30. Partial Synthesis of 3′-Hydroxy-2′-deoxy-2″,3″,4″,5″-tetrahydroverrucarin A

Verrucarins and Roridins, 38th Communication [1]

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Summary

The macrocyclic trichothecene triester 3′-hydroxy-2′-deoxy-2″,3″,4″,5″-tetrahydroverrucarin A (**37**), has been synthesized starting from the sesquiterpene alcohol verrucarol (**3**), adipic acid and a derivative of mevalonic acid (**14**). The latter has been prepared from 4-(tetrahydro-2-pyranyloxy)-2-butanone (**9**).

1. Introduction. – The verrucarins are members of a growing class of natural products whose structures are characterized either as macrocyclic diesters or as triesters of sesquiterpene alcohols which belong to the trichothecene group [2]. The family includes mainly secondary metabolites isolated from moulds, such as verrucarin A (**1**) [3], verrucarin B [4], verrucarin J [5], 2′,*O*-didehydroverrucarin A [6], verrucarin K [7], roridin A [8], roridin D [9], roridin E [10], roridin H [11], isororidin E, 7β,8β-epoxyroridin E, 7β,8β-epoxyroridin H, 7β,8β,2′,3′-diepoxyroridin H [12], roridin J [13], vertisporin [14], satratoxin H [15], satratoxin F and G [16]. Recently macrocyclic trichothecene derivatives have been discovered also in higher plants, namely baccharin, baccharinol, isobaccharinol and isobaccharin [17]. Many of these natural compounds exhibit remarkable biological effects such as antibiotic, antifungal and antitumor, and especially antileukemic activity; but they are also highly toxic [2] [18]. It is known that these biological characteristics are to a large extent due to the presence of the macrocyclic ester system. However, very little is known about the structural requirements of the ring systems for an optimal biological activity. In order to clarify this problem we have started a program for the synthesis of macrocyclic esters of trichothecene alcohols leading either to natural verrucarins or to unnatural analogs. After completion of the partial synthesis of tetrahydroverrucarin J (**2**) as the first example of a macrocyclic triester [19], we now wish to report the partial synthesis of 3′-hydroxy-2′-deoxy-2″,3″,4″,5″-tetrahydroverrucarin A (**37**), which contains mevalonic acid and adipic acid as building blocks of the macrocyclic system, starting from verrucarol (**3**) and 4-(tetrahydro-2-pyranyloxy)-2-butanone (**9**).

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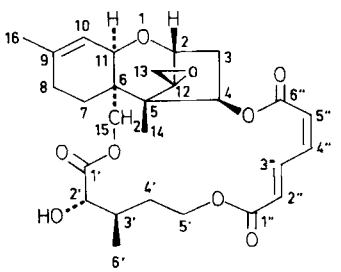
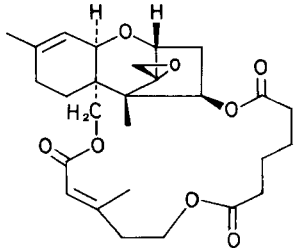


1 Verrucarin A



2 Tetrahydroverrucarin J

2. Partial Synthesis. – In our first approach it was planned to cyclize the seco-acid **4** *(cf. Scheme 1)* using the 5′-hydroxy group and the 1″-carboxylic group. In order to reach this goal a selective protection of the various hydroxyl and carboxylic groups present in the building blocks used for the synthesis was required. Esterification with phenacyl bromide proved to be the most convenient method for the protection of the carboxylic groups of adipic acid. The phenacyl half ester **5** of adipic acid was obtained with phenacyl bromide in the presence of triethylamine. Ester **5** was converted with *N,N′*-carbonyldiimidazole (CDI) in benzene into the corresponding amide [20]. This derivative was reacted *in situ* with verrucarol (**3**) in the presence of catalytic amounts of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) as base [20] to give the diester **6** (54%) besides the tetraester **7** (15%; *cf. Table*).

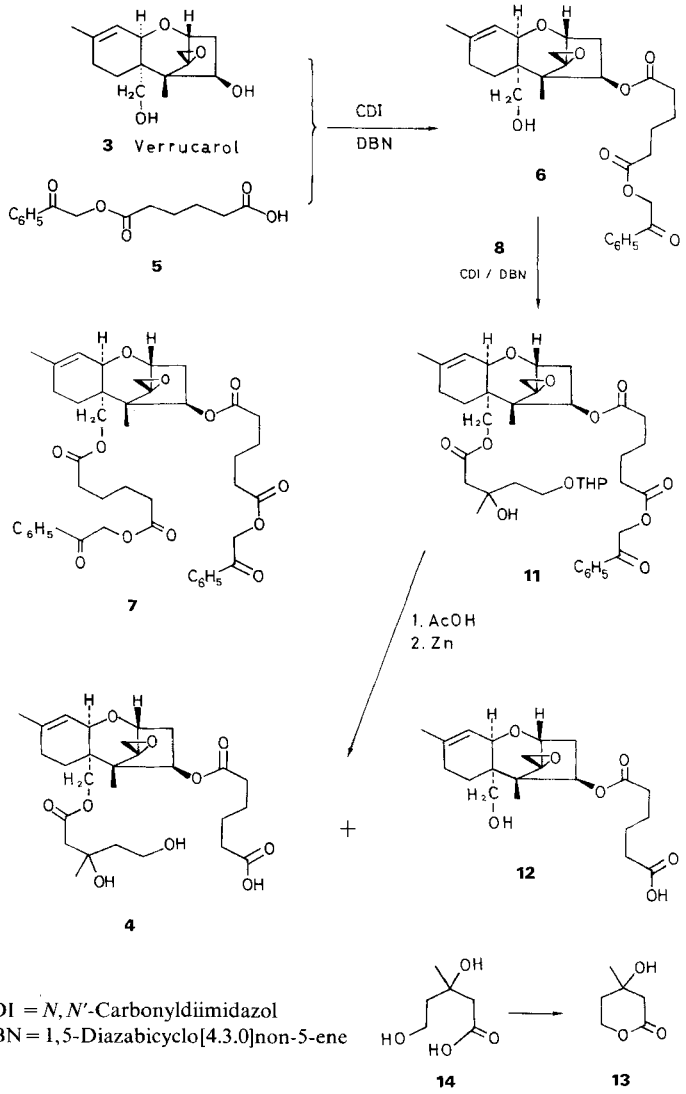
Table. *Condensation reactions of verrucarol* (**3**) *and verrucarol derivatives*

Alcohol	Acid	Method[a])	Product	Yield[b]) [%]
3	**4**	CDI/DBN, Be	**6**	54
			7	15
6	**8**	CDI/DBN, Be	**11**	32
15	**5**	MSC, Py/Be 1:1	**20**	69
		1) Oxalyl chloride, CH_2Cl_2/DMF		
		2) $(C_2H_5)_3N$, CH_2Cl_2		80
	30	MSC, Py/Be 1:1	**34**	28
		MSC, $(C_2H_5)_3N$, THF		28
	5	CDI/DBN, Be	**21**	52
16		MSC, Py/Be 1:1		72
		1) Oxalyl chloride, CH_2Cl_2/DMF		
		2) $(C_2H_5)_3N$, CH_2Cl_2		69
	22	CDI/DBN, Be	**23**	25
	29	CDI/DBN, Be	**31**	27
	30	CDI/DBN, Be	recovery	
		DCC/DMAP, CH_2Cl_2	complex mixture	

[a]) CDI = 1,1′-carbonyldiimidazole, DBN = 1,5-diazabicyclo[4.3.0]non-5-ene, Be = benzene, MSC = mesitylenesulfonyl chloride, Py = pyridine, DCC = *N,N′*-dicyclohexylcarbodiimide, DMAP = 4-(dimethylamino)pyridine.

[b]) Yield refers to isolated compounds.

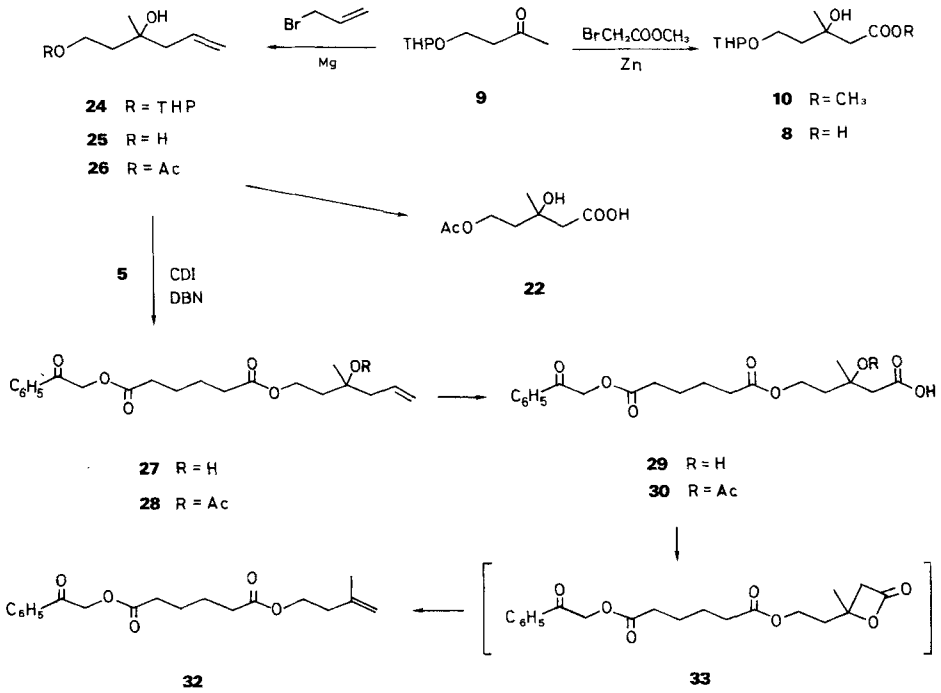
Scheme 1



The ^{1}H-NMR. spectrum of **6** showed signals at 5.78 ppm as double doublets which are characteristic for a 4*a*-proton. The IR. spectrum exhibited bands at 3500 (OH), 1730 (C=O, ester) and 1705 (C=O, ketone) cm^{-1}. The ^{1}H-NMR. spectrum of **7** revealed twice as many aromatic protons as the one of **5**. In the IR. no absorption bands characteristic of hydroxy groups were present.

For the second condensation 5-*O*-(tetrahydro-2-pyranyl)mevalonic acid (**8**; s. *Scheme 2*) was used which was prepared from the known 4-(tetrahydro-2-pyranyloxy)-2-butanone (**9**) by a *Reformatzki* reaction (→ **10**) [21] followed by treatment with sodium hydroxide in methanol. With CDI as condensing agent **8** and **6** reacted in the presence of DBN to the triester **11** (32%; *cf. Table*).

Scheme 2

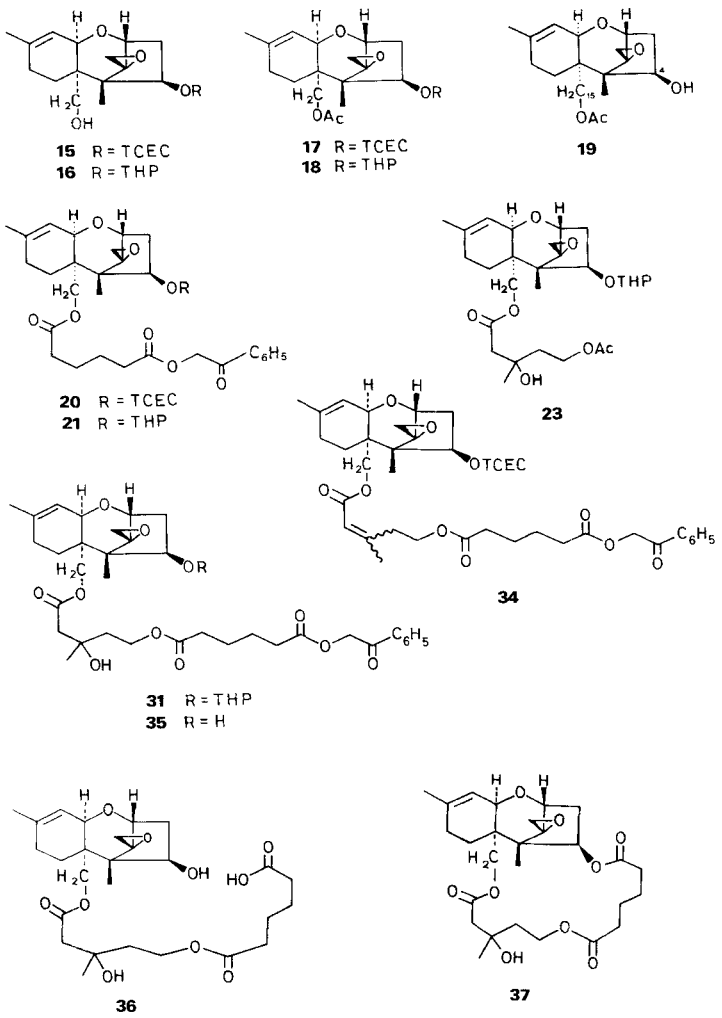


In the ^{1}H-NMR. spectrum of **11** the 4α-proton appeared as expected at 5.78 ppm. The signal at 4.58 ppm, which was assigned to H–C(2) of the tetrahydropyranyl ether group, was complex due to the additional chiral centre of the protecting group.

The removal of both protecting groups in **11** was achieved by hydrolysis with 50% aqueous acetic acid followed by treatment with an excess of zinc dust [22]. The unprotected hydroxyacid **4** was obtained in 55% yield. As by-products the monoester **12** (25% yield) and mevalono-lactone (**13**) were isolated. These undesired products are due to the great lability of **4**, and are also formed on purification of crude **4** or even on standing (*cf.* [23]). Therefore, no attempts to cyclize hydroxyacid **4** were made.

In order to overcome these unexpected difficulties we decided to form the cyclizing ester bond rather between C(4) and C(6″) than between C(5′) and C(1″). For this purpose a derivative of verrucarol (**3**) with a free HO–C(15) group and carrying a protecting group at the HO–C(4) group was required as starting material. Treatment of verrucarol (**3**) with 2,2,2-trichloroethyl chloroformate in pyridine at 0° yielded the desired 4-*O*-(2,2,2-trichloroethoxycarbonyl)-verrucarol (=4-*O*-TCEC-verrucarol; **15**; s. *Scheme 3*) in high yield (*cf.* [24]). When verrucarol (**3**) was reacted with dihydropyran and pyridinium *p*-toluenesulfonate [25] at room temperature 4-*O*-(tetrahydro-2-pyranyl)verrucarol (=4-*O*-THP-verrucarol; **16**) was obtained, again in very good yield (*cf.* [24]). Acetylation of both compounds with acetic anhydride/pyridine gave the acetyl derivatives **17** and **18**, respectively. The removal of the TCEC-group was achieved by treat-

Scheme 3



TCEC = 2,2,2-Trichloroethoxycarbonyl

ment of **17** with zinc in acetic acid [26] to give 15-*O*-acetylverrucarol (**19**) in 97% yield. On the other hand when **18** was reacted with pyridinium *p*-toluenesulfonate in absolute methanol [25] the same monoacetylated verrucarol derivative **19** was obtained in 92% yield.

Preliminary condensations of the verrucarol derivatives **15** and **16**, respectively, with the monophenacylester **5** of adipic acid were performed by applying three procedures: (1) the acid chloride method (oxalyl chloride), (2) the mesitylensulfonyl chloride method [27], and (3) the carbonyldiimidazole method [20] *(cf. Table)*. The yield of the isolated ester **20** and **21**, respectively, was 52–80%.

However, when **16** was treated with 5-*O*-acetylmevalonic acid (**22**; s. *Scheme 2*) using CDI/DBN as condensing agent, the yield of ester **23** was only 25%. As it will also be shown below the condensation of bulky carboxylic acids with the HO–C(15) group of verrucarol, which is of neopentyl alcohol type, proceeds in relatively low yields.

For the construction of the acidic moiety to be connected by esterification to C(15) of **15** or **16** we proceeded as follows (s. *Scheme 2*): The ketone **9** was subjected to a *Grignard* reaction with allyl bromide (→ **24**) followed by treatment with *p*-toluenesulfonic acid in methanol [28] (→ **25**; 71%). The vinyl group of **25** (acetyl derivative **26**) served for the formation of the carboxylic group of the mevalonic acid moiety in a later stage of the synthesis. Selective esterification of **25** with monophenacyl adipate **5** by the carbonyldiimidazole method gave ester **27** (85% after chromatographic purification), characterized by its acetyl derivative **28** (s. exper. part).

The IR. spectrum of **27** exhibited absorptions at 3500 (OH), 1735 (C=O, ester), and 1705 (C=O, ketone) cm^{-1}. In the ^{1}H-NMR. spectrum the phenacyl group was characterized by signals at 5.24 ppm (*s*, 2 H) and 7.4–8.0 ppm (*m*, 5 H). The vinylic protons appeared at 4.8–6.2 ppm (*m*, 3 H) and the tertiary methyl group at 1.14 ppm (*s*, 3 H).

Ozonolysis of **27** in methanol at −78° followed by oxidation of the ozonide with H_2O_2 and formic acid gave the desired hydroxy acid **29** (65% after chromatographic purification). Its acetyl derivative **30** was prepared from **28** (s. exper. part). The presence of the phenacyl, the carboxylic, the tertiary hydroxy and the tertiary methyl group in **29** was indicated by the IR. and ^{1}H-NMR. spectra.

The reaction of the acid **29** with 4-*O*-THP-verrucarol (**16**) using CDI/DBN in dry benzene as condensing agent above 70° yielded the desired product **31** (s. *Scheme 3*), only in 7% yield. It could be raised to 27% by very careful experimentation. The main product proved to be the olefin **32** (s. *Scheme 2*). We assume that the reason for the low yield of **31** is the instability of β-hydroxycarboxylic acids like **29** at higher temperatures. It is known that such systems can form β-lactones if an acidic medium is avoided. The latter can undergo thermic cycloreversion which leads to an olefin and CO_2 with retention of the original geometry and without isomerization of the double bond [29]. Treatment of the carboxylic acid **29** with mesitylenesulfonyl chloride in pyridine/benzene at 70° in the absence of an alcohol gave indeed as the only product the olefin **32**. We were not able to isolate the intermediary β-lactone **33**.

The ^{1}H-NMR. spectrum of **31** (mixture of 4 diastereoisomers) was very complex and difficult to analyze. It showed signals at 7.4–8.0 ppm (*m*, 5 H) and 5.34 ppm (*s*, 2 H) for the phenacyl group, and at 4.66 ppm (br., 1 H) for H–C(2) of the tetrahydropyranyl ether. In the IR. spectrum bands at 3490 (OH), 1730 (C=O, esters), 1705 (C=O, ketone) and 1600 (benzene ring) cm^{-1} appeared.

The condensation of the acetyl derivative **30** (s. *Scheme 2*) with 4-*O*-THP-verrucarol (**16**) by the carbonyldiimidazole method yielded mainly starting material. With mesitylenesulfonyl chloride in pyridine/benzene at 50° or in tetrahydrofuran in the presence of triethylamine at room temperature, condensation took place, but acetic acid was eliminated at the same time leading to the α,β-unsaturated triester **34** (*cf. Scheme 3* and *Table*).

Selective removal of the tetrahydropyranyl group in the triester **31** was easily effected by treatment with pyridinium *p*-toluenesulfonate in absolute methanol [25] to yield hydroxytriester **35**.

The ^{1}H-NMR. spectrum of **35** (mixture of two diastereoisomers) was relatively simple. It showed signals at 7.4–8.0 ppm (*m*, 5 H) and 5.35 ppm (*s*, 2 H) for the phenacyl group, at 5.45 ppm (*d*, 1 H) for the vinylic proton at C(11), at 3.10 and 2.79 ppm (*AB*-system, J = 4 Hz, 2 H) for the oxirane group, at 1.71 ppm (*s*, 3 H) for H_3C(16), at 1.29 ppm (*s*, 3 H) for H_3C–C(3′) and at 0.86 ppm (*s*, 3 H) for H_3C(14). The IR. spectrum was also in agreement with structure **35**.

The phenacylester **35** was transformed to the free acid **36** by treatment with zinc dust in acetic acid/tetrahydrofuran/water 3:1:1 [22]. After purification by column chromatography the yield was 64%.

The ^{1}H-NMR. spectrum of **36** showed two significant signals at 1.30 and 1.29 ppm which were assigned to H_3C–C(3′) because the product was a mixture of two epimers with respect to C(3′).

The last step of the synthesis leading to the desired macrocyclic triester 3′-hydroxy-2′-deoxy-2″,3″,4″,5″-tetrahydroverrucarin A (**37**) was successfully achieved by the use of the *Corey-Mukaiyama* method [30]. A solution of 2-pyridylthiolate in dry xylene, prepared from **36** by reaction with 2,2′-dipyridyl disulfide and triphenylphosphine, was added to a large volume of boiling xylene under nitrogen and heated under reflux. The cyclized product **37** was obtained in 45% yield after chromatographic purification.

In the mass spectrum of **37** the molecular ion appeared as expected at *m/z* 506. The IR. spectrum showed absorptions at 3500 cm^{-1} for the 3′-hydroxy group and at 1730 cm^{-1} for the ester bonds. The ^{1}H-NMR. spectrum indicated a mixture of two diastereoisomers as anticipated. The characteristic signals assigned to the 4*a*-proton appeared at 5.99 and 5.64 ppm as double doublets (J = 4 and 8 Hz). The H_3C(14) gave two singlets at 0.81 and 0.83 ppm. Finally H_3C–C(3′) appeared as two singlets at 1.23 and 1.34 ppm.

The separation of the two epimers of **37** could not yet be achieved. However, with the completion of this partial synthesis a second example of an unnatural verrucarin analogue has become available. The triester **37** is the first compound containing mevalonic acid (**14**), which is the biogenetic precursor of the corresponding unit in the natural metabolites [4].

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Experimental Part

General. Cf. [19]. *Preparation of phenacyl hydrogen adipate* (**5**). To a stirred solution of 8.3 g of adipic acid and 7 ml of triethylamine in 200 ml of acetone were added 10 g of phenacyl bromide at RT. The mixture was stirred overnight, and the precipitates were filtered off. The solvent was removed under reduced pressure, ether was added and the resulting solution extracted with 2N aqueous $KHCO_3$-solution. The aqueous extract was acidified with conc. HCl-solution in an ice bath and 8.2 g of crude product were collected. Recrystallization from EtOH/H_2O gave 7.5 g of pure **5**, m.p. 71–73°. – IR. (KBr): 1745, 1725, 1675, 1595, 1385, 1160, 760, 690. – ^{1}H-NMR. (90 MHz, $CDCl_3$): 7.4–8.0 (*m*, C_6H_5); 5.35 (*s*, $C_6H_5COCH_2O$); 2.45 (*m*, 2 H–C(2) and 2 H–C(5)); 1.76 (*m*, 2 H–C(3) and 2 H–C(4)).

$C_{14}H_{16}O_5$ (264.28) Calc. C 63.62 H 6.10% Found C 63.58 H 6.20%

Preparation of 4-O-(5'-phenacyloxycarbonylpentanoyl)verrucarol (**6**). To a stirred solution of 210 mg of CDI in 2 ml of dry benzene at RT. were added portionwise 264 mg of **5**. After the evolution of CO_2 had ceased, 270 mg of verrucarol (**3**) and 10 µl of DBN were added. The mixture was stirred at RT. for 48 h. Usual work-up afforded 420 mg of crude product as a yellow oil. Purification by column chromatography on SiO_2 (with CH_2Cl_2/Et_2O 4:1) yielded 115 mg of **7** as a colourless foam and 280 mg of **6** as a colourless oil, which was crystallized from CH_2Cl_2/Et_2O/petroleum ether to afford 265 mg of pure colourless needles, m.p. 106–107°. – IR. (KBr): 3500, 3070, 1730, 1705, 1600, 1220, 1085, 965, 755, 690. – ^{1}H-NMR. (90 MHz, DMSO-d_6): 5.78 (*d*×*d*, *J* = 8 and 4, H–C(4)); 5.47 (*s*, $C_6H_5COCH_2O$); 5.29 (br. *d*, *J* = 4.5, H–C(10)); 3.01 and 2.76 (*AB*-system, *J* = 4, 2 H–C(13)); 1.64 (*s*, H_3C(16)); 0.75 (*s*, H_3C(14)).

$C_{29}H_{36}O_8$ (512.50) Calc. C 67.95 H 7.08% Found C 67.81 H 7.03%

Preparation of 4-O-(5'-phenacyloxycarbonylpentanoyl)-15-O-[5'-O-(tetrahydro-2''-pyranyl)mevalonyl]-verrucarol (**11**). To a stirred solution of 281 mg of 5-*O*-(tetrahydro-2-pyranyl)mevalonic acid (**8**) in dry benzene were added portionwise at RT. 200 mg of CDI. After the evolution of CO_2 had ceased, 456 mg of **6** and 10 µl of DBN were added. The mixture was stirred at 50° for 48 h. Usual work-up gave 530 mg of crude product, which was purified by column chromatography on SiO_2 with CH_2Cl_2/Et_2O 1:1 to yield 206 mg of **11** as a colourless foam. – ^{1}H-NMR. (90 MHz, $CDCl_3$): 7.4–8.0 (*m*, C_6H_5); 5,78 (*m*, H–C(4)); 5.37 (*s*, $C_6H_5COCH_2O$); 4.58 (br., 1 H, H–C(2) of THP); 4.14 (*AB*-system, *J* = 12, 2 H–C(15)); 2.95 (*AB*-system, *J* = 4, 2 H–C(13)); 1.90 (*t*, *J* = 6, 2 H–C(4')); 1.71 (*s*, H_3C(16)); 1.30 (*s*, H_3C–C(3')); 0.81 (*s*, H_3C(14)). – MS.: 479 ($M^+ - 247$), 265, 231.

Preparation of 4-O-(5'-carboxypentanoyl-15-O-mevalonyl)verrucarol (**4**). A solution of 300 mg of **11** in 2 ml of 50% aqueous acetic acid was kept at 50° for 6 h. After cooling, 200 mg of activated zinc dust were added at RT. and the mixture was stirred for 1 h at RT. Excess zinc was filtered off and washed with ethyl acetate. The filtrate was diluted with Et_2O and washed with 2N HCl and H_2O. Evaporation, after drying, gave 250 mg of crude product as a yellow oil. Purification by column chromatography on SiO_2 with Et_2O/AcOH 99:1 afforded 39 mg of **12** and 116 mg of **4** as a colourless foam. Compound **4**: ^{1}H-NMR. (90 MHz, $CDCl_3$): 5.81 (*d*×*d*, *J* = 7.5 and 4, H–C(4)); 5.47 (br., H–C(10)); 4.16 (*AB*-system, *J* = 12, 2 H–C(15)); 2.98 (*AB*-system, *J* = 4, 2 H–C(13)); 1.72 (*s*, H_3C(16)); 1.31 (*s*, H_3C–C(3')); 0.82 (*s*, H_3C(14)).

4-O-(5'-Carboxypentanoyl)verrucarol (**12**). ^{1}H-NMR. (90 MHz, $CDCl_3$): 6.00 (*d*×*d*, *J* = 7.5 and 4, H–C(4)); 5.46 (*d*, *J* = 5, H–C(10)); 2.97 (*AB*-system, *J* = 4, 2 H–C(13)); 1.72 (*s*, H_3C(16)); 0.82 (*s*, H_3C(14)).

Preparation of 3-methyl-1-(tetrahydro-2-pyranyloxy)-5-hexen-3-ol (**24**). To a stirred solution of allyl magnesium bromide, prepared from 15.3 g of magnesium turnings and 35 g of allyl bromide in ether, were added slowly at 0° 22 g of ketone **9**. After standing at RT. for 1 h, 40 ml of AcOH in 150 ml of H_2O were added carefully under cooling. Usual work-up afforded 47 g of crude product, which was distilled under reduced pressure yielding 29.8 g of pure **24**, b.p. 136–138°/11 Torr; [28]. – IR. (film): 3460, 3075, 1640, 1130, 1075, 1023, 980, 905. – ^{1}H-NMR. (60 MHz, CCl_4): 4.7–6.2 (*m*, H_2C=HC(5)); 4.52 (br. *s*, H–C(2) of THP); 2.2 (*d*, *J* = 7, 2 H–C(4)); 1.69 (*t*, *J* = 6, 2 H–C(1)); 1.14 (*s*, H_3C–C(3)).

Preparation of 3-methyl-5-hexen-1,3-diol (**25**). To a solution of 27.8 g of **24** in 100 ml of dry MeOH were added 100 mg of *p*-toluenesulfonic acid and the mixture was kept at RT. for 1 h. After usual work-up, 21.2 g of crude product were obtained and distillation under reduced pressure yielded 16.0 g of **25** as a colourless liquid, b.p. 121–123°/11 Torr; [23]. – IR. (film): 3360, 3070, 1635, 1120, 1015, 990, 910. – ^{1}H-NMR. (60 MHz, CCl_4): 4.8–6.2 (*m*, H_2C=HC(5)); 3.77 (*t*, *J* = 6, 2 H–C(1)); 2.24 (*d*, *J* = 7, 2 H–C(4)); 1.64 (*t*, *J* = 6, 2 H–C(2)); 1.16 (*s*, H_3C–C(3)).

Preparation of 1-acetoxy-3-methyl-5-hexen-3-ol (**26**). A solution of 6.5 g of **25** in 6 ml of pyridine was treated with 6 ml of acetic anhydride at 70° for 1 h. After usual work-up and distillation, 7.2 g of **26** were obtained, b.p. 62–64°/0.03 Torr. – IR. (film): 3460, 3075, 1735, 1640, 1240, 1030, 915. – ^{1}H-NMR. (60 MHz, CCl_4): 4.8–6.2 (*m*, H_2C=HC(5)); 4.16 (*t*, *J* = 7, 2 H–C(1)); 2.21 (*d*, *J* = 7, 2 H–C(4)); 1.98 (*s*, CH_3COO); 1.73 (*t*, *J* = 7, 2 H–C(2)); 1.15 (*s*, H_3C–C(3)).

Preparation of methyl 5-O-(tetrahydro-2-pyranyl)mevalonate (**10**). A mixture of 27 g of **9** and 25 g of methyl bromoacetate in 100 ml of dry ether was added to 15 g of zinc wool in 20 ml of dry ether

to maintain gentle reflux of ether. The mixture was heated under reflux for 4 h after the addition was completed. Then 10 ml of acetic acid in 50 ml of water were added slowly. The organic layer was separated, and the aqueous phase extracted with ether (3 times 50 ml). The combined ether extracts were washed with 5% aqueous $Na_2S_2O_3$- and sat. NaCl-solution, dried, and evaporated to give 30 g of crude product as an oil. Distillation *in vacuo* afforded 25.6 g of colourless oil, b.p. 110–112°/1.0 Torr. – IR. (film): 3500, 1730, 1120, 1075, 1025. – ^{1}H-NMR. (90 MHz, $CDCl_3$): 4.59 (br. *s*, H–C(2) of THP); 3.70 (*s*, $COOCH_3$); 2.59 (*s*, 2 H–C(2)); 1.91 (*t*, $J = 6$, 2 H–C(4)); 1.31 (*s*, H_3C–C(3)). – MS.: 85 ($M^+ - 17$).

Preparation of 5-O-(tetrahydro-2'-pyranyl)mevalonic acid (**8**). A mixture of 13.0 g of **10**, 30 ml of 2N aqueous NaOH-solution, and 70 ml of MeOH was heated on a steam bath for 5 h. After evaporation of MeOH, 100 ml of H_2O were added. Then the mixture was extracted with ether (3 times 50 ml). The aqueous layer was acidified with conc. HCl-solution under cooling and the resulting acidic solution extracted with ether (5 times 50 ml). The ether extract was washed with conc. NaCl-solution, dried, and evaporated to give 11.0 g of crude product as a yellow oil. Purification by column chromatography on SiO_2 with Et_2O/AcOH 99:1 yielded 9.2 g of **8** as a colourless oil. – ^{1}H-NMR. (90 MHz, $CDCl_3$): 4.60 (br., H–C(2) of THP); 2.59 (*s*, 2 H–C(2)); 1.92 (*t*, $J = 6$, 2 H–C(4)); 1.35 (*s*, H_3C–C(3)).

Preparation of 5-O-acetylmevalonic acid (**22**). Ozone was bubbled through a solution of 615 g of **26** in 10 ml of MeOH at −70° until the blue colour persisted. After the solvent was removed, 26 ml of 96% HCOOH-solution and 14 ml of 35% H_2O_2-solution were added, and the resulting solution was kept at 70° for 2 h. After evaporation, 100 ml of Et_2O were added, and the solution was washed with 5% aqueous $Na_2S_2O_3$-solution and water before extraction with 2N aqueous K_2CO_3-solution. The aqueous extract was acidified with conc. HCl-solution and continuously extracted with CH_2Cl_2 yielding 5.3 g of crude product, which was purified by column chromatography on 200 g of SiO_2 with Et_2O/Acetone 4:1 followed by bulb to bulb distillation to afford 4.9 g of **22** as a colourless oil. – IR. (film): 1720, 1250, 1130, 1070, 1030. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 4.26 (*t*, $J = 6$, 2 H–C(5)); 2.59 (*s*, 2 H–C(2)); 2.04 (*s*, CH_3COO); 1.96 (*t*, $J = 6$, 2 H–C(4)); 1.35 (*s*, H_3C(6)).

Preparation of 3'-hydroxy-3'-methyl-5'-hexenyl phenacyl adipate (**27**). To a stirred solution of 4.49 g of **5** in dry benzene were added portionwise at RT. 3.03 g of CDI. Then a solution of 2.5 g of **25** in 26 ml of dry benzene and 50 µl of DBN were added, and the mixture was kept at RT. for 4 h. By usual work-up 6.2 g of crude product were obtained, and purification by column chromatography on 300 g of SiO_2 with Et_2O yielded 5.3 g of pure **27** as a colourless oil. – IR. (film): 3520, 3070, 1735, 1705, 1640, 1595, 1220, 1150, 755, 690. – ^{1}H-NMR. (60 MHz, CCl_4): 7.4–8.0 (*m*, C_6H_5); 4.8–6.2 (*m*, H_2C=HC(5')); 5.24 (*s*, $C_6H_5COCH_2O$); 4.19 (*t*, $J = 6$, 2 H–C(1')); 2.18 (*d*, $J = 7$, 2 H–C(4')); 1.73 (*t*, $J = 6$, 2 H–C(2')); 1.14 (*s*, H_3C–C(3')). – MS.: 358 ($M^+ - 18$).

Preparation of 3'-acetoxy-3'-methyl-5'-hexenyl phenacyl adipate (**28**). A mixture of 3 g of **27**, 10 ml of acetic anhydride, 71 mg of DMAP, and 10 ml of pyridine was stirred at RT. overnight. Ether (200 ml) was added and usual work-up gave 3.3 g of crude products. Purification by column chromatography on 320 g of SiO_2 with CH_2Cl_2/EtO_2 100:0 to 95:5 (as a gradient) gave 1.9 g of pure **28** as a colourless oil. – IR. (CCl_4): 3075, 1730, 1705, 1635, 1595, 1230, 1160, 680. – ^{1}H-NMR. (60 MHz, CCl_4): 7.4–8.0 (*m*, C_6H_5); 5.20 (*s*, $C_6H_5COCH_2O$); 4.09 (*t*, $J = 7$, 2 H–C(1')); 2.56 (*d*, $J = 7$, 2 H–C(4')); 1.91 (*s*, CH_3COO); 1.41 (*s*, H_3C–C(3')). – MS.: 419 ($M^+ + 1$), 377 ($M^+ - 41$), 359 ($M^+ - 59$), 265 ($M^+ - 153$).

Preparation of 5-O-(5'-phenacyloxycarbonylpentanoyl)mevalonic acid (**29**). A slow stream of ozone was bubbled through a solution of 2.0 g of **27** in 10 ml of MeOH at −70° until the blue colour persisted. After evaporation of the solvent, 7 ml of 96% HCOOH-solution and 3 ml of 35% H_2O_2-solution were added, and the mixture was kept at 70° for 1 h. After evaporation, ether was added and the solution washed with 5% aqueous $Na_2S_2O_3$-solution (several times) and water followed by drying and evaporation giving 2.4 g of crude products. By column chromatography on 200 g of SiO_2 with Et_2O/Acetone 4:1 1.3 g of pure **29** were obtained. – IR. (CH_2Cl_2): 3600–2300, 1730, 1700, 1595, 1220, 1160, 960. – ^{1}H-NMR. (90 MHz, $CDCl_3$): 7.4–8.0 (*m*, C_6H_5); 5.36 (*s*, $C_6H_5COCH_2O$); 4.25 (*t*, $J = 6$, 2 H–C(5)); 2.58 (*s*, 2 H–C(2)); 1.94 (*t*, $J = 6$, 2 H–C(4)); 1.32 (*s*, H_3C–C(3)). – MS.: 377 ($M^+ - 17$), 247 ($M^+ - 147$), 105.

Preparation of 3-O-acetyl-5-O-(5'-phenacyloxycarbonylpentanoyl)mevalonic acid **30**. Ozone was bubbled through a solution of 2.2 g of **28** in 70 ml of MeOH at −78° for 1 h until the blue colour persisted. After removal of MeOH, the residue was treated with 4 ml of 30% H_2O_2 solution and 10 ml of HCOOH solution at 70° for 2 h. Work-up as described before gave 1.6 g of crude product, which was purified by column chromatography on 50 g of SiO_2 with Et_2O and Et_2O/acetone 1:1 yielding 1.2 g of **30** as a colourless oil. – IR. (film): 3700–2500 br., 1740, 1710, 1600, 1450. – ^{1}H-NMR. (60 MHz, CCl_4): 7.4–8.0 (*m*, C_6H_5); 5.24 (*s*, $C_6H_5COCH_2O$); 4.14 (*t*, $J=6$, 2 H–C(5)); 2.94 (br. *s*, 2 H–C(2)); 1.94 (*s*, CH_3COO); 1.54 (*s*, H_3C–C(3)).

Formation of 3'-methyl-3'-butenyl phenacyl adipate (**32**) *from* **29**. A solution of 200 mg of **29** and 120 mg of mesitylenesulfonyl chloride in 1 ml of pyridine/benzene 1:1 was kept at 70° for 5 h. After usual work-up, 123 mg of crude products were obtained. Purification by column chromatography on SiO_2 with CH_2Cl_2/Et_2O 95:5 gave 107 mg of pure **32** as a colourless oil. – IR. (film): 3080, 1740, 1720, 1650, 1600, 1450, 760, 690. – ^{1}H-NMR. (60 MHz, CCl_4): 5.20 (*s*, $C_6H_5COCH_2O$); 4.73 (br. *s*, 2 H–C(4')); 4.13 (*t*, $J=7$, 2 H–C(1')); 2.28 (*t*, $J=7$, 2 H–C(2')); 1.74 (*s*, H_3C–C(3')).

Preparation of 4-O-(2',2',2'-trichloroethoxycarbonyl)verrucarol (**15**). To a stirred solution of 1.33 g of **3** in 2 ml of pyridine were added within 1 h 0.7 ml of 2,2,2-trichloroethyl chloroformate at 0° so that the temp. was lower than 5°. Then the mixture was stirred for 1 h more at 0°. Usual work-up gave 2.21 g of crude product, which was recrystallized from CH_2Cl_2/Et_2O to afford 1.98 g of pure **15**, m.p. 202–203°. – IR. (KBr): 3450, 1755, 1250, 1075, 950, 810, 715. – ^{1}H-NMR. (90 MHz, $CDCl_3$): 5.99 (*d*×*d*, $J=7.5$ and 4, H–C(4)); 5.48 (*d*, $J=5$, H–C(10)); 4.85 and 4.72 (*AB*-system, $J=11.5$, 2 H–C(1')); 3.14 and 2.83 (*AB*-system, $J=4$, 2 H–C(13)); 1.73 (*s*, H_3C(16)); 0.93 (*s*, H_3C(14)).

$C_{18}H_{23}Cl_3O_6$ (441.74) Calc. C 48.93 H 5.25% Found C 48.93 H 5.32%

Preparation of 4-O-(tetrahydro-2'-pyranyl)verrucarol (**16**). A mixture of 2.6 g of **3**, 10 ml of dihydropyran, 100 mg of pyridinium *p*-toluenesulfonate, and 15 ml of CH_2Cl_2 was stirred at RT. for 2 days. The mixture was washed with 2N aqueous K_2CO_3-solution. The aqueous phase was extracted with ether (2 times, 30 ml), and the combined organic phase dried and evaporated to give 3.88 g of crude product. Purification by column chromatography on 200 g of SiO_2 with Et_2O yielded 2.46 g of pure **16** as a colourless foam. – IR. (KBr): 3460, 1675, 1075, 1020, 960. – ^{1}H-NMR. (90 MHz, $CDCl_3$): 5.43 (*d*, $J=5.5$, H–C(10)); 4.70 (br., H–C(2) of THP); 3.09 and 2.81 (*AB*-system, $J=4$, 2 H–C(13)); 1.71 (*s*, H_3C(16)); 0.98 and 0.91 (2 *s*, H_3C(14)). – MS.: 349 (M^+-1), 335 (M^+-15), 319 (M^+-31).

Preparation of 15-O-acetyl-4-O-(2',2',2'-trichloroethoxycarbonyl)verrucarol (**17**). A solution of 250 mg of **15** in 0.75 ml of pyridine was treated with 0.5 ml of acetic anhydride at RT. overnight. After usual work-up, 260 mg of crude product was obtained. Purification by column chromatography on 20 g of SiO_2 with CH_2Cl_2/Et_2O 3:1 gave 225 mg of pure **17** as a colourless foam. – IR. (film): 3060, 1750, 1680, 1260, 960, 815, 730. – ^{1}H-NMR. (90 MHz, $CDCl_3$): 5.73 (*d*×*d*, $J=8$ and 3.5, H–C(4)); 5.44 (br. *d*, $J=5.5$, H–C(10)); 4.80 and 4.75 (*AB*-system, $J=12$, 2 H–C(1')); 4.16 and 4.07 (*AB*-system, $J=12$, 2 H–C(15)); 3.15 and 2.83 (*AB*-system, $J=4$, 2 H–C(13)); 2.08 (*s*, CH_3COO); 1.71 (br. *s*, H_3C(16)); 0.87 (*s*, H_3C(14)). – MS.: 487, 485, 483 (M^++1); 471, 469, 467 (M^+-15); 445, 443, 441, 439 (M^+-43); 428, 426, 424, 422 (M^+-60); 400, 398, 396, 394 (M^+-89); 291 (M^+-191).

Preparation of 15-O-acetyl-4-O-(tetrahydro-2'-pyranyl)verrucarol (**18**). As usual 400 mg of **16** were acetylated to afford 330 mg of **18** after purification. – IR. (film): 1740, 1675, 1240, 1080, 1020. – ^{1}H-NMR. (90 MHz, $CDCl_3$): 5.41 (*d*, $J=5$, H–C(10)); 4.74 (br. *s*, H–C(2) of THP); 4.23 and 3.91 (*AB*-system, $J=12$, 2 H–C(15)); 3.09 and 2.82 (*AB*-system, $J=4$, 2 H–C(13)); 2.07 (*s*, CH_3COO); 1.71 (*s*, H_3C(16)); 0.92 and 0.81 (*s*, H_3C(14)). – MS.: 391 (M^+-1), 349 (M^+-43), 307 (M^+-85), 290, 277.

Preparation of 15-O-acetylverrucarol (**19**). a) *From* **17**. A solution of 110 mg of **17** in 1 ml of AcOH was treated with 40 mg of activated zinc dust. The mixture was stirred at RT. for 3 h. Then 10 ml of CH_2Cl_2 were added, and the mixture was filtered and washed with CH_2Cl_2 several times. The organic solution was washed with 2N aqueous $KHCO_3$, dried, and evaporated to give 73 mg of crude product. Recrystallization from CH_2Cl_2/Et_2O yielded 68 mg of pure **19** as fine needles, m.p. 149–150°.

b) *From* **18**. A mixture of 200 mg of **18**, 10 mg of pyridinium *p*-toluenesulfonate, and 2 ml of dry EtOH was kept at RT. overnight. Usual work-up and crystallization yielded 145 mg of **19**, m.p. 149–150°. – IR. (KBr): 3450, 1720, 1675, 1385, 1255, 1070, 955. – ^{1}H-NMR. (90 MHz, $CDCl_3$): 5.41 (*d*, *J* = 5, H–C(10)); 4.48 (*d* × *d* × *d*, *J* = 9, 8, and 3, H–C(4)); 4.13 and 3.92 (*AB*-system, *J* = 12, 2 H–C(15)); 3.82 (*d*, *J* = 5, H–C(11)); 3.60 (br. *d*, *J* = 5.5, H–C(2)); 3.11 and 2.80 (*AB*-system, *J* = 4, 2 H–C(13)); 2.06 (*s*, CH_3COO); 1.71 (*s*, $H_3C(16)$); 0.87 (*s*, $H_3C(14)$).

$C_{17}H_{24}O_5$ (308.37) Calc. C 66.21 H 7.85% Found C 66.31 H 7.99%

Preparation of 4-O-(2′,2′,2′-trichloroethoxycarbonyl)-15-O-(5′-phenacyloxycarbonylpentanoyl)verrucarol (**20**). – a) To a stirred solution of 130 mg of **5** in 2 ml of dry CH_2Cl_2 were added 45 µl of oxalyl chloride and 10 µl of DMF at 0°, and the mixture was stirred for 15 min at 0°. Then a solution of 220 mg of **15** in 0.7 ml of triethylamine/CH_2Cl_2 2:5 was added. The mixture was kept at 0° for 30 min, and usual work-up afforded 320 mg of crude product, which was purified by column chromatography on 30 g of SiO_2 with CH_2Cl_2/Et_2O 95:5 to yield 276 mg of pure **20** as a colourless foam.

b) A mixture of 130 mg of **5**, 220 mg of **15**, 113 mg of mesitylenesulfonyl chloride, and 1 ml of pyridine/benzene 1:1 was kept at 5–10° for 2 days. Usual work-up and purification gave 239 mg of pure **20**. – IR. (film): 1750, 1705, 1600, 1380, 1250, 1080, 965, 730. – ^{1}H-NMR. (90 MHz, $CDCl_3$): 7.4–8.0 (*m*, C_6H_5); 5.69 (*d* × *d*, *J* = 7 and 3.5, H–C(4)); 5.47 (*d*, *J* = 5.5, H–C(10)); 5.35 (*s*, $C_6H_5COCH_2O$); 4.80 and 4.75 (*AB*-system, *J* = 12, 2 H–C(1′)); 4.20 and 4.07 (*AB*-system, *J* = 15, 2 H–C(15)); 3.14 and 2.83 (*AB*-system, *J* = 4, 2 H–C(13)); 1.72 (*s*, $H_3C(16)$); 0.88 (*s*, $H_3C(14)$).

Preparation of 4-O-(tetrahydro-2′-pyranyl)-15-O-(5′-phenacyloxycarbonylpentanoyl)verrucarol (**21**). – a) From 130 mg of **5** and 165 mg of **16** 194 mg of **21** were prepared as above for **20** (method a)).

b) A mixture of 132 mg of **5**, 165 mg of **16**, 113 mg of mesitylenesulfonyl chloride, and 1 ml of pyridine/benzene 1:1 was kept at 5–10° for 3 days. Usual work-up and purification gave 202 mg of pure **21**.

c) To a stirred solution of 88 mg of CDI in 2 ml of dry THF were added portionwise at RT. 137 mg of **5**. After the evolution of CO_2 had ceased, 165 mg of **16** and 10 µl of DBN were added. The mixture was kept at 50° for 3 days. Usual work-up and purification yielded 146 mg of **21**. – IR. (film): 1740, 1705, 1600, 1080, 1020, 965, 915. – ^{1}H-NMR. (90 MHz, $CDCl_3$): 7.4–8.0 (*m*, C_6H_5); 5.35 (*s*, $C_6H_5COCH_2O$); 3.09 and 2.82 (*AB*-system, *J* = 4, 2 H–C(13)); 1.71 (*s*, $H_3C(16)$); 0.92 and 0.81 (2 *s*, $H_3C(14)$).

Preparation of 15-O-(5′-O-acetylmevalonyl)-4-O-(tetrahydro-2′-pyranyl)verrucarol (**23**). To a stirred solution of 190 mg of **22** in 1 ml of dry benzene were added 160 mg of CDI at RT. Then 260 ml of **16** and 20 µl of DBN were added, and the mixture was kept at 50° for 5 days. After usual work-up 310 mg of crude product were obtained. Column chromatography on 30 g of SiO_2 with CH_2Cl_2/Et_2O 4:1 gave 47 mg of **16** and 97 mg of **23**. – IR. (film): 3480, 1735, 1235, 1075, 1020. – ^{1}H-NMR. (90 MHz, $CDCl_3$): 5.46 (*d*, *J* = 6, H–C(10)); 4.23 (*t*, *J* = 7, 2 H–C(5′)); 3.09 and 2.81 (*AB*-system, *J* = 4, 2 H–C(13)); 2.54 (*s*, 2 H–C(2′)); 2.04 (*s*, CH_3COO); 1.88 (*t*, *J* = 7, 2 H–C(4′)); 1.71 (*s*, $H_3C(16)$); 1.28 (*s*, $H_3C–C(3′)$); 0.91 and 0.80 (2 *s*, $H_3C(14)$). – MS.: 438 ($M^+ - 84$), 333 ($M^+ - 189$).

Preparation of 15-O-[3′-methyl-5′-(5″-phenacyloxycarbonyl-pentanoyloxy)-2′-pentenoyl-4-O-(β,β,β-trichloroethoxycarbonyl)verrucarol (**34**). To a stirred solution of 54 mg of **30**, 0.3 ml of Et_3N, and 30 mg of mesitylenesulfonyl chloride in 0.5 ml of dry THF were added 43 mg of **15**. The mixture was stirred at RT. for 2.5 h. Usual work-up and purification by prep. TLC. yielded 25 mg of **15** and 22 mg of **34**. – IR. (film): 1740, 1710, 1650, 1600, 1450. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 7.4–8.0 (*m*, C_6H_5); 5.20 (*s*, $C_6H_5COCH_2O$); 5.75–5.35 (br. *m*, H–C(4), H–C(10), and H–C(2′)); 1.70 (*s*, $H_3C(16)$ and $H_3C–C(3′)$); 0.80 (*s*, $H_3C(14)$).

Preparation of 15-O-[5′-O-(5″-phenacyloxycarbonylpentanoyl)mevalonyl]-4-O-(tetrahydro-2′-pyranyl)-verrucarol (**31**). To a stirred solution of 325 mg of **29** in 2 ml of dry benzene were added at RT. under N_2 portionwise 263 mg of CDI. After the evolution of CO_2 had ceased, the mixture was stirred for additional 20 min. Then a solution of 267 mg of **16** and 0.07 ml of DBN in 2 ml of dry benzene was added in several portions, and the mixture was stirred at 50° for 62 h under N_2. Usual work-up gave 383 mg of crude products. Chromatography on 50 g of SiO_2 with CH_2Cl_2/Et_2O 10:1 to 0:10, then Et_2O as a gradient, afforded 153 mg of **31**. – IR. (film): 3490, 1730, 1705, 1600, 1450. –

^{1}H-NMR. (90 MHz, $CDCl_3$): 7.4–8.0 (*m*, C_6H_5); 5.44 (*d*, $J=5$, H–C(10)); 5.34 (*s*, $C_6H_5COCH_2O$); 4.66 (br. *m*, H–C(2) of THP); 4.25 (*t*, $J=7$, 2 H–C(5′)).

Preparation of 15-O-[5′-O-(5″-phenacyloxycarbonylpentanoyl)mevalonyl)]verrucarol (**35**). To a stirred solution of 235 mg of **31** in 5 ml of dry MeOH were added 90 mg of pyridinium *p*-toluenesulfonate at RT. under N_2. The mixture was stirred overnight, the solvent removed under vacuum and the residue chromatographed on 25 g of SiO_2. After the elution with CH_2Cl_2/Et_2O 1:1, the fractions eluted with MeOH/Et_2O 1:9 were collected yielding 190 mg of **35**. – IR. (film): 3490, 1730, 1705, 1595. – ^{1}H-NMR. (90 MHz, $CDCl_3$): 7.4–8.0 (*m*, C_6H_5); 5.35 (*s*, $C_6H_5COCH_2O$); 4.25 (*t*, $J=7$, 2 H–C(5′)); 3.82 (*d*, $J=5$, H–C(11)); 3.10 and 2.79 (*AB*-system, $J=4$, 2 H–C(13)); 1.71 (*s*, H_3C(16)); 1.29 (*s*, H_3C–C(3′)); 0.86 (*s*, H_3C(14)).

Preparation of 3′-hydroxy-2′-deoxy-2″,3″,4″,5″-tetrahydro-4(6″-O)-secoverrucarin A (**36**). To a stirred solution of 116 mg of **35** in 3 ml of AcOH/THF/H_2O 3:1:1 were added 369 mg of activated zinc dust. The mixture was stirred at RT. overnight under N_2. Excess zinc dust was filtered off and washed with CH_2Cl_2 several times. The filtrate was washed with 2N HCl and sat. NaCl-solution, dried over magnesium sulfate, and evaporated to afford 90.9 mg of crude product. Chromatography on 6 g of SiO_2 with Et_2O and acetone/Et_2O 1:4 yielded 61 mg of **36** as a colourless oil. – IR. ($CHCl_3$): 3600–2300, 1720, 1175, 1075, 960. – ^{1}H-NMR. (90 MHz, $CDCl_3$): 5.45 (*d*, $J=6$, H–C(10)); 4.26 (*t*, $J=7$, 2 H–C(5′)); 3.12 and 2.80 (*AB*-system, $J=4$, 2 H–C(13)); 2.54 (br. *s*, 2 H–C(2′)); 1.71 (br. *s*, H_3C(16)); 1.30 and 1.29 (2 *s*, H_3C(6′)); 0.86 (*s*, H_3C(14)). – MS.: no peaks over 309, 309, 307, 293, 251, 249, 235.

Preparation of 3′-hydroxy-2′-deoxy-2″,3″,4″,5″-tetrahydroverrucarin A (**37**). To a stirred solution of 24 mg of **36** in 2 ml of dry xylene were added 21 mg of triphenylphosphine and 15 mg of 2,2′-dipyridyl disulfide at RT. under N_2. The mixture was stirred overnight. This solution was diluted with 2 ml of dry xylene and added to 25 ml of boiling dry xylene in small portions within 8 h and through a syringe under N_2. Then heating under reflux was continued overnight, the solvent was evaporated, and the residue purified several times by prep. TLC. to yield 10.5 mg of **37**. An analytical sample was obtained by recrystallization from Et_2O/CH_2Cl_2, m.p. 196–198°. – IR. ($CHCl_3$): 3500, 1720, 1075, 960, 900. – ^{1}H-NMR. (90 MHz, $CDCl_3$): 5.99 and 5.64 (2 $d\times d$, $J=8$ and 4, H–C(4)); 5.51 and 5.45 (2 *d*, $J=5$, H–C(10)); 3.14 and 2.82 (*AB*-system, $J=4$, H_2C(13)); 1.72 (*s*, H_3C(16)); 1.34 and 1.23 (2 *s*, H_3C(6′)); 0.83 and 0.81 (2 *s*, H_3C(14)). – MS.: 506 (M^+), 491 (M^+-15), 488 (M^+-18), 478 (M^+-28), 463 (M^+-43), 259, 249, 248, 247, 187.

$C_{27}H_{38}O_9$ (506.60) Calc. C 64.01 H 7.56% Found C 63.85 H 7.78%

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