196. Approaches to the Total Synthesis of Cytochalasans. A Convergent Synthesis of the Octahydroisoindolone Moiety Related to Proxiphomin.

Preliminary Communication[1])

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Summary

The octahydroisoindolone moiety related to proxiphomin (**1**) has been synthesized by condensation of *N*-benzyloxycarbonyl-protected D,L-phenylalaninal (**7**) with methyl-(4-methyl-sorbyl)-malonate (**11**) to yield the branched ethylene derivative **12**. Consecutive intramolecular [2+4]-cycloaddition and lactam ring closure of **12** gave the desired octahydroisoindolone derivative **15**, possessing adaptable functional groups for the attachment of the macrocyclic ring system.

The cytochalasans are secondary metabolites of microorganisms which exhibit unusual biological effects on mammalian cells [1]. Their unusual structures [1] represent an exciting and difficult challenge for partial and total synthesis.

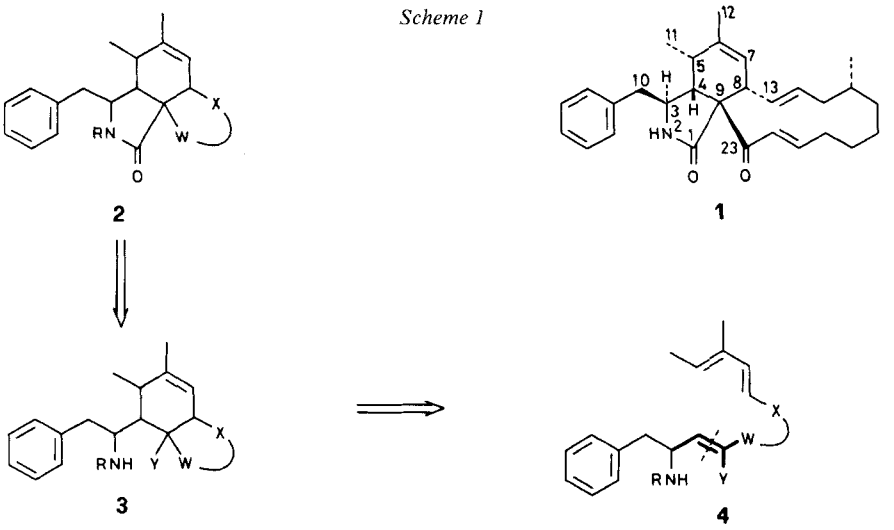
Any rational approach to this type of molecule involves two major synthetic problems, namely the formation of the bicyclic octahydroisoindolone moiety and the attachment of the macrocyclic ring. Hitherto no approach has provided a satisfactory solution of these problems [2–5].

In this communication we wish to report the regiospecific construction of the octahydroisoindolone portion related to proxiphomin (**1**) based on the principle of a convergent synthesis. Analysis of the cytochalasane structure reveals the importance of the linkage between carbon atoms C(4) and C(9). A suitable creation of this unit should permit pseudo-symmetrical functionalisation leading to the formation both of the heterocyclic five-membered ring system as well as of the carbocyclic six-membered ring as shown in *Scheme 1*. According to the aforementioned dislocations[2]), we decided to prepare first a *Synthon A* containing the atoms N(2), C(3), C(4) and C(10) (connected to a phenyl group) and secondly a *Synthon B* including the centers C(1), C(5), C(6), C(7), C(8), C(9), C(11), C(13) and C(23) *(Scheme 2)*.

[1]) Presented in a lecture given by *Ch. T.* at the *Euchem Stereochemistry Conference Bürgenstock*, 30th April–6th May 1978.

[2]) The term 'dislocation' is used to denote an antithetic step. *Cf. Ian Fleming*, 'Selected Organic Syntheses', J. Wiley & Sons Ltd., London, New York, Sydney, Toronto, 1972.

Scheme 1



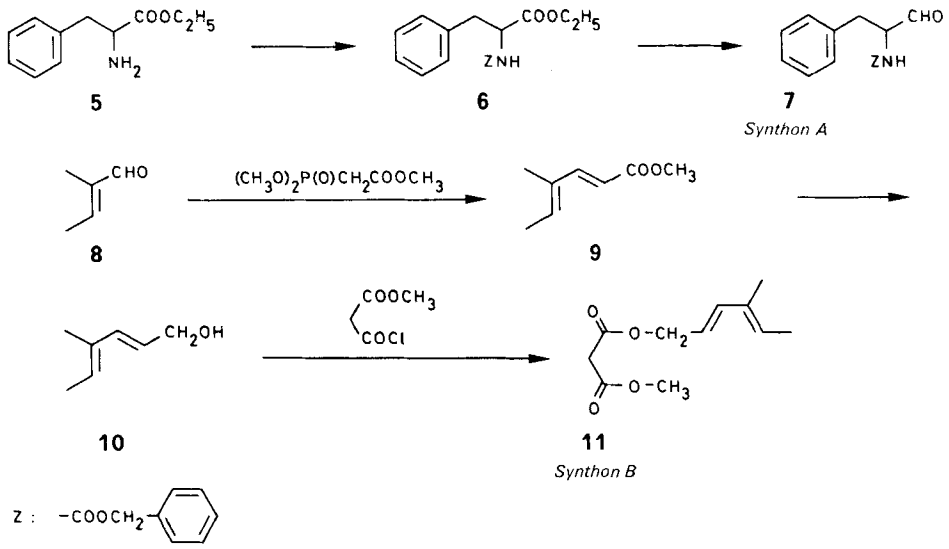
The benzyloxycarbonyl derivative **6** [6] of D,L-phenylalanine ethyl ester (**5**) was reduced by diisobutylaluminium hydride in benzene/toluene [6] to give D,L-*N*-benzyloxycarbonyl-phenylalaninal (**7**) *(Synthon A)* of m.p. 77–78° [7]. A small amount of the corresponding alcohol was obtained as well. The overall yield of pure **7** starting from **5** was about 56%.

The preparation of *Synthons of type B* containing conjugated systems was more difficult due to the tendency for intra- and intermolecular condensation. The most suitable compound possessing adequate stability proved to be the mixed malonic ester **11**. It was obtained in 65% yield by the reaction of malonic methylester chloride and 4-methyl-sorbinol (**10**) in dichloromethane in the presence of one equivalent of triethylamine. For the synthesis of 4-methyl-sorbinol (**10**) [2], tiglic aldehyde (**8**) served as starting material. Condensation of **8** with trimethyl phosphonoacetate in benzene using sodium hydride as base gave methyl 4-methyl-sorbate (**9**). The latter was reduced by lithium aluminium hydride in ether. The overall yield of **10** was 38%. Compound **11** was characterized by mass spectrometry showing *m/e* 212 (M^+) and *m/e* 194 ($M^+ - H_2O$) as typical heavy ions and by the ^{1}H-NMR. spectrum (60 MHz, $CDCl_3$): 1.73 (*m*, 6 H, 2 CH_3); 3.37 (*s*, 2 H, $CO-CH_2-CO$); 3.73 (*s*, 3 H, $O-CH_3$); 4.67 ($d \times d$, $J=7$, $J'<1$, 2 H, $O-CH_2$); 5.25–5.85 (*m*, 2 H, $CH=CH-C(CH_3)=CH-CH_3$); 6.31 ($d \times d$, $J=15$, $J'<1$, 1 H, $CH=CH-C(CH_3)=CH-CH_3$).

The condensation of *Synthon A* (**7**) with *Synthon B* (**11**) was successfully performed in benzene solution under the conditions of a *Knoevenagel-Cope* reaction with piperidinium benzoate as catalyst. The reaction yielded a mixture of several compounds as identified by TLC. using UV.-absorption for detection[3]).

[3]) A detailed analysis of the reaction mixture is under way.

Scheme 2



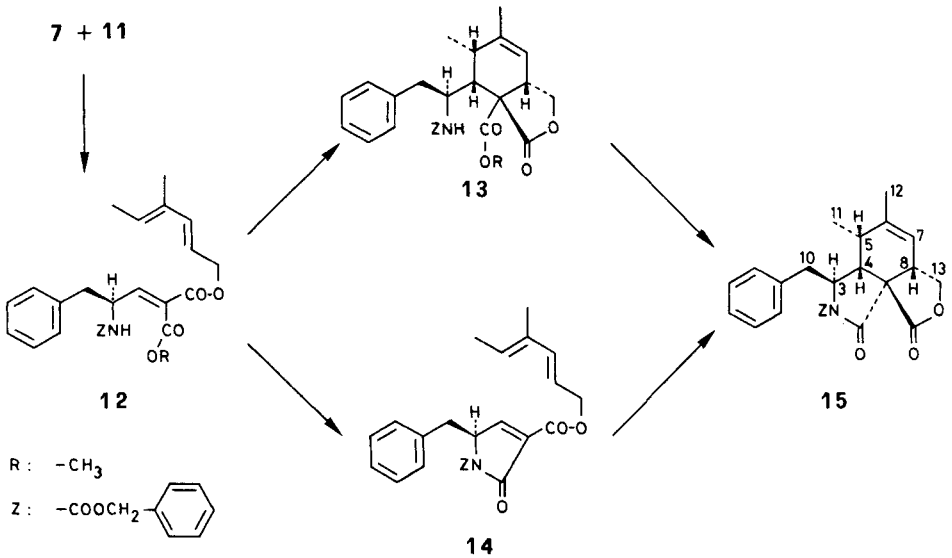
Fractionation of the mixture by column chromatography on silica gel resulted in the isolation of pure tricyclic compound **15**, m.p. 174–175° in *ca.* 10% yield. The pertinent pathways leading to **15** are outlined in *Scheme 3*[4]).

Evidently, initial condensation occurs between the aldehyde **7** and the active methylene compound **11** to form the (*E*)-olefin **12** as a primary product. Further conversion of **12** to **15**, effected by prolonged heating of the reaction mixture, may proceed formally either with the *Diels-Alder* reaction occuring first to yield the bicyclic cyclohexene derivative **13** or by prior closure of the pyrrolinone ring to form the monocyclic product **14**. An intramolecular [2+4]-cycloaddition of this type may lead to four different isomers. The assignment of structure **15** is based on the following evidences: elemental analysis (Calc. C 72.79, H 6.11, N 3.14%; Found C 72.60, H 6.22, N 3.07%) confirming the molecular formula $C_{27}H_{27}NO_5$, is in agreement with the peak of the heaviest ion *m/e* 446 ($M^+ + 1$) in the mass spectrum which additionally exhibits typical fragments at *m/e* 354, 338, 310, 147, 133 and 91. Carbonyl stretching frequencies in the IR. spectrum of **15** appear as strong bands at 1716, 1745 and 1763 cm^{-1} belonging to the γ-lactam, the carbamate (ZN) and the γ-lactone, respectively. Further information concerning structure **15** emerged from the 400 MHz ^{1}H-NMR. spectrum ($CDCl_3$)[5]). Application of selective decoupling techniques resulted in the unequivocal assignment of all relevant H-atoms: 0.89 (*d*, $J(5,11)=7.0$, 3 H–C(11)); 1.71 (br. *s*, $J(8,12)=1.8$, 3 H–C(12)); 2.03–2.13 (*m*, $J(4,5)=5.7$, $J(5,11)=7.0$, 1 H–C(5)); 2.17 (*d*×*d*, $J(3,4)=9.2$, $J(4,5)=5.7$, 1 H–C(4)); 3.07–3.12 (*m*, 1 H–C(8)); 3.15 (*d*×*d*, *J (gem)*=

[4]) All reactions have been performed with racemic compounds, but only the natural enantiomers are depicted.

[5]) We thank Dr. *H.P. Kellerhals* and Mr *R. Hoerdt*, Spectrospin AG., Fällanden, for the measurement of this spectrum.

Scheme 3



14.0, $J(3,10)=7.0$, 1 H–C(10)); 3.31 ($d\times d$, $J(gem)=14.0$, $J'(3,10)=3.0$, 1 H–C(10)); 4.04 (d, $J(gem)=8.4$, $J(8,13)=0$, 1 H–C(13)); 4.64 ($d\times d$, $J(gem)=8.4$, $J'(8,13)=6.0$, 1 H–C(13)); 5.10 ($d\times d\times d$, $J(3,4)=9.2$, $J(3,10)=7.0$, $J'(3,10)=3.0$, 1 H–C(3)); 5.31–5.35 (m, 1 H–C(7)); 5.35 and 5.39 (AB, $J(gem)=12.0$, CH_2 of Z-group); 7.01–7.53 (m, 10 H, 2 phenyl). The observed values of the coupling constants $J(3,4)=9.2$ Hz and $J(4,5)=5.7$ Hz are in agreement with a *trans* relationship of the H-atoms at C(3) and C(4) and a *cis* relationship between the H-atoms at C(4) and C(5) according to formula **15**. The formation of **15** corresponds to the expected course of the *Diels-Alder* reaction for which a *pseudo-endo* addition from the less hindered side of the olefinic double bond bearing the asymmetric substituent, is kinetically favoured.

The synthetic route described above starts from a derivative of phenylalanine, a chiral natural product. Consequently, any other natural or unnatural α-amino acid may be used as starting material for the synthesis of structural analogues.

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