Supplementary Information for "Construction of Azaspirocyclic Ketones Through α-Hydroxy Iminium Ion or α-Siloxy Epoxide Semipinacol Rearrangements"

Michaël D.B. Fenster, Brian O. Patrick and Gregory R. Dake; Department of Chemistry, 2036 Main
Mall, The University of British Columbia, Vancouver BC V6T 1Z1

Experimental

General

All reactions were performed under a nitrogen atmosphere in flame-dried glassware. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Thin layer chromatography (TLC) was performed on DC-Fertigplatten SIL G-25 UV_{254} pre-coated TLC plates. Analytical gas-liquid chromatography (GC) was performed on a Hewlett-Packard 5880A or 5890A gas chromatograph, equipped with a split mode capillary injection system and a flame ionization detector. The stationary phase consisted of an OV-101 capillary column of dimensions 0.20 mm x 12 m or an HP-5 MS capillary column of dimensions 0.25 mm x 30 m. Helium was used as the carrier gas. Melting points were performed using a Mel-Temp II apparatus (Lab devices USA) and are uncorrected. Infrared (IR) spectra were obtained using a Perkin Elmer 1710 FT-IR spectrometer. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded in deuterochloroform using a Bruker WH-400 spectrometer. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded in deuterochloroform using a Bruker AV-300 spectrometer. Chemical shifts are reported in parts per million (ppm) and are referenced to the centerline of deuterochloroform (δ 7.24 ppm ^1H NMR; 77.0 ppm ^{13}C NMR). Low resolution mass spectra (LRMS) and high resolution mass spectra (HRMS) were recorded on either a Kratos-AEI model MS 50 spectrometer (for EI) or a Kratos MS 80 spectrometer (for CI+ or DCI+). Microanalyses were performed by Mr. Peter Borda in the Microanalytical Laboratory at the University of British Columbia on a Carlo Erba Elemental Analyzer Model 1106 or a Fisions CHN-O Elemental Analyzer Model 1108.

Representative Procedure for Acid Mediated Ring Expansion (4a/5a)

To a solution of alcohol **1a** (13 mg, 0.042 mmol) in dichloromethane (2 mL) was added concentrated hydrochloric acid (4 μL, 0.05 mmol). The solution was stirred at room temperature for 2 h. The solvent was removed by evaporation *in vacuo* and the resulting solid was absorbed onto silica. Purification by column chromatography (1/4 ethyl acetate-hexanes) yielded 8.6 mg (67%) of a white solid.

mp: 104-106 ^{o}C (ethyl acetate-hexanes). IR (KBr): 2954, 2859, 1746, 1321, 1154, 1094 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J*= 8.5 Hz, 2H), 7.26 (d, *J*= 8.2 Hz, 2H), 3.22-3.14 (m, 1H), 2.96 (td, *J*= 12.5 Hz, 2.7 Hz, 1H), 2.77 (dt, *J*=18.3 Hz, 10.1 Hz, 1H), 2.39 (s, 3H), 2.45-2.35 (m, 1H), 2.29 (ddd, *J*=18.3 Hz, 8.2 Hz, 2.4 Hz, 1H), 2.20-2.09 (m, 1H), 1.77-1.55 (m, 4H), 1.49-1.22 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ _216.4, 143.4, 136.9, 129.3, 128.0, 66.7, 44.3, 35.8, 32.6, 32.0, 24.5, 21.5, 19.6, 18.3. LRMS (EI+) *m/z* (relative intensity): 307 (M^+,13), 280 (12), 279 (67), 187 (90), 186 (100), 152 (7), 124 (6), 105 (6), 91 (16), 55 (6). HRMS:Calcd for $C_{16}H_{21}NO_3S$ (M^+): 307.1242. Found: 307.1234.

Azaspirocyclic Ketone 4b

Isolated as a colorless oil
$[\alpha]_D^{25}$ = +22 ± 1 (c 0.17, $CHCl_3$). IR (CCl_4 solution): 2953, 2859, 1752, 1337, 1159, 1109, 874, 582 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J*=8.2 Hz, 2H), 7.27 (d, *J*=7.9 Hz, 2H), 3.39 (m, 1H), 3.21 (ddd, *J*=12.2 Hz, 4.9 Hz, 1.5 Hz, 1H), 2.85-2.71 (m, 2H), 2.46-2.23 (m, 6H), 2.22-2.11 (m, 1H), 1.85-1.77 (m, 1H), 1.75-1.64 (m, 1H), 1.61-1.34 (m, 3H), 0.77 (s, 9H), -0.10 (s, 3H), -0.12 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.1, 143.6, 136.8, 129.4, 127.8, 67.3, 66.0, 50.4, 40.2, 36.2, 32.3, 31.2, 29.7, 25.7, 21.5, 18.5, 18.0, -5.0. LRMS (DCI+) *m/z* (relative intensity): 455 (M^++18, 17), 439 (M^++2, 31), 438 (M^++1,100), 381 (21), 380 (81), 353 (17), 352 (72), 324 (13), 282 (13), 261 (11), 260 (49), 224 (23), 213 (14), 150 (13), 149 (10), 122 (10). HRMS: Calcd for $C_{22}H_{36}NO_4SSi$ (M^++1) 438.2134. Found: 438.2139.

Azaspirocyclic Ketone 5b

Isolated as a colorless oil
$[\alpha]_D^{25}$ = +1.7 ± 0.5 (c 0.33, $CHCl_3$). IR (CCl_4 solution): 2953, 2859, 1752, 1337, 1159, 1109, 874, 582 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, *J*=8.2 Hz, 2H), 7.22 (d, *J*=8.5 Hz, 2H), 3.90 (t, *J*=2.7Hz, 1H), 3.10 (d, *J*=2.1 Hz, 2H), 2.74 (dt, *J*=18.3 Hz, 10.5 Hz, 1H), 2.43-1.98 (m, 9H), 1.76-1.59 (m, 2H), 1.33 (dt, *J*=13.4 Hz, 3.5 Hz, 1H), 0.07 (s, 9H), -0.10 (s, 3H), -0.28 (s, 3H). _^{13}C NMR (75 MHz, $CDCl_3$): δ 215.5, 143.1, 136.9, 129.2, 128.2, 66.5, 63.8, 50.3, 35.9, 32.1, 27.0, 26.5, 25.6, 21.5, 18.3, 17.8, -5.1 (d, *J*=3.4 Hz), -5.3 (d, *J*=5.0 Hz). LRMS (DCI+) *m/z* (relative intensity): 455 (M^++18, 6), 439 (M^++2, 33), 438 (M^++1,100), 382 (11), 381 (22), 380 (85), 354 (10), 353 (16), 352 (62), 324 (11), 260 (43), 213 (11), 139 (11). HRMS: Calcd for $C_{22}H_{36}NO_4SSi$ (M^++1) 438.2134. Found: 438.2134.

Azaspirocyclic Ketone 4c/5c

Purification by column chromatography (1/2 ether-petroleum ether) yielded an inseparable mixture of diastereomers **4c** and **5c** as a colorless oil.

IR (KBr): 2948, 1747, 1328, 1154, 946, 688, 584 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J*=8.2 Hz, 2H), 7.83 (d, *J*=8.5 Hz, 2H), 7.33-7.23 (m, 10H), 7.19 (d, *J*=7.3 Hz, 2H), 7.14 (d, *J*=7.0 Hz, 2H), 3.73 (dd, *J*=12.5 Hz, 6.1 Hz, 1H), 3.36-3.28 (m, 1H), 3.16 (td, *J*=12.8 Hz, 2.7 Hz, 1H), 2.86-2.68 (m, 2H), 2.58-2.46 (m, 2H), 2.41 (s, 3H), 2.34-2.15 (m, 2H), 2.07-1.90 (m, 2H), 1.88-1.48 (m, 6H), 0.91-0.79 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ _215.8, 215.7, 144.7, 143.9, 143.6, 143.3, 138.5, 136.7, 129.5, 129.4, 128.6, 128.0, 127.5, 126.8, 126.7, 126.6, 67.3, 66.4, 44.7, 42.6, 39.9, 38.9, 37.8, 36.6, 35.8, 35.2, 34.4, 32.5, 32.1, 30.9, 29.7, 21.6, 18.4, 17.5. LRMS *m/z* (relative intensity): 385 (M^++2, 26), 384 (M^++1, 26), 356 (22), 355 (87), 264 (10), 263 (45), 262 (50), 228 (23), 201 (11), 200 (65), 158 (71), 132 (14), 131 (68), 123 (10), 109 (13), 96 (14), 95 (18), 91 (22), 81 (11). HRMS: Calcd for $C_{22}H_{26}NO_3S$ (M^++1): 384.1633. Found: 384.1632.

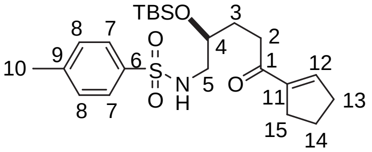
Enone 7

To alcohol **7** (21.4 mg, 0.047 mmol) was added a solution of (*S*)-(+)-10-camphorsulfonic acid (13 mg, 0.056 mmol) in dichloromethane (2.0 mL). The mixture was stirred at rt for 3 h. The solvent was removed by evaporation *in vacuo*. Purification by column chromatography (1/4 ethyl acetate-hexanes) yielded 8.9 mg (42%) of a yellow oil.

$[\alpha]_D^{25}$ = -15.3 ± 0.17 (c 0.17, $CHCl_3$). IR (NaCl): 3289, 2955, 2857, 1663, 1163, 838, 739 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J*=8.2 Hz, 2H), 7.28 (d, *J*=7.9 Hz, 2H), 6.72-6.67 (m, 1H), 4.68 (dd, *J*=7.3 Hz, 5.2 Hz, 1H), 3.86- 3.79 (m, 1H), 2.95-2.88 (m, 1H), 2.84-2.77 (m, 1H), 2.71-2.59 (m, 2H), 2.58-2.45 (m, 4H), 2.40 (s, 3H), 1.94-1.85 (m, 2H), 1.84-1.67 (m, 2H), 0.81 (s, 9H), -0.01 (s, 3H), -0.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.3, 145.4, 143.7, 143.4, 136.7, 129.7, 127.1, 69.7, 47.6, 33.9, 33.8, 30.7, 28.4, 25.7, 22.7, 21.5, 17.9, -4.7, -4.8. LRMS: *m/z* (relative intensity): 452 (M^++1, 32), 451 (M^+, 5), 410 (7), 376 (4), 350(5), 336 (7), 320 (30), 306 (5), 283 (8), 267 (81), 263 (6), 239 (10), 223 (23), 210 (13), 197 (20), 179 (12), 155(27), 149

(26), 123 (43), 109 (49), 95 (92), 75 (100). HRMS: Calcd for $C_{23}H_{38}NO_4SSi$ (M^++1): 452.2291. Found: 452.2296.

Table 1: HMBC Correlation Data for 7



Assignment (C-x)	**^{13}C NMR (δ ppm)**	**HMBC ^{1}H NMR Correlation (δ ppm)**
1	198.3	H_2 (2.71-2.59), H_3 (1.84-1.67)
3	28.4	H_2 (2.71-2.59), H_5 (2.95-2.88),
4	69.7	H_2 (2.71-2.59), H_3 (1.84-1.67), H_5 (2.95-2.88),
12	143.7	H_{13}, H_{15} (2.58-2.45), H_{14} (1.94-1.85)
13	33.9	H_{12} (6.72-6.67)
14	33.8	H_{12} (6.72-6.67)
15	30.7	H_{12} (6.72-6.67)

Azaspirocyclic Ketone 9

To a solution of epoxide **8** (89 mg, 0.17 mmoL) in dichloromethane (8 mL) was added 180 µL of a 1.0 M solution of titanium tetrachloride (0.18 mmol) at –78°C. The reaction mixture was stirred for 0.5h at –78°C and then warmed to rt and poured into a saturated solution of sodium chloride. The two layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation *in vacuo*. Purification by column chromatography (1/3 ethyl acetate-hexanes) yielded 75 mg (96%) of a white solid.

m.p. = 137-138 °C (methanol). $[\alpha]_D^{26}$ = -8.6 ± 0.5 (c 0.25, $CHCl_3$). IR (KBr): 3505, 2941, 2858, 1718, 1329, 1149 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J*=8.4 Hz, 2H), 7.30 (d, *J*=8.0 Hz, 2H), 4.13-4.00 (m, 2H), 3.58 (s, 1H), 3.32 (dd, *J*=12 Hz, 8.0 Hz, 1H), 3.06-2.86 (m, 2H), 2.64-2.53 (m, 1H), 2.52-2.44 (m, 1H), 2.41 (s, 3H), 2.10-1.97 (m, 2H), 1.88-1.54 (m, 5H), 0.81 (s, 9H), -0.04 (s, 3H), -0.06 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.9, 143.6, 137.6, 129.6, 127.7, 69.9, 69.5, 62.0, 47.7, 40.9, 35.1, 33.7, 26.9, 25.7, 21.5, 20.2, 17.9, -4.9. LRMS *m/z* (relative intensity): 468 (M^++1, 17), 410 (26), 382 (9), 312 (24), 284 (21), 162 (52), 161 (46), 92 (32), 91 (20), 84 (11), 75 (100), 74 (66), 73 (24). HRMS (DCI+) *m/z* (M^++1) calcd 468.2240, obsd 468.2239. Anal. Calcd for $C_{23}H_{37}NO_5SSi$: C, 59.07; H, 7.97; N, 2.99. Found: C, 59.29; H, 8.09; N, 3.09.

Azaspirocyclic Ketone 11

To a mixture of cyclopentanol silyl ether **10** (54.4 mg, 0.138 mmol) and anhydrous potassium carbonate (192 mg, 1.39 mmol) was added a 0.07 M solution of dimethyldioxirane (10 mL, 0.70 mmol) at 0°C. The reaction mixture was stirred at 0°C for 0.5 h and warmed to rt and stirred for 5h. A saturated solution of sodium chloride was added and the layers were separated. The aqueous layer was extracted with diethyl ether. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation *in vacuo*. Purification by column chromatography (1/6 ethyl acetate-hexanes, 1% triethylamine) yielded 55.6 mg (98%) of a white solid.

m.p. = 74-75 °C (methanol). IR (KBr): 2953, 1351, 1162, 1084, 842, 666 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J*=8.2Hz, 2H), 7.25 (d, *J*=9.8 Hz, 2H), 3.43 (dt, *J*=14.6 Hz, 3.1 Hz, 1H), 3.22 (d, *J*=2.4 Hz, 1H), 2.79 (td, *J*=12.5 Hz, 2.4 Hz, 1H), 2.40 (s, 3H), 2.19-2.06 (m, 1H), 1.97-1.48 (m, 9H), 1.14-1.02 (m, 1H), 0.93-0.77 (m, 1H), 0.16 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.5, 137.4, 129.3, 128.7, 86.2, 72.3, 53.5, 45.1, 40.0, 35.9, 23.5, 21.7, 21.6, 21.5, 17.8, 2.0. LRMS *m/z* (relative intensity): 410 (M^++1, 6), 394 (6), 326 (21), 325 (41), 320 (9), 255 (9), 254 (22), 239 (16), 238 (7), 180 (11), 170 (20), 158 (15), 157 (100), 156 (22), 90 (14), 75 (10), 74 (9), 73 (40), 71 (13). HRMS: Calcd for $C_{20}H_{32}NO_4SSi$ (M^++1) 410.1821. Found: 410.1826.

To a solution of the 2,3-epoxide derivative of **10** (46 mg, 0.11 mmoL) in dichloromethane (5 mL) was added 125 µL of a 1.0 M solution of titanium tetrachloride (0.13 mmol) at –78°C. The reaction mixture was stirred for 0.5 h at –78°C and then warmed to rt and poured into a saturated solution of sodium chloride. The two layers were separated and the aqueous layer was extracted with dicholromethane. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation *in vacuo*. Purification by column chromatography (1/1 ethyl acetate-hexanes) yielded 36 mg (95%) of a waxy oil.

IR (KBr): 3516, 2936, 1707, 1325, 1153 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.84 (d, *J*=8.4 Hz, 2H), 7.27 (d, *J*=8.8 Hz, 2H), 3.93 (dd, *J*=6.2 Hz, 3.0 Hz, 1H), 3.38 (d, *J*=3.05, 1H), 3.27-3.13 (m, 2H), 2.98-2.89 (m, 1H), 2.55-2.41 (m, 2H), 2.39 (s, 3H), 2.39 (s, 3H), 2.09-1.71 (m, 7H), 1.65-1.53 (m, 1H), 1.34 (dt, *J*=13.4 Hz, 3.4 Hz, 1H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 210.3, 143.4, 137.5, 129.4, 127.8, 69.5, 66.9, 42.3, 40.4, 33.2, 25.2, 25.1, 21.5, 20.8, 17.8. LRMS *m/z* (relative intensity): 337 (0.5), 319 (0.4), 309 (0.6), 245 (19), 182 (76), 166 (10), 164 (29), 155 (11), 154 (100), 124 (11), 112 (12), 96 (19), 92 (19), 91 (54), 84 (28), 83 (13), 71 (39), 65 (21), 55 (20), 54 (14). HRMS: Calcd for $C_{17}H_{23}NO_4S$ (M$^+$): 337.1348. Found: 337.1355.

***p*-Nitrobenzoate derivative of 11**

Azaspirocyclic ketone **11** (10.8 mg, 0.0320 mmol) and 4-(dimethylamino)pyridine (15.4 mg, 0.126 mmol) were dissolved in dichloromethane (0.5 mL) and cooled to 0^{o}C. A solution of 4-nitrobenzoyl chloride (14.6 mg, 0.0787 mmol) in dichloromethane (1.0 mL) was added. The cold bath was removed and the solution was stirred at rt for 4 h. Dichloromethane was added and the reaction mixture was poured into a saturated solution of sodium bicarbonate. The two layers were separated and the organic layer was washed with a saturated aqueous solution of sodium chloride. The organic layer was dried over magnesium sulfate, filtered, and concentrated by evaporation *in vacuo*. Purification by column chromatography (3/1 diethyl ether-petroleum ether) yielded 15.6 mg (100%) of a white solid.

m.p. = 203-204 ^{o}C (methanol). IR (KBr): 2945, 1719, 1528, 1324, 1154, 1104, 720 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.29 (d, *J*=8.7 Hz, 2H), 8.23 (d, *J*=8.7 Hz, 2H), 7.93 (d, *J*=8.2 Hz, 2H), 7.33 (d, *J*=8.2 Hz, 2H), 5.56 (t, *J*=3.0 Hz, 1H), 3.42 (dt, *J*=14.2 Hz, 3.8 Hz, 1H), 3.30 (td, *J*=14.2 Hz, 3.8 Hz, 1H), 2.84 (m, 1H), 2.67 (m, 1H), 2.45 (s, 3H), 2.44-2.38 (m, 1H), 2.18-1.94 (m, 5H), 1.91-1.66 (m, 3H), 1.61-1.51 (m, 1H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 204.1, 164.1, 150.5, 143.6, 138.1, 135.6, 131.3, 129.6, 127.4, 123.4, 69.9, 69.7, 65.8, 42.2, 40.3, 34.7, 26.5, 23.5, 21.5, 21.1, 18.7, 15.3. LRMS *m/z* (relative intensity): 488 (23), 487 (81), 458 (23), 395 (18), 394 (74), 331 (19), 308 (12), 303 (12), 244 (100), 228 (25), 187 (11), 166 (10), 165 (11), 164 (21), 150 (62), 136 (24), 120 (16), 109 (12), 108 (15), 96 (10), 91 (14), 89 (11). HRMS: Calcd for $C_{24}H_{27}N_2O_7S$ (M$^+$+1) 487.1539. Found: 487.1530.

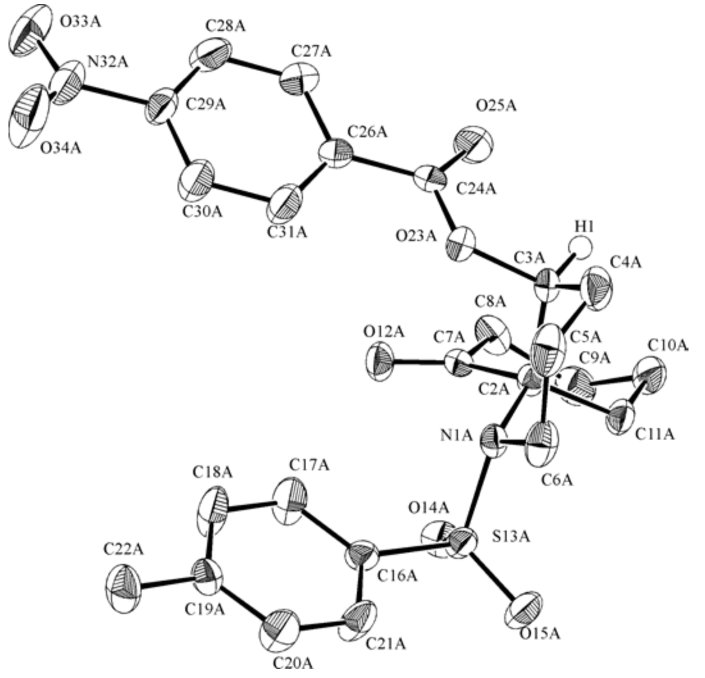


Fig. A. Ortep structure of *p*-nitrobenzoate derivative of **11**