Tetrahedron Letters,Vol.27,No.26,pp 3001-3004,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

ENANTIOSELECTIVE PHOTODECONJUGATION OF α,β-UNSATURATED ESTERS: EFFECT OF THE NATURE OF THE CHIRAL AGENT

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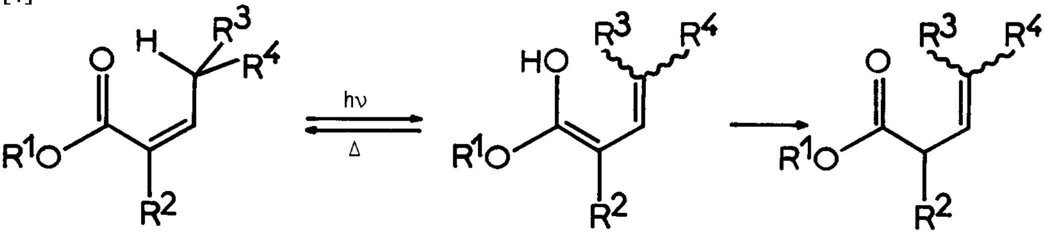
Abstract : A synergism exists between the effect of the amino and hydroxy groups of chiral amino alcohols on the enantiomeric excess of the photodeconjugation of α,β-unsaturated esters.

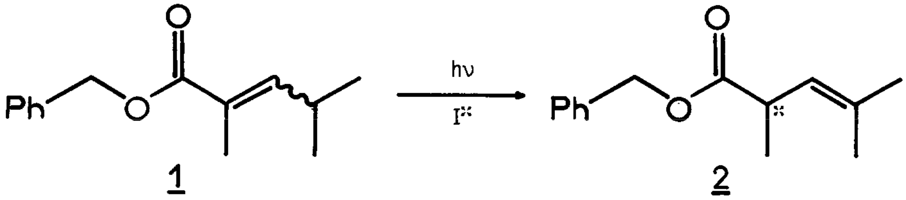
The photodeconjugation of α,β-unsaturated esters and lactones involves a photodienolic intermediate as shown in equation [1] (1).

[1]



When conjugated esters or lactones are substituted at the α -position, the above deconjugation creates a new asymmetric center. In the presence of catalytic amounts of a chiral inductor such as (-) ephedrine the deconjugated molecule is produced with an enantiomeric excess of up to 30% (2). In the aim of understanding the mechanism of this asymmetric induction, we have now examined the efficiency of various inductors on the photodeconjugation of benzyl-2,4-dimethyl-2-pentenoate and the results are summarized in equation [2] and Table 1.

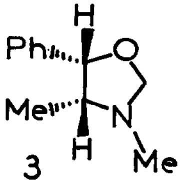
[2]



To avoid competition of the solvent with the chiral catalyst in the tautomery of the photoenol, we have excluded solvents having either acidic or basic properties hence all the experiments have been carried out at -78°C in methylene chloride.

Table 1

Run	Inductor (a)	Configuration C*–O	 C*–N	Conv. %	Yield %	$\|\alpha\|_D$ CH_2Cl_2	Major. conf.	ee %
1	(-) ephedrine	R	S	99	71	-25.5° ± 0.5 (c = 0.96)	R	28
2	(+) ephedrine	S	R	97	78	+28.1° ± 0.4 (c = 0.62)	S	31
3	(+) menthol	R	-	86	81	0	-	-
4	(-) octanol	R	-	90	57	0	-	-
5	L-diisopropyltartrate	R,R	-	(b)	84	+0.6° ± 0.1 (c = 0.8)	-	< 1
6	(-) Methyllactate	S	-	(b)	35	-1.3° ± 0.3 (c = 1.3)	R	1.5
7	(-) α-phenylethylamine	-	S	92	60	-3.8° ± 0.4 (c = 0.65)	R	4
8	(+) O-methylephedrine	S	R	91	70	+6.4° ± 0.5 (c = 0.64)	S	7
9	Cinchonidine	R	S	(b)	73	-33.9° ± 0.2 (c = 1.06)	R	37
10	(-) oxazolidine 3	S	R	77	51	+1.5° ± 0.3 (c = 1.3)	S	< 2
11	(-) N-methylephedrine	R	S	100	80	-5.4° ± 0.5 (c = 0.46)	R	6
12	(-) nor-ephedrine	R	S	95	72	-12.6° ± 0.4 (c = 0.67)	R	14
13	(+) ψ-ephedrine	S	S	97	70	-4.0° ± 0.4 (c = 0.62)	R	4
14	(+) N-methylvalinol	-	S	98	71	-13.1° ± 0.3 (c = 0.73)	R	14
15	L-isoleucinol	-	S	96	75	-13.0° ± 0.4 (c = 0.65)	R	14



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(a) The irradiations were carried out at 254 nm and -78°C in CH_2Cl_2. The initial concentration of the conjugated ester was 10^{-2} M.L^{-1} and the concentration of the inductor was 10^{-3} M.L^{-1}

(b) not determined.

When 1 was irradiated in dry methylene chloride in the presence of 0.1 equivalents of (-) ephedrine a very clean transformation into the deconjugated ester 2 was observed. The reaction was enantioselective (ee = 28%) and the major enantiomer possesses the (R) configuration.

When ephedrine was replaced by a chiral alcohol in the reaction mixture (entries 3-6) clean deconjugation took place and almost no chiral induction was observed. Thus at low temperature there was little chiral discrimination in the protonation step of the prochiral enol using a chiral alcohol alone.

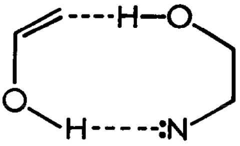
The transformation of the photoenol into the deconjugated ester is catalyzed by small amounts of base (1e-1f). The strong interaction developed between the acidic enolic proton (3) and the nitrogen atom of a chiral amine might influence the enantioselectivity (4). However the chiral amines bearing no hydroxyl group in the molecule led to a considerably lower enantioselectivity than ephedrine. Thus the O-methylation of (+) ephedrine (run 8) lowered the enantiomeric excess by a factor of 4. The effect of the substitution of the nitrogen atom can be important as shown also by comparison of runs 1, 11 and 12. The replacement of the secondary amino group of (-) ephedrine by a primary amine in (-) nor-ephedrine or a tertiary amine in (-) N-methyl-ephedrine lowered the enantioselectivity of the photodeconjugation of 1. However, the use of cinchonidine (run 8) as chiral inductor increased the enantioselectivity.

The improvement of the enantiomeric excess when the chiral inductor possesses an amino and a hydroxy group simultaneously was confirmed by the results of runs 12, 14 and 15 obtained with (-) nor ephedrine, (+) N-methylvalinol and L-isoleucinol.

Another important observation appeared from the comparison of the results : the configuration of the major enantiomer of 2 seems to depend only on the configuration of the carbon atom linked to the nitrogen atom. Thus the (2R) configuration of the major enantiomer of the deconjugated ester is obtained when the configuration of the carbon linked to the nitrogen of the inductor has the (S) configuration whatever the configuration of the carbon linked to the hydroxy group.

The tautomery of the photoenol can be considered as the rate determining step because of the high activation energy required for the process (5). The synergistic effect of the amino and hydroxy groups of the chiral inductor on the selectivity can be rationalized if we assume that the removal of enolic proton by the basic amine and the protonation of the double bond by the hydrogen group of the β-amino alcohol is a concerted process (figure 1). The chiral discrimination would result from differences of steric interaction in the two diastereoisomeric transition states involving each face of the prochiral enol.

Figure 1



Further work in agreement with this model and especially the influence of the steric hindrance on the starting conjugated ester is reported in the accompanying communication (6).

Acknowledgments : Professor F. PETIT from the Université des Sciences et Techniques de Lille is greatly acknowledged for a gift of (+) N-methylvalinol.

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3. The acidity of a photoenol has been recently determined by flash photolysis. For 4-methyl-2,4-pentadien-2-ol the equilibrium constant dienol-dienolate is $K = 3.8 \times 10^{-11}$
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4. The acidity of photodienol is similar to the acidity of a phenol. The thermodynamic data for hydrogen bonds between phenol and an amine in carbon tetrachloride indicates negative ΔH and ΔS values and the association constant $K^{20°C} > 29$.
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   In the strong association between the amine and the acidic dienol, the highly ordered state might help the chiral discrimination between the diastereomeric transitions states involved in the tautomery of the enol.

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(Received in France 27 April 1986)