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CONDURITOLS AND RELATED COMPOUNDS

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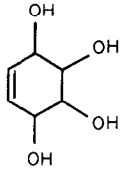
1. INTRODUCTION

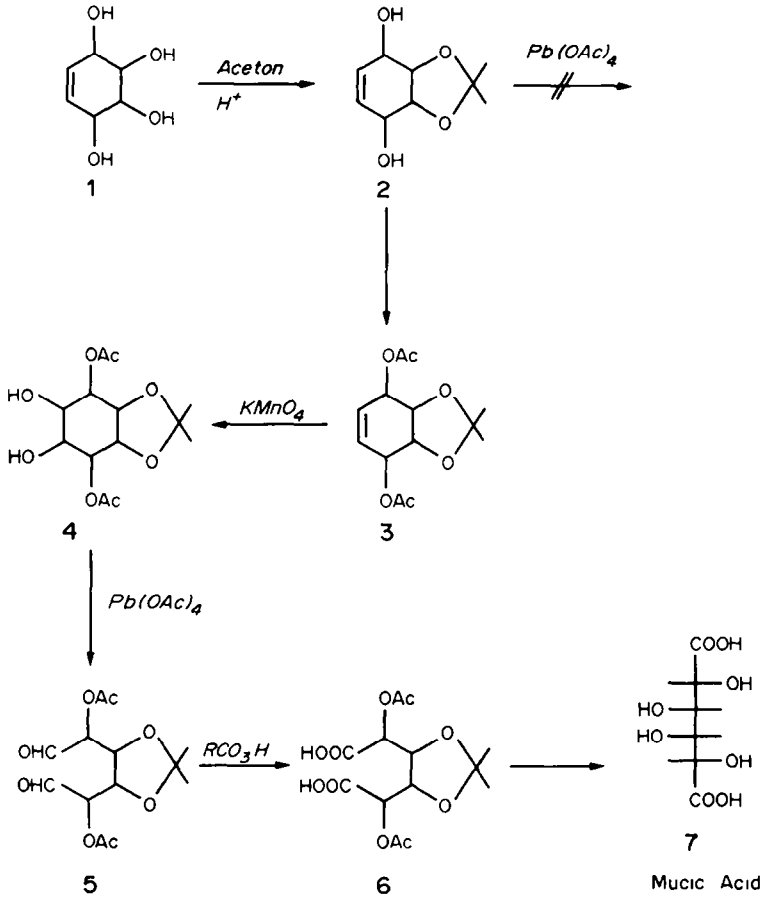
In 1908 Kübler[1] isolated a new alcohol from the bark of the vine *Marsdenia condurango* which he named conduritol.[2] It was optically inactive and apparently of unsaturated cyclic constitution. Heating with aqueous hydrochloric acid yielded pyrocatechol and treatment with bromine gave an



Conduritol

Fig 1

addition product. Kübler did not determine the constitution of conduritol and the constitution and the configuration of conduritol were established 30 years later by Dangschat and Fischer.[3] Conduritol **1** and acetone yielded a mono-acetonide **2**. The fact that the other two hydroxyl groups were indifferent to $Pb(OAc)_4$ indicated that the hydroxyl groups at C_2 and C_3 were blocked. Furthermore, the diacetate **3** was oxidised by neutral $KMnO_4$ to dihydroxy-compound **4** which upon treatment with $Pb(OAc)_4$ in benzene, further oxidation with $EtCO_3H$ and saponification yielded mucic acid **7** (Scheme 1).



Scheme 1.

On the basis of these reactions the configuration of conduritol was established as conduritol-A **8**. Full details of this work were never published. Fischer was planning to publish this work in the

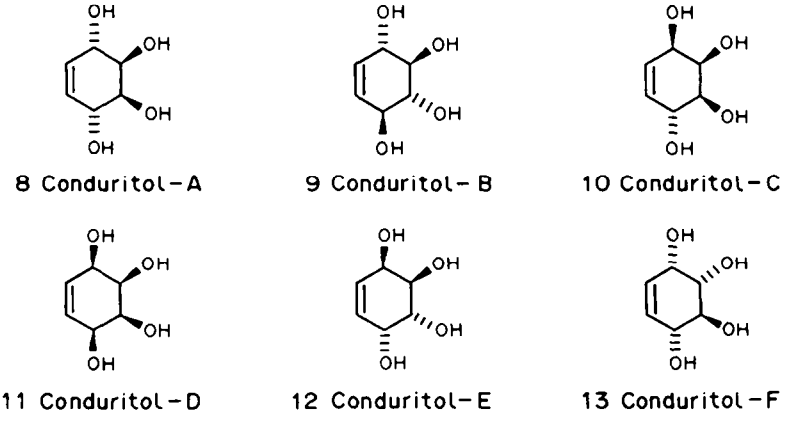


Fig. 2.

early 1950s and asked Professor D. L. McDonald to translate this work into English. Fortunately, Professor McDonald retained a copy of the English translation and published[4] the details after 50 years in a memoir of Professor Fischer. Six diastereomers of conduritol are possible. To avoid ambiguity the diastereoisomers have been labelled A, B, C, D, E and F.[5]

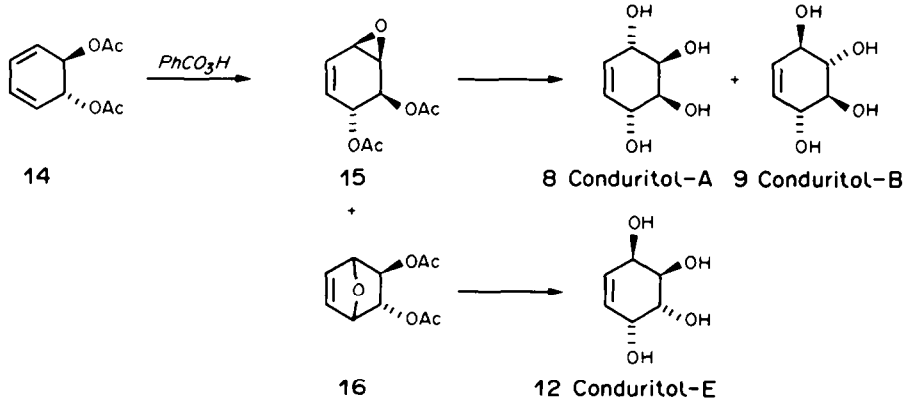
All the possible conduritol isomers have been synthesised and their biological importance has been studied. The double bond in these compounds participates in a variety of addition reactions. The discovery of conduritol-A opened up the way to the synthesis of numerous isomers as well as derivatives of inositol by Dangschat and Fischer.[3a]

In this Report we give an overview of the synthesis, reactions and biological importance of conduritol isomers and their conversion to the other biologically important compounds.

2. CONDURITOLS

2.1. *Conduritol-A* **8**

The first successful and non-stereospecific synthesis of conduritol-A was carried out by Nakajima *et al.*[6] starting from *trans*-benzenediol. For the first time, Nakajima *et al.* also used *trans*- and *cis*-benzenediols for the synthesis of conduritol isomers (Scheme 2). Oxidation of the diacetate **14** with perbenzoic acid yielded a mixture of **15** and **16**. Without separation of the products, this mixture was hydrolysed with 2N H_2SO_4 and gave the three isomeric conduritols-A, -B, and -E which were separated by crystallisation and column chromatography.

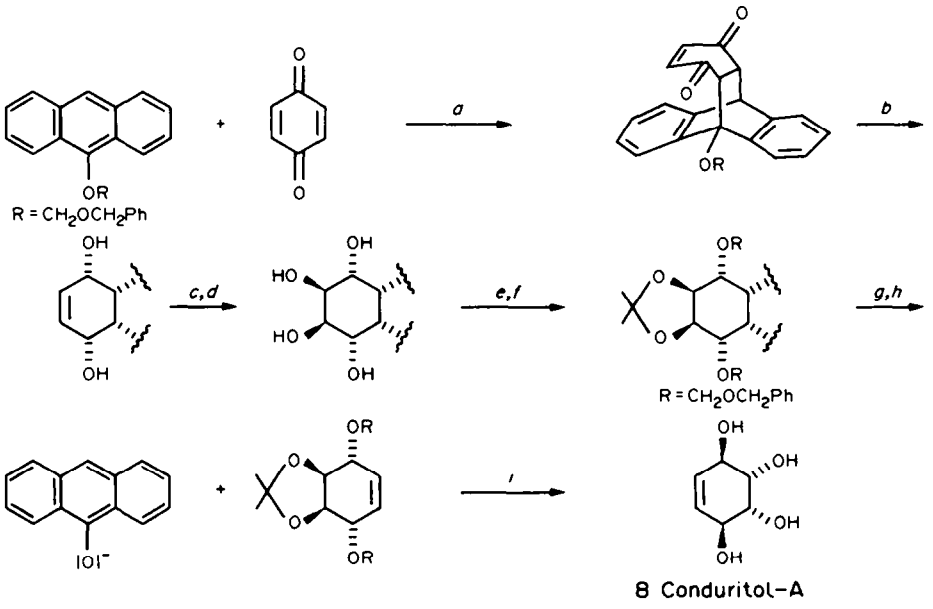


Scheme 2.

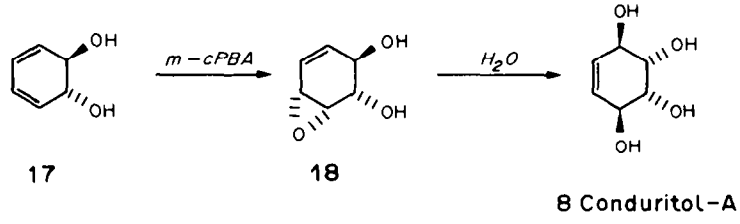
Recently, Knapp *et al.*[7] described the first stereospecific synthesis of conduritol-A **8** from *p*-benzoquinone by protecting one double bond of benzoquinone with 9-[(benzyloxy)methoxy] anthracene. With this protecting group they also blocked one face of *p*-benzoquinone in order to direct *cis* reduction at C_3 and C_6 and *cis* functionalisation of the remaining C=C double bond (Scheme 3). Disadvantages of this stereospecific synthesis are the protection of the double bond and hydroxyl groups and deprotection reactions which increase the number of steps.

Recently, Aleksejczyk and Berchtold[8] described a new synthesis of conduritol-A **8** from the dihydrodiol **17**.[9] Epoxidation of **17** provided **18** (61%) and solvolysis of **18** in water at room temperature for several days gave conduritol-A (Scheme 4).

Recently we developed a new, efficient and stereospecific synthesis of conduritol-A[10a] starting from cyclohexa-1,4-diene. This synthetic strategy is based upon the introduction of two oxygen functionalities at the C_2 and C_3 positions by $KMnO_4$ oxidation followed by two oxygen func-

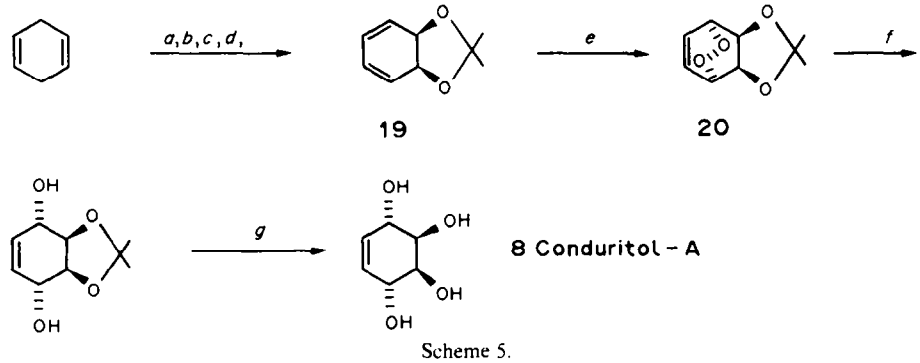


Scheme 3.
(a) Toluene, 15 h, 68 C, (b) $NaBH_4$, $CeCl_3$, MeOH, Toluene, −78 C, (c) OsO_4, NMO, Acetone, water, (d) TFA, MeOH, 40 C, (e) Acetone, TFA, 65 C, (f) $PhCH_2OCH_2Cl$, NaH, THF, (g) KH, dioxane, 35 C, 12 h, (h) Na, NH_3, EtOH, ether, −78 C, (i) TFA, MeOH.



Scheme 4.

tionalities at C_1 and C_4 positions by photo-oxygenation. The key compound **19** in the synthesis of conduritol-A was synthesised as described in the literature.[11] Suitable ring opening reactions of **20** provided conduritol-A (Scheme 5). Catalytic reduction of the double bond provided the dihydro-

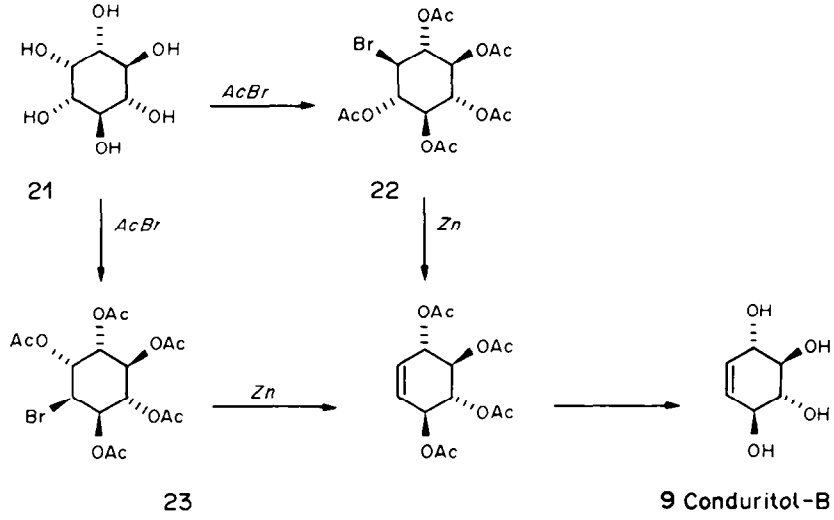


Scheme 5.
(a) Br_2, $CHCl_3$, −40 C, (b) $KMnO_4$, EtOH, H_2O, −10 C, (c) 2,2-dimethoxypropane, H_2SO_4, (d) 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU), benzene, (e) $^1O_2$, TPP, (f) Thiourea, MeOH, (g) HCl, MeOH.

conduritol.[12] *cis*-Benzenediol is now a commercial product which is synthesised by stereospecific microbial oxidation of benzene using *Pseudomonas putida* strains.[13] After our publication,[10a] Carless and Oak[10b] independently applied the same method to the synthesis of conduritol-A **8**.

2.2. *Conduritol-B* **9**

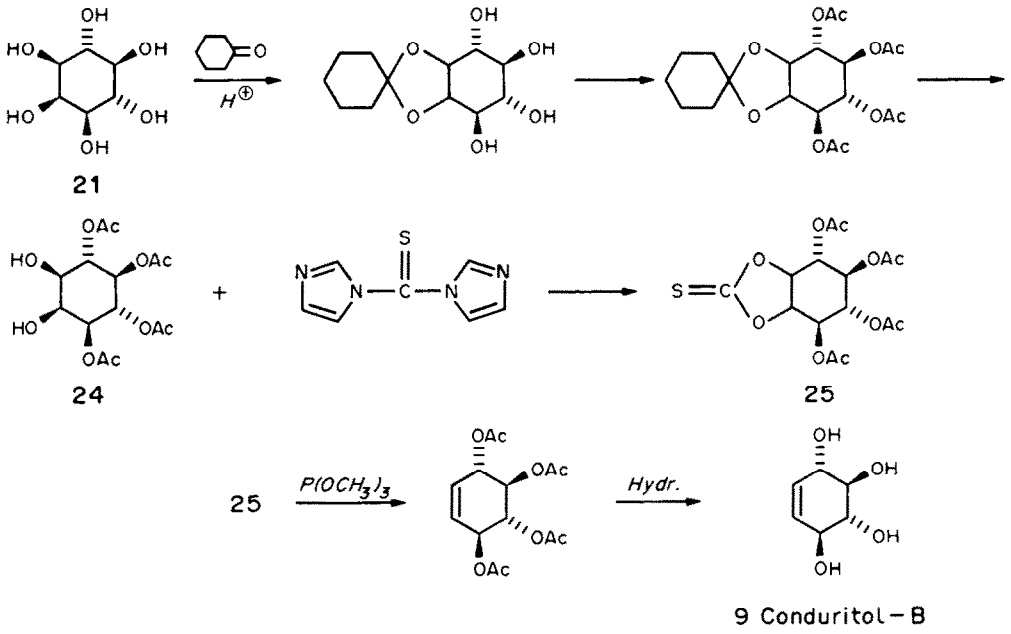
The first attempted synthesis of any conduritol isomers by the dehydration of inositol or other cyclitols resulted in the introduction of three double bonds (aromatisation) instead of one. Müller reported[14] that the penta-acetate **22** of 6-bromoquercitol on treatment with zinc in acetic acid gave a product, $C_{14}H_{18}O_8$. These results were reinvestigated by McCasland and Horswill.[15] They prepared two different bromoquercitol penta-acetates **22** and **23** from myo-inositol **21** by reaction with acetyl bromide. On repetition of Müller's debromination-procedure[14] with **22** and **23**, they isolated the tetracetate of conduritol-B which gave conduritol-B **9** on deacetylation (Scheme 6). Its structure was established by hydrogenation to the known 1,2,3,4 cyclohexanetetrol.[16]



Scheme 6.

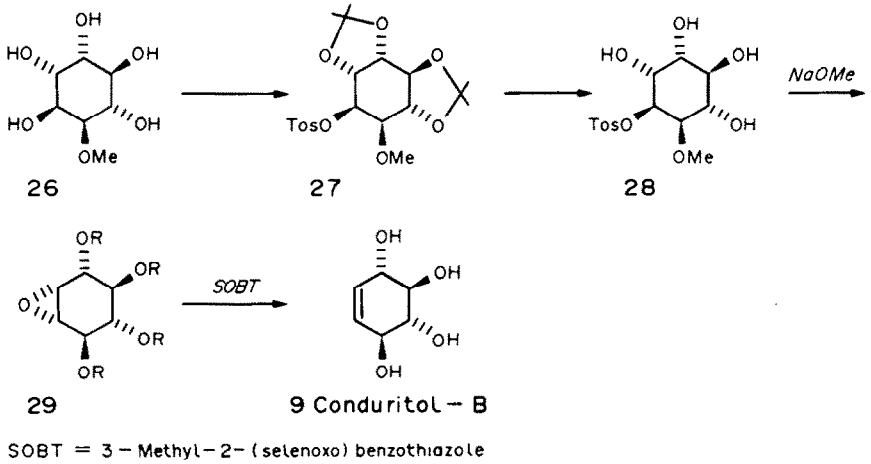
Later, conduritol-B **9** was synthesised as a mixture with conduritol-A **8** and -E **12** by Nakajima *et al.*[6] (Scheme 2). Although the first preparation of conduritol-B **9** starting from myo-inositol was stereospecific, the low yields of the intermediate penta-acetates **22** and **23** prompted Nagabhushan to develop a new synthesis from 1,4,5,6-tetra-O-acetylmyoinositol **24**.[17] Condensation of myo-inositol **21** with cyclohexanone yielded 1,2,-O-cyclohexylidene myo-inositol (2%) and three diketals. Although satisfactory conditions could not be found for the preparation of the monoketal, this compound was obtained in good yield (90%) by partial hydrolysis of the diketals. By acetylation and subsequent deketalisation, Nagabhushan[17] obtained the intermediate **24** which with N,N'-thiocarbonyldiimidazole by the method of Corey and Winter[18] gave the thiocarbonate **25**. Treatment of **25** with trimethylphosphite gave the tetra-acetate **9a**. Deacetylation with NEt_3 gave conduritol-B **9** (Scheme 7).

More recently, the synthesis of conduritol-B **9** described by Nagabhushan[17] and Angyal *et al.*[19] was modified and improved by Radin *et al.*[20] All syntheses leading to conduritol-B **9** yielded a racemic mixture. An enantioselective synthesis of conduritol-B **9** was described by Paulsen *et al.*[21]



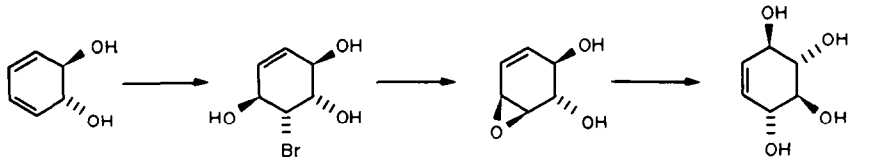
Scheme 7

The key intermediate, the 1-O-tosylate **28** was synthesised starting from optically active quebrachitol **26**. The reductive deoxygenation of **29** with SOBT[22] followed by hydrogenolysis of the protecting groups provided optically active conduritol-B **9** in high yield (Scheme 8).



Scheme 8.

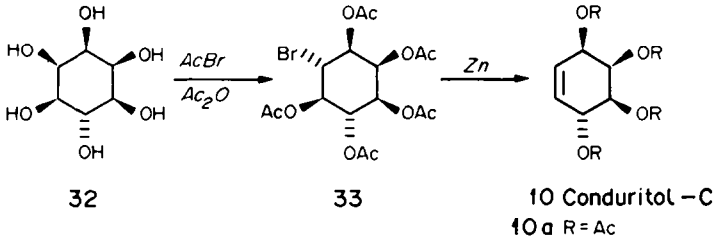
Berchtold[8] developed an efficient synthetic pathway for conduritol-B **9** starting from dihydrobenzene diol **17** which with N-bromosuccinimide in aqueous tetrahydrofuran gave the bromide **30** the configuration of which was established by X-ray crystal structure determination. Dehydrobromination of **30** gave **31** as a hygroscopic oil the solvolysis of which, in water, provided conduritol-B **9** (Scheme 9).



Scheme 9.

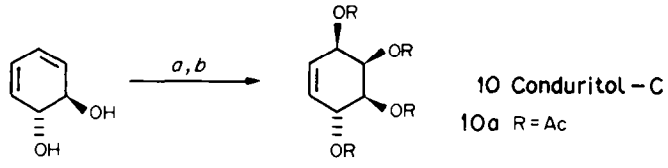
2.3. *Conduritol-C* **10**

McCasland and Reeves[23] have applied similar synthetic methodology (Scheme 6) leading to the synthesis of conduritol-C **10** (Scheme 10). When *epi*-inositol **32** was heated with acetyl bromide-acetic anhydride, a new bromoquercitol penta-acetate **33** was obtained. This penta-acetate **33** on reaction with zinc-acetic acid gives **10a** from which the free tetrol **10** can be obtained by ammonolysis. The configuration of conduritol-C was established by hydrogenation, giving a saturated tetrol which was identical with the compound previously reported by Posternak and Friedli.[12]



Scheme 10.

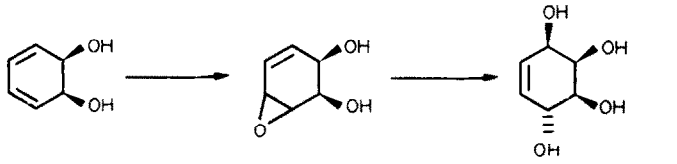
Nakajima *et al.*[6] have synthesised conduritol-C **10** starting from *trans*-benzenediol **17** as in the case of conduritol-A **8** and conduritol-B **9** (see Scheme 2). *Trans*-benzene diol **17** was treated with osmium tetroxide in the presence of silver perchlorate. The product was acetylated and was identical with the tetracetate reported by McCasland and Reeves[23] (Scheme 11). One would also expect the



(a) OsO_4, $AgClO_4$, (b) Ac_2O, pyridine

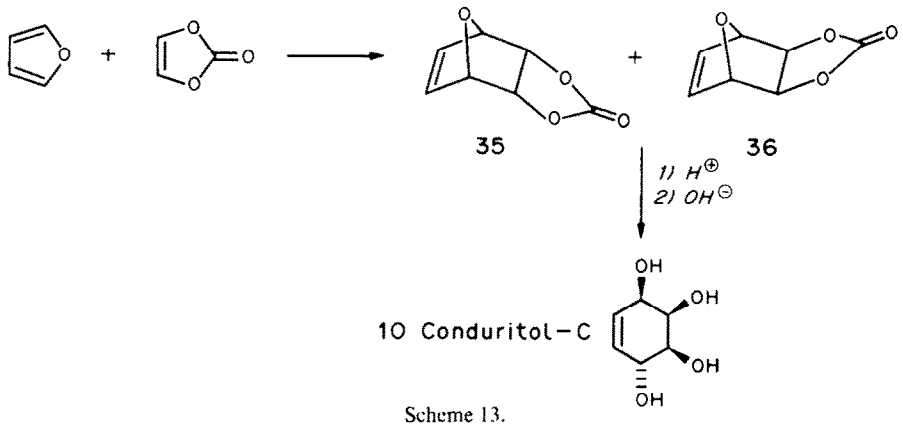
Scheme 11.

formation of conduritol-F by this reaction but the authors indicate that they could not isolate it. From *cis*-benzenediol, conduritol-C **10** was also synthesised by *trans*-hydroxylation. Benzenediol **34** was oxidized with perbenzoic acid giving a monoepoxide the exact structure of which was not described. Hydrolysis with acid gave the *trans*-hydroxylation product, conduritol-C **10**[8] (Scheme 12).



Scheme 12.

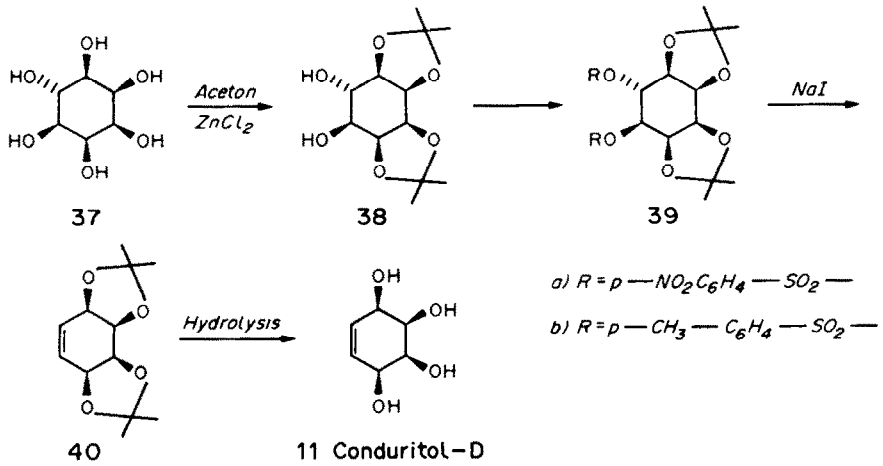
Yurev and Zefirov[24] have developed a short, elegant stereospecific route to conduritol-C **10**. The *endo*- and *exo*-adduct mixture **35** and **36** obtained by [4+2]cycloaddition of furan and ethylene-carbonate was hydrolysed under acidic conditions. Basic cleavage of the carbonate gave conduritol-C **10** (Scheme 13).



Scheme 13.

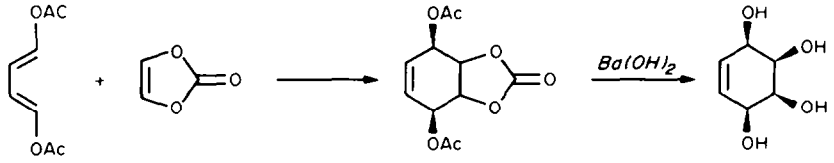
2.4. *Conduritol-D* **11**

The first synthesis of conduritol-D[25] **11** was achieved from suitably substituted inositols. The di-O-isopropylidene derivative of 5,6-di-O-nitrobenzenesulphonyl-*epi*-inositol **39a** was eliminated at 100°C yielding the di-O-isopropylidene derivative of conduritol-D **40**. In contrast the di-O-isopropylidene derivative **39b** did not react with sodium iodide even under more drastic reaction conditions (Scheme 14).



Scheme 14.

Criegee and Becher[26] used a different synthetic method in which the cyclohexane ring was formed by a Diels–Alder reaction. They key compound **41** was obtained (30%) by reaction of known *trans-trans*-diacetoxybutadiene with vinylenecarbonate at high temperature and high pressure. The free tetrol was obtained by saponification of **41** with $Ba(OH)_2$ (Scheme 15). The configuration of the product was established by oxidation of the double bond with OsO_4 giving the known allo-inositol.

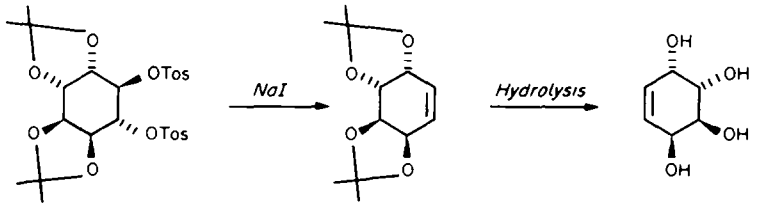


41 11 Conduritol-D

Scheme 15.

2.5. *Conduritol-E* **12**

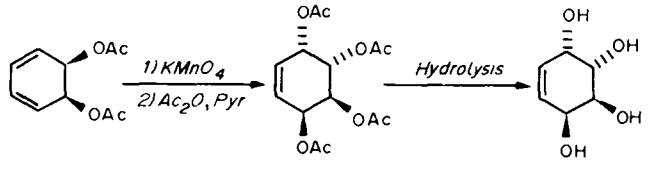
The first synthesis of conduritol-E **12** was described by Nakajima *et al.*[6] in 1957 (Scheme 2). Epoxidation of *trans*-diacetoxybenzene followed by hydrolysis gave a mixture of conduritol-E **12**, conduritol-A **8** and conduritol-B **9**. This synthetic approach is not stereospecific and is not useful. A stereospecific synthesis of conduritol-E **12** has been reported by Angyal and Gilham[25] using a similar synthetic route to that reported for the synthesis of conduritol-D **11** (Scheme 14). The preparation involved elimination of the two vicinal sulphonyloxy groups by iodide ion which has been used in carbohydrate chemistry.[27] The readily available di-O-isopropylidene derivative of 3,4-di-O-tosylinositol **42** reacted smoothly with sodium iodide and gave cyclohex-5-ene-1,2,3,4-tetrol as its diisopropylidene derivative **43**. Hydrolysis of **43** gave conduritol-E **12** (Scheme 16).



42 43 12 Conduritol-E

Scheme 16

Conduritol-E **12** has also been synthesised starting from *cis*-benzenediol.[28] Direct oxidation of *cis*-benzenediol with OsO_4 in the presence of silver salts gave conduritol-E **12**. Furthermore, the diacetate **44** by $KMnO_4$ oxidation under neutral conditions, followed by acetylation, yielded the tetracetate of conduritol-E **12** (61%) (Scheme 17). Conduritol-D **11** was not formed under these reaction conditions, due to steric interaction caused by the hydroxyl groups.



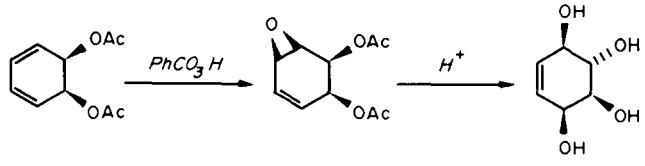
44 12 a 12 Conduritol-E

Scheme 17.

2.6. *Conduritol-F* **13**

The occurrence in Nature of only two conduritols, namely conduritol-A **8** and conduritol-F **13** has been established. Conduritol-A **8** was discovered by Kübler from the bark of the vine *Marsdenia condurango* in 1908. A systematic study of tropical Asclepiadaceae shows that *Marsdenia abyssinica*, *M. zambesica*, *M. erecta*, *M. angolensis* and *Dragea faulknerae* contain conduritol-A **8** as their main cyclitol component. These findings mean that conduritol can be found only in the subfamily Cynanchoidea of the Asclepiadaceae.[29] In 1962 Plouvier[30] discovered a new optically active conduritol isomer from *Chrysanthemum leucanthemum* which was named L-leucanthemitol **13** (conduritol-F). The very restricted distribution of conduritol-A **8** contrasts with that of its isomer, L-leuchanthemitol which at least in traces can be detected in almost all green plants.

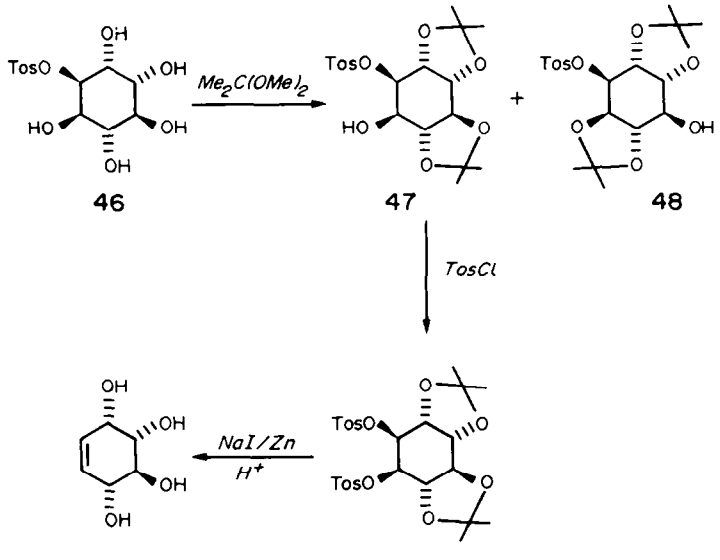
The first successful synthesis of conduritol-F **13** was achieved by Nakajima *et al.*[28] in 1959 before its discovery as a natural product. Nakajima *et al.* first prepared *cis*-benzenediol **34** starting from tetrachlorocyclohexene. Epoxidation of the diacetate **44** followed by hydrolysis with sulphuric acid provided in contrast with the epoxidation and hydrolysis of free benzenediol (Scheme 12) only conduritol-F **13** (30%) (Scheme 18). From the acid-catalysed ring opening reaction of **45** one would expect the formation of a pair of diastereoisomers. The authors do not mention the formation of conduritol-C **10**: the regiospecific ring opening of **45** is remarkable.



44 45 13 Conduritol – F

Scheme 18.

Paulsen *et al.*[21] have discovered an enantioselective synthesis of conduritol-F **13** using similar approaches as described for conduritol-B **9**(Scheme 8) and conduritol-E **12** (Scheme 16). 1-O-Tosylate of quebrachitol (L-chiro-inositol) was converted into its isopropylidene derivatives **47** and



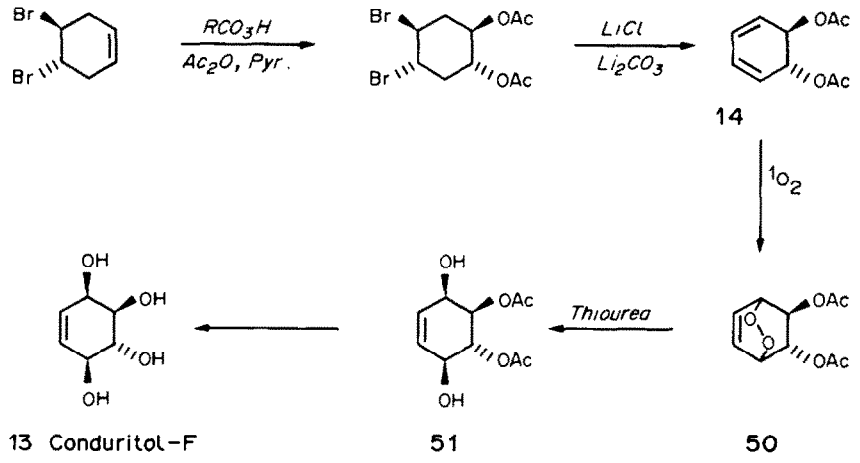
46 47 48

13 Conduritol-F 49

Scheme 19.

48 which were easily separated by column chromatography. Reaction of **47** with tosyl chloride followed by elimination with sodium iodide and zinc provided the isopropylidene derivative of conduritol-F **13**. Removal of the protecting groups gave the L-enantiomer **13** which was optically active, $[\alpha]_D^{20} = -70.5°$ (Scheme 19). Conduritol-F **13**, isolated by Plouvier from *Chrysanthemum leucanthemum* showed the specific rotation, $[\alpha]_D^{20} = +101.5$. This indicates that the natural conduritol-F **13** has D-configuration. The difference in the specific rotation values was not explained.

More recently, we discovered an efficient, stereospecific pathway leading to conduritol-F **13**[31] in which we used the bicyclic-endoperoxide **50** as the key intermediate. Our starting material, *trans*-benzene diacetate **14**[32] was synthesised as described in the literature. Photooxygenation of **3** afforded the bicyclic endoperoxide **50** in high yield. Selective reduction of the peroxide linkage was performed with thiourea[33] under very mild conditions giving **51** (Scheme 20). Since only the oxygen oxygen bond breaks in this reaction, the configuration at all four carbon atoms is preserved. Deacetylation of **51** gave pure conduritol-F **13**.



Scheme 20.

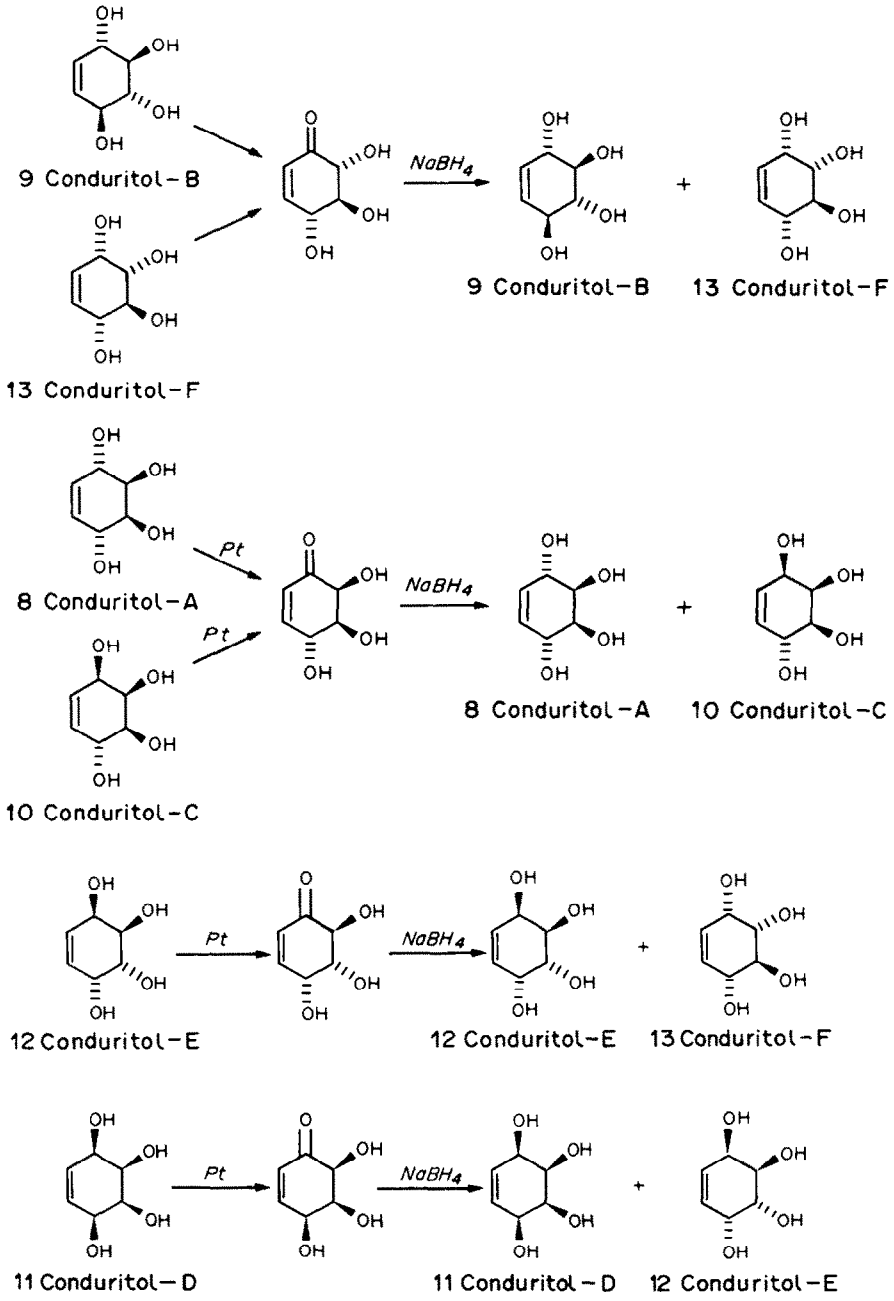
2.7. *Conduritol oxidation*

Paulsen *et al.*[34] have studied the catalytic oxidation of all the conduritol isomers A, B, C, D, E and F. Earlier studies concerning selective catalytic oxidation of polyhydroxy-cyclohexane derivatives have revealed that only axial hydroxyl groups are oxidised.[35] Equatorial hydroxyl groups are not attacked. If there is more than one axial hydroxyl group only one of them is oxidised. The catalytic oxidation of all conduritol isomers with oxygen in the presence of platinum catalyst proceeded smoothly giving the corresponding monoketo-derivatives (Scheme 21). Easy oxidation of conduritols can be explained on the basis of the formation of conjugated ketones. Reduction of these ketones with $NaBH_4$ provided conduritol isomers as expected.[36]

The oxidation of various inositol,[37] quercitol and cyclohexanetetrol[38] derivatives by resting cells of *Acetobacter suboxydans* have been studied by various groups. Only some conduritol isomers can be oxidised by *Acetobacter suboxydans*.

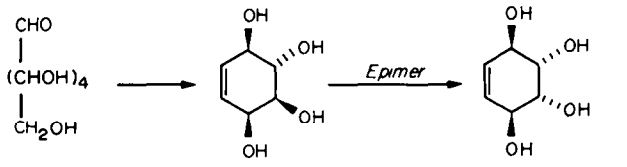
2.8. *Biosynthesis of conduritols in* Marsdenia *species*

The occurrence of cyclitols in plants has been studied using the method of photoassimilation in the atmosphere of $^{14}CO_2$: radioactive ^{14}C was incorporated into the conduritols.[39] Experiments with radioactively labelled precursors gave more insight into the mechanism of formation of conduritols. Infusion experiments with ^{14}C-labelled possible precursors of conduritol in *Marsdenia abyssinica*



Scheme 21.

showed the incorporation of D-glucose and D-galactose into the conduritol. The hexose molecules seem to be built into conduritol-A **8** as such without prior fragmentation.[40] L-Leuchanthemitol (conduritol-F **13**) is also incorporated into conduritol with a much better radiochemical yield than the two hexoses. These results suggest that the last step in the biosynthesis of conduritol-A **8** is the epimerisation of conduritol-F **13** to conduritol-A **8** (Scheme 22).



Scheme 22.

2.9. *Biological importance of conduritol derivatives*

Metabolism of benzene proceeds by enzyme-catalysed oxidation to benzene-oxide **52** which can then undergo either spontaneous isomerisation to phenol or enzyme-catalysed hydration to the dihydrodiol **17**. The role of diol-epoxides as carcinogens in the metabolic activation of polycyclic aromatic hydrocarbons is under detailed investigation.[41] Dihydrodiol **17**, by analogy with the dihydrodiols derived from polycyclic aromatic hydrocarbons, is a potential substrate for further enzyme-catalysed oxidation to diol epoxides **18** and **31**. Diol epoxides **18** and **31** are important precursors for conduritols[42] (see Schemes 4 and 9). Bacterial mutagenesis of **18** and **31** was measured by the *Salmonella typhimurium* forward mutation assay of Skopek *et al.*[43] Dihydrodiol **17** requires exogenous metabolism for mutagenic activity. Diol epoxide **18** was equally mutagenic in the presence or absence of an exogenous metabolising system, while **31** was inactive.[8]

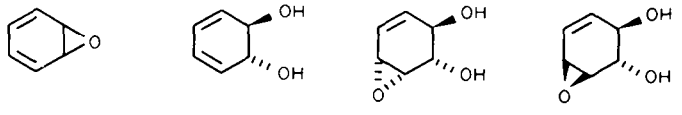


Fig. 3

Conduritol epoxides and aminoconduritols are inactivating inhibitors of several D-glycosidases, particularly the mammalian enzyme which cleaves glycosylceramide.[44] Epoxyconduritols with a configuration of their hydroxyl groups corresponding to that of the substrate glycose residue are potential active site directed inhibitors for glycohydrolases for two reasons.

(i) They can bond specifically by interaction with complementary groups of the substrate binding site and

(ii) the epoxide function can be activated by a suitably oriented acidic group, subsequently forming a covalent bond with a nucleophilic group at the catalytic site.[45]

Specific b-galactosidases, from *Escherichia coli* and from *Aspergillus wentii* and b-glycosidases that catalyse the hydrolysis of both galacto- and glyco-sides are readily inactivated by the *cis*-epoxyconduritol **53** but not by *trans*-epoxide **54**.[46]

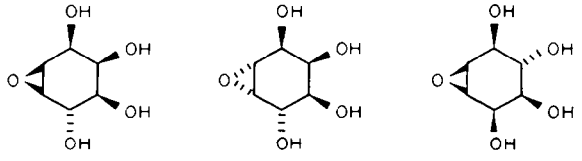
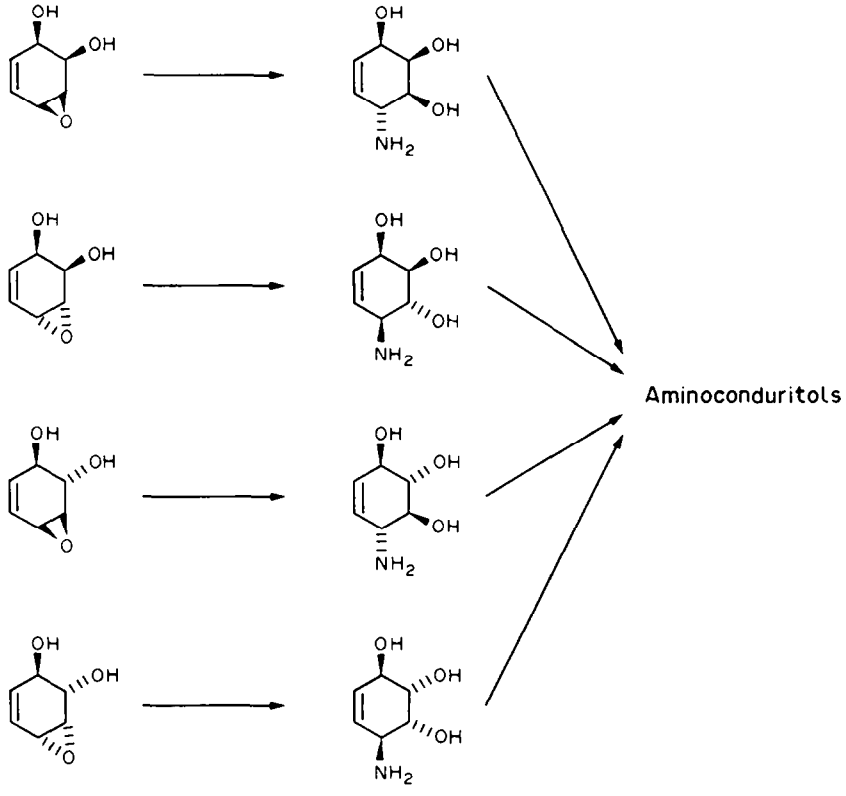


Fig. 4.

β-Glycosidases which are strictly specific for glycosides are not inhibited by *cis*-epoxide **53** or their reaction with **53** is several orders of magnitude slower than with conduritol-B **9** epoxide[47] with its configuration corresponding to that of glucose. More recently, it has been shown that b-mannosidase B (liver specific form) isolated from goat liver was inactivated by conduritol-F **13** epoxide[48] **55**.

3. AMINOCONDURITOLS

As mentioned in the preceding section the aminoconduritols show interesting inhibitor activity for some glycosidases. Synthesis of some aminoconduritols has been reviewed.[49] In this section we give a survey of the general synthetic ways leading to aminoconduritols. Nakajima *et al.*[50] have applied similar synthetic methodology as in the case of the synthesis of conduritols starting from *cis*- and *trans*-benzenediols. Epoxidation of *cis*- and *trans*-benzenediols gave two epoxy-diol isomers in both cases. Opening of the epoxide rings by NH_3 provided the corresponding aminoconduritols (Scheme 23). In all cases the other isomers are not formed because ammonia attacks the epoxide-ring at the allylic position.



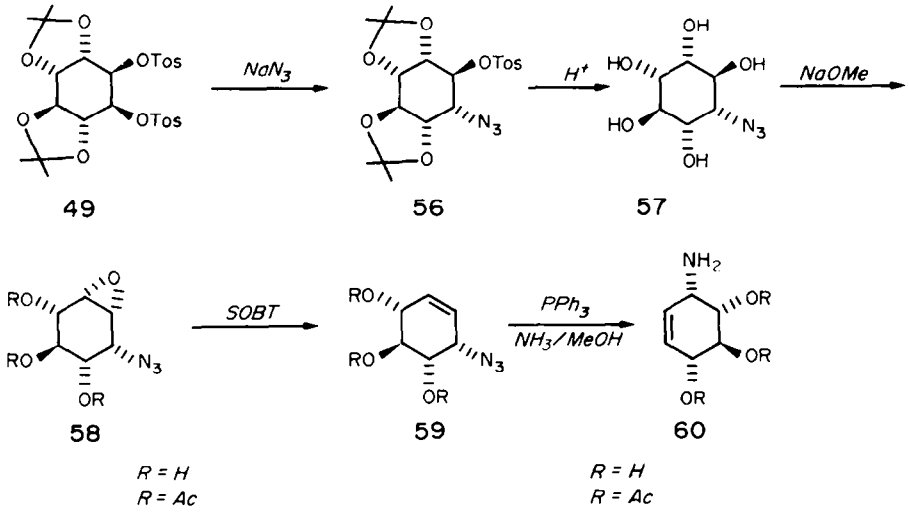
Scheme 23.

Aminoconduritols serve as important intermediates for the synthesis of aminoinositols.[50] For this conversion two different methods have been applied.

(i) *cis*-Hydroxylation of aminoconduritol tetra-acetates by $KMnO_4$ under neutral conditions and

(ii) *trans*-hydroxylation, by epoxidation of N-acetyl-aminoconduritols by perbenzoic acid, followed by hydrolysis of the epoxide ring by acid.[50,51]

Paulsen *et al.*[21] have synthesised optically active aminoconduritols from optically active starting materials (Scheme 19). The ditosylate **49** was synthesised as described. Selective displacement of the equatorial tosyloxy group by azide gave **56**. From **56**, the epoxide **58** and corresponding olefin **59** were synthesised. Treatment of **59** with triphenylphosphine gave the optically active aminoconduritol **60** (Scheme 24).



Scheme 24.

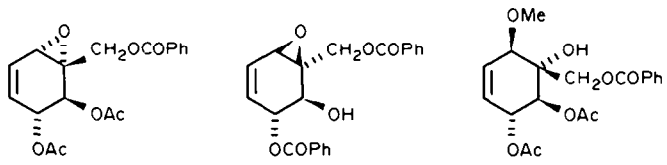
4. RELATED COMPOUNDS

In this section we do not intend to discuss all compounds related to the conduritols. We plan to discuss only those compounds which have four oxygen bonded substituents on a cyclohexene-ring and not six oxygen derivatives like inositol. Of the highly oxygenated cyclohexane derivatives, crotepoxide **61** first discovered by Kupchan *et al.*[52] is of biological interest. Crotepoxide **61** belongs to a small group of naturally occurring highly oxygenated cyclohexane derivatives. Crotepoxide **61** and newly discovered boesenoxide[53] **62** are members of this group which possess the diepoxide functionality.[54]

61 Crotepoxide **62 Boesenoxide**

Fig. 5.

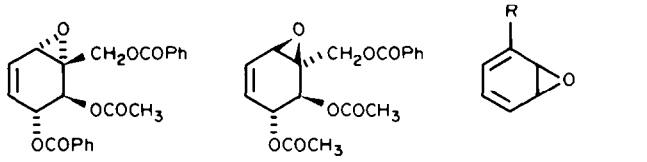
Plant metabolites like crotepoxide **61**, senepoxide **63**, pipoxide **64** belong to a family of highly oxygenated cyclohexane epoxides exhibiting interesting biological properties including tumour-inhibitory, antileukaemic and antibiotic activities.



63 Senepoxide **64** Pipoxide **65** Seneol

Fig. 6.

The crystalline compounds, senepoxide **63** and seneol **65** have been isolated from *Uvaria catocarpa* (Annonaceae).[55] Shortly after this, Atal *et al.* isolated a new compound, pipoxide **64** from the leaves of *Piper hookeri* L., the structure of which was proposed to be 1-benzoyloxy-methyl-2-benzoyl-3-hydroxy-1,6-epoxy-cyclohexene.[56] Later, a more abundant source for pipoxide was discovered in the leaves of *Uvaria purpurea*.[57] It has been shown that the proposed structure[56] by Atal *et al.* for pipoxide was not supported by NMR measurements. The correct structure was established by X-ray crystallography and total synthesis. Two new epoxides, tingtanoxide **66** and *β*-senepoxide **67** were recently added to this family.[58]



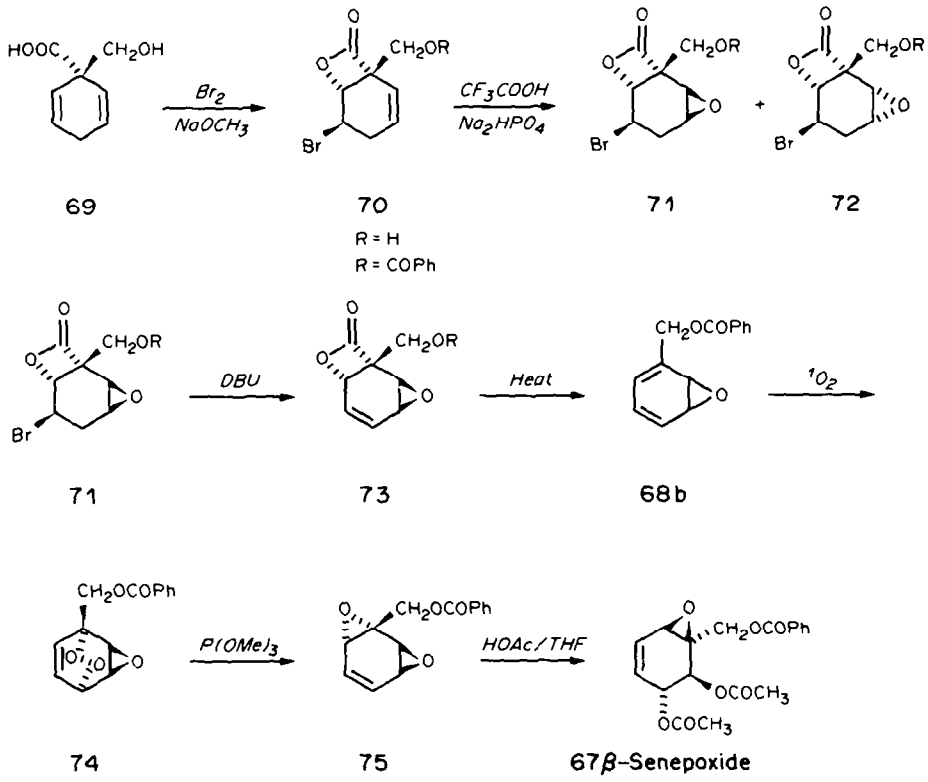
66 Tingtanoxide **67***β*–Senepoxide **68a** R = COOH
68b R = CH_2COOPh

Fig. 7.

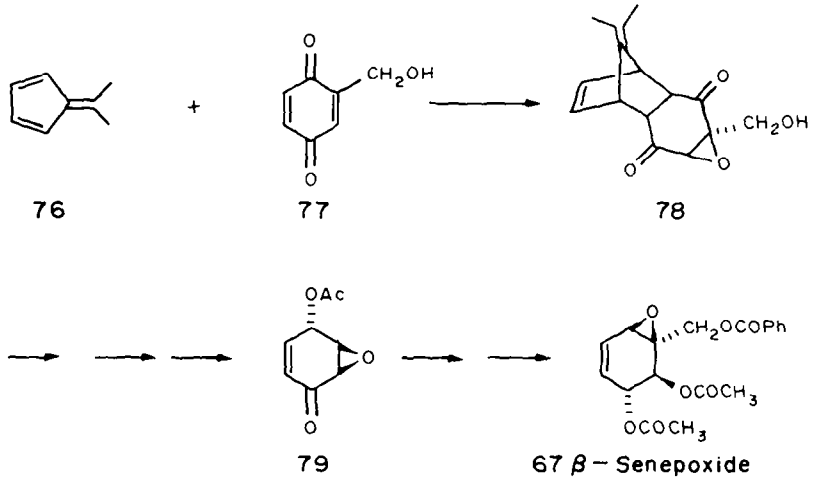
Holbert and Ganem postulated that arene oxides **68a**/**68b**[59] are the precursors in Nature, of senepoxide, crotepoxide and pipoxide and they have developed stereospecific synthesis of senepoxide **63** in accordance with their biogenetic plan (Scheme 25).[60] The conversion of **75** to senepoxide **67** necessitated a selective acid-catalysed *trans*-opening of the epoxide ring. Optimum conditions for selective opening utilized 1 : 1 THF-10% aqueous HOAc whereupon **67** was formed (32%) with the isomeric diol and tetrol.

The first stereospecific synthesis of DL-senepoxide **67** was carried out by Ichihara *et al.*[61] (Scheme 26). Diels–Alder reaction of 2-hydroxymethyl-1,4-benzoquinone with dimethylfulvene and subsequent epoxidation gave **78** which after sequential reduction, benzoylation, and acetylation underwent a retro-Diels–Alder reaction giving the epoxy-cyclohexenone **79**. Sequential epoxidation, reductive cleavage of the epoxide ring, and acetylation gave the senepoxide **67**, identical with that isolated from *Uvaria catocarpa*.

More recently, during the course of investigation of the methanol extracts of the roots of *Uvaria zeylenica* L. (Annonaceae) for tumour inhibitory constituents, two new crystalline compounds (−)zeylenol **80** and zeylena **81** were isolated.[62] Both compounds were found inactive in the P-338 lymphocytic leukaemia test system. The assignment of stereochemistry to zeylenol, originally based on NMR studies was conclusively established by its partial synthesis from (+)pipoxide **64**.[63] Thus (+)pipoxide was hydrolysed in a two phase system (97% H_2SO_4—CH_2Cl_2) giving (−)-zeylenol (30%).



Scheme 25.

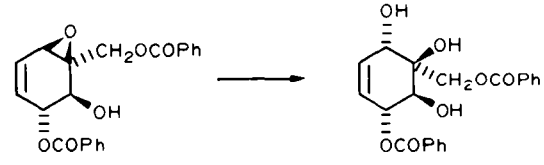


Scheme 26.

80 Zeylenol 81 Zeylena

Fig. 8.

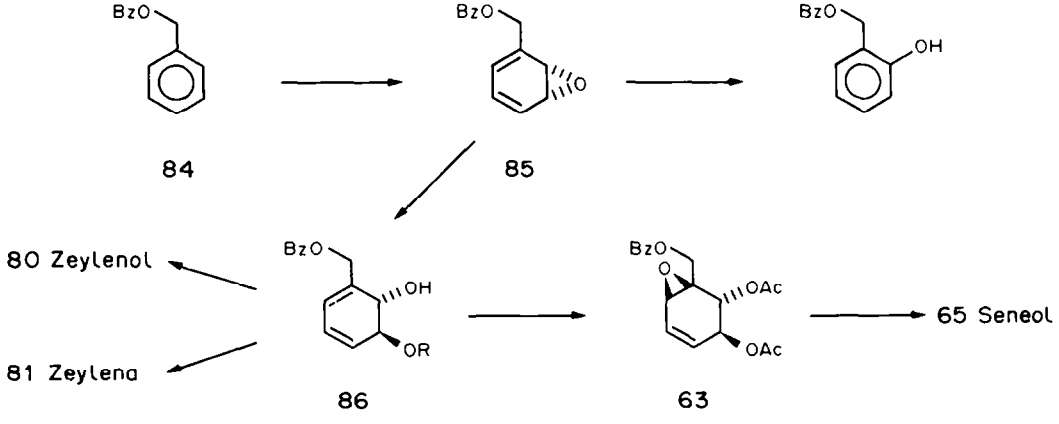
More recently, Tuntiwachwuttikul *et al.*[53] isolated (+)zeylenol from a chloroform extract of the rhizomes of a *Boesenbergia* species (Zingiberaccae). Zeylenol isolated from *Uvaria zeylenica* L. has a negative rotation $[\alpha]^{25} = -116.3^{\circ}$. However, zeylenol isolated from Boesenbergia has positive rotation $[\alpha]^{25} = +113.5^{\circ}$ and their circular dichroism curves were opposite in sign. During an investigation of the methanol extract of the roots of *Uvaria zeylenica* L. a third inactive compound was isolated which was isomeric with zeylenol. This new compound was named 1-epizeylenol[64] **83**.



64 Pipoxide 80 (−) Zeylenol

Scheme 27.

The finding of zeylenol **80** and zeylena **81** in a *Uvaria* species makes clear the biogenetic routes to some related substances found in this genus. Ganem[59] put forward an ingenious scheme to rationalise this biogenetic pathway in terms of cyclohexene oxides and their cleavage products (Scheme 28). Benzyl benzoate **84** is epoxidised to the key intermediate **85**. Compound **85** adds (*E*)-



Scheme 28.

cinnamic acid giving **86** which then undergoes an intramolecular Diels Alder reaction giving zeylena **81**. Compound **85** also adds water, acetic acid, or benzoic acid and becomes further epoxidised, eventually giving three other natural products: zeylenol **80**, senepoxide **67** and seneol **65**. This proposal was supported strongly by the discovery and structural elucidation of (−)1,6-desoxypipoxide **87**,[65] a key intermediary metabolite isolated from *Uvaria purpurea*. This intermediate metabolite may be envisioned as arising by the addition of benzoic acid to **85**.

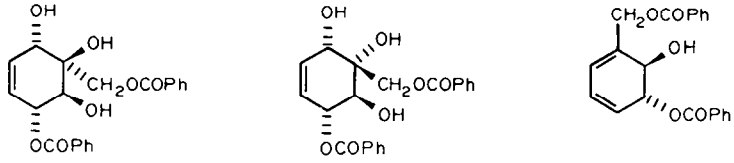


Fig. 9.

Shortly after this, further diene intermediates **88** and **89** together with their epoxidised products, β-senepoxide **67** and tingtanoxide **66**, from *Uvaria ferruginea* (Annonaceae) or 'Ting-tang' as the plant is known in Thailand,[66] were discovered.

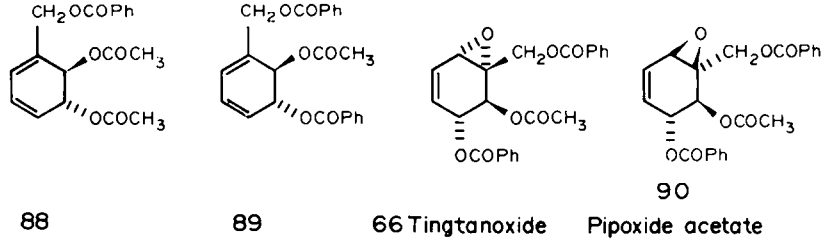
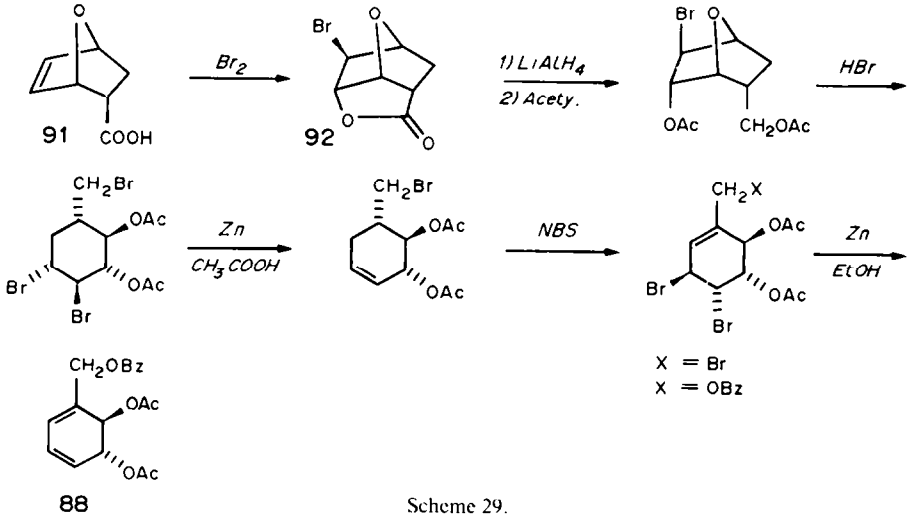


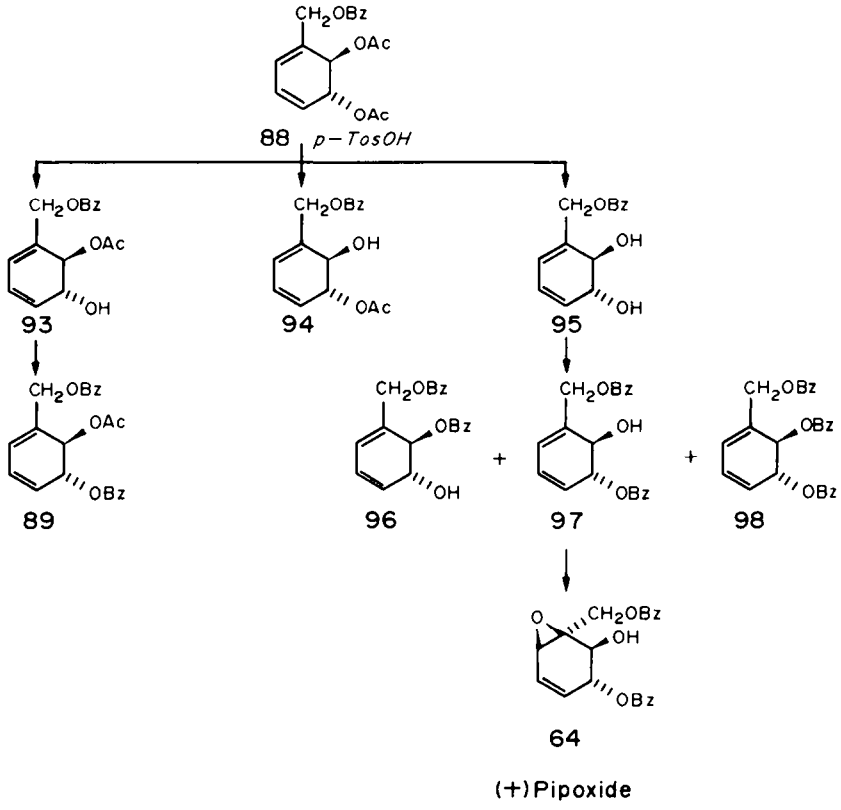
Fig. 10.

Acetylation of (−)1,6-desoxypipoxide **87** of known absolute stereochemistry[65] afforded the diene **89** identical with the natural product. Epoxidation of the natural product **89** yields tingtanoxide **66** and pipoxide acetate **90**. Furthermore, epoxidation of the diene **88** gave β-senepoxide **67** and senepoxide **63**.



Scheme 29.

Optically active **88**, a diene precursor in the biosynthesis of highly oxygenated cyclohexene epoxides has been synthesised by Ogawa and Takagaki[67] starting from the bromolactone **92** derived from (1*S*)-endo-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid **91**[68] and adapting the procedure formerly used for the preparation of racemic **88**[69] (Scheme 29). Selective O-deacetylation of **88** was carried out with *p*-toluenesulfonic acid in methanol giving two monoacetates **93**, **94** and the dihydroxy-compound **95**. Compound **93** was benzoylated giving the dibenzoate which was identical with the natural product **89**.[66] Selective benzoylation of **95** afforded two dibenzoates **96** and **97** as well as the tribenzoate **98**. Direct epoxidation of **97** gave crystalline (+)pipoxide **64** (Scheme 30).



Scheme 30.

Another new metabolite, ferrudiol[70] **100**, possessing a polyoxygenated cyclohexane skeleton was isolated in Thailand from *Uvaria ferruginea*. More recently streptol[71] **101**, a plant growth regulator, was isolated from a culture filtrate of an unidentified *Streptomyces* sp. Streptol **101** inhibited the root growth of lettuce seedlings at a concentration above 13 ppm. Some other isomeric compounds **102** and **103** have been synthesised.[72]

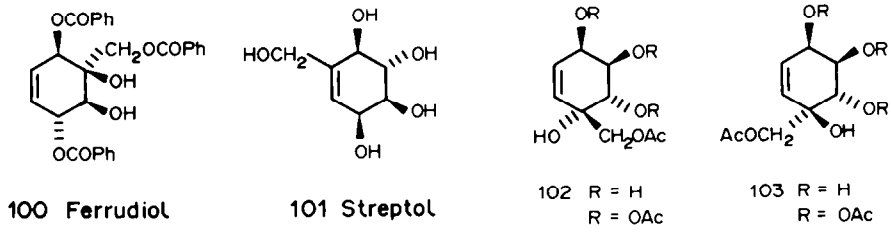
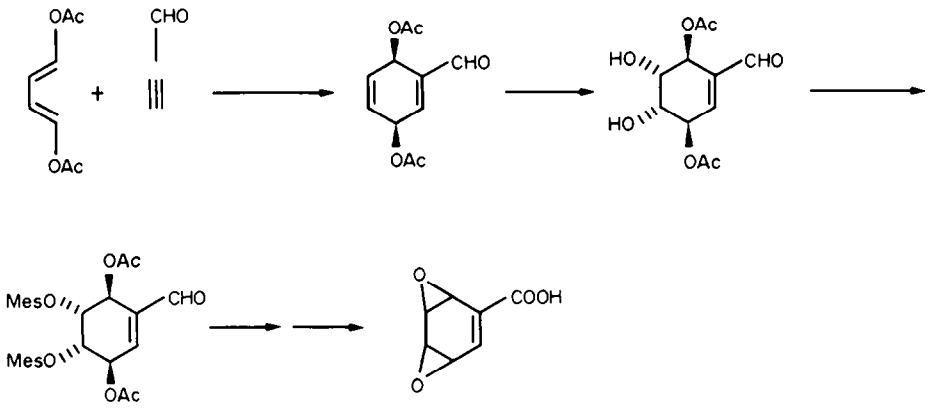


Fig. 11.

A completely different synthetic route to cyclohexenetetrol derivatives was developed by Vogel *et al.*[73] in the course of the synthesis of benzenedioxide (Scheme 31).

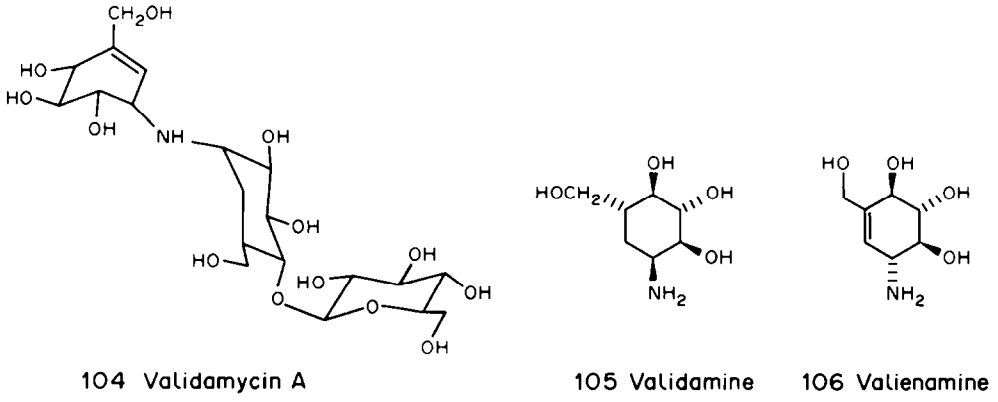


Scheme 31.

Naturally occurring cyclohexene oxides have been reviewed by Thebtaranonth *et al.*[74]

5. DERIVATIVES OF AMINOCYCLITOLS

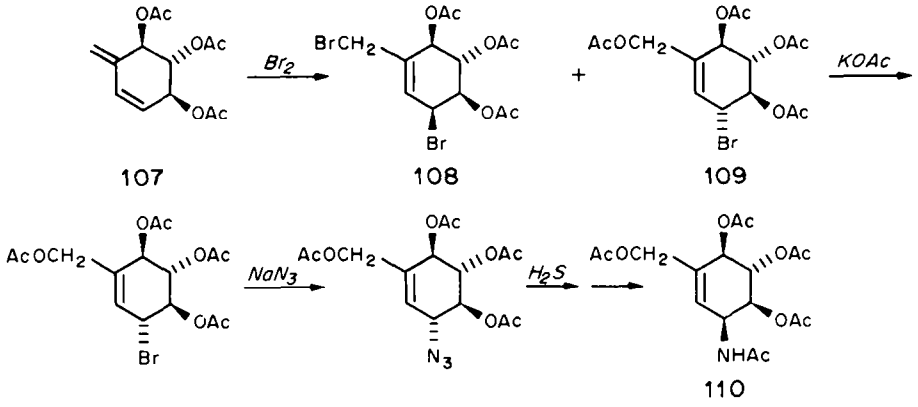
Validamycin A[75] **104** is the major and most active component of the antibiotic validamycins, produced by *Streptomyces hygroscopicus* var. *limoneus* and widely used to control sheath blight in rice plants.



104 Validamycin A 105 Validamine 106 Valienamine

Fig. 12.

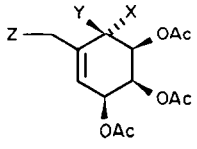
Microbial degradation of validamycin A with a cell suspension of *Pseudomonas denitrificans* gave validamine[76] **105** and the unsaturated aminocyclitol valienamine[77] **106**. Valienamine **106** itself has been found to show both the a-glycosidase inhibition and antibiotic activity against *Bacillus* species.[78] The synthesis of penta-N,O-acetyl-DL-valienamine was described recently by Suami *et al.*[79] Treatment of the readily available tri-O-acetyl-DL-(1,3/2)-4-methylene-5-cyclohexene-1,2,3-triol[77] **107** with bromine in acetic acid at room temperature gave **108** and **109**. These dibromides were converted easily to valienamine **106** (Scheme 32).

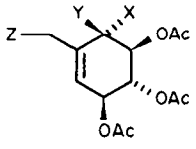


Scheme 32.

From the dibromides **108** and **109** several branch-chain unsaturated cyclitols, related to the biologically interesting valienamine **106**[80] were selectively prepared.

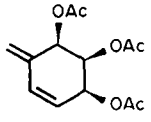
Table 1.



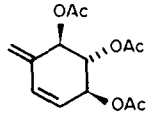


X	Y	Z	X	Y	Z
H	Br	Br	H	Br	Br
Br	H	Br	Br	H	Br
N_3	H	N_3	OAc	H	Br
NHAc	H	NHAc	H	OAc	Br
OAc	H	Br	N_3	H	N_3
OAc	H	OAc	NHAc	H	NHAc
OAc	H	N_3	H	N_3	N_3
OAc	H	NHAc	OAc	H	N_3
H	OAc	Br	OAc	H	NHAc
H	OAc	OAc	Br	H	OAc
H	OAc	Br			

Starting from the two isomers **107**[81] and **111**[82] many related compounds have also been synthesised successfully.



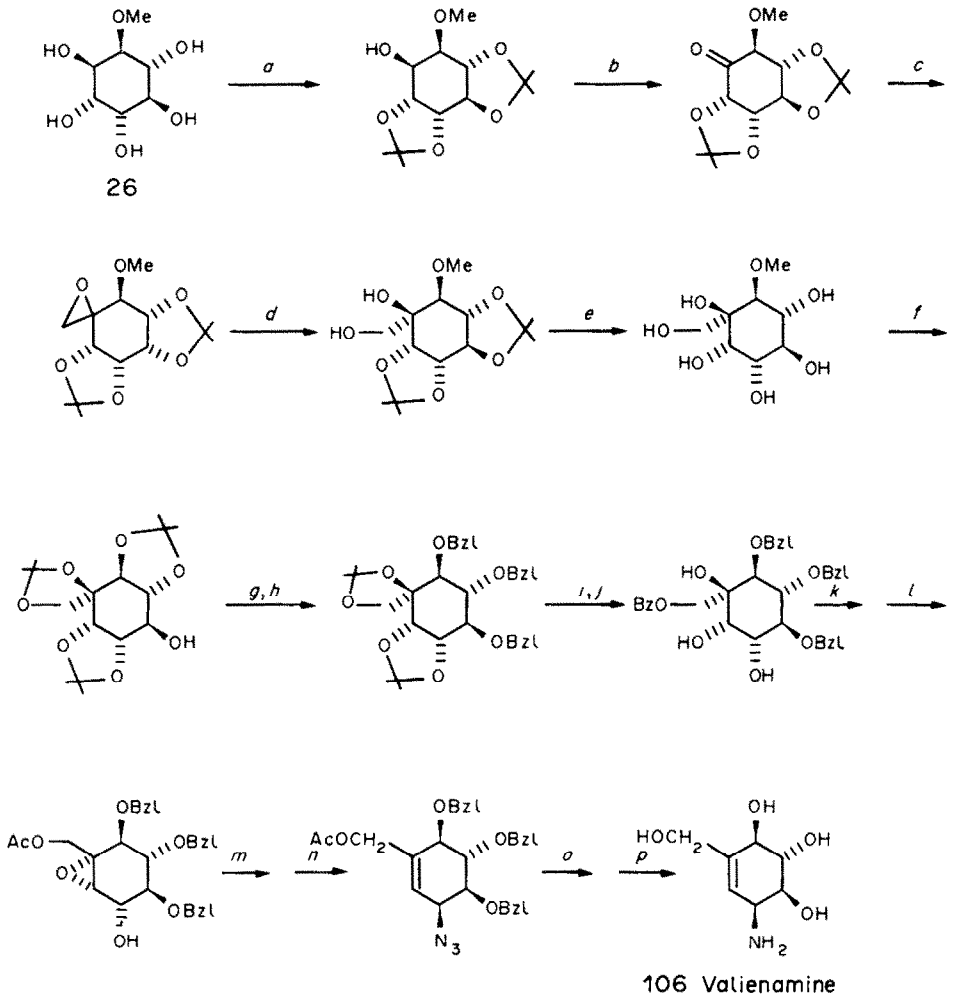
111



107

Fig. 13.

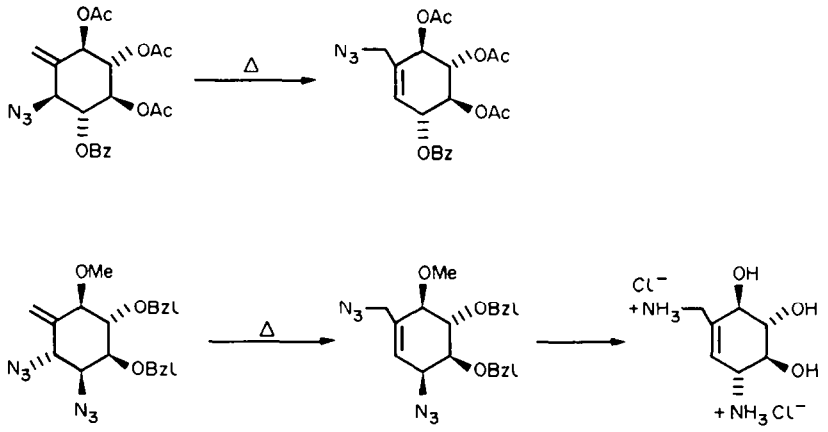
Optically active valienamine **106** was also synthesised by Paulsen and Heiker[83] using a different approach from that described by Suami *et al.*[79] Quebrachitol was used as the optically active starting material (Scheme 33).



Scheme 33.
(a) $CH_3C(OCH_3)_2CH_3$, (b) RuO_4, $NaIO_4$, (c) $(CH_3)_2CSO_2CH_2Li$, (d) OH^-, (e) BF_3, (f) $CH_3C(O\text{-}CH_3)_2CH_3$, (g) selective hydrolysis, (h) Base/Benzylchloride, (i) Hydrolysis, (j) Benzoylation, (k) selective mesylation, (l) NaOEt, (m) NaI, $POCl_3$, (n) HN_3, PPh_3, ROOC—N=N—COOR, (o) PPh_3, hydrolysis (p) Na/NH_3

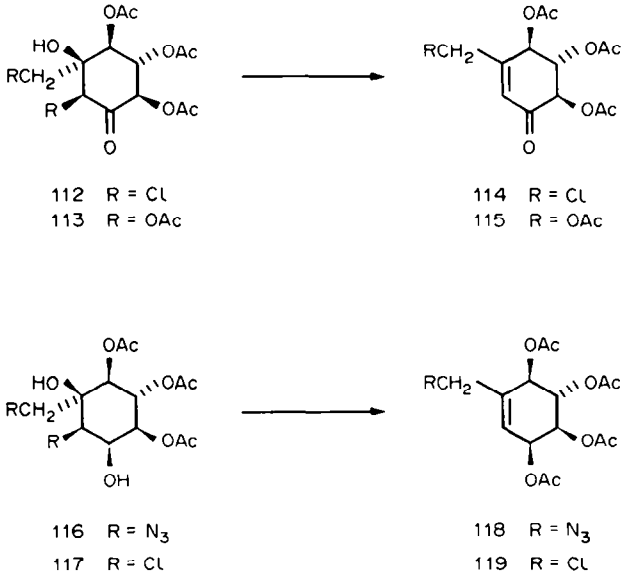
Paulsen and Heiker[84] have used [1.3]sigmatropic rearrangements successfully for the synthesis of 7-amino-valienamine **106** and other conduritol derivatives.[84]

[1.3]Sigmatropic rearrangements occur easily in inositol derivatives bearing an exocyclic methylene group when a substituent capable of migration occupies a position vicinal to the double bond. This rearrangement leads to a thermodynamically more stable product having an endocyclic double bond. With suitable substrates, this effectively transposes the double bond into the ring and the substituent onto the side-chain. Some of the aminoconduritol isomers which have been synthesised in this way are given (Scheme 34).



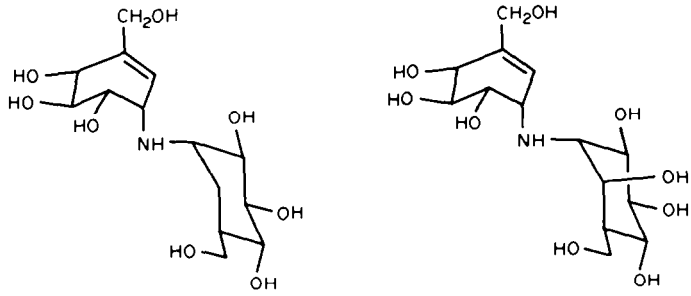
Scheme 34.

Another synthetic approach leading to side-branched conduritol derivatives was developed by Riordan and Kiely[85] starting from chloromethyl cyclose **112** and acetoxymethylcyclose **113**. Each underwent regiospecific loss of water giving α-β-unsaturated cyclohexanone derivatives **114** and **115** (Scheme 35). Electron withdrawing azido substituents on the cyclitol **116** and **117** promoted the base-catalysed regiospecific elimination yielding **118** and **119** (Scheme 35).



Scheme 35.

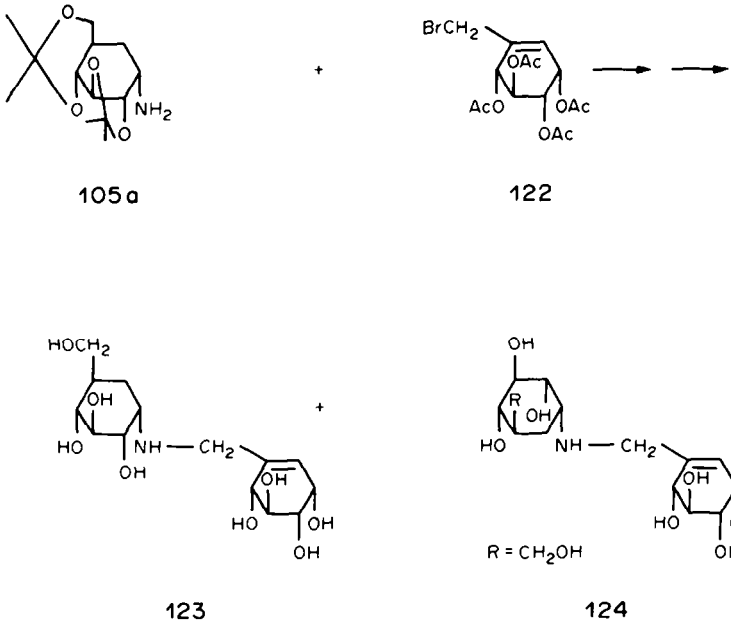
Validoxylamine A[86] **120** was first isolated from the hydrolysate of the antibiotic validamycin A with sulphuric acid. It was later found to be present in the fermentation broth of *Streptomyces hygroscopicus* var. *limoneus*.[87] It shows a very low activity compared to the parent validamycin A, in the dendrite test method but exhibited considerable activity in the green house test.[87] Some



120 Validoxylamine A 121 Validoxylamine B

Fig. 14.

isomers of validoxylamine A **120** have been synthesised by Suami *et al.*[88] in order to study structure - activity relationships of this type of pseudo-disaccharide. For this purpose, the blocked DL-validamine **105a** was condensed with the allyl bromide **122** to give a mixture of **123** and **124** (Scheme 36).

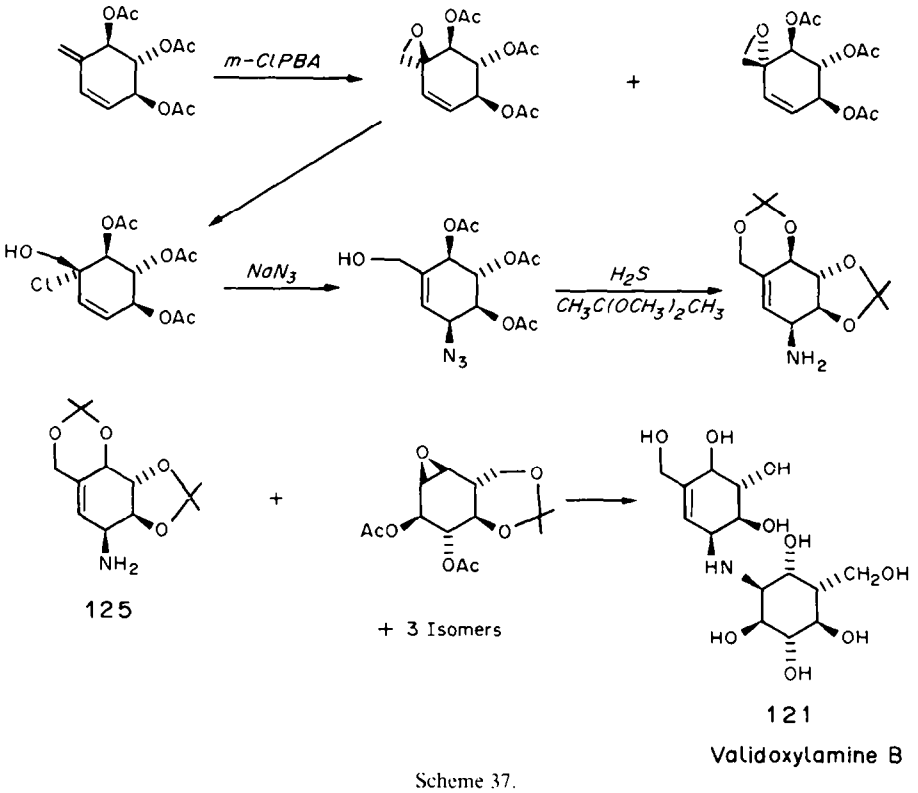


105a 122

123 124

Scheme 36

Validoxylamine B[87], which was first isolated by acid hydrolysis of the antibiotic validamycin B and was isolated also from the fermentation broth of *Streptomyces hygroscopius* var. *limoneus*, was recently synthesised by Ogawa *et al.*[89] The key compound in their total synthesis was the di-O-isopropylidene derivative of DL-valienamine **125** prepared by the reaction sequence (Scheme 37).



Scheme 37.

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REFERENCES

1. Kübler, K. *Arch. Pharm.* **1908,** *346*, 620
2. For conduritol isolation see: [a]Kern, W.; Fricke, W. *Pharm Zentralhalle* **1939,** *80*, 349–352; [b]Manni, P. E.; Sinsheimer, J. E. *J. Pharm. Sci.* **1965,** *54*, 1541; [c]Dominguez, X. A.; Marroquin, J.; Olguin, L. M.; Morales, F.; Valdez, V. *Phytochemistry* **1974,** *13*, 2617–2618.
3. [a]Dangschat, G.; Fischer, H. O. L. *Naturwissenschaften* **1939,** *27*, 756–757; [b]For structure determination see also: Kern, W.; Fricke, W.; Steger, H. *Arch. Pharm.* **1940,** *278*, 145–156; [c]For Proton Magnetic Resonance Spectra and Conformations of the conduritols see: Abraham, R. J.; Gottschalck, H.; Thomas, W. A. *J. Chem. Soc.* **1965,** 6268–6277
4. Dangschat, G.; Fischer, H. O. L. *Carbohydr. Res.* **1987,** *164*, 343–355.
5. McCasland, G. E.; Horswill, E. C. *J. Am. Chem. Soc.* **1953,** *75*, 4020–4026.
6. Nakajima, M.; Tomida, I.; Takei, S. *Chem. Ber.* **1957,** *90*, 246–250.
7. Knapp, S.; Ornof, R. M.; Rodriques, K. E. *J. Am. Chem. Soc.* **1983,** *105*, 5494–5495
8. Aleksejczyk, R. A.; Berchtold, G. A. *J. Am. Chem. Soc.* **1985,** *107*, 2554–2555.
9. Platt, K. L.; Oesch, F. *Synthesis* **1977,** *7*, 449–450.
10. [a]Sütbeyaz, Y.; Seçen, H.; Balci, M. *J. Chem. Soc., Chem. Commun.* **1988,** 1331–1332; [b]Carless, H. A. J.; Oak, O. Z. *Tetrahedron Lett.* **1989,** *30*, 1719–1720.
11. Yang, N. C.; Chen, M. J.; Chen, P. *J. Am. Chem. Soc.* **1984,** *106*, 7310–7317.
12. Posternak, T.; Friedli, H. *Helv. Chim. Acta* **1953,** *36*, 251.
13. [a]Ley, S. V.; Sterfeld, F.; Taylor, S. *Tetrahedron Lett.* **1987,** *28*, 225–228; [b]Ballard, D. G. H.; Courtis, A.; Shirley, I. M.; Taylor, S. C. *J. Chem. Soc., Chem. Commun.* **1983,** 954–955.
14. [a]Muller, H. *J. Chem. Soc.* **1907,** *91*, 1790; [b]Müller, H. *J. Chem. Soc.* **1912,** *101*, 2383.

15. McCasland, G. E.; Horswill, E. C. *J. Am. Chem. Soc.* **1953,** *75*, 4020–4026.
16. Bedos, P.; Ruyer, A. *Compt. rend.* **1933,** *196*, 625.
17. Nagabhushan, T. L. *Can. J. Chem.* **1970,** *48*, 383–384.
18. Corey, E. J.; Winter, R. A. E. *J. Am. Chem. Soc.* **1963,** *85*, 2677.
19. Angyal, S. Y.; Tate, M. E.; Gero, S. D. *J. Chem. Soc.* **1961,** 4116.
20. Lee, K. J.; Boyd, S. F.; Radin, N. S. *Carbohyd. Res.* **1985,** *144*, 148–154.
21. Paulsen, H.; Röben, W.; Heiker, F. R. *Chem. Ber.* **1981,** *114*, 3242–3252.
22. [a]Calo, V.; Lopez, L.; Mincuzzi, A.; Pesce, G. *Synthesis* **1976,** 200; [b]Paulsen, H.; Heiker, F. R.; Feldmann, J.; Heyns, K. *Synthesis* **1980,** 636.
23. McCasland, G. E.; Reeves, J. M. *J. Am. Chem. Soc.* **1955,** *77*, 1812–1814.
24. Yurev, Y. K.; Zefirov, N. S. *Zh. Obshchei Khim.* **1961,** *31*, 685–686.
25. Angyal, S. J.; Gilham, P. T. *J. Chem. Soc.* **1955,** 375–379.
26. Criegee, R.; Becher, P. *Chem. Ber.* **1957,** *90*, 2516–2521.
27. Tipson, T. *Carbohydr. Chem.* **1953,** 8, 201.
28. Nakajima, M.; Tomida, I.; Takei, S. *Chem. Ber.* **1959,** *92*, 163–172.
29. Kindl, H.; Hoffmann-Ostenhof, O. *Fortschrit. Chem. Organ. Naturst.* **1966,** *24*, 149.
30. Plouvier, V. *C.r. hebd. Se'Acad. Sci.* Paris **1962,** *225*, 360.
31. Seçen, H.; Sütbeyaz, Y.; Balcı, M. *Tetrahedron Lett.* in press.
32. Demuth, M. R.; Garret, P. E.; White, J. D. *J. Am. Chem. Soc.* **1976,** *98*, 634–635.
33. Balcı, M. *Chem. Rev.* **1981,** *81*, 91.
34. [a]Heyns, K.; Paulsen, H. *Chem. Ber.* **1953,** *86*, 333; [b]Heyns, K.; Paulsen, H. *Chem. Ber.* **1956,** *89*, 1152.
35. Post, G. G.; Anderson, L. *J. Am. Chem. Soc.* **1956,** *84*, 1152.
36. Heyns, K.; Gottschalck, H.; Paulsen, H. *Chem. Ber.* **1962,** *95*, 2660.
37. [a]Magasanik, B.; Chargaff, E. *J. Biol. Chem.* **1948,** *174*, 173; [b]Magasanik, B.; Ranzl, R. E.; Chargaff, E. *J. Am. Chem. Soc.* **1952,** *74*, 2618; [c]Posternak, T.; Reymond, D. *Helv. Chim. Acta* **1953,** *36*, 260; [d]Posternak, T., Ravenna, F. *Helv. Chim. Acta* **1947,** *30*, 441.
38. [a]Anderson, L., Takeda, R., Angyal, S. Y.; Mueltugh, D. *J. Arch. Biochem. Biophys.* **1958,** *78*, 518–531; [b]Posternak, T.; Reymond, D. *Heh. Chim. Acta* **1955,** *38*, 195–205.
39. [a]Kindl, H.; Hoffmann-Ostenhof, O. *Phytochemistry* **1966,** 1091–1102; [b]Kindl, H.; Hoffmann-Ostenhof, O. *Monatsh. Chem.* **1966,** *97*, 1778–1782; [c]Kindl, H.; Hoffmann-Ostenhof, O. *Monatsh. Chem.* **1966,** *97*, 1783–1788.
40. [a]Wober, G.; Hoffmann-Ostenhof, O. *Monatsh. Chem.* **1969,** *100*, 369–375; [b]Kindl, H., Hoffmann-Ostenhof, O. *Monatsh Chem.* **1970,** *101*, 1704–1711.
41. [a]Jerina, D. M.; Daly, J. W.; Witkop, B.; Zaltzmann-Nierenberg, P.; Udenfreid, S. *Arch. Biochem. Biophys.* **1968,** *128*, 176–183; [b]Jerina, D. M.; Daly, J. M. *Science* (Washington DC) **1974,** *185*, 573–582; [c]Oesch, F.; Bentley, P.; Platt, K. L.; Galan, D. M. *Arch. Biochem. Biophys.* **1980,** *199*, 538–544; [d]Sato, T., Fukuyama, T., Suzuki, T., Yoshikowa, H. *J. Biochem* **1963,** *53*, 23–27.
42. Ferrel, J. E. Jr; Loew, G. H. *J. Am. Chem. Soc.* **1979,** *101*, 1385.
43. Skopek, T. R.; Liber, H. L.; Krolewski, J. J.; Thilly, W. G. *Proc. Natl. Acad. Sci. U.S.A.* **1978,** *75*, 410–414.
44. [a]Legler, G., Bause, E. *Carbohyd. Res.* **1973,** *28*, 45; [b]Legler, G.; Lotz, W.; *Hoppe-Seyler's Z. Physiol. Chem.* **1973,** *354*, 243.
45. Legler, G. *Methods Enzymol.* **1977,** *46*, 368–381.
46. Legler, G.; Herrchen, M. *FEBS Lett.* **1981,** *135*, 139–144.
47. Legler, G. *Moll. Cell. Biochem.* **1973,** *2*, 31–38.
48. Cavanagh, K. T.; Fischer, R. A.; Legler, G.; Herchen, M.; Jones, M. Z.; Julich, E.; Sewell-Alger, R. P.; Sinnoth, M. L., Wilkinson, F. E. *Enzyme* **1985,** *34*, 75–82.
49. Posternak, T. *The Cyclitols* Hermann, Paris, 1965.
50. Nakajima, M.; Hasegawa, A.; Kurihara, N. *Chem. Ber.* **1962,** *95*, 2709–2713.
51. [a]Nakajima, M.; Kurihara, N. *Chem. Ber.* **1961,** *94*, 515–523; [b]Nakajima, M., Hasegawa, A.; Kurokawa, T. *Ann. Chem.* **1965,** *689*, 299–234; [c]Nakajima, M.; Hasegawa, A., Kurokawa, T. *Ann. Chem.* **1965,** *689*, 235–242; [d]Nakajima, M., Kurihara, N., Hasegawa, A.; Kurokawa, T. *Ann. Chem.* **1965,** *689*, 243–247.
52. [a]Kupchan, S. M.; Hemingway, R. J., Coggon, P., Mephail, A. T., Sim, G. A. *J. Am. Chem. Soc.* **1968,** *90*, 2982; [b]Kupchan, S. M.; Hemingway, R. J.; Smith, R. M. *J. Org. Chem.* **1969,** *34*, 3898; [c]Takahashi, S. *Phytochemistry.* **1969,** *8*, 321; [d]Pancharoen, O.; Patrick, V. A., Reutrakul, V. Tuntiwachwuttikul, P.; White, A. H. *Aust. J. Chem.* **1984,** *37*, 221; [e]Oda, K.; Ichiara, A., Sakamura, S. *Tetrahedron Lett.* **1977,** 2467–2470.; [f]Demuth, M. R.; Garratt, P. E., White, J. D. *J. Am. Chem. Soc.* **1976,** *98*, 634; [g]Matsumote, M.; Dobashi, S., Kuroda, K. *Tetrahedron Lett.* **1977,** 3361–3364.
53. Tuntiwachwuttikul, P.; Pancharoen, O.; Bubb, W. A., Hambley, T. W.; Taylor, W. C., Reutrakul, V. *Aust. J. Chem.* **1987,** *40*, 2049–2061.
54. For a review on Cyclic Polyepoxides see. Adam, W., Balcı, M. *Tetrahedron*, **1980,** *36*, 833–858.
55. [a]Hollands, R., Becher, D.; Gaudemer, A.; Polansky, J.; Rieroch, N. *Tetrahedron* **1968,** *24*, 1633–1650; [b]Ducruix, A., Pascard, C., Polansky, J. *Acta Cryst. (B)* **1976,** *32*, 1589.
56. [a]Singh, J.; Dhar, K. L., Atal, C. K. *Tetrahedron* **1970,** *26*, 4403–4406; [b]Singh, J.; Dhar, K. L.; Atal, C. K. *Curr. Sci. India* **1969,** *38*, 471; Singh, J.; Atal, C. K. *Indian J. Pharm.* **1969,** *31*, 129–130.
57. Holbert, G. W.; Ganem, B., Eugen, D. V., Clardy, J., Borsub, L., Chantrapromma, K.; Sadavongvivad, C.; Thebtaranonth, Y. *Tetrahedron Lett.* **1979,** 715–718.
58. Kopimd, M., Sadavongvivad, C.; Thebraranonth, C.; Thebtaranonth, Y. *Tetrahedron Lett.* **1983,** *24*, 2019–2022.
59. Ganem, B., Holbert, G. W.; *Biorg. Chem.* **1977,** *6*, 393.

60. [a]Holbert, G. W.; Ganem, B. *J. Am. Chem. Soc.* **1978,** *100*, 352–353; [b]Ganem, B.; Holbert, G. W.; Weiss, L. B.; Ishizumi, K. *J. Am. Chem. Soc.* **1978,** *100*, 6483.
61. Ichiara, A.; Oda, K.; Kobayashi, M.; Sakamura, S. *Tetrahedron Lett.* **1974,** 4235–4238.
62. Jolad, S. D.; Hoffmann, J. J.; Schram, K. H.; Cole, J. R.; Tempesta, M. S.; Bates, R. B. *J. Org. Chem.* **1981,** *46*, 4267–4272.
63. Schulte, G. R., Ganem, B. *Tetrahedron Lett.* **1982,** *23*, 4299–4302.
64. Jolad, S. D.; Hoffmann, J. J.; Cole, J. R.; Tempesta, M. S.; Bates, R. B. *Phytochemistry* **1984,** *23*, 935.
65. Schulte, G. R.; Kodpinid, M.; Thebtaranonth, C.; Thebtaranonth, Y. *Tetrahedron Lett.* **1982,** *23*, 4303–4304.
66. Kodpinid, M.; Sadavongvivad,C.; Thebtaranonth, C.; Thebtaranonth, Y. *Tetrahedron Lett.* **1983,** *24*, 2019–2022
67. Ogawa, S.; Takageki, T. *J. Org. Chem.* **1985,** *50*, 2356.
68. [a]Suami, T.; Ogawa, S.; Nakamoto, K.; Kasahara, I. *Carbohyd. Res.* **1977,** *58*, 240; [b]Ogawa, S.; Iwasawa, Y.; Suami, T. *Chem. Lett.* **1984,** 355; [c]Ogawa, S.; Iwasawa, Y.; Noso, T.; Suami, T.; Ohbo, S.; Ito, M.; Saito, Y. *J. Chem. Soc. Perkin Trans* 1, **1985,** 903.
69. [a]Ogawa, S.; Toyokuni, T.; Ara, M.; Suetsuge, M.; Suami, T. *Chem. Lett.* **1980,** 379; [b]Ogawa, S.; Toyokuni, T.; Ara, M.; Suetsuge, M.; Suami, T. *Bull. Chem. Soc. Jpn* **1983,** *56*, 1710.
70. Schulte, G. R.; Ganem, B.; Chantrapomma, K.; Kodpinid, M.; Sudsuansri, K. *Tetrahedron Lett.* **1982,** *23*, 289.
71. Isogai, A.; Sakude, S.; Nakayama, J.; Watanabe, S.; Suzuki, A. *Agric. Biol. Chem.* **1987,** *51*, 2277–2279.
72. [a]Ogawa, S., Shibata, Y. *Carbohyd. Res.* **1986,** *156*, 273–281; [b]Ogawa, S.; Tsukiboshi, Y.; Iwasawa, Y.; Suami, T. *Carbohyd. Res.* **1985,** *136*, 77–89.
73. Altenbach, H.-J.; Voss, B.; Vogel, E. *Angew. Chem.* **1983,** *95*, 424–426.
74. Thebtaranonth, C.; Thebtaranonth, Y. *Acc. Chem. Res.* **1986,** *19*, 84–90.
75. [a]Iwasa, T.; Yamamoto, H.; Shibata, M. *J. Antibiot.* **1970,** *23*, 595; [b]Horii, S.; Kameda, Y. *J. Chem. Soc., Chem. Commun.* **1972,** 747; [c]Suami, T.; Ogawa, S.; Chida, N. *J. Antibiot.* **1980,** *33*, 98.
76. Ogawa, S.; Shibata, Y., Chida, N.; Suami, T. *Chem. Lett.* **1980,** 135.
77. Kameda, Y.; Horii, S. *J. Chem. Soc., Chem. Commun.* **1972,** 746.
78. Kameda, Y.; Asao, N.; Yoshikawa, M.; Matsui, K. *J. Antibiot.* **1980,** *33*, 1575.
79. Ogawa, S., Toyokuni, T.; Suami, T. *Chem. Lett.* **1980,** 713–716.
80. Toyokuni, T., Abe, Y.; Ogawa, S.; Suami, T. *Bull. Chem. Soc. Jpn* **1983,** *56*, 505–513.
81. Toyokuni, T.; Ogawa, S.; Suami, T. *Bull. Chem. Soc. Jpn* **1983,** *56*, 1161–1170.
82. Ogawa, S.; Hattori, T.; Toyokuni, T.; Suami, T. *Bull. Chem. Soc. Jpn* **1983,** *56*, 2077.
83. Paulsen, H.; Heiker, F. R. *Angew. Chem.* **1980,** *92*, 930–931.
84. Paulsen, H.; Heiker, F. R. *Carbohyd. Res.* **1982,** *102*, 83–98.
85. Riordon, J. M.; Kiely, D. E. *J. Carbohydr. Chem.* **1983,** *2*, 201–205.
86. Horii, S.; Iwasa, T.; Kameda, Y. *J. Antibiot.* **1971,** *24*, 57.
87. Horii, S.; Kameda, Y.; Kawahara, K. *J. Antibiot.* **1972,** *25*, 48.
88. [a]Ogawa, S.; Toyokuni, T., Suami, T. *Chem. Lett.* **1981,** 947–950; [b]Toyokuni, T.; Ogawa, S.; Suami, T. *Bull. Chem. Soc. Jpn* **1983,** *56*, 2994–3304.
89. Ogawa, S.; Toyokuni, T.; Iwasawa, Y.; Abe, Y., Suami, T. *Chem. Lett.* **1982,** 279–282