Total Synthesis of Proxiphomin, a Naturally Occurring [13]Cytochalasan

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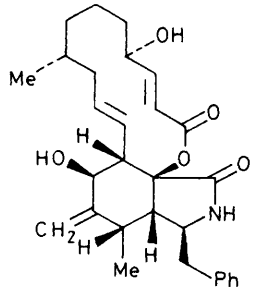
Proxiphomin (**2**) has been synthesized by a route which uses an intramolecular Diels–Alder reaction of triene-pyrrolinone (**3**) to form the [13]cytochalasan skeleton.

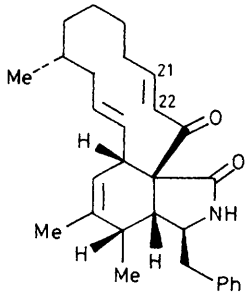
The cytochalasans[1] are an important group of biologically active fungal metabolites which provide challenging targets for total synthesis.[2] The macrolide [14]cytochalasans, *e.g.* cytochalasin B, (**1**), are the only naturally occurring cytochalasans to have been synthesized to date.[3,4] We here describe the first total synthesis of proxiphomin (**2**), a naturally occurring [13]cytochalasan.[5,6] The key feature of our synthesis is the use of an intramolecular Diels–Alder reaction of a long-chain triene-pyrrolinone to close the macrocyclic ring forming simultaneously the desired hydrogenated isoindolone unit. Model studies have shown the viability of this approach,[7] which was also used by Stork in his second synthesis of cytochalasin B.[4] However, the conditions required by Stork (180—190 °C, 6 days; 30%) for the Diels–Alder reaction using a 3-acyloxypyrrolinone as dienophile, were much more vigorous than those required here.

The plan of the proposed synthesis is outlined in Scheme 1. A convergent route to the Diels–Alder precursor (**3**) was envisaged using phosphonate (**5**),[4] aldehyde-ester (**6**), and pyrrolidinone (**7**),[7] as building blocks for triene-pyrrolidinone (**4**, R = H). Phenylselenenylation and oxidative elimination could then be used to provide triene-pyrrolinone (**3**). To avoid possible complications in the Diels–Alder reaction, it was felt that the C(21)–C(22) double bond should be introduced after the cyclization step.

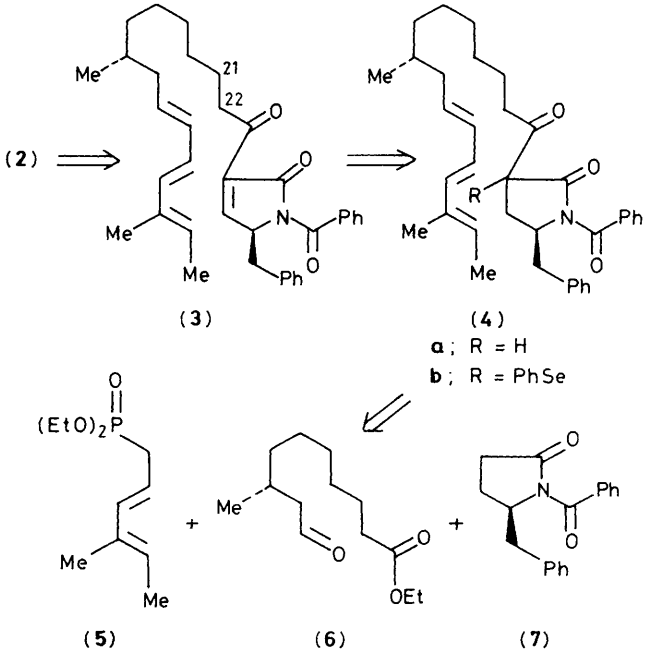
(3*R*)-(+)-Citronellol (**8**) was chosen as the starting material for the synthesis of aldehyde-ester (**6**). Protection (t-butyldimethylsilyl chloride, imidazole; 98%) and ozonolysis (dimethyl sulphide work-up; 80—85%) gave the aldehyde



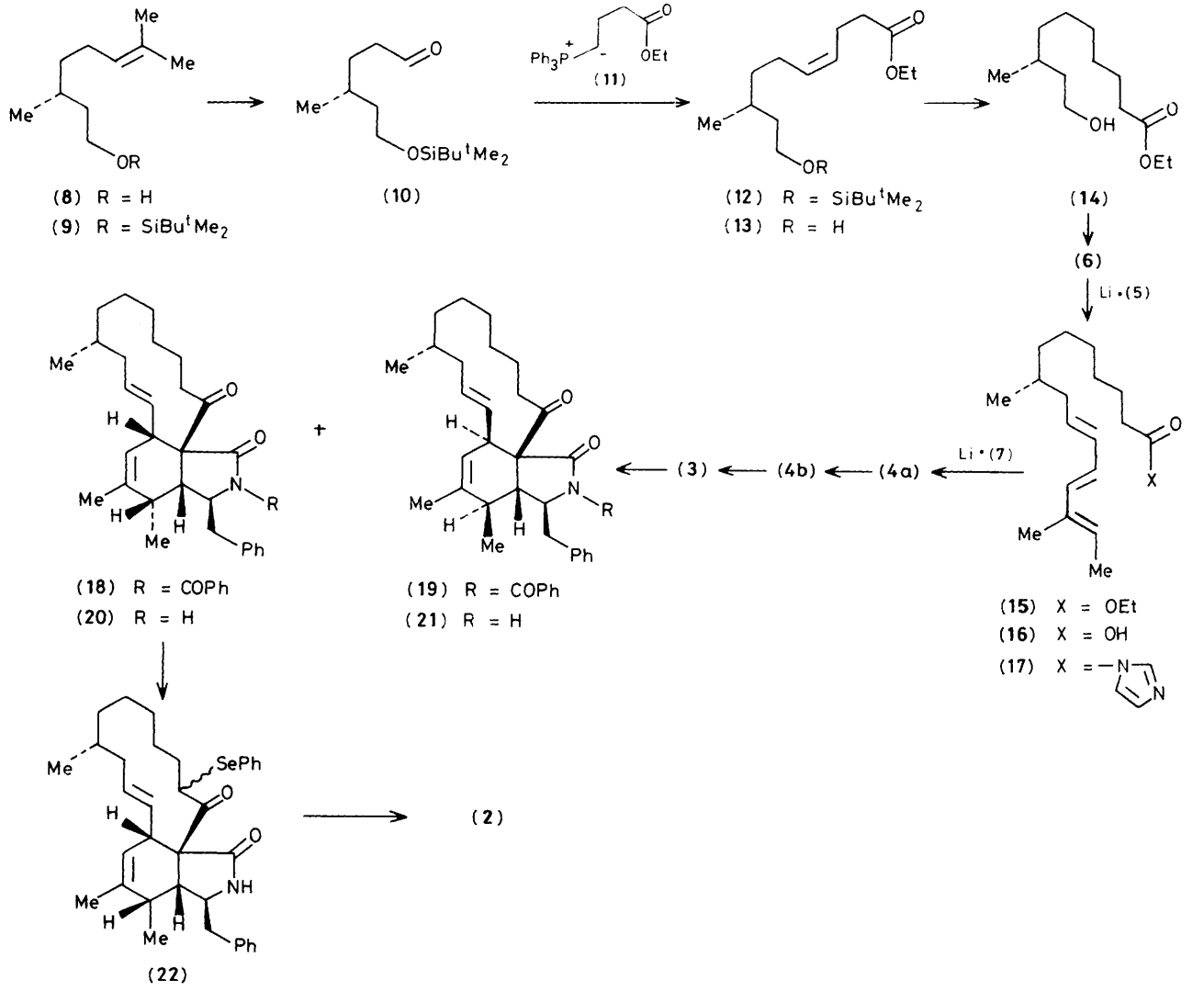
(**1**)



(**2**)



Scheme 1



(**10**), b.p. 78 °C at 0.2 mmHg.† This was treated (at −78 °C for 2 h, then at 20 °C for 1 h) with phosphorane (**11**), generated at −78 °C from the corresponding phosphonium salt[8] using potassium hexamethyldisilazide, to give the alkene (**12**) (70—90%), b.p. 114—116 °C at 0.1 mmHg. Deprotection of the silylated alkene (Bu^n_4NF, $KF{\cdot}2H_2O$; 85—90%), and catalytic hydrogenation gave ethyl (8*R*)-10-hydroxy-8-methyldecanoate (**14**) as a colourless liquid, b.p. 170—180 °C at 0.1 mmHg.

Oxidation of this alcohol using dimethylsulphoxide–oxalyl chloride[9] gave aldehyde (**6**) (87%) which was treated at −78 °C for 3 h with the lithium salt of dienylphosphonate (**5**), generated using n-butyl-lithium, (1 h at −78 to −50 °C) in tetrahydrofuran (THF). The reaction mixture was then allowed to warm to 0 °C, and hexamethylphosphoric triamide added, to give the desired triene-ester (**15**) (60%) as an acid-sensitive oil which could be chromatographed on base washed silica.‡ Several alternative methods for carrying out this condensation reaction were investigated, but this procedure, modelled on that described by Stork,[4] was found to be the most reliable and stereoselective, less than 5% of the *cis*-isomer being formed. Hydrolysis of triene-ester (**15**) (NaOH–H_2O–EtOH, followed by acidification using tartaric acid), and treatment of the acid obtained with 1,1′-carbonyldiimidazole, gave the crystalline imidazolide (**17**) (90%), m.p. 47 °C. This imidazolide was found to be quite stable, and could be stored in the crystalline form under argon at −30 °C.

(5*R*)-5-Benzylpyrrolidinone was prepared from L-phenylalanine as described in the literature,[10] and benzoylated (benzoyl chloride, pyridine) to give the *N*-benzoylpyrrolidinone (**7**) (81%). This was converted into its lithium enolate using lithium hexamethyldisilazide (THF, −78 °C, 1 h), and two equivalents of the enolate added to imidazolide (**17**) in THF at −78 °C. Work-up after 8 h at −78 °C gave the 3-oxopyrrolidinone (**4a**) (60—80%), isolated as a mixture of diastereoisomers after flash chromatography. Phenylselenenylation was then achieved by deprotonation [LiN($SiMe_3$)$_2$, −78 °C, 1 h], and addition of phenylselenenyl chloride (−78 °C, 2 h), to give the desired pyrrolidinone (**4b**) (60—70%).

Having prepared the pyrrolinone percursor (**4b**), the stage was set for the key Diels–Alder reaction. It was found that oxidative-elimination of the phenylselenenyl moiety from (**4b**) could best be achieved by treatment with *m*-chloroperoxyben-

† All new compounds were characterized spectroscopically and by analytical or accurate mass data.

‡ Chromatography of trienes (**4**), (**15**)—(**17**) was carried out using flash silica washed with saturated aqueous $NaHCO_3$ and rinsed with distilled water until the washings were neutral.

zoic acid (1 equiv.) and an excess of 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. Dilution of the organic phase, after washing with dilute aqueous sodium hydrogen carbonate and drying (Na_2SO_4), then gave a solution of the Diels–Alder precursor, triene-pyrrolinone (**3**). This intermediate polymerized on attempted isolation, but could be characterized in solution by its high-field ^1H n.m.r. spectrum which showed all the expected resonances including a doublet, δ 7.96 (1H, *J* 1 Hz), assigned to H(4) of the pyrrolinone ring.

The chloroform solution of pyrrolinone (**3**) was then diluted with toluene (to give a concentration of *ca.* 100 mg/100 ml), and the solution obtained heated at 100 °C under an inert atmosphere for 12 h. Flash chromatography gave a mixture of the two Diels–Alder adducts (**18**) and (**19**), ratio 52:48, in a combined yield of 50—55%. These adducts could not be separated but were debenzoylated (KOH–benzene–MeOH; 75%) to give the NH-compounds (**20**) and (**21**) which were separated by short column chromatography (using CH_2Cl_2 and MeOH, 99:1). The less polar diastereoisomer was identified as the desired adduct (**20**) on the basis of nuclear Overhauser effect (n.O.e.) observations, *e.g.* an enhancement of both H(4) and H(5) on irradiation of H(8) and would appear to have been formed by cycloaddition of the triene onto the less-hindered face of the pyrrolinone with the imide carbonyl C(1) controlling the *endo–exo* selectivity. The more polar diastereoisomer was provisionally identified as adduct (**21**) again on the basis of n.O.e. observations, and had involved cycloaddition of the triene on the less-hindered face of the pyrrolinone, but now with the ketone carbonyl C(23) controlling the *endo–exo* selectivity.

The final step in the synthesis involved the introduction of the C(21)–C(22) double-bond. This was achieved by phenylselenenylation of ketone (**20**) (lithium di-isopropylamide, −78 °C, 1 h, then PhSeCl, −78 °C, 4 h), and oxidative-elimination (using hydrogen peroxide and pyridine in CH_2Cl_2–H_2O) to give proxiphomin (**2**) isolated as an amorphous solid. The product obtained was found to be homogeneous after purification by flash chromatography as judged by spectroscopic and chromatographic methods including high-field (500 MHz) ^1H n.m.r. spectroscopy, and had spectroscopic data identical to data reported for proxiphomin, $[\alpha]_D^{20}$ −136 ± 5° (*c* 0.4725, $CHCl_3$) {lit. $[\alpha]_D^{22}$ −140 ± 2° (*c* 0.156, $CHCl_3$)}.§

This synthesis of proxiphomin would appear to confirm its stereochemistry which was initially assigned by analogy with other cytochalasans, and the convergent strategy used may provide an efficient general entry into compounds of the cytochalasan type.

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