standing of bonding in these and other solid-state systems. But if compounds have not been prepared, their physical properties cannot be measured! The present eclectic compilation of novel and interesting structure types underscores the enormous potential of the reactive flux method for the synthesis of new solid-state materials.

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Cytochalasan Synthesis: Macrocycle Formation via Intramolecular Diels–Alder Reactions

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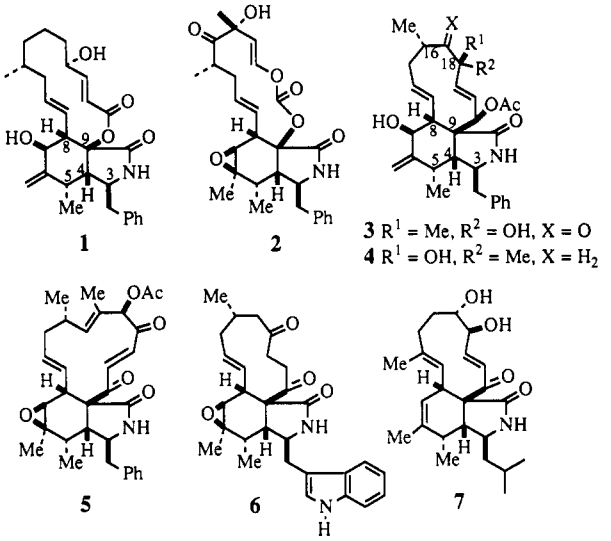
The cytochalasans are fungal metabolites of considerable importance because of their potent biological activities, including effects on transport across mammalian cell membranes and cell morphology.[1,2] Structurally they are characterized by the presence of a reduced isoindolone nucleus fused to a macrocyclic ring, which can be either a lactone, as in cytochalasin B (1),[2] a carbonate, as in cytochalasin E (2),[3] or a carbocycle, as in cytochalasins D,[2] H,[4] and K (3–5).[5] The biosynthesis of the cytochalasans has been studied[6] and the N(2)–C(4) fragment shown to be derived from an amino acid, usually phenylalanine,[7] although other amino acids can be incorporated, e.g., tryptophan into cytochalasin G (6)[8] and leucine into the aspochalasans, e.g., aspochalasin C (7)[9] (Scheme I).

In developing a synthesis of the cytochalasans, two problems that have to be overcome are the control of stereochemistry, particularly around the heavily functionalized isoindolone nucleus, and the efficient formation of the macrocyclic ring. Most approaches to the isoindolone have used Diels–Alder reactions. However, the efficient formation of macrocyclic rings is still a major problem in organic synthesis because of competing intermolecular processes, and several approaches have been developed for the introduction of the macrocyclic ring into cytochalasan precursors including ring-expansion and fragmentation processes, together with direct ring formation. The *simultaneous* formation of the isoindolone and the large ring via an intramolecular Diels–Alder reaction is the focus of the present Account, although relevant intermolecular Diels–Alder reactions will be discussed first to introduce the chemistry that is involved.

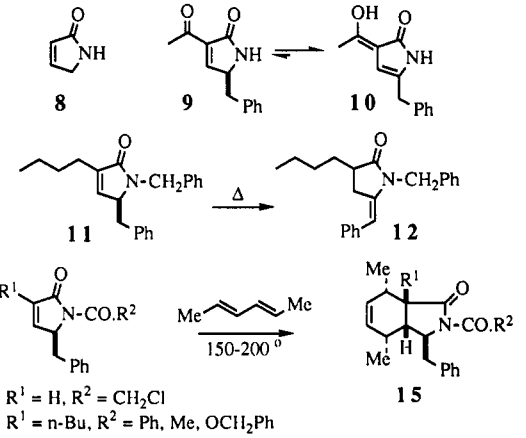
Hydroisoindolone Synthesis via Intermolecular Diels–Alder Reactions

Synthesis of the isoindolone fragment of the cytochalasans via Diels–Alder reactions of pyrrol-2(5*H*)-ones has been widely investigated, with the nature of the N-substituent being found to be particularly important.

Scheme I
Representative Cytochalasans



Scheme II
Pyrrol-2(5*H*)-ones as Dienophiles



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(1) Pendse, G. S. *Recent Advances in Cytochalasans*; Chapman and Hall: London, 1986.
(2) Binder, M.; Tamm, C. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 370–380.

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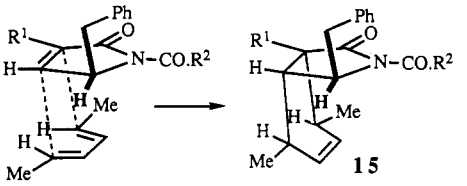


Figure 1. Stereoselectivity of diene approach to pyrrol-2-(5*H*)-ones.

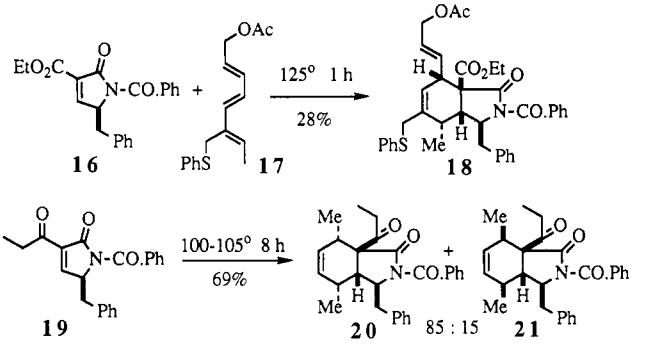
The parent pyrrol-2(5*H*)-one (**8**)[10] is thermally unstable, and the 3-acetylpyrrol-2(5*H*)-one **9** undergoes irreversible tautomerism to its enol **10**,[11] and so these are unsuitable for use as dienophiles. Moreover, the 1,5-dibenzyl-3-butylpyrrol-2(5*H*)-one (**11**) isomerizes to its 5-benzylidene isomer **12** rather than undergoing Diels–Alder reaction with (*E,E*)-2,4-hexadiene or cyclopentadiene.[12] However, the introduction of an electron-withdrawing substituent at N(1) dramatically changes the chemistry of pyrrol-2(5*H*)-ones, and they become useful Diels–Alder dienophiles, e.g., the *N*-acylpyrrol-2(5*H*)-ones **13**[13] and **14**[12] both react stereoselectively with (*E,E*)-2,4-hexadiene (Scheme II).

The difference in reactivity between the *N*-acyl- and *N*-alkylpyrrol-2(5*H*)-ones has been attributed to an increase in the antiaromatic character of the enol tautomer of the *N*-acyl compounds due to delocalization of the N lone pair of electrons into the exocyclic carbonyl group.[14] This phenonemon also prevents racemization of the 1-acyl-5-benzylpyrrol-2(5*H*)-ones during Diels–Alder reactions.

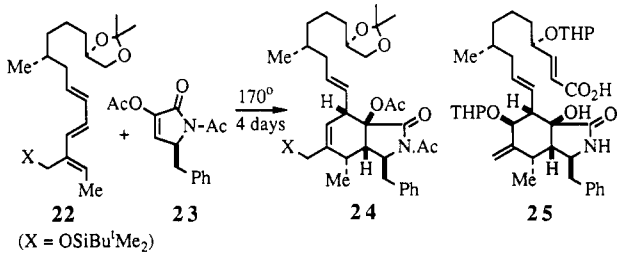
Of particular interest in connection with cytochalasan synthesis is the stereoselectivity of these reactions. It appears that there is a preference for the diene to approach the less hindered face of the dienophile, away from the benzyl substituent at C(5), endo to the pyrrol-2(5*H*)-one ring (see Figure 1). This mode of addition gives rise to the stereochemistry required for a cytochalasan synthesis at all five stereogenic centers and is a key feature of this synthetic approach.

Rather vigorous conditions were required for Diels–Alder addition of the monoactivated pyrrol-2(5*H*)-ones **13** and **14** to conjugated dienes. However, *N*-acylpyrrol-2(5*H*)-ones with electron-withdrawing groups at the 3-position, being doubly activated dienophiles, are more reactive, although somewhat unstable, and undergo Diels–Alder reactions with a wider range of conjugated dienes and trienes. For example, the 3-(ethoxycarbonyl)pyrrol-2(5*H*)-one **16** reacts with triene **17**

Scheme III
3-Acylpyrrol-2(5*H*)-ones as Dienophiles



Scheme IV
Synthesis of Cytochalasin B (1)



to give adduct **18**,[14] and the 3-acylpyrrol-2(5*H*)-one **19** reacts with (*E,E*)-2,4-hexadiene to give a mixture of adducts **20** and **21**.[12] Again the major product of these reactions was formed by addition of the diene to the less hindered face of the dienophile endo to the pyrrol-2-(5*H*)-one ring (Figure 1; Scheme III).

An intermolecular Diels–Alder reaction was used in the first synthesis of cytochalasin B (**1**),[15] in which the triene **22** and the monoactivated 3-acetoxypyrrol-2-(5*H*)-one **23** were combined to give adduct **24** (170 °C, 4 days, 40% conversion). Conversion into the seco acid **25**, which had previously been transformed into cytochalasin B (**1**),[16] completed the total synthesis (Scheme IV).

Simultaneous Macrocycle and Hydroisoindolone Formation by Intramolecular Diels–Alder Cyclization

The work outlined above demonstrated that Diels–Alder reactions can be used to synthesize the isoindolone fragment of the cytochalasans. However, there remained the difficulty of assembling the macrocyclic ring. One attractive approach appeared to be to use the Diels–Alder reaction in an *intra*molecular mode to assemble the isoindolone and the macrocyclic ring simultaneously. This strategy would avoid complications of regioselectivity encountered in an intermolecular Diels–Alder approach, but it was not clear whether polymerization of the diene–dienophile via intermolecular cycloaddition reactions would interfere.

Formation of the large-ring system of the cytochalasans via an intramolecular Diels–Alder reaction was first investigated using diene anhydride **26**. Heating a dilute solution of **26** in toluene under reflux induced cyclization to give the adducts **27** and **28**, so demonstrating

(3) Buchi, G.; Kitaura, Y.; Yuan, S.-S.; Wright, H. E.; Clardy, J.; Demain, A. L.; Glinsukon, T.; Hunt, N.; Wogan, G. N. *J. Am. Chem. Soc.* **1973**, *95*, 5423–5425.
(4) Beno, M. A.; Cox, R. H.; Wells, J. M.; Cole, R. J.; Kirksey, J. W.; Christoph, G. G. *J. Am. Chem. Soc.* **1977**, *99*, 4123–4130.
(5) Fex, T. *Tetrahedron Lett.* **1981**, *22*, 2703–2706.
(6) Wyss, R.; Tamm, C.; Vederas, J. C. *Helv. Chim. Acta* **1980**, *63*, 1538–1541.
(7) Vederas, J. C.; Tamm, C. *Helv. Chim. Acta* **1976**, *59*, 558–566.
(8) Cameron, A. F.; Freer, A. A.; Hesp, B.; Strawson, C. J. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1741–1744.
(9) Neupert-Laves, K.; Dobler, M. *Helv. Chim. Acta* **1982**, *65*, 1426–1431.
(10) Bocchi, V.; Chierici, L.; Gardini, G. P. *Tetrahedron* **1970**, *26*, 4073–4082.
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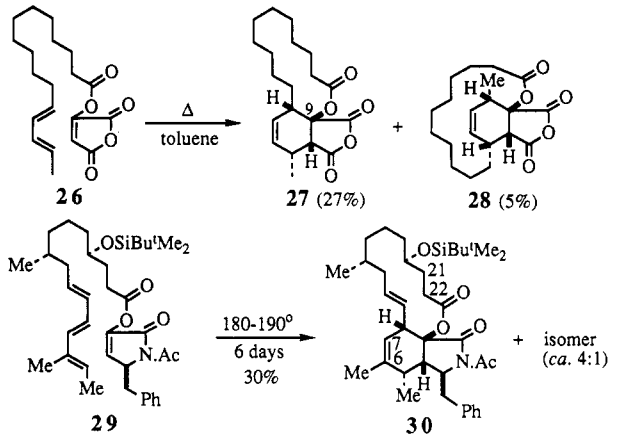
(12) Harkin, S. A.; Singh, O.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1489–1499.
(13) Vedejs, E.; Gadwood, R. C. *J. Org. Chem.* **1978**, *43*, 376–378.
(14) Vedejs, E.; Campbell, J. B., Jr.; Gadwood, R. C.; Rodgers, J. D.; Spear, K. L.; Watanabe, Y. *J. Org. Chem.* **1982**, *47*, 1534–1546.
(15) Stork, G.; Nakahara, Y.; Nakahara, Y.; Greenlee, W. J. *J. Am. Chem. Soc.* **1978**, *100*, 7775–7777.
(16) Masamune, S.; Hayase, Y.; Schilling, W.; Chan, W. K.; Bates, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 6756–6758.

Scheme V
Macrolide Cytochalasans by Intramolecular Diels–Alder Reactions

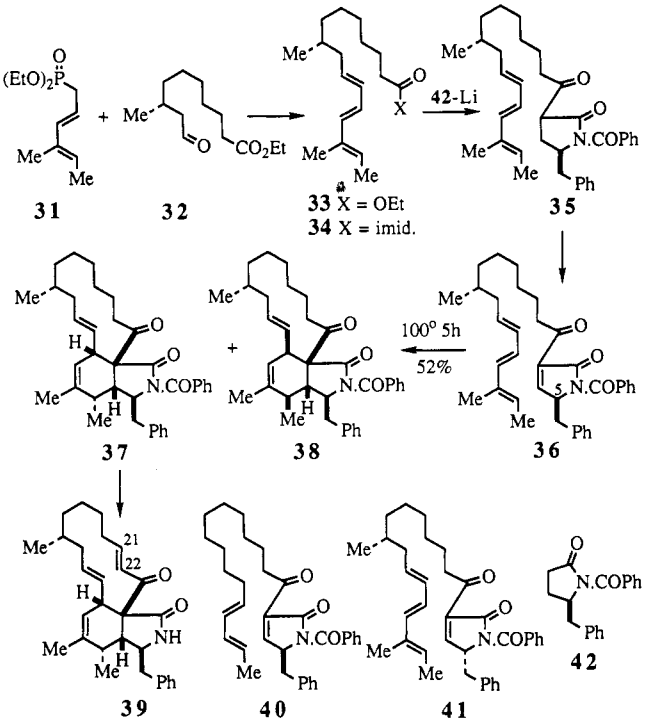


the viability of this approach. However, the yield was only modest because of competing hydrolysis of the enol ester under the high dilution conditions.[17,18] Nevertheless, this strategy was used successfully in the second synthesis of cytochalasin B (1), in which the trienyl pyrrol-2(5*H*)-one **29** was heated at 180–190 °C for 6 days to give a mixture of Diels–Alder products, yield 30%, ratio *ca.* 4:1, with the required isomer **30** as the major component. Introduction of the 21,22-double bond and oxidation at C(6)–C(7) completed the synthesis of cytochalasin B[19] (Scheme V).

The greater reactivity of the doubly activated 3-acylpyrrol-2(5*H*)-ones, e.g., **19**, as dienophiles, suggested that intramolecular Diels–Alder reactions of these compounds would provide useful access to carbocyclic cytochalasans. Difficult steps in the synthesis were identified as the stereoselective synthesis of the conjugated triene, the assembly of the sensitive 3-acylpyrrol-2(5*H*)-one incorporating the conjugated triene, and the Diels–Alder cyclization itself. Procedures for carrying out these reactions were developed during a synthesis of proxiphomin (**39**)[20,21] (Scheme VI).

The dienyl phosphonate **31**[20] was condensed with the homochiral aldehyde **32** to give the acid-sensitive (*E*,*E*,*E*)-trienyl ester **33** (60%), only minor amounts of other stereoisomers being detected, and the ester was converted into the acyl imidazolide **34**. The homochiral pyrrolidinone **42**, available from (*S*)-phenylalanine, was deprotonated by using lithium hexamethyldisilazide, and the enolate so obtained was acylated by using imidazolide **34** to give the 3-acylpyrrolidinone **35**. Oxidation to the 3-acylpyrrol-2(5*H*)-one **36** was achieved by phenylselenation, and oxidative elimination using *m*-chloroperoxybenzoic acid at low temperature, in the presence of an excess of hydrogen peroxide, a procedure that effected selective oxidation of the selenide in the presence of the conjugated triene. The acylpyrrol-2(5*H*)-one **36** was unstable and polymerized on attempted isolation, but could be detected in solution by ^{1}H NMR. Nevertheless, on heating in a dilute solution

Scheme VI
Synthesis of Proxiphomin (39)



at 100 °C, Diels–Alder cyclization occurred, to give two adducts, **37** and **38**, 50–55%, ratio 52:48. N-Debenzoylation and phenylselenation–oxidative elimination, to introduce the 21,22-double bond, gave proxiphomin (**39**).[21]

It was reassuring that the Diels–Alder reaction of the trienoyl pyrrol-2(5*H*)-one **36** had been reasonably efficient and that it could be carried out under relatively mild conditions. This contrasted with the behavior of the analogous diene **40**, which gave poor yields of Diels–Alder products on thermolysis, the lower reactivity of the conjugated diene allowing increased decomposition of the unstable 3-acylpyrrol-2(5*H*)-one to compete with cyclization.[20] However, the lack of exo–endo selectivity observed during the cyclization of **36** was disappointing, although this appeared to be a feature of 13-membered-ring formation, since cyclization of 11-membered-ring precursors was much more stereoselective, vide infra.[20] No epimerization at C(5) of the pyrrol-2(5*H*)-one **36** was detected during its cyclization. A mixture of the 5*S* and 5*R* diastereoisomers **36** and **41** was synthesized from racemic pyrrolidinone and shown to give four adducts, i.e., **37** and **38** and the analogous adducts from the (5*R*)-pyrrol-2(5*H*)-one **41**, which were not detected as products from **36**.[21]

This intramolecular Diels–Alder strategy was applied to synthesize cytochalasin H (**4**).[22] The chiral centers at C(16) and C(18) were introduced by stereoselective peracid epoxidation of the allylic alcohol **44**, available from methyl (2*S*)-3-hydroxy-2-methylpropanoate (**43**), followed by reduction of the epoxide **45** using lithium aluminum hydride to give diol **46**. Conventional chemistry was used to convert the diol into the long-chain aldehyde ester **47**, which was converted into the conjugated triene **48**, and into the 3-acylpyrrol-2(5*H*)-one **49** using the chemistry developed during the proxi-

(17) Bailey, S. J.; Thomas, E. J.; Turner, W. B.; Jarvis, J. A. J. *J. Chem. Soc., Chem. Commun.* **1978**, 474–475.
(18) Bailey, S. J.; Thomas, E. J.; Vather, S. M.; Wallis, J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 851–859.
(19) Stork, G.; Nakamura, E. *J. Am. Chem. Soc.* **1983**, *105*, 5510–5512.
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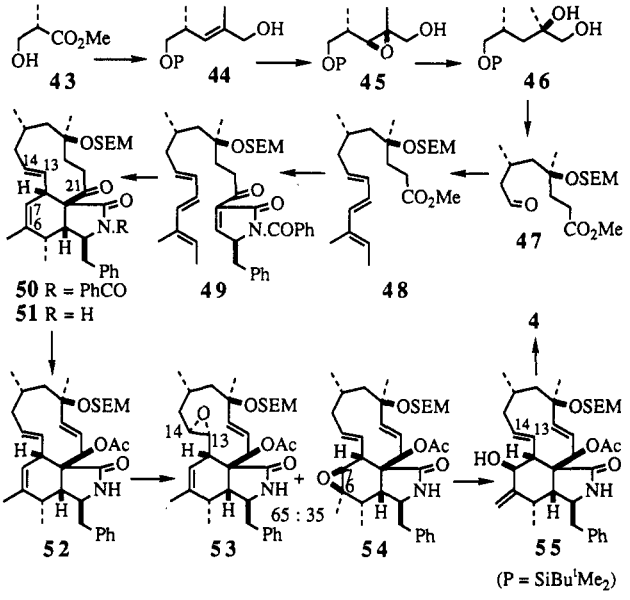
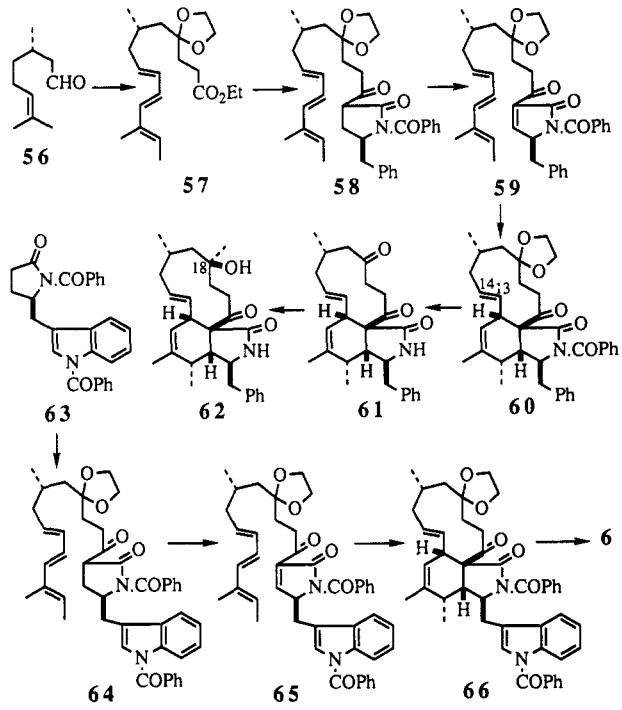
(21) Thomas, E. J.; Whitehead, J. W. F. *J. Chem. Soc., Perkin Trans. 1* **1989**, 499–505.
(22) Thomas, E. J.; Whitehead, J. W. F. *J. Chem. Soc., Perkin Trans. 1* **1989**, 507–518.

Scheme VII
Synthesis of Cytochalasin H (4)



Scheme VIII
Alternative Approach to Cytochalasin H (4) and Synthesis of Cytochalasin G (6)



phomin synthesis. The Diels–Alder reaction of pyrrol-2(5*H*)-one **49** was carried out by heating a dilute solution in toluene at 80–100 °C for 5 h and was highly stereoselective, giving the required adduct **50** (38%) as the only isolable product. Mild base hydrolysis gave the N-deprotected lactam **51** (Scheme VII).

Modification of the 11-membered ring was carried out by phenylselenation–oxidative elimination, followed by reduction of the enone using sodium borohydride, this reduction being highly stereoselective due to the screening of the carbonyl group by the 11-membered ring. Acetylation gave allylic acetate **52**, which was epoxidized to give a mixture of epoxides **53** and **54**, although epoxidation of the ketone **51** gave only the C(6)–C(7) epoxide, perhaps because of through-bond electron withdrawal from the 13,14-double bond by the carbonyl group at C(21). Rearrangement of epoxide **54** gave the allylic alcohol **55**, which was deprotected to provide cytochalasin H (**4**).[22]

As an alternative procedure for introduction of the chiral centers at C(16) and C(18), citronellal (**56**) was converted via trienyl ester **57** and pyrrolidinone **58** into the 3-acylpyrrol-2(5*H*)-one **59**. Diels–Alder cyclization was stereoselective and gave the adduct **60** (58%) together with a small amount, 1–2%, of its 13(14)-*Z* isomer. N-Deprotection and acetal hydrolysis gave the diketone **61**, which reacted regio- and stereoselectively with methylmagnesium chloride in THF to give the tertiary alcohol **62** (84%), which has the same stereochemistry at C(18) as cytochalasin H (**4**)[23] (Scheme VIII).

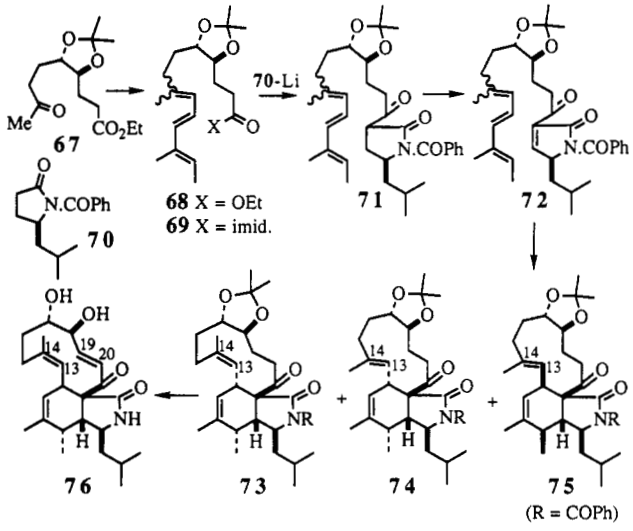
Triene **57** was also incorporated into a synthesis of cytochalasin G (**6**).[24] The pyrrolidinone required for this synthesis, **63**, was obtained from tryptophan ethyl ester and acylated by using the imidazolide derived from ester **57** to give the pyrrol-2(5*H*)-one **65** after oxidation. Diels–Alder cyclization gave **66**, which was converted into cytochalasin G (**6**) by acetal hydrolysis, cyclohexene epoxidation, and N-deprotection.[24]

Problems were encountered during attempts to use the intramolecular Diels–Alder approach to synthesize aspochalasin C (**7**).[25] Condensation of the dienyl phosphonate **31** with the methyl ketone **67**, available from diethyl tartrate, gave the conjugated triene **68** as a mixture of 8*E* and 8*Z* isomers, ratio *E*:*Z* = 75:25. This mixture was not separated, but was converted to the imidazolide **69**, which was used to acylate the lithium salt of the leucine-derived pyrrolidinone **70**. Phenylselenation–oxidative elimination gave the pyrrol-2(5*H*)-ones **72**, which were heated as a dilute solution in toluene at 85 °C to effect Diels–Alder cyclization. Three Diels–Alder products were isolated, which were identified as the 13(14)-*Z* isomer **73** together with the two 13(14)-*E* isomers **74** and **75**, ratio 3:1:2, respectively, combined yield 30%. It appeared that the *major* Diels–Alder product **73** had been derived from the *minor* (*Z*)-trienyl pyrrol-2(5*H*)-one (8′*Z*)-**72**, which had cyclized stereoselectively as usual, whereas the *major* (*E*)-trienyl pyrrol-2(5*H*)-one (8′*E*)-**72** had cyclized nonstereoselectively to give a mixture of endo and exo isomers in which the usually observed endo product **74** was the *minor* component. On the basis of isolated yields, it was not clear whether *E*–*Z* isomerization of the trienes had been taking place under the reaction conditions, but the overall result was that the 13(14)-*E* isomer **74** required for aspochalasan synthesis was only a minor product. The major product **73** was converted into the 13(14)-*Z* isomer **76** of aspochalasin C, by deprotection and phenylselenation–oxidative elimination[25] (Scheme IX).

The intramolecular Diels–Alder approach was finally applied to synthesize cytochalasin D (**3**).[26] Meth-

(23) Sauter, R.; Thomas, E. J.; Watts, J. P. *J. Chem. Soc., Perkin Trans. 1* **1989**, 519–523.
(24) Dyke, H.; Steel, P. G.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 525–528.
(25) Craven, A. P.; Dyke, H.; Thomas, E. J. *Tetrahedron* **1989**, *45*, 2417–2429.
(26) Merifield, E.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1990**, 464–466.

Scheme IX
Synthesis of Isoaspochalasin C (76)



acrolein was treated with (*E*)-2-butenyldiisopinocampheylborane (**77**), to give the anti homoallylic alcohol **78** after oxidative workup, together with a small amount (<10%) of its syn diastereoisomer. Claisen rearrangement using triethyl orthoacetate gave the ester **79**, which was hydroborated and oxidized to give aldehyde **80**. Condensation with the dienyl phosphonate **31** gave the conjugated triene **81**, which as its imidazolide **82** was condensed with the pyrrolidinone **42**. Oxidation by the usual procedure gave the 3-acylpyrrol-2(5*H*)-one **84**, which on heating in dilute solution in toluene cyclized to give the Diels–Alder product **85** (25–35%), together with a minor diastereoisomer (ca. 4%) (Scheme X).

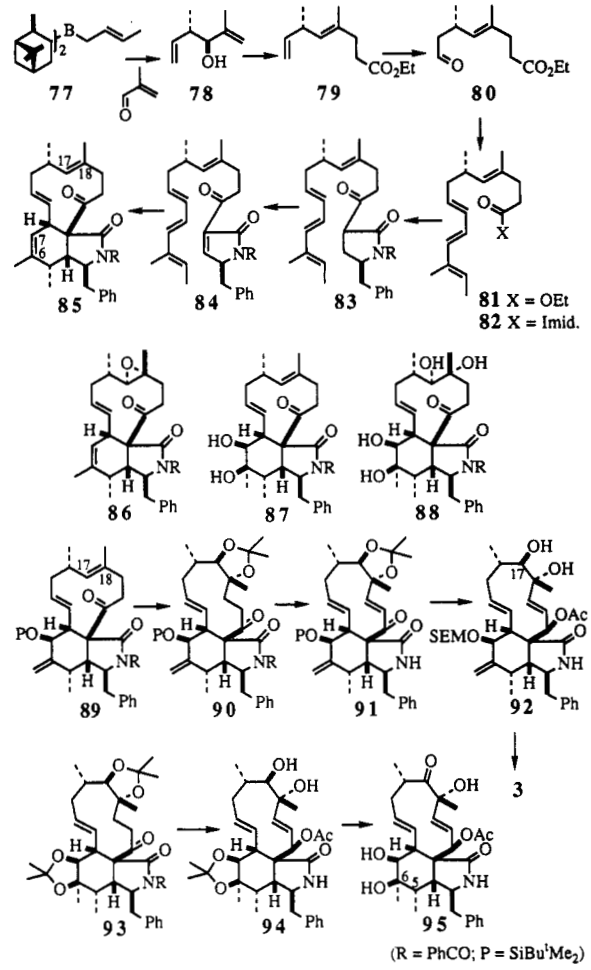
Whereas *m*-chloroperoxybenzoic acid reacted on the less hindered face of the 17,18-double bond of the adduct **85** to give epoxide **86**, osmium tetraoxide reacted selectively on the 6,7-double bond to give diol **87** together with a small amount of the tetrol **88**. Perhaps the peracid is reacting selectively at the more electron rich trisubstituted double bond, while osmium tetraoxide reacts at the more accessible.

Selective protection of diol **87**, followed by dehydration, gave the exocyclic alkene **89**, which was oxidized stereoselectively with osmium tetraoxide, to give acetonide **90** after diol protection. Phenylselenation, N-deprotection, and oxidative elimination gave the enone **91**, which was reduced with sodium borohydride–cerium(III) chloride and acetylated, followed by desilylation, SEM protection, and acetonide hydrolysis to give the diol **92**. Finally, selective oxidation of the secondary alcohol at C(17) with oxalyl chloride–DMSO gave cytochalasin D (**3**) after deprotection.[26]

During the course of this work, selective modifications based on tetrol **88** were investigated.[27] This tetrol could be isolated in an improved yield (69%) by using 2 molar equiv of osmium tetraoxide and was protected as its bis-acetonide **93**. Introduction of the allylic acetate into the 11-membered ring was carried out as in the cytochalasin D synthesis, and selective hydrolysis of the 17,18-acetal gave diol **94**. Swern oxidation of the C(17) secondary alcohol followed by acetal hydrolysis gave the trihydroxy ketone **95**, which had spectroscopic data

(27) Merifield, E.; Thomas, E. J., unpublished observations.

Scheme X
Syntheses of Cytochalasins D and O (3 and 95)



identical with those of cytochalasin O,[28] so establishing the stereochemistry of this natural product at C(5) and C(6). An alternative approach to cytochalasin D has been reported.[29]

Other Approaches to Cytochalasan Synthesis

Imides have been used as dienophiles during syntheses of the isoindolone fragment of the cytochalasans with regioselective reduction of the adducts **96** being developed to provide hydroxy lactams **97** (R′ = H).[30] Treatment with acidic methanol then gave the ethers **97** (R′ = Me), which with tribenzylaluminum gave the isoindolones **98**. Oxidation at C(9) gave **99**, which may be useful for a cytochalasan B synthesis.[30] The intermolecular Diels–Alder reaction between the dienol **100** and the alkylidenemalonate **101** gave the adduct **102** with the wrong stereochemistry at C(9), but this was corrected by a ring-opening and -closing sequence to complete an efficient synthesis of the isoindolone **103**.[31,32] An alternative intramolecular Diels–Alder approach, developed in connection with a fragmentation route to the 11-membered ring, is based

(28) Edwards, R. L.; Maitland, D. J.; Whalley, A. J. S. *J. Chem. Soc., Perkin Trans. 1* **1989**, 57–65.
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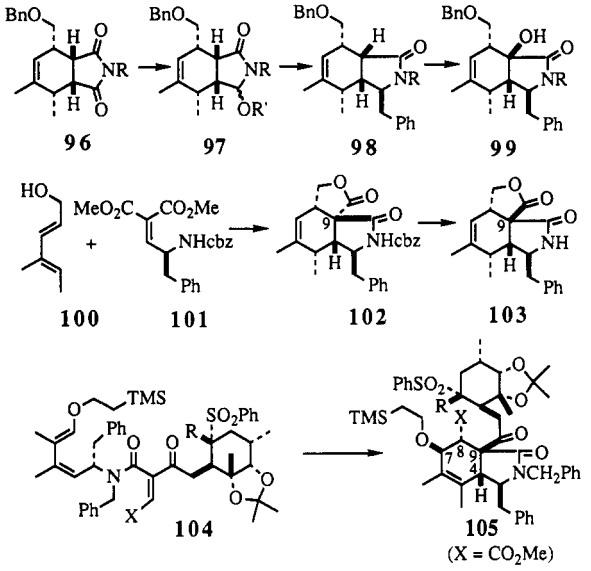
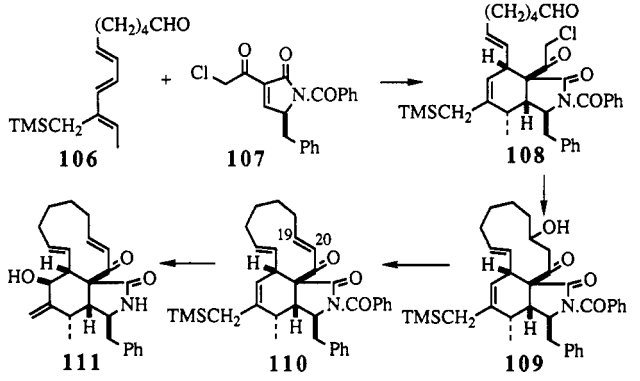
Scheme XI
Other Isoindolone Syntheses



Scheme XII
Synthesis of Cytochalasans via a Reformatski Reaction

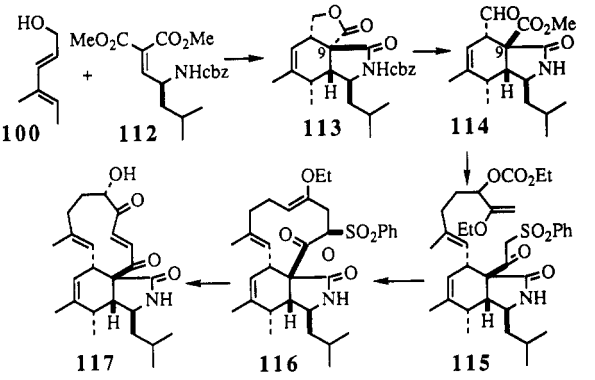


on a Diels–Alder process using (*Z*)-dienes in which the C(4)–C(9) and C(7)–C(8) bonds are formed. For example, cyclization of the diene **104** gave a good yield of the isoindolone **105**[33,34] (Scheme XI).

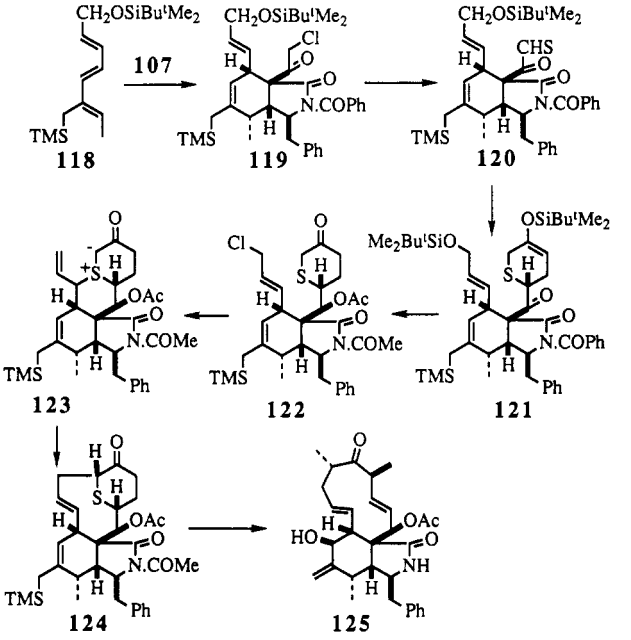
Other procedures for the formation of the 11-membered ring of the carbocyclic cytochalasans include a modified Reformatski procedure[35] and a transition-metal-mediated process.[36] Diels–Alder addition of the triene **106** with the 3-acylpyrrol-2(5*H*)-one **107** gave the isoindolone **108** (79%), which cyclized on slow addition of Rieke zinc in THF to give the cytochalasan **109** (75%) as a 1:1 mixture of epimers; samarium iodide was more selective but less efficient (46%). Dehydration of one of the isomers gave mainly the (19(20)-*E*)-alkene **110**, which was taken through to the methylenecyclohexanol **111**.[35] The other epimer of **109** gave mainly the 19(20)-*Z* isomer of **110** on dehydration and led to a mixture of **111** and its 19(20)-*Z* diastereoisomer[35] (Scheme XII).

Aspochalasin B (**117**) has been synthesized via a transition-metal-mediated cyclization of the 11-membered ring.[36] Isoindolone **113** was prepared via an intermolecular Diels–Alder reaction between diene **100** and the leucine-derived dienophile **112** and was converted into aldehyde **114**, with the correct configuration at C(9), by the ring-opening and -closing sequence. Modification of the ester and aldehyde groups gave the sulfone **115**, which was cyclized by using a palladium catalyst, to give the aspochalasan precursor **116** as a single diastereoisomer (49%). Stereoselective epoxidation of the enol ether double bond followed by hydrolysis and elimination of the sulfone gave aspochalasin B (**117**)[36] (Scheme XIII).

Scheme XIII
Synthesis of Aspochalasin B (117)



Scheme XIV
Synthesis of Zygosporin E (125) via Sulfur Ylide Chemistry



In addition to the direct formation of the 11-membered ring of the cytochalasans, ring-expansion and ring-fragmentation procedures have been developed, one useful route being based upon the 2,3-rearrangement of sulfonium ylides.[37,38] The intermolecular Diels–Alder reaction between the triene **118** and the acylpyrrol-2(5*H*)-one **107** gave adduct **119** (93%). This was used to generate the thioaldehyde **120**, which was trapped by a 2-silylated butadiene to give the dihydrothiopyran **121** as the major product after equili-

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bration under basic conditions. Conversion into the thiopyranone **122** followed by treatment with sodium iodide generated the sulfonium ylide **123**, which rearranged to form the sulfur-bridged cytochalasan **124** (65%) together with minor isomeric products.[38] Further modification gave rise to zygosporin E (**125**)[39] (Scheme XIV).

Another approach to the 11-membered-ring system of the cytochalasans based on fragmentation of keto toluene-*p*-sulfonates has been described.[40]

Conclusion

Intramolecular Diels–Alder reactions of 3-acylpyrrol-2(5*H*)-ones would appear to provide useful access to macrocyclic compounds including [11]cytochalasans, although improved methods are required for stereoselective 13-membered-ring formation. Conformational factors affecting the endo–exo selectivities of these reactions have not been elucidated, although it is likely that they are under kinetic control. Further work on other approaches to cytochalasan synthesis is expected, thus making these complex, biologically active molecules, and their analogues, more readily available for chemical and biological study. Further insights into the processes involved in their biosynthesis are of interest. Is an enzymically mediated Diels–Alder reaction involved?[41,42]

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Calicheamicins: Discovery, Structure, Chemistry, and Interaction with DNA

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Introduction

The enediyne class of antitumor antibiotics represented in Chart I by calicheamicin γ_1^I (**1**),[1] esperamicin A_1 (**2**),[2] dynemicin A (**3**),[3] and neocarzinostatin (**4**)[4] are some of the most potent antitumor agents ever discovered. Calicheamicin γ_1^I is over 1000 times more potent than adriamycin, a clinically useful antitumor antibiotic, when tested in murine tumor models. The remarkable biological properties of this class of compounds appear to be a consequence of their ability to interact with cellular DNA and initiate double-stranded cleavage by carbon-centered diradical hydrogen abstraction processes. The elucidation of the chemical structures of **1** and **2** has stimulated intense synthetic efforts in a number of academic laboratories.

Similarities between the calicheamicins and the esperamicins were recognized quite early in our studies of the calicheamicins due to the extreme potency of both families of compounds, the presence of a thio sugar in both, and characteristic proton signals of their aglycons. However, the close structural relationships between these two families of compounds were not recognized until the structures of calicheamicin γ_1^I and the esperimicins were published simultaneously.[1,2] Dynemicin A shares with the calicheamicins in having a 10-membered enediyne ring system, although the remainder of its structure is very different. The chemical structure of the neocarzinostatin chromophore is only remotely related to that of the calicheamicins. The conjugated diacetylenic ring systems of these potent antitumor antibiotics can undergo cycloaromatization

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