# Fungal Metabolites. Part 5.[1] Uvidins, New Drimane Sesquiterpenes from *Lactarius uvidus* Fries

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Uvidin A (IIa) and uvidin B (IIc) along with (−)-drimenol have been isolated from *Lactarius uvidus* Fries (Basidiomycetes). The structure and the stereochemistry of the two uvidins have been determined both by spectroscopic data and chemical reactions. Compound (IIa) has been correlated with (+)-drimanol (VIII) by transformations into (VI) and then (VII). Reactions and spectroscopic data are discussed.

In this paper we report the presence of sesquiterpenes with the drimane skeleton in Basidiomycetes and in particular in *Lactarius* mushrooms. In the last decade the structure of many sesquiterpenes isolated from *Lactarius* species (Russulaceae, Basidiomycetes) have been determined. *Lactarius deliciosus*, an edible species which has a characteristic orange-red juice, contains guaiane sesquiterpenes.[2] From other species (*Lactarius blennius*,[1,3] *L. helvus*,[4] *L. necator*,[5-7] *L. pallidus*,[1] *L. pergamenus*,[4,8-11] *L. rufus*,[6,12-14] *L. scrobiculatus*,[1,15,16] *L. vellereus*,[4,8-11] which are mainly inedible because of their pungent or peppery taste) sesquiterpenes with the lactarane skeleton, or with a skeleton biogenetically correlated with lactarane, have been isolated.

Pursuing our research on *Lactarius* metabolites we examined *Lactarius uvidus* Fries. This mushroom grows in humid woods and is easily identifiable by the colour change of the flesh and of the milky juice from white to violet. The taste, mild at the beginning, later becomes pungent. Ingestion of this mushroom is not recommended though toxicity has not been proved.

An extract of *L. uvidus*, examined by g.l.c.–m.s., showed the presence of at least five sesquiterpenes with molecular weights 222, 238, 252, 254, and 268. The three main components (molecular weights 222, 252, and 268) were separated and purified by column chromatography.

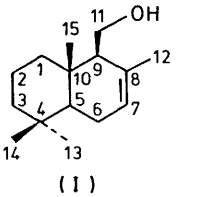
The lowest molecular weight product was identified as (−)-drimenol[17] (I) by spectroscopic data and comparison with an authentic sample. The other two compounds were named uvidin A and B, respectively.

Uvidin A (IIa) (*M* 252, $C_{15}H_{24}O_3$) showed i.r. bands at 3 430 (OH) and 1 710 (CO) $cm^{-1}$. Acetylation with $Ac_2O$–pyridine afforded a monoacetyl derivative (IIb) as shown by i.r. and $^1H$ n.m.r. spectra (see Experimental section).

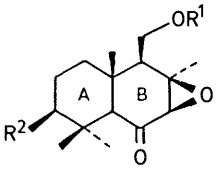
The $^1H$ n.m.r. signals of (IIa) showed the presence of four tertiary methyl groups, one geminal to an oxygen atom, an isolated $CHCH_2OH$ group, as demonstrated by decoupling experiments, and two low field isolated methyne protons. The $^{13}C$ n.m.r. data confirmed the presence of these groups and of a ketone and in addition showed three methylene groups and a trisubstituted epoxide ring clearly shown by the large C–H coupling constant (172 Hz) of the doublet at δ 60.7 p.p.m. characteristic of a three-membered ring.

The presence of epoxide, ketone, and two fused six-membered rings explains the level of unsaturation and accommodates the functional groups. At this point several structures could be assumed for (IIa) but the following data led us to determine the exact position of the substituents.

In the mass spectrum of (IIa) the base peak occurred at *m/e* 151 and could be attributed to ion (IIIa), indicating the position of the ketone at C-6; furthermore

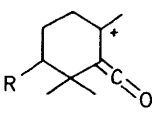



(I)




(II)

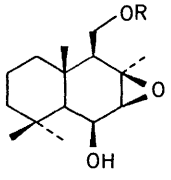
a ; $R^1 = R^2 = H$
b ; $R^1 = Ac, R^2 = H$
c ; $R^1 = H, R^2 = OH$
d ; $R^1 = Ac, R^2 = OAc$




(III)

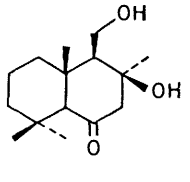
a ; R = H
b ; R = OH

the ions at *m/e* 109 and 123 precluded the presence of substituents in ring A.[19] $NaBH_4$ reduction of the carbonyl group afforded the diol (IVa) ($M^+$ 254, $\nu_{max.}$ 3 400 $cm^{-1}$, no CO absorption) which showed a new n.m.r. signal at δ 4.52 (1 H, m, C*H*OH) coupled with the epoxy proton and with 5-H. The unusual high-field chemical shift of 5-H is difficult to rationalize but




(IV)

a ; R = H
b ; R = Ac




(V)

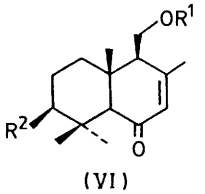
decoupling experiments left no doubt about the attribution. $NaBH_4$ reduction of (IIb) led to similar results.

Hydrogenation of uvidin A with Pd–C caused the epoxide ring to open and gave 8-hydroxy-6-oxodrimanol (V) ($M^+$ 254) as was clearly indicated by the n.m.r. spectrum which showed, besides three tertiary methyl

groups, a methyl geminal to an hydroxy-group, an isolated methylene near the CO, an isolated methyne, and a $CHCH_2OH$ group. The i.r. spectrum indicated that the ketone has not been reduced. Compound (V) was also obtained by treatment of (IIa) with hydrazine hydrate and acetic acid instead of the expected allylic alcohol [20] probably because epoxide opening occurred faster than attack on the ketone.

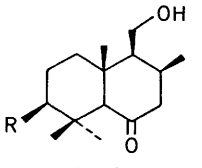
These data established the sequence of all the ring B functional groups, 6-oxo- 7,8-epoxy, and 9-$CHCH_2OH$ flanked by two quaternary carbon atoms which bear two of the four tertiary methyl groups. The structure of uvidin A was definitely confirmed by correlating it with the known (+)-drimanol through the following chemical reactions, thus also confirming the *trans* (10β-$CH_3$) configuration of the AB ring junction and the β configuration of C-11.

By treatment of (IIa) with KI in acetic acid de-epoxidation of uvidin A occurred yielding 6-oxodrimenol (VIa) ($M^+$ 236), as shown by absorptions in the i.r. and u.v. spectra characteristic of an αβ-unsaturated ketone. In the n.m.r. spectrum the vinylic proton showed allylic coupling with 8-methyl and 9-H appeared as a broad multiplet. Hydrogenation of (VIa) with Adams' catalyst led to 6-oxodrimanol (VIIa) ($M^+$ 238) as was demonstrated by the n.m.r. and i.r. spectra. Drastic Wolff–Kishner reduction of (VIIa) then yielded (+)-drimanol (VIII),[17] identical with the product of hydrogenation of (−)-drimenol (I).



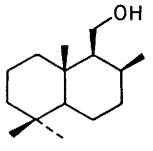

(VI)

a ; $R^1 = R^2 = H$
b ; $R^1 = H, R^2 = OH$
c ; $R^1 = Ac$ $R^2 = OAc$




(VII)

a ; R = H
b ; R = OH




(VIII)

At this point, given the stereochemistry of the AB ring junction, the configuration of the epoxide can be determined in various ways together with the stereochemistry of 8-$CH_3$ in (V) and (VII).

In the c.d. spectra of uvidin A the ketone exhibited a strong positive Cotton effect (peak $[\theta]_{320}$ +13 101) which according to the anti-octant rule for αβ-epoxyketones [21] indicated that the epoxy ring had the β configuration. Moreover the quartet at δ 31.0 p.p.m.[18] for the 8-$CH_3$ in the $^{13}C$ n.m.r. spectrum of 8-hydroxy-6-oxodrimanol (V) suggested that the methyl was equatorial to ring B, the geminal OH being axial. Since hydrogenolysis of the epoxy ring occurs with retention of configuration, these data confirm that the epoxide must be β.

Finally in the $^1H$ n.m.r. spectrum of the diol (IVa) the signals for 5-, 6-, and 7-H formed a clean AMX system. The magnitudes of the coupling constants revealed that these three protons were in a *syn*-relationship and since 5-H was axial, 7-H had the α-configuration and therefore the epoxy ring was β. The presence of the 7,8-β-epoxide caused an upfield shift of the singlet for 10-$CH_3$ in (IIa) by comparison with the corresponding signal of 6-oxodrimenol (VIa). It is interesting to note that both $NaBH_4$ reduction and hydrogenolysis of the epoxide in (IIa) were highly stereoselective: reduction took place from the less hindered α-side of the molecule and introduced a new β-axial hydroxy-group. As expected the chemical shift of 10-$CH_3$ in the diols (IVa) (6-OH) and (V) (8-OH) moved downfield relative to that of 10-$CH_3$ in (IIa) because of the new 1,3-axial interaction.

Also hydrogenation of (VIa) occurred from the more accessible α-side of the molecule yielding (VIIa) but in this case the configuration of 8-$CH_3$ is β-axial ($^{13}C$ n.m.r. absorption at δ 15.9 p.p.m.[18]) and therefore opposite to that of the uvidins.

Uvidin B (IIc) ($M^+$ 268, $C_{15}H_{24}O_4$) showed spectra very similar to those of uvidin A and the differences could be explained by the presence in (IIc) of a CHOH instead of a $CH_2$ group. This was indicated, in the $^1H$ n.m.r. spectrum, by a signal (four lines) at δ 3.13 and, in the $^{13}C$ n.m.r. spectrum, by a doublet at δ 78.3 p.p.m. This hydroxy-group could only be in ring A; this was confirmed by the appearance in the mass spectrum of the base peak at *m/e* 167 corresponding to (IIIb).

Acetylation of uvidin B with $Ac_2O$–pyridine gave the expected diacetyl derivative (IId) as shown by the i.r. bands at 1 750 and 1 738 $cm^{-1}$ (AcO) and the absence of any OH absorptions. As usual, upon acetylation the CHO signals shifted downfield in the $^1H$ n.m.r. spectrum.

De-epoxidation of (IIc) with KI in acetic acid afforded 3-hydroxy-6-oxodrimenol (VIb) ($M^+$ 252) as was shown by the formation of an αβ-unsaturated ketone with a methyl on the β-carbon of the double bond. Similar results were obtained by de-epoxidation of (IId). Hydrogenation of (VIb) with Adams' catalyst gave 3-hydroxy-6-oxodrimanol (VIIb) ($M^+$ 254).

We could verify that uvidin B (IIc) had the *trans*-configuration at the AB ring junction [as (IIa)] not only on the basis of the positive Cotton effects of the ketones (VIb) and (VIIb), which do not of themselves exclude a *cis*-junction, but also by the shielding of the angular methyl carbon in the $^{13}C$-n.m.r. spectrum of (IIc). It is known that the methyl signal of the *trans*-isomer should occur *ca.* 11—12 p.p.m. upfield than that of the *cis*-isomer,[22] the latter being δ *ca.* 30 p.p.m.[18] The $^{13}C$ n.m.r. spectrum of uvidin B showed, besides the signal for the methyl linked to the epoxide ring, methyl group signals at δ 18.7, 21.9, and 33.3 p.p.m. The lowest field signal must be assigned to the 4α-methyl group, while

TABLE 1

$^1$H N.m.r. data [a] of uvidins and their derivatives

| Compd. | Solvent | 3-H | 5-H | 6-H | 7-H | 8-H | 9-H | 11-,11′-H | 8-$CH_3$ | 10-$CH_3$ | 4β-$CH_3$ | 4α-$CH_3$ | Coupling constants (Hz) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (IIa) | $CDCl_3$ | | 1.92(s) | | 2.91(s) | | 1.84(t) | 4.04(d) | 1.50(s) | 0.94(s) | 1.07(s) | 1.16(s) | $J_{9,11}$ 4.5; |
| (IIb) [b] | $CDCl_3$ | | 1.92(s) | | 2.92(s) | | 2.10(dd) | 4.49(dd), 4.36(dd) | 1.40(s) | 0.92(s) | 1.07(s) | 1.16(s) | $J_{11,11'}$ 12.0; $J_{9,11}$ 3.2 $J_{9,11'}$ 6.5 |
| (IIc) | $(CD_3)_2CO$ | 3.13(dd) | 2.17(s) | | 2.88(s) | | 1.94(dd) | 3.95(dd), 3.85(dd) | 1.46(s) | 0.88(s) | 1.11(s) | 1.17(s) | $J_{2,3} + J_{2',3}$ 15.0; $J_{11,11'}$ 11.0; $J_{9,11}$ 3.5; $J_{9,11'}$ 6.0 |
| (IId) [b] | $CDCl_3$ | 4.40(t) | 2.18(s) | | 2.95(s) | | 2.00(dd) | 4.52(dd), 4.30(dd) | 1.42(s) | 0.98(s) | 1.10(s) | 1.22(s) | $J_{2,3} + J_{2,3'}$ 15.0; $J_{11,11'}$ 12.0; $J_{9,11}$ 3.5; $J_{9,11'}$ 6.0 |
| (IVa) | $CDCl_3$ | | 0.79(d) | 4.52br(m) | 3.25(d) | | *ca.* 1.5 [c] | 4.0(d) | 1.46(s) | 1.16(s) | 1.28(s) | 1.06(s) | $J_{5,6}$ 4.0; $J_{6,7}$ 6.0; $J_{9,11}$ 4.0 |
| | $C_6D_6$ | | 0.46(d) | 4.26(dd) | 2.88(d) | | 1.16(t) | 3.69(d) | 1.41(s) | 1.09(s) | 1.28(s) | 1.02(s) | $J_{5,6}$ 4.0; $J_{6,7}$ 5.5; $J_{9,11}$ 4.5 |
| (IVb) [b] | $CDCl_3$ | | 0.68(d) | 4.56br(m) | 3.26(d) | | 1.64(dd) | 4.48(dd), 4.30(dd) | 1.37(s) | 1.13(s) | 1.28(s) | 1.07(s) | $J_{5,6}$ 4.5; $J_{6,7}$ 6.0; $J_{11,11'}$ 12.5; $J_{9,11}$ 3.7; $J_{9,11'}$ 6.0 |
| | $C_5D_5N$ | | 0.85(d) | 4.70(dd) | 3.28(d) | | 1.69(dd) | 4.67(dd), 4.45(dd) | 1.42(s) | 1.33(s) | 1.52(s) | 1.15(s) | $J_{5,6}$ 4.5; $J_{6,7}$ 5.8; $J_{11,11'}$ 12.0; $J_{9,11}$ 3.6; $J_{9,11'}$ 6.0 |
| (V) | $CDCl_3$ | | 2.14(s) | | 2.55(d) 2.36(d) | | 1.51(t) | 4.18(d) | 1.45(s) | 1.22(s) [d] | 0.94(s) | 1.27(s) [d] | $J_{7,7'}$ 13.5; $J_{9,11}$ 3.0 |
| | $C_5D_5N$ | | 2.29(s) | | 2.67(s) | | | 4.46(dd), 4.26(dd) | 1.66(s) | 1.46(s) [d] | 1.08(s) | 1.44(s) [d] | $J_{11,11'}$ 11.5; $J_{9,11} = J_{9,11'} = 3.0$ |
| (VIa) | $CDCl_3$ | | 2.10(s) | | 5.84(m) | | 2.32br(m) | 3.98(dd), 3.84(dd) | 2.06(t) | 0.93(s) | 1.12(s) | 1.17(s) | $J_{11,11'}$ 11.2; $J_{9,11}$ 3.5; $J_{9,11'}$ 5.5; $J_{8-CH_3,9} = J_{7,9} = J_{8-CH_3,7} = 1.2$ |
| (VIb) | $CD_3OD$ | 3.10(m) | 2.18(s) | | 5.75(m) | | 2.30br | 3.87(dd), 3.71(dd) | 2.02(t) | 0.89(s) | 1.08(s) | 1.19(s) | $J_{11,11'}$ 11.3; $J_{9,11}$ 3.0; $J_{9,11'}$ 5.7; $J_{7,9} = J_{8-CH_3,7} = J_{8-CH_3,9} = 1.0$ |
| (VIc) [b] | $CDCl_3$ | 4.48(dd) | 2.20(s) | | 5.88(m) | | 2.5br | 4.38(dd), 4.22(dd) | 1.95(t) | 0.96(s) | 1.14(s) | 1.23(s) | $J_{2,3} + J_{2',3}$ 15.0; $J_{11,11'}$ 12.0; $J_{9,11}$ 2.2; $J_{9,11'}$ 5.2; $J_{8-CH_3,7} = J_{8-CH_3,9} = 1.0$ |
| (VIIa) | $C_6D_6$ | | 1.90(s) | | 1.9—2.7 | 2.45(m) | 1.59(m) | 3.53(dd), 3.24(dd) | 0.89(d) | 0.73(s) | 1.36(s) | 1.00(s) | $J_{8,9}$ 4.5; $J_{11,11'}$ 11.3; $J_{9,11}$ 5.0; $J_{9,11'}$ 9.0; $J_{8-CH_3,8}$ 7.5 |
| | $C_5D_5N$ | | 2.29(s) | | 2.73(dd) 2.21(dd) | 3.03(m) | 2.20(m) | 4.10(dd), 3.84(dd) | 1.08(d) | 0.92(s) | 1.86(s) | 0.99(s) | $J_{7,7'}$ 12.5; $J_{7,8}$ 7.0 $J_{7',8}$ 1.5; $J_{11,11'}$ 10.0; $J_{9,11}$ 4.5; $J_{9,11'}$ 9.5; $J_{8,9}$ 4.5; $J_{8-CH_3,8}$ 7.5 |
| (VIIb) | $CDCl_3$ | *ca.* 2.7(m) | 2.20(s) | | | *ca.* 2.7(m) | 2.00(m) | 3.94(dd), 3.66(dd) | 0.99(d) | 0.89(s) | 0.91(s) | 1.23(s) | $J_{8,9}$ 4.5; $J_{11,11'}$ 10.5; $J_{9,11}$ 4.5; $J_{9,11'}$ 9.0; $J_{8-CH_3,8}$ 7.5 |
| (VIII) | $CDCl_3$ | | | | | | | 3.86(dd), 3.58(dd) | 0.95(d) | 0.80(s) [d] | 0.83(s) [d] | 0.83(s) [d] | $J_{11,11'}$ 10.5; $J_{9,11}$ 4.7; $J_{9,11'}$ 9.0; $J_{8-CH_3,8}$ 7.5 |

[a] At 100 MHz. Chemical shifts are quoted in δ units relative to $Me_4Si$. The proton signals not reported (*i.e.* for 1- and 2-H) appeared as overlapping multiplets. [b] Chemical shifts of $CH_3CO$: (IIb) δ 2.07(s); (IId) δ 2.04(s) and 2.07(s); (IVb) δ 2.07(s); (Vc) δ 2.08(s). [c] Data determined by decoupling experiments. [d] The assignments of these signals may be reversed.

the upfield chemical shifts of the other methyls were consistent only with *trans*-stereochemistry at the AB ring junction.

The c.d. curve of (IIc) (peak $[\theta]_{320}$ +10 923) again indicated [21] a β-configuration of the epoxide ring as in uvidin A.

The position and configuration of the secondary hydroxy in (IIc) were determined by comparison of the $^{13}$C n.m.r. spectra of (IIa and c) which showed that the introduction of a new OH group in ring A did not affect the shift of 10-$CH_3$, but caused significant effects on the resonances of 4-$CH_3$ and C-4. The two 4-$CH_3$ signals were shifted upfield by *ca.* 5—6 p.p.m. while the C-4 signal moved downfield by 6 p.p.m. These data agreed with the known shielding γ-effect and the deshielding β-effect exerted on adjacent carbon atoms by a hydroxy-group which had replaced an hydrogen atom.[23] Thus the secondary OH in (IIc) must be at C-3 and equatorial to ring A, since the chemical shifts of the two geminal 4-$CH_3$ were affected in the same way. Further evidence for the β-configuration of 3-OH was obtained from the $^1$H n.m.r. spectrum of (IIc) by the width of the signal for 3-H (which is the X part of an ABX system). The value of 15 Hz is characteristic of axial–axial and axial–equatorials coupling with the vicinal protons and indicated that 3-H is axial and thus 3-OH is equatorial.

This is the first time that drimane sesquiterpenes, which are peculiar to some plants,[17,24-40] have been found in Basidiomycetes. To our knowledge (−)-drimenol has been found previously only in liverworts (*Bazzania trilobata*,[41] *B. tricrenata*, *Scapania undulata*,[42] *Porella verniciosa*, *P. macroloba*, and *P. gracillima* [34]), and in shrubs (*Walburgia ugandensis* [29] and *Drimys winteri* [17]).

So far as we are aware, uvidin B is the first drimane found in nature with a hydroxy-group at the 3 position. Such a hydroxy-group is always present in the iresane

TABLE 2

$^{13}$C N.m.r. data * of drimenol, uvidins, and their derivatives

| Compd. | C-1 | C-2 | C-3 | C-4 | C-5 | C-6 | C-7 | C-8 | C-9 | C-10 | C-11 | C-12 | C-13α | C-14β | C-15 | Solvent |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (I) | 39.9(t) | 18.8(t) | 42.2(t) | 32.9(s) | 49.9(d) | 23.6(t) | 124.1(d) | 132.8(s) | 57.4(d) | 36.1(s) | 60.9(t) | 21.9(q) | 33.3(q) | 22.1(q) | 14.9(q) | $CDCl_3$ |
| (IIa) | 40.5(t) | 17.8(t) | 42.6(t) | 32.2(s) | 65.0(d) | 204.7(s) | 60.7(d) | 61.4(s) | 55.2(d) | 37.2(s) | 60.5(t) | 21.5(q) [a] | 33.2(q) | 21.6(q) [a] | 18.7(q) | $CDCl_3$ |
| | 40.7(t) | 18.4(t) | 43.4(t) | 32.6(s) | 64.7(d) | 205.9(s) | 61.8(d) | 62.1(s) | 55.8(d) | 37.5(s) | 60.7(t) | 21.9(q) [a] | 33.3(q) | 21.9(q) [a] | 18.7(q) | $(CD_3)_2CO$ |
| (IIc) | 39.2(t) | 27.3(t) | 78.3(d) | 38.3(s) [b] | 64.6(d) | 205.0(s) | 62.1(d) | 62.5(s) | 55.8(d) | 37.6(s) [b] | 60.6(t) | 21.8(q) | 28.5(q) | 15.6(q) | 19.0(q) | $(CD_3)_2CO$ |
| (IVb) [c] | 43.2(t) [c] | 18.4(t) | 44.3(t) [c] | 34.2(s) [b] | 54.4(d) [d] | 65.2(d) | 63.8(d) | 62.8(s) | 52.3(d) [d] | 35.8(s) [b] | 62.8(t) | 21.1(q) [a] | 33.2(q) | 22.6(q) [a] | 18.7(q) | $CDCl_3$ |
| (V) | 40.3(t) | 18.2(t) | 42.5(t) | 32.4(s) | 66.2(d) | 209.5(s) | 58.5(t) | 78.7(s) | 58.5(d) | 44.1(s) | 59.7(t) | 31.0(q) [a] | 32.8(q) [a] | 21.8(q) | 18.1(q) | $CDCl_3$ |
| (VIa) | 39.3(t) | 18.2(t) | 43.1(t) | 32.3(s) | 63.0(d) | 200.1(s) | 129.1(d) | 157.3(s) | 58.3(d) | 42.1(s) | 60.0(t) | 21.6(q) [a] | 33.6(q) | 21.9(q) [a] | 15.9(q) | $CDCl_3$ |
| (VIb) | 38.2(t) | 27.4(t) | 79.3(d) | 38.8(s) | 63.7(d) | 201.9(s) | 129.3(d) | 161.2(s) | 59.1(d) | 43.1(s) | 59.8(t) | 22.1(q) | 28.9(q) | 16.2(q) [a] | 15.7(q) [a] | $CD_3OD$ |
| (VIIa) | 40.1(t) | 18.1(t) | 42.5(t) | 32.2(s) | 65.9(d) | 212.3(s) | 51.0(t) | 33.2(d) | 54.9(d) | 43.7(s) | 60.3(t) | 15.9(q) | 32.6(q) | 21.7(q) | 18.1(q) | $CDCl_3$ |

* At 25.2 MHz. Chemical shifts in p.p.m. from $Me_4Si$. Signal multiplicity obtained by off-resonance decoupling experiments.

[a–c] The assignments of these signals may be reversed. [d] Assigned on the basis of $^1J_{C-H}$. [e] $CH_3CO$: δ 24.5(q) and 170.7 p.p.m. (s).

sesquiterpenes.[43,44] It is known that the bicyclofarnesane sesquiterpenes can be derived biogenetically, when the 3 position is not substituted, by synchronized cyclization of farnesyl pyrophosphate caused by proton attack on the terminal double bond (as for drimanes), and, when the 3 position is hydroxylated, by cyclization of epoxyfarnesyl pyrophosphate (as for iresane). In the case of uvidin B it would be interesting to check whether it is formed by cyclization of epoxyfarnesyl pyrophosphate or by hydroxylation at C-3 of the pre-formed uvidin Z.

## EXPERIMENTAL

M.p.s are uncorrected and were determined with a Fisher–Johns hot plate. I.r. spectra were recorded on a Perkin-Elmer 257 spectrophotometer, u.v. spectra for solutions in methanol with a Perkin-Elmer 200 spectrophotometer, and $^1H$ and $^{13}C$ n.m.r. spectra with a Varian XL-100 spectrometer. Mass spectra were run on a Du Pont 21-492B instrument at 70 eV. C.d. curves were measured for solutions in methanol with a Jobin Yvon instrument; specific rotations refer to $CHCl_3$ solutions, unless otherwise indicated, and were taken on an automatic Perkin-Elmer polarimeter. T.l.c. was carried out on silica gel (Merck 60 $GF_{254}$) and spots were visualized by spraying with vanillin–sulphuric acid solution and then heating at 120° for 10 min. Column chromatography was performed on silica gel 60 (0.063—0.200 mm; Merck) or on neutral $Al_2O_3$ (activity III, Merck). G.l.c.–m.s. analyses were run on a glass column of 3% OV-1 on Varaport 30 (100—120 mesh), carrier gas He, flow rate 20 ml $min^{-1}$, programmed temperature from 135 to 275° at 2° $min^{-1}$.

N.m.r. data are reported in Tables 1 and 2.

*Isolation of Drimenol* (I), *Uvidin A* (IIa), *and Uvidin B* (IIc) *from* Lactarius uvidus.—Fresh fruitbodies of *Lactarius uvidus* (*ca.* 2.7 kg), collected during the autumn in the mountains of the Trentino region (Italy), were extracted in the cold with acetone and then homogenized in a mixer with ethanol. The water phase, obtained after removal *in vacuo* of the solvent from both extracts, was extracted with ethyl acetate. The concentrated extract was washed with aqueous 5% w/v $NaHCO_3$ and then filtered on alumina (80 g) (eluant ethyl acetate) to remove the free fatty acids (*ca.* 400 mg). T.l.c. plates of the sesquiterpene residue (3.2 g) showed many yellow and red spots while g.l.c.–m.s. analysis showed three main peaks with $M^+$ 222, 252, and 268 and two minor products with $M^+$ 238 and 254.

The residue (3.0 g) was chromatographed on silica gel (150 g) using a benzene–ethyl acetate gradient as eluant. The first fractions, eluted with benzene–ethyl acetate (2 : 1), were rechromatographed on alumina using cyclohexane–benzene (3 : 1) as eluant to yield, after crystallization from pentane, drimenol (I) (32 mg), m.p. 97—98° (lit.,[17] 97—98°), $[\alpha]_D^{20}$ −22° [lit.,[17] −18° (benzene)], identical, m.p., mixed m.p., and spectral data with an authentic sample of (−)-drimenol.

The second fraction eluted by benzene–ethyl acetate (1 : 1) gave, after crystallization from pentane–$Et_2O$, *uvidin A* (IIa) (471 mg), m.p. 123—124°, $[\alpha]_D^{20}$ +151.1°; c.d. $[\theta]_{320}$ +13 101; $\nu_{max.}$ (KBr) 3 430 (OH) and 1 710 (CO) $cm^{-1}$; $\lambda_{max.}$ 204 (log ε 3.18) and 233sh nm; *m/e* 252 ($M^+$, 4%), 237 ($M$ − $CH_3$, 7), 224 ($M$ − CO, 28), 221 ($M$ − $CH_2OH$, 3), 219 ($M$ − $CH_3$ − $H_2O$, 5), 209 (10), 193 (20), 167 (9), 151 [(IIIa), 100], 135 (17), 123 (62), 109 (61), 95 (37), 83 (40), 81 (35), 69 (43), 67 (28), 55 (42), 43 (55), and 41 (40).

Crystallization of mother-liquors of (IIa) afforded further crops (175 mg) of uvidin A, m.p. 122—123°. The last fractions, eluted from a silica gel column with benzene–ethyl acetate (1 : 2) were concentrated and on standing at −20 °C deposited fine needles (280 mg) of *uvidin B* (IIc), recrystallized from ethyl acetate, m.p. 180—181°, $[\alpha]_D^{20}$ +171° ($Me_2CO$), c.d. $[\theta]_{320}$ +10 923; $\nu_{max.}$ (KBr) 3 470 (OH) and 1 722 (CO) $cm^{-1}$; $\lambda_{max.}$ 206 nm (log ε 3.01); *m/e* 268 ($M^+$, 9%), 253 ($M$ − $CH_3$, 2), 250 ($M$ − $H_2O$, 4), 239 (12), 221 (15), 203 (8), 191 (17), 167 [(IIIb), 100], 149 (32), 139 (22), 123 (28), 121 (50), 109 (17), 107 (19), 96 (34), 83 (47), 69 (18), 55 (28), 43 (47), and 41 (28).

*Acetylation of* (IIa).—Uvidin A (IIa) (50 mg) was acetylated by $Ac_2O$–pyridine overnight at room temperature. Recovery of the product in the usual way gave the monoacetate (IIb), m.p. 81.5—82.5° (EtOH–$H_2O$); $[\alpha]_D^{20}$ +155.6°; $\nu_{max.}$ (KBr) 1 752 (acetate) and 1 718 (ketone) $cm^{-1}$; *m/e* 294 ($M^+$, 2%), 252 ($M$ − 42, 2), 234 ($M$ − $CH_3COOH$, 29), 215 ($M$ − $CH_3COOH$ − $CH_3$, 13), 205 (25), 191 (13), 173 (23), 163 (11), 151 (58), 135 (45), 123 (58), 109 (69), 95 (26), 83 (69), 69 (51), 55 (32), and 43 (100).

$NaBH_4$ *Reduction of Uvidin A Acetate* (IIb) *to* (IVb).—To a solution of (IIb) (30 mg) in MeOH (3 ml) was added $NaBH_4$ (30 mg) and the mixture was stirred at room temperature for 20 min. Work-up in the usual way afforded by crystallization from EtOH–$H_2O$, 6-dihydrouvidin A acetate (IVb) (29 mg, 95%), m.p. 75—77°; $\nu_{max.}$ (KBr) 3 538 (OH), 1 735, and 1 250 (acetate) $cm^{-1}$.

$NaBH_4$ *Reduction of Uvidin* A (IIa) *to* (IVa).—Reduction of (IIa) in a way similar to (IIb) gave 6-dihydrouvidin A (IVa), m.p. 107—111° (hexane); $\nu_{max.}$ 3 400 (OH) $cm^{-1}$; *m/e* 254 ($M^+$, 1%), 239 ($M$ − $CH_3$, 5), 236 ($M$ − $H_2O$, 7), 223 ($M$ − $CH_2OH$, 4), 221 ($M$ − $CH_3$ − $H_2O$, 9), 218 ($M$ − 2 $H_2O$, 7), 205 ($M$ − $CH_2OH$ − $H_2O$, 13), 203 (10), 191 (11), 177 (18), 175 (16), 166 (17), 153 (31), 151 (23), 139 (24), 135 (27), 123 (38), 121 (31), 109 (78), 97 (50), 95 (51), 84 (95), 83 (92), 81 (45), 69 (75), 55 (72), 43 (88), 41 (100), and 31 (60).

*Hydrogenolytic Opening of the Epoxide* (IIa) *to* (V).—Uvidin A (20 mg) in EtOH (2 ml) was hydrogenated over Pd–C for 8 h at 20° and 1 atm. Work-up in the usual way gave after crystallization from hexane–$Et_2O$ 8β-hydroxy-6-oxodrimanol (V) (11 mg), m.p. 168—169°; $[\alpha]_D^{20}$ +44.76°; c.d. $[\theta]_{299}$ +3 069; $\nu_{max.}$ (KBr) 3 470, 3 375 (OH), and 1 700 (CO) $cm^{-1}$; $\lambda_{max.}$ 204 nm (log ε 2.99); *m/e* 254 ($M^+$, *ca.* 1%), 239 ($M$ − $CH_3$, 7), 236 ($M$ − $H_2O$, 3), 218 (22), 203 (15), 175 (10), 161 (11), 155 (12), 153 (14), 152 (12), 151 (44), 149 (16), 148 (15), 147 (13), 136 (18), 135 (100), 123 (30), 122 (13), 121 (18), 112 (14), 109 (25), 107 (15), 105 (14), 95 (19), 91 (18), 83 (16), 81 (17), 79 (14), 77 (13), 69 (24), 67 (17), 55 (23), 53 (12), 43 (22), and 41 (27).

*Action of Hydrazine Hydrate–Acetic Acid on Uvidin A* (IIa) *to* (V).—To a solution of uvidin A (75 mg) in anhydrous MeOH (1 ml) was added at 0° with stirring 100% hydrazine hydrate (45 mg) in MeOH (0.5 ml) followed by addition of few drops of glacial acetic acid. The mixture was kept at 0° for 45 min and then at room temperature for 24 h. No evolution of nitrogen was detected and the solution turned pale yellow. Evaporation of MeOH without heating left a residue which was dissolved in $CH_2Cl_2$ and the organic phase was then dried ($Na_2SO_4$) and evaporated. The residue gave two spots on t.l.c. (eluant $Et_2O$): a red spot for the less polar product and a yellow one for the more

polar component. The mixture was separated by preparative t.l.c. ($Et_2O$–$Me_2CO$ 50 : 9). The higher $R_F$ compound (6 mg) was shown to be identical to 8β-hydroxy-6-oxodrimanol (V) obtained as described above by catalytic hydrogenation of (IIa). The second compound (9 mg) was not identified.

*De-epoxidation of Uvidin A* (IIa) *with* KI *in Acetic Acid to* (VIa).—The epoxy-ketone (IIa) (120 mg) and a few crystals of KI in glacial AcOH (2 ml) were heated on a steam-bath (60—70°) for 10 min. The solution turned yellowish brown due to liberation of iodine. After cooling and dilution with MeOH the solution was percolated on a strong basic ion exchange resin column to remove AcOH and $I_2$. The crude product (which showed only one spot on t.l.c.) was chromatographed on a silica gel column (eluant $CH_2Cl_2$–$Et_2O$, 5 : 1) which gave, in quantitative yields, 6-oxodrimenol (VIa), m.p. 84° (hexane); c.d. $[\theta]_{333}$ ×4 950; $\nu_{max.}$ 3 490, 3 400 (OH), and 1 650 (conjugated CO) $cm^{-1}$; $\lambda_{max.}$ 239.5 (log ε 3.76); *m/e* 236 ($M^+$, 15%), 221 ($M - CH_3$, 6), 218 ($M - H_2O$, 40), 205 ($M - CH_2OH$, 6), 203 ($M - CH_3 - H_2O$, 22), 175 (16), 163 (10), 161 (14), 153 (33), 149 (21), 148 (18), 147 (17), 136 (29), 135 (100), 124 (20), 123 (84), 122 (18), 121 (27), 119 (13), 112 (45), 111 (25), 109 (35), 107 (19), 105 (20), 97 (21), 95 (28), 91 (24), 83 (14), 81 (18), 79 (16), 77 (17), 69 (28), 67 (20), 65 (10), 56 (13), 55 (26), 53 (16), 43 (25), and 41 (29).

*Catalytic Hydrogenation of* 6-*Oxodrimenol* (VIa) *to* (VIIa).—Compound (VIa) (71 mg) in ethyl acetate (2 ml) was hydrogenated at room temperature at atmospheric pressure in the presence of Adams' catalyst (16 mg). One mole of hydrogen was taken up during 20 min. Work-up in the usual way gave a solid (68 mg, 95%) which was crystallized from hexane to give 6-oxodrimanol (VIIa), m.p. 108—110° (hexane); $[\alpha]_D^{20}$ +34.30°; c.d. $[\theta]_{301}$ +4 818; $\nu_{max.}$ 3 460 (OH) and 1 700 (CO) $cm^{-1}$; $\lambda_{max.}$ 203 nm (log ε 2.97); *m/e* 238 ($M^+$, 18%), 223 ($M - CH_3$, 12), 220 ($M - H_2O$, 2), 205 ($M - H_2O - CH_3$, 5), 155 (26), 153 (14), 152 (24), 151 (100), 137 (13), 135 (10), 125 (12), 124 (22), 123 (38), 111 (16), 110 (20), 109 (49), 108 (16), 107 (15), 98 (11), 97 (18), 96 (19), 95 (30), 93 (13), 91 (11), 83 (31), 82 (18), 81 (26), 79 (13), 77 (11), 72 (10), 71 (19), 69 (40), 68 (22), 67 (21), 57 (16), 55 (33), 53 (16), 43 (35), 41 (32), and 31 (11).

*Synthesis of* (+)-*Drimanol* (VIII).—(a) *Catalytic hydrogenation of drimenol* (I). Drimenol (I) (28 mg) was hydrogenated in ethyl acetate (2 ml) and two drops of acetic acid with Adams' catalyst (6 mg) at 20° and 1 atm. Work-up in the usual way afforded drimanol (VIII) (29 mg), needles from $Me_2CO$–$H_2O$, m.p. 106—108° (lit.,[17] 110—111°); $[\alpha]_D^{20}$ +9.2° ($C_6H_6$) [lit.,[17] +15° ($C_6H_6$)]; $\nu_{max.}$ (KBr) 3 360 (OH) $cm^{-1}$; *m/e* 224 ($M^+$, 29%), 209 ($M - CH_3$, 40), 206 ($M - H_2O$, 10), 191 (23), 163 (10), 150 (13), 149 (18), 138 (18), 137 (21), 135 (20), 125 (19), 124 (30), 123 (100), 121 (23), 111 (20), 110 (17), 109 (63), 107 (22), 105 (14), 99 (14), 97 (25), 96 (24), 95 (72), 93 (25), 91 (20), 85 (21), 83 (30), 82 (39), 81 (74), 79 (24), 77 (21), 71 (27), 69 (78), 67 (43), 59 (35), 57 (73), 55 (25), 43 (46), and 41 (95).

(b) *Wolff–Kishner reduction of* 6-*oxodrimanol* (VIIa). 6-Oxodrimanol (VIIa) (57 mg), triethylene glycol (4 ml), 100% hydrazine hydrate (5 ml), and hydrazine hydrochloride (800 mg) were heated under reflux (internal temperature 130—140°) for 4 h in a stream of nitrogen. After addition of 85% KOH (1.11 g), excess of hydrazine was distilled off and the mixture heated at 220° (internal temperature) for 2 h. Dilution with $H_2O$ and extraction with $Et_2O$ gave a crude product (53 mg) which was purified by column chromatography on silica gel (<0.063 mm, Merck; eluant $CH_2Cl_2$–$Et_2O$ 6 : 1) and then crystallized from aqueous acetone to give drimanol (VIII) (14 mg), m.p. 109—110° (lit.,[17] 110—111°); $[\alpha]_D^{20}$ +12.7° ($C_6H_6$) [lit.,[17] +15° ($C_6H_6$)], identical with the product obtained by hydrogenation of drimenol.

*Acetylation of Uvidin B* (IIc) *to* (IId).—Uvidin B (IIc) (30 mg) was acetylated by $Ac_2O$–pyridine overnight at room temperature. Recovery of the product as usual and crystallization from EtOH–$H_2O$ gave the diacetate (IId), m.p. 150—152°; $[\alpha]_D^{20}$ +140.2°; $\nu_{max.}$ (KBr) 1 750 and 1 738 (acetate) and 1 715 (ketone) $cm^{-1}$.

*De-epoxidation of Uvidin B* (IIc) *with* KI *in Acetic Acid to* (VIb).—Uvidin B (100 mg) and a few crystals of KI in acetic acid (2 ml) were heated at 60—70° for 10 min. After cooling, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The extract was successively washed with sodium thiosulphate, sodium hydrogencarbonate, and water and dried ($Na_2SO_4$). Removal of the solvent and crystallization from $Et_2O$–pentane gave 7,8-deoxyuvidin B (VIb) (45 mg), m.p. 222—226°; $[\alpha]_D^{20}$ +14.71° (MeOH); c.d. $[\theta]_{333}$ +3 234; $\nu_{max.}$ (KBr) 3 400 (OH) and 1 655 (unsaturated CO) $cm^{-1}$; $\lambda_{max.}$ 239.5 nm (log ε 3.83); *m/e* 252 ($M^+$, 13%), 237 (3), 234 ($M - H_2O$, 18), 221 ($M - CH_2OH$, 5), 219 (12), 216 (20), 201 (18), 193 (18), 191 (12), 189 (18), 176 (12), 175 (20), 173 (15), 164 (19), 163 (73), 161 (16), 159 (12), 153 (20), 149 (23), 147 (18), 137 (19), 136 (21), 135 (58), 134 (24), 124 (22), 123 (100), 122 (35), 121 (30), 119 (20), 112 (46), 111 (33), 109 (27), 108 (21), 107 (30), 105 (25), 97 (33), 96 (31), 95 (36), 93 (22), 91 (28), 84 (16), 83 (30), 82 (18), 81 (28), 79 (24), 77 (25), 71 (15), 69 (37), 67 (27), 65 (18), 64 (16), 57 (24), 56 (27), 55 (47), 53 (26), 43 (64), and 41 (57).

*De-epoxidation of Uvidin B Diacetate* (IId) *to* (VIc).—From uvidin B diacetate (IId) (43 mg), with work-up as described for (IIc), 7,8-deoxyuvidin B diacetate (VIc) (29 mg) was obtained, m.p. 104—106° (EtOH–$H_2O$); $[\alpha]_D^{20}$ +60.78°; $\nu_{max.}$ (KBr) 1 730 and 1 745 (acetate) and 1 665 (unsaturated ketone) $cm^{-1}$.

*Catalytic Hydrogenation of* 7,8-*Deoxyuvidin B* (VIb) *to* (VIIb).—The enone (VIb) (42 mg) in EtOH (5 ml) and a few drops of acetic acid was hydrogenated with Adams' catalyst (10 mg) at 20° and 1 atm. for 40 min. Work-up as usual afforded 3β-hydroxy-6-oxodrimanol (VIIb) (42 mg), m.p. 207—209°, needles from $Et_2O$–pentane, $[\alpha]_D^{20}$ +30.64° (MeOH); c.d. $[\theta]_{301}$ +4 653; $\nu_{max.}$ (KBr) 3 420 (OH) and 1 700 (ketone) $cm^{-1}$; $\lambda_{max.}$ 204 nm (log ε 2.78); *m/e* 254 ($M^+$, 18%), 239 ($M - CH_3$, 3), 236 ($M - H_2O$, 2), 221 ($M - H_2O - CH_3$, 9), 195 (26), 178 (13), 168 (28), 167 (100), 155 (26), 149 (27), 139 (28), 137 (24), 135 (19), 125 (31), 124 (20), 123 (43), 122 (31), 121 (54), 111 (29), 109 (35), 107 (34), 105 (18), 99 (17), 98 (18), 97 (31), 96 (52), 95 (44), 93 (26), 91 (23), 85 (20), 83 (86), 82 (27), 81 (45), 79 (23), 77 (23), 72 (16), 71 (30), 69 (60), 68 (22), 67 (34), 58 (36), 57 (98), 55 (30), 43 (95), and 41 (88).

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