Catalytic Asymmetric Induction from Prochiral Cyclic Acid Anhydrides using Cinchona Alkaloids

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Asymmetric ring-opening of prochiral cyclic acid anhydrides (**1**) with methanol was effected by a catalytic amount of cinchona alkaloids (**2**) with an enantiomeric excess of up to 70% and the product was converted into optically active lactones.

Enzymes such as dehydrogenases[1] or hydrolases[2] have been widely used in asymmetric induction reactions from symmetrical molecules having enantiotopic groups. We recently reported a non-enzymic procedure for differentiation between enantiotopic carbonyl groups of cyclic acid anhydrides using axially dissymmetric binaphthyldiamines.[3] These procedures, however, required stoicheiometric quantities of chiral amines. There is only one report of asymmetric induction with moderate selectivity from prochiral cyclic acid anhydrides involving hydrogenation using a chiral ruthenium catalyst.[4]

In this communication we describe the catalytic enantioselective ring-opening of cyclic acid anhydrides (**1a,b**) by methanol in the presence of a catalytic amount of cinchona alkaloids (**2a—d**). This reaction, followed by selective reduction of the initially formed half esters, gave optically active *cis*-2,4-dimethyl-δ-valerolactone and mevalonic lactone.

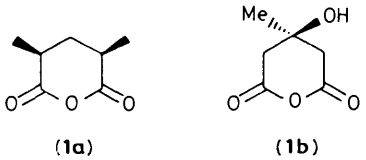
The acid anhydrides (**1a,b**) were treated with methanol (4—20 mol equiv.) in the presence of (**2a—d**) (0.1 mol equiv.) in dry toluene or dry diethyl ether at room temperature to give the optically active monoesters (**3a,b**)† quantitatively. In order to determine the enantiomeric excess (e.e.) of the product, (**3a,b**) were converted into a mixture of diastereoisomeric amide esters (**4a,b**) with (*R*)-1-(1-naphthyl)ethylamine and thionyl chloride (Scheme 1). The diastereoisomer ratios (d.r.) in the products (**4a,b**) and the

† The spontaneous methanolysis of (**1a**) was much slower than that catalysed by (**2a**); pseudo-first-order reaction rates ($k_{obs.}$) for (**2a**)-catalysed and spontaneous reactions were 2.3×10^{-3} and 3.7×10^{-5} min^{-1}, respectively [(**1a**), 0.2 mmol; (**2a**), 0.02 mmol; methanol, 2.0 mmol; 5 ml of dry toluene; room temperature; the reaction was monitored by g.l.c. (5% XE-60, 155 °C)].

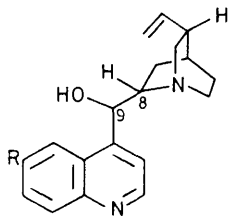
Table 1. Ring opening of acid anhydrides (**1a**,**b**) with methanol catalysed by (**2a**,**b**).[a]

Substrate	Catalyst[b]	Solvent	MeOH/mmol	Reaction period/days	D.r. of (**4**)	Selectivity[e]
(**1a**)	(**2a**)	toluene	0.4	4	15:85[c]	*pro-S*
(**1a**)	(**2b**)	toluene	0.4	4	82:18[c]	*pro-R*
(**1a**)	(**2c**)	toluene	0.4	4	80:20[c]	*pro-R*
(**1a**)	(**2d**)	toluene	0.4	4	16:84[c]	*pro-S*
(**1b**)	(**2a**)	Et_2O	2.0	1	36:64[d]	*pro-R*
(**1b**)	(**2b**)	Et_2O	2.0	1	62:38[d]	*pro-S*
(**1b**)	(**2c**)	Et_2O	2.0	1	74:26[d]	*pro-S*
(**1b**)	(**2d**)	Et_2O	2.0	1	26:74[d]	*pro-R*

[a] Acid anhydride (0.1 mmol), solvent (5 ml), room temperature, quantitative. [b] 0.01 mmol (0.1 equiv.). [c] The d.r. is given in the order of elution by h.p.l.c.; hexane:propan-2-ol:triethylamine = 15:1:0.16, retention volume, R_v = 10.2 and 12.6 ml, separating factor α = 1.38. [d] The d.r. was determined by 400 MHz ^{1}H n.m.r. spectroscopy using the diastereoisomeric proton resonance of CO_2Me; the first number corresponds to the lower frequency resonance. [e] Preferentially attacked carbonyl group.



(**1a**) (**1b**)



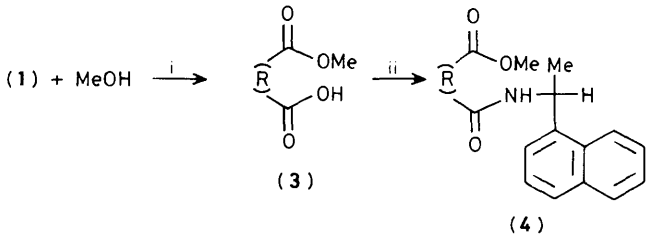
(**2**)

Configuration

	C-8	C-9	R
(**2a**)	*R*	*S*	H
(**2b**)	*S*	*R*	H
(**2c**)	*S*	*R*	OMe
(**2d**)	*R*	*S*	OMe

e.e.s of (**3a**,**b**) were then determined by h.p.l.c. or ^{1}H n.m.r. spectroscopy (Table 1).‡ The absolute configurations of the products were assigned by the specific rotation of the corresponding lactones (**5**) and (**6**) (*vide infra*).

The largest optical yield (70% e.e.) was observed when cinchonine (**2a**) was employed as a catalyst in the reaction of the anhydride (**1a**). Cinchonine (**2a**) or quinidine (**2d**) was shown to promote preferential attack of methanol on the *pro-S* and *pro-R* carbonyl groups of (**1a**) and (**1b**), respectively, whereas cinchonidine (**2b**) or quinine (**2c**) showed the opposite stereoselectivity for both anhydrides (Table 1). It is worthy of note that the direction of stereoselectivity corresponded to the stereochemistry of C-9 and C-8 in (**2a**—**d**). Product (**3a**), which was prepared using (**2a**) as catalyst, was reduced with lithium borohydride[5]§ to afford (−)-(2*R*,4*S*)-*cis*-2,4-dimethyl-δ-valerolactone (**5**) with $[\alpha]_D^{25}$ −27.0° (*c* 1.94, $CHCl_3$) in an overall yield of 56% from (**1a**). The monoester (**3a**) was also reduced by BH_3–Me_2S[6] to give the counterpart, (+)-(2*S*,4*R*)-(**5**), with $[\alpha]_D^{25}$ +28.7° (*c* 1.97, $CHCl_3$) in an overall yield of 48% from (**1a**). Based on a maximum rotation of $[\alpha]_D^{25}$ −41.1°,[2a] the optical purities of (−)-(**5**) and (+)-(**5**) were calculated to be 66 and 70%, respectively. These values agreed with the e.e. of (**3a**) (66%) which was estimated from the d.r. of the corresponding amide ester (**4a**). The optically active (−)-(*R*)-mevalonic lactone (**6**) was also synthesized by $LiBH_4$ reduction of (**3b**) which was derived from (**1b**) and (**2c**), in an overall yield of 74%. The optical purity of (**6**) {$[\alpha]_D^{25}$ −7.2° (*c* 6.89, EtOH)} was determined to be 31%¶ based on a maximum rotation of $[\alpha]_D^{20}$ −23.0°.[7] The e.e. of (**6**) was somewhat lower than that for (**3b**) (40% e.e.). This result is due to partial racemization of (**6**) during isolation.[3]



(**3**) (**4**)

a; R = –CH(Me)CH_2CH(Me)–
b; R = –CH_2C(Me)(OH)CH_2–

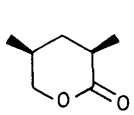
Scheme 1. *Reagents and conditions:* i, (**2a**—**d**) (0.1 equiv.), dry toluene or dry diethyl ether (5 ml), room temp., 1—4 days; ii, (*R*)-1-(1-naphthyl)ethylamine (1.1 equiv.), $SOCl_2$ (1.2 equiv.), Et_3N (3.3 equiv.), dry toluene, 0 °C, 1 h.

To investigate the reaction mechanism, (**1a**) was treated with a large excess of methanol or [$^2H_1$]methanol (20 mol equiv.) in the presence of (**2a**) (0.1 mol equiv.). The pseudo-first-order reaction rate constants, $k_{obs.}$(H) and $k_{obs.}$(D), were determined to be 10.5 × 10^{-3} and 4.5 × 10^{-3} min^{-1}, respectively. The deuterium isotope effect [$k_{obs.}$(H)/$k_{obs.}$(D)] was calculated to be 2.3. The reported value of the deuterium isotope effect in base-catalysed hydrolysis of acetic anhydride was *ca.* 3 in which general-base catalysis was established.[8] Thus the present reaction is thought to proceed by a general-base catalysis mechanism.

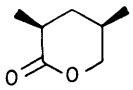
‡ Racemic (**3**) gave a 50:50-diastereoisomeric mixture of (**4**) in the presence (0.1 mol equiv.) or absence of cinchonine using this amidation method. Thus the d.r. of (**4**) correctly reflects the e.e. of (**3**).

§ Lithium borohydride was prepared *in situ* from lithium perchlorate (5 mol equiv.) and sodium borohydride (5 mol equiv.) in dry tetrahydrofuran.

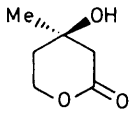
¶ The e.e. of (**6**) was also determined by n.m.r. spectroscopy using a chiral shift reagent, tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III); W. K. Wilson, T. J. Scallen, and C. J. Morrow, *J. Lipid Res.*, 1982, **23**, 645.



(-)-(2*R*,4*S*)-(**5**)



(+)-(2*S*,4*R*)-(**5**)



(-)-(*R*)-(**6**)

Of the two basic moieties in the structure of (**2a**), the quinoline and quinuclidine rings, the latter ring was responsible for the catalytic activity of (**2a**), since quinuclidine catalysed the reaction as effectively as (**2a**), whereas quinoline did not catalyse the reaction [$k_{obs.}$(quinuclidine)/$k_{obs.}$(spontaneous) = 61, $k_{obs.}$(**2a**)/$k_{obs.}$(spont.) = 61, $k_{obs.}$(quinoline)/$k_{obs.}$(spont.) = 1.2]. From these results, it was concluded that the reaction proceeds *via* general-base catalysis by the quinuclidine moiety of (**2**) with the orientation of hydroxy group on C-9 playing an important role in the stereoselection.

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References

1 I. J. Jokovac, H. B. Goodbrand, K. P. Lok, and J. B. Jones, *J. Am. Chem. Soc.*, 1982, **104**, 4659.
2 (a) C.-S. Chen, Y. Fujimoto, and C. J. Sih, *J. Am. Chem. Soc.*, 1981, **103**, 3580; (b) M. Ohno, S. Kobayashi, T. Iimori, Y.-F. Wang, and T. Izawa, *ibid.*, 1981, **103**, 2405; (c) S. Iriuchijima, K. Hasegawa, and G. Tsuchihashi, *Agric. Biol. Chem.*, 1982, **46**, 1907; (d) D. W. Brooks and J. T. Palmer, *Tetrahedron Lett.*, 1983, **24**, 3059.
3 Y. Kawakami, J. Hiratake, Y. Yamamoto, and J. Oda, *J. Chem. Soc., Chem. Commun.*, 1984, 780.
4 K. Osakada, M. Obana, T. Ikariya, M. Saburi, and S. Yoshikawa, *Tetrahedron Lett.*, 1981, **22**, 4297.
5 J. W. Cornforth, R. H. Cornforth, G. Popják, and L. Yengoyan, *J. Biol. Chem.*, 1966, **241**, 3970.
6 C. F. Lane, H. L. Myatt, J. Daniels, and H. B. Hopps, *J. Org. Chem.*, 1974, **39**, 3052.
7 R. H. Cornforth, J. W. Cornforth, and G. Popják, *Tetrahedron*, 1962, **18**, 1351.
8 R. J. E. Talbot, in 'Comprehensive Chemical Kinetics,' ed. C. H. Bamford and C. F. H. Tipper, Elsevier, Amsterdam, 1972, vol. 10, p. 286.