SUPPORTING INFORMATION

1,2,4-Trioxepanes: Redox Cleavable Protection for Carbonyl Groups

Aqeel Ahmed and Patrick H. Dussault*

Department of Chemistry

University of Nebraska-Lincoln, Lincoln, NE 68588-0304

pdussault1@unl.edu

Contents

Experimental Procedures and Characterization: pp 1-11

¹H and ¹³C spectra form 2,2-dibutyl-1,3-dioxolane pp 12-13

Experimental Procedures and Compound Characterization

Standard experimental conditions have been reported.¹ Unless otherwise indicated, NMR spectra were acquired at 400 (¹H) or 100 (¹³C) MHz. Calorimetry was performed on a TA 2960 DSC/TGA.

3-Triethylsilyldioxy-3-methyl-1-butanol (1):² To a solution of 3-methyl-3-butenol or 3-methyl-2-butenol (1.0eq) and triethylsilane (2.0eq) under O₂ atmosphere was added 0.05 eq. Co (thd)₂ or 0.1 eq. Co(acac)₂.³ The reaction mixture was stirred for 8-12h and then solvent was removed under reduced pressure. The residue was filtered through a plug of silica with 10%EA/hex to obtain a mixture of 3-methyl-3-triethylsilyldioxy-1-butanol (**1**) accompanied by variable amounts (see table, below) of the bis triethylsilyl ether of 3-methyl-3-hydroperoxy-1-butanol, (**2**), and occasionally a small amount of 3-methyl-3-triethylsiloxy-1-butanol. Although pure samples of **1** were available upon chromatography (EA/hex), the reagent was typically used as a crude mixture.

(Table 1, duplicated from manuscript)

catalyst	Solvent	1	2
Co(acac) ₂	CH ₂ Cl ₂	27%	25%
	EtOH	30-35%	5%
	EtOH:CH ₂ Cl ₂ (1:1)	30%	5%
Co(thd) ₂	ClCH ₂ CH ₂ Cl	50%	5%
	EtOH	40%	1-2%
	CH ₂ Cl ₂	20%	18%

General procedure for the formation of Trioxepanes: To a 1.0M solution of carbonyl compound in CH₂Cl₂ was added the peroxide **1** (1.5-3.0mmol, neat) and 0.5-1.0 eq. of *p*-TsOH. The reaction was continued for 1-2 hours or until the disappearance of the starting materials by TLC. The reaction mixture was diluted with 20-30 ml of ether. The residue obtained after concentration of the ether layer was subjected to flash chromatography to furnish pure trioxepanes.

4-(7,7-Dimethyl-1,2,4-trioxepan-3-yl)-benzoic acid methyl ester (3): Protection of 4-formyl benzoic acid methyl ester (300mg, 1.8mmol) using the general procedure furnished **3** (438mg, 90%); *R_f* = 0.39 (10% EA/hex); ¹H δ 8.01(d, 2H, 8.3), 7.54 (bd, 2H, 8.3), 6.06 (s, 1H), 4.14-4.04(2H), 3.88(s, 3H), 2.32 (broad dd, 1H, 14.0, 10.0), 1.93 (dd, 1H, 15.1, 4.8), 1.36(s, 3H), 1.94(s, 3H); ¹³C δ 166.6, 140.2, 130.6, 129.4, 126.8, 106.4, 83.0, 65.1, 52.1, 43.8, 27.2, 25.1; IR (cm⁻¹) 2973, 2950, 2860, 1717, 1611, 1438, 1360, 1226, 1192, 1136, 1097, 1025, 974, 907, 852, 762, 706; HRFAB calc. for C₁₄H₁₉O₅⁺: (M+H)⁺: 267.1232; found: 267.1230, 1.1ppm; Analysis calc. for C₁₄H₁₈O₅: C, 63.15, H, 6.81; found: C, 62.72, H, 6.79.

4-(3,7,7-Trimethyl-1,2,4-trioxepane-3-yl)-benzoic acid ethyl ester (4): Protection of 4-acetyl-benzoic acid ethyl ester (325mg, 1.7mmol) furnished **4** (453mg, 91%); *R_f* = 0.55 (10% EA/hex); ¹H: δ 8.02(d, 1H, 8.3), 8.01(d, 1H, 8.3), 7.58(d, 1H, 8.3), 7.49(d, 1H, 8.6), 4.35(q, 2H, 7.0), 4.02(m, 0.5H), 3.87-3.72(1.5H), 2.00 (0.5H, app. ddd, 14.0, 10.0, 4.0), 1.88-1.85(1H), 1.67(s, 1.5H). 1.63-1.58(0.5H), 1.43(s, 1.5H), 1.41(s, 1.5H), 1.36(t, 3H,

7.0), 1.32(s, 1.5H), 1.20(s, 1.5H), 0.94(s, 1.5H); ^{13}C δ 166.4, 166.1, 147.1, 145.4, 130.3, 129.6, 129.5, 129.3, 126.0, 125.7, 107.3, 106.9, 81.9, 81.7, 60.9, 60.7, 60.5, 60.3, 43.4, 43.2, 26.8, 26.3, 26.1, 26.0, 24.9, 23.8, 14.3, 14.2; IR (cm^{-1}) 2978, 2939, 1717, 1611, 1460, 1365, 1270, 1164, 1092, 1025, 919, 863, 773, 701; HRFAB calc. for $\text{C}_{16}\text{H}_{23}\text{O}_5^+$: (M+H) $^+$: 295.1545; found: 295.1536, 3.1ppm; Analysis calc. for $\text{C}_{16}\text{H}_{22}\text{O}_5$: C, 65.29, H, 7.53; found: C, 65.49, H, 7.57.

3,3-Dibutyl-7,7-dimethyl-1,2,4-trioxepane (5): Protection of 5-nonanone (200mg, 1.4mmol) furnished **5** (335mg, 97%); R_f = 0.58 (5% EA/hex); ^1H δ (-35 $^\circ\text{C}$): 3.92(broad t, 1H, 11.82), 3.66(ddd, 1H, 12.6, 4.4, 3.1), 1.89(dd, 1H, 12.9, 3.0), 1.84(dd, 1H, 11.0, 3.1) 1.70-1.63(2H), 1.43(t, 2H, 8.2), 1.37(s, 3H), 1.36-1.17(8H), 1.14(s, 3H), 0.93 (t, 3H, 6.8), 0.88 (t, 3H, 6.8); ^{13}C (125 MHz, RT): δ 109.4, 81.1, 58.9, 43.9, 33.5, 31.8, 26.6, 26.0, 25.7, 24.1, 23.0, 23.0, 14.0, 13.9; IR (cm^{-1}): 2958, 2872, 1458, 1379, 1336, 1361, 1311, 1275, 1146, 1089, 1039, 967, 871; HRFAB calc. for (M+H) $^+$: $\text{C}_{14}\text{H}_{29}\text{O}_3^+$: 245.2117 found: 245.2105, 5.0 ppm; Analysis calc. for $\text{C}_{14}\text{H}_{28}\text{O}_3$: C, 68.81, H, 11.55; found: C, 68.26, H, 11.66; The differential scanning calorimetry (DSC-TGA) revealed an exotherm between 184 and 206 $^\circ\text{C}$.

DSC-TGA

3-(9-Decen-1-yl)-7,7-dimethyl-1,2,4-trioxepane(6): Protection of 10-undecenal (500mg, 3.0mmol) furnished **6** (690mg, 86%); $R_f = 0.47$ (5% EA/hex); ^1H δ 5.79(ddt, 1H, 16.9, 10.4, 6.8), 5.04(t, 1H, 5.6), 4.97(bd, 1H, 17.0), 4.90(bd, 1H, 10.0), 3.92-3.83(2H), 2.17(ddd, 1H, 14.9, 9.2, 3.2), 2.01(app. q, 2H, 7.0), 1.82(app. ddd, 1H, 15.0, 4.0, 2.0), 1.55-1.50(2H), 1.38-1.39(5H, includes a s, at 1.34, 3H), 1.26(broad, 9H), 1.12(3H); ^{13}C δ 139.2, 114.1, 108.2, 82.6, 64.6, 43.9, 33.8, 32.2, 29.35, 29.31, 29.0, 28.9, 27.4, 25.2, 25.5; IR (cm^{-1}): 2974, 2922, 2851, 1639, 1457, 1358, 1227, 1144, 1104, 962, 906, 879, 732, 641; HRFAB calc. for $\text{C}_{16}\text{H}_{31}\text{O}_3^+$: $(\text{M}+\text{H})^+$: 271.2273; found: 271.2280, 2.4ppm; Analysis calc. for $\text{C}_{16}\text{H}_{30}\text{O}_3$: C, 71.07, H, 11.18; found: C, 70.55, H, 11.16.

7,7-Dimethyl-3-hexyl-1,2,4-trioxepane-3-propionic acid, methyl ester (7): Protection of 4-oxo-decanoic acid methyl ester (558mg, 2.8mmol) furnished **7** (758mg, 90%); $R_f = 0.45$ (10% EA/hex); ^1H δ 3.86-3.80(1H), 3.63-3.57(4H, including 3.60, s, 3H), 2.45-2.37(0.5H), 2.32-2.24(1.5H), 2.19-2.12(0.5H), 2.04-1.94(0.5H), 1.9-1.54(4H), 1.41-1.29(5H, includes two broad singlets at 1.30, 1.29), 1.22, 1.20(broad s, 7H), 1.06(s, 3H), 0.81(t, 3H, 6.4); ^{13}C δ 173.8, 173.5, 108.3, 108.1, 81.3, 81.2, 59.1, 59.0, 51.5, 51.4, 43.6, 33.5, 32.6, 31.6, 31.5, 29.41, 29.37, 29.1, 29.0, 28.5, 27.5, 26.4, 26.3, 24.1, 23.9, 23.6,

23.3, 22.5, 22.4, 13.94, 13.91; IR (cm⁻¹): 2945, 2861, 1739, 1449, 1371, 1320, 1281, 1147, 1086, 1231, 863, 991, 729; HRFAB calc. for (M+H)⁺ : C₁₆H₃₁O₅⁺: 303.2171 found: 303.2173 0.5ppm ; Analysis calc. for C₁₆H₃₀O₅: C, 63.55, H, 10.00; found: C, 63.42, H, 10.16. The differential scanning calorimetry (DSC-TGA) revealed an exotherm between 195 and 224°C.

3-tert-Butyl-9, 9-dimethyl-7, 8, 12-trioxa-spiro (5.6)dodecane (8): Protection of 4-tert-butyl cyclohexanone (242mg, 1.6mmol) furnished **8** (358mg, 89%); *Diastereomer 1*: m.p. 90-91°C; R_f = 0.74 (10% EA/hex); ¹H δ 3.88(t, 1H, 11.6), 3.69(dt, 1H, 12.4, 3.6), 2.33(ddd, 1H, 12.8, 7.6, 4.0), 1.87(m, 1H), 1.67-1.62(4H), 1.45-1.37(1H), 1.36(s, 3H), 1.25-1.19(3H), 1.13(s, 3H), 1.0-0.94(1H), 0.84(s, 9H); ¹³C δ 105.9, 81.2, 58.8, 47.5, 43.7, 34.2, 32.3, 30.7, 27.6, 26.6, 24.2, 23.7, 23.5; IR (cm⁻¹): 2950, 2863, 1461, 1441, 1366, 1310, 1275, 1200, 1148, 1104, 1025, 954, 906, 867, 744.

Diastereomer 2: m.p. 65-66°C; R_f = 0.6 (10% EA/hex); ¹H δ 3.95(t, 1H, 11.6), 3.68(dt, 1H, 12.6, 4.5, 3.7), 2.39(app. tt, 1H, 10.0, 3.0), 1.92-1.80(2H), 1.66-1.57(3H), 1.40-1.36(1H), 1.38(s, 3H), 1.33-1.25(2H), 1.23-1.16(1H), 1.14(s, 3H), 1.0-0.96(1H), 0.84(s,

9H); ^{13}C δ 105.9, 81.1, 58.8, 47.7, 44.0, 33.7, 32.6, 32.3, 27.7, 26.6, 24.15, 24.12, 23.7; HRFAB calc. for $\text{C}_{15}\text{H}_{29}\text{O}_3^+$: $(\text{M}+\text{H})^+$: 257.2116; found: 257.2113; Analysis calc. for $\text{C}_{15}\text{H}_{28}\text{O}_3$: C, 70.27, H, 11.01; found: C, 70.28, H, 11.36.

1-Methoxymethoxy-16-heptadecene-5-yn-7-one: A 1.0M solution of the corresponding propargyl alcohol (3.5g, 11.4mmol) in CH_2Cl_2 was oxidized with PDC (8.5g, 22.7mmol) to furnish alkynone in 3.3g (94% yield). $R_f = 0.34$ (10% EA/hex); ^1H δ 5.69(ddt, 1H, 16.9, 10.4, 6.8), 4.88(bdd, 1H, 17.0, 2.0), 4.82(broad dd, 1H, 10.0, 2.0), 4.50(s, 2H), 3.44(t, 2H, 5.8), 3.25(s, 3H), 2.41(t, 2H, 7.3), 2.31(t, 2H, 6.8), 1.93(app. q, 2H, 7.0), 1.62-1.53(7H), 1.28-1.23(2H) 1.19(broad, 9H); ^{13}C δ 187.9, 138.7, 113.9, 96.1, 93.1, 80.8, 66.6, 54.8, 45.2, 33.5, 28.99, 28.98, 28.8, 28.65, 28.60, 28.57, 24.3, 23.8, 18.4; IR (cm^{-1}): 3073, 2928, 2766, 2855, 2213, 1672, 1633, 1466, 1354, 1226, 1142, 1108, 1036, 913, 718; HRFAB calc. for $(\text{M}+\text{H})^+$: $\text{C}_{19}\text{H}_{33}\text{O}_3^+$: 309.2429 found: 309.2429 3.2ppm; Analysis calc. for $\text{C}_{19}\text{H}_{32}\text{O}_3$: C, 73.98, H, 10.46; found: C, 73.74, H, 10.46.

3-(9-Decen-1-yl)-3-(6-methoxymethoxy-1-hexynyl)-7,7-dimethyl-1,2,4-trioxepane (9): Protection of the alkynone (650mg, 2.1mmol) furnished **9** (706mg, 82%) $R_f = 0.33$ (10% EA/Hexane); ^1H δ 5.79(ddt, 1H, 16.9, 10.1, 6.6), 4.97(dd, 1H, 16.9, 1.6), 4.90(dd, 1H, 10.4, 1.0), 4.6(s, 2H), 4.19(s, 1H), 3.71(1H), 3.53(t, 2H, 6.2), 3.34(s, 3H), 2.33-2.24(2H), 2.02(dd, or app. q, 2H, 6.8-7.3), 1.94-1.78(2H), 1.75-1.64(6H), 1.50-1.46(2H), 1.4-1.24(14H), 1.13(b singlet, 3H); ^{13}C δ 139.1, 114.0, 103.3, 96.2, 86.4, 84.9, 81.6, 70.0, 61.5, 60.6, 55.0, 43.6, 43.0, 38.4, 37.7, 29.4, 29.3, 29.0, 28.8, 28.7, 26.7, 25.4, 25.1, 24.2, 24.0, 23.7, 22.6, 18.3, 14.0; IR (cm^{-1}): 2923, 2846, 1642, 1461, 1364, 1297, 1230, 1153, 1111, 1050, 911, 859, 725; HRFAB calc. for $(\text{M}+\text{H})^+$: $\text{C}_{24}\text{H}_{43}\text{O}_5^+$: 411.3110 found: 411.3123, 3.0ppm; Analysis calc. for $\text{C}_{24}\text{H}_{42}\text{O}_5$: C, 70.21, H, 10.31; found: C, 70.16, H, 10.45.

7,7-Dimethyl-3-(2E-phenylethenyl)-1, 2, 4-trioxepane (10): Protection of cinnamaldehyde (314mg, 2.4mmol) furnished **10** (461mg, 83%); $R_f = 0.64$ (10% EA/hex); ^1H δ 7.43-7.41(2H), 7.36-7.26(3H), 6.84(d, 1H, 16.0), 6.13(dd, 1H, 16.4, 4.8), 5.73(d, 1H, 4.8), 4.09-3.99(2H), 2.28(m, 1H), 1.93(m, 1H), 1.42(s, 3H), 1.21(s, 3H); ^{13}C δ 135.8, 134.6, 128.5, 128.3, 126.8, 122.4, 106.2, 82.8, 64.6, 43.9, 27.2, 25.2; IR (cm^{-1}) 3061, 3025, 2970, 2871, 1655, 1497, 1453, 1366, 1334, 1275, 1231, 1184, 1093, 1033,

970, 875, 744, 693; HRFAB calc. for $C_{14}H_{19}O_3^+$: (M+H) $^+$: 235.1334 found: 235.1339, 1.9ppm; Analysis calc. for $C_{14}H_{18}O_3$: C, 71.77, H, 7.74; found: C, 72.01, H, 7.80.

3-Decyl-7,7-dimethyl-1,2,4-trioxepane (11): Catalytic hydrogenation of **6** (94mg, 0.35mmol) furnished **11** (86mg, 91%) $R_f = 0.53$ (10% EA/hex); 1H δ 5.05(t, 1H, 5.6), 3.93-3.84(2H), 2.18(ddd, 1H, 14.9, 9.1, 2.8), 1.83 (broad dd, 1H, 15.0, 11.0), 1.57-1.51 (2H), 1.39-1.35{5H includes 1.39-1.38(2H), 1.35(s, 3H)}, 1.29-1.24(14H), 1.13(s, 3H), 0.87(t, 3H, 6.8); ^{13}C δ 108.3, 82.6, 64.7, 43.9, 32.3, 31.9, 29.6, 29.5, 29.4, 29.4, 29.3, 27.4, 25.2, 24.6, 22.7, 14.1; IR (cm^{-1}): 2928, 2855, 1466, 1365, 1281, 1226, 1198, 1147, 1108; HRFAB calc. for (M+H) $^+$: $C_{16}H_{33}O_3^+$: 273.2430, found: 273.2419, 4.1ppm; Analysis calc. for $C_{16}H_{32}O_3$: C, 70.54, H, 11.84; found: C, 70.49, H, 11.92.

4-(7,7-Dimethyl-1,2,4-trioxepane)-phenyl methanol (12): $LiAlH_4$ reduction of **3** (578mg, 2.2mmol) furnished **12** (515mg, quant.); $R_f = 0.54$ (50% EA/hex); 1H δ 7.45(bd, 2H, 7.0), 7.31(bd, 2H, 8.0), 6.04(s, 1H), 4.62(s, 2H), 4.14-4.03(2H), 2.33(ddd, 1H, 14.5, 9.5, 1.8), 2.12(broad s, 1H), 1.94(broad dd, 1H, 14.9, 4.67), 1.38(s, 3H), 1.2(3H); ^{13}C δ 142.0, 135.0, 127.02, 126.97, 107.0, 83.0, 65.1, 64.9, 44.0, 27.4, 25.3; IR (cm^{-1}): 3394, 2975, 2920, 2869, 1527, 1457, 1421, 1366, 1270, 1230, 1199, 1149, 1093, 1038, 1023, 902, 972; HRFAB calc. for (M+H) $^+$: $C_{13}H_{19}O_4^+$: 239.1283 found: 239.1281 1.1ppm; Analysis calc. for $C_{13}H_{18}O_4$: C, 65.53, H, 7.61; found: C, 66.06, H, 7.59.

4-(3,7,7-Trimethyl-1,2,4-trioxepan-3-yl)-phenyl methanol (13): $LiAlH_4$ reduction of **4** (162mg, 0.5mmol) furnished **13** (137mg, quant.); $R_f = 0.73$ (50% EA/hex); 1H δ 7.54(broad d, 0.8H, 8.3), 7.44(broad d, 1.2H, 8.0), 7.36(broad d, 2.0H, 8.0), 4.7(s, 2H), 4.04(app ddd, 0.4H, 12.0, 9.0, 2.0), 3.90-3.83(1H, includes a 3.85, ddd of one conformer and a dt of the other conformer), 3.77(dt, 0.6H, 12.6, 3.5), 2.02(app. ddd, 1H, 15.0, 11.0, 3.0), 1.89(broad t, 1H, 5.0), 1.69(s, 2.0H), 1.64-1.60(2H, includes O-H), 1.46(s, 1.6H), 1.43(s, 1.4H), 1.35(s, 1.8H), 0.98(s, 1.2H); ^{13}C δ 141.7, 140.9, 140.1, 140.0, 126.9, 126.7, 126.2, 126.0, 107.5, 107.1, 81.8, 81.6, 65.1, 64.9, 60.4, 60.2, 43.5, 43.4, 26.9, 26.5, 26.1, 24.9, 23.9. IR (cm^{-1}): 3405, 2982, 2942, 2875, 1457, 1409, 1366, 1283, 1259, 1203, 1160, 1227, 1077, 1227, 1009, 819; HRFAB calc. for (M+H) $^+$: $C_{14}H_{21}O_4^+$:

253.1440 found: 253.1444, 1.7 ppm; Analysis calc. for $C_{14}H_{20}O_4$: C, 66.65, H, 7.99; found: C, 66.43, H, 8.12.

7,7-Dimethyl-3-hexyl-3-(3-hydroxypropyl)-1,2,4-trioxepane (14): $LiAlH_4$ reduction of **7** (335mg, 1.1mmol) furnished **14** (300mg, quant.) $R_f = 0.67$ (50% EA/hex); 1H δ 3.92(broad t, 1H, 11.6), 3.70(broad t, 0.3H, 4.0), 3.68-3.60(2.7H), 2.04-1.42(10H), 1.36(s, 3H), 1.31-1.25(7H), 1.13(s, 3H), 0.87(t, 3H, 6.7); ^{13}C δ 109.31, 109.26, 81.4, 81.3, 63.0, 62.9, 59.04, 58.98, 43.75, 43.72, 33.6, 32.1, 31.7, 31.6, 30.1, 29.5, 29.5, 29.1, 27.3, 26.9, 26.6, 26.5, 24.2, 24.0, 23.7, 23.5, 22.6, 22.56, 14.1, 14.0; IR (cm $^{-1}$): 3405, 2942, 2863, 1457, 1382, 1362, 1279, 1227, 1148, 1200, 1065, 942, 871; HRFAB calc. for $(M+Li)^+$: $C_{15}H_{30}O_4Li^+$: 281.2304 found: 281.2291, 4.6ppm; Analysis calc. for $C_{15}H_{30}O_4$: C, 65.66, H, 11.02; found: C, 65.27 H, 11.00.

(1R, 2S, 5R)-2-(1-Triethylsilylperoxy-1-methyl-ethyl)-5-methyl-cyclohexanol (15): Co-mediated peroxidation of (-)-isopulegol (183mg, 1.2mmol) upon similar conditions as for 3-methyl-3-butenol furnished **15** (323mg, 80%); $R_f = 0.71$ (10% EA/hex); $[\alpha]_D^{26}C = +26.4$ (C = 6.8, $CHCl_3$) 1H δ 4.11(s, 1H), 3.53(td, 1H, 4.0, 10.4), 1.88(bd, 1H, 12-13), 1.67(app. td, 1H, 11.0, 3.4), 1.62-1.54(2H), 1.36-1.26(1H, very broad), 1.20(s, 3H), 1.15(s, 3H), 0.97-0.96(2H), 0.90(t, 9H, 7.9), 0.83(d, 3H, 6.4), 0.61(q, 6H, 7.9); ^{13}C δ 88.19, 71.3, 48.8, 43.5, 34.4, 30.8, 26.6, 24.6, 21.8, 19.1, 6.5, 3.6; IR (cm $^{-1}$): 3536, 2945, 2922, 2872, 1454, 1410, 1371, 1315, 1237, 1142, 1002, 974, 891, 835, 801, 734; HRFAB calc. for $(M+H)^+$: $C_{16}H_{35}O_3^+$: 303.2355 found: 303.2367, 3.9ppm; Analysis calc. for $C_{16}H_{35}O_3$: C, 63.52, H, 11.33; found: C, 63.62 H, 11.33.

(1R, 6S, 9R)-3,3-Dibutyl-6,6,9-trimethyl-hexahydro-2,4,5-benzotrioxepane (16): Protection of 5-nonanone (112mg, 0.8mmol) with peroxide **15** under the conditions described in the general procedure furnished **16** (206mg, 84%); $R_f = 0.71$, 5% EA/Hexanes; $[\alpha]_D^{26}C = +98.4$ (C = 10.2, $CHCl_3$); 1H δ 3.74-3.67(td, 1H, 5.0, 10.4), 1.86-1.78(2H), 1.61-1.48(3H), 1.40-1.24(11H), 1.21(s, 3H), 1.18-1.12(1H), 1.06-0.96(2H), 1.09(s, 3H), 0.88(d, 3H, 6.8), 0.87(t, 6H, 7.1), 0.86-0.75(2H); ^{13}C δ 108.1, 84.2, 69.4, 54.5, 42.4, 34.0; 31.7, 30.2, 27.6, 26.3, 25.9, 25.3, 23.05, 22.97, 22.1, 20.9, 14.0,

13.98; IR: 2943, 2865, 1458, 1384, 1314, 1256, 1227, 1161, 1070, 976, 893, 868, 736; HRFAB calc. for (M+H)⁺: C₁₉H₃₇O₃⁺: 313.2742; found: 313.2757, 4.6ppm; Analysis calc. for C₁₉H₃₆O₃: C, 73.03, H, 11.61; found: C, 73.38 H, 11.64.

2,2-Dibutyl-1,3-dioxolane^{4a, 5-9} has been previously reported without a detailed procedure or spectral characterization. A solution of 5-Nonanone (1g, 7.0mmol), ethylene glycol(3mL, 50 mmol) and cat. *p*-TsOH (130mg, 0.3 mmol) in benzene was refluxed for 12h, with azeotropic removal of water. The reaction was then quenched into water and the separated aqueous layer extracted with ether. The combined organic layers were washed with dilute base. ([Alternatively, a solution of 5-nonanone (1g, 7.0mmol) and 0.1eq.CuCl₂.H₂O^{4b} in ethylene glycol (3mL, 53.4mmol), was stirred for 30 min and then quenched with sat. aq. NH₄Cl. The aqueous layer was extracted with 20% EA/Hexanes (3x, 50mL).

The organic layers from either procedure were dried over Na₂SO₄ and the solvent was removed under reduced pressure. The residue was purified through flash chromatography (5%EA/Hexanes) to typically furnish a mixture of 5-nonanone and 2,2-dibutyl-1,3-dioxolane. The mixture was subjected to NaBH₄ (151mg, 4mmol) reduction in MeOH (0°C to R.T). After 1 hour the reaction mixture was diluted with Et₂O (50mL) and quenched with 10% aqueous NaOH; the aqueous layer was extracted with 20% EA/Hexanes (3x, 30mL) and the solvent was removed under reduced pressure. A second purification by flash chromatography (5% EA/Hexanes) furnished 2,2-dibutyl-1,3-dioxolane (570mg, 45% overall yield from 5-nonanone). R_f = 0.79(5% EA/hex); ¹H δ 3.90(s, 4.0H), 1.59-1.55(4H), 1.33-1.26(8.0H), 0.87(t, 6.0H, 6.8); ¹³C δ 111.9, 64.8, 36.8, 26.0, 23.0, 14.0; IR (cm⁻¹): 2956, 2872, 1471, 1336, 1337, 1315, 1265, 1159, 1086, 969, 946, 880, 773.

Relative Rates of Acidic Deprotection: Trioxepane vs. 1,3-Dioxolane:

A mixture of 2,2-dibutyl-[1,3]dioxolane (150mg, 0.8mmol) and 3,3-dibutyl-7,7-dimethyl-1,2,4-trioxepane (100mg, 0.4mmol) was stirred in a solution of 10% aq. HCl:THF(1:2). The GC-MS analysis of the reaction mixture after 2 h revealed an absence of 1,3-dioxolane and the presence of 5-nonanone. The reaction mixture was quenched with DI water (10mL); the aqueous layer was extracted with 20% EA/Hexanes (3x, 20mL). The

combined organic layers were sequentially washed with sat. NaHCO_3 solution (2x, 25mL) and DI water (2x, 25mL) and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the residue purified by flash chromatography to furnish trioxepane (94 mg, >90%) and 5-nonanone (126 mg, 84%, yield based on 1,3-dioxolane). A separate experiment measuring the stability of **5** towards 10% aq. $\text{HCl}:\text{THF}$ (1:2) revealed little decomposition for 4 hours, some decomposition after 6 h, and predominant decomposition after 12 h.

Deprotections with Mg/MeOH were conducted using the procedure of Dai, et al.¹⁰ To a 0.5-1.0M solution of trioxepane in warm methanol, was added freshly scratched Mg (5.0-7.0 eq) and a crystal of iodine. Following disappearance of starting material (TLC, usually 4-6 h), the reactions were quenched with water and extracted with ether or ethyl acetate/hexane. The organic layer was dried (Na_2SO_4) and concentrated, and the residue subjected to flash chromatography to provide the carbonyl compound. Small scale reactions were not quenched; instead, the crude reaction mixture was concentrated and the residue directly submitted to chromatography.

Deprotections to form aldehydes, aryl ketones, or unsaturated ketones were conducted using the procedure of Dai, et al.¹⁰ To a solution of trioxepane in glacial acetic acid (5.0-6.0mL) was added Zn powder (5.0-8.0eq). The reaction was stirred until the trioxepane had disappeared (TLC). The reaction mixture was diluted with water (10mL) and diethyl ether (20mL). The ether layer was washed with sat. aq. NaHCO_3 and dried over Na_2SO_4 . The residue obtained after concentration was subjected to flash chromatography.

Differential Scanning Calorimetry was performed on neat samples (approximately 30 mg) of trioxepanes using a gradient of $5^\circ\text{C}/\text{minute}$ over a range of 25 – 400 $^\circ\text{C}$.

(1) Dussault, P. H.; Eary, C. T.; Lee, R. J.; Zope, U. R. *J. Chem. Soc., Perkins Trans. I* **1999**, 2189-2204.

(2) Ito, T.; Tokuyasu, T.; Masuyama, A.; Nojima, M.; McCullough, K. J. *Tetrahedron* **2003**, 59, 525-36.

(3) O'Neill, P. M.; Hindley, S.; Pugh, M. D.; Davies, J.; Bray, P. G.; Park, B. K.; Kapu, D. S.; Ward, S. A.; Stocks, P. A. *Tetrahedron Lett.* **2003**, 44, 8135-8.

(4) a. Daignault, R. A.; Eliel, E. L.; *Org. Synth., Coll. Vol. V.*, **1973**, 303.
Greene, T. W.; Wuts, P. G. M. *Protecting Groups in Organic Synthesis*, 3rd ed. **1999**, Wiley-Interscience, 313. b. Satoh, J. Y.; Yokoyama, C. T.; Haruta, A. M.; Nishizawa, K.; Hirose, M.; and Hagitani, A. *Chem. Lett.*, **1974**, 12, 1521-2.

Preparation of 2,2-Dibutyl-1,3-dioxolane has been reported using several methods:

- (5) "An efficient procedure for the preparation of cyclic ketals and thioketals catalyzed by zirconium sulfophenyl phosphonate" Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. *Synlett*. **2001**, 1182-4.
- (6) "Microwave-assisted acetalization of carbonyl compounds catalyzed by reusable Envirocat supported reagents" Beregszaszi, T.; Molnar, A. *Synth. Commun.* **1997**, 27, 3705-9.
- (7) "Conversion of ketals to ketones by nitrogen dioxide in the presence of silica gel" Nishiguchi, T.; Ohosima, T.; Nishida, A.; Fujisaki, S. *J. Chem. Soc., Chem. Commun.* **1995**, 11, 1121-2.
- (8) "Deketalization induced by phenyl dichlorophosphate and sodium iodide" Liu, J. H.; Yuan, S. U. *Synth. Commun.* **1986**, 16, 1357-61;
- (9) "Studies on the terpenoids and related alicyclic compounds. XXXI. Bis (diisobutylaluminum) 1,2-ethanedithiolate: a reagent in the conversion of oxyacetals to thioacetals: Satoh, T.; Uwaya, S.; Yamakawa, K. *Chem. Lett.* **1983**, 5, 667-70.
- (10) Dai, P.; Dussault, P. H.; Trullinger, T., K. *J. Org. Chem.* **2004**, 69, 2851-2.

2,2-Dibutyl-[1,3]dioxolane

2,2-Dibutyl-[1,3]dioxolane