Participation of Ambident Neighbouring Groups in Hypobromous Acid Addition to some Steroidal Olefins. Competition of Electronic and Stereoelectronic Effects

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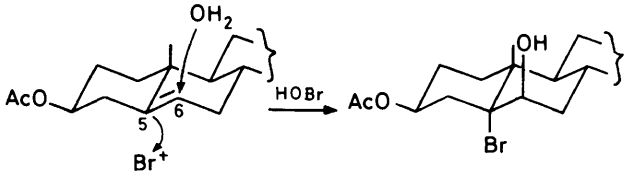
The participation propensity, in hypobromous acid addition, of various ambident neighbouring groups containing a carbonyl moiety has been studied for steroidal olefins (**1**)—(**3**). The carbamoyloxy group (–$OCONH_2$) has been found to be superior to other groups. The relative importance of the electronic (Markownikoff) and stereoelectronic effects in electrophilic additions has also been elucidated. In cases where these effects are dissonant, the neighbouring group participation may alter the regioselectivity of the reaction. A new method of synthesis of unsubstituted carbamates has been developed.

The course of electrophilic additions to carbon–carbon double bonds is controlled by effects which can be generally characterised as electronic, stereoelectronic, and steric.[1,2] The Markownikoff rule,[1,3] which summarises the electronic effects of substituent, predicts that the electrophilic part of the reagent will become bonded to the less substituted terminus of the double bond. The stereoelectronic effect is most pronounced in cyclohexene systems, where the addition as a rule leads to 1,2-*trans*-diaxial products (Fürst–Plattner rule).[4] Finally, the steric effects result from steric hindrance which makes one of the faces of the double bond less accessible to the electrophilic reagent.[1,2]

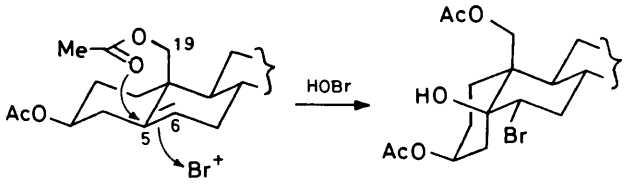
Depending on the structure of the olefinic substrate, the electronic (Markownikoff) and stereoelectronic (Fürst–Plattner) effects can be either consonant or dissonant. The latter case may be illustrated by the hypobromous acid addition to cholesteryl acetate (Scheme 1) (ref. 2): Although the



Scheme 1.

Markownikoff rule requires that the corresponding 5α,6α-bromonium ion be cleaved by water at C-5, the reaction course is dominated by stereoelectronic factors which prefer cleavage at C-6 to afford the diaxial bromohydrin.

As we have shown earlier,[5,6] anchoring a suitable functional group near the reaction centre may, in certain instances, alter the relative importance of the Markownikoff and the stereoelectronic effects. Thus, introduction of an acetoxy group into position 19 of cholesteryl acetate (Scheme 2)[5] reverses the



Scheme 2.

cleavage of the 5α,6α-bromonium ion in favour of the Markownikoff rule. This results in the formation of diequatorial bromohydrin *via* a process that can be classified as $6(O)^{\pi,n}$-*exo-Trig* participation.† This and other examples[8] clearly show that participation of a neighbouring group can effectively reverse the regioselectivity of the electrophilic addition.

If the neighbouring group is of a bidentate character, there are—*a priori*—two different nucleophilic centres which have to be considered for the reaction. Thus, for instance, the acetoxy group can react either with its ether or with its carbonyl oxygen.[5,9] In our previous papers[6,10] we were mainly concerned with participation of hydroxy, methoxy, and acetoxy groups and their mutual competition[6] in electrophilic additions to a double bond located in the steroid skeleton. Whereas the neighbouring groups were standardly attached to C-19, the position of the double bond was systematically changed. We have studied the reactivity of steroidal 19-substituted olefins with a double bond located in positions 1,2, 2,3, 3,4, 4,5, 5,6, or 6,7 and have found examples of $5(O)^n$, $6(O)^n$, $5(O)^{\pi,n}$, $6(O)^{\pi,n}$, and $7(O)^{\pi,n}$ participation, respectively.[6,9,11] It appears that the series can be divided topologically into compounds with the participating functionality in bis-homoallylic (type A) and

(A) (B)

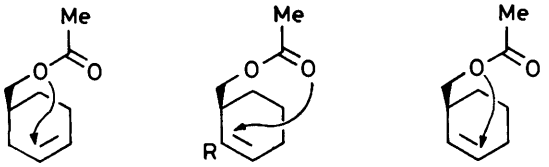
R = H, Me

homoallylic (type B) positions. Compounds with a double bond in positions 2,3, 3,4, and 6,7 fit the former group, whereas 1,2-, 4,5-, and 5,6-olefins belong to the latter. In the cases of OH and OMe as participating groups, both A and B types prefer $5(O)^n$ participation[5,10] leading to the formation of cyclic bromo ethers.‡

† Here we use a combination of notations proposed earlier by us[5] and by Baldwin.[7] 'O' Stands for the nature of the participating atom (oxygen), the superscript characterises the participating atom orbitals, *i.e.* 'π,n' for the carbonyl, or 'n' for ether oxygen.[5] The remaining symbols are commonly known from the Baldwin rules.[7]

‡ The participation is somewhat more pronounced with the type A, for it reacts *via* a favoured $5(O)^n$-*exo-Trig* process, while the type B must react *via* a disfavoured $5(O)^n$-*endo-Trig* route.

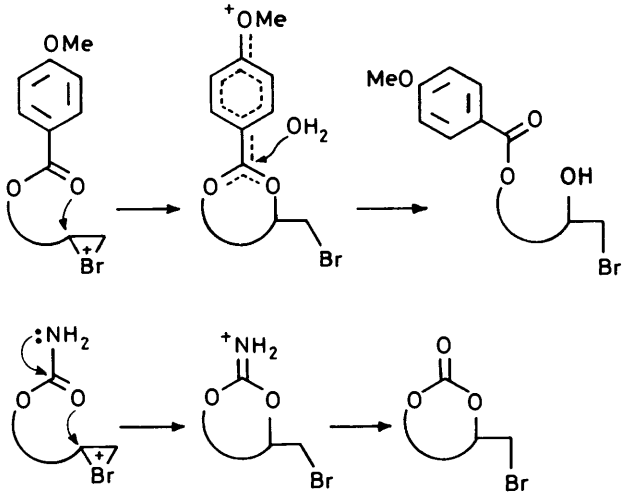
By contrast, compounds containing an ambident ester group (*e.g.* acetoxy) exhibit a marked qualitative difference in reactivity: whereas the bis-homoallylic type A, reacts again with 5(O)^{n}-*exo-Trig* participation giving the same product as does the corresponding alcohol or methyl ether, the homoallylic type B_1 reacts differently, *via* a 6(O)^{n,n}-*exo-Trig* pathway.[5] The latter reaction has been observed, however, only with compounds containing a trisubstituted double bond, *i.e.* with type B_1 (4,5-



and 5,6-olefins).[5,6] Here, the regioselectivity of the reaction is apparently reversed due to the favourable Markownikoff bias (see also Scheme 2). On the other hand, this pathway does not operate with compounds containing a disubstituted double bond (1,2-olefin), *i.e.* type B_2 (still homoallylic), and other reaction channels [mainly 5(O)^{n}-*endo-Trig*] are preferred.[11]

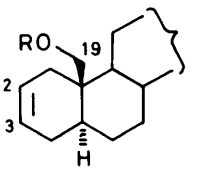
From these findings it may be concluded that the stringent stereoelectronic control may be suppressed only if a dissonant Markownikoff effect operates together with neighbouring group participation. This conclusion raises the question of whether or not a neighbouring group can be designed which could alter the reaction course even without such a supporting effect. Here we report our effort at finding a group more nucleophilic than acetoxy, the strongest internal carbonyl nucleophile thus far used in our experiments.*

We reasoned that the carbonyl nucleophilicity should be increased in *p*-methoxybenzoate and carbamate groups according to the expected mechanisms (Scheme 3).† As



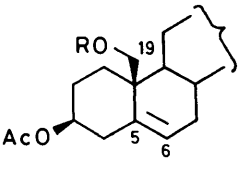
Scheme 3.

representatives for the different patterns of the types A_1, B_1, and B_2 we chose derivatives (**1**)—(**3**) with a double bond in the position 2,3 (Type A_1), 5,6 (Type B_1), and 1,2 (Type B_2) which are most readily accessible by synthesis.



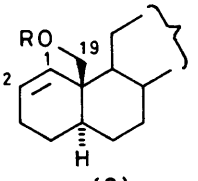
(**1**)

a; R = H
b; R = MeCO
c; R = PhCO
d; R = CF_3CO
e; R = EtOCO
f; R = *p*-$MeOC_6H_4CO$
g; R = H_2NCO



(**2**)

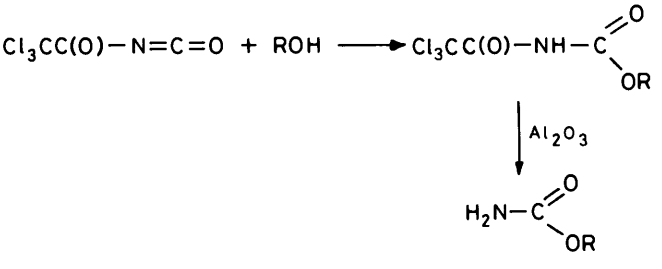
a; R = H
b; R = MeCO
c; R = PhCO
d; R = CF_3CO
e; R = EtOCO
f; R = *p*-$MeOC_6H_4CO$
g; R = H_2NCO



(**3**)

a; R = H
b; R = MeCO
g; R = H_2NCO

The *p*-methoxybenzoates (**1f**) and (**2f**) were prepared in conventional manner from the alcohols (**1a**)[5] and (**2a**)[5] by acylation with *p*-methoxybenzoyl chloride in pyridine. Direct acylation with *p*-methoxybenzoic acid mediated by 2-chloro-*N*-methylpyridinium iodide and 4-(*N*,*N*-dimethylamino)pyridine (DMAP)[12] was used for small-scale preparation of (**1f**) and (**2f**). Carbamates were synthesized in two steps: treatment of the alcohols (**1a**), (**2a**), and (**3a**) with trichloroacetyl isocyanate (TAI) led to *in situ* formation of the corresponding trichloroacetyl carbamates[13] (Scheme 4) that were surprisingly



Scheme 4.

smoothly hydrolysed to carbamates (**1g**), (**2g**), and (**3g**) upon filtration through a pad of neutral aluminium oxide. This procedure for preparation of unsubstituted carbamates (–OCO-NH_2) appears to be superior to other methods known to date[14] with regard to the mild reaction conditions and high yields achieved even with tertiary alcohols.[15] It turned out that the method also tolerated a variety of labile functional groups.[15]

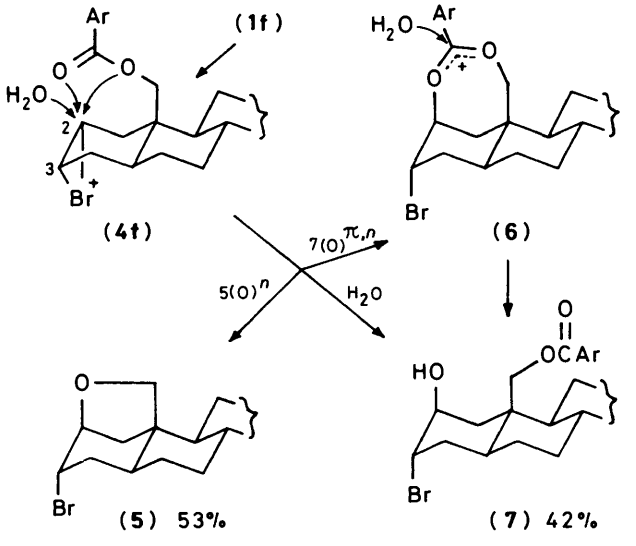
Hypobromous Acid Addition.—The model compounds (**1f**), (**1g**), (**2f**), (**2g**), and (**3g**) were treated with hypobromous acid

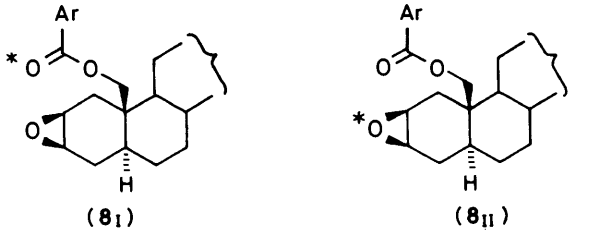
* For a comparison of selected neighbouring groups see ref. 10.
† For similar effects in S_N reactions see *e.g.* K. Wiesner, T. Y. R. Tsai, and H. Jin, *Helv. Chim. Acta*, 1985, **68**, 300; K. Wiesner and T. Y. R. Tsai, *Pure Appl. Chem.*, 1986, **58**, 799.

Table. Isolated percentage in yields in hypobromous acid addition to 19-substituted steroidal olefins (**1**)—(**3**)

Starting compound	Neighbouring group	Mode of reaction					
		5(O)^n	6(O)$^{\pi,n}$	7(O)$^{\pi,n}$	+	External[a]	Ref.
(**1b**)	$MeCO_2$	79 (**5**)	*b*	9	+	2	5, 6[b]
(**1c**)	$PhCO_2$	37 (**5**)	*b*		60[c]		10
(**1d**)	CF_3CO_2	0	*b*	0	+	70	10
(**1e**)	$EtOCO_2$	0	*b*		87[c,d]		5
(**1f**)	*p*-$MeOC_6H_4CO_2$	53 (**5**)	*b*	28 (**7**)	+	14 (**7**)	
(**1g**)	H_2NCO_2	31 (**5**)	*b*	31 (**10**)	+	0	
(**2b**)	$MeCO_2$	0	67	3	+	7[e]	5, 6[b]
(**2c**)	$PhCO_2$	0	62		21[c,f]		10
(**2d**)	CF_3CO_2	0	0	0	+	53	10
(**2e**)	$EtOCO_2$	0	75 (**13**)[d]		5[c]		5
(**2f**)	*p*-$MeOC_6H_4CO_2$	0	27 (**12**)[g]		?[h]		
(**2g**)	H_2NCO_2	0	89 (**13**)		0		
(**3b**)	$MeCO_2$	36 (**15**)	0	22[d]	+	28	11
(**3g**)	H_2NCO_2	13 (**15**)	0	43 (**17**)	+	0	

[a] External = attack by water as an external nucleophile. [b] Cannot be expected for structural reasons. [c] Ratio of the two pathways has not been established. [d] Two products are formed by this mechanism. [e] Further by-product (9%) is formed from the 5β,6β-bromonium ion. [f] Further by-product (11%) is formed from the 5β,6β-bromonium ion. [g] The only (major) product isolated from a complex reaction mixture of unstable products. [h] T.l.c. indicated formation of by-products which could not be isolated.



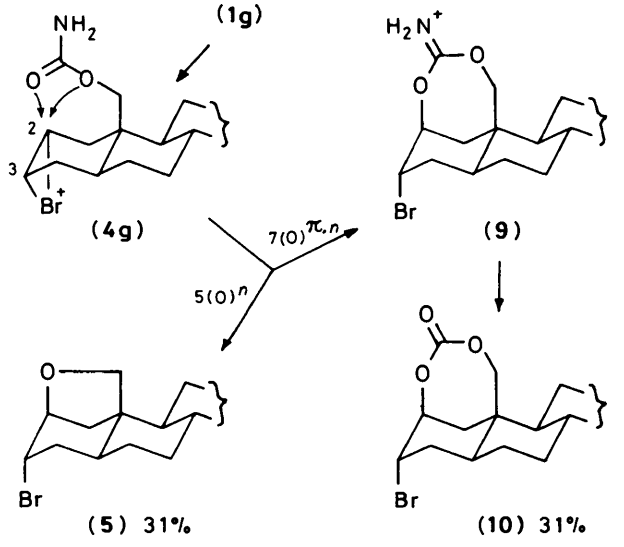


Scheme 5. Ar = *p*-$MeOC_6H_4CO$

[generated *in situ* from *N*-bromoacetamide (NBA) and perchloric acid] in aqueous dioxane. The products were isolated and subjected to spectral analysis. The results are compared with those obtained earlier with other esters (**1b**)—(**1e**), (**2b**)—(**2e**), and (**3b**) (Table).

On hypobromous acid treatment, the 2,3-unsaturated 19-*p*-methoxybenzoate (**1f**) afforded a mixture of two products (**5**) and (**7**), with the former being formed in a slight excess (Scheme 5). Whereas the known[5] cyclic ether (**5**) arises from the 2α,3α-bromonium ion (**4f**) by 5(O)^n-*exo-Trig* participation, two mechanistic pathways could be suggested for the formation of the bromohydrin (**7**) from the same bromonium ion, namely the 7(O)$^{\pi,n}$-*exo-Trig* participation *via* (**6**) or a direct reaction with water as an external nucleophile. The actual role of these two routes to (**7**) was investigated by running the experiment in dioxane solution containing water enriched in ^{18}O isotope (27%). Since the resulting labelled bromohydrin (**7**) could not be unequivocally analysed by mass spectrometry, it was converted into the epoxide (**8**) by alkali treatment. Mass spectral analysis of compound (**8**) then revealed 27.8 ± 0.5% ^{18}O in $M^{\cdot+}$, 9.3 ± 0.1% in $(M - CH_3OC_6H_4CO)^+$, and 17.1 ± 0.7% in $CH_3OC_6H_4CO^+$. The distribution of the label is thus about 67% in the carbonyl of the *p*-methoxybenzoate group ($\mathbf{8_I}$) and 33% in the oxirane ring ($\mathbf{8_{II}}$). Hence, the bromohydrin (**7**) is formed by two reaction pathways, *i.e.* by 7(O)$^{\pi,n}$ participation of the ester group and by the reaction with water as an external nucleophile in a 2:1 ratio.

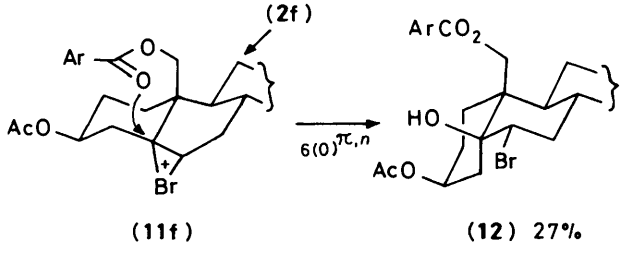
The 2,3-unsaturated carbamate (**1g**) also gave two products on hypobromous acid addition (Scheme 6), namely (**5**) and (**10**)



Scheme 6.

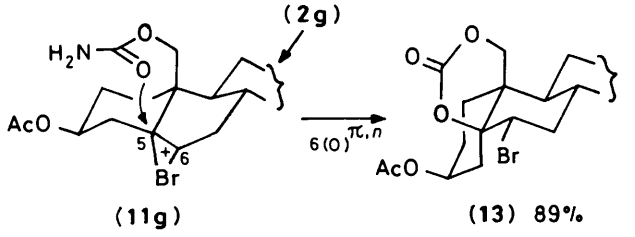
in a 1:1 ratio. While the bromo epoxide (**5**) is, again, formed by 5(O)^{n}-*exo-Trig* participation, the cyclic carbonate (**10**) arising by 7(O)$^{\pi,n}$-*exo-Trig* path *via* intermediate (**9**).

The 5,6-unsaturated derivatives (**2f**) and (**2g**) share the same general reactivity. The *p*-methoxybenzoate (**2f**) produced a complex mixture of unstable compounds from which the 6(O)$^{\pi,n}$-*exo-Trig* participation product (**12**) could be isolated as the major component (Scheme 7). By contrast, the reaction of



Scheme 7.

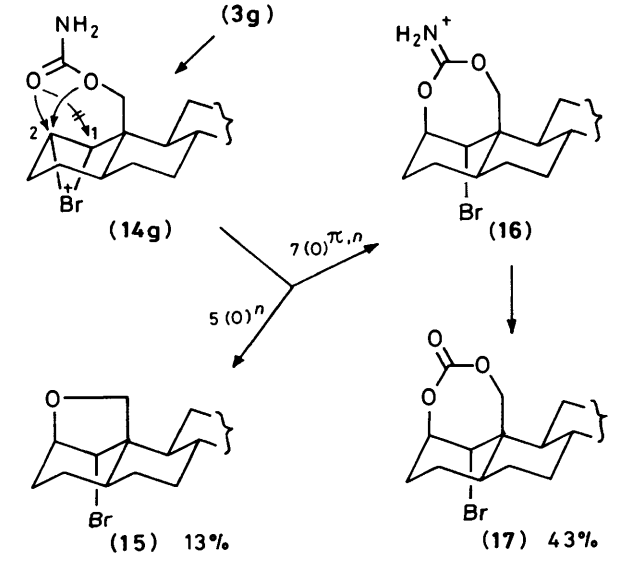
carbamate (**2g**) was clean and gave essentially one product (**13**) as a result of 6(O)$^{\pi,n}$-*exo-Trig* participation (Scheme 8). This and the above results demonstrate the superiority of carbamate



Scheme 8.

over the *p*-methoxybenzoate group as a powerful nucleophilic neighbouring functionality. Hence, in the 1,2-unsaturated series only the carbamate (**3g**) was studied.

Analysis of the reaction mixture after treatment of compound (**3g**) with hypobromous acid showed two major products (Scheme 9). The lipophilic one was identified as the known [11]



Scheme 9.

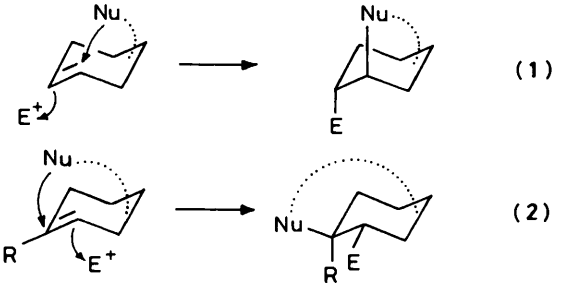
bromo epoxide (**15**) whereas the polar component turned out to be a carbonate with a seven-membered ring, (**17**). The former compound arises from the 1α,2α-bromonium ion (**14g**) by 5(O)^{n}-*endo-Trig* participation, while the latter must be formed from the same bromonium ion by the 7(O)$^{\pi,n}$-*endo-Trig* route *via* intermediate (**16**). Since only trace amounts of other components could be detected by t.l.c., it is obvious that the third pathway, *i.e.* the 6(O)$^{\pi,n}$-*exo-Trig* process, does not operate.

Discussion

The different reactivity of 19-substituted olefins (**1**)—(**3**) can be qualitatively correlated with the effective nucleophilicity of the participating carbonyl group (Table). Thus, for instance, the 2α,3α-bromonium ion derived from the acetate (**1b**) is preferentially cleaved by the ether oxygen of the acetoxy group, *i.e.* by a 5(O)^{n}-*exo-Trig* process.[5] The bromohydrin arising mainly by 7(O)$^{\pi,n}$-*exo-Trig* participation is formed in a yield as low as 11% (Table). On the other hand, benzoyloxy (**1c**) and *p*-methoxybenzoyloxy (**1f**) groups display a relative decrease of the (O)^{n} nucleophilicity, while the reactivity of the carbonyl oxygen dominates, particularly with (**2c**) and (**2f**). The carbonate carbonyl also exhibits a fairly high nucleophilicity, as in (**2e**).[5] In contrast, the CF_3CO_2 group in (**1d**) and (**2d**) does not participate at all by either of its oxygens [10] (Table).

An increase of the carbonyl nucleophilicity is particularly dramatic with the carbamoyloxy group in compounds (**1g**), (**2g**), and (**3g**). Thus the 5,6-unsaturated carbamate (**2g**) gives an almost clean reaction leading to the 6(O)$^{\pi,n}$-*exo-Trig* participation product (**13**), whereas the corresponding acetate (**2b**),[5] benzoate (**2c**),[10] carbonate (**2e**),[5] and formate [16] produce certain amounts of products * due to competing reactions. Even the 7(O)$^{\pi,n}$-*exo-Trig* participation by the carbamate group (**1g**) is more pronounced than that by the acetoxy group (**1b**).[6b] Moreover, 7(O)$^{\pi,n}$-*endo-Trig* participation is the main reaction pathway with the 1,2-unsaturated carbamate (**3g**), while the corresponding acetate (**3b**) is known to react predominantly with an external nucleophile and *via* a 5(O)^{n} pathway [11] (Table).

In spite of the strong carbonyl nucleophilicity the carbamate group is, however, still unable to reverse the course of hypobromous acid addition to a symmetrically substituted double bond in the 1,2-unsaturated derivative (**3g**), *i.e.* in compounds of Type B_2. Instead, an apparently less entropically favoured 7(O)$^{\pi,n}$-*endo-Trig* participation occurs. This indicates that a strong nucleophilicity of the neighbouring group alone does not suffice for overriding the stereoelectronic control in the cleavage of 'symmetrical' bromonium ions whose preference for the S_N2-like reactivity is strong [Scheme 10, equation (1)].† In



Scheme 10.

* For other examples of participation by -OCONHR groups see *e.g.* W. R. Roush, R. J. Brown, and M. DiMare, *J. Org. Chem.*, 1983, **48**, 5083; W. R. Roush and R. J. Brown, *ibid.*, p. 5093; W. R. Roush and M. A. Adam, *ibid.*, 1985, **50**, 3752; M. Hirama, M. Iwashita, Y. Yamazaki, and S. Itô, *Tetrahedron Lett.*, 1984, **25**, 4963; M. Hirama and M. Uei, *ibid.*, 1982, **23**, 5307; M. Minami, S. S. Ko, and Y. Kishi, *J. Am. Chem. Soc.*, 1982, **104**, 1109; L. E. Overman, C. B. Campbell, and F. M. Knoll, *ibid.*, 1978, **100**, 4822.

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

other words, formation of the diequatorial (thermodynamic) product can be boosted by neighbouring group participation only with olefins containing a non-symmetrically substituted double bond, where S_N1-like or a borderline mechanism can be assumed to support this reaction course [Scheme 10, equation (2)].*

Experimental

M.p.s were taken on a Kofler block and are uncorrected. Optical rotations were recorded with an Opton polarimeter with an error of $\pm 3°$ and refer to solution in chloroform. The i.r. spectra were recorded on a Perkin-Elmer 580 spectrometer for CCl_4 solutions unless otherwise stated. The ^1H n.m.r. spectra were recorded on a Varian XL-200 apparatus (FT-mode) and on a Tesla BS 476 instrument (60 MHz) for $CDCl_3$ solutions at 30 °C with Me_4Si as internal reference. Chemical shifts are given in δ-scale p.p.m. 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 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 composition of ions was determined by accurate mass measurements. The identity of samples prepared by different routes was checked by mixed m.p. determination, t.l.c., and i.r. and ^1H n.m.r. spectra. Yields are given in mg of isolated product showing one spot on a chromatoplate and no trace of impurities detectable in the n.m.r. spectrum. Usual work-up of an ethereal solution means washing the solution with 5% HCl acid, 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.

5α-*Cholest*-2-*en*-19-*yl* p-*Methoxybenzoate* (**1f**).—A mixture of the alcohol (**1a**) (150 mg), *p*-methoxybenzoic acid (63 mg), DMAP (175 mg) and 2-chloro-*N*-methylpyridinium iodide (131 mg) in dichloromethane (5 ml) was refluxed and stirred under nitrogen for 3 h. The mixture was then cooled and filtered, and the solid residue was washed with dichloromethane. The filtrate was evaporated and the residue was chromatographed on a column of silica gel (9 g) with light petroleum–ether (9:1) as eluant to give the oily p-*methoxybenzoate* (**1f**) (74 mg); $[\alpha]_D^{20}$ +32° (*c* 1.9); δ_H 0.58 (3 H, s, 18-H_3), 3.82 (3 H, s, MeO), 4.43 and 4.72 (2 H, 2 × d, AB system, J_{gem} 13 Hz, 19-H_2), and 5.62 (2 H, m, Σ*J* 9 Hz, 2- and 3-H); $\nu_{max.}$ 1 514, 1 583, 1 609, and 1 717 cm^{-1} (Found: C, 80.5; H, 10.1. $C_{35}H_{52}O_3$ requires C, 80.7; H, 10.0%).

5α-*Cholest*-2-*en*-19-*yl Carbamate* (**1g**).—The alcohol (**1a**) (0.20 mmol) was dissolved in dry chloroform (3 ml) and treated with a solution of TAI (0.25 mmol) in benzene (2 ml) at room temperature for 15 min under nitrogen. The solution was then soaked into a pad of neutral aluminium oxide (activity II, Brockmann) and after 5 min was washed with a mixture of benzene and chloroform (2:1) to give, after work-up, the oily *carbamate* (**1g**) (73 mg, 84%); $[\alpha]_D^{20}$ +14° (*c* 1.8); δ_H 0.67 (3 H, s, 18-H_3), 4.03 and 4.35 (2 H, 2 × d, AB system, J_{gem} 12 Hz, 19-H_2), 4.60 (2 H, m, Σ*J* 25 Hz, NH_2), and 5.60 (2 H, br, s, 2- and 3-H); $\nu_{max.}$ 1 658 and 3 030 (HC=CH), 1 580, 1 598, 1 732, 3 175, 3 265, 3 330, 3 440, 3 490, 3 510, and 3 555 cm^{-1} ($OCONH_2$) (Found: C, 78.0; H, 11.2; N, 3.0. $C_{28}H_{47}NO_2$ requires C, 78.3; H, 11.0; N, 3.3%).

Cholest-5-*ene*-3β,19-*diol* 3-*Acetate* 19-p-*Methoxybenzoate* (**2f**).—*Method A.* A mixture of the alcohol (**2a**) (1.23 g), *p*-methoxybenzoic acid (444 mg), DMAP (1.432 g) and 2-chloro-*N*-methylpyridinium iodide (1.076 g) in dichloromethane (10 ml) was treated and worked up as given for the preparation of (**1f**) to yield the oily p-*methoxybenzoate* (**2f**) (497 mg); $[\alpha]_D^{20}$ −61° (*c* 3.1); δ_H 0.61 (3 H, s, 18-H_3), 1.98 (3 H, s, $MeCO_2$), 3.84 (3 H, s, MeO), 4.24 and 4.54 (2 H, 2 × d, AB system, J_{gem} 12 Hz, 19-H_2), and 5.63 (1 H, m, Σ*J* 11 Hz, 6-H); $\nu_{max.}$ 1 240, 1 515, 1 583, 1 607, 1 720, and 1 745 cm^{-1} (Found: C, 76.6; H, 9.3. $C_{37}H_{54}O_5$ requires C, 76.8; H, 9.4%).

Method B. To a solution of the alcohol (**2a**) (250 mg) in pyridine (4 ml) was added a solution of *p*-methoxybenzoyl chloride (140 mg) in benzene (2 ml) and the mixture was kept at 0 °C for 2 h before being poured into ice–water, the product was extracted with ether, and the extract was worked up. The product was dissolved in chloroform and the solution was filtered through a pad of aluminium oxide to afford after work-up, the pure *p*-methoxybenzoate (**2f**) (183 mg).

Cholest-5-*ene*-3β,19-*diol* 3-*Acetate* 19-*Carbamate* (**2g**).—The *compound* was prepared similarly to (**1g**) in 69% yield and had m.p. 166—167 °C (from aqueous acetone); $[\alpha]_D^{20}$ −63° (*c* 1.4); δ_H 0.68 (3 H, s, 18-H_3), 2.00 (3 H, s, $MeCO_2$), 4.05 and 4.40 (2 H, 2 × d, AB system, J_{gem} 12 Hz, 19-H_2), 4.70 (2 H, br s, NH_2), and 5.65 (1 H, m, Σ*J* 11 Hz, 6-H); $\nu_{max.}$ 1 244 and 1 738 ($MeCO_2$), 1 592 (C=CH), 1 738, 3 275, 3 355, 3 492, and 3 510 cm^{-1} ($OCONH_2$) (Found: C, 73.8; H, 10.3; N, 2.8. $C_{30}H_{49}NO_4$ requires C, 73.8; H, 10.1; N, 2.9%).

5α-*Cholest*-1-*en*-19-*yl Carbamate* (**3g**).—The *compound* was prepared, in a similar manner to that given for (**1g**), in 77% yield and had m.p. 125—126 °C (from aqueous acetone); $[\alpha]_D^{20}$ −18° (*c* 1.2); δ_H 0.69 (3 H, s, 18-H_3), 4.17 and 4.38 (2 H, 2 × d, AB system, J_{gem} 6 Hz, 19-H_2), 4.58 (2 H, br s, NH_2), and 5.81 (2 H, br, s, 1- and 2-H); $\nu_{max.}$ 1 596 and 3 028 (HC=CH), 1 730, 3 280, 3 335, 3 490, and 3 510 cm^{-1} ($OCONH_2$) (Found: C, 78.1; H, 11.2; N, 3.2. $C_{28}H_{47}NO_2$ requires C, 78.3; H, 11.0; N, 3.3%).

Addition of Hypobromous Acid to Compounds (**1f**), (**1g**), (**2f**), (**2g**), *and* (**3g**).—The unsaturated compound (0.5 mmol) was dissolved in dioxane (5 ml) and treated with 10% 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, dried with Na_2SO_4, and the solvent was evaporated off. The residue was chromatographed on three preparative silica gel plates (20 × 20 cm) with light petroleum–ether–acetone (90:5:5) or (80:10:10) as developer. Zones containing the desired compound were collected, and eluted with ether, and the eluates were evaporated. The yields are given in the Table.

Addition of Labelled Hypobromous Acid to Compound (**1f**).—The unsaturated *p*-methoxybenzoate (**1f**) (100 mg) was dissolved in dry dioxane (2 ml), water (0.2 ml) containing 27% $H_2{}^{18}O$ was added under argon, and the mixture was treated with 70% perchloride acid (0.01 ml) and NBA (45 mg) at room temperature for 15 min. The mixture was worked up and chromatographed as given in the previous experiment to give labelled bromohydrin identical with (**7**) except for its ^{18}O content.

3α-*Bromo*-5α-*cholestane*-2β,19-*diol* 19-p-*Methoxybenzoate* (**7**). —M.p. 186—187 °C (from aq. acetone); $[\alpha]_D^{20}$ +37° (*c* 1.5); δ_H 0.61 (3 H, s, 18-H_3), 3.87 (3 H, s MeO), 4.21 (1 H, m, Σ*J* 19 Hz, 3β-H), 4.37 (1 H, m, Σ*J* 10 Hz, 2α-H), and 4.51 and 4.68 (2 H, 2 × d, AB system, J_{gem} 11.5 Hz, 19-H_2) (Found: C, 67.8; H, 9.0; Br, 13.0. $C_{35}H_{53}BrO_4$ requires C, 68.1; H, 8.7; Br, 12.9%).

* Another route might be by thermodynamic equilibration of the kinetic product, which is, however, not the case in our reactions.

2β,3β-*Epoxy*-5α-*cholestan*-19-*yl* p-*Methoxy*[carbonyl-^{18}O]-*benzoate* (**8$_I$**) *and* 2β,3β-[^{18}O]*Epoxy*-5α-*cholestan*-19-*yl* p-*Methoxybenzoate* (**8$_{II}$**).—A mixture of the ^{18}O-labelled (carbonyl) bromohydrin (**7**) (25 mg) obtained by addition of labelled hypobromous acid to compound (**1f**) in methanol (5 ml), acetone (0.5 ml), and water (0.5 ml) was refluxed with potassium hydroxide (100 mg) for 10 min. The mixture was then cooled, diluted with ether, washed with water, and dried with Na_2SO_4, and the solvent was evaporated off. The residue was dissolved in benzene and the solution was filtered through a pad of aluminium oxide. The filtrate was evaporated to yield the oily mixture of labelled epoxides (**8$_I$**) and (**8$_{II}$**) (14 mg), $[\alpha]_D^{20}$ +67° (*c* 2.2); δ_H 0.55 (3 H, s, 18-H$_3$), 3.15 (2 H, m, $W_{\frac{1}{2}}$ 5 Hz, 2α- and 3α-H), 3.85 (3 H, s, MeO), and 4.30 and 4.57 (2 H, 2 × d, AB system, J_{gem} 12 Hz, 19-H$_2$). For distribution of the label, see text.

3α-*Bromo*-5α-*cholestane*-2β,19-*diol carbonate* (**10**) had $[\alpha]_D^{20}$ +73° (*c* 2.1); δ_H 0.68 (3 H, s, 18-H$_3$), 4.04 and 4.22 (2 H, 2 × d, AB system, J_{gem} 12.5 Hz, 19-H$_2$), 4.46 (1 H, m, Σ*J* 10.4 Hz, 3β-H), and 4.64 (1 H, m, Σ*J* 9.4 Hz, 2α-H); $\nu_{max.}$ 1 777 cm^{-1} (C=O) (Found: C, 65.8; H, 9.2; Br, 15.8. $C_{28}H_{45}BrO_3$ requires C, 66.0; H, 8.9; Br, 15.6%).

6α-*Bromo*-5β-*cholestane*-3β,5,19-*triol* 3-*acetate* 19-p-*methoxybenzoate* (**12**) had $[\alpha]_D^{20}$ +34° (*c* 1.0); δ_H 0.54 (3 H, s, 18-H$_3$), 2.10 (3 H, s, MeCO$_2$), 3.20 (1 H, s, OH), 3.87 (3 H, s, MeO), 4.58 and 4.65 (2 H, 2 × d, AB system, J_{gem} 12 Hz, 19-H$_2$), 4.70 (1 H, dd, $J_{6\beta\text{-H},7\alpha\text{-H}}$ 12, $J_{6\beta\text{-H},7\beta\text{-H}}$ 5 Hz, 6β-H), and 5.28 (1 H, m, $W_{\frac{1}{2}}$ 8 Hz, 3α-H) (Found: C, 65.7; H, 8.4; Br, 11.6. $C_{37}H_{55}BrO_6$ requires C, 65.8; H, 8.2; Br, 11.8%).

6α-Bromo-5β-cholestane-3β,5,19-triol 3-acetate 5,19-carbonate (**13**) had $[\alpha]_D^{20}$ −8° (*c* 2.0) (*lit.*,[5] −6°); δ_C 11.97, 18.55, 21.27, 21.35, 21.91, 22.53, 22.78, 23.54, 23.75, 27.96, 28.00, 29.69, 30.35, 35.60, 35.97, 36.70, 37.84, 39.40, 39.45, 40.14, 41.64, 42.58, 55.70, 55.87, 55.91, 66.71, 71.12, 84.49, 146.68, and 170.89.

1α-*Bromo*-5α-*cholestane*-2β,19-*diol* 2,19-*carbonate* (**17**) had $[\alpha]_D^{20}$ +30° (*c* 2.1); δ_H 0.67 (3 H, s, 18-H$_3$), 4.19 and 4.46 (2 H, 2 × d, AB systems, J_{gem} 12.6 Hz, 19-H$_2$), 4.64 (1 H, dd, $J_{1\beta\text{-H},2\alpha\text{-H}}$ 3.6, $J_{1\beta\text{-H},3\beta\text{-H}}$ 1.4 Hz, 1β-H), and 4.70 (1 H, q, $J_{2\alpha\text{-H},1\beta\text{-H}}$ 3.6, $J_{2\alpha\text{-H},3\alpha\text{-H}} = J_{2\alpha\text{-H},3\beta\text{-H}}$ = 2.8 Hz, 2α-H); $\nu_{max.}$ 1 778 cm^{-1} (C=O) (Found: C, 65.7; H, 9.2; Br, 15.6. $C_{28}H_{45}BrO_3$ requires C, 66.0; H, 8.9; Br, 15.6%).

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