Approaches to Cytochalasan Synthesis: Macrocycle Formation using an Intramolecular Diels–Alder Reaction

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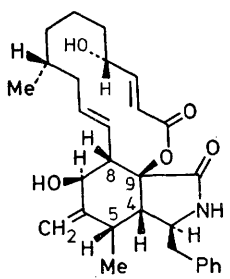
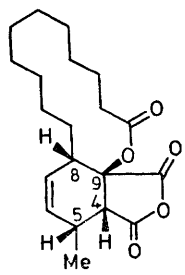
Summary Thermolysis of the long-chain diene-anhydride (**3**) gives a mixture of macrocyclic lactones (**2**; 27%) and (**10**; 5%) *via* an intramolecular Diels–Alder reaction.

THE cytochalasans,[1] *e.g.* cytochalasin B (**1**), are fungal metabolites which produce unique effects on mammalian cells. Several approaches to cytochalasan synthesis have recently been reported, but no total synthesis has yet been achieved.[2] We report a stereoselective synthesis of the macrocyclic lactone (**2**) by a route which has implications for cytochalasan biosynthesis. Although the origin of the carbon atoms of the cytochalasans is known, the biosynthetic formation of the tricyclic ring system poses a mechanistic problem. A possible solution to this problem[3] involves an intramolecular Diels–Alder reaction which is not only mechanistically feasible, but also establishes the correct relative stereochemistry at four asymmetric centres (C-4, C-5, C-8, and C-9, cytochalasan numbering[1]) and provides a 6,7-double bond for the introduction of the remaining functionality of the cyclohexane ring.



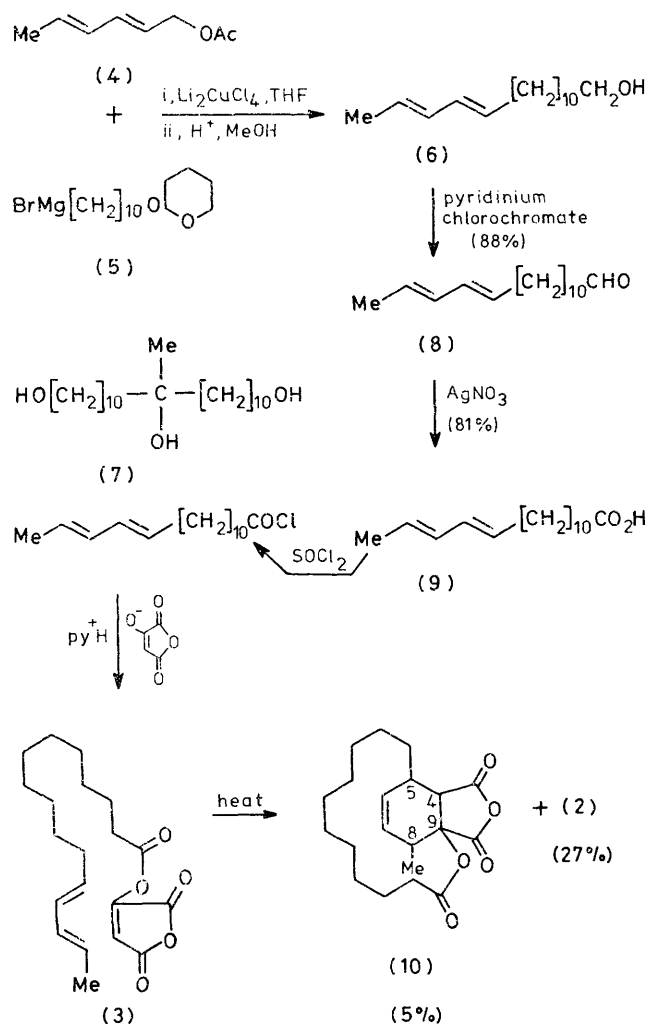
(1)



(2)

We considered a similar approach to the synthesis of the macrolide cytochalasans and since the formation of macrocycles *via* intramolecular Diels–Alder reactions is not usually regioselective,[4] we tested the feasibility of this approach by studying the intramolecular Diels–Alder reaction of the diene-anhydride (**3**).

The synthesis of the diene-anhydride (**3**) is shown in the Scheme. Sorbyl acetate (**4**) was treated in tetrahydrofuran (THF) with the Grignard reagent (**5**) derived from 10-bromodecanyl tetrahydropyran-2-yl ether, at −78 °C in the presence of Li_2CuCl_4.[5,6] The mixture was allowed to warm up to room temperature and stirred overnight; the crude product was isolated in the usual way and hydrolysed (*p*-$MeC_6H_4SO_3H$; refluxing MeOH; 1 h) to give a mixture



SCHEME

containing *trans,trans*-hexadeca-12,14-dien-1-ol (**6**; 60—70%) as the major component.† Little 11-methylheneicosane-1,11,21-triol (**7**), the product of carbonyl attack, was formed under these conditions. The pure dienol (**6**; 40—50%) was obtained by crystallization and chromatography of the crude reaction mixture and was converted

† Satisfactory analytical or accurate mass data were obtained for all new compounds.

into *trans,trans*-hexadeca-12,14-dienoic acid (**9**) *via* the aldehyde (**8**). Treatment of the crude acid chloride prepared from the acid (**9**) using thionyl chloride, with the pyridinium salt of hydroxymaleic anhydride,[7] gave the desired diene-anhydride (**3**) in 79% yield (from **9**) after recrystallization.

Intramolecular Diels–Alder reactions of the diene-anhydride (**3**) were studied under high dilution conditions (100 mg per 100 ml) in refluxing toluene. No unchanged starting material could be detected by t.l.c. after 96 h reflux. Instead two new products were observed and these were separated by column chromatography. The major product (m.p. 117—118·5 °C), isolated in 27% yield, was identified as the desired Diels–Alder adduct (**2**) on the basis of its spectroscopic data. In particular the regioselectivity of the cycloaddition was established by a spin-decoupling experiment (220 MHz) since irradiation of one of the allylic protons, presumably H-5, caused both the doublet due to H-4 and the doublet due to the exocyclic methyl group to collapse to singlets. The minor product, m.p. 110—112 °C, was isolated in 5% yield, and was identified as the regioisomer (**10**) of the major product. The gross spectroscopic data of the minor product were similar to those of the major product. However, irradiation of one of the allylic protons, presumably H-5, caused the doublet due to H-4 to collapse to a singlet but had no effect on the exocyclic methyl group, whereas irradiation of the other allylic proton, presumably H-8, caused the exocyclic methyl doublet to collapse to a singlet but had no effect on the doublet due to H-4 (see formula **10** for numbering). In addition to these Diels–Alder adducts, some *trans,trans*-hexadeca-12,14-dienoic acid (**9**) possibly formed by adventitious hydrolysis of the enol-ester unit of the diene-anhydride (**3**), was always found in the crude Diels–Alder reaction mixtures.

Although the regiochemistry of the Diels–Alder adduct was assigned on the basis of the spin-decoupling experiments described above, our spectroscopic data did not unambiguously define the stereochemistry of the adducts. The relative stereochemistry of the minor adduct (**10**) has not been defined. However, the relative stereochemistry of the major adduct has unambiguously been established as that depicted in formula (**2**) by an *X*-ray diffraction study.‡

Therefore the intramolecular Diels-Alder reaction of the diene-anhydride (**3**) is both regio- and stereoselective, the major product being the lactone (**2**) which is structurally related to cytochalasin B (**1**).

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‡ Details of the *X*-ray diffraction work will be published elsewhere.

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