remaining diazomethane. It may be stored for several days under argon or sealed under vacuum, but a change in composition is noted by capillary GC after a few weeks. Pressures, amounts of materials, irradiation times, etc., for each photolysis are given in Ehlhardt's dissertation[23] (for the results of photolyses involving unlabeled materials, see Figure 2 and Ehlhardt's Table III; for photolyses with dideuteriodiazomethane, Ehlhardt's Table IV; and for photolyses of diazomethane in labeled 1-(2,2-dideuteriocyclopropyl)-2-vinylacetylene, Ehlhardt's Table V).

The mixtures are analyzed by capillary GC by using either Carbowax column. A sample trace from a photolysis at 15 torr of unlabeled materials can be seen in Ehlhardt's[23] Figure 16. Peaks corresponding to allylcyclopropylacetylene and cyclopropyl-*trans*-propenylacetylene are first identified by coinjection of authentic materials. Amounts of allylcyclopropylacetylene (D) vary from 0.4–25.0% of the main product, dicyclopropylacetylene (S), in photolyses carried out between 200 and 0.06 torr, respectively. Reproducibility of the integrations is within 0.2–0.3% for the ratios of products. The measured ratios tend to rise or fall if the amounts of material injected are much greater or smaller than the normal injection (0.5 μL of a 10% solution of the photolysis mixture in ether). Overall, the photolysis produces about 100 products in quantity greater than 0.01% of the starting material. Solvents used for the diazomethane solutions are present in amounts of less than 0.5% of the total and do not interfere with the measurement of any of the products.

Isolation of Allylcyclopropylacetylene (d_0 or d_2) and Cyclopropyl-*trans*-propenylacetylene (d_0 or d_2) from Gas-Phase Photolyses. Allylcyclopropylacetylene-d_2 is isolated and purified by preparative GC in four stages, except where otherwise noted. First, column CW1 is used to separate the main components (He flow 60 mL/min, column 110 °C). Unreacted cyclopropylvinylacetylene (retention time 22 min) and dicyclopropylacetylene (retention time 55 min) are recovered in greater than 95% purity, as assessed by capillary GC. Allylcyclopropylacetylene (retention time 30 min) and cyclopropyl-*trans*-propenylacetylene (retention time 33 min) are collected as a single fraction containing all materials eluting between cyclopropylvinylacetylene and dicyclopropylacetylene. In the second stage, column CW2 is used (He flow 60 mL/min, column 100 °C) to separate allylcyclopropylacetylene and cyclopropyl-*trans*-propenylacetylene (retention time 40 and 45 min, respectively), each as mixtures containing 2–3 other main components. Third, impure allylcyclopropylacetylene is enriched to 90–95% of purity by chromatography on column Ag (He flow 120 mL/min, column 55 °C, retention 5.5 min). Fourth, chromatography on column Ph (He flow 60 mL/min, column 130 °C, retention time 25 min) allows isolation of allylcyclopropylacetylene in 98% of purity, most of the impurity being butyl alcohol from the column. This material is suitable for ^{2}H NMR analysis and shows peaks for isomers **1**, **2**, and **3** only.

Two photolyses, carried out at 15 torr with CD_2N_2 and cyclopropylvinylacetylene, were processed by using the first three steps of the above preparative GC separation procedure and yielded allylcyclopropylacetylene-d_2 in 94% of purity in one experiment and 93% of purity in another. To remove the impurity, the two samples were united after measurement of ^{2}H NMR spectra (each 2–4 mg in 2 mL of CCl_4), concentrated by distilling CCl_4 slowly (over 5 h) through a 30 in. Vigreux column until 0.5 mL of solution remained, and rechromatographed on column Ag to give A in 98% of purity.

The mixture from the series of photolyses carried out at 1.5 torr using CD_2N_2 and cyclopropylvinylacetylene was separated by the procedure consisting of the first three steps outlined above. The resulting material was 92% pure and contained an impurity interfering with the ^{2}H NMR analysis. The ^{2}H NMR sample (5 mg in 2 mL of CCl_4) was concentrated by removing CCl_4 by slow distillation (over 5 h) through a 30 in. Vigreux column, leaving 0.3 mL of solution, which was chromatographed by using column Ph and afforded material 100% of purity with respect to known deuterium-containing compounds and 98% of purity overall (capillary GC). The results are recorded in Table II.

A sample of allylcyclopropylacetylene (d_0 from photolyses with unlabeled materials was isolated by preparative GC by using the first three steps of the procedure outlined above. The resulting material was 93–96% of purity (capillary GC) and served in identification of samples of allylcyclopropylacetylene produced in gas-phase photolyses by comparison of IR and NMR spectra.

Acknowledgment. We note with gratitude that this material is based upon work supported by the National Science Foundation under Grants CHE 76-24300 and 80-19427. W.v.E.D. expresses his thanks to Professor B. S. Rabinovitch for encouragement (June 1965 meeting of the National Academy of Sciences in Seattle, WA) to pursue the new strategy[7] in its implications for the premise of RRKM theory and to Professor W. R. Roth for highly valued criticisms incorporated into this manuscript.

Studies on the Synthesis of the Antitumor Agent CC-1065. Synthesis of the Unprotected Cyclopropapyrroloindole A Portion Using the 3,3′-Bipyrrole Strategy

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Contribution from the Department of Chemistry, Indiana University, Bloomington, Indiana 47405. *Received August 8, 1986*

Abstract: The total synthesis of the unprotected A portion of the potent cytotoxic agent CC-1065 **1** using the 3,3′-bipyrrole strategy is described. Treatment of ethyl sorbate with (*p*-tolylsulfonyl)methyl isocyanide (TosMIC)/NaH gave the pyrrole **7**, which was *N*′-phenylsulfonated and treated again with TosMIC/NaH/HMDS to give the 3,3′-bipyrrole **11**. Through a sequence of transformations involving the Mannich reaction and standard homologation, the bipyrrole **11** was converted into the carboxylic acid **18**, which was readily induced to undergo intramolecular cyclodehydration to give the tricyclic phenol **20**. Alternative methods for converting **11** into **20** were examined, but the sequence described above was the most efficient. The 2,3-double bond in **20** was selectively reduced by using $HSiEt_3$/TFA to give **33**, after acetylation during the workup. Reduction of the ester **33** gave **34**, which upon exposure to the Mitsunobu conditions, namely, $EtO_2CN{=}NCO_2Et/Ph_3P$/THF, gave the cyclopropapyrroloindole **35**. Deprotection of **35** to give first **36** and subsequently **2** was achieved by treatment with MeONa/MeOH. The substrate **35** was exposed to *p*-ClC_6H_4SH to give **37** and *p*-TsOH to give **38**. Initially, coupling studies demonstrated that the sodium salt of **2** on treatment with indole-2-carbonyl chloride gave **41**, albeit in low yield.

The potent cytotoxic agent CC-1065 has the unusual triindole structure **1**.[1] It is more active than actinomycin, vinblastine, or maytansine. The overall molecule has a helical topology, and as such, is able to bind into the minor groove of DNA, where the

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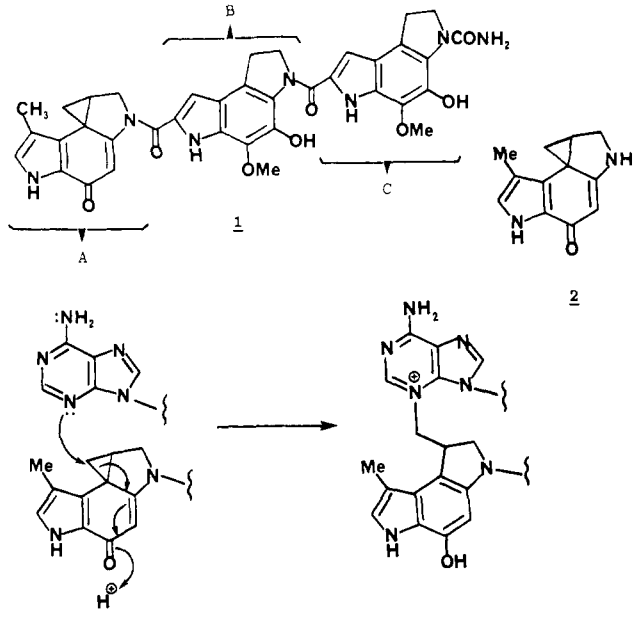
Scheme I



spirocyclopropane alkylates N-3 of adenine, Scheme I.[2] The interesting biology of CC-1065 has motivated a considerable amount of synthetic effort, not only to make CC-1065 itself, but simpler analogues with the prospect of reduced liver toxicity.[3] Since the spirocyclopropane A portion is responsible for irreversible DNA covalent bonding, it would be most desirable to construct the A portion as the free diamine **2**. This would allow the preparation of CC-1065 through amide coupling; a variety of simpler analogues are readily conceivable. In this paper we describe the complete details of the synthesis of **2** and related information.[4]

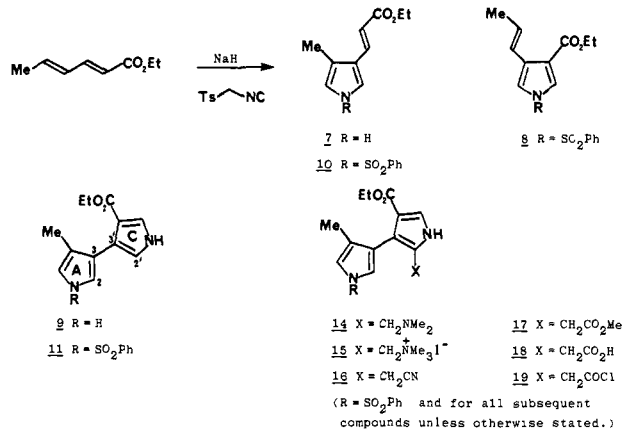
Strategy

While there are numerous ways to make substituted indoles, none of these methods provides a particularly convenient solution for constructing highly oxygenated and functionalized derivatives.[5] A possible solution, applicable to each portion of CC-1065, is to construct an appropriately substituted pyrrole and annulate on to it the additional benzenoid ring. For the specific problem of the A portion of **2** such a strategy requires the synthesis of a 3,3′-bipyrrole, **3**, and the subsequent placement of a two-carbon unit (acetic acid residue) at the 2- or 2′-position of **4**, in order to complete the central benzenoid ring. This strategy is outlined in Scheme II. An important feature of this approach is the need to differentiate between the two pyrrole systems at two crucial junctures in the synthesis. First, the regiospecific attachment of a two-carbon fragment either at C-2 or C-2′ (depending on the manner of attachment) is required (see **4**) and secondly, the selective reduction of the indole 2,3-double bond in **5**, without competitive reduction of the other indole ring. This can be accomplished by deactivation of the 3-methylpyrrole ring through N-sulfonylation. This type of deactivation is also necessary in order to be able to make the required 3,3′-bipyrrole. The final ring closure of the spirocyclopropane can be achieved by using the Winstein Ar-3′ reaction, **6**, paralleling the work of Wierenga.[3]

To implement this scheme a method for constructing the requisite 3,3′-bipyrrole **3** was needed. An ideal solution to this problem is to make use of the van Leusen (*p*-tolylsulfonyl)methyl isocyanide (TosMIC) chemistry for the synthesis of 3-substituted pyrroles.[6]

Results

Treatment of a suspension of NaH in ether at 0 °C with a Me_2SO solution of ethyl sorbate and TosMIC gave the 1,6-addition adduct **7** (80%). If this same reaction is carried out under aprotic conditions with THF as solvent and $LiN(SiMe_3)_2$ as the base, the 1,4-adduct **8** (61%) becomes the only product (isolated after N-phenylsulfonation). Excess TosMIC and NaH does not convert **7** into the 3,3′-bipyrrole **9**, because the electrophilicity of the α,β-unsaturated ester (presumably present as the N–Na salt) is drastically curtailed by the attached pyrrole ring (vinylogous amide). To add the second pyrrole ring, and also to provide the necessary differential protection between the two pyrrole rings, **7** was treated with $NaH/THF/PhSO_2Cl$ to give **10** (87%). When a solution of **10** and TosMIC in THF was added to a suspension of NaH in THF containing $HN(SiMe_3)_2$, the 3,3′-bipyrrole **11** was isolated in 85% yield after recrystallization. 3,3′-Bipyrroles are an extremely rare class of compounds; in fact, prior to this study, the only known example was the parent unsubstituted 3,3′-bipyrrole.[7]



The next part of the synthesis involves conversion of **11** into **4** or an equivalent. There are several viable methods by which this may be accomplished, and we chose to examine in detail two different and complementary strategies. The first involves the regiospecific electrophilic substitution preference of **11**, and the second utilizes alkylated TosMIC derivatives. In either case we have to attach a two-carbon appendage at 2′ in **11**.

Since both pyrrole rings in **11** are electron deficient relative to pyrrole itself and all of the more reactive positions are available for electrophilic substitution, it is not clear that **11** will undergo clean regiospecific substitution reactions with carbon electrophiles under Friedel–Crafts type conditions. On an optimistic note,

(1) CC-1065 was isolated from *Streptomyces zelensis*: Hanka, L. J.; Dietz, A.; Gerpheide, S. A.; Kuentzel, S. L.; Martin, D. G. *J. Antibiot.* **1978**, *31*, 1211. Structure: Martin, D. G.; Chidester, C. G.; Duchamp, D. J.; Mizsak, S. A. *Ibid.* **1980**, *33*, 902. Chidester, C. G.; Krueger, W. C.; Mizsak, S. A.; Duchamp, D. J.; Martin, D. G. *J. Am. Chem. Soc.* **1981**, *103*, 7629.

(2) Hurley, L. H.; Rokem, J. S. *J. Antibiot.* **1983**, *36(4)*, 383. Hurley, L. H.; Reynolds, V. L.; Swenson, D. H.; Petzold, G. L.; Scahill, T. A. *Science (Washington, DC)* **1984**, *226*, 843.

(3) Wierenga, W. *J. Am. Chem. Soc.* **1981**, *103*, 5621. Kraus, G. A.; Yue, S.; Sy, J. *J. Org. Chem.* **1985**, *50*, 284. Kraus, G. A.; Yue, S. *J. Chem. Soc., Chem. Commun.* **1983**, 1198. For the synthesis of an *o*-cyclohexadienone version of **2**, see: Sundberg, R. J.; Nishiguchi, T. *Tetrahedron Lett.* **1983**, *4773*. Rawal, V. H.; Jones, R. J.; Cava, M. P. *Tetrahedron Lett.* **1985**, *2423*. Rawal, V. H.; Cava, M. P. *J. Chem. Soc., Chem. Commun.* **1984**, 1526. For references to the B/C components of CC-1065, see the following paper in this issue.

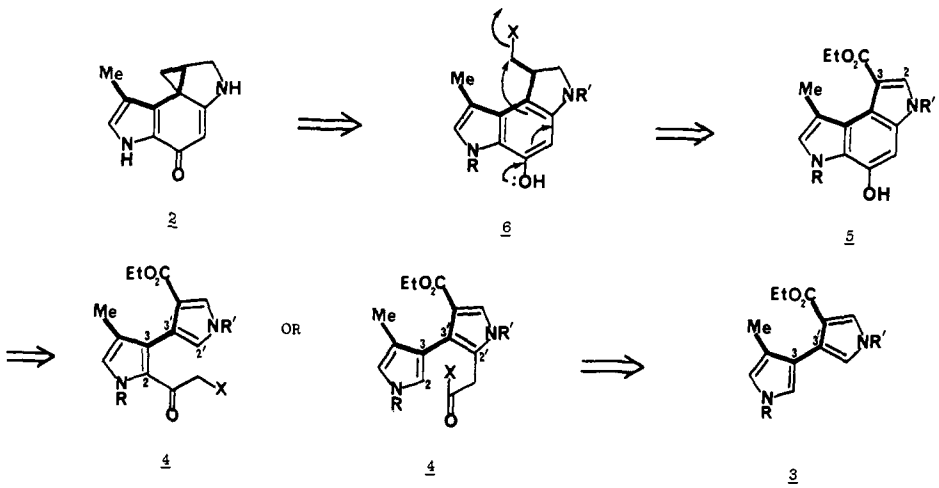
(4) For our initial studies on the A portion of CC-1065, see: Magnus, P.; Or, Y.-S. *J. Chem. Soc., Chem. Commun.* **1983**, 26. Magnus, P.; Gallagher, T. *Ibid.* **1984**, 389.

(5) Indoles can be synthesized by cyclization (electrophilic aromatic substitution) onto a preformed pyrrole ring. Trost, B. M.; Reiffen, M.; Crimmin, M. *J. Am. Chem. Soc.* **1979**, *101*, 257. Oikawa, Y.; Yonemitsu, O. *J. Org. Chem.* **1976**, *41*, 1118. Sundberg, R. J. *The Chemistry of Indoles*; Academic: New York, 1970. Houlihan, W. J. *Indoles*; Wiley-Interscience: New York, 1972; Vol. I, II, III.

(6) van Leusen, A. M.; Siderius, H.; Hoogenboom, B. E.; van Leusen, D. *Tetrahedron Lett.* **1972**, 5337. van Leusen, A. M.; Bouma, R. J.; Possel, O. *Ibid.* **1975**, 3487. van Nispen, S. P. J. M.; Mensink, C.; van Leusen, A. M. *Ibid.* **1980**, 3723. van Leusen, A. M.; Possel, O. *Heterocycles* **1977**, *7*, 77. Schöllkopf, U. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 339.

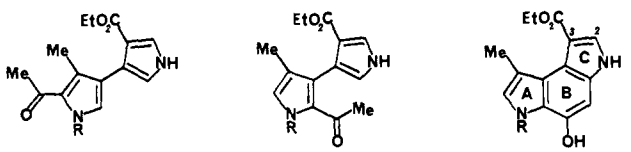
(7) The parent 3,3′-bipyrrole is known: Farnier, M.; Soth, S.; Fournari, P. *Can. J. Chem.* **1976**, *54*, 1083. See also: Galasso, V.; Trinajstic, N. *Tetrahedron* **1972**, *28*, 4419.

Scheme II[a]



[a] The heavy lines indicate that these carbon atoms are derived from ethyl sorbate; see text.

N-(phenylsulfonyl)pyrrole has recently been shown to react with electrophiles in the 3-position, thus reversing the normal preference for 2-substitution.[8] Treatment of **11** with $SnCl_4/AcCl/CH_2Cl_2$ gave a mixture of monoacetyl derivatives **12** and **13** (55%; 4;1). Presumably the Lewis acid has complexed with the pyrrole nitrogen in the C ring and further deactivated it toward acetylation. It was planned to oxidatively rearrange the $COCH_3$ group into a CH_2CO_2Me group by using $Tl(NO_3)_3$ had this electrophilic substitution been successful.[9]



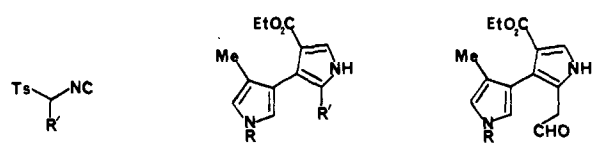
12 **13** **20**

In general, the Mannich reaction proceeds under milder conditions than Friedel–Crafts acylation.[10] In the event, treatment of **11** with Me_2NHHCl/aqueous CH_2O/MeOH at 55 °C for 7 h gave **14** (82%). Its structure was established by the subsequent transformations. Quaternization of **14** with MeI/EtOH gave the methiodide **15**, which was treated with NaCN/THF/H_2O to furnish the cyano compound **16** (66%). Methanolysis (MeOH/HCl) of **16** gave **17** (>87%), with approximately 20% ester exchange of the β-ethyl ester. A solution of the diester **17**, in dry pyridine heated at reflux, was treated with LiI, and the carboxylic acid **18** was isolated in 76% yield. A more convenient procedure, particularly on a large scale, involves treatment of **17** with LiOH/THF/H_2O to give **18** (100%).

The conversion of the acid **18** into the phenol **20** was achieved by two methods. Treatment of **18** with oxalyl chloride/pyridine in CH_2Cl_2 at 0 °C gave the acid chloride **19**, which was directly treated with $SnCl_4$ at −78 °C to give the tricyclic phenol **20** (71%). Most indicative of the structure is the presence of a one-proton singlet at δ 6.85. A superior method, that directly converts the acid **18** into the phenol **20** in 90% yield, involves treatment of the acid **18** with a dichloromethane solution of trimethylsilyl polyphosphate (PPSE) at 20 °C. Trimethylsilyl polyphosphate was first introduced into the chemical literature by Yokoyama and is readily prepared by heating P_2O_5 in $Me_3SiOSiMe_3$ in refluxing CH_2Cl_2.[11]

While the sequence of transformations from **11** to **20** through the Mannich sequence is a very practical route (six steps, overall yield 44%) and is readily scaled up, it would be useful to develop other routes to the key carboxylic acid **18**.

It was found that various alkylated TosMIC derivatives such as the methyl, (trimethylsilyl)methyl, and allyl compounds **21**, **22**, and **23**, respectively, reacted with the monopyrrole **10** under the usual conditions (NaH/HMDS/THF) to give the 3,3′-bipyrroles **25** (70%), **26** (40%), and **27** (96%). Unfortunately, the

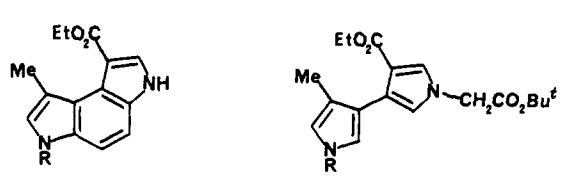


21 R^1 = Me
22 R^1 = CH_2SiMe_3
23 R^1 = $CH_2CH{=}CH_2$
24 R^1 = $CH_2CO_2Bu^t$

25 R^1 = Me
26 R^1 = CH_2SiMe_3
27 R^1 = $CH_2CH{=}CH_2$
28 R^1 = $CH_2CH(OH)CH_2OH$

29

most direct route to the *tert*-butyl ester of **18** using the alkylated TosMIC reagent **24**, under a variety of conditions that worked for the above mentioned examples, only leads to the elimination of *p*-toluenesulfinate to give NCCH=$CHCO_2Bu$-*t* and recovered **10**. Treatment of either **25** or **26** with a range of oxidizing agents that have commonly been used to functionalize 2-alkylpyrroles (SO_2Cl_2, $Pb(OAc)_4$, NBS, etc.) only resulted in nuclear oxidation.[12] Consequently, it was decided to concentrate on the 2′-allylbipyrrole **27**. Treatment of **27** with OsO_4 (catalyst)/*N*-methylmorpholine *N*-oxide/THF gave the diol **28**, which was cleaved with HIO_6/Na_2HPO_4 to the unstable aldehyde **29** in 79% yield from **27**.[13] Exposure of **29** to mild acids, even chromatography over silica gel, resulted in extremely ready cyclization to the pyrrolo[*b*]indole **30** in 98% yield. To avoid this unwanted



30 **31**

pathway, the aldehyde **29** was immediately treated with $NaOCl_2$,

(8) Rokach, J.; Hamel, P.; Kakushima, M.; Smith, G. M. *Tetrahedron Lett.* **1981**, 4901. Xu, R. X.; Anderson, J.; Gogan, N. J.; Loader, C. E.; McDonald, R. *Ibid.* **1981**, 4899. Kakushima, M.; Hamel, P.; Frenette, R.; Rokach, J. *J. Org. Chem* **1983**, *48*, 3214.

(9) For an application of the Taylor–McKillop rearrangement to pyrrole chemistry, see: Kenner, G. W.; Smith, K. M.; Unsworth, J. F. *J. Chem. Soc., Chem. Commun.* **1973**, 43.

(10) Blicke, F. F. *Org. React.* **1942**, *1*, 303. Herz, W.; Dittmer, K.; Cristol, S. *J. Am. Chem. Soc.* **1947**, *69*, 1698.

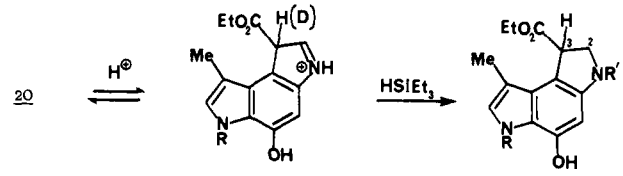
(11) Yokoyama, M.; Yoshida, S.; Imamoto, T. *Synthesis* **1982**, 591.

(12) Jones, R. A.; Bean, G. P. *The Chemistry of Pyrroles* Academic: New York, 1977. Baltazzi, E., Krimen, L. I. *Chem. Rev.* **1963**, *63*, 511.

(13) Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.

buffered with NaH_2PO_4, to give the required acid **18** (90%).[14] While the sequence from **10** via the allylbipyrrole **27** to **18** is shorter than the Mannich route (five steps) and proceeds in good overall yield (55%), we could not scale up this sequence in a reliable and reproducible manner without attendant side reactions, such as the intervention of the pyrrolo[*b*]indole **30**. In passing, it should be noted that attempted direct C-alkylation of the 3,3′-bipyrrole **11** with $BrCH_2CO_2Bu$-*t* only gave the N-alkylated product **31**.[15] Further experiments involving more concise routes to **18** did not provide any improvements over the Mannich route, which, although somewhat lengthy, does provide multigram quantities of **18** in a very reliable sequence.

The stage was now set for the crucial selective reduction of the 2,3-double bond in the pyrroloindole **20**. The *N*-phenylsulfonyl group should inductively deactivate the A ring and prevent protonation. We reasoned that exposure of **20** to strong acid should lead to C-3 protonation, and the resulting iminium ion **20a** would be reduced to **32**. While **20** was inert to Zn/AcOH and



20a

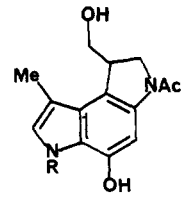
32 R^1 = H

33 R^1 = Ac

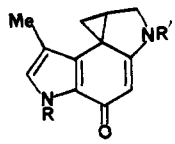
$NaCNBH_3/H^+$,[16] treatment with trifluoroacetic acid/$HSiEt_3$ (ionic hydrogenation)[17] gave **32** (80%). The proton at C-3 appears as part of an ABX system at δ 4.29 (dd,J = 4, 10 Hz). When the above reduction is carried out in deuteriotrifluoroacetic acid/$HSiEt_3$, the proton at C-3 is absent and those at C-2 are a simple AB quartet, thus supporting the formation of an intermediate iminium ion **20a**. Because of the lability of **32**, it was experimentally expedient to work up the above reduction with acetic anhydride to give the corresponding acetate **33**. The ester group in **33** was selectively reduced with $LiAlH_4$/THF/0 °C to give the alcohol **34** (85%) with no trace of amide reduction or removal of the *N*-phenylsulfonyl group.

The Ar-3′ cyclopropane ring closure was best conducted by making use of the intramolecular Mitsunobu reaction.[18] Treatment of **34** with $EtO_2CN{=}NCO_2Et$/THF/PPh_3 resulted in clean conversion into the spirocyclopropane **35** (>90%). We anticipated that the final removal of the N-protecting groups would be sequential under basic conditions, with the N–Ac group being more readily deprotected than the N–SO_2Ph group. In the event, treatment of **35** with NaOMe/MeOH at 20 °C rapidly (5 min) gave **36**, which, on prolonged exposure (18 h) to the above conditions, gave the completed unprotected cyclopropapyrroloindole **2** (75%). This material was identical with an authentic sample kindly supplied by Dr. Warpehoski and Dr. Martin, the Upjohn Company.

With ready access to the cyclopropapyrroloindole systems **35**, **36**, and **2**, it was of some considerable interest to examine potential amide coupling protocols and cyclopropane ring-opening reactions. Some preliminary observations are presented.



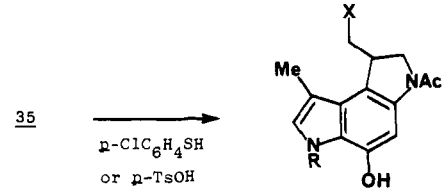
34



35 R^1 = Ac; 2 R = R^1 = H

36 R^1 = H; 39 R = R^1 = Ac

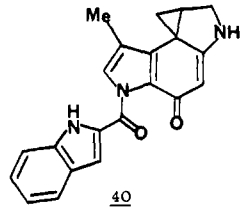
The completely protected system **35** on exposure to *p*-ClC_6H_4SH gave the adduct **37**, thus paralleling Scheme I. In an effort to model the cyclopropane ring-cleavage process depicted in Scheme I, **37** was treated with adenine/THF in the presence of a catalytic amount of *p*-TsOH. Upon increasing the amount of *p*-TsOH to equimolar, a single adduct was formed, namely, **38**, which rapidly reformed into **35** when contacted with DBU.



37 X = SC_6H_4Cl-*p*

38 X = OTs

The diamine **2** gave the diacetate **39** when treated with Ac_2O/DMF; there was no discernable selectivity between the pyrrole nitrogen reactivity and the β-amino acrylate nitrogen atom. Dicyclohexylcarbodiimide-mediated coupling of the diamine **2** with indole-2-carboxylic acid only gave **40**. Whereas, treatment of the diamine **2** with NaH/THF, followed by indole-2-carbonyl chloride, gave a low yield (ca. 10%) of **41**.



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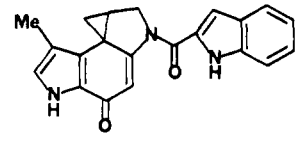

41

Conclusion. 3,3′-Bipyrrole strategy provides convenient access, for the first time, to the A portion of CC-1065 in an unprotected form. The following paper in this issue shows how the same strategy can be used to make the separated B and C components.

Experimental Section

Ethyl 3-(4-Methyl-3-pyrrolyl)acrylate (7). A solution of tosylmethyl isocyanide (15 g, 75 mM) and ethyl sorbate (10 g, 71.3 mM) in dry Me_2SO (50 mL) and ether (100 mL) was added to an ice-cold suspension of NaH (3.6 g, 88.5 mM, 59% dispersion in oil) in ether (100 mL). The mixture was stirred for 3 h at 20 °C, poured into saturated aqueous NH_4Cl solution (50 mL), and extracted with ether (4 × 50 mL). The combined extracts were washed with saturated aqueous NH_4Cl solution and dried ($MgSO_4$). Evaporation of the extract gave **7** (13 g, crude). Crystallization from EtOH gave pure **7**: 10.6 g, 80%; mp 88–89 °C; IR ($CHCl_3$) 3450, 3300, 1695, 1635, 1440, 1280, 1270, 1180, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 8.3 (1 H, brs), 7.8 (1 H, d, J = 15 Hz), 7.05 (1 H, m), 7.60–7.5 (1 H, m), 6.15 (1 H, d, J = 15 Hz), 4.23 (2 H, q, J = 7 Hz), 2.2 (3 H, s), 1.3 (3 H, t, J = 7 Hz). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.81. Found: C, 66.94; H, 7.48; N, 7.69.

Ethyl 4-Methyl-1-(phenylsulfonyl)-3,3′-bipyrrole-4′-carboxylate (11). The pyrrole **10** (3.06 g, 9.5 mM) and tosylmethyl isocyanide (2.25 g, 11.5 mM) in dry THF (50 mL) were added dropwise to a suspension of NaH (0.765 g, 18.8 mM) in THF (50 mL) and $HN(SiMe_3)_2$ (3.6 mL, 17.05 mM) at 0 °C. After 15 min the mixture was poured into saturated aqueous NH_4Cl solution, extracted with ether (4 × 40 mL), and dried ($MgSO_4$). The extract was evaporated and the residue crystallized from ethanol to give the bipyrrole **11**: 2.75 g, 85%; mp 138–139 °C; IR ($CHCl_3$) 3440, 3290, 1695 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 8.53

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(1 H, brs), 7.87 (2 H, m), 7.57–7.45 (4 H, m), 7.23 (1 H, m), 6.93 (1 H, t, J = 2 Hz), 6.53 (1 H, t, J = 2 Hz), 4.12 (2 H, q, J = 7 Hz), 1.9 (3 H, s), 1.2 (3 H t, J = 7 Hz). Anal. Calcd for $C_{18}H_{18}N_2SO_4$: C, 60.32; H, 5.06; N, 7.83. Found: C, 60.24; H, 5.02; N, 7.63.

Ethyl 2′-((*N*,*N*-Dimethylamino)methyl)-4-methyl-1-(phenylsulfonyl)-3,3′-bipyrrole-4′-carboxylate (14). To a solution of the bipyrrole **11** (5.03 g, 14.04 mM) in warm methanol (100 mL) was added a solution of the Mannich reagent (72 mL) [prepared from $Me_2N^+H_2Cl^-$ (28.7 g), water (21 mL), methanol (35 mL), and 37% aqueous formaldehyde (15 mL)]. The solution was kept at 55 °C for 7 h, with an additional 17 mL of the Mannich reagent added after 4.5 h. The mixture was concentrated in vacuo to one-third its volume and basified by 10% aqueous $NaHCO_3$ (150 mL), followed by 2 N NaOH (30 mL). Extraction of the above solution with dichloromethane (3 × 50 mL), drying ($MgSO_4$), and evaporation in vacuo gave crude **14** (6.63 g) as a pale-yellow foam. The product was recrystallized from EtOH to give **14**: 4.81 g, 82%, mp 123–125 °C; IR (Nujol) 3120, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$, 220 MHz) δ 10.5 (1 H, br), 7.95–7.8 (2 H, m), 7.6–7.4 (4 H, m), 7.0–6.9 (2 H, m), 4.05 (2 H, q, J = 7 Hz), 3.2 (3 H, s), 2.1 (6 H, s), 1.8 (3 H, s), 0.95 (3 H, t, J = 7 Hz), MS, m/e calcd for $C_{19}H_{19}N_2O_4S$ (M^+ − NMe_2) 371.1065, found 371.1067.

Ethyl 2′-(Cyanomethyl)-4-methyl-1-(phenylsulfonyl)-3,3′-bipyrrole-4′-carboxylate (16). The amine **14** (4.18 g, 11.59 mM) in absolute ethanol (80 mL) and methyl iodide (3 mL, 48.81 mM) was stirred at 20 °C for 3 h. The mixture was concentrated in vacuo and the residue triturated with dry ether to give the methiodide **15** (6.15 g, 95%). A solution of **15** (4.7 g, 8.95 mM), sodium cyanide (3.5 g, 71 mM) in THF (100 mL), and water (100 mL) was heated at 75 °C for 2.5 h. The mixture was diluted with water (150 mL) and extracted with dichloromethane (4 × 50 mL). The combined extracts were dried (Na_2SO_4) and evaporated to give the nitrile **16** (2.2 g, 66%) after recrystallization from $CHCl_3$–hexane: mp 168–170 °C; IR ($CHCl_3$) 3440, 2250, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 220 MHz) δ 9.41 (1 H, br), 8.0–7.91 (2 H, m), 7.75–7.55 (4 H, m), 7.11–6.00 (2 H, m), 4.09 (2 H, q, J = 7 Hz), 3.52 (2 H, s), 1.82 (3 H, s), 0.93 (3 H, t, J = 7 Hz); MS, m/e calcd for $C_{20}H_{19}O_4SN_3$ 397.1096, found 397.1074.

Ethyl 2′-((Methoxycarbonyl)methyl)-4-methyl-1-(phenylsulfonyl)-3,3′-bipyrrole-4′-carboxylate (17). A solution of the nitrile **16** (1.95 g, 4.9 mM) in dry methanol (120 mL) was saturated with dry HCl gas at 0 °C. After 20 h at 25 °C the solution was evaporated, and the residue was extracted into CH_2Cl_2 (70 mL), washed with saturated aqueous $NaHCO_3$ solution (2 × 40 mL) and water (2 × 50 mL), dried ($MgSO_4$), and evaporated, to give **17** (1.85 g, 87%) as a 5:2 mixture of ethyl/methyl esters at the 4-position: IR (Nujol) 3260, 1735, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 mHz) δ 9.5 (1 H, br), 8.0–7.8 (2 H, m), 7.65–7.4 (4 H, m), 7.05–6.95 (2 H, m), 4.1 (2 H, q, J = 7 Hz), 3.7 (3 H, s), 3.58 (3 H, s, 4-CO_2Me), 3.40 (2 H, s), 1.8 (3 H, s), 0.95 (3 H, t, J = 7 Hz); MS, m/e calcd for $C_{21}H_{22}N_2O_6S$ (for carboethoxy ester) 430.1198, found 430.1201, m/e calcd for $C_{20}H_{20}N_2O_6S$ (for carbomethoxy ester) 416.1042, found 416.1039.

Ethyl 2′-(Carboxymethyl)-4-methyl-1-(phenylsulfonyl)-3,3′-bipyrrole-4′-carboxylate (18). A solution of the diester **17** (404 mg, 0.92 mM, as a 5:2 mixture of ethyl/methyl esters) and anhydrous LiI (553 mg) in dry pyridine (5 mL) was heated at reflux for 7 h under argon [additional LiI (503 mg) was added after 4 h]. The mixture was concentrated, and the residue was dissolved in 2 N HCl (15 mL), extracted with dichloromethane (4 × 20 mL), and dried ($MgSO_4$). The extract was evaporated and the residue purified by flash chromatography (successive elution with 50%, 60%, and 70% EtOAc–hexane) to give **18** (316 mg, 76%).

An alternative, and milder, procedure is as follows: The diester **17** (1.06 g) in THF (2.4 mL) and water (2.4 mL), was treated with LiOH (106 mg). After 5 h at 20 °C the mixture was worked up as before to give **18**: 0.998 g, 100%; IR ($CHCl_3$) 3600–2400, 1700; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 9.6 (1 H, brs), 8.4 (1 H, brs), 7.95–7.75 (2 H, m), 7.6–7.4 (4 H, m), 7.1–6.9 (2 H, m), 4.05 (2 H, q, J = 7 Hz), 3.55 (3 H, s), 3.35 (2 H, s), 1.75 (3 H, s), 0.95 (3 H, t, J = 7 Hz). Anal. Calcd for $C_{20}H_{20}O_6SN_2$: C, 57.69; H, 4.80; N, 6.73. Found: C, 57.45; H, 4.60; N, 6.70.

Ethyl 3,6-Dihydro-5-hydroxy-8-methyl-6-(phenylsulfonyl)benzo[1,2-*b*:4,3-*b*′]dipyrrole-1-carboxylate (20). To a solution of the carboxylic acid **18** (250 mg, 0.6 mM) in CH_2Cl_2 (5 mL) at −5 °C was added pyridine (10 μL) and freshly distilled oxalyl chloride (400 μL). The mixture was kept at 0 °C for 3 h and then evaporated in vacuo to give a brown foam, which was immediately redissolved in CH_2Cl_2 (6 mL) and cooled to −78 °C, and $SnCl_4$ (800 μL) was added. The mixture was stirred at −78 °C for 30 min and then quenched with water (40 mL). Dichloromethane (50 mL) was added, and the mixture was rapidly stirred for 10 min to complete hydrolysis. The mixture was filtered through a Celite pad, and the organic layer was separated, dried (Na_2SO_4), and evaporated in vacuo to give **20**. Purification by flash chromatography over silica gel eluting with 15% EtOAc–85% hexane gave **20**: 170 mg, 71%, mp 160–162 °C (from benzene–hexane); IR ($CHCl_3$) 3460, 3350, 1710, 1630, 1580, 1170, 1150 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.96 (1 H, s), 8.56 (1 H, brs), 7.75–7.73 (2 H, m), 7.58 (1 H, m), 7.5–7.3 (4 H, m), 6.87 (1 H, s), 4.31 (2 H, q, J = 7 Hz), 2.38 (3 H, s), 1.35 (3 H, t, J = 7 Hz). Anal. Calcd for $C_{20}H_{18}N_2O_5S$: C, 60.29; H, 4.55; N, 7.03. Found: C, 60.44; H, 4.63; N, 6.97. The small amount of methyl ester is removed in the purification step, although this can be carried into the next stage.

The acid **18** (311 mg) in toluene (2.9 mL) at 20 °C was treated with PPSE (1.85 mL, 2.35 M, in CH_2Cl_2). After 16 h at 20 °C the mixture was quenched with aqueous NaOAc, extracted with CH_2Cl_2 (2 × 20 mL), and dried (Na_2SO_4). Purification as before gave **20** (260 mg, 87%).

Ethyl 2′-(Formylmethyl)-4-methyl-1-(phenylsulfonyl)-3,3′-bipyrrole-4′-carboxylate (29). To a solution of **27** (147 mg, 0.373 mM) in THF (1 mL)/H_2O (0.25 mL) was added *N*-methylmorpholine *N*-oxide (75 mg, 2 equiv) followed by a small crystal of OsO_4. After 15 h at 20 °C the mixture was quenched with aqueous $Na_2S_2O_4$ solution, extracted with EtOAc (3 × 5 mL), and dried ($MgSO_4$). Evaporation gave the crude diol **28** (81%).

To a solution of the diol **28** (100 mg, 0.233 mM) in acetone (7.8 mL) was added H_5IO_6 (107 mg) in 10% aqueous Na_2HPO_4 (4 mL) to maintain the pH at ca. 5.5. After 2 h at 0 °C H_5IO_6 (20 mg) was added, followed by Na_2HPO_4 (100 mg). The mixture was extraced with EtOAc (50 mL), washed with 10% aqueous Na_2HPO_4/10% aqueous $NaHSO_4$ and saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated at 20 °C to give a labile aldehyde **29**: 73 mg, 79%, IR ($CDCl_3$) 1710, 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 9.55 (1 H, d, J = 2 Hz), 9.42 (1 H, brs), 7.88–7.72 (2 H, m), 7.50–7.32 (4 H, m), 6.9 (2 H, s), 3.97 (2 H, q, J = 7 Hz), 3.45 (2 H, brs), 1.72 (3 H, s), 0.93 (3 H, t, J = 7 Hz). This material readily cyclized to the benzenoid adduct **30** (98%) on treatment with *p*-toluenesulfonic acid in CH_2Cl_2 or on standing for several days in the freezer. Compound **30**: mp 179–180 °C (from EtOH); IR ($CHCl_3$) 3455, 1700, 1360, 1290, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 9.1 (1 H, brs), 8.07 (1 H, d, J = 10 Hz), 8.0–7.4 (7 H, m), 7.29 (1 H, d, J = 10 Hz), 4.43 (2 H, q; J = 7 Hz), 2.52 (3 H, s), 1.40 (3 H, t, J = 7 Hz). Anal. Calcd for $C_{20}H_{18}N_2O_4S$: C, 62.81; H, 4.74. Found: C, 62.79; H, 4.90.

The labile aldehyde **29** (15 mg, 0.038 mM) in acetone (200 μL)/isopropenyl acetate (200 μL) was treated with $NaClO_2$ (1 M, 227 μL, 6 equiv)/sulfamic acid (34 mg, 8 equiv) and 10% aqueous Na_2HPO_4 (200 μL) at 0 °C. After 15 min the solution was diluted with water and extracted with Et_2O (3 × 5 mL). Evaporation of the dried ($MgSO_4$) extract gave **18** (15 mg, 90%). Treatment of **18** with diazomethane gave **17**, thus confirming the structure.

Ethyl 1,2,3,6-Tetrahydro-5-hydroxy-8-methyl-6-(phenylsulfonyl)-3-acetylbenzo[1,2-*b*:4,3-*b*′]dipyrrole-1-carboxylate (33). To a rapidly stirred ice-cold solution of the phenol **20** (368 mg, 0.85 mM) in dry trifluoroacetic acid (3 mL was added freshly distilled triethylsilane (1.5 mL). After 15 min the mixture was warmed to 20 °C and kept for 1.5 h. The dark-green solution was evaporated in vacuo; the residue was dissolved in CH_2Cl_2 (10 mL) and washed with saturated aqueous $NaHCO_3$. The dried ($MgSO_4$) dichloromethane layer was evaporated and the residue treated with Ac_2O (1 mL)/CH_2Cl_2 (1 mL) for 2 h at 20 °C. Evaporation of the mixture and chromatography of the residue over silica gel eluting with CH_2Cl_2/EtOAc (3:1) gave **33**: 271 mg, 71%; mp 206–208 °C; IR ($CHCl_3$) 3360, 3100, 1720, 1650, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 8.89 (1 H, brs), 7.95 (1 H, brs), 7.83–7.68 (2 H, m), 7.58–7.12 (4 H, m), 4.48–3.90 (3 H, m), 4.03 (2 H, q, J = 7 Hz), 2.22 (6 H, brs), 1.03 (3 H, t, J = 7 Hz). Anal. Calcd for $C_{22}H_{22}N_2O_6S$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.49; H, 5.10; N, 6.12.

The amine **32** is sufficiently stable to record its spectra: ^{1}H NMR ($CDCl_3$, 220 MHz) δ 8.82 (1 H, brs), 7.82–7.73 (2 H, m), 7.59–7.39 (3 H, m), 7.11 (1 H, s), 6.34 (1 H, s), 4.29 (1 H, dd, J = 4, 10 Hz), 4.18–4.02 (2 H, m), 3.93–3.79 (2 H, m), 2.18 (3 H, s), 1.09 (3 H, t, J = 7 Hz).

Running the above reduction in CF_3CO_2D gave the 1-deuterio analogue: δ 4.38 (1 H, d, J = 11 Hz), 4.19 (1 H, d, J = 11 Hz).

1,2,3,6-Tetrahydro-5-hydroxy-8-methyl-6-(phenylsulfonyl)-3-acetyl-1-(hydroxymethyl)benzo[1,2-*b*:4,3-*b*′]dipyrrole (34). The ester **33** (90 mg, 0.20 mM) in dry THF (10.2 mL) at 0 °C was treated with $LiAlH_4$ (46 mg, 6 equiv). After 0.5 h the mixture was quenched with water (five drops), neutralized with 3 N HCl, and extracted with EtOAc (20 mL). The dried ($MgSO_4$) extract was evaporated to give crude **34**, which was used directly in the next stage: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.80 (1 H, brs), 7.97 (1 H, s), 7.77 (2 H, m), 7.55–7.44 (4 H, m), 7.20 (1 H, brs), 4.18–4.05 (2 H, m), 2.29 (3 H, s), 2.27 (3 H, s).

2-Acetyl-1,2,8,8a-tetrahydro-7-methyl-5-(phenylsulfonyl)cyclopropa[*c*]pyrrolo[3,2-*e*]indol-4(5*H*)-one (35). To a solution of the crude alcohol **34** [prepared by reduction of **33** (512 mg) with $LiAlH_4$, as above] in CH_2Cl_2 (50 mL) was added Ph_3P (512 mg), followed by diethyl diazo-

dicarboxylate (512 μL). The mixture was stirred at 20 °C for 5 min and evaporated, and the residue was chromatographed over silica gel, eluting with EtOAc/5% Et_3N to give **35**: 392 mg, 80.2%; mp 92-94 °C; IR ($CHCl_3$) 1625, 1380, 1280, 1163, 1120 cm^{-1}; ^1H ($CDCl_3$, 360 MHz) δ 8.08 (2 H, d), 7.45-7.60 (5 H, m), 4.15 (1 H, b), 3.96 (1 H, b), 2.95 (1 H, m), 2.23 (3 H, brs), 2.04 (3 H, s), 1.97 (1 H, m), 1.35 (1 H, m), the signals are broadened due to amide resonance; MS, *m/e* calcd for $C_{20}H_{18}N_2O_4S$ 368.0956, found 368.0945.

Starting with the phenol **20** (620 mg) through four steps, Et_3SiH, Ac_2O, $LiAlH_4$, and finally cyclopropane ring closure, gives **35** (392 mg, 70.7%).

1,2,8,8a-Tetrahydro-7-methylcyclopropa[*c*]pyrrolo[3,2-*e*]indol-4-(5*H*)-one (2). A solution of **35** (73 mg, 0.19 mM) in 1 M MeONa (1.91 mL, 10 equiv) was stirred at 20 °C for 16 h. The mixture was quenched with 10% aqueous Na_2HPO_4 solution (5 mL) and extracted with dichloromethane (6 × 5 mL). The dried ($MgSO_4$) extract was evaporated and the residue chromatographed over silica gel, eluting with THF/EtOAc (1:1)/5% Et_3N to give **2** (30 mg, 75%) as an off-white foam: IR ($CHCl_3$) 3450, 1610 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 9.00 (1 H, brs), 6.70 (1 H, d, *J* = 2 Hz), 5.51 (1 H, s), 4.56 (1 H, brs), 3.79 (1 H, ddd, J = 10, 5, 2 Hz), 3.63 (1 H, d, *J* = 10 Hz), 2.95 (1 H, m), 2.00 (3 H, s), 1.86 (1 H, dd, *J* = 8, 4 Hz), 1.20 (1 H, t, *J* = 4 Hz); MS, *m/e* calcd for $C_{12}H_{12}N_2O$: 200.0949, found 200.0960. The above material was compared with an authentic sample supplied by Dr Warpehoski and Dr. Martin (The Upjohn Company) and was identical by TLC, NMR, and IR.

If the methoxide treatment of **35** is stopped after 15 min and the solution is worked up as above, the deacetylated product **36** is isolated: IR ($CHCl_3$) 3440, 1620, 1260, 1140 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.97 (2 H, d), 7.5-7.36 (5 H, m), 4.58 (1 H, brs), 3.68 (1 H, m), 3.63 (1 H, d, *J* = 10 Hz), 2.94 (1 H, m), 1.93 (3 H, s), 1.78 (1 H, dd, *J* = 8, 4 Hz), 1.22 (1 H, t, *J* = 4 Hz); MS, *m/e* calcd for $C_{18}H_{16}N_2O_3S$: 340.0882, found 340.0875.

Reaction of the Cyclopropapyrroloindole 35 with Nucleophiles. To a solution of **35** (10 mg) in THF (200 μL) was added *p*-chlorothiophenol (7 mg). After 4 h at 20 °C clean conversion into **38** had taken place: ^1H NMR ($CDCl_3$, 360 MHz) δ 8.75 (1 H, s), 7.85 (1 H, s), 7.71 (2 H, d), 7.5-7.3 (5 H, m), 7.2 (3 H, m), 7.1 (1 H, s), 4.12 (1 H, d, *J* = 12 Hz), 3.94 (1 H, t), 3.50 (1 H, t), 2.98 (1 H, d), 2.67 (1 H, t), 2.15 (3 H, s), 1.98 (3 H, s).

Similar treatment of **35** (10 mg) with *p*-toluenesulfonic acid (excess) gave **38**: 13 mg, >95% ^2H NMR ($CDCl_3$, 360 MHz) δ 8.87 (1 H, s), 7.90 (1 H, s), 7.77 (2 H, d, *J* = 8 Hz), 7.68 (2 H, d, *J* = 8 Hz), 7.57 (1 H, t), 7.43 (2 H, t), 7.30 (2 H, d, *J* = 8 Hz), 7.18 (1 H, s), 4.02 (3 H, m), 3.81 (1 H, m), 3.70 (1 H, t, *J* = 7 Hz), 2.46 (3 H, s), 2.16 (3 H, s), 2.18 (3 H, s).

2-(1*H*-Indol-2-ylcarbonyl)-1,2,8,8a-tetrahydro-7-methylcyclopropa[*c*]pyrrolo[3,2-*c*]indol-4(5*H*)-one (41). To the diamine **2** (10 mg) suspended in THF (200 μL) at 0 °C was added NaH (2.3 mg). After 15 min at 0 °C a clear solution was formed. To this solution was added indole-2-carbonyl chloride (9.9 mg), and the mixture was stirred at 0 °C for 1 h. Workup and chromatography of the residue over silica gel eluting with THF/EtOAc (1:1) gave **41** (2 mg), identical with an authentic sample (TLC, NMR) kindly supplied by Dr. Warpehoski (The Upjohn Company).

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Supplementary Material Available: Description of experimental and characterization details for compounds **8**, **10**, **13**, **21**, **22**, **23**, **24**, **25**, **26**, and **27** (3 pages). Ordering information is given on any current masthead page.

Studies on the Synthesis of the Antitumor Agent CC-1065. Synthesis of PDE I and PDE II, Inhibitors of Cyclic Adenosine-3′,5′-monophosphate Phosphodiesterase Using the 3,3′-Bipyrrole Strategy

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Abstract: In the model series *tert*-butyl 2,4-pentadienoate was treated with TosCHMeNC/NaH to give the pyrrole **18**, which was converted into the 3,3′-bipyrrole **20**. Treatment of the pyrrole **20** with oxalyl chloride gave the *o*-quinone **21**, which was reduced and concomitantly protected to give **24**. O-Methylation of **24** using **29** gave **26**. Subsequently, transformations converted **29** into the PDE I/II model **33**. Application of this strategy to the 5-carboxymethyl series gave the 3,3′-bipyrrole **36**. It was converted into the *o*-quinone **42** and subsequently into PDE I (**2**) and PDE II (**3**).

In the preceding paper in this issue we have described the synthesis of the unprotected A portion of CC-1065, **1**, using the 3,3′-bipyrrole strategy.[1] This strategy, in principle, should be equally applicable to the synthesis of the separated constituents of the B/C portion, which are natural products in their own right and known as PDE I (**2**; R = $CONH_2$) and PDE II (**3**; R = Ac).[2] They are inhibitors of cyclic adenosine-3′,5′-monophosphate phosphodiesterase, and they have been the subject of three total syntheses.[3] It appears that the B/C portion of CC-1065 is necessary for binding into the minor groove of DNA.[4]

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