Asymmetric Reduction of α-Ketoesters with Hantzsch Esters (Dialkoxycarbonyldihydropyridines)

By KAZUYOSHI NISHIYAMA, NAOMICHI BABA, JUN'ICHI ODA, and YUZO INOUYE*
(Institute for Chemical Research, Kyoto University, Uji, Kyoto, Japan)

Summary Single and double asymmetric inductions were achieved by the reduction of pyruvates and benzoylformates with 2,6-dimethyl-3,5-dialkoxycarbonyl-1,4-dihydropyridine in the presence of a mono-ionised zinc species; differentiation is made between enantiotopic faces of the substrate carbonyl by diastereotopic hydrogen, and between diastereotopic faces by equivalent and diastereotopic hydrogen.

ASYMMETRIC reduction of carbonyl compounds by the use of dihydropyridine derivatives is of particular interest from the viewpoint of models of the NAD(P)H reaction as well as for their synthetic utility.

Recently, we found [1] that the direct transfer of hydrogen from the Hantzsch ester (IIa) to α-ketoesters was greatly accelerated by the mono-ionised zinc species formed in the Reformatsky reaction, and that the reduction yield was considerably improved by the addition of *p*-t-butylcathecol (III).

We now describe the single and double asymmetric inductions obtained by combining achiral or chiral α-ketoesters (Ia—d) with achiral or chiral Hantzsch esters (IIa—b) to give the corresponding enantiomeric or diastereomeric hydroxy-esters (IVa—d) with asymmetric bias ranging over 8—78%.

The following procedure to give (—)-methyl mandelate

TABLE. Asymmetric reductions of pyruvates and benzoylformates with Hantzsch esters.

Run	Substrate	Hantzsch ester	Additive	% Yield	Configuration of hydroxy-acid	% Asymmetric yield
1	(Ia)	(IIb)	—	18	*R*	16[a]
2	(Ia)	(IIb)	(III)	35	*R*	8[a]
3	(Ic)	(IIb)	—	50	*R*	17[b]
4	(Ic)	(IIb)	(III)	82	*R*	21[b]
5	(Ib)	(IIa)	—	19	*R*	47
6	(Ib)	(IIa)	(III)	40	*R*	35
7	(Id)	(IIa)	—	54	*R*	17
8	(Id)	(IIa)	(III)	60	*R*	15
9	(Ib)	(IIb)	—	18	*R*	78
10	(Ib)	(IIb)	(III)	41	*R*	70
11	(Id)	(IIb)	—	26	*R*	77
12	(Id)	(IIb)	(III)	37	*R*	70

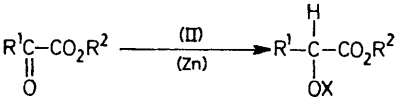
[a] Based on the reported maximum rotation[6] of methyl *O*-acetyl-lactate: $[\alpha]_D^{9.2}$ +57·20° (nitrobenzene). [b] Based on the reported maximum rotation[2] of methyl mandelate: $[\alpha]_D^{18}$ +173° (benzene).

(run 3; Table) is typical. Methyl bromoacetate (184 mg), benzophenone (215 mg), and zinc dust (76 mg), in dry benzene (20 ml) were refluxed for 1·5 h. To the Reformatsky mixture thus formed, the dihydropyridine† (IIb), m.p. 159—161 °C, $[\alpha]_D^{30.5}$ −94·0° (420 mg), and methyl benzoylformate (Ic) (128 mg) were added at room temperature, and the mixture was kept in the dark at room temperature for 4·5 h. After the usual work-up, the reduction product, methyl mandelate {(IVc) (64 mg; 50%), $[\alpha]_D^{26}$ −30·44°, optical yield 17% based on the reported maximum rotation[2] of −173° of methyl *R*-mandelate[3]} was isolated pure by silica gel column and then gas–liquid chromatography. 2,6-Dimethyl-3,5-dimenthoxycarbonylpyridine, $[\alpha]_D^{26}$ −96·6° was recovered (380 mg, 90%) from the silica gel column.

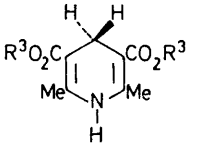
In runs 5—12 where mixtures of diastereomeric (−)-menthyl hydroxy-esters resulted from reduction, the asymmetric yield and the absolute configuration of the predominant product were determined by g.l.c. comparison with authentic samples of (−)-menthyl (*R*)- and (*S*)-lactates, and (*R*)- and (*S*)- mandelates.[4]

The Table shows that the predominant hydroxy-esters possessed the *R*-configuration at the newly created chiral carbinol centre where (−)-(3*R*)-menthol was used as the chirality-inducing centre.

The addition of (III) did improve the reduction yields in the present asymmetric systems too, but did not affect the stereochemistry. The asymmetric yields (70—78%) found for double inductions (runs 9—12) were much higher than those for individual inductions (runs 1—8), which clearly shows that the chirality-inducing centres in both substrates (Ib), (Id), and the Hantzsch ester (IIb) acted together to enhance the steric effects in the same direction. It is noteworthy that the diastereotopic hydrogen atoms in (IIb) discriminated between the enantiotopic faces of methyl pyruvate and benzoylformate (runs 1—4), leading to asymmetric syntheses of lactate and mandelate in lower optical yields (8—21%). This fact clearly shows that the present asymmetric reductions proceeded through diastereomeric transition-state ternary complexes: α-keto-ester – – – – – –Zn – – Hantzsch ester. The important role zinc plays in the present systems may be understood in



a; $R^1 = R^2 = Me$, (X = Ac)
b; $R^1 = Me$, R^2 = (-)-menthyl, (X = H)
c; $R^1 = Ph$, $R^2 = Me$, (X = H)
d; $R^1 = Ph$, R^2 = (-)-menthyl, (X = H)



(III)
a; $R^3 = Et$
b; R^3 = (-)-menthyl

terms of a proposal [5] for the function of magnesium ions in a similar NAD(P)H model reaction; it is assumed that the metal ions bind closely the substrate carbonyl and the dihydropyridine derivatives and stabilise the transition state by chelation, as would probably be the case with the metal-dependent alcohol dehydrogenase in biological systems.

(*Received*, 10*th November* 1975; *Com.* 1257.)

† All the compounds reported herein gave i.r., u.v., and n.m.r. spectra consistent with the assigned structures and satisfactory elementary analyses.

[1] K. Nishiyama, N. Baba, J. Oda, and Y. Inouye, *Chem. Letters*, in the press.
[2] P. Walker, *Chem. Ber.*, 1905, **38**, 400.
[3] P. Pratesi, A. La Manna, A. Campiglio, and V. Ghislandi, *J. Chem. Soc.*, 1958, 2069; 1959, 4062.
[4] A. McKenzie, *J. Chem. Soc.*, 1904, **85**, 1249; A. McKenzie and H. B. Thompson, *ibid.*, 1905, **87**, 1004.
[5] Y. Ohnishi, M. Kagami, and A. Ohno, *J. Amer. Chem. Soc.*, 1975, **97**, 4766.
[6] T. S. Patterson and W. C. Forsyth, *J. Chem. Soc.*, 1913, **103**, 2263.