[Chem. Pharm. Bull. 24(6)1288—1292(1976)]

UDC 547.913.6.057 : 547.677.6.04

Stereochemical Studies. XLII.[1] Asymmetric Synthesis of naturally Occurring Podocarpic Acid

TAKANORI SONE, SHIRO TERASHIMA, and SHUN-ICHI YAMADA

Faculty of Pharmaceutical Sciences, University of Tokyo[2]

(Received October 4, 1975)

Optically active methyl deoxypodocarpate ((*S*) (+)-**5b**), 92% optically pure, was synthesized from (*R*) (+)-δ-ketoaldehyde ((*R*) (−)-**3a**) which was obtainable by the asymmetric synthesis using D-proline-derived pyrrolidine ((*R*)-**4** (R_2=$CH_2NC_4H_8$)) as a chiral additive. The chemical scheme which was previously developed, was used for the conversion of (*R*) (−)-**3a** to (*S*) (+)-phenanthrone derivative ((*S*) (+)-**1a**), and a combination of reductive carbomethoxylation and reductive alkylation was adopted for preparing (*S*) (+)-**5b** from (*S*) (+)-**1a**.

Since (*S*) (+)-**5b** had already been converted to naturally occurring podocarpic acid ((*S*) (+)-**5a**), the asymmetric synthesis of (*S*) (+)-**5a** was accomplished.

In the previous report,[1] it was established that optically active (*R*)(−)-phenanthrones[3] ((*R*)(−)-**1a** and (*R*)(−)-**1b**) could be prepared from (*R*)(+)-2-cyclohexenones ((*R*)(+)-**2a** and (*R*)(+)-**2b**) or (*S*)(+)-δ-ketoaldehydes ((*S*)(+)-**3a** and (*S*)(+)-**3b**) which were produced by the asymmetric synthesis using optically active L-proline-derived pyrrolidines ((*S*)-**4**) as chiral additives.[4] Completion of the synthetic scheme mentioned above, clearly discloses that when D-proline-derived pyrrolidines ((*R*)-**4**) are used as chiral additives for the asymmetric synthesis, or when (*R*)(*S*) conversion is carried out with (*R*)(+)-**2**,[5] (*S*)(+)-**1** should be successfully obtained by the asymmetric synthesis.

Racemic **1** have been widely employed as starting materials for the total syntheses of racemic tri- and tetracyclic diterpenes and steroids such as podocarpic acid, nimbiol, (−)-kaurene, stachene, phyllocladene, 5α-pregnan-3β-ol-20-one, and so on.[6] Among them, few diterpenes such as (−)-kaurene, atisirene, and stachene, contain α-methyl groups at A—B ring junction, whose absolute configurations are identical with those of the C_{4a}-methyl groups of (*R*)(−)-**1**. The methyl groups of the other large number of diterpenes and steroids at A—B ring junction, have the same absolute configurations (β-configurations) as those of the C_{4a}-methyl groups of (*S*)(+)-**1**. Therefore, starting from (*R*)(−)- or (*S*)(+)-**1**, various tri- and tetracyclic diterpenes and steroids which contain α or β-methyl groups at A—B ring junction, should be synthesized freely.

In order to visualize the above-mentioned applicability of the synthetic route developed here, to total syntheses of optically active diterpenes and steroids, synthesis of naturally occurring (*S*)(+)-podocarpic acid ((*S*)(+)-**5a**), one of the most popular diterpene resin acids,

1) Part XLI: T. Sone, S. Terashima, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **24**, 1273 (1976).
2) Location: *Hongo, Bunkyo-ku, Tokyo, 113, Japan.*
3) Throughout this work, (*R*) (*S*) expression is used to designate the absolute configuration of the chiral center produced by asymmetric synthesis except for (*R*)- and (*S*)-**4**.
4) *a*) G. Otani and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **21**, 2112, 2119, 2125 (1973); *b*) T. Sone, K. Hiroi, and S. Yamada, *ibid.*, **21**, 2331 (1973).
5) T. Sone, S. Terashima, and S. Yamada, *Synthesis*, **1974**, 725.
6) See ref. 1, footnote 9.

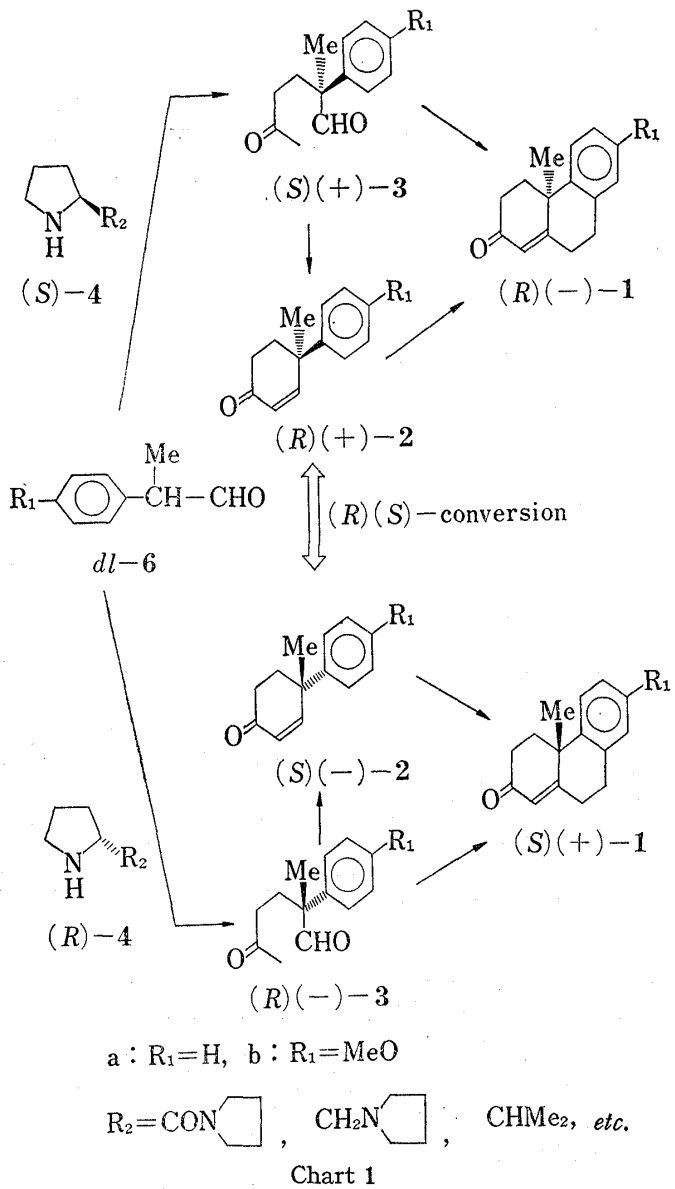

Chart 1

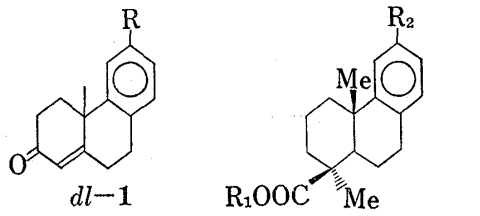

Chart 2

was examined. Although syntheses of **5a** have been attempted by many groups[7] in optically active[7a,b,c] or racemic modifications,[7d–l] and some synthetic studies have utilized *dl*-**1a**[7a,b,c] or its 6-methoxy derivative (*dl*-**1c**)[7k,l] as a starting material, synthesis of (*S*)(+)-**5a** by asymmetric synthesis has not yet been reported.

In this report, (*S*)(+)-**1a** was prepared from (*R*)(−)-**3a** which was obtained by the asymmetric synthesis using (*R*)-**4** ($R_2=CH_2NC_4H_8$) as a chiral additive and *dl*-2-phenylpropionaldehyde (*dl*-**6a**) as a substrate for the enamine formation. The best reaction conditions which were established in the previous studies,[1] were also applied to the preparation of (*S*)(+)-**1a**. As a method for converting (*S*)(+)-**1a** to (*S*)(+)-**5a**, a combination of reductive carbomethoxylation and reductive alkylation, which was developed by Welch, *et al.*,[7l] was adopted because of its simplicity. By these studies, optically active (*S*)(+)-methyl deoxypodocarpate ((*S*)(+)-**5b**), which had already been converted to (*S*)(+)-**5a**,[7c] was prepared with more than 90% optical integrity.

Some preliminary experiments which were performed by racemic compounds, were described in detail in experimental part.

Result and Discussion

As shown in Chart 3, the asymmetric Michael addition of the enamine, prepared from *dl*-**6a** and (*R*)-**4** ($R_2=CH_2NC_4H_8$), $[\alpha]_D^{20}$−9.2° (ethanol), to methyl vinyl ketone (MVK), gave

7) *a*) E. Wenkert and B.G. Jackson, *J. Am. Chem. Soc.*, **80**, 217 (1958); *b*) *Idem, ibid.*, **81**, 5601 (1959); *c*) E. Wenkert and A. Tahara, *ibid.*, **82**, 3229 (1960); *d*) F. Giarrusso and R.E. Ireland, *J. Org. Chem.*, **33**, 3560 (1968); *e*) M.E. Kuehne and J.A. Nelson, *ibid.*, **35**, 161 (1970); *f*) R.D. Haworth and B.P. Moore, *J. Chem. Soc.*, **1946**, 633; *g*) F.E. King, T.J. King, and J.G. Topliss, *Chem. Ind.*, **1956**, 113; *h*) V.R. Ghatak, *J. Am. Chem. Soc.*, **82**, 1728 (1960); *i*) T.A. Spencer, R.J. Friary, W.W. Schmiegel, J.F. Simeone, and D.S. Watt, *J. Org. Chem.*, **33**, 712, 719 (1968); *j*) W.L. Meyer and K.K. Maheshwari, *Tetrahedron Letters*, **1964**, 2175; *k*) M. Kuehne, *J. Am. Chem. Soc.*, **85**, 1492 (1961); *l*) S.C. Welch and C.P. Hagan, *Synth. Comm.*, **1972**, 221, and **1973**, 29.

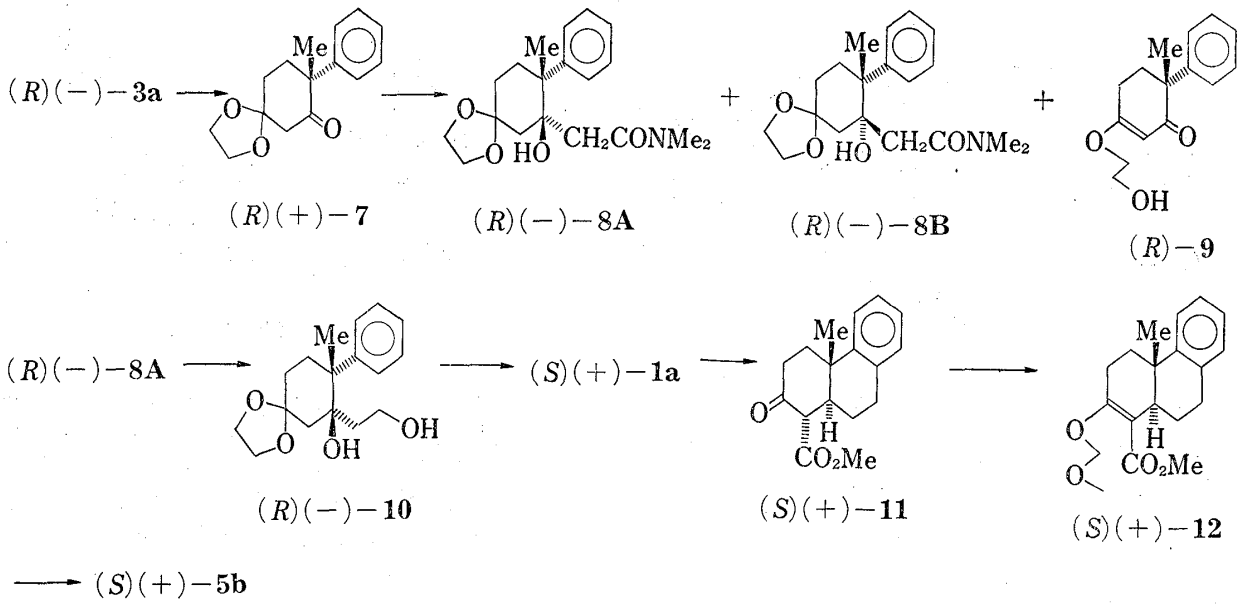

Chart 3

(*R*)(−)-**3a**, $[\alpha]_D^{20}$−12.0° (ethanol), 42% optically pure,[8] in 74% yield. Cyclization of (*R*)(−)-**3a** in the presence of dilute aqueous base, followed by ketalization with ethylene glycol and Jones oxidation, yielded (*R*)(+)-cyclohexanone ((*R*)(+)-**7**), $[\alpha]_D^{20}$+63.3° (ethanol), in 73% yield (overall from (*R*)(−)-**3a**). Addition of N,N-dimethyl lithioacetamide-1,4-diazabicyclo[2,2,2]octane (DABCO) complex[1] gave two kinds of the addition products[9] ((*R*)(−)-**8A** and (*R*)(−)-**8B**), $[\alpha]_D^{20}$−26.6° (ethanol) and $[\alpha]_D^{20}$−14.4° (ethanol), in 82% and 11% yields, and (*R*)-enol ether ((*R*)-**9**)[10] in 4.0% yield. The optical purity of (*R*)(−)-**8A** was raised by the same procedure as that developed before,[1] and (*R*)(−)-**8A** showing $[\alpha]_D^{20}$−57.5° (ethanol) was finally obtained. Repeated reduction of (*R*)(−)-**8A** with sodium aluminium bis (methoxyethoxy)hydride (Vitride)[1] afforded (*R*)(−)-diol ((*R*)(−)-**10**), $[\alpha]_D^{20}$−49.5° (ethanol), in 69% yield (overall from (*R*)(−)-**8A**). Cyclization of (*R*)(−)-**10** with polyphosphoric acid (PPA) gave a 62% yield of (*S*)(+)-**1a**, $[\alpha]_D^{27}$+297° (95% ethanol), 89% optically pure.[11]

According to the reported procedure,[7l] reductive carbomethoxylation of (*S*)(+)-**1a** by sequential treatment with lithium in liquid ammonia, dry carbon dioxide gas, and diazomethane, afforded (*S*)(+)-β-ketoester ((*S*)(+)-**11**), $[\alpha]_D^{20}$+70.0° (ethanol), in 23% yield. Treatment of (*S*)(+)-**11** with sodium hydride in hexamethylphosphoramide (HMPA), followed by quenching with chloromethyl methyl ether, gave (*S*)(+)-vinyl ether ((*S*)(+)-**12**), $[\alpha]_D^{20}$+23.6° (ethanol), in 75% yield. Reductive alkylation of (*S*)(+)-**12** by treatment with lithium in liquid ammonia-1,2-dimethoxyethane, followed by quenching with methyl iodide, afforded (*S*)(+)-**5b**, $[\alpha]_D^{20}$+127° (ethanol), 92% optically pure,[12] in 49% yield.

Since (*S*)(+)-**5b** had already been converted to (*S*)(+)-**5a**,[7c] the asymmetric synthesis of (*S*)(+)-**5a** was completed.

8) The optical purity was determined by converting (*R*) (−)-**3a** to (*S*) (−)-**2a** (see ref. 1).
9) For detailed studies on the elucidation of structures of these compounds, see ref. 1.
10) The optical rotation was not measured. For the elucidation of the structure, see the accompanying paper (T. Sone, S. Terashima, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **26**, 1293 (1976).
11) (*S*) (+)-**1a**, $[\alpha]_D^{27}$ +332° (95% ethanol), which was prepared by chemical resolution, was assumed to be optically pure (W.R. Adams, O.L. Chapman, J.B. Sieja, and W.L. Welstead, Jr., *J. Am. Chem. Soc.*, **88**, 162 (1966)).
12) The optical purity was calculated by the assumption that (*S*) (+)-**5b**, $[\alpha]_D$ +138.2° (ethanol), mp 141—142°, derived from naturally occurring (*S*) (+)-**5a**, was optically pure (see ref. 7*a*,*c*).

Experimental[13]

(*R*) (−)-2-(1-Pyrrolidinomethyl)pyrrolidine ((*R*) (−)-4(R_2=$CH_2NC_4H_8$))——This compound was prepared from commercially available D-proline according to the published procedure.[4b] Bp 87—88° (7 mmHg), $[\alpha]_D^{20}$ −9.2° (c=4.28, EtOH) (lit.,[4b] bp 99—101° (12 mmHg), $[\alpha]_D^{20}$ +8.5° (c=2.40, EtOH) for (*S*) (+)-**4** (R_2=$CH_2NC_4H_8$)). IR and NMR spectra of this oil were superimposable on those of (*S*) (+)-compound measured in the same states.

(*R*) (−)-2-Methyl-2-phenyl-1,5-hexanedione ((*R*) (−)-3a)——Michael addition of the crude enamine, prepared from *dl*-**6a** (6.7 g, 0.050 mole) and (*R*) (−)-**4** (R_2=$CH_2NC_4H_8$) ($[\alpha]_D^{20}$ −9.2° (c=4.28, EtOH)) (7.7 g, 0.050 mole), to MVK in a mixture of benzene and methanol (9: 1) at 5° for 3 days, followed by the hydrolytic work-up with 10% HCl and by usual extractive isolation, afforded pure (*R*) (−)-**3a** as an oil (7.53 g, 74%), bp 130—132° (2 mmHg), $[\alpha]_D^{20}$ −12.0° (c=3.168, EtOH) (lit.,[1] bp 111—114° (1 mmHg), $[\alpha]_D^{20}$ +12.8° (c=0.972, EtOH) for (*S*) (+)-**3a**). Spectral (IR) and chromatographic properties of this oil were identical with those of (*S*) (+)-**3a**.

In order to determine the degree of asymmetric induction for the alkylation step, a part of (*R*) (−)-**3a** (1.00 g, 4.9 mmole) was converted to (*S*) (−)-**2a** (720 mg, 80%), bp 125—126° (3 mmHg), $[\alpha]_D^{20}$ −54.0° (c= 1.524, EtOH), according to the published procedure.[1,4a] Since optically pure (*R*) (+)-**2a** was reported to show $[\alpha]_D^{20}$ +130° (EtOH),[1,4a] the degree of asymmetric induction could be calculated as 42%.

(*R*) (+)-5,5-Ethylenedioxy-2-methyl-2-phenylcyclohexanone ((*R*) (+)-7)——Cyclization of (*R*) (−)-**3a** ($[\alpha]_D^{20}$ −12.0° (c=3.168, EtOH)) (6.53 g, 0.032 mole) with 0.3N KOH (6.4 ml, 1.9 mmole) in a cold room, followed by ketalization with ethylene glycol (5 ml, *ca.* 90 mmole) and *p*-toluenesulfonic acid monohydrate (50 mg, catalytic amount), and oxidation with 2.5M Jones reagent (1,1 eq.) at −25°, according to the same procedures as those established,[1] afforded pure (*R*) (+)-**7** as an oil (5.77 g, 73% overall yield from (*R*) (−)-**3a**), $[\alpha]_D^{20}$ +63.3° (c=0.980, EtOH) (lit.,[1] $[\alpha]_D^{20}$ −59.8° (c=0.894, EtOH) for (*S*) (−)-**7**). The structure of this compound was confirmed by spectral (IR) and chromatographic (TLC) comparisons with (*S*) (−)-**7**.

(*R*) (−)-N,N-Dimethyl-2-(5,5-ethylenedioxy-1-hydroxy-2-methyl-2-phenylcyclohexyl)acetamide ((*R*) (−)-8A and (*R*) (−)-8B)——Similar treatment of (*R*) (+)-**7** ($[\alpha]_D^{20}$ +63.3° (c=0.980, EtOH)) (3.20 g, 13 mmole) with N,N-dimethyl lithioacetamide-DABCO complex (2.0 eq.) to the case for the reaction with (*S*) (−)-**7**, afforded two kinds of the addition products ((*R*) (−)-**8A** and (*R*) (−)-**8B**) as oils (3.56 g, 82% and 490 mg, 11%), $[\alpha]_D^{20}$ −26.6° (c=3.552, EtOH) and $[\alpha]_D^{20}$ −14.4° (c=2.012, EtOH), and (*R*)-enol ether ((*R*)-**9**)[10] (130 mg, 4.0%) as an oil, after separation by column chromatography (silica gel, solvent ether). Recrystallization of the major adduct ((*R*) (−)-**8A**) (3.56 g) from ether gave *dl*-**8A** as colorless prisms (1.62 g), mp 147—149° (lit.,[1] mp 149—150°), and (*R*) (−)-**8A** (1.91 g), $[\alpha]_D^{20}$ −57.5° (c=1.028, EtOH), could be obtained as a colorless oil by evaporation of the combined mother liquors from the recrystallization. The structures of these compounds obtained here, were definitely confirmed by comparisons of their spectral (IR) and chromatographic (TLC) behavior with those of the authentic samples prepared before.[1]

(*R*) (−)-3-Hydroxy-3-(2-hydroxyethyl)-4-methyl-4-phenylcyclohexanone Ethylene Ketal ((*R*) (−)-10)—— Similar repeated reductions of (*R*) (−)-**8A** ($[\alpha]_D^{20}$ −57.5° (c=1.028, EtOH)) (1.00 g, 3.0 mmole) with Vitride (1.1 eq.) in a mixture of benzene and ether to the case for (*S*) (+)-**8A**,[1] afforded pure (*R*) (−)-**10** as a pale yellow oil (605 mg, 69%), $[\alpha]_D^{20}$ −49.5° (c=0.798, EtOH) (lit.,[1] $[\alpha]_D^{20}$ +48.7° (c=1.902, EtOH) for (*S*) (+)-**10**). Spectral (IR) and chromatographic (TLC) properties of this oil were identical with those of (*S*) (+)-**10** recorded in the same states.

(*S*) (+)-4a-Methyl-4,4a,9,10-tetrahydro-2(3H)-phenanthrone ((*S*) (+)-1a)——The same treatment of (*R*) (−)-**10** ($[\alpha]_D^{20}$ −49.5° (c=0.798, EtOH)) (584 mg, 2.0 mmole) with PPA as that of (*S*) (+)-**10**,[1] gave pure product as a pale yellow oil (262 mg, 62%), $[\alpha]_D^{27}$ +297° (c=0.296, 95% EtOH), 89% optically pure.[11] This oil showed the identical spectral (IR and NMR) and chromatographic (TLC) behavior with those of the authentic sample[1] recorded in the same states.

***dl*-Methyl 4a-Methyl-1,2,3,4,4a,9,10,10a-octahydro-2-oxophenanthrene-1-carboxylate (*dl*-11)**——A solution of *dl*-**1a**[1] (1.06 g, 5.0 mmole) in ether (20 ml) was added to a solution of Li(105 mg, 15 mg atom) in liquid ammonia (30 ml). The ammonia was evaporated at room temperature and ether (*ca.* 30 ml) was added to the residual mixture. Dry carbon dioxide gas was bubbled through the ethereal solution at room temperature for 2 hr, then the mixture was poured onto ice. The aqueous layer was separated, and the upper organic layer was extracted with ice-water. The combined aqueous layers were acidified with 10% HCl at 0°, and extracted with ether. An ethereal solution of diazomethane was added to the combined ethereal extracts until the

13) All melting and boiling points are uncorrected. Infrared (IR) spectra measurements were carried out using spectrometers, JASCO Infrared Spectrometer Model DS-402G and JASCO IRA-1 Grating Infrared Spectrometer. Nuclear magnetic resonance (NMR) spectra were measured with spectrometers, JNM-PS 100 Spectrometer (100 Mc) and Hitachi R-24 High Resolution NMR Spectrometer (60 Mc). All signals are expressed by the ppm downfield from tetramethylsilane used as an internal standard (δ value). Following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br). Measurements of optical rotation were carried out with YANACO OR-50 Automatic Polarimeter.

color of diazomethane remained. Excess diazomethane was decomposed by 10% HCl, and the organic layer was washed with satd. NaCl. After drying over anhyd. $MgSO_4$, filtration and evaporation *in vacuo*, followed by separation with column chromatography (silica gel, solvent ether: hexane 2: 3) gave pure *dl*-**11** as a colorless solid (272 mg, 20%). Recrystallization from ether–petr. ether gave pure sample showing mp 127—129° (lit.,[7i] mp 126—127°). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1745 (COOMe), 1714 (CO). NMR (in CCl_4): 1.32 (3H, s, CH_3), 3.86 (3H, s, $COOCH_3$).

(*S*)(+)-Methyl 4a-Methyl-1,2,3,4,4a,9,10,10a-octahydro-2-oxophenanthrene-1-carboxylate ((*S*) (+)-11)——The same treatment of (*S*) (+)-**1a** ($[\alpha]_D^{27}$ +297° (*c*=0.296, EtOH)) (195 mg, 0.92 mmole) as that of *dl*-**1a** gave pure (*S*) (+)-**11** as a solid (56 mg, 23%), $[\alpha]_D^{20}$ +70.0° (*c*=1.102, EtOH), mp 128—136°. Spectral (IR and NMR) and chromatographic (TLC) behavior of this solid were identical with those of *dl*-**11** recorded in the same states.

***dl*-Methyl 2-(Methoxymethoxy)-4a-methyl-3,4,4a,9,10,10a-hexahydrophenanthrene-1-carboxylate (*dl*-12)**——A solution of *dl*-**11** (136 mg, 0.50 mmole) in HMPA (1.5 ml) was added to a suspension of sodium hydride (50% oil dispersion) (27 mg, 0.56 mmole) in HMPA (1 ml). The whole was stirred at room temperature for 2 hr, and chloromethyl methyl ether (50 mg, 0.62 mmole) was added to the HMPA solution obtained here, under ice cooling. After stirring at room temperature for 3 hr, the mixture was poured into a mixture of ice and satd. $NaHCO_3$ and extracted with ether–hexane (1: 2). The combined organic extracts were washed with satd. NaCl, then dried over anhyd. $MgSO_4$. Filtration and evaporation *in vacuo*, followed by purification with preparative TLC (Merck precoated TLC plate, 0.2 mm, silica gel, solvent ether: hexane 1: 2) gave pure *dl*-**12** as a pale yellow oil (140 mg, 88%). IR ν_{max}^{film} cm^{-1}: 1730 (COOMe). NMR (in CCl_4): 1.10 (3H, s, CH_3), 1.8—2.8 (9H, m, $4\times CH_2+CH$), 3.41 (3H, s, OCH_3), 3.66 (3H, s, $COOCH_3$), 4.84 (2H, q, J=4 Hz, OCH_2O).

(*S*) (+)-Methyl 2-(Methoxymethoxy)-4a-methyl-3,4,4a,9,10,10a-hexahydrophenanthrene-1-carboxylate ((*S*) (+)-12)——The same treatment of (*S*) (+)-**11** ($[\alpha]_D^{20}$ +70.0° (*c*=1.102, EtOH)) (55 mg, 0.20 mmole) as that of *dl*-**11** gave pure (*S*) (+)-**12** as a pale yellow oil (47 mg, 75%), $[\alpha]_D^{20}$ +23.6° (*c*=0.440, EtOH). This oil showed the same spectral (IR and NMR) and chromatographic (TLC) properties as those of the racemic compound recorded in the same states.

***dl*-Methyl Deoxypodocarpate (*dl*-5b)**——Metal Li (7 mg, 1.0 mg atom) was added to a solution of *dl*-**12** (53.7 mg, 0.17 mmole) in a mixture of 1,2-dimethoxyethane (1 ml) and liquid ammonia (3.5 ml). The whole was stirred at reflux temperature (−33°) for 10 min, and at −70° for 5 min. Methyl iodide (0.2 ml) was added to the reaction mixture and the whole solution was stirred at −70° for 30 min, and at room temperature for 4 hr. After diluted with ether (15 ml), the ethereal solution was washed with satd. NaCl, and dried over anhyd. $MgSO_4$. Filtration and evaporation *in vacuo* gave an oily residue, which was purified by preparative TLC (Merck precoated TLC plate, 0.2 mm, silica gel, solvent ether: hexane 1: 9) to afford pure *dl*-**5b** as a colorless crystalline solid (17 mg, 37%), mp 131—132° (lit.,[14] mp 130—131°). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1722 (COOMe). NMR (in CCl_4): 1.00 (3H, s, CH_3), 1.24 (3H, s, CH_3), 3.70 (3H, s, $COOCH_3$). Mass Spectrum *m/e*: 272 (M^+), 215, 197.

(*S*) (+)-Methyl Deoxypodocarpate ((*S*) (+)-5b)——The same treatment of (*S*) (+)-**12** ($[\alpha]_D^{20}$ +23.6° (*c*=0.440, EtOH)) (36.5 mg, 0.12 mmole) as that of *dl*-**12** gave pure (*S*) (+)-**5b** as a colorless crystalline solid (15.3 mg, 49%), mp 136—140°, $[\alpha]_D^{20}$ +127° (*c*=0.270, EtOH), 92% optically pure.[12] This sample showed the same spectral (IR and NMR) and chromatographic (TLC) behavior as those of *dl*-**5b** recorded in the same states.

Acknowledgement The authors are indebted to members of the Central Analysis Room of This Faculty for spectra measurements.

14) E. Wenkert, A. Afonso, J.B. Bredenberg, C. Kaneko, and A. Tahara, *J. Am. Chem. Soc.*, **86**, 2038 (1964).