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Stereochemical Studies. XXXV.[1] A Biogenetic-type Asymmetric Cyclization. Syntheses of optically Active α-Cyclocitral and *trans*-α-Damascone[2,3]

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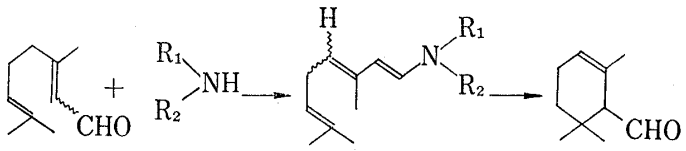
Application of the biogenetic-type cyclization of citral (**2**) *via* its enamine, which was developed by us as described in the preceding paper, to the asymmetric synthesis, has been found to give (*R*) (+)-α-cyclocitral ((*R*) (+)-**4**) in at most 33% optical yield.

(*R*) (+)-**4** thus prepared was successfully converted to (*R*) (+)-*trans*-α-damascone ((*R*) (+)-**6**), a famous perfume which has fragrant odor, without racemization.

Introduction

It is well known that many kinds of naturally occurring optically active terpenes having many asymmetric centers are biosynthesized from the corresponding acyclic terpenes carrying no asymmetric carbon by the enzyme-catalyzed cyclization reaction.[5] For example, the enzyme-catalyzed reaction which affords (*R*) (+)-carotene *in vivo* from mevalonic acid through neurosporene, has been elucidated to proceed with 100% asymmetric induction at the cyclization step.[6]

As mentioned in the preceding paper,[1] we developed a new biogenetic-type cyclization of the dienamine (**1**)[7] derived from citral (**2**)[8] and several kinds of secondary amines (**3**), to *dl*-α-cyclocitral (*dl*-**4**), with the intention of achieving transformations similar to those observed *in vivo*, by organic synthesis *in vitro*.



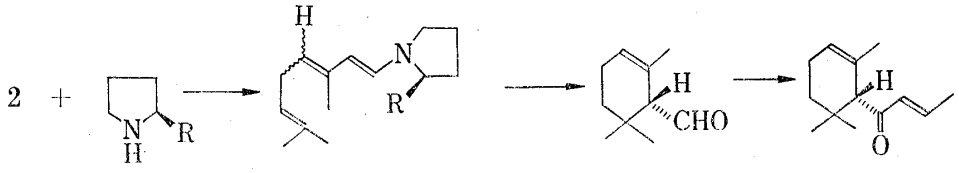
2 3 1 *dl*-4

Chart 1

This report concerns with the results of application of the cationic cyclization reaction exploited previously,[1] to the asymmetric synthesis of optically active **4**, using optically active pyrrolidines (**5a**—**e**) easily obtainable from L-proline (**5f**)[9] as shown in Chart 2, and with the

1) Part XXXIV: M. Shibasaki, S. Terashima, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **23**, 272 (1975).
2) Presented at the 92nd Annual Meeting of the Pharmaceutical Society of Japan, Osaka, April, 1972, and at the 17th Sympodium on the Chemistry of Natural Products, Tokyo, October, 1973.
3) Part of this report has been a subject of the preliminary communication: S. Yamada, M. Shibasaki, and S. Terashima, *Tetrahedron Letters*, **1973**, 381.
4) Location: *Hongo, Bunkyo-ku, Tokyo, 113, Japan.*
5) *a*) G. Rücker, *Angew. Chem. Internat. Edit.*, **12**, 793 (1973); *b*) D.V. Banthorpe and B.V. Charlwood, "Biogenesis of Terpenes," in "Chemistry of Terpenes and Terpenoids," ed., by A.A. Newman, Academic Press, London and New York, 1972, pp. 337—441; *c*) G. Britton, "General Aspects of Carotenoid Biosynthesis," in "Aspects of Terpenoid Chemistry and Biochemistry," ed., by T.W. Goodwin, Academic Press, New York and London, 1971, pp. 255—289.
6) See ref. 5*c*, pp. 267—271.
7) For studies on the structure of **1**, see ref. 1.
8) Throughout this work, a mixture of *cis*- and *trans*-isomer (ratio determined by gas–liquid chromatography (GLC) was 5 : 6) was employed (see ref. 1).
9) L-Proline itself was used as an asymmetric source (*vide infra*).

subsequent successful conversion of optically active (*R*) (+)-**4** (*vide infra*)[10] thus obtained, to optically active (*R*) (+)-*trans*-α-damascone ((*R*) (+)-**6**).[10,11] *trans*-α-Damascone, a famous perfume which is known to be a component of tea,[12] has been synthesized by many research groups in racemic modification[13] and/or optically active form[14] because of its fragrant odor.



5 7 (*R*)(+)−4 (*R*)(+)−6

a : R=Me
b : R=iso-Pr
c : R=CON
d : R=CONEt$_2$
e : R=CO$_2$Et
f : R=COOH

Chart 2

Result and Discussion

A. Asymmetric Cyclization Reaction Using Optically Active Pyrrolidine Derivatives (5a—f)

Reaction condition for the preparation of optically active dienamines (citral-optically active pyrrolidine enamines) (**7a—f**) was identical with that reported previously,[1] except for the molar ratio of **5a—f** and **2** which was shown in Table I. Among all the asymmetric sources employed here, (*R*) (−)-2-methylpyrrolidine ((*R*) (−)-**5a**) was prepared according to the method reported by Paquette, *et al.*,[15] and (*S*) (−)-2-isopropylpyrrolidine ((*S*) (−)-**5b**),[16] (*S*) (−)-proline pyrrolidide ((*S*) (−)-**5c**),[17] and (*S*) (−)-proline diethylamide ((*S*) (−)-**5d**)[17] were synthesized by the methods developed by us. Preparation of (*S*) (−)-ethyl prolinate ((*S*) (−)-**5e**) was carried out using the conventional method with thionyl chloride as an esterification reagent.[18–20]

The dienamines (**7a—f**) which showed a complete absence of the absorption due to α,β-unsaturated aldehyde group of **2** in their infrared (IR) spectra, were directly submitted to the cyclization reaction, since it had been already found by us[17] that distillation of enamines

10) In the communication (see ref. 3), this compound was erroneously expressed to have (*S*)-configuration, because of the complicated sequence rule for a class of this compound (see for example, G. Ryback, *Chem. Comm.*, **1972**, 1190, and T. Oritani, K. Yamashita, and H. Meguro, *Agr. Biol. Chem.*, **36**, 885 (1972)).
11) As described in ref. 1, (*R*) (+)-**6** has the same absolute configuration as those of (*R*) (+)-carotene and (*R*) (+)-α-ionone.
12) G. Ohloff, V. Rautenstrauch, and K.H. Schulte-Elte, *Helv. Chim. Acta*, **56**, 1503 (1973).
13) *a*) E. Demole, P. Enggist, U. Säuberli, M. Stoll, and E. sz. Kováts, *Helv. Chim. Acta*, **53**, 541 (1970); *b*) K.H. Schulte-Elte, B.L. Muller, and G. Ohloff, *ibid.*, **56**, 310 (1973); *c*) R.C. Cookson and R.M. Tuddenham, *Chem. Comm.*, **1973**, 742.
14) G. Ohloff and G. Uhde, *Helv. Chim. Acta*, **53**, 531 (1970).
15) L.A. Paquette, J.P. Freeman, and S. Maiorara, *Tetrahedron*, **27**, 2599 (1971).
16) T. Sone, K. Hiroi, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **21**, 2331 (1973).
17) G. Otani and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **21**, 2112 (1973).
18) J. Kapfhammer and A. Matthes, *Hopper-Seylers Zeit. Physiol. Chem.*, **223**, 47 (1934).
19) H. Seki, K. Koga, H. Matsuo, S. Ohki, I. Matsuo, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **13**, 995 (1965).
20) K. Hiroi, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **20**, 246 (1972).

prepared with the optically active pyrrolidines such as (*S*) (−)-**5c** and (*S*) (−)-**5d**, brought about racemization concerning asymmetric center in pyrrolidine part.

All cyclization reactions were carried out using the best condition (0°, in a mixture of 95% sulfuric acid and water (ratio by volume 10: 1), 3.0 hr), which had afforded *dl*-**4** from **2** in 41% yield.[1] Hydrolytic treatment, followed by the purification with column chromatography, gave pure (*R*) (+)-**4**,[21,22] on which optical purity was determined. Results of the asymmetric cyclization were summarized in Table I.

TABLE I. Asymmetric Synthesis of (*R*) (+)-α-Cyclocitral ((*R*)(+)-4) from Citral (**2**) *via* the Dienamines (**7a—f**)

Run	Optically active pyrrolidines		(*R*)(+)-α-Cyclocitral ((*R*)(+)-4)		
	Nature	Molar ratio of **5** to **2**	Yield (%)[a]	$[\alpha]_D^{20}$ (*c*, EtOH)[b]	Optical yield[c] (%)
1	**5a**	1.2[d]	26	+72.3° (0.678)	12.2
2	**5b**	1.2[d]	26	+159° (0.710)	26.7
3	**5c**	1.0	8	+131° (0.810)	22.0
4	**5d**	1.0	4	+198° (0.284)	33.0
5	**5e**	1.0	9	+1.8° (1.108)	0.3
6	**5f**	1.0[e]	7	+1.9° (0.728)	0.3

a) Based on **2** employed. This was determined on the sample obtained by the purification with column chromatography.
b) measured on the sample purified by column chromatography
c) (*R*) (+)-**4** showing $[\alpha]_D^{20}$ +594.5° (ethanol), was assumed to be 100% optically pure. For a detailed description, see the section B.
d) This molar ratio was selected because of the volatility of pyrrolidine used.
e) Dienamine (**7f**) was prepared by refluxing the reaction mixture for 2.0 hr.

As it is clear from the Table, the highest asymmetric induction (33%)[22] was observed when (*S*) (−)-**5d** was used as an optically active pyrrolidine counterpart, and all L-proline-derived pyrrolidines (**5a—e**) and L-proline (**5f**) itself gave (*R*) (+)-**4** whose absolute configuration was the same as those of (*R*) (+)-**6** and (*R*) (+)-carotene.

The reason why (*R*) (+)-**4** was isolated in very low yields in runs 3, 4, 5, and 6 in Table I, is probably due to competition of the decomposition of **7c, d, e,** and **f** in concd. sulfuric acid with the cyclization reaction. This interpretation would be verified by the fact that when **7a,** and **b** having an acid-stable alkyl group at the α position of pyrrolidine ring, were used for the cyclization, a fair improvement of the yield of (*R*) (+)-**4** was achieved.

B. Determination of Pure Optical Rotation of (*R*) (+)-α-Cyclocitral ((*R*) (+)-4)

In order to precisely calculate the degree of asymmetric induction for asymmetric synthesis, it is necessary that pure optical rotations of original asymmetric source and final reaction product are clearly established. Since the absolute configuration of (+)-**4** had been determined by the chemical correlation with (+)-manool and (+)-ambrein,[23] confirmation of the

21) GLC analysis of the crude reaction mixture showed a presence of a small amount of β-cyclocitral (see ref. 1). However, isolation of β-cyclocitral by column chromatography, was not attempted throughout this work.
22) Absolute configuration and pure optical rotation of (+)-**4** will be discussed in the section B.
23) *a*) C.H. Eugster, R. Buchecker, C. Tscharner, G. Uhde, and G. Ohloff, *Helv. Chim. Acta*, **52**, 1729 (1969); *b*) R. Bucheker, R. Egli, H. Regelwild, C. Tscharner, C.H. Eugster, and G. Ohloff, *ibid.*, **56**, 2548 (1973).

pure optical rotation was examined by our hands, because it seemed to be easily accomplished according to the chemical scheme shown in Chart 3.

(*S*) (−)-α-Cyclogeranic acid ((*S*) (−)-**8**),[24] $[\alpha]_{546}^{20}$ −334.3° (ethanol), 84.4% optically pure, prepared by the resolution of *dl*-**8**[25] according to the procedure reported by Bennet, *et al.*,[26] was reduced with lithium aluminium hydride, giving (*S*) (−)-α-cyclogeraniol ((*S*) (−)-**9**) which showed $[\alpha]_D^{20}$ −103.1° (ethanol). On the other hand, reduction of (+)-**4**, $[\alpha]_D^{20}$ +131.1°, obtained by the asymmetric synthesis, with sodium borohydride, gave (*R*) (+)-**9**, $[\alpha]_D^{20}$ +26.9° (ethanol).

The above transformation clearly established that the pure optical rotation of (*R*) (+)-**4** could be estimated to be $[\alpha]_D^{20}$ +594.5° (ethanol).[27]

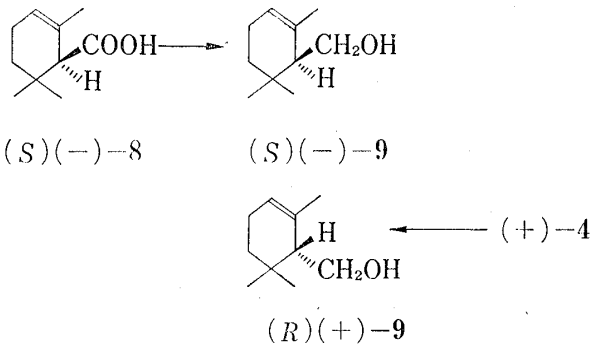


Chart 3

C. Mechanistic Consideration on the Asymmetric Cyclization

Mechanistic studies were carried out in the preceding paper.[1] Since it is conceivable that the same reaction mechanism as that presented before[1] should be valid for the asymmetric cyclization with **5a**—**f**, kinetic discrimination during the attack of double bond in the immonium salt derived from **7** in the acidic cyclization condition, to the terminal tertiary carbonium ion, would give the optically active cyclized immonium salt. That (*R*) (+)-**4** was found to be stable and nonracemizable under the condition similar to that for hydrolysis of the cyclized product, might mean that degree of the asymmetric induction observed here, directly reflected the above-mentioned kinetic differentiation.

D. Synthesis of (R) (+)-trans-α-Damascone ((R) (+)-6)

As stated in the introduction of the preceding paper,[1] we studied the asymmetric synthesis of **4** since it was expected that (*R*) (+)-**4** would be one of the best key intermediates for total synthesis of several kinds of optically active terpenes.

We visualized the above-cited expectation by converting (*R*) (+)-**4** prepared by the asymmetric synthesis to (*R*) (+)-**6**[28] without racemization.

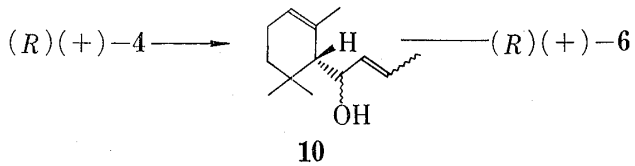


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Chart 4

As shown in Chart 4, addition of 1-lithio-1-propene (a mixture of *cis*- and *trans*-isomer) to (*R*) (+)-**4**, $[\alpha]_D^{20}$ +172° (ethanol), 28.9% optically pure, in ether, gave a mixture of the diastereomeric alcohol (**10**). Oxidation of **10** with chromium trioxide in pyridine and the subsequent isomerization of the olefinic double bond in the reaction medium, afforded (*R*) (+)-**6**, $[\alpha]_D^{20}$ +89.2° (chloroform), 27.5% optically pure,[29] in 66% yield based on (*R*) (+)-**4**. (*R*) (+)-**6** thus prepared, was confirmed by comparing its spectral properties with those reported.[13a,14]

24) (−)-**8** had been determined to have (*S*)-configuration (see ref. 23).
25) *a*) G. Stork and A.W. Burgstahler, *J. Am. Chem. Soc.*, **77**, 5068 (1955); *b*) K. Bernhauer and R. Forster, *J. Prakt. Chem.*, **147**, 199 (1936).
26) D.J. Bennet, G.R. Ramage, and J.L. Simonser, *J. Chem. Soc.*, **1940**, 418.
27) Although (*R*) (+)- and (*S*) (−)-**4** were reported to have $[\alpha]_D^{22}$ +618° (ethanol), and $[\alpha]_D^{20}$ −637° (ethanol), in ref. 23, these values were not adopted by us because their optical purities were not clearly established.
28) In ref. 23, optically active **4** has been converted to optically active ionones without racemization.
29) This optical purity was calculated by the assumption that (+)-**6** $[\alpha]_D$ +324° (chloroform), prepared from optically pure (+)-α-ionone, was 100% optically active (see ref. 14).

Experimental[30,31]

(*R*) (−)-2-Methylpyrrolidine ((*R*) (−)-5a)——Prepared according to the procedure reported by Paquette, *et al.*,[15] bp 84—99° (760 mmHg), $[\alpha]_D^{22}$ −11.0° (*c*=1.512, H_2O) (lit.,[15] bp 88—94° (760 mmHg), $[\alpha]_D^{24}$ −11.5° (*c*=2.5, H_2O)).

(*S*) (−)-2-Isopropylpyrrolidide ((*S*) (−)-5b)——This sample was synthesized according to the published procedure,[16] bp 120° (760 mmHg), $[\alpha]_D^{20}$ −14.0° (*c*=1.004, EtOH) (lit.,[16] bp 130—137° (760 mmHg), $[\alpha]_D^{20}$ −14.4° (*c*=0.450, EtOH)).

(*S*) (−)-Proline Pyrrolidide ((*S*) (−)-5c)——Preparation of this sample was carried out by the reported procedure,[17] bp 140—141° (2 mmHg), $[\alpha]_D^{20}$ −112.4° (*c*=1.528, EtOH) (lit.,[17] bp 134—136° (4 mmHg), $[\alpha]_D^{26}$ −112.5° (*c*=0.91, EtOH)).

(*S*) (−)-Proline Diethylamide ((*S*) (−)-5d)——A sample prepared by the reported method,[17] showed bp 110—111.5° (2 mmHg), $[\alpha]_D^{27}$ −94.9° (*c*=1.182, EtOH) (lit.,[17] bp 107—108° (5 mmHg), $[\alpha]_D^{29}$ −96.4° (*c*=2.49, EtOH)).

(*S*) (−)-Ethyl Prolinate ((*S*) (−)-5e)——Thionyl chloride (27.4 g, 0.23 mole) was gradually added to a stirred suspension of **5f** (17.4 g, 0.15 mole) in absolute ethanol (180 ml) in an ice-bath.[19] The mixture was stirred at room temperature for 0.5 hr, then refluxed for 3.0 hr. Evaporation *in vacuo* gave a yellow viscous oil, which was dissolved in chloroform (100 ml). The chloroform solution was made basic with excess ammonia saturated in chloroform. Filtration and evaporation *in vacuo* afforded crude ester as a yellow oil, which was distilled *in vacuo* to give pure (*S*) (−)-**5e** as a colorless oil (17.1 g, 81%), bp 75—78° (16 mmHg), $[\alpha]_D^{22}$ −45.0° (*c*=1.782, EtOH) (lit.,[18] bp 78° (12—14 mmHg)). IR spectrum of this sample was in agreement with the assigned structure. This oil was directly submitted to the next step.

Asymmetric Synthesis of (*R*) (+)-α-Cyclocitral ((*R*) (+)-4)——Reaction procedure for the asymmetric synthesis of (*R*) (+)-4 with (*S*) (−)-**5b** (run 2 in Table I) was described as an example. Other asymmetric reactions were conducted under the same reaction condition as that described here.

A mixture of **2**[8] (0.61 g, 4.0 mmole) and (*R*) (−)-**5b** (0.54 g, 4.8 mmole) in anhyd. benzene (17.0 ml) was refluxed for 1.0 hr in the presence of Molecular Sieves 4A. Filtration and evaporation *in vacuo* gave crude **7b** as a pale brown oil (1.01 g, quantitative yield). IR ν_{max}^{film} cm^{-1}: 1640, 1633, 1620, 1613 (olefinic double bond), 930 (*trans*-disubstituted olefin).

An ethereal solution (0.4 ml) of **7b** (1.01 g) prepared above, was gradually added to a stirred mixture of 95% sulfuric acid (4.0 ml) and water (0.4 ml) in an ice-bath. After the addition was over, the stirring was continued for 3.0 hr in an ice-bath, then the whole mixture was poured into ice-water (57 ml). The aqueous solution was made to pH 3—4 by the addition of 10% aq. NaOH, then covered with benzene (17 ml). A two layer solution was refluxed for 1.0 hr with stirring. After cooled, the benzene layer was separated, and the lower aqueous phase was further extracted with benzene (X2). Combined organic extracts were washed with satd. NaCl, and dried over anhyd. Na_2SO_4. Filtration and evaporation *in vacuo* gave a brown oil, which was purified with column chromatography (silica gel, solvent, benzene–hexane 1:1) to afford pure (*R*) (+)-**4** as a yellow oil (0.16 g, 26% based on **5**). Spectral (IR and NMR) and chromatographic (TLC and GLC) properties were completely identical with those of the authentic *dl*-**4**.[1] This oil showed $[\alpha]_D^{20}$ +159° (*c*=0.810, EtOH). ORD (*c*=0.778, EtOH) $[M]^{20}$ (mμ)[32]: +187° (700), +247° (589), +396° (500), +816° (400), +4830° (321, peak), 0° (298), −3260° (272, trough). Optical yield for this asymmetric reaction was calculated as 26.7%, based on the assumption that (*R*) (+)-**4** showing $[\alpha]_D^{20}$ +594.5° (EtOH) was optically pure.

(*S*) (−)-α-Cyclogeraniol ((*S*) (−)-9)——(*S*) (−)-**8** prepared according to the reported procedure,[26] showed mp 100—103.5° and $[\alpha]_{546}^{20}$ −334.3° (*c*=1.096, EtOH). Optical purity of this sample was calculated as 84.4% since optically pure (*S*) (−)-**8** was reported to have mp 104° and $[\alpha]_{5461}$ −395.7° (*c*=4.865, EtOH).[26]

A solution of (*S*) (−)-**8** (0.91 g, 5.4 mmole) in anhyd. ether (8.0 ml) was gradually added to a stirred suspension of lithium aluminium hydride (0.26 g, 6.8 mmole) in ether (10. 0ml) at room temperature. The

30) 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 measured with spectrometers, JNM-PS 100 and Hitachi R-24 High Resolution NMR Spectrometers. All signals are expressed by the ppm downfield from tetramethylsilane used as an internal standard. Optical activities were determined with YANACO OR-50 Automatic Polarimeter. Optical rotatory dispersion (ORD) curve measurements were carried out with a spectrometer, Model ORD/UV-5, Japan Spectroscopic Co. Ltd. Gas-liquid chromatography (GLC) were performed using Hitachi K 23-D Gas Chromatograph.

31) Extraction solvent for all volatile compounds was not completely evaporated in order to prevent a loss of the reaction product, so weight measurements for these samples at the stage of crude evaporation residue were not performed throughout this work.

32) This ORD curve was measured on (*R*) (+)-**4** having $[\alpha]_D^{20}$ +162° (*c*=0.778, EtOH), obtained by the same reaction as that described here.

whole mixture was stirred at room temperature overnight, then the reaction was quenched by the addition of water (4.5 ml) with ice-cooling. After 10% sulfuric acid (4.5 ml) was added to the mixture, the upper organic phase was separated. The lower aqueous layer was further extracted with ether (X2), and the combined ethereal extracts were successively washed with 10% Na_2CO_3, and satd. NaCl, and finally dried over anhyd. Na_2SO_4. Filtration and evaporation *in vacuo* gave almost pure (*S*) (−)-**9** as a colorless oil (0.57 g, 69%), which showed bp 66° (10 mmHg) and $[\alpha]_D^{20}$ −103.1° (*c*=0.686, EtOH). IR and NMR spectra of this oil were superimposable on those of the authentic racemic alcohol[1] measured in the same states. Chromatographic (TLC and GLC) behaviors of this sample were also identical with those of the racemic compound.[1]

Based on the above experiment, the optical rotation of optically pure (*S*) (−)-**9** was calculated to be $[\alpha]_D$ −122.0° (EtOH).

(*R*) (+)-α-Cyclogeraniol ((*R*) (+)-9)——A mixture of (*R*) (+)-**4** (0.17 g, 1.1 mmole) ($[\alpha]_D^{20}$ +131.1° (*c*=0.810, EtOH)) prepared by the asymmetric synthesis, and sodium borohydride (0.08 g, 2.1 mmole) in absolute ethanol (10.0 ml) was stirred at room temperature overnight. The residue obtained by evaporation *in vacuo*, was dissolved in 10% aq. HCl, then the acidic solution was extracted with ether (X3). Combined organic extracts were washed with satd. NaCl, and dried over anhyd. Na_2SO_4. Filtration and evaporation *in vacuo* gave an oily residue, which was successively purified by column chromatography (silica gel, solvent, benzene) and distillation *in vacuo*, giving pure (*R*)(+)-**9** as a colorless oil (0.05 g, 29%), bp 80° (10 mmHg) (bath temperature), $[\alpha]_D^{20}$ +26.9° (*c*=0.610, EtOH). This sample showed identical IR spectrum and TLC behavior with those of the authentic racemic compound.[1]

The optical purity of (*R*)(+)-**4** showing $[\alpha]_D^{20}$ +131.1° (*c*=0.810, EtOH), was calculated as 22.0%. Then, it became obvious that optically pure (*R*)(+)-**4** should have $[\alpha]_D^{20}$ +594.5° (EtOH).

Optical Stability of (*R*)(+)-α-Cyclocitral ((*R*)(+)-4) under the Acidic Condition——A two layer solution prepared with benzene (15.0 ml) containing (*R*)(+)-**4** (0.15 g, 1.0 mmole) ($[\alpha]_D^{20}$ +102.6° (*c*=0.696, EtOH)) and 10% aq. acetic acid (pH *ca.* 4.0), was refluxed for 1.0 hr with stirring. The upper benzene layer was separated, and the lower aqueous phase was further extracted with benzene (X2). Combined benzene extracts were washed with 10% aq. $NaHCO_3$ and satd. NaCl, then dried over anhyd. Na_2SO_4. Filtration and evaporation *in vacuo* recovered (*R*)(+)-**4** (0.14 g, 93% recovery), whose spectral (IR) and chromatographic (TLC) behaviors were identical with those of the starting (*R*)(+)-**4**. This sample showed $[\alpha]_D^{20}$ +97.5° (*c*=0.162, EtOH).

This experiment clearly discloses that optically active (*R*)(+)-**4** is not only prone to racemize, but is stable under almost the same condition as that employed for the hydrolysis of the immonium salt.

(*R*)(+)-trans-α-Damascone ((*R*)(+)-6)——Commercially available 1-chloro-1-propene (a mixture of *cis*- and *trans*-isomer) (0.99 g, 4.5 mmole) in anhyd. ether (4.5 ml) was added to a stirred suspension of lithium (38 mg, 5.7 mg atom) in anhyd. ether (4.5 ml) under a nitrogen atmosphere. Stirring was continued for 2.0 hr at room temperature under a nitrogen atmosphere, affording an ethereal solution of 1-lithio-1-propene (a mixture of *cis*- and *trans*-isomer), to which was added a solution of (*R*)(+)-**4** ($[\alpha]_D^{20}$ +172° (*c*=0.282, EtOH), 28.9% optically pure) (0.15 g, 1.0 mmole) in anhyd. ether (1.5 ml). The whole mixture was stirred at room temperature overnight, then was diluted with satd. NH_4Cl (10 ml). The upper ethereal layer was separated, and the lower aqueous phase was further extracted with ether (X2). Combined organic phases were washed with satd. NH_4Cl, and dried over anhyd. Na_2SO_4. Filtration and evaporation *in vacuo* afforded a diastereomeric mixture of the crude addition product (**10**) as a pale yellow oil (0.20 g), which was immediately used for the next oxidation.

To a stirred mixture of chromium trioxide (0.19 g, 2.9 mmole) and pyridine (9.5 ml), was added a pyridine solution (9.5 ml) of **10** prepared above, over a period of 3.0 min at room temperature. After the mixture was stirred at room temperature overnight, it was poured into an ice-water (50 ml). The aqueous mixture was extracted with ether (X3), and the combined organic extracts were successively washed with 10% aq. HCl and satd. NaCl (X3), and finally dried over anhyd. Na_2SO_4. Filtration and evaporation *in vacuo* gave crude (*R*)(+)-**6** as a yellow oil, which was purified with column chromatography (silica gel, solvent, benzene–hexane 4: 1) to give pure (*R*)(+)-**6** as a colorless oil (0.12 g, 66% based on (*R*)(+)-**4**). IR ν_{max}^{film} cm^{-1}: 1690 (conjugated ketone), 1660, 1625 (olefinic double bond), 970 (*trans*-disubstituted olefin). NMR (in CCl_4): 0.83, 0.91 (6H, two singlets, >C($C\underline{H}_3$)$_2$), 1.53 (3H, singlet, =Ç–$C\underline{H}_3$), 1.89 (3H, doubled doublet, =CH–$C\underline{H}_3$, *J*=6.5 and 1.0 cps), 1.5—2.3 (4H, multiplet, –($C\underline{H}_2$)$_2$–), 2.75 (1H, singlet, >C$\underline{H}$–CO), 5.51 (1H, broad singlet, CH_2–C$\underline{H}$=Ç–CH_3), 6.20 (1H, doubled qualtet, –CO–C$\underline{H}$=CH–CH_3, *J*=16.0 and 1.0 cps), 6.80 (1H, doubled quartet, –CO–CH=C$\underline{H}$–CH_3, *J*=6.5 and 16.0 cps). These spectral properties were the same as those reported in the literature.[13a] TLC (silica gel, solvent, benzene): *Rf*=*ca.* 0.5. GLC (15% Carbowax, 2m, 170°, 1 kg/cm^2): retention time, 4.8 min. These chromatographic analyses showed that this oil was completely homogeneous. This oil showed $[\alpha]_D^{20}$ +89.2° (*c*=1.058, $CHCl_3$). ORD (*c*=1.058, $CHCl_3$) $[M]^{20}$ (mμ): +145° (700), +182° (589), +306° (500), +854° (400), +1380° (370, peak), 0° (334), −510° (314, trough). Optical purity of (*R*)(+)-**6** thus prepared was calculated as 27.5% by the assumption that (*R*)(+)-**6** showing $[\alpha]_D$ +324° (*c*=10, $CHCl_3$)[14] was optically pure.

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