Pergamon

Tetrahedron Letters, Vol. 37, No. 19, pp. 3407-3410, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00558-8

On the Dihydroxylation of Cyclic Allylic Alcohols

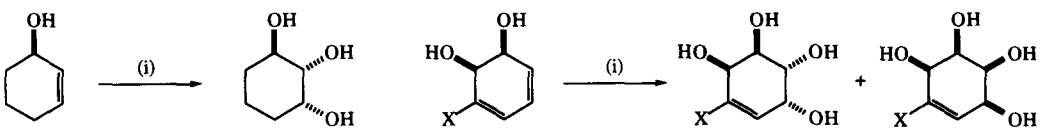
Timothy J. Donohoe,* Rina Garg and Peter R. Moore

Department of Chemistry, The University of Manchester, Oxford Road, Manchester, M13 9PL, U. K.

Abstract: The preparation and dihydroxylation (OsO_4) of a series of conformationally constrained allylic alcohols is described. By using dichloromethane as solvent, the selectivity that favours the anti triol is substantially reduced by hydrogen-bonding effects. This principle is applied to the stereoselective synthesis of syn tetraols from the oxidation of (1S,2S)-1,2-dihydroxy-3-bromo-3,5-cyclohexadiene.

The transformation of an alkene into a vicinal diol under the action of osmium tetraoxide is a particularly mild and reliable reaction that has found use in numerous organic syntheses.[1] Moreover, the stereospecific nature of the reaction and the development of oxidising systems that are capable of imposing absolute stereochemistry onto the diol products further augment the value of such a reaction.[1]

It has been shown that stereogenic centres close to an alkene can affect the diastereoselectivity of a subsequent dihydroxylation step: Kishi and co-workers reported that the oxidation of allylic alcohols (both cyclic and acyclic) occurs preferentially from the face of the olefin that is *opposite* to the hydroxyl group (*e.g.* **1**→**2**, **Scheme 1**).[2] However, this rule does not apply to all cyclic allylic alcohols and (for example) Carless and co-workers have shown that the dihydroxylation of 1,2-dihydroxy-3,5-cyclohexadienes proceeds with little or no facial selectivity (*e.g.* **3** and **6**, **Scheme 1**).[3] The value that stereoselective dihydroxylation of cyclic allylic alcohols holds for synthesis can be in no doubt, and is demonstrated by the large number of naturally occurring compounds that are accessible by such a reaction (*e.g* inositols, conduritols *etc.*).[4]



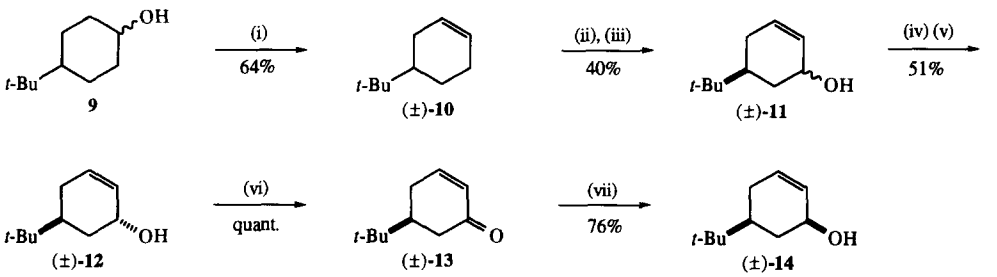
3 X=H
6 X=Br

4 X=H 71:29 5 X=H
7 X=Br 53:47 8 X=Br

Scheme 1: Reagents: (i) OsO_4, NMO, acetone/water.

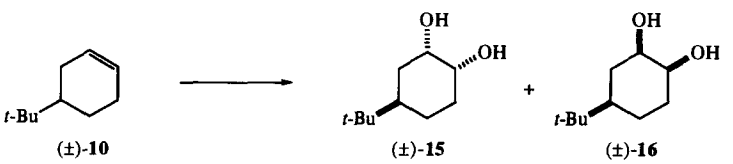
We were intrigued by the factors behind the diastereoselective reactions outlined above, and this prompted an investigation of the oxidation of conformationally locked cyclohexenols in order to study the relationship between the orientation of the hydroxyl group and the facial selectivity of subsequent dihydroxylation reactions.

Three alkenes (**10**, **12** and **14**) were prepared as outlined in **Scheme 2**, starting from commercially available *t*-butylcyclohexanol (**9**, **Scheme 2**).[5] Noteworthy steps are the regioselective bromination of *t*-butylcyclohexene (**10**) with NBS and the fact that the *para*-nitrobenzoate derivative of the epimeric mixture of alcohols (**11**) can be crystallised to yield only the *trans* isomer. Reduction of enone **13** proceeds with good regio- and stereoselectivity (complete 1,2- addition and 97:3 diastereoselectivity).



Scheme 2: Reagents: (i) $KHSO_4$, Δ; (ii) NBS; (iii) (aq.) K_2CO_3; (iv) *p*-$NO_2C_6H_4COCl$ then crystallise; (v) (aq.) NaOH; (vi) CrO_3, H_2SO_4; (vii) $LiAlH_4$, Et_2O, -78°C.

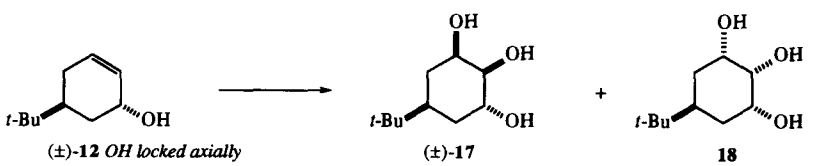
With the three derivatives in hand, the stereoselectivity of dihydroxylation available with osmium tetraoxide was examined. We chose to utilise two sets of conditions, namely catalytic osmium tetraoxide in acetone/water (4:1) with N-methylmorpholine-N-oxide (NMO) as a reoxidant, and stoichiometric osmium tetraoxide in dichloromethane.[6] A check on the neutrality of the *t*-butyl group as an influence on the facial selectivity of dihydroxylation was made by oxidising **10** (**Scheme 3**). With each oxidation reaction that was examined, alkene **10** exhibited only very modest diastereofacial selectivity; a 55:45 ratio of diols was obtained with the major compound assumed to be the *anti* diol **15**, although this was not proven.[7]



cat. OsO_4, NMO, acetone/water 57:43 (93%)
OsO_4, DCM 55:45 (46%)

Scheme 3

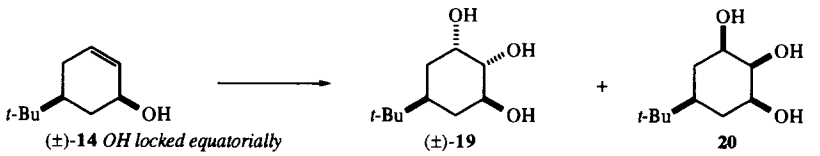
As far as oxidation of the axially-locked allylic alcohol **12** was concerned, it was clear that osmium tetraoxide displayed a penchant for the face of the alkene that was opposite to the alcohol functionality, in accordance with Kishi's rule (**Scheme 4**).[2]



cat. OsO_4, NMO, acetone/H_2O 94:6 (90%) *Reaction 1*
OsO_4, DCM 75:25 (97%) *Reaction 2*

Scheme 4

This effect holds true (although it is less pronounced) for the oxidation of isomer **14** under aqueous acetone conditions: however, under anhydrous conditions very poor *anti:syn* stereoselectivity was observed (**Scheme 5**).

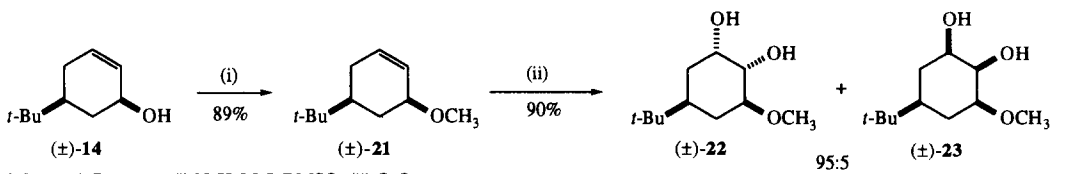


Scheme 5

Analysis of these results suggests that under aqueous acetone/NMO conditions the stereodirecting effect of an equatorial hydroxyl group is less than that of an axial hydroxyl- presumably this is a steric effect (compare Reaction 1 and 3).[8] However, the *anti* selectivity that is observed upon oxidation of these two allylic alcohols can be ameliorated by performing the oxidations in dichloromethane, (compare Reaction 1 with 2, and 3 with 4). We choose to assign this effect to hydrogen bonding between the allylic alcohol and the osmium tetraoxide.[9] Unfortunately, the magnitude of this directing effect is less than is commonly observed for other useful transformations such as epoxidation and cyclopropanation *etc.*,[10] and cannot overcome the (opposing) steric effect of the hydroxyl group. In keeping with other hydrogen-bonding directed reactions, the best opportunity for formation of the *syn* product comes *via* reaction of an equatorial allylic alcohol rather that an axial one, although the ratios are very close to each other (compare Reaction 2 with 4).

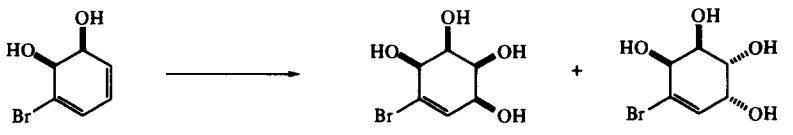
It should be noted that oxidation of **14** with stoichiometric quantities of osmium tetraoxide in dichloromethane gave only a 45% yield of the diastereoisomeric triols: this was subsequently shown to be a consequence of competing oxidation of the allylic alcohol to the enone **13**, which appeared to be resistant to further oxidation under these conditions. This observation may be taken as circumstantial evidence of some kind of association between the osmium tetraoxide and the allylic alcohol, prior to osmate ester formation.

Further evidence for the operation of hydrogen-bonding was sought in the oxidation of methyl ether **21** under anhydrous conditions (**Scheme 6**). In contrast to the low stereoselectivity observed in the oxidation of **14**, the ether (which cannot act as a hydrogen-bond donor) displayed remarkably high facial selectivity (95:5) with the major diol assigned as the *anti* isomer **22**.[8]



Scheme 6: Reagents: (i) NaH, MeI, DMSO; (ii) OsO_4, DCM.

In order to obtain a more accurate value of this directing effect, we decided to oxidise a substrate that showed little or no bias under standard dihydroxylation conditions (catalytic OsO_4, NMO, acetone/water). The most obvious candidate for oxidation was (1*S*, 2*S*)-1,2-dihydroxy-3-bromo-3,5-cyclohexadiene (**6**), as illustrated in **Scheme 1**.[3] Unfortunately, this substrate did not appear to be compatible with stoichiometric amounts of osmium tetraoxide and low yields of tetraols (<30%) were obtained. However, preliminary experiments have shown that the 'hydrogen-bonding' conditions may be duplicated using *catalytic* amounts of osmium tetraoxide in dichloromethane by using trimethylamine-N-oxide dihydrate as a reoxidant.[11] Therefore, when (1*S*, 2*S*)-**6** was reacted under these conditions, an 82:18 mixture of tetraols was obtained in 79% yield (**Scheme 7**). In this case the major product was the *syn* tetraol (1*S*, 2*S*, 3*S*, 4*S*)-**8**, and this contra-steric facial selectivity has clear implications for the efficient synthesis of natural products such as the conduritols.



(1*S*, 2*S*)-**6** (1*S*, 2*S*, 3*S*, 4*S*)-**8** (1*R*, 2*R*, 3*S*, 4*S*)-**7**

OsO_4 (cat), Me_3NO, DCM	82:18	(79%)	
OsO_4 (cat), NMO, acetone/water	47:53	(84%)	Ref 3

Scheme 7

We assume that the *syn* selectivity described above originates from hydrogen-bonding between the allylic hydroxyl group (and possibly the homo-allylic hydroxyl) and the oxidant. The use of catalytic amounts of osmium tetraoxide (1 mol %) to effect this transformation is significantly more practicable than procedures which involve stoichiometric quantities of transition metal.

In conclusion this study has outlined the facial selectivity and directing effect of cyclic allylic alcohols by utilising conformationally locked derivatives. The presence of hydrogen-bonding appears to influence the diastereoselectivity of oxidation, and this effect has been extended to the stereoselective synthesis of *syn* tetraols. Futher work is continuing in this area.

Acknowledgments: We would like to thank Rhône-Poulenc Rorer (TJD), Zeneca Pharmaceuticals (RG) and the Leverhulme Trust (PRM) for financial support. We would also like to express our gratitude to Johnson-Matthey Ltd. for a loan of osmium tetraoxide and to Dr G. H. Whitham for encouragement.

References

1. (i) Schroeder, M. *Chem. Rev.*, **1980**, *80*, 187; (ii) Lohray, B. B. *Tetrahedron: Asymmetry*, **1992**, *3*, 1317; (iii) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.*, **1994**, *94*, 2483.
2. Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.*, **1983**, *24*, 3943; Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.*, **1983**, *24*, 3947; Cha, J. K.; No-Soo Kin, *Chem. Rev.*, **1995**, *95*, 1761.
3. Carless, H. A. J.; Busia, K.; Dove, Y.; Malik, S. S. *J. Chem. Soc., Perkin Trans. 1*, **1993**, 2505; see also Burdisso, M.; Gandolfi, R.; Rastelli, A. *Tetrahedron Lett.*, **1991**, *32*, 2659.
4. For some representative examples see: Hudlicky, T.; Price, J. D.; Rulin, F.; Tsunoda, T. *J. Am. Chem. Soc.*, **1990**, *112*, 9439; Motherwell, W. B.; Williams, A. S. *Angew. Chem. Int. Ed. Engl.*, **1995**, *34*, 2031; Carless, H. A. J.; Malik, S. S. *J. Chem. Soc. Chem. Commun.*, **1995**, 2447; Blacker, A. J.; Booth, R. J.; Davies, G. M.; Sutherland, J. K. *J. Chem. Soc., Perkin Trans. 1*, **1995**, 2861.
5. (i) Ferrier, R. J.; Prasad, N. *J. Chem. Soc. C*, **1967**, 1417; (ii) Chamberlain, P.; Roberts, M. L.; Whitham, G. H. *J. Chem. Soc. B*, **1970**, 1374.
6. All oxidations were performed with 0.01M of alkene, at room temperature. The catalytic osmium tetraoxide conditions employed 5 mol% OsO_4 and 4 e.q NMO in acetone/water (4:1).
7. All new compounds have been fully characterised (^1H, ^{13}C nmr, MS, IR, elemental analysis or HRMS): triol **20** was characterised as its triacetate. Diastereoisomeric ratios were determined by ^1H nmr spectroscopy. Selected experimental data follow: **18** $\delta_H(D_2O)$ 4.04-4.07 (2H, m), 3.52 (1H, t, *J* 3.1), 1.85-2.00 (2H, m), 1.55-1.70 (1H, m), 1.20-1.24 (2H, m), 0.83 (9H, s); $\delta_C(D_2O)$ 74.38, 73.44, 36.05, 34.66, 33.49, 29.57 ppm. **20** (triacetate) $\delta_H(CDCl_3)$ 5.50-5.42 (1H, m), 4.78-4.90 (2H, m), 2.15 (3H, s), 2.00 (6H, s), 1.20-2.10 (5H, m), 0.91 (9H, s); $\delta_C(CDCl_3)$ 170.8, 170.5, 71.30, 69.83, 42.27, 32.82, 27.95, 26.79, 21.45 ppm.
8. It is possible that in these cases electrostatic repulsion between the electronegative oxygen and the osmium tetraoxide contributes to the stereoselectivity see Vedejs, E.; McClure, C. K. *J. Am. Chem. Soc.*, **1986**, *108*, 1094.
9. Kon. K; Isoe, S. *Tetrahedron Lett.*, **1980**, *21*, 3399; Smith III, A. B.; Boschelli, D. *J. Org. Chem.*, **1983**, *48*, 1217; see also- Ref 1(iii).
10. Rickborn, B.; Chan, J. H. -H. *J. Org. Chem.*, **1967**, *32*, 3576; Ref 5(ii); see also Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.*, **1993**, *93*, 1307.
11. Poli, G. *Tetrahedron Lett.*, **1989**, *30*, 7385. These conditions are 1 mol% OsO_4, 1.3 eq. $Et_3NO.2H_2O$ and 1 eq. alkene (0.05M) in dichloromethane.

(*Received in UK* 24 *February* 1996; *revised* 18 *March* 1996; *accepted* 22 *March* 1996)