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EVALUATION OF THE STERIC INTERACTIONS RESPONSIBLE FOR THE ENANTIOSELECTIVE PHOTODECONJUGATION OF α,β-UNSATURATED ESTERS

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Abstract : A model is proposed to explain the configuration and the proportion of the preponderant enantiomer in the enantioselective photodeconjugation of α,β-unsaturated esters. The major interactions in the transition state are developed between the inductor and the β-carbon of the intermediate dienol.

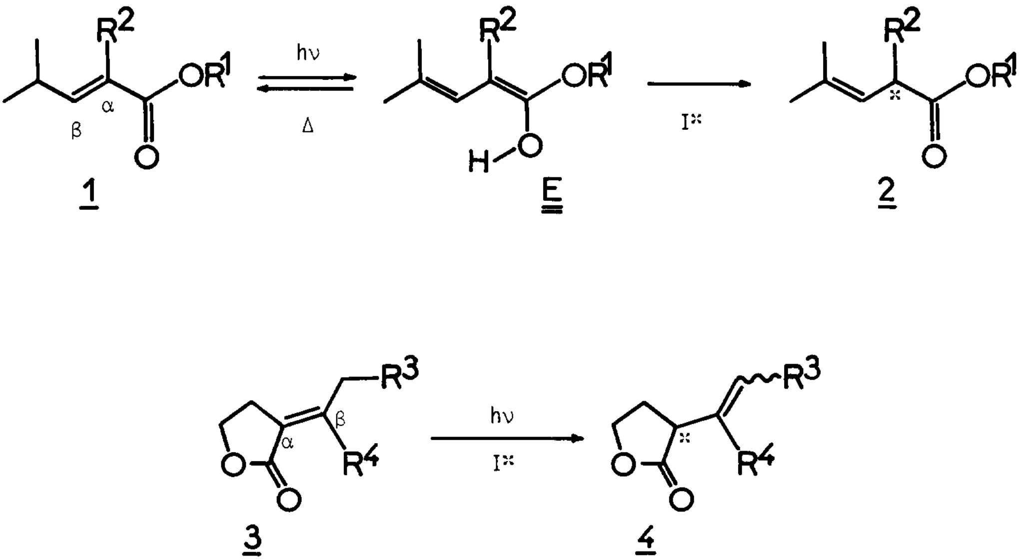
The photolysis of α-alkylidene lactones or α-alkyl α,β-unsaturated esters affords the corresponding deconjugated lactones and esters respectively (1). In the presence of small quantities of chiral aminoalcohols, the deconjugation is enantioselective (2) and we have recently shown the cumulative effect of amino and hydroxyl groups on the enantiomeric excess (3). An abstraction of the enolic proton by the amino group concerted with the protonation step by the hydroxyl group of the chiral inductor was proposed to explain the results. In order to define more precisely the transition state and the interactions responsible for the chiral discrimination, we have now examined the effect of the substitution of the starting conjugated ester or lactone on the configuration of the deconjugated compound and on the importance of the enantiomeric excess. Ephedrine was used as the chiral catalyst and methylene chloride as the solvent. The results are summarized in scheme 1 and table 1.

The first conclusion which can be made from the observation of the results is that the configuration of the new asymmetric center in 2 does not depend on the nature of the alkoxy group of the starting ester. With (+) ephedrine as the chiral inductor the configuration at C-2 is (S) whatever the nature of the substituents. Furthermore the configuration is still the same when the α-methyl is replaced by an α-ethyl substituent.

The indication that only small steric interactions are present between ephedrine and the alkoxy group of the photoenol E is confirmed by the observation of a very low modification of the enantiomeric excess when the size of this chain is considerably increased. When the methoxy group of 1a is replaced by ethoxy (1b), isopropoxy (1c) and even cyclohexanemethyloxy (1g) almost the same enantioselectivity is observed. Interestingly, the presence of a phenyl entity in the alkoxy group leads to an increase of the enantiomeric excess. This might indicate secondary interactions between the phenyl and ephedrine, such as hydrogen bonding able to increase the chiral discrimination in the transition state. However, the real nature of these interactions is still unknown.

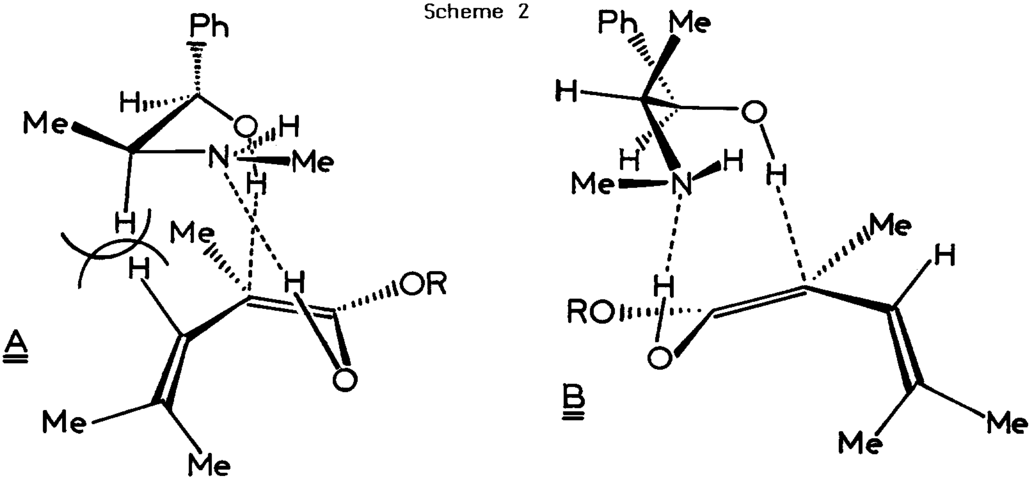
A modification of the steric hindrance on the acid part of the starting ester has a far more important effect on the selectivity. When the α-methyl (1a) is replaced by an α-ethyl substituent (1i) there is a significant diminution of the enantiomeric excess. Furthermore, a β-disubstitution as in 3b or 3c impedes an efficient asymmetric synthesis. This can be rationalised if we consider the probable transition state for the base catalyzed tautomery of the photoenol. The major steric interaction should be developed between the substituents of the β-carbon atom of the enol and the carbon atom of ephedrine which is linked to the nitrogen. We have indeed shown (3) that an inversion of the configuration of the carbon in the inductor reverses the configuration at C-2 in the deconjugated ester although the configuration of the carbon atom bearing the hydroxyl group of the amino alcohol has no effect on the configuration of the major enantiomer of 2.

Scheme 1



As the tautomery is base catalyzed we may anticipate that the transformation of the enol into the deconjugated ester is the rate determining step (4). The acidity of the photoenol (5) is of the same

Scheme 2



order as the acidity of a phenol and the strength of the hydrogen bonds between the amine function and the acidic proton in non polar solvents should be very similar (6). Furthermore, the hydrogen bond N...HO is stronger than O...H-O (7) and a bond distance lower than 3 Å for the N...HO bond has been estimated (8). Therefore we propose that che chiral discrimination can be explained by a competition between the two diastereomeric transition states represented in scheme 2 for (-) ephedrine.

In these two diastereofacial approaches of (-) ephedrine with the prochiral dienol a) the hydroxylic proton of the inductor interacts strongly with the π orbital of the enol ; b) the larger substituents on the inductor, phenyl and methyl are as far as possible from the dienol ; c) the less hindered conformation of ephedrine is retained.

Table 1

Starting Material	R_1 or R_3	R_2 or R_4	Inductor	Yield %	<u>2</u> or <u>4</u> Configuration at C-2	ee% (b)
<u>1a</u>	CH_3	CH_3	(-) ephedrine	67	R	18 (c)
<u>1b</u>	C_2H_5	CH_3	(-) ephedrine	68	R	16 (c)
<u>1c</u>	$(CH_3)_2CH$	CH_3	(+) ephedrine	63	S	20
<u>1d</u>	C_6H_5-CH_2	CH_3	(+) ephedrine (-) ephedrine	78 71	S R	31 28
<u>1e</u>	C_6H_5-$(CH_2)_2$	CH_3	(+) ephedrine	64	S	29
<u>1f</u>	C_6H_5-$(CH_2)_3$	CH_3	(+) ephedrine	70	S	22
<u>1g</u>	C_6H_{11}-CH_2	CH_3	(+) ephedrine	73	S	17
<u>1h</u>	$(CH_3)_2C{=}CHCH_2$	CH_3	(+) ephedrine	84	S	19.5
<u>1i</u>	CH_3	C_2H_5	(-) ephedrine	96	R	12 (c)
<u>3a</u>	CH_3	H	(-) ephedrine	80	R	10 (c)
<u>3b</u>	H	CH_3	(-) ephedrine	60	(e)	0.5
<u>3c</u>	$(CH_2)_4$		(-) ephedrine	72	-	0 (d)

a) Unless stated, the ester or lactone (10^{-2}M.L^{-1}) were irradiated in CH_2Cl_2 at -78°C with low pressure mercury lamps (254 nm) in the presence of ephedrine (10^{-3}M.L^{-1}).

b) The configuration of the major enantiomer was established by correlation with a known reference; the enantiomeric excess was determined by NMR in the presence of $Eu(hfc)_3$.

c) Ref. 2.

d) The reaction was carried out at room temperature.

e) $|\alpha|_D$ = -0.64. The configuration of the major enantiomer should be (R).

In the transition state A leading to the (2S) configuration of the deconjugated ester there is a steric interaction between the vinylic β-hydrogen of the dienol and the C-H bond of the carbon linked to the nitrogen atom of ephedrine. This transition state A is then less favourable than B where no such important steric interaction of the inductor appears with the dienol part or with the alkoxy group.

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