

Lactate as Chiral Auxiliary in Asymmetric Photodeconjugation of Unsaturated Esters

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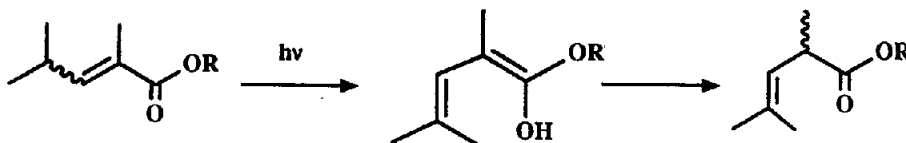
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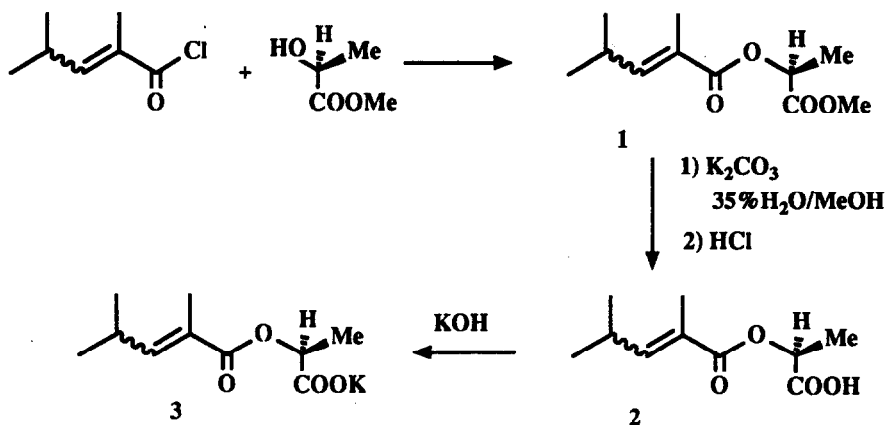
Abstract: The asymmetric photodeconjugation of the α,β -unsaturated esters 1, 2 and 3, to the corresponding β,γ -unsaturated esters having a new chiral center at the α position, has been studied in a variety of solvents. In most solvents, the (*S*)-lactyl chiral auxiliary induced the *S* configuration at the new chiral center. However, irradiation of 1 in methanol or 2-propanol/water mixtures gave an unusual reversal of diastereoselectivity to produce the *R* configuration at the new chiral center.

Photodeconjugation of α,β -unsaturated esters to β,γ -unsaturated esters can produce a new chiral center at the α carbon, and the asymmetric induction at this center can be controlled either by the presence of a chiral catalyst, or by a chiral auxiliary present in the ester.¹⁻¹¹ The mechanism of the photodeconjugation involves intramolecular hydrogen abstraction to form an enol that subsequently tautomerizes to the nonconjugated ester.



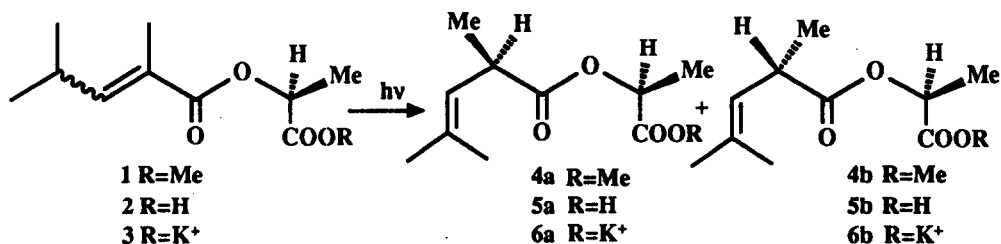
In our efforts to improve the asymmetric induction in this reaction, and to better understand its mechanism, we have continued to search for more efficient chiral auxiliaries. Because of the known efficiency of the lactyl chiral auxiliary in certain Diels-Alder reactions,¹²⁻¹⁵ we chose to study its effect on the deconjugation reaction. The lactyl chiral auxiliary was considered especially appropriate for this reaction as the diastereoselective protonation of the dienol might be directed by a direct involvement of the carboxylate group in the protonation mechanism. To test this possibility, compounds 1, 2 and 3 were

synthesized, as illustrated below. 2,4-Dimethylpent-2-enoyl chloride (mixture of E and Z isomers)⁸ and one equivalent of methyl (S)-lactate were refluxed in CCl₄ for 15 hrs to produce the methyl lactate ester **1** in 59% yield (after chromatography on silica, 5% EtOAc/petroleum ether) as a mixture of E and Z isomers.¹⁶ The lactate ester **1** could be selectively hydrolysed by stirring with 2 equivalents of K₂CO₃ in 35% H₂O/MeOH at room temperature for 24 hrs to give, after acidification, the acid **2** in 91% yield.¹⁶



The potassium salt **3** was produced, when needed, by dissolving the acid **2** in the solvent of choice and then treating it with exactly one equivalent of powdered KOH.

Irradiation of oxygen free solutions of (S)-**1** with a low pressure mercury lamp in a variety of solvents gave a quantitative conversion of **1** to the mixture of diastereomers **4a** and **4b**.



Although the two isomers could not be fully separated by column chromatography the nmr spectrum of each diastereomer could be completely assigned at 300 MHz.¹⁶ The absolute configurations (and structures) of **4a** and **4b** were established by conversion of an 18:82 mixture of **4a**:**4b** (ratio measured by nmr integration) to methyl (S)-2,4-dimethylpent-3-enoate (64% ee) by treatment with 3% HCl/MeOH at 50°C for 6 hrs. The configuration and optical purity of this latter ester were in turn confirmed by nmr in the presence of Eu(hfc) and by the sign of its rotation.^{8,17,18} To quantify the diastereoselectivity of the deconjugation, 10⁻⁴ M solutions of (S)-**1** were deoxygenated with nitrogen, sealed, and irradiated at 254 nm at 0°C in hexane, methanol, ethanol, 2-propanol, 2-propanol/water and at 20°C in t-butyl alcohol.¹⁹ The irradiated solutions were analysed by gas chromatography-mass spectroscopy.²⁰ It was found that (S)-**1** preferentially produced **4b** (SS) with modest to good de in ethanol, 2-propanol, t-butyl alcohol and hexane,

while in methanol and 2-propanol/water with >40% water, diastereomer 4a (RS) was the major product (see Table 1).

The acid 2 was similarly irradiated in methanol, ethanol, 2-propanol and t-butyl alcohol to give mixtures of the corresponding nonconjugated acids 5a and 5b. Analysis, after conversion of 5 to the ester 4 (diazomethane), showed that the acid 2 preferentially produced the nonconjugated ester 5a (SS) with excellent selectivity in all solvents.

The carboxylate salt 3 was prepared by dissolving 35 mg 2 and 10 mg KOH in 10 mL of water, methanol, ethanol and 2-propanol (0.018 M). These solutions were deoxygenated with argon and irradiated at 254 nm at 30°C. Analysis by nmr was carried out after evaporation, acidification and conversion of the products to ester 4. In all solvents the preferred product was 6a (SS)¹⁹ (see Table 1).

TABLE 1

Compound	Solvent	Temp (°C)	Ratio SS/RS	de (%)
1 ^a	methanol	0	24:76	-52
	ethanol	0	65:35	30
	2-propanol	0	79:21	58
	t-butyl alcohol	20	84:16	68
	hexane	0	73:27	46
	20% 2-propanol in H ₂ O	0	35:65	-30
	40% 2-propanol in H ₂ O	0	44:56	-12
	60% 2-propanol in H ₂ O	0	48:52	4
	80% 2-propanol in H ₂ O	0	53:47	6
2 ^a	methanol	0	71:29	42
	ethanol	0	91:9	82
	2-propanol	0	92:8	84
	t-butyl alcohol	20	93:7	86
3 ^b	water	30	80:20	60
	methanol	30	80:20	60
	ethanol	30	80:20	60
	2-propanol	30	80:20	60

a) Product analysis by GC-MS +/-3%

b) Product analysis by nmr +/-10%

As indicated in Table 1, the methyl (S)-lactyl chiral auxiliary induces the S configuration at the newly produced chiral center for all three compounds, except for compound 1 in methanol and 2-propanol/water mixtures. Models indicate that it is sterically easier for the carboxylate group in the S auxiliary to approach the *re* face of the α carbon of the dienol which would produce S induction if the carboxylate were directing protonation. The exact mechanism as well as the reasons for the unusual solvent induced reversal of induction is under investigation.²¹

ACKNOWLEDGMENTS

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REFERENCES and NOTES

1. Henin, F.; Mortezaei, R.; Muzart, J.; Pete, J-P. *Tetrahedron Lett.*, **1985**, 26, 4945.
2. Mortezaei, R.; Henin, H.; Muzart, J.; Pete, J-P. *Tetrahedron Lett.*, **1985**, 26, 6079.
3. Mortezaei, R.; Piva, O.; Henin, F.; Muzart, J.; Pete, J-P. *Tetrahedron Lett.*, **1986**, 27, 2997.
4. Piva, O.; Henin, F.; Muzart, J.; Pete, J-P. *Tetrahedron Lett.*, **1986**, 27, 3001.
5. Pete, J-P.; Henin, H.; Mortezaei, R.; Muzart, J.; Piva, O. *Pure and Appl. Chem.*, **1986**, 58, 1257.
6. Piva, O.; Henin, F.; Muzart, J.; Pete, J-P. *Tetrahedron Lett.*, **1987**, 28, 2845.
7. Mortezaei, R.; Awandi, D.; Henin, F.; Muzart, J.; Pete, J-P. *J. Am. Chem. Soc.*, **1988**, 110, 4824.
8. Henin, F.; Mortezaei, R.; Muzart, J.; Pete, J-P.; Piva, O. *Tetrahedron*, **1989**, 45, 6171.
9. Piva, O.; Pete, J-P. *Tetrahedron Lett.*, **1990**, 31, 5157.
10. Piva, O.; Mortezaei, R.; Henin, F.; Muzart, J.; Pete, J-P. *J. Am. Chem. Soc.*, **1990**, 112, 9263.
11. Awandi, D.; Henin, F.; Muzart, J.; Pete, J-P. *Tetrahedron: Asymmetry*, **1991**, 2, 1101.
12. Helmchen, G.; Karge, R.; Weetman, J. In *Modern Synthetic Methods Vol 4*; Scheffold, R.; Ed.; Springer-Verlag, New York, 1986, p. 261.
13. Hartmann, H.; Hady, A. F. A.; Sartor, K.; Weetman, J.; Helmchen, G. *Angew. Chem. Int. Ed. Engl.*, **1987**, 26, 1143.
14. Charlton, J. L.; Plourde, G. L.; Koh K.; Secco, A. S. *Can. J. Chem.*, **1989**, 67, 574.
15. Charlton, J. L.; Koh, K.; Plourde, G. L. *Tetrahedron Lett.*, **1989**, 30, 3279.
16. Nmr spectra, 300 MHz in CDCl₃ (ref TMS): 1-Z 0.997 (6H, d, J=6.61), 1.527 (3H, d, J=7.07), 1.913 (3H, s), 1.918 (3H, s), 3.255 (1H, m), 3.756 (3H, s), 5.142 (1H, q, J=7.07), 5.774 (1H, dq, J=1.37, 9.74); 1-E 1.034 (3H, d, J=6.65), 1.039 (3H, d, J=6.65), 1.529 (3H, d, J=7.06), 1.863 (3H, s), 1.868 (3H, s), 2.658 (1H, m), 3.752 (3H, s), 5.119 (1H, q, J=6.98), 6.665 (1H, dq, J=1.37, 9.68); 2-Z 0.999 (6H, d, 6.62), 1.580 (3H, d, J=7.09), 1.918 (3H, d, J=1.28), 2.663 (1H, m), 5.160 (1H, q, J=7.10), 5.800 (1H, dd, J=9.85, 1.35); 2-E 1.043 (6H, d, J=6.60), 1.580 (3H, d, 7.09), 1.872 (3H, d, J=1.25), 3.256 (1H, m), 5.15 (1H, q, J=7.15), 6.677 (1H, dd, J=1.37, 9.72); 4a 1.241 (3H, d, J=7.03), 1.485 (3H, d, 7.13), 1.677 (3H, d, J=1.40), 1.729 (3H, d, J=1.54), 3.387 (1H, dq, J= 6.95, 8.99), 3.729 (3H, s), 5.082 (1H, q, J=7.06), 5.17 (1H,m); 4b 1.242 (3H, d, J=7.04), 1.475 (3H, d, J=7.0), 1.674 (3H, d, J=1.50), 1.723 (3H, d, J=1.59), 3.402 (1H, dq, J=6.97, 9.16), 3.738 (3H, s), 5.071 (1H, q, J=7.06), 5.17 (1H, m).
17. Mortezaei, R. *Photodéconjugaison Asymétrique*, Université de Reims-Champagne-Ardenne, 1987.
18. Methyl (S)-2,4-dimethylpent-3-enoate, 64% ee, gave $[\alpha]_D^{25} = +81.5$ (c 0.75, ether), a value higher than that previously reported.⁸
19. t-Butyl alcohol solutions were supercooled to 20°C and would remain liquid for the 10 minute irradiation period.
20. Determination of the ratios of 4a:4b were made by both nmr in benzene-D₆ (300 or 80 MHz) and/or capillary gas chromatography-mass spectrometry (Varian 3400, Finnegan MAT 800).
21. There are also other chiral auxiliaries presently under investigation which show equally high asymmetric induction. Pete, J-P.; Piva, O. *Tetrahedron: Asymmetry*, **1992**, 3, accepted for publication.

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