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Selective Oxidation of Tertiary-secondary *vic*-Diols to α-Hydroxy Ketones by Dioxiranes

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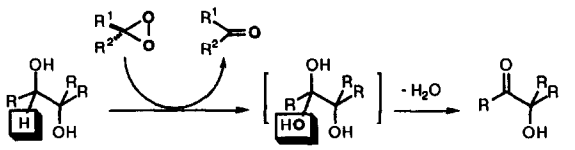
Abstract. Isolated dimethyldioxirane (**1a**) and methyl(trifluoromethyl)dioxirane (**1b**) efficiently afford the conversion of bicyclic diols bicyclo[2.2.2]octane-1,2-diol (**2**) and (+)-pinane-2,3-diol (**6**), of tricyclic diols adamantane-1,2-diol (**3**), homoadamantane-3,4-diol (**4**), and of homopentaprismane-3,4-diol (**5**) into the corresponding α-hydroxy ketones in high yields and under mild conditions. In the oxidation of (+)-pinane-2,3-diol (**6**), (-)-2-hydroxy-3-pinanone (**11**) is obtained in optical yield >97% with retention of configuration.

In recent times, the availability of dioxiranes $R^1R^2CO_2$ (**1**) (i.e., the smallest ring peroxides containing carbon) *in situ* generated,[1] as well as in isolated form,[2] precipitated an intensive utilization of these powerful oxidants to carry out a variety of synthetically useful transformations.[3] Among these a truly remarkable one is the efficient oxyfunctionalization of simple, "non activated" alkane C-H bonds,[4] and the selective conversion of secondary and primary alcohols into carbonyls;[5] for these transformations methyl(trifluoromethyl)dioxirane (**1b**) appears better suited than dimethyldioxirane (**1a**), leading to higher yields and much faster conversions.

We have now turned to the oxidation of either simple or complex *vic*-diols by dioxiranes, finding that these powerful (and yet selective) reagents allow their transformation into the corresponding α-hydroxy ketones in high yield and mild conditions (eq 1).



(1)

In this paper we report on the facile conversion of representative polycyclic tertiary-secondary *vic*-diols, such as bicyclo[2.2.2]octane-1,2-diol (**2**),[6a] adamantane-1,2-diol (**3**),[6a] homoadamantane-3,4-diol (**4**),[6a] hexacyclic homopentaprismane-3,4-diol (**5**),[6b,c] and (+)-pinane-2,3-diol (**6**).

Solutions of 0.06-0.08 M dimethyldioxirane (**1a**: $R^1=R^2=CH_3$)[4a,b] in acetone or of 0.5-0.8 M methyl-(trifluoromethyl)dioxirane (**1b**: $R^1=CH_3$, $R^2=CF_3$)[4d] in 1,1,1-trifluoropropanone (its ketone precursor, hereafter TFP) were obtained by reported procedures;[4] the oxidations simply involved addition of aliquots of standardized [4] dioxirane solution to the diol substrates at the conditions given in Table 1.

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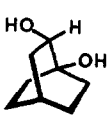
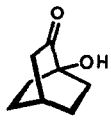
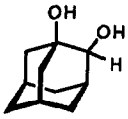
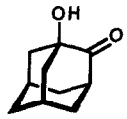
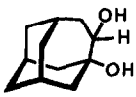
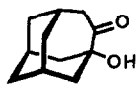
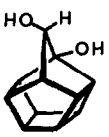
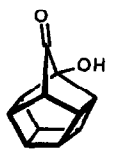
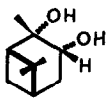
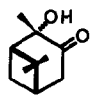
Table 1. Selective Oxidation of Polycyclic *vic*-Diols by Dioxiranes. [a]

Entry	Substrate	Dioxirane	Reactn. time	% Conv.[b]	Product	% Yield[c]
1	 (2)	1b	15 min	> 96	 (7)	96
		1a	4 h	68		95
2	 (3)	1b	15 min	> 98	 (8)	99
		1a	4 h	52		95
3	 (4)	1b	10 min	96	 (9)	> 96
		1a	2 h	88		95
4	 (5)	1a[d]	70 h	99	 (10)	99
5	 (6)[e]	1a	4 h	> 96	 (11)	98[f]

[a] Reactions were routinely run at 0 °C, with initial dioxirane to substrate molar ratio ca. 1.2 : 1 : mixed solvent composition was CH_2Cl_2/TFP ca. 9:1 for oxidations with 1b, and CH_2Cl_2/acetone ca 7:3 for oxidations with 1a. [b] As determined (± 2%) by gc (DB5, 0.20 μm film thickness, 15 m × 0.32 mm i.d., wide-bore capillary column). [c] Unless noted otherwise, yields were determined by gc or gc/ms (Hewlett-Packard mod. 5970 mass selective detector and mod. 5890 gas chromatograph) and based on the amount of substrate consumed; products were identified upon comparison of their ^1H nmr spectra (Varian XL 200 or VXR 400) and/or gc/ms with those of reported compounds. [d] A two-fold molar excess of dioxirane over substrate was employed in solvent acetone. [e] Commercial (Aldrich) (1S,2S,3R,5S)-(+)-pinanediol, $[\alpha]_D$= +8.5° (*c* 6.5, $PhCH_3$). [f] (1S,2S,5S)-(-)-2-Hydroxy-3-pinanone, $[\alpha]_D$= -36° (*c* 0.5, $CHCl_3$); based on a literature (ref. 14c) value of $[\alpha]_D$= -37° (*c* 0.5, $CHCl_3$) for the pure enantiomer, the optical yield is in excess of 97%.

The following example is representative of the simple oxidation procedure. To a stirred solution of 1,2-adamantanediol (**3**) (113 mg, 0.67 mmol) in CH_2Cl_2 (15 mL) at 0° C, 0.95 mL (0.7 mmol) of a cold standardized (ca. 0.78 M) methyl(trifluoromethyl)dioxirane solution in TFP was added in one portion; gc monitoring revealed that substrate conversion was practically complete after 15 min. Then, removal of solvent in vacuo afforded pure 1-hydroxy-2-adamantanone (**8**)[7] (111 mg, 0.67 mmol, yield > 99%).

Data in Table 1 indicate that dioxirane oxidation cleanly allows the conversion of the given *vic*-diols into the corresponding α-hydroxy carbonyls under mild conditions. For instance, oxidation of bicyclo[*2.2.2*]octane-1,2-diol (**2**) gives bicyclic α-hydroxy ketone **7**[8] in nearly quantitative yield (entry 1). By way of comparison, either with the Jones reagent[9a,b] or with Ag_2CO_3/Celite[9c] the same transformation is unsatisfactory,[10] so that (dioxirane oxidation aside) one has eventually to depend on a synthetic route[10] other than oxidation in order to obtain **7**.

Employing dioxiranes, we were also able to perform in high yields the selective transformation of tricyclic adamantane-1,2-diol (**3**) and of homoadamantane-3,4-diol (**4**) into the corresponding α-hydroxy ketones **8**[7] and **9**,[11] respectively (entry 2 and 3, Table 1). It is worthy of note that Jones oxidation of adamantane-1,2-diol (**3**) has been reported[12] to give **8** in 70% yield; however, silver carbonate oxidation gives 26% yield only. By way of contrast, Ag_2CO_3 oxidation of homoadamantane-3,4-diol (**4**) works nicely to provide **9** in 83% yield, although the Jones reagent or pyridinium chlorocromate (PCC)[9d] give low yields (i.e., 18% and 30%, respectively).[11b]

3-Hydroxyhomopentaprismane-4-one (**10**) is the critical intermediate in the only known synthesis of pentaprismane.[6b,c] It can be obtained by the Corey-Kim oxidation (Me_2S/Cl_2) of diol (**5**), but the best yield obtained was about 85%, and then only on 5 mmol scale or less; larger scale oxidations resulted in a precipitous drop in yield. Other usual oxidation methods (MnO_2, Br_2/HMPT, DMSO/TFA, etc.) gave lower yields and/or resulted in oxidative cleavage.[6c] Fortunately, in an early successful application of dioxirane **1a** to the oxidation of tertiary-secondary 1,2-diols, homopentaprismane diol **5** (30 mM in acetone, at 0 °C) could be converted into **10**[13] in nearly quantitative yield (entry 4, Table 1); and this even on >7 mmol (1.3 g) scale. Under the conditions given, over-oxidation did not occur.

Of interest is the oxidation of optically active pinane-2,3-diol (**6**) (entry 5, Table 1); here, the corresponding α-hydroxyketone **11**[14] is obtained in practically quantitative yield, and with an optical yield in excess of 97%. Actually, recent data[15] indicate that not only tertiary-secondary but *also secondary-secondary* vic-*diols* can be converted by isolated dioxiranes into *α-hydroxy ketones in high enantiomeric excess*, with virtually total retention of configuration at the chiral center adjacent to the one undergoing transformation into carbonyl.

Thus, dioxiranes should be the reagents of choice for the transformation of structurally complex *vic*-diols (such as those at hand) into the corresponding α-hydroxy carbonyls under mild conditions. Of course, the more reactive[2d,4a-c,5] methyl(triluoromethyl)dioxirane (**1b**) allows higher conversions with far shorter reaction times as compared to dimethyldioxirane (**1a**) (Table 1). No doubts the high selectivities recorded are to be ascribed to the mild conditions, close to neutrality, attainable by using isolated dioxiranes.[3] They can hardly be reconciled with a radical mechanism. Rather, an "oxenoid" *O*-insertion mechanism is likely to apply, akin to that envisaged to occur in the transformation of secondary alcohols to ketones.[5]

Concerning this, it is interesting that some *vic*-diols appear to be more reactive than alcohols toward dioxiranes. In the case at hand this was verified by kinetic experiments, comparing the rate of conversion of adamantane-1,2-diol (**3**) into 1-hydroxy-2-adamantanone (**8**) with that of commercial adamantan-2-ol (**12**) into adamantan-2-one by dimethyldioxirane (**1a**). By adopting a described[4a,5] competition kinetics technique, the two substrates (**3** and **12**) in the same solution were allowed to react with excess dioxirane **1a**, making $([\mathbf{3}]_o+[\mathbf{12}]_o) << [\text{dioxirane}]_o$. With dimethyldioxirane initial concentration 6.9×10^{-2} M, $[\mathbf{3}]_o = 0.65\times10^{-3}$ M, and $[\mathbf{12}]_o = 2.1\times10^{-3}$ M in acetone at 0 °C, aliquots were withdrawn at time intervals within the first 30 -50% reaction and quenched (with excess Ph_3P in $CHCl_3$). Gc analyses of the samples (methyl perfluorooctanoate internal standard) allowed to estimate a relative rate $k_r = (k^3/k^{12}) = 2.8$, as $(k^3/k^{12}) = \{\log([\mathbf{3}]/[\mathbf{3}]_o)/(\log([\mathbf{12}]/[\mathbf{12}]_o)\}$; in each experiment, at least three values were measured and averaged (estimated error $\leq \pm 5\%$).

Thus, the secondary alcohol moiety is oxidized to carbonyl about three times faster in tricyclic diol **3** than in its mono functional analog adamantan-2-ol (**12**). This is in spite of the fact that in **3** the electron withdrawing OH functionality at C-1 should decrease the electron density at the site of *O*-insertion by the dioxirane (i.e., the HOC-*H* bond at C-2). Therefore, it is likely that some "cooperative" effect can be exercised by the proximal OH functionality even in conformationally rigid diol **3**, to the effect of assisting dioxirane attack through *H*-bonding in the transition state. This would have several well-established precedents in peroxide chemistry.[16]

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7. (a) **1-Hydroxyadamantan-2-one (8)**: mp 279-281 °C (lit.:[7b] mp 278-281 °C); ^{1}H nmr ($CDCl_3$, 200 MHz): δ 1.707- 2.25 (complex m, 10 H), 2.41 (2 H), 2.78 (broad, s, 1 H) ; {^{1}H}^{13}C nmr ($CDCl_3$, 50 MHz): δ 30.42, 34.72, 38.80, 45.87, 47.04, 75.70 (*C*-OH), 215.86 (*C*=O); ms (70 eV): *m/z* (r.i.) 166 (M^+, 9), 138 (23), 95 (100); ir (KBr): 3819-3559 (O-H str.), 1717 (C=O str.), 1147 cm^{-1} (C-OH str.) , etc. (b) Ree, B. R.; Martin, J. C. *J. Amer. Chem. Soc.* **1970**, *92*, 1660.

8. (a) **1-Hydroxybicyclo[*2.2.2*]octan-2-one (7)**: mp 183-186 °C; after recrystallization (n-hexane): mp 186-187 °C (lit:[8b] mp 187.5-188 °C); ^{1}H nmr ($CDCl_3$, 200 MHz): δ 1.5-2.05 (complex m, 8 H), 2.15 (q, 1 H, *J* = 3 Hz), 2.42 (CH_2, 2 H); {^{1}H}^{13}C nmr ($CDCl_3$, 50 MHz): δ 26.18, 27.54, 30.36, 43.30, 74.58, (*C*-OH), 216.10 (*C*=O); ms (70 eV): *m/z* (r.i.) 140 (M^+, 1), 96 (49), 83 (100) 70 (9), 55 (24); ir (KBr): 3513-3249 (O-H str), 1729 (C=O str), 1171 cm^{-1} (C-OH str), etc. (b) Takeuchi, K.; Kitagawa, T.; Ohga, Y.; Yoshida, M.; Akiyama, F.; Tsugeno, A. *J. Org. Chem.* **1992**, *57*, 280.

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11. (a) **3-Hydroxyhomoadamantan-4-one (9)**: mp 243-245°C (lit.:[11b] mp 242.5-244.5 °C); ^{1}H nmr ($CDCl_3$, 200 MHz): δ 1.98-1.58 (complex m, 8 H), 2.16 (broad, 1 H), 2.42 (m, 4 H), 2.65 (d, 2 H, *J* = 6 Hz); {^{1}H}^{13}C nmr ($CDCl_3$, 50 MHz): δ 26.19, 28.29, 34.16, 36.27, 40.69, 46.57, 77.22 (*C* -OH), 215.35 (*C* =O); ms (70 eV): *m/z* (r.i.) 180 (M^+, 4), 152 (10), 134 (25), 95 (100); ir (KBr): 3430-3398 (O-H str), 1695 (C=O str.), 1174 cm^{-1} (C-OH str), etc. (b) Takeuchi, K.; Akiyama, F.; Miyazaki,T.; Kitagawa, I.; Okamoto, K. *Tetrahedron Lett.* **1987**,*43*, 701.

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13. Sufficiently pure by nmr[6c] to be used without further purification: ^{1}H nmr ($CDCl_3$, 400 MHz): δ 2.32 (bs, 1 H), 2.43 (t, 1 H, *J* = 5.5 Hz), 3.16 (m, 2 H), 3.31 (m, 4 H), 3.50 (m, 4 H).

14. (a) **(1S,2S,5S)-(-)-2-Hydroxy-3-pinanone (11)**: mp 34-35°C;[14b,c] ^{1}H nmr (200 MHz, $CDCl_3$): δ 0.82 (s, 3 H, C^9H_3), 1.30 (s, 3 H, C^8H_3), 1.32 (s, 3 H, $C^{10}H_3$), 2.89 (s, 1 H, O*H*); {^{1}H}^{13}C nmr (50 MHz, $CDCl_3$): δ 214 (C=O), etc.; ir (neat): 3449-3425 (O-H str), 1723 (C=O str.), 1164 cm^{-1} (C-OH str.), etc.; ms (70 eV), *m/z* (r.i.): 168 (2, M+), 99 (77), 71 (97), 43 (100); $[\alpha]_D$= -35° (*c* 0.5, $CHCl_3$); lit.[14c]: $[\alpha]_D$= -37° (*c* 0.5, $CHCl_3$). (b) Suga, T.; Shishibori, T.; Hirata, T.; Matsuura, T. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 1180. (c) Oki, M.; Iwamura, H.; Aihara, J. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 176.

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