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STRUCTURE AND ABSOLUTE STEREOCHEMISTRY OF VANILLOSMIN, A GUAIANOLIDE FROM *VANILLOSMOPSIS ERYTHROPAPPA*

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Abstract—The structure and absolute stereochemistry of vanillosmin were established by chemical and spectral evidence and by comparison with *O*-acetyl-isophoto-α-santonic lactone and tetrahydroartabsin "C".

INTRODUCTION

THE ESSENTIAL oil from the wood of *Vanillosmopsis erythropappa* Sch.-Bip. (Compositae),[1] contains (−)α-bisabolol, accompanied by small amounts of β-bisabolene and isovaleric acid.[2] More recently, Gilbert *et al.*[3] reported that this oil displays schistosomicidal activity.

We have examined the acetone extract of the same wood and isolated in high yield, besides the above mentioned compounds, a new sesquiterpenoid, which we named vanillosmin (**1**).* In this paper we report the determination of its structure and assign absolute configuration to all the asymmetric centers present in the molecule (C-1, C-5, C-6, and C-7).

* A preliminary communication of this finding was presented at the 7th Int. Symp. on the Chemistry of Natural Products, Riga 1970 (Communication E-10). Very recently, W. Vichnewski and B. Gilbert[4] isolated a compound from *Eremanthus elaeagnus*, which they named eremanthine and for which they proposed a structure identical with that of vanillosmin, except for the configuration at C-1 which was unspecified. The reported PMR, MS and IR data of eremanthine closely resemble those of vanillosmin, whereas the m.p. and particularly the optical rotation are different.

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[2] GOTTLIEB, O. R. and MAGALHÃES, M. T. (1958) *Perfumery Essential Oil Record* **49**, 711; *Chem. Abstr.* **53**, 10667.
[3] GILBERT, G., DE SOUZA, J. P., FASCIO, M., KITAGAWA, M., NASCIMENTO, S. S. C., FORTES, C. C., DO PRADO SEABRA, A. and PELLEGRINO, J. (1970) *Anais Acad. Bras. Ciências* **42** supl. 397.
[4] VICHNEWSKI, W. and GILBERT, B. (1972) *Phytochemistry* **11**, 2563.

Vanillosmin belongs to the guaianolides, many of which have a double bond or an oxygen function at C-1 or C-5. Only a limited number bear two hydrogens in these positions, such as estafiatin, the zaluzanins, ligustrin and the cumambrins,[5] the lipidiols,[6] grosheimin,[6-8] cynaropicrin and isoamberboin,[7] and viscidulin.[9] The determination of the geometry of the ring junction is essential in order to understand the way in which an acyclic precursor undergoes cyclization in the biosynthesis of guaianolides.[10] In the past, this problem has been examined only by physico-chemical methods which have given rise, in many cases, to ambiguities.[11] More recently, X-ray analysis[12-14] and chemical correlation[7-9] have clearly shown that in all the known guaianolides the hydrogens at C-1 and C-5 are in the α position, the only exceptions being centaurepensin,[13] in which they are both β, and gaillardin,[14] which is, to our knowledge, the only guaianolide having the two hydrogens of the junction in a *trans* relationship, 1-β and 5-α.*

RESULTS AND DISCUSSION

Structure of Vanillosmin

Vanillosmin (**1**), a crystalline compound m.p. 62–62·5°, has the molecular formula $C_{15}H_{18}O_2$ as shown by elemental analysis and MS (M^+ 230 *m/e*). It exhibits absorption bands at 1755, 1655, 895 and 820 cm^{-1} in the IR spectrum and a maximum at 218 nm in the UV, typical of a γ-lactone ring conjugated with an exocyclic methylene. The presence of two vinyl protons β to a carbonyl group is confirmed by the PMR spectrum which displays two doublets at 6·18 and 5·48δ (1H each, *J* 3·2 Hz); the protons of a second non conjugated exocyclic methylene resonate at 5·22 and 5·04δ as two one-proton broad signals. Other resonances in the spectrum are in keeping with the presence of a vinyl proton (5·58δ, 1H, *m*), a vinyl methyl (1·82δ, 3H *b s*) and a proton on a carbon bearing an acyloxy group, coupled with two other separate protons (3·93δ, 1H, *t*, *J* 9·5 Hz).

$NaBH_4$ reduction of vanillosmin (**1**) under mild conditions and for a short time affords a dihydroderivative $C_{15}H_{20}O_2$ (**4**). Only the conjugated double bond is reduced and the reaction is highly stereospecific;[6,7,15] the compound (**4**) lacks any absorption above

* We thank the Referee who informed us that, after the mailing of this note, a paper appeared where the structure of two new guaianolides with *trans* ring junction is proposed mainly on the basis of NMR analysis (FURUKAWA, H., LEE, K. H., SHINGU, T., MECK, R. and PIANTADOSI, C. (1973) *J. Org. Chem.* **38,** 1722).

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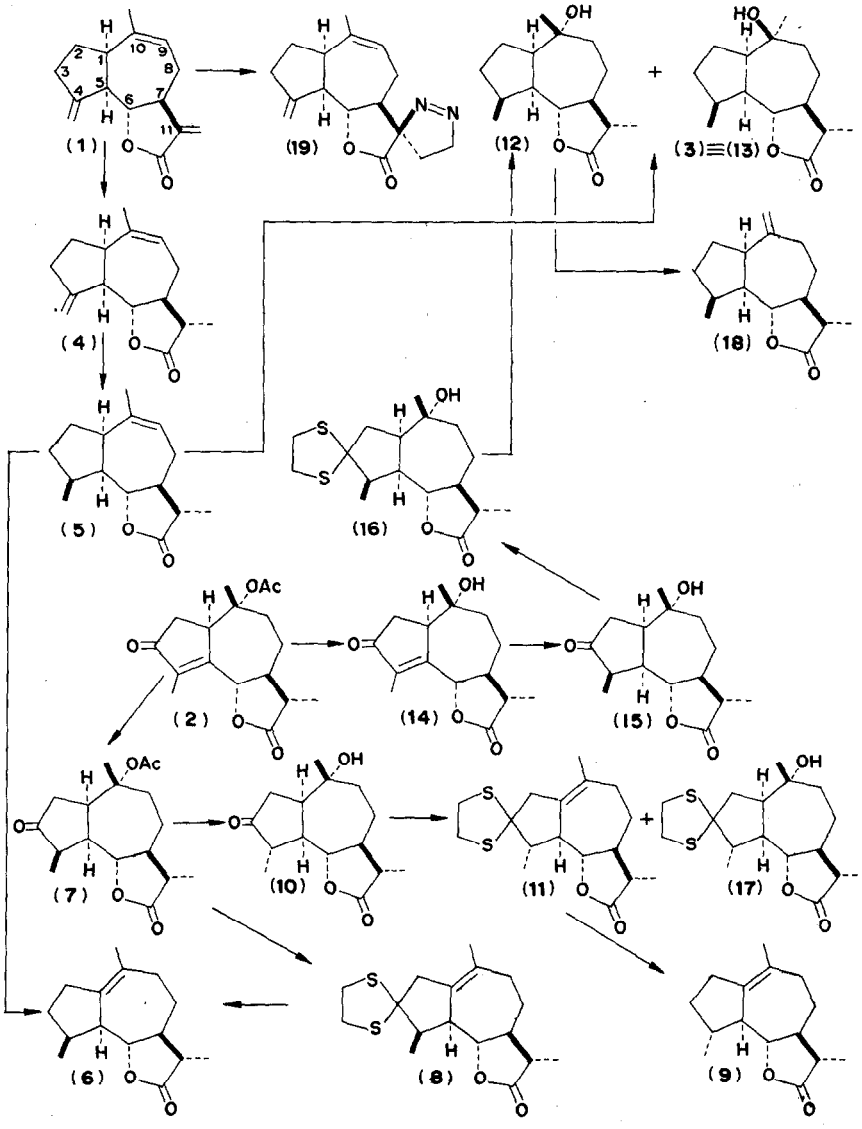

205 nm in the UV, whereas in the IR spectrum shows the absorption bands of a saturated γ-lactone at 1770 cm^{-1} and of double bonds at 1660 and 895 cm^{-1}. Comparison of the PMR spectrum of (**4**) with that of (**1**) shows that the signals at 6·18 and 5·48δ are replaced by a new three proton doublet at 1·22δ (J 6 Hz), thus indicating the presence of a secondary methyl group.

Reduction of dihydrovanillosmin (**4**) with H_2 in the presence of Wilkinson's soluble catalyst[16] affords tetrahydrovanillosmin (**5**), $C_{15}H_{22}O_2$, an oily compound derived from saturation of the exocyclic double bond. Spectral data are in agreement with the structure (**5**): a band at 1650 cm^{-1} in the IR clearly indicates that a double bond is still present in

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the molecule; in the PMR a new doublet at 1·15δ (J 6 Hz) attributable to a secondary methyl replaces the signals of the two vinyl protons at 5·22 and 5·04δ in the spectrum of (**1**), whereas the signals of the vinyl methyl and vinyl proton are unchanged. This hydrogenation is highly stereospecific; GC–MS examination of the crude reaction mixture shows that only traces of the epimer at C-4 are formed during the reaction.

The three products, (**1**), (**4**) and (**5**) are very sensitive to light and heat; they must be stored in the dark and below 0 °, or insoluble polymeric substances are formed.

Treatment of (**5**) with H_2 in EtOAc in the presence of Pd/C results in the isomerization of the double bond to the tetrasubstituted position: the main product of the reaction is isotetrahydrovanillosmin (**6**), together with very small amounts of hexahydroderivatives of (**1**).

Structure and absolute stereochemistry of isotetrahydrovanillosmin

Isotetrahydrovanillosmin (**6**), $C_{15}H_{22}O_2$, is a crystalline compound; in its PMR spectrum there are no more signals attributable to vinyl protons, but the broad singlet of a vinyl methyl at 1·75δ and the doublets of two secondary methyls at 0·92 and 1·22δ are still present.

Hydrogenation under pressure of *O*-acetyl-isophoto-α-santonic lactone (**2**)[17] in anhydrous ethanol and in the presence of Pd/C affords in good yield the dihydroderivative (**7**) of known absolute stereochemistry.[18] On treatment of (**7**) with 1,2-ethanedithiol and BF_3–Et_2O, the thioacetal (**8**) is formed with elimination of acetic acid. Reductive removal of the thioacetal group of (**8**) with Raney–Nickel affords a crystalline compound identical in all respects with isotetrahydrovanillosmin (**6**).[19]

To ensure that the acidic treatment of (**7**) has not affected the configuration of the methyl group at C-4, which is known to be more stable in the α than in the β position,[18,20] we prepared the C-4 epimer of (**6**). Alkaline treatment of *O*-acetyl-dihydroisophoto-α-santonic lactone (**7**) gives (**10**) as a consequence of hydrolysis of the acetate and epimerization at C-4. Thioacetalization of (**10**) yields two products in comparable amounts: one (**17**) still bears he tertiary hydroxyl, the other (**11**) has lost a molecule of water. Desulphurization of (**11**) affords a crystalline substance (**9**), which is different from isotetrahydrovanillosmin (**6**) and has recently been prepared also by Šorm *et al.*[21] in a similar way.

The described correlation confirms the structure proposed for isotetrahydrovanillosmin (**6**) and establishes the absolute configuration at C-5, C-6 and C-7 of vanillosmin as shown in (**1**).

Absolute configuration at C-1 of vanillosmin

The reaction of oxymercuration-demercuration according to Brown[22] on tetrahydrovanillosmin (**5**) affords two isomeric hydroxy-lactones (**12**) and (**13**) in a molar ratio 1:12. The less abundant of these hydroxy-lactones, (**12**), is a crystalline compound, m.p. 127°, with a molecular formula $C_{15}H_{24}O_3$, as shown by elemental analysis and MS. The IR spectrum indicates the presence in its molecule of an hydroxyl (3590 cm^{-1}) and a γ-lactone

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(1762 cm^{-1}). The tertiary nature of the hydroxyl is supported by the PMR spectrum which displays, besides the signals of two secondary methyls at 0·92 and 1·20δ, a singlet for a tertiary methyl bound to an oxygen bearing carbon (1·22δ). The structure of (**12**) has been unambiguously established by the following synthesis.

Alkaline hydrolysis of (**2**) gives isophoto-α-santonic lactone (**14**)[17] accompanied by small amounts of an isomeric substance whose spectral data suggest epimerization at C-1. Catalytic hydrogenation under pressure converts (**14**) into its dihydroderivative (**15**)[20] in high yields; treatment of the latter with ethanedithiol and BF_3–Et_2O at low temperature to avoid dehydration of the tertiary alcohol, affords the thioacetal (**16**), $C_{15}H_{26}O_3S_2$, a crystalline compound, m.p. 220–222°. After reduction of (**16**) with Raney–Nickel, a product identical with the hydroxylactone (**12**) derived from tetrahydrovanillosmin (**5**) is obtained. Recently, Šorm *et al.*[21] obtained the same compound as a by-product of the hydrogenation of (**14**) over palladium catalyst.

The most abundant product of the oxymercuration–demercuration reaction on tetrahydrovanillosmin (**5**) is the hydroxy-lactone (**13**), a crystalline compound, m.p. 136°, which is the C-10 epimer of (**12**), according to its analytical data. In the IR spectrum, the absorption band at 1740 cm^{-1} indicates that the carbonyl of the γ-lactone is hydrogen bonded with the tertiary hydroxyl; the PMR spectrum is very similar to the one of (**12**) showing the presence of two secondary methyls (0·93 and 1·20δ) and one tertiary methyl on oxygen bearing carbon (1·21δ). To ensure that the configuration at C-10 is the only difference between (**12**) and (**13**), the former was dehydrated with thionyl chloride and pyridine at −20°. The anhydroderivative (**18**) exhibits two bands at 1640 and 900 cm^{-1} in the IR attributable to an exocyclic methylene; in the PMR spectrum, the resonances of the two secondary methyls at C-4 and C-11 appear at the usual chemical shift, whereas two vinyl protons resonate as a broad singlet at 4·97δ. Oximercuration–demercuration reaction on (**18**) affords as the main product a crystalline compound identical in all its physico-chemical properties with the hydroxy-lactone (**13**).

Furthermore, the identity of (**13**) with tetrahydroartabsin "C", one of the isomers obtained on catalytic hydrogenation of artabsin,[23] has been established by direct comparison.

The above described results demonstrate that the hydrogen at C-1 of vanillosmin has an α-configuration and, consequently, the absolute stereochemistry of the compound has to be as in (**1**).

The CD of vanillosmin (**1**) shows a negative band at 253 nm ($\Delta\epsilon$ −1·0) which corresponds to the $n \rightarrow \pi^*$ transition of the α-methylene-γ-lactone; CD curves of its pyrazoline derivative (**19**) displays a strong positive azo-band Cotton effect at 327 nm ($\Delta\epsilon$ +15·5) besides bands at 242 nm ($\Delta\epsilon$ +1·4) and 202 nm ($\Delta\epsilon$ −20·8). These data are very similar to those reported for dehydrocostus lactone[24] and are consistent with a lactone *trans*-fused at C-6[25] and with the C-11 configuration shown for the pyrazoline derivative (**19**).

EXPERIMENTAL

M.ps are uncorrected. IR spectra were run in nujol on crystalline compounds and in $CHCl_3$ or liquid film for oily substances. UV spectra were determined in isooctane and optical rotations in $CHCl_3$ solution (*c* 1). PMR spectra were registered on a 60 MHz Varian NV 14 apparatus. A 3 m glass column packed with 2·5% EGS

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on Chromosorb CWS 80–100 mesh was used for GC, with N_2 (25 ml/min) as carrier gas. CD curves were registered on a Roussel–Jouan Dichrograph CD 185 in MeOH soln. For column chromatography, silica gel Merck 0·05–0·2 mm and for TLC thin layer plates Merck 60 F_{254} (0·25 mm) were used.

Isolation of vanillosmin (**1**). The crude acetonic extract of the pulverized trunk wood of *V. erythropappa* (7 kg) was concentrated *in vacuo* and taken up in MeOH H_2O (2:1). It was then extracted several times with light petrol. (1·5 l.) giving 120 g of a smelling greenish oil after removal of the solvent. A portion of this oil (23 g) was chromatographed over a 30% $AgNO_3$–silica gel (850 g) column. Four fractions were collected: fraction A (petrol.–EtOAc(95:5) 10 l. eluate) contained 5 g of fatty oils; fraction B (petrol.–EtOAc(9:1) 8 l. eluate) contained 12 g of (−)-α-bisabolol with small amounts of vanillosmin; fraction C (petrol.–EtOAc(9:1) 8 l. eluate) contained 3 g of pure vanillosmin; fraction D (petrol.–EtOAc(3:1) 8 l. eluate) contained 1 g of vanillosmin mixed with more polar substances. Fraction C and D were crystallized twice from *n*-hexane, giving 3·4 g of pure vanillosmin in long needles, m.p. 62–62·5°; b.p. 175–180°/0·2 mm (Found: C, 78·0; H, 7·8. $C_{15}H_{18}O_2$ requires: C, 78·2; H, 7·9%). $[\alpha]_D^{20}$ −110°; λ_{max} 218 nm (ε 10000); ν_{max} 1755, 1655, 895, 820 cm^{-1}. PMR: ($CDCl_3$) 1·82 (3H, *b s*, Me), 3·93 (1H, *t*, *J* 9·5 Hz, C-6 H), 5·04 and 5·22 (1H each, *b s*, C-4 $=CH_2$), 5·48 and 6·18 (1H each, *d*, *J* 3·2 Hz, C-11 $=CH_2$) and 5·58δ (1H, *m*, C-9 H). The MS showed prominent peaks at *m/e* 230 (M^+, 30%), 215 (2%), 187 (5%), 172 (34%), 150 (100%), 122 (40%) and 91 (98%). CD: $\Delta\epsilon_{253}$ −1·0 (*c* 0·164). On exposure to light and heat, vanillosmin becomes insoluble in the common organic solvents. The pyrazoline derivative (**19**) of vanillosmin was prepared by action of CH_2N_2 in Et_2O on a $CHCl_3$ soln of (**1**), m.p. 84°. CD: $\Delta\epsilon_{292}$ −20·8 (*c* 0·0038), $\Delta\epsilon_{232}$ +1·4 (*c* 0·0038) and $\Delta\epsilon_{327}$ +15·5 (*c* 0·19).

Dihydrovanillosmin (**4**). A soln of 1 g vanillosmin (**1**) was dissolved in 13 ml MeOH and treated under stirring with 70 mg $NaBH_4$ in small portions with occasional cooling. After 30 min, further 60 mg of $NaBH_4$ were added. After 30 min the reaction mixture was acidified with AcOH, concentrated under reduced pressure, taken up in H_2O and extracted 4× with $CHCl_3$. The extract was dried (Na_2SO_4) and the solvent evaporated, obtaining 923 mg crude product. Crystallization from *n*-hexane yielded 600 mg pure (**4**). The mother liquors were chromatographed on silica gel; by elution with petrol.–EtOAc(3:7) further 250 mg pure (**4**) were obtained, m.p. 70·5–72·5°; $[\alpha]_D^{20}$ −63°; ν_{max} 1770, 1660, 1050, 895 cm^{-1}. PMR: ($CDCl_3$) 1·22 (3H, *d*, *J* 6 Hz, C-11 Me), 1·83 (3H, *b s*, C-10 Me), 3·97 (1H, *t*, *J* 9·5 Hz, C-6 H), 5·00 and 5·18 (1H each, *b s*, C-4 $=CH_2$) and 5·51δ (1H, *m*, C-9 H) (Found: C, 77·65; H, 8·62. $C_{15}H_{20}O_2$ requires: C, 77·55; H, 8·68%).

Tetrahydrovanillosmin (**5**). To a soln of 400 mg (**4**) in 7 ml C_6H_6, 150 mg Wilkinson catalyst were added and the soln hydrogenated at room temp. till consumption of 1 mol H_2 (*ca.* 4 hr). The reaction mixture was evaporated to dryness and taken up in 6 ml petrol.–Et_2O(1:1). The suspension was filtered over a silica gel column (20 g); prolonged elution with the same solvent mixture yielded 390 mg crude product. It gave only one spot in TLC (petrol.–EtOAc, 7:3), but revealed a small impurity in GC (column temp. 200°), probably the corresponding C-4 epimer (MS gave M^+ 234 *m/e*). As the product resisted all attempts of crystallization, it was purified by preparative GC, using the same type of column and conditions. The pure product collected was still a thick colorless oil, very sensitive to light and heat. It shows: ν_{max} 1765, 1650 cm^{-1}. PMR: ($CDCl_3$) 1·15 (3H, *d*, *J* 6 Hz, C-4 Me), 1·20 (3H, *d*, *J* 6 Hz, C-11 Me), 1·77 (3H, *b s*, C-10 Me), 4·10 (1H, *t*, *J* 9·5 Hz, C-6 H) and 5·45δ (1H, *m*, C-9 H) (Found: C, 76·52; H, 9·39. $C_{15}H_{22}O_2$ requires: C, 76·88; H, 9·46%).

Isotetrahydrovanillosmin (**6**). Tetrahydrovanillosmin (**5**) (300 mg), dissolved in anhyd. EtOAc (30 ml), was shaken with 900 mg palladium black in H_2 for 2 hr. The catalyst was filtered off and the crude product chromatographed on silica gel (40 g). The fraction eluted with *n*-hexane–EtOAc (4:1), was crystallized from *n*-hexane and 150 mg of pure (**4**) were obtained, m.p. 128°; $[\alpha]_D^{20}$ +37·7°; ν_{max} 1765 cm^{-1}. PMR: ($CDCl_3$) 0·92 (3H, *d*, *J* 6 Hz, C-4 Me), 1·22 (3H, *d*, *J* 6 Hz, C-11 Me), 1·75 (3H, *b s*, C-10 Me) and 3·73δ (1H, *t*, *J* 9·5 Hz, C-6 H).

O-Acetyl-dihydroisophoto-α-santonic lactone (**7**). *O*-Acetyl-isophoto-α-santonic lactone (**2**) (3·5 g) in anhyd. EtOH (200 ml) was hydrogenated for 4 hr over freshly prepared 10% Pd/C (1 g) at 15 atm. The reaction mixture was filtered on celite and evaporated to dryness. The residue crystallized from petrol.–EtOAc yielding 2 g pure (**7**), m.p. 171–172°; $[\alpha]_D^{20}$ −61·7°, identical to those already reported by White *et al.*[18] Purification of the mother liquors by chromatography never afforded further amounts of (**7**) owing to the easy epimerization at C-4 induced by the absorbent.

Guai-1(10)-en-6,12-olide (**6**) *from* (**7**). The same procedure adopted by Suchý *et al.*[19] was followed.

Thioacetalization of (**10**). 4-*epi*-Dihydroisophoto-α-santonic lactone (**10**) (1 g) was dissolved in 1,2-ethanedithiol, 4 drops of BF_3–Et_2O were added, directly distilled into the reaction flask. After 3 hr at room temp., the reaction mixture was diluted with $CHCl_3$ and washed thoroughly with aq. 10% $NaHCO_3$. Evaporation of the solvent afforded 1·2 g of crude product containing both thioacetals (**11**) and (**17**) in a ratio 3:7. The mixture was chromatographed on AlOX-3 (36 g); elution with petrol.–Et_2O(1:1) gave 300 mg amorphous (**11**), which resulted pure both in TLC (petrol.–EtOAc, 1:1) and GC (column temp. 290°), and lacked OH bands in its IR spectrum. By further elution with Et_2O, 700 mg pure (**17**) were obtained, m.p. 230° (from EtOAc); $[\alpha]_D^{20}$ −2·78°; $[\alpha]_{365}^{20}$ +14·1° (lit.[21] m.p. 233·5–234°); $[\alpha]_D^{20}$ ±0°.

Desulphurization of (**11**). The thioacetal (**11**) (200 mg) was refluxed in anhyd. EtOH under vigorous stirring with a large excess of Raney–Nickel for 1 hr. After filtration and evaporation of the solvent, 150 mg (**9**) were obtained. It was purified by micropreparative GC (Column temp. 200°) and crystallized from *n*-hexane, m.p. 75–76°; $[\alpha]_D^{20}$ −31·19° identical to those previously reported.[21]

Oxymercuration-demercuration of tetrahydrovanillosmin (**5**). Tetrahydrovanillosmin (**5**) (100 mg) in purified THF was added to a stirred soln of $Hg(OAc)_2$ (136 mg in 0·5 ml H_2O). After 2 hr at room temp. the reaction mixture was first treated with 3 M NaOH (0·5 ml), then with a soln of $NaBH_4$ (0·5 M) in 3 M NaOH, till complete precipitation of metallic Hg. After acidification with AcOH and filtration, the soln was extracted with $CHCl_3$. Evaporation of the solvent yielded 108 mg of residue, which was chromatographed on silica gel (10 g). Elution with petrol.–EtOAc, 7:3, gave 60 mg pure (**13**) which crystallized from diisopropyl ether, m.p. 135–6°; $[\alpha]_D^{20}$ + 22·6°, ν_{max}: 3468, 1740 cm^{-1}, PMR: ($CDCl_3$) 0·93 (3H, *d*, *J* 7 Hz, C-4 Me), 1·20 (3H, *d*, *J* 7 Hz, C-11 Me), 1·21 (3H, *s*, C-10 Me) and 4·45δ (1H, *b s*, C-6 H) (Found: C, 71·48; H, 9·31. $C_{15}H_{24}O_3$ requires: C, 71·50; H, 9·51%). Elution with petrol.–EtOAc(4:6) afforded 5 mg of pure (**12**) which was crystallized from diisopropyl ether, m.p. 127° (lit.[21] 125·5–127·5°); $[\alpha]_D^{20}$ +20°.

Saponification of O-acetyl-isophoto-α-santonic lactone (**2**). *O*-Acetyl-isophoto-α-santonic lactone (**2**) (5 g) was stirred with 5% aq. KOH (250 ml) till complete soln (*ca.* 4 hr). After addition of H_2SO_4 till pH 3, the soln was left for 45 min, then extracted with EtOAc. Evaporation of the solvent afforded 4·2 g of a thick oil which was crystallized from petrol.–EtOAc, obtaining 2·8 g of pure (**14**). The mother liquors revealed two spots in TLC and were chromatographed on silica gel (50 g). Elution with petrol.—EtOAc (3:7), afforded 700 mg of a crystalline compound, m.p. 115–118°; $[\alpha]_D^{20}$ 128°, whose IR and MS were almost superimposable to those of (**14**). PMR: (C_5D_5N) 1·23 (3H, *d*, *J* 6 Hz, C-11 Me), 1·48 (3H, *s*, C-10 Me), 2·20 (3H, *b s*, C-4 Me), 5·20 (1H complex *d*, main *J* 10·2 Hz, C-6 H) and 4·80δ (1H, broad signal, OH): this compound is probably the C-1 epimer of (**14**). Elution with petrol.–EtOAc (1:4) afforded further 800 mg pure (**14**).

Dihydroisophoto-α-santonic lactone (**15**). Isophoto-α-santonic lactone (**14**) (5 g), in anhyd. EtOH (200 ml) was hydrogenated for 4 hr at 18 atm over freshly prepared 10% Pd/C. The mixture was filtered on celite and the solvent evaporated. Crystallization of the crude product afforded 3 g pure (**15**). By rapid chromatography on silica gel of the mother liquors, using peroxide-free anhyd. Et_2O as eluent, further 800 mg pure (**15**) could be recovered. Physical and chemical properties were identical to those previously reported.[20]

Thioacetalization of (**15**). Dihydroisophoto-α-santonic lactone (**15**) (2·39 g) was dissolved in 1,2-ethanedithiol (32 ml) and the soln cooled in ice. Few drops of BF_3–Et_2O were distilled directly into the reaction flask and the soln was left overnight at 0°. After dilution with $CHCl_3$, the soln was washed thoroughly with aq. 5% $NaHCO_3$, dried over Na_2SO_4 and evaporated to dryness. Crystallization of the crude product from EtOAc gave 2·1 g of pure (**16**), m.p. 220–222°; $[\alpha]_D^{20}$ −41°. PMR: (C_5D_5N) 1·23 (6H, two superimposed *d*, *J* 6·5 Hz, C-11 and C-4 Me), 1·37 (3H, *s*, C-10 Me), 3·23 (4H, *s*, —S—CH_2—CH_2—S—), 4·35 (1H, unresolved signal, C-6 H) and 4·92δ (1H, broad signal, OH) (Found: C, 59·71; H, 7·21. $C_{17}H_{26}O_3S_2$ requires: C, 59·65; H, 7·10%).

Dethioacetalization of (**16**). The same procedure adopted for the preparation of (**9**) was followed. From 200 mg (**16**), 140 mg crystalline (**12**) were obtained.

Dehydration of (**12**). The hydroxylactone (**12**) (450 mg) was dissolved in a small vol. of dry pyridine and the soln cooled at −20°. 3 ml of $SOCl_2$ soln (1 ml) in cold dry pyridine (19 ml) were added and the reaction mixture left overnight at −20°. The soln was poured in ice and extracted with $CHCl_3$; the extract, dried over Na_2SO_4 and evaporated *in vacuo*, gave a crude product, which was purified over 15% $AgNO_3$–silica gel. Elution with petrol.–EtOAc(9:1) afforded the anhydrolactone (**18**) (110 mg) which could not be crystallized, $[\alpha]_D^{20}$ + 26°; $\nu_{max}^{CHCl_3}$ 1765, 1640, 1605, 900 cm^{-1}. PMR: ($CDCl_3$) 0·95 (3H, *d*, *J*, 6·5 Hz, C-4 Me), 1·22 (3H, *d*, *J* 6·5 Hz, C-11 Me), 4·05 (1H, *t*, *J* 9·5 Hz, C-6 H) and 4·97δ (2H, *b s*, C-10 =CH_2).

Oxymercuration of (**18**). The same procedure adopted for the oxymercuration of (**5**) was followed. The crude reaction product was purified by preparative TLC. Starting from 40 mg (**18**), 20 mg pure crystalline (**13**) were obtained.

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