



Solid phase cyclization and cleavage of enol acetate **14**: To a suspension of selenium bromide resin[c] (300 mg, 0.528 mmol, 1.0 equiv) in CH_2Cl_2 (4.0 mL) at 25 °C was added a solution of enol acetate **14**[a] (513 mg, 1.58 mmol, 3.0 equiv) in CH_2Cl_2 (2.0 mL). The resulting suspension was cooled to -23 °C and $SnCl_4$ (1.58 mL of 1.0 M solution in CH_2Cl_2, 1.58 mmol, 3.0 equiv) was added and the mixture was stirred at -23 °C for 20 min. Triethylamine (1.0 mL) was then added and the reaction mixture was allowed to warm to 25 °C. The suspension was filtered through a sintered funnel and the resin was washed alternately with CH_2Cl_2 (5 x 30 mL) and MeOH (5 x 30 mL) and then finally with Et_2O (30 mL). To a suspension of this resin (100 mg, 0.171 mmol, 1.0 equiv) in THF at 0 °C was added 30% H_2O_2 (200 μL) and the resulting mixture was stirred at 0 °C for 2 h. The suspension was then filtered through a sintered funnel and the resin was washed alternately with CH_2Cl_2 (5 x 30 mL) and MeOH (5 x 30 mL) and then finally with Et_2O (30 mL). After drying under high vacuum for 10 h the resin mass was determined to be 378 mg suggesting approximately 91% loading. This resin was then suspended in CCl_4 (2.0 ml) and heated to 80 °C for 10 min after which time the resin was removed by filtration and the filtrate was concentrated to afford bicycle **32** (98% pure as determined by crude ^{1}H-NMR). FT-IR (neat) ν_{max} 2954, 1789, 1731, 1531, 1454, 1260, 1184, 1102, 1043 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (d, *J* = 9.6 Hz, 1 H, C-4), 5.13 (d, *J* = 9.8 Hz, 1 H, C-3), 4.04 (dd, *J* = 10.9, 5.2 Hz, 1 H, C-6), 3.72 (s, 3 H, OMe), 3.05 (d, *J* = 16.9 Hz, 1 H, C-10), 2.52 (ddd, *J* = 14.9, 4.2, 2.7 Hz, 1 H), 2.39 (d, *J* = 16.9 Hz, 1 H, C-10), 2.33-2.19 (m, 2 H), 2.04-1.94 (m, 1 H), 1.34 (s, 3 H, Me), 1.12 (s, 3 H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 201.2, 174.1, 170.1, 143.6, 120.5, 82.6, 64.2, 57.1, 52.0,

[c] Nicolaou, K. C.; Pastor, J.; Barluenga, S.; Winssinger, N. *Chem. Commun.* **1998**, 1947-1948.

47.5, 46.1, 35.5, 29.8, 26.9, 23.9, 23.1, 19.3; HRMS calcd for $C_{15}H_{18}O_5$ [M + Na^+] 301.1053, found 301.1049.