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FACILE SYNTHESIS OF α–HYDROXY CARBONYL COMPOUNDS BY ENOLATE OXIDATION WITH DIMETHYLDIOXIRANE

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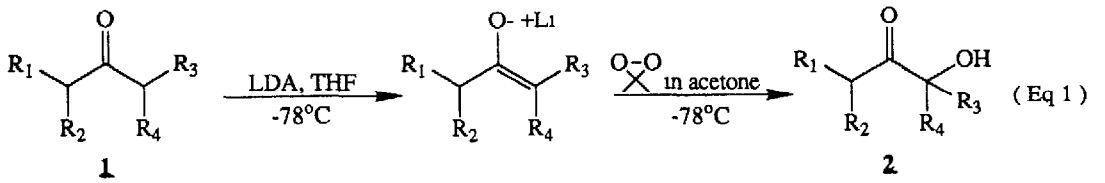
Abstract The direct oxidation of enolates with dimethyldioxirane (as a solution in acetone) provides the α-hydroxy derivatives in excellent yield

The conversion of enolizable ketones to their corresponding α-hydroxy derivatives is an important synthetic transformation and has received a great deal of attention [1,2] The classical method of achieving this transformation is direct enolate oxygenation with subsequent reduction of the hydroperoxide [1a,b,c] More recently, Vedejs and co-workers have introduced the molybdenum peroxide reagent MoO_5 pyridine HMPA[2] (MoOPH) for this purpose Similarly, Davis and co-workers have utilized both chiral and achiral oxaziridines for the direct oxidation of enolates [1i,j,k]

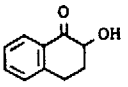
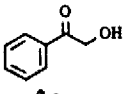
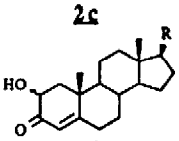
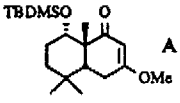
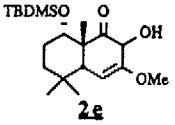
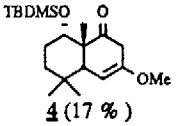
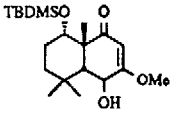
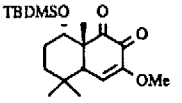
The direct oxidation of enolates however, is often complicated by other competing reactions In the case of enone, methyl and unhindered ketone enolates, aldol condensation is often a problem[2], and yields of the desired acyloin products are often low Furthermore, α-diketone products due to over oxidation are common and sometimes the predominant species

Recently, dimethyldioxirane (DD)[3] has been shown to be a mild selective oxidant converting enol ethers[4], γ-methylene-γ–butyrolactones[5], sugar-derived dihydropyrans[6], α,β-unsaturated ketones , esters and acids[7], enol silyl ethers[8] and aflatoxin B_1[9] to their corresponding epoxides, polycyclic arenes[10] to their oxides and allenes[11] to their dioxides These results prompt us to report our work on the direct oxidation of enolates with DD Indeed, DD was found to oxidize the enolates of ketones **1** to their α-hydroxy derivatives **2** (Eq 1) in high yield (see Table 1) An illustrative procedure is given below



1 **2** (Eq 1)

Table 1 Enolate oxidation with DD [a]

Carbonyl Compound	Oxid [b] Method	Oxid Temp (oC)	Time (min)	Product	% Yield [c]	Recovered Carbonyl [c] Compound (%)	Other [c] % Yield	Ref [d]
α-tetralone **1a**	A	-78	10	 **2a**	82	8	-	12
	B	-78	20	**2a**	52	31	-	--
	C[e]	-22	-	**2a**	48	0	-	--
Camphor **1b**	A	-78	15	 **2b**	74[f]	18	-	16
	B	-78	30	**2b**	50[f]	39	-	16
	C[e]	-22	10	**2b**	70[g]	15	-	--
Acetophenone **1c**	A	-78	30	 **2c**	77	4	-	13
Cholestenone **1d**	A	-78	10	 **2d**	60[h]	26	-	--
	C[e]	-	-	**2d**	40[h]	0	-	--
 **1e**[i]	A	-78	30	 **2e**	60J	0	 **4** (17 %)	14a
				 **3**	15J			14b
	C	+22	930	**2e**, **3**	0	48	 **5** (8 %)	15

[a] DD solutions in acetone were prepared (small scale) and standardized (thioanisole assay) according to the procedure of Adam and co-workers (ref 3c) and dried over 3A molecular sieves for 2 days at -20°C before using [b] Method A , inverse addition (see text) Method B regular addition (ie the DD solution in acetone at -78°C is added dropwise to the enolate in THF at -78°C) Method C The MoOPH reagent (approx 1 5 equiv) is added to the enolate in THF at -78°C and then warmed to the specified temperature [c] Refers to isolated yield (after chromatography) [d] Selected spectral data are given in refs 12 - 15 IR data were recorded on an Analect AQS-18 instrument, MS on a Kratos MS25RFA and ^{1}H NMR on a Varian XL-200 ($CDCl_3$ reference line) [e] These results were taken from ref 2 Cholestenone was oxidized using inverse MoOPH addition. [f] Mixture of 2 diastereomers (exo endo = 2 2 · 1) [g] Reported as a single diastereomer (see ref 2) [h] Mixture of 2 diastereomers, stereochemistry not determined [i] For successful generation of the enolate, 5 0 Equivalents of HMPA is required J Isolated as a single diastereomer

Preparation of 2-hydroxy-α-tetralone (inverse addition, method A)

To a stirring solution of diisopropylamine (87 µL , 0 62 mmol , 1 5 Equiv) in 2 0 mL of dry THF under argon at -78°C was added n-butyllithium solution (0 32 mL of 1 7M solution in pentane , 0.54 mmol , 1 3 Equiv) dropwise After 10 min , a solution of α-tetralone (40 mg , 0 27 mmol) in 0 5 mL of dry THF was added dropwise (cannula), washing the transfer vessel twice with 1 0 mL portions of dry THF to insure complete transfer After allowing the enolate to generate (1 h), the mixture was transferred dropwise (cannula) to a second flask containing anhydrous DD solution [3c] in acetone (5 80 mL of 0 062 M solution , 1 4 Equiv) also cooled to -78°C After allowing to stir for 10 min , the mixture was quenched at -78°C with 0 3 mL of pH 7 buffer solution and then allowed to come to room temperature The solvent was removed *in vacuo* and the residue taken into CH_2Cl_2 (10 mL) and washed with 5 mL of water The aqueous phase was further extracted twice with 5 mL of CH_2Cl_2 The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a crude oily residue Flash chromatography on silica gel (eluent 35 % ether / hexanes) gave 36 4 mg (82 %) of 2-hydroxy-α-tetralone **2a** as a slightly yellow colored oil which darkens on exposure to air A small amount (3 2 mg, 8 %) of α-tetralone was also recovered

A few general comments concerning the results (Table 1) are warranted Remarkably, no products resulting from aldol condensation with acetone are formed On the other hand, despite taking all precautions to dry solvents and reagents, some of the starting ketone was recovered in each case This is presumably due to the competing proton transfer reaction between the ketone enolate and acetone The amount of recovered ketone could be minimized in most cases using the inverse addition technique (Method A, see Table 1) In the case of cholestenone **1d**, the results demonstrate that the α-hydroxy products are derived, as expected, from the kinetic enolate in regiochemistry Moderate stereoselectivity was observed for the derivatives **2b** (2 2 1 exo endo) and **2d** (2 1 mixture of diastereomers, stereochemistry not determined) It is possible that proton transfer with acetone is affecting the ratio of products through epimerization Recently, Baumstark [17] has observed a rapid zero order decomposition of dimethyldioxirane solutions to give α -hydroxyacetone upon exposure to aqueous potassium hydroxide This result would suggest a rapid oxidation of the enolate of acetone by DD, which is consistent with our results

In the oxidation of the enolate of **1e**, the α-hydroxy product **2e** is favored over the γ-product **3** Both of these products were isolated as single diastereomers, however their stereochemistries were not determined It is interesting to compare the results of MoOPH (method C) and DD oxidations of the enolate of **1e** The MoOPH oxidation gave only the α-diketone **5** in low yield, while DD oxidation gave as the major product, the α-hydroxy compound **2e** and none of the diketone **5**

In conclusion, the present methodology for enolate oxidation provides the α-hydroxy derivatives under mild conditions in high yield For the compounds examined (in Table 1), the yields are generally superior to the MoOPH methodology and further oxidation of the acyloin products to the α-diketones is effectively suppressed.

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FOOTNOTES AND REFERENCES

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12 **2a** IR (film, cm^{-1}) 3407, 1686
^1H NMR ($CDCl_3$, ppm) 8 06-7 24 (m, 4H), 4 38 (dd, J=13 6, 5 4 Hz, 1H), 3 91 (s, exch D_2O, 1H), 3 24-3 95 (m, 2H), 2 59-2 46 (m, 1H), 2 14-1 92 (m, 1H)
MS (EI, % rel int) 162 (M^+ , 50), 144 (16), 130 (26), 118 (100), 90 (48), 77 (10)

13 The identity was confirmed by comparison of spectral data with the litterature values in Sadtler standard spectra (^1H NMR 17161M, IR, grating, 24179K)

14 (a) **2e** IR ($CHCl_3$, cm^{-1}) 3585, 1722
^1H NMR ($CDCl_3$, ppm) 4 94 (d, J=6 9 Hz, 1H), 4 10 (s, 1H), 3 67 (s, 3H), 3 35 (dd, J=11.5, 3 7 Hz, 1H), 3 02 (bs, exch D_2O, 1H), 2 05-1 83 (m, 1H), 1 95 (d, J=6 9 Hz, 1H), 1 65-1 24 (m, 3H), 1 38 (s, 3H), 0 89 (s, 9H), 0 87 (s, 3H), 0 56 (s, 3H), 0 07 (s, 3H), 0 02 (s, 3H)
MS (EI, % rel int) 368 (M^+ , 2), 311 (30), 295 (10), 159 (7), 101 (8), 81 (9), 75 (100).
(b) **3** IR ($CHCl_3$, cm^{-1}) 3585, 1636
^1H NMR ($CDCl_3$, ppm) · 5 26 (s, 1H), 4 27 (d, J=2 9 Hz, 1H), 3 70 (s, 3H), 3 41 (dd, J=8 5, 2 9 Hz, 1H), 2 45 (bs, exch D_2O, 1H), 1 90-1 11 (m, 5H), 1 43 (s, 3H), 1 06 (s, 3H), 0 87 (s, 9H), 0 78 (s, 3H), 0 04 (s, 3H), -0 02 (s, 3H)
MS (EI, % rel int.) 368 (M^+ , 1), 353 (4), 311 (100), 279 (40), 251 (21), 159 (14), 101 (9), 81 (12), 75 (39)

15 **5** · Pale yellow solid mp 191-193 °C (dec) IR ($CHCl_3$, cm^{-1}) 1734, 1693, 1622
^1H NMR ($CDCl_3$, ppm) 6 04 (d, J=7 1Hz, 1H), 3 71 (s, 3H), 3 39 (dd, J=11 7, 4 0 Hz, 1H), 2 29 (d, J=7 1Hz, 1H), 2 03 (m, 1H), 1 75-1 20 (m, 3H), 1 37 (s, 3H), 1 00 (s, 3H), 0 87 (s, 9H), 0 64 (s, 3H), 0 09 (s, 3H), 0 02 (s, 3H)
MS (EI, % rel int.) 309 (M^+ -57, 19), 281 (4), 265 (8), 167 (11), 149 (35), 129 (16), 75 (100), 57 (28)

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