UTILIZATION OF PROTOPINE AND RELATED ALKALOIDS. XVIII.[1] SOME REACTIONS OF ANHYDROISODIHYDROCORYCAVIDINE AND ITS N-OXIDE

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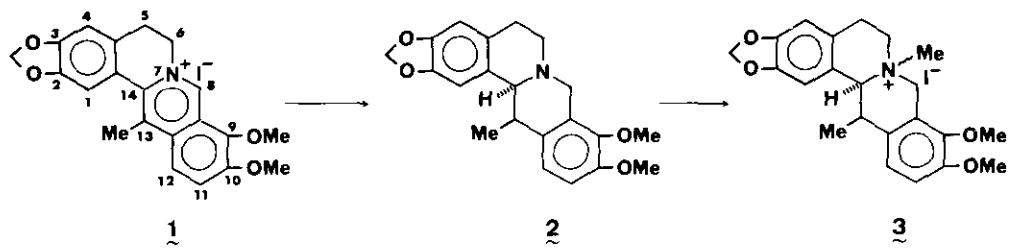
Abstract —— Hydroxylation of anhydroisodihydrocorycavidine 4 with osmium tetroxide affords the α-glycol 7 and the 13,14-seco keto aldehyde 8. Treatment of the N-oxide 6 with acetic anhydride/acetic acid gives the 7,8-seco diacetate 10 and the indene acetate 11. The formation paths to these products are briefly discussed.

The total synthesis of protopines via the transannular rearrangement of 7-methyl-5,6,7,8-tetrahydrodibenz(c,g)azecine N-oxides was achieved by Perkin et al.[2] Subsequently, several protopines were synthesized according to this method by other groups.[3] We now report the interesting findings obtained from a study on the reactions of a 7,13-dimethyl-5,6,7,8-tetrahydrodibenz(c,g)azecine, anhydroisodihydrocorycavidine, and its N-oxide.

Preparation of Anhydroisodihydrocorycavidine 4 and Its N-Oxide 6

Sodium borohydride reduction of 13-methylberberinium iodide 1, which was readily derived from berberinium chloride,[4] gave (±)-thalictricavine 2 (86%). The stereochemistry (trans ring juncture and 13ax-Me) of 2 was confirmed by means of spectroscopy (IR, 2800, 2768, 2752 cm^{-1} (Bohlmann bands); ^{1}H-NMR, $J_{13,14}$ 3.5 Hz). Treatment of 2 with methyl iodide afforded the methiodide 3 (82%) as a mixture of the α- and the β-isomers. The isomer ratio of 1/1 was assessed on the basis of the 13-methyl signal intensity in the ^{1}H-NMR spectrum.

Hofmann degradation of 3 afforded anhydroisodihydrocorycavidine 4 (75%) and 3,4-dihydro-4-methylanhydromethylberberine 5 (6%). The ^{1}H-NMR spectrum of 4 showed an olefinic proton (14-H) as a singlet (δ 6.44), and that of 5 revealed three



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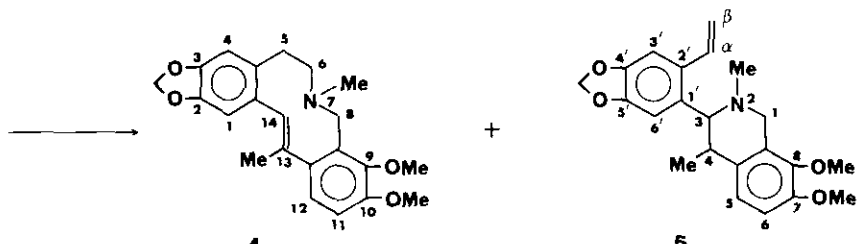

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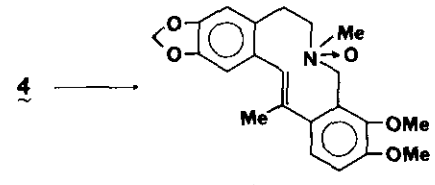

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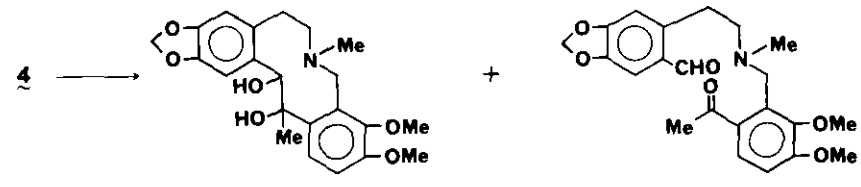


7 8

Chart 1

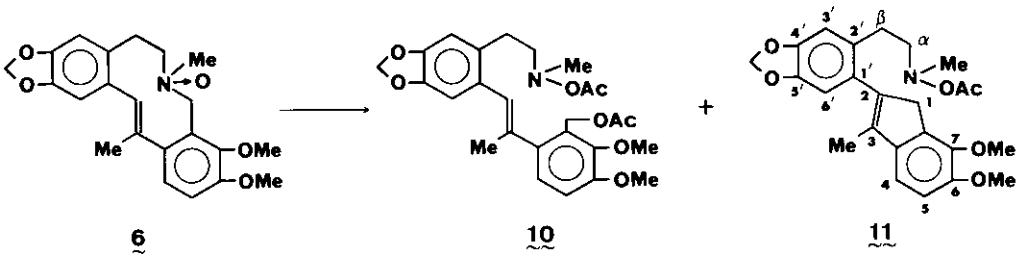
olefinic protons (α-H and β-H_2) as three double doublets (δ 7.05, 5.42, 5.15, $J_{\alpha,\beta}$ 17.5, 11 Hz, $J_{\beta,\beta}$ 1 Hz). Oxidation of 4 with m-chloroperbenzoic acid gave the N-oxide 6 (67%) which was characterized by the ^{1}H-NMR spectrum showing the presence of an olefinic proton (δ 6.22, s, 14-H) and a down-field shift of the 7-methyl group ($\Delta\delta_{6-4}$=1.28 ppm).

Reactions of 4 and 6

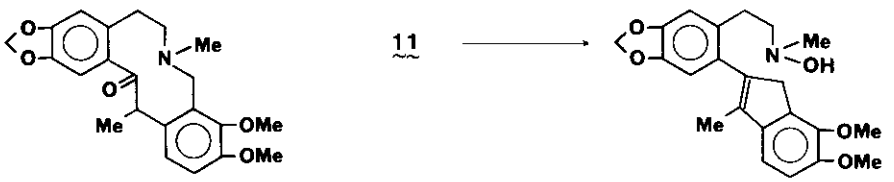
Hydroxylation of 4 with osmium tetroxide/D-mannitol gave the α-glycol 7 (47%) (IR, 3580, 3400 cm^{-1}) and the 13,14-seco keto aldehyde 8 (18%) (IR, 1690, 1678 cm^{-1}). The ^{1}H-NMR spectrum of 7 indicated two signals for each proton, suggesting the existence of two isomers. The isomer ratio of 12/1 was assessed on the basis of the 2,3-methylenedioxy signal intensity in the ^{1}H-NMR spectrum, and the major one would correspond to the 13R*,14R*-configuration.[5] The use of sodium sulfite instead of D-mannitol provided 8 (39%) as a sole product. An attempt to dehydrate 7 in the presence of p-toluenesulfonic acid or 4A molecular sieve was unsuccessful, and instead, 8 (58%) was obtained as a sole product. The formation of 8 is considered to be a result of a retro-pinacol formation of 7 caused by air oxidation.

On acid treatment (HCl/AcOH),[2,3] 6 did not rearrange to give corycavidine 9 and gave a number of unidentified products. On the other hand, treatment of 6 with acetic anhydride/acetic acid afforded the 7,8-seco diacetate 10 (26%) and the indene acetate 11 (25%). The ^{1}H-NMR spectrum of 10 showed the existence of an olefinic proton (δ 6.29, q, J 1 Hz, 14-H) long-range coupled to a methyl group (δ 1.94, d, J 1 Hz, 13-Me) in addition to two acetoxy groups (δ 2.01, 1.93, 7- and 8-OAc's). The ^{1}H-NMR spectrum of 11 indicated the presence of an acetoxy group (δ 1.75, N-OAc), and no olefinic proton signal was observed. On lithium aluminum hydride reduction, 11 was converted into the hydroxylamine 12 (56%) in which no acetoxy signal was observed in the ^{1}H-NMR spectrum.

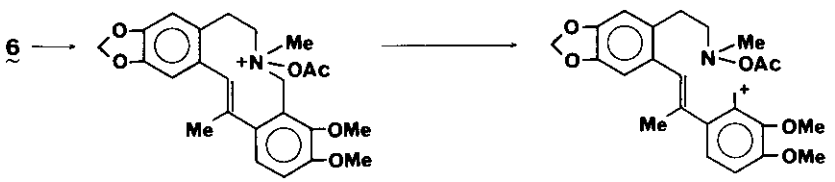
Since 10 was not converted into 11 under the same reaction conditions as above, the formation paths to 10 and 11 are considered as follows. The ammonium ion 13, which is derived from 6 by acetylation, is converted into the cation 14 by the cleavage of 7,8-bond, and 14 competitively affords 10 and 11. Alternative path to 10 *via* the attack of acetoxy group upon the 8-position in 13 cannot be ruled out.



6 10 11



9 12



13 14

10 10 + 11

Chart 2

EXPRIMENTAL

Melting points are uncorrected. Spectral data were recorded on the following spectrometers: IR, Hitachi 260-30; ^{1}H-NMR, Varian EM-390 (90 MHz) and XL-400 (400 MHz); MS, JEOL JMS DX-300.

(±)-Thalictricavine 2

A mixture of 1 (202.3 mg) and $NaBH_4$ (90 mg) in anhydrous ethanol (5 ml) was refluxed for 2 h, and water (1 ml) was added. The precipitate was collected and recrystallized from ethanol/water to yield 2 (127.9 mg, 86%) as colorless needles of mp 220-223°C (lit.,[6,7] mp 205-207 and 211.5-212.5°C). IR ($CHCl_3$): 2800, 2768, 2752 cm^{-1} (Bohlmann bands). ^{1}H-NMR (90 MHz) ($CDCl_3$) δ: 6.87, 6.76 (each 1H, d, J 9 Hz, 11- and 12-H's), 6.65, 6.55 (each 1H, s, 1- and 4-H's), 5.89 (2H, s, 2,3-OCH_2O), 4.16, 3.46 (each 1H, d, J 16 Hz, 8-H_2), 3.84 (6H, s, 9- and 10-OMe's), 3.64 (1H, d, J 3.5 Hz, 14-H), 3.32-2.40 (5H, m, 5-, 6-H_2's and 13-H), 0.95 (3H, d, J 7 Hz, 13-Me). MS Calcd for $C_{21}H_{23}NO_4$: M, 353.163. Found m/z: M^+, 353.163.

(±)-Thalictricavine Methiodide 3

A mixture of 2 (503.6 mg) and methyl iodide (2 ml) was heated at 90°C in a sealed tube for 4 h. The precipitate was collected and recrystallized from ethanol to yield 3 (576.2 mg, 82%) as colorless needles of mp 255-257°C (dec.) (lit.,[6] mp 244°C (dec.)). This compound consists of two isomers. ^{1}H-NMR (90 MHz) ($CDCl_3$) δ: 7.07, 6.93 (1H, each d, J 9 Hz), 6.91 (1H, s) (11- and 12-H's), 6.75, 6.65 (2H, each s, 1- and 4-H's), 5.94 (2H, s, 2,3-OCH_2O), 5.47 (1H, d, J 4 Hz, 14-H), 5.22, 5.11 (1H, each d, J 7 Hz), 5.09 (1H, s) (8-H_2), 4.47-2.74 (5H, m, 5-, 6-H_2's and 13-H), 3.87, 3.80 (each 3H, s, 9- and 10-OMe's), 3.63, 3.11 (each 3H, s, 7-Me), 1.29, 0.94 (each 3H, s, 13-Me). Anal. Calcd for $C_{22}H_{26}INO_4$: C, 53.34; H, 5.29; N, 2.83. Found: C, 53.40; H, 5.25; N, 2.77.

Anhydroisodihydrocorycavidine 4 and 3,4-Dihydro-4-methylanhydromethylberberine 5

A mixture of 3 (300 mg) and Ag_2O, which was obtained from $AgNO_3$ (230 mg), in methanol (10 ml) was stirred at room temperature for 2 h. The reaction mixture was filtered, and the filtrate was concentrated in vacuo. The oily residue was heated at 100°C in vacuo for 1 h, and the resulting solid was recrystallized from methanol to yield 4 (166.9 mg, 75%) as colorless needles of mp 176-179°C (lit.,[8] mp 162-163°C). ^{1}H-NMR (90 MHz) ($CDCl_3$) δ: 6.97, 6.72 (each 1H, d, J 9 Hz, 11-

and 12-H's), 6.75, 6.66 (each 1H, s, 1- and 4-H's), 6.44 (1H, s, 14-H), 5.91 (2H, s, 2,3-OCH_2O), 3.85 (3H, s, 9- or 10-OMe), 3.62 (5H, s, 8-H_2 and 10- or 9-OMe), 2.66 (4H, br s, 5- and 6-H_2's), 2.13 (3H, s, 7-Me), 1.75 (3H, s, 13-Me). NOE: 13-Me —— 14-H (0%). MS Calcd for $C_{22}H_{25}NO_4$: M, 367.178. Found m/z: M^+, 367.178.

The mother liquor from the recrystallization was concentrated in vacuo, and preparative TLC (alumina, $CHCl_3$) of the residue gave 5 (13 mg, 6%) as a colorless oil, Rf 0.32. IR ($CHCl_3$): 2788, 2776 cm^{-1} (Bohlmann bands). ^{1}H-NMR (90 MHz) ($CDCl_3$) δ: 7.05 (1H, dd, J 17.5, 11 Hz, α-H), 6.81, 6.75 (each 2H, s, 5-, 6- and 3'-, 6'-H's), 5.90 (2H, s, 4',5'-OCH_2O), 5.42 (1H, dd, J 17.5, 1 Hz), 5.15 (1H, dd, J 11, 1 Hz) (β-H_2), 4.16, 3.44 (each 1H, d, J 16.5 Hz, 1-H_2), 3.91 (1H, d, J 4.5 Hz, 3-H), 3.84 (6H, s, 7- and 8-OMe's), 3.10 (1H, m, 4-H), 2.27 (3H, s, 2-Me), 1.02 (3H, d, J 7 Hz, 4-Me). MS Calcd for $C_{22}H_{25}NO_4$: M, 367.178. Found m/z: M^+, 367.179.

Anhydroisodihydrocorycavidine N-Oxide 6

A solution of 4 (63.4 mg) in chloroform (0.3 ml) was added to a solution of m-chloroperbenzoic acid (43 mg) in ether (8 ml), and the whole was stirred at −15°C for 20 h. The precipitate was collected and recrystallized from chloroform/ether to yield 6 (44.7 mg, 67%) as colorless needles of mp 198–202°C. ^{1}H-NMR (90 MHz) ($CDCl_3$) δ: 7.03 (2H, s, 11- and 12-H's), 6.77, 6.65 (each 1H, s, 1- and 4-H's), 6.22 (1H, s, 14-H), 5.94 (2H, s, 2,3-OCH_2O), 4.88 (2H, s, 8-H_2), 3.90, 3.88 (each 3H, s, 9- 10-OMe's), 3.88–3.52, 3.35–3.05 (each 2H, m, 5- and 6-H_2's), 3.41 (3H, s, 7-Me), 1.95 (3H, s, 13-Me). MS Calcd for $C_{22}H_{25}NO_5$: M, 383.173. Found m/z: M^+, 383.174.

13-Hydroxydihydrocorycavidine 7 and 13-Oxo-13,14-secocorycavidine 8

a) A solution of 4 (75 mg) in anhydrous benzene (5 ml) was added to a mixture of OsO_4 (65 mg) and anhydrous pyridine (6 drops) in anhydrous benzene (5 ml), and the whole was stirred at room temperature for 18 h. The precipitate was collected and dissolved in chloroform (10 ml). A mixture of D-mannitol (2 g) and KOH (400 mg) in water (20 ml) was added to the above chloroform solution, and the whole was stirred at room temperature for 1 h. The organic phase was washed with water and dried over Na_2SO_4. Removal of the solvent in vacuo and preparative TLC (alumina, $CHCl_3$) of the residue gave 7 (38.4 mg, 47%), Rf 0.45 and 8

(14.6 mg, 18%), Rf 0.74.

α-Glycol 7: A colorless oil. This compound consists of two isomers. IR ($CHCl_3$): 3580, 3400 cm^{-1} (OH). ^{1}H-NMR (90 MHz) ($CDCl_3$) δ[9]: 7.11 (6.88) (1H, each d J 9 Hz), 6.81 (6.61) (1H, each d, J 9 Hz) (11- and 12-H's), 6.71 (6.68) (1H, each s), 6.53 (6.42) (1H, each s) (1- and 4-H's), 5.89 (5.86) (2H, each s, 2,3-OCH_2O), 4.79 (4.69) (1H, each s, 14-H), 4.02 (3.66) (1H, each d, J 14 Hz), 3.82 (3.53) (1H, each d, J 14 Hz) (8-H_2), 3.87 (3.79) (3H, each s), 3.75 (3.67) (3H, each s) (9- and 10-OMe's), 2.90–2.00 (6H, m, 5-, 6-H_2's and 13-, 14-OH's exchangeable with D_2O), 2.18 (2.28) (3H, each s, 7-Me), 1.84 (1.64) (3H, each s, 13-Me); δ5.89/δ5.86=12/1. MS Calcd for $C_{22}H_{27}NO_6$: M, 401.184. Found m/z: M^+, 401.185.

13,14-Seco Keto Aldehyde 8: A colorless oil. IR ($CHCl_3$): 1690, 1678 cm^{-1} (C=O). ^{1}H-NMR (90 MHz) ($CDCl_3$) δ: 10.03 (1H, s, 14-H), 8.76 (1H, d, J 9 Hz, 12-H), 7.25 (1H, s, 1-H), 7.13 (1H, d, J 9 Hz, 11-H), 6.65 (1H, s, 4-H), 5.97 (2H, s, 2,3-OCH_2O), 3.97, 3.70 (each 1H, d, J 17 Hz, 8-H_2), 3.87, 3.74 (each 3H, s, 9- and 10-OMe's), 3.23–2.86 (2H, m), 2.68–2.30 (2H, m) (5- and 6-H_2's), 2.39 (3H, s, 7-Me), 2.21 (3H, s, 13-Me). MS Calcd for $C_{22}H_{25}NO_6$: M, 399.168. Found m/z: M^+, 399.166.

b) A solution of 4 (76.3 mg) in anhydrous benzene (7 ml) was added to a mixture of OsO_4 (88 mg) and anhydrous pyridine (5 drops) in anhydrous benzene (5 ml), and the whole was stirred at room temperature for 16 h. The precipitate was collected and dissolved in ethanol (20 ml). A solution of Na_2SO_3 (1 g) in water (8 ml) was added to the above ethanol solution, and the whole was refluxed for 3.5 h. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was extracted with chloroform. Work-up of the organic phase gave 8 (32.6 mg, 39%) as a colorless oil.

Formation of 8 from 7

a) A mixture of 7 (20.3 mg) and p-toluenesulfonic acid (5 mg) in anhydrous benzene (1 ml) was refluxed for 7 h. The organic phase was washed with 5% aqueous $NaHCO_3$ and water, and then dried over Na_2SO_4. Removal of the solvent *in vacuo* and preparative TLC (alumina, $CHCl_3$) of the residue gave 8 (14.7 mg, 73%) as a colorless oil, Rf 0.74.

b) A mixture of 7 (12.7 mg) and 4A molecular sieve 1/16-in. pellets (154 mg) in anhydrous toluene (3 ml) was refluxed for 3 h. Work-up of the reaction mixture

gave 8 (7.3 mg, 58%) as a colorless oil, and unreacted 7 (3.1 mg, 24%) was recovered.

7,8-Diacetoxy-7,8-secoanhydroisodihydrocorycavidine 10 and 2-2'-N-Acetoxy-N-methylaminoethyl-4',5'-methylenedioxyphenyl-6,7-dimethoxy-3-methylindene 11

A mixture of 6 (20 mg) and acetic anhydride (0.1 ml) in acetic acid (0.4 ml) was stirred at 55°C for 3.5 h. The reaction mixture was concentrated in vacuo, and preparative TLC (alumina, benzene/$CHCl_3$=1/1) of the residue gave 10 (6.5 mg, 26%), Rf 0.20 and 11 (5.4 mg, 25%), Rf 0.31.

7,8-Seco Diacetate 10: Colorless prisms of mp 98–100°C ($CHCl_3$/hexane). IR ($CHCl_3$): 1741 cm^{-1} (OC=O). ^{1}H-NMR (90 MHz) ($CDCl_3$) δ: 6.94 (2H, s, 11- and 12-H's), 6.74, 6.69 (each 1H, s, 1- and 4-H's), 6.29 (1H, q, J 1 Hz, 14-H), 5.92 (2H, s, 2,3-OCH_2O), 5.18 (2H, s, 8-H_2), 3.87 (6H, s, 9- and 10-OMe's), 2.81 (4H, m, 5- and 6-H_2's), 2.74 (3H, s, 7-Me), 2.01, 1.93 (each 3H, s, 7- and 8-OAc's), 1.94 (3H, d, J 1 Hz, 13-Me). Decoupling: 14-H ⟶ 13-Me (d ⟶ s). MS Calcd for $C_{26}H_{31}NO_8$: M, 485.205. Found m/z: M^+, 485.205.

Indene Acetate 11: A colorless oil. IR ($CHCl_3$): 1742 cm^{-1} (OC=O). ^{1}H-NMR (400 MHz) ($CDCl_3$) δ: 6.98, 6.91 (each 1H, d, J 8 Hz, 4- and 5-H's), 6.77, 6.63 (each 1H, s, 3'- and 6'-H's), 5.95 (2H, s, 4',5'-OCH_2O), 3.95, 3.90 (each 3H, s, 6- and 7-OMe's), 3.59 (2H, q, J 2 Hz, 1-H_2), 2.90, 2.70 (each 2H, m, α- and β-H_2's), 2.67 (3H, s, N-Me), 1.91 (3H, t, J 2 Hz, 3-Me), 1.75 (3H, s, N-OAc). Decoupling: 1-H_2 ⟶ 3-Me (t ⟶ s). MS Calcd for $C_{24}H_{27}NO_6$: M, 425.185. Found m/z: M^+, 425.184.

6,7-Dimethoxy-2-2'-N-hydroxy-N-methylaminoethyl-4',5'-methylenedioxyphenyl-3-methylindene 12

A mixture of 11 (5 mg) and $LiAlH_4$ (1 mg) in anhydrous ether/anhydrous tetrahydrofuran (3/1) (3 ml) was stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuo, and water (2 ml) was added. The mixture was extracted with chloroform. Work-up of the organic phase and preparative TLC (alumina, $CHCl_3$/MeOH=100/1) of the products afforded 12 (2.5 mg, 56%) as colorless prisms of mp 102–104°C ($CHCl_3$/hexane), Rf 0.44. IR ($CHCl_3$): 3450 cm^{-1} (OH). ^{1}H-NMR (400 MHz) ($CDCl_3$) δ: 6.99, 6.92 (each 1H, d, J 8 Hz, 4- and 5-H's), 6.80, 6.62 (each 1H, s, 3'- and 6'-H's), 5.95 (2H, s, 4',5'-OCH_2O), 3.96, 3.91 (each 3H, s, 6- and 7-OMe's), 3.61 (2H, q, J 2 Hz, 1-H_2), 2.78 (4H, m, α- and β-H_2's), 2.60

(3H, s, N-Me), 1.93 (3H, t, J 2 Hz, 3-Me), 1.60 (1H, s, N-OH exchangeable with D_2O). MS Calcd for $C_{22}H_{25}NO_5$: M, 383.173. Found m/z: M^+, 383.172.

REFERENCES AND NOTES

1. Part XVII: H. Takahashi, M. Iguchi, and M. Onda, Chem. Pharm. Bull., 1985, 33, 4775.
2. R. D. Haworth and W. H. Perkin, Jr., J. Chem. Soc., 1926, 445; R. D. Haworth, W. H. Perkin, Jr., and T. S. Stevens, ibid., 1926, 1769.
3. P. B. Russell, J. Am. Chem. Soc., 1956, 78, 3115; D. Giacopello, V. Deulofeu, and J. Comin, Tetrahedron, 1964, 20, 2971; D. Giacopello and V. Deulofeu, ibid., 1967, 23, 3265; R. M. Sotelo and D. Giacopello, Aust. J. Chem., 1972, 25, 385.
4. M. Onda, K. Yuasa, J. Okada, K. Kataoka (nee Yonezawa), and K. Abe, Chem. Pharm. Bull., 1973, 21, 1333.
5. The stereochemistry of osmium tetroxide hydroxylation is generally cis. The 13R*,14R*-configuration corresponds to the structure resulted from the cis addition.
6. C. Tani, N. Takao, S. Takao, and K. Tagahara, Yakugaku Zasshi, 1962, 82, 751.
7. T. Takemota and Y. Kondo, Yakugaku Zasshi, 1962, 82, 1408.
8. F. V. Bruchhausen, Arch. Pharm., 1925, 263, 570.
9. The chemical shifts shown in the square brackets correspond to those of the protons in the minor isomer.

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