Stereoselective Homogeneous Hydrogenation of 3-Substituted Itaconate Esters

John M. Brown and Alun P. James

The Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY, U.K.

Hydrogenation of the title compounds occurs with high diastereoselectivity when catalysed by cationic rhodium compounds, and with efficient kinetic resolution when the catalyst is chiral.

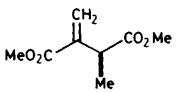
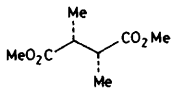
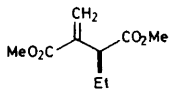
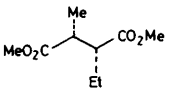
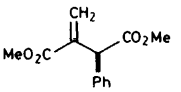
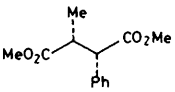
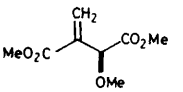
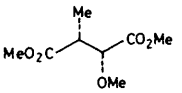
Examples of efficient kinetic resolution in organic synthesis by purely chemical means are rare[1—3] but include the catalytic homogeneous hydrogenation of α-(hydroxyalkyl)acrylate esters with optically active rhodium biphosphine complexes.[3] We report that in the analogous case of 3-substituted itaconate esters, the ester group at the chiral site exerts a powerful directing effect leading to high diastereoselectivity in the reduced product and kinetic resolution of the starting material with enantiomer discrimination up to 16 : 1.

Ester (**3a**) was prepared from compound (**1**) according to the literature procedure[4] or alternatively by the reaction of the allylic bromide (**2**)[5] with $LiCuMe_2$. It was readily hydrogenated in MeOH using catalyst (**5**) (Table 1) giving essentially pure (*R**,*R**)-dimethyl 2,3-dimethylsuccinate (**4a**). Since itaconate esters are hydrogenated in good optical yield when the (*RR*)-dipamp-derived catalyst (**6**) is employed,[6] this encouraged an attempt at kinetic resolution of compound (**3a**). It was hydrogenated to 65% completion with the optically active catalyst, starting material and product were separated by preparative g.l.c. (15 ft OV225; 160 °C), and the recovered (**3a**) was hydrogenated with catalyst (**5**). Hydrolysis gave (*S,S*)-2,3-dimethylsuccinic acid, $[\alpha]_D^{20}$ −8.3° (*c* 1, H_2O) {lit.[7] $[\alpha]_D^{20}$ −8.0° (c → 0, H_2O)}. Similarly, hydrolysis of product (**4a**) from the hydrogenation gave (*R,R*)-dimethylsuccinic acid of 53% optical purity (predicted 54% at 65% reduction).

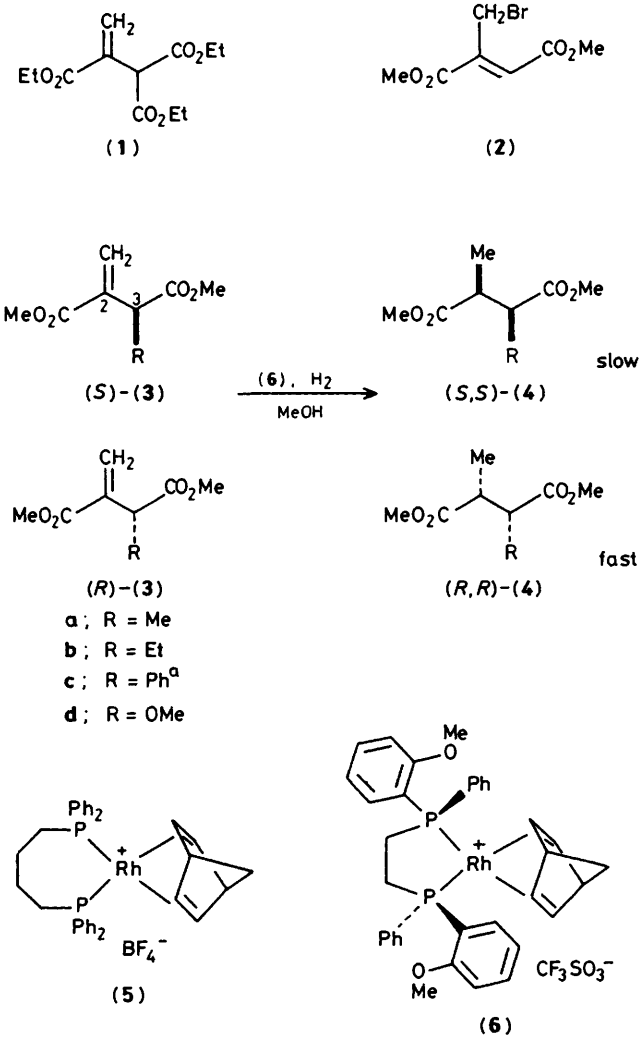
The ethyl analogue (**3b**) was prepared by alkylation of compound (**1**), and the phenyl derivative (**3c**) by the cuprate route; in the latter case comparable quantities of S_N2 and S_N2' products were formed[8] and these were separated by flash chromatography. All hydrogenations with catalyst (**5**) occurred with high diastereoselectivity, irrespective of solvent (Table 1). Reductions were carried out to 50—60% completion with catalyst (**6**), and the optical purity of the starting material was determined by ^1H n.m.r. spectroscopy using tris(dicampholylmethanato)europium.[9] (The extent of kinetic resolution was uniformly high, up to 16 : 1, with preference for the *R*-configuration at the new asymmetric centre.)

Thus the direction and magnitude of stereoselection induced by the CO_2Me group in the hydrogenation of (**3**) is comparable to that induced by OH in hydrogenation of α-(hydroxyalkyl)acrylates.[3] It is also known that OMe is a good directing group, although inferior to OH in this regard.[10] It was found that the methoxyitaconate (**3d**) was readily prepared from the bromide (**2**) in a clean S_N2' reaction (KOH, MeOH, 20 °C), affording the opportunity to compare the directing ability of OMe and CO_2Me. Hydrogenation proceeded smoothly with the catalyst (**5**) giving >98% (2*R*,3*R*)-reduced product (**4d**),[11] resulting from participation

Table 1.

Reactant (3)[a,g]	Product[b]	Catalyst θ/°C[c]	% Reaction[d]	Enantiomer excess,[e] %	k_R/k_S	(*R**,*R**) : (*R**,*S**)
		(**5**); 20	C[f]	—	—	250 : 1
		(**6**); 20	65	(100)	≥10	
		(**5**); 20	C	—	—	250 : 1
		(**6**); 0	64.6	≥96	≥12	
		(**6**); 0	52.7	81	15.8	
		(**6**); 20	56.6	81	10.3	
		(**6**); 50	55.3	64	5.8	
		(**5**); 20	C	—	—	(1 : 200)
		(**6**); 20	32.0	35	9.5	
		(**6**); 20	62.3	82	7.2	
		(**5**); 20	C	—	—	98 : 2
		(**6**); 20	62.2	93	11.5	

[a] The enantiomer enriched by kinetic resolution is drawn. [b] The product formed faster by asymmetric hydrogenation is drawn. [c] All reactions conducted in MeOH. Comparable diastereoselectivity was observed in tetrahydrofuran or CH_2Cl_2 but rates were slower. [d] Conditions for g.c. analysis: (**3a**), (**3b**), (**3d**), 5 ft OV225, 120 °C; (**3c**) 50 ft OV1, 120—250 °C 5 °C min^{-1}. [e] Determined for recovered starting material as described in the text. Shift reagent experiments were carried out in C_7D_8, monitoring the ester OCH_3 resonances and adding reagent until baseline resolution of (*R*) and (*S*)-enantiomers was attained. For (**3d**) Eu(hfc)$_3$ was employed. [f] C signifies complete reaction. [g] Rotations for optically pure reactants: (*S*)-(**3a**) $[\alpha]_D^{20}$ +16.4 (*c* 2, Et_2O); (*S*)-(**3b**) $[\alpha]_D^{20}$ +40.7 (*c* 0.73, Et_2O) (extrapolated from 81% enantiomeric excess); (*S*)-(**3d**) $[\alpha]_D^{20}$ −57.1 (*c* 1, Et_2O).



[a] (*S*,*R*)-Product from (*S*)-(**3**), (*R*,*S*)-product from (*R*)-(**3**).

of CO_2Me. Kinetic resolution using catalyst (**6**) was as successful as earlier cases cited.†

In asymmetric hydrogenation of dehydroamino acids, optical yields increase with increasing temperature.[12] By inference from the kinetic resolution experiments, the reverse is true in the present case since the rate ratio for hydrogenation of the enantiomers of (**3b**), k_R/k_S, is highest at the lowest temperature, and diminished at 50 °C.

Rhodium and iridium enamide complexes have an essentially planar chelate ring incorporating N–C=O–M and the α-carbon of the alkene.[13] If a similar model is employed in the present case replacement of trigonal-NH by tetrahedral-CHR results in a non-planar chelate. It then becomes clear why the precursor of (*R*,**R**) (**4**) is preferred over the precursor of (*R*,**S**)-(**4**), since the substituent of C-3 is antiperiplanar to the co-ordinated double bond and interacts unfavourably with the α-ester (Figure 1). Future work will underpin the mechanistic details more securely.

† An initial experiment with the Rh-complex of commercially available *R*-BINAP gave slightly inferior discrimination.

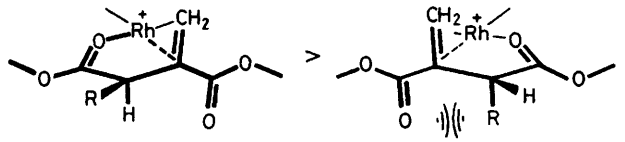


Figure 1. Diastereoisomeric chelates formed by co-ordination of (**3**) to rhodium.

In summary, the hydrogenation of 3-substituted itaconate esters provides a simple route to a range of stereoisomerically pure 2,3-disubstituted succinates, often not readily accessible by other means. The unsaturated precursor may itself be kinetically resolved in the catalytic reaction and isolation followed by further hydrogenation using complex (**5**) leads to the (*S*,*S*) isomer in a state of high optical purity.

We thank the S.E.R.C. for postdoctoral support (A. P. J.) and Johnson-Matthey for loans of rhodium salts. Mr. Peter Maddox was very helpful with chiral shift n.m.r. experiments, and Mr. Phillip Evans kindly supplied a sample of catalyst (**6**).

Received, 18th July 1986; Com. 1008

References

1 S. Miyano, L. D-L. Lu, S. M. Viti, and K. B. Sharpless, *J. Org. Chem.*, 1985, **50**, 4350, and references therein.
2 A. Mori and H. Yamamoto, *J. Org. Chem.*, 1985, **50**, 5446.
3 J. M. Brown and I. Cutting, *J. Chem. Soc., Chem. Commun.*, 1985, 578; *cf.* J. M. Brown and S. A. Hall, *J. Organomet. Chem.*, 1985, **285**, 333; A. G. Shultz and P. J. McCloskey, *J. Org. Chem.*, 1985, **50**, 5905, for prior examples of carboxy participation in directed hydrogenation.
4 P. Dowd, M. Shapiro, and J. Kang, *Tetrahedron*, 1984, **40**, 3069.
5 S. C. Welch and J. M. Gruber, *J. Org. Chem.*, 1982, **47**, 385; J. Nokami, T. Tamaoka, H. Ogawa, and S. Wakabayashi, *Chem. Lett.*, 1986, 541.
6 W. C. Christopfel and B. D. Vineyard, *J. Am. Chem. Soc.*, 1979, **101**, 4406.
7 E. Berner and R. Leonardsen, *Liebigs. Ann. Chem.*, 1939, **538**, 1; H. Brockmann and D. Müller-Enoch, *Chem. Ber.*, 1971, **104**, 3704.
8 *Cf.* T. Ibuka, T. Aoyagi, and F. Yoneda, *J. Chem. Soc., Chem. Commun.*, 1985, 1452.
9 J. D. McCreary, D. W. Lewis, D. L. Wernick, and G. M. Whitesides, *J. Am. Chem. Soc.*, 1974, **96**, 1038.
10 J. M. Brown and S. A. Hall, *Tetrahedron*, 1985, **41**, 4639.
11 W. Trowitzsch, G. Höfle, and W. S. Sheldrick, *Tetrahedron Lett.*, 1981, **22**, 3829.
12 R. Selke and H. Pracejus, *J. Mol. Catal.*, 1986, **38**, 213, and references therein.
13 A. S. C. Chan, J. J. Pluth, and J. Halpern, *Inorg. Chim. Acta.*, 1979, **37**, L477; A. S. C. Chan and J. Halpern, *J. Am. Chem. Soc.*, 1980, **102**, 5952; N. W. Alcock, J. M. Brown, A. E. Derome, and A. R. Lucy, *J. Chem. Soc., Chem. Commun.*, 1985, 575; N. W. Alcock, J. M. Brown, and P. J. Maddox, *ibid.*, 1986, 1532.