Oxidation of Natural Targets by Dioxiranes. 2.[1] Direct Hydroxylation at the Side-Chain C-25 of Cholestane Derivatives and of Vitamin D_3 Windaus–Grundmann Ketone

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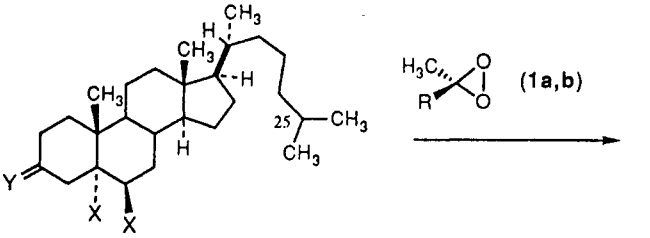
Summary: The direct, high-yield oxyfunctionalization of the side-chain C-25 of 5α-cholestan-3-one, 3β-acetoxy-5α-cholestane, and 5α,6β-Br_2-3β-acetoxycholestane as well as of the vitamin D_3-derived Windaus–Grundmann ketone has been achieved under mild conditions employing either dimethyldioxirane or its trifluoromethyl analogue.

The biological significance and uses of 25-hydroxyvitamin D_3 and its metabolites[2] continue to stimulate interest in 25-hydroxycholesterol derivatives;[2,3] these, in fact, can act as suitable precursors in the synthesis of 25-OH-D_3 or 1,25-$(OH)_2$-D_3.[3,4] However, effective methods[5] for the direct selective C-25 side-chain oxyfunctionalization of cholestane derivatives are still lacking. With the advent of dioxiranes[6] on the chemical scene, the combination of high reactivity, neutral pH, and ease of product isolation offered by these reagents has spurred their application (either in situ[7] or in isolated form[8,9]) to the oxyfunctionalization of non-natural[10] as well as natural[1,11,12] target molecules. The results have been encouraging so far; in the steroid area,[1,12] for instance, we have recently shown inter alia that the site-selective C-9 hydroxylation of estrone acetate can be achieved[1] using isolated dimethyldioxirane (**1a**)[8b,c] or methyl(trifluoromethyl)dioxirane (**1b**).[9]

We now report on the selective C-25 hydroxylation of three saturated cholestane derivatives using isolated **1a** and **1b** (eq 1); the dioxiranes were obtained by following a general protocol.[8,9] Typical reaction conditions and results are presented in Table I.

The reactions were carried out by addition of an aliquot (usually from 4 to 10 mL) of standardized[6,8,9] cold solution of ca. 0.1 M dimethyldioxirane (**1a**) in acetone or of ca. 0.8 M methyl(trifluoromethyl)dioxirane (**1b**) in 1,1,1-trifluoro-2-propanone (TFP) to a stirred solution of the substrate **2**, **4**, or **6**[13] (100–300 mg) in CH_2Cl_2 or acetone (5–10 mL), kept in a thermostat at the given temperature (Table I). After the reaction was carried out to a suitable conversion (GC or TLC monitoring) product isolation was achieved by removal of solvent in vacuo, followed by column chromatography (silica gel, *n*-hexane/Et_2O).

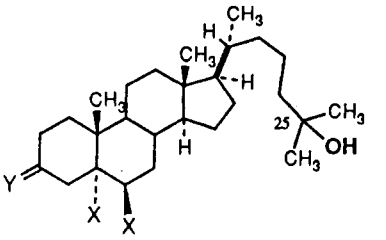
Inspection of data in Table I reveals that in the oxyfunctionalization of substrates **2** and **4** similar results are obtained using either dioxirane **1a** or **1b** (first two entries), except for percent conversions. Both transformations are much faster with the more reactive[9] methyl(trifluoromethyl)dioxirane (**1b**); there is no change in selectivity, however. In the spectra of reaction products **3**[14] and **5**,[15] most telling is a ^{13}C NMR (50-MHz) resonance at ca. 71.1 ppm due to the C^{25}-OH. Also of interest is the high yield transformation of 3β-acetoxy-5α,6β-dibromocholestane (**6**) into its 25-hydroxy derivative (**7**)[16] (last entry, Table I). In fact, the latter could be cleanly (yield 93%) converted into 25-hydroxycholesteryl acetate (**8**)[17] upon debromination with Zn/AcOH,[13c] thus restoring the $\Delta^{5,6}$ unsaturated moiety that had been masked in **6**.



(**2**) (Y = O; X = H)

(**4**) (Y = β-OAc, H; X = H)

(**6**) (Y = β-OAc, H; X = Br)



(**1**)

(**3**)

(**5**)

(**7**)

Alternative to employing cholestanol or cholesterol derivatives as starting materials,[3,4] in a convergent approach[18]

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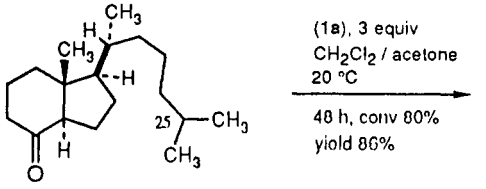
Table I. Dioxirane Oxyfunctionalization of Steroids 2, 4, and 6

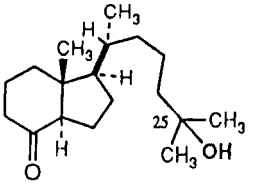
substrate	dioxirane	T (°C)	reactn time (h)	conversn[a] (%)	product	yield[b] (%)
5α-cholestan-3-one (2)	1a[c]	20	24	35	25-hydroxy- (3)	83
	1b[d]	0	3	87		85
3β-acetoxy-5α-cholestane (4)	1a[c]	20	24	30	25-hydroxy- (5)	81
	1b[d]	0	3	78		85
3β-acetoxy-5α,6β-dibromocholestane (6)	1a[c]	20	24	50	25-hydroxy- (7)	88
	1b[d]	-40	3	78		80

[a] As determined (±2%) by GC (SPB-1, 0.25-μm film thickness, 15-m × 0.25-mm i.d., capillary column); the progress of the reactions was monitored by GS or GC–MS (Hewlett-Packard Model 5970 mass selective detector and Model 5890 gas chromatograph). [b] Isolated yields (±4%), based on the amount of substrate consumed; products were identified by ^{13}C and/or ^{1}H NMR (Varian XL 200 or Bruker AM 500) (see text). [c] Initial dioxirane to substrate molar ratio (hereafter D/S) = 2.5:1; solvent CH_2Cl_2/acetone (40:60). [d] D/S = 3/1; solvent CH_2Cl_2/TFP (70:30).

to vitamin D_3 synthesis, the C-25-hydroxylated[19] Windaus–Grundmann ketone **10** can act as precursor of the ring C,D-side-chain fragment.[18] Therefore, satisfactory methods for the direct oxyfunctionalization at C-25 of these key intermediates are actively pursued. For instance, Uskokovic et al. have recently reported[18a] that **10** can be obtained in 44% yield upon reaction of Windaus–Grundmann ketone **9**[20] with $NaIO_4/RuCl_3$. We find that dioxiranes can also be applied to the synthesis of this important synthon. In fact, employing dimethyldioxirane (**1a**), the ketone **9**[21] could be selectively transformed into its hydroxy derivative **10**[22] in 86% yield under the reaction conditions shown in eq 2.



(9)



(10) (2)

The high selectivities displayed by dioxiranes in achieving the oxyfunctionalizations above is remarkable. Their origin might be traced to rather stringent steric and stereoelectronic demands.[1,9a,23] High tertiary over secondary C–H selectivity has been recorded in the dioxirane oxyfunctionalization of alkanes and cycloalkanes.[9a] Also, the sensitivity of dioxirane O-insertions to steric factors is well established in many instances,[10b,24] including oxidation of steroidal substrates.[1,12] As for the cases presented herein, the site-selective oxyfunctionalization at side chain C-25 of cholestane derivatives **2**, **4**, and **6**, as well as of ketone **9** points to enhanced steric availability of these centers to dioxirane *O*-insertion as compared to the other available tertiary C–H positions. Whatever the mecha-

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(13) (a) Commercial (Aldrich) 5α-cholestan-3-one (**2**) was recrystallized from EtOH: mp 128–130 °C; 3β-acetoxy-5α-cholestane (**4**) was obtained upon reaction of commercial (Aldrich) 3β-hydroxy-5α-cholestane with Ac_2O/Py, and was purified by column chromatography (silica gel, *n*-hexane/Et_2O (9:1)): mp 109 °C (lit.[13b] mp 109–110 °C). By following a literature[13c] procedure, treatment of cholesteryl acetate (Aldrich) with Br_2 in Et_2O gave 3β-acetoxy-5α,6β-dibromocholestane (**6**); flash column chromatography (silica gel, *n*-hexane/Et_2O (9:1)) afforded pure **6**: mp 121 °C (lit.[13d] mp 118–121 °C); ^{1}H NMR and ^{13}C NMR spectra agreed with literature data.[13d,e] (b) Heath-Brown, B.; Heilbron, I. M.; Jones, E. R. H. *J. Chem. Soc.* **1940**, 1482. (c) Fieser, L. F. *J. Am. Chem. Soc.* **1953**, *75*, 5421. (d) Kasal, A. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1642. (e) Römer, J.; Scheller, D. *J. Prakt. Chem.* **1983**, *325*, 422.

(14) (a) **25-Hydroxy-5α-cholestan-3-one (3)**: mp 168–170 °C; $[\alpha]^{20}_D$ +24.8° (*c* 0.3, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.65 (s, 3 H, C^{18}-*H*), 0.89 (d, *J* = 6.5 Hz, 3 H, C^{21}-*H*), 0.98 (s, 3 H, C^{19}-*H*), 1.18 (s, 6 H, C^{26}-*H* and C^{27}-*H*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.46, 12.06, 18.62, 20.76, 21.43, 24.20, 28.25, 28.95, 29.20, 29.34, 31.70, 35.37, 35.62, 35.73, 36.38, 38.19, 38.54, 39.87, 42.58, 44.38, 44.72, 46.67, 53.75, 56.16, 56.24, 71.10 (C^{25}), 212.3 (C^{3}); IR (KBr) 1714 cm^{-1} (C=O, str), etc. Anal. Calcd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.51. Found: C, 80.12; H, 11.75. (b) The MS of this compound has been reported: Aringer, L.; Nordström, L. *Biomed. Mass Spectrom.* **1981**, *8*, 183.

(15) **3β-Acetoxy-25-hydroxy-5α-cholestane (5)**: mp 124–125 °C;[5a] ^{1}H NMR spectrum in agreement with literature[5a] data; ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.06, 12.20, 18.62, 20.78, 21.18, 21.49, 24.18, 27.46, 28.25, 28.58, 29.20, 29.32, 29.69, 31.96, 34.00, 34.45, 35.75, 36.40, 36.73, 39.95, 42.58, 44.40, 44.62, 54.18, 56.16, 56.38, 71.11 (C^{25}), 73.77 (C^{3}), 170.72 (CH_3C=O).

(16) **3β-Acetoxy-5α,6β-dibromo-25-hydroxycholestane (7)**: mp 127–128 °C; $[\alpha]^{20}_D$ -54.0° (*c* 0.3, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.69 (s, 3 H, C^{18}-*H*), 0.91 (d, *J* = 6.5 Hz, 3 H, C^{21}-*H*), 1.20 (s, 6 H, C^{26}-*H* and C^{27}-*H*), 1.44 (s, 3 H, C^{19}-*H*), 2.03 (s, 3 H, CH_3CO), 4.81 (dd, J_{ae} = 4.2 Hz, J_{ee} = 2.0 Hz, 1 H, C^{6}-*H*), 5.46 (m, 1 H, C^{3}-*H*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.18, 18.61, 20.11, 20.76, 21.25, 21.34, 24.02, 26.15, 28.16, 29.21, 29.30, 30.78, 35.70, 36.35, 36.45, 37.16, 39.54, 41.82, 41.91, 42.68, 44.37, 47.20, 55.10, 56.00, 56.08, 71.10 (C^{25}), 72.01 (C^{3}), 88.07 (C^{5}), 170.4 (CH_3CO). Anal. Calcd for $C_{29}H_{48}Br_2O_3$: C, 57.62; H, 8.00. Found: C, 56.95; H, 8.09.

(17) (a) Mp 142–143 °C (lit.[17b] mp 141–142 °C); ^{1}H NMR spectrum in agreement with literature.[3b] (b) Fieser, L. F.; Huang, W.-Y.; Bhattacharrya, B. K. *J. Org. Chem.* **1957**, *22*, 1380.

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(21) (a) According to a literature[21b] procedure, ozonolysis of commerical (+)-vitamin D_3, and flash column chromaography (silica gel, *n*-hexane/Et_2O (9:1)) of the reaction mixture, afforded [1*R*-[1α-(*R**),3aβ,7aα]]-Octahydro-1-(1,5-dimethylhexyl)-7a-methyl-4*H*-inden-4-one (**9**): bp 115–120 °C (0.001 mmHg) (lit.[21c] bp 105–110 °C (0.5×10^{-3} mmHg)). (b) Story, P. R.; Alford, J. A.; Ray, W. C.; Burgess, J. R. *J. Am. Chem. Soc.* **1971**, *93*, 3042. (c) Inhoffen, H. H.; Quinkert, G.; Schutz, S.; Kampe, D.; Domagk, G. F. *Chem. Ber.* **1957**, *90*, 664.

(22) **[1*R*-[1α(*R**),3aβ,7aα]]-Octahydro-1-(5-hydroxy-1,5-dimethylhexyl)-7a-methyl-4*H*-inden-4-one (10)**. Colorless oil: $[\alpha]^{25}_D$ +17.5° (*c* 0.3, EtOH) (lit.[18b] $[\alpha]^{25}_D$ +17.9° (*c* 0.3, EtOH)); ^{1}H NMR spectrum in agreement with literature[18b] data; ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.27, 18.51, 18.87, 20.53, 23.88, 27.36, 29.03, 29.23, 35.33, 36.09, 38.84, 40.84, 44.17, 49.83, 56.55, 61.92, 71.02 (C^{25}),[19] 212.6 (*C*=O).

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nistic details, dioxirane oxyfunctionalization of vitamin D_3 metabolite precursors shows promise of considerable practical value because of its efficiency and simplicity of approach.

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How Can High Diastereoselectivity Be Attained in the Michael Addition of Ketene Silyl Acetals?

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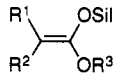
Summary: Criteria for attaining high diastereoselectivity in the title reaction are elucidated in terms of suppressing an electron-transfer process.

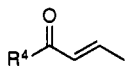
Michael addition of ketene silyl acetals to α-enones (Mukaiyama–Michael reaction) is a powerful means for carbon–carbon bond formation.[1] Stereocontrol of this reaction would be highly desired in the context of "acyclic stereoselection".[2] Nonetheless, it has been generally accepted that the reaction is virtually nonstereoselective, in particular, with regard to the relative topicity between two prochiral centers (simple diastereoselection).[3] Recently, we disclosed that this reaction, especially when β-substituted acetals were employed, involved an electron-transfer process which necessarily gave rise to loss of the stereoselectivity as a consequence of double-bond isomerization of the reactants.[4] In other words, the high stereoselectivity may be achievable if the electron transfer is suppressed and the transition-state geometry of an alternative nucleophilic reaction is sterically controlled. This hypothesis has prompted us to address the entitled problem.

The only precedent of the high stereoselection was put forth by Heathcock et al.[5] $TiCl_4$-promoted reaction between ketene silyl acetal **1b** and enone **2a** resulted in an exceptionally high syn/anti ratio (99:1 simple diastereoselection) (see Table I, entry 1), a very promising clue to the present subject. The *E* isomer **1c** provides the same outcome (entry 2).[6] Accordingly, we have begun with the scrutiny of this reaction.

One of the grounds on which we advanced the electron-transfer mechanism lies in unexpected competition reaction where β-substituted ketene silyl acetals react in preference to the corresponding less substituted ones.



1a	R^1 = Me	R^2 = Me	Sil = TBS	R^3 = ^{t}Bu
b	= Me	= H	= TBS	= ^{t}Bu
c	= H	= Me	=TBS	= ^{t}Bu
d	= H	= H	= TBS	= ^{t}Bu
e	= Me	= Me	= TBS	= bornyl
f	= H	= Me	= TBS	= bornyl
g	= H	= H	= TBS	= bornyl
h	= H	= Me	= TMS	= bornyl
i	= H	= Me	= TES	= ^{t}Bu
j	= H	= Me	= TBS	= $CH_2{}^t$Bu
k	= H	= Me	= TBS	= Me



2a R^4 = ^{t}Bu
b = 2,4,6-$Me_3C_6H_2$
c = 4-$MeOC_6H_4$

When a similar competition is run employing *tert*-butyldimethylsilyl (TBS) enolates of *tert*-butyl esters, **1a**, **1c**, and **1d**, the preference is completely opposite from that of conventional less bulky ketene silyl acetals such as triethylsilyl (TES) enolates of ethyl esters.[4] The less sterically crowded products always predominate, suggesting that the electron-transfer process is unlikely (Scheme I). Apparently, incorporation of TBS and *tert*-butoxy groups dramatically changes the reactivity of the ketene silyl acetals. The PM_3 semiempirical molecular orbital calculations[7,8] demonstrate that introduction of these elec-

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(2) Oare, D. A.; Heathcock, C. H. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1991; Vol. 20, p 87.

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