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).

**Acknowledgment.** The National Institutes of Health (GM 32718) are thanked for their support of this research. The National Science Foundation is acknowledged for their contribution toward the purchase of a 360-MHz NMR spectrometer (CHE 81-05004). Drs. Warpehoski, Martin, Kelly, and Wierenga (The Upjohn Company) are thanked for many discussions and exchanges of information. Dr. Craig Wilcox, University of Texas at Austin, is thanked for suggesting the deuterium experiment.

**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

**Paul Carter, Steven Fitzjohn, Serge Halazy, and Philip Magnus***

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

**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]

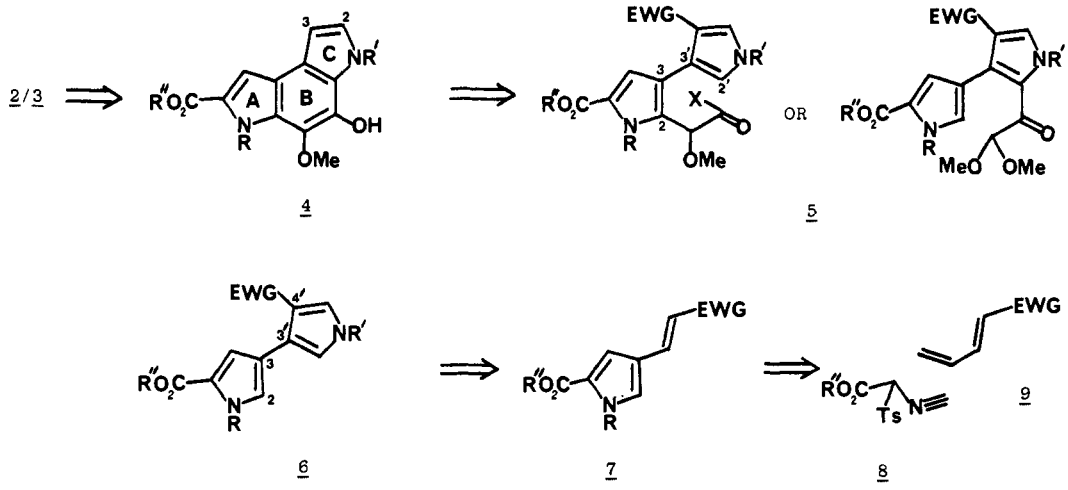
(1) Magnus, P.; Gallagher, T.; Schultz, J.; Or, Y.-S.; Ananthanarayan, T. P. *J. Am. Chem. Soc.*, preceding paper in this issue.

(2) Enomoto, Y.; Furutani, Y.; Naganawa, H.; Hamada, M.; Takenchi, T.; Umezawa, H. *Agric. Biol. Chem.* **1978**, *42*, 1331.

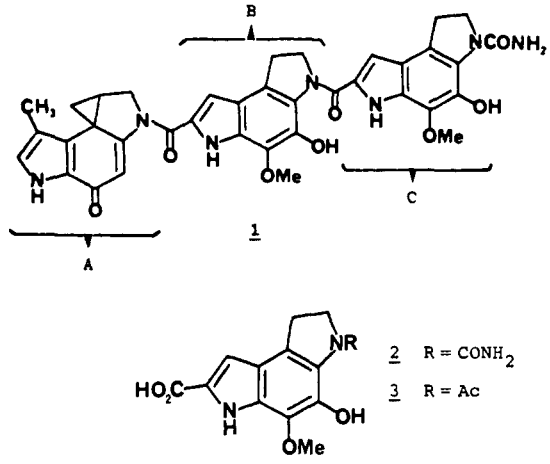
(3) Komoto, N.; Enomoto, Y.; Miyagaki, M.; Tanaka, Y.; Nitani, K.; Umezawa, H. *Agric. Biol. Chem.* **1979**, *43*, 555. Komoto, N.; Enomoto, Y.; Tanaka, Y.; Nitani, K.; Umezawa, H. *Ibid.* **1979**, *43*, 559. Bolton, R. E.; Moody, C. J.; Rees, C. W.; Tojo, G. *J. Chem. Soc., Chem. Commun.* **1985**, 1775. Rawal, V. H.; Cava, M. P. *J. Am. Chem. Soc.* **1986**, *108*, 2110. For references to approaches to the B/C portion, see: Rawal, V. H.; Cava, M. P. *J. Chem. Soc., Chem. Commun.* **1984**, 1526. Boger, D. L.; Coleman, R. S. *J. Org. Chem.* **1984**, *49*, 2240. Sundberg, R. J.; Pearce, B. C. *Ibid.* **1985**, *50*, 425. For preliminary studies toward the synthesis of the B/C portion from these laboratories, see: Magnus, P.; Halazy, S. *Tetrahedron Lett.* **1985**, 2985. Carter, P.; Fitzjohn, S.; Magnus, P. *J. Chem. Soc., Chem. Commun.* **1986**, 1162.

0002-7863/87/1509-2711$01.50/0 

**Scheme I**



In order to apply the 3,3′-bipyrrole strategy (as outlined in Scheme II of the preceding paper in this issue), a few extra considerations must be evaluated.

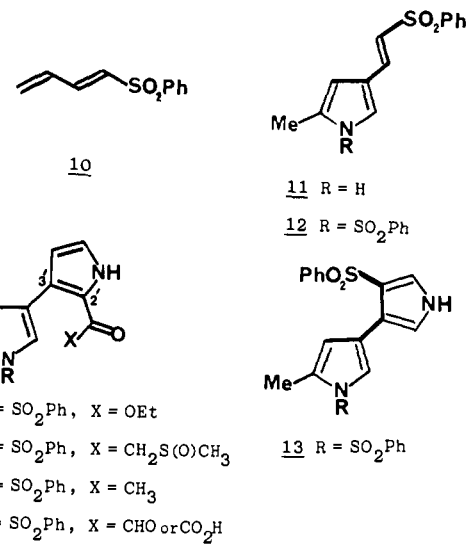




The presence of an electron-withdrawing group (EWG) at C-4′ in **6** is essential for the conversion of **7** into **6** using TosMIC chemistry. This functional group (EWG) must be removed at a later stage to arrive at **4**.

The construction of **4** requires that the OMe group in ring B is placed into position in a regiospecific manner, perhaps by precursors such as **5** or their equivalents. To explore Scheme I in a general way, it was decided to conduct some model work where the $CO_2R''$ group had been replaced by a $CH_3$ group. The reasons for this are twofold. First, the required carboalkoxy TosMIC derivatives **8** are not available. Attempts to make them always result in oxazoles, which do not enter into the required pyrrole annulation process.[5] Second, it might be possible at an appropriate stage in the synthesis to oxidize an $\alpha$-methylpyrrole to the corresponding carboxylate derivative, thus converting a "model" compound into the "real" system.

**Model Systems.** A suitable diene to act as a Michael acceptor for TosMIC is 1-(phenylsulfonyl)-1,3-butadiene (**10**).[6] When this electron-deficient diene was treated with TosCHMeNC/NaH/THF/$Me_2SO$/20 °C, the 2,4-disubstituted pyrrole **11** was isolated in 64% yield. This result is remarkable considering the extreme ease with which **10** undergoes anionic polymerization when exposed to bases. The pyrrole **11** was converted into the



*N*-phenylsulfonyl derivative **12** and was treated with TosMIC/NaH/THF/$Me_2SO$/20 °C to give the required 3,3′-bipyrrole **13** (72%). All attempts to conduct regioselective acylation chemistry on **13** lead to mixtures, and reduction (Raney nickel) removed the *N*-phenylsulfonyl group, rather than the *C*-phenylsulfonyl group. Consequently, we required a method for selectively removing the *C*-phenylsulfonyl group, which would at the same time introduce a useful functional group at C-2′ (see **14**). Treatment of **12** with $EtO_2CCH_2NC$/NaH/HMDS/$Me_2SO$/THF/20 °C gave the 3,3′-bipyrrole **14** (70%),[7] where the *C*-phenylsulfonyl group has been lost.[8] Attempts to further manipulate **14** via the derived sulfoxide **15** or methyl ketone **16** in order to arrive at the glyoxal or glyoxalic acid **17** were not successful.[9]

To avoid the strongly deactivating effect of the *C*-phenylsulfonyl substituent, it was decided to examine the possibility of having an ester at C-4′ (in **6**, EWG = $CO_2R$), which would eventually have to be dealkylated and the resulting acid decarboxylated.

(4) Hurley, L. H.; Rokem, J. S. *J. Antibiot.* **1983**, *36*, 383. Hurley, L. H.; Reynolds, V. L.; Swenson, D. H.; Petzold, G. L.; Scahill, T. A. *Science (Washington, DC)* **1984**, *226*, 843. Needham-Vandevanter, D. R.; Hurley, L. H.; Reynolds, V. L.; Theriault, N. Y.; Krueger, W. C.; Wierenga, W. *Nucleic Acids Res.* **1984**, *12*, 6159.

(5) Hantke, K.; Schöllkopf, U.; Hansberg, H.-M. *Liebigs Ann. Chem.* **1975**, 1531. van Leusen, A. M.; Possel, O. *Heterocycles* **1977**, *7*, 77.

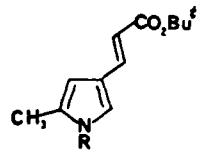
(6) Tanaskov, M. M.; Stadnichuk, M. D.; Kekisheva, L. V. *Zh. Obshch. Khim.* **1980**, *50*, 1738.

(7) Schöllkopf, U.; Hoppe, D.; Jentsch, R. *Chem. Ber.* **1975**, *108*, 1580. Schölkopf, U.; Hantke, K. *Liebigs Ann. Chem.* **1973**, 1571.

(8) Halazy, S.; Magnus, P. *Tetrahedron Lett.* **1984**, 1421.

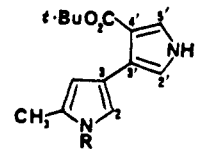
(9) Ajello, T.; Sprio, V.; Madonis, P. *Gazz. Chim. Ital.* **1957**, *87*, 11. Sprio, V.; Madonia, P. *Ibid.* **1957**, *87*, 171. Ingraffia, F. *Ibid.* **1934**, *64*, 784. Meinwald, J.; Ottenheym, H. C. J. *Tetrahedron* **1971**, 3307. De Kimpe, N.; Verhē, R.; De Buyck, L.; Schamp, N. *J. Org. Chem.* **1978**, *43*, 2933. Oikawa, Y.; Yonemitsu, O. *Ibid.* **1976**, *41*, 1118. Moore, T. L. *Ibid.* **1967**, *32*, 2786. Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1974**, 2653. Becker, H.-D.; Mikol, G. J.; Russell, G. A. *J. Am. Chem. Soc.* **1963**, *85*, 3410. Russell, G. A.; Mikol, G. J. *Ibid.* **1966**, *88*, 5498. Russell, G. A.; Ochrymowycz, L. A. *J. Org. Chem.* **1969**, *34*, 3618.

*tert*-Butyl 2,4-pentadienoate was treated with TosCHMeNC/NaH/THF/20 °C to give **18** (75%), which directly converted into the *N*-phenylsulfonyl derivative **19** (65%). Pyrrole annulation of **19** with TosMIC/NaH/THF/20 °C gave the required 3,3′-bipyrrole **20** (75%).

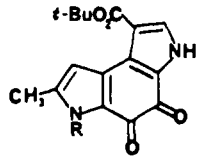


**18** R = H

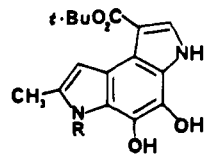
**19** R = $SO_2Ph$



**20**

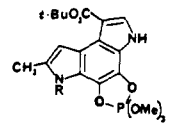


**21**



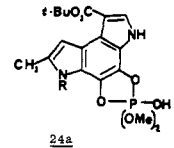
**22**

When a solution of the bipyrrole **20** in $CH_2Cl_2$ at −78 °C was treated with oxalyl chloride in ether, and the mixture warmed to 20 °C, the *o*-quinone **21** (85%) crystallized directly from the reaction mixture.[10] If the quinone **21** is reduced to the corresponding hydroquinone **22**, this compound is too unstable and cannot be O-methylated. As a result, we required a method which would reduce the quinone **21** to the hydroquinone oxidation level and at the same time selectively protect it against reoxidation. Reduction of the quinone **21** with $P(OMe)_3$ in benzene gave the cyclic oxyphosphorane **23**, which was readily hydrolyzed in wet THF to a *single* phenolic phosphate ester **24** (100%).[11] The regiochemistry depicted for **24** is based upon steric considerations that place the phosphate ester group on the least hindered hydroxyl group. Moreover, the phosphate ester can migrate to the adjacent hydroxyl group, especially under basic conditions.

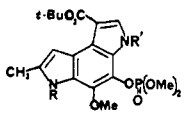


**23**

**24**

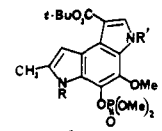


**24a**



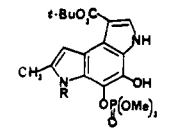
**25** $R^1$ = Me

**26** $R^1$ = H

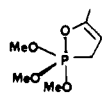


**27** $R^1$ = Me

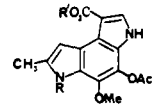
**28** $R^1$ = H



**24b**

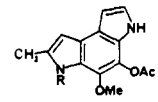


**29**

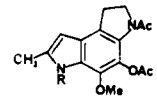


**30** $R^1$ = But

**31** $R^1$ = H



**32**



**33**

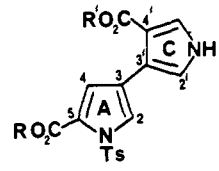
(R = $SO_2Ph$ throughout)

When **24** was exposed to $Me_2SO_4/Ba(OH)_2$/DMF a mixture of **25** and **27** (1:1) was isolated, whereas $Me_2SO_4/K_2CO_3$/acetone gave **25** and **27** in a 9:1 ratio. The regiochemistry of the O-methylation in **25** was confirmed by single-crystal X-ray crystallography.[12] Unfortunately, while the above methylation conditions gave predominantly the required regiochemistry, the problem of N-methylation could not be avoided. Treatment of **24** with a wide range of methylating agents[13] (*O*-methyl-*N*,*N*′-diisopropylisourea, MeI/*n*-$Bu_4NF$, $Me_3O^+BF_4^-/CH_2Cl_2$, $CH_2N_2$/MeOH, $CH_2N_2/Et_2OBF_3/CH_2Cl_2$, $Ag_2O$/MeI/acetone, and many others) did not produce any detectable amount of the desired methyl ether **26**. Fortunately, we found that the *N*-methylation of **24** was avoided by treatment of **24** with the cyclic oxaphospholene **29** [prepared from $P(OMe)_3$ and methyl vinyl ketone] in THF/20 °C to give **26** (50%).[14] The structure of **26** was established by N-methylation with NaH/MeI to give **25**.

Removal of the phosphate ester group with NaOMe/MeOH followed by $Ac_2O$ gave **30**. The *tert*-butyl ester was readily hydrolyzed by trifluoroacetic acid at 20 °C in chloroform to give **31**.[15] After considerable experimentation, it was found that **31** could be decarboxylated by heating with excess $NEt_3$ in toluene at 110 °C to give **32**. The 2,3-double bond in **32** was selectively reduced by exposure to $Et_3SiH$/TFA/0 °C followed by $Ac_2O$ to give the diacetate **33** (60%).[16]

The above model study has solved the problem of constructing the B ring with correct regiochemistry, and a method for removing the $CO_2Bu$-*t* group (EWG), Scheme I, is available. Since we were unable to oxidize the 2-methyl group to a carboxylic acid in any of the tricyclic compounds **26**, **30**, or **33**, this functional group must be present in the correct oxidation state from an early stage.[17]

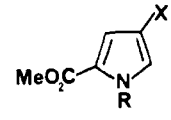
**5-$CO_2$Me Pyrrole Series.** Since the model series has established that we need the EWG at C-4′ (Scheme I, structure **6**) to be an ester, it is therefore necessary to be able to distinguish between the two esters (C-5 and C-4′). Originally, we carried out several



**34** R = Me, $R^1$ = $Bu^t$

**35** R = Bn, $R^1$ = Me

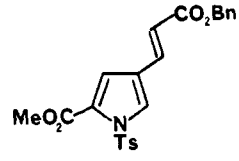
**36** R = Me, $R^1$ = Bn



**37** R = X = H

**38** R = H , X = CHO

**39** R = Ts, X = CHO



**40**

transformations with the substrates **34** and **35**, but found that the *tert*-butyl ester was incompatible with the oxalyl chloride *o*-quinone step (unlike the model series!),[18] and the benzyl ester **35** did not

(10) Treibe, A.; Kreuzer, F. H. *Liebigs Ann. Chem.* **1969**, 105. Archibald, J. L.; Freed, M. E. *J. Heterocycl. Chem.* **1967**, 335.

(11) Ramirez, F.; Desai, N. B. *J. Am. Chem. Soc.* **1960**, *82*, 2652; **1963**, *85*, 3252.

(12) The structure of **25** has been determined crystallographically. Details are available on microfiche, from the Indiana University Chemistry Library—request Structure Report No. 83128.

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(18) Oxalyl chloride cleaved the *tert*-butyl ester group to give an acid chloride, which did not subsequently provide an *o*-quinone.

Scheme II

provide the necessary distinction between the C-5 (benzyl) and C-4′ (methyl) esters.[19] Consequently, it was decided to reverse the ester alkyl groups, C-5 (methyl) and C-4′ (benzyl).

Methyl pyrrole-2-carboxylate[20] (**37**) was formylated with $Cl_2CHOMe/AlCl_3/CH_2Cl_2$[21] to give the aldehyde **38** (80%), which was activated toward addition reactions to the formyl group by N-tosylation, TsCl/NaH/THF, to furnish **39**. Treatment of **39** with $(EtO)_2P(O)CH_2CO_2Bn/NaH/THF$ provided the *E* α,β-unsaturated ester **40** (80%), which on exposure to TosMIC/LiHMDS/THF/−78 °C gave the crucial 3,3′-bipyrrole **36** (65%). Both pyrrole rings in **36** are deactivated toward electrophilic substitution, but the A ring, by virtue of the N-Ts group, is more so. Treatment of **36** with oxalyl chloride/$CH_2Cl_2$/0 °C cleanly gave **41**; further exposure of **41** to $SnCl_4/CH_2Cl_2$/−78 °C accomplished ring closure into the 2-position to yield the *o*-quinone **42** (72%), $\lambda_{max}$ 460, 355, and 262 nm.

By use of the reduction procedure developed in the model sequence, the *o*-quinone **42** was treated with triethyl phosphite/$CH_2Cl_2$, followed immediately by aqueous hydrolysis of the cyclic oxyphophorane **43** to give a single phenolic phosphate ester **44** (83%). While the regioisomer, depicted as **44**, is the least sterically encumbered adduct compared to **47**, the phenolic hydroxyl group is correspondingly more hindered. Treatment of **44** with a variety of O-methylating agents, including the oxaphospholene **29** (used successfully in the model series), gave the wrong regioisomer **48**. In the series derived from **35**, with the benzyl and methyl esters transposed, the structure was established by single-crystal X-ray crystallography.[22] Presumably, the difference between **44** ⇌ **47** and the model series **24** ⇌ **24b** is the increased acidity of the phenolic hydroxyl group in **47**. Fortunately, a solution to the problem of regiospecific O-methylation of **44** was discovered when it was found that treatment of **44** with $CH_2N_2$ in $CH_2Cl_2/Et_2O$/−78 °C gave **45** (50%) along with **48** in ratios of 3:1 (1-mM scale) to 9:1 (10-mM scale). The specific ratios of solvents and scale are vital to the success of this reaction, and the details are given in the Experimental Section.

Reductive cleavage of the N-Ts group of **45** with Al/Hg amalgam/*THF* gave **49** (90%), which was hydrogenolyzed over 10% Pd/C/EtOAc to give the carboxylic acid **50** (90%). The decarboxylation conditions that were successful in the model series did not work. After considerable experimentation it was found that treatment of **50** in anisole at 130 °C in the presence of Cu powder (8 equiv) and *i*-$Pr_2NEt$ (150 equiv)/DMF (catalyst) gave **51** (50–60%).

**49** X = $CO_2Bn$
**50** X = $CO_2H$
**51** X = H

**52** R = H
**53** R = Ac
**54** R = $CONH_2$

**55** R = Ac
**56** R = $CONH_2$

Reduction of the indole 2,3-double bond in **51** was carried out by using $Et_3SiH/TFA/CH_2Cl_2$/0–20 °C to give the dihydro derivative **52**, which was directly treated with $Ac_2O$ to give **53** (60% from **51**). Similarly, treatment of **52** with NaOCN/AcOH produced the corresponding carbamate **51** (56% from **51**).

Standard methods for the hydrolysis of phenolic phosphate esters did not result in the required phenols **55**/**56**; only extensive decomposition occurred. Since it is known that alkoxy groups in phosphate esters are readily exchanged by alcoholysis,[23] we reasoned that treatment of a dialkoxy phosphate with a triol would result in exchange, followed by intramolecular attack of the third hydroxyl group on phosphorus to give a pentacoordinate species that could readily expel the phenolate leaving group (Scheme II).

When **53** was treated with KOH/MeOH/$MeC(CH_2OH)_3$, the phenol **55** (80%) was produced. Similarly, **54** gave **56** (68%). If the triol $MeC(CH_2OH)_3$ is omitted, neither **55** nor **56** is formed. Base hydrolysis of **55** with 1 N KOH/EtOH gave PDE II (**3**) (60%), and treatment of **56** with 0.01 N KOH/$H_2O$ gave PDE I (**2**) (75%).

The recent studies from the Upjohn group have described methods for coupling the A portion of CC-1065 to the B/C portion, and more importantly, the synthesis of analogues such as **57**, which do not exhibit the liver toxicity problems associated

**57**

with CC-1065 yet are equipotent in both in vitro and in vivo assays. In view of this extensive program, and to avoid unnecessary duplication of effort, the studies reported here complete our own program on CC-1065.[24]

**Conclusion.** In summary, the 3,3′-bipyrrole approach to the synthesis of the separate components of CC-1065 has proven successful in all respects and has provided a unified strategy. The future of CC-1065 as a chemotherapeutic agent must evolve from

(19) Attempts to hydrolyze **49** where the methyl and benzyl esters are transposed did not lead to any useful selectivity; consequently, we used the sequence shown.

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(22) The structure of **48** (with the methyl and benzyl esters transposed) has been determined crystallographically. Details are available on microfiche, from the Indiana University Chemistry Library—request Structure Report No. 84048.

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(24) The coupling of the A portion to the B/C portion has been carried out by Dr. Kelly (The Upjohn Company).

the construction of analogues of similar topology and hopefully reduced toxicity.[25]

## Experimental Section

**Ethyl 5-Methyl-1-(phenylsulfonyl)-3,3′-bipyrrole-2′-carboxylate (14).** The pyrrole **12** (200 mg, 0.51 mM) and ethyl isocyanoacetate (68 mg, 0.6 mM) dissolved in THF (3 mL) were added to a suspension of NaH (17 mg, 0.7 mM) in ether (2 mL) containing HMDS (85 mg, 0.7 mM) at 0 °C. To this mixture, $Me_2SO$ (0.3 mL) was added, and the immediate evolution of hydrogen was observed. After 10 min at 0 °C, followed by 4 h at 20 °C, the mixture was quenched with saturated aqueous $NH_4Cl$ (5 mL) and extracted with EtOAc (3 × 20 mL). The combined extracts were washed with water and brine and dried ($Na_2SO_4$). Evaporation in vacuo followed by chromatography of the residue over silica gel eluting with petroleum ether/EtOAc (1:1) gave **14**: 128 mg, 70%; mp 119–121 °C (from petroleum ether/EtOAc); IR ($CHCl_3$) 3380, 2985, 1680, 1560, 1440, 1410, 1350, 1270, 1180, 1090, 1060 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) $\delta$ 9.25 (1 H, m), 7.3–8.0 (6 H, m), 6.92 (1 H, t), 6.45 (2 H, m), 4.4 (2 H, q, $J$ = 7 Hz), 2.35 (3 H, s), 1.40 (3 H, t). Anal. Calcd for $C_{18}H_{18}O_4SN_2$: C, 60.32; H, 5.06; N, 7.82. Found: C, 60.53; H, 5.20; N, 7.60.

***tert*-Butyl 3-[1-(Phenylsulfonyl)-5-methylpyrrol-3-yl]acrylate (19).** A solution of methyl TosMIC (6.27 g, 30 mM) and *tert*-butyl penta-2,4-dienoate (4.62 g, 30 mM) in THF (25 mL) was added dropwise to a suspension of NaH (840 mg, 35 mM) in THF (10 mL) and HMDS (4.83 g, 30 mM) at 20 °C. A few drops of $Me_2SO$ were added, and rapid hydrogen evolution was observed. After 15 h at 20 °C, the mixture was evaporated in vacuo, and the residue was dissolved in EtOAc (200 mL) and hydrolyzed with saturated aqueous $NH_4Cl$ (50 mL). The mixture was extracted with EtOAc (3 × 40 mL), and the combined extracts were dried ($Na_2SO_4$) and evaporated to give **18** as a brown oil, used directly in the next step.

The crude material prepared as above was dissolved in THF (25 mL) and added to a suspension of NaH (720 mg, 30 mM) in THF (10 mL) containing HMDS (4.83 g, 30 mM) at 20 °C (ca. 10 mg of imidazole was also added). After 2 h at 20 °C, phenylsulfonyl chloride (5.295 g, 30 mM) was slowly added to the above mixture. After 1 h at 20 °C, the mixture was evaporated under reduced pressure, and the residue, was dissolved in $CH_2Cl_2$ (200 mL), hydrolyzed with saturated aqueous $NH_4Cl$ (50 mL), and extracted with $CH_2Cl_2$ (3 × 40 mL). The combined extracts were washed with water, dried ($Na_2SO_4$) and evaporated in vacuo to give a brown oil, which was purified by chromatography over silica gel eluting with petroleum ether/EtOAc (1:1) to give **19**: 6.76 g, 65%; mp 122–124 °C (from petroleum ether/EtOAc); IR ($CHCl_3$) 3120, 1690, 1630 $cm^{-1}$ NMR (90 MHz, $CDCl_3$) $\delta$ 7.1–7.8 (7 H, m), 6.08 (1 H, m), 5.95 (1 H, d, $J$ = 16 hZ), 2.25 (3 H, s), 1.75 (9 H, s). Anal. Calcd for $C_{18}H_{21}NO_4S$: C, 62.23; H, 6.09; N, 4.03. Found: C, 62.08; H, 5.95; N, 3.90.

***tert*-Butyl 5-Methyl-1-(phenylsulfonyl)-3,3′-bipyrrole-4′-carboxylate (20).** A solution of TosMIC (4.095 g, 21 mM) and the pyrrole **19** (6.94 g, 20 mM) in THF (20 mL) was slowly added to a suspension of NaH (600 mg, 25 mM) in THF (10 mL) containing HMDS (3.22 g, 20 mM) at 20 °C. After 1.5 h at 20 °C, the mixture was worked up as above to give an oil, which was purified by chromatography over silica gel eluting with petroleum ether/EtOAc (1:1) to give **20**: 5.79 g, 75%; mp 160–161 °C (from MeOH); IR ($CHCl_3$) 3440, 1680, 1430 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) $\delta$ 9.73 (1 H, m), 7.3–7.8 (6 H, m), 7.23 (1 H, t), 6.6 (1 H, t), 6.15 (1 H, m), 2.25 (3 H, s), 1.4 (9 H, s). Anal. Calcd for $C_{20}H_{22}O_4N_2S$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.22; H, 5.90; N, 7.15.

***tert*-Butyl 3,4,5,6-Tetrahydro-6-(phenylsulfonyl)-4,5-dioxobenzo[1,2-*b*:4,3-*b*′]dipyrrole-7-carboxylate (21).** The 3,3′-bipyrrole **20** (1.73 g, 4.5 mM) in $CH_2Cl_2$ (4 mL) was added to a solution of oxalyl chloride (700 mg, 5.5 mM) in ether (4 mL) at −78 °C. The mixture was warmed to 20 °C, and a red-orange precipitate separated. After 2 h at 20 °C ether (50 mL) was added and the precipitate filtered. The orange-red solid was washed with ether (5 × 30 mL) and dried in vacuo to give **21**: 1.68 g, 85%; mp 320 °C (dec); UV (MeOH) 365, 255, 220 nm ($\epsilon$ 3800, 4500, 7500). Anal. Calcd for $C_{22}H_{20}N_2O_6S$: C, 59.99; H, 4.58; N, 6.36. Found: C, 59.66; H, 4.53; N, 6.04. The compound was too insoluble (even in $Me_2SO$) to give presentable $^1H$ NMR data.

***tert*-Butyl 3,6-Dihydro-4-((dimethoxyphosphinyl)oxy)-5-hydroxy-7-methyl-6-(phenylsulfonyl)benzo[1,2-*b*:4,3-*b*′]dipyrrole-1-carboxylate (24).** Trimethyl phosphite (496 mg, 4 mM) in benzene (3 mL) was added to a suspension of the *o*-quinone **21** (240 mg) in benzene (20 mL). The mixture was stirred at 80 °C for 2 h and evaporated, and the crude product **23** (300 mg) was used directly in the next stage: IR ($CHCl_3$) 3200, 2920, 1680, 1580, 1495, 1440, 1360, 1280, 1140, 1080 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) $\delta$ 9.3 (1 H, m), 7.05–7.9 (7 H, m), 3.63 (9 H, d, $J$ = 13 Hz), 2.60 (3 H, s), 1.45 (9 H, s).

The dioxaphospholene **23** (300 mg, 0.53 mM) was dissolved in THF (20 mL) and water (5 mL). After 1 h at 20 °C, the mixture was evaporated and the residue extracted with $CH_2Cl_2$ (3 × 20 mL). The combined extracts were washed with water and saturated brine, dried ($Na_2SO_4$), and evaporated in vacuo to give **24**: 218 mg, 75%; mp 169–172 °C (from benzene/hexane); IR ($CHCl_3$) 3300, 2990, 1690, 1510, 1440, 1390, 1285, 1260, 1135, 1035 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) $\delta$ 10.1 (1 H, m), 9.5 (1 H, s), 7.25–7.85 (7 H, m), 3.90 (6 H, d, $J$ = 12 Hz), 2.55 (3 H, s), 1.45 (9 H, s). Anal. Calcd for $C_{24}H_{27}O_9N_2SP$: C, 52.36; H, 4.94; N, 5.09. Found: C, 52.19; H, 4.82; N, 5.04.

**Methylation of 24.** Treatment of **24** (30 mg, 0.055 mM) in acetone (5 mL) with $Me_2SO_4$ (100 mg) and $K_2CO_3$ (100 mg) under the usual experimental conditions gave **25**: 70%; $^1H$ NMR (90 MHz, $CDCl_3$) $\delta$ 7.3–7.8 (7 H, m), 4.03 (3 H, s), 3.7 (3 H, s), 3.63 (6 H, d, $J$ = 14 Hz), 2.75 (3 H, s), 1.58 (9 H, s). **27**: 8%; $^1H$ NMR (90 MHz, $CDCl_3$) $\delta$ 7.2–7.55 (7 H, m), 4.05 (3 H, s), 4.00 (3 H, s), 3.9 (6 H, d, $J$ = 13 Hz), 2.55 (3 H, s), 1.50 (9 H, s). The structure of **25** was proven by single-crystal X-ray crystallography.

The oxaphospholene **29** (58 mg, 0.3 mM) in THF (10 mL) was added to a solution of **24** (86 mg, 0.15 mM) in THF (6 mL) at 20 °C. After 15 h at 20 °C, water (3 mL) and $NaHSO_3$ (150 mg) were added. After 3 h at 20 °C, the mixture was extracted with $CH_2Cl_2$ (3 × 10 mL), dried ($Na_2SO_4$), and evaporated in vacuo to give **26**: 45 mg, 50%, purified by preparative TLC [silica gel, eluting with hexane/EtOAc (7:3)]; mp 102–103 °C; IR ($CHCl_3$) 3360, 1690, 1625 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) $\delta$ 10.25 (1 H, m), 7.7 (1 H, m), 7.25–7.65 (6 H, m), 3.70 (3 H, s), 3.68 (6 H, d, $J$ = 12 Hz), 2.7 (3 H, s), 1.52 (9 H, s). Anal. Calcd for $C_{25}H_{29}O_9N_2SP$: C, 53.19; H, 5.18; N, 4.96. Found: C, 53.00; H, 5.18; N, 4.75.

Treatment of **26** (25 mg, 0.043 mM) in THF (2 mL)/$Me_2SO$ (1 mL) at 20 °C with NaH (5 mg, 0.25 mM) and MeI (50 mg) gave **25**.

**3,6-Dihydro-4-acetoxy-5-methoxy-7-methyl-6-(phenylsulfonyl)benzo-[1,2-*b*:4,3-*b*′]dipyrrole (32).** The phosphate ester **26** (34 mg, 0.06 mM) in MeOH (0.5 mL) at 25 °C was treated with NaOMe (0.2 mL of a 16.6 M soln). After 3 h at 25 °C, $Ac_2O$ (0.5 mL) was added, and the mixture was evaporated in vacuo. The residue was dissolved in $CH_2Cl_2$ (20 mL) and washed successively with 2 N HCl (5 mL) and water (5 mL). The dried ($Na_2SO_4$) extract was evaporated in vacuo to give **30**: 80%; IR ($CHCl_3$) 3300, 1770, 1695 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) $\delta$ 8.6 (1 H, m), 7.25–7.8 (7 H, m), 3.78 (3 H, s), 2.78 (3 H, s), 2.27 (3 H, s), 1.64 (9 H, s). This material was used directly in the next stage.

To a solution of **30** (50 mg, 0.1 mM) in $CHCl_3$ (3 mL) at 0 °C was added trifluoroacetic acid (0.3 mL). After 1 h at 20 °C the mixture was concentrated under reduced pressure, and the residue was washed with hexane/ether (20 mL, 1:1). The residue was dissolved in toluene (10 mL), triethylamine (500 mg) was added, and the resulting solution was heated at 110 °C for 6 h. The mixture was evporated to give **32**: 32 mg, 80%; IR ($CHCl_3$) 3200, 1760, 1440, 1350, 1190, 1120, 1090 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) $\delta$ 8.2 (1 H, m), 7.25–7.75 (6 H, m), 7.1 (1 H, m), 6.55 (1 H, m), 3.7 (3 H, s), 2.7 (3 H, s), 2.28 (3 H, s); MS, $m/e$ calcd for $C_{20}H_{18}N_2O_5S$ 398, found 398.

**1,2-Dihydro Derivative 33.** To a solution of **32** (20 mg) in trifluoroacetic acid (0.3 mL) was added triethylsilane (0.3 mL), and the mixture was stirred at 20 °C in 1 h. The mixture was concentrated under reduced pressure, and the residue was dissolved in $CH_2Cl_2$ (15 mL), washed with saturated aqueous $NaHCO_3$ solution (2 × 5 mL), dried ($Na_2SO_4$), and evaporated. The residue was dissolved in $Ac_2O$ (1 mL) and evaporated in vacuo to give **33**: 12 mg, 60%; IR ($CHCl_3$) 1765, 1640, 1440, 1360, 1170; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 7.77–7.43 (5 H, m), 6.23 (1 H, s), 4.16 (2 H, t, $J$ = 6 Hz), 3.77 (3 H, s), 3.06 (2 H, t, $J$ = 6 Hz), 2.69 (3 H, s), 2.27 (3 H, s), 2.21 (3 H, s); MS, $m/e$ calcd for $C_{22}H_{22}N_2O_6S$ 442, found 442.

**(*E*)-Benzyl 3-[1-((4-Methylphenyl)sulfonyl)-5-(methoxycarbonyl)-pyrrol-3-yl]acrylate (40).** To a suspension of NaH (1.2 g, 25 mM) in THF (30 mL) at −30 °C was added $(EtO)_2P(O)CH_2CO_2Bn$ (6.136 g, 21.45 mM) dropwise, and the mixture was warmed to 0 °C. After the mixture recooled to −30 °C, the pyrrole **39** (6.2 g, 20 mM) in THF (30 mL) was added, with the temperature maintained at about −10 °C. After 5 min the mixture was quenched with 10% aqueous $NH_4Cl$ solution (20 mL), and the THF was evaporated under reduced pressure. The residue was extracted with $CH_2Cl_2$ (3 × 50 mL), dried ($Na_2SO_4$), and evaporated to give a tan solid (8.77 g). Recrystallization from acetone gave **40**: 6.26 g, 70%; mp 131–133 °C; IR (Nujol) 3140, 1735, 1700,

(25) For the synthesis of **57**, see: Warpehoski, M. A. *Tetrahedron Lett.*, in press. Warpehoski, M. A.; Kelly, R. C.; McGovren, J. P.; Wierenga, W. *Proc. Am. Assoc. Cancer Res.* **1985**, *26*, 870. For syntheses of model B and C portions, related to analogues of CC-1065, see: Warpehoski, M. A.; Bradford, V. S. *Tetrahedron Lett.* **1986**, 2735.

1635 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) $\delta$ 7.93–7.80 (3 H, m), 7.60 (1 H, d, $J$ = 16 Hz), 7.33–7.13 (8 H, m), 6.23 (1 H, d, $J$ = 16 Hz), 5.23 (2 H, s), 3.72 (3 H, s), 2.39 (3 H, s). Anal. Calcd for $C_{23}H_{21}NO_6S$: C, 62.86; H, 4.82; N, 3.19. Found: C, 63.03; H, 4.86; N, 3.29.

**Benzyl 5-(Methoxycarbonyl)-1-((4-methylphenyl)sulfonyl)-3,3′-bipyrrole-4′-carboxylate (36).** To a solution of TosMIC (2.240 g, 11.48 mM) and the pyrrole **40** (4 g, 9.2 mM) in THF (80 mL) at −78 °C was added LiHMDS [prepared from HMDS (4 mL, 19 mM) and 1.36 M *n*-BuLi (13.6 mM) in THF (20 mL)]. After 15 min at −70 °C, the mixture was quenched with 10% aqueous $NH_4Cl$ solution (20 mL) and evaporated under reduced pressure to remove the THF. The residue was extracted with $CH_2Cl_2$ (4 × 20 mL), dried ($Na_2SO_4$), and filtered, and silica gel (10 g) was added. After evaporation the residue (absorbed on the added silica gel) was chromatographed over silica gel (30 g) eluting with 5% EtOAc/25% petroleum ether/70% $CH_2Cl_2$ to give **36** (3.962 g) as a pale-yellow solid. Recrystallization from acetone gave **36**: 2.826 g, 65%; mp 152–154 °C; IR (Nujol) 3480, 1720, 1687, 1455 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) $\delta$ 8.93 (1 H, s), 8.13 (1 H, d, $J$ = 2 Hz), 7.90, 7.80 (2 H, AB q, $J$ = 8 Hz), 7.60–7.13 (9 H, m), 6.80 (1 H, t, $J$ = 2 Hz), 5.23 (2 H, s), 3.77 (3 H, s), 2.77 (3 H, s). Anal. Calcd for $C_{25}H_{22}N_2O_6S$: C, 62.75; H, 4.63; N, 5.85. Found: C, 62.58; H, 4.51; N, 5.80. The crude material can be used directly in the next stage.

**Benzyl 7-(Methoxycarbonyl)-3,4,5,6-tetrahydro-4,5-dioxo-6-((4-methylphenyl)sulfonyl)benzo[1,2-*b*:4,3-*b*′]dipyrrole-1-carboxylate (42).** To a solution of the bipyrrole **36** (1.912 g, 4.0 mM) in $CH_2Cl_2$ (50 mL) at 0 °C was added dropwise oxalyl chloride (450 μL, 52 mM). Further oxalyl chloride (0.15 mL) was added, and the mixture was left at 0 °C for 24 h. The mixture was cooled to −78 °C, and $SnCl_4$ (468 μL) was added dropwise. After 1.5 h, the mixture was quenched by dropwise addition of water (10 mL). The $CH_2Cl_2$ layer was separated, and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic phases was dried ($Na_2SO_4$) and filtered, and silica gel (5 g) was added to the filtrate and evaporated under reduced pressure. The residue was chromatrographed on silica gel (15 g) eluting with 5% EtOAc/25% petroleum ether/70% $CH_2Cl_2$ to give **42** (1.542 g, 72%) as a red solid: mp 180 °C (slow dec); IR (Nujol) 3160, 1705, 1660, 660 $cm^{-1}$; UV (MeOH) 262, 355, 460 nm (ε 12950, 8690, 320); $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 11.26 (1 H, s), 8.43, 8.41 (2 H, d, $J$ = 8 Hz), 7.55 (1 H, d, $J$ = 3 Hz), 7.76 (1 H, s), 7.48–7.30 (7 H, m), 5.36 (2 H, s), 3.99 (3 H, s), 2.39 (3 H, s). Anal. Calcd for $C_{27}H_{20}N_2O_8S$: C, 60.90; H, 3.79; N, 5.26. Found: C, 60.71; H, 4.08; N, 4.97.

**Benzyl 3,6-Dihydro-4-((diethoxyphosphinyl)oxy)-5-hydroxy-7-(methyloxycarbonyl)-6-((4-methylphenyl)sulfonyl)benzo[1,2-*b*:4,3-*b*′]dipyrrole-1-carboxylate (44).** To a solution of the quinone **42** (1.24 g 2.3 mM) in $CH_2Cl_2$ (10 mL) was added $(EtO)_3P$ (420 μL 2.45 mM). The red color of the quinone was discharged almost immediately, and the mixture evaporated at 20 °C in vacuo to give **43**, which was dissolved in 2% aqueous THF (10.2 mL). After 1 h the solution was evaporated in vacuo, and the residue treated with $Et_2O$ (5 mL) and filtered. The solid was washed with ether (2 × 10 mL), and dried to give **44** (1.216 g 78%), mp 152–153 °C (dec) (from acetone/cyclohexane). IR (Nujol) 3400–2600, 1710, 1460 and 1150 $cm^{-1}$. NMR (360 MHz, $CDCl_3$) $\delta$ 10.63 (1 H, s), 8.75 (1 H, bs), 8.42 (1 H, s), 7.88 (1 H, d, $J$ = 3 Hz), 7.68, 7.74 (2 H, AA′ q, $J$ = 8 Hz), 7.5–7.3 (5 H, m), 7.16, 7.14 (2 H, BB′ q, $J$ = 8 Hz), 5.37 (2 H, s), 4.32 (4 H, m), 3.98 (3 H, s), 2.34 (3 H, s), 1.36 (6 H, t, $J$ = 8 Hz). Anal. Calcd for $C_{31}H_{31}N_2O_{11}PS$: C, 55.52; H, 4.66. Found: C, 55.23; H, 4.58. The nitrogen analysis was low, and satisfactory MS data could not be obtained.

**Benzyl 3,6-Dihydro-4-((diethoxyphosphinyl)oxy)-5-methoxy-7-(methoxycarbonyl)-6-((4-methylphenyl)sulfonyl)benzo[1,2-*b*:4,3-*b*′]dipyrrole-1-carboxylate (45).** Diazomethane in $Et_2O$ (30 mL) [prepared from Diazald (2.4 g)] was added to a solution of the phosphate ester **44** (1.97 g) in $CH_2Cl_2$ (100 mL) at −78 °C. After 20 h at −78 °C additional diazomethane [prepared from Diazald (1.2 g)] was added, and stirring was continued for 28 h. The mixture was quenched with AcOH (2 mL) and evaporated at 20 °C to give an oil (1.953 g), which was crystallized from acetone to give **45**: 1.085 g, 53%; mp 170–171 °C (dec); IR (Nujol) 3270, 1720, 1460 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) $\delta$ 10.75 (1 H, s), 8.40 (1 H, s), 8.33, 8.26 (2 H, AA′ q, $J$ = 8 Hz), 7.99 (1 H, d, $J$ = 3 Hz), 7.5–7.27 (7 H, m), 5.42 (2 H, s), 4.20 (4 H, q, $J$ = 8 Hz), 3.97 (3 H, s), 3.38 (3 H, s), 2.37 (3 H, s), 1.30 (6 H, t, $J$ = 8 Hz). Anal. Calcd for $C_{32}H_{33}N_2O_{11}PS$: C, 56.13; H, 4.86; N, 4.09. Found: C, 56.21; H, 5.00; N, 4.27. Evaporation of the mother liquors and chromatography over silica gel gave **48**: 140 mg, 7%; mp 168–170 °C (dec); $^1H$ NMR (90 MHz, $CDCl_3$) $\delta$ 10.25 (1 H, br s), 8.30 (1 H, s), 7.65, 7.55 (2 H, AA′ q, $J$ = 8 Hz), 7.40 (6 H, br s), 7.10, 6.95 (2 H, BB′ q, $J$ = 8 Hz), 5.30 (2 H, s), 4.40 (4 H, q, $J$ = 8 Hz), 3.87 (3 H, s), 3.84 (3 H, s), 2.30 (3 H, s), 1.30 (6 H, t, $J$ = 8 Hz).

**Benzyl 3,6-Dihydro-4-((diethoxyphosphinyl)oxy)-5-methoxy-7-(methoxycarbonyl)benzo[1,2-*b*:4,3-*b*′]dipyrrole-1-carboxylate (49).** A solution of the phosphate ester **45** (1.928 g, 2.8 mM) in THF (25 mL)/water (0.3 mL) at 0 °C was treated with Al/Hg amalgam [prepared from Al foil (310 mg)], and the mixture was stirred for 15 h at 20 °C. The mixture was diluted with $CH_2Cl_2$ (25 mL) and filtered through Celite. The Celite was washed with $CH_2Cl_2$ (6 × 25 mL), and the filtrate was concentrated to approximately 5 mL and filtered through silica gel, eluting with EtOAc. Evaporation of the filtrate in vacuo gave **49**: 1.582 g, 90%; mp 135–137 °C (from acetone/hexane); IR (Nujol 3330, 3190, 1705 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 10.70 (1 H, s), 9.24 (3 H, s), 8.18 (1 H, d, $J$ = 3 Hz), 7.92 (1 H, d, $J$ = 3 Hz), 7.5–7.3 (5 H, m), 5.42 (2 H, s), 4.26 (4 H, q, $J$ = 8 Hz), 4.08 (3 H, s), 3.90 (3 H, s), 1.27 (6 H, t, $J$ = 8 Hz). Anal. Calcd for $C_{25}H_{27}N_2O_9P$: C, 56.60; H, 5.13; N, 5.28. Found: C, 56.38; H, 5.39; N, 5.48.

**3,6-Dihydro-4-((diethoxyphosphinyl)oxy)-5-methoxy-7-(methoxycarbonyl)benzo[1,2-*b*:4,3-*b*′]dipyrrole (51).** The phosphate ester **49** (1.110 g, 2.09 mM) in EtOAc (100 mL) was hydrogenated over 10% Pd/C (120 mg) until no starting material (TLC) remained (ca. 20 h). Filtration and evaporation gave **50**: 810 mg, 88%; mp 246 °C (dec) (EtOAc); IR (Nujol) 3320, 3220, 1710, 1665 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$/$Me_2SO$-$d_6$) $\delta$ 11.40 (1 H, s), 11.13 (1 H, s), 8.10 (1 H, d, $J$ = 2 Hz), 7.85 (1 H, d, $J$ = 3 Hz), 4.23 (4 H, q, $J$ = 8 Hz), 4.00 (3 H, s), 3.90 (3 H, s), 1.27 (6 H, t, $J$ = 8 Hz). Anal. Calcd for $C_{18}H_{21}N_2O_9P$: C, 49.10; H, 4.81; N, 6.36. Found: C, 49.34; H, 4.96; N, 6.56.

A mixture of the acid **50** (500 mg, 1.136 mM), copper powder (600 mg), diisopropylethylamine (30 mL), and anisole (40 mL) was heated at 130 °C for 48 h. The mixture was evaporated under reduced pressure, and the residue was suspended in 10% aqueous HCl (20 mL) and extracted with $CH_2Cl_2$ (3 × 10 mL). The dried ($Na_2SO_4$) extract was evaporated and the residue (532 mg) chromatographed over silica gel eluting with 20% EtOAc/petroleum ether to give **51**: 285 mg, 60%; mp 118–119 °C (acetone/hexane); IR (Nujol) 3365, 3220, 1710, 1460, 1255 $cm^{-1}$; UV (MeOH) 208, 247, 316 nm (ε 22000, 11400, 17400); $^1H$ NMR (90 MHz, $CDCl_3$) $\delta$ 10.13 (1 H, s), 9.33 (1 H, s), 7.40 (1 H, d, $J$ = 2 Hz), 7.20 (1 H, t, $J$ = 3 Hz), 6.70 (1 H, t, $J$ = 3 Hz), 4.23 (4 H, q, $J$ = 8 Hz), 4.00 (3 H, s), 3.97 (3 H, s), 1.27 (6 H, t, $J$ = 8 Hz). Anal. Calcd for $C_{17}H_{21}N_2O_7P$: C, 57.52; H, 5.34; N, 7.07. Found: C, 57.44; H, 5.56; N, 7.20.

**Methyl 1,2,3,6-Tetrahydro-4-((diethoxyphosphinyl)oxy)-5-methoxybenzo[1,2-*b*:4,3-*b*′]dipyrrole-7-carboxylate (52).** To a solution of the phosphate ester **51** (109 mg, 0.275 mM) in $HSiEt_3$ (2 mL)/$CH_2Cl_2$ (4 mL) at −20 °C was added trifluoroacetic acid (2 mL) over 15 min. The mixture was warmed to 20 °C and after 17 h was evaporated under reduced pressure to give a green oil. Chromatography over silica gel eluting with EtOAc gave **52**: 48 mg, 44%; mp 93–96 °C (from $Et_2O$/hexane); IR ($CHCl_3$) 3460, 3320, 1706, 1280, 1260, 1025 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) $\delta$ 9.29 (1 H, br s), 6.98 (1 H, d, $J$ = 2 Hz), 4.68 (1 H, br s), 4.26 (4 H, q, $J$ = 7 Hz), 3.94 (3 H, s), 3.87 (3 H, s), 3.68 (2 H, t, $J$ = 7 Hz), 3.17 (2 H, t, $J$ = 7 Hz), 1.30 (6 H, t, $J$ = 7 Hz); MS, $m/e$ calcd for $C_{17}H_{23}N_2O_7P$ $M^+$ 398.1243, found 398.1251. It is best to use the crude **52** in the next step. In this way the overall yields through to **53** and **54** are substantially improved.

Carrying out the above reduction on **51** (353 mg, 0.891 mM), followed by direct acetylation with $Ac_2O$ (1 mL), gave **53**: 317 mg, 81%; mp 144–145 °C (from acetone/hexane); IR ($CHCl_3$) 3450, 1708, 1642, 1532, 1420, 1370, 1264, 1136, 1016 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 9.34 (1 H, br), 7.04 (1 H, d, $J$ = 2 Hz), 4.24 (6 H, m), 4.08 (3 H, s), 3.95 (3 H, s), 3.12 (2 H, t, $J$ = 7 Hz), 2.16 (3 H, s), 1.37 (6 H, t, $J$ = 7 Hz); MS, $m/e$ calcd for $C_{19}H_{25}N_2O_8P$ $M^+$ 440.1348, found 440.1344.

Treatment of the amine **52** (13 mg) in $CH_2Cl_2$ (0.5 mL) with NaOCN (61 mg) and AcOH (1 mL)/water (two drops) for 2.25 h followed by workup with water (1 mL)/$CH_2Cl_2$ (1 mL) and extraction of the aqueous phase with $CH_2Cl_2$ (3 × 1 mL) gave crude **54**. Chromatography over silica gel eluting with 10% MeOH/EtOAc gave **54**: 11 mg, 76%; mp 163–165 °C (from $CHCl_3$); IR ($CHCl_3$) 3510, 3450, 1707, 1651, 1586, 1426, 1284, 1250, 1025 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 9.25 (1 H, br s), 7.05 (1 H, d, $J$ = 2 Hz), 5.39 (2 H, br s), 4.37 (2 H, t, $J$ = 7 Hz), 4.27 (4 H, m), 4.07 (3 H, s), 3.95 (3 H, s), 3.12 (2 H, t, $J$ = 7 Hz), 1.36 (6 H, t, $J$ = 7 Hz); MS, $m/e$ calcd for $C_{18}H_{24}N_3O_8P$ $MH^+$ 442, found 442, base peak 399.

**Methyl 1,2,3,6-Tetrahydro-4-hydroxy-5-methoxybenzo[1,2-*b*:4,3-*b*′]-dipyrrole-7-carboxylate (55).** The phosphate **53** (317 mg, 0.72 mM), $MeC(CH_2OH)_3$ (864 mg), and $Na_2S_2O_5$ (274 mg) in INKOH/MeOH (12 mL, degassed) were stirred at 20 °C for 3 h. The mixture was quenched with 2 M HCl to pH 6 (ca. 5 mL), water (1 mL) was added, and the mixture was extracted with $CH_2Cl_2$ (4 × 8 mL). The dried ($MgSO_4$) extract was evaporated in vacuo to give a brown solid (322 mg). Further extraction of the aqueous phase with EtOAc (2 × 5 mL) gave 55 mg of crude product. Chromatography of the total crude solids over silica gel, eluting with 5% MeOH/EtOAc successively to 100% MeOH, gave **55**: 103 mg, 49%, 72% based upon recovered **53**; mp 244–246 °C

(from acetone); IR (Nujol) 3320, 2600, 1686, 1640, 1578, 1535, 1296, 1260 $cm^{-1}$; $^1H$ NMR (300 MHz, $Me_2SO$-$d_6$) $\delta$ 12.26 (1 H, s), 11.68 (1 H, br s), 7.04 (1 H, d, $J$ = 2 Hz), 4.22 (2 H, t, $J$ = 8 Hz), 3.83 (3 H, s), 3.80 (3 H, s), 3.21 (2 H, t, $J$ = 8 Hz), 2.29 (3 H, s); MS, $m/e$ calcd for $C_{15}H_{16}O_5N_2$ $M^+$ 304.1059, found 304.1056.

An exactly comparable procedure carried out on **54** (208 mg, 0.472 mM) gave **56**: 93 mg, 68%; mp 221-222 °C (dec) (from acetone); IR (Nujol) 3300, 1694, 1632 $cm^{-1}$; $^1H$ NMR (300 MHz, $Me_2SO$-$d_6$) $\delta$ 12.93 (1 H, s), 11.49 (1 H, br s), 6.96 (1 H, d, $J$ = 2 Hz), 6.89 (2 H, b), 4.00 (2 H, t, $J$ = 8 Hz), 3.82 (3 H, s), 3.79 (3 H, s), 3.20 (2 H, t, $J$ = 8 Hz); MS, $m/e$ calcd for $C_{14}H_{15}N_3O_5$ $M^+$ 305.1011, found 305.1008.

**PDE I (2) and PDE II (3).** A solution of **56** (14.3 mg, 46.9 $\mu$M) in 0.01 N KOH (21 mL degassed) was allowed to stand at 20 °C for 31.5 h. The solution was acidified with 2 N HCl (15 mL) and brine (7 mL) and extracted with EtOAc (10 × 5 mL). The dried ($Na_2SO_4$) extract was evaporated in vacuo to give a tan solid, which was crystallized from MeOH to give **2**: 3 mg; mp 230-233 °C; IR (Nujol) 3450, 3340, 3200, 1662, 1634, 1335, 1298, 1261, 1088 $cm^{-1}$; UV (in water) 251, 308 nm ($\epsilon$ 40 000, 15 000), (in 0.01 N NaOH) 236, 254 (shoulder), 338 nm ($\epsilon$ 35 000, 24 000); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 12.83 (1 H, s), 11.26 (1 H, br s), 6.87 (3 H, b), 3.99 (2 H, t, $J$ = 9.0 Hz), 3.77 (3 H, s), 3.19 (2 H, t, $J$ = 9.0 Hz).

To a stirred suspension of the ester **55** (13.1 mg, 45.2 $\mu$M) in EtOH (0.5 mL degassed) containing $Na_2S_2O_5$ (25 mg) was added INKOH (0.5 mL degassed). After 11.5 h at 20 °C, 2 N HCL (1 mL)/brine (1 mL) and EtOAc (2 mL) were added. The aqueous phase was extracted with EtOAc (4 × 2 mL), washed with brine (2 mL), dried ($Na_2SO_4$), and evaporated to give crude **3** (8.0 mg). Purification by chromatography over Celite eluting with EtOAc, then $CHCl_3$, and finally MeOH gave **3**: 2 mg; mp slow dec at ca. 180 °C; IR (Nujol) 3280, 2500-3700, 1663, 1640, 1600, 1565 $cm^{-1}$; UV (in water) 265, 324 nm ($\epsilon$ 55 000, 40 000), (in 0.01 N NaOH) 262, 333 nm ($\epsilon$ 21 000, 7 000); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 12.19 (1 H, s), 11.46 (1 H, br s), 6.95 (1 H, br s), 4.20 (2 H, t, $J$ = 8.1 Hz), 3.77 (3 H, s), 3.19 (2 H, t, $J$ = 8 Hz), 2.28 (3 H, s).

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**Supplementary Material Available:** Experimental and characterization details for **11**, **12**, **13**, **38**, and **39** (2 pages). Ordering information is given on any current masthead page.

# Diels-Alder Reactions of Heterocyclic Azadienes: Total Synthesis of PDE I, PDE II, and PDE I Dimer Methyl Ester

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**Abstract:** Full details of the total synthesis of PDE I (**2**) and PDE II (**3**), two 3',5'-cAMP phosphodiesterase inhibitors possessing the identical, functionalized 1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole structure constituting the central and right-hand segments of the potent antitumor antibiotic CC-1065 (**1**), are described. The linkage of two 1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole units in the preparation of PDE-I dimer methyl ester (**4**) is detailed and constitutes the preparation of the fully assembled central and right-hand segments of CC-1065.

CC-1065 (**1**, NSC-298223), an antitumor antibiotic isolated from *Streptomyces zelensis*,[2] initially identified by spectroscopic methods[3a] and confirmed by single-crystal X-ray structural analysis,[3b] has been shown to possess exceptional, potent in vitro cytotoxic activity,[4] antimicrobial activity,[2] and confirmed, potent in vivo antitumor activity.[2] Recent studies have shown that CC-1065 binds to double-stranded B-DNA in an initial, high-affinity, five base pair sequence-specific (A/GNTTA or AAAAA), nonintercalative fashion along the minor groove[5] and subsequently forms an irreversible, covalent adduct.[6] The covalent alkylation of DNA has been shown to proceed by N-3 adenine alkylation of the 4,4-spirocyclopropylcyclohexa-2,5-dienone (spirobicyclo-[5.2.0]octa-2,5-dien-4-one) unit present in the left-hand segment of CC-1065.[6] Consequently, the mechanism of CC-1065 cytotoxicity has been proposed to be derived from the overstabilization of the DNA helix and the inhibition of the normal unwinding and melting process necessary for DNA synthesis.[5] The binding specificity and cytotoxic potency associated with this agent may be attributed to two complementary structural features: the repeating, identical 1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole units constituting the central and right-hand segments of CC-1065 appear to be responsible for the high-affinity, sequence-specific

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