An Approach to Cytochalasin D; 11-Membered Ring Formation using an Intramolecular Diels–Alder Reaction

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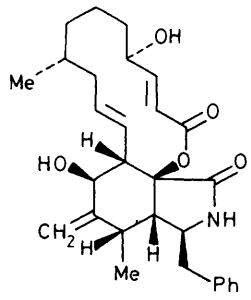
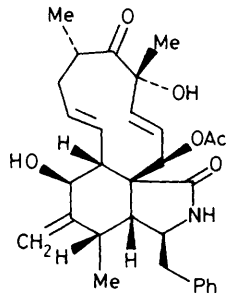
As preparation for a proposed synthesis of cytochalasin D, the triene-pyrrolinone (**12**) was shown to cyclize stereoselectively on heating (12 h, 100 °C) in toluene to give the Diels–Alder product (**13**) (40—45%), and a synthesis of the protected dihydroxyaldehyde (**26**) was developed.

Synthesis of the cytochalasans, a group of biologically active fungal metabolites,[1] is of some considerable interest at the present time.[2] Cytochalasin B (**1**), a macrolide cytochalasan, has been synthesized by Stork,[3] and in the preceding communication we report the first synthesis of the naturally occurring 'carbocyclic' cytochalasan, proxiphomin, using an intramolecular Diels–Alder reaction to form the 13-membered carbocyclic ring.[4] Since a large group of cytochalasans, *e.g.* cytochalasin D (**2**),[5] possess an 11-membered ring, it would be of interest to see whether the direct intramolecular Diels–Alder strategy is suitable for the preparation of these [11]cytochalasans. However ring-closing reactions forming 11-membered rings can be rather inefficient, sometimes, taking place more slowly than when analogous reactions are used to form 12-membered and larger rings.[6] Indeed the two other reported approaches to the 11-membered ring of cytochalasin D which are being developed use fragmentation[7] and ring expansion[8] procedures rather



(1)



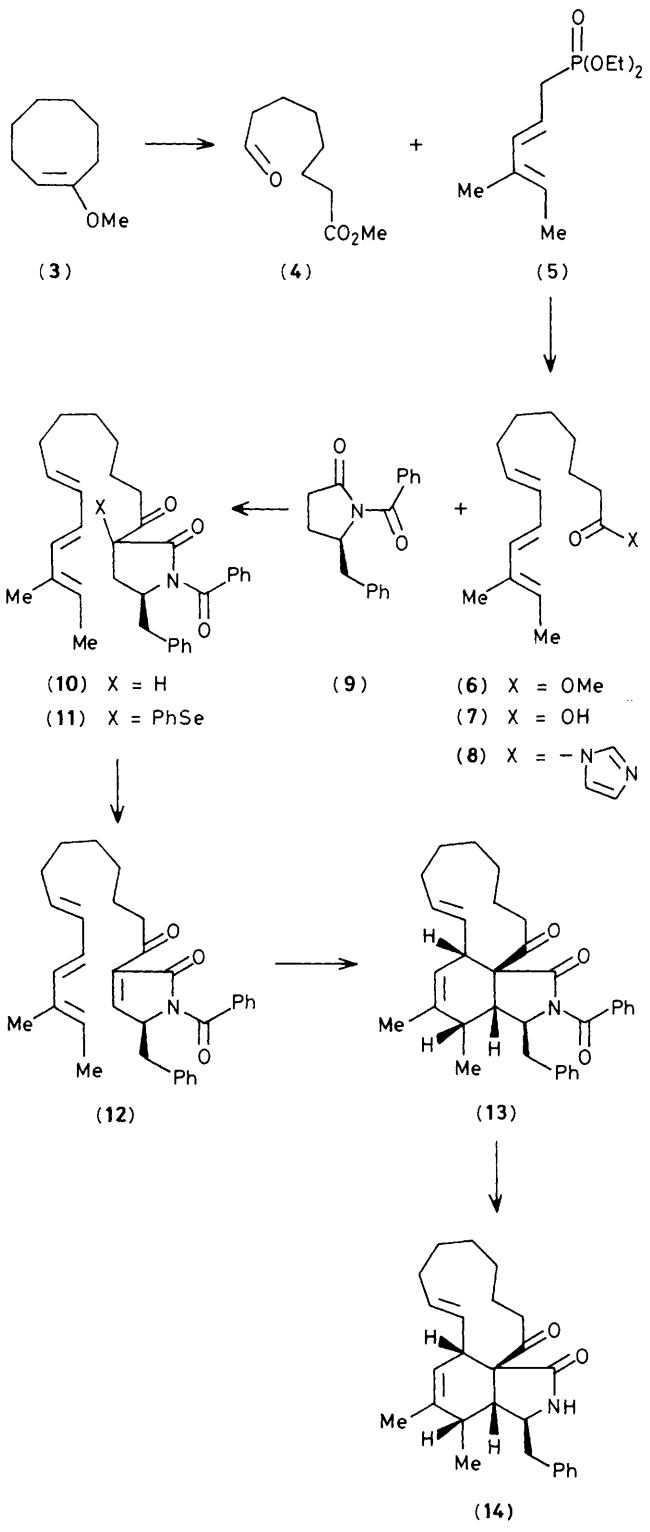
(2)

than direct cyclization. We here describe an intramolecular Diels–Alder reaction of a triene-pyrrolinone which is found to provide rapid access to the [11]cytochalasan skeleton.† We also describe some preliminary studies on establishing the functionality and stereochemistry of the C(14) to C(21) portion of cytochalasin D.

The synthesis of the Diels–Alder precursor (**12**) follows that used in the proxiphomin synthesis,[4] and is outlined in Scheme 1. Cyclo-octanone was converted into its enol ether (**3**) (94%)[9] which was ozonolysed (with a triphenylphosphine work-up) to give the aldehyde-ester (**4**) (50%).‡ Treatment of this aldehyde at −78 °C with the lithium salt of the dienylphosphonate (**5**)[3] gave, after the addition of hexamethylphosphoric triamide at 0 °C, the trienyl ester (**6**) (60%) which contained only small amounts of its *cis*-isomer.§ Hydrolysis of the ester (**6**) (NaOH, H_2O, EtOH, quenched after 2—4 h with tartaric acid), and treatment of the acid (**7**) with 1,1′-carbonyldiimidazole, gave the crystalline imidazolide (**8**) (87%), m.p. 36 °C. This imidazolide was treated with the lithium enolate (2 equiv.) of *N*-benzoyl-5-benzylpyrrolidinone (**9**)[10] (generated at −78 °C using lithium hexamethyldisilazide), to give, after 6 h at −78 °C, the oxopyrrolidinone (**10**) (70—90%), as a mixture of diastereoisomers. This mixture was phenylselenenylated (lithium hexamethyldisilazide, PhSeCl, −78 °C) to give the pyrrolinone precursor (**11**) (70—80%).

Oxidative elimination of the phenylselenenyl moiety was achieved using *m*-chloroperoxybenzoic acid–hydrogen peroxide in a two-phase mixture ($CHCl_3$–H_2O), at −50 °C for 15 min, followed by warming to 0 °C for 15 min. This procedure generated the unstable triene-pyrrolinone (**12**) which could not be isolated, but which was characterized in solution by high-field ^1H n.m.r. spectroscopy. The chloroform solution of pyrrolinone (**12**) was then dried (Na_2SO_4), diluted with toluene, and the mixture heated at 100 °C under an argon atmosphere for 12 h. Flash chromatography gave the Diels–Alder product (**13**) isolated in 40—45% yield based upon the phenylselenopyrrolidinone (**11**).

The Diels–Alder product so obtained was found to be essentially one diastereoisomer, less than 5% of a second isomer being present. The stereochemistry of this major isomer was established as shown in formula (**13**) on the basis of



(3) (4) (5) (10) X = H (11) X = PhSe (9) (6) X = OMe (7) X = OH (8) X = −N=CH−N (12) (13) (14)

Scheme 1

nuclear Overhauser effect (n.O.e.) difference spectra,¶ and was found to be that required for cytochalasan synthesis. Diels–Alder cyclization of triene-pyrrolinone (**12**) would appear to have taken place on the less-hindered face of the pyrrolinone, with the imide carbonyl controlling the *exo*–

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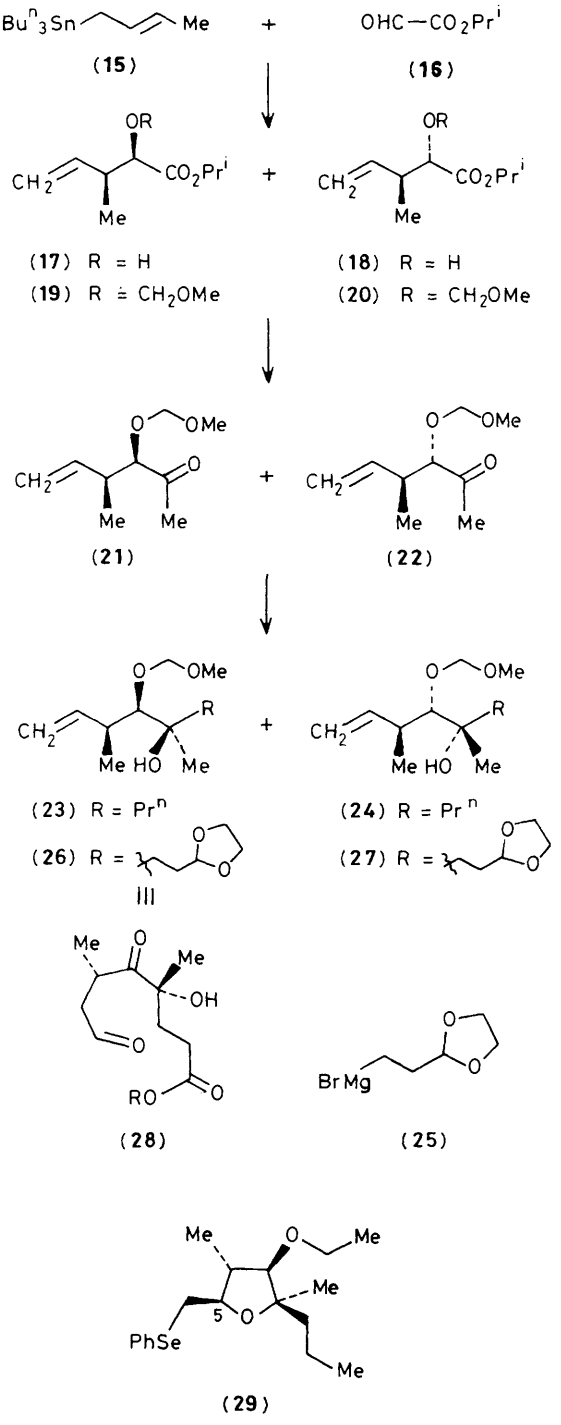
‡ New compounds were characterized by spectroscopic and analytical or accurate mass data.

§ Trienes (**6**), (**10**), and (**11**) were chromatographed on flash silica which had been washed with saturated aqueous $KHCO_3$, and with distilled water until the washings were neutral.

¶ The structure of adduct (**13**) has now been confirmed by an *X*-ray structure determination. Details will be presented in a full paper.



Scheme 2

endo-selectivity. Removal of the *N*-benzoyl group then gave lactam (**14**) (70—80%), which has the same skeleton as cytochalasin D (**2**).

Extension of this strategy to include a synthesis of cytochalasin D requires a synthesis of an aldehyde-ester which incorporates, albeit in protected form, the functionality present in the 11-membered ring of cytochalasin D. A short, stereoselective synthesis of the protected dihydroxyaldehyde (**26**), which is synthetically equivalent to aldehyde-ester (**28**), is outlined in Scheme 2.

As reported in the literature,[11] it was found that treatment of isopropyl glyoxalate (**16**) with *trans*-crotyl-tri-n-butylstannane (**15**) in the presence of boron trifluoride–diethyl ether at −78 °C; gave a mixture of *syn*- and *anti*-adducts (**17**) and (**18**) in which the *syn*-adduct (**17**) predominated, (**17**) : (**18**) = 85 : 15 (^{1}H n.m.r. spectroscopy). Protection of the hydroxy group (chloromethyl methyl ether, Pr^i_2NEt), ester hydrolysis (LiOH, H_2O–tetrahydrofuran, THF), and treatment with methyl-lithium, then gave a mixture of the *syn*- and *anti*-ketones (**21**) and (**22**) without any appreciable equilibration. The addition of Grignard reagents to α-alkoxyketones in THF is known to proceed with good stereoselectivity *via* chelation control.[12] It was found that treatment of the 85 : 15 mixture of ketones (**21**) and (**22**) with propylmagnesium bromide, and with the acetal Grignard reagent (**25**), gave mixtures of products, (**23**) and (**24**), (**26**) and (**27**), which had been formed *via* chelation-controlled addition. The configuration of the major propylmagnesium bromide adduct (**23**) was established by cyclization using phenylselenenyl chloride to give tetrahydrofuran (**29**) together with its epimer at C(5). The structure of this tetrahydrofuran was shown using n.O.e. difference data, which confirmed the stereoselectivity of the initial crotylstannane addition and the stereochemistry of the Grignard addition step. The structure of the major acetal Grignard addition product (**26**) was assigned by analogy, the ratio of adducts (**26**) and (**27**), 85 : 15, reflecting the ratio of starting ketones (**21**) and (**22**); racemic adduct (**26**) is synthetically equivalent to the cytochalasin D synthon (**28**).

Work is in progress to develop a synthesis of an optically active synthetic equivalent of aldehyde-ester (**28**) and a total synthesis of cytochalasin D.

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