Enantiotopic-group Differentiation. Catalytic Asymmetric Ring-opening of Prochiral Cyclic Acid Anhydrides with Methanol, using Cinchona Alkaloids

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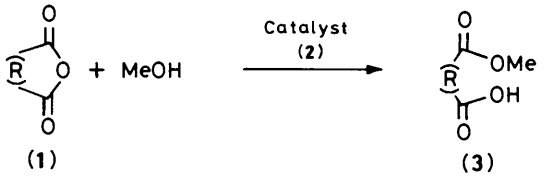
Asymmetric ring-opening of prochiral acid anhydrides (**1**) with methanol has been achieved by a catalytic quantity of cinchona alkaloids (**2**). The product, the optically active half-ester (**3**), has been subjected to functional-group-selective reduction to give the optically active lactones (**5**). The reaction rate of the ring-opening and the extent of selectivity are dependent on the nature of the reaction medium, the polarity of solvent, and substrate concentration. By selecting the reaction conditions, an enantiometric excess of up to 70% has been obtained. The kinetic isotope effect and other mechanistic investigations suggest that the reaction proceeds *via* general-base catalysis by the quinuclidine moiety of the base (**2**), and that the relative configuration of the C-9 hydroxy group with respect to the C-8 quinuclidine amino function determines the selectivity of the reaction.

Asymmetric induction based on the differentiation between enantiotopic groups of prochiral molecules has now been recognised as a new, promising strategy for asymmetric synthesis.[1] This strategy has been attained with high stereoselectivity in enzyme-mediated synthesis of optically active lactones by means of such enzymes as dehydrogenases[2] and hydrolases.[3] Non-enzymic methods have also been reported,[4,1b] but one equivalent (or more) of chiral reagent is required. Catalytic processes, on the other hand, are the most attractive methods for developing economical asymmetric synthesis.[5,6] As regards a catalytic procedure for differentiation between enantiotopic groups, we now report an asymmetric ring-opening of prochiral cyclic acid anhydrides with methanol, catalysed by cinchona alkaloids,[7] and the synthesis of optically active lactones. The base-catalysed addition of methanol to cyclic acid anhydrides (1) afforded ring-opened half-ester (3) (Scheme 1). The ring-



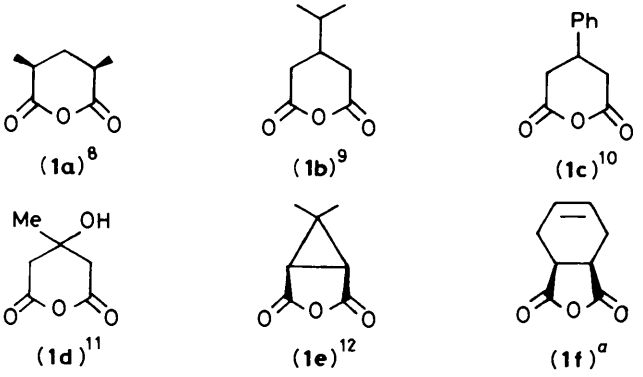
a; R = -CH(Me)CH_2CH(Me)-
b; R = -CH_2CH(Pr^i)CH_2-
c; R = -CH_2CH(Ph)CH_2-
d; R = -CH_2C(OH)(Me)CH_2-
e; R = *cis*-CHCMe$_2$CH-
f; R = *cis*-CHCH$_2$CH=CHCH$_2$CH-

Scheme 1.

opening reaction of cyclic acid anhydrides is suitable for designing an asymmetric induction based on enantiotopic-group differentiation, because only one of the two enantiotopic carbonyl groups is attacked by a nucleophile and the other remains unattacked as an intramolecular leaving group.[4] The relationship between the configuration of the catalysts and the stereoselectivity of the reaction is discussed in addition to their reaction features and mechanistic considerations.

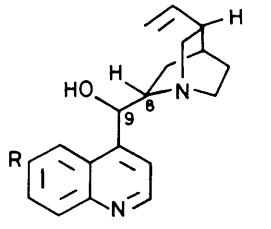
Results and Discussion

The substrates examined are the *meso* or prochiral acid anhydrides (**1a**—**f**) which were prepared according to the literature methods cited below[8-12] [(**1f**) was commercially available].

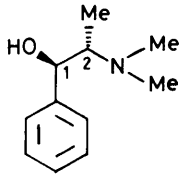


(**1a**)[8] (**1b**)[9] (**1c**)[10]
(**1d**)[11] (**1e**)[12] (**1f**)[a]

[a] Commercially available.



(**2a**—**h**)

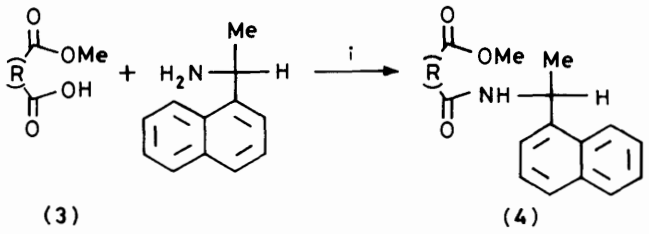


(1*R*,2*S*)-(**2i**)

		config'n C-8	C-9	R
(**2a**)	Cinchonine	*R*	*S*	H
(**2b**)	Cinchonidine	*S*	*R*	H
(**2c**)	Quinine	*S*	*R*	OMe
(**2d**)	Quinidine	*R*	*S*	OMe
(**2e**)	Epicinchonine	*R*	*R*	H
(**2f**)	Epicinchonidine	*S*	*S*	H
(**2g**)	Epiquinine	*S*	*S*	OMe
(**2h**)	Epiquinidine	*R*	*R*	OMe

The catalysts (**2a**—**d**) are naturally occurring cinchona alkaloids. Their diastereoisomers (**2e**—**h**) were prepared by the inversion of C-9 hydroxy group *via* the tosylates of (**2a**—**d**) according to the procedure reported by Suszko and Szelag.[13]† The acid anhydrides (**1a**—**f**) were treated with methanol (4—20 mol equiv.) in the presence of a base (**2a**—**i**) (0.1—0.2 mol

† We failed to obtain the tosylates of bases (**2a**—**d**) by the reported procedure, so we synthesized the tosylates by the modified method (see Experimental section).



(3) (4)

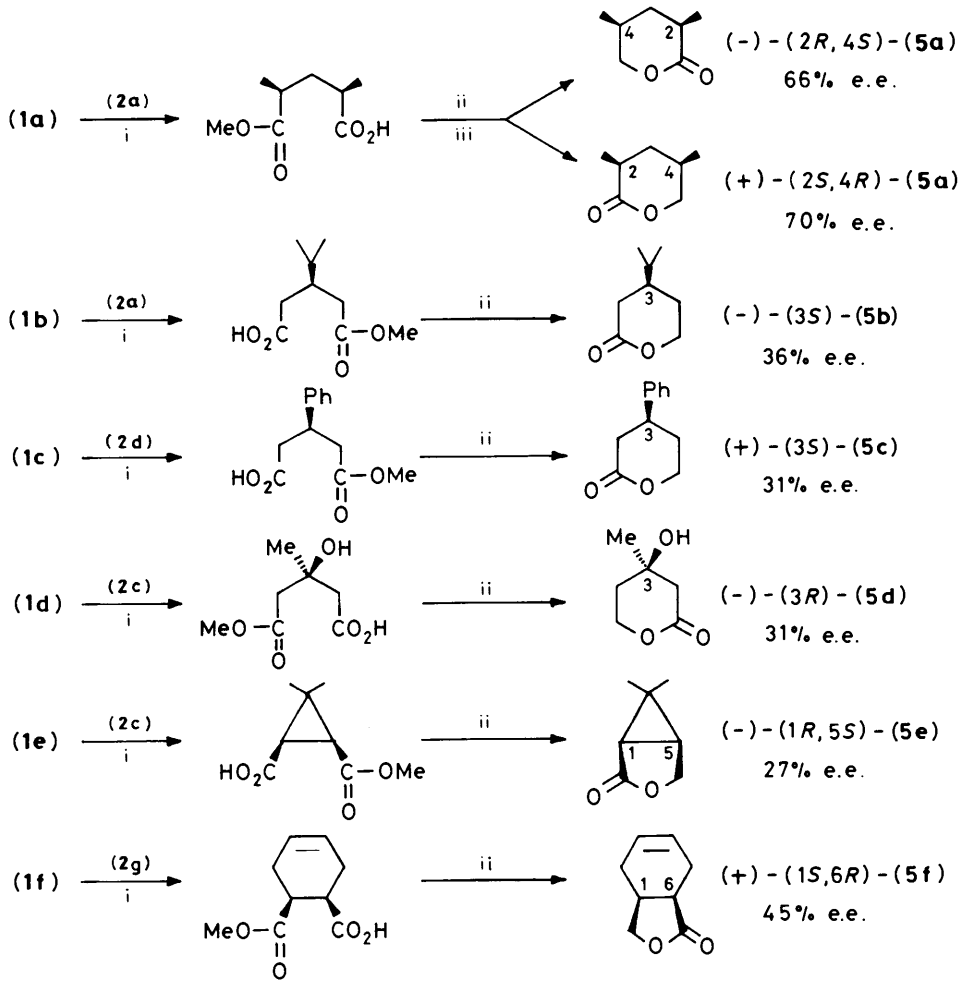
Scheme 2. *Reagents and conditions*: i, $SOCl_2$, NEt_3, dry toluene, 0 °C, 1 h

equiv.) in dry toluene or dry diethyl ether at room temperature to give the chiral half-ester (**3a**—**f**). The consumption of anhydride (**1**) and the formation of mono ester (**3**) were followed by g.l.c. or t.l.c. In a control experiment without catalyst, the product (**3**) could not be detected after 2 days. The enantiomeric excess (e.e.) of each product (**3a**—**f**) was determined by h.p.l.c. or ^1H n.m.r. analyses of the corresponding diastereoisomeric amide-ester (**4a**—**f**) which was derived from mono ester (**3a**—**f**) respectively, without isolation (Scheme 2). Racemic (**3**) prepared from triethylamine-catalysed methanolysis of anhydride (**1**) showed 0—1.5% e.e. by this method. These values did not change when racemic (**3**) was converted into product (**4**) in the presence of the chiral amine (**2a**). Thus the method allows the extent of the asymmetric induction to be determined within an error of ±1.5% e.e. on a <0.1 mmol scale of the substrate (**1**) without isolation. The results are summarised in Table 1. The direction of the stereoselection was fixed by the absolute configuration of the optically active lactones (**5a**—**f**) which were derived from compounds (**3a**—**f**), respectively (*vide infra*). Toluene or diethyl ether was the solvent of our choice in all small-scale reactions because non-polar solvents such as toluene and diethyl ether gave favourable results as to the reactivity and the selectivity of the ring-opening as shown in Table 2. The *erythro* bases (**2a**—**d**) showed high catalytic activity for all the anhydrides examined, especially for the six-membered anhydrides (**1a**—**d**). Under the standard conditions (Table 1, entry 1), the reaction proceeded smoothly and went to completion in a day. By reducing the amount of methanol the reaction rate was diminished and the selectivity was improved up to 70% e.e. (entry 2). One striking feature of the results presented in Table 1 is that the *threo* bases (**2e**—**h**) had practically no activity for (**1a**) and the e.e. of the product was extremely low (entries 6—9). It has been pointed out that the *threo* bases (**2e**—**h**) showed lower asymmetric induction in cyanohydrin formation[14] and the thiol addition to conjugated enones.[5] As to rate-enhancement, this indication also holds for the present reaction. The *threo* bases (**2e**—**h**) were the less effective catalysts for (**1a**—**d**), with slower reaction and lower e.e.s. For the five-membered anhydrides (**1e,f**), however, the *threo* catalysts (**2e**—**h**) exhibited higher asymmetric induction (entries 39—42 and 47—50; 44—60% e.e.) than did the *erythro* catalysts (**2a**—**d**) (entries 35—38 and 43—46; 11—33% e.e.). Another remarkable feature of the reaction is that the stereochemistry of the reaction was controlled by the configurations at C-8 and C-9 in the catalyst. For example, the cinchonine (**2a**)–quinidine (**2d**) series having the C-8(*R*)–C-9(*S*) configuration promoted preferential attack of methanol on the *pro-S* carbonyl group of anhydride (**1a**), and the cinchonidine (**2b**)–quinine (**2c**) series having the C-8(*S*)–C-9(*R*) stereochemistry showed *pro-R* selectivity in almost equally high e.e.s for the same substrate. These configuration biases were applicable not only to the other anhydrides (**1b**—**e**) but also to the reaction catalysed by the *threo* bases (**2e**—**h**) and (1*R*,2*S*)-*N*-methylephedrine (**2i**) which has the stereochemistry corresponding to the C-8(*S*)–C-9(*R*) bases. This type of stereocontrol is also observed in cinchona-alkaloid-catalysed asymmetric induction such as thiol-addition

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

Entry	Substrate	Catalyst	MeOH (mmol)	Time[b] (day)	e.e. (%)	Selectivity[c]
1	(**1a**)	(**2a**)	2.0	1	56	*pro-S*
2	(**1a**)	(**2a**)	0.4	4	70	*pro-S*
3	(**1a**)	(**2b**)	0.4	4	64	*pro-R*
4	(**1a**)	(**2c**)	0.4	4	60	*pro-R*
5	(**1a**)	(**2d**)	0.4	4	67	*pro-S*
6	(**1a**)	(**2e**)	1.0	12 (29%)	5.4	*pro-R*
7	(**1a**)	(**2f**)	1.0	12 (21%)	4.0	*pro-R*
8	(**1a**)	(**2g**)	1.0	12 (4%)	6.2	*pro-R*
9	(**1a**)	(**2h**)	1.0	12 (16%)	1.8	*pro-R*
10	(**1a**)	(**2i**)	2.0	5	8.8	*pro-R*
11	(**1b**)	(**2a**)	1.0	1	23	*pro-R*
12	(**1b**)	(**2b**)	1.0	1	6.3	*pro-S*
13	(**1b**)	(**2c**)	1.0	1	6.8	*pro-S*
14	(**1b**)	(**2d**)	1.0	1	19	*pro-R*
15	(**1b**)	(**2e**)	1.0	12 (89%)	13	*pro-R*
16	(**1b**)	(**2f**)	1.0	12 (90%)	5.4	*pro-S*
17	(**1b**)	(**2g**)	1.0	12 (88%)	5.3	*pro-S*
18	(**1b**)	(**2h**)	1.0	12 (90%)	11	*pro-R*
19	(**1c**)	(**2a**)	1.0	1	33	*pro-R*
20	(**1c**)	(**2b**)	1.0	1	7.8	*pro-S*
21	(**1c**)	(**2c**)	1.0	1	7.4	*pro-S*
22	(**1c**)	(**2d**)	1.0	1	48	*pro-R*
23	(**1c**)	(**2e**)	1.0	12	10	*pro-R*
24	(**1c**)	(**2f**)	1.0	12	2.2	*pro-S*
25	(**1c**)	(**2g**)	1.0	12	5.1	*pro-S*
26	(**1c**)	(**2h**)	1.0	12	10	*pro-R*
27	(**1d**)[d]	(**2a**)	2.0	1	28[e]	*pro-R*
28	(**1d**)[d]	(**2b**)	2.0	1	24[e]	*pro-S*
29	(**1d**)[d]	(**2c**)	2.0	1	48[e]	*pro-S*
30	(**1d**)[d]	(**2d**)	2.0	1	48[e]	*pro-R*
31	(**1d**)[d]	(**2e**)	1.0	3	3.1[e]	*pro-S*
32	(**1d**)[d]	(**2f**)	1.0	3	0.2[e]	
33	(**1d**)[d]	(**2g**)	1.0	3	3.7[e]	*pro-R*
34	(**1d**)[d]	(**2h**)	1.0	3	2.2[e]	*pro-S*
35	(**1e**)	(**2a**)	1.0	7	16	*pro-R*
36	(**1e**)	(**2b**)	1.0	3	11	*pro-S*
37	(**1e**)	(**2c**)	1.0	3	33	*pro-S*
38	(**1e**)	(**2d**)	1.0	4	32	*pro-R*
39	(**1e**)	(**2e**)	1.0	9	60	*pro-S*
40	(**1e**)	(**2f**)	1.0	9	47	*pro-R*
41	(**1e**)	(**2g**)	1.0	9	52	*pro-R*
42	(**1e**)	(**2h**)	1.0	9	56	*pro-S*
43	(**1f**)	(**2a**)	1.0	7[f]	14	*pro-R*
44	(**1f**)	(**2b**)	1.0	7[f]	18	*pro-S*
45	(**1f**)	(**2c**)	1.0	7[f]	21	*pro-R*
46	(**1f**)	(**2d**)	1.0	7[f]	30	*pro-S*
47	(**1f**)	(**2e**)	1.0	7[f]	51	*pro-R*
48	(**1f**)	(**2f**)	1.0	7[f]	44	*pro-S*
49	(**1f**)	(**2g**)	1.0	7[f]	47	*pro-S*
50	(**1f**)	(**2h**)	1.0	7[f]	52	*pro-R*

[a] The ring-opening was carried out under the following conditions: (**1**) (0.1 mmol), MeOH (0.4—2.0 mmol), (**2**) (0.01 mmol), dry toluene (5 ml) unless otherwise specified, room temperature. [b] The conversion was monitored by g.l.c.: 5% XE-60; 130–190 °C for (**1a**, **b**, **e**, and **f**); 2% DC-QF-1; 140—170 °C for (**1c** and **d**). The chemical yield was quantiative or >95% unless otherwise specified. Chemical conversion is shown in parentheses if needed. [c] Indicates the preferentially attacked carbonyl group. [d] Solvent: dry diethyl ether (5 ml). [e] Determined by 400 MHz ^1H n.m.r. spectroscopy, by comparison with the diastereoisomeric proton resonance of CO_2Me of the corresponding amide-ester (**4d**). [f] The reactant (**1f**) was consumed after 7 days (t.l.c.; $CHCl_3$–EtOH (9:1)].



Scheme 3. *Reagents and conditions*: i, MeOH (10 mol equiv.), dry toluene, room temperature, quantitative yield; ii, $LiClO_4$, $NaBH_4$, dry THF; iii, BH_3–Me_2S, dry THF

to α,β-unsaturated carbonyl compounds[5] and nitro olefins[15a], and other Michael reactions.[15b,16]

The preparative-scale reaction (3 mmol of substrate) was effected and the optically active lactones (**5a**—**f**) were synthesised (Scheme 3). The chiral half-ester (**3a**) was prepared using (**2a**) as the catalyst, and the ester group of compound (**3a**) was reduced selectively with lithium borohydride[17,*] to afford (−)-(2*R*,4*S*)-*cis*-2,4-dimethyl-δ-valerolactone (**5a**) with $[\alpha]_D^{25}$ −27.0° (*c* 1.94 in $CHCl_3$) in an overall yield of 56% from (**1a**). The carboxy group of compound (**3a**) was also selectively reduced by BH_3–Me_2S[18] to give the other enantiomer, (+)-(2*S*,4*R*)-(**5a**), with $[\alpha]_D^{25}$ +28.7° (*c* 1.97 in $CHCl_3$) in an overall yield of 48% from (**1a**). Based on the maximum rotation of $[\alpha]_D^{25}$ −41.1°,[3a] the optical purities of (−)- and (+)-(**5a**) were calculated to be 66 and 70%, respectively. These values agreed with the e.e. of (**3a**) (66%) which was determined from the diastereoisomeric excess of the corresponding amide-ester (**4a**). Thus both enantiomers (−)- and (+)-(**5a**) with almost equal optical purity were prepared from the identical precursor (**3a**). The same procedure was applied to other half-esters (**3b**—**f**) to give the optically active lactones (**5b**—**f**) having 30—50% e.e.s. The optical purities of compounds (**5b**,**f**) were determined by h.p.l.c. according to Mori's method[10] (see Experimental section). The absolute configuration of compounds (**5a**—**f**) thus obtained enabled the direction of asymmetric induction of each catalyst (**2**) to be determined.

* Lithium borohydride was prepared *in situ* from lithium perchlorate and sodium borohydride (see Experimental section).

Table 2. Solvent effect on the reaction of anhydride (**1a**) with methanol, catalysed by cinchonine (**2a**)[a]

Entry	Solvent	ε (25 °C)	Time	e.e. (%)	Selectivity
1	Methanol[b]	32.7	10 h	5.4	*pro-S*
2	Ethyl acetate	6.02	5 day	64	*pro-S*
3	Chloroform	4.64	2 day	44	*pro-S*
4	Diethyl ether	4.20	12 h	69	*pro-S*
5	Toluene	2.38	20 h	64	*pro-S*
6	Toluene[c]	2.38	9 h	46	*pro-S*
7	Benzene	2.28	2 day	58	*pro-S*

[a] Compound (**1a**) (0.1 mmol), base (**2a**) (0.02 mmol), methanol (1 mmol), solvent (5 ml), room temperature, quantitative yield. [b] The solvent is itself the nucleophile. [c] 2.5 ml of solvent.

Some aspects of the reaction were investigated with a combination of compounds (**1a**) and (**2a**) as the substrate and the catalyst, respectively. The reaction was effected in several kinds of solvents from methanol to benzene with varying polarity of the solvent. The results are summarised in Table 2. The reaction rates and the e.e.s of the products were influenced by the nature of the solvent. The highest asymmetric induction was obtained in diethyl ether (entry 4). In general, less polar

Table 3. Reactivity of alcohols[a]

Entry	Nucleophile	(mmol)	Time	e.e. (%)	Selectivity
1	Methanol	2.0	36 h	64	*pro-S*
2	Ethanol	2.0	10 day	56	*pro-S*
3	CF_3CH_2OH	1.0	43 h	32	*pro-S*
4	Propan-2-ol	2.0	No reaction[b]		

[a] Compound (**1a**) (0.1 mmol), base (**2a**) (0.01 mmol), dry toluene (5 ml), room temperature, quantitative yield. [b] None of the product was detected after 1 week (g.l.c.; 5% XE-60; 160 °C).

Table 4. Pseudo-first-order reaction rate constant of the reaction of anhydride (**1a**) catalysed by cinchonine (**2a**), quinuclidine, and quinoline[a]

Catalyst	$k_{obs.}$ (min^{-1})	$k_{obs.}/k_{spont.}$[b]
None	3.71×10^{-5}	1
(**2a**)	2.26×10^{-3}	60.9
Quinuclidine	2.26×10^{-3}	60.9
Quinoline	4.34×10^{-5}	1.17

* See footnote *. [b] $k_{spont.}$ = spontaneous reaction rate in the absence of catalyst.

solvents such as toluene or diethyl ether gave favourable results with respect to the reaction rate and the extent of asymmetric induction. The direction of selectivity (*pro-S*) did not change with a change in reaction medium. When the solvent was itself the nucleophile, namely in methanol (entry 1), the extent of asymmetric induction was extremely diminished (5.4% e.e.). The reaction rate in methanol did not increase as remarkably as had been expected from the high concentration of nucleophile (solvent) compared with the standard conditions, thus suggesting that the polar solvent retarded the reaction rate. The e.e. of the product was also dependent upon the concentration of the reactant. By increasing the concentration of the reactant, an increase in the reaction rate and a decrease in e.e. were observed (entries 5 and 6).

An attempt was made to test the ability of several alcohols as the nucleophile. Table 3 shows the reactivity and the selectivity of methanol, ethanol, 2,2,2-trifluoroethanol, and propan-2-ol for anhydride (**1a**). Methanol was the most reactive nucleophile and propan-2-ol was unreactive. It is worth noting that 2,2,2-trifluoroethanol exhibited considerable reactivity (entry 3) in contrast with low reactivity of ethanol, but the extent of selectivity was not so high as in the case of methanol.

Of the two basic moieties in the structure of cinchonine (**2a**), the quinoline and the quinuclidine rings, the latter ring was responsible for the catalytic activity of cinchonine (**2a**) because quinuclidine catalysed the present reaction as effectively as did the base itself, whereas quinoline did not (Table 4). In addition, the absence of a hydroxy group in the catalyst did not influence the reaction rate, since quinuclidine exhibited almost the same reaction rate as cinchonine (**2a**). To clarify the reaction mechanism, the deuterium isotope effect was assessed under pseudo-first-order reaction conditions.* The anhydride (**1a**) was treated with a large excess of methanol or methan[^{2}H]ol (20 mol equiv.) in the presence of cinchonine (**2a**) (0.1 mol equiv.) in dry toluene. The reaction was well simulated by pseudo-first-order kinetics (Figure). The pseudo-first-order reaction rate

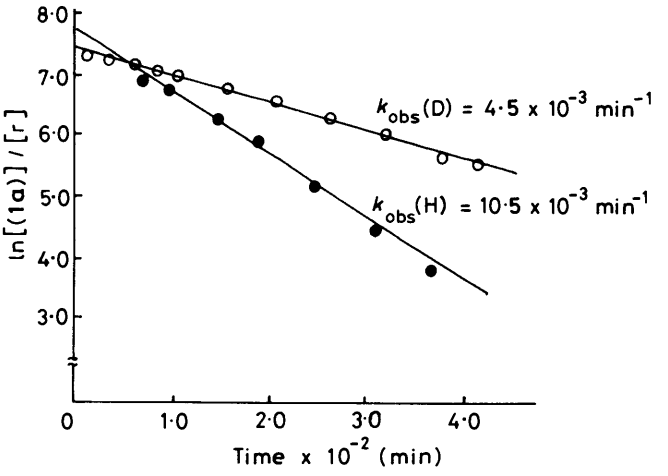


Figure. Plots of ln[(**1a**)]/[r] *vs.* reaction time for the reaction of anhydride (**1a**) (0.2 mmol) with methanol (●) (4 mmol) or methan-[^{2}H]ol (○) (4 mmol) catalysed by cinchonine (**2a**) (0.02 mmol). [r], concentration of internal standard (diethyl phthalate) (see footnote *)

constants, k_{obs}(H) and k_{obs}(D), were determined as 10.5×10^{-3} and 4.5×10^{-3} min^{-1}, respectively. The deuterium isotope effect [k_{obs}(H)/ k_{obs}(D)] was calculated as 2.3. The reported value of deuterium isotope effect in base-catalysed hydrolysis of acetic anhydride was *ca.* 3 in which general-base catalysis was established.[19] The observed data suggest that the reaction proceeded *via* general-base catalysis by the quinuclidine moiety of cinchonine (**2a**). This is consistent with the fact that the more acidic 2,2,2-trifluoroethanol (pK_a 12.4[20]) was more reactive than ethanol (pK_a 16.0[20]). Hiemstra and Wynberg[5] proposed a mechanism for base-catalysed addition of thiols to electron-poor olefins, in which they pointed out that the base catalyst activated the thiols *via* ion-pair formation (1:1 complex) in rapid equilibrium, followed by reaction with conjugated enones in the rate-determining step. As to the present reaction, however, this is not the case. The addition of alcohols to acid anhydrides seems to proceed *via* general-base catalysis without formation of such a charge-separated tight complex as in the thiol-addition. Taking into account the difference of acidity of thiols (pK_a 6—8) and alcohols (pK_a 16—18), the present mechanistic differences are rational.

Experimental

General Details.—The high-field ^{1}H n.m.r. results for compounds marked* have been treated as a Supplementary publication [SUP. No 56668 (4 pp.)]†. ^{1}H N.m.r. spectra were measured on a Varian EM 360 (60 MHz) and a JEOL GX-400 (400 MHz) spectrometer. ^{13}C N.m.r. spectra were recorded on a JEOL JNM-FX 100 (25 MHz). Deuteriochloroform was used as the solvent with tetramethylsilane as internal standard throughout unless otherwise specified. I.r. spectra were measured on a Hitachi 215 spectrophotometer. Elemental analyses were performed by a Yanaco MT-3. Mass spectra were measured with a JEOL JMS-DX-300. A Perkin-Elmer 241 polarimeter was used for measurement of optical rotations. G.l.c. analyses were performed on a Shimadzu GC-4B equipped with a flame ionisation detector. For preparative g.l.c., a Varian model 920 equipped with a thermal conductivity detector was used. H.p.l.c. analyses were carried out with a Jasco BIP-1 chromatograph system [column; silica gel NUCLEOSIL 50–5, 25 cm × 4 mm; eluant hexane–propan-2-ol–NEt_3 (15:1:0.16)

* Compound (**1a**) (0.2 mmol), catalyst (0.02 mmol), methanol (4 mmol), dry toluene (5 ml), room temperature. The consumption of compound (**1a**) was followed by g.l.c. with an internal standard, diethyl phthalate (4.32×10^{-2} mmol); 5% XE-60; 150 °C.

† For details of the Supplementary publication, scheme, see Instructions for Authors (1987), *J. Chem. Soc., Perkin Trans. 1*, 1987, Issue 1.

unless otherwise specified; detection 280 nm]. Data-processing was performed on a Hitachi M833 Chromato-Processor. M.p.s and b.p.s were uncorrected. Toluene and methanol were distilled over CaH_2 and stored over molecular sieves type 4Å. Diethyl ether and tetrahydrofuran (THF) were distilled over sodium wire immediately before use. Commercially available cinchonine (**2a**) and cinchonidine (**2b**) were recrystallised from ethanol. Commercial grade quinine (**2c**) was purified by conversion into its tartrate.[21] Quinidine (**2d**) was purchased and used without further purification. Compound (**2i**) was prepared from commercially accessible (−)-ephedrine hydrochloride by reductive alkylation using formaldehyde and sodium cyanoborohydride.[22]

Preparation of Epi-bases (**2e—h**).—The general procedure for the preparation of compounds (**2e—h**) is exemplified by the preparation of epiquinine (**2g**). Quinine (**2c**) (3.00 g, 9.25 mmol) was allowed to react with sodium hydride (444 mg, 18.5 mmol) in dry THF (100 ml) at 50—60 °C for 2 h. The mixture was then cooled to 0 °C, and a solution of toluene-*p*-sulphonyl chloride (2.65 g, 13.9 mmol) in dry THF (25 ml) was added dropwise to the mixture. After the addition was completed, the mixture was heated under gentle reflux for 9 h. The reaction mixture was evaporated to dryness under reduced pressure and the residue was diluted with 1M-HCl (200 ml). The acidic solution was washed with ether (2 × 100 ml) and the aqueous layer was made alkaline with Na_2CO_3 powder (*ca.* 25 g) and extracted with ether (3 × 100 ml). The combined extracts were washed with saturated aq. NaCl and dried over anhydrous Na_2SO_4, and evaporated to give a syrup (4.53 g). The crude product was subjected to silica gel column chromatography [$CHCl_3$–MeOH (40:1)] to afford O-*tosylquinine* (2.03 g, 46%), $[\alpha]_D^{26}$ +12.7° (*c* 1.10 in EtOH) (Found: C, 65.6; H, 6.2; N, 5.6. $C_{27}H_{30}N_2O_4S{\cdot}H_2O$ requires C, 65.30; H, 6.50; N, 5.64%); δ_H 1.50—3.20 (11 H, m), 2.16 (3 H, s), 3.90 (3 H, s), 4.8—5.1 (2 H, m), 5.6—6.2 (2 H, m), 6.75 (2 H, d, *J* 8.0 Hz), 7.1—7.4 (5 H, m), 7.85 (1 H, d, *J* 9.2 Hz), and 8.50 (1 H, d, *J* 4.4 Hz).

A mixture of *O*-tosylquinine (1.29 g, 2.70 mmol) and (+)-tartaric acid (422 mg, 2.81 mmol) in distilled water (30 ml) was heated under reflux for 20 min. The reaction mixture was then made alkaline with Na_2CO_3 powder (*ca.* 300 mg), and extracted with ether (4 × 70 ml). The combined extracts were washed with saturated aq. $NaHCO_3$, and work-up gave a syrup (0.86 g). Purification by t.l.c. on silica gel [Chromatotron; hexane–$CHCl_3$–MeOH–NEt_3 (20:20:1:1)] yielded epiquinine (**2g**)* (0.74 g, 84%), $[\alpha]_D^{28}$ +39.9° (*c* 1.13 in EtOH) {lit.,[23] $[\alpha]_D^{25}$ +43.3° (*c* 0.949 in EtOH)} (Found: C, 73.1; H, 7.4; N, 8.5. Calc. for $C_{20}H_{24}N_2O_2$: C, 74.05; H, 7.46; N, 8.63%); δ_C 25.2, 27.3, 28.0, 39.8, 40.8, 55.5, 55.9, 61.5, 71.4, 102.6, 114.7, 120.1, 121.3, 128.2, 131.6, 141.3, 144.4, 144.8, 147.5, and 157.4; *m/z* 324 (M^+, 6%).

Epicinchonine (**2e**),* $[\alpha]_D^{26}$ +114.5° (*c* 1.07 in EtOH) {lit.,[23] $[\alpha]_D^{22}$ +120.3° (*c* 0.806 in EtOH)} (Found: C, 77.1; H, 7.5; N, 9.4. Calc. for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52%); δ_C 23.9, 26.4, 27.4, 39.1, 47.0, 49.2, 62.5, 69.9, 115.1, 119.8, 123.9, 126.4, 127.1, 129.1, 130.3, 139.8, 146.5, 148.6, and 150.1.

Epicinchonidine (**2f**),* $[\alpha]_D^{28}$ +56.9° (*c* 1.29 in EtOH) {lit.,[23] $[\alpha]_D^{20}$ +62.8° (*c* 0.804 in EtOH)} (Found: C, 77.0; H, 7.6; N, 9.3%); δ_C 25.0, 27.3, 27.8, 39.8, 40.8, 55.8, 62.1, 70.6, 114.6, 119.8, 124.0, 126.4, 127.2, 128.9, 130.3, 141.3, 146.5, 148.6, and 150.1.

Epiquinidine (**2h**),* $[\alpha]_D^{26}$ +96.3° (*c* 1.15 in EtOH) {lit.,[23] $[\alpha]_D^{19}$ +102.4° (*c* 0.865 in EtOH)}; δ_C 24.0, 26.7, 27.4, 39.0, 46.9, 49.3, 55.5, 62.3, 70.1, 102.0, 114.8, 120.0, 121.7, 128.1, 131.6, 140.2, 144.7, 145.0, 147.6, and 157.5; *m/z* 324 (M^+, 5.7%).

Asymmetric Ring-opening of Anhydrides (**1a—f**).—A typical procedure is illustrated by the reaction of compound (**1a**) catalysed by cinchonine (**2a**). *cis*-2,4-Dimethylglutaric anhydride (**1a**)[8] (14.2 mg, 0.1 mmol) and cinchonine (**2a**) (2.9 mg, 0.01 mmol) were dissolved in dry toluene (5 ml), and MeOH (64.1 mg, 2 mmol) was added to the solution. The mixture was stirred at room temperature and the progress of the reaction was monitored by g.l.c. (5% XE-60; 160 °C; carrier gas flow rate 40 ml min^{-1}; R_t (**1a**) 7.2 min, R_t (**3a**) 4.5 min). The anhydride (**1a**) was quantitatively converted into (**3a**) within a day. The solvent was removed and the residual oil was converted into the diastereoisomeric amide-ester (**4a**) by the following procedure.

Determination of Diastereomeric Excess of Compounds (**4**).—A representative procedure is as follows. To a solution of the mono ester (**3a**) (17.4 mg, 0.1 mmol) in dry toluene (3 ml) at 0 °C was added thionyl chloride (14.3 mg, 0.12 mmol). The mixture was stirred at 0 °C for 10 min, and then (*R*)-1-(1-naphthyl)ethylamine (18.8 mg, 0.11 mmol) and triethylamine (33.4 mg, 0.33 mmol) were added successively. The mixture was stirred at 0 °C for 1 h, then at room temperature for an additional 1 h. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (20 ml). The solution was washed successively with 1M-HCl, saturated aq. $NaHCO_3$, and saturated aq. NaCl. The organic layer was dried (Na_2SO_4) and evaporated to give a diastereoisomeric mixture (**4a**) (25 mg, 76%), δ_H (400 MHz) 1.05—1.18 (6 H, 4 × d, $CHMeCH_2$-$CHMe$: 1.05, d, *J* 6.84 Hz; 1.10, d, *J* 6.35 Hz; 1.15, d, *J* 6.38 Hz; 1.18, d, *J* 6.84 Hz), 1.44 (1 H, m), 1.67 (3 H, m, $NHCHMe$), 1.97—2.25 (2 H, m), 2.52 (1 H, m), 3.61 and 3.63 (3 H, 2 × s, diastereoisomeric CO_2Me), 5.81 (1 H, m, CONH), 5.92 (1 H, m, $NHCHMe$), and 7.26—8.09 (7 H, m, ArH). The diastereoisomeric excess (d.e.) of compound (**4a**) was determined as 63% by h.p.l.c. (flow rate 2 ml min^{-1}; R_t 5.1 and 6.3 min). The d.e. was calculated as 61% from calculation of the peak areas at δ 3.61 and 3.63 in ^1H n.m.r. spectrum.

Preparation of Optically Active Lactones (**5a—f**).—The general procedure for the preparation of lactones (**5**) from monoesters (**3**) is exemplified by the reduction of the CO_2Me group of compound (**3a**). To a solution of compound (**3a**) [370 mg, 2.11 mmol; prepared from (**1a**) and (**2a**)] in dry THF (60 ml) was added lithium hydroxide (50.5 mg, 2.11 mmol), and the mixture was stirred at 40—50 °C until the LiOH had completely dissolved. Anhydrous lithium perchlorate (1.12 g, 10.5 mmol) was added to the solution and allowed to dissolve completely, and then sodium borohydride (400 mg, 10.5 mmol) was added all at once to the solution at room temperature. Gentle effervescence was observed immediately, but this ceased within 10 min. The solution was then heated at 50 °C (further effervescence). After the effervescence had ceased (*ca.* 40 min), the reaction mixture was evaporated to dryness. The residue was treated with 1.5 M-HCl, and an oily substance was liberated. The mixture was extracted with ether (3 × 30 ml), and work-up gave an oil, which was distilled (Kugelrohr) to yield (−)-(2*R*,4*S*)-*cis*-2,4-dimethyl-δ-valerolactone (**5a**) [150 mg, 56% yield from (**1a**); 66% e.e.], b.p. 131—134 °C (oven temp.) at 15.5 mmHg; $[\alpha]_D^{25}$ −27.0° (*c* 1.94 in $CHCl_3$) {lit.,[3a] $[\alpha]_{D\,max.}^{25}$ −41.1° (*c* 5—10 in $CHCl_3$)}; $\nu_{max.}$ 1 740 cm^{-1} (C=O); δ_H 1.0 (3 H, d, *J* 6.4 Hz), 1.28 (3 H, d, *J* 6.8 Hz), 1.1—1.6 (1 H, m), 1.81—2.77 (3 H, m), and 3.70—4.50 (2 H, m).

The half-ester (**3a**) (370 mg, 2.11 mmol) was also reduced by BH_3–SMe_2 (192 mg, 2.53 mmol) in dry THF (4 ml) containing trimethoxyborane (660 mg, 6.33 mmol)[18] to give (+)-(2*S*,4*R*)-*cis*-2,4-dimethyl-δ-valerolactone (**5a**) [130 mg, 48% yield from (**1a**); 70% e.e.], $[\alpha]_D^{25}$ +28.7° (*c* 1.97 in $CHCl_3$). An aliquot of compound (**3a**) was converted into amide-ester (**4a**), d.e. 66% (h.p.l.c.).

(−)-(3S)-3-*Isopropyl*-δ-*valerolactone* (**5b**). 3-Isopropylglutaric anhydride (**1b**)[9] (500 mg, 3.20 mmol), MeOH (1.03 g, 32.0 mmol), and cinchonine (**2a**) (94.2 mg, 0.32 mmol) in dry toluene (160 ml) at room temperature for 2 days yielded compound (**3b**)

quantitively. The half-ester (**3b**) was reduced with $LiBH_4$ to afford (−)-(3*S*)-3-isopropyl-δ-valerolactone (**5b**) [370 mg, 88% from (**1b**)], b.p. 91.5—94 °C (oven temp.) at 0.9 mmHg; $[\alpha]_D^{24}$ −5.93° (*c* 1.13 in EtOH) {lit.,[10] $[\alpha]_{D\,max.}^{24}$ +16.3° (*c* 1.04 in EtOH)}; $\nu_{max.}$ 1 743 cm^{-1} (C=O); δ_H 0.88 and 0.97 (6 H, m, 2 × Me), 1.20—2.95 [6 H, m, $CH_2CH(CHMe_2)CH_2$] and 4.31 (2 H, m, CH_2O). The e.e. of compound (**5b**) was found to be 36% by h.p.l.c. analysis[10] as described below.

The lactone (**5b**) (40 mg, 0.28 mmol) and (*R*)-1-(1-naphthyl)ethylamine (53 mg, 0.31 mmol) were mixed and heated at 90 °C for 12 h. The consumption of lactone (**5b**) was monitored by g.l.c. (5% XE-60; 165 °C) and the formation of the diastereoisomeric amide-alcohols was confirmed by t.l.c. [hexane–AcOEt (1:1)]. The resulting mixture of diastereoisomeric amide-alcohols was analysed by h.p.l.c. [hexane–AcOEt (2:3); flow rate 3 ml min^{-1}; R_t 7.4 and 11.7 min].

(+)-(3S)-3-*Phenyl*-δ-*valerolactone* (**5c**). 3-Phenylglutaric anhydride (**1c**)[10] (500 mg, 2.63 mmol), MeOH (0.84 g, 26.3 mmol), and quinidine (**2d**) (85.3 mg, 0.26 mmol) in dry toluene (130 ml) at room temperature for 1 day gave compound (**3c**) quantitatively, e.e. 30% (h.p.l.c.).

The half-ester (**3c**) was reduced to yield (+)-(3*S*)-3-phenyl-δ-valerolactone (**5c**) [280 mg, 62% from (**1c**); 31% e.e.], b.p. 170—173 °C (oven temp.) at 1.0 mmHg; $[\alpha]_D^{25}$ +1.16° (*c* 5.45 in $CHCl_3$) {lit.,[24] b.p. 124—126 °C at 0.07 mmHg; $[\alpha]_{D\,max.}^{25}$ +3.71° (*c* 5.3 in $CHCl_3$)}; $\nu_{max.}$ 1 727 cm^{-1} (C=O); δ_H 1.8—3.5 (5 H, m, $CH_2CHPhCH_2$), 4.1—4.6 (2 H, m, CH_2O), and 7.2 (5 H, m, Ph).

(−)-(R)-*Mevalonolactone* (**5d**). 3-Hydroxy-3-methylglutaric anhydride (**1d**)[11] (500 mg, 3.47 mmol), MeOH (1.11 g, 34.7 mmol), and quinine (**2c**) (115 mg, 0.35 mmol) in a mixture of dry toluene (200 ml) and dry ether (100 ml) at room temperature for 3 days yielded compound (**3d**) quantitatively, e.e. 40% [^1H n.m.r. (400 MHz)].

The half-ester (**3d**) was reduced with $LiBH_4$, and the product was purified by preparative t.l.c. [silica gel; benzene–AcOEt (1:3)] to give (−)-(*R*)-mevalonolactone (**5d**) [330 mg, 73% from (**1d**); 31% e.e.], $[\alpha]_D^{25}$ −7.17° (*c* 6.89 in EtOH) {lit.,[25] $[\alpha]_{D\,max.}^{20}$ −23.0° (*c* 6 in EtOH)}; δ_H 1.55 (3 H, s, Me), 2.06 (2 H, m, CH_2), 2.74 (2 H, m, $CH_2C{=}O$), 3.14 (1 H, br s, OH), and 4.28—4.99 (2 H, m, CH_2O). The e.e. of (**5d**) was ascertained by 400 MHz ^1H n.m.r. spectroscopy in the presence of the chiral shift reagent tris-[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]-europium(III).[26]

(−)-(1R,5S)-6,6-*Dimethyl*-3-*oxabicyclo*[3.1.0]*hexan*-2-*one* (**5e**). *cis*-3,3-Dimethylcyclopropane-1,2-dicarboxylic anhydride (**1e**)[12] (500 mg, 3.57 mmol), MeOH (1.14 g, 35.7 mmol), and quinine (**2c**) (117 mg, 0.36 mmol) in dry toluene (180 ml) at room temperature for 9 days afforded compound (**3e**) in >90% yield (g.l.c.; 5% XE-60; 150 °C), e.e. 27% (h.p.l.c.).

The half-ester (**3e**) was reduced with $LiBH_4$, and the product was purified by preparative g.l.c. (5% XE-60; 170 °C) to yield (−)-(1*R*,5*S*)-6,6-dimethyl-3-oxabicyclo[3.1.0]hexan-2-one (**5e**) [240 mg, 55% from (**1e**); 27% e.e.], $[\alpha]_D^{21}$ −23.90° (*c* 1.41 in $CHCl_3$) {lit.,[27] $[\alpha]_{D\,max.}^{25}$ −89.9° (*c* 1.4 in $CHCl_3$)}; $\nu_{max.}$ 1 770 cm^{-1} (C=O); δ_H 1.20 (6 H, s, 2 × Me), 1.87—2.16 (2 H, m, 2 × CH), and 4.00—4.50 (2 H, m, CH_2).

(+)-(1S,6R)-8-*Oxabicyclo*[4.3.0]*non*-3-*en*-7-*one* (**5f**). *cis*-Cyclohex-4-ene-1,2-dicarboxylic anhydride (**1f**)* (540 mg, 3.56 mmol), MeOH (1.14 g, 35.6 mmol), and epiquinine (**2g**) (115 mg, 0.36 mmol) in dry toluene (180 ml) at room temperature for 3 days gave compound (**3f**) (43% e.e. by h.p.l.c.) quantitatively.

The half-ester (**3f**) was reduced with $LiBH_4$ to yield (+)-(1*S*,6*R*)-8-oxabicyclo[4.3.0]non-3-en-7-one (**5f**) [260 mg, 54% from (**1f**)], $[\alpha]_D^{24}$ +23.29° (*c* 1.05 in $CHCl_3$) {lit.,[2] $[\alpha]_{D\,max.}^{25}$ −67.1° (*c* 1 in $CHCl_3$)}; $\nu_{max.}$ 1 770 cm^{-1} (C=O); δ_H 1.60—2.69 (6 H, m, 2 × CH_2 and 2 × CH), 4.13 (2 H, m, CH_2O), and 5.72 (2 H, m, CH=CH). The lactone (**5f**) was converted into the corresponding diastereoisomeric mixture of amide-alcohols by the same procedure as described in the preparation of compound (**5b**), and the e.e. of (**5f**) was found to be 45% by h.p.l.c. [hexane–AcOEt (2:3); flow rate 2 ml min^{-1}; R_t 5.70 and 8.05 min].

* Commercially obtained and recrystallised from benzene–light petroleum.

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