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NEW FATTY ACID ESTERS OF DRIMANE SESQUITERPENES FROM *LACTARIUS UVIDUS*[1]

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ABSTRACT.—This study of lipids of *Lactarius uvidus* has revealed the presence of new fatty acid esters of uvidin A [**2a–d**] and drimenol [**6a–d**]. Treatment of uvidin A [**1**] with base induced a Favorskii-like rearrangement leading to compounds with a new sesquiterpenoid skeleton. Uvidin A [**1**] showed insect antifeedant and cytotoxic activities.

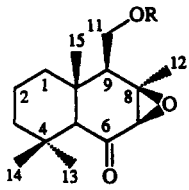
Large quantities of tasteless and biologically inactive fatty acid esters of sesquiterpenoid alcohols are stored in intact cells of *Lactarius* fruiting bodies and can be isolated when such mushrooms are worked up under carefully controlled conditions. These fatty acid esters are transformed by esterases and other enzymes into free sesquiterpene aldehydes and alcohols in response to injury (2–5). The latter compounds usually impart an intense pungent or bitter taste to the latex and flesh of the mushrooms and possess potent antibiotic, antifungal, and insect antifeedant activities. Therefore, they are considered to function as a chemical defense system protecting the mushrooms (2).

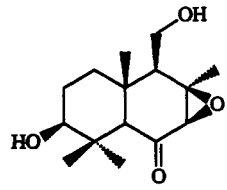
Uvidins A [**1**], B [**4**], C, D, and E, along with drimenol [**5**], have been isolated from an Me_2CO extract of *Lactarius uvidus* Fr. (Russulaceae) (6,7). Drimane-type sesquiterpenoids have not been found so far in other Russulaceae species and their distribution in wild higher fungi (Basidiomycetes) is not well documented (8,9). Because uvidins A–E and drimenol possess free hydroxy groups, it was of interest to determine whether they were artifacts and if the corresponding fatty acid esters or other precursors could be found among the lipids of *L. uvidus*.

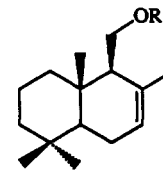
RESULTS AND DISCUSSION

When previously used as an extraction solvent of *L. uvidus*, Me_2CO has been shown to induce formation of chemical artifacts during extraction of *Lactarius* sesquiterpenoids (10). Therefore, during this investigation, frozen fruiting bodies of *L. uvidus* were rapidly minced in the cold and extracted with CH_2Cl_2 at $-20°$. For comparison, intact fruiting bodies, apparently undamaged by parasites or insects, were extracted with CH_2Cl_2 at $-20°$. The two extracts were identical by tlc, showing a large number of low polar compounds with chromatographic behavior typical of fats. Prep. cc on Si gel led to isolation of the following in order of increasing polarity: saturated and unsaturated fatty acid esters of drimenol [**6a–c**], fatty acid methyl esters, triglycerides, 6-ketostearoyldrimenol [**6d**], fatty acid esters of uvidin A [**2a–c**], and 6-ketostearoyluvidin A [**2d**]. No attempt was made to separate further the mixtures of esters and triglycerides because of their similar chromatographic properties. In more polar fractions (see Experimental) drimenol [**5**], and uvidins A [**1**], B [**4**], and D were isolated. The structures of isolated compounds were established by nmr spectroscopy and comparison with authentic samples. In addition, gc and gc-ms analysis of methyl esters obtained by separate transesterification of fatty acid esters and triglycerides indicated the identity and distribution of each fatty acid in ester mixtures (Table 1). For identification, the retention times and ms were compared with those of standard samples and the reference

[1]Part 32 in the series "Fungal Metabolites." For part 31, see L. Garlaschelli *et al.* (1).







1 R=H
2a R=$CO(CH_2)_nCH_3$, n=14, 16
2b R=$CO(CH_2)_7CH{=}CH(CH_2)_7CH_3$
2c R=$CO(CH_2)_7(CH{=}CHCH_2)_2(CH_2)_3CH_3$
2d R=$CO(CH_2)_4CO(CH_2)_{11}CH_3$
3 R=$CH(CH_3)OCH_2CH_3$
4
5 R=H
6a R=$CO(CH_2)_nCH_3$, n=14, 16
6b R=$CO(CH_2)_7CH{=}CH(CH_2)_7CH_3$
6c R=$CO(CH_2)_7(CH{=}CHCH_2)_2(CH_2)_3CH_3$
6d R=$CO(CH_2)_4CO(CH_2)_{11}CH_3$

ms of commercial libraries (11,12). A representative sample of the initial CH_2Cl_2 extract was also transesterified and analyzed by gc-ms. In this way, the overall content of each fatty acid occurring in the lipids of *L. uvidus* was determined (Table 1).

Our findings confirm that large amounts of sesquiterpenoid alcohols occur as fatty acid esters in the fruiting bodies of *Lactarius* species. However, in contrast with other *Lactarius* species (2–5, 13–19), sesquiterpenoid esters of C-16 saturated and C-18 unsaturated acids, instead of stearic or 6-ketostearic acids, are among the major metabolites of *L. uvidus*. Compounds **2a–d** and **6a–d** are new and represent the first examples of drimane fatty acid esters found in mushrooms. Interestingly, among the lipids of *L. uvidus*, 6-ketostearic acid is specifically esterified to drimenol and uvidin A, proving that the enzyme pool controlling the esterification step of sesquiterpenoid alcohols is different from that of other lipids. Sesquiterpenes with free alcoholic groups, such as **1**, **4**, and **5**, were also found in extracts of apparently undamaged samples of *L. uvidus* (see above), while in other *Lactarius* species (2–5, 13–19) intact fruiting bodies contain only fatty ester derivatives. It is possible that the lipases of *L. uvidus* are not completely deactivated during extraction in the cold. However, it is intriguing that no esters of uvidin B [**4**], one of the major free alcohols, could be found in significant amounts.

Free uvidin A [**1**] showed an LC_{50} value of 48.8 ppm in the brine shrimp (*Artemia salina*) lethality assay (20) and 97% and 21% inhibition of ^{3}H-thymidine incorporation into HL-60 human leukemia cells at the concentration of 50 γ/ml and 0.05 γ/ml, respectively. In the same test uvidin B [**4**] showed 61% and 0% inhibition, respectively. Moreover, antifeedant activity of uvidin A [**1**], B [**4**], and uvidin A lactarinate [**2d**] was tested on two phytophagous insects: *Spodoptera littoralis* (Boids) and *Leptinotarsa decemlineata* (Say). The measured antifeedant ratio and anorexic ratio values, as defined in Ref. 21, are reported in Table 2. These data show that drimane sesquiterpenes of *L. uvidus*,

TABLE 1. Distribution of Fatty Acids in the Various Esters of *L. uvidus*.[a]

Sample	Fatty Acids[b] (% in the mixture)
Esters of drimenol [**6a–c**]	$C_{16:0}$ (21.1); $C_{18:0}$ (6.5); 9Z-$C_{18:1}$ (19.0); 9Z,12Z-$C_{18:2}$ (27.0)
Triglycerides	$C_{16:0}$ (21.6); $C_{18:0}$ (2.7); 9Z-$C_{18:1}$ (52.9); 9Z,12Z-$C_{18:2}$ (16.6)
Esters of uvidin A [**2a–c**]	$C_{16:0}$ (8.0); $C_{18:0}$ (7.0); 9Z-$C_{18:1}$ (41.8); 9Z,12Z-$C_{18:2}$ (35.2)
CH_2Cl_2 total extract	$C_{16:0}$ (4.9); $C_{18:0}$ (2.3); 9Z-$C_{18:1}$ (11.5); 9Z,12Z-$C_{18:2}$ (11.5); 6-CO-$C_{18:0}$ (70)

[a]Minor unidentified acids are not reported.
[b]$C_{16:0}$=hexadecanoic acid; $C_{18:0}$=octadecanoic acid; $C_{18:1}$=octadecenoic acid; $C_{18:2}$=octadecadienoic acid.

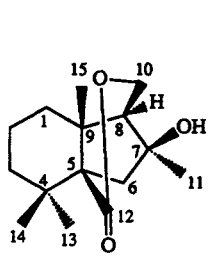
TABLE 2. Antifeedant Activity of Uvidins A [**1**] and B [**4**], and Uvidin A Lactarinate [**2d**].

Sample	*Spodoptera littoralis*				*Leptinotarsa decemlineata*		
	concentration (ppm)	Antifeedant ratio	Anorexic ratio	Death (%)	Antifeedant ratio	Anorexic ratio	Death (%)
Uvidin A [**1**]	100	94	41	0	28	34	0
	20	23	10	0	—	—	—
Uvidin B [**4**]	100	41	16	0	6	4	0
Uvidin A lactarinate [**2d**] ...	100	68	4	0	4	27	0
	20	7	0	0	0	1	0

particularly uvidin A [**1**], have the same biological role as other sesquiterpenes previously found in Russulaceae species (2–5, 13–19).

On treatment with methanolic KOH, uvidin A esters **2a–d** gave, besides the expected free uvidin A [**1**], an isomer of **1** possessing a new sesquiterpene skeleton. Exposure of free uvidin A [**1**] to base produced the same compound. This rearrangement product was assigned structure **7** based on the following spectral evidence: an ir band at 1700 cm^{-1} and a signal at δ 171.15 ppm in the ^{13}C-nmr spectrum for the δ-lactone C-12 carbonyl; an OH band at 3510 cm^{-1} and a quaternary C-O signal at δ 74.3 ppm for the tertiary C_7-OH group; four methyl singlets at δ 1.14, 1.18, 1.32, and 1.61 in the ^1H-nmr spectrum; an AB quartet centered at δ 2.31 for the isolated C-6 methylene group; and three signals at δ 34.0, 59.8, and 43.2 for the three vicinal quaternary carbon atoms C-4, C-5, and C-9, respectively. This **1** to **7** Favorskii-like rearrangement can easily occur as the *p*-orbital of the enolate anion formed by deprotonation of uvidin A [**1**] at C-5 is aligned in an antiperiplanary fashion to the C_7-O σ-orbital of the oxirane ring, thus fulfilling the stereochemical requirements for the reaction (22).

As expected, this rearrangment takes place also in *O*-protected uvidin A, for example in *O*-ethoxyethyl uvidin A [**3**]. In this case, we obtained the tricyclic rearrangement product **8**, still containing a lactone ring, but now involving the tertiary hydroxy group at C-7. We propose the name isothapsane for the hitherto unknown 1,2,2,6,7,8-hexamethylbicyclo[4.3.0]-nonane sesquiterpenoid skeleton of compounds **7** and **8**. This structure is isomeric to the thapsane skeleton **9**, but it contains an alkyl substituent at C-8 instead of at C-6.



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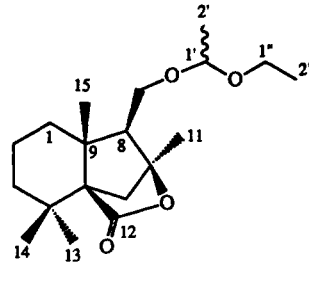

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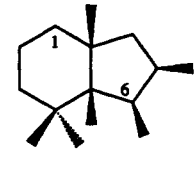

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EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mps were determined on a Fisher-Johns hot plate and are uncorrected. The ir spectra were recorded (film or KBr pellets) with a Perkin-Elmer model 257 spectrophotometer. ^1H- and ^{13}C-nmr spectra were recorded in $CDCl_3$ solution, unless otherwise indicated, using a Bruker WP80SY or ACE 300 or Varian XL-100 instrument. Chemical shifts (δ) are reported in ppm with Me_4Si as internal standard. Coupling constants (*J*) are reported in Hz. In the ^{13}C-nmr spectra the number

of hydrogens attached to the corresponding carbons was determined from DEPT experiments. Assignments with superscripts a–e may be interchanged. Ms were recorded with a Finnigan MAT 8222 or with a Du Pont 21-492B instrument, operating at 70 eV and using a direct inlet system. Specific optical rotations were determined with a Perkin-Elmer model 241 digital polarimeter. Cc was performed at atmospheric pressure on Kieselgel 60 (Merck) 0.040–0.063 mm, slurry packed, or Woelm neutral Al_2O_3 (activity III). Analytical GF_{254} tlc plates (0.25 mm) were obtained from Merck. The spots were visualized under uv light or by spraying the plates with 0.5% vanillin solution in H_2SO_4-EtOH (4:1) followed by heating at 120° for ca. 1 min. Gc capillary analysis was performed with an HRGC-5160 Mega Series Carlo Erba apparatus (SupelCowax TM10 capillary column, 30 m long, 0.32 mm i.d., 0.25 μm film thickness) under the following conditions: injection "on column," fid detector at 300°; H_2 as a carrier gas at 0.3 kg/cm^2 pressure; the temperature of the column oven increased from 90° to 180° at 40°/min, then from 180° to 270° at 5°/min, and finally was kept at 270° for 20 min. Gc-ms analysis was performed with a Finnigan-MAT ITS-40 instrument equipped with a DB-5MS capillary column, 30 m long, 0.25 mm i.d., 0.25 μm film thickness; chromatographic conditions: injector 250°, detector 270°; the temperature of the column oven increased from 40° to 300° at 8°/min, then kept at 300° for 20 min; He as a carrier gas. Standard fatty acids were purchased from Sigma and were methylated with CH_2N_2 in Et_2O. Details of the methodology used for the insect feeding inhibition bioassays are reported elsewhere (21).

EXTRACTION AND ISOLATION.—*Lactarius uvidus* (2 kg) was collected in a mixed wood near Cecina, Tuscania, Italy, in October 1982 and was identified by Ilario Filippi (Florence) of the Mycological Association Unione Micologica Italiana. A voucher specimen has been deposited in the herbarium of the mycological group G. Bresadola, Fara Novarese, Italy (No. GMFN 1909). The mushrooms were brought to the laboratory in Pavia a few hours after collection and frozen at −20°. The fruiting bodies were rapidly broken and then extracted three times with CH_2Cl_2 (2 liters each) at −20°. The combined extracts were dried rapidly ($MgSO_4$) and concentrated below 30° under reduced pressure. The residue (8.5 g) was adsorbed on the top of an Al_2O_3 column (225 g) and eluted with a gradient of Me_2CO in hexane (from 5 to 100% Me_2CO) and then with Me_2CO-MeOH (98:2). Fractions 1–11 were collected after tlc analysis. Crystallization of fraction 4 (0.78 g) from petroleum ether gave 0.6 g of 6-ketostearoyluvidin A [**2d**], while crystallization of fraction 5 (0.72 g) from hexane afforded drimenol [**5**] (0.26 g), mp 96–97° [lit. 97–98° (6)], identical (mixed mp, ir, nmr spectra) with an authentic sample of (−)-drimenol (6). Crystallization of fraction 9 (1.6 g) from hexane/Et_2O gave 0.86 g of uvidin A [**1**], mp 124–125° [lit. 123–124° (6)], identical (mixed mp and spectral data) with authentic (+)-uvidin A (6), while crystallization (hexane/Et_2O) of fraction 10 (0.3 g) afforded ergosterol peroxide (85 mg), mp 175–178° [lit. 181.5–183° (23)], and crystallization of fraction 11 (0.4 g) from EtOAc yielded uvidin B [**2**] (0.52 g), mp 179–181° (6), identical with an authentic sample (6). Fraction 1 (2.15 g), containing non-polar compounds with very close chromatographic properties, was further chromatographed on several Si gel columns, eluted with hexane to which different percentages (2–15%) of EtOAc were added. We obtained, in order of polarity, a mixture of fatty acid esters of drimenol [**6a–c**] (130 mg), 2-heptadecanone, fatty acid methyl esters (150 mg), triglycerides (230 mg), 6-ketostearoyldrimenol [**6d**] (150 mg), and fatty acid esters of uvidin A [**2a–c**] (70 mg).

The mixture of fatty acid methyl esters was directly analyzed by gc and gc-ms. Methyl linoleate, methyl oleate, and methyl palmitate were identified by comparison of their retention times and mass spectra with authentic reference compounds.

METHANOLYSIS OF TRIGLYCERIDES AND ESTERS **2a–d** AND **6a–d** (GENERAL PROCEDURE).—About 25 mg of the esters were stirred in 3 ml methanolic 10% KOH at room temperature until tlc indicated the disappearance of starting material. The mixture was diluted with Et_2O (20 ml) and extracted with H_2O, then with brine. The organic phase was dried ($MgSO_4$), concentrated, and separated on a Si gel column with a hexane/EtOAc mixture. Uvidin A [**1**] and drimenol [**5**] were identical with authentic samples (6). Fatty acid methyl esters were obtained as an inseparable mixture and were identified by gc and gc-ms. Methyl 6-ketostearate (mp 45°) was identical with an authentic sample.

DRIMENOL ESTERS **6a–c**.—Ir ν max 2915, 2840, 1730, 1450, 1380, 1360, 1160, 1110, 810, 720 cm^{-1}; ^{1}H nmr (80 MHz) δ 0.83, 0.87, 0.88 (3H each, 3s, H_3-13, H_3-14, H_3-15), 0.88 (3H, br t, ω″-H_3), 1.30 (br s, $-(CH_2)_n$-ester chain), 1.68 (3H, br s, H_3-12), 1.75–2.12 (m, H_2-6 and allylic methylenes of ester chain), 2.30 (2H, t, J=7.0 Hz, H_2-2″), 2.77 (t, J=5.0 Hz, diallylic methylene of ester chain), 4.09 (1H, dd, $J_{11,11'}$=12.0 Hz, $J_{11,9}$=6.0 Hz, H-11), 4.29 (1H, dd, $J_{11,11'}$=12.0 Hz, $J_{11',9}$=4.0 Hz, H-11′), 5.13–5.62 (m, H-7 and olefinic protons of ester chain); eims *m/z* [M−RCOOH]$^+$ 204 (100), 189 (21), 161 (25), 148 (18), 135 (21), 133 (13), 122 (19), 121 (20), 119 (15), 109 (39), 108 (29), 105 (11), 97 (11), 95 (24), 93 (12), 85 (31), 83 (53), 81 (28), 69 (27), 67 (16), 57 (18), 55 (32), 43 (26), 41 (26).

6-KETOSTEAROYLDRIMENOL (DRIMENOL LACTARINATE) [**6d**].—Waxy solid, mp 22–23°; $[\alpha]^{20}$D +7.24° (c=1.3, $CHCl_3$); ir ν max 2920, 2850, 1735, 1715, 1455, 1410, 1385, 1365, 1165, 1095, 1050, 1030, 980,

810, 720 cm^{-1}; ^1H nmr (300 MHz) δ 0.83, 0.87, 0.90 (3H each, 3s, H_3-13, H_3-14, H_3-15), 0.89 (1H, t, J=6.5 Hz, H_3-18″), 1.28 (18H, br s, H_2-9″-H_2-17″), 1.57–1.65 (6H, m, H_2-3″, H_2-4″, H_2-8″), 1.67 (3H, br s, H_3-12), 2.31, 2.39, and 2.42 (2H each, 3t, J=7.2 Hz, H_2-2″, H_2-5″, H_2-7″), 4.09 (1H, dd, $J_{11,11'}$=11.5 Hz, $J_{11,9}$=6.5 Hz, H-11), 4.29 (1H, dd, $J_{11,11'}$=11.5 Hz, $J_{11',9}$=3.3 Hz, H-11′), 5.51 (1H, m, H-7); ^{13}C nmr (75.5 MHz) δ 210.8 (s, C-6″), 173.3 (s, C-1″), 132.3 (s, C-8), 123.6 (d, C-7), 62.9 (t, C-11), 53.3 (d, C-5)[a], 49.7 (d, C-9)[a], 42.7 (t, C-5″)[b], 42.1 (t, C-7″)[b], 41.9 (t, C-3), 39.4 (t, C-1), 35.8 (s, C-10), 34.2 (t, C-2″), 33.1 (q, C-13), 32.8 (s, C-4), 31.8 (t, C-16″), 29.5 (t, C-9″)[c], 29.5 (t, C-10″)[c], 29.5 (t, C-11″)[c], 29.3 (t, C-12″)[c], 29.3 (t, C-13″)[c], 29.2 (t, C-14″)[c], 29.1 (t, C-15″)[c], 24.3 (t, C-3″)[d], 23.7 (t, C-4″)[d], 23.4 (t, C-6)[d], 23.1 (t, C-8″)[d], 22.5 (t, C-17″)[d], 21.8 (q, C-12)[e], 21.6 (q, C-14)[e], 18.6 (t, C-2), 14.4 (q, C-15), 14.0 (q, C-18″); eims *m/z* $[M-RCOOH]^+$ 204 (100), 189 (25), 161 (32), 148 (17), 135 (22), 133 (15), 122 (21), 121 (33), 120 (13), 119 (19), 109 (35), 108 (30), 105 (13), 95 (24), 93 (14), 83 (17), 81 (25), 69 (19), 57 (26), 55 (31), 43 (33), 41 (25).

UVIDIN A ESTERS **2a–c**.—Ir ν max 2920, 2845, 1730, 1710, 1380, 1225, 1160, 1115, 890, 870, 810 cm^{-1}; ^1H nmr (80 MHz) δ 0.85 (3H, br t, ω″-H_3), 0.88, 1.02, 1.10 (3H, 3s each, H_3-13, H_3-14, H_3-15), 1.25 (br s, $-(CH_2)_n$-ester chain), 1.32 (3H, s, H_3-12), 1.88 (1H, s, H-5), 1.90–1.22 (m, allylic methylenes of ester chain), 2.30 (2H, t, J=7.0 Hz, H_2-2″), 2.75 (t, J=5.0 Hz, diallylic methylenes of ester chain), 2.88 (1H, s, H-7), 4.25 (1H, dd, $J_{11,11'}$=12.0 Hz, $J_{11,9}$=6.0 Hz, H-11), 4.50 (1H, dd, $J_{11,11'}$=12.0 Hz, $J_{11',9}$=3.0 Hz, H-11′), 5.20–5.50 (m, olefinic protons of ester chain); eims *m/z* 518 (5), 516 (3), 514 (2), 267 (22), 252 (19), 235 (55), 234 (39), 224 (15), 219 (25), 206 (55), 191 (40), 178 (11), 163 (12), 151 (80), 123 (65), 109 (62), 97 (37), 95 (37), 83 (100), 82 (87), 71 (35), 69 (52), 57 (61), 55 (55), 43 (65), 41 (44).

6-KETOSTEAROYLUVIDIN A (UVIDIN A LACTARINATE) [**2d**].—Waxy solid, mp 52–53°; $[\alpha]^{20}D$ +101.8° (c=0.7, $CHCl_3$); ir ν max 2910, 2840, 1725, 1705, 1465, 1410, 1385, 1315, 1295, 1280, 1258, 1230, 1205, 1170, 1155, 1125, 1095, 1045, 1015, 1005, 985, 970, 915, 890, 875, 860, 810, 770, 755, 715, 690 cm^{-1}; ^1H nmr (300 MHz) δ 0.87 (3H, br t, J=6.0 Hz, H_3-18″), 0.92, 1.07, 1.17 (3H each, 3s, H_3-13, H_3-14, H_3-15), 1.25 (18H, br s, H_2-9″-H_2-17″), 1.40 (3H, s, H_3-12), 1.91 (1H, s, H-5), 1.6–1.7 (6H, m, H_2-3″, H_2-4″, H_2-8″), 1.96 (1H, dd, $J_{11,9}$=6.3 Hz, $J_{11',9}$=3.0 Hz, H-9), 2.3–2.5 (6H, m, H_2-2″, H_2-5″, H_2-7″), 2.92 (1H, s, H-7), 4.37 (1H, dd, $J_{11,11'}$=12.0 Hz, $J_{11,9}$=6.3 Hz, H-11), 4.62 (1H, dd, $J_{11,11'}$=12.0 Hz, $J_{11',9}$=3.0 Hz, H-11′); ^{13}C nmr (75.5 MHz) δ 210.8 (s, C-6″), 204.0 (s, C-6), 173.0 (s, C-1″), 64.8 (d, C-5), 62.3 (t, C-11), 61.0 (d, C-7), 60.6 (s, C-8), 52.1 (d, C-9), 42.8 (t, C-5″)[a], 42.6 (t, C-7″)[a], 42.1 (t, C-3)[a], 40.3 (t, C-1), 37.1 (s, C-10), 34.1 (t, C-2″), 33.1 (q, C-13), 32.2 (s, C-4), 31.8 (t, C-16″), 29.5 (t, C-9″)[b], 29.5 (t, C-10″)[b], 29.4 (t, C-12″)[b], 29.3 (t, C-13″)[b], 29.2 (t, C-14″)[b], 29.1 (t, C-15″)[b], 24.3 (t, C-3″)[c], 23.8 (t, C-4″)[c], 23.0 (t, C-8″)[c], 22.6 (t, C-17″)[c], 21.4 (q, C-14)[d], 21.3 (q, C-12)[d], 18.3 (q, C-15), 17.6 (t, C-2), 14.0 (q, C-18″); eims *m/z* $[M]^+$ 532 (2), $[M-CH_3(CH_2)_8CH=CH_2]^+$ 378 (4), 281 (13), 263 (16), 235 (78), $[M-RCOOH]^+$ 234 (47), 219 (31), 218 (20), $[234-CO]^+$ 206 (100), 151 (50), 135 (35), 126 (15), 123 (36), 111 (24), 109 (42), 97 (19), 95 (39), 83 (53), 71 (28), 69 (33), 57 (41), 55 (46), 43 (55).

REARRANGEMENT OF UVIDIN A [**1**] TO LACTONE **7**.—Uvidin A [**1**] (18 mg) was stirred in 2 ml 1% methanolic KOH at 65° for 5 h. The mixture was diluted with H_2O (15 ml) and extracted with Et_2O (3×15 ml). The organic phase was washed with 3% aqueous HCl, H_2O, dried ($MgSO_4$), and taken to dryness. Crystallization of the residue from hexane/Et_2O gave lactone **7** (15 mg), mp 206–208° (closed capillary tube); $[\alpha]^{21}D$ −25.7° (c=0.4, $CHCl_3$); ir ν max 3510, 2910, 1700, 1460, 1376, 1258, 1205, 1185, 1160, 1100, 1065, 1015, 955, 940, 890 cm^{-1}; ^1H nmr (300 MHz) δ 1.14, 1.18, 1.32, 1.61 (3H each, 4s, H_3-11, H_3-13, H_3-14, H_3-15), 1.2–1.8 (6H, m, H_2-1, H_2-2, H_2-3), 1.70 (1H, dd, $J_{8,10}$=2.8 Hz, $J_{8,10'}$=1.5 Hz, H-8), 1.98 (1H, d, $J_{6,6'}$=15.0 Hz, H_6), 2.64 (1H, d, $J_{6,6'}$=15.0 Hz, H-6′), 4.40 (1H, dd, $J_{10,10'}$=10.7 Hz, $J_{10,8}$=2.8 Hz, H-10), 4.73 (1H, dd, $J_{10,10'}$=10.7 Hz, $J_{10',8}$=1.5 Hz, H-10′); ^{13}C nmr (75.5 MHz) δ 18.3 (t, C-2), 22.6 (q, C-15)[a], 23.9 (q, C-14)[a], 29.3 (q, C-11), 32.0 (t, C -1), 32.6 (q, C-13), 34.0 (s, C-4), 37.8 (t, C-3), 43.2 (s, C-9), 50.0 (t, C-6), 56.9 (d, C-8), 59.8 (s, C-5), 67.5 (t, C-10), 74.3 (s, C-7), 171.5 (s, C-12); eims *m/z* $[M]^+$ 252 (13), $[M-H_2O]^+$ 234 (12), 193 (34), 177 (28), 176 (22), 139 (54), 138 (35), 137 (46), 135 (20), 123 (46), 121 (42), 119 (25), 109 (30), 108 (24), 107 (38), 95 (39), 93 (25), 83 (23), 81 (35), 79 (20), 71 (34), 69 (51), 67 (23), 55 (43), 43 (100).

REARRANGEMENT OF *O*-1′-ETHOXYETHYL UVIDIN A [**3**] TO LACTONE **8**.—*O*-1′-Ethoxyethyl uvidin A [**3**] (65 mg) was obtained as a mixture of 1′ diastereomers from uvidin A [**1**] (80 mg) and ethylvinyl ether, following a standard procedure (24). Ir ν max 2970, 2920, 1710, 1440, 1380, 1340, 1290, 1228, 1130, 1090, 1055, 985, 968, 928, 810 cm^{-1}; ^1H nmr (300 MHz) δ 0.88, 1.08, 1.16 (3H each, 3s, H_3-13, H_3-14, H_3-15), 1.23 (3H, br t, J=7.0 Hz, H_3-2″), 1.35 (3H, br d, J=5.5 Hz, H_3-2′), 1.43 and 1.45 (3H overall, 2s, H_3-12), 1.90 (1H, s, H-5), 2.90 (1H, s, H-7), 3.42–3.95 (4H, m, H_2-11 and H_2-1″), 4.7 (1H, m, H-1′). Compound **3** (33 mg) was stirred in 1.3 ml of 12% aqueous KOH at 40° for 6 h. The mixture was diluted with H_2O and extracted with CH_2Cl_2 (3×10 ml). The organic solution was washed with brine, dried ($MgSO_4$), and evaporated. Cc on a Si gel column, eluted with EtOAc-hexane (1:9), gave 12 mg of rearranged

product **8**, as a mixture of diastereomers at C-1′, $[\alpha]^{21}D$ +40.4° (c=0.5, $CHCl_3$); ir ν max 2960, 2920, 1770, 1450, 1380, 1300, 1248, 1130, 1080, 1050, 990, 920, 890 cm^{-1}; ^1H nmr (300 MHz) δ 0.98 (3H), 1.16 and 1.17 (3H overall), 1.43 (3H), 1.48 (3H) (H_3-11, H_3-13, H_3-14, H_3-15), 1.20 (3H, br t, J=7.0 Hz, H_3-2″), 1.28 (3H, d, J=5.5 Hz, H_3-2′), 1.80 (1H, m, H-8), 1.89 (1H, d, J=11.0 Hz, H-6a), 2.23 (1H, d, J=11.0 Hz, H-6b), 3.35–3.80 (4H, m, H_2-10 and H_2-1″), 4.62 (1H, 2 overlapped q, J=5.5 Hz, H-1′); ^{13}C nmr (75.5 MHz) δ 176.3 (s, C-12), 99.3 and 98.8 (2d, C-1′), 85.0 (s, C-7), 62.1 and 61.4 (2t, C-10)[a], 60.7 and 60.6 (2s, C-7), 60.5 and 60.3 (2t, C-1″)[a], 56.7 and 56.6 (2d, C-8), 44.4 (t, C-6), 41.9 (s, C-9), 38.6 and 38.5 (2t, C-3), 38.0 (t, C-1), 30.9 (s, C-4), 29.7 (q, C-13), 21.7 (q, C-11)[b], 19.1 and 18.9 (2q, C-14)[b], 18.5 and 18.4 (2q, C-15)[b], 17.7 (t, C-2), 17.5 and 17.4 (2q, C-2′)[b], 14.4 and 14.3 (2q, C-2″); eims *m/z* $[M]^+$ 324 (2), 309 (5), 278 (11), 236 (20), 235 (20), 207 (20), 192 (10), 177 (10), 139 (10), $[C_2H_4OC_2H_5]^+$ 73 (100), $[OC_2H_5]^+$ 45 (40).

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