A VERY ENANTIOSELECTIVE PHOTODECONJUGATION OF α , β -UNSATURATED ESTERS

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Abstract : An enantiomeric excess up to 70% can be obtained in the photodeconjugation of conjugated esters in the presence of (1R, 2S) 1-phenyl, 2-isopropylamino-propanol.

It was shown previously that chiral β_{γ} -unsaturated esters can be produced when conjugated esters are irradiated in the presence of a catalytic amount of a chiral protonating agent I*(1).



The deconjugation involves a photodienol intermediate which can return to the conjugated ester in a thermal and concerted [1,5] sigmatropic shift or lead to the deconjugated ester in a process which can be catalyzed either by bases or by protic acids (2). The discrimination step is then the tautomerisation of the dienol catalyzed by a chiral inductor. The enantiomeric excess is largely increased when this inductor is a chiral β -aminoalcohol, containing both an amino group as a basic function and a hydroxyl group as a possible proton source (3). A model involving a 9-membered cyclic transition state was proposed to rationalize the chiral discrimination (4).

The best enantiomeric excess obtained up to now (ee \leq 37%) was, to our knowledge, thehighest described for an enantioselective photochemical reaction carried out in solution (5, 6). This selectivity was however far too low to envisage a practical application. We decided to prepare new chiral inductors (7), which might be more selective according to the proposed model for chiral discrimination. A selectivity up to 70%, obtained with (1R, 2S) 1-phenyl, 2-isopropylamino-propanol, used as the chiral inductor, is reported in this communication. When the benzyl ester <u>1a</u> (R₁=R₂=Me, R=CH₂Ph) was irradiated at 254 nm in the presence of 0,1 equivalent of the chiral amino-alcohol <u>3</u> or <u>4</u>, the deconjugated ester <u>2a</u> was the only new product except for polar residues which can be easily removed from the reaction mixture. The results are summarized in scheme 1 and table 1. 4826

Scheme 1



As shown in table 1, the enantiomeric excess is very sensitive to the nature of the substituents R' and R" of the inductor. For instance, a two fold enantiomeric excess was observed when the primary amino group of (-) nor ephedrine $\underline{3a}$ was replaced by a methyl amino group as in ephedrine $\underline{4}$. The selectivity was also considerably improved if inductors $\underline{3e}$, $\underline{3f}$ and $\underline{3h}$ having a secondary alkyl group on the nitrogen atom were used.

Furthermore, in agreement with the proposed model examined precedingly (3b, 4), the presence of a bulky substituent on the nitrogen, as in case <u>3b</u> or <u>3c</u>, creates unfavorable interactions; then, the transition state leading to the major enantiomer is less favored. This effect is enhanced when the nitrogen atom is disubstituted as for <u>3i</u>, and the selectivity is almost destroyed.

At -40°C, the best enantiomeric excess (ee = 70%) indicates that seven pure chiral molecules were produced by molecule of amino alcohol 3e.

The model proposed for the chiral discrimination indicates that the main unfavorable interactions are developped between the inductor and the β , γ unsaturated group of the dienolic intermediate. The modification of the substitution at the γ position should influence the selectivity. As expected, this effect is strengthened if the inductor $\underline{4}$ is replaced by $\underline{3}e$ in the reaction mixture.

The results obtained for various unsaturated esters are summarized in scheme I and table 2. As shown in this last table, regardless of the substituents R, R_1 , R_2 , the use of <u>3e</u> rather than (+)<u>4</u> or (-)<u>4</u> as the chiral agent, and a disubstitution at the γ -position results in better selectivities.

Inductor	R'	R"	t (°C)	Isolated yields (%)	ee (%) (b)	
<u>3a</u>	Н	Н	-78	75	14	
(+)4	-	-	-78	78	31	
(+) <u>4</u>	~	-	-40	64	37	
<u>3b</u>	н	Ph-CH ₂	-40	75	8.5	
<u>3c</u>	н	p CH3OC6H4-CH2	-40	57	4.5	
<u>3d</u>	н	(CH ₃) ₂ CH-CH ₂	-40	68	31.5	
<u>3e</u>	н	(CH ₃) ₂ CH	-40	69	70	
<u>3f</u>	н	3-pentyl	-40	47	62	
<u>3g</u>	н	cyclopentyl	-40	61	26	
<u>3h</u>	н	cyclohexyl	-40	68	44	
<u>3i</u>	СН3	CH3	-78	80	6	

Table 1 : Irradiation of <u>la</u> (R=CH₂Ph, R₁=R₂=Me) in CH₂Cl₂, in the presence of aminoalcohols (a)

(a)

starting concentrations for $\underline{1a} = 10^{-2} \text{M} \cdot \text{L}^{-1}$, for $\underline{3}$ or $\underline{4} = 10^{-3} \text{M} \cdot \text{L}^{-1}$. the enantiomeric excess was determined either using polarimetry or by ¹H NMR, in the presence of Eu(hfc)₃. Except in the case of (+) $\underline{4}$, the configuration of the major enantiomer was (R). (b)

Table	2	:	Influence	e of	the	γ -sub	stitution	of	lpha,eta-unsaturated	esters
on the asymmetric photodeconjugation										

S	tarting R ₁	g ester (a) R ₂ R		Inductor (b)	Conversion (%)	lsolated yield (%)	^[α] D (CH ₂ CI ₂)	Configuration of the major enantiomer	e.e. % (e)
<u>la</u>	сн3	СН3	benzyl	(+) <u>4</u> <u>3e</u>	100 94	64 65	+33.3 -62.2	S R	37 70
<u>16</u>	сн3	СН3	ethyl	(-) <u>4</u> (c) <u>3e</u>	100 100	68 84	-28.4 -70.8	R R	16 40
<u>lc</u>	н	nC ₅ H ₁₁	ethyl	(+) <u>4</u> <u>3e</u>	88 87	63 69	+1.5 (d) -5.7 (d)	S (f)	9 38
<u>1d</u>	-(сн ₂) ₄ -	ethyl	(+) <u>4</u> <u>3e</u>	98 97	68 67	+11.0 -34.9	$\frac{S}{R}$ (f)	10 32
<u>le</u>	(0	CH ₂) ₅ -	ethyl	(+) <u>4</u> <u>3e</u>	100 100	61 62	+29 -76	$\frac{S}{R}$ (f)	24 63

(a) $[1] = 10^{-2} \text{ M}^{-1} \text{ L}^{-1}$; (b) [3] or $[4] = 10^{-3} \text{ M}^{-1} \text{ L}^{-1}$; (c) the reaction was carried out at -78°C; (d) $[\alpha]_D$ of the hydrogenated compound, the e.e., in this case was determined for the hydrogenated ester; (e) the e.e. were determined by ¹H NMR using Eu(hfc)₃; (f) the configurations were not verified by chemical correlations but postulated from analysis of the preferred transition state in our model and ¹H NMR deplacements in presence of Eu(hfc)₃. In conclusion, these results proved that photochemical reactions can be very enantioselective when a photochemically produced intermediate is able to develop strong interactions such as

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hydrogen bonding, with the chiral inductor.

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