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STEREOSELECTIVE TOTAL SYNTHESIS AND STEREOCHEMISTRY OF DIPLODIATOXIN, A MYCOTOXIN FROM DIPLODIA MAYDIS[1]

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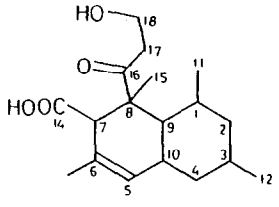
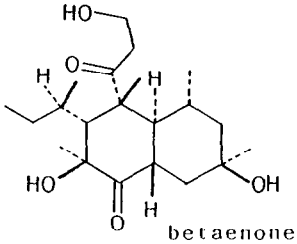
Abstract: The stereochemistry of diplodiatoxin has been deduced, and the assumed stereostructure has been confirmed by the synthesis using highly stereocontrolled strategy, in which the intramolecular Diels-Alder reaction of a(E, E, E)-triene is involved.

Diplodiatoxin is a mycotoxin isolated from infected maize with Diplodia maydis which causes a well known disease, diplodiosis, among cattle and sheep in Southern Africa. The first symptoms are lachrymation, salivation and a slight quivering of the muscles of shoulder and flank, and the causes of death is muco-enteritis and nephritis.[2] The toxic



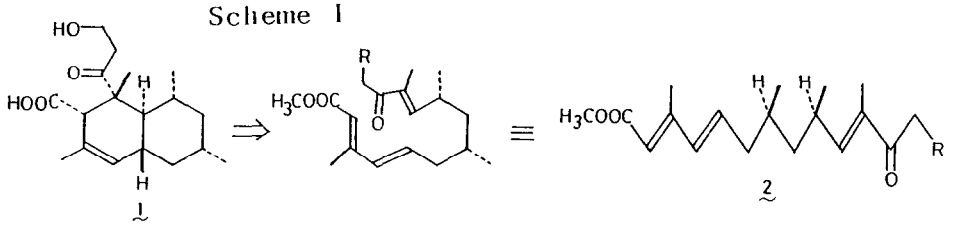
diplodiatoxin

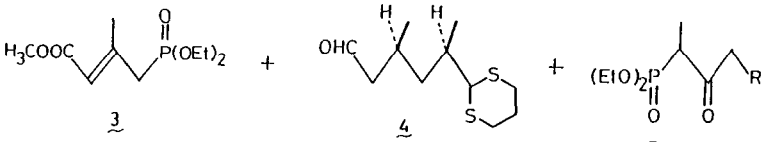


betaenone B

principle, diplodiatoxin, was extracted from the infected maize and the planar structure was elucidated on the basis of spectroscopic data and chemical reactions in 1972.[3] Tentative configuration of the mycotoxin has been deduced as 1 from the known data[3] and extensive comparison of ^{1}H NMR spectra of 1 with those of betaenone B.[4]

Scheme I

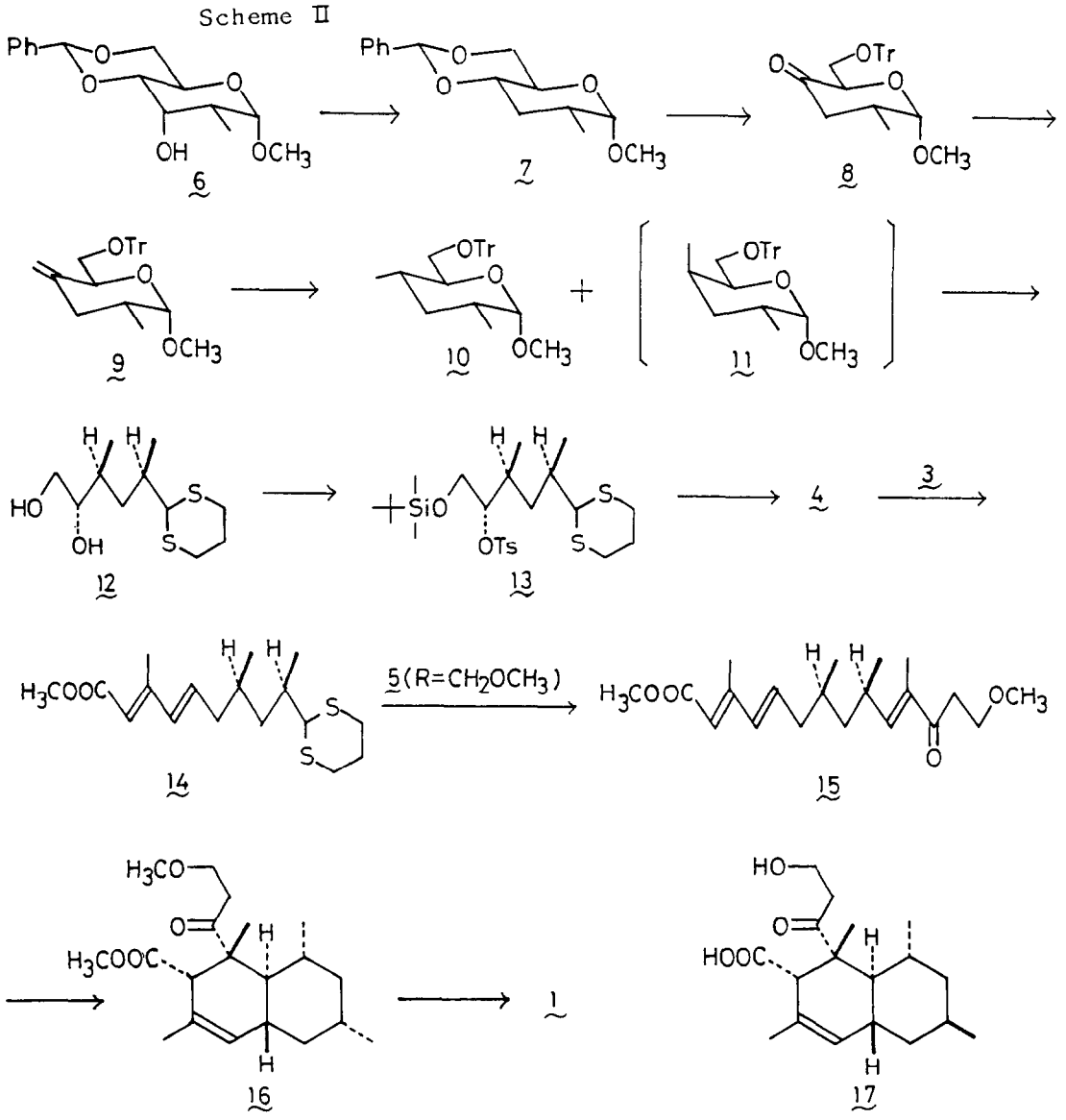




In order to confirm the stereochemistry including the absolute configuration, and to develop an effective synthetic method to supply this type of bioactive molecules,[5] a stereoselective synthesis of chiral diplodiatoxin was undertaken according to the general tactics as shown in Scheme I. In the retro synthetic analysis, the intramolecular Diels-Alder

reaction of a(E, E, E)-trienone 2 is the key step, and may involve four possible transition states. The endo transition state leading to the trans decaline framework is most favorable, since the three other transition states involve severe interaction between non-bonded atoms.

Scheme II



The trienone 2 may be devided into the three segments A, B and C. The segments A (3) and C (5) are known or readily accessible compounds. Tatal synthesis of (+)-diplodiatoxin (1) has been completed as shown in Scheme II.

The alcohol 6 which was derived from D-glucose through 8 steps[6] was converted to the xanthate (CS_2, CH_3I, NaH, THF),[7] which was reduced to 7, mp 77 - 79°C, with nBu_3SnH refluxing in toluene for 2 days (75.1% from 6). Removal of protective group (TsOH, CH_3OH, r.t. 3hr) of 7 and subsequent protection with trityl group (TrCl, Py, r.t. overnight) and oxidation (PDC, DMF, r.t. overnight), yielded the ketone 8 (syrup, 95% from 7). The Wittig reaction

(CH_3PPh_3Br, nBuLi, toluene, 0°C→r.t. 3hr) of 8 gave the olefin 9, mp 107 - 111°C, (86.8%). Reduction of the olefin 9 with diimide ($N_2H_4 \cdot H_2O$, O_2, EtOH, reflux, 6hr) yielded quantitatively two diastereoisomers 10, mp 102 - 104°C, and 11, mp 76 - 77°C in a ratio of 2 : 1.[8] The stereochemistry of these isomers, 10 and 11, was assigned on the basis of the coupling constants (10, δ 1.24, ddd, J=12.7, 12.7, 12.7 Hz, 11, δ 1.75, ddd, J=13.2, 13.2, 4.4 Hz) of 3-Hax and the difference NOE experiments in ^{1}H NMR spectra. Treatment of 10 with propanedithiol (BF_3 -etherate, 0°C, 4hr) produced the ring opening product 12 (oil) in essentially quantitative yield. After protection of primary hydroxyl group (t-$BuMe_2SiCl$, imidazole, -10°C, 4hr), 12 was converted to the tosylate 13 (TsCl, DMAP, $CHCl_3$, r.t. 12hr) (80% from 12). Elimination of p-toluenesulfonic acid (DBU, Py, 100°C, 19hr) afforded directly the desirable aldehyde 4 (40%).[9]

The Wittig-Horner reaction (LDA, THF, HMPT, -60°C, 6hr) of segment B (4) with the known phosphonate 3[10] gave the diene 14 (oil, 95.1%), in which the geometry of newly formed double bond was exclusively trans, as deduced from a comparison of the ^{1}H NMR spectrum with those of four geometrical isomers of methyl 3-methyl-2,4-decadienoates.[10] Treatment of 14 with mercuric perchlorate, $Hg(ClO_4)_2$ $3H_2O$, ($CHCl_3$-THF, r.t. 10 min.) yielded an aldehyde, which was immediately allowed to react with the phosphonate 5 ($R=CH_2OCH_3$)[11] (nBuLi, DMF, THF, -1.5° r.t. 24hr) to give a mixture of the trienones (56.5%), which contains less than 5% of Z isomer about the newly formed double bond on the basis of the ^{1}H NMR spectrum compared with those of (E)-and (Z)-4,6-dimethyl-4-octen-3-one (manicone).[12]

The intramolecular Diels-Alder reaction was effected by heating a toluene solution of the trienone 15 at 140°C in a sealed tube for 37hr to afford the adduct 16 (oil, 85%) as a single product. The ^{1}H NMR spectrum which shows the signal at δ 2.00 (1H, dd, J=9.90, 9.90 Hz) due to 9-H is exactly compatible with the predicted stereostructure 16,[13] and is inconsistent with the other diastereomer of 16. Removal of two protective groups ($AlCl_3$, tetrahydrothiophene, r.t. 15 hr)[14] produced (+)-diplodiatoxin (1), mp 186 - 188°C (lit.[3] 186 - 187°C), (64%), whose spectroscopic data (IR, ^{1}H NMR and MS) are identical with those of natural sample. Since the CD spectrum ($\Delta\varepsilon$: 293 nm -0.50, 225 nm +11.0, c 1.0 x 10^{-3} M in CH_3OH) is also identical with that of natural specimen, the absolute configuration of (+)-diplodiatoxin must be as depicted in 1.

In the same way, the diastereoisomer 11 was converted to 3-epidiplodiatoxin (17) (oil), whose spectroscopic data are very similar but slightly different with those of (+)-diplodiatoxin (1).

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References and Notes

1. Taken from the Ph. D. thesis of H. Kawagishi, Hokkaido University, 1985.

2. J. M. Watt, M. G. Breyer-Grandwijk, "The Medicinal and Poisonous Plants of Southern and Eastern Africa" p 1127, E. S. Livingstone, London (1962).

3. P. S. Steyn, P. L. Wessels, C. W. Holzapfel, D. J. J. Potgieter, W. K. A. Louw, Tetrahedron 28, 4775 (1972).

4. A. Ichihara, H. Oikawa, K. Hayashi, S. Sakamura, A. Furusaki, T. Matsumoto, J. Am. Chem. Soc., 105, 2907 (1983). A. Ichihara, H. Oikawa, M. Hashimoto, S. Sakamura, T. Haraguchi, H. Nagano, Agric. Biol. Chem. 47, 2965 (1983). H. Oikawa, A. Ichihara, S. Sakamura, Agric. Biol. Chem. 48, 2603 (1984): The stereochemistry of 1 was elucidated by the

following reasoning: 1. the signal at δ 2.04 (1H, dd, J=9.0, 9.0 Hz) due to 9-H exhibited characteristic trans diaxial coupling; 2. unusual upfield shift (δ 0.59) of 11-CH_3 would be caused by the anisotropy of 16-CO group; 3. reduction of 16-CO with $NaBH_4$ involves readily lactone formation with 14-COOH. The facts, 1 and 2, are very similar to observation with betaenone B. The fact 3 indicates that the 14-COOH is cis to the 16-CO. The configurations at 3-C (12-CH_3) and absolute configuration of 1 are tentative.

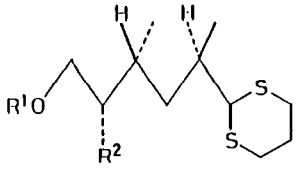
5. Other compounds having the similar structural feature are antibiotic LL-N313γ, W. J. McGahren, G. A. Ellestad, J. E. Lancaster, G. O. Morton, M. P. Kunstmann, J. Am. Chem. Soc., 96, 1616 (1974); 3-(1', 2', 4a', 5', 6', 7', 8', 8a'-octahydro-2'-methyl-5'-hydroxynaphthyl) pripionic acid, Sankyo Co. Ltd., Japanese patent, J5 5100 335.; stemphyloxin, I. Barash, S. Manulis, Y. Kashman, J. P. Springer, M. H, A. Chen, J. Clardy, G. A. Strobel, Science 20, 1055 (1983); betaenones.[4]

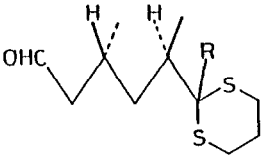
6. S. Hanessian, G. Rancourt, Can. J. Chem., 55, 111 (1977).

7. Satisfactory elemental composition (exact mass spectroscopy) and spectral data were obtained on all new compounds.

8. Catalytic hydrogenation of 9 on PtO_2 and Pd-C yielded 1 : 1 (100%) and 2 : 1 (86%) mixtures of 10 and 11 respectively.[2] These diastereomers have been prepared by an alternate route: S. Jarosz, B. Fraser-Reid, Tetrahedron Lett., 22, 2533 (1981).

9. In the preliminary conversion of a diastereomer i through ii, iii and iv to the aldehyde v, oxidation of iv with various reagents (PCC, PDC, DMSO-oxalyl chloride), afforded mainly the alcohol vi (~60%) and small amount of the aldehyde v.





i $R^1 = H$ $R^2 = OH$ iii $R^1 = OSi$–|– $R^2 = H$ v R = H

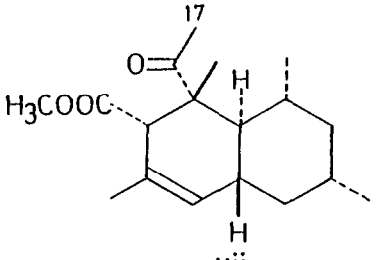
ii $R^1 = OSi$–|– $R^2 = OTs$ iv $R^1, R^2 = H$ vi R = OH

10. E. J. Corey, J. A, Katzenellenbogen, S. A. Roman, N. W. Gilman, Tetrahedron Lett., 1821 (1971). E. J. Corey, B. W. Erickson, J. Org. Chem., 39, 821 (1974). Very minor amount of 7'Z-isomer was contained in the Wittig-Horner reaction product.

11. The phosphonate 5 ($R=CH_2OCH_3$) was prepared from methyl 3-methoxypropionate and diethylethylphosphonate (nBuLi, THF, HMPT, -78°→ -50°, 3hr).

12. J. A. Katzenellenbogen, T. Utawanit, J. Am. Chem. Soc., 96, 6153 (1974).

13. Initially, the methyl ketone vii was synthesized by the intramolecular Diels-Alder reaction of the trienone 2 (R=H). However, all attempts to introduce a hydroxymethyl group at 17-CH_3 in vii were failed.



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14. M. Node, K. Nishide, M. Sai, K. Fuji, E. Fujita, J. Org. Chem., 46, 1991 (1981).

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