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Stereochemical Studies. XXXVIII.[1] Asymmetric Synthesis of the Key Compounds for the Synthesis of optically Active Diterpenes. Asymmetric Synthesis of optically Active 1,2,3,4,5,6,-7,8,8a-Octahydro-8a-methyl-3,8-naphthalenedione Derivatives with L-Proline Derivatives

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We attempted the asymmetric synthesis of key compounds for optically active diterpenes and obtained some optically active key compounds (Ib, c).

The effects of solvents and reaction temperatures were examined and the results are discussed.

Recently there have been reports on the total synthesis of diterpenes published by many investigators.[3]

However, the total synthesis of optically active diterpenes by asymmetric induction has not been reported until now.

Initially, we studied the asymmetric synthesis of key compounds for diterpenes. This paper is concerned with the asymmetric synthesis of the key compounds (Ia—c) for the total synthesis of diterpenes.

We have already reported the asymmetric synthesis of α-alkyl carbonyl compounds through optically active enamines[4] and further succeeded in obtaining optically active Wieland–Miescher ketone (Id)[4i] by an application of our method. We extended this method for the purpose of asymmetric synthesis of key compounds (Ia—c).

The key intermediates leading to the important optically active compounds (Ia—c) by asymmetric cyclization are triketones (IVa—c), which will be formed upon condensation of 2-methyl-1,3-cyclohexanedione (II) and methyl vinyl ketone derivatives (IIIa—c).

The synthesis of methyl 4-(2,6-dioxo-1-methylcyclohexyl)-2-oxovalerate (IVa) from II and methyl 3-oxo-4-pentenoate (IIIa)[5] was studied under various reaction conditions. How-

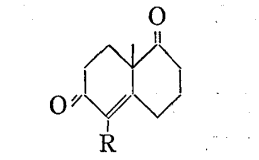
1) Part XXXVII: T. Sone, S. Terashima, and S. Yamada, *Synthesis*, **1974**, 1725

2) Location: *Hongo, Bunkyo-ku, Tokyo, 113, Japan.*

3) *a*) Y. Kitahara, A. Yoshikoshi, and S. Oida, *Kagaku no Ryoiki*, **19**, 57 (1965); *b*) K. Mori and M. Matsui, *ibid.*, **20**, 829 (1966); *c*) R. McCrindle and K.H. Overton, "Advances in Organic Chemistry: Methods and Results," Vol. 5, Interscience Publishers, Inc., New York, 1965, p. 47; *d*) J.R. Hanson, "The Tetracyclic Diterpenes," Pergamone Press, 1968; *e*) E. Wenkert, *Rec. Chem. Progress*, **31**, 1 (1970) and cited therein; *f*) "Terpenoids and Steroids," ed. by K.H. Overton, The Chemistry Society, London, Vol. 1 (1971), Vol. 2 (1972), Vol. 3 (1973); *g*) R.B. Kelly, J. Eber, and H.K. Hung, *Can. J. Chem.*, **51**, 2534 (1973); *h*) E. Fujita, M. Shibuya, S. Nakamura, Y. Okada, and T. Fujita, *J. Chem. Soc.*, (*L*) **1974**, 165.

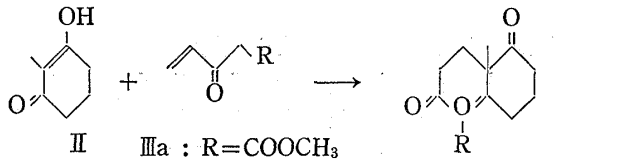
4) *a*) S. Yamada, K. Hiroi, and K. Achiwa, *Tetrahedron Letters*, **1969**, 4233; *b*) S. Yamada, and G. Otani, *ibid.*, **1969**, 4237; *c*) *Idem, ibid.*, **1971**, 1133; *d*) K. Hiroi, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **26**, 246 (1972); *e*) K. Hiroi and S. Yamada, *ibid.*, **21**, 47, 54 (1973); *f*) G. Otani and S. Yamada, *ibid.*, **21**, 2112, 2125, 2130 (1973); *g*) T. Sone, K. Hiroi, and S. Yamada, *ibid.*, **21**, 2331 (1973); *h*) M. Kitamoto, K. Hiroi, S. Terashima, and S. Yamada, *ibid.*, **22**, 459 (1974); *i*) K. Nagasawa, H. Takahashi, K. Hiroi, and S. Yamada, *Yakugaku Zasshi*, **95**, 33 (1975); *j*) K. Nagasawa, K. Hiroi, and S. Yamada, *ibid.*, **95**, 46 (1975).

5) I.N. Nazarov and S.I. Zavyalov, *Zh. Obshch. Khim.*, **23**, 1703 (1953).



Ia : R=$COOCH_3$
Ib : R=CH_3
Ic : R=CH_2OCH_3
Id : R=H
Ie : R=$CH_2SCH_2CH_3$

Chart 1

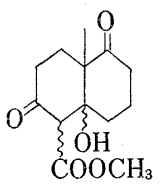


II

IIIa : R=$COOCH_3$
IIIb : R=CH_3
IIIc : R=CH_2OCH_3

IVa : R=$COOCH_3$
IVb : R=CH_3
IVc : R=CH_2OCH_3

Chart 2

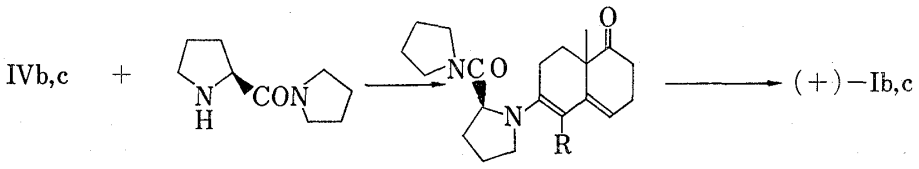


V

Chart 3

ever, we could not obtain IVa, but rather the cyclized product under the reaction condition using catalysts such as Et_3N, N-methylmorpholine, pyridine, ion exchangers Amberlite IR-45, and AcOH. For example, the reaction of II with IIIa in refluxing tetrahydrofuran (THF) in the presence of a catalytic amount of Et_3N gave not only Ia,[6] but also crystals which were identified as the cyclized product (V).[7] This result is probably due to the high reactivity of the β-keto ester of IVa.

Therefore, we synthesized 2-methyl-2-(3-oxopentyl)-1,3-cyclohexanedione (IVb) and 2-methyl-2-(5-methoxy-3-oxopentyl)-1,3-cyclohexanedione (IVc), which have no reactive methylene. Then the asymmetric cyclization[8] of triketone (IVb, c) with optically active secondary amine (VI) was investigated and the effect of the substituent R of IVb, c on the asymmetric induction was examined.



VI

VIIa : R=CH_3
VIIb : R=CH_2OCH_3

Chart 4

1) Asymmetric Synthesis of (*S*)-(+)-1,2,3,5,6,7,8,8a-Octahydro-4,8a-dimethyl-3,8-naphthalenedione ((*S*)-(+)-Ib)

IVb was prepared from II and ethyl vinyl ketone (IIIb) in refluxing THF in the presence of Et_3N.

We employed, as an optically active amine, L-proline pyrrolidine amide (VI), which had already been observed to be the most effective secondary amine in our asymmetric synthesis.

We reacted IVb with VI (equimolar amount of IVb) in several solvents at various reaction temperatures for appropriate reaction time using molecular sieves 4A as a dehydrating agent. After filtration of molecular sieves, the filtrate was evaporated to afford dienamine VIIa, which was assigned by the data of nuclear magnetic resonance (NMR), infrared, and ultraviolet (UV) spectra described in the experimental part. This was hydrolyzed by refluxing 30 min in a mixture of benzene and 10% HCl. The product ((+)-Ib) could not be purely isolated by silica gel column chromatography, and a mixture of the starting material (IVb) and (+)-Ib was obtained.

6) I.N. Nazarov and S.I. Zavyalov, *Zh. Obshch. Khim.*, **25**, 508 (1955) [*C.A.*, **50**, 3359 (1956)].
7) S.W. Pelletier, R.L. Chappel, and S. Prabhakar, *J. Am. Chem. Soc.*, **90**, 2889 (1968).
8) While our research was in progress, the similar asymmetric synthesis was published, U. Eder, G. Sauer, and R. Wiechert, *Angew. Chem.*, **10**, 496 (1971), and most recently another paper was also published, Z.G. Hajos and D.R. Parrish, *J. Org. Chem.*, **39**, 1615 (1974).

The angular methyl group of IVb appeared as a singlet at τ 8.78 in its NMR spectrum, while that of Ib appeared as a singlet at τ 8.60, so, we estimated the ratios of IVb to Ib in the reaction products by their NMR spectral analysis. Based on these ratios, the yields and the optical yields of the product (+)-Ib were calculated.

Solvent Effects——The solvent effects on asymmetric induction of IVb with VI were examined by refluxing IVb and VI in several solvents; *i.e.* $CHCl_3$, THF, CH_3CN, CCl_4, MeOH, and benzene, for 6 hours with molecular sieves 4A. The results are summarized in Table I.

Table I. Effects of Solvents on Asymmetric Cyclization of IVb with VI

Solvents[a]	Product Ib			
	Yields (%)	$[\alpha]_D^{20}$ (MeOH)	Absolute configuration	Optical[b] yields (%)
$CHCl_3$	47	+39°, c=1.534	*S*	49
THF	48	+39°, c=2.268	*S*	49
CH_3CN	40	+32°, c=1.272	*S*	41
CCl_4	24	+37°, c=1.768	*S*	47
MeOH	40	+17°, c=0.880	*S*	22
Benzene	43	+6°, c=0.630	*S*	8

a) reaction condition: IVb was refluxed with VI for 6 hours in each solvent with molecular sieves 4A under stirring, and hydrolyzed by heating in 10% HCl and benzene for 30 min.
b) Optical yields were calculated from the value of optically pure Ib, $[\alpha]_D^{20}$ +79° (MeOH) obtained in this report.

The yields of Ib were, as shown in Table I, about 40—47% in several solvents. Table I indicates that when Ib was prepared in $CHCl_3$ or THF the best yield and the best optical yield were obtained, while the use of higher boiling (benzene) and protic (MeOH) solvents resulted in poor optical yields.

Effects of Reaction Temperatures——The effects of the reaction temperatures on this asymmetric induction were summarized in Table II.

The cyclization reaction of IVb with VI was very slow at the low reaction temperature and a long reaction time was required in order to increase the yield. As shown in Table II,

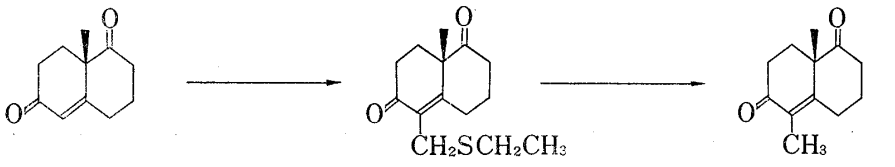
Table II. Effects of Reaction Temperature on Asymmetric Cyclization of IVb with VI

Reaction Conditions			Product Ib			
Solvents	Reaction temp.	Reaction time	Yields (%)	$[\alpha]_D^{20}$ (MeOH)	Absolute confign.	Optical yields (%)
Benzene	40°	24 hr	32	+36°, c=1.020	*S*	46
	room temp.	3 days	28	+44°, c=1.814	*S*	56
Toluene	0°	7 days	45	+50°, c=1.264	*S*	63
$CHCl_3$	room temp.	3 days	20	+40°, c=0.935	*S*	51
	0°	7 days	18	+44°, c=0.935	*S*	56
MeOH	0°	7 days	38	+48°, c=1.322	*S*	61

Ib was prepared in the higher optical yield at the low reaction temperature as we expected.

Determination of optically Pure Ib and Its Absolute Configuration——The optical yield and the absolute configuration of Ib were obtained from Id, for which the absolute configuration and the optical rotation are known.[9] (+)-Ib was prepared from (*S*)-(+)-Id by Kirk's method[10] described as follows: thiomethylation of (+)-Id, followed by desulfurization.

The reaction of (*S*)-(+)-Id ($[\alpha]_D^{20}$ +63° (*c*=1.006, MeOH), optical purity 63%) with formalin and ethanethiol in refluxing EtOH gave (*S*)-(+)-Ie ($[\alpha]_D^{20}$ +56.5° (*c*=0.620, MeOH)), and subsequent desulfurization of this (+)-Ie with Raney Ni[11] gave (*S*)-(+)-Ib ($[\alpha]_D^{20}$ +50° (*c*=0.640, MeOH)).



(*S*)−(+)−Id (*S*)−(+)−Ie (*S*)−(+)−Ib

Chart 5

Based on these data, the specific optical rotation of optically pure (+)-Ib was calculated to be $[\alpha]_D^{20}$ +79° (MeOH), and the optical yields of Ib are listed in Table I and II.

Ib was obtained in rather good optical yields in contrast to those of Id reported in the previous paper.[4d]

2) Asymmetric Synthesis of (+)-1,2,3,5,6,7,8,8a-Octahydro-4-methoxymethyl-8a-methyl-3,8-naphthalenedione ((+)-Ic)

The asymmetric cyclization reaction was further investigated using IVc and VI. IVc was prepared by the reaction of II with 5-methoxy-1-penten-3-one (IIIc) in refluxing THF in the presence of Et_3N.

The reaction of IVc with VI was carried out in the same manner as described in the previous section to give (+)-Ic. The product (+)-Ic could not be purely isolated by silica gel column chromatography (7% EtOH in $CHCl_3$) and a mixture of Ic and IVc was obtained.

Table III. Asymmetric Cyclization of IVc with VI

Reaction conditions[a]			Product Ic	
Solvents	Reaction temp.	Reaction time	Yields (%)	$[\alpha]_D^{20}$ (MeOH)
Benzene	reflux	8 hr	19	+18°, *c*=0.346
THF	reflux	8 hr	7	+36°, *c*=0.191
$CHCl_3$	reflux	24 hr	20	+30°, *c*=0.275
CH_3CN	reflux	24 hr	22	+34°, *c*=0.268

a) IVc was refluxed with VI in each solvent using molecular sieves 4A as a dehydrating agent.

9) W. Acklin, V. Prelog, and A.P. Pietro, *Helv. Chim. Acta.*, **41**, 1416 (1958).
10) D.N. Kirk and U. Petrow, *J. Chem. Soc.*, **1962**, 1091.
11) R. Mozingo, D.E. Wolf, S.A. Harris, and K. Folkers, *J. Am. Chem. Soc.*, **65**, 1013 (1943).

The angular methyl group of Ic appeared as a singlet at τ 8.55 in its NMR spectrum, while that of IVc appeared as a singlet at τ 8.76, so, we estimated the ratios of IVc to Ic in the reaction products by their NMR spectral analysis, and calculated the yields and the optical rotation of the product (+)-Ic based on these ratios.

The effects of solvents on this asymmetrics induction were described in Table III. (+)-Ic was obtained in low yield, as shown in Table III, even after a long reaction time. The optical yields and the absolute configuration of the product (+)-Ic are not known.

Thus, we succeeded in obtaining some optically active key compounds for optically active diterpenes *via* asymmetric induction.

Investigations are now in progress on approaching optically active diterpenes.

Experimental[12]

The Reaction of 2-Methyl-1,3-cyclohexanedione (II) with Methyl 3-Oxo-4-pentenoate (IIIa) in the Presence of a Catalytic Amount of Et_3N——A solution of II (0.82 g, 0.00650 mole) and IIIa (0.68 g, 0.00670 mole), freshly distilled, in THF (12 ml) was refluxed for 2 hr in the presence of a catalytic amount of Et_3N (0.065 g, 0.00065 mole). After the solvent was removed in reduced pressure, benzene was added to the residue and the precipitates were filtered off to recover the starting material (II) (0.36 g, recovered yield 44%). The filtrate was evaporated to dryness to afford semisolids (1.02 g), from which 0.35 g of solids and 0.55 g of yellow oil were obtained. The solids were recrystallized from iso-Pr_2O–MeOH for several times to give two crystals which are diastereoisomers of V as follows: One of the solids was colorless prisms melting at 107—108°: IR ν_{max}^{KBr} cm^{-1}: 3500 (OH), 1735 ($COOCH_3$), 1707 (C=O). NMR (in $CDCl_3$) τ: 8.70 (3H, singlet, CH_3), 7.2—8.5 (11H), 6.20 (3H, singlet, $COOCH_3$), 5.48 (1H, singlet, OH). *Anal.* Calcd. for $C_{13}H_{18}O_5$: C, 61.40: H, 7.14. Found: C, 61.53: H, 7.20.

The second crystal was colorless prisms melting at 161—162°: IR ν_{max}^{KBr} cm^{-1}: 3520 (OH), 1733 ($COOCH_3$), 1707 (C=O). NMR (in $CDCl_3$) τ: 8.60 (3H, singlet, CH_3), 7.2—8.5 (11H), 6.20 (3H, singlet, $COOC\underline{H}_3$), 6.05 (1H, singlet, OH). *Anal.* Calcd. for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.26; H, 7.11.

The oily fraction was purified by silica gel column chromatography (5% EtOH in CH_2Cl_2) to give Ia (0.35 g), of which identity was established by the comparison of its infrared spectrum with that of the authentic sample.[6]

2-Methyl-2-(3-oxopentyl)-1,3-cyclohexanedione (IVb)——A solution of II (7.56 g, 0.0600 mole) and ethyl vinyl ketone (IIIb)[13] (4.40 g, 0.060 mole) in THF (50 ml) was refluxed for 3 hr with Et_3N (0.5 ml). The reaction solution was evaporated under reduced pressure to give semisolids. Benzene was added to the semisolids and the precipitates were filtered off to recover II (3.8 g, recovered yield 50%). The filtrate was condensed to give a brown oil (6.75 g), which was distilled to afford IVb (4.4 g, yield 43%): bp 120° (0.05 mmHg). (Reported[14] bp 129—131° (1 mmHg)). IR ν_{max}^{film} cm^{-1}: 1715, 1694. NMR (in $CDCl_3$) τ: 9.00 (3H, triplet, $COCH_2C\underline{H}_3$), 8.78 (3H, singlet, CH_3), 7.2—8.4 (12H). *Anal.* Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.31; H, 8.59.

Asymmetric Cyclization of 2-Methyl-2-(3-oxopentyl)-1,3-cyclohexanedione (IVb) with L-Proline Pyrrolidine Amide (VI)

(*S*)-(+)-1,2,3,5,6,7,8,8a-Octahydro-4,8a-dimethyl-3,8-naphthalenedione ((*S*)-(+)-Ib)——A solution of IVb (0.50 g, 0.0024 mole) and VI (0.50 g, 0.0024 mole) in benzene (20 ml) was refluxed for 6 hr with Dean-Stark apparatus. The solvent was evaporated *in vacuo* to give a brown oil (VIIa) (0.83 g). This was confirmed by the spectral data NMR (in $CDCl_3$) τ: 8.60 (3H, singlet, CH_3), 7.4—8.5 (16H), 6.0—7.3 (7H), 5.55 (1H, singlet, C=C–H). IR ν_{max}^{film} cm^{-1}: 1705 (C=O), 1640—1610 (amide and C=C). UV λ_{max}^{MeOH} $m\mu$ (ε): 315 (12000)).[15] This was hydrolyzed by refluxing in a mixture of benzene (17 ml) and 10% HCl (7 ml) for 30 min.

12) 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. Nuclear magnetic resonance (NMR) spectra were measured at 100 MC (Japan Electron Optics LAB) with Me_4Si as an internal reference.

13) *a*) E.M. McMahon, J.N. Roper, Jr., W.P. Utermohlen, Jr., R.H. Hasek, R.C. Harris, and J.H. Brant, *J. Am. Chem. Soc.*, **70**, 2927 (1948); *b*) B. Woodward, F. Sondheimer, D. Taub, K. Hensler, and W.M. Mclamore, *ibid.*, **74**, 4223 (1952).

14) Y. Kitahara, A. Yoshikoshi, and S. Oida, *Tatrahedron Letters*, **1964**, 1763.

15) J. Szmuszkovicz, "Advances in Organic Chemistry: Methods and Results," Vol. 4, edited by R.A. Raphael, E.C. Taylor, and H. Wynberg, Interscience Publishers, Inc., New York, 1963, p. 84.

The benzene layer was separated and the aqueous layer was extracted with benzene. The benzene layer and benzene extracts were combined, washed with 10% HCl and a satd. NaCl solution, and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residual yellow oil was distilled to afford Ib (0.20 g, yield 43%): bp 115° (0.05 mmHg). (Reported[16] bp 145—150° (3 mmHg). IR ν_{max}^{film} cm^{-1}: 1712 (C=O), 1665 (C=C–O), 1614 (C=C). NMR (in $CDCl_3$) τ: 8.60 (3H, singlet, angular CH_3), 8.20 (3H, singlet, C=C–$C\underline{H}_3$), 7.0—8.2 (10H). *Anal.* Calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.68; H, 8.42.

The optical rotation of (+)-Ib obtained was shown in Table I.

The Solvent Effects (General Procedure)——A solution of IVb (0.30 g, 0.0014 mole) and VI (0.24 g, 0.0014 mole) in a solvent (12 ml; $CHCl_3$, THF, CH_3CN, CCl_4 or MeOH) was refluxed for 6 hr with molecular sieves 4A (0.5 g) under stirring. The molecular sieves were filtered off and the filtrate was evaporated under reduced pressure. The brown oil obtained was refluxed in a mixture of benzene (10 ml) and 10% HCl (5 ml) for 30 min. The following working-up was made in the same way as described above. The pale yellow oil obtained was purified by silica gel column chromatography (6% EtOH in $CHCl_3$). The product (Ib) could not be separated from the starting material (IVb) by this column chromatography. So the ratios of these mixtures of Ib and IVb were estimated by NMR spectral analyses. The yields and optical data were calculated on the basis of these data, and summarized in Table I.

The Effects of Reaction Temperatures——A solution of IVb (0.30 g, 0.0014 mole) and VI (0.24 g, 0.0014 mole) in each solvent (12 ml); *i.e.* benzene, toluene, $CHCl_3$ or MeOH, was stirred with molecular sieves 4A (0.5 g) at each reaction temperature (0—40°). The following working-up was carried out in the same way as described earlier. The results were summarized in Table II.

The Determination of optically Pure Ib and Its Absolute Configuration

(*S*)-(+)-Ib from (*S*)-(+)-1,2,3,5,6,7,8,8a-Octahydro-8a-methyl-4,8-naphthalenedione ((*S*)-(+)-Id)[9]——A solution of (*S*)-(+)-Id (0.60 g, 0.0034 mole, $[\alpha]^{20}+63°$ ($c=1.00$, benzene), optical purity 63%), mercaptoethanol (0.5 g, 0.0069 mole), Et_3N (0.36 g, 0.0036 mole), and 37% aqueous formaldehyde (0.36 g) in EtOH (12 ml) was refluxed for 36 hr. The reaction solution was condensed under reduced pressure. The residual oil was dissolved in AcOEt and the AcOEt solution was washed with 10% NaOH, satd. aqueous NaCl solution, and dried over anhydrous Na_2SO_4. The solvent was evaporated *in vacuo* and the residual oil was purified by silica gel column chromatography (AcOEt: *n*-hexane, 1: 3) to give (+)-4-ethylthiomethyl-1,2,3,5,6,7,8,8a-octahydro-8a-methyl-4,8-naphthalenedione (Ie) (0.37 g, yield 44%): IR ν_{max}^{film} cm^{-1}: 1710 (C=O), 1667 (α,β-unsaturated ketone), 1602 (C=C). NMR (in $CDCl_3$) τ: 8.75 (3H, triplet, $J=7.5$ cps, $SCH_2C\underline{H}_3$), 8.56 (3H, singlet, CH_3), 6.9—8.5 (12H), 6.55 (2H, quartet, $SC\underline{H}_2CH_3$). $[\alpha]_D^{20}+56.5°$ ($c=0.620$, EtOH). The desulfurization of (+)-Ie (0.2 g, 0.0004 mole), thus obtained, was carried out with Raney Ni (8 ml) by refluxing for 9 hr in acetone (20 ml) in the same method as Kirk[10] reported.

The same working-up as Kirk's method and the purification by silica gel column chromatography (AcOEt: *n*-hexane, 1: 3) gave (*S*)-(+)-Ib (0.09 g, 58% yield from Ie). This was identified by the comparison of its infrared and NMR spectra with those of the authentic sample. The optical rotation of this product (Ib) thus obtained was $[\alpha]_D^{20}+50°$ ($c=0.640$, MeOH). Therefore, the optical rotation of optically pure Ib, corrected for optical purity of the starting material (+)-Id used, was $[\alpha]_D^{20}+79°$ (MeOH).

Asymmetric Synthesis of (+)-Ic

1-(5-Methoxy-3-oxopentyl)-1-methyl-1,3-cyclohexanedione (IVc)——A solution of II (5.40 g, 0.043 mole), 5-methoxy-1-penten-3-one[17] (IIIc) (4.90 g, 0.043 mole), and Et_3N (1.4 ml) in THF (55 ml) was refluxed for 5.5 hr. The solvent was evaporated *in vacuo* and benzene was added to the residue. The precipitates separated were filtered to recover II (1.5 g, recovered yield 31%). The filtrate was evaporated under reduced pressure and the residual oil was distilled to give IVc (5.0 g, yield 48%): bp 150° (0.04 mmHg). IR ν_{max}^{film} cm^{-1}: 1715, 1695. NMR (in $CDCl_3$) τ: 8.76 (3H, singlet, CH_3), 7.2—8.4 (12H), 6.65 (3H, singlet, OCH_3), 6.40 (2H, triplet, $J=6$ cps, $C\underline{H}_2OCH_3$). Semicarbazone: white crystals. mp>295°. *Anal.* Calcd. for $C_{16}H_{29}O_4N_9\cdot 1H_2O$: C, 43.84; H, 7.30; N, 28.76. Found: C, 43.86; H, 7.53; N, 28.85.

(±)-1,2,3,5,6,7,8a-Octahydro-4-methoxymethyl-8a-methyl-3,8-naphthalenedione ((±)-Ic)——A solution of IVc (0.84 g, 0.0036 mole) and pyrrolidine (0.52 g, 0.0072 mole) in abs. benzene (24 ml) was refluxed for 6 hr with molecular sieves 4A (1.0 g) under stirring. The molecular sieves were filtered off and the filtrate was evaporated to give enamine (VIIb) (IR ν_{max}^{film} cm^{-1}: 1706, 1620, 1600). This was hydrolyzed by refluxing it in a mixture of benzene (12 ml) and 10% HCl (6 ml) for 25 min and the product was extracted with AcOEt. The AcOEt layers were washed with satd. aqueous NaCl solution and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residual oil was purified by silica gel column chromatography (7% EtOH in $CHCl_3$) to give(±) Ic (0.16 g, yield 21%): IR ν_{max}^{film} cm^{-1}: 1710 (C=O), 1670 (α,β-unsaturated ketone), 1615 (C=C). NMR (in $CDCl_3$) τ: 8.55 (3H, singlet, CH_3), 7.2—8.3 (10H), 6.70 (3H, singlet, OCH_3), 6.60 (2H, Singlet, OCH_2). bp 145° (0.03 mmHg). *Anal.* Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.85; H, 7.87.

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Asymmetric Synthesis of (+)-1,2,3,5,6,7,8,8a-Octahydro-4-methoxymethyl-8a-methyl-3,8-naphthalenedione ((+)-Ic)——A solution of IVc (0.24 g, 0.0010 mole) and VI (0.15 g, 0.0010 mole) in various solvents (12 ml; benzene, TEF, $CHCl_3$ or CH_3CN) was refluxed for 8 or 24 hours with molecular sieves 4A (0.5 g) under stirring. The molecular sieves were filtered off and the filtrate was evaporated *in vacuo*. The resultant oil was hydrolyzed by refluxing in a mixture of benzene (10 ml) and 10% HCl (5 ml) for 30 min. The following working-up was made in the same way as described in (*S*)-(+)-Ib. The product could not be separated from the starting material (IVc) by silica gel column chromatography (5% EtOH in CH_2Cl_2). So the ratios of these mixtures of Ic and IVc were estimated by NMR spectral analyses. For example (refluxing in benzene for 8 hr), the angular methyl group of Ic appeared as a singlet at τ 8.55 (33%), while that of IVc appeared as a singlet at τ 8.76 (67%). The yields and the optical data were calculated on the basis of these data, and summarized in Table III.