CC-1065 and the Duocarmycins: Synthetic Studies

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Received October 7, 1996

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I. Introduction

(+)-CC-1065 was isolated in trace quantities from cultures of *Streptomyces zelensis* at Upjohn and disclosed in 1978.[1,2] Subsequently, it was shown to be identical to rachelmycin which was isolated from

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Born August 22, 1953, Dale L. Boger (seated) received his B.Sc. in chemistry from the University of Kansas (1975) and Ph.D. in chemistry from Harvard University (1980). Immediately following graduate school, he returned to the University of Kansas as a member of the faculty in the Department of Medicinal Chemistry (1979–1985), moved to the Department of Chemistry at Purdue University (1985–1991), and joined the faculty at The Scripps Research Institute (1991 to present) as the Richard and Alice Cramer Professor of Chemistry. His research interests span the fields of organic and bioorganic chemistry and include the development of synthetic methodology, the total synthesis of natural products, heterocyclic chemistry, bioorganic chemistry, medicinal chemistry, the study of DNA–agent and protein–ligand interactions, and antitumor agents.

Christopher W. Boyce (standing left) was born January 30, 1972, and grew up in Richmond, MA. Following a year abroad at the Swiss Federal Institute (ETH-Zurich), he received his B.Sc. in chemistry from Rensselaer Polytechnic Institute (1994, *summa cum laude*). He is currently pursuing a Ph.D. under the direction of Professor Dale L. Boger where he is addressing the synthesis and evaluation of potent DNA alkylation agents related to the CC-1065 and duocarmycin families.

Robert M. Garbaccio (standing right) was born on January 20, 1972, and grew up in Old Tappan, NJ. He received his B.A. in chemistry and graduated *summa cum laude* from Boston University in 1994 where he conducted research in the laboratory of Professor James S. Panek. Presently, he is pursuing a Ph.D. in chemistry at The Scripps Research Institute under the guidance of Professor Dale L. Boger where he is addressing the synthesis and evaluation of potent DNA alkylating agents from the duocarmycin and mitomycin families of antitumor antibiotics.

Joel A. Goldberg (standing center) was born June 17, 1972, and grew up in Bedford, NH. After receiving his B.Sc. from Tufts University he joined Professor Boger's laboratory at The Scripps Research Institute where he is pursuing his Ph.D. in Chemistry. His research concentrates on the synthesis and evaluation of potent alkylating agents related to CC-1065 and the duocarmycins.

S0009-2665(96)00095-7 CCC: $28.00

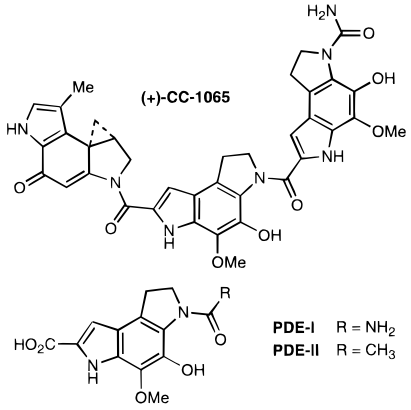


Figure 1. Structure of (+)-CC-1065 and related agents.

Streptomyces C-329 at Bristol-Myers,[3] and it has also been isolated from *Streptomyces canulus*.[4] The structure of CC-1065 was disclosed in 1980[5] based largely on spectroscopic and chemical degradation studies and subsequently confirmed by X-ray analysis.[6] Its remarkable structure was shown to consist of two identical central and right-hand subunits further linked to a related left-hand pyrrolo[3,2-*e*]indole subunit containing an unprecedented spirocyclic cyclopropane that was subsequently established to be responsible for its characteristic DNA alkylation properties (Figure 1). The highly functionalized central and right-hand subunits of CC-1065 had been previously isolated and characterized[7] by Umezawa and co-workers and disclosed in 1978 as the effective *c*-AMP phosphodiesterase inhibitors PDE-I and PDE-II. At the time of its identification, (+)-CC-1065 constituted the most potent antitumor antibiotic identified exhibiting cytotoxic activity approximately 10^3 times more potent than classical agents.[8]

More recently, two new members of this class of exceptionally potent antitumor agents have been disclosed by groups in Japan along with a series of structurally related congeners (Figure 2).[9] The first of these is (+)-duocarmycin A which was isolated from *Streptomyces* DO-88 collected at the foot of Mt. Fuji and disclosed in 1988[10] by Kyowa Hakko Kogyo concurrent with a series of structurally related agents isolated from *Streptomyces* DO-89 collected in Hyogo, Japan: duocarmycins B_1 and B_2, C_1 and C_2, and D_1 and D_2.[9−14] Pyrindamycins A and B which proved identical to duocarmycins C_2 and C_1, respectively, were simultaneously disclosed by Meiji Seika Kaisha with isolation from *Streptomyces* SF2582 collected in Sagamihara, Japan.[15,16] The single-crystal X-ray structure determination of pyrindamycin A unambiguously established its relative and absolute stereochemistry[15] and through chemical interconversions independently conducted by the Kyowa Hakko Kogya group[9] and our group[17] served to establish the structures and absolute stereochemistry for the entire class. Notably, the transannular Ar-3′ spirocyclization of duocarmycin C_1 to provide duocarmycin A conducted in these studies[17] represented its first implementation and provided the basis for synthetic strategies that departed from those introduced in preceding efforts directed toward CC-1065.

The newest and most exciting of the natural products identified is (+)-duocarmycin SA which was isolated from *Streptomyces* DO-113 collected at the

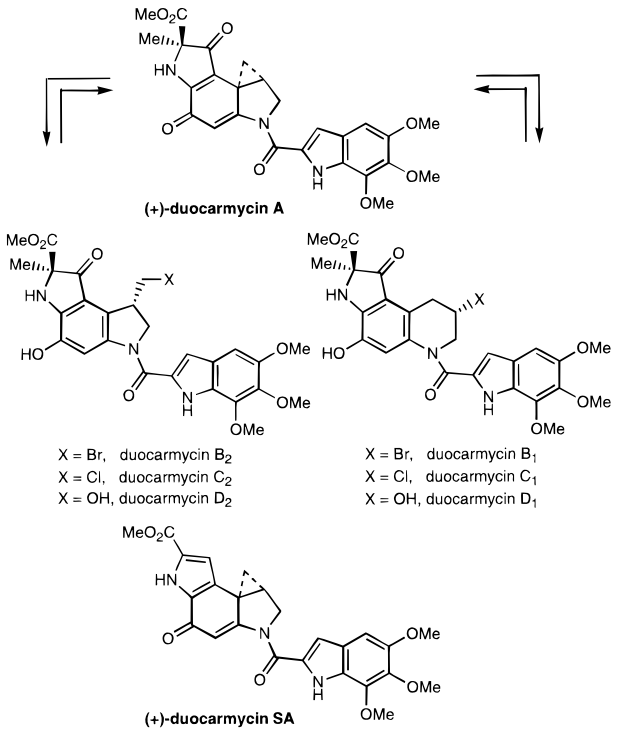


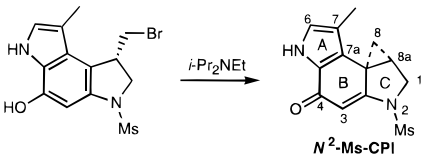
Figure 2. Structures of the duocarmycins.

Rokkakudo temple in Kyoto, Japan, by Kyowa Hakko Kogya. Disclosed in 1990,[18] it possesses a combination of chemical and biological properties that surpasses its predecessors.[19,20] Like duocarmycin A and its related congeners, (+)-duocarmycin SA lacks the delayed, fatal toxicity characteristic of (+)-CC-1065.[14,21−25] In addition, it is the most stable and most potent member of this class of agents. In fact, the name duocarmycin SA is a shortened abbreviation of its original referral name, duocarmycin stable A, which was used prior to the establishment of its structure. As defined in studies conducted in the interim and extrapolated from those addressing CC-1065,[26] this combination of properties is not fortuitous. The enhanced chemical and functional stability of duocarmycin SA is directly responsible for its increased biological potency.

Since the disclosure of CC-1065 and the duocarmycins, extensive efforts have been devoted to defining, understanding, and exploiting their properties.[26−41] In these studies, they have been shown to exert their biological effects through a characteristic sequence-selective alkylation of duplex DNA.[26,42−60] The reversible,[46,58] stereoelectronically controlled adenine N3 addition to the least substituted cyclopropane carbon has been shown to occur within selected AT-rich minor groove sites. Extensive and ongoing efforts have been devoted to establishing the origin of the DNA alkylation selectivity,[26] to determining the link between DNA alkylation and the ensuing biological properties,[61] and to defining the fundamental principles underlying the relationships between structure, chemical reactivity, and biological activity.[26]

A powerful complement to the examination of the natural products themselves is the preparation and examination of key partial structures, agents containing deep-seated structural modifications, and

Scheme 1. Wierenga Ar-3′ Spirocyclization



their corresponding unnatural enantiomers. Well-conceived deep-seated structural modifications have been used to address the structural basis of their interaction with DNA and to define important relationships between structure and properties. Central to such studies is the development of dependable synthetic strategies and the advent of new synthetic methodology to permit the preparation of the natural products, key partial structures, and their analogs. Herein we summarize[31−33,40,62] efforts directed at the total synthesis of CC-1065, the duocarmycins, and structurally related analogs that complements a recent review which summarizes their evaluation and properties.[26]

II. CC-1065

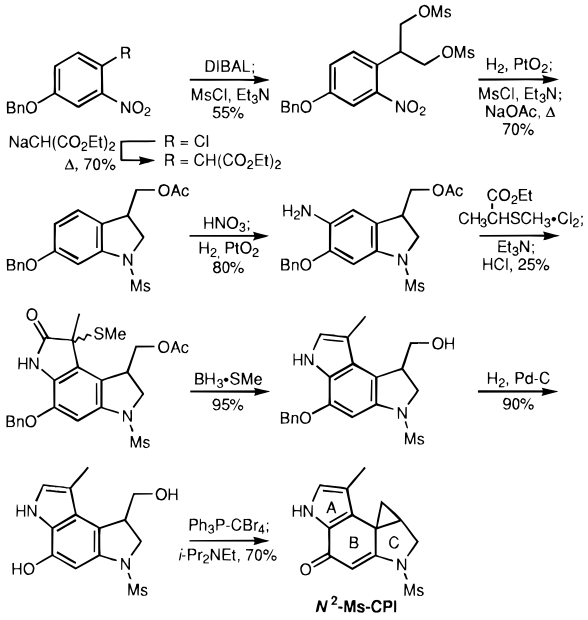
A. Synthesis of the Left-Hand Subunit of CC-1065 (CPI)

1. Wierenga Synthesis

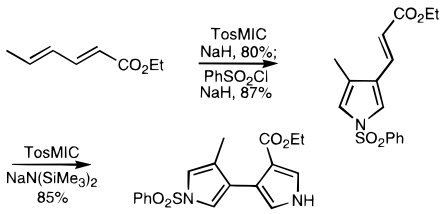
The first synthesis of the left-hand segment of CC-1065 was described by Wierenga in 1981,[63] three years after the reported isolation[1] and less than one year after the disclosed structural elucidation[5] of the natural product. Strategically, this synthesis is based on a key Winstein Ar-3′ alkylation[64] for introduction of the cyclopropane ring (Scheme 1), a modified Gassman oxindole synthesis[65] to form the A-ring, and an efficient route to 6-alkoxyindolines.

The nucleophilic aromatic substitution of commercially available 4-(benzyloxy)-1-chloro-2-nitrobenzene with the sodium anion of diethyl malonate was employed to introduce a three-carbon unit used for construction of the C-ring (Scheme 2). Conversion of this diester to the 6-(benzyloxy)indoline preceded regiospecific nitration followed by catalytic hydrogenation to install an amine at the C5 position which set the stage for introduction of the A-ring employing a modified Gassman oxindole synthesis. Thus, *in situ* generation and subsequent [2,3] sigmatropic rearrangement of a stabilized sulfur ylide, followed by acid-induced cyclization provided an α-(methylthio)lactam and this intramolecular reaction served to introduce a substituent at the hindered C4 aryl position. Subsequent improvements[66] in this sequence have addressed the low conversions initially reported. Borane reduction of the lactam completed the tricyclic core of CPI. Finally, deprotection of the benzyl ether, conversion of the primary alcohol to the corresponding bromide and Winstein Ar-3′ alkylation effected by treatment with Hunig's base provided *N*-Ms-CPI. The demonstration of this facile spirocyclization first investigated by Winstein and Baird in pioneering studies of the Ar anchimeric assistance or neighboring group participation reactions has provided the basis for most subsequent efforts, and the examination of this key subunit established its

Scheme 2. Wierenga Synthesis of CPI



Scheme 3. Magnus 3,3′-Bipyrrole Synthesis



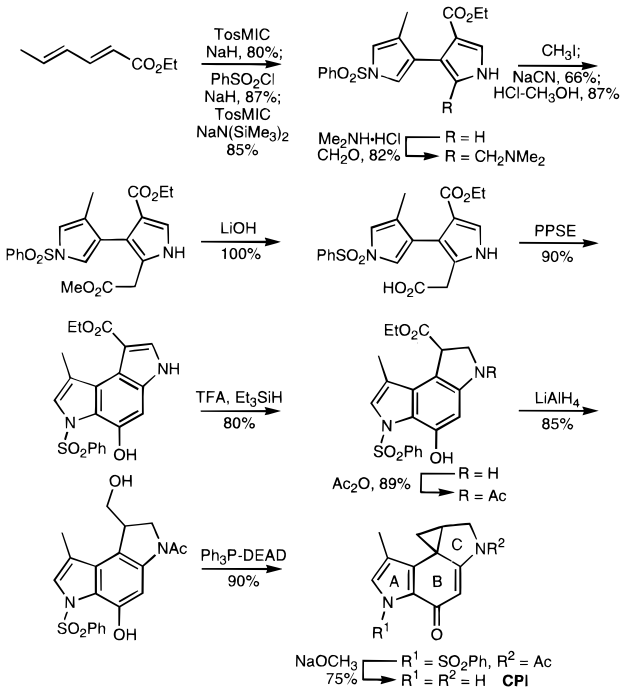
unusual and readily managed stability. Continued development of the Upjohn approach has resulted in improved yields, and CPI has been reported to be prepared by this 14-step sequence in 4% overall yield.[66]

2. Magnus Synthesis

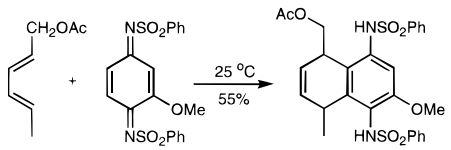
Magnus was first to report the preparation of unprotected CPI.[67] The approach commenced with an extension of the van Leusen 3-substituted pyrrole synthesis[68] to the construction of a 3,3′-bipyrrole, followed by completion of the CPI skeleton by benzannulation of the central ring, and subsequent selective reduction of the C-ring pyrrole.[69] In an effective three-step sequence, the required 3,3′-bipyrrole was prepared from ethyl sorbate (Scheme 3). The 1,6-addition of (*p*-tolylsulfonyl)methyl isocyanide (TosMIC) to ethyl sorbate, with concomitant cyclization and aromatization introduced the first pyrrole. Although the second addition of TosMIC did not occur directly with this substrate, protection of the free pyrrole as a sulfonamide, and subsequent 1,4-addition of TosMIC completed the 3,3′-bipyrrole synthesis.

To effect benzannulation of the central ring, a regioselective Mannich reaction introduced a one-carbon unit onto the desired, most electrophilic position (Scheme 4). Following three-step homologation to the ester and subsequent hydrolysis to the carboxylic acid, an effective Friedel−Crafts acylation conducted in trimethylsilyl polyphosphate (PPSE) completed the benzannulation onto the 3,3′-bipyrrole. A number of alternative and interesting approaches to the completion of this tricyclic core of CPI were

Scheme 4. Magnus Synthesis of CPI



Scheme 5. Kraus Regioselective Diels–Alder Reaction



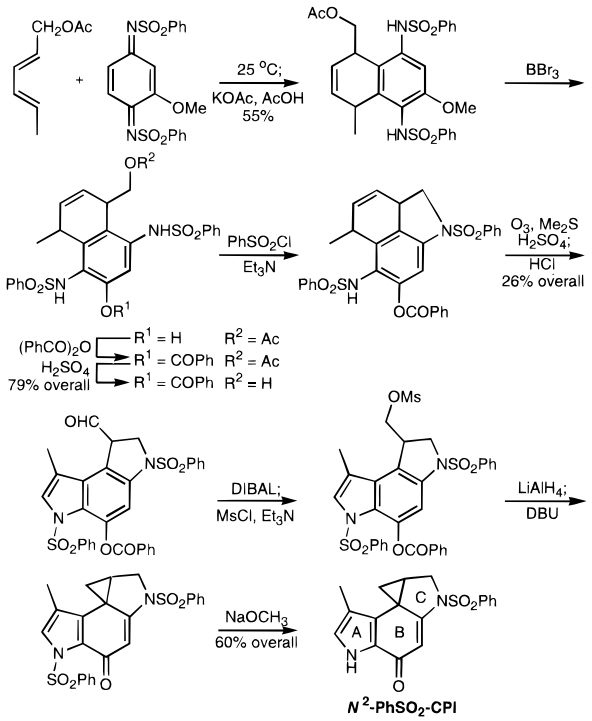
also examined in this work. Selective reduction of the C-ring pyrrole was accomplished with TFA/Et_3-SiH and may be attributed in part to the deactivating nature of the A-ring sulfonamide. Following N3 protection and C1 ester reduction, direct spirocyclization of the alcohol upon Mitsunobu activation[70] afforded protected CPI in 90% yield. Exhaustive deprotection completed the first reported synthesis of fully deprotected CPI in 14 steps from ethyl sorbate in 10% overall yield.

3. Kraus Synthesis

An imaginative route to CPI disclosed by Kraus[71] was based on a regioselective Diels–Alder reaction of an unsymmetrical 1,4-dialkyl-substituted diene with an iminoquinone to quickly access the requisite number of carbons in CPI followed by the cleavage of the resulting cyclohexene to introduce the differentiated fused 5-membered rings (Scheme 5). Embodied in this approach was the demonstration that an allylic acetate can produce unusual and useful levels of regioselectivity in the key Diels–Alder reaction.

Thus, the [4 + 2] cycloaddition of the unsymmetrical *N*,*N*′-bis(phenylsulfonyl)benzoquinone diimine, obtained in 90% yield by oxidation of the corresponding sulfonamide, with 1-acetoxy-2,4-hexadiene at 25 °C provided a single cycloadduct (55%) with greater than 25:1 regioselectivity. After cleavage of the methyl ether and replacement with a more easily removed protecting group, hydrolysis of the acetate, benzenesulfonate formation with activation

Scheme 6. Kraus Synthesis of CPI



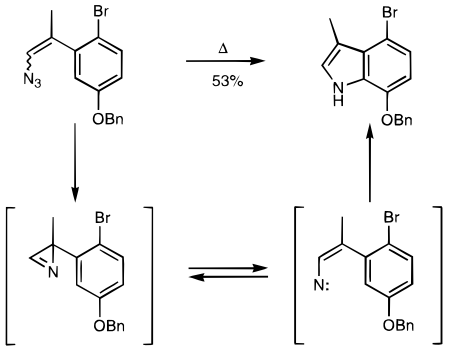
of the primary alcohol, and displacement by the adjacent sulfonamide formed the C-ring indoline (Scheme 6). In what may be the cleverest approach to introduction of the functionalized fused 5-membered rings at their appropriate oxidation level, cleavage of the cyclohexene by ozonolysis with reductive workup followed by acid-catalyzed cycloaromatization yielded the tricyclic core of CPI. Following conversion of the aldehyde to the mesylate and debenzoylation, introduction of the cyclopropane was effected by base-promoted spirocyclization to form N^2,N^5-bis(benzenesulfonyl) CPI. Selective deprotection of the N5 benzenesulfonyl group was achieved with NaOMe. This Diels–Alder-based route provided N^2-$PhSO_2$-CPI in 12 steps with an overall yield of 6% starting from the readily available benzoquinone diimide.

4. Rees–Moody Synthesis

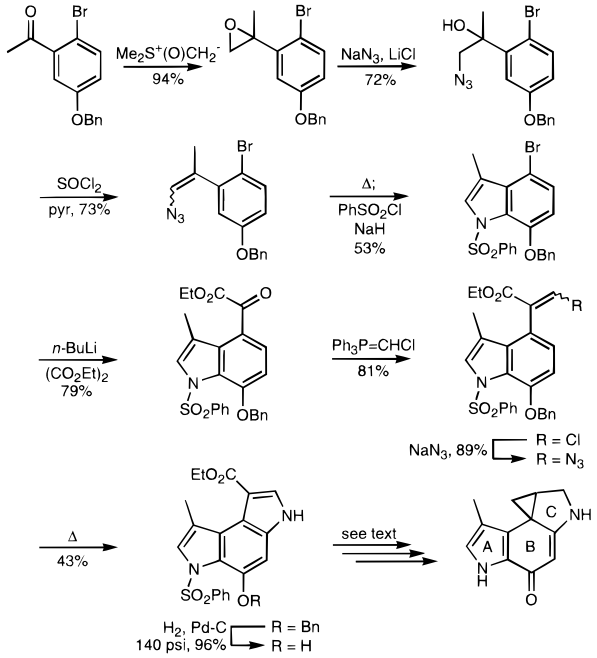
Rees and co-workers[72] employed their development[73] of the styryl azide thermolysis methodology discovered by Hemetsberger[74] for the preparation of 3-substituted indoles to introduce both fused 5-membered rings of CPI onto the central benzene ring (Scheme 7).

Conversion of 5-(benzyloxy)-2-bromoacetophenone, which was prepared in two steps from 3-hydroxyacetophenone (83%), to the first key styryl azide required three steps (Scheme 8). Thermolysis with generation of the intermediate nitrene led to introduction of the A-ring pyrrole in 53%. The second styryl azide was formed from an α-keto ester derived from lithium–halogen exchange and trap of the resulting aryllithium with diethyl oxalate. The α-keto ester was converted to the β-chlorostyrene through a Wittig reaction, and subsequent introduction of the azide was effected by a Michael addition with *in situ* elimination of chloride. The second

Scheme 7. Rees Styryl Azide Thermolysis



Scheme 8. Rees−Moody Synthesis of CPI



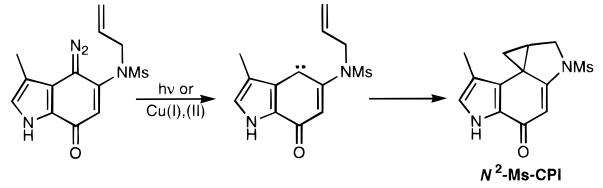
thermolysis provided the tricyclic core of CPI (43%) and intersected with the Magnus route[67] (Scheme 4) after phenol deprotection. The synthesis was completed using the Magnus protocol providing CPI in 17 steps with an overall yield of 3%.

5. Sundberg Synthesis

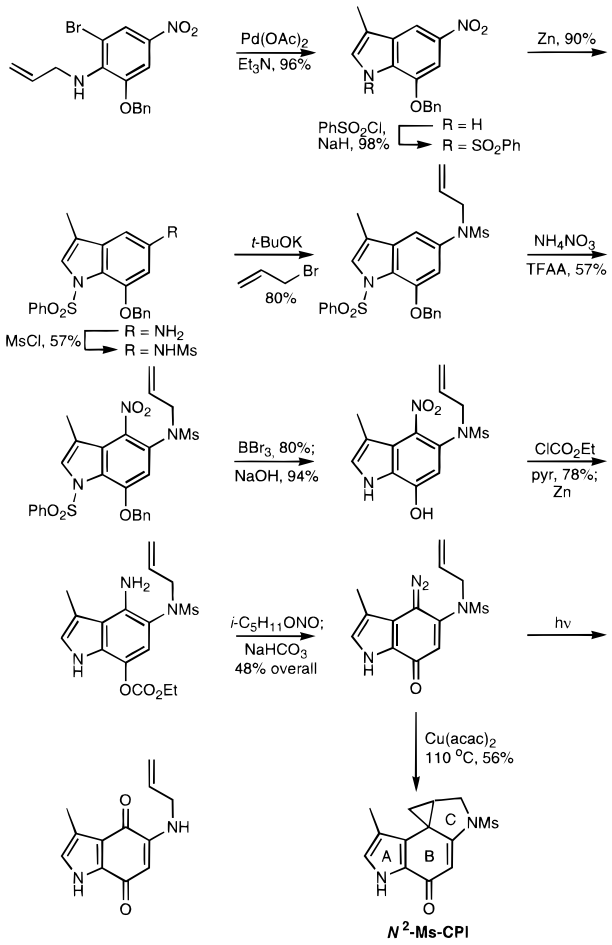
Sundberg and co-workers have described what may be the most interesting approach to the CPI subunit[75] which successfully diverged from the Winstein spirocyclization strategy for introduction of the activated cyclopropane. Initial efforts demonstrated that the cyclopropane could be introduced by an intramolecular carbene addition to an alkene tethered to a quinone monodiazide. Although early studies resulted in the inadvertent preparation of an agent isomeric with CPI[75a] and derived from *o*-quinone monodiazide, subsequent efforts provided the required *p*-quinone monodiazide and resulted in the synthesis of CPI utilizing this intramolecular carbene addition as the key step (Scheme 9). Notably, efforts to photochemically generate and subsequently trap the carbene with intramolecular alkene addition analogous to intermolecular alkene addition reactions[76] were not very successful. Rather, a metal-catalyzed carbenoid addition reaction was implemented.

The parent indole was constructed though a palladium(II)-catalyzed Hegedus[77] cyclization of 2-bromo-

Scheme 9. Sundberg Intramolecular Carbene Insertion

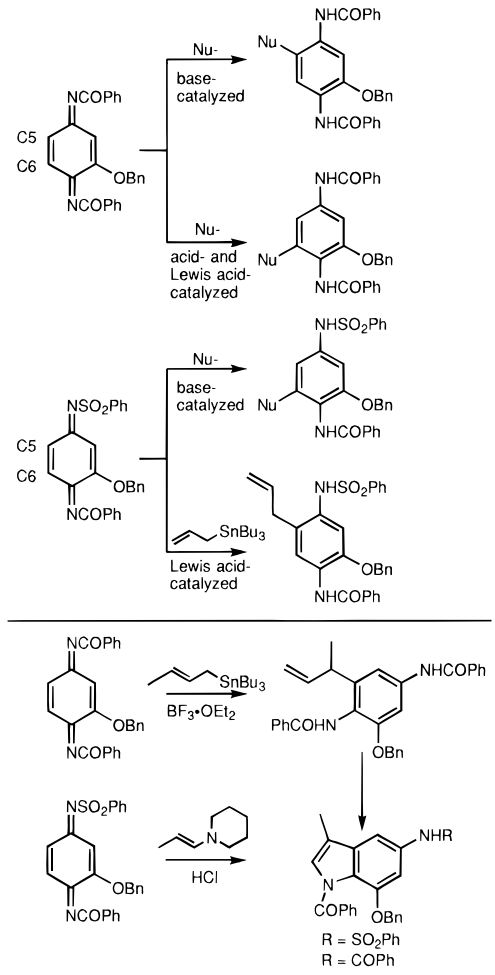


Scheme 10. Sundberg Synthesis of CPI



6-(benzyloxy)-4-nitro-*N*-(2-propenyl)aniline (Scheme 10). This indole was converted to the corresponding 5-(allylamino)indole which was subjected to a selective C4 nitration using NH_4NO_3−TFAA. This regioselective nitration successfully addressed the synthetic problem encountered in Sundberg's early efforts which resulted in the isomeric CPI preparation. After protecting group interchange, the nitro group was reduced and diazotization was carried out using isoamyl nitrite. Without isolation, the intermediate diazonium salt was converted directly to the 4-diazoindol-7-one. Photolysis of the *p*-quinone monodiazide yielded a 2:1 ratio of *p*-quinone to the desired N^2-Ms-CPI. This undesired side reaction was proposed to arise by oxygen atom transfer from the adjacent methanesulfonyl group to the carbene, which leads to hydrolysis of the resulting unstable sulfinamide. In contrast, efforts employing a thermal, metal-catalyzed carbene addition provided N^2-Ms-CPI in 50−80% accompanied by only minor amounts of the *p*-quinone. Although $Cu(acac)_2$ was utilized in the original disclosure of the work[75c] and

Scheme 11. Boger Addition to *p*-Quinone Diimines



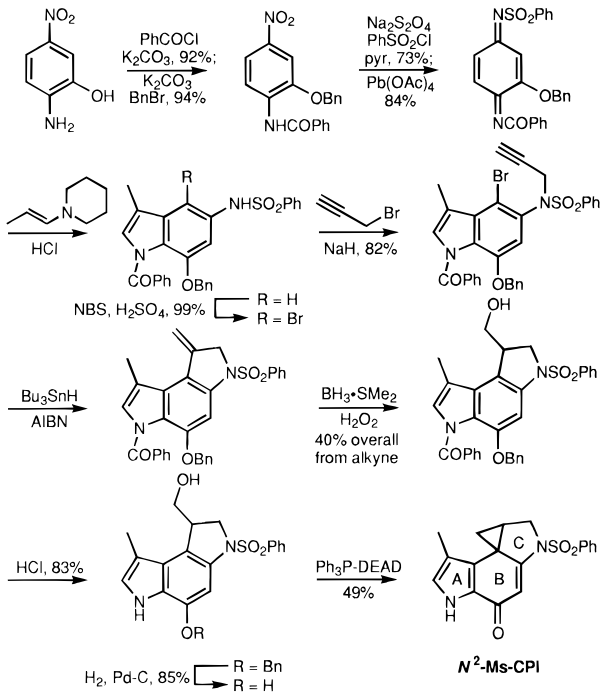
proved generally more useful than $Rh_2(OAc)_4$, (tfpd)-Cu(CO)−$BuNH_2$ was subsequently found to be superior, and a detailed study of Cu(I) and Cu(II) complexes as catalysts has been disclosed.[75d] The Sundberg synthesis of N^2-Ms-CPI was completed in 13 steps in 3% overall yield.

6. Boger–Coleman Synthesis

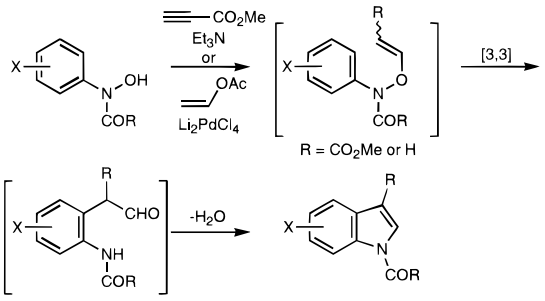
Our approach to CPI[78] was based on the regioselective addition of nucleophiles to selectively activated *p*-quinone diimines[79,80] to effectively introduce the 3-methylpyrrole A-ring (Scheme 11), subsequent implementation of a 5-*exo*-*dig* aryl radical−alkyne cyclization[81] to install the C-ring, and the Winstein Ar-3′ alkylation to complete the synthesis of CPI.

Use of the selectively activated N^4-(phenylsulfonyl)-2-(benzyloxy)-*p*-benzoquinone diimine, prepared in five steps from 2-amino-5-nitrophenol, in the regioselective addition of 1-piperidino-1-propene, followed by acid-catalyzed elimination of piperidine and concomitant aromatization provided the key substituted 5-amino-3-methylindole (Scheme 12). The selective electrophilic activation of the C6 position of the *p*-quinone diimine by the N4 benzenesulfonyl group proved sufficient to override the inherent preference for the C5 nucleophilic addition of the parent N^1,N^4-dibenzoyl-2-(benzyloxy)-*p*-benzoquinone diimine. The modest conversions initially disclosed were subsequently improved employing the Lewis acid-catalyzed addition of allyltributyltin (Scheme 11).[80] The reversed and complementary regioselectivity of this latter reaction no longer required the N^4-benzenesulfonyl activation for C6 nucleophilic addition. Regioselective C4 bromination, introduction of the alkyne, and 5-*exo*-*dig* aryl radical−alkyne cyclization[81] provided the unstable 3-methyleneindoline. Immediate hydroboration−oxidation afforded the primary alcohol and completed the construction of the appropriately functionalized CPI skeleton. After deprotection, direct Winstein Ar-3′ alkylation upon Mitsunobu activation of the primary alcohol afforded N^2-$PhSO_2$-CPI in 4% overall yield over eight steps from the starting *p*-quinone diimine.

Scheme 12. Boger−Coleman Synthesis of CPI



Scheme 13. Martin Hetero-Cope Rearrangement

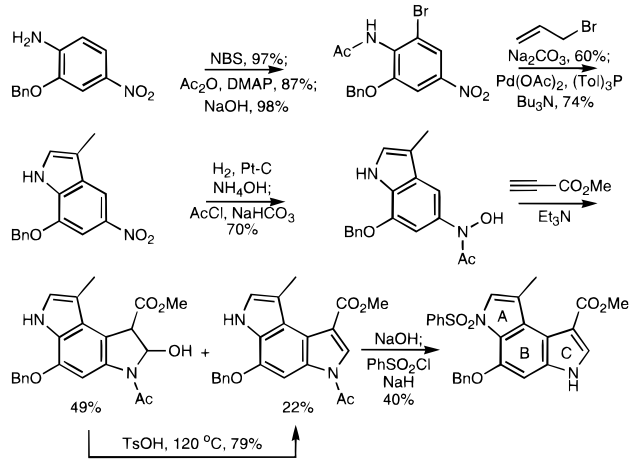


7. Martin Synthesis

Martin's formal synthesis of CPI[82] was based on a methodology developed for the construction of substituted *N*-acylindoles. Hetero-Cope rearrangement of a substituted *N*-phenyl *O*-vinylhydroxylamine, generated *in situ* from the corresponding *N*-phenylhydroxamic acid, secured efficient access to the BC-ring indole of CPI (Scheme 13) following adoption of a Pd(II)-catalyzed cyclization[77] for introduction of the A-ring pyrrole.

Following regioselective bromination of 2-(benzyloxy)-4-nitroaniline and two-step *N*-acetylation, *N*-alkylation with allyl bromide and Hegedus cyclization

Scheme 14. Martin Formal Synthesis of CPI



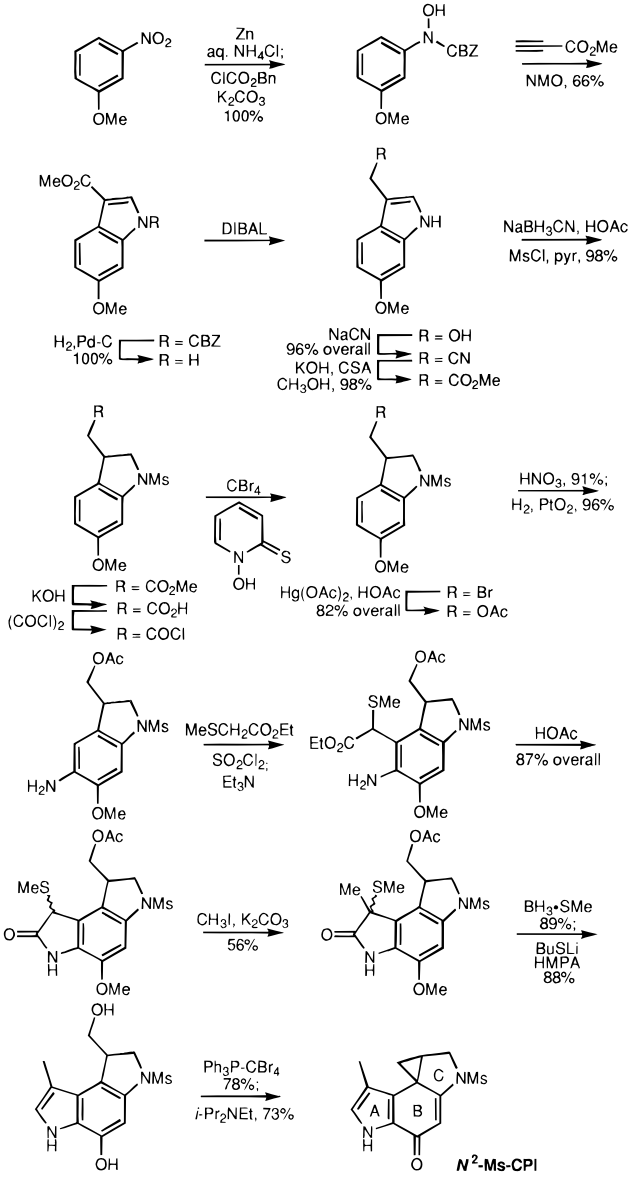
formed the A-ring pyrrole (Scheme 14). Partial reduction of the nitro group effected by hydrogenation over Pt in the presence of NH_4OH, and subsequent *N*-acylation provide the key *N*-phenylhydroxamic acid. Base-catalyzed Michael addition to methyl propiolate generated *in situ* the vinyl ether, which underwent a [3,3] hetero-Cope rearrangement, followed by dehydration and aromatization to form the desired indole in 22% along with the corresponding carbinol amide in 49%. Conversion of the latter to the desired indole (79%) provided overall conversions approaching 60% for this key reaction. Hydrolysis of the *N*-acetyl group, and sulfonylation of the more nucleophilic pyrrole yielded the methyl versus ethyl ester of the key intermediate in the Magnus and Rees−Moody syntheses of CPI (Schemes 4 and 8).

8. Fukumoto Synthesis

Fukumoto's synthesis of CPI[83] disclosed three years later was also based on a tandem Michael addition−[3,3] sigmatropic rearrangement for the formation of substituted indoles analogous to Martin's disclosure.[82] Strategically, the route reversed the order of A- and C-ring introductions relying on the reaction of a substituted phenylhydroxylamine with methyl propiolate to form the desired BC-ring indole first, and then adopted modifications in approaches detailed by Cava[84] and Wierenga[63] (Scheme 2) to complete the synthesis of CPI.

The key precursor, benzyl *N*-hydroxy-*N*-(3-methoxyphenyl)carbamate was prepared from *m*-nitroanisole in a two-step sequence. This substituted phenylhydroxylamine added in Michael fashion to methyl propiolate in the presence of NMO and underwent *in situ* [3,3] sigmatropic rearrangement, carbamate addition to the formyl group, and dehydration with aromatization to the desired indole in 66% yield. By using a modification of Cava's approach (Scheme 48), the *N*-(methylsulfonyl)indoline was formed, and the ester was degraded to an acetate similarly using a Barton free radical decarboxylation reaction. The A-ring was installed using the improved modified Gassman oxindole synthesis[65] developed in the Wierenga route. Finally, conversion to N^2-Ms-CPI was achieved following Wierenga's two-step protocol for Ar-3′ spirocyclization, completing the synthesis in 21 steps with an overall yield of 9% (Scheme 15).

Scheme 15. Fukumoto Synthesis of CPI

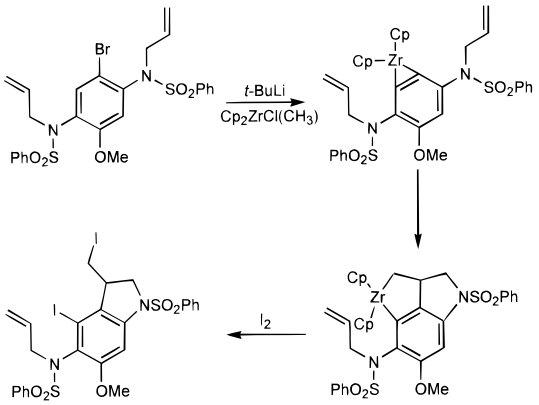


9. Tietze Synthesis

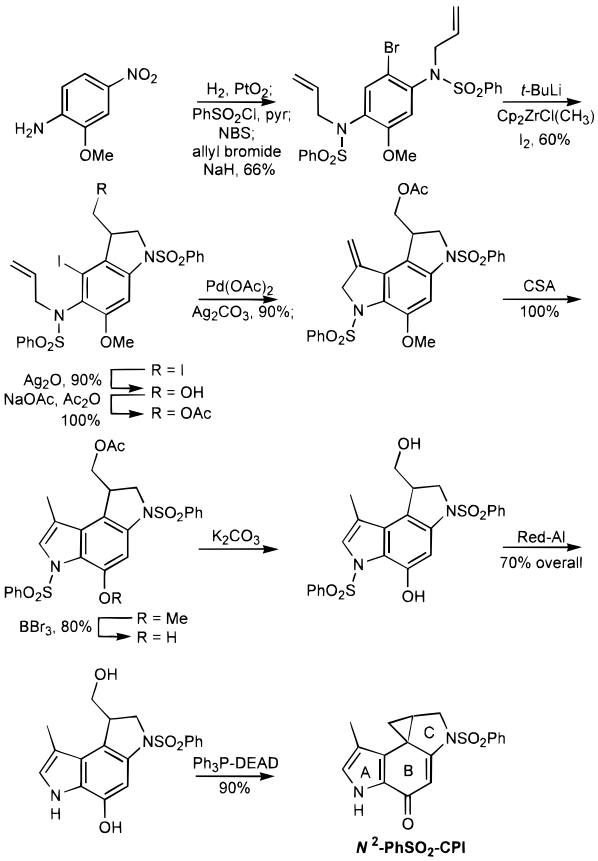
Tietze has completed the latest synthesis of CPI disclosed to date.[85] On the basis of an approach and methodology introduced by Buchwald,[86] two metal-catalyzed cyclizations were employed to sequentially form the pyrroline C-ring and the pyrrole A-ring of CPI (Scheme 16). The first cyclization is catalyzed by zirconocene which cleverly sets up the ensuing Pd(II)-catalyzed cyclization first implemented in the work of Sundberg[75d] and Martin[82] (Schemes 10 and 14).

The key precursor to the zirconocene cyclization was synthesized in four steps, 66% yield from 2-methoxy-4-nitroaniline (Scheme 17). Lithium−halogen exchange and subsequent reaction with $Cp_2ZrCl(CH_3)$ proceeded through a zirconocene−benzyne complex to the zirconacyclopentene. After quenching with 2 equiv of I_2, the diiodoindoline was isolated as the single reaction product in 60% yield. Following conversion of the primary iodide to the acetate, a Pd(II)-catalyzed cyclization and subsequent acid-catalyzed double-bond isomerization produced the C-ring

Scheme 16. Buchwald−Tietze Zirconocene Cyclization



Scheme 17. Tietze Synthesis of CPI



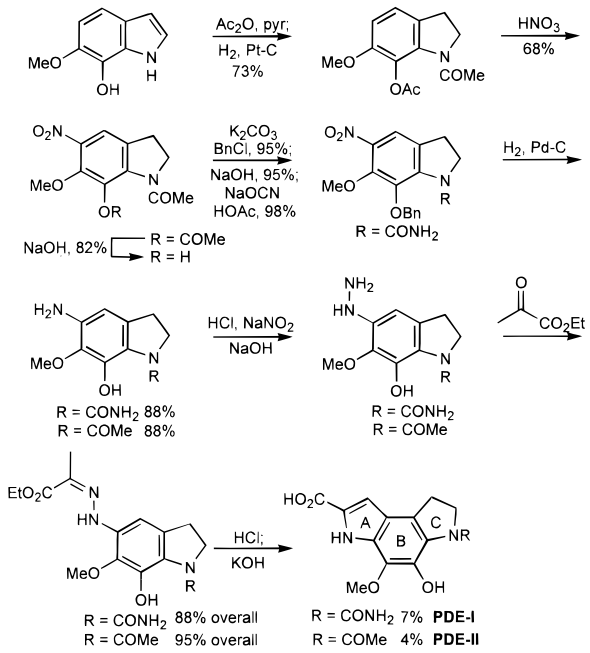
pyrrole, and completed the tricyclic core of CPI. After three sequential deprotections, Winstein spirocyclization of the primary alcohol upon Mitsunobu activation completed the synthesis. N^2-PhSO$_2$-CPI was synthesized in 12 steps in 12% overall yield.

B. Synthesis of the Central and Right-Hand Subunits of CC-1065: PDE-I and PDE-II

1. Umezawa Synthesis

Shortly following the the discovery of PDE-I and PDE-II (Figure 1) as natural products,[7] Umezawa and co-workers conducted the first synthesis in conjunction with their structure identification studies.[87] The dihydropyrrolo[3,2-*e*]indole core was constructed by building two pyrrole rings onto a central benzene ring using classical chemistry. The first of

Scheme 18. Umezawa Synthesis of PDE-I and PDE-II



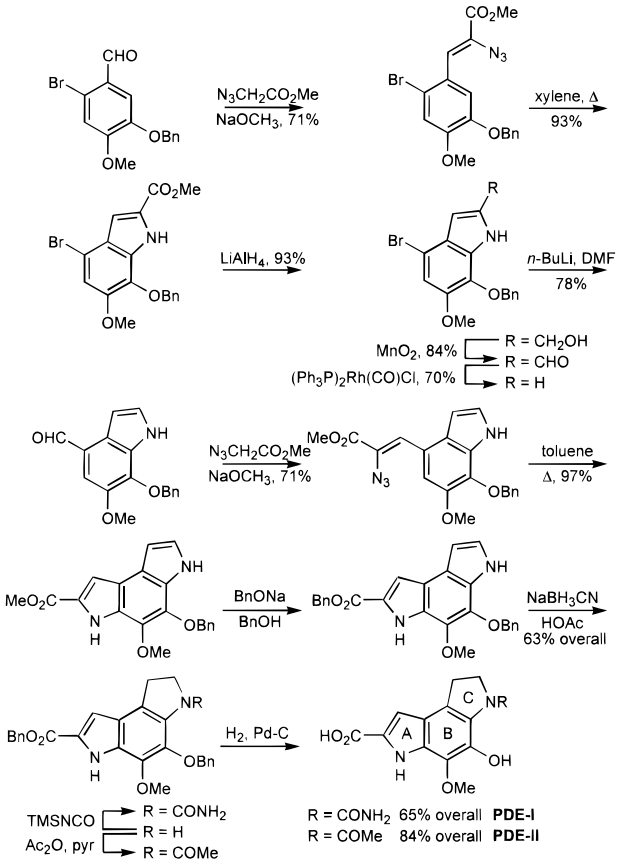
these, 7-hydroxy-6-methoxyindole, was synthesized from isovanillin in a three-step sequence (Scheme 18). The acetylated indole was reduced to the indoline and regiospecific C5 nitration set up the introduction of the second indole. At this stage, the indoline was maintained as the acetamide or converted to the corresponding urea for the purposes of accessing both PDE-I and PDE-II. The C5 nitro group was reduced, converted to the hydrazone using Japp-Klingemann conditions,[88] and, upon reaction with ethyl pyruvate in the presence of acid, underwent Fischer indole cyclization, albeit in low yields. Final hydrolysis of the ethyl esters gave PDE-I in 14 steps from isovanillin in 0.07% yield and PDE-II in 0.1% yield after 11 steps.

2. Rees–Moody Synthesis

The Rees−Moody synthesis[89] further extended their application of vinyl azides in heterocyclic synthesis[73] by highlighting the use of α-azidocinnamates, which are easily prepared from aromatic aldehydes, in styryl nitrene cyclizations. Its successful application in the synthesis of PDE-I and PDE-II illustrated the ability of this methodology to address all three subunits of CC-1065. Their strategy, which was analogous to that employed for CPI (Scheme 8), utilized two sequential thermal azide cyclizations for introduction of two pyrroles onto an appropriately substituted central benzene ring followed by selective reduction of the C-ring.

5-(Benzyloxy)-2-bromo-4-methoxybenzaldehyde was prepared from isovanillin in a two-step sequence in 77% yield (Scheme 19). Low-temperature condensation of the aldehyde with methyl α-azidoacetate cleanly provided the α-azidocinnamate and subsequent thermolysis formed the first indole in 93%. The methyl ester was removed in a three-step sequence that included a Rh(I)-catalyzed decarbonylation employing Wilkinson's catalyst. Conversion of the C4 bromide to an aldehyde effected by a lithium−

Scheme 19. Rees–Moody Synthesis of PDE-I and PDE-II



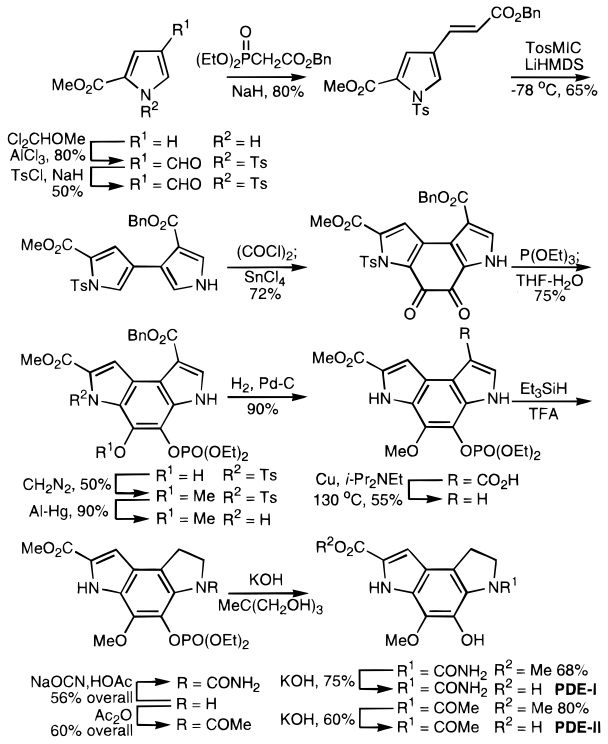
halogen exchange and reaction of the resulting aryllithium reagent with DMF, followed by condensation with methyl α-azidoacetate provided the second key α-azidocinnamate. Thermolysis and nitrene cyclization proceeded in 97%, and was followed by transesterification with benzyl alcohol and selective $NaBH_3CN$ reduction of the more nucleophilic indole. After divergent *N*-acylation with trimethylsilyl isocyanate or Ac_2O to accommodate both natural products, deprotection of the benzyl ether yielded PDE-I and PDE-II in 14 steps and 4% and 5% overall yields, respectively.

3. Magnus Synthesis

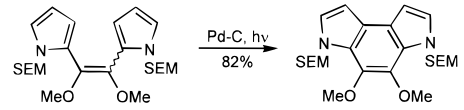
The Magnus approach[90] relied on an extension of their 3,3′-bipyrrole strategy used in the synthesis of CPI (Scheme 4).[67] Although tactically similar, the implementation of this strategy of constructing the central aromatic ring onto a differentiated 3,3′-bipyrrole proved more challenging. This was accomplished by a double acylation with oxalyl chloride for fused annulation of an *o*-quinone, reduction to a catechol, and selective C4 *O*-methylation. Subsequent selective C-ring reduction provided access to PDE-I and PDE-II and followed protocols introduced in their CPI synthesis.

Thus, the 3,3′-bipyrrole was assembled by the addition of TosMIC to the α,*β*-unsaturated ester derived from methyl pyrrole-2-carboxylate in three steps (Scheme 20). Treatment with oxalyl chloride followed by $SnCl_4$ provided the key *o*-quinone via sequential Friedel–Crafts acylations. Reduction of the quinone with triethyl phosphite and subsequent

Scheme 20. Magnus Synthesis of PDE-I and PDE-II



Scheme 21. Cava–Rawal Mallory-type Photocyclization

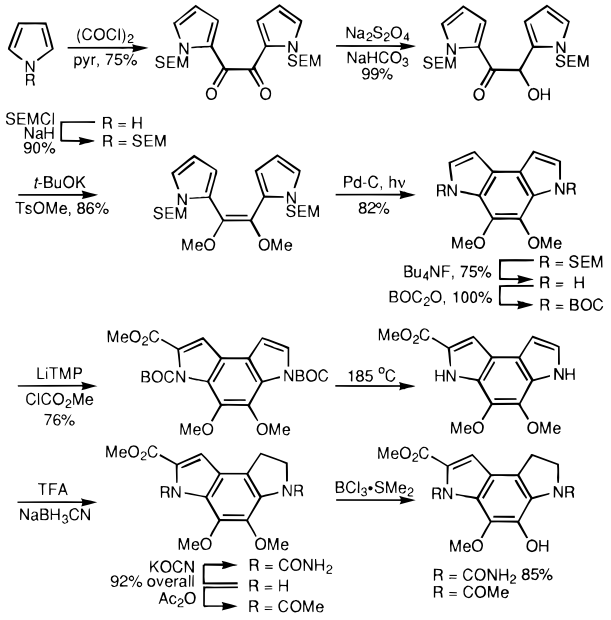


hydrolysis in aqueous THF gave a single phosphate ester. The regioselectivity of the intermediate cyclic oxaphosphorane hydrolysis is rationalized as a steric preference for formation of the less hindered phosphate. Since the phosphate ester easily migrated under basic conditions, carefully defined reaction conditions were required for methylation of the free phenol (CH_2N_2) and provided the desired C5 methyl ether in 3:1 to 9:1 ratios with the undesired isomer. Removal of the sulfonamide with Al(Hg), hydrogenolysis of the benzyl ester, and copper-catalyzed thermal decarboxylation gave the appropriately substituted pyrrolo[3,2-*e*]indole. Selective reduction of the electron-rich indole proceeded smoothly under the conditions developed for CPI. Final *N*-acylation followed by ester and phosphate ester hydrolysis produced PDE-I and PDE-II in 16 steps in 1% overall yield.

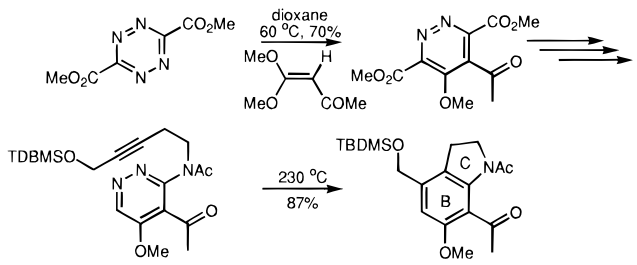
4. Cava–Rawal Synthesis

Cava developed an efficient approach that utilizes the symmetry inherent in the subunits.[91] It is similar to the Magnus strategy in that it constructed the central aromatic ring on a precursor that contains the two existing pyrroles, but differed in that it is the 3,3′-bipyrrole linkage that was formed in the key cyclization reaction. A Mallory-type stilbene photocyclization[92] was employed to install the central benzene ring (Scheme 21). The authors were able to effectively break the symmetry of their intermediates using an unusually successful directed metala-

Scheme 22. Cava−Rawal Synthesis of PDE-I and PDE-II



Scheme 23. Boger−Coleman 1,2,4,5-Tetrazine → 1,2-Diazine → Indoline Strategy

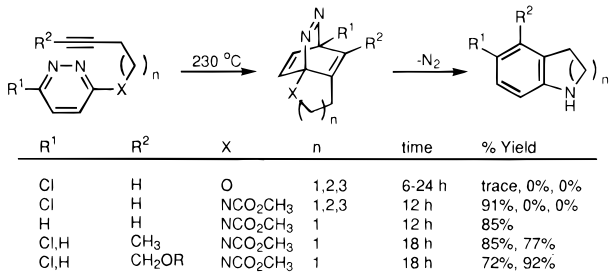


tion and were able to selectively deprotect the C-4/C-5 catechol required of the natural products thereby substantially simplifying the synthetic challenge.

The electrocyclic photocyclization substrate was prepared as outlined in Scheme 22. A cis−trans mixture of olefins was photocyclized in the presence of Pd−C[93] to insure efficient dehydrogenation of the intermediate and provided the symmetrical pyrrolo-[3,2-*e*]indole. After replacing the SEM protecting groups with BOC, a directed orthometalation and subsequent trap with $ClCO_2Me$ effectively afforded the methyl pyrrolo[3,2-*e*]indole-2-carboxylate in a key reaction that served to break the symmetry of the intermediates. Following thermal removal of the BOC protecting groups[94] and selective reduction of the unsubstituted pyrrole, divergent *N*-acylation provided the immediate precursors to PDE-I and PDE-II. Selective Lewis acid-promoted C4 *O*-demethylation with BCl_3 provided the natural products in 11 steps and in greater than 20% overall yield.

5. Boger–Coleman Synthesis

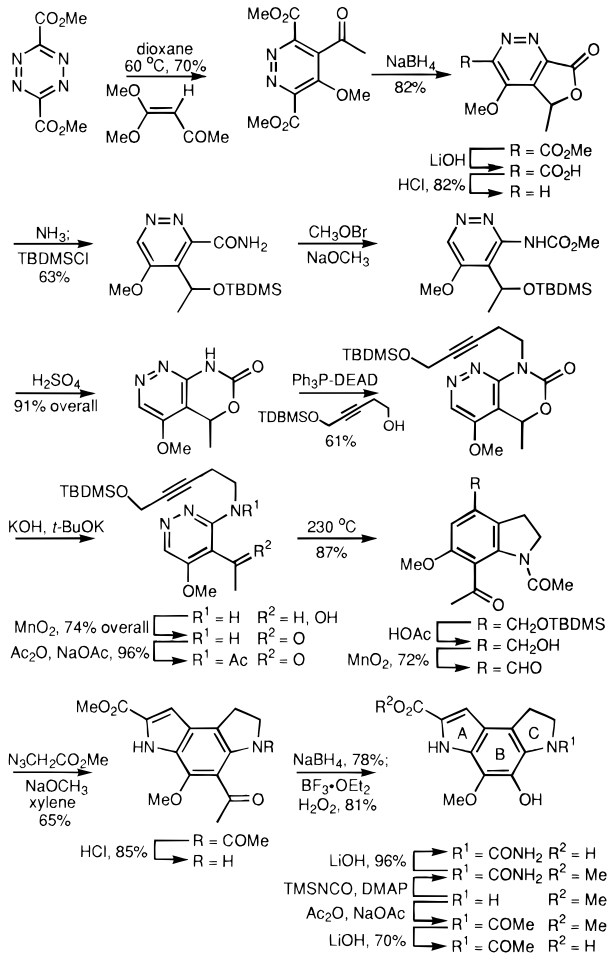
Our approach to PDE-I and PDE-II[95] was based on two heterocyclic azadiene Diels−Alder reactions[96] in the implementation of a 1,2,4,5-tetrazine → 1,2-diazine → indoline strategy[97] for construction of the BC ring system (Scheme 23). Concurrent with its development, the feasibility and scope of the key intramolecular alkyne/1,2-diazine cycloaddition reaction was first defined (Figure 3).[97] Following installation of the pyrrole-2-carboxylate A-ring employing the Rees α-azidocinnamate thermolysis (Scheme 7),[73] a regiospecific introduction of the C4 phenol permitted effective differentiation of the C4/C5 catechol and was achieved through implementation of a newly developed Lewis acid-promoted benzylic hydroperoxide rearrangement.[98]



R^1	R^2	X	n	time	% Yield
Cl	H	O	1,2,3	6-24 h	trace, 0%, 0%
Cl	H	NCO_2CH_3	1,2,3	12 h	91%, 0%, 0%
H	H	NCO_2CH_3	1	12 h	85%
Cl,H	CH_3	NCO_2CH_3	1	18 h	85%, 77%
Cl,H	CH_2OR	NCO_2CH_3	1	18 h	72%, 92%

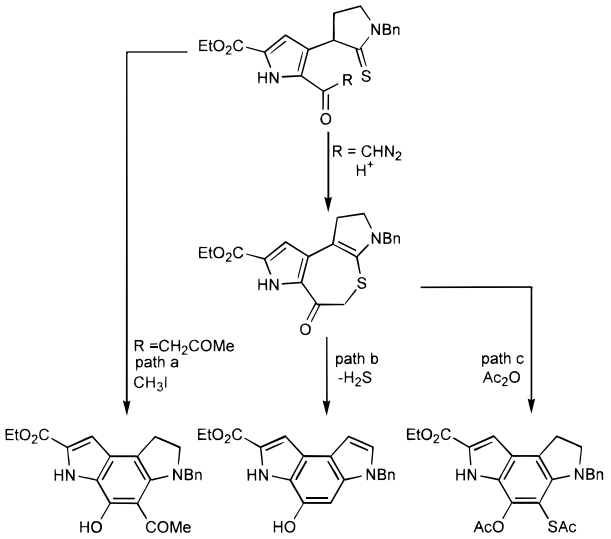
Figure 3. Boger 1,2-diazine alkyne Diels−Alder reaction.

Scheme 24. Boger−Coleman Synthesis of PDE-I and PDE-II



The alkyne 1,2-diazine required for incorporation into the total synthesis of PDE-I and PDE-II was derived from the product of a Diels−Alder reaction of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate[99] with 4,4-dimethoxybut-3-en-2-one which proceeded in 70% yield at 60 °C (Scheme 24). Reduction of the resulting ketone followed by *in situ* closure to the lactone led to differentiation of the C3 and C6 carboxylates. Subsequent hydrolysis of the remaining methyl ester followed by acidification provided a surprisingly facile, room temperature decarboxylation of the C3

Scheme 25. Sundberg Cyclizations of 3-(3-Pyrrolyl)thiopyrrolidones



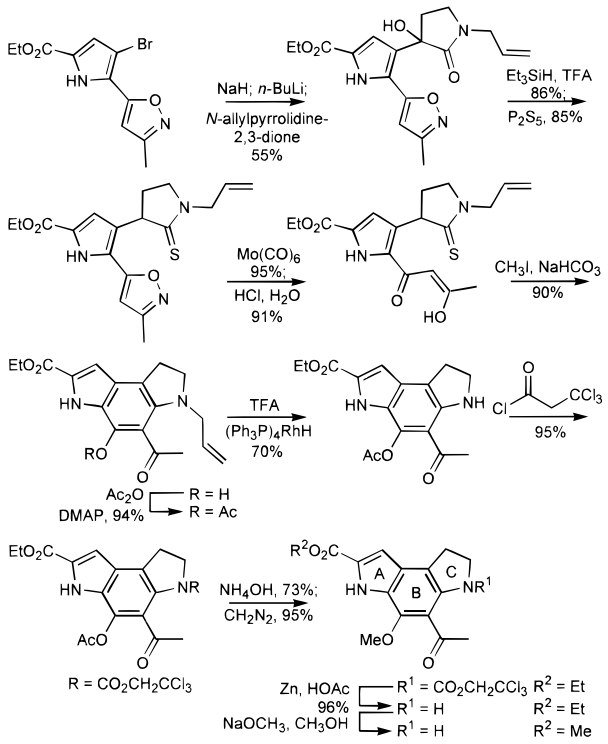
carboxylate presumably derived from aryl ipso protonation. Introduction of the nitrogen required for the BC indoline ring construction was accomplished by a modified Hofmann rearrangement[100] of the primary amide derived from aminolysis of the lactone. Subsequent deprotection of the TBDMS ether and closure to the carbamate preceded *N*-alkylation with the functionalized alkyne side chain under Mitsunobu conditions. This alkyne failed to undergo the desired intramolecular Diels−Alder reaction due to the geometrical constraints imposed by the fused oxazinone. Thus, hydrolysis of the oxazinone[101] followed by *N*-acetylation to confer stability on the emerging indole gave the successful Diels−Alder substrate. At 230 °C, the intramolecular [4 + 2] cycloaddition produced the BC-ring indoline in 87%. The A-ring pyrrole-2-carboxylate was introduced by preparation and thermolysis of the α-azidocinnamate. A mild Lewis acid-catalyzed benzylic hydroperoxide rearrangement was developed to convert the benzylic alcohol to the corresponding phenol and this rearrangement could be conducted under conditions where even a basic amine was not competitively oxidized. Divergent *N*-acylation and ester hydrolysis provided PDE-I and PDE-II in 19 steps with overall yields of 2.5% and 1.7%, respectively.

6. Sundberg Synthesis

In initial studies, Sundberg[102] demonstrated that 3-(3-pyrrolyl)thiopyrrolidones could serve as intermediates in the synthesis of substituted dihydropyrrolo[3,2-*e*]indoles or pyrrolo[3,2-*e*]indoles potentially suitable as precursors to PDE-I and PDE-II. The most efficient approach was the intramolecular condensation[103] (path a), but two additional routes were explored where path b is an Eschenmoser ring contraction reaction with sulfur extrusion,[104] and path c employs a related ring contraction (Scheme 25). All three pathways proceeded in good yield. Yet, due to the ease of oxidative aromatization of the dihydropyrrolo[3,2-*e*]indoles that accompanied *N*-debenzylation, their conversion to PDE-I and PDE-II was not achieved.

Continued developments established the viability of this approach.[105] The addition of ethyl 4-lithio-1-

Scheme 26. Sundberg Formal Synthesis of PDE-I and PDE-II



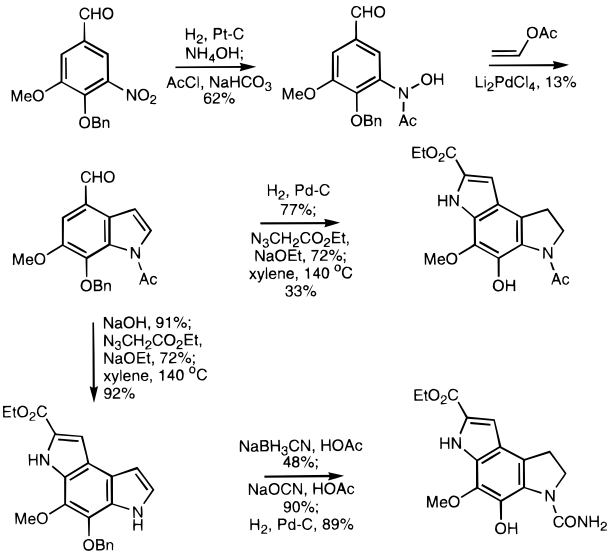
sodio-5-(3-methylisoxazol-5-yl)pyrrole-2-carboxylate to *N*-allylpyrrolidine-2,3-dione, and subsequent conversion to the thiolactam was completed in a five-step sequence (Scheme 26). Molybdenum hexacarbonyl effected cleavage of the isoxazole and subsequent hydrolysis provided the key cyclization substrate. Cyclization in the presence of 2−3 equiv of MeI with intermediate generation of the *S*-(methylthio)iminium ion occurred in 90%. Metal-catalyzed isomerization and subsequent hydrolysis of the *N*-allyl group, followed by four-step conversion to a key intermediate in our approach to PDE-I and PDE-II[95] (Scheme 24) completed a formal synthesis of the natural products.

7. Martin Synthesis

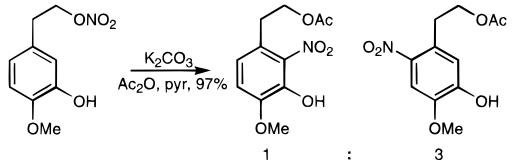
Martin extended his study of the hetero-Cope rearrangement of *N*-phenylhydroxamic acids (Schemes 13 and 14) to the preparation of the central and right-hand subunits of CC-1065[82] and although it was successfully implemented, the yield of the key step to form the BC-ring indole was low. In these studies, the hetero-Cope rearrangement was found to suffer from a lack of regioselectivity when an electron-donating group was located ortho or para to the hydroxamic acid. Subsequent to the BC ring introduction, the Rees−Moody α-azidocinnamate thermolysis and nitrene cyclization[73] for formation of the A-ring pyrrole was adopted.

4-(Benzyloxy)-3-methoxy-5-nitrobenzaldehyde was converted to the hydroxamic acid by Pt-catalyzed partial hydrogenation of the nitro group in the presence of NH_4OH, followed by *N*-acetylation (Scheme 27). The hydroxamic acid was treated with vinyl acetate in the presence of catalytic Li_2PdCl_4 to generate *in situ* the *O*-vinyl-*N*-phenylhydroxylamide which underwent hetero-Cope rearrangement, dehy-

Scheme 27. Martin Synthesis of PDE-I and PDE-II



Scheme 28. Tojo Intramolecular Nitration of Phenols



dration, and aromatization to give the BC-ring indole in 13%. Subsequent catalytic hydrogenation served to remove the benzyl ether and reduce the indole. Condensation of the aldehyde with ethyl α-azidoacetate and subsequent thermolysis yielded PDE-II ethyl ester in six steps in 1.5% overall yield. PDE-I was synthesized in a similar manner following the exchange of the *N*-acetyl group for the *N*-carbamoyl group and a selective reduction of the C-ring pyrrole. PDE-I was synthesized in nine steps in 1.8% yield.

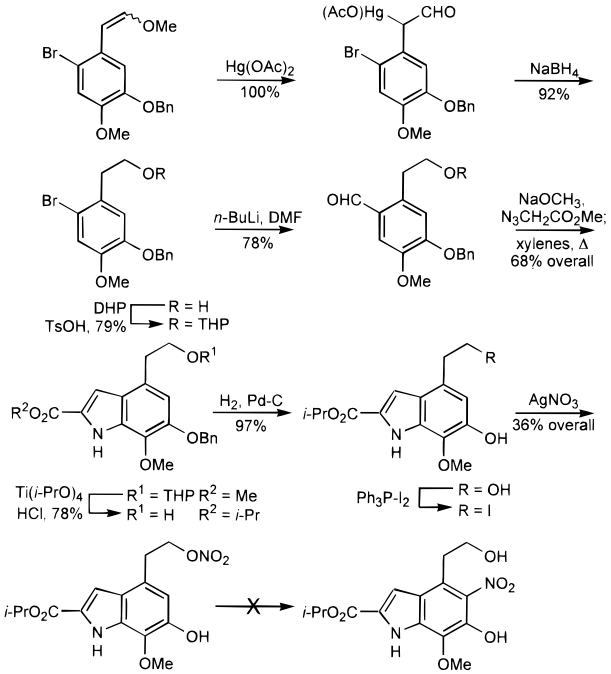
8. Tojo Approach

Although unsuccessful to date, the recent efforts of Tojo and co-workers to prepare PDE-I and PDE-II[106] constitute an interesting extension of the approach disclosed by Rees.[72] Tojo adopted the thermolysis of an α-azidocinnamate to construct the first indole and then planned to install the dihydropyrrole ring directly avoiding the necessity for selective reduction. For this purpose, a mild intramolecular *o*-nitration was developed using aryl ethyl nitrates[107] (Scheme 28).

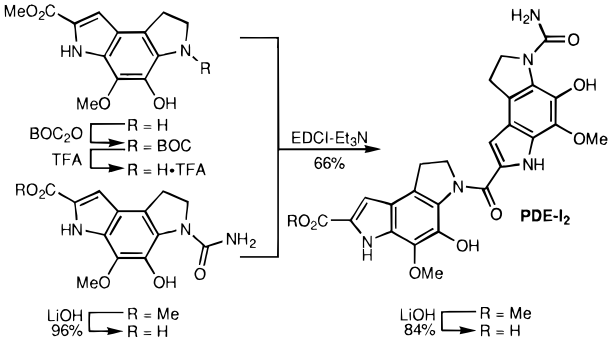
Thus, Wittig conversion of the Rees aldehyde (Scheme 19) to the corresponding methyl enol ether, subsequent hydrolysis, reduction, and THP protection of the free alcohol provided the key starting material (Scheme 29). Introduction of the first pyrrole ring was accomplished in the fashion described by Rees.[72] Unfortunately, all conventional C5 nitration attempts failed due to the susceptibility of the 6-hydroxyindole-2-carboxylate to oxidize to the *o*-quinone.

In expectations that the tethered nitration might alleviate this problematic reaction, the primary alcohol was converted to the nitrate, and the intramolecular transfer was explored. Unfortunately, this

Scheme 29. Tojo Approach to the Synthesis of PDE-I and PDE-II



Scheme 30. Boger−Coleman Synthesis of PDE-I_2



also led to complex mixtures and the desired product was not detected.

C. Synthesis of PDE-I_2 and CC-1065

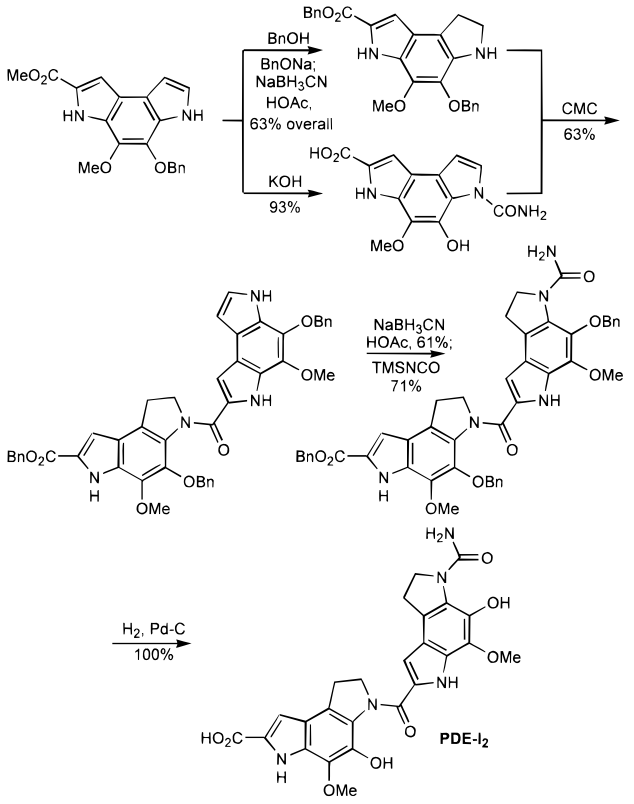
1. Boger–Coleman Synthesis of PDE-I_2

Following successful studies with readily available model systems which established that the terminal carbamoyl and free phenol of PDE-I would not interfere with a direct coupling,[108] the trifluoroacetate salt of the deprotected indoline was coupled with PDE-I using EDCI to afford PDE-I_2 methyl ester in 66% (Scheme 30).[109] Base-promoted ester hydrolysis provided PDE-I_2 in 84%. This approach was also utilized to prepare PDE-I_3,[108] a key analog of the natural product which proved to be an effective DNA minor groove binding agent lacking the capabilities of DNA alkylation.

2. Rees–Moody Synthesis of PDE-I_2

Having prepared both PDE-I and PDE-II,[72] Rees and co-workers incorporated their intermediates in an indirect synthesis of PDE-I_2.[110] From the common C4-benzyl-protected phenol, the precursor to the left-hand portion was transesterified and reduced to form

Scheme 31. Rees−Moody Synthesis of PDE-I_2

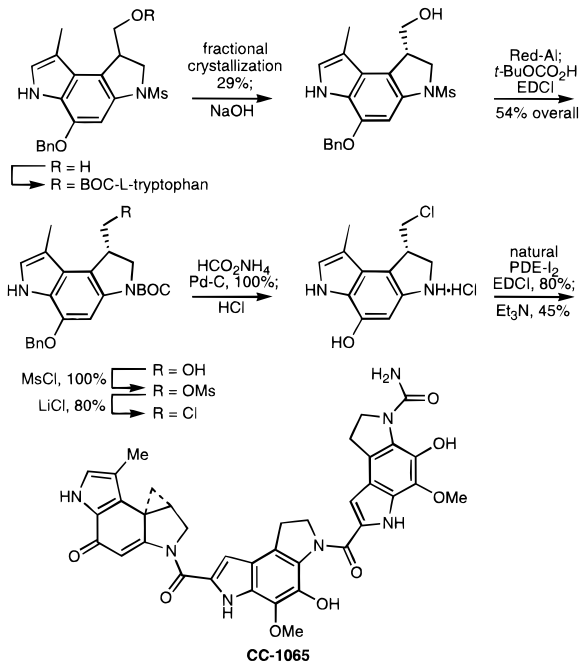


the unprotected indoline, while the right-hand segment was prepared by methyl ester hydrolysis (Scheme 31). These two intermediates were coupled using the carbodiimide reagent CMC to produce the dimer in 63%. Selective reduction of the unsubstituted pyrrole followed by introduction of the *N*-carbamoyl group and hydrogenolysis of the benzyl ethers provided PDE-I_2 and together with their synthesis of CPI[72] completed a formal total synthesis of CC-1065.[111]

3. Upjohn Preparation of (+)- and ent-(–)-CC-1065

Kelly and co-workers reported[112] the reconstitution of (+)-CC-1065 and its unnatural enantiomer from synthetic precursors to the CPI subunit and PDE-I_2 derived from natural sources using technology developed in their preparation of CC-1065 analogs.[66,113] The primary alcohol precursor to CPI was resolved by fractional crystallization of the corresponding BOC-L-tryptophan ester and subsequent hydrolysis of the chiral auxiliary provided both enantiomers (Scheme 32). The *N*-Ms was exchanged for a BOC protecting group by Red-Al reduction and *N*-acylation. The primary alcohol was first activated by formation of the mesylate. However, attempts to employ this intermediate resulted in difficulties arising from its reactivity. Competitive spirocyclization versus coupling with PDE-I_2 discouraged the use of the corresponding phenol, and upon coupling the benzyl ether with PDE-I_2, deprotection also afforded products that resulted from hydrogenolysis of the spirocyclopropane. Thus, exchanging the primary mesylate for the less reactive chloride and hydrogenolysis of the benzyl ether afforded the coupling precursor. Acid-catalyzed deprotection provided the unstable indoline hydrochloride salt which was

Scheme 32. Kelly Reconstitution of CC-1065

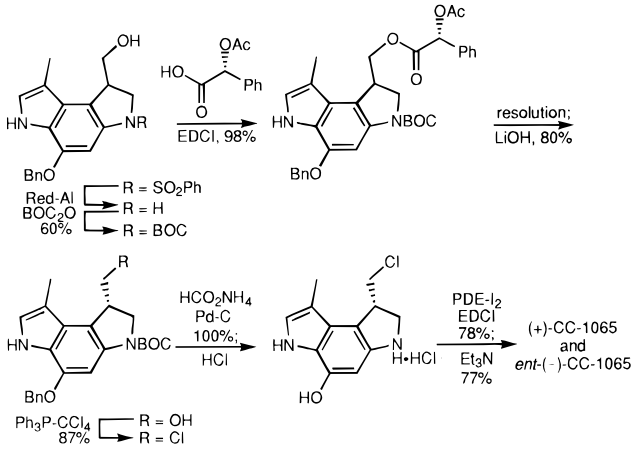


coupled with naturally derived PDE-I_2 in 80%. Using the Kelly protocol ($Et_3N-H_2O-CH_3CN$) to effect spirocyclization, (+)-CC-1065 and *ent*-(−)-CC-1065 were prepared. Concurrent with this effort, the direct coupling of CPI with PDE-I_2 was investigated and found to be unsuccessful. The important and unusual observation was made that the unnatural enantiomer of CC-1065 constituted a cytotoxic agent equipotent with the natural enantiomer and subsequent studies established its comparable DNA alkylation efficiency but distinguishable sequence selectivity. Interestingly, the unnatural enantiomer of CC-1065 was found to lack the characteristic, delayed fatal toxicity of the natural product.

4. Boger–Coleman Total Synthesis of (+)- and ent-(–)-CC-1065

The first total synthesis of (+)-CC-1065 was achieved shortly thereafter.[78,114] Red-Al removal of the *N*-benzenesulfonyl group of our CPI precursor and BOC protection of the resulting free indoline afforded the key CPI resolution intermediate (Scheme 33). Chromatographic separation of the (*R*)-(−)-*O*-acetylmandelate followed by hydrolysis of the optically active ester provided the individual enantiomers of the CPI precursor.[115] Although this protocol was initially developed for the synthesis of CC-1065, it has proven general and widely adopted for the resolution of other alkylation subunits and their analogs (sections III−IV). The differential potencies often observed between the natural and unnatural enantiomers require that the quality of such resolutions or the enantioimeric excess achieved by asymmetric synthesis be carefully assessed. In general, >99.0−99.9% ee is required in order to accurately define the potency and properties of the less potent enantiomer. The more potent, contaminant enantiomer will dominate the observed properties of the less potent enantiomer if this is not achieved. After conversion to the primary chloride, hydrogenolysis of the benzyl ether, and removal of the BOC group

Scheme 33. Boger−Coleman Total Synthesis of CC-1065



following the Kelly protocol[112] afforded the unstable indoline hydrochloride salt which was coupled directly with synthetic PDE-I_2 in the presence of EDCI. Final spirocyclization was affected by treatment with 1:1:1 $Et_3N-H_2O-CH_3CN$ providing both enantiomers of CC-1065. In conjunction with these efforts, both enantiomers of CPI-PDE-I, which lacks the right-hand subunit of the natural product, were prepared and evaluated.[59] The natural enantiomer, (+)-CPI-PDE-I, proved to be equipotent with (+)-CC-1065 illustrating that the entire right-hand subunit of the natural product was not required for its activity.

III. Duocarmycins

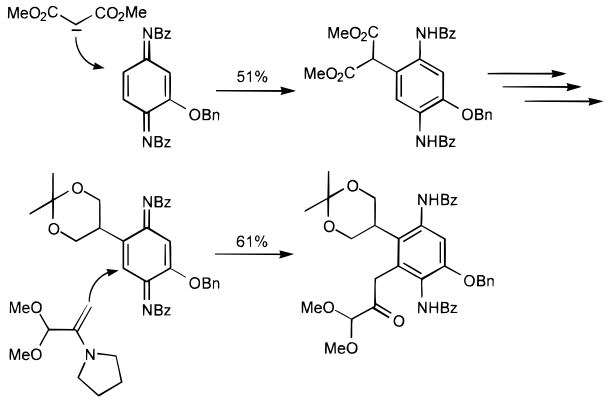
A. Duocarmycin SA

1. Boger Total Synthesis of (+)- and ent-(−)-Duocarmycin SA

The first disclosed total synthesis of duocarmycin SA (Figure 2) relied on sequential regiospecific nucleophilic substitution reactions of appropriately substituted *p*-quinone diimines[79,80] (Scheme 34) followed by acid-catalyzed cyclization to produce the functionalized indole skeleton.[28,116−119] Following intramolecular alkylation of a prochiral diol upon Mitsunobu activation for closure of the A-ring, Winstein Ar-3′ cyclization[64] provided the natural product. Thus, treatment of N^1,N^4-dibenzoyl-2-(benzyloxy)-*p*-benzoquinone diimine[80] with dimethyl malonate in the presence of catalytic NaOMe provided regiospecific C5 nucleophilic substitution. Following reduction of the diester under remarkably mild conditions ($NaBH_4$, EtOH) and acetonide protection of the resulting diol, oxidation with $Pb(OAc)_4$ afforded the second *p*-quinone diimine substrate. Nucleophilic addition of the pyrrolidine enamine of pyruvaldehyde dimethyl acetal[120] followed by mild acid hydrolysis cleanly provided the C6 adduct.

Cyclization to the indole was accomplished by treatment with $HCl-CH_3OH$ and completion of the dihydropyrrolo[3,2-*e*]indole skeleton was accomplished by intramolecular alkylation of the diol upon Mitsunobu activation (Scheme 35). Both *N*-benzoyl groups were removed and the more reactive C3 amine was acylated with BOC_2O. Acid-catalyzed

Scheme 34. Sequential Nucleophilic Additions to *p*-Quinone Diimines



deprotection of the dimethyl acetal was accomplished under conditions that did not lead to competitive BOC deprotection. Subsequent oxidation of the resulting aldehyde directly to the methyl ester and removal of the benzyl ether afforded the intermediate alcohol which was resolved by conversion to the bis-(*R*)-*O*-acetylmandelate ester (Scheme 36). Independent methanolysis of the separated diastereomers provided enantiomerically pure intermediates. Conversion of the primary alcohol to the chloride and acid-catalyzed deprotection followed by coupling of the unstable indoline hydrochloride with 5,6,7-trimethoxyindole-2-carboxylic acid[17,121] provided the enantiomerically pure penultimate intermediates. Final Winstein spirocyclization completed the synthesis of (+)-and *ent*-(−)-duocarmycin SA. Overall the synthesis required 14 steps and proceeded in 6% overall yield from the readily available *p*-quinone diimine.

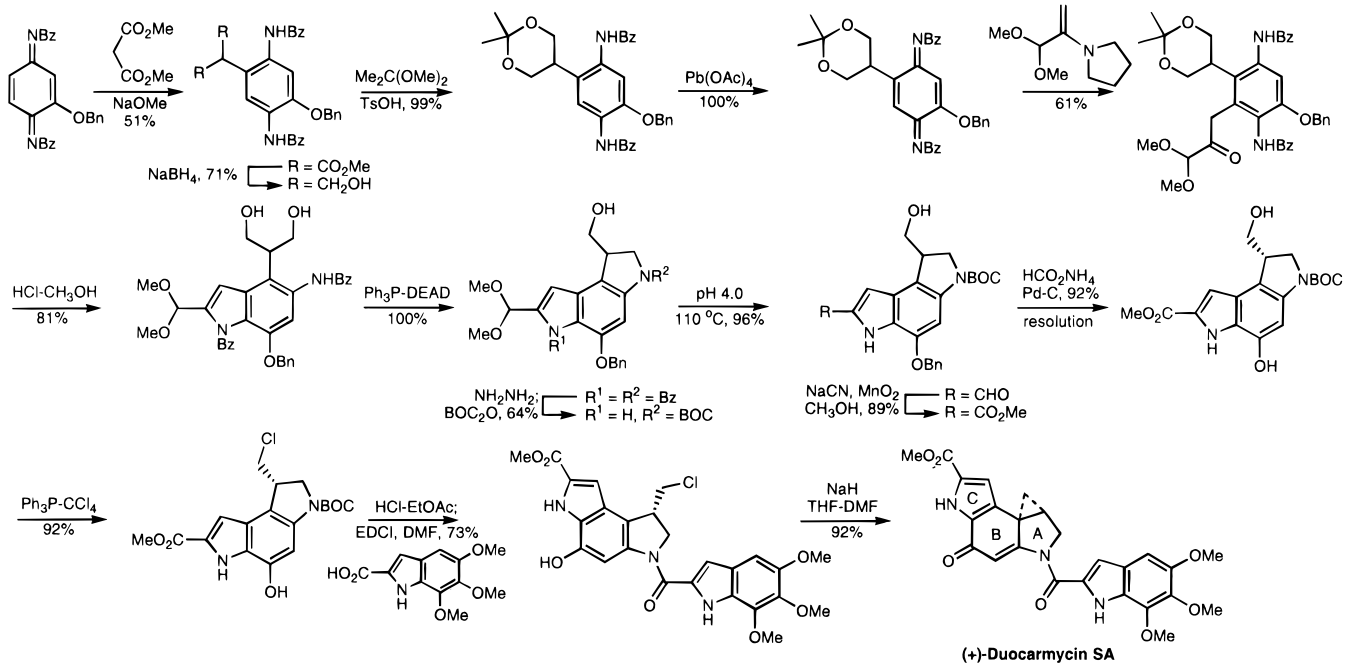
More recently, it was found that racemic *N*-BOC-DSA, derived from spirocyclization of the primary chloride, could be directly resolved on a Chiralcel OD HPLC column ($\alpha = 1.19$). Use of this direct resolution and subsequent HCl deprotection with concomitant ring opening provided an alternative synthesis of the optically active natural product (Scheme 36). Like *ent*-(−)-CC-1065, the unnatural enantiomer of duocarmycin SA was found to be a potent cytotoxic agent and effective DNA alkylating agent.[43]

2. Natsume Total Synthesis of Duocarmycin SA

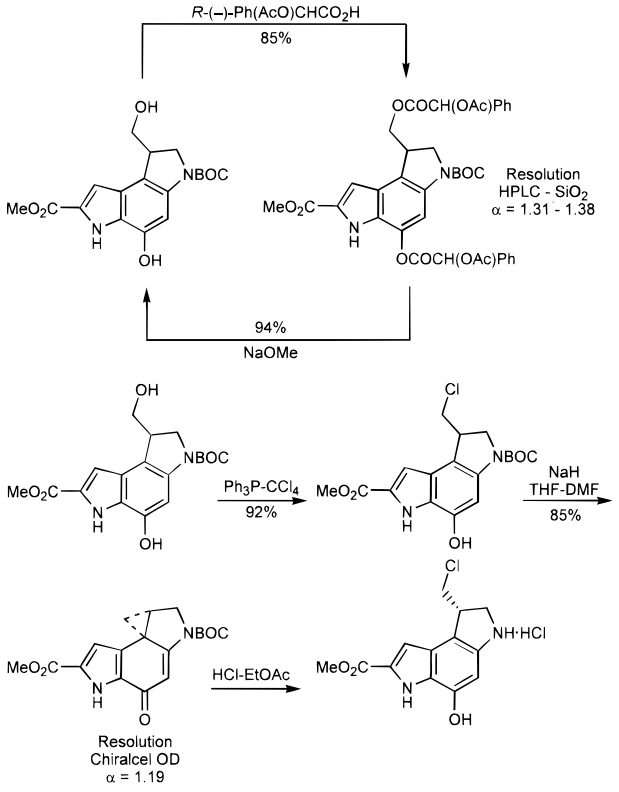
This concise synthesis[122,123] began with the C-ring pyrrole intact, linked a 6-membered A-ring precursor, and completed the skeleton of the alkylation subunit by formation of the central ring employing a Pd(II)-catalyzed intramolecular Heck reaction.[124] A transannular Ar-3′ alkylation[9,17] was employed for introduction of the activated cyclopropane, and the intact alkylation subunit complete with cyclopropane installed was coupled with an active ester derivative of 5,6,7-trimethoxyindole-2-carboxylic acid.

C5 Acetylation of methyl 4-bromopyrrole-2-carboxylate and conversion to its silyl enol ether preceded condensation with the singlet oxygen adduct of 1-(benzyloxy)carbonyl-1,2-dihydropyridine conducted in the presence of $SnCl_2$[125] (Scheme 37). Palladium(II)-catalyzed cyclization provided the key tricyclic structure. Following direct conversion to the dimethyl ketal, the central ring was aromatized by

Scheme 35. Boger Total Synthesis of (+)- and *ent*-(−)-Duocarmycin SA

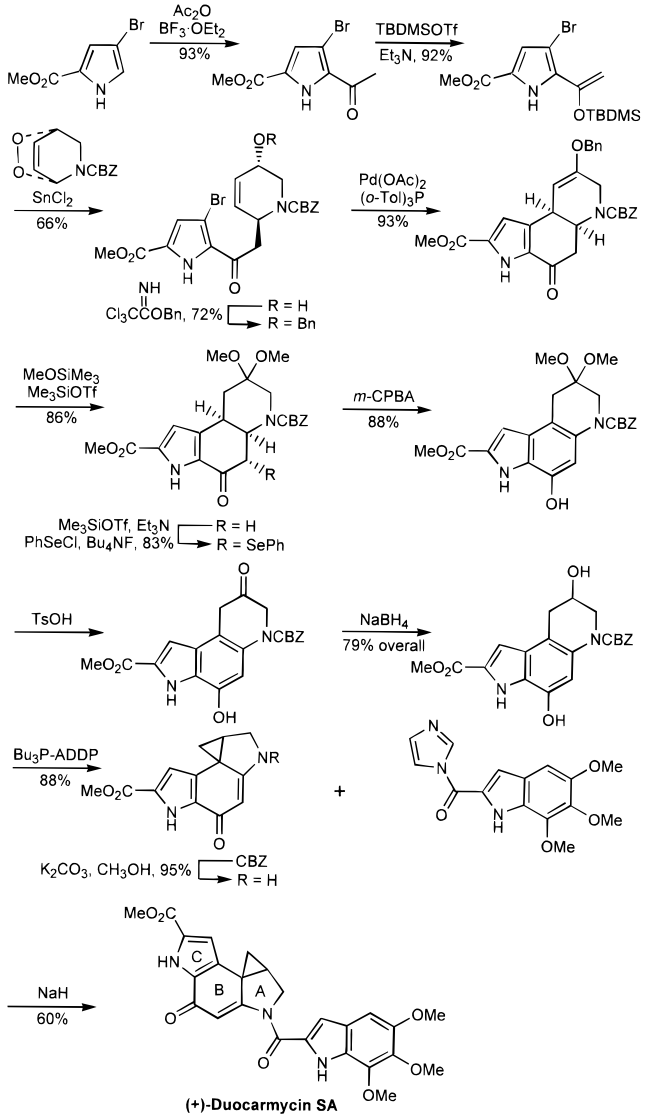


Scheme 36. Resolution of Key Intermediates

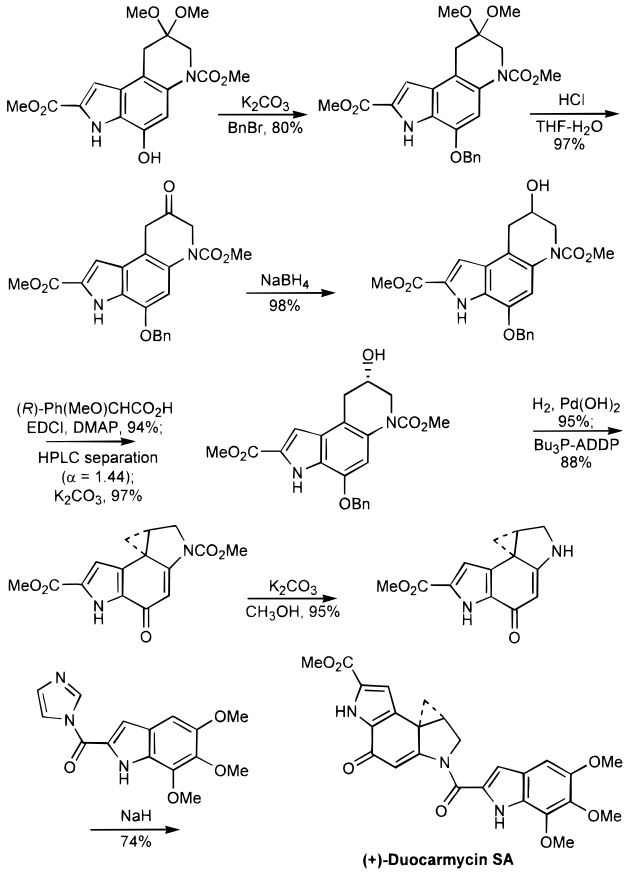


formation of the α-phenylselenyl ketone and subsequent *m*-CPBA oxidation with *in situ* elimination of the selenoxide. After deprotection of the dimethyl ketal and reduction of the ketone to give the secondary alcohol, the cyclopropane was installed by direct transannular Ar-3′ cyclization upon Mitsunobu activation, yielding the intact alkylation subunit. Base-catalyzed cleavage of the CBZ group followed by deprotonation (NaH) and coupling with the acyl imidazole of 5,6,7-trimethoxyindole-2-carboxylic acid provided racemic duocarmycin SA. The overall yield for this 13-step synthesis was 9%.

Scheme 37. Natsume Total Synthesis of (±)-Duocarmycin SA



Scheme 38. Natsume Total Synthesis of (+)- and *ent*-(−)-Duocarmycin SA

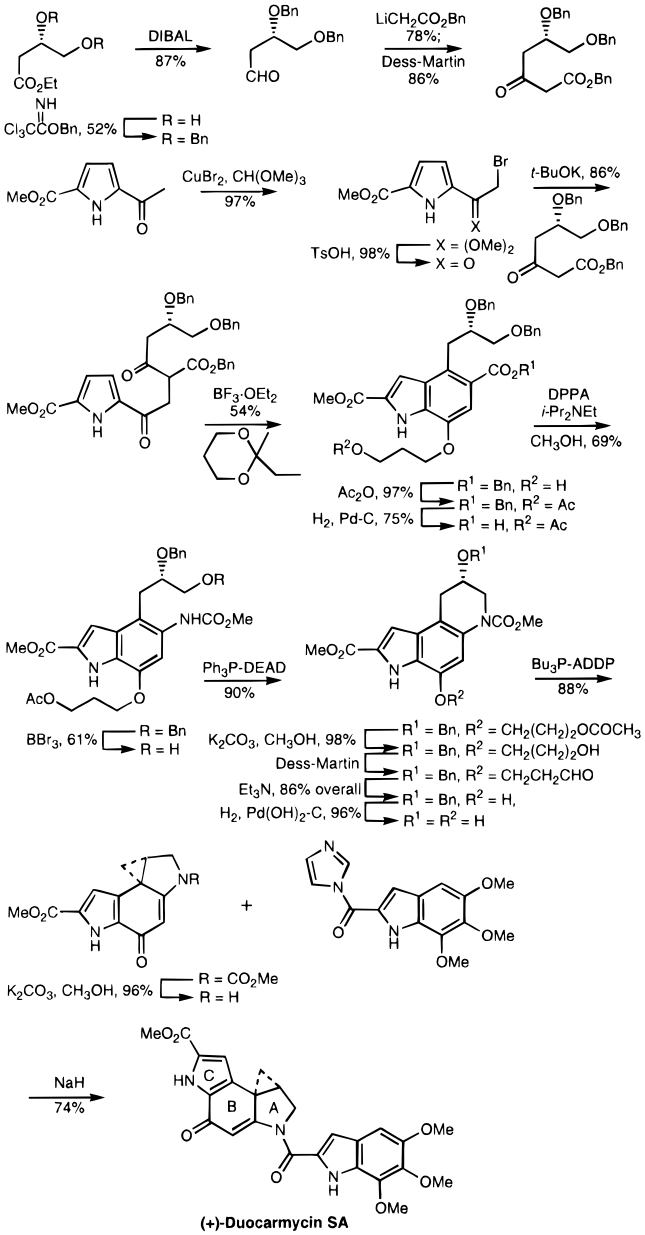


After disclosure of the racemic synthesis, Natsume and co-workers described a modification which permitted resolution of a key intermediate and allowed the synthesis of (+)- and *ent*-(−)-duocarmycin SA[122] (Scheme 38). In order to conduct the resolution it was necessary to protect the free phenol as a benzyl ether. Since this was to be removed by hydrogenation, an alternative to *N*-CBZ was used as the protecting group for the C3 amine. The initial stages of the synthesis were identical to that detailed in Scheme 37 except for the use of the singlet oxygen adduct of 1-(methoxycarbonyl)-1,2-dihydropyridine which was adopted to introduce the methyl carbamate rather than CBZ protecting group. The modified synthesis diverges slightly after the *m*-CPBA oxidization and aromatization when the benzyl protecting group is installed (Scheme 38). The ketone was then deprotected and reduced as before and the chiral auxiliary was coupled to the resultant secondary alcohol. (*R*)-*O*-Methylmandelate was found to provide the greatest diastereomer separability (α = 1.44). After cleavage of the mandelate ester and debenzylation, transannular spirocyclization proceeded as before. The methyl carbamate was removed by methanolysis and the natural product and its unnatural enantiomer were obtained by coupling to 5,6,7-trimethoxyindole-2-carboxylic acid as previously described.

3. Natsume Total Synthesis of (+)-Duocarmycin SA

One year after completion of their racemic synthesis, Natsume and co-workers disclosed a synthesis of optically active (+)-duocarmycin SA in which

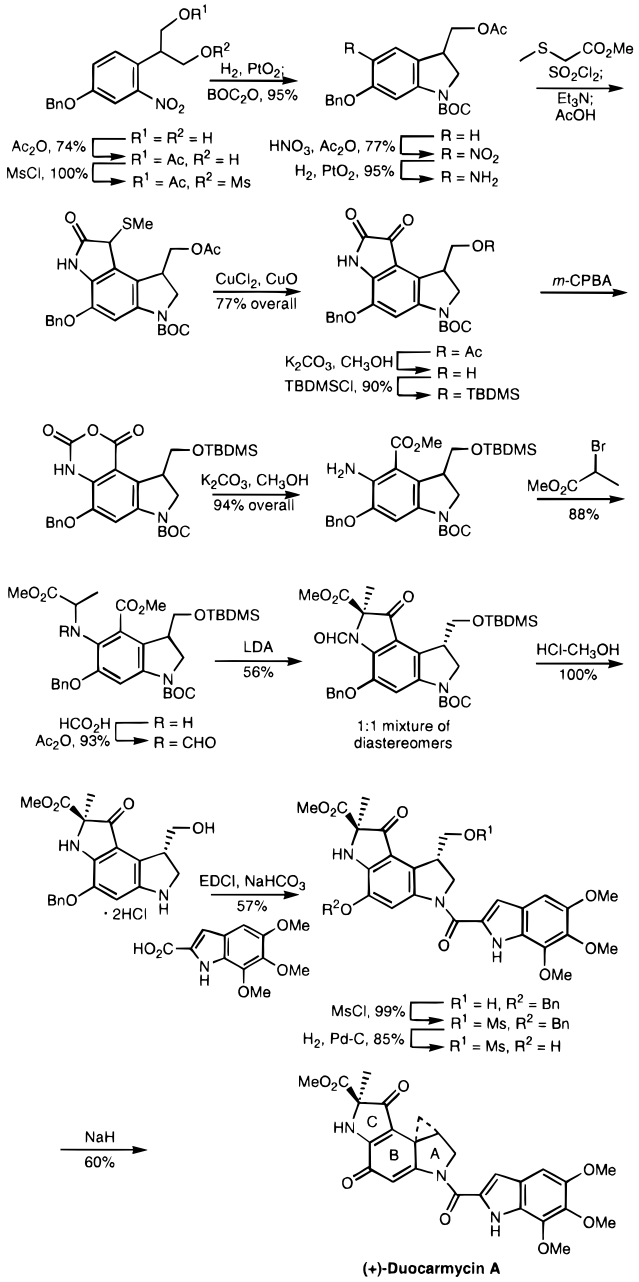
Scheme 39. Natsume Total Synthesis of (+)-Duocarmycin SA



L-malic acid served as the chiral starting material[126] (Scheme 39). The synthesis began with the C-ring pyrrole intact and sequentially constructed the B and A rings of a tetrahydropyrrolo[3,2-*f*]quinoline precursor. Analogous to their prior efforts, a transannular spirocyclization was utilized to introduce the cyclopropane.

After α-bromination of methyl 2-acetylpyrrole-5-carboxylate, alkylation by the β-keto ester derived from L-malic acid provided the key cyclization precursor. Cyclization with formation of the indole was accomplished under Lewis acid-catalyzed conditions in the presence of 2-ethyl-2-methyl-1,3-dioxane. During the cyclization reaction, a 3-hydroxypropyl group was incorporated onto the phenol and conveniently served as an interim protecting group. A Curtius rearrangement installed the C5 amine and an intramolecular Mitsunobu alkylation served to close the third A-ring. Following three-step removal of the phenol protecting group and debenzylation, transannular spirocyclization, and coupling with the acyl

Scheme 40. Terashima Total Synthesis of (±)-Duocarmycin A



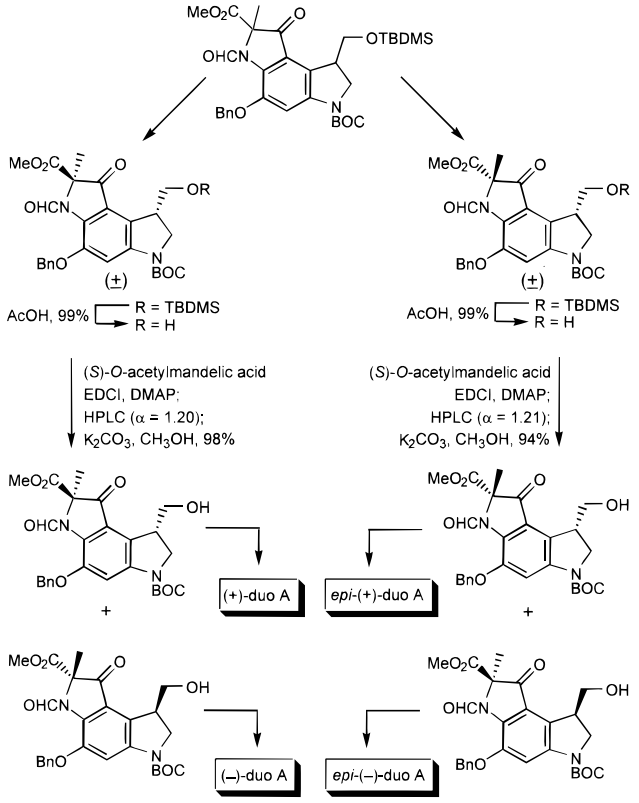
imidazole of 5,6,7-trimethoxyindole-2-carboxylic acid as implemented in their racemic synthesis (Scheme 37) provided (+)-duocarmycin SA. This synthesis was completed in 18 steps with an overall yield of 2%.

B. Duocarmycin A

1. Terashima Total Synthesis of Duocarmycin A

In this first disclosed synthesis of duocarmycin A (Figure 2), Terashima's strategy sequentially constructed the C-ring and A-ring on a preexisting central aromatic precursor and completed the functionalizations necessary for the conventional Winstein Ar-3′ alkylation before coupling to 5,6,7-trimethoxyindole-2-carboxylic acid.[127,128] The C-ring introduction as well as the Gassman oxindole synthesis[65] adopted from Wierenga's CPI synthesis[63,66] was used to access a C4 functionalized 5-aminoindo-

Scheme 41. Resolution Leading to (+)-Duocarmycin A, *epi*-(+)-Duocarmycin A, and Their Unnatural Enantiomers

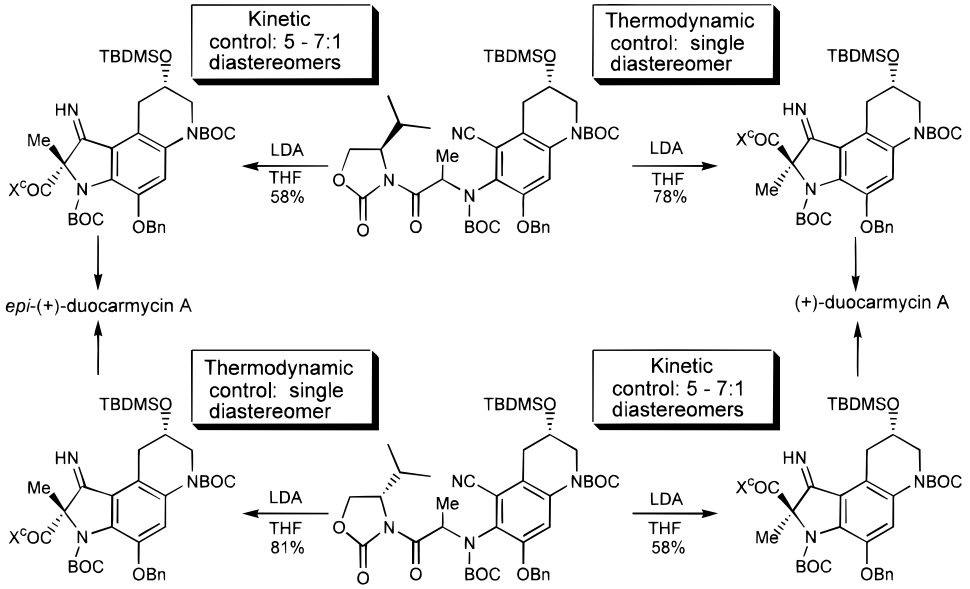


line, and a Dieckmann condensation was used to install the substituted A-ring in a nondiastereoselective manner (Scheme 40).

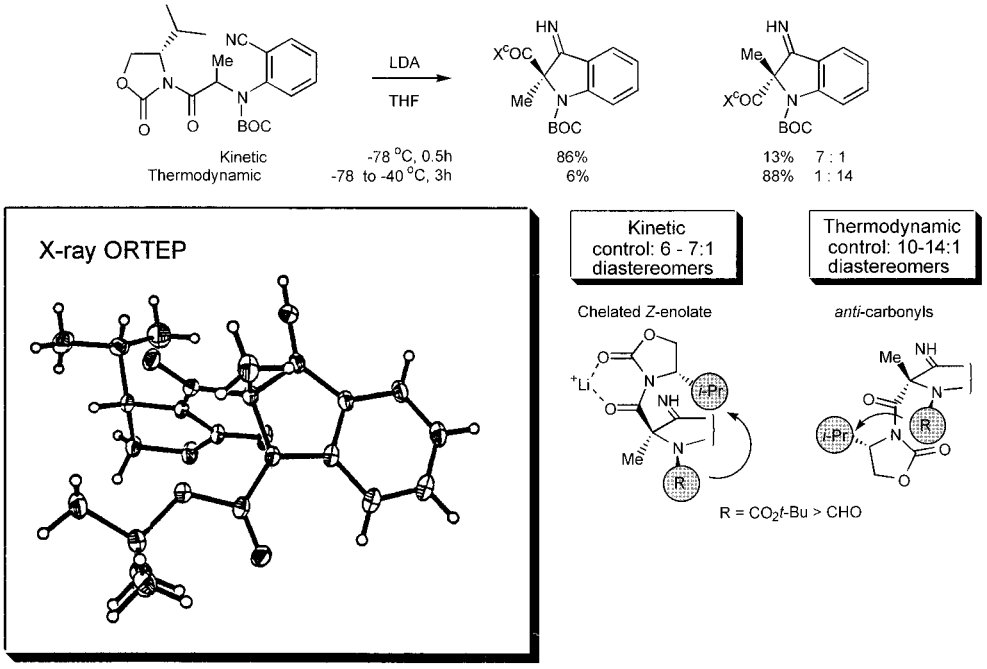
The synthesis began with selective monoacetylation and subsequent mesylation of the symmetrical diol first described by Wierenga (Scheme 2). Reduction of the nitro group and *in situ* indoline formation followed by immediate BOC protection completed the introduction of the C-ring. Analogous to the Wierenga synthesis of CPI, nitration and reduction provided the 5-aminoindoline derivative that was subjected to Gassman's oxindole synthesis to install a one-carbon unit at the hindered C4 position. At this stage the synthesis diverged from the Wierenga route with oxidation to the isatin derivative accomplished by treatment with $CuCl_2-CuO$. Following replacement of the acetate protecting group with a TBDMS ether, Baeyer−Villiger oxidation and methanolysis of the resulting anhydride provided the key precursor required for introduction of the A-ring. Alkylation of the primary amine with methyl 2-bromopropionate followed by *N*-formylation produced the substrate for the key Dieckmann cyclization and treatment with LDA yielded a separable 1:1 mixture of diastereomers. The BOC and TBDMS groups were removed and 5,6,7-trimethoxyindole-2-carboxylic acid was coupled to the less hindered and more reactive C3 amine hydrochloride. Final Winstein spirocyclization was carried out by mesylation of the primary alcohol, hydrogenation of the benzyl ether, and treatment with sodium hydride. This 21-step synthesis proceeded in an overall yield of 5%.

Subsequently, Terashima reported the synthesis of (+)-duocarmycin A, *epi*-(+)-duocarmycin A and their

Scheme 42. Divergent Control of C6-Stereochemistry



Scheme 43. Origin of the Stereochemistry of the Dieckmann-like Cyclization



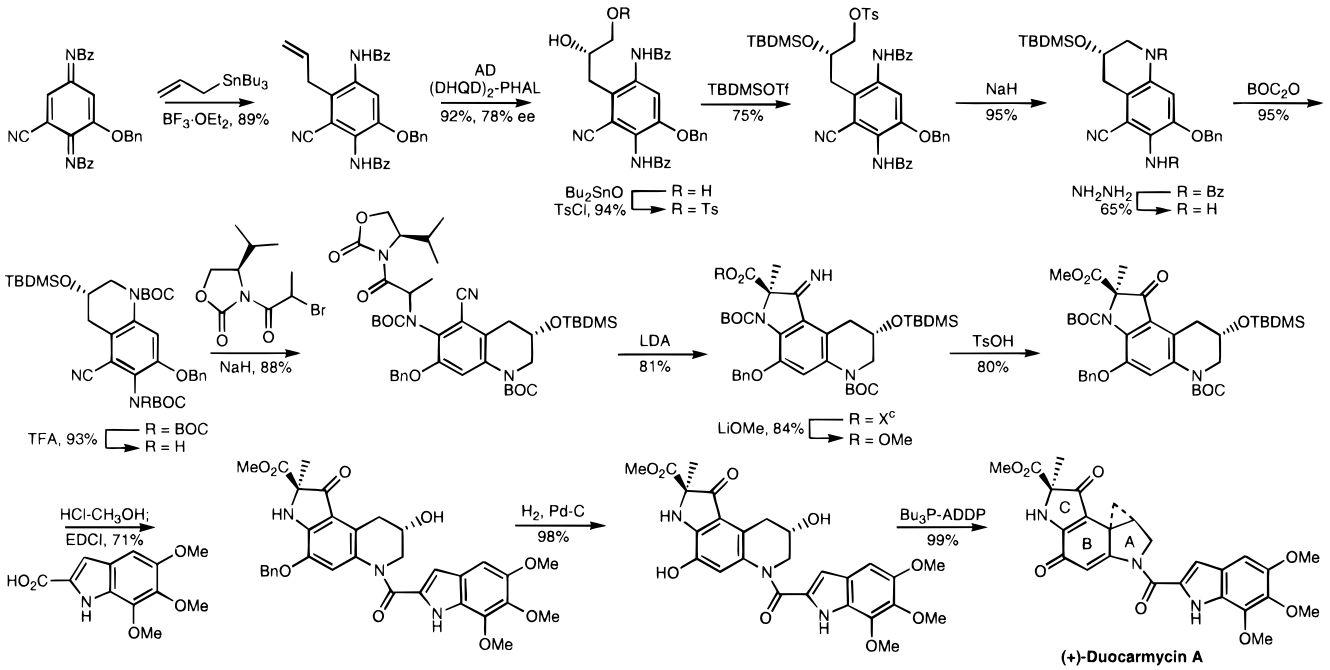
unnatural enantiomers by resolution of racemic intermediates following the key Dieckmann cyclization (Scheme 41).[128,129]

2. Boger Enantiospecific Total Synthesis of (+)-Duocarmycin A, epi-(+)-Duocarmycin A, and Their Unnatural Enantiomers

Duocarmycin A constitutes the most reactive and synthetically challenging member of this class of agents and approaches to the control of relative and absolute stereochemistry of its remote stereocenters had not been previously addressed.[130,131] Central to the strategy was the ability to prepare both enantiomers of the cyclopropane stereochemistry while maintaining the opportunity to independently control the C6 absolute stereochemistry thereby providing access to the natural and unnatural enantiomers of both duocarmycin A and *epi*-duocarmycin A (Scheme 42). Key elements of the approach included a diastereoselective Dieckmann-like condensation for introduction of the C6 quaternary center and a transannular Ar-3′ spirocyclization[17] of duocarmycin D_1 for introduction of the reactive cyclopropane for which the absolute stereochemistry was set through use of the Sharpless asymmetric dihydroxylation reaction.[132] Employing Evans' optically active *N*-acyl oxazolidinones,[133] the Dieckmann-like reaction permitted the introduction of either the 6*R* or 6*S* stereochemistry through use of enantiomeric auxiliaries or, more interestingly, by conducting the reaction of a given auxiliary under thermodynamic versus kinetic reaction conditions for this reversible reaction.[134]

Thus, simply changing the reaction conditions allowed for either kinetic or thermodynamic control of the Dieckmann-like condensation with excellent

Scheme 44. Boger Enantioselective Total Synthesis of (+)-Duocarmycin A



diastereoselection in both cases. The kinetic product is the result of the reaction of the chelated (*Z*)-enolate while the thermodynamic product is the result of equilibration of a reversible ring closure providing the most stable of the two possible diastereomers (Scheme 43).[131,134]

Lewis acid-catalyzed addition of allyltributyltin to a *p*-quinone diimine[80] provided the first key intermediate (Scheme 44). Sharpless asymmetric dihydroxylation of this olefin was found to proceed with an enantioselectivity opposite that predicted from established models. Thus, the $(DHQD)_2$-PHAL catalyzed dihydroxylation reaction[135] provided the *S*-enantiomer (78% ee) required of the natural enantiomers while $(DHQ)_2$-PHAL provided the *R*-enantiomer (77% ee) from which the unnatural enantiomers were prepared. Selective tosylation of the primary alcohol, TBDMS protection of the secondary alcohol and base-catalyzed alkylation with closure of the 6-membered ring provided the second key intermediate. This intermediate was further directly resolved on a Chiralcel OD semipreparative HPLC column (α = 2.30, 150−250 mg/injection) to provide optically pure material (>99.9% ee).

The *N*-benzoyl protecting groups were replaced with *N*-BOC protecting groups, and the exocyclic amine was alkylated with an Evans' optically active 2-(bromopropionyl)oxazolidinone, setting up the key Dieckmann-like condensation. Treatment with LDA under thermodynamic reaction conditions (−78 to −50 °C, 0.5 h) cleanly provided the desired 2*R*,8*S* diastereomer in 78% yield with ≥10:1 diastereoselection. The introduction of the 2*S* stereochemistry required for *epi*-duocarmycin A could be achieved in similar yield and diastereoselectivity using the enantiomer of the Evans' oxazolidinone. Alternatively, the same condensation reactions could be run under kinetic reaction conditions (LDA, −78 °C, 10 min) providing the reversed diastereoselection to that observed under thermodynamic control, but with lower diastereoselectivities (4−5:1).

Methanolysis of the acyloxazolidinone, hydrolysis of the imine followed by acid-catalyzed removal of both the BOC and the TBDMS protecting groups, and coupling with 5,6,7-trimethoxyindole-2-carboxylic acid provided the penultimate precursor. The natural product was then attained by debenzylation and direct transannular spirocyclization[17] upon Mitsunobu activation of the free alcohol. Overall, this first asymmetric synthesis of (+)-duocarmycin A was also utilized to prepare 6-*epi*-(+)-duocarmycin A, as well as the unnatural enantiomers, and was accomplished in 8% yield in 15 steps.

IV. Key Partial Structures and Analogs of the Alkylation Subunits

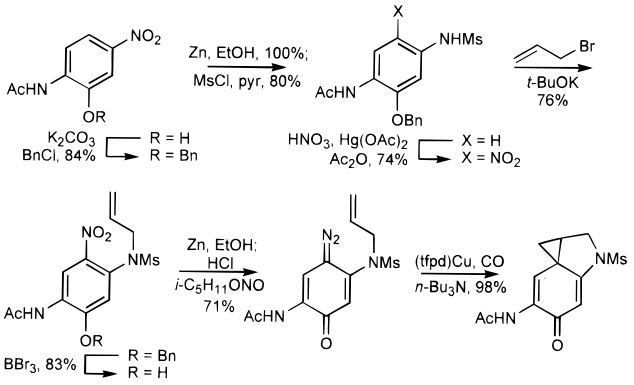
A. 1,2,7,7a-Tetrahydrocyclopropa[*c*]indol-4-one (CI)

1. Sundberg Synthesis

Sundberg disclosed the first report of an agent incorporating the CI structure in the development of a synthetic approach to CPI.[75b−d] *N*-Ms-5-acetamido-CI was obtained by intramolecular metal-catalyzed carbene insertion into a tethered olefin employing a key *p*-quinone monodiazide precursor (Scheme 45).

Thus, 2-acetamido-5-(*N*-allyl-*N*-mesylamino)-4-diazocyclohexadienone was prepared from 2-amino-5-nitrophenol in nine steps with an overall yield of approximately 20%. The intramolecular carbene insertion of the diazocyclohexadienone into the tethered olefin was examined under several conditions including photolysis and thermolysis catalyzed by a variety of Rh, Cu, and Mo complexes (*cf.* Schemes 9 and 10).[75c] In initial studies, dirhodium tetrapivalate provided the highest yield of the desired CI compound (73%) with little quinone byproduct (10%), while photolysis provided 56% of the undesired quinone and only 26% of *N*-Ms-5-acetamido-CI. Upon continued examination, this model system for CPI underwent (tfpd)Cu(I)-catalyzed addition in a re-

Scheme 45. Sundberg Synthesis of CI



markable 98%.[75d] Enantioselective addition catalyzed by optically active Cu(I) catalysts has not yet proven successful.

2. Boger Synthesis

In early studies, the CI-based agents were shown to bear the common and minimum potent pharmacophore of the duocarmycin/CC-1065 alkylation subunits (Figure 4).[17,44,60,136] Our synthesis of the CI subunit featured a self-terminating aryl radical−alkene cyclization for the preparation of a 3-(hydroxymethyl)indoline precursor and the Winstein Ar-3′ alkylation[64] for introduction of the exceptionally reactive cyclopropane.

Thus, regioselective, acid-catalyzed bromination of commercially available 3-(benzyloxy)aniline was followed by BOC protection of the aryl amine (Scheme 46). *N*-Alkylation with 1-bromo-4-(phenylthio)-2-butene followed by implementation of the self-terminating 5-*exo*-*trig* aryl radical−alkene cyclization afforded the 3-vinylindoline in superb yield (91%). Following oxidative cleavage of the olefin and $NaBH_4$ reduction of the resulting aldehyde, the 3-(hydroxymethyl)indoline intermediate was resolved into its enantiomers via the (*R*)-*O*-acetylmandelate ester.[137] Primary alcohol activation, catalytic hydrogenolysis, and base-promoted Ar-3′ alkylation provided (+)- and (−)-*N*-BOC-CI in 11 steps with an overall yield of 11%. *N*-BOC-CI and the related compound, *N*-$PhSO_2$-CI, were found to be exceptionally reactive and particular care was required for their isolation and final purification.

CI was incorporated into a full set of analogs of the natural products (Scheme 47).[17,44,137] Thus, acid-catalyzed deprotection of *seco*-*N*-BOC-CI followed by immediate coupling with the appropriate carboxylic acid in the presence of EDCI provided the key penultimate intermediates. Subsequent treatment with NaH led to spirocyclization with introduction of the reactive cyclopropane. Given the challenge of isolating and characterizing the reactive agents, an

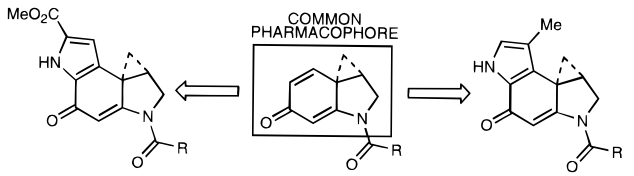
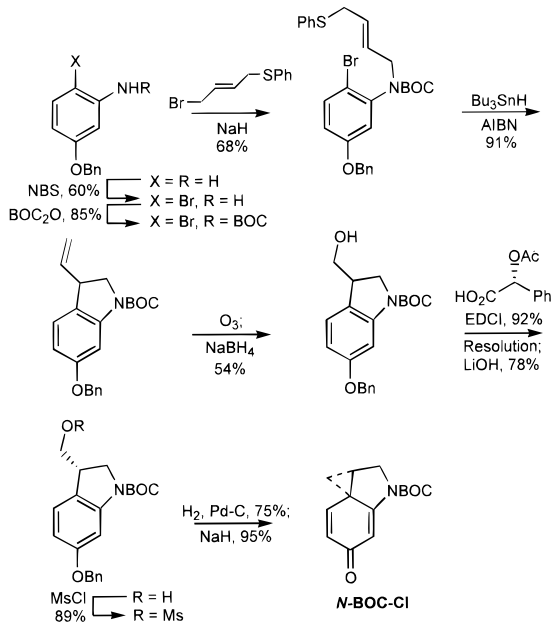
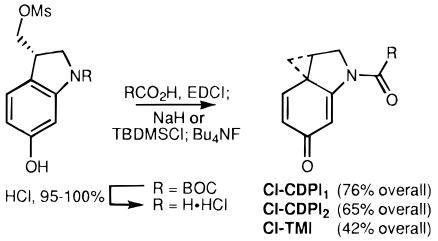


Figure 4. Common pharmacophore of CC-1065 and the duocarmycins.

Scheme 46. Boger Synthesis of CI



Scheme 47. Synthesis of CI Analogs



alternative protocol illustrated with CI-TMI was also devised, utilizing the Bu_4NF-catalyzed deprotection of the phenol TBDMS ether with *in situ* spirocyclization which could be conducted dependably under mild, anhydrous reaction conditions.[17,44]

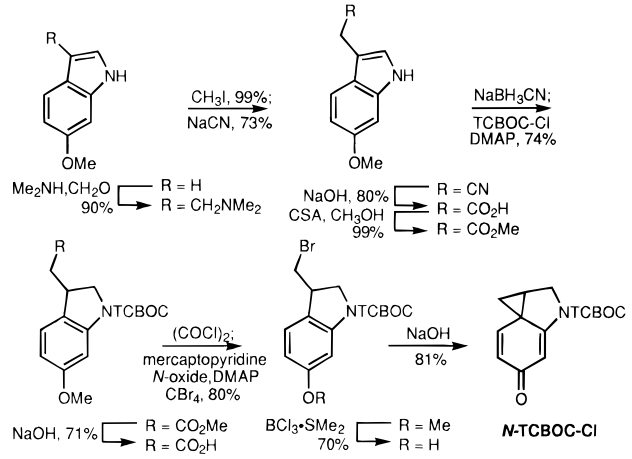
3. Cava Synthesis

A synthesis of racemic CI disclosed by Cava began with the substituted bicyclic core of CI intact in the form of an indole and introduced the additional functionalized carbon necessary for the cyclopropane ring through a Mannich reaction.[138] Thus, reaction of 6-methoxyindole with aqueous dimethylamine and formaldehyde followed by sequential treatment with CH_3I, NaCN, and NaOH provided 6-methoxyindole-3-acetic acid (Scheme 48). After converting the carboxylic acid to the corresponding methyl ester, the indole was smoothly reduced[69] and protected. Following hydrolysis of the methyl ester, Barton free-radical decarboxylation[139] and *in situ* trap of the resulting primary radical with CBr_4 provided the key precursor to CI. Following phenol deprotection, the ring closure was conducted with sodium hydroxide to provide racemic *N*-TCBOC-CI in 12 steps with an overall yield of 12%.

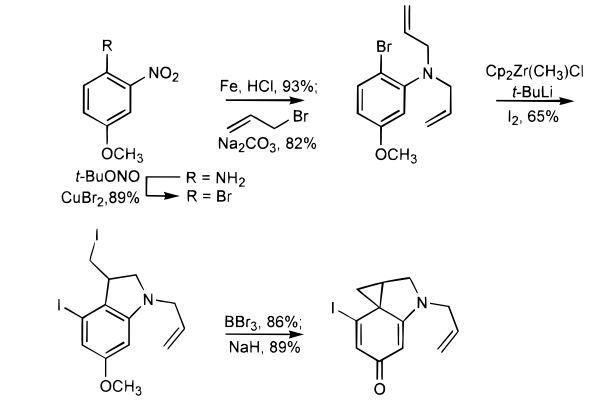
4. Buchwald–Tietze Synthesis

Having pioneered methodology for the synthesis of 3,4-disubstituted indoline and indole derivatives via zirconocene−benzyne complexes (Schemes 16 and 17), Buchwald and co-workers extended the efforts

Scheme 48. Cava Synthesis of CI



Scheme 49. Buchwald Synthesis of *N*-Allyl-6-iodo-CI



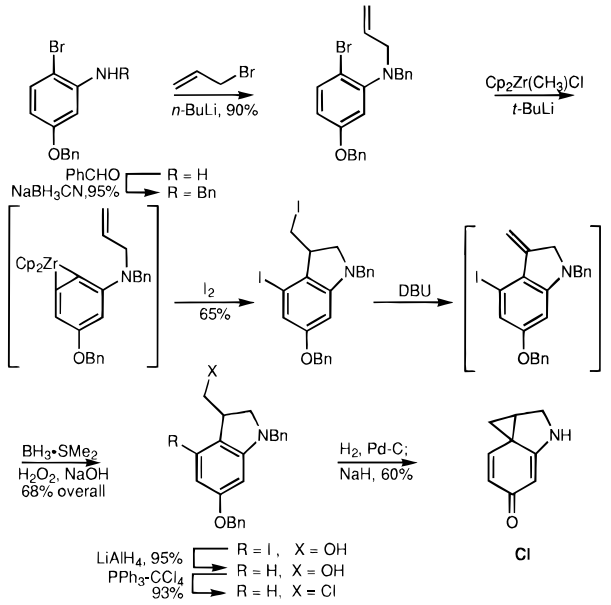
to the synthesis of *N*-allyl-6-iodo-CI (Scheme 49).[86] The intermediate benzyne complex, formed upon sequential treatment of a *N*,*N*-diallyl-2-bromoaniline with *t*-BuLi and $Cp_2Zr(CH_3)Cl$, underwent intramolecular insertion into the adjacent olefin to form a zirconacycle which is cleaved by I_2 to give the corresponding diiodoindoline. The synthesis of *N*-allyl-6-iodo-CI was completed following phenol deprotection and spirocyclization in six steps in 33% overall yield.

Tietze and co-workers later reported an analogous synthesis of CI utilizing Buchwald's zirconocene procedure (Scheme 50).[140] Reductive amination of 5-(benzyloxy)-2-bromoaniline and subsequent *N*-allylation was followed by formation of the diiodoindoline. Elimination of HI upon base treatment and hydroboration of the exocyclic olefin afforded the 3-(hydroxymethyl)-4-iodoindoline which was deiodinated upon treatment with $LiAlH_4$. Conversion to the primary chloride, catalytic hydrogenolysis, and final Winstein Ar-3′ alkylation completed the synthesis of CI in eight steps with an overall yield of 20%.

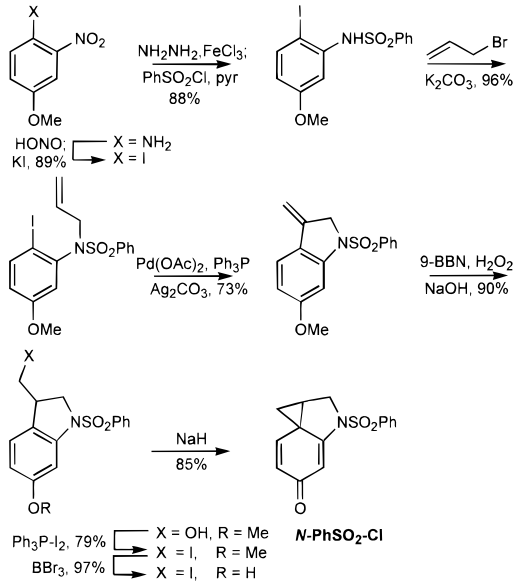
5. Sakamoto Synthesis

Sakamoto and co-workers have developed a synthesis of CI on the basis of a Pd(II)-catalyzed cyclization of a *N*-allyl-2-iodoaniline derivative to form a 3-methyleneindoline.[141] Following synthesis of *N*-(phenylsulfonyl)-*N*-allyl-2-iodo-5-methoxyaniline from commercially available 4-methoxy-2-nitroaniline, a

Scheme 50. Tietze Synthesis of CI



Scheme 51. Sakamoto Synthesis of CI

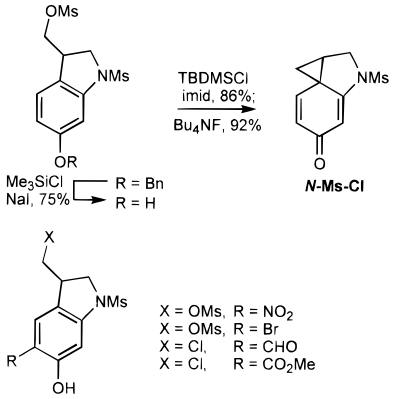


palladium(II)-catalyzed Mori−Hegedus indole cyclization[77,142] in the presence of Ag_2CO_3 was utilized to provide the 3-methyleneindoline (Scheme 51). The employment of bases other than Ag_2CO_3 lead to indole/indoline mixtures derived from double-bond isomerization. Hydroboration−oxidation of the alkene analogous to efforts in our CPI synthesis[78] (Scheme 46) afforded a 3-(hydroxymethyl)indoline which was transformed to the final product. Overall, *N*-$PhSO_2$-CI was prepared in 10 steps in a yield of 32%.

6. Lown Synthesis

In an effort to further examine the properties of agents in the CC-1065 and duocarmycin family, Lown and co-workers prepared a series of substituted CI analogs adopting the early stages of the Upjohn synthesis of CPI (Scheme 2).[143] Thus, racemic *N*-Ms-CI was prepared from the Wierenga indoline bismesylate intermediate in three steps (Scheme 52). In addition, several *seco*-CI agents bearing electron-

Scheme 52. Lown Synthesis of CI and C5-Substituted Analogs



withdrawing groups at the 5-position were synthesized by electrophilic aromatic substitution. Due to the reactivity of the ring-closed materials, they were evaluated as the precursor *seco* agents.

B. 1,2,9,9a-Tetrahydrocyclopropa[*c*]benzo[*e*]indol-4-one (CBI)

1. Boger Syntheses of CBI

Several investigations of the natural enantiomers of the CBI-based analogs of CC-1065 have shown that they are chemically more stable, biologically more potent, and considerably more synthetically accessible than the corresponding CPI-based agents.[144−153] Importantly, their initial examination in our group revealed that *in vivo* antitumor efficacy may be observed in agents containing deep-seated and simplifying structural changes and that the potency of the naturally derived materials may be enhanced by simply improving the inherent chemical stability. Moreover, the inherent regioselectivity for nucleophilic addition to the least substituted cyclopropane carbon of CBI (≥20:1) substantially exceeds that of the CC-1065 (*ca.* 4:1) and the duocarmycin alkylation subunits (6−1:1) and may be attributed to the near idealized stereoelectronic alignment of the breaking cyclopropane bond with CBI (Figure 5).[147]

In a series of reports, the synthesis of CBI has served as the structural template on which a free radical cyclization could be studied for preparation of a functionalized indoline suitable for use in the installation of the key spirocyclopropane (Scheme 53). In initial efforts, a 3-(hydroxymethyl)indoline precursor was derived from a 5-*exo*-*dig* aryl radical−alkyne cyclization of a *N*-propynyl-1-bromonaphthylamine followed by immediate hydroboration−oxidation of the inherently unstable 3-methyleneindoline (approach A).[148] Although adherence to carefully defined reaction conditions led to satisfactory conversions (50−62%), isomerization to the corresponding indole could not be completely suppressed. Nonetheless, this method proved more successful than an indirect approach based on a self-terminating 5-*exo*-*trig* aryl radical−alkene cyclization in which subsequent oxidative conversion of the 3-vinylindoline to the 3-(hydroxymethyl)indoline precursor proved more problematic (approach B). This may be attributed to a competitive oxidative cleavage[148] of the electron-rich naphthalene with strongly electrophilic reagents like O_3 and is less problematic with substrates bearing

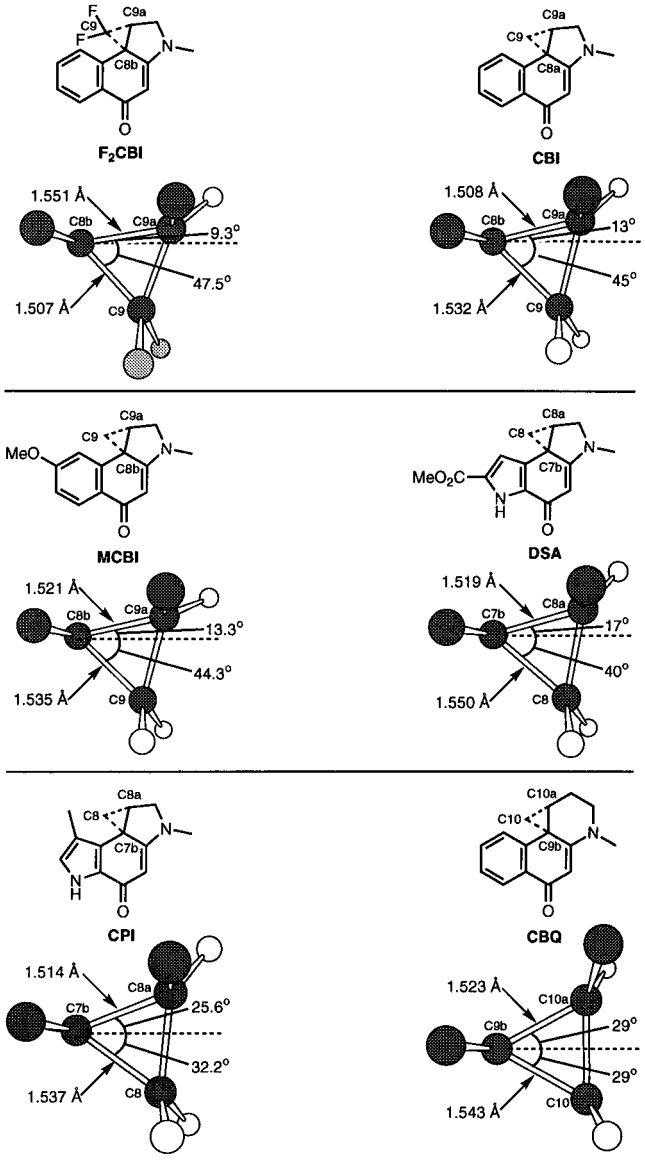
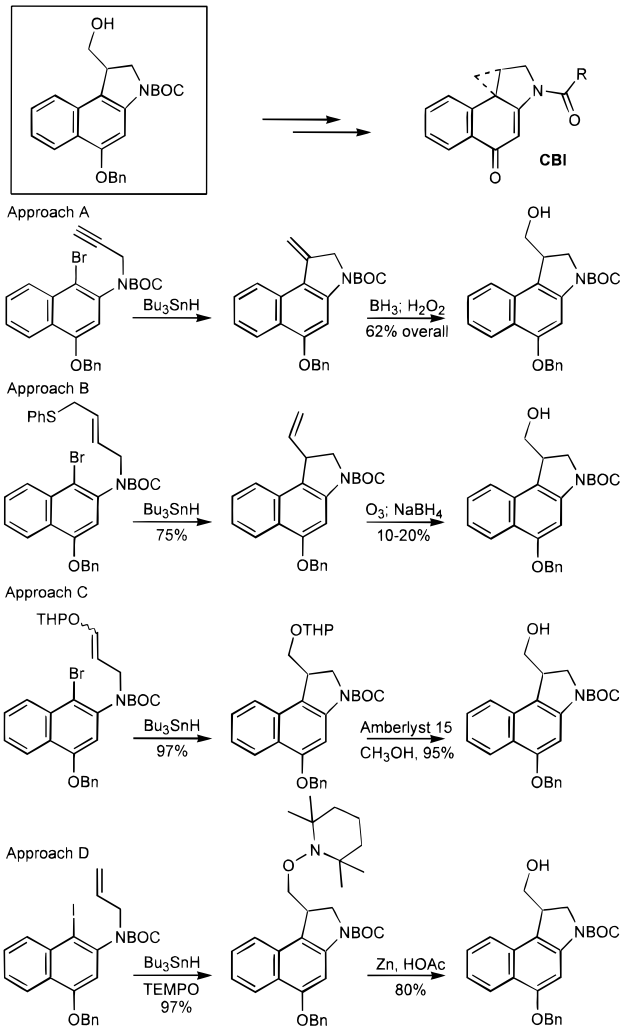


Figure 5. Stick models of the side view of the activated cyclopropanes of F_2CBI, CBI, MCBI, DSA, CPI, and CBQ using data taken from the X-ray crystal structures.

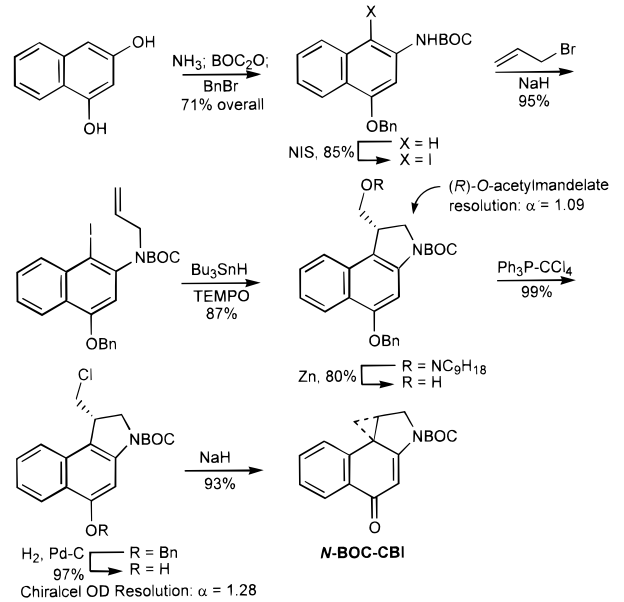
more nucleophilic alkenes[148,154,155] or which lack the naphthalene structure.[137] Subsequent efforts featured a 5-*exo*-*trig* aryl radical−alkene cyclization employing a vinyl ether as the acceptor alkene which solved the problem of postcyclization functionalization and served to reinforce the inherent cyclization regioselectivity (approach C).[150] The limitation of this approach is the precyclization functionalization of the acceptor alkene which required ozonolysis and a subsequent Wittig reaction to provide the vinyl ether. The most efficient preparation of the 3-(hydroxymethyl)indoline CBI precursor disclosed to date in these studies is based on the TEMPO trap of an aryl radical−alkene 5-*exo*-*trig* cyclization of an unfunctionalized alkene that replaces the need for pre- or postcyclization functionalization (approach D).[152]

Thus, selective C4 iodination of *N*-BOC-4-(benzyloxy)naphthylamine, readily accessible in three steps (71%) from commercially available 1,3-dihydroxynaphthalene,[148] followed by *N*-alkylation with allyl bromide provided the required substrate for implementation of the key 5-*exo*-*trig* aryl radical−alkene

Scheme 53. Boger Radical Cyclization Strategies for the Synthesis of CBI

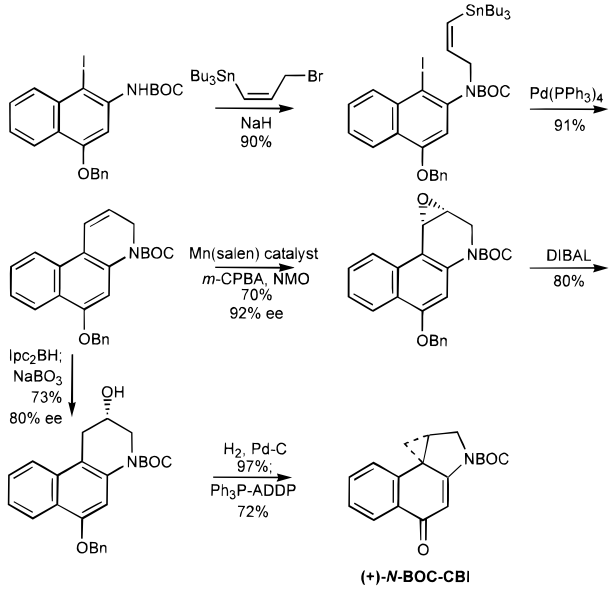


Scheme 54. Boger Synthesis of *N*-BOC-CBI



cyclization (Scheme 54). Treatment with Bu_3SnH–TEMPO and subsequent reduction with Zn afforded the 3-(hydroxymethyl)indoline CBI precursor in excellent yields. Formation and chromatographic resolution of the corresponding (*R*)-*O*-acetylmandelate

Scheme 55. Boger Asymmetric Synthesis of CBI

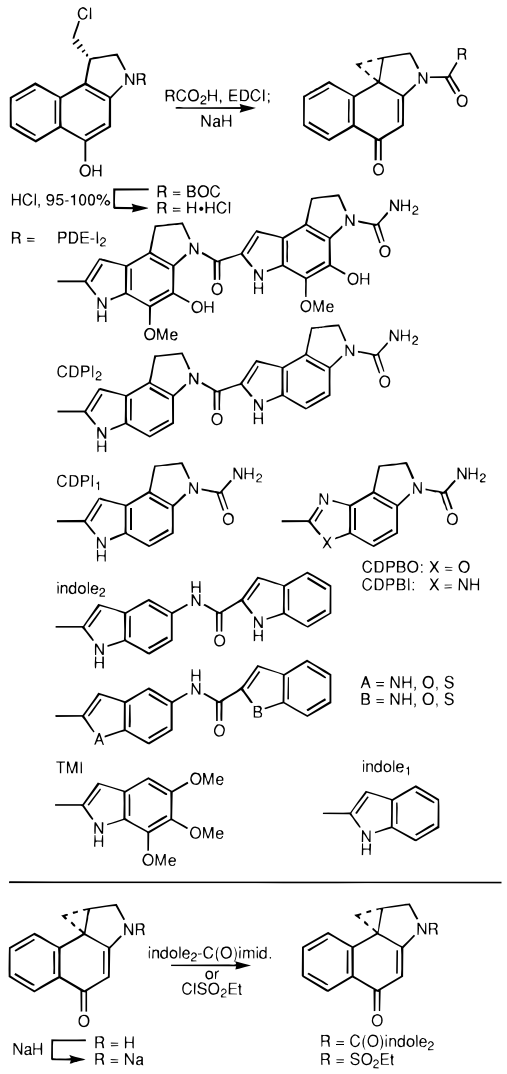


ester followed by hydrolysis provided the optically pure enantiomers (≥99.9% ee).[148] Alternatively, conversion to the primary chloride and catalytic hydrogenolysis of the benzyl ether followed by direct resolution on a semipreparative Daicel Chiralcel OD HPLC column ($\alpha = 1.28$) also afforded both enantiomers.[151] Subsequent Winstein spirocyclization completed the synthesis of (+)- and *ent*-(−)-*N*-BOC-CBI in nine steps in 36% overall yield.

More recently, two related asymmetric syntheses of *N*-BOC-CBI have been developed (Scheme 55).[156] Both rely on the asymmetric oxidation of a 1,2-dihydrobenzo[*f*]quinoline precursor rapidly accessed by an intramolecular Pd(II)-catalyzed cross-coupling reaction. Either asymmetric hydroboration−oxidation employing Ipc_2BH or Jacobsen epoxidation with an optically active Mn(salen) catalyst and DIBAL reduction of the resulting epoxide provided the optically active secondary alcohol which was subjected to direct transannular Ar-3′ spirocyclization upon Mitsunobu activation to provide (+)-*N*-BOC-CBI.

Both the (+)- and *ent*-(−)-enantiomers of an extensive series of CBI-based agents including CBI-$CDPI_1$, CBI-$CDPI_2$, CBI-$indole_2$, and CBI-TMI were prepared first by our group[148,149,151,153] and, more recently, by the Upjohn group[157] because of their promising *in vitro* and *in vivo* antitumor activity. Typically, acid-catalyzed deprotection of the *seco*-*N*-BOC-CBI, immediate coupling with the appropriate carboxylic acid conducted in the presence of EDCI and in the deliberate absence of added base, and spirocyclization upon base treatment provided the final CBI analogs in good overall yield (Scheme 56). A number of conditions have been disclosed for conducting the Ar-3′ alkylation including treatment with NaH, DBU, DBN, P_4-*t*Bu, 5% aqueous $NaHCO_3$–THF, and Et_3N–CH_3CN–H_2O. The ease of spirocyclization and the range of successful conditions that may be employed increase with the increasing inherent stability of the final cyclopropane containing agents. Table 1 summarizes many of the properties of the *N*-BOC derivatives of the alkylation subunits examined to date including their inherent reactivities. In selected

Scheme 56. Synthesis of CBI Analogs



instances, the deprotected CBI bearing the installed cyclopropane could be deprotonated with NaH and coupled with activated acylating agents.[153,157]

2. Cava Synthesis of CBI

Cava's route to CBI utilized a clever photocyclization of a heterostilbene first disclosed in his work on PDE-I and PDE-II[91] (Schemes 21 and 22) to establish the tricyclic CBI core followed by introduction of an additional functionalized carbon necessary for formation of the cyclopropane.[158] Thus, photolysis of the alkene formed from condensation of the α-methoxybenzyl phosphonate with *N*-benzylpyrrole-2-carboxaldehyde in the presence of Pd−C provided the tricyclic CBI core (Scheme 57).[159] Since the utilization of a Mannich reaction at this stage followed by CH_3I−NaCN treatment provided a mixture of regioisomers, a four-step debenzylation sequence followed by a regioselective Mannich alkylation was employed to provide the key CBI intermediate. Analogous to their efforts with CI (Scheme 48),[138] a similar reaction sequence provided racemic *N*-TCBOC-CBI in 18 steps with an overall yield of 15%.

3. Aristoff Synthesis of CBI

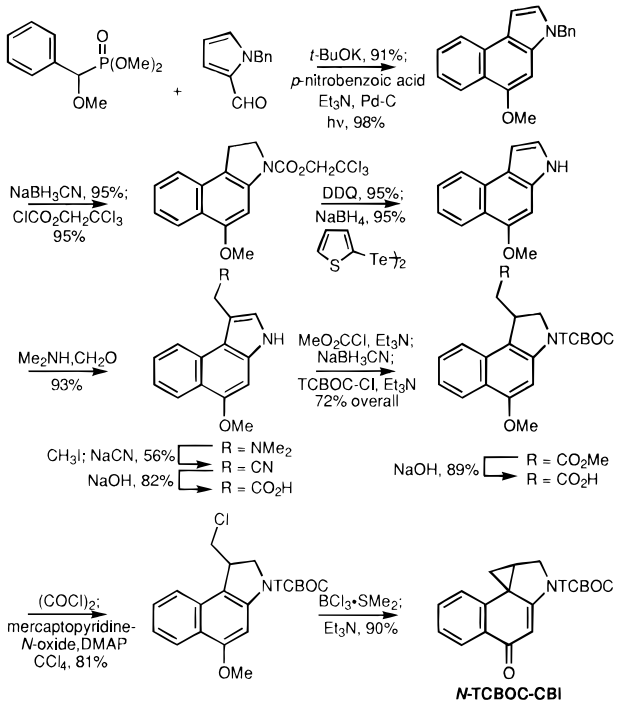
An alternative approach to the CBI subunit was recently described by Aristoff[157] which constructed a tricyclic tetrahydrobenzo[*f*]quinoline and subsequently implemented a transannular Ar-3′ alkylation for introduction of the activated cyclopropane reminiscent of that detailed in the duocarmycin structure correlations.[17] Although the possibility of an asymmetric synthesis based on the Sharpless asymmetric dihydroxylation reaction[132,135] was examined, resolution of the (*R*)-*O*-acetylmandelate ester analogous to that originally detailed in our efforts[137,148] was utilized to prepare the optically pure enantiomers. 1-Allyl-2-(benzylamino)-1-hydroxydihydronaphtha-

Table 1

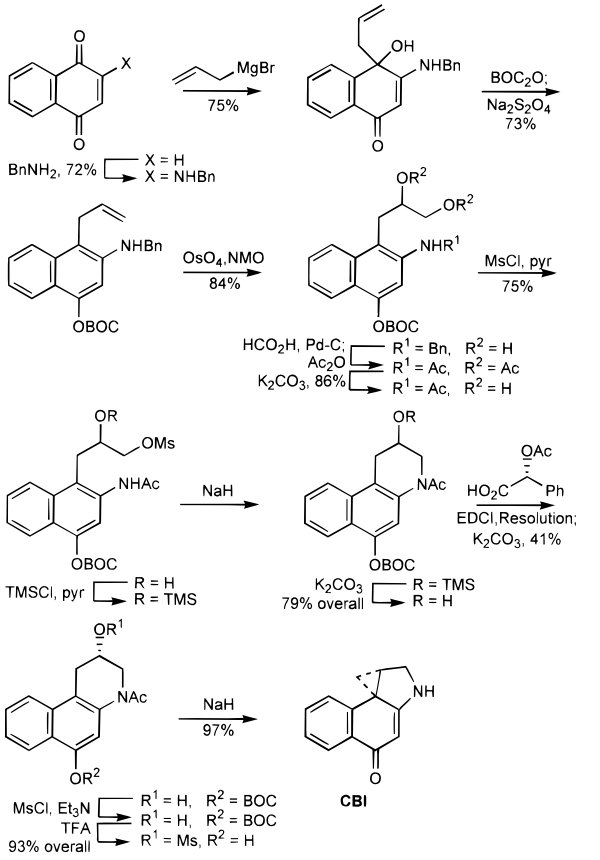
agent	k, s^{-1} (pH 3)[a]	$t_{1/2}$, h (pH 3)[a]	IC_{50}, μM (L1210)	UV, nm (λ_{max}, ϵ)	IR (C=O), cm^{-1}
N-BOC-DSA	1.08×10^{-6}	177	0.006	339 (18 000)[b] 301 (14 000) 255 (10 000)	1719, 1610[c]
N-BOC-CCBI	0.99×10^{-6}	213	0.02	300 (12 000)[d] 267 (24 000) 259 (22 200)	1727, 1634 1608[e]
N-BOC-CBI	1.45×10^{-6}	133	0.08	300 (19 000)[d] 264 (5700)	1718, 1628 1602[e]
N-BOC-MCBI	1.75×10^{-6}	110	0.09	301 (25 000)[d] 270 (20 000)	1724, 1622 1599[e]
N-BOC-CPI	5.26×10^{-6}	37	0.3	344 (12 000)[b] 278 (17 000)	1725, 1570[f]
N-BOC-*iso*-CBI	6.97×10^{-6}	27	nd	387 (3 000)[b] 302 (6 000) 293 (6 000) 250 (20 000)	1716, 1670 1635[e]
N-BOC-DA	1.75×10^{-5}	11	2	nd	1725, 1677, 1560[e]
N-BOC-CBQ	9.07×10^{-5}	2.1	2	314 (19 000)[b] 260 (9 000) 218 (17 000)	1705, 1639 1604[c]
N-BOC-F_2CBI	7.05×10^{-4}	0.26	110[g]	nd	1727, 1634[e]
N-BOC-CNA	6.78×10^{-3}	0.03	nd	nd	1698, 1647
N-BOC-CI	1.98×10^{-2}	0.01	18	294 (14 000)[d] 258 (21 000)	1705, 1617[c]

[a] pH = 3: 50% CH_3OH−buffer, buffer is 4:1:20 (v:v:v) 0.1 M citric acid, 0.2 M Na_2HPO_4, and H_2O, respectively. [b] CH_3OH. [c] KBr. [d] THF. [e] Film. [f] Nujol. [g] Racemate.

Scheme 57. Cava Synthesis of CBI



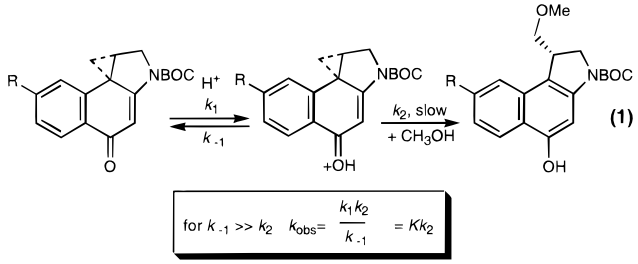
Scheme 58. Aristoff Synthesis of CBI



lenone was prepared in two steps from 1,4-naphthoquinone in 54% (Scheme 58). Reduction and rearomatization was accomplished by treatment with BOC_2O followed by sodium dithionite. The racemic diol was prepared by OsO_4-catalyzed dihydroxylation. Although several variations of the Sharpless asymmetric dihydroxylation were investigated, low chemical yields or low levels of enantioselectivity as well as oxidation of the amine precluded its useful application. Deprotection of the benzylamine, *N*- and *O*-acetylation, acetate hydrolysis, followed by selective mesylation of the primary alcohol and TMS ether protection of the secondary alcohol preceded 6-membered ring closure upon treatment with NaH. Alcohol deprotection and resolution by chromatographic separation of the diastereomeric (*R*)-*O*-acetylmandelate esters provided the optically active materials. Primary alcohol activation, BOC deprotection, and transannular cyclization upon treatment with NaH provided CBI with hydrolysis of the intermediate *N*-Ac-CBI by adventitious water present in the reaction mixture. CBI was prepared in 17 steps with an overall yield of 15% by this approach.

4. Boger Synthesis of 7-Cyano- and 7-Methoxy-1,2,9,9a-tetrahydrocyclopropa[c]benzo[e]indol-4-one (CCBI and MCBI)

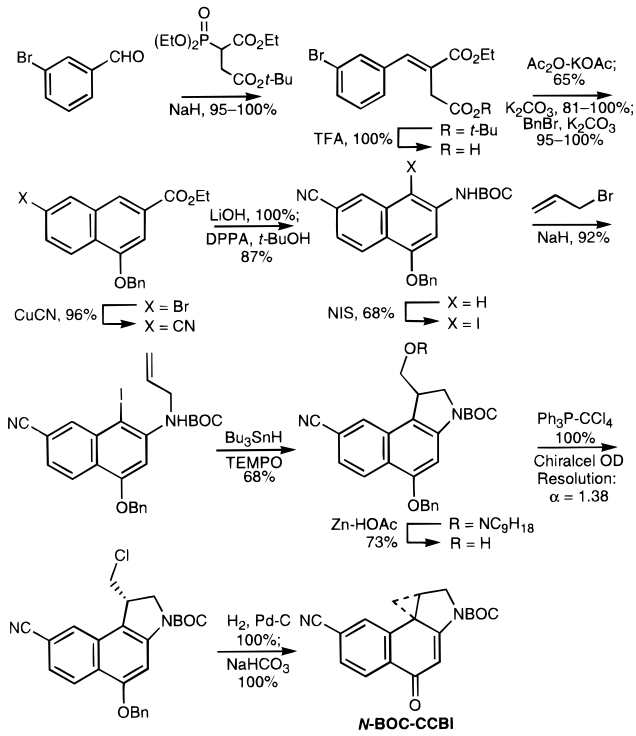
In an extension of our efforts, the substituted CBI derivatives bearing either a C7 methoxy[154] or cyano[155] group para to the C4 carbonyl were prepared in efforts that established the magnitude of electronic effects on the chemical and functional reactivity of the agents. Studies of the solvolysis reactivity of this classical Hammett series revealed that C7 substitution predictably affected the rate of solvolysis but only to a surprisingly small extent ($\rho = -0.3$). Additional kinetic studies of the acid-catalyzed nucleophilic addition reaction established a first-order dependence on both the acid and nucleophile concentration defining the rate-determining step as nucleophilic addition to the cyclopropane following rapid and reversible C4 carbonyl protonation (eq 1).[155] This suggests that the



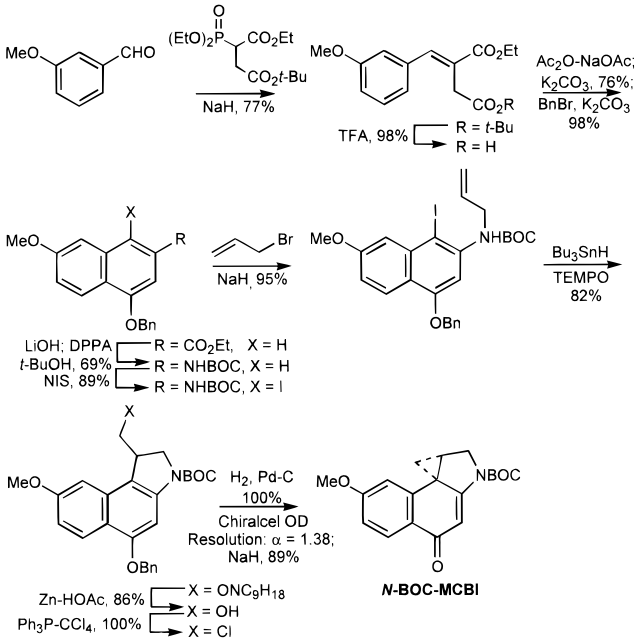
positioning of an accessible nucleophile (adenine N3) and not C4 carbonyl protonation is the rate-determining step controlling the sequence selectivity of the DNA alkylation reaction. More importantly, the examination of this series of agents revealed that the relative rates of DNA alkylation did not follow the relative rates of acid-catalyzed solvolysis.[155] A subsequent demonstration that the rates of DNA alkylation exhibit little pH dependence led to the investigation of alternative sources of catalysis for the DNA alkylation reaction and the discovery that it is derived from a DNA binding-induced conformation change in the agents that reduces the vinylogous amide stabilization of the alkylation subunit.

The MCBI and CCBI alkylation subunits were prepared by a modified Stobbe condensation/Friedel–Crafts acylation[160] for generation of the appropriately functionalized naphthalene precursors followed by 5-*exo*-*trig* aryl radical–alkene cyclization and final Winstein Ar-3′ alkylation (Schemes 59 and 60). Thus, Wadsworth–Horner–Emmons condensation of the appropriate benzaldehyde with the Sargent phos-

Scheme 59. Boger Synthesis of CCBI

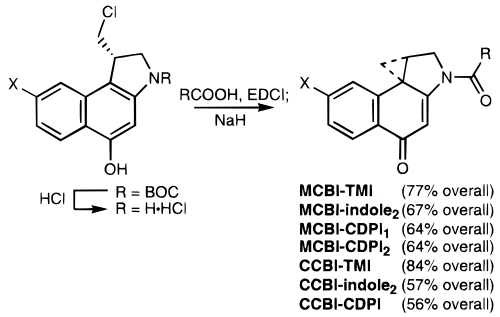


Scheme 60. Boger Synthesis of MCBI

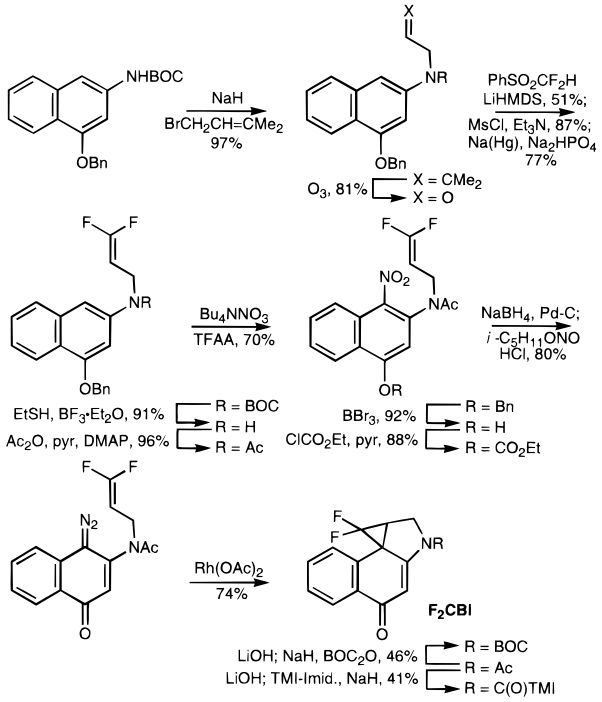


phonate[161] predominately provided the *E*-isomer which then underwent acid-catalyzed deprotection and Friedel−Crafts acylation. Ester hydrolysis and Curtius rearrangement effected by treatment with the Shioiri−Yamada reagent (DPPA)[162] was followed by regioselective C4 bromination and *N*-alkylation with 1-bromo-3-methyl-2-butene. Conversion to the enol ether, aryl radical−alkene cyclization, and further conversions to provide *N*-BOC-MCBI and *N*-BOC-CCBI followed protocols introduced in our CBI synthesis (Schemes 53 and 54). The shortest and most efficient preparation of both *N*-BOC-MCBI (14 steps, 25−30%) and *N*-BOC-CCBI (16 steps, 15−20%) relied on the TEMPO trap of an aryl radical−alkene

Scheme 61. Synthesis of MCBI (X = OMe) and CCBI Analogs (X = CN)



Scheme 62. Boger Synthesis of F_2CBI



cyclization employing an unactivated and unfunctionalized alkene as described in our synthesis of CBI.[152]

Resolution of the penultimate precursors on a Chiralcel OD semipreparative HPLC column and acid-catalyzed deprotection of the *N*-BOC-MCBI and *N*-BOC-CCBI precursors followed by EDCI-promoted coupling with appropriate carboxylic acids and subsequent cyclopropane closure provided an important series of CC-1065/duocarmycin analogs (Scheme 61).

5. Boger Synthesis of 9,9-Difluoro-1,2,9,9a-tetrahydrocyclopropa[c]benzo[e]indol-4-one (F_2CBI)

Our synthesis of F_2CBI, a difluoro-substituted cyclopropane analog of CBI, represents the first agent to incorporate substitution or functionalization at the reactive center.[163] It was found to be 500 times more reactive than CBI, a result of the increased strain introduced by the difluorocyclopropane substitution. The core structure of F_2CBI was prepared through an intramolecular metal-catalyzed carbene insertion reaction into a 1,1-difluoroalkene employing a key *p*-quinondiazide precursor following an approach first disclosed by Sundberg (Scheme 9).[75c] *N*-Alkylation of *N*-BOC-4-(benzyloxy)-2-naphthylamine with 1-bromo-3-methyl-2-butene followed by ozonolysis provided the tethered aldehyde (Scheme 62). The dif-

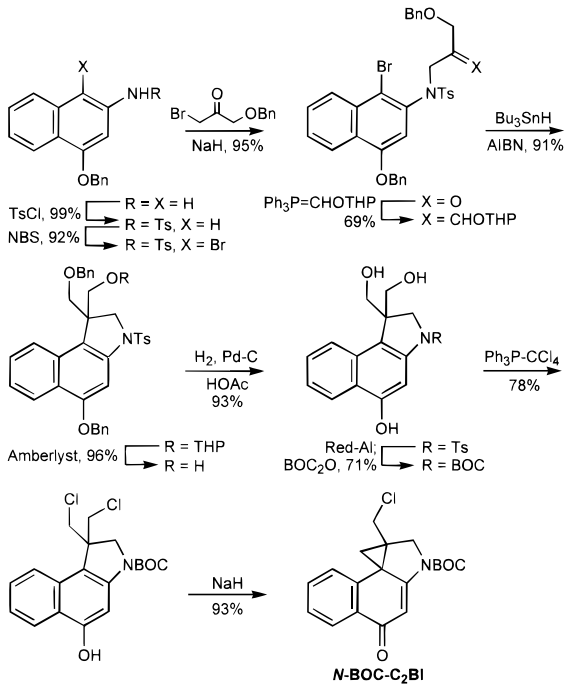
luoroalkene was introduced following a three-step protocol developed by Sabol and McCarthy[164] in which an *in situ*-generated α-lithio difluoromethyl sulfone was added to the aldehyde. Subsequent mesylation of the resulting alcohol followed by reductive elimination provided the key difluoroalkene. Regiospecific C4 nitration with Bu_4NNO_3−TFAA, reduction of the nitro group with $NaBH_4$/Pd−C, and subsequent diazotization with isoamyl nitrite with *in situ* acid-catalyzed deprotection of the phenol led to direct generation of the key *p*-quinone monodiazide. The preparation of *N*-Ac-F_2CBI was completed by treatment with catalytic $Rh_2(OAc)_4$ in refluxing toluene. This approach provided *N*-Ac-F_2CBI in 13 steps in 8% overall yield. The *N*-acetyl group was hydrolyzed and converted to the *N*-BOC and *N*-TMI derivatives with the latter constituting an analog of the duocarmycins. The F_2CBI-TMI analog represents one of the few agents formed by direct coupling of a fully intact alkylation subunit with a DNA binding subunit.[153,157]

6. Boger Synthesis of 9a-(Chloromethyl)-1,2,9,9a-tetrahydrocyclopropa[c]benzo[e]indol-4-one (C_2BI)

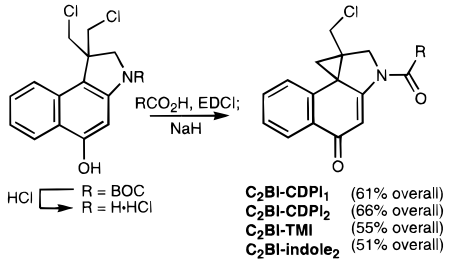
Through the process of preparing analogs of naturally occurring agents possessing deep-seated changes in the alkylation subunit, a great deal of progress has been made in defining the fundamental structural features contributing to polynucleotide recognition and functional reactivity. The C_2BI-based agents represent the exquisite level to which this understanding has been established.[165] Site-specific interstrand adenine−adenine DNA cross-linking by the agents was predicted and ultimately observed based on the emerging models of the natural and unnatural enantiomer alkylations of duplex DNA. The C_2BI agents were additionally anticipated to be important targets since the precursor acyclic *seco* agents not only display properties indistinguishable from the ring closed agents but they are achiral. This greatly simplified the synthetic considerations by avoiding the resolution or asymmetric synthesis required for the preparation of optically active agents and also removed the requirement to carefully document the biological properties of both enantiomers. These features enhanced the interest in the C_2BI-based analogs as potential DNA alkylating and cross-linking agents.

Our approach to the preparation of the C_2BI alkylation subunit was based on the implementation of a 5-*exo*-*trig* aryl radical−alkene cyclization with direct introduction of an appropriately functionalized and protected 3,3-bis(hydroxymethyl)indoline. Thus, reaction of 1-(benzyloxy)-3-naphthylamine with TsCl followed by regioselective acid-catalyzed C4 bromination and *N*-alkylation with 3-(benzyloxy)-1-bromo-2-propanone provided a key intermediate (Scheme 63). Subsequent Wittig reaction provided the enol ether substrate for the free radical cyclization. Treatment with Bu_3SnH effected clean 5-*exo*-*trig* aryl radical−alkene cyclization without competitive 6-*endo*-*trig* closure despite the formation of the carbon−carbon bond at a quaternary center.[166] In part, this may be attributed to the directing effect of the enol ether acceptor alkene. Acid-catalyzed THP deprotection and catalytic hydrogenolysis of the benzyl

Scheme 63. Boger Synthesis of C_2BI



Scheme 64. Boger Synthesis of C_2BI Analogs



ethers afforded the 3,3-bis(hydroxymethyl)indoline. Conversion to the dichloride and spirocyclization upon treatment with NaH provided *N*-BOC-C_2BI. Overall, *N*-BOC-C_2BI was prepared in 10 steps with 25% yield from 1-(benzyloxy)-3-naphthylamine.

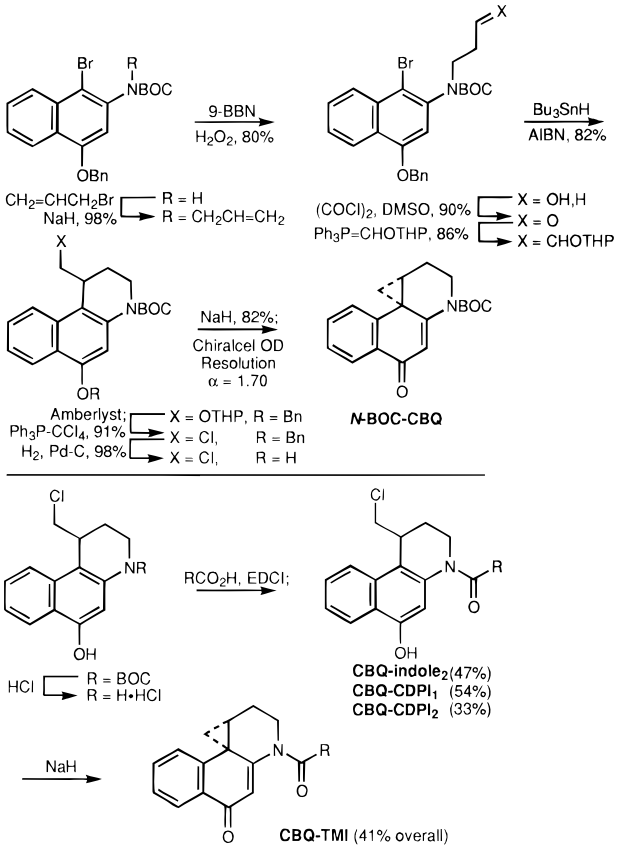
Several important analogs of CC-1065 and the duocarmycins were prepared including C_2BI-$CDPI_1$, C_2BI-$CDPI_2$, C_2BI-TMI, and C_2BI-$indole_2$ (Scheme 64).

C. C-Ring Expansion Analogs of CBI

1. Boger Synthesis of 2,3,10,10a-Tetrahydro-1H-cyclopropa[d]benzo[f]quinol-5-one (CBQ)

Our preparation and study of agents derived from the ring expansion of the fused 5-membered ring found in CBI to the 6-membered ring found in CBQ revealed important insights into the structural origin of the unusual stability and solvolysis regioselectivity of the naturally occurring alkylation subunits.[28,147,167] The increased reactivity and loss of stereoelectronic control for cyclopropane ring opening observed with CBQ could be attributed to an idealized alignment and conjugation of the activated cyclopropane with the cyclohexadienone π-system as observed in the X-ray structure (Figure 5). Thus, the unusual stability and solvolysis regioselectivity of CBI and the naturally occurring alkylation subunits is imposed by fusion of the activated cyclopropane to the 5-membered ring which constrains it to a nonideal align-

Scheme 65. Boger Synthesis of CBQ



ment and overlap with the cyclohexadienone π-system.

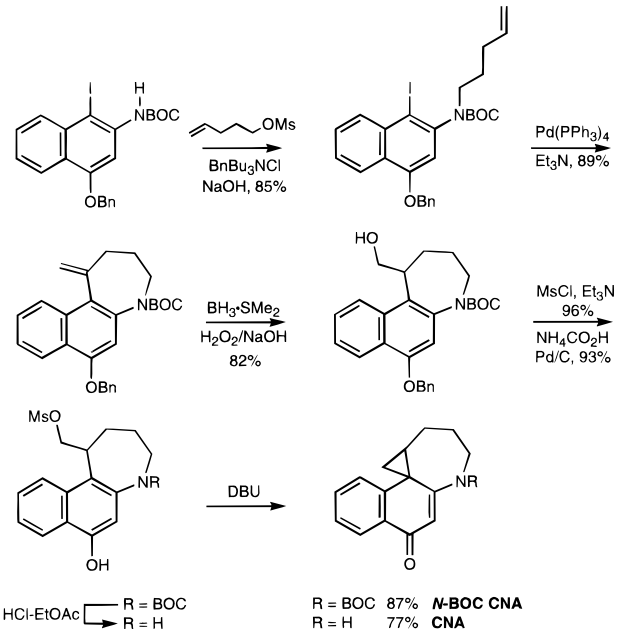
The key to our preparation of the CBQ nucleus rested with the implementation of a 6-*exo*-*trig* versus 7-*endo*-*trig* aryl radical−alkene cyclization for construction of the functionalized 1,2,3,4-tetrahydrobenzo[*f*]quinoline nucleus central to its core structure. Thus alkylation of the sodium salt of *N*-BOC-4-(benzyloxy)-1-bromo-2-naphthylamine, readily prepared in three steps (71%) from 1,3-dihydroxynaphthalene, with allyl bromide was followed by hydroboration−oxidation and Swern oxidation to provide the key aldehyde (Scheme 65). Subsequent Wittig reaction afforded the enol ether in excellent conversions as a 2:3 mixture of *Z*- and *E*-isomers. Exclusive 6-*exo*-*trig* free radical cyclization completed the preparation of the functionalized CBQ skeleton. Alcohol deprotection and activation followed by phenol deprotection and base-promoted cyclopropane ring closure provided *N*-BOC-CBQ. Direct chromatographic resolution on a semipreparative Chiralcel OD HPLC column provided the optically active materials. The synthesis of *N*-BOC-CBQ was accomplished in eight steps with an overall yield of 36%.

The (−)- and *ent*-(+)-enantiomers of CBQ-TMI as well as the racemic precursors to CBQ-indole$_2$, CBQ-CDPI$_1$, and CBQ-CDPI$_2$ were prepared by acid-catalyzed deprotection and immediate EDCI coupling to the appropriate carboxylic acid.

2. Boger Synthesis of 1,2,3,4,11,11a-Hexahydrocyclopropa[c]naphtho[3,4-b]azepin-6-one (CNA)

Recent efforts have resulted in the synthesis of the next member in this series of agents derived from

Scheme 66. Boger Synthesis of CNA



further ring expansion of the C-ring of CBQ. This synthesis of CNA[168] conducted as a logical extension of the efforts on CBI and CBQ provided compelling evidence revealing the source of the catalysis for the sequence selective alkylation of DNA. The origin of the remarkable reactivity of *N*-BOC-CNA ($t_{1/2}$ = 1.7 min, pH 3; 3.2 h, pH 7) was revealed in its X-ray structure[168] and confirmed that it is derived from disruption of the vinylogous amide stabilization of the alkylation subunit by twisting of the nitrogen lone pair out of conjugation with the cyclohexadienone.

The preparation of CNA (Scheme 66) relied on a Pd(0)-catalyzed 7-*exo*-*trig* cyclization of a tethered alkene for clean introduction of the appropriately functionalized fused 7-membered ring. Hydroboration−oxidation of the exocyclic alkene[78] afforded the 1-(hydroxymethyl)naphthazepine which was transformed into the sensitive final products through formation of the primary mesylate, hydrogenolysis of the benzyl ether, and DBU-promoted spirocyclization. Overall, *N*-BOC-CNA was synthesized in six steps from *N*-(*tert*-butyloxycarbonyl)-4-(benzyloxy)-1-iodo-2-naphthylamine in a yield of 33%.

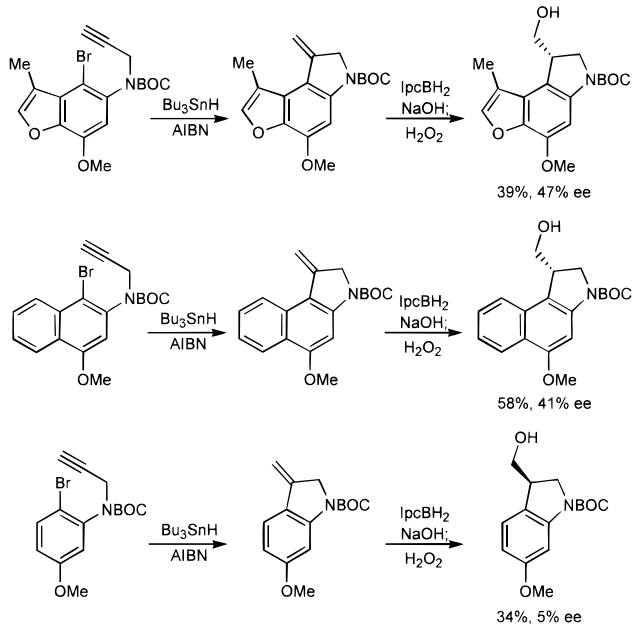
D. Modified Heteroaromatic Core Structures of the Alkylation Subunits

To date, only a limited number of modified heteroaromatic core structures of the CC-1065 or duocarmycin alkylation subunits have been described in which the fused pyrrole is replaced with a different heterocycle.

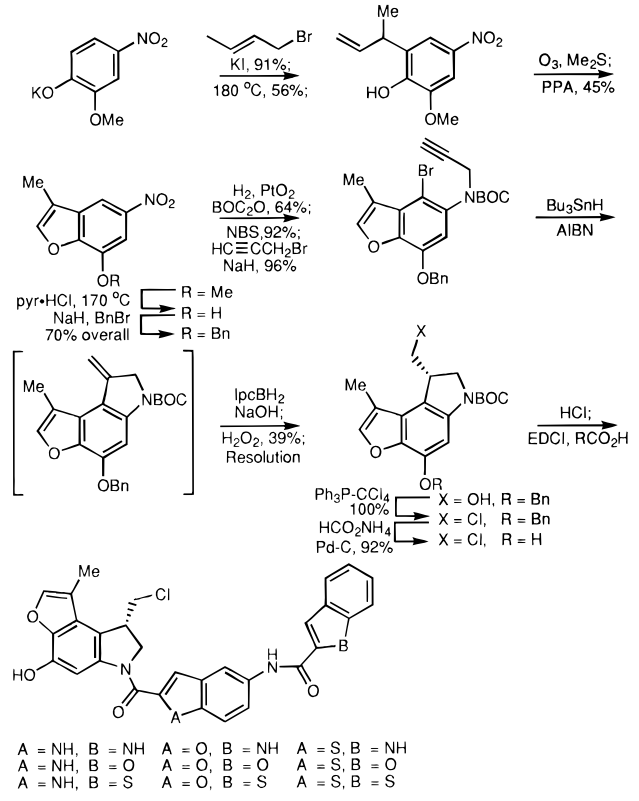
1. Mohamadi Synthesis of 1,2,8,8a-Tetrahydrocyclopropa[c]furano[3,2-e]indol-4-one (CFI)

Mohamadi's efforts with CFI in which a furan was substituted for the CPI A-ring pyrrole was among the first published studies to address a potential asymmetric synthesis of the alkylation subunits.[169] The study of an asymmetric hydroboration reaction of an intermediate 3-methyleneindoline was extended to the CFI, CBI, and CI precursors (Scheme 67).

Scheme 67. Mohamadi Asymmetric Hydroboration



Scheme 68. Mohamadi Synthesis of CFI



Thus, the potassium salt of 4-nitroguaiacol was alkylated with crotyl bromide and the resulting ether underwent a thermal Claisen rearrangement to provide 6-(but-3-en-2-yl)-4-nitroguaiacol (Scheme 68). Ozonolysis followed by a reductive workup provided a benzylic aldehyde that underwent dehydration to afford 7-methoxy-3-methyl-5-nitrobenzofuran. Nitro reduction and *N*-BOC protection provided an intermediate analogous to that used in the our CPI[78] (Scheme 12) and original CBI syntheses (Scheme 53). Adopting our approach,[148] C4 bromination, *N*-alkylation with propargyl bromide followed by free radical cyclization provided the key 3-methyleneindoline. Asymmetric hydroboration with (+)-IpcBH$_2$ afforded the desired enantiomer of the primary alcohol in 50% ee. Although 1,1-disubstituted alkenes generally afford much lower levels of asymmetric induction,[170] atypical preferential reaction through one of two possible transition states was observed due to the extremely large and small olefin substituents held in a rigid structural framework. Consistent with this, the extent of asymmetric induction diminished as the relative size of the two substituents was diminished. The asymmetric hydroboration of the 3-methyleneindoline CBI precursor proceeded with 41% ee, while the CI precursor exhibited little asymmetric induction (Scheme 67). Subsequent derivatization as the (*R*)-*O*-mandelate ester and chromatographic resolution of the racemic CFI intermediate[137,148] or recrystallization of the optically enriched derivative was followed by conversion to the primary chloride, debenzylation, and coupling with a variety of carboxylic acids which were evaluated as the *seco* precursors without ring closure. The synthesis of the CFI alkylation subunit was accomplished in 12 steps with an overall yield of 3%.

2. Boger Synthesis of 1,2,9,9a-Tetrahydrocyclopropa[c]pyrido[3,2-e]indol-4-one (CPyI)

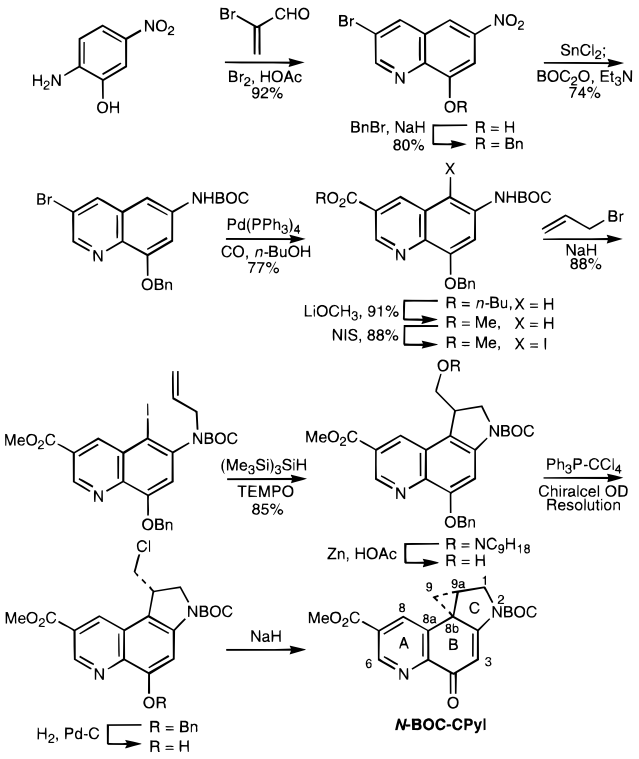
As extrapolated from prior work,[26] the substitution of a fused pyridine for the fused pyrrole found in duocarmycin SA with ring expansion from a 5-membered to a 6-membered ring was expected to produce one of the more potent, stable, and selective alkylation subunits examined to date.[171] The incorporation of the C7 methyl ester analogous to that found in the duocarmycins not only productively contributed to its properties and stability, but also permitted the preparation of reversed and sandwiched analogs which contain DNA binding subunits linked as amides to the C7 carboxylate. The strategy for the CPyI synthesis was based on a modified Skraup quinoline synthesis[172] to provide the quinoline core structure, followed by our TEMPO trap of an aryl radical−alkene 5-*exo*-*trig* cyclization for introduction of the A-ring, and final Winstein Ar-3′ spirocyclization.

Thus, 3-bromo-8-hydroxy-6-nitroquinoline was prepared from α-bromoacrolein and the appropriately substituted aniline according to the procedure developed by Tinsley[172] (Scheme 69). The mechanism is proposed to proceed by formation of tribromopropanal, dehydrohalogenation, and 1,4-addition of the aryl amine to dibromoacrolein. The final quinoline is formed through ring closure and dehydrobromination. Following *O*-benzylation, nitro reduction, and *N*-BOC protection, the 3-bromoquinoline was subjected to Pd(0)-catalyzed carboxybutylation and treatment with LiOCH$_3$. Iodination and *N*-alkylation with allyl bromide preceded aryl radical−alkene cyclization and reduction to provide the 3-(hydroxymethyl)-indoline CPyI precursor. The synthesis of (+)-*N*-BOC-CPyI was completed in a fashion analogous to our *N*-BOC-CBI synthesis (Scheme 54).

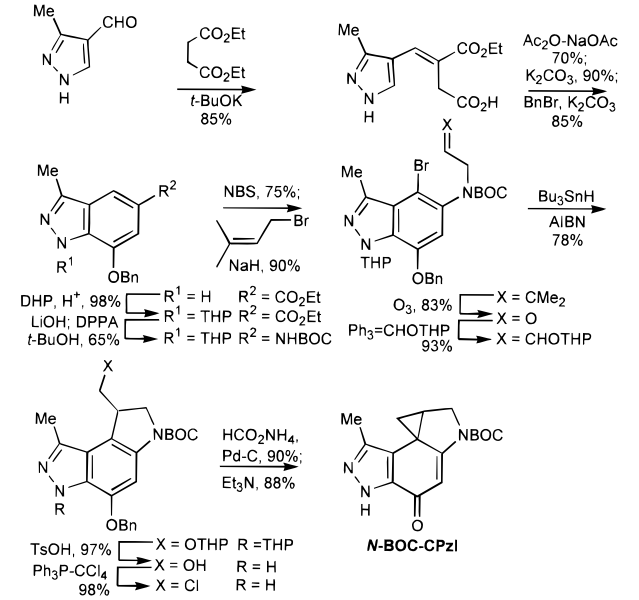
3. Baraldi Synthesis of 1,2,8,8a-Tetrahydro-5H-cyclopropa[c]pyrazolo[4,3-e]indol-4-one (CPzI)

Following our initial strategy developed for the synthesis of CBI, MCBI, and CCBI (Schemes 54, 59,

Scheme 69. Boger Synthesis of *N*-BOC-CPyI



Scheme 70. Baraldi Synthesis of *N*-BOC-CPzI



and 60),[154,155] Baraldi and co-workers have prepared *N*-BOC-CPzI (Scheme 70).[173]

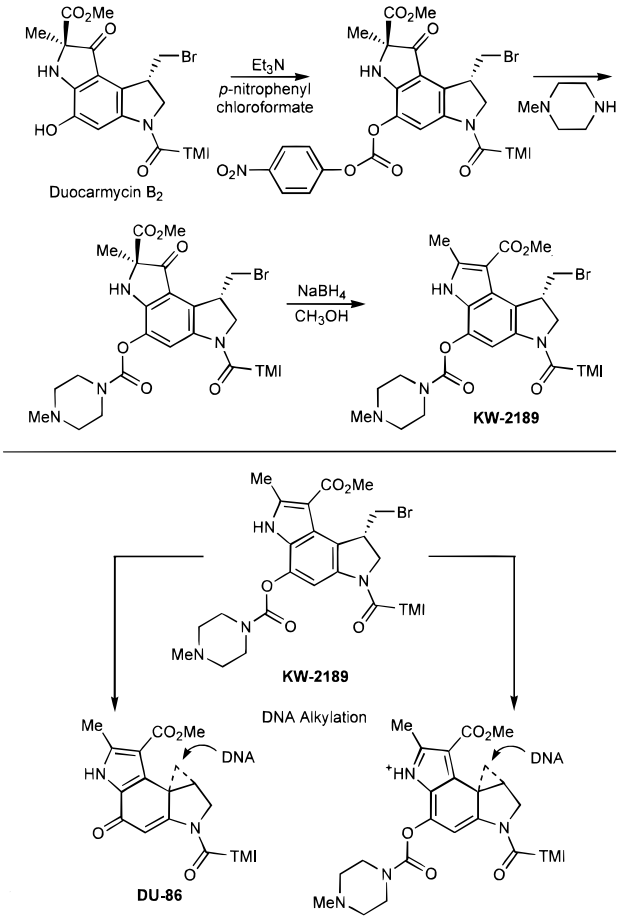
E. Additional Substituted 1,2,8,8a-Tetrahydrocyclopropa[*c*]pyrrolo[3,2-*e*]indol-4-ones (CPI)

1. Kyowa Hakko Kogya Synthesis of DU-86 and KW-2189

Kyowa Hakko Kogyo has recently disclosed preliminary synthetic details for the preparation of KW-2189, an agent currently in phase I clinical trials, in three steps from duocarmycin B_2 (Scheme 71).

Treatment with Et_3N and *p*-nitrophenyl chloroformate yielded the activated carbonate. Displacement

Scheme 71. Synthesis and DNA Alkylation of KW-2189



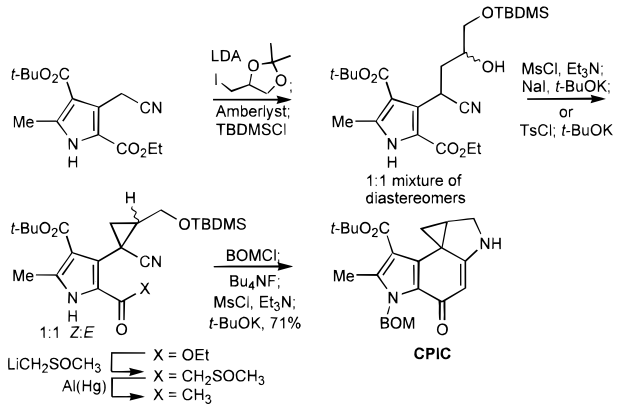
of *p*-nitrophenol with *N*-methylpiperazine[174] provided the more hydrophilic protected phenol, which, upon reduction with $NaBH_4$ in CH_3OH underwent an unusual rearrangement to form KW-2189.[175] This agent was designed as a prodrug, which after enzymatic hydrolysis of the carbamoyl moiety and subsequent spirocyclization, would provide DU-86, an effective analog of the duocarmycins. KW-2189 was found to possess superior stability, solubility, and *in vivo* antitumor activity when compared to duocarmycin A and DU-86. Moreover, recent studies have revealed that KW-2189 itself may alkylate DNA without hydrolysis of the carbamoyl moiety, through a proposed imminium intermediate.[176]

2. Bryson Synthesis of a 1,2,8,8a-Tetrahydro-6-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-7-carboxylate (CPIC)

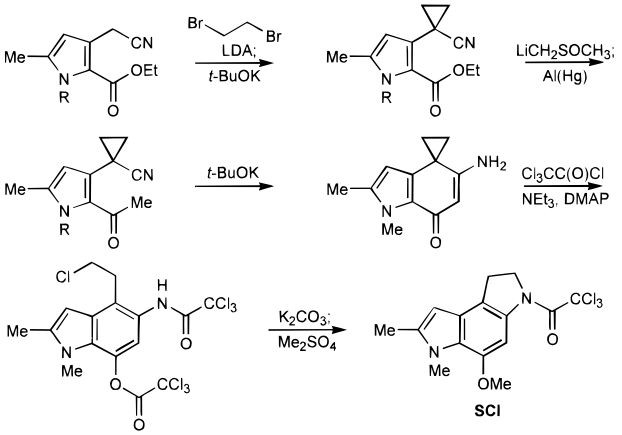
Bryson and co-workers had prepared an analogous CPI analog[177] even before the Kyowa Hakko Kogya disclosure of the structure and importance of DU-86[174−176] and its prodrugs. The insightful design resulted from the development of a clever approach that sequentially closed the B- and C-rings in a single reaction employing a precursor in which the A-ring pyrrole and cyclopropane were already installed. As such, it constitutes only the second approach which does not rely on a final Winstein Ar-3′ alkylation for introduction of the cyclopropane.

Thus, the dianion of a highly substituted 3-(cyanomethyl)pyrrole underwent alkylation with 3-iodopropane-1,2-diol acetonide (Scheme 72).[177] Ketal

Scheme 72. Bryson Synthesis of CPIC



Scheme 73. Bryson Synthesis of SCI

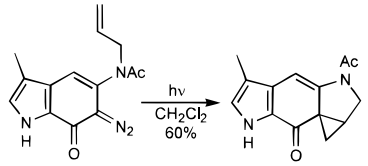


cleavage and selective TBDMS ether protection of the primary alcohol preceded activation of the secondary alcohol by conversion to the corresonding mesylate. *In situ* iodide formation and subsequent intramolecular alkylation with closure to the cyclopropane was accomplished upon treatment with *t*-BuOK but provided a 1:1.2 mixture of *Z*(desired)/*E*(undesired) diastereomers. Alternatively, conversion of the secondary alcohol to the corresponding tosylate followed by intramolecular alkylation improved the *Z*/*E* ratio to 1:1.[178] Conversion of the ethyl ester to the methyl ketone using the Corey protocol[179] followed by BOM protection of the pyrrole and primary alcohol activation provided the key intermediate. Treatment with *t*-BuOK afforded *tert*-butyl CPIC via sequential intramolecular attack of the methyl ketone enolate on the nitrile to close ring B followed by *N*-alkylation of the resulting imine anion/metalloenamine to close ring C.[177]

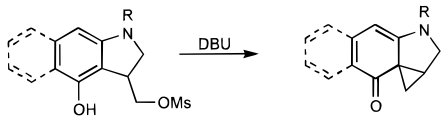
3. Bryson Synthesis of 5′-Amino-2′-methylspiro[cyclopropane-1,4′-indol-7′-one] (SCI)

In an extension to their investigations, Bryson and co-workers developed a synthesis of a stable SCI lacking the characteristic pyrrolidine ring which was further converted to a 1,2-dihydro-3*H*-pyrrolo[3,2-*e*]-indole characteristic of the CC-1065 central and right-hand subunits.[177] Thus, the cyclopropane was introduced onto a 3-(cyanomethyl)pyrrole via dialkylation with 1,2-dibromoethane (Scheme 73). Subsequent base-catalyzed intramolecular ring closure provided the substituted SCI which was surprisingly resistant to nucleophilic addition under basic conditions. Cyclopropane cleavage with Cl_3CCOCl and concomitant *O*- and *N*-acylation followed by intramolecular *N*-alkylation and final *O*-methylation established the tricylic CDPI core and completed the effort.

Scheme 74. Sundberg Synthesis of *iso*-CPI



Scheme 75. Boger Ar-3′ Spirocyclization



F. Isomeric Spiro(cyclopropyl-1,*X*′-indolones)

Even more pronounced structural changes in the naturally occurring alkylation subunits have been investigated in efforts that address directly the importance of the location of the conjugated carbonyl to the expression of the agents properties and the impact such a structural perturbation might have on the reactivity and reaction regioselectivity of the activated cyclopropane.

1. Sundberg Synthesis of 1,1a,2,3-Tetrahydro-6-methylcyclopropa[c]pyrrolo[2,3-f]indol-8-one (iso-CPI)

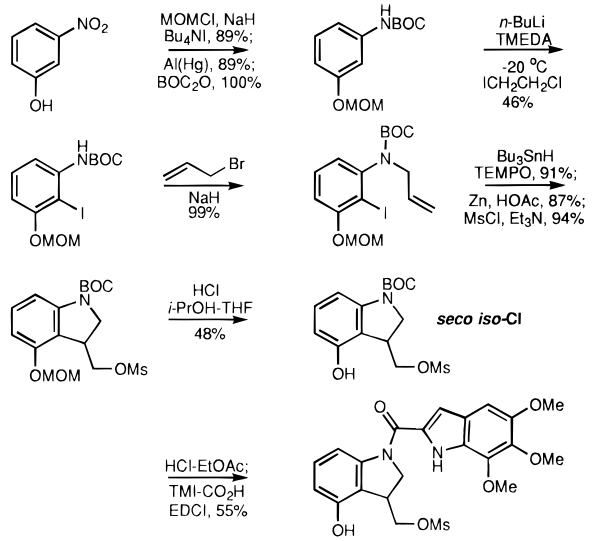
In the course of preparing CPI (Scheme 10), Sundberg and co-workers inadvertently synthesized an agent isomeric with CPI.[75a,c] *Iso*-CPI was derived from an intramolecular carbene insertion of an *o*-quinone monodiazide onto a tethered alkene. The *o*-quinone monodiazide resulted, after reduction and diazotization, from a regiospecific nitration that occurred at the undesired C6 position (Scheme 74). Because of the perceived unique character of the authentic CPI alkylation subunit of CC-1065 at the time of this work, the chemical behavior, biological characteristics and DNA alkylation properties of *iso*-CPI unfortunately were not pursued.

2. Boger Synthesis of 1,1a,2,3-Tetrahydrocyclopropa[c]indol-7-one (iso-CI)

Recently, we have completed an alternative route to the preparation of isomeric analogs of the CC-1065 and duocarmycin alkylation subunits, which has resulted in the synthesis of *iso*-CI and *iso*-CI-TMI.[180] The strategy for the synthesis included a cooperative directed *ortho*-metalation to regiospecifically install a C2 versus C4 halide. Following TEMPO trap of a 5-*exo*-*trig* aryl radical−alkene cyclization onto an unfunctionalized tethered alkene, an isomeric variant of the classical Winstein Ar-3′ alkylation was used to introduce the cyclopropane in which the electrophilic C3′ position is alkylated *ortho* to the C4 phenol (Scheme 75).

This Ar-3′ alkylation selectively afforded the tetrahydrocyclopropa[*c*]indol-6-one core isomeric with that found in the natural products (Scheme 76).[180] Conversion to both the *N*-BOC-*iso*-CI and *iso*-CI-TMI penultimate precursors proceeded in excellent yields.

Scheme 76. Boger Synthesis of *seco iso*-CI



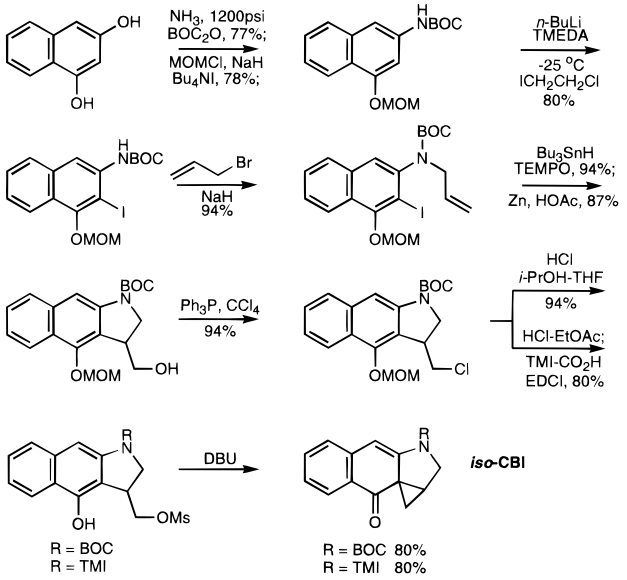
Although the spirocyclization to *iso*-CI could be effected by treatment with DBU, its exceptional reactivity discouraged attempts to isolate and characterize the ring-closed cyclopropane agents. Consequently, they were evaluated as the precursor *seco* agents and were shown to exhibit biological properties and DNA alkylation capabilities analogous to the corresponding CI derivatives.

3. Boger Synthesis of 1,1a,2,3-Tetrahydrocyclopropa[c]benzo[f]indol-9-one (iso-CBI)

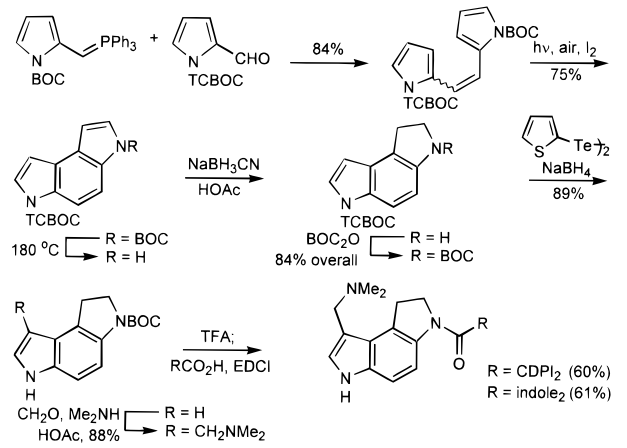
The synthesis of *iso*-CBI also employed a cooperative directed *ortho*-metalation of *N*-BOC-4-(methoxymethoxy)naphthylamine with subsequent trap of the resulting aryllithium to regiospecifically install the C2 iodide (80%).[180] In a fashion analogous to our synthesis of CBI (Scheme 54), a 5-*exo-trig* radical cyclization with *in situ* TEMPO trap, and subsequent N−O bond cleavage effected by Zn yielded the key 3-(hydroxymethyl)indoline in excellent yield. Activation of the primary alcohol by conversion to the corresponding chloride and selective acid-catalyzed deprotection of the MOM ether afforded the precursor to *iso*-CBI. Treatment with DBU effected selective spirocyclization in 80% yield, and provided *N*-BOC-*iso*-CBI in nine steps in 13% overall yield (Scheme 77).

The aqueous solvolysis of this agent ($t_{1/2}$ = 27 h, pH 3) compared to that of *N*-BOC-CBI ($t_{1/2}$ = 133 h, pH 3) documented the reduced stability of this isomeric system due in part to the lost vinylogous amide stabilization. Nonetheless, it proved to be comparable in stability to *N*-BOC-CPI ($t_{1/2}$ = 37 h, pH 3) and *N*-BOC-DA ($t_{1/2}$ = 11 h, pH 3), the authentic alkylation subunits of CC-1065 and duocarmycin A, respectively. In addition, *iso*-CBI-TMI was prepared and shown to exhibit a DNA alkylation selectivity identical to (+)-CBI-TMI and (+)-duocarmycin SA.[26] In addition to providing an important new series of analogs, the evaluation of the *iso*-CBI-based agents provided further definitive evidence that the Upjohn−Hurley proposal of a sequence dependent phosphate protonation of the alkylation subunit carbonyl responsible for the observed DNA alkylation sequence[37,56,57] specificity cannot be accurate. More importantly, the studies have illustrated that larger structural changes in the alkylation subunits may be more tolerated than perceived.

Scheme 77. Boger Synthesis of *iso*-CBI



Scheme 78. Cava Synthesis of Gramine Analog



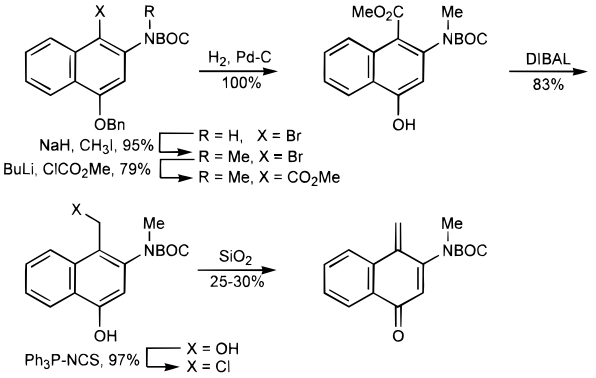
G. Gramine-type Analog

Building on previous photocyclization methodology employed for the synthesis of PDE-I and PDE-II (Scheme 22),[91] Cava and co-workers reported the synthesis and biological testing of a gramine type analog of CC-1065.[181] Following linkage of two differentially protected pyrroles,[159] photocyclization to form a pyrrolo[3,2-*e*]indole and further Mannich functionalization provided their desired agent (Scheme 78).

H. *p*-Naphthoquinone Methide Analog

The synthesis of the inherently reactive *p*-quinone methide analog of the alkylation subunits afforded one of the few unsubstituted *p*-quinone methides[182] and the only recorded *p*-naphthoquinone methide that is sufficiently stable for isolation and characterization. *N*-Methylation of *N*-BOC-4-(benzyloxy)-1-bromo-2-naphthylamine followed by lithium−halogen exchange and reaction with $ClCO_2Et$ provided a methyl naphthalene-4-carboxylate (Scheme 79). Deprotection of the benzyl ether and treatment with DIBAL provided clean conversion to the stable 4-(hy-

Scheme 79. Boger Synthesis of an Isolable *p*-Naphthoquinone Methide



droxymethyl)-1-naphthol. Subsequent reaction with Ph_3P-NCS afforded the 4-(chloromethyl)-1-naphthol. Although reactive, the *p*-quinone methide itself could be isolated and characterized upon chromatography of this precursor. The surprising ease of generation of the final product and its stability relative to typical *p*-quinone methides may be attributed to vinylogous amide stabilization. This same vinylogous amide stabilization contributes significantly to the stability of the CC-1065 and duocarmycin alkylation subunits and its DNA binding-induced disruption is responsible for the rapid catalysis in their reaction with duplex DNA.

I. Other Modifications in the DNA Alkylation Subunits

A small number of agents incorporating additional modifications in the DNA alkylation subunits have been disclosed without detail in abstracts and are shown in Figure 6.[180,183,184]

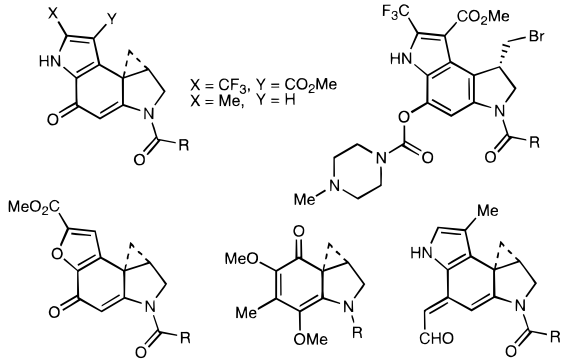


Figure 6. Other modifications in the DNA alkylation subunits.

V. Deep-Seated Modifications in the DNA Binding Subunits

A. CPI Derivatives

In early studies conducted with the intention of reducing or eliminating the acute and delayed toxicity[21−24] of CC-1065, an extensive series of simplified analogs in which the central and right-hand subunits were replaced with more accessible subunits were prepared and evaluated (Figure 7).[185,186]

This included the disclosure that CPI-indole$_2$ (U-71,184)[113] and adozelesin[112] possessed not only the exceptional potency of the natural product, but

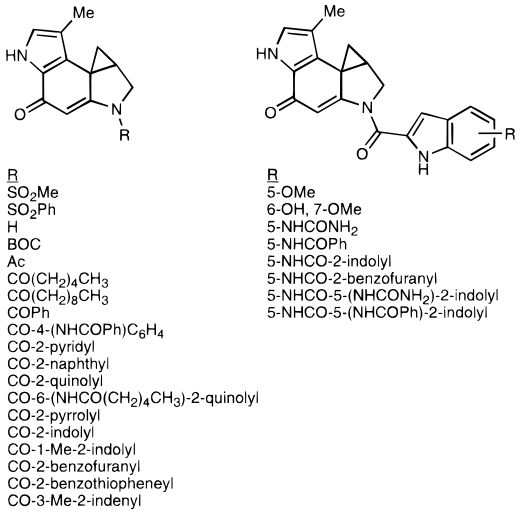
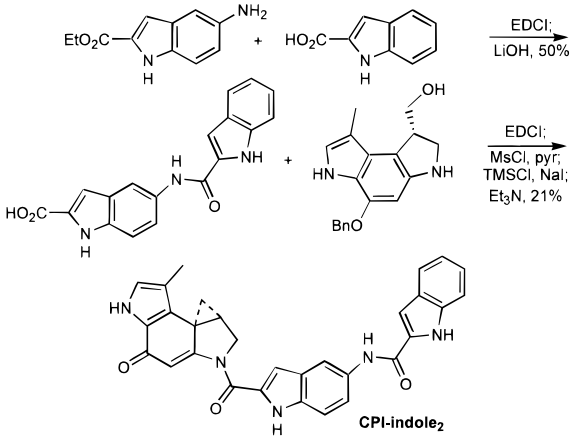


Figure 7. Upjohn CPI analogs.

Scheme 80. Upjohn Synthesis of CPI-Indole$_2$ (U-71,184)



greatly surpasses its antitumor efficacy, without possessing the delayed lethal toxicity. The synthesis of U-71,184 and related agents was effected by EDCI coupling of the indole dimer with the *seco*-CPI precursor and subsequent spirocyclization (Scheme 80).

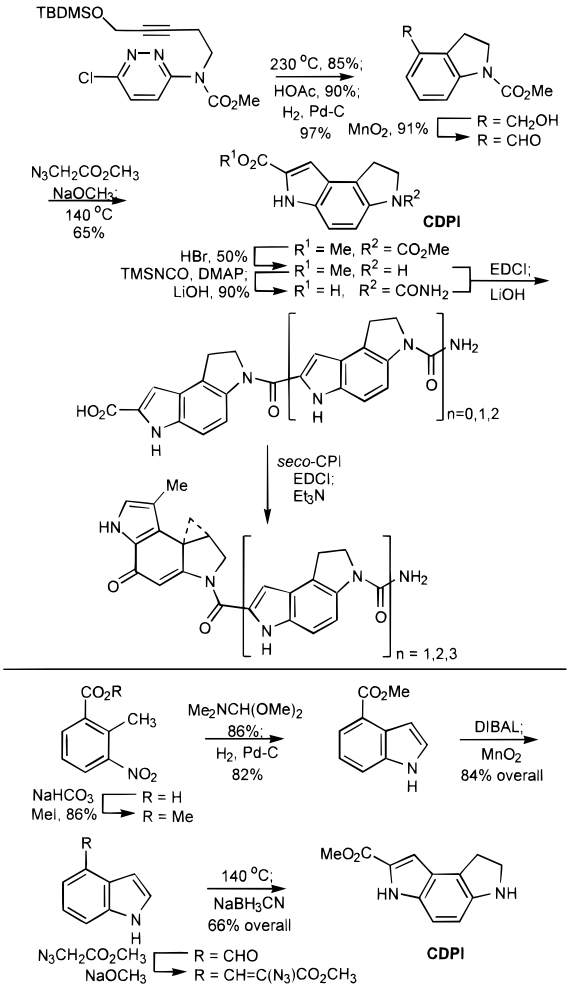
Mohamadi has described a related series of the CFI-based analogs[168] and we have detailed an extensive set of similar CBI analogs.[153,186]

B. 3-Carbamoyl-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indoles (CDPI)

1. Boger CDPI$_n$ Synthesis

In order to address on the contribution of the central and right-hand segments of CC-1065 to the affinity and selectivity of the DNA association, we prepared an analog of CC-1065 which lacked the 4-hydroxy and 5-methoxy groups.[59,108,114,115,187] When this 3-carbamoyl-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-carboxylate (CDPI) was incorporated into an analog of CC-1065 it proved to be a precise analog with indistinguishable properties. The early evaluation of CPI-CDPI$_2$ demonstrated not only that the 4-hydroxy and 5-methoxy groups do not contribute to the observed DNA alkylation efficiency or selectivity, but also that the hydrophobic core of central and right-hand segments of CC-1065 were responsible for the high-affinity, sequence-selective minor groove DNA binding.[59,108]

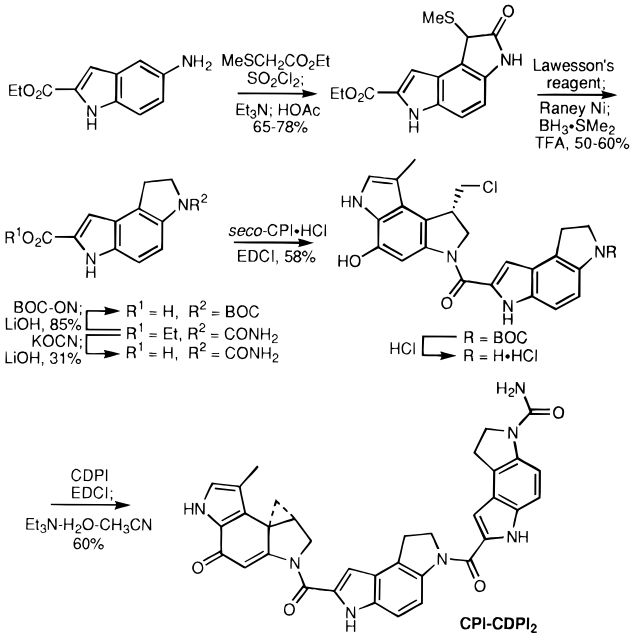
Scheme 81. Boger Synthesis of CDPI and CPI-CDPI$_n$



The agents were prepared using a strategy similar to that employed in our synthesis of PDE-I and PDE-II (Scheme 23).[95] Intramolecular heterocyclic azadiene Diels−Alder cycloaddition,[96] followed by application of the Rees−Hemetsberger α-azidocinnamate thermolysis[73] for introduction of the pyrrole-2-carboxylate yielded the methyl 3-(methoxycarbonyl)-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-carboxylic acid (Scheme 81). Selective *N*-deprotection, and divergent *N*-acylation with ester hydrolysis yielded the coupling partners which provided CDPI$_2$ methyl ester. Hydrolysis of the ester yielded CDPI$_2$ which was coupled to both enantiomers of the CPI precursor and subjected to spirocyclization to provide (+)- and *ent*-(−)-CPI-CDPI$_2$. The full set of CPI-CDPI$_n$ (n = 1−3) were prepared and studied.[59,108] An alternative and more direct preparation of CDPI was subsequently developed.[108] Condensation of indole-4-carboxaldehyde[188] with methyl α-azidoacetate and subsequent thermolysis of the resulting azidocinnamate followed by selective reduction[69] of the unsubstituted, fused indole provided CDPI methyl ester.

A range of CDPI$_n$ oligomers (n = 1−5)[108] as well as linked oligomers, CDPI$_3$−linker−CDPI$_n$,[32] were also prepared in these studies and their examination proved important to defining the preferential AT-rich noncovalent minor groove binding properties of the agents and its structural origin.[108,189] Affinity cleavage agents have also been prepared from CDPI$_3$ and

Scheme 82. Upjohn Synthesis of CPI-CDPI$_2$



have served to demonstrate AT-rich noncovalent binding coincidental with all observed (+)- or *ent*-(−)-CPI-CDPI$_2$ or CC-1065 alkylation sites.[190] In addition, the linkage of CDPI$_n$, and especially CDPI$_3$, to short oligonucleotides has been shown to dramatically increase their duplex and triplex stability with targeted sequences providing a useful approach to the inhibition of gene transcription.[191]

2. Upjohn CDPI$_n$ Synthesis

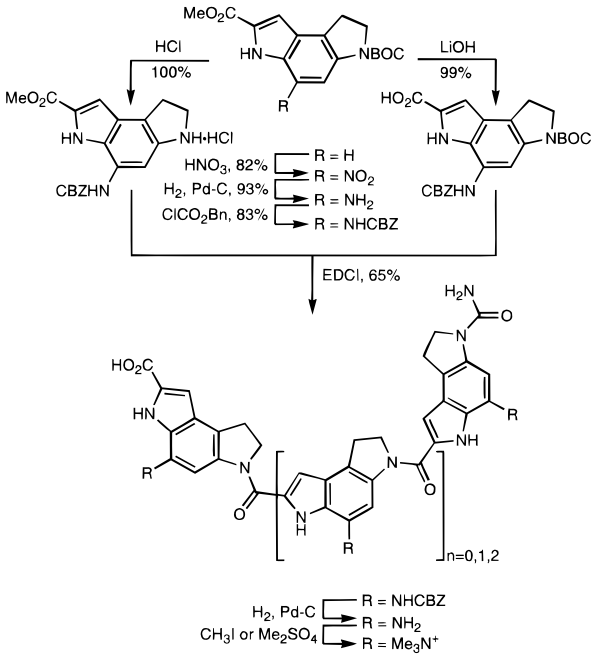
The Upjohn group synthesized CDPI$_2$ and described its incorporation into CPI-CDPI$_2$ with the expectation that it would bind to DNA differently than CC-1065.[56,113,185,192] Their synthesis and subsequent studies determined that, despite identical biological properties, CPI-CDPI$_2$ exhibited a lower induced CD upon DNA alkylation. Although initially misinterpreted as indicating a weaker binding to DNA,[192] this has since been accurately attributed to a smaller DNA binding induced conformational change with CPI-CDPI$_2$ versus CC-1065 since both agents exhibit indistinguishable DNA alkylation selectivities and efficiences. Importantly, the Upjohn studies established that C-4 hydroxy and C-5 methoxy groups were not contributing to the fatal, delayed toxicity of CC-1065.[192] The Upjohn synthesis of CDPI extends the strategy developed in Wierenga synthesis of CPI (Scheme 2),[63] and constructs the C-ring dihydropyrrole ring onto an existing indole.

This route began with the readily available ethyl-5-aminoindole-2-carboxylate and utilized a Gassman oxindole synthesis[65] followed by reduction to provide the 1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole (Scheme 82). After functional group interconversions, the *N*-BOC-protected monomer was coupled to the CPI precursor. *N*-BOC deprotection and coupling with CDPI and base-promoted spirocyclization completed the synthesis.

3. Boger Synthesis of ACDPI$_n$, TACDPI$_n$

In the course of investigating the effects of peripheral substituents on the noncovalent DNA minor

Scheme 83. Boger Synthesis of ACPDI and TACPDI



groove binding affinity and selectivity of agents related to CC-1065, two analogs were prepared that include a strong electronegative or a strong electropositive substituent on the periphery.[189] It was found that ACDPI, the C5 amino-substituted CDPI, exhibited reduced DNA binding affinity through introduction of unfavorable electrostatic interactions with the phosphate backbone. In contrast, TACDPI, the C5 trimethylammonium-substituted CDPI, exhibited increased DNA binding affinity through introduction of stabilizing electrostatic interactions.

The synthesis of these agents began with the *N*-BOC-protected CDPI, which underwent regiospecific C5 nitration (Scheme 83). Nitro reduction, amine protection, and iterative coupling provided the dimer, trimer, and tetramer. Amine deprotection completed the ACDPI$_n$ synthesis and exhaustive *N*-methylation provided the corresponding TACDPI$_n$ agents.

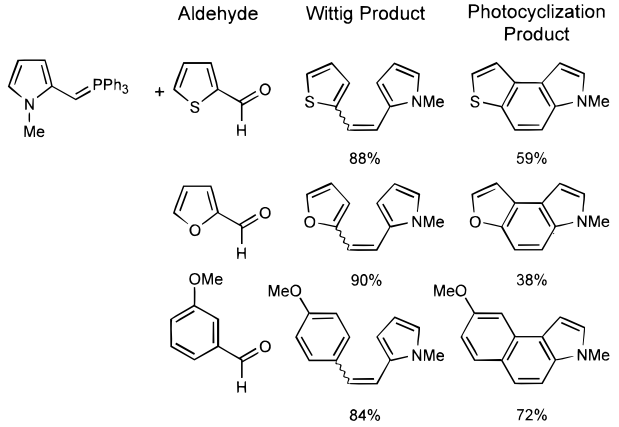
C. Modified Heteroaromatic Core Structures

1. Cava Synthesis of CDPI, Thiophene, and Furan Analogs

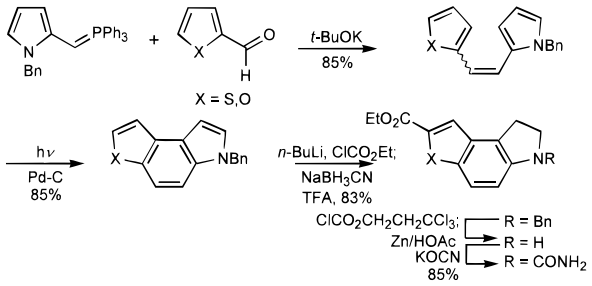
The photocyclization of heterostilbeniods, which proved successful in the synthesis of PDE-I and PDE-II (Scheme 21),[91] has also proved to be a flexible strategy for the synthesis of many analogs (Scheme 84).[159,193] By exchanging the A-ring pyrrole for a thiophene and using an identical sequence of reactions employed in their efficient PDE-I total synthesis, the thiophene analog of PDE-I was prepared.[193]

The synthesis of CDPI as well as its furan and thiophene analogs were also completed (Scheme 85) following an analogous approach. The Wittig reaction with the thiophene or furan aldehyde gave the heterostilbenoid precursors in good yields.[194] Photocyclization of the heterostilbenoids in the presence of Pd−C as described for the natural products[91,159] proceeded smoothly and directed lithiation of the resulting tricycle followed by $ClCO_2Et$ trap installed

Scheme 84. Cava Wittig/Photocyclization Strategy for Analog Synthesis



Scheme 85. Cava Synthesis of CDPI (X = NH), Thiophene (X = S), and Furan (X = O) CDPI Analogs



the required carboxylate. Two-step debenzylation with β,β,β-trichloroethyl chloroformate overcame difficulties experienced by both Cava and Sundberg[102] with this readily oxidized system. *N*-Acylation provided CDPI and its analogs in greater than 30% overall yield.

2. Boger Synthesis of 3-Carbamoyl-1,2-dihydro-3H-pyrrolo[3,2-e]benzoxazole (CDPBO)

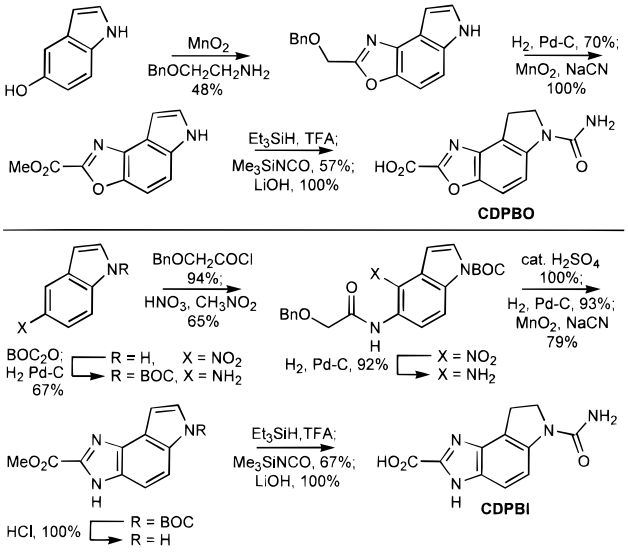
The CDPBO and CDPBI analogs of CC-1065 were designed to study the effects of heteroatoms on the inside convex face of the agent which is in intimate contact with the DNA minor groove floor.[186] These modified agents incorporate a nitrogen atom capable of functioning as a hydrogen-bond acceptor (CDPBO, CDPBI) or hydrogen-bond donor (CDPBI).

In a previous study, we reported an unusual oxidative coupling of methyl 6-hydroxyindole-2-carboxylate with primary amines mediated by MnO_2 to form 2-substituted pyrrolo[2,3-*e*]benzoxazole-5-carboxylates.[195] This methodology was exploited in the synthesis of these analogs, and extended to accommodate the isomeric benzoxazole. When 5-hydroxyindole was treated with 2-(benzyloxy)ethylamine the resulting benzoxazole was isolated in 48% yield (Scheme 86). After conversion of the benzyl alcohol to the methyl ester and selective reduction of the unsubstituted pyrrole, *N*-acylation, and hydrolysis of the ester provided CDPBO in just six steps with an overall yield of 19%.

3. Boger Synthesis of 3-Carbamoyl-1,2-dihydro-3H-pyrrolo[3,2-e]benzimidazole (CDPBI)

CDPBI was synthesized from 5-nitroindole (Scheme 86).[186] After *N*-BOC protection and conversion of the

Scheme 86. Boger Synthesis of CDPBO and CDPBI



nitro group to the acylated amine, regiospecific nitration and subsequent reduction gave the substituted 4-aminoindole which upon treatment with acid cyclized to form the benzimidazole. This intermediate was converted into CDPBI in 11 steps with an overall yield of 4%.

D. Substituted Indoles

More recent efforts conducted in the context of examining the properties of the duocarmycins have addressed the minimum indole substitution required to provide full potentiation of the properties. From these studies, it was established that the C5 indole substituent which lies in the minor groove when the agents are bound to DNA is especially important.

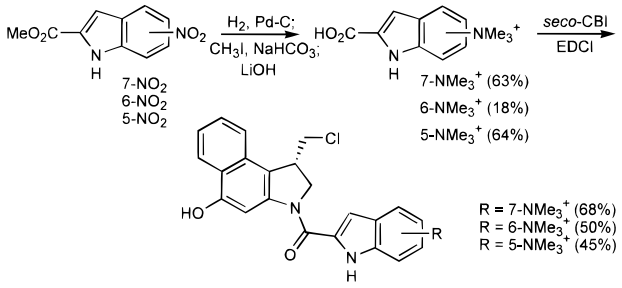
1. Indole–NMe_3

In a continuing effort to examine the DNA binding affinity and selectivity impact of electropositive substituents placed on the peripheral face of the agents, a series of CBI analogs were synthesized which contained a single indole substituted with a trimethylammonium group.[196] It was found that these substituted indoles proved to be 100 times more efficient at alkylating DNA than the unsubstituted indole and the agents themselves were inherently water soluble. The synthesis of the compounds was accomplished by catalytic reduction of the readily available methyl 7-, 6-, and 5-nitroindole-2-carboxylates, exhaustive *N*-methylation, hydrolysis of the ester and coupling to the *seco*-CBI precursor (Scheme 87).

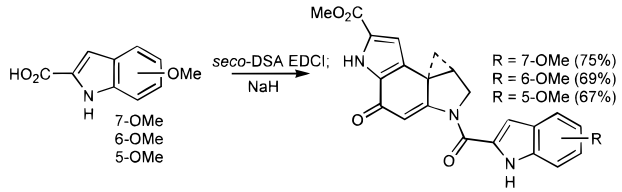
2. Role of the Duocarmycin Indole Methoxy Substituents

More recent studies have systematically examined the role of the three methoxy substituents on the trimethoxyindole DNA binding subunit of the duocarmycin SA.[197] The trimethoxyindole C6 and C7 methoxy substituents which lie on the outer or peripheral face of the DNA−agent complexes individually contribute little to the cytotoxic potency and the relative efficiency of DNA alkylation (C6 > C7) while the C5 methoxy substituent which is deeply imbedded in the minor groove contributes fully to

Scheme 87. Boger Synthesis of Indole-NMe_3^+



Scheme 88. Boger Synthesis of Indole-OMe



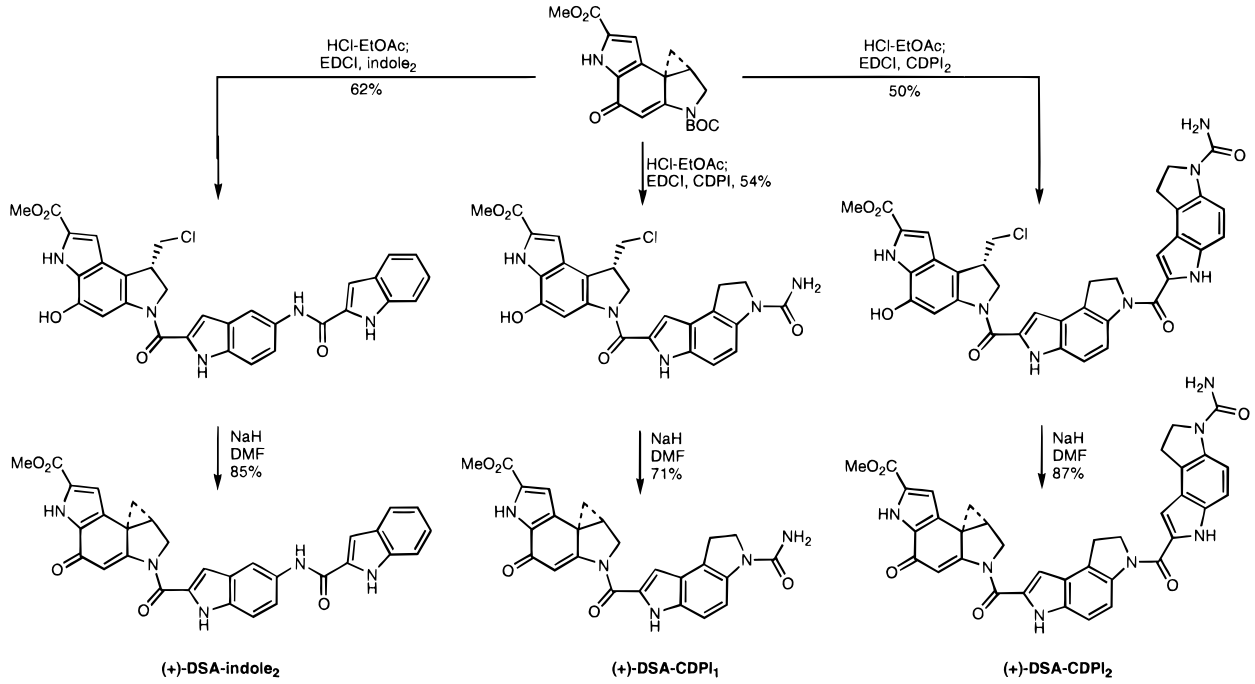
such properties. In fact, the agent with a single C5 methoxy substituent proved indistinguishable from the natural product, indicating that it alone is sufficient for full potentiation of the properties. Consistent with the results of modeling studies detailed in early studies on CC-1065,[31,32] this may be attributed to the additional noncovalent binding stabilization provided by the C5 methoxy substituent imbedded in the minor groove and its role in inducing a bound conformation containing a twisted N^2 amide.[197] The agents were prepared by EDCI promoted coupling of the appropriately substituted indole carboxylic acid with the alkylation subunit precursor followed by NaH-promoted spirocyclization (Scheme 88).

E. Reversed and Sandwiched versus Extended Analogs of the Duocarmycins

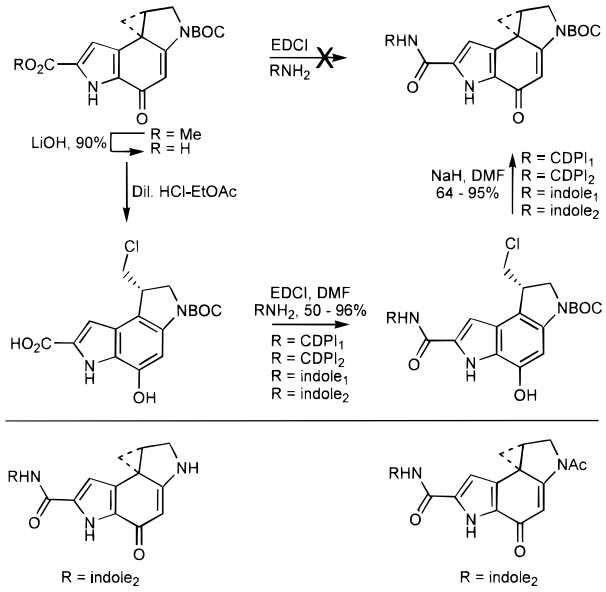
The duocarmycin SA alkylation subunit provided an ideal template on which to study the effects of the structure and orientation of the attached DNA binding subunit(s). The N2 nitrogen provided a site for attaching binding subunits to the right side via amide formation with carboxylic acids affording extended analogs of duocarmycin SA resembling CC-1065[198] while the C6 carboxylate allowed linking binding subunits on the left side providing a unique class of reversed analogs of duocarmycin SA.[199,200] Sequential coupling of binding subunits to both the left and right-hand sides of the alkylation subunit provided a third class of analogs referred to as sandwiched analogs.[201]

EDCI coupling of CDPI, $CDPI_2$, and $indole_2$ to the N2 amine hydrochloride on the right-hand side of the duocarmycin SA alkylation subunit produced a series of extended agents (Scheme 89). The reversed analogs which contain the binding subunits extended to the left side of the alkylation subunit were prepared by coupling an appropriate free amine to the C6 carboxylic acid (Scheme 90). The latter coupling was most efficiently carried out on the *seco* precursor to the alkylation subunit. Both enantiomers of $CDPI_2$-DSA, $indole_2$-DSA, and indole-DSA, and a series of related agents were prepared in this manner. The

Scheme 89. Synthesis of Extended Analogs of Duocarmycin SA



Scheme 90. Synthesis of Reversed Analogs of Duocarmycin SA



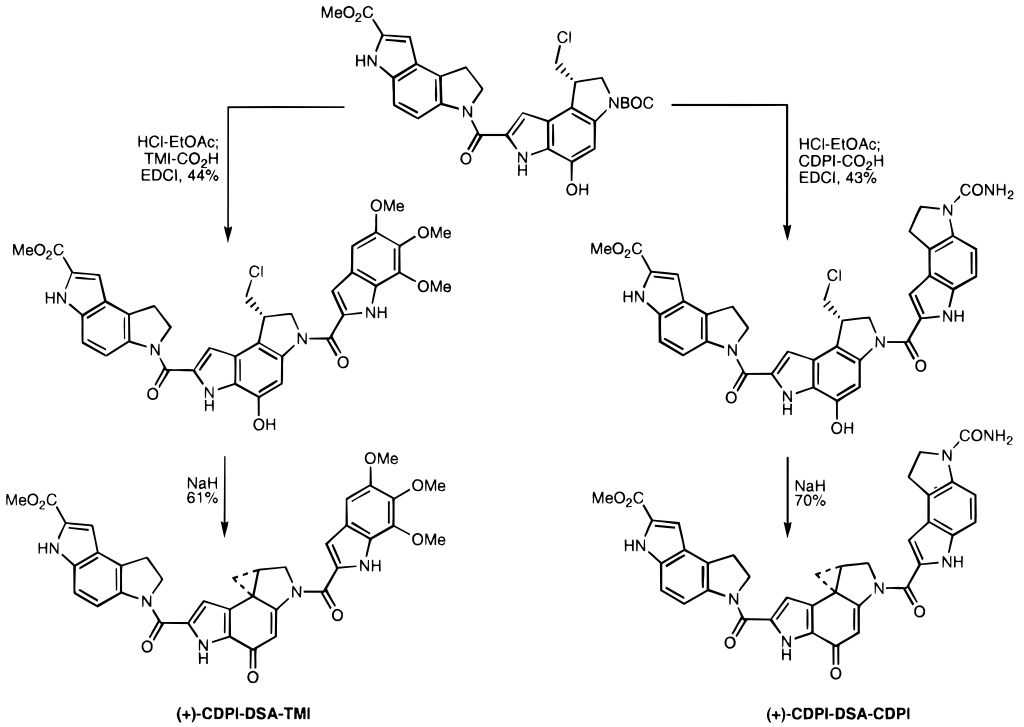
sandwich agents, CDPI-DSA-TMI and CDPI-DSA-CDPI, were prepared by deprotecting CDPI-*seco*-DSA-BOC and coupling with the appropriate right-hand subunit followed by spirocyclization (Scheme 91).

The examination of these three classes of analogs proved instrumental in defining or confirming the origin of the DNA alkylation selectivity of the natural products. The reversal of the inherent enantiomeric alkylation selectivity upon comparison of the reversed versus extended analogs confirmed that both enantiomers are subject to the same polynucleotide recognition principles and that the noncovalent binding selectivity exerts a dominant control. Similarly, the distinct alkylation sites and selectivity of the sandwiched analogs independent of their absolute configuration further confirmed the structural basis for the DNA alkylation selectivity and additionally illustrated that the sites of DNA alkylation were not uniquely imbedded in the DNA structure or controlled by the nature of the alkylation reaction. Moreover, their examination proved instrumental in defining the source of catalysis for the DNA alkylation reaction. The activation for DNA alkylation which is nearly independent of pH was found to result from a binding-induced conformational change on the agents which increases their inherent reactivity.[201] This binding-induced ground-state destabilization results from a twist in the linking N^2 amide that disrupts the N^2 vinylogous amide stabilization of the alkylation subunit and activates the agent for nucleophilic addition. This leads to preferential activation of the agents for DNA alkylation within the narrower, deeper AT-rich minor groove sites where the inherent twist in the linking N^2 amide and helical rise of the bound conformation is greatest. Thus, shape-selective recognition (preferential AT-rich noncovalent binding) and shape-dependent catalysis (induced twist in linking N^2 amide) combine to restrict S_N2 alkylation to accessible adenine N3 nucleophilic sites within the preferred binding sites. In addition, the results of the study illustrate the unique importance of the C5′ methoxy substituent and the C6 methyl ester of duocarmycin SA and a previously unrecognized role for these substituents was disclosed.

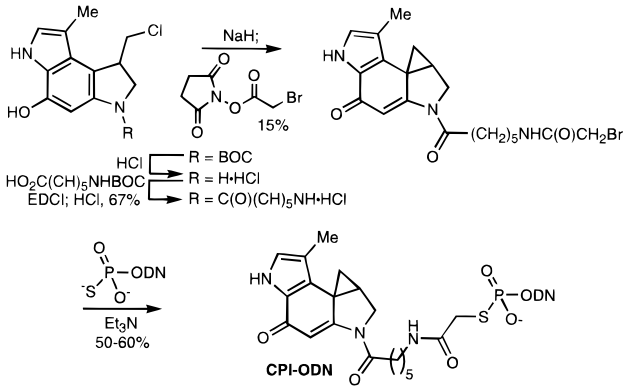
F. CPI–ODN

An interesting set of CC-1065 analogs was reported by Kutyavin and co-workers in which an oligodeoxynucleotide (ODN) was attached to CPI to create a new class of sequence-specific, hybridization-directed DNA alkylating agents.[191,202] The authors suggest this class of agents should find application as inhibitors of single-stranded viral DNA replication or as gene selective inhibitors of transcription. The synthesis of such analogs proceeded with coupling to a linker,

Scheme 91. Synthesis of the Duocarmycin SA Sandwiched Analogs



Scheme 92. Kutyavin Synthesis of CPI-ODN



spirocyclization, and reaction with bromoacetic acid *N*-hydroxysuccinimide ester. The resulting terminal bromide was displaced with an ODN containing a terminal phosphorothioate in the presence of Et_3N (Scheme 92).

G. Additional Cross-Linking Agents

An exciting new class of CC-1065 analogs are the bifunctional alkylating agents containing two alkylation subunits.[203] The CPI units were introduced in their benzyl ether protected *seco* form as hydrochloride salts, coupled one at a time to carboxylic acid linkers, debenzylated through catalytic hydrogenolysis, and simultaneously spirocyclized. Using this methodology, CPI dimers with methylene linkers ranging from 2 to 11 and 14 carbons, as well as a rigid bis-indole linker were synthesized (Figure 8).

H. CBI and Bleomycin A_2 Hybrid Agents

Several hybrid agents containing the C-terminus DNA binding domain of bleomycin A_2 linked to CBI were recently reported (Figure 9).[204] The hybrid

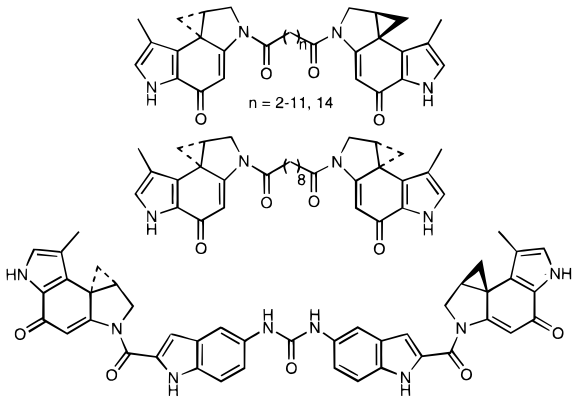


Figure 8. Upjohn cross-linking agents.

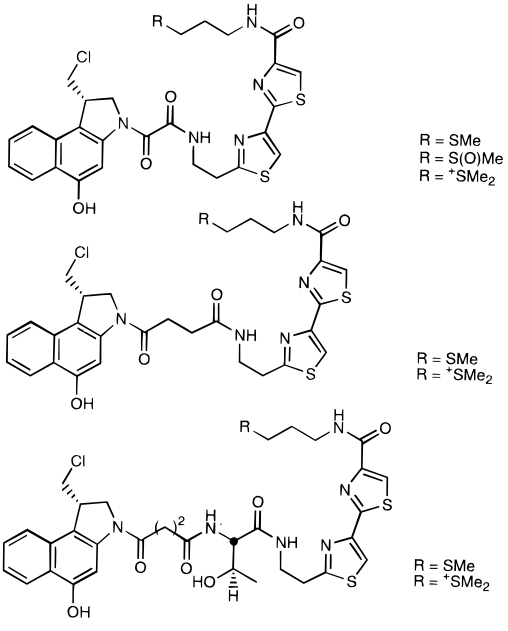


Figure 9. CBI and bleomycin A_2 hybrid agents.

compounds were prepared by acid-catalyzed deprotection of *seco*-*N*-BOC-CBI and coupling with the corresponding di- and tripeptide S DNA binding domains of bleomycin A_2 through a rigid two-carbon or flexible four-carbon linker. The agents exhibited little or no enhancement of DNA alkylation efficiency and demonstrated identical selectivity to that of simple CBI derivatives such as *N*-BOC-CBI.

VI. Conclusions and Future Prospects

An extensive series of studies have led to the development of synthetic approaches to the natural products CC-1065 and the duocarmycins. The extension of these studies to the preparation and evaluation of analogs containing deep-seated structural changes have provided agents that have helped define the nature of the characteristic DNA alkylation reaction, the origin of the DNA alkylation selectivity, the unique source of catalysis for the DNA alkylation reaction, and fundamental relationships between structure, chemical reactivity, and biological activity. As a consequence of these efforts and despite expectations of the unique behavior of the natural products, potent and efficacious antitumor activity has not only been observed with such analogs but both their potency and efficacy may even exceed those of the natural products. The design principles that have been defined in the studies to date, including the fundamental relationship between functional stability and biological potency[26] coupled with the studies that have defined structural features contributing to their functional stability[26] suggest that the most exciting of the potential analogs are yet to be prepared.

VII. Acknowledgments

We gratefully acknowledge the financial support of the National Institutes of Health (CA 55276 and 41986) in support of our efforts.

VIII. Abbreviations

ACDPI	5-*a*mino-3-*c*arbamoyl-1,2-*d*ihydro-3*H*-*p*yrrolo[3,2-*e*]*i*ndole-7-carboxylate
CBI	1,2,9,9a-tetrahydro*c*yclopropa[*c*]*b*enzo[*e*]*i*ndol-4-one
iso-CBI	1,1a,2,3-tetrahydro*c*yclopropa[*c*]*b*enzo[*f*]*i*ndol-9-one
C_2BI	9a-(*c*hloromethyl)-1,2,9,9a-tetrahydro*c*yclopropa-[*c*]*b*enzo[*e*]*i*ndol-4-one
CBQ	2,3,10,10a-tetrahydro-1*H*-*c*yclopropa[*d*]*b*enzo[*f*]-*q*uinol-5-one
CCBI	1,2,9,9a-tetrahydro-7-*c*yano*c*yclopropa[*c*]*b*enzo[*e*]-*i*ndol-4-one
CDPBI	3-*c*arbamoyl-1,2,-*d*ihydro-3*H*-*p*yrrolo[3,2-*e*]*b*enz-*i*midazole-7-carboxylate
CDPBO	3-*c*arbamoyl-1,2-*d*ihydro-3*H*-*p*yrrolo[3,2-*e*]*b*enz*o*xazole-7-carboxylate
CDPI	3-*c*arbamoyl-1,2-*d*ihydro-3*H*-*p*yrrolo[3,2-*e*]*i*ndole-7-carboxylate
CFI	1,2,8,8a-tetrahydro-7-methyl*c*yclopropa[*c*]*f*urano-[3,2-*e*]*i*ndol-4-one
CI	1,2,7,7a-tetrahydro*c*yclopropa[*c*]*i*ndol-4-one
iso-CI	1,1a,2,3-tetrahydro*c*yclopropa[*c*]*i*ndol-7-one
CNA	1,2,3,4,11,11a-hexahydrocyclopropa[*c*]naphtho-[2,1-*b*]azepin-6-one
CPI	1,2,8,8a-tetrahydro-7-methyl*c*yclopropa[*c*]*p*yrrolo-[3,2-*e*]*i*ndol-4-one
iso-CPI	1,1a,2,3-tetrahydro-6-methyl*c*yclopropa[*c*]*p*yrrolo-[2,3-*f*]*i*ndol-8-one
CPIC	1,2,8,8a-tetrahydro-6-methyl-4-oxo*c*yclopropa[*c*]-*p*yrrolo[3,2-*e*]*i*ndole-7-*c*arboxylate
CPyI	1,2,9,9a-tetrahydro*c*yclopropa[*c*]*py*rido[3,2-*e*]*i*n-dol-4-one
CPzI	1,2,8,8a-tetrahydro-5*H*-*c*yclopropa[*c*]*p*yrazolo[4,3-*e*]*i*ndol-4-one
DSA	*d*uocarmycin *SA* alkylation subunit
DA	*d*uocarmycin *A* alkylation subunit
F_2CBI	9,9-di*f*luoro-1,2,9,9a-tetrahydro*c*yclopropa[*c*]*b*enzo[*e*]*i*ndol-4-one
MCBI	1,2,9,9a-tetrahydro-7-*m*ethoxy*c*yclopropa[*c*]*b*enzo[*e*]*i*ndol-4-one
SCI	spiro(*c*yclopropane-1,4′-*i*ndol-7′-one)
TACDPI	5-(*t*rimethyl*a*mmonio)-3-*c*arbamoyl-1,2-*d*ihydro-3*H*-*p*yrrolo[3,2-*e*]*i*ndole-7-carboxylate
TMI	5,6,7-*tri*-*m*ethoxy*i*ndole-2-carboxylate

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CR960095G