[Chem. Pharm. Bull. 24(2) 315—322 (1976)] UDC 547.381.057 : 547.787.04

Stereochemical Studies. XXXIX.[1] A Novel Method for the Preparation of Optically Active Aldehydes. Syntheses of Optically Active (*R*)(+)-α-Cyclocitral, (*S*) (+)-Dehydrovomifoliol, and (*S*) (+)-Abscisic Acid[2]

Masakatsu Shibasaki, Shiro Terashima, and Shun-ichi Yamada

Faculty of Pharmaceutical Sciences, University of Tokyo[3]

(Received June 7, 1975)

It was found that direct hydrolysis of the crude oxazolidine derivatives (**3a**, **b**), prepared with *dl*-α-cyclocitral (*dl*-**1a**), or its 6-benzoxy derivative (*dl*-**1b**) and (*S*) (+)-prolinol ((*S*) (+)-**4**), with aqueous acetic acid, afforded (*R*) (+)-**1a**, 19% optically pure, and (*S*) (+)-6-hydroxy-α-cyclocitral ((*S*) (+)-**2b**), 63% optically pure, respectively. A merit of the resolution method is that optically active (*R*) (+)-**1a** or (*S*) (+)-**2b** can be obtained without any recrystallizations.

Some mechanistic studies and discussions on the hydrolysis were also examined.

Optically active (*S*) (+)-**2b**, thus obtained, was successfully converted into (*S*) (+)-dehydrovomifoliol ((*S*) (+)-**5**) *via* (*S*) (+)-6-hydroxy-α-ionone ((*S*) (+)-**9**). By this chemical conversion, (*S*) (+)-abscisic acid could be formally synthesized from *dl*-**1b**.

Although there have been reported various methods including resolutions[4] and asymmetric syntheses[5] for preparation of optically active compounds, methods which are effective for producing optically active carbonyl compounds are quite limited.[6,7]

Recently, it was reported[8] that the resolution of racemic aldehyde and ketone, which were key intermediates for prostaglandin synthesis, could be achieved by repeated recrystallizations of the diastereomeric mixtures of oxazolidines prepared with *d*-ephedrine.

In the course of our effort[7] for preparing optically active carbonyl compounds using optically active α-amino acid derivatives, the authors have found that the racemic aldehydes such as *dl*-α-cyclocitral (*dl*-**1a**)[7] and *dl*-6-benzoxy-α-cyclocitral (*dl*-**1b**) can be readily converted into the corresponding optically active aldehydes ((*R*) (+)-**1a** and (*S*) (+)-**2b**[9]) by the direct acidic hydrolysis of oily diastereomeric mixtures of the oxazolidines (**3**). Since **3** is obtained by the condensation of *dl*-**1** with (*S*) (+)-prolinol ((*S*)-(+)-**4**),[10] and moreover, since fairly high degrees of optical purity for (*R*) (+)-**1a** and (*S*) (+)-**2b** are obtained without any recrystallizations of **3**, the method developed here, could be considered to be one of the effective methods for preparation of optically active aldehydes.

1) Part XXXVIII: K. Hiroi and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **23**, 1103 (1975).
2) Presented at the 94th Annual Meeting of the Pharmaceutical Society of Japan, Sendai, April, 1974, and at the 17th Sympodium on the Chemistry of Natural Products, Tokyo, October, 1973.
3) Location: *Hongo, Bunkyo-ku, Tokyo, 113, Japan.*
4) E.L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, Inc., New York, 1962, pp. 47—83.
5) J.D. Morrison and H.S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Inc., Engelwood Cliffs, New Jersy, 1971.
6) *a*) ref. 4, p. 56; *b*) E.J. Corey and R.B. Mitra, *J. Am. Chem. Soc.*, **84**, 2938 (1962); *c*) J. Casanova, Jr. and E.J. Corey, *Chem. Ind.*, **1961**, 1664; *d*) W.R. Adams, O.L. Chapmann, J.B. Seija, and W.L. Welstead, Jr., *J. Am. Chem. Soc.*, **88**, 162 (1966); *e*) R. Pappo, P. Collins, and C. Jung, *Tetrahedron Letters*, **1973**, 943.
7) M. Shibasaki, S. Terashima, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **23**, 272, 279 (1975), and references therein.
8) *a*) R. Kelly and V. VanRheenen, *Tetrahedron Letters*, **1973**, 1709; *b*) R.C. Kelly, V. VanRheenen, I. Schletter, and M.D. Pillai, *J. Am. Chem. Soc.*, **95**, 2746 (1973).
9) For the cleavage of benzoyl group, see the later description.
10) P. Karrer, P. Portmann, and M. Suter, *Helv. Chim. Acta*, **31**, 1617 (1948).

This report deals with a full account of the novel resolution method and its successful application to the synthetic approach to naturally occurring (*S*) (+)-dehydrovomifoliol ((*S*) (+)-**5**)[11] from which (*S*) (+)-abscisic acid ((*S*) (+)-**6**), a plant growth regurator, have been synthesized by many groups.[11,12]

Result and Discussion

A. Preparation of Optically Active (*R*) (+)-α-Cyclocitral ((*R*) (+)-1a) and (*S*) (+)-6-Hydroxy-α-cyclocitral ((*S*) (+)-2b)

It has been already established that when secondary amino alcohols react with carbonyl compounds, stable oxazolidine derivatives are formed.[13] Therefore, we first examined the applicability of (*S*) (+)-**4** to the resolution of *dl*-**1a**[14] by way of its oxazolidine derivative (**3a**).

Condensation of *dl*-**1a** with an equimolar amount of (*S*) (+)-**4** in the presence of *p*-toluenesulfonic acid and Molecular Sieves 4A gave an almost quantitative yield of the crude oily **3a**. As shown in Chart 2, presence of four diastereoisomers are theoretically possible for **3a** due to the asymmetric center inherently present in *dl*-**1a** and to the newly created C_2-position of oxazolidine system. Moreover, it is probable that one of four possible pairs of the diastereoisomers[15] was selectively formed in a manner similar to the case for the resolution in prostaglandin synthesis[8] if the oxazolidine formation proceeds stereoselectively concerning the C_2-position. However, attempted separation of one of the formed diastereoisomers as crystalline picrate or perchlorate[16] turned out to be unpromising, and the relative ratio of the formed

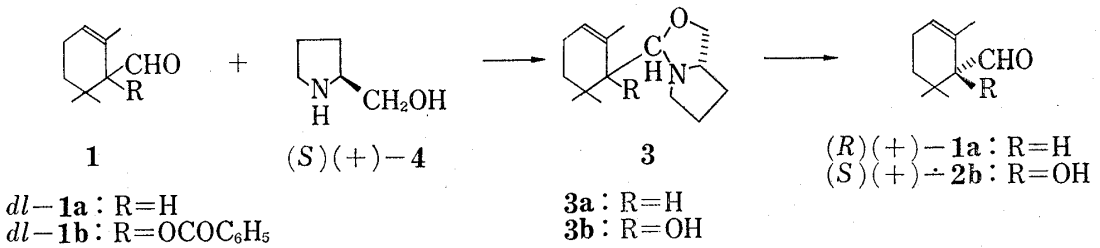


Chart 1

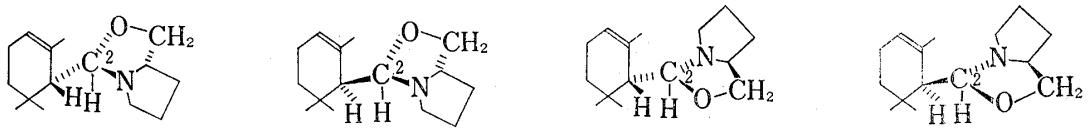


Chart 2

11) *a*) M. Takasugi, M. Anetai, N. Katsui, and T. Masamune, *Chemistry Letters*, **1973**, 245; *b*) K. Mori, *Tetrahedron Letters*, **1973**, 2635, and *idem*, *Tetrahedron*, **30**, 1065 (1974).
12) M. Koreeda, G. Weiss, and K. Nakanishi, *J. Am. Chem. Soc.*, **95**, 239 (1973).
13) *a*) D.E. Bergmann, *Chem. Rev.*, **53**, 309 (1953); *b*) L. Neelakantan, *J. Org. Chem.*, **36**, 2256 (1971).
14) Optically active (*R*) (+)-**1a** was recently synthesized by the asymmetric synthesis, and could be converted into optically active (*R*) (+)-*trans*-α-damascone, a famous perfume due to its fragrant odor (see ref. 7).
15) These pairs are as follows: **3aA** and **3aB**, **3aA** and **3aD**, **3aC** and **3aB**, and **3aC** and 3aD.
16) In ref. 13, some oxazolidine derivatives are reported to give well-crystalline picrates or perchlorates.

isomers could not be determined. The structure of **3a** was definitely confirmed by the following spectral data: IR (film): 1200, 1140, and 1050 cm^{-1} (oxazolidine ring)[13]; NMR (in carbon tetrachloride): δ 4.50—4.30 (1H, multiplet, C_2-proton of the oxazolidine ring).

Since oxazolidine is expected to be readily hydrolyzed to aldehyde by acidic treatment, the direct hydrolysis of crude **3a** was next undertaken.

A two layer solution of benzene containing crude **3a**, and 10% aqueous acetic acid, was stirred at room temperature for 0.5 hr, regenerating oily (*R*) (+)-**1a**, $[\alpha]_D^{20}$ +112.0° (ethanol), in 26% yield from *dl*-**1a** after extractive isolation and purification by column chromatography. The optical purity of this oil could be calculated as 19%, based on the assumption that (*R*) (+)-**1a** showing $[\alpha]_D^{20}$ +594.5° (ethanol) was optically pure.[7] Kinetic difference of the hydrolysis rates of diastereoisomers might explain the observed result. However, inspection of the stereo-structures of four diastereoisomers (**3aA-D**) using Dreiding model could not elucidate the reason why **3aA** and/or **3aC** were hydrolyzed preferentially to the others (**3aB** and/or **3aD**).

When the hydrolysis time was changed, the optical purity of (*R*) (+)-**1a** varied as was shown in Table I. It is clear that the optical purity of (*R*) (+)-**1a** reaches at a maximum

Table I. Effect of the Hydrolysis Time on the Chemical Yield and Optical Purity of (*R*)(+)-α-Cyclocitral ((*R*)(+)-**1a**)

Hydrolysis time (hr)	(*R*)(+)-α-Cyclocitral(hr) ((*R*)(+)-**1a**)	
	Chem. yield (%)[a]	Optical yield (%)[b]
0.13	15	14
0.5	26	19
2.0	45	13
3.0	57	10
21	60	4

a) Based on *dl*-**1a** used for the preparation of **3a**.
b) (*R*)(+)-**1a** showing $[\alpha]_D^{20}$ +594.5° (EtOH) was assumed to be optically pure.

after 0.5 hr hydrolysis and gradually decreased with increase of the chemical yield of (*R*) (+)-**1a** at longer hydrolytic treatment. These phenomena are clearly compatible with the speculation that the optical activity observed in (*R*) (+)-**1a** is due to kinetic difference of the hydrolysis rates of diastereoisomers.

Next, we applied the above-mentioned method to the resolution of *dl*-**1b**, aiming to synthesize optically active dehydrovomifoliol ((*R*) (−)-**5** or (*S*) (+)-**5**).

As shown in Chart 3, preparation of *dl*-**1b** was readily accomplished by the treatment of *dl*-α-cyclocitral-pyrrolidine enamine (**7**) with benzoyl peroxide.[17] The benzoxylation also afforded *dl*-4-benzoxy-β-cyclocitral (*dl*-**8**) as a byproduct, but it could be easily separated from the desired *dl*-**1b** by column chromatography.

Condensation of *dl*-**1b** with (*S*) (+)-**4** was carried out under a similar condition to that for *dl*-**1a** except for the relative amount of (*S*) (+)-**4** (3.0 equivalents) and refluxing time (75 hr).[18] Sequential extraction of the reaction mixture afforded crude *dl*-**1b** in 54% recovery from the neutral fraction, and benzoic acid in 23% yield from the acidic fraction. From the basic fraction,[19] crude oily **3b** was obtained as a mixture of diastereoisomers.[20] Separation of

17) *a*) R.L. Augustine, *J. Org. Chem.*, **28**, 581 (1962); *b*) S.O. Lawesson, H.J. Jakobsen, and E.H. Larsen, *Acta. Chem. Scand.*, **17**, 1188 (1963).
18) Even under this forcing condition, more than 50% of *dl*-**1b** was recovered from the reaction mixture. This is probably due to the increased steric hindrance to aldehyde group of *dl*-**1b**.
19) Since **3b** was found to be stable to 10% aqueous hydrochloric acid at room temperature, the separation of crude **3b** could be easily accomplished by simple extraction of the reaction mixture with 10% aqueous hydrochloric acid, followed by basification and re-extraction. Unreacted (*S*) (+)-**4** was not contaminated in crude **3b** by the above-mentioned isolation method due to its large solubility in water.
20) Four kinds of diastereoisomers similar to **3aA-D** were theoretically possible for **3b**.

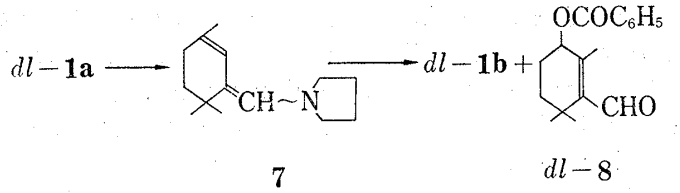


Chart 3

one of the possible diastereoisomers and determination of the formation ratio of four isomers were again unsuccessful. However, the structure of **3b**, that is, exclusive cleavage of the benzoyl group during oxazolidine formation, was ascertained by its spectral data.

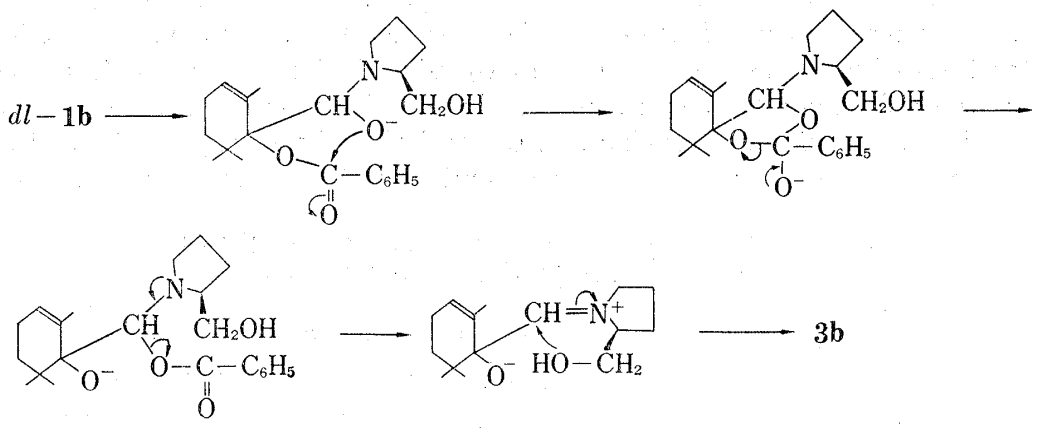


Chart 4

Cleavage of the benzoyl group is conceivably due to the result of intramolecular catalysis as is shown in Chart 4.[21,22]

Hydrolysis of crude **3b** was attempted by refluxing a two layer solution of benzene containing **3b** and 10% aqueous acetic acid for 5.0 hr. Extractive isolation and purification by preparative thin-layer chromatography (TLC) afforded (*S*) (+)-**2b**, $[\alpha]_D^{20}$ +472.4° (benzene), 63% optically pure,[23] in 14% yield based on *dl*-**1b** (in 26% yield from *dl*-**1b** when corrected for the recovered *dl*-**1b**). Infrared and nuclear magnetic resonance spectra (IR and NMR) of (*S*) (+)-**2b** were identical with those of *dl*-**2b** prepared independently from *dl*-**1b**.

Since the optical purity of (*S*) (+)-**2b** was amazingly high when compared with that of (*R*) (+)-**1a**, the same hydrolysis as that mentioned above, was repeated two more times to check the reproducibility of the reaction. The following optical rotations, optical purities, and chemical yields based on *dl*-**1b** were observed: $[\alpha]_D^{20}$ +362.7° (benzene), 49% optically pure,[23] 8%; $[\alpha]_D^{20}$ +406.0° (benzene), 54% optically pure,[23] 10%. The reason why the optical purity of (*S*) (+)-**2b** was about three times higher than that of (*R*) (+)-**1a** is obscure,[24] but these results definitely discloses that the resolution method developed here, usually gives (*S*) (+)-**2b** which is 50 to 60% optically pure.

21) Similar intramolecular mechanism was presented for the ester cleavage of methyl *o*-formylbenzoate with secondary amine. See, M.L. Bender and M.S. Silver, *J. Am. Chem. Soc.*, **84**, 4589 (1962), and M.L. Bender, J.A. Reinstein, M.S. Silver, and R. Mikulak, *ibid.*, **87**, 4545 (1965).

22) Refluxing a benzene solution of cyclohexyl benzoate and (*S*) (+)-**4** for 25 hr under the same condition as that used for the preparation of **3b** recovered cyclohexyl benzoate in a quantitative yield. This observation further supports the mechanism shown in Chart 4.

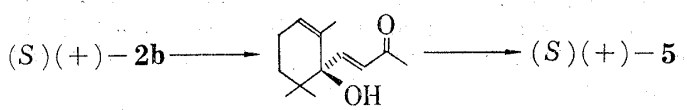
23) The optical purity and absolute configuration of (*S*) (+)-**2b** were clearly established by converting (*S*) (+)-**2b** into (*S*) (+)-6-hydroxy-α-ionone ((*S*) (+)-**9** (see Section B).

24) Although there is no experimental evidence, the preferential decomposition of one or two diastereoisomers of **3b** leading to (*R*) (−)-**2b**, in addition to the selective hydrolysis of **3b** similar to the case for **3a**, might significantly increase the optical purity of (*S*) (+)-**2b**.

B. Preparation of Optically Active (*S*) (+)-Dehydrovomifoliol ((*S*) (+)-5)

In order to establish the optical purity and absolute configuration of (+)-**2b**, and moreover, to exploit the synthetic route to optically active **5**,[11] the chemical scheme shown in Chart 5 was studied.

Base-catalyzed condensation of (+)-**2b**, $[\alpha]_D^{20}$ +298.5° (benzene),[25] with acetone gave a 23% yield of (+)-6-hydroxy-α-ionone ((+)-**9**), $[\alpha]_D^{20}$ +103.7° (ethanol). The structure of (+)-**9** was confirmed by comparing its spectral (IR and NMR) and chromatographic (TLC) behavior with those of the authentic racemic compound independently prepared from racemic α-ionone.[26] Since (−)-**9** showing $[\alpha]_D^{20}$ −260° (ethanol), was reported to be optically pure and to have (*R*)-configuration,[26,27] (+)-**9** obtained here was determined to have (*S*)-configuration and to be 40% optically pure. This conversion further elucidated that the absolute configuration and optical purity of (+)-**2b**, $[\alpha]_D^{20}$ +298.5° (benzene) were (*S*)-configuration and 40% optically pure, and that the pure optical rotation of (*S*) (+)-**2b** could be calculated as $[\alpha]_D^{20}$ +746.3 (benzene). Oxidation of (*S*) (+)-**9**, $[\alpha]_D^{20}$ +103.7° (ethanol), with *t*-butyl chromate[26b,c] yielded (*S*) (+)-**5**, $[\alpha]_D^{20}$ +99.8° (chloroform), in 5% yield with a large amount of recovered starting material. Spectral (IR and NMR) and chromatographic (TLC) behavior of (*S*) (+)-**5** were identifical with those of the authentic racemic compound.[28]



(*S*)(+)−**9**

Chart 5

As the conversion of (*S*) (+)-**5** to (*S*) (+)-**6** has been well documented,[11,12] completion of the synthetic route to (*S*) (+)-**5** means that (*S*) (+)-**6** has been formally synthesized from *dl*-**1b**.

Experimental[29,30]

(*S*) (+)-Prolinol ((*S*) (+)-4)——Prepared from optically pure L-proline according to the reported procedure.[10] This sample showed bp 87—89.5° (12 mmHg), and $[\alpha]_D^{20}$ +2.8° (c=2.046, EtOH), α_D^{20} +0.446° (l=0.1, neat) (lit.,[10] bp 100—105° (9 mmHg)).

***dl*-α-Cyclocitral (*dl*-1a)**——This compound was prepared from commercially available citral (a mixture of *cis*- and *trans*-isomer whose ratio was *ca.* 5: 6) by the reported procedure.[7] The oily sample obtained, showed a single spot on TLC analysis. *Rf* value was *ca.* 0.5 (silica gel, solvent benzene: hexane 1: 1)

Preparation of (*R*) (+)-α-Cyclocitral ((*R*) (+)-1a) from *dl*-α-Cyclocitral (*dl*-1a) *via* the Oxazolidine Derivative (3a)——Procedure which could afford (*R*) (+)-**1a** showing the highest optical activity, was given as an example.

25) This sample was prepared by combining several lots of (+)-**2b** accumulated during the study on the hydrolysis condition for **3b**.

26) *a*) T. Oritani and K. Yamashita, *Tetrahedron Letters*, **1972**, 2521; *b*) T. Oritani, K. Yamashita, and H. Meguro, *Agr. Biol. Chem.*, **36**, 885 (1972); *c*) T. Oritani and K. Yamashita, *ibid.*, **37**, 1115 (1973).

27) In ref. 26, (*R*) (−)-**9** was erroneously expressed as (*S*) (−)-**9** because of the misunderstanding of the 1966 Cahn-Ingold-Prelog convention (see G. Ryback, *Chem. Comm.*, **1972**, 1190).

28) D.L. Roberts, R.A. Heckman, B.P. Hege, and S.A. Bellin, *J. Org. Chem.*, **33**, 3566 (1968).

29) All melting and boiling points are uncorrected. IR spectra measurements were performed with spectrometers, JASCO Infrared Spectrometer Model DS-402G and JASCO IRA-1 Grating Infrared Spectrometer. NMR spectra were recorded with spectrometers, JNM-PS100 and Hitachi R-24 High Resolution NMR Spectrometers. All signals are expressed by the ppm downfield from tetramethylsilane used as an internal standard. Following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). Optical rotations were determined with a Yanaco OR-50 Automatic Polarimeter. Mass spectra measurements were carried out using a JEOL JMS-OlSG-2 Mass Spectrometer.

30) Extraction solvent used for the isolation of volatile compound was not completely evaporated in order to prevent a loss of the reaction product, so weight measurement at the stage of crude evaporation residue was not performed throughout this work.

Preparation of **3a** from *dl*-**1a**: A solution of *dl*-**1a** (0.30 g, 2.0 mmole) and (*S*) (+)-**4** (0.20 g, 2.0 mmole) in anhyd. benzene (10 ml) was heated at reflux for 25 hr in the presence of anhyd. *p*-toluenesulfonic acid (10 mg) and Molecular Sieves 4A (*ca.* 0.6 g) under nitrogen atmosphere. After filtration, the benzene layer was concentrated *in vacuo*, giving crude **3a** as a pale yellow oil (0.44 g, 97% yield). IR ν_{max}^{film} cm^{-1}: 1200, 1140, 1050 (O–C–N system of oxazolidine ring).[13] NMR (in CCl_4): 4.50—4.30 (1H, m, O–C<u>H</u>–N), 5.37 (1H, braod s, =C<u>H</u>–). Mass Spectrum *m/e*: 234 ($[M-1]^+$).

Hydrolysis of **3a**: 10% Aqueous acetic acid (6 ml) was gradually added to a stirred benzene solution (6 ml) of crude **3a** (0.44 g) in an ice-bath. The whole mixture was stirred at room temperature for 0.5 hr, then the upper benzene layer was separated. The residual aqueous layer was twice extracted with benzene. The combined benzene layers were washed with satd. $NaHCO_3$ and satd. NaCl solutions, then dried over anhyd. Na_2SO_4. Filtration followed by evaporation *in vacuo*, afforded a yellow oil, which was purified by column chromatography (silica gel, solvent benzene: hexane 1: 1), to give (*R*) (+)-**1a** as a pale yellow oil (79 mg, 26% yield based on *dl*-**1a**), $[\alpha]_D^{20}$ +112.0° (*c*=0.866, EtOH). The optical purity of this sample could be calculated as 19% by the assumption that (*R*) (+)-**1a** showing $[\alpha]_D^{20}$ +594.5° (EtOH) was optically pure.[7] Spectral (IR and NMR) and chromatographic (TLC) behavior were completely identical with those of the authentic sample.[7]

***dl*-6-Benzoxy-α-cyclocitral (*dl*-1b) and *dl*-4-Benzoxy-β-cyclocitral (*dl*-8)**[17]——A mixture of *dl*-**1a** (0.30 g, 2.0 mmole) and pyrrolidine (0.57 g, 8.0 mmole) in anhyd. benzene (10 ml) was heated at reflux for 25 hr in the presence of Molecular Sieves 4A (*ca.* 2.0 g) under nitrogen atmosphere. Filtration and evaporation *in vacuo* gave the crude enamine (**7**) as a pale brown oil (0.42 g). IR ν_{max}^{film} cm^{-1}: 1680, 1640, 1610 (olefinic double bonds). NMR (in CCl_4): 5.22 (1H, broad s, olefinic proton), 5.65 (1H, broad s, =C<u>H</u>–N). Crude **7** was immediately used for the next benzoxylation.

A benzene solution (2 ml) of crude **7** (0.42 g) was added to a stirred solution of benzoyl peroxide (1.94 g, 8.0 mmole) in anhyd. benzene (8 ml) in an ice bath and under nitrogen atmosphere. The whole mixture was stirred at room temperature for 96 hr under nitrogen atmosphere and interception of light.[17] The reaction was quenched by the addition of 10% aqueous acetic acid (10 ml) and potassium iodide (2.66 g, 16 mmole) to the mixture in an ice-bath, then the whole was refluxed with stirring for 1.0 hr. After the upper benzene layer was separated, the lower aqueous phase was further extracted with benzene (×2). The combined organic extracts were successively washed with satd. $Na_2S_2O_3$, satd. $NaHCO_3$, and satd. NaCl solutions, and finally dried over anhyd. Na_2SO_4. Filtration and evaporation *in vacuo* gave a brown viscous oil (1.44 g), which was chromatographed on silica gel column (solvent benzene: hexane 1: 1) to afford *dl*-**1b** as a pale yellow solid (89 mg, 17% yield based on *dl*-**1a**). Repeated recrystallizations from hexane gave pure sample as colorless prisms, mp 96—98°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1733 (sh), 1725 (sh), 1712 (ester and aldehyde), 1285, 1150 (ester). NMR (in CCl_4): 1.05, 1.19 (6H, two s, –C<u>Me</u>$_2$), 1.74 (3H, s, =C–<u>Me</u>), 1.50—2.40 (4H, m, –(C<u>H</u>$_2$)$_2$–), 5.66 (1H, broad s, =C<u>H</u>–), 7.20—8.30 (5H, m, aromatic protons), 9.67 (1H, s, C<u>H</u>O). TLC analysis of this sample showed a single spot whose *Rf* value was *ca.* 0.4 (silica gel, solvent benzene: hexane 1: 1). *Anal.* Calcd. for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.80; H, 7.39.

Further elution of the silica gel column with the same solvent system as that used for *dl*-**1b**, followed by evaporation of the eluates, gave *dl*-**8** as a yellow viscous oil (0.12 g, 22% yield based on *dl*-**1a**). IR ν_{max}^{film} cm^{-1}: 1730 (ester), 1685 (α,β-unsaturated aldehyde), 1265, 1110 (ester). NMR (in CCl_4): 1.15, 1.23 (6H, two s, –C<u>Me</u>$_2$), 2.05 (3H, s, =C–<u>Me</u>), 1.32—2.02 (4H, m, –(C<u>H</u>$_2$)$_2$–), 5.42 (1H, t, *J*=6 Hz, C<u>H</u>–O), 7.12—8.12 (5H, m, aromatic protons), 10.02 (1H, s, C<u>H</u>O). Mass Spectrum *m/e*: 273 ($[M+1]^+$). TLC analysis showed that this sample was completely homogeneous (*Rf ca.* 0.35, silica gel, solvent benzene: hexane 1: 1).

***dl*-6-Hydroxy-α-cyclocitral (*dl*-2b)**——A mixture of *dl*-**1b** (0.19 g, 0.70 mmole) and sodium ethoxide (0.12 g, 1.8 mmole) in absolute ethanol (8.8 ml) was stirred in an ice-bath for 1.5 hr. After ethanol was removed *in vacuo* below 0°, the yellow residue obtained was dissolved in H_2O (20 ml). The aqueous solution was extracted with benzene (×3), and the combined benzene layers were successively washed with 10% aqueous acetic and satd. NaCl solutions, then dried over anhyd. Na_2SO_4. Filtration and evaporation *in vacuo* afforded a yellow oil, which was purified by column chromatography (silica gel, solvent benzene: hexane 1: 1) to give pure *dl*-**2b** as a colorless oil (80 mg, 68% yield). IR ν_{max}^{film} cm^{-1}: 3520, 1140 (alcohol), 1720 (aldehyde). NMR (in CCl_4): 0.87, 0.96 (6H, two s, –C<u>Me</u>$_2$), 1.44 (3H, broad s, =C–<u>Me</u>), 1.34—2.34 (4H, m, –(C<u>H</u>$_2$)$_2$–), 3.38 (1H, broad s, O<u>H</u>), 5.71 (1H, broad s, =C–<u>H</u>), 9.51 (1H, s, C<u>H</u>O).

Preparation of (*S*) (+)-6-Hydroxy-α-cyclocitral ((*S*) (+)-2b) from *dl*-6-Benzoxy-α-cyclocitral (*dl*-1b) *via* the Oxazolidine Derivative (3b)——Procedure which could afford (*S*) (+)-**2b** having the highest optical activity, was given as an example.

Preparation of **3b** from *dl*-**1b**: A benzene solution (13 ml) of *dl*-**1b** (0.24 g, 0.90 mmole) and (*S*) (+)-**4** (0.27 g, 2.7 mmole) was heated at reflux for 75 hr in the presence of anhyd. *p*-toluenesulfonic acid (30 mg) and Molecular Sieves 4A (*ca.* 0.9 g) under nitrogen atmosphere. After cooling, the Molecular Sieves 4A was filtered off, and washed with anhyd. benzene (13 ml). The combined filtrates were successively washed with 10% HCl (13 ml×1, then 4 ml×2), satd. $NaHCO_3$ (15 ml×2), and satd. NaCl (15 ml×2), and finally dried over anhyd. $MgSO_4$. Filtration and evaporation *in vacuo* recovered crude *dl*-**1b** as colorless plates (0.13 g,

54% recovery), $[\alpha]_D^{20}$ *ca.* 0° (c=1.074, benzene).[31] Spectral (IR and NMR) and chromatographic (TLC) behavior were completely identical with those of the authentic racemic compound.

The combined sodium bicarbonate washings were acidified with 10% HCl, and extracted with ether (50 ml×3). The combined ether extracts were washed with satd. NaCl (30 ml×2), and dried over anhyd. $MgSO_4$. Filtration and evaporation *in vacuo* gave benzoic acid (25 mg, 23% yield) as a colorless solid. This solid was recrystallized from H_2O to give pure sample, mp 123—123.5°, which was identified with the authentic sample by comparing their spectral (IR and NMR) data and measuring the mixed melting point, mp 123.5—124°.

The remaining 10% HCl washings were combined and made basic (pH>10) with 10% NaOH under ice-cooling. The basic aqueous solution was extracted with benzene (17 ml×3). The combined benzene extracts were dried over anhyd. K_2CO_3. Filtration and evaporation *in vacuo* afforded crude **3b** as a yellow oil (0.13 g). IR ν_{max}^{film} cm^{-1}: 3440 (alcohol), 1200, 1140, 1080, 1050 (alcohol and O–C–N system of oxazolidine ring[13]). NMR (in CCl_4): 4.45 (1H, s, O–C<u>H</u>–N), 5.30 (1H, broad s, =C<u>H</u>–). This NMR spectrum clearly showed an almost complete absence of the signals due to aromatic and aldehyde protons.

Hydrolysis of **3b**: 10% aqueous acetic acid (5 ml) was added to a solution of crude **3b** (0.13 g) in benzene (5 ml) with stirring in an ice-bath. After the mixture was heated at reflux for 5.0 hr with stirring, the upper benzene layer was successively washed with satd. $NaHCO_3$ and satd. NaCl solutions, then dried over anhyd. $MgSO_4$. Filtration and evaporation *in vacuo* gave a yellow oil, which was purified by preparative TLC (silica gel, solvent hexane: ether 4: 1) to give pure (*S*) (+)-**2b** as soft crystals (18 mg, 14% yield based on *dl*-**1b** or 26% yield from *dl*-**1b** when corrected for the recovered *dl*-**1b**), mp 40—52°, $[\alpha]_D^{20}$ +472.4° (c=0.362, benzene). The optical purity of this sample could be calculated as 63% since (*S*) (+)-**2b** showing $[\alpha]_D^{20}$ +298.5° (c=1.150, benzene) gave (*S*) (+)-**9**, $[\alpha]_D^{20}$ +103.7° (c=0.108, EtOH), and the pure optical rotation of (*R*) (−)-**9** was reported to be $[\alpha]_D^{12}$ −260° (c=0.6, EtOH) (*vide infra*). IR and NMR spectra of this sample were completely identical with those of the authentic racemic compound recorded in the same states. TLC analysis of this solid showed a single spot whose *Rf* value was the same as that of the pure racemic compound.

***dl*-6-Hydroxy-α-ionone (*dl*-9)**——The compound was prepared from commercially available *dl*-α-ionone by using selenium dioxide as an oxidizing agents.[26] Recrystallization from hexane gave colorless needles, mp 85—87.5°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1692 (sh), 1672 (α,β-unsaturated ketone), 1622 (double bond), 1110 (alcohol). NMR (in CCl_4): 0.90, 0.93 (6H, two s, –C<u>Me</u>$_2$), 1.56 (3H, broad s, =C–<u>Me</u>), 2.19 (3H, s, CO<u>Me</u>), 1.30—2.30 (5H, m, –(C<u>H</u>$_2$)$_2$– and O<u>H</u>), 5.43 (1H, broad s, =C–<u>H</u>), 6.24 (1H, d, J=16 Hz, –CH=C<u>H</u>–CO), 6.64 (1H, d, J=16 Hz, –C<u>H</u>=CH–CO). *Anal.* Calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.49; H, 10.03.

(*S*) (+)-6-Hydroxy-α-ionone ((*S*) (+)-9)——Sodium ethoxide (0.23 g, 3.4 mmole) in absolute ethanol (1.9 ml) was added to an acetone solution (1.9 ml) of (*S*) (+)-**2b** ($[\alpha]_D^{20}$ +298.5° (c=1.150, benzene)) (58 mg, 0.34 mmole) under ice-cooling. The whole mixture was stirred for 3.5 hr in an ice-bath, then neutralized with 10% HCl. After addition of H_2O (7 ml), ethanol and acetone were evaporated *in vacuo* to give an aqueous solution, which was extracted with ether (×3). The combined ether extracts were washed with satd. NaCl (×2), and dried over anhyd. $MgSO_4$. Filtration and evaporation *in vacuo* gave an yellow oil (0.16 g), which was purified by preparative TLC (silica gel, solvent hexane: ether 7: 3) to afford pure (*S*) (+)-**9** as a colorless semisolid (16 mg, 23% yield), mp 78—86°, $[\alpha]_D^{20}$ +103.7° (c=0.108, EtOH). Since optically pure (*R*) (−)-**9** was reported to show mp 90—91° and $[\alpha]_D^{12}$ −260° (c=0.6, EtOH),[25] the optical purity of this semisolid could be calculated as 40%. IR and NMR spectra of this sample were superimposable on those of the authentic racemic compound measured in the same states. TLC analysis of this product showed a single spot whose *Rf* value was the same as that of the authentic racemic compound (*Rf ca.* 0.3, silica gel, solvent hexane: ether 7: 3).

***dl*-Dehydrovomifoliol (*dl*-5)**——Preparation of the authentic *dl*-**5** was carried out by the reported procedure.[28] This sample showed mp 113.5—114° after recrystallizations from toluene (lit,[28] mp 112—113°). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1665 (α,β-unsaturated ketones), 1625 (olefinic double bonds). NMR (in $CDCl_3$): 1.00, 1.07 (6H, two s, C–<u>Me</u>$_2$), 1.88 (3H, d, J=1.5 Hz, =C–<u>Me</u>), 2.28 (3H, s, CO<u>Me</u>), 2.15—2.60 (3H, m, –C<u>H</u>$_2$– and O<u>H</u>), 5.92 (1H, broad s, =C–<u>H</u>), 6.42 (1H, d, J=16 Hz, –CH=C<u>H</u>–CO), 6.82 (1H, d, J=16 Hz, –C<u>H</u>=CH–CO). These spectral properties are the same as those reported.[28] TLC analysis of this sample showed a single spot (*Rf ca.* 0.1, silica gel, solvent ether: hexane 6: 4).

(*S*) (+)-Dehydrovomifoliol ((*S*) (+)-5)——*t*-Butyl chromate solution was prepared by the successive addition of chromium trioxide (0.60 g, 6.0 mmole) and acetic anhydride (0.56 ml, 6.0 mmole) to *t*-butyl alcohol.[26c]

A solution of (*S*) (+)-**9** ($[\alpha]_D^{20}$ +103.7° (c=0.503, EtOH)) (0.21 g, 1.0 mmole) in *t*-butyl alcohol (0.8 ml) was gradually added to the stirred *t*-butyl chromate solution prepared above, at room temperature. The

31) This sample was converted to (*S*) (+)-**2b**, $[\alpha]_D^{20}$ +6.3° (c=1.052, benzene), according to the same method as that employed for the preparation of *dl*-**2b** from *dl*-**1b**. Since (*S*) (+)-**2b**, being 63% optically active, was found to exhibit $[\alpha]_D^{20}$ +472.4° (c=0.362, benzene) (*vide infra*), the optical purity of the benzoate showing $[\alpha]_D^{20}$ *ca.* 0° (c=1.074, benzene) could be calculated as about 0%.

reaction mixture was stirred for 30 hr at room temperature. After evaporation of *t*-butyl alcohol *in vacuo*, H_2O (4 ml) was added to the residue. Then, 10% aqueous oxalic acid (15 ml) was added to the aqueous solution to decompose excess *t*-butyl chromate, and the whole solution was extracted with $CHCl_3$ ($\times 3$). The combined chloroform extracts were successively washed with satd. $NaHCO_3$ ($\times 1$), and satd. NaCl solutions ($\times 2$), and dried over anhyd. $MgSO_4$. Filtration and evaporation *in vacuo* afforded a pale brown viscous oil (0.14 g), which was purified by preparative TLC (silica gel, solvent ether: hexane 6: 4) to give pure (*S*) (+)-**5** (10 mg, 5%) as a colorless viscous oil, $[\alpha]_D^{20}$ +99.8° ($c=0.200$, $CHCl_3$)[32] Spectral (IR and NMR) properties of this oil were identical with those of *dl*-**5** recorded in the same states. This sample showed the identical *Rf* value with that of the authentic racemic compound on TLC analysis.

Separation with preparative TLC attempted here, recovered crude starting material (90 mg, 43% recovery) as a pale yellow viscous oil.

Acknowledgement The authors are grateful to the members of the Central Analysis Room of this Faculty for elemental analyses and spectral data. A part of this work was supported by a Grant-in-Aid for Fundamental Scientific Research from the Ministry of Education Science and Culture, to which the authors' thanks are due.

32) Following optical rotations have been reported for (*S*) (+)-**5** of natural origin,[11a] $[\alpha]_D$ +159° ($CHCl_3$), and $[\alpha]_D$ +172° ($CHCl_3$), and that of chemical synthesis,[11b] $[\alpha]_D^{21}$ +266.3° ($c=0.3$, $CHCl_3$). The optical purity of this product could be calculated as 38% by the assumption that (*S*) (+)-**5**, $[\alpha]_D^{21}$ +266.3° ($c=0.3$, $CHCl_3$), was optically pure.