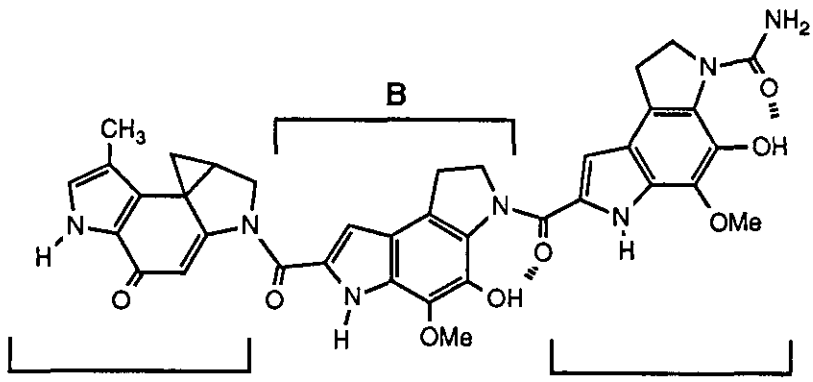
REVIEW OF SYNTHETIC STUDIES TOWARD CC-1065, PDE-I, AND PDE-II†

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.

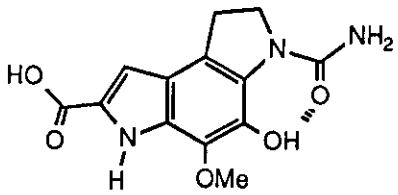
Abstract – The synthetic approaches to the potent antitumor agent CC-1065 (1) and the closely related phosphodiesterase inhibitors PDE-I (2) and PDE-II (3) are reviewed.

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 adriamycin[2], 10 times more potent than actinomycin D, xanthomycin or quinomycin C and about twice as potent as maytansine[3] 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 DNA[4].



CC-1065
(1)

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



PDE-I
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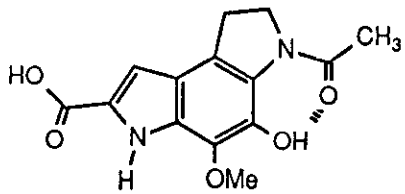


PDE-II
(3)

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.

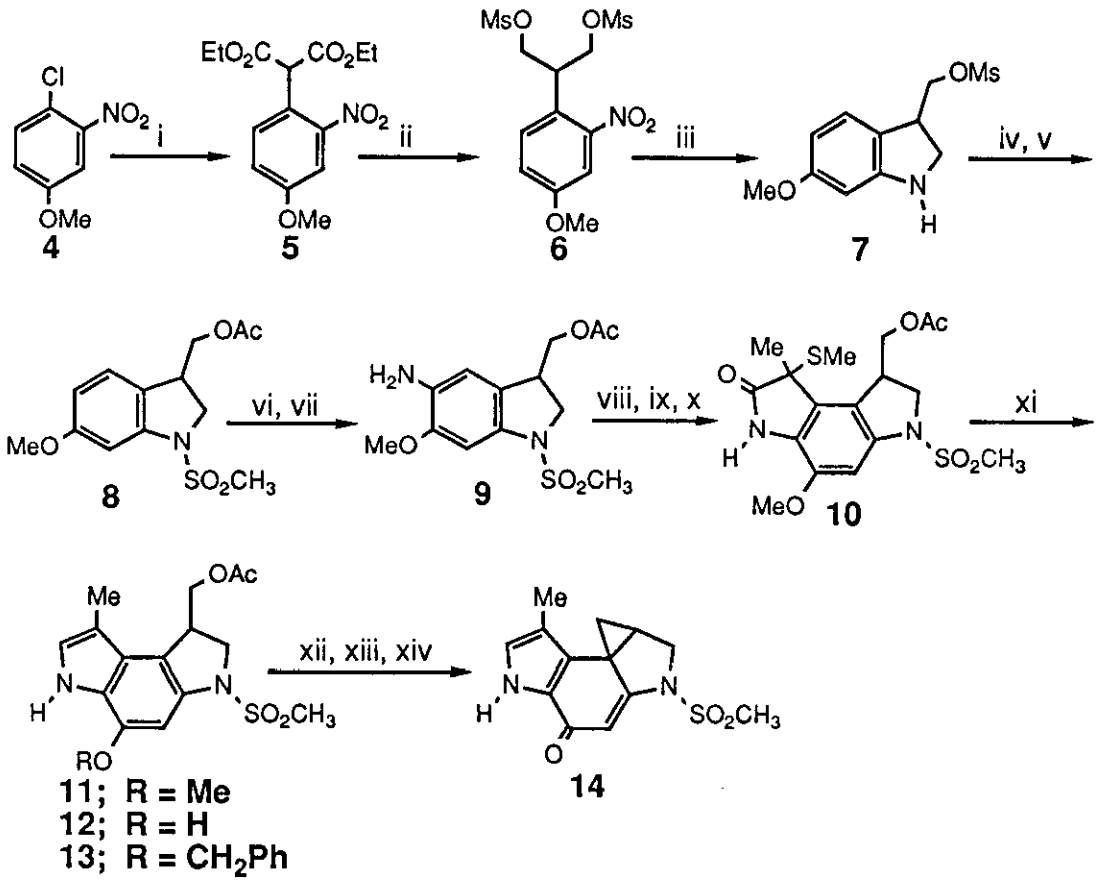
1. Syntheses of Unit A of CC-1065

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 Ar_3 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) $NaCH(CO_2Et)_2$, DMF, Δ; ii) DIBAL, THF/toluene; iii) H_2,PtO_2, Et_3N; iv) MsCl, Et_3N; v) NaOAc; vi) HNO_3, CH_3NO_2; vii) H_2,PtO_2; viii) $CH_3CH(CO_2Et)SCH_3{\cdot}Cl_2$, R_3N, CH_2Cl_2, -75°C; ix) Et_3N; x) 2 N HCl; xi) $BH_3{\cdot}Me_2S$, THF; xii) LiSBu, HMPA, 110°C; xiii) CBr_4, PPh_3, CH_3CN; xiv) $(C_3H_7)_2NC_2H_5$, CH_2Cl_2.

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 quailfications, 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]

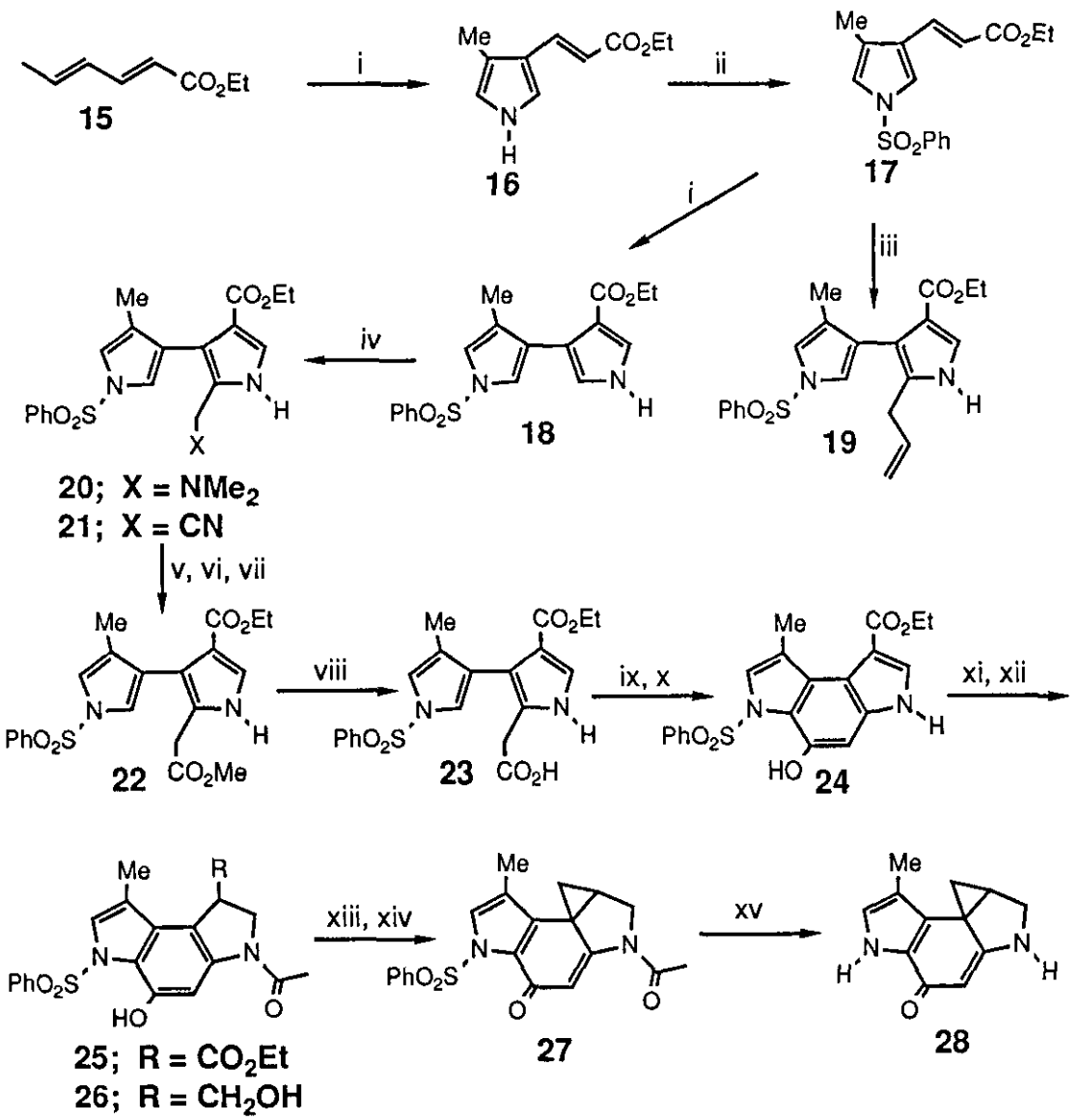
Whereas Van Leusen had examined the monoaddition reaction of TOSMIC, Magnus looked into the possibility of adding two of these units onto a dieneoate (scheme 2). Unfortunately, the dieneoate ester, ethyl sorbate **15**

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 Guillerm 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 clevage 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 Mitsunobu[17] 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-Et_2O; ii) NaH, $PhSO_2Cl$, THF; iii) C-allyl TOSMIC, *NaH, DMSO*; iv) $Me_2NH{\cdot}HCl$, CH_2O, H_2O, *MeOH, 50°C*; v) *MeI*; vi) *NaCN*; vii) MeOH, HCl; vii) LiI, pyridine, reflux; ix) oxalyl chloride, CH_2Cl_2, pyridine; x) $SnCl_4$, CH_2Cl_2; xi) TFA, $HSiEt_3$, 50°C; xii) Ac_2O; xiii) LAH, THF, 0°C; xiv) DEAD, PPh_3; xv) NaOMe, MeOH.

c. KRAUS' SYNTHESIS

In Kraus' ingeneous 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,]

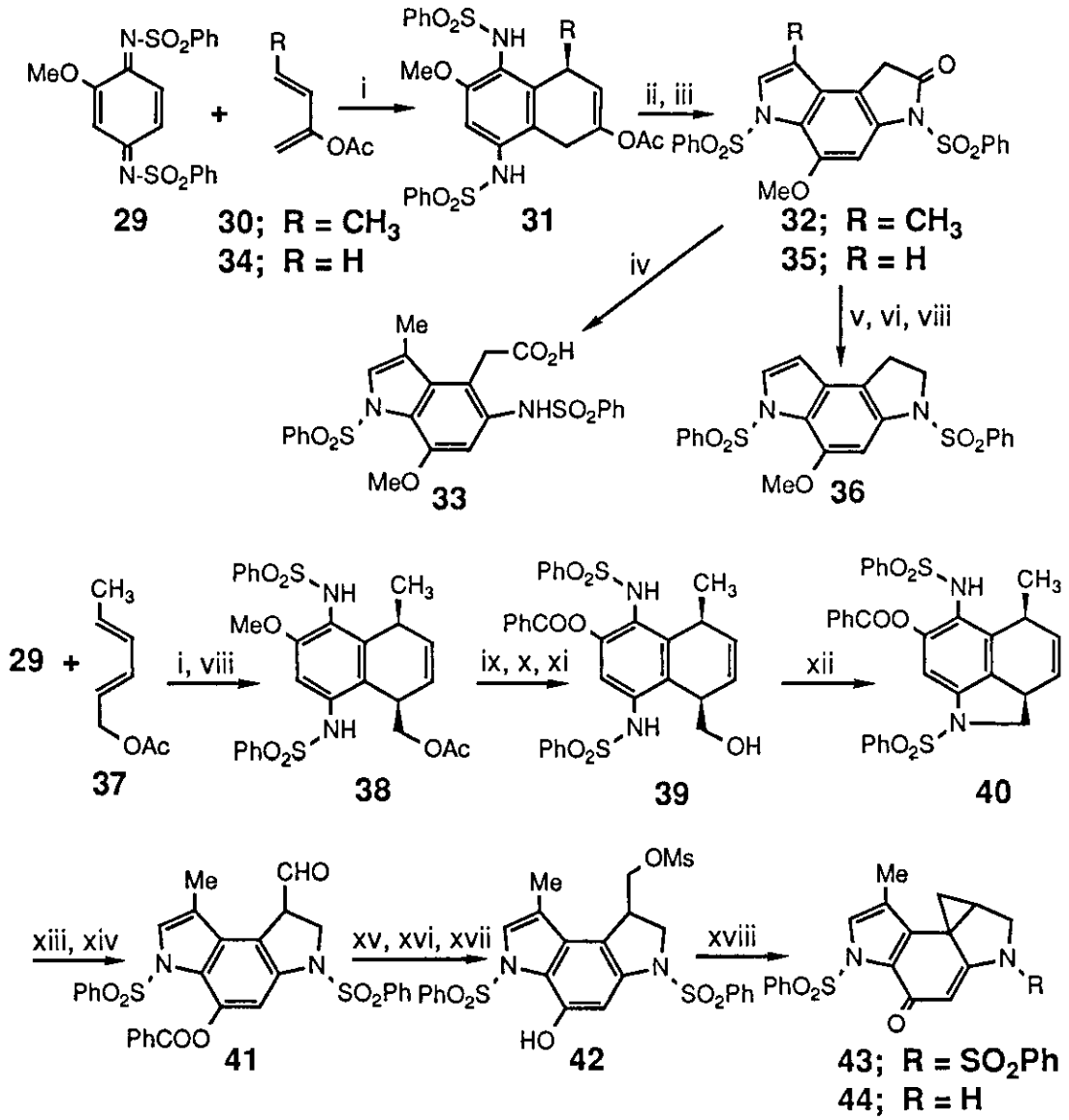
Results of his preliminary studies are detailed in Scheme 3.[6c] Cycloaddition reaction between methoxybenzoquinone bis(benzenesulfonamide) **29**, which was obtained in 90% yield from methoxy-*p*-phenylenediamine, and diene **30** gave the unsymmetrical dihydronaphthalene **31**. Rupture of the enol 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 BBr_3 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**.

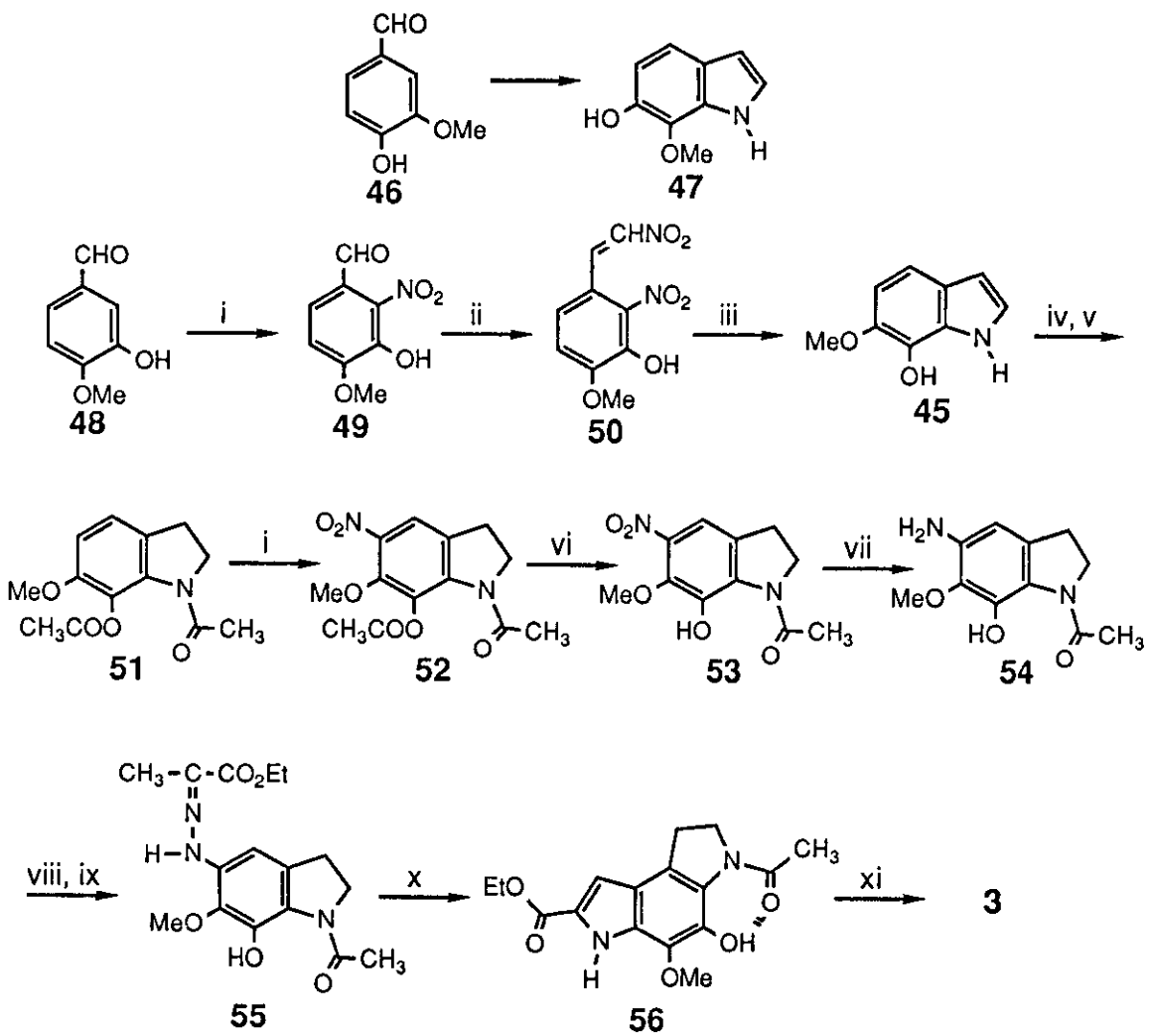
This aldehyde was reduced with Dibal and the resulting alcohol was converted to a mesylate. Debenzoylation, achieved with $LiAlH_4$, afforded phenol **42**, which closely resembles the penultimate intermediates in Wierenga's and Magnus' syntheses. Cyclization to the spiro-cyclopropane **43** was accomplished with DBU. Treatment

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



Scheme 3. **Reagents:** i) RT, 4 days; ii) O_3, -78°C, then Me_2S; iii) HCl, dioxane; iv) NaOH; v) NaOMe; vi) Red-Al; vii) NaH, $MeSO_2Cl$; viii) KOAc, HOAc; ix) BBr_3, hexane, CH_2Cl_2 -78°C to 30°C; x) $(PhCO)_2O$, Et_3N CH_2Cl_2, 0°C; xi) dioxane, 4 M H_2SO_4, MeOH (4:1:1); xii) $PhSO_2Cl$, Et_3N, CH_2Cl_2, 0°C; xiii) O_3, 1:1 CH_2Cl_2, MeOH, -78°C then excess Me_2S, cat H_2SO_4, 0°C; xiv) HCl, dioxane; xv) DIBAL, THF, 0°C; xvi) CH_3SO_2Cl, Et_3N, CH_2Cl_2; 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 nitromethane[19] followed by reductive cyclization afforded the required indole **45**.[20]

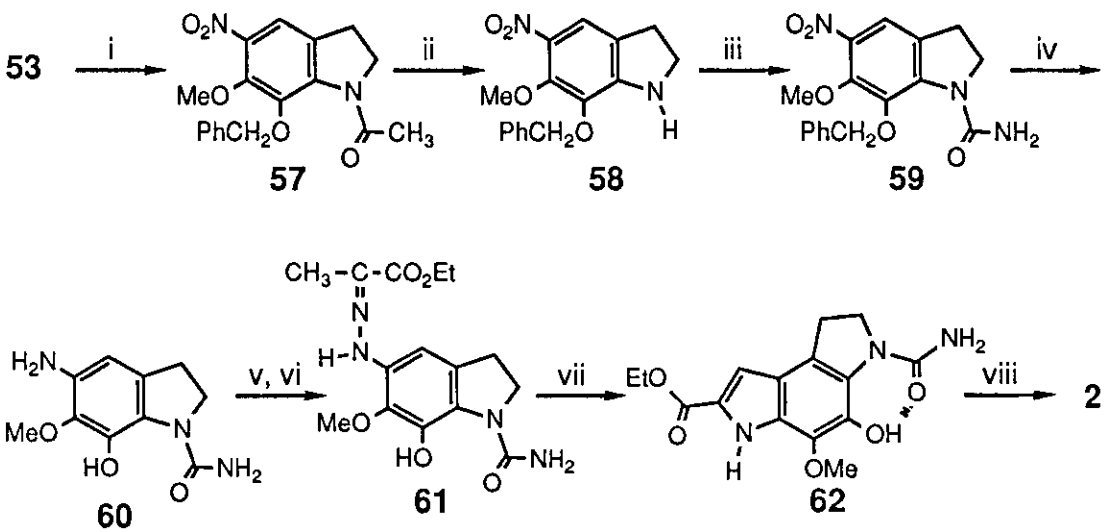
This indole was hydrogenated in an autoclave and the resulting, unpurified indoline was acetylated directly to give amide **51**. Nitration of **51** proceeded regioselectively to give **52** which was hydrolyzed to phenol **53**, the common intermediate for the synthesis of both PDE-I (**2**) and PDE-II (**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.

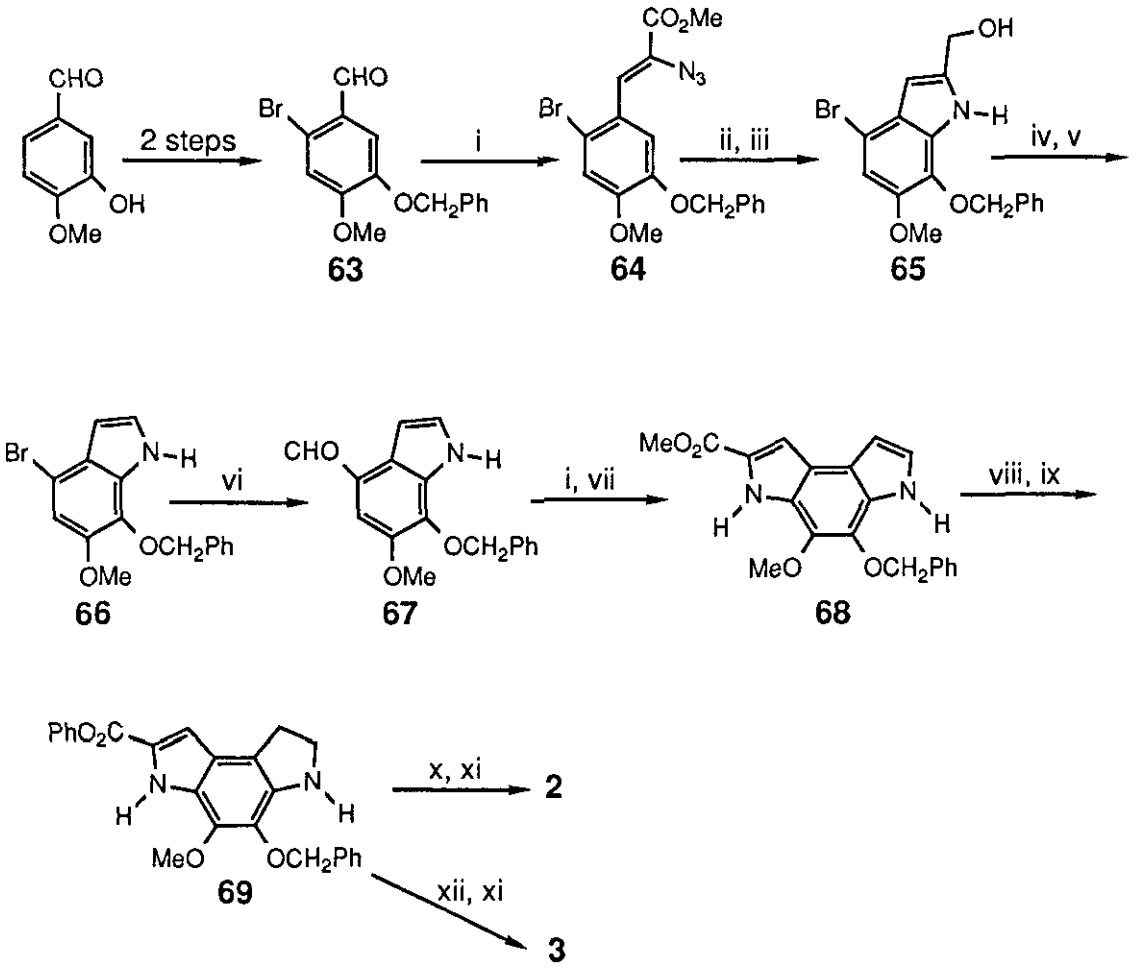
c. *REES' SYNTHESIS OF PDE-I AND PDE-II.*

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 synthesis[22].

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 $(PH_3P)_2Rh(CO)Cl$ gave the indole **66**. Other groups reported difficulties in the hydrolysis and decarboxylation of indole-2-carboxylic acid derivatives[23] 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 acid[24] 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) $MeO_2CCH_2N_3$, NaOMe, MeOH, 4°C; ii) xylene, reflux; iii) LAH, ether, reflux; iv) MnO_2, CH_2Cl_2, reflux; v) $(Ph_3P)_2Rh(CO)Cl$ (0.06 eq.), dppp (0.12 eq.), mesitylene, reflux; vi) ^{t}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 reaction[25] 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) group[26] 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]

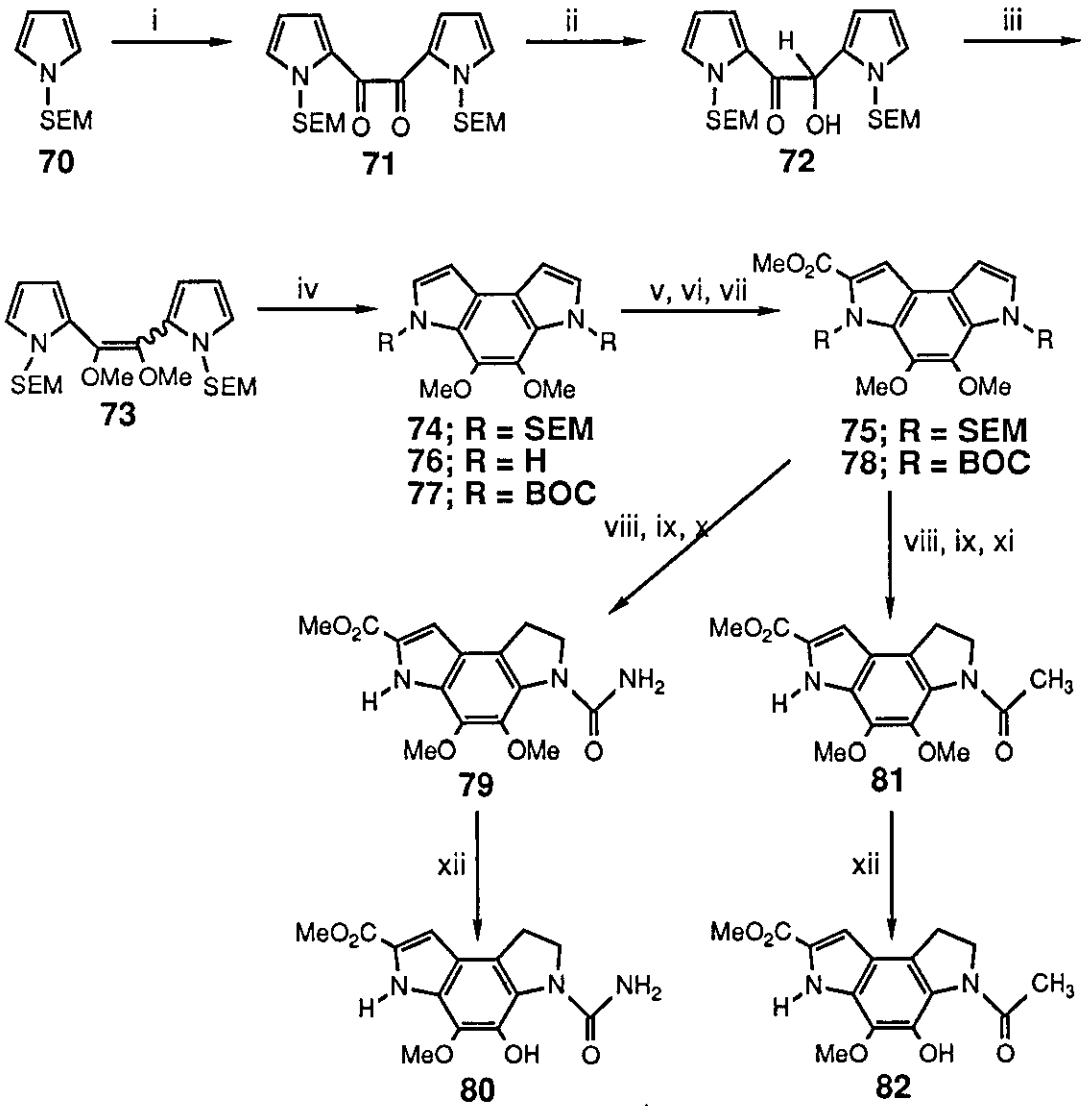
Conversion of hydroxyketone **72** *into a suitably protected enediol proved to be unexpectedly difficult.* After considerable experimentation, exclusive *O*-alkylation was achieved when a DMSO solution of **72** was treated with an excess of *t*-BuOK and methyl tosylate, and the desired, light and acid 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 lithiated[26] in DME at 0°C, then chilled to -78°C and quenched with an excess of $ClCO_2Me$ 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*-Bu_4NF, 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*-butyloxycarbonyl (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 $ClCO_2Me$ 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*t*Bu (5 eq.), MeOTs (5 eq.), DMSO; iv) hν, 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; vix) $NaCNBH_3$, AcOH, -20°C; x) KOCN, AcOH, H_2O; xi) Ac_2O, pyridine; xii) $BCl_3 \cdot Me_2S$, 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 complex[32] 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%.

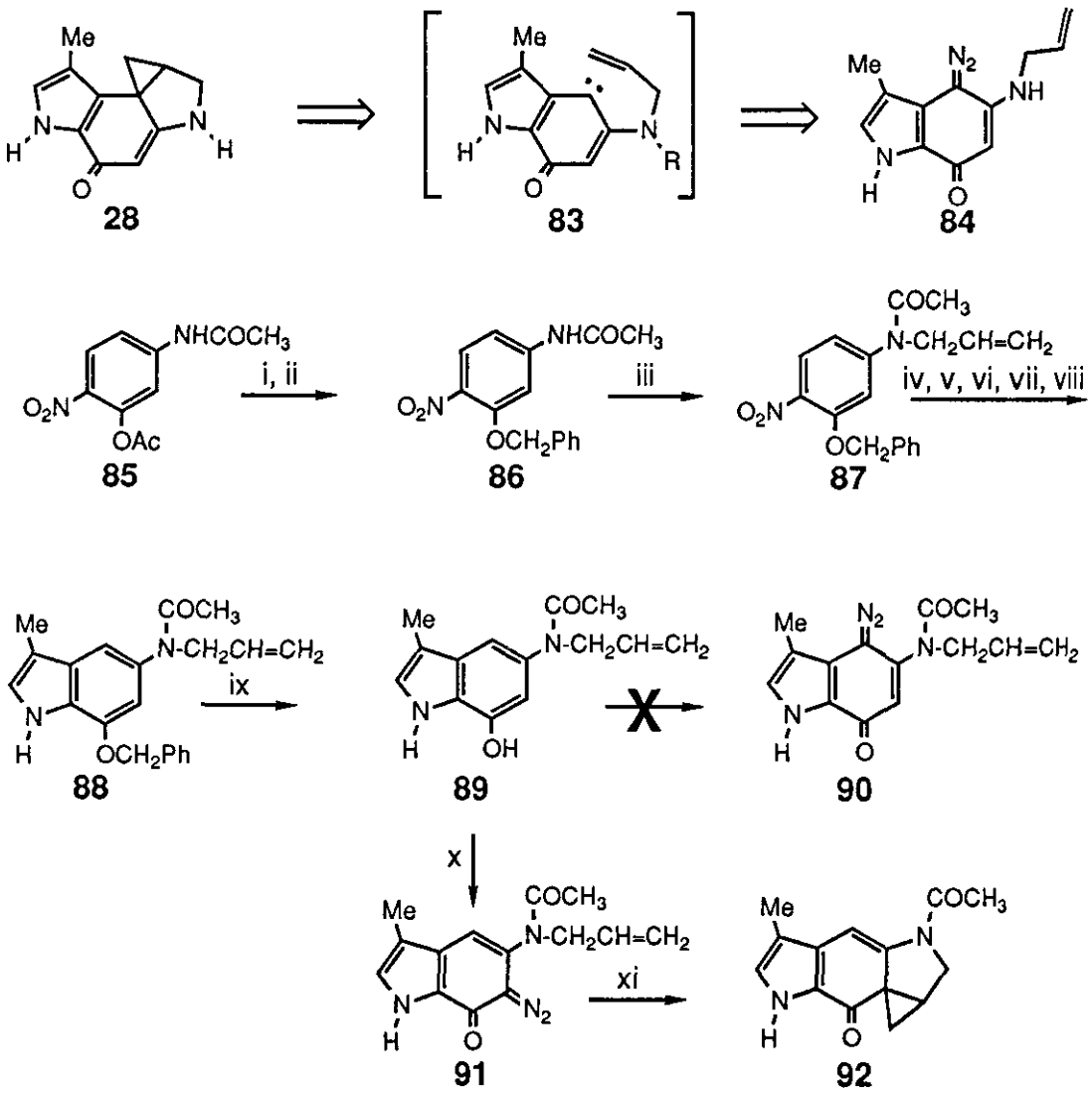
3. Approaches toward the Units of CC-1065

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**. Reducton 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^{t}Bu, DMF, allyl bromide; iv) Zn, $CaCl_2$, EtOH, 80°C; v) HCl, $NaNO_2$; vi) $SnCl_2$, HCl, -5°C; vii) CH_3CH_2CHO, DMF, 0°C, *then* NaOAc, 5°C; *viii)* TsOH, THF; ix) BBr_3, CH_2Cl_2, -40°C; *x) m-nitrobenzenesulfonyl azide;* xi) *hν* > 400 nm.

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

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

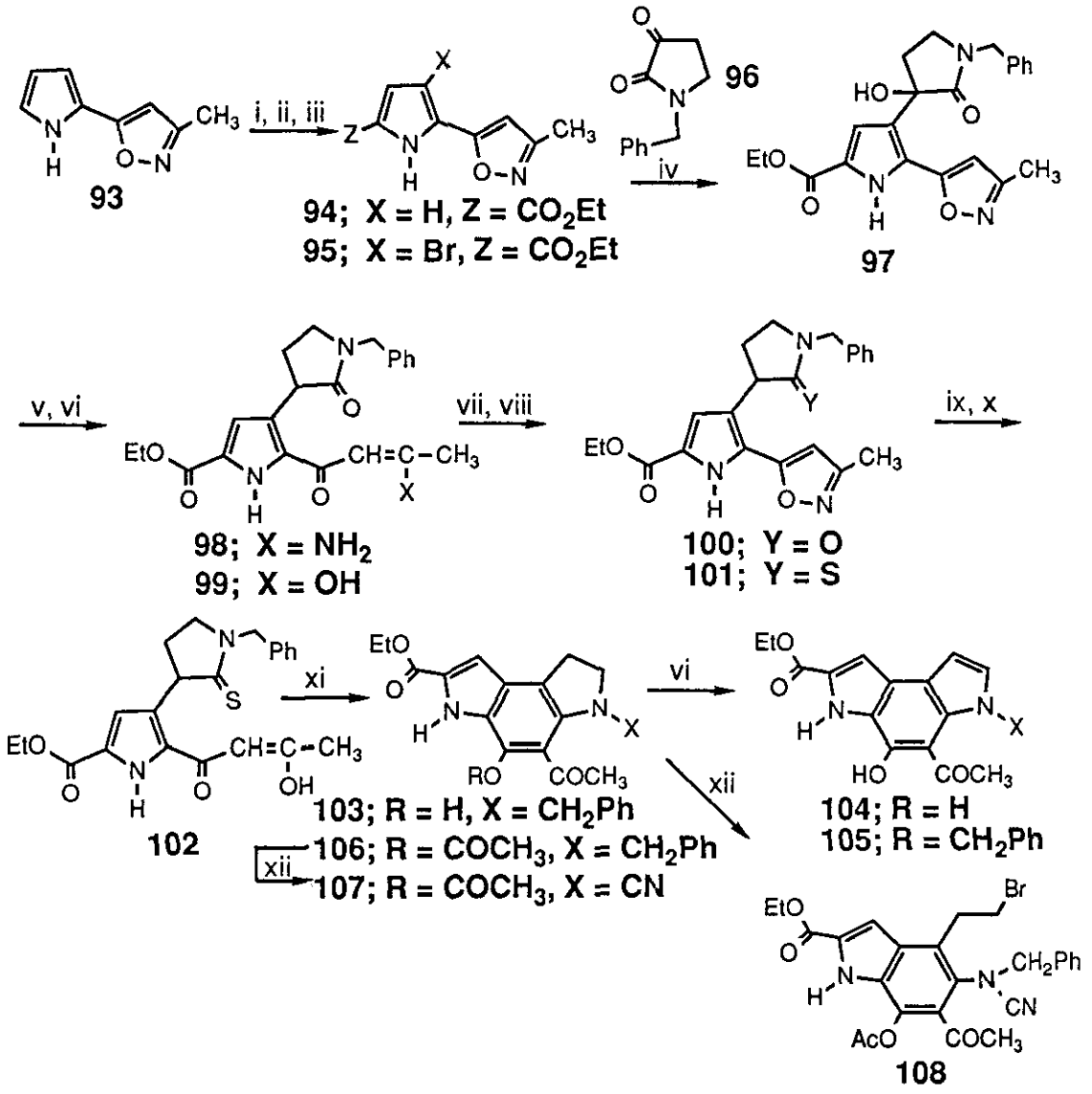
Having abandoned the carbene strategy, Sundberg then embarked on an approach[7b] where, in the key step, the central ring was formed by either a sulfur extrusion reaction of the type Eschenmoser has used so elegantly in his vitamin B-12 synthesis,[33,34] or by an aldol-type condensation with an activated 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 clevage of the isoxazole ring by reaction with molybdenum hexacarbonyl[37] followed by hydrolysis afforded ß-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.

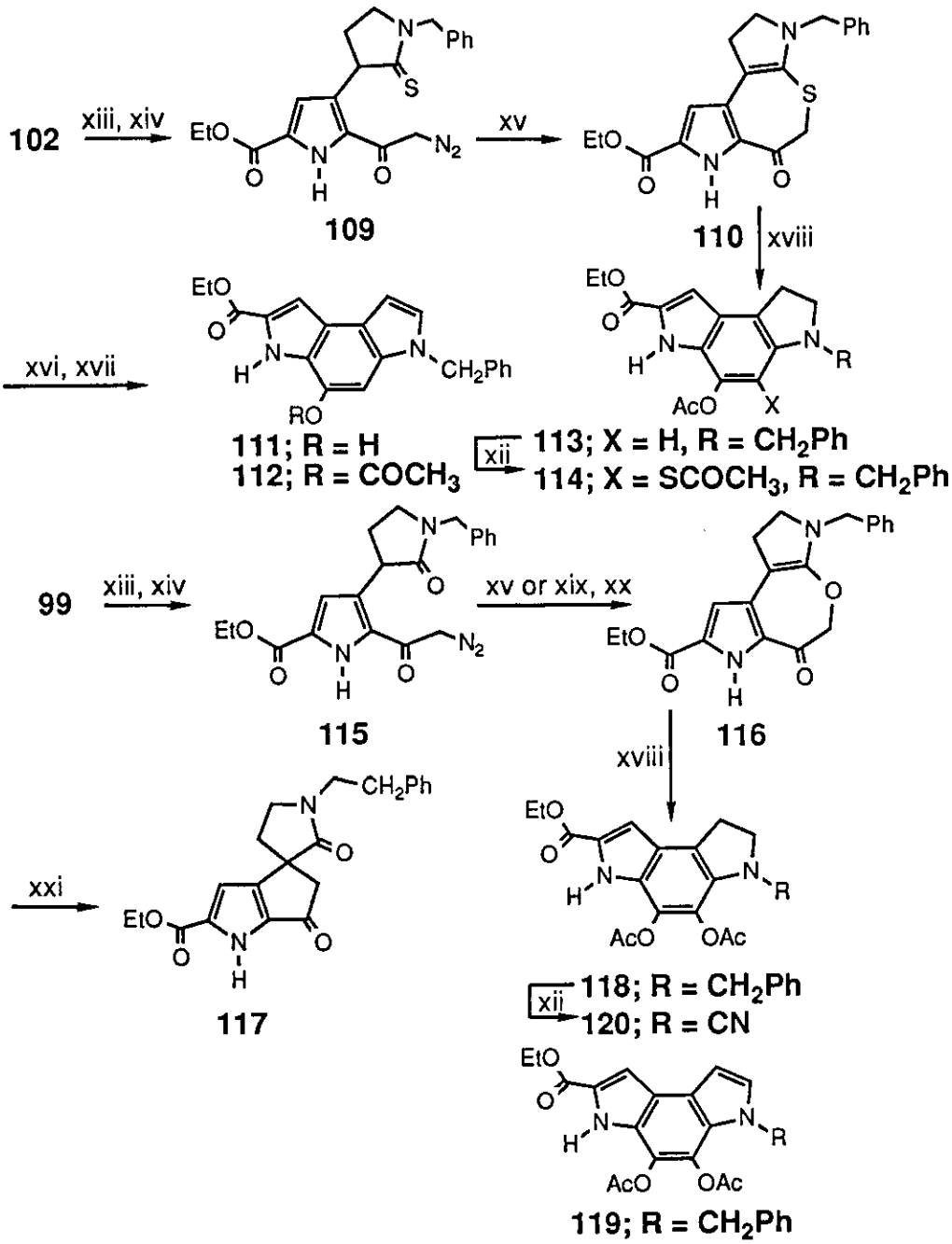
To test the feasibility of the Eschenmoser type of cyclization, diketone **102** was converted in two steps to the diazoketone **109**. Treatment of **109** with either HBr or $BF_3{\cdot}Et_2O$ gave the thiopinone **110**. The ring

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



Scheme 9. **Reagents:** i) Cl_3CCOCl, $ClCH_2CH_2Cl$, reflux; ii) NaOEt, EtOH; iii) NaOAc, HOAc, Br_2; iv) NaH, THF, RT then -98°C, ^{t}Buli, **96**; v) HCl (conc); vi) EtOH, H_2, Pd/C; vii) $H_2OH{\cdot}HCl$, EtOH, 80°C; viii) P_4S_{10}, toluene, reflux; ix) $Mo(CO)_6$, CH_3CN(wet), reflux; x) THF, 5%HCl, 55°C; xi) MeI or Br_2 then aq. $NaHCO_3$; xii) BrCN, $ClCH_2CH_2Cl$;

Scheme 9. cont.



xiii) p-nitrobenzenesulfonyl azide, Et_3N, THF; xiv) EtOH, pyrrolidine; xv) $BF_3{\cdot}OEt_2$, CH_2Cl_2; xvi) 100°C; xvii) Ac_2O, DMAP; xviii) HOAc, Ac_2O, Δ; xix) $Me_3O^+BF_4^-$, $ClCH_2CH_2Cl$, CH_3NO_3; 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 preceeding 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.

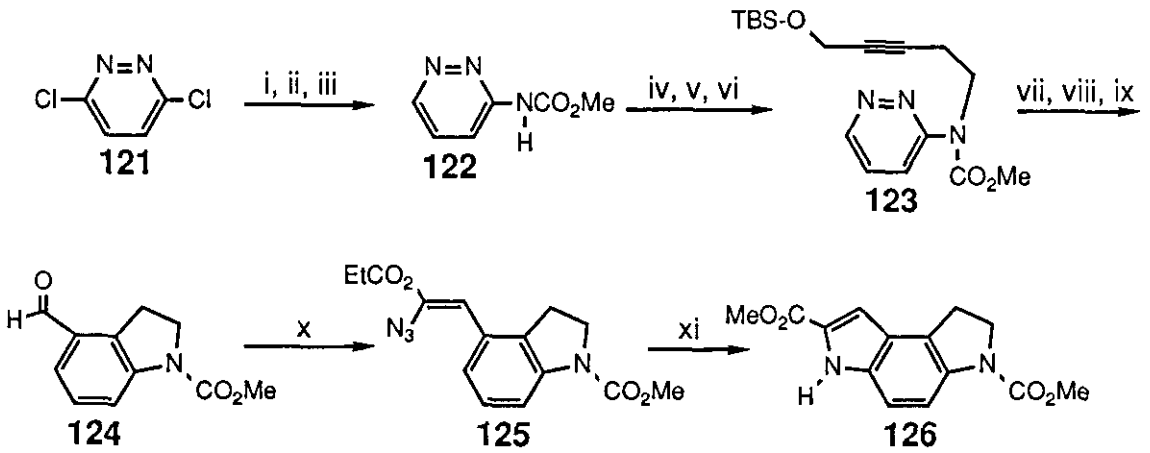
c. BOGER'S APPROACH

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 begans 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 Mitsunobu[39] 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

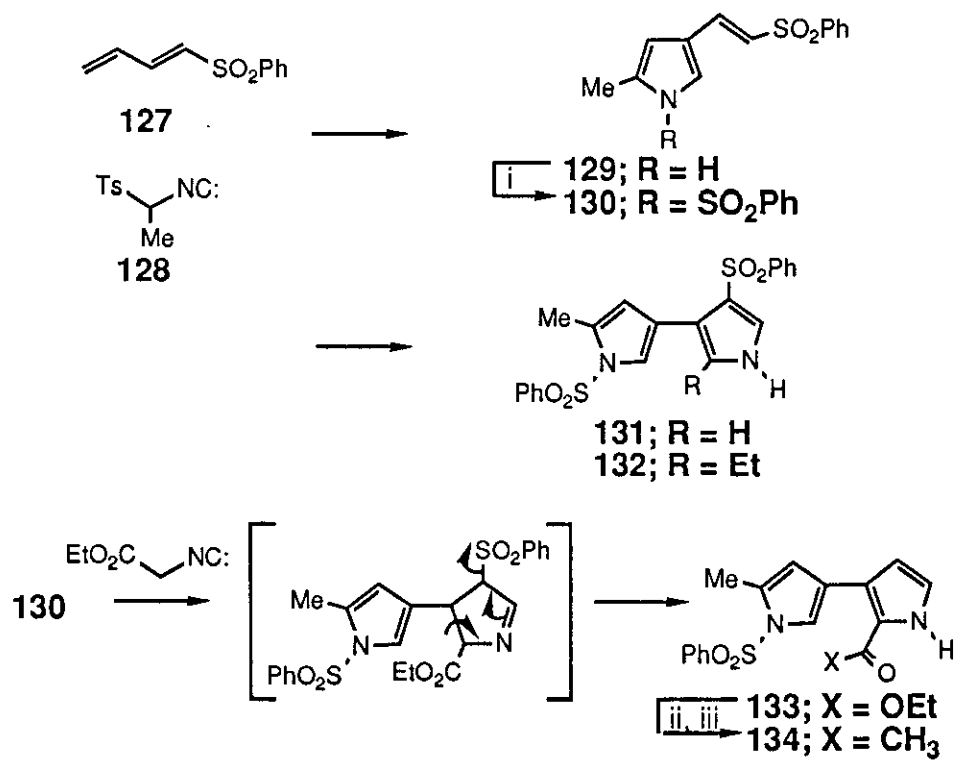


Scheme 10. **Reagents:** i) NH_4OH(conc), 130°C; ii) K_2CO_3, THF, $ClCO_2Me$; iii) NaOH, 10% Pd/C, EtOH, H_2; iv) PPh_3, 5-(tetrahydro-2-pyranyl)-3-pentyn-1-ol, THF, DEAD; v) PPTS, EtOH, 60°C; vi) TBS-Cl, imidazole, DMF; vii) triisopropylbenzene, 230°C; viii) tetrabutylammonium fluoride, THF; ix) MnO_2, CH_2Cl_2; x) methyl azidoacetate, benzene, NaOMe, MeOH, 0°C; xi) xylene, reflux.

d. MAGNUS' APPROACH TO THE B AND C UNITS

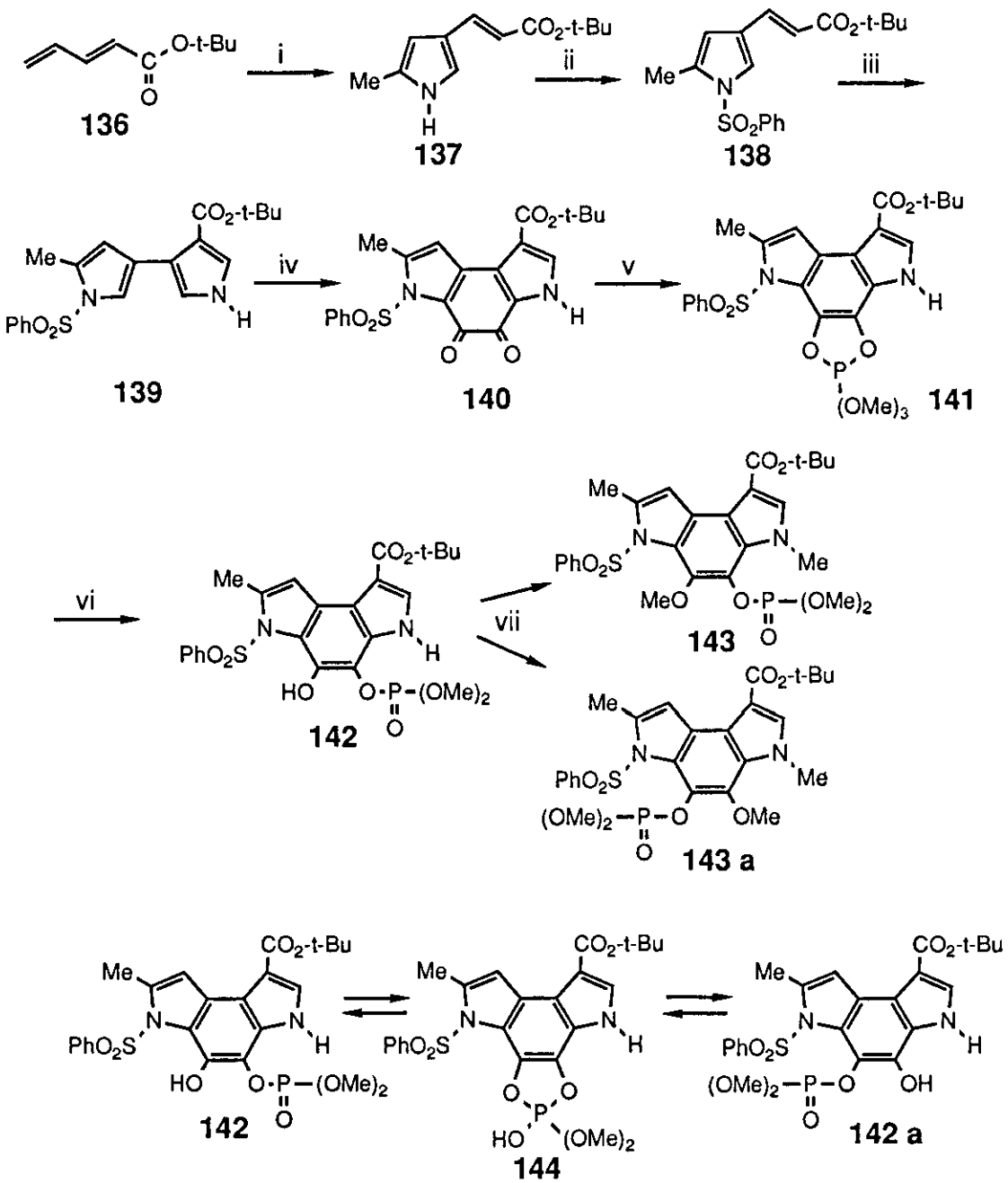
In order to extend his bipyrrole approach to make the **B** and **C** units, Magnus looked into the use of other electrophilic dienes (Scheme 11).[7c] When 1-phenylsulfonyl-1,3-butadiene **127**, which is easily polymerized by base, was treated with the anion of methyl TOSMIC **128**, the 2,4-disubstituted, 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 dimsyl 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, $PhSO_2Cl$; ii) $LiCH_2S(O)CH_3$; iii) Zn, HOAc.

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

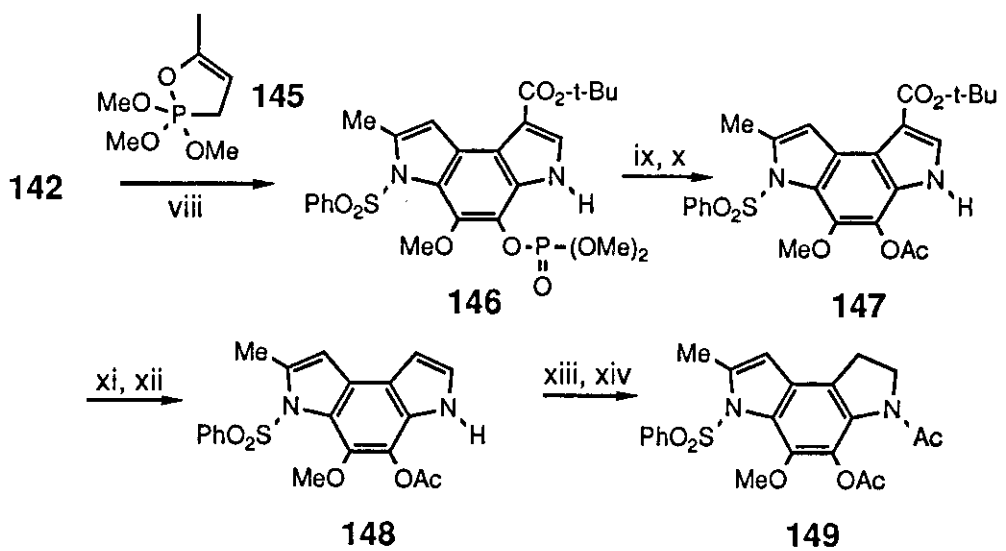


Scheme 12. **Reagents:** i) Methyl TOSMIC, NaH, THF; ii) NaH, $PhSO_2Cl$; iii) TOSMIC, NaH, THF; iv) oxalyl chloride, ether, -78°C to 20°C; v) $P(OMe)_3$, benzene; vi) THF (wet); vii) Me_2SO_4, K_2O_3, acetone;

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 phosphite[43] 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 existance 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) Ac_2O; xi) TFA; xii) Et_3N, toluene, 110°C; xiii) Et_3SiH, TFA, 0°C; xiv) Ac_2O.

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 succeptibility of indoles to oxidizing agents. Magnus' synthesis of diacetate **149** required 12 steps from dienoate **136**; the overall yield was 4.5%.

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