THE SYNTHESIS AND CHEMISTRY OF BENZODIPYRROLES

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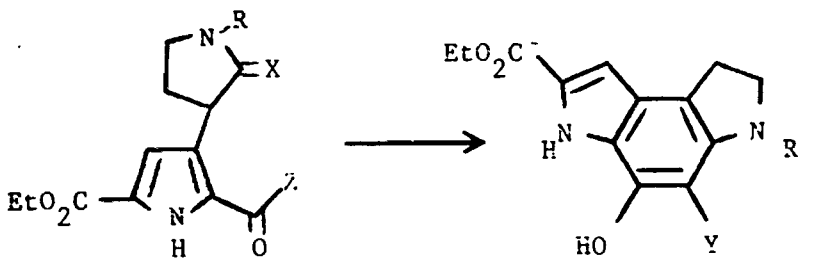
Abstract

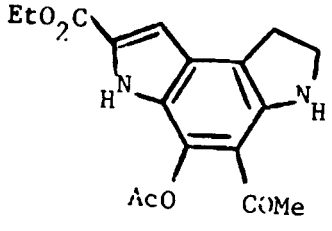
Two cyclization routes for the synthesis of substituted benzo[1,2-b:4,3-b']dipyrroles were investigated. These compounds are of interest for the synthesis of the B and C rings of the potent antitumor antibiotic CC-1065. Also, the preparation of deoxy analogues was considered of significance due to the possibility of synthesizing less toxic analogues of CC-1065 that retain the antitumor activity of the parent compound. The key intermediates in both routes were 3-(3-pyrrolyl)thiopyrrolidines. The use of both the allyl and benzyl groups as nitrogen-protecting groups was investigated.



A B

In the first case, where Z = $COCH_3$, the 5-acetyl substituted benzodipyrrole (Y = $COCH_3$) was obtained by an aldol-type cyclization. The key goal in this path was the elaboration of this substrate to the natural products PDE-I and PDE-II, which would in essence constitute a synthesis

of the B and C rings of CC-1065. It proved not to be possible to methylate the phenolic moiety when R was an alkyl group. Dealkylation of the indoline nitrogen when R = benzyl or allyl also did not prove feasible by electrophilic reagents. However, treatment of the N-allyl benzodipyrrole with tetrakis(triphenylphosphine)rhodium hydride provided an efficient method for the obtention of indoline 44. Conversion of this compound to either an amide or carbamate allowed for high-yielding methylation of the phenol to obtain methoxy benzodipyrroles 50 and 53. Deprotection of the carbamate with zinc and acetic acid provided compound 54 in good yield. Since the



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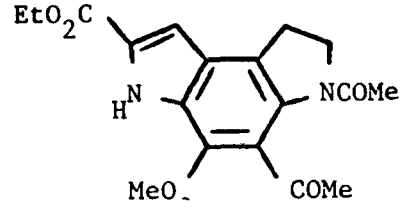

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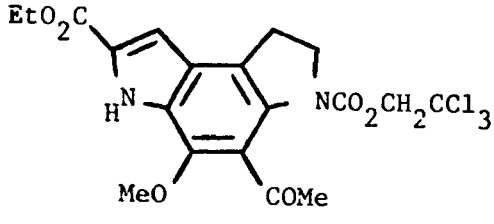

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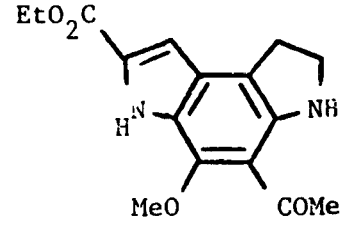
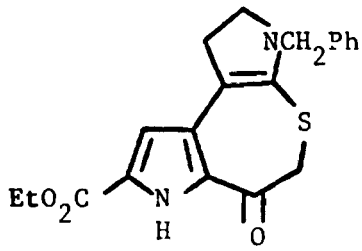


54

oxidation of such substrates to the 5-hydroxy compounds has been described by Boger, this route constitutes a formal total synthesis of PDE-I and PDE-II.

In the case where Z = CH=N=N, decomposition of the diazoketone with boron trifluoride-etherate delivered the stable thiepinone 10 in excellent yield. Treatment of this compound with Raney nickel in refluxing ethanol effected ring contraction-desulfurization to furnish the 5-unsubstituted benzodipyyrole in acceptable yield. Methylation of this compound with diazomethane led to the methoxy compound 91, which could be converted to the trichloroethoxycarbonyl



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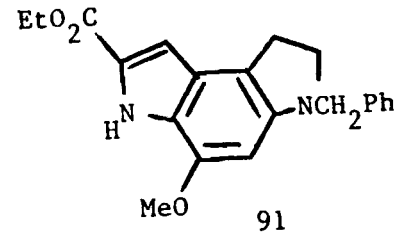

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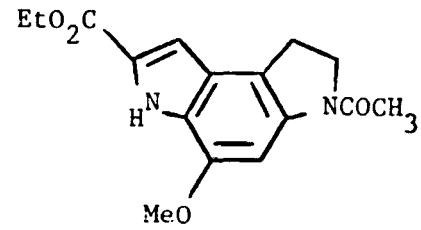

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derivative. Deprotection of this compound and conversion to the amide provides a 5-deoxy analogue of rings B/C of CC-1065.

ACKNOWLEDGEMENTS

The patience, guidance, and inspiration of my adviser, Prof. Richard J. Sundberg, throughout my graduate school years is gratefully acknowledged. Dr. Sundberg's intellectual rigor and scientific integrity stand as models for my own aspirations. I also thank various colleagues and faculty members for their help and advice. In addition to Dr. Sundberg, Dr. Glenn J. McGarvey deserves special thanks for inspiring and shaping my fascination with and appreciation of organic chemistry.

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DEDICATED

To All True Seekers Of The Light

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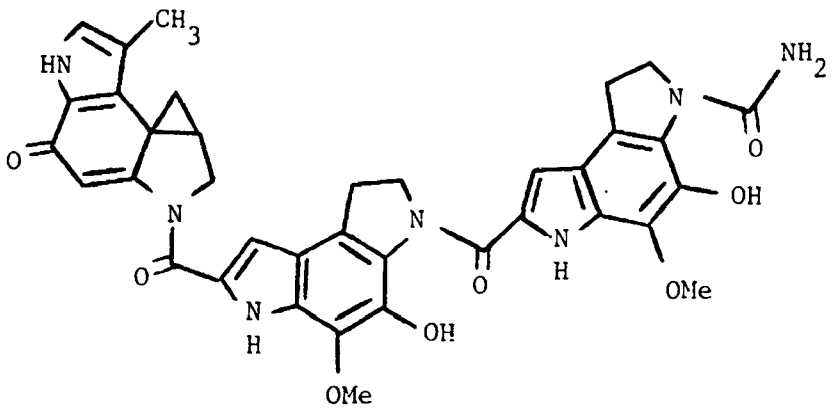
CHAPTER I

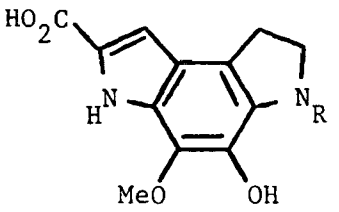
The isolation of the extremely potent antitumor antibiotic CC-1065 in 1978 from the fermentation liquors of Streptomyces zelensis[1] and its subsequent structure elucidation in 1981[2] sparked a surge of interest in the synthesis and chemistry of the benzodipyrrole ring system. Previously, this ring system had been found in nature only in the cyclic adenosine 3',5'-monophosphate (cAMP) phosphodiesterase inhibitors PDE-I and PDE-II, which were isolated by Umezawa and co-workers from the culture filtrate of Streptomyces MD 769-C6[3], and subsequently synthesized by them[4].

The CC-1065 molecule consists of three benzodipyrrole structures A, B, and C, linked by amide bonds; rings B and C have identical substitution patterns and are essentially the same as PDE-I and PDE-II.



CC-1065

PDE-I is non-toxic in mice at 200 mg/kg; CC-1065, in contrast, is toxic at a dose of 0.1 mg/kg[2a]. CC-1065 is, in fact, one of the most cytotoxic substances known. As discussed below, this is thought to be due to its ability to disrupt DNA synthesis.



PDE-I R = $CONH_2$

PDE-II R = $COCH_3$

In initial in vitro tests, CC-1065 was found to be strongly active against L1210 leukemia cells[5,6]. By way of comparison, CC-1065 is about four hundred times more active against this cell line than adriamycin; ten times more potent than quinomycin C, xanthomycin or actinomycin C; and about twice as active as maytansine. Subsequent in vivo tests have demonstrated antitumor activity against a variety of murine and human tumors, including P388 leukemia, B16 melanoma, CD8F mammary and colon 26. CC-1065 has been found to prolong the lives, but not to cure, tumor-bearing mice[7]. It is now known that CC-1065 itself will never be clinically useful due to an unusual delayed lethality. Preliminary studies by McGovren et. al. indicate that CC-1065 causes delayed lethal hepatotoxicity at therapeutic antineoplastic doses. Changes in mitochondrial

structure and function have been implicated in this delayed toxicity, possibly indicative of binding of the drug to mitochondrial DNA[8].

CC-1065 inhibits DNA synthesis more than it does the synthesis of RNA or proteins. Concentrations required for the 50% inhibition of DNA or RNA synthesis are 4 to 6 ng/ml and 45-60 ng/ml, respectively[9,10].

Chidester published the structure of CC-1065 in 1981[2], based on X-ray crystallographic analysis and circular dichroism studies. As noted previously, the molecule consists of three benzodipyrrole subunits. The 'left-hand side', or ring A, contains a cyclopropane moiety conjugated with an indolequinone system. It was postulated, and subsequently demonstrated, that this electrophilic spiro-cyclopropane-cyclohexadienone structure is the site of covalent DNA binding. The cyclopropane portion of ring A also contains the only two asymmetric carbons in the CC-1065 molecule. The X-ray analysis, while not allowing certain assignment of the absolute stereochemistry, gave an accurate value for most of the bond lengths and angles. Based on subsequent knowledge of the structure of a DNA-CC-1065 adduct, it appears rather certain that the 3bR, 4aS configuration is the correct one. As will be subsequently discussed, the structure of a DNA-1065 adduct has been elucidated by Hurley and his co-workers; accomodation of the CPK model of this adduct with the polarity of drug-

binding can be done only if the stereochemistry of the C-4a position in the adduct is S[13]. Recently, Wierenga and his colleagues at the Upjohn Company have been working to independently confirm the absolute stereochemistry of CC-1065[29].

The CC-1065 molecule is curved and possesses a definite right-handed twist along the long axis. The individual subunits (A, B and C) are planar but the entire molecule possesses a helicity which mimics that of B-DNA. The outer surface of CC-1065, with its array of hydrogen bond donors and acceptors, is hydrophilic, while the interior is hydrophobic (ie, lipophilic). From the X-ray data, the angle between the A and B rings was found to be roughly 55^0, while that between the B and C rings was approximately 16^0. The twist between the B and C rings is probably constrained by the hydrogen-bonding between the phenolic hydroxyl and the amide carbonyl.

CC-1065 is one of the strongest DNA-binding drugs discovered to date. In contrast to most other antitumor agents, there is evidence that CC-1065 stabilizes the DNA helix. The cytotoxicity of CC-1065 is believed to be due to its ability to inhibit DNA synthesis by irreversible binding[7a]. The curvature and shape of the molecule are such that, as indicated by models, a good fit into the minor groove of double-stranded DNA is possible. Furthermore, the presence of the electrophilic cyclopropane ring

suggested that the mode of action may be non-intercalative alkylation of DNA. Much work was undertaken to elucidate the mode of action of CC-1065 with DNA. Early results indicated an affinity with A-T rich regions in the minor groove.

Experimental results indicate strongly that DNA is indeed the cellular target of CC-1065. The interaction of CC-1065 with various biomacromolecules was examined by three methods: 1) difference circular dichroism 2) analysis of differential drug toxicity following pre-mixing of the drug with biopolymers, and 3) Sephadex chromatography and UV absorption measurements.

The CD data indicated that CC-1065 binds only to double-stranded DNA, with little or no interaction with heat-denatured single-strand DNA or with RNA or protein[11]. Furthermore, a strong preference for A-T rich regions was shown, clearly indicating that AT-containing, double-stranded DNA is required for binding[9].

Pre-mixing CC-1065 with calf thymus DNA resulted in a marked decrease in drug potency; pre-mixing with albumin resulted in only a small loss of potency[11]. This latter reduction in potency is thought to be due to weak, reversible interactions between the drug and protein.

Saturation binding studies have also been carried out. After a four-hour incubation period at 37^{0}C, binding levels of approximately 1 drug molecule/11 base pairs were found.

This figure was increased to 1 drug molecule/ 7 base pairs after prolonged incubation[9].

It was noted above that binding of CC-1065 to double-stranded DNA results in marked stabilization of the DNA helix. This has been demonstrated in three types of experiment: 1) examining the effects of drug binding on DNA-helix melting temperature, 2) effects of drug binding on S. nuclease digestion of DNA, and 3) effects of drug binding on ability of ethidium bromide to intercalate and unwind supercoiled DNA. It was found that binding of CC-1065 to DNA resulted in a marked increase in the melting temperature of the DNA[9]. It was also found that drug binding greatly inhibited DNA degradation by S1 nuclease[9]. Since S1 nuclease degrades single-stranded DNA, this result was interpreted to mean that binding of CC-1065 to DNA suppresses DNA "breathing" (local, transient strand separation). Studies also discovered that the binding of the drug inhibited ethidium-induced unwinding[9].

The conclusion that CC-1065 binding occurs in the minor groove of DNA rests on three pillars of evidence. Netropsin, which is known to bind non-covalently in the minor groove of AT-rich regions of DNA, has been shown to inhibit subsequent binding by CC-1065. Over prolonged times, CC-1065 was able to displace netropsin, but netropsin could not displace bound CC-1065[12]. In addition, CC-1065 reacted with bacteriophage T-4 DNA, which was 65%

glycosylated in the major groove, to nearly the same extent as with unmodified calf thymus DNA[9]. Finally, inhibition of methylation at minor groove sites by such alkylating agents as methyl- and ethylnitrosourea was shown to result from binding of CC-1065 to DNA[9].

On the basis of these results it is likely that CC-1065 binds to DNA in a non-intercalative fashion. The mechanism of binding was postulated to involve alkylation by CC-1065 of either N-3 of adenine or O-2 of thymine. In addition, two possible alkylation reactions of the cyclopropane moiety were considered, as shown in Fig. 1.

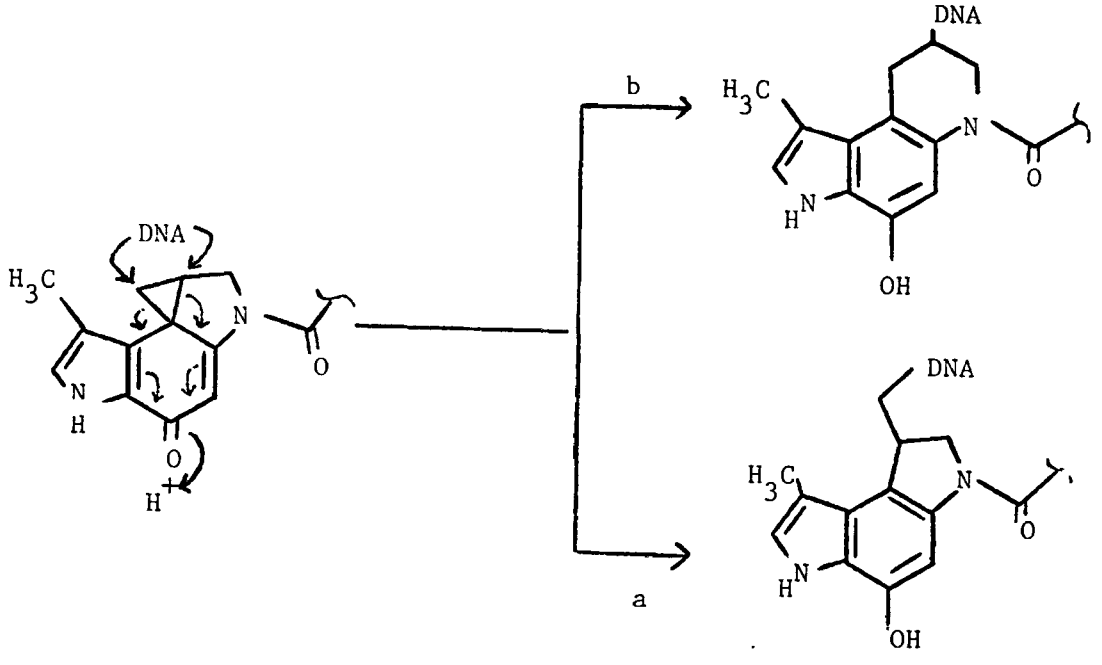


FIGURE 1

In 1984 Hurley and co-workers isolated and

characterized a CC-1065-(N-3 adenine)-DNA adduct which provided definitive evidence for a covalent bond between N-3 of adenine and CC-1065[13]. It was also shown that the drug binding is as-sociated with a sequence specificity for 4-5 base pair domains. The two sequences which were identified as preferred for binding were A/GNTTA and AAAAA. The reaction between CC-1065 and N-3 of adenine is shown in Figure 2. The experimental results show that alkylation is proceeding by path a in Figure 1.

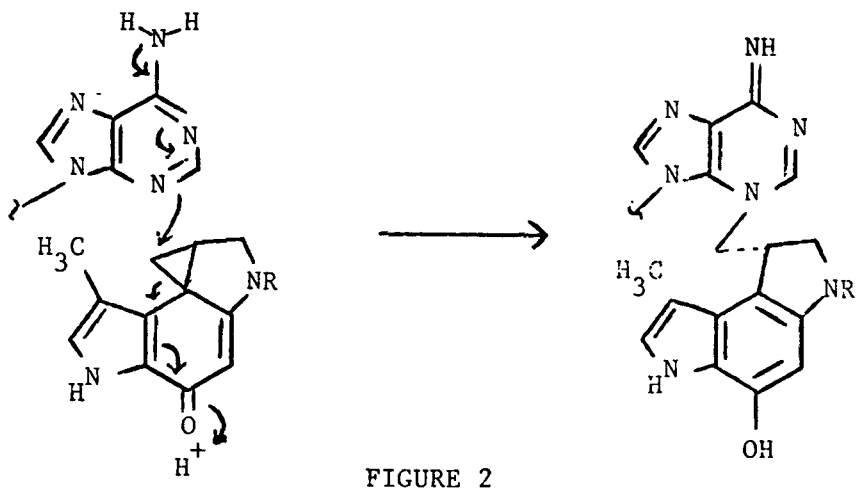


FIGURE 2

Hurley and his colleagues have also characterized a defined CC-1065-oligodeoxynucleotide adduct, using a 14 base pair DNA sequence (5'-CGGAGTTAGGGGCG) that contained a single adenine binding site[14]. Reaction of this oligo-duplex with CC-1065 delivered an adduct which was characterized and shown to be the result of CC-1065 binding to the 5'-TTA sequence of the oligomer.

CPK models of the CC-1065-(N-3-adenine)-DNA indicate

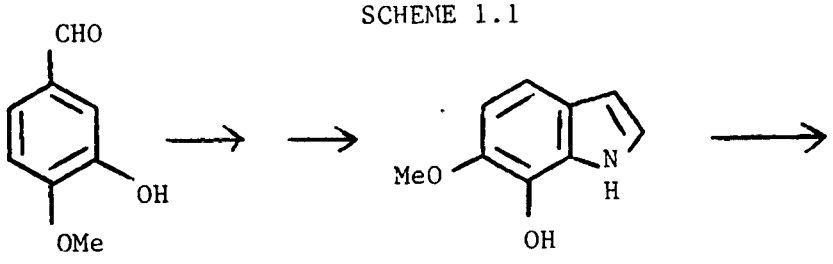
that the drug molecule lies cradled in the minor groove of DNA with a defined stereochemistry and orientation, and should cover approximately five base pairs. The conclusion that the absolute stereochemistry of the asymmetric centers in the A ring is 3bR, 4aS arises from the fact that the observed polarity of drug binding can be accomodated only if the stereochemistry at the C-4a position of the CC-1065 adduct is S[15].

The biosynthesis of CC-1065 has also been investigated by Hurley[16]. Using radioisotope techniques, tyrosine, DOPA, serine and methionine were shown to be precursors of CC-1065. DOPA appears to be incorporated in to the B and C subunits, whereas tyrosine is thought to be a precursor of all three subunits. The role of serine is proposed to be the contribution of 2-carbon units to all three subunits. Methionine is believed to contribute, by way of S-CH3, four C1 units, possibly including the cyclopropane ring of unit A.

As noted previously, preparation of the B/C rings of CC-1065 is essentially equivalent to synthesis of the phosphodiesterase inhibitors PDE-I and PDE-II. These compounds were first synthesized by classical methods by Umezawa[4] in order to verify the proposed structures, assigned initially by NMR spectroscopy and X-ray crystallography. Umezawa's routes start with isovanillin and proceed with overall yields of 0.02-0.04%. The route

to PDE-II is depicted in Scheme 1.1; the synthesis of PDE-I is completely analogous. Mononitration of isovanillin provided the desired 2-nitro isomer in 31% yield, the 6-isomer predominating. Condensation of the nitro-aldehyde with nitromethane and reduction of the resultant nitrostyrene (iron-acetic acid) furnished the hydroxy indole; treatment with palladium on carbon and treatment of the unstable indoline with acetic anhydride furnished the O,N-diacetyl compound. This intermediate was nitrated in the 5-position with acetyl nitrate; after catalytic reduction of the nitro group to the amine and removal of the O-acetyl group, condensation of the amine with ethyl 2-methyl-3-oxobutanoate in a Japp-Klingeman reaction gave the hydrazone which was cyclized by Fischer methodology (mineral acid) to provide the pyrroloindole, albeit in poor yield. Saponification of the ester delivered authentic PDE-I.

SCHEME 1.1



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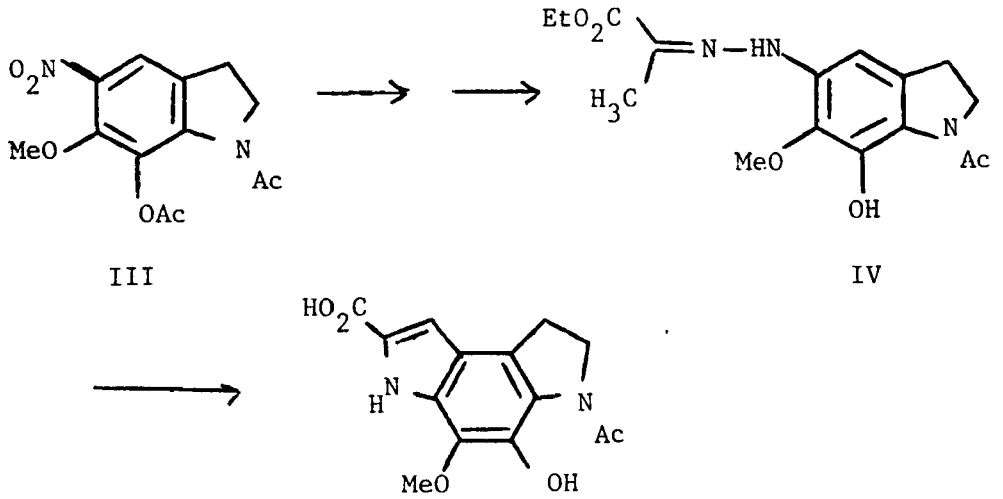
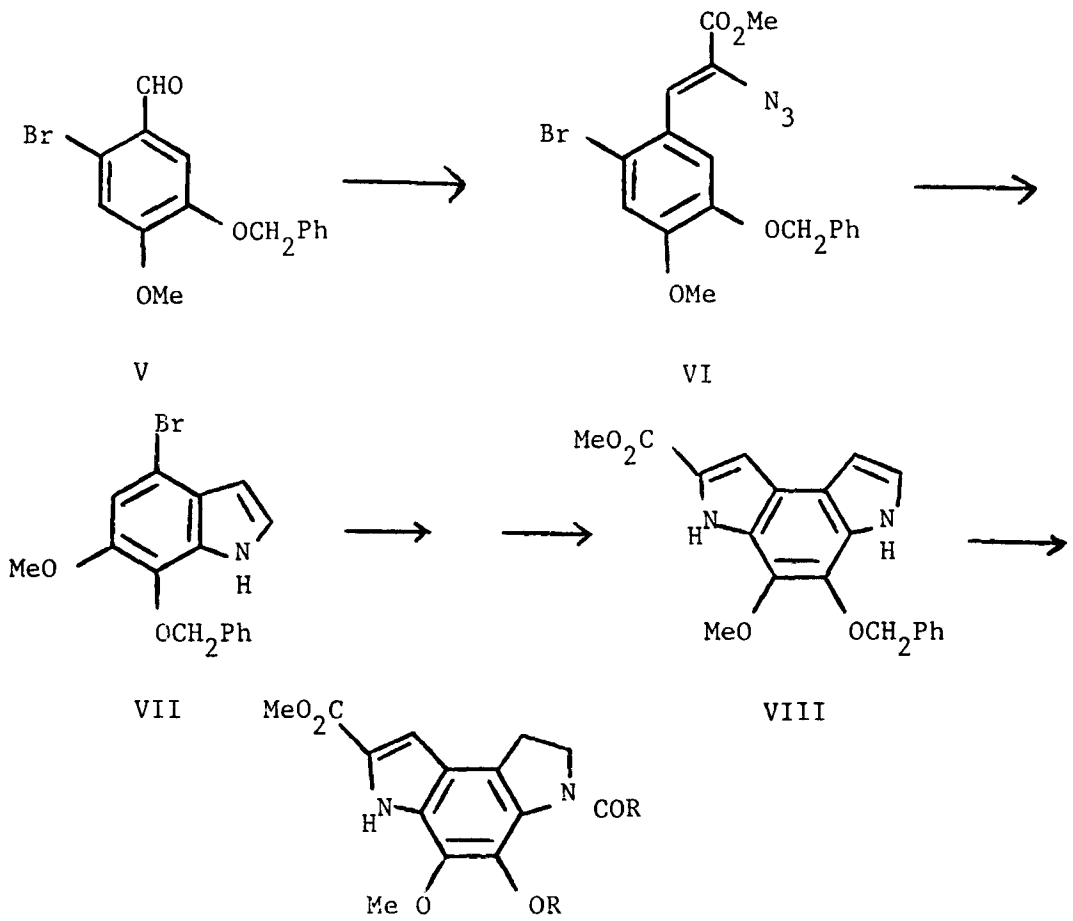


III IV

Rees has recently reported a more efficient and modern synthesis of both PDE-I and -II starting from isovanillin, which utilizes thermolysis of azidoacrylates to form both pyrrole rings[17]. The latter compounds are readily derived from benzaldehydes. Thus, the known bromobenzaldehyde V (prepared in two steps in 77% yield from isovanillin) was condensed with methyl azidoacetate and the resultant vinyl azide was refluxed in xylene to generate the indole. Rees found that the indole-2-carboxylic acid was difficult to decarboxylate; therefore the ester was reduced to the alcohol (lithium aluminum hydride), oxidized to the aldehyde, and decarbonylated. The organolithium reagent derived from this bromoindole by halogen-metal exchange (t-butyllithium, -78^{0}C) was quenched with DMF to afford the

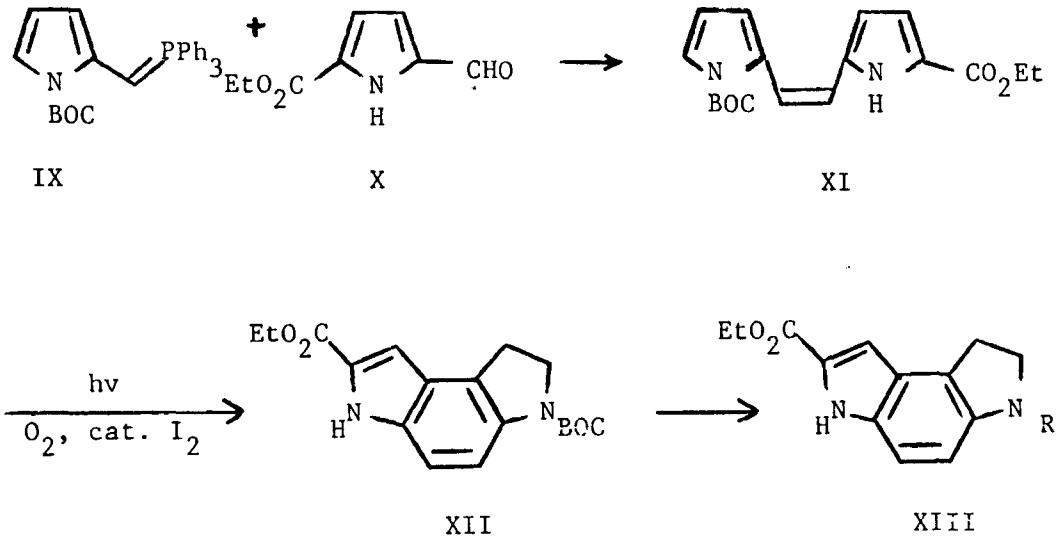
aldehyde. Repetition of the methyl azidoacetate condensation-thermolysis procedure delivered the benzodipyrrole skeleton in good yield. Transesterification with benzyl alcohol, followed by selective reduction to the desired indoline ($NaCNBH_3$, HOAc) gave the pyrroloindole, which could be converted to either PDE-I (treatment with trimethylsilyl isocyanate followed by hydrogenolysis of the benzyl groups) or PDE-II (treatment with acetic anhydride followed by hydrogenolysis).

SCHEME 1.2



Cava has developed syntheses of PDE-I, PDE-II, their dideoxy analogues, and furan and thiophene analogues, based on a Mallory-type photocyclization of stilbenoid hetero-cycles[18]. In initial work on the dideoxy analogue (Scheme 1.3)[18a], the di-pyrrylethene XI was synthesized

SCHEME 1.3



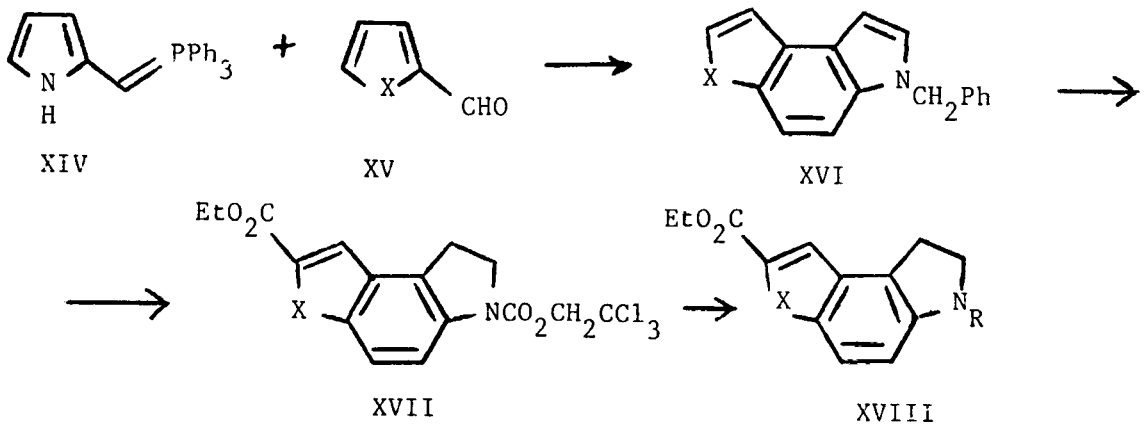
IX X XI

XII XIII

via a Wittig reaction between the phosphonium ylide and pyrrole aldehyde shown. Air-mediated photocyclization of the olefin provided the tricyclic framework in acceptable yield (55-65%). Thermolysis effected removal of the tBOC group in nearly quantitative yield. Selective reduction of the unsubstituted indole ring, acylation of the resultant indoline (potassium isocyanate or acetic anhydride) and hydrolysis of the ester liberated dideoxy PDE-I and -II,

respectively. Synthesis of the thieno and furo analogues of PDE-I and PDE-II (Scheme 1.4, X=S or O)[18e] proceeded in an analogous vein, this time making use of a palladium-mediated photocyclization of the key stilbenoid heterocycles. Regioselective lithiation of the cyclized compounds allowed introduction of the 2-carboethoxy substituent by reaction with ethyl chloroformate. Removal of the benzyl protecting group on the indoline nitrogen in this case was accomplished with 2,2,2-trichloroethyl

SCHEME 1.4



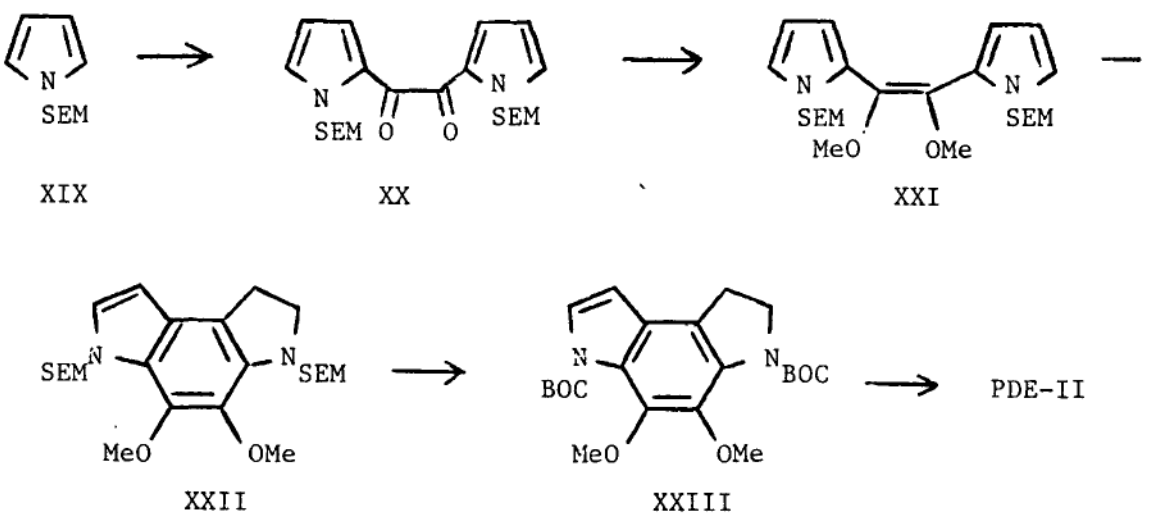
XIV XV XVI XVII XVIII

chloroformate; the resulting carbamate was reductively cleaved with zinc in acetic acid and the free indoline was treated with the appropriate acylating reagent.

A modification of this strategy was necessary in order to accomodate the oxygen functionality required for synthesis of PDE-I/II[18c]. As shown in Scheme 1.5, pyrrole was protected with the SEM group, 2-(trimethylsilyl) ethoxymethyl, and reacted with oxalyl chloride to provide

the diketone. The desired dimethoxy stilbenoid was obtained by treatment of this material with potassium t-butoxide in the presence of methyl tosylate. Photocyclization by Cava's Pd/C protocol proceeded in good yield. Removal of the SEM groups and replacement by tBOC allowed for lithiation followed by quenching with 1 equivalent of ethyl

SCHEME 1.5

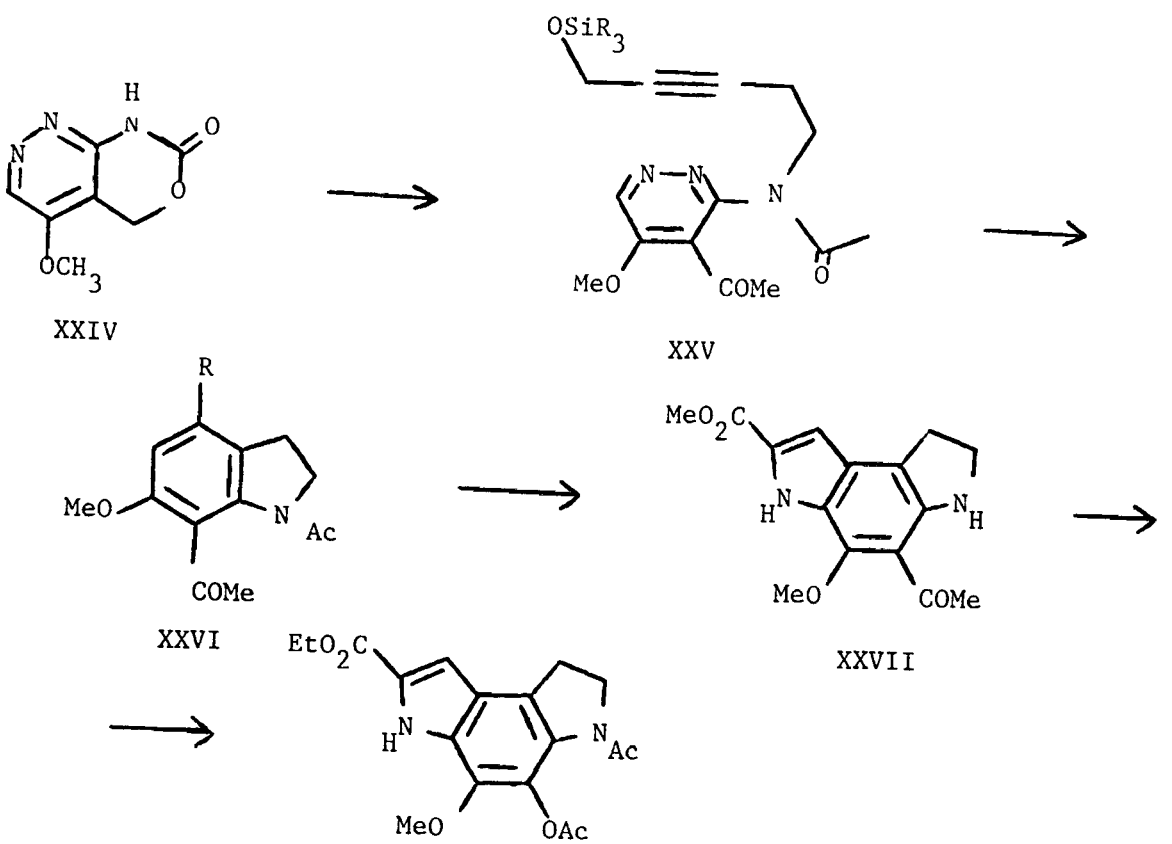


chloroformate to deliver the ester. Thermolytic deprotection, selective reduction to the indoline, and treatment with either KOCN or acetic anhydride furnished

the urea or amide, respectively. Demethylation of XXIII with BCl_3-Me_2S proceeded with the desired regioselectivity to give the proper substitution pattern for the B/C ring system of CC-1065.

Boger has published a synthesis of the B/C subunits and, in addition, has coupled them together to generate PDE-I dimer methyl ester in good yield[19]. His synthetic strategy is based on the intramolecular heterocyclic azadiene Diels-Alder reaction of an appropriately substituted alkyne 1,2-diazine as shown in Scheme 1.6.

SCHEME 1.6

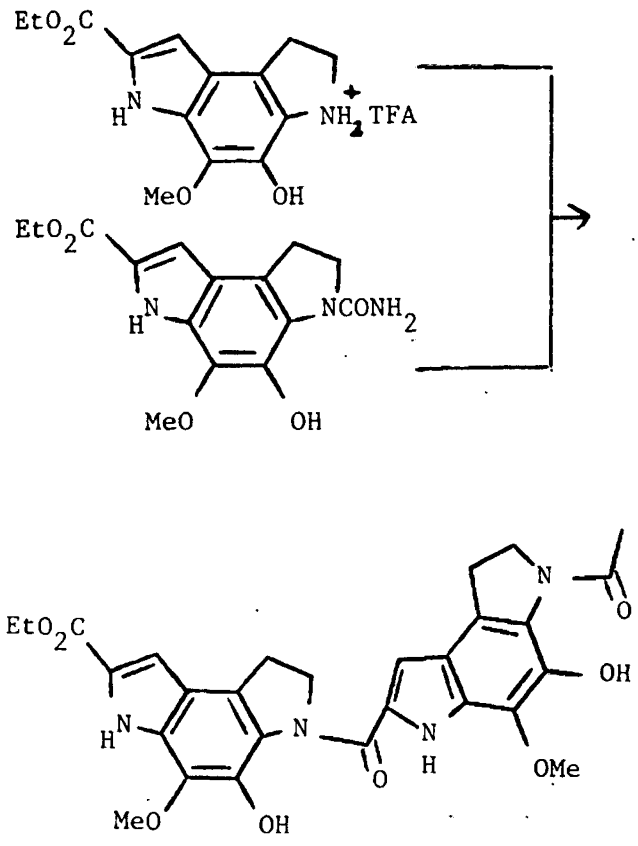


Reaction of 4,4-dimethoxybut-3-en-2-one with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate furnished the basic diazine skeleton XXIV which was elaborated in several steps to the key alkyne 1,2-diazine. Conversion to the amide and thermolyzing at 230^0C provided the indole shown in high yield. Use of the Hemetsberger methodology, previously described for the work of Rees, served for the introduction of the indole ring; removal of the silyl protecting group, followed by oxidation of the primary alcohol to the aldehyde, condensation with methyl azidoacetate and thermolysis provided the benzodipyrrole structure. Introduction of the final oxygen substituent on the central ring was done by a benzylic hydroperoxide rearrangement. Reduction of the acetyl side chain to the secondary alcohol, after removal of the N-acetyl group, followed by treatment with hydrogen peroxide and boron trifluoride etherate and thence with acetic anhydride, provided PDE-II methyl ester.

Boger has also published the results of studies on the coupling of these subunits into dimers, trimers and tetramers[19d]. Dimerization has been achieved in good yield with PDE-I methyl ester and also with the dideoxy analogue. Treatment of PDE-I itself and the trifluoroacetate salt of the methyl ester (Scheme 1.7) with triethylamine followed by 2.0 equivalents of the carboxyl activating reagent 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride

(EDCI) afforded PDE-I dimer methyl ester in 60% isolated yield. Boger has extended this methodology to the preparation of trimers and tetramers of the dideoxy analogue of the B/C subunits.

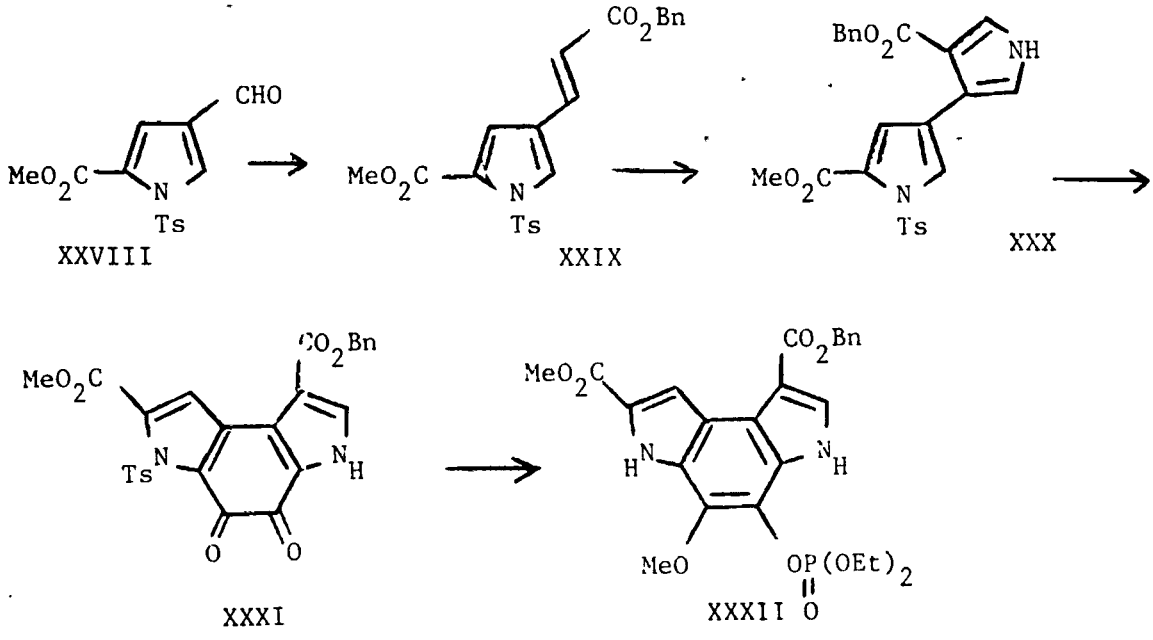
SCHEME 1.7



Magnus has developed a synthesis of the subunits of CC-1065 based on the utilization of p-tolylsulfonylmethyl isocyanide (TOSMIC) for the construction of 3,3'-bipyrrole structures[20]. For the synthesis of the B/C rings, the

pyrrole aldehyde XXVIII in Scheme 1.8 was tosylated on nitrogen and reacted with the phosphonate Wittig reagent to provide the acrylic ester, which upon exposure to TOSMIC

SCHEME 1.8



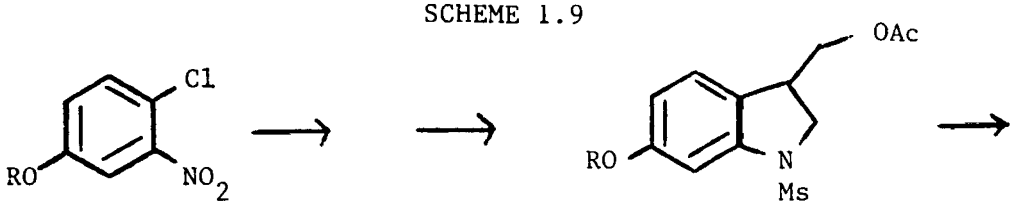
delivered the key bispyrrole intermediate. Electrophilic substitution on the less deactivated pyrrole ring with oxalyl chloride introduced the necessary two carbon unit, and the resulting compound was cyclized in good yield with $SnCl_4$ to afford the ortho-quinone XXXI. Treatment with triethyl phosphite followed by aqueous hydrolysis resulted in a single phenolic phosphate ester, which was methylated

with diazomethane in 50% yield. Reductive removal of the N-tosyl group, sapponification and decarboxylation of the 3-carboxylate group and selective indole to indoline reduction followed by treatment with acetic anhydride or NaOCN gave the urea or carbamate; removal of the phenolic phosphate completed the synthesis of PDE-I and PDE-II.

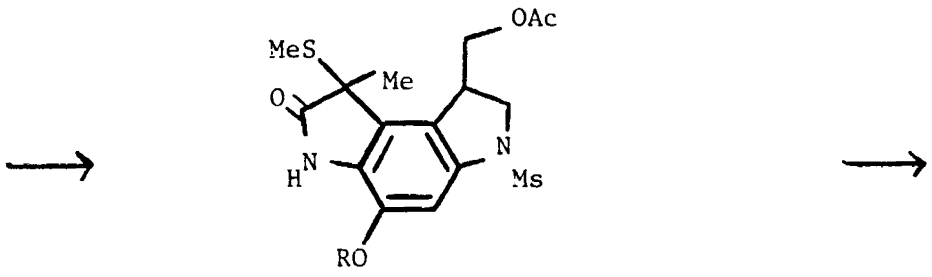
Several syntheses of the A ring of CC-1065 have been developed and these will be briefly reviewed here. In general, two strategies have been used for the formation of the spiro-cyclopropanecyclohexadienone moiety. In the majority of cases, intramolecular para alkylation in an appropriately substituted indole is utilized. A different approach has been developed by Sundberg, which makes use of an intramolecular carbenoid addition to an N-allyl group.

Wierenga was the first to publish a pathway to ring A. In his synthesis[21] (Scheme 1.9), 4-chloro-3-nitroanisole is converted in several steps to the 6-hydroxy indoline XXXIV. Regiospecific nitration of this intermediate and conversion to the amino compound, followed by treatment with ethyl 2-(methylthio)propionate in a modified Gassman oxindole synthesis, delivered compound XXXV which was converted to the 3-methylindole XXXVI by diborane reduction. Conversion of the primary acetate to the alcohol and thence to the bromide, followed by treatment of the phenol with base resulted in formation of the cyclopropyl ring.

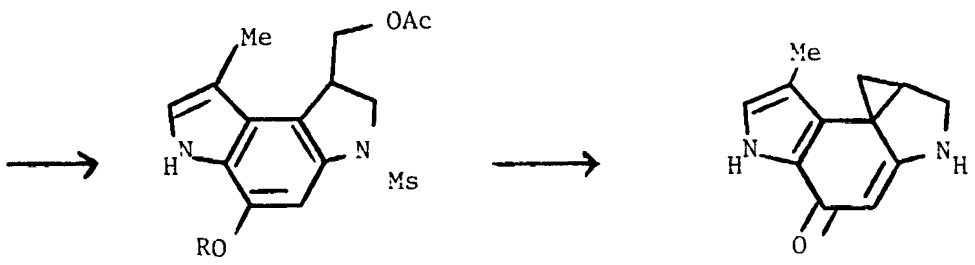
SCHEME 1.9



XXXIII XXXIV



XXXV

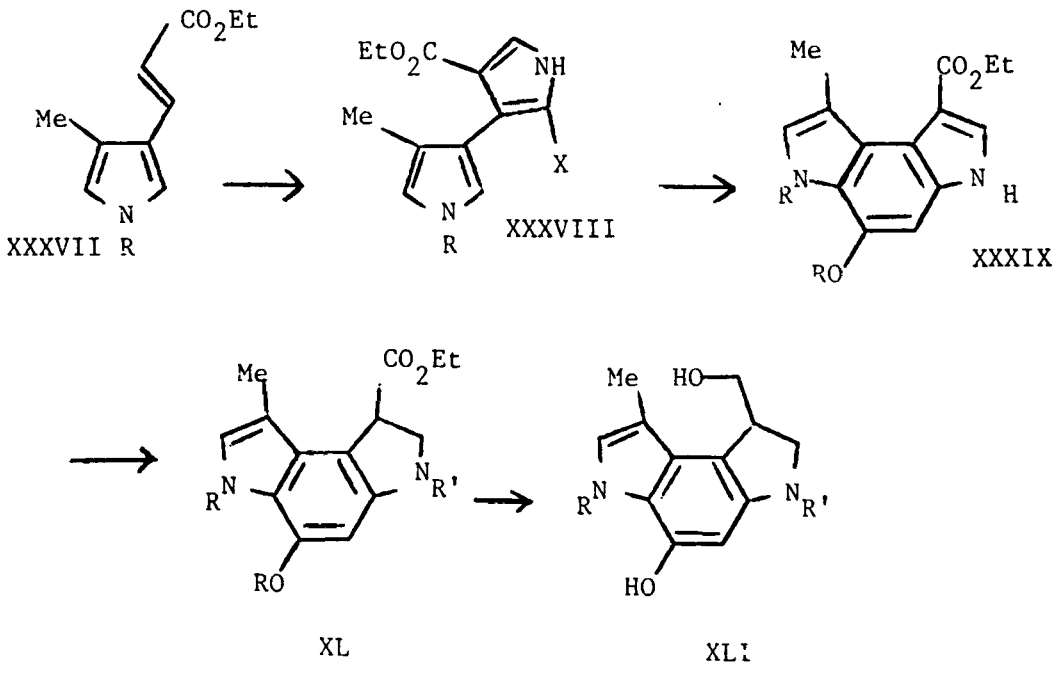


XXXVI

Magnus has published a ring A synthesis based on his 3,3'-bipyrrole strategy discussed above[22]. Sequential conjugate addition of TOSMIC to ethyl sorbate provided the bispyrrole (XXXVIII, X=$CO_2C_2H_5$) (Scheme 1.10), which was converted to the acid chloride (XXXVIII, X=COCl) and

cyclized to the benzodipyrrole in a series of reactions closely related to those discussed in his ring B

SCHEME 1.10

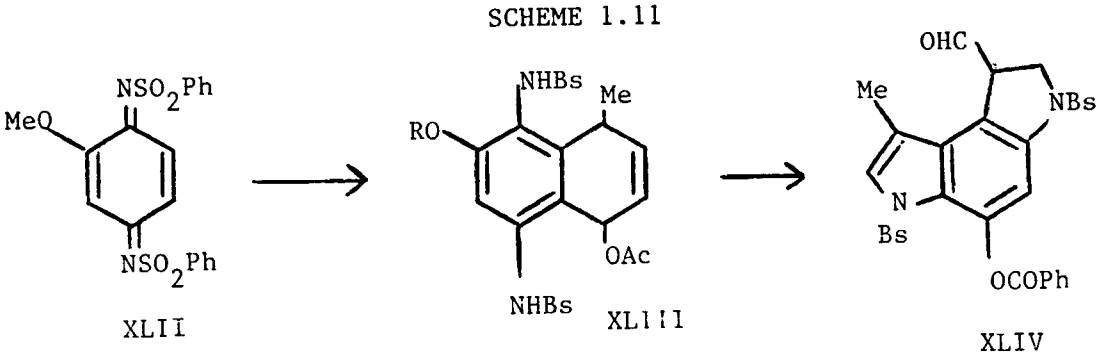


synthesis. Selective reduction and conversion to the primary alcohol followed by intramolecular alkylation via a modified Mitsonobu reaction completes the ring A synthesis.

Kraus[23] has published a route based on the Diels-Alder reaction between the quinoneimine XLII in Scheme 1.11 and 2-acetoxypenta-1,3-diene to produce the bicyclic intermediate XLIII. This compound was converted in several steps to the tricyclic intermediate XLIV. Reduction of the

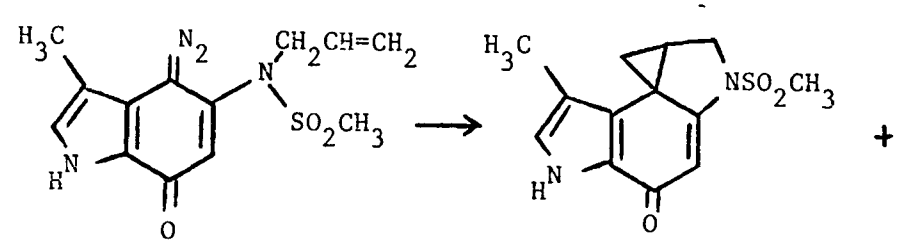
aldehyde to the alcohol and conversion to the mesylate, followed by debenzylation and treatment of the hydroxy-mesylate with DBU, furnished the cyclopropyl system.

SCHEME 1.11

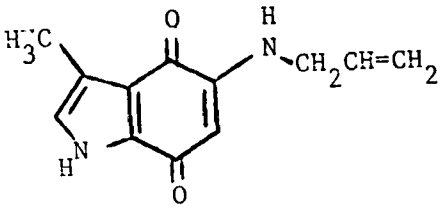


A synthesis of ring A has been achieved in our group based on the generation of the carbene from an appropriately substituted quinone diazide (Scheme 1.12)[24]. Intramolecular addition of the carbene to the N-allyl group was expected to provide the cyclopropyl moiety. Whereas photolysis of the indole quinone diazide delivered only the quinone XLVII, carbenoid formation using metal catalysts has proven more successful and has generated the methanesulfonyl-protected ring A in acceptable yield. The quinone diazide has been approached in two ways. Synthesis of the nitro-indole followed by reduction to the amine and subsequent diazotization provides the desired substrate. Methods for effecting direct para-diazo transfer on phenols of the type shown are currently under investigation in our laboratories.

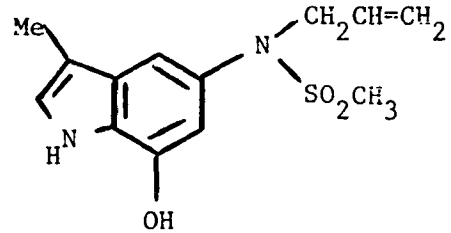
SCHEME 1.12

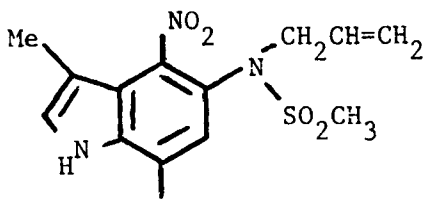


XLV XLVI



XLVII



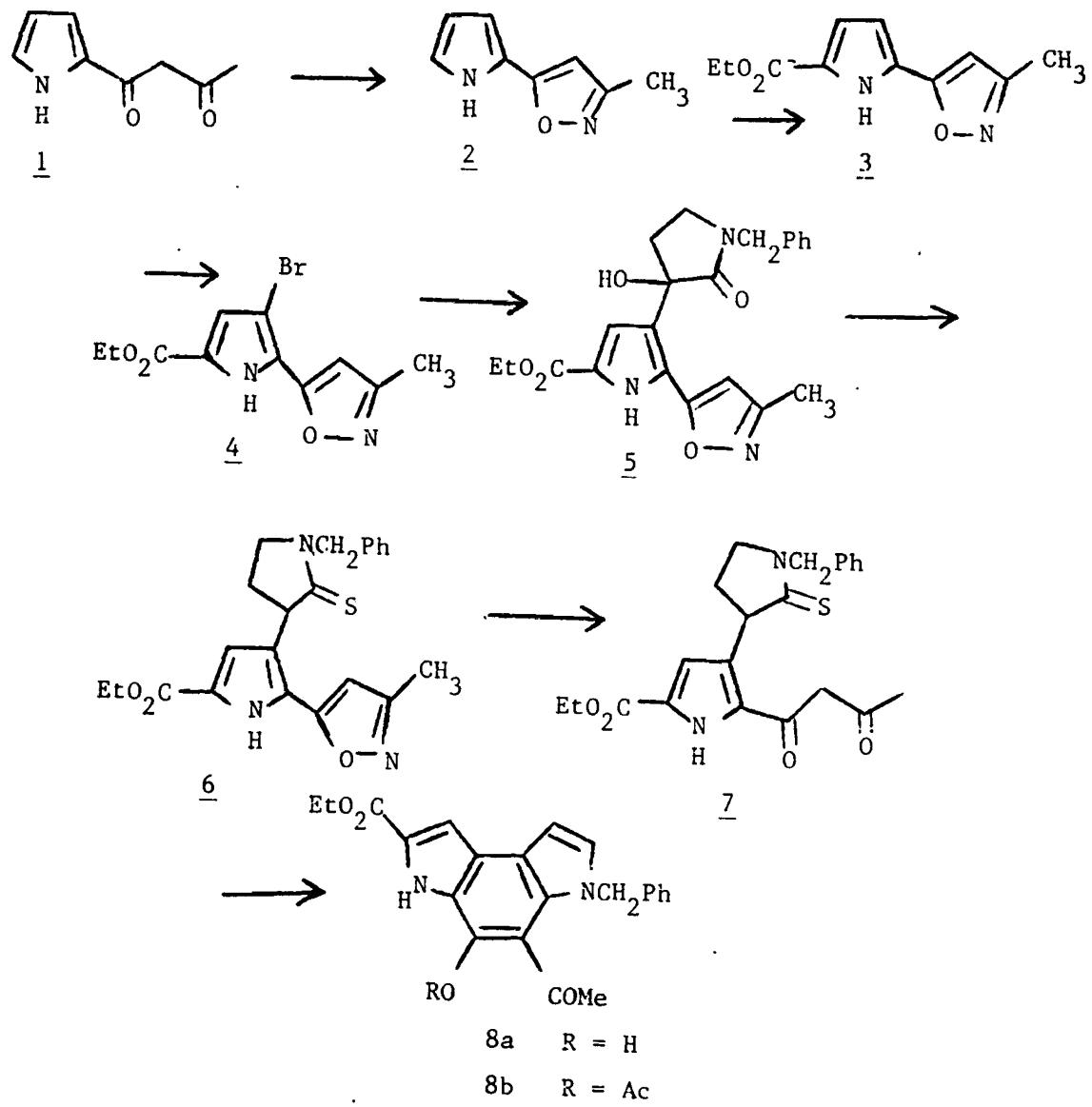


OR

Work in our group on the ring B/C subunits has centered on the use of 3-(3-pyrrolyl)thiopyrrolidines as precursors for PDE-I and PDE-II type structures. Initial work by Pearce demonstrated the basic utility of such routes[25]. The tri-substituted pyrrole 4 (Scheme 1.13), which is readily available in multigram quantities, was deprotonated with NaH and the organolithium reagent was generated by lithium-halogen exchange. The lithiated intermediate was treated immediately with N-benzyl-2,3-pyrrolidinone to provide the key 3-(3-pyrrolyl) thiopyrrolidinol intermediate 5, which was converted in several steps to the thiolactam 6. Reductive cleavage of

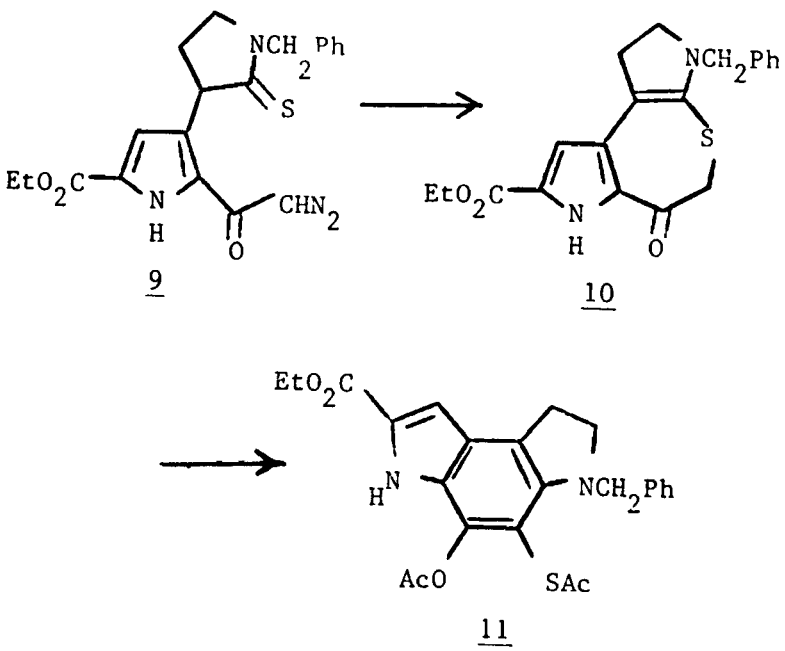
the isoxazole ring with molybdenum hexacarbonyl and subsequent acid hydrolysis afforded the dicarbonyl compound 7. Cyclization with either bromine or excess methyl

SCHEME 1.13



iodide proceeded efficiently to yield the N-benzyl benzodipyrrole 8a. Unfortunately, attempted debenzylation with either Pearlman's catalyst or palladium on carbon gave mixtures of benzylated and debenzylated materials in which the dihydropyrrole ring had been oxidized to the indole. Also, while acylation of the phenolic hydroxyl occurred readily with acetyl chloride to afford the acetate 8b in nearly quantitative yield, the phenolic moiety resisted attempts at methylation with diazomethane. Reaction of acetate 8b with cyanogen bromide delivered the N-cyano derivative in erratic and low yield, accompanied by substantial quantities of ring-opened material and decomposition products.

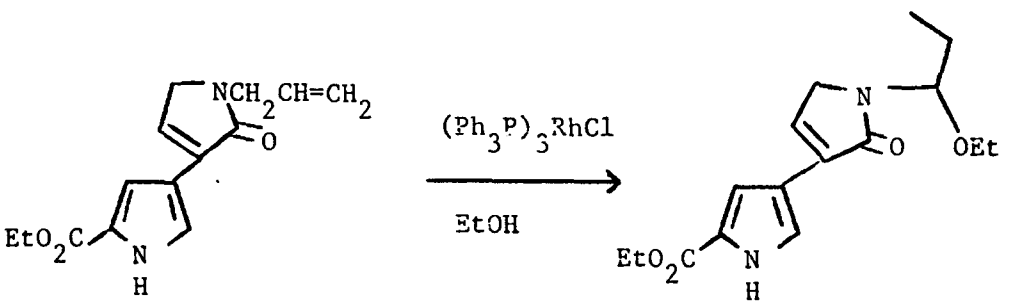
SCHEME 1.14



In an alternate cyclization route shown in Scheme 1.14, the diazo ketone, available from the diketone 7 in two high-yielding steps, could be quantitatively decomposed with boron trifluoride-etherate to furnish the thiepinone 10. Heating this compound in a mixture of acetic acid and acetic anhydride produced the acetylthio-substituted benzodipyrrole in 40-45% yield.

Due to the recalcitrance of the benzyl group towards removal, an investigation of the possibility of using other nitrogen protecting groups in the Pearce synthesis was initiated by Laurino. In view of published methods for the N-deallylation of both amines and amides[26], the allyl group appeared promising. Laurino demonstrated that the N-allyl dione could be made by the Southwick procedure used in the N-benzyl case[27], and that the corresponding N-allyl 3- (3-pyrrolyl)thiopyrrolidinol[28] could be synthesized by Pearce's methods. Unfortunately, however, the method

SCHEME 1.15



of Pearce for removal of the carbinol oxygen from the initial adduct (dehydration followed by catalytic

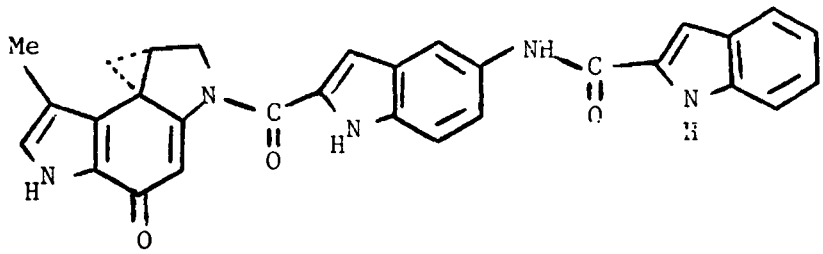
hydrogenation of the olefin) was obviously not applicable in the N-allyl case, and this problem remained unsolved. The ethoxypropyl derivative was obtained by treatment of the dehydrated compound with Wilkinson's catalyst in ethanol (Scheme 1.15).

The current research was undertaken with several objectives in mind: 1) to extend the work of Pearce to a workable total synthesis of PDE-I and/or II, the B/C subunits of CC-1065; 2) to investigate the use of these routes for the synthesis of potentially less toxic analogues; 3) to explore some of the largely unknown chemistry of these electron-rich benzodipyrrole systems. The two basic pathways developed by Pearce were studied: the cyclization of β-dicarbonyl compounds to provide 5-acetyl substituted benzodipyrroles, and possible cyclization modes of diazoketones. The elaboration of these two routes is detailed in the next two chapters.

Some work on the synthesis and evaluation of potentially less toxic analogues has been published. The structural modifications explored have involved substitution of other heteroatoms for the pyrrole nitrogen, as in the work of Cava, the removal of the oxygen functionality from the B/C rings, and the use of indole subunits rather than benzodipyrrole structures for the B/C rings. It has been postulated that the cytotoxicity of CC-1065 may be related to the oxygenation of the B/C rings[19d].

This ortho-catechol functionality may not contribute to the affinity or specificity of the binding. Recent experimental and modeling studies have indicated that these o-catechol units lie on the outer, unbound peripheral face; the high affinity binding is likely to be due to the mimicking of the topological pitch of B-DNA by the natural product. Boger has speculated that the oxidation of the B/C ring to provide an extended reactive p-quinone methide imine subject to nucleophilic attack may provide a mechanism for the observed toxicity[19d].

The CC-1065 analogues U-71,184 and U-71,185 have been prepared and biologically evaluated by Wierenga and Warpehoski and their colleagues[29]. The selective antitumor



U-71,184 (Pictured)
U-71,185 (Other enantiomer)

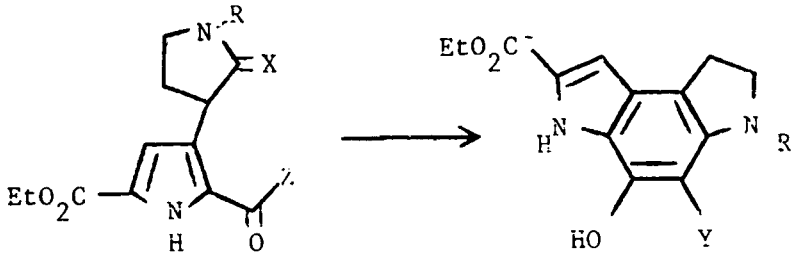
potency and DNA alkylation of the 3bS; 4aR pair of the two analogues lends support to the assignment of the absolute stereochemistry of the natural product. In addition, the

active analogue (U-71,184) has been found to display decreased toxicity relative to CC-1065 itself. In a different approach to analogue development, Boger has synthesized the trimer and tetramer of the dideoxy analogue of the B/C subunits, as detailed previously, with the expectation that these compounds, which lack the alkylating ring A moiety of CC-1065 itself, will prove to be selective, high affinity, non-covalent B-DNA minor-groove binding agents.

CHAPTER II

II.1. Introduction

As discussed in the previous chapter, earlier work by Pearce had established the utility of 3-(3-pyrrolyl)thiopyrrolidines as precursors for benzodipyrrole structures.



A B

8b: Y = COMe
R = Bn

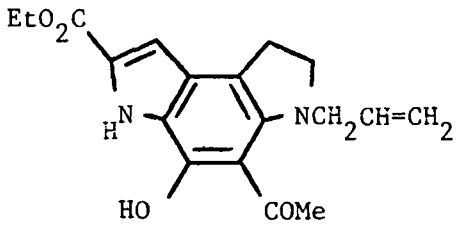
The use of these compounds as intermediates for the synthesis of targets of type B has several advantages: 1) the variation possible in the nature of the group Z 2) the variation possible in the nature of the nitrogen protecting group R 3) the compounds of type A are generally quite stable, crystalline substances which may be stored and worked with conveniently 4) the products B are formed at the correct oxidation level 5) the compounds A are available routinely in multigram quantities. Three major problems to be solved in order to complete the synthesis of B/C ring structures remain: the methylation of the phenolic

moiety, the dealkylation of the pyrrolidine nitrogen and its subsequent conversion to the amide or the urethane, and incorporation of oxygen at the 5-position of the benzodipyrrole.

As mentioned in the previous chapter, a number of methods were explored by Pearce in order to effect debenzylation of 8b. Catalytic hydrogenation was carried out under a variety of conditions; use of 10% Pd/C in ethanol, ethanolic HCl, ethanolic triethylamine and in acetic acid proved fruitless. Hydrogenation with Pearlman's catalyst or with $Pd(OH)_2$ in ethanol gave a mixture of both aromatized starting material and debenzylated but aromatized product. Attempts to cleave the benzyl group by benzylic oxidation were also in vain. Benzylic bromination and Polonovsky type oxidation were not successful; reaction with lead tetraacetate resulted in primarily oxidation of the indoline ring to the indole. Reaction of 8b with acetyl bromide (Staedel reaction) led to primarily the ring-opened product; with cyanogen bromide, the debenzylated N-cyano compound was obtained as the major product, albeit in poor yield.

The initial goal undertaken was the synthesis of N-allyl benzodipyrrole 12. It was felt that this compound might prove more amenable to deprotection than the N-benzyl compound. The study of the methylation of 12 and its derivatives, and the oxidation of the 5-position, were the

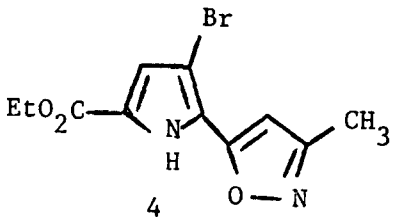
planned objects of subsequent study.



12

II.2. Synthesis of Ethyl 5-Acetyl-6-allyl-4-hydroxy-3,6,7,8-tetrahydrobenzo[1,2-b:4,3-b']dipyrrole-2-carboxylate

Trisubstituted pyrrole 4 was synthesized in multigram quantities by the method of Pearce[25]. 1-Allylpyrrolidin-2,3-dione was prepared by the method described by Sundberg, Pearce and Laurino[27]. Hydrolysis and decarboxylation of 13



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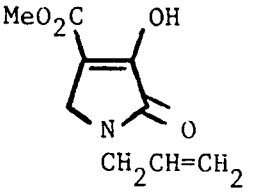

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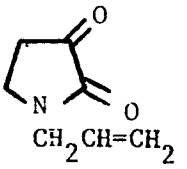
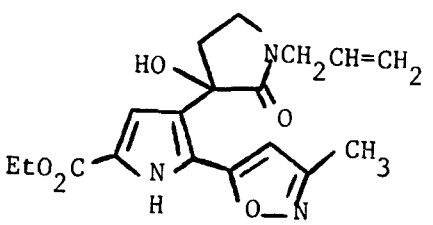


14

in 10% HCl provided 14 along with unreacted 13. It was

necessary to distill 14 from the product mixture in order to obtain material for use in the subsequent organometallic reaction. Kugelrohr distillation of the dione under vaccuum using a mercury diffusion pump (ca. 0.01mm Hg) at 170°C in the presence of 5 mol% of terephthalic acid routinely provided dione 14 as a light yellow oil in 2-3 gram quantities.

Addition of a THF solution of dione 14 to a solution of the 4-lithio-1-sodio dianion of 4 in THF at -98°C provided the key intermediate adduct 15 in typical yields of 50-54%. Along with alcohol 15, debrominated pyrrole 3 was recovered in these reactions and resulted in good overall mass balance. Compound 3 could then be recycled to provide more bromo compound 4, making the overall process quite efficient. Alcohol 15 was obtained as a snow-white crystalline compound, mp 174°C. This compound was unambiguously characterized by NMR and mass spectrometry as



15

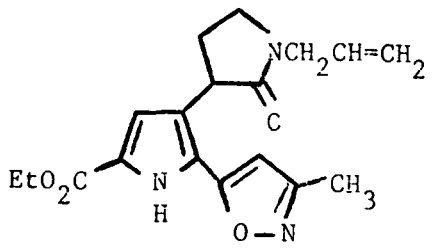
well as elemental analysis. The NMR spectrum (δ 1.40, t, 3H; 2.25, s, 3H; 2.35-2.50, m, 2H; 3.40, d of m, 2H; 4.00-

4.20, AB q, 2H; 4.35, q, 2H; 5.36, m, 2H; 5.90, m, 1H; 6.55, s, 1H, 6.74, d, 1H) was in full accord with expectations. The mass spectrum confirmed the correct formula weight of 359 for compound 15.

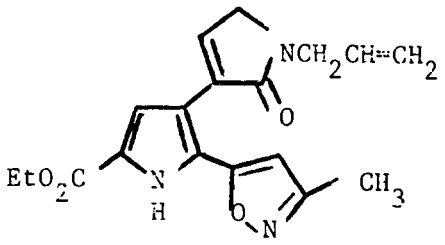
With alcohol 15 in hand, immediate attention was focused on the necessity of reducing the alcohol to the hydrocarbon. The triethylsilane / trifluoroacetic acid procedure for benzylic alcohols[30] was considered promising. Treatment of a vigorously stirred solution of alcohol 15 in trifluoroacetic acid at room temperature with several aliquots of triethylsilane over a two hour period, followed by workup and chromatography, delivered a solid material whose NMR and mass spectra showed it to be almost entirely pure deoxy compound 16. The mass spectrum showed the molecular ion to be 343, corresponding to 16. (NMR: δ 1.37, t, 3H; 2.15, m, 1H; 2.32, s, 3H; 2.55, m, 1H; 3.50, m, 2H; 3.90-4.10, m, 3H; 4.35, q, 2H; 5.25, m, 2H; 5.80, m, 1H; 6.45, s, 1H; 6.80, d, 1H; 9.65, broad, 1H).

In various runs, differing amounts of the dehydration product 17 were also obtained, accounting for 1-20% of the product mixture. Compound 17 was synthesized separately by dehydration of 16 in HCl, and characterized by NMR and mass spectrometry. In addition to the molecular weight indicated by the mass spectrum (341), 17 was identified by the absence of the pyrrolidine methylene and methine multiplets, and the appearance of a triplet at 7.20 (1H)

for the vinyl proton and a sharp doublet at 4.05 ppm for the methylene protons adjacent to nitrogen. The allyl methylene signals also appeared as a doublet, having lost the additional complexity due to the chiral center. Compounds 16 and 17 could not be readily resolved



16

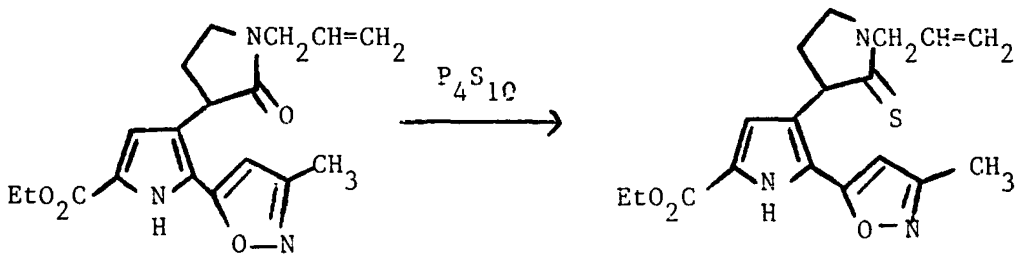


17

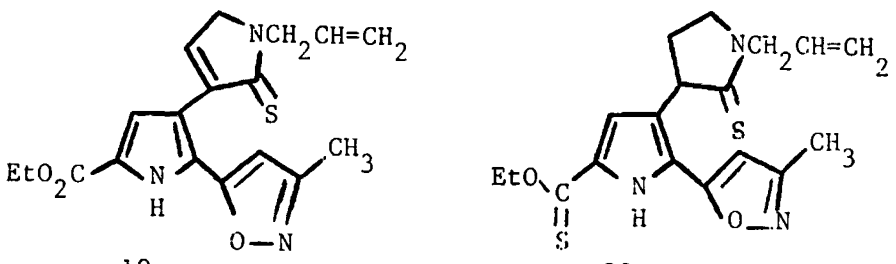
by preparative scale chromatography. It was found that the two could be readily separated after the thionation reaction to form the respective thiolactams. Mass balances were consistently high in the reductive deoxygenations (>98%) and the percentage of deoxy compound 16 in the product mixture was usually quite high (typically 90%).

Treatment of the product from the reduction reaction with tetraphosphorus decasulfide in refluxing toluene led to rapid disappearance of the starting material and formation of the desired thiolactam. Three products were isolated in these reactions. Thiolactam 18 was isolated as the major product in 68% yield. The overall yield of

thiolactam 18 for the two steps from alcohol 15 was typically 60-65%. Thiolactam 18 was obtained as a white crystalline compound, mp 149-150°C, and was fully characterized by NMR, mass spectrometry and elemental analysis (NMR: δ 1.35, t, 3H; 1.90-2.60, m, 2H; 2.30, s, 3H; 3.60, m, 2H; 4.10-4.60, m, 5H; 5.25, m, 2H; 5.90, m, 1H; 6.40, s, 1H; 6.70, d, 1H; 9.70, broad, 1H). Trace amounts



16 18

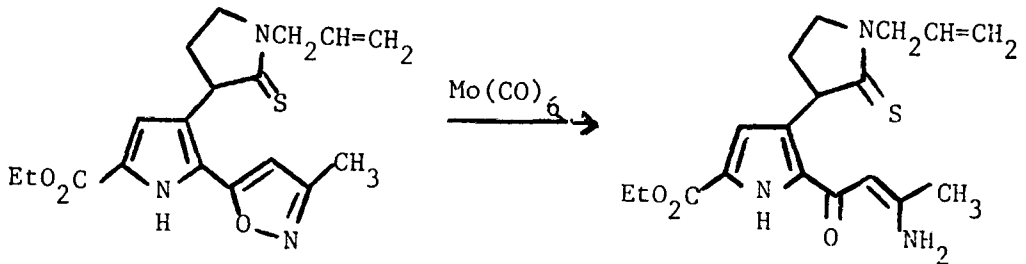


19 20

of two less polar compounds were also isolated off the column. One, a highly fluorescent compound under UV, was assigned structure 19 on the basis of NMR and mass spectral data. The NMR spectrum indicates a compound of the type of 17 but with slight variations in chemical shift (NMR: δ 1.40, t, 3H; 2.28, s, 3H; 4.35, q plus d, 4H; 5.22, m, 2H; 6.00, m, 1H; 6.35, s, 1H; 6.68, t, 1H; 6.91, d, 1H; 9.10, broad, 1H). The mass spectrum indicated the incorporation of sulfur. Compound 19 is evidently a byproduct arising from the olefin 17 carried over from the deoxygenation process. The other component was characterized only by mass spectrometry, as only very small amounts were obtained. The molecular ion, 375, indicated that two sulfur atoms were incorporated into the compound, and structure 20 was postulated as the most reasonable. Pearce reported finding trace amounts of the corresponding N-benzyl thioester in his work.

It remained to convert the isoxazole of 18 to the dioxobutyl side chain necessary for the aldol condensation. Pearce had found that molybdenum hexacarbonyl served to reductively cleave the isoxazole moiety to the corresponding enaminone in the benzyl series. There was no interference due to reduction of the thioamide functionality. In the case of thiolactam 18, treatment with 0.5 eq of molybdenum hexacarbonyl in refluxing moist acetonitrile delivered, after chromato-graphy, enaminone 21

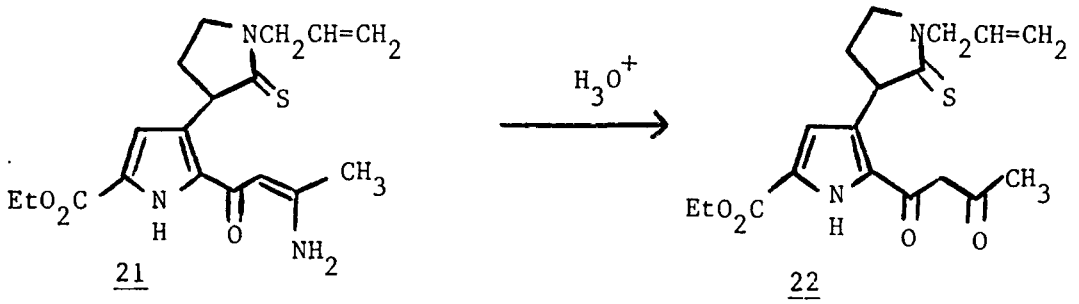
in good yield. Compound 21 was always obtained as an oil and was characterized by NMR spectroscopy. (NMR: δ 1.35, t, 3H; 2.05, s, 3H; 2.00-2.15, m, 1H; 2.60, m, 1H; 3.65-3.80, m, 2H; 4.30, q, 2H; 4.40-4.55, AB m, 2H; 4.80, t, 2H; 5.35, m, 2H; 5.57, s, 1H; 5.90, m, 1H; 6.70, d, 1H; 9.55, broad, 1H.)



18 21

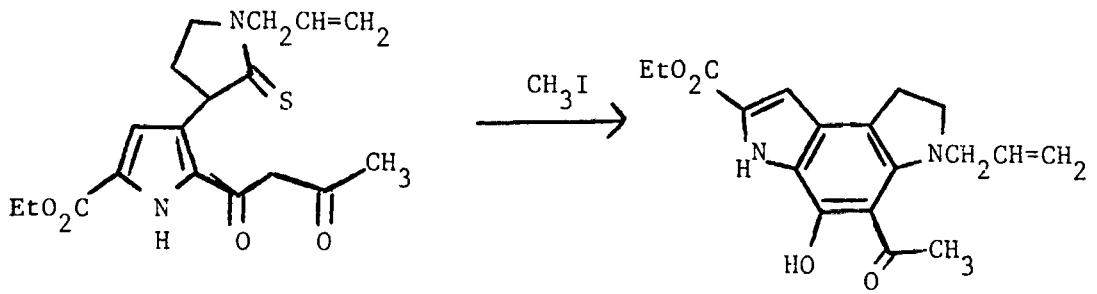
Acidic hydrolysis of 21 under mild conditions led, as expected, to an excellent yield of β-dicarbonyl compound 22. This key compound was obtained as off-white crystals, mp 144-145^{0}C, and was characterized by NMR, mass spectrometry, and elemental analysis (NMR: 1.37, t, 3H; 2.10, m, 1H; 2.18, s, 3H; 2.60, m, 1H; 3.70-3.85, m, 2H; 4.35, q, 2H; 4.40-4.60, AB m, 2H; 4.70, t, 1H; 5.35, m, 2H; 5.90, m, 2H; 6.05, s, 1H; 6.77, d, 1H; 9.58, broad, 1H).

Heating thiolactam 22 in a sealed tube with excess methyl iodide led, as in the case of the benzyl compound, to a nearly quantitative yield of N-allyl benzodipyrrole 12 as a bright orange-yellow crystalline compound.



21 22

Benzodipyrrole 12 was characterized by NMR and mass spectrometry. The NMR spectrum was perfectly in accord



22 12

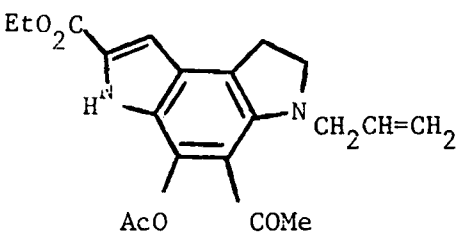
with expectations (NMR: δ 1.40, t, 3H; 2.80, s, 3H; 3.07, t, 2H; 3.44, d, 2H; 3.57, t, 2H; 4.42, q, 2H; 5.19-5.39, m, 2H; 5.90, m, 1H; 6.95, d, 1H; 9.25, broad, 1H). The pyrrolidine ring protons were clear triplets at 3.07 and

3.57 ppm, and the allyl methylene had become the expected doublet at 3.44 ppm. These features of the spectrum are con-sistent with the achiral nature of 12.

Treatment of compound 12 with acetic anhydride and dimethylaminopyridine furnished the acetate 23 in excellent yield. Acetate 23 was obtained as an oil which was not successfully crystallized. Compound 23 was well characterized by NMR and mass spectrometry, however. Conversion of phenol 12 to the acetate was confirmed by a gain of 42 amu in the mass spectrum and the appearance of a methyl singlet at 2.37 in the NMR (NMR: δ 1.42, t, 3H; 2.37, s, 3H; 2.58, s, 3H; 3.20, t, 2H; 3.45-3.60, m, 4H; 4.40, q, 2H; 5.10-5.30, m, 2H; 5.85, m, 1H; 7.00, d, 1H; 8.67, broad, 1H).

Two minor side products were occasionally isolated from chromatography of the acetate. These are apparently derived from byproducts arising in the cyclizations. The fully aromatized indole 24, characterized as the acetate 25, was obtained in some acetylation reactions (NMR: δ 1.42, t, 3H; 2.40, s, 3H; 2.60, s, 3H; 4.42, q, 2H; 4.67, m, 2H; 4.80-5.20, m, 2H; 5.80-5.95, m, 1H; 6.80, d, 1H; 7.15, d, 1H; 7.45, d, 1H; 8.80, broad, 1H). A somewhat more interesting compound was isolated on several occasions isolated by chromatography of acetylation product 23. This compound, slightly more polar than 23, was assigned structure 26 on the basis of NMR and mass spectrometry

(NMR: δ 1.40, t, 3H; 2.39, s, 3H; 2.59, s, 3H; 2.69, s, 3H; 3.17, t, 2H; 3.50, t, 2H; 4.40, q, 2H; 7.00, d, 1H; 8.66, broad, 1H). The NMR spectrum of this by-product lacked any



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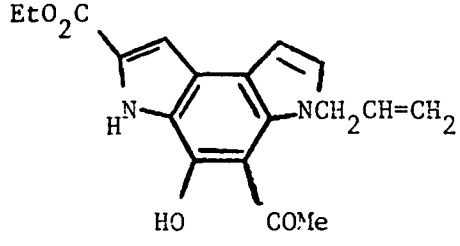

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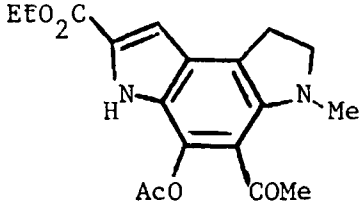

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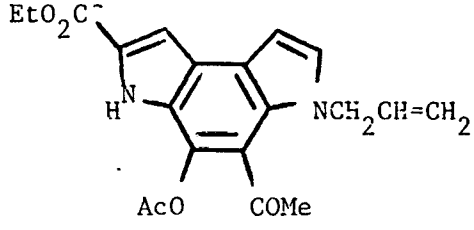


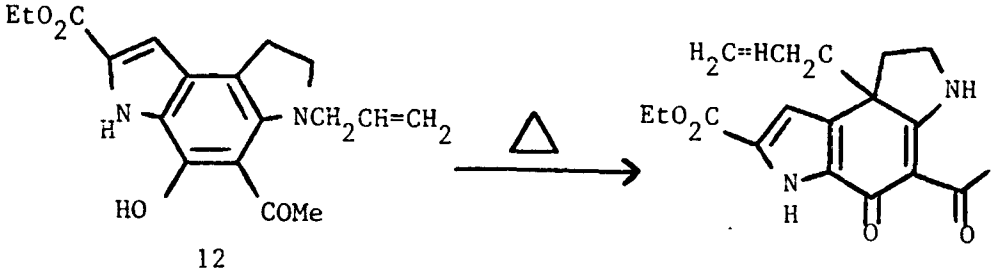
25

signals from the allyl group. A methyl singlet at 2.69 ppm was reasonable for a methyl substituted aniline type compound. Mass spectrometry confirmed that the formula weight of the compound was 344, correct for structure 26. Compound 26 presumably arises from a small amount of deallylation of 12 by methyl iodide by a mechanism analogous to that of the von Braun reaction. It was found

that keeping the quantity of methyl iodide used to 2-3 equivalents minimized the formation of 26.

II.3. Synthesis and Chemistry of Pyrroloindolone 27

When a solution of N-allyl benzodipyrrole 12 in ethanol is thermolyzed at 80°C in a sealed glass tube, a conversion to the considerably more polar enone compound 27 takes place. This conversion may also be effected, in lesser yield, by stirring 12 with base at room temperature for a prolonged period to deliver 27 along with unchanged 12. Compound 27 may be formulated as the product of a N→C Claisen rearrangement of the allyl group. Rearrangement product 27 is an extremely stable rather high-melting (208-210°C) crystalline compound which was characterized by NMR, elemental analysis and mass spectrometry.



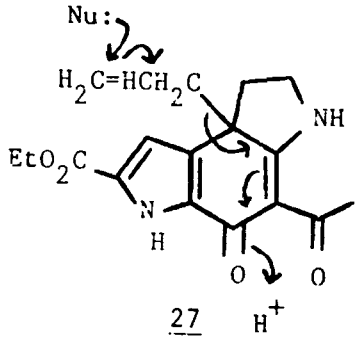
12 27

The enone structure 27 was assigned after considering all of the data. The most striking feature of the NMR spectrum of 27 is the non-equivalence of the pyrrolidine ring protons. A set of four complex multiplets has replaced the pair of triplets which is characteristic of the planar achiral benzodipyrrole12. Nontheless, the compound does not have the appearance of a ring-opened structure, and there is no signal attributable to a bridgehead proton. In addition, the methylene signal from the allyl group is no longer a doublet but has become an AB system, indicating the presence of a chiral center in the molecule. These protons are found to be shifted considerably upfield in this compound, to a chemical shift of 2.40 ppm, indicating that the methylene carbon is no longer bonded to a heteroatom. Both the mass spectrum and elemental analysis establish that the thermolysis product 27 has the same molecular weight as the starting material and is thus an isomer of 12. Structure 27 is the only logical possibility which fits the data. Sigmatropic rearrangement of 12 would result in migration of the allyl group to the bridgehead (8a) position, generating the observed chiral center. The upfield shift in the allyl methylene protons would be expected to result since this carbon is no longer bonded to nitrogen. It should be pointed out that the Claisen rearrangement here is normal enough except that it leads to dearomatization. The stability of the highly substituted

vinylogous amide structure of 27 must account for the facile formation of this compound.

Compound 27 was also detected as a minor by-product (<5%) from the cyclization of 22 to 12. In later experiments involving attempted methylation of 12, rearrangement compound 27 and its N-methylated derivative 28 were frequently encountered.

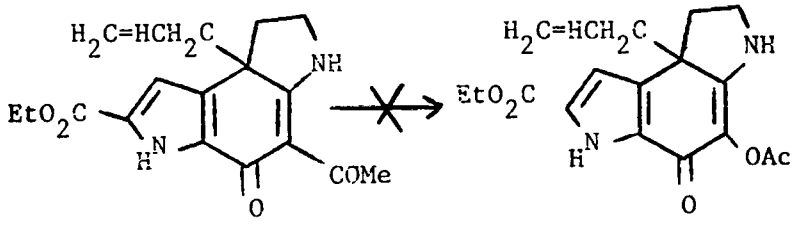
Enone 27 proved to be an extremely stable compound and was inert to all attempts to convert it to useful intermediates. It was thought that 27 might be susceptible to deallylation by appropriate nucleophiles as shown below.



27

Reaction with a buffered mixture of thiophenoxide and thiophenol in ethanol was attempted several times, with no success; only unchanged starting material was recovered. Likewise, attempted deallylation with palladium(II), under the same conditions as described in the next section for

the N-deallylation of 23, returned only enone 27. Attempts to achieve Baeyer-Villager type oxidation of 27 to acetate 29 delivered only starting material.



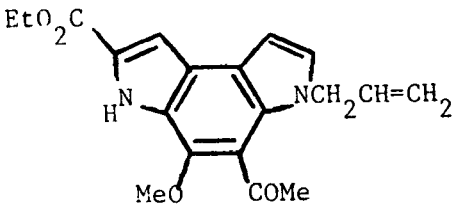
29

II.4. Attempts to O-Methylate N-Allyl Benzodipyrrole 12

With the acquisition of N-allyl benzodipyrole 12 in good yield, attention was turned towards the study of the methylation of the phenolic moiety. While the acetate 23 was readily available in high yield, the ortho-acetyl phenol proved to be extremely resistant to O-methylation. This lack of reactivity is characteristic of tightly hydrogen bonded o-acetyl phenols[31]. A variety of methylating techniques were investigated; ultimately, it did not prove possible to satisfactorily O-methylate the N-alkyl benzodipyrroles. As will be discussed in section II.6., this problem was finally solved after successful dealkylation of the indoline nitrogen and subsequent conversion to the amide had been accomplished.

Treatment of a methanolic solution of 12 with ethereal diazomethane led to recovery of products in rather low

(50%) mass balance. The majority of the material obtained consisted of rearrangement compound 27 and its N-methylated derivative 28. A small amount of the aromatized methoxy compound 30 was obtained; this compound was well characterized by NMR and mass spectrometry (NMR: δ 1.45, t, 3H; 2.75, s, 3H; 3.95, s, 3H; 4.45, q, 2H; 4.68, m, 2H; 4.75, d, 1H; 5.10, d, 1H; 5.90, m, 1H; 6.75, d, 1H; 7.10, d, 1H; 7.43, t, 1H; 9.05, broad, 1H). The formula weight was in accordance with structure 30 and the presence of a methyl singlet at 3.95 ppm confirmed that O-methylation had occurred. The lack of pyrrolidine methylene signals and the appearance of three indole signals verified that oxidation to the indole had occurred, as indicated by the mass spectrum.



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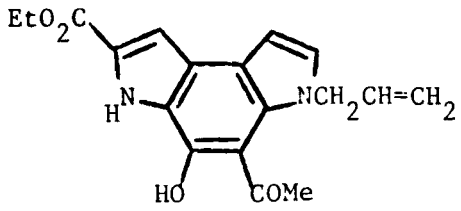
Treatment of 12 with diazomethane in methylene chloride at -78^{0}C led to no methylation product of any kind and a high recovery of unchanged starting material. Pre-treatment of 12 with boron trifluoride-etherate, in hopes

of activating the phenol, followed by ethereal diazomethane, also resulted in no methylation product. The primary product recovered in this reaction was simply the aromatized phenol 24, as characterized by NMR (NMR: 1.43, t, 3H; 2.60, s, 3H; 4.40, q, 2H; 5.20-5.33, m, 2H; 5.80, m, 1H; 6.80, d, 1H; 7.05, d, 1H; 7.32, d, 1H; 9.39, broad).

Next, the methylation of the phenoxide anion of 12 was investigated. It was hoped that the careful addition of one equivalent of an appropriate base would allow selective alkylation of the phenol over the indole nitrogen. Treatment of 12 with one equivalent of potassium tert-butoxide and methyl iodide led to the isolation of material, in poor mass balance, that was primarily 30. An additional methyl singlet at 4.38 in the NMR and a peak at 354 in the mass spectrum indicated the presence of a minor amount of the dimethylated compound 31. Additionally, a small amount of compound was 28 was isolated from the product mixture. This product was characterized by NMR and mass spectrometry and found to be identical to rearrangement compound 27 with the addition of a methyl group on the indole nitrogen (NMR: δ 1.40, t, 3H; 2.15, m, 1H; 2.35, m, 2H; 2.50, m, 1H; 2.65, s, 3H; 3.80, m, 2H; 4.30, q, 2H; 4.35, s, 3H; 4.95-5.15, m, 2H; 5.60, m, 1H; 6.75, s, 1H). The use of methyl sulfate as the alkylating agent in this reaction led to similar products and yields. Use of sodium hydride as the base, with methyl iodide as

the electrophile, led to 27 as the major product. A mixture of compounds 24 and 30 was also recovered in low yield.



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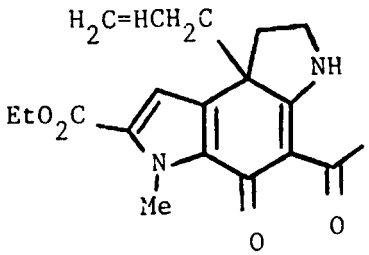

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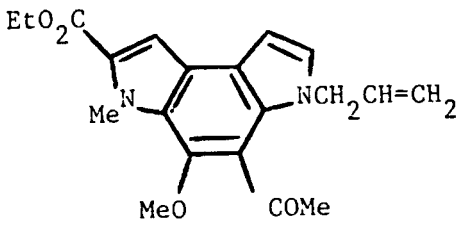
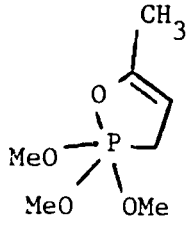


31

Phase transfer conditions for the methylation of phenols were also tried on compound 12[32]. Typically, 12 was stirred in a two-phase mixture (methylene chloride and water) containing a base (sodium or potassium carbonate), a phase transfer catalyst (tetrabutylammonium hydroxide) and an alkylating agent (methyl sulfate). Consistently poor mass balances were obtained from these reactions. Products consisted of O,N-dimethylated compound 31 (well characterized by NMR and mass spectrometry) (NMR: δ 1.45, t, 3H; 2.75, s, 3H; 3.85, s, 3H; 4.38, s, 3H; 4.40, q, 2H;

4.68, m, 2H; 5.10-5.20, m, 2H; 5.90, m, 1H; 6.75, d, 1H; 7.07, d, 1H; 7.50, s, 1H) and N-methylated rearrangement compound 28.

Cyclic oxaphospholene 33[33] was briefly investigated as a potential O-alkykating agent. In the case of compound 12, this reagent gave only methylation on the indole nitrogen. Treatment of 12 with the oxaphospholene 33 in THF delivered a mixture of N-methylated compound 32 (NMR: 1.42, t, 3H; 2.80, s, 3H; 3.05, t, 2H; 3.40, d, 2H; 3.55, t, 2H; 4.40, q, 2H; 4.43, s, 3H; 5.15-5.35, m, 2H; 5.87, m, 1H; 6.95, s, 1H) and the N-methylated rearrangement compound 28.



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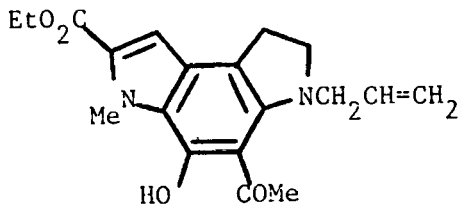
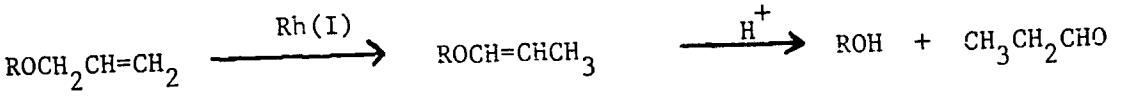


32

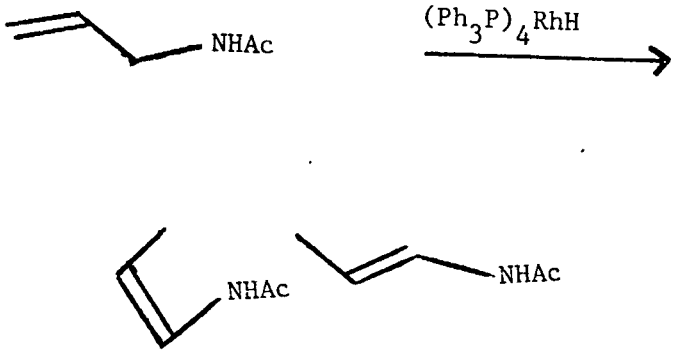
II.5. Studies on the Dealkylation of N-Allyl Benzodipyrroles

As noted previously, the synthesis of the N-allyl benzodipyrroles was originally undertaken in hopes of finding dealkylation procedures superior to those attempted on the N-benzyl compound. Several methods have appeared in the literature for the deallylation or transformation of

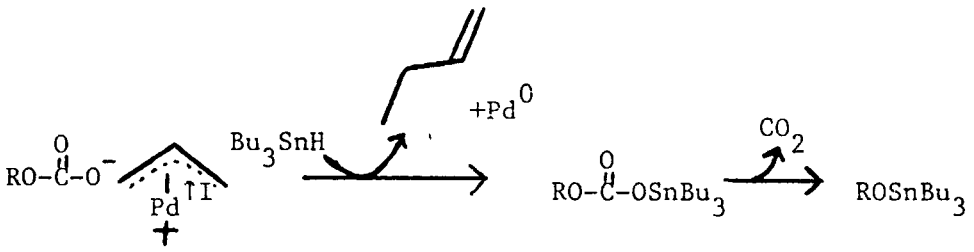
allyl amines, amides and related structures. The utilization of transistion metal catalysts to effect double bond migration has provided the basis for several of these procedures. Moreau and colleagues found that treatment of diphenyl allylamine with Wilkinson's catalyst in moist ethanol gave a quantitative yield of diphenylamine[26a]. This product presumably arises from aqueous hydrolysis of the intermediate enamine. In a related type of chemistry, Corey used the rhodium(I) catalyzed isomerization of allyl ethers to the corresponding enol ethers as a means for



selectively converting allyl ethers to alcohols[26d]. Stille has published a procedure for the isomerization of N-allylamides and imides to enamides by complexes containing iron, ruthenium or rhodium[26b]. In a typical example, isomerization of N-allyl acetamide by tetrakis (triphenylphosphine)rhodium hydride afforded the enamide in 80% yield as a mixture of cis and trans isomers, with the cis isomer predominating. Use of a molybdenum complex for the isomerization of allyl amines to enamines has also been reported[26c].



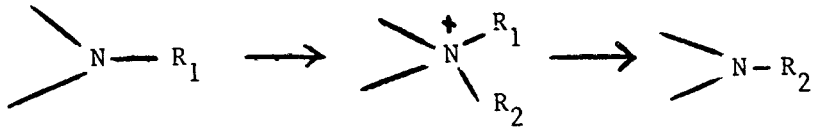
Guibe has described a method for the selective deprotection of allyl and allyloxycarbonyl derivatives of acids and amino acids based on generation of the



corresponding π-allyl palladium complexes[34]. Benzyl allyl carbonate was found to be quantitatively converted to benzyl alcohol when treated with a catalytic amount of Pd(0) followed by tributyltin hydride and subsequent acid hydrolysis. It is likely that this reaction proceeds by way of oxidative addition of palladium(0) to the allylic moiety to generate the π-allyl complex. Reduction by tin hydride

regenerates the zero-valent palladium and forms the intermediate tin ester, which upon loss of CO_2 and acid hydrolysis furnishes the observed alcohol product. In more recent work Guibe has used the air stable palladium(II) dichloro-bis-triphenylphosphine with equivalent results[35]. Allyloxycarbonylbenzylamine was converted to benzylamine by this methodology in nearly quantitative yield.

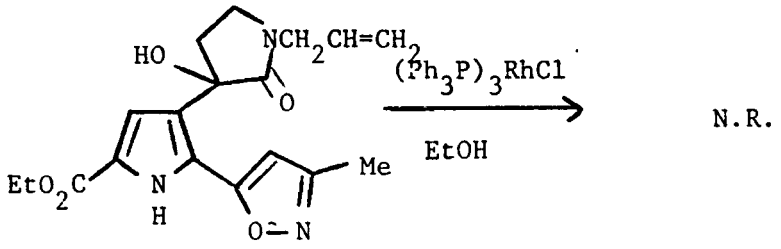
Several deprotection procedures of the type depicted below have been successfully used with allyl amines.



Charles and Kapnang studied the reaction of various chloroformates with tertiary amines, assaying the competition between the alternate pathways of deamination, N-demethylation and dealkylation[36]. N-debenzylation and -deallylation were generally preferred, particularly with the reagents vinyl chloroformate and 2,2,2-trichloroethyl chloroformate. More recently, the reagent ∝-chloroethyl chloroformate has been reported to give good results in the selective dealkylation of tertiary amines[37].

The use of rhodium reagents for the deallylation of potential intermediates for benzodipyrrole synthesis was

briefly investigated by Laurino[28]. Treatment of either of the pyrrolidinols 34 or 35 with rhodium trichloride or Wilkinson's catalyst returned only unchanged starting



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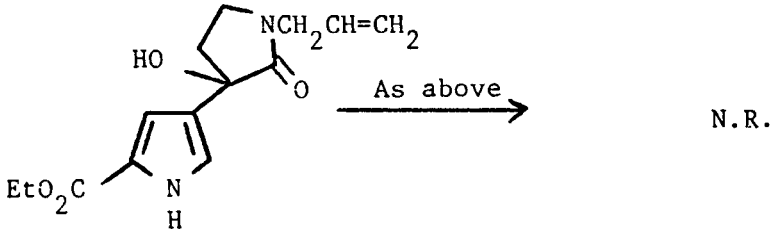
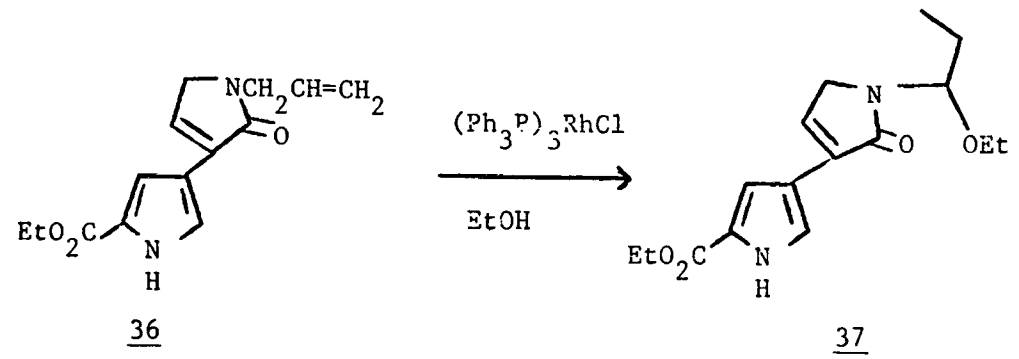


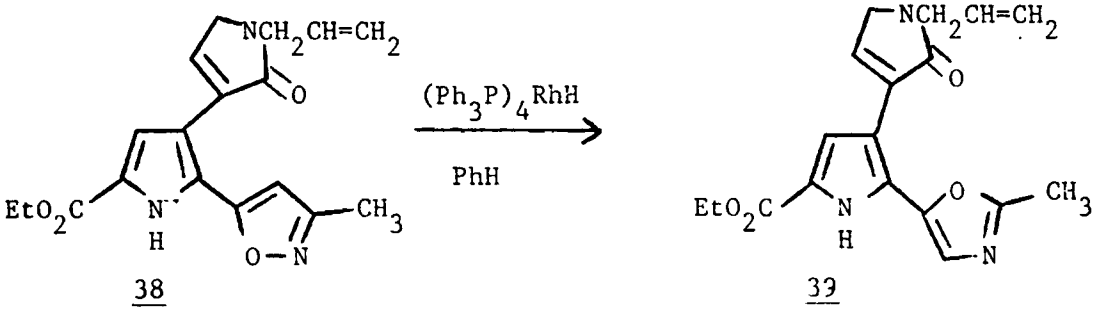
35

material in good recovery. It may be that coordination of the rhodium atom to the hydroxyl function impedes the isomerization of the allyl group. Treatment of the enone 36, prepared by dehydration of 35, with Wilkinson's catalyst in ethanol led to the ethoxy propyl derivative 37. This product presumably arises from solvolysis of the initial isomerization product. Treatment of this

ethoxypropyl compound with methanolic HCl produced the corresponding methyl ether; aqueous acid provided the



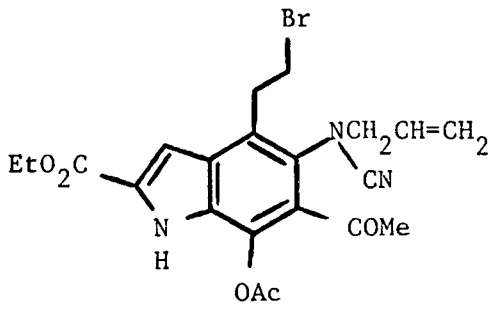
36 37



38 39

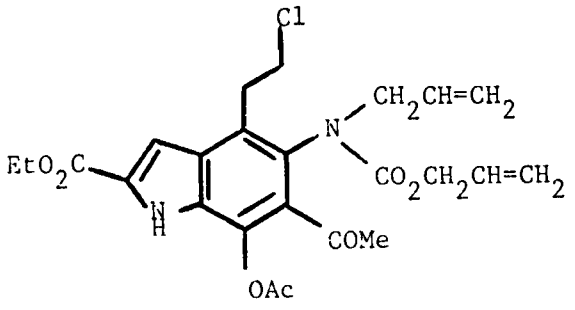
deallylated compound. Reaction of Wilkinson's catalyst with the corresponding isoxazolyl dehydro compound 38, however, produced only compound 39. This material was identical to starting material except that the isoxazole ring had rearranged to the oxazole. No products from reaction of the allyl group were found in this case. It was subsequently shown that the isomerization of 38 to 39 is a purely thermal process.

With this background of dealkylation methods the deprotection of compound 23 was examined. N-allyl benzodipyrrole 23 was reacted with cyanogen bromide in a manner identical to that followed for the N-benzyl compound. Heating 23 in a sealed tube with several equivalents of CNBr in dichloroethane at 92°C for three hours led to a large amount of complex unidentifiable material. Also isolated was a compound whose NMR and mass spectrum indicated it to be the ring-opened product 40. The NMR had some unusual broadening but the main features and chemical shifts could be accomodated quite well to structure 40 (NMR: 1.42, t, 3H; 2.42, s, 3H; 2.67, s, 3H; 3.57, m, 2H?; 3.70-4.00, m, 4H?; 4.45, q, 2H; 5.40, d of m, 2H; 6.00, m, 1H; 7.30, d, 1H; 9.13, broad, 1H). The reason for the complexity in the signals for the alkyl chain methylene protons is unclear. The mass spectrum showed the expected bromine isotope effect and gave the correct molecular weight (477/475) for structure 40.



40

A cleaner reaction was achieved using vinyl chloroformate. Unfortunately, the product was again the result of ring-opening rather than deallylation. The mass spectrum of this product exhibited an isotope pattern expected for the presence of a single chlorine atom in the structure, and indicated the correct formula weight for structure 41 (476).



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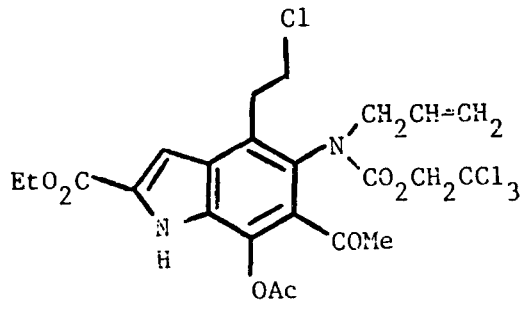
The NMR was cleaner than that for the product of the cyanogen bromide reaction, and was in accord with expectations for 41 (NMR: δ1.45, t, 3H; 2.40, s, 3H; 2.42, s, 3H; 3.20-3.30, m, 2H; 3.68, m, 2H; 3.80, m, 2H; 4.40-4.50, q plus m, 4H total; 4.60, m, 1H; 5.15, m, 2H; 5.85-6.00, m, 1H; 7.30, d, 1H; 9.13, broad, 1H). The presence of two terminal double bonds in the product was clearly seen from the number and multiplicity of vinyl protons in the NMR. In addition, the side chain methylenes were well resolved and integrated multiplets.

The reagent 2,2,2-trichloroethyl chloroformate gave the cleanest and highest-yielding reaction; unfortunately,

it was the ring-opened material 42 that was produced in



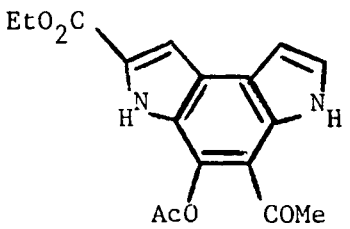
42

good yield as the sole product. This nicely crystalline compound was characterized by NMR and mass spectrometry. The presence of four chlorine atoms in the structure of product 42 was strikingly conveyed by the isotope pattern in the mass spectrum. The quite clean NMR was again in accordance with the assigned structure of this compound (NMR: δ 1.43, t, 3H; 2.40, s, 3H; 2.48, s, 3H; 3.20-3.40, m, 2H; 3.55-3.85, m, 2H; 4.45, q, 2H; 4.80, s, 2H; 5.13, m, 2H; 6.00, m, 1H; 7.30, d, 1H; 9.30, broad, 1H).

It is apparent from these results that ring-opening is favored over deallylation in reaction of 23 with electrophilic reagents. It may be that a steric effect hindering the attainment of the transistion state for dealkylation is partly responsible. The yields of ring-opened products are higher with the more sterically demanding chloroformate reagents.

The use of the rhodium induced isomerization of the

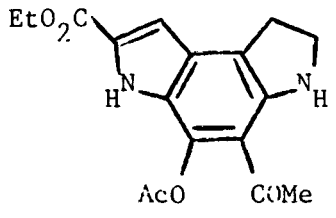
allyl group was therefore explored. Heating acetate 23 in ethanol with tris(triphenylphosphine)rhodium chloride (Wilkinson's catalyst) did not produce any ethoxypropyl compound but gave, in addition to aromatized starting material, deallylated oxidized compound 43 in poor yield. The structure of 43 is readily deduced from the NMR spectrum, which shows loss of the allyl group and the replacement of the pyrrolidine ring triplets with two new indole signals. The appearance of these signals as triplets at 6.77 and 7.35 ppm is indicative of their coupling to an indole -NH. (NMR: δ 1.42, t, 3H; 2.55, s, 3H; 2.74, s, 3H; 4.42, q, 2H; 6.77, t, 1H; 7.35, t, 1H; 7.44, d, 1H; 8.97, broad, 1H.)



43

Reaction of 23 with tetrakis(triphenylphosphine) rhodium hydride under identical conditions (ethanol, sealed tube, 100^{0}C for three hours) furnished, after chromatography, three products. Rearrangement product 27 was isolated in low (10-15%) yield in several runs. This

product presumably arises from solvolysis of the O-acetyl group and subsequent thermal rearrangement. Two deallylated products were also obtained. The desired indoline 44 was obtained in varying amounts (typically 25%). This compound was characterized initially by NMR. The spectrum of this product, a reddish colored compound, showed loss of all signals from the allyl group, and the triplets at 3.18 and

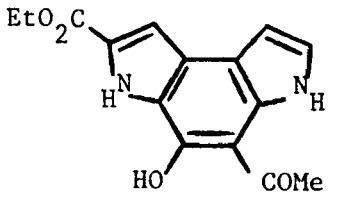


44

3.75 ppm were clearly indicative of the indoline structure 44 (NMR: 1.42, t, 3H; 2.50, s, 3H; 2.55, s, 3H; 3.18, t, 2H; 3.75, t, 2H; 4.40, q, 2H; 6.80. d, 1H; 8.40, broad, 1H). In addition to 44, the aromatized dealkylated compounds 43 and 45 were isolated in larger amount. Most often 45, without the acetyl group on oxygen, was isolated. This compound was well characterized by NMR and mass spectrometry (H NMR: δ 1.42, t, 3H; 2.86, s, 3H; 4.43, q, 2H; 6.80, d, 1H; 7.17, d, 1H; 7.35, d, 1H; 8.40, broad, 1H. EI MS: m/z 286, 240, 212).

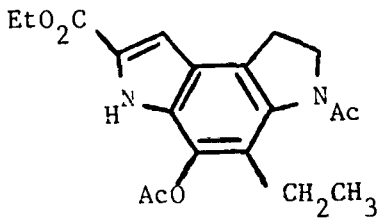
An experiment with the reduction of deallylated indole

43 to the indoline 44 led instead to the 5-ethyl



45

benzodipyrrole 46. Treatment of 43 in trifluoroacetic acid with triethysilane followed by acetylation of the crude pro-duct furnished compound 46, characterized by NMR and mass spectrometry (NMR: δ 1.15, t, 3H; 1.40, t, 3H; 2.30, broad s, 3H; 2.45, s, 3H; 2.75, q, 2H; 3.20, t, 2H; 4.40, q, 2H; 7.10, d, 1H; 8.60, broad, 1H).



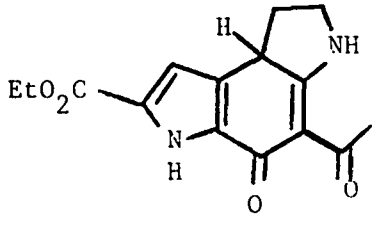
46

Numerous deallylation runs with varying amounts of rhodium catalyst and different reaction times were employed, but general mixtures of dealkylated products were obtained in erratic and generally rather low yield.

It seemed reasonable that protonation of the pyrrolidine nitrogen would furnish a better leaving group for the deallylation process. It would be expected that this nitrogen should be the most basic site in the molecule and that treatment of 23 with one equivalent of acid should result in complete protonation at this site. Accordingly, treatment of 23 in ethanol with one equivalent of trifluoroacetic acid in ethanol, followed by addition of 0.25 equivalent of the rhodium hydride and heating to reflux for 90 minutes, resulted in conversion of 23 to the bright red indoline 44 as observed by TLC. After workup and purification, indoline 44, identical to previous samples, was obtained in good yield. This compound was well characterized by NMR and mass spectrometry. The deallylation procedure described proved quite amenable to scale-up and made indoline 44 routinely available in acceptable (70%) yield.

The use of π-allyl palladium intermediates for the deallylation of 44 was also investigated, with results that were interesting though somewhat unexpected. The stable complex bis(triphenylphosphine)palladium(II) chloride was used in catalytic amounts (5-10 mol%) in conjunction with tri-n-butyltin hydride as a reducing agent. Moist dichloromethane was found to be the most reliable solvent/proton donor combination. The initial experiments were carried out on phenol 12. Treatment of this compound

with the palladium complex and 1.2 equivalents of butyltin hydride, followed by hydrolytic acidic workup, delivered three products, isolated after chromatographic purification. Previously characterized compounds 45 and 27 were present in the reaction mixture in small amount. The main product was a compound whose NMR was.

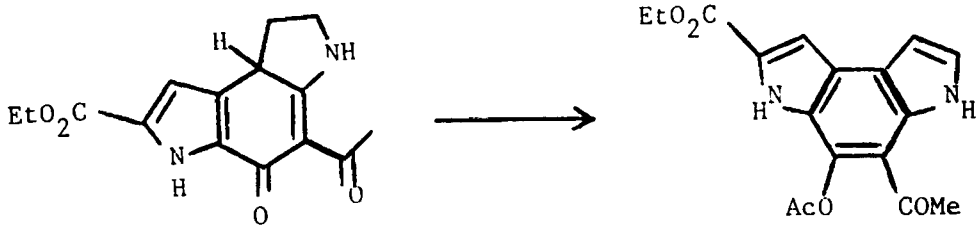


47

unusually complex (NMR: 1.40, t, 3H; 1.95-2.10, m, 1H; 2.68, s, 3H; 2.70-2.80, m, 1H; 3.75-3.82, m, 1H; 3.85-3.95, m, 1H; 3.98-4.05, m, 1H; 4.35, q, 2H; 6.83, d, 1H; 9.75, broad, 1H). The appearance of the pyrrolidine ring protons as AB multiplets in compound 47 was strongly reminiscent of compound 27. In addition, a fifth multiplet at 4.03 ppm seemed plausible for the bridgehead proton in structure 47. This proton was found to be coupled to the adjacent pyrrolidine methylene protons by coupling constants of 7 and 14 Hz. In addition to this coupling, the pyrrolidine signals exhibited geminal and vicinal couplings similar to those in 27.

The surprising appearance of enone tautomer 47 as the

product in this reaction is perhaps indicative of the unusual stability of its highly substituted indolone structure. It may be that the formation of the π-allyl palladium complex provides a low-energy pathway for the rearrangement to the enone tautomer of the deallylated product. The palladium reaction proved to be quite capricious and gave widely varying yields and product ratios from run to run. It was not possible to obtain reliably quantities of 47. Several experiments aimed at elucidating the chemistry of 47 were inconclusive. Attempted reaction with methyl triflate, in hopes of effecting O-methylation and concomitant rearrangement to the indole to pro-vide the methoxy compound, returned only unchanged starting material. Reaction of 47 with acetic



47 43

anhydride and DMAP, on the other hand, led to a clean high yielding conversion to a compound that appeared to be a fully aromatized structure. This product was characterized by NMR and assigned the structure 43. This compound was

identical to the previously obtained and characterized 43. (NMR: δ 1.45, t, 3H; 2.55, s, 3H; 2.75, s, 3H; 4.45, q, 2H; 6.80, t, 1H; 7.35, t, 1H; 7.45, d, 1H; 8.90, broad, 1H).

It was clearly of interest to see what the reaction product would be from treatment of acetate 23 with the palladium(II)/tin hydride system. The presence of the acetate functionality would be expected to preclude formation of the enone tautomer. It might therefore be expected to obtain deallylated compound 44. Indeed, subjection of compound 23 to the same conditions used for 12 did result in the formation of 44 in addition to recovery of lesser amounts of starting material and rearrangement product 27. Unfortunately, the maximum yield of 44 was 44%, and the reaction again proved unreliable, often giving poor yields. The procedure developed using trifluoroacetic acid and the rhodium hydride reagent, described previously, proved to be the most efficient and reliable method found for the conversion of 23 to 44.

Phenol 12 was reacted with trifluoroacetic acid and tetrakis(triphenylphosphine)rhodium hydride in hopes of obtaining enone 47 more reliably. Unfortunately, while 47 was obtained in several attempts at this reaction, the yields were quite poor, the major products being aromatized starting material 24 and compound 27. In this case, presence of the phenolic moiety may inhibit the desired

deallylation by complexation with the rhodium.

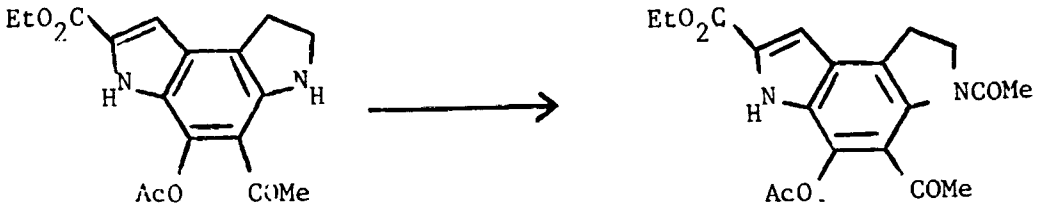
II.6. Subsequent Transformations of Indoline 44. Formal Total Synthesis of PDE-I and PDE-II

The dealkylation method using rhodium hydride under acidic conditions, described in the previous section, made deprotected benzodipyrrole 44 available in good overall yield. Converting this compound to the amide or urethane would set the stage for elaboration to PDE-I and PDE-II. Methylation of the phenol, followed by insertion of oxygen at the 5-position by a Baeyer-Villiger type process or its synthetic equivalent, would complete the synthesis of the B/C rings of CC-1065.

During the course of this work a study of the Baeyer-Villiger oxidation of electron rich acetophenones such as 44 was published by Boger and Coleman[38]. These workers found that these compounds were quite resistant to oxidation by the usual reagents employed for this reaction (MCPBA, peroxytrifluoroacetic acid). A modified version of the benzylic hydroperoxide rearrangement was found to give superior results, however. It was subsequently found by these workers that conversion of the ketone 44 to the tertiary alcohol, followed by treatment with boron trifluoride-peroxyacetic acid, gave a good yield of the desired 5-acetoxy compound. This process was found to work

well only on the free indoline rather than the N-acyl derivative. Synthesis of the dealkylated methoxy indoline 55 would thus constitute a formal total synthesis of PDE-I and PDE-II.

Acetylation of indoline 44 (acetyl chloride, pyridine) provided the amide 48 in excellent yield. Compound 48 was a



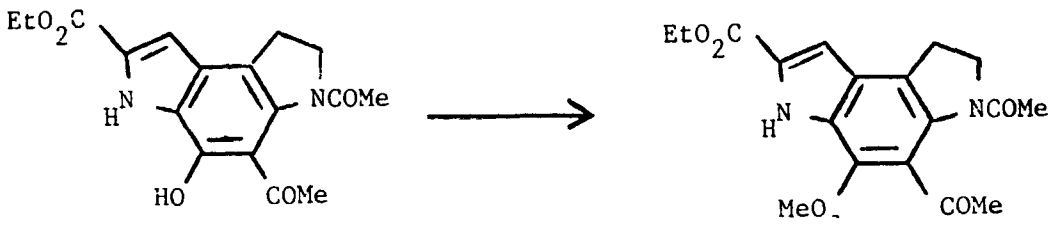
44 48

crystalline substance, mp 162-164^{0}C, which was characterized by NMR and mass spectrometry. The NMR spectrum (δ 1.35, t, 3H; 2.18, s, 3H; 2.35, s, 3H; 2.45, s, 3H; 3.25, t, 2H; 4.20, t, 2H; 4.35, q, 2H; 7.04, d, 1H; 8.80, broad, 1H) is interesting in that no splitting of the amide methyl due to presence of rotamers is seen. This indicates that the steric effect of the adjacent acetyl group causes one of the rotamers to be dominant.

Hydrolysis of the acetate with ammonium hydroxide in ethanol liberated the phenol 49 as a fluorescent yellow oil characterized by NMR. Phenol 49, in strong contrast to the N-alkyl analogues, was readily methylated by diazomethane (methanol:trifluoroethanol solvent) in very good yield.

Methoxy amide 50 was obtained as a crystalline compound, mp 192-194^{0}C, which was completely characterized by NMR and elemental analysis (NMR: 1.45, t, 3H; 2.25, s, 3H; 2.75, s, 3H; 3.30, t, 2H; 3.93, s, 3H; 4.25, t, 2H; 4.45, q, 2H; 7.10, d, 1H; 9.05, broad, 1H).

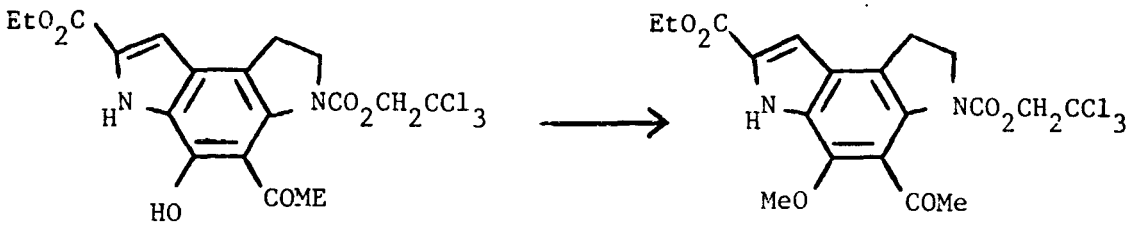
The greater reactivity of the amide 49 as compared to N-alkyl benzodipyrroles 8a and 12 is most likely due to a weakening of the hydrogen bonding of the ortho-acetyl phenol. Inspection of models indicates that the amide carbonyl, in adopting the preferred planar conformation, should push the acetyl group somewhat out-of-plane from the position for maximum hydrogen bonding with the hydroxyl.



49 50

The methylation of the corresponding N-trichloroethoxycarbonyl compound was likewise found to be quite facile. Treatment of indoline 44 with 2,2,2-trichloroethyl chloroformate delivered the carbamate in good yield, which was characterized by NMR and mass spectrometry (NMR: δ 1.43, t, 3H; 2.42, s, 3H; 2.49, s, 3H; 3.33, t, 2H; 4.43, t plus q, 4H; 4.85, s, 2H; 7.11, d, 1H;

8.92, broad, 1H). Hydrolysis of the acetate and methylation of the phenol in methanol with diazomethane resulted in isolation of methoxy compound 53 in nearly quantitative yield (NMR: δ 1.45, t, 3H; 2.70, s, 3H; 3.28, t, 2H; 3.95, s, 3H; 4.35, t, 2H; 4.42, q, 2H; 4.83, s, 2H; 7.10, d, 1H; 9.05, broad, 1H).

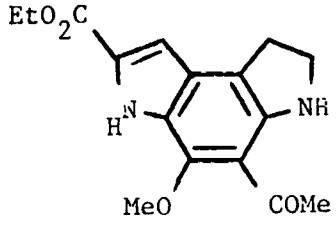


52 53

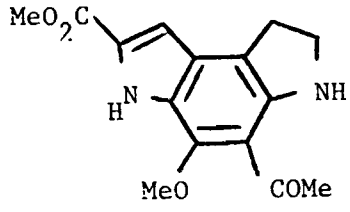
Compound 53 was reductively deprotected with zinc in acetic acid[39] to furnish the bright red methoxy indoline 54 in excellent yield. Compound 54 gave an NMR spectrum in full accord with expectations (NMR: δ 1.42, t, 3H; 2.70, s, 3H; 3.14, t, 2H; 3.73, t, 2H; 3.93, s, 3H; 4.42, q, 2H; 6.95, d, 1H; 8.68, broad, 1H). In order to complete the formal total synthesis of PDE-I and II, compound 54 was treated with sodium methoxide in excess methanol in order to effect conversion to the methyl ester 55, the key intermediate in Boger's synthesis.

Compound 55 was thoroughly characterized by NMR, IR and mass spectrometry and found to be completely identical to the compound obtained by Boger. TLC comparisons (1:1

hexanes:ethyl acetate, 1:2 hexanes:ethyl acetate) against an authentic sample of 55 generously supplied by Professor



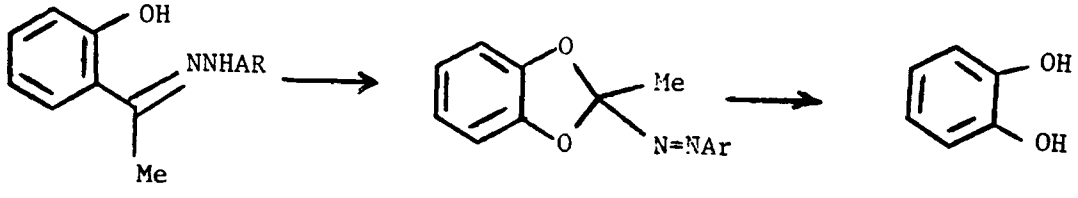
54



55

Boger confirmed the identity of 55. (NMR: δ 2.70, s, 3H; 3.13, t, 2H; 3.72, t, 2H; 3.96, s, 6H; 6.92, d, 1H; 8.70, broad, 1H. IR(neat): 3413, 3339, 3276, 2949, 1721, 1631, 1578, 1435, 1311, 1284, 1243, 1210, 1138, 1101, 755 cm^{-1}).

A report by Nishinaga et al[40] that substituted 2'-hydroxyacetophenone 4-bromophenylhydrazones are oxygenated



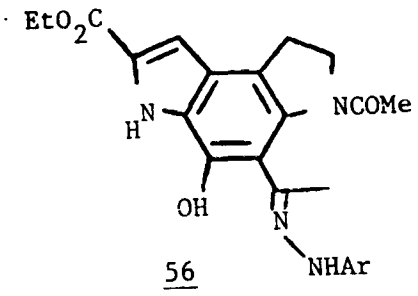
in the presence of complexes of cobalt(II) suggested that conversion of hydroxy amide 49 to the phenylhydrazone,

followed by treatment with dioxygen in the presence of a Co(II) Schiff base complex, might provide a novel method for the introduction of the 5-oxygen functionality. In the work by Nishinaga, the initial products isolated from the reaction were the benzodioxoles. Treatment with methanolic HCl liberated the corresponding catechols in good yield.

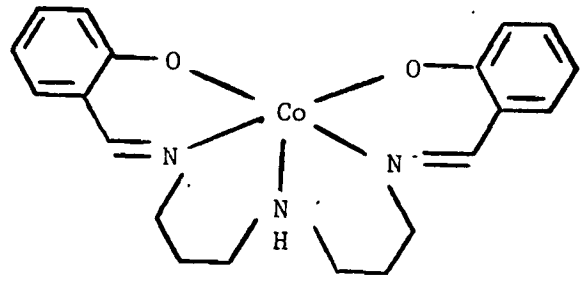
With hydroxy amide 49 in hand, the synthesis of the requisite phenylhydrazone and its subsequent reaction with the oxygen/cobalt complex was investigated. Para-bromo phenylhydrazine was synthesized by the tin(II) chloride reduction of the corresponding diazonium species. The free hydrazine was found to rapidly decompose to oily red by-products; this compound was thus isolated and stored as its complex tin salt. Treatment of 49 with the hydrazine salt in the presence of sodium acetate led, after prolonged stirring, to a mediocre yield of hydrazone 56. Hydrazone 56 was obtained as a mixture of syn and anti isomers, as observed by its NMR spectrum (δ 1.42, t, 3H; 2.20 and 2.30, broad singlets, 2.40 and 2.50, broad singlets, total 6H; 3.20, t, 2H; 4.25, t, 2H; 4.42, q, 2H; 6.95, d; 7.07, d, 1H; 7.35, d; 7.38, d; 7.63, d; 9.20, broad, 1H). The mass spectrum of this compound exhibited a bromine isotope pattern and gave the correct formula weight for hydrazone 56 (500/498).

The reaction of hydrazone 56 with oxygen in the presence of Co(II) SALPR (57) led to disappearance of

starting material but the product mixture proved to be mostly unidentifiable. A major fraction had numerous



56

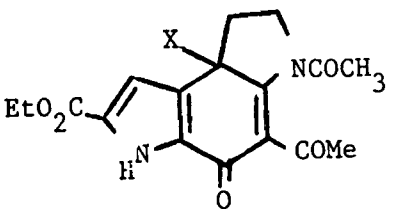


57

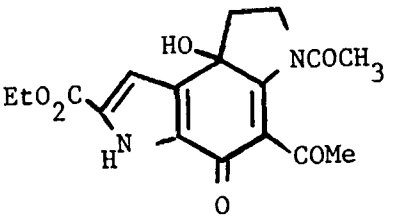
signals in the aromatic region of the NMR spectrum. The mass spectrum of this fraction was also complex and showed high mass peaks at 514 and 512 amu. These weights would correspond to incorporation of one oxygen atom into 56 with concomitant oxidation of the pyrrolidine ring.

It was decided to see how the parent hydroxy ketone would react under identical conditions. When oxygen was bubbled through a stirred mixture of 49 and the cobalt(II) complex, disappearance of starting material was rapid, with the formation of a more polar product spot on TLC. After workup and chromatography, this product was obtained quite clean and in good yield. The NMR spectrum of this product

suggested that a structure of type 58 had formed (NMR: δ 1.40, t, 3H; 2.15, t, 1H; 2.25, s, 3H; 2.60, s, 3H; 2.63-2.75, m, 1H; 4.00, t, 1H; 4.20, m, 1H; 4.40, q, 2H; 7.00, d, 1H; 9.80, broad, 1H). Comparison of this spectrum to that of 27 showed similar coupling patterns and J-values for the pyrrolidine ring protons. The lack of a bridgehead proton suggests that X in structure 58 is -OH. The mass spectrum (M+ 346) confirmed that oxygen had been incorporated into the structure. Structure 59 was assigned to this product on the basis of these considerations.



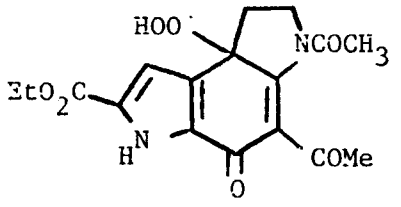
58



59

On a repetition of the above reaction, a fraction was isolated that appeared to consist of of a compound whose NMR spectrum was extremely similar to that of 59 but which exhibited small but significant chemical shift differences (NMR: δ 1.45, t, 3H; 2.25, s, 3H; 2.30, m, 1H; 2.65, s, 3H; 2.80, d of d, 1H; 4.00, t, 1H; 4.10, m, 1H; 4.40, q, 2H; 6.97, d, 1H; 9.88, broad, 1H). The molecular weight

indicated by the mass spectrum (362), showing that this structure had an additional atom of oxygen in its structure, suggested that this compound may be the hydroperoxide 60, a likely intermediate in the oxi-



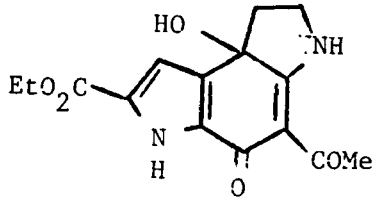
60

dation to the alcohol. Phosphites are known to effect the reduction of hydroperoxides[41]. Treatment of a sample of 60 with trimethyl phosphite resulted in complete conversion to 59, as verified by NMR.

Subjection of methoxy amide 50 to the reaction conditions above resulted in recovery of unchanged starting material in 70% yield. A small amount of product was recovered that appeared to have aromatized in the pyrrolidine ring, as indicated by signals at 6.50, 7.50, and 7.55 ppm. This compound was completely inert to Baeyer-Villiger oxidation conditions; this observation is in keeping with the results of Boger's studies.

In hopes of gaining enone 47 by rearrangement of the parent phenol, indoline 44 was treated with ammonium hydroxide in ethanol. The product of the reaction, however,

did not appear to be the same as compound 47 (NMR: δ 1.40, t, 3H; 2.20, m, 1H; 2.52, s, 3H; 2.70, d of d, 1H; 3.82, m, 1H; 4.18, m, 1H; 4.35, q, 2H; 6.95, d, 1H; 9.68, broad, 1H). The conspicuous absence of a bridgehead proton made the compound appear to be of the same type as 59; there were however, slight changes in chemical shifts. Mass spectral evidence that this compound has incorporated oxygen (MW 304) led to the conclusion that the product was most likely 61. The effects of the amide

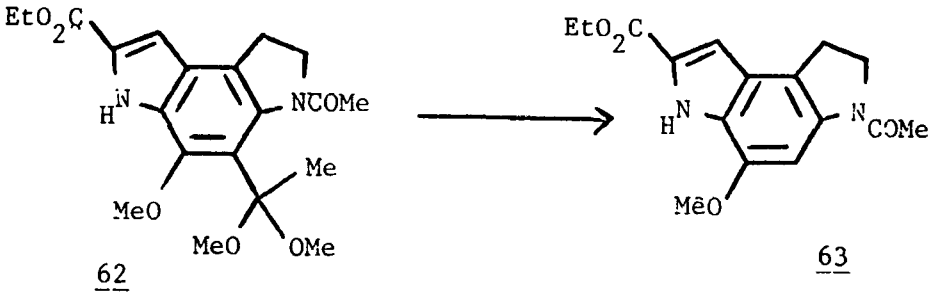


61

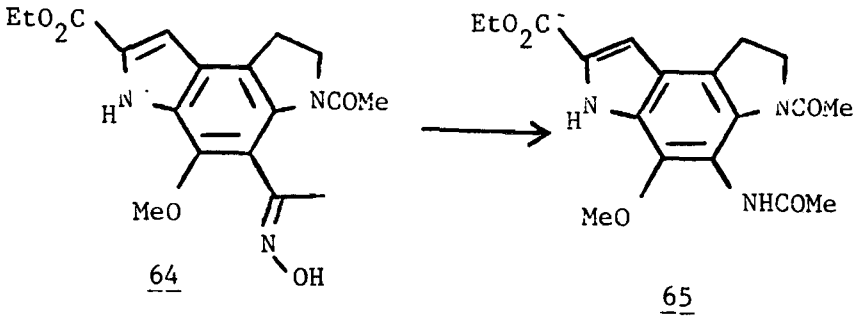
functionality account for the slight variation in the pyrrolidine proton chemical shifts. In hopes of converting this compound to 59 for purposes of verifying this relationship, 61 was refluxed in ethanolic HCL for 12 hours; however, only complex degradation products were obtained from this reaction.

Several attempts were made to functionalize the ketone moiety in methoxy amide 50. It was thought that ketal 62, if subjected to acid treatment, might undergo fragmentation to produce the deoxy compound 63. However, treatment of

either hydroxy amide 49 or the corresponding methoxy compound with trimethyl orthoformate in the presence of a catalytic amount of p-toluenesulfonic acid resulted in the recovery of starting material in 70 and 96% yield, respectively. No products of ketalization were found.



The ketone carbonyl of 50 likewise resisted oxime formation. It was hoped that synthesis of the oxime would



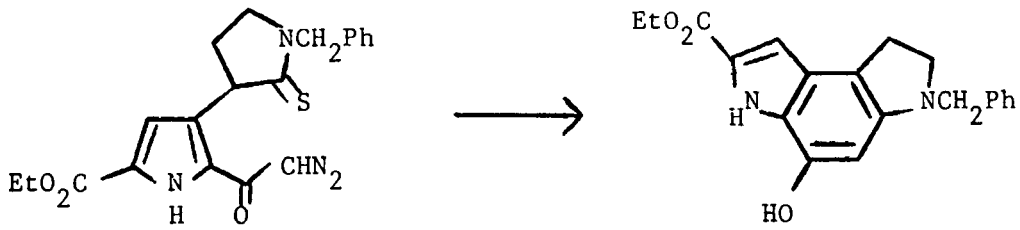
allow, via Beckmann rearrangement, access to the amide derivative 65. Stirring 50 in ethanol with excess hydroxylamine for a prolonged period led only, in addition to recovered starting material, to a small amount of indoline 54. These results undoubtedly reflect the fact that the

ketone moiety of 50 is sluggish in its reactivity, due to the congested steric environment surrounding this center.

CHAPTER III

III.1. Introduction

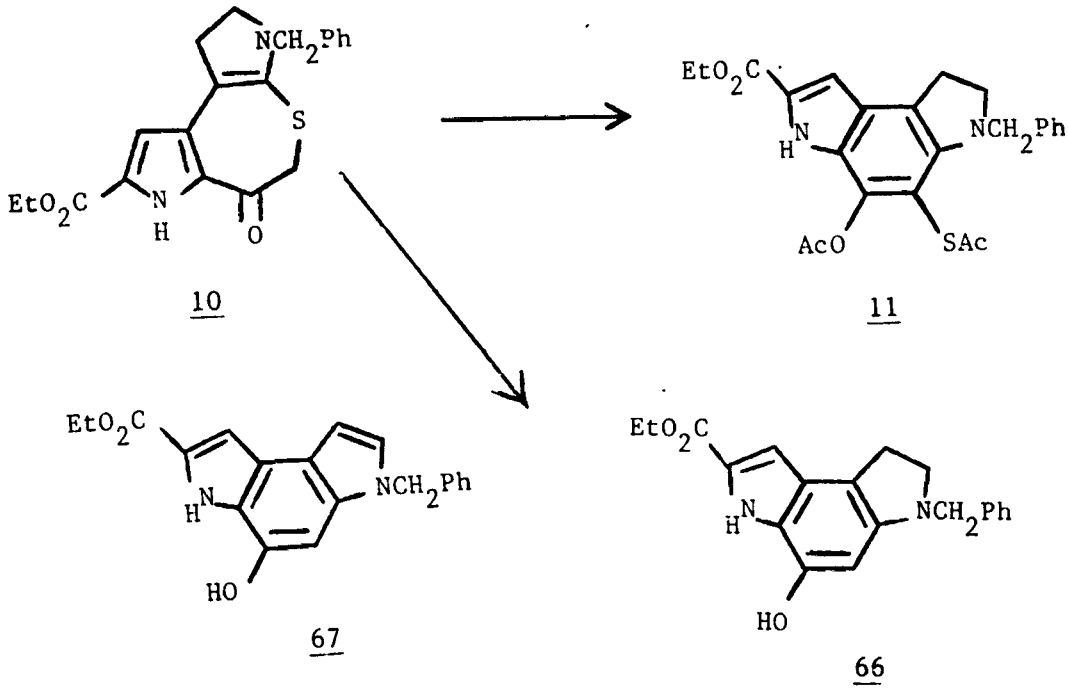
The synthesis and cyclization of diazo ketone 9 had originally been undertaken by Pearce with the end in mind of gaining synthetic access to monosubstituted benzodipyrrole 66. Due to the problems associated with the manipulation and functionalization of the N-benzyl 5-acetyl benzodipyrroles, it was hoped that synthesis of such compounds would provide an alternate route to the dioxy substitution pattern of PDE-I/II by way of oxidation of the 5-position of 66.



9 66

Pearce found that treatment of thiolactam diazo ketone 9 with hydrobromic acid led to a quantitative yield of thiepinone 10. Heating this compound in a mixture of acetic

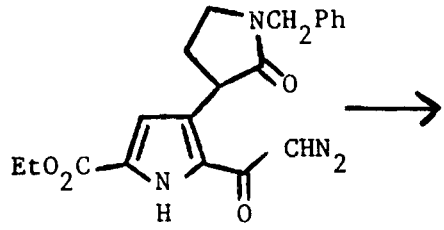
acid and acetic anhydride gave rise to 5-acetylthio benzodipyrrole 11 in good yield. Heating in acetonitrile, on the other hand, resulted in the oxidized monosubstituted phenol 67 in somewhat lower yield. In the presence of acid, it is likely that cyclization of the iminium species occurs followed by opening of the thiirane ring and acetylation of the sulfur and oxygen. In the non-acidic case, aromatiza-



tion may be occurring by loss of H_2S. Compound 11 could be converted to 68 in 60% yield by treatment with Raney nickel. In a subsequent experiment, thermolyzing 10 in the presence of tributylphosphine delivered a 1:1 mixture of dehydro and dihydro compounds 66 and 67.

The results with thiepinone 10 led to the hope that

cyclization of the corresponding lactam diazo ketone might provide, by way of oxepin 70, direct access to the dioxy substitution pattern of the B/C rings of CC-1065.



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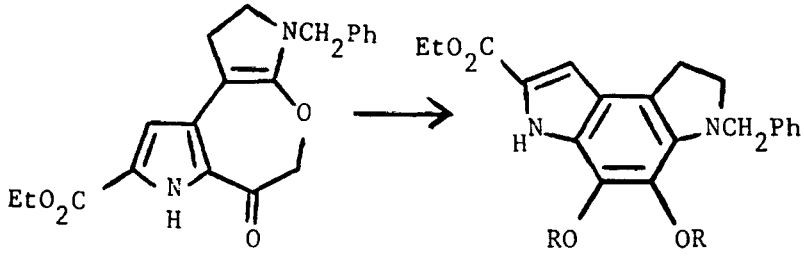
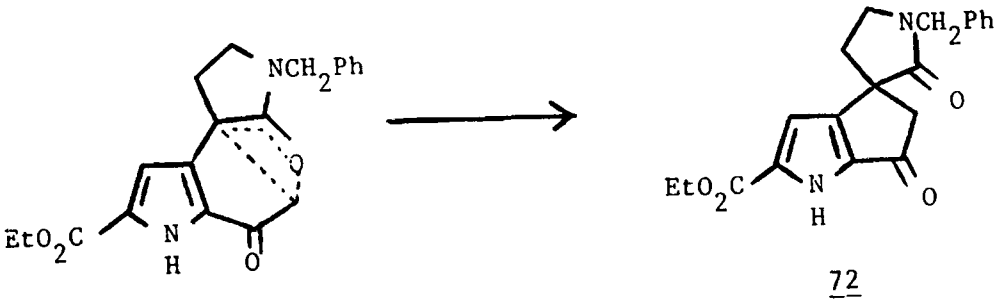


70 71

Unfortunately, it was found that the oxepin, in contrast to the quite stable sulfur compound, was much more reactive and gave rise to unwanted rearrangement products.

Treatment of diazo ketone 69 with either boron trifluoride-etherate or trimethyloxonium tetrafluoroborate in nitromethane produced, after treatment of the initial reaction mixture with base, a bright red solution from which was obtained primarily the spiro compound 72. This may be the product of a 1,3 shift in the oxepin as shown. Thermolysis of the crude product mixture from the cyclization did produce some desired product 71, but in

erratic yield due to the instability of intermediate 70. In another experiment, the lability of imino ether 73 was demonstrated. Solvolysis of 73 delivered, upon workup, hydroxy ketone 74.



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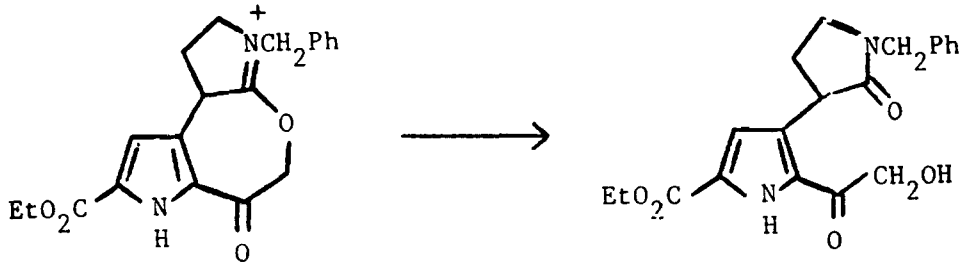


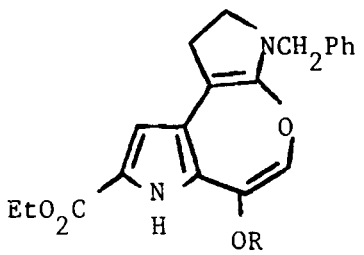
73 74

Two issues were addressed in the following studies. With respect to diazoacetyl lactams such as 69, it was sought to determine whether cyclization and contraction to compounds such as 71 was a workable method. Concerning the thiolactam compounds, it was hoped to develop a synthesis of compound 66 to allow the preparation of deoxy analogues

of PDE-I/II.

III.2. Reactions of Diazoacetyl Lactam 69.

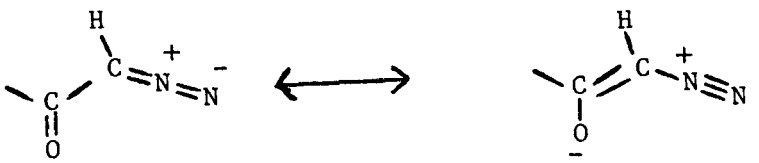
The results discussed in the previous section indicated that cyclization modes which passed through intermediate 70 were unlikely to be profitable. The synthesis of enol ethers 75 was considered with the hope that such a species, once generated, might contract to the desired benzodipyrrole. Species 75, with participation of an oxygen electron pair, would be formally antiaromatic and very electron-rich.



75 a R = CH_3
b R = SiR_3

In order to obtain access to enols 75, the alkylation of diazo ketone 69 was studied. The nucleophilic character

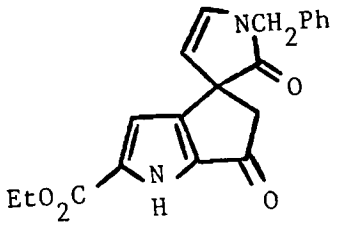
of the carbonyl oxygen in α-diazo ketones may be understood by consideration of resonance forms:



It was felt that, with sufficiently reactive alkylating reagents, it should be possible to generate the enol ether directly[42]. Use of a methylating agent would thus provide direct access to the PDE-I/II oxygenation pattern.

Treatment of diazo ketone 69 with a solution of methyl trifluoromethanesulfonate in methylene chloride led to rapid formation of a more polar substance, as monitored by TLC. Addition of dimethylaminopyridine generated a dark red colored solution. The red color faded before and during workup of the reaction. Three products were isolated and characterized. Spiro compound 72 was obtained as the major product, and was identical to a previously characterized sample (NMR: δ 1.38, t, 3H; 2.20-2.40, m, 2H; 2.74, d (J=18 Hz), 1H; 3.33, d of t, 1H; 3.42, d (J=18 Hz), 1H; 3.45, m, 1H; 4.36, q, 2H; 4.43 and 4.65, AB q, 2H; 6.60, d, 1H; 7.24-7.40, m, 5H; 9.52, broad, 1H). Also obtained in significant amount was the hydroxy ketone 74 (NMR: 1.38,

t, 3H; 2.05, m, 1H; 2.50, m, 1H; 3.37, m, 2H; 3.75, broad, 1H; 4.20, t, 1H; 4.35, q, 2H; 4.50, AB q, 2H; 4.60 and 4.80, AB m, 2H; 6.78, d, 1H; 7.20-7.40, m, 5H). Curiously, a compound was isolated which appeared to be the dehydro spiro compound 76. This compound was characterized by NMR and mass spectrometry. The presence of a chiral center in 76 is clearly seen from the appearance of the benzylic methylene protons as an AB quartet. The vinyl protons are



76

seen as a clean pair of doublets at 5.45 and 6.50. The molecular weight of 76 was found to be 350, two mass units lower than 72 (NMR: δ 1.38, t, 3H; 2.95 and 3.20, AB q (J=18 Hz), 2H; 4.35, q, 2H; 4.60 and 4.75, AB q, 2H; 5.45, d, 1H; 6.50, d, 1H; 7.20, d, 1H; 7.22-7.40, m, 5H; 9.52, broad, 1H). The appearance of an AB pair at 2.95 and 3.20 ppm with a J value of 18 Hz strongly implicates the spiro cyclopentanone structure since the saturated analogue 72 has a nearly identical spectral feature.

It seems likely that the red colored solution obtained

by treating the reaction mixture with base must contain oxepin 70. The cyclization of the diazo ketone is evidently going by way of the acid catalyzed route described previously. It may be that traces of acid from decomposition of the highly labile triflate reagent are sufficient to preclude the desired cyclization path.

Next, the silylating agent tert-butyldimethylsilyl trifluoromethanesulfonate was assayed with the hopes of generating the corresponding silyl enol ether. Diazo ketone 69 was treated with the silyl triflate and the resulting reaction mixture was treated with a non-nucleophilic base (1,8-bis(dimethylamino)napthalene; 'Proton Sponge'). Again, a dark red solution was obtained which rather quickly lightened in color. The crude material obtained from removal of the solvent was thermolyzed in acetonitrile without further purification. The products of the thermolysis were complex and uninterpretable. The only components present in the reaction mixture appeared to be non-cyclized products, as gauged by NMR.

The reaction of 69 with the silyl triflate was repeated, this time isolating the intermediate products. Chromatography of the reaction mixture delivered only compounds 72 and 74.

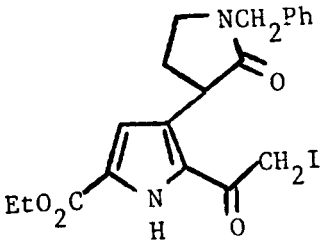
For comparison, thiolactam diazo ketone 9 was reacted with tert-butyldimethylsilyl triflate in the same manner as the lactam. After stirring together for several hours, TLC

indicated conversion to a compound which appeared to be the known thiepinone. Workup and purification of the reaction mixture provided 10 in excellent yield, with no trace of products incorporating silicon. Again, cyclization appears to be going by way of acid induced decomposition of the diazo ketone.

In another experiment, the silyl triflate was added to a stirred mixture of diazo ketone 69 and an excess of Proton Sponge. In this case, prolonged reaction led to the recovery of unchanged starting material in 87% mass balance, along with a small amount of hydroxy ketone 74.

These results indicated that the triflate reagents were not suitable for effecting the desired transformation. Accordingly, the use of the more reactive iodotrimethylsilane was investigated. Reaction of 69 with this reagent followed by treatment with base led to the formation of a compound that did not appear to be the oxepin. The crude material from removal of the solvent was thermolyzed in acetonitrile and the resulting mixture was analyzed for products. A small amount of hydroxy ketone 74 was isolated. The major product, however, was the iodo ketone 77. The NMR spectrum was clearly that of an open ring compound of type 74. The spectrum was virtually the same as that of 74 but with some variations in chemical shifts (NMR: 1.37, t, 3H; 2.00-2.10, m, 1H; 2.50-2.55, m, 1H; 2.57, s, 2H; 3.35, m, 2H; 4.25, t, 1H; 4.30, q, 2H;

4.55, AB q, 2H; 6.78, d, 1H; 7.25-7.40, m, 5H; 9.80, broad, 1H). In addition the methylene protons adjacent to the



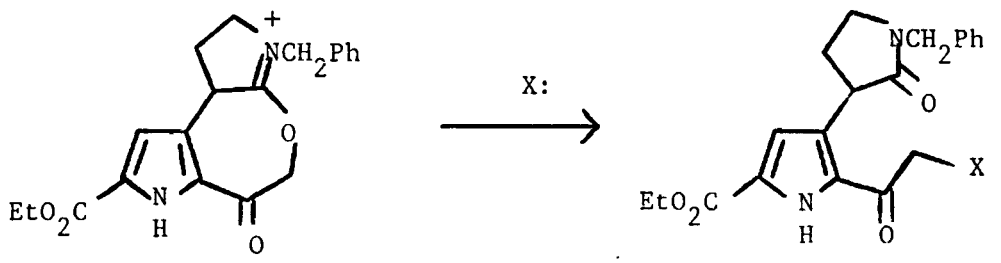
77

carbonyl appeared as a clean singlet. Mass spectral data were also in accord with structure 77, showing an ion (352) corresponding to facile loss of HI.

At this point the study of the cyclizations of the diazoacetyl lactam 69 was abandoned in favor of the study of the corresponding thiolactam. However, the results obtained here do suggest some other lines of further investigation that might prove worthwhile. The ease with which protonated imino ether 73 undergoes solvolysis suggests a possible synthesis of functionalized compounds of type 78.

If X is a suitable activating group for aldol type condensations, such compounds could provide alternate routes to benzodipyrroles. For example, treatment of imino ether 73 with cyanide might deliver the cyano ketone (78, X=CN). Cyclization of this compound with base might then

give a 5-cyano benzodipyrrole. Alternatively, the phosphonate reagent (78, X=PO(OC_2H_5)$_2$ might arise from treatment of 73 with triethyl phosphite. Cyclization of this compound could provide the phenol 66.

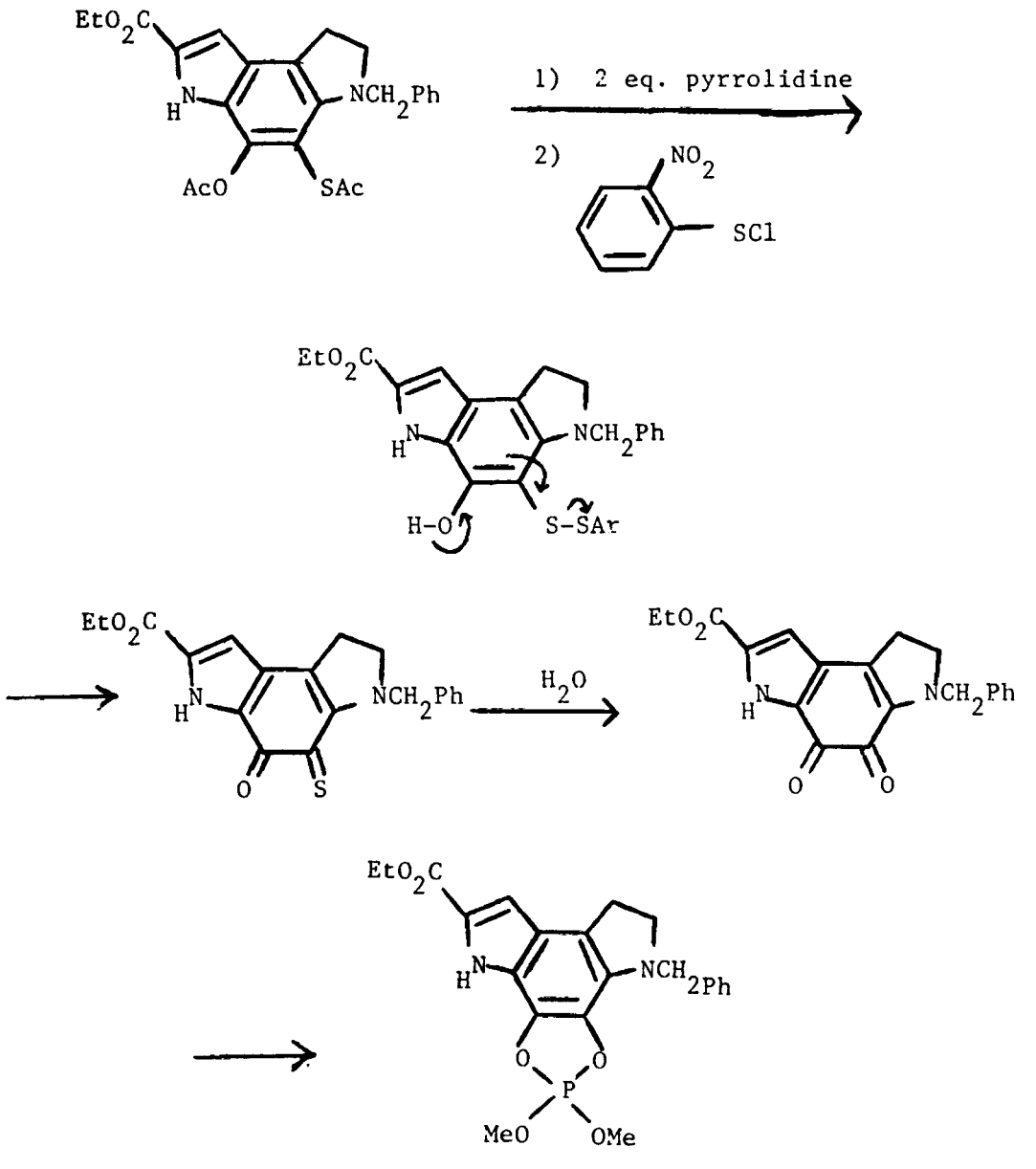


78

III.3. Cyclizations of Diazoacetyl Thiolactams. Synthesis of Ethyl 6-Alkyl-4-methoxybenzo[1,2-b:4,3-b']dipyrrole-2-carboxylates

One pathway utilizing the diazo ketones was envisioned as providing access to the dioxygenated substitution pattern by way of the 5-acetylthio benzodipyrrole 11 which had been synthesized by Pearce. It was planned that treatment of this compound with pyrrolidine to effect hydrolysis of the thioacetyl group, followed by treatment with 2-nitro benzenesulfenyl chloride, would result in

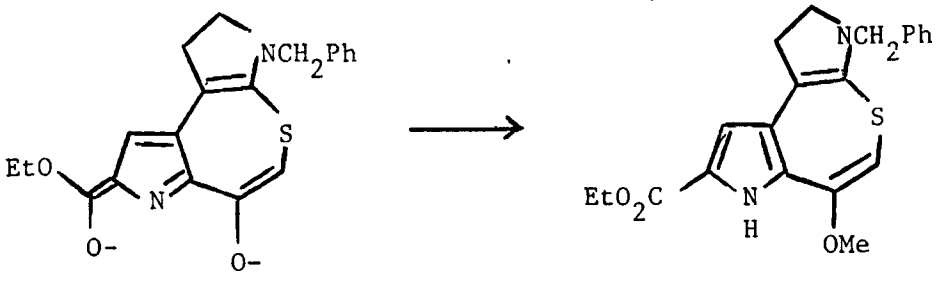
formation of the disulfide. This compound could undergo base-catalyzed cleavage to the ortho-thioquinone, which upon aqueous treatment should provide the quinone. Magnus



79

has shown that such compounds may be reduced with trimethyl phosphite to produce the cyclic oxyphosphorane 79. Treatment of 11 with two equivalents of pyrrolidine followed by one equivalent of the sulfenyl chloride, resulted in conversion to a single more polar spot as monitored by TLC. Addition of DABCO produced a single, less polar spot. Extractive workup and chromatography delivered this product, which proved to be the phenol 67. This compound was further characterized by conversion to the acetate, which was identical to previously obtained samples[25]. The mechanism of the conversion of the (presumed) intermediate to the product is not clear.

The possibility of alkylating the dianion of

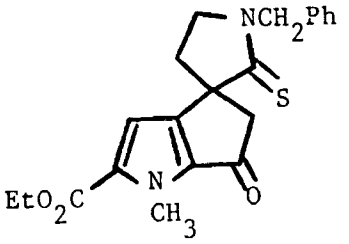


80 81

thiepinone 10 was briefly investigated. It was envisioned that O-alkylation of the dianion 80 would generate the enol ether 81, which could then contract to the methoxy

compound.

Treatment of compound 10 with two equivalents of LDA followed by HMPA and methyl sulfate resulted in a complex mixture of products. In addition to recovered starting material, N-methylated starting material was also obtained. The largest fraction isolated from the reaction mixture was assigned structure N-methyl spiro lactam 82.



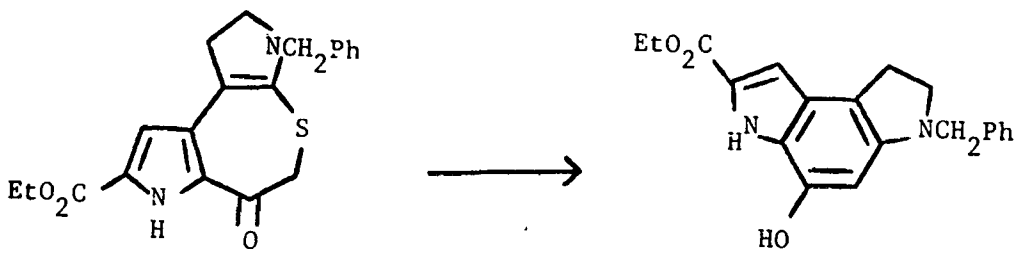
82

Assignment of structure 82 was based on comparison of the NMR spectrum of 82 with that of previously characterized spiro compound 72 and consideration of the mass spectral data. The NMR of compound 82 (1.39, t, 3H; 2.30 and 2.40, m, 2H; 2.80 and 3.68, AB q, 2H; 3.60 and 3.75, AB m, 2H; 4.08, s, 3H; 4.30, q, 2H; 4.95 and 5.20, AB q, 2H; 6.55, s, 1H; 7.40, m, 5H) clearly indicated it to be closely related to 72. The addition of a methyl singlet at 4.10 ppm, together with the lack of an indole -NH signal and loss of coupling in the signal from the indole 3-position, suggested that methylation had taken place on the indole nitrogen. The characteristic 18 Hz geminal coupling

for the methylene protons next to the carbonyl, at 2.80 and 3.68 ppm, was strong evidence for structure 82. The incorporation of sulfur was indicated by the mass spectrum, which gave a formula weight of 382, correct for structure 82 ($C_{21}H_{22}O_3S$).

Interest in the cyclizations of diazoacetyl thiolactams such as 9 also lay in the ability to access deoxy analogues of PDE-I and PDE-II. As noted previously, it is thought that the hepatotoxicity of CC-1065 may be related to the oxygenated functionality of the B/C rings. A decrease in toxicity of the dideoxy analogue of Warpehoski and Wierenga relative to CC-1065 has been documented. Thus, the 5-deoxy analogue of PDE-1/II was considered a desirable target.

The direct reaction of Raney nickel with thiepinone 10 was considered of interest and was investigated with

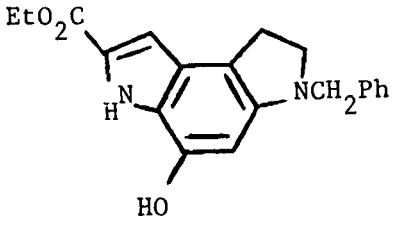


10 66

encouraging results. Recall that Raney nickel desulfurization of 11 led to compound 68 in 60% yield, with concomitant oxidation of the pyrrolidine ring (page 71). In order to elaborate this intermediate into a suitable B/C ring analogue, the acetyl group must be hydrolyzed to the phenol, methylated, and the methoxy compound reduced to the indoline oxidation level and dealkylated. It was hoped that a more direct, high-yielding route to compounds such as 66 might be found.

Reaction of 10 with moist activated Raney nickel in refluxing ethanol resulted, after 1 1/2 - 2 1/2 hours reaction time, in disappearance of the starting material and appearance of several new spots by TLC. Two upper spots appeared to be cyclized aromatic compounds. One was considerably more brightly fluorescent blue than the other. After the crude mixture had been left standing under vaccuum overnight, the darker, more polar spot of the pair had disappeared, leaving only the less polar fluorescent material. This observation suggested that these two spots consisted of the pair of dehydro- and dihydro- phenols 66 and 67. Also present in the mixture was a very polar material that appeared similar by TLC to the previously obtained spiro type compounds. The crude mixture was treated with acetic anhydride and DMAP and the products from this step were isolated by flash chromatography. Acetate 68 was isolated as the main product from this

process. Compound 68 was characterized by MS and NMR (NMR: 1.45, t, 3H; 2.42, s, 3H; 4.42, q, 2H; 5.36, s, 2H; 6.77, d, 1H; 7.10, d, 1H; 7.17, d, 1H; 7.30-7.40, m. 5H; 7.47, d, 1H; 8.89, broad, 1H). Also isolated from this reaction was



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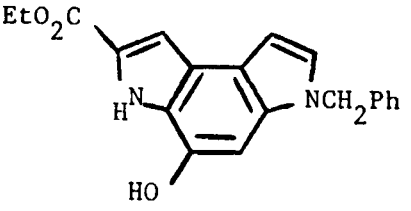

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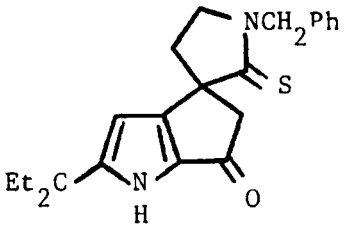

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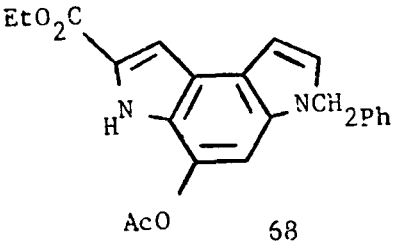


68

the polar spot from the cyclization reaction. This compound (NMR: δ 1.39, t, 3H; 2.35 and 2.45, m, 2H; 2.80 and 3.70, AB q, 2H; 3.60 and 3.75, m, 2H; 4.35, d of d, 2H; 4.95 and 5.20, AB q, 2H; 6.57, d, 1H; 7.35-7.40, m, 5H; 9.40, broad, 1H) was assigned structure 83, identical to previously characterized spiro lactam 82, but lacking the N-methylation. The NMR spectra of 82 and 83 were virtually identical, including the 18 Hz geminal coupling for the

methylene group adjacent to the carbonyl. The mass spectrum indicated the correct formula weight for structure 83 (368). Spiro lactam 83 was found to be a common by-product in these types of cyclizations.

In initial work with the Raney nickel reaction mixtures, the crude mixture of products obtained by filtering and concentrating the reaction mixture was used for subsequent reactions. Filtering did not completely remove metallic material, however, and the yields of subsequent reactions with diazomethane seemed to suffer due to the use of this crude material. It was found that phenol 67 was sufficiently stable to allow chromatographic purification before proceeding to subsequent steps. The products were generally obtained as an off-white solid containing a mixture of indole and indoline compounds 66 and 67.

Thermolysis of thiepinone 10 in acetonitrile at 100^{0}C for 7 hours led to a mixture of three components, closely spaced on the TLC plate. This mixture was subjected to phase transfer methylation conditions as described in Chapter II (methylene chloride, aqueous sodium carbonate, tetrabutylammonium hydroxide and methyl sulfate). The mass balance for this reaction was quite poor and only a small amount of material judged to be methylated indole 84 by NMR was isolated from the reaction mixture.

Several variations in the reaction conditions for the

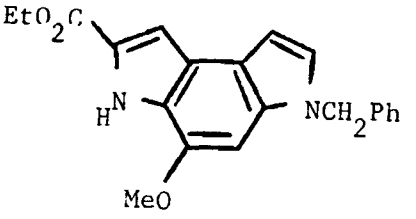
ring contraction of 10 were explored. Heating the thiepinone in trimethyl phosphite at 100^{0}C for a prolonged period led to a recovery of starting material in good yield (69%). A smaller amount of material appeared to be a mixture of a spiro type compound and the desired ring contraction product. Heating 10 with methyl iodide in THF resulted in the isolation of two materials in approximately equal amounts. The less polar of the two was unchanged starting material; the other appeared to be the spiro thione 83, identical to previously obtained and characterized samples.

The use of a nickel boride catalyst ('NiBo') was investigated as an alternative to Raney nickel for the desulfurization - ring contraction of 10. The use of this reagent for the desulfurization of thiophene substrates has been reported to give conjugated dienes in 50-55% yields[43]. The reagent is easily made by the addition of sodium borohydride to nickel(II) chloride. Refluxing thiepinone 10 in ethanol with the nickel catalyst did produce phenol 67 but in inferior yield as compared with Raney nickel.

Treatment of phenol 67 with the cyclic oxaphospholene was fraught with the same problems as in the case of the 5-acetyl benzodipyrroles discussed in the previous chapter. Inseparable mixtures of the desired O-methylated compound 84 along with O,N-dimethylated material were obtained using this reagent. The presence of two methylation

products was readily deduced from the NMR spectrum of the product mixture, which contained methyl singlets at 3.85, 3.95 and 4.40 ppm.

Treatment of phenol 67 in ether with ethereal diazomethane provided methoxy compound 84 in yields of 30-40%. The methylation of phenols is reported to frequently be expedited by the use of protic solvents[44], and for this reason methanol is frequently used in such reactions. Use of methanol as the solvent for the methylation of 67 provided, after reaction overnight, methoxy compound 84 in improved yield. The possibility of using the more acidic



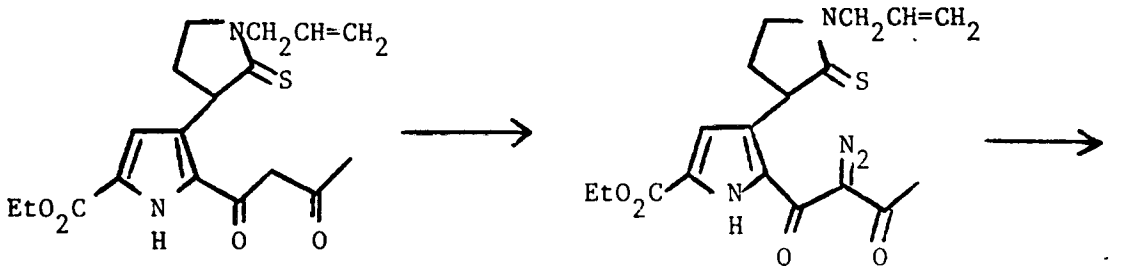
84

2,2,2-trifluoroethanol as the solvent was considered. Compound 67 proved to be poorly soluble in this solvent. However, a 1:1 mixture of methanol and 2,2,2-trifluoroethanol was found to be ideal for these diazomethane methylations, and routinely provided methyl aryl ether 84 in 70-80% yield after two hours reaction time. In this manner methoxy indole 84 was available in two

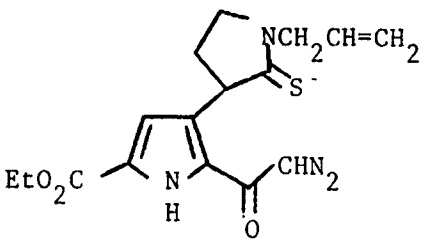
steps and 50-60% overall yield from thiepinone 10. Though the phenolic material used for the methylations was generally a mixture of the indole and indoline compounds, the product of the diazomethane reaction was invariably only the fully aromatized indole 84. Compound 84 was obtained quite pure as judged by NMR and was characterized by MS as well. (NMR: δ 1.43, t, 3H; 3.90, s, 3H; 4.40, q, 2H; 5.35, s, 2H; 6.63, s, 1H; 6.73, d, 1H; 7.05, d, 1H; 7 .20-7.40, m, 5H; 7.43, d, 1H; 9.10, broad, 1H.)

With a reasonable route to the 4-methoxy N-benzyl benzodipyrrole 84 established, it was considered prudent to obtain the analogous compounds with the allyl group as the nitrogen protecting functionality. This would allow for greater versatility in deprotection methodology since at this time deprotection procedures for the N-allyl 5-acetyl benzodipyrroles were being successfully worked out. As expected, synthesis of the necessary diazo ketone 86 proceeded in parallel with that of the N-benzyl case. Thus, treatment of diketone 22 with p-nitrobenzenesulfonyl azide and triethylamine produced diazo compound 85 in good yield (NMR: 1.40, t, 3H; 2.05, m, 1H; 2.51, s, 3H; 2.58, m, 1H; 3.70, m, 2H; 4.37, q, 2H; 4.50, m, 2H; 4.95, t, 1H; 5.32, m, 2H; 5.87, m, 1H; 6.85, d, 1H). Deacetylation of this compound with pyrrolidine in ethanol provided diazo ketone 86 (NMR: 1.35, t, 3H; 2.20, m, 1H; 2.60, m, 1H; 3.75, m,

1H; 3.87, m, 1H; 4.32, q, 2H; 4.45, m, 2H; 4.60, t, 1H; 5.35, m, 2H; 5.85, m, 1H; 6.73, d, 1H; 6.80, s, 1H; 9.75, broad, 1H) in overall yield of 75% from 22. Compounds 85



85

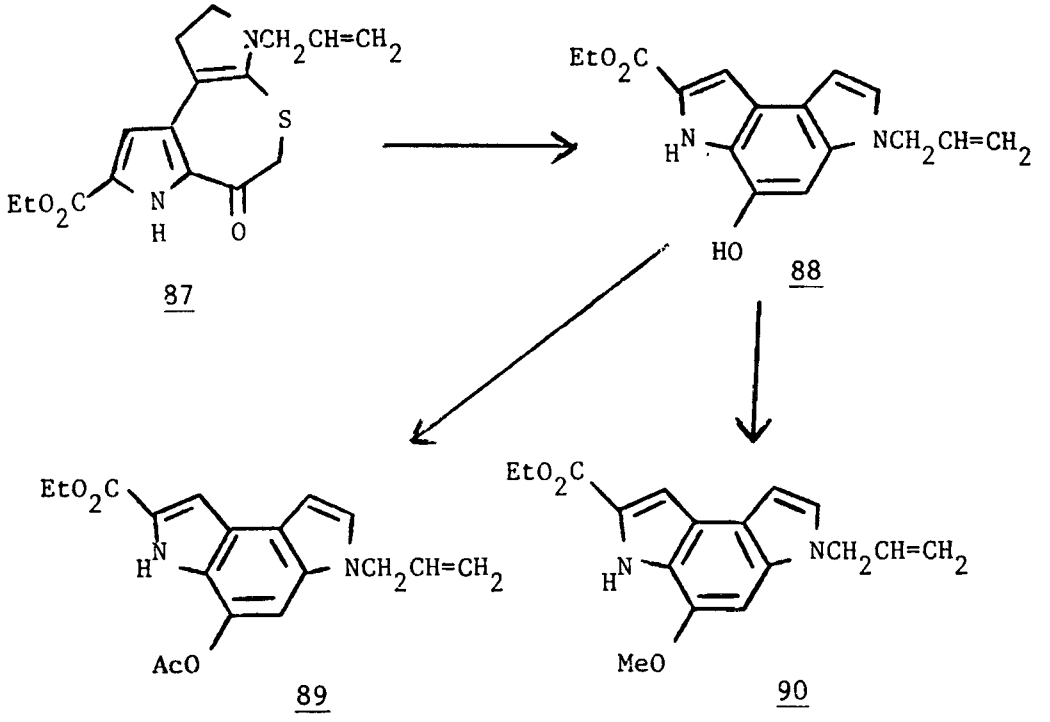


86

and 86 were obtained consistently as oils and did not lend themselves to recrystallization, but were well characterized by NMR spectroscopy and comparison with the corresponding benzyl compounds.

Decomposition of N-allyl diazo ketone 86 with BF_3-Et_2O in methylene chloride resulted, as in the case of the benzyl compound, in a nearly quantitative yield of N-allyl

thiepinone 87. Thiepinone 87 was obtained as a bright orange crystalline material which could be recrystallized from chloroform-hexanes. Compound 87 was fully characterized by NMR, mass spectrometry and elemental analysis. The NMR spectrum of 87 (NMR: δ1.40, t, 3H; 2.90, t, 2H; 3.40, t plus overlapping s, 4H total; 3.75, d, 2H; 4.38, q, 2H; 5.25, m, 2H; 5.82, m, 1H; 6.70, d, 1H; 9.68, broad, 1H) was fully in accord with expectations for this compound and completely analogous to the N-benzyl case.



Treatment of N-allyl thiepinone 87 with Raney nickel in refluxing ethanol delivered, after treatment of the crude product 88 with acetic anhydride and DMAP and chromatographic resolution, acetate 89, characterized by NMR, in slightly better than 50% yield (NMR: δ1.43, t, 3H; 2.45, s, 3H; 4.42, q, 2H; 4.75, d, 2H; 5.05-5.25, m, 2H; 6.00, m, 1H; 6.75, d, 1H; 7.13, d, 1H; 7.45, d, 1H; 8.95, broad, 1H). Treatment of the ring contraction product 88 in methanol:trifluoroethanol with ethereal diazomethane furnished N-allyl methoxy indole 90 in good yield. Compound 90 was characterized by NMR (NMR: δ1.43, t, 3H; 4.00, s, 3H; 4.40, q, 2H; 4.75, m, 2H; 5.05-5.25, m, 2H; 6.05, m, 1H; 6.70, s plus d, 2H; 7.01, d, 1H; 7.41, d, 1H; 9.10, broad, 1H).

III.4. Subsequent Transformations of N-Alkyl-4-methoxybenzodipyrroles. Synthesis of 5-Deoxy PDE-II Ethyl Ester.

With 4-methoxy benzodipyrroles 84 and 90 in hand, the remaining tasks to address were the removal of the nitrogen protecting group and the reduction of the C ring to the necessary indoline oxidation state. Treatment of the free indoline with the appropriate acylating reagent should provide the 5-deoxy analogues of PDE-I and PDE-II.

It was felt that reduction to the indoline stage would

most likely be required in order to effect smooth dealkylation of the nitrogen, due to the expected lack of reactivity of the indole nitrogen. Initial experiments bore this out. Treatment of N-allyl 4-methoxy benzodipyrrole 90 with tetrakis(tri-phenylphosphine)rhodium hydride resulted only in recovery of starting material. Likewise, treatment with palladium(II) / butyltin hydride did not effect the desired dealkylation. Attempted catalytic hydrogenation of N-benzyl methoxy indole 84 with 10% palladium on carbon in acetic acid and acetic anhydride led only to degradation products.

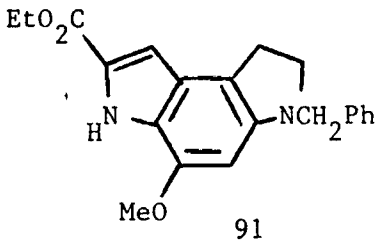
The study of the reduction of indoles 84 and 90 to the corresponding indolines was therefore undertaken. It was neccessary that the reduction method distinguish between the two indole rings in compounds 84 and 90. A number of methods for the reduction of indoles to indolines have been reported. Protonation of the indole 3-position and reduction of the resultant iminium species is a common mechanistic pathway of these procedures. A frequently used method first described by Gribble involves treating the indole in acetic acid with sodium cyanoborohydride[45]. In a related method, the triethylsilane/ trifluoroacetic acid combination has been successfully used[46]. The reduction of indoles to indolines using a complex of trifluoroacetic acid and diborane has been reported by Maryanoff[47]. Addition of borane-THF to trifluoroacetic acid produces

the acid stable complex bis(tri-fluoroacetoxy)borane. Treatment of a TFA solution of the indole with borane-THF is reported to rapidly produce the indoline in good yield. Experience of other workers in the reduction of 2-carboalkoxy benzodipyrroles related to 84 confirms that, as expected, selective reduction of the more basic (unsubstituted) indole ring occurs[18,19,20].

Treatment of either the N-benzyl or N-allyl compound in trifluoroacetic acid with triethylsilane led to complex mixtures that contained other products in addition to the desired indoline compounds. Treatment of a solution of N-benzyl methoxy indole 84 in TFA with borane-THF provided, after workup and chromatography, the N-benzyl indoline in moderately good yield (60%). The indoline was characterized by its NMR spectrum (NMR: δ 1.43, t, 3H; 3.05, t, 2H; 3.40, m, 2H; 3.90, s, 3H; 4.30, s, 2H; 4.43, q, 2H; 6.34, s, 1H; 7.00, d, 1H; 8.90, broad, 1H).

The borane reduction procedure, though moderately successful in the case of the N-benzyl compound, could not be used on N-allyl compound 90 due to the presence of the olefin functionality. It was found, however, that reduction of the indoles 84 and 90 by the procedure of Gribble ($NaCNBH_3$ and acetic acid) was considerably more convenient and provided the indolines in consistently high yields. Treatment of either 84 or 90 in acetic acid with several equivalents of sodium cyanoborohydride over the course of

two hours resulted in the conversion of the starting material to the more polar, red-colored indoline, as followed by TLC. Here again, the reaction proceeds by way of the protonated iminium species, which is reduced by cyanoborohydride.



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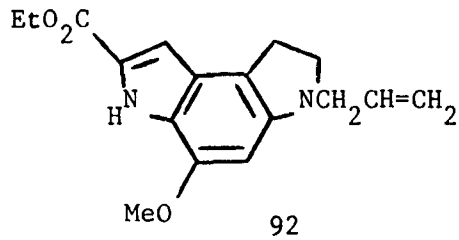
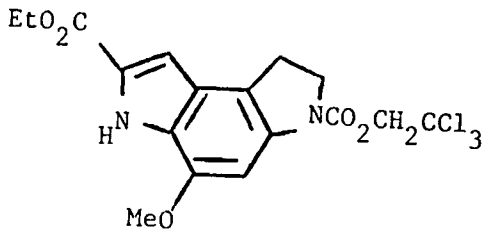


92

Indolines 91 and 92 were found to be considerably more labile towards re-oxidation to the indole than the corresponding 5-acetyl compounds. Initially obtained indoline compounds, after storage under vaccuum overnight, began to show oxidation to the indole, as seen by the appearance in TLC of a fluorescent blue spot corresponding to the aromatized material.

For this reason, indolines 91 and 92 were not isolated but used immediately for the deprotection reactions. The reaction of indolines 91 and 92 with 2,2,2-trichloroethyl chloroformate was investigated[18e]. It will be recalled that, in the case of the 4-acetoxy-5-acetyl compounds discussed in chapter II, treatment with this reagent gave only ring-opened product. It was hoped that, in the absence

of the steric effect of the 5-acetyl substituent, dealkylation would be favored over ring-opening. In the event, treatment of either 91 or 92 with the chloroformate in acetonitrile resulted in good conversions to the trichloroethoxycarbonyl compound 93. Comparable dealkylation yields were obtained using either the N-allyl or N-benzyl substrate. Carbamate 93 was obtained as a

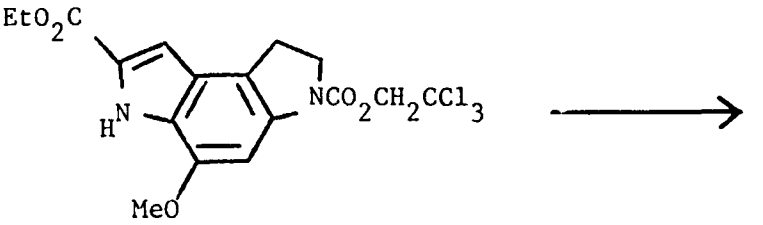


93

beautifully crystalline compound which was fully characterized by NMR, mass spectrometry and elemental analysis. The NMR spectrum of 93 was in full accord with the structure expected (1.42, t, 3H; 3.30, t, 2H; 4.00, s, 3H; 4.30, t, 2H; 4.42, q, 2H; 4.85, s, 2H; 7.05, d, 1H; 7.65, s, 1H; 9.03, broad, 1H) and the mass spectrum indicated the correct formula weight and showed the expected isotope pattern for three chlorines.

Treatment of carbamate 93 with zinc in acetic acid resulted in conversion to a polar reddish-orange compound, presumably the free indoline 94. Due to the expected

lability of this compound towards oxidation, it was immediately treated with acetyl chloride and pyridine. Methoxy amide 95, the methyl ester of 5-deoxy PDE-II, was obtained in 65% yield from carbamate 93. In addition to 95, some unreacted carbamate was recovered which could be recycled. The NMR spectrum of 95 was in accord with the proposed structure (NMR: δ 1.42, t, 3H; 2.25, s, 3H; 3.30, t, 2H; 4.00, s, 3H; 4.20, t, 2H; 4.42, q, 2H; 7.07, d, 1H; 8.05, s, 1H; 9.01, broad, 1H) and the compound was further characterized by mass spectrometry and elemental analysis.



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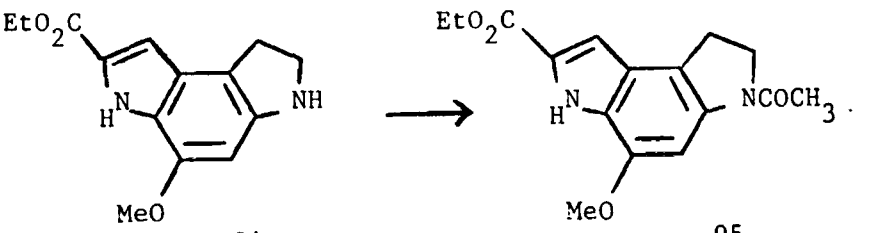


94 95

With the acquisition of deoxy compound 95, the possibility of oxidizing the 5-position to the phenol was of interest to consider. Taylor has developed a method for the oxidation of electron rich aromatic systems to phenols

via an arylthallium intermediate[48]. Such electron rich systems generally form the products of thallium substitution on the ring readily when treated with thallium(III) trifluoroacetate[49]. In addition, 95 potentially benefits from the directing effect of the N-acetyl substituent. These arylthallium compounds are generally stable and may be elaborated by a variety of methods developed by Taylor and his colleagues. It was found by these workers that treatment of the thallated intermediates with lead tetraacetate, followed by addition of tributylphosphine and then hydrolytic workup, provided a one-pot synthesis of phenols in moderately good yields. It is thought that an aryllead species, the product of metal-metal exchange, may be an intermediate in this process. Direct reaction of the arylthallium intermediates with hydroxide cannot be used to make phenols, as the products of this reaction are stable arylthallium oxides.

Treatment of a solution of 95 in trifluoroacetic acid with thallium(III) trifluoroacetate led to immediate formation of a dark red solution. Upon treatment with lead tetraacetate the mixture quickly changed to a brown color. The addition of 6N HCl led to the formation of a precipitate, presumably chloride salts of thallium(II) and lead(I). The reaction mixture was treated with triphenylphosphine, made alkaline, and stirred for 30 minutes. After neutralization and extraction into methylene

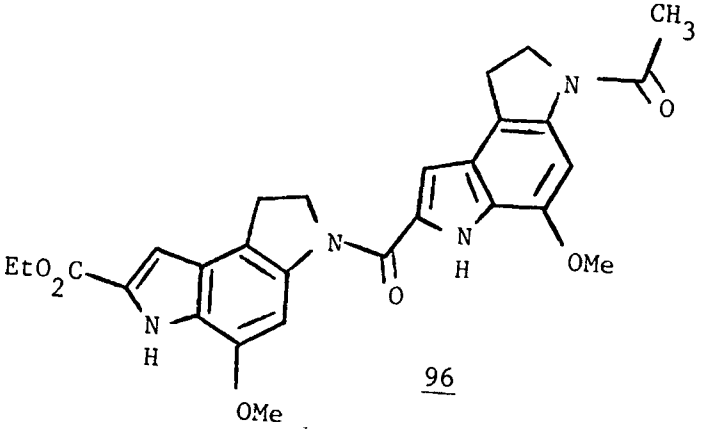
chloride, drying and removal of the solvent did not produce any characterizable organic material. Extraction of the aqueous fraction under both basic and acidic conditions did not lead to the isolation of any further material.

In order to determine whether thallation of the aromatic ring was indeed taking place, the procedure published for synthesis of the corresponding iodo compound from the arylthallium species was followed[50]. Compound 95 was treated with 1.1 equivalents of thallium trifluoroacetate followed by an aqueous solution of excess potassium iodide. After reductive workup two components were isolated in poor yield. Neither gave a good NMR spectrum but it appeared that the products were starting material and oxidized (aromatized) starting material, as indicated by mass spectra of the two fractions; formula weights of 302 and 300 were indicated. The aromatized material was the predominate fraction. The thallium reagent may thus be acting as an oxidant towards the pyrrolidine ring. This reaction was not investigated further.

III.5. Summary and Prospects for Analogue Synthesis

The route described herein should allow for the synthesis of 5-deoxy compound 95 in sufficient quantities to allow coupling to form the dimer 96. The conditions for such dimerization have been worked for similar systems have been worked out by Boger and should be applicable to the 4-

methoxy compound. Coupling of this dimer with the A ring moiety should provide 5-deoxy-CC-1065. This compound may prove of interest in biological testing. Such an analogue may show reduced cytotoxicity while retaining the helical pitch and thus DNA-binding characteristics of the parent molecule. Saponification of the ester of 95 would provide the acid as one component of the coupling, which would be reacted with the indoline 94, obtained from reductive cleavage of 93 in the presence of a suitable carbonyl activating agent.



96

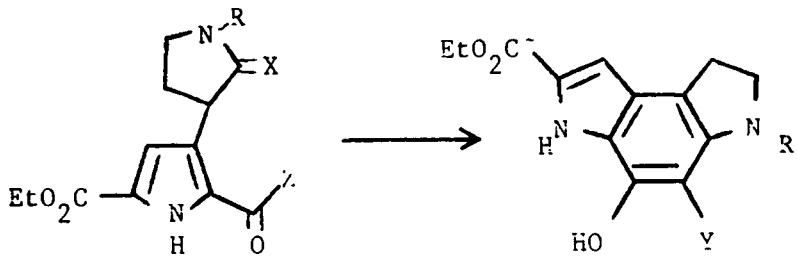
Other methods to functionalize the 5-position of 95 may also be worth considering. Electrophilic mercuration may occur to provide the organomercury compound, though this reagent may also show a tendency to oxidize the non-aromatic ring.

Bromination of the 5-position with N-bromosuccinimide may prove to be a method for obtaining the 5-halo compound.

CHAPTER IV

SUMMARY AND SIGNIFICANCE OF RESULTS

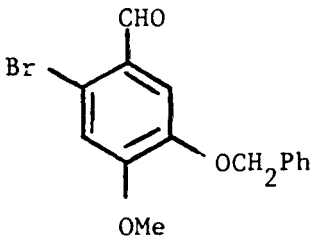
The work discussed herein demonstrates that 3-(3-pyrrolyl)thiopyrrolidines are useful intermediates for the synthesis of interesting and potentially significant benzodipyrrole structures. In the case where Z = $COCH_3$, it



has been shown that the benzodipyrrole obtained by aldol type cyclization (Y = $COCH_3$) may be elaborated into an intermediate which constitutes a formal total synthesis of the natural products PDE-I and PDE-II. When Z is a good leaving group (Z = CH=N=N), cyclization proceeds to provide the 5-unsubstituted compounds (Y = H). This route has provided access to the 5-deoxy analogue of PDE-II ethyl

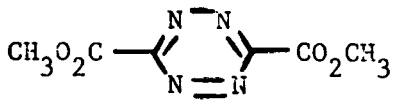
ester, a compound which may be of interest in the ongoing search for active, less toxic analogues of CC-1065.

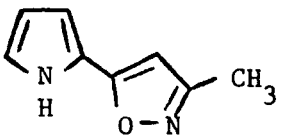
It is instructive to compare the overall yields of the PDE-II synthesis developed in this work with those of other workers. The synthesis of PDE-I and PDE-II described by Cava (Chapter I) is the most efficient published to date. His synthesis proceeds in 10 steps from SEM-protected pyrrole to PDE-II in 20% overall yield. The synthesis



of Rees, beginning with the bromobenzaldehyde shown, delivers PDE-I in 11 steps and net yield of 7.1%. Boger's synthesis requires 16 steps from 1,2,4,5-tetrazine-3,6-dicarboxylate to PDE-II and provides the product in overall yield of 3.7%. Comparably, the synthesis described herein proceeds in 18 steps and 3.7% overall yield from 2-(isoxazolyl)pyrrole to PDE-II. Finally, Magnus, starting from methyl pyrrole-2-carboxylate, obtained PDE-I and

II in 13 steps in a net yield of 0.9%.





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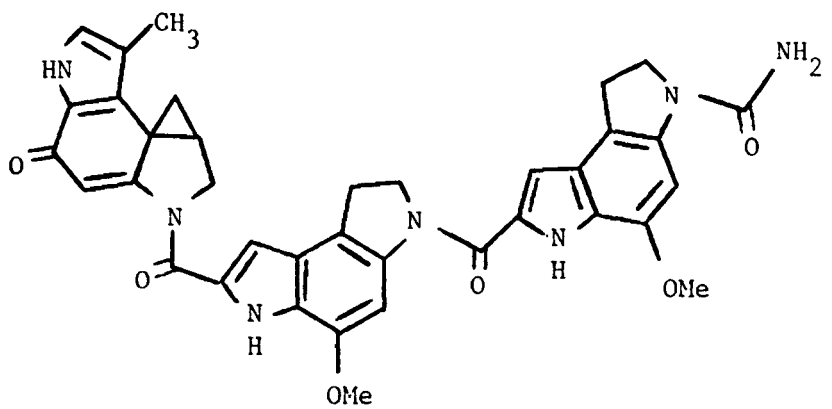
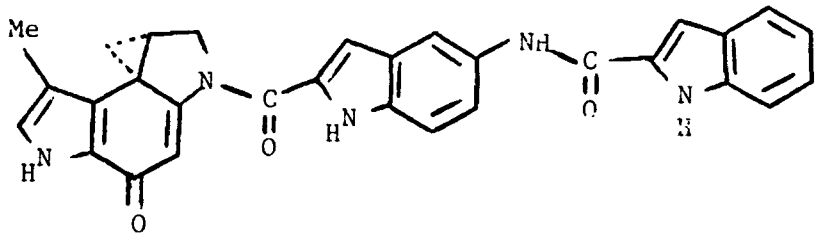
As noted previously, the synthesis of the 5-deoxy compound 95 provides a new, previously unreported analogue of the B/C rings of CC-1065. This material is available in 17 steps and 3% overall yield from 2. Synthethesis



sis of the corresponding CC-1065 analogue molecule (above) and comparison of its biological properties with those of

CC-1065 and wirenga's dideoxy analogue U-71,184 may provide increased understanding regarding the role of the oxygenation substitution in the cytotoxicity of CC-1065.



U-71,184

Chapter V

General Experimental Methods

Nitrogen was dried by bubbling through concentrated sulfuric acid followed by passing through sodium hydroxide pellets. A dry nitrogen atmosphere was routinely used for all experiments involving air and/or moisture sensitive reagents. Transfers of air and/or moisture liquids were done using oven dried syringes. All organometallic reactions were carried out in oven and/or flame dried glassware. Evaporation of solvents was done using a Buchler rotary evaporator.

Reagents and Solvents

Commercially available reagents were used as purchased unless otherwise noted. Diethyl ether, hexanes, tetrahydrofuran, toluene and xylenes were distilled from the sodium ketyl of benzophenone for anhydrous use. Methanol and ethanol were obtained in anhydrous form by distilling from the magnesium alkoxide by the procedure of Gordon and Ford[51]. Diisopropylamine, pyridine, pyrrolidine and triethylamine were distilled from calcium hydride.

Chromatography

Flash chromatography was performed according to the procedure of Still[52]. Analytical thin layer chromatography

was done using Merck 60 F-254 silica gel plates. Visualization was done by UV illumination, iodine development or vanillin spray followed by heating.

Analytical Data and Instrumentation

Melting points are uncorrected. Proton NMR spectra were recorded on a Varian EM 390-instrument (90 MHz) or a Nicolet NT-360 with 1280/293B data system (360 MHz) using chloroform or tetramethylsilane as a reference. The low resolution mass spectra were recorded on a Finnegan Model 3200 by UVa chemistry personnel. Elemental analyses were performed by Atlantic Micro-lab Inc., Atlanta, Georgia.

Experimental Procedures

Ethyl 4-(1-Allyl-3-hydroxy-2-oxopyrrolidin-3-yl)-5-(3-methyl-isoxazol-5-yl)pyrrole-2-carboxylate (15).

Sodium hydride (500mg of a 60% oil disperion; 300mg net; 12.5mmol) was added to a solution of bromo pyrrole 4 (MW 299; 3.31g; 11.1mmol) in 150ml of dry THF. The mixture was stirred for 10 minutes at room temperature and then cooled to -98^{0}C (liquid nitrogen/methanol bath). A solution of tert-butyllithium (1.7M in hexane; 14ml; 23.0mmol) was added via syringe, giving rise to a deep red solution. There was quickly added a solution of 1-allylpyrrolidine-

2,3-dione (MW 139; 2.01g; 14.4mmol) in 10ml of THF pre-cooled to -78^{0}C. The reaction mixture was stirred for an hour at -98^{0}C, allowed to come to room temperature, and stirred for an additional hour. Acetic acid, several milliliters, was added, and the mixture was poured into 200ml of water. Dilute HCl was added until the color lightened to a pale brownish orange (~pH 5). The product was extracted into ethyl acetate. Chromatography of the crude material obtained by drying and evaporation of the solvent (1:1 hexanes:ethyl acetate) delivered 15 (MW 359; 2.10g; 53%) as a white crystalline compound, mp 174^{0}C. There was also recovered from the column 1.03g of debrominated compound 3. 15:^{1}H NMR (360 MHz): 1.40, triplet, 3H; 2.25, singlet, 3H; 2.35-2.50, m, 2H; 3.40, doublet of multiplets, 2H; 4.00-4.20, AB quartet, 2H; 4.35, quartet, 2H; 5.36, multiplet, 2H; 5.90, m, 1H; 6.55, singlet, 1H; 6.74, doublet, 1H. EI MS: m/z 359, 341, 263, 247, 201 amu. Anal. Calcd. for $C_{18}H_{21}N_3O_5$: C 60.16, N 11.69, H 5.89. Found: C 60.33, N 11.60, H 5.93.

Ethyl 4-(1-Allyl-2-oxopyrrolidin-3-yl)-5-(3-methyl-isoxazol-5-yl)pyrrole-2-carboxylate (16).

Adduct 15 (129mg; 0.36mmol) was dissolved in 5ml of trifluoroacetic acid in a 25ml flask. Triethylsilane, 1.0ml, was immediately added and the mixture was stirred vigorously at room temperature for 2 hours. Additional

0.5ml aliquots of triethylsilane were added at 30min intervals. The volatiles were removed on a vaccuum aspirator to afford a tan gummy sub-stance which was purified by flash chromatography (1:1 hexanes:ethyl acetate). There was obtained 108mg (0.31 mmol; 86%) of 16 as a solid material. ^{1}H NMR (360 MHz): 1.37, t, 3H; 2.15, m, 1H; 2.32, s, 3H; 2.55, m, 1H; 3.50, m, 2H; 3.90-4.10, m, 3H; 4.35, q, 2H; 5.25, m, 2H; 5.80, m, 1H; 6.45, s, 1H; 6.80, d, 1H; 9.65, broad, 1H. EI MS: m/z 343, 228, 145, 123 amu.

Ethyl 4-(1-Allyl-2-oxo-Δ^3-pyrrolidin-3-yl)-5-(3-methyl-isoxazol-5-yl)pyrrole-2-carboxylate (17).

Alcohol 15 (24.9 mg; 0.07mmol) was dissolved in 3ml of concentrated hydrochloric acid and stirred at room temperature for 20 min. The mixture was poured into water and extracted into ethyl acetate; purification of the crude material obtained by evaporation of the solvent (flash chromatography; 1:1 hexanes:ethyl acetate) delivered olefin 17 as a crystalline solid (MW 341; 19.3mg; 0.06mmol; 86%). ^{1}H NMR (360 MHz): 1.37, t, 3H; 2.32, s, 3H; 4.05, d, 2H; 4.17, d, 2H; 4.35, q, 2H; 5.25, m, 2H; 5.85, m, 1H; 6.29, s, 1H; 7.20, t, 1H; 7.32, d, 1H; 9.71, broad, 1H.

Ethyl 4-(1-Allyl-2-thioxopyrrolidin-3-yl)-5-(3-methyl-isoxazol-5-yl)pyrrole-2-carboxylate (18).

Isoxazole 16 (MW 343, 1.54mmol; 527mg) and P_4S_{10} (103 mg, 0.23mmol) were heated to reflux in 30ml of toluene for 30min, at which point TLC indicated disappearance of starting material and appearance of a major, less polar spot along with two minor, still less polar substances. The toluene was decanted off and the residue was triturated with several portions of hot toluene. The combined toluene fractions were concentrated to a crude material which was purified by flash chromatography (1:1 hexane:ethyl acetate). Thiolactam 18 was obtained as an off-white solid (377mg; 1.05mmol; 68%). Recrystallization from ethyl acetate/hexanes provided fluffy, snow-white crystals, mp 149 -150^{0}C. Trace amounts of two compounds assigned structures 19 and 20 were also isolated from the column. 18:^{1}H NMR (360 MHZ): 1.35, t, 3H; 1.90-2.60, m, 2H; 2.30, s, 3H; 3.60, m, 2H; 4.10- 4.60, m, 5H; 5.25, m, 2H; 5.90, m, 1H; 6.40, s, 1H; 6.70, d, 1H; 9.70, broad, 1H. Anal. Calcd. for $C_{18}H_{21}N_3O_3S$: C 60.15, H 5.89, N 11.69 Found: C 60.06, H 5.91, N 11.62 19:^{1}H NMR (360 MHz): 1.40, t, 3H; 2.28, s, 3H; 4.35, q plus d, 4H; 4.53, d, 2H; 5.22, m, 2H; 6.00, m, 1H; 6.55, s, 1H; 6.68, t, 1H; 6.91, d, 1H; 9.10, broad, 1H. EI MS: m/z 357, 342, 325, 279 amu. 20: EI MS: m/z 375, 356, 342, 325, 298, 279 amu.

Ethyl 4-(1-Allyl-2-thioxopyrrolidin-3-yl)-5-(3-amino-1-oxobut-2-enyl)pyrrole-2-carboxylate (21).

Thiolactam 18 (MW 359, 88.3mg; 0.25mmol) and molybdenum hexacarbonyl (MW 264; 35.9mg; 0.14mmol) were dissolved in 20ml of moist acetonitrile (15 drops of water added) and heated to reflux for 90 minutes. During this time the mixture turned black. Removal of the solvent under reduced pressure furnished a black gum; purification of this material via flash chromatography removed the black residue and delivered enaminone 21 (MW 361; 84.5mg; 95%) as a brownish oil. 21: ^{1}H NMR (360 MHZ): 1.35, t, 3H; 2.05, s, 3H; 2.00-2.15, m, 1H; 2.60, m, 1H; 3.65-3.80, m, 2H; 4.30, q, 2H; 4.40-4.55, AB m, 2H; 4.80, t, 1H; 5.35, m, 2H; 5.57, s, 1H; 5.90, m, 1H; 6.70, d, 1H; 9.55, broad, 1H.

Ethyl 4-(1-Allyl-2-thioxopyrrolidin-3-yl)-5-(1,3-dioxobutyl)pyrrole-2-carboxylate (22).

Enaminone 21 (MW 361; 127mg; 0.35mmol) was dissolved in 15ml of THF and treated with 15ml of 5% HCl. After stirring at 50^{0}C for 20 minutes the mixture was poured into water and extracted into ethyl acetate. The organic portions were dried and concentrated, and the residue was recrystallized from chloroform/hexanes to furnish diketone 22 (MW 362, 115mg, 0.32mmol; 91%) as an off-white solid, mp 144 -145^{0}C. 14:^{1}H NMR (360 MHz): 1.37, t, 3H; 2.10, m, 1H; 2.18, s, 3H; 2.60, m, 1H; 3.70-3.85, m, 2H; 4.35, q, 2H; 4.40-4.60, AB m, 2H; 4.70, t, 1H; 5.35, m, 2H; 5.90, m, 1H; 6.05, s, 1H; 6.77, d, 1H; 9.58, broad, 1H. Anal. Calcd.

for $C_{18}H_{22}N_2O_4S$: C 59.65, H 6.12, N 7.73. Found: C 59.68, H 6.16, N 7.70

Ethyl 5-Acetyl-6-allyl-4-hydroxy-3,6,7,8-tetrahydrobenzo [1,2-b:4,3-b']dipyrrole-2-carboxylate (12).

To a solution of ketothiolactam 22 (MW 362; 215mg; 0.59mmol) in 3ml of THF was added 0.1ml of methyl iodide (MW 142; 1.80mmol; 3eq). This mixture was placed in a Pyrex glass tube, sealed, and heated to 80°C for 15 hr. A thick precipitate of light yellow crystals formed during this time. After cooling to -78°C, the tube was opened and its contents poured into 10ml of water. The aqueous mixture was made slightly basic with sodium bicarbonate and extracted with several portions of methylene chloride. The organic portions were dried (Na_2SO_4) and concentrated to provide the product as a bright yellow-orange solid, which was recrystallized from chloroform/hexanes to provide 12 as yellow needles, mp 132-134°C (MW 328; 184mg; 95%). 12: ^{1}H NMR (360 MHz): 1.40, t, 3H; 2.80, s, 3H; 3.07, t, 2H; 3.44, d, 2H; 3.57, t, 2H; 4.42, q, 2H; 5.19-5.39, m, 2H; 5.90, m, 1H; 6.95, d, 1H; 9.25, broad, 1H.

On some runs a trace amount of a slightly more polar compound was noticed by TLC. This compound was isolated and characterized as the acetate and assigned structure 25: ^{1}H NMR (360 MHz): 1.40, t, 3H; 2.39, s, 3H; 2.59, s, 3H; 2.69, s, 3H; 3.17, t, 2H; 3.50, t, 2H; 4.40, q, 2H; 7.00, d, 1H;

8.66, broad, 1H. EI MS: 344, 302, 256, 228 amu.

Ethyl 4-Acetyl-8b-allyl-1,2-dihydropyrrolo[3,2-e] indol-5-one (27).

A. By thermolysis. Compound 12 (MW 328, 24.1mg; 0.07mmol) placed in a Pyrex tube with 2ml of ethanol, frozen and degassed, and sealed under nitrogen. The tube was heated to 100^{0}C for eight hours, during which time the bright red-orange color of the initial solution faded to a light yellow. The tube was cooled, opened, and its contents concentrated in vacuo. The crude material was chromatographed (1:1 hexanes:ethyl acetate) to obtain the rearrangement product 27 as the major component (MW 328, 14.5mg; 60%). There was also recovered 0.8mg of starting material, the remainder of the mass balance being polar tarry material. 27: ^{1}H NMR (360 MHz): 1.40, t, 3H; 2.15-2.55, multiplets, 4H total; 2.65, s, 3H; 3.85, m, 2H; 4.35, q, 2H; 4.95, d, 1H; 5.13, d, 1H; 5.6, m, 1H; 6.75, d, 1H; 9.70, broad, 1H. CI MS: m/z 329 (M+1) EI MS: m/z 328, 286, 241 amu. Anal. Calcd. for $C_{18}H_{20}O_4N_2$: C 65.84, H 6.13, N 8.53 Found: C 65.70, H 6.18, N 8.47.

B. By treatment with base. A sample of compound 12 (15.4mg; 0.05mmol) was dissolved in ethanol and treated with several mg of potassium carbonate. This mixture was stirred overnight. Removal of the solvent, after neutralization, and chromatographic resolution of the

residue delivered aromatized starting material 24 (4.4mg) and enone 27 (3.6mg)

Ethyl 4-Acetoxy-5-acetyl-6-allyl-3,6,7,8-tetrahydro benzo[1,2-b:4,3-b']dipyrrole-2-carboxylate (23).

N-allyl benzodipyrrole 12 (MW 328; 180mg; 0.54mmol) was dissolved in 5ml of dry methylene chloride and treated with acetic anhydride (10 drops) and dimethylaminopyridine (10mg). After stirring at room temperature for 15min, TLC indicated complete conversion to a more polar, bright orange compound. The reaction mixture was concentrated to a crude material which was subjected to flash chromatography (1:1 hexanes/ethyl acetate). Acetate 23 was obtained as an orange oil (MW 370; 190mg; 0.51mmol; 94%). In some runs, a small amount of the fully aromatized indole 25 was obtained and characterized. 23: ^{1}H NMR (360 MHz): 1.42, t, 3H; 2.37, s, 3H; 2.58, s, 3H; 3.20 t, 2H; 3.45-3.60, m, 4H; 4.40, q, 2H; 5.10-5.30, m, 2H; 5.85, m, 1H; 7.00, d, 1H; 8.67, broad, 1H. EI MS: m/z 370, 326, 310, 264, 168, 85. 25: ^{1}H NMR (360 MHz): 1.42, t, 3H; 2.40, s, 3H; 2.60, s, 3H; 4.42, q, 2H; 4.67, m, 2H; 4.80-5.20, m, 2H; 5.80-5.95, m, 1H; 6.80, d, 1H; 7.15, d, 1H; 7.45, d, 1H; 8.80, broad, 1H.

Attempted Deallylation of 27 with Thiophenoxide

Sodium metal (2.2mg; 0.01mmol) was dissolved in 2ml of

absolute ethanol. To this sodium ethoxide solution was added a solution of thiophenol (MW 110; 30.7mg; 0.3mmol) in 3ml of ethanol. After stirring this mixture for several minutes at room temperature a solution of 27 (15.0mg; 0.05mmol) in 3ml of ethanol was added and the mixture was heated to reflux for 10 hours. TLC indicated that only starting material was present. Workup delivered unchanged starting material in virtually quantitative mass balance.

Attempted Deallylation of 27 with Palladium(II) / Tri-n-Butyl Hydride

Compound 27 (13.0mg; 0.04mmol) and bis(triphenylphosphine)palladium(II) chloride (3.5mg; 0.005mmol) were stirred together in 1.5ml of moist methylene chloride and treated with freshly distilled tri-n-butyltin hydride (19.3mg; 0.07mmol) in 5ml of methylene chloride. After stirring for four hours, TLC indicated only starting material was present. The reaction was quenched with 1.5ml of 10% HCl, poured into water, and extracted with methylene chloride. The methylene chloride extracts were dried and concentrated to afford pure unchanged starting material after chromatography.

Attempted Baeyer-Villiger Oxidation of 27

A solution of meta-chloroperoxybenzoic acid (8.7mg; 0.05mmol) in 1ml of dry methylene chloride was stirred at

room temperature and treated with a solution of compound 27 (12.2mg; 0.04mmol) in 2ml of methylene chloride. This mixture was stirred at room temperature for four hours; no change was discernible by TLC. An additional equivalent of MCPBA was added and stirring was continued overnight. No product appeared to have developed. Workup and chromatography delivered, in addition to m-chlorobenzoic acid, only pure unchanged 27.

Attempts to O-Methylate 12 with Diazomethane

A. In Ether, With Boron Trifluoride-Etherate

Boron trifluoride-etherate (MW 142; 23.7mg; 0.17mmol) was added via syringe to a solution of N-allyl benzodipyrrole 12 (54.8mg; 0.17mmol) in 20ml of dry ether. The mixture quickly turned red with the formation of a precipitate. Diazomethane, ca. 30mg (MW 42; 0.71mmol; 4.3eq) was added as an ethereal solution and the mixture was stirred overnight. The reaction was quenched with several drops of acetic acid, poured into aqueous sodium bicarbonate, and extracted with several portions of methylene chloride. The combined organic extracts were dried (Na_2SO_4) and concentrated to afford 46.1mg of crude material. Chromatography of this material delivered starting material (3.9mg) and aromatized starting material 24 (MW 326; 16.8mg) in addition to a small amount of compound 27(2.4mg). 24: ^{1}H NMR (360 MHz): 1.43, t, 3H;

2.60, s, 3H; 4.40, q, 2H; 4.60, d, 2H; 5.20-5.33, m, 2H; 5.80, m, 1H; 6.80, d, 1H; 7.05, d, 1H; 7.32, d, 1H; 9.39, broad, 1H.

B. In Methanol

Compound 12 (17.8mg; 0.05mmol) was dissolved in 3ml of absolute methanol and treated with diazomethane (13.0mg; 0.30mmol) as an ethereal solution. After stirring under nitrogen at room temperature for 3 1/2 hours the reaction was worked up as above. After chromatography, only 8.6mg of identifiable material was obtained. The majority of the recovered material (70%) consisted of the rearrangement compound 27 and its N-methylated derivative. The remainder consisted of the O-methylated indole 30. 30: ^{1}H NMR (360 MHz): 1.45, t, 3H; 2.75, s, 3H; 3.95, s, 3H; 4.45, q, 2H; 4.68, m, 2H; 4.75 and 5.10, m, 2H total; 5.90, m, 1H; 6.75, d, 1H; 7.10, d, 1H; 7.43, t, 1H; 9.05, broad, 1H.

C. In Methylene Chloride

Benzodipyrrole 12 (15.0mg; 0.05mmol) was dissolved in 10ml of methylene chloride, cooled to -78^{0}C, and treated with an ethereal solution of diazomethane (10mg in 1.5ml of ether; 0.23mmol). After 1 1/2 hours of stirring, an additional aliquot of diazomethane was added and stirring was continued for another 5 1/2 hours. TLC indicated only starting material present. Workup and purification

delivered only unchanged starting material.

Methylation with Cyclic Oxaphospholene 33

Benzodipyrrole 12 (15.0mg; 0.05mmol) was dissolved in THF (1.5ml) and treated with a solution of oxaphospholene 33[33] (MW 194; 26.2mg; 0.14mmol) in 2.0ml of THF. After stirring overnight, TLC showed a new, less polar spot appearing. Several additional drops of methylating agent were added, and stirring was continued for a total of 120 hours; at this point, no starting material could be detected by TLC. After aqueous extractive workup (methylene chloride) and chromatography (1:1 hexanes:ethyl acetate) two products were isolated in rather poor mass balance (6.8mg). Roughly 2/3 of the product was compound 32, consisting entirely of N-methylated starting material with no O-methylated product; the remainder (2.4mg) was assigned structure 28, the rearrangement product 27 methylated on the indole nitrogen. This assignment was supported by NMR and mass spectral data. 32: ^{1}H NMR (360 MHz): 1.42, t, 3H; 2.80, s, 3H; 3.05, t, 2H; 3.40, d, 2H; 3.55, t, 2H; 4.40, q, 2H; 4.43, s, 3H; 5.15-5.35, m, 2H; 5.87, m, 1H; 6.95, s, 1H. 28: ^{1}H NMR (360 MHz): 1.40, t, 3H; 2.15, 2.35, and 2.50, m, 4H total; 2.65, s, 3H; 3.80, m, 2H; 4.30, q, 2H; 4.35, s, 3H; 4.95-5.15, m, 2H; 5.60, m, 1H; 6.75, s, 1H. EI MS: m/z 342, 300, 275 amu.

Reaction of 12 with Potassium Tert-Butoxide / Methyl Iodide

Potassium tert-butoxide (MW 112; 9.1mg; 0.08mmol) was added in one portion to a stirred solution of 12 (23.0mg; 0.07mmol) in 5ml of dry THF at -23^{0}C. This mixture was stirred together for 30min and then treated with a solution of methyl iodide (MW 142; 14.2mg; 0.1mmol) in 1.0ml of THF. This mixture was stirred at -23^{0}C for one hour and allowed to slowly come to room temperature. TLC indicated several components present in addition to unreacted starting material. An additional aliquot of methyl iodide (13.9mg; 0.1mmol) was added and the reaction mixture was stirred overnight at room temperature. It was poured into water and extracted into methylene chloride; the organic extracts were dried and concentrated to deliver 18.9mg of crude product mixture. This consisted largely of intractable material. A small amount (5.2mg) of material was obtained after chromatography that appeared to consist of primarily the O-methylated indole 30. An additional weak signal at 4.29 ppm in in the NMR and a mass signal at 356 amu in the mass spectrum indicated the presence of some of the dimethylated material 31 EI MS: m/z 356, 354, 342, 340 amu.

Reaction of 12 with Potasasium Tert-Butoxide / Methyl Sulfate

To a stirred suspension of potassium tert-butoxide in

1.5ml of dry THF, cooled to -20^{0}C under a nitrogen atmosphere, was added compound 12 (11.7mg; 0.04mmol) as a THF solution (1.5ml). After stirring at -20^{0}C for 30min, freshly distilled methyl sulfate, 2 drops, was added, and after stirring together at -20^{0}C for 30 minutes the mixture was allowed to come to room temperature. After 2 hours of stirring, TLC indicated that the starting material was roughly half gone. An additional 2 drops of methyl sulfate was added and the mixture was stirred at room temperature overnight. The reaction mixture was poured into water and extracted into methylene chloride; the organic layers were washed with several portions of 2N aqueous ammonia and with brine, dried, and concentrated to furnish 8.7mg of material. Again, chromatography delivered organic product in very poor mass balance.Several mg each of two fractions were obtained; one was a mixture of O- and N-methylated products 30 and 31 similar to the previous experiment, the other was a pure sample of rearranged enone 27.

Reaction of 12 with Sodium Hydride / Methyl Iodide

A suspension of sodium hydride (60% dispersion in oil; 3.3mg; 0.08mmol) in 1.5ml of dry THF stirred at -20^{0}C was treated with a solution of 12 (24.7mg; 0.08mmol) in 2.0ml of THF. This mixture was stirred at -23^{0}C for 30 minutes and then treated with 2 drops of methyl iodide. The mixture was allowed to come to room temperature and treated with 2

more drops of methyl iodide. TLC after several hours showed that three components were present; a pair of non-polar spots and a more polar fluorescent blue one. The reaction was worked up in the usual way to obtain 23.1mg of crude material. Chromatography delivered three fractions totaling 17.1mg. The uppermost spot, 4.3mg, was a mixture of 30 and oxidized starting material. The next fraction was pure 24 (3.5mg). The major fraction (9.3mg) was the rearranged compound 27.

Methylation of 12 under Phase Transfer Conditions

Compound 14 (14.7mg; 0.05mmol) was dissolved in 3ml of methylene chloride. To this was added a solution of 14.9mg of sodium carbonate in 3ml of water, 3 drops of a 40% aqueous solution of tetrabutylammonium hydroxide in water, and 2 drops of freshly distilled methyl sulfate. This mixture was stirred vigorously at room temperature for 14 hours. It was poured into sodium bicarbonate solution and the layers were separated; the aqueous layer was washed with methylene chloride and the combined organic fractions were washed with 2N ammonia and brine, dried, and concentrated to a greenish oily substance. This was passed through a flash column (1:1 hexane:ethyl acetate). Again, the mass balance was poor; only 3.0mg of characterizable material was obtained, divided equally between two fractions. The uppermost spot was the dimethylated compound

31, characterized by NMR and mass spectroscopy. The more polar material was compound 28, identical to other characterized samples. In another run using potassium carbonate as the base, similar yields and product mixtures were obtained, with the N-methylated rearrangement compound 28 predominating. 31: ^{1}H NMR (360 MHz): 1.45, t, 3H; 2.75, s, 3H; 3.85, s, 3H; 4.38, s, 3H; 4.40, q, 2H; 4.68, m, 2H; 5.10-5.20, m, 2H; 5.90, m, 1H; 6.75, d, 1H; 7.07, d, 1H; 7.50, s, 1H. EI MS: m/z 354, 340, 314, 251, 149 amu.

Reaction of 23 with Cyanogen Bromide

Acetate 23 (MW 370; 25.8mg; 0.07mmol) and cyanogen bromide (MW 106; 23.4mg; 0.22mmol) were dissolved in 2ml of dry 1,2-dichloroethane. The solution was placed in a Pyrex tube, flushed with nitrogen, and frozen and degassed several times. The tube was sealed under vaccuum and heated on an oil bath to 92^{0}C for 3 hrs; during this time the tube's contents darkened The tube was cooled, opened, and its contents were poured into water and extracted into methylene chloride. TLC of the crude product indicated two major components. The crude material was purified by flash chromatography to furnish the two spots. The first, 7.9mg, gave a very rough NMR which was not interpretable. The second component, 6.3mg, was assigned the structure 40 on the basis of NMR and mass spectral data. 40: ^{1}H NMR (360 MHz): 1.42, t, 3H; 2.42, s, 3H; 2.67, s, 3H; 3.57, m,

2H?; 3.70-4.00, m, 4H?; 4.45, q, 2H; 5.40, d of m; 2H; 6.0, m, 1H; 7.30, d, 1H; 9.13, broad, 1H. EI MS: m/z 475, 477 (bromine isotope pattern), 433, 369, 354, 340, 327, 286, 240 amu.

Reaction of 23 with Vinyl Chloroformate

Acetate 23 (41.4mg; 0.11mmol) and vinyl chloroformate (MW 107; 45.0mg; 0.42mmol) were dissolved in 2ml of dichloroethane and placed in a Pyrex tube. After repeated freezing and degassing, the tube was sealed under vaccuum and heated to 100^0 C for 15 hrs. After cooling and opening, the tube's contents were poured into water and extracted into methylene chloride. TLC indicated the crude material to consist primarily of a single new product; no trace of starting material was left. Purification by flash chromatography (1:1 hexanes:ethyl acetate) afforded 36.8mg of ring-opened material 41. ^{1}H NMR (360 MHz): 1.45, t, 3H; 2.40, s, 3H; 2.42, s, 3H; 3.20-3.40, m, 2H; 3.68, m, 2H; 3.80, m, 2H; 4.40-4.50, q plus m, 4H; 4.60, m, 1H; 5.15, m, 2H; 5.85-6.00, m, 1H; 7.30, d, 1H; 9.13, broad, 1H. EI MS: m/z 478, 476, 463 461, 435, 433 (bromine isotope pattern), 391, 349, 301 amu.

Reaction of 23 with 2,2,2-Trichloroethyl Chloroformate

Acetate 23 (20.0mg; 0.05mmol) was dissolved in 5ml of acetonitrile and treated with 10 drops of 2,2,2-

trichloroethyl chloroformate. After stirring at room temperature for 30min the bright yellow-orange color of the starting material had disappeared. TLC indicated complete conversion to a new, slightly more polar compound. The reaction mixture was concentrated in vacuo and passed through a flash column, eluting with 2:1 hexanes:ethyl acetate. A single compound was isolated (24.8mg; 0.04mmol; 85%) which was assigned structure 42 on the basis of spectral data. 42: ^{1}H NMR (360 MHz): 1.43, t, 3H; 2.40, s, 3H; 2.48, s, 3H; 3.20-3.40, m, 2H; 3.55-3.85, m, 2H; 4.45, q, 2H; 4.80, s, 2H; 5.13, m, 2H; 6.0, m, 1H; 7.30, d, 1H; 9.30, broad, 1H. EI MS: m/z 542, 540, 538 (Cl4 isotope pattern), 522, 498, 433, 298, 267 amu.

Reaction of 23 with Tris(Triphenylphosphine)Rhodium Chloride (Wilkinson's Catalyst)

The acetylated N-allyl benzodipyrrole 23 (8.0mg; 0.02mmol) and Wilkinson's catalyst (MW 925; 8.9mg; 0.01mmol) in 1ml of absolute ethanol were placed in a Pyrex tube, frozen and degassed repeatedly, and sealed under vaccuum. The tube was heated to 100^{0}C for 3 hours, cooled, opened and its contents poured into aqueous sodium bicarbonate solution. The products were extracted into methylene chloride. TLC indicated three components were present; unreacted starting material and two new compounds. The crude product mixture obtained by evaporation of the

solvent was passed through a flash column (1:1 hexanes:ethyl acetate). In addition to unchanged starting material, 1.9mg of aromatized starting material (compound 25) was recovered. Also isolated from the column were 2.0mg of de-allylated, aromatized compound 43: ^{1}H NMR (360 MHz): 1.42, t, 3H; 2.55, s, 3H; 2.65, s, 3H; 4.42, q, 2H; 6.77, t, 1H; 7.35, t, 1H; 7.44, d, 1H; 8.97, broad, 1H.

Reaction of 23 with Tetrakis(Triphenylphosphine)Rhodium Hydride

Acetate 23 (8.0mg; 0.02mmol) and tetrakis(triphenylphos-phine)rhodium hydride (4.8mg; 0.005mmol; 0.25eq) were placed in a Pyrex tube with 1ml of absolute ethanol, frozen and degassed several times, and sealed under vaccuum. The tube was heated in an oil bath to 100^{0}C for 3 hours. After cooling, the tube was opened and its contents poured into aqueous sodium bicarbonate solution. The product was extracted into methylene chloride, and the organic portions were filtered to remove solid residue and dried over Na_2SO_4. TLC indicated that the starting material was completely gone, replaced by three new spots. Two had similar R_f's (0.5) and appeared reddish and blue, respectively, under UV light. The third was more polar, R_f 0.1. The mixture was separated on a flash column (1:1 hexanes ethyl acetate> 1:2 hexanes:ethyl acetate. The uppermost, reddish-appearing spot, 1.6mg, proved to be the

deallylated benzodipyrrole 44 (MW 330; 0.005mmol; 25%). The bluish material immediately below on TLC was assigned the structure 45; this was identical to 43 except for having lost its acetyl group (MW 286; 3.0mg; 0.01mmol; 50%). The most polar material, 1.1mg, proved to be the rearrangement compound 27. 45: ^{1}H NMR (360 MHz): 1.42, t, 3H; 2.86, s, 3H; 4.43, q, 2H; 6.8, d, 1H; 7.17, d, 1H; 7.35, d, 1H; 8.4, broad, 1H. EI MS: m/z 286, 240, 212 amu. 44: ^{1}H NMR (360 MHz): 1.42, t, 3H; 2.50, s, 3H; 2.55, s, 3H; 3.18, t, 2H; 3.75, t, 2H; 4.40, q, 2H; 6.80, d, 1H; 8.40, broad, 1H.

Ethyl 6-Acetyl-5-ethyl-4-hydroxy-3,6-dihydrobenzo [1,2-b:4,3-b']dipyrrole-2-carboxylate

Indole 43 (5.0mg; 0.02mmol) was dissolved in 0.5ml of trifluoroacetic acid and cooled to 0^{0}C. Triethylsilane (0.06ml) was added and the mixture was stirred for 2 hours. An additional 0.1ml of triethylsilane was added and stirring was continued for another 3 hours. The reaction mixture was concentrated in vacuo to a crude solid. This was dissolved in dry methylene chloride and treated with 6 drops each of acetic anhydride and a small amount of DMAP. This mixture was stirred under nitrogen for several hours, concentrated, and chromatographed (1:1 hexanes:ethyl acetate). The major component isolated (MW 358; 3.0mg; 50%) was the 5-ethyl compound 46, resulting from reduction of the ketone. This assignment was supported by NMR and mass

spectra. 46: ^{1}H NMR (360 MHz): 1.15, t, 3H; 1.40, t, 3H; 2.30, broad s, 3H; 2.45, s, 3H; 2.75, q, 2H; 3.20, t, 2H; 4.20, t, 2H; 4.40, q, 2H; 7.10, d, 1H; 8.60, broad, 1H. EI MS: m/z 358, 316, 270, 228, 175, 120 amu.

Reaction of 12 with Palladium(II) / Tri-n-Butyltin Hydride

A mixture of benzodipyrrole 12 (21.8mg; 0.07mmol) and bis(triphenylphosphine)palladium(II) chloride (MW 702; 4.8mg; 0.007mmol) in 3ml of dry methylene chloride was stirred at room temperature under a nitrogen atmosphere. To this mixture was added dropwise via syringe, over 5 minutes, freshly distilled tri-n-butyltin hydride (MW 291; 25.0mg; 0.09mmol) in 1.0ml of methylene chloride. After stirring for 30 minutes, TLC showed virtually complete loss of starting material; several new spots were present. Aqueous 10% HCl, 3ml, was added, causing the formation of a precipitate. After stirring for several minutes, the mixture was poured into 20ml of water and neutralized with sodium bicarbonate. The layers were separated and the aqueous layer was washed with several portions of methylene chloride; the organic fractions were dried and concentrated to a crude solid. This was passed through a flash column eluting with 1:1 hexanes:ethyl acetate. Three components were isolated having an overall mass of 17mg. A small amount (2mg) of the dealkylated aromatized product 45 was identified, and a larger fraction (4mg) proved to be the

rearranged compound 27. The major fraction consisted of a compound assigned structure 47 (MW 288; 11mg; 58%) on the basis of spectral data and comparison with those of compound 27. 47: ^{1}H NMR(360MHz): 1.40, t, 3H; 1.95-2.10, m, 1H; 2.68, s, 3H; 2.70-2.80, m, 1H; 3.75-3.82, m, 1H; 3.85-3.95, m, 1H; 3.98-4.05, m, 1H; 4.35, q, 2H; 6.83, d, 1H; 9.75, broad, 1H. EI MS: m/z 288, 260, 242, 227, 214, 143, 77 amu.

Reaction of Enone Tautomer 47 with Acetic Anhydride / DMAP

Compound 47 (MW 288; 3.0mg; 0.01mmol) was dissolved in 1.0ml of dry methylene chloride and treated with 2 drops of acetic anhydride and a bit of DMAP. TLC indicated rapid conversion to a less polar compound. Chromatography of the crude material obtained by evaporation of the solvent yielded compound 43 in nearly quantitative yield (3.4mg). 43: ^{1}H NMR (360 MHz): 1.45, t, 3H; 2.55, s, 3H; 2.75, s, 3H; 4.45, q, 2H; 6.80, t, 1H; 7.35, t, 1H; 7.45, d, 1H; 8.90, broad, 1H.

Reaction of Enone 47 with Methyl Triflate

Compound 47 (3.0mg; 0.01mmol) in 1ml of anhydrous THF was treated with methyl triflate (7.3mg; 0.04mmol) as a THF solution (1ml). After stirring at room temperature for 7 hours, the reaction mixture was poured into water and extracted into methylene chloride. Chromatography provided

as the main fraction unchanged starting material (2.5mg).

Reaction of 12 with Tetrakis(triphenylphosphine)Rhodium Hydride / Trifluoroacetic Acid

Benzodipyrrole 12 (20.0mg; 0.06mmol) was dissolved in 3ml of absolute ethanol and treated with trifluoroacetic acid (7.0mg; 0.06mmol) and tetrakis(triphenylphosphine)rhodium hydride (MW 1152; 20.4mg; 0.3mmol). This mixture was refluxed under nitrogen for 90 minutes. TLC indicated virtually complete loss of starting material. The reaction mixture was concentrated and chromatographed (1:1 hexanes:ethyl acetate> 1:2 hexanes:ethyl acetate) to provide three products. Aromatized compound 24 was isolated cleanly (7.3mg). The previously characterized rearrangement product 27 was also identified (5.0mg). The largest fraction (21.9mg) consisted mainly of triphenylphosphine-derived material, but also clearly contained compound 47 in ca. 5mg quantity.

On a repeat run, in addition to the above products a small amount of dealkylated indole 45 was also isolated.

Reaction of 23 with Palladium(II) / Tri-n-Butyltin Hydride

Acetate 23 (MW 370; 25.5mg; 0.07mmol) was dissolved in 2ml of moist methylene chloride and stirred at room temperature with bis(triphenylphosphine)palladium(II) chloride (MW 702; 10.2mg; 0.01mmol), treating this mixture

with tri-n-butytin hydride (MW 291; 36.4mg; 0.12mmol) added dropwise over the course of 10 minutes. After stirring for 45 minutes, TLC indicated that several components were present. The reaction was quenched with several drops of 10% HCl, poured into water, neutralized with sodium bicarbonate, and extracted into methylene chloride. The crude material was chromatographed to provide three products in overall high mass balance. The major product was the deallylated acetate 44, obtained quite pure (MW 330, 10.1mg; 44%) and characterized by NMR and mass spectroscopy. A smaller quantity (5.9mg) of the rearrangement compound 27 was also isolated, as well as a third fraction (10mg) that contained primarily unchanged starting material in addition to some tarry material. 44: ^{1}H NMR (360MHz): 1.40, t, 3H; 2.47, s, 3H; 2.57, s, 3H; 3.20, t, 2H; 3.75, t, 2H; 4.40, q, 2H; 6.19, broad s, 1H; 6.93, d, 1H; 8.45, broad, 1H. EI MS: m/z 330, 288, 242, 214 amu.

Reaction of 23 with Tetrakis(Triphenylphosphine)Rhodium Hydride/Trifluoroacetic Acid. Ethyl 4-Acetoxy-5-acetyl-3,6,7,8-tetrahydrobenzo[1,2-b:4,3-b']dipyrrole-2-carboxylate 44

Acetate 23 (78.0mg; 0.21mmol) was dissolved in 3ml of absolute ethanol and treated with trifluoroacetic acid (31.0mg; 0.27mmol) in 1.5ml of ethanol. Tetrakis(triphenylphosphine)rhodium hydride[26c] (MW 1152;

0.46mg; 0.04mmol) was added to the solution and this mixture was stirred under reflux for 90min. TLC indicated conversion of the starting material to a more polar red substance. The reaction mixture was concentrated to a crude solid and chromatographed (1:1 hexanes ethyl acetate> 1:2 hexanes:ethyl acetate) to provide compound 44 as a bright red semi-solid (MW 330; 48.5mg; 70%). 44:^{1}H NMR (360 MHz): 1.40, t, 3H; 2.49, s, 3H; 2.58, s, 3H; 3.17, t, 2H; 3.75, t, 2H; 4.41, q, 2H; 6.94, d, 1H; 8.45, broad, 1H. EI MS: m/z 330, 288, 242, 214, 84 amu.

Ethyl 4-Acetoxy-5,6-diacetyl-3,6,7,8-tetrahydrobenzo [1,2-b:4,3-b']dipyrrole-2-carboxylate 48

Indoline 44 (MW 330, 48.5mg; 0.15mmol) was dissolved in dry methylene chloride (5ml) and treated with acetyl chloride and pyridine (3 drops each). After stirring for 15min TLC indicated complete conversion to a very polar compound. The reaction mixture was poured into water, extracted into methylene chloride, and the organic extracts were dried, concentrated, and chromatographed (1:2 hexanes/ ethyl acetate> ethyl acetate) to obtain amide 48 as an off-white solid, mp 162-164^{0}C (MW 372; 53.3mg; 98%). 48:^{1}H NMR (360 MHz): 1.35, t, 3H; 2.18, s, 3H; 2.35, s, 3H; 2.45, s, 3H; 3.25, t, 2H; 4.20, t, 2H; 4.35, q, 2H; 7.04, d, 1H; 8.80, broad, 1H.

Ethyl 5,6-diacetyl-4-hydroxy-3,6,7,8-tetrahydrobenzo [1,2-b:4,3-b']dipyrrole-2-carboxylate 49

Amide 48 (MW 372; 32.0mg; 0.09mmol) was dissolved in 2ml of ethanol and treated with 2 drops of ammonium hydroxide. After stirring for 10min, TLC showed complete conversion to a less polar yellow compound. Removal of the solvent under reduced pressure and chromatography of the crude residue (1:1 hexanes:ethyl acetate) resulted in phenol 49 (MW 330; 24.4mg) as a bright yellow oil in 86% yield. 49: ^{1}H NMR (360 MHz): 1.42, t, 3H: 2.30, s, 3H; 2.40, s, 3H; 3.20, t, 2H; 4.30, t, 2H; 4.43, q, 2H; 7.07, d, 1H; 9.35, broad, 1H.

Ethyl 5,6-Diacetyl-4-methoxy-3,6,7,8-tetrahydrobenzo [1,2-b:4,3-b']dipyrrole-2-carboxylate 50.

Phenol 49 (MW 330; 17.0mg; 0.05mmol) was dissolved in 2ml of absolute methanol and 1.5ml of 2,2,2-trifluoroethanol was added. This mixture was treated with an ethereal solution of diazomethane (ca. 18mg diazomethane) and stirred at room temperature for 1 1/2 hours. TLC indicated that the starting material was mostly gone. An additional aliquot of diazomethane was added, and stirring was continued for another hour. At this time TLC indicated complete disappearance of 49. The reaction was quenched with several drops of acetic acid, poured into water, and extracted into methylene chloride. The methylene

chloride extracts were dried, concentrated, and the residue was chromatographed (1:2 hexanes:ethyl acetate) to furnish methoxy amide 50 (MW 344; 16.0mg; 90%) as a white crystalline substance, mp 192-194^{0}C. 50:^{1}H NMR (360 MHZ): 1.45, t, 3H; 2.25, s, 3H; 2.75, s, 3H; 3.30, t, 3H; 3.93, s, 3H; 4.25, t, 2H; 4.45, q, 2H; 7.10, d, 1H; 9.05, broad, 1H. Anal. Calcd. for C18H20N2O5: C 62.78, H 5.85, N 8.13 Found: C 62.66, H 5.92, N 8.10.

Ethyl 4-Acetoxy-5-acetyl-6-(2,2,2-trichloroethoxycarbonyl)-3,6,7,8-tetrahydrobenzo[1,2-b:4,3-b']dipyrrole-2-carboxylate 51

Indoline 44 (MW 330; 32.1mg; 0.1mmol) was dissolved in dry methylene chloride (3ml) and treated with 2,2,2-trichloroethyl chloroformate (5 drops). After stirring for 10min TLC showed complete conversion to a new, less polar substance. Workup and chromatography using 1:1 hexane:ethyl acetate as eluent delivered the carbamate 51 (MW 505, 47.0mg; 95%) as a greenish-gray oil. 51:^{1}H NMR (360 MHz): 1.43, t, 3H; 2.42, s, 3H; 2.49, s, 3H; 3.33, t, 2H; 4.43, t + q, 4H total; 4.85, s, 2H; 7.11, d, 1H; 8.92, broad, 1H. EI MS: m/z 506, 504, 466, 464, 462 (Cl3 isotope pattern), 422, 374, 241 amu.

Ethyl 5-Acetyl-4-hydroxy-6-(2,2,2-trichloroethoxycarbonyl)-3,6,7,8-tetrahydrobenzo[1,2-b:4,3-b']dipyrrole-2-carboxylate 52

Carbamate 51 (MW 505; 53.4mg; 0.11mmol) was dissolved in 3ml of absolute ethanol and treated with 2 drops of ammonium hydroxide. After stirring together for 20min, the reaction mixture was concentrated and chromatographed to obtain phenol 52 as a bright yellowish-green oil (MW 463; 36.4mg; 73%).

Ethyl 5-Acetyl-4-methoxy-6-(2,2,2-trichloroethoxycarbonyl)-3,6,7,8-tetrahydrobenzo[1,2-b:4,3-b']dipyrrole-2-carboxylate 53

Phenol 52 (MW 463; 36.4mg; 0.08mmol) in 5ml of methanol was treated with diazomethane (ca. 15mg) as an ethereal solution. After stirring for 1 1/2 hours TLC indicated conversion to a slightly more polar compound. THe reaction was quenched with acetic acid, poured into water, and extracted into methylene chloride. Chromatographic purification of the crude material obtained by evaporation of the solvent afforded methoxy compound 53 in excellent yield (MW 477; 37.7mg; 99%) as a light yellow crystalline compound. 53: ^{1}H NMR (360 MHz): 1.45, t, 3H; 2.70, s, 3H; 3.28, t, 2H; 3.95, s, 3H; 4.35, t, 2H; 4.42, q, 2H; 4.83, s, 2H; 7.10, d, 1H; 9.05, broad, 1H. EI MS: m/z 480, 478, 476, 434, 432, 430 (Cl3 isotope pattern), 329, 286, 255

amu.

Ethyl 5-Acetyl-4-methoxy-3,6,7,8-tetrahydrobenzo [1,2-b:4,3-b']dipyrrole-2-carboxylate 54

Carbamate 53 (MW 477; 12.2mg; 0.03mmol) was stirred in 2ml of acetic acid at room temperature and zinc dust was added in portions over two hours (50mg total). TLC showed complete conversion to a more polar, orange-red compound. The reaction mixture was diluted with water, filtered, and the filtrate was extracted with several portions of methylene chloride. Purification by flash chromatography of the crude material obtained by evaporation of the solvent furnished indoline 54 as a bright red solid (MW 302; 7.5mg; 96%). 54: ^{1}H NMR (360 MHz): 1.42, t, 3H; 2.70, s. 3H; 3.14, t, 2H; 3.73, t, 2H; 3.93, s, 3H; 4.42, q, 2H; 6.95, d, 1H; 8.68, broad, 1H.

Methyl 5-Acetyl-4-methoxy-3,6,7,8-tetrahydrobenzo [1,2-b:4,3-b']dipyrrole-2-carboxylate 55

Indoline 54 was dissolved in a solution of sodium methoxide in methanol and stirred for 5 hours. TLC indicated conversion to a similar, very slightly less polar compound. Extractive workup delivered the methyl ester 55, identical in all ways to a verified sample of 55 provided by Professor Dale Boger. 55: ^{1}H NMR (360 MHz): 2.70, s, 3H; 3.13, t, 2H; 3.72, t, 2H; 3.96, s, 6H; 6.92, d, 1H; 8.70,

broad, 1H. IR(neat): 3413, 3339, 3276, 2949, 1721, 1631, 1578, 1435, 1311, 1284, 1243, 1210, 1138, 1101, 755 cm^{-1}. EI MS: 288, 256, 241, 228, 213 amu.

Synthesis of Hydrazone 56

Hydroxy amide 49 (MW 330; 6.7mg; 0.02mmol) was dissolved in 0.5ml of absolute ethanol and treated with the complex tin salt of p-bromophenylhydrazine[53] (7.0mg). After stirring for several hours at room temperature the mixture was poured into water and extracted into ethyl acetate. The crude material obtained (11.5mg) was chromatographed with 1:1 hexanes:ethyl acetate. A non-polar fraction from the column consisted of hydrazine-derived decomposition products (5mg). A considerably more polar fraction (6.5mg) consisted of the desired hydrazone as a mixture of syn and anti isomers, as characterized by NMR and mass spectroscopy. 56: ^{1}H NMR (360 MHz): 1.42, t, 3H; 2.20 and 2.30, broad singlets, 2.40 and 2.50, broad singlets, total 6H; 3.20, t, 2H; 4.25, t, 2H; 4.42, q, 2H; 6.95, d; 7.07, d, 1H; 7.35, d; 7.38, d; 7.63, d; 9.20, broad, 1H. EI MS: m/z 500, 498, 288, 277, 242, 171, 90 amu.

Reaction of Hydrazone 56 with Dioxygen / Co(II) SALPR[54]

A mixture of hydrazone 56 (5.0mg; 0.01mmol) and 2mg of the cobalt complex in 1ml of ethanol was stirred at room temperature and O_2 was bubbled through for 30 minutes. The

reaction mixture was concentrated in vacuo, dissolved in a small amount of methylene chloride, and chromatographed (2:1 hexanes:ethyl acetate). The major fraction, 2.2mg, gave a very rough NMR but appeared to be primarily the hydrazone starting material. A trace amount of a more polar material which was not hydrazone was isolated, but the quantity was insufficient for characterization.

Reaction of Hydroxy Amide 49 with Dioxygen / Co(II) SALPR

Oxygen was bubbled through a stirred mixture of hydroxy amide 49 (MW 330; 10.7mg; 0.03mmol) and Co(II) SALPR (6.8mg) in 3ml of ethanol. After 45 minutes the mixture was concentrated to a crude solid and chromatographed (1:1 hexanes:ethyl acetate> ethyl acetate). Two polar spots were isolated off the column. The less polar (4.7mg) consisted of a complex mixture containing at least three components and was not resolved further. The lower spot (7.5mg) was obtained quite pure. The NMR spectrum of this compound was highly reminiscent of the rearrangement compound 27 and enone tautomer 47, though not identical to either. Mass spectrometry indicated incorporation of an additional oxygen. On the basis of the spectral data, structure 59 was assigned to this product. 59: ^{1}H NMR (360 MHz): 1.40, t, 3H; 2.15, t, 1H; 2.25, s, 3H; 2.60, s, 3H; 2.63-2.75, m, 1H; 4.00, t, 1H; 4.20, m, 1H; 4.40, q, 2H; 7.00, d, 1H; 9.80, broad, 1H. EI MS: m/z

346, 304, 287, 276, 243, 230 amu.

On a second run, a mixture was isolated that appeared to consist of 59 and a major amount of a second, closely related material. This second compound had an NMR spectrum very similar to 59 but with slight variations in chemical shifts for the pyrrolidine ring protons. The mass spectrum indicated inclusion of a second oxygen atom into the structure. Hydroperoxide 60 was proposed for the structure of this compound. 60: ^{1}H NMR (360 MHz): 1.45, t, 3H; 2.25, s, 3H; 2.30, m, 1H; 2.65, s, 3H; 2.80, d of d, 1H; 4.00, t, 1H; 4.10, m, 1H; 4.40. q, 2H; 6.97, d, 1H; 9.88, broad, 1H. EI MS: m/z 362, 346, 304, 287, 276, 243, 230 amu.

The material from the above reaction was dissolved in 2ml of trimethyl phosphite and stirred overnight in order to effect reduction of the hydroperoxide to the alcohol. Removal of the phosphite and chromatography of the crude product delivered pure 59.

Reaction of 50 with Dioxygen / Co(II) SALPR

Methoxy amide 50 (MW 344; 8.1mg; 0.02mmol) was dissolved in 3ml of absolute ethanol and treated with the cobalt complex (13.1mg). Oxygen was bubbled through this stirred mixture for 45 minutes. TLC indicated that mostly starting material was present. The reaction mixture was concentrated to driness and chromatographed. Starting material (5.7mg; 70% recovery) was isolated from the column. There was also isolated a small amount (1.8mg) of material which gave a crude NMR spectrum. From the appearance of three aromatic signals (6.50, 7.00 and 7.55) it appears as though this component may be the aromatized starting material.

Reaction of 50 with MCPBA

Compound 50 (5.7mg; 0.016mmol) in 1ml of dry methylene chloride at room temperature was treated with MCPBA (7.0mg; 0.4mmol). After stirring at room temperature for 24 hours, TLC indicated no change. An additional equivalent of MCPBA was added and the mixture was gently warmed for 5 hours. The reaction mixture was poured into water, neutralized with sodium bicarbonate, and extracted into methylene chloride. Chromatography of the crude product mixture delivered, in addition to m-chlorobenzoic acid, only unchanged starting material.

Reaction of 44 with Ammonium Hydroxide

Indoline 44 (MW 330; 12.0mg; 0.04mmol) was dissolved in 5ml of absolute ethanol and treated with several drops of ammonium hydroxide. After stirring for several minutes TLC indicated conversion of the starting material to two new substances, one more and one less polar. Chromatography of the crude material delivered two products. The less polar material (1.4mg) proved to be the aromatized compound 45, verified by mass spectroscopy and NMR. The other, more polar material (7.9mg) was assigned structure 61 on the basis of NMR and mass spectral data. 61: ^{1}H NMR: 1.40, t, 3H; 2.20, m, 1H; 2.70, d of d, 1H; 3.82, m, 1H; 4.18, m, 1H; 4.35, q, 2H; 6.95, d, 1H; 9.68, broad, 1H. EI MS: m/z 304, 288 286, 276, 240, 212 amu.

Attempted Ketalization of 49

A solution of hydroxy amide 49 (MW 330; 6.2mg; 0.02mmol) in 2ml of trimethyl orthoformate was placed in a Pyrex glass tube with 0.5mg of p-toluenesulfonic acid. The tube was sealed and heated to 100^{0}C for 4 hours. The tube was opened and its contents concentrated in vacuo. TLC indicated only a single component which appeared to be unchanged starting material. Chromatography delivered exclusively 49 (4.3mg; 70% recovery).

Attempted Ketalization of 50

Methoxy amide 50 (MW 344; 14.0mg; 0.04mmol) in 1.5ml of trimethyl orthoformate was treated with 1.0mg of p-toluenesulfonic acid and sealed in a glass tube. After heating to 100^{0}C for 4 hours, concentration of the tube's contents and chromatography returned unchanged starting material (13.4mg) in 96% mass balance.

Reaction of 50 with Hydroxylamine Hydrochloride

Methoxy amide 50 (MW 344; 10.0mg; 0.03mmol) in 2ml of absolute ethanol was treated with hydroxylamine hydrochloride (MW 69.5; 6.8mg; 0.1mmol) and triethylamine (2 drops). After stirring for several hours at room temperature there was no change by TLC. An additional 2 equivalents of hydroxylamine hydrochloride and drop of triethylamine were added and stirring was continued overnight. TLC indicated mostly starting material present with a small amount of a less polar, reddish material. After stirring for an additional 24 hours, the reaction mixture was poured into water and extracted into methylene chloride. The crude product mixture was chromatographed (1:1 hexanes:ethyl acetate) to obtain two compounds. The more polar of the two was unchanged starting material (3.6mg; 0.1mmol). The less polar red material (3.1mg) was found to be the deacetylated indoline 54, identical to previously obtained samples.

Ethyl 4-(1-Allyl-2-thioxopyrrolidin-3-yl)-5-(2-diazo-1,3-dioxobutyl)pyrrole-2-carboxylate 85

Thiolactam 22 (MW 362; 187mg; 0.52mmol), p-nitrobenzenesulfonyl azide (MW 228; 132mg; 0.58mmol) and triethylamine (MW 102; 60.6mg; 0.59mmol) were stirred in 15ml of THF at room temperature for 4 hours. The mixture was poured into water (50ml), extracted into ethyl acetate, and the organic extracts were dried and concentrated. Stirring the crude material with 25ml of chloform precipitated most of the sulfonamide byproduct. The chloroform solution was filtered, concentrated and chromatographed (1:1 hexanes:ethyl acetate) to afford 85 as a yellow foam (MW 388, 170.3mg; 84%). 85: ^{1}H NMR (360 MHz): 1.40, t, 3H; 2.05, m, 1H; 2.51, s, 3H; 2.58, m, 1H; 3.70, m, 2H; 4.37, q, 2H; 4.50, m, 2H; 4.95, t, 1H; 5.32, m, 2H; 5.87, m, 1H; 6.85, d, 1H.

Ethyl 4-(1-Allyl-2-thioxopyrrolidin-3-yl)-5-(diazoacetyl) pyrrole-2-carboxylate 86

Diazoketone 85 (MW 388; 170mg; 0.44mmol) was dissolved in 30ml of ethanol, treated with 20 drops of pyrrolidine, and stirred at room temperature for 45 min. The reaction mixture was concentrated to a crude solid and this was passed through a flash column eluting with 1:1 hexanes:ethyl acetate to obtain diazo ketone 86 (MW 346;

138.3mg; 91%) as an oil. 86: ^{1}H NMR (360MHz): 1.35, t, 3H; 2.20, m, 1H; 2.60, m, 1H; 3.75, m, 1H; 3.87, m, 1H; 4.32, q, 2H; 4.45, m, 2H; 4.60, t, 1H; 5.35, m, 2H; 5.85, m, 1H; 6.73, d, 1H; 6.80, s, 1H; 9.75, broad, 1H.

Ethyl 7-Allyl-4-oxo-3,4,5,7,8,9-hexahydrothiepin [2,3-b:5,4-b]dipyrrole-2-carboxylate 87

Diazo ketone 86 (MW 346; 35.0mg; 0.1mmol) in 2.0ml of dry methylene chloride was treated with boron trifluoride-etherate (MW 142; 20mg; 0.14mmol) in 1.0ml of methylene chloride. There was immediate evolution of gas and the solution darkened in color. After stirring for 20 minutes at room temperature, the reaction mixture was poured into aqueous sodium carbonate and extracted into methylene chloride, giving a bright red extract. Drying and removal of the solvent afforded thiepinone 87 (MW 318; 31.6mg; quantitative yield) as a bright orange-red solid. Recrystallization from chloform-hexanes gave an analytical sample, mp 133-134^{0}C. 87: ^{1}H NMR (360 MHz): 1.40, t, 3H; 2.90, t, 2H; 3.40, t plus overlapping s, 4H total; 3.75, d, 2H; 4.38, q, 2H; 5.25, m, 2H; 5.82, m, 1H; 6.70, d, 1H; 9.68, broad, 1H. EI MS: m/z 318, Anal. Calcd. for $C_{16}H_{18}N_2O_3S$: C 60.36; N 8.80; H 5.70. Found: C 60.34; N 8.78; H 5.75.

Reaction of Ethyl 4-(1-Benzyl-2-oxopyrollidin-3-yl)-5-(diazoacetyl)pyrrole-2-carboxylate (69) with Methyl Triflate

Diazo ketone 69 (MW 368; 45.1mg; 0.11mmol) was stirred under nitrogen at room temperature in dry methylene chloride (7ml) and treated with a solution of methyl triflate (MW 164; 41.0mg; 0.25mmol) in 2ml of methylene chloride. The reaction was stirred at room temperature and monitored by TLC. A more polar spot was observed to slowly grow. After stirring for 65 hours, dimethylaminopyridine (MW 122; 17.1mg; 0.14mmol) was added; the solution immediately turned bright red. The reaction mixture was diluted with additional methylene chloride and the organic phase was washed with aqueous sodium bicarbonate, dried, and concentrated to deliver 40mg of crude material. After passing through a flash column, three products were isolated. The major product (17.4mg; 70% of the mixture) was the spiro compound 72, identical to the previously characterized samples[25]. Hydroxy ketone 74, the hydrolysis product of the protonated oxepin, was also isolated (MW 370; 4.6mg; 18% of mixture). Curiously, a fraction was also isolated which, on the basis of NMR and mass spectral data and comparison with spectra of 72, appeared to be the dehydro spiro compound 76 (3.0mg). 72: ^{1}H NMR (360MHz) 1.38, t, 3H; 2.20-2.40, m, 2H; 2.74, d, 1H; 3.33, d of t, 1H; 3.42, d, 1H; 3.45, m, 1H; 4.36, q, 2H;

4.43 and 4.65, AB q, 2H; 6.60, d, 1H; 7.24-7.40, m, 5H; 9.52, broad, 1H. EI MS: m/z 352, 324, 310, 296, 261, 232, 91 amu. 76:^{1}H NMR (360 MHz): 1.38, t, 3H; 2.95 and 3.20, AB q, 2H; 4.35, q, 2H; 4.60 and 4.75, AB q, 2H; 5.45, d, 1H; 6.50, d, 1H; 7.20, d, 1H; 7.22-7.40, m, 5H; 9.52, broad, 1H. EI MS: m/z 350, 312, 304, 259, 213, 91. 74:^{1}H NMR (360MHz): 1.38, t, 3H; 2.05, m, 1H; 2.50, m, 1H; 3.37, m, 2H; 3.75, broad, 1H; 4.20, t, 1H; 4.35, q, 2H; 4.50, AB q, 2H; 4.60 and 4.80, AB m, 2H; 6.78, d, 1H; 7.20-7.40, 5H. EI MS: m/z 370, 352, 340, 312, 293, 192, 173, 91 amu.

Reaction of 69 with Tert-Butyldimethylsilyl Triflate

Run 1. Diazo ketone 69 (MW 380; 20.2mg; 0.05mmol) was dissolved in 1ml of dry methylene chloride in a 10ml flask. A solution of tert-butyldimethylsilyl triflate (MW 264; 15.9mg; 0.06mmol) in 1ml of methylene chloride was added dropwise via syringe. Evolution of gas was observed and the color of the solution changed from yellow to a darker, amber color. Over the course of an hour it became increasingly reddish. TLC indicated the disappearance of starting material and the appearance of two new spots. Proton Sponge, 1,8-bis (dimethylamino)napthalene, (MW 214; 21.2mg) was added; the solution immediately became very dark red and then lightened to its original medium red color. The reaction mixture was rapidly concentrated in

vacuo, and the residue was dissolved in 2ml of acetonitrile, placed in a Pyrex tube, and sealed under vaccuum after repeated freezing and degassing. The tube was heated to 80 C for 2.5 hours; after cooling, it was opened and its contents poured into water and extracted with methylene chloride. The crude material obtained by removal of the solvent was chromatographed. The mass balance of the recovered material was very poor, and the only components present appeared to be ring-opened type compounds.

Run 2. Diazo ketone 69 (10.11mg; 0.03mmol) in 1ml of dry methylene chloride was treated with tert-butyldimethylsilyl triflate (MW 264; 13.2mg; 0.05mmol) in 1ml of methylene chloride; evolution of gas ocurred immediately and the solution turned orange-red over 30 minutes. Proton Sponge was added and the dark red mixture was poured into water and extracted into methylene chloride. NMR of the crude material obtained by evaporation of the solvent indicated that it consisted of roughly 75% of hydroxy ketone 74 and 25% of spiro compound 72. Chromatography delivered 6.1mg of pure 74 and 1.3mg of the spiro material 72.

Run 3. The reaction was done in the presence of a non-nucleophilic base ('Proton Sponge'). A stirred mixture of 69 (13.3mg; 0.04mmol) and Proton Sponge (13.5ml; 0.06mmol) in 1.5ml of dry methylene chloride at room temperature was treated with tert-butyldimethylsilyl triflate (13.6mg;

0.05mmol). There was no obvious reaction or evolution of gas. After several hours of stirring, TLC indicated that only starting material was present. The reaction mixture was worked up and chromatographed as previously. In addition to recovery of unchanged starting material in high (87%) mass balance, there was isolated only a trace amount of hydroxy ketone 74.

Reaction of 69 with Iodotrimethylsilane

Diazo ketone 69 (20.0mg; 0.05mmol), stirred at room temperature in 2ml of dry methylene chloride, was treated with iodotrimethylsilane (3 drops). Instantly, the yellow solution turned red. TLC showed that the starting material was gone, replaced by a new more polar spot. Proton Sponge (15.3mg; 0.07mmol) was added and TLC indicated that the polar spot had been replaced by a less polar one (R_f= 0.5) as a major product and several faint spots. The mixture was concentrated, dissolved in acetonitrile, and sealed in a Pyrex tube under vaccuum. The tube was heated to 85^{0}C for 4.5 hours and then worked up as usual. A total of 9.2mg of organic material was obtained after chromatography. A minor component, 2.0mg, was primarily hydroxy ketone 74 , as shown by NMR and mass spectroscopy. The major component, 7.0mg, was the product of substitution of the diazo group by iodide ion, com-pound 77:^{1}H NMR (360MHz): 1.37, t, 3H; 2.00-2.10, m, 1H; 2.50-2.55, m, 1H; 2.57, s, 2H; 3.35, m,

2H; 4.25, t, 1H; 4.30, q, 2H; 4.55, AB q, 2H; 6.78, d, 1H; 7.25-7.40, m, 5H; 9.80, broad, 1H. EI MS: m/z 352, 310, 214, 168, 119, 91.

Reaction of Diazoacetyl Thiolactam 9 with Tert-Butyl-dimethylsily Triflate

A solution of 9 (MW 396; 15.0mg; 0.04mmol) in 2ml of dry methylene chloride was treated with tert-butyldimethylsilyl triflate (MW 264; 11.2mg; 0.04mmol) in 1ml of methylene chloride. After stirring for several hours TLC indicated that all the starting material was gone. Proton Sponge (MW 214; 10mg; 0.05mmol) was added and the solution quickly turned bright red. Ether, 5ml, was added, causing the formation of a precipitate. The solvent was decanted and the solid residue was washed with methylene chloride. The combined organic portions were dried and concentrated to deliver a material whose NMR indicated it to be nearly pure thiepinone 10. Purification through a chromatography column delivered 10 in excellent yield (MW 368; 13.0mg; 0.036mmol; 90%).

Thermolysis of Ethyl 7-Benzyl-4-oxo-3,4,5,7,8,9-hexahydro-thiepino [2,3-b:5,4-b']dipyrrole-2-carboxylate 10 and Subsequent Phase Transfer Methylation

Thiepinone 10 (MW 368, 29.4mg; 0.08mmol) in 2ml of acetonitrile was sealed in a Pyrex tube under vaccuum and

heated to 100^{0}C on an oil bath for 7 hours. The tube was cooled, opened, and its contents concentrated. TLC indicated three components, closely spaced on the plate. Without further treatment the material was dissolved in 1ml of methylene chloride; a solution of 8mg of potassium carbonate in 2ml of water was added, followed by 5 drops of tetrabutylammonium hydroxide (40% solution) and 5 drops of methyl sulfate. This mixture was stirred vigorously at room temperature for 5 hours. The reaction was poured into water and the layers were separated and the organic layer was washed with 2N aqueous ammonia. After drying of the organic phase and removal of the solvent, the crude residue was purified by chromatography to deliver a total of 12.4mg of recovered material. A minor component, 2.6mg, appeared to be primarily the methoxy indole 84. The remaining material was complex and could not be interpreted.

Attempted Synthesis of Compound 79.

Ethyl 4-Acetoxy-5-(acetylthio)-6-benzyl-3,6,7,8-tetrahydrobenzo[1,2-b:4,3-b']dipyrrole-2-carboxylate 11 (MW 452; 25.0mg; 0.06mmol) was prepared from thiepinone 10 as described by Pearce. This material was dissolved in 2ml of anhydrous THF in a 25ml flask equipped with nitrogen inlet and magnetic stirrer. Pyrrolidine (8.90mg; 0.125mmol; 2.1eq) was added as a THF solution and the mixture was stirred at room temperature for 1 hour, at which point TLC

indicated complete disappearance of starting material. A solution of 2-nitrobenzenesulfenyl chloride (16.0mg; 0.08mmol) in 1ml of THF was added via syringe. The reaction mixture, intially cloudy, turned a clear yellow. After stirring for an hour, TLC indicated conversion to a new, more polar material. At this point 1,4-diazabicyclo[2.2.2.]octane (28.0mg; 0.25mmol) was added; a precipitate immediately formed. After stirring this mixture for several minutes water, 3ml, was added and the mixture rapidly darkened in color. TLC showed that the former spot was gone, replaced by a new, less polar material. The reaction mixture was poured into water and extracted into methylene chloride. The methylene chloride extracts were washed with 3% HCl and brine, dried, and concentrated to deliver 43.0mg of solid material, which was subjected to flash chromatography. There was isolated from the column 15mg of organic material. NMR indicated that the main product is probably the mono-substituted phenol 67. The postulated molecular weight (334) was verified by the mass spectrum of the compound. 67: ^{1}H NMR (360 MHz): 1.45, t, 3H; 4.48, q, 2H; 5.33, s, 3H; 6.70, d, 1H; 6.75, s, 1H; 7.05, d, 1H; 7.25, broad m, 5H; 7.50, d, 1H. EI MS: m/z 334, 288, 260, 197, 91 amu.

For purposes of further characterization, the above material (5.0mg) was dissolved in 1ml of methylene chloride and treated with acetic anhydride and DMAP. After 1 hour of

stirring, conversion to a less polar substance was complete. Workup and chromatography delivered 4.7mg of a material identified by NMR as 68, previously obtained and characterized by an alternate route. 68: ^{1}H NMR (360 MHz): 1.45, t, 3H; 2.41, s, 3H; 4.43, q, 2H; 5.36, s, 2H; 6.78, d, 1H; 7.18, d plus overlapping s, 2H; 7.29, m, 5H; 7.47, d, 1H; 8.90, broad, 1H.

Reaction of 10 with LDA / Methyl Sulfate

A mixture of diisopropylamine (MW 101; 16mg; 0.16mmol) in 1.0ml of THF at 0^{0}C was treated with 0.08ml of 1.6M nBuLi (0.13mmol) and the resulting LDA solution was cooled to -42^{0}C. Thiepinone 10 (22.7mg; 0.06mmol) was added as a THF solution, followed by HMPA (1.15mmol). After stirring at -42^{0}C for 30 minutes this mixture was treated with methyl sulfate (8.0mg; 0.06mmol) in 0.5ml of THF. The mixture was stirred for three hours while allowing it to slowly come to room temperature; it was poured into aqueous ammonium chloride, extracted into ethyl acetate, and the ethyl acetate portions were washed with 2N ammonia, brine and water and dried over magnesium sulfate. TLC indicated a number of components. These were resolved by flash chromatography. The main component (4.6mg) was assigned the structure spiro lactam 82. The other components (6.8mg) consisted of a mixture of unchanged starting material, N-

methylated starting material, and non-methylated spiro compound 83. 83: ^{1}H NMR (360MHz): 1.39, t, 3H; 2.30 and 2.40, m, 2H; 2.80 and 3.68, AB q, 2H; 3.60 and 3.75, AB m, 2H; 4.08, s, 3H; 4.30, q, 2H; 4.95 and 5.20, AB q, 2H; 6.55, s, 1H; 7.40, m, 5H. EI MS: m/z 382, 353, 291, 91 amu.

Reaction of 10 with Trimethyl Phosphite

Thiepinone 10 (MW 368; 26.2mg; 0.07mmol) was dissolved in 2ml of trimethyl phosphite, sealed in a tube, and heated to 80^0 C for 6 hours. There was no observed change in the color of the solution. The temperature was increased to 100^{0}C and held there for 20 hours. The tube was cooled to -78^{0}C, opened, and its contents concentrated on a roto-vap. The crude material was passed through a flash column. Unchanged starting material (18.2mg; 69% recovery) was the major fraction. A smaller amount of material (6.1mg) appeared to be a mixture of a spiro type compound and some of the desired ring contraction product, as judged by NMR.

Reaction of Thiepinone 10 with Methyl Iodide

Thiepinone 10 (MW 368; 17.3mg; 0.05mmol) in 1.5ml of THF was treated with 0.1ml of methyl iodide, sealed in a Pyrex glass tube, and heated to 80^{0}C for 15 hours. The tube was cooled and opened and its contents were poured into water. The aqueous mixture was made slightly alkaline with

sodium bicarbonate and extracted with methylene chloride. TLC indicated a spot with the same Rf as starting material and a very polar fluorescent blue material. The crude material obtained by removal of the solvent was chromatographed. The less polar fraction (5.1mg) was contaminated with other material but appeared to be primarily the starting material. The more polar component of the mixture (5.3mg) proved to be identical to samples of spiro thiolactam 83 obtained in other reactions.

Reaction of 10 with Raney Nickel. Ethyl 4-Acetoxy-6-benzyl-3,6-dihydrobenzo[1,2-b:4,3-b']dipyrrole-2-carboxylate

Thiepinone 10 (15.5mg; 0.42mmol) was placed in a Pyrex tube with 109mg of moist activated Raney nickel and 3ml of ethanol. The tube was sealed under vaccuum, after repeated freezing and degassing, and heated to 80^{0}C for 5 hours. The tube was opened and the contents were filtered through Celite to remove the nickel. TLC indicated the complete loss of starting material, and replacement by two fluorescent blue spots and a more polar darker spot. The ethanol solution was concentrated and the residue was dissolved in methylene chloride (5ml) and treated with 6 drops of acetic anhydride and a bit of DMAP. After 30 minutes TLC showed complete conversion to a less polar substance. This was concentrated and chromatographed to obtain acetylated indole 68 as the major product (6.0mg;

36%). There was also isolated off the column 1.5mg of spiro thiolactam 83. 68: ^{1}H NMR (360 MHz): 1.45, t, 3H; 2.42, s, 3H; 4.42, q, 2H; 5.36, s, 2H; 6.77, d, 1H; 7.10, d, 1H; 7.17, d, 1H; 7.30-7.40, m, 5H; 7.47, d, 1H; 8.89, broad, 1H. EI MS: m/z 376, 334, 288, 260, 197, 91 amu. 83: ^{1}H NMR (360MHz): 1.39, t, 3H; 2.35 and 2.45, m, 2H; 2.80 and 3.70, AB q, 2H; 3.60 and 3.75, m, 2H; 4.35, d of q, 2H; 4.95 and 5.20, AB q, 2H; 6.57, d, 1H; 7.35-7.40, m, 5H; 9.40, broad, 1H. EI MS: m/z 368, 339, 293, 91 amu.

Reaction of 10 with 'Nickel Boride'[43]

To a cooled solution of $NiCl_2$-$6H_2O$ (FW 238; 64.3mg; 0.27mmol) at 0^0C was added sodium borohydride (FW 38; 30.9mg; 0.81mmol). The mixture immediately turned black with apparent evolution of gas. The solution was allowed to warm up to room temperature over a period of 45 minutes. The ethanol was decanted off, leaving a black material behind. To this residue was added thiepinone 10 (MW 368; 55.5mg; 0.15mmol) and 5ml of fresh ethanol, and this mixture was refluxed for 1 1/2 hours. TLC indicated loss of starting material. Concentrative workup and chromatography delivered the phenol (12.0mg) which was methylated with diazomethane to deliver the methoxy compound 84 (10.8mg; 0.03mmol) in overall yield of 21% from 10.

Ethyl 6-Benzyl-4-methoxy-3,6-dihydrobenzo[1,2-b:4,3-b']dipyrrole-2-carboxylate

A. By methylation of 67 with Diazomethane

Thiepinone 10 (MW 368, 200.0mg; 0.54mmol) was dissolved in 50ml of ethanol and treated with moist activated Raney nickel (125mg). After refluxing this mixture for 90 minutes TLC indicated essentially complete disappearance of starting material. The reaction mixture was cooled, filtered through Celite and concentrated to a crude material. This was passed through a flash column (1:1 hexane:ethyl acetate) to obtain an off-white solid (151mg). This material was immediately dissolved in 10ml of methanol, an equal amount of 2,2,2-trifluoroethanol was added, and this solution was treated with several aliquots of ethereal diazomethane. After 2 hours TLC indicated complete conversion to a less polar material. The reaction was quenched and worked up as usual to deliver, after chromatography, methoxy compound 84 as a light brown semi-solid (MW 348; 102mg; 0.30mmol; 54% overall from thiepinone 10. 84: ^{1}H NMR (360MHz): 1.43, t, 3H; 3.90, s, 3H; 4.40, q, 2H; 5.35, s, 2H; 6.63, s, 1H; 6.73, d, 1H; 7.05, d, 1H; 7.20-7.40, m, 5H; 7.43, d, 1H; 9.10, broad, 1H.

B. By Methylation of 67 with Phospholene 33.

Phenol 67 (MW 334; 32.0mg; 0.1mmol) was dissolved in 2.0ml of THF and treated with a solution of cyclic oxaphospholene 33 (MW 194; 75.6mg; 0.4mmol) in 1ml of THF.

This mixture was stirred at room temperature and monitored by TLC. After three days of stirring, all starting material appeared to be gone. The reaction was worked up as previously described and chromatographed. The purest fraction from the column (5mg) consisted of the desired product 84. A larger fraction (10mg) appeared to consist of a 50/50 mixture of O-methylated and O- and N-dimethylated products as judged by NMR signals at 3.85, 3.95 and 4.40 ppm.

Ethyl 4-Acetoxy-6-allyl-3,6-dihydrobenzo[1,2-b:4,3-b'] dipyrrole-2-carboxylate 89

Thiepinone 87 (MW 318; 20.0mg; 0.06mmol) and moist Raney nickel (100mg) were refluxed under a nitrogen atmosphere for 2 1/2 hours. After cooling, the reaction mixture was filtered through Celite, concentrated to a crude solid, dissolved in methylene chloride, and treated with 2 drops of acetic anhydride and a bit of DMAP. After stirring at room temperature for 40 minutes, the reaction mixture was concentrated and chromatographed (1:1 hexanes:ethyl acetate) to deliver 89. (11.0mg; 53% from 87). 89: ^{1}H NMR (360 MHz): 1.43, t, 3H; 2.45, s, 3H; 4.42, q, 2H; 4.75, d, 2H; 5.05-5.25, m, 2H; 6.00, m, 1H; 6.75, d, 1H; 7.13, d, 1H; 7.45, d, 1H; 8.95, broad, 1H.

Ethyl 6-Allyl-4-methoxy-3,6-dihydrobenzo[1,2-b:4,3-b']dipyrrole-2-carboxylate 90

A. Methylation of 88 with Oxaphospholene 33[33].

Phenol 88 (MW 284; 10.6mg; 0.04mmol) was dissolved in 3ml of THF and treated with a solution of oxaphospholene 33 (MW 194 19.8mg; 0.1mmol) in 1.0ml of THF. This mixture was stirred overnight at room temperature. Several more drops of methylating agent were added, and stirring was continued for another 24 hours. TLC indicated the reaction mixture to be a roughly 50/50 mixture of starting material and a new, less polar compound. The reaction mixture was poured into water, extracted into methylene chloride, and the methylene chloride extracts were dried, concentrated and chromatographed to deliver, in addition to starting material (2mg), methoxy compound 90 (MW 298; 3.0mg; 25%).

B. Methylation of 88 with Diazomethane

Phenol 88 (14.2mg; 0.05mmol) was dissolved in 10ml of absolute methanol and treated with an ethereal solution of diazomethane (ca. 30mg; 0.7mmol). After stirring at room temperature for 1 1/2 hours, the reaction was quenched with several drops of acetic acid and poured into water. The product was extracted into methylene chloride and the organic portions were dried and concentrated; the crude material so obtained was purified by flash chromatography to afford methoxy compound 90 as a light brown semi-solid (MW 298; 10.6mg; 0.04mmol; 80%). 90: ^{1}H NMR (360 MHz):

1.43, t, 3H; 4.00, s, 3H; 4.40, q, 2H; 4.75, m, 2H; 5.05-5.20, m, 2H; 6.05, m, 1H; 6.70, s plus d, 2H; 7.01, d, 1H; 7.41, d, 1H; 9.10, broad, 1H.

Attempted Deallylation of 90 With Tetrakis(triphenylphosphine)rhodium Hydride

Methoxy compound 90 (MW 298; 2.5mg; 0.008mmol) was dissolved in 2ml of absolute ethanol, treated with 2mg of tetrakis(triphenylphosphine)rhodium hydride, and this mixture was refluxed under a nitrogen atmosphere for 4 1/2 hours. The reaction mixture was poured into sodium bicarbonate, filtered, and extracted into methylene chloride; the organic extracts were dried, concentrated, and chromatographed to deliver 1.9mg of unchanged starting material (76% recovery).

Reduction of 84 with Borane-Trifluoroacetic Acid. Ethyl 6-Benzyl-4-methoxy-3,6,7,8-tetrahydrobenzo[1,2-b:4,3-b']dipyrrole-2-carboxylate 91

Indole 84 (MW 334; 5.2mg; 0.016mmol) was dissolved in a minimal amount of dry methylene chloride, cooled to 0^0C, and treated with 1.5ml of trifluoroacetic acid and 2 equivalents of diborane-THF complex[47]. After stirring for several minutes, an additional 2 equivalents of borane were added. The reaction mixture was stirred an additional 15 minutes before quenching with water (5ml). The aqueous

mixture was stirred for 5 minutes, poured into 20ml of additional water, and extracted into methylene chloride. Evaporation of the solvent delivered a crude material which was purified by column chromatography to provide the indoline 91 (MW 336; 3.2mg; 60%). 91: ^{1}H NMR (360 MHz): 1.40, t, 3H; 3.05, t, 2H; 3.40, m, 2H; 3.90, s, 3H; 4.30, s, 2H; 4.40, q, 2H; 6.34, s, 1H; 7.00, d, 1H; 8.90, broad, 1H.

Ethyl 4-Methoxy-6-(2,2,2-trichloroethoxycarbonyl)-3,6-dihydrobenzo[1,2-b:4,3-b']dipyrrole-2-carboxylate 93

Compound 84 (MW 348; 18.1mg; 0.05mmol) was dissolved in several ml of glacial acetic acid and treated with sodium cyanoborohydride[45] (MW 63; 20mg total; 0.03mmol; 6eq) in several portions over two hours while stirring at room temperature. The mixture was poured into aqueous sodium hydroxide and extracted into methylene chloride to provide, after drying and removal of the solvent, crude indoline 91 as an orange-red solid. This material was dissolved in 3ml of acetonitrile and treated with 5 drops of 2,2,2-trichloroethyl chloroformate. After stirring for one hour at room temperature TLC indicated complete conversion to a less polar fluorescent blue material. The reaction mixture was concentrated and chromatographed (1:1 hexanes:ethyl acetate) to deliver carbamate 93 (MW 436; 13.1mg; 58% overall). Recrystallization from ethyl

acetate:hexanes gave an analytical sample, mp 190-191 C. 93: ^{1}H NMR (360 MHz): 1.42, t, 3H; 3.30, t, 2H; 4.00, s, 3H; 4.30, t, 2H; 4.42, q, 2H; 4.85, s, 2H; 7.05, d, 1H; 7.65, s, 1H; 9.03, broad, 1H. EI MS: m/z 434, 390, 259, 186, 91 amu. Anal. Calcd. for $C_{17}H_{17}N_2O_5Cl_3$: C 46.87, H 3.93, N 6.43 Found: C 46.91, H 3.98, N 6.39.

Use of the same methodology utilizing N-allyl methoxy compound 90 as the starting material resulted in identical product in comparable yields.

Ethyl 6-Acetyl-4-methoxy-3,6,7,8-tetrahydrobenzo [1,2-b:4,3-b']dipyrrole-2-carboxylate 95 (5-Deoxy PDE-II Ethyl Ester).

Carbamate 93 (MW 436; 11.4mg; 0.026mmol) was dissolved in 2ml of glacial acetic acid. Zinc dust was added, with stirring, in portions over 2 hours (20mg total). The reaction mixture was diluted with water, methylene chloride (10ml) was added, and the mixture was filtered to remove unreacted zinc. The layers were separated and the aqueous layer was washed with methylene chloride. The combined organic extracts were dried and concentrated. The crude residue was dissolved in dry methylene chloride and treated with 2 drops each of acetyl chloride and pyridine. After several minutes of stirring TLC indicated conversion to a very polar substance. The mixture was poured into water and extracted into methylene chloride; chromatography of the

crude product (1:2 hexanes:ethyl acetate> ethyl acetate) afforded compound 95 as a white crystalline solid (MW 302; 5.1mg; 65% overall). Recrystallization from ethyl acetate: hexanes provided an analytical sample, mp 234-236^{0}C. 95:^{1}H NMR (360 MHz): 1.42, t, 3H; 2.25, s, 3H; 3.30, t, 2H; 4.00, s, 3H; 4.20, t, 2H; 4.42, q, 2H; 7.07, d, 1H; 8.05, s, 1H; 9.01, broad, 1H. EI MS: m/z 302, 256, 214, 186.

Reaction of 95 With Thallium(III) Trifluoroacetate

Compound 95 (MW 302; 7.0mg; 0.02mmol) was dissolved in several ml of trifluoroacetic acid and treated with thallium (III) trifluoroacetate (MW 543; 13.4mg; 0.025mmol) in 1ml of TFA. The mixture initially turned dark red-purple and then became an inky blue. A solution of potassium iodide (10 mg) in water was added and a yellow precipitate immediately formed. After several minutes, sodium bisulfite was added, and the mixture was stirred an additional 20 minutes before neutralizing with 10% aqueous sodium hydroxide. Methylene chloride was added and the two phase mixture was filtered. Separation of the layers and drying and concentration of the organic phase furnished a crude material which was run through a flash column to deliver two compounds in rather poor (ca. 50%) mass balance. The primary product appeared to be the oxidized aromatic starting material. The mass spectrum, indicating a molecular weight of 300, was consistent with this

assignment. The lesser of the two fractions was simply unchanged starting material.

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