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STUDIES ON THE ANTITUMOR AGENT CC-1065

Regiospecific Introduction of the Oxygen Functionality for the Synthesis of the B/C Component of CC-1065.

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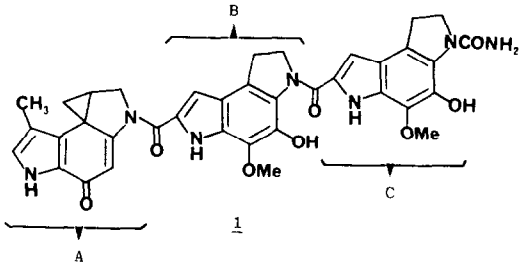
SUMMARY: The 3,3¹-bipyrrole 4 is readily converted into o-quinone 5, which was regiospecifically elaborated into the CC-1065 B/C-model component 15 by sequential reduction, alkylation and reduction reactions.

Recently, we have reported the successful application of the 3,3¹-bipyrrole strategy for synthesizing the A-portion of CC-1065 1.[1] *Here we describe the use of this strategy for the construction of the key features of the B/C components.*



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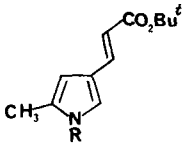
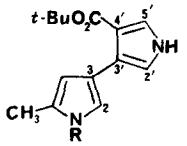


2 R = H
3 R = SO_2Ph



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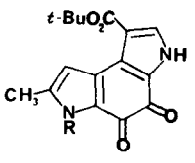

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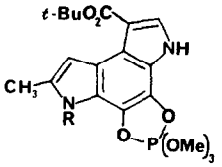

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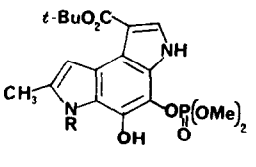

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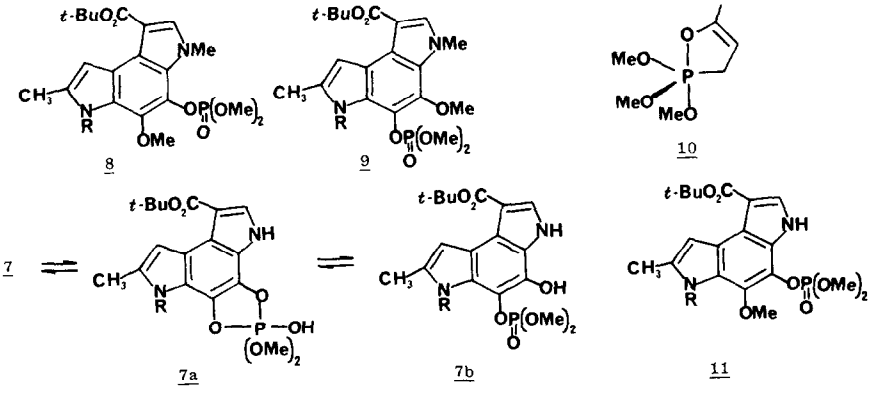
Treatment of t-butyl 2,4-pentadienoate[2] with MeCH(Ts) NC/NaH/THF/20°C gave the 1,6-addition product 2 (75%), which was directly converted into the N-phenylsulfonyl derivative 3 (65%) by standard methods. Pyrrole annulation of 3 using TOSMIC/NaH/THF/20°C resulted in the 3,3¹-bipyrrole 4 (75%). The purpose of the -CO_2Bu^t group is to block electrophilic substitution in the adjacent 5¹-position, and to provide the necessary electrophilicity needed to make 2 and 4.

When a solution of the bipyrrole 4 in CH_2Cl_2 at -78°C was treated with oxalyl chloride[3] in ether, and the mixture warmed to 20°C, the o-quinone 5 crystallized (85%), λ_{max}^{MeOH} 365, 255 and 220nm (ε, 3800, 4500 and 7500). Reduction of the o-quinone 5 using $P(OMe)_3$[4] in benzene gave the cyclic oxyphosphorane 6 (75%), which was rapidly hydrolyzed in wet THF to a single phenolic phosphate ester 7 (100%), m.p. 169-172°C (benzene/hexane). Treatment of 7 with Me_2SO_4/acetone/K_2CO_3 gave 8 (70%) and 9 (8%). Presumably, 7 can equilibrate via 7a to 7b, and thus give rise to the undesired regioisomer 9. The structure of 8 was established by single crystal X-ray crystallography.[5]



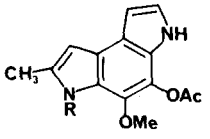
The N-methylation of 7 was avoided by treatment of 7 with the cyclic oxaphospholene 10 [prepared from $P(OMe)_3$ and methylvinylketone][6] in THF/20°C (neutral conditions) to give 11 (50%), m.p. 102-103°C. The structure of 11 was established by N-methylation, NaH/MeI, to give 8.

Removal of the phosphate group with NaOMe/MeOH, followed by Ac_2O gave

12 (80%). When a solution of 12 in $CHCl_3$ was treated with trifluoroacetic acid, at 20°C, the acid 13 was formed. While 13 proved to be resistant to the usual decarboxylation conditions associated with indole and pyrrole 3-carboxylic acids, triethylamine in toluene at 110°C/6h. gave 14 (80%). The unsubstituted 2,3-double bond in 14 was selectively reduced by exposure of 14 to $Et_3SiH/TFA/0°C$,[7] followed by Ac_2O to give the diacetate 15 (60%).

12 $R^1 = Bu^t$

13 $R^1 = H$



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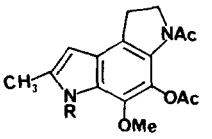

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In summary, the 3,3[1]-bipyrrole strategy, combined with o-quinone formation, $P(OMe)_3$ reduction, and oxaphospholene O-methylation provides a practical solution for constructing the requisite oxygenation pattern in the B/C portion of CC-1065.[8]

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References and Footnotes

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5. The structure of 8 has been determined crystallographically - see ortep below. Details are available on microfiche, from the Indiana University Chemistry Library - request Structure Report No. 83128.

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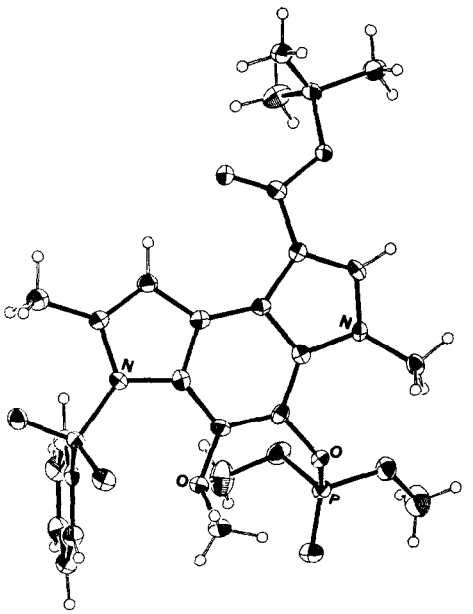
7. G. Guillerm, F. Frappier, J.C. Tabet, and A. Marquet, J. Org. Chem., 3776, 42 (1977).

8. All new compounds were characterized by ^{1}H NMR, IR and micro-analytical/ MS data.



ORTEP DRAWING OF 8

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