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Selective Dimethyldioxirane Oxidation of Bile Acid Methyl Esters

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Abstract: DMDO oxidation of the hydroxy groups of bile acid methyl esters establishes the positional order of reactivity as 3~7 > 6 > 12 and supports a mechanism involving C-H oxygen insertion through a planar intramolecularly hydrogen bonded transition state.

Dioxiranes are now well established oxidants which show selectivity dependent upon substrate and reaction conditions.[1,2] Although the dioxirane-mediated oxidations of secondary alcohols are well known[3-6] and selectivity for secondary versus primary alcohols has been established,[7] little has been reported on the selectivity of oxidations of secondary polyhydric alcohols. The selective oxidation of polyhydroxy steroids with a variety of oxidising agents has been extensively studied[8] and the use of Ag_2CO_3-Celite has found particular applications[9] in the oxidation of bile acid methyl esters. We report here an investigation of dimethyldioxirane (DMDO) oxidation of bile acid methyl esters which complements our earlier mechanistic study[4] of the DMDO oxidation of cholestanols and provides further insight into the mechanism of DMDO oxidations of alcohols.

The oxidations of esters **1-4** were carried out at 0-5°C in acetone using one or two equivalents of DMDO. After approximately 16h, during which the reaction mixtures were allowed to warm to room temperature, evaporation and column chromatography afforded the products (Table), all of which are known compounds, and were identified by their ^{1}H nmr spectra.

As can be seen from the Table, oxidation occurs readily at positions 3 and 7, relatively slowly at position 6 and not at all at position 12. It is presumed that the reactions take place *via* the *gem*-diol resulting from insertion of oxygen into the C-H bond.[3,4] Recently reported[10] intramolecular dioxirane mediated oxygen insertions into C-H bonds of alkyl groups are best explained by a spiro (Figure 1a) rather than a planar ("butterfly" type) transition state (Figure 1b or 1c) and calculations[11,12] for hydrocarbon DMDO mediated C-H oxygen insertions support a concerted process involving a form of polarised spiro transition state which may approach planarity depending on the substrate (O-C-O-H dihedral angle $\leq 167°$ and O-O-C angle ~160-180°). It appears that the most stable arrangement is arrived by rotation of the DMDO around the O-O-CH axis relative to the HCR^1 plane thereby minimising steric crowding. The transition states described in Figure 1 all involve the electrophilic oxygen approaching in the CHR^1 plane[11,12] but owing to the presence of the OH

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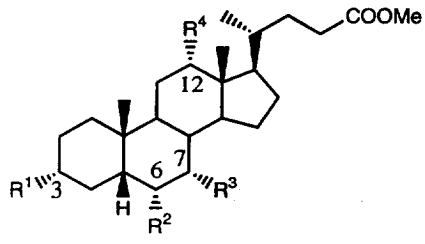
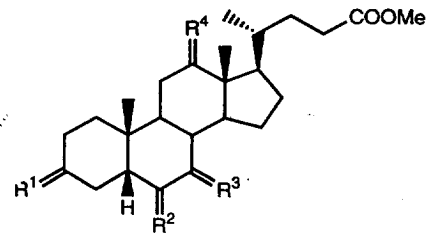




1	$R^1 = R^3 = R^4 = OH;\ R^2 = H$	**5**	$R^1 = O;\ R^2 = H_2;\ R^3 = R^4 = \alpha$ - OH, H
2	$R^1 = R^4 = OH;\ R^2 = R^3 = H$	**6**	$R^1 = R^4 = \alpha$ - OH, H; $R^2 = H_2;\ R^3 = O$
3	$R^1 = R^3 = OH;\ R^2 = R^4 = H$	**7**	$R^1 = R^3 = O;\ R^2 = H_2;\ R^4 = \alpha$ - OH, H
4	$R^1 = R^2 = OH;\ R^3 = R^4 = H$	**8**	$R^1 = O;\ R^2 = R^3 = H_2;\ R^4 = \alpha$ - OH, H
		9	$R^1 = O;\ R^2 = R^4 = H_2;\ R^3 = \alpha$ - OH, H
		10	$R^1 = \alpha$ - OH, H; $R^2 = R^4 = H_2;\ R^3 = O$
		11	$R^1 = R^3 = O;\ R^2 = R^4 = H_2$
		12	$R^1 = O;\ R^2 = \alpha$ - OH, H; $R^3 = R^4 = H_2$
		13	$R^1 = R^2 = O;\ R^3 = R^4 = H_2$

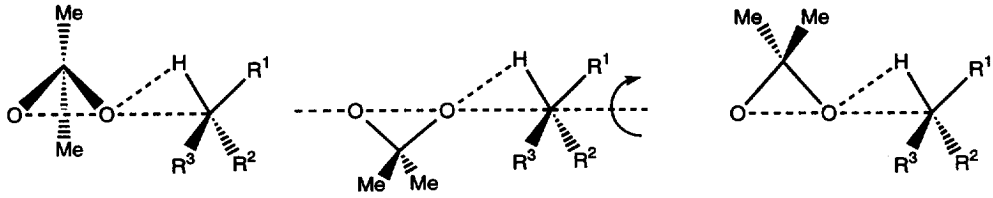
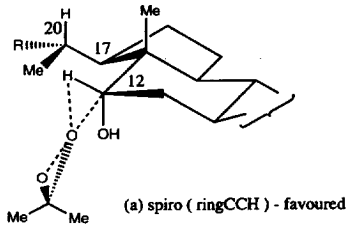
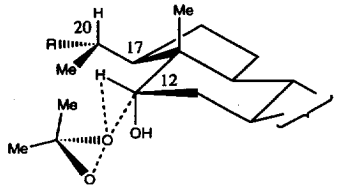


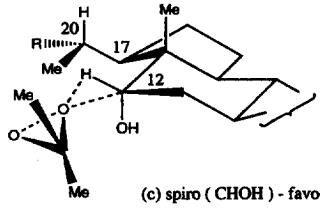
Figure 1



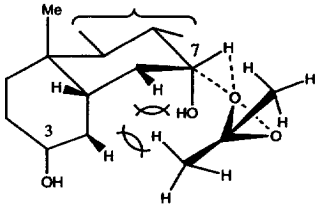
(a) spiro (ringCCH) - favoured



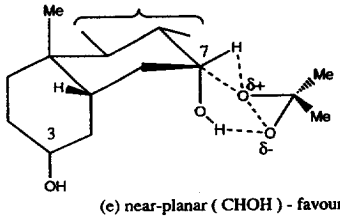
(b) near-planar (ringCCH) - favoured



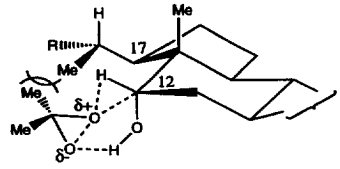
(c) spiro (CHOH) - favoured



(d) spiro (CHOH) - disfavoured



(e) near-planar (CHOH) - favoured



(f) near-planar (CHOH) - disfavoured

Figure 2

group and the possibility of significant hydrogen bonding, approach in the CHOH plane has also been considered.[21]

TABLE. PRODUCTS OF OXIDATION OF BILE ACID METHYL ESTERS USING DMDO

	Isolated yields %			
Methyl cholate 1	**3-oxo-7α,12α-dihydroxy 5**[9]	**7-oxo-3α,12α-dihydroxy 6**[16]	**3,7-dioxo-12α-hydroxy 7**[16]	
1 equ DMDO	26	21	25	
2 equ DMDO	9	6	61	
Methyl deoxycholate 2	**3-oxo-12α-hydroxy 8**[9]	**starting material 2**		
1 equ DMDO	59	25		
2 equ DMDO	75	-		
methyl chenodeoxycholate 3	**3-oxo-7α-hydroxy 9**[9]	**7-oxo-3α-hydroxy 10**[17]	**3,7-dioxo 11**[18]	**starting material 3**
1 equ DMDO	36	25	14	18
2 equ DMDO	-	-	91	-
methyl hyodeoxycholate 4	**3-oxo-6α-hydroxy 12**[19]	**3,6-dioxo 13**[20]		
1 equ DMDO	78	8		
2 equ DMDO	69	18		

Crucially, oxidation at C12 would be expected to be similar to that at C7 and the other positions if a spiro transition state or near-planar transition state is involved and approach is in the ring C-CH plane (Figure 2a/b).[21] Likewise for approach in the CHOH plane a spiro transition state would be relatively unhindered at C12 (Figure 2c). However, for a similar approach a spiro transition state would not satisfactorily explain the observations reported here since, in particular, oxidation of the 7-hydroxy group would be expected to be strongly inhibited by steric interactions between the DMDO methyl groups and either the 4β, 6α - or the 15α - hydrogen atoms (Figure 2d). However, an approximately planar and polarised transition state in which there is intramolecular hydrogen bonding to the second oxygen of the DMDO[4] may more readily be accommodated (Figure 2e). Furthermore, in such a transition state (Figure 2f), reaction at position 12 would be severely inhibited by steric interaction between the methyl groups of DMDO and the 20-methyl group in the side chain.[13] Also, the relatively slow reaction at position 6 may be explained by some steric repulsion between the incoming DMDO and the 10-methyl group particularly if the axial 6β-H to oxygen bond is almost completely formed as suggested by calculation.[11,12]

Hydrogen bonding is recognised as having an important influence in dioxirane reactions in general[1,2,14] and intramolecular hydrogen bonding has more particularly been observed to be influential in DMDO mediated C-H oxygen insertion reactions.[15] If, as suggested, intramolecular hydrogen bonding facilitates the oxidation of secondary alcohols, it would be expected that the use of a hydrogen bonding solvent would inhibit the oxidation by disruption of the intramolecular hydrogen bond.[22] This prediction was confirmed by

the observation that the oxidation of methyl deoxycholate to the ketone **8** in methanol: acetone (44:56), as determined by ^{1}H nmr spectroscopy, was reduced from 63 to 30% and in chloroform: acetone (44:56) to 44%. In the proposed transition state (e.g. Figure 2e), it is likely that C-O-O is not linear in order to accommodate a sensible hydrogen bonding distance between the OH and the dioxirane second oxygen. A non-linear arrangement is indicated for some of the calculated transition states for dioxirane mediated CH insertions[11,12] and, in particular, for that proposed for reactions assisted by intramolecular hydrogen bonding.[15]

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REFERENCES

1. Adam, W; Smerze, A.K. *Bull. Soc. Chim. Belg.* **1996**, *105*, 581-599.
2. Curci, R.; Dinoi, A.; Rubino, M.F. *Pure Appl. Chem.* **1995**, *67*, 811-822.
3. Mello, R.; Cassidei, L.; Fiorentino, M.; Fusco, C.; Hümmer, W.; Jäger, V.; Curci, R. *J. Am. Chem. Soc.* **1991**, *113*, 2205-2208.
4. Marples, B.A.; Muxworthy, J.P.; Baggaley, K.H. *Tetrahedron Lett.* **1991**, *32*, 533-536.
5. D'Accolti, L.; Detomaso, A; Fusco, C.; Rosa, A.; Curci, R. *J. Org. Chem.* **1993**, *58*, 3600-3601.
6. Curci, R.; D'Accolti, L.; Detomaso, A.; Fusco, C.; Takeuchi, K.; Ohga, Y.; Eaton, P.E.; Yip, Y.C. *Tetrahedron Lett.* **1993**, *34*, 4559-4562.
7. Bovicelli P.; Lupattelli, P.; Sanetti, A.; Mincione, E. *Tetrahedron Lett.* **1994**, *35*, 8477-8490.
8. Neustaedter, P.J., In *Steroid Reactions An Outline for Organic Chemists*; Djerassi C., Ed.; Holden Day, Inc. : San Francisco, 1993; Chapter 2, pp 89-154.
9. Tserng, K.-Y. *J. Lipid Res.* **1978**, *19*, 501-504.
10. Yang, D.; Wong, M.-K.;Wang, X.-C.; Tang, Y.-C. *J. Am. Chem. Soc.* **1998**, *120*, 6611-6612.
11. Du, X.; Houk, K.N. *J. Org. Chem.* **1998**, *83*, 6480-6483.
12. Glukhovtsev, M.N.; Canepa, C.; Bach, R.D. *J. Am. Chem. Soc.* **1998**, *120*, 10528-10533.
13. Atkinson, K.F.; Blickenstaff, R.T. *Steroids* **1974**, *23*, 895-908.
14. Buxton, P.C., Ennis, J.N.; Marples, B.A., Waddington, V.L.; Boehlow, T.R. *J. Chem. Soc. Perkin, Trans. 2* **1998**, 265-268.
15. Murray, R.W.; Gu, H. *J. Phys. Org. Chem.* **1996**, *9*, 751-758.
16. Mitra, M.N.; Elliott, W.H. *J. Org. Chem.* **1968**, *33*, 2814-2818.
17. Hauser, E.; Baumgartner, E.; Meyer, K. *Helv. Chim. Acta* **1960**, *43*, 1595-1600.
18. Mappus, E.; Cuilleron, Cl.Y. *Steroids* **1979**, *33*, 693-718.
19. Justoni, R.; Pessina, R. *Farmaco Ed. sci.* **1953**, *8*, 332-341.
20. Windaus, A.; Bohne, A. *Liebigs Ann.* **1923**, *433*, 278-287.
21. Bach, R.D.; Andrés, J.L.; Su, M.-D.; McDouall, J.J.W. *J. Am. Chem. Soc.* **1993**, *115*, 5768-5775.
22. In the DMDO epoxidation of cyclohex-2-en-1-ol the level of the competing oxidation to cyclohex-2-en-1-one is reduced in hydrogen bonding solvents; see Murray, R.W.; Singh, M.; Williams, B.L.; Moncrieff, H.M. *Tetrahedron Lett.* **1995**, *36*, 2437-2440.