Formation of Bicyclic Ethers from Lewis Acid Promoted Cyclizations of Cyclic Oxonium Ions

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Supporting Information

Experimental Section

General. ^1H and ^{13}C NMR: Bruker AC 250, Bruker Avance 400, spectra were recorded in CDCl_3 ; chemical shifts are calibrated to the residual proton and carbon resonance in CDCl_3 (7.25 ppm, 77.00 ppm). EI-MS; Finnigan Triple-Stage-Quadrupol (TSQ-70). HRMS (EI): modified AMD Intectra MAT 711 A. Flash chromatography: J. T. Baker silica gel 43-60 μm . Thin-layer chromatography Machery-Nagel Polygram Sil G/UV₂₅₄. Solvents were distilled prior to use; petroleum ether with a boiling range of 40-60 °C was used.

General procedure for Grignard reaction. Under nitrogen atmosphere, a stirred solution of aldehyde **1a-c** (1 eq) in THF was treated dropwise with a solution of vinylmagnesium bromide in THF (1.1 eq) at 0 °C. The cooling bath was removed and the reaction mixture stirred at room temperature for 6 h. The reaction mixture was quenched with aqueous NH_4Cl solution and extracted with ether three times. The combined organic layers were washed with water, brine, and dried (Na_2SO_4), filtered, and concentrated with a rotavapor to give colorless viscous oils **2a-d**. The crude product was pure enough for the next step.

General procedure for cyclic acetal formation. To a solution of the allyl alcohol derivatives **2a-d** in dichloromethane (0.06 M) was added camphor-10-sulphonic acid (10 mol %) at room temperature. After stirring the reaction mixture at the same temperature for 5 h, solid NaHCO_3 (5 eq) was added, and stirring was continued for 15 min. Then the mixture was filtered and washed with dichloromethane. The combined filtrate and washings were concentrated and the crude product was subjected to flash chromatography using pentane/ether as eluent to give the cycli hemiacetals **3a-d** as thin oils (82-91% yield for two steps).

General procedure for Suzuki reaction. To a stirred solution of the olefin (**3a-d**, **10**) (1 eq) in THF was added 9 BBN (0.5 M in THF, 1.2 eq) at 0 °C. The reaction mixture was stirred at the same temperature for 1 h and then at room temperature for 3 h. The excess borane reagent was quenched with degassed water (1 eq) and diluted with benzene (double of the total volume of THF). To the mixture were added aqueous 3N NaOH (4 eq), $\text{Pd}(\text{PPh}_3)_3$ (3 mol %), and the vinyl bromide (**6a** or **6b**) (1 eq)

and the reaction mixture was refluxed for 4 h. After cooling to room temperature the organic layer was separated and the aqueous layer was extracted with ether twice. The combined organic layers were washed with water, brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexane) afforded the alkenes **7a-d**, **8a-d**, **9a-d** as pale yellow viscous oils (59-79% yield).

General procedure for bicyclic ether formation. To a stirred solution of the acetal-alkene derivative (**7a-d**, **8a-d**, **8aOEt**, **9a-d**, **11**, **12**) (0.02 M in the reported solvent) was added SnCl_4 (1.5 eq, 1.0 M in dichloromethane) or TMSOTf (1.5 eq) or $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (2.0 eq) at -78°C . After stirring for 1 h at the same temperature, the reaction mixture was slowly warmed up to -10°C over a period of 4 h and then quenched with 2N aq NaOH solution. The organic layer was separated and the aqueous layer was extracted with dichloromethane twice. The combined organic layers were washed with water, brine, dried (Na_2SO_4), filtered, and concentrated in vacuo using a rotavapor. The crude products were subjected to flash chromatography (ethyl acetate/hexane) to furnish the bicyclic ethers.

Hydrolysis of the thio enol ether 22: To a stirred solution of the alkenyl phenyl sulfide **22** in THF was added aqueous HCl solution (3 N, 3 eq) at 0°C and the reaction mixture was stirred overnight at room temperature. Solid NaHCO_3 was added to neutralize the acid. The reaction mixture was treated with water and was extracted with ether three times. The combined organic layers were washed with water, brine, dried over Na_2SO_4 , filtered and concentrated in vacuo. Chromatographic purification furnished the desired ketone **23** as a colorless oil (90% yield).

(1S*,2S*)-2-methyl-4-oxo-5-cyclodecen-1-yl acetate (24). To a solution of LDA in THF (2 mL) [generated from $n\text{BuLi}$ (2.5 eq) and $i\text{Pr}_2\text{NH}$ (3.0 eq) at -10°C] at 0°C was added a solution of (1R*,5S*,6S*)-5-methyl-11-oxabicyclo[4.4.1]undecan-3-one (**23**) (40 mg, 0.22 mmol) in THF (1 mL). The reaction mixture was warmed to room temperature and stirred for 48 h and then quenched with aqueous NH_4Cl solution and extracted with ether thrice. The combined organic layer was washed with water, brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was dissolved in dichloromethane and treated with DMAP (1 eq), triethylamine (10 eq) and acetic anhydride (6 eq) at 0°C

°C. The reaction mixture was warmed to room temperature and stirred for 2 h. Then it was quenched with aqueous NaHCO₃ solution and extracted with dichloromethane. The dichloromethane layer was washed with water, brine, dried over Na₂SO₄, and filtered. Concentration and chromatographic purification afforded the desired acetate **24** as a colorless viscous oil (74% yield) together with the starting ketone **23** (22%).

Spectral Data

Compound **2d**: ¹H NMR (400 MHz): δ 4.90 (s, 1H), 4.80 (s, 1H), 4.33 (t, *J* = 5.8 Hz, 1H), 4.02 (t, *J* = 6.5 Hz, 1H), 3.28 (s, 6H), 1.69 (s, 3H), 1.62-1.48 (m, 4H), 1.43-1.22 (m, 4H); ¹³C NMR (100 MHz): δ 147.6, 110.9, 104.4, 75.8, 52.6, 52.5, 34.8, 32.4, 25.4, 24.5, 17.4; IR (neat): 3444, 2844, 1651, 1454, 1386, 1129, 1052 cm⁻¹.

Compound **3d**: ¹H NMR (400 MHz): δ 4.95 (s, 1H), 4.75 (s, 1H), 4.65 (dd, *J* = 5.5, 8.5 Hz, 1H-major), 4.49 (dd, *J* = 3.5, 7.5 Hz, 1H-minor), 4.15 (d, br., *J* = 10.5 Hz, 1H-major), 3.89 (dd, *J* = 4.0, 9.0 Hz, 1H-minor), 3.39 (s, 3H-minor), 3.30 (s, 3H-major), 2.14-2.05 (m, 1H), 1.96-1.84 (m, 1H), 1.75 (s, 3H-minor), 1.74 (s, 3H-major), 1.82-1.24 (m, 6H); ¹³C NMR (100 MHz), major isomer: δ 146.8, 109.9, 102.4, 73.7, 55.1, 35.2, 34.7, 29.7, 22.5, 18.9; minor isomer: δ 146.3, 109.9, 106.1, 80.2, 55.6, 35.9, 35.0, 25.2, 22.9, 19.1; IR (neat): 2934, 1652, 1452, 1371, 1204, 1132, 1066 cm⁻¹.

Compound **9d**: ¹H NMR (400 MHz), major isomer: δ 7.47-7.40 (m, 2H), 7.35-7.24 (m, 3H), 5.11 (s, 1H), 4.85 (s, 1H), 4.59 (dd, *J* = 5.5, 9.0 Hz, 1H), 3.68 (dd, *J* = 3.5, 10.0 Hz, 1H), 3.36 (s, 3H), 2.42 (dd, *J* = 3.0, 12.0 Hz, 1H), 2.07-1.93 (m, 3H), 1.88-1.77 (m, 1H), 1.65-1.50 (m, 3H), 1.47-1.16 (m, 3H), 0.92 (d, *J* = 6.5 Hz, 3H); ¹³C NMR (100 MHz): δ 145.1, 133.5, 133.0, 129.0, 127.8, 113.3, 102.9, 73.8, 55.5, 39.8, 37.5, 34.9, 31.5, 29.3, 22.6, 15.1; IR (neat): 2932, 1607, 1439, 1066, 1025 cm⁻¹; EIMS, *m/z*: 306 [M]⁺, 275 [M - OMe]⁺, 197, 177, 156, 149; HRMS: calcd for C₁₈H₂₆O₂S 306.1654, found 306.1668.

Compound **22a**: ¹H NMR (400 MHz), major isomer: δ 7.40-7.15 (m, 5H), 5.85 (dd, *J* = 2.8, 4.5 Hz, 1H), 4.49-4.38 (m, 1H), 3.62 (ddd, *J* = 5.0, 5.0, 9.5 Hz, 1H), 2.72 (dddd, *J* = 2.3, 2.3, 11.0, 16.0 Hz,

1H), 2.30-2.17 (m, 1H), 2.16-1.98 (m, 1H), 2.04 (dd, $J = 1.8, 16.0$ Hz, 1H), 1.90-1.45 (m, 7H), 0.81 (d, $J = 6.8$, 3H); ^{13}C NMR (100 MHz): δ 136.8, 135.1, 132.6, 130.6, 129.0, 126.7, 84.0, 76.5, 40.9, 37.9, 37.3, 33.9, 25.6, 25.5, 20.2; IR (neat): 2925, 1582, 1477, 1438, 1157, 1129, 1024 cm^{-1} ; EIMS, m/z : 274 (M), 232, 197, 189, 165; HRMS: calcd for $\text{C}_{17}\text{H}_{22}\text{OS}$ 274.1391, found 274.1406.

Compound **23**: ^1H NMR (400 MHz): δ 4.15 (dddd, $J = 5.0, 6.5, 10.0, 15.0$ Hz, 1H), 3.73 (ddd, $J = 5.0, 5.0, 9.5$ Hz, 1H), 2.74 (ddd, $J = 1.0, 7.0, 13.0$ Hz, 1H), 2.62 (dd, $J = 10.5, 13.0$ Hz, 1H), 2.55 (ddd, $J = 1.5, 5.0, 13.0$ Hz, 1H), 2.34 (ddd, $J = 2.0, 2.0, 13.0$ Hz, 1H), 2.06 (m, 1H), 1.94-1.66 (m, 5H), 1.64-1.44 (m, 3H), 0.94 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (100 MHz): δ 210.0, 82.9, 72.5, 50.5, 49.7, 36.2, 33.4, 32.5, 25.5, 24.8, 20.3; IR (neat): 2927, 1704, 1462, 1141, 972 cm^{-1} ; EIMS, m/z : 182 (M), 165, 154, 139, 123, 111, 97; HRMS: calcd for $\text{C}_{11}\text{H}_{18}\text{O}_2$ 182.1307, found 182.1314.

Compound **24**: ^1H NMR (400 MHz): δ 6.32 (d, $J = 12.0$ Hz, 1H), 5.76 (ddd, $J = 5.5, 12.0, 12.0$ Hz, 1H), 4.70 (ddd, $J = 1.8, 3.5, 12.0$ Hz, 1H), 2.81-2.69 (m, 1H), 2.69 (d, $J = 14.0$ Hz, 1H), 2.68-2.58 (m, 1H), 2.16 (dd, $J = 1.0, 14.0$ Hz, 1H), 2.10 (m, 1H), 2.04 (s, 3H), 1.60-1.23 (m, 5H), 1.14-1.02 (m, 1H), 1.00 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz): δ 206.7, 170.7, 138.6, 132.9, 76.8, 46.6, 31.7, 27.2, 24.4, 23.6, 21.1, 20.1, 20.0; IR (neat): 2933, 1736, 1687, 1625, 1469, 1369, 1245 cm^{-1} ; EIMS, m/z : 224 $[\text{M}]^+$, 182, 164, 135, 121, 107, 84; HRMS: calcd for $\text{C}_{13}\text{H}_{20}\text{O}_3$ 224.1412, found 224.1425.