

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

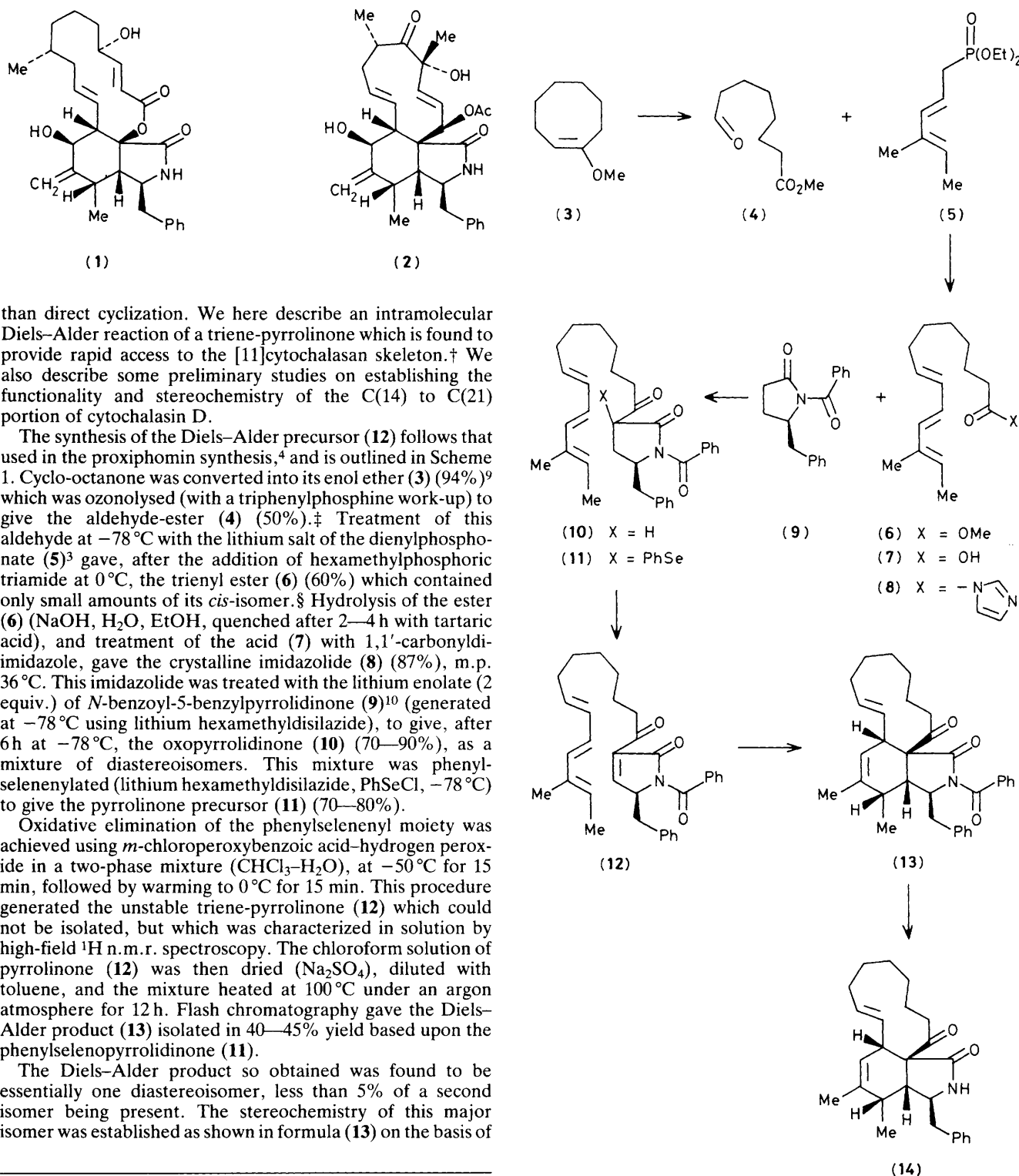
Andrew Craven, David J. Tapolczay, Eric J. Thomas,* and John W. F. Whitehead

The Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY, U.K.

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 fragmentation⁷ and ring expansion⁸ procedures rather



Scheme 1

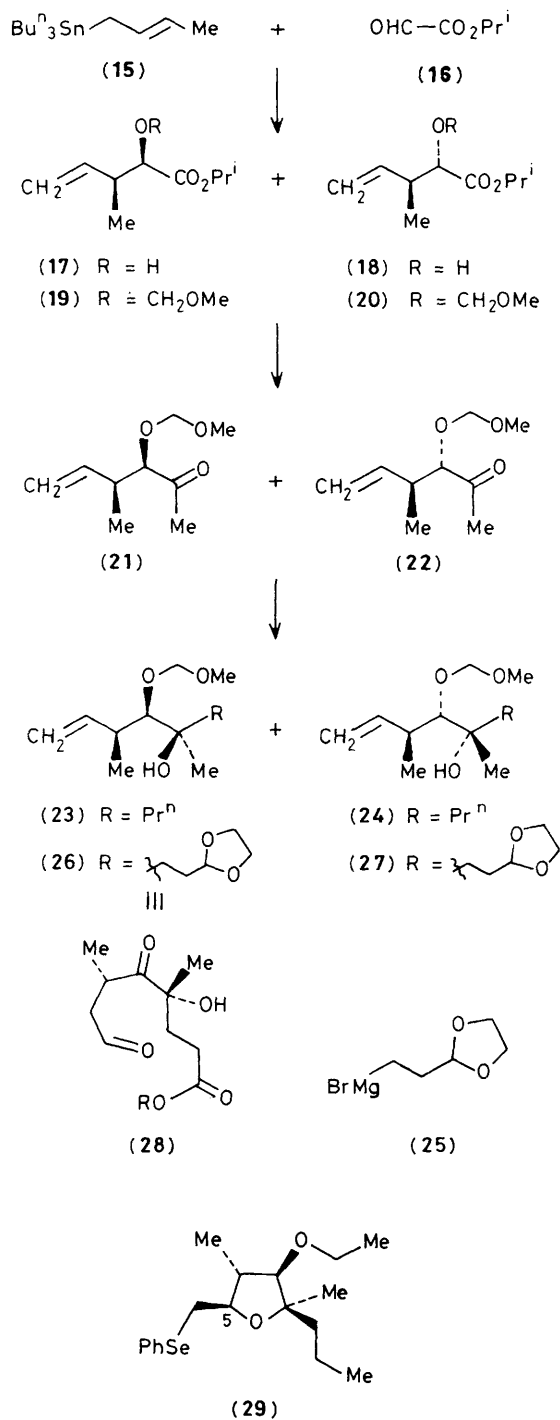
† Presented in part at the Royal Society of Chemistry Symposium on Carbanion Chemistry, Durham, July, 1984.

‡ 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.

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*-

¶ 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 (¹H n.m.r. spectroscopy). Protection of the hydroxy group (chloromethyl methyl ether, Pr₂NEt), ester hydrolysis (LiOH, H₂O–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.

We thank the S.E.R.C. for support (to D. J. T. and J. W. F. W.), the Royal Society of Chemistry for a Hickinbottom Fellowship (to E. J. T.), and Wellcome Pharmaceuticals for support under the C.A.S.E. scheme. We are also grateful to Dr. A. Derome and Mrs. E. McGuinness for n.m.r. spectra, and Dr. R. T. Aplin for mass spectra.

Received, 9th October 1984; Com. 1432

References

- M. Binder and C. Tamm, *Angew. Chem., Int. Ed. Engl.*, 1973, **12**, 370.
- E. Vedejs, J. B. Campbell, R. C. Gadwood, J. D. Rogers, K. L. Spear, and Y. Watanabe, *J. Org. Chem.*, 1982, **47**, 1534; T. Schmidlin, R. Gamboni, P. Strazewski, and C. Tamm, *Helv. Chim. Acta*, 1983, **66**, 1796; T. Schmidlin, P. E. Burckhardt, N. Waespe-Sačević, and C. Tamm, *ibid.*, p. 450; R. Brett and I. A. Jafri, *J. Chem. Soc., Perkin Trans. 1*, 1983, 387; M. Y. Kim, J. E. Starrett, and S. M. Weinreb, *J. Org. Chem.*, 1981, **46**, 5383.
- G. Stork, Y. Nakahara, Y. Nakahara, and W. J. Greenlee, *J. Am. Chem. Soc.*, 1978, **100**, 7775; G. Stork and E. Nakamura, *ibid.*, 1983, **105**, 5510.
- D. J. Tapoleczay, E. J. Thomas, and J. W. F. Whitehead, *J. Chem. Soc., Chem. Commun.*, preceding communication.
- D. C. Aldridge and W. B. Turner, *J. Chem. Soc. (C)*, 1969, 923; Y. Tsukada and H. Koyama, *J. Chem. Soc., Perkin Trans. 2*, 1972, 739.
- G. Illuminati and L. Mandolini, *Acc. Chem. Res.*, 1981, **14**, 95.
- S. G. Pyne, D. C. Spellmeyer, S. Chen, and P. L. Fuchs, *J. Am. Chem. Soc.*, 1982, **104**, 5728.
- E. Vedejs, M. J. Arnost, J. M. Eustache, and G. A. Krafft, *J. Org. Chem.*, 1982, **47**, 4384.
- R. A. Wohl, *Synthesis*, 1974, 38.
- S. A. Harkin, O. Singh, and E. J. Thomas, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1489.
- Y. Yamamoto, N. Maeda, and K. Maruyama, *J. Chem. Soc., Chem. Commun.*, 1983, 774.
- W. C. Still and J. H. McDonald, *Tetrahedron Lett.*, 1980, 1031.