Stereo- and Regio-control of Electrophilic Additions to Cyclohexene Systems by Neighbouring Groups: Participation of Allylic and Homoallylic Ester Groups in Hypobromous Acid Addition to some 5-Unsaturated Cholestane Derivatives

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Hypobromous acid addition to 3β,7β-, 3β,7α-, 3α,7β-, and 3α,7α-diacetoxycholest-5-ene (**8**)—(**11**) and 3β,7β,19- and 3β,7α,19-triacetoxycholest-5-ene (**12**) and (**13**) involves intramolecular participation of the neighbouring acetoxy group(s). Competing reaction pathways responsible for the product distribution are discussed. The relative importance of steric, electronic (Markownikoff), and stereoelectronic effects has been elucidated. The findings may be used for prediction of the reaction outcome. They also demonstrate that the purposeful introduction of a neighbouring group can direct the addition along the desired route.

Electrophilic additions to acyclic, non-symmetrically substituted olefins are governed by the Markownikoff rule which states that the nucleophile attacks the most electrophilic centre, usually the more substituted carbon atom.[1–3] Reactions that proceed through cyclic 'onium' ions generally exert high stereospecificity resulting in overall *anti*-addition, since in the transition state all the four atoms involved can lie in a plane (Figure 1).[2] As a consequence, such reactions have stringent stereoelectronic demands that become particularly apparent in cyclohexene systems which afford preferentially 1,2-*trans*-diaxial products (Fürst–Plattner rule).[4]

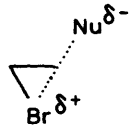
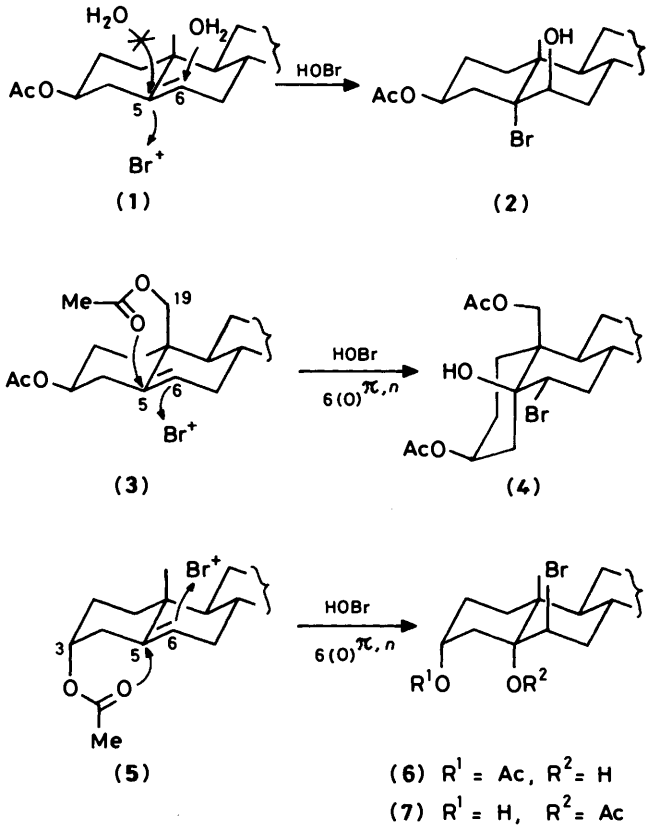


Figure 1. S_N2-Like cleavage of 'onium' intermediate in electrophilic addition

Depending on the structure of the unsaturated substrate the electronic (Markownikoff) and stereoelectronic (Fürst–Plattner) effects can be either consonant or dissonant.[5] The latter case may be illustrated with the hypobromous acid addition to cholesteryl acetate[2] (**1**) in Scheme 1: although the Markownikoff rule requires that the corresponding 5α,6α-bromonium ion be cleaved by water as external nucleophile at C-5, the reaction course is dominated by stereoelectronic factors that prefer cleavage at C-6, leading to the diaxial bromohydrin (**2**).[2]

The reaction course can be dramatically affected by the presence of a functional group located near the reaction centre.[6] As we have reported earlier,[7,8] an analogous 19-acetate (**3**) affords upon hypobromous acid addition mainly the diequatorial bromohydrin (**4**) which arises by Markownikoff cleavage at C-5 of the 5α,6α-bromonium ion by the carbonyl oxygen of the 19-acetoxy group.[7] This and other examples[5,7,8] show that participation by a neighbouring group can effectively reverse the regioselectivity of the reaction in certain instances. Moreover, the neighbouring group can also alter the steric course of the addition. Thus, for instance, the 3α-acetoxycholest-5-ene (**5**) (Scheme 1) is unusually attacked by the electrophile

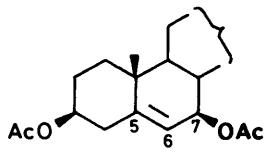


Scheme 1.

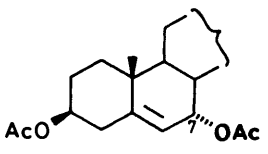
from the β-side, and the resulting 5β,6β-bromonium ion is then cleaved at C-5 with participation of the 3α-acetoxy group to give a mixture of acetates (**6**) and (**7**).[9] Furthermore, we have found that the participating group can even enforce electrophilic addition across an otherwise unreactive double bond.[10]

The introduction of neighbouring groups to control the course of electrophilic addition has recently been utilized in

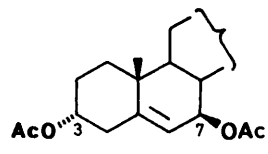
numerous syntheses of natural products with cyclic[11,12] or acyclic[13,14] skeletons. However, relatively little attention has been paid to a systematic investigation of steric, electronic, and stereoelectronic factors that govern neighbouring group participation in biased cyclohexane systems.[5,8,9,15] The aim of this work is to show how a purposeful introduction of ester group(s) as control element(s) into allylic and homoallylic positions of cyclohexene systems can affect the course of electrophilic addition and steer its regio- and stereo-selectivity in the desired direction. In order to study these effects we prepared cholestene derivatives (**8**)—(**13**)[16] with the double bond constantly located at C-5–C-6 and with one or two acetoxy groups (bold) capable of independent or competitive participation in hypobromous acid addition. The results are summarized in Schemes 2—7.



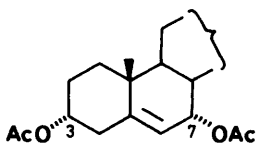
(**8**)



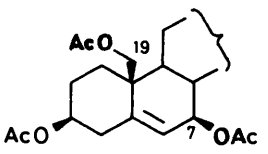
(**9**)



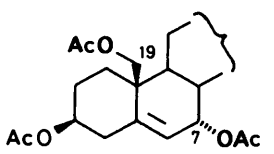
(**10**)



(**11**)



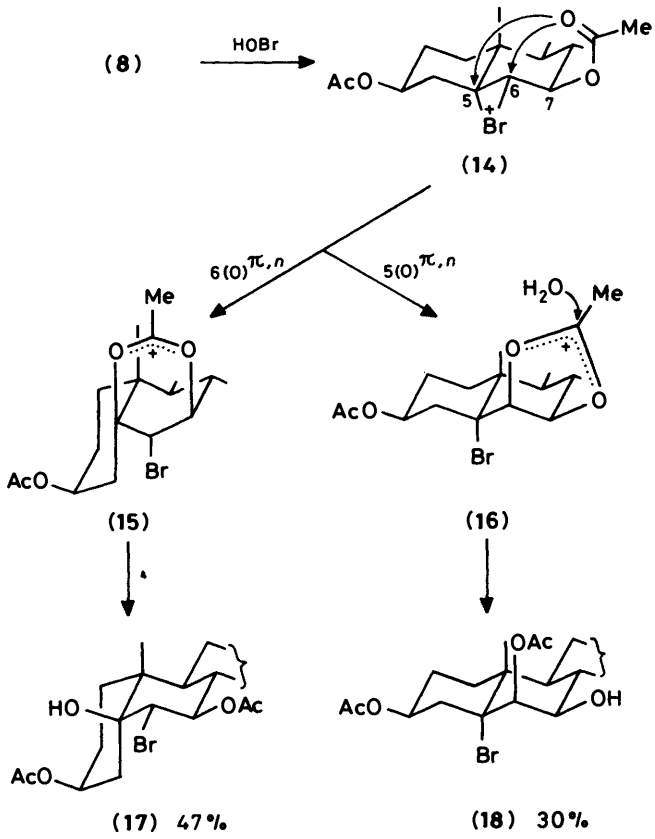
(**12**)



(**13**)

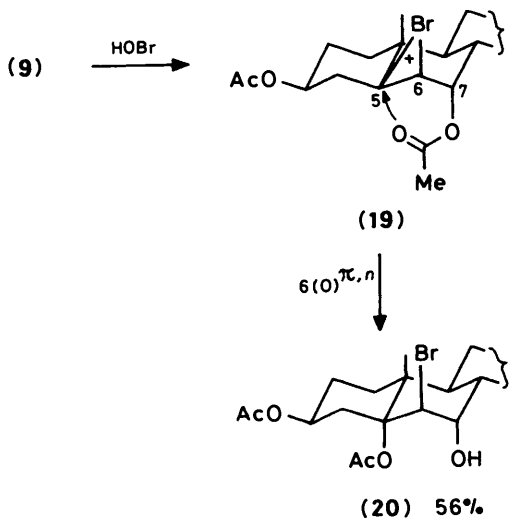
Results

Hypobromous acid addition to the unsaturated 7β-acetoxy derivative (**8**) afforded mainly the diequatorial bromohydrin (**17**). The reaction course can be visualized as being initiated by electrophile attack across the double bond in (**8**) from the more accessible α-side (Scheme 2). The intermediary 5α,6α-bromonium ion (**14**) is cleaved at C-5 by the carbonyl oxygen of the vicinal acetoxy group, in accordance with the Markownikoff rule, to give an acyloxonium ion (**15**) which is eventually hydrolysed to (**17**). A competing cleavage of the bromonium ion (**14**) at C-6 leads to the diaxial isomer (**18**) *via* the acetoxonium ion (**6**). The structures of both major products (**17**) and (**18**) were confirmed by i.r. and n.m.r. spectroscopy. The ^{1}H n.m.r. spectrum of (**17**) shows the signal of 3α-H as a multiplet of Σ*J* 21 Hz which corresponds to an axial 3β-acetoxy group and hence to a *cis*-AB ring junction. *In situ* acylation of 5β-OH with trichloroacetyl isocyanate (TAI)[17] shifts the signal of 6β-H downfield (Δδ 1.08 p.p.m.), consistent with the known β-effect of the 5β-hydroxy group.[7,15b] The chemical shift of 7α-H was practically unchanged. The ^{1}H n.m.r. spectrum of (**18**) displayed a broad multiplet for the axial 3α-H (Σ*J* 32 Hz) which confirmed a *trans*-junction of the AB rings. The coupling pattern and constants of 6-H and 7-H were consistent with a 6β-X–7β-Y arrangement. The position of the hydroxy group as 7β-OH was established through a downfield shift of 7α-H (Δδ 1.31 p.p.m.) upon TAI acylation.



Scheme 2.

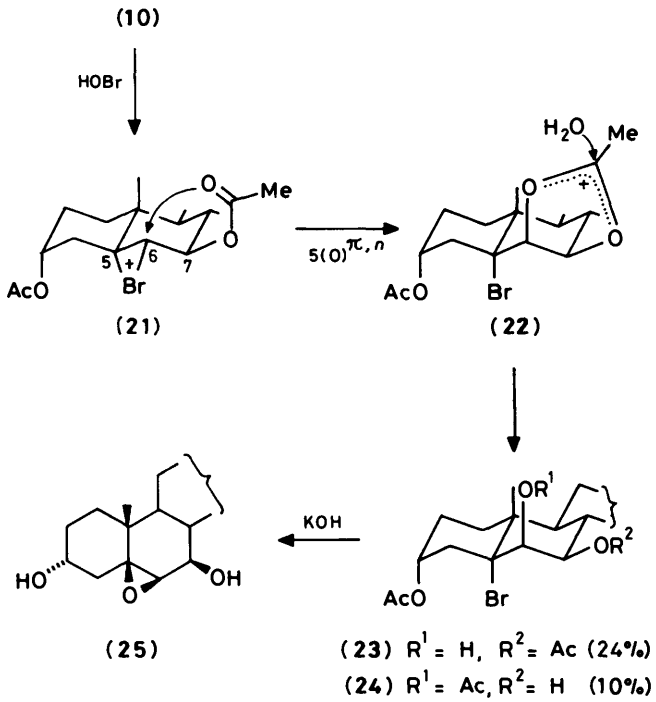
The unsaturated 7α-acetate (**9**) reacts with hypobromous acid to furnish a single bromohydrin (**20**) (Scheme 3). The addition apparently proceeds *via* the 5β,6β-bromonium ion (**19**) that is cleaved by the carbonyl terminus of the 7α-acetoxy group in a process of 6(O)$^{\pi,n}$-*endo*-*Trig* participation (for notation see refs.[5,7]). This reaction course is in line with both the Markownikoff and the Fürst–Plattner rules. The basic structural features supporting the suggested structure of compound (**20**) were deduced from the ^{1}H and ^{13}C n.m.r. spectra. The signal of 3α-H appears as a broad multiplet (Σ*J* 28 Hz), confirming the *trans*-annulation of the AB rings. The



Scheme 3.

coupling constants of 6-H and 7-H show a 6β-X–7α-Y arrangement. *In situ* TAI acylation induced a downfield shift of 7-H (Δδ 1.16 p.p.m.), which confirmed the location of the hydroxy group at C-7. The position of the bromine substituent followed from the chemical shifts and attached proton multiplicities of C-5 (87.20, s) and C-6 (48.36, d). The structure is also corroborated by the presence of the intramolecular hydrogen bond apparent in the i.r. spectrum.

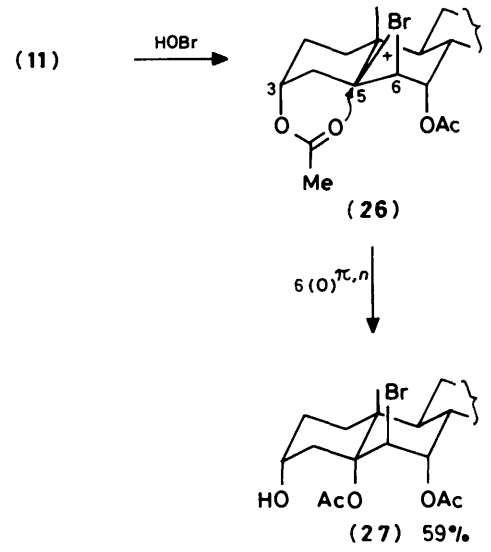
With the 3α,7β-diacetate (**10**) it was *a priori* possible to expect a competitive participation by either acetoxy group [*cf.* the reactivity of (**5**) and (**8**), above]. The addition afforded two major isolable products, (**23**) and (**24**) (Scheme 4), besides several unstable minor products which were not further examined. The structures of products (**23**) and (**24**) were established through their ^{1}H n.m.r. spectra after TAI acylation (see Experimental section). The addition in this case is initiated by α-attack from the more accessible face of the skeleton. The transient bromonium ion (**21**) is cleaved at C-6 by axial attack of the 7-acetoxy group, followed by hydrolysis of the acetoxonium ion (**22**) to yield the positional isomers (**23**) and (**24**). An alternative mechanism leading to (**23**) and (**24**), *via* an external cleavage of the bromonium ion (**21**) by water, was disproved by a labelling experiment. When using an $H_2{}^{18}O/H{}^{18}OBr$ reagent, generated *in situ* from *N*-bromoacetamide (NBA), $H_2{}^{18}O$ (50% ^{18}O), and a trace of perchloric acid in dioxane,[5,8] a direct cleavage of (**21**) by water would have resulted in incorporation of the ^{18}O label into the 6β-hydroxy group. According to our previous results,[5,8] the standard conditions employed make it possible to introduce a high proportion



Scheme 4.

(> 90%) of the available label. Unfortunately, the molecular ion of (**23**) very rapidly eliminated the 7β-acetoxy group, and so the crude mixture of products (**23**) and (**24**) was converted into a common epoxide (**25**) which still contained the original 6β-oxygen. The mass spectrum of the epoxide (**25**) showed no ^{18}O content above the natural abundance level, which excluded the alternative mechanistic path without acetate participation.

The reaction of the 3α,7α-diacetoxy derivative (**11**) with hypobromous acid gave a single product (**27**) in good yield (Scheme 5). The structure of compound (**27**) was inferred from its ^{1}H n.m.r. spectrum which showed a multiplet for equatorial 3β-H (Σ*J* 17 Hz) corresponding to a *trans*-AB annulation. *In situ* acylation with TAI led to a downfield shift of 3β-H (Δδ 1.07 p.p.m.) which confirmed the presence of the free hydroxy group at C-3, while the original acetyl group migrated to position 5α. Confirmation of the arrangement at C-6, C-7 (6β-Br–7α-OAc) came from the corresponding coupling constants.

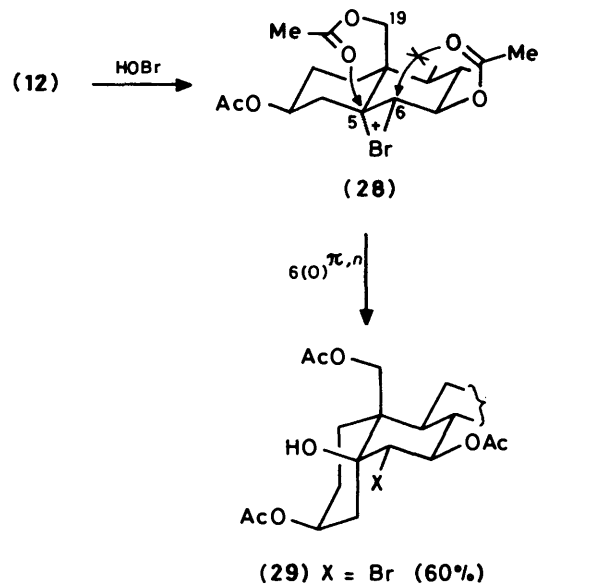


Scheme 5.

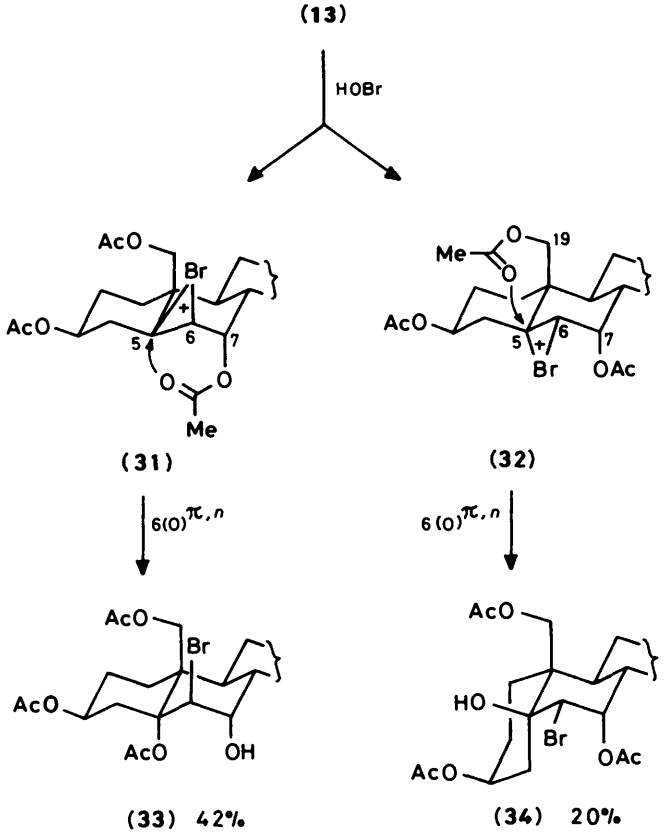
Having explored the behaviour of the four isomeric diacetates (**8**)—(**11**), we turned our attention to the triacetates (**12**) and (**13**). With this pair of isomers the 3β-acetoxy group is too remote from the double bond to be active in participation. The reactivity control therefore should be due to competitive participation of the 19- and 7-acetoxy groups.

The triacetate (**12**) reacted with hypobromous acid, giving a single major product (**29**) (Scheme 6) the structure of which was deduced from the ^{1}H n.m.r. spectrum (the position and width of the 3α-H multiplet, coupling constants of 6-H and 7-H, and TAI-induced shifts of signals of 4β-H and 6β-H. Reductive replacement of bromine by hydrogen in (**29**) gives the hydroxy triacetate (**30**) which further corroborates the structural assignment for the product of hypobromous acid addition. The double bond in compound (**12**) is attacked preferentially from the α-side and the 5α,6α-bromonium ion (**28**) is then cleaved at C-5 according to the Markownikoff rule. Although participation by 19-OAc and 7β-OAc could not be discerned in this case, the former acetoxy group appears to be a more probable candidate because of its better access to the reaction centre.

The isomeric triacetate (**13**) afforded two major products, (**33**) and (**34**) (Scheme 7). The ^{1}H n.m.r. spectra confirmed *trans*-annulation of the AB ring system in the former product, while the latter contained *cis*-annulated AB rings. The configuration at C-7 in both compounds corresponded to that in the reactant (**13**) while the configuration at C-6 was assigned on the basis of coupling constants as done for the 19-unsubstituted derivatives (*vide supra*). The position of the acetoxy and hydroxy groups in products (**33**) and (**34**) was established from TAI-induced shifts. The formation of (**33**) and (**34**) can be rationalized by competing attacks of the electrophile from opposite sides of the skeleton in compound (**13**). Compound (**33**) arises from a 5β,6β-bromonium ion (**31**) that is cleaved at C-5 by the carbonyl



Scheme 6.



Scheme 7.

oxygen of the 7α-acetoxy group, according to the Markownikoff and Fürst–Plattner rules. The isomeric 5α,6α-bromonium ion (**32**) is quenched by participation of the carbonyl oxygen of the 19-acetoxy group to give the minor product (**34**). Thus, the latter reaction obeys the Markownikoff rule, but violates the Fürst–Plattner rule.

Discussion

In a sterically biased cyclohexene system the electrophile approaches the molecule from the sterically less hindered side. The following reaction with a nucleophile obeys the stereoelectronic effect (Fürst–Plattner rule) rather than the electronic (Markownikoff) effect [see (A) in Figure 2]. Our findings show

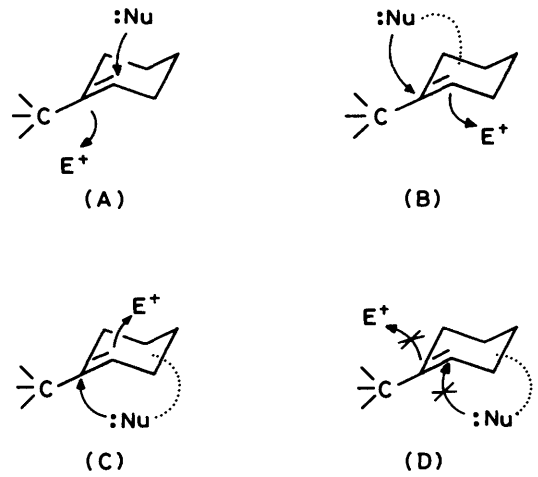
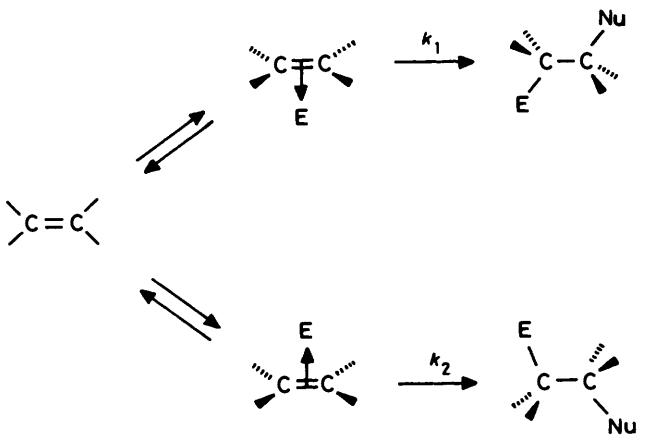


Figure 2. The role of the neighbouring group in electrophilic addition

that intervention of a properly situated neighbouring group may alter the regioselectivity of the second step in favour of the electronic effect [see (B) in Figure 2]. However, we have shown earlier[5] that this can be achieved only with olefins containing a non-symmetrically substituted double bond, where the inherent tendency toward S_N1-like or a borderline mechanism can be boosted by the neighbouring group. With 'symmetrical' bromonium ions whose preference for the S_N2-like mechanism is strong, the presence of the neighbouring group alone does not suffice to override the stringent stereoelectronic control.[5] Finally, intervention of a neighbouring group residing on the less hindered face of the double bond [as in (C), Figure 2] can alter the overall stereochemistry. The last case (D) that would violate both the electronic and the stereoelectronic factors has not been observed in our conformationally rigid cyclohexene systems.

Comparison of the structures (A)—(C) in Figure 2 shows an interesting point: although the approach from the top-side is assumed to be sterically more hindered, the third process (C) appears to be the most effective one in some instances [see *e.g.* the reactivity of (**13**)]. This can be rationalised as follows (Scheme 8): better accessibility of the bottom face of the double bond leads to a higher concentration of the corresponding intermediate in the first, reversible step.[18] If the quenching of this intermediate is fast enough ($k_1 \geqslant k_2$) the reaction follows the (A) or (B) pattern.[19] However, if the less populated diastereoisomeric intermediate is consumed faster ($k_1 < k_2$, or, better, $k_1 \ll k_2$) the reaction can switch to the pathway (C). Note that in (C) the second step is boosted by consonant electronic and stereoelectronic effects. Hence, the second step in (C) should be faster than that in (A) or (B) where these effects are dissonant.* However, $k_1 \ll k_2$ only when the second step is

* One can argue that introduction of a substituent on the originally more accessible face of the double bond could alter the relative steric hindrance, which might result in reversal of the overall stereochemistry. However, this is certainly not the case in our 5-unsaturated 7α-acetoxy derivatives (**9**) and ((**13**), since (**9**) is known to be oxidized with peroxy acids preferentially from the α-side.[16b]



Scheme 8.

intramolecular.[20] Therefore, without intervention of a neighbouring group, the reaction usually follows path (A).*

Our observation leads to the conclusion that the purposeful introduction of a neighbouring group can control the course of electrophilic additions not only to aliphatic compounds[14] but also to highly biased and fastidious cyclohexene systems. Careful evaluation of the relative importance of the factors governing the addition (as above) can lead to a reliable prediction of the favoured and disfavoured reaction pathway.† Such an analysis may be useful for driving the addition in the desired direction and for designing syntheses of complex polysubstituted molecules.

Experimental

M.p.s were determined on a Kofler block and are uncorrected. Optical rotations were measured with an Opton polarimeter with an error of ±3° and refer to solutions in chloroform. The i.r. spectra were recorded on a Perkin-Elmer 580 spectrometer for CCl_4 unless otherwise stated. The ^1H n.m.r. spectra were recorded on a Varian XL-200 apparatus (FT-mode) and on Tesla BS 497 instrument (100 MHz) for $CDCl_3$ solutions at 22 °C with Me_4Si as internal reference. Chemical shifts are given as δ values. The ^{13}C n.m.r. spectra were measured on a Varian XL-200 instrument (50.309 MHz, FT-mode) for $CDCl_3$ solutions with Me_4Si as internal reference. The degree of carbon protonation was obtained from single-frequency off-resonance decoupling. The mass spectra were recorded on a Jeol JMS D-100 spectrometer operating at 75 eV. The samples were introduced using a direct inlet at the lowest temperature enabling evaporation. The elemental compositions of ions were determined by accurate mass measurements. Yields are given in mg of isolated products showing one spot on a chromatoplate and no trace of impurities detectable in the n.m.r. spectrum. Work-up of an ethereal solution means washing the solution successively with 5% HCl, water, 5% aqueous $KHCO_3$, 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.

Addition of Labelled Hypobromous Acid to Compound (**10**).—The unsaturated compound (**10**) (145 mg) was dissolved in dry dioxane (5 ml), water (0.15 ml) containing 50% $H_2{}^{18}O$ was added, and the mixture was treated with 70% aqueous perchloric acid (*ca.* 0.02 ml) and NBA (70 mg) at room temperature for 15 min. The mixture was worked up as given in the following experiment to yield a non-separable mixture of two compounds, identical (t.l.c.) with the mixture of compounds (**23**) and (**24**) obtained from the unlabelled experiment (except for its ^{18}O content). The mixture of labelled products was saponified without further attempts at purification.

Addition of Hypobromous Acid to Compounds (**8**)—(**13**).—The unsaturated compound (0.5 mmol) was dissolved in dioxane (5 ml) and treated with 10% aqueous perchloric acid (0.5 ml) and NBA (80 mg, 0.6 mmol) at room temperature for 15 min. The mixture was then diluted with ether and washed successively with water, 5% aqueous $KHCO_3$, 5% aqueous $Na_2S_2O_3$, and water, and then dried with Na_2SO_4 and evaporated. The residue was chromatographed on three preparative silica gel plates (20 × 20 cm) using a mixture of light petroleum–ether–acetone (80:10:10) as developer. Zones containing products were collected, eluted with ether, and evaporated. The yields are given in Schemes 2—7.

6α-*Bromo*-5β-*cholestane*-3β,5,7β-*triol* 3,7-*diacetate* (**17**) had $[\alpha]_D^{20}$ +23° (*c* 3.9); δ_H 0.67 (3 H, s, 18-H_3), 1.05 (3 H, s, 19-H_3), 2.06 (3 H, s, $MeCO_2$), 2.09 (3 H, s, $MeCO_2$), 3.06 (1 H, br s, 5β-OH), 4.38 [1 H, d, *J*(6β-H, 7α-H) 11 Hz, 6β-H], 4.96 (1 H, m, Σ*J* 21 Hz, 3α-H), and 5.23 [1 H, dd, *J*(6β-H, 7α-H) 11, *J*(7α-H, 8β-H) 7.6 Hz, 7α-H]; after treatment with TAI: δ_H 5.46 (6β-H); $\nu_{max.}$ 1 226 and 1 744 ($MeCO_2$), and 3 598 cm^{-1} (OH) (Found: C, 63.5; H, 9.0; Br, 13.5. $C_{31}H_{51}BrO_5$ requires C, 63.79; H, 8.81; Br, 13.69%).

5-*Bromo*-5α-*cholestane*-3β,6β,7β-*triol* 3,6-*diacetate* (**18**) had $[\alpha]_D^{20}$ −16° (*c* 2.1); δ_H 0.71 (3 H, s, 18-H_3), 1.28 (3 H, s, 19-H_3), 2.03 (3 H, s, $MeCO_2$), 2.15 (3 H, s, $MeCO_2$), 4.46 [1 H, dd, *J*(7α-H, 8β-H) 10.8, *J*(6α-H, 7α-H) 4 Hz, 7α-H], 5.47 [1 H, d, *J*(6α-H, 7α-H) 4 Hz, 6α-H], and 5.48 (1 H, m, Σ*J* 32 Hz, 3α-H); after treatment with TAI: δ_H 5.45 (3α-H), 5.58 (6α-H), and 5.77 (7α-H); $\nu_{max.}$ 1 238 and 1 739 ($MeCO_2$), and 3 606 cm^{-1} (OH) (Found: C, 63.6; H, 9.0; Br, 13.9%).

6β-*Bromo*-5α-*cholestane*-3β,5,7α-*triol* 3,5-*diacetate* (**20**) had m.p. 145—147 °C (decomp., from acetone–methanol–water); $[\alpha]_D^{20}$ −7° (*c* 2.9); δ_H 0.72 (3 H, s, 18-H_3), 1.36 (3 H, s, 19-H_3), 2.01 (3 H, s, $MeCO_2$), 2.04 (3 H, s, $MeCO_2$), 2.23 [1 H, dd, *J*(3α-H, 4β-H) 11.7, J_{gem} 13.6 Hz, 4β-H], 2.91 [1 H, ddd, J_{gem} 13.6, *J*(3α-H, 4α-H) 4.9, *J*(2α-H, 4α-H) 1.6 Hz, 4α-H], 4.04 (1 H, m, Σ*J* 9.5 Hz, 7β-H), 4.72 (1 H, m, Σ*J* 28 Hz, 3α-H), and 5.28 [1 H, d, *J*(6α-H,7β-H) 1.9 Hz, 6α-H]; after treatment with TAI: δ_H 5.20 (7β-H); δ_C 11.94 (q, C-18), 18.69 (q, C-21), 18.95 (q, C-19), 20.94 (q, *Me*CO_2), 21.30 (t, C-11), 22.57 (q, *Me*CO_2), 22.63 (q, C-26), 22.80 (q, C-27), 23.59 (t, C-15), 23.69 (t, C-23), 26.32 (t, C-2), 28.02 (d, C-25), 28.10 (t, C-12), 32.51 (t, C-4), 33.51 (d, C-8), 33.51 (t, C-1), 35.75 (d, C-20), 36.13 (t, C-22), 37.62 (d, C-9), 39.34 (t, C-16), 39.52 (t, C-24), 41.01 (s, C-10), 42.54 (s, C-13), 48.36 (d, C-6), 48.88 (d, C-14), 56.00 (d, C-17), 69.96 (d, C-3), 74.18 (d, C-7), 87.20 (s, C-5), 170.32 (s, MeCO_2), and 170.80 (s, $MeCO_2$); $\nu_{max.}$ 1 240 and 1 735 ($MeCO_2$), 3 586 (OH bonded), and 3 622 cm^{-1} (OH free) (Found: C, 63.6; H, 9.1; Br, 13.5%).

5-*Bromo*-5α-*cholestane*-3α.6β,7β-*triol* 3,7 *diacetate* (**23**) had δ_H [in admixture with (**24**)] 0.70 (3 H, s, 18-H), 1.24 (3 H, s, 19-H_3), 2.05 ($MeCO_2$), 2.07 ($MeCO_2$), 2.95 [1 H, dd, *J*(4α-H, 3β-H) 4.8, J_{gem} 16.6 Hz, 4α-H], 4.14 [1 H, d, *J*(6α-H, 7α-H_3) 3.8 Hz, 6α-H], 5.12 (1 H, m, $w_{\frac{1}{2}}$ 10 Hz, 3β-H), and 5.69 [1 H, dd, *J*(6α-H, 7α-H) 3.8, *J*(7α-H, 8β-H) 10.6 Hz, 7α-H] (Found: C, 63.65; H, 8.9; Br, 13.55%).

5-*Bromo*-5α-*cholestane*-3α,6β,7β-*triol* 3,6-*diacetate* (**24**) had δ_H [in admixture with (**23**)] 0.72 (3 H, s, 18-H_3), 1.26 (3 H, s, 19-H_3), 2.05 ($MeCO_2$), 2.12 ($MeCO_2$), 2.47 [1 H, dd, J_{gem} 16.4, *J*(4α-H, 3β-H) 4.6 Hz, 4α-H], 4.57 (1 H, dd, *J*(6α-H, 7α-H) 4.3, *J*(7α-H,

* An extremely bulky external nucleophile can alter the reaction stereochemistry in favour of (C) even in the absence of a neighbouring group: R. D. Evans and J. H. Schaube, *Synthesis*, 1987, 551.

† This analysis applies for rigid systems which cannot attain other conformations by ring flipping.

8β-H) 9.8 Hz, 7α-H], 5.12 (1 H, m, ΣJ 10 Hz, 3β-H), and 5.42 (1 H, d, J(6α-H, 7α-H) 4.3 Hz, 6α-H).

5,6β-*Epoxy*-5β-*cholestane*-3α,7β-*diol* (**25**).—A mixture of labelled diacetates (**23**) and (**24**) (50 mg), benzene (0.5 ml), methanol (5 ml), and potassium hydroxide (300 mg) was heated at 60 °C for 2 h. The mixture was then cooled, diluted with water, and extracted with ether. The organic phase was washed with water and dried with Na_2SO_4. The solvent was evaporated off and the residue was chromatographed on one preparative silica gel plate (20 × 20 cm) with benzene–methanol (85:15) as developer. The zone corresponding to the product was collected, and eluted with ether, and the eluate was evaporated to afford the oily *epoxy diol* (**25**) (24 mg); $[\alpha]_D^{20}$ +36° (*c* 3.7); δ_H 0.66 (3 H, s, 18-H_3), 1.00 (3 H, s, 19-H_3), 2.22 [1 H, dd, J_{gem} 14, *J*(3β-H, 4α-H) 4 Hz, 4α-H], 3.15 [1 H, d, *J*(6α-H, 7α-H) 1.4 Hz, 6α-H], 3.58 [1 H, br d, *J*(7α-H, 8β-H) 8.5 Hz, 7α-H], and 4.20 (1 H, m, ΣJ 18 Hz, 3β-H) (Found: C, 77.4; H, 11.1. $C_{27}H_{46}O_3$ requires C, 77.46; H, 11.05%); *m/z* 418 ($M^{+\bullet}$), 400 ($M^+ - H_2O$), 382 ($M^+ - 2H_2O$, 371 (400 − CHO), 367 (382 − CH_3), 278 ($M - C_{10}H_{20}$), and 123 ($C_8H_{11}O$).

6β-*Bromo*-5α-*cholestane*-3α,5,7α-*triol* 5,7-*diacetate* (**27**) had $[\alpha]_D^{20}$ +30° (*c* 2.8); δ_H 0.71 (3 H, s, 18-H_3), 1.28 (3 H, s, 19-H_3), 2.016 (3 H, s, $MeCO_2$), 2.021 (3 H, s, $MeCO_2$), 2.25 [1 H, dd, J_{gem} 15.8, *J*(3β-H,4β-H) 3.9 Hz, 4β-H], 2.80 [1 H, dd, J_{gem} 15.8, *J*(3β-H, 4α-H) 2 Hz, 4α-H], 4.17 (1 H, m, ΣJ 17 Hz, 3β-H), 5.15 [1 H, dd, *J*(6α-H, 7β-H) 1.8, *J*(7β-H, 8β-H) 3.6 Hz, 7β-H], and 5.22 [1 H, d, *J*(6α-H, 7β-H) 1.8 Hz, 6α-H]; after treatment with TAI: δ_H 5.24 (3β-H), 3.04 (4α-H), and 2.45 (4β-H) (Found: C, 63.9; H, 8.9; Br, 13.8%).

6α-*Bromo*-5β-*cholestane*-3β,5,7β,19-*tetraol* 3,7,19-*triacetate* (**29**) had $[\alpha]_D^{20}$ +39° (*c* 1.9); δ_H 0.65 (3 H, s, 18-H_3), 1.92 [1 H, dd, J_{gem} 15.9, *J*(3α-H,4α-H) 3.8 Hz, 4α-H], 2.06 (3 H, s, $MeCO_2$), 2.09 (3 H, s, $MeCO_2$), 2.12 (3 H, s, $MeCO_2$), 2.41 (1 H, br d, J_{gem} 15.9 Hz, 4β-H), 4.28 and 4.37 (2 H, 2 × d, AB system, J_{gem} 11.8 Hz, 19-H_2), 4.57 [1 H, br d, *J*(6β-H, 7α-H) 10.7 Hz, 6β-H], 5.00 (1 H, m, ΣJ 20 Hz, 7α-H), and 5.21 (1 H, m, $w_{\frac{1}{2}}$ 6 Hz, 3α-H); after treatment with TAI: δ_H 3.13 (4β-H) and 5.55 (6β-H) (Found: C, 61.6; H, 8.4; Br, 12.4. $C_{33}H_{53}BrO_7$ requires C, 61.76; H, 8.34; Br, 12.45%).

5β-*Cholestane*-3β,5,7β,19-*tetraol* 3,7,19-*Triacetate* (**30**).—A solution of the bromo derivative (**29**) (35 mg) in benzene (3 ml) was refluxed with a 1M benzene solution of tributyltin hydride (0.3 ml) and a catalytic amount of 2,2′-azoisobutyronitrile for 1 h. The mixture was worked up and the residue, after evaporation of the solvent, was chromatographed on one preparative silica gel plate (20 × 20 cm) with light petroleum–ether–acetone (70:20:10) as developer to yield the *oily product* (**30**) (29 mg), $[\alpha]_D^{20}$ +64° (*c* 3.2); δ_H 0.68 (3 H, s, 18-H_3), 2.00 (3 H, s, $MeCO_2$), 2.090 (3 H, s, $MeCO_2$), 2.092 (3 H, s, $MeCO_2$), 2.16 [1 H, dd, J_{gem} 16, *J*(3α-H, 4β-H) 4 Hz, 4β-H], 4.35 and 4.42 (2 H, AB system, J_{gem} 12 Hz, 19-H_2), 4.62 [1 H, ddd, *J*(6α-H, 7α-H) 6.4, *J*(6β-H, 7α-H) 10.3, *J*(7α-H, 8β-H) 10.3 Hz, 7α-H], and 5.20 (1 H, m, $w_{\frac{1}{2}}$ 6 Hz, 3α-H); after treatment with TAI: δ_H 3.06 (4α-H) (Found: C, 70.2; H, 9.9. $C_{33}H_{54}O_7$ requires C, 70.43; H, 9.67%).

6β-*Bromo*-5α-*cholestane*-3β,5,7α,19-*tetraol* 3,5,19-*triacetate* (**33**) had $[\alpha]_D^{20}$ −18° (*c* 1.9); δ_H 0.71 (3 H, s, 18-H_3), 2.01 (3 H, s, $MeCO_2$), 2.05 (3 H, s, $MeCO_2$), 2.09 (3 H, s, $MeCO_2$), 2.97 [1 H, ddd, J_{gem} 13.8, *J*(3α-H, 4α-H) 5, *J*(2α-H, 4α-H) 1.9 Hz, 4α-H], 4.03 (1 H, m, ΣJ 5 Hz, 7β-H), 4.50 and 4.67 (2 H, 2 × d, AB system, J_{gem} 12.8 Hz, 19-H_2), 4.76 (1 H, m, ΣJ 32 Hz, 3α-H), and 5.30 [1 H, d, *J*(6α-H, 7β-H) 2.1 Hz, 6α-H]; after treatment with TAI: δ_H 0.84 (18-H_3), 2.83 (4α-H), and 4.73 (7β-H) (Found: C, 61.5; H, 8.6; Br, 12.2%).

6α-*Bromo*-5β-*cholestane*-3β,5,7α,19-*tetraol* 3,7,19-*triacetate* (**34**) had $[\alpha]_D^{20}$ +28° (*c* 5.9); δ_H 0.64 (3 H, s, 18-H_3), 2.08 (3 H, s, $MeCO_2$), 2.09 (3 H, s, $MeCO_2$), 2.14 (3 H, s, $MeCO_2$), 2.24 (1 H, br d, J_{gem} 15.8 Hz, 4α-H), 2.53 [1 H, dd, J_{gem} 15.8, *J*(3α-H, 4β-H) 3.7 Hz, 4β-H), 4.33 (2 H, m, ΣJ 30 Hz, 19-H_2), 4.70 [1 H, d, *J*(6β-H, 7β-H) 3.6 Hz, 6β-H], 5.23 (1 H, m, $w_{\frac{1}{2}}$ 9 Hz, 3α-H), and 5.49 (1 H, m, ΣJ 7 Hz, 7β-H); after treatment with TAI: δ_H 2.50 (4α-H) and 3.17 (4β-H) (Found: C, 61.5; H, 8.5; Br, 12.2%).

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