**Stereochemical Studies. XXVI.¹⁾ Asymmetric Synthesis using Proline
Derivatives of optically Active Various 4,4-Disubstituted
2-Cyclohexenones with Enamine Alkylation²⁾**

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Enamines III, prepared from some disubstituted acetaldehydes I and L-proline pyrrolidide (II), were alkylated with methyl vinyl ketone to generally afford optically active 4,4-disubstituted 2-cyclohexenones V. This asymmetric synthesis is found to be widely applicable, their absolute configurations could be deduced by a comparison of the two substituents.

In a previous paper,⁴⁾ we reported that asymmetric synthesis with alkylation of the enamines prepared from L-proline derivatives and 2-phenylpropanal, as a model compound of disubstituted acetaldehyde, with methyl vinyl ketone, gave (*R*)-(+)-4-methyl-4-phenyl-2-cyclohexenone. In the present investigation we extended the bounds of this asymmetric synthesis by using some disubstituted acetaldehydes.

The enamines III were prepared from disubstituted acetaldehydes I and L-proline pyrrolidide in benzene by eliminating water with azeotropic distillation with benzene or by dehydration with a molecular sieve. The crude enamines III were dissolved in methanol and alkylated with methyl vinyl ketone at 0° for 3–6 hr in methanol. After hydrolysis of the alkylated enamines, the keto aldehydes IV obtained were cyclized to give 4,4-disubstituted 2-cyclohexenones (V). Results are summarized in Table I. All the cyclohexenones V were optically active. Thus, this asymmetric synthesis was shown to be generally applicable to synthesis for optically active 4,4-disubstituted 2-cyclohexenones.

The absolute configuration of (+)-4-methyl-4-phenyl-2-cyclohexenone (Vf, $R_1 = \text{CH}_3$, $R_2 = \text{C}_6\text{H}_5$) was determined as *R* configuration in a previous paper¹⁾ and the absolute configuration of (–)-4-methyl-4-isopropyl-2-cyclohexenone here obtained (Vc) was determined as *S* configuration as follows. (–)-4-Methyl-4-isopropyl-2-cyclohexenone (Vc) was oxidized with KMnO_4 in acetone. The unpurified 2-methyl-2-isopropylglutaric acid (VI) produced,

Chart 1

1) Part XXV: G. Otani and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **21**, 2119 (1973).

2) This work was the subject of a preliminary reported: S. Yamada and G. Otani, *Tetrahedron Letters*, **1969**, 4237.

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4) G. Otani and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **21**, 2112 (1973).

TABLE I. Asymmetric Synthesis of 4,4-Disubstituted 2-Cyclohexenones (V)

V	R ₁	R ₂	bp °C (mmHg)	Yield (%) ^{a)}	[α] _D (c, MeOH)
a	CH ₃	C ₂ H ₅	92—94(15)	15	+ 1.11(2.16)
b	CH ₃	<i>n</i> -C ₃ H ₇	101—103(14)	13	+ 4.96(2.26)
c	CH ₃	iso-C ₃ H ₇	96—98(10)	10	— 5.96(1.11)
d	CH ₃	CH ₂ CH ₂ CO ₂ CH ₃	124—126(3)	46	+12.4 (1.35)
e	C ₂ H ₅	CH ₂ CH ₂ CO ₂ CH ₃	139—140(3) ^{b)}	11.4	+ 7.55(1.06)
f	CH ₃	C ₆ H ₅	125—128(3)	50	+54.3 (1.05)
g	C ₂ H ₅	C ₆ H ₅	126—129(5)	35	+42.8 (1.13)

a) yield based on II

b) The (±) compound has been synthesized by G. Stork and his co-workers.⁵⁾

was heated with acetic anhydride, and (–)-2-methyl-2-isopropylglutaric anhydride ((–)-VII), [α]_D²⁵ –8.2° (CHCl₃) was obtained by column chromatography on silica gel followed by distillation *in vacuo*. The absolute configuration of (–)-VII has been determined as the structure shown in Chart 2 by E.J. Eisenbraun and his co-workers⁶⁾ based on its chemical correlation to (+)-2-methyl-2-isopropylsuccinic acid ((+)-VIII) whose absolute configuration had been established by X-ray crystallography.⁷⁾ Consequently, the absolute configuration of (–)-4-methyl-4-isopropyl-2-cyclohexenone (Vc) was proved to be S configuration, as illustrated in Chart 2.

4,4-Disubstituted 2-cyclohexenones can be present in two stable conformations,⁸⁾ IX and X. The conformation energies of the two substituents, R₁ and R₂, determine which conformation is preferred.⁹⁾

- 5) G. Stork, A. Brizzlara, H. Landesman, J. Szmuszkowicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).
- 6) M.V. Kurkarni, E.J. Eisenbraun, and M.M. March, *J. Org. Chem.*, **33**, 1661 (1968); E.J. Eisenbraun, F. Burian, J. Osiecki, and C. Djerassi, *J. Am. Chem. Soc.*, **82**, 3476 (1960).
- 7) M.R. Cox, H.P. Koch, W.B. Whalley, M.B. Hursthouse, and D. Rogers, *Chem. Commun.*, **1967**, 212.
- 8) E. Toromanoff assumed in his brief review^{8a)} of "Stable Conformations of Cyclohexenones" that the most stable conformations for cyclohexenones are analogous to those of the corresponding cyclohexene derivatives, *i.e.*, the half-chair form is most stable. G. Snatzke^{8b)} discussed the relation between the chirality and the sign of circular dichroism (CD) in cyclohexenones from the standpoint that the most stable conformation is the half-chair form; a) E. Toromanoff, "Stable Conformations of Cyclohexenones," in "Topics in Stereochemistry," Vol. 2, ed. by N.L. Allinger and E.L. Eliel, Interscience Publishers, Ind., New York, 1967, p. 160; b) G. Snatzke, *Tetrahedron*, **21**, 413, 421 (1965).
- 9) In cyclohexenones the conformer, having an equatorial substituent of larger conformation energy, is more stable than the another, having an axial substituent of larger conformation energy.^{9a)} Based on the assumption by E. Toromanoff,^{8a)} the stabilities of two conformations, IX and X, depend on the balance of the conformation energies of the two substituents, R₁ and R₂; a) E.L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, 1962, p. 239, and cited herein.

In both Vc ($R_1 = \text{CH}_3$, $R_2 = \text{iso-C}_3\text{H}_7$) and Vf ($R_1 = \text{CH}_3$, $R_2 = \text{C}_6\text{H}_5$) the conformation energies¹⁰⁾ of R_2 (iso- C_3H_7 and C_6H_5) are larger than that of R_1 (both CH_3). Thus, the preferred conformation is IX, in which R_1 is quasi-axial and R_2 is quasi-equatorial.

The Cotton effect for the $n \rightarrow \pi^*$ transition of 2-cyclohexenone is known^{8b)} to be dependent on the disymmetric chromophore, based on the chirality of the conjugated system of the preferred conformation. All the 4,4-disubstituted 2-cyclohexenones (Va—g), obtained by the asymmetric synthesis, exhibited positive Cotton effects in the 350 $m\mu$ region (Fig. 1). This showed that their preferred conformation was IX, as was that of Vc and Vf. Thus the absolute configurations of the 4,4-disubstituted 2-cyclohexenones obtained by our asymmetric synthesis are illustrated by structure XI when the conformation energy of R_1 is less than that of R_2 .

These results indicate that asymmetric synthesis with enamine alkylation is generally applicable and that the absolute configuration of the product is predictable.

An application of this method for synthesizing optically active organic compounds is reported in a subsequent paper.

Fig. 1. ORD Curves of the 4,4-Disubstituted 2-Cyclohexenones Va—g

Experimental¹¹⁾

Methyl 4-Formylpentanoate (Id)—The compound was prepared by following the procedure for methyl 4-formylhexanoate reported by G. Stork and his co-workers.⁵⁾ bp 92–93° (14 mmHg). NMR (CCl_4) τ : 1.07 (1H, doublet, $J=1$ cps), 6.37 (3H, singlet), 7.5–8.5 (5H, multiplet), 8.87 (3H, doublet, $J=7$ cps). *Anal.* Calcd. for $\text{C}_7\text{H}_{12}\text{O}_3$: C, 58.31; H, 8.39. Found: C, 58.10; H, 8.35.

(+)-4-Ethyl-4-methyl-2-cyclohexenone (Va)—A solution of 2-methylbutanal¹²⁾ (860 mg, 10 mmoles) and L-proline pyrrolidide⁴⁾ (1.68 g, 10 mmoles) in benzene (30 ml) was heated to reflux, and the water produced was azeotropically distilled off. The solution was evaporated after which the residue was dissolved in methanol (20 ml). Methyl vinyl ketone (1.0 ml, 12 mmoles) was added to the solution cooled at 0° and the mixture was allowed to stand at 0° for 2 hr. Aqueous acetic acid (30%, 6 ml) was added, then the solution was heated under reflux for an hour and evaporated. The residue was dissolved in benzene, then washed with 10% hydrochloric acid and water. The organic layer was dried over sodium sulfate and evaporated. Dis-

10) J.A. Hirsch, "Table of Conformational Energies—1967," in "Topics in Stereochemistry," Vol. 1, ed. by N.L. Allinger and E.L. Eliel, Interscience Publishers, Inc., New York, p. 199.

11) All melting and boiling points are uncorrected. Optical rotations were measured with a Yanagimoto Model OR-10 polarimeter. Optical rotatory dispersion (ORD) curves were recorded on Nippon Bunko Model ORD/UV-5 spectropolarimeter. Infrared (IR) spectra were obtained with Nippon Bunko Models IR-S and DS-403G spectrophotometers. Nuclear magnetic resonance (NMR) spectra were recorded at 60 Mc on a Japan Electron Optical Models JNM C-60 NMR spectrometer. Gas-liquid chromatography (GLC) analyses were carried out with Shimadzu Model GC-1 and Perkin-Elmer Model 800 gas-chromatographs with dual flame ionization detectors.

12) These aldehydes were prepared following the procedure for 2,3-dimethylbutanal reported by H. Brunner and E.H. Farmer. H. Brunner and E.H. Farmer, *J. Chem. Soc.*, 1937, 1039.

tillation of the residue gave (+)-4-ethyl-4-methyl-2-cyclohexenone (Va), (210 mg, 15%), bp 92–94° (15 mmHg) as colorless liquid, $[\alpha]_D^{25} +1.11^\circ$ ($c=2.16$, MeOH). GLC (5% Carbowax 20M, column length 2.25 m, column temp. 125°) retention time: 7 min 45 sec, one peak. ORD ($c=2.16$, MeOH) $[M]^{13}$ (m μ): +1.0° (700), +1.53° (589), +25.7° (340) (peak), 0° (280). IR $\nu_{\max}^{\text{carb}}$ cm⁻¹: 1680. NMR (CCl₄) τ : 3.41 (1H, doublet, $J=10.5$ cps), 4.27 (1H, doublet, $J=10.5$ cps), 7.5–9.2 (12H, multiplet).

Its semicarbazone, mp 168–170°, as white prisms, was prepared as usual and recrystallized from methanol. Anal. Calcd. for C₁₀H₁₇ON₃: C, 61.51; H, 8.78; N, 21.52. Found: C, 61.45; H, 8.72; N, 21.38.

(+)-4-Methyl-4-*n*-propyl-2-cyclohexenone (Vb)——The solution of 2-methylpentanal¹² (1.0 g, 10 mmoles) and L-proline pyrrolidide (1.68 g, 10 mmoles) in benzene (30 ml) was heated to reflux, then water produced was azeotropically distilled off. The solution was evaporated and the residue dissolved in methanol (30 ml). Methyl vinyl ketone (1.0 ml, 12 mmoles) was added to the solution cooled at 0° and the mixture was allowed to stand at 0° for 3 hr. Aqueous acetic acid (30%, 3 ml) was added and the solution was heated under reflux for an hour, then evaporated. The residue was dissolved in benzene and washed with 10% hydrochloric acid and water after which it was dried over sodium sulfate. The solution was evaporated and the residue was distilled to give (+)-4-methyl-4-*n*-propyl-2-cyclohexenone (Vb) (0.20 g, 13%), bp 101–103° (14 mmHg) as colorless liquid, $[\alpha]_D^{25} +4.96^\circ$ ($c=2.26$, MeOH). ORD ($c=2.26$, MeOH) $[M]^{13}$ (m μ): +5.6° (700), +8.6° (589), +74.1° (345) (peak), +33.7° (290). IR $\nu_{\max}^{\text{carb}}$ cm⁻¹: 1677. NMR (CCl₄) τ : 3.41 (1H, doublet, $J=10$ cps), 4.28 (1H, doublet, $J=10$ cps), 7.5–9.2 (14H, multiplet). GLC (5% Carbowax 20M, column length 2.25 m, column temp. 125°) retention time: 11 min 0 sec.

Its semicarbazone was prepared as usual and was recrystallized from benzene–hexane, mp 138–140°, as white powder. Anal. Calcd. for C₁₁H₁₉ON₃: C, 63.12; H, 9.15; N, 20.08. Found: C, 63.25; H, 9.28; N, 20.37.

(–)-4-Methyl-4-isopropyl-2-cyclohexenone (Vc)——Molecular sieves 4A (3 g) were added to a solution of 2,3-dimethylbutanal¹² (3.0 g, 30 mmoles) and L-proline pyrrolidide (5.04 g, 30 mmoles) in ether (50 ml), and the mixture was allowed to stand for 30 min. The solution was evaporated and the residue was dissolved in methanol (75 ml). Methyl vinyl ketone (3.0 ml, 36 mmoles) was added to the solution cooled at 0° and the mixture was allowed to stand at 0° for 6 hr. Aqueous acetic acid (30%, 10 ml) was added and the solution was evaporated under reduced pressure. Dilute sulfuric acid (10%, 10 ml) was added to the residue and the mixture was extracted with ether (15 ml $\times$ 3). The extract was washed with saturated sodium chloride solution and evaporated. Aqueous acetic acid (30%, 2 ml) and pyrrolidine (0.5 ml) were added to a solution of the residue in methanol (20 ml) and the solution was heated under reflux for 2 hr. After evaporation, water was added to the residue and the whole was extracted with benzene. The extract was washed with water, then dried over sodium sulfate and evaporated. The residue was chromatographed on silica gel (90 g) with chloroform. The desired fractions were collected and distilled to give (–)-4-methyl-4-isopropyl-2-cyclohexenone (Vc) (0.45 g, 10%), bp 89–90° (8 mmHg), as colorless liquid. $[\alpha]_D^{25} -5.96^\circ$ ($c=1.11$, MeOH). ORD ($c=1.11$, MeOH) $[M]^{26}$ (m μ): –5.2° (700), –6.7° (589), 0° (398), +96.8° (350) (peak), 0° (328), –327° (300). IR $\nu_{\max}^{\text{carb}}$ cm⁻¹: 1678. NMR (CCl₄) τ : 3.45 (1H, doublet, $J=10$ cps), 4.31 (1H, doublet, $J=10$ cps), 7.5–9.2 (14H, multiplet). GLC (5% Carbowax 20M, column length 1.5 m, column temp. 127°) retention time: 4 min 40 sec.

Its semicarbazone was prepared as usual and was recrystallized from n-ethanol, mp 168–170°, as white needles. Anal. Calcd. for C₁₁H₁₉ON₃: C, 63.12; H, 9.15; N, 20.08. Found: C, 63.38; H, 9.05; N, 19.96.

(+)-4-Methyl-4-(2-carbomethoxyethyl)-2-cyclohexenone (Vd)——A solution of methyl 4-formylpentanoate (Id) (0.72 g, 5 mmoles) and L-proline pyrrolidide (0.84 g, 5 mmoles) in benzene was heated to reflux and the water produced was azeotropically distilled off. The solution was evaporated and its residue was dissolved in methanol (15 ml). Methyl vinyl ketone (1.0 ml, 12 mmoles) was added to the solution cooled at 0° and the mixture was allowed to stand at 0° for 5.5 hr. Aqueous acetic acid (30%, 2 ml) was added to the solution and the whole was heated under reflux for an hour, then evaporated. Dilute sulfuric acid was added to the residue and extracted with benzene. The extract was dried over sodium sulfate after which it was evaporated. Distillation of the residue gave (+)-4-methyl-4-(2-carbomethoxyethyl)-2-cyclohexenone (Vd) (0.45 g, 46%), bp 124–126° (3 mmHg), $[\alpha]_D^{25} +12.4^\circ$ ($c=1.35$, MeOH). ORD ($c=1.35$, MeOH) $[M]^{18.5}$ (m μ): +16° (700), +26.1° (589), +177° (344) (peak), +92° (305) (trough), +580° (260). IR $\nu_{\max}^{\text{carb}}$ cm⁻¹: 1742, 1680. NMR (CCl₄) τ : 3.44 (1H, doublet, $J=10$ cps), 4.25 (1H, doublet, $J=10$ cps), 6.39 (3H, singlet), 7.5–8.4 (8H, multiplet), 8.84 (3H, singlet). GLC (SE-30, column length 2.25 m, column temp. 160°C) retention time: 4 min 15 sec.

Its semicarbazone was prepared as usual and was recrystallized from methanol, mp 124–126°, as white powder. Anal. Calcd. for C₁₂H₁₉O₃N₃: C, 56.90; H, 7.56; N, 16.59. Found: C, 56.82; H, 7.52; N, 16.49.

(+)-4-Ethyl-4-(2-carbomethoxyethyl)-2-cyclohexenone¹³ (Ve)——Using methyl 4-formylhexanoate⁹

13) A (±) compound was reported by G. Stork and his co-workers.⁹ The bp 118–122° (0.25 mmHg) was given. With respect to IR, NMR spectra and GLC, the (+) compound was identical with the (±) compound, bp 134–136° (3 mmHg), prepared by us following the procedure reported by Stork and his co-workers.

(790 mg, 5 mmoles), asymmetric synthesis was carried out following the procedure for (+)-4-methyl-4-(2-carbomethoxyethyl)-2-cyclohexenone (Vd) described above. (+)-4-Ethyl-4-(2-carbomethoxyethyl)-2-cyclohexenone (Ve) (110 mg, 11%), bp 139–140° (3 mmHg),¹³ $[\alpha]_D^{25} + 7.55^\circ$ ($c=1.06$, MeOH), was obtained. ORD ($c=1.06$, MeOH) $[M]^{16}$ ($m\mu$): +11.7° (700), +18.5° (589), +95° (345) (peak), +20° (317) (trough), +238° (270). IR $\nu_{\max}^{\text{carb}}$ cm^{-1} : 1742, 1682. NMR (CCl_4) τ : 3.38 (1H, doublet, $J=10$ cps), 4.17 (1H, doublet, $J=10$ cps), 6.38 (3H, singlet), 7.5–8.6 (10H, multiplet), 9.06 (3H, triplet). GLC (SE-30, column length 2.25 m, column temp. 160°) retention time: 6 min 20 sec.

(+)-4-Ethyl-4-phenyl-2-cyclohexenone (Vg)—Using 2-phenylbutanal¹⁴ (0.74 g, 5 mmoles), asymmetric synthesis was carried out following the procedure for (+)-4-methyl-4-phenyl-2-cyclohexenone (Vf) reported⁴ earlier. (+)-4-Ethyl-4-phenyl-2-cyclohexenone (Vg) (0.35 g, 35%), bp 126–129° (5 mmHg), $[\alpha]_D^{25} + 42.8^\circ$ ($c=1.13$, MeOH), was obtained. ORD ($c=1.13$, MeOH) $[M]^{15}$ ($m\mu$): +52.5° (700), +85.6° (589), +800° (350) (peak), -40° (317) (trough), +1410° (280). IR $\nu_{\max}^{\text{carb}}$ cm^{-1} : 1685. NMR (CCl_4) τ : 2.77 (5H, singlet), 3.00 (1H, doublet, $J=10$ cps), 3.94 (1H, doublet, $J=10$ cps), 7.84 (4H, singlet), 8.14 (2H, quartet, $J=6.7$ cps), 9.20 (3H, triplet, $J=6.7$ cps). Anal. Calcd. for $\text{C}_{14}\text{H}_{16}\text{O}$: C, 83.96; H, 8.05. Found: C, 83.78; H, 7.94.

Its semicarbazone was prepared as usual and was recrystallized from aqueous ethanol, mp 150–152°, as white small prisms. Anal. Calcd. for $\text{C}_{15}\text{H}_{19}\text{ON}_3$: C, 70.00; H, 7.44; N, 16.33. Found: C, 70.25; H, 7.50; N, 16.35.

(-)-2-Methyl-2-isopropylglutaric anhydride ((-)-VII)—Potassium permanganate (1.19 g, 7.4 mmoles) was added to a solution of (-)-4-methyl-4-isopropyl-2-cyclohexenone (Vc) (0.45 g, 2.96 mmoles). $[\alpha]_D^{25} - 5.96^\circ$ ($c=1.11$, MeOH), in acetone (25 ml) portionwise with stirring. After the color of permanganate had disappeared the precipitate was obtained by filtration and was washed with acetone. This precipitate was then washed with water (3 ml $\times$ 4). The washings were collected and acidified (pH 1) with hydrochloric acid after which they were extracted continuously with ether. The extract was evaporated and its residue was dissolved in acetic anhydride (10 ml), after which the solution was heated under reflux for 2 hr. The solution was then evaporated under reduced pressure and its residue was chromatographed on a silica gel column (40 g) with chloroform. The desired fractions were collected and evaporated after which the residue was distilled under reduced pressure to give (-)-2-methyl-2-isopropylglutaric anhydride ((-)-VII) (70 mg), bp 115–120° (3.5 mmHg), $[\alpha]_D^{25} - 11.6^\circ$ ($c=1.37$, CHCl_3).¹⁵ ORD ($c=1.37$, CHCl_3) $[M]^{24}$ ($m\mu$) τ : -17.8° (700), -18.9° (589), -102° (286) (trough), 0° (256). IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1} : 1805, 1770. NMR (CCl_4) τ : 7.26 (2H, triplet), 7.7–8.5 (3H, multiplet), 8.76 (3H, singlet), 8.98 (3H, singlet), 9.10 (3H, singlet). Anal. Calcd. for $\text{C}_9\text{H}_{14}\text{O}_3$: C, 63.51; H, 8.29. Found: C, 63.13; H, 8.28.

14) D.J. Cram and R. Davis, *J. Am. Chem. Soc.*, **71**, 3871 (1949).

15) E.J. Eisenbraun and his co-workers reported⁵ mp 55–56°, $[\alpha]_D - 6.1^\circ$ ($c=0.99$), IR $\lambda_{\max}^{\text{CHCl}_3}$ μ : 5.56 and 5.67, for (-)-2-methyl-2-isopropylglutaric anhydride.