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SUBSTITUENT EFFECT ON THE DIASTEREOSELECTIVITY OF THE ACID HYDROLYSIS AND TRICHLOROACETOLYSIS OF 9,10-OXIDES DERIVED FROM trans-1,2,3,4,4a,10a--HEXAHYDROPHENANTHRENE. MECHANISM OF THE EPOXIDE RING OPENING

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Abstract: The mechanism of the acidic ring opening reactions of 2-aryloxiranes which are simple models of arene oxides, is still under discussion. Two different mechanisms have been suggested to rationalise the product distributions of the acid hydrolysis of the two types of conformationally restricted 2-aryloxiranes (2 and 3, and 5 and 6) : it would appear to be difficult to reconcile the two rationales. In order to gain insight into the reactions of benzo-epoxides of type 5 and 6, the 6-methoxy (5c and 6c) and the 7-bromo derivatives (5a and 6a) were synthesised and their acid hydrolysis (1:1 dioxane/water) and trichloroacetolysis in benzene were studied and compared with those of the unsubstituted compounds (5b and 6b). Contrary to expectations based on the results obtained with the epoxides of type 2 and 3, the introduction of the substituent on the aromatic moiety, in particular the strong electron-donating 6-methoxy, does not modify the complete anti diastereoselectivity observed in the acid hydrolysis of the unsubstituted epoxide 6b. In the case of the epoxides 5, on the contrary, the percentage of syn adduct increases noticeably with the ability of the aromatic moiety to stabilise the benzylic carbocationic centre. As for the trichloroacetolysis reactions, significant amounts of syn adducts are observed for both the epoxides 5 and 6 ; the syn stereoselectivity increases for both the epoxides 5 and 6 with the ability of the aryl to stabilise a benzylic carbocationic centre. A Hammett-type linear correlation was found between the diastereoselectivity and the σ^+ constants for the acid hydrolysis of 5a-c and for the trichloroacetolysis reactions of 5a-c and 6a-c. The results obtained are difficult to explain on the basis of either of the mechanisms hypothesised for 2-aryloxiranes, at least as they were originally proposed.

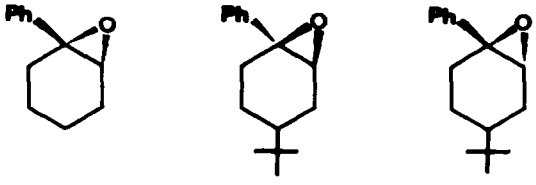
Polycyclic aromatic hydrocarbons (PAHs) are considered to be an important class of environmental mutagenic and carcinogenic compounds.[1] The carcinogenic activity of PAHs has been considered to be elicited through their metabolic transformation into reactive arene oxides,[2,3] which become covalently bonded to cellular biomolecules such as DNA through the oxirane function.[3,4] A knowledge of the ring opening mechanisms of such arene oxides should be fundamental in understanding the more complex biological reactions. The study of the nucleophilic reactions of 2--aryl-substituted oxiranes, which can be considered as models of arene oxides, in the condensed phase has been regarded of significance in understanding the biological behaviour of these last compounds.[5]

It is well known that the steric course of the ring opening of both aliphatic and cycloaliphatic 1,2-epoxides generally occurs with complete or near complete inversion of configuration.[6-8] However, when aryl or other unsaturated systems are directly linked to the oxirane ring, the stereochemistry of the acidic ring opening can range from complete retention to complete inversion of configuration

depending on the structure of the epoxide and the reaction conditions.[9-11]

Although much work has been carried out, in recent years, on the acid-catalysed reactions of 2-aryl-substituted oxirane derivatives, the papers on this topic are not at all unanimous.[9,10] The mechanism of the ring opening processes is still under discussion.[9,10]

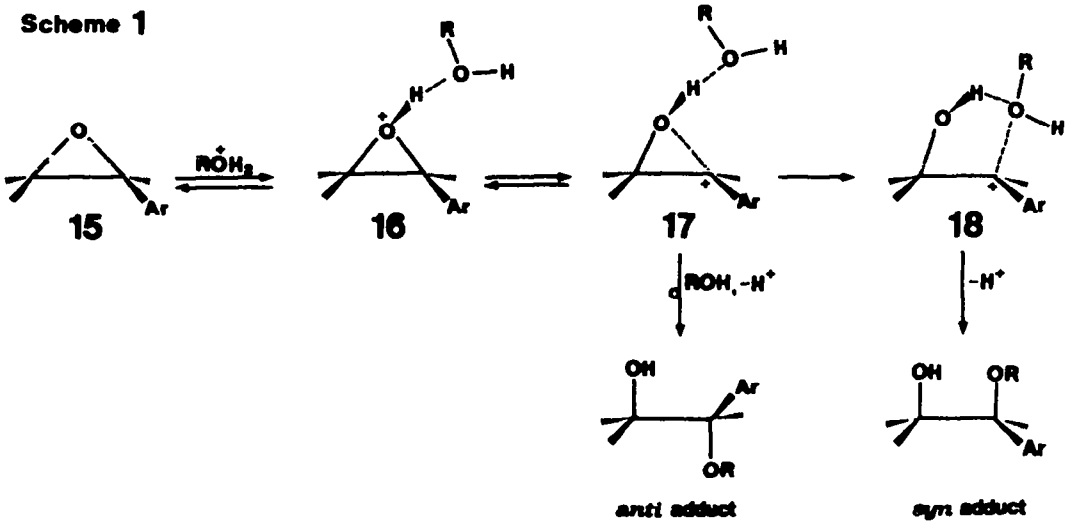
Studies of the acidic ring opening reactions (hydrolysis, alcoholysis, and trichloroacetolysis) of a series of 2-aryloxiranes of type 1 and of the corresponding conformationally rigid derivatives 2 and 3 suggest the mechanistic



1 2 3

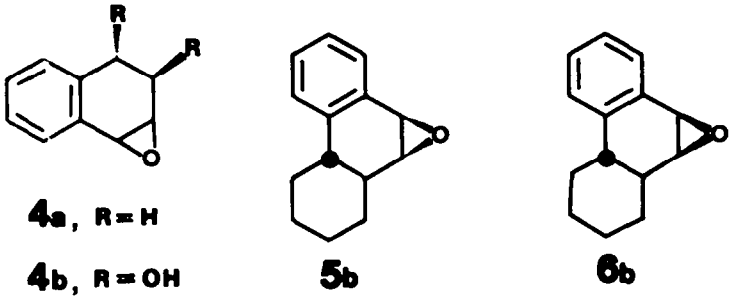
scheme summarised in Scheme 1: this presentation, which rationalises the product distribution in the ring opening process, uses simplified general formulas which should be valid for any aryl-substituted epoxide. The mechanism,[10] which implies two different carbocationic species, can be related to the "ion-dipole pair"

Scheme 1



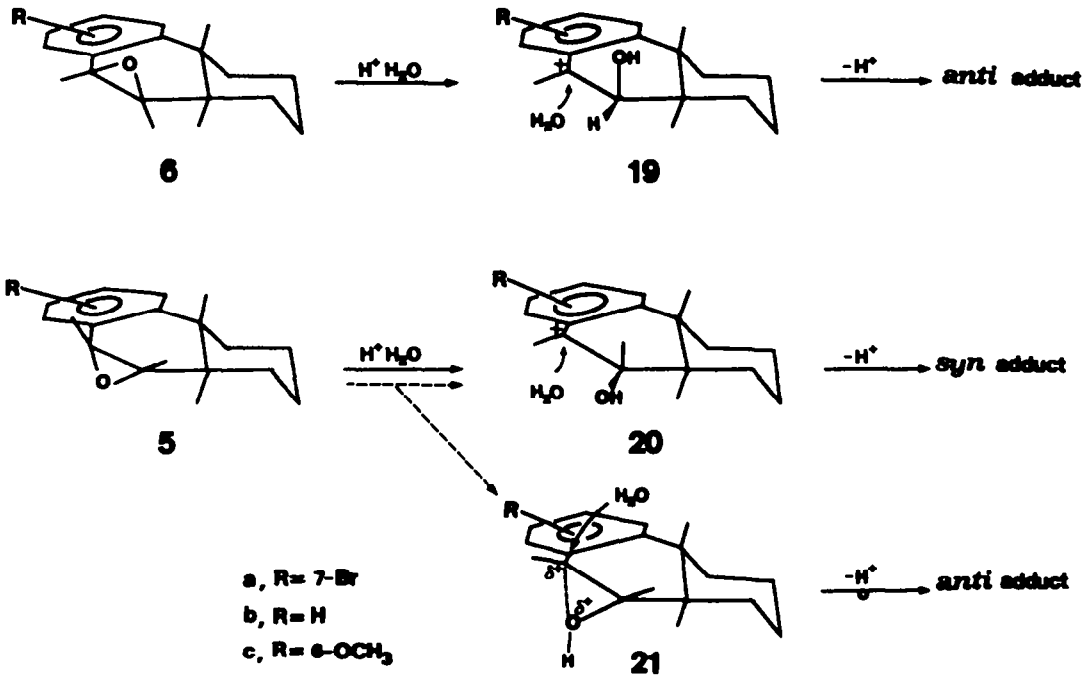
mechanism,[12] a close analogue of the Winstein ion-pair scheme of nucleophilic substitution.[13-15] According to this rationale the protonated oxirane 16 affords an intimate ion-dipole pair 17 which on attack of the nucleophile gives the anti adduct. On the other hand, internal rearrangement of the intimate ion-dipole pair 17 leads to a nucleophile-separated ion-dipole pair 18 (a more carbocationic structure) which collapses to yield the syn adduct.[10] Any factor increasing the stability of the benzylic carbocationic centre should favour the more carbocation-like intermediate (18), thus favouring the formation of the syn adduct.[10] Actually the syn diastereoselectivity, that is the syn/anti product ratio, was found, through a Hammett-type treatment, to be directly linked to the

ability of the aromatic system to stabilise the benzylic carbocationic centre both for the mobile epoxides 1[16] and for both the rigid derivatives 2 and 3.[16] The preferential reactivity of mobile epoxides 1 through a conformation corresponding to 3 and the higher syn diastereoselectivity of the epoxide 3 compared to 2 were explained through the proposed mechanism, on the hypothesis that the "axial cleavage" of the oxirane ring is energetically favoured over the "equatorial" one.[16] On the other hand the diastereoselectivity observed in the acid-catalysed hydrolysis (1:9 dioxane/water) of the conformationally rigid fused benzo-ring epoxides 6b and 5b (100% trans diol from 6b, and a 75:25 mixture of cis and trans



diols from 5b) was explained by assuming the preferential pseudoaxial attack of the nucleophile (H_2O) on the corresponding fully developed benzylic carbenium ion 19b and 20b respectively (see Scheme 2).[9] As an extension of this rationale it was

Scheme 2



suggested[9] that the product distribution observed for mobile tetrahydro- (4a) and diol epoxides of type 4b was determined by the conformation of the carbenium ion which is initially formed from the predominant ground state conformation of the

epoxide, which can undergo a pseudoaxial attack by the nucleophile.[9] However, in the case of the mobile epoxides, if the carbenium ion is stable enough to undergo conformational equilibrium prior to capture by the solvent, the axial attack of the nucleophile on the alternative carbenium ion can be decisive.[9] According to the extension of this mechanism[9] to mobile epoxides of type 4, factors increasing the stability of the benzylic carbenium ion (e.g. electron-donating group on the aryl) favour its conformational equilibrium and consequently the formation of products arising from the alternative carbenium ion.[9]

It appears to us very likely that the mechanism by which 2-aryloxiranes react under acidic conditions should be the same in all cases, independently of the structure of the epoxide.[10] Consequently, the rationalisation of the product distributions in the reactions of the epoxides of type 1 and 4 and in general of 2-aryloxiranes should follow either the same mechanistic scheme or schemes which are closely inter-connected. However, the two mechanisms suggested[9,10] are completely different in nature and cannot be easily reconciled.[10] When the mechanism implying a fully developed benzylic carbenium ion was suggested,[9] in order to rationalise the stereochemical outcome of the reactions in the 1-arylcyclohexene oxide system (1), it was shown to be completely inadequate.[10] However, attempts to rationalise the steric course of the reactions of the rigid benzo-epoxides **5b** and **6b** of type 4, through a mechanism analogous to the one proposed by us for the 1-arylcyclohexene oxide system, were unsuccessful.[10] It appears that significant differences between the two systems must be present and further clarification is required.

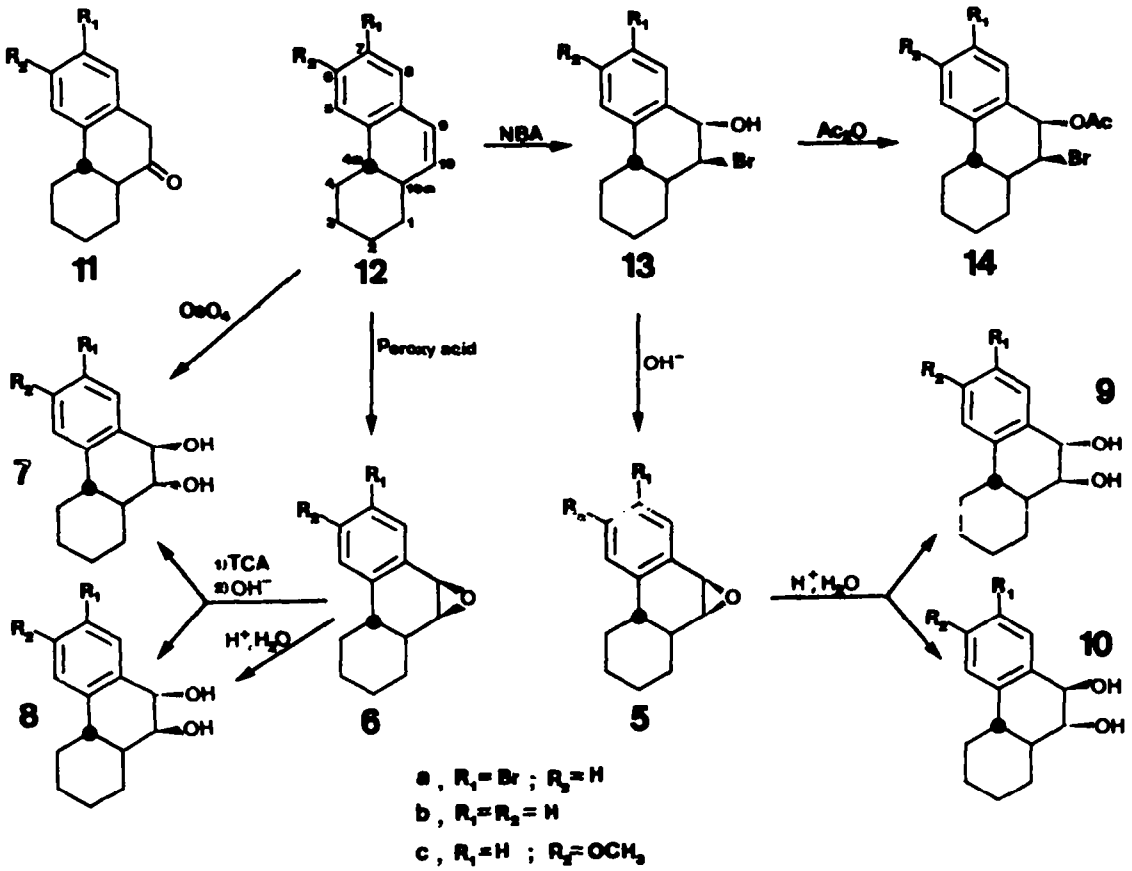
To get a better insight into the reactions of the benzo-epoxides of type 4, it was thought worth while to verify how far the product distribution of the rigid derivatives **5b** and **6b** is influenced by different aryl substituents. Therefore the 7-bromo- **5a** and **6a**, and the 6-methoxy-derivatives **5c** and **6c** were synthesised and their acid hydrolysis (1:1 dioxane/water) and trichloroacetolysis in anhydrous benzene were studied. Trichloroacetolysis in benzene and hydrolysis under acidic conditions are distinct reactions; however, it may be pointed out that the mechanisms of the ring opening of oxiranes under acidic catalysis, even if in different conditions, should be somewhat related. Therefore information from the comparison of the two different types of reactions could be reasonably useful for a complete understanding of the acidic (hydrolysis and trichloroacetolysis) ring opening mechanism of these systems.

Results

The epoxides **5a,c** and **6a,c** were prepared from the corresponding olefins **12a,c**[17] following as closely as possible the procedures used for the corresponding

derivatives (5b and 6b) having no substituents on the aromatic ring.[9,18] Treatment of 12a and 12c with N-bromoacetamide in aqueous THF[9] affords the trans diaxial bromohydrins 13a and 13c respectively, which on treatment with a base give the corresponding epoxides 5a and 5c (see Scheme 3). Direct epoxidation of 12a with m-chloroperoxybenzoic acid in anhydrous THF, in accordance with the method previously used for 6b,[9] gave the epoxide 6a. On the contrary,

Scheme 3



treatment of olefin 12c under the same conditions yielded a complex mixture mostly consisting of products, very likely hydroxy m-chlorobenzoates, deriving from the ring opening of 6c with m-chlorobenzoic acid, together with only a very small amount of the desired epoxide 6c. Pure epoxide 6c was obtained by direct epoxidation of 12c at 0°C in a two-phase system (Et_2O and saturated aqueous $NaHCO_3$ solution) using an ether solution of peroxybenzoic acid. The trans diaxial diols 8a and 8c were the only products obtained in the acid hydrolysis of epoxides 6a and 6c respectively. The corresponding cis diols 7a and 7c (see Scheme 3) were obtained by cis-dihydroxylation with OsO_4 of the olefins 12a and 12c, respectively. The cis 9a and trans 10a, and cis 9c and trans 10c diols were obtained as mixtures from the acid hydrolysis of the corresponding epoxides 5a and 5c in 1:1 dioxane/water: the diols 9c and 10c were directly separated from this mixture and

purified by preparative TLC, whereas from the mixture of **9a** and **10a** only pure diol **10a** was obtained by fractional crystallization. As for the diol **9a**, it was separated (as a diacetate) by preparative TLC, only when the starting mixture of diols **9a** and **10a** was transformed into a mixture of the corresponding diacetates (**Dia-9a** and **Dia-10a**), because of the very low solubility of these 7-bromo diols in most of the usual solvents. Saponification of **Dia-9a** afforded pure diol **9a**.

In order to perform the acid-hydrolysis of all the epoxides (**5a-c** and **6a-c**) under the same conditions and in homogeneous solutions, the reactions were carried out in 1:1 dioxane/water, that is under conditions different from those (1:9 dioxane/water) originally used for the unsubstituted epoxides **5b** and **6b**.[9] The same hydrolytic conditions were used in the analogous study of epoxides of type 1-3.[10]

The relative percentages of *syn* and *anti* adducts obtained in the acid-catalysed hydrolysis in 1:1 dioxane/water and in the trichloroacetolysis in anhydrous benzene of epoxides **5a-c** and **6a-c** are shown in Table 1. While the hydrolysis reaction mixtures were analysed by GLC after transformation of the diols obtained into their trimethylsilyl derivatives, the reaction mixtures from the trichloroacetolysis reactions were examined only after saponification of the mono-esters obtained (primary reaction products) into the corresponding diols and subsequent conversion of the latter into the trimethylsilylethers.

It should have been possible to infer the structure and configuration of the epoxides **5a,c** and **6a,c** and of diols **7-10a,c**, simply on the basis of their methods of synthesis; these resemble those of the corresponding derivatives without any substituent on the aromatic ring, whose structure and configuration has been firmly established.[9,15,16] The stereoselectivity of the attack of all the electrophilic reagents (peroxyacid, positive bromine, osmium tetroxide) on the olefins 12[9,15,16] should not be modified by the presence of different substituents on the aromatic moiety: to confirm this point, the structure of the acetate (**14c**) of the 6-methoxybromohydrin (**13c**) was determined by an X-ray diffractometric method.[17] However, the structure and configuration of both the epoxides **5a,c** and **6a,c** and of diols **7-10a,c** can be demonstrated by a comparison of the ^{1}H NMR spectra of the epoxides **5a,c** and **6a,c**, and of the diacetates (**Dia-7a,c - Dia-10a,c**) of the diols **7-10a,c** with those of the corresponding derivatives of the **b** series having no substituent on the aromatic ring. Apart from the pattern of the aromatic moiety in both the **a** and the **c** series, and the signal of the methoxy group for the compounds of the **c** series, the spectra of the compounds of the **a** and the **c** series correspond closely to those of the **b** series. The $J_{9,10}$ and $J_{10,10a}$ coupling constants measured for the diacetates (**Dia-7a,c - Dia-10a,c**) of the diols **7-10a,c** (Table 2) offer further support for the structure and configuration assigned to the diols.[9]

Table 1. Stereochemistry of the ring opening of epoxides 5a-c and 6a-c under acid conditions at 25°C.

Epoxide	Solvent	Acid	Reaction time	syn adduct%	anti adduct%
5a	Dioxane-H_2O (1:1)	H_2SO_4	2 min	31.0[a]	69.0[b]
5b	Dioxane-H_2O (1:1)	H_2SO_4	2 min	51.4[c]	48.6[d]
5c	Dioxane-H_2O (1:1)	H_2SO_4	2 min	81.1[e,p]	18.9[f,p]
5a	Benzene	CCl_3COOH	24 h	14.3[a,o]	85.7[b,o]
5b	Benzene	CCl_3COOH	2 min	22.4[c,o]	77.6[d,o]
5c	Benzene	CCl_3COOH	2 min	56.1[e,o,q]	43.9[f,o,q]
6a	Dioxane-H_2O (1:1)	H_2SO_4	2 min	0[g]	100[h]
6b	Dioxane-H_2O (1:1)	H_2SO_4	2 min	0[i]	100[j]
6c	Dioxane-H_2O (1:1)	H_2SO_4	2 min	0[m]	100[n]
6a	Benzene	CCl_3COOH	24 h	7.7[g,o]	92.3[h,o]
6b	Benzene	CCl_3COOH	2 min	15.3[i,o]	84.7[j,o]
6c	Benzene	CCl_3COOH	2 min	38.7[m,o]	61.3[n,o]

[a] Diol 9a; [b] Diol 10a ; [c] Diol 9b ; [d] Diol 10b ; [e] Diol 9c ; [f] Diol 10c ; [g] Diol 7a ; [h] Diol 8a; [i] Diol 7b ; [j] Diol 8b ; [m] Diol 7c ; [n] Diol 8c ; [o] After saponification of the crude reaction mixture ; [p] Ketone 11c was also present (5%) ; [q] Ketone 11c was the main reaction product (65%).

Discussion

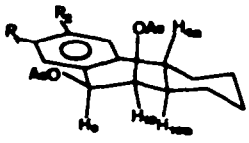
Before discussing the results of the effects of the aryl substituents on the diastereoselectivity of the reactions of epoxides 5a-c and 6a-c, we would like to make a few comments on the mechanism originally suggested, in order to rationalise the diastereoselectivity of the acid-hydrolysis of epoxides 5b and 6b in 1:9 dioxane/water.[9] As pointed out above, this rationalisation[9] implies the intermediate formation of the carbenium ions 19b and 20b, followed by a stereoselective pseudoaxial attack of the nucleophilic solvent. This mechanism, however, does not give any explanation for the different stereoselectivity of the reactions of the two epoxides 6b and 5b (100% anti adduct from 6b and a 75:25 mixture of syn and anti adduct from 5b).[9] While the complete pseudoaxial attack by the solvent on the carbenium ion 19b (derived from epoxide 6b) must have occurred, only 75% of the same type of attack on the diastereoisomeric related ion 20b, derived from 5b, is envisaged; but the only difference between the carbenium ions 19b and 20b appears to be in the position of the vicinal OH, axial in 19b and equatorial in 20b.Coming back to the studies on the effects of the substituent on the aryl, it may be noted

that the behaviour of the epoxides 5a-c and 6a-c is somewhat intriguing. The substituent effect on the diastereoselectivity of the hydrolysis and trichloroacetolysis of the epoxides 5a-c and 6a-c is not univocal, and it is not easy to give a complete explanation for it on the basis of either of the two mechanisms proposed for 2-aryloxiranes.[9,10] Contrary to expectations based on the results obtained with the epoxides of type 2 and 3,[10] the introduction of the substituents, in particular the strong electron-donating 6-methoxy group, on the aromatic moiety of epoxides 6, does not modify the complete anti diastereoselectivity observed in the acid hydrolysis of the unsubstituted epoxide 6b. In the case of the hydrolysis of the epoxides 5a-c, on the contrary, the percentage of syn adduct increases noticeably with the ability of the aromatic moiety to stabilise the benzylic carbocationic centre, that is to say on passing from the 7-bromo derivative, through the unsubstituted one, to the 6-OMe derivative. As for the trichloroacetolysis reactions, significant amounts of syn adducts are observed for both the epoxides 5a-c and 6a-c; however, in this case, the syn stereoselectivity increases, for both the epoxides 5a-c and 6a-c, with the ability of the aryl group to stabilise a benzylic positive charge. In the case of the reactions of the p-methoxy derivative 5c, different amounts of the ketone 11c were revealed (5% in the hydrolysis, and 65% in the trichloroacetolysis) (GLC).

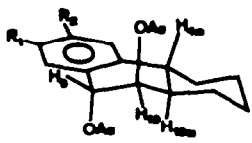
As for the hydrolysis reactions of 5a-c and the trichloroacetolysis of the epoxides 5a-c and 6a-c, a Hammett-type linear correlation was found between the diastereoselectivity and the σ^+ constants,[20] in accordance with equation 1.[10,16,21] The $\varrho_{syn} - \varrho_{anti}$ values obtained are summarised in Table 3 together with their correlation coefficients (r) and standard deviations (s). An analogous correlation was found for the acid hydrolysis of both the mobile epoxides of type 1[16] and the rigid epoxides of type 2 and 3.[10]

The complete anti stereoselectivity of the hydrolysis of the epoxides 6a-c, independently of the presence of any type of substituent on the aromatic ring, tends to favour the mechanism[9] implying the fully developed carbonium ion 19 preferentially attacked in a pseudoaxial fashion.[9] On the contrary, the data from epoxides 5a-c show a highly variable syn diastereoselectivity ranging from 31% to 81% depending on the substituent (see Table 1). Keeping in mind that epoxides 5, and consequently the corresponding completely developed carbonium ions 20 derived from them, are conformationally locked, it is difficult to explain the results observed by such a mechanism.[9] According to this mechanism, the syn diastereoselectivity should be practically invariable with the substituent. In order to reconcile the data obtained with the mechanism originally suggested,[9] one could suggest that in the case of the epoxides of type 5 there is competition between a completely developed benzylic carbenium ion 20 pseudoaxially attacked to give the syn adduct, and an incipient benzylic carbenium ion 21, similar to the

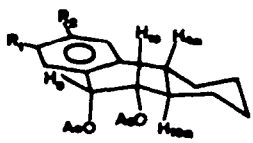
Table 2. ^{1}H NMR Parameters for diacetates (Dia7a,c - Dia10a,c) of diols (7-10a,c) from epoxides 5a,c and 6a,c.[a]



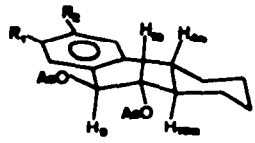
Dia-7



Dia-8



Dia-9



Dia-10

a, R_1=Br, R_2=H ; c, R_1=H R_2=OCH_3

Compound	δH_9	δH_{10}	$J_{9,10}$	$J_{10,10a}$
Dia-7a	6.03	5.42	3.7	0.5
Dia-7c	6.05	5.41	4.0	0.5
Dia-8a	5.82	5.04	2.7	1.8
Dia-8c	5.84	5.05	2.7	1.8
Dia-9a	6.13	5.00	3.8	10.8
Dia-9c	6.17	5.00	3.7	11.1
Dia-10a	6.12	5.13	8.3	10.9
Dia-10c	6.14	5.12	8.0	10.8

[a] Spectra were measured in $CDCl_3$ at 80 MHz. Chemical shift are in ppm, and coupling constants are in Hz

Table 3. $\varrho_{syn} - \varrho_{anti}$ Values obtained for the acid-catalysed hydrolysis of epoxides 5a-c and trichloroacetolysis of epoxides 5a-c and 6a-c according to equation 1.

$$\log \frac{[S][A^\circ]}{[A][S^\circ]} = (\varrho_{syn} - \varrho_{anti})\sigma^+ \qquad (1)$$

Epoxide	Reagents	$\varrho_{syn} - \varrho_{anti}$	Correlation coefficient (r)	Standard deviation(s)
5	H_2SO_4-Dioxane/H_2O	-0.82	0.999	0.016
5	TCA-Benzene	-0.75	0.996	0.031
6	TCA-Benzene	-0.73	0.999	0.016

one (17) suggested in our mechanism, which on attack of the nucleophile from the back side, because of the strong shielding at the front side,[19] gives the anti adduct with inversion of configuration. According to this modified mechanism, an increase in the stability of the benzylic carbenium ion would favour the more carbocation-like structure 20, thus favouring the syn adduct. However, it would

appear to us somewhat unreasonable to assume that epoxides **6a-c** yield fully--developed carbenium ions and that epoxides **5a-c** do not. Alternatively the results obtained in the acid hydrolysis of epoxides of type **5** could be equally explained by a mechanism like the one described in Scheme 2,[10] even if no explanation can be given on the basis of this mechanism, for the complete lack of syn adducts from epoxides **6**. Anyway, in both the two alternative rationalisations a Hammett-type correlation of the syn diastereoselectivity of the acidic hydrolysis of epoxides **5** could be expected, as actually found.

As for the trichloroacetolysis reactions, the presence of noticeable amounts of syn adduct from the epoxides **5a-c** and **6a-c**, which in both the two systems are directly linked to the ability of the aromatic system to stabilise the benzylic carbocation (see Table 1), is not explained by the mechanism implying the pseudoaxially attacked carbocation,[9] even in our modified version. According to this scheme (Scheme 2), in the case of epoxides of type **6**, the syn adduct should be expected to decrease as the ability of the aryl to stabilise the benzylic carbenium ion increases, contrary to the results observed (see Table 1). On the contrary, the mechanism depicted in Scheme 1[10] could rationalise these results.

In conclusion, it appears to us that the significant differences in behaviour between the epoxides of type **2** and **3**, and **5** and **6** pointed out above, still remain. It is difficult to give a complete explanation for the results obtained on the basis of either of the mechanisms hypothesised for 2-aryloxiranes,[9,10] even in a modified version. Much further work must therefore be done in order to arrive at a full understanding of the acidic ring opening of this class of biologically important compounds.

Experimental

Melting points were determined on a Kofler apparatus and are uncorrected. IR spectra for the comparison of compounds were taken on paraffin oil mulls on a Perkin-Elmer Model 137 infracord. ^1H NMR spectra were determined in ca 10% $CDCl_3$ solution with a Varian EM 360 spectrometer using Me_4Si as the internal standard. In the case of compounds **5a,c**, **6a,c**, **Dia-7a,c - Dia10a,c** the ^1H NMR spectra were also measured with a Varian CFT 20 spectrometer. GLC analyses of mixtures of diols **9** and **10a-c**, and **7** and **8a-c** obtained in the acid hydrolysis and trichloroacetolysis of the corresponding epoxides **5a-c** and **6a-c**, were performed only after transformation of the crude diols mixture into the corresponding mixture of their trimethylsilyl derivatives. In all cases GLC analyses were run on a Carlo Erba Fractovap 4200 apparatus with a flame ionization detector and a glass column (2 m x 2.5 mm) packed with 10% diethylene glycol succinate on 80-100 mesh silanized Chromosorb W in the following conditions: diols **7-10a**, column 205°C, evaporator and detector 240°C; diols **7-10b**, column 180°C, evaporator and detector 210°C; diols **7-10c**, column 205°C, evaporator and detector 240°C; the nitrogen flow in all cases, was 40 ml/min. Semipreparative TLC was performed on 0.5-mm silica gel plates (Merck F_{254}) containing a fluorescent indicator. Petroleum ether refers to the fraction with bp 40-70°C. In a typical run, diacetates (**Dia-7a,c - Dia-10a,c**) were prepared as follows: the diol (0.15 g) in anhydrous pyridine (1.5 ml) was treated at 0°C with Ac_2O (2.5 ml) then left 24 h at room temperature. Ice-water was added and after 2 h the reaction mixture was extracted with ether. Evaporation of the washed (10% aqueous HCl, saturated aqueous $NaHCO_3$, and water) ether extracts afforded the corresponding diacetate which was recrystallised from petroleum ether bp 60-80°C. Only **Dia-8c** was recovered as a viscous oil which did not crystallise. Epoxides **5b** and **6b** and diols **7-10b** were prepared as previously described.[9] All the compounds described in this paper gave satisfactory elemental analyses.

(4aβ,9α,10β)-7,10-Dibromo-9-hydroxy-trans-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (13a)
A solution of olefin 12a (0.52 g, 2.0 mmol) in 75% THF-H_2O was treated with NBA (0.303 g, 2.2 mmol), then left overnight at room temperature. Ice-water was added and the reaction mixture was extracted with ether. Evaporation of the washed (water) ether extracts afforded a solid residue (0.70 g) which was recrystallised from hexane to give pure 13a (0.45 g) as a solid, mp 112-113°C; IR 3300 cm^{-1} (OH); ^1H NMR δ 7.58-7.13 (m,3H,aromatic protons), 4.83 (d,1H, J=2.2 Hz, H_9), 4.23 (m,1H,H_{10}).

(4aβ,9α,10α)-7-Bromo-9,10-epoxy-trans-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (5a)
A solution of bromohydrin 13a (0.30 g, 0.83 mmol) in anhydrous benzene (10 ml) was treated with potassium t-butoxide (0.090 g, 0.83 mmol). After 1 h stirring at room temperature, another portion (0.090 g) of the same base was added, followed by another 1 h stirring. The organic solution was washed (water), and evaporated to give a solid residue (0.21 g) consisting of 5a which was recrystallised from hexane at -10°C to give pure 5a (0.17 g) as a solid, mp 106.5-107°C; ^1H NMR δ 7.63 (d,1H, J=2.1 Hz, H_8), 7.47-7.02 (m,2H,H_5 and H_6), 3.68 (d,1H, $J_{9,10}$= 4.1 Hz,H_9), 3.27 (dd,1H, $J_{9,10}$=4.1 Hz, $J_{10,10a}$=1.2 Hz, H_9).

(4aβ,9α,10α)-9,10-Epoxy-6-methoxy-trans-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (5c)
Bromohydrin 13c[17] (0.34 g, 1.09 mmol) in anhydrous benzene (20 ml) was treated with potassium t-butoxide (0.147 g x 2) as indicated in the analogous preparation of 5a. Evaporation of the organic solution afforded an oily residue (0.23 g) which slowly solidifies. Recrystallisation from pentane at -20°C afforded pure 5c (0.15 g) as a solid, mp 75-76°C; ^1H NMR δ 7.30 (d,1H, J=9.0 Hz, H_8), 6.85-6.61 (m,2H,H_5 and H_6), 3.79 (s,3H,OCH_3), 3.71 (d,1H, $J_{9,10}$= 4.2 Hz, H_9), 3.25 (dd,1H, $J_{9,10}$=4.2 Hz, $J_{10,10a}$=1.3 Hz, H_{10})

(4aβ,9β,10β)-7-Bromo-9,10-epoxy-trans-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (6a)
A solution of olefin 12a (0.25 g) in anhydrous THF (10 ml) was treated with MCPBA (1.0 g) at room temperature and left 4 h at the same temperature. Ether was added and the organic solution was washed (10% aqueous NaOH solution, and water), then evaporated to give a solid residue (0.23 g) consisting of crude 6a which was recrystallised from petroleum ether at -10°C to give pure 6a as a solid, mp 74-75°C; ^1H NMR δ 7.52-7.03 (m,3H,aromatic protons), 3.80 (d,1H, $J_{9,10}$=4.3 Hz, H_9), 3.45 (d,1H, $J_{9,10}$=4.3 Hz, H_{10}).

(4aβ,9β,10β)-9,10-Epoxy-6-methoxy-trans-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (6c)
A two phase system made from a solution of olefin 12c (0.64 g, 3 mmol) in Et_2O (40 ml) and saturated aqueous $NaHCO_3$ solution (40 ml) was treated at 0°C,under vigorous stirring,with a 0.32 M peroxybenzoic (PBA) solution in Et_2O (9.3 ml) (addition time 15 min). The same amount of the PBA solution was added at 1 h intervals, with the temperature rigorously kept at 0°C, while the proceeding reaction was followed by TLC. When only few traces of the starting olefin were revealed, the reaction mixture was quenched with 10% aqueous $Na_2S_2O_3$ solution. After 10 min stirring at room temperature the ether was separated, washed (water, 5% aqueous NaOH solution, and water) then evaporated to give a semisolid residue (0.60 g) mostly consisting of 6c which was taken up in pentane. After concentration of the pentane solution, pure 6c was obtained at -20°C as crystals, mp 70-71°C; ^1H NMR δ 7.30 (d,1H, J=7.8 Hz, H_8), 6.80-6.78 (m,2H, H_5 and H_7), 3.95 (d,1H, $J_{9,10}$=4.4 Hz, H_9), 3.80 (s,3H,OCH_3), 3.44 (d,1H, $J_{9,10}$=4.4 Hz, H_{10}).
When the direct epoxidation of olefin 12c was performed with MCPBA in the same conditions as described above for the corresponding reaction of olefin 12a, only carbonylic products, presumably deriving from the ring opening of the initially formed oxirane 6c, were obtained.

Reaction of epoxide 6a in a 1:1 aqueous 0.2 N H_2SO_4/dioxane solution
A solution of epoxide 6a (0.050 g) in a 1:1 aqueous 0.2 N H_2SO_4/dioxane (50 ml) was stirred at 25°C for 2 min, then quenched with solid $NaHCO_3$,and saturated aqueous $NaHCO_3$ and extracted with ether. Evaporation of the washed (water) ether extracts yielded a solid residue consisting of diol 8a as the only product (GLC) which was recrystallised from petroleum ether bp 60-80°C and a few drops of benzene to give pure (4aβ,9α,10β)-7-bromo-trans-1,2,3,4,4a,9,10,10a-octahydrophenanthren-9,10-diol (8a) (0.035 g) as a solid, mp 173-174 °C, IR 3300 cm^{-1} (OH). Diacetate (Dia-8a), solid, mp 171-172 °C, IR 1735 cm^{-1}(C=O); ^1H NMR, see Table 2.

(4aβ,9β,10β)-7-Bromo-trans-1,2,3,4,4a,9,10,10a-octahydrophenanthren-9,10-diol (7a)
A solution of olefin 12a (0.16 g, 0.60 mmol) in anhydrous pyridine (5 ml) was treated with OsO_4 (0.152 g, 0.60 mmol) then left 64 h at room temperature. The reaction mixture was treated with solid $Na_2S_2O_5$ (0.50 g), water (5 ml) and pyridine (2 ml), stirred 1 h at room temperature, and then extracted with CH_2Cl_2. Evaporation of the washed (cold 10% aqueous HCl, water, saturated aqueous $NaHCO_3$, and water) organic solution afforded a solid residue consisting of 7a which was recrystallised from petroleum ether bp 60-80°C and a few drops of benzene to give pure 7a (0.11 g) as a solid, mp 177-178°C; IR 3330 cm^{-1} (OH). Diacetate(Dia-7a), solid, mp 137-138°C; IR 1735 cm^{-1} (C=O); ^1H NMR, see Table 2.

Reaction of epoxide 5a in a 1:1 aqueous 0.2 N H_2SO_4/dioxane solution
A solution of epoxide 5a (0.35 g) in a 1:1 aqueous 0.2 N H_2SO_4/dioxane (100 ml) was stirred for 1 h at room temperature. The usual work-up, as described above for the analogous reaction of epoxide 6a, afforded a solid residue (0.35 g) consisting of the two diols cis 9a and trans 10a in the ratio as reported in Table 1. In one experiment a portion (0.050 g) of this crude reaction product was subjected to semipreparative TLC (a 35:55:10 mixture of hexane, ethyl acetate, and methanol was used as the eluant: elution was repeated twice). Extraction of the most intense band afforded a solid residue still consisting of 9a and 10a which on recrystallisation from petroleum ether and a few drops of benzene afforded pure (4aβ,9β,10α)-7-bromo-trans-1,2,3,4,4a,9,10,10a-octahydrophenanthren-9,10-diol (10a) as a solid, mp 176-177°C; IR 3325 cm^{-1} (OH).Diacetate (Dia-10a), solid, mp 168-169°C, IR 1730 cm^{-1} (C=O); ^1H NMR, see Table 2.

In another experiment, in order to recover the cis diol **9a** in the pure state, the crude reaction mixture (0.30 g) from the acid-catalysed hydrolysis of **5a** in 1:1 0.2 N H_2SO_4/dioxane, consisting of the two diols cis **9a** and trans **10a** (see Table 1), was transformed into a mixture of the corresponding diacetates (**Dia-9a** and **Dia-10a**) by the usual method. The crude reaction product (0.37 g) was subjected to preparative TLC on 1-mm silica gel plate (a 8:2 mixture of petroleum ether and ether was used as the eluant; elution was repeated twice). Extraction of the two most intense bands (the slower moving band contained **Dia-10a**) afforded **Dia-10a** (0.13 g) and **Dia-9a** (0.070 g) as a solid, mp 145-146°C; IR 1730 cm^{-1} (C=O); ^1H NMR, see Table 2.

Dia-9a (0.050 g) was saponified in THF (4 ml) with 1 M KOH in EtOH (1.4 ml) as below described for the analogous reaction on trichloroacetates, to give a crude solid product consisting of cis diol **9a** which was recrystallised from benzene to give pure (4aβ,9a,10a)-7-bromo-trans-1,2,3,4,4a,9,10,10a-octahydrophenanthren-9,10-diol (**9a**)(0.020 g) as a solid, mp 196-197°C; IR 3350 cm^{-1} (OH).

Reaction of epoxide **6c** in a 1:1 aqueous 0.2 N H_2SO_4/dioxane solution

A solution of epoxide **6c** (0.20 g) in a 1:1 aqueous 0.2 N H_2SO_4/dioxane (50 ml) was stirred at room temperature for 2 min then worked up as usual to yield a crude product, as a very dense oil, consisting of the only trans diol **8c** (GLC). **8c** did not crystallise and so it was purified by preparative TLC (a 5:5:0.1 mixture of petroleum ether, ether and methanol was used as the eluant; elution was repeated three times) to give pure (4aβ,9a,10β)-6-methoxy-trans-1,2,3,4,4a,9,10,10a-octahydrophenanthren-9,10-diol (**8c**) (0.12 g) as a glass; IR 3400 cm^{-1} (OH). Diacetate (**Dia-8c**), as a glass, IR 1730 cm^{-1} (C=O), ^1H NMR, see Table 2.

(4aβ,9β,10β)-6-Methoxy-trans-1,2,3,4,4a,9,10,10a-octahydrophenanthren-9,10-diol (**7c**)

Reaction of olefin **12c** (0.16 g, 0.74 mmol) in anhydrous pyridine (2 ml) with OsO_4 (0.208 g, 0.82 mmol) for 12 h at room temperature, following the procedure previously described for the corresponding reaction of olefin **12a**, afforded a crude semisolid residue (0.16 g), which on recrystallisation from petroleum ether afforded pure **7c** (0.060 g) as a solid , mp 60-61°C; IR 3400 cm^{-1} (OH) Diacetate (**Dia-7c**), solid, mp 130-132°C; IR 1735 cm^{-1} (C=O); ^1H NMR, see Table 2.

Reaction of epoxide **6c** with trichloroacetic acid in anhydrous benzene

A solution of epoxide **6c** (0.20 g, 0.87 mmol) in anhydrous benzene (20 ml) was treated at 25°C with a 1 M CCl_3COOH solution in anhydrous benzene (0.95 ml), and the resulting reaction mixture was left 2 min at the same temperature. The organic solution was washed (saturated aqueous $NaHCO_3$ solution) dried and evaporated to give an oily residue (0.33 g), consisting of a mixture of the monotrichloroacetates of diols **7c** and **8c** which was dissolved in THF (16 ml), treated with 1 M KOH in EtOH (5 ml), then left 5 h at room temperature. Dilution with water, extraction with ether and evaporation of the ether extracts afforded a solid residue (0.18 g) consisting of the two diols cis **7c** and trans **8c**, in the ratio shown in Table 1, which was subjected to semipreparative TLC (a 5:5:0.1 mixture of petroleum ether, ether, and methanol was used as the eluant; elution was repeated several times). Extraction of the two main bands (the slower moving band contained **8c**) afforded **7c** (0.030 g) and **8c** (0.060 g).

Reaction of epoxide **5c** in a 1:1 aqueous 0.2 N H_2SO_4/dioxane solution

Following the procedure as described above, reaction of epoxide **5c** (0.20 g) in a 1:1 aqueous H_2SO_4/dioxane solution (50 ml) for 2 min at 25°C afforded a crude solid reaction product (0.19 g) consisting of mixture of diols cis **9c** and trans **10c** in the ratio shown in Table 1, which was subjected to semipreparative TLC (a 5:5:0.1 mixture of petroleum ether, ether, and methanol was used as the eluant; elution was repeated four times). Extraction of the two main bands (the slower moving band contained **10c**) gave the following: (4aβ,9a,10a)-6-methoxy-trans-1,2,3,4,4a,9,10,10a-octahydrophenanthren-9,10-diol (**9c**) (0.090 g) as a solid, mp 178-179°C; IR 3450 cm^{-1} (OH). Diacetate (**Dia-9c**), solid, mp 123-125°C; IR 1720 cm^{-1} (C=O); ^1H NMR, see table 2. (4aβ,9β,10a)-6-methoxy-trans-1,2,3,4,4a,9,10,10a-octahydrophenanthren-9,10-diol (**10c**) (0.030 g), as a solid, mp 102-103°C; IR 3300 cm^{-1} (OH). Diacetate (**Dia-10c**), solid, mp 127-128°C, IR 1720 cm^{-1} (C=O); ^1H NMR, see Table 2.

Reaction of epoxide **5c** with trichloroacetic acid in anhydrous benzene

A solution of epoxide **5c** (0.15 g, 0.65 mmol) in anhydrous benzene (15 ml) was treated with 1 M CCl_3COOH in anhydrous benzene (0.71 ml). After 2 min at room temperature the benzene solution was washed (saturated aqueous $NaHCO_3$) dried and evaporated to give an oily residue (0.20 g) which was divided into two portions and separately treated as follows:

a) a 0.10 g portion was saponified in THF (5 ml) with 1 M KOH in EtOH (1.5 ml) as usual to give a semisolid residue (0.080 g) which was subjected to semipreparative TLC (a 5:5:0.1 mixture of petroleum ether, ether, and methanol was used as the eluant; elution was repeated several times). Extraction of the two nicely separated slower moving bands afforded cis **9c** (0.010 g) and trans diol **10c** (0.010 g).

b) a second 0.10 g portion was directly subjected to semipreparative TLC (a 8:2 mixture of petroleum ether and ether was used as the eluant; elution was repeated twice). Extraction of the most intense band (R_f=0.35) afforded pure 6-methoxy-trans-1,2,3,4,4a,10a-hexahydro-10(9H)-phenanthrenone (**11c**) (0.023 g) as a liquid; IR 1700 cm^{-1} (C=O); ^1H NMR δ 7.1-6.66 (m,3H,aromatic protons), 3.83 (s,3H,OCH_3), 3.50 (s,2H,$COCH_2$)

Reactions of epoxides **5a-c** and **6a-c** in dioxane-water in the presence of acid

A solution of the epoxide (0.020 g) in a thermostated (25°C) 1:1 aqueous 0.2 N H_2SO_4/dioxane (20 ml) was stirred at 25°C for the time shown in Table 1, quenched with solid $NaHCO_3$ and saturated aqueous $NaHCO_3$, and extracted with ether. Evaporation of the washed (water) and dried ether extracts yielded mixtures consisting of diols **9a-c** and **10a-c** from epoxides **5a-c** and diols **8a-c** from epoxides **6a-c** which were analysed by GLC (as trimethylsilyl derivatives). The diols (**7-10a-c**) were completely stable under the reaction conditions used.

Reactions of epoxides 5a-c and 6a-c with trichloroacetic acid in anhydrous benzene

A solution of the epoxide (0.15 mmol) in anhydrous benzene (3 ml) was treated at 25°C with a 1 M solution of CCl_3COOH in the same solvent (0.165 ml) and then left at the same temperature for the time shown in Table 1. The reaction mixture was then washed (saturated aqueous $NaHCO_3$, and water), dried and evaporated to give an oily residue consisting of monotrichloroacetates which were hydrolysed by dissolving the crude product in THF (2.5 ml) and subsequent treatment with 1 M KOH in EtOH (1 ml). After 5 h at room temperature the reaction mixture was diluted with water and extracted with ether. Evaporation of the washed (water) and dried ether extracts yielded a crude reaction product consisting of a mixture of the corresponding cis and trans diols which were analysed by GLC. The diols 7-10a-c were completely stable under the reaction conditions used. Experiments were carried out in order to verify if the diols 7-10a-c are stable under the saponification conditions and if the method of saponification used does not alter the stereoselectivity of the reactions under investigation. In the case of the trichloroacetolysis of epoxide 5c, the percentage of the ketone 11c relative to diols 9c and 10c, were determined by reducing the crude product from 5c with $LiAlH_4$ and measuring (GLC) the peaks of diols relative to the only two other peaks present, which could easily be attributed to the reduced ketone by their comparison with an analytical sample of 11c reduced under the same experimental conditions. The values given in Table 1 are the average of at least three measurements taken on at least two different runs for each point.

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21. Equation 1 can be obtained[16] by term-by-term subtraction of the Hammett equation relative to the formation of the anti adduct (A) from the one relative to the syn adduct (S), under the very likely assumption that the two parallel reactions follow the same kinetic equation and therefore the rate ratios k_s/k_a can be equated to the concentration ratios S/A. This type of correlation affords the difference $Q_{syn} - Q_{anti}$.