chemical shifts with solid-state structures, or on speculating coordination geometries from these shifts alone, are potentially completely incorrect. Upfield shifts in one element of the shielding tensor may be canceled by opposing effects of the other elements, leading to isotropic chemical shifts whose similarity hides gross differences in stereochemistry. Given the current interest in ^{113}Cd NMR as a probe of divalent metal sites in proteins, these dangers should not be taken lightly.

The large anisotropies of the chemical shielding tensors are also of significance for the ^{113}Cd NMR of proteins and other macromolecular systems. The chemical shielding anisotropies (CSAs) reported here are among the largest yet measured for this nucleus. For cadmium with similar coordination geometry in high molecular weight systems, it is likely that CSA relaxation will have a dominant effect on line width and perhaps preclude observation of the nucleus in larger proteins and/or proteins bound to DNA. For cadmium in the solid state, high spinning speeds will be necessary to reduce the comb of sidebands exemplified by Figure 7. In both solution and solid-state NMR, the advantages of going to higher field will be minimal, since sensitivity gains will be small and resolution in solution may actually be diminished.

We are currently studying related systems to further elucidate the effects of geometry and ligand type and number on the magnitude and direction of tensor elements in the ^{113}Cd NMR spectrum. Hopefully, a meaningful set of structure–shift correlations can be established.

Conclusion

Several potential models for $[Cd(S\text{-}Cys)_2(His)_2]$ sites cadmium-substituted metalloproteins have been synthesized and characterized by X-ray crystallography and solution and solid-state ^{113}Cd NMR. A small change of nitrogen donor ligand from bipyridine to phenanthroline causes a completely different solid-state structure to be adapted, which is also reflected in the ^{113}Cd NMR chemical shift tensors. Single-crystal NMR of **1** confirms that the sulfur atoms of the thiolate ligands bound to the cadmium atom are primarily responsible for the magnitude of the least shielded tensor element (σ_{11}), but there is an unexpected and large deshielding tensor element (σ_{22}), which arises largely from the contribution of the bipyridine ligand. Preliminary studies on related compounds indicate that both σ_{22} and σ_{33} reflect the effect of the nitrogen donor ligands. The isotropic solution shifts of **1-4** are significantly different from the solid-state shifts of these compounds. This difference can be explained in the phenanthroline compound by dissolution of the dimer in solution and by a small (but significant) change in the metal–ligand bond distances for the other compounds. We are continuing the study of these $[Cd(SR)_x(N\text{-donor})_{4-x}]$ systems in order to answer these questions.

Finally, the large chemical shielding anisotropy of **1** indicates that CSA would be the likely relaxation pathway for Cd-substituted metalloproteins. This would imply a short T_2 for these systems, which would make ^{113}Cd solution NMR study more difficult. Similarly, the large CSA dictates high spinning speeds in solid-state NMR studies of such materials.

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Supplementary Material Available: Tables of atomic coordinates, thermal parameters, bond distances, and bond angles for **1–3** (21 pages); tables of observed and calculated structure factors for **1–3** (31 pages). Ordering information is given on any current masthead page.

Highly Enantioselective Photodeconjugation of α,β-Unsaturated Esters. Origin of the Chiral Discrimination

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Abstract: The photodeconjugation of α-methyl conjugated esters can be highly enantioselective when carried out in CH_2Cl_2 or hexane in the presence of catalytic amounts of chiral β-amino alcohols. Enantiomeric excesses (ee %) up to 70% are described. A correspondence is established between the configuration of the new asymmetric center of the deconjugated ester and the configuration of the asymmetric carbon linked to the nitrogen of the chiral auxiliary. A model involving a nine-membered-ring transition state is proposed to rationalize the results. The effects of the reaction conditions on the level of enantioselectivity are examined. Discrimination parameters $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ can be determined from experiments at various temperatures. For a given ester and β-amino alcohol pair, $\Delta\Delta S^{\ddagger}$ and $\Delta\Delta H^{\ddagger}$ are shown to have the same sign which indicates that the major enantiomer corresponds to the most ordered diastereoisomeric transition state. Among the great variety of chiral β-amino alcohols used in this study, 2-(*N*-isopropylamino)-1-phenyl-1-propanol appears to be the best choice to induce high ee %. The scope and limits of the enantioselective photodeconjugation and the generality of the model are discussed.

Despite considerable efforts of organic chemists in the field of asymmetric synthesis, only a few photochemical studies have been concerned with asymmetric induction in solution, and the reported selectivities are usually quite low.[1] Among the processes available to photochemists, the photocycloaddition of chiral substrates to alkenes is very promising since diastereoselectivities higher than 80% have already been described[2] for stoichiometric amounts of the chiral inductor. A search for enantioselective photochemical reactions involving only catalytic amounts of a chiral auxiliary seems to us to be very important even if the reported selectivities

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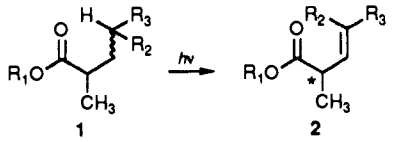
Scheme I



(1)

1 2

	R_1	R_2	R_3
a	$C_6H_5CH_2$	CH_3	CH_3
b	C_2H_5	C_2H_5	C_2H_5
c	C_2H_5	$-(CH_2)_4-$	
d	C_2H_5	$-(CH_2)_5-$	
e	$C_6H_5CH_2$	$-(CH_2)_5-$	
f	$C_6H_5CH_2$	H	C_6H_{13}
g	C_2H_5	H	C_6H_{13}
h	$C_6H_5CH_2$	H	H
i	C_2H_5	CH_3	CH_3
j	*i*-Pr	CH_3	CH_3
k	$C_6H_5(CH_2)_2$	CH_3	CH_3
l	$(CH_3)_2C{=}CHCH_2$	CH_3	CH_3
m	*t*-Bu	CH_3	CH_3
n	3-pentyl	CH_3	CH_3
o	$C_6H_{11}-CH_2$	CH_3	CH_3

for this approach have been so far very low. In this connection, the use of chiral sensitizers[3] or chiral solvents[4] has not yet been very successful.

If chiral centers can be produced photochemically from a prochiral substrate, in principle it would be possible to induce some enantioselectivity as soon as a chiral catalyst is introduced into the reaction mixture. Furthermore if the chiral additive is not consumed during the reaction, small amounts of this agent should be sufficient to direct the reaction of the unstable intermediates produced photochemically and an amplification of the chirality would be anticipated. The induction of high enantioselectivities requires reactions in which a very strong interaction between the chiral inductor and a photochemically produced intermediate can be developed. Among the strong and reversible interactions which can be considered, hydrogen bonding seemed to us to be attractive. To test these ideas we turned to the well-studied photodeconjugation reaction[5] which is known to produce a very polar and long-lived photodienolic intermediate.

In the photodeconjugation of α-substituted α,β-unsaturated esters, the dienol possesses a prochiral α-carbon. When carried out in the presence of a chiral catalyst **I***, the protonation of the two enantiofaces should not occur at the same rate and thus the deconjugated ester should be produced enantioselectively.

The tautomerization of the photodienol to the deconjugated ester is catalyzed either by bases such as amines[6] or by protic acids.[7] Taking advantage of the highly acidic properties of such an enol,[8] we achieved enantioselective photodeconjugation in the presence of chiral β-amino alcohols.[9] When catalytic amounts of (+)- or (−)-ephedrine were introduced into the reaction mixture, an enantiomeric excess (ee) of up to 30% was observed which was indicative of a significant amplification of chirality. Furthermore, it appeared that the chiral discrimination between the two diastereoisomeric transition states did not involve strong steric interactions between the alkoxy group R_1O and the inductor.[9h]

However, it remained necessary to understand the origin of the discrimination in order to propose a model explaining the chirality of the new asymmetric carbon and to increase the selectivities as much as possible to make this reaction of synthetic value. For this purpose, we have examined the varying effect of the structure of the chiral catalyst and the effect of different reaction conditions on the enantioselectivity of photodeconjugation of α-substituted α,β-unsaturated esters.

Table I. Effect of the Solvent on the Enantioselective Photodeconjugation of **1a** (10^{-2} mol L^{-1}) (λ = 254 nm) in the Presence of (+)-Ephedrine (**3b**) (10^{-3} mol L^{-1}) at −40 °C

solvent	conversion, %	yield, %	configuration of the major enantiomer	$[\alpha]^{20}_D$ (*c*, CH_2Cl_2)	ee %
CH_2Cl_2	100	64	*S*	+33.3 (0.4)	37
n-hexane	100	70	*S*	+25.6 (0.5)	28
Et_2O	94	70	*S*	+5.4 (0.6)	6
CH_3OH	100	75	-	0	-
CH_3CN	100	65	-	0	-

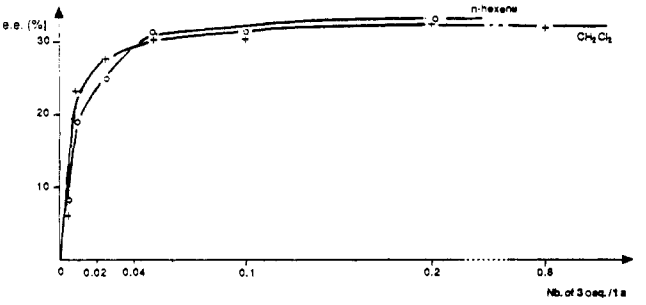


Figure 1. Influence of the concentration of (−)-ephedrine (**3c**) on the enantioselective deconjugation of **1a** (10^{-2} mol L^{-1}) at −78 °C.

Results

Before examining the role of the structure of the chiral inductor on the optical purity of the deconjugated ester **2a**, (Scheme I, eq 1) we studied the influence of the solvent and of the concentration of the chiral auxiliary. These results are reported in Table I and Figure 1.

It appeared that very dry solvents were needed in order to obtain enantioselectivity since whenever any moisture was introduced into the reaction mixture the ester **2** was isolated in racemic form. A rationale for this result is that water can compete with the chiral inductor during the protonation step. This explanation is consistent with the observation of the low selectivities observed when protic or basic solvents are used for the reaction. Alkanes such as *n*-hexane and CH_2Cl_2 were found to be convenient for these enantioselective photodeconjugation studies. The starting material **1** and the deconjugated ester **2** are stable in the dark under the

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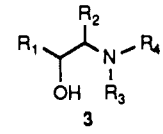
Table II. Enantioselective Photodeconjugation of **1a** in the Presence of Chiral Alcohols or Amines[a]

chiral auxiliary	solvent	temperature, °C	conversion, %	isolated yield, %	ee %	configuration of the major enantiomer
(+)-menthol	CH_2Cl_2	−78	86	81	0	-
(−)-2-octanol	CH_2Cl_2	−78	90	57	0	-
(+)-1-phenylethanol	CH_2Cl_2	−40	100	71	0	-
(−)-1-phenylethylamine	CH_2Cl_2	−40	98	71	2	*R*
	n-hexane	−78	91	57	2	*R*
(−)-1-phenylethylamine and (+)-1-phenylethanol	CH_2Cl_2	−40	93	76	2[b]	*R*
(−)-1-phenylethylamine and (−)-octanol-2	CH_2Cl_2	−40	96	75	2	*R*
3b	CH_2Cl_2	−40	100	64	37	*S*
(+)-ephedrinium chlorohydrate	CH_2Cl_2	−78	100	81	2	*R*
10	CH_2Cl_2	−78	91	70	7	*S*
13	CH_2Cl_2	−78	77	51	2	*S*

[a] Irradiation conditions are those of Table I. [b] A very similar selectivity was observed when the two additives were introduced at a relative concentration of 0.1 equiv of **1a**.

Chart I



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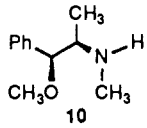
	R_1	R_2	R_3	R_4	Configuration at C_1	Configuration at C_2
3a	C_6H_5	CH_3	H	H	*R*	*S*
3b	C_6H_5	CH_3	CH_3	H	*S*	*R*
3c	C_6H_5	CH_3	CH_3	H	*R*	*S*
3d	C_6H_5	CH_3	CH_3	H	*S*	*S*
3e	C_6H_5	CH_3	CH_3	CH_3	*R*	*S*
3f	C_6H_5	CH_3	$C_6H_5CH_2$	H	*R*	*S*
3g	C_6H_5	CH_3	*i*-Pr	H	*R*	*S*
3h	C_6H_5	CH_3	*i*-Bu	H	*R*	*S*
3i	C_6H_5	CH_3	3-pentyl	H	*R*	*S*
3j	C_6H_5	CH_3	cyclopentyl	H	*R*	*S*
3k	C_6H_5	CH_3	cyclohexyl	H	*R*	*S*
3l	C_6H_5	CH_3	2,4-dimethyl 3-pentyl	H	*R*	*S*
3m	C_6H_5	CH_3	*t*-Bu	H	*R*	*S*
4	H	$C_6H_5CH_2$	CH_3	H	-	*S*
5	H	*i*-Pr	CH_3	H	-	*S*
6	H	*s*-Bu	H	H	-	*S*
7	H	C_6H_5	H	H	-	*S*
8	C_6H_5	H	*i*-Pr	H	*R*	-
9	H	$-(CH_2)_3-$		H	-	*S*



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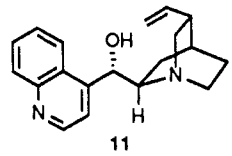

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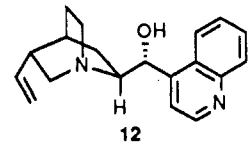

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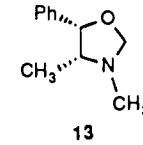

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reaction conditions and no epimerization of **2** can be detected in the presence of any chiral amine used in this study.

As shown in Figure 1, a limit was reached for the ee % as soon as 0.1 equiv of ephedrine is introduced into the reaction mixture. Similar curves were obtained either in CH_2Cl_2 or *n*-hexane. However, high concentrations of β-amino alcohols could not be used in alkanes at low temperatures due to solubility limits.

When the irradiations were carried out in the presence of 0.1 equiv or more of the chiral amino alcohol, the ee did not seem to be sensitive to the percentage conversion. This can be easily rationalized if we assume that under our conditions of irradiation there is at any moment a large excess of the chiral inductor with respect to the photodienol.

To study the influence of the structure of the inductor on the enantiomeric excess, we first examined the nature of the functional groups needed for an asymmetric tautomerism of the photodienol. Chiral alcohols in catalytic amounts led to a racemic mixture of **2** and only low enantioselectivities were obtained when either simple chiral amines, ammonium salts, or a mixture of a chiral amine and a chiral alcohol were utilized as chiral auxiliaries (Table II).

By contrast, selectivity of 37% was obtained in the presence of (+)-ephedrine (**3b**). The need for the amino and the hydroxyl groups in the same molecule for a good enantioselection became more evident when we found that only poor optical yields were obtained by replacement of (+)- or (−)-ephedrine by either its *O*-methyl ether **10** or the corresponding isoxazolidine **13** (Chart I).

The synergy observed on the enantioselectivity, when the two functional groups are present in the same molecule, might be indicative of a cyclic transition state as shown in Figure 2: The abstraction of the hydroxylic proton from the photodienol by the amine might be concerted with the protonation of C-2 by the hydroxyl group of the amino alcohol.

Various β-amino alcohols readily available from natural amino acids were next considered in order to determine the relationship

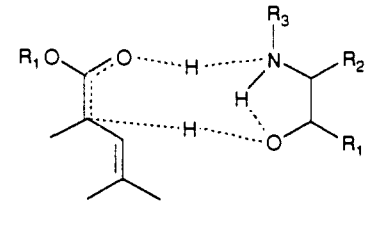


Figure 2.

Table III. Photodeconjugation of **1a** in the Presence of a β-Amino Alcohol[a]

run	catalyst[b]	configuration of the inductor at C*–O	configuration of the inductor at C*–N	solvent	temperature, °C	conversion, %	yield,[c] %	$[\alpha]^{20}_D$ (c, CH_2Cl_2)	ee %	configuration[d] of **2a**
1	**3b**	*S*	*R*	CH_2Cl_2	−40	100	64	+33.3 (0.42)	37	*S*
2	**3d**	*S*	*S*	CH_2Cl_2	−78	97	70	−4.0 (0.62)	4	*R*
3	**3d**	*S*	*S*	*n*-hexane	−78	98	57	−6.1 (0.49)	7	*R*
4	**4**	–	*S*	CH_2Cl_2	−78	86	67	−2.9 (0.58)	3	*R*
5	**5**	–	*S*	*n*-hexane	−78	95	65	−28.7 (0.49)	31	*R*
6	**5**	–	*S*	CH_2Cl_2	−78	98	71	−13.1 (0.72)	14	*R*
7	6	–	*S*	CH_2Cl_2	−78	96	75	−13.0 (0.61)	14	*R*
8	6	–	*S*	CH_2Cl_2	−40	94	64	−11.8 (0.50)	13	*R*
9	**7**	–	*R*	CH_2Cl_2	−40	100	64	−25.4 (0.50)	28	*R*
10	**8**	*R*	–	CH_2Cl_2	−40	100	64	0	0	–
11	**9**	–	*S*	CH_2Cl_2	−40	100	51	+10.4 (0.63)	11	*S*
12	**11**	*S*	*R*	CH_2Cl_2	−40	74	40	+39.3 (0.2)	41	*S*
13	**12**	*R*	*S*	CH_2Cl_2	−78	83	66	−33.9 (1.0)	37	*R*

[a] Irradiation conditions are those of Table I. [b] The optical purity of chiral auxiliary was >97%. [c] Yield of pure isolated **2a**. [d] Configuration at C-2 of the major enantiomer of **2a**. The % ee was determined by ^1H NMR in the presence of $Eu(hfc)_3$ and from the comparison of the $[\alpha]^{20}_D$ of a pure enantiomer of **2a**.

Table IV. Influence of the Substitution of the Amino Group of the Inductor on the Enantioselectivity of the Photodeconjugation of **1a**[a]

run	chiral auxiliary	solvent	temperature, °C	conversion, %	yield, %	$[\alpha]^{20}_D$ (c, CH_2Cl_2)	ee %[c]	configuration[b]
1	**3a**	CH_2Cl_2	−78	95	72	−12.6 (0.67)	14	*R*
2	**3a**	*n*-hexane	−78	100	65	−18.8 (0.66)	21	*R*
3	**3b**	CH_2Cl_2	−78	97	78	+28.1 (0.62)	31	*S*
4	**3b**	*n*-hexane	−78	98	66	+37.2 (0.80)	41	*S*
5	**3c**	CH_2Cl_2	−78	98	70	−25.7 (0.70)	28	*R*
6	**3c**	*n*-hexane	−78	98	65	−32.0 (1.0)	37	*R*
7	**3e**	CH_2Cl_2	−78	100	80	−5.4 (0.4)	6	*R*
8	**3f**	CH_2Cl_2	−40	93	70	−7.8 (0.33)	9	*R*
9	**3g**	CH_2Cl_2	−40	94	65	−62.2 (0.10)	70	*R*
10	**3g**	toluene	−40	100	78	−64.4 (0.5)	71	*R*
11	**3h**	CH_2Cl_2	−40	92	63	−28.6 (0.4)	31	*R*
12	**3i**	CH_2Cl_2	−40	98	63	−52.2 (0.45)	57	*R*
13	**3j**	CH_2Cl_2	−78	100	47	−56.7 (0.25)	62	*R*
14	**3j**	CH_2Cl_2	−40	100	57	−25.5 (0.41)	28	*R*
15	**3k**	CH_2Cl_2	−40	96	68	−39.8 (0.60)	44	*R*
16	**3l**	CH_2Cl_2	−40	100	56	−7.7 (0.3)	8	*R*
17	**3m**	CH_2Cl_2	−50	100	68	+4.8 (1.09)	5	*S*

[a] Irradiations conditions are those of Table I. [b] Configuration of the major enantiomer of **2a**. [c] Determined as in Table III.

between the chirality of the inductor and the induced chirality in the deconjugated molecule (Table III).

In the absence of a chiral center on the carbon directly linked to the amino group of the inductor, photodeconjugation is not enantioselective (run 10). By contrast, an asymmetric center on the carbinol group of the inductor is not needed and significant ee % are observed with (+)-*N*-methylvalinol (**5**), (+)-isoleucinol (**6**), or (+)-prolinol (**9**) (runs 5–9 and 11).

The important role of the configuration of the asymmetric carbon bearing the amine function is confirmed by observation of the inversion of the configuration at C-2 of the deconjugated ester when the inductors have an inverted configuration of the asymmetric carbon bearing the nitrogen. This effect is observed even if other asymmetric carbons are present in the chiral auxiliary (runs 1–2 and 12–13). In most cases, the C-2(*S*) configuration of the major enantiomer **2** can be correlated with the *R* configuration of the asymmetric carbon linked to the nitrogen in the chiral catalyst.

Interestingly use of the ephedrinium salt rather than ephedrine leads to almost racemic mixtures of **2**. The differences in selectivities obtained from diastereoisomeric inductors **3b** and **3d** (runs 1, 2, and 3) and the apparent exception to the previously reported observation that the C-2(*R*) configuration of **2** arises from β-amino alcohols having the *S* configuration of the C*–N (runs 9 and 11) might be indicative of some conformational effects.

To test the importance of the steric hindrance of the substituents on the nitrogen, we prepared various 2-amino-1-phenylpropanols derived from (−)-norephedrine and determined the efficiency of their asymmetric induction (Table IV). The ee % were lower for norephedrine (**3a**) and *N*-methylephedrine (**3e**) than for (+)-ephedrine (**3b**). This led us to consider only various 2-(*N*-alkylamino)-1-phenylpropanols. 2-(*N*-Isopropylamino)-1-phenylpropanol (NIAPP) (**3g**) gave the best results, and a 70% ee was determined for **2a**. When the size of the N substituent was increased further, the ee % began to decrease (runs 8, 11–17) and NIAPP looked to be the best compromise for the chiral inductors derived from ephedrine in the enantioselective photodeconjugation of **1a**. As these inductors were very poorly soluble in alkanes we also examined the enantioselectivity of the same reaction carried out in toluene at −40 °C in the presence of NIAPP. The results indicated that very similar selectivities can be obtained in *n*-hexane, CH_2Cl_2, and toluene.

For the photodeconjugation of esters **1**, the selectivity was always higher with NIAPP rather than ephedrine (Table V). The selectivity in the presence of NIAPP was particularly high when the γ position was doubly substituted (compare **1a**, **1f**, and **1h**). If the γ position was monosubstituted, a mixture of *Z* and *E* diastereoisomers, which could not be separated, was isolated. Fortunately, hydrogenation of the double bond[10] easily transformed the mixture of diastereoisomers into a mixture of enantiomers, and the optical purity could be determined on the hydrogenated compound by NMR in the presence of (+)-$Eu(hfc)_3$.

As pointed out previously, the enantioselectivity of the photodeconjugation of **1** in the presence of ephedrine was not very sensitive to the steric hindrance of the alkoxy group of the ester.[9d,e,h] The same observation could now be made with NIAPP as the chiral auxiliary. The observed selectivities for the photodeconjugation were very similar for benzyl, isopropyl, phenylethyl, and 3-methyl-2-butenyl esters **1a**, **1j**, **1k**, and **1l**, respectively; fur-

(10) Suzukamo, G.; Fukao, M.; Tamura, M. *Tetrahedron Lett.* **1984**, *25*, 1595.

Table V. Enantioselectivities of the Photodeconjugation of Esters **1** in the Presence of (+)-Ephedrine (**3b**) or (−)-NIAPP (**3g**) at −40 °C[a]

starting ester	inductor	solvent	conversion, %	yield, %	$[\alpha]^{20}_D$ (c, CH_2Cl_2)	ee %	configuration
1a	**3b**	CH_2Cl_2	100	64	+33.3 (0.4)	37	*S*
	3g	CH_2Cl_2	94	65	−62.2 (0.10)	70	*R*
1b	**3b**	CH_2Cl_2	100	70	+13.4 (0.4)	6	*S*
	3b	*n*-hexane	100	77	−5.4 (0.4)	3	*R*
	3g	CH_2Cl_2	100	65	−52.9 (0.5)	25	*R*
1c	**3b**	CH_2Cl_2	100	68	+11.0 (0.3)	10	*S*
	3g	CH_2Cl_2	100	67	−34.9 (0.2)	32	*R*
1d	**3b**	CH_2Cl_2	100	72	+24.9 (0.5)	21	*S*
	3g	CH_2Cl_2	100	59	−75.4 (0.2)	63	*R*
1e	**3b**	CH_2Cl_2	100	60	+38.8 (0.8)	31	*S*
	3b	*n*-hexane	100	60	+27.1 (0.5)	22	*S*
	3g	CH_2Cl_2	100	60	−65.2 (0.6)	52	*R*
1f	**3b**	CH_2Cl_2	100	75	+4.6 (0.8)	9	*S*
	3b	*n*-hexane	100	52	+10.1 (0.6)	20	*S*
	3g	CH_2Cl_2	93	70[c]	−2.5 (0.4)	38[d]	*R*
1g	**3b**	CH_2Cl_2	88	63[c]	+1.5 (0.5)[e]	9[d]	*S*
	3b	*n*-hexane	88	52[c]	+0.7 (0.3)[e]	4[d]	*S*
	3g	CH_2Cl_2	87	69[c]	−5.7 (0.3)[e]	36[d]	*R*
1h	**3g**	CH_2Cl_2	100	56	−1.5 (0.7)[e]	10[d]	*R*
1i	**3c**	CH_2Cl_2[f]	100	68	−28.4 (0.9)[g]	16	*R*
	3g	CH_2Cl_2	100	84	−70.8 (0.4)[g]	40	*R*
1j	**3b**	CH_2Cl_2[f]	97	63	+16.8 (1.0)	20	*S*
	3g	CH_2Cl_2	100	76	−57.0 (0.7)	68	*R*
1k	**3b**	CH_2Cl_2[f]	100	64	+23.7 (0.6)	29	*S*
	3g	CH_2Cl_2	90	67	−44.2 (0.3)	53	*R*
1l	**3b**	CH_2Cl_2[f]	92	80	+21.6 (0.8)	21	*S*
	3g	CH_2Cl_2	100	74	−69.7 (0.3)	68	*R*
1m	**3b**	CH_2Cl_2[f]	44	20	+11.6 (1.2)	17	*S*
	3b	*n*-hexane	88	59	−7.6 (0.7)	11	*R*
	3g	CH_2Cl_2	100	54	−34.5 (0.3)	45	*R*
1n	**3b**	CH_2Cl_2	100	60	+5.1 (0.4)	5	*S*
	3g	CH_2Cl_2	100	48	−26.4 (0.4)	24	*R*
1o	**3b**	CH_2Cl_2[f]	92	73	+17.8 (0.4)	17	*S*
	3g	CH_2Cl_2	100	74	−46.9 (0.4)	43	*R*

[a] Irradiation conditions are those of Table I. [b] Configuration postulated; see the text. [c] Mixture of the stereoisomers where the *E* isomer is predominant. [d] ee % determined on the hydrogenated ester. [e] $[\alpha]_D$ of the saturated ester. [f] The reaction was carried out at −78 °C. [g] $[\alpha]_D$ in Et_2O.

Table VI. Discrimination Parameters $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ in the Enantioselective Photodeconjugation of **1**

starting ester	inductor	solvent	$\Delta\Delta H^{\ddagger}$, kJ mol^{-1}	$\Delta\Delta S^{\ddagger}$, J mol^{-1} K^{-1}	$T\Delta\Delta S^{\ddagger}$ at 229 K, kJ mol^{-1}	$\Delta\Delta G^{\ddagger}$ at 229 K, kJ mol^{-1}
1a	**3c**	CH_2Cl_2	−2.9	−6	−1.6	−1.5
		n-hexane	−3.9	−10	−2.5	−1.7
	3b	*n*-pentane	−3	−8	−1.8	−1.2
		n-octane	−5.7	−16	−3.7	−2
	3g	CH_2Cl_2	−10	−29	−6.6	−3.4
1o	**3b**	CH_2Cl_2	−3.7	−13	−3	−0.7
		n-hexane	−2.9	−10	−2.3	−0.6
	3g	CH_2Cl_2	−5.8	−17	−3.9	−1.9

thermore the ee % was still 45% for the *tert*-butyl ester **1m**.

Preliminary studies indicated that the enantioselectivity increased when we lowered the temperature. A more complete study of this effect was undertaken to see if the chiral discrimination involved one or several competitive processes. Assuming that the two enantiomers are formed through the same mechanism, the concentration of each of the **2**-(*R*) and **2**-(*S*) isomers is proportional to the rate constants k_R and k_S of protonation of the two respective enantiofaces of the photodienol. If only one process is responsible for the formation of **2**, the plot of log [major isomer]/[minor isomer] against $1/T$, expected to be linear, should give some quantitative information about the discrimination process. Such typical plots are given in Figures 3 and 4 for the photodeconjugation of **1a** in the presence of (+)-ephedrine or (−)-NIAPP. Over the range of −40 to 70 °C we observed a linear relationship from which we can deduce the discrimination parameters $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ according to eq 2. $\Delta\Delta G^{\ddagger}$, $\Delta\Delta H^{\ddagger}$, and

$$\log [R]/[S] = -\Delta\Delta H^{\ddagger}/2.3RT + \Delta\Delta S^{\ddagger}/2.3R = \Delta\Delta G^{\ddagger}/2.3RT \quad (2)$$

$\Delta\Delta S^{\ddagger}$ represent the differences of the free energy, enthalpy, and entropy of activation between the two protonation pathways of the photodienol respectively. These parameters are reported in Table VI.

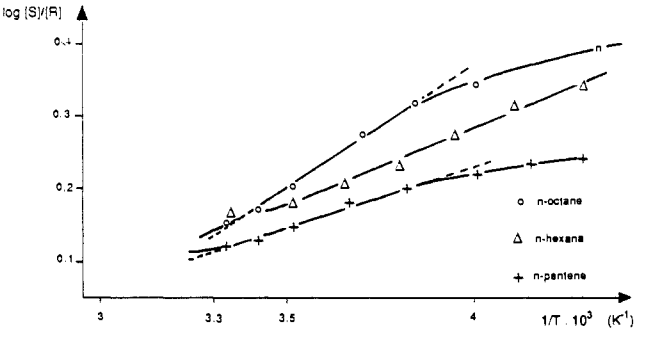


Figure 3. Influence of the temperature on the enantioselectivity of the photodeconjugation of **1a** (10^{-2} mol L^{-1}) in the presence of (+)-ephedrine (**3b**) (10^{-3} mol L^{-1}).

Surprisingly the enantioselectivity in CH_2Cl_2 is lower at −78 °C than at −40 °C. This observation suggests a competitive nonasymmetric protonation which is more favorable at very low temperatures. Methylene chloride can react with secondary

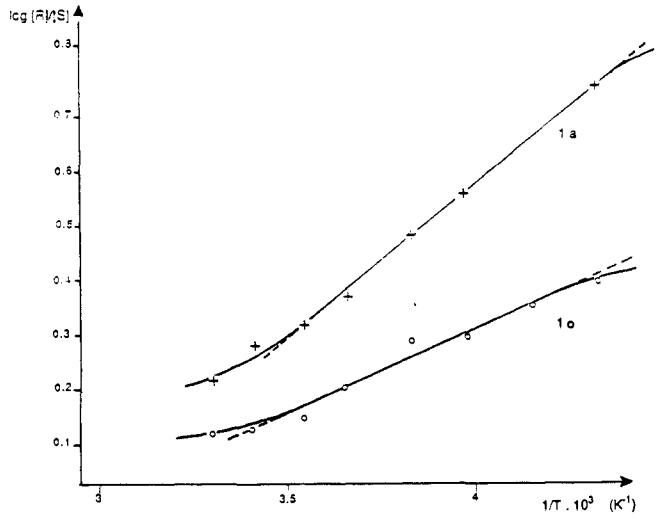


Figure 4. Influence of the temperature on the enantioselectivity of the photodeconjugation of **1a** or **1o** (10^{-2} mol L^{-1}) in the presence of **3g** (10^{-3} mol L^{-1}).

amines at room temperature either in the ground state[11] or the excited state.[12] If such reactions are competitive at low temperature with the photodeconjugation process, the new chiral compounds produced from the starting chiral inductor might interfere with it in the discrimination process. We found that the nucleophilic reaction of ephedrine on methylene chloride in the dark was very slow and could be neglected at low temperature. When irradiated at 254 nm a solution of ephedrine in CH_2Cl_2 produced ephedrinium hydrochloride which partly precipitated at very low temperature. A small amount of this salt was also characterized from the photodeconjugation experiments at low temperature. When ephedrine was replaced by its hydrochloride salt in the solution of **1a** in CH_2Cl_2, the irradiation led to the photodeconjugated ester **2a** with a chemical yield not significantly modified but its enantiomeric excess was very low (2%).

Discussion

Transition States Involved in the Enantioselective Protonation of the Dienol. The acidities of the photodienol and phenol have been shown to be of the same order,[8] and very strong hydrogen bonding have been observed in nonpolar solvents between phenol and amines.[13] In the absence of bases, conjugated enols can have quite long lifetimes[14] but the rate of their tautomerism in water is increased by a factor of at least 7 orders of magnitude in the presence of a base.[15] Similarly, in nonpolar solvents, the hydrogen bonding of the photodienol with the amine should also be a favorable process and should precede the protonation of the α-carbon of the enol. However, it has been proposed that the base-catalyzed isomerization process involves the intermediacy of an enolate,[6,15] and, in the presence of strong bases or in polar solvents, enolate intermediates seem probable. When the enantioselective photodeconjugation is carried out in nonpolar solvents and in the presence of chiral amino alcohols, enolates are probably not intermediates for the following reasons. In nonpolar solvents, the strong hydrogen bonding between phenol and tertiary amines indicates that the O–H bond is not cleaved in solution, and there is no evidence for a N–H vibration.[13] The same effect should be

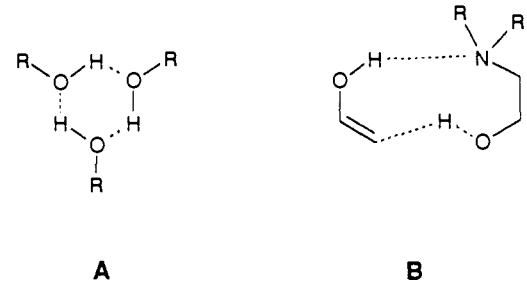
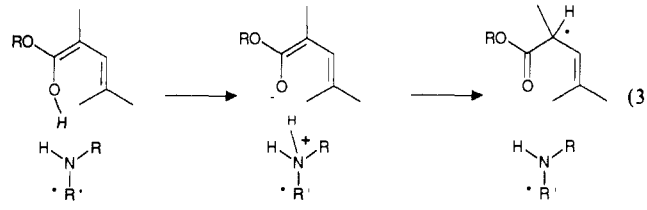


Figure 5.

expected for enols. An enolate, if produced, should exist as a very tight ion pair and protonation should be a very fast process.[8] The acidity of an ammonium salt is at least 10^5 times higher than the corresponding acidity of an alcohol and the enolate should be protonated by the ammonium ion rather than by the hydroxylic proton. Furthermore, it is known that the protonation of a lithium enolate is an enantioselective process when carried out in the presence of a chiral amine and a protic agent. The protonation involves the selective transfer of a proton from the nitrogen of the secondary amine group to the enolic carbon and an "intrasupramolecular" proton transfer from this secondary amine to the lithium enolate linked together by complexation has already been proposed.[16] The protonation of the naked enolate by the ammonium ion formed in situ according to eq 3 does not need



any hydroxylic protons. When ephedrine is replaced by (–)-1-phenylethylamine, **10**, or **13** (Table II), only low enantioselectivities are observed although the photodeconjugation is still a very efficient process and probably involves an ion pair intermediate. When a chiral alcohol is added to the reaction mixture in the presence of a chiral amine, the enantioselectivities observed are very close to the selectivities observed in the presence of the chiral amine as the only additive. The synergy between the hydroxyl and amino groups when situated in the same molecule requires another mechanism to rationalize the results.

When chiral amino alcohols are used in aprotic, nonpolar solvents a new mechanism can compete and even replace the ion pair process.[17] Cooperative hydrogen bonding has great importance in biological structures when, for example, three hydrogen bonds are arranged in a cyclic array[18] as in complex A (Figure 5). Complex intermediates like B, where the enol and the β-amino alcohol are linked by hydrogen bonds, can be similarly considered to explain the tautomerism of dienols. The N–H and C_α–O bond making might occur simultaneously with the π_{CC} and O–H bond breaking without any enolate–ammonium ion pair formation. An early transition state has already been proposed for the ketonization of enols.[19] The hydrogen bonding between the enolic proton and the nitrogen atom increases the electron density on the β-carbon and favors a nine-membered cyclic transition state.

Geometry of the Transition State. An important activation energy has already been calculated for the base-catalyzed tautomerism of enols in water.[8c] According to the Curtin–Hammett

(11) Mills, J. E.; Maryanoff, C. A.; McComsey, D. F.; Stanzione, R. C.; Scott, L. *J. Org. Chem.* **1987**, *52*, 1857, and references therein.

(12) (a) Erra Balsells, R.; Frasca, A. R. *Rev. Latinoamer. Quim.* **1986**, *17*, 43. (b) Erra Balsells, R.; Frasca, A. R. *Tetrahedron Lett.* **1984**, *25*, 5363.

(13) (a) Gramstad, T. *Acta Chem. Scand.* **1962**, *16*, 807. (b) See also; Abraham, M. H.; Grellier, P. L.; Prior, D. V.; Taft, R. W.; Morris, J. J.; Taylor, P. J.; Laurence, C.; Berthelot, M.; Doherty, R. M.; Kamlet, J. M.; Abboud, J. L. M.; Sraidi, K.; Guihéneuf, G. *J. Am. Chem. Soc.* **1988**, *110*, 8534.

(14) Chin, C. S.; Lee, S. Y.; Park, J.; Kim, S. *J. Am. Chem. Soc.* **1988**, *110*, 8244, and references therein.

(15) Kresge, A. J. *L'Actualité Chimique* **1988**, 233. (b) Chiang, Y.; Kresge, A. J.; Santaballa, J. A.; Wirz, J. *J. Am. Chem. Soc.* **1988**, *110*, 5506. (c) Capon, B.; Guo, B. *J. Am. Chem. Soc.* **1988**, *110*, 5144.

(16) (a) Eleveld, M. B.; Hogeveen, H. *Tetrahedron Lett.* **1986**, *27*, 631. (b) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624 and references therein.

(17) The difference of mechanism of the tautomerism of the dienol catalyzed by amines is also detected in the diastereoselective photodeconjugation of very hindered esters derived from 2,3-dihydroxybornane. Very different selectivities can be obtained in the presence of achiral bases as diisopropylamine and 2-benzylaminoethanol.

(18) Saenger, W. *Principles of nucleic acid structure*; Springer: Berlin, 1984; p 117.

(19) Zimmerman, H. E. *Acc. Chem. Res.* **1987**, *20*, 263.

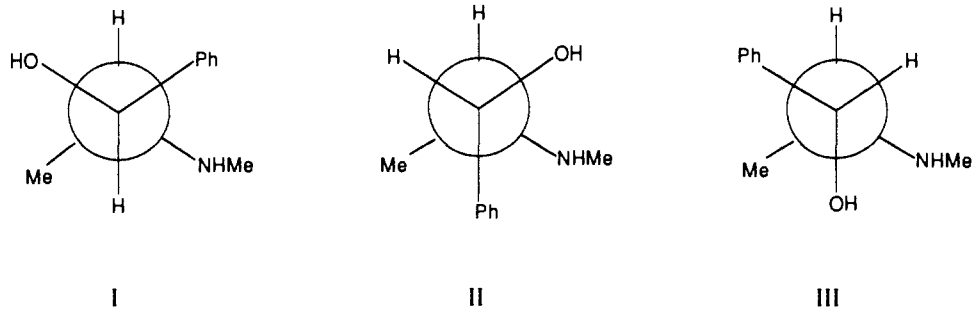


Figure 6.

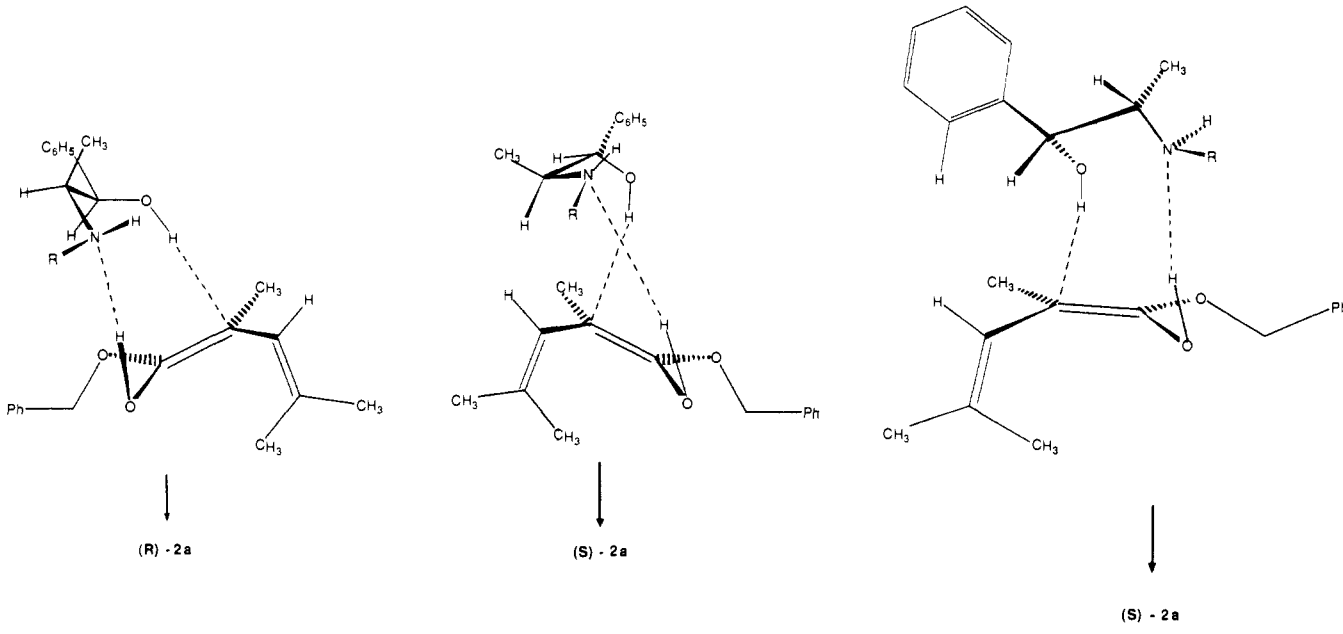
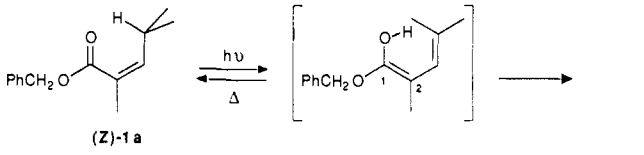
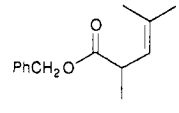


Figure 7.

principle, we can assume that the chiral discrimination between the two transition states of **2** (see Figure 7 parts a–c) is determined by the differences in the activation energy for the protonation step and does not depend on the conformational equilibrium of the dienol.

To try to define a model explaining the enantioselective photodeconjugation we will first consider the reaction between the benzyl ester **1a** and (−)-ephedrine (**3c**) (eq 4). During the





(4)

photochemical step, the dienol formed exclusively from the *Z* isomer possesses the *E* configuration of $C_1{=}C_2$. As 0.05 equiv of (−)-ephedrine is sufficient to produce the maximum enantioselectivity (Figure 1), we can assume that the dienol does not accumulate in the reaction mixture. The *Z*/*E* photoisomerization process of the dienol is then unlikely and can be neglected under the conditions of the reaction. The stereospecific formation[6b,6c] of the dienol in its *E* configuration is very important with respect to an enantioselective protonation on prochiral C_2. Very good selectivities can be expected if high discrimination takes place between the two enantiofaces of this unique dienol in the presence of a chiral proton source.

Conformational studies of (−)-ephedrine have shown that an intramolecular hydrogen bond is formed[20] and that the most probable conformations can be represented as in Figure 6 with a preference for II. As soon as there is an interaction between the acidic dienol and (−)-ephedrine, we can expect that the intramolecular hydrogen bond will be replaced by an intermolecular one between the enol and the amino group of the inductor.

As shown earlier, the major steric interactions responsible for the discrimination between the two diastereoisomeric transitions states do not involve the alkoxy group of the starting ester.[9] If we consider the approach of (−)-ephedrine to either of the two enantiofaces of the dienol, keeping the largest substituents as far as possible, the transition states A–C represented in Figure 7 can be examined. In these transition states, only gauche conformations of (−)-ephedrine are considered. For (−)-ephedrine and the dienol formed from **1a**, no major steric interaction can be detected in the transition state A and the formation of the 2-*R* configuration of **2a** seems to be favorable. When the inductor approaches the *pro-S* enantioface of the dienol, two cyclic transition states B and C derived from different orientations of the interaction of the amino group with the enolic proton can be considered. In B and C, steric interactions appear to take place between the unsaturated chain of the dienol and the carbons linked either to the nitrogen or to the hydroxyl group of ephedrine respectively. Thus the formation of the resulting 2-*S* configuration of **2a** seems unfavorable.

In general, the selectivity of an asymmetric synthesis is usually highest when the chiral center of the inductor is as close as possible

(20) (a) Schneider, H. J.; Lonsdorfer, M. *Org. Magn. Reson.* **1981**, *16*, 133. (b) Solmajer, P.; Kocjan, D.; Solmajer, T. *Z. Naturforsch.* **1983**, *38*, 758. (c) Spassov, S. L.; Radeglia, R. *Dokl. Bolg. Akad. Nauk.* **1980**, *33*, 1085.

to the prochiral center of the substrate. Although the chirality of the C*–N asymmetric center determines the chirality on C-2 of the deconjugated ester, it would be very difficult to decide which of the transition states B or C is in competition with A, due to the small differences of activation energies involved.

The preference for transition states of type A can be generalized for other dienols and many β-amino alcohols. Particularly we can anticipate that an increase in the size of the substituents on the γ-carbon of the starting ester and on the nitrogen of the chiral auxiliary will increase the steric interactions in transition states B and C. An increase of ee % is indeed observed under these conditions. The results obtained with (+)-cinchonine (**11**) and (−)-cinchonidine (**12**) can be rationalized with the same model if we assume that only the more basic nitrogen interacts with the dienol in the transition state. However, this interpretation has to be examined with great prudence. Very small free energy differences $\Delta\Delta G^{\ddagger}$ are indeed involved and the maximum ee value observed (ee = 70%) requires only $\Delta\Delta G^{\ddagger}$ = 3.3 kJ M^{-1} at −40 °C. The ionic character, and exact geometry of the transition states, and the true distances between the dienol and the amino alcohol are not known, and a discussion dealing with such small free energy differences is still very speculative.

Finally, spectroscopic studies carried out on β-amino alcohols in aqueous solution have led to the conclusion that the usual OH···:N intramolecular hydrogen bond can be replaced in acidic medium by an NH···:O bond.[20b] In the presence of amines, we can assume that dienols have a very polar character. In the transition state, the amino group develops a new N–H bond and an ammonium character, allowing a new intramolecular NH···:O hydrogen bonding as shown in Figure 2. At the end of the reaction, the hydroxylic proton of the amino alcohol is transferred to C_α of the deconjugated ester, and a proton might be transferred intramolecularly from the nitrogen to the oxygen of the inductor. Then the deconjugated ester **2** might be formed and the β-amino alcohol be regenerated without the intermediacy of polar intermediates. The consequence of the appearance of such an NH···:O bond would be the lowering of the activation energy for nine-membered-ring transition states. The synergy between the hydroxyl and the amino groups of β-amino alcohols could be rationalized on this basis and from the preference of bimolecular rather than termolecular interactions.

Such cyclic transition states should be very ordered and very sensitive to temperature.

Temperature Effects. The linearity of the plots of log [major isomer]/[minor isomer] as a reciprocal function of the temperature between −40 to +25 °C indicates that only one protonation process of the dienol is probably involved over this range of temperature. The discrimination parameters $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ deduced from these curves possess the same sign for the ester and inductor pairs studied. This means that, from the two diastereoisomeric transition states involved in the protonation of prochiral dienols, the lower activation enthalpy corresponds to the more ordered transition state. The chiral discrimination energy of 3.35 kJ mol^{-1} was obtained at −40 °C when NIAPP was the inductor.

The increase in the viscosity of the solvent from *n*-pentane to *n*-octane decreases simultaneously the two discrimination parameters. However, at low temperature, the relative contribution of the entropic factor becomes lower in viscous solvent and the selectivity increases from *n*-pentane to *n*-octane.

At temperatures lower than −70 °C, the deviation of the Eyring plots from linearity can be attributed to several factors and first to a decrease in the rate of tautomerism. Activation energies of about 12 kcal mol^{-1} have been determined for the protonation of vinyl alcohols and dienols in water.[8c,21] If we assume activation energies of the same order in aprotic solvents and in the presence of amino alcohols, the protonation process might be slow enough at temperatures lower than −60 °C to allow other processes to occur. As shown earlier, there is a process in methylene chloride involving electron transfer and the formation of ephedrinium salts which may compete with ephedrine in the protonation step. Autoassociation of amino alcohols, known to occur for quinine in nonpolar solvents, might also contribute to the decrease of the ee % at low temperature.[22]

Photolysis of conjugated esters in the presence of amines can also induce electron transfer processes and radical coupling of the amine and the ester.[23] We did not detect significant amounts of such adducts and in every case the deconjugated ester represented the major product. Furthermore, the absence of variation of the ee with the percentage conversion indicates that, under the conditions used, the starting chiral catalyst is probably the only species involved in the enantioselective protonation process.

At temperatures higher than 20 °C we observe another curvature of the Eyring plots. This can be attributed to competing tautomerism processes involving molecules of the starting ester since the amino group and the hydroxyl function can act independently as catalysts. The catalysis of the tautomerism of the dienol by the starting ester has already been proposed[6] and amines such as diisopropylamine can catalyze the formation of the deconjugated ester even in the absence of another proton source besides the enolic proton.[9g]

During a study of the Paternò–Büchi reaction of chiral phenyl glyoxylates, it was recently shown that the temperature dependence of diastereoselectivity yielded two linear functions in the corresponding Eyring diagrams. Temperatures of inversion and two distinct temperature areas, in which the selection was either mostly enthalpy or entropy determined, were recognized.[24] The changes of the slopes observed in the curves of Figures 3 and 4 at high and at very low temperatures might also have a similar origin. Further experiments are however required to determine which of these factors plays the major role.

The enantioselective photodeconjugation can now be compared with similar processes involving enolate intermediates. Use of (2*R*,3*R*)-*O*,*O*-diacyltartaric acids as the proton source allows the enantioselective protonation of enolates with selectivities up to 82%[25] and similar selectivities were recently reported with ephedrine derivatives as the proton source.[26] In all these cases, the reaction process needs stoichiometric amounts of a chiral catalyst. The enantioselective photodeconjugation of esters involves enol rather than enolate intermediates, and it can be carried out in neutral medium. The chiral catalyst is not consumed in the reaction process. This represents the best result yet obtained (ee up to 70%) for an enantioselective photoreaction carried out in solution when the chiral auxiliary is not directly linked to the reactants. On the basis of the principles discussed in this paper we can anticipate that photoreactions leading to polar intermediates and even polar excited states should be considered in connection with asymmetric synthesis. The high chiral discrimination reported for α-amino esters in the presence of chiral alcohols,[27] the interesting selectivities described in electrocyclic reactions,[28] and photocycloadditions[2] indicate that studies on enantio- and diastereoselective photoreactions might lead to important developments in the near future.

Experimental Section

General. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ as solvent (80 MHz) on a CW80 or AC300 (300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR) Bruker instrument and are referenced to tetramethylsilane as an internal standard. IR spectra were obtained in $CHCl_3$ on a SP 3.300 Philips spectrophotometer. Mass spectra were taken on

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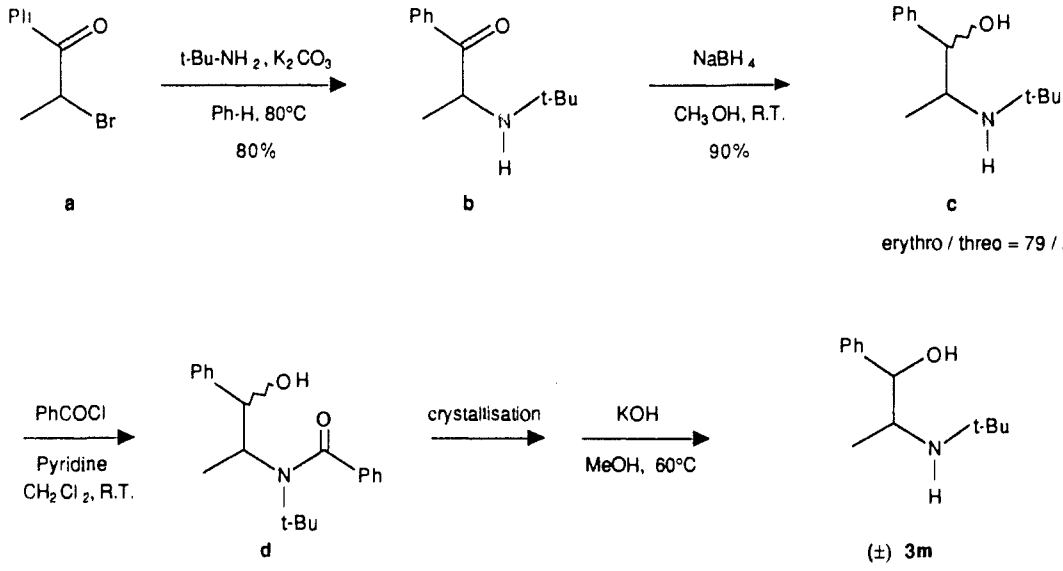
Scheme II



a DNM 300 JEOL apparatus and optical rotations at 20 °C on a Perkin-Elmer Model 241 polarimeter.

Starting materials **1a–o** were prepared as described in ref 9h. Hexane and CH_2Cl_2 as irradiation solvents were freshly distilled from CaH_2 under an argon atmosphere. Photolysis experiments were performed as follows: a 10^{-2}M solution of substrate **1** containing 0.1 equiv of inductor **3–13** was poured into quartz tubes, degassed with argon, and placed in a temperature controlled ethanol bath; irradiations were realized with an OSRAM H.N.S. 10 lamp; after complete disappearance of ester **1**, as indicated by TLC, solvent was eliminated, and the deconjugated compound **2** was purified by preparative thin-layer chromatography.

Synthesis of Inductors. The following amino alcohols available from Aldrich or Fluka Company were used as received: (+)- and (−)-ephedrine (**3b** and **3c**, respectively), (+)-pseudoephedrine (**3d**), (+)-isoleucinol (**6**), (−)-phenylglycinol (**7**), (+)-prolinol (**9**), (+)-cinchonine (**11**), and (−)-cinchonidine (**12**). Ephedrine derivates were prepared by the procedure mentioned: (−)-*N*-methylephedrine (**3e**) by the Eschweiler-Clarke procedure,[29] (+)-*O*-methylephedrine (**10**) and (−)-oxazoline (**13**), respectively, according to refs 30 and 31; (+)-*N*-methyl-3-phenylalaninol (**4**) and (+)-*N*-methylvalinol (**5**) have been furnished.[32] Inductors **3f–l** were obtained by reductive alkylation of (−)-norephedrine (**3a**) with sodium borohydride in presence of the appropriate carbonyl compound.[33]

(1*R*,2*S*)-2-(Benzylamino)-1-phenyl-1-propanol (3f):[34] Yield 80%; mp (hexane) 56 °C; IR 3500–3100, 3000, 1490, 1450, 1380, 1110, 990; $[\alpha]_D$ −20.4 (*c* = 0.5, $CHCl_3$); ^{1}H NMR 0.84 (d, *J* = 6.5, 3H), 2.20–2.70 (2 H), 2.95 (dq, *J* = 6.5, 3.9, 1 H), 3.83 (s, 2 H), 4.75 (d, *J* = 3.9, 1 H), 7.21–7.34 (m, 10 H); ^{13}C NMR 14.73 (q), 51.38 (t), 57.90 (d), 73.39 (d), 126.25 (d), 127.17 (d), 127.26 (d), 127.66 (d), 128.19 (d), 128.65 (d), 128.75 (d), 140.21 (s), 141.53 (s); MS *m/e* 242 (M^+, <1), 134 (42), 91 (100).

(1*R*,2*S*)-2-(Isopropylamino)-1-phenyl-1-propanol (3g) [(−)-NIAPP]:[33] Yield 80%; mp (hexane) 89 °C; IR 3600, 3600–3100, 2960, 2870, 1595, 1490, 1450, 1380, 1220, 1165, 700; $[\alpha]_D$ −5° (*c* = 1, CH_2Cl_2); ^{1}H NMR 0.80 (d, *J* = 6.5, 3 H), 1.08 (d, *J* = 6.3, 3 H), 1.09 (d, *J* = 6.3, 3 H), 2.30–2.70 (m, 2 H), 2.97 (qq, *J* = 6.3, 6.3, 1 H), 3.05 (dq, *J* = 6.5, 4, 1 H), 4.70 (d, *J* = 4, 1 H), 7.22–7.36 (m, 5 H); ^{13}C NMR 15.30 (q), 23.59 (q), 23.69 (q), 45.64 (d), 55.29 (d), 73.58 (d), 126.32 (d), 127.14 (d), 128.18 (d), 141.65 (s); MS *m/e* 194 (M^+ + 1, 49), 160 (25), 91 (27), 87 (83), 86 (100), 79 (61), 77 (100), 70 (34).

(1*R*,2*S*)-2-(Isobutylamino)-1-phenyl-1-propanol (3h):[33] Yield 93%; mp (hexane) 65 °C; IR 3500–3150, 2980, 1490, 1465, 1450, 1180, 990; $[\alpha]_D$ −17.5° (*c* = 0.5, $CHCl_3$); ^{1}H NMR 0.73 (d, *J* = 6.5, 3 H), 0.84 (d, *J* = 6.3, 3 H), 0.86 (d, *J* = 6.3, 3 H), 1.63 (m, 1 H), 2.36 (dd, *J* = 11.4, 6.9, 1 H), 2.49 (dd, *J* = 11.4, 6.4, 1 H), 2.80 (dq, *J* = 6.5, 3.9, 1 H), 4.65 (d, *J* = 3.9, 1 H), 7.23 (s, 5 H); ^{13}C NMR 14.96 (q), 20.76 (q), 21.05 (q), 28.87 (d), 55.39 (t), 58.66 (d), 73.07 (d), 126.21 (d), 127.08 (d), 128.18 (d), 141.64 (s).

(1*R*,2*S*)-2-(3-Pentylamino)-1-phenyl-1-propanol (3i): Yield 43%; mp (hexane) 68 °C; IR 3650, 3550–3200, 2980, 1455, 1380, 980; $[\alpha]_D$ +7.8° (*c* = 0.6, EtOH); ^{1}H NMR 0.69 (d, *J* = 6.5, 3 H), 0.79 (t, *J* = 7, 3 H), 0.83 (t, *J* = 6.9, 3 H), 1.26–1.42 (m, 4 H), 2.44 (tt, *J* = 5.8, 5.8, 1 H), 2.90 (dq, *J* = 6.5, 3.9, 1 H), 4.58 (d, *J* = 3.9, 1 H), 7.22 (s, 5 H); ^{13}C NMR 9.82 (q), 10,11 (q), 15,25 (q), 26.45 (t), 26.89 (t), 55.59 (d), 57.18 (d), 73.36 (d), 126.15 (d), 126.94 (d), 128.07 (d), 141.70 (s); MS *m/e* 222 (M^+ + 1, <1), 164 (74), 115 (90), 114 (100), 79 (82), 77 (100), 70 (62), 58 (52). Anal. Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 75.90; H, 10.45; N, 6.42.

(1*R*,2*S*)-2-(Cyclopentylamino)-1-phenyl-1-propanol (3j): Yield 87%; mp (hexane) 132 °C; IR 3600–3100, 2940, 1230–1200, 1080; $[\alpha]_D$ +15° (*c* = 0.3, EtOH); ^{1}H NMR 0.81 (d, *J* = 6.5, 3 H), 1.15–1.45 (m, 2 H), 1.45–1.75 (m, 4 H), 1.75–2.00 (m, 2 H), 2.98 (dd, *J* = 6.5, 4.1, 1 H), 3.22 (d, *J* = 6.7, 1 H), 4.69 (d, *J* = 4.1, 1 H), 7.21–7.36 (m, 5 H); ^{13}C NMR 15.48 (q), 23.93 (t), 33.75 (t), 34.02 (t), 56.81 (d), 57.15 (d), 73.65 (d), 126.36 (d), 127.11 (d), 128.15 (d), 141.76 (s); MS *m/e* 220 (M^+ + 1, <1), 112 (100). Anal. Calcd for $C_{14}H_{21}NO$: C, 76.66; H, 9.65; N, 6.39. Found: C, 76.46; H, 9.74; N, 6.48.

(1*R*,2*S*)-2-(Cyclohexylamino)-1-phenyl-1-propanol (3k): Yield 87%; mp (hexane) 128 °C; IR (CCl_4) 3700–3200, 2950, 1460, 1250, 1220, 1160, 1080, 1010; $[\alpha]_D$ +6° (*c* = 0.2, EtOH); ^{1}H NMR 0.79 (d, *J* = 6.5, 3 H), 1.04–1.32 (m, 5 H), 1.59–1.64 (m, 1 H), 1.70–1.76 (m, 2 H), 1.88–1.93 (m, 2 H), 2.00–2.60 (2 H), 2.52–2.62 (m, 1 H), 3.07 (dq, *J* = 6.5, 3.9, 1 H), 4.66 (d, *J* = 3.9, 1 H), 7.20–7.31 (m, 5 H); ^{13}C NMR 15.59 (q), 25.21 (t), 25.35 (t), 26.25 (t), 34.48 (t), 34.57 (t), 53.85 (d), 54.99 (d), 73.71 (d), 126.33 (d), 127.09 (d), 128.15 (d), 141.78 (s); MS *m/e* 234 (M^+ + 1, 22), 127 (64), 126 (100), 82 (44), 77 (33). Anal. Calcd for $C_{15}H_{23}NO$: C, 77.20; H, 9.93; N, 6.00. Found: C, 77.03; H, 9.94; N, 6.02.

(1*R*,2*S*)-2-[[3-(2,4-Dimethylpentyl)]amino]-1-phenyl-1-propanol (3l): Yield 90%; oil; IR 3600, 3600–3300, 2960, 2880, 1610, 1575, 1490, 1385, 1220, 1090, 1050; $[\alpha]_D$ −20.1° (*c* = 0.7, Et_2O); ^{1}H NMR 0.91 (d, *J* = 6.7, 12 H), 1.00 (d, *J* = 6.5, 3 H), 1.75 (dqq, *J* = 6.7, 6.7, 5.9, 2 H), 2.10–2.40 (m, 2 H), 3.00 (t, *J* = 5.9, 1 H), 3.29 (dq, *J* = 6.5, 4.3, 1 H), 4.68 (d, *J* = 4.3, 1 H), 7.24–7.33 (m, 5 H); ^{13}C NMR 16.64 (q), 19.79 (q), 30.53 (d), 52.17 (d), 76.37 (d), 81.83 (d), 126.35 (d), 127.58 (d), 128.27 (d), 140.78 (s).

(1*R*,2*S*)-2-(*tert*-Butylamino)-1-phenyl-1-propanol (3m). The racemic **3m** was prepared from (±)-2-bromo-1-phenyl-1-propanone (a)[35] as shown in Scheme II.

The $NaBH_4$ reduction of b led to an amino alcohol c which was a 79/21 mixture of erythro and threo isomers as indicated by ^{1}H NMR. The erythro isomer was purified by crystallization of the *N*-benzoyl derivative: a methylene chloride solution (10 mL) containing compound c (1.26 g, 6 mmol), benzoyl chloride (1 mL, 8 mmol), and pyridine (0.8 mL) was stirred for 4 h at room temperature. The mixture was diluted with CH_2Cl_2, washed with water, and dried over Na_2SO_4, and the solvent

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was removed under reduced pressure. The residue was triturated with ethyl acetate and gave a solid compound which was filtered off and heated for 1 h at 60 °C with KOH (0.61 g, 11 mmol) in methanol (10 mL). The cooled solution was filtered on alumina. Evaporation of solvent gave 285 mg (23% from c) of (±)-**3m** as a viscous material.

S-(−)-Carbamalactic acid was used as resolving agent[36] for racemic **3m**. The salt obtained from **3m** (285 mg, 1.4 mmol) presented a constant optical rotation after two crystallizations (MeOH/ether): $[\alpha]_D$ −43° (*c* = 1.1, CH_2Cl_2) and led to (+)-**3m** (89 mg, 0.43 mmol); $[\alpha]_D$ +2.5° (*c* = 2.4, CH_2Cl_2): mp (salt from benzoic acid, CH_2Cl_2) 170 °C; IR 3600–3200, 2960, 1450, 1360, 1130, 970; ^{1}H NMR 0.78 (d, *J* = 6.6, 3 H), 1.15 (s, 9 H), 1.73 (dq, *J* = 6.3, 4.2, 1 H), 7.19–7.31 (m, 5 H); ^{13}C NMR 17.93 (q), 30.03 (q), 51.11 (s), 51.93 (d), 74.79 (d), 126.12 (d), 126.74 (d), 127.83 (d), 141.82 (s); MS *m/e* 208 (M^+ + 1, 43), 174 (21), 100 (100).

The configuration of (+)-**3m** was established as 1-*R*, 2-*S* by comparison of its circular dichroism spectrum with those of **3b** and **3g**. Observed molar ellipticity were the following: (+)-(1*S*,2*R*)-ephedrine (**3b**) $[\theta]^{20}_{267.5}$ = −1062, $[\theta]^{20}_{261}$ = −1136; (−)-(1*R*,2*S*)-2-(isopropylamino)-1-phenyl-1-propanol (**3g**) $[\theta]^{20}_{267.5}$ = +1437, $[\theta]^{20}_{261}$ = +1555, and (+)-(1*R*,2*S*)-2-(*tert*-butylamino)-1-phenyl-1-propanol (**3m**) $[\theta]^{20}_{267.5}$ = + 1666, $[\theta]^{20}_{261}$ = +1825.

(*R*)-2-(Isopropylamino)-1-phenylethanol (8). The procedure reported in ref 37 was used. Isopropylamine (6.8 mL, 79.3 mmol) in dry ether (20 mL) was added to an ice-cooled solution of acetylmandelyl chloride (8.43 g, 39.6 mmol)[38] in ether (30 mL). The mixture was stirred for 12 h, hydrolyzed with saturated brine, extracted with CH_2Cl_2 and dried over magnesium sulfate. After evaporation the residue was crystallized from hexane to afford 6.4 g (27.2 mmol, 69%) of *N*-isopropyl-*O*-acetylmandelamide: mp 98 °C; IR 3420, 2980, 1745, 1675, 1520, 1460, 1375, 1230–1210, 1030; $[\alpha]_D$ −105.4 (*c* = 0.46, CH_2Cl_2); ^{1}H NMR 1.13 (d, *J* = 6.6, 3 H), 1.15 (d, *J* = 6.5, 3 H), 2.16 (s, 3 H), 4.08 (m, 1 H), 6.02 (s, 1 H), 7.32–7.43 (m, 5 H).

The mandelamide (2.5 g, 10.6 mmol) in THF was added at 0 °C to a stirred suspension of $LiAlH_4$ (1.61 g, 42.5 mmol) in THF. The mixture was refluxed overnight, cooled, and carefully hydrolyzed with wet ether. The product was isolated after filtration of the ether layer, evaporation, and crystallization from hexane to give 838 mg (44% yield) of **8**: mp 91 °C; IR 3620, 3540–3200, 3020, 2980, 1490, 1450, 1230–1200, 1060; $[\alpha]_D$ −2° (*c* = 0.2, $CHCl_3$); ^{1}H NMR 1.03 (d, *J* = 6.2, 3 H), 1.04 (d, *J* = 6.2, 3 H), 2.63 (dd, *J* = 12, 9.1, 1 H), 2.78 (qq, *J* = 6.2, 6.2, 1 H), 2.86 (dd, *J* = 12, 3.7, 1 H), 4.68 (dd, *J* = 9.1, 3.7, 1 H), 7.28–7.36 (m, 5 H); ^{13}C NMR 23.13 (q), 48.81 (d), 54.93 (t), 72.19 (d), 125.96 (d), 127.52 (d), 128.47 (d), 143.28 (s); MS *m/e* 180 (M^+ + 1.76), 146 (50), 91 (37), 79 (63), 77 (100), 73 (14), 72 (100). Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.93; H, 9.50; N, 7.83.

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Supplementary Material Available: Tables showing the influence of temperature on the enantioselectivity of various photodeconjugations (8 pages). Ordering information is given on any current masthead page.

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New Tandem Radical Cyclizations Directed toward the Synthesis of Crinipellin A

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Abstract: We describe a new tandem radical cyclization strategy for the construction of the congested angular triquinane portion of the naturally occurring tetraquinane crinipellin A. The preparation and cyclization of three 5,5-disubstituted-1,4-dimethyl-1,3-cyclopentadienes are detailed. This cyclization strategy results in a 1,4-functionalization of the cyclopentadiene nucleus, mediated by an allylic radical cyclization. Each tandem cyclization produces two diastereomeric triquinanes in a ratio of 5:1. The minor diastereomer possesses the correct relative stereochemistry for the D-ring isopropyl group of crinipellin A. A tandem cationic cylization, paralleling the radical cyclizations, is also described. The generation and subsequent addition or cyclization reactions of acyl radicals has been accomplished by the reduction of acyl methyl selenides with tin hydride. This new method is the most direct route for conversion of a methyl ester to an acyl radical.

Introduction

Several years ago, we initiated a program to develop a unified approach to the synthesis of triquinane natural products.[1] Our strategy is based on tandem radical cyclizations, wherein the two outer rings of a triquinane (linear or angular) are formed around a central, preformed cyclopentene ring. Variations in both the placement and degree of functionality of the side chains on the central ring allow for an efficient entry to a variety of cyclopentanoids, as demonstrated by the syntheses of the linear triquinanes hirsutene,[2] capnellene,[3] coriolin, and hypnophilin,[4] the angular triquinane silphiperfolene,[5] and the propellane triquinane modhephene.[6] We now report our initial studies on a new tandem radical cyclization strategy directed toward the synthesis of the tetraquinane crinipellin A (**1a**, Figure 1).

Crinipellis stipitaria (Agaricales) is a fungus that grows on both the dead and living parts of grasses. It produces an antibacterial metabolite that was isolated and named crinipellin.[7a]

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