

Sesquiterpenoids. Part VI. The Absolute Configuration of Caryophyllene.*

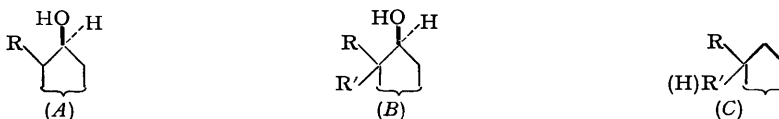
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By a consideration of the molecular rotations of tricyclic derivatives of caryophyllene of established stereochemistry, the absolute configuration of the hydrocarbon has been deduced.

DETERMINATION of the absolute configuration of a molecule requires either direct or indirect correlation with D-glyceraldehyde. Direct correlation is always desirable, but in complex alicyclic systems it is not in every case easily attainable. Amongst indirect methods of correlation should be mentioned the use of asymmetric synthesis (Prelog, *Helv. Chim. Acta*, 1953, **36**, 308; Prelog and Meier, *ibid.*, p. 320; Dauben, Dickel, Jeger, and Prelog, *ibid.*, p. 325; and subsequent papers) and the application of molecular-rotation considerations. Using the latter method Klyne (*J.*, 1952, 2916) was able to correlate correctly the triterpenoids with the steroids, and Mills (*J.*, 1952, 4976) the steroids with D-glyceraldehyde (Cornforth, Youhotsky, and Popjak, *Nature*, 1954, **173**, 536; Riniker, Arigoni, and Jeger, *Helv. Chim. Acta*, 1954, **37**, 546).

Klyne and Stokes (*J.*, 1954, 1979; see also Stokes and Bergmann, *J. Org. Chem.*, 1952, **17**, 1194; Mills, *Chem. and Ind.*, 1953, 212) recently proposed a useful molecular-rotation rule for the correlation of appropriately substituted cyclohexanols or cyclopentanols with D-glyceraldehyde. Thus cyclic secondary alcohols of the absolute stereochemistry depicted in (A) or (B) (R and R' = alkyl or part of a further ring) usually afford positive molecular-rotation increments on acylation. The molecular-rotation contribution of the



secondary hydroxyl group with respect to the parent saturated structure (C) is also, in general, positive. Conversely parallel negative molecular-rotation changes are observed for the epimeric alcohol. The present paper is concerned with the application of this rule to the elucidation of the absolute configuration of caryophyllene.

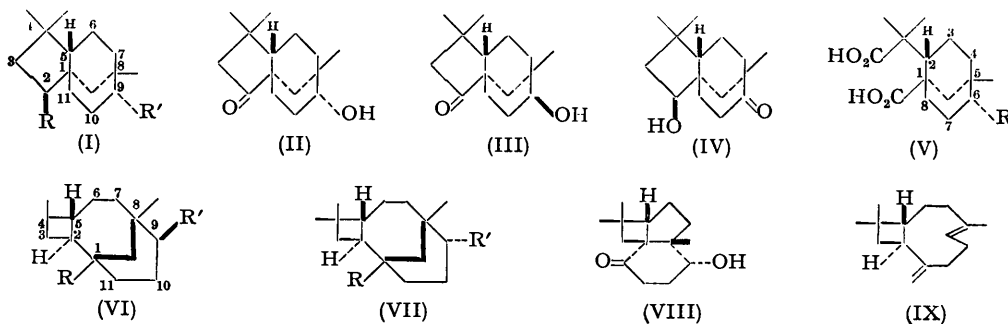
In previous parts of this series (Barton and Lindsey, *J.*, 1951, 2988; Barton, Bruun, and Lindsey, *ibid.*, 1952, 2210; Aebi, Barton, and Lindsey, *ibid.*, 1953, 3124) the preparation of a number of tricyclic derivatives of caryophyllene has been described. The relative configurations of these compounds have also been established (Aebi, Barton, Burgstahler, and Lindsey, preceding paper). In particular three different tricyclic ring systems have been

* Part V, preceding paper.

studied, that of clovane (I; $R = R' = H$), that of caryolane (VI; $R = R' = H$), and that represented by the hydroxy-ketone (VIII). In the Table we have correlated a considerable number of derivatives of these three ring systems according to the method of Klyne and Stokes (*loc. cit.*). If the absolute configurations of these substances are taken as given in the formulæ and in previous parts of this series (Aebi, Barton, and Lindsey, *loc. cit.*; Aebi, Barton, Burgstahler, and Lindsey, *loc. cit.*) then there is an excellent agreement between the signs of the predicted and the observed molecular-rotation contributions. Of the 28 correlations summarised in the Table, 25 are in agreement with one another and with the proposed absolute configuration (IX) of caryophyllene. We discuss, first, the method of correlation used in the Table and then the data that are not in agreement.

The molecular-rotation data in the Table are presented either as the $[M]_D$ contributions of the hydroxyl, acetoxyl, etc., group to the molecular rotation, with the use of the parent unsubstituted compound as reference standard, or as molecular-rotation increments based on the hydroxy-derivative as reference standard. Both procedures are equally applicable (see Klyne and Stokes, *loc. cit.*). The procedure adopted is indicated in the Table.

The validity of molecular-rotation correlations depends on the absence, or control, of "vicinal action" (see Barton and Cox, *J.*, 1948, 783). Vicinal action is, in general, more serious the more unsaturated are the substances under consideration. Two of the



anomalous figures are provided by the benzoate and the 3 : 5-dinitrobenzoate of clovane-2 β : 9 α -diol 2-benzoate (I; $R = OBz$; $R' = OH$). These are the two compounds in the Table where vicinal action might be most expected (Barton and Cox, *loc. cit.*) to invalidate the results. The results do not, therefore, constitute a serious criticism of the proposed absolute configuration. The third anomalous value is provided by the acetate of (VIII); the numerical value of the discrepancy is, however, small. Molecular-rotation correlations are most reliably applied when an adequate number of compounds is examined. We regard the number of examples cited in the Table as adequate for our purpose (cf. Klyne and Stokes, *loc. cit.*).

The constitution and stereochemistry* of most of the tabulated parent compounds, from which derivatives are obtained, have been established in earlier papers of this series. The preparation of 2 β -hydroxyclovan-9-one (IV) requires mention. Clovane-2 β : 9 α -diol was monobenzoyleated; oxidation of the product and hydrolysis gave a keto-alcohol shown to be (IV) by its non-identity with (II) (Aebi, Barton, and Lindsey, *loc. cit.*) and by its infra-red spectrum (max. at 1704 cm^{-1} , indicative of a *cyclohexanone*).

In order to prepare clovan-2 α -ol, the epimeric clovan-2 β -ol, obtained from 2 β -hydroxyclovan-9-one (see above) by Wolff-Kishner reduction, was oxidised to clovan-2-one. This ketone was not obtained crystalline, but on perchloric acid-catalysed hydrogenation it afforded the desired clovan-2 α -ol. That a rearrangement was not involved in the hydrogen-

* The configuration of the secondary hydroxyl group in (VIII) is determined by the mechanism of genesis (Barton and Lindsey, *loc. cit.*) and by the established configuration (Aebi, Barton, Burgstahler and Lindsey, *loc. cit.*) of caryophyllene oxide. This corrects an earlier (tentative) assignment of configuration (Barton, Bruun, and Lindsey, *loc. cit.*) based on the existence of only one (strained) chair conformation for the six-membered ring. In fact two such conformations are possible and the earlier (and more speculative) argument can also be reconciled with the correct configuration without difficulty.

ation was confirmed by re-oxidation of the clovan-2 α -ol to clovan-2-one, identified as its 2 : 4-dinitrophenylhydrazone. It is of interest that neither clovan-2 α - nor -2 β -ol is identical with " α -caryophyllene alcohol," as would have been expected on the basis of the known properties of this compound (Bell and Henderson, *J.*, 1930, 1971; see Barton, Bruun, and Lindsey, *J.*, 1952, 2210).

The following two cases, not conveniently included in the Table, are also in agreement with our proposed absolute configurations. Although the parent compound (clovan-2-one)

| Parent compound | Hydroxy-derivative (or equiv. process) | Hydroxyl | Molecular-rotation contributions | | | Predicted sign | References | |
|--|---|----------|----------------------------------|-------------------------|---|----------------|-------------|---------|
| | | | Acetyl or acetate | Benzoyl-oxo or benzoate | 3 : 5-Dinitro-benzoyl-oxo or 3 : 5-dinitro-benzoate | | Parent cpd. | Derivs. |
| Clovan-2 β -ol (I; R' = H) | Clovan-2 β -ol (I; R = OH, R' = H) | +61° | — | +141° | +183° | + | 1 | 2 |
| Clovan-2 α -ol (I; R' = H) | Clovan-2 α -ol | -43 | — | — | — | — | 1 | 2 |
| Clovan-9 α -ol (I; R' = H) | Clovan-9 α -ol (I; R = H, R' = OH) | -39 * | — | — | -136 | — | 1 | 2 |
| Clovan-2 β : 9 α -diol (I; R = R' = OH) | (Acylation at C ₍₉₎) | — | — | +146 | +178 | + | 3 | 1, 2 |
| Clovan-2 β -ol (I; R = OH, R' = H) | Clovan-2 β : 9 α -diol (I; R = R' = OH) | -39 | — | — | — | — | 2 | 3 |
| 9 α -Hydroxyclovan-2-one (II) | (Acylation at C ₍₉₎) | — | -121° | -91 | -9 | — | 3 | 2, 3 |
| 9 β -Hydroxyclovan-2-one (III) | " | — | — | — | +68 | + | 3 | 2 |
| 2 β -Hydroxyclovan-9-one (IV) | " | — | — | — | +153 | + | 2 | 2 |
| Clovenic acid (V; R = H) | 6 α -Hydroxyclovenic acid (V; R = OH) | -90 | — | — | — | — | 5 | 5 |
| Clovenic anhydride | 6 α -Hydroxyclovenic acid anhydride | — | -151 | — | — | — | 2, 6 | 2 |
| Caryolane-1 : 9 β -diol (VI; R = R' = OH) | (Acylation at C ₍₉₎) | — | +88 | +94 | +98 | + | 4 | 2, 4 |
| 1-Chlorocaryolane (VI; R = Cl, R' = H) | 1-Chlorocaryolane-9 β -ol (VI; R = Cl, R' = OH) | — | +107 | — | — | + | 4 | 4 |
| Caryolane-1 : 9 α -diol (VII; R = R' = OH) | (Acylation at C ₍₉₎) | — | -29 | -99 | — | — | 5 | 2 |
| <i>Anomalous</i> Clovan-2 β : 9 α -diol 2-benzoate (I; R = OBz, R' = OH) | (Acylation at C ₍₉₎) | — | -77 | +141 | +239 | — | 2 | 2 |
| Hydroxy-ketone (VIII) | (Acylation) | — | +26 | -99 | -137 | — | 7 | 2, 7 |

* Not obtained crystalline.

1, Lutz and Reid, *Chem. and Ind.*, 1953, 278; *J.*, 1954, 2265. 2, Experimental, this paper. 3, Aebi, Barton, and Lindsey, *J.*, 1953, 3124. 4, Barton, Bruun, and Lindsey, *J.*, 1952, 2210. 5, Aebi, Barton, Burgstahler, and Lindsey, *J.*, 1954, preceding paper. 6, Ruzicka and Gibson, *Helv. Chim. Acta*, 1931, 14, 570. 7, Barton and Lindsey, *J.*, 1951, 2988.

corresponding to the two epimeric hydroxy-ketones (II) and (III) was not obtained crystalline (see above), the difference in molecular rotation between (III) and (II) is positive (+47°) as predicted. The molecular rotation (-174°) of clovan-2 β : 9 α -diol diacetate (I; R = R' = OAc) less than (+27°) for clovan-2 β : 9 α -diol 2-benzoate 9-acetate (I; R = OBz, R' = OAc) is negative (-201°), as expected.

EXPERIMENTAL

For general experimental directions see *J.*, 1952, 2339. Infra-red spectra, in CS_2 solution, were kindly determined by Messrs. Glaxo Laboratories Ltd. $[\alpha]_D$'s are in CHCl_3 . Spence's Grade H alumina was used for chromatography.

General Procedures.—Acetates were prepared in the following way. The alcohol (200 mg.) in acetic anhydride (2 ml.) and pyridine (3 ml.) was left overnight at room temperature. Ethanol (3 ml.) was added and, after 15 min., the solution was concentrated *in vacuo* to 1–2 ml. Extraction with ether, washing successively with aqueous hydrochloric acid (5%), dilute sodium carbonate solution, and water, and removal of the ether (after drying; Na_2SO_4) gave the required derivative.

For the preparation of benzoates, the alcohol (200 mg.) in pyridine (3 ml.) was treated with benzoyl chloride (300 mg.) and left overnight at room temperature. After the addition of water (slight excess), the solution was poured into sodium hydrogen carbonate solution (5%). Extraction with ether and processing as above gave the required derivative.

For the preparation of 3 : 5-dinitrobenzoates, the alcohol (200 mg.) in pyridine (5 ml.) was treated with 3 : 5-dinitrobenzoyl chloride (600 mg.) and the solution heated on the steam-bath for $\frac{1}{2}$ hr. After concentration *in vacuo* the solution was poured into sodium hydrogen carbonate solution (5%) and left for 15 min. Extraction with ether and processing as above gave the required 3 : 5-dinitrobenzoates. For purification all the 3 : 5-dinitrobenzoates were filtered in benzene solution through alumina (10 g.).

Clovan-2 β : 9 α -diol and its Derivatives.—The diol was prepared from caryophyllene oxide as described by Aebi, Barton, and Lindsey (*J.*, 1953, 3124). The 2 β -benzoate (prepared by use of only 1.1 mols. of benzoyl chloride) had m. p. 132–133° [needles from light petroleum (b. p. 60–80°)], $[\alpha]_D + 46^\circ$ (*c.* 1.26) (Found : C, 77.15; H, 8.95. $\text{C}_{22}\text{H}_{30}\text{O}_3$ requires C, 77.15; H, 8.85%). The 2 β : 9 α -dibenzoate (needles from methanol) had m. p. 128.5–129°, $[\alpha]_D + 67^\circ$ (*c.* 1.32) (Found : C, 78.05; H, 7.6. $\text{C}_{28}\text{H}_{34}\text{O}_4$ requires C, 78.0; H, 7.65%). The 9 α -acetate-2 β -benzoate had m. p. 84–85° (from methanol at low temperature), $[\alpha]_D + 7^\circ$ (*c.* 1.07) (Found : C, 75.1; H, 8.45. $\text{C}_{24}\text{H}_{32}\text{O}_4$ requires C, 74.95; H, 8.4%). The 2 β -benzoate-9 α -(3 : 5-dinitrobenzoate), needles [from chloroform–light petroleum (b. p. 40–60°)], had m. p. 178–179°, $[\alpha]_D + 74^\circ$ (*c.* 1.10) (Found : C, 65.0; H, 5.95; N, 5.2. $\text{C}_{29}\text{H}_{32}\text{O}_8\text{N}_2$ requires C, 64.9; H, 6.0; N, 5.2%). The 2 β -(3 : 5-dinitrobenzoate), prepared according to Lutz and Reid (*J.*, 1954, 2265) had m. p. 209–211° [from chloroform–light petroleum (b. p. 60–80°)], $[\alpha]_D + 44^\circ$ (*c.* 1.16).

2 β -Hydroxyclovan-9-one.—The 2 β -monobenzoate (see above) (2.8 g.) in “AnalaR” acetic acid (20 ml.) was treated with sodium dichromate dihydrate (0.91 g.) in the same solvent (12 ml.) and left at room temperature for 20 hr. The product {2.33 g.; $[\alpha]_D - 21^\circ$ (*c.* 1.96)} was not obtained crystalline. For hydrolysis the oily oxo-benzoate (930 mg.) in methanol (7 ml.) containing excess of potassium hydroxide was refluxed for 45 min. Chromatography over alumina and crystallisation from light petroleum (b. p. 40–60°) gave 2 β -hydroxyclovan-9-one, m. p. 77–78°, $[\alpha]_D - 92^\circ$ (*c.* 1.04) (Found : C, 76.35; H, 10.15. $\text{C}_{15}\text{H}_{24}\text{O}_2$ requires C, 76.2; H, 10.25%). The derived 3 : 5-dinitrobenzoate [from light petroleum (b. p. 80–100°)] had m. p. 135.5–136.5°, $[\alpha]_D - 15^\circ$ (*c.* 1.50) (Found : C, 61.5; H, 6.05; N, 6.9. $\text{C}_{22}\text{H}_{26}\text{O}_7\text{N}_2$ requires C, 61.4; H, 6.1; N, 6.5%).

Clovan-2 β -ol.—2 β -Hydroxyclovan-9-one (395 mg.) in ethanol (6 ml.) containing sodium (190 mg.) and anhydrous hydrazine (3 ml.) was heated at 185° for 15 hr. Sublimation of the product at 70°/0.5 mm. gave clovan-2 β -ol, needles, m. p. 95–96°, $[\alpha]_D + 23^\circ$ (*c.* 1.23) (Found : C, 81.3; H, 11.75. $\text{C}_{15}\text{H}_{26}\text{O}$ requires C, 81.0; H, 11.8%). The benzoate sublimed at 80°/0.1 mm., m. p. 46–47.5°, $[\alpha]_D + 40^\circ$ (*c.* 1.12) (Found : C, 81.35; H, 9.3. $\text{C}_{23}\text{H}_{30}\text{O}_2$ requires C, 80.95; H, 9.25%). The 3 : 5-dinitrobenzoate, needles [from light petroleum (b. p. 80–100°)], had m. p. 134–135°, $[\alpha]_D + 44^\circ$ (*c.* 1.12) (Found : C, 63.8; H, 7.0; N, 6.85. $\text{C}_{22}\text{H}_{28}\text{O}_6\text{N}_2$ requires C, 63.45; H, 6.8; N, 6.75%).

Clovan-2-one and Clovan-2 α -ol.—Clovan-2 β -ol (375 mg.) in “AnalaR” acetic acid (3 ml.) was treated with sodium dichromate dihydrate (185 mg.) in the same solvent (2 ml.) and left overnight at room temperature. The resulting ketone, which was an oil { $[\alpha]_D + 20^\circ$ (*c.* 2.32)}, was converted into the 2 : 4-dinitrophenylhydrazone. After filtration through alumina in benzene solution and crystallisation from ethyl acetate–methanol, this had m. p. 152–153° (Found : N, 14.3. $\text{C}_{21}\text{H}_{28}\text{O}_4\text{N}_4$ requires N, 14.0%).

Clovan-2-one (820 mg.) in ethyl acetate (30 ml.) containing perchloric acid (72% aqueous; 10 drops) was hydrogenated over platinum in the usual way. Chromatography of the product over alumina and elution with light petroleum (b. p. 40–60°)–benzene gave clovan-2 α -ol, m. p.

97—98.5° (from aqueous methanol), $[\alpha]_D -24^\circ$ (*c*, 1.10) (Found, in material sublimed at 75—80°/5 mm.: C, 81.3; H, 11.7. $C_{15}H_{26}O$ requires C, 81.0; H, 11.8%). On oxidation with sodium dichromate in acetic acid this gave back clovan-2-one, identified by its 2:4-dinitrophenylhydrazone (m. p. and mixed m. p.).

Reduction of clovan-2-one with sodium and *n*-propanol in the usual way gave a crystalline mixture (90%) of alcohols which could not be separated by crystallisation or chromatography. The mixture had m. p. 71—74°, $[\alpha]_D -3^\circ$ (*c*, 2.26), and thus corresponded to equal parts of clovan-2 α - and -2 β -ol.

Clovan-2 α - and -2 β -ol gave marked m. p. depressions both with each other and with " α -caryophyllene alcohol," m. p. 118°, $[\alpha]_D +5^\circ$ (*c*, 0.47), kindly prepared by Dr. T. Bruun.

9 α -Hydroxyclovan-2-one and its Derivatives.—The keto-alcohol was prepared according to Aebi, Barton, and Lindsey (*loc. cit.*). The *benzoate*, rods [from light petroleum (b. p. 60—80°)], had m. p. 134—135°, $[\alpha]_D -19^\circ$ (*c*, 1.75) (Found: C, 77.85; H, 8.25. $C_{22}H_{28}O_3$ requires C, 77.6; H, 8.3%). The 3:5-*dinitrobenzoate*, needles [from chloroform—light petroleum (b. p. 60—80°)], had m. p. 166—167°, $[\alpha]_D +4^\circ$ (*c*, 1.25) (Found: C, 61.5; H, 6.15; N, 6.7. $C_{22}H_{26}O_7N_2$ requires C, 61.4; H, 6.1; N, 6.5%). 9 α -Hydroxyclovan-2-one (120 mg.) in ethanol (1.5 ml.) containing dissolved sodium (70 mg.) and anhydrous hydrazine (1 ml.) was heated at 185° for 15 hr. The oily product {170 mg.; $[\alpha]_D -22^\circ$ (*c*, 1.05)} was converted into *clovan-9 α -yl 3:5-dinitrobenzoate*, needles [from light petroleum (b. p. 60—80°), m. p. 192—193°, $[\alpha]_D -35^\circ$ (*c*, 0.84) (Found: C, 63.4; H, 6.85. $C_{22}H_{26}O_6N_2$ requires C, 63.45; H, 6.8%).

2-Oxoclovan-9 β -yl 3:5-Dinitrobenzoate.—9 β -Hydroxyclovan-2-one was prepared from *isocaryophyllene oxide* according to Aebi, Barton, and Lindsey (*loc. cit.*). The derived 3:5-*dinitrobenzoate* had m. p. 191—192° [from benzene—light petroleum (b. p. 60—80°)], $[\alpha]_D +33^\circ$ (*c*, 1.07) (Found: C, 61.9; H, 6.2; N, 6.85. $C_{22}H_{26}O_7N_2$ requires C, 61.4; H, 6.1; N, 6.5%).

Clovenic Anhydride and its Derivatives.—The anhydride (Ruzicka and Gibson, *Helv. Chim. Acta*, 1931, 14, 570) had m. p. 50° [from light petroleum (b. p. 40—60°)], $[\alpha]_D -11^\circ$ (*c*, 2.84). 6 α -Hydroxyclovenic acid (Aebi, Barton, Burgstahler, and Lindsey, *loc. cit.*) on acetylation in the usual way (see above) gave 6 α -*acetoxyclovenic anhydride*, needles (from cold aqueous methanol), m. p. 114—115°, $[\alpha]_D -58^\circ$ (*c*, 0.84) (Found: C, 66.05; H, 7.8. $C_{17}H_{24}O_5$ requires C, 66.2; H, 7.85%).

1-Hydroxycaryolan-9 β -yl Benzoate.—Caryolane-1:9 β -diol was prepared according to Treibs (*Chem. Ber.*, 1947, 80, 56). The 9 β -*benzoate* had m. p. 130—131° (from aqueous methanol), $[\alpha]_D +24^\circ$ (*c*, 1.06) (Found: C, 76.8; H, 9.05. $C_{22}H_{30}O_3$ requires C, 77.15; H, 8.85%). The 3:5-*dinitrobenzoate* [from benzene—light petroleum (b. p. 60—80°)] had m. p. 201—202°, $[\alpha]_D +20^\circ$ (*c*, 1.05) (Found: C, 60.7; H, 6.4. $C_{22}H_{28}O_7N_2$ requires C, 61.1; H, 6.55%).

Caryolane-1:9 α -diol and its Derivatives.—The diol was prepared according to Aebi, Barton, Burgstahler, and Lindsey (*loc. cit.*). The derived 9 α -*acetate* (needles from light petroleum (b. p. 40—60°)) had m. p. 102—103°, $[\alpha]_D -16^\circ$ (*c*, 1.07) (Found: C, 72.85; H, 9.95. $C_{17}H_{28}O_3$ requires C, 72.8; H, 10.05%). The corresponding *benzoate* had m. p. 157—158° (from aqueous methanol), $[\alpha]_D -32^\circ$ (*c*, 1.02) (Found: C, 77.4; H, 8.95. $C_{22}H_{30}O_3$ requires C, 77.15; H, 8.85%).

Derivatives of the Hydroxy-ketone (VIII).—The hydroxy-ketone (Barton and Lindsey, *J.*, 1951, 2988) gave an *acetate*, m. p. 57—58° (from aqueous methanol), $[\alpha]_D -17^\circ$ (*c*, 1.07) (Found: C, 72.85; H, 9.3. $C_{16}H_{24}O_3$ requires C, 72.7; H, 9.15%). The corresponding *benzoate* (from aqueous methanol) had m. p. 98—99°, $[\alpha]_D -52^\circ$ (*c*, 1.74) (Found: C, 77.05; H, 8.05. $C_{21}H_{28}O_3$ requires C, 77.25; H, 8.05%). The dinitrobenzoate, already described by Barton and Lindsey (*loc. cit.*), had $[\alpha]_D -50^\circ$ (*c*, 1.76).

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