Tetrahedron Vol 45, No 8, pp 2385 to 2415, 1989
Printed in Great Britain

0040-4020/89 $3 00 + 00
Pergamon Press plc

SYNTHESIS OF MACROCYCLIC TRICHOTHECENE MYCOTOXINS

Christoph Tamm* and Nicolas Jeker

Institut für Organische Chemie
der Universität, St.Johanns-Ring 19
CH-4056 Basel, Switzerland

(*Received in South Africa* 20 *June* 1988)

Abstract

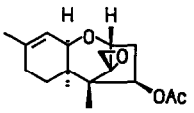
In the first part synthetic approaches and total syntheses of the trichothecenes are summarized. Special attention is paid to not naturally occurring derivatives of the sesquiterpenoids. In the second part the syntheses of macrocyclic trichothecenes are reviewed, with special reference to the preparation of the macrolidic building blocks, protecting groups and methods of macrolactonization. The preparation of several new unnatural macrocyclic analogues is reported. Finally the biological activity of the simple and macrocyclic trichothecenes are briefly discussed

1. Introduction

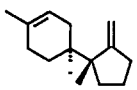
The trichothecenes belong to a class of sesquiterpenoid secondary metabolites produced by moulds, especially various species of Fungi imperfecti (Fusarium, Stachybotrys, Trichothecium, Myrothecium, Cephalosporium etc.). Many members of the family display a wide range of biological properties such as antibacterial, antifungal and cytostatic activities [1-5]. Moreover, their general toxicity is very high Therefore they can be responsible for alimentary toxic aleukia, vomiting, skin inflammation, weight loss and death in humans and agricultural animals. The trichothecenes can be divided into three groups according to their chemical structure. (1) the simple sesquiterpenes being either alcohols or simple esters, (2) the trichoverroids, which are esters with one or two more complex C_6- or C_8-carboxylic acids, and (3) the macrocyclic di- and triesters. A considerable number of studies on the structure-activity relationship have established the requirement of certain structure elements of the trichothecane moiety. However less is known about the structural requirements of the macrolidic part of the cyclic esters. Owing to their extraordinary biological properties, the trichothecenes have been the target of many synthetic efforts [6,7]. It is the goal of this article to briefly summarize the earlier highlights and to present the recent developments in this area

2. Total Synthesis of Simple Trichothecenes

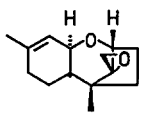
The first synthesis of a natural trichothecene, trichodermin (1), was reported by Colvin et al.[8] in 1973. Since then, numerous studies on the synthesis of either natural trichothecenes or model compounds have been published. The construction of the trichothecene skeleton made use of either the aldol or the biomimetic approach, according to the categorization of McDougal & Schmuff[7] (Scheme 1). Whereas in the aldol approach, the final ring closure takes place between C(2) and C(3) or a correspondingly functionalized A/B-synthon (path A and B), the biomimetic approach uses trichodiene (2) as a key intermediate (path C and D).



1

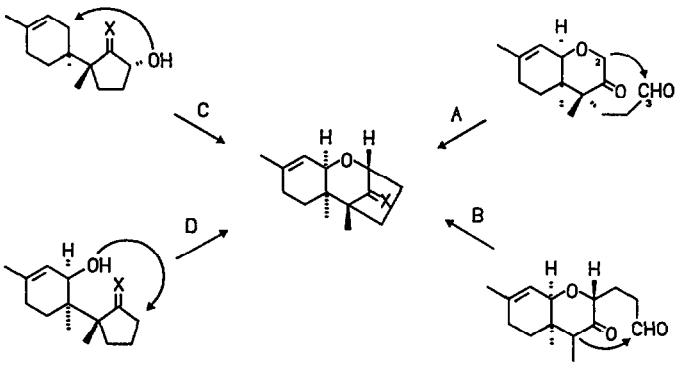


2

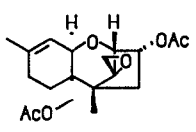


3

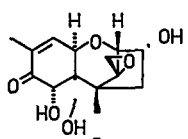
Scheme 1



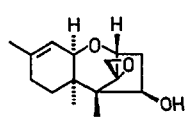
The subsequent syntheses of 12,13-epoxytrichothec-9-ene (3)[9], calonectrin (4)[10], an optically active synthon for 4[11], building blocks for rings A and B[12], and an approach to deoxynivalenol (5)[13] were based on the aldol scheme
However a much higher number of syntheses were required for the biomimetic approach which made use of a modified trichodiene (2) structure as an intermediate The first example was 12,13-epoxytrichothec-9-ene (3)[14]. Four years later a synthesis



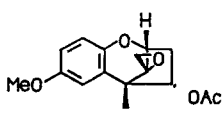
4



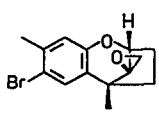
5



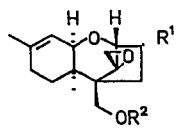
6



7



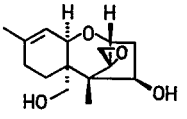
8



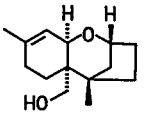
9 R^1=H, R^2=Me

10 R^1=OH, R^2=H

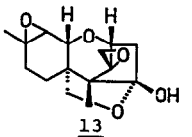
of trichodermol (6) was completed by Still & Tsai[15]. Noteworthy are the model compounds 7 and 8, in which ring A is aromatic[16,17]. In the naturally occuring trichothecenes the 14-methyl group is not functionalized, however, the 14-methoxytrichothecene 9[18] and the 3,14-dihydroxy derivative 10[19] were prepared by Pearson et al. So far three syntheses of verrucarol (11), which is the sesquiterpenoid moiety of the majority of the trichoverroids and the macrocyclic trichothecene derivatives, are known. The first approach leading to the model compound 12 was undertaken by Roush and D'Ambra[20] in 1980. Three years later the same authors[21] completed a synthesis of (+)-verrucarol (11). Optically active verrucarol (11) was synthesized by Schlessinger and Nugent[22]. The third synthesis was accomplished by Trost and McDougal[23]. The same authors also prepared the 11-epi-derivative 13. A trichodiene derivative served as an intermediate for the synthesis of anguidine (14)[24]. An approach for the synthesis of sambucinol (15)[25], a metabolite possesing a modified



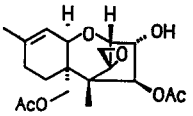
11



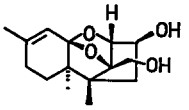
12



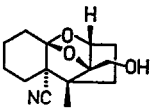
13



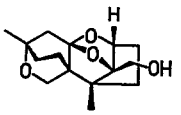
14



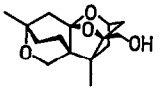
15



16



17

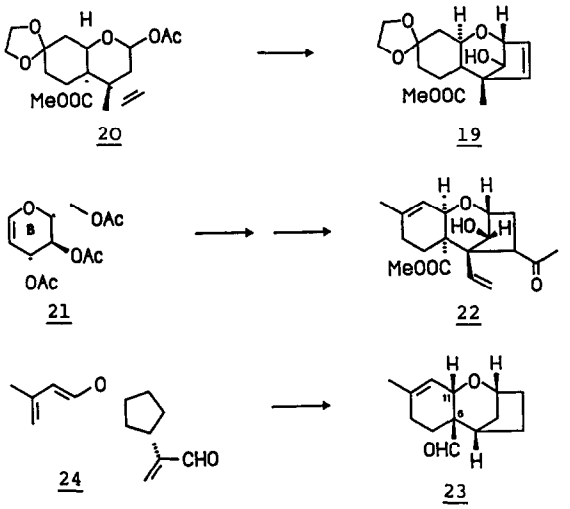


18

trichothecene skeleton but biosynthetically derived from trichodiene (2), led to the 1,3-dioxolane derivative 16. Originally sporol (18) was assigned to structure 17[26]; however the synthesis of 17 proved it to be neosporol, which has not been isolated from a natural source[27,28].

The following syntheses were designed on the basis of neither the aldol nor the biomimetic concept. White et al.[29] constructed the tricyclic compound 19 by making use of a "cationic ring expansion" of the cyclobutene 20. Fraser-Reid and Tsang[30] converted the triacetate 21, which was obtained from D-glucose, into the trichothecene 22. The 6,11-di-epi-trichothecene skeleton 23 was the result of an intramolecular Diels-Alder reaction of the triene 24[31].

Scheme 2



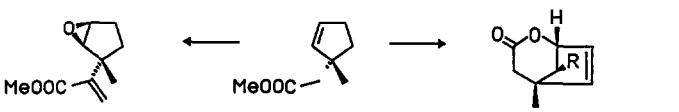
20 19 21 22 24 23

The ketone 25 was synthesized as a C-ring fragment by Hua & Venkataraman[32]. Starting from tri-O-acetyl-D-glucal (21) Fétizon et al.[33] carried out a chiral synthesis of the B/C-fragment 26. The bicyclic compound 27 which is similar to 26

25 26 R = OCHO

resulted from the conversion of the cyclopentene derivative 28 by a series of reactions[34]. However the authors failed to attach a methylene group adjacent to

Scheme 3



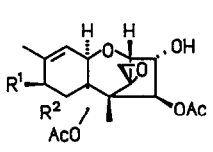
29 28 27 R = OTBDMS

the δ-lactone function. It therefore was introduced at an earlier stage of the synthesis. It ended with the preparation of intermediate 29 (Scheme 3).

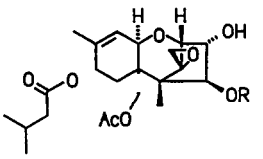
3. Conversions of Simple Trichothecenes

In order to prepare larger quantities of rare metabolites or of unnatural trichothecenes numerous transformations of naturally occurring major metabolites were carried out. Anguidine (14) proved to be very convenient because it can be isolated readily from cultures of various Fusarium species. The pronounced cytostatic activity of the metabolite was an additional important factor for its use.

Besides the preparation of standard derivatives mainly by acylation and deacylation[35,36,37] oxygenations and deoxygenations represent the main reactions leading to modified structures. Hydroxylation of anguidine (14) at C(8) with SeO_2 led to the 8β-hydroxy derivative 30. It was epimerized to neosolaniol (31) via the 8-ketone[36]. Later neosolaniol monoacetate (32) and the epimer 33 were prepared via the bromides 34 and 35 respectively[38]. T-2-toxin (36) and HT-2-toxin (37) were also prepared[39]. The Mitsunobu methodology[40] proved to be most useful for the in-



30 R^1 = OH, R^2 = H
31 R^1 = H, R^2 = OH
32 R^1 = H, R^2 = OAc
33 R^1 = OAc, R^2 = H
34 R^1 = Br, R^2 = H
35 R^1 = H, R^2 = Br

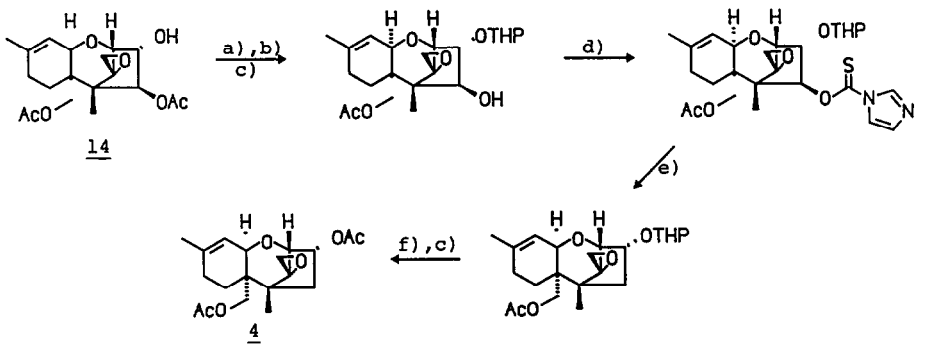


36 R = Ac
37 R = H

version of configuration of the 8-hydroxy group. Oxidation of calonectrin (4) at C(7) and C(8) yielded deoxynivalenol (5)[41].

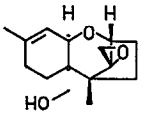
For the deoxygenation of hydroxyl groups Barton's method[42], which proceeds by the homolytic C-O-cleavage of thioesters, or the modification according to Robins & Wilson[43], were applied successfully for the conversion of anguidine (14) into verrucarol (11) and trichodermol (6)[44,45]. More recently Tamm et al.[46] transformed anguidine (14) into calonectrin (4) in this way as outlined in Scheme 4

Scheme 4

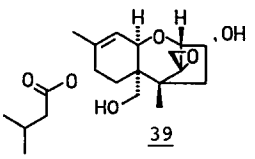


a) DHP, PPTS b) NaOH, MeOH c) Ac_2O, py d) 1,1-thiocarbonyldiimidazole
e) Bu_3SnH f) PPTS, MeOH
DHP = dihydropyrane PPTS = pyridinum-p-toluolsulfonate

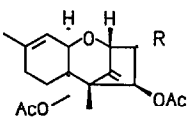
The same conversion was achieved via base catalyzed regiospecific elimination of a 3,4-dimesyloxy derivative[41]. Deoxygenations by Robins procedure of verrucarol (11)[47] and T-2-toxin (36)[48] yielded 4-deoxyverrucarol (38) and anguidine (14) respectively. Anguidine (14) again served as starting material for the partial synthesis of sporotrichiol (39) by subsequent removal of the 4-acetoxy group and allylic oxidation of C(8)[39].



38



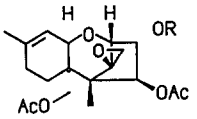
39



40 R = H

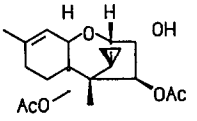
41 R = OH

The replacement of the 12,13-spiroepoxide by an exocyclic vinyl group was reported for the first time in 1964 by Tamm et al.[49]. The key reaction was the reduction of the epoxide with $LiAlH_4$. The tertiary alcohol obtained from the diacetate of verrucarol (11) was acetylated and subjected to a thermal elimination reaction yielding 4,15-di-O-acetyl-12,13-deoxyverrucarol (40). Removal of the epoxide was also possible by subsequent treatment with thiophenolate, oxidation of the sulfide formed to the sulfone and reduction of the latter by sodium amalgam as demonstrated by the conversion of anguidine (14) into 12,13-deoxyanguidine (41)[50] Efficient deoxygenation of the 12,13-epoxy group was also achieved by using WCl_6-BuLi[51] as demonstrated by Colvin & Cameron[52]. The authors used the same method for the synthesis of the 12,13-epi-trichothecene 42[53]. The exocyclic vinyl group obtained by deoxygenation was converted to the 12-ketone. Treatment of the latter with dimethylsulfonium methylide yielded the desired 12,13-epi-epoxide. 12,13-epi-anguidine (43) and 12,13-deoxy-12,13-methanoanguidine (44) were also synthesized[54].



42 R = Ac

43 R = H



44

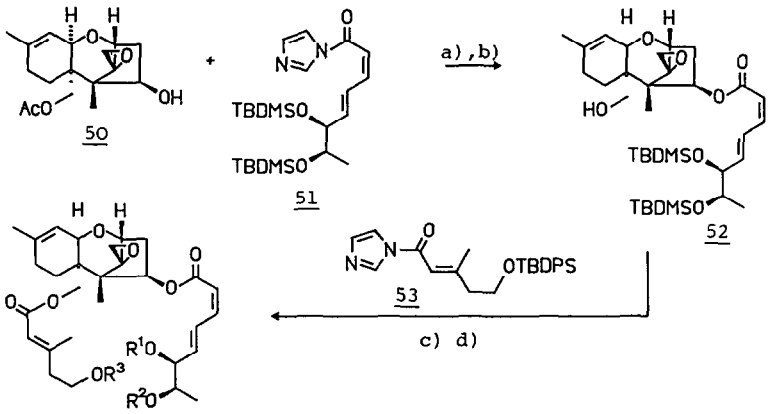
4 Synthesis of Trichoverroids

In the trichoverroids verrucarol (11) is esterified with one or two more complex carboxylic acids They also function as building blocks of the macrolidic moiety of the macrocyclic trichothecenes. It is therefore very likely that the trichoverroids are the biogenetic precursors of the macrolides[55] The first synthesis of the epimeric esters 45 and 46 was reported by Tulshian & Fraser-Reid[56] in 1981 They used the chiral cyclic enol ethers 47 and 48 as starting material They were obtained from D-glucose and D-galactose respectively A synthesis which

47 45 48 46

leads to all four possible diastereoisomers was designed by Roush and Spada[57] For the synthesis of trichoverrin B (49)[45], 15-O-acetyl-verrucarol (50) was condensed with the imidazole 51 to yield the monoester 52 after the acetyl group had been removed by selective hydrolysis. Subsequent condensation with the imidazole 53 gave the diester 54 in a relatively low yield. Cleavage of the silyl groups led to trichoverrin B (49) (Scheme 5).

Scheme 5



50 51 52 53

54 R^1,R^2 = TBDMS, R^3 = TBDPS

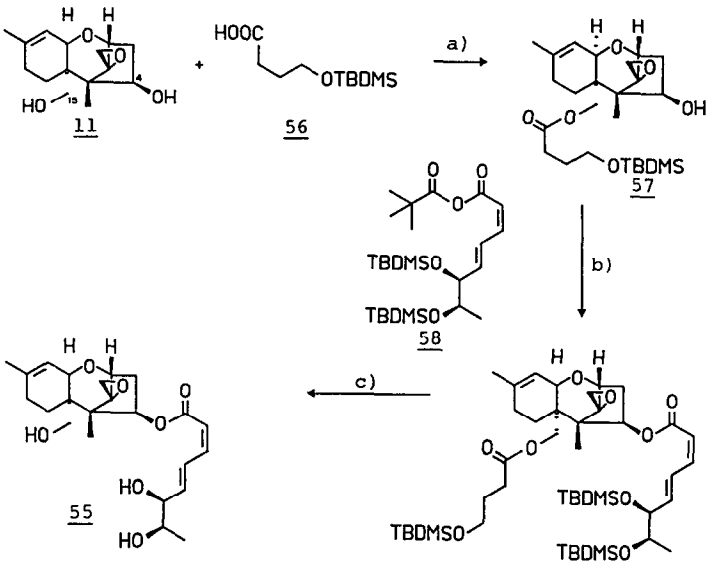
49 R^1,R^2,R^3 = H

a) NaH,HMPA b) NaOH c) NaH, Bu_4NI d) Bu_4NF

TBDMS = tert. butyldimethylsilyl TBDPS = tert. butyldiphenylsilyl

Trichoverrol B (55) is the second member of the trichoverroid family which was synthesized[58] Selective protection of the 15-hydroxy group of verrucarol (11) was achieved by the reaction with the acid 56 yielding the monoester 57 Condensation of the latter with the mixed anhydride 58, removal of the protecting silyl groups and partial hydrolysis of the 15-O-acyl group yielded trichoverrol B (55) (Scheme 6).

Scheme 6



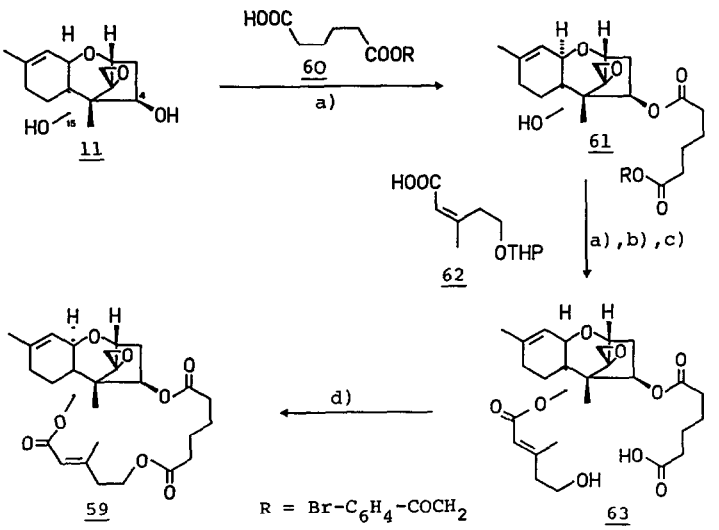
a) DCC,DMAP b) NaH c) Bu_4NF
DCC = dicyclohexylcarbodiimide
DMAP = 4-dimethylaminopyridine

5. Synthesis of Macrocyclic Trichothecenes

5 1 Model Compounds

Synthetic work was initiated by Tamm et al.[59,60] in 1978, who synthesized tetrahydroverrucarin J (59), which contains adipic acid in place of Z,E-muconic acid as a building block. The synthesis of this model compound was carried out in order to establish the conditions for the regioselective acylation of the hydroxyl groups of verrucarol (11) and the macrolactonization. The methods are limited because of the sensitivity of the spiroexpoxy group. Selective condensation of 11 with the phenacylmonoester 60 of adipic acid led to the 4-O-acyl derivative 61 Subsequent reaction of the 15-hydroxy group with the acid 62 and removal of the protecting groups gave the seco-acid 63 which was cyclized to tetrahydroverrucarin J (59) using the Corey-Nicolaou[61] method (Scheme 7).

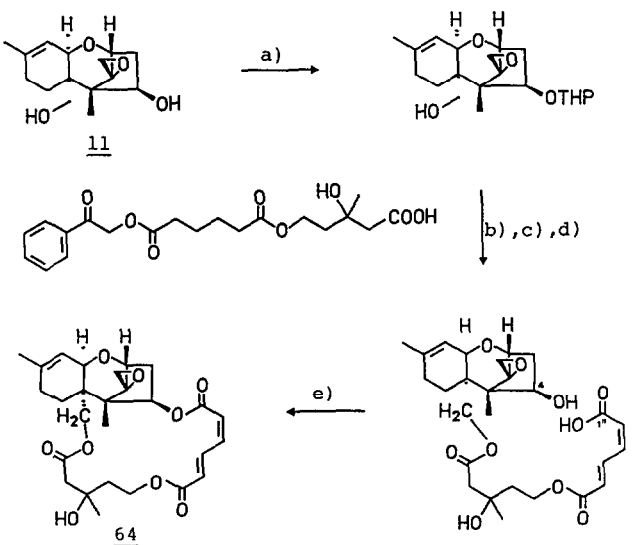
Scheme 7



a) CDI, DBN b) HOAc c) Zn, HOAc d) DPDS, Ph_3P
CDI = N,N-carbonyldiimidazole DBN = 1,5-diaza-bicyclo[4 3 0]non-5-ene DPDS = dipyridyldisulfid

In contrast to this approach, the cyclization was performed between the 4-hydroxy group and the 1"-carboxy group in the synthesis of 3'-hydroxy-2'-deoxy-2",3",4",5"-tetrahydro-verrucarin A (64)[60] as outlined in Scheme 8. The yields of the final cyclization reaction were 45-50% in both cases.

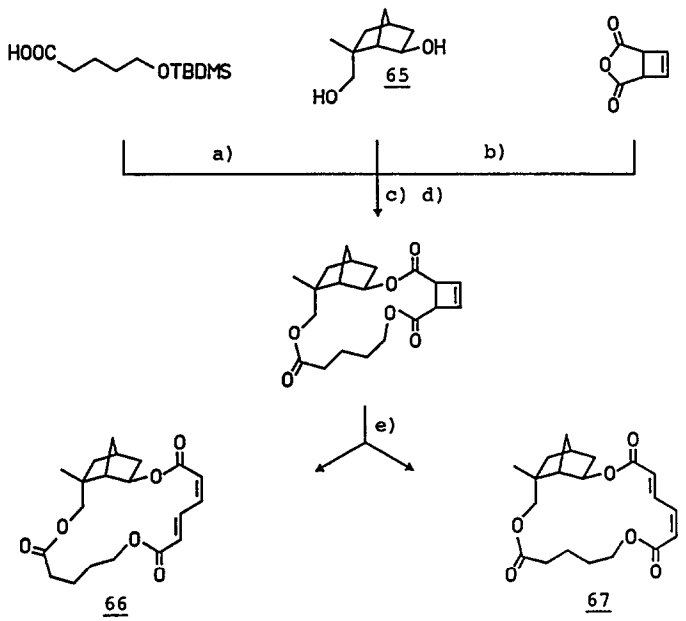
Scheme 8



a) DHP, PPTS b) CDI, DBN c) PPTS, MeOH
d) Zn, HOAc e) DPDS, Ph_3P

The first synthesis of a model compound containing the Z,E-conjugated diene system of the natural verrucarins was reported by Trost and McDougal[62]. They used the diol 65 in place of verrucarol (11). The diene system was generated by thermolysis of a cyclobutene. Both isomers 66 and 67 were formed in a ratio of 2:1 in favour of the desired product (Scheme 9).

Scheme 9



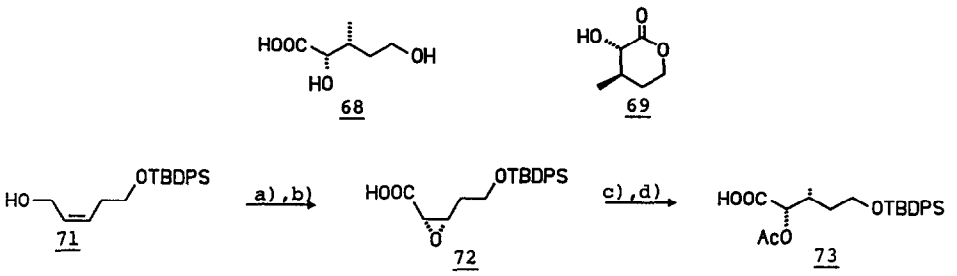
a) DCC, DMAP b) DMAP c) Bu_4NF d) DEAD, Ph_3P e) 106°C, toluene
DEAD = diethylazodicarboxylate

5.2. Verrucarin A

5.2.1. Verrucarinic Acid

Several syntheses of verrucarinic acid (68) and verrucarinolactone (69), which are building blocks of verrucarin A (70) are available. Sharpless epoxidation of the allylic alcohol 71 and subsequent treatment with pyridinium dichromate yielded the glycidic acid 72[63]. The optically active verrucarinic acid derivative 73 resulted from the regioselective opening of the epoxide (Scheme 10).

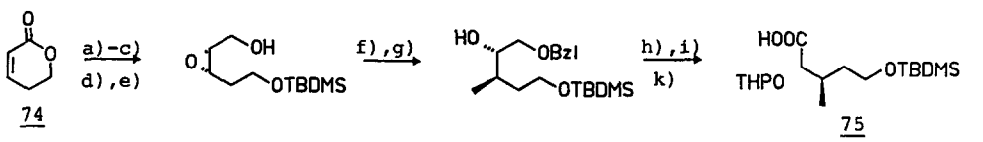
Scheme 10



a) $Ti(OiPr)_4$, DET, tBuOOH b) $RuCl_3$, $NaIO_4$ c) Me_3Al d) Ac_2O, py
DET = diethyl tartrate

A Sharpless epoxidation was also the key reaction in a synthesis reported by Tamm et al.[64]. Starting from the unsaturated δ-lactone 74, doubly protected verrucarinic acid 75 was obtained in good yield (Scheme 11).

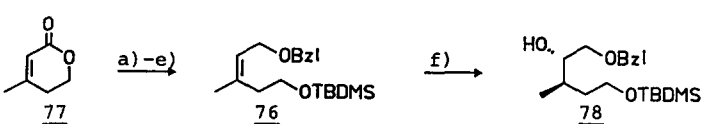
Scheme 11



a) KOH b) MeI c) TBDMSCl, Et_3N, d) DIBAH e) $Ti(OiPr)_4$, tBuOOH
f) BzlBr, NaH, Bu_4NI g) Me_3Al, BuLi h) DHP, PPTS i) H_2, Pd/C k) $RuCl_3$, $NaIO_4$
DIBAH = diisobutylaluminium hydride Bzl = benzyl

Asymmetric hydroboration was applied for the introduction of both centres of chirality as demonstrated by Tamm et al.[64] (Scheme 12). The protected allylic alcohol 76, which was prepared from the methylated unsaturated δ-lactone 77 was treated with optically active dilongifolylborane. Subsequent oxidation of the product obtained yielded the desired enantiomer 78 (Selectivity 50% ee).

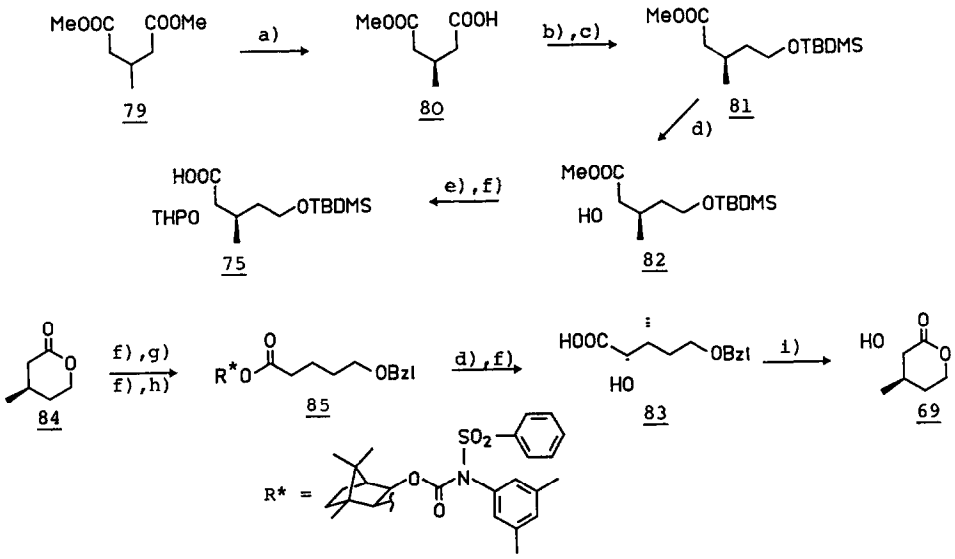
Scheme 12



a) KOH b) MeI c) TBDMSCl, Et_3N, DMAP d) DIBAH
e) BzlBr, NaH, Bu_4NI f) dilongifolylborane, NaOH, H_2O_2

Tamm et al [65] used dimethyl glutarate 79 as starting material in their third synthesis. The first centre of chirality was introduced by enantioselective hydrolysis with pig liver esterase. Reduction of the carboxyl group of the obtained monoester 80, and protection of the hydroxy group, gave the ester 81. The stereoselectivity of the asymmetric hydroxylation of 81 was rather modest. It yielded the hydroxy ester 82, which was converted to the desired building block 75 (Scheme 13).

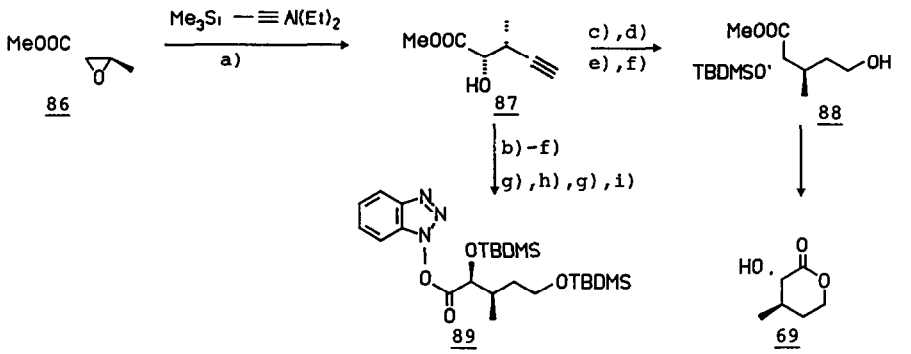
Scheme 13



a) PLE, NaOH b) $BH_3 \cdot S(Me)_2$ c) TBDMSCl, Et_3N, DMAP d) LDA, $MoO_5 \cdot py \cdot HMPT$
e) DHP, PPTS f) KOH g) BzlCl, NaH, Bu_4NI h) CDI, NaH, R*OH i) H_2,Pd, HOAc
PLE = pig liver esterase HMPT = hexamethylphosphorus triamide

By application of a newly developed hydroxylation method of ester enolates which allows high diastereoselectivity[66], Tamm et al.[67] obtained the hydroxy acid 83 starting from the lactone 84 via the intermediate 85. 83 was readily converted to verrucarinolactone (69). Independently Roush et al [68] and Trost & McDougal[69] prepared derivatives of verrucarinic acid by nearly the same sequence of reactions The epoxyester 86 was converted to the racemic key intermediate 87. Whereas Roush's synthesis ended with the racemic verrucarinic acid derivative 88, Trost & McDougal resolved the racemate 87 via the corresponding ester of (S)-mandelic acid leading to the optically active compound 89 (Scheme 14)

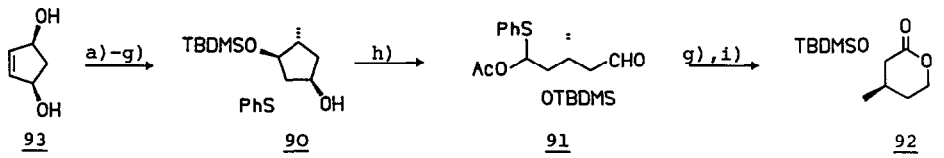
Scheme 14



a) NaOMe, MeOH b) (S)-O-methylmandelic acid, DCC, HBT, py c) H_2, Lindlar d) $BHSia_2$, MCPBA e) TBDMSCl, DMAP f) NaOMe, MeOH g) TBDMSCl, imidazole, DMF h) LiSMe, HMPT i) DCC, DMAP, HBT
HBT = N-hydroxybenzotriazole

In the second synthesis of Trost & McDougal[69], cleavage of the cyclic hydroxysulfide 90 with lead tetraacetate led to 91 It was readily converted to the desired product 92. The preparation of 90 from the cis-diol 93 required 7 steps (Scheme 15).

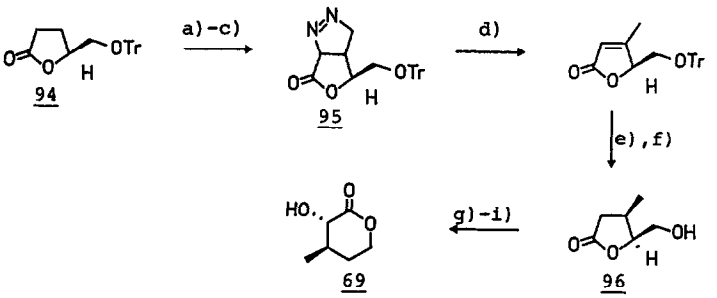
Scheme 15



a) PhCOCl, py b) $LiCuMe_2$ c) MCPBA d) BzCl, NaH e) Li thiophenoxide f) TBDMSCl, imidazole g) DIBAH h) $Pb(OAc)_4$ i) $CrO_3 \cdot 2py$
Bz = Benzoyl

The chiral γ-butyrolactone (94) served as starting material in a synthesis reported by Koga et al.[70]. The methyl group was introduced by pyrolysis of the pyrazoline derivative 95. Stereoselective hydrogenation generated the second centre of chirality, forming the saturated γ-lactone 96. The latter was converted to verrucarinolactone (69) in 3 steps (Scheme 16).

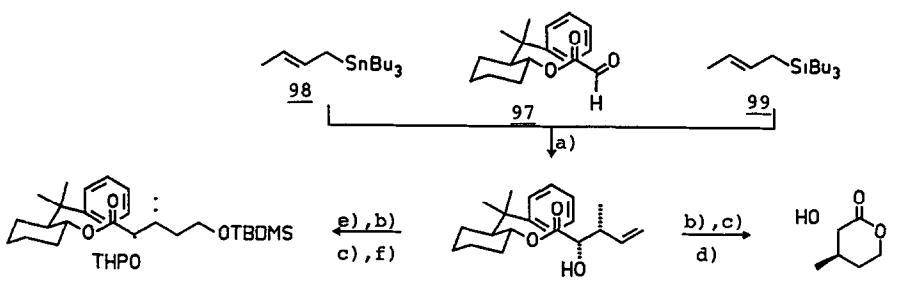
Scheme 16



a) LDA, PhSeBr b) $NaIO_4$, 18-crown-6 c) CH_2N_2 d) 100°, dioxane
e) PtO_2, H_2 f) HCl g) $K_2Cr_2O_7$, H_2SO_4 h) $LiBH_4$ i) HCl
Tr = trityl

The concept of reacting the glyoxylate 97, which contains a chiral directing group, with the allylstannane 98 or the allylsilane 99 was realized independently by Yamamoto et al.[71] and Tamm et al.[72] (Scheme 17).

Scheme 17

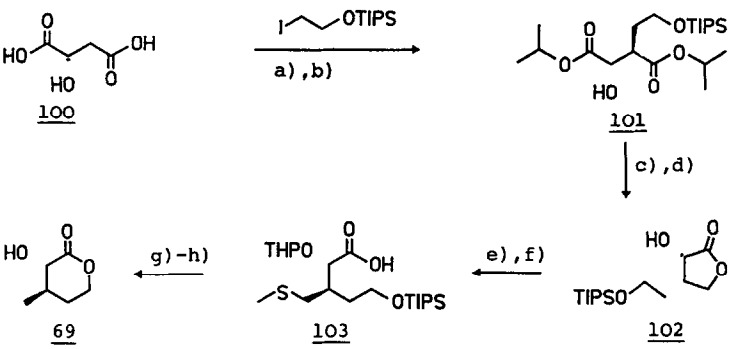


a) $BF_3 \cdot Et_2O$ b) $BH_3 \cdot S(Me)_2$ c) NaOH, H_2O_2 d) PTS f) TBDMSCl, imidazole
PTS = p-toluolsulfonic acid e) DHP, PPTS

In their fifth synthesis of verrucarinic acid Tamm et al.[72] made use of malic acid (100) as a chiral synthon and used a diastereoselective alkylation leading to the desired diastereoisomer 101 (Scheme 18). Regioselective ester hydrolysis followed by reduction of the half ester yielded lactone 102. O-alkyl cleavage gave the sulfide 103. It was readily converted to verrucarinolactone (69).

2-Hydro-3-methyl-carboxylic acids are also available by Claisen[73,74,75] and [2,3]-Wittig rearrangments[76,77] Similarly the unnatural enantiomer of verrucarinolactone (69) was also prepared.

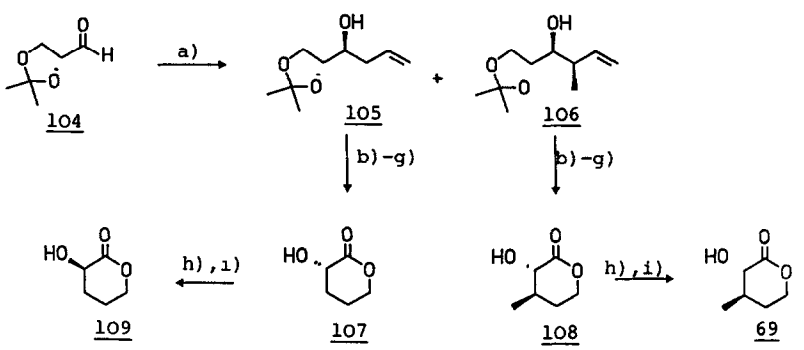
Scheme 18



a) iPrOH, cat $SOCl_2$ b) LDA, HMPT, TIPSCl, Et_3N, DMAP
c) KOH d) $LiBH_4$ e) DHP, PPTS f) NaSMe, HMPT g) CH_2N_2
h) Raney-Ni i) TSOH
TIPS = triisopropylsilyl

Finally, Mulzer & Salımi[78] reported very recently the stereocontrolled synthesis of all four stereoisomers of verrucarinolactone (69) (Scheme 19). Addition of crotylchromium (II) to (R)-2,3-O-isopropylidene glyceraldehyde (104) yielded both diastereoisomers 105 and 106. They were transformed to the lactones 107 and 108 respectively by standard reactions. Inversion of the hydroxyl group by the Mitsunobu method[40] gave the enantiomers 109 and 69.

Scheme 19

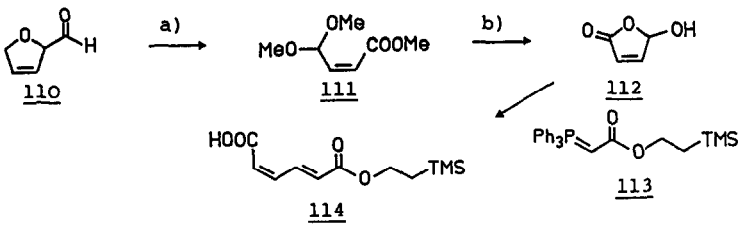


a) $CrCl_3$, $LiAlH_4$ $MeCHCHCH_2Br$ b) BzlBr, NaH c) 9-BBN, H_2O_2 d) TSOH e) $NaIO_4$ f) PCC g) H_2Pd/c h) DEAD, Ph_3P, C_6H_5COOH i) KOH
9-BBN = 9-borabicyclo[3.3.1]nonane

5.2.2. Muconic Acid

The second macrolidic fragment of the verrucarins Z,E-muconic acid and derivatives there of, were synthesized in three ways. The first synthesis reported by Still & Ohmizu[79] started from furfural (110). Electrochemical oxidation gave the ester acetal 111. It was converted to 112 which, by treatment with the ylide 113, yielded the silylprotected half ester of Z,E-muconic acid 114 (Scheme 20). The

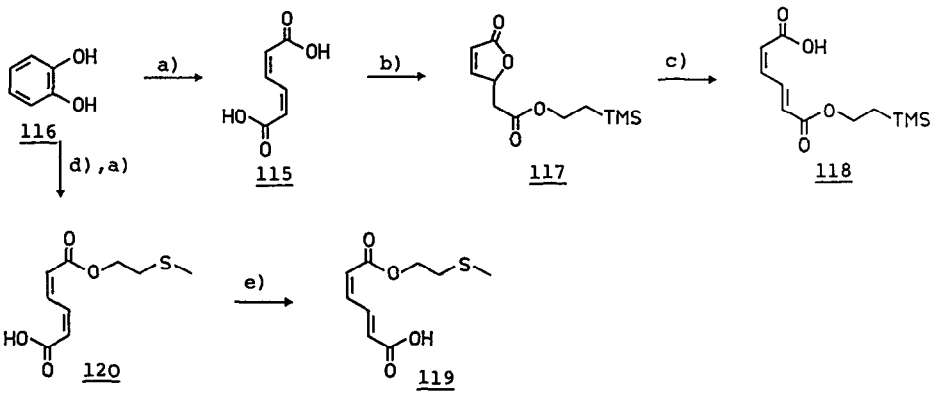
Scheme 20



a) Pt(1.5 amps), $EtNClO_4$, MeOH b) H_2SO_4

same compound was synthesized independently by Tamm et al.[65] from Z,Z-muconic acid (115), which results from oxidative cleavage of catechol (116). Condensation of 115 with trimethylsilylethanol resulted in the formation of the lactone 117. Treatment of the latter with Eschenmoser base induced β-elimination leading to the E-protected half ester 118. The Z-protected halfester 119 resulted from the isomerization of the halfester 120 (Scheme 21).

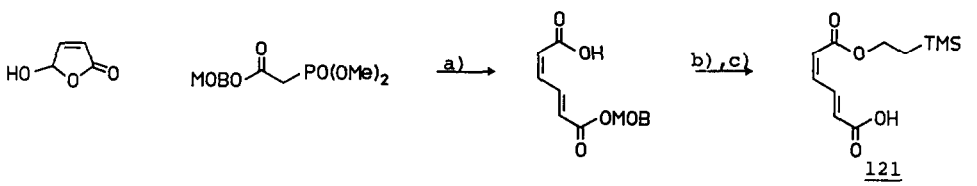
Scheme 21



a) $CuCl,O_2$ or $MeCO_3H$, $FeAc_3$ b) $Me_3SiCH_2CH_2OH$, DCC, DMAP c) Eschenmoser's base
d) $MeS(CH_2)_2OH$, py e) Δ, H_2O
Eschenmoser's base = 3,3,6,9,9-pentamethyl-2,10-diazabicyclo[4.4.0]-1-decene

The Z-protected halfester 121, was synthesized by Roush & Blizzard[80]. Trost & McDougal[62] prepared several monoprotected derivatives of Z/E-muconic acid using the cyclobutene thermolysis method.

Scheme 22

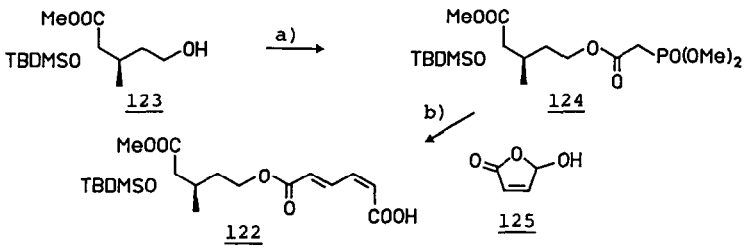


a) KOtBu b) $Me_3SiCH_2CH_2OH$, DEAD, Ph_3P c) HCOOH
MOB = p-methoxybenzyl

5 2.3. Verrucarin A

The complete macrolidic moiety 122 of verrucarin A (70) was constructed by Roush et al.[68] in 1982. The verrucarinic acid derivative 123 was transformed into the phosphonate 124. The Horner-Emmons reaction of 124 with the pseudocarboxylic acid 125 yielded the desired product 122 (Scheme 23).

Scheme 23

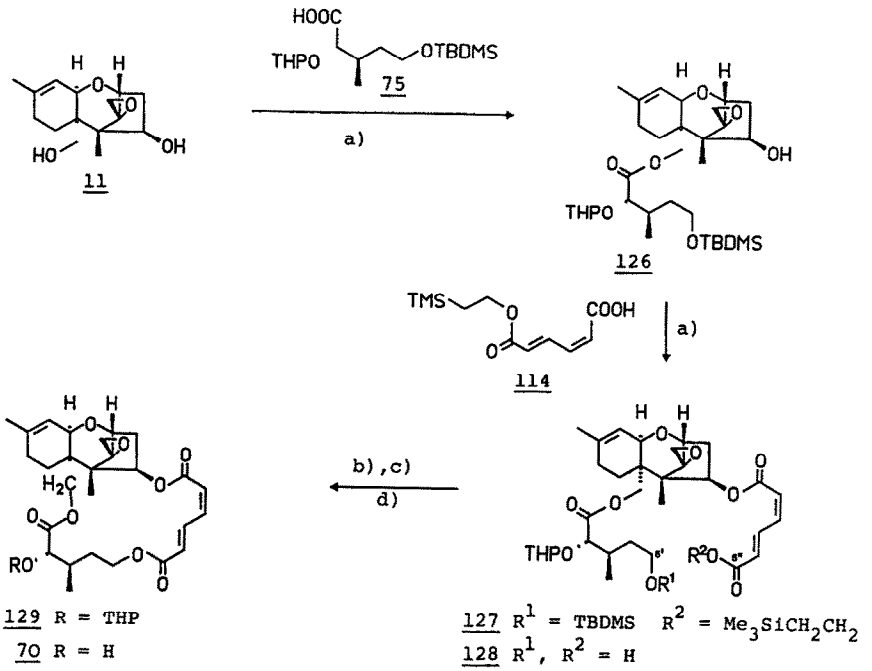


a) $CF_3CO_2COCH_2PO(OMe)_2$, py b) KOtBu, tBuOH

Verrucarin A (70) was the first natural macrocyclic trichothecene which was synthesized, almost simultaneously and independently by Still & Ohmizu[63] and Tamm et al.[65] using similar methods. In both syntheses the final macrolactonization was effected between the sterically least hindered 5'-hydroxy and the 6"-carboxy groups. In order to avoid unnecessary repetition only our synthesis is presented in detail (Scheme 24) Selective condensation of verrucarol (11) with the verrucarinic acid derivative 75 (Still & Ohmizu used the acetyl and the tert. butyldiphenylsilyl groups for protection) gave the monoester 126. Esterification with 114 led to the diester 127, which consisted of a 2:1 mixture of the Z,E- and E,E-isomers respectively Removal of the protection groups gave the seco-acid 128 which was cyclized using Yamaguchi's mixed anhydride method[81] (in Still's synthesis cyclization was effected applying the Mitsunobu procedure 82) to give tetrahydropyranyl verru-

carin A (128) underwent cyclization. The same observation was made by Still & Ohmizu (Scheme 24).

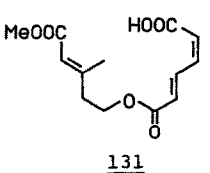
Scheme 24



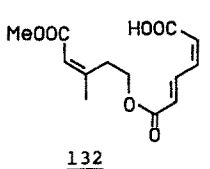
a) DCC, DMAP b) Bu_4NF c) TCBACl, Et_3N, DMAP d) PPTS, MeOH
TCBACl = 2,4,6-trichlorobenzoyl chloride

5.3. Verrucarin J

Derivatives of anhydromevalonic acid, which is a building block of verrucarin J (130) were made available[83,59,45], but not used for the synthesis of the metabolite Also syntheses of the complete macrolidic moiety, the dicarboxylic acid 131 as well as of the isomer 132 have been reported. Roush et al [68] prepared the diacid in the same way as they synthesized the corresponding building block of verrucarin A (70) A very similar procedure was used by White et al.[83] for the synthesis of 131 and 132



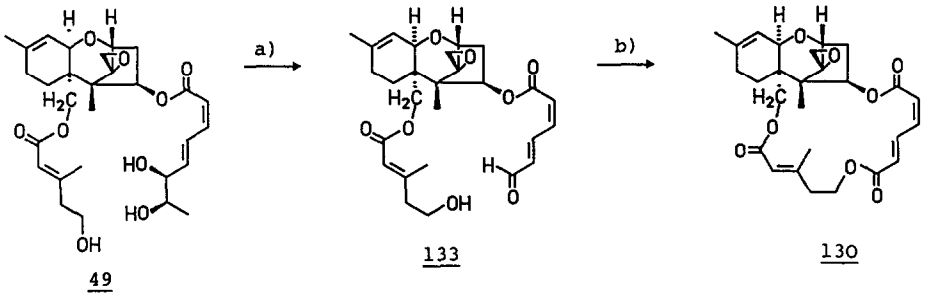
131



132

The synthesis of verrucarin J (130) was achieved successfully by two groups. Fraser-Reid et al.[45] followed an unconventional pathway by starting from trichoverrin B (49). Oxidation with periodate gave the aldehyde 133 which was cyclized via the semiacetal to 130 (Scheme 25).

Scheme 25



49 133 130

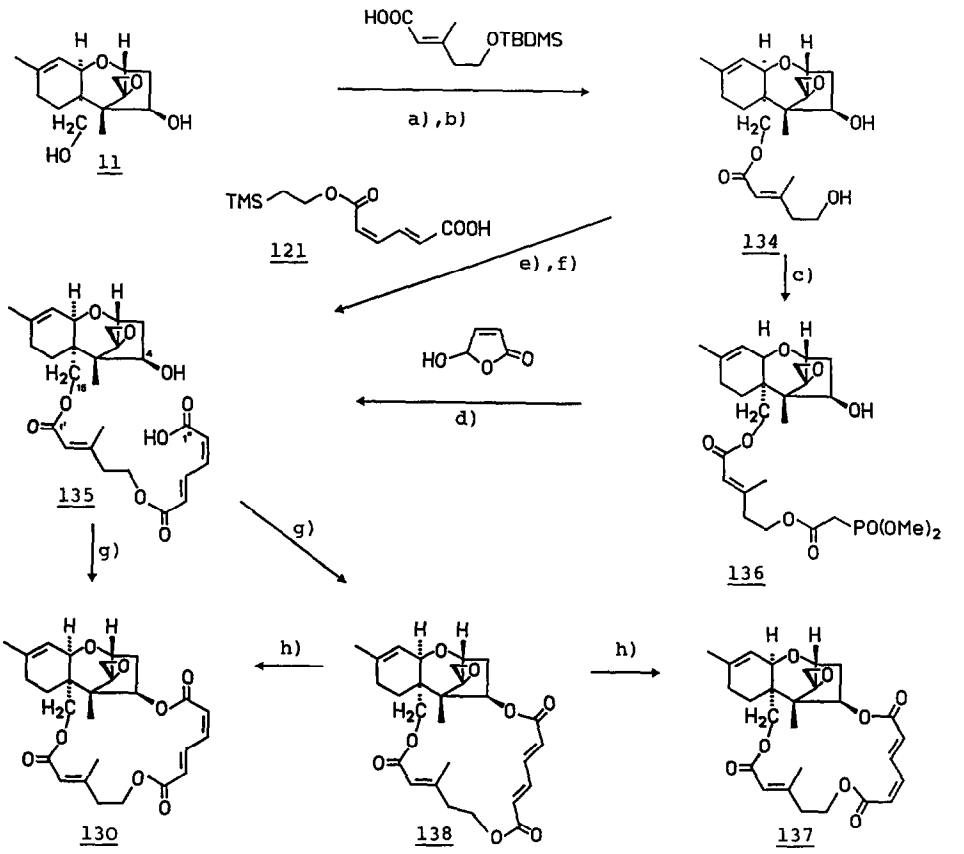
a) $NaIO_4$ b) PDC

In a first approach Roush & Blizzard[80] tried unsuccessfully to attach the ester 131 at the 4-hydroxy group of verrucarol (11) without isomerization. Therefore ring closure between the 15-hydroxy group and the 1'-carboxy group was not tried. However the second approach with the reversal of the site of the macrolactonization led to verrucarin J (130) as outlined in scheme 26
Verrucarol (11) was converted to the monoester 134. The next step consisted of a chain elongation to the seco-acid 135 either via the phosphonate 136 or by condensation of 134 with the acid 121. The latter reaction gave higher yield. For the cyclization of 135, the mixed anhydride with pivalic acid gave the best results. Surprisingly, also the unnatural E,E-isomer 137 was formed. However it was possible to convert the E,E-isomer into both Z,E-isomers 130 and 138 by treatment with iodine

5.4. Verrucarin B

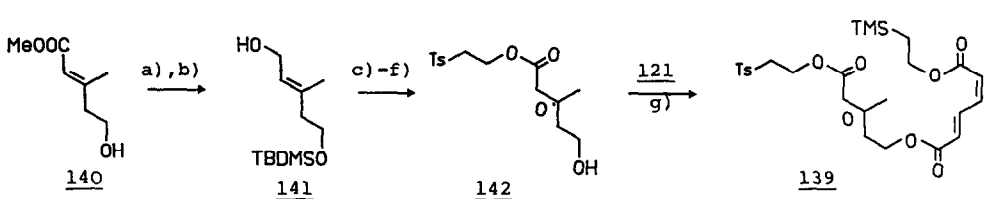
Roush & Blizzard[84] constructed the macrolidic building block 139 starting from the unsaturated ester 140 via the intermediates 141 and 142 (Scheme 27). However, 139 turned out to be too labile to survive selective condensation with the 15-hydroxy group of verrucarol (11). Therefore the same authors solved the problem of the regioselectivity by protecting the 4-hydroxy group of 11 as silylcarbonate

Scheme 26



a) DCC, DMAP b) HOAc c) $(MeO)_2POCH_2COOH$, DCC d) KOtBu
e) DEAD, Ph_3P f) KF g) Me_3CCOCl, Et_3N, DMAP h) I_2, benzene

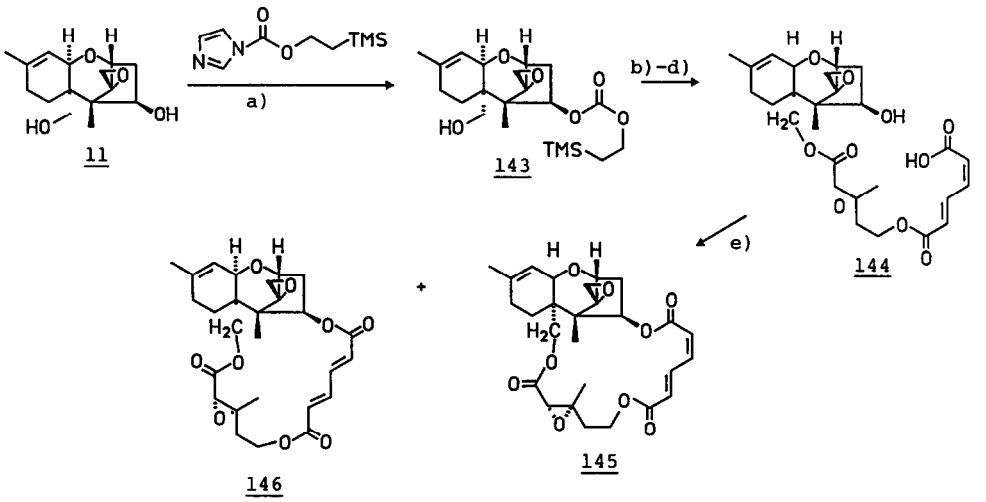
Scheme 27



a) TBDMSCl b) DIBAH c) tBuOOH, $Ti(OiPr)_4$, (-)-DET d) $KMnO_4$, Bu_4NBr
e) $TsCH_2CH_2OH$, BOPCl, Et_3N, DMAP f) AcOH g) Me_3CCOCl, Et_3N, DMAP
BOP = N,N-bis(2-OxO-3-oxazolidinyl)phosphordiamidic

143. The subsequent reaction of 143 with deprotected 139 gave the seco-acid 144 partially after removal of the remaining protecting groups. Cyclization to verrucarin B (145) was successfully achieved via the mixed anhydride with pivalic acid generated in situ. The E/E-isomer 146 was formed as well. It could be converted to 145 by treatment with iodine (Scheme 28)

Scheme 28



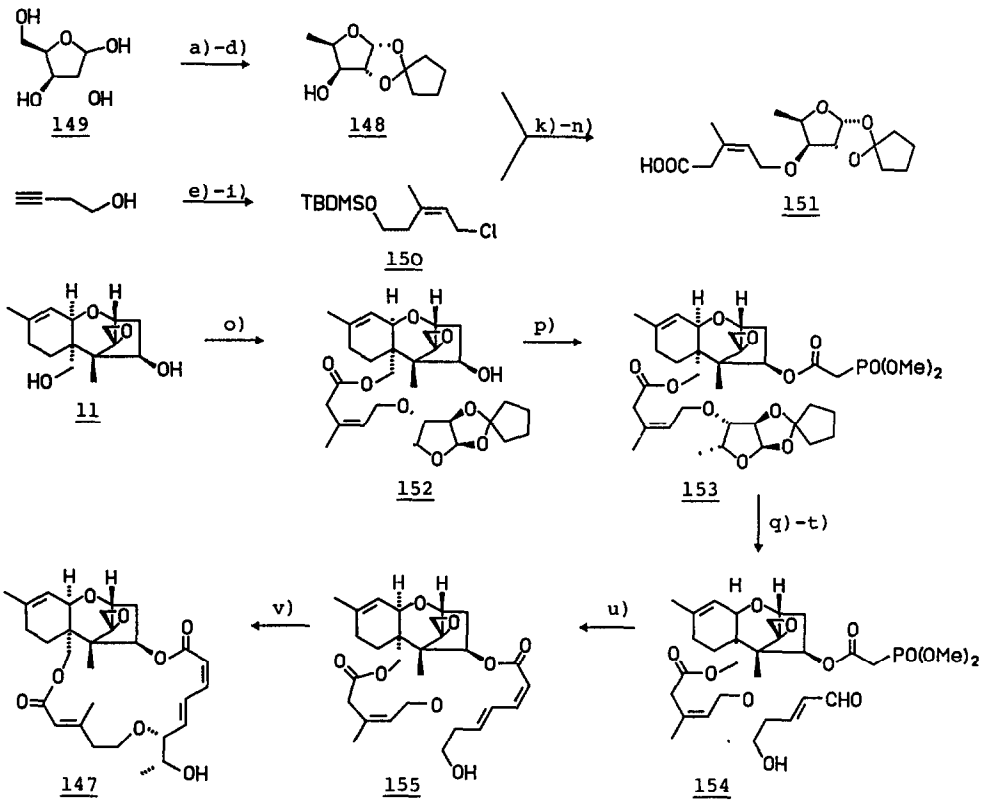
a) DBU b) 139, NaH, cat. DBU c) BOPCl, Et_3N, DMAP d) KF e) Me_3CCOCl, Et_3N,DMAP

5 5 Roridins and Baccharins

Roridin E (147) is the only member of the roridins which has been synthesized[85] to date In contrast to the syntheses of the macrocyclic triesters previously described, ring closure was achieved by an intramolecular Horner-Emmons reaction. The use of the xylose derivative 148, which was prepared from D-xylose (149) guaranteed the correct stereochemistry of C(6') and C(13'). By condensation of 148 with synthon 150 and subsequent oxidation, acid 151 was obtained (Scheme 29) Esterification of the latter with verrucarol (11) yielded the monoester 152 in very high yield It was converted into the phosphono-ester 153. Further transformation led to the unsaturated aldehyde 154. Cyclization produced both the desired product 155 as well as the E/E-isomer.

The final step, i.e shift of the isolated olefinic double bond, succeeded by treatment of 155 with potassium tert.-butoxide. The only product obtained was roridin E (147)

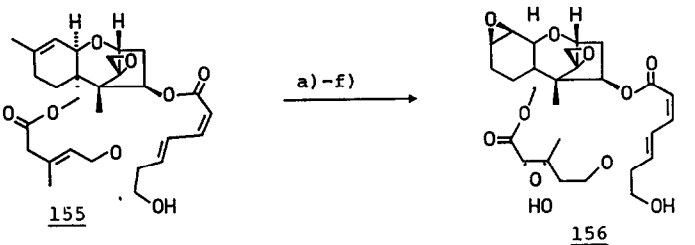
Scheme 29



a) cyclopentanone, $CuSo_4$, cat. H_2SO_4 b) HCl c) TsCl, py d) $LiAlH_4$
e) TBDMSCl f) BuLi, ClCOOEt g) Me_2CuLi h) $LiAlH_4$ i) NCS
k) NaH l) cat. Bu_4NI, HMPT m) Bu_4NF n) CrO_3, H_2SO_4 o) 151, DCC, Ppy
p) $HOOCCH_2PO(OMe)_2$, DCC, PPy q) TSOH r) $NaIO_4$ s) Et_3N, MeOH
t) Ph_3PCH_2CHO u) K_2CO_3, 18-crown-6 v) KOtBu

Baccharin B5 (156) was synthesized using the macrolide 155[85]. The transformation required 7 steps (Scheme 30).

Scheme 30

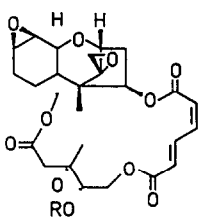


155 156

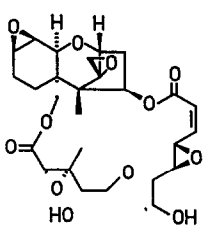
a) TBDMS-OTf, lutidine b) MCPBA c) KOtBu d) tBuOOH, $VO(acac)_2$
e) HCOOH, DEAD, Ph_3P f) Bu_4NF

5.6. Derivatives and Unnatural Analogues

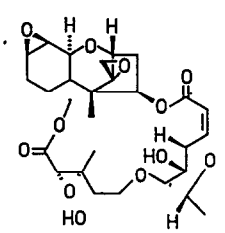
The observation that the cytostatic activity in vivo of the baccharins is enhanced by the presence of additional epoxy groups in the 9β,10β-position, prompted Jarvis et al.[86,87] to prepare derivatives of verrucarins and roridins which contain this additional functional group. Moreover, they introduced hydroxyl groups at C(8) or C(16) by allylic oxidation. Very recently Jarvis et al.[88] obtained new macrocyclic trichothecenes by selective oxidation in the macrolidic part of baccharin B5. In persuing this goal the unnatural macrolides 157 - 160 were made available for biological testing.



157 R = H
158 R = Ac



159

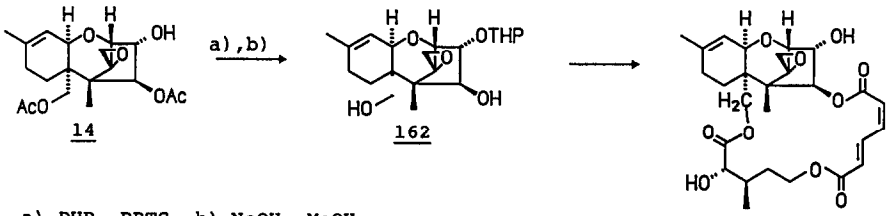


160

Having synthesized verrucarin A (70) Tamm et al.[65] also prepared 3α-hydroxy-verrucarin A (161) in order to study the influence of the additional hydroxyl group on the biological activity. The synthesis, which started from anguidine (14), was carried out according to the same concept described for the case of verru-

carin A. It required more steps because anguidine (14) had to be protected in the 3-position and deacetylated in order to obtain the compound (162) suitable for the macrolactonization (Scheme 31).

Scheme 31

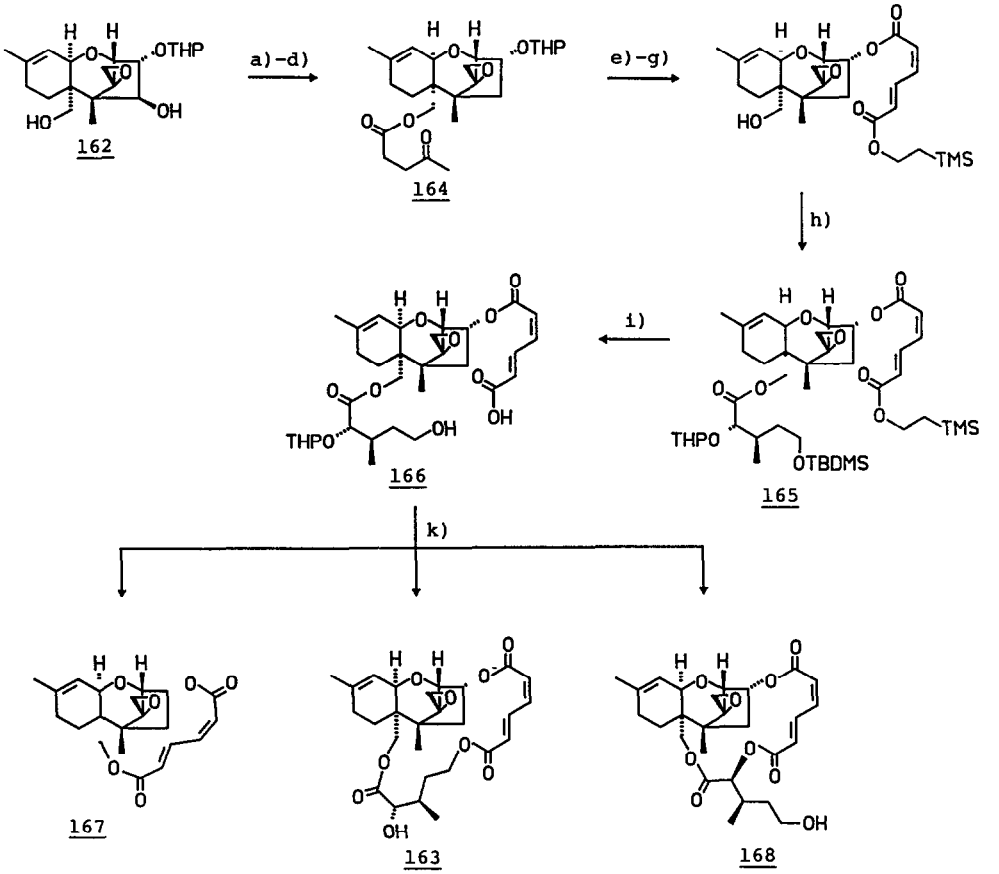


14 162 161

a) DHP, PPTS b) NaOH, MeOH

Very recently Jeker & Tamm[89] have synthesized several new unnatural macrocyclic trichothecenes in order to gain more detailed insight into the relationships between chemical structure and biological activity. The first compound of this series is 3-iso-verrucarin A (163) (Scheme 32). Again anguidine (14) was chosen as starting material. The first operation consisted in the removal of the 4-hydroxy group by selective deoxygenation. The subsequent steps involved, in contrast to the verrucarin A synthesis, the initial attachment of the muconic acid moiety. It was followed by the introduction of verrucarinic acid and the final macrolactonization The primary hydroxyl group of diol 162 was protected by esterification with levulinic acid. Subsequent Barton-deoxygenation gave ester 164. The condensation with the half-ester 114 of Z,E-muconic acid proceeded successfully without isomerization. The next step was the formation of the diester 165 with protected verrucarinic acid 75. After removal of the silyl groups the seco-acid 166 obtained was subjected to cyclization using Yamaguchi's method[81]. Three products were isolated: The desired 3-isoverrucarin A (163), and compounds 167 and 168, which were named verrucene and verrucinol respectively The yields and ratios of the three cyclization products depend very much on the methods and conditions of the condensation reaction. The formation of the by-products 167and 168 did not occur using either the Mitsunobu method[82] or the mixed anhydride with privalic acid[80]. Verrucene (167) is the first case in which the macrolidic part consists exclusively of Z,E-muconic acid It was not possible to achieve an analogous cyclization between the 4β- and 15-hydroxy groups. Surprisingly, verrucinol (168) proved to be relatively unstable in comparison to 163 and 167.

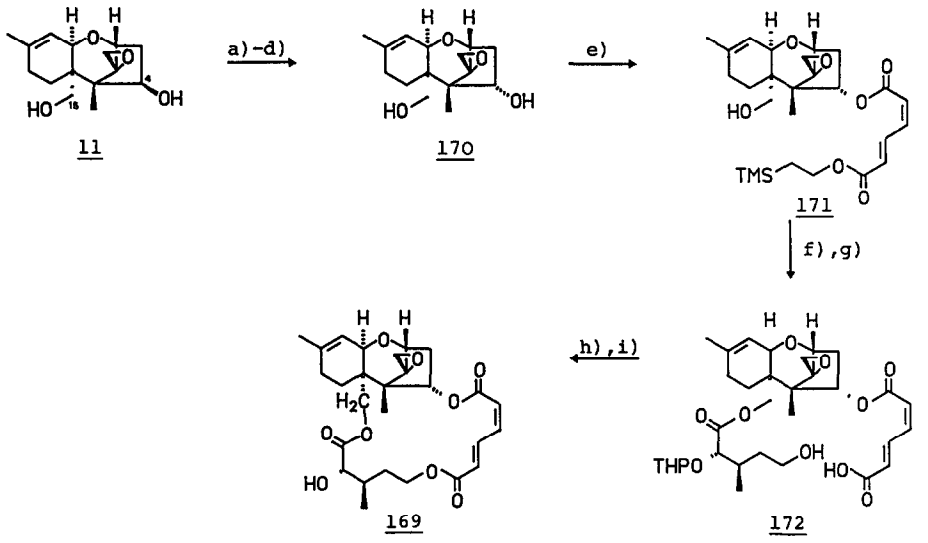
Scheme 32



a) DHP, PPTS b) levulinic acid, DCC, DMAP c) 1,1-thiocarbonyldiimidazole
d) Bu_3SnH e) PPTS, MeOH f) 114, DCC, DMAP g) H_2N-NH_2, py, HOAc
h) 75, DCC, DMAP i) Bu_4NF k) TCBACl, Et_3N, DMAP

Jeker and Tamm[89] also synthesized 5-epi-verrucarin A (169) (Scheme 33). Verrucarol (11) served as starting material. The epimerization at C(4) was preformed via 4-dehydroverrucarol. Because the 15-hydroxy group needed protection 4 steps were required for the conversion of 11 to 4-epi-verrucarol (170). Surprisingly the reactivity of the hydroxyl groups in 170 was reversed in comparison to verrucarol (11) Therefore the condensation with the muconic half ester 114 in the presence of DCC took place at the 4-position regioselectively without isomerization of the 2-double bond. However the condensation of the resulting monoester 171 with the verrucarinic acid moiety 75 turned out to be more difficult. After deprotection of the seco-acid 172 the finally obtained cyclization via the mixed anhydride[80] yielded the desired 4-epi-verrucarin A (169).

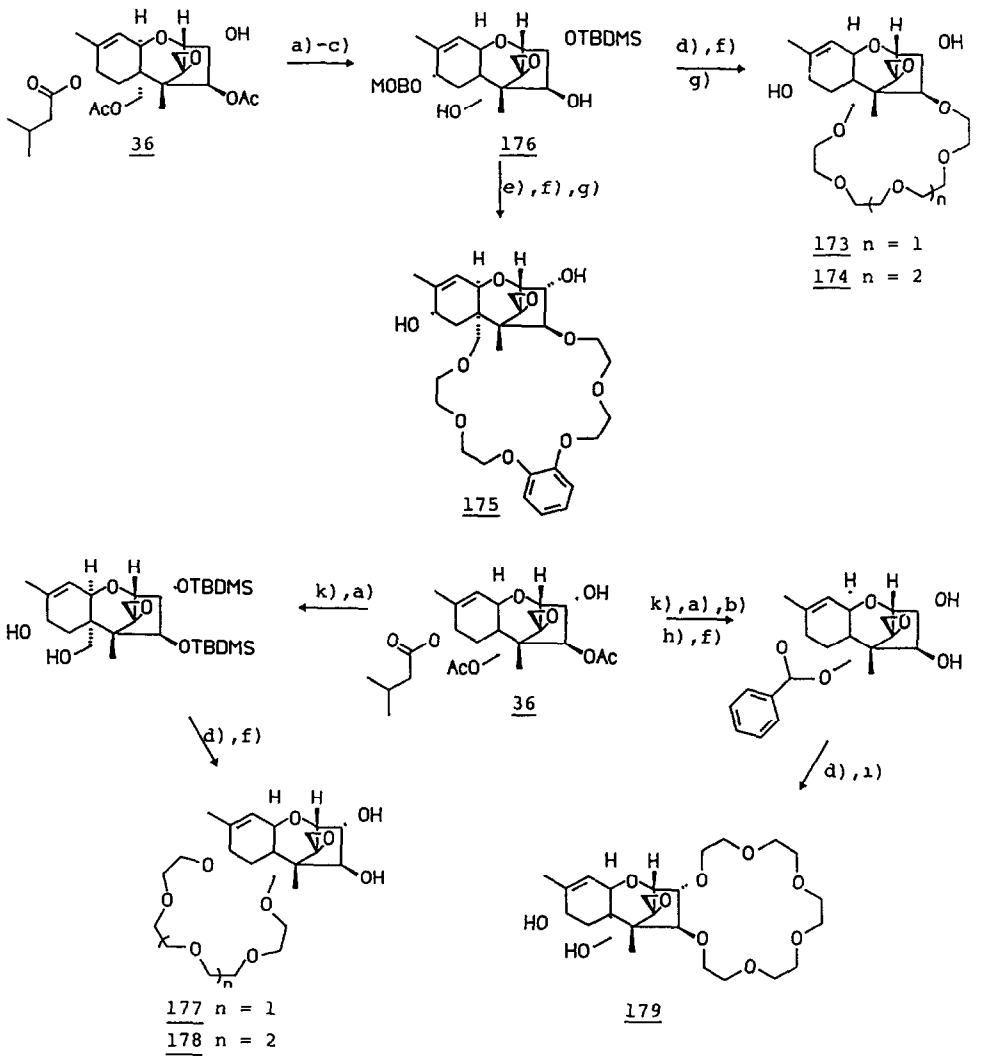
Scheme 33



a) Ac_2O, py b) DMSO, TFAA, Et_3N c) $NaBH_4$ or $LiAl(OtBu)_3$ d) NaOH
e) 114, DCC, DMAP f) 75, DCC, DMAP g) Bu_4NF h) Me_3CCOCl, Et_3N, DMAP
i) PPTS, EtOH

Anderson et al [90] constructed a new type of macrocyclic trichothecene by combining the sesquiterpenoid moiety with a polyether block. The products obtained are crown-ethers. For the synthesis of the macrocycles 173 - 175 T-2-toxin (36) was converted into the diol 176. Treatment of the latter with the polyether ditosylates yielded the desired products (Scheme 34). In a similar way the crown-ethers 177 - 179 were prepared also starting from T-2-toxin (36) [91]

Scheme 34



a) TBDMSCl, ımıdazole b) NaOMe, MeOH c) MOBBr, NaH d) TEGBT or PEGBT, NaH
e) 1,2-bis-(5-p-toluenesulfonyloxy-3-oxapentoxy)benzene f) Bu_4NF g) DDQ
h) PhCHO, $SnCl_2$, DME i) $SnCl_2$, TSOH k) NH_4OH
TEGT = tetraethylenglycolbıstosylate PEGT = pentaethylenglycolbıstosylate

6. Biological Activity

General toxicity, mode of action, metabolism, cytostatical and immunosuppressive activity of the trichothecenes have been investigated by several authors[92,5,3]. The conclusions concerning the structure - activity relationship which emerge from these studies can be summarized as follows. The presence of the 12,13-epoxy group is essential for the biological activity of the sesquiterpene alcohols and their simple esters. The unnatural 12,13-epi-epoxide leads to a loss of activity. β-Configuration of the substituents at C(4) is required for the cytostatic activity *in vitro*. In the series of the macrocyclic trichothecenes introduction of a 9,10β-epoxy group enhances the cytostatic activity whereas 9,10-epoxy groups with α-configuration have no influence. The 12,13-epoxy group which is present in the majority of the natural metabolites, contributes to biological activity, although this does appear not to be essential as shown by verrucarin K (12,13-deoxyverrucarin A) It is possible that the macrolidic moiety possesses cytostatic activity independently from the trichothecene skeleton. It might contribute in a synergistic mode of action. The activity of the synthetic model compounds 66 and 67 supports this hypothesis The inversion of configuration at C(4) as demonstrated by 4-epi-verrucarin A (169)[90] is less dramatic as in the case of the sesquiterpene alcohols The change in the attachment of the macrolidic bridge from the C(4) to C(3) position leads to a complete loss of biological activity as shown by 3-isoverrucarin A (163) and verrucene (167). The additional 3α-hydroxy group does not change the *in vitro* activity of verrucarin A (70). In general the conjugated Z,E-diene system contributes to an enhancement of activity. However with the data available at present it is too early to draw final conclusions for the structural requirements for the whole spectrum of biological activity More detailed studies are necessary.

Acknowledgment. Our investigations in the trichothecene field have been supported generously by grants of the Swiss National Science Foundation and by Sandoz AG, Basel.

References

1. Bamburg J.R. & Strong F.M. in "Microbial Toxins"; Kadis S., Ciegler A , Ajl C.J., Eds.; Academic Press: New York 1973.
2. Tamm Ch., Progr. Chem. Org. Nat. Prod. 31, 63 (1974).
3 Doyle T.W. & Bradner W.T. in "Anticancer Angents Based on Natural Product Models" Cassidy I.M. and Duro J.; Academic Press New York, 1980.
4 Tamm Ch. & Tori M. in "Mycotoxin-Production, Isolation, Separation and Purification", Betina V., Ed. Elsevier: Amsterdam-Oxford-London, 1984.
5 Ueno Y. in "Development in Food Science 4: Trichothecenes-Chemical, Biological and Toxicological Aspects", Elsevier: Amsterdam-Oxford-London, 1983.
6. Ong C.W., Heterocycles 19, 1685 (1982).
7 McDougal P.G. & Schmuff N.R., Progr. Chem Org. Nat. Prod. 47, 153 (1985).
8 Colvin E.W , Malchenko S., Raphael R.A , Roberts J.S., J. Chem. Soc Perk Trans I, 1989 (1973).
9. Fujimoto Y , Yokua S., Nakamura T., Morikawa T. & Tatsuno T., Tetrahedron Lett. 2523 (1974)
10 Kraus G.A , Roth B., Frazier K. & Shimagaki M , J. Am Chem. Soc. 104, 1114 (1982).
11. Tomioka, K., Sugimori M. & Koga K., Chem. Pharm. Bull. 35, 906 (1987).
12. Welch S.C. & Wong R.V., Synth. Commun. 2, 291 (1972).
Goldsmith D.J., Lewis A.J. & Still W.C., Tetrahedron Lett. 4807 (1973)
Snider B.B. & Amin S.G., Synth Commun. 8, 117 (1978).
Trost B.M & Rigby J.H., J. Org. Chem. 43, 2938 (1978).
Nakahara Y & Tatsuno T , Chem. Pharm. Bull. 28, 1981 (1980)
Banks R.E., Miller J A., Nunn M.J., Stanley P., Weakley T.J.R. & Ullah Z , J. Chem. Soc Perkin Trans I 1096 (1981)
Kraus G.A & Frazier K , J. Org. Chem. 45, 4820 (1982).
13. Colvin E.W. & Thom F G., Tetrahedron 42, 3137 (1986).
14 Masuoka N., Kamikawa T. & Kubota T., Chem. Lett. 751 (1974).
15. Still W.C & Tsai M.-Y., J. Am. Chem. Soc. 102 3654 (1980).
16. Anderson W.K. & Lee G.E , J. Org. Chem. 45, 501 (1980).
17. Goldsmith D.J., John T.K., Kwong C.D. & Rainter G.R , J Org. Chem. 45, 3989 (1980).
18 Pearson A J. & Ong W.C., J. Am Chem. Soc 103, 6686 (1981).
19 Pearson A J & Chen Y -S., J. Org. Chem 51, 1939 (1986)
20 Roush W.R & D'Ambra T E., J. Org Chem 45, 3927 (1980)
21 Roush W.R & D'Ambra T.E., J. Am Chem. Soc 105, 1058 (1983)
22. Schlessinger R.H & Nugent R.A., J. Am. Chem. Soc. 104, 1116 (1982).
23. Trost B.M & McDougal P.G., J. Am. Chem. Soc. 104, 6110 (1982).
24 Brooks D W , Grothaus P.G. & Palmer J.T., Tetrahedron Lett. 23, 4187 (1982).
25 Ziegler F.E , Nangia A & Schulte G., J. Am. Chem. Soc. 109, 3987 (1987).
26. Corley D.G., Rottinghaus G E. & Tempesta M.S., Tetrahedron Lett 27, 427 (1986)
27 Ziegler F.E., Nangia A. & Tempesta M.S., Tetrahedron Lett 29, 1665 (1988)
28. Ziegler F.E., Nangia A. & Schulte G., Tetrahedron Lett 29, 1669 (1988)
29 White J D., Matsui T & Thomas J.A., J Org. Chem. 46, 3376 (1981)
30. Tsang R & Fraser-Reid B., J Org. Chem. 50, 4659 (1985)
31 Koreeda M. & Luengo J I , J. Org Chem 49, 2079 (1984).
32 Hua D H. & Venkataraman S., Tetrahedron Lett 26, 3765 (1985)

33. Fétizon M., DoKhak D. & Dinh Tho N., Tetrahedron Lett. 26, 1777 (1986).
34. Pearson A.J. & Hsu S.-Y., J. Org. Chem. 51, 2505 (1986).
35. Claridge C.A., Schmitz H. & Bradner W.T., Cancer Chemother. Pharmacol 2, 181 (1979).
36. Kaneko, T., Schmitz H., Essery J.M., Rose W., Howell H.G., O'Herren F.A. Nachfolger S., Huftalen J., Bradner W.T., Partyka R.A., Doyle T.W., Davies J. & Cundliffe E., J. Med. Chem. 25, 579 (1982).
37. Kaneko T., Wong H., Howell H.G., Rose W.C., Bradner W.T. & Doyle T.W., J. Med. Chem. 28, 958 (1985).
38. Dillen J.L.M., Gorst-Allman Ch.P. & Steyn P.S., S. Afr. J. Chem. 39, 111 (1986).
39. Wani M.C., Rector D.H. & Cook C.E., J. Org. Chem. 52, 3468 (1987).
40. Mitsunobu O., Synthesis 1 (1981).
41. Colvin E.W. & Cameron S., Tetrahedron Lett. 29, 493 (1988).
42. Barton D.H.R. & McCombie S.W., J. Chem. Soc. Perkin Trans I, 1574 (1975)
43. Robins M.J. & Wilson J.S., J. Am. Chem. Soc. 103, 932 (1981).
44. Tulshian D.B. & Fraser-Reid B., Tetrahedron Lett. 21, 4549 (1980).
45. Esmond R., Fraser-Reid B. & Jarvis B.B., J. Org. Chem. 47, 3358 (1982).
46. Jeker N., Mohr P. & Tamm Ch., Tetrahedron Lett. 25, 5637 (1984).
47. Schuda P.F., Potlock S.J. & Wannemacher R.W., J. Nat. Prod. 47, 514 (1984).
48. Anderson D.W., Black R.M., Leigh D.A., Stoddart J.F. & Williams N.E., Tetrahedron Lett. 28, 2661 (1987).
49. Gutzwiller J., Mauli R., Sigg H.P. & Tamm Ch., Helv. Chim. Acta 47, 2234 (1964).
50. Roush W.R., Russo-Rodriguez S., J. Org. Chem. 50, 5465 (1985).
51 Sharpless K.B., Umbreit M.A., Nieh M.T. & Flood T.C., J. Am. Chem. Soc. 94, 6538 (1972).
52. Colvin E.W. & Cameron S., J. Chem. Soc. Chem. Commun. 1084 (1986).
53 Colvin E.W. & Cameron S., J. Chem. Soc. Chem. Commun. 1642 (1986).
54. Roush W.R. & Russo-Rodriguez S., J. Org. Chem. 52, 603 (1987)
55. Jarvis B.B., Pavanasasivam G., Holmlund C.E., De Silva T.& Stahly G.P., J. Am. Chem. Soc. 103, 472 (1981).
56 Tulshian D.B. & Fraser-Reid B., J. Am. Chem. Soc. 103, 474 (1981).
57. Roush W.R. & Spada A.P , Tetrahedron Lett. 23, 3773 (1982).
58. Roush W.R. & Spada A.P., Tetrahedron Lett. 24, 3693 (1983)
59. Breitenstein W. & Tamm Ch., Helv. Chim. Acta 61, 1975 (1978).
60 Notegen E.A., Tori M. & Tamm Ch., Helv Chim. Acta 64, 316 (1981)
61. Corey E.J. & Nicolaou K.C., J. Am. Chem. Soc. 96, 5614 (1974).
62 Trost B.M. & McDougal P.G., J. Org. Chem. 49, 458 (1984).
63. Still W.C. & Ohmizu H., J. Org. Chem. 46, 5242 (1981).
64. Herold P., Mohr P. & Tamm Ch., Helv. Chim. Acta 66, 744 (1983).
65. Mohr P., Tori M., Grossen P., Herold P. & Tamm Ch., Helv. Chim. Acta 65, 1412 (1982).
66 Gamboni R., Mohr P., Waespe-Sarcevic N. & Tamm Ch., Tetrahedron Lett. 26, 203 (1985).
Gamboni R. & Tamm Ch., Helv. Chim. Acta 69, 615 (1986).
67. Gamboni R. & Tamm Ch., Tetrahedron Lett. 27, 3999 (1986).
68. Roush W.R., Blizzard T.A. & Basha F.Z., Tetrahedron Lett. 23, 2331 (1982)
69. Trost B.M. & McDougal P.G., Tetrahedron Lett. 23, 5497 (1982).
70. Tomioka K., Sato F. & Koga K., Hetereocycles 17, 311 (1982).

71. Yamamoto Y., Maeda N. & Maruyama K., J. Chem. Soc., Chem. Commun. 774 (1983).
72. Grossen P., Herold P., Mohr P. & Tamm Ch., Helv. Chim. Acta 67, 1625 (1984).
73. Bartlett P.A., Tanzella D.J. & Barstow J.F., J. Org. Chem. 47, 3941 (1982).
74. Sato T., Tajima K. & Fujisawa T., Tetrahedron Lett. 24, 729 (1983).
75 Burke S D., Fobare W.F. & Pacofsky G.J., J. Org. Chem. 48, 5221 (1983).
76. Mikami K., Fujimoto K. & Nakai T., Tetrahedron Lett. 24, 513 (1983).
77. Mikami K , Fujimoto K., Kasuga T. & Nakai T., Tetrahedron Lett. 25, 6011 (1984)
78. Mulzer J. & Salimi N., Liebigs Ann. Chem. 1172 (1986).
79 Still W.C. & Ohmizu H , J Org. Chem. 46, 5244 (1981).
80. Roush W.R. & Blizzard T.A., J. Org. Chem. 49, 1772 (1984).
81. Inanaga J.,Hirata K. ,Saeki H., Katsuki T & Yamaguchi M., Bull Chem. Soc. Jpn. 52, 1989 (1979).
Honda M , Hirata K., Sueka H., Katsuki T. & Yamaguchi M., Tetrahedron Lett. 2679 (1981).
82. Kurihara T , Nakajima N. & Mitsunobu O., Tetrahedron Lett. 2445 (1976).
83 White J D., Carter J.P. & Kezar H.S., J. Org. Chem. 47, 929 (1982).
84. Roush W.R. & Blizzard T.A., J. Org. Chem. 49, 4332 (1984).
85. Still W.C., Gennari C., Noguez J.A. & Pearson D.A , J Am. Chem. Soc 106, 260 (1984).
86 Jarvis B.B., Stahly G.P. & Pavanasasivam G., J. Med. Chem. 23, 1054 (1980)
87. Jarvis B.B., Midiwo J.O. & Mazzola E.P., J. Med. Chem. 27, 239 (1984).
88. Jarvis B.B , Comezoglu S.N. & Alvarez M.E., J. Org. Chem. 53, 1918 (1988).
89. Jeker N & Tamm Ch., papers in preparation.
90. Anderson D.W., Black R.M., Leigh D.A. & Stoddart J.F., Tetrahedron Lett 28, 2653 (1987)
91. Anderson D.W., Black R.M., Leigh D.A. & Stoddart J.F., Tetrahedron Lett. 28, 2657 (1987)
92 Bamburg J.R in "Progress in Molecular and Subcellular Biology: Biological and Biochemical Actions of Trichothecene Mycotoxins" Hahn F.E., Kopecko D.J. & Müller W.E.G., Eds.; Springer Verlag, Berlin-Heidelberg-New York, 1983