Efficient synthesis of *trans*-fused polycyclic ethers including tetrahydropyrans and oxepanes based on SmI_2-induced reductive cyclization

Nobuyuki Hori, Hiroko Matsukura, and Tadashi Nakata*

The Institute of Physical and Chemical Research (RIKEN), Wako-shi, Saitama 351-0198, Japan.

Supporting Information

Thioacetal 9:

To a stirred solution of **8** (732.5 mg, 3.46 mmol) in toluene (30 mL) at room temperature under Ar was added DIBAH (0.95 M in *n*-hexane, 4.40 mL, 4.15 mmol). After stirring at room temperature for 1 h, the reaction mixture was quenched with *i*-PrOH (1 mL) and H_2O (0.5 mL) at –78 °C and allowed to room temperature. After addition of SiO_2 and $MgSO_4$, the mixture was diluted with EtOAc and stirred for 1 h. The mixture was filtrated through a Celite-pad and then evaporated to give lactol (720.0 mg). To a stirred solution of the lactol in CH_2Cl_2 (30 mL) at 0 °C were added 1,3-propanedithiol (0.65 mL, 6.45 mmol) and $BF_3{\cdot}Et_2O$ (0.79 mL, 6.45 mmol). After stirring at 0 °C for 1 h, the mixture was diluted with EtOAc, washed with 10% aqueous NaOH. The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with saturated aqueous NH_4Cl and brine, dried over $MgSO_4$, and evaporated. The residue was purified by flash column chromatography (SiO_2; *n*-hexane/EtOAc = 3:2) to give **9** (995.3 mg, 95%) as colorless crystals.

9: mp 102-103 °C (Et_2O); $[\alpha]^{25}_D$ +39.6 (*c* 0.83, $CHCl_3$); IR (nujol) 3462, 2949, 2728, 2676, 1456, 1378 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.20 (dd, *J* = 10.1, 4.1 Hz, 1H), 3.88 (m, 1H), 3.70 (br, 1H), 3.59 (ddd, *J* = 10.1, 7.3, 2.8 Hz, 1H), 3.31 (ddd, *J* = 11.0, 11.0, 4.1 Hz, 1H), 3.16 (ddd, *J* = 11.0, 9.6, 4.6 Hz, 1H), 2.96 (ddd, *J* = 9.2, 8.7, 4.6 Hz, 1H), 2.89-2.78 (m, 4H), 2.18-2.08 (m, 3H), 1.93-1.83 (m, 6H), 1.68-1.66 (m, 3H), 1.44 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 83.3, 83.2, 82.5, 74.5, 67.8, 43.9, 40.5, 31.2, 30.8, 30.0, 29.5, 27.2, 26.0, 25.8. Anal. Calcd for $C_{14}H_{24}O_3S_2$: C, 55.23; H, 7.95. Found: C, 55.19; H, 8.01.

Aldehyde 10:

To a stirred solution of **9** (595.9 mg, 1.96 mmol) in CH_2Cl_2 (20 mL) at room temperature under Ar were added *N*-methylmorpholine (0.43 mL, 3.92 mmol) and ethyl propiolate (0.40 mL, 0.76 mmol). After stirring at room temperature for 16 h, the reaction mixture was diluted with EtOAc, washed with H_2O. The aqueous layer was extracted with EtOAc and the combined organic extracts were dried over $MgSO_4$, and evaporated. The residue was purified by falsh column chromatography (SiO_2; *n*-hexane/EtOAc = 3:1) to give ester (830.5 mg). To a stirred solution of the ester in MeCN (16 mL) and H_2O (4 mL) at room temperature were added $NaHCO_3$ (494.0 mg, 5.88 mmol) and MeI (0.33 mL, 5.22 mmol). After stirring for 18 h, the reaction mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc and the combined organic extracts were dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (SiO_2; *n*-hexane/EtOAc = 3:1, 1:1) to give **10** (595.2 mg, 98%) as a colorless oil.

10: $[\alpha]^{25}_D$ +50.7 (*c* 0.83, $CHCl_3$); IR (neat) 3088, 2943, 2851, 2733, 1709, 1644, 1622 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.75 (dd, *J* = 1.9, 1.3 Hz, 1H), 7.44 (d, *J* = 12.4 Hz, 1H), 5.25 (d, *J* = 12.4 Hz, 1H), 4.16 (q, *J* = 6.9 Hz, 2H), 4.13 (m, 1H), 4.00 (ddd, *J* = 10.1, 6.9, 3.2 Hz, 1H), 3.87 (m, 1H), 3.30 (m, 1H), 3.24 (ddd, *J* = 11.0, 9.2, 4.1 Hz, 1H), 2.96 (ddd, *J* = 9.2, 9.2, 5.0 Hz, 1H), 2.65 (ddd, *J* = 17.0, 9.2, 2.3 Hz, 1H), 2.58 (ddd, *J* = 17.0, 3.7, 1.4 Hz, 1H), 2.10-2.00 (m, 2H), 1.92-1.80 (m, 3H), 1.77-1.65 (m, 2H), 1.38 (m, 1H), 1.27 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.6, 167.5, 160.5, 98.8, 84.0, 82.8, 82.5, 77.7, 67.7, 59.9, 48.1, 31.0, 27.0, 26.1, 25.6, 14.3; HRMS (FAB) calcd for $C_{16}H_{25}O_6$ ($M+H^+$) 313.1651, found 313.1634.

6,7,6-Membered tricyclic ether 11:

To a stirred solution of **10** (111.6 mg, 0.36 mmol) in MeOH (44 μL, 1.08 mmol) and THF (3 mL) at 0 °C under Ar was added SmI_2 (0.1 M in THF, 10.8 mL, 1.08 mmol). After stirring at 0 °C for 10 min, the reaction mixture was diluted with

EtOAc, washed saturated aqueous $Na_2S_2O_3$. The aqueous layer was extracted with EtOAc and the combined organic extracts were dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (SiO_2; *n*-hexane/EtOAc = 1:2) to give **11** (107.1 mg, 95%) as a colorless solid.

11: $[\alpha]^{25}_D$ +18.2 (*c* 0.67, $CHCl_3$); IR (nujol) 3419, 2924, 2854, 1702, 1459, 1376 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.16 (q, *J* = 7.3 Hz, 2H), 3.86 (m, 1H), 3.48 (ddd, *J* = 9.3, 7.3, 4.4 Hz, 1H), 3.42 (m, 1H), 3.28 (m, 2H), 3.20 (ddd, *J* = 10.7, 8.8, 3.9 Hz, 1H), 3.17 (ddd, J = 9.3, 9.3, 5.9 Hz, 1H), 3.07 (ddd, J = 9.3, 8.8, 5.9 Hz, 1H), 2.78 (dd, J = 15.1, 4.4 Hz, 1H), 2.47 (dd, *J* = 15.1, 7.3 Hz, 1H), 2.40 (ddd, *J* = 11.7, 4.4, 4.4 Hz, 1H), 2.11 (br d, *J* = 4.4 Hz, 1H), 2.07 (m, 1H), 1.97 (m, 1H), 1.95 (m, 1H), 1.86 (m, 1H), 1.84 (m, 1H), 1.66 (m, 2H), 1.50 (ddd, J = 11.7, 11.2, 11.2 Hz, 1H), 1.43 (m, 1H), 1.26 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.0, 82.5, 81.9, 80.8, 78.7, 78.6, 70.0, 67.9, 60.7, 40.8, 38.3, 31.4, 29.9, 29.0, 25.9, 14.2; HRMS (FAB) calcd for $C_{16}H_{27}O_6$ ($M+H^+$) 315.1808, found 315.1814.

6,7-Membered bicyclic ether having *trans*-γ-Lactone 8:

Colorless crystals, mp 83-84 °C (Et_2O); $[\alpha]^{27}_D$ +17.1 (*c* 0.78, $CHCl_3$); IR (nujol) 2923, 2854, 1780, 1457, 1416, 1376 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.22 (ddd, *J* =10.8, 8.3, 8.3 Hz, 1H), 4.14 (ddd, *J* = 10.3, 8.3, 7.8 Hz, 1H), 3.88 (m, 1H), 3.26 (m, 1H), 3.18 (ddd, *J* = 11.2, 8.3, 4.4 Hz, 1H), 3.08 (ddd, *J* = 10.8, 8.3, 2.0 Hz, 1H), 2.83 (dd, *J* = 17.6, 7.8 Hz, 1H), 2.64 (dd, *J* = 17.6, 10.3 Hz, 1H), 2.39 (dddd, *J* = 14.2, 10.8, 8.3, 8.3 Hz, 1H), 2.11 (m, 1H), 2.01 (dddd, *J* = 14.7, 8.3, 2.0, 2.0 Hz, 1H), 1.96 (dddd, *J* = 14.7, 10.8, 10.8, 8.3 Hz, 1H), 1.79 (dddd, *J* = 14.2, 10.8, 8.3, 2.0 Hz, 1H), 1.68 (m, 2H), 1.44 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.0, 83.4, 81.6, 79.6, 76.5, 67.6, 36.3, 30.4, 30.2, 25.4, 25.2. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.33; H, 7.66.

6,7,7-Membered tricyclic ether having *trans*-γ-Lactone 14:

Colorless crystals, mp 175-179 °C (Et_2O); $[\alpha]^{26}_D$ -9.5 (*c* 0.78, $CHCl_3$); IR (nujol) 2923, 2854, 1790, 1780, 1740, 1640, 1622, 1460, 1377 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.17 (ddd, *J* =13.2, 8.3, 4.9 Hz, 1H), 3.87 (m, 1H), 3.85 (ddd, *J* = 11.2, 8.3, 7.8 Hz, 2H), 3.54 (ddd, *J* = 7.8, 5.4, 2.9 Hz, 1H), 3.47 (ddd, *J* = 11.2, 7.8, 3.9 Hz, 1H), 3.31 (m, 1H), 3.11 (ddd, *J* = 11.2, 9.3, 3.9 Hz, 1H), 2.92 (ddd, *J* = 9.8, 9.3, 4.4 Hz, 1H), 2.81 (dd, *J* = 17.1, 7.8 Hz, 1H), 2.68 (dd, *J* = 17.1, 11.2 Hz, 1H), 2.37 (dddd, *J* = 13.7, 10.7, 5.4, 4.9 Hz, 1H), 2.19 (dddd, *J* = 13.7, 10.7, 5.4, 3.9 Hz, 1H), 2.04 (m, 1H), 2.02 (m, 1H), 1.94 (m, 1H), 1.93 (dddd, *J* = 13.7, 11.2, 10.3, 5.4 Hz, 1H), 1.84 (m, 1H), 1.81 (m, 1H), 1.73 (dddd, *J* = 13.7, 13.2, 10.3, 5.4 Hz, 1H), 1.68 (m, 2H), 1.45 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.6, 85.3, 85.1, 83.6, 83.5, 82.4, 80.8, 67.9, 36.3, 31.6, 30.0, 29.7, 27.9, 26.0, 25.2; HRMS (FAB) calcd for $C_{15}H_{23}O_5$ ($M+H^+$) 283.1545, found 283.1537. Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.76; H, 7.95.

6,7,7-Membered tricyclic ether having *cis*-γ-Lactone 15:

Colorless crystals, mp 211-216 °C (Et_2O-EtOAc); $[\alpha]^{24}_D$ +41.5 (*c* 1.46, $CHCl_3$); IR (nujol) 2925, 2855, 1771, 1736, 1708, 1641, 1621, 1456, 1374 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.55 (ddd, *J* = 9.8, 5.4, 3.9 Hz, 1H), 4.41 (ddd, *J* = 7.8, 5.4, 3.9 Hz, 1H), 3.87 (m, 1H), 3.43 (ddd, *J* = 9.3, 9.3, 3.4 Hz, 1H), 3.29 (m, 1H), 3.22 (ddd, *J* = 9.3, 5.9, 5.9 Hz, 1H), 3.17 (ddd, *J* = 11.2, 8.8, 3.9 Hz, 1H), 2.98 (ddd, *J* = 8.8, 7.8, 4.4 Hz, 1H), 2.84 (dd, *J* = 18.5, 7.8 Hz, 1H), 2.57 (dd, *J* = 18.5, 3.9 Hz, 1H), 2.14 (m, 2H), 2.06 (m, 1H), 2.03 (m, 1H), 1.93 (m, 1H), 1.90 (m, 1H), 1.85 (m, 1H), 1.83 (m, 1H), 1.68 (m, 1H), 1.45 (m, 1H), 1.40 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.5, 85.4, 83.5, 83.1, 82.5, 81.8, 77.6, 67.9, 36.3, 31.4, 30.7, 29.6, 29.2, 25.9, 25.2; HRMS (FAB) calcd for $C_{15}H_{23}O_5$ ($M+H^+$) 283.1545, found 283.1547. Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.11; H, 7.80.

6,7,7,6-Membered ethers 20:

Colorless crystals, mp 111-114 °C (Et_2O); $[\alpha]^{24}_D$ +9.3 (*c* 1.53, $CHCl_3$); IR (nujol) 3522, 2954, 2924, 2854, 1716, 1460, 1377 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.16 (q, *J* = 7.3 Hz, 2H), 3.86 (m, 1H), 3.52 (m, 1H), 3.51 (m, 1H), 3.47 (ddd, *J* = 9.3, 7.3, 4.4 Hz, 1H), 3.42 (m, 1H), 3.28 (m, 1H), 3.13 (ddd, *J* = 11.2, 8.8, 4.4 Hz, 1H), 3.06 (m, 2H), 2.94 (ddd, *J* = 9.3, 9.3, 3.4 Hz, 1H), 2.77 (dd, *J* = 15.6, 4.4 Hz, 1H), 2.46 (dd, *J* = 15.6, 7.3 Hz, 1H), 2.38 (ddd, *J* = 11.7, 4.4, 4.4 Hz, 1H), 2.04 (m, 1H), 2.02 (m, 1H), 1.97 (d, *J* = 5.4 Hz, 1H), 1.97 (m, 1H), 1.88 (m, 1H), 1.85 (m, 1H), 1.84 (m, 2H), 1.79 (m, 1H), 1.75 (m, 1H), 1.66 (m, 2H), 1.48 (ddd, *J* = 11.7, 11.2, 11.2 Hz, 1H), 1.41 (m, 1H), 1.26 (t, *J* = 7.3 Hz, 3H); ^{13}C

NMR (150 MHz, $CDCl^3$) δ 171.9, 83.1, 83.0, 82.6, 82.5, 81.4, 80.7, 78.4, 70.0, 67.8, 60.7, 40.7, 38.2, 31.4, 29.9, 29.8, 28.8, 28.3, 25.9, 14.2. Anal. Calcd for $C_{20}H_{32}O_7$: C, 62.48; H, 8.39. Found: C, 62.34; H, 8.44.