Stereochemistry of Epoxidation of Allylic and Homoallylic Cyclohexene Alcohols

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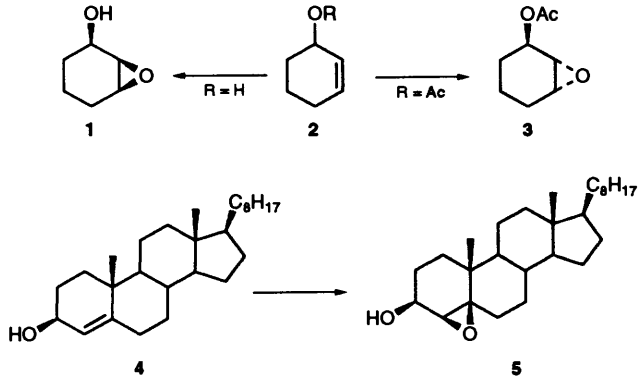
The reactivity of cyclohexene-type allylic alcohols towards epoxidation reagents (peroxy acids and Bu^tO_2H with transition metal catalysts) is largely dependent on the magnitude of steric hindrance in the substrate molecules. With unhindered [**2** (R = H)] or slightly hindered allylic alcohols (**4**, **8** and **12**) the reaction is dominated by the *syn*-stereodirecting effect of the hydroxy group which results in the exclusive or predominant formation of *cis*-epoxy alcohols. In contrast, this well established type of stereocontrol fails with sterically congested substrates (**23**, **26** and **27**), which give *trans*-epoxy alcohols on *m*-chloroperoxybenzoic acid treatment while the transition metal-catalysed oxidation with Bu^tO_2H affords conjugated ketones as the sole products. The latter reaction can serve as a mild procedure for the selective oxidation of hindered allylic alcohols to α,β-unsaturated ketones.

Epoxidation of cyclic alcohols, such as **2** (R = H) with peroxy acids in non-coordinating solvents is known to proceed in a *syn*-fashion[1] giving *cis*-epoxy alcohols (**1**; ≥10:1) as the major products (see Scheme 1).[2,3] By contrast, epoxidation of the corresponding esters [*e.g.* **2** (R = Ac)] proceeds either non-stereospecifically, or produces predominantly *trans*-epoxides (**3**; ≥4:1)[1] which clearly points to the steering effect of the hydroxy group in the former case (*via* a coordination of the reagent through a hydrogen bond).[1–5]

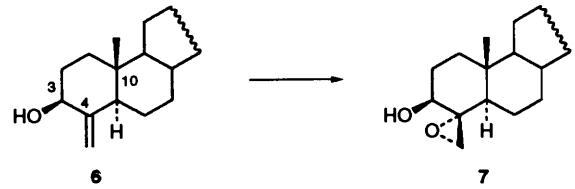
Henbest[1] pioneered this concept and showed that this control is strong enough to override the steric bias of the steroid skeleton and to drive the epoxidation of, *e.g.*, **4** to occur predominantly from the sterically more hindered β-side (see Scheme 1). Later on, epoxidation with *tert*-butyl hydroperoxide, catalysed by transition metals, was developed, using mainly V and Mo as the catalysts.[5–8] Sharpless[7,9] and others[5,6,8] soon demonstrated that the catalytic method often exhibits higher selectivity than the classical peroxy acids epoxidation.[5,10,11] These efforts culminated in the Sharpless–Katsuki asymmetric epoxidation,[12] with its extraordinary enantioselectivity and versatility.[13]



Scheme 1

However, a survey of the literature on epoxidation reveals that, occasionally, lower selectivity[5] or allylic oxidation have been encountered.[14] Thus, for instance, transition metal-catalysed oxidation of cyclooct-2-enol (with Bu^tO_2H) gives a substantial amount of the corresponding ketone as well as the expected epoxide and the products of its fission.[14b] Moreover, there are a few examples of the tendency for $Mo(CO)_6$-mediated oxidations to take on a sharply different diastereofacial course from that of *m*-chloroperoxybenzoic acid (MCPBA).[15] Reports by Robinson[16] and others,[17] and our own occasional observations of the absence of stereocontrol with an allylic hydroxy group (both in MCPBA and catalytic epoxidations) prompted us to carry out a systematic study on the influence of steric effects on the epoxidation of cyclic allylic alcohols.

Robinson *et al.*[16] have found that, although the allylic alcohol **6** seems to be an obvious candidate for a stereocontrolled *syn*-epoxidation, it is approached by MCPBA solely from the α-side to furnish the *trans*-epoxy alcohol **7** (see Scheme 2). Furthermore, Sharpless asymmetric epoxidation afforded the same product regardless of the absolute configuration of the catalyst.[16] The authors attributed this absence of *syn*-stereocontrol to steric effects that prevent the reagent from attacking the β-side of the skeleton.



Scheme 2

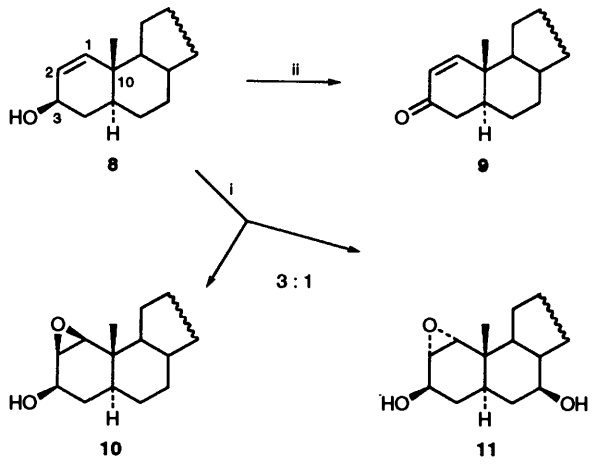
In this paper we report on limitations of the *syn*-stereocontrol in the epoxidation of cyclic allylic alcohols as inferred from the study of a set of the model steroid derivatives **4**, **6**, **8**, **12**, **16**, **20**, **23**, **26** and **27**.[18]

Results

Henbest[1] has shown that the allylic alcohol **4** gives mainly the β-epoxide **5** on reaction with peroxy acids.† We have now found that oxidation with Bu^tO_2H catalysed by vanadyl acetylacetonate [$(acac)_2VO$] affords the same β-epoxide **5** as the sole product (see Scheme 1).[19]

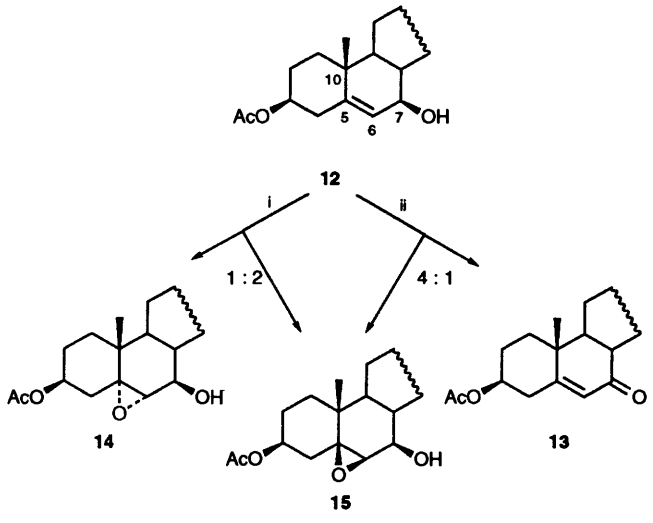
The 1,2-unsaturated alcohol **8** (itself a positional isomer of **4**) is known to react with peroxybenzoic acid in a less selective way, giving a 3:1 mixture of **10** and **11** (see Scheme 3).[20] We

† By contrast, the corresponding acetate gives predominantly the 4α,5α-epoxide on treatment with peroxy acids.[1] On the other hand, the *N*,*N*-dimethylcarbamate affords exclusively the 4β,5β-epoxide.[3c]



Scheme 3 *Reagents and conditions:* i, MCPBA, CH_2Cl_2, 0 °C; ii, Bu^tO_2H, $(acac)_2VO$ cat.

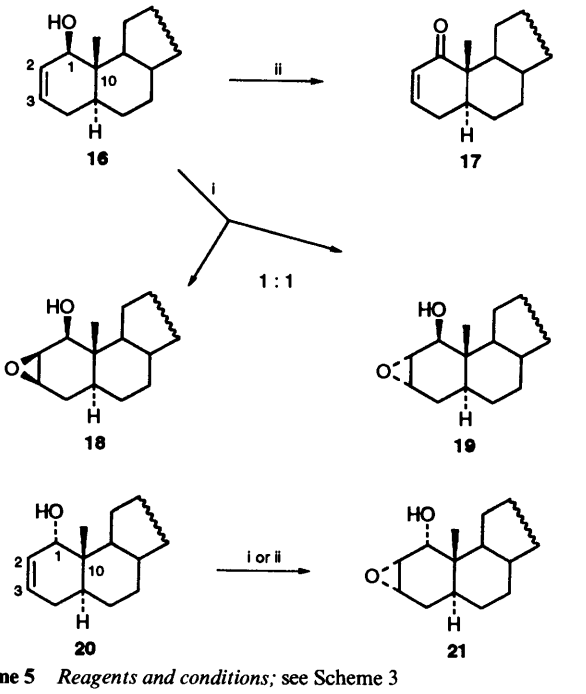
have now found that epoxidation using MCPBA proceeds with the same diastereofacial selectivity,*,† In contrast, the Bu^tO_2H–$(acac)_2VO$ oxidation resulted in clean formation of the α,β-unsaturated ketone **9**.[21] The 5,6-unsaturated alcohol **12** gave a 1 : 2 mixture of **14** and **15** on MCPBA treatment (see Scheme 4),*,[22] whereas the Bu^tO_2H–$(acac)_2VO$ oxidation afforded a mixture of ketone **13** and *cis*-epoxy alcohol **15** in a 1 : 4 ratio.



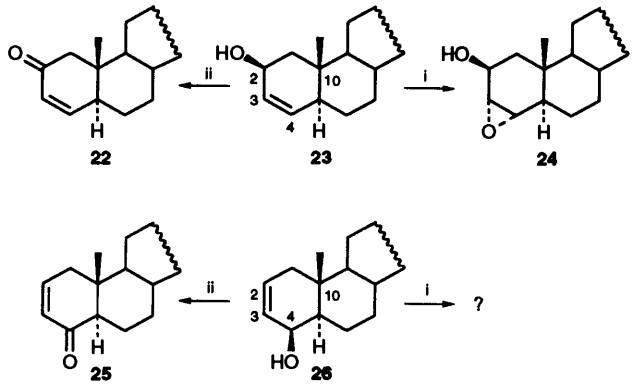
Scheme 4 *Reagents and conditions:* see Scheme 3

The MCPBA epoxidation of **16** is even less selective, giving a 1 : 1 mixture of *cis*- and *trans*-epoxy alcohols **18** and **19** (see Scheme 5);[23] the $(acac)_2VO$-catalysed oxidation has now been found to give solely the α,β-unsaturated ketone **17**. In contrast, epoxidation of the epimeric 1α-alcohol **20** either with MCPBA[19e] or with Bu^tO_2H–$(acac)_2VO$ furnished the *cis*-product **21** (> 20 : 1) in quantitative yield.*

The allylic alcohol **23** afforded exclusively the *trans*-epoxy alcohol **24** on reaction with MCPBA;‡,§ catalytic oxidation with Bu^tO_2H and $(acac)_2VO$ furnished ketone **22** as the only product (see Scheme 6).

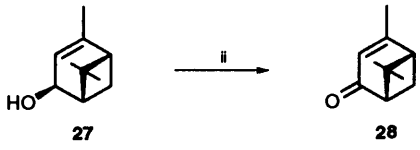


Scheme 5 *Reagents and conditions;* see Scheme 3



Scheme 6 *Reagents and conditions;* see Scheme 3

The allylic alcohol **26** is cleanly oxidized with Bu^tO_2H–$(acac)_2VO$ to ketone **25** (see Scheme 6) while the reaction with MCPBA is considerably slower than with other olefins and affords a mixture of polar compounds in which no epoxide could be identified.‡ Similarly, *cis*-verbenol **27** afforded verbenone **28** on the attempted catalytic epoxidation (see Scheme 7) whereas MCPBA furnished a mixture of polar compounds.



Scheme 7 *Reagents and conditions;* see Scheme 3

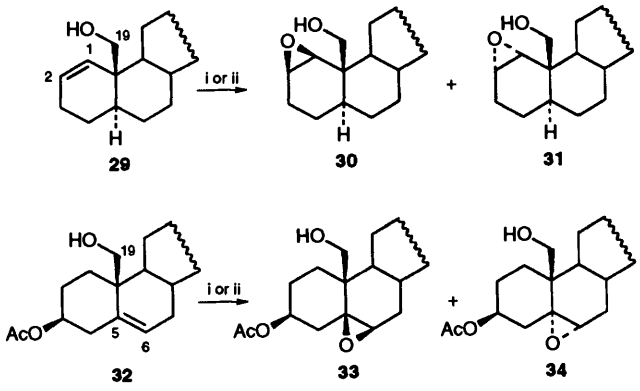
* The ratio of the products (*i.e. cis*/*trans*-epoxides or epoxide/ketone) was determined from the 200 MHz ^1H NMR spectra of the crude mixtures by integrating the oxirane or vinylic protons.

† The corresponding acetate[21] and *N*-benzylcarbamate[3c] are both attacked by MCPBA preferentially from the α-side.

‡ The corresponding *N*,*N*-dimethylcarbamate is also exclusively epoxidized with MCPBA from the α-face.[3c]

§ The configuration of **24** was established on the basis of its IR spectrum (namely the absence of an intramolecular hydrogen bond) and confirmed by NMR as follows. The coupling pattern of 3-H and 4-H in the ^1H NMR spectrum of **24** is identical with that of the corresponding carbamate (whose stereostructure was unequivocally determined by an independent synthesis[3c]) and dramatically different from the coupling pattern in the spectrum of the diastereoisomeric 3β,4β-epoxycarbamate.[3c]

Finally, both homoallylic alcohols **29** and **32** are known to undergo epoxidation with MCPBA predominantly from the more hindered β-side (see Scheme 8) affording mixtures of **30**



Scheme 8 *Reagents and conditions;* see Scheme 3

and **31** (7:1),*,[24] and **33** and **34** (5:1),†,[25] respectively. The Bu^tO_2H–$(acac)_2VO$ epoxidation gives the β-epoxides **30** and **33** as the sole products.

Other systems for catalytic epoxidation employing $Mo(CO)_6$ and $(Pr^iO)_4Ti$ exhibit a reactivity similar to that of $(acac)_2VO$. However, in accord with earlier observations,[6] the reaction rates have been found to be considerably lower in several instances so that no systematic study has been carried out with these systems.

Discussion

The failure of the hydroxy group to stereodirect epoxidation in some allylic alcohols can apparently be rationalized by steric effects, as suggested previously.[16] Molecular models reveal striking differences in the magnitude of the steric hindrance to the attack on the *syn*-face in our set of allylic alcohols **4**, **8**, **12**, **16**, **23**, **26** and **27**; partial structures of the representative compounds are shown in Fig. 1.‡ Thus, for instance, in **4**, there is relatively little steric shielding exercised by the 10β-Me group. As a result, coordination of the reagent to the hydroxy group can easily occur and the *cis*-epoxy alcohol **5** is formed with high selectivity, regardless of the reagent employed.§ Allylic alcohols **8** and **12** react less selectively. Although their structural pattern is similar to that of **4**, there are apparently subtle differences that are difficult to assess. For instance, one of the reasons for the preferential oxidation of **8** to **9** by means of Bu^tO_2H may be the lower nucleophilicity of the double bond, which, in this case, is disubstituted, as opposed to the trisubstituted one in **4**. On the other hand, the reactivity of **12** (with a trisubstituted double bond) more closely resembles that of **4**. In all three alcohols, the hydroxy group is pseudoequatorial, which should be favourable for the peroxy acid epoxidation[1,2,5,9] but unfavourable for the catalytic method.[5,9,26] However, while the A-ring of **4** can relatively easily assume another half-chair conformation with a pseudoaxial hydroxy group (which should be favourable for the catalytic epoxidation), similar flipping of **8** can only produce a

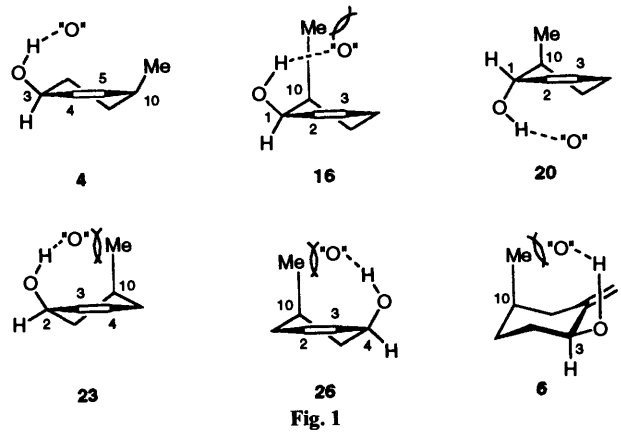


Fig. 1

boat form. Hence, attaining a conformation with a pseudoaxial hydroxyl is less likely in the latter instance. This difference can contribute to the distinct preference of **8** to yield enone rather than epoxide on the reaction with Bu^tO_2H–$(acac)_2VO$.

In the 2,3-unsaturated 1β-alcohol **16**, coordination of the reagent to the hydroxy group is partially impaired by the axial 10β-Me, which results in the formation of a 1:1 mixture of diastereoisomeric epoxides **18** and **19** on MCPBA treatment. Apparently, the steric shielding of the β-face is more serious here than, *e.g.*, in **4**.[23] The transition metal complex is probably too bulky to coordinate from the β-side so that the competing reaction producing ketone **17** is now entirely favoured.|| By contrast, α-attack on epimer **20** is free of any hindrance and yields solely the corresponding *cis*-epoxide **21** with both reagents.

Even higher steric hindrance, namely the 1,3-(axial–pseudo-axial) interaction, operates in the allylic alcohols **23** and **26**. This congestion apparently precludes the hydroxyl-directed approach of the reagent from the *syn*-face and, as a result, MCPBA gives *trans*-epoxides whereas Bu^tO_2H–$(acac)_2VO$ affords ketones.¶ Similar effects can account for the reported epoxidation of the steroidal derivative **6**[16] and for *cis*-verbenol **27**.**

The reactivity of the rigid, homoallylic alcohols **29** and **32** is of interest; here the hydroxy group protrudes above the π-system. The steric hindrance to attack on the 1,2- and 5,6-double bonds, respectively, in these compounds may be regarded similar to that in **8** and **12**, respectively, which is reasonably well reflected in the mixtures of α- and β-epoxides obtained from MCPBA epoxidation of both pairs of compounds.†† However, the Bu^tO_2H–$(acac)_2VO$ reagent, although bulkier, gives solely the *cis*-epoxides, since no other competing reaction (such as allylic oxidation) is possible for these structures.

The present analysis shows that with relatively non-hindered olefinic alcohols, epoxidation is, indeed, directed by the hydroxy group. However, increased steric shielding of the *syn*-face renders other competing pathways more favourable, namely the formation of a *trans*-epoxy alcohol with MCPBA or the oxidation to an enone for the catalytic reaction. When, in the catalytic reaction, formation of enones is not possible, as with the homoallylic alcohols **29** and **32**, the *cis*-epoxides are produced selectively.

* The corresponding acetate gives exclusively the 1α,2α-epoxide on reaction with MCPBA.[24]

† The corresponding benzoate gives a 10:1 mixture of 5α,6α- and 5β,6β-epoxides on treatment with monoperoxyphthalic acid.[25c]

‡ For the sake of brevity, the formulae in Fig. 1 are confined to show the peroxy acid epoxidation. Similar pictures can be considered for the catalytic method.

§ By contrast, the corresponding acetate gives predominantly the 4α,5α-epoxide on treatment with peroxy acids.[1] On the other hand, the *N*,*N*-dimethylcarbamate affords exclusively the 4β,5β-epoxide.[3c]

|| The catalytic epoxidation is further disfavoured by the pseudo-equatorial disposition of the hydroxy group. For discussion, see refs. 5 and 9.

¶ Since both **23** and **26** have a pseudoaxial hydroxy group, epoxidation should be favoured with Bu^tO_2H–V which, however, is not the case here.

** See also the epoxidation of *cis*-pinocarveol.[17e]

†† Primary homoallylic alcohols generally tend to give lower stereoselectivity.[25a]

It can be argued that the ease of the catalytic oxidation to a ketone stems from a stereoelectronic effect, *i.e.* that molecules with a better overlap of the allylic C–H with the π-system may favour allylic oxidation at the expense of epoxidation. However, this would be an oversimplification, since it would predict that, *e.g.* **4** (with a pseudoaxial allylic hydrogen), should be preferentially oxidized whereas **23** and **26** (with pseudoequatorial hydrogen) should give the corresponding *cis*-epoxides. Since the reverse is the case, the mutual orientation of the π-orbitals and the orbital of the allylic C–H bond in the starting materials cannot be solely responsible for the reaction outcome. A more likely explanation is that if the hydroxy-coordinated transition metal complex cannot effectively overlap with the orbitals of the double bond (due to steric congestion or to lower nucleophilicity of the double bond), it will, instead, abstract the allylic hydrogen, effecting oxidation to a ketone. The latter process is certainly assisted by the allylic double bond (note that non-allylic hydroxy groups are not oxidized). In summary, our data suggest that it is the steric hindrance to attack of the double bond, rather than the initial orientation of the allylic C–H, which plays the primary role in deciding which of the two reactions will be preferred.

Conclusions.—The reactivity of a range of allylic cyclohexenols toward the established epoxidation reagents [MCPBA and Bu^tO_2H–$(acac)_2VO$] clearly shows that the reaction course is heavily dependent on steric effects and that, in conflict with the general belief, it may often not give the expected *cis*-epoxide. Our results can be summarized as follows: (*a*) the *syn*-stereodirecting effect of an allylic hydroxy group does operate in sterically unhindered or slightly hindered allylic alcohols (such as **2** or **4**) which give *cis*-epoxy alcohols as the sole products regardless of the reagent employed [MCPBA or Bu^tO_2H–$(acac)_2VO$].* (*b*) Increased steric hindrance imposed by, *e.g.*, an axial alkyl group in a vicinal position to the hydroxy group (as in **16**) impairs the hydroxyl-directed *syn*-epoxidation to some extent. As a result, peroxy acids give diastereoisomeric mixtures of epoxy alcohols while the transition metal-catalysed reactions with Bu^tO_2H produce α,β-unsaturated ketones. (*c*) With more sterically crowded molecules having, *e.g.*, a 1,3-(axial–pseudoaxial) interaction of the allylic hydroxy and alkyl groups, the stereodirecting effect of the hydroxy group is entirely absent; while peroxy acids will approach exclusively from the less hindered *anti*-face, the transition metal-catalysed Bu^tO_2H oxidation will, again, lead to ketones and may even be used as a mild, high-yielding preparative method. On the other hand, with homoallylic alcohols, where enone formation is precluded by the structure, the catalytic epoxidation may exhibit much better *syn*-selectivity than peroxy acids in certain instances.

Experimental

M.p.s (uncorrected) were obtained on a Kofler block. Optical rotation was measured in $CHCl_3$ with an error of ±3°. The IR spectra were recorded on a Perkin-Elmer 580 spectrometer in CCl_4 solution. The ^1H NMR spectra were recorded on a Varian XL-200 or a Bruker AM 300 spectrometer in $CDCl_3$ solution at 25 °C; chemical shifts are given in ppm values relative to the signal of Me_4Si (0.00 ppm). Apparent coupling constants were obtained from the first-order analysis. Ether refers to diethyl ether. Standard work-up of an ethereal solution refers to washing the solution with water, 5% aqueous $KHCO_3$, 5% aqueous $Na_2S_2O_3$ and water, drying with Na_2SO_4 and evaporation of the solvent under reduced pressure. Light petroleum refers to the fraction boiling in the range 40–60 °C. The identity of samples prepared by different routes was checked by mixed m.p. determination, TLC, and NMR spectra.

General Procedure for Epoxidation with m-*Chloroperoxybenzoic Acid.*—The allylic alcohol (0.5 mmol) was dissolved in dichloromethane (5 cm^3) and treated with *m*-chloroperoxybenzoic acid (0.6 mmol) at 0 °C for 0.5–2 h (depending on the reactivity). The mixture was then diluted with dichloromethane and worked up. The crude product was chromatographed on a column of silica gel (10 g) with benzene–ether (97:3 or 95:5) as eluent.

General Procedure for the Catalytic Oxidation with tert-*Butyl Hydroperoxide.*—To a stirred solution of an allylic alcohol (0.5 mmol) and vanadyl acetylacetonate (2 mol %) in dichloromethane (5 cm^3) was added 70% aqueous *tert*-butyl hydroperoxide (0.7 mmol) and the mixture was stirred at room temperature for 0.5–4 h (depending on the reactivity). The mixture was then filtered through a pad of aluminium oxide to remove inorganic materials, the filtrate was worked up and the crude product was chromatographed as given in the previous experiment.

3α,4α-*Epoxy*-5α-*cholestan*-2β-*ol* **24**.—(Found: C, 71.1; H, 9.8%. $C_{27}H_{46}O_2$ requires C, 80.54; H, 10.51%), $[\alpha]_D^{20}$ +26° (*c* 3.1); ν_{max}/cm^{-1} 3620sh and 3633 (free OH); δ_H 0.66, (3 H, s, 18-H), 0.97 (3 H, s, 19-H), 2.87 (1 H, d, *J* 3.5, 4β-H), 3.13 (1 H, d, *J* 3.5, 3β-H) and 4.30 (1 H, br d, *J* 5.5, 2α-H).

Acknowledgements

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* In this instance, the outcome of the catalytic reaction appears to be dependent on the nucleophilicity of the double bond. Thus, **4** (with a trisubstituted C=C bond) gives solely the *cis*-epoxy alcohol **5** despite the equatorial hydroxy. Similarly, **12** affords mainly the 5β,6β-epoxide **15**. By contrast, **8** and *cis*-4-*tert*-butylcyclohex-2-enol[5] (with disubstituted C=C bonds) are oxidized to the corresponding enones.

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