An Examination of the Extent of Diastereofacial Selection in the Reactions of a Chiral Nitrile Oxide with Achiral Alkenes: a Route to β-Hydroxy Carboxylic Acids

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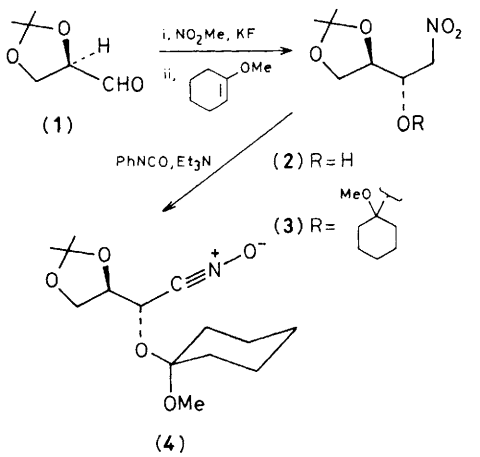
A new synthesis of optically active β-hydroxy carboxylic acids has been developed which is based on the (modest) diastereoselective addition of the chiral nitrile oxide (**4**) to 1,2-disubstituted alkenes.

We have been concerned recently with the extent of diastereofacial selection that might be achieved in both inter- and intra-molecular nitrile oxide cycloaddition (NOC) reactions.[1] While we have reported in part on such selection in the addition of achiral nitrile oxides to chiral olefins,[2] we now report on diastereoselective reactions of chiral nitrile oxides with achiral alkenes. Only a few examples of this use of chiral nitrile oxides have been recorded.[3]

We thought that the diastereoselectivity in these reactions might prove useful in the synthesis of optically active β-hydroxy acids.[4] We thus used a nitrile oxide derived from a chiral nitroethanol, for we had previously used the tetrahydropyranyl ether derivative of 2-nitroethanol in the *cis*-carboxyhydroxylation of various olefins.[5] The readily available aldehyde (**1**) was used to prepare the optically active nitroethanol (**2**) *via* the Henry reaction. While the stereoselectivity of this addition reaction was only moderate (80 : 20), the major isomer of the product could be separated readily from the minor one by fractional crystallization. A detailed ^{1}H n.m.r. analysis showed that the major isomer had the structure (**2**)† with stereochemistry that corresponds to addition *via* a Felkin–Anh type transition state.[6] The hydroxy group of (**2**) was protected, as its 1-methoxycyclohexyl derivative to give the key reagent (**3**). The reaction sequence in Scheme 1 was chosen so that the aldehyde (**1**) could be recycled from the β-hydroxy acid forming stage.

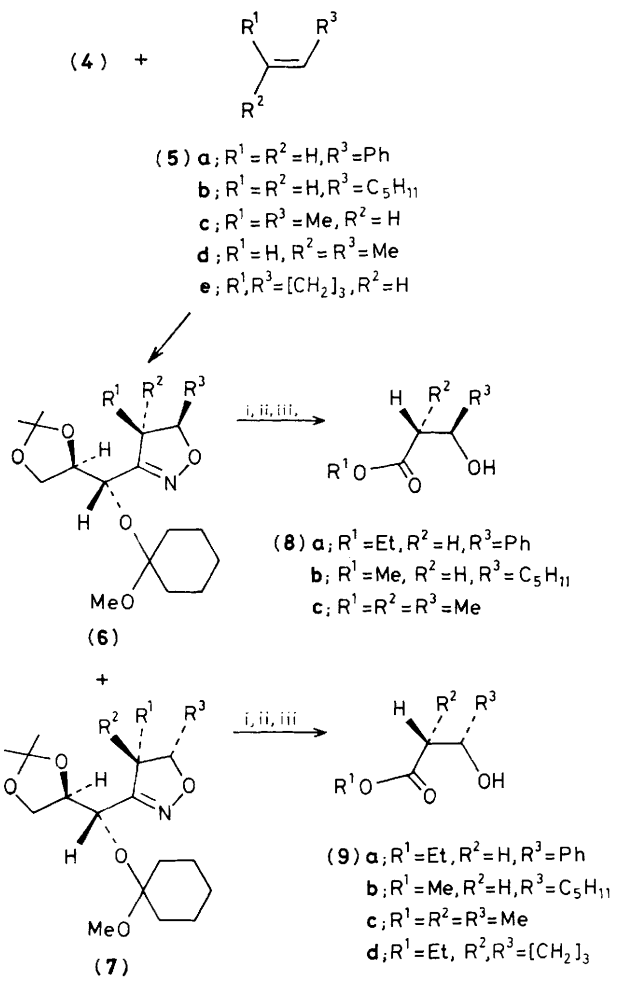


Scheme 1

The nitrile oxide (**4**) was generated *in situ* by treatment of (**3**) with phenyl isocyanate and triethylamine and then trapped in good yields (50—90%) by the five alkenes shown in Table 1.‡ Not unexpectedly, *no* diastereoselection was found for either styrene (**5a**) or hept-1-ene (**5b**). This is a consequence of the

† Compound (**2**) has the following physical and spectral properties: m.p. 58—59.5 °C; 300 MHz ^{1}H n.m.r. ($CDCl_3$) δ 4.70 (dd, 1 H, *J* 14, 2 Hz), 4.46 (dd, 1 H, *J* 14, 9 Hz), 4.15—4.28 (m, 1 H), 4.14 (ddd, 1 H, *J* 8, 8, 2.5 Hz), 4.02 (dd, 1 H, *J* 10, 2.5 Hz), 4.00 (dd, 1 H, *J* 10, 8 Hz), 2.96 (br. d, 1 H, *J* 5 Hz), 1.43 (s, 3 H), 1.34 (s, 3 H); mass spectrum (70 eV) *m/z* 176, 158, 115, 101 (base).

‡ The major isomer (**7**, $R^1 = R^3 = Me$, $R^2 = H$) from the reaction of (**4**) with *cis*-but-2-ene has the following spectral properties: i.r. (thin film) 1618 cm^{-1}; 300 MHz ^{1}H n.m.r. ($CDCl_3$) δ 4.65 (d, 1 H, *J* 5.5 Hz), 4.59 (dq, 1 H, *J* 9, 6.5 Hz), 4.33 (ddd, 1 H, *J* 6.5, 6.5, 5.5 Hz), 4.11 (dd, 1 H, *J* 8.5, 6.5 Hz), 3.91 (dd, 1 H, *J* 8.5, 6.5 Hz), 3.32 (dq, 1 H, *J* 9, 7.5 Hz), 3.19 (s, 3 H), 1.40 (s, 3 H), 1.35 (s, 3 H), 1.30 (d, 3 H, *J* 6.5 Hz), 1.14 (d, 3 H, *J* 7.5 Hz); mass spectrum (70 eV) *m/z* 341, 326, 229, 219, 212, 154, 129 (base), 113, 101.



Scheme 2. i, H_2/Raney Ni–$AlCl_3$–MeOH–H_2O; ii, $NaIO_4$, $NaHCO_3$; iii, (CH_2N_2 or $MeCHN_2$).

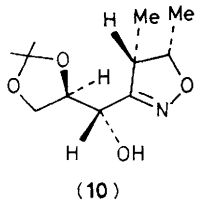
Table 1

Alkene (5)	Product ratio (6):(7) (^{1}H n.m.r.)	β-Hydroxy ester	$[\alpha]_D^{24}$ (c, $CHCl_3$)	Lit. $[\alpha]_D^t$/°
a	1:1	(8a)	−50.4° (0.96)	−54.9[a]
		(9a)	+49.9° (1.23)	+53.2[a]
b	1:1	(8b)	−24.6° (0.33)	−18.4[b]
		(9b)	+21.8° (0.92)	+24[b]
c	1:2.9	(9c)	+3.8° (0.71)	−11.39[c]
				−4.04(2S,3R)[c]
d	1.6:1	(8c)	−28.3° (0.42)	−34.72[c]
				+32.51(2S,3R)[c]
e	1:2.4	(9d)	+13.9° (0.4)	+14.1[d]

[a] For (**8a**), t = 22 °C (c 3.5, $CHCl_3$); (**9a**), t = 22 °C (c 3.4, $CHCl_3$); S. G. Cohen and S. Y. Weinstein, *J. Am. Chem. Soc.*, 1964, **86**, 725. [b] For (**9b**), $CHCl_3$; (**8b**), (c 1, $CHCl_3$); R. V. Lemieus and J. Giguere, *Can. J. Chem.*, 1951, **29**, 678. The laevorotatory compound was prepared by phytochemical reduction and probably is not optically pure. [c] For (**9c**), t = 20 °C (neat); (2*S*,3*R*), (c 0.5, $CHCl_3$); for (**8c**), t = 20 °C (neat); (2*S*,3*R*), (c 0.5, $CHCl_3$); A. Tai and M. Imaida, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 1114. [d] For (**9d**), t = 20 °C (c 1.7, $CHCl_3$); B. S. Deol, D. D. Ridley, and G. W. Simpson, *Aust. J. Chem.*, 1976, **29**, 2459.

developing asymmetric centre being quite remote from the existing asymmetric centre. The diastereoisomeric products were, however, easily separated by gravity column chromatography after removal of the 1-methoxycyclohexyl protecting group. Hydrogenolysis of the isoxazoline ring (70—93%) and sodium periodate cleavage of the resulting dihydroxyketone (50—77%) gave the optically pure β-hydroxy acids (Scheme 2). The optical rotations of their esters are compared with the literature values in Table 1.

With the 1,2-disubstituted olefins, *cis*- and *trans*-but-2-ene (**5c**) and (**5d**) respectively and cyclopentene (**5e**), some diastereoselection was observed (Table 1). Formation of a new chiral centre close to the original chiral centre could explain the diastereoselection in these cases. To ascertain the nature of the cycloaddition step, it was necessary to define the stereochemistry of the major isoxazoline generated in each case which could again be done by converting the isoxazolines into their β-hydroxy acids. Hydroxy group deprotection and isoxazoline ring cleavage were effected in a single step by treatment with Raney nickel–$AlCl_3$–MeOH–H_2O. Additionally, to support the stereochemical assignments, and particularly, that of the stereocentre generated in the Henry reaction, an *X*-ray analysis was carried out on the alcohol (**10**) formed by removing the 1-methoxycyclohexyl group from the 'major' NOC product of (**4**) with *cis*-but-2-ene.§ This compound was transformed into the (+)-β-hydroxy ester, which by literature precedent was given the 2*R*,3*S* stereochemistry. The *X*-ray structure in Figure 1 (ref. 9) fully supported this assignment,



(**10**)

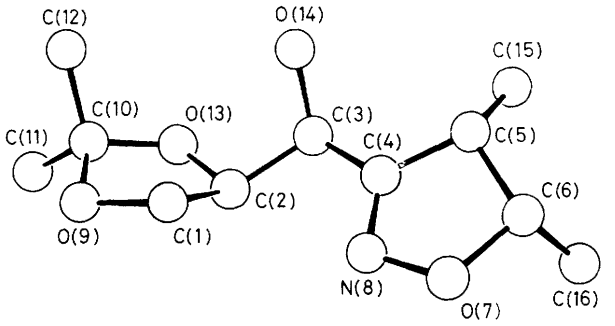


Figure 1. The *X*-ray structure of (**10**) without the hydrogen atoms which shows the absolute stereochemistry.

§ Suitable crystals of (**10**) for a single crystal *X*-ray analysis formed from ether–hexane mixtures. *Crystal data:* orthorhombic, space group $P2_12_12_1$, a = 7.015(1), b = 8.765(1), c = 19.742(4) Å, Z = 4, D_c = 1.256 g cm^{-3}. Of the 1004 unique reflections on the diffractometer with $2\theta \leqslant 114°$ using Cu-K_α radiation, 915 were treated as observed [$I \geqslant 3\sigma(I)$]. The structure was solved by routine methods (ref. 7) and refined using full matrix least-squares (ref. 8) with anisotropic temperature parameters for the non-hydrogen atoms and fixed isotropic temperature parameters for the hydrogen atoms. The final unweighted R factor was 0.05. The configurations of the four stereochemical centres in (**10**) are 2-*R*, 3-*S*, 5-*S*, and 6-*S*. The ketal ring has a half-chair conformation while the isoxazoline ring has an envelope conformation. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Rd., Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

as well as revealing the correctness of our assignment of stereochemistry in the Henry reaction.

The conversions of the *trans*-but-2-ene and the cyclopentene cycloadducts into their β-hydroxy acid esters showed that the sense of the additions of the three alkenes (**5c**—**e**) to (**4**) was the same. The C-4 centre of the major isoxazoline assumes the *R* configuration.

While the diastereoselection in the reactions discussed is not overwhelming, we do nonetheless believe that these syntheses of β-hydroxy acids may prove advantageous as the manipulations required are quite simple.

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