189. Further Syntheses of Optically Active Verrucarinic Acid

43rd Communication of Verrucarins and Roridins[1])

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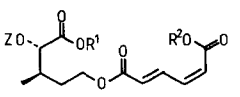
Summary

Two new syntheses of verrucarinic acid ((2*S*,3*R*)-2,5-dihydroxy-3-methylpentanoic acid) and its derivatives, suitably protected for the further conversion to macrocyclic trichothecenes, are described. The first one makes use of a diastereoselective alkylation of a (−)-(*S*)-malic acid ester and the regioselective reduction of one carboxyl function to a methyl group. The second approach involves a stereoselective addition of an allylsilane to a chiral glyoxylate.

The trichothecenes belong to a class of sesquiterpenoid metabolites which have attracted much attention during the past years owing to a wide range of biological activity [2]. They are produced by various *fungi imperfecti* and can be divided into three groups: 1) the simple sesquiterpenes, 2) the macrocyclic di- and triesters, most often derived from verrucarol, and 3) the trichoverroids discovered by *Jarvis et al.* [3]. The latter possess only a portion of the macrolidic moiety.

Owing to their extraordinary properties, many trichothecenes have been the target of synthetic efforts, which have recently culminated in the synthesis of *e.g.* verrucarol [4], anguidine [5] and calonectrin [6] and of verrucarin A [7], verrucarin J [8], baccharin B5 [9] and trichoverrol B [10]. In continuation of our work in this field, we explored the possibilities of synthesizing a triester of type **1** with two goals in mind. By switching the sequence of the deblocking reactions for R^1 and R^2, it should be possible to close



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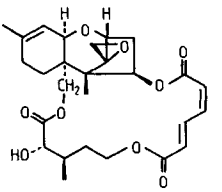


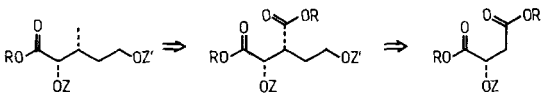
Verrucarin A

the macrolide ring with either the C(4)- or the C(15)-OH group of the trichothecene nucleus. On the other hand, it would be advantageous to condense the latter synthon, limited from natural sources, at the latest possible stage. Since we needed more material for the left-hand side portion of compound **1** for our model studies, we developed

[1]) 42nd Commun.: [1].

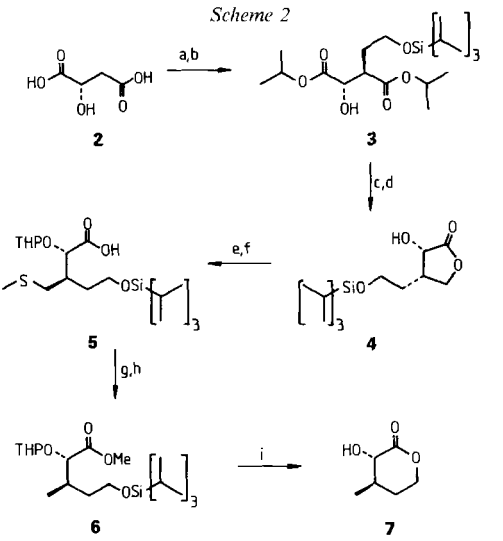
two new syntheses of verrucarinic acid *((2S,3R)-2,5-dihydroxy-3-methylpentanoic acid)*, suitably protected for the transformation to macrocyclic trichothecenes. They are presented in this communication[2]) [7a] [11].

Scheme 1



Scheme 1 shows the retrosynthetic analysis leading to the first synthesis. The key steps involve a diastereoselective alkylation of a (−)-(*S*)-malic acid ester and the regioselective reduction of one carboxyl function to a CH_3-group. *Scheme 2* summarizes the reaction sequence which was realized. (−)-(*S*)-Malic acid (**2**) was esterified with 2-propanol and then alkylated by a slightly modified procedure according to *Seebach & Wasmuth* [12] with 1-iodo-2-(triisopropylsilyloxy)ethane. The electrophile entered the molecule with 90% diastereoselectivity (^{1}H-, ^{13}C-NMR) yielding predominantly the desired isomer **3**. Careful akaline hydrolysis was highly regioselective by the anchimeric assistance of the free OH-group [13]. Reduction of the resulting half-ester led directly to the 5-membered lactone **4**, which was protected by forming the THP(tetrahydropyranyl)-ether. Alkyl-*O*-fission proceeded smoothly with NaSMe in HMPA to yield the

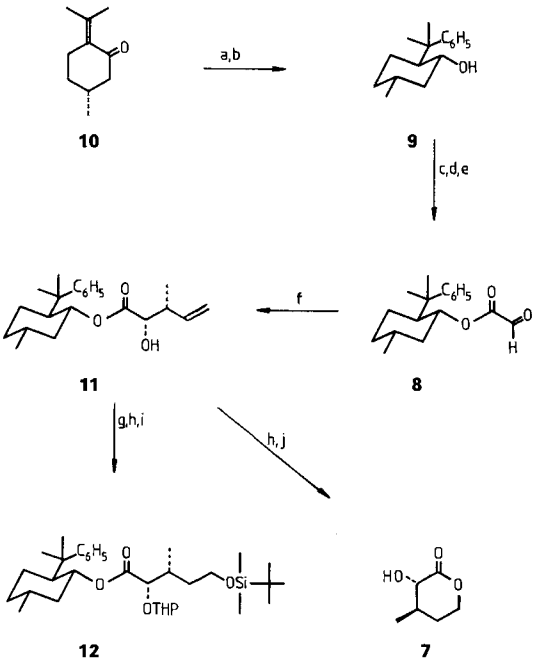
Scheme 2



a) i-PrOH, cat. $SOCl_2$, Δ; 70%. b) 2 equiv. Li-cyclohexylisopropylamide, THF/20% HMPA, −78°→−20°, 45 min; 1.1 equiv. 1-iodo-2-(triisopropylsilyloxy)ethane (prepared from 2-iodoethanol; 1.1 equiv. TIPS-Cl (triisopropylsilyl chloride), DMAP (4-(dimethylamino)pyridine), Et_3N, CH_2Cl_2 [14]; 80%) −78°→−50°, 34 h; 70%. c) 1 equiv. KOH, dioxane/H_2O, 0°; 93%. d) $LiEt_3BH$, THF, −40°→r.t. [15]; 60%; or $LiBH_4$, THF/Et_2O, Δ; [16]; 65%. e) DHP, PPTS (pyridinium *p*-toluenesulfonate), CH_2Cl_2; 90%. f) 1 equiv. NaSMe, HMPA, 2 h; 85%. g) CH_2N_2; 95%. h) Freshly prepared *Raney*-Ni *W2*, MeOH, Δ; 87%. i) TsOH, MeOH, Δ; 70%.

[2]) Prof. *W. Oppolzer*, Genève, has informed us on an independent synthesis of entiomerically pure verrucarino-lactone along similar lines.

Scheme 3



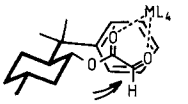
a) Ph_2CuLi, Et_2O, −20°, **10** added drop by drop→r.t., 48 h; 23%. b) 6 equiv. Na, toluene/i-PrOH, Δ, 1 h; 48%. c) $BrCH_2COOH$, DCC, DMAP, CH_2Cl_2, r.t., 14 h; 77%. d) $AgNO_3$, MeCN, 40°, 14 h; 95%. e) NaOAc, DMSO, 35°, 3 h, bulb-to-bulb dist. (0.01 Torr, 200° oven temp.); 73%. f) (*E*)−$CH_3CH{=}CHCH_2Si(CH_3)_3$/$BF_3 \cdot Et_2O$, CH_2Cl_2, −78°, 8 h; 63% (ratio 80:10.5:7.5:2). g) DHP, PPTS, CH_2Cl_2, r.t., 14 h; 98%. h) Borane dimethylsulfide, THF, r.t., 3 h; H_2O_2, NaOH, r.t., 1 h; 71%. i) TBDMS-Cl ((*tert*-butyl)dimethylsilyl chloride), imidazole, DMF, r.t., 14 h; 74%. j) TsOH, Et_2O, r.t., 14 h; 90% (crude yield).

carboxylic acid **5**. The reaction was followed by the disappearance of the C=O band of the lactone in the IR spectrum. We prefer this method using the commercially available NaSMe to the procedures using LiSMe [17] and NaC_6H_5Se [18]. After esterification with CH_2N_2 the synthesis was finally completed by desulfuration with *Raney*-Ni [19] yielding the protected verrucarinic acid methyl ester **6**. Conversion to verrucarinolactone **7** was achieved by treatment with TsOH in MeOH. The data of the crystalline product (m.p. 100–102°, $[\alpha]_D^{r.t.} = -10.0$ ($c = 1.1$; $CHCl_3$)), were in agreement with those of an authentic sample.

The second synthesis involved a stereoselective addition of an allylsilane to a chiral glyoxylate. This concept which is similar to that of *Yamamoto et al.* [11f] [11g] is based on *Hayashis* observation that [(*E*)-2-butenyl]trimethylsilane shows excellent *erythro*-selectivity in the reaction with aldehydes in the presence of $TiCl_4$ [20]. This selectivity was found as good as in the [(*E*)-2-butenyl]stannane/$BF_3 \cdot Et_2O$ system. To test this approach, we prepared the glyoxylate **8** according to known procedure *(Scheme 3)*. As a chiral directing group, we chose 8-phenylmenthol (**9**), which has already been successfully used by *Corey & Ensley* [21], *Oppolzer et al.* [22], *Whitesell et al.* [23] and *Yamamoto et al.* [11f] [11g]. It is accessible from (+)-(*R*)-pulegone (**10**) in two steps.

Esterification with bromoacetic acid according to *Neises & Steglich* [24] followed by a *Kornblum* oxidation [25] yielded the key intermediate **8**. Since this aldehyde was readily hydrated, it had to be purified by bulb-to-bulb distillation. However, when **8** was treated with [(*E*)-2-butenyl]trimethylsilane and $TiCl_4$ as catalyst [20], we isolated a rather complex mixture. The two major products were obtained in a 2:1 ratio (GC, ^{1}H-NMR), the minor isomer thereof being the desired one. Fortunately, exchanging the catalyst by $BF_3 \cdot Et_2O$ dramatically influenced the steric course of the reaction. The *erythro*-alcohol **11** was the predominant product, the ratio of isomers being found to be 80:10.5:7.5:2 (GC) (total yield 63%). For comparison, the reaction mixture was converted to crystalline verrucarinolactone **7** (m.p. 100–102°, $[\alpha]_D^{r.t.} = -9.6°$ ($c = 0.78$, $CHCl_3$)). The value of the optical rotation indicated an e.e. of 95%. For the purposes of our synthesis the final conversion to the doubly protected verrucarinic acid ester **12** was performed using standard procedures.

Obviously the proper choice of the *Lewis*-acid catalyst seems to be crucial. We were rather surprised by the failure of the $TiCl_4$-mediated reaction. *Reetz et al.* have recently shown that α- and β-alkoxy-aldehydes undergo chelation-controlled addition reactions with $TiCl_4$/allylsilanes with high 1,2- and 1,3-induction [26]. We therefore had anticipated that the glyoxylate **8** would be forced by complexation into *syn*-geometry (**13**).



13

Thus, the attack of the allylsilane would occur from the *si*-face, the *re*-face being blocked by the phenyl group. On the other hand, the effect of $BF_3 \cdot Et_2O$ was also unexpected but always in a desired direction. Boron, without the involvement of d-orbitals, would not be likely to undergo chelation, unless a F-atom is displaced by another ligand [27]. However, the 'chelation-controlled' product **11** dominated in agreement with the observation of *Reetz et al.* [27] and *Yamamoto et al.* [11f] [11g] [28].

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REFERENCES

[1] *N. Jeker, P. Mohr & Ch. Tamm,* Tetrahedron Lett., in press.

[2] a) *J.R. Bamburg & F.M. Strong,* in 'Microbial Toxins', eds. S. Kadis, A. Ciegler and C.J. Ajl, Vol. 7, Academic Press, New York, 1971, p. 207; b) *Ch. Tamm,* Fortschr. Chem. Org. Naturst. *31,* 63 (1974); c) *J.R. Bamburg,* in 'Mycotoxins and other Fungal Related Food Problems', ed. J.V. Rodricks, American Chemical Society, Washington D.C., 1976, Adv. Chem. Ser. No. 149, p. 144; d) *T.W. Doyle & W.T. Bradner,* in 'Anticancer Agents Based on Natural Product Models', eds. J.M. Cassidy and D. Douros, Academic Press, New York, 1980, p. 43; e) *B.B. Jarvis & E.P. Mazzola,* Acc. Chem. Res. *15,* 388 (1982); f) *C.W. Ong,* Heterocycles *19,* 1685 (1982).

[3] a) *B.B. Jarvis, J.O. Midiwo, G.P. Stahly, G. Pavanasasivam & E.P. Mazzola,* Tetrahedron Lett. *21,* 787 (1980); b) *B.B. Jarvis, V.M. Vrudhula & J.O. Midiwo,* J. Org. Chem. *48,* 2576 (1983).

[4] a) *R.H. Schlessinger & R.A. Nugent,* J. Am. Chem. Soc. *104,* 1116 (1982); b) *W.R. Roush & T.E. D'Ambra,* J. Am. Chem. Soc. *105,* 1058 (1983); c) *B.M. Trost, P.G. McDougal & K.J. Haller,* J. Am. Chem. Soc. *106,* 383 (1984).

[5] *D. W. Brooks, P. G. Grothaus & H. Mazdiyasni*, J. Am. Chem. Soc. *105*, 4472 (1983).
[6] *G. A. Kraus, B. Roth, K. Frazier & M. Shimagaki*, J. Am. Chem. Soc. *104*, 1114 (1982).
[7] a) *W. C. Still & H. Ohmizu*, J. Org. Chem. *46*, 5242 (1981); b) *P. Mohr, M. Tori, P. Grossen, P. Herold & Ch. Tamm*, Helv. Chim. Acta *65*, 1412 (1982).
[8] a) *R. Esmond, B. Fraser-Reid & B. B. Jarvis*, J. Org. Chem. *47*, 3358 (1982); b) *W. R. Roush & T. A. Blizzard*, J. Org. Chem. *49*, 1772 (1984).
[9] *W. C. Still, C. Gennari, J. A. Noguez & D. A. Pearson*, J. Am. Chem. Soc. *106*, 260 (1984).
[10] *W. R. Roush & A. P. Spada*, Tetrahedron Lett. *24*, 3693 (1983).
[11] For other syntheses of verrucarinic acid see: a) *K. Tomioka, F. Sato & K. Koga*, Heterocycles *17*, 311 (1982); b) *W. R. Roush, T. A. Blizzard & F. Z. Basha*, Tetrahedron Lett. *23*, 2331 (1982); c) *B. M. Trost & P. G. McDougal*, Tetrahedron Lett. *23*, 5497 (1982); d) *P. Herold, P. Mohr & Ch. Tamm*, Helv. Chim. Acta *66*, 744 (1983); e) *S. D. Burke, W. F. Fobare & G. J. Pacofsky*, J. Org. Chem. *48*, 5221 (1983); f) *Y. Yamamoto, N. Maeda & K. Maruyama*, J. Chem. Soc., Chem. Commun. *1983*, 774; g) *Y. Yamamoto, H. Yatagai, Y. Ishihara, N. Maeda & K. Maruyama*, Tetrahedron *40*, 2239 (1984).
[12] *D. Seebach & D. Wasmuth*, Helv. Chim. Acta *63*, 197 (1980).
[13] *J. S. Bajwa & M. J. Miller*, J. Org. Chem. *48*, 1114 (1983).
[14] *R. F. Cunico & L. Bedell*, J. Org. Chem. *45*, 4797 (1980).
[15] a) *H. C. Brown, S. C. Kim & S. Krishnamurthy*, J. Org. Chem. *45*, 1 (1980); b) *D. Wasmuth, D. Arigoni & D. Seebach*, Helv. Chim. Acta *65*, 344 (1982).
[16] *H. C. Brown, S. Narasimhan & Y. M. Choi*, J. Org. Chem. *47*, 4702 (1982).
[17] *T. Ross Kelly, H. M. Dali & W.-G. Tsang*, Tetrahedron Lett. *18*, 3859 (1977).
[18] *D. Liotta, U. Sunay, H. Santiesteban & W. Markiewicz*, J. Org. Chem. *46*, 2605 (1981).
[19] *R. Mozingo, D. E. Wolf, S. A. Harris & K. Folkers*, J. Am. Chem. Soc. *65*, 1013 (1943).
[20] *T. Hayashi, K. Kabata, I. Hamachi & M. Kumada*, Tetrahedron Lett. *24*, 2865 (1983).
[21] *E. J. Corey & H. E. Ensley*, J. Am. Chem. Soc. *97*, 6908 (1975).
[22] a) *W. Oppolzer, M. Kurth, D. Reichlin, Ch. Chapuis, M. Mohnhaupt & F. Moffatt*, Helv. Chim. Acta *64*, 2802 (1981); b) *W. Oppolzer & H. J. Löher*, ibid. *64*, 2808 (1981).
[23] a) *J. K. Whitesell, A. Bhattacharya & K. Henke*, J. Chem. Soc., Chem. Commun. *1982*, 988; b) *J. K. Whitesell, A. Bhattacharya, D. A. Aguilar & K. Henke*, ibid. *1982*, 989; c) *J. K. Whitesell, D. Deyo & A. Bhattacharya*, ibid. *1983*, 802.
[24] *B. Neises & W. Steglich*, Angew. Chem. *90*, 556 (1978).
[25] *N. Kornblum & H. W. Frazier*, J. Am. Chem. Soc. *88*, 865 (1966).
[26] a) *M. T. Reetz & A. Jung*, J. Am. Chem. Soc. *105*, 4833 (1983); b) *M. T. Reetz, K. Kesseler, S. Schmidtberger, B. Wenderoth & R. Steinbach*, Angew. Chem. *95*, 1007 (1983); *M. T. Reetz*, Angew. Chem. *96*, 542 (1984).
[27] *M. T. Reetz, K. Kesseler & A. Jung*, Tetrahedron Lett. *25*, 729 (1984).
[28] *K. Maruyama, Y. Ishikara & Y. Yamamoto*, Tetrahedron Lett. *22*, 4235 (1981).