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REMOTE OH-GROUP DIRECTING EFFECT IN THE STEREOCHEMISTRY OF INTRAMOLECULAR ALKOXIDE ADDITION TO CONJUGATED DOUBLE BOND

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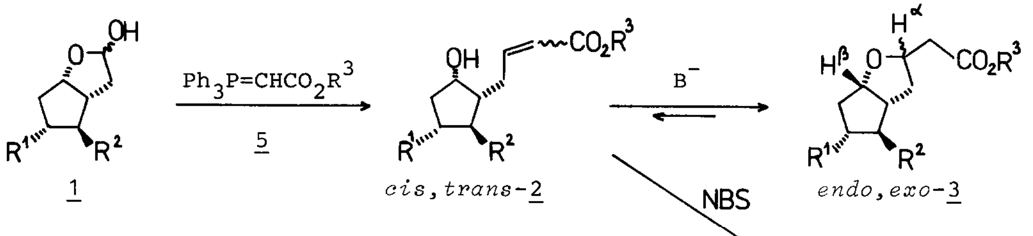
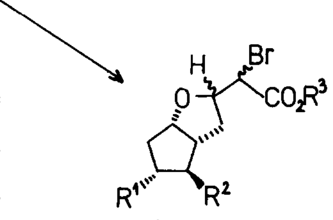
Abstract: Preferential formation of less stable (endo) product in intramolecular Michael reaction is explained by the participation of structurally remote OH group in the transition state.

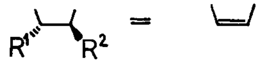
In the course of a study[1] concerning the stereochemistry of intramolecular haloalkoxylation of $PGF_{2\alpha}$ and related derivatives - a route that gained outstanding importance in the synthesis of PGI_2[2,3] - we prepared a series of ε-hydroxy-α,β-unsaturated esters that are capable to undergo base induced cyclization *via* intramolecular Michael addition. The resulting products of type 3 are versatile intermediates in the synthesis of stable prostacyclin analogues. The unique stereochemistry observed in the cyclization process will be discussed in this paper.



1 cis,trans-2 *endo,exo*-3



endo,exo-4

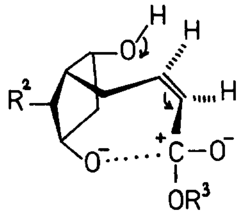
	R^1	R^2	R^3
a	H	H	Me
b	HO	CH_2OCH_2Ph	Et
c	HO	(R)-$CH\overset{t}{=}CH-CH(OH)C_5H_{11}$	Et
d	THPO	(S)-$CH\overset{t}{=}CH-CH(OTHP)C_5H_{11}$	Me
e			Me

Reaction of lactols 1a-e with the stable phosphorane 5 in THF, benzene or dichloromethane gave *cis-trans* mixtures of unsaturated esters 2a-e in excellent yields[4] ($\geq 80\%$). Chromatography on silica gel colums afforded pure *cis*-2 and *trans*-2 isomers [R_f, H^1-NMR for $CH^A=CH^B-CO$, δ_A and δ_B in ppm (J_{AB} in Hz): *a,* 0.41, 0.37 (hexane-EtOAc,3:1), 6.32, 5.84(5.5), 7.08, 5.9(8); *b,* 0.36, 0.30 (hexane-acetone,2:1), 6.22, 5.85(5.5), 7.08, 5.9(8); *c,* 0.33, 0.28(chloroform -acetone,1:1), 6.22, 5.90(5.5), 6.96, 5.90(8); *d,* 0.39, 0.29 (CH_2Cl_2-acetone, 7:1), 6.25, 5.86(6), 7.03, 5.90(8); *e,* 0.50, 0.45 (hexane-EtOAc,1:1), 6.28, 5.90(5.5), 7.04, 5.9(8)] . Base catalysed cyclization was initiated in dry ether (0.01 mmole/ml) by the addition of ≤ 0.1 mole equivalent sodium hydride at 25° under argon. The progress[5] of the reaction could easily be detected by TLC since under these conditions cyclizations required 1-3 hours giving rise to kinetically controlled products (see Table 1.). Attainment of the thermodynamic equilibrium (*exo:endo* ratio 1.5~2) required 3-5 days. After consumption of the starting material, the reaction was quenched by the addition of water. Chromatography of the isomeric products on silica gel columns afforded pure *endo*- and *exo*-3[6].

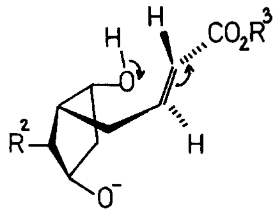
Table 1.

starting material	*exo:endo* ratio in prod. 3	R_f(eluent) H^1-NMR, δ_α, δ_β, in ppm } of *exo,endo*-3, resp.
cis-2a	2	0.28, 0.32 (CH_2Cl_2-acetone, 40:1)
trans-2a	2	4.54, 4.33 ; 4.38 4.0
cis-2b	0.1	0.22, 0.27 (CH_2Cl_2-acetone, 8:1)
trans-2b	10	4.45, 4.44 ; 4.32, 4.07
cis-2c	0.2	0.23, 0.25 (CH_2Cl_2-acetone, 2:1)
trans-2c	6	4.50, 4.45 ; 4.3 4.0
cis-2d	2	0.15, 0.18 (CH_2Cl_2-acetone, 15:1)
trans-2d	2	- - ; - -
cis-2e	1	0.55, 0.52 (benzene-MeOH, 15:1)
trans-2e	1	0.8 , 4.2 ; - -

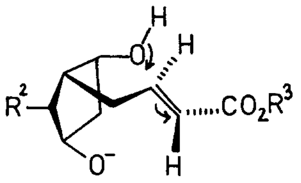
Highly preferred formation of *endo*-3 from *cis*-2b,c seems to be unique[7] and could not be expected from purely stereochemical reasons. However, α, β, unsaturated carbonyl compounds are known to behave as ambident electrophiles bearing the largest positive charge at the carbonyl-C[8]. Electrostatic interaction of this center with hard (negatively charged) nucleophiles, represented by the Coulombic term of Klopman equation[8,9], generally exceeds the importance of frontier orbital term. Energy gain associated to such Coulombic interaction of $R^1 = O^-$ with favourably disposed carbonyl group might conceivably overcome steric repulsion due to congestion in a transition state like A which in turn itself should collapse to *endo*-3.



A



B



C

In *trans*-2b,c derivatives R^1 and the carbonyl group are separated by relatively large distances (B and C) at which the Coulombic term becomes less important and the stereochemistry is controlled primarily by steric factors favouring *exo*-selectivity. Similarly, blocking or replacement of the remote $OH(R^1)$ group in the *cis* series causes the Coulombic term to vanish which is manifested in the preferential formation of *exo*-3a,d,e from *cis*-2a,d,e, respectively. Indirect corroboration of the above interpretation can be inferred from the fact that the reaction of either *cis*- or *trans*-2b with N-bromosuccinimide (1.1. equiv, 25°, 3-5 hrs in CH_2Cl_2) gave *exo*-4b[10] as the major product (stereochemistry of the double bond effected only the configuration of halogen bearing C). This finding reveals that *endo*-selectivity is not an inherent property of the models (*cis*-2b,c) but depends rather on the nature of interactions encountered along the reaction path. Halocyclization is most probably controlled by the frontier orbital term due to the interaction of the HOMO of the conjugated double bond with the LUMO of soft electrophilic

N-bromosuccinimide. In lack of charged alkoxide group the contribution of Cculomb interaction may be negligible.

References and notes

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2. (*a*) E. J. Corey, G. E. Keck, and I. Szêkely, J. Amer. Chem. Soc., 99, 2006 (1977); (*b*) R. A. Johnson, F. H. Lincoln, J. L. Thompson,E.G. Nidy, S. A. Mizsak, and U. Axen, ibid.,99, 4182 (1977); (*c*) I. Tömösközi, G. Galambos, V. Simonidesz, and G. Kovâcs, Tetrahedron Letters, 2627 (1977); (*d*) N. Whittaker, ibid., 2805 (1977); (*e*) K. C. Nicolaou, W. E. Barnette, G. P. gasic, R. L. Magolda, and W. J. Sipio, J. Chem. Soc. Chem. Commun., 630 (1977); (*f*) R. A. Johnson, F.H. Lincoln, E. G. Nidy, W. P. Schneider, J. L. Thompson, and U. Axen, J. Amer. Chem. Soc.,100, 7690 (1978).
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4. The rate of the Wittig reaction proved to be markedly influenced by the chemical character of the R^1 group. In those cases where R^1= OH (1b,c) completion of the reaction occured 10-20 times faster than in those cases where R^1=H or protected OH group (1a,d,e).
5. The ratio $k_{trans}:k_{cis}$ = 2 was estimated for the apparent rate constants of *trans*-2b and *cis*-2b by recording the decrease of absorbance at 224 and 227 nm, resp., in 10^{-4} molar EtOH solution in the presence of 10-fold excess of NaOEt.
6. For the assignment of stereochemistry see ref. 1 and 3.
7. H. O. Hosuse, Modern Synthetic Reactions, Benjamin Inc., Menlo Park, 2nd Ed., 1974, p. 595-622.
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10. For the assignment of stereochemistry see ref. 1.

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