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SIMPLIFIED CYTOCHALASINS. 1. SYNTHESIS OF VERSATILE PERHYDROISOINDOLONE INTERMEDIATES.

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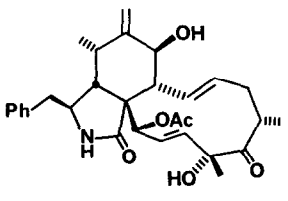
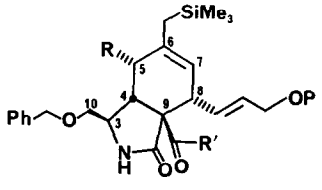
Summary: The chiral synthesis of key intermediates in the preparation of simplified cytochalasin based biological probes is described.

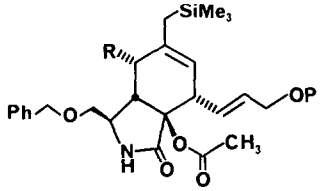
The cytochalasins are a group of naturally occurring cytotoxic fungal metabolites which have been shown to elicit a plethora of unusual responses in biological systems.[2] Structure activity studies[3] of these cytochalasins have been unable to elucidate the molecular interactions responsible for these responses, primarily due to the complexity of these molecules and the broad spectrum of responses elicited by any single cytochalasin molecule. In an effort to simplify the spectrum of biological responses, facilitate identification of receptor sites, and probe the mechanism of the biological processes with which the cytochalasins interfere, we are preparing structurally simplified analogs of the cytochalasins, which retain what we anticipate to be the key pharmacophoric structural characteristics.



Cytochalasin D



R = H, CH_3
R′ = CH_3, Ph
1



R = H, CH_3
2

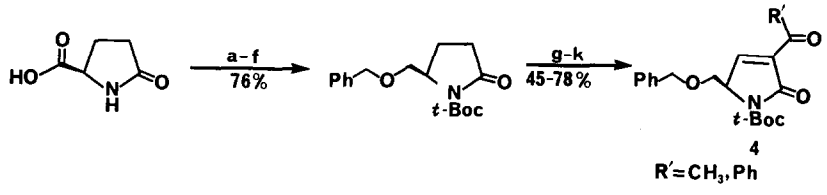
In this communication we report the design and chiral synthesis of versatile perhydroisoindolone intermediates **1** and **2**, which serve as starting points for the preparation of a variety of simplified cytochalasin-like target molecules that lack an intact macrocycle. These intermediates are capable of functional and structural elaboration in four important regions of the molecule. The allylic silane facilitates incorporation of alkyl or heteroatom electrophiles at C-7, and the introduction of other functionality in the C-5 - C-7 region. The allylic oxygen at C-8 and the acyl group at C-9 permit elaboration or extension of the "northern" and

"southern" appendages. Finally, the benzyloxy group at C-10 imparts aromaticity known to be necessary for biological activity, and also serves as a protected hydroxymethyl which may be elaborated into other useful aromatic moieties.

The key step in the construction of **1** and **2** is a Diels-Alder reaction between the trienes **3a** and **3b**, and the pyrrolidenones **4** and **5**.[4] The cycloaddition reaction, proceeding via an endo transition state with respect to the cyclic imide,[5] should provide the perhydroisoindolone ring system with the correct relative stereochemistry at all five asymmetric centers. Moreover, the use of an optically active pyrrolidenone dienophile would result in complete asymmetric induction in the perhydroisoindolone framework.

Our synthesis of the optically active pyrrolidenone dienophiles **4** proceeds from L-pyroglutamic acid as outlined in Scheme I. The t-butyloxycarbonyl protected lactam is obtained in 76% yield by nitrogen protection/O-benzylation, a sequence which unfortunately required intermediate hydroxyl protection as its ethoxyethyl ether.[6] Acylation and subsequent phenyl selenation provided a 1.5:1 mixture of diastereomeric selenides. This mixture was the immediate precursor to the pyrrolidenone **4**, which was typically generated via the selenoxide immediately prior to the cycloaddition reaction. The pyrrolidenone **4** ($R=CH_3$) has been isolated by rapid flash chromatography as a reasonably pure oil; however, substantial decomposition of this material occured at room temperature within 24 hours, precluding prolonged storage.

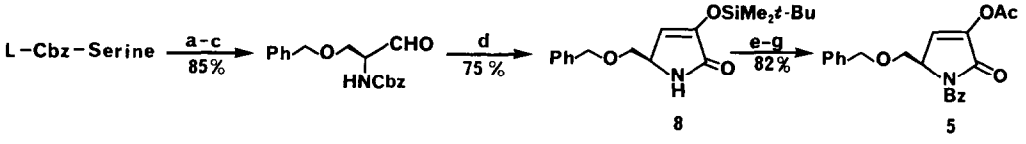
Scheme I



Reagents:
a) MeOH, $SOCl_2$; b) $NaBH_4$; c) EVE, H^+; d) $t\text{-BuO})_2C{=}O$, NaH; e) PPTS, MeOH;
f) NaH, $PhCH_2Br$; g) $LiN(TMS)_2$,THF,-78°C; h) $R'COCl$; i) $KN(TMS)_2$, 0°C; j) PhSeCl; k) m-CPBA

The acetoxy substituted pyrrolidenone **5** has been prepared by the synthetic pathway outlined in Scheme II. L-Cbz-serine was converted in 78% yield to the corresponding aldehyde via DIBAL reduction of the Weinreb amide. This aldehyde was condensed with the t-butyldimethylsilyl protected phosphonate[7] to form the α,β-unsaturated ester which cyclized under the reaction conditions to give **8**.[8] Benzoylation, desilylation and acetylation provided pyrrolidenone **5**, in 82% yield.

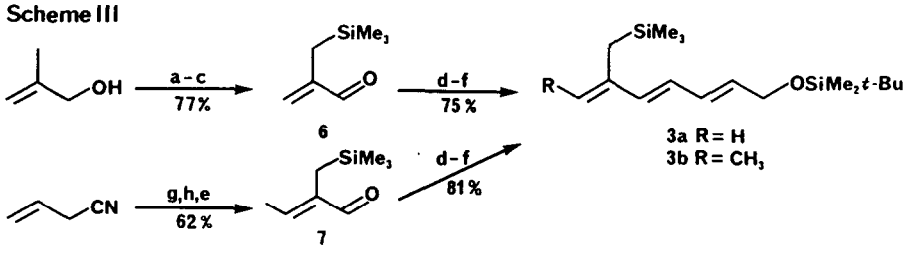
Scheme II



a) NaH, $PhCH_2Br$; b) MeONHMe, DCC; c) $i\text{-}Bu_2AlH$, -78°C; d) $(EtO)_2P(O)\bar{C}(OTBS)CO_2Et$ Li^+
e) LDA, PhCOCl; f) $Et_3NH^+F^-$; g)Ac_2O, Pyridine, DMAP

The trienes **3a** and **3b** were prepared as outlined in Scheme III.[9] Aldehydes **6** and **7** were prepared from methallyl alcohol and allyl cyanide in 77% and 62% yield respectively. Olefination with the crotyl phosphonate reagent, DIBAL reduction and protection provided the trienes in 75% and 81% respectively from the aldehydes.

Scheme III



Reagents:
a) 2 n-BuLi; b) 2 TMSCl, H_3O^+; c) Swern Oxidation; d) $(EtO)_2P(O)\overset{-}{C}H\overset{Li^+}{}CH{=}CHCO_2Et$;
e) i-Bu_2AlH; f) t-$BuMe_2SiCl$, DMAP; g) LDA, -78°C; h) $TMSCH_2I$, 0°C

The Diels-Alder reactions between the pyrrolidenone dienophile **4** and the trienes **3a** and **3b** proceeded readily in refluxing dichloromethane.[9] The predominant product of these reactions was **1**, isolated in 78-83% yield by flash chromatography on silica gel. The identity of the adducts was established by PMR decoupling experiments, and by comparison with spectra of a similar Diels-Alder adduct reported in the total synthesis of cytochalasin G.[4a] The designated regiochemistry was verified by the allylic methine proton at C-5, which is coupled to the bridgehead methine proton at C-4 and collapses to a quartet upon irradiation of the C-4 proton at 2.55 ppm. The stereochemistry between C-4 and C-5, resulting from an endo transition state, places the two protons cis, as verified by the 2.6 Hz coupling constant.[4a]

Cycloaddition of the pyrrolidenone dienophile **5** with the triene **3a** occurred after 4 hours in refluxing toluene (with $Eu(fod)_3$ as a mild Lewis acid catalyst) providing perhydroisoindolone **2** in 50-65% yield. Pyrrolidenone **5** is significantly less reactive than the doubly activated pyrrolidenone dienophile **4** and some decomposition occurred at the elevated temperatures. No other Diels-Alder cycloadducts were isolated in this reaction.

We have developed conditions for the selective removal of the tert-butyldimethylsilyl protecting group, and the benzoyl protecting group, and elaboration of the allyl silane into exocyclic and endocyclic olefins at C-6 - C-7. These transformations, and the interesting biological activity of several target molecules will be reported elsewhere.

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1. G. A. Krafft is a fellow of the American Cancer Society, 1983-1986.

2. Tanenbaum, S. W., Ed. (1978) "Cytochalasins, Biochemical and Cell Biological Application"; North-Holland Publishing Co.: Amsterdam.

3. a. Yahara, I., Harada, F., Sekita, S., Yoshihira, K., and Natori, S. (1982) J. Cell Biol., **92**, 69-78; b. Rampal, A. L., Pinkosky, H. B., and Jung, C. Y. (1980) Biochemistry, **19**, 679-684; c. Weiland, T. and Low, I. (1980) Biochemistry, **19**, 3363-3369.

4. For similar approaches in total synthetic efforts see: a. Vedejs, E. and Reid, J. G.(1984), J. Amer. Chem. Soc. 106, 4617-4618; b. Stork, G. and Nakamura, E. (1983), ibid. 105, 5510-5512.

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6. All intermediates and target compounds were fully characterized and gave satisfactory ^{1}H and ^{13}C NMR, IR, and mass spectral data. ^{1}H NMR data for key compounds are as follows:
Selenide precursor to **4** (R=Ph), δ ($CDCl_3$): 8.35 - 7.06 (m, 20H, aromatic), 4.97 (d, J = 14.7 Hz, 1H, benzylic CH_2, minor), 4.75 (d, J = 15.3 Hz, 1H, benzylic **CH_2**, major), 4.36 - 4.09 (m, 3H, benzylic, CH_2O), 3.83 (m, 1H, minor, N methine), 3.58 (m, 1H, major, N methine), 3.08 (dd, J_1 = 14.0 Hz, J_2 = 7.0 Hz, 1H, β-CH_2, minor), 3.00 (dd, J_1 = 14.6 Hz, J_2 = 6.71 Hz, 1H, β-CH_2, major), 2.42 (dd, J_1 = 14.6Hz, J_2 = 7.63 Hz, 1H, β-CH_2, major), 2.30 (dd, J_1 = 14.0 Hz, J_2 = 7.02 Hz, 1H, β-CH_2 minor).

5($CDCl_3$): 7.70 - 7.30 (m, 10H, aromatic), 7.12 (d, J = 3.0 Hz, 1H, vinyl) 5.16 (m, 5 line overlapping ddd, J_1 = J_2 = 3.0 Hz, J_3 = 6.1 Hz), 4.53 (s, 2H, **OCH_2**Ph), 3.94 (dd, J_1 = 10.5 Hz, J_2 = 3.0 Hz, 1H, OCH_2), 3.78 (dd, J_1 = 10.5 Hz, J_2 = 6.1 Hz, 1H, OCH_2), 2.26 (s, 3H, CH_3)

1 (R=H R^1=Ph, P=Bz, $CDCl_3$): 8.06 - 7.22 (m, 15H, aromatic), 5.77 (dd, J_1 = 7.83 Hz, J_2 = 15.6 Hz, 1H, E vinyl) 5.68 (dt, J_1 = 15.6 Hz, J_2 = 6.02 Hz, 1H, E vinyl), 5.26 (d, J = 4.88 Hz, 1H, C-7 vinyl), 4.73 (2m, 4H, **CH_2**Ph, **CH_2**OBz), 4.60 (m, 2H, CH_2O), 4.25 (m, 1H, N methine), 3.98 (dd, J_1 = 7.83 Hz, J_2 = 4.88 Hz, C-8 methine), 3.63 (dd, J_1 = 3.96 Hz, J_2 = 8.15 Hz, 1H, C-4 methine), 2.59 (dd, J_1 = 3.96 Hz, J_2 = 16.0 Hz, 1H, C-5 CH_2), 2.33 (dd, J_1 = 16.0 Hz, J_2 = 8.15 Hz, 1H, C-5 CH_2), 1.57 (s, 2H, **CH_2**$SiMe_3$), 0.0 (s, 9H, $SiMe_3$)

7. Nakamura, E. (1981) Tetrahedron Lett. 22, 663-66.

8. The Cbz group was lost in this reaction, which also produced 10-20% E olefin, incapable of cyclization.

9. Triene **3b** has been reported (ref. 5b), but the synthesis reported here is shorter and more efficient.

10. Generation of pyrrolidenone **4** and subsequent Diels-Alder reaction were carried out as follows: The selenide, 1,3-di-benzoyl-3-phenylselenyl-5-benzyloxy methyl-2-pyrrolidinone (30mg, 5.26 x 10^{-5} mole) was dissolved in CH_2Cl_2 (3mL) and cooled to -78°C. m-CPBA (18mg, 10.5 x 10^{-5} mole) in CH_2Cl_2 (3mL) was added dropwise and the mixture stirred for 30 minutes at -78°C. The mixture was warmed to 0° for 3 min. and then Me_2S (29mL, 33 mg, 5.26 x 10^{-4} mole) was added. The mixture was poured over saturated $NaHCO_3$ (10mL) and CH_2Cl_2 (10 mL) and after vigorous shaking the layers were separated. The organic layer was washed once more with saturated $NaHCO_3$ (10 ml), dried over $MgSO_4$ and filtered directly into a flask containing neat triene, 2-trimethylsilylmethyl-1,3,5-heptatrienol benzoate (79mg. 2, 63 x 10^{-4} mole). The mixture was stirred overnight at room temperature and then refluxed for 3 h. The solvent was removed and the mixture purified by flash chromatography on silica gel (7g) using 100:1 hexane-EtOAc to remove excess triene and 7:1 hexane-EtOAc to remove product, 29 mg (78%), R_f = 0.61 (1:2 EtOAc-hexane).

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