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Stereochemical Studies. IX.[1] Asymmetric Synthesis of 2-Alkylcyclohexanones with Enamine Alkylation[2]

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This paper is concerned with the asymmetric synthesis of 2-alkylcyclohexanones (VI) by alkylation of cyclohexanone enamines (III) of L-proline ester derivatives. Acrylonitrile, methyl acrylate, allyl bromide and ethyl bromoacetate were used as alkylating agents. Several reaction conditions were examined, and plausible reaction mechanisms were proposed. Rates of racemization for VIa and VIc were determined.

Many recent investigations have been explored on asymmetric synthesis.[4] The present paper is concerned with the asymmetric synthesis of 2-alkylcyclohexanone derivatives which are the key intermediates in the total synthesis of optically active steroids, terpenes and alkaloids. Syntheses of optically active 2-alkylcyclohexanone derivatives by resolution[5] or the previously reported asymmetric synthesis[6] are tedious, troublesome and very difficult; no convenient methods has been reported until now.

Enamines are very reactive species which are widely used in synthesis. Alkylation of enamines is the most popular tool to obtain α-alkyl carbonyl compounds.

To this end, fundamental studies for asymmetric alkylation of cyclohexanone enamine were undertaken. Only few published papers[6a,7] concern asymmetric synthesis with enamines. The stereochemistry[8] and reactivities[9] of enamine on alkylation have been well explored, especially for pyrrolidine enamine of cyclohexanone derivatives,[8,9] which is very reactive.[9] Instead of pyrrolidine, we tried to use optically active pyrrolidine derivatives; L-proline esters (I) which are now readily available, as the amine component of cyclohexanone enamines.

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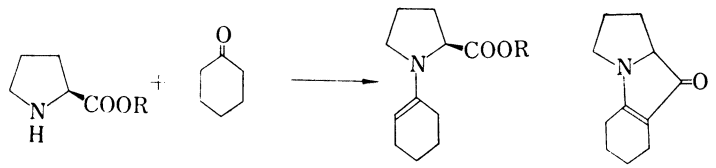
3) Location: *Hongo, Bunkyo-ku, Tokyo.*
4) Reviews of asymmetric synthesis recently been published: *a*) D.R. Boyd and M.A. McKervey, *Quart. Rev. (London)*, **22**, 95 (1968); *b*) J. Mathieu and J. Weill-Raynal, *Bull. Soc. Chim. France*, **1968**, 1211.
5) *a*) W.R. Adams, O.L. Chapman, J.B. Sieja, and W.J. Welstead, Jr., *J. Am. Chem. Soc.*, **88**, 162 (1966) and cited therein; *b*) E.J. Corey and R.B. Mitra, *ibid.*, **84**, 2938 (1962); *c*) R. Bucourt, L. Nedelec, J.C. Gasc, and J. Weill-Raynall, *Bull. Soc. Chim. France*, **1967**, 561; *d*) M. Luche-Ronteix, S. Bory, and M. Dvolaitzky, *ibid.*, **1970**, 2564.
6) *a*) D. Méa-Jacheet and A. Moreau, *Bull. Soc. Chim. France*, **1968**, 4571; *b*) R. Kuhn, H.E. Driesen, and H.J. Haas, *Ann.*, **718**, 78 (1968).
7) After our preliminary communication on the subject appeared, the following paper was reported: L.A. Paquette and J.P. Freeman, *J. Am. Chem. Soc.*, **91**, 7548 (1969).
8) *a*) W.R.N. Williamson, *Tetrahedron*, 3, 314 (1958); *b*) F. Johnson and A. Whitehead, *Tetrahedron Letters*, **1964**, 3825; *c*) H.J. Schaeffer and V.K. Jain, *J. Org. Chem.*, **29**, 2594 (1964); *d*) F. Johnson and S.K. Malhotra, *J. Am. Chem. Soc.*, **87**, 5492, 5493 (1965); *e*) S. Danishefsky and M. Feldman, *Tetrahedron Letters*, **1965**, 1135; *f*) S.K. Malhotra and F. Johnson, *ibid.*, **1965**, 4027; *g*) W.D. Gurowitz and M.A. Joseph, *ibid.*, **1965**, 4433; *h*) S.K. Malhotra, D.F. Moakley, and F. Johnson, *Chem. Comm.*, **1967**, 448; *i*) M. Charles, G. Descotes, J-C Martin, and Y. Querou, *Bull. Soc. Chim. France*, **1968**, 4159; *j*) W.D. Gurowitz and M.A. Joseph, *J. Org. Chem.*, **32**, 3289 (1967); *k*) F. Johnson, *Chem. Rev.*, **68**, 375 (1968); *l*) F.P. Colonna, M. Forchiassin, A. Risaliti, and E. Valentin, *Tetrahedron Letters*, **1970**, 571.
9) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

By alkylation of these enamines (III) with electrophilic olefins, *e.g.* acrylonitrile and methyl acrylate, and also with strongly electrophilic halides, *e.g.* allyl bromide, ethyl bromoacetate, and benzyl bromide, we succeeded in obtaining optically active 2-alkylcyclohexanones induced by L-proline derivatives.



I II III IV

Ia : R = CH_3
Ib : R = CH_2CH_3
Ic : R = *t*-Bu

IIIa : R = CH_3
IIIb : R = CH_2CH_3
IIIc : R = *t*-Bu

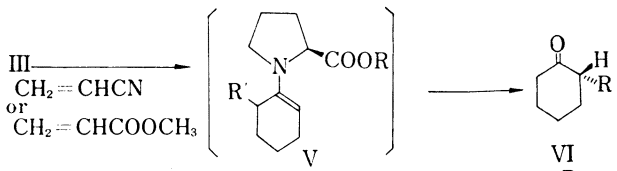
Chart 1

Formation of Enamines (III) with Cyclohexanone and L-Proline Esters

Condensation of L-proline methyl or ethyl ester (Ia or Ib) with cyclohexanone (II) in benzene under reflux in the presence of molecular sieves 4A for 2 hours gave the corresponding enamines (IIIa, b) which easily undergo intramolecular acylation[10] to afford the cyclized product, IV,[11] with distillation under reduced pressure in the working-up process. With L-proline *t*-butyl ester (Ic),[12] the expected enamine (IIIc) was obtained in a 72% yield under conditions similar to those above. This did not cyclize to give IV under high vacuum distillation. However, some racemization occurred during distillation; depending on the distilling temperature, since distilled enamine (IIIc) ($[\alpha]_D^{29}$ −28.0° (MeOH), bp 107° (0.02 mmHg)) prepared from Ic showing $[\alpha]_D^{30}$ −42.2° (MeOH), was hydrolyzed with a 10% aqueous solution of phosphorous acid to recover Ic, $[\alpha]_D^{33}$ −24.2° (EtOH). Hence, the L-proline ester enamines (IIIa,b,c) obtained were used for asymmetric synthesis without distillation, as shown in the experimental section.

I. Alkylation of Enamines (III) with Electrophilic Olefins

The enamines (III) obtained above were alkylated with electrophilic olefins, such as methyl acrylate and acrylonitrile, under various reaction conditions. 1,4-Asymmetric induction was observed and optically active 2-alkylcyclohexanones were obtained by the usual hydrolysis. The various reaction conditions were examined as follows.



III —CH_2=CHCN or CH_2=$CHCOOCH_3$

V VI

Va : R′ = $-CH_2CH_2CN$ VIa : R = $-CH_2CH_2CN$
Vb : R′ = $-CH_2CH_2COOCH_3$ VIb : R = $-CH_2CH_2COOCH_3$

Chart 2

10) *a*) N.A. Nelson, J.E. Ladbury, and R. Hsi, *J. Am. Chem. Soc.*, **80**, 6633 (1958); *b*) U.K. Pandit, K. de Jongo, and G.T. Koomen, *Tetrahedron Letters*, **1967**, 3529; *c*) Z. Horii, K. Morikawa, C. Iwata, and I. Ninomiya, *Chem. Pharm. Bull.* (Tokyo), **16**, 1686 (1968); *d*) A.I. Meyers, A.H. Reine, J.C. Sircar, K.B. Rao, S. Singh, H. Weidmann, and M. Fitzpatrick, *J. Heterocyclic Chem.*, **5**, 151 (1968); *e*) R.J. Friary, R.W. Franck, and J.F. Tobin, *Chem. Comm.*, **1970**, 283.

11) Further studies on IV will be reported in a subsequent paper.

12) G.W. Anderson and F.M. Callahan, *J. Am. Chem. Soc.*, **82**, 3359 (1960).

Solvent Effects——The effects of solvents on this asymmetric induction are summarized in Table I. After the reflux of Ib with cyclohexanone in benzene for 2 hours with molecular sieves 4A, the benzene was removed and was replaced with CH_3OH, C_2H_5OH, CH_3CN or dioxane. Alkylation of IIIb with acrylonitrile was carried out under reflux for 8 hours in each solvent. As shown in Table I, non-polar aprotic solvents, *i.e.* dioxane and benzene, produced VIa in poor yields, but in good optical yields. In polar protic solvents results were reversed.

TABLE I. Solvent Effects on Alkylation of Enamine IIIb with Acrylonitrile

	Solvents	Dioxane	Benzene	CH_3CN	MeOH	EtOH
VIa	yields (%)	9	8	18	48	55
	$[\theta]_{290}$ (MeOH)	−546 25°	−528 21.5°	−297 19°	−248 28°	−214 27.5°

Effects of Ester Moiety of L-Proline Esters——Methyl, ethyl, and *t*-butyl groups were used as a moiety of proline ester and their steric effects on asymmetric induction were examined. Enamines IIIa–c were refluxed in EtOH or MeOH for 3 hours with 1,2 molar equivalents of acrylonitrile or methyl acrylate respectively. Results are described in Table II, which shows that *t*-butyl group is 2—3 times as great as methyl and ethyl groups in asymmetric induction.

The optical yield of VIb in Tables II and IV will be discussed in the appropriate section of this paper.

TABLE II. Effects of the Ester Moiety of L-Proline Esters on Asymmetric Induction

Alkylating agents	Products	Proline ester R	Me[a]	Et[a]	*t*-Bu	
					Enamine isolated[b]	Enamine not isolated[a]
Acrylonitrile	VIa	yields (%)	34[c]	36[c]	61[d]	41[c]
		$[\alpha]_D$ (MeOH)	+1.2° *c*=3.05 21°	+1.2° *c*=3.37 26.5°	+2.2° *c*=3.03 13°	+2.6° *c*=3.06 12°
		$[\theta]_{290}$ (MeOH)	−160 21°	−218 29°	−281 11°	−384 11°
Methyl acrylate	VIb	yields (%)	32[c]	38[c]	43[d]	33[c]
		$[\alpha]_{460}$ (MeOH)	−1.7° *c*=4.11 23°	−2.3° *c*=4.35 28°	−2.0° *c*=2.02 13°	−4.8° *c*=2.51 14.5°
		$[\theta]_{290}$ (MeOH)	−332 30.5°	−406 24°	−371 14°	−915 13°
		optical yields (%)[e]	15	21	18	43

a) Enamine was not isolated by distillation.
b) Enamine IIIc isolated by distillation was used (IIIc: bp 115° (0.2 mmHg), $[\alpha]_D^{13}$ −29.1° (*c*=1.808, MeOH)).
c) Yields based on L-proline ester (I).
d) Yield based on enamine.
e) Calculated from the $[\alpha]_{460}$ value of optically pure VIb, $[\alpha]_{460}^{12}$ −11.2° (MeOH), obtained by resolution of VII, followed by esterification with diazomethane and deketalization.

Effects of Reaction Temperatures——The effects of reaction temperatures on asymmetric synthesis were examined. Enamine IIIc was alkylated at 20°, 40° or under reflux in EtOH or MeOH with acrylonitrile or methyl acrylate, respectively. Products obtained by subsequent hydrolysis are summarized in Table III and IV. As shown in these tables, at high temperatures VIa and VIb are obtained in poor optical yields. On the other hand, at low temperatures VIa and VIb are obtained in good optical yields although their yields are poor.

TABLE III. Effects of Reaction Temperatures on Asymmetric Induction of Enamine IIIc with Acrylonitrile

Reaction[a] conditions	Product VIa		
	Yields (%)[b]	$[\alpha]_D$ (MeOH)	$[\theta]_{290}$ (MeOH)
20°	15	+3.0°	−549
5 hr		c=2.13, 23°	23.5°
40°	18	+3.0°	−531
3 hr		c=1.61, 18°	20°
Reflux in	41	+2.6°	−384
EtOH, 3 hr		c=3.06, 12°	11°

a) Alkylated in EtOH with 1.2 molar equiv. of acrylonitrile.
b) Yields based on L-proline *t*-butyl ester (Ic).

TABLE IV. Effects of Reaction Temperatues on Asymmetric Induction of Enamine IIIc with Methyl Acrylate

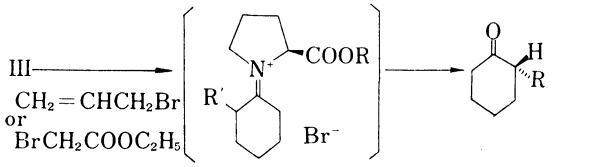
Reaction conditions[a]	Product VIb			
	Yields (%)[b]	$[\alpha]_{460}$ (MeOH)	$[\theta]_{290}$ (MeOH)	Optical yields (%)[c]
20°	17	−6.7°	−1241	59
5 hr		c=2.30, 22°	22°	
40°	22	−6.0°	−1145	53
3 hr		c=3.45, 20°	22°	
Reflux in	33	−4.8°	−915	43
MeOH, 3 hr		c=2.51, 14.5°	13°	

a) Alkylated in MeOH with 1.2 molar equiv. of methyl acrylate.
b) Yields based on L-proline *t*-butyl ester (Ic).
c) Based on the $[\alpha]_{460}$ value of optically pure VIb, ($[\alpha]_{460}$ −11.2° (MeOH)).

II. Alkylation of Enamines (III) with Allyl Bromide

In preliminary experiments, we found that methyl iodide and ethyl bromide showed poor reactivities for the alkylation of the L-proline ester enamines (III). Hence, strongly electrophilic halides such as allyl bromide, ethyl bromoacetate and benzyl bromide were selected as the alkylating agents of III, and the corresponding optically active 2-alkylcyclohexanones (VIc, d) were obtained. Reactions were examined in detail using allyl bromide. The reaction of the cyclohexanone enamines (III) of L-proline derivatives with allyl bromide gave optically active 2-allylcyclohexanone (VIc) by subsequent hydrolysis. Enamines (III) were prepared as above and used without distillation.

Solvent Effects——Solvent effects on the asymmetric induction were examined by reacting enamine IIIb with the 1.5 molar equivalents of allyl bromide in various solvents. Enamine IIIb was prepared as above and the solvent was replaced with the required solvents, *i.e.* dioxane, acetonitrile, chloroform and tetrahydrofuran. A solution of IIIb and allyl bromide in each solvent was refluxed for 12 hours. This was followed by hydrolysis to give optically active 2-allylcyclohexanone (VIc). Results are summarized in Table V. This shows that VIc was obtained in benzene in the best yield,



V
Vc: R′ = −CH2CH=CH2
Vd: R′ = −CH2COOC2H5

VI
VIc: R = −CH2CH=CH2
VId: R = −CH2COOC2H5

Chart 3

and in tetrahydrofuran in the best optical yield. Optical yields of VIc can be calculated from the rotation $[\alpha]_D$ of optically pure VIc, as described in the following section of this paper.

TABLE V. Solvent Effects on Asymmetric Synthesis of 2-Allylcyclohexanone (VIc) through Alkylation of Enamine (IIIb)

Solvents	Product VIc			
	Yields[a] (%)	$[\alpha]_D$ (MeOH)	$[\theta]_{290}$ (MeOH)	optical yields[b] (%)
Benzene	24	−2.7° (c=2.046, 27.5°)	−389 (28°)	20
Dioxane	16	−0.6° (c=4.138, 25°)	−83 (25°)	4
CH_3CN	19	−0.3° (c=3.712, 20°)	−45 (20°)	2
$CHCl_3$	15	−2.7° (c=4.108, 23°)	−383 (23°)	20
THF	11	−3.9° (c=2.316, 26°)	−571 (27°)	29

a) Yields based on L-proline ethyl ester (Ib).
b) Based on the $[\alpha]_D$ value of optically pure VIc.

Effects of Ester Moiety of Proline Esters——Methyl, ethyl, *t*-butyl groups were used as the ester part of proline esters and steric effects on this asymmetric induction were investigated. Enamines (IIIa, b, c) were reacted with 1,5 molar equivalents of allyl bromide in refluxing benzene for 12 hours. Results are given in Table VI.

TABLE VI. Effect of the Ester Moiety of L-Proline Esters on Asymmetric Synthesis of 2-Allylcylclohexanone (VIc) through Enamine Alkylation

III R	Product VIc			
	Yields (%)	$[\alpha]_D$ (MeOH)	$[\theta]_{290}$ (MeOH)	Optical yields[a] (%)
Me	24[b]	−0.6° (c=3.232, 26°)	−86 (26°)	4
Et	24[b]	−2.7° (c=2.046, 27.5°)	−389 (28°)	20
t-Bu	20[b]	−4.0° (c=4.212, 20°)	−594 (20°)	30
t-Bu[c]	24	−2.8° (c=2.004, 10°)	−416 (11.5°)	21

a) Based on the $[\alpha]_D$ value of optically pure VIc.
b) Yields based on L-proline ester(I).
c) Enamine IIIc purified by distillation was used (IIIc: $[\alpha]_D^{14}$ −27° (MeOH)).

The table shows that the degree of asymmetric synthesis on allylation in benzene is enhanced with the increasing bulkiness of the ester moiety of proline esters. When IIIc, purified by distillation, was used as a starting enamine, the optical yields of VIc obtained was smaller than when undistilled IIIc was used. This suggests that IIIc is racemized during distillation.

III. Alkylation of Enamines (III) with Other Alkyl Halides

Besides allyl bromide, asymmetric alkylations of enamines III with ethyl bromoacetate and benzyl bromide were undertaken. The reaction of IIIb with 1,2 molar equivalents of

ethyl bromoacetate in the presence of 1,2 molar equivalents of triethylamine in a solvent and its subsequent hydrolysis gave optically active ethyl 2-oxocyclohexaneacetate (VId). Solvent effects on this asymmetric synthesis are shown in Table VII. Moreover, alkylation of IIIb with benzyl bromide in refluxing benzene gave optically active 2-benzylcyclohexanone VIe, whose optical rotation is very small. Both alkylations were unsatisfactory under the reaction conditions used.

Table VII. Solvent Effects on Asymmetric Synthesis of Ethyl 2-Oxocyclohexaneacetate (VId) by the Reaction of Enamine IIIc with Ethyl Bromoacetate

Solvents	Product VId		
	Yields[a] (%)	$[\alpha]_D$ (MeOH)	$[\theta]_{285}$ (MeOH)
Benzene	13	−5.8° (c=1.816, 9°)	−707 11°
Dioxane	13	−5.2° (c=1.070, 20°	−660 20°
CH_3CN	10	−7.0° (c=1.687, 12°	−849 13.5°

a) Yields based on L-proline *t*-butyl ester (Ic).

Determination of the Absolute Configuration of Obtained Cyclohexanones (VIa—d) and Optically Pure VIb and VIc

All products (VIa—d) obtained from the L-proline enamines III show a negative (CD) circular dichroism maximum at 290 or 285 mμ in methanol (Fig. 1, 2, 3, and 4). They have the same (*S*)-configuration, based on the octant rule.[13,14] We also found that optically active (*S*)-α-substituted cyclohexanones VI are always formed from L-proline enamines III.

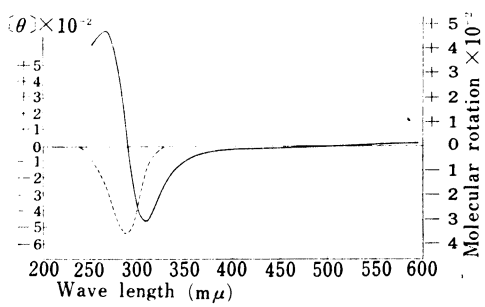


Fig. 1. ORD and CD Curves of the (+)-2-Cyanoethylcyclohexanone (VIa) obtained

——: ORD of VIa
------: CD of VIa (in MeOH at 23°)

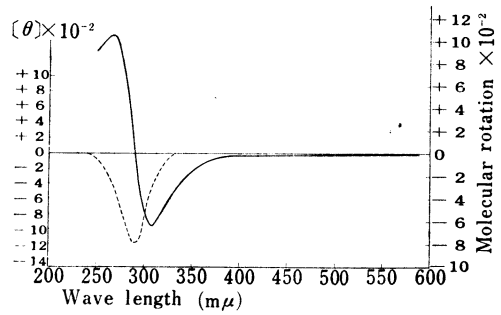


Fig. 2. ORD and CD Curves of the Methyl (−)-3-(2-oxocyclohexyl) propionate (VIb) obtained

——: ORD of VIb
------: CD of VIb (in MeOH at 22°)

To establish the specific rotation of optically pure VIb and VIc, an optically pure reference compound, (−)-2-ethylenedioxycyclohexanepropionic acid (VII), $[\alpha]_D^{10}$ −18.7° (CH_3OH) was obtained by resolution of its racemic modification prepared with quinine as described in the Experimental section. Transformation of (−)-VII to (−)-VIb showed that specific rotation of optically pure (−)-VIb is estimated to be $[\alpha]_{460}^{12}$ −11.2° (CH_3OH). The optical yield of VIb obtained by asymmetric induction was calculated based on this $[\alpha]_{460}$ value.

13) C. Djerassi, *Proc. Chem. Soc.*, **1963**, 299.
14) J.C. Tai and N.L. Allinger, *J. Am. Chem. Soc.*, **88**, 2179 (1966).

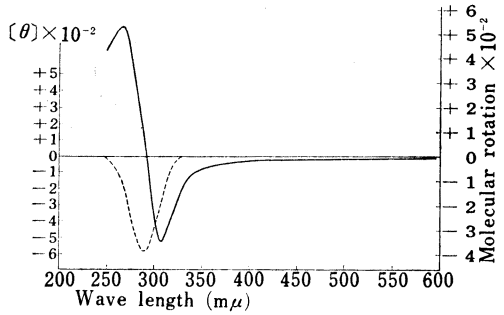


Fig. 3. ORD and CD Curves of the (−)-2-Allylcyclohexanone (VIc) obtained

——: ORD of (−)-VIc in MeOH at 23°
------: CD of (−)-VIc in MeOH at 24°

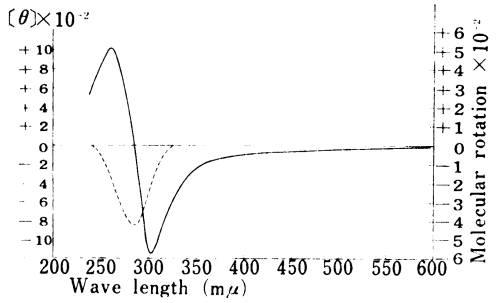


Fig. 4. ORD and CD Curves of the Ethyl (−)-2-oxocylohexaneacetate (VId) obtained

——: ORD of (−)-VId in MeOH at 22°
------: CD of (−)-VId in MeOH at 13.5°

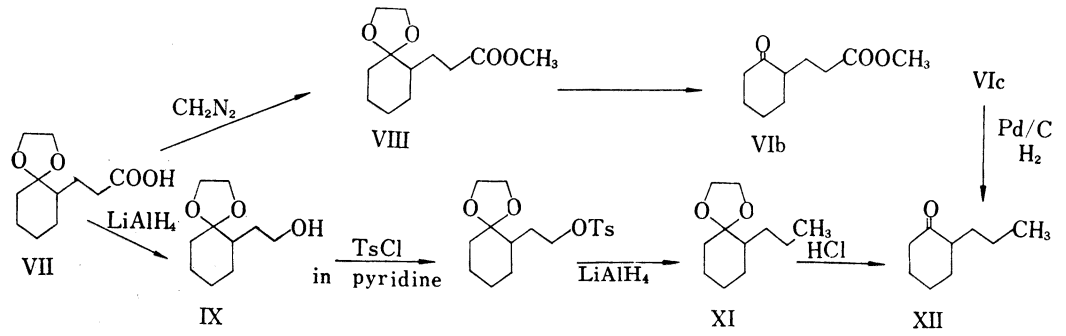


Chart 4

The optical yield of (−)-VIc was obtained as follows: (−)VII ($[\alpha]_D^{10}$ −15.0° (CH_3OH), optical purity 80%) obtained as above was reduced with $LiAlH_4$ to give (−)-2-ethylenedioxycyclohexanepropanol, (−)-(IX) ($[\alpha]_D^{20}$ −18.8° (CH_3OH)). This compound, (−)-IX, was tosylated with *p*-toluenesulfonyl chloride in pyridine to afford (−)-2-ethylenedioxycyclohexanepropanol tosylate, (−)-(X) ($[\alpha]_D^{20}$ −9.4° (CH_3OH)). Reduction of (−)-X with lithium aluminium hydride in refluxing tetrahydrofuran gave (−)-2-propyl-1-ethylenedioxycyclohexane, (−)-(XI) ($[\alpha]_D^{20}$ −22.0° (CH_3OH)). Hydrolysis of this (−)-(XI) by shaking it vigorously in 3N HCl-benzene gave a 7:3 mixture of XI and XII, $[\alpha]_D^{20}$ −22.1° (CH_3OH), determined by gas chromatography. Based on these data, the specific rotation of optically pure (−)-XII was calculated to be $[\alpha]_D^{20}$ −27.9° (CH_3OH). On the other hand, (−) VIc ($[\alpha]_D^{27.5}$ −2.7° (CH_3OH)) obtained by asymmetric synthesis was catalytically reduced with Pd-C to give (−)-XII ($[\alpha]_D^{20}$ −5.5° (CH_3OH)). Therefore, the optical yield of VIc in Table VI can be calculated from these data. Specific rotation of optically pure VIa and VId could not be found because of easy racemization in the course of transformation to VIb or VIc. Optical yields of these compounds VIa and VId are not described in Table I, II, III, and V.

Mechanism of Asymmetric Synthesis

All the optically active 2-substituted cyclohexanones (VIa—d) obtained from L-proline ester derivatives (IIIa—c) show (*S*)-configuration. The following mechanism now seems to account for the observed stereospecificity. Among the conformers of L-proline ester cyclohexanone enamines XIII, XIV, XV, and XVI, XIII and XV seem preferable to XIV and XVI. The trivalency of nitrogen probably causes the ester group of proline to interfere with a hydrogen attached to the double bond in XIV and XVI, if electron overlap is to be maintained

between nitrogen unshared electrons and the π-electrons of the double bond. In XIII and XV, a quasi-equatorial hydrogen at C_6 in XV interferes more with the ester group sterically than a quasi-axial hydrogen at C_6 in XIII.[8] Hence, XIII is the preferable conformation. Axial attack of an entering group at C_2 in XIII results in (*S*)-configuration of 2-substituted cyclo hexanones.

In alkylation of aldehyde enamines with allyl bromide, carbon-alkylated aldehydes were obtained.[15] It appeared that nitrogen alkylation might indeed have occurred first, followed by rearrangement to the carbon-alkylated product.[15d,e] Opitz, *et al.*[16] reported that alkylation of cyclohexanone pyrrolidine enamine with allyl bromide directly gave 2-allyl cyclohexanone. No mechanism for this carbon allylation has been reported. If direct carbon-allylation occurs in this case stereochemical course is to be explained by above mechanism. However, if asymmetric carbon allylation of III proceeds by nitrogen-allylation and a subsequent rearrangement from nitrogen to carbon, as in the allylation of aldehyde enamines,[15d,e] the reaction path can be assumed to be that shown in Chart 6.

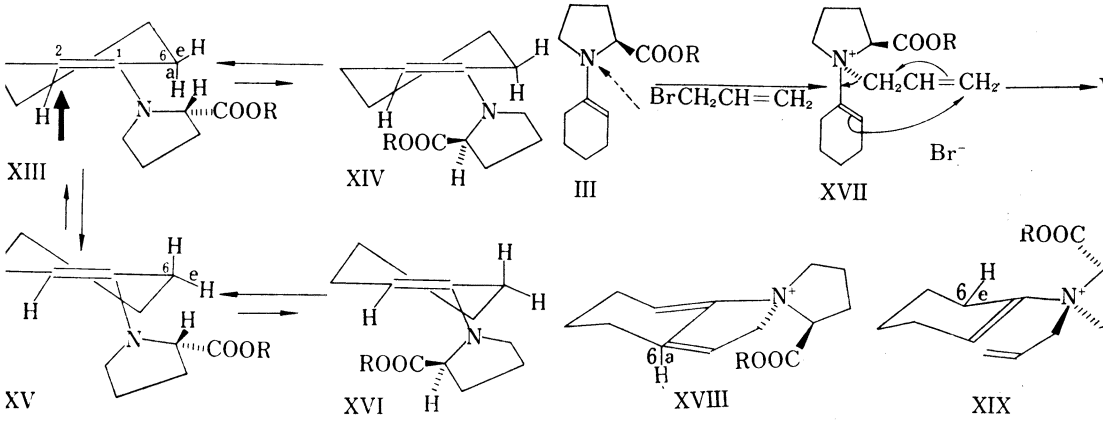


Chart 5 Chart 6

The attack of the allyl group to the nitrogen of the enamine (III), occurs from the backside of the L-proline ester group to form the intermediate (XVII). To rearrange the allyl group, attached to the nitrogen, to the cyclohexene ring, the allyl group should approach the double bond of the cyclohexene ring. For this purpose, two conformers XVIII and XIX are to be considered. According to the Dreiding model, XVIII has greater steric hindrance between an ester group and the quasi-axial hydrogen at C_6 position than dose XIX. Hence, rearrangement of the allyl group by way of XIX is preferable to one through XVIII, and (*S*)-VIc is formed.

Investigation of Racemization of 2-Alkylcyclohexanones

Few studies on the racemization[17] of optically active α-alkyl ketones have been reported. Optically active α-alkyl ketones, having an enolizable hydrogen at the asymmetric center, are easily racemized with strong acids or bases. In general, they are rather stable with acid. The ease of racemization of VIa and VIc obtained by this new asymmetric induction was investigated.

15) *a*) E. Elkik, *Bull. Soc. Chim. France*, **1960**, 972; *b*) G. Opitz and H. Mildenberger, *Ann.*, **649**, 26 (1961); *c*) G. Opitz, H. Hellmann, H. Mildenberger, and H. Suhr, *ibid.*, **649**, 36 (1961); *d*) K.C. Brannock and R.D. Burpitt, *J. Org. Chem.*, **26**, 3576 (1961); *e*) E. Elkik, *Bull. Soc. Chim. France*, **1969**, 903.

16) G. Optitz, H. Mildenberger, and H. Suhr, *Ann.*, **649**, 47 (1961).

17) A.K. Mills and A.E. Wilder Smith, *Helv. Chim. Acta*, **43**, 1915 (1960).

Compound VIa was not racemized at all with AcOH at 25° or at 40°. The racemization rate of VIa with 5% H_2SO_4 in dioxane was measured at 25°. Logarithms of the term α_0/α, where α_0 and α are the initial rotation and the rotation after time t, respectively. At appropriate intervals of time these were plotted against time t in order to draw a good linear graph, as shown in Fig. 5. Half-life time was 16 min. VIa was neither racemized with NEt_3 at 25° and 40°, nor with 1% $NaHCO_3$ in 50% aq. EtOH at 25°. However VIa was racemized very quickly with a strong base. The racemization rate of VIa with 0.008N NaOH in 80% aq. EtOH, as shown in Fig. 6, was in the pseudo-first order at 25°, and half-life time was 5.5 min.

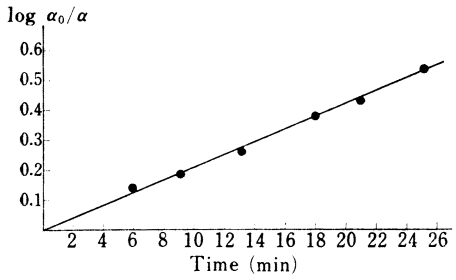


Fig. 5. Racemization of (+)-2-Cyanoethylcyclohexanone (VIa) with 5% H_2SO_4 in Dioxane at 25°

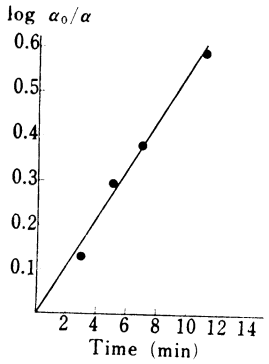


Fig. 6. Raceimzation of (+)-2-Cyanoethylcyclohexanone (VIa) with 0.008N NaOH 80% aq. EtOH at 25°

The compound, (−) VIc, was not racemized at all with AcOH at 25° or at 40°. It was also not racemized by shaking its benzene solution vigorously with 3N HCl for 50 min. The racemization rate of (−)-VIc with 2% H_2SO_4 in dioxane was measured at 25°. Logarithms of the term α_0/α, where α_0 and α are the initial rotation $[\alpha]^{25}_{460}$ and the rotation $[\alpha]^{25}_{460}$ after time t, respectively. At appropriate intervals of time these were plotted against time t producing the good linear graph shown in Fig. 7. Half-life time was 8 min. (−)-VIc was not racemized with NEt_3 (27% Et_3N in benzene) at 25° and 40°.

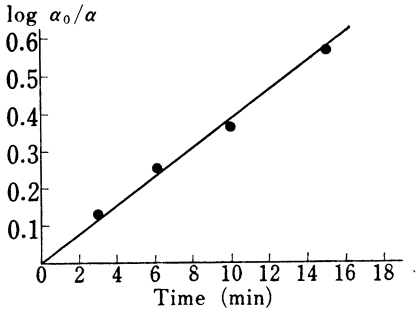


Fig. 7. Racemization of (−)-2-Allylcyclohexanone (VIc) with 2% H_2SO_4 in Dioxane at 25°

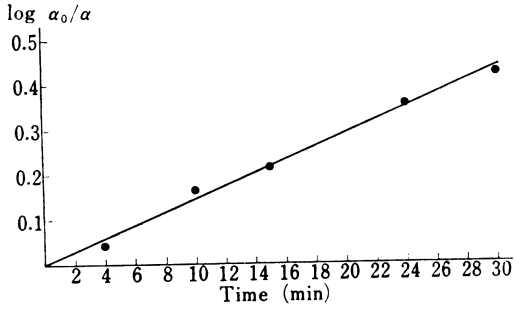


Fig. 8. Racemization of (−)-2-Allylcyclohexanone (VIc) with 0.008N NaOH in 80% aq. EtOH at 25°

However, it was racemized with a strong base. The racemization rate of (−)-VIc with 0.008N NaOH in 80% aq. EtOH, as shown in Fig. 8, was in the pseudo-first order at 25°, and half-life time was 21 min.

Experimental[18]

General Procedure for Preparation of Cyclohexanone Enamines (III) of L-Proline Esters

Enamines (III) were prepared by treating cyclohexanone (II) with L-proline esters (I) in the presence of molecular sieves 4A as the dehydrating agent in refluxing benzene for 2 hours with stirring.

Cyclohexanone Enamine (IIIc) of L-Proline *t*-Butyl Ester——A solution of 5.56 g (0.0325 mole) of L-proline *t*-butyl ester (Ic) and 5.00 g (0.0488 mole) of cyclohexanone (II) in 30 ml of benzene was refluxed for 2 hours with stirring, using 5.0 g of molecular sieves 4A as the dehydrating agent. Molecular sieves were filtered off and the solvent was removed from the filtrate under reduced pressure. Residual oil was distilled under a high vacuum to give 5.86 g (yield 72%) of enamine (IIIc), bp 115° (0.2 mmHg). $[\alpha]_D^{22}$ −29.1° (c=1.808, MeOH), IR ν_{max}^{film} cm^{-1}: 1730 (ester), 1645 (enamine double bond).

Hydrolysis of IIIc——The solution of 2.0 g of IIIc ($[\alpha]_D^{29}$ −28.0° (c=1.420, MeOH)), prepared from L-proline *t*-butyl ester (Ic) ($[\alpha]^{30}$ −42.0° (c=0.920, EtOH)) and cyclohexanone (II), in 30 ml of ether was shaken with 10% aqueous solution of phosphorous acid. The aqueous layer was washed with ether, alkalized with 20% Na_2CO_3 under cooling and extracted with ether. The organic layer was washed with a saturated solution of NaCl, then dried over anhydrous Na_2SO_4. The solvent was evaporated and the residual oil was distilled under reduced pressure to afford 0.30 g of Ic: bp 87° (18 mmHg) $[\alpha]_D^{33}$ −24.2° (c=1.176, EtOH). This was identified by infrared and gas chromatographic analyses.

1,2,3,5,6,7,8,9a-Octahydro-9H-pyrrolo[1,2-*a*]indol-9-one (IV)——A solution of 8.0 g (0.063 mole) of L-proline ethyl ester (Ib) and 6.2 g (0.063 mole) of cyclohexanone (II) in 60 ml of benzene was refluxed for 21 hours in the presence of a catalytic amount of *p*-toluenesulfonic acid with Dean–Stark apparatus. The solvent was evaporated and residual oil was distilled to give 6.4 g (yield 58%) of IV: bp 150° (2.5 mmHg), IR ν_{max}^{film} cm^{-1}: 1665 (α,β-unsaturated ketone). NMR (in CCl_4) τ: 7.5—8.5 (12H, multiplet), 6.75—7.0 (2H, multiplet, -CH_2N-), 6.38 (1H, quartet, J=7 cps, N-CH-CO-).

Alkylation of Enamines (III) with Electrophilic Olefins

(−)-2-Cyanoethylcyclohexanone (VIa)——A solution of 2.00 g (0.0160 mole) of L-proline ethyl ester (Ib) and 1.92 g (0.0192 mole) of cyclohexanone (II) in 20 ml of benzene was refluxed under stirring for 2 hours with 2.0 g of molecular sieves 4A. The molecular sieves were filtered off and the filtrate was evaporated under reduced pressure. Residual oil was dissolved in 20 ml of EtOH, then 1.57 g (0.0192 mole) of acrylonitrile was added to the solution. The reaction mixture was refluxed for 8 hours. The solvent was evaporated under reduced pressure and benzene was added to the residue. The solution of benzene was shaken with ice cooling in 10% hydrochloric acid. The benzene layer was separated and the aqueous layer was extracted with benzene. Benzene layers and benzene extracts were combined, washed with water, neutralized with some drops of sat. $NaHCO_3$ aqueous solution, then dried over anhyd. Na_2SO_4. The solvent was evaporated. The residual oil was distilled to give 1.65 g (yield 55%) of VIa: bp 119° (2.5 mmHg) ((±) VIa: reported[9] bp 141—145° (10 mmHg)) $[\alpha]_D^{25}$ +1.2° (c=4.072, MeOH), CD (c=4.072, MeOH) $[\theta]^{27.5}$ (mμ): −214 (290) (negative maximum). IR ν_{max}^{film} cm^{-1}: 2250 (CN), 1713 (C=O). *Anal.* Calcd. for $C_9H_{13}ON$: C, 71.47; H, 8.67; N, 9.26. Found: C, 71.34; H, 8.43; N, 9.05. Semicarbazone: colorless leaves, mp 162—163°. *Anal.* Calcd. for $C_{10}H_{16}ON_4$: C, 57.67; H, 7.74; N, 26.90. Found: C, 57.71; H, 7.86; N, 26.88. The ORD spectrum of VIa obtained by the reaction of IIIc with acrylonitrile in EtOH at 20° is as follows: ORD (c=2.13, MeOH) $[\alpha]^{23}$ (mμ): +3.0° (589), −1.1° (500), −3.6° (450), −10.3° (400), −33.0° (350), −192° (304) (trough), 0° (290), +295° (267) (peak).

Methyl (−)-2-Oxocyclohexanepropionate (VIb)——The reaction of 3.00 g (0.0240 mole) of L-proline ethyl ester (Ib) with 2.89 g (0.0288 mole) of cyclohexanone (II) was carried out in a manner similar to the procedure described above. The obtained enamine (IIIb), which was not isolated by distillation, was dissolved in 30 ml of MeOH and 2.48 g (0.0288 mole) of methyl acrylate was added to the solution. The reaction mixture was refluxed for 3 hours. The work-up was the same as mentioned above and gave 1.7 g (yield 38%) of VIb; bp 118° (4 mmHg) $[\alpha]_{460}^{28}$ −2.3° (c=4.350, MeOH), CD (c=4.350, MeOH) $[\theta]^{24}$ (mμ): −406 (290) (negative maximum). IR ν_{max}^{film} cm^{-1}: 1738 (ester), 1711 (C=O). *Anal.* Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.97; H, 8.81. Semicarbazone: (recryst. from EtOH–$(iso\text{-}Pro)_2O$), colorless prisms, mp 123—123.5°. *Anal.* Calcd. for $C_{11}H_{19}O_3N_3$: C, 54.75; H, 7.94; N, 17.42. Found: C, 54.92; H, 7.93; N, 17.12. The ORD spectrum of VIb obtained by the reaction of IIIc with methyl acrylate in MeOH at 20° is as follows: ORD (c=2.30, MeOH) $[\alpha]^{22}$ (mμ): −6.7° (460), −20.9° (400), −70.0° (350), −352° (304) (trough), 0° (290), +548° (peak).

18) All melting points are uncorrected. Infrared (IR) spectra were measured using a spectrometer, Model DS-402 Japan Spectroscopic Co., Ltd. Optical activities were determined with a Yanagimoto Photo Direct Reading Polarimeter, Model OR-20. Optical rotatory dispersion (ORD) measurements were carried out with a spectrometer, Model ORD UV-5, Japan Spectroscopic Co., Ltd. Gas chromatographic analyses were performed using a Shimadzu Gas Chromatograph, Model GC-1B (hydrogen flame ionization detector). Nuclear magnetic resonance (NMR) spectra were measured at 60 MC (Japan Electron Optics LAB) in CCl_4 with Me_4Si as the internal reference.

Alkylation of Enamines (III) with Alkyl Halides

(−)-2-Allylcyclohexanone (VIc)——A solution of 5.00 g (0.0400 mole) of L-proline ethyl ester (Ib) and 4.00 g (0.0408 mole) of cyclohexanone (II) in 50 ml of benzene was refluxed for 2 hours with 5.0 g of molecular sieves 4A under stirring. The molecular sieves were filtered off and a solution of 7.25 g (0.0600 mole) of allyl bromide in 20 ml of benzene was added to the filtrate. The reaction solution was refluxed for 12 hours. The same work-up, as described earlier, and distillation gave 1.31 g (yield 24%) of VIc: bp 100° (36 mmHg) (lit.[16] bp 79—80° (12 mmHg)). IR ν_{max}^{film} cm^{-1}: 1716 (C=O), 1642 (C=C), 997, 910 (vinyl). *Anal.* Calcd. for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 77.99; H, 10.33. Optical data are shown in Table V. ORD (c=2.046, MeOH) $[\alpha]^{27.5}$ (mμ): −1.8° (700), −2.7° (589), −3.5° (550), −5.2° (500), −8.5° (450), −15.6° (400), −44.0° (350), −191° (307) (trough), 0° (290), +260° (269) (peak). 2,4-Dinitrophenylhydrazone: orange needles, mp 150° (recryst. from EtOH) (lit.[19] mp 149°). *Anal.* Calcd. for $C_{15}H_{18}O_4N_4$: C, 56.59; H, 5.70; N, 17.60. Found: C, 56.54; H, 5.82; N, 17.71.

Ethyl (−)-2-Oxocyclohexaneacetate (VId)——L-Proline *t*-butyl ester enamine (IIIc) of cyclohexanone was prepared from 2.00 g (0.0116 mole) of L-proline *t*-butyl ester (Ic) and 1.36 g (0.0140 mole) of cyclohexanone (II) in the manner described earlier. The solution of enamine (IIIc), thus, obtained and 2.34 g (0.0140 mole) of ethyl bromoacetate in 40 ml of CH_3CN was refluxed for 3 hours with 1.41 g (0.0140 mole) of Et_3N. The solvent was evaporated under reduced pressure and the residual oil was dissolved in benzene. The same work-up, as described earlier, and silica gel column chromatography gave 0.20 g (yield 10%) of VId: bp 118° (6 mmHg) (lit.[20] bp 130° (10 mmHg). IR ν_{max}^{film} cm^{-1}: 1741 (ester), 1716 (C=O). Optical rotation is shown in Table VII. ORD (c=1.695, MeOH) $[\alpha]^{12.5}$ (mμ): −4.7° (700), −7.0° (589), −8.8° (550), −12.3° (500), −18.0° (450), −30.0° (400), −67.5° (350), −320° (302) (trough), 0° (285), +284° (262) (peak). *Anal.* Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.13; H, 8.70. Semicarbazone ($C_{11}H_{19}O_3N_3$): colorless needles, mp 181.5—182.5° (recryst. from EtOH). *Anal.* Calcd. for $C_{11}H_{19}O_3N_3$: C, 54.75; H, 7.94; N 17.42. Found: C, 55.00; H, 7.94; N, 17.50.

(−)-2-Benzylcyclohexanone (VIe)——Enamine IIIb was prepared from 5.00 g (0.040 mole) of L-proline ethyl ester (Ib) and 4.82 g (0.048 mole) of cyclohexanone (II) in the manner described earlier. The solution of enamine IIIb, thus, obtained and 6.83 g (0.040 mole) of benzyl bromide in 50 ml of benzene was refluxed for 24 hours. The same work-up as described earlier and distillation gave 1.03 g (yield 16.5%) of VIe: bp 130° (2.5 mmHg) (lit.[21] bp 165—166° (18 mmHg)). IR ν_{max}^{film} cm^{-1}: 1712 (C=O), 1607 (phenyl). $[\alpha]_D^{31}$ −0.6° (c=3.012, MeOH). ORD (c=3.012, MeOH) $[\alpha]^{32.5}$ (mμ): −0.4° (700), −0.6° (589), −0.6° (500), −0.7° (450), −1.2° (400), −1.6° (370). Semicarbazone ($C_{14}H_{19}ON_3$): colorless needles, mp 163—164° (recryst. from MeOH) (lit.[21] mp 166—167°). *Anal.* Calcd. for $C_{14}H_{19}ON_3$: C, 68.54; H, 7.81; N, 17.13. Found: C, 68.48; H, 7.58; N, 17.31.

Determination of Optically Pure VIb

Methyl (±)-2-oxocyclohexanepropionate (VIb) was prepared according to the usual enamine method reported by G. Stork.[9]

Methyl (±)-2-Ethylenedioxycyclohexanepropionate (VIII)——(±)-VIII was prepared by the usual method; refluxing azeotropically the solution of (±)-VIb and ethyleneglycol in benzene for 3.5 hours in the presence of a catalytic amount of *p*-toluenesulfonic acid. The work-up was made in the usual manner and distillation gave (±)-VIII in 90% yield; bp 134° (3.5 mmHg). IR ν_{max}^{film} cm^{-1}: 1735 (ester), lack of C=O.

(±)-2-Ethylenedioxycyclohexanepropionic Acid (VII)——(±)-VII was prepared by hydrolyzing (±)-VIII in a methanol solution of KOH at room temperature. The work-up in the usual manner gave (±)-VII in 77% yield: bp 174° (3.0 mmHg). IR ν_{max}^{film} cm^{-1}: 2670 (broad), 1739, 1711 (carboxylic acid). *Anal.* Calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.22; H, 8.54.

2-Ethylenedioxycyclohexanepropionic Acid Quinine Salt (VII-quinine salt)——To a solution of 27.2 g (0.0841 mole) of quinine in 100 ml of EtOH was added 18.00 g (0.0841 mole) of (±)-VII, then the solvent was evaporated to dryness. The residual oil was dissolved in 100 ml of ether and an undissolved precipitate was filtered off. After the ether solution had been kept standing at room temperature for one day, the separated crystals of quinine salt were collected. Systematic recrystallization of these crystals from acetone gave 2.0 g of VII-quinine salt; colorless needles, mp 98°. $[\alpha]_D^7$ −133.1° (c=1.608, MeOH). *Anal.* Calcd. for $C_{31}H_{42}O_6N_2 \cdot H_2O$: C, 66.88; H, 7.97; N, 5.03. Found: C, 66.88; H, 7.90; N, 5.38.

(−)-2-Ethylenedioxycyclohexanepropionic Acid (VII)——A solution of 1.9 g of the VII-quinine salt obtained above in 40 ml of $CHCl_3$ was shaken twice with 20 ml of 10% hydrochloric acid, washed with water, then dried over anhyd. Na_2SO_4. The solvent was removed *in vacuo*. Distillation of the residual oil gave 0.5 g of (−)-VII: bp 143° (1.5 mmHg), $[\alpha]_D^{10}$ −18.7° (c=1.494, MeOH) $[\alpha]_{460}^{10}$ −33.6° (c=1.494, MeOH). Its infrared spectrum was identical with that of (±)-VII prepared as described earlier.

Methyl (−)-2-Ethylenedioxycyclohexanepropionate (VIII)——Esterification of (−)-VII ($[\alpha]_D^{10}$ −18.7° (c=1.494, MeOH)) was worked up in the usual manner by diazomethane. The obtained crude oil underwent

19) G. Optiz and H. Mildenberger, *Ann.*, **650**, 115 (1961).
20) H.E. Baumgarten, P.L. Creger, and C.E. Villars, *J. Am. Chem. Soc.*, **80**, 6609 (1958).
21) M. Tiffeneau and M. Porcher, *Bull. Soc. Chim. France*, **31**, 331 (1931).

purification by column chromatography on silica gel using $CHCl_3$ as an eluent. Distillation gave (−)-VIII: bp 108° (2 mmHg), $[\alpha]_D^{10}$ −16.6° (c=1.454, MeOH) $[\alpha]_{460}^{10}$ −27.1° (c=1.454, MeOH). This infrared spectrum was identical with that of (±)-VIII prepared as described earlier.

Methyl (−)-2-Oxocyclohexanepropionate (VIb) from (−)-VIII——A solution of 0.35 g of (−)-VIII ($[\alpha]_D^{10}$ −16.6° (c=1.454, MeOH)) in 20 ml of benzene was vigorously shaken with 20 ml of 3 N HCl in 100 ml of Magen for 30 min. The benzene layer was separated, and washed with water, then dried over anhyd. Na_2SO_4. The solvent was removed *in vacuo* and the residual oil was distilled to give 0.15 g of a mixture of VIII and VIb: bp 2 mmHg 130°—140° (bath temperature) $[\alpha]_D^{12}$ −4.1° (c=1.726, MeOH), $[\alpha]_{460}^{12}$ −15.2° (c=1.726, MeOH). IR ν_{max}^{film} cm^{-1}: 1714 (C=O), 1741 (eater). This was estimated to be a 25: 75 mixture of VIII to VIb using gas chromatography on a column 1.5 m long packed with 5% SE-30 on Diasolid L. No racemization of (−)-VIb was observed in this acidic condition.

So from this ratio, the optical rotation of pure VIb was estimated to be $[\alpha]_{460}^{12}$ −11.2° (c=1.726, MeOH). From this value the optical yields of VIb, which was synthesized asymmetrically using this enamine method, were calculated. They are summarized in Table II, III, and IV.

Determination of Optically Pure VIc

(−)-2-Ethylenedioxycyclohexanepropanol (IX)——The solution of 1.60 g (0.0075 mole) of (−)-VII ($[\alpha]_D^{10}$ −15.0° (c=1.060, MeOH), optical purity 80%) was hydrogenated with 0.29 g of $LiAlH_4$ in 25 ml of abs. ether under reflux for 2.5 hours. The usual work-up and distillation gave 1.32 g (yield 88%) of (−)-IX: bp 135° (9 mmHg). IR ν_{max}^{film} cm^{-1}: 3400 (OH). NMR (in $CDCl_3$) τ: 8.0—9.0 (13H), 7.60 (1H, singlet, OH), 6.35 (2H, multiplet, CH_2OH), 6.05 (4H, singlet, $\langle O_O]$). *Anal.* Calcd. for $C_{11}H_{20}O_3$. C, 65.97; H, 10.07. Found: C, 65.74; H, 10.07. $[\alpha]_D^{20}$ −18.8° (c=1.000, MeOH).

(−)-2-Ethylenedioxycyclohexanepropanol Tosylate (X)——1.00 g (0.0055 mole) of (−)-XI ($[\alpha]_D^{20}$ −18.8° (c=1.000, MeOH)) was tosylated with 1.26 g (0.0066 mole) of tosyl chloride in 7.5 ml of abs. pyridine under ice cooling for 4 hours. The reaction mixture was dissolved in AcOEt. The AcOEt solution was washed with ice water several times, ice cooling 10% HCl, sat. $NaHCO_3$ and H_2O, then dried over anhydrous Na_2SO_4. The solvent was evaporated and the residual oil was purified by silica gel column chromatography to give 1.56 g of (−)-X (yield 80%) as a viscous oil. IR ν_{max}^{film} cm^{-1}: 1600 (aromatic), 1362, 1177 (SO_2) $[\alpha]_D^{20}$ −9.4° (c=1.022, MeOH). NMR (in $CDCl_3$) τ: 7.9—9.1 (13H), 7.55 (3H, singlet, $SO_2C_6H_4CH_3$), 6.12 (4H, singlet, $\langle O_O]$), 5.85—6.40 (2H, multiplet, $CH_2OSO_2C_6H_4CH_3$), 2.15—2.85 (4H, $SO_2C_6H_4CH_3$).

(−)-1-Ethylenedioxy-2-propylcyclohexane (XI)——The solution of 1.15 g (0.0032 mole) of (−)-X ($[\alpha]_D^{20}$ −9.4° (c=1.022, MeOH)) in 20 ml of abs. THF was refluxed with 0.17 g of $LiAlH_4$ for 2.5 hours. The usual work-up was followed, and the liquid obtained was distilled to afford 0.49 g of (−)-XI (yield 83%): bp 98° (15 mmHg). $[\alpha]_D^{20}$ −22.0° (c=1.002, MeOH). NMR (in $CDCl_3$) τ: 8.05—9.30 (16H), 6.08 (4H, singlet, $\langle O_O]$). *Anal.* Calcd. for $C_{11}H_{20}O_2$: C, 71.73; H, 10.87. Found: C, 71.44; H, 10.76.

Hydrolysis of (−)-1-Ethylenedioxy-2-propylcyclohexane (XI)——The solution of 0.20 g of (−)-(XI) ($[\alpha]_D^{20}$ −22.0° (c=1.002, MeOH)) in 6 ml of benzene was shaken vigorously with 10 ml of 3N HCl for 45 min in Magen. The benzene layer was washed with H_2O, neutralized with $NaHCO_3$, then dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residual liquid was distilled to give 80 mg of a colorless liquid (bp 100—110° (65 mmHg)), which was a 3: 7 mixture of XII to XI based on gas chromatographic analysis. The optical rotation of this mixture was $[\alpha]_D^{20}$−22.1° (c=0.920, MeOH). No racemization of (−)-XII was observed in this acidic condition. Therefore, the pure optical rotation of XII, corrected for optical purity of the starting carboxylic acid (VII), was $[\alpha]_D^{20}$ −27.9° (MeOH).

(−)-2-Propylcyclohexanone (XII) from (−)-2-Allylcyclohexanone (VIc)——0.40 g (0.0029 mole) of (−)-VIc ($[\alpha]_D^{27.5}$−2.7° (c=2.046, MeOH), $[\theta]_{290}^{28}$−389 (0.148 mole/liter, MeOH)) was catalytically reduced in 10 ml of EtOH with 0.10 g of 5% Pd/C under shaking for 15 min. The catalyst was filtered off and the filtrate was evaporated. The residual liquid was distilled to give 0.37 g (yield 90%) of (−)-XII: bp 105° (45 mmHg). (lit.[22] bp 95—96° (25 mmHg). IR ν_{max}^{film} cm^{-1}: 1715 (C=O). $[\alpha]_D^{20}$−5.5° (c=1.738, MeOH). ORD (c=1.738, MeOH) $[\alpha]^{20}$ (mμ): −3.9° (700), −5.5° (589), −9.2° (500), −14.0° (450), −24.2° (400), −58.0° (350), −241.6° (305) (trough), 0° (290), +236.0° (265) (peak). CD (0.124 mole/liter, MeOH) $[\theta]^{22}$ (mμ): −452 (290) (negative maximum). This sample (XII) was identical with that obtained by hydrolysis of (−)-XI. Identity was established by comparison of infrared spectra, and retention time in the gas chromatogram.

Semicarbazone: colorless needles, mp 130° (recryst. from EtOH) (lit.[22] mp 130°). *Anal.* Calcd. for $C_{10}H_{19}ON_3$: C, 60.88; H, 9.71; N, 21.30. Found: C, 60.92; H, 9.82; N, 21.36.

22) Marc Tiffenneau, M.B. Tchoubar, M. Saiaslambert, and M. LeTellier-Dupre, *Bull. Soc. Chim. France*, **1947**, 445.