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CONSTRUCTION OF AN ISOINDOLONE PRECURSOR FOR SYNTHESIS OF THE MACROLACTONE CYTOCHALASINS

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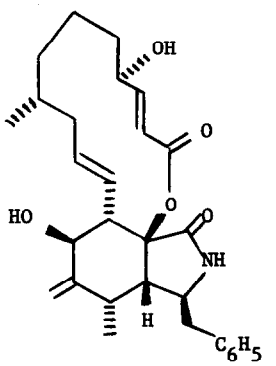
The cytochalasins are a group of about two dozen structurally related fungal metabolites having a wide range of biological activity.[2] Considerable effort has recently been described towards synthesis of these compounds.[3] Masamune, et al. have reported a partial synthesis of cytochalasin B (1) by an elegant series of transformations on naturally derived seco-compound 2.[3b] Thus a synthesis of 2 now will constitute a total synthesis of cytochalasin B. In this paper we describe an approach to the isoindolone portion of 2. We hope to use this strategy in total synthesis of a number of macrolactone-containing cytochalasins. Our synthetic



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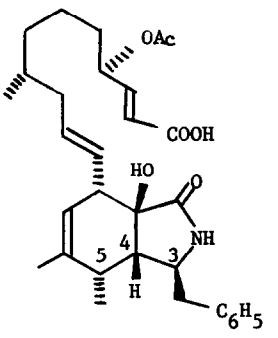

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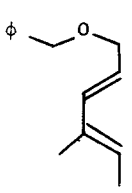
approach is based upon a novel coupling reaction of tribenzylalane.

Diene 3, prepared from the corresponding alcohol[3a] in 90% yield by treatment with benzyl bromide/NaH in DME, was combined with N-ethylmaleimide in a Diels-Alder reaction (5 hr, refluxing toluene) to afford adduct 4 (88%). Reduction of 4 with $NaBH_4$ gave about a 1/2 mixture of



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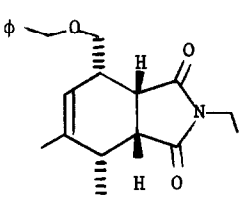

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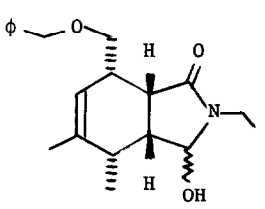

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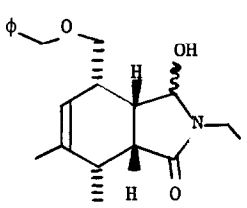

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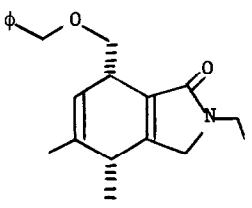

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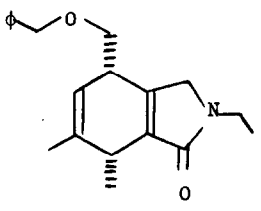

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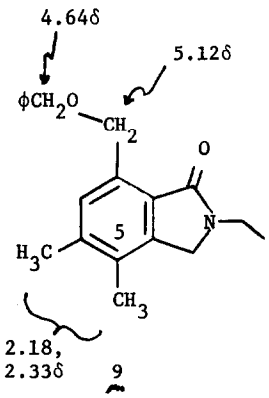
hydroxylactams 5 and 6 along with some unreacted starting material.[4] The structures of 5 and 6 were firmly established as follows: Treatment of 5 and 6 individually with p-TsOH/CH_3OH at



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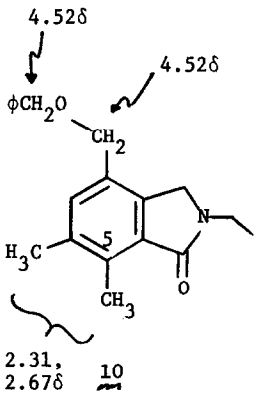

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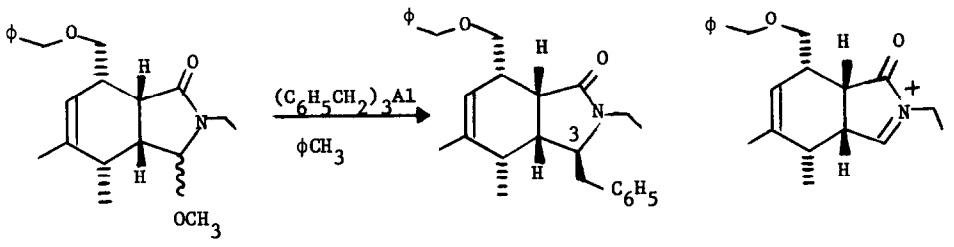
room temperature caused dehydration and double bond migration, yielding lactams 7 and 8 (60% yields). Dehydrogenation of these compounds (5%Pd/C, refluxing toluene) gave the phthalides 9 and 10, respectively, in 55% yields. The NMR spectra of 9 and 10 clearly supported these structural assignments. In particular, it is evident (see data on structures) that the lactam carbonyl of 9 deshields the benzyl protons, and similarly the carbonyl of 10 deshields the

methyl group at C-5.

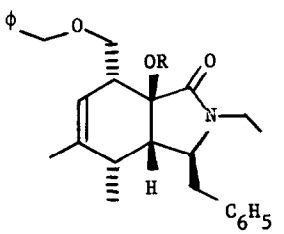


11 12 13

Reduction of imide 4 with diisobutylaluminium hydride in toluene at -78° to our delight produced only the desired hydroxylactam 5 (68%). We cannot satisfactorily rationalize this selectivity at present.[4]

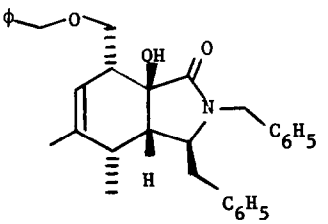
Careful treatment of 5 with methanolic hydrochloric acid (0°, 30 min) afforded crystalline methyl ether 11 in quantitative yield. We have found that ether 11 can be coupled with tribenzyl aluminum, generated in situ from benzyl magnesium chloride and aluminum chloride,[5] in refluxing toluene to produce a single benzylated product 12 in about 40% yield.[6] Although we cannot unequivocably establish C-3 stereochemistry at present, we believe that 12 must have the β-benzyl configuration, since the coupling probably occurs via transfer of a benzyl group from an alanate complex to the least hindered face of acyl imine 13.[6]

Introduction of an angular hydroxyl group into lactam 12 was readily accomplished by treatment with lithio hexamethyldisilazane in THF at -78°, followed by bubbling oxygen through the solution for one hour at 0°, and then allowing the mixture to stand at room temperature for 2 hours in the presence of excess trimethyl phosphite. A single product was isolated (60% yield) to which we have assigned structure 14.[7] This alcohol was further characterized as its



14 R = H

15 R = $COCH_3$



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acetate 15 formed by treatment of 14 with acetic anhydride/pyridine containing 4-dimethylamino-pyridine (100% yield).[7]

Once again, our stereochemical assignment is based upon mechanistic considerations: ie attack of oxygen on the anion derived from lactam 12 will occur from the unhindered β-face of the molecule, thus resulting in the β-alcohol 14.

Since the N-ethyl group of 14 is not readily removable we have also studied the N-benzyl series of compounds, and by an identical route have prepared hydroxylactam 16.[8,9] The regio-chemical and stereochemical specificity of reactions in this series was identical to that in preparing the N-ethyl compounds. Yields were comparable in both sequences.

Work is currently in progress on synthesis of compound 2 using the approach described above

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References and Notes

1. Fellow of the A. P. Sloan Foundation, 1975-79; Recipient of Career Development Award HL-00176 from the National Heart and Lung Institute, 1975-80; address correspondence to this author at The Pennsylvania State University.
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4. cf J. C. Hubert, J. B. P. A. Wijnberg and W. N. Speckamp, *Tetrahedron, 31,* 1437 (1975); *ibid, 34,* 179 (1978).
5. (a) R. Koster and G. Bruno, *Ann., 629,* 89 (1960); (b) J. J. Eisch and J. Biedermann, *J. Organometal. Chem., 30,* 167 (1971).
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7. Compound 14: IR ($CHCl_3$): 3350, 1660 cm^{-1}; NMR ($CDCl_3$)δ 7.26 (10H, m), 5.1 (1H, br s), 4.52 (1H, OH), 4.6 (2H, AB quartet, J=11 Hz), 2.1-4.3 (10H, m), 1.68 (3H, br s), 0.96 (3H, t, J=7 Hz), 0.76 (3H, d, J=7 Hz). Compound 15: IR: 1720, 1755 cm^{-1}; NMR: δ 7.2 (10H, m), 5.4 (1H, br s), 4.52 (1H, S), 2.4-4.2 (10H, m), 2.02 (3H, s), 1.7 (3H, br s), 0.9 (3H, t, J=7 Hz), 0.72 (3H, d, J=7 Hz).
8. The NH substituted imide related to 4 could not be reduced cleanly to a hydroxylactam using either dibal or $NaBH_4$. Also, attempted coupling of 11 with benzyl magnesium chloride gave only lactam 7 and no coupled product 12.
9. A beautiful total synthesis of cytochalasin B has just been reported: G. Stork, Y. Nakahara, Y. Nakahara and W. J. Greenlee, *J. Am. Chem. Soc., 100,* 7775 (1978).

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