[Chem. Pharm. Bull. 23(2) 272—278 (1975)]

UDC 547.91.057 : 542.98

# Stereochemical Studies. XXXIV.[1] A Novel Biogenetic-type Cyclization of Citral to α-Cyclocitral *via* an Enamine[2,3]

Masakatsu Shibasaki, Shiro Terashima, and Shun-ichi Yamada

*Faculty of Pharmaceutical Sciences, University of Tokyo*[4]

(Received June 12, 1974)

Aminig to develop a new biogenetic-type cyclization of acyclic terpene derivatives which is applicable to the asymmetric synthesis of optically active terpenes, a novel acid-catalyzed cyclization of the dienamines (**7**) easily prepared with citral (**1**) and several kinds of secondary amines, was studied. Treatment of citral-pyrrolidine enamine (**7a**) with a mixture of concd. sulfuric acid and water, followed by hydrolysis, was found to exclusively afford α-cyclocitral (**2**) in 41% yield.

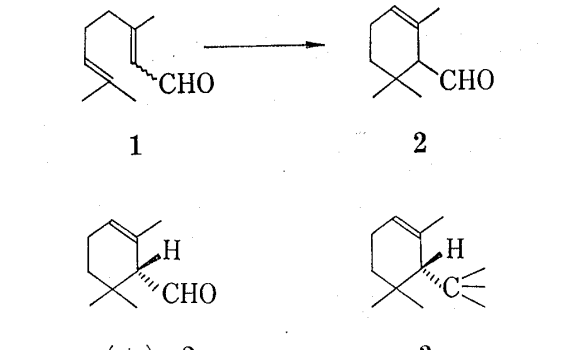
Detailed studies on the structure of **7** and the reaction mechanism for the new cyclization reaction were also carried out.

## Introduction

*In vivo*, acyclic terpenes having no asymmetric center are generally converted to cyclic terpenes carrying several asymmetric carbons by enzymic cyclization reaction.[5] Aiming to achieve similar chemical transformations[6] *in vitro*, numerous acyclic terpene structure types have been synthesized and submitted to the non-enzymic cationic cyclization reactions which are recognized as model reactions for biosyntheses of cyclic terpenes.[5,7] However, only few reports[8] are concerned with the so-called asymmetric syntheses[9] of optically active cyclic terpenes from achiral acyclic ones.

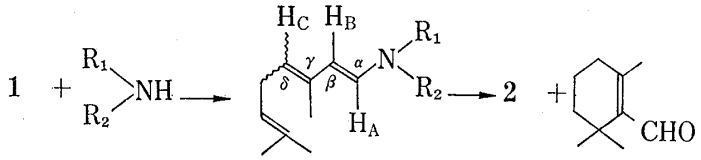
1) Part XXXIII: K. Nagasawa, K. Hiroi, and S. Yamada, *Yakugaku Zasshi*, **95**, 46 (1975).
2) Presented at the 92nd Annual Meeting of the Pharmaceutical Society of Japan, Osaka, April, 1972, and at the 17th Sympodium on the Chemistry of Natural Products, Tokyo, October, 1973.
3) Part of this report has been communicated in the paper: S. Yamada, M. Shibasaki, and S. Terashima, *Tetrahedron Letters*, **1973**, 377.
4) Location: *Hongo, Bunkyo-ku, Tokyo, 113, Japan.*
5) *a*) M.J.O. Francis, "Monoterpene Biosynthesis" in "Aspects of Terpenoid Chemistry and Biochemistry," ed. by T.W. Goodwin, Academic Press, New York and London, 1971, pp. 29—51; *b*) G. Rücher, *Angew. Chem. Internat. Edit.*, **12**, 793 (1973); *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; *d*) 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—411.
6) For reviews dealing with this field, see *a*) W.S. Johnson, *Accounts Chem. Res.*, **1**, 1 (1968); *b*) E.E. van Tamelen, *ibid.*, **1**, 111 (1968); *c*) T. Kato and Y. Kitahara, *J. Synth. Org. Chem. Japan*, **28**, 559 (1970); *d*) S. Yamada and M. Shibasaki, *Kagaku*, **28**, 737 (1973).
7) For example, see *a*) E.E. van Tamelen and R.J. Anderson, *J. Am. Chem. Soc.*, **94**, 8225 (1972), and accompanying papers; *b*) W.S. Johnson, M.M. Gravestock, and B.E. McCarry, *ibid.*, **93**, 4332 (1971), and accompanying papers; *c*) R.L. Markezick, W.E. Willy, B.E. McCarry, and W.S. Johnson, *ibid.*, **95**, 4414 (1973), and references cited therein; *d*) M.A. Schwarz, J.D. Crowell, and J.H. Musser, *ibid.*, **94**, 4361 (1972), and references cited therein; *e*) A.S. Kumanireng, T. Kato, and Y. Kitahara, *Chemistry Letters*, **1973**, 1045, and its preceding papers.
8) *a*) W.S. Johnson, C.A. Harbert, and R.D. Stipanovic, *J. Am. Chem. Soc.*, **90**, 5279 (1968); *b*) T. Kato, S. Kumazawa, and Y. Kitahara, *Synthesis*, **1972**, 573; *c*) S. Kumazawa, T. Kato, and Y. Kitahara, *Chemistry Letters*, **1973**, 633.
9) For the definition of asymmetric synthesis, see J.D. Morrison and H.S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Inc., Englewood Cliffs, New Jersey, 1971, p. 4.

In the course of our studies[10] on the asymmetric syntheses in the field of natural products using optically active amino acid derivatives as chiral additives, we paid much attention to the possible biogenetic-type asymmetric cyclization of achiral and acyclic monoterpene, citral (**1**),[11] to optically active cyclic one, α-cyclocitral (**2**),[12] which carries only one asymmetric carbon, since optically active **2** (for example, (+)-**2**)[13] could be a versatile key intermediate for the syntheses of several physiologically active terpenes having a partial structure such as **3**, that is, (+)-α-ionone ((+)-**4**),[14] (+)-*trans*-α-damascone ((+)-**5**),[15] and (+)-α-carotene ((+)-**6**).[14]



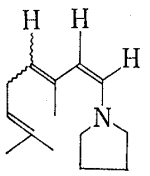

1 2 (+)−2 3 (+)−4 (+)−5 (+)−6

Chart 1




8 7 9

a : $R_1$, $R_2 = -(CH_2)_4-$
b : $R_1$, $R_2 = -(CH_2)_5-$
c : $R_1$, $R_2 = -(CH_2)_2-O-(CH_2)_2-$
d : $R_1$, $R_2 = C_6H_5CH_2-$




10a

Chart 2

In order to study whether L-proline derivatives, which showed unique asymmetric induction abilities in some alkylation reactions,[10] are usable as asymmetric origins for the above-mentioned asymmetric synthesis of optically active **2** from **1**, the biogenetic-type cyclization of the dienamines (citral-secondary amine enamines) (**7**) easily obtainable from **1** and secondary amines (**8**) was first examined. Being different from the method reported by Colombi, *et al.*,[16] featuring the acid-catalyzed cyclization of the citral-aniline Schiff base which usually gives a

10) *a*) K. Hiroi, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **20**, 246 (1972); *b*) K. Hiroi and S. Yamada, *ibid.*, **21**, 47 (1973); *c*) M. Kitamoto, K. Hiroi, S. Terashima, and S. Yamada, *ibid.*, **22**, 459 (1974); *d*) G. Otani and S. Yamada, *ibid.*, **21**, 2112, 2119, 2125, 2130 (1973); *e*) T. Sone, K. Hiroi, and S. Yamada, *ibid.*, **21**, 2331 (1973); *f*) K. Nagasawa, H. Takahashi, K. Hiroi, and S. Yamada, *Yakugaku Zasshi*, **95**, 33 (1975); *g*) K. Nagasawa, K. Hiroi, and S. Yamada, *ibid.*, **95**, 46 (1975).

11) Throughout this work, a mixture of *cis*- and *trans*-isomer whose ratio could be determined as 5: 6, was employed (*vide infra*).

12) Since all chiral compounds prepared or used in this report were of racemates, structual formula which ignored absolute configuration, were used for convenience except for (+)-**2**,**3**, (+)-**4**, (+)-**5**, and (+)-**6**.

13) For the absolute configuration of (+)-**2**, see ref. 17.

14) C.H. Eugster, R. Buchecker, Ch. Tscharner, G. Uhde, and G. Ohloff, *Helv. Chim. Acta*, **52**, 1729 (1969).

15) G. Ohloff and G. Uhde, *Helv. Chim. Acta*, **53**, 531 (1970).

16) L. Colombi, A. Bosshard, H. Schniz, and C.F. Seidel, *Helv. Chim. Acta*, **34**, 265 (1951).

mixture of **2** and β-cyclocitral (**9**) in a ratio of 2: 1, our new chemical scheme shown in Chart 2, was found to afford **2** with concomitant formation of a trace amount of **9**.

This report deals with a full account of the successful biogenetic-type cyclization of **1** to **2** *via* **7**, and its some machanistic studies. An application of this novel reaction to the asymmetric synthesis of optically active (+)-**2** *via* optically active dienamines prepared with L-proline derivatives, and a synthesis of optically active (+)-**5** from (+)-**2**, will be reported in the accompanying paper.[17]

## Result and Discussion

### A. Preparation of the Dienamines (7) from Citral (1) and Secondary Amines (8)

Reflux of a benzene solution containing **1**[11] and two equivalents of pyrrolidine (**8a**) in the presence of Molecular Sieves 4A for 1.0 hr[18] gave **7a** in a quantitative yield. Throughout this work, **1** was used as a mixture of *cis*- and *trans*-isomer since both isomers were anticipated to afford the same **7** through double bond migration during the dienamine formation. Infrared (IR) spectrum of **7a** showed a strong absorption at 930 $cm^{-1}$ due to *trans*-disubstituted olefin, and its nuclear magnetic resonance (NMR) spectrum disclosed one of four olefinic protons ($H_B$) at $\delta$ 6.33 and 6.41 ppm as doubled doublets having identical coupling constants ($J_{AB}$=14.0 cps). These spectral properties could be reasonably explained by assuming that **7a** is a mixture of the double bond isomers concerning γ-double bond as shown in Chart 2. The other two possible structures having *cis*-double bond at the α-position such as **10a**, might be excluded from steric reason and the spectral data cited above.

Similar spectral characteristics could be observed for the dienamines (**7b, c,** and **d**) prepared with **1** and secondary amines, piperidine (**8b**), morpholine (**8c**), and dibenzylamine (**8d**).

Without further purification, **7a**—**d** thus obtained, were submitted for the next cyclization reaction.

### B. Cyclization Reaction of the Dienamines (7) under Acidic Conditions

As it had been generally accepted that dienamine could be converted to stable conjugated immonium salt by the action of mineral acid,[19] it was expected that the treatment of **7** with acid could afford the corresponding stabilized immonium salt (**11**), which would cyclize to the monocyclic product (**12**) through the protonation of terminal double bond, followed by the simultaneous nucleophilic ring closure (see **13**) as visualized in Chart 3. The cyclic product (**12**) was considered to be easily converted to **2** under hydrolytic condition.

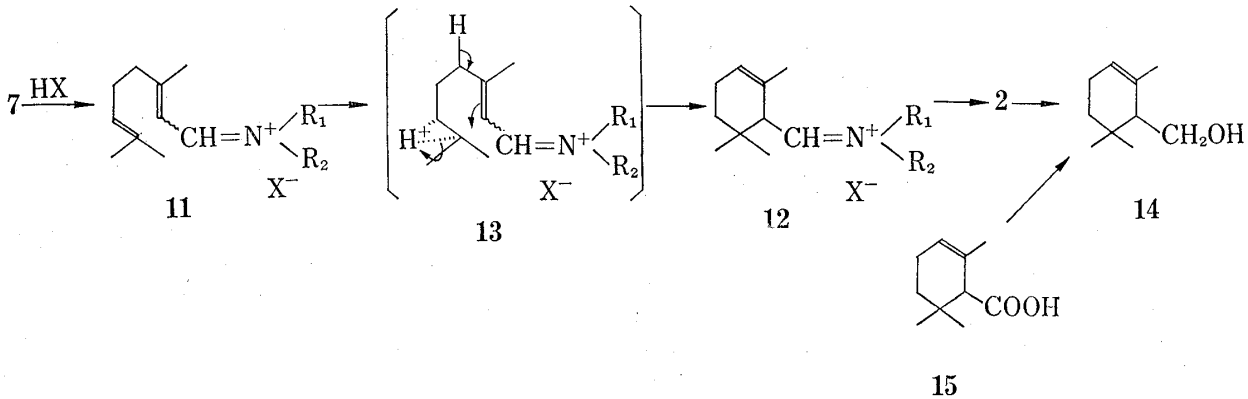



Chart 3

17) M. Shibasaki, S. Terashima, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **23**, 279 (1975).
18) K. Taguchi and F.H. Westheimer, *J. Org. Chem.*, **36**, 1570 (1971).
19) J. Szmuszkovicz, "Enamines" in "Advances in Organic Chemistry, Methods and Results," ed. by R.A. Raphael, E.C. Taylor, and H. Wynberg, Interscience Publishers, New York and London, 1963, p. 84.

Table I. Preparation of α-Cyclocitral (2) from the Dienamine (7a) under Several Acidic Conditions

| Run | Acidic conditions: Nature | Ratio by Vol. | Temp.[a] (°C) | Time (hr) | Products: α-Cyclocitral (2) yield (%)[b] | Products: β-Cyclocitral (9) yield (%)[c] |
|---|---|---|---|---|---|---|
| 1 | 95% $H_2SO_4$–$H_2O$ | 10:1 | 0 | 3.0 | 41 | 1 |
| 2 | 99% HCOOH–95% $H_2SO_4$ | 8:5 | 30 | 0.75 | 26 | —[d] |
| 3 | 85% $H_3PO_4$–95% $H_2SO_4$ | 1.1:1 | 30 | 0.75 | 14[e] | —[d] |
| 4 | $BF_3$·ether–benzene | 1:3.3 | 80 | 24.0 | 6[e] | —[d] |

a) external temperature
b) isolated yield based on 1 used
c) determined by the GLC analysis on the crude reaction product
d) Presence of 9 in the crude reaction product could not be detected by TLC analysis. GLC analysis was not performed
e) isolated as 14 after reduction of the crude reaction product

In fact, the treatment of **7a** with a mixture of 95% sulfuric acid and water in an ice bath, followed by the hydrolysis at pH 3—4,[20] was found to afford **2** in 41% yield with a trace amount of **9** (*ca.* 1%). The hydrolysis condition employed here was chosen for preventing the unfavorable isomerization of **2** to **9**. Results on the cyclization reaction of **7a** under various reaction conditions are summarized in Table I. Characterization of the reaction products was performed by comparing their spectral and chromatographic behaviors with those of the authentic samples prepared by the reported method.[16] For runs 3 and 4 in Table I, **2** was reduced to α-cyclogeraniol (**14**) with sodium borohydride, which was similarly identified with the authentic **14** prepared from α-cyclogeranic acid (**15**).[21]

That **2** could be exclusively prepared according to the condition shown in run 1, cleanly shows that the new cationic cyclization reaction developed here is absolutely superior to the method by Colombi, *et al.*[16]

In order to further improve the yield of **2**, the cyclizations of **7b, c,** and **d** were carried out under the same condition as for run 1 in Table I. However, as shown in Table II, improvement of the yield of **2** could not be achieved.

Table II. Preparation of α-Cyclocitral (2) from the Dienamines (7b, c, d)[a]

| Run | Dienamines | Products: α-Cyclocitral (2) yield (%)[b] | Products: β-Cyclocitral (9) yield (%)[c] |
|---|---|---|---|
| 1 | **7b** | 33 | 1 |
| 2 | **7c** | 12 | 1 |
| 3 | **7d** | 8 | 1 |

a) All reactions were conducted under the same condition as that for run 1 in Table I.
b) isolated yield based on 1 used
c) determined by the GLC analysis on the crude reaction product

20) Treatment of **12a** under a strongly acidic condition (10% hydrochloric acid, reflux for 10 min) was not effective for the hydrolysis.
21) *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).

## C. Mechanistic Consideration on the Cyclization Reaction

Although the above-mentioned cyclization was developed by assuming that **7** should cyclize to **12** *via* **11** which was produced by the protonation of **7** with mineral acid, such mechanism could be further verified by the experiment shown in Chart 4.

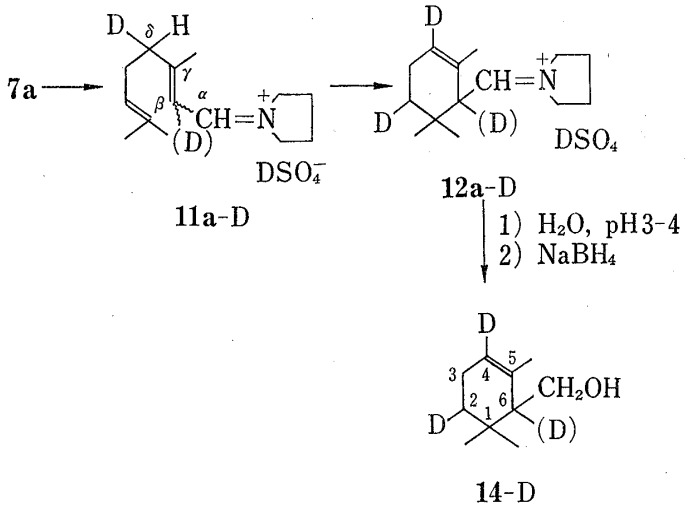



Chart 4

When the cyclization of **7a** was carried out with a mixture of concd. deuterosulfuric acid and deuterium oxide, NMR spectrum of the reaction product isolated as deuterated α-cyclogeraniol (**14**-D), cleanly showed that the $C_4$-position of **14**-D incorporated deuterium in 78% conversion. Although whether the deuteration of **7a** occurred directly at the δ position or first at the β position, then at the δ position to afford **11a**-D, is still ambiguous,[22] it is evident that the cyclization of **7a** has occurred from the deuterated immonium salt (**11a**-D) which carries deuterium at the δ position. Presence of deuterium at the $C_2$- and $C_6$-positions of **14**-D was anticipated when two possible modes of deuteration of **7a** with concd. deuterosulfuric acid and the subsequent cyclization of **11a**-D by the deuteration of the terminal double bond were considered. However, the quantities of deuterium incorporated into the $C_2$- and $C_6$-positions of **14**-D could not be determined by the NMR spectrum because the signals due to the protons which remained at the $C_2$- and $C_6$-positions of **14**-D overlapped with the signals of the $C_3$-methylene group and appeared as multiplet.

### Experimental[23,24]

**Purification of Citral (1)**——Commercially available **1** was purified according to the reported procedure.[25] Distillation *in vacuo* gave pure **1** as a colorless oil, bp 123—125° (21 mmHg) (lit.,[25] bp 119° (20 mmHg)). Gas–liquid chromatography (GLC) (15% SE-30 on Diasolid L, 2m, 110°, 0.7 kg/cm²) showed that **1** thus obtained was a mixture of *cis*- and *trans*-isomer: *cis*-isomer (neral), retention time 12.2 min; *trans*-isomer (geranial), retention time, 14.3 min. A ratio of *cis*- to *trans*-isomer determined by GLC was *ca.* 5 : 6.

**Preparation of the Authentic α-Cyclocitral (2) and β-Cyclocitral (9)**——Authentic samples of **2** and **9** were prepared according to the method reported by Colombi, *et al.*[16] Spectral and chemical properties of these compounds were as follows.

**2**: IR $\nu_{max}^{film}$ $cm^{-1}$: 1730 (saturated aldehyde). NMR (in $CCl_4$): 0.90, 0.98 (6H, two singlets, $-C-(C\underline{H}_3)_2$), 1.58 (3H, singlet, $=C-C\underline{H}_3$), 1.10—1.50 (2H, multiplet, $-C\underline{H}_2-$), 1.98—2.38 (3H, multiplets, allylic protons), 5.04 (1H, broad singlet, olefinic proton), 9.32 (1H, doublet, $J$=5.0 cps, $-C\underline{H}O$). GLC (15% SE-30 on Dia-

22) Due to this reason, deuterium at the β position of **11a**-D and **12a**-D, and that at the $C_6$-position of **14**-D were expressed in parentheses.

23) 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. GLC analyses were carried out using Hitachi K-23-D Gas Chromatograph.

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

25) H. Hibbet and L.T. Cannon, *J. Am. Chem. Soc.*, **46**, 119 (1924).

solid L, 2m, 110°, 1.5 kg/cm²): retention time, 2.5 min. Thin-layer chromatography (TLC) (silica gel, solvent, benzene–hexane 1: 1): *Rf*=*ca.* 0.5. Semicarbazone: mp 208—211° (lit.,[26] mp 201—203°).

**9**: IR $\nu_{max}^{film}$ cm$^{-1}$: 1680 ($\alpha,\beta$-unsaturated aldehyde). NMR (in $CCl_4$): 1.23 (6H, singlet, >C–(C$\underline{H}_3$)$_2$), 1.23—1.79 (4H, multiplet, –C$\underline{H}_2$–C$\underline{H}_2$–), 2.90 (3H, singlet, =C–C$\underline{H}_3$), 2.15—2.35 (2H, multiplet, allylic protons), 10.03 (1H, singlet, –C$\underline{H}$O). GLC (15% SE-30 on Diasolid L, 2m, 110°, 1.5 kg/cm²): retention time, 4.3 min. TLC (silica gel, solvent, benzene–hexane 1: 1): *Rf*=*ca.* 0.35. Semicarbazone; mp 168—171° (lit.,[26] mp 165—168°).

**Preparation of the Authentic $\alpha$-Cyclogeraniol (14)**——An ethereal solution (18 ml) of **15** (2.00 g, 12.0 mmole), prepared according to the literature,[21] was gradually added to a suspension of lithium aluminium hydride (0.57 g, 15.0 mmole) in anhyd. ether (22 ml) with stirring at room temperature. The whole mixture was stirred at room temperature overnight, then water (10 ml) was gradually added with ice-cooling. After 10% sulfuric acid (10 ml) was added to the aqueous mixture, the upper organic layer was separated, and the lower aqueous phase was extracted twice with ether. Combined ethereal layers 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 pure **14** as a colorless oil (1.08 g, 59%). This oil was homogeneous by TLC analysis (silica gel, solvent, benzene), *Rf*=*ca.* 0.2, and showed bp 78—79° (3 mmHg). IR $\nu_{max}^{film}$ cm$^{-1}$: 3340, 1015 (OH). NMR (in $CCl_4$): 0.88, 1.00 (6H, two singlets, –C–(C$\underline{H}_3$)$_2$), 1.72 (3H, singlet, =C–C$\underline{H}_3$), 1.04—2.12 (6H, multiplet, –C$\underline{H}_2$–, three allylic protons, and O$\underline{H}$), 3.61 (2H, doublet, $J$=4.0 cps, C$\underline{H}_2$OH), 5.50 (1H, broad singlet, olefinic proton). GLC (15% SE-30 on Diasolid L, 2m, 110°, 0.5 kg/cm²): retention time, 4.8 min. *Anal.* Calcd. for $C_{10}H_{18}O$: C, 77.86, 11.76. Found: C, 77.32; H, 11.76.

**Citral-Pyrrolidine Enamine (7a)**——A mixture of **1** (1.07 g, 7.0 mmole) and **8a** (1.00 g, 14.0 mmole) in anhyd. benzene (30 ml) was refluxed for 1.0 hr in the presence of Molecular Sieves 4A under a nitrogen atmosphere.[18] Filtration and evaporation *in vacuo* afforded **7a** as a pale brown oil (1.70 g, quantitative yield). IR $\nu_{max}^{film}$ cm$^{-1}$: 1639, 1631, 1618, 1613 (olefinic double bonds), 930 (*trans*-disubstituted olefin). NMR (in $CDCl_3$): 6.33, 6.41 (1H, doubled doublets, $J$=14.0 cps, –C$\underline{H}$=CH–N), 4.48—5.28 (3H, multiplets, olefinic protons). This oil was immediately used for the next cyclization step.

**Dienamines (7b, c, and d)**——Treatment of **1** with **8b**, c, and **d** in place of **8a** similarly gave **7b**, **c**, and **d** as a pale brown oil in quantitative yields. Spectral properties of **7b**, **c**, and **d** are shown in the following.

**7b**: IR $\nu_{max}^{film}$ cm$^{-1}$: 1650, 1640, 1620 (olefinic double bonds), 930 (*trans*-disubstituted olefin). NMR (in $CDCl_3$): 6.01, 6.14 (1H, doubled doublets, $J$=14.0 cps, –C$\underline{H}$=CH–N), 4.60—5.70 (3H, multiplets, olefinic protons).

**7c**: IR $\nu_{max}^{film}$ cm$^{-1}$: 1640, 1630, 1610 (olefinic double bonds), 930 (*trans*-disubstituted olefin). NMR (in $CDCl_3$): 5.97, 6.06 (1H, doubled doublets, $J$=14.0 cps, –C$\underline{H}$=CH–N), 4.79—5.55 (3H, multiplets, olefinic protons).

**7d**:[27] IR $\nu_{max}^{film}$ cm$^{-1}$: 1645, 1640, 1620 (olefinic double bonds), 930 (*trans*-disubstituted olefin). NMR (in $CDCl_3$): 6.39. 6.49 (1H, doubled doublets, $J$=14.0 cps, –C$\underline{H}$=CH–N), 4.73—5.49 (3H, multiplets, olefinic protons).

These dienamines were directly used for the next cyclization.

**Cyclization Reactions of the Dienamines (7a, b, c, and d)**——General procedures for cyclizations under different conditions were described on the reactions with **7a** as examples.

Cyclization with a Mixture of 95% Sulfuric Acid and Water (Run 1 in Table I): An ethereal solution (0.7 ml) of **7a** prepared from 1.07 g (7.0 mmole) of **1**, was gradually added to a mixture of 95% $H_2SO_4$ (7.0 ml) and $H_2O$ (0.7 ml) with stirring and external ice-cooling. The mixture was stirred for 3.0 hr in an ice bath, then a dark brown viscous oil formed was poured into a stirred ice-water (100 ml) with external ice-cooling. The pH of the acidic solution was adjusted to 3—4 with 10% aq. NaOH, and the aqueous solution was covered with benzene (30 ml). A two layer solution was refluxed for 1.0 hr with stirring, and the upper organic phase was separated. The lower aqueous solution was further extracted with benzene (X2), and the combined benzene extracts were washed with satd. NaCl (X2). After drying over anhyd. $Na_2SO_4$, filtration and evaporation *in vacuo* afforded a brown oil, which was purified with column chromatography (silica gel, solvent, benzene–hexane 1: 1), to give pure **2** as a yellow oil (0.44 g, 41% based on 1). Spectral (IR and NMR) and chromatographic (TLC and GLC) properties of this oil were completely identical with those of the authentic sample. GLC (15% SE-30 on Diasolid L, 2 m, 110°, 1.5 kg/cm²) analysis on the crude cyclization product disclosed that **9** was formed in *ca.* 1% yield by this reaction.

Cyclization with a Mixture of 99% Formic Acid and 95% Sulfuric Acid (Run 2 in Table I): A mixture of 99% formic acid (5.78 g) and 95% sulfuric acid (3.0 ml) (ratio by volume 8: 5) was gradually added to neat **7a** prepared from 1.07 g (7.0 mmole) of **1**, with stirring and external ice-cooling. The whole mixture was stirred for 0.75 hr in a water bath of 30°. After ice-water (30 ml) was added to the reaction mixture with external ice-cooling, the pH of the acidic solution was adjusted to 3—4 with 10% aq. NaOH, then the aqueous solution was covered with benzene (30 ml). A two layer solution was refluxed for 1.0 hr, and then

26) H.B. Henbest, B.L. Shaw, and G. Woods, *J. Chem. Soc.*, **1952**, 1154.
27) An equivalent amount of **8d** was used for the reaction.

worked up in a manner similar to the case for run 1 in Table I. Purification of the crude evaporation residue with column chromatography (silica gel, solvent, benzene–hexane 1 : 1) afforded pure **2** as a yellow oil (0.27 g, 25% based on **1**). This oil was identified with the authentic sample by its spectral (IR and NMR) and chromatographic (TLC) properties. Presence of **9** in the crude reaction product could not be detected by the TLC analysis.

Cyclization with a Mixture of 85% Phosphoric Acid and 95% Sulfuric Acid (Run 3 in Table I): To **7a** prepared from 1.07 g (7.0 mmole) of **1**, was gradually added a mixture of 85% phosphoric acid (5.78 g) and 95% sulfuric acid (3.0 ml) (ratio by volume 1.1 :1) with stirring in an ice-bath. The reaction mixture was stirred for 0.75 hr in a water bath of 30°, then was diluted with ice-water (30 ml). After neutralized to pH 3—4 with 10% aq. NaOH in an ice-bath, the whole solution was treated the same as the case for run 1 in Table I, giving a brown oil after evaporation of the benzene extract. Sodium borohydride (0.26 g, 7.0 mmole) was added to an ethanolic solution (11 ml) of the brown oil obtained above, and the mixture was stirred at room temperature overnight, then evaporated *in vacuo* to give a residue, which was diluted with 10% aq. HCl. The acidic solution was extracted with ether (X3), and the combined ethereal extracts were washed with satd. NaCl, then 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), giving pure **14** as an almost colorless oil (0.15 g, 14% based on **1**). Spectral (IR and NMR) and chromatographic (TLC and GLC) behaviors of this oil were completely identical with those of the authentic sample. TLC analysis showed a complete absence of **9** in the crude cyclization product.

Cyclization with a Mixture of Boron Trifluoride–etherate and Benzene (Run 4 in Table I): A mixture of boron trifluoride–etherate (2.10 g, 17.8 mmole) and anhyd. benzene (4.2 ml) was gradually added to a stirred solution of **7a** prepared from 1.00 g (6.6 mmole) of **1**. The mixture was refluxed for 20.0 hr, then was diluted with water (20 ml) after cooled in an ice-bath. The pH of the aqueous solution was made to 3—4 with 10% aq. NaOH in an ice-bath, then the neutralized mixture was worked up in a manner similar to the case for run 3 in Table I, to give an oily residue after evaporation of benzene extract. Reduction with sodium borohydride in an ethanolic solution, followed by purification with column chromatography (silica gel, solvent, benzene), yielded pure **14** as an almost colorless oil (0.06 g, 6% based on **1**). IR spectrum and TLC behavior of this oil were identical with those of the authentic sample. Presence of **9** was not observed by the TLC analysis on the crude cyclization product.

**Cyclization of the Dienamine (7a) with a Mixture of Concd. Deuterosulfuric Acid and Deuterium Oxide**—— Treatment of **7a** (1.03 g, 5.0 mmole) with a mixture of concd. deuterosulfuric acid (5.0 ml) and deuterium oxide (0.5 ml) (ratio by volume 10: 1) similar to the case for run 1 in Table I, followed by the same work-up procedure as those described before, gave crude deuterated $\alpha$-cyclocitral as an oily residue after evaporation of the benzene extract. Sodium borohydride reduction and subsequent purification with column chromatography (silica gel, solvent, benzene) afforded **14**–D as an almost colorless oil (0.11 g, 15%), whose chromatographic (TLC and GLC) behaviors were identical with those of **14**. NMR spectrum (in $CCl_4$) of this oil cleanly showed that the $C_4$-position of **14**–D incorporated deuterium in 78% conversion when the absorption area due to the protons which remained at the $C_4$-position of **14**–D, was compared with that of the methylene protons adjacent to hydroxyl group.

**Acknowledgements** The authors were indebted to members of the Central Analysis Room of this Faculty for elemental analyses and spectral data.