STUDIES ON ASYMMETRIC INDUCTION BASED ON ENANTIOTOPIC GROUP DIFFERENTIATION

HIRATAKE JUN

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CHAPTER 1

INTRODUCTION

1-1. General Introduction

One of the most fundamental processes encountered in organic synthesis is stereoselective construction of new chiral centers on a chiral or an achiral substrate. This process, asymmetric synthesis, has been a challenging area of endeavor for all synthetic chemists in both academic and industrial fields.

Recently much attention has been focused on asymmetric induction based on enantiotopic-group differentiation, in which one of the enantiotopic functional groups attached to a prochiral center or the centers of opposite chiralities within meso-compounds is differentiated, new chiral centers thereby being created.

The concept of this methodology was introduced for the first time in 1975 by Fischli et al.[1] They proposed an ingeniously simple scheme by which a starting material with enantiotopic groups can be converted completely to a predetermined enantiomer. The original idea is shown in Fig. 1. Its essence is the reversal in the order of transformations. First, a bifunctional prochiral starting material is allowed to react with one equivalent of a chiral auxiliary (C^*) to give a pair of diastereomer (D_1 and D_2).

These must be separated, and then the unreacted group (X) is transformed to group B in diastereomer D_1 and to A in D_2. Removal of the chiral auxiliary group and transformation of the liberated functional groups to groups A and B, respectively, gives in both cases, the same enantiomer. Interchanging the order of transformations at both branches provides an antipodal end product.

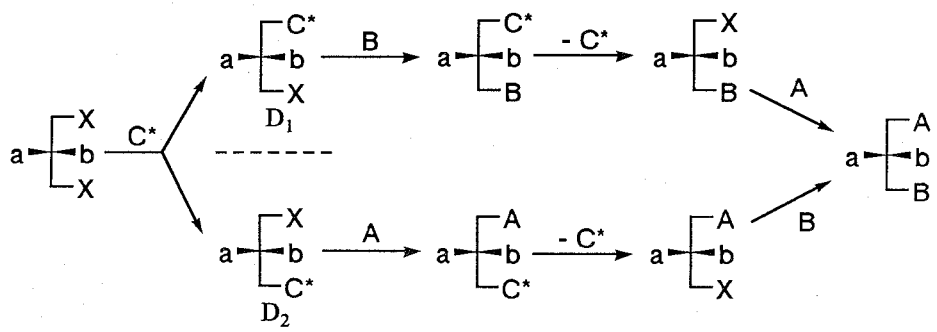


Fig.1

The major advantages of this methodology exist in that both enantiomeric configurations of products can be prepared from either of the enantiomeric intermediates by simply altering the sequence of reactions and that one enantiomer having the undesired configuration is readily converted to the desired antipode through selective transformation of functional groups.[2a-c)]

Terashima et al.[2c)] demonstrated these advantages in their report on the synthesis of optically active prostaglandin intermediates. They prepared both enantiomers of the cyclopentenyl

lactone from either of the enantiomers of the intermediary half-esters through a series of transformation of functional groups as shown in Fig. 2.

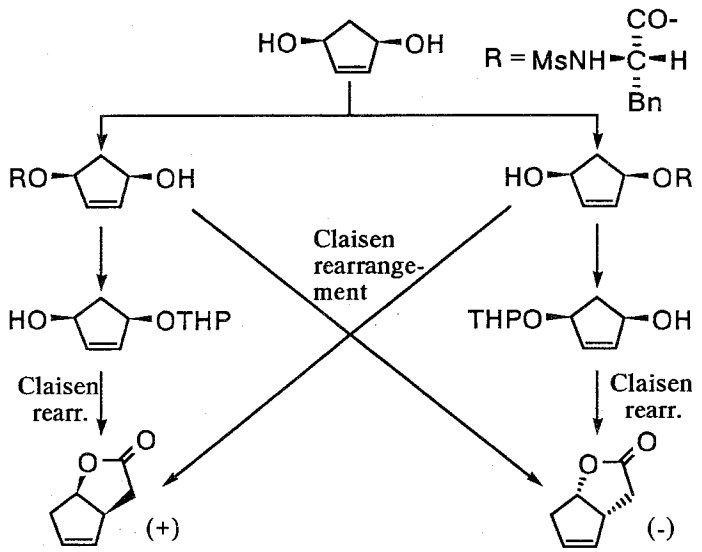
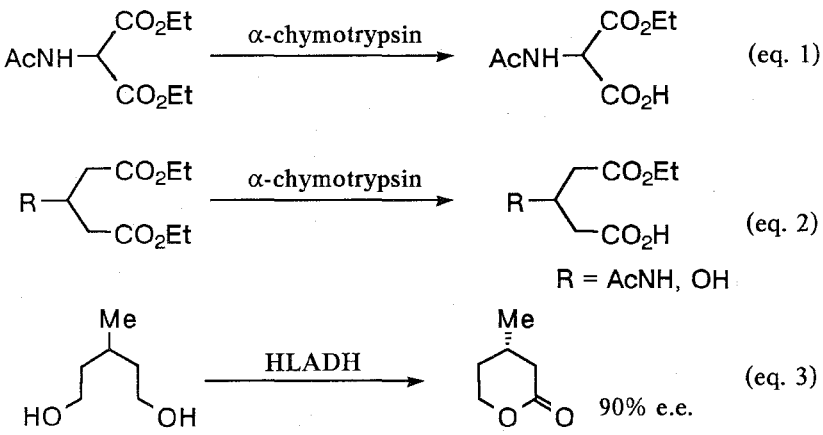
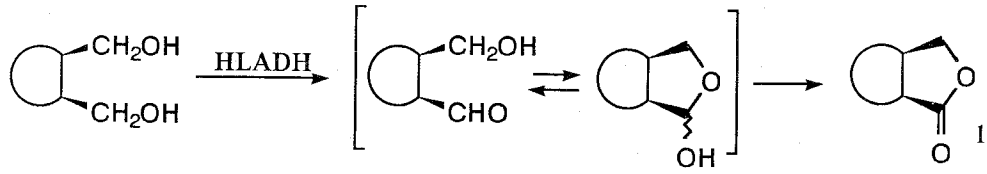


Fig. 2

Asymmetric synthesis based on this methodology has been extensively developed in the area of enzyme-catalyzed reactions. The early works were presented by Cohen et al.[3] They examined the ability of α-chymotrypsin to hydrolyze the enantiotopic ester groups of prochiral malonic or glutaric acid diesters; they prepared optically active half-esters through this enzymatic hydrolysis (eq. 1 and 2). Jones et al.[4a] reported that horse liver alcohol dehydrogenase (HLADH) effectively catalyzed the enantioselective oxidation of prochiral pentane-1,5-diols to give opti-

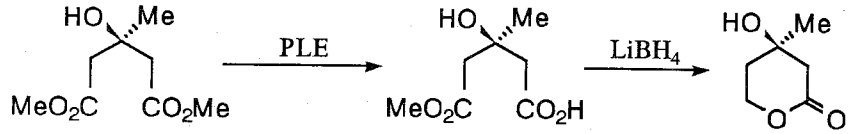
cally active lactones (eq. 3). This enzymatic oxidation was successfully applied to meso-diols and gave optically pure lactones (eq. 4).[4b,c] In 1975, Sih et al. found that pig liver esterase (PLE) showed high stereoselectivity in hydrolyzing enantiotopic ester groups of prochiral glutaric acid diesters (eq. 5).[5a] Afterwards enzymatic or microbial hydrolyses of prochiral or meso-diesters were extensively studied[5b-f] and their practical use in asymmetric synthesis of biologically active compounds has been widely appreciated. Ohno et al. demonstrated an elegant example of producing a chiral synthon for β-lactam antibiotics by using PLE (eq. 6).[6] They also prepared L- and D-riboses through PLE-catalyzed hydrolysis of meso-diesters and subsequent chemoselective transformation of functional groups (eq. 7).[7] The optically active precursor for (+)-biotin was also prepared by PLE-catalyzed hydrolysis (eq. 8 and 9).[8),9]





(eq. 4)

100% e.e.



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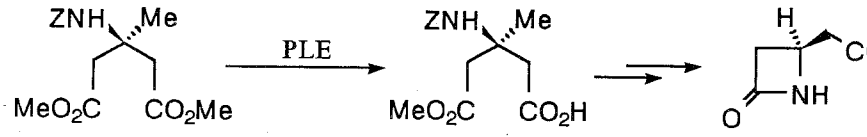
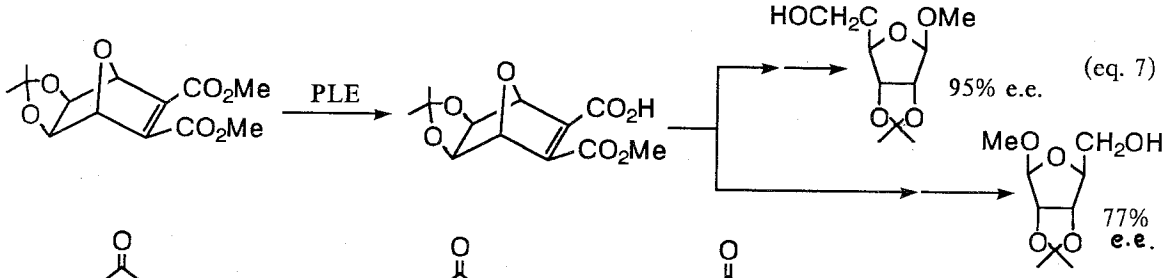
(eq. 5)



>96% e.e.

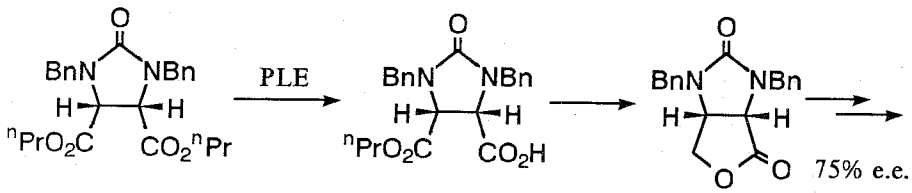
(eq. 6)



95% e.e.

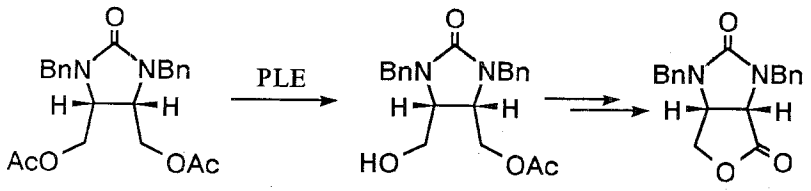
77% e.e.

(eq. 7)



75% e.e.

(+)-biotin (eq. 8)

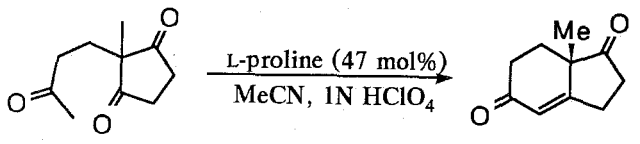


93% e.e.

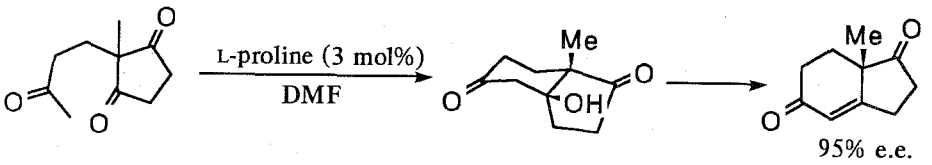
(eq. 9)

On the other hand, some non-enzymatic methods so far been reported are based on enantiotopic-group differentiation. One of

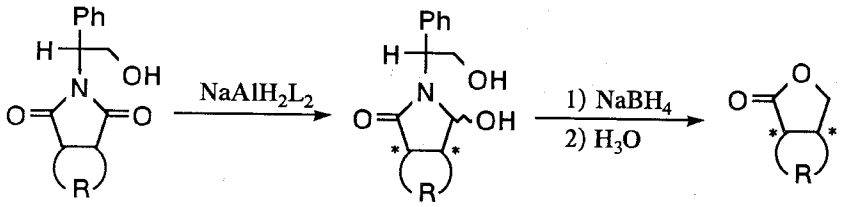
the most fascinating works was offered by the two groups of Schering A.G. (eq. 10)[10] and Hoffmann-La Roche, Inc. (eq. 11).[11] They reported that a L-proline-catalyzed cyclization of prochiral triketones yielded an optically active ketol or enone, a key intermediate for C,D-ring system in steroid synthesis. Mukaiyama et al.[12] reported a method for asymmetric synthesis of bicyclic lactones through diastereoselective reduction of chiral cyclic imides, derived from meso-1,2-cis-dicarboxylic acids and chiral 2-amino-2-phenylethanol (eq. 12). They also reported a diastereoselective acylation of meso-cyclic tin alkoxides prepared from meso-diols and dibutyltin oxide, and obtained diastereomeric monoacylated products in utmost 90% d.e. (eq. 13).[13] The first report on the enantioselective deprotonation of symmetrical epoxide with chiral lithium amide was presented by Whitesell et al.[14a] The reaction was then used for the synthesis of optically active 4-hydroxy-2-cyclopentenone, a versatile chiral synthon for cyclopentenoid natural products (eq. 14).[14b]



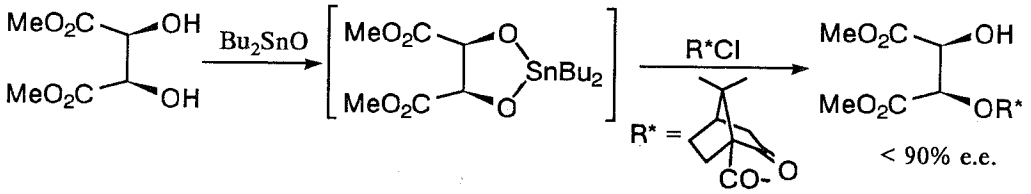
(eq. 10)



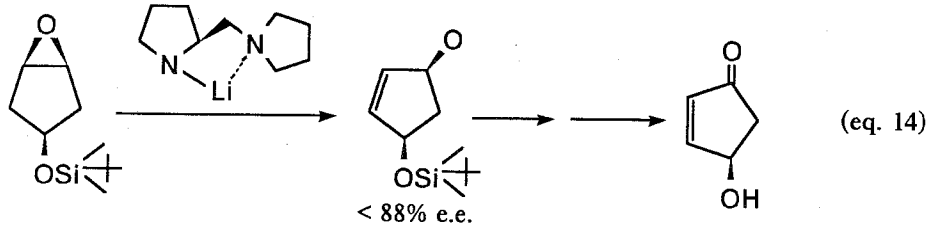
(eq. 11)



(eq. 12)



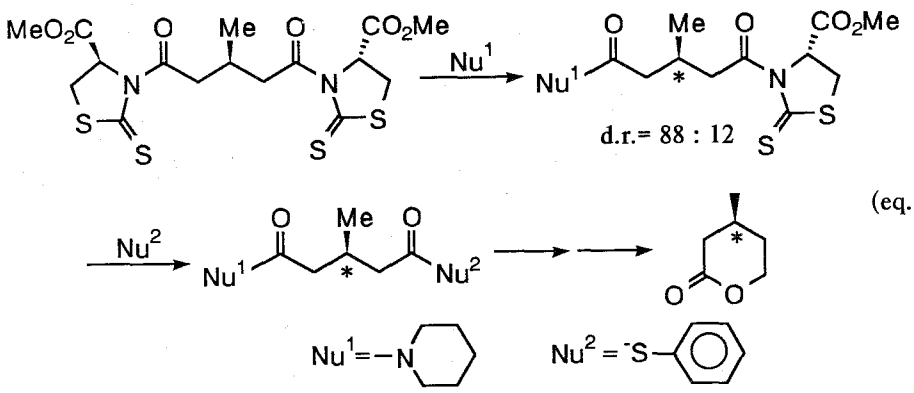
(eq. 13



(eq. 14)

These non-enzymatic methods described above are indeed based on enantiotopic-group differentiation; however, the advantages of this methodology have not yet been fully appreciated. In some cases transformation of functional groups in the products would be difficult and therefore one enantiomer having the undesired configuration would be useless for further chemical elaboration. Consequently, it is desirable to develop a method which permits the subsequent transformation of functional groups to be effected easily. On this basis, Fujita et al.[15] proposed a method for differentiating between enantiotopic carboxyl groups in prochiral or meso-dicarboxylic acids by using 2 molar equiv. of an opti-

cally active 1,3-thiazolidine-2-thione derivative as a chiral adjuvant. In designing the reaction, they attached importance to the substitution on the enantiotopic carboxyl groups for further chemical elaboration and on a chromatographic separation of the diastereomeric products, and thereby prepared optically pure 3-methyl-δ-valerolactone (eq. 15).



(eq. 15)

1-2. Outline of the Present Study

Considering those advantages of the asymmetric induction based on enantiotopic-group differentiation, this author intended to develop novel chemical processes for differentiating enantiotopic carboxyl groups of prochiral or meso-diacids. In designing these processes, the author chose cyclic derivatives of the diacids as the substrates. Prochiral cyclic acid anhydrides, for example, react irreversibly with alcohols or amines to yield chiral half-esters or half-amides without overreaction yielding achiral diesters or diamides (Fig. 3).

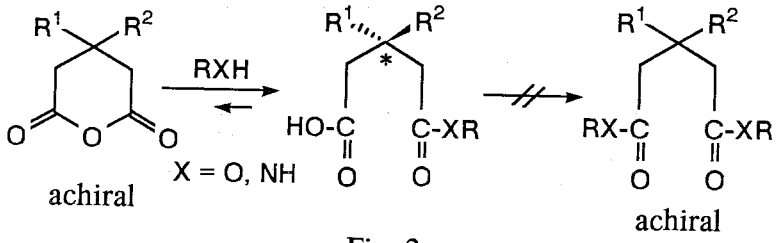


Fig. 3

In Chapter 1, the author describes a diastereoselective ring-opening of prochiral or meso-cyclic acid anhydrides by using chiral binaphthyldiamine derivatives as nucleophiles, and the preparation of optically active lactones are also described.

Catalytic process, on the other hand, is highly desirable in the light of effective asymmetric synthesis. In Chapter 2, the author describes a catalytic asymmetric ring-opening of prochiral or meso-cyclic acid anhydrides with methanol, using cinchona alkaloids as the catalysts.

Malonic acid derivatives having two enantiotopic carboxyl groups attached directly to a prochiral center are also promising substrates for enantiotopic-group differentiation. On this basis, in Chapter 3, the author describes an asymmetric monoesterification of 2-methyl-2-phenylmalonic acid through stereoselective ring-opening of prochiral cyclic acylal derived from the acid.

As will be discussed in Chapter 2, cinchona alkaloid is a naturally occurring chiral tertiary amine and has unique properties as a chiral base catalyst in various asymmetric reactions.

One way to improve its utility as a chiral catalyst is to fix it onto a solid support. In Chapter 4, the author describes the preparation of polymer-supported quinine with spacer groups between the polymer matrix and the alkaloid molecule; the author examined the catalytic activity of those polymer-catalyst in three types of base-catalyzed asymmetric reactions.

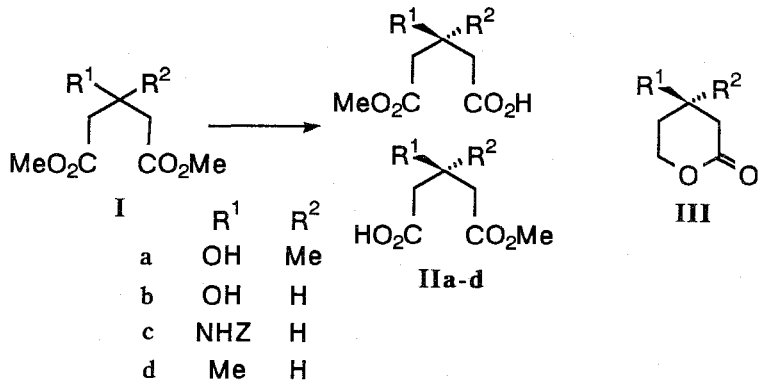
CHAPTER 2

ASYMMETRIC SYNTHESIS OF LACTONES BY STEREOSELECTIVE RING-OPENING OF PROCHIRAL AND MESO-CYCLIC ACID ANHYDRIDES WITH CHIRAL BINAPHTHYLDIAMINES

2-1. Introduction

Optically active glutaric acid monoesters (**II**) and the related lactones (**III**) are of considerable interest not only as target molecules but also as chiral building blocks in the synthesis of many biologically active compounds.[16]

In the past decade, the enzyme-catalyzed or microbial hydrolysis of prochiral diesters (**I**) has been extensively developed for the synthesis of biologically active compounds such as (R)- and (S)-mevalonolactone [from (**IIa**)],[5a] pimaricin fragment [from (**IIb**)],[17] β-lactam antibiotics [from (**IIc**)],[6] negamycin [from (**IIc**)],[18] and verrucarinic acid [from (**IId**)].[19]



	R^1	R^2
a	OH	Me
b	OH	H
c	NHZ	H
d	Me	H

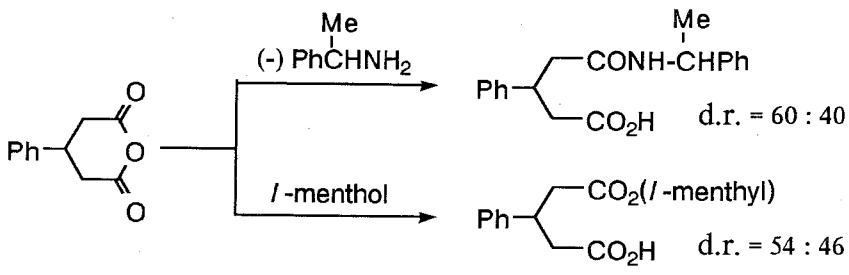
On the other hand, only a limited number of study has been reported on non-enzymatic processes for discriminating enantiotopic carbonyl groups of prochiral glutarates, except the work presented by Fujita et al.[15] as described in Chapter 1. They reported a chemical method for enantioselective transformation of prochiral 3-substituted glutaric acids or meso-diacids by using 2 molar equivalent of optically active 1,3-thiazolidine-2-thione as a chiral adjuvant.

In designing a chemical process for enantiotopic-group differentiation, diesters or diamides of prochiral diacids are not necessarily suitable because decrease in chemical or optical yields may result if both of the chemically equivalent enantiotopic groups react simultaneously or reversibly with reagents to yield achiral products or the opposite enantiomer.

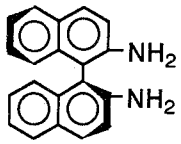
Cyclic acid anhydrides, as described in Chapter 1, would be a satisfactory derivative of prochiral diacids, reacting irreversibly with alcohols or amines to afford chiral half-esters or half-amides solely without overreaction yielding achiral diesters or diamides.

Schwartz[20] and Cohen[21] reported independently that the reaction of 3-phenylglutaric anhydride with (S)-1-phenylethylamine or l-menthol yielded a product mixture which consisted of unequal amounts of the diastereomers of the half-amide or the half-ester, respectively. The observed asymmetric yields of these reactions were very low; however, they can be improved by select-

ing an appropriate nucleophile.



In this respect, the author undertook the asymmetric ring-opening of cyclic acid anhydrides with axially dissymmetric 2,2'-diamino-1,1'-binaphthyl (**1**) and its derivatives as the nucleophile.



(**1**)

The potential of this axially dissymmetric binaphthyl moiety as a chiral recognition unit has been well documented in its use as a chiral hydrogenation catalyst[22a] or a chiral host compound.[22b] In addition to this structural feature, this amine can be easily prepared[23] and both enantiomers are readily accessible in optical pure form by conventional optical resolution.[24]

On the basis of this conception, the author started the investigation by synthesizing the axially dissymmetric amines (**2**)-(**4**) from (S)-(**1**).

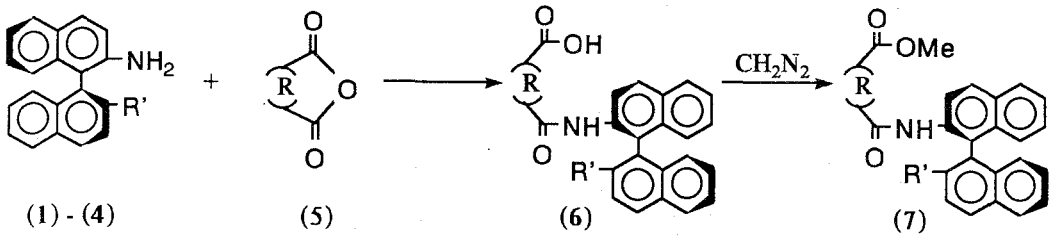
2-2. Results and Discussion

Selective monoacylation of (**1**) with trifluoroacetic anhydride afforded the trifluoroacetyl derivatives (**2**) in a 67% yield. The piperidino derivative (**3**) was synthesized in a 38% yield by reductive N-alkylation with glutaraldehyde and sodium cyanoborohydride. A one-pot synthesis through ozonolysis of 2,5-dihydrofuran and the subsequent reductive N-alkylation gave the morpholino derivative (**4**) in a 42% yield.

Taking account of the synthetic utility of products as chiral building blocks, the prochiral and meso-cyclic acid anhydrides (cis-**5a**, **5b-d**) were subjected to the present asymmetric reaction.

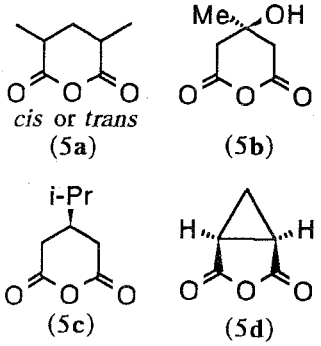
The reaction is shown in Scheme 1. The anhydride (**5**), except trans-(**5a**), was allowed to react with an equal amount of the chiral amine (**1**)-(**4**) in dry solvent at room temperature. The ring-opening reaction proceeded smoothly (TLC) to yield a diastereomeric mixture of the half-amide (**6**) quantitatively.

In addition to this asymmetric synthesis, the author conducted kinetic resolution of a racemic anhydride, trans-(**5a**). The racemic substrate trans-(**5a**) was subjected to react with a 0.2 molar equiv. amount of the chiral amine (**3**) or (**4**); in this condition, a limited amount of the chiral amine reacted preferentially with one of the enantiomers of trans-(**5a**) to yield a diastereomeric mixture of the corresponding half-amide (**6**) in une-



(1) - (4) (5) (6) (7)

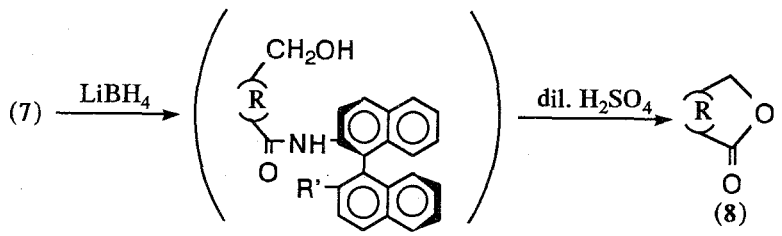
(1): R' = NH_2
(2): R' = $NHCOCF_3$
(3): R' = piperidino
(4): R' = morpholino

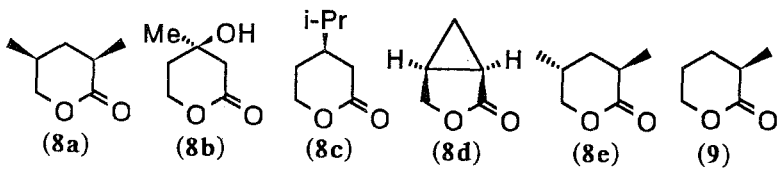


cis or *trans* (5a) (5b) (5c) (5d)

(6a), (7a) :	R = *cis*-$CH(Me)CH_2CH(Me)$	R' = NH_2
(6b), (7b) :	R = *cis*-$CH(Me)CH_2CH(Me)$	R' = $NHCOCF_3$
(6c), (7c) :	R = *cis*-$CH(Me)CH_2CH(Me)$	R' = piperidino
(6d), (7d) :	R = *cis*-$CH(Me)CH_2CH(Me)$	R' = morpholino
(6e), (7e) :	R = $CH_2C(OH)(Me)CH_2$	R' = piperidino
(6f), (7f) :	R = $CH_2C(OH)(Me)CH_2$	R' = morpholino
(6g), (7g) :	R = $CH_2CH(i\text{-}Pr)CH_2$	R' = NH_2
(6h), (7h) :	R = $CH_2CH(i\text{-}Pr)CH_2$	R' = $NHCOCF_3$
(6i), (7i) :	R = *cis*-cyclopropanediyl	R' = NH_2
(6j), (7j) :	R = *cis*-cyclopropanediyl	R' = $NHCOCF_3$
(6k), (7k) :	R = t*rans*-$CH(Me)CH_2CH(Me)$	R' = piperidino

Scheme 1. Asymmetric Ring-opening of the Cyclic Acid Anhydrides (5) with the Chiral Amines (1) - (4).





(8a) (8b) (8c) (8d) (8e) (9)

Scheme 2. Preparation of the Optically Active Lactones (8).

qual amounts. (vide infra).

The resulting half-amide (6), prepared from both the prochiral and racemic anhydrides, was then treated with diazomethane without isolation and converted to the corresponding amide-ester (7). The stereoselectivity of the asymmetric ring-opening was estimated by the diastereomeric ratio in (7) measured with HPLC. The results of the preliminary experiments are shown in Table 1.

Table 1. Stereoselective Ring-opening of the Cyclic Acid Anhydrides (5)[a]

				Amide-ester (7)		
Entry	Anhydride	Amine	Solvent	Compound	D.r.[b]	α[c]
1	*cis*-(5a)	(1)	benzene	(7a)	20 : 80	1.40[d]
2	*cis*-(5a)	(2)	toluene	(7b)	48 : 52	1.39[e]
3	*cis*-(5a)	(3)	toluene	(7c)	10 : 90	1.05[f]
4	*cis*-(5a)	(4)	toluene	(7d)	10 : 90	1.39[g]
5	(5b)	(3)	CH_2Cl_2	(7e)	24 : 76	1.05[h]
6[i]	(5b)	(4)	CH_2Cl_2	(7f)	17 : 83	1.16[j]
7	(5c)	(1)	benzene	(7g)	80 : 20	1.09[d]
8	(5c)	(2)	toluene	(7h)	79 : 21	1.22[e]
9	(5d)	(1)	benzene	(7i)	56 : 44	1.14[d]
10	(5d)	(2)	toluene	(7j)	29 : 71	1.06[e]
11[k]	*trans*-(5a)	(3)	toluene	(7k)	87 : 13	1.20[f]

[a]Conditions: anhydride (0.7 mmol), amine (0.7 mmol), dry solvent (10 mL), room temperature, overnight. [b]Diastereomeric ratio determined by HPLC (silica gel, Nucleosil 50-5; 280 nm). [c]Separation factor in HPLC analysis. [d]Hexane-AcOEt-NEt_3, 2 : 1 : 0.03, 3 mL/min. [e]Hexane-AcOEt-NEt_3, 3 : 2 : 0.05, 3 mL/min. [f]Hexane-AcOEt-NEt_3, 7.5 : 1 : 0.05, 3 mL/min. [g]Hexane-AcOEt-NEt_3, 4 : 1 : 0.05, 3 mL/min. [h]Hexane-isopropyl alcohol-NEt_3, 20 : 1 : 0.02, 0.4 mL/min. [i]The reaction was conducted at -20°C. [j]Hexane-isopropyl alcohol-NEt_3, 20 : 1 : 0.02, 2 mL/min. [k]Kinetic resolution: anhydride (2.5 mmol), amine (0.5 mmol), dry toluene (5 mL).

The stereoselection varied with the combination of the anhydride and the amine: the reaction of the anhydride cis-(**5a**) with (**3**) or (**4**), the anhydride (**5b**) with (**4**), the anhydride (**5c**) with (**1**), and the anhydride (**5d**) with (**2**) gave good results respectively in the light of stereoselection.

On the basis of these results, optically active lactones were synthesized (Scheme 2). The results are shown in Table 2. An equimolar amount of cis-2,4-dimethylglutaric anhydride [cis-(**2**)][25] reacted with the piperidino amine (**3**) at -20°C to afford the half-amide (**6c**) quantitatively. After treating with diazomethane, the diastereomeric ratio of the resulting amide-ester (**7c**) was determined by HPLC and found to be 4:96. The amide-ester (**7c**) was then reduced with lithium borohydride and subsequent acid-hydrolysis afforded (-)-(2R,4S)-cis-2,4-dimethyl-δ-valerolactone (**8a**) with $[\alpha]_D^{25}$ -37.8° in an overall yield of 77% from cis-(**5a**). The optical purity of (**8a**) was calculated from the reported maximum rotation value and found to be 92%; this value was consistent with the diastereomeric ratio in (**7c**).

As expected from the separation factor of (**7a**) (α=1.40), the chromatographic separation of each diastereomer was successfully performed. The major isomer of (**7a**), isolated in a 45% yield from cis-(**5a**), was N-acylated and then subjected to reduction and hydrolysis as described for (**7c**) to give optically pure (-)-(**8a**) having $[\alpha]_D^{25}$ -42.4°.

Table 2. Preparation of the Optically Active Lctones (**8**)[a]

Entry	Anhydride	Amine	Temp. (°C)	Time[b] (day)	D.r. of (7)[c]	Lactone	Yield (%)	$[\alpha]_D$ (deg)	E.e. (%)	Abs. config.
1	*cis*-(**5a**)	(**3**)	-20	3	4 : 96	(**8a**)	77	-37.8[d]	92[e]	(2*R*, 4*S*)
2[f]	(**5b**)	(**4**)	-20	7	17 : 83	(**8b**)	44	-12.2[g]	58[h]	(*R*)
3	(**5c**)	(**2**)	25	0.5	79 : 21	(**8c**)	38	+7.1[i]	42[j]	(*R*)
4	(**5d**)	(**2**)	25	0.5	29 : 71	(**8d**)	65	+28.0[k]	46[l]	(2*R*, 3*S*)
5[m]	*trans*-(**5a**)	(**3**)	-20	2	87 : 13	(**8e**)	47	-60.1[n]	74[o]	(2*R*, 4*R*)
6[m]	*trans*-(**5a**)	(**4**)	-20	2	- [p]	(**8e**)	41	-53.4[q]	66[r]	(2*R*, 4*R*)

[a]Conditions: anhydride (1.5 mmol), amine (1.5 mmol), dry toluene (6 - 17 mL). [b]Reaction time for ring-opening. [c]Diastereomeric ratio (d.r.) of the corresponding amide-ester (7), determined by HPLC. [d] c 1.3, $CHCl_3$. [e]Calculated from the maximum optical rotation value: $[\alpha]_D^{25}$ -41.1° ($CHCl_3$).* [f]Solvent, CH_2Cl_2 (23 mL). [g] c 6.0, EtOH. [h]Determined by 400 MHz ^1H NMR in the presence of Eu(hfc)$_3$. [i] c 0.83, EtOH. [j]Calculated from the maximum optical rotaion value: $[\alpha]_D^{24}$ +16.9° (c 1.04, EtOH).* [k] c 6.41, $CHCl_3$. [l]Calculated from the maximum optical rotation value: $[\alpha]_D$ -61.8° (c 6.6, $CHCl_3$).* [m]Kinetic resolution: anhydride (7.5 mmol), amine (1.5 mmol), dry toluene (25mL). [n] c 2.13, $CHCl_3$. [o]Calculated from the d.r. of (**7c**) (87 : 13). [p]HPLC separation of the diastereomers of (**7d**) was insufficient to calculate the d.r. [q] c 1.9, $CHCl_3$. [r]Calculated from the maximum rotation value ($[\alpha]_D^{20}$ -81.2° calculated from the result in entry 5).

The author also prepared the optically active lactones (**8b-d**) by the same procedure. After the ring-opening of 3-hydroxy-3-methylglutaric anhydride (**5b**),[26] 3-isopropylglutaric anhydride (**5c**),[27] and cis-1,2-cyclopropanedicarboxylic anhydride (**5d**)[28] with the appropriate amines, the resulting amide-esters (**7f**), (**7h**), and (7j) were reduced and hydrolyzed to afford (-)-(R)-mevalonolactone [(**8b**), 58% e.e., entry 2], (+)-(R)-3-isopropyl-δ-valerolactone [(8c), 42% e.e., entry 3], and (+)-(2R,3S)-2,3-methylene-γ-butyrolactone [(**8d**), 46% e.e., entry 4], respective-

ly. Since the rotatory method for determining the e.e. of (**8b**) was reported to be unreliable,[29] the e.e. was determined by ^1H NMR using a chiral shift reagent. The e.e. value in (**8b**) obtained was somewhat lower than that expected from the diastereomeric ratio in (**7f**). This may be due to partial racemization of (**8b**) in acidic solution during isolation.

The kinetic resolution of racemic trans-2,4-dimethylglutaric anhydride [trans-(**5a**)] was carried out by using the piperidino amine (**3**) and the morpholino amine (**4**). The amine (**3**) reacted with five-fold molar excess of racemic trans-(**5a**) and yielded a diastereomeric mixture of the half-amide (**6k**) and the unreacted trans-(**5a**). After removing the excess trans-(**5a**), the stereoselectivity of this kinetic resolution was evaluated on the diastereomeric ratio in (**7c**) (Table 1, entry 11). In the same procedure as for the synthesis cis-lactone (**8a**), (-)-trans-2,4-dimethyl-δ-valerolactone (**8e**) having $[\alpha]_D^{20}$ -60.1° was obtained in an overall yield of 47% based on (**3**). The e.e. of (**8e**) was calculated from the diastereomeric ratio in (**7k**) and found to be 74%. Therefore the maximum specific rotation value of (-)-(**8e**) was calculated as -81.2°. When the morpholino amine (**4**) was used, the trans-lactone (**8e**) with $[\alpha]_D^{20}$ -53.4° was obtained. The e.e. of this lactone was calculated from the maximum specific rotation value for (**8e**) determined as above, and found to be 66%.

The author established the absolute configuration of (-)-(**8e**) by the chiroptical method as follows: both (-)-cis-(2R,4S)-

lactone (**8a**) and (-)-trans-lactone (**8e**) have a negative maximum around the wavelength of the lactone n-π^* transition (Table 3).

Table 3. CD-maxima of the Optically Active 2-Methylated δ-valerolactones

Lactone	$[\alpha]_D$ (deg)	Ellipticity[a] $[\theta]$ (deg·cm^2·dmol^{-1})	(nm)
(2*R*,4*R*)-(**8e**)	-53.4	-2930	221
(2*R*,4*S*)-(**8a**)	-21.8	-1550	227
(2*R*)-(**9**)[b]	-40.7	-3910	225

[a]Measured in hexane. [b]The data were reported in the literature: A. I. Meyers, Y. Yamampto, E. D. Mihelich, and R. A. Bell, *J. Org. Chem.*, **45**, 2792 (1980).

As to the cis-lactone (**8a**), a half-chair conformation with the two methyl groups oriented pseudoequatorially can be assigned tentatively. The positive chirality between C(1)-O and C(2)-C(3) in this lactone corresponds to that predicted from the chirality rule based on the CD spectrum; the rule has been also supported by the relationship between the chiroptical property and the

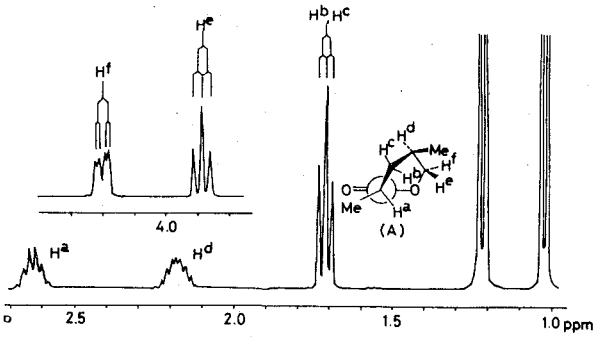


Fig. 1 ^{1}H NMR Spectrum (400 MHz) of *trans*-2,4-Dimethyl-δ-valerolactone (**8e**) in $CDCl_3$-CCl_4 (1:2).

configuration of (-)-(2S)-2-methylvalerolactone (**9**). As shown in

Fig. 1, on the other hand, the chemical shifts and the coupling constants of (-)-trans-lactone (**8e**) presented the structure [A] as the predominant conformer, in which the two methyl groups oriented pseudoequatorially. Consequently, the negative maximum in the CD spectrum indicated the positive chirality also between C(1)-O and C(2)-C(3) in (-)-trans-lactone (**8e**), and therefore (2R,4R)-configuration was assigned to the (-)-trans-2,4-dimethyl-δ-valerolactone (8e). The author thus confirmed that the (2R,4R)-isomer of racemic trans-(**5a**) reacted preferentially with (**3**) and (**4**).

Experimental

The following instrumentation is common to all the experimental parts of this thesis.

^{1}H NMR spectra were measured on a Varian EM-360 (60 MHz) and a Varian VXR-200 (200 MHz), and a JEOL GX-400 (400 MHz) spectrometer. ^{13}C NMR spectra were recorded on a JEOL JNM-FX 100 (25 MHz), and a Varian VXR-200 (50 MHz), and a JEOL GX-400 (100 MHz) spectrometer. Deuteriochloroform was used as the solvent with tetramethylsilane as an internal standard for NMR spectra unless otherwise specified. IR spectra were measured on a Hitachi 215 spectrophotometer. Elemental analyses were performed on a Yanaco MT-3. Mass spectra were recorded on a JEOL JMS-DX-300. A Perkin-Elmer 241 polarimeter was used for measuring optical rotations. A Jasco Model J-20 spectropolarimeter was employed for CD spectra. GLC analyses were performed on a Shimadzu GC-4B equipped with a flame ionization detector. A Varian model 920 gas chromatograph equipped with a thermal conductivity detector was used for preparative GLC. HPLC analyses were carried out on a Jasco BIP-I chromatograph system [column: silica gel NUCLEOSIL 50-5, 25cm x 4mm]. Data-processing was performed on a Hitachi M833 Chromato-Processor. The products were isolated through bulb-to-bulb distillation on a Büchi Kugelrohr apparatus or by column chromatography on silica gel [Kieselgel 60 (230-400 mesh), Merck Co., Ltd.]. Melting and boiling points were uncorrected.

Diethyl ether and THF were dried by distillation from sodium wire immediately before use, using benzophenone ketyl as an indicator. Benzene, toluene, CH_2Cl_2, MeOH, and EtOH were distilled over calcium hydride and stored over molecular sieves type 4Å.

Preparation of Binaphthyldiamine Derivatives

(S)-(-)-2,2'-Diamino-1,1'-binaphthyl (1) was prepared according to the procedure reported by Clemo;[23] $[\alpha]_D^{25}$ -151.5° (c 1.47, pyridine) [lit.[24] $[\alpha]_D^{20}$ +149.5° (c 1.482, pyridine) for optically pure (R)-isomer[67]].

(S)-2-Trifluoroacetylamino-2'-amino-1,1'-binaphthyl(2). Trifluoroacetic anhydride (1.62 g, 7.7 mmol) was added at 0°C to a mixture of (S)-(1) (2.0 g, 7.0 mmol), trifluoroacetic acid (5.4 mL), and CH_2Cl_2 (10 mL). The mixture was stirred at room temperature overnight and poured into sat. $NaHCO_3$ (50 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined extracts were washed with sat. NaCl (50 mL) and dried over anhydrous Na_2SO_4. After evaporation, the residue was subjected to silica gel column chromatography (hexane-AcOEt, 93:7) to afford (S)-(2) as an amorphous powder (1.8 g, 67% yield): $[\alpha]_D^{25}$ +29.0° (c 0.99, $CHCl_3$); MS m/e 380(M^+); ^1H NMR (60 MHz) δ 3.7 (br s, 2H, NH_2), 6.7-8.2 (m, 12H, aromatic protons), 8.50 and 8.66 (2 x s, 1H, NHCO). IR(KBr) 3380, 1730, 1620, 1530,

1505, 815, and 755 cm^{-1}.

(S)-2-Piperidino-2'-amino-1,1'-binaphthyl (3). To a solution of (S)-(**1**) (2.0 g, 7.0 mmol) in a mixture of DMF (8 mL) and acetonitrile (25 mL), were added sodium cyanoborohydride (0.44 g, 7.0 mmol) and an aqueous solution of glutaraldehyde (25%, 2.8 mL, 7.0 mmol) with ice-cooling. The mixture was then stirred at room temperature for 2 h with maintaining the pH around 7 by adding a solution of acetic acid (1.3 g, 21 mmol) in acetonitrile (5 mL). After stirring overnight, 3N HCl (50 mL) was added to the mixture and the resulting acidic solution was washed with ether (30 mL). The aqueous layer was made alkaline with 15% NaOH and extracted with CH_2Cl_2 (3 x 50mL). The combined extracts were washed with sat. NaCl and dried over anhydrous Na_2SO_4. After evaporation, the residue was subjected to silica gel column chromatography (hexane-AcOEt, 86:14) to afford (**3**) as an amorphous powder (0.95 g, 38% yield): $[\alpha]_D^{20}$ -12.3° (c 1.97, $CHCl_3$); MS m/e 352 (M^+); ^1H NMR (60 MHz) δ 0.9-1.5 [m, 6H, $(CH_2)_3$], 2.8-3.1 [m, 4H, $N(CH_2-)_2$], 3.7 (br s, 2H, NH_2), 6.9-8.1 (m, 12H, aromatic protons). IR (KBr) 3380, 1620, 1505, 810, and 750 cm^{-1}.

(S)-2-Morpholino-2'-amino-1,1'-binaphthyl (4). Ozone gas was passed through a solution of 2,5-dihydrofuran (1.12 g, 16 mmol) in MeOH (25 mL) at -60°C until a permanent blue color persisted. The excess ozone was expelled by passing argon gas into the reac-

tion mixture at -60°C for 20 min. To this MeOH solution was added a solution of (**1**) (4.3 g, 15 mmol) and sodium cyanoborohydride (3.0 g, 48 mmol) in DMF (30 mL) at -50°C. The mixture was stirred at 0°C for 2.5 h with adding acetic acid (8.6 g, 0.14 mol) portionwise to maintain the pH around 7. After evaporation, the residue was treated with 5% NaOH (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined extracts were washed with sat. NaCl and dried over anhydrous Na_2SO_4. After evaporation, the residue was subjected to silica gel column chromatography (hexane—isopropyl alcohol, 97:3) to give (**3**) as an amorphous powder (2.3 g, 42% yield): $[\alpha]_D^{25}$ -53.3° (c 1.1, $CHCl_3$); MS m/e 354(M^+); ^1H NMR (60 MHz) δ 2.8-3.1 [m, 4H, $N(CH_2-)_2$], 3.1-3.4 (m, 4H, $O(CH_2-)_2$), 3.6 (br s, 2H, NH_2), 6.9-8.2 (m, 12H, aromatic protons); IR (KBr) 3360, 1620, 1510, 820, and 750 cm^{-1}.

Preparation of Cyclic Acid Anhydrides (5a-d)

cis-2,4-Dimethylglutaric anhydride [cis-(5a)] was prepared according to the procedure of Wiley[25] with modification using ethyl methacrylate instead of ethyl α-bromoisobutyrate; yield 23.0 g (23.4 %): mp 92.5-93°C (lit.[25] mp 95-95.5°C); ^1H NMR (60 MHz) δ 1.35 (d, 6H, 2 x CH_3), 1.61-2.30 (m, 2H, CH_2), 2.40-3.12 (m, 2H, 2 x CH). The purity was confirmed with GLC (5% XE-60, 130°C).

trans-2,4-Dimethylglutaric anhydride [trans-(5a)] was obtained from the mother liquor from which cis-(5a) was crystallized out. After evaporation of the mother liquor, the residual crude trans-(5a) was hydrolyzed in boiling water (2 h); the resulting diacid was recrystallized from AcOEt three times (mp 140-141°C). Treatment with acetic anhydride (100°C, 1 h) and distillation afforded trans-(5a); bp 152-154°C/20mmHg: ^{1}H NMR (60 MHz) δ 1.43 (d, J=7.6Hz, 6H, 2 x CH_3), 1.96 (t, J=6.6Hz, 2H, CH_2), 2.7-3.1 (m, 2H, 2 x CH). The purity was confirmed with GLC (5% XE-60, 120°C).

3-Hydroxy-3-methylglutaric anhydride (5b).[26] Yield 1.62 g (39.4%): recrystallization from $CHCl_3$; mp 101-102°C; ^{1}H NMR (60 MHz, $CDCl_3$ and acetone-d_6) δ 1.49 (s, 3H, CH_3), 2.56-3.16 (m, 4H, 2 x CH_2), 4.25 (br s, 1H, OH); IR (KBr) 3530(br, OH), 1810, and 1775(C=O) cm^{-1}.

3-Isopropylglutaric anhydride (5c) was prepared from isobutyraldehyde and cyanoacetamide according to the procedure reported by Nelson;[27] yield 10.1 g (27.0 %): bp 112-115°C/0.5mmHg; ^{1}H NMR (60 MHz) δ 1.00 (d, J=6.8Hz, 2 x CH_3), 1.40-2.20 (m, 2H, 2 x CH), 2.28-3.15 (m, 4H, 2 x CH_2).

cis-1,2-Cyclopropanedicarboxylic anhydride (5d):[28] recrystallization from CH_2Cl_2-hexane; yield 14 g (58 %); mp 96-97°C; ^{1}H NMR (60MHz) δ 1.5-1.8 (m, 2H, CH_2), 2.7-2.95 (m, 2H, 2 x CH).

Asymmetric Ring-Opening of Cyclic Acid Anhydrides (5a-c)

Typical Procedure. A solution of cis-(**5a**) (0.49 g, 3.5 mmol) in dry benzene (15 mL) was added to a solution of the amine (**1**) (1.0 g, 3.5 mmol) in dry benzene (35 mL) at room temperature. After stirring at room temperature overnight, the reaction mixture was treated with a ethereal solution of diazomethane. The mixture was evaporated and subjected to silica gel column chromatography (hexane-AcOEt, 80:20) to afford each diastereomer of (**7a**).

(2S,4R)-(**7a**): yield 0.24 g (15.5 %), amorphous powder; $[\alpha]_D^{25}$ -50.0° (c 1.03, $CHCl_3$); MS m/e 440(M^+); ^1H NMR (100 MHz) δ 0.82 and 0.96 (2 x d, J=7.2Hz, 6H, 2 x CH_3), 1.0-1.4, 1.7-2.1, and 2.2-2.5 [m, 4H, -CH(CH_3)CH_2CH(CH_3)-], 3.48 (s, 3H, OCH_3), 3.8 (br s, 2H, NH_2), 6.8-8.0 (m, 12H, aromatic protons), 8.43 and 8.52 (2 x s, 1H, NHCO).

(2R,4S)-(**7a**): yield 0.69 g (44.5 %), crystalline mass, mp 149-150°C; $[\alpha]_D^{25}$ -52.6° (c 1.07, $CHCl_3$); MS m/e 440(M^+); ^1H NMR (100 MHz) δ 0.77 and 0.94 (2 x d, J=7.2Hz, 6H, 2 x CH_3), 1.1-1.3 and 1.5-2.4 [m, 4H,-CH(CH_3)CH_2CH(CH_3)-], 3.4 (br s, 2H, NH_2), 3.51 (s, 3H, OCH_3), 6.8-8.1 (m, 12H, aromatic protons), 8.50 and 8.59 (2 x s, 1H, NHCO).

Synthesis of Optically Active Lactones (8a-e)

(2R,4S)-2,4-Dimethyl-δ-valerolactone (8a). cis-2,4-Dimethylgluta-

ric anhydride [cis-(**5a**), 0.19 g, 1.3 mmol] was added to a solution of the amine (**3**) (0.47 g, 1.3 mmol) in dry toluene (15 mL) at -20°C. The mixture was allowed to stand at -20°C for 3 days and then treated with diazomethane to yield a diastereomeric mixture of (**7c**). Lithium chloride (0.17 g, 3.9 mmol) and sodium borohydride (0.15 g, 3.9 mmol) were added successively to a solution of (**7c**) in dry EtOH (10 mL) at 0°C. The mixture was then heated at 50°C for 24 h. After cooling, 3N HCl (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined extracts were washed with sat. NaCl, dried over anhydrous Na_2SO_4, and evaporated. Dilute sulfuric acid (2N, 20 mL) and dioxane (4 mL) were added to the residue, and the mixture was heated at 80°C for 2 h. After cooling, the solution was extracted with ether (5 x 30 mL). The combined extracts were washed successively with 3N HCl three times and with sat. NaCl, and then dried over anhydrous Na_2SO_4. Evaporation gave (**8a**) as an oil (0.16 g, 77 % yield). An analytical sample was obtained by preparative GLC (10% SE-30, 150°C): $[\alpha]_D^{23}$ -37.8° (c 1.3, $CHCl_3$) [lit.[5b] $[\alpha]_D^{25}$ -41.1° (c 5-10, $CHCl_3$) for optically pure (2R,4S)-(**8a**)], 92% e.e.; ^1H NMR (60 MHz) δ 1.0 (d, J=6.4Hz, 3H, CH_3), 1.28 (d, J=6.8Hz, 3H, CH_3), 1.1-1.6 (m, 1H), 1.81-2.77 (m, 3H), 3.70-4.50 (m, 2H, CH_2O); IR (NaCl) 1740(C=O) cm^{-1}.

Optically pure (2R,4S)-(**8a**) was obtained from (2R,4S)-(**7a**) as follows: acetic anhydride (0.29 g, 2.8 mmol) and triethylamine (0.28 g, 2.8 mmol) were added to a solution of (2R,4S)-(**7a**) (0.60

g, 1.4 mmol) in CH_2Cl_2 (5 mL) at 0°C. The mixture was stirred at room temperature overnight. After adding sat. $NaHCO_3$ (10 mL), the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined extracts were washed with sat. NaCl and dried over anhydrous Na_2SO_4. Evaporation gave the acetylated (**7a**) (0.63 g). This product was reduced and hydrolyzed as above to afford optically pure (2R,4S)-(**8a**); yield 0.08g (46 %): $[\alpha]_D^{25}$ -42.4° (c 1.75, $CHCl_3$).

(R)-Mevalonolactone (8b). To a solution of 3-hydroxy-3-methylglutaric anhydride [(**5b**), 0.29 g, 2.0 mmol] in dry CH_2Cl_2 (30 mL) was added the amine (**4**) (0.79 g, 2.0 mmol) at -20°C. The mixture was allowed to stand at -20°C for 7 days. After treating with diazomethane, the resulting amide-ester (**7f**) was reduced as described in the preparation of (**8a**). After working up, alkaline hydrolysis was carried out using 10% KOH in MeOH (20 mL) at 60°C for 4 h. After the pH of the solution was adjusted to 7.0 with 2N H_2SO_4, MeOH was evaporated under reduced pressure. The residual aqueous solution was adjusted to pH 3 with 2N H_2SO_4 and then continuously extracted with ether for 3 days. The extract was dried over anhydrous Na_2SO_4 and evaporated. The extract was subjected to preparative TLC (silica gel, benzene-AcOEt, 3:1) to afford (**8b**) as a syrup (0.11 g, 44% yield): $[\alpha]_D^{25}$ -12.2° (c 6.0, EtOH); ^1H NMR (60 MHz) δ 1.55 (s, 3H, CH_3), 2.06 (m, 2H, CH_2CO), 2.74 (m, 2H, CH_2O), 3.14 (br s, 1H, OH), 4.28-4.99 (m, 2H, CH_2O). The e.e. of (**8b**) was determined by ^1H NMR (400 MHz) in the pres-

ence of a chiral shift reagent, tris[3-(heptafluorohydroxymethylene)-(+)-camphorato], europium (III) [Eu(hfc)$_3$][29] and found to be 58 % e.e.

(R)-3-Isopropyl-δ-valerolactone (8c). 3-Isopropylglutaric anhydride [(**5c**), 0.23 g, 1.5 mmol] was added to a solution of the amine (**2**) (0.5 g, 1.3 mmol) in dry toluene (10 mL) at room temperature. After stirring overnight, the reaction mixture was treated with diazomethane. The resulting mixture (**7h**) was subjected to reduction followed by acidolysis by the same procedure as for the preparation of (**8a**) to give the lactone (**8c**) as a colorless oil (0.05 g, 38 % yield): $[\alpha]_D^{25}$ +7.1° (c 0.83, EtOH) [lit.[35] $[\alpha]_D^{24}$ +16.3° (c 1.037, EtOH) for (R)-(**8c**) with 96.6% optical purity], 42% e.e.; ^{1}H NMR (60 MHz) δ 0.95 (d, J=6.0Hz, 6H, 2 x CH_3), 1.2-2.8 (m, 6H, 2 x CH and 2 x CH_2), 4.1-4.9 (m, 2H, CH_2O).

(2R,3S)-2,3-methylene-γ-butyrolactone (8d). 1,2-Cyclopropanedicarboxylic anhydride (**5d**) (0.40 g, 3.6 mmol) was added to a solution of the amine (**2**)(1.14 g, 3.0 mmol) in dry toluene (15 mL) at room temperature. After stirring overnight, diazomethane was added. By the same treatment as described in the synthesis of (**8c**) from (**7c**), the amide-ester (**7j**) was converted to (**8d**) (0.19 g, 65% yield): $[\alpha]_D^{25}$ +28.0° (c 6.41, $CHCl_3$) [lit.[4b] $[\alpha]_D$ -61.8° (c 6.6, $CHCl_3$) for optically pure (2S,3R)-(**8d**)], 46% e.e.; ^{1}H NMR

(60 MHz) δ 0.75-1.55 (m, 2H, CH_2), 1.9-2.55 (m, 2H, 2 x CH_2), 4.1-4.6 (m, 2H, CH_2O).

(2R,4R)-Dimethyl-δ-valerolactone (8e) through kinetic resolution. To a solution of the amine (**3**) (0.53 g, 1.5 mmol) in dry toluene (25 mL) was added racemic trans-(**5a**) (1.1 g, 7.5 mmol) at -20°C. After stirring at -20°C for 2 days, diazomethane was added to the reaction mixture. The mixture was evaporated and the residue was treated with a solution of n-propylamine (0.47 g, 7.9 mmol) in CH_2Cl_2 (3 mL) at room temperature for 1 h to remove unreacted trans-(**5a**). The mixture was washed with sat. $NaHCO_3$ three times and dried over anhydrous Na_2SO_4. Evaporation gave the amide-ester (**7k**) whose diastereomeric ratio was found to be 87:13 (HPLC). Reduction and hydrolysis of (**7k**) by the same procedure for the preparation of (**8a**) gave the lactone (**8e**) as an oil (0.09 g, 47% yield): bp 135°C/15mmHg, $[\alpha]_D^{20}$ -60.1° (c 2.13, $CHCl_3$), 74% e.e. calculated from the diastereomeric ratio in (**7k**); ^1H NMR spectrum (400 MHz) was depicted in Fig.1.

CHAPTER 3

CATALYTIC ASYMMETRIC RING-OPENING OF PROCHIRAL OR MESO-CYCLIC ACID ANHYDRIDES, USING CINCHONA ALKALOIDS AS CATALYSTS

3-1. Introduction

In recent years, catalytic process has been a most intense area of research in asymmetric synthesis, because a small amount of a chiral catalyst affords a large number of chiral molecules in an enantiomeric form, but not in a diastereomeric form.

This process has been extensively developed in asymmetric hydrogenation,[30] epoxidation,[31] and carbonyl addition;[32] however, these asymmetric reactions are all based on enantio-face differentiation. In the field of enantiotopic group differentiation, on the other hand, very few catalytic processes have been so far developed except the enzymatic catalyses in enantioselective hydrolysis of prochiral or meso-diesters.[3),5)-9)]

In the preceding chapter, the author described the asymmetric ring-opening of prochiral or meso-cyclic acid anhydrides. This reaction was a chemical method for differentiating enantiotopic carboxyl groups of α,ω-symmetric diacids; however, the reaction was stoichiometric and required an equimolar amount of optically active binaphthyldiamines as a chiral reagent. Very few catalytic reactions for these cyclic acid anhydrides have been so

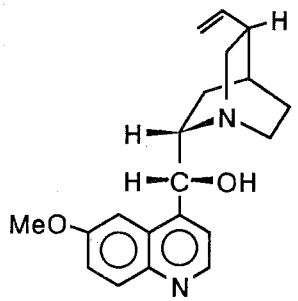
far reported except the work presented by Yoshikawa et al.[33] They effected an asymmetric hydrogenation of prochiral or meso-cyclic acid anhydrides, using a chiral ruthenium complex as a catalyst. The reaction, however, required a drastic condition; the chemical and optical yields were both unsatisfactory. Hence, it would be desirable to develop a catalytic process in the asymmetric ring-opening of prochiral or meso-cyclic acid anhydrides.

The author found that a catalytic amount of triethylamine effectively catalyzed the alcoholysis of glutaric anhydride to yield the corresponding half-esters quantitatively. This reaction could provide optially active half-esters if prochiral or meso-cyclic acid anhydrides are ring-opened with alcohols, using a chiral tertiary amine as a catalyst. On the basis of this conception, the author undertook a catalytic and asymmetric methanolysis of prochiral or meso-cyclic acid anhydrides with chiral tertiary amines as the catalysts.

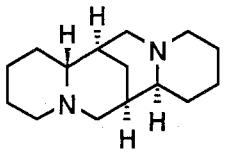
3-2. Results and Discussion

As a preliminary experiment, the author chose the methanolysis of cis-2,4-dimethylglutaric anhydride (**1a**) as a standard reaction and examined the catalytic activity of naturally occurring chiral alkaloids such as quinine, sparteine, and brucine for this reaction. Quinine is a well known representative of cinchona alkaloid and its properties as a chiral base-catalyst have been

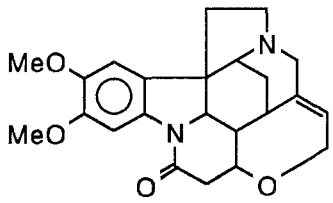
well appreciated in a number of base-catalyzed asymmetric synthesis.[34]



quinine



sparteine



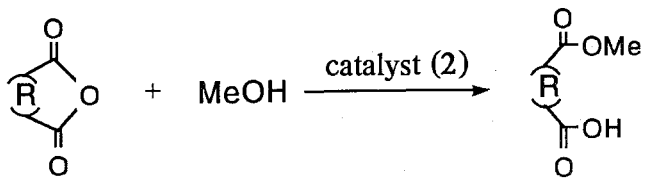
brucine

As will be described later in detail, quinine showed marked rate-enhancement with fairly good stereoselectivity, yielding optically active cis-2,4-dimethylglutaric acid monomethylester quantitatively. Sparteine and brucine, on the other hand, exhibited fair to moderate rate-enhancement but with no notable stereoselectivity.

On this basis, the author examined the catalytic activity of all the diastereomers of cinchona alkaloid (**2a-h**) and the related chiral amines (**2i,j**) shown in Fig. 1 for the methanolysis of the prochiral or the meso-cyclic acid anhydrides (**1a-f**).

The anhydrides (**1a-e**) were prepared according to the reported procedure cited below, and the compound (**1f**) was commercially available.

The erythro-bases (**2a-d**) are also commercially available. The threo-bases (**2e-h**), which are the C(9)-epimers of the erythro-bases (**2a-d**) respectively, were prepared from (**2a-d**) by



(1a-f) (3a-f)

a: R = *cis*-CH(Me)CH_2CH(Me)-

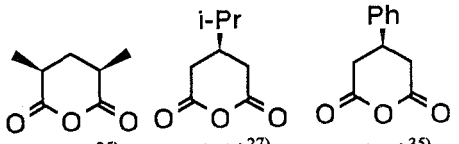
b: R = -CH_2CH(i-Pr)CH_2-

c: R = -CH_2CH(Ph)CH_2-

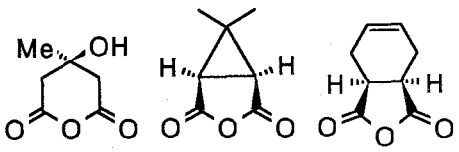
d: R = -CH_2C(OH)(Me)CH_2-

e: R = *cis*-CHC(Me)$_2$CH-

f: R = *cis*-CHCH$_2$CH=CHCH$_2$CH-

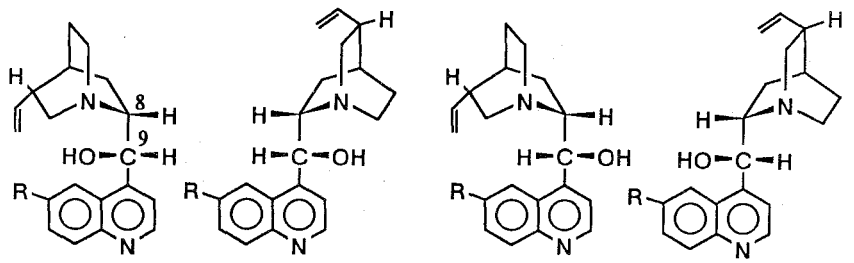


(1a)[25] (1b)[27] (1c)[35]



(1d)[26] (1e)[36] (1f)

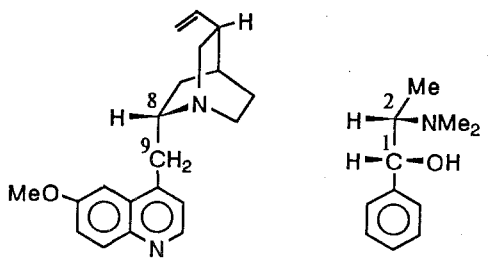
Scheme 1



(8*R*,9*S*) *erythro* (8*S*,9*R*) *erythro* (8*R*,9*R*) *threo* (8*S*,9*S*) *threo*

R=H cinchonine (2a) cinchonidine (2c) epicinchonine (2e) epicinchonidine (2g)

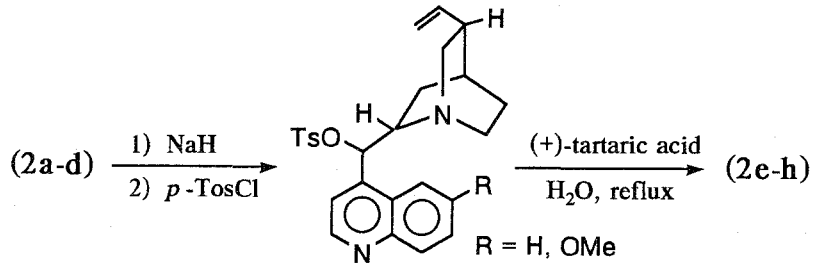
R=OMe quinidine (2b) quinine (2d) epiquinidine (2f) epiquinine (2h)



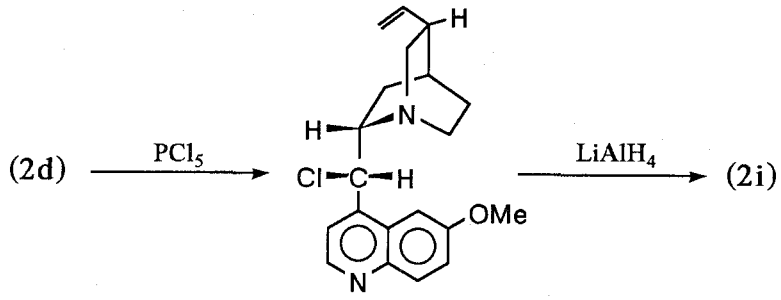
deoxyquinine (2i) (1*R*,2*S*)-(2j)

Fig. 1

the inversion of the C(9)-hydroxyl group via the corresponding tosylates according to the reported procedure by Suszko and Szelag.[37] They reported that the tosylate of (**2d**) was prepared by treating (**2d**) with p-toluenesulfonyl chloride in the presence of pyridine or sodium hydroxide as a base; however, the author failed to synthesize the tosylates of (**2a-d**) by this method. The author hence converted the alkaloids (**2a-d**) in advance into the corresponding alkoxides with sodium hydride and then treated them with p-toluenesulfonyl chloride, thus obtaining the tosylates of (**2a-d**) in good yields. Deoxyquinine (**2i**) was synthesized by $LiAlH_4$-reduction of epichloroquinine prepared by treating quinine (**2d**) with phosphorus pentachloride according to the reported procedure.[38]

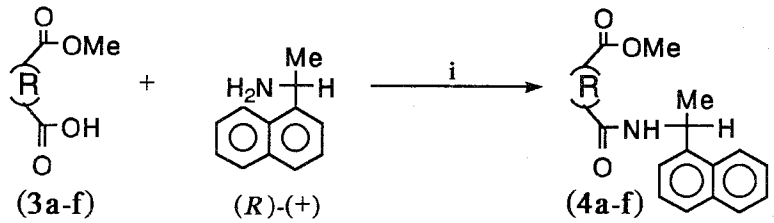


tosylate of (**2a-d**)



epichloroquinine

The acid anhydrides (**1a-f**) were allowed to react with methanol (4-20 molar equiv.) in the presence of the alkaloids (**2a-j**) (0.1-0.2 molar equiv.) in dry toluene or dry diethyl ether at room temperature to yield the corresponding chiral half-esters (**3a-f**) (Scheme 1). The consumption of (**1**) and the formation of (**3**) were monitored with GLC or TLC. Without catalysts, the anhydrides (**1a-f**) were virtually inactive to methanol under the reaction conditions employed: no product (**3**) was detected with GLC after 3 days. To determine the enantiomeric excess (e.e.) of the product half-esters (**3a-f**), they were converted without isolation into the corresponding diastereomeric amide-esters (**4a-f**) with (R)-1-(1-naphthyl)ethylamine (1.1 molar equiv.) by the aid of thionyl chloride (1.2 molar equiv.) and triethylamine (3.0 molar equiv.) in dry toluene (Scheme 2).



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

The diastereomeric ratio in (**4**) was successfully determined by HPLC and/or ^1H NMR (diastereomeric $CO_2\underline{Me}$ protons), and thereby the enantiomeric ratio in (**3**) was determined easily. Racemic (**3a**), which was prepared by the triethylamine-catalyzed methanolysis of the anhydride (**1a**), showed 0 - 1.5% e.e. by this method;

these values did not change when racemic (**3a**) was converted into (**4a**) in the presence of the chiral amine (**2a**). This method hence allows the e.e. of the half-ester (3) to be determined without isolation within an error of ±1.5% e.e. for less than 0.1 mmol scale of the reaction.

The results are summarized in Table 1. The preferentially attacked carbonyl group, i.e. the direction of stereoselection, was determined from the absolute configuration of the optically active lactones (**5a-f**) derived from the half-esters (**3a-f**), respectively (vide infra). Toluene or diethyl ether was the solvent of the author's choice in all the small-scale reactions, because non-polar solvents such as toluene and diethyl ether gave good results in the light of both the reactivity and the stereoselectivity of the reaction as described later (Table 3).

The erythro-bases (**2a-d**) showed high catalytic activity for all the anhydrides examined, particularly 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; the e.e. of the half-ester (**3a**) was found to be 56%. Reducing the amount of methanol slowed down the reaction, but improved the extent of stereoselection up to 70% e.e. (entry 2).

One striking feature of the results in Table 1 is that the threo-bases (**2e-h**) had practically no activity for (**1a**); besides, the e.e. of the product was extremely low (entry 6-9). As to rate-enhancement, the threo-bases (**2e-h**) were inferior to the

Table 1. Ring-opening of the Cyclic Acid Anhydrides (1) with Methanol, Catalyzed by the Chiral Amines (2)[a]

Entry	Anhydrides	Amines	MeOH (mmol)	Time[b] (day)	E.e.[c] (%)	Selectivity[d]
1	(1a)	(2a)	2.0	1	56	(*S*)-side[e]
2	(1a)	(2a)	0.4	4	70	(*S*)-side[e]
3	(1a)	(2b)	0.4	4	67	(*S*)-side[e]
4	(1a)	(2c)	0.4	4	64	(*R*)-side[e]
5	(1a)	(2d)	0.4	4	60	(*R*)-side[e]
6	(1a)	(2e)	1.0	12 (29%)	5.4	(*R*)-side[e]
7	(1a)	(2f)	1.0	12 (16%)	1.8	(*R*)-side[e]
8	(1a)	(2g)	1.0	12 (21%)	4.0	(*R*)-side[e]
9	(1a)	(2h)	1.0	12 (4%)	6.2	(*R*)-side[e]
10	(1a)	(2i)	1.0	8	0.7	-
11	(1a)	(2j)	2.0	5	8.8	(*R*)-side[e]
12	(1a)	sparteine	1.0	2	2.6	(*S*)-side[e]
13	(1a)	brucine	2.0	7	6.4	(*S*)-side[e]
14	(1b)	(2a)	1.0	1	23	*pro-R*
15	(1b)	(2b)	1.0	1	19	*pro-R*
16	(1b)	(2c)	1.0	1	6.3	*pro-S*
17	(1b)	(2d)	1.0	1	6.8	*pro-S*
18	(1b)	(2e)	1.0	12 (89%)	13	*pro-R*
19	(1b)	(2f)	1.0	12 (90%)	11	*pro-R*
20	(1b)	(2g)	1.0	12 (90%)	5.4	*pro-S*
21	(1b)	(2h)	1.0	12 (88%)	5.3	*pro-S*
22	(1c)	(2a)	1.0	1	33	*pro-R*
23	(1c)	(2b)	1.0	1	48	*pro-R*
24	(1c)	(2c)	1.0	1	7.8	*pro-S*
25	(1c)	(2d)	1.0	1	7.4	*pro-S*
26	(1c)	(2e)	1.0	12	10	*pro-R*
27	(1c)	(2f)	1.0	12	10	*pro-R*
28	(1c)	(2g)	1.0	12	2.2	*pro-S*
29	(1c)	(2h)	1.0	12	5.1	*pro-S*
30	(1d)[f]	(2a)	2.0	1	28[g]	*pro-R*
31	(1d)[f]	(2b)	2.0	1	48[g]	*pro-R*
32	(1d)[f]	(2c)	2.0	1	24[g]	*pro-S*
33	(1d)[f]	(2d)	2.0	1	48[g]	*pro-S*
34	(1d)[f]	(2e)	1.0	3	3.1[g]	*pro-S*

35	(1d)[f]	(2f)	1.0	3	2.2[g]	*pro-S*
36	(1d)[f]	(2g)	1.0	3	0.2[g]	-
37	(1d)[f]	(2h)	1.0	3	3.7[g]	*pro-R*
38	(1e)	(2a)	1.0	7	16	(*R*)-side[e]
39	(1e)	(2b)	1.0	4	32	(*R*)-side[e]
40	(1e)	(2c)	1.0	3	11	(*S*)-side[e]
41	(1e)	(2d)	1.0	3	33	(*S*)-side[e]
42	(1e)	(2e)	1.0	9	60	(*S*)-side[e]
43	(1e)	(2f)	1.0	9	56	(*S*)-side[e]
44	(1e)	(2g)	1.0	9	47	(*R*)-side[e]
45	(1e)	(2h)	1.0	9	52	(*R*)-side[e]
46	(1f)	(2a)	1.0	7[h]	14	(*R*)-side[e]
47	(1f)	(2b)	1.0	7[h]	30	(*S*)-side[e]
48	(1f)	(2c)	1.0	7[h]	18	(*S*)-side[e]
49	(1f)	(2d)	1.0	7[h]	21	(*R*)-side[e]
50	(1f)	(2e)	1.0	7[h]	51	(*R*)-side[e]
51	(1f)	(2f)	1.0	7[h]	52	(*R*)-side[e]
52	(1f)	(2g)	1.0	7[h]	44	(*S*)-side[e]
53	(1f)	(2h)	1.0	7[h]	47	(*S*)-side[e]

[a]Reacion 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 with GLC; 5% XE-60, 130-190°C for (**1a**,**b**,**e**, and **f**); 2% DC-QF-1, 140-170°C for (**1c**,**d**). The conversion yield was quantitative or >95% unless otherwise specified, or shown in parentheses if needed. [c]Determined by HPLC analysis (silica gel; hexane-isopropyl alcohol-NEt_3, 15 : 1 : 0.16) of the corresponding amide-ester (**4**). [d]Indicates the preferentially attacked carbonyl group. [e]Indicates the carbonyl group attached to (*R*) or (*S*)-chiral carbon of the *meso* -anhydride (**1a**,**e**,**f**). [f]Solvent: dry diethyl ether (5 mL). [g]Determined by 400MHz ^1H NMR analysis of (**4d**). [h]The consumption of the reactant (**1f**) was monitored with TLC ($CHCl_3$ - EtOH, 9 : 1).

erythro-bases (2a-d) for all the anhydrides (1) tested: the reactions with the threo-bases proceeded much more slowly than those with the erythro-bases. The threo-bases were also less effective than the erythro-bases as to the stereoselection for the anhydrides (**1b-d**): the extent of the stereoselection with the threo-bases was lower (entry 18-21, 26-29, and 34-37; 0 - 13% e.e.) than that with the erythro-bases (entry 14-17, 22-25, and 30-33; 6 - 48% e.e.). It has been pointed out that the threo-bases (**2e-h**) exhibited lower asymmetric induction than the erythro-bases (**2a-d**) in cyanohydrin formation,[39] thiol-addition to conjugated enones,[40] and 2+2 cycloaddition of ketene to chloral.[41]

For the five-membered anhydrides (**1e,f**), however, the threo-bases (**2e-h**) exhibited higher asymmetric induction (entries 42-45 and 50-53; 44-60% e.e.) than did the erythro-bases (**2a-d**) (entries 38-41 and 46-49; 11-33% e.e.), although the reactions with (**2e-h**) were slower than those with (**2a-d**).

Another notable feature of the reaction is that the stereochemistry of the products was controlled by the configurations at C(8) and C(9) in the alkaloid. For example, the cinchonine (**2a**)—quinidine (**2b**) series having the (8R,9S)-configuration promoted the attack of methanol preferentially on the (S)-side carbonyl group of the anhydride (**1a**), whereas the cinchonidine (**2c**)—quinine (**2d**) series with the (8S,9R)-configuration promoted the (R)-side attack in almost equally high e.e.'s (entry 2, 3 and 4, 5). These configurational biases are applicable not only to the

reactions with other anhydrides (**1b-e**) but also to those catalyzed by the threo-bases (**2e-h**) and (1R,2S)-N-methylephedrine (**2j**), which has the configuration corresponding to the (8S,9R) erythro-bases.

This type of stereocontrol is observed generally in the cinchona alkaloid-catalyzed asymmetric induction such as thiol-addition to α,β-unsaturated carbonyl compounds[40] or nitro olefins,[42] 2+2 cycloaddition of ketene to chloral,[41] and other Michael additions.[43]

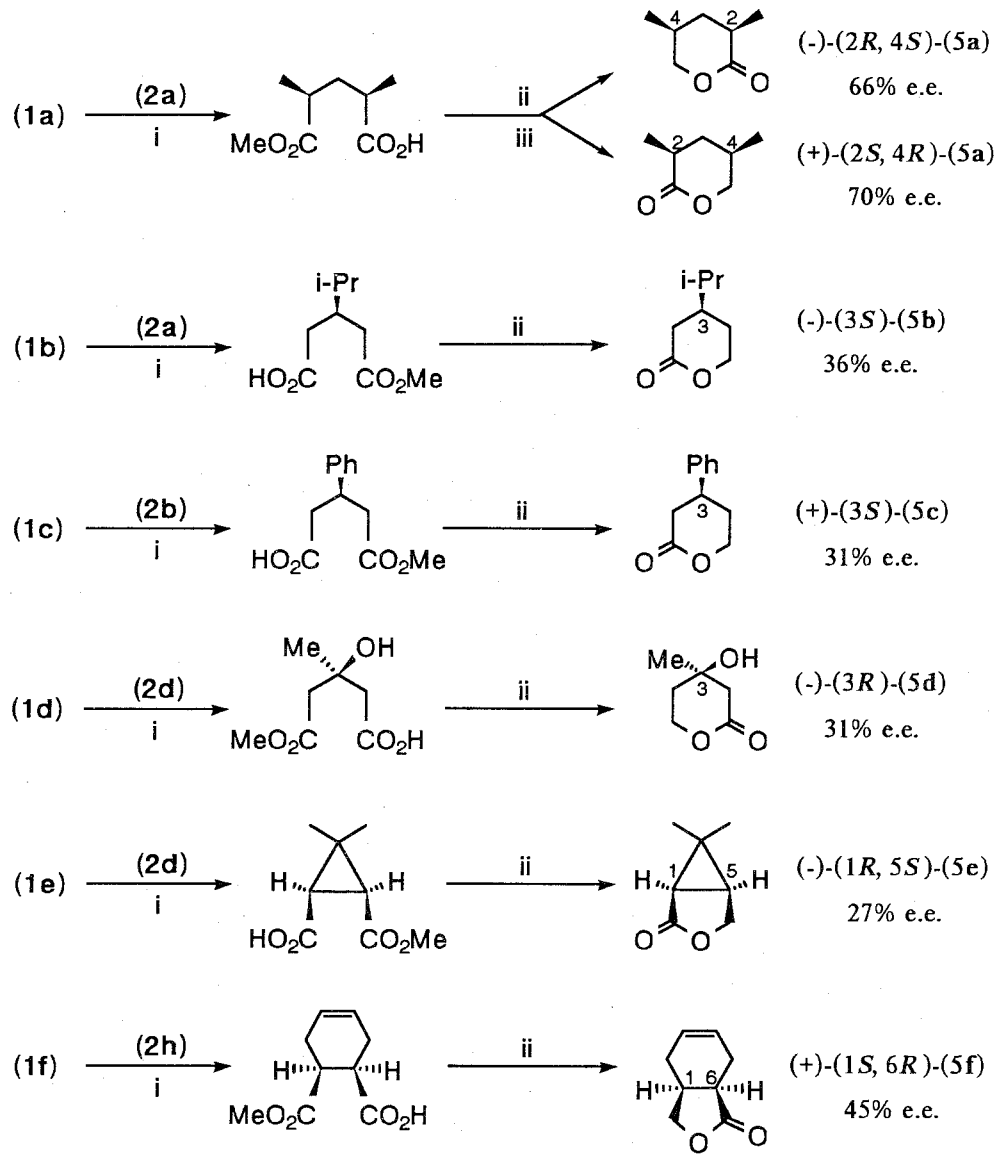
As will be discussed later, the β-hydroxyamine portion at C(8)-C(9) of cinchona alkaloid is the critical site responsible for the catalytic action. Cinchonine (**2a**) and cinchonidine (**2c**), as well as quinidine (**2b**) and quinine (**2d**), are diastereomeric pairs, but enantiomeric at this site (Fig. 1); hence the stereochemistry of the products is determined by the configuration around C(8)-C(9) in the alkaloid molecule. The results with (**1f**), however, deviated from this rule (entry 46-49). The reason for these unexpected results are obscure.

The role of the C(9)-hydroxyl function is critical for the stereoselection. Deoxyquinine (**2i**), which lacks the C(9)-hydroxyl group, showed no stereoselection in the methanolysis of (**1a**) (entry 10), whereas quinine (**2d**) having the C(9)-hydroxyl group arranged in a proper position gave the product (**3a**) with 50% e.e. in the same reaction conditions.

The author effected preparative scale reactions (3 mmol

of substrate) and synthesized the optically active lactones (**5a-f**) (Scheme 3). The chiral half-ester (**3a**) was prepared using (**2a**) as the catalyst; the ester group of (**3a**) was then reduced with lithium borohydride to afford (-)-(2R,4S)-cis-2,4-dimethyl-δ-valerolactone (**5a**) with $[\alpha]_D^{25}$ -27.0° in an overall yield of 56% from (**1a**). The lithium borohydride was successfully prepared in situ from lithium perchlorate and sodium borohydride. The carboxyl group of (**3a**) was also selectively reduced with BH_3-SMe_2 to give the other enantiomer (+)-(2S,4R)-(**5a**) having $[\alpha]_D^{25}$ +28.7° in an overall yield of 48% from (**1a**). The optical purity of (-) and (+)-(**5a**) was calculated from the maximum rotation of $[\alpha]_D^{25}$ -41.1° for (2R,4S)-(**5a**)[5b] and found to be 66 and 70%, respectively. These values were consistent with the e.e. of (**3a**) (66% e.e.) calculated from the diastereomeric ratio in the corresponding amide-ester (**4a**). Either of the enantiomers of the lactone (**5a**) with almost equal optical purity was thus prepared from the identical precursor (**3a**).

The same procedure was applied to the other half-esters (**3b-f**) to yield the optically active lactones (**5b-f**) with 30-50% e.e., respectively. The optical purity of (**5b**) and (**5f**) was determined by HPLC analysis of the corresponding amide-alcohols derived from the lactone (**5b,f**) and (R)-1-(1-naphthyl)ethylamine according to Mori's method[35] (see Experimental). The absolute configuration of the lactones (**5a-f**) thus obtained enabled the direction of the asymmetric induction of each reaction to be



Scheme 3. Reagents and conditions: i, (1) (3 mmol), MeOH (30 mmol), (2) (0.3 mmol), room temperature, dry toluene (150 mL), quantitative yield. ii, LiOH (3 mmol), $LiClO_4$ (15 mmol), $NaBH_4$ (15 mmol), dry THF(85 mL), 50°C, 40 min; iii, BH_3-SMe_2 (3.6 mmol), dry THF (6 mL), 0°C, 1 h.

determined.

Some features of the present ring-opening reaction were investigated, using (**1a**) and (**2a**) as the standard substrate and catalyst, respectively.

First, the author examined the ability of several alcohols as the nucleophile. Table 2 shows the reactivity and the selectivity of methanol, ethanol, 2,2,2-trifluoroethanol, and 2-propanol for the anhydride (**1a**). Methanol was the most reactive nucleophile, whereas 2-propanol was unreactive. It is worth noting that 2,2,2-trifluoroethanol exhibited fairly good reactivity (entry 3) compared with ethanol, although the extent of stereoselection was not as high as those for ethanol or methanol.

Table 2. Reactivity of Alcohols as the Nucleophile[a]

Entry	Alcohol	(mmol)	Time	E.e. (%)	Selectivity[b]
1	Methanol	2.0	36 h	64	(*S*)-side
2	Ethanol	2.0	10 day	56	(*S*)-side
3	CF_3CH_2OH	1.0	43 h	32	(*S*)-side
4	2-propanol	2.0	no reaction[c]	-	-

[a]Conditions: (**1a**) (0.1 mmol), catalyst (**2a**) (0.01 mmol), dry toluene (5 mL), room temperature, quantitative conversion. [b]Indicates the preferentially attacked carbonyl group. [c]No product was detected after 1 week (GLC; 5% XE-60, 160°C).

The reaction was conducted in several kinds of solvents from methanol to benzene with varying polarity of the solvents. The

results are summarized in Table 3.

Table 3. Solvent Effect on the Reaction of (**1a**) with Methanol, Catalyzed by Cinchonine (**2a**)[a]

Entry	Solvent	ε (25°C)	Time	E.e. (%)	Selectivity[c]
1	Methanol[b]	32.7	10 h	5.4	(*S*)-side
2	Ethyl acetate	6.02	5 day	64	(*S*)-side
3	Chloroform	4.64	2 day	44	(*S*)-side
4	Diethyl ether	4.20	12 h	69	(*S*)-side
5	Toluene	2.38	20 h	64	(*S*)-side
6	Toluene[d]	2.38	9 h	46	(*S*)-side
7	Toluene + NEt_4Cl[e]	-	24 h	26	(*S*)-side
8	Benzene	2.28	2 day	58	(*S*)-side

[a]Conditions: (**1a**) (0.1 mmol), catalyst (**2a**) (0.02 mmol), MeOH (1 mmol), solvent (5 mL), room temperature, quantitative conversion. [b]Solvent itself is the nucleophile. [c]Indicates the preferentially attacked carbonyl group. [d]2.5 mL of the solvent. [e]The reaction was conducted in the presence of tetraethyl ammonium chloride (0.02 mmol).

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 when the reaction was conducted in diethyl ether (entry 4). In general, less polar solvents such as toluene or diethyl ether gave favorable results in the light of the reaction rate and the extent of asymmetric induction. The direction of the stereoselection, the preference for the (S)-side attack of methanol, remained unchanged by a change in the reaction medium. When methanol was used as the solvent (entry 1), in which the

solvent itself was the nucleophile, the extent of asymmetric induction was greatly diminished (5.4% e.e.). Surprisingly, the reaction in methanol was much slower than that had been expected from the extremely high concentration of the nucleophile (1240 molar equiv!), compared with that in the standard conditions (10 molar equiv., entry 4). These results suggested that the protic solvent retarded the reaction as well as reduced the stereoselection.

The e.e. of the product was also dependent upon the concentration of the reactant; increasing the substrate-concentration resulted in an increase in the reaction rate and a decrease in e.e. (entry 5 and 6). The addition of a catalytic amount of tetraethylammonium chloride to the reaction mixture also resulted in a great loss in stereoselection (entry 7).

These results described above can be explained by an assumption that hydrogen-bonding between the catalyst and the substrate was important for the stereoselection and that the protic solvent or the ionic species disturbed this specific hydrogen-bonding. Since the lack of the C(9)-hydroxyl function in the catalyst resulted in a complete loss in the stereoselection (Table 1, entry 10), the C(9)-hydroxyl function was responsible for this specific hydrogen-bonding and therefore indispensable to the present asymmetric induction.

Of the two basic moieties in the alkaloid molecule, quinuclidine- or quinoline-ring, which was responsible for the

catalytic activity? In order to identify the catalytic site of cinchonine (2a), the author conducted the methanolysis of (1a) in the presence of (2a), quinuclidine, and quinoline as the catalyst respectively under pseudo-first-order reaction conditions. The reaction was monitored with GLC; the pseudo-first-order reaction rate constants were calculated from the slope of the linear rate plot obtained. The results are compiled in Table 4.

Table 4. Pseudo-first-order Reaction Rate Constant of the Methanolysis of (**1a**) Catalyzed 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

[a]Conditions: (**1a**) (0.2 mmol), catalyst (0.02 mmol), MeOH (4 mmol), dry toluene (5 mL), 25°C, diethyl phthalate as the internal standard (4.32×10^{-2} mmol). The consumption of (**1a**) was monitored with GLC (5% XE-60, 150°C). [b]$k_{spont.}$: spontaneous reaction rate in the absence of the catalyst.

Quinuclidine catalyzed the methanolysis of (1a) as effectively as did cinchonine (2a), whereas quinoline was practically inactive. Therefore the quinuclidine moiety in (2a) was responsible for the catalytic function.

In order to elucidate the mode of the catalytic action, deuterium isotope effect was assessed under pseudo-first-order reac-

tion conditions. The anhydride (**1a**) was subjected to react with a large excess (20 molar equiv.) of methanol or methanol-$\underline{d}_1$ in the presence of cinchonine (**2a**) (0.1 molar equiv.) in dry toluene. The reaction was well simulated by pseudo-first-order kinetics (Fig. 2).

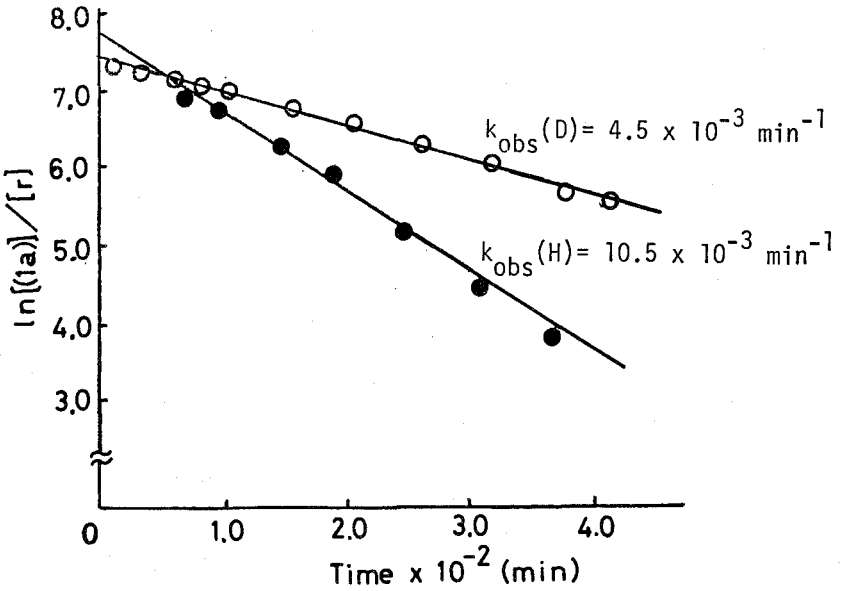


Fig. 2. Plots of ln[(**1a**)]/[r] vs. reaction time for the reaction of (**1a**) (0.2 mmol) with methanol (●) (4 mmol) or methanol-d_1 (○) (4 mmol) catalyzed by cinchonine (**2a**) (0.02 mmol) in dry toluene (5 mL), 25°C; monitored with GLC (5%, XE-60, 150°C). [r]: concentration of the internal standard, diethyl phthalate (8.64×10^{-3} mmol/mL). The observed psedo-first order reaction rate constant, k_{obs} (H) for methanol and k_{obs} (D) for methanol-d_1, was calculated from the slope of each linear rate prot.

The observed pseudo-first-order reaction rate constants, $\underline{k}_{obs}$(H) and $\underline{k}_{obs}$(D), were calculated from the slope of each linear rate plot and found to be 10.5×10^{-3} and 4.5×10^{-3} min^{-1}

, respectively. The deuterium isotope effect [$\underline{k}_{obs}(H)/\underline{k}_{obs}(D)$] was calculated as 2.3. The reported value of deuterium isotope effect in base-catalyzed hydrolysis of acetic anhydride was ca. 3 in which the general-base catalysis was established.[44] Hence the reaction proceeded at the quinuclidine-nitrogen of cinchonine (2a) *via* general-base catalysis, in which alcohols were activated possibly through partial proton-abstraction by the quinuclidine-nitrogen. This is consistent with the fact that the more acidic 2,2,2-trifluoroethanol (pKa 12.4)[45] was more reactive than ethanol (pKa 16.0)[45] (Table 2).

Hiemstra and Wynberg[40] proposed a mechanism for cinchona-alkaloid-catalyzed addition of thiols to conjugated enones, in which the base catalyst activated thiols by proton-abstraction to form an ion-pair (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. Taking into account the acidity of alcohols (pKa 16—18) compared with benzenethiols (pKa 6—8), it seems unlikely to form such a charge separated tight ion-complex between alcohols and the quinuclidine-nitrogen.

Wynberg et al. also observed a large rate difference between the reactions catalyzed by quinine and *O*-acetylquinine in conjugate-addition of benzenethiol to 2-cyclohexenone.[40] They offered an assumption that the hydrogen-bonding between the C(9)-hydroxyl function and the carbonyl oxygen introduced additional polariza-

tion into the carbonyl group of the substrate and facilitated the development of charge on this oxygen in the transition state, compared to the case in which no hydrogen-bonding is present. Considering the present result that quinuclidine exhibited the same catalytic activity as cinchonine (**2a**) for the methanolysis of (**1a**) as shown in Table 4, the C(9)-hydroxyl function has no or little effect on the rate-acceleration in the present ring-opening, although this hydroxyl function is essential for the stereoselection.

As described earlier, threo-bases (**2e-h**) exhibited lower catalytic activity than erythro-bases (**2a-d**). Chekhlor et al. reported that the crystal structure of 10-bromo-10,11-dihydroepi-quinidine, a derivative of epiquinidine (**2f**), revealed a strong intramolecular hydrogen-bonding between the hydroxyl group and the nitrogen in the quinuclidine ring.[46] The intramolecular hydrogen-bonding in epiquinidine (**2f**) and epiquinine (**2h**) was also supported by a large solvent-effect on the chemical shifts in ^{13}C NMR[47] or the H(8)-H(9) vicinal coupling constant (J=9.5Hz) in ^{1}H NMR.[40]

On the other hand, the erythro-bases (**2a-d**) have no intra-molecular hydrogen-bonding. Crystal studies of cinchonine (**2a**)[48a], cinchonidine (**2c**)[48b], and quinidine (**2b**)[48c] indicated that the C(9)-hydroxyl group and the quinuclidine-nitrogen are so positioned that they cannot form the intramolecular hydrogen-bonding between them. Moreover, a crystal structure of quinidine

ethanolate, a 1:1-complex of quinidine and ethanol, revealed that the nitrogen in the quinuclidine ring was hydrogen-bonded to the hydroxyl group of ethanol, instead of being hydrogen-bonded to the C(9)-hydroxyl group intramolecularly.[49] Lack of the intramolecular hydrogen-bonding thus permits the nitrogen in the quinuclidine ring to abstract a proton from alcohols, thereby providing them with enough nucleophilicity to attack the carbonyl group of the anhydrides; hence the catalytic activity of the erythro-bases (**2a-d**) were higher than the threo-bases (**2e-h**). In other words, the low catalytic activity of the latter bases can be attributed to the intramolecular hydrogen-bonding which reduces the basicity of the nitrogen in the quinuclidine ring.

The assumption that the hydrogen-bonding at the quinuclidine-nitrogen diminishes the activity of the catalyst also offers an explanation of the result that excess methanol retarded the ring-opening of (**1a**) (Table 3, entry 1): in this condition, a large excess of methanol forms unfavorable hydrogen bonding between the quinuclidine-nitrogen intermolecularly, thus reducing the basicity of the nitrogen atom.

Experimental

Preparation of the Cyclic Acid Anhydrides (1a-f)

The preparation of the anhydrides (**1a-b, d**) was described in Chapter 2. The anhydride (**1f**) was commercially available and recrystallized from benzene—light petroleum.

3-Phenylglutaric anhydride (1c) was prepared from ethyl cinnamate and diethyl malonate[35], and recrystallized from benzene; yield 15.7 g (53.6 %): mp 107-108 °C; ^{1}H NMR (60 MHz) δ 2.8-3.5 [m, 5H, $C\underline{H}_2C\underline{H}(Ph)C\underline{H}_2$], 7.1-7.6 (m, 5H, aromatic protons).

3,3-Dimethyl-cis-1,2-cyclopropanedicarboxylic anhydride (1e) was prepared from commercially available cis/trans mixture of chrysanthemic acid by ozonolysis and the subsequent cyclization of the resulting cis/trans mixture of 3,3-dimethylcyclopropanedicarboxylic acid with acetic anhydride, resinous solid; yield 3.3 g, (13.2 %): bp 88-94°C/0.4 mmHg; ^{1}H NMR (60 MHz) δ 1.39 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 2.74 (s, 2H, 2 x CH); IR (NaCl) 3100, 2950, 1860, and 1770(C=O) cm^{-1}.

Preparation of the Catalysts (2e-j)

Commercially available cinchonine (**2a**) and cinchonidine (**2c**)

were recrystallized from EtOH. Commercial grade quinine (**2d**) was purified by being converted into its tartrate[68]. Quinidine (**2b**) was purchased and used without further purification.

The threo-bases (**2e-h**) were prepared from the corresponding erythro-bases (**2a-d**) according to the procedure of Suszko[37] but with considerable modification as described below.

Epiquinine (2h); typical procedure. Quinine (**2d**) (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 p-toluenesulfonyl 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 1N HCl (200 mL). After the acidic solution was washed with ether (2 x 100 mL), the aqueous layer was made alkaline with Na_2CO_3 powder (25 g) and extracted with ether (3 x 100 mL). The combined extracts were washed with sat. NaCl and dried over anhydrous Na_2SO_4. After evaporation, the residual syrup (4.53 g) was subjected to silica gel column chromatography ($CHCl_3$-MeOH, 40:1) to afford **O-tosylquinine** as a colorless syrup (2.03 g, 46% yield): $[\alpha]_D^{26}$ +12.7° (c 1.10, EtOH). Found: C, 65.58; H, 6.22; N, 5.59. Calcd for $C_{27}H_{30}N_2O_4S \cdot H_2O$: C, 65.30; H, 6.50; N, 5.64%. ^1H NMR (60 MHz) δ 1.50-3.20 (m, 11H), 2.16 (s, 3H), 3.90 (s, 3H),

4.8-5.1 (m, 2H), 5.6-6.2 (m, 2H), 6.75 (d, J=8.0Hz, 2H), 7.1-7.4 (m, 5H), 7.85 (d, J=9.2Hz, 1H), 8.50 (d, J=4.4Hz, 1H).

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 (300 mg) and extracted with ether (4 x 70 mL). The combined extracts were washed with sat. $NaHCO_3$; an usual work-up gave a syrup (0.86 g). Purification with preparative TLC on silica gel (Chromatotron; hexane—$CHCl_3$—MeOH—triethylamine, 20:20:1:1) yielded epiquinine (**2h**) as a colorless syrup (0.74 g, 84 % yield): $[\alpha]_D^{28}$ +39.9° (c 1.13, EtOH) [lit.[69] $[\alpha]_D^{22}$ +43.3° (c 0.949, EtOH)]. Found: C, 73.14; H, 7.42; N, 8.54. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.05; H, 7.46; N, 8.63%. MS m/e 324 (M^+, 6%). ^1H NMR (400 MHz) 0.94-1.73 [m, 5H, CH_2CHCH_2 and $CH(CH_2CH=CH_2)$], 2.33 (m, 1H, CH_2CHCH_2), 2.77-3.30 [m, 5H, $CHN(CH_2-)CH_2-$], 3.94 (s, 3H, OCH_3), 4.20 (br s, 1H, OH), 5.0 (m, 3H, CHOH and $CH=CH_2$), 5.74 (m, 1H, $-CH=CH_2$), 7.38 (dd, J=9.27 and 2.93Hz, 1H, 7'-H), 7.41 (d, J=4.39Hz, 1H, 3'-H), 7.66 (d, J=2.44Hz, 1H, 5'-H), 8.04 (d, J=9.27Hz, 1H, 8'-H), and 8.74 (d, J=4.39Hz, 1H, 2'-H). ^{13}C NMR (100 MHz) δ 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 ppm.

Epicinchonine (2e): a colorless syrup, $[\alpha]_D^{26}$ +114.5 (c 1.07, EtOH) [lit.[69] $[\alpha]_D^{22}$ +120.3° (c 0.806, EtOH)]. Found: C, 77.08;

H, 7.53; N, 9.37. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N,9.52%. ^1H NMR (400 MHz) δ 1.0-2.4 [m, 6H, $C\underline{H}_2C\underline{H}C\underline{H}_2$ and $C\underline{H}(CH_2CH{=}CH_2)$], 3.05 [m, 5H, $C\underline{H}N(C\underline{H}_2\text{-})C\underline{H}_2\text{-}$], 3.96 (br s, 1H, OH), 5.2 (m, 3H, $C\underline{H}OH$ and $CH{=}C\underline{H}_2$), 5.90 (m, 1H, $C\underline{H}{=}CH_2$), 7.53 (d, $\underline{J}$=4.40Hz, 1H, 3'-H), 7.57-7.73 (m, 2H, 6'-H and 7'-H), 8.14 (d, $\underline{J}$=8.30Hz, 1H, 5'-H), 8.33 (d, $\underline{J}$=7.81Hz, 1H, 8'-H), and 8.90 (d, $\underline{J}$=4.40Hz, 1H, 2'-H). ^{13}C NMR (100 MHz) δ 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 ppm.

Epiquinidine (2f): a colorless syrup, $[\alpha]_D^{26}$ +96.3° (c 1.15, EtOH) [lit.[69] $[\alpha]_D^{19}$ +102.4° (c 0.865, EtOH)]; MS m/e 324 (M^+, 5.7%); ^1H NMR (400 MHz) δ 1.04—1.74 [m 5H, $C\underline{H}_2CHC\underline{H}_2$ and $C\underline{H}(CH_2CH{=}CH_2)$], 2.34 (m, 1H, $CH_2C\underline{H}CH_2$), 2.90-3.08 [m, 5H, $C\underline{H}N(C\underline{H}_2\text{-})C\underline{H}_2\text{-}$], 3.94 (s, 3H, OCH_3), 4.5 (br s, 1H, OH), 5.1 (m, 3H, $C\underline{H}OH$ and $CH{=}C\underline{H}_2$), 5.93 (m, 1H, $C\underline{H}{=}CH_2$), 7.37 (dd, $\underline{J}$=9.28 and 2.44Hz, 1H, 7'-H), 7.48(d, $\underline{J}$=4.64Hz, 1H, 3'-H), 7.58 (d, $\underline{J}$=2.93Hz, 1H, 5'-H), 8.03 (d, $\underline{J}$=9.28Hz, 1H, 8'-H), and 8.75 (d, $\underline{J}$=4.64Hz, 1H, 2'-H). ^{13}C NMR (100 MHz) δ 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 ppm.

Epicinchonidine (2g): a colorless syrup, $[\alpha]_D^{28}$ +56.9° (c 1.29, EtOH) [lit.[69] $[\alpha]_D^{20}$ +62.8° (c 0.804, EtOH)]. Found: C, 77.03; H, 7.58; N, 9.28. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52%.

^{1}H NMR (400 MHz) δ 1.0-1.7 [m, 5H, $C\underline{H}_2CHC\underline{H}_2$ and $C\underline{H}(CH_2CH{=}CH_2)$], 2.32 (m, 1H, $CH_2C\underline{H}CH_2$), 2.8-3.3 [m, 5H, $C\underline{H}N(C\underline{H}_2{-})C\underline{H}_2{-}$], 4.74 (br s, 1H, OH), 4.96 (m, 2H, $CH{=}C\underline{H}_2$), 5.15 (d, J=9.77Hz, 1H, $C\underline{H}OH$), 5.72 (m, 1H, $C\underline{H}{=}CH_2$), 7.50 (d, J=4.40Hz, 1H, 3'-H), 7.57-7.71 (m, 2H, 6'-H and 7'-H), 8.14 (d, J=9.28Hz, 1H, 5'-H), 8.36 (d, J=7.81Hz, 8'-H), and 8.90 (d, J=4.40Hz, 1H, 2'-H). ^{13}C NMR (100 MHz) δ 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 ppm.

Deoxyquinine (2i) was prepared by $LiAlH_4$-reduction (THF, reflux 3 h) of epichloroquinine[38] and purified with preparative TLC (hexane—$CHCl_3$—triethylamine, 15:15:2); a colorless syrup, $[\alpha]_D^{20}$ -97.4° (c 1.94, EtOH) [lit.[38] $[\alpha]_D^{20}$ -97.7° (c 2.021, EtOH)], MS m/e 136, 172, 184, 293, and 308 (M^+); ^{1}H NMR (400 MHz) δ 1.20 (m, 1H), 1.55-1.85 (m, 2H), 2.30 (m, 1H), 2.73 (dq, J=13.7 and 2.44 Hz, 1H), 2.80 (dq, J=14.7 and 4.89 Hz, 1H), 3.03 (dd, J=13.7 and 8.79 Hz, 1H), 3.23 (m, 3H), 3.39 (dd, J=13.9 and 5.5 Hz, 1H), 3.95 (s, 3H, OCH_3), 5.0 (m, 2H, $CH{=}C\underline{H}_2$), 5.80 (m, 1H, $C\underline{H}{=}CH_2$), 7.24 (d, J=4.39Hz, 1H, 3'-H), 7.28 (d, J=2.93Hz, 1H, 5'-H), 7.37 (dd, J=2.93 and 9.28 Hz, 1H, 7'-H), 8.02 (d, J=9.28Hz, 1H, 8'-H), 8.67 (d, J=4.39Hz, 1H, 2'-H).

(1R,2S)-N-Methylephedrine (2j) was prepared from (-)-ephedrine hydrochloride through reductive alkylation using formaldehyde and

sodium cyanoborohydride; recrystallization from light petroleum-ether, yield 490 mg (55 %): mp 86-87°C, $[\alpha]_D^{25}$ -29.0° (c 3.91, MeOH) [lit.[70] mp 87-87.5°C, $[\alpha]_D^{20}$ -29.0° (c 3.89, MeOH)].

Asymmetric Ring-Opening of the Anhydrides (1a-f)

A Typical procedure is illustrated by the reaction of cis-2,4-dimethylglutaric anhydride (**1a**) catalyzed by cinchonine (**2a**). The anhydride (**1a**) (14.2 mg, 0.1 mmol) and (**2a**) (2.9 mg, 0.01 mmol) were dissolved in dry toluene (5 mL). The reaction was initiated by adding dry MeOH (64.1 mg, 2 mmol) to the mixture at room temperature. The mixture was stirred at room temperature, the progress of the reaction being monitored with GLC [5% XE-60, 1 m, 160°C, carrier gas flow rate 40 mL/min; t_R(**1a**) 7.2 min and t_R(**3a**) 4.5 min]. The anhydride (**1a**) was quantitatively converted into (**3a**) within a day. The solvent was removed and the residual oil was transformed into the diastereomeric amide-ester (**4a**) by the following procedure.

Determination of Enantiomeric Excess of the Half-esters (3)

A representative procedure is as follows. To a solution of the half-ester (**3a**) (17.4 mg, 0.1 mmol) in dry toluene (3 mL) was added thionyl chloride (14.3 mg, 0.12 mmol) at 0°C. The mixture was stirred at 0°C for 10 min; 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 30 min and at room temperature for further 1 h. The solvent was removed under reduced pressure and the residue was diluted with AcOEt (20 mL). The solution was washed successively with 1N HCl, sat. $NaHCO_3$, and sat. NaCl. The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give a diastereomeric mixture of (**4a**) as a colorless syrup (25 mg, 76 % yield): ^{1}H NMR (400 MHz) 1.05-1.18 [4 x d, 6H, $CH(C\underline{H}_3)CH_2CH(C\underline{H}_3)$: 1.05, d, J=6.84Hz; 1.10, d, J=6.35Hz; 1.15, d, J=6.38Hz; 1.18, d, J=6.84Hz], 1.44 (m, 1H, CH_2), 1.67 (m, 3H, $NHCHC\underline{H}_3$), 1.97-2.25 (m, 2H, $C\underline{H}CONH$ and CH_2), 2.52 (m, 1H, $CHCO_2$), 3.61 and 3.63 (2 x s, 3H, diastereomeric CO_2CH_3), 5.81 (m, 1H, CONH), 5.92 (m, 1H, $NHC\underline{H}CH_3$), 7.26-8.09 (m, 7H, aromatic protons). The diastereomeric excess (d.e.) of compound (**4a**) was determined by HPLC (hexane—isopropyl alcohol—triethylamine, 15:1:0.16; flow rate 2 mL/ min; t_R 5.1 and 6.3 min; 280 nm) and found to be 63%. The d.e. was also found to be 61 % from the calculation of the peak areas at δ 3.61 and 3.63 ppm in ^{1}H NMR spectrum. The enantiomeric excess (e.e.) of (**3a**) was thus determined from the d.e. of (**4a**).

Preparation of Optically Active Lactones (5a-f)

(-)-(2R,4S)-cis-2,4-Dimethyl-δ-valerolactone (5a). The standard procedure for the preparation of the lactones (**5**) from the half-

esters (**3**) is exemplified by the reduction of the CO_2Me group of compound (**3a**). To a solution of (**3a**) [370 mg, 2.11 mmol, prepared from (**1a**) with the catalyst (**2a**)] in dry THF (60 mL) was added finely powdered lithium hydroxide (50.5 mg, 2.11 mmol). The mixture was stirred at 40-50°C until the lithium hydroxide was completely dissolved (ca. 30 min). Anhydrous lithium perchlorate (1.12 g, 10.5 mmol) was then added to the solution and dissolved completely (ca. 10 min). Finally, sodium borohydride (400 mg, 10.5 mmol) was added to the solution at room temperature. Gentle effervescence was observed immediately, but 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 1.5N HCl (60 mL), liberating an oily substance. The mixture was extracted with ether (3 x 30 mL). The combined extracts were washed with sat. NaCl and dried over anhydrous Na_2SO_4. Evaporation and distillation gave (-)-(2R,4S)-cis-2,4-dimethyl-δ-valerolactone (**5a**) as a colorless oil [150 mg, 56 % yield from (**1a**)]: bp 131-134°C/15.5mmHg, $[\alpha]_D^{25}$ -27.0° (c 1.94, $CHCl_3$) [lit.[5b] $[\alpha]_D^{25}$ -41.1° (c 5-10, $CHCl_3$) for (2R,4S)-(**5a**) with >98% e.e.], 66% e.e.; ^1H NMR (60 MHz) δ 1.0 (d, J=6.4Hz, 3H, CH_3), 1.28 (d, J=6.8Hz, 3H, CH_3), 1.1-1.6 (m, 1H, CH_2), 1.81-2.77 (m, 3H, CH_2 and 2 x CH), and 3.70-4.50 (m, 2H, CH_2O). IR(NaCl) 1740(C=O) cm^{-1}.

The half-ester (**3a**)(370 mg, 2.11 mmol) was also reduced with

BH_3-SMe_2 (2.53 mmol) in dry THF (4 mL) at 0°C for 1 h. The same work-up as above gave (+)-(2S,4R)-cis-2,4-dimethyl-δ-valerolactone (**5a**) as a colorless oil [130 mg, 48% yield from (**1a**)]: $[\alpha]_D^{25}$ +28.7° (c 1.97, $CHCl_3$), 70% e.e. An aliquot of compound (**3a**) was converted into amide-ester (**4a**), 66% d.e. (HPLC).

(-)-(3S)-3-Isopropyl-δ-valerolactone (5b). 3-Isopropylglutaric anhydride (**1b**) (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 the half-ester (**3b**) quantitatively. Compound (**3b**) was reduced with lithium borohydride by the standard procedure described in the preparation of (-)-(**5a**) to afford (-)-(3S)-3-isopropyl-δ-valerolactone (**5b**) as a colorless oil [370 mg, 88 % yield from (**1b**)]: bp 91.5-94°/0.9mmHg, $[\alpha]_D^{24}$ -5.93 (c 1.13, EtOH) [lit.[35] $[\alpha]_D^{24}$ +16.9° (c 1.037, EtOH) for (R)-(**5b**) of 96.6% optical purity]; ^1H NMR (60 MHz) δ 0.88 and 0.97 (m, 6H, 2 x CH_3), 1.20-2.95 [m, 6H, $C\underline{H}_2C\underline{H}(C\underline{H}(CH_3)_2)C\underline{H}_2$], 4.31 (m, 2H, CH_2O). The e.e. of the lactone (**5b**) was found to be 36% by HPLC analysis[35] as follows.

A mixture of the lactone (**5b**) (40 mg, 0.28 mmol) and (R)-1-(1-naphthyl)ethylamine (53 mg, 0.31 mmol) was heated at 90°C for 12 h. The consumption of (**5b**) was monitored with GLC (5% XE-60, 165°C); the formation of the diastereomeric amide-alcohol was confirmed by TLC (hexane-AcOEt, 1:1). The resulting mixture of the diastereomeric amide-alcohol was analyzed by HPLC (hexane-

AcOEt, 2:3; flow rate 3 mL/min; t_R 7.4 and 11.7 min).

(+)-(3S)-3-Phenyl-δ-valerolactone (5c). 3-Phenylglutaric anhydride (**1c**) (500mg, 2.63 mmol), MeOH (0.84 g, 26.3 mmol), and quinidine (**2b**)(85.3 mg, 0.26 mmol) in dry toluene (130 mL) at room temperature for a day gave the half-ester (**3c**) quantitatively. The e.e. of (**3c**) was determined by the standard method [amide-ester (**4c**), HPLC] and found to be 30%. Compound (**3c**) was reduced with lithium borohydride to yield (+)-(3S)-3-phenyl-δ-valerolactone (**5c**) as a colorless oil [280 mg, 62% yield from (**1c**)]: bp 170-173°C/1.0mmHg, $[\alpha]_D^{25}$ +1.16° (c 5.45, $CHCl_3$) [lit.[4a] $[\alpha]_D^{25}$ +0.78° (c 5.3, $CHCl_3$) for (3S)-(**5c**) with 21% optical purity]; ^1H NMR (60 MHz) 1.8-3.5 [m, 5H, $CH_2CH(Ph)CH_2$], 4.1-4.6 (m, 2H, CH_2O), 7.2 (m, 5H, aromatic protons); IR (NaCl) 1727(C=O) cm^{-1}.

(-)-(R)-Mevalonolactone (5d). 3-Hydroxy-3-methylglutaric anhydride (500 mg, 3.47 mmol), MeOH (1.11 g, 34.7 mmol), and quinine (**2d**) (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 the half-ester (**3d**) quantitatively. The e.e. of (**3d**) was determined by the standard method [amide-ester (**4d**), ^1H NMR] and found to be 40%. Compound (**3d**) was reduced with lithium borohydride; the product was purified with preparative TLC (silica gel, benzene-AcOEt, 1:3) to give (-)-(R)-mevalonolactone (**5d**) [330 mg, 73% yield from (**1d**), 31% e.e.]: $[\alpha]_D^{25}$ -7.17 (c 6.89, EtOH) [lit.[71]

$[\alpha]_D^{20}$ -23.0° (c 6, EtOH) for optically pure (R)-(**5d**)]; ^{1}H NMR (60 MHz) δ 1.55 (s, 3H, CH_3), 2.06 (m, 2H, CH_2), 2.74 (m, 2H, CH_2CO), 3.14 (br s, 1H, OH), 4.28-4.99 (m, 2H, CH_2O). The e.e. of (**5d**) was ascertained with 400 MHz ^{1}H NMR in the presence of a chiral shift reagent, Eu(hfc)$_3$.[29]

(-)-(1R,5S)-6,6-Dimethyl-3-oxabicyclo[3.1.0]hexan-2-one (5e). 3,3-Dimethyl-cis-1,2-cyclopropanedicarboxylic anhydride (**1e**) (500 mg, 3.57 mmol), MeOH (1.14 g, 35.7 mmol), quinine (**2d**) (117 mg, 0.36 mmol) in dry toluene (180 mL) at room temperature for 9 days afforded the half-ester (**3e**) in a 90 % yield (GLC, 5% XE-60, 150°C). The e.e. of (**3e**) was determined by the standard method [amide-ester (**4e**), HPLC] and found to be 27%. Compound (**3e**) was reduced with lithium borohydride and the product was purified with preparative GLC (5% XE-60, 170°C) to yield (-)-(1R,5S)-6,6-dimethyl-3-oxabicyclo[3.1.0]hexan-2-one (**5e**) [240 mg, 55% yield from (**1e**), 27% e.e.]: $[\alpha]_D^{21}$ -23.90° (c 1.41, $CHCl_3$) [lit.[12] $[\alpha]_D^{25}$ -72.8° (c 1.4, $CHCl_3$) for (1R,5S)-(**5e**) with 81% optical purity]; ^{1}H NMR (60 MHz) δ 1.20 (s, 6H, 2 x CH_3), 1.87-2.16 (m, 2H, 2 x CH), 4.00-4.50 (m, 2H, CH_2O); IR (NaCl) 1770(C=O) cm^{-1}.

(+)-(1S,6R)-8-Oxabicyclo[4.3.0]non-3-en-7-one (5f). 4-Cyclohexene-cis-1,2-dicarboxylic anhydride (**1f**) (540 mg, 3.56 mmol), MeOH (1.14 g, 35.6 mmol), and epiquinine (**2h**) (115 mg, 0.36 mmol) in dry toluene (180 mL) at room temperature for 3 days gave the

half-ester (**3f**) quantitatively (43% e.e. by the standard method using HPLC). Compound (**3f**) was reduced with lithium borohydride to yield (+)-(1S,6R)-8-oxabicyclo[4.3.1]non-3-en-7-one (**5f**) [260 mg, 54% yield from (**1f**)]: $[\alpha]_D^{24}$ +23.29° (c 1.05, $CHCl_3$) [lit.[4b] $[\alpha]_D^{25}$ -67.1° (c 1, $CHCl_3$) for optically pure (1R,6S)-(**5f**)]; ^1H NMR (60 MHz) δ 1.60-2.69 (m, 6H, 2 x CH_2 and 2 x CH), 4.13 (m, 2H, CH_2O), 5.72 (m, 2H, CH=CH). The lactone (**5f**) was converted to a diastereomeric mixture of the corresponding amide-alcohol by the same procedure described in determining the e.e. of (**5b**); the e.e. of (**5f**) was found to be 45% with HPLC (hexane-AcOEt, 2:3; flow rate 2 mL/min; t_R 5.70 and 8.05 min).

CHAPTER 4

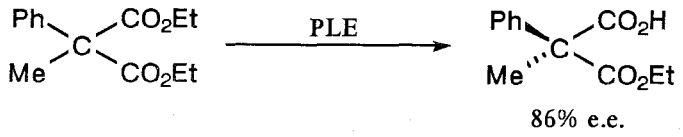
ASYMMETRIC INDUCTION WITH A PROCHIRAL MALONIC ACID DERIVATIVE

4-1. Introduction

Malonic acid derivatives having a prochiral center between the two carboxyl groups are also promising candidates for the substrates for enantiotopic group-differentiation. The absence of the two methylene groups, as compared with glutaric acids, would bring the site of the reaction closer to the center of asymmetry; the more restrictive steric situation might lead to greater selectivity in discriminating the two enantiotopic carbonyl groups. In addition to this structural feature, optically active malonic acid monoesters are useful chiral building blocks for the synthesis of optically active α-alkyl amino acids[8),50)] and barbiturates.[51)]

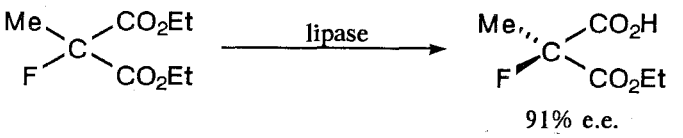
Enzymatic processes have been so far successfully used for the preparation of optically active malonic acid monoesters: enantioselective hydrolysis of disubstituted malonic acid diesters catalyzed by porcine liver esterase (Eq. 1)[51)] or microbial lipases (Eq. 2).[52)]

As a non-enzymatic method, on the other hand, monosubstituted chiral malonic monoesters were prepared by using l-menthol



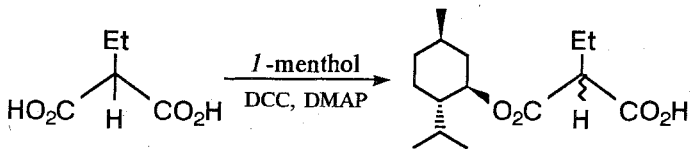
86% e.e.

(Eq. 1)



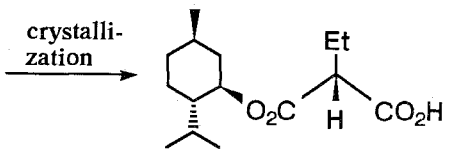
91% e.e.

(Eq. 2)



d.r. = 11 : 9

(Eq. 3)



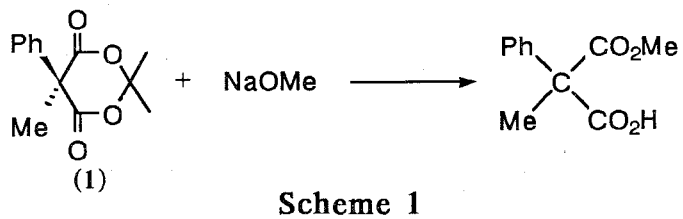
100% d.e.

as an auxiliary (Eq. 3).[53] Nevertheless, little has been reported on the non-enzymatic processes which enable the two carboxyl groups to be differentiated enantioselectively to yield optically active malonic monoesters. Hence, the author undertook chemical asymmetric induction with prochiral malonic acid derivatives through enantioselective monoesterification of one of the two carboxyl groups.

As described in Chapter 2, one of the principal advantages of the reaction using cyclic anhydrides as the substrates is that they afford half-esters solely, when treated with alcohols, without yielding achiral diesters by overreaction.

Unfortunately, malonic acids cannot form anhydrides; moreover, rapid enolization of α-hydrogen would lead to racemization.

Scheuer et al.[54] reported that a cyclic acylal, 2,2-dimethyl-5-methyl-5-phenyl-4,6-dioxo-1,3-dioxane (**1**) derived from α,α-disubstituted malonic acids, reacted with sodium methoxide and afforded the corresponding monomethylester quantitatively (Scheme 1).



(1)

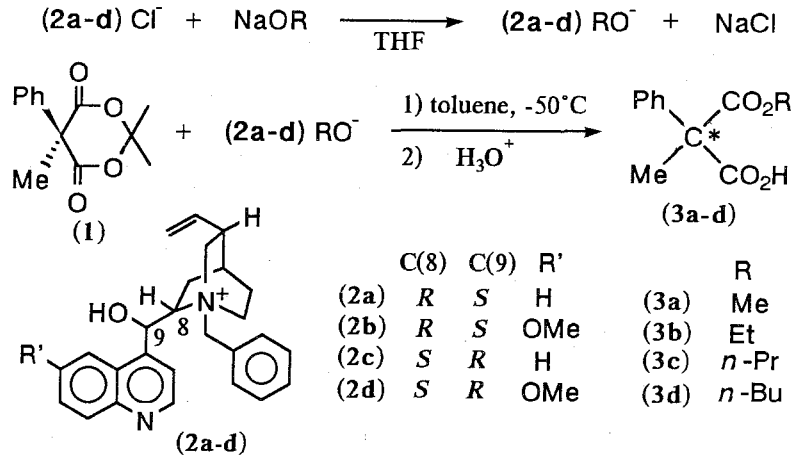
Scheme 1

On this basis the author designed the asymmetric ring-opening of (**1**) by using alkoxide anions paired with chiral quaternary ammonium cations (**2a-d**) derived from cinchona alkaloid, and prepared optically active half-esters (**3**).

4-2. Results and discussion

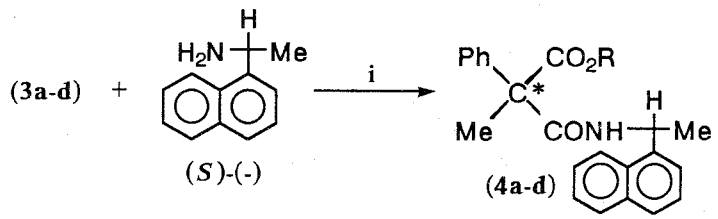
N-Benzylquininium methoxide [(**2d**)MeO^-] was prepared in situ by mixing N-benzylquininium chloride [(**2d**)Cl^-] and an equimolar amount of sodium methoxide in dry THF. The resulting mixture, a slightly cloudy solution, was added as such to a cold solution of the acylal (**1**) under an argon atmosphere (Scheme 2). The ring-opening proceeded rapidly and went to completion in a few minutes. Quenching of the reaction mixture with dilute citric

acid afforded the monomethyl ester (3a) quantitatively.



Scheme 2

The e.e. of (3a) was determined by ^{1}H NMR or HPLC-analyses of the corresponding diastereomeric amide-ester (**4a**) prepared from (3a) and (S)-1-(1-naphthyl)ethylamine (Scheme 3).



Scheme 3. Reagents and conditions: i, (**3a-d**) (0.3 mmol), (*S*)-1-(1-naphthyl)ethylamine (0.36 mmol), 2-chloro-1-methylpyridinium iodide (0.36 mmol), NEt_3 (0.72 mmol), CH_2Cl_2 (5 mL), reflux, 2 h.

Racemic (3a), a test compound for detecting the accuracy of this method, was analyzed and found to be 2.4% e.e., thus indica-

ting that the e.e. of (3) can be calculated within an error of ca. ±2 % by this method. When the amidation of racemic (3a) was conducted with thionyl chloride as a coupling reagent according to the procedure described in Scheme 2 in Chapter 3, partial kinetic resolution occurred and a mixture of unequal amounts of the diastereomers (4a) (62:38, ^{1}H NMR) was obtained in poor chemical yield (25%).

Preliminary experiments with [(2d)MeO$^-$] as the nucleophile revealed that the relatively non-polar and aprotic solvents such as toluene, diethyl ether, THF, and 1,2-dimethoxyethane were found to be desirable in the light of chemical and optical yields of the monoester (3a) (Table 1).

Table 1. Solvent Effect on the Reactivity and the Stereoselectivity[a]

Solvent	Reaction time (min)	Yield[b] (%)	E.e. (%)
Toluene	15	73	33
Diethyl ether	15	64	35
THF	15	84	34
DME[c]	15	94	34
Dichloromethane	15	100	11
Carbon tetrachloride[d]	15	77	21
Toluene-hexane (1 : 1)	15	88	21
Acetonitrile	15	87	5
Methanol	15	85	11

[a]Conditions: (1) (0.3 mmol), [(2d)MeO$^-$] (0.33 mmol), solvent (15 mL), -50°C. [b]Overall yield of (4a) based on (1). [c]1,2-Dimethoxyethane. [d]The reaction was conducted at -20°C.

The nucleophile [(**2d**)MeO^-] was, however, sparingly soluble in diethyl ether or less polar solvents such as carbon tetrachloride and a mixture of toluene and hexane (1:1); the chemical yield of (3) was lowered as a result. The reaction was hence carried out in a mixture of dry THF and dry toluene throughout the experiments.

The results are summarized in Table 2. The ring-opening reaction was completed within a few minutes; the conversion was 100% (GLC) for all the experiments with methoxide anion as the nucleophile. The yield was given as the isolated yield of the diastereomeric mixture of (**4a**). The sense of stereoselectivity, i.e. pro-R or pro-S preference of the alkoxide-attack on (1), was determined from the absolute configuration of α-methyltropic acid (5) prepared from (3a) by reducing the ester group of (3a) selectively (vide infra). When the reaction was conducted at room temperature, decarboxylation of (3a) occurred to some extent and gave methyl 2-phenylpropionate as a by-product. This undesired decarboxylation was completely avoided by lowering the reaction temperature to -50°C.

The reactions with the ammonium cations (**2a**) and (**2c**), derived from cinchonine and cinchonidine respectively, gave the monoester (3a) in high chemical yields, but with much lower e.e.'s (entry 1 and 3) than those with quinidinium (**2b**) or quininium cation (**2d**) (entry 2 and 4). The low e.e.'s for those reactions with (**2a**) and (**2c**) can be attributed to the fact that the

Table 2. Asymmetric Ring-opening of (**1**) with Alkoxide Anions Paired with the Chiral Ammonium Cations (**2**)[a]

Entry	Nucleophile	Temp. (°C)	Time (h)	Yield[b] (%)	E.e.[c] (%)	Selectivity[d]
1	(**2a**)MeO$^-$	-50	0.25	88	4	pro-*S*
2	(**2b**)MeO$^-$	-50	0.25	89	27	pro-*S*
3	(**2c**)MeO$^-$	-50	0.25	92	8	pro-*R*
4	(**2d**)MeO$^-$	-50	0.25	73	34	pro-*R*
5	(**2d**)MeO$^-$	-78	0.5[e]	100[f]	37	pro-*R*
6	(**2d**)MeO$^-$	20	5 min	65	23	pro-*R*
7	(**2d**)MeO$^-$	-82	0.25	81	34	pro-*R*
8	(**2a**)EtO$^-$	-50	2	81	8	pro-*S*
9	(**2b**)EtO$^-$	-50	2	82	45	pro-*S*
10	(**2b**)EtO$^-$	-78	2.5[e]	90[f]	45	pro-*S*
11	(**2c**)EtO$^-$	-50	2	44	20	pro-*R*
12	(**2d**)EtO$^-$	-50	2	65	43	pro-*R*
13	(**2b**)*n*-PrO$^-$	-78	3.5[e]	91[f]	51	pro-*S*
14	(**2d**)*n*-PrO$^-$	-50	2	57	39	pro-*R*
15	(**2d**)*i*-PrO$^-$	-50	1	- [g]	-	-
16	(**2b**)*n*-BuO$^-$	-50	2	69	45	pro-*S*
17	(**2d**)*n*-BuO$^-$	-78	3.5[e]	77f	40	pro-*R*

[a]Conditions: (**1**) (0.3 mmol), nucleophile (0.36 mmol), dry toluene (13 mL), dry THF (2 mL). [b]Overall yield of (**4**) based on (**1**). [c]Calculated from the diastereomeric ratios in (**4**). [d]Preferentially attacked carbonyl group of (**1**). [e]Preparative scale reaction [(**1**): 1.2 - 2.1 mmol]. [f]Yield of (**3**). [g]No product was detected and (**1**) was recovered.

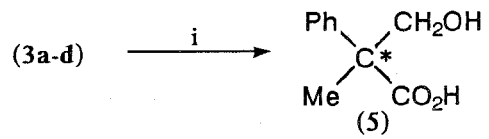
salts [(**2a**)MeO^-] and [(**2c**)MeO^-] are sparingly soluble in THF; hence, the undesirable ion-pairing of methoxide anion with achiral Na^+ may precede the desired ion-pairing with chiral ammonium cations (**2a**) or (**2c**), when they are prepared *in situ* from the salts [(**2a**)Cl^-] or [(**2c**)Cl^-] and sodium methoxide in THF.

It is worth noting that the cations (**2a**) and (**2b**), both having the (8*R*,9*S*)-configuration, promoted the attack of MeO^- preferentially on the pro-*S* carbonyl group of (**1**) (entry 1 and 2); whereas, the cations (**2c**) and (**2d**) with (8*S*,9*R*)-configuration showed pro-*R* selectivity (entry 3 and 4). The same stereochemical biases were observed for all the alkoxides examined. This type of stereocontrol, in which the configuration around the C(8) and C(9) in the alkaloid are of fundamental importance in determining the stereochemistry of products, is generally observed in cinchona alkaloid-mediated asymmetric induction such as 1,4-addition of nucleophiles to α,β-unsaturated carbonyl compounds[34] and asymmetric methanolysis of cyclic acid anhydrides described in Chapter 3. A plausible explanation of those stereochemical biases is, as described in Chapter 3, that the β-hydroxyamine portion at C(8)-C(9) of cinchona alkaloid is the critical site responsible for the stereoselection and that the ammonium cations (**2a**) and (**2c**), as well as (**2b**) and (**2d**), are diastereomeric pairs but enantiomeric at this site.

Primary alkoxide, EtO^-, *n*-PrO^-, and *n*-BuO^- also reacted with (**1**), giving the corresponding monoester (**3b-d**) in high chemical

yields. The reactions for these alkoxides were much slower than that with MeO^- and required 1.5-2 h for completion at -50°C; however, the optical yields were improved generally to 40-50% e.e. On the other hand, the secondary alkoxide $i\text{-}PrO^-$ was unreactive and the substrate (1) was recovered quantitatively. Scheuer et al.[54] reported that the acylal (1) reacted with 2 molar equiv. of sodium isopropoxide to yield a mixture of methylphenylmalonic acid and the unreacted (1).

A preparative scale reaction was effected. The selective reduction of the ester group of the monoester (3) with lithium borohydride afforded optically active 3-hydroxy-2-methyl-2-phenylpropionic acid [α-methyltropic acid (5)] (Scheme 4). Optically active α-methyltropic acid has attracted much attention as the chiral constituent of an anticholinergic drug, tropine α-methyltropate, which is an optically stable analogue of atropine;[55] moreover, (-)-tropine α-methyltropate was reported to show a cholinergic blocking activity in vitro about fifty times greater than the (+)-isomer.[56]



Scheme 4. Reagents and conditions: i, (**3a-d**) (2.0 mmol), LiOH (2.0 mmol), $LiClO_4$ (8.0 mmol), $NaBH_4$ (8.0 mmol), dry THF (60 mL), room temperature, 2.5 h.

The results of the preparation of optically active (5) are shown in Table 3. The treatment of (1) with [(**2d**)MeO^-] and the

subsequent reduction gave the optically active (S)-(5) having $[\alpha]_D^{20}$ -10.9° (c 1.0, EtOH) in an overall yield of 82% from (1). The optical purity of (5) was calculated from the reported maximum rotation {$[\alpha]_D^{20}$ +28.7° (EtOH) for optically pure (R)-(5)}[57] and found to be 38% e.e. This value was consistent with the e.e. of the monoester (3a) (37% e.e.) calculated from the diastereomeric ratio of the corresponding amide-ester (4a). The same procedure was applied to the reactions of (1) with alkoxides [(2b)EtO$^-$], [(2b)n-PrO$^-$], and [(2d)n-BuO$^-$]. In all cases the selective reduction of the ester group was well achieved and optically active (5) was obtained in 77-86% yields from (1). The absolute configuration of (5) obtained thus determined the sense of asymmetric induction, i.e. pro-R or pro-S attack, for each monoester studied.

Table 3. Preparation of α-Methyltropic acid (5) from (1)[a]

Entry	Alkoxide	Yield (%)	$[\alpha]_D^{20}$ (c 1, EtOH)	Optical purity (%)	Configuration
1	(2d)MeO$^-$	82	-10.9°	38	*S*
2	(2b)EtO$^-$	86	+11.3°	39	*R*
3	(2b)*n*-PrO$^-$	86	+12.3°	43	*R*
4	(2d)*n*-BuO$^-$	77	-11.0°	38	*S*

[a]Reaction conditions of ring-opening: (1) (1.2 - 2.1 mmol), alkoxide [1.2 molar equiv. of (1)], dry toluene—THF (40—90 mL), -78°C, 2-3 h. [b]c 1, EtOH. [c]Calculated from the reported value, $[\alpha]_D^{20}$ +28.7° (EtOH).[57]

Experimental

Preparation of 2,2-Dimethyl-5-methyl-5-phenyl-4,6-dioxo-1,3-dioxane (1)

Diethyl methylphenylmalonate: A solution of diethyl phenylmalonate (45 g, 0.19 mol) in dry DMF (45 mL) was added dropwise to a suspension of NaH (5.49 g, 0.23 mol) in dry DMF (65 mL) at 0°C with stirring. The mixture was stirred at 0°C for 15 min. To this slightly turbid solution, was added dropwise a solution of methyl iodide (58.1 g, 0.38 mol) in dry DMF (45 mL) at 0°C. After addition, the mixture was stirred at room temperature for 2 h. The reaction mixture was poured onto crushed ice and water (500 mL), and the mixture was extracted with ether (3 x 150 mL). The combined extracts were washed with sat. NaCl (2 x 100 mL) and dried over anhydrous Na_2SO_4. After evaporation, the residual oil was distilled to afford diethyl methylphenylmalonate as a colorless oil (43.4 g, 90.9% yield): bp 128-136°C/0.9 mmHg; ^1H NMR (60 Mhz) δ 1.3 (t, $\underline{J}$=7Hz, 6H), 1.9 (s, 3H), 4.3 (q, $\underline{J}$=7Hz, 4H), 7.4 (s, 5H).

Methylphenylmalonic acid: A solution of diethyl methylphenylmalonate (3.0 g, 12.1 mmol) and potassium hydroxide (1.4 g, 24.6 mmol) in 95% EtOH (60 mL) was allowed to stand at room temperature for 20 h. The solvent was removed under reduced pressure to

give a colorless solid. The solid was air-dried, crushed, washed with ether (3 x 30 mL), and dissolved in distilled water (5 mL). Ether (40 mL) was layered over this aqueous solution and 6N HCl was added dropwise to the mixture with ice-cooling until it tested acidic with Congo red as an indicator (ca. pH 4.0). The ethereal layer was separated and the aqueous layer was extracted with ether (3 x 20 mL). The combined extracts were washed with sat. NaCl and dried over anhydrous Na_2SO_4. Evaporation gave methylphenylmalonic acid as a colorless syrup; this syrup was immediately crystallized by adding hexane (30 mL) (1.63 g, 75.8% yield): ^1H NMR (60 MHz) δ 1.8 (s, 3H), 4.6 (s, 2H, 2 x CO_2H), 7.3 (s, 5H).

2,2-Dimethyl-5-methyl-5-phenyl-4,6-dioxo-1,3-dioxane (1): Methylphenylmalonic acid (7.5 g, 38.6 mmol) was suspended in acetic anhydride (13.5 mL). Concentrated sulfuric acid (0.75 mL, 14.1 mmol) was added to the suspension at room temperature; the mixture immediately became a clear solution. To this solution was added acetone (4.5 mL) dropwise over a period of 15 min at room temperature. The mixture was stirred for 30 min and afforded colorless crystals. The crystals were collected and washed with distilled water (30 mL) and dried in a desiccator. The crude product was recrystallized from acetone-water (5 : 1) to give (**1**) as colorless crystals (7.25 g, 80% yield): mp 142-144°C (lit.[54] mp 146-148°C). Found: C, 66.66; H, 6.02. Calcd for $C_{13}H_{14}O_4$: C,

66.52; H, 6.03%. ^{1}H NMR (60 MHz) δ 1.2 and 1.7 [2 x s, 6H, $(CH_3)_2C$], 1.85 [s, 3H, $C(C_6H_5)C\underline{H}_3$], 7.4 (s, 5H, C_6H_5).

Preparation of the Quaternary Ammonium Salts (2a-d)Cl$^-$

Quaternary salts of cinchona alkaloid (**2a-d**)Cl$^-$ were prepared according to the procedure by Jacobs[72] but with modification as shown below.

N-Benzylquininium chloride (2d)Cl$^-$; typical procedure. To a suspension of quinine (6.00 g, 18.5 mmol) in dry acetone (30 mL) was added benzyl chloride (3.98 g, 31.4 mmol). The mixture was heated at 60°C in an autoclave for 4 h. The reaction mixture was evaporated The residual dark brown syrup was dissolved in dry acetone (50 mL) and precipitated by adding ether (50 mL). The powder was collected and recrystallized from EtOH (60 mL) to yield (**2d**) as a colorless crystals (7.08 g, 84.9% yield): mp 180-183°C (dec.), $[\alpha]_D^{22}$ -218.2° (c 1.48, H_2O) [lit.[72] $[\alpha]_D^{22}$ -230.5° (c 1.48, H_2O)]. Found: C, 70.73; H, 6.96; N, 6.09. Calcd for $C_{27}H_{31}N_2O_2Cl \cdot 1/2$ EtOH: C, 70.94; H, 7.23; N, 5.91%.

N-Benzylcinchoninium chloride (2a)Cl$^-$: a colorless crystal from hot water (1.65 g, 39% yield), mp 265-266°C (dec.), $[\alpha]_D^{25}$ +165.2° (c 0.72, H_2O) [lit.[72] $[\alpha]_D^{22}$ +164.8° (c 0.716, H_2O)]. Found: C, 73.98; H, 6.91; N, 6.68. Calcd for $C_{26}H_{29}N_2OCl$: C, 74.18; H,

6.94; N, 6.65%.

N-Benzylquinidinium chloride (2b)Cl$^-$: a colorless crystal from hot acetone (4.46 g, 80.2% yield), mp 173-174°C (dec.), $[\alpha]_D^{22}$ +197.6° (c 0.630, H_2O) [lit.[72] $[\alpha]_D^{21.5}$ +219.9° (0.632, H_2O)]. Found: C, 71.08; H, 6.97; N, 6.14. Calcd for $C_{27}H_{31}N_2O_2Cl$ 1/3 H_2O: C, 70.96; H, 6.84; N, 6.13%.

N-Benzylcinchonidinium chloride (2c)Cl$^-$: a colorless crystal from hot acetone (8.48 g, 74% yield), mp 217-219°C (dec.), $[\alpha]_D^{22.5}$ -186.5° (c 0.712, H_2O) [lit.[73] $[\alpha]_D^{20}$ -175.4° (c 0.5, H_2O)]. Found: C, 74.00; H, 6.93; N, 6.76. Calcd for $C_{26}H_{29}N_2OCl$: C, 74.18; H, 6.94; N, 6.65%.

Asymmetric Monoesterification of (1); Typical Procedure.

N-Benzylquininium chloride [(**2d**)Cl$^-$, 162 mg, 0.36 mmol] was suspended in dry THF (2 mL). A methanol solution of sodium methoxide (3.0 mmol/mL, 120 μL, 0.36 mmol) was added to the suspension at room temperature. The suspension immediately became opaque solution. The mixture was stirred at room temperature for 10 min and then added dropwise to a solution of (**1**) (70.3 mg, 0.3 mmol) in dry toluene (13 mL) at -50°C. The reaction was monitored with GLC [5% XE-60, 1 m, 160°C, carrier gas flow rate 40 mL/min; t_R 0.52 min {product (**3a**) detected as methyl 2-phenylpropionate},

6.1 min (**1**)]. The substrate (**1**) was completely consumed within 5 min. After the mixture was stirred for additional 10 min at -50°C, the reaction mixture was quenched by adding 3% citric acid aqueous solution (30 mL). The organic layer was separated and the aqueous layer was extracted with ether (3 x 20 mL). The combined organic layers were washed with sat. NaCl and dried over anhydrous Na_2SO_4. Evaporation below 50°C gave methyl hydrogen methylphenylmalonate (**3a**) quantitatively as a colorless oil (130 mg): ^{1}H NMR (60 MHz) δ 1.88 (s, 3H, CH_3), 3.68 (s, 3H, OCH_3), 7.23 (s, 5H, C_6H_5), 9.5 (br s, 1H, CO_2H).

Ethyl hydrogen methylphenylmalonate (3b): ^{1}H NMR (60 MHz) δ 1.25 (t, J=7.2Hz, 3H, $CH_2\underline{C}H_3$), 1.87 (s, 3H, CH_3), 4.20 (q, J=7.2Hz, 2H, $C\underline{H}_2CH_3$), 7.23 (s, 5H, C_6H_5), 8.3 (br s, 1H, CO_2H).

n-Propyl hydrogen methylphenylmalonate (3c): ^{1}H NMR (60 MHz) δ 0.9 (t, J=7.0Hz, $CH_2\underline{C}H_3$), 1.5-1.9 (m, 2H, $C\underline{H}_2CH_3$), 1.88 (s, 3H, CH_3), 4.1 (t, J=7.0Hz, 2H, CO_2CH_2), 7.23 (s, 5H, C_6H_5), 8.2 (br s, 1H, CO_2H).

n-Butyl hydrogen methylphenylmalonate (3d): ^{1}H NMR (60 MHz) δ 0.8-1.8 (m, 7H, $CH_2CH_2CH_3$), 1.90 (s, 3H, CH_3), 4.2 (t, J=6.4Hz, 2H, CO_2CH_2), 7.30 (s, 5H, C_6H_5), 10.7 (br s, 1H, CO_2H).

To determine the e.e. of the monoester (**3a**), compound (**3a**) was allowed to react with (S)-1-(1-naphthyl)ethylamine according

to the procedure given below.

Determination of Enantiomeric Excess of (3); Typical Procedure for (3a).

A mixture of (S)-1-(1-naphthyl)ethylamine (61.6 mg, 0.36 mmol), 2-chloro-1-methylpyridinium iodide[74] (92.0 mg, 0.36 mmol), triethylamine (72.9 mg, 0.72 mmol), and (**3a**) (0.3 mmol) in dry CH_2Cl_2 (5 mL) was heated under reflux for 2 h. The mixture was evaporated and the residual oil was passed through a short-pass silica gel column with AcOEt as an eluent. Evaporation gave a diastereomeric mixture of the amide-ester (**4a**) as an oil [88.2 mg, 81% yield from (**1**)]: MS m/e(%) 361(M^+,12), 164(70), 155(100); ^1H NMR (200 MHz) δ 1.6 (2 x d, J=6.8Hz, 3H, $NHCHC\underline{H}_3$), 1.85 [s, 3H, $C(C_6H_5)C\underline{H}_3$], 3.58 and 3.79 (2 x s, 3H, CO_2CH_3), 5.94 (m, 1H, CH), 6.8 and 6.9 (2 x d, br, 1H, NH), 7.2-8.1 (m, 12H, aromatic protons). The e.e. of (**3a**) was calculated from the integration of the diastereomeric proton peaks (δ 3.58 and 3.79 ppm) of (**4a**), or by HPLC analysis of (**4a**) (hexane—isopropyl alcohol, 100 : 3; flow rate 0.7 mL/min; t_R 9.7 and 10.5 min).

Amide-ester (4b): MS m/e(%) 375 (M^+,14), 178(85), 155 100); ^1H NMR (200 MHz) δ 1.0 and 1.3 (2 x t, J=7.2Hz, 3H, $CH_2C\underline{H}_3$), 1.6 (2 x d, J=6.5Hz, 3H, $NHCHC\underline{H}_3$), 1.8 [2 x s, 3H, $C(C_6H_5)C\underline{H}_3$], 4.03(m) and 4.26 (q, J=7.2Hz, 2H, $OC\underline{H}_2CH_3$), 5.9 (m, 1H, CH), 6.85 (br m,

1H, NH), 7.2-8.1 (m, 12H, aromatic protons).

Amide-ester (4c): MS m/e(%) 389(M^+,13), 192(77), 155(100); ^1H NMR (200 MHz) δ 0.7 and 0.9 (2 x t, J=7.4Hz, 3H, $CH_2C\underline{H}_3$), 1.4 (m, 2H, $C\underline{H}_2CH_3$), 1.6 (2 x d, J=6.5Hz, 3H, $NHCHC\underline{H}_3$), 1.8 [2 x s, 3H, $C(C_6H_5)C\underline{H}_3$], 3.93(m) and 4.16 (t, J=6.6Hz, 2H, CO_2CH_2), 5.9 (m, 1H, CH), 6.9 (br m, 1H, NH), 7.2-8.1 (m, 12H, aromatic protons).

Amide-ester (4d): MS m/e(%) 403(M^+,10), 206(62), 155(100); ^1H NMR (200 MHz) δ 0.8-1.4 (m, 5H, CH_2CH_3), 1.55-1.7 (m, 5H, $OCH_2C\underline{H}_2$ and $NHCHC\underline{H}_3$), 1.80 [2 x s, 3H, $C(C_6H_5)C\underline{H}_3$], 3.96(m) and 4.20 (t, J=6.6Hz, 2H, CO_2CH_2), 5.9 (m, 1H, CH), 6.93 (br m, 1H, NH), 7.2-8.1 (m, 12H, aromatic protons).

Selective Reduction of Ester-Group of (3); Typical Procedure.

Finely powdered anhydrous lithium hydroxide (47.7 mg, 1.99 mmol) was dissolved in dry THF (60 mL); methyl hydrogen methylphenylmalonate (**3a**) [415 mg, 1.99 mmol, prepared from (1) and (**2d**)CH_3O^-, 37% e.e.] was added to the solution at 0°C. The mixture was stirred until homogenous, the temperature being kept below 0°C to avoid decarboxylation of (**3a**). To this slightly cloudy solution were added successively anhydrous lithium perchlorate (848 mg, 7.97 mmol) and sodium borohydride (302 mg, 7.97 mmol) at 0°C. The mixture was stirred at 0°C for 3 h, then at

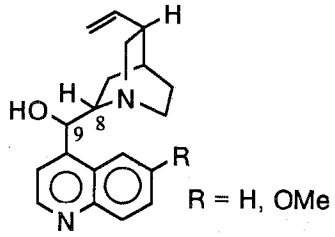
room temperature for 2.5 h. The solvent was evaporated and the residue was extracted with ether (4 x 30 mL). The combined extracts were washed with sat. NaCl and dried over anhydrous Na_2SO_4. Evaporation and distillation gave (S)-3-hydroxy-2-methyl-2-phenylpropanoic acid (**5**) as a colorless syrup which crystallized upon standing [294 mg, 82% yield from (**1**)]: bp 156-159 °C/0.7 mmHg, mp 79-81°C, $[\alpha]_D^{20}$ -10.9° (c 1.0, EtOH) [lit.[57] mp 77-79°C, $[\alpha]_D^{20}$ +28.7° (EtOH) for optically pure (R)-(**5**)]. Found: C, 66.90; H, 6.76. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71%; ^1H NMR (200 MHz) δ 1.68 (s, 3H, CH_3), 3.66 and 4.10 (2 x d, J=11.4Hz, 1H each, CH_2O), 6.9 (br s, 2H, OH and CO_2H), 7.3 (m, 5H, C_6H_5).

CHAPTER 5

ASYMMETRIC INDUCTION USING POLYMER-SUPPORTED QUININES WITH SPACER GROUPS

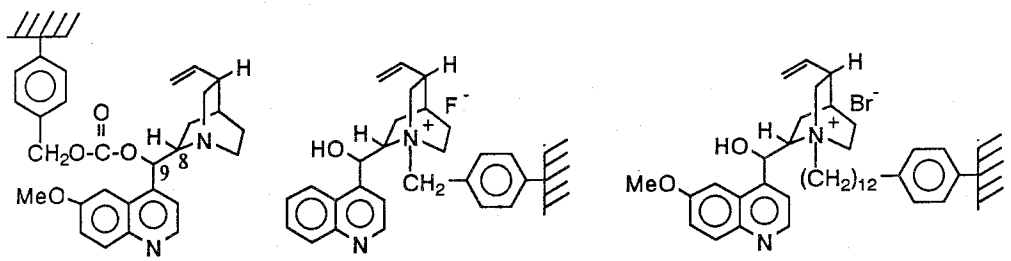
5-1. Introduction

In Chapter 3, the author described a catalytic asymmetric ring-opening of cyclic acid anhydrides catalyzed by cinchona alkaloid. The unique catalytic properties of these alkaloids have been well appreciated in a number of asymmetric reactions developed so far.[34]



The mechanism of their excellent catalytic function, mechanism which has found general acceptance, is that the amine portion of the alkaloids enhances the nucleophilicity of nucleophiles, whereas the hydroxyl group enhances the acceptor qualities of electrophiles; the alkaloids thus serve as the bifunctional catalysts in which the β-hydroxyamine portion at C(8)-C(9) of the alkaloid molecule is the critical site responsible for their catalytic function.[40] These unique properties of the alkaloids

prompted the author further to improve the utility of them as chiral base-catalysts. One of the attractive methods to improve the utility of cinchona alkaloid is to fix it onto a solid support. Several polymer-bound cinchona alkaloids have been synthesized so far; in some of them, the alkaloid molecule was attached to the polymer matrices by either C(9)-hydroxyl group[58a] or C(8)-tertiary amino function[58b,c] (Fig. 1). These polymers, however, seem to have limited potential as catalysts in asymmetric synthesis, because the amino-alcohol part at C(8)-C(9), the catalytic site of the alkaloids, was modified and used as the connecting site to the polymer matrices.

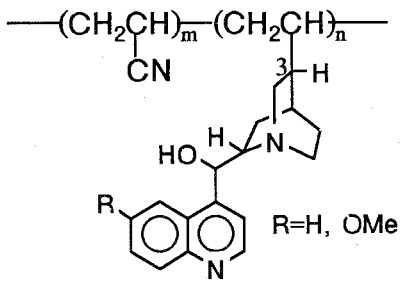


Wynberg (1977) Hodge (1983) Kobayashi (1981)

Fig. 1

Another type of polymeric cinchona alkaloid was synthesized by Kobayashi et al.[59] They prepared the polymer-catalyst by copolymerizing the alkaloids with acrylonitrile, the C(3)-vinyl group of the alkaloid being used as the connecting site to the polymer matrix (Fig. 2). Since the alkaloid moiety in this polymer has a non-modified C(8)-C(9) catalytic site, this polymer-

catalyst has been successfully used in a number of base-catalyzed asymmetric syntheses.[43]



Kobayashi (1978)

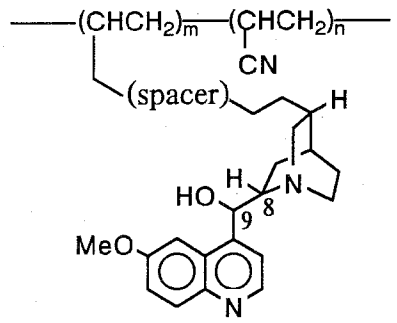
Fig. 2

The author examined the catalytic activity of Kobayashi's polymer for the asymmetric methanolysis of cis-2,4-dimethylglutaric anhydride (cf. Chapter 3); however the asymmetric yield was unsatisfactory. It has been pointed out that the activity of catalysts or reagents is often reduced by being supported to polymers,[60] a plausible explanation of this phenomenon being that the polymer matrices exert unfavorable steric effects on the reaction site.

One approach to overcome this drawback would be the insertion of a spacer between the catalytic center and the polymeric support. Some researchers reported that the catalytic activity of polymeric phase-transfer catalysts was improved by inserting a spacer between the catalytic site and the polymer matrix.[61] This spacer-effect was observed not only for a polymer-supported acylating catalyst,[62] but also for immobilized enzymes.[63] Hence

the reactivity and the stereoselectivity of the polymer-supported cinchona alkaloids could be improved by inserting a spacer chain between the alkaloid molecule and the polymer matrix.

The author therefore synthesized polymer-supported quinines with spacer groups between the C(3)-vinyl function of quinine and the polyacrylonitrile backbone and examined their catalytic activity for three types of asymmetric reactions.



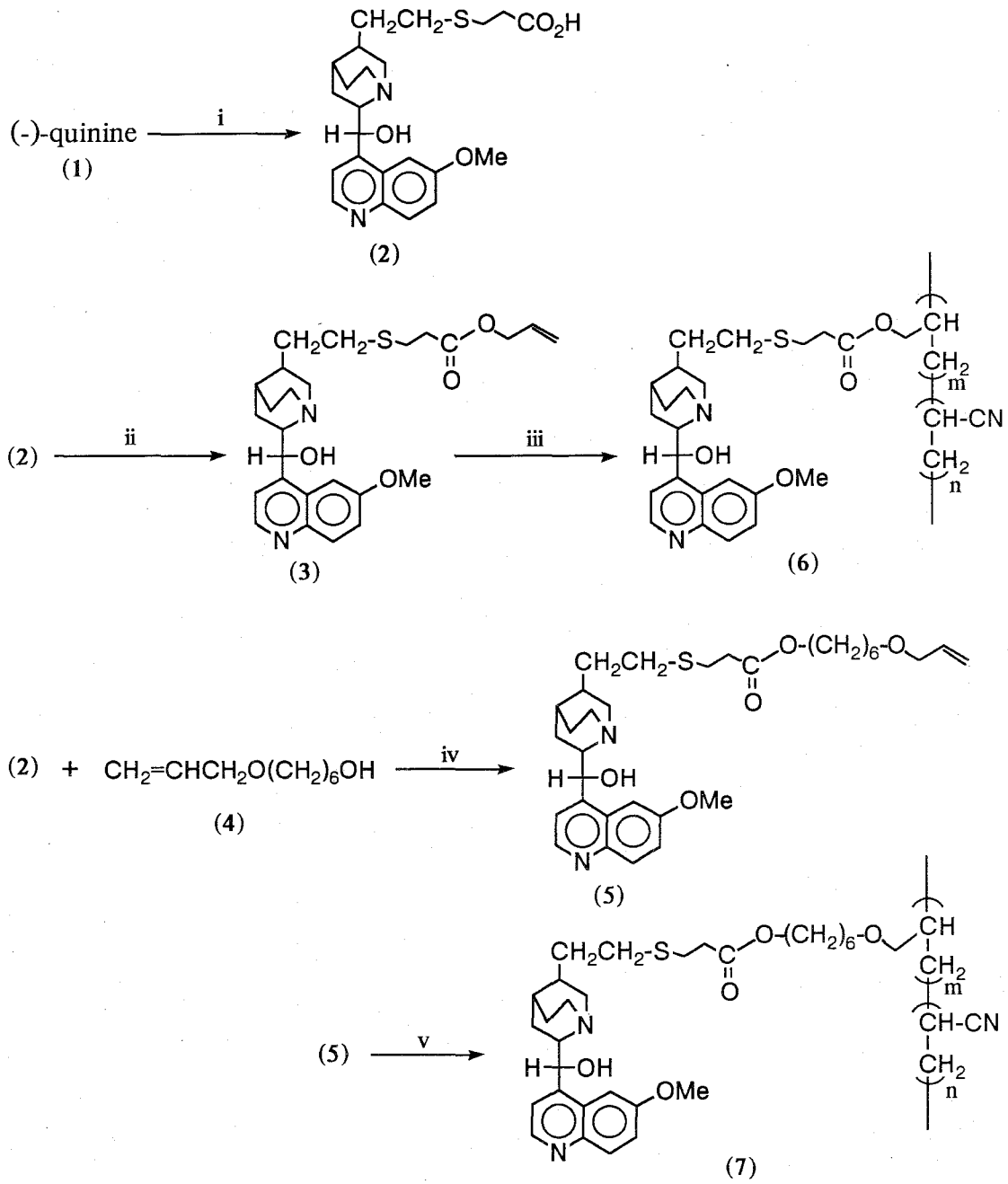
5-2. Results and Discussion

The synthetic route of the polymeric quinines is shown in Scheme 1 and 2. The key reaction was the radical addition of thiols to the C(3)-vinyl group of quinine (**1**).[64] The author's first attempt to introduce methyl 3-mercaptopropionate into (**1**) was unsuccessful. However, 3-mercaptopropionic acid successfully reacted with (1) in the presence of 2,2'-azobisisobutyronitrile (AIBN) as a radical initiator and gave the acid (**2**) as a colorless powder in an 82% yield. In order to introduce a polymerizable double bond, compound (**2**) was allowed to react with allyl

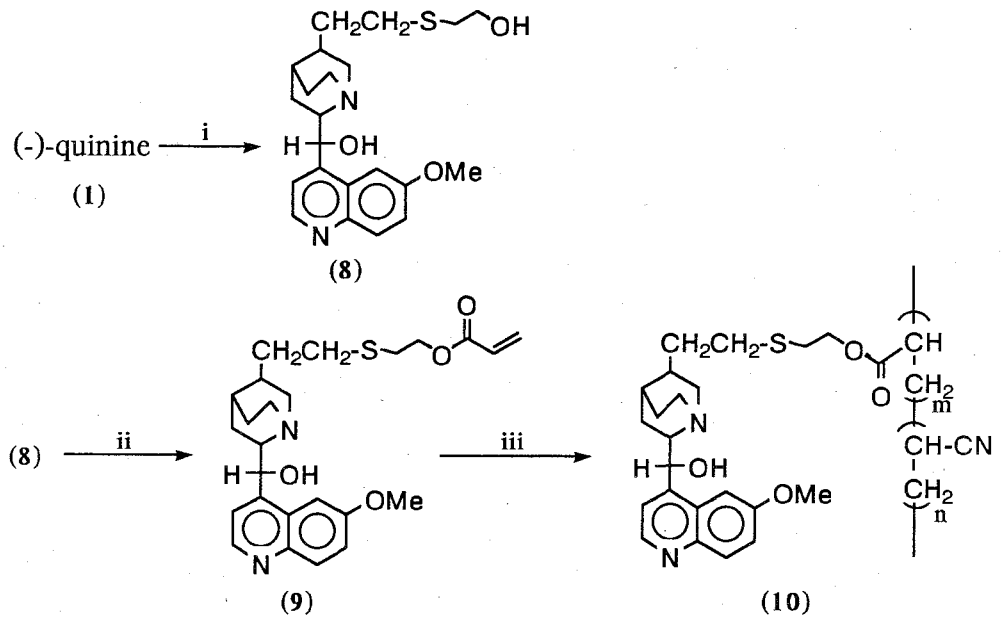
alcohol to afford the allyl ester (3) having a spacer as long as 8 atoms from the quinuclidine ring to the terminal double bond. Compound (2) was also esterified with the alcohol (4) by the Mitsunobu reaction to give the ester (5) having a spacer of 15-atoms length.

The quinine derivatives (3) and (5) thus obtained were copolymerized with acrylonitrile in dry DMF to afford the polymers (6) and (7), respectively. The crude polymers obtained were dissolved in DMF and reprecipitated by dropping the polymer solution into methanol, and then Soxhlet-extracted to remove the unreacted monomers. The alkaloid content of (6) and (7) was determined by an elemental analysis and found to be 1.10 and 1.24 mol%, respectively. These values were lower than those expected from the initial quinine concentration (5 mol%) in the reactant mixtures.

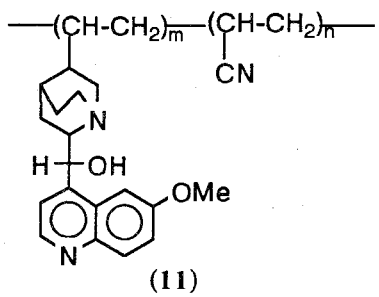
To obtain a copolymer with higher alkaloid content, the author synthesized another type of monomer. Because acrylonitrile copolymerizes more easily with a compound having a conjugated double bond than that having an isolated double bond,[65] the author prepared the monomer having an acryloyl group as a polymerizable unit (Scheme 2). Quinine (1) was allowed to react with 2-mercaptoethanol to give the alcohol (8). Compound (8) was then converted to the acrylic ester (9) by selective esterification of the primary hydroxyl group with acrylic acid by the Mitsunobu reaction. It is worth noting that the C(8)-hydroxyl group in (8)



Scheme 1. Reagents and conditions: i, (1) (30 mmol), 3-mercaptopropionic acid (300 mmol), AIBN (6 mmol), benzene (80 mL), 70°C, 17 h; 82% yield. ii, (2) (5.81 mmol), thionyl chloride (12 mmol), allyl alcohol (40 mL), room temperature, 3 h; 72% yield. iii, (3) (4.06 mmol), acrylonitrile (77.1 mmol), AIBN (0.11 mmol), dry DMF (14.8 mL), 60°C, 21 h; 57% yield. iv, (2) (5.81 mmol), (4) (6.98 mmol), triphenylphosphine (6.98 mmol), diethyl azodicarboxylate (6.98 mmol), dry THF (60 mL), room temperature, overnight; 94% yield. v, (5) (4.52 mmol), acrylonitrile (85.9 mmol), AIBN (0.13 mmol), dry DMF (17.5 mL), 60°C, 22 h, 43% yield.



Scheme 2. Reagents and conditions: i, (**1**) (30 mmol), 2-mercaptoethanol (240 mmol), AIBN (6 mmol), benzene (80 mL), 70°C, 28 h; 77% yield. ii, (**8**) (9.94 mmol), acrylic acid (10.3 mmol), triphenylphosphine (10.3 mmol), diethyl azodicarboxylate (10.3 mmol), dry THF (100 mL), room temperature, overnight; 67% yield. iii, (**9**) (4.27 mmol), acrylonitrile (38.4 mmol), AIBN (0.07 mmol), dry DMF (10 mL), 65°C, 42 h; 57% yield.



(**11**)

was exclusively esterified when (8) was treated with an equal amount of acryloyl chloride.

Copolymerization of (9) with acrylonitrile (1:9 molar ratio) afforded the copolymer (10) with an alkaloid content of 8.04 mol%, this value being consistent with that expected from the initial molar ratio in the reactant mixture.

The author also synthesized the polymer (11) without a spacer, according to the method reported by Kobayashi et al.[59b] The physical properties of the polymers (6), (7), (10) and (11) are compiled in Table 1.

Table 1. Physical Properties of the Polymer-supported Quinines with the Spacers

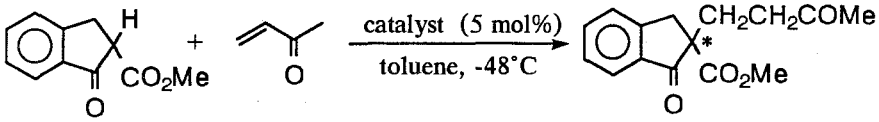
Polymer	Spacer length	Initial molar ratio[a]	$[\alpha]_D$[b] (deg.)	Elemental analysis (%) C	H	N	Alkaloid content (mol %)
(6)	8	1 : 19	-5.6[c]	67.41	5.78	24.44	1.10
(7)	15	1 : 19	-6.5	67.62	5.95	23.81	1.24
(10)	7	1 : 9	-26.0	65.82	6.15	17.69	8.04
(11)	0	1 : 19	-10.4[d]	68.33	5.93	24.39	1.99

[a]Initial molar ratio of the monomers (3), (5), (9), and (1) vs. acrylonitrile before polymerization, respectively. [b]Measured in DMF at 25°C. [c]At 27°C. [d]At 28°C.

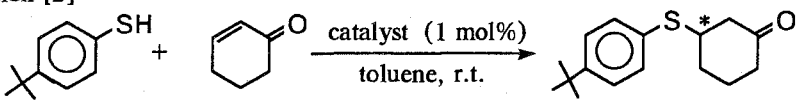
The catalytic activity of the polymers (6), (7), (10), and (11) was examined in the three types of base-catalyzed reactions: the Michael addition of methyl 1-oxo-2-indancarboxylate to 3-buten-2-one (reaction [1])[66], the conjugate addition of p-t-butylbenzenethiol to 2-cyclohexenone (reaction [2])[40], and the methanolysis of cis-2,4-dimethylglutaric anhydride (reaction [3],

see Chapter 3).

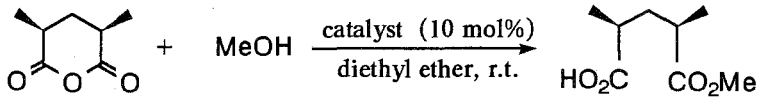
Reaction [1]



Reaction [2]



Reaction [3]



The results of the reaction [1] catalyzed by the polymers (**6**), (**7**), (**10**), and (**11**) are shown in Table 2. To evaluate the effect of polymerization on the catalytic activity, the reaction was also conducted by using the corresponding monomeric alkaloids (**3**), (**5**), (**9**), and (**1**) as the catalysts.

The monomers (**3**), (**5**), and (**9**) catalyzed the reaction [1] as effectively as quinine (**1**) and gave (S)-methyl 1-oxo-2-(3-oxobutyl)-2-indancarboxylate with 75-76% optical purity in quantitative yield (Table 2, entries 6-9). These results suggested that the spacer arms attached to the C(3)-position of quinine (**1**) did not affect the catalytic activity of the alkaloid; in other words, the stereochemical environment of the catalytic center, around the C(9)-hydroxyl group and the C(8)-nitrogen atom, was conserved after attaching the pendant groups to the C(3)-position.

Table 2. Asymmetric Addition of Methyl 1-Oxo-2-indancarboxylate to 3-Buten-2-one Catalyzed by the Polymers (**6**), (**7**), (**10**), and (**11**); the Reaction [1].[a]

Entry	Catalyst	Spacer length	Reaction period (h)	Isolated yield (%)	$[\alpha]_{578}^{25}$ (deg.)	E.e.[b] (%)	Abs. config.
1	(**7**)	15	28	88	-50.4	65	*S*
2	(**6**)	8	28	96	-47.4	62	*S*
3	(**10**)	7	6.6 d	2[c]	-[d]	-	-
4	(**10**)[e]	7	3.9 d	92	-34.4	45	*S*
5	(**11**)	0	28	99	-37.8	49	*S*
6	(**5**)	-	14	quant.	-58.1	75	*S*
7	(**3**)	-	14	quant.	-58.7	76	*S*
8	(**9**)	-	27	quant.	-57.9	75	*S*
9	(**1**)	-	28	quant.	-58.7	76	*S*

[a]Reagents and conditions: methyl 1-oxo-2-indancarboxylate (0.25 mmol), 3-buten-2-one (0.50 mmol), catalyst (0.0125 mmol of alkaloid), dry toluene (1.5 mL), -48°C. [b]Based on $[\alpha]_{578}$ = -77° (c 2, benzene) for the optically pure product. [c]Determined by HPLC. [d]Not measured. [e]The reaction was conducted at room temperature.

The polymer-catalysts (**6**), (**7**), and (**11**) gave the product in 88-99% chemical yields, but in somewhat lower asymmetric yields than the corresponding monomers. The polymers (**6**) and (**7**) with the spacer groups, as expected, showed higher stereoselectivity (62 and 65% e.e., respectively) than that without a spacer [(**11**), 49% e.e.](entries 1, 2, and 5). On the other hand, the polymer (**10**) prepared from a different type of monomer was practically inactive at -48°C, in spite of higher quinine content (entry 3). When the reaction was carried out at room temperature, however, the polymer (**10**) slowly catalyzed the reaction and gave the (S)-

enantiomer of the product in a 45% e.e. (entry 4). This result suggested that the stereochemical environment of the alkaloid moiety was retained after copolymerization in this polymer, although its catalytic activity was much lower than the other polymers. The low catalytic activity of the polymer (**10**) at -48°C may be ascribed to a defect in the diffusion of the substrates into the polymer matrix at this temperature.

The results of the reaction [2] are shown in Table 3. The monomers (**1**), (**3**), (**5**), and (**9**) afford (R)-3-[(p-t-butylphenyl)-thio]cyclohexanone with 25-45% e.e. in high chemical yields. The

Table 3. Asymmetric Addition of *p*-*t*-Butylbenzenethiol to 2-Cyclohexenone Catalyzed by the Polymers (**6**), (**7**), (**10**), and (**11**); the Reaction [2].[a]

Entry	Catalyst	Spacer length	Isolated yield (%)	$[\alpha]_{578}^{25}$ (deg.)	E.e.[b] (%)	Abs. config.
1	(**7**)	15	89	+5.8	8	*R*
2	(**6**)	8	90	+4.8	6	*R*
3	(**10**)	7	7[c]	-[d]	-	-
4	(**11**)	0	98	+4.2	5	*R*
5	poly (AN)[e]	-	7[c]	-[d]	-	-
6	(**5**)	-	83	+19.4	25	*R*
7	(**3**)	-	96	+27.1	35	*R*
8	(**9**)	-	87	+23.1	30	*R*
9	(**1**)	-	97	+31.5	41	*R*

[a]Reagents and conditions: *p*-*t*-butylbenzenethiol (1.81 mmol), 2-cyclohexenone (1.56 mmol), catalyst (0.015 mmol of alkaloid), dry toluene (3 mL), room temperature. [b]Based on $[\alpha]_{578}^{21}$ = +77° (c 1, CCl_4) for the optically pure product. [c]Determined by HPLC. [d]Not measured. [e]Poly(acrylonitrile) homopolymer without a quinine moiety.

polymers (6), (7), and (11) also well catalyzed the reaction and gave the product in 89-98% chemical yields; however, the optical yields were much lower than those with the monomeric catalysts (3), (5), and (1), respectively. The reason for these results is not clear at present; these undesirable results could not be ascribed to the spontaneous reaction occurring on the polymer matrix, because poly(acrylonitrile) without the quinine moiety had no catalytic activity (Table 3, entry 5).

On the other hand, the polymers (6), (7), (10), and (11) effectively catalyzed the reaction [3] as shown in Table 4.

Table 4. Asymmetric Methanolysis of *cis*-2,4-Dimethylglutaric Anhydride Catalyzed by the Polymers (6), (7), (10), and (11); the Reaction [3].[a]

Entry	Catalyst	Spacer length	Reaction period (d)	E.e.[b] (%)	Selectivity[c]
1	(7)	15	4.0	32	*R*-side
2	(6)	8	3.8	22	*R*-side
3	(10)	7	8.6[d]	20	*R*-side
4	(11)	0	2.6	14	*R*-side
5	(5)	-	1.5	12	*R*-side
6	(3)	-	2.0	57	*R*-side
7	(9)	-	2.0	29	*R*-side
8	(1)	-	3.8	50	*R*-side
9	(7)[e]	15	9.0	28	*R*-side
10	(6)[e]	8	12.2	33	*R*-side

[a]Reagents and conditions: *cis*-2,4-dimethylglutaric anhydride (0.1 mmol), methanol (1.0 mmol), catalyst (0.01 mmol of alkaloid), dry ether (5 mL), room temperature, conversion >95%. [b]Determined by HPLC after converting the product to the diastereomeric amide-ester (see Chapter 3). [c]The author has defined the selectivity as *R*-side when methanol preferentially attacked the carbonyl group attached to the (*R*)-chiral carbon of the anhydride. [d]Conversion, ca. 40%. [e]Reuse of the catalyst.

Although they showed lower stereoselectivity than the corresponding monomers, the effect of the spacer groups was observed clearly. The asymmetric yield was improved from 14 to 22% e.e. by inserting the spacer group of 8-atoms length; the spacer of 15-atoms length further improved the asymmetric yield up to 32% (Table 4, entries 1, 2, and 4). As had been observed for the reaction [1], the polymer (**10**) showed practically no or very low activity for the reaction [2] and [3], respectively.

One of the advantages of polymer-catalysts is that they can be recovered by filtration and reused. The polymers (**6**) and (**7**) were recovered and reused as the catalysts for the reaction [3]. The recovered polymers exhibited lower catalytic activity than the first use, but showed almost the same stereoselectivity as that with the first use. (entry 1 vs. 9, and entry 2 vs. 10).

In summary, polymer-supported quinines were prepared in which a spacer arm was inserted to keep the catalytic center apart from the polymer chains. The catalytic activity of these polymers were examined for the three types of base-catalyzed asymmetric reactions and found to vary with the reactions tested. In some cases the stereoselectivity was improved by inserting a spacer and approached to those of the corresponding non-immobilized catalysts.

Experimental

11-(2-Carboxyethylthio)-10,11-dihydroquinine (2): A mixture of quinine [(**1**), 9.73 g, 30 mmol], 3-mercaptopropionic acid (31.67 g, 300 mmol), and 2,2'-azobisisobutyronitrile (AIBN) (0.99 g, 6 mmol) in benzene (80 mL) was heated at 70 °C for 17h under an argon atmosphere. The reaction mixture was extracted with 2N HCl (3 x 50 mL). The combined extracts were washed with ether (2 x 50 mL) and made alkaline (pH 8) with Na_2CO_3 powder to afford (**2**) as a colorless syrup. The syrup became powder by cooling at 4°C overnight. The powder was collected and dried in a desiccator; it was used for the next step without further purification (10.55 g, 82% yield): $[\alpha]_D^{25}$ -211° (c 1.022, 0.1N HCl), MS m/e(%) 430 (M^+, 6), 242 (8), 44 (100). Found: m/e 430.1927. Calcd for $C_{23}H_{30}N_2O_4S$: M, 430.1927. ^1H NMR (200MHz, DMSO-d_6) δ 1.30-3.55 (m, 19H, protons of quinuclidine ring and spacer arms), 3.91 (s, 3H, CH_3O), 5.54 (d, 1H, J=4.4Hz, CHOH), 6.15 (br s, 3H, OH and CO_2H), 7.37 (dd, J=9.2 and 2,5 Hz, 1H, 7'-H), 7.50 (d, J=2.5Hz, 1H, 5'-H), 7.54 (d, J=4.7Hz, 1H, 3'-H), 7.92 (d, J=9.2Hz, 1H, 8'-H), 8.68 (d, J=4.7Hz, 1H, 2'-H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 21.427, 24.991, 26.705, 26.972, 28.969, 33.537, 33.592, 35.724, 41,844, 55.652, 56.051, 59.605, 68.936, 102.143, 118.958, 121.119, 126.501, 131.106, 143.768, 147.363, 148.007, 157.073, and 174.080 ppm; IR (KBr) 3410(OH), 1620(C=O) cm^{-1}.

11-[2-(Allyloxycarbonyl)ethylthio]-10,11-dihydroquinine (3): Thionyl chloride (1.45 g, 12.16 mmol) was added to a suspension of (2) (2.50 g, 5.81 mmol) in allyl alcohol (40 mL) at 0 °C with stirring. The mixture was stirred at room temperature for 3 h. The reaction mixture was evaporated and quenched with 1N NaOH at 0°C, and extracted with CH_2Cl_2 (4 x 25 mL). The combined extracts were washed with sat. NaCl and dried over anhydrous Na_2SO_4. Evaporation followed by column chromatography on silica gel ($CHCl_3$—MeOH—triethylamine, 70 : 2 : 1) gave (3) as a colorless syrup (1.96 g, 72% yield): $[\alpha]_D^{28}$ -122° (c 0.968, EtOH); MS m/e(%) 470 (M^+,27), 282 (42), 32 (100). Found: m/e 470.2235. Calcd for $C_{26}H_{34}N_2O_4S$: M, 470,2239. ^1H NMR (400 MHz) δ 1.35-1.82, 2.32, 2.58, 2.99-3.05, and 3.47 (m, 13H, protons of quinuclidine ring and 10-H), 2.41 (m, 2H, 11-H), 2.57 (m, 2H, CH_2CO_2), 2.71 (m, 2H, $SCH_2CH_2CO_2$), 3.90 (s, 3H, CH_3O), 4.56 (m, J=5.9 and 1.5 Hz, 2H, allyl protons), 5.21 [m, J=10.3, 2.5, and 1.5Hz, 1H, (Z)-vinyl protons], 5.29 [m, J=17.1, 3.2, and 1.5 Hz, 1H, (E)-vinyl protons], 5.36 (br s, 1H, OH), 5.50 (d, J=3.4 Hz, 1H, 9-H), 5.88 (m, 1H, J=17.1, 10.3 and 5.9 Hz, =CH), 7.21 (d, J=2.4 Hz, 1H, 3'-H), 7.25 (dd, J=9.3 and 2.9 Hz, 1H, 7'-H), 7.44 (d, J=4.4 Hz, 1H, 5'-H), 7.87 (d, J=9.3 Hz, 1H, 8'-H), 8.43 (d, J=4.9 Hz, 1H, 2'-H); ^{13}C NMR (100 MHz) δ 20.959, 25.512, 26.987, 27.483, 30.022, 34.182, 34.255, 34.678, 43.144, 55.681, 57.739, 59.695, 65.036, 70.670, 100.839, 117.798, 117.973, 120.980, 125.899, 130.905, 131.416, 143.530, 146.493, 146.741, 157.162, and 170.662 ppm;

IR (NaCl) 3080(OH), 1735(C=O) cm^{-1}.

6-Allyloxy-1-hexanol (4): The allyl ether (**4**) was prepared from allyl alcohol and tetrahydropyranyl ether of 6-chloro-1-hexanol (2.20 g, 37 % yield based on 6-chloro-1-hexanol): bp 142-148 °C/13mmHg; ^1H NMR (200 MHz) δ 1.20-1.60 (m, 8H, 4 x CH_2), 2.65 (s, 1H, OH), 3.22-3.68 (m, 4H, 2 x OCH_2), 4.83-4.92 (m, 2H, allyl protons), 5.05-5.26 (m, 2H, CH_2=), 5.70-5.95 (m, 1H, =CH).

11-[2-[6-(Allyloxy)hexyloxycarbonyl]ethylthio]-10,11-dihydroquinine (5): The carboxylic acid (**2**) (2.50 g, 5.81 mmol), the alcohol (**4**) (1.10 g, 6.98 mmol), and triphenylphosphine (1.83 g, 6.98 mmol) were suspended in dry THF (60 mL). Diethyl azodicarboxylate (1.21 g, 6.98 mmol) was added dropwise to the suspension with stirring at 0 °C with stirring over a period of 15 min. The mixture was stirred overnight at room temperature and evaporated to dryness. The residue was extracted with 2N HCl (4 x 25 mL). The combined acid extracts were washed with ether (6 x 35 mL) and made alkaline with NaOH pellet, and then extracted with CH_2Cl_2 (4 x 25 mL). The combined extracts were washed with sat. NaCl and dried over anhydrous Na_2SO_4. Evaporation gave (**5**) as a colorless syrup (3.12 g, 94 % yield): $[\alpha]_D^{24}$ -101° (c 1.156, EtOH); MS m/e(%) 570 (M^+, 4), 382 (5), 32 (100). Found: m/e 570.31328. Calcd for $C_{32}H_{46}N_2O_5S$: M, 570.31278. ^1H NMR (400 MHz)

δ 1.30-1.85, 2.35, 2.61, 3.02-3.08, and 3.47 (m, 21H, protons of quinuclidine ring, 10-H, and 4 x CH_2), 2.42 (t, J=7.3Hz, 2H, 11-H), 2.53 (t, J=7.3Hz, 2H, CH_2CO_2), 2.70 (t, J=7.3Hz, 2H, $SCH_2CH_2CO_2$), 3.40 (t, J=6.4Hz, 2H, CH_2OCH_2-CH=), 3.87 (s, 3H, CH_3O), 3.94 (m, J=5.4 and 1.5 Hz, 2H, allyl protons), 4.05 (t, J=6.8Hz, 2H, CO_2CH_2), 4.88 (br s, 1H, OH), 5.16 [m, J=10.3 and 1.5 Hz, 1H, (Z)-vinyl protons], 5.25 [m, J=17.1, 3.4 and 1.5Hz, 1H, (E)-vinyl protons], 5.52 (m, 1H, 9-H), 5.90 (m, J=17.1, 10.3 and 5.4 Hz, 1H, =CH), 7.22 (d, J=2.4 Hz, 1H, 5'-H), 7.27 (dd, J=9.3 and 2.4 Hz, 1H, 7'-H), 7.46 (d, J=4.4 Hz, 1H, 3'-H), 7.90 (d, J=9.3 Hz, 1H, 8'-H), 8.51 (d, J=4.4 Hz, 1H, 2'-H); ^{13}C NMR (50 MHz) δ 21.404, 25.688, 25.835, 25.908, 27.157, 28.013, 28.586, 29.683, 30.196, 34.452, 34.631, 34.882, 43.627, 55.805, 58.202, 59.876, 64.770, 70.242, 71.580, 71.811, 101.370, 116.688, 118.423, 121.382, 126.527, 131.343, 134.941, 144.029, 147.326, 147.725, 157.657, and 171.846 ppm; IR (NaCl) 3150(OH), 1740(C=O) cm^{-1}.

Alkaloid (3)—Acrylonitrile Copolymer, (6): A mixture of the alkaloid (3) (1.91 g, 4.06 mmol), freshly distilled acrylonitrile (4.09 g, 77.14 mmol), and AIBN (0.018 g, 0.11 mmol) in dry DMF (14.8 mL) was heated at 60 °C for 21 h under an argon atmosphere. The reaction mixture was poured into boiling MeOH (1000 mL). A polymer precipitated was filtered and reprecipitated twice from DMF into MeOH followed by Soxhlet-extraction with MeOH

(5 h) to remove unreacted monomers. The residue was dried over P_2O_5 *in vacuo* at 70 °C (4 h) to give the polymer (**6**) as a colorless solid (3.39 g, 57 % yield): $[\alpha]_D^{27}$ -5.6° (*c* 1.022, DMF). Found: C, 67.41; H, 5.78; N, 24.44 %, alkaloid content 1.10 mol%.

Alkaloid (5)—Acrylonitrile Copolymer, (7): A solution of the alkaloid (5) (2.58 g, 4.52 mmol), freshly distilled acrylonitrile (4.56 g, 85.89 mmol), and AIBN (0.021 g, 0.13 mmol) in dry DMF (17.5 mL) was heated at 60 °C for 22 h under an argon atmosphere. The same purification process described above afforded the polymer (7) as a colorless solid (3.08 g, 43 % yield): $[\alpha]_D^{25}$ -6.5° (*c* 1.086, DMF). Found: C, 67.62; H, 5.95; N, 23.81 %, alkaloid content 1.24 mol%.

11-(2-Hydroxyethylthio)-10,11-dihydroquinine (8): A mixture of quinine [(1), 9.73 g, 30 mmol], 2-mercaptoethanol (18.75 g, 240 mmol), and AIBN (0.99 g, 6 mmol) in benzene (80 mL) was heated at 70°C for 28 h under an argon atmosphere. The reaction mixture was extracted with 2*N* HCl (2 x 50 mL). The combined extracts were washed with ether (2 x 50 mL) and then made alkaline with NaOH pellet. The liberated oil was taken up with CH_2Cl_2 (3 x 50 mL). The combined extracts were washed with sat. NaCl and dried over anhydrous Na_2SO_4. Evaporation and chromatography on silica gel ($CHCl_3$—MeOH—triethylamine, 70 : 2 : 1) afforded (**8**) as a pale yellow syrup (9.25 g, 77 % yield): $[\alpha]_D^{25}$

-108° (c 1.030, EtOH) [lit[64]. $[\alpha]_D^{25}$ -140.6° (EtOH)]; MS m/e(%) 402 (M^+,57), 357 (49), 214 (100); ^{1}NMR (400 MHz) δ 1.22-1.80, 2.26, 2.52, 2.90-3.00 and 3.48 (m, 13H, protons of quinuclidine ring, 10-H), 2.37 (m, 2H, 11-H), 2.59 (t, J=6.4 Hz, 2H, SCH_2), 3.63 (t, J=6.4 Hz, 2H, CH_2O), 3.83 (s, 3H, CH_3O), 4.36 (br s, 1H, OH), 5.49 (m, 1H, CHOH), 5.59 (br s, 1H, OH), 7.13-7.26, 7.43, 8.79, and 8.42 (m, 5H, protons of quinoline ring); ^{13}C NMR (50 MHz) δ 20.880, 25.633, 27.945, 29.956, 34.586, 35.154, 43.189, 55.742, 58.157, 59.681, 60.700, 68.403, 71.322, 101.509, 118.476, 121.377, 126.532, 130.996, 143.709, 147.110, 148.461, and 157.733 ppm.

11-[2-(Acryloyloxy)ethylthio]-10,11-dihydroquinine (9): A solution of diethyl azodicarboxylate (1.80 g, 10.33 mmol) in dry THF (5 ml) was added dropwise to a suspension of (8) (4.00 g, 9.94 mmol), acrylic acid (0.745 g, 10.33 mmol), and triphenylphosphine (2.71 g, 10.33 mmol) in dry THF (100 mL) at 0°C over a period of 15 min. The mixture was stirred at 0 °C for 30 min and then at room temperature overnight. The reaction mixture was evaporated to dryness; the residue was dissolved in 2N HCl (80 mL). The acidic solution was washed with ether (6 x 30 mL) and made alkaline with Na_2CO_3 powder, and extracted with CH_2Cl_2 (2 x 50 mL). The combined extracts were washed with sat. NaCl and dried over anhydrous Na_2SO_4. After evaporation, the residue was flash-chromatographed on silica gel ($CHCl_3$—MeOH—triethylamine,

50 : 2 : 1) to afford (**9**) as a colorless syrup (3.02 g, 67% yield): $[\alpha]_D^{25}$ -105° (c 1.044, EtOH); MS m/e(%) 456 (M^+,87), 357 (99), 268 (100). Found: m/e 456.20527. Calcd for $C_{25}H_{32}N_2O_4S$: M, 456.20817; ^1H NMR (400 MHz) δ 1.34-1.83, 2.38, 2.61, 3.02-3.08, and 3.53 (m, 13H, protons of quinuclidine ring and 10-H), 2.45 (t, J=7.3 Hz, 2H, 11-H), 2.70 (t, J=6.8 Hz, 2H, SCH_2), 3.84 (s, 3H, CH_3O), 4.23 (t, J=6.8 Hz, 2H, CH_2O), 5.56 (m, 2H, CHOH), 5.80 [m, J=10.3, 2.4 and 1.5 Hz, 1H, (Z)-vinyl protons], 6.07 (m, J=17.1 and 10.3 Hz, 1H, =CH), 6.34 [m, J=17.1 and 1.5 Hz, 1H, (E)-vinyl protons], 7.21 (d, J=2.9 Hz, 1H, 5'-H), 7.23(dd, J=9.3, and 2.4 Hz, 1H, 7'-H), 7.46 (d, J=4.4 Hz, 1H, 3'-H), 7.86 (d, J=9.3 Hz, 1H, 8'-H), 8.45 (d, J=4.4 Hz, 1H, 2'-H); ^{13}C NMR (50 MHz) δ 20.931, 25.543, 27,738, 30.221, 30.403, 33.723, 34.431, 43.182, 55.699, 58.008, 59.781, 63.433, 71.111, 101.338, 118.456, 121.338, 126.457, 128.059, 131.142, 131.142, 143.832, 147.202, 148.059, 157.676, and 165.846 ppm; IR (NaCl) 3160(OH), 1725(C=O) cm^{-1}.

Alkaloid (9)—Acrylonitrile Copolymer, (10): A solution of the alkaloid (**9**) (1.95 g, 4.27 mmol), acrylonitrile (2.04 g, 38.40 mmol), and AIBN (0.012 g, 0.07 mmol) in dry DMF (10.0 mL) was heated at 65 °C for 42 h under an argon atmosphere. The same purification process described for the polymer (**5**) gave the polymer (**10**) as a colorless solid (2.29 g, 57 % yield): $[\alpha]_D^{25}$ -26.0° (c 1.008, DMF). Found: C, 65.82; H, 6.15; N, 17.69%, alkaloid

content 8.04 mol%.

Quinine--Acrylonitrile Copolymer, (11): According to the reported procedure,[59] a mixture of quinine (**1**) and acrylonitrile (molar ratio, 1 : 19) was copolymerized in dry DMF. The crude polymer was purified as above to give the polymer (**11**) having no spacer (8.09 g, 29 % yield): $[\alpha]_D^{28}$ -10.4° (c 1.00, DMF), Found: C, 68.33, H, 5.93, N, 24.39%, alkaloid content 1.99 mol%.

Asymmetric Addition of Methyl 1-Oxo-2-indancarboxylate to 3-Buten-2-one Catalyzed by (7). Typical Procedure for the Reaction [1]: A mixture of the polymer-catalyst (**7**) (59.0 mg, 0.0125 mmol of alkaloid), methyl 1-oxo-2-indancarboxylate (47.5 mg, 0.25 mmol), and freshly distilled 3-buten-2-one (35.0 mg, 0.50 mmol) in dry toluene (1.5 mL) was stirred at -48 °C. The conversion was monitored with HPLC (hexane—isopropyl alcohol, 100 : 5, 280 nm). The reaction mixture was filtered and the filtrate was evaporated to afford the pure adduct (TLC); its optical rotation was measured at 578 nm (25°C) in benzene. The purity and structural integrity were certified with ^{1}H NMR and TLC.

Asymmetric Addition of p-t-Butylbenzenethiol to 2-Cyclohexenone Catalyzed by (6). Typical Procedure for the Reaction [2]: A mixture of the polymer catalyst (**6**) (80.0 mg, 0.015 mmol), p-t-butylbenzenethiol (301 mg, 1.81 mmol), and 2-cyclohexenone (150

mg, 1.56 mmol) in dry toluene (3 mL) was stirred overnight at room temperature. The reaction mixture was washed successively with 2N HCl (2 x 10 mL), 2N KOH (2 x 10 mL), and sat. NaCl (1 x 10 mL), and then dried over anhydrous Na_2SO_4. The optical rotation was measured at 578 nm (25 °C) in CCl_4.

Asymmetric Methanolysis of cis-2,4-Dimethylglutaric Anhydride Catalyzed by (6). Typical Procedure for the Reaction [3]: The polymer-catalyst (**6**) (52.6 mg, 0.01 mmol of alkaloid), cis-2,4-dimethylglutaric anhydride (14.2 mg, 0.1 mmol), and dry methanol (32.0 mg, 1.0 mmol) in dry ether (5 mL) were mixed and stirred at room temperature. The conversion was monitored with GLC (2% XE-60, 2 m, 160°C). After removing polymer-catalyst by filtration, the half-ester obtained was converted to the diastereomeric amide ester using (R)-1-(1-naphthyl)ethylamine as described in Chapter 3. The diastereomeric ratio of the amide ester was determined by HPLC (hexane—isopropyl alcohol, 100 : 6, 280 nm).

SUMMARY

The present study deals with novel chemical methods for the asymmetric induction based on the differentiation between the enantiotopic carboxyl groups of prochiral or meso-dicarboxylic acids. The essence is the use of cyclic derivatives of these acids as the substrates; the nucleophilic ring-opening of these derivatives, e.g. cyclic acid anhydrides, with a chiral amine would provide the corresponding chiral half-amides quantitatively without yielding achiral di-amides.

On the basis of this conception, the author designed a nucleophilic ring-opening of prochiral 3-substituted or meso-glutaric anhydrides, using chiral binaphthyldiamine derivatives as the nucleophile. The reaction of (S)-2-piperidino-2'-amino-1,1'-binaphthyl with cis-2,4-dimethylglutaric anhydride proceeded highly stereoselectively and gave the corresponding diastereomeric half-amide in a 92% d.e. This half-amide was then successfully converted to optically active (+)-(2R,4S)-2,4-dimethyl-δ-valerolactone with 92% optical purity. The author also synthesized optically active lactones including (-)-(R)-mevalonolactone in 42—74% asymmetric yields by this reaction.

Catalytic process, on the other hand, is highly desired in the light of effective asymmetric synthesis. The author found that a catalytic amount of cinchona alkaloid effectively catalyzed the methanolysis of prochiral or meso-glutaric anhydrides

to yield the corresponding chiral monomethyl esters. The reaction of cis-2,4-dimethylglutaric anhydride with methanol in the presence of cinchonine (0.1 eq.) afforded (2S,4R)-1-methyl hydrogen 2,4-dimethylglutarate in a 66% e.e. The carboxyl group or the ester group of this half-ester was selectively reduced to yield (+)-(2S,4R)-2,4-dimethyl-δ-valerolactone or its antipode with 70% or 66% optical purities, respectively. Mechanistic studies and a series of experiments with various stereoisomers of cinchona alkaloid revealed that the ring-opening proceeded via general-base catalysis at the quinuclidine-nitrogen in cinchona alkaloid and that the C(9)-hydroxyl group in the alkaloid was essential for the stereoselection possibly through hydrogen-bonding in the transition state.

Prochiral 2,2-di-substituted malonic acids are also promising candidates for enantiotopic-group differentiation. The author conducted an asymmetric monoesterification of 2-methyl-2-phenylmalonic acid through stereoselective ring-opening of the corresponding prochiral cyclic acylal, isopropylidene methylphenylmalonate, using an alkoxide anion paired with a chiral ammonium cation. The reaction of the acylal with N-benzylquinidinium n-propoxide afforded (S)-2-methyl-2-phenylmalonic acid mono(n-propyl)ester in a 51% e.e.; the selective reduction of the ester group yielded optically active α-methyltropic acid.

Cinchona alkaloid is a naturally occurring chiral tertiary amine with unique properties as a chiral base-catalyst. To im-

prove the utility of this alkaloid as a catalyst, the author synthesized polymer-supported quinines with spacer groups of 7 to 15 atoms length between the polymer matrix and the C(3)-position of the alkaloid, in order to keep the catalytic center apart from the polymer chains. Although the catalytic activity of these polymers was found to vary with the reactions tested, the effect of the spacers was observed for the Michael addition of methyl 1-oxo-2-indancarboxylate to 3-buten-2-one and for the methanolysis of cis-2,4-dimethylglutaric anhydride; the asymmetric yields were improved by inserting the spacers and approached to those with the corresponding non-immobilized quinines.

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