and ^{1}H NMR comparison with authentic material.

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Supplementary Material Available: Procedures and spectral data for the preparation of starting ketones, spectral data for the trisylhydrazones, and experimental details for proof of stereochemistry of the cyclization product from **2** are available (13 pages). Ordering information is given on any current masthead page.

Total Synthesis of (±)-N^2-(Phenylsulfonyl)-CPI, (±)-CC-1065, (+)-CC-1065, *ent*-(−)-CC-1065, and the Precise, Functional Agents (±)-CPI-CDPI$_2$, (+)-CPI-CDPI$_2$, and (−)-CPI-CDPI$_2$ [(±)-(3b*R**,4a*S**)-, (+)-(3b*R*,4a*S*)-, and (−)-(3b*S*,4a*R*)-Deoxy-CC-1065]†

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Abstract: Full details of the total synthesis of (±)-N^2-(phenylsulfonyl)-CPI (**3**), the spiro[2.5]octa-4,7-dien-6-one bearing left-hand segment of CC-1065, the coupling of the racemic and resolved immediate precursors (±)-(1*R**)-**33**, (−)-(1*S*)-**33**, and (+)-(1*R*)-**33** with synthetic PDE-I dimer (PDE-I$_2$, **39**), and incorporation into the total syntheses of (±)-CC-1065, natural (+)-CC-1065, and enantiomeric (−)-CC-1065 are described. The approach to the CC-1065 CPI left-hand segment is based on the regioselective, nucleophilic addition of 1-piperidino-1-propene to the selectively activated N^4-(phenylsulfonyl)-*p*-quinone diimide **11** for direct introduction of the CPI 3-methylpyrrole A ring and the subsequent implementation of a 5-*exo*-*dig* aryl radical–alkyne cyclization for indirect introduction of the CPI 3-(hydroxymethyl)pyrroline C ring (**23** → **24** → **25**). Adoption of the Winstein Ar-3′ spirocyclization provided the final introduction of the CPI spirocyclopropylquinone. Full details of additional incorporation of (±)-(1*R**)-**33**, (−)-(1*S*)-**33**, and (+)-(1*R*)-**33** into the total syntheses of (±)-, (+)-, and (−)-CPI-CDPI$_2$ [(±)-(3b*R**,4a*S**)-, (+)-(3b*R*,4a*S*)-, and (−)-(3b*S*,4a*R*)-deoxy-CC-1065] are described. CPI-CDPI$_2$ was anticipated and found to possess the precise structural and functional features that are responsible for the CC-1065 sequence-selective B-DNA minor groove association and the resulting expression of potent cytostatic activity. CC-1065, and the precise functional agent CPI-CDPI$_2$, constitute reactive alkylating agents *superimposed* on the CDPI trimer skeleton and derive their B-DNA associative properties through a common underlying mechanism: accessible hydrophobic binding-driven-bonding. It is predominantly hydrophobic interactions of the concave face of CC-1065 and its B-DNA minor-groove complementary shape (curvature and pitch) that permit (binding) the association with accessible AT-rich minor-groove regions and promote (bonding) the irreversible adenine N-3 covalent alkylation.

CC-1065 (**1**, NSC-298223), an antitumor–antibiotic isolated from cultures of *Streptomyces zelensis*,[2] has been shown to possess exceptionally potent in vitro cytotoxic activity,[3] broad-spectrum antimicrobial activity,[2] and potent in vivo antitumor activity.[4] The structure of CC-1065 was determined initially through a combination of spectroscopic and chemical degradation studies[5] and subsequently was confirmed in a single-crystal X-ray structure determination.[6] At the time of this initial structure determination, CC-1065 constituted the most potent antitumor–antibiotic identified to date, and consequently extensive investigations ensued to define the site and mechanism of the CC-1065 antitumor activity. CC-1065 has been shown to bind to double-stranded B-DNA within the minor groove in an initial high-affinity, nonintercalative manner and subsequently forms an irreversible covalent adduct.[6-9] The (+)-CC-1065 irreversible B-DNA minor groove covalent alkylation has been shown to proceed by acid-catalyzed, 3′-adenine N-3 alkylation of the electrophilic spiro-[2.5]octa-4,7-dien-6-one unit present in the left-hand segment (CPI) of (+)-CC-1065[10] within two consensus sequences, 5′-d-(A/GNTTA)-3′ and 5′-d(AAAAA)-3′.[11-16] Consequently, the mechanism of CC-1065 antitumor activity has been proposed to be derived from (1) the inhibition of the normal unwinding and melting process required for DNA synthesis,[7,13] (2) the inhibition or alteration of replication and transcription enzyme action proximal or distal to its binding regions of DNA,[17] or (3) through the induction of unbalanced cell growth.[18]

† This paper is dedicated to Professor E. J. Corey on the occasion of his 60th birthday.

(1) (a) National Institutes of Health research career development award recipient, 1983–1988 (Grant CA 01134). Alfred P. Sloan research fellow, 1985–1989. (b) National Institutes of Health predoctoral trainee, 1984–1985 (Grant GM 07775). David Ross Fellow, Purdue University, 1986–1987.

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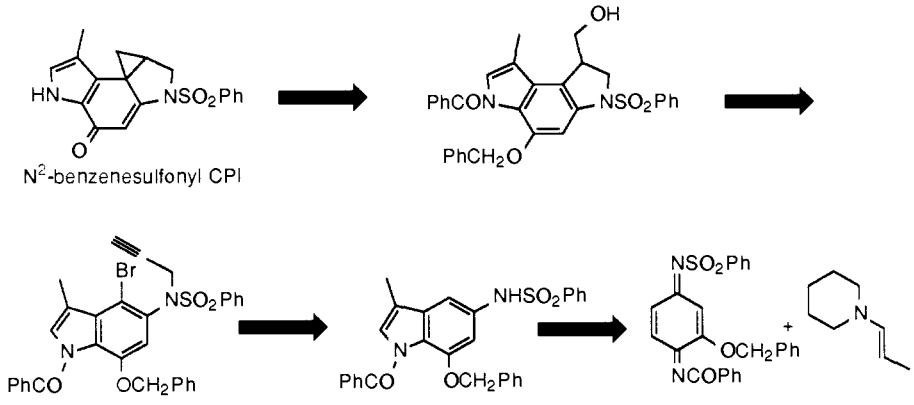
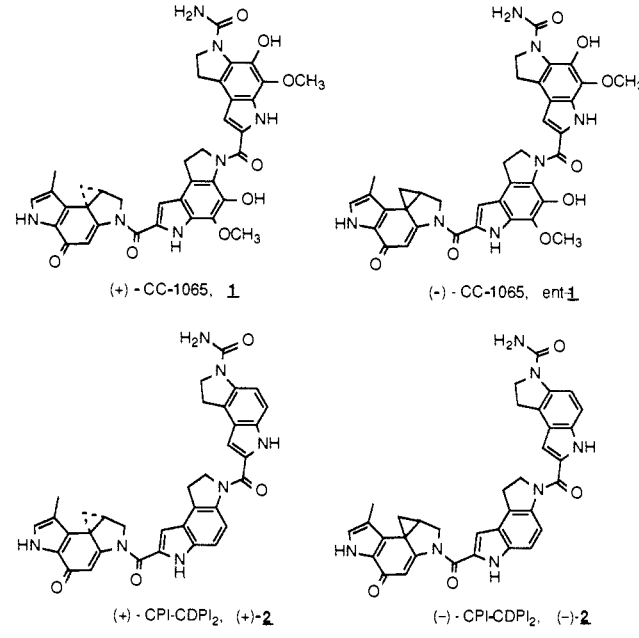
0002-7863/88/1510-4796$01.50/0

Scheme I



Early efforts disclosed in the work of Kelly, Warpehoski, and Wierenga have described the preparation and evaluation of simplified analogues of CC-1065 bearing modified central and right-hand subunits that possess comparable in vitro cytotoxic activity and improved in vivo antitumor activity,[17-19] possess comparable although less discriminate sequence-selective, adenine N-3 alkylation of DNA;[17] lack the characteristic delayed, fatal toxicity of CC-1065;[15,19] and in which the antitumor activity and DNA binding properties were determined to be restricted principally to the agent enantiomer bearing the natural 3b*R*,4a*S*-CPI left-hand segment.[17,20] In sharp contrast, recent efforts have demonstrated that *ent*-(−)-CC-1065, which possesses the unnatural, enantiomeric 3b*S*,4a*R*-CPI left-hand segment, and natural (+)-CC-1065 possess comparable in vitro cytotoxic and in vivo antitumor activity and comparable, albeit altered, B-DNA minor groove binding properties.[17] Consequently, our examination of the CC-1065 structural features that are responsible for the nonintercalative binding within the B-DNA minor groove has focused on the role and the extent to which the CC-1065 central and right-hand segments contribute to the affinity, specificity, and enantioselectivity of the DNA:CC-1065 association.[12,21-25]



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(12) A detailed molecular mechanics simulation conducted with AMBER[21] (MacroModel, Version 1.1) of the covalent and noncovalent association of (+)-CC-1065 [(+)-**1**], (+)-CPI-CDPI$_2$ [(+)-**2**], and structurally related CDPI$_n$-based agents[22] within the minor groove of the deoxydecanucleotide d(A)$_{10}$·d(T)$_{10}$ had been conducted for predictive comparison. A partitioning of the effects of both the covalent and noncovalent association of the agents within the d(A)$_{10}$·d(T)$_{10}$ minor groove revealed that the CC-1065 adenine N-3 alkylation is promoted and rendered irreversible (bonding) by the strong, stabilizing noncovalent association derived principally and predictably from van der Waals contacts of the agent within the d(A)$_{10}$-d(T)$_{10}$ minor groove (binding); i.e., hydrophobic binding-driven-bonding. Moreover, the overall comparative association of (+)-CC-1065 and (+)-CPI-CDPI$_2$ derived from the AMBER-simulated d(A)$_{10}$·d(T)$_{10}$:CC-1065 and d(A)$_{10}$·d(T)$_{10}$:CPI-CDPI$_2$ covalent complexes (−51.4 kcal versus −48.0 kcal)[26] suggested indistinguishable properties for the two agents. The comparison of the results derived from the AMBER full structure energy optimization of the simulated d(A)$_{10}$·d(T)$_{10}$:CPI-CDPI$_2$ covalent complex, in which the 3′-adenine residue **3** was covalently bound (N-3 alkylation) to (+)-CPI-CDPI$_2$ with those derived from the comparative d(A)$_{10}$·d(T)$_{10}$:CC-1065 covalent complex indicated that the hydrophobic, rigid, helical skeleton introduced by the repeating 1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole units of CPI-CDPI$_2$ precisely complements the topological curvature and pitch of the d(A)$_{10}$·d(T)$_{10}$ B-DNA minor groove. This is accurately reflected in the comparison of the MM2 (Allinger, 1985; MacroModel, Version 1.1) low-energy conformations of (+)-CC-1065 and (+)-CPI-CDPI$_2$ (Allinger MM2; MacroModel, Version 1.1) with the covalently bound conformations of (+)-CC-1065 and (+)-CPI-CDPI$_2$ taken from the AMBER simulated d(A)$_{10}$·d(T)$_{10}$:CC-1065 and d(A)$_{10}$·d(T)$_{10}$:CPI-CDPI$_2$ covalent complexes (Figure 2 and 3, supplementary material). It is predominantly hydrophobic interactions of the concave face of CC-1065 and CPI-CDPI$_2$ and their B-DNA minor groove complementary shape (curvature and pitch) that permit (binding) the association with accessible AT-rich minor-groove regions and promote (bonding) the irreversible, adenine N-3 alkylation. This analysis permitted the anticipation of the comparable properties of (+)-CC-1065 and (+)-CPI-CDPI$_2$ [(+)-deoxy-CC-1065]. In addition, the comparison of the d(A)$_{10}$·d(T)$_{10}$-bound and low-energy conformations of (+)-CC-1065, Figure 2 (supplementary material), reveal that the pitch of the low-energy conformation of the agent is more pronounced than that of the B-DNA minor groove. In contrast, the comparison of the CPI-CDPI$_2$ low energy and d(A)$_{10}$·d(T)$_{10}$-bound conformations, Figure 3 (supplementary material), as well as the direct comparison of the low-energy conformations of CC-1065 and CPI-CDPI$_2$ suggest that the CDPI$_n$-based agents more closely follow the precise pitch of the B-DNA minor groove. Consequently, the CC-1065 C-4 phenol present in the central and right-hand segments once projected as the structural feature responsible for induction and maintenance of the agent pitch through hydrogen bonding appears to actually introduce an exaggerated pitch into the agent.

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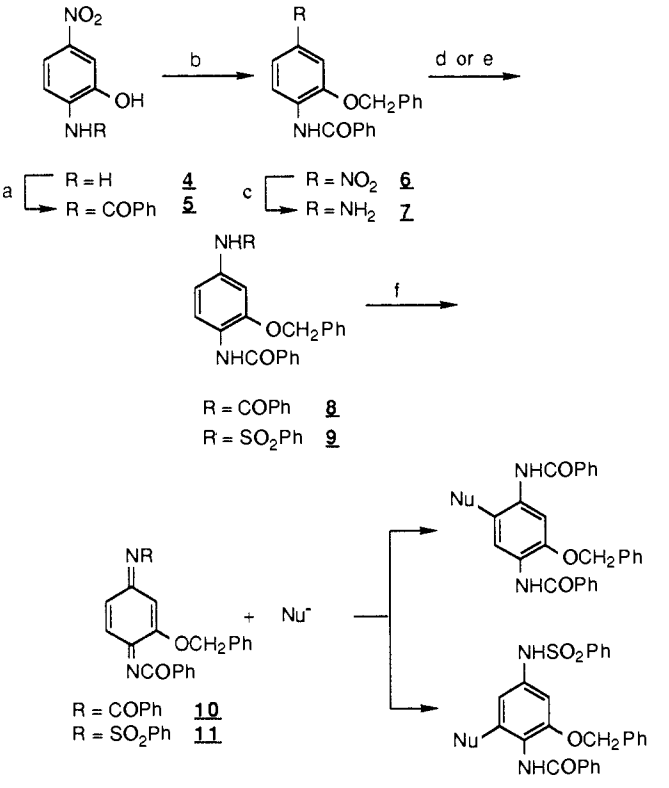
Herein, we provide full details of the total synthesis of N^2-(phenylsulfonyl)-CPI (**3**),[23] the spiro[2.5]octa-4,7-dien-6-one bearing left-hand segment of CC-1065; the coupling of the racemic and resolved immediate precursors (±)-(1*R**)-**33**, (−)-(1*S*)-**33**, and (+)-(1*R*)-**33** with synthetic PDE-I dimer (**39**, PDE-I_2);[24b] and incorporation into the total syntheses of (±)-CC-1065, natural (+)-CC-1065, and enantiomeric (−)-CC-1065.[23] The additional details of the incorporation of (±)-(1*R**)-**33**, (−)-(1*S*)-**33**, and (+)-(1*R*)-**33** into the total syntheses of (±)-CPI-$CDPI_2$, (+)-CPI-$CDPI_2$, and (−)-CPI-$CDPI_2$ [(±)-(3b*R**,4a*S**)-, (+)-(3b*R*,4a*S*)-, and (−)-(3b*S*,4a*R*)-deoxy-CC-1065 (**2**)][25] are provided. As anticipated,[12] **2** was found to embody the precise structural and functional features responsible for the CC-1065 sequence-selective B-DNA minor groove association and the resulting expression of potent cytotoxic activity.

Preparation of N^2-(Phenylsulfonyl)-CPI (3): The Left-Hand Segment of CC-1065.[26] The synthetic approach to the preparation of the cyclopropa[*c*]pyrrolo[3,2-*e*]indol-4(5*H*)-one (CPI) left-hand segment of CC-1065, Scheme I, is based on the regioselective, nucleophilic addition of 1-piperidino-1-propene to the selectively activated N^4-(phenylsulfonyl)-*p*-quinone diimide **11** for direct introduction of the CPI 3-methylpyrrole A ring.[27] The subsequent implementation of a 5-*exo*-*dig* aryl radical–alkyne cyclization[28] was anticipated to provide an indirect approach to the introduction of the CPI 3-(hydroxymethyl)pyrroline C ring and represented the completion of a five-step preparation of the parent 1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole ring system. Adoption of the Winstein Ar-3′ spirocyclization,[29] originally introduced by Wierenga[26a] for final introduction of the electrophilic spiro-[2.5]octa-4,7-dien-6-one ring system, was anticipated to provide N^2-(phenylsulfonyl)-CPI (**3**).

Scheme II[a]



[a] (a) 1.1 equiv of PhCOCl, 1.2 equiv of K_2CO_3, catalytic 4-(dimethylamino)pyridine, THF, 23 °C, 4 h, 92%; (b) 1.05 equiv of $PhCH_2Br$, 1.2 equiv of K_2CO_3, catalytic *n*-Bu_4NI, acetone, reflux, 16 h, 94%; (c) 5 equiv of $Na_2S_2O_4$, THF/H_2O (2:1), reflux, 30 h, 90%; (d) 1.1 equiv of PhCOCl, 1.2 equiv of K_2CO_3, THF, 23 °C, 64% from **5**; (e) 1.2 equiv of $PhSO_2Cl$, 2 equiv of pyridine, THF, 22 °C, 18 h, 73% from **5**; (f) 1.05 equiv of $Pb(OAc)_4$, benzene, 23 °C, 65% for **10**, 84% for **11**.

Preliminary studies[30] revealed the previously unrecognized regiocontrol available to direct nucleophilic addition[31] to *p*-quinone diimides **10** and **11** suitable for the introduction of the CPI 3-methylpyrrole A ring. The preparation of the *p*-quinone diimides **10** and **11** was achieved in five steps from commercially available 2-amino-5-nitrophenol (**4**), Scheme II. Sequential protection of the amine and phenol through reaction of **4** with benzoyl chloride (K_2CO_3, catalytic DMAP, THF, 23 °C, 92%) followed by treatment of the resulting amide **5** with benzyl bromide (K_2CO_3, acetone, catalytic *n*-Bu_4NI, reflux, 94%) afforded **6**. Subsequent reduction of the nitro group of **6** with sodium dithionite (2:1 THF/H_2O, reflux) was followed by treatment of the resulting amine **7** with benzenesulfonyl chloride (pyridine, THF, 23 °C) or benzoyl chloride (K_2CO_3, THF, 22 °C) and afforded *p*-phenylenediamines **8** and **9** (73% and 64% overall from **6**), respectively. Oxidation of *p*-phenylenediamines **8** and **9** with lead tetraacetate[31] (benzene, 23 °C) afforded the *p*-quinone diimides **10** and **11**. Nucleophilic addition to N^1,N^4-dibenzoyl *p*-quinone diimide **10** proceeded with selective C-5 substitution.[30,31] In contrast, this inherent regioselectivity of the symmetrically activated *p*-quinone diimide **10** was reversed by introduction of the N^4-phenylsulfonyl group of *p*-quinone diimide **11**, and nucleophilic addition to **11** was found to proceed with selective C-6 substitution (Scheme II).[30] Thus, the selective electrophilic activation of the C-6 position of 2-(benzyloxy)-*p*-quinone diimide **11** by the N^4-phenylsulfonyl group proved sufficient to override the inherent preference for C-5 nucleophilic addition observed with N^1,N^4-

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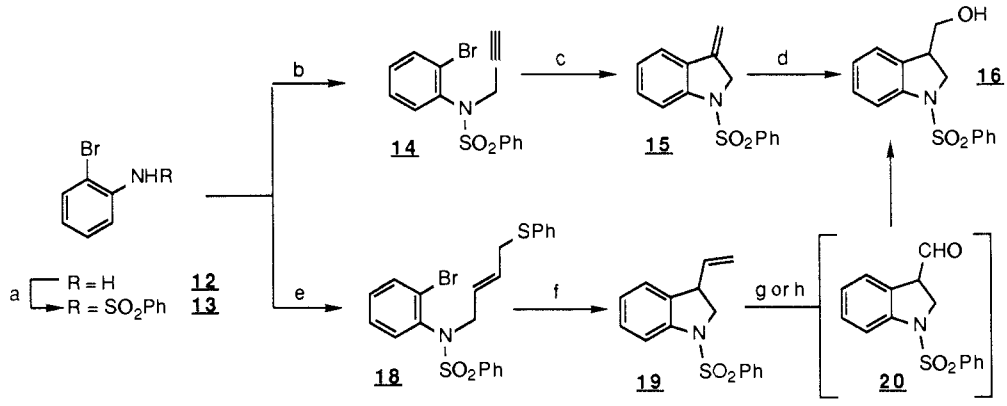
Scheme III[a]

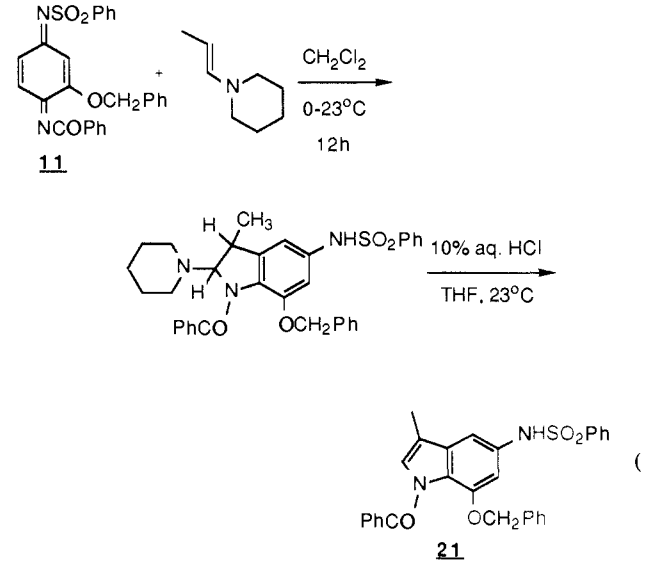


[a] (a) 1.2 equiv of $PhSO_2Cl$, 5 equiv of pyridine, THF, reflux, 86%; (b) 1.1 equiv of NaH, DMF, 22 °C, 1 h; 1.5 equiv of 3-bromopropyne, DMF, 22 °C, 24 h, 88%; (c) 2.1 equiv of *n*-Bu_3SnH, catalytic AIBN, benzene, 80 °C, 12 h, 72%; (d) 1.1 equiv of $BH_3{\cdot}SMe_2$, THF, 22 °C, 2.5 h; 2 N NaOH, 30% H_2O_2, 22 °C, 12 h, 60%; (e) 1.1 equiv of NaH, DMF, 20 °C, 30 min; 1.2 equiv of **17**, DMF, 20 °C, 12 h, 70%; (f) 2.1 equiv of *n*-Bu_3SnH, catalytic AIBN, benzene, 80 °C, 3 h, 82%; (g) O_3, CH_3OH, 0 °C, 20 min; $NaBH_4$, $EtOH/H_2O$ (2:1), 23 °C, 59% from **19**; (h) 2 mol % OsO_4, 3 equiv of $NaIO_4$, acetone/H_2O (3:1), 23 °C, 4 h; $NaBH_4$, EtOH, 0 °C, 30 min, 67% from **19**.

dibenzoyl-2-(benzyloxy)-*p*-quinone diimide (**10**).[30,31]

Prior to initiation of efforts on the preparation of the CPI left-hand segment of CC-1065, the feasibility for the implementation of an aryl radical–alkyne or –alkene cyclization[32] for direct and indirect introduction of the 3-(hydroxymethyl)pyrroline C ring was examined with the substrates **14** and **18** (Scheme III). Treatment of *o*-bromoaniline (**12**) with benzenesulfonyl chloride (pyridine, THF, reflux) afforded 2-bromo-*N*-(phenylsulfonyl)-aniline (**13**, 86%), which upon treatment with sodium hydride in *N*,*N*-dimethylformamide (22 °C, 1 h) followed by 3-bromopropyne (22 °C) or phenyl 4-bromo-2-butenyl sulfide (**17**, 20 °C) afforded **14** and **18**, respectively. 5-*exo-dig* Aryl radical–alkyne cyclization of **14** was effected by treatment with tri-*n*-butyltin hydride (2.1 equiv, catalytic AIBN, benzene, 80 °C) and provided 3-methylidene-*N*-(phenylsulfonyl)indoline (**15**, 72%) (Scheme III). Subjection of **15** to the conditions of hydroboration ($BH_3{\cdot}SMe_2$, THF, 0–22 °C, 2.5 h) followed by oxidation with basic hydrogen peroxide (NaOH, 30% aqueous H_2O_2, 22 °C) afforded 3-(hydroxymethyl)-*N*-(phenylsulfonyl)indoline (**16**, 60%). In a complementary approach, self-terminating 5-*exo-trig* aryl radical–alkene cyclization of allyl sulfide **18** was initiated by treatment with tri-*n*-butyltin hydride (2.1 equiv, catalytic AIBN, benzene, 80 °C) under the conditions described by Ueno and co-workers[33] and afforded *N*-(phenylsulfonyl)-3-vinylindoline (**19**, 82%) (Scheme III). Oxidative cleavage of the carbon–carbon double bond of **19** and subsequent introduction of the C-3 hydroxymethyl group of **16** was achieved by ozonolysis (CH_3OH, 0 °C) and subsequent reduction of the crude ozonide ($NaBH_4$, $EtOH/H_2O$, 23 °C) and afforded 3-(hydroxymethyl)-*N*-(phenylsulfonyl)-indoline (**16**, 59%). Alternatively, subjection of *N*-(phenylsulfonyl)-3-vinylindoline (**19**) to the conditions of the Johnson–Lemieux oxidation[34] (2 mol % OsO_4, $NaIO_4$, 3:1 acetone/H_2O, 23 °C, 4 h) afforded the intermediate *N*-(phenylsulfonyl)-indoline-4-carboxaldehyde (**20**), which was reduced directly to **16** ($NaBH_4$, EtOH, 0 °C, 67% overall from **19**). Additional attempts to introduce the 3-(hydroxymethyl)pyrroline C ring through a direct free-radical cyclization reaction have not proven successful.[30]

Treatment of the selectively activated 2-(benzyloxy)-N^4-(phenylsulfonyl)-*p*-quinone diimide **11** with 1-piperidino-1-propene (CH_2Cl_2, 0–23 °C), which proceeded with selective C-6 nucleophilic addition, followed by acid-catalyzed elimination of piperidine (10% aqueous HCl, THF, 23 °C)[35] provided the direct introduction of the 3-methylpyrrole A ring of the left-hand segment of CC-1065 and afforded **21** (eq 1).



(1)

Implementation of the indirect aryl radical–alkyne and –alkene cyclization to introduction of the 3-(hydroxymethyl)pyrroline C ring of the CPI precursor **25** is detailed in Scheme IV. Selective C-4 bromination of indole **21** was achieved by low-temperature, acid-catalyzed treatment with *N*-bromosuccinimide (THF, catalytic H_2SO_4, –23 °C, 1 h) and afforded aryl bromide **22** (99% crude yield) as the exclusive reaction product. N^5-Benzenesulfonamide alkylation of **22** with 3-bromopropyne (NaH, DMF, 23 °C) provided the alkyne free radical cyclization substrate **23** (67% overall yield from **21**). 5-*exo-dig* Aryl radical–alkyne cyclization[28] of **23** was effected by treatment with tri-*n*-butyltin hydride (2.1 equiv, catalytic AIBN, benzene, reflux) and afforded the unstable methylideneindoline **24** as the predominate reaction product. 3-Methylideneindoline **24**, which proved unstable to chromatographic purification (SiO_2 or neutral Al_2O_3) and underwent isomerization to the corresponding 1,8-dimethylpyrrolo[3,2-*e*]indole,[36] was subjected immediately to the conditions

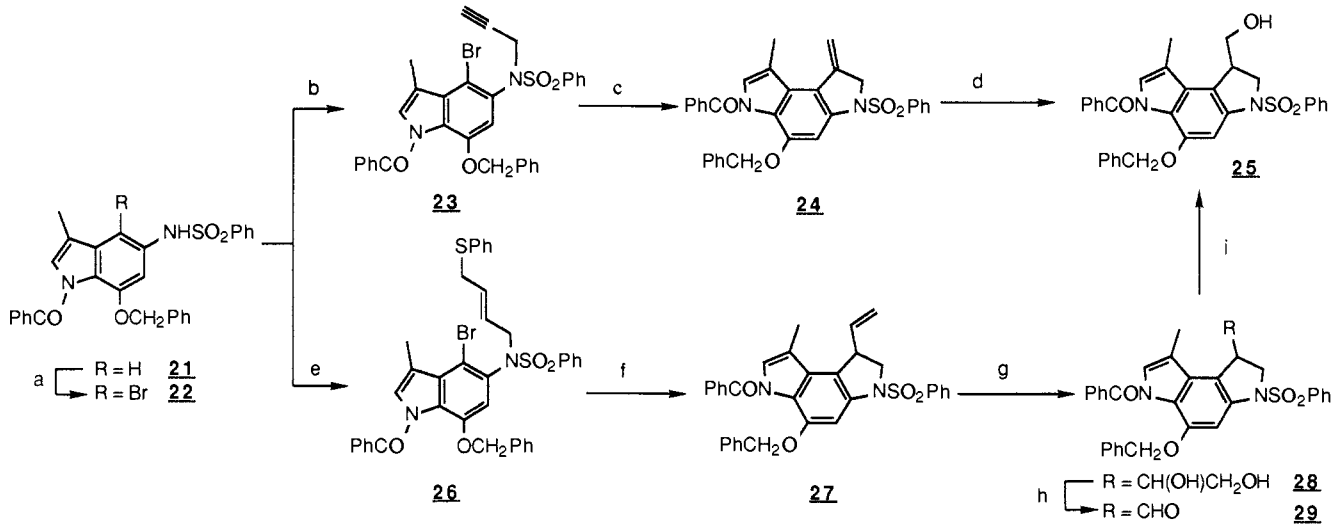
(32) For recent reviews and monographs on free radical reactions in organic synthesis, see: Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. Hart, D. J. *Science (Washington, D.C.)* **1984**, *223*, 883. Giese, B. *Radicals in Organic Synthesis*; Pergamon: New York, 1986.

(33) Ueno, Y.; Chino, K.; Okawara, M. *Tetrahedron Lett.* **1982**, *23*, 2575. See also: Dittami, J. P.; Ramanathan, H. *Tetrahedron Lett.* **1988**, *29*, 45.

(34) Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.

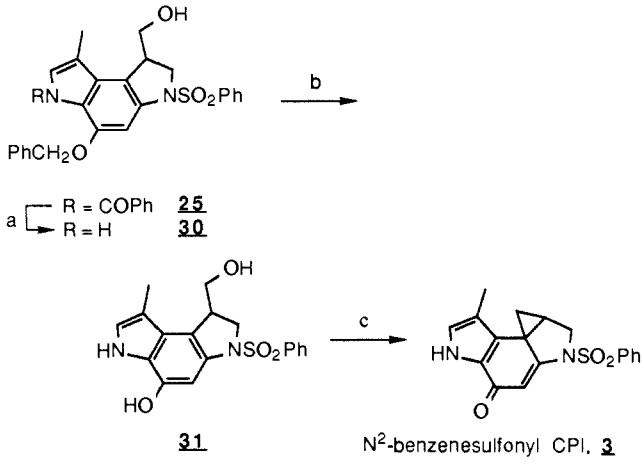
(35) *p*-Toluenesulfonic acid (benzene, 80 °C, 24 h) and Amberlyst 15 (THF, 23 °C, 36–40 h) proved as effective as 10% aqueous hydrochloric acid at promoting the acid-catalyzed elimination of piperidine, whereas other acids (CF_3CO_2H, 23 °C; CH_3CO_2H, 22–70 °C; 4-Å molecular sieves, 23 °C) and reagents (*m*-CPBA, 22 °C; CH_3I, 22 °C; $CF_3SO_3CH_3$, 23 °C; $LiOCH_3/CH_3OH$, 23 °C; *t*-BuOK, THF, 23 °C) were ineffective at promoting this elimination.

Scheme IV[a]



[a](a) 1 equiv of *N*-bromosuccinimide, catalytic H_2SO_4, THF, −23 °C, 1 h, 99%; (b) 1.15 equiv of NaH, DMF, 25 °C, 30 min; 3 equiv of 3-bromopropyne, 25 °C, 1 h, 82% from **21**; (c) 2.1 equiv of *n*-Bu_3SnH, catalytic AIBN, benzene, 80 °C, 4 h; (d) 6 equiv of BH_3·SMe_2, THF, 0–25 °C, 3 h; 2 N NaOH, 30% H_2O_2, 45 °C, 30 min, 40% from **23**; (e) 1.1 equiv of NaH, DMF, 24 °C, 10 min; 1.4 equiv of **17**, DMF, 24 °C, 16 h, 67%; (f) 2.05 equiv of *n*-BuSnH, catalytic AIBN, benzene, 80 °C, 2.5 h, 95%; (g) 1.2 equiv of OsO_4, pyridine, 0–23 °C, 20 h; aqueous $NaHSO_3$, 23 °C, 39%; (h) 1.0 equiv of $Pb(OAc)_4$, benzene, 23 °C, 2 h, 29% from **27**; (i) $NaBH_4$, EtOH, 23 °C.

Scheme V[a]



[a](a) 5% anhydrous HCl in CH_3OH, 50 °C, 2 h, 83%; (b) 1 atm of H_2, 10% Pd/C, EtOAc, 23 °C, 20 h, 85%; (c) 1.2 equiv of Ph_3P, 1.2 equiv of diethyl azodicarboxylate, THF, 23 °C, 8 h, 49%.

of hydroboration (BH_3-SMe_2, THF, 0–23 °C, 1–3 h) followed by treatment with basic hydrogen peroxide (NaOH, 30% aqueous H_2O_2, 45 °C, 30 min) and afforded 3-(hydroxymethyl)indoline **25** (40% overall from **23**) and completed construction of the parent 1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole ring system in five steps from *p*-quinonediimide **11**.

In the exploration of an alternative approach to introduction of the 3-(hydroxymethyl)pyrroline ring of the left-hand segment of CC-1065, the allyl sulfide **26** was examined as a substrate for self-terminating aryl radical–alkene cyclization[33] (Scheme IV). *N*-Benzenesulfonamide alkylation of **22** with phenyl 4-bromo-2-butenyl sulfide (**17**; NaH, DMF, 23 °C) provided the free radical cyclization substrate **26** (72%). Allyl sulfide **26** underwent clean self-terminating 5-*exo*-*trig* aryl radical–alkene cyclization with elimination of thiophenoxy radical[33] to afford 3-vinylindoline **27** (95%). Initial attempts to cleave the carbon–carbon double bond of alkene **27** by treatment with ozone in methanol (0 °C) or dichloromethane (−78 °C) followed by reductive workup (Me_2S or $NaBH_4$/EtOH) failed to provide aldehyde **29** or alcohol **25**, respectively. In each instance, it appeared that the 3-methylindole A ring of **27** was reacting competitively with ozone. Although attempts to promote oxidative cleavage of the carbon–carbon double bond of **27** employing the Johnson–Lemieux oxidation[34] (5–20 mol % OsO_4, $NaIO_4$, 3:1 acetone/water) proved unsuccessful in providing aldehyde **29**, treatment of alkene **27** with excess osmium tetraoxide in pyridine[37] (0–23 °C) followed by reduction of the intermediate cyclic osmate ester with aqueous sodium bisulfite afforded 1,2-diol **28** (39%).[38a] Treatment of crude 1,2-diol **28** with lead tetraacetate (benzene, 23 °C) afforded aldehyde **29**[38b] (29% overall from **27**), and sodium borohydride reduction of aldehyde **29** provided 3-(hydroxymethyl)indoline **25**. Thus, although the self-terminating aryl radical–alkene cyclization of **26** has proven more effective than the aryl radical–alkyne cyclization of **23**, the subsequent transformation of the free radical cyclization products, **24** versus **27**, to the 3-(hydroxymethyl)-indoline **25** at present has proven most expedient through use of the aryl radical–alkyne cyclization approach (**23** → **24** → **25**).

Completion of the total synthesis of the left-hand segment of CC-1065, Scheme V, was achieved by acid-catalyzed methanolysis of the *N*-benzoylindole protecting group of **25** (5% anhydrous HCl, CH_3OH, 50 °C) and provided 1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole **30** (83%). Hydrogenolysis of the benzyl ether of **30** (1 atm of H_2, 10% Pd/C, EtOAc) afforded phenol **31** (85%). Final Ar-3′ cyclization of **31** directly to spirocyclopropylquinone **3** was effected by employing the Mitsunobu activation[39] and intramolecular alkylation conditions described by Magnus and co-workers[26c] (triphenylphosphine, diethyl azodicarboxylate, THF, 23 °C) and

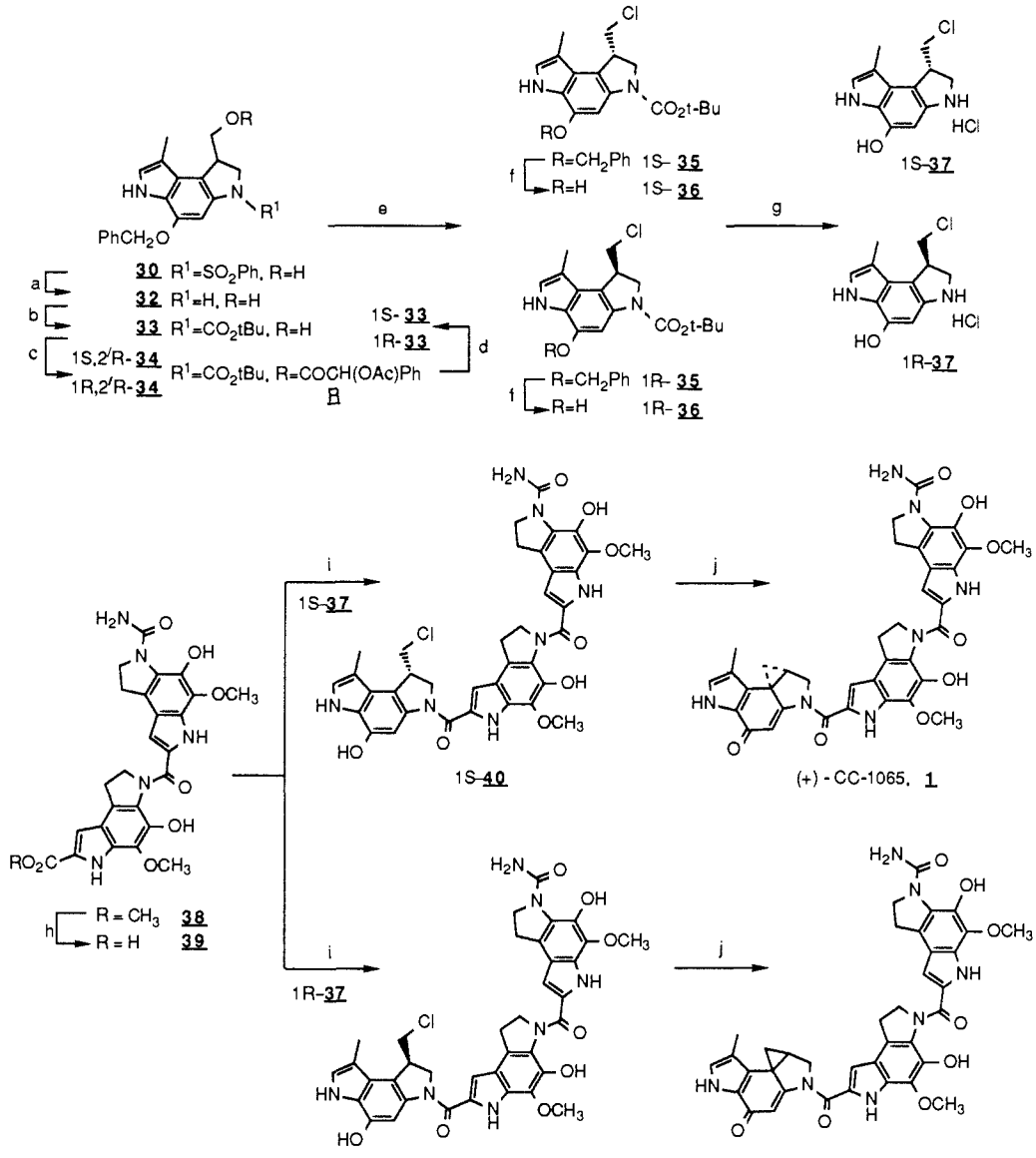
(36) The reaction product was characterized: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.8–7.2 (m, 17 H, Ar H), 5.21 (s, 2 H, PhCH_2O), 2.52 (d, 3 H, *J* = 1 Hz, Ar CH_3), 2.49 (d, 3 H, *J* = 1 Hz, Ar CH_3); EIMS, *m*/*e* (relative intensity) 534 (M^+, 3), 443 (6), 303 (3), 248 (3), 105 (base); CIMS (isobutane), *m*/*e* 535 (M^+ + H, base).

(37) Baran, J. S. *J. Org. Chem.* **1960**, *25*, 257.

(38) (a) **28**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.85–7.20 (m, 15 H, Ar H), 7.09 (s, 1 H, C7-H), 5.27 (s, 2 H, PhCH_2O), 4.15 (d, 1 H, *J* = 9 Hz), 3.80–3.40 (m, 5 H), 2.40 (br s, 1 H, OH), 2.37 (s, 3 H, Ar CH_3), 1.78 (br s, 1 H, OH); IR (KBr) ν_{max} 3462, 3061, 2926, 1690, 1601, 1581, 1490, 1446, 1403, 1353, 1279, 1236, 1204, 1166, 1091, 1052, 899, 831, 720, 691, 667, 629 cm^{-1}; EIMS, *m*/*e* (relative intensity) 582 (M^+, 2), 521 (7), 417 (3), 381 (3), 380 (3), 290 (3), 289 (3), 185 (6), 105 (base); CIMS (isobutane), *m*/*e* (relative intensity) 583 (M^+ + H, 52), 521 (18), 479 (20), 442 (base), 381 (35), 361 (30), 344 (27), 338 (77); HRMS, *m*/*e* 582.1824 ($C_{33}H_{30}N_2O_6S$ requires 582.1825). (b) **29**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.13 (d, 1 H, *J* = 2.5 Hz, C*H*O), 7.9–7.3 (m, 15 H, Ar H), 7.10 (d, 1 H, *J* = 1.1 Hz, C7-H), 5.14 (s, 2 H, PhCH_2O), 4.43 (d, 1 H, *J* = 10 Hz), 4.16–3.95 (m, 2 H), 2.17 (d, 3 H, *J* = 1.1 Hz, Ar CH_3); IR (neat) ν_{max} 3061, 2925, 1725, 1700, 1600, 1489, 1446, 1405, 1354, 1277, 1237, 1167, 1092, 1019, 903, 832, 721, 690, 665 cm^{-1}; CIMS (isobutane), *m*/*e* (relative intensity) 551 (M^+ + H, 86), 410 (base).

(39) Mitsunobu, O. *Synthesis* **1981**, 1. Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679.

Scheme VI[a]



[a] (a) 6 equiv of sodium *bis*(2-methoxyethoxy)aluminum hydride, toluene, N_2, 100 °C, 3 h; (b) 3 equiv of $(t\text{-BuOCO})_2O$, THF, N_2, 23 °C, 20 h, 60% from **30**; (c) 1.5 equiv of (*R*)-(−)-*O*-acetylmandelic acid, 1.7 equiv of EDCI, catalytic 4-(dimethylamino)pyridine, 23 °C, 1 h, 98%, chromatographic resolution;[25] (d) 5 equiv of LiOH, $THF/CH_3OH/H_2O$ (3:2:1), 20 °C, 3 h, 76–83% from (±)-(1*R**)-**33**; (e) 1.5 equiv of Ph_3P, 1.5 equiv of CCl_4, CH_2Cl_2, 23 °C, 12 h, 87%; (f) 25% aqueous HCO_2NH_4/THF 1:4, 10% Pd/C, 23 °C, 30–45 min, 100%; (g) 3 N anhydrous HCl/EtOAc, 23 °C, 30–45 min; (h) 10 equiv of LiOH, 1–3 equiv of $Na_2S_2O_4$, $THF/CH_3OH/H_2O$ 3:2:1, 50 °C, 10 h, 84%; (i) 0.9 equiv of **39**, 3 equiv of 1-((3-dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (EDCI), $NaHCO_3$, DMF, 23 °C, 24 h, 78%; (j) 1:1:1 $Et_3N/H_2O/CH_3CN$, 23 °C, 30 min, 34% from **39**.

afforded N^2-(phenylsulfonyl)-CPI (**3**, 49% yield).

Total Synthesis of (±)-CC-1065, (+)-CC-1065, and *ent*-(−)-CC-1065. Completion of the total synthesis of (+)- and (−)-CC-1065 from the optically active CPI precursors (1*S*)-**33** and (1*R*)-**33** and synthetic PDE-I dimer (**39**) required the development of a procedure for resolution, which has been previously described,[25] and the subsequent incorporation of (1*S*)-**33** and (1*R*)-**33** into the total synthesis of natural (+)- and enantiomeric (−)-CC-1065 (Scheme VI).[40-43] Independent conversion of *primary* alcohols (1*S*)-**33** and (1*R*)-**33**[25] to the corresponding the *primary* chlorides (Ph_3P, CCl_4, CH_2Cl_2, 23 °C)[44] afforded (1*S*)-**35** and (1*R*)-**35**, respectively, constituting the resolved substrates for incorporation into the total synthesis of natural (+)-CC-1065 and *ent*-(−)-CC-1065.[23]

Following the conditions described by Kelly and co-workers,[40] removal of the benzyl ether of (1*R**)-**35**, (1*S*)-**35**, and (1*R*)-**35** by phase-transfer catalytic hydrogenolysis (25% aqueous HCO_2NH_4/THF 1:5, 10% Pd/C, 23 °C) afforded phenols (1*R**)-**36**, (1*S*)-**36**, and (1*R*)-**36** (95–100%) (Scheme VI). Treatment of (1*R**)-**36**, (1*S*)-**36**, and (1*R*)-**36** with anhydrous hydrochloric acid (3 N HCl in EtOAc, 23 °C, 45 min)[45] afforded unstable indoline hydrochlorides (1*R**)-**37**, (1*S*)-**37**, and (1*R*)-**37**, which were coupled directly with synthetic PDE-I dimer (**39**)[24b] in the presence of 1-[(3-dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI; 0.9 equiv **39**, $NaHCO_3$, DMF, 23 °C, 20–24 h) to afford (1*R**)-**40**, (1*S*)-**40**, and (1*R*)-**40**

(40) Kelly, R. C.; Gebhard, I.; Wicnienski, N.; Aristoff, P. A.; Johnson, P. D.; Martin, D. G. *J. Am. Chem. Soc.* **1987**, *109*, 6837.
(41) Martin, D. G.; Mizsak, S. A.; Krueger, W. C. *J. Antibiot.* **1985**, *38*, 746.
(42) Gold, E. H.; Babad, E. *J. Org. Chem.* **1972**, *37*, 2208.
(43) Resolution of alcohol **33** was achieved by chromatographic separation of the corresponding diastereomeric (*R*)-(−)-*O*-acetylmandelate esters **34**. This procedure routinely afforded (1*R*,2'*R*)-**34** of ≥99% purity and (1*S*,2'*R*)-**34** of 93–98% diastereomeric purity. The separated diastereomeric esters (1*S*,2'*R*)-**34** and (1*R*,2'*R*)-**34** were subjected independently to lithium hydroxide promoted ester hydrolysis (LiOH, $THF/CH_3OH/H_2O$, 3:2:1, 23 °C) to remove the chiral auxiliaries and provided the enantiomeric alcohols (1*S*)-**33** and (1*R*)-**33**.[25]
(44) Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801.
(45) Stahl, G. L.; Walter, R.; Smith, C. W. *J. Org. Chem.* **1978**, *43*, 2285.

Table I. In Vitro Cytotoxic Activity of CC-1065 and CPI-CDPI$_2$[a]

agent	configuration	IC_{50},[b] μg/mL L1210[c]	B16[d]	9PS (P388)[e]	9KB[f]
natural (+)-CC-1065	natural	1.1×10^{-5}	1.4×10^{-5}	0.6×10^{-5}	0.4×10^{-3}
synthetic (+)-CC-1065 [(+)-**1**]	natural	1.2×10^{-5}	1.8×10^{-5}	0.8×10^{-5}	0.2×10^{-3}
ent-(−)-CC-1065 [(−)-**1**]	enantiomeric	1.3×10^{-5}	1.3×10^{-5}	1.6×10^{-5}	0.3×10^{-3}
(1*S*)-*seco*-CC-1065 [(1*S*)-**40**]	natural	1.5×10^{-5}	11×10^{-5}	0.4×10^{-5}	0.4×10^{-3}
(1*R*)-*seco*-CC-1065 [(1*R*)-**40**]	enantiomeric	1.3×10^{-5}	11×10^{-5}	3.0×10^{-5}	0.5×10^{-3}
(±)-CPI-CDPI$_2$ [(±)-**2**]		1.2×10^{-5}	11×10^{-5}	1.0×10^{-5}	1.2×10^{-3}
(+)-CPI-CDPI$_2$ [(+)-**2**]	natural	1.2×10^{-5}	11×10^{-5}	1.0×10^{-5}	1.5×10^{-3}
(−)-CPI-CDPI$_2$ [(−)-**2**]	enantiomeric	1.3×10^{-5}	8.0×10^{-5}	0.4×10^{-5}	1.4×10^{-3}
(1*S*)-*seco*-CPI-CDPI$_2$[(1*S*)-**43**]	natural	1.8×10^{-5}	12×10^{-5}	0.6×10^{-5}	1.4×10^{-3}
(1*R*)-*seco*-CPI-CDPI$_2$ [(1*R*)-**43**]	enantiomeric	1.8×10^{-5}	12×10^{-5}	0.3×10^{-5}	1.3×10^{-3}

[a] The cell culture cytotoxicity assays were performed as described: Boger, D. L.; Yasuda, M.; Mitscher, L. A.; Drake, S. D.; Kitos, P. A.; Thompson, S. C. *J. Med. Chem.* **1987**, *30*, 1918. [b] IC_{50} = inhibitory concentration for 50% cell growth relative to untreated controls. [c] L1210 mouse lymphocytic leukemia cell culture. [d] B16 mouse melanoma cell culture. [e] P388 mouse leukemia cell culture. [f] Human epidermoid carcinoma of the nasopharynx.

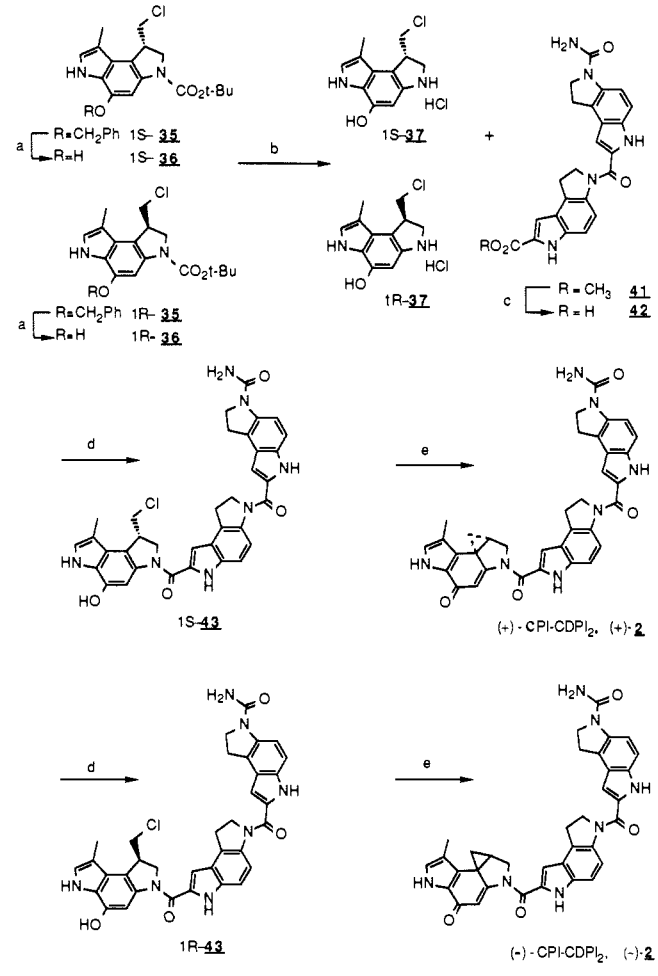
[(1*R**)-*seco*-CC-1065, (1*S*)-*seco*-CC-1065, and (1*R*)-*seco*-CC-1065], respectively. Final Ar-3′ spirocyclization (Wierenga–Kelly Winstein Ar-3′ alkylation) was effected by treatment of (1*R**)-**40**, (1*S*)-**40**, and (1*R*)-**40** with 1:1:1 $Et_3N/H_2O/CH_3CN$[40] (23 °C, 30 min) and afforded synthetic (±)-CC-1065 [(±)-**1**], (+)-CC-1065 [(+)-**1**, $[\alpha]^{23}_{578}$ +90° (*c* 0.065, DMF)], and synthetic *ent*-(−)-CC-1065 [(−)-**1**, $[\alpha]^{23}_{578}$ −92° (*c* 0.075, DMF)], respectively.[46] Synthetic (+)-CC-1065 proved identical in all comparable respects [SiO_2 TLC (20% DMF/toluene), $[\alpha]^{23}_{578}$, ^1H NMR (DMSO-d_6, 300 MHz), IR (KBr), and FABMS] with an authentic sample of (+)-CC-1065 isolated from natural sources.[41]

Total Synthesis of (±)-(3b*R,4a*S**)-CPI-CDPI$_2$, (+)-(3b*R*,4a*S*)-CPI-CDPI$_2$, and (−)-(3b*S*,4a*R*)-CPI-CDPI$_2$ [(±)-Deoxy-CC-1065, (+)-Deoxy-CC-1065, and (−)-Deoxy-CC-1065].**[25] CPI-CDPI$_2$ (deoxy-CC-1065, **2**), composed of the cyclopropa[*c*]pyrrolo[3,2-*e*]indol-4(5*H*)-one (CPI) left-hand segment of CC-1065 coupled to 3-carbamoyl-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-carboxylate dimer (CDPI dimer, **42**),[22] constitutes the agent anticipated[12] to possess the precise CC-1065 structural and functional features responsible for the initial high-affinity, noncovalent B-DNA minor groove association (binding) and the subsequent adenine N-3 covalent alkylation of DNA (bonding).

The preparation of (±)-CPI-CDPI$_2$, (+)-CPI-CDPI$_2$,[47] and (−)-CPI-CDPI$_2$ proceeded from indoline hydrochlorides (1*R**)-**37**, (1*S*)-**37**, and (1*R*)-**37** and CDPI dimer (**42**)[22] in a manner identical with that described for the preparation of (+)- and (−)-CC-1065 (Scheme VII). Thus, the direct coupling of indoline hydrochlorides (1*R**)-**37**, (1*S*)-**37**, and (1*R*)-**37** with CDPI dimer (**42**)[22] in the presence of EDCI (0.95 equiv of **42**, $NaHCO_3$, DMF, 23 °C, 24 h) afforded (1*R**)-**43**, (1*S*)-**43**, and (1*R*)-**43** [(1*R**)-*seco*-CPI-CDPI$_2$, (1*S*)-*seco*-CPI-CDPI$_2$, and (1*R*)-*seco*-CPI-CDPI$_2$], respectively. Final Ar-3′ spirocyclization was effected by treatment of (1*R**)-**43**, (1*S*)-**43**, and (1*R*)-**43** with 1:1:1 $Et_3N/H_2O/CH_3CN$[40] (23 °C, 4 h) and afforded (±)-CPI-CDPI$_2$ [(±)-**2**], (+)-CPI-CDPI$_2$ [(+)-**2**, $[\alpha]^{25}_{578}$ +65° (*c* 0.11, DMF)],[48] and (−)-CPI-CDPI$_2$ [(−)-**2**, $[\alpha]^{25}_{578}$ −74° (*c* 0.17 DMF)], respectively, in 50% overall yields from CDPI dimer (**42**).

In Vitro Cytotoxic Evaluation. The preliminary results of the comparative in vitro cytotoxic evaluation of (±)-CPI-CDPI$_2$, (+)-CPI-CDPI$_2$, and (−)-CPI-CDPI$_2$ with natural (+)-CC-1065,[41] synthetic (+)-CC-1065, synthetic (±)-CC-1065, and synthetic *ent*-(−)-CC-1065 are presented in Table I. Within the limits of experimental error, synthetic (+)-CC-1065, natural (+)-CC-1065, and (+)-CPI-CDPI$_2$ have proven indistinguishable from one another. In sharp contrast to the simplified functional analogues of CC-1065,[17-20] *ent*-(−)-CC-1065 and (−)-CPI-CDPI$_2$ likewise have proven indistinguishable from one another *and* comparable in cytotoxic potency to the natural (+) enantiomers. The seco agents, (1*S*)- and (1*R*)-*seco*-CC-1065 and (1*S*)- and (1*R*)-*seco*-CPI-CDPI$_2$, exhibited cytotoxic activity at comparable levels to (+)- and (−)-CC-1065 and (+)- and (−)-CPI-CDPI$_2$ and presumably suffer Ar-3′ alkylative ring closure in vitro.[49] The

Scheme VII[a]



[a] (a) 25% aqueous HCO_2NH_4/THF 1:4, 10% Pd/C, 23 °C, 30–45 min, 100%; (b) 3 N anhydrous HCl/EtOAc 23 °C, 30–45 min; (c) 5 equiv of LiOH, $THF/CH_3OH/H_2O$ (3:2:1), 50–55 °C, 10 h, 98%; (d) 0.95 equiv of **42**, 3 equiv of 1-((3-dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (EDCI), $NaHCO_3$, DMF, 23 °C, 20–24 h, 88%; (e) 1:1:1 $Et_3N/H_2O/CH_3CN$, 23 °C, 4 h, 77%, 50% for (+)-2 and (−)-2 from **42**.

(46) The $[\alpha]^{25}_D$ for natural (+)-, semisynthetic (+)-, and semisynthetic *ent*-(−)-CC-1065 have been reported to be +97°, +98°, and −96° (*c* 0.2, DMF),[40] respectively. In the present investigation, the $[\alpha]^{23}_{578}$ for natural (+)-CC-1065 was determined to be +93° (c 0.067, DMF).

(47) For an alternative approach to the total synthesis of (+)-CPI-CDPI$_2$, see: Warpehoski, M. A.; Bradford, V. S. *Tetrahedron Lett.* **1988**, *29*, 131. For preliminary studies, see: Warpehoski, M. A.; Bradford, V. S. *Tetrahedron Lett.* **1986**, *27*, 2735. Wierenga, W.; Griffin, J.; Warpehoski, M. A. *Tetrahedron Lett.* **1983**, *24*, 2437. See also: ref 19 and 20.

(48) This material was 93–94% enantiomerically pure as determined by HPLC analysis of the corresponding precursor (*R*)-(−)-*O*-acetylmandelate ester (1*S*,2′*R*)-**34**.

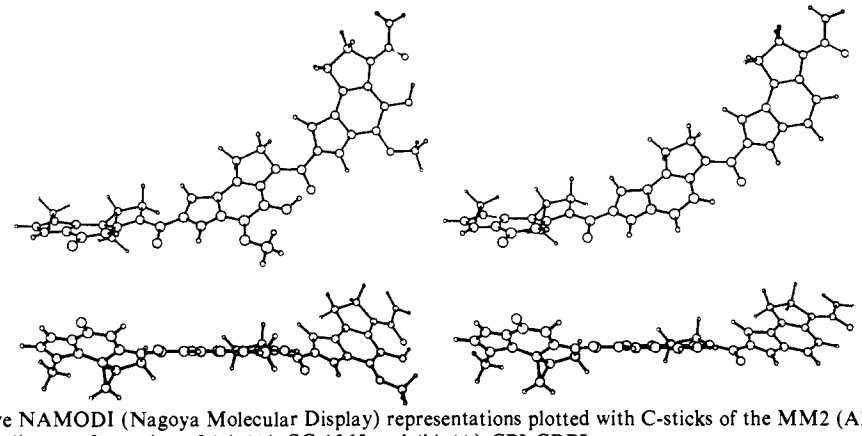


Figure 1. Two comparative NAMODI (Nagoya Molecular Display) representations plotted with C-sticks of the MM2 (Allinger, 1985; MacroModel, Version 1.1) low-energy helical conformation of (a) (+)-CC-1065 and (b) (+)-CPI-$CDPI_2$.

indistinguishable cytotoxic properties of (+)-CC-1065 and (+)-CPI-$CDPI_2$, the indistinguishable and unique cytotoxic activity of the enantiomeric agents *ent*-(−)-CC-1065 and (−)-CPI-$CDPI_2$, coupled with the report of the recognition of the (+)-CPI-$CDPI_2$ maintenance of the unusual delayed toxicity characteristic of (+)-CC-1065,[47] confirmed the expectation that CPI-$CDPI_2$ possesses the precise structural and functional features of CC-1065 that are responsible for B-DNA minor groove association and resultant expression of the potent cytostatic properties exhibited by the naturally occurring agent.

CC-1065 and the precise functional agent CPI-$CDPI_2$ constitute reactive alkylating agents superimposed on the CDPI trimer skeleton and derive their B-DNA associative properties through a common underlying mechanism: accessible hydrophobic binding-driven-bonding.[12,26] It is predominantly hydrophobic interactions of the concave face of the agents and their B-DNA minor groove complementary shape, Figure 1,[12] that permit (binding) the association with accessible AT-rich minor groove regions and promote (bonding) the irreversible, adenine N-3 covalent alkylation.

Experimental Section[50]

3-Methylidene-1-(phenylsulfonyl)indoline (15). A solution of **14** (105 mg, 0.30 mmol), tri-*n*-butyltin hydride (0.17 mL, 0.63 mmol, 2.1 equiv), and AIBN (ca. 3 mg, catalytic) in 30 mL of benzene was warmed at reflux under nitrogen for 12 h. The benzene was removed in vacuo, the residue was dissolved in 30 mL of ether, and the solution was stirred with 30 mL of saturated aqueous potassium fluoride[52] at 22 °C for 45 min. The mixture was diluted with 100 mL of ether, the aqueous layer was separated, and the organic layer was washed with water (50 mL) and saturated aqueous NaCl (50 mL) and was dried ($MgSO_4$). Removal of the solvent in vacuo and purification of the residue by flash chromatography (1 × 12 cm SiO_2, 0–10% Et_2O/hexane gradient elution) afforded **15** (58.6 mg, 81.1 mg theoretical, 72%) as a colorless oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 7.9–7.0 (m, 9 H, Ar H), 5.37 (t, 1 H, J = 2.7 Hz, *cis*-C=C*H*), 4.98 (t, 1 H, J = 2.6 Hz, *trans*-C=C*H*), 4.55 (t, 2 H, J = 2.8 Hz, NCH_2); EIMS, *m/e* (relative intensity) 271 (M^+, 12), 130 (base), 103 (11), 77 (47); CIMS (isobutane), *m/e* 272 (M^+ + H, base); HRMS, *m/e* 271.0666 ($C_{15}H_{13}NO_2S$ requires 271.0667).

1-(Phenylsulfonyl)-3-vinylindoline (19). A solution of **18** (168 mg, 0.354 mmol), tri-*n*-butyltin hydride (0.20 mL, 0.743 mmol, 2.1 equiv), and AIBN (ca. 5 mg, catalytic) in 35 mL of benzene was warmed at reflux under nitrogen for 3 h. The benzene was removed in vacuo, and the residue was dissolved in 20 mL of acetonitrile. The acetonitrile solution was extracted with hexane[53] (4 × 10 mL), and the acetonitrile layer was concentrated in vacuo. The residue was purified by flash chromatography (5 × 150 mm SiO_2, 10% Et_2O/hexane eluant) to afford **19** (83.1 mg, 101.0 mg theoretical, 82%) as a white, crystalline solid: mp 101–103 °C (CH_2Cl_2/hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.85–6.95 (m, 9 H, Ar H), 5.50 (ddd, 1 H, J = 17.0, 10.0, 8.2 Hz, C*H*=CH_2), 5.05 (dm, 1 H, J = 17.0 Hz, *cis*-CH=C*H*H), 5.04 (dm, 1 H, J = 10.0 Hz, *trans*-CH=CH*H*), 4.16 (dd, 1 H, J = 10.5, 9.1 Hz), 3.73 (dd, 1 H, J = 16.8, 8.2 Hz), 3.60 (dd, 1 H, J = 10.5, 7.7 Hz); IR (KBr) ν_{max} 3059, 3006, 2867, 1643, 1598, 1475, 1465, 1461, 1347, 1310, 1289, 1233, 1166, 1103, 1090, 1065, 1027, 997, 988, 926, 763, 755, 740 cm^{-1}; EIMS, *m/e* (relative intensity) 285 (8), 144 (base), 117 (20), 116 (23), 115 (36); CIMS (isobutane), *m/e* 286 (M^+ + H, base); HRMS, *m/e* 285.0826 ($C_{16}H_{15}NO_2S$ requires 285.0823).

3-(Hydroxymethyl)-1-(phenylsulfonyl)indoline (16). Method A. A solution of **15** (53.0 mg, 0.195 mmol) in 0.65 mL of tetrahydrofuran was cooled to 0 °C under nitrogen and was treated with neat borane methyl sulfide[54] (7.2 μL, 72 μmol, 1.1 equiv). The reaction mixture was allowed to warm to 22 °C and was stirred 2.5 h (22 °C). The reaction mixture was cooled to 0 °C and was treated sequentially with water (0.5 mL), 2 N aqueous sodium hydroxide (0.13 mL, 0.26 mmol), and 30% aqueous hydrogen peroxide (25 μL, 0.25 mmol). The reaction mixture was allowed to warm to 22 °C and was stirred 12 h (22 °C) before it was diluted with 5 mL of water and extracted with EtOAc (30 mL). The organic extract was washed with saturated aqueous NaCl (10 mL) and dried ($MgSO_4$) and the solvent was removed in vacuo. Flash chromatography (1 × 15 cm SiO_2, 30–100% Et_2O/hexane gradient elution) afforded **16** (34.1 mg, 56.4 mg theoretical, 60%) as a colorless oil.

Method B. A solution of 3-vinylindoline **19** (65 mg, 0.23 mmol) in 2.0 mL of methanol was cooled to 0 °C and was treated with a stream of 3–8% ozone in oxygen (300 mL/min, 20 min). The reaction mixture was stirred for an additional 20 min (0 °C) before the excess ozone was removed by passing a stream of nitrogen through the reaction mixture (10 min). Fifty percent aqueous ethanol (1.0 mL) was added at 0 °C followed by the *careful* addition of excess sodium borohydride (20 mg, 2.1 mmol, 10 equiv). The reaction mixture was allowed to warm to 23 °C and was stirred 1 h (23 °C). The reaction mixture was poured onto 10 mL of 10% aqueous hydrochloric acid and was extracted with EtOAc (30 mL). The organic extract was washed with saturated aqueous $NaHCO_3$ (10 mL), water (10 mL), and saturated aqueous NaCl (10 mL) and was dried ($MgSO_4$). Removal of the solvent in vacuo and flash chromatography (1 × 15 cm SiO_2, 30–100% Et_2O/hexane gradient elution) afforded **16** (38.6 mg, 66.0 mg theoretical, 59%).

Method C. A solution of 3-vinylindoline **19** (34.2 mg, 0.12 mmol) in 1.2 mL of acetone/water (3:1) was cooled to 0 °C and was treated sequentially with a solution of osmium tetraoxide (30 μL, 2% solution in acetone, 2.4 μmol, 2 mol %) and sodium periodate (78 mg, 0.36 mmol, 3 equiv).[34] The reaction mixture was allowed to warm to 23 °C and was stirred for 4 h (23 °C). The reaction mixture was diluted with 10 mL of water and was extracted with EtOAc (30 mL). The organic extract was dried ($MgSO_4$) and evaporated in vacuo to afford the crude aldehyde **20**. A solution of the aldehyde **20** in 1 mL of ethanol was treated directly with sodium borohydride (5 mg, 0.13 mmol, 4.4 equiv) at 0 °C (30 min).

(49) The comparable cytotoxic activity of 1-(chloromethyl)-*seco*-CPI versus CPI-derived agents has been previously disclosed: Kelly, R. C., 21st Great Lakes Regional ACS Meeting, June, 1987. See also: Kelly, R. C.; Warpehoski, M. A.; Wierenga, W. U.S. patent 581 836 21; *Chem. Abstr.* **1986**, **104**, 148641*w*.

(50) Flash chromatography[59] was performed on 230–400 mesh silica gel. Ozone in oxygen was generated with a Welsbach T-23 Ozonator. (*R*)-(−)-*O*-Acetylmandelic acid, lead tetraacetate, tri-*n*-butyltin hydride, borane methylsufide, sodium bis(2-methoxyethoxy)aluminum hydride, 3-bromopropyne, and 1-[3-(dimethylamino)-3-propyl]-3-ethylcarbodiimide hydrochloride (EDCI) were purchased from Aldrich Chemical Co. 2-Amino-5-nitrophenol was purchased from Pfaltz and Bauer, Inc.

(51) Opitz, G.; Hellman, H.; Schubert, H. W. *Justus Liebigs Ann. Chem.* **1959**, *623*, 112.

(52) Leibner, J. E.; Jacobus, J. *J. Org. Chem.* **1979**, *44*, 449.

(53) Berge, J. M.; Roberts, S. M. *Synthesis* **1979**, 471.

(54) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis via Boranes*; Wiley-Interscience: New York, 1975.

The reaction mixture was poured onto 10 mL of 10% aqueous hydrochloric acid and was extracted with EtOAc (30 mL). The organic extract was washed with saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous NaCl (10 mL) and was dried ($MgSO_4$). Removal of the solvent in vacuo and flash chromatography (1 × 15 cm SiO_2, 30–100% Et_2O/hexane gradient elution) afforded **16** (23.2 mg, 34.7 mg theoretical, 67%): ^1H NMR ($CDCl_3$, 200 MHz) δ 8.0–7.0 (m, 9 H, Ar H), 4.07 (dd, 1 H, J = 11, 9 Hz, C2-H), 3.94 (dd, 1 H, J = 11, 5 Hz, C2-H), 3.7–3.3 (m, 3 H, C3-H and CH_2OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.1 (s), 136.7 (s), 133.3 (d), 131.7 (s), 129.0 (2d), 128.6 (d), 127.2 (2 d), 124.9 (d), 123.8 (d), 114.8 (d), 64.6 (t), 52.7 (t), 42.5 (q); IR (neat) ν_{max} 3538, 3065, 2940, 2878, 2600, 1478, 1460, 1446, 1354, 1246, 1168, 1110, 1091, 1029, 991, 754, 712, 689 cm^{-1}; EIMS, m/e (relative intensity) 289 (6), 258 (11), 141 (20), 130 (20), 118 (34), 117 (27), 91 (19), 77 (base); ClMS (isobutane), m/e 290 (M^+ + H, base); HRMS, m/e 289.0774 ($C_{15}H_{15}NO_3S$ requires 289.0773).

N-[4-(Benzoylimino)-3-(benzyloxy)-2,5-cyclohexadien-1-ylidene]benzenesulfonamide (11). A slurry of **9** (2.0 g, 4.4 mmol) in 40 mL of dry benzene at 22 °C was treated with lead tetraacetate (2.08 g, 4.7 mmol, 1.07 equiv), and the reaction mixture was stirred for 8 h (22 °C). The reaction mixture was filtered through Celite (CH_2Cl_2 wash), and the filtrate was concentrated in vacuo. Flash chromatography (2 × 20 cm SiO_2, CH_2Cl_2/Et_2O/hexane, 2:1:7 to 2:2:6, gradient elution) afforded **11** (1.68 g, 2.0 g theoretical, 84%; typically 82–84%, 4–11-mmol scale) as a bright yellow, crystalline solid: mp 158–159.5 °C dec (CH_2Cl_2/hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.1–7.2 (m, 15 H, Ar H), 7.11 (m, 1 H, C3-H), 6.94 (d, 1 H, J = 10 Hz, C6-H), 6.74 (dd, 1 H, J = 10, 2 Hz, C5-H), 5.01 (s, 2 H, PhCH_2O); IR (KBr) ν_{max} 3062, 1666, 1606, 1576, 1533, 1446, 1307, 1261, 1221, 1176, 1150, 1134, 1089, 1061, 1022, 1001, 859, 839, 815, 802, 757, 756, 730, 711, 699, 686, 623, 613 cm^{-1}; EIMS, m/e (relative intensity) 458 (M^+ + 2 H, 2), 317 (3), 212 (3), 105 (base), 91 (90), 77 (44); CIMS (isobutane), m/e (relative intensity) 459 (M^+ + 3 H, 34), 369 (3), 319 (19), 318 (12), 251 (10), 215 (5), 158 (9), 143 (71), 123 (36), 107 (base), 91 (75). Anal. Calcd for $C_{26}H_{20}N_2O_4S$: C, 68.41; H, 4.42; N, 6.14. Found: C, 68.21; H, 4.49; N, 6.12.

5-Amino-1-benzoyl-7-(benzyloxy)-3-methyl-N^5-(phenylsulfonyl)indole (21). A solution of **11** (0.99 g, 2.17 mmol) in 30 mL of dry methylene chloride was cooled to 0 °C under nitrogen, and 1-piperidino-1-propene[51] (0.33 mL, 2.23 mmol, 1.02 equiv) was added in one portion. The reaction mixture was allowed to warm to 23 °C and was stirred for 10 h (23 °C). The solvent was removed in vacuo, and the residue was dissolved in 20 mL of tetrahydrofuran. The solution was treated with 4 mL of 10% aqueous hydrochloric acid, and the reaction mixture was stirred for 20 h (23 °C). The reaction mixture was poured onto saturated aqueous $NaHCO_3$ (75 mL) and extracted with EtOAc (200 mL). The organic extract was washed with saturated aqueous NaCl (50 mL), dried ($MgSO_4$), and concentrated in vacuo. Chromatography (65 g of Al_2O_3, activity grade III, 20–50% EtOAc/hexane gradient elution) afforded **21** (0.315 g, 1.08 g theoretical, 29%; typically 22–33%, 1–2-mmol scale) as a white, crystalline solid: mp 189–190.5 °C (CH_2Cl_2); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.8–7.2 (m, 15 H, Ar H), 7.12 (d, 1 H, J = 1.2 Hz, C2-H), 6.77 (d, 1 H, J = 1.8 Hz, C6-H), 6.70 (br s, 1 H, NH), 6.60 (d, 1 H, J = 1.8 Hz, C4-H), 4.87 (s, 2 H, PhCH_2O), 2.14 (d, 3 H, J = 1.2 Hz, Ar CH_3); IR (KBr) ν_{max} 3285, 1699, 1616, 1600, 1580, 1499, 1448, 1356, 1340, 1276, 1240, 1157, 1147, 1089, 1002, 835, 755, 720, 687, 668 cm^{-1}; EIMS, m/e (relative intensity) 496 (M^+, 2), 355 (6), 249 (1), 169 (3), 141 (1), 125 (1), 105 (base), 91 (48), 77 (40); CIMS (isobutane), m/e 497 (M^+ + H, base); HRMS, m/e 496.1452 ($C_{29}H_{24}N_2O_4S$ requires 496.1457).

5-Amino-1-benzoyl-7-(benzyloxy)-4-bromo-3-methyl-N^5-(phenylsulfonyl)indole (22). A solution of **21** (0.77 g, 1.55 mmol) in 15 mL of tetrahydrofuran under nitrogen was cooled to −23 °C and treated with concentrated sulfuric acid (1 drop) and *N*-bromosuccinimide (277 mg, 1.55 mmol, 1.0 equiv). The reaction mixture was stirred for 1 h (−23 °C) and then treated with solid sodium bicarbonate (ca. 20 mg) and saturated aqueous sodium thiosulfate (4 mL). The reaction mixture was poured onto 50 mL of water and extracted with EtOAc (200 mL). The organic layer was washed with water (50 mL) and saturated aqueous NaCl (50 mL) and was dried ($MgSO_4$). Removal of the solvent in vacuo afforded crude **22** (0.86 g, 0.87 g theoretical 99%; typically 96–99%, 1.5–2.0-mmol scale) as a light brown, crystalline solid, which was used directly in the next reaction. An analytical sample of **22** was purified by flash chromatography (SiO_2, 50–75% CH_2Cl_2/hexane gradient elution) and afforded pure **22** as a white, crystalline solid: mp 146.5–147.5 °C (EtOAc/hexane); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.8–7.2 (m, 15 H, Ar H), 7.11 (d, 1 H, J = 1.1 Hz, C2-H), 7.01 (s, 1 H, C6-H), 5.01 (s, 2 H, PhCH_2O), 2.35 (d, 3 H, J = 1.1 Hz, ArCH_3); IR (KBr) ν_{max} 3319, 1698, 1600, 1573, 1481, 1448, 1394, 1373, 1351, 1326, 1277, 1243, 1201, 1165, 1102, 1090, 988, 935, 892, 718, 703 cm^{-1}; EIMS, m/e (relative intensity) 574/576 (M^+, 3/3), 433/435 (2/2), 193/195 (1/1), 179/181 (1/1), 163/165 (2/2), 151/153 (2/2), 137/139 (2/2), 125 (6), 111 (12), 105 (base), 97 (21), 91 (40), 83 (21), 77 (39), 71 (27), 69 (27); CIMS (isobutane), m/e 575/577 (M^+ + H, 1/1, base); HRMS, m/e 574.0548 ($C_{29}H_{23}N_2O_4SBr$ requires 574.0562). Anal. Calcd for $C_{29}H_{23}N_2O_4SBr$: C, 60.53; H, 4.03; N, 4.87. Found: C, 60.79; H, 3.90; N, 4.56.

1-Benzoyl-7-(benzyloxy)-4-bromo-3-methyl-N^5-(phenylsulfonyl)-5-(2-propyn-1-ylamino)indole (23). A solution of crude **22** (0.86 g, 1.49 mmol) in 8 mL of dry *N*,*N*-dimethylformamide at 25 °C under argon was treated with sodium hydride (70 mg, 60% oil dispersion 1.77 mmol, 1.15 equiv). The reaction mixture was stirred for 30 min (25 °C) before 3-bromopropyne (0.5 mL, 80% in toluene, 4.5 mmol, 3 equiv) was added. The reaction mixture was stirred for 1 h (25 °C) and then was poured onto 100 mL of water. The mixture was extracted with EtOAc (200 mL), and the organic extract was washed with water (50 mL) and saturated aqueous NaCl (50 mL) and dried ($MgSO_4$). Removal of the solvent in vacuo and purification of the residue by flash chromatography (2 × 20 cm SiO_2, 50–75% CH_2Cl_2/hexane gradient elution) afforded **23** (0.76 g, 0.91 g theoretical, 82% from **21**; typically 77–82%, 1.0–1.7-mmol scale) as a light yellow, crystalline solid: mp 144–144.5 °C (Et_2O); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.95–7.05 (m, 16 H, Ar H), 6.46 (s, 1 H, C6-H), 4.86 and 4.09 (2 dd, 1 H each, J = 18.4, 2.4 Hz, NCH_2), 4.80 and 4.62 (2 d, 1 H each, J = 12.5 Hz, PhC*H*HO and PhCH*H*O), 2.48 (d, J = 1.2 Hz, Ar CH_3), 1.77 (t, 1 H, J = 2.4 Hz, C≡C*H*): IR (KBr) ν_{max} 3289, 2120, 1706, 1599, 1569, 1462, 1447, 1393, 1355, 1274, 1241, 1201, 1164, 1093, 1023, 1000, 906, 791, 753, 717 cm^{-1}; EIMS, m/e (relative intensity) 612/614 (M^+, 1/1), 533 (2), 471/473 (1/1), 392 (2), 380/382 (1/1), 363 (1), 353 (1), 315 (1), 301 (1), 105 (base), 91 (15), 77 (33); CIMS (isobutane), m/e 613/615 (M^+ + H, 1/1 base); HRMS, m/e 613.0774 ($C_{32}H_{25}N_2O_4SBr$ requires 613.0797). Anal. Calcd for $C_{32}H_{25}N_2O_4SBr$: C, 62.65; H, 4.11; N, 4.57. Found: 62.52; H, 4.02; N, 4.52.

6-Benzoyl-5-(benzyloxy)-1,2-dihydro-8-methyl-1-methylidene-3-(phenylsulfonyl)-3*H*-pyrrolo[3,2-*e*]indole (24). A solution of **23** (302 mg, 0.49 mmol) in 33 mL of dry benzene at 23 °C under nitrogen was treated with tri-*n*-butyltin hydride (0.28 mL, 1.04 mmol, 2.1 equiv) and AIBN (10 mg, catalytic), and the reaction mixture was warmed at reflux under nitrogen for 4 h. The reaction mixture was cooled, and the solvent was removed in vacuo. The residue was dissolved in 50 mL of acetonitrile, and the solution was extracted with hexane[53] (3 × 20 mL). The acetonitrile layer was concentrated in vacuo to afford crude **24** as a yellow foam, which was used directly in the next reaction: ^1H NMR ($CDCl_3$, 200 MHz) δ 7.9–7.2 (m, 16 H, Ar H), 7.12 (d, 1 H, J = 1 Hz, C7-H), 5.52 (t, 1 H, J = 2.4 Hz, *cis*-C=C*H*), 5.07 (s, 2 H, PhCH_2O), 4.94 (t, 1 H, J = 2.4 Hz, *trans*-C=C*H*), 4.50 (t, 2 H, J = 2.4 Hz, C2-H), 2.38 (d, 3 H, J = 1 Hz, Ar CH_3); EIMS, m/e (relative intensity) 534 (M^+, 4), 443 (5), 394 (1), 303 (1), 273 (1), 225 (1), 169 (1), 122 (2), 105 (base), 91 (36), 77 (57); CIMS (isobutane), m/e 535 (M^+ + H, base).

6-Benzoyl-5-(benzyloxy)-1,2-dihydro-1-(hydroxymethyl)-8-methyl-3-(phenylsulfonyl)-3*H*-pyrrolo[3,2-*e*]indole (25). A solution of crude **24** (from 0.49 mmol of **23**) in 2.0 mL of tetrahydrofuran under argon was cooled to 0 °C and treated with borane methyl sulfide (0.1 mL, 1.0 mmol, 6 equiv).[54] The reaction mixture was allowed to warm to 25 °C and was stirred for 3 h (25 °C). The reaction mixture was cooled to 0 °C and was treated sequentially with water (0.5 mL), 2 N aqueous sodium hydroxide (0.5 mL, 1 mmol), and 30% aqueous hydrogen peroxide (0.3 mL, 3 mmol). The reaction mixture was allowed to warm to room temperature and then was warmed at 45 °C for 30 min. The reaction mixture was cooled to room temperature and was poured onto 30 mL of saturated aqueous NaCl. The mixture was extracted with EtOAc (3 × 30 mL), the combined organic extracts were dried ($MgSO_4$), and the solvent was removed in vacuo. Flash chromatography (1 × 20 cm SiO_2, 0–10% EtOAc/CH_2Cl_2 gradient elution) afforded **25** (108 mg, 271 mg theoretical, 40% from **23**; typically 37–40% from **23**, 0.3–0.5-mmol scale) as a colorless oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 7.9–7.3 (m, 16 H, Ar H), 7.07 (d, 1 H, J = 1 Hz, C7-H), 5.13 (s, 2 H, PhCH_2O), 4.22 (dd, 2 H, J = 11, 1 Hz, C2-H), 3.86–3.50 (m, 3 H, C1-H and CH_2OH), 3.02 (br t, 1 H, J = 10 Hz, CH_2OH), 2.24 (d, 3 H, J = 1 Hz, Ar CH_3); IR (KBr) ν_{max} 3437, 1696, 1685, 1602, 1490, 1448, 1403, 1354, 1277, 1237, 1209, 1167, 1092, 1037, 903, 834, 720 cm^{-1}; EIMS, m/e (relative intensity) 552 (M^+, 3), 521 (2), 431 (1), 411 (4), 381 (1), 290 (1), 275 (1), 185 (2), 105 (base); CIMS (isobutane), m/e 553 (M^+ + H, base); HRMS, m/e 552.1705 ($C_{32}H_{28}N_2O_5S$ requires 552.1719).

1-Benzoyl-7-(benzyloxy)-4-bromo-3-methyl-N^5-(phenylsulfonyl)-5-[(4-(phenylthio)-2-buten-1-yl)amino]indole (26). A solution of crude **22** (867 mg, 1.51 mmol) in 15 mL of *N*,*N*-dimethylformamide at 24 °C under nitrogen was treated with sodium hydride (65 mg, 60% oil dispersion, 1.6 mmol, 1.07 equiv). The reaction mixture was stirred 10 min (24 °C) before a solution of **17** (520 mg, 2.14 mmol, 1.4 equiv) in 2 mL of *N*,*N*-dimethylformamide was added. The reaction mixture was stirred 16 h (24 °C) and then was poured onto 75 mL of water. The mixture

was extracted with EtOAc (200 mL), and the organic layer was washed with water (75 mL) and saturated aqueous NaCl (50 mL) and was dried ($MgSO_4$). The solvent was removed in vacuo, and the residue was purified by flash chromatography (2 × 20 cm SiO_2, 60–80% CH_2Cl_2/hexane gradient elution) to afford **26** (770 mg, 1.14 g theor., 70% overall from **21**; typically 70–74% from **21**, 0.1–1.5-mmol scale) as a yellow foam: ^1H NMR ($CDCl_3$, 200 MHz) δ 7.9–7.1 (m, 21 H, Ar H), 6.23 (s, 1 H, C7-H), 5.52 (dt, 1 H, J = 15.3, 6.4 Hz, C=C*H*CH_2SPh), 5.32 (dt, 1 H, J = 15.3, 6.7 Hz, C=C*H*CH_2N), 4.79 and 4.63 (2 d, 1 H each, J = 12.5 Hz, PhC*H*HO and PhCH*H*O), 4.14 and 3.99 (2 dd, 1 H each, J = 14.5, 7.0 Hz, NC*H*HC=C and NCH*H*C=C), 3.30 (d, 2 H, J = 6.4 Hz, PhSCH_2C=C), 2.47 (d, 3 H, J = 1.2 Hz, Ar CH_3); IR (KBr) ν_{max} 3061, 2925, 1706, 1598, 1569, 1447, 1393, 1350, 1273, 1242, 1199, 1165, 1090, 1024, 1000, 966, 909, 787, 741, 717, 690, 667 cm^{-1}; CIMS (isobutane), m/e (relative intensity) 737/739 (M^+ + H, 55/44), 629 (22), 549 (base); CIHRMS, m/e 737.1101 ($C_{39}H_{33}N_2O_4S_2Br$ requires 737.1143).

6-Benzoyl-5-(benzyloxy)-1,2-dihydro-8-methyl-3-(phenylsulfonyl)-1-vinyl-3*H*-pyrrolo[3,2-*e*]indole (27). A solution of **26** (300 mg, 0.407 mmol) in 27 mL of benzene at 23 °C under nitrogen was treated with tri-*n*-butyltin hydride (0.225 mL, 0.836 mmol, 2.05 equiv) and AIBN (5 mg, catalytic), and the reaction mixture was warmed at reflux under nitrogen for 2.5 h.[33] The reaction mixture was cooled to room temperature, and the solvent was removed in vacuo. The residue was dissolved in 20 mL of acetonitrile, and the solution was extracted with hexane[53] (3 × 15 mL). The acetonitrile layer was concentrated in vacuo and the residue was purified by flash chromatography (1 × 17 cm SiO_2, 5–10% Et_2O/hexane gradient elution) to afford **27** (212 mg, 223 mg theoretical, 95%; typically 79–95%, 0.1–0.4-mmol scale) as a yellow semisolid: ^1H NMR ($CDCl_3$, 470 MHz) δ 7.8–7.2 (m, 16 H, Ar H), 7.04 (d, 1 H, J = 1 Hz, C7-H), 5.50 (ddd, 1 H, J = 17.1, 10.2, 6 Hz, C*H*=CH_2), 5.17 (d, 1 H, J = 12.8 Hz, PhC*H*HO), 5.12 (d, 1 H, J = 12.8 Hz, PhCH*H*O), 4.76 (d, 1 H, J = 10.2 Hz, *trans*-CH=CH*H*), 4.60 (d, 1 H, J = 17.1 Hz, *cis*-CH=CH*H*), 4.05–3.90 (m, 3 H, C1-H and C2-H), 2.20 (d, 3 H, J = 1 Hz, Ar CH_3); IR (KBr) ν_{max} 1706, 1616, 1490, 1456, 1447, 1401, 1354, 1325, 1276, 1234, 1168, 1158, 1092, 1014, 920, 902, 737, 719, 712, 691, 667 cm^{-1}; EIMS, m/e (relative intensity) 548 (M^+, 6), 407 (20), 105 (base), 91 (30), 77 (38); CIMS (isobutane), m/e 549 (M^+ + H, base); HRMS, m/e 548.1762 ($C_{33}H_{28}N_2O_4S$ requires 548.1770).

5-(Benzyloxy)-1,2-dihydro-1-(hydroxymethyl)-8-methyl-3-(phenylsulfonyl)-3*H*-pyrrolo[3,2-*e*]indole (30). A slurry of **25** (113 mg, 0.204 mmol) in 2.5 mL of dry methanol was cooled to 0 °C under nitrogen, and acetyl chloride (0.25 mL, 3.5 mmol) was added dropwise (2–3 min, *caution*: exothermic reaction) with stirring. The reaction mixture was warmed at 50 °C for 2 h. The solvent was removed in vacuo, and the residue was dissolved in methylene chloride and treated with solid $NaHCO_3$ (10 mg). Flash chromatography (1 × 15 cm SiO_2, 0–10% EtOAc/CH_2Cl_2 gradient elution) afforded **30** (76 mg, 91.5 mg theoretical, 83%; typically 83–86%, 0.2–0.5-mmol scale) as a light green-brown, crystalline solid: mp 184–185 °C (CH_2Cl_2/hexane); ^1H NMR ($CDCl_3$, 200 MHz) δ 8.23 (br s, 1 H, NH), 7.7–7.2 (m, 11 H, Ar H), 6.91 (d, 1 H, J = 1 Hz, C7-H), 5.30 (s, 2 H, PhCH_2O), 4.19 (dd, 2 H, J = 11, 1 Hz, C2-H), 3.85 (dd, 2 H, J = 11, 9 Hz, CH_2OH), 3.60 (m, 1 H, C1-H), 2.80 (br t, 1 H, J = 9 Hz, OH), 2.28 (d, 3 H, J = 1 Hz, Ar CH_3); IR (KBr) ν_{max} 3420, 1584, 1498, 1445, 1347, 1308, 1164, 1090, 1024, 821, 736, 720, 690, 607 cm^{-1}; EIMS, m/e (relative intensity) 448 (M^+, 17), 417 (15), 307 (37), 276 (7), 277 (7), 186 (32), 185 (22), 157 (7), 91 (base); CIMS (isobutane), m/e 449 (M^+ + H, base); HRMS, m/e 448.1452 ($C_{25}H_{24}N_2O_4S$ requires 448.1457).

1,2-Dihydro-5-hydroxy-1-(hydroxymethyl)-8-methyl-3-(phenylsulfonyl)-3*H*-pyrrolo[3,2-*e*]indole (31). A solution of **30** (8.0 mg, 17.8 μmol) in 0.5 mL of EtOAc at 23 °C was treated with 10% palladium/carbon (5 mg), and the reaction mixture was placed under hydrogen (1 atm). The reaction mixture was stirred for 20 h (23 °C), and the catalyst was removed by filtration of the reaction mixture through Celite. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography (0.5 × 15 cm SiO_2, 10–20% EtOAc/CH_2Cl_2 gradient elution) to afford **31** (5.4 mg, 6.4 mg theoretical, 85%) as a colorless oil: ^1H NMR (acetone-d_6, 200 MHz) δ 9.90 (br s, 1 H, NH), 8.69 (s, 1 H, OH), 7.95–7.50 (m, 5 H, $PhSO_2$), 7.22 (s, 1 H, C4-H), 7.06 (d, 1 H, J = 1 Hz, C7-H), 4.34 (dd, 2 H, J = 11, 1 Hz, C2-H), 4.05–3.50 (m, 3 H, C1-H, and CH_2OH), 2.35 (d, 3 H, J = 1 Hz, Ar CH_3); IR (KBr) ν_{max} 3406, 2934, 1587, 1497, 1446, 1375, 1347, 1162, 1089, 1039, 837, 753, 721 cm^{-1}; EIMS, m/e (relative intensity) 358 (M^+, 15), 327 (24), 217 (36), 199 (17), 186 (63), 77 (base); CIMS (isobutane), m/e (relative intensity) 359 (M^+ + H, 5), 250 (13), 235 (5), 219 (24), 218 (17), 201 (6), 187 (7), 143 (base).

1,2,8,8a-Tetrahydro-7-methyl-2-(phenylsulfonyl)cyclopropa[*c*]-pyrrolo[3,2-*e*]indol-4(5*H*)-one (N^2-(phenylsulfonyl)-CPI, 3). A solution of **31** (4.1 mg, 11.4 μmol) and triphenylphosphine (3.6 mg, 13.7 μmol, 1.2 equiv) in 0.2 mL of tetrahydrofuran at 23 °C was treated with diethyl azodicarboxylate (2.1 μL, 13.7 μmol, 1.2 equiv), and the reaction mixture was stirred for 8 h (23 °C). The solvent was removed in vacuo, and the residue was purified by flash chromatography (5 × 12 mm SiO_2 pretreated with 10% Et_3N/CH_2Cl_2, $CH_2Cl_2/Et_2O/CHCl_3$, 3:1:1, eluant) to afford **3** (1.9 mg, 3.9 mg theor., 49%) as a light brown solid: ^1H NMR ($CDCl_3$, 200 MHz) δ 9.4 (br s, 1 H, NH), 7.92 (dd, 2 H, J = 8, 1 Hz, C2-H and C6-H $PhSO_2$), 7.7–7.5 (m, 3 H, $PhSO_2$), 6.77 (dd, 1 H, J = 2, 0.5 Hz, C6-H), 6.57 (s, 1 H, C3-H), 4.16 (d, 1 H, J = 10.1 Hz, C1-H), 3.99 (dd, 1 H, J = 10.1, 4.7 Hz, C1-H), 2.83 (m, 1 H, C9-H), 1.95 (s, 3 H, Ar CH_3), 1.78 (dd, 1 H, J = 7.5, 4.7 Hz, C8-H), 0.95 (apparent t, 1 H, J = 4.7 Hz, C8-H); IR (KBr) ν_{max} 3429, 3198, 1616, 1554, 1476, 1447, 1413, 1359, 1164, 1090, 1034, 1005, 913, 852, 799, 758, 724, 683, 626 cm^{-1}; EIMS, m/e (relative intensity) 340 (M^+, 18), 326 (8), 310 (7), 281 (5), 275 (19), 248 (18), 233 (8), 199 (base); CIMS (isobutane), m/e (relative intensity) 341 (M^+ + H, 56), 279 (92), 201 (base), 143 (95); CIHRMS, m/e 341.0960 ($C_{18}H_{16}N_2O_3S$ + H requires 341.0959).

(±)-(1*R)-, (+)-(1*R*)-, and (−)-(1*S*)-5-(Benzyloxy)-3-[(*tert*-butyloxy)carbonyl]-1-(hydroxymethyl)-8-methyl-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole [(±)-(1*R**)-33, (+)-(1*R*)-33, and (−)-(1*S*)-33].** A stirred slurry of **30** (38.5 mg, 85.8 μmol) in 0.7 mL of toluene at 23 °C under argon was treated with a solution of sodium bis(2-methoxyethoxy)aluminum hydride (0.15 mL of 3.4 M in toluene, 0.51 mmol, 6 equiv), and the reaction mixture was warmed at 100 °C (bath temperature) under argon for 3 h.[40,42] The reaction mixture was cooled to 0 °C and the excess bis(2-methoxyethoxy)aluminum hydride was quenched by the careful addition of ice. The mixture was diluted with nitrogen-saturated water (5 mL), and solid $NaHCO_3$ was added to pH 8–9. The mixture was extracted with nitrogen-saturated EtOAc (4 × 5 mL) under nitrogen, and the organic extracts were dried (Na_2SO_4) under nitrogen.[40] The solvent was removed in vacuo to afford crude, unstable **32** as a yellow oil. The crude oil was dissolved immediately in 0.8 mL of tetrahydrofuran at 23 °C under nitrogen, and the solution was treated with di-*tert*-butyl dicarbonate (59 μL, 0.26 mmol, 3 equiv) and was stirred for 20 h (23 °C). The solvent was removed in vacuo, and the residue was purified by flash chromatography (1 × 12 cm SiO_2, 0–10% EtOAc/CH_2Cl_2 gradient elution) to afford **33** (21.0 mg, 35.0 mg theoretical, 60%; typically 52–60%, 0.1–0.18-mmol scale) as a light brown oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 8.10 (br s, 1 H, NH), 7.72 (br s, 1 H, C4-H), 7.5–7.35 (m, 5 H, *Ph*CH_2O), 6.92 (s, 1 H, C7-H), 5.21 (s, 2 H, PhCH_2O), 4.3–3.6 (m, 5 H, C1-H, C2-H, CH_2OH), 2.41 (s, 3 H, Ar CH_3), 1.58 (s, 9 H, CO_2-*t*-Bu); IR (neat) ν_{max} 3428, 3334, 2928, 1684, 1588, 1503, 1453, 1419, 1405, 1367, 1345, 1320, 1242, 1171, 1141, 1029, 896 cm^{-1}; EIMS, m/e (relative intensity) 408 (M^+, 24), 352 (28), 321 (75), 231 (44), 187 (20), 186 (15), 91 (base), 57 (58); CIMS (isobutane), m/e (relative intensity) 409 (M^+ + H, 37), 308 (31), 391 (6), 353 (base), 309 (11); HRMS, m/e 408.2052 ($C_{24}H_{28}N_2O_4$ requires 408.2049). (1*R*)-**33**:[55,56] $[\alpha]^{23}_D$ +7.0° (*c* 0.63, CH_2Cl_2); $[\alpha]^{23}_{578}$ +8.1° (*c* 0.63, CH_2Cl_2). (1*S*)-**33**:[55,57] $[\alpha]^{23}_D$ −7.1° (*c* 0.74, CH_2Cl_2), 95% optically pure; calcd $[\alpha]^{23}_D$ −7.5° (*c* 0.74, CH_2Cl_2); $[\alpha]^{23}_{578}$ −8.3° (*c* 0.74, CH_2Cl_2), 95% optically pure; calcd $[\alpha]^{23}_{578}$ −8.7° (*c* 0.74, CH_2Cl_2).

(±)-(1*R)-, (+)-(1*R*)-, and (−)-(1*S*)-5-(Benzyloxy)-3-[(*tert*-butyloxy)carbonyl]-1-(chloromethyl)-8-methyl-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole [(±)-(1*R**)-35, (+)-(1*R*)-35, and (−)-(1*S*)-35].** A solution of **33** (35.5 mg, 86.9 μmol) and triphenylphosphine (34.6 mg, 132 μmol, 1.5 equiv) in 0.4 mL of methylene chloride at 23 °C under argon was treated with carbon tetrachloride (13 μL, 135 μmol, 1.5 equiv), and the reaction mixture was stirred for 14 h (23 °C).[44] Flash chromatography (5 × 150 mm SiO_2, 30–50% CH_2Cl_2/hexane gradient elution) afforded **35** (32.4 mg, 37.1 mg theoretical, 87%) as a white, crystalline solid: mp 206–208 °C dec; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.12 (br s, 1 H, NH), 7.67 (br s, 1 H, C4-H), 7.5–7.3 (m, 5 H, *Ph*CH_2O), 6.93 (s, 1 H, C7-H), 5.19 (s, 2 H, PhCH_2O), 4.3–3.75 (m, 3 H, C1-H and C2-H), 3.38 (apparent t, 2 H, J = 10.7 Hz, CH_2Cl), 2.40 (s, 3 H, Ar CH_3), 1.59 (s, 9 H, CO_2-*t*-Bu); IR (KBr) ν_{max} 3400, 1677, 1586, 1502, 1421, 1405, 1349, 1321, 1217, 1203, 1174, 1164, 1143, 1126, 1092, 1038, 1012, 986, 889,

(55) The alcohol **33** was resolved through formation and chromatographic separation of the diastereomeric (*R*)-(−)-*O*-acetylmandelate esters **34** as previously detailed: cf. ref 25. Measurements of the optical rotation of (1*S*)-**33** and (1*R*)-**33** in solvents (CH_3OH, CH_2Cl_2) in which the sample is not completely soluble (opaque suspension) but easily recovered (e.g., versus DMF) has resulted in the observation that the observed sign of rotation may invert. We thank Dr. Robert C. Kelly for bringing this to our attention.

(56) This material was ≥99% enantiomerically pure as determined by HPLC analysis of the corresponding precursor (*R*)-(−)-*O*-acetylmandelate ester (1*R*,2′*R*)-**34**.

(57) This material was 97–98% enantiomerically pure as determined by HPLC analysis of the corresponding precursor (*R*)-(−)-*O*-acetylmandelate ester (1*S*,2′*R*)-**34**.

829, 802, 748, 696 cm^{-1}; EIMS, *m/e* (relative intensity) 426/428 (13/5), 370/372 (43/14), 321 (42), 279/281 (54/18), 199 (18), 91 (base); CIMS (isobutane), *m/e* (relative intensity) 427/429 (M^+ + H, 36/12), 426/428 (39/20), 371/373 (base/33); HRMS, *m/e* 426.1715 ($C_{24}H_{27}N_2O_3Cl$ requires 426.1710). (1*R*)-**35**:[56] $[\alpha]^{23}_D$ +13.4° (*c* 0.66, CH_2Cl_2); $[\alpha]^{23}_{578}$ +13.1° (*c* 0.66, CH_2Cl_2). (1*S*)-**35**:[57] $[\alpha]^{23}_D$ −12.8° (*c* 0.51, CH_2Cl_2), 95% optically pure; calcd $[\alpha]^{23}_D$ −13.5° (*c* 0.51, CH_2Cl_2); $[\alpha]^{23}_{578}$ −12.6° (*c* 0.51, CH_2Cl_2), 95% optically pure; calcd $[\alpha]^{23}_{578}$ −13.3° (*c* 0.51, CH_2Cl_2).

(1*R)-, (1*R*)-, and (1*S*)-3-[(*tert*-Butyloxy)carbonyl]-1-(chloromethyl)-5-hydroxy-8-methyl-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole [(1*R**)-36, (1*R*)-36, and (1*S*)-36].** A solution of **35** (7.7 mg, 18.0 μmol) in 0.25 mL of tetrahydrofuran at 24 °C was treated sequentially with a 25% aqueous ammonium formate (50 μL) and 10% palladium/carbon (5 mg), and the reaction mixture was stirred vigorously for 30 min (24 °C).[40] The catalyst was removed by filtration of the reaction mixture through Celite (EtOAc wash), and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (5 × 25 mm SiO_2, 0–25% EtOAc/CH_2Cl_2 gradient elution) to afford **36** (6.1 mg, 6.1 mg theoretical, 100%; typically 96–100%, 10–20-μmol scale) as an unstable, white crystalline solid: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.20 (br s, 1 H, OH), 7.48 (br s, 1 H, C4-H), 6.96 (s, 1 H, C7-H), 6.74 (br s, 1 H, NH), 4.32–3.76 (m, 3 H, C1-H and C2-H), 3.38 (apparent t, 2 H, *J* = 11 Hz, CH_2Cl), 2.38 (s, 3 H, Ar CH_3), 1.58 (s, 9 H, CO_2-*t*-Bu); IR (KBr) ν_{max} 3377, 2976, 2927, 1662, 1590, 1499, 1409, 1368, 1333, 1256, 1165, 1141, 1043, 896, 834, 759, 737, 705 cm^{-1}; EIMS, *m/e* (relative intensity) 336 (M^+, 1), 302 (1), 280 (1), 246 (3), 231 (9), 199 (4), 187 (4), 56 (base); CIMS (isobutane), *m/e* (relative intensity) 303 (M^+ + 2 H − Cl, 31), 302 (M^+ + H − Cl, 17), 301 (M^+ + H − HCl, 26), 281 (9), 278 (12), 247 (base), 203 (13), 201 (14).

6-[[6-(Aminocarbonyl)-3,6,7,8-tetrahydro-5-hydroxy-4-methoxybenzo-[1,2-*b*:4,3-*b*']dipyrrol-2-yl]carbonyl]-3,6,7,8-tetrahydro-5-hydroxy-4-methoxybenzo[1,2-*b*:4,3-*b*']dipyrrole-2-dicarboxylic Acid [PDE-I Dimer (39)]. A slurry of PDE-I dimer methyl ester[24b] (**38**; 4.3 mg, 8.0 μmol) in 0.1 mL of nitrogen-saturated tetrahydrofuran/methanol (3:2) at 23 °C under nitrogen was treated with sodium dithionite[58] (4.2 mg, 24 μmol, 3 equiv) and a nitrogen-saturated aqueous solution of lithium hydroxide (20 μL of 4 N, 80 μmol, 10 equiv). The reaction mixture was warmed at 45 °C (bath temperature) under nitrogen for 10 h. The solvents were evaporated under a stream of nitrogen, and the yellow residue was dissolved in 0.5 mL of water. Ten percent aqueous hydrochloric acid (2 drops) was added, producing a yellow, gelatinous precipitate that was collected by centrifugation and washed with water (4 × 0.5 mL). Drying in vacuo afforded **39** (3.5 mg, 4.2 mg theoretical, 84%) as a grey-green solid:[41] ^{1}H NMR (DMSO-d_6, 200 MHz) δ 13.0 (br s, 1 H, OH), 11.6 (s, 1 H, NH), 11.4 (s, 1 H, NH), 11.0 (s, 1 H, OH), 7.04 (d, 1 H, *J* = 1 Hz), 6.92 (s, 2 H, $CONH_2$), 6.90 (d, 1 H, *J* = 1 Hz), 4.64 (t, 2 H, *J* = 8 Hz, NCH_2CH_2), 4.04 (t, 2 H, *J* = 8 Hz, NCH_2CH_2), 3.84 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.4–3.1 (m, 4 H, NCH_2CH_2, partially obscured by H_2O); IR (KBr) ν_{max} 3432, 1700, 1636, 1562, 1523, 1488, 1469, 1441, 1418, 1383, 1375, 1332, 1317, 1250, 1173, 1153, 1106, 1075, 1052, 1020, 960 cm^{-1}; FABMS (dithiothreitol/dithioerythritol), *m/e* 522 (M^+ + H).

(1*R)-, (1*R*)-, and (1*S*)-*seco*-CC-1065 [(1*R**)-40, (1*R*)-40, and (1*S*)-40].** Phenol **36** (1.5 mg, 4.5 μmol) was treated with anhydrous 3 N hydrochloric acid in ethyl acetate (0.5 mL) at 21 °C for 45 min.[45] The solvent wsa removed in vacuo to afford crude, unstable **37** as a red-brown oil.

A mixture of crude **37**, sodium bicarbonate (2.0 mg, 24 μmol, 5 equiv), 1-[(3-dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI, 3.0 mg, 15 μmol, 4 equiv), and PDE-I dimer (**39**, 1.9 mg, 3.65 μmol) was slurried in 0.1 mL of *N,N*-dimethylformamide at 21 °C under nitrogen, and the reaction mixture was stirred vigorously for 22 h (21 °C). The solvent was removed in vacuo, and the residue was slurried in 0.5 mL of water. Ten percent aqueous hydrochloric acid (1 drop) was added, and the mixture was stirred vigorously for 15 min (21 °C). The solids were collected by centrifugation and were washed with water (3 × 0.5 mL). Drying in vacuo afforded **40** (2.1 mg, 2.7 mg theoretical, 78%) as a grey-green solid: ^{1}H NMR (DMSO-d_6, 200 MHz) δ 12.93 (s, 1 H, OH), 11.36 (br s, 2 H, NH), 10.90 (s, 1 H, OH), 10.71 (br s, 1 H, NH), 9.78 (s, 1 H, OH), 7.58 (br s, 1 H, C4-H), 7.07 (s, 1 H), 7.04 (s, 1 H), 6.99 (s, 1 H), 6.92 (s, 2 H, $CONH_2$), 4.9–4.3 (m, 1 H, NCH_2), 4.04 (br t, 2 H, *J* = 9 Hz, CH_2NCONH_2), 3.89 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 3.58 (apparent t, 2 H, *J* = 10 Hz, CH_2Cl), 3.4–3.1 (m, 5 H, partially obscurred by H_2O), 2.35 (s, 3 H, Ar CH_3); IR (KBr) ν_{max} 3422, 2929, 2854, 2617, 1636, 1570, 1522, 1466, 1442, 1420, 1378, 1318, 1268, 1240, 1200, 1168, 1129, 1050, 1023, 963, 801, 739 cm^{-1}; FABMS (dithiothreitol/dithioerythritol), *m/e* 740 (M^+ + H).

(±)-(3b*R,4a*S**)-, (+)-(3b*R*,4a*S*)-, and (−)-(3b*S*,4a*R*)-CC-1065 [(±)-(3b*R**,4a*S**)-1, (+)-(3b*R*,4a*S*)-1, and (−)-(3b*S*,4a*R*)-1].** Compound **40** (1.5 mg, 2.0 μmol) was treated with 0.3 mL of 1:1:1 Et_3N/H_2O/CH_3CN[40] at 22 °C, and the reaction mixture was stirred for 30 min (22 °C). The solvents were removed in vacuo, and the residue was slurried in 0.5 mL of water. Saturated aqueous ammonium chloride (3 drops) was added, and the solid was collected by centrifugation and was washed with water (3 × 0.5 mL). Drying the solid in vacuo and flash chromatography (5 × 50 mm SiO_2, 0–20% DMF/toluene gradient elution) afforded CC-1065 (0.6 mg, 1.4 mg theoretical, 43%; typically 37–43%) identical in all comparable respects with a sample of authentic, naturally occurring material:[41,46] ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.93 (s, 1 H, OH), 11.53 (br s, 2 H, NH), 11.35 (br s, 1 H, NH), 11.05 (s, 1 H, OH), 7.07 (d, 1 H, *J* = 1.9 Hz), 7.06 (d, 1 H, *J* = 1.9 Hz), 6.91 (br s, 2 H, $CONH_2$), 6.87 (d, 1 H, *J* = 0.5 Hz), 6.44 (s, 1 H), 4.69 (t, 2 H, *J* = 9 Hz), 4.45 (dd, 1 H, *J* = 10, 5 Hz), 4.34 (d, 1 H, *J* = 9 Hz), 4.03 (t, 2 H, *J* = 9 Hz), 3.86 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 3.6–3.2 (m, 5 H, partially obscured by H_2O), 2.00 (s, 3 H, Ar CH_3), 1.95 (m, 1 H), 1.45 (apparent t, 1 H, *J* = 5 Hz); IR (KBr) ν_{max} 3431, 1634, 1577, 1465, 1443, 1419, 1376, 1351, 1330, 1305, 1267, 1152, 1118, 1079, 1048, 857, 802, 736 cm^{-1}; UV (DMF) λ_{max} 365 nm; FABMS (dithiothreitol/dithioerythritol), *m/e* 704 (M^+ + H). (+)-CC-1065:[46,57] $[\alpha]^{23}_{578}$ +90° (*c* 0.059, DMF), 95% optically pure, calcd $[\alpha]^{23}_{578}$ +95° (*c* 0.059, DMF). (−)-C-1065:[46,56] $[\alpha]^{23}_{578}$ −92° (*c* 0.075, DMF).

(1*R)-, (1*R*)-, and (1*S*)-*seco*-CPI-CDPI$_2$ [(1*R**)-43, (1*R*)-43, and (1*S*)-43].** Phenol **36** (6.1 mg, 18.1 μmol) was treated with anhydrous 3 N hydrochloric acid in ethyl acetate (0.5 mL) at 24 °C for 45 min.[45] The solvent was removed in vacuo to afford crude, unstable **37** as a light brown solid.

A mixture of crude **37**, sodium bicarbonate (7.8 mg, 93 μmol, 5 equiv), 1-[(3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDCI, 10.3 mg, 54 μmol, 3 equiv), and **42** (CDPI dimer, 7.0 mg, 16.3 μmol)[22] was slurried in 0.3 mL of dry *N,N*-dimethylformamide at 24 °C under nitrogen, and the reaction mixture was stirred vigorously for 17 h (24 °C). The solvent was removed in vacuo, and the residue was slurried in 0.5 mL of water; 10% aqueous hydrochloric acid (1 drop) was added, and the mixture was stirred vigorously for 30 min (24 °C). The solids were collected by centrifugation and were washed with water (0.5 mL), dilute aqueous hydrochloric acid (0.5 mL), and water (0.5 mL). Drying the solids in vacuo afforded **43** (9.3 mg, 10.6 mg theoretical, 88%; typically 88–96%) as a grey-green powder: ^{1}H NMR (DMSO-d_6, 200 MHz) δ 11.73 (s, 1 H, NH), 11.55 (s, 1 H, NH), 10.72 (s, 1 H, NH), 9.76 (s, 1 H, OH), 8.26 (d, 1 H, *J* = 8.6 Hz), 7.97 (d, 1 H, *J* = 8.8 Hz), 7.62 (br s, 1 H), 7.37 (d, 1 H, *J* = 8.6 Hz), 7.23 (d, 1 H, *J* = 8.8 Hz), 7.07 (s, 1 H), 7.05 (s, 1 H), 6.97 (s, 1 H), 6.10 (s, 2 H, $CONH_2$), 4.8–4.5 (m, 4 H), 4.00 (t, 2 H, *J* = 8 Hz), 3.7–3.2 (m, 7 H, partially obscurred by H_2O), 2.36 (s, 3 H, ArCH_3); IR (KBr) ν_{max} 3419, 1635, 1610, 1583, 1506, 1411, 1364, 1343, 1286, 1203, 1148, 1129, 1022, 806, 756, 667 cm^{-1}; FABMS (dithiothreitol/dithioerythritol), *m/e* 648 (M^+ + H), 585, 492, 440, 412.

(±)-(3b*R,4a*S**)-, (+)-(3b*R*,4a*S*)-, and (−)-(3b*S*,4a*R*)-CPI-CDPI$_2$ [(±)-(3b*R**,4a*S**)-2, (+)-(3b*R*,4a*S*)-2, and (−)-(3b*S*,4a*R*)-2].**[25] Compound **43** (4.6 mg, 7.1 μmol) was slurried in 1:1:1 $Et_3N/H_2O/CH_3CN$[40] (0.5 mL), and the reaction mixture was stirred vigorously at 24 °C for 4 h. The phenol **43** dissolved after 15–30 min, and **2** slowly precipitated from the reaction mixture. The solids were collected by centrifugation and were washed with water (2 × 0.5 mL). Drying in vacuo afforded **2** (3.3 mg, 4.3 mg theoretical, 77%) as a brown powder: ^{1}H NMR (DMSO-d_6, 200 MHz) δ 11.85 (s, 1 H, NH), 11.54 (br s, 2 H, NH), 8.28 (d, 1 H, *J* = 9.3 Hz), 7.97 (d, 1 H, *J* = 8.8 Hz), 7.36 (d, 1 H, *J* = 9.3 Hz), 7.22 (d, 1 H, *J* = 8.8 Hz), 7.14 (s, 1 H), 6.96 (d, 1 H, *J* = 0.7 Hz), 6.88 (d, 1 H, *J* = 1.7 Hz), 6.67 (s, 1 H), 6.10 (s, 2 H, $CONH_2$), 4.65 (br t, 2 H, *J* = 8 Hz), 4.50 (dd, 2 H, *J* = 10, 5 Hz), 3.99 (t, 2 H, *J* = 9 Hz), 3.6–3.1 (br m, 5 H), 2.01 (s, 3 H), 1.95 (m, 1 H), 1.41 (t, 1 H, *J* = 5 Hz); IR (KBr) ν_{max} 3409, 1635, 1605, 1576, 1505, 1432, 1394, 1362, 1339, 1265, 1146, 1120, 803, 758, 697, 667 cm^{-1}; FABMS (dithiothreitol/dithioerythritol), *m/e* 612 (M^+ + H). (+)-CPI-CDPI$_2$ [(+)-**2**]:[48] $[\alpha]^{25}_{578}$ +65° (*c* 0.11, DMF), 86% optically pure, calcd $[\alpha]^{25}_{578}$ +75.6° (*c* 0.11, DMF). (−)-CPI-CDPI$_2$ [(−)-**2**]:[56] $[\alpha]^{25}_{578}$ −74° (*c* 0.17, DMF).

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(58) Conducting the lithium hydroxide promoted methyl ester hydrolysis in the absence of sodium dithionite afforded discolored PDE-I dimer of unsuitable purity for subsequent use.

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and the assistance of Daniel L. Severance with molecular modeling and computer graphics. We especially wish to thank Dr. Robert C. Kelly and Dr. Martha A. Warpehoski of the Upjohn Company for a sample of natural (+)-CC-1065, for many helpful discussions, for comparative optical rotations of intermediates, and for preprints of their work (ref 18, 19, 40, and 47).

Supplementary Material Available: Synthetic procedures and full spectral and physical characterizations of **5-10**, **14**, **17** and **18**, figures 2 and 3 (footnote 12), and preliminary, comparative B-DNA binding properties of CC-1065 and CPI-CDPI$_2$ (ΔT_m, poly[dA]·poly[dT]) are provided (11 pages). Ordering information is given on any current masthead page.

Acromelic Acids A and B. Potent Neuroexcitatory Amino Acids Isolated from *Clitocybe acromelalga*†

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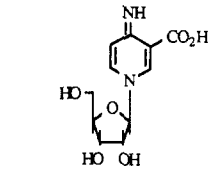
Abstract: The minute amount of toxic principles, acromelic acids A (ca. 110 μg) and B (ca. 40 μg), was isolated from a poisonous mushroom *Clitocybe acromelalga*. Spectral analyses and biogenetic consideration led to the structures **1** and **2** for acromelic acids A and B, respectively. The syntheses of **1** and **2** starting from L-α-kainic acid **3** established the proposed structures. Both amino acids show extremely potent neuroexcitatory action.

The poisonous mushroom *Clitocybe acromelalga* Ichimura (Japanese name, Dokusasako), found only in Japan, has been known for many years to exhibit unique symptoms similar to acromelalgia and erythromelalgia. Ingestion of the mushroom causes a sharp pain and a marked reddish edema in hand and foot (after several days), and it continues for about a month.

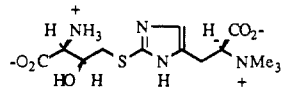
These characteristic properties prompted us to study the chemical constituents of the fungus. Fractionation monitored by lethal effect in mice led to the isolation of four new compounds: clitidine, a toxic nucleoside;[1] clithioneine, an unusual nontoxic betaine;[2] and acromelic acids A (**1**) and B (**2**), powerful neuroexcitatory amino acids. We describe here the isolation, characterization, and syntheses of acromelic acids A and B in detail.[3]

Isolation and Structure. From the water extract of fresh fruiting bodies (16.2 kg), pure acids A and B (ca. 110 and 40 μg, respectively) were isolated. Both compounds showed yellow coloration with a ninhydrin test and the behavior of a strong acid on ion-exchange chromatography and paper electrophoresis.

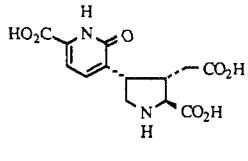
Due to the scarcity of the samples, spectral data available were limited. For example, no ^{13}C NMR signals could be observed even after 35912 transients (25.0 MHz), and all attempts to measure the mass spectrum (FD-MS, SIMS) were unsuccessful. Thus, the data obtained were only those of ^1H NMR (360 MHz), UV, and CD spectra. The formulas **1** and **2**, however, could be inferred from the data comparing with those of related compounds.



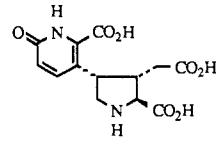
clitidine



clithioneine



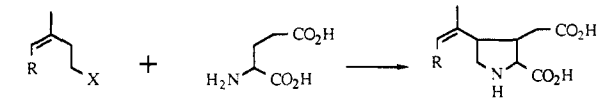
acromelic acid A (1)



acromelic acid B (2)

† Dedicated to Professor E. J. Corey on the occasion of his 60th birthday.
‡ Hokkaido University.
§ Suntory Institute for Bioorganic Research.

Scheme I. Biogenesis of Kainic Acid and Domoic Acid



isoprene unit glutamic acid kainic acid , domoic acid

The ^1H NMR spectra of both **1** and **2** consisted of the signals of two aromatic protons, three methine, and two methylene groups. The sequence of the methine and methylene groups was a readily suggested presence of a partial structure (**A**) in both compounds by the decoupling experiments (Figure 1). The terminal methine proton was thought to be an α-proton of amino acid,[4] judging from chemical shift values (4.13 in **1** and 4.16 in **2**). On the other hand, one of the methylene groups was indicated to be α to the carbonyl group because of its chemical shifts (2.01, 2.54 in **1** and 2.23 in **2**) and a large J value (hertz) between geminal protons (16.5 Hz). These analyses led to a partial structure (**B**) possessing a glutamic acid moiety, which was in accord with the strongly acidic nature of **1** and **2** on chromatography. Another partial structure (**C**) (including the proline moiety) was suggested from the facts that both **1** and **2** gave a yellow coloration with a ninhydrin test and the chemical shifts of the other methylene (3.73, 3.76 in **1** and 3.67, 3.78 in **2**) were assignable to a methylene α to an ammonium nitrogen. Taking all these evidence into consideration, a structure of 4-substituted 2-carboxy-3-(carboxymethyl)pyrrolidine (**D**) was inferred for each of **1** and **2**. Indeed, as shown in Table I, the ^1H NMR spectral data (360 MHz) of **1** and **2** closely resembled those of domoic acid (**4**)[5] and kainic acid (**3**),[6] respectively, except

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(2) (a) Konno, K.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1981**, *22*, 1617-1618. (b) Konno, K.; Shirahama, H.; Matsumoto, T. *Phytochemistry* **1984**, *23*, 1003-1006.
(3) Preliminary accounts of this work: (a) Konno, K.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1983**, *24*, 939-942. (b) Konno, K.; Hashimoto, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Ibid.* **1986**, *27*, 607-610. (c) Hashimoto, K.; Konno, K.; Shirahama, H.; Matsumoto, T. *Chem. Lett.* **1986**, 1399-1400.
(4) Roberts, G. C. K.; Jardetzky, O. *Adv. Protein Chem.* **1970**, *24*, 447-545.
(5) (a) Isolation and structure: Takemoto, T.; Daigo, K.; Kondo, Y.; Kondo, K. *J. Pharm. Soc. Jpn.* **1966**, *86*, 874-877. (b) Total synthesis: Ohfune, Y.; Tomita, M. *J. Am. Chem. Soc.* **1982**, *104*, 3511-3513.
(6) For review see: McGeer, E. G.; Olney, J. W.; McGeer, P. L. *Kainic Acid as a Tool in Neurobiology*; Raven: New York, 1978.

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