[Chem. Pharm. Bull. 21(1) 47—53 (1973)]

UDC 547.743.1'592.2.04 : 547.594.3.057

Stereochemical Studies. XIX.[1] Asymmetric Synthesis of 2-Alkyl-4-substituted Cyclohexanones with Enamine Alkylation

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(Received May 1, 1972)

2-, or 4-Alkylcyclohexanone enamines of L-proline *t*-butyl ester were formed. Asymmetric syntheses of 2-alkylcyclohexanone derivatives were carried out by these enamines reacting with alkylating agents, *i.e.* acrylonitrile, methyl acrylate, and allyl bromide.

The mechanism of this asymmetric induction was deduced from the experimental results.

In a previous paper,[3] the successful asymmetric synthesis of 2-alkylcyclohexanone derivatives through alkylation of the cyclohexanone enamines of L-proline esters was reported. In extending this work, we performed a similar asymmetric synthesis of 2-alkyl-4-substituted cyclohexanones by alkylation of the 4-substituted cyclohexanone enamine of L-proline *t*-butyl ester reported to be the most effective amine component of this enamine for asymmetric synthesis.[3]

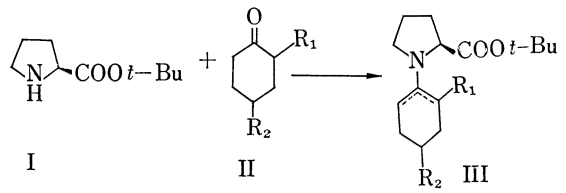
The stereochemistry of 2-alkylcycohexanone pyrrolidine enamines has been well investigated,[4] but few studies have been done on the double bond isomers of the pyrrolidine enamines of cyclohexanones,[4b,h,i] with a substituent at the 3 or 4 position of cyclohexanone or at the 2 position of the pyrrolidine ring.[4g] Little is known about the alkylation of these substituted cyclohexanone pyrrolidine enamines since the products are very complicated.

Instead of pyrrolidine, L-proline *t*-butyl ester (I) was used as the amine component of 2 or 4-substituted cyclohexanone enamine for asymmetric induction. Reaction of I with IIa—c afforded the respective optically active enamines (III—V) which subsequently were alkylated with acrylonitrile, methyl acrylate, and allyl bromide and then were hydrolyzed to give optically active 2-alkylcyclohexanone derivatives.

I. Formation of Enamines (III—V)

The L-proline *t*-butyl ester enamines (III—V) of cyclohexanone derivatives were prepared by refluxing I and 2-, or 4-alkycyclohexanone (II) in benzene for 2 hours using molecular sieves 4A as the dehydrating agent. Yields, optical rotations, and physical data for enamines (III—V) are summarized in Table I. All the enamines obtained can be distilled and their distillates show optical rotation. However, it was found that they also partially racemize during distillation even under reduced pressure.[3] Thus, we used enamines without distillation in the following asymmetric synthesis. As shown in Table I, enamines IV and V were prepared in about 70% yields from I and 4-alkylcyclohexanones (IIb and IIc). As reported in a previous paper,[3] the cyclohexanone enamine (VI) of L-proline *t*-butyl ester

1) Part XVIII: M. Yoh, K. Koga, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **20**, 2017 (1972).
2) Location: *Hongo, Bunkyo-ku, Tokyo.*
3) K. Hiroi, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **20**, 246 (1972).
4) *a*) W.D.N. Williamson, *Tetrahedron*, **3**, 314 (1958); *b*) M.E. Kuehne, *J. Am. Chem. Soc.*, **81**, 5400 (1959); *c*) H.J. Schaeffer and V.K. Jain, *J. Org. Chem.*, **29**, 2595 (1964); *d*) F. Johnson and A. Whitehead, *Tetrahedron Letters*, **1964**, 3825; *e*) S.K. Malhotra and F. Johnson, *ibid.*, **1965**, 4027; *f*) W.D. Gurowitz and M.A. Joseph, *ibid.*, **1965**, 4433; *g*) *Idem*, *J. Org. Chem.*, **32**, 3289 (1967); *h*) S.K. Malhotra, D.F. Moakley, and F. Johnson, *Chem. Comm.*, **1967**, 448; *i*) M. Charles, G. Descates, J-C. Mertin, and Y. Querou, *Bull. Soc. Chim. France*, **1968**, 4159; *j*) E.P. Colonna, M. Forchiassin, A. Risaliti, and E. Valentin, *Tetrahedron Letters*, **1970**, 571.



I II III

	R_1	R_2		R_1	R_2
IIa:	CH_3	H	III :	CH_3	H
IIb:	H	CH_3	IV:	H	CH_3
IIc:	H	*t*-Bu	V :	H	*t*-Bu
			VI:	H	H

Chart 1

was obtained in a 72% yield. Thus, substituents at 4 position do not sterically affect the formation of enamines (IV and V). With 2-methylcyclohexanone (IIa), enamine III was obtained in only a 12% yield even though reflux was continued for 9.5 hours in the presence of a small amount of *p*-toluenesulfonic acid. This is probably due to steric interference between the 2-methyl group and *t*-butyl ester.

It has been shown[4b,c,d,e,f,g,h] that the methyl group of the cyclohexene ring in the pyrrolidine enamine (VII) of 2-methylcyclohexanone sterically interferes with the methylene at the 2′ position attached to nitrogen. Therefore, severe steric interaction must exist between the methyl group and *t*-butyl ester in III.

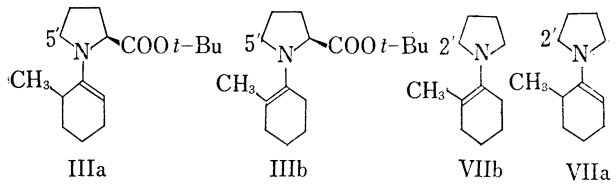
Table I. Enamine Formation (III—V)

Enamine	bp (mmHg)	Yield %	IR ν_{max}^{neat} cm^{-1}	$[\alpha]_D$ (MeOH)[a]
III[b]	112—115° (0.10)	12	1743, 1737 (ester) 1645 (enamine)	−1.4° (c=1.596, 28.5°)
IV[c]	116° (0.06)	70	1741, 1727 (ester) 1644 (enamine)	−29.5° (c=1.458, 20°)
V[c]	128° (0.025)	65	1741, 1727 (ester) 1648 (enamine)	−38.4° (c=1.220, 18.5°)

a) Optical rotations of distilled enamines.
b) Refluxed in benzene for 9.5 hours in the presence of a small amount of *p*-toluenesulfonic acid with Dean-Stark Apparatus.
c) Refluxed in benzene for 2 hours with stirring, using molecular sieves 4A as the dehydratiog agent.

Double Bond Isomer of Enamine (III) by Nuclear Magnetic Resonance (NMR) Spectral Analysis[5]

With the 2-methylcyclohexanone enamine (III) of L-proline *t*-butyl ester, the less substituted double bond isomer and the more substituted one should be considered. IIIa and IIIb may be considered as having the predicted isomer of III under the overlap of a lone pair of nitrogen with double bond π electrons because of steric hindrance between *t*-butyl ester and the methyl group. Recently Gurowitz[4f] reported on the structure of enamines derived from 2-methylcyclohexanone and estimated the ratio of VIIa to VIIb as 90:10 using an NMR technique. We tried to analyze enamine III in the same manner.



IIIa IIIb VIIb VIIa

Chart 2

We analyzed the two isomers (IIIa and IIIb) by comparing the

5) All NMR spectra were measure at 60Mc (Japan Electron Optics LAB) in CCl_4 (5—10%) with Me_4Si as the internal reference.

area of a vinyl proton (at 5.84 τ) of III, with that of the *t*-butyl group (9H, at 8.50 τ) in the NMR spectrum. According to this analysis enamine III exists in IIIa at about 100% but does not exist in IIIb.

Perhaps this result can be explained by the large steric effect between the methyl substituent and 5′-methylene, caused by the overlap of a lone pair of nitrogen with double bond π-electrons in IIIb. This steric effect has already been observed many times.[4b,e,f]

With the 4-alkylcyclohexanone enamines (IV and V) of L-proline *t*-butyl ester, vinyl protons appear at 5.92 τ in IV and at 5.40 τ in V.

II. Alkylation of 2-, or 4-Methylcyclohexanone Enamines (III, and IV) of L-Proline *t*-Butyl ester with Acrylonitrile

The 2-methylcyclohexanone enamine (III) of L-proline *t*-butyl ester could not be alkylated with acrylonitrile. This seems to be due to steric hindrance of the 2-methyl group and *t*-butyl ester in enamine alkylation.

The 4-methylcyclohexanone enamine (IV) of L-proline *t*-butyl ester was alkylated with acrylonitrile in EtOH. In this solvent the best yield was obtained as a diastereoisomeric mixture of optically active 2-cyanoethyl-4-methylcyclohexanone (IX) after hydrolysis. This mixture, IXa and IXb, was analyzed by gas chromatography, then separated by column chromatography on silica gel. Yields, and optical data are shown in Table II and III.

Stereochemical assingment of the diastereoisomers (IX) was made by converting the less stable *trans*-isomer (IXb) to the more stable *cis*-isomer (IXa) with ion exchanger Amberlite IRA-400 (OH^- type). The ratio of diastereoisomers obtained at various reaction temperatures is summarized in Table II. The ratio of the less stable isomer (IXb) increased at lower reaction temperatures. It is to be notable that the less stable isomer (IXb) was preferentically produced by this enamine method.

Table II. Yields and Ratios of Diastereoisomers of IXa and IXb at Various Reaction Temperatures

Reaction conditions[a]	Yield of IX (%)	Ratio of IXa to IXb	
		cis-IXa (%)	*trans*-IXb (%)
20°	14	17	83
40°	19	22	78
78°	46	32	68

a) Reacted IV with acrylonitrile in EtOH for 3 hours.

Table III. Optical Data for 2-Cyanoethyl-4-methylcyclohexanone Derivatives (IXa and IXb) obtained by Asymmetric Cyanoethylation

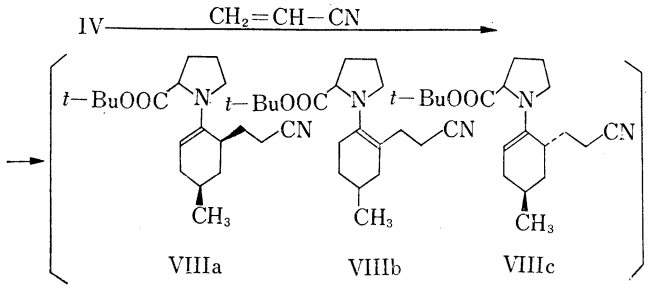
Product	Yield[a] (%)	Isomer	$[\alpha]_D$ (MeOH)	$[\theta]$ (MeOH)	Absolute configuration
IX	46[b]	*cis* IXa	−0.9° c=2.227 25°	+307 291 mμ, 27.5°	2(*S*), 4(*S*)
		trans IXb	−4.4° c=1.953 25°	−561 291 mμ, 25.5°	2(*R*), 4(*S*)

a) yields based on I
b) IV was refluxed with acrylonitrile in EtOH for 3 hours.

Enamine IV was alkylated with acrylonitrile in EtOH at constant temperatures and a portion of reaction mixture was hydrolyzed with dil. hydrochloric acid at a definite interval, to give a mixture of IXa and IXb, whose diastereoisomeric ratio was determined by gas

chromatography. No change of ratio was observed during times measured.[6] Therefore, no isomerization between VIIIa and VIIIc *via* the more substituted double bond isomer VIIIb exists after alkylation, and a new asymmetric center was induced when alkylation occurred.

cis isomer IXa had a positive circular dichroism (CD) maximum at 291 mμ in MeOH and *trans* isomer IXb had a negative one at the same wave length in MeOH. The absolute configurations of *cis*-(—)-IXa and *trans*-(—)-IXb were 2(*S*), 4(*S*)-(—)-IXa and 2(*R*), 4(*S*)-(—)-IXb based on the octant rule.[7]



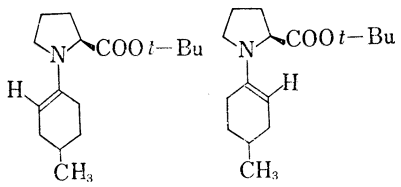


Chart 4

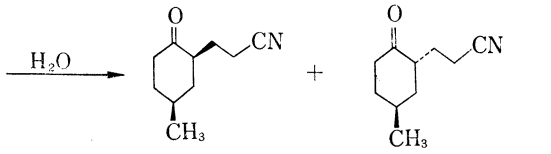


Chart 3

These results are explainable as follows: In the two conformers, IVa and IVb, IVa is more stable than IVb, because of steric interference between an ester group and a hydrogen attached to the double bond in IVb. IVa shows that it has four conformations; Xa, Xb, XIa, and XIb. Xa and XIa equilibrate with Xb and XIb by flipping the cyclohexene ring. XIa and XIb are formed from Xa and Xb by isomerization of the double bond. From the conformational free energy difference of the methyl group in the cyclohexane system,[8] the methyl substituent at the 4 position of enamine IV must be mostly equatorially orientated at these reaction temperatures. Among these four conformations, Xa and XIa are the preferred ones, and XIa is more preferable to Xa due to considerable steric interference of the ester group with a quasi-equatorial hydrogen at the 6 position in Xa when a lone pair on the nitrogen in the enamine is conjugated with the double bond.[3]

An axial attack to conformer XIa occurrs preferectially to give the main product (IXb), which has a negative CD maximum. Equatorial attack to the same conformer (XIa) gives the minor product (IXa), which shows a positive CD maximum.

III. Alkylation of 4-Alkylcyclohexanone Enamine (IV and V) of L-Proline *t*-Butyl Ester with Methyl Acrylate

In alkylation of IV and V with methyl acrylate as the alkylating agent, no diastereometric products could be analyzed by gas chromatography, through all our efforts with various columns, and none could be separated by column chromatography under various conditions.

The reaction of enamine IV with methyl acrylate in refluxing MeOH for 3 hours and subsequent hydrolysis gave a diastereoisomeric mixture of methyl (—)-2-oxo-5-methylcyclohexanepropionate (XII), which had a negative CD maximum at 294 mμ in MeOH.

6) Refer to our following report.
7) C. Djerassi, *Proc. Chem. Soc.*, **1963**, 299.
8) E.L. Eliel, N.L. Allinger, S.J. Angyal, and G.A. Morrison, "Conformational Analysis," John Wiley and Sons, Inc., New York, 1965, p. 11, 44.

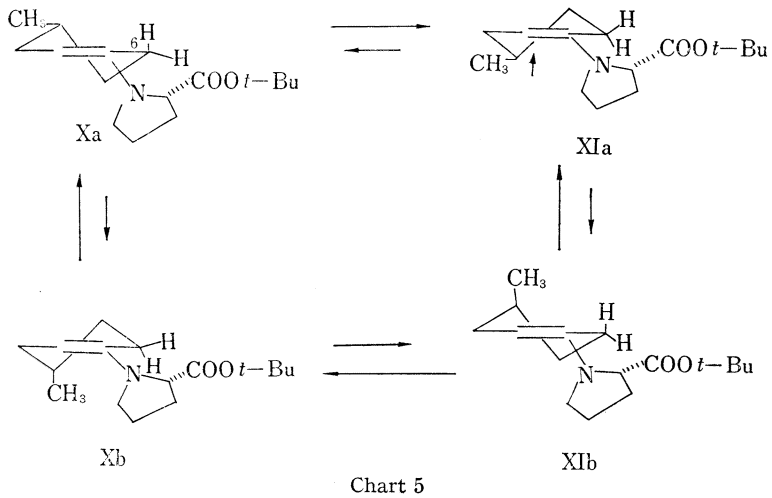
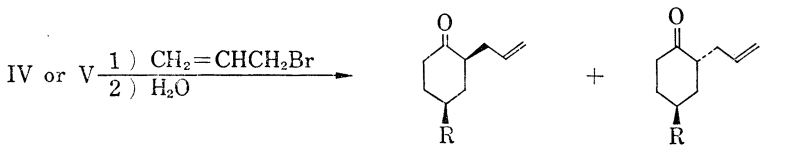


Chart 5

The reaction of enamine V with methyl acrylate in refluxing MeOH for 3 hours gave a diastereoisomeric mixture of methyl (−)-2-oxo-5-*t*-butylcyclohexane propionate (XIII) in 43% yield when followed by hydrolysis.

IV. Alkylation of 4-Alkylcyclohexanone Enamine (IV and V) of L-Proline *t*-Butyl Ester with Allyl Bromide

Enamines IV and V underwent a reaction with a allyl bromide for 20 hours in refluxing benzene. By subsequent hydrolysis the corresponding optically active ketones, 2-allyl-4-methylcyclohexanone (XIV) and 2-allyl-4-*t*-butylcyclohexanone (XV) were obtained as a mixture of diastereoisomers, although their yields were very poor. Diastereoisomeric ratios were analyzed by gas chromatography and stereochemical assignment was made as described in the experimental section. A mixture of diastereoisomers (XIV) could not be separated by silica gel column chromatography under various condition.



XIVa : R=CH_3 XIVb : R=CH_3
XVa : R=*t*−Bu XVb : R=*t*−Bu

Chart 6

TABLE IV. Asymmetric Synthesis of 2-Allylcyclohexanone Derivatives

Product	Yield[a] (%)	Ratio of diastereomers cis %	Ratio of diastereomers trans %	$[\alpha]_D$ (MeOH)	$[\theta]$ (MeOH)
XIV	20	13	87	−8.6°[b] c=1.067, 31.5° trans (XVb)	−637[b] 290 mμ, 31° trans (XVb)
XV	16	13	87	−2.1° c=0.95, 30°	−219 292 mμ, 18°

a) yields based on L-proline *t*-butyl ester (I)
b) Optical data for the diastereomeric mixtures whose ratios are shown in this table.

In the case of XV, *cis* isomer (XVa) could not be purely isolated by column chromatography on silica gel, only *trans* isomer (XVb) with a negative CD maximum at 292 mμ in MeOH was purely isolated. The absolute configuration of (−)-XVb obtained was determined to be 2-(*R*)-4-(*S*) using the octant rule. Ratios of the diastereoisomers and their optical data are summarized Table IV.

As mentioned above, we succeeded in obtaining various kinds of optically active cyclohexanone derivatives by asymmetric synthesis, but the optical yields of these asymmetric reactions could not be calculated because the optically pure products are unknown.

Experimental[9]

General Procedure for the Preparation of Enamines III—V——The most useful method for preparing enamines III—V consisted of heating one equivalent of L-proline *t*-butyl ester (I) with 1.2 equivalent of 2-, or 4-alkylcyclohexanone (IIa—c) in about 30 ml of benzene per 0.05 mole of ketone. Refluxing was continued for 2 hours using molecular sieves 4A as the dehydrating agent. Molecular sieves were filtered off, then the filtrate was evaporated under reduced pressure to give an oil. Distillation of this residual oil gave the expected enamines III—V. Their yields and their spectral and optical data are summarized in Table 1. 2-Methylcyclohexanone enamine III requires the use of *p*-toluenesulfonic acid and longer refluxing periods (9.5 hours). In the following experiments, the enamines formed were used without distillation, or if necessary, only after the evaporation of benzene.

I) Asymmetric Synthesis with Acrylonitrile——*cis*(−)- and *trans*-(−)-2-Cyanoethyl-4-methylcyclohexanone (IXa and IXb): Enamine IV, was prepared from L-proline *t*-butyl ester (2.00 g, 0.0116 mole) (I) and 4-methylcyclohexanone (1.56 g, 0.0139 mole) (IIb) as described above, then it was alkylated with acrylonitrile (0.92 g, 0.0174 mole) in EtOH (40 ml) under reflux for 3 hours. After the solvent was evaporated, the residual oil was dissolved in benzene (40 ml) and the benzene solution was shaken with ice cooling 10% hydrochloric acid. The benzene layer was separated and the aqueous layer was extracted with benzene. Benzene layers and benzene extracts were combined, and washed with water, then were dried over anhydrous Na_2SO_4 and evaporated. The residual oil was distilled to give 0.89 g (46% yield from I) of IX: bp 137° (6 mmHg) (reported[10] bp 92° (0.5 mmHg).

A diastereomeric mixture was analyzed by gas chromatography on a column 1.5 m long packed with 5% SE-30 on Diasolid L (column temperature 150°), which showed that it was a 32: 68 mixture of IXa and IXb. Analysis was based on peak areas and stereochemical assignment of the diastereoisomers was made by transformation of the less stable isomer (IXb) to the more stable one (IXa) with ion exchanger Amberlite IRA-400 (OH^- type). The diastereoisomers were isolated by column chromatography on silica gel using 3% EtOH in benzene as the eluent. *trans* isomer (IXb) was first eluted.

cis Isomer (IXa): bp 126° (5.5 mmHg). IR ν_{max}^{film} cm^{-1}: 2250 (CN), 1714 (C=O). ORD (c=2.227, MeOH) $[\alpha]^{26.5}$ (mμ): −0.9° (700), −0.9° (589), −0.7° (550), −0.4° (500), 0° (460), +2.7° (400), +14.3° (350) (peak), 0° (291), −139.0° (265) (trough). *Anal.* Calcd. for $C_{10}H_{15}ON$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.50; H, 9.07; N, 8.52. Semicarbazone: colorless needles mp 141—142° (recrystallized from (iso-Pr)$_2$O-EtOH). *Anal.* Calcd. for $C_{11}H_{18}ON_4$: C, 59.43; H, 8.16; N, 25.21. Found: C, 59.36; H, 8.19; N, 24.90.

trans Isomer (IXb): bp 115° (4 mmHg). IR ν_{max}^{film} cm^{-1}: 2240 (CN), 1714 (C=O). ORD (c=1.950, MeOH) $[\alpha]^{24.5}$ (mμ): −3.1° (700), −4.5° (589), −5.7° (550), −8.2° (500), −12.1° (450), −19.7° (400), −48.2° (350), −164.1° (310) (trough), 0° (291), +205.1° (270) (peak). Semicarbazone: colorless needles mp 151—152° (recrystallized from (iso-Pr)$_2$O-EtOH). *Anal.* Calcd. for $C_{11}H_{18}ON_4$: C, 59.43; H, 8.16; N, 25.21. Found: C, 59.43; H, 8.24; N, 25.06.

Optical rotations and CD maxima of these isomers are listed in Table III.

This reaction was carried out at 20° or 40° for 3 hours in the same way and with the same work-up described above, producing diastereoisomeric mixtures of IX in respective yields of 14% or 19%. Diastereoisomers were not separated. Their ratios were estimated by gas chromatography (5% SE-30 on Diasolid L, 1.5 m, column temperature 150°). The ratios of IXa to IXb are shown in Table II.

Isomerization of *trans*-IXb to *cis*-IXa: A solution of a 4: 6 mixture (0.3 g) of IXa and IXb in MeOH (10 ml) was stirred at room temperature (23°) for 2 hours with ion exchanger Amberlite IRA-400 (OH^- type) (0.3 g).

9) All melting points are uncorrected. Infrared (IR) spectra were measured with a spectrophotometer, Model 402 equipped with NaCl optics. All gas chromatograms were measured with a Shimazu GC-1B (hydrogen flame ionization detector). Optical activities were determined with a Yanagimoto Photo Direct Reading Polarimeter, Model OR-20. ORD measurements were carried out with a Spectrometer, Model ORD UV-5, Japan Spectroscopic Co., Ltd.

10) R.L. Frand and R.C. Pierle, *J. Am. Chem. Soc.*, 73, 724 (1951).

After filtration of the ion exchanger and evaporation of the solvent, IX was recovered quantitatively and was estimated by gas chromatography (5% SE-30 on Diasolid L, 1.5 m, column temperatutes 150°) to be almost the only more stable isomer (IXa).

II. Asymmetric Synthesis with Methyl Acrylate——Methyl (−)-2-Oxo-5-methylcyclohexanepropionate (XII): Enamine IV, prepared from L-proline *t*-butyl ester (3.00 g, 0.0174 mole) (I) and 4-methylcyclohexanone (2.34 g, 0.0209 mole) (IIb) in the usual way, was alkylated with methyl acrylate (2.24 g, 0.0261 mole) in MeOH (60 ml) under reflux for 3 hours. After working it up as above, distillation gave 1.46 g (42% yield from I) of XII: bp 127° (4 mmHg). An attempt to analyze the diastereoisomers by gas chromatography was unsuccessful. Spectral and optical data for this diastereomeric mixture are as follows. IR ν_{max}^{film} cm^{-1}: 1743 (ester), 1716 (ketone). $[\alpha]_D^{37.5}$ −8.7° (c=2.412, MeOH). ORD (c=2.412, MeOH) $[\alpha]_D^{37.5}$ (mμ): −5.4° (700), −8.4° (589), −10° (550), −13° (500), −18.3° (450), −28.8° (400), −62.2° (350), −200° (313) (trough), 0° (294), +183.3° (272) (peak). CD (0.121 mole/l, MeOH) $[\theta]^{37.5}$ (mμ): −518° (294) (negative maximum). *Anal.* Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.46; H, 8.92.

Methyl (−)-2-Oxo-5-*t*-butylcyclohexanepropionate (XIII): Enamine V, prepared from L-proline *t*-butyl ester (3.00 g, 0.0174 mole) (I) and 4-*t*-butylcyclohexanone (2.68 g, 0.0174 mole) (IIc) by the usual method, was alkylated with methyl acrylate (2.25 g, 0.0261 mole) in MeOH (45 ml) under reflux for 3 hours. The same work-up as above gave 1.79 g (43% yield from I) of XIII: bp 139° (6 mmHg).

An attempt to analyze the diastereoisomers by gas chromatography was unsuccessful. Spectral, optical, and analytical data were measured with a diastereomeric mixture. IR ν_{max}^{film} cm^{-1}: 1744 (ester), 1716 (ketone). $[\alpha]_D^{13}$ −4.7° (c=2.380, MeOH). ORD (c=2.380, MeOH) $[\alpha]^{18.5}$ (mμ): −3.2° (700), −4.2° (589), −4.7° (550), −5.7° (500), −7.6° (450), −10.0° (400), −15.7° (350), −26.0° (320) (trough), 0° (257) (peak). *Anal.* Calcd. for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 70.07; H, 9.98.

III. Asymmetric Synthesis with Allyl Bromide——2-Allyl-4-methylcyclohexanone (XIV): Enamine (IV) was formed from I (4.00 g, 0.0234 mole) and IIb (3.10 g, 0.0281 mole) as described above. The solution of enamine obtained and allyl bromide (4.2 g, 0.0351 mole) in benzene (80 ml) was refluxed for 20 hours. The same work-up and distillation gave a 0.71 g (yield 20%) of XIV: bp 100° (25 mmHg). (reported[11] bp 95° (8 mmHg)). IR ν_{max}^{film} cm^{-1}: 1714 (C=O), 1640 (C=C), 1000, 912 (vinyl). This product was judged to be a 13: 87 mixture of XIVa and XIVb by gas chromatographic analysis (5% SE-30 on Diasolid L, 0.75×3 m, column temp. 90°). Assignment of this diastereoisomer was made by converting the less stable isomer (XIVb) to the more stable one (XIVa) with ion exchanger Amberlite IRA-400 (OH^- type). Optical data for this mixture are shown in Table IV. ORD (c=1.067, MeOH) $[\alpha]^{30.5}$ (mμ): −5.6° (700), −8.6° (589), −13.7° (500), −18.0° (460), −31.1° (400), −71.2° (350), −234.3° (311) (trough), 0° (294), +290.7° (268) (peak). *Anal.* Calcd. for $C_{10}H_{16}O$: C, 79.00; H, 10.52. Found: C, 79.12; H, 10.35.

Isomerization of XIVb to XIVa: A solution of 0.2 g of a 13: 87 mixture of XIVa and XIVb in MeOH (8 ml) was stirred at room temperature (20°) for 2 hours with ion exchanger Amberlite IRA-400 (OH^- type) (0.2 g). After filtration of the ion exchanger and evaporation of the solvent, XIV was recovered quantitatively and judged to be composed almost only of the more stable isomer (XIVa) by gas chromatography (5% SE-30 on Diasolid L, 0.75×3 m, column temperature 90°).

2-Allyl-4-*t*-butylcyclohexanone (XV): Enamine V was formed by refluxing a solution of I (6.00 g, 0.0348 mole) and IIc (5.36 g, 0.0348 mole) in benzene (90 ml) with molecular sieves 4A (6.0 g) for 2 hours, as described earlier. The molecular sieves were filtered off, and a solution of allyl bromide (6.32 g, 0.0522 mole) in 10 ml of benzene was added to the filtrate. The reaction solution was refluxed for 20 hours. The same work-up as above and silica gel column chromatography gave 1.08 g of XV (yield 16%). This was estimated as a 13: 87 mixture of XVa and XVb by gas chromatography (5% SE-30 on Diasolid L, 0.75×5 m, column temp. 162°). A mixture of diastereoisomers (XV) was submitted to silica gel column chromatography using benzene as the eluent. However *cis* isomer (XVa) could not be obtained and only *trans* isomer (XVb) was isolated purely.

trans Isomer (XVb): bp 98—99° (4 mmHg) (reported[12] bp 120° (10 mmHg)). IR ν_{max}^{film} cm^{-1}: 1716 (C=O), 1642 (C=O), 996, 912 (vinyl). *Anal.* Calcd. for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.61; H, 11.42. Optical data for XVb are shown in Table IV. ORD (c=0.950, MeOH) $[\alpha]^{30}$ (mμ): −1.8° (700), −2.1° (589), −2.5° (550), −3.8° (500), −5.1° (450), −7.6° (400), −15.6° (350), −48.4° (310) (trough), 0° (292), +84.2° (270) (peak).

Isomerization of XVb to XVa: A solution of 0.2 g of a 13: 87 mixture of XVa and XVb in MeOH (8 ml) was stirred at room temperature (18°) for 2 hours with ion exchanger Amberlite IRA-400 (OH^- type) (0.2 g). After filtration of the ion exchanger and evaporation of the solvent, XV was recovered quantitatively and judged to be almost completely composed of the more stable isomer (XVa) by gas chromatography (5% SE-30 on Diasolid L, 0.75×5 m, column temperature 162°).

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