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Novel Solution and Solid Phase Chemistry of α-Sulfonated Ketones Applicable to Combinatorial Chemistry

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Supporting Information

Synthesis of resin 8: To a suspension of polystyrene (1% DVB crosslinked, 100-200 mesh) (15.0 g) in cyclohexane/TMEDA (100 mL/21.4 mL) at 25 °C was added *n*BuLi (112 mL, 1.6 M hexanes).[1] The mixture was heated to 65 °C for 4.5 h and cooled to 25 °C. The solvent was removed via cannula, the resin was washed with dry THF (2 x 100 mL) and then suspended in THF (100 mL). To this suspension at 0 °C was added a solution of freshly purified SO_3-NMe_2[2] (10.5 g, 1.15 equiv) in THF and the mixture was allowed to warm to 25 °C and stirred for 8 h. After filtering, the resin was washed with THF (2 x 500 mL) and then suspended in THF/6 N aq. HCl (2:1) and stirred for 3 h. The resin was then washed sequentially with THF (2 x 500 mL), MeOH (2 x 500 mL), CH_2Cl_2 (2 x 500 mL), Et_2O (500 mL), and then dried *in vacuo* to furnish 16.2 g of **8**. (see attached IR spectrum).

Loading of substrates onto resin: To a solution of epoxide (2-3 equiv) (used directly or synthesized in the same pot using DMDO (4.0 equiv)) in CH_2Cl_2 (0.1 M) was added resin **8**. After *ca.* 4 h at 25 °C, $NaHCO_3$ (6.0 equiv) and DMP (2.0 equiv) were added and the reaction mixture was stirred for an additional 12 h period at 25 °C. Filtration, washing with THF (2 x 500 mL), MeOH (2 x 500 mL), CH_2Cl_2 (2 x 500 mL), and Et_2O (500 mL), and then drying *in vacuo* furnished the corresponding α-sulfonated ketones (**9-14**) (see attached IR spectra). All

compounds were released from the resin with K_2CO_3 (cat.) in THF/H_2O (2:1) to furnish the corresponding α-hydroxy ketones in order to verify loading yields determined by mass gain (hydrolysis nearly quantitative) and to verify the structural assignments.

General procedure for "heterocycle-release" leading to heterocycles 3, 18, 23-26, 29, and 32-34: To a suspension of **11** in benzene or toluene was added the appropriate bis-nucleophile (or thioacetamide for **29**) (*ca.* 10 equiv) and PPTS (cat.), and the solution was heated to reflux with a Dean-Stark apparatus. Standard aqueous workup followed by flash column chromatography furnished the corresponding heterocycles.

3: Colorless syrup; R_f = 0.62 (silica gel, hexane:Et_2O 2:1); IR (film) ν_{max} (cm^{-1}) 3356, 3064, 2922, 2852, 1650, 1578, 1469, 1396, 1307, 1261, 1119, 1064, 1024, 741; ^1H NMR (500 MHz, $CDCl_3$) δ 7.03 (dd, J_1 = 7.6 Hz, J_2 = 1.1 Hz, 1 H), 6.88 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1 H), 6.72 (dt, J_1 = 7.6 Hz, J_2 = 1.1 Hz, 1 H), 6.63 (dd, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1 H), 4.04 (brs, 1 H), 2.28-2.23 (m, 2 H), 2.21-2.15 (m, 2 H), 1.83-1.45 (m, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0, 128.0, 127.4, 125.2, 124.9, 122.1, 120.8, 111.5, 83.2, 38.4, 28.0 (2 C), 24.4, 22.3 (2 C); HRMS (MALDI) calcd for $C_{14}H_{17}NS$ 232.1154 (MH^+), found 232.1151.

17: Known compound; see ref 3.

18: White powder; R_f = 0.32 (silica gel, pentane); IR (film) ν_{max} (cm^{-1}) 2920, 2851, 1451, 1430, 1384, 1255, 1010, 862, 800, 744; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, J_1 = 4.0 Hz, J_2 = 2.2 Hz, 2 H), 7.19 (dd, J_1 = 4.0 Hz, J_2 = 2.2 Hz, 2 H), 2.53-2.45 (m, 4 H), 1.73 - 1.67 (m, 4 H), 1.40-1.24 (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 134.7, 127.8, 127.1, 31.3, 30.3, 24.5, 24.3, 22.5; HRMS (MALDI) calcd for $C_{18}H_{24}S_2$ (M+) 304.3133, found 304.1324.

19: To a solution of ethyl acetoacetate (20 equiv) and methyl amine (40% solution in H_2O, 20 equiv) in toluene was added resin **11**. The mixture was heated to 60 °C for 24 h. After filtration, the solution was washed with Et_2O (2 x 1 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give a light yellow syrup. Flash column chromatography (silica gel, hexane:Et_2O 2:1) gave colorless needles. m.p. 105-106 °C (Et_2O); R_f = 0.36 (silica gel, hexane:Et_2O 2:1); IR (film) ν_{max}

(cm^{-1}) 2930, 2854, 1692, 1570, 1524, 1464, 1437, 1403, 1377, 1343, 1289, 1258, 1198, 1147, 1094, 1072; ^1H NMR (500 MHz, $CDCl_3$) δ 4.24 (q, J = 7.5 Hz, 2 H), 3.40 (s, 3 H), 2.59 (t, J = 7.2, 2 H), 2.55 (t, J = 7.2 Hz, 2 H), 2.47 (s, 3 H), 1.67-1.57 (m, 4 H), 1.55-1.43 (m, 4 H), 1.41-1.28 (m, 11 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 135.9, 130.0, 121.8, 110.1, 59.3, 31.0, 29.4, 27.9, 26.2, 25.7, 25.6, 25.3, 23.4, 22.8, 22.7, 21.7, 14.8, 12.3; HRMS (MALDI) calcd for $C_{19}H_{31}NO_2$ 306.2428 (MH^+), found 306.2422.

23: White powder; R_f = 0.72 (silica gel, hexane:Et_2O 1:1); IR (film) ν_{max} (cm^{-1}) 3351, 2925, 2856, 1651, 1517, 1489, 1420, 1371, 1309, 1236, 1136, 1089, 927, 885, 803; ^1H NMR (600 MHz, $CDCl_3$) δ 6.60 (d, J = 7.9 Hz, 1 H), 6.51 (d, J = 7.9 Hz, 1 H), 6.49 (s, 1 H), 4.57 (brs, 1 H), 2.21 (s, 3 H), 1.97-1.92 (m, 2 H), 1.70 - 1.21 (m, 17 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 139.4, 130.5, 128.6, 120.8, 116.6, 115.3, 84.1, 33.8, 29.7, 25.5 (2 C), 24.2 (2 C), 23.3 (2 C), 20.8, 20.6 (2 C); HRMS (MALDI) calcd for $C_{19}H_{27}NO$ 285.2087 (MH^+), found 285.2089.

24: Known compound, see ref 4.

25: Known compound, see ref 5.

26: White powder; R_f = 0.35 (silica gel, hexane:EtOAc 2:1); IR (film) ν_{max} (cm^{-1}) 2929, 2855, 1712, 1627, 1566, 1440, 1387, 1296, 1149, 1057, 871, 734; ^1H NMR (500 MHz, $CDCl_3$) δ 7.10 (s, 1 H), 6.84 (s, 1 H), 6.30 (d, J = 1 Hz, 1 H), 2.34 (d, J = 1 Hz, 3 H), 2.05-1.90 (m, 4 H), 1.80-1.60 (m, 4 H), 1.45 - 1.25 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.7, 152.4, 149.8, 145.9, 140.6, 114.4, 112.8, 111.7, 105.8, 98.9, 75.8, 35.1, 30.1, 27.3, 26.3, 25.8, 23.7, 23.1, 22.8, 22.3, 19.1; HRMS (MALDI) calcd for $C_{22}H_{26}O_4$ 355.1904 (MH^+), found 355.1894.

29: Known compound, see ref 6.

32: Colorless syrup; R_f = 0.22 (silica gel, hexane:Et_2O 2:1); IR (film) ν_{max} (cm^{-1}) 2929, 2857, 1637, 1600, 1506, 1450, 1398, 1347, 1290, 1199, 1120, 1063, 1029, 732; ^1H NMR (500 MHz, $CDCl_3$) δ 2.93 - 2.90 (m, 2 H), 2.79 (t, J = 7.6 Hz, 2 H), 1.90-1.87 (m, 2 H), 1.84-1.78 (m, 2 H), 1.70 - 1.20 (m, 20 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.3, 149.1, 31.6, 31.0, 28.0, 25.9, 25.2, 22.9, 22.8; HRMS (MALDI) calcd for $C_{18}H_{28}N_2$ 273.2325 (MH+) found 273.2327.

33: Colorless syrup; R_f = 0.29 (silica gel, hexane:Et_2O 1:1); IR (film) ν_{max} (cm^{-1}) 3414, 2925, 2854, 1646, 1466, 1450, 1381, 1260, 1055, 803, 757; ^1H NMR (500 MHz, $CDCl_3$) δ 5.71 (s, 1 H), 3.93 (t, J = 6.1 Hz, 2 H), 3.82 - 3.76 (m, 2 H), 2.59 (t, J = 6.8 Hz, 2 H), 2.32 (bt, J = 7.5 Hz, 2 H), 1.63 - 1.20 (m, 16 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.9, 107.1, 70.8, 46.0, 30.7, 30.2, 28.7, 25.9, 25.5, 24.4, 23.4, 23.2, 22.7, 21.7; HRMS (MALDI) calcd for $C_{14}H_{25}NO$ 224.2009 (MH^+), found 224.2010.

34: Light yellow syrup; R_f = 0.58 (silica gel, hexane:Et_2O 2:1); IR (film) ν_{max} (cm^{-1}) 3364, 3067, 2932, 2855, 1584, 1467, 1396, 1346, 1305, 1258, 1120, 1074, 1023, 910, 802, 740; ^1H NMR (400 MHz, $CDCl_3$) δ 7.04 (dd, J_1 = 7.5 Hz, J_2 = 1.2 Hz, 1 H), 6.89 (td, J_1 = 7.5 Hz, J_2 = 1.2 Hz, 1 H), 6.72 (td, J_1 = 7.5 Hz, J_2 = 1.2 Hz, 1 H), 6.43 (dd, J_1 = 7.5 Hz, J_2 = 1.2 Hz, 1 H), 4.03 (brs, 1 H), 2.10-2.03 (m, 2 H), 2.00 - 1.92 (m, 2 H), 1.60-1.30 (m, 16 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0, 127.9, 127.5, 124.9, 122.2, 120.6, 111.1, 82.1, 36.1, 26.1 (2 C), 25.9, 22.5 (2 C), 22.1 (2 C), 20.6 (2 C); HRMS (MALDI) calcd for $C_{18}H_{25}NS$ 288.1780 (MH^+), found 288.1790.

Spectral data for compounds 2, 4, 15-17, 21, 28, 30, 31 and 35:

2: Colorless syrup; R_f = 0.44 (silica gel, hexane:Et_2O 2:1); IR (film) ν_{max} (cm^{-1}) 3044, 2931, 2863, 1725, 1598, 1450, 1405, 1364, 1243, 1176, 1092, 1031, 987, 946, 898, 818, 671, 555; ^1H NMR (500 MHz, $CDCl_3$) δ 7.79 (bd, J = 8.1 Hz, 2 H), 7.33 (bd, J = 8.1 Hz, 2 H), 4.92 (dd, J_1 = 7.3 Hz, J_2 = 3.3 Hz, 1 H), 2.54 (ddd, J_1 = 13.4 Hz, J_2 = 8.4 Hz, J_3 = 3.3 Hz, 1 H), 2.44 (s, 3 H), 2.35 (ddd, J_1 = 13.9 Hz, J_2 = 9.9 Hz, J_3 = 3.3 Hz, 1 H), 2.12-1.93 (m, 3 H), 1.87-1.79 (m, 1H), 1.73-1.65 (m, 1 H), 1.59-1.44 (m, 4 H), 1.39-1.33 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.4, 145.0, 133.6, 129.9 (2 C), 127.9 (2 C), 83.3, 38.8, 32.8, 27.3, 24.6, 24.5, 22.8, 21.1; HRMS (MALDI) calcd for $C_{15}H_{20}O_4SNa$ (MNa^+) 319.0974, found 319.0976.

4: Colorless syrup; R_f = 0.31 (silica gel, hexane:Et_2O 2:1); IR (film) ν_{max} (cm^{-1}) 3033, 2927, 2859, 1681, 1598, 1457, 1362, 1303, 1257, 1175, 1131, 1096, 1010, 965, 872, 846, 816, 786, 667, 556, 524; ^1H NMR (500 MHz, $CDCl_3$) δ 7.81 (td, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 2 H), 7.31 (td, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 2 H), 6.42 (ddd, J_1 = 12.5, J_2 = 8.3, J_3 = 7.2 Hz, 1 H), 6.06 (dd, J_1 = 12.5 Hz, J_2 = 2.0 Hz, 1 H), 5.54 (dd, J_1 = 9.2 Hz, J_2 = 6.7 Hz, 1 H), 2.52-2.46 (m, 2 H), 2.43 (s, 3 H),

2.11-2.04 (m, 1 H), 1.97-1.94 (m, 1 H), 1.69-1.52 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.3, 144.8, 142.5, 133.7, 131.8, 129.7, 127.9, 82.3, 30.3, 28.6, 22.8, 21.7, 21.3; HRMS (MALDI) calcd for $C_{15}H_{18}O_4SNa$ (MNa^+) 317.0818, found 317.0831.

15: Colorless needles; m.p. 102-103 °C (Et_2O); R_f = 0.53 (silica gel, hexane:Et_2O 2:1); IR (film) ν_{max} (cm^{-1}) 3063, 2932, 2860, 1722, 1582, 1562, 1467, 1438, 1376, 1288, 1248, 1132, 1103, 1016, 975, 875, 741; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (dd, J_1 = 7.5 Hz, J_2 = 0.8 Hz, 1 H), 7.94 (dd, J_1 = 7.5 Hz, J_2 = 1.6 Hz, 1 H), 7.41 (td, J_1 = 7.5 Hz, J_2 = 0.8 Hz, 1 H), 7.16 (td, J_1 = 7.5 Hz, J_2 = 1.6 Hz, 1 H), 5.38 (dd, J_1 = 6.6 Hz, J_2 = 3.0 Hz, 1 H), 2.82 (ddd, J_1 = 18.1 Hz, J_2 = 10.8 Hz, J_3 = 3.3 Hz, 1 H), 2.47 (ddd, J_1 = 18.1 Hz, J_2 = 6.3 Hz, J_3 = 3.5 Hz, 1 H), 2.16 - 2.09 (m, 1 H), 2.06-1.96 (m, 2 H), 1.64-1.58 (m, 1 H), 1.40 - 1.15 (m, 14 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.8, 165.8, 141.3, 134.4, 132.9, 131.5, 128.0, 94.2, 79.6, 34.9, 27.6, 26.3, 26.0, 23.8, 22.7, 22.4, 22.0, 21.1, 19.6; HRMS (MALDI) calcd for $C_{19}H_{25}IO_3Na$ 451.0741 (MNa^+), found 451.0746.

16: Known compound, see ref 7.

20: Known compound, see ref 8.

21: Known compound, see ref 9.

22: Yellow needles; m.p. 71-72 °C (CH_2Cl_2); R_f = 0.57 (silica gel, hexane:Et_2O 2:1); IR (film) ν_{max} (cm^{-1}) 2927, 2855, 1716, 1580, 1468, 1440, 1273, 1241, 1050, 1018, 801, 748; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (dd, J_1 = 7.7 Hz, J_2 = 1.5 Hz, 1 H), 7.19 (ddd, J_1 = 8.4 Hz, J_2 = 1.5 Hz, J_3 = 0.8 Hz, 1 H), 6.69 (t, J = 7.7 Hz, 1 H), 6.61 (dd, J_1 = 8.4 Hz, J_2 = 1.0 Hz, 1 H), 4.53 (dd, J_1 = 9.9 Hz, J_2 = 4.0 Hz, 1 H), 3.04 (ddd, J_1 = 18.0 Hz, J_2 = 11.0 Hz, J_3 = 3.5 Hz, 1 H), 2.15-1.90 (m, 4 H), 1.50-1.20 (m, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.7, 156.0, 139.8, 129.5, 123.1, 112.3, 86.6, 84.2, 33.4, 29.3, 26.5, 26.4, 23.7, 22.6, 22.2, 22.1, 20.9, 19.6; HRMS (MALDI) calcd for $C_{18}H_{25}IO_2Na$ (MNa^+) 423.0791, found 423.0783.

28: colorless syrup; R_f 0.30 (silica gel, hexane:EtOAc 2:1); IR (film) ν_{max} (cm^{-1}) 2928, 2854, 1711, 1643, 1467, 1448, 1262, 1118, 1012, 873, 800; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.63-3.50 (m, 5 H), 2.65 (t, J = 4.0 Hz, 4 H), 2.45-2.30 (m, 1 H), 2.30-2.25 (m, 1 H), 1.50 - 1.05 (m, 18 H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 211.8, 74.5, 67.1 (2 C), 51.2 (2 C), 36.5, 27.0, 26.2, 25.7, 23.9, 23.7, 23.2, 22.2, 21.6, 21.2; HRMS (MALDI) calcd for $C_{16}H_{29}NO_2$ 268.2271 (MH^+), found 268.2266.

30: White powder; R_f = 0.42 (silica gel, hexane:EtOAc 2:1); IR (film) ν_{max} (cm^{-1}) 3401, 2931, 2849, 1710, 1604, 1460, 1100, 597; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (dd, J_1 = 8.0 Hz, J_2 = 1 Hz, 1 H), 7.30 (ddd, J_1 = 12.1 Hz, J_2 = 5.1 Hz, J_3 = 0.7 Hz, 1 H), 6.53 (ddd, J_1 = 12.1 Hz, J_2 = 5.1 Hz, J_3 = 0.7 Hz, 1 H), 6.4 (d, J = 8.0 Hz, 1 H), 5.25 (brs, 1 H), 4.69 (m, 1 H), 2.95 (ddd, J_1 = 18.0 Hz, J_2 = 11.0 Hz, J_3 = 3.0 Hz, 1 H), 2.29 (dq, J_1 = 18.0 Hz, J_2 = 3.0 Hz, 1 H), 2.1-1.9 (m, 3 H), 1.4-1.15 (m, 15 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 220.9, 167.5, 158.0, 147.8, 123.4, 119.1, 70.8, 45.8, 38.6, 36.7, 36.5, 34.2, 33.2, 32.6, 32.5, 31.8, 29.8; HRMS (MALDI) calcd for $C_{17}H_{26}N_{20}$ 275.2118 (MH^+), found 275.2129.

31: Known compound, see ref 7.

35: (labile methoxy epoxide) Colorless oil; IR (film) ν_{max} (cm^{-1}) 2922, 2851, 1463, 1259, 1107, 601; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.38 (s, 3 H), 2.41 (s, 1 H), 1.52-1.05 (m, 20 H).

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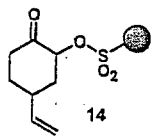

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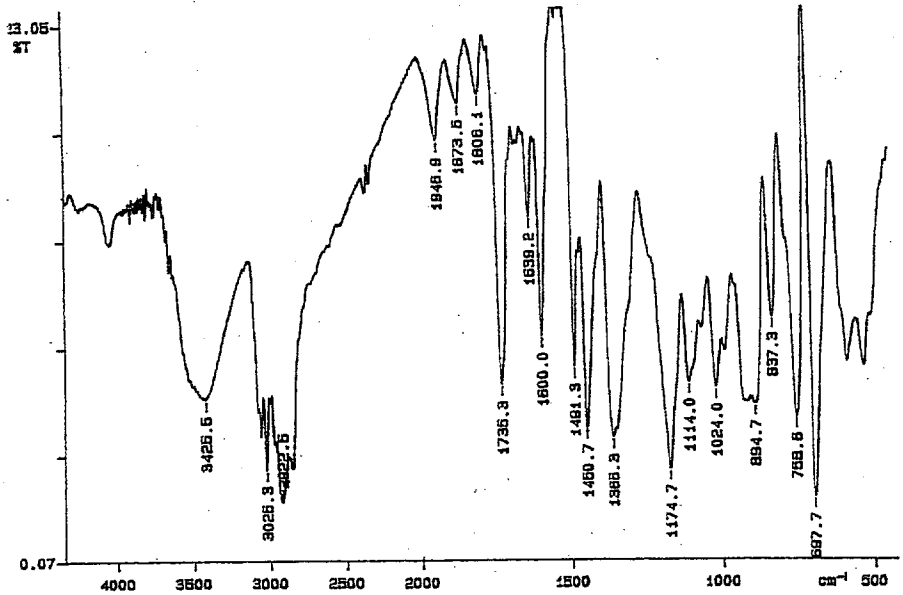

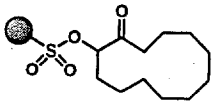

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Derived from *E* olefin
(entry 5)