Supporting Information

Osmium Tetroxide Promoted Catalytic Oxidative Cleavage of Olefins. An Organometallic Ozonolysis

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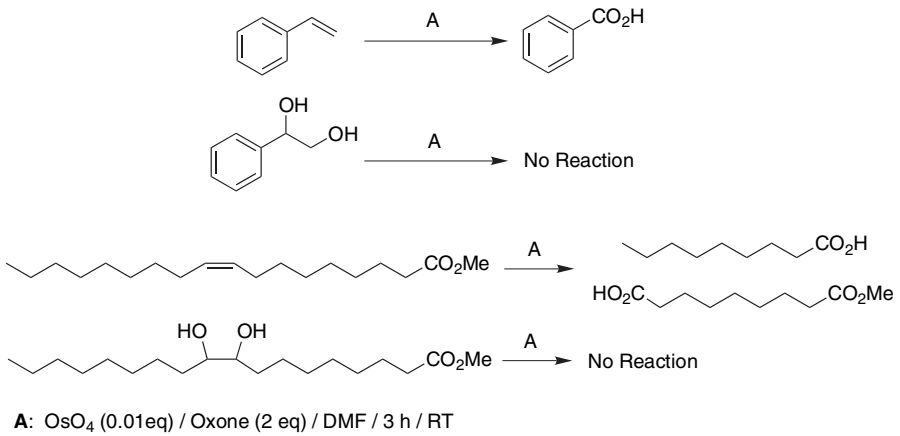
General: All commercially available starting materials were used without further purification. Except for cyclohexene **6** (Fisher), methyl oleate **11** (Nu-Chek-Prep), and Nootkatoone **23** (Lancaster) all commercially available starting materials (**1**-**5**, **7**-**10**, **14**, **16**-**20**, **22**) were obtained from Aldrich. Compounds **21**[1] and **24**[2] were prepared as reported, previously. ^{1}H, ^{13}C, 2D-COSY and DEPT spectra were recorded on 300 MHz NMR spectrometer (VARIAN INOVA) in $CDCl_3$. IR spectra were recorded on Nicolet IR/42 spectrometer using NaCl cells. Column chromatography was performed using Silicycle (40-60 μm) silica gel. Analytical TLC was done using pre-coated silica gel 60 F_{254} plates. GC analysis was performed using HP (6890 series) GC system (Column type-AltechSE-54, 30 m x 320 μm x 0.25 μm). ***Caution***: OsO_4 is a known to be highly toxic and should be handled with appropriate precautions. Although Oxone® appears to be a very stable and easily handled reagent, as with all peroxides, it has the potential to be explosive. In this study; however, no problems were encountered with either reagent.

Reference 13 from manuscript:



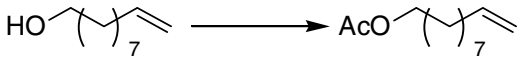
A: OsO_4 (0.01eq) / Oxone (2 eq) / DMF / 3 h / RT

To highlight the fact that 1,2-diols do not oxidize under our reaction conditions to yield product, and thus are not intermediates during the cleavage, two test reactions were performed with both styrene glycol and methyl 9,10-dihydroxyoctadecanoate. In both cases, their corresponding olefinic counterparts; i.e., styrene and methyl 9,10-octadecenoate were also subjected to the oxidative cleavage reaction, simultaneously [Oxone® (2eq), OsO_4 (0.01 eq), 3 h, RT]. The reactions were monitored by ^{1}H-NMR, TLC, and GC and clearly showed that the olefins were cleanly oxidized to the corresponding carboxylic acids, however, the diols in both cases remained untouched and were recovered in near quantitative yields.

OsO_4 does not cleave 1,2-diols independently. From the latter experiment and literature precedent, it is clear that Oxone® also does not cleave or oxidize alcohols or 1,2-diols with out other cofactors present.[3-6] Thus, it is reasonable to assume that the oxidative cleavage reported herein proceeds without the formation of an intermediate 1,2-diol, and in fact the osmate ester is activated for the direct cleavage of the C-C bond.

EXPERIMENTAL

9-Decenyl acetate (13):[7]



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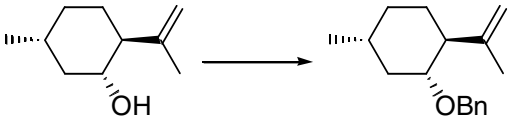
To a solution of 9-decene-1-ol (500 mg, 3.2 mmol) in pyridine (10 mL) was added acetic anhydride (0.91 mL, 9.6 mmol). The mixture was stirred and heated for 3 h at 60 ^{0}C. The reaction was then extracted with EtOAc (25 mL) and washed with 1N HCl (25 mL x 5) and brine (25 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to provide a crude, slightly yellow oil. Column chromatography (5% EtOAc / Hexanes) provided the desired acetate (630 mg, 99% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.74-5.83 (m, 1H), 4.89-4.99 (m, 2H), 4.03 (t, 2H, *J*=6.9 Hz), 2.02 (s, 3H), 2.01-2.07 (m, 2H), 1.56-1.62 (m, 2H), 1.27-1.38 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.2, 139.0, 114.1, 64.6, 33.7, 29.3, 29.1, 28.9, 28.7, 28.5, 25.8, 20.9; IR (neat, NaCl, cm^{-1}) 3077, 2927, 2856, 1741, 1641, 1242; LRMS (70 eV, EI) *m/z* 138 $[M\text{-}OAc]^+$.

(1R, 2S, 5R)-(2-isoprenyl-5-methyl-cyclohexyl) benzyl ether (15):[8]



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Sodium hydride (68 mg, 60% dispersion in mineral oil, 1.7 mmol) was suspended in dry THF (9 mL). The reaction was cooled to 0 ^{0}C and isopulegol (200 mg, 1.3 mmol) dissolved in dry THF (1 mL) was added and stirred for 30 min. Benzyl bromide (289 mg, 1.7 mmol) and KI (63 mg, 1.7 mmol) were added sequentially at 0 ^{0}C. The reaction mixture was allowed to warm to RT and stirred for an additional 3 h, after which it was quenched with water and sat. NH_4Cl, and then extracted into EtOAc (20 mL x 2). The combined organics were washed with water (40 mL) and brine (40 mL), dried over Na_2SO_4, and the solvent was removed under reduced pressure to obtain a slightly colored oil. Column chromatography (10% EtOAc / Hexanes) provided the desired benzyl ether (278 mg, 88%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25-7.43 (m, 5H), 4.83 (s, 2H), 4.61 (t, 1H, *J*=11.5 Hz), 4.52 (d, 1H, *J*=11.8 Hz), 3.31 (dt, 1H, *J*=4.1, 10.7 Hz), 2.11 (m, 2H), 1.71 (s, 3H), 1.64 (m, 2H), 1.28-1.45 (m, 2H), 0.95-1.06 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 147.8, 139.1, 128.3, 128.1, 127.7, 127.6, 127.2, 110.9, 79.1, 70.3, 51.7, 40.2, 34.3, 31.5, 31.0, 22.3, 20.0; IR (neat, NaCl, cm^{-1}) 2923, 2867, 1106; LRMS (70 eV, EI) *m/z* 243 $[M\text{-}H]^+$, 138 $[M\text{-}OBn]^+$.

General Procedure for the Oxidative Cleavage of Mono and Disubstituted Olefins (Condition A):

The olefin (1 eq) was dissolved in DMF (0.2 M), and OsO_4 (0.01 eq, 2.5% in *t*BuOH) was added and stirred for 5 min. Oxone® (4 eq) was added in one portion and the reaction was stirred at RT for 3 h or until the solution becomes colorless. This usually marks the completion of the reaction which was verified by TLC or GC. Na_2SO_3 (6 eq w/w) was added, to reduce the remaining Os(VIII), and stirred for an additional hour or until solution became dark brown / black. EtOAc was added to extract the products and 1N HCl was used to dissolve the salts. The organic extract was washed with 1N HCl (3x) and brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure to obtain the crude product. Products were purified by silica gel column chromatography.

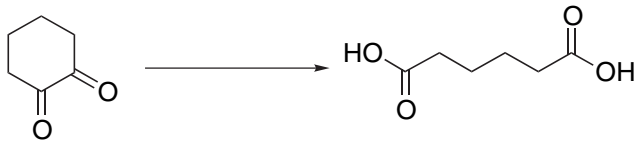
General Procedure for the Oxidative Cleavage of Tri and Tetrasubstituted Olefins (Condition B):

The olefin (1 eq) was dissolved in DMF (0.2 M), and OsO_4 (0.01 eq, 2.5% in *t*BuOH) was added and stirred for 5 min. A solid mixture of Oxone® (4 eq) and $NaHCO_3$ (4 eq) was then added in one portion and the reaction was stirred at RT for 3h. or until solution becomes colorless. This usually marks the completion of the reaction which was verified by TLC or GC. Na_2SO_3 (6 eq w/w) was added, to reduce the remaining Os(VIII), and stirred for an additional hour or until solution became dark brown / black. EtOAc was added to extract the products and 1N HCl was used to dissolve the salts. The organic extract was washed with 1N HCl (3x) and brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure to obtain the crude product. Products were purified by silica gel column chromatography.

Large scale preparation of 1a from 2:

The olefin (9 g) was dissolved in DMF (250 mL), and OsO_4 (0.2 mL, 2.5% in *t*BuOH) was added and stirred for five minutes. Oxone® (123 g) was then added slowly via a solid addition funnel over 2 h. The reaction was stirred at RT for 6 h followed by addition of Na_2SO_3 (54 g) and stirred for an additional hour. The reaction was diluted with Et_2O (750 mL) and stirred for 10 min. The solid was filtered off and washed with Et_2O (75 mL x 3). The organic extract is washed with 1N HCl (200 mL x 3) and brine (200 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to obtain the product at 11.60 g and 95% yield. The final product was crystallized from hot chloroform to obtain **1a** (10.74 g, 88%).

Oxidation of 1,2-Cyclohexanedione to Adipic acid

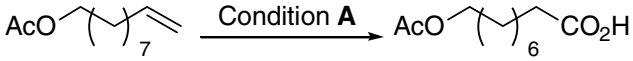


1,2-Cyclohexanedione (1 eq) was dissolved in DMF (0.2 M), and Oxone® (4 eq) was added in one portion. The reaction was stirred at RT for 3 h and an aliquot was removed and diluted with EtOAc for GC analysis. This showed an 80% conversion to adipic acid.

Spectral Data:

Spectral properties of Benzoic acid (**1a**), Adipic acid (**6a**), Suberic acid (**7a**), Nonanoic acid (**8a**), Octanoic acid (**9a**), Heptanoic acid (**10a**), 4-Methylbenzoic acid (**16a**), 4-Nitrobenzoic acid (**17a**), Glutaric acid (**18a**)**,** Acetophenone (**21a**), and 3R-Methyladipic acid (**22a**) match those reported by Aldrich and comparison to authentic samples.

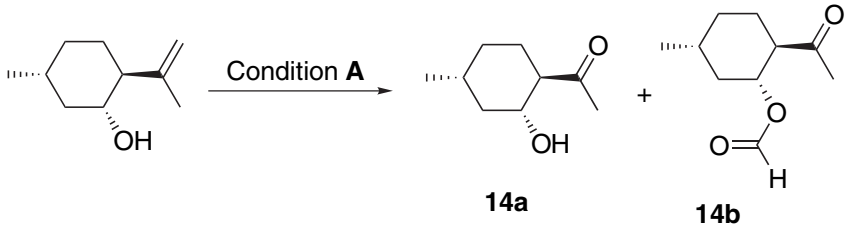
9-Acetoxy nonanoic acid (13a):[9]



13a

^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.02 (t, 2H, *J*=6.9 Hz), 2.32 (t, 2H, *J*=7.4 Hz), 2.02 (s, 3H), 1.56-1.61 (m, 4H), 1.29 (bs, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 179.6, 171.4, 64.5, 33.9, 29.0, 28.9, 28.8, 28.4, 25.7, 24.5, 20.9; IR (neat, NaCl, cm^{-1}) 3455, 2931, 2856 1739, 1737, 1242; LRMS (70 eV, EI) *m/z* 199 $[M-H_2O]^+$, 157 $[M-OAc]^+$.

(1R, 2R, 5R)-2-Acetyl-5-methyl cyclohexanol (14a):[10]



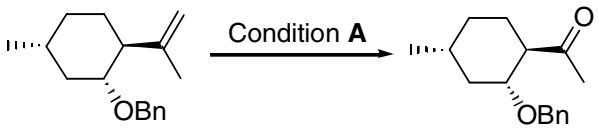
14a **14b**

^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.80 (ddd, 1H, *J*=4.4, 9.6, 11.1 Hz), 2.27 (ddd, 1H, *J*=3.6, 9.6, 12.9 Hz), 2.17 (s, 3H), 1.91-2.00 (m, 2H), 1.68-1.74 (m, 1H), 1.38-1.52 (m, 1H), 1.22-1.27 (m, 1H), 0.91-1.03 (m, 1H), 0.92 (d, 3H, *J*=6.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 212.9, 70.4, 58.5, 42.2, 34.0, 31.1, 29.2, 27.5, 22.0; IR (neat, NaCl, cm^{-1}) 3417, 2952, 2927, 2869, 1705; LRMS (70eV, EI) *m/z* 156 M^+, 138 $[M-H_2O]^+$, 95 $[M-H_2O-C(O)Me]^+$.

(1R, 2R, 5R)-2-Acetyl-5-methyl cyclohexanyl formate (14b):

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.95 (s, 1H), 5.06 (ddd, 1H, *J*=4.4, 9.6, 11.2 Hz), 2.59 (ddd, 1H, *J*=6.9, 8.9, 14.5 Hz), 2.15 (s, 3H), 2.11-2.13 (m, 1H), 1.93 (qd, 1H, *J*=3.9, 6.9 Hz), 1.68-1.77 (m, 1H), 1.50-1.62 (m, 1H), 1.27-1.41 (m, 1H), 0.87-1.06 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 209.4, 160.3, 73.1, 55.2, 39.3, 33.3, 30.0, 29.3, 27.8, 21.7; IR (neat, NaCl, cm^{-1}) 2952, 2929, 2869, 1728, 1178; LRMS (70 eV, EI) *m/z* 185 $[M+H]^+$, 149 $[M-HCO_2H]^+$; HRMS $[M+H]^+$ Calcd for $C_{10}H_{16}O_3$: 184.1099 *m/z* . Observed 184.1095 *m/z* .

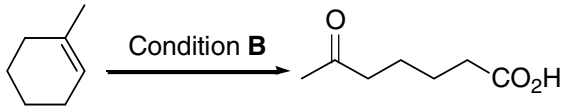
(1R, 2R, 5R)-(2-Acetyl-5-methylcyclohexyl) benzyl ether (15a):



15a

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.21-7.32 (m, 5H), 4.56 (d, 1H, *J*=11.3 Hz), 4.37 (d, 1H, *J*=11.3 Hz), 3.6 (dt, 1H, *J*=6, 10.4 Hz), 2.53 (ddd, 1H, *J*=3.8, 10.1, 12.6 Hz), 2.16 (s, 3H), 2.12-2.19 (m, 1H), 1.75 (qd, 1H, *J*=3.6, 10.2 Hz), 1.64-1.70 (m, 1H), 1.25-1.52 (m, 2H), 0.93 (d, 2H, *J*=3.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 212.3, 138.5, 128.2, 127.6, 127.4, 79.1, 70.9, 56.6, 39.4, 33.5, 30.9, 27.7, 22.1; IR (neat, NaCl, cm^{-1}) 2950, 2927, 2867, 1739, 1712; LRMS (70 eV, EI) *m/z* 228 $[M-H_2O]^+$, 140 $[M-OBn]^+$; HRMS $[M+H]^+$ Calcd. for $C_{16}H_{22}O_2$: 246.1620 *m/z* . Observed 246.1631 *m/z* .

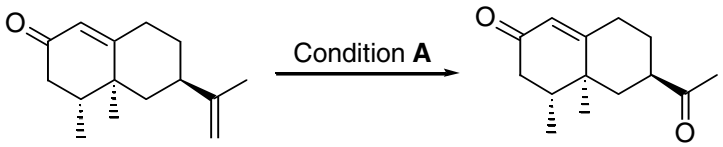
6-Oxyheptanoic acid (20a):[11]



20a

^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.41-2.45 (m, 2H), 2.31-2.36 (m, 2H), 2.11 (s, 3H), 1.56-1.62 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 208.8, 179.1, 43.2, 33.7, 29.9, 24.0, 22.9; IR (neat, NaCl, cm^{-1}) 3455, 2939, 1714; LRMS (70 eV, EI) *m/z* 144 M^+, 126 $[M-H_2O]^+$.

(4S, 4aR, 6R)-6-Acetyl-4,4a-dimethyl-4,4a,5,6,7,8-hexahydro-3*H*-naphthalen-2-one (23a):[12]



23a

^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.72 (s, 1H), 2.71 (m, 1H), 2.33-2.48 (m, 2H), 2.20-2.25 (m, 2H), 2.1 (s, 2H). 1.94-2.06 (m, 4H), 1.40 (m, 1H), 1.21 (t, 1H, *J*=12.5 Hz), 1.06 (s, 3H), 0.93 (dd, 3H, *J*=6.6, 1.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 10.4, 199.2, 168.5, 125.1, 46.6, 41.9, 40.1, 39.8, 38.8, 31.9, 28.4, 28.1, 16.6, 14.8; IR (neat, NaCl, cm^{-1}) 2966, 2939, 2883, 1708, 1668, 1617; LRMS (70 eV, EI) *m/z* 220 M^+, 177 $[M\text{-}COMe]^+$.

References:

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