3β,19-Oxidoisopimara-7,15-diene as Intermediate in the Conversion of Virescenol B† into Isopimara-7,15-dien-19-ol

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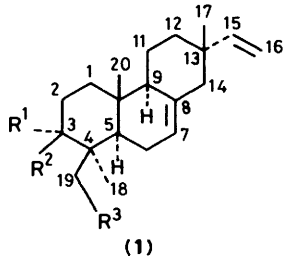
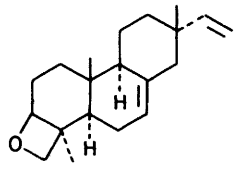
Several methods for the conversion of virescenol B tosylate (**1c**) into the oxetane (**2**) are described. On exposure to triphenyldi-iodophosphorane, (**2**) was transformed into the iodohydrin (**1g**), whose lithium–ammonia reduction led to the known isopimara-7,15-dien-19-ol (**1b**).

In connection with a study of the chemistry of virescenol B (**1a**), the aglycone of several of the fungal virescenoside metabolites,[1] the oxetane (**2**) has been encountered frequently and now has been utilized for the conversion of virescenol B (**1a**) into isopimara-7,15-dien-19-ol (**1b**). The latter was found as a minor constituent of the *Acremonium luzulae* (Fuckel) Gams fungus[2] and of *Amaracus akhdarensis* (Labiatae).[3] Treatment of virescenol B (**1a**) with toluene-*p*-sulphonyl chloride in pyridine yielded the 19-tosyl derivative (**1c**),[4] whose reduction with lithium aluminium hydride[5a] led to the 3β,19-oxidoisopimara-7,15-diene (**2**) and a mixture of isopimara-7,15-dien-3β-ol (**1d**)[5b] and isopimara-7,15-dien-19-ol (**1b**).[2]

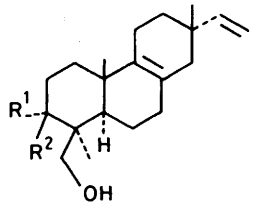


(**1**)



(**2**)

a; R^1 = H, R^2 = OH, R^3 = OH
b; R^1 = H, R^2 = H, R^3 = OH
c; R^1 = H, R^2 = OH, R^3 = OTs
d; R^1 = H, R^2 = OH, R^3 = H
e; R^1 = H, R^2 = OTs, R^3 = H
f; R^1 = Cl, R^2 = H, R^3 = OH
g; R^1 = I, R^2 = H, R^3 = OH



(**3**)

a; R^1 = Cl, R^2 = H
b; R^1 = H, R^2 = OH
c; R^1 = H, R^2 = H

The structure of (**2**) was elucidated by analytical and spectroscopic data; the ^{1}H n.m.r. spectrum showed oxymethylene proton signals at δ 3.88 and 4.68 (dd, *J* 7 Hz). ^{13}C N.m.r. carbon shifts are listed in the Table.

The oxetane (**2**), which resulted from alkaline action of the reagent, was not involved in the formation of the abnormal alcohol (**1b**). The ether (**2**) was stable toward hydrides in accord with previously observed attempts at reductive cleavage of tri- and tetra-substituted oxetanes.[6] The transformation of (**1c**) into (**1b**) required the intermediacy of tosyl derivative (**1e**).

† Virescenol B is isopimara-7,15-diene-3β,19-diol.

Table. ^{13}C N.m.r. data for compounds

Carbon	(**1b**)	(**2**)	(**3a**)	(**3c**)
C-1	39.8 t	32.5 t	27.2 t	36.6 t
C-2	18.4 t	29.6 t	29.6 t	18.7 t
C-3	35.5 d	86.2 d	66.9 d	35.0 t
C-4	37.8 s	39.0 s	45.0 s	37.4 s
C-5	51.5 d	47.1 d	45.0 d	52.6 d
C-6	23.0 t	22.9 t	21.0 t	21.2 t
C-7	121.5 d	121.2 d	32.4 t	32.9 t
C-8	135.5 s	136.2 s	124.4 s	124.3 s
C-9	52.2 d	49.9 d	136.0 s	136.8 s
C-10	35.4 s	34.4 s	37.2 s	38.6 s
C-11	20.3 t	20.4 t	18.3 t	19.1 t
C-12	36.2 t	36.1 t	34.8 t	35.4 t
C-13	36.7 q	36.8 s	34.8 s	35.0 s
C-14	46.1 t	46.4 t	41.9 t	42.0 t
C-15	150.3 d	150.0 d	146.0 d	146.1 d
C-16	109.0 t	109.3 t	110.8 t	110.7 t
C-17	21.5 q	21.5 q	27.4 q	28.0 q
C-18	26.8 q	27.6 q	24.6 q	26.7 q
C-19	65.3 t	77.4 t	65.3 t	65.3 t
C-20	15.9 q	13.9 q	20.3 q	20.0 q

When lithium triethylborohydride[7] was used in the reduction of (**1c**) instead of lithium aluminium hydride, the oxetane (**2**) was obtained as the only product. The selective formation of the ether (**2**) was observed also during attempts to reduce (**1c**) with zinc and sodium iodide in hexamethylphosphoric triamide.[8] The preparation of the oxetane (**2**) was performed by treating (**1c**) with potassium t-butoxide in benzene. Treatment of the ether (**2**), thus prepared by a variety of paths from virescenol B (**1b**) (*vide supra*), with hydrogen chloride gas in chloroform produced the halohydrin (**3a**) by a regioselective oxetane ring opening[9] and migration of the endocyclic double bond.‡ The C-3 stereochemistry of (**3a**) is based on the ^{13}C n.m.r. analysis (see Table): the strong shielding of C-1 and C-5 (27.3 and 45.1) of the compound compared with C-1 and C-5 (35.4 and 52.1) of isovirescenol B (**3b**)[10] indicating the axial nature of the 3-chloro group.

Whereas substituted oxetanes have been shown to form predominantly primary halides on hydrochloric acid treatment,[9] the oxetane (**2**) appeared to behave abnormally in the acid-catalysed ring opening. The remarkable regioselectivity of this process can be explained by the steric hindrance of the hydrogens at C-6 preventing the attack of the halide ion at C-19. Reduction of (**3a**) with lithium in liquid ammonia yielded the alcohol (**3c**), identical in all respects with a compound prepared from natural (**1b**) (see Experimental section).

In order to prevent the migration of the endocyclic double

‡ For the acid-catalysed migration of Δ^7 double bond in the isopimaric compound see ref. 4.

bond observed in the transformation (2)→(3a), the oxetane (2) was treated with 10% hydrogen chloride in acetone. Following this procedure, the oxetane (2) was converted into the halohydrin (1f) in poor yield. Lithium–ammonia reduction of (1f) produced the expected alcohol (1b).[2,3]

The recent finding of tertiary phosphine dihalides being effective in the conversion of epoxides into halohydrins[11] led us to explore the possible use of tryphenyldihalogenophosphoranes for the oxetane ring opening. Treatment of (2) with the reagent at room temperature led to an iodohydrin, identified as 3α-iodoisopimara-7,15-dien-19-ol (1g) from the analytical and spectroscopic data. Lithium–ammonia reduction of the iodo derivative (1g) afforded the expected alcohol (1b).

The (2)→(1g)→(1b) reaction sequence constitutes the best procedure for the partial synthesis of the natural product isopimara-7,15-dien-19-ol (1b).

Experimental

M.p.s were determined on a Kofler hot-stage and are uncorrected. I.r. spectra were obtained with a Perkin-Elmer 1320 spectrophotometer in $CHCl_3$ solutions. ^1H N.m.r. spectra were recorded on a Varian EM-390 spectrometer (solutions in $CDCl_3$ with internal $SiMe_4$ as standard). ^{13}C N.m.r. spectra were produced on a Varian XL-100-15 spectrometer operating at 25.2 MHz in the Fourier transform mode. Column chromatography was performed with 0.063—0.0200 mm Merck silica gel adsorbant. Ether refers to diethyl ether.

Treatment of Virescenol B 19-*Toluene*-p-*sulphonate* (**1c**) *with Lithium Aluminium Hydride.*—A solution of virescenol B toluene-*p*-sulphonate (**1c**) (0.40 g) in THF (15 ml) was added to a suspension of lithium aluminium hydride (0.15 g) in THF (15 ml) and the reaction mixture was stirred at reflux under nitrogen for 30 min. It was then cooled, decomposed with water, acidified with dilute aqueous hydrochloric acid, and extracted with chloroform. The organic layer was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. Chromatography of the residue (0.22 g) on silica gel and elution with benzene–ethyl acetate (49:1) gave 3β,19-*oxidoisopimara*-7,15-*diene* (**2**) (0.04 g), m.p. 58—60 °C (Found: C, 83.5; H, 10.8. $C_{20}H_{30}O$ requires C, 83.86; H, 10.56%); δ_H 0.84, 1.10, 1.31 (9 H, each s, Me_3), 3.88, 4.68 (2 H, dd, *J* 7 Hz, 19-H), 4.65—4.88 (2 H, m, 16-H), and 5.50—5.80 (1 H, m, 15-H). Further elution gave a mixture (0.160 g) of isopimara-7,15-dien-19-ol (**1b**) and isopimara-7,15-dien-3β-ol (**1d**). Rechromatography of the mixture on silica gel and elution with benzene gave pure (**1b**) (0.04 g) (t.l.c. and i.r. and ^1H n.m.r. spectra were identical with an authentic sample[2]), and a mixture of (**1b**) and (**1d**) (0.06 g), and pure (**1d**) (0.03 g), m.p. 143—144 °C (lit.,[5b] 146—147 °C) (Found: C, 83.4; H, 11.3. $C_{20}H_{32}O$ requires C, 83.27; H, 11.18); δ_H 0.88, 0.88, 0.90, 1.00 (12 H, each s, Me_4), 3.32 (1 H, m, 3-H), 5.70—5.92 (2 H, m, 16-H), and 5.54—5.84 (1 H, m, 16-H).

Treatment of Virescenol B 19-*Toluene*-p-*sulphonate* (**1c**) *with Lithium Triethylborohydride.*—A 1M solution of lithium triethylborohydride in THF (3 ml) was added to a stirred solution of virescenol B 19-toluene-*p*-sulphonate (**1c**) (0.50 g) in THF (20 ml) at 0 °C under nitrogen and the stirring continued for 4 h. 3M-Sodium hydroxide (1 ml) and 36% hydrogen peroxide (1 ml) were added successively and the reaction mixture stirred at room temperature for 30 min. It then was diluted with water and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. Chromatography of the residue (0.25 g) on silica gel and elution with chloroform gave 3β-19-oxidoisopimara-7,15-diene (**2**) (0.20 g) (*vide supra*).

Treatment of Virescenol B 19-*Toluene*-p-*sulphonate* (**1c**) *with Zinc and Sodium Iodide in Hexamethylphosphoric Triamide.*—Powdered zinc (1g) was added to a solution of virescenol B 19-toluene-*p*-sulphonate (**1c**) (0.5 g) and sodium iodide (**1g**) in hexamethylphosphoric triamide (20 ml) and the mixture was stirred at 90 °C, under nitrogen, for 12 h. It was then diluted with water and extracted with ether. The organic layer was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. Chromatography of the residue (0.20 g) on silica gel and elution with chloroform gave 3β,19-oxidoisopimara-7,15-diene (**2**) (0.18 g) (*vide supra*).

Treatment of Virescenol B 19-*Toluene*-p-*sulphonate* (**1c**) *with Potassium t-Butoxide.*—A solution of virescenol B 19-toluene-*p*-sulphonate (**1c**) (1 g) and potassium t-butoxide (1.1 g) in benzene (150 ml) was stirred at 20 °C for 2 h. It was then diluted with water and extracted with chloroform. The organic layer was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. Chromatography of the residue (0.55 g) on silica gel and elution with chloroform gave 3β,19-oxidoisopimara-7,15-diene (**2**) (0.42 g) (*vide supra*).

Treatment of 3β,19-*Oxidoisopimara*-7,15-*diene* (**2**) *with Hydrogen Chloride Gas.*—A solution of 3β,19-oxidoisopimara-7,15-diene (**2**) (1 g) in chloroform (300 ml) saturated with hydrogen chloride gas was kept at room temperature for 24 h. It then was washed with saturated aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4), and evaporated under reduced pressure. Chromatography of the residue (0.95 g) on silica gel and elution with chloroform gave 3α-*chloroisopimara*-8(9),15-*dien*-19-ol (**3a**) as a semisolid (0.90 g) (Found: C, 74.5; H, 9.5. $C_{20}H_{31}ClO$ requires C, 74.37; H, 9.69%); δ_H 0.90, 0.92, 1.09 (9 H, each s, Me_3), 3.34, 3.62 (2 H, dd, *J* 11 Hz, 19-H), 4.53 (1 H, broad s, $W_{\frac{1}{2}}$ 5 Hz, 3-H), 4.50—4.72 (2 H, m, 16-H), and 5.32—5.60 (1 H, m, 15-H).

Treatment of 3β,19-*Oxodoisopimara*-7,15-*diene* (**2**) *with Hydrogen Chloride.*—10% Aqueous hydrogen chloride (70 ml) was added to a solution of 3β,19-oxidoisopimara-7,15-diene (**2**) (0.5 g) in acetone (25 ml) and the reaction mixture stirred at room temperature for 4 h. It was then diluted with water and extracted with chloroform. The organic layer was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. Chromatography of the residue (0.42 g) and elution with chloroform gave the oxetane (**2**) (0.18 g) and 3α-*chloroisopimara*-7,15-*dien*-19-*ol* (**1f**) as a semisolid (0.20 g) (Found: C, 74.1; H, 9.8. $C_{20}H_{31}ClO$ requires C, 74.37; H, 9.6%); δ_H 0.86, 0.86, 1.15 (9 H, each s, Me_3), 3.58, 3.93 (2 H, dd, *J* 11 Hz, 19-H), 4.60 (1 H, br s, $W_{\frac{1}{2}}$ 5 Hz, 3-H), 4.81—5.01 (2 H, m, 16-H), and 5.65—6.0 (1 H, m, 16-H).

Treatment of 3β,19-*Oxidoisopimara*-7,15-*diene* (**2**) *with Triphenyldi-iodophosphorane.*—Triphenylphosphine (0.3 g) was added to a stirred solution of iodine (0.3 g) in anhydrous dichloromethane (40 ml). The brown solution turned immediately to a pale yellow colour and then 3β,19-oxidoisopimara-7,15-diene (**2**) (0.40 g) in dichloromethane (10 ml) was added and the reaction mixture stirred at room temperature for 30 min. It then was washed with M-aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4), and evaporated under reduced pressure. Chromatography of the residue (0.43 g) on silica gel and elution with chloroform gave 3α-*iodoisopimara*-7,15-*dien*-19-*ol* (**1g**) (0.38 g), m.p. 81—83 °C (Found: C, 58.1; H, 7.3. $C_{20}H_{31}IO$ requires C, 57.96; H, 7.55%); δ_H 0.86, 0.86, 1.16 (9 H, each s, Me_3), 3.55, 4.04 (2 H, dd, *J* 11 Hz, 19-H), 5.05 (1 H, br s, $W_{\frac{1}{2}}$ 5 Hz, 3-H), 4.86—5.01 (2 H, m, 16-H), and 5.60—5.90 (1 H, m, 16-H).

Isopimara-8(9),15-*dien*-19-*ol* (**3c**).—A solution of the chloro alcohol (**3a**) (0.15 g) in THF (8 ml) was added slowly to a stirred solution of lithium (0.03 g) in liquid ammonia (50 ml) under nitrogen at −40 °C, and the mixture stirred for 30 min. Enough ammonium chloride was added to discharge the blue colour and the ammonia allowed to evaporate. The residue was shaken with a mixture of water and chloroform and the organic layer dried (Na_2SO_4), and evaporated under reduced pressure. Chromatography of the residue (0.1 g) and elution with benzene–ethyl acetate (49:1) gave isopimara-8(9),15-dien-19-ol (**3c**) (0.08 g) (*vide infra*).

Treatment of Isopimara-7,15-*dien*-19-*ol* (**1b**) *with Hydrogen Chloride Gas*.—A solution of isopimara-7,15-dien-19-ol (**1b**) (0.1 g) in chloroform (100 ml) saturated with hydrogen chloride gas was kept at room temperature for 24 h. Work-up as above and chromatography of the residue (0.1 g) on silica gel and elution with benzene–ethyl acetate (49:1) gave *isopimara*-8(9),15-*dien*-19-*ol* (**3c**) (0.08 g), m.p. 92—95 °C (Found: C, 83.1; H, 11.3. $C_{20}H_{32}O$ requires C, 83.27; H, 11.18%); δ_H 0.97, 1.00, 1.02 (9 H, each s, Me_3), 3.41, 3.71 (2 H, dd, *J* 11 Hz, 19-H), 4.63—4.90 (2 H, m, 16-H), and 5.50—5.80 (1 H, m, 15-H).

Isopimara-7,15-*dien*-19-*ol* (**1b**).—A solution of the chloro alcohol (**1f**) (0.2 g) in THF (10 ml) was added to a stirred solution of lithium (0.05 g) in liquid ammonia (50 ml). Work-up as above and chromatography of the residue (0.13 g) on silica gel and elution with benzene–ethyl acetate (49:1) gave isopimara-7,15-dien-19-ol (**1b**) (0.11 g, 62%); t.l.c. and i.r. and ^{1}H n.m.r. spectra were identical with those of an authentic sample.[2]

A solution of the iodo alcohol (**1g**) (0.2 g) in THF (10 ml) was added to a stirred solution of lithium (0.05 g) in liquid ammonia (50 ml). Work-up as above and chromatography of the residue (0.13 g) on silica gel and elution with benzene–ethyl acetate 49:1 gave isopimara-7,15-dien-19-ol (**1b**) (0.09 g, 65%); t.l.c. and i.r. and ^{1}H n.m.r. spectra were identical with those of an authentic sample.[2]

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