

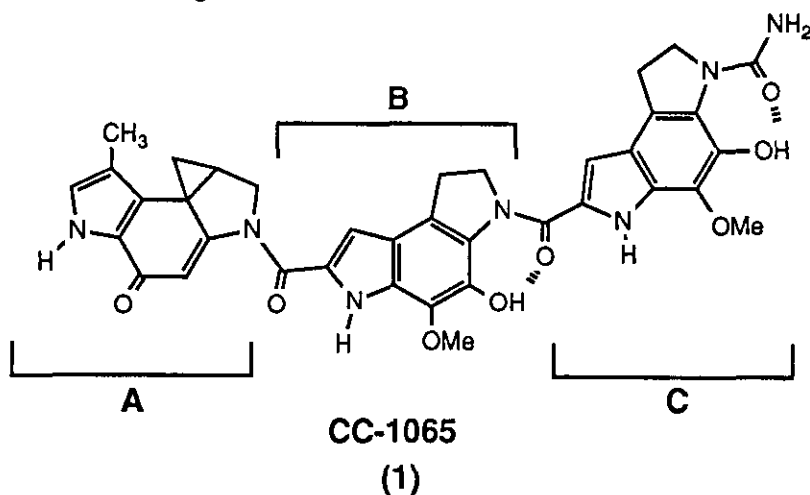
REVIEW OF SYNTHETIC STUDIES TOWARD CC-1065, PDE-I, AND PDE-II[†]

Viresh H. Rawal, Robert J. Jones, and Michael P. Cava*

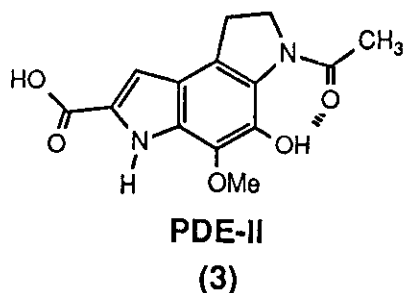
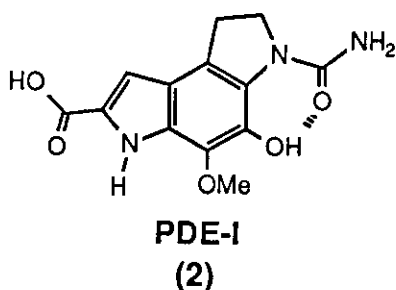
Department of Chemistry, University of Alabama, P. O. Box H, Tuscaloosa, Alabama 35487-9671
U.S.A.

Abstract – The synthetic approaches to the potent antitumor agent CC-1065 (1) and the closely related phosphodiesterase inhibitors PDE-I (2) and PDE-II (3) are reviewed.

The antitumor antibiotic CC-1065 (1), isolated from *Streptomyces zelensis*¹ is one of the most cytotoxic compounds known. As compared to other antineoplastic agents, CC-1065 is about 400 times more potent than adriamycin², 10 times more potent than actinomycin D, xanthomycin or quinomycin C and about twice as potent as maytansine³ against L1210 leukemia cells *in vitro*. It has been shown to bind covalently to N-3 of adenine and to lie within the minor groove of DNA⁴.



[†]Dedicated to Professor Gilbert Stork on the occasion of his 65th birthday.



The remarkable potency and unique structure of CC-1065 have initiated considerable effort toward the syntheses of the individual units A, B and C, and these include the syntheses of phosphodiesterase inhibitors PDE-I (2) and PDE-II (3),^{5,6,7} essentially the B and C units which have significant action in cyclic adenosine-3', 5'-monophosphate (c-AMP) regulation. This review covers the synthetic efforts directed towards these unique compounds up to the end of April 1986.

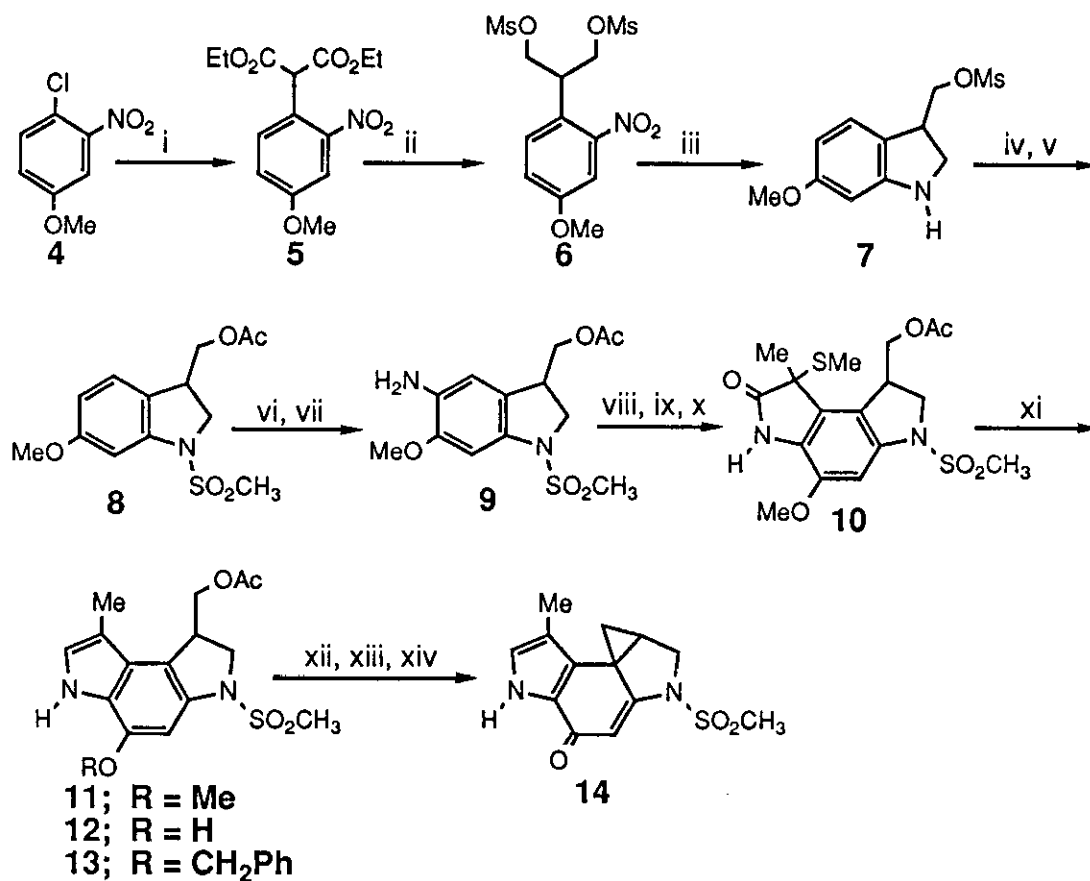
1. Syntheses of Unit A of CC-1065

a. WIERENGA'S SYNTHESIS

Soon after its isolation at Upjohn, Wierenga, who is also from the same company, reported the first synthesis of a CC-1065 segment.^{6a} In terms of strategy, the synthesis is similar to Umezawa's synthesis of PDE-I and PDE-II. The author begins with a functionalized benzene ring onto which is grafted first the indoline portion, then the indole ring. The synthesis, shown in Scheme 1, is noteworthy in a number of ways, including the clever formation of the substituted indoline and its subsequent functionalization to the tricyclic indole using Gassman's oxindole procedure.^{8,9} Most important, the synthesis established the feasibility of carrying out a Winstein Ar₃ type of cyclization to give the cyclopropane-conjugated dienone moiety found in unit A.¹⁰

Wierenga's synthesis began with 4-chloro-3-nitroanisole 4, which was transformed to the aryl malonate 5 by means of a nucleophilic aromatic substitution reaction. Reduction to the diol followed by mesylation gave the bismesylate 6. Subsequent reduction of the nitro group in the presence of triethylamine also effected cyclization to give the unstable indoline 7. The nucleophilic indoline nitrogen was blocked and the *O*-mesylate was displaced with an acetate. Nitration of the resulting acetate 8 proceeded regioselectively and gave, after catalytic

Scheme 1. Wierenga's synthesis of N-methanesulfonyl protected A unit



Scheme 1. Reagents: i) NaCH(CO₂Et)₂, DMF, Δ; ii) DIBAL, THF/toluene; iii) H₂, PtO₂, Et₃N; iv) MsCl, Et₃N; v) NaOAc; vi) HNO₃, CH₃NO₂; vii) H₂, PtO₂; viii) CH₃CH(CO₂Et)SCH₃·Cl₂, R₃N, CH₂Cl₂, -75°C; ix) Et₃N; x) 2 N HCl; xi) BH₃·Me₂S, THF; xii) LiSBu, HMPA, 110°C; xiii) CBr₄, PPh₃, CH₃CN; xiv) (C₃H₇)₂NC₂H₅, CH₂Cl₂.

hydrogenation, amine 9. Next, the 3-methylindole moiety was introduced using a modification of Gassman's oxindole synthesis.^{8,9} Thus, 9 was alkylated with the chlorine complex of ethyl α -(mercaptomethyl)propionate in the presence of a non-nucleophilic, hindered base such as 1,8-bis(dimethylamino)naphthalene or isopentyldiisopropylamine; then, it was rearranged using triethylamine and cyclized to give oxindole 10, which was reduced cleanly and in good yield with the dimethylsulfide complex of borane.

At this stage, the author encountered the common but nontrivial problem of demethylation. Acidic reagents were unsuitable for demethylating 11, presumably because of destruction of the resulting electron-rich indole 12. Although mercaptide anion did allow the desired transformation, the yield was unacceptable. This forced the author to repeat the whole sequence using the benzyl protecting group (yields not specified). Indole 13, so obtained, was debenzylated by catalytic hydrogenation to afford a good yield of 12. The acetate group was removed and the resulting alcohol was converted to a bromide using carbon tetrabromide and triphenylphosphine. This compound was highly reactive and on exposure to Hunig's base gave the desired cyclopropane containing A unit, masked as its methanesulfonyl derivative 14.

The synthesis of 14 required 14 steps from 4-chloro-3-nitroanisole. The overall yield is difficult to state since yields were not given for a couple of steps, and for the entire sequence which used the benzyl group. It also has to be assumed that the benzyl group survived fully the two PtO_2 catalyzed hydrogenations prior to the final debenzylation. With these qualifications, the overall yield is in the 3% range.

b. MAGNUS' SYNTHESIS

Not unlike the Chemical Abstracts nomenclature for these systems, Magnus and coworkers have employed a strategy where the individual units of CC-1065 are viewed as arising from suitably functionalized 3,3'-dipyrroles.^{6b,d} In the first of their series of communications on the synthesis of CC-1065 is described an extension of the Van Leusen pyrrole synthesis where the anion of *p*-tolylsulfonylmethyl isocyanide (TOSMIC) is reacted with various Michael acceptors such as α , β -unsaturated ketones, esters or nitriles.¹¹⁻¹⁴

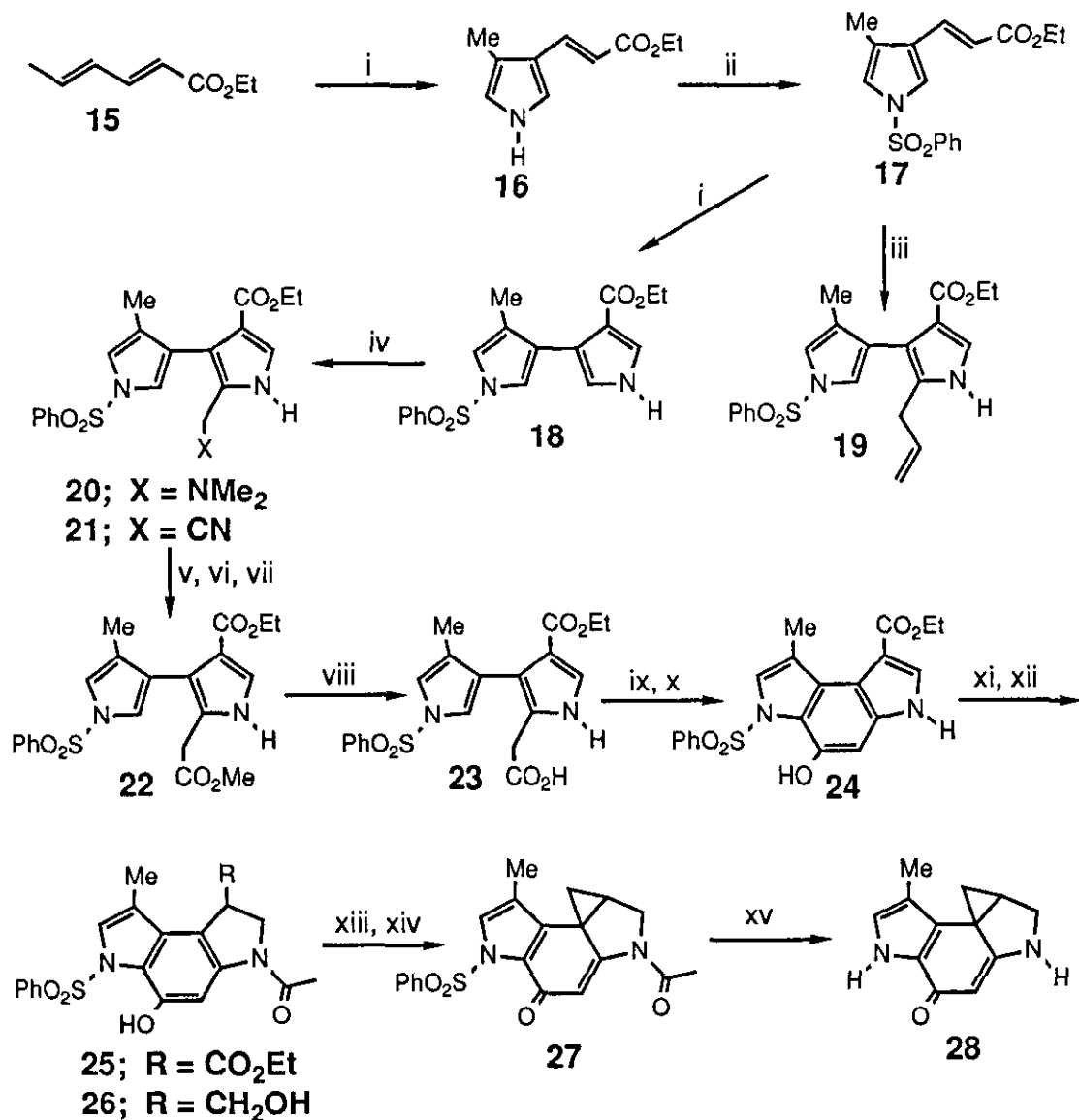
Whereas Van Leusen had examined the monoaddition reaction of TOSMIC, Magnus looked into the possibility of adding two of these units onto a dieneoate (scheme 2). Unfortunately, the dieneoate ester, ethyl sorbate 15

reacted with only one equivalent of TOSMIC to afford pyrrole 16. The powerful electron-donating character of pyrrole is undoubtedly deactivating the resulting α,β -unsaturated ester toward a second addition. To enable further reaction, the pyrrole nitrogen was blocked with the strongly electron-withdrawing benzenesulfonyl group. Rendered more electrophilic, the resulting ester 17 reacted smoothly with both TOSMIC and its *C*-allyl derivative to give the 3,3'-bipyrrole systems 18 and 19, respectively. This three step sequence allowed an efficient conversion of the readily available ethyl sorbate, into potentially useful, differentiated 3,3'-bipyrroles.^{6b} The efficacy of the bipyrrole approach was soundly established in a later paper on the synthesis of unit A.^{6d} Mannich reaction of 18 allowed a one carbon homologation at the desired, most electrophilic position to give 20, which was converted by quaternization with methyl iodide and treatment with sodium cyanide to the nitrile 21. Methanolysis of the nitrile gave the desired diester 22, along with approximately 20% of the β -ester exchange product. Selective hydrolysis of the methyl ester was effected using lithium iodide in refluxing pyridine.¹⁵ Conversion of 23 to the acid chloride followed by treatment with SnCl_4 accomplished the formation of the tricyclic phenol 24 in 61% overall yield. Selective reduction of the indole, on the right-hand side, was carried out under the "ionic hydrogenation" conditions of Guillerme et al.,¹⁶ and the indoline which was produced was acetylated with acetic anhydride to afford the pyrroloindoline 25. The ester moiety was reduced cleanly to the alcohol 26 without concomitant reduction of the amide group or cleavage of the *N*-phenylsulfonyl group.

The stage was now set to carry out the Winstein Ar_3 cyclization. The authors reported obtaining a complex mixture when alcohol 26 was subjected to Wierenga's two-step cyclization procedure. This problem was solved by making use of the Mitsunobu¹⁷ reaction in a novel intramolecular fashion. Thus 26 was converted directly to 27 in fair yield. Treatment of 27 with sodium methoxide in methanol quickly removed the acetyl group and, after prolonged treatment (18 h), also removed the phenylsulfonyl group. The resulting cyclopropyl-conjugated enone 28 bears no protecting groups and thus constitutes a true synthesis of the A unit of CC-1065.

Starting from ethyl sorbate the overall synthesis required 14 steps and upto the protected unit 27 the overall yield is reported to be around 5%. The yield was not disclosed for the last step, where two protecting groups are removed from a rather labile substrate.

Scheme 2. Magnus' 3,3'-bipyrrole synthesis of the A unit



Scheme 2. Reagents: i) TOSMIC, NaH, DMSO-Et₂O; ii) NaH, PhSO₂Cl, THF; iii) C-allyl TOSMIC, NaH, DMSO; iv) Me₂NH·HCl, CH₂O, H₂O, MeOH, 50°C; v) MeI; vi) NaCN; vii) MeOH, HCl; viii) LiI, pyridine, reflux; ix) oxalyl chloride, CH₂Cl₂, pyridine; x) SnCl₄, CH₂Cl₂; xi) TFA, HSiEt₃, 50°C; xii) Ac₂O; xiii) LAH, THF, 0°C; xiv) DEAD, PPh₃; xv) NaOMe, MeOH.

c. KRAUS' SYNTHESIS

In Kraus' ingenious approach to unit A, a Diels-Alder reaction was used to add the required number of carbons to an iminoquinone, and the resulting cyclohexene, having very little resemblance to the final product, was broken open and its appendages were wrapped around to construct the two indolic rings.^{6c}

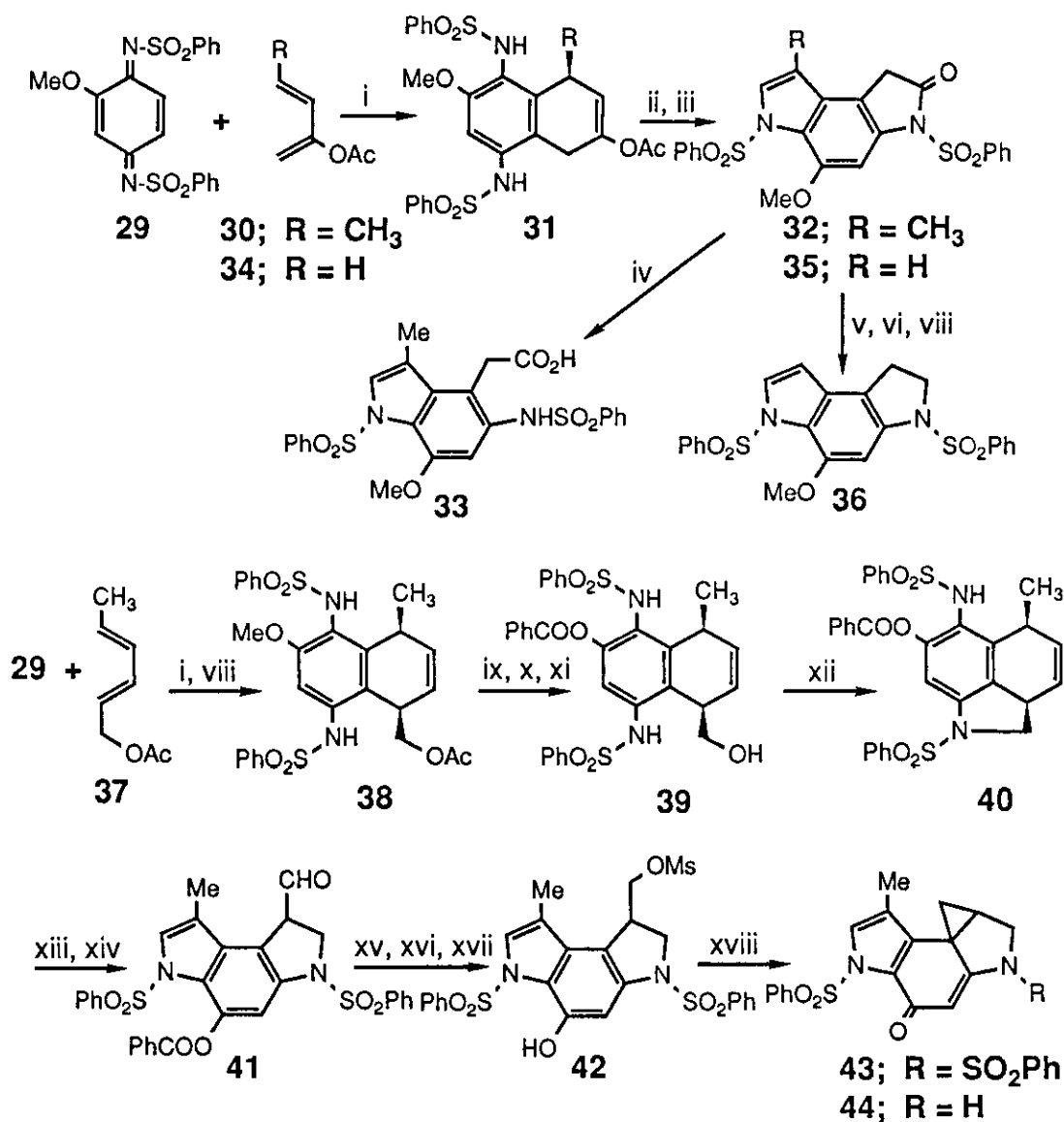
Results of his preliminary studies are detailed in Scheme 3.^{6c} Cycloaddition reaction between methoxybenzoquinone bis(benzenesulfonamide) **29**, which was obtained in 90% yield from methoxy-*p*-phenylenediamine, and diene **30** gave the unsymmetrical dihydronaphthalene **31**. Rupture of the enol ether linkage followed by acid-mediated cyclization of both of the resulting segments gave the indolelactam **32**, the identity of which was confirmed by x-ray analysis of its hydrolysis product **33**. An identical sequence of reactions with 2-acetoxybutadiene **34** afforded the desmethyl indole-lactam **35**. Hydrolysis of this lactam, followed by reduction and recyclization generated the tricyclic unit **36**, which closely resembles that found in the A unit of CC-1065.

A second communication from the Iowa group described the successful application of the Diels-Alder route to the synthesis of unit A, protected as a benzene sulfonamide.^{6e} Critical for the success of their strategy was the regiochemistry of the Diels-Alder reaction between a protected 2,4-hexadien-1-ol and an unsymmetrical dienophile. The authors examined the reaction of a number of such dienes with carbomethoxybenzoquinone and found very good regioselectivity with the acetoxy group^{6e}.

When diene **37** was allowed to react at room temperature with iminoquinone **29**, the cycloaddition proceeded with excellent regioselectivity, and afforded, after aromatization, a mixture enriched in the desired isomer **38** by better than a 25:1 ratio. The methyl ether of **38** was removed with BBr₃ and the resulting phenol was reprotected as a benzoate. The acetate group was removed selectively under acidic conditions to yield the primary alcohol **39**. Benzenesulfonylation of **39** led directly to ring formation, generating specifically the indoline ring **40**. Cleavage of the olefinic bond by ozonolysis and workup under reducing conditions, followed by acid-mediated ring formation, produced aldehyde **41**, which contains the tricyclic framework of unit A.

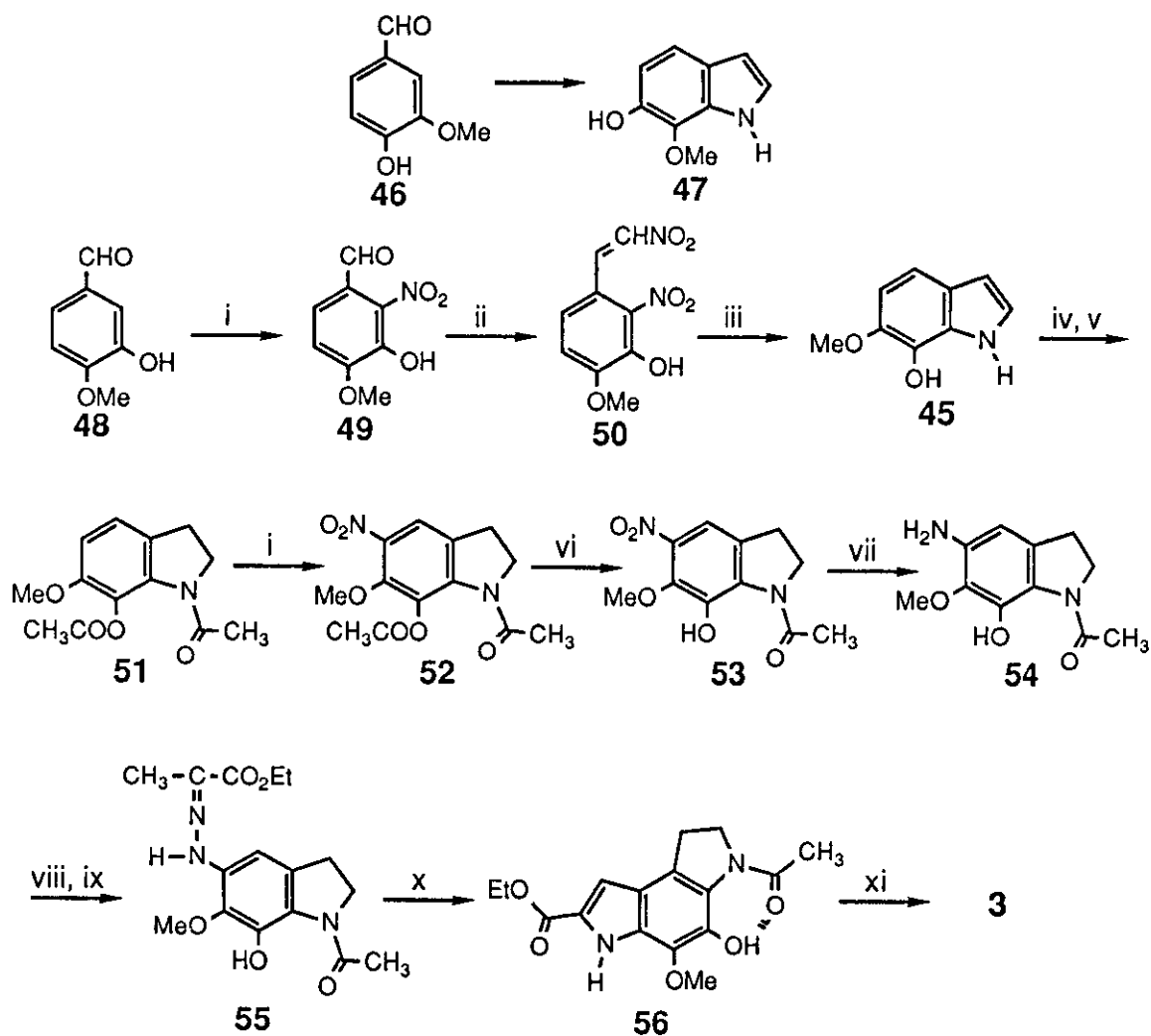
This aldehyde was reduced with Dibal and the resulting alcohol was converted to a mesylate. Debenzoylation, achieved with LiAlH₄, afforded phenol **42**, which closely resembles the penultimate intermediates in Wierenga's and Magnus' syntheses. Cyclization to the spiro-cyclopropane **43** was accomplished with DBU. Treatment

Scheme 3. Kraus' synthesis of phenylsulphonyl-protected A Unit



Scheme 3. Reagents: i) RT, 4 days; ii) O₃, -78°C, then Me₂S; iii) HCl, dioxane; iv) NaOH; v) NaOMe; vi) Red-Al; vii) NaH, MeSO₂Cl; viii) KOAc, HOAc; ix) BBr₃, hexane, CH₂Cl₂ -78°C to 30°C; x) (PhCO)₂O, Et₃N CH₂Cl₂, 0°C; xi) dioxane, 4 M H₂SO₄, MeOH (4:1:1); xii) PhSO₂Cl, Et₃N, CH₂Cl₂, 0°C; xiii) O₃, 1:1 CH₂Cl₂, MeOH, -78°C then excess Me₂S, cat H₂SO₄, 0°C; xiv) HCl, dioxane; xv) DIBAL, THF, 0°C; xvi) CH₃SO₂Cl, Et₃N, CH₂Cl₂; xvii) LAH, THF, 0°C; xviii) DBU, toluene, 50°C.

Scheme 4. Umezawa's synthesis of PDE-II



Scheme 4. Reagents: i) Ac_2O fuming HNO_3 ; ii) CH_3NO_2 , HOAc , NaOAc ; iii) Fe , HOAc ; iv) H_2 , Pt-C , HOAc ; v) Ac_2O , pyridine; vi) NaOH , EtOH ; vii) H_2 , Pd/C , EtOH ; viii) conc. HCl , H_2O , NaNO_2 ; ix) Ethyl 2-acetylpropionate, NaOH , H_2O ; x) EtOH , conc. H_2SO_4 , 70°C ; xi) EtOH , NaOH , then HCl , H_2O .

with sodium methoxide gave **44**, resulting from removal of only the benzenesulfonyl group on the indole nitrogen. Kraus' Diels-Alder based synthesis afforded the benzenesulfonyl protected indoline **44** in 12 steps with an overall yield of 5.5%, starting from the readily available methoxy benzoquinone bis(benzenesulfonamide) **29**.

2. Syntheses of PDE-I and PDE-II

a. UMEZAWA'S SYNTHESIS OF PDE-II

In a series of papers appearing in *Agricultural and Biological Chemistry*, these researchers described first the isolation and characterization^{5a,b} and later the syntheses^{5c,d} of PDE-I and PDE-II, which are structurally very similar to the B and C units of CC-1065. Their synthetic strategy was classical in nature and involved sequential functionalization of a benzene ring into an indoline ring, onto which was then grafted by Fisher indolization the last, indole-ester containing ring. The structural similarity between PDE-I and PDE-II enabled the authors to utilize a somewhat advanced, common synthetic intermediate.

The starting material for the synthesis was 7-hydroxy-6-methoxyindole **45**, which the authors stated was prepared in five steps from vanillin **46** by an established procedure. (Inspection of the substitution pattern of vanillin, however, reveals that it would give rise to 6-hydroxy-7-methoxyindole **47**, not the desired compound **45**.) As shown in Scheme 4, this preparation began with isovanillin **48**, which was nitrated by the method of Pschorr to give **49**.¹⁸ Condensation with nitromethane¹⁹ followed by reductive cyclization afforded the required indole **45**.²⁰

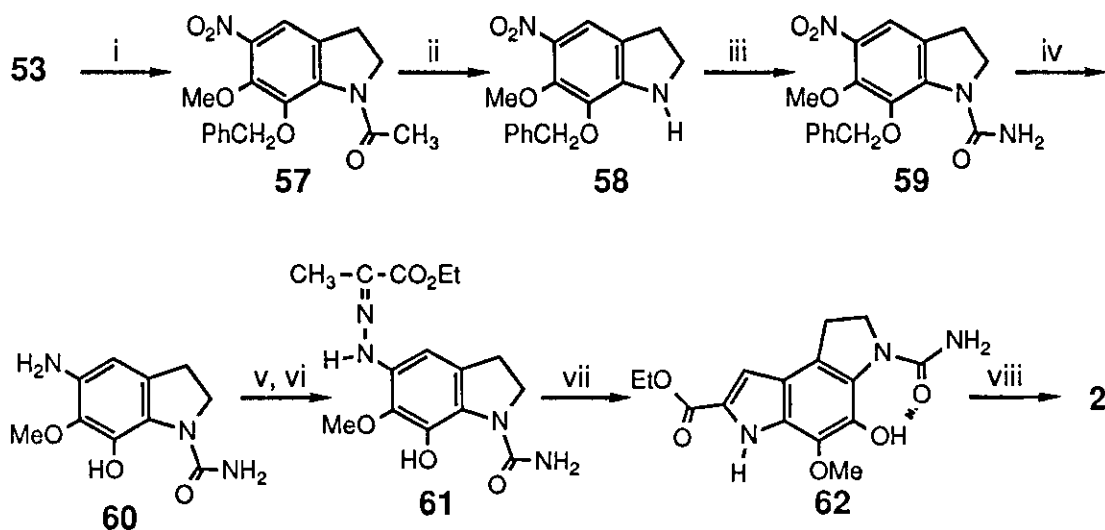
This indole was hydrogenated in an autoclave and the resulting, unpurified indoline was acetylated directly to give amide **51**. Nitration of **51** proceeded regioselectively to give **52** which was hydrolyzed to phenol **53**, the common intermediate for the synthesis of both PDE-I (**2**) and PDE-II (**3**). Conversion of **53** to PDE-II was accomplished in a straightforward manner, with Fisher indolization as the pivotal, ring-forming step. Catalytic reduction of the nitro group gave amine **54** in quantitative yield. Using the Japp-Klingemann conditions,²¹ this amine was diazotized, and then treated with an alkaline solution of ethyl 2-acetylpropionate to afford hydrazone **55** as a mixture of syn and anti isomers which were not separated. Fisher indolization of **55** in

ethanol saturated with dry hydrogen chloride gave the ethyl ester of PDE-II (56), but in a rather low yield (11%). By using ethanol and sulfuric acid the yield was improved slightly, to 18%. Hydrolysis of 56 using dilute ethanolic potassium hydroxide gave PDE-II (3) which was identical in all respects with the naturally derived product. The synthesis required just 8 steps from the relatively advanced starting material, indole 45, and 11 steps from isovanillin 48. Unfortunately, the overall yield of PDE-II was only 1.1% from 45 and 0.1% from isovanillin.

b. UMEZAWA'S SYNTHESIS OF PDE-I

Starting from the common intermediate 53, Umezawa's synthesis of PDE-I follows essentially the same route used for PDE-II (Scheme 5).^{5d} To enable conversion of the N-acetyl to an N-aminocarbonyl group, phenol 53 was first blocked with a benzyl group. Hydrolysis of compound 57 by refluxing in ethanol and aqueous sodium

Scheme 5. Umezawa's synthesis of PDE-I



Scheme 5. Reagents: i) PhCH_2Cl , K_2CO_3 , DMF, 110°C ; ii) EtOH, NaOH, 79°C ; iii) NaOCN, HOAc, H_2O ; iv) H_2 , 10% Pd/C, EtOH; v) Ac_2O , pyridine; vi) NaOH, EtOH; vii) H_2 , Pd/C, EtOH; viii) conc. HCl, H_2O , NaNO_2 ; ix) Ethyl 2-acetylpropionate, NaOH, H_2O ; x) EtOH, conc. H_2SO_4 , 70°C ; xi) EtOH, NaOH, then HCl, H_2O .

hydroxide proceeded nicely to give indoline 58, which was converted quantitatively to urea 59. Catalytic hydrogenation effected both the reduction of the nitro group and the cleavage of the benzyl ether. The resulting aniline 60 was subjected to the Japp-Klingmann conditions to provide hydrazone 61 in good overall yield. Fisher indolization was again a bad reaction, giving the ethyl ester of 62 in only 12% yield. Basic hydrolysis gave PDE-I. This synthesis required 14 steps from isovanillin and proceeded in 0.07% overall yield. Clearly, the low yields makes this synthetic route impractical, especially for preparing significant quantities of these units, required for the synthesis of CC-1065.

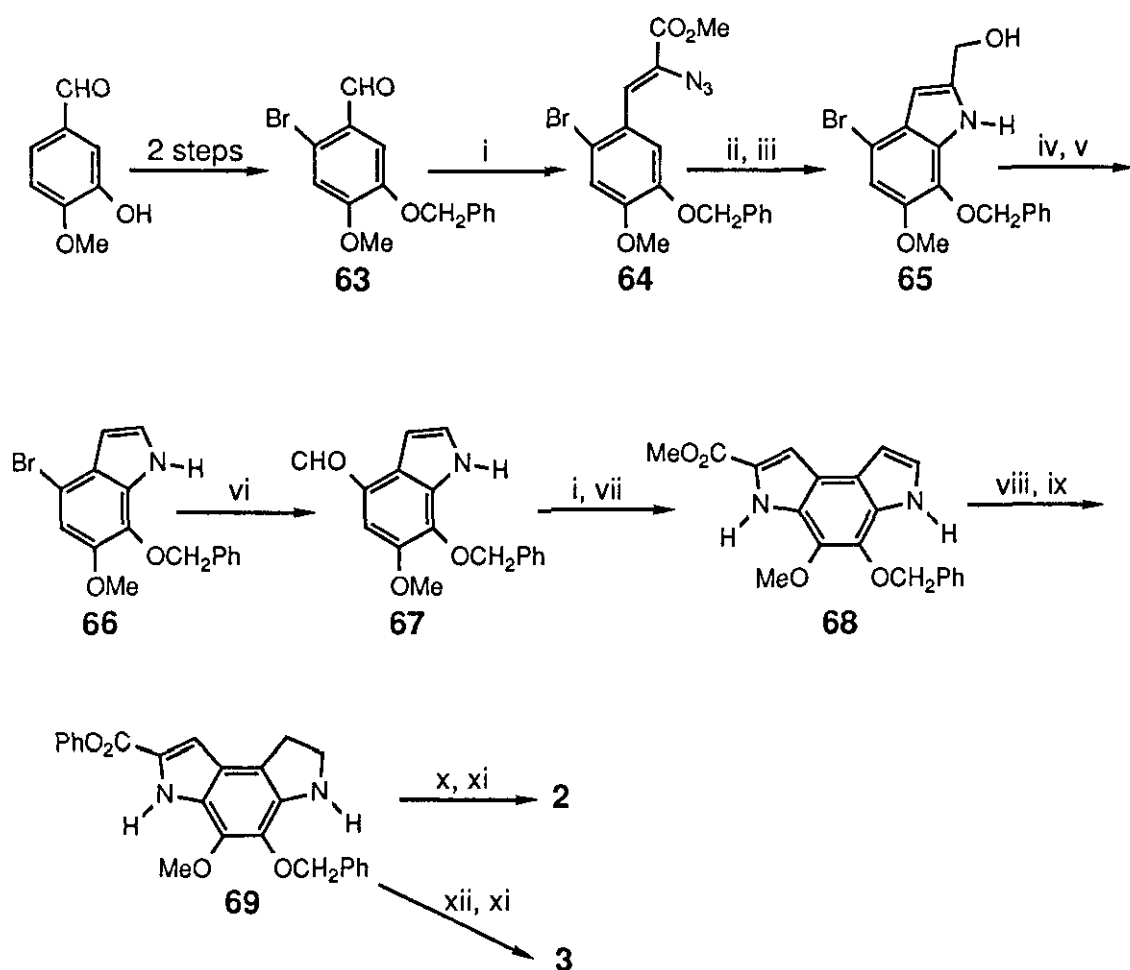
c. REES' SYNTHESIS OF PDE-I AND PDE-II.

Rees and coworkers followed a similar strategy as Umezawa and Wierenga in that they began with a functionalized benzene ring and subsequently annulated the pyrrole rings.^{5e} The pyrrole rings were formed by decomposing azidoacrylate derivatives which were easily prepared from the corresponding aldehydes; a similar sequence was utilized in Rees' methoxatin synthesis²².

The synthesis, as shown in Scheme 6, begins with the bromobenzaldehyde 63, which is readily prepared on large scale from isovanillin in two steps. The aldehyde 63 was condensed with methyl azidoacetate to give the azide 64. This azide was thermolyzed to form the indole ring, and the aldehyde functionality was reduced with LAH to give the alcohol 65. Manganese dioxide oxidation followed by decarbonylation with $(\text{PH}_3\text{P})_2\text{Rh}(\text{CO})\text{Cl}$ gave the indole 66. Other groups reported difficulties in the hydrolysis and decarboxylation of indole-2-carboxylic acid derivatives²³ and this represents an alternative solution to this problem.

The second pyrrole ring was annulated in a similar fashion. Aldehyde 67 was prepared by metal-halogen exchange of bromoindole 66 with excess *tert*-butyllithium, followed by quenching with DMF. Condensation of aldehyde 67 with methyl azidoacetate and subsequent thermolysis gives the tricyclic compound 68. Transesterification with benzyl alcohol and selective reduction with sodium cyanoborohydride in acetic acid²⁴ gave the indoline 69. Treatment of 69 with trimethylsilylcyanate, followed by hydrogenolysis gives PDE-I in 14 steps and 4.2% overall yield. Similar acylation of 69 with acetic anhydride and hydrogenolysis gives PDE-II in 14 steps and 5.5% yield.

Scheme 6. Rees' Synthesis of PDE-I and PDE-II



Scheme 6. Reagents: i) $\text{MeO}_2\text{CCH}_2\text{N}_3$, NaOMe, MeOH, 4°C ; ii) xylene, reflux; iii) LAH, ether, reflux; iv) MnO_2 , CH_2Cl_2 , reflux; v) $(\text{Ph}_3\text{P})_2\text{Rh}(\text{CO})\text{Cl}$ (0.06 eq.), dppp (0.12 eq.), mesitylene, reflux; vi) $t\text{BuLi}$ (6.5 eq) THF, -78°C , then DMF, -78°C to RT; vii) toluene reflux; viii) PhCH_2OH , PhCH_2ONa , benzene, reflux; ix) NaCNBH_3 , AcOH; x) Me_3SiNCO , benzene; xi) H_2 (4 atm), Pd/C, MeOH; xii) Ac_2O , pyr.

d. THE CAVA GROUP SYNTHESIS OF PDE-I AND PDE-II

The synthesis of PDE-I and PDE-II by Rawal and Cava is similar to Magnus' in that they start with the two pyrrole rings and form the benzene ring last. The key step is a novel variation of the Mallory reaction²⁵ using palladized carbon as the "oxidant".^{7f} The starting material for the synthesis (Scheme 7) was the simple heterocycle pyrrole, which was protected in high yield with the 2-(trimethylsilyl)ethoxymethyl (SEM) group²⁶ giving **70**. The two carbons and two oxygens required for the benzenoid portion were provided by oxalyl chloride,²⁷ and the resulting diketone **71** was reduced selectively to the benzoin-like hydroxyketone **72** using sodium dithionite.²⁸

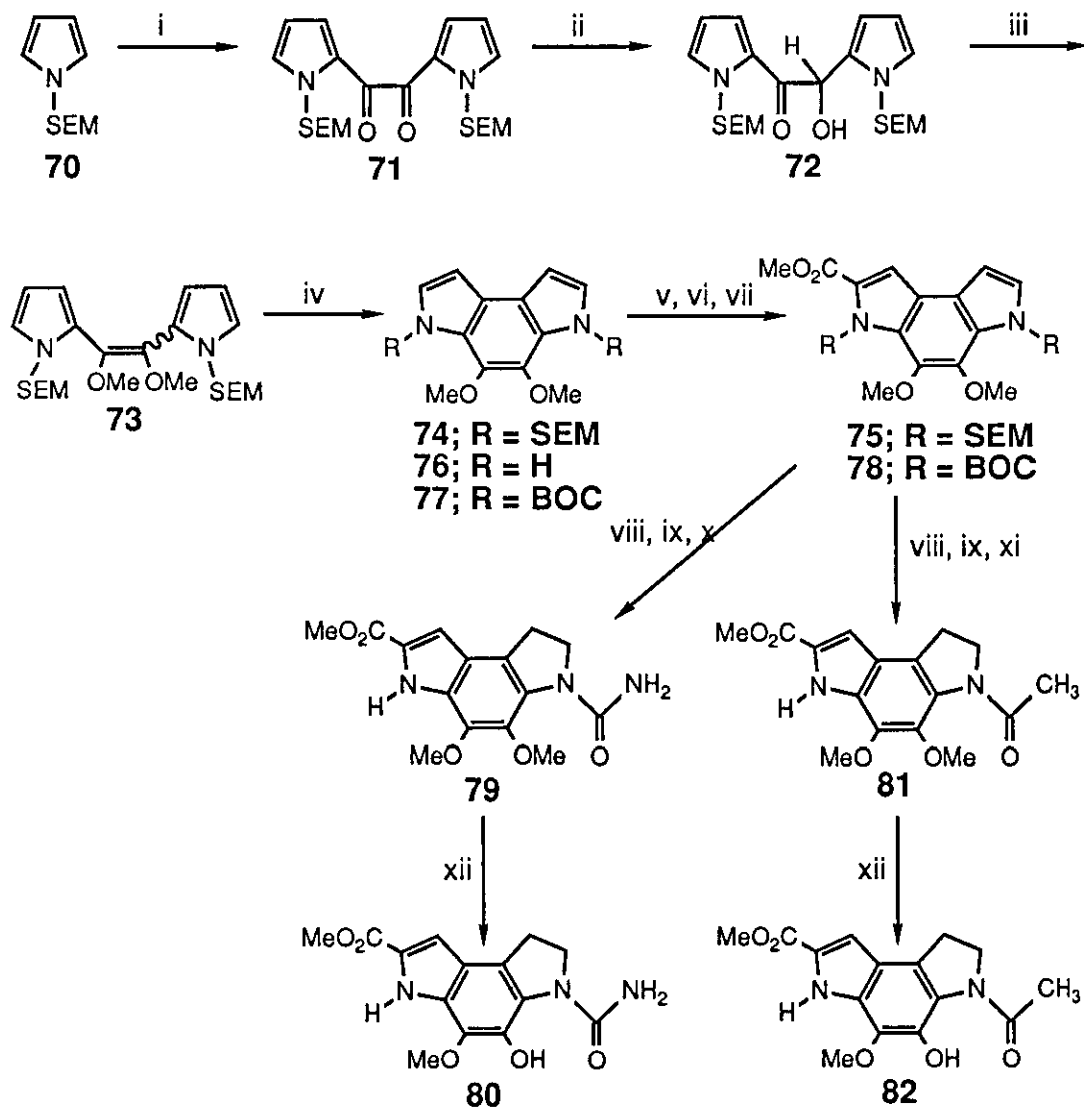
Conversion of hydroxyketone **72** into a suitably protected enediol proved to be unexpectedly difficult. After considerable experimentation, exclusive *O*-alkylation was achieved when a DMSO solution of **72** was treated with an excess of *t*-BuOK and methyl tosylate, and the desired, light and acid sensitive stilbenoid heterocycles **73** were obtained.

A *cis-trans* mixture of these enediol-dimethyl ethers **73** was photocyclized under anaerobic conditions, using the novel palladium protocol ^{7f} to give **74**. The cyclization product was lithiated²⁶ in DME at 0°C, then chilled to -78°C and quenched with an excess of ClCO₂Me to give the desired ester **75**. Unfortunately, after numerous attempts using a variety of fluoride sources, it was not possible to isolate any of the desired product from ester **75**. By contrast, removal of the SEM groups from **74** proceeded smoothly in DMF at 85 °C using *n*-Bu₄NF, with ethylenediamine as the formaldehyde sponge.^{26b}

To allow functionalization at the α -position, indole **76** was first blocked in quantitative yield with the *t*-butoxycarbonyl (BOC) group,²⁹ which is known to direct lithiation on indoles,³⁰ and is easily removable under both acidic and basic conditions. The resulting protected indole **77** was lithiated in THF with lithium 2,2,6,6-tetramethylpiperidide (LTMP) and, after cooling to -100 °C, treated with ClCO₂Me to effect the desired homologation. Deprotection of the resulting ester **78** was accomplished most efficiently under thermolytic conditions.³¹ As this substance was clean by both TLC and 250 MHz NMR, the next two steps were also carried out in the same flask. Thus reduction of the unprotected indole proceeded chemoselectively to the indoline,²⁴ which upon quenching with aqueous KOCN and warming generated urea **79**.

Selective demethylation of **79**, on the side with the urea, was expected, since the resulting hydroxyl is strongly

Scheme 7. The Cava Group Synthesis of PDE-I and PDE-II



Scheme 7. Reagents: i) oxalyl chloride, pyridine, CH_2Cl_2 , -78°C to RT; ii) Na_2SO_4 , NaHCO_3 , DMF, H_2O (1:1); iii) KO^tBu (5 eq.), MeOTf (5 eq.), DMSO; iv) $h\nu$, 5% Pd/C, CH_3CN , triethylammonium-p-nitrobenzoate; v) tetrabutylammonium fluoride, DMF, ethylenediamine; vi) BOC_2O , DMAP, CH_3CN ; vii) LTMP, -78°C , followed by excess ClCO_2Me , -100°C to RT; viii), 180°C , neat; ix) NaCNBH_3 , AcOH , -20°C ; x) KOCN , AcOH , H_2O ; xi) Ac_2O , pyridine; xii) $\text{BCl}_3\cdot\text{Me}_2\text{S}$, CH_2Cl_2 .

hydrogen bonded in both CC-1065 and the PDE's. Using the dimethyl sulfide complex of BBr_3 ,³² the demethylation was indeed selective, but was accompanied by appreciable amounts of the didemethylated compound. The related BCl_3 complex³² was milder and gave a good yield of urea 80. An analogous sequence of reactions, using acetic anhydride instead of KOCN, afforded the amide 81, which was demethylated to 82. Since the deprotection, reduction, and acylation are all performed in one pot, this synthesis of the B and C units requires only ten steps from pyrrole, and the overall yield is in excess of 20%.

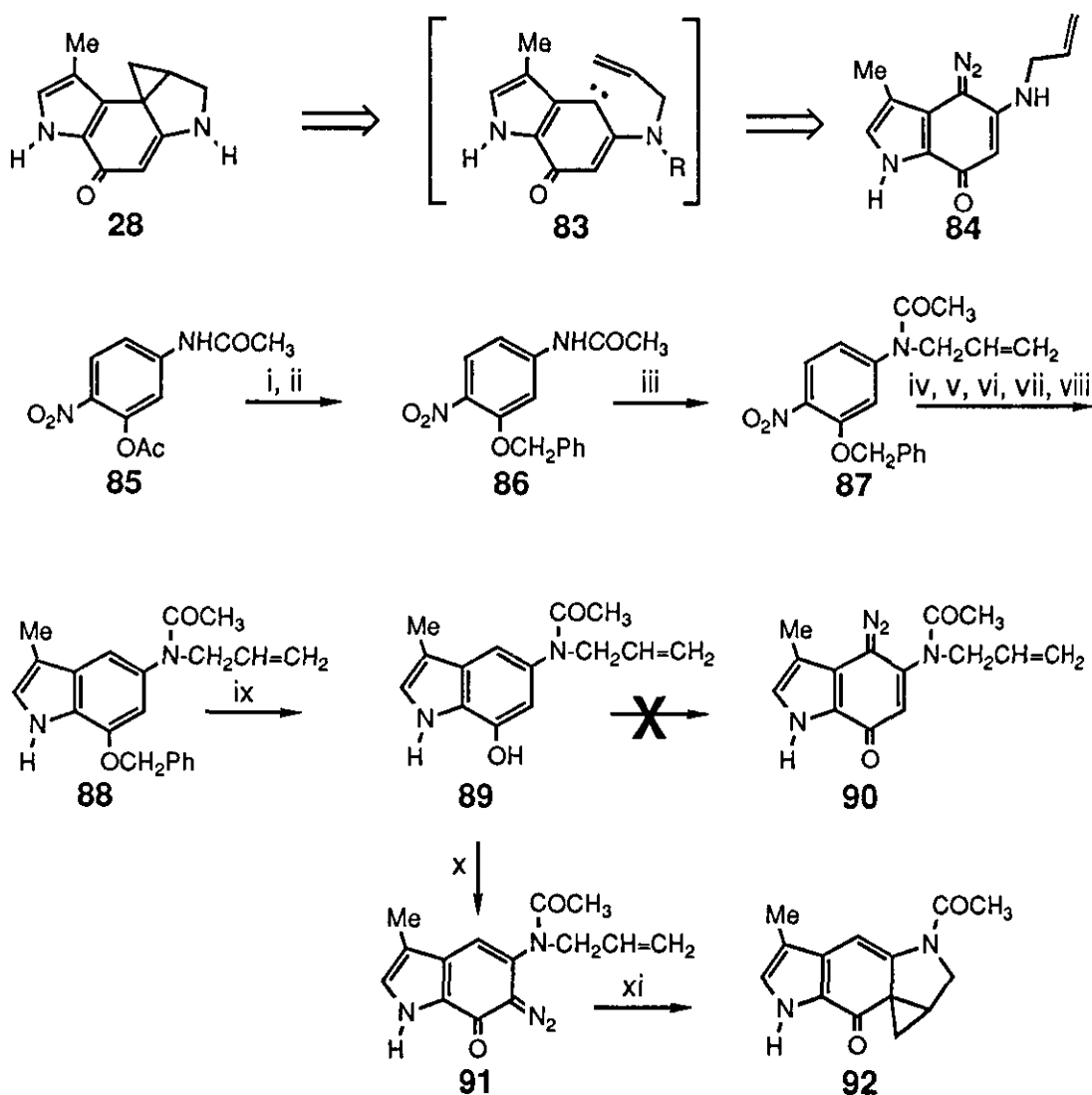
3. Approaches toward the Units of CC-1065

a. SUNDBERG'S APPROACH TO UNIT A

Sundberg and Nishiguchi have described an interesting approach to unit A (28) which ultimately proved to be unsuccessful.^{6f} The authors cleverly viewed the cyclopropane moiety as arising from intramolecular insertion of an appropriately placed carbene 83, which would derive from the diazoketone 84.

The synthetic strategy involved preparation of a functionalized indole system by a classical route requiring 9 steps and proceeding in 25% yield, starting from the diacetate 85 (Scheme 8). Partial hydrolysis of 85 followed by benzylation gave 86, which was allylated using *t*-BuOK to give the nitro compound 87. Reduction of the nitro group, diazotization, and conversion to the hydrazone, followed by Fisher indole cyclization afforded the functionalized indole 88. On treatment with BBr_3 , indole 88 was debenzylated to afford the required phenol 89. Direct diazotization of 89 was achieved when *m*-nitrobenzenesulfonyl azide was used as the diazo transfer agent in trifluoroethanol. None of the expected quinone diazide 90, however, was formed. Instead, isolated in 45% yield was the isomeric compound 91, as deduced by comparing its UV spectrum with that of both 2- and 4-diazonaphthalen-1-one. As further evidence of its structure, irradiation of 91 in methylene chloride with light in the visible region (>400 nm) produced a compound which possessed the spectral properties necessary for a cyclopropane conjugated dienone moiety. Direct comparison of the ^1H NMR chemical shifts and multiplicities, however, showed this product to be different from the desired A unit, which had been supplied by Wierenga and coworkers. Consequently, the product was assigned structure 92. Solvent insertion was the predominant process when 91 was photolyzed in benzene. The authors did not discuss the possibility of blocking the *ortho*

Scheme 8. Sundberg's approach to the A unit



Scheme 8. Reagents: i) K_2CO_3 , MeOH; ii) K_2CO_3 , KI, $PhCH_2Cl$, DMF; iii) KO^tBu , DMF, allyl bromide; iv) Zn, $CaCl_2$, EtOH, $80^\circ C$; v) HCl, $NaNO_2$; vi) $SnCl_2$, HCl, $-5^\circ C$; vii) CH_3CH_2CHO , DMF, $0^\circ C$, then $NaOAc$, $5^\circ C$; viii) TsOH, THF; ix) BBr_3 , CH_2Cl_2 , $-40^\circ C$; x) *m*-nitrobenzenesulfonyl azide; xi) $h\nu > 400\text{ nm}$.

position, so as to force the diazotization to the *para* position.

b. SUNDBERG'S APPROACH TO THE B AND C UNITS

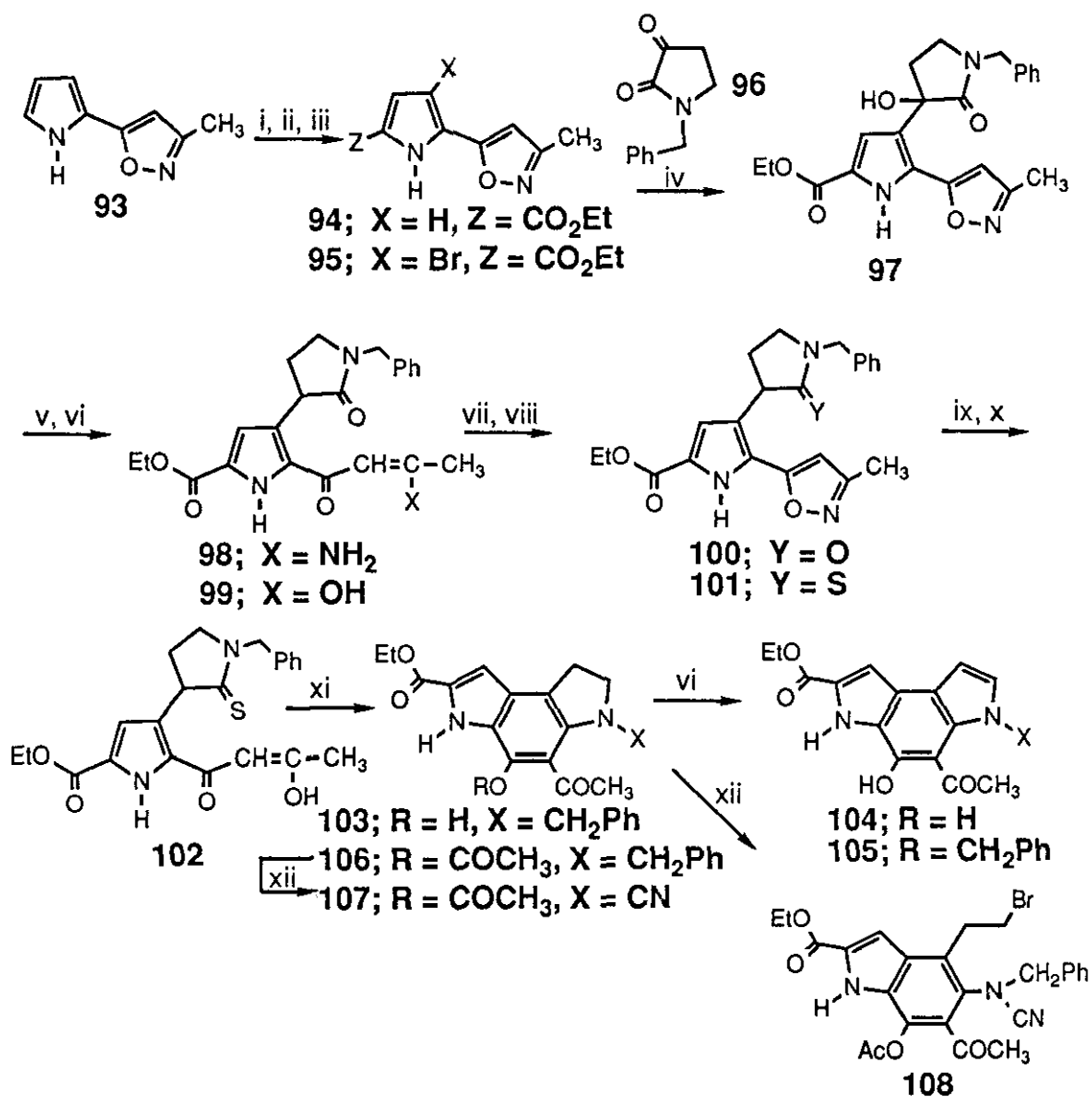
Having abandoned the carbene strategy, Sundberg then embarked on an approach^{7b} where, in the key step, the central ring was formed by either a sulfur extrusion reaction of the type Eschenmoser has used so elegantly in his vitamin B-12 synthesis,^{33,34} or by an aldol-type condensation with an activated thiolactam.³⁵ A tremendous amount of work has been carried out in order to use this strategy for the synthesis of CC-1065. Although eventually this approach also met with serious problems, the exercise, overall, did produce some interesting chemistry.

The first part of their approach is shown in Scheme 9 and begins with the known 2-(3-methylisoxazol-5-yl) pyrrole 93 which was prepared in two steps from pyrrole by a modification of Trieb's procedure.³⁶ The carboethoxy group was then introduced by way of the trichloroacetyl group which was saponified to 94 in a two step, high yielding process. To attach the pyrrolidinone unit, the 4-lithio salt of 94, obtained by a low temperature metal-halogen exchange reaction of bromo-pyrrole 95, was treated with dione 96 to furnish in fair yield alcohol 97. Dehydration and catalytic reduction gave the critical intermediate, enaminone 98, which could be hydrolyzed to 99. Direct conversion of 99 to the thiolactam 102 was not possible, so the isoxazole ring was reformed, and the resulting lactam 100 was thionated with P_4S_{10} to give 101.

Mild, selective cleavage of the isoxazole ring by reaction with molybdenum hexacarbonyl³⁷ followed by hydrolysis afforded β -diketone 102, which was used to test the condensation-cyclization path. Treatment of 102 with either methyl iodide or bromine effected the cyclization. Hydrogenolysis of the resulting benzyl protected indoline 103 with palladium catalysts, however, gave none of the desired product. Produced, instead, was a mixture of the aromatized compounds 104 and 105. When the *O*-acetate of 103 was treated with cyanogen bromide, a 30% yield of nitrile 107 was obtained along with some ring-opening product 108. Although conversion to a PDE-type of unit would be quite difficult, 107 could conceivably be used for preparing analogs of CC-1065.

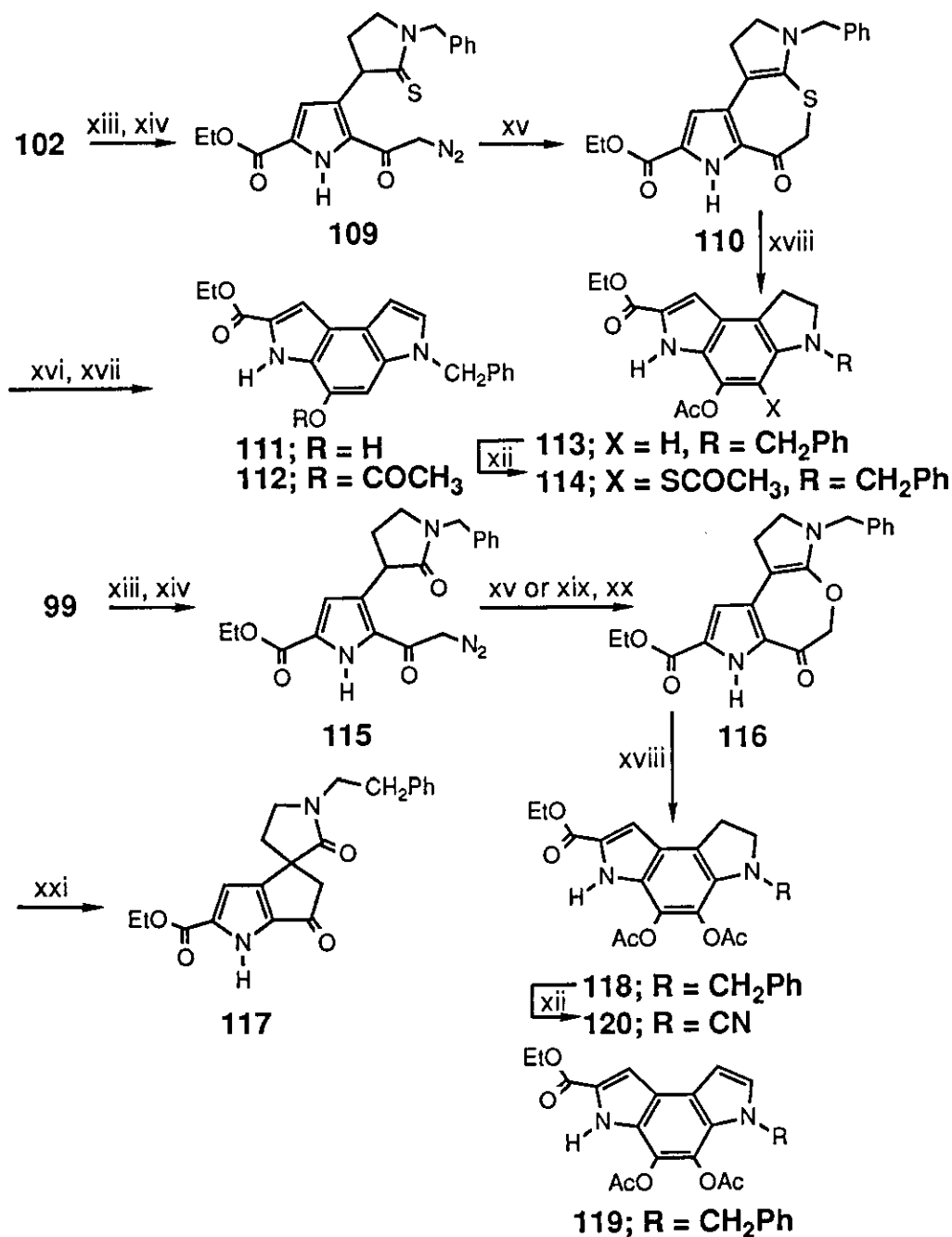
To test the feasibility of the Eschenmoser type of cyclization, diketone 102 was converted in two steps to the diazoketone 109. Treatment of 109 with either HBr or $BF_3 \cdot Et_2O$ gave the thiopinone 110. The ring

Scheme 9. Sundberg's Activated Thiolactam Approach to the PDEs



Scheme 9. Reagents: i) Cl₃CCOCl, ClCH₂CH₂Cl, reflux; ii) NaOEt, EtOH; iii) NaOAc, HOAc, Br₂; iv) NaH, THF, RT then -98°C, ^tBuLi, 96; v) HCl (conc); vi) EtOH, H₂, Pd/C; vii) H₂OH-HCl, EtOH, 80°C; viii) P₄S₁₀, toluene, reflux; ix) Mo(CO)₆, CH₃CN(wet), reflux; x) THF, 5% HCl, 55°C; xi) MeI or Br₂ then aq. NaHCO₃; xii) BrCN, ClCH₂CH₂Cl;

Scheme 9. cont.



xiii) p-nitrobenzenesulfonyl azide, Et₃N, THF; xiv) EtOH, pyrrolidine; xv) BF₃·OEt₂, CH₂Cl₂; xvi) 100°C; xvii) Ac₂O, DMAP; xviii) HOAc, Ac₂O, Δ; xix) Me₃O⁺BF₄⁻, ClCH₂CH₂Cl, CH₃NO₃; xx) aq base or DMAP; xxi) 25°C.

contraction was accomplished by heating 110 in acetonitrile. The product, however, was the aromatized compound 111, isolated as its acetate 112, and evidently resulting from dehydrogenation by the elemental sulfur which was produced. When tributylphosphine was included to assist in the desulfurization, the cyclization was slower and gave a 1:1 mixture of 112 and its dihydro compound 113. Because of this difference in rates, the authors propose that the H_2S liberated in the reaction may catalyze the ring contraction. Cyclization also occurred in a solution of acetic acid-acetic anhydride to give the *O,S*-diacetate 114; Raney nickel desulfurization of 114 gave 112, presumably as a result of concomitant aromatization. Overall this particular sequence of reactions required between 17 and 18 steps and led to mono-oxygenated systems which resemble neither the A nor the B/C units of CC-1065.

The third pathway examined by these authors, also detailed in Scheme 9, is similar to the preceding route and utilized diazoketone 115, a compound which was obtained by diazotizing and deacylating 99. Conversion of 115 to the unstable oxepin 116 was effected by treatment either with $BF_3 \cdot Et_2O$ followed by base or with $Me_3O^-BF_4^+$ followed by DMAP. Compound 116, so obtained, was highly reactive and rearranged at room temperature to lactam 117. If, however, the crude 116 was heated immediately in the presence of acetic anhydride, small amounts of the desired cyclization product 118 and its dehydro system 119 were obtained as a mixture of unspecified composition. Treatment of a crude sample, enriched in 118, with cyanogen bromide afforded a fair yield of the cyanamide 120. Compared with the other two, this particular sequence is much superior aesthetically, since it requires considerably fewer steps and leads to units resembling the PDE's. In practice, however, there were many problems due to the instability of the intermediates.

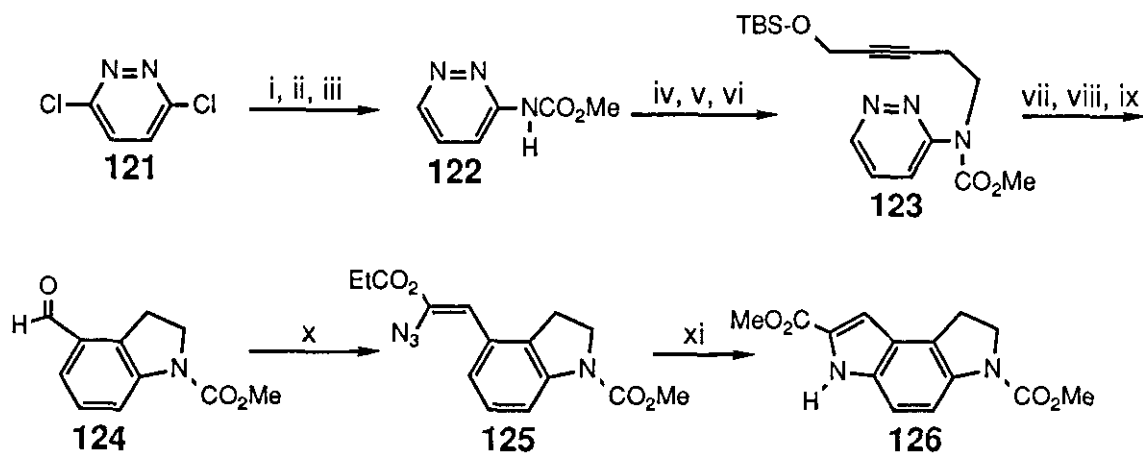
c. BOGER'S APPROACH

The strategy reported by Boger and Coleman^{7a} for the synthesis of a PDE-type unit demonstrates yet another application of the Diels-Alder reaction of 1,2-diazine derived dienes.³⁸ The key step in their approach was the intramolecular Diels-Alder reaction of 123 to give an indoline, to which was then appended the indole-ester portion (Scheme 10).

The synthesis began with 1,4-dichloro-1,2-diazine 121, which was converted by a three step process to urethane 122. Direct alkylation of 122 was unsuccessful under standard conditions. Eventually alkylation

was accomplished using the Mitsunobu³⁹ conditions. After deprotection and reprotection with the *t*-butyldimethylsilyl (TBS) group, the necessary Diels-Alder precursor **123** was obtained in 10% yield. The critical Diels-Alder reaction was performed by thermolyzing a solution of **123** in 1,3,5-triisopropylbenzene at 230 °C in a sealed tube. The resulting product was deprotected and oxidized to aldehyde **124**. This aldehyde has been prepared by other routes and is a key intermediate in several synthetic approaches to ergot alkaloids.⁴⁰ Condensation of **124** with methyl azidoacetate gave the expected *Z*-azido ester **125** which was thermolyzed in refluxing xylene to afford the desired ester **126**, a deoxygenated version of the tricyclic B and C units of CC-1065. To convert **126** to a deoxy analog of PDE-I or PDE-II would still require both replacement of the carbamate with an aminocarbonyl or an acetyl group, and hydrolysis of the ester moiety. Overall the synthesis of **126** required 11 steps from 1,4-dichloro-1,2-diazine, and proceeded in an overall yield of about 2%.

Scheme 10. Boger's Approach to the PDEs

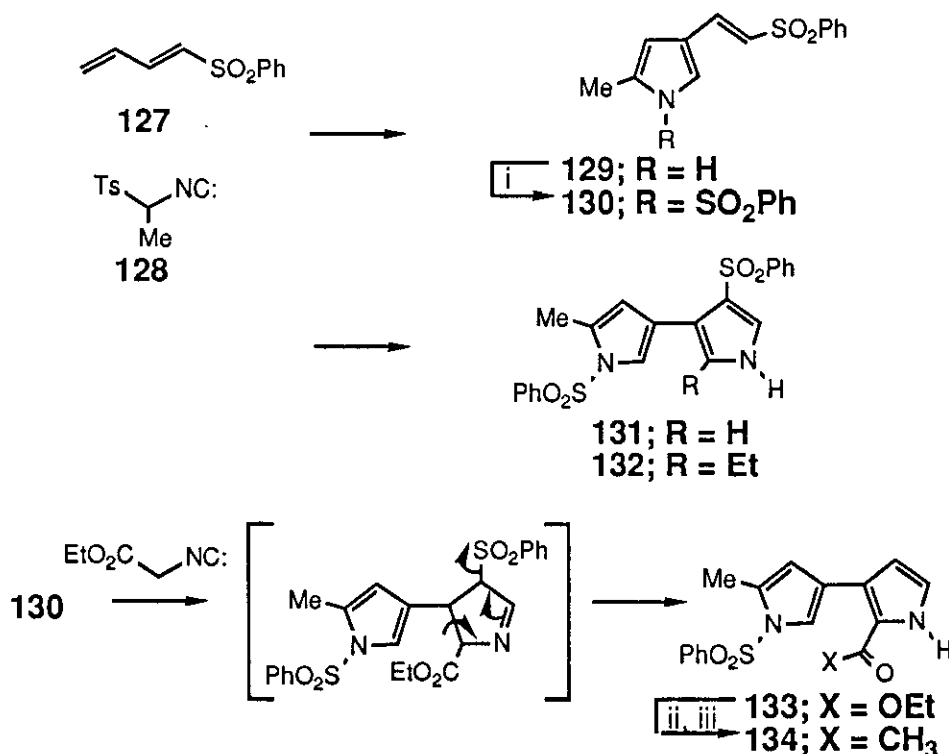


Scheme 10. Reagents: i) $\text{NH}_4\text{OH}(\text{conc})$, 130°C; ii) K_2CO_3 , THF, ClCO_2Me ; iii) NaOH , 10% Pd/C , EtOH , H_2 ; iv) PPh_3 , 5-(tetrahydro-2-pyranyl)-3-pentyn-1-ol, THF, DEAD; v) PPTS, EtOH , 60°C; vi) TBS-Cl, imidazole, DMF; vii) triisopropylbenzene, 230°C; viii) tetrabutylammonium fluoride, THF; ix) MnO_2 , CH_2Cl_2 ; x) methyl azidoacetate, benzene, NaOMe , MeOH , 0°C; xi) xylene, reflux.

d. MAGNUS' APPROACH TO THE B AND C UNITS

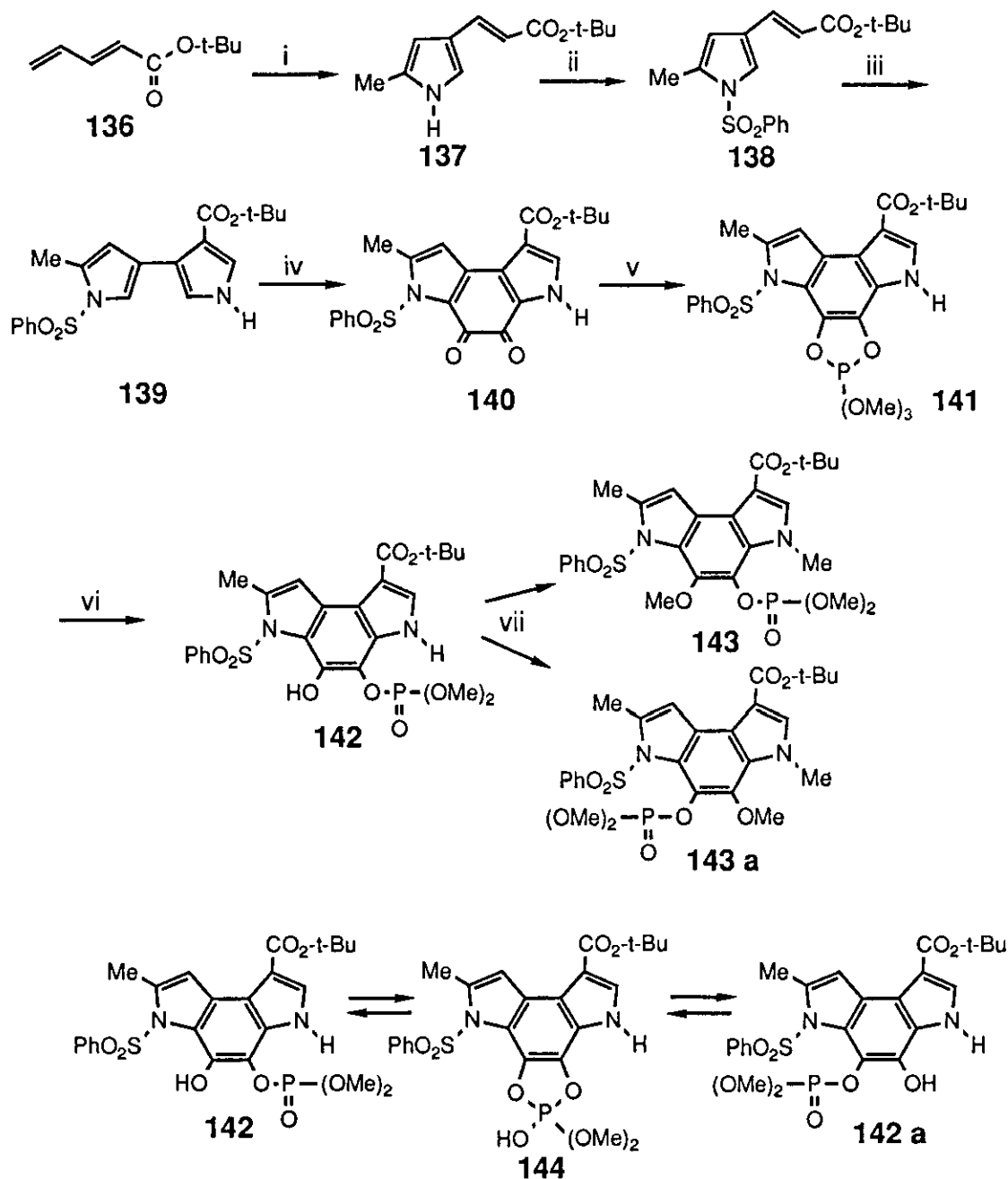
In order to extend his bipyrrole approach to make the B and C units, Magnus looked into the use of other electrophilic dienes (Scheme 11).^{7c} When 1-phenylsulfonyl-1,3-butadiene **127**, which is easily polymerized by base, was treated with the anion of methyl TOSMIC **128**, the 2,4-disubstituted, monoaddition product **129** was obtained. Protection with phenylsulfonyl and further treatment with either TOSMIC or ethyl TOSMIC anion gave the 3,3'-bipyrroles **131** and **132**. The authors encountered problems in removing the C-phenylsulfonyl group, so an alternate method was tried. When **130** was allowed to react with ethyl isocyanoacetate,^{41,42} the desired bipyrrole **133** was obtained as a result of elimination of the C-phenylsulfonyl group. Homologation with dimethyl lithium followed by reduction with zinc and acetic acid produced the methyl ketone **134**. As would be anticipated, attempted oxidation of the methyl ketone to a glyoxal or a glyoxylic acid led to destruction of the substrate.

Scheme 11. Magnus' 3,3'-bipyrrole approach



Scheme 11. Reagents: i) NaH, PhSO₂Cl; ii) LiCH₂S(O)CH₃; iii) Zn, HOAc.

Scheme 12. Magnus' bipyrrrole approach to PDE-type units

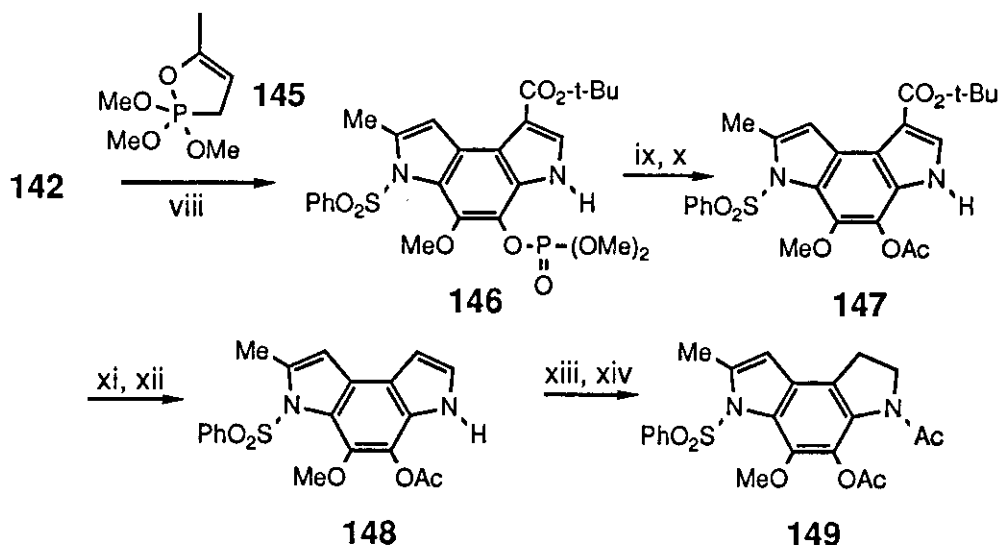


Scheme 12. Reagents: i) Methyl TSMIC, NaH, THF; ii) NaH, PhSO_2Cl ; iii) TSMIC, NaH, THF; iv) oxalyl chloride, ether, -78°C to 20°C ; v) $\text{P}(\text{OMe})_3$, benzene; vi) THF (wet); vii) Me_2SO_4 , K_2O_3 , acetone;

As further proof of the viability of the 3,3'-bipyrrole approach, Magnus and Halazy reported the synthesis of a dioxygenated unit resembling PDE-II (Scheme 12).^{7d} The starting material in this case was *t*-butyl 2,4-pentadienoate 136, which was treated with the anion of methyl TOSMIC to give the mono-addition product 137. As in the earlier work, the pyrrole was blocked with a benzenesulfonyl group, and the resulting α,β -unsaturated ester 138, with greater electrophilic character, was allowed to react with TOSMIC to give the 3,3'-bipyrrole 139. Treatment of 139 with oxalyl chloride and reduction of the resulting *o*-quinone 140 with trimethyl phosphite⁴³ gave the cyclic oxyphospholane 141. Hydrolysis of 141 can, potentially, give rise to two phosphate esters 142 and 142a; however, the former, presumably more stable isomer was produced exclusively. Methylation of 142 under standard conditions gave two dimethylation products, 143 and 143a, the desired regioisomer being predominant (ca. 9:1).

The authors explain the formation of these two products by invoking the existence of an equilibrium between 142 and 142a by way of the cyclic intermediate 144. No explanation, however, is given for the preferred formation of one isomer over the other. Arguments involving steric interactions between the benzenesulfonyl group and the R group on the adjacent phenol may offer an answer.

Scheme 12. cont.



viii) **145**, THF; ix) NaOMe, MeOH; x) Ac₂O; xi) TFA; xii) Et₃N, toluene, 110°C; xiii) Et₃SiH, TFA, 0°C; xiv) Ac₂O.

Selective monomethylation of **142** was accomplished under remarkably mild conditions using the cyclic oxaphospholane **145**, the adduct of $P(OMe)_3$ with methylvinylketone.¹⁶ Subsequent hydrolysis and acetylation gave **147**. Acid hydrolysis of the *t*-butyl ester followed by base mediated decarboxylation afforded the mono-acetate **148**, which was reduced selectively using the "ionic hydrogenation" conditions,¹⁶ then acetylated to afford diacetate **149**. The most important difference between **149** and PDE-II is the oxidation state of the carbon on the indole ring. While the oxidation of this methyl group to a carboxylic acid is not an insurmountable problem, it may prove to be quite difficult, particularly in light of the known susceptibility of indoles to oxidizing agents. Magnus' synthesis of diacetate **149** required 12 steps from dienoate **136**; the overall yield was 4.5%.

ACKNOWLEDGEMENT

This work was supported by a grant from the National Institutes of Health (Grant No. NIH-CA 41995).

REFERENCES

1. L. J. Hanka, A. Dietz, S. A. Gerpheide, S. L. Kuentzel, and D. G. Martin, *J. Antibiot.*, **1978**, *31*, 1211. D. G. Martin, C. G. Chidester, D. J. Duchamp, and S. A. Mizak, *J. Antibiot.*, **1980**, *33*, 902. D. G. Martin, C. Biles, S. A. Gerpheide, L. J. Hanka, W. C. Krueger, J. P. McGovern, S. A. Mizak, G. L. Neil, J. C. Stewart, and J. Visser, *J. Antibiot.*, **1981**, *34*, 1119.
2. D. H. Swenson, W. C. Krueger, A. H. Lin, S. L. Schpok, and L. H. Li, *Proc. Am. Assoc. Cancer Res.*, **1981**, *22*, 857.
3. D. G. Martin, L. J. Hanka, and G. L. Neil, *Proc. Am. Assoc. Cancer Res.*, **1978**, *19*, 99. B. K. Bhuyan, K. A. Newell, E. G. Adams, S. L. Crampton, and D. D. Von Hoff, *Proc. Am. Assoc. Cancer Res.*, **1981**, *22*, 224.
4. D. H. Needham-VanDevanter, L. H. Hurley, V. L. Reynolds, N. Y. Theriault, W. C. Krueger, and W. Wierenga, *Nucleic Acids Research*, **1984**, *12*, 6159. L. H. Hurley, V. L. Reynolds, D. H. Swenson, G. L. Petzold, and T. A. Scahill, *Science*, **1984**, *226*, 843.
5. PDE-I and PDE-II.
Isolation:
 a) Y. Enomoto, Y. Furutani, H. Naganawa, M. Hamada, T. Takeuchi, and H. Umezawa, *Agric. Biol. Chem.*, **1978**, *42*, 1331.
 b) H. Nakamura, Y. Enomoto, T. Takeuchi, H. Umezawa, and Y. Litaka, *Agric. Biol. Chem.*, **1978**, *42*, 1337.
Synthesis:
 c) N. Komoto, Y. Enomoto, M. Miyagaki, Y. Tanaka, K. Nitani, and H. Umezawa, *Agric. Biol. Chem.*, **1979**, *43*, 555.

- d) N. Komoto, Y. Enomoto, Y. Tanaka, K. Nitani, and H. Umezawa, *Agric. Biol. Chem.*, **1979**, *43*, 559.
 - e) R. E. Bolton, C. J. Moody, C. W. Rees, and G. Tojo, *J. Chem. Soc., Chem. Commun.*, **1985**, 1775.
 - f) V. H. Rawal, and M. P. Cava, *J. Am. Chem. Soc.*, **1986**, *108*, 2110.
6. Studies directed towards unit A:
- a) W. Wierenga, *J. Am. Chem. Soc.*, **1981**, *103*, 5621.
 - b) P. Magnus, and Y-S. Or, *J. Chem. Soc., Chem. Commun.*, **1983**, 26.
 - c) G. A. Kraus, and S. Yue, *J. Chem. Soc., Chem. Commun.*, **1983**, 1198.
 - d) P. Magnus, and T. Gallager, *J. Chem. Soc., Chem. Commun.*, **1984**, 389.
 - e) G. A. Kraus, S. Yue, and J. Sy, *J. Org. Chem.*, **1985**, *50*, 284.
 - f) R. J. Sundberg, and T. Nishigushi, *Tetrahedron Lett.*, **1983**, *24*, 4473.
7. Studies directed toward units B and C:
- a) D. L. Boger, and R. S. Coleman, *J. Org. Chem.*, **1984**, *49*, 2240.
 - b) R. J. Sundberg, and B. C. Pearce, *J. Org. Chem.*, **1985**, *50*, 425.
 - c) P. Magnus, and S. Halazy, *Tetrahedron Lett.*, **1984**, *25*, 1421.
 - d) P. Magnus, and S. Halazy, *Tetrahedron Lett.*, **1985**, *26*, 2985.
 - e) V. H. Rawal, and M. P. Cava, *J. Chem. Soc., Chem. Commun.*, **1984**, 1526.
 - f) V. H. Rawal, R. J. Jones, and M. P. Cava, *Tetrahedron Lett.*, **1985**, *26*, 2423.
8. P. G. Gassman, and T. J. van Bergen, *J. Am. Chem. Soc.*, **1974**, *96*, 5508.
9. P. G. Gassman, G. Gruetzmacher, and T. J. van Bergen, *J. Am. Chem. Soc.*, **1974**, *96*, 5512.
10. R. Baird, and S. Winstein, *J. Am. Chem. Soc.*, **1963**, *85*, 567.
11. A. M. van Leusen, H. Siderius, B. E. Hoogenboom, and D. van Leusen, *Tetrahedron Lett.*, **1972**, 5337.
12. A. M. van Leusen, R. J. Bouma, and O. Possel, *Tetrahedron Lett.*, **1975**, 3487.
13. S. P. J. M. van Nispen, C. Mensink, and A. M. van Leusen, *Tetrahedron Lett.* **1980**, 3723
14. U. Schollkopf, *Angew. Chem., Int. Ed. Engl.*, **1977**, *16*, 339.
15. J. E. McMurry, *Org. React.*, **1976**, *24*, 187.
16. G. Guillermin, F. Frappier, J. C. Tabet, and A. Marquet, *J. Org. Chem.*, **1977**, *42*, 3776.
17. O. Mitsunobu, *Synthesis*, **1981**, *21*, 1.
18. R. Pschorr, and W. Stohrer, *Chem. Ber.*, **1902**, *35*, 4396.
19. L. C. Raiford, and D. E. Fox, *J. Org. Chem.*, **1944**, *9*, 170.
20. R. J. S. Beer, K. Clarke, H. F. Davenport, and A. Robertson, *J. Chem. Soc.*, **1951**, 2029.
21. R. R. Phillips, *Org. Reactions*, **1959**, *10*, 143.
22. A. R. MacKenzie, C. J. Moody, and C. W. Rees, *J. Chem. Soc., Chem. Commun.*, **1983**, 1372.
23. M. D. Meyer, and L. I. Kruse, *J. Org. Chem.*, **1984**, *49*, 3195.

24. G. W. Gribble, and J. Hoffman, *Synthesis*, 1977, 859.
25. F. B. Mallory, and C. W. Mallory, *Org. React.*, 1984, 30, 1.
26. a) E. P. Martin, S. V. Ley, S. G. Lister, and B. D. Palmer, *J. Chem. Soc., Chem. Comm.*, 1983, 630.
b) J. M. Muchowski, and D. R. Solas, *J. Org. Chem.*, 1984, 49, 203.
27. D. Bher, S. Brandange, and B. Lindstrom, *Acta Chem. Scand.*, 1973, 27, 2411.
28. M. J. Haddadin, G. E. Zahr, T. N. Rawdah, N. C. Chelhot, and C. H. Issidorides, *Tetrahedron*, 1974, 30, 659.
29. L. Grehn, and U. Ragnarsson, *Angew. Chem. Int. Ed. Engl.*, 1984, 23, 296.
30. a) I. Hasan, E. R. Marinelli, L. C. Lin, F. W. Fowler, and A. B. Levy, *J. Org. Chem.*, 1981, 46, 157.
b) T. Kline, *J. Heterocyclic Chem.*, 1985, 22, 505.
31. V. H. Rawal, and M. P. Cava, *Tetrahedron Lett.*, 1985, 26, 6141.
32. a) P. G. Willard, and C. B. Fryhle, *Tetrahedron Lett.*, 1980, 21, 3731.
b) S. Teitel, J. O'Brien, and A. Brossi, *J. Org. Chem.*, 1972, 37, 3368.
c) D. H. R. Barton, L. Bould, D. L. J. Clive, P. D. Magnus, and T. Hase, *J. Chem. Soc. (C)*, 1971, 2204.
d) F. M. Dean, J. Goodchild, L. E. Houghton, J. A. Martin, R. B. Morton, B. Parton, A. W. Price, and N. Somvichien, *Tetrahedron Lett.*, 1966, 4153.
33. V. M. Roth, P. Dubbs, E. Gotschi, and A. Eschenmoser, *Helv. Chim. Acta*, 1971, 54, 710.
34. R. E. Ireland, and F. R. Brown, Jr., *J. Org. Chem.*, 1980, 45, 1868.
35. M. M. Gugelchuk, D. J. Hart, and Y. M. Tasi, *J. Org. Chem.*, 1981, 46, 3671.
36. A. Triebs, and K.-M. Michl, *Liebigs Ann. Chem.*, 1952, 577, 129.
37. M. Nitta, and T. Koyabashi, *J. Chem. Soc., Chem. Commun.*, 1982, 877.
38. D. L. Boger, *Tetrahedron*, 1983, 39, 2869.
39. O. Mitsunobu, M. Wada, and T. Sano, *J. Am. Chem. Soc.*, 1972, 94, 679.
40. A. P. Kozikowski, *Heterocycles*, 1981, 16, 267.
41. U. Schollkopf, D. Hoppe, and R. Jentsch, *Chem. Ber.*, 1975, 108, 1580.
42. U. Schollkopf, and K. Hantke, *Liebigs Ann. Chem.*, 1973, 1571.
43. F. Ramirez, and N. B. Desai, *J. Am. Chem. Soc.*, 1960, 82, 2652.

Received, 29th May, 1986