

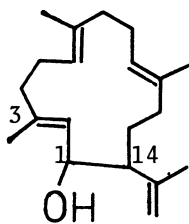
PREPARATION OF ENANTIOMERICALLY PURE 1-HYDROXY-NEOCEMBRENES TO DETERMINE THE UNSOLVED ABSOLUTE CONFIGURATION OF CEMBRENIDS<sup>1)</sup>Mario AOKI, Tadao UYEHARA, Tadahiro KATO,\* Kuninobu KABUTO,\*<sup>†</sup> and Shozo YAMAGUCHI<sup>†</sup>

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Cis and trans 1-hydroxy-neocembrenes were prepared in an enantiomerically pure form by reduction of dl-ketone with respective (+)- and (-)-Darvon-LiAlH<sub>4</sub> complex followed by purification with the aids of esterification with d- and l-menthoxyacetyl chlorides and (-)-camphanic acid chloride, respectively. Absolute configuration of naturally occurring (+)-mayol and (+)-cembrenene was determined by correlation with enantiomerically pure compounds.

An increasing number of cembrene type natural products possessing 14-membered ring have been accumulated from nature. Among them there remain not a few member of compounds whose absolute configuration have not yet been determined. With the view of determination of the unsolved absolute configuration of cembrenoids by the synthetic work, we undertook the asymmetric preparation of 1-hydroxy neocembrene (1) which can serve as a valuable intermediate for the synthesis of various target molecules.<sup>2)</sup> This paper concerns with the preparation of 1 in an enantiomerically pure form and its preliminary application to determine the absolute configuration of naturally occurring cembrenoids.

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The 14-membered ring ketone (2), readily available from geranylgeranic acid chloride in a dl-form,<sup>3)</sup> was submitted to the reaction with (+)-Darvon-LiAlH<sub>4</sub> complex<sup>4)</sup> under several conditions, resulting in partially enantiocontrolled reduction as shown in Table 1. The absolute stereochemistry of the resultant alcohols (1a and 1b) was rigorously established as follows. The enantiomerically enriched trans-(+)-alcohol (1b) was converted into d-menthoxyacetate by the action of d-menthoxyacetyl chloride (excess py in C<sub>6</sub>H<sub>6</sub>, rt, 12 h) and the resulting ester was recrystallized repeatedly from MeOH to get diastereomerically pure ester, mp 80°C, [α]<sub>D</sub><sup>21</sup> +71.4°(c 1.72).<sup>5)</sup> The ester was reduced with Li in EtNH<sub>2</sub> at -78°C to (-)-neocembrene (cembrene-A) (3), [α]<sub>D</sub><sup>21</sup> -19°(c 1.52) in 54% yield.<sup>6)</sup> Since S. Dev has unequivocally assigned 3 to have 14R-configuration by chemical degradation,<sup>7)</sup> C-14 of 1b is conclusively determined. The pure d-menthoxyacetate was hydrolyzed with KOH in aqueous MeOH, affording the enantiomerically purified trans alcohol (1b), [α]<sub>D</sub><sup>21</sup> +65.7°(c 1.75). Oxidation of 1b with CrO<sub>3</sub> in pyridine gave the corresponding ketone (2a), [α]<sub>D</sub><sup>20</sup> -196°(c 1.29) in 48% yield, which was then reduced with AlH<sub>3</sub> at -78°C to afford the isomeric cis alcohol (1c), [α]<sub>D</sub><sup>21</sup> -156°(c 1.89) after purification with SiO<sub>2</sub> column chromatography. Since the relative stereochemistry of C<sub>1</sub>-hydroxy group with respect to the neighboring isopropenyl moiety was established previously,<sup>8)</sup> the absolute stereochemistry of 1a, 1b and 1c must therefore be as depicted in the scheme.

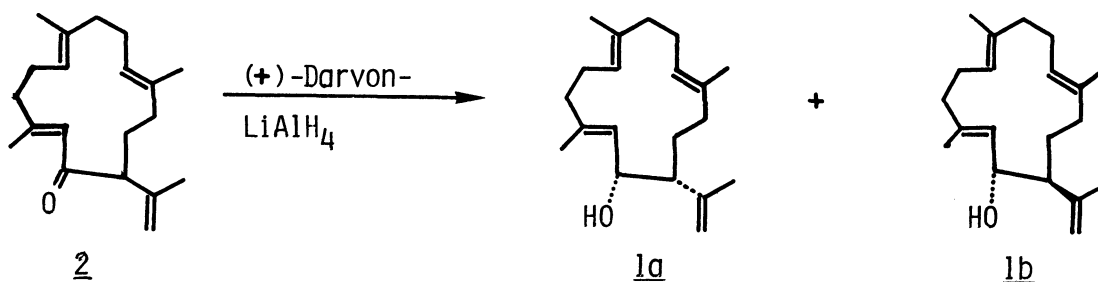


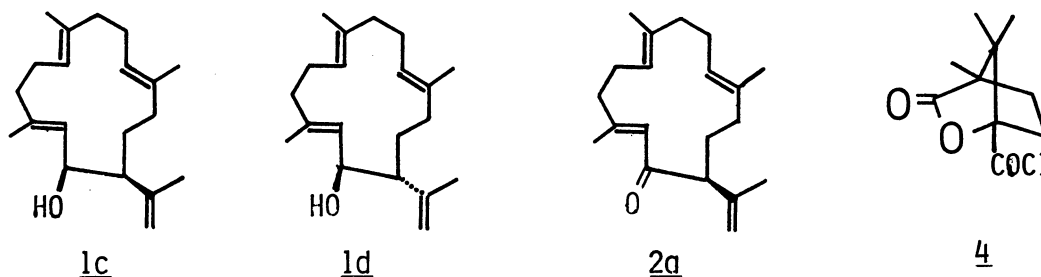
Table 1  
Reduction of ketone (2) with (+)-Darvon-LiAlH<sub>4</sub> complex<sup>a)</sup>

dl-Ketone ( <u>2</u> ) mmol	Reaction temp C	ee% (chemical yield%) <u>1a</u>	<u>1b</u>	Recovered ketone (%)
1.0	-20	14 (20)	27 (14)	63
1.0	0	33 (30)	56 (20)	42
1.5	0	28 (41)	49 (29)	22
3.8	0	trace	trace	88

a) Molar ratio of 2 : LiAlH<sub>4</sub> : Darvon = 1.0 : 2.34 : 5.4.

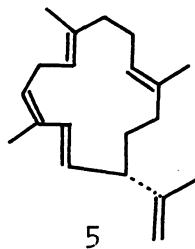
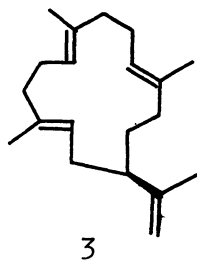
The enantiomerically enriched cis-(+)-alcohol (1a), obtained by the (+)-Darvon  $\text{LiAlH}_4$  complex reduction, was converted to d-camphanate by treatment with (-)-camphanic acid chloride<sup>9)</sup> (4) (py, rt). The resultant diastereomeric mixture, which was characterized by the carbonyl bands ( $1800$  and  $1730 \text{ cm}^{-1}$ ) in the IR spectrum, was subjected to  $\text{SiO}_2$  column chromatography eluted with hexane-AcOEt (20:1), leading to the isolation of d-camphanate of 1a, oil,  $[\alpha]_{\text{D}}^{21} +41^\circ$  (c 2.18). Saponification of the diastereomerically pure ester under usual conditions regenerated cis alcohol (1a),  $[\alpha]_{\text{D}}^{21} +156^\circ$  (c 2.23).

When dl-ketone (2) was reduced with the use of (-)-Darvon- $\text{LiAlH}_4$  complex, a pair of enantiomerically enriched alcohols (1c and 1d) was formed with the similar enantiomeric preference. These were purified by the same procedure as described above to obtain the enantiomerically pure alcohols 1c  $[\alpha]_{\text{D}}^{21} -155^\circ$  (c 1.70) and 1d  $[\alpha]_{\text{D}}^{21} -67.1^\circ$  (c 1.89).<sup>11)</sup> Thus, we could prepare cis and trans 1-hydroxy neocembrenes in an enantiomerically pure form. These compounds lend themselves conveniently to the synthesis of a variety of compounds whose absolute configuration have not yet been determined. Our preliminary experiment is illustrated below.



Recently, two cembrenoids were isolated from the soft coral, Sinularia Mayi,<sup>12)</sup> named mayol ( $[\alpha]_{\text{D}} +139^\circ$  ( $\text{CHCl}_3$ )) and cembrenene (5) ( $[\alpha]_{\text{D}} +78^\circ$  ( $\text{CHCl}_3$ )), respectively. The former was determined to be cis-1-hydroxy neocembrene by comparison of physical data with those of our dl-cis alcohol. However, its absolute configuration remains undetermined. The same sign of optical rotation with 1a indicates clearly that (+)-mayol has 1S,14R-absolute stereochemistry. When the enantiomerically pure trans alcohol (1d) was treated with  $\text{MsCl}$  in pyridine at  $0^\circ\text{C}$ , a hydrocarbon with  $[\alpha]_{\text{D}}^{22} +111^\circ$  (c 1.89) was obtained in 80% yield.<sup>13)</sup> The physical evidence including the sign of optical rotation was identical with that of natural (+)-cembrenene (5). Thus, the conversion of 1d to the (+)-cembrenene not only means its synthesis but also leads to the independent determination of the absolute stereochemistry of the cembrenene.

It should be noted that the values of optical rotation of mayol and cembrenene are less than those of synthetic compounds. In this regard the complete identity of PMR spectra of each compound strongly suggests that the naturally occurring cembrenoids are enantiomerically mixed with the corresponding antipode to some extent.



#### References

- 1) This constitutes part 38 of the series of "Cyclization of Polyenes."
- 2) T. Kato, T. Kobayashi, and Y. Kitahara, *Tetrahedron Lett.*, 1975, 3299; See also T. Kato, "Synthesis of Macrocyclic Terpenoids by Cyclization, Kagaku No Ryoiki Zokan No. 128," Nankodo, Tokyo, 1980, p 119.
- 3) Y. Kitahara, T. Kato, T. Kobayashi, and B. P. Moore, *Chem. Lett.*, 1976, 219.
- 4) S. Yamaguchi and H. S. Mosher, *J. Org. Chem.*, 38, 1870 (1973); K. Kabuto and H. Ziffer, *ibid.*, 40, 3467 (1975).
- 5) All the measurements of optical rotation were carried out in  $\text{CHCl}_3$ .
- 6) T. Kato, M. Suzuki, T. Kobayashi, and B. P. Moore, *J. Org. Chem.*, 45, 1126 (1980).
- 7) V. D. Patil, U. R. Nayak, and S. Dev, *Tetrahedron*, 29, 341 (1973).
- 8) T. Kato, M. Suzuki, M. Takahashi, and Y. Kitahara, *Chem. Lett.*, 1977, 456.
- 9) (-)-Camphanic acid chloride (4),  $[\alpha]_D -4.3^\circ$  (c 1.2,  $\text{C}_6\text{H}_6$ ) was prepared according to the Gerlach's procedure.<sup>10)</sup>
- 10) H. Gerlach, *Helv. Chim. Acta*, 61, 2773 (1978) and references cited therein.
- 11) The intermediates showed the following data. d-Camphanate of 1c: mp 76-77°C (MeOH);  $[\alpha]_D^{20} -58^\circ$  (c 1.47); PMR( $\text{CDCl}_3$ ) 0.91, 1.06, 1.08 (each 3H, s), 1.55 (6H, s), 1.70 (6H, s), 4.70 (1H, bs), 4.81 (1H, bs), 4.8-5.1 (2H, m), 5.25 (1H, d, 9 Hz), and 5.66 (1H, d, 9 Hz) ppm. l-Menthoxyacetate of 1d: mp 79-80°C (MeOH);  $[\alpha]_D^{21} -70.6^\circ$  (c 1.39).
- 12) Y. Uchio, H. Nabeya, M. Nakayama, S. Hayashi, and T. Hase, *Tetrahedron Lett.*, 1981, 1689.
- 13) The same treatment of 1b afforded the antipode of 5 with  $[\alpha]_D -111^\circ$  (c 1.30).

(Received May 20, 1983)