137. Synthesis of Verrucarin A and 3α-Hydroxyverrucarin A from Verrucarol and Diacetoxyscripenol (Anguidine)[1])

39th Communication on Verrucarins and Roridins[2])

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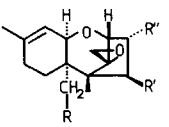
Summary

The title compounds have been synthesized starting from verrucarol and diacetoxyscripenol (anguidine), (*E*, *Z*)-muconic half ester and a derivative of verrucarinic acid. The latter has been prepared in optically active form from dimethyl 3-methylglutarate.

The verrucarins and roridins belong to an important and still growing class of macrocyclic di- and triesters produced by various strains of microorganisms[3]). Some metabolites are transformed by higher plants to yield oxygenated derivatives named baccharins [4]. The majority of these trichothecane esters exhibit interesting biological effects such as antibiotic, antifungal and antitumor activities. However, their general toxicity is very high [5]. It has been found that the macrocyclic lactone moiety and the epoxy group are essential structural requirements for the biological properties. However, these vary substantially with the individual nature of the macrocyclic system and the oxygenation pattern of the trichothecane part of the metabolites in a manner which is not yet well understood.

During the past decade many synthetic approaches to this family of natural products have been published, including successful routes which led to racemic trichodermol (**1**) [6], verrucarol (**2**) [7] and calonectrin (**3**) [8] *(Scheme 1)*. A first

Scheme 1



1	R = H	R' = OH	R'' = H
2	R = OH	R' = OH	R'' = H
3	R = OAc	R' = H	R'' = OAc
6	R = OAc	R' = OAc	R'' = OH

[1]) Part of this work was reported at the Meeting of the Swiss Chemical Society in Bern, October 16, 1981.

[2]) 38th Commun.: [1].

[3]) Reviews, see [2]; for recently isolated metabolites, see [3].

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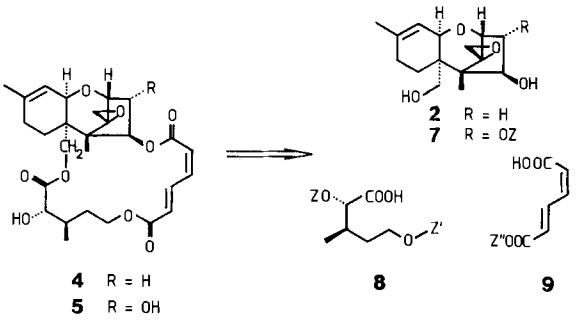
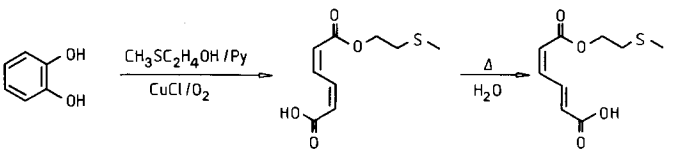
synthesis of a naturally occurring macrocyclic trichothecane ester, verrucarin A (**4**), was reported very recently by *Still et al.* [9]. The latter communication prompts us to disclose briefly our own results, by which not only the synthesis of verrucarin A (**4**) but also of 3α-hydroxyverrucarin A (**5**) has been successfully completed. The latter compound is an unnatural macrocyclic derivative of diacetoxyscirpenol (anguidine) (**6**, *Scheme 1*). These syntheses made use of the experience gained during the synthesis of tetrahydroverrucarin J and 2'-deoxy-3'-hydroxy-tetrahydroverrucarin A [1] [10].

Scheme 2



The obvious building blocks for the synthesis of **4** and **5** are verrucarol (**2**) and 3-*O*-protected 4,15-deacetylanguidine (**7**), respectively, a suitable functionalized derivative of verrucarinic acid (**8**) and a monoprotected (*E*/*Z*)-muconic acid (**9**) *(Scheme 2)*. We have pursued two different approaches. One of these focussed on the cyclization of a seco-acid containing a (*Z*)-enoic group with the secondary 4-hydroxy group of verrucarol (**2**). The other approach, which is described in this communication in more detail, uses a similar strategy to that applied in the meantime by *Still et al.* [9]. The first idea seemed attractive because of the ready availability of the required (*Z*/*E*)-muconic half ester **10**. This ester is prepared in a two step sequence from catechol and a primary alcohol *(Scheme 3)*. ^{13}C-NMR. spectrum of the product obtained showed the absence of any significant contamination by the isomer **9**. By this procedure the methyl mercaptoethyl half ester **10** was prepared [11][5]). However, it was difficult to condense the less reactive 4-hydroxyl group of verrucarol (**2**) with the very unstable (*Z*)-enoic function.

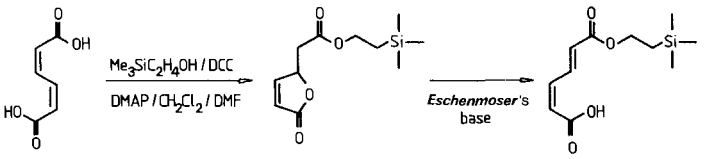
Scheme 3



[5]) Our findings disagree with the structures and mechanisms postulated by *Jaroszewski & Ettlinger* in the case of the 3-methyl-muconic acid derivatives [12]. However, independent syntheses of both **9** and **10**, which gave significantly different ^{13}C-NMR. spectra, support our assignments.

The observation that the muconic acid fragment **9** can also be prepared in the following straightforward manner *(Scheme 4)* allowed us to complete the synthesis of **4** and **5** by the second approach. Freshly recrystallized (*Z*/*Z*)-muconic acid (**12**) prepared by peracid oxidation of catechol [13] was condensed with β-trimethylsilylethanol in the presence of dicyclohexylcarbodiimide and 4-(dimethylamino)pyridine in CH_2Cl_2/DMF [14]. The lactone **13** obtained (yield ca. 80%) underwent elimination on treatment with *Eschenmoser's* base[6]) in CH_2Cl_2 or acetone to give **9** (yield *ca.* 75%[7]), m.p. 69–71° [^{1}H-NMR. ($CDCl_3$): 8.38 (br. $d \times d$, 1 H, $J = 16$ and 12); 6.72 (br. *t*, 1 H, $J = 12$); 6.11 (br. *d*, 1 H, $J = 16$); 5.96 (br. *d*, 1 H, $J = 12$); *cf.* [9]].

Scheme 4



12 **13** **9**

DMAP = 4-(Dimethylamino)pyridine

The verrucarinic acid fragment **8** was synthesized in optically active form starting from dimethyl 3-methylglutarate (**14**) *(Scheme 5)*. The diester was hydrolyzed enantioselectively by pig liver esterase [15] to the half ester **15** in 95% yield. Reduction of the carboxyl group by $BH_3 \cdot Me_2S$ [16] and silylation [17] of the primary alcohol formed led to the protected methyl ester **17**[8]). α-Hydroxylation was achieved by treatment of the Li-enolate (LDA/THF) of **17** with $MoO_5 \cdot Py \cdot HMPA$ (1.2 mol-equiv., −78°, 2 h) [20]. Separation of the resulting mixture of **19** and **20** (yield *ca.* 80%) by column chromatography (silicagel, ethyl acetate/petroleum ether 1:10) afforded the desired isomer **19** in *ca.* 40% yield. Treatment of **19** with dihydropyrane/pyridinium *p*-toluenesulfonate [21] and alkaline hydrolysis completed the synthesis of the verrucarinic acid segment **21**. The absolute configuration and optical purity of the product were established as follows: The hydroxy ester **19** was converted by mineral acid to verrucarinolactone (**22**)[9]), m.p. 101.5–103°, $[\alpha]_D^{23} = -10.7° \pm 0.4$ ($c = 1$, $CHCl_3$) (Lit. [23]: m.p. 103–104°, $[\alpha]_D^{22} = -9°$ ($c = 1$, $CHCl_3$);

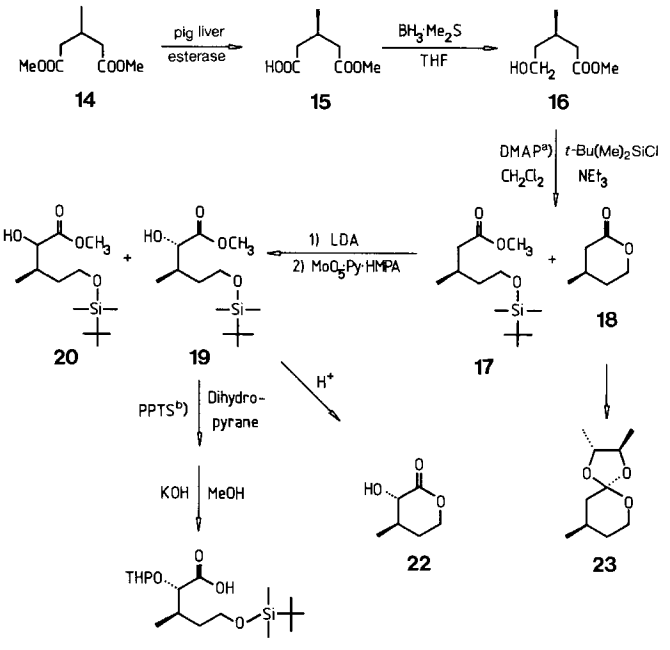
[6]) = 3,3,6,9,9-Pentamethyl-2,10-diazabicyclo[4.4.0]-1-decene.

[7]) The reaction seemed to be quite tricky. In the case of the methylmercapto-ethylester the corresponding lactone could be cleaved by the much cheaper DBU (= 1,8-Diazabicyclo[5.4.0]-7-undecene) in good yield and high purity, whilst **13** gave complex mixtures under these reaction conditions, as well as with DBN (= 1,5-diazabicyclo[4.3.0]-5-nonene). According to ^{1}H-NMR. the product was contamined with not more than 5% of the undesired (*Z*,*Z*)-isomer, as could be anticipated from a conformational analysis.

[8]) Formation of the lactone **18** could not be entirely suppressed in this reaction, nor when the silylimidazole procedure [18] was used. However, **18** could easily be separated and recycled to the desired ester **18** with a) KOH/methanol, b) 2.2 mol-equiv. (*t*-butyl)dimethylsilyl chloride/DMF/imidazole, c) KOH/methanol and d) CH_2N_2 [19] (yield *ca.* 70%).

[9]) A synthesis of optically active verrucarinolactone (**22**) starting with glutamic acid has been recently described [22].

Scheme 5



a) DMAP = 4-(dimethylamino)pyridine
b) PPTS = pyridinium *p*-toluenesulfonate

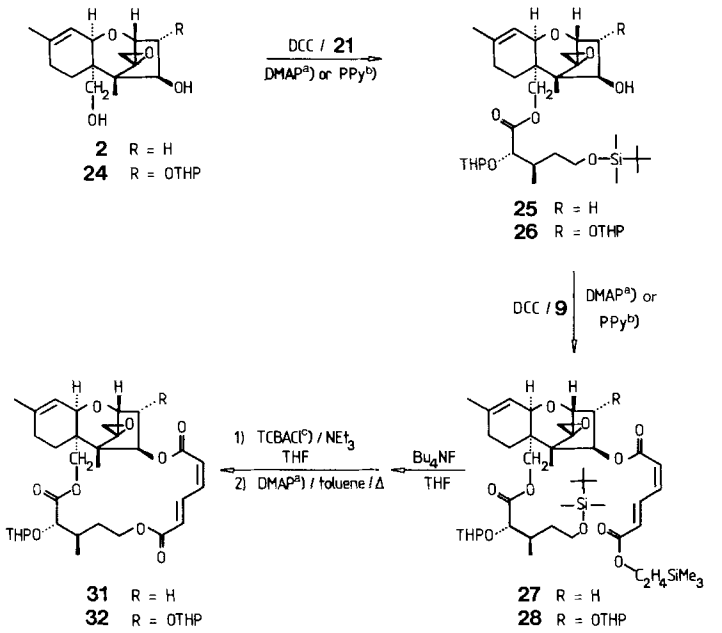
Lit. [24]: $[\alpha]_D^{23} = -11°$ ($c = 0.33$, $CHCl_3$); Lit. [9]: m.p. 103°, $[\alpha]_D^{23} = -10.4°$; Lit. [22]: m.p. 102–102.5°, $[\alpha]_D^{20} = -8.60°$ ($c = 0.93$, $CHCl_3$)). Compound **22** is a degradation product of verrucarin A (**4**). Optically active 3-methylvalerolactone (**18**) is known and its optical rotation can be compared with the reported data (found: $[\alpha]_D^{23} = +23.4°$ ($c = 5.8$, $CHCl_3$); Lit. [25]: $[\alpha]_D = 23.1°$ ($c = 1.31$, $CHCl_3$); Lit. [26]: $[\alpha]_D^{27} = -24.8°$ ($c = 5.6$, $CHCl_3$) for a sample with 90% e.e.; Lit. [27]: $[\alpha]_D^{27} = -26.18°$ ($c = 0{,}83$, $CHCl_3$)).

Finally, the orthoester **23**, prepared from (2*R*,3*R*)-butanediol, was subjected to capillary GC. in order to determine the diastereomer ratio [28]. On the basis of these methods the enantiomeric excess of (3*R*)-**15** is estimated as being 90%[10]).

The remaining steps of the synthesis of the macrocyclic triesters **4** and **5**, *i.e.* the combination of the three building blocks, were performed as given in *Scheme 6*. Anguidine (**6**) was converted to 3*a*-*O*-THP-verrucarol (**24**): *a*) dihydropyrane/pyridinium *p*-toluenesulfonate/CH_2Cl_2; *b*) KOH/MeOH (yield 95%). The primary hydroxyl groups of verrucarol (**2**), obtained by alkaline hydrolysis of verrucarin A (**4**), and of the THP-ether **24** were then condensed with **21** according to *Steglich*'s procedure [14] to give **25** and **26** in about 55% yield. The muconic acid part **9** was attached to the 4-hydroxyl group of **2** using the same reaction conditions (yield

[10]) It is noteworthy that the enzyme cleaved diethyl 3-methylglutarate with much lower selectivity (about 75% e.e.) than the dimethylester **14**.

Scheme 6



a) DMAP = 4-(dimethylamino)pyridine
b) PPy = 4-pyrrolidinopyridine
c) TCBACl = 2,4,6-trichlorobenzoyl chloride

95%), whereby significant isomerization was observed. According to ^{1}H-NMR. the crude product contained about 33% of the undesired (*E*,*E*)-muconate which was separated to a large extent by column chromatography on silica gel. With 4-pyrrolidinopyridine as catalyst [9] the same results were obtained with compound **26**. Preliminary experiments suggest that *Mukaiyama*'s method (CsF/2-bromopyridiniumtetrafluoroborate/CH_2Cl_2) which is recommended for α,β-unsaturated systems [29], should yield **27** and **28** in pure form. The two silyl protecting groups were removed by treatment with tetrabutylammoniumfluoride (THF, 0°, 30 min) to give the seco-acids **29** and **30** in moderate yield. Both underwent smooth cyclization using *Yamaguchi*'s mixed anhydride method [30] (2,4,6-trichlorobenzoylchloride/NEt_3/THF, followed by 6 mol-equiv. 4-(dimethylamino)pyridine/toluene/110°) to give the verrucarin derivatives **31** and **32** in *ca.* 50% yield. In the course of this reaction the (*E*,*E*)-isomers were lost. Finally, deprotection (pyridinium *p*-toluenesulfonate/MeOH/50°) completed the synthesis of verrucarin A (**4**) and 3*a*-hydroxyverrucarin A (**5**), identified by ^{1}H-NMR. and MS., the former also being compared with an authentic sample of natural verrucarin A (**4**).

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