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Unexpected Effect of Protecting Group and Solvent on the Stereoselectivity of *m*-CPBA Epoxidation of Diprotected *cis*-4,5-Dihydroxycyclohexenes

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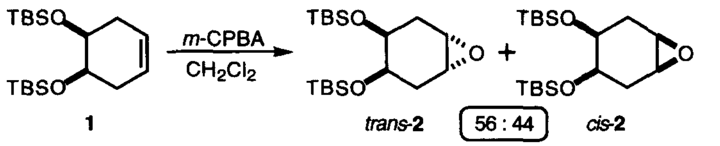
Abstract: The stereoselectivity of *m*-CPBA epoxidation of diprotected *cis*-4,5-dihydroxycyclohexenes has been studied as a function of protecting group, solvent and in one example, epoxidising reagent. Three different ways of obtaining high levels of *trans* diastereoselectivity have been uncovered. In addition, the results suggest that bulky silyl protecting groups (*eg* triethylsilyl and *tert*-butyldimethylsilyl) can, in CH_2Cl_2, behave as moderate *cis*-directors *via* hydrogen bonding to *m*-CPBA.

Keywords: epoxidation; diastereoselection; protecting groups; solvents and solvent effects

We have previously reported that epoxidation of cyclohexene **1** using *m*-CPBA in CH_2Cl_2 generated a 56:44 mixture of epoxides *trans*- and *cis*-**2**.[1] Initially, we were quite surprised at the poor level of stereoselectivity observed as we had anticipated an even greater preference for attack *trans* to the axial *tert*-butyldimethylsilyloxy group (Figure 1). In search of better stereoselectivity, the protecting groups in diprotected 4,5-dihydroxycylohexenes like **1**, the solvent and the epoxidising reagent were varied and we now wish to disclose our somewhat unexpected results.



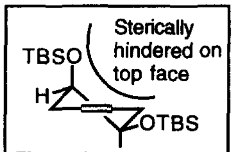


Figure 1

Since Henbest's pioneering work,[2] the stereoselectivity of epoxidation of cyclic *allylic* alcohols is well understood and has become an important method in organic synthesis.[3,4] For cyclohexenes, *free* allylic alcohols give *cis* selectivity *via* hydrogen bonding of a lone pair on one of the oxygens of *m*-CPBA to the hydroxyl group's proton. However, *protected* allylic alcohols generate *trans* epoxides preferentially due to steric hindrance.[2,5,6] It has also been reported that *protected* allylic alcohols can be involved in *cis* selective epoxidations if trifluoroperacetic acid[7] or perbenzimidic acid (Payne conditions)[8] are used; in these cases, hydrogen bonding must be from the oxygen lone pair on the protected hydroxyl group to the peracid's proton.

In contrast to allylic alcohols, there have only been sporadic reports on stereoselective epoxidations of six-membered cyclic homoallylic alcohols with examples of *cis* selectivity when *free homoallylic* alcohols

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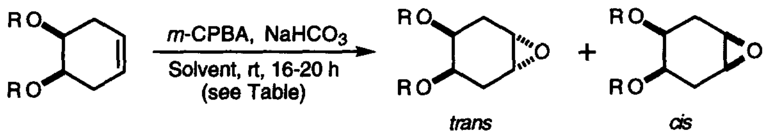
were employed.[9-11] However, no-one has investigated the effect of hydroxyl protecting group, solvent and epoxidising reagent on the stereoselectivity of such epoxidation reactions. Due to the arrangement of substituents in alkenes like **1** (see Figure 1), we were in an unprecedented[12] position of carrying out a detailed study into the effect of a protected *axial homoallylic* hydroxyl group on the stereoselectivity of epoxidation.

A range of diprotected cyclohexenes (see Table) were prepared from known[1,12] diol **3** using standard conditions.[13,14] Epoxidation reactions were initially carried out using $NaHCO_3$-buffered *m*-CPBA in CH_2Cl_2. The crude product mixtures were analysed by ^1H NMR spectroscopy to determine the *trans* : *cis* ratios and then purified by chromatography to give diastereomerically pure epoxides (see Table for full details). All of the relative stereochemistry of the epoxide products (except for **10**) were established by synthesis (*vide infra*).

Table: *Stereoselective Epoxidation of Diprotected cis-4,5-Dihydroxycyclohexenes*



Entry	R	SM[a]	Prod[b]	Product(s) (% yield)[c] from CH_2Cl_2 reactions	CH_2Cl_2[d] *trans* : *cis*	THF[e] *trans* : *cis*	% Completion[f] (THF reactions)
1	H	**3**	**4**	–	31 : 69	–	–
2	Me	**5**	**6**	*trans*-**6** (54); *cis*-**6** (22)	75 : 25	76 : 24	≥65%[g]
3	Bn	**7**	**8**	*trans*-**8** (22)	60 : 40	90 : 10	71%
4	–CMe₂–	**9**	**10**	*trans*-**10** (77)	90 : 10[h]	98 : 2	–[i]
5	Ac	**11**	**12**	*trans*-**12** (66)	85 : 15	98 : 2	40%[j]
6	Bz	**13**	**14**	–	80 : 20	–	–
7	TES	**15**	**16**	*trans*-**15** (38); *cis*-**15** (53)	39 : 61	88 : 12	90%[k]
8	TBS	**1**	**2**	*trans*-**2** (51); *cis*-**2** (41)	56 : 44	97 : 3	93%
9	TIPS	**17**	**18**	*trans*-**18** (77)	89 : 11	98 : 2	97%[j]
10	TBDPS	**19**	**20**	*trans*-**20** (92)	98 : 2	98 : 2	97%[j]

[a] Starting material; [b] Product; [c] Isolated yield after flash column chromatography; [d] CH_2Cl_2 as solvent, ratio determined by ^1H NMR spectroscopy on crude product; [e] THF as solvent, ratio determined by ^1H NMR spectroscopy on crude product; [f] Determined by ^1H NMR spectroscopy on crude product; [g] Unable to determine accurate % completion as starting alkene is volatile and is lost during work up; [h] Likely stereochemistry of epoxides *trans*- and *cis*-**10** is indicated but this has not been proven unequivocally; [i] Unable to determine % completion as starting alkene is volatile and is lost during work up; [j] After 44 h; [k] After 72 h.

The epoxidation of free diol **3** only generated an approximately 2:1 ratio of epoxides *cis*- and *trans*-**4** (Entry 1) indicating that the axial homoallylic hydroxyl group in **3** is not as good a *cis* director as the well documented[2-4] allylic alcohol. Surprisingly, a similarly *cis* selective epoxidation was observed with triethylsilyl protected alkene **15** (Entry 7); other sterically small alkyl and silyl ethers showed low levels of *trans* selectivity (Entries 2, 3 and 8). In contrast, with sterically more demanding silyl protecting groups (Entries 9 and 10), an isopropylidene acetal (Entry 4) and esters (Entries 5 and 6), considerably better *trans* selectivity was observed; epoxidation of di-*tert*-butyldiphenylsilyl protected alkene **19** generated only epoxide *trans*-**20** in an excellent and synthetically useful 92% isolated yield (Entry 10).

To explain these results, we wish to suggest that with certain protecting groups, the expected sterically controlled *trans* selectitivity is compromised by a degree of *cis* directed epoxidation; as shown in Figure 2, the oxygen lone pair of the axial protected hydroxyl group could hydrogen bond to *m*-CPBA.[15] Such a hydrogen bonding interaction would be minimised if the lone pair was unavailable (as in esters **11** and **13**, Entries 5 and 6) or if the protecting group was very large sterically (as in silyl ethers **17** and **19**, Entries 9 and 10). Alternatively, making the protecting group sterically smaller (as in alkyl ethers **5** and **7** or in silyl ethers **15** and **1**, Entries 2, 3, 7 and 8) leads to lower levels of *trans* selectivity.

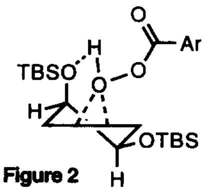
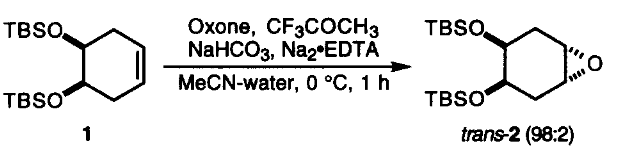
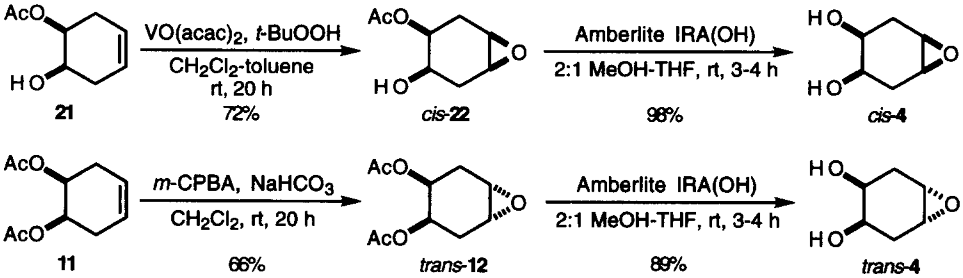


Figure 2

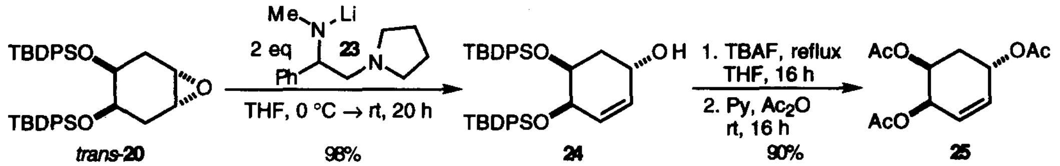


1 *trans*-**2** (98:2)

Next, we repeated most of the epoxidation reactions using THF as solvent as literature precedent[9,11] suggested that this solvent should interfere with intramolecular hydrogen bonding with *m*-CPBA. The results are shown in the Table for comparison. As expected, the epoxidations proceeded more sluggishly[16] and sometimes did not reach completion. However, in every case investigated (Entries 2-5 and 7-10), greater proportions of *trans* epoxides were produced. In some cases, the results were spectacular with only *trans* epoxides now being generated (Entries 4, 6, 8, 9 and 10). To further support our hydrogen bonding theory, we carried out epoxidation of alkene **1** using a reagent (*in situ* generated dioxirane[17]) that could not hydrogen bond to a silyl ether. Thus, alkene **1** was epoxidised using Yang's conditions[17] to give a quantitative yield of *trans*-**2** as a single diastereoisomer; this reaction clearly proceeds under complete steric control. Other examples of stereoselective epoxidations which compare *m*-CPBA and an *in situ* generated dioxirane are documented in the accompanying paper.[18]



The stereochemistry of all of the epoxides described in this paper has been established unequivocally. First of all, monoacetate **21** was subjected to a $VO(acac)_2$ directed *cis* epoxidation to give epoxide *cis*-**22** which on methanolysis produced epoxy diol *cis*-**4**. A different diastereomeric epoxy diol (*trans*-**4**) was obtained from diacetate alkene **11** (*m*-CPBA epoxidation then methanolysis) This is the first time that diasteromerically pure epoxy diols *cis*- and *trans*-**4** have been prepared. Finally, epoxy diol *trans*-**4** was diprotected to give *trans*-**20** and subsequent rearrangement[1] using lithium amide base *rac*-**23** gave allylic alcohol **24**. Removal of the silyl groups in **24** required refluxing TBAF and acetylation then gave triacetate **25** which was identical (^{1}H and ^{13}C NMR spectroscopy) to the same compound recently synthesised by Haines *et al.*[19] Epoxy diol *trans*-**20** has been converted into all of the diprotected epoxides in the Table (except for **10** and **12**) thus establishing their stereochemistry.



To summarise, we believe that the results of our epoxidation reactions indicate that sterically bulky silyl ethers can participate in hydrogen bonding with *m*-CPBA in CH_2Cl_2 provided the orientation of the silyl ether and the alkene are suitable (see Figure 2). Even the *tert*-butyldimethylsilyl protecting group appears to participate in some degree of hydrogen bonding. Knight has used a related hydrogen bond between a tri-*iso*-propyl silyl ether and a carboxylic acid to rationalise a stereoselective cyclisation reaction.[20] From a synthetic viewpoint, the observed *trans* stereoselectivity of epoxidation of cyclohexenes like **1** can be improved in three ways: (i) increasing the size or electronic properties of the protecting groups; (ii) changing the solvent to one which disrupts hydrogen bonding of reagent to substrate; or (iii) changing to a non-peracid based reagent.

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References and Notes

1. O'Brien, P.; Poumellec, P. *Tetrahedron Lett.* **1996**, *37*, 8057-8058; O'Brien, P.; Poumellec, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2435-2441.
2. Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc.* **1959**, 1958-1965.
3. Berti, G. *Top. Stereochem.* **1973**, *7*, 93-251.
4. Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307-1370.
5. Chavdarian, C. G.; Heathcock, C. H. *Synth. Commun.* **1976**, *6*, 277-280.
6. Sabol, J. S.; Cregge, R. J. *Tetrahedron Lett.* **1989**, *30*, 3377-3380.
7. McKittrick, B. A.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 4895-4898.
8. Bachmann, C.; Gesson, J-P.; Renoux, B.; Tranoy, I. *Tetrahedron Lett.* **1998**, *39*, 379-382.
9. Garside, P.; Halsall, T. G.; Hornby, G. M. *J. Chem. Soc., C,* **1969** 716-721.
10. Ye, D.; Fringuelli, F.; Piermatti, O.; Pizzo, F. *J. Org. Chem.*, **1997** *62*, 3748-3750; Christol, H.; Duval, D.; Solladie, G. *Bull. Soc. Chim. France* **1968** (2), 689-692; Armour, A. G.; Büchi, G.; Eschenmoser, A.; Storni, A. *Helv. Chim Acta* **1959**, *42*, 2233-2244.
11. For examples with five-membered rings, see: Asami, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1402-1408; Zurflüh, R.; Wall, E. N.; Siddall, J. B.; Edwards, J. A. *J. Am. Chem. Soc.* **1968**, *90*, 6224-6225.
12. Only the epoxidation of isopropylidene acetal **9** (see Entry 4 in the Table) has been reported previously: Krow, G. R.; Carmosin, R.; Mancuso, A. *Org. Prep. Proc. Int.* **1977**, *9*, 285-288.
13. Yields from diol **3**: **5** (92%); **7** (74%); **9** (86%); **11** (99%); **13** (94%); **15** (93%); **1** (97%); **17** (65%); **19** (94%). Compounds **5** and **9** are more volatile and were best purified by distillation; the remainder were purified by flash chromatography.
14. All novel compounds gave satisfactory microanalysis and/or high resolution mass spectrometry data.
15. The interaction shown in Figure 2 is our preferred one but other interactions cannot be ruled out.
16. Kavcic, R.; Plesnicar, B. *J. Org. Chem.* **1970**, *35*, 2033-2035.
17. Yang, D.; Wong, M-K.; Yip, Y-C. *J. Org. Chem.* **1995**, *60*, 3887-3889.
18. de Sousa, S. E.; O' Brien, P.; Pilgram, C. D.; Roder, D.; Towers, T. D. *Tetrahedron Lett.* **1999**, *40*, 391-392.
19. Haines, A. H.; King, A. S. H.; Knight, J. R.; Nguyen, V-A. *Tetrahedron Lett.* **1998**, *39*, 4393-4396.
20. Bedford, S. B.; Fenton, G.; Knight, D. W.; Shaw, D. E. *J. Chem. Soc., Pekin Trans. 1* **1996**, 1505-1509. For information on basicity of silyl ethers, see: Shambayati, S.; Blake, J. F.; Wierschke, S. G.; Jorgensen, W. L.; Schreiber, S. L., *J. Am. Chem. Soc.* **1990**, *112*, 697-703.