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# PARTIAL SYNTHESIS OF OLEUROPEIN[1]

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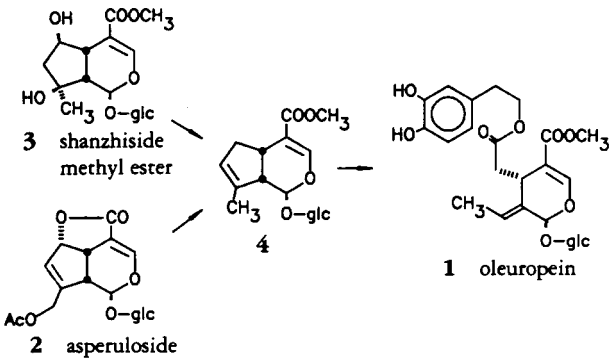
ABSTRACT.—The partial synthesis of oleuropein [**1**], the first secoiridoid isolated, is described. A biomimetic approach has been chosen, focusing on the oxidative cleavage of 10-deoxygeniposide [**4**], a suitable iridoid, obtained from asperuloside [**2**] and shanzhiside methyl ester [**3**].

Oleuropein [**1**] is a bitter glucoside present in the leaves and in the fruits of *Olea europaea* L. (Oleaceae). Its structure was elucidated in 1960 by Panizzi *et al.* (1). *Ol. europaea* is known to be relatively immune to microbe and insect attack, and at least a part of this immunity may be attributed to high concentrations of oleuropein [**1**], demethyloleuropein, and the related secoiridoid ligstroside (2).

We focused our attention on the problem of the biomimetic conversion of an iridoid into a secoiridoidic target. Several transformations have been reported for iridoid glycosides in the literature (3), but few have presented data on the conversion of iridoids into secoiridoids. Oleuropein [**1**] was chosen as the target because it was the first member of the secoiridoid family to be isolated (1).

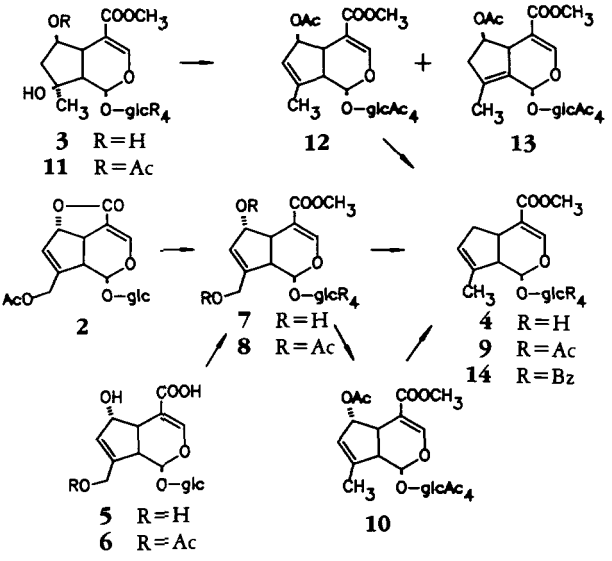
The strategy for the partial synthesis of oleuropein [**1**] follows a biogenetic approach and consists of the oxidative opening of the cyclopentane ring of a suitable iridoid intermediate, 10-deoxygeniposide [**4**], as summarized in Scheme 1.




SCHEME 1

The key compound **4** was prepared following two different strategies, as depicted in Scheme 2, starting from four readily available iridoids: asperuloside [**2**] (or asperulosidic acids **5** and **6**), isolated from different species of *Rubia* and *Galium*, or shanzhiside methyl ester [**3**], extracted from two species of *Odontites* (see Experimental). Asperuloside [**2**] was transformed into the corresponding methyl ester **7** with MeONa in MeOH (4) and subsequently converted into the hexaacetate **8**. Compound **8** was also obtained from a mixture of the acids **5** and **6** by esterification with $CH_2N_2$ and successive acetylation (5,6).

[1]This paper is dedicated to the memory of Prof. Luigi Panizzi, who pioneered iridoid chemistry in Italy with the isolation of oleuropein.

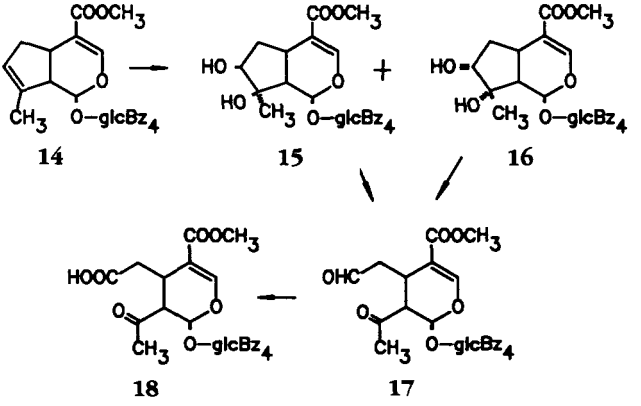



SCHEME 2

The iridoid intermediate 10-deoxygeniposide tetraacetate [**9**] was obtained from compound **8** by transfer hydrogenolysis with $Pd(OH)_2C$/cyclohexene, according to methodology recently described (7). In this reaction the monodeoxyderivative **10** was also obtained and can be easily reconverted into **9**. The degree of formation of **10** depends upon the reaction time.

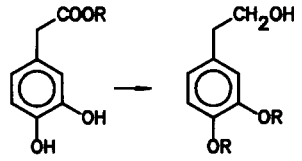
A slightly different strategy was utilized for the transformation of shanzhiside methyl ester [**3**] into **9**. Compound **3** was selectively converted into the pentaacetyl-derivative **11** which was then dehydrated with $POCl_3$/pyridine. Because of the anti configuration of the C-8 hydroxyl and C-7 hydrogen, this reaction afforded compound **12** with a regioselectivity of almost 95%; however, small amounts of olefin **13** were also recovered. Compound **12** was then hydrogenolyzed, using the same experimental conditions as with **8**, to give the 10-deoxygeniposide tetraacetate **9**.

A simple work up allowed conversion of acetate **9** into the benzyl derivative **14**, which is the key compound of this synthesis. The synthetic strategy for cleavage of the cyclopentane ring of **14** was outlined by Inouye *et al.* (8), but little attention was given to the yields (almost 30%) and regioselectivity of the transformation. We have improved the procedure for the oxidative opening of **14**, giving secoderivative **17** in an overall yield of almost 80% (Scheme 3).




SCHEME 3

10-Deoxygeniposide tetrabenzylether [**14**] was selectively hydroxylated at the C-7–C-8 double bond with $OsO_4$/trimethylamine-*N*-oxide, a method useful for the osmylation of hindered olefins (9). This reaction afforded the two cis diols **15** and **16** (93:7), the predominance of **15** presumably reflecting easier access to the β side of the molecule. The total yield of this step is 85%, and both **15** and **16** are suitable for the subsequent reaction. Structures and absolute configurations of both diols were established by examining their nmr spectra and by using the known effects on chemical shifts of C-7 and C-8 due to the presence of cis hydroxyls located on the α or β side of the iridoid molecule (10–12). The oxidative cleavage of the cis diol function of **15** and **16** was performed with $NaIO_4$ in $Me_2CO$ and provided the secoderivative **17** in 90% yield.



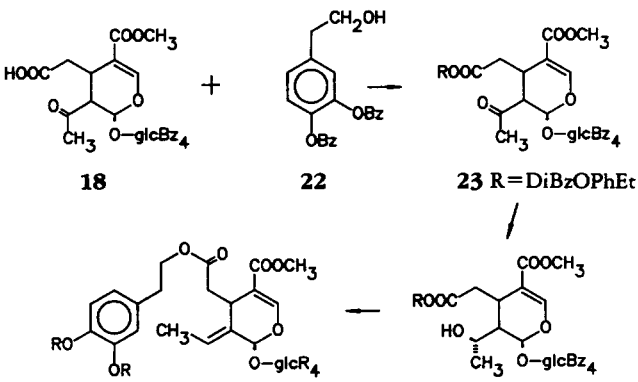

**19** R=H **21** R=H
**20** R=Me **22** R=Bz

SCHEME 4

The final steps of the synthesis are depicted in Scheme 5, starting from acid **18**, which is easily prepared from **17** by oxidizing the formyl group with Jones reagent.

At this stage it was necessary to insert the dihydroxyphenylethylalcohol moiety which blocks the acid function at C-7 in oleuropein [**1**]. In fact the free carboxyl group at C-7 easily undergoes lactonization (see structures **25** and **26**) with the C-8 hydroxyl, which has to be prepared by reduction of C-8 carbonyl, in order to obtain, by dehydration, the C-8–C-9 double bond.

The dihydroxyphenylethylalcohol **21** was obtained from 3,4-dihydroxyphenylacetic acid [**19**] by a simple workup (Scheme 4). Compound **19** was transformed into its methyl ester **20**, which was reduced to **21** with $NaBH_4$ in $H_2O$ according to a method recently described by us (13). The phenolic functions of **21** were then protected with benzyl groups to furnish dibenzylether **22**.




**18** **22** **23** R=DiBzOPhEt

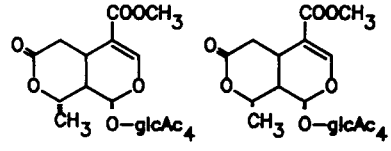
**1** R=R′=H
**28** R=R′=Ac
**27** R=R′=Bz

**24** R=DiBzOPhEt

SCHEME 5

Esterification of acid **18** with **22** was performed in good yield with dicyclohexylcarbodiimide, according to the method of Holmberg and Hansen (14), and the resulting ester **23** was then converted into oleuropein [**1**] following the procedure depicted in Scheme 5.

The carbonyl function of **23** was reduced with $NaBH_4$ in MeOH with a diastereomeric excess higher than 95% (checked by nmr). The absolute *R* configuration of the C-8 chiral center of alcohol **24** was foreseeable on the basis of the Cramm rule and was demonstrated from its molar optical rotation, MD = −234°, which is comparable with that of the corresponding *R* lactone **25** described by Inouye *et al.* (8) (MD = −260°) and very different from that (MD = −541°) of the epimeric *S* lactone **26**. The high diastereoselectivity observed in the reduction of the C-8 carbonyl probably reflects a strict steric requirement due to the dibenzyloxyphenylethyl moiety at C-7.




**25** **26**

Alcohol **24** was then dehydrated with $SOCl_2$/pyridine to olefin **27** which, after removing the benzyl groups (15), afforded oleuropein [**1**], which was identified also as the acetylderivative **28**. The yield of this synthesis, starting from asperuloside [**2**] or shanzhiside methyl ester [**3**], was 18%.

## EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—$^1$H- and $^{13}$C-nmr spectra were recorded with Varian XL-300 or Bruker 90 spectrometers and ir spectra with a Perkin-Elmer 247 spectrometer. Optical rotation was measured with a Perkin-Elmer 241 instrument at 20°. Compounds were purified by cc on Merck Si gel and yields are calculated after purification. Physical data of compounds **2**, **5**, **6**, **7**, and **8** are reported by Bianco *et al.* (16), and data of **3** and **11** are reported by Bianco *et al.* (17).

ISOLATION OF NATURAL COMPOUNDS.—Asperuloside [**2**] was extracted, together with asperulosidic acid [**5**] and 10-deacetylasperulosidic acid [**6**], from *Rubia tinctorum*, *Rubia peregrina*, *Galium mollugo*, and *Galium aquaticum* (16). Shanzhiside methyl ester [**3**] was extracted from *Odontites serotina* and *Odontites lutea* (17). Voucher specimens of plants are in the herbarium of Dipartimento di Biologia Vegetale–Università di Roma "La Sapienza."

PREPARATION OF COMPOUNDS **7** AND **8** FROM ASPERULOSIDE [**2**].—Asperuloside [**2**] (800 mg) was dissolved in 50 ml of anhydrous MeOH, and 1 ml of a 30% solution of MeONa in anhydrous MeOH was added at room temperature. After 10 min, the base was destroyed by bubbling $CO_2$ into the solution, and MeOH was then evaporated in vacuo. The residue was chromatographed in *n*-BuOH saturated with $H_2O$ to give 700 mg of **7** (90% yield) (5). Compound **7** (700 mg) was treated with 3 ml of $Ac_2O$ and 6 ml of anhydrous pyridine at room temperature for 2 h. Excess $Ac_2O$ was destroyed by adding 10 ml of MeOH, the volatile materials were evaporated in vacuo, and the residue was chromatographed in $C_6H_6$-EtOAc (6:4) to give 1.1 g of pure **8** (97% yield) (4).

PREPARATION OF COMPOUNDS **7** AND **8** FROM ACIDS **5** AND **6**.—A mixture of **5** and **6** (800 mg) was dissolved in 100 ml of MeOH and treated at −15° with ethereal $CH_2N_2$. The volatile materials were evaporated in vacuo, and the residue of crude **7** was acetylated, as previously described, to furnish pure **8** (1.25 g, 95% yield) (5).

HYDROGENOLYSIS OF **8**.—A solution of **8** (1.5 g) in 20 ml of EtOH and 10 ml of cyclohexene containing 500 mg of 20% $Pd(OH)_2$ on carbon (50% moist) was stirred under reflux for 48 h. The catalyst was removed by filtration and, after elimination of volatile materials, the residue was purified by chromatography in $C_6H_6$-EtOAc (6:4). Pure **9** (980 mg, 80% yield) (7) was obtained together with 120 mg (yield 9%) of monodeoxyderivative **10**. Compound **10** can be recycled so that the yield of the bisdeoxyderivative **9**

approaches 90%. Compound **9**: $^1$H nmr ($CDCl_3$) δ 5.10 (H-1, d, $J_{1,9}$ = 7.5), 7.30 (H-3, s), 5.35 (H-7, m), 1.75 ($H_3$-10, bs), 3.65 (OMe, s), 2.05, 1.90, 1.95, 2.00 (4 × Ac, s); $^{13}$C nmr ($CDCl_3$) δ 95.7 (C-1), 150.8 (C-3), 112.8 (C-4), 33.4 (C-5), 38.5 (C-6), 127.1 (C-7), 137.7 (C-8), 49.3 (C-9), 15.3 (C-10), 167.5 (C-11), 51.1 (OMe), 96.1 (C-1′), 70.1 (C-2′), 75.5 (C-3′), 68.5 (C-4′), 76.2 (C-5′), 61.8 (C-6′), 170.5, 170.1, 169.3, 169.1 (4 × Me*CO*), 20.6 (4 × *Me*CO). Compound **10**: $^1$H nmr ($CDCl_3$) δ 5.10 (H-1, d, $J_{1,9}$ = 7.5), 7.45 (H-3, s), 5.75 (H-7, m), 1.90 ($H_3$-10, bs), 3.78 (OMe, s), 2.00 (5 × Ac, s); $^{13}$C nmr ($CDCl_3$) δ 100.4 (C-1), 153.0 (C-3), 107.5 (C-4), 39.1 (C-5), 78.1 (C-6), 127.2 (C-7), 148.7 (C-8), 47.9 (C-9), 16.7 (C-10), 167.1 (C-11), 51.4 (OMe), 97.4 (C-1′), 71.1 (C-2′), 72.2 (C-3′), 68.5 (C-4′), 72.6 (C-5′), 61.2 (C-6′), 170.3, 170.1, 169.9, 169.4 (5 × Me*CO*), 21.1, 20.6 (5 × *Me*CO). Found: C 54.12, H 5.63; $C_{27}H_{33}O_{15}$ requires C 54.26, H 5.57.

DEHYDRATION OF SHANZHISIDE METHYL ESTER **3** TO **12** AND **13**.—Shanzhiside methyl ester [**3**] (300 mg) was converted to pentaacetate **11** by a mild acetylation (1.5 h at room temperature) with 3 ml of anhydrous pyridine and 6 ml of $Ac_2O$. Workup as before and chromatography in $Et_2O$-EtOAc (8:2) afforded 410 mg of pure **11**. Compound **11** (400 mg) was dissolved in 10 ml of anhydrous pyridine and treated with 10 ml of pyridine-$SOCl_2$ (30:1) at room temperature for 1 h. The reaction mixture was diluted with 150 ml of EtOAc, and the cooled solution was washed with 2 N HCl, $NaHCO_3$ saturated solution, and $H_2O$. The organic phase was dried over anhydrous $Na_2SO_4$ and evaporated in vacuo, and the residue was chromatographed in $C_6H_6$-EtOAc (7:3). Pure **12** (350 mg, yield 95%) was obtained together with 20 mg of **13** (yield 5%). Compound **12**: $^{13}$C nmr ($CDCl_3$) δ 94.3 (C-1), 151.3 (C-3), 109.7 (C-4), 39.0 (C-5), 82.1 (C-6), 126.9 (C-7), 144.8 (C-8), 48.5 (C-9), 15.2 (C-10), 166.8 (C-11), 51.4 (OMe), 96.1 (C-1′), 70.7 (C-2′), 72.3 (C-3′), 68.3 (C-4′), 72.3 (C-5′), 61.7 (C-6′), 170.5, 170.1, 169.3, 169.0 (5 × Me*CO*), 22.3, 21.2, 20.6, 20.2 (5 × *Me*CO). Found C 54.08, H 5.62; $C_{27}H_{33}O_{15}$ requires C 54.26, H 5.57. Compound **13**: $^1$H nmr ($CDCl_3$) δ 5.80 (H-1, s), 7.25 (H-3, s), 1.70 ($H_3$-10, bs), 3.70 (OMe, s), 2.02, 1.98, 1.95, 1.85 (5 × Ac, s). Found: C 54.11, H 5.68; $C_{27}H_{33}O_{15}$ requires C 54.26, H 5.57.

HYDROGENOLYSIS OF **12**.—Compound **12** (350 mg) in 5 ml of EtOH, 150 mg of palladium catalyst, and 2.5 ml of cyclohexene was refluxed for 24 h. Workup as before afforded, after chromatography in $C_6H_6$-EtOAc (8:2), 310 mg of pure **9** (yield 99%).

TETRABENZYL DERIVATIVE **14**.—Compound **14** (1.0 g) was dissolved in 50 ml anhydrous MeOH, and 1 ml of a 30% solution of NaOMe in anhydrous MeOH was added at room temperature. After 30 min the base was destroyed by bubbling $CO_2$ into the solution. MeOH was evaporated in vacuo and the residue chromatographed in *n*-BuOH-saturated $H_2O$ to give 620 mg of **4** (yield 90%). Compound **4** (620 mg) was dissolved in 150 ml of anhydrous THF, 1.0 g of NaH and 3.0 ml of benzyl bromide were added, and the suspension was refluxed until complete benzylation (tlc monitoring, 3 days). NaH excess was destroyed with MeOH, and the suspension was diluted with 150 ml of EtOAc, filtered, washed with 1 N HCl and $H_2O$, and dried over anhydrous $Na_2SO_4$. After elimination of volatile materials, the residue was chromatographed in $C_6H_6$-EtOAc (8:2), affording 1.8 g of pure **14** (yield 81%): $^1$H nmr ($CDCl_3$) δ 5.13 (H-1, d, $J_{1,9}$ = 7.5), 7.33 (H-3, s), 5.45 (H-7, m), 1.73 ($H_3$-10, bs), 3.62 (OMe, s), 5.0–5.2 (4 × $CH_2$Ph), 7.2–7.4 (4 × $CH_2$*Ph*); $^{13}$C nmr δ 94.2 (C-1), 150.8 (C-3), 112.8 (C-4), 33.3 (C-5), 38.4 (C-6), 127.3 (C-7), 137.5 (C-8), 49.1 (C-9), 15.0 (C-10), 167.3 (C-11), 51.0 (OMe), 99.2 (C-1′), 82.2 (C-2′), 85.2 (C-3′), 78.1 (C-4′), 75.5 (C-5′), 69.1 (C-6′), 73.9, 73.8, 72.8, 71.6 (4 × $CH_2$Ph), 139.0, 138.8, 138.7, 138.6 (4 × C-1Ph), 128.9 (4 × C-2Ph, 4 × C-4Ph, 4 × C-6Ph), 128.1 (4 × C-3Ph, 4 × C-5Ph). Found C 73.62, H 6.68; $C_{45}H_{48}O_9$ requires C 73.75, H 6.60.

OSMYLATION OF **14** INTO **15** AND **16**.—Compound **14** (600 mg) was dissolved in 0.2 ml of pyridine and 6 ml of *t*-BuOH; trimethylamine-*N*-oxide (380 mg in 2 ml of $H_2O$) and $OsO_4$/*t*-BuOH solution (1.2 ml) (100 mg of $OsO_4$ in 5 ml of *t*-BuOH) were added; and the reaction was warmed at 60° for 36 h. Excess $OsO_4$ was destroyed with $NaHSO_3$, the reaction mixture was diluted with MeOH, and the volatile materials were evaporated in vacuo. The residue was washed with $CHCl_3$, suspended in $H_2O$, and extracted with EtOAc. The collected organic phases were evaporated in vacuo and chromatographed in $CHCl_3$-EtOAc (4:6) affording 500 mg of **15** (6) and 40 mg of **16** (total yield 85%). Compound **15**: ir ($CHCl_3$) ν max 3260, 1750, 1650 $cm^{-1}$; $^1$H nmr ($CDCl_3$) δ 5.35 (H-1, d, $J_{1,9}$ = 2.0), 1.20 ($H_3$-10, s), 3.60 (OMe, s), 5.0–5.2 (4 × $CH_2$Ph), 7.3–7.5 (4 × $CH_2$*Ph*); $^{13}$C nmr ($CDCl_3$) δ 93.8 (C-1), 149.1 (C-3), 113.8 (C-4), 26.2 (C-5), 37.7 (C-6), 78.3 (C-7), 78.7 (C-8), 47.5 (C-9), 21.3 (C-10), 167.1 (C-11), 51.3 (OMe). Found C 70.21, H 6.58; $C_{45}H_{50}O_{11}$ requires C 70.49, H 6.52. Compound **16**: ir ($CHCl_3$) ν max 3240, 1740, 1650 $cm^{-1}$; $^{13}$C nmr ($CDCl_3$) δ 93.1 (C-1), 147.5 (C-3), 113.0 (C-4), 26.5 (C-5), 36.4 (C-6), 77.2 (C-7), 78.7 (C-8), 38.2 (C-9), 21.3 (C-10), 166.3 (C-11), 51.0 (OMe).

OXIDATION OF **15** AND **16** INTO **17**.—Compound **15** (825 mg) was dissolved in 50 ml of $Me_2CO$, 40 ml of an aqueous saturated solution of $NaIO_4$ was added, and the reaction was left at room temperature for 2 h. The reaction mixture was diluted with $H_2O$ and extracted with EtOAc; the organic phase was dried

over anhydrous $Na_2SO_4$ and evaporated in vacuo to give 750 mg (90% yield) of chromatographically pure **17**. The same procedure was used for the oxidation of **16** into **17** with identical isolated yields. Compound **17**: $^1$H nmr ($CDCl_3$) δ 5.35 (H-1, d, $J_{1,9}$ = 8.0), 9.40 (H-7, bs) 2.20 ($H_3$-10, s), 3.60 (OMe, s); $^{13}$C nmr ($CDCl_3$) δ 95.1 (C-1), 152.3 (C-3), 109.3 (C-4), 32.3 (C-5), 45.1 (C-6), 209.1 (C-7), 199.7 (C-8), 51.6 (C-9), 26.3 (C-10), 169.4 (C-11), 51.0 (OMe).

OXIDATION OF **17** INTO **18**.—Compound **17** (670 mg) was dissolved in 40 ml of $Me_2CO$ and treated at −10° with 3 ml of Jones reagent. After 30 min the reaction was complete, and $Na_2S_2O_5$ was added until a green color appeared. The reaction mixture was treated with 0.1 ml of pyridine and concentrated to small volume. The suspension was acidified with cold 2 N HCl and extracted with EtOAc. The organic phase was washed with $H_2O$, dried over anhydrous $Na_2SO_4$, and evaporated in vacuo, affording 620 mg of pure **18** (90% yield): ir ($CHCl_3$) ν max 3050, 1760, 1650 cm$^{-1}$; $^1$H nmr ($CDCl_3$) δ 5.45 (H-1, d, $J_{1,9}$ = 7.0), 10.05 (H-7, bs), 2.25 ($H_3$-10, s), 3.70 (OMe, s); $^{13}$C nmr ($CDCl_3$) δ 95.3 (C-1), 152.3 (C-3), 109.1 (C-4), 32.3 (C-5), 34.9 (C-6), 175.5 (C-7), 199.7 (C-8), 51.6 (C-9), 28.4 (C-10), 166.5 (C-11), 50.8 (OMe). Found C 68.95, H 6.42; $C_{45}H_{50}O_{12}$ requires C 69.05, H 6.39.

PREPARATION OF **22**.—Acid **19** was esterified with MeOH/$H_2SO_4$, yielding ester **20** which was reduced to dihydroxyphenylethyl alcohol **21** with $NaBH_4$ in $H_2O$-dioxane (1:1) (80% yield) as previously described (13). Compound **21** was transformed into the dibenzyl derivative **22** by means of the standard procedure (benzyl bromide/anhydrous $K_2CO_3$ in refluxing $Me_2CO$). Crude **22** was purified by chromatography in $CHCl_3$-EtOAc (7:3) (65% yield).

ESTERIFICATION OF **18** WITH **22**.—Compounds **18** (100 mg) and **22** (60 mg) were dissolved in 0.5 ml of anhydrous pyridine and 30 mg of dicyclohexylcarbodiimide, and 2 mg of *p*-toluenesulfonic acid was added. The reaction mixture was stirred at room temperature for 24 h and after addition of 0.05 ml of glacial HOAc, left at −10° for 12 h. The reaction was diluted with 20 ml of $Et_2O$ and washed with 2 N HCl, $NaHCO_3$-saturated solution, and $H_2O$. The organic phase was dried on anhydrous $Na_2SO_4$ and evaporated in vacuo, and the residue was chromatographed in hexane-EtOAc (1:1) to give 100 mg of pure **23** (65% yield): [α]D ($Me_2CO$, *c* = 0.5) −22°; $^1$H nmr ($CDCl_3$) δ 5.48 (H-1, d, $J_{1,9}$ = 9.0), 7.44 (H-3, s), 3.51 (H-5, m), 2.47 ($H_2$-6, m), 3.00 (H-9, dd, $J_{9,1}$ = 9.0, $J_{9,5}$ = 5.0), 2.23 ($H_3$-10, s), 3.71 (OMe, s), 4.88 (H-1′, d, $J_{1',2'}$ = 7.5), 3.72 (H-5′, m), 3.82 and 4.11 ($H_2$-6′, AB system, $J_{A,B}$ = 13.0, $J_{A,5'}$ = 2.0, $J_{B,5'}$ = 5.5), 5.2–4.9 (H-2′, H-3′, H-4′, 6 × *CH*$_2$Ph), 2.81 ($H_2$-β, t, $J_{b,a}$ = 7.5), 4.15 ($H_2$-α, t, $J_{a,b}$ = 7.5), 6.83 (H-2″, d, $J_{2'',6''}$ = 2.0), 6.87 (H-5″, d, $J_{5'',6''}$ = 7.5), 6.72 (H-6″, dd, $J_{6'',2''}$ = 2.0, $J_{6'',5''}$ = 7.5), 7.20–7.50 (6 × $CH_2$*Ph*); $^{13}$C nmr ($CDCl_3$) δ 95.2 (C-1), 152.0 (C-3), 109.0 (C-4), 28.4 (C-5), 34.5 (C-6), 171.6 (C-7), 206.8 (C-8), 50.7 (C-9), 24.9 (C-10), 166.3 (C-11), 51.6 (OMe), 137.4 (C-1″), 116.0 (C-2″), 147.7 (C-3″), 148.9 (C-4″), 155.4 (C-5″), 121.8 (C-6″), 32.3 (C-α), 65.3 (C-β). Found C 73.25, H 6.28; $C_{67}H_{68}O_{14}$ requires C 73.36, H 6.20.

REDUCTION OF **23** TO **24**.—Compound **23** (50 mg) was reduced in 2.0 ml of MeOH with 20 mg of $NaBH_4$. Excess hydride was destroyed by bubbling $CO_2$ into the solution, $H_2O$ was added, and the solution was extracted with EtOAc. After drying with anhydrous $Na_2SO_4$ and evaporation of the volatile material the residue was chromatographed in hexane-EtOAc (4:6), affording 45 mg of pure **24** (yield 90%): [α]D ($Me_2CO$, *c* = 0.5) −13°; ir ($CHCl_3$) ν max 3500, 1720 cm$^{-1}$; $^1$H-nmr ($CDCl_3$) δ 5.70 (H-1, d, $J_{1,9}$ = 8.5), 7.43 (H-3, s), 3.50 (H-5, m), 2.35 ($H_2$-6, m), 4.0–4.5 (H-8, $H_2$-6′, $H_2$-α), 2.7–2.9 (H-9, $H_2$-β), 1.61 ($H_3$-10, d, $J_{10,8}$ = 7.5), 3.72 (OMe, s), 4.88 (H-1′, d, $J_{1',2'}$ = 7.5), 3.70 (H-5′, m), 5.4–4.9 (H-2′, H-3′, H-4′, 6 × *CH*$_2$Ph), 7.1–7.4 (H-2″, H-5″, H-6″, 6 × $CH_2$*Ph*).

DEHYDRATION OF **24**.—Compound **24** (50 mg) was dissolved in 1 ml of anhydrous pyridine and treated with 1 ml of a solution of pyridine-$SOCl_2$ (30:1) for 1 h at room temperature. The reaction was diluted with EtOAc and washed with 2 N HCl, $NaHCO_3$-saturated solution, and $H_2O$. The dried organic phase was evaporated in vacuo and chromatographed in hexane-EtOAc (1:1), affording 42 mg of pure **27** (85% yield): $^1$H nmr ($CDCl_3$) δ 5.70 (H-1, s), 7.44 (H-3, s), 3.96 (H-5, dd, $J_{5,6a}$ = 9.0, $J_{5,6b}$ = 4.5), 2.38 and 2.65 ($H_2$-6, AB system, $J_{A,B}$ = 13.5, $J_{6a,5}$ = 9.0, $J_{6b,5}$ = 4.5), 5.98 (H-8, q, $J_{8,10}$ = 7.0), 1.66 ($H_3$-10, d, $J_{10,8}$ = 7.0), 3.71 (OMe, s), 5.01 (H-1′, d, $J_{1',2'}$ = 8.0), 3.73 (H-5′, m), 5.4–5.0 (H-2′, H-3′, H-4′, 6 × *CH*$_2$Ph), 4.0–4.5 ($H_2$-6′, $H_2$-α), 2.81 ($H_2$-β, t, $J_{b,a}$ = 7.5), 6.83 (H-2″, d, $J_{2'',6''}$ = 2.5), 6.87 (H-5″, d, $J_{5'',6''}$ = 7.5), 6.72 (H-6″, dd, $J_{6'',2''}$ = 2.0, $J_{6'',5''}$ = 7.5), 7.2–7.5 (6 × $CH_2$*Ph*).

TRANSFORMATION OF **27** INTO OLEUROPEIN [**1**].—Compound **27** (45 mg) was dissolved in 5 ml of EtOH; 1 ml of cyclohexene and 25 mg of 20% $Pd(OH)_2$ on carbon (50% moist) were added; and the suspension was stirred under reflux for 2 h. The catalyst was removed by filtration and, after removal of volatile materials, the residue was chromatographed in $CHCl_3$-MeOH (85:15) affording 20 mg of oleuropein [**1**] (1) (yield 90%), identical to an authentic sample. Compound **1**: $^1$H nmr ($D_2O$) δ 5.66 (H-1, s), 7.41 (H-3, s), 3.79 (H-5, dd, $J_{5,6a}$ = 7.5, $J_{5,6b}$ = 4.5), 2.36 and 2.56 ($H_2$-6, AB system, $J_{A,B}$ = 13.5, $J_{6a,5}$ = 7.5, $J_{6b,5}$ = 4.5), 5.98 (H-8, q, $J_{8,10}$ = 7.5), 1.48 ($H_3$-10, d, $J_{10,8}$ = 7.5), 3.63 (OMe, s), 4.79 (H-1′, d,

$J_{1',2'}$ = 7.5), 3.3–3.6 (H-2', H-3', H-4', H-5'), 3.64 and 3.82 ($H_2$-6', AB system, $J_{A,B}$ = 12.5, $J_{6'a,5'}$ = 4.5, $J_{6'b,5'}$ = 2.5), 2.71 ($H_2$-β, t, $J_{\beta,\alpha}$ = 6.0), 4.07 and 4.20 ($H_2$-α, AB system, $J_{A,B}$ = 11.0, $J_{A,\beta}$ = $J_{B,\beta}$ = 6.0), 6.71 (H-2", d, $J_{2",6"}$ = 3.0), 6.76 (H-5", d, $J_{5",6"}$ = 7.5), 6.59 (H-6", dd, $J_{6",2"}$ = 3.0, $J_{6",5"}$ = 7.5); $^{13}$C nmr ($D_2O$) δ 95.6 (C-1, d, 172.0), 155.4 (C-3, d, 193.0), 108.8 (C-4, s), 31.1 (C-5, d, 138.5), 40.8 (C-6, t, 136.0), 174.7 (C-7, s), 125.8 (C-8, d, 156.5), 131.8 (C-9, s), 13.4 (C-10, q, 126.5), 169.7 (C-11, s), 52.7 (OMe, q, 148.0), 100.4 (C-1', d, 165.5), 73.5 (C-2', d, 145.5), 76.5 (C-3', d, 144.0), 70.3 (C-4', d, 148.5), 77.1 (C-5', d, 143.0), 61.5 (C-6', t, 144.0), 129.1 (C-1", s), 122.0 (C-2", d, 160.5), 143.3 (C-3", s), 144.8 (C-4", s), 117.0 (C-5", d, 159.0), 117.5 (C-6", d, 152.0), 34.2 (C-α, t, 126.5), 67.0 (C-β, t, 153.0).

ACETYLOLEUROPEIN [**28**].—Oleuropein [**1**] (20 mg) was acetylated with 0.1 ml of pyridine and 0.2 ml of $Ac_2O$ at room temperature for 2 h. The reaction was worked up as described for **8** and, after chromatography in $C_6H_6$-*t*-butyl methyl ether (4:6), 28 mg of **28** (1) was obtained (90% yield), identical to an authentic sample. Compound **28**: $^1$H nmr ($CDCl_3$) δ 5.69 (H-1, s), 7.46 (H-3, s), 3.96 (H-5, dd, $J_{5,6a}$ = 9.0, $J_{5,6b}$ = 4.5), 2.42 and 2.72 ($H_2$-6, AB system, $J_{A,B}$ = 13.5, $J_{6a,5}$ = 9.0, $J_{6b,5}$ = 4.5), 5.99 (H-8, q, $J_{8,10}$ = 7.0), 1.68 ($H_3$-10, d, $J_{10,8}$ = 7.0), 3.72 (OMe, s), 5.03 (H-1', d, $J_{1',2'}$ = 8.0), 3.77 (H-5', m), 5.4–5.1 (H-2', H-3', H-4'), 4.05–4.35 ($H_2$-6', $H_2$-α), 2.91 ($H_2$-β, t, $J_{b,a}$ = 8.0), 7.05 (H-2", d, $J_{2",6"}$ = 2.0), 7.12 (H-5", d, $J_{5",6"}$ = 7.5), 7.85 (H-6", dd, $J_{6",2"}$ = 2.0, $J_{6",5"}$ = 7.5), 2.29, 2.04, 2.03, 2.02 (6 × Ac, s); $^{13}$C nmr δ 93.8 (C-1), 153.0 (C-3), 108.7 (C-4), 30.3 (C-5), 39.9 (C-6), 171.0 (C-7), 127.0 (C-8), 128.1 (C-9), 13.5 (C-10), 166.7 (C-11), 51.4 (OMe), 97.1 (C-1'), 70.8 (C-2'), 72.2 (C-3'), 68.3 (C-4'), 72.6 (C-5'), 61.7 (C-6'), 136.6 (C-1"), 124.9 (C-2"), 140.8 (C-3"), 142.0 (C-4"), 123.4 (C-5"), 123.8 (C-6"), 34.3 (C-α), 64.5 (C-β), 170.6, 170.1, 169.4, 169.3, 168.3, 168.1 (6 × $CH_3CO$), 20.7, 20.6, 20.5 (6 × $CH_3$CO).

## LITERATURE CITED

1. L. Panizzi, M.L. Scarpati, and G. Oriente, *Gazz. Chim. Ital.*, **90**, 1449 (1960).
2. I. Kubo, A. Matsumoto, and I. Takase, *J. Chem. Ecol.*, **11**, 251 (1985).
3. A. Bianco, in: "Studies in Natural Products Chemistry." Ed. by Atta-ur-Rahman, Elsevier Sciences Publishers, Amsterdam, 1990, Vol. 7, p. 439.
4. M. Guiso and A. Kocsis, 1st Int. Conf. Chem. Biotechnol. Biol. Act. Nat. Prod., Varna, Bulgaria, Sept. 21–26, 1981. Proceedings, Vol. 3, p. 22.
5. A. Bianco, M. Guiso, C. Iavarone, P. Passacantilli, and C. Trogolo, *Gazz. Chim. Ital.*, **108**, 13 (1978).
6. H. Inouye, T. Yoshida, S. Tobita, and M. Okigawa, *Tetrahedron*, **26**, 3905 (1970)
7. A. Bianco, P. Passacantilli, and G. Righi, *Tetrahedron Lett.*, **30**, 1405 (1989).
8. H. Inouye, T. Yoshida, S. Tobita, K. Tanaka, and T. Nishioka, *Tetrahedron Lett.*, 2459 (1970).
9. R. Ray and D.S. Matteson, *Tetrahedron Lett.*, **21**, 449 (1980).
10. R.K. Chaudhuri, F.U. Afifi-Yazar, O. Sticher, and T. Winkler, *Tetrahedron*, **36**, 2317 (1980).
11. S. Damtoft, S.R. Jensen, and B.J. Nielsen, *Phytochemistry*, **20**, 2717 (1981).
12. A. Bianco, P. Passacantilli, G. Polidori, M. Nicoletti, and I. Messana, *Gazz. Chim. Ital.*, **113**, 829 (1983).
13. A. Bianco, P. Passacantilli, and G. Righi, *Synth. Commun.*, **18**, 1765 (1988).
14. K. Holmberg and B. Hansen, *Acta Chem. Scand.*, **33**, 410 (1979).
15. S. Hasnessian, T.J. Liak, and B. Vanasse, *Synthesis*, 396 (1981).
16. A. Bianco, M. Guiso, C. Iavarone, P. Passacantilli, and C. Trogolo, *Gazz. Chim. Ital.*, **108**, 13 (1978).
17. A. Bianco, A. Francesconi, and P. Passacantilli, *Phytochemistry*, **20**, 1421 (1981).

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