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STERIC CONTROL OF EPOXIDATION BY ALLYLIC AND HOMOALLYLIC CARBAMATE GROUPS

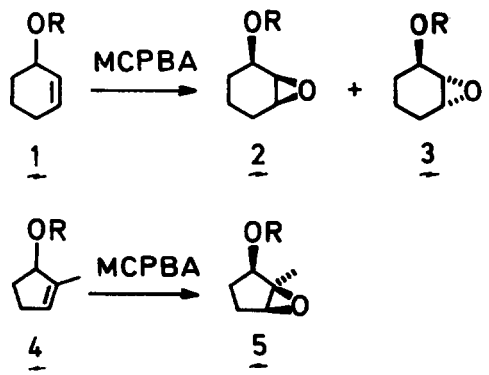
Pavel Kočovský

Institute of Organic Chemistry and Biochemistry
Czechoslovak Academy of Sciences, 166 10 Prague 6, Czechoslovakia

Abstract: Carbamoyloxy groups show syn-stereodirecting effect on epoxidation of allylic and homoallylic double bonds similar to that of hydroxy groups. Allylic carbamates 1c-1f, 4d, 6d, and 6f and their homoallylic counterparts 8c-8e thus produce corresponding cis-epoxides as the major products on reaction with MCPBA. Mechanism of this steering is discussed.

Epoxidation of cyclic allylic alcohols (e.g. 1a) is known to proceed in a syn-fashion[1] giving cis-epoxides[2]. In contrast, allylic esters (1b) produce trans-epoxides under the same conditions[1] (Scheme 1). Here we describe syn-stereodirecting effect of various carbamoyloxy groups similar to that of hydroxyl.

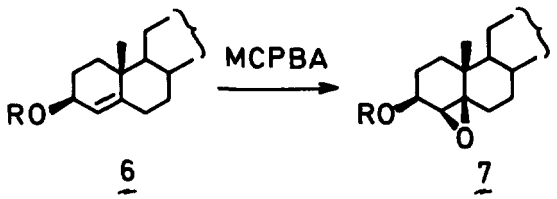
We have found that carbamates derived from allylic alcohols 1 and 4 are predominantly oxidised with m-chloroperoxybenzoic acid (MCPBA) in CH_2Cl_2 or $CHCl_3$ at 0°C from the syn-side to give the corresponding cis-epoxides 2 and 5 as



Scheme 1

Compound	R	cis/trans
1a	H	10 : 1
1b	Ac	1 : 4
1c	$CONH_2$	3 : 1
1d	$CONHCH_2Ph$	5 : 1
1e	CONHTs	3 : 1
1f	$CONMe_2$	10 : 1
4a	H	>20 : 1
4d	$CONHCH_2Ph$	>20 : 1

the major products (Scheme 1 and Table)[3,6,7]. It turned out that this effect is strong enough to override the steric bias of the steroid skeleton, whose α-side is usually less hindered[8], and to drive the epoxidation to occur predominantly from the ß-side (Scheme 2). Thus the steroidal carbamates 6d and 6f afford the cis-epoxides 7 as the sole products similarly to the parent alcohol 6a.

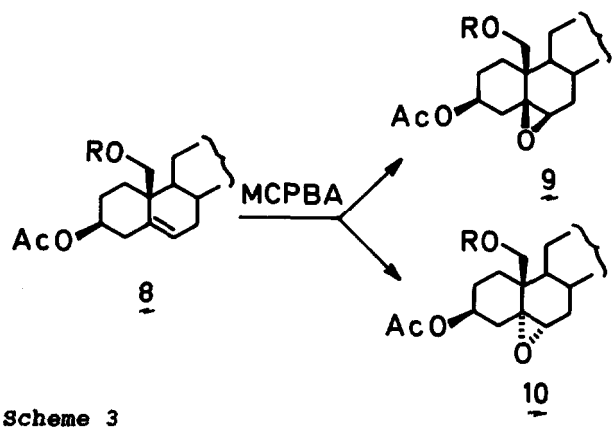


6 7

Compound	R	7
6a	H	major[1]
6d	$CONHCH_2Ph$	>20 : 1
6f	$CONMe_2$	>20 : 1

Scheme 2

This steric control appears not to be confined to allylic carbamates, but can be observed with some homoallylic derivatives. Thus 19-carbamoyloxy (8c), 19-N-benzyl carbamoyloxy (8d), and 19-N-tosyl carbamoyloxy (8e) groups steer the epoxidation from the ß-side which leads to predominant formation of 5ß,6ß-epoxides 9. Note that carbamates 8c-8e furnish even higher cis/trans ratio than does the parent alcohol 8a. This neighboring group effect is, however, considerably less manifested with the N,N-dimethyl carbamate 8f (Scheme 3 and Table).



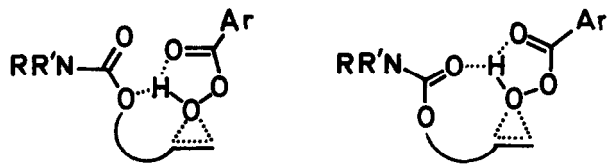
8 9 10

Compound	R	Ratio 9/10
8a[9]	H	5 : 1
8b[10]	PhCO	1 : 10
8c	H_2NCO	6 : 1
8d	$PhCH_2NHCO$	>10 : 1
8e	TsNHCO	>10 : 1
8f	Me_2NCO	1 : 2

Scheme 3

Our findings show that the carbamate group can serve as an alternative to the hydroxyl in steric control of epoxidation[11]. This behavior raises the question as to the mechanism. The steering effect of hydroxy group was attributed by Henbest to the hydrogen bonding between OH and the reagent[1] and since then this mechanism has been widely accepted[2]. Similar syn-epoxidation of allylic amides[12] was rationalized by analogous NH-bonding[13]. However, our allylic N,N-dimethyl carbamoyloxy group in 1f and 6f cannot offer any OH or NH and still con-

trols the epoxidation in a syn-fashion. Therefore an alternative mechanism should be suggested to account for this behavior. We can speculate on hydrogen bonding in a reversed way, i.e. from the reagent (MCPBA) to one of the oxygen atoms of the carbamate group (Scheme 4). Although the ether oxygen seems to be an entropically better candidate (A), the carbonyl oxygen in carbamates is known to be much stronger nucleophile[14] and might also play a role in binding the electrophile (B)[15]. Participation of the nitrogen lone-pair does not seem probable in the light of general reactivity of the carbamate and amide groups[14]. Another mechanism can simply involve Coulombic interaction of the electrophile with the nucleophilic allylic center[16]. Further study of this issue is in progress in this Laboratory.



Scheme 4

In principle, the cis-carbamoyloxy epoxides 2, 5, 7, and 9 could also be synthesized in the reversed way, i.e. by epoxidation of allylic alcohols followed by derivatization with the corresponding isocyanates. However, some epoxy alcohols do not react cleanly with isocyanates (particularly 7a) and give large amounts of by-products. Furthermore, preparation of N,N-dimethyl carbamoyloxy epoxides 2f, 7f, and 9f would require drastic conditions (cf. ref.5) which are not compatible with this sensitive functionality. Our epoxidation of carbamates thus seems to be a cleaner process. Moreover, diastereoselectivity of epoxidation of certain carbamates is better than that of the parent alcohols. As the carbamate groups have been frequently employed to control the opening of oxirane ring[17] we believe that our stereocontrolled epoxidation method may become a useful alternative for the stereoselective synthesis of epoxy carbamates.

References and Notes

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2. For review see e.g.: Kočovský P., Tureček F., Hájíček J.: "Synthesis of Natural Products : Problems of Stereoselectivity", Vol. I and II, CRC Press, Boca Raton FL, 1986.
3. Carbamates 1c and 8c were prepared by our new method[4], i.e. by reaction of alcohols with trichloroacetyl isocyanate followed by hydrolysis on alumina. N-Benzyl carbamates 1d, 4d, 6d, and 8d were obtained from the alcohols by

treatment with benzyl isocyanate at r.t. for 3 days. Shorter time (several minutes) was required for prepartion of N-tosyl carbamates 1e and 8e. Preparation of N,N-dimethyl carbamates 1f and 6f required reaction of Li-salts of the alcohols with Me_2NCOCl in agreement with the Overman's observation[5]. Synthesis of 8f was more complex and included several steps, as the presence of the acetoxy group was not compatible with the method of generating the lithium salt (details will be published in full paper).

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5. Overman L.E., Campbell C.B., Knoll F.M.: J. Am. Chem. Soc. 100, 4822 (1978).
6. All new compounds gave satisfactory elemental analyses and spectral data (IR, ^{1}H-NMR). Configuration of the epoxides was confirmed by an independent synthesis involving epoxidation of parent alcohols followed by derivatization with isocyanates. However, the epoxy N,N-dimethyl carbamates cannot be synthesized in this way. Their configuration was inferred from the comparison of their H-NMR spectra with those of the epoxy alcohols and of the corresponding carbamates and N-benzyl carbamates. For steroidal derivatives 7 the coupling constant $J_{3,4} \approx 4$ Hz is characteristic [see: Collins D.J., Hobbs J.J.: Tetrahedron Lett. 623 (1963)].
7. cis/trans-Ratio was determined from ^{1}H-NMR spectra of the crude products.
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11. Attempted epoxidation of 1c-1f and 8d with $(acac)_2VO$ and TBHP or $Mo(CO)_6$ and TBHP in CH_2Cl_2 or C_6H_6 either at r.t. or at reflux gave no reaction, whereas the use of $(i\text{-}PrO)_4Ti$ and THBP at elevated temperature led to a complex mixture of products.
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14. The carbonyl oxygen of the carbamate group is strongly nucleophilic; see: Kočovský P., Stieborová I.: J. Chem. Soc. Perkin Trans. 1, 1969 (1987).
15. Stereocontrolled epoxidations effected by ketone carbonyl have been occasionally reported. Thus P. Baeckström (personal communication) has noticed selective endo-epoxidation that can be attributed to this effect:

For further examples see e.g.: (a) Takeda K., Hamamoto K., Sasaki K., Maezono N., Murabayashi A.: Steroids 2, 27 (1963); (b) Černý V., Buděšínský M., Ryba M., Tureček F.: Collect. Czech. Chem. Commun., in press (1988).
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