71. Syntheses of Optically Active Verrucarinic Acid

40th Communication on Verrucarins and Roridins[1])

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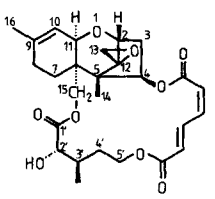
Summary

Three syntheses of (2 *S*, 3 *R*)-2, 5-dihydroxy-3-methylpentanoic acid (verrucarinic acid) and its derivatives suitably protected for the further transformation to macrocyclic trichothecenes are described. These involve an enantioselective ester hydrolysis by pig liver esterase, a *Sharpless* epoxidation and an asymmetric hydroboration.

The verrucarins and roridins are two important classes of macrocyclic trichothecene metabolites produced by various *fungi imperfecti* [2]. Since the discovery of the first member verrucarin A (**1**) in 1962 [3], these compounds have attracted much attention owing to their biological properties such as antibacterial, antifungal and cytostatic activity, which is connected with the macrocyclic ring system and with the epoxy group in the trichothecene moiety [4]. Therefore, many synthetic studies have been carried out recently. The synthesis of the model compounds tetrahydroverrucarin J [5] and 2′-deoxy-3′-hydroxyverrucarin A [6], as well as of the naturally occurring metabolites, verrucarin A (**1**) [1] [7] and verrucarin J (**2**) [8] have been completed. In the course of our own program directed towards the synthesis of macrocyclic trichothecenes we have developed three approaches to optically active verrucarinic acid (**3**), which is suitably protected for the subsequent



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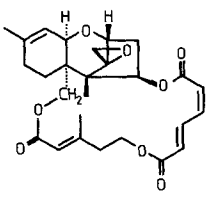

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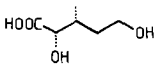

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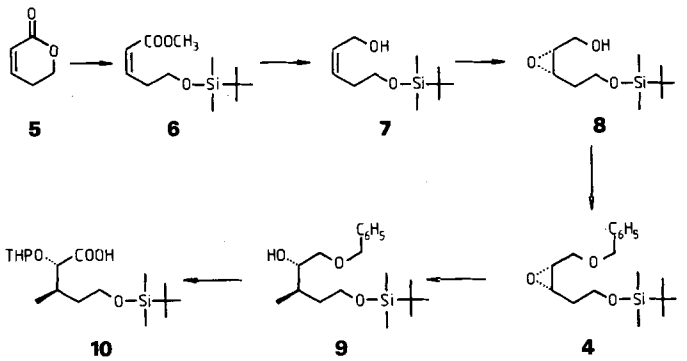
[1]) 39th Commun.: [1].

[2]) Author to whom correspondance should be addressed.

condensation with the C(15)-hydroxyl group of the sesquiterpene moiety. The increasing number of reports on the synthesis of verrucarinic acid derivatives [7] [9] prompts us to disclose our own results. In this paper are also given the experimental details of the enzymatic approach which has already been communicated [1].

The first route *(cf. Scheme 1)* using a *Sharpless* epoxidation [10] for introducing the chirality was based on the assumption that an epoxy group substituted simultaneously with an α-alkoxy and a β'-alkoxy group can be regioselectively opened.

Scheme 1



This prediction was deduced from the observation of *Pfaltz & Mattenberger* [11] that α-benzyloxy-epoxides are attacked by trimethylaluminum at lower temperatures and with higher selectivity than the β-substituted analogues. Key substrate for testing this hypothesis was the epoxide **4**. It was synthesized in a straightforward manner from the unsaturated lactone **5**[3]). Base-catalyzed hydrolysis (KOH/H_2O) of **5** followed by treatment with CH_3I/DMF[4]) led to the hydroxyester. This was subsequently protected as *t*-butyldimethylsilylether (**6**) [13] and then reduced to the allylic alcohol **7**. Epoxidation [10] gave the (2*R*,3*S*)-isomer **8** as shown below. Benzylation [14] of **8** yielded the intermediate **4** which was treated with trimethylaluminum/0.1 mol-equiv. BuLi [11]. A single product, later proven to be **9**, was isolated in high yield while treatment of **4** with dimethyllithiumcuprate [15] afforded a nearly 1:1 mixture of both regioisomers as expected, which could be separated on TLC. Finally the secondary hydroxyl group was protected as THP-ether [16], the benzyl group removed by hydrogenolysis and the primary alcohol transformed to the verrucarinic acid derivative **10** by applying the *Sharpless* procedure[5]) (cat. $RuCl_3/NaIO_4/CH_3CN/H_2O/CCl_4$) [17]. The latter is suitable to be used for the direct condensation with the trichothecene moiety.

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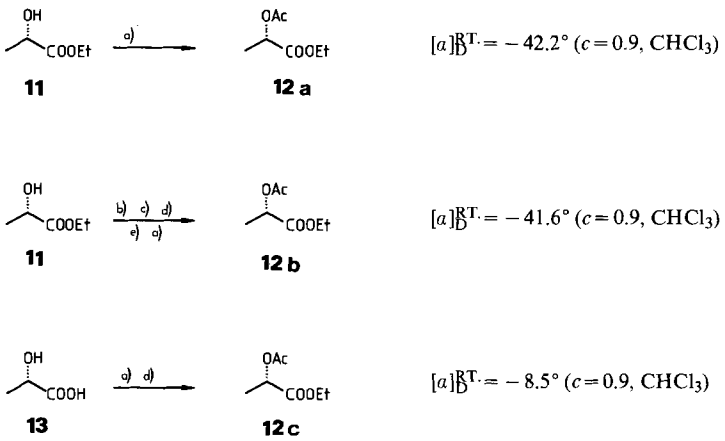
[3]) Prepared from vinylacetic acid and paraformaldehyde according to [12]. For details of this synthesis see *Exper. Part.*

[4]) *O*-Alkylation of the potassium carboxylate is convenient to perform and prevents ring closure always observed when the free acid is esterified with diazomethane.

[5]) *Attempts to* oxidize with pyridinium dichromate/DMF [18] completely failed.

The choice of the protecting group of the hydroxy group at C(2) proved to be critical to the success of the further synthesis. It must be quite stable because it has to be maintained till the last step of the synthesis and it has to be removed under conditions which must suit the many different functional groups. The influence on the acidity of the H-atom on the C(α)-atom represents a second problem. *Steglich* mentions [19] that partial racemization occurred during esterification of Z-protected amino acids when treated with *t*-butylalcohol, dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP). Similar observations were reported by *Trost et al.* with (*S*)-*O*-methylmandelic acid[6]), and have also been made in our laboratory with (*R*)-*O*-acetylmandelic acid[7]). In order to clarify the influence of the particular protecting groups we have carried out the following reactions *(Scheme 2)* with lactic acid as the most simple model for aliphatic α-hydroxy acids. Ethyl (*S*)-*O*-Acetyllactat **12a** which was prepared as a reference, showed a somewhat lower rotation than reported in [20] ($-47.6°$, $c = 0.9$, $CHCl_3$); however, the value was within the experimental error the same as for compound **12b** which was prepared by a five step synthesis. The reaction sequence contained the crucial reactions: 1) base-catalyzed hydrolysis and 2) esterification of the O-THP-protected α-hydroxy acid. Thus the results removed our doubts. However, we were very surprised to learn that the enantiomeric excess of ester **12c** was strongly decreased indicating that the DCC/DMAP procedure is probably too vigorous for O-acyl-α-hydroxyacids.

Scheme 2



[a]) Ac_2O/Py; [b]) dihydropyrane/pyridinium *p*-toluenesulfonate; [c]) KOH/EtOH; [d]) EtOH/dicyclohexylcarbodiimide/dimethylaminopyridine; [e]) HCl-solution.

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[6]) *Cf.* footnote 15 in [9c].

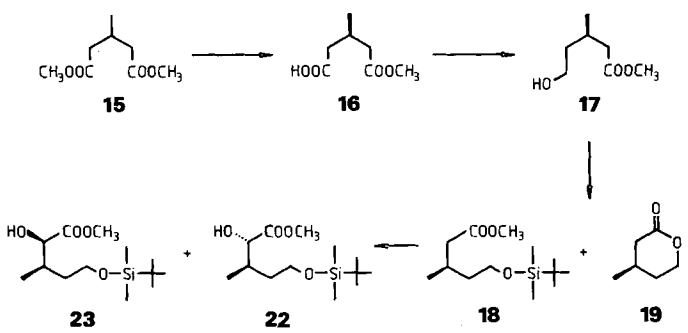
[7]) A sample of (*R*)-*O*-acetylmandelic acid of 61.3% e.e. showed substantial racemization yielding a 40.5:59.5 diastereomeric ratio after standard esterification with (*S*)-2-methylbutanol/DCC/DMAP as determined by GC.-analysis.

In order to confirm the structural assignments and the optical purity **10** was converted with *p*-toluenesulfonic acid/CH_2Cl_2 to (−)-verrucarinolactone (**14a**), whose m.p. and optical rotation were almost identical with those of an authentic sample prepared by hydrolysis of natural verrucarin A (**1**) as well as with those of a sample of (−)-verrucarinolactone (**14b**) which was synthesized by the enzymatic approach described further below.

However, this analysis feigns a too high enantioselectivity because the predominant enantiomer is probably enriched during crystallization of the lactone. *Data of* **14a**: m.p. 102–102.5°, $[\alpha]_D^{RT.} = -10.6$ ($c = 1.1$, $CHCl_3$); *data of* **14b**: m.p. 101.5–103°, $[\alpha]_D^{RT.} = -10.7°$ ($c = 1$, $CHCl_3$) ([21]: m.p. 103–104°, $[\alpha]_D^{RT.} = -9°$ ($c = 1$, $CHCl_3$); [22]: m.p. 103.5–104°, $[\alpha]_D^{RT.} = -11°$ ($c = 0.33$, $CHCl_3$)).

The second synthesis *(cf. Scheme 3)* utilizes the enantioselective hydrolysis of dimethyl 3-methylglutarate (**15**) by pig liver esterase [1] [23][8]). The free carboxyl group of **16** was reduced with borane dimethylsulfide [24] and the resulting hydroxyester **17** protected as *t*-butyldimethylsilylether (**18**) [13]. The six membered lactone **19**, obtained as side product[9]), is easily separable and can be used for the determination of the optical purity. The value of $[\alpha]_D^{RT.} = +23.4°$ ($c = 5.8$, $CHCl_3$) was found ([25]: $[\alpha]_D^{27} = -24.8°$ ($c = 5.6$, $CHCl_3$) for a sample with 90% e.e.). These data were in good agreement with the results of a ^{1}H-NMR. analysis of the diol **20** (obtained with MeLi) in the presence of Eu(tfc)$_3$ [26] as well with that of a capillary GC.-analysis of the orthoester **21** which was prepared with (2*R*,3*R*)-butan-2,3-diol [27]. The two latter measurements indicated an e.e. of 90% in lactone **19**. The crucial step consisted of the direct hydroxylation of the ester enolate. Kinetic deprotonation with lithium diisopropylamide (LDA) followed by treatment with

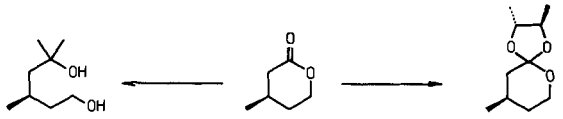
Scheme 3



[8]) The diethyl ester is hydrolyzed with significantly lower selectivity than the substrate **15** (*cf.* footnote 10 in [1] and [23]). A sample of (−)-verrucarinolactone (**14**) synthesized by the same route but starting with diethyl 3-methylglutarate showed $[\alpha]_D^{RT.} = -8.5°$ ($c = 1$, $CHCl_3$), m.p. = 98–101°.

[9]) The silylation step gives poorly reproducible yields with varying amounts of cyclization product. However, this 3-methylvalerolactone (**19**) can be transformed to **18** by a sequence involving a) KOH/MeOH; b) 2 mol-equiv. *t*-butyldimethylsilylchloride/imidazole/DMF; c) KOH/MeOH; d) CH_2N_2.

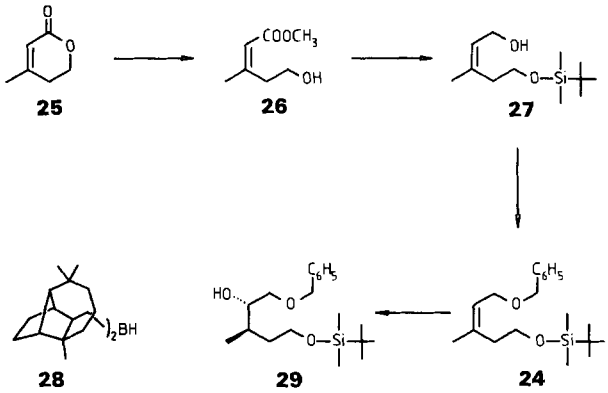
$MoO_5 \cdot Py \cdot HMPA$ [28] yielded a mixture of both α-hydroxy derivatives. As anticipated, the directing effect of the asymmetric center in 3-position is low, thus favouring the desired (2*S*)-epimer **22** over **23** in the ratio of 2:1[10]). After careful column chromatography **22** was obtained in pure form. It was transformed to the THP-ether and the latter cleaved with KOH/MeOH to yield the free acid, identical to **10**.



20 **19** **21**

The key step of the third synthesis *(cf. Scheme 4)* consists of an asymmetric hydroboration of the olefin **24** using dilongifoylborane as external chiral reagent. Although this sesquiterpene is available only in one enantiomeric form, comparison with the model compounds studied by *Brown et al.* [29] allowed us to assume that the attack should occur preferably from the *si,si*-side yielding predominantly the natural enantiomer. The well known anhydromevalonolactone (**25**) [30] served as starting material. For its preparation a new two step synthesis was developed. It began with a *Jones* oxidation of 3-methyl-3-buten-1-ol[11]) which was followed by an acid catalyzed *Prins*-type reaction of the resulting β,γ-unsaturated acid with paraformaldehyde in analogy to the synthesis of **5**. The shortness and simplicity of the new procedure compensates the modest overall yield of 19%. The subsequent reactions of the synthesis were analogous to those of the first approach. They included base-catalyzed hydrolysis (KOH/H_2O) and esterification (CH_3I/DMF) of the lactone **25** to yield compound **26** which again was transformed to the silyl-ether. Reduction of the α,β-unsaturated ester with diisobutylaluminumhydride

Scheme 4



25 **26** **27**

28 **29** **24**

[10]) Direct hydroxylation of the lactone enolate could not be achieved in acceptable yields.
[11]) Commercially available from *EGA*.

(DIBAH) afforded the allylic alcohol **27** which was finally protected as its benzyl-ether **24**. Treatment of the latter olefin with dilongifolylborane (**28**) gave after oxidative workup (H_2O_2/NaOH) a mixture of longifolol and of the desired compound **27**. Since both components had nearly the same polarity, they were separated by column chromatography after silylation of the crude product[12]). To establish the enantiomeric excess, the optical rotation of the relay compound **29**, which was identical with **9** with respect to its spectral data, was compared with that of the alcohol **9**. The latter was obtained by epoxide opening and estimated to be $\geq 95\%$ optically pure. Based on the $[\alpha]_D^{RT}$-values of distilled and analytically pure samples of **9** and **29**, the enantiomeric excess of the hydroboration product was found to be 50%. This value is somewhat lower than those observed for the model olefins studied by *Brown et al.* [29]. The subsequent transformations leading to verrucarinic acid (**3**) has been described already.

In conclusion, three approaches to optically active verrucarinic acid have been developed, two of which yield products of good to excellent enantiomeric excess. We are presently utilizing these building blocks for the synthesis of preformed side chains suitably protected for the further elaboration to macrocyclic trichothecenes.

The support of these investigations by the *Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung* is gratefully acknowledged.

Experimental Part

General remarks. Water-sensitive reactions were carried out in an Ar-atmosphere, CH_2Cl_2 and ether were dried by passing them through an Al_2O_3-column, THF by distilling it over $LiAlH_4$. All organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure below 50°. Pig liver esterase was purchased from *Boehringer.* Capillary GC.-analyses were carried out with a *Perkin-Elmer Sigma 3B* chromatograph on a *SE 54* column. Thin layer chromatograms (TLC.) were prepared on silica gel 60 F_{254} *(Merck)* and the spots were observed by spraying them with 10% H_2SO_4-solution in MeOH or $KMnO_4$-solutions. For column chromatography *silica gel 60* (0.04–0.063 or 0.063–0.200 mm, *Merck*) was used. The melting points (m.p.) were determined on a *Kofler* block and are corrected. The boiling points (b.p.) (Kugelrohr) refer to not corrected oven temperatures. Optical rotations and IR. (cm^{-1}) were measured with a *Perkin-Elmer model 141* polarimeter and a *Perkin-Elmer model 177* grating spectrometer, respectively. The 60-MHz-^{1}H-NMR. spectra were recorded on a *Varian EM 360* spectrometer, the 90-MHz-^{1}H-NMR. and 22.63-MHz ^{13}C-NMR. spectra on a *Bruker WH-90* spectrometer with *Fourier* transform, respectively. Chemical shifts are reported in ppm downfield from internal $SiMe_4$, if indicated in parentheses, or from the Me_2Si-singlet in TBDMS-protected compounds. Abbreviations: TBDMS-Cl = *t*-butyldimethylsilyl chloride, DMAP = dimethylaminopyridine, PPTS = pyridinium *p*-toluenesulfonate.

Preparation of methyl (Z)-5-t-butyldimethylsilyloxy-2-pentenoate (**6**). To a solution of 1.78 g (18.3 mmol) of 5,6-dihydro-2-pyrone (**5**) in 18 ml of water were added 1.28 g (1.2 mol-equiv.) of KOH. After 2.5 h at r.t. the solvent was removed *i.v.* and the residue dried for 24 h over P_4O_{10} in high vacuum. The K-salt was dissolved in 13 ml of DMF and 5.5 ml of CH_3I were added under stirring. After 5 h at r.t. the mixture was poured onto crashed ice and extracted with ether. The combined organic layers were washed with brine and dried to afford, after removal of the solvent, virtually pure methyl (*Z*)-5-hydroxy-2-pentenoate and small amounts of DMF. To a solution of this crude product in 25 ml of CH_2Cl_2 were added at 0° subsequently 3.3 ml of NEt_3, 3.3 g of TBDMS–Cl and 200 mg of DMAP. After 10 min the stirring was continued for 1 h at r.t. The mixture was diluted with ether, washed with 1N HCl, brine and dried. After evaporation of the solvent the residue was distilled

[12]) Under the conditions introduced by *Chaudhary & Hernandez* (NEt_3, TBDMS-Cl/DMAP, see *Exper. Part*) [13] primary alcohols can be selectively protected.

(Kugelrohr, 110°/0.1 Torr) to afford 2.59 g (58%) of **6** pure according to TLC. (ether/petrol ether 1:1). – IR. (film): 1725, 1640. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 0 (*s*, 6 H, $(CH_3)_2Si$); 0.8 (*s*, 9 H, $(CH_3)_3C$); 2.6–2.9 (*m*, 2 H, $H_2C(4)$); 3.55 (*s*, 3 H, $COOCH_3$); 3.6 (*t* overlapped, 2 H, $H_2C(5)$); 5.7 ($d \times d$, $^3J = 11$, $^4J = 1$, 1 H, H–C(2)); 6.05–6.45 (*m*, 1 H, H–C(3)).

*Preparation of (Z)-5-*t*-butyldimethylsilyloxy-2-penten-1-ol* (**7**). At 0° to a solution of 10.3 g (42 mmol) of **6** in 100 ml of abs. toluene. 80 ml of 1.2N DIBAH (hexane) were added dropwise. After stirring for 1 h at this temp. the mixture was quenched with 250 ml of sat. K/Na-tartrate-solution and extracted with ether. The combined organic layers were washed with brine, dried and evaporated *i.v.* to yield 8.3 g (91%) of an oil which was pure according to TLC. (ether/petrol ether 1:1). It can be distilled at 100°/0.05 Torr (Kugelrohr). – IR. (film): 3350 br., 3020. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 0 (*s*, 6 H, $(CH_3)_2Si$); 0.8 (*s*, 9 H, $(CH_3)_2C$); 2.15–2.45 (*m*, 2 H, $H_2C(4)$); 2.6 (br. *s*, 1 H, OH); 3.55 (*t*, $J = 6$, 2 H, $H_2C(5)$); 4.05 (*d*, $J = 5$, 2 H, $H_2C(1)$); 5.2–5.9 (*m*, 2 H, H–C(2), H–C(3)). – ^{13}C-NMR. ($CDCl_3$, TMS): 5.4 (*qa*, $(CH_3)_2Si$); 18.4 (*s*, $(CH_3)_3C$); 25.9 (*qa*, $(CH_3)_3C$); 31.0 (*t*, C(4)); 58.1 (*t*, C(5)); 62.4 (*t*, C(1)); 129.0 (*d*, C(2) or C(3)); 130.9 (C(3) or C(2)).

$C_{11}H_{24}O_2Si$ (216.40) Calc. C 61.06 H 11.18% Found C 61.02 H 11.37%

*Preparation of (2R,3S)-5-*t*-butyldimethylsilyloxy-2,3-epoxypentan-1-ol* (**8**). To 370 ml of abs. CH_2Cl_2 12.4 ml (41.8 mmol) of $Ti(OiPr)_4$ were added at –30° followed by 7.4 ml (43.2 mmol) of diethyl (–)-D-tartrate in 10 ml of CH_2Cl_2. After 10 min a solution of 8.24 g (38.1 mmol) of **7** in 20 ml of CH_2Cl_2 and 23 ml of 4.1N *t*-butylhydroperoxide in $C_2H_4Cl_2$ were added. The mixture was kept for 4 days at this temp. and then quenched with 100 ml of 10% aq. solution of tartaric acid. After stirring for 30 min at –30° and 1 h at r.t. the aqueous phase was separated and extracted with 50 ml of CH_2Cl_2. The combined organic layers were washed with water, dried and evaporated *i.v.* Then, 120 ml of 1N NaOH were added at 0° to the residue, which was dissolved in 300 ml of ether, with vigorous stirring. After 30 min the aqueous phase was separated and extracted with 50 ml of ether. Finally, the combined organic layers were washed with brine (2 times), dried and evaporated *i.v.* to yield 8.43 g (95%) of **8**. – IR. (film): 3400 br. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 0 (*s*, 6 H, $(CH_3)_2Si$); 0.8 (*s*, 9 H, $(CH_3)_3C$); 1.55–1.95 (*m*, 2 H, $H_2C(4)$); 2.85–3.25 (*m*, 3 H, H–C(2), H–C(3) and OH); 3.3–3.85 (*m*, 4 H, $H_2C(1)$ and $H_2C(5)$).

*Preparation of (2R,3S)-1-benzyloxy-5-*t*-butyldimethylsilyloxy-2,3-epoxypentan* (**4**). To a solution of 8.43 g (36.3 mmol) of **8** in 120 ml of abs. THF were added at 0° 1.2 g of NaH from which the white oil had been removed with hexane prior to use. After 5 min 1.3 g (3.5 mmol) of Bu_4NI and 5.35 ml (45 mmol) of benzylbromide were added and the mixture stirred for 3 h at r.t. The solution was diluted with 200 ml of petrol ether, washed with brine (3 times), dried and evaporated *i.v.* to afford 13 g of crude product which was purified by column chromatography (ether/petrol ether 2:3) to yield 11.0 g (94%) of pure **4**. – IR. (film): 1250, 1100. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 0 (*s*, 6 H, $(CH_3)_2Si$); 0.8 (*s*, 9 H, $(CH_3)_3C$); 1.45–1.8 (*m*, 2 H, $H_2C(4)$); 2.85–3.3 (*m*, 2 H, H–C(2) and H–C(3)); 3.45–3.8 (*m*, 4 H, $H_2C(1)$ and $H_2C(5)$); 4.5 (*AB*-system, 2 H, $CH_2C_6H_5$); 7.2 (br. *s*, 5 H, C_6H_5).

*Preparation of (2S,3R)-1-benzyloxy-5-*t*-butyldimethylsilyloxy-3-methylpentan-2-ol* (**9**). At –40° 34 ml of 3M Me_3Al (toluene) followed by 6.5 ml of 1.6M BuLi (hexane) were added to a solution of 10.87 g (33.7 mmol) of **4** in 120 ml of abs. toluene. The reaction mixture was kept over night at –30° and hydrolyzed by careful addition of 150 ml of 2N NaOH at 0°. After dilution with 300 ml of ether stirring was continued until two clearly separable layers appeared. The aqueous phase was again extracted with ether and the combined organic layers washed with brine, dried and evaporated *i.v.* The residue, after purification by column chromatography (ether/petrol ether 8:2), afforded 10.81 g (94%) of **9**. The product was homogeneous on TLC. It could be distilled at 180°/0.5 Torr (Kugelrohr); $[\alpha]_D^{RT} = +2.82$ ($c = 6.59$, $CHCl_3$). – IR. (film): 3450 br., 3090, 3070, 3035. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 0 (*s*, 6 H, $(CH_3)_2Si$); 0.8 (*s*, 9 H, $(CH_3)_3C$); 0.8 (*d*, overlapped, 3 H, H_3C–C(3)); 1.4–2.0 (*m*, 3 H, H–C(3), $H_2C(4)$); 2.75 (*d*, $J = 3$, 1 H, OH); 3.35–3.8 (*m*, 5 H, $H_2C(1)$, H–C(2) and $H_2C(5)$); 4.5 (*s*, 2 H, $CH_2C_6H_5$); 7.3 (br. *s*, 5 H, C_6H_5). – ^{13}C-NMR. ($CDCl_3$): 4.9 (*qa*, $(CH_3)_2Si$); 14.4 (*qa*, H_3C–C(3)); 18.7 (*s*, $(CH_3)_3C$); 26.3 (*qa*, $(CH_3)_3C$); 33.3 (*d*, C(3)); 36.8 (*t*, C(4)); 61.5 (*t*, C(5)); 73.4, 73.6 and 73.8 (C(1), C(2) and $CH_2C_6H_5$); 128.0 (*d*, arom., *ortho* and *para*); 128.8 (*d*, arom., *meta*); 138.7 (*s*, arom.).

$C_{19}H_{34}O_3Si$ (338.56) Calc. C 67.40 H 10.12% Found C 67.19 H 10.28%

Reaction of epoxide **4** *with* Me_2CuLi. To a well stirred suspension of 286 mg (1.5 mmol) of CuI in 5 ml of abs. ether were added by a syringe 2 ml of 1.5 M MeLi in ether at 0°. After 5 min 135 mg (0.42 mmol) of **4** dissolved in 5 ml of ether were added and the mixture allowed to stand for 3 h at 0°. After quenching with sat. NH_4Cl-solution the layers were separated, the aqueous solution extracted with 30 ml of ether and the combined organic phases washed with brine, dried and evaporated *i.v.* to afford 123 mg of crude product consisting of **9** and the 3-hydroxy-2-methyl-regioisomer in a ratio of about 1:1, which could be separated on TLC. (ether/petrol ether 1:1, Rf 0.43 (**9**) and 0.49, respectively). The unnatural isomer was isolated by column chromatography (ether/petrol ether 1:3). – ^{1}H-NMR. (60 MHz, $CDCl_3$): 0 (*s*, 6 H, $(CH_3)_2Si$); 0.8 (*s*, 9 H, $(CH_3)_3C$); 0.85 (*d*, overlapped, 3 H, $H_3C-C(2)$); 1.2–2.0 (*m*, 3 H, H–C(2), $H_2C(4)$); 3.1 (br. *s*, 1 H, OH); 3.3–4.0 (*m*, 5 H, $H_2C(1)$, H–C(3) and $H_2C(5)$); 4.4 (*s*, 2 H, $CH_2C_6H_5$); 7.25 (br. *s*, 5 H, C_6H_5).

Preparation of (2S,3R)-1-benzyloxy-5-t-butyldimethylsilyloxy-3-methyl-2-tetrahydropyranyloxy-pentan. A mixture of 370 mg (1.09 mmol) of **9**, 0.65 ml of dihydropyrane and 80 mg of PPTS in 4 ml of CH_2Cl_2 were allowed to stand at r.t. over night. After filtration through a short column (10 g Al_2O_3 (neutral), ether) 450 mg (97%) of pure THP-ether were obtained (diastereoisomers separable on TLC. (ether/petrol ether 1:4)). – IR. (film): 3030, 1255. – ^{1}H-NMR. (90 MHz, $CDCl_3$): 0 (*s*, 6 H, $(CH_3)_2Si$); 0.85 (*s*, 9 H, $(CH_3)_3C$); 0.8 (*d*, overlapped, 3 H, $H_3C-C(3)$); 1.4–1.9 (*m*, 9 H, H–C(3), $H_2C(4)$, $H_2C(3')$, $H_2C(4')$ and $H_2C(5')$); 3.2–4.0 (*m*, 7 H, $H_2C(1)$, H–C(2), $H_2C(5)$ and $H_2C(6')$); 4.48 and 4.50 (2 *s*, 2 H, $CH_2C_6H_5$); 4.6 and 4.8 (br., 1 H, H–C(2')); 7.28 (br. *s*, 5 H, C_6H_5).

Preparation of (2S,3R)-5-t-butyldimethylsilyloxy-3-methyl-2-tetrahydropyranyloxy-pentan-1-ol. The solution of 450 mg (1.06 mmol) of 1-benzyloxy-5-*t*-butyldimethylsilyloxy-3-methyl-2-tetrahydropyranyloxy-pentane in 6 ml of ethyl acetate and 2.5 ml of abs. ethanol was shaken over 150 mg of Pd/C (10%) under 1 H_2-atm. for 15 min. The catalyst was removed by filtration through *Celite* and the solvents removed *i.v.* to leave 330 mg (93%) of free alcohol, separable on TLC. into the diastereomers (ether/petrol ether 7:3). – IR. (film): 3450 br., 1260. – ^{1}H-NMR. (90 MHz, $CDCl_3$): 0 (*s*, 6 H, $(CH_3)_2Si$); 0.85 (*s*, 9 H, $(CH_3)_3C$); 0.85 (*d*, overlapped, 3 H, $H_3C-C(3)$); 1.0–2.2 (*m*, 9 H, H–C(3), $H_2C(4)$, $H_2C(3')$, $H_2C(4')$ and $H_2C(5')$); 3.35–4.15 (*m*, 8 H, $H_2C(1)$, H–C(2), $H_2C(5)$, $H_2C(6')$ and OH); 4.4 and 4.7 (br., 1 H, H–C(2')).

Preparation of (2S,3R)-5-t-butyldimethylsilyloxy-3-methyl-2-tetrahydropyranyloxy-pentanoic acid (**10**). To 330 mg (0.95 mmol) of 5-*t*-butyldimethylsilyloxy-3-methyl-2-tetrahydropyranyloxy-pentan-1-ol suspended in a mixture of 2 ml of CCl_4, 2 ml of CH_3CN and 3 ml of H_2O were added 660 mg (3.08 mmol) of $NaIO_4$ followed by 8.5 mg of $RuCl_3 \cdot$ aq. After vigorous stirring for 1 h the mixture was extracted with CH_2Cl_2, the combined organic layers washed with brine, dried and evaporated *i.v.* The residue was dissolved in ether, filtered through *Celite* and yielded after removal of the solvent 294 mg (89%) of protected verrucarinic acid (**10**). – IR. (film): 3000 br., 1720, 1250. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 0 (*s*, 6 H, $(CH_3)_2Si$); 0.85 (*s*, 9 H, $(CH_3)_3C$); 0.9 (*d*, overlapped, 3 H, $H_3C-C(3)$); 1.0–2.8 (*m*, 9 H, H–C(3), $H_2C(4)$, $H_2C(3')$, $H_2C(4')$ and $H_2C(5')$); 3.3–4.4 (*m*, 4 H, $H_2C(5)$ and $H_2C(6')$); 4.05 and 4.25 (*d*, 1 H, H–C(2)); 4.4–4.8 (br., 1 H, H–C(2')); 8.7 (br., 1 H, COOH).

The spectra were identical except for the diastereomeric ratio to those of a sample prepared from natural (–)-verrucarinolactone (**14**) by a reaction sequence involving a) dihydropyrane/PPTS; b) KOH/MeOH; c) 2.2 mol-equiv. TBDMS-Cl/imidazole; d) KOH/MeOH.

Preparation of 1-methyl hydrogen (3R)-3-methylglutarate (**16**). To 15.0 g (86 mmol) of dimethyl 3-methylglutarate (**15**) suspended in 100 ml of 0.1 M phosphate buffer of pH 8 were added 1000 units of pig liver esterase with vigorous stirring. The pH-value was kept constant by adding 1 N NaOH. After consumption of 1 mol-equiv. of base (overnight) the mixture was homogeneous. The pH-value was adjusted to 9, the aqueous phase extracted with ether, the organic layer washed with water and the combined aqueous solutions acidified to pH 2. These were again extracted with ether, dried and evaporated *i.v.* to yield 11.90 g (86%) of pure half-ester **16** as an oil. – IR. (film): 3100 br., 1735, 1705. – ^{1}H-NMR. (60 MHz, CCl_4, TMS): 1.0 (br. *d*, $J = 5$, 3 H, $H_3C-C(3)$); 2.0–2.6 (*m*, 5 H, $H_2C(2)$, H–C(3) and $H_2C(4)$); 3.60 (*s*, 3 H, $COOCH_3$); 11.0 (*s*, 1 H, COOH).

Preparation of methyl (3R)-5-hydroxy-3-methyl-pentanoate (**17**). To a solution of 9.59 g (59.9 mmol) of **16** in 40 ml of abs. THF were added 5.87 ml (62 mmol) of $BH_3 \cdot (CH_3)_2S$ at such a rate that the temp. did not exceed 30°. After stirring for 1.5 h at r.t. 3.6 ml of water were carefully added and the solvent removed *i.v.* The white residue was taken up in ethyl acetate, dried, filtered and evaporated to yield 8.53 g (97%) of **17** as an oil shown to be 97% pure according to GC. (*carbowax* 3%). – IR. (film):

3500 br., 1735. – ^{1}H-NMR. (60 MHz, $CDCl_3$, TMS): 0.95 (br. *d*, J=6, 3 H, H_3C–C(3)); 1.2–2.6 (*m*, 6 H, H_2C(2), H–C(3), H_2C(4) and OH); 3.65 (*s*, 3 H, $COOCH_3$); 3.75 (*t*, J=6, 2 H, H_2C(5)).

Preparation of methyl (3R)-5-t-butyldimethylsilyloxy-3-methyl-pentanoate (**18**). To a solution of 1.04 g (7.1 mmol) of **17** in 10 ml of abs. CH_2Cl_2 were subsequently added 1.16 g (7.7 mmol) of TBDMS-Cl, 780 mg (7.7 mmol) of NEt_3 and 50 mg of DMAP. After 2 h at r.t. the precipitate was filtered off and washed with CH_2Cl_2, the combined filtrates washed with sat. NH_4Cl-solution and brine, dried and evaporated *i.v.* Column chromatography of the residue (CH_2Cl_2) afforded 1.60 g (87%) of **18**. However, the yields were not reproducible. From the most unfavourable run only 21% of **18** and 69% of **19** were obtained.

Data of **18**. B.p. 120°/0.2 Torr (Kugelrohr). – IR. (film): 1740, 1255. – ^{1}H-NMR. (60 MHz, CCl_4): 0 (*s*, 6 H, $(CH_3)_2Si$); 0.85 (*s*, 9 H, $(CH_3)_3C$); 0.9 (*d*, overlapped, 3 H, H_3C–C(3)); 1.1–2.4 (*m*, 5 H, H_2C(2), H–C(3) and H_2C(4)); 3.55 (*s*, 3 H, $COOCH_3$); 3.6 (*t*, J=6, 2 H, H_2C(5)).

Preparation of methyl (2S,3R)-5-t-butyldimethylsilyloxy-2-hydroxy-3-methyl-pentanoate (**22**). A solution of 13.9 mmol of LDA was prepared by adding 9.3 ml of 1.5 M BuLi (hexane) to 1.96 ml of diisopropylamine in 10 ml of abs. THF at 0°. After stirring for 5 min, the LDA-solution was cooled to −78°. A solution of 3.30 g (12.7 mmol) of **18** in 60 ml of abs. THF was then added during 20 min. After an additional ¼ h 6.94 g (16 mmol) of $MoO_5 \cdot Py \cdot HMPA$ were added within a few seconds and the whole mixture stirred for 2¼ h at −78°. The cooling bath was removed and as soon as the temp. reached −30° 15 ml of sat. Na_2SO_3-solution were added, followed by additional 20 ml of water. After stirring for 10 min at r.t. the layers were separated, the aqueous phase extracted with ether and the combined organic layers washed with sat. NH_4Cl-solution and brine. Drying and removal of the solvents yielded a crude product which consisted according to GC.-analysis of 11% of starting material, 56% of desired **22** and 28% of unnatural (2*R*)-epimer **23**. Column chromatography (ethyl acetate/petrol ether 1:10) afforded 495 mg (14%) of pure **22**, 1.067 g (30%) of enriched **22** (82%), which was purified by a second column, and 1.03 g (29%) of a nearly 1:1 mixture of **22** and **23**. – IR. (film): 3500 br., 1735, 1255. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 0 (*s*, 6 H, $(CH_3)_2Si$); 0.85 (*s*, 9 H, $(CH_3)_3C$); 0.85 (*d*, overlapped, 3 H, H_3C–C(3)); 1.0–2.4 (*m*, 3 H, H–C(3) and H_2C(4)); 3.0 (*s*, 1 H, OH); 3.65 (*t*, J=5.5, 2 H, H_2C(5)); 3.7 (*s*, 3 H, $COOCH_3$); 4.20 (*d*, J=3, 1 H, H–C(2)). – In **23** the H–C(2)-*d* appears at 4.05 (J=4).

Preparation of (2S,3R)-5-t-butyldimethylsilyloxy-3-methyl-2-tetrahydropyranyloxy-pentanoic acid. A solution of 267 mg (0.96 mmol) of **22** in 5 ml of CH_2Cl_2 was treated with 0.5 ml of dihydropyrane and 25 mg of PPTS. After 12 h the mixture was diluted with CH_2Cl_2, washed with 2 N K_2CO_3, dried and evaporated *i.v.* Column chromatography of the crude product (CH_2Cl_2) yielded 250 mg (72%) of pure THP-protected ester which was hydrolyzed by refluxing it in 4 ml MeOH/H_2O 4:1 for 3 h. Water was added, the organic solvent removed *i.v.* and the residual aqueous phase washed with small amounts of ether (attention: the carboxylate is bad water-soluble!). Acidifying to pH 2.5 and extraction with ether yielded finally, after washing with brine, drying and removal of the solvent, 170 mg (71%) of the acid, identical to **10**.

Preparation of 3-methyl-3-butenoic acid. To 30 g (0.35 mol) of 3-methyl-3-buten-1-ol in 300 ml of acetone were added slowly at 0° 185 ml of 8 N *Jones* reagent. After stirring for 5 h at r.t. the supernatant solution was decanted and the organic solvent thereof removed *i.v.*, while the residue was dissolved in H_2O and extracted with ether. After combination of these ethereal extracts with the first crop an aqueous layer separated which was discarded. The organic phase, after being concentrated to half the volume, was extracted with 2 N $KHCO_3$ (180 ml), acidified with 32 ml of conc. HCl-solution (cooling!) and saturated with NaCl. The acid layer was separated, the aqueous phase extracted with ether (2 times) and the combined organic layers washed with brine, dried and evaporated *i.v.* Distillation (77–79°/15 Torr) yielded 19.5 g (56%) of pure 3-methyl-3-butenoic acid. – IR. (film): 3000 br., 1710, 1650. – ^{1}H-NMR. (60 MHz, $CDCl_3$, TMS): 1.85 (br. *s*, 3 H, CH_3); 3.05 (br. *s*, 2 H, H_2C(2)); 4.8 (*m*, 2 H, H_2C(4)); 11.5 (*s*, 1 H, COOH).

Preparation of anhydromevalonolactone (**25**). A mixture of 2.35 g (23.5 mmol) of 3-methyl-3-butenoic acid, 0.7 g of paraformaldehyde, 6 ml of acetic acid and 0.1 ml of conc. sulfuric acid were refluxed for 8 h. After cooling 0.47 g of anh. NaOAc were added and the solvent evaporated *i.v.* The residue was dissolved in 30 ml of CH_2Cl_2 and the starting material extracted with 8 ml of sat. $NaHCO_3$-solution. The organic layer was dried, the solvent removed *i.v.* and the residue again dissolved in ether. By shaking with 20 ml of 2 N NaOH the lactone was hydrolyzed and went into the aqueous phase.

After acidifying with conc. HCl-solution and saturation with NaCl, the solution was extracted 3 times with 40 ml of CH_2Cl_2. The combined organic layers were dried, the solvent removed *i.v.* and the residue distilled (Kugelrohr/65°/0.4 Torr) to yield finally 870 mg (30%) of pure **25**. – IR. (film): 1720. – ^{1}H-NMR. (60 MHz, $CDCl_3$, TMS): 2.0 (br. *s*, 3 H, CH_3); 2.4 (br. *t*, J = 6.5, 2 H, $H_2C(4)$); 4.3 (*t*, J = 6.5, 2 H, $H_2C(5)$); 5.7 (*qa*, J = 1.5, 1 H, H–C(2)).

Preparation of (Z)-1-benzyloxy-5-t-butyldimethylsilyloxy-3-methyl-2-buten (**24**). A solution of 870 mg (7.76 mmol) of **25** and of 520 mg of KOH in 7.5 ml of H_2O were heated for 15 min on a steam bath. The water was then removed *i.v.* and the residue dried over P_4O_{10} on high vacuum. The K-salt was dissolved in 7.5 ml of DMF, and 1.85 ml of CH_3I were added. After stirring for 24 h at r.t. the mixture was poured on ice and extracted with ether (3 times). The combined organic layers were washed with brine, dried and evaporated *i.v.* to yield crude *methyl (Z)-5-hydroxy-3-methyl-2-pentenoate* (**26**), which was immediately silylated by adding subsequently at 0° 10 ml of CH_2Cl_2, 1.0 ml of NEt_3, 1.0 g of TBDMS-Cl and 100 mg of DMAP. After 10 min stirring was continued for 1 h at r.t., the mixture diluted with ether, washed with 1N HCl and brine and dried. After removal of the solvents Kugelrohr-distillation (120°/0.4 Torr) afforded 1.17 g (58%) of pure product which was directly used for the following reduction. This reaction was run completely analogously to the synthesis of **7** by using 6.5 ml of 1.2N DIBAH (hexane). Workup as described above yielded 1.0 g (95%) of *(Z)-5-t-butyldimethylsilyloxy-3-methyl-2-penten-1-ol* **27** pure by TLC., which was benzylated according to the preparation of **4** by using 300 mg of NaH, 140 mg of BU_4NI and 0.66 ml of benzylbromide. Flash chromatography of the crude product (ether/petrol ether 1:11) afforded 1.30 g (93%) of pure **24**. – IR. (film): 3090, 3060, 3030. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 0 (*s*, 6 H, $(CH_3)_2Si$); 0.85 (*s*, 9 H, $(CH_3)_3C$); 1.7 (br. *s*, 3 H, CH_3); 2.2 (br. *t*, J = 7, 2 H, $H_2C(4)$); 3.55 (*t*, J = 7, 2 H, $H_2C(5)$); 3.95 (br. *d*, J = 6, 2 H, $H_2C(1)$); 4.4 (*s*, 2 H, $CH_2C_6H_5$); 5.45 (br. *t*, J = 6, 1 H, H–C(2)); 7.25 (br. *s*, 5 H, C_6H_5).

$C_{19}H_{32}O_2Si$ (320.55) Calc. C 71.19 H 10.06% Found C 71.23 H 10.28%

Preparation of (2S,3R)-1-benzyloxy-5-t-butyldimethylsilyloxy-3-methyl-pentan-2-ol (**29**). To a suspension of 3.6 g (8.53 mmol) of dilongifolylborane (**28**, prepared from 4.2 g of longifolen and 1.4 ml of $BH_3 \cdot (CH_3)_2S$ in abs. ether) in 15 ml of abs. THF were added 2.2 g (6.86 mmol) of **24**. After stirring over night at r.t. 3.2 ml of 3N NaOH followed by 3.5 ml of 30% H_2O_2-solution were added by cooling so that the internal temp. remained below 30°. After heating for 1 h at 55° the layers were separated and the aqueous phase extracted with ether. The combined organic layers were washed with brine, dried and evaporated *i.v.* to afford 6.0 g of a mixture consisting of longifolol and of **29**. For separating the mixture was selectively silylated by dissolving it in 40 ml of CH_2Cl_2 and adding subsequently at 0° 2.65 ml of NEt_3, 2.5 g (16.6 mmol) of TBDMS-Cl and 80 mg of DMAP. After stirring over night at r.t. the mixture was diluted with ether, washed with 1N HCl and brine, dried and evaporated *i.v.* Flash chromatography of the crude product (ether/petrol ether 3:7) yielded 1.0 g of **29** which was liberated from last traces of longifolol by Kugelrohr-distillation (180°/0.5 Torr) to yield 700 mg (30%) of pure **29**. – IR. and ^{1}H-NMR. identical with **9**. $[\alpha]_D^{T.} = +1.68°$ (c = 6.3, $CHCl_3$).

$C_{19}H_{34}O_3Si$ (338.56) Calc. C 67.40 H 10.12% Found C 67.17 H 10.41%

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