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Stereochemical Studies. XX.[1] Asymmetric Synthesis of α-Bromoketones

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Optically active 2-bromocyclohexanone derivatives were asymmetrically synthesized for the first time. Absolute configurations of products were determined using the axial α-haloketone rule. The solvent effect of (—)-V on optical rotatory dispersion and circular dichroism was studied in various solvents.

Racemization of (—)-V catalyzed with acid or base was examined. Asymmetric synthesis using other ketones was also studied.

Optically active α-haloketones are particularly interesting for their spectroscopic and physical properties. The stereochemistries of 2-bromocyclohexanone derivatives have been well studied by their infrared (IR) and ultraviolet (UV) spectra,[3] and their dipole moments.[3b,4]

The effect of optically active α-haloketones on their optical rotatory dispersions (ORD) and circular dichroisms (CD) is known as the rule of axial α-haloketones.[5] This rule is very useful in the assignment of the absolute configuration of α-halocarbonyl compounds and has been especially useful in the stereochemical studies of steroids. However, the synthesis of optically active α-haloketones from racemic compounds is very difficult because of difficulties in the resolution of carbonyl compounds and the very active reactivity of α-haloketones.

To obtain optically active α-haloketones easily, studies on asymmetric bromination through enamines were undertaken. No asymmetric synthesis of α-haloketones has been reported, though α-bromination of carbonyl compounds through enamines has been known.[6] Asymmetric alkylation in enamines of L-proline esters has been successfully carried out in our laboratories.[7] L-Proline esters are now readily available and are excellent secondary amines for cyclohexanone enamines. Bromination of enamines prepared from cyclohexanone derivatives and L-proline esters produced optically active 2-bromocyclohexanone derivatives in fairly good optical yields.

1) Part XIX: K. Hiroi and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **21**, 47 (1973).
2) Location: *Hongo, Bunkyo-ku, Tokyo.*
3) *a*) E.J. Corey, *J. Am. Chem. Soc.*, **75**, 2301 (1953); *b*) J. Allinger and N.L. Allinger, *Tetrahedron*, **2**, 64 (1958); *c*) N.L. Allinger and J. Allinger, *J. Am. Chem. Soc.*, **80**, 5476 (1958).
4) *a*) W.D. Kumler and A.C. Huitric, *J. Am. Chem. Soc.*, **78**, 3369 (1956); *b*) N.L. Allinger, J. Allinger, and N.A. Lebel, *ibid.*, **82**, 2926 (1960); *c*) N.L. Allinger, J. Allinger, L.W. Chow, and G.L. Wang, *J. Org. Chem.*, **32**, 522 (1967).
5) *a*) C. Djerassi and W. Klyne, *J. Am. Chem. Soc.*, **79**, 1506 (1957); *b*) C. Djerassi and L.E. Geller, *Tetrahedron*, **3**, 319 (1958); *c*) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Company, Inc., New York, 1960, p. 115; *d*) C. Djerassi, L.E. Geller, and E.J. Eisenbraun, *J. Org. Chem.*, **25**, 1 (1960); *e*) N.L. Allinger, J. Allinger, L.E. Geller, and C. Djerassi, *ibid.*, **25**, 6 (1960); *f*) C. Djerassi, E.J. Warawa, R.E. Wolff, and E.J. Eisenbraun, *ibid.*, **25**, 917 (1960); *g*) C. Djerassi and J. Staunton, *J. Am. Chem. Soc.*, **83**, 736 (1961); *h*) J. Allinger, N.L. Allinger, L.E. Geller, and C. Djerassi, *J. Org. Chem.*, **26**, 3521 (1961); *i*) K.M. Wellman, E. Bunnenberg, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 1870 (1963); *j*) A. Moscowitz, K.M. Wellman, and C. Djerassi, *Proc. Nat. Acad. Science*, **50**, 799 (1963); *k*) *Idem*, *J. Am. Chem. Soc.*, **85**, 3515 (1963).
6) *a*) M.E. Kuehne, *J. Am. Chem. Soc.*, **83**, 1492 (1961); *b*) J. Szmuszkovicz, "Advances in Organic Chemistry," Vol. 4, ed. by R.A. Raphael, E.C. Tayler, and H. Wynberg, Interscience Publishers, Inc., New York, 1963, p. 61.
7) *a*) S. Yamada, K. Hiroi, and K. Achiwa, *Tetrahedron Letters*, **1969**, 4233; *b*) S. Yamada and G. Otani, *ibid.*, **1969**, 4237; *c*) *Idem*, *ibid.*, **1971**, 1133; *d*) K. Hiroi, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **20**, 246 (1972).

I. Asymmetric Synthesis of 2-Bromocyclohexanone Derivatives

a) Asymmetric Synthesis of 2-Bromocyclohexanone——Optically active 2-bromocyclohexanone was obtained by reacting bromine as an electrophile with cyclohexanone enamines (III) of L-proline esters followed by hydrolysis.

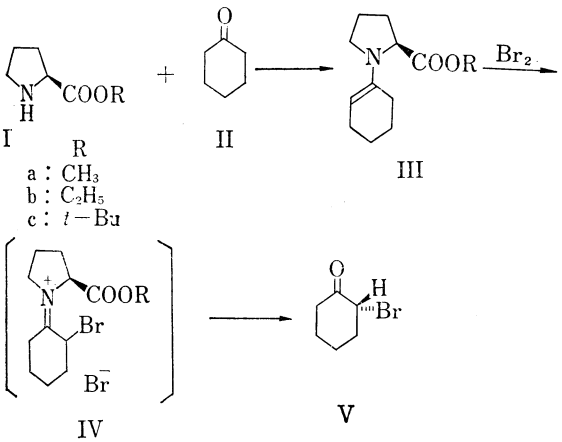

Chart 1

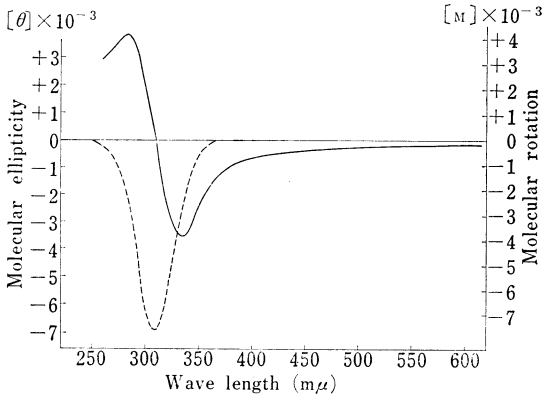

Fig. 1. ORD and CD Spectra of 2-Bromocyclohexanone obtained from Cyclohexanone Enamine of L-Proline Et ester and Br_2

——: ORD curve in CCl_4 ---------: CD curve in CCl_4

Enamines (III) were prepared, as reported in a previous paper,[7d] from L-proline esters (I) and cyclohexanone (II) in refluxing benzene with molecular sieves 4A. These enamines were brominated with bromine in chloroform under cooling. After the reaction was completed, the solvent was evaporated under reduced pressure. The residual oil was hydrolyzed by shaking it vigorously in a mixture of 10% HCl and benzene followed by purification through silica gel column chromatography which gave optically active 2-bromocyclohexanone (V), with a negative CD maximum at 310 mμ.

No racemization of (−)-V obtained was observed in these work-up treatments on shaking (−)-V with a mixture of 10% HCl and benzene then submitting it to silica gel column chromatography with CH_2Cl_2–*n*-hexane (1: 1) as the eluent. However (−)-V was racemized by distillation. The effects of L-proline ester moieties on this asymmetric induction were examined using methyl, ethyl, and *t*-butyl groups (Ia—c). Results are summarized in Table

Table I. Effect of Ester Moieties of L-Proline Esters on Asymmetric Synthesis of (−)-V

I R	Yield[b] (%)	Product V[a] Optical data $[\alpha]_D^{15}$ (CCl_4)	Molecular amplitude (CCl_4)	$[\theta]_{310}$ (CCl_4)	Optical yield (%)
CH_3	48	−82° (c=0.600)	7310° 20°	−5082 20°	33
C_2H_5	48	−95° (c=1.564)	8137° 14°	−6963 14°	37
t-Bu	47	−75° (c=1.216)	6584° 23°	−4653 23°	30

a) Product V was purified by column chromatography.
b) Based on cyclohexanone.

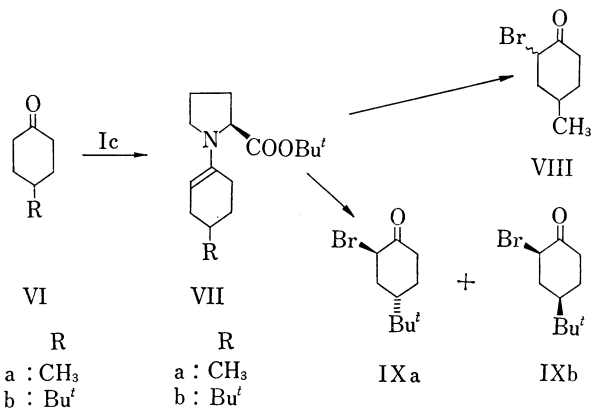

Chart 2

I. In contrast to results reported for the asymmetric alkylation of cyclohexanone enamines of L-proline esters,[7a,d] no significant differences in optical yields of (—)-V were observed by changing the ester part of L-proline esters; the bulkiest ester (IIIc) being less effective in this asymmetric synthesis. Optical yields, are discussed in another part of this paper.

b) Asymmetric Synthesis of 2- Bromo-4-substituted Cyclohexanones——4-Substituted cyclohexanone enamines (VIIa and VIIb) were brominated as above.

With 4-methylcyclohexanone (VIa), the products were a mixture of diatereoisomers VIII. This was not separable by column chromatography, nor were their ratios analyzable by gas chromatography. This mixture shows a negative CD maximum at 308 mμ, but further investigation was interrupted.

The ratio of a diastereomeric mixture of IXa and IXb obtained by a similar reaction was estimated by nuclear magnetic resonance (NMR) analysis.[8] This mixture shows two peaks corresponding to α-hydrogens at the 2 position of IXa and IXb in its NMR spectrum: equatorial hydrogen of IXa at τ 5.72 and axial hydrogen of IXb at τ 5.44. This was estimated to be a 6 :4 mixture of IXa and IXb by analysis of the peak areas. The stereochemistry of IXa and IXb has already been reported.[3c]

Diastereoisomers IXa and IXb were isolated by silica gel column chromatography. A negative Cotton effect was observed at 308 mμ in both compounds. One (IXa) shows a clear negative CD maximum, while the other (IXb) shows a very small negative CD maximum. Their optical data are shown in Table II.

Table II. Asymmetric Synthesis of IX with VIIb

Diastereo-isomer	Yield (%)	Product IX [α]$_D$ (MeOH)	Molecular amplitude (MeOH)	Molecular ellipticity [θ] (MeOH)	Absolute configu-ration	Optical yield (%)
IXa	33	−44°	3635°	−2772	2*R*, 4*S*	17
		c=2.340, 24°	24°	308 mμ, 23.5°		
IXb		−3°	91°	−70	2*R*, 4*R*	15-5
		c=0.600, 24°	24°	308 mμ, 25°		

a) Based on use of VIb.

c) Absolute Configuration and Optical Yields of Products——Effects of the α-halogen of cyclic carbonyl compounds on ORD have often been studied in the steroid fields[9] and the axial α-haloketone rule[5] has been generally applied for stereochemical studies of α-halocyclic ketones.

8) K.M. Wellman and F.G. Bordwell, *Tetrahedron Letters*, **1963**, 1703.

9) *a*) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6377 (1956); *b*) C. Djerassi, J. Osiecki, R. Riniker, and B. Riniker, *ibid.*, **80**, 1216 (1958); *c*) C. Djerassi, I. Fornaguera, and O. Mancera, *ibid.*, **81**, 2383 (1959); *d*) C. Djerassi, N. Finch, and R. Mauli, *ibid.*, **81**, 4997 (1959); *e*) C. Djerassi, N. Finch, R.C. Cookson, and C.W. Bird, *J. Am. Chem. Soc.*, **82**, 5488 (1960); *f*) H.P. Sigg and Ch. Tamm, *Helv. Chim. Acta*, **43**, 1402 (1960); *g*) C. Djerassi and W. Klyne, *J. Chem. Soc.*, **1963**, 2390; *h*) P. Crabbe, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," by Holden-Day, Inc., 1965, p. 158.

The absolute configuration of product (—)-V was shown to be *R*-configuration by application of this rule. Allinger[5h] estimated the molecular amplitude of ORD curve of 2-axial bromocyclohexanone to be 29670° and that of 2-equatorial bromocyclohexanone to be very small. Equilibrium constants of 2-bromocyclohexanone (Va⇄Vb) in various solvents have been reported as listed in Table IV.[3b,4a,b] The various equilibrium constants were shown in several solvents by infrared spectra and dipole moment analyses. Infrared spectral data indicated, as shown in Table IV, that V was an equilibrium mixture in carbon tetrachloride solution containing 74% Va and 26% Vb at 25°.[3b]

The molecular amplitude of V obtained by asymmetric synthesis with L-proline ethyl ester (Ib), as shown in Table I, was 8137° in carbon tetrachloride. Therefore, the optical yield of V obtained with Ib was calculated to be about 37%. Optical yields of V obtained with Ia—c are summarized in Table I.

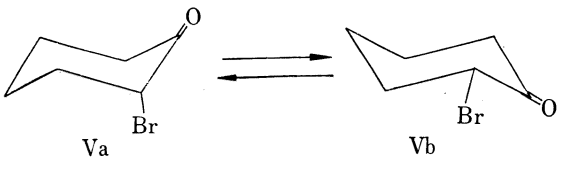

Chart 3

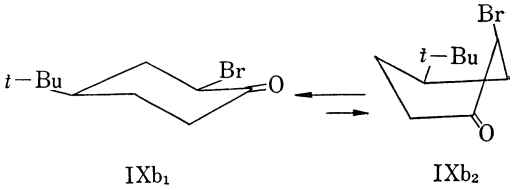

Chart 4

The absolute configuration of *trans*-(—)-2-bromo-4-*t*-butylcyclohexanone (IXa) was 2-(*R*)-4-(*S*), based on the axial α-haloketone rule. The optical yield of *trans*-(—)-IXa could be obtained without considering the above equilibrium because of fixation of the cyclohexanone ring in any solvents by the *t*-butyl group. The molecular amplitude of the IXa obtained, as shown in Table II, was 3635° in MeOH. The optical yield of IXa was calculated to be about 17% as above.

Allinger[4c] reported that IXb is a 98—91%: 2—9% conformational equilibrium mixture of IXb_1 and IXb_2 in various solevnts from conformational analysis of IXb by means of its dipole moment.

From these conformations, we can suggest that (—)-IXb might show a small negative CD maximum, this suggestion is in accordance with the experimental data shown in Table II. Thus, we induced the absolute configuration of the (—)-IXb obtained to be 2-(*R*)-4-(*R*).

Molecular amplitude of the IXb obtained, as shown in Table II, was 91° in MeOH. The optical yield of IXb was calculated, as above, from the conformational equilibrium ratio of IXb_1 to IXb_2, to be about 15—5%.

II. Asymmetric Synthesis of Other Ketones

When cyclopentanone was used as a carbonyl compound, enamine XIa was easily prepared. But bromination of XIa did not proceed smoothly and the color of bromine remained throughout the reaction, thus 2-bromocyclopentanone (XIIa) obtained was optically inactive.

However, the reaction of cycloheptanone enamine XIb with bromine gave optically active 2-bromocycloheptanone (XIIb), with a negative CD maximum at 310 mμ. Since the axial α-haloketone rule can not be applied to 2-bromocycloheptanone (XIIb) due to flexibility of the cycloheptanone ring, the absolute configuration and the optical yield of XIIb could not be estimated.

The reaction of enamine XIV with bromine unexpectedly gave N-naphthyl-L-proline ethyl ester (XV)[10] instead of 1-bromo-2-tetralone. XV was confirmed by IR, NMR spectral, elemental analyses, and by comparison of its UV spectrum with that of 2-naphthylamine.[11] The yields and optical data of the products are shown in Table III.

10) R.T. Parfitt, *J. Chem. Soc.*, **1967**, 140.
11) H. Baba and S. Suzuki, *Bull. Chem. Soc. Japan*, **34**, 82 (1961).

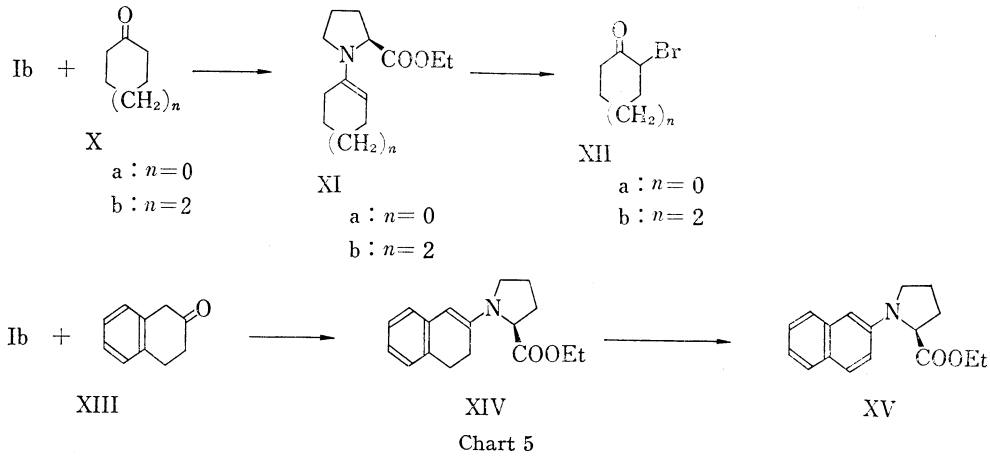

Chart 5

TABLE III. Asymmetric Synthesis with Other Ketones

Ketone	Product	Yiekd (%)	$[\alpha]_D$ (concentration, solvent)	$[\theta]$
Xa	XIIa	36	0°	0°
Xb	XIIb	37	−4.2°, 20° (c=1.040, CCl_4)	−241, 23° 310 mμ, CCl_4
XIII	XV	78	−83.2°, 18° (c=1.002, EtOH)	—

III. Solvent Effects of Optically Active 2-Bromocyclohexanone on Optical Rotatory Dispersion

Striking solvent effects of 2-halocyclohexanone derivatives on ORD and CD are widely known. As a typical example of solvent effects on ORD and CD, 2-halo-5-methylcyclohexanone has been cited by many investigators.[5b,d,e,f,h,i,k] They determined this solvent effect as due to change in conformational equilibrium.

Solvent effects of (−)-2-bromocyclohexanone (V) obtained on ORD and CD are summarized in Table IV.

TABLE IV. Solvent Effects of (−)-2-Bromocyclohexanone (V) on ORD and CD Measurements

	Solvent	$[\alpha]_D^{15}$ (c, 1.500)	Molecular amplitude	Molecular ellipticity $[\theta]$ mμ, (°C)	Reported ratio of Va in V (%)	
					Infrared[3b]	Dipole moments
1	isooctane	−95°	8257° 25°	−6869 310 25°		
2	*n*-heptane	−92°	8177° 18°	−6653 314 18°	45	68[3b] 85[4a, b]
3	cyclohexane	−96°	8560° 16°	−7294 314 17°	55	
4	CCl_4	−95°	8137° 24°	−6963 316 24.5°	74	
5	benzene	−62°	5640° 23°	−5321 304 24°	60	60[3b] 76[4a]
6	dioxane	−37°	4204° 20°	−4039 314 20°	57	51[3b] 62[4a]
7	tetrahydrofuran	−32°	3584° 25.5°	−3089 320 24.5°		
8	$CHCl_3$	−52°	5221° 21°	−4918 309 22°	68	
9	MeOH	−35°	3690° 25°	−3449 303 25°		
10	pyridine	−26°	2805° 25.5°	−2664 313 25.5°		

The equilibrium constants of 2-bromocyclohexanone (Va⇄Vb) in various solvents have been obtained, as shown in Table IV, by infrared spectroscopic and dipole moment analyses.[3b,4a,b]

We found that (−)-V had a greater CD maximum in non-polar than in polar solvents, as shown in Table IV. In non-polar solvents the repulsion of dipole-dipole moment is larger in the equatorial conformer (Vb) than in the axial one (Va). This result is attributed to a preference for the axial conformer (Va) in non-polar solvents, which is more effective on optical rotation.

The position of the predicted Va⇄Vb equilibrium should be displaced to the right in solvents of high dielectric constant.

IV. Investigation of Racemization of 2-Bromocyclohexanone

Optically active 2-bromocyclohexanone was stable in carbon tetrachloride and iso-octane at room temperature even for 10 days. We then studied the racemization of (−)-V catalyzed with acid. (−)-V was not racemized with AcOH at 25° even for 2 days. The racemization rate of (−)-V with 10% 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 at appropriate intervals of time, were plotted against time t producing a good linear graph as shown in Fig. 2. Half-life time was 125 min. Thus, (−)-V was rather stable with acid.

With strong base, however, it was dehydrobrominated. While in pyridine it was racemized, as shown in Fig. 3, in the pseudo-first order reaction rate at 25°. Half-life time was 5 hours. The recovered sample in these racemization reactions was identified as V by gas chromatographic and infrared spectroscopic analyses.

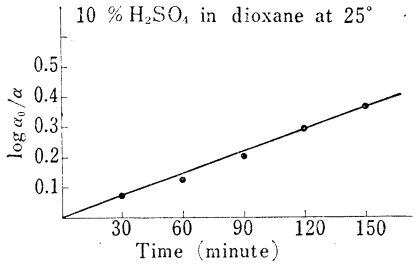

Fig. 2. Racemization of (−)-2-Bromocyclohexanone I

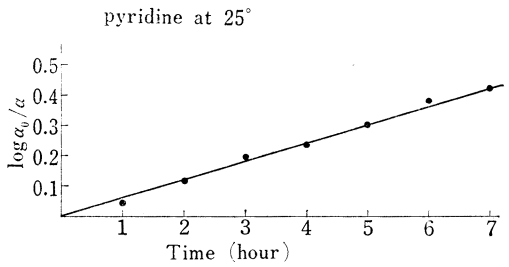

Fig. 3. Racemization of (−)-2-Bromocyclohexanone II

Synthesis of optically active α-haloketones have usually been done by bromination of optically active ketones obtained by resolution of racemic compounds or from natural sources, *i.e.* steroids and terpenes. No synthesis of optically active α-haloketones from optically inactive compounds has been reported until now. Moreover, optical resolution of racemic α-haloketones is very difficult because of the very active reactivity of the α-haloketones and the lack of availability of resolving agents for carbonyl compounds. Therefore, this asymmetric synthesis which we have reported here, is a general and easily available synthetic method for optically active α-bromoketones.

Experimental[12]

I. The Asymmetric Synthesis of 2-Bromocyclohexanone Derivatives *via* Enamines

Preparation of Cyclohexanone Enamine (III) of L-Proline Ester——Enamine (III) was prepared in the usual method as previously reported[7d] and was used without isolation by distillation.

12) All melting points are uncorrected. IR spectra were measured using Spectrometers, Model DS-402 Japan Spectroscopic Co., Ltd. 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. NMR spectra were measured at 60 MC (Japan Electron Optics LAB) with Me_4Si as the internal reference.

(*R*)-(−)-2-Bromocyclohexanone (V)——Enamine IIIb was prepared from L-proline ethyl ester (2.0 g, 0.014 mole) (Ib) and cyclohexanone (1.4 g, 0.014 mole) (II) in benzene (30 ml) by the usual method. The solvent was removed and replaced with $CHCl_3$ (20 ml). A solution of bromine (2.2 g, 0.014 mole) in $CHCl_3$ (10 ml) was added dropwise to the solution IIIb in $CHCl_3$ (20 ml) under ice NaCl cooling (−15°) for 30 min, then the reaction mixture was stirred at −15° for 1.5 hr. The solvent was removed under reduced pressure without heating and replaced with benzene. The benzene solution was shaken with ice cooling 10% hydrochloric acid. The aqueous layer was extracted with benzene 3 times. Combined benzene layers were washed with water, neutralized with $NaHCO_3$, and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residual oil was purified with silica gel column chromatography (CH_2Cl_2: *n*-hexane, 1:1) to give 1.2 g (yield 48%) of V: The optical rotation and CD maximum ([θ] molecular ellipticity) of V are shown in Table I. ORD (Fig. 1) (*c*=0.422, CCl_4) $[\alpha]^{14}$ (mμ): −79° (650), −95° (589), −125° (550), −169° (500), −251° (450), −474° (400), −1659° (350), −2227° (335) (trough), 0° (310), +1422° (300), +2370° (284) (peak). (−)-V was racemized by its distillation. bp 102° (29 mmHg) (lit.[13] bp 89—90° (14 mmHg)) IR ν_{max}^{film} cm^{-1}: 1716 (C=O in Va), 1734 (C=O in Vb). *Anal.* Calcd. for C_6H_9OBr: C, 40.68; H, 5.08. Found: C, 40.31; H, 5.06.

(−)-*trans*- and (−)-*cis*-2-Bromo-4-t-butylcyclohexanone (IXa and IXb)——Enamine VIIb was prepared from L-proline *t*-butyl ester (1.09 g, 0.0064 mole) (Ic) and 4-*t*-butylcyclohexanone (1.00 g, 0.0064 mole) (VIb) in benzene (16.5 ml) by the usual method reported previously.[7d] The solvent was removed and replaced with $CHCl_3$ (40 ml). A solution of bromine (1.0 g, 0.0064 mole) in $CHCl_3$ (5 ml) was added dropwise to the solution of enamine (VIIb) in $CHCl_3$ (40 ml) under ice cooling (2—3°) for 15 min. The reaction mixture was stirred for 1 hr at 2—3° then at room temperature for 1 hr. The work-up mentioned earlier and purification by silica gel column chromatography (CH_2Cl_2: *n*-hexane=1:1) gave 0.50 g (yield 33%) of IX. This was estimated to be a 6:4 mixture of IXa and IXb by NMR analysis.[8] Diastereoisomers were isolated by silica gel column chromatography. Trans isomer IXa was eluted first with CH_2Cl_2 and *n*-hexane (1:1) and was oily. *cis* Isomer IXb was eluted later and solidified.

trans Isomer IXa: bp 117° (7 mmHg) (reported[3c] at 0.5 mm, bath temp. 110°). IR ν_{max}^{film} cm^{-1}: 1728 (C=O). ORD (*c*=2.340, MeOH) $[\alpha]^{23}$ (mμ): −30° (700), −36° (650), −44° (589), −56° (550), −75° (500), −107° (450), −175° (400), −534° (350), −780° (335) (trough), 0° (310), +427° (300), +780° (286) (peak). *Anal.* Calcd. for $C_{10}H_{17}OBr$: C, 51.50; H, 7.29. Found: C, 51.80; H, 7.40.

cis Isomer IXb: colorless needles mp 65—66° (reported[3c] mp 67—68°). IR ν_{max}^{KBr} cm^{-1}: 1732 (C=O). ORD (*c*=0.600, MeOH) $[\alpha]^{24.5}$ (mμ): −3° (589), −5° (450), −7° (400), −15° (350), −22° (330) (trough), 0° (300), +17° (285) (peak). *Anal.* Calcd. for $C_{10}H_{17}OBr$: C, 51.50; H, 7.29. Found: C, 51.51; H, 7.43.

Optical rotations and CD maxima for IXa and IXb are shown in Table II.

(−)-2-Bromo-4-methylcyclohexanone (VIII)——Enamine VIIa was prepared from L-proline *t*-butyl ester (2.50 g, 0.0145 mole) (Ic) and 4-methylcyclohexanone (1.95 g, 0.0174 mole) (VIa) in benzene (40 ml) by the usual method as reported previously.[7d] The solvent was removed and replaced with $CHCl_3$ (30 ml).

A solution of bromine (2.3 g, 0.0145 mole) in chloroform (10 ml) was added to the solution of this enamine in $CHCl_3$ (30 ml) under ice cooling (2—3°) for 1 hr. The reaction solution was stirred for 1.5 hr at the same temperature (2—3°). The work-up described above and purification by silica gel column chromatography (CH_2Cl_2: *n*-hexane=1:1) gave 1.15 g (yield 42%) of VIII. This had a single peak in gas chromatography with several columns packed with SE-30 on Diasolid L, Carbowax 20M on diasolid L, *etc.* So the ratio of the diastereoisomer (VIIIa and VIIIb) could not be estimated. (−)-VIII: bp 105—110° (32 mmHg). IR ν_{max}^{film} cm^{-1}: 1727 (C=O). $[\alpha]_D^{28}$ −22° (*c*=0.390, MeOH). ORD (*c*=0.390, MeOH) $[\alpha]^{28}$ (mμ): −13° (700), −22° (589), −24° (550), −33° (500), −46° (450), −71° (400), −185° (350), −282° (330) (trough), 0° (308), +226° (238) (peak). CD (*c*=0.390, MeOH) $[\theta]^{29}$ (mμ): −231° (308) (negative maximum). *Anal.* Calcd. for $C_7H_{11}OBr$: C, 43.98; H, 5.76. Found: C, 43.72; H, 6.10.

II. Asymmetric Synthesis with Other Ketones

2-Bromocyclopentanone (XIIa)——Enamine XIa was prepared by refluxing the solution of L-proline ethyl ester (1.70 g, 0.0119 mole) (Ib) and cyclopentanone (1.00 g, 0.0119 mole) (Xa) in benzene (30 ml) for 2 hr using a Dean Stark Apparatus. (XIa: IR ν_{max}^{film} cm^{-1}: 1742 (ester), 1633 (enamine double bond)). The solvent was replaced with chloroform (30 ml). A solution of bromine (2.9 g, 0.0179 mole) in $CHCl_3$ (20 ml) was added to the chloroform solution under ice cooling (ice-NaCl, −5°) for 30 min. The reaction solution was stirred at −5—0° for 5 hr. The work-up described in V and purification by silica gel column chromatography (CH_2Cl_2: *n*-hexane=1:1) gave 0.70 g (36% yield from Ib) of XIIa, which had no optical activity. bp 100° (30 mmHg) (reported,[14] bp 79.8—80° (7 mmHg)). IR ν_{max}^{film} cm^{-1}: 1750 (ketone) (reported[3a] 1750). *Anal.* Calcd. for C_5H_7OBr: C, 36.81; H, 4.30. Found: C, 36.52; H, 4.37.

(−)-2-Bromocycloheptanone (XIIb)——Enamine XIb was prepared by refluxing the solution of L-proline ethyl ester (1.29 g, 0.0090 mole) (Ib) and cycloheptanone (1.00 g, 0.0090 mole) (Xb)[15] in benzene

13) A. Kotz and C. Gotz, *Ann.*, **358**, 195 (1908).
14) V.A. Barkhash, G.P. Smirnova, and I.V. Machinskaya, *Zh. Obshch. Khim.*, **31**, 3197 (1962) [*C. A.*, **57**, 685b (1962)].
15) E.P. Kohler, M. Tishler, and H. Potter, *J. Am. Chem. Soc.*, **61**, 1059 (1939).

(20 ml) for 3 hr using a Dean-Stark apparatus (XIb IR ν_{max}^{film} cm^{-1}: 1740 (ester), 1640 (enamine double bond)).

The solvent was replaced with chloroform (20 ml). Then a solution of bromine (1.4 g, 0.0090 mole) in chloroform (10 ml) was added dropwise to the chloroform solution of XIb under ice-NaCl cooling (−8°) for 30 min, after which the reaction mixture was stirred at −8——5° for 3 hr. The following work-up was done as described in V. The oil obtained was purified with silica gel column chromatography (CH_2Cl_2: *n*-hexane; 1:1) to give 0.64 g (37% yield from Ib) of XIIb: ORD (c=1.040, CCl_4) $[\alpha]^{19}$ (mμ): −3.1° (700), −4.3° (589), −5.0° (550), −7.0° (500), −9.6° (450), −16.5° (400), −57.7° (350), −69.2° (342) (trough), 0° (310), +115.4° (264) (peak). The optical rotation and CD maximum of XIIb are shown in Table III.

XIIb: bp 110° (20 mmHg) (reported[14] bp 99° (6 mmHg)). IR ν_{max}^{film} cm^{-1}: 1712 (ketone). NMR (in $CDCl_3$) τ: 7.0—9.0 (10H), 5.3—5.8 (1H, multiplet, O=C-CHBr). *Anal.* Calcd. for $C_7H_{11}OBr$: C, 43.98; H, 5.76. Found: C, 43.60; H, 5.69.

N-Naphthyl-L-proline Ethyl Ester (XV)——Enamine XIV was prepared by refluxing 2-tetralone (1.00 g, 0.0068 mole) and L-proline ethyl ester (0.97 g, 0.0068 mole) in benzene (20 ml) for 1 hr using a Dean Stark apparatus (XIV: IR ν_{max}^{film} cm^{-1}: 1745 (ester), 1615 (enamine double bond)).

The solvent was replaced with chloroform (30 ml). Then a solution of bromine (1.1 g, 0.0068 mole) in chloroform (10 ml) was added to the chloroform solution of XIV under ice cooling (0°) for 30 min, after which the reaction mixture was stirred for 1.5 hr at 0°. The reaction solution was shaken twice with ice water (30 ml). The aqueous layers were extracted with chloroform, then the combined organic layers were washed with water, and dried over anhydrous Na_2SO_4.

The solvent was evaporated *in vacuo*, after which the residual oil was purified by silica gel column chromatography (C_6H_6) to give, instead of 1-bromo-2-tetralone, 1.4 g (Y. 78%) of XI: bp 180° (0.10 mmHg). $[\alpha]_D^{18}$ −83.2° (c=1.002, EtOH). IR ν_{max}^{film} cm^{-1}: 1745 (ester), 1630, 1604 (aromatic). UV ν_{max}^{MeOH} mμ (ε): 248 (1.7×10^5), 278 (2.7×10^4), 288 (4.0×10^4), 298 (3.8×10^4), 355 (1.0×10^4). NMR (in CCl_4) τ: 8.81 (3H, triplet, CH_3), 7.1—8.2 (4H, CH_2CH_2), 6.48 (2H, quartet, CH_2N-), 5.6—6.1 (3H, methylene of ester and a proton of asymmetric carbon), 2.3—3.4 (7H, multiplet, aromatic proton). *Anal.* Calcd. for $C_{17}H_{19}O_2N$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.40; H, 6.82; N, 5.28.