on standing. Also obtained was (Z)-enelactam **4a** (11.4 mg, 3%) from the column as a side product.

2d (cis and trans, 1:1): mp 136–137 °C (ethyl acetate and hexanes); IR ($CHCl_3$) 1735 cm^{-1} (C=O); $[\alpha]_D$ −117.8 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.05 (d, *J* = 6.5 Hz, 3 H, CH_3), 2.15 (d, *J* = 6.5 Hz, 3 H, CH_3), 3.25 (dd, *J* = 2.5 and 8.6 Hz, 1 H, C-H_4), 3.66 (s, 6 H, OCH_3), 3.95 (dd, *J* = 5.12 and 8.6 Hz, 1 H, C-H_4), 4.40 (ddd, *J* = 2.5, 5.20, and 7.5 Hz, 2 H, C-H_3), 4.75 (m, 2 H, CH), 6.05–6.55 (m, 2 H, CH), 7.40–7.61 (m, 20 H, aromatic); EIMS, *m/e* 433 (M^+), 157 (base); HRMS for $C_{20}H_{20}NO_2I$ requires 433.0537, found 433.0545. Anal. Calcd for $C_{20}H_{20}NO_2I$: C, 55.44; H, 4.65; N, 3.23. Found: C, 55.61; H, 4.98; N, 3.16.

***rel*-(1′*S*,3*S*,4*R*)- and (1′*S*,3*S*,4*S*)-1-(4-Methoxyphenyl)-3-[1′-[(*N*-thiocarbonylimidazolyl)oxy]ethyl]-4-(2′-phenylethenyl)-2-azetidinone (3).** A solution of **2a** (350 mg, 1.08 mmol) in tetrahydrofuran (4 mL) was refluxed in the presence of 1,1-thiocarbonyldiimidazole (420 mg, 2.32 mmol) for 5 h under an atmosphere of nitrogen. The solution was poured into 15 mL of water, and the aqueous layer was extracted with ether (2 × 10 mL), dried (magnesium sulfate), and evaporated to give almost pure **3** as a oil containing 1:1 mixture of cis and trans isomers. For analytical purposes, the compound was purified by chromatography (silica gel; ethyl acetate–hexanes, 1:1) to yield 387 mg (98%) of compound **3**: IR ($CHCl_3$) 1745 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ (cis–trans, 1:1), 1.65 (t, *J* = 6.2 Hz, 3 H, CH_3), 1.70 (t, *J* = 6.2 Hz, 3 H, CH_3), 3.45 (m, 1 H, C-H_3), 3.55 (m, 1 H, C-H_3), 3.75 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.15 (m, 2 H, CH), 4.52 (dd, *J* = 2.5 and 8.0 Hz, 1 H, C-H_4), 4.85 (t, *J* = 5.0 Hz, 1 H, C-H_4), 6.25 (dd, *J* = 8.0 and 15.0 Hz, 2 H, CH), 6.70–7.90 (m, 24 H, aromatic), 8.25 (s, 2 H, aromatic); EIMS, *m/e* 433 (M^+), 157 (base); HRMS for $C_{24}H_{23}N_3O_3S$ requires 433.1459, found 433.1463.

(*Z*)-Enelactam 4a: mp 97–98 °C; IR ($CHCl_3$) 1740, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.11 (d, *J* = 8 Hz, 3 H, CH_3), 3.79 (s, 3 H, OCH_3), 4.91 (d, *J* = 8 Hz, C-H_4), 5.75 (m, 1 H, CH), 6.21 (q, *J* = 8 Hz, 1 H), 6.79–7.61 (m, 11 H, CH, ArH); EIMS, *m/e* 305 (M^+, base); HRMS for $C_{20}H_{19}NO_2$ requires *m/e* 305.1415, found 305.1404.

(*E*)-Enelactam 4b: oil; IR ($CHCl_3$) 1740, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72 (d, *J* = 7.5 Hz, 3 H, CH_3), 3.75 (s, 3 H, OCH_3), 4.98 (d, *J* = 8.0 Hz, 1 H, C-H_4), 6.0–6.42 (m, 2 H, CH), 6.70–7.45 (m, 10 H, aromatic); EIMS, *m/e* 305 (M^+, base); HRMS for $C_{20}H_{19}NO_2$ requires *m/e* 305.1415, found 305.1404.

***rel*-(3*R*,4*R*)- and (3*R*,4*S*)-3-Ethyl-1-(4-methoxyphenyl)-4-(2′-phenylethenyl)-2-azetidinone (5).** To a solution of **3** (75 mg, 0.18 mmol) in 5 mL of dry dimethyl sulfoxide was added, in portions, sodium borohydride (20 mg, 0.5 mmol) under an inert atmosphere of nitrogen. The solution was stirred for 2 h at 90 °C and then poured into a cold solution of saturated ammonium chloride (5 mL). The aqueous layer was extracted with ether, dried (magnesium sulfate), and evaporated to give a yellow oil, which was purified by chromatography over silica gel with ethyl acetate and hexanes (1:1) as eluents to give **5** (43 mg, 79%) as a mixture of cis–trans (1:1) isomers: IR ($CHCl_3$) 1740 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.09 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.26 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.81–1.94 (m, 4 H, CH_2), 2.90–3.45 (m, 2 H, CH_3), 3.75 (s, 6 H, OCH_3), 4.25 (dd, *J* = 2.5 and 8.0 Hz, 1 H, C-H_4), 4.65 (dd, *J* = 5.5 and 8.0 Hz, 1 H, C-H_4), 6.25 (ddd, *J* = 2.5, 8.0, and 16.0 Hz, 2 H, CH), 7.45–7.70 (m, 20 H, aromatic); EIMS, *m/e* 307 (M^+), 134 (base); HRMS for $C_{20}H_{21}NO_2$ requires 307.1571, found 307.1566.

β-Lactam 5 from 2c. The same procedure as employed for the conversion of **3** to **5** was used. Yield 70%.

(3*R*,4*R*)- and (3*R*,4*S*)-3-Ethyl-1-(4-methoxyphenyl)-4-(2-phenylethenyl)-2-azetidinone (5) from 2d. The same procedure was utilized as employed for the conversion of **3** to **5** with sodium borohydride. Yield 80% as a mixture of cis–trans (1:1) isomers, $[\alpha]_D$ +67.98 (*c* 1.44, $CHCl_3$).

β-Lactam 5 from 2d. A solution of **2d** (75 mg, 0.17 mmol) in dry benzene (10 mL) was refluxed in the presence of tributyltin hydride (0.1 mL, 0.34 mmol) and a catalytic amount of AIBN (8 mg) for a period of 2 h under an atmosphere of nitrogen. The solution was cooled, and the benzene layer was washed with water (2 × 3 mL) and brine (2 × 3 mL), dried (magnesium sulfate), and evaporated to give a yellow oil, which was purified further by chromatography (silica gel; ethyl acetate–hexanes, 1:1) to give 41 mg (80%) of the pure compound **5**.

β-Lactam 2d from 2a. To a solution of **2a** (323 mg, 1.0 mmol) in 5 mL of dry tetrahydrofuran at room temperature was added triphenylphosphine (576 mg, 2.2 mmol), diethyl azodicarboxylate (576 mg, 2.2 mmol), and methyl iodide (310 mg, 2.2 mmol) under an atmosphere of nitrogen. After the mixture was stirred for 16 h, the mixture was poured into the flask containing 15 mL of brine, and then the aqueous layer was extracted with ether (3 × 10 mL), dried (magnesium sulfate), and evaporated to give a dark brown oil. On chromatography (silica gel; ethyl acetate–hexanes, 1:4, three different products were isolated: β-lactam **2d** in 30% yield, enelactam **4a** in 20% yield, and enelactam **4b** in 20% yield.

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Registry No. **1**, 67007-79-8; **2a** (isomer 1), 101977-76-8; **2a** (isomer 2), 101977-77-9; **2b** (isomer 1), 112245-38-2; **2b** (isomer 2), 112245-39-3; **2c** (isomer 1), 112113-94-7; **2c** (isomer 2), 112245-40-6; **2d** (isomer 1), 112113-95-8; **2d** (isomer 2), 112245-41-7; **3** (isomer 1), 112113-96-9; **3** (isomer 2), 112245-42-8; **4a**, 112113-97-0; **4b**, 112113-98-1; **5** (isomer 1), 103733-13-7; **5** (isomer 2), 112245-43-9; **6** (isomer 1), 112113-99-2; **6** (isomer 2), 112245-44-0; **7** (isomer 1), 112114-00-8; **7** (isomer 2), 112245-45-1; **8** (isomer 1), 112114-01-9; **8** (isomer 2), 112245-46-2; **9** (isomer 1), 103775-03-7; **9** (isomer 2), 103775-02-6; **10**, 93788-48-8; **11**, 83997-55-1; **12**, 79252-31-6.

Supplementary Material Available: Physical data for compounds **6–9**, **11**, and **12** (4 pages). Ordering information is given on any current masthead page.

Total Synthesis of (+)- and (−)-CPI-CDPI$_2$: (+)-(3b*R*,4a*S*)- and (−)-(3b*S*,4a*R*)-Deoxy-CC-1065

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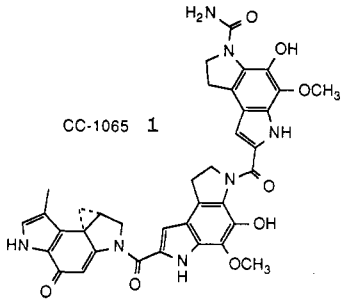
CC-1065 (**1**, NSC-298223), an antitumor antibiotic isolated from *Streptomyces zelensis*[2a] initially identified by spectroscopic techniques[2b] and confirmed in a single-crystal X-ray structure determination,[2c] possesses exceptional, potent in vitro cytotoxic activity, antimicrobial activity, and confirmed, potent in vivo antitumor activity.[3] The



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

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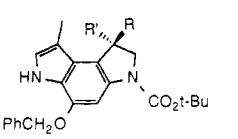
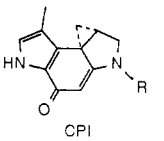
naturally occurring agent, (+)-CC-1065, and structurally related synthetic agents bearing the natural (3b*R*,4a*S*)-CPI left-hand segment of CC-1065[4] have been shown to bind within the double-stranded B-DNA minor groove in an initial, high-affinity, five base-pair sequence-selective [5′-d(A/GNTTA)-3′ or 5′-d(AAAAA)-3′] nonintercalative manner and subsequently form irreversible, covalent adducts.[5] The double-stranded B-DNA minor groove covalent alkylation has been shown to proceed by an acid-catalyzed 3′-adenine N-3 alkylation of the reactive, electrophilic (3b*R*, 4a*S*)-4,4-spirocyclopropylcyclohexadienone (spirobicyclo[5.2.0]octa-2,5-dien-4-one) unit found in the natural left-hand segment of CC-1065.[6] Consequently, the mechanism of CC-1065 antitumor activity (inhibition of DNA synthesis) has been proposed to be derived from overstabilization of double-stranded B-DNA and inhibition of the normal unwinding and melting process required of DNA synthesis[5] or selective alkylation of replication-related recognition regions of DNA.[7]

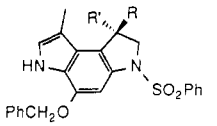
Early efforts disclosed in the work of Kelly, Warpehoski, and Wierenga[8] have led to the preparation and subsequent evaluation of simplified analogues of CC-1065, e.g. U-71,184,[8a] bearing modified central and right-hand subunits that possess comparable in vitro and in vivo antitumor activity, possess comparable sequence-selective 3′-adenine N-3 alkylation of DNA,[8d] possess reduced and/or no delayed, fatal hepatotoxicity,[8b] and in which the antitumor activity and DNA binding properties have been found to be restricted principally to the agent enantiomer bearing the natural (3b*R*,4a*S*)-CPI left-hand segment.[8a,d] In sharp contrast, recent efforts have unexpectedly demonstrated that *ent*-(−)-CC-1065 bearing the unnatural (3b*S*,4a*R*)-CPI left-hand segment and naturally occurring (+)-CC-1065 possess comparable, potent in vitro cytotoxic activity.[9] As a result, the examination of the structural features of CC-1065 that are responsible for the high-affinity, sequence-selective nonintercalative binding within the B-DNA minor groove has focused on the role and the extent to which the central and right-hand segments of CC-1065 may contribute to the affinity, specificity, and enantioselectivity of this binding. Recent studies[6a,10] have indicated that the selectively protected C-4/C-5 catechol units of CC-1065 lie on the unbound, peripheral face of the DNA:CC-1065 complex and that the initial, selective, high-affinity binding of the natural product may be attributed predominately to hydrophobic interactions and to the B-DNA minor groove complementary shape of CC-1065. Consequently, structural analogues of CC-1065 that possess the hydrophobic, rigid, helical skeleton introduced by two repeating 1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole units would be expected to mimic the topological pitch of B-DNA, possess the sequence-selective, high-affinity nonintercalative binding to double-stranded B-DNA, and exhibit properties associated with the naturally occurring material.

Herein, we detail a procedure for the resolution of **2**, a penultimate precursor to the left-hand segment (CPI) of CC-1065, and the subsequent incorporation of (−)-(1*S*)-**2** and (+)-(1*R*)-**2** into the preparation of (+)-CPI-$CDPI_2$ and (−)-CPI-$CDPI_2$ [(+)-(3b*R*,4a*S*)- and (−)-(3b*S*,4a*R*)-deoxy CC-1065 (**14**)]. A series of diastereomeric esters and

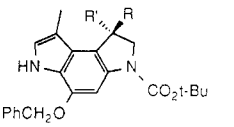




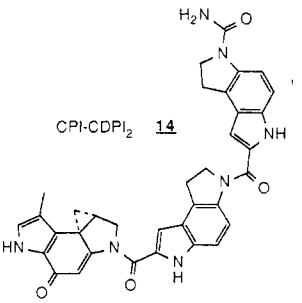
R = CH_2OH, R' = H (+)-1R-**2**
R = H, R' = CH_2OH (-)-1S-**2**



R = CH_2OH, R' = H 1R-**3**
R = H, R' = CH_2OH 1S-**3**



R = CH_2Cl, R' = H (+)-1R-**10**
R = H, R' = CH_2Cl (-)-1S-**10**



carbamates of (±)-**2** and (±)-**3**, which were prepared in the course of the total synthesis of (±)-CC-1065,[11] were examined as potential substrates for chromatographic separation

(3) For a recent review of the chemistry, mechanism of action, and biological properties of CC-1065, see: Reynolds, V. L.; McGovren, P. J.; Hurley, L. H. *J. Antibiot.* **1986**, *31*, 319 and references cited therein.

(4) The assignment of the absolute configuration of naturally occurring (+)-CC-1065 was initially based on the defined site of B-DNA minor groove alkylation combined with the directional sequence-selective binding of this agent, as predicted by employing molecular models of the covalent adduct between (+)-CC-1065 and DNA.[6] This assignment of absolute configuration has been unambiguously established in a single-crystal X-ray analysis of N^2-*p*-chlorobenzoyl CPI derived from natural (+)-CC-1065, David G. Martin (The Upjohn Company), unpublished observations. The assignment of the absolute configuration of (−)-(1*S*)-**2** is based on a successful correlation with natural (+)-CC-1065.[9,11]

(5) Swenson, D. H.; Li, L. H.; Hurley, L. H.; Rokem, J. S.; Petzold, G. L.; Dayton, B. D.; Wallace, T. L.; Lin, A. H.; Krueger, W. C. *Cancer Res.* **1982**, *42*, 2821. Li, L. H.; Swenson, D. H.; Schpok, S. L. F.; Kuentzel, S. L.; Dayton, B. D.; Krueger, W. C. *Cancer Res.* **1982**, *42*, 999. Reynolds, V. L.; Molineux, I. J.; Kaplan, D. J.; Swenson, D. H.; Hurley, L. H. *Biochemistry* **1985**, *24*, 6228. For a review on the covalent binding of CC-1065 to the minor groove of DNA, see: Hurley, L. H.; Needham-VanDevanter, D. A. *Acc. Chem. Res.* **1986**, *19*, 230 and references cited therein.

(6) (a) Hurley, L. H.; Ryenolds, V. L.; Swenson, D. H.; Petzold, G. L.; Scahill, T. A. *Science (Washington, D.C)* **1984**, *226*, 843. (b) Needham-VanDevanter, D. R.; Hurley, L. H.; Reynolds, V. L.; Theriault, N. Y.; Krueger, W. C.; Wierenga, W. *Nucleic Acids Res.* **1984**, *12*, 6159.

(7) For a recent discussion of sequence-specific DNA binding agents, see: Hurley, L. H. *Ann. Rep. Med. Chem.* **1987**, *22*, 259.

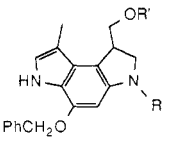
(8) (a) Warpehoski, M. A. *Tetrahedron Lett.* **1986**, *27*, 4103. (b) Warpehoski, M. A.; Gebhard, I.; Kelly, R. C.; Krueger, W. C.; Li, L. H.; McGovren, J. P.; Prairie, M. D.; Wicnienski, N.; Wierenga, W. *J. Med. Chem.*, submitted for publication. (c) Li, L. H.; Wallace, T. L.; DeKoning, T. F.; Warpehoski, M. A.; Kelly, R. C.; Prairie, M. D.; Krueger, W. C. *Invest. New Drugs*, in press. (d) For a review of the biological activity of analogues of CC-1065, see: Wierenga, W.; Bhuyan, B. K.; Kelly, R. C.; Krueger, W. C.; Li, L. H.; McGovren, J. P.; Swenson, D. H.; Warpehoski, M. A. *Adv. Enzyme Regul.* **1986**, *25*, 141. (e) **Note added in proof**: Warpehoski, M. A.; Bradford, V. S. *Tetrahedron Lett.*, in press.

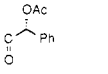
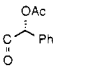
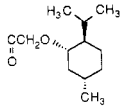
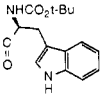
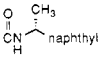
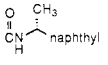
(9) Kelly, R. C.; Gebhard, I.; Wicnienski, N.; Aristoff, P. A.; Johnson, P. D.; Martin, D. G. *J. Am. Chem. Soc.* **1987**, *109*, 6837.

(10) (a) Zakrzewska, K.; Randrianarivelo, M.; Pullman, B. *Nucleic Acids Res.* **1987**, *15*, 5775. (b) Boger, D. L., submitted for publication. (c) Coleman, R. S.; Boger, D. L. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, in press.

(11) Boger, D. L.; Coleman, R. S. *J. Am. Chem. Soc.*, in press. Boger, D. L.; Coleman, R. S. *J. Am. Chem. Soc.* **1987**, *109*, 2717.

Table I. Normal-Phase Chromatographic Separation of Diastereomers[a]



diastereomers	α value[b]	solvent system
4 R = $CO_2{}^tBu$, R' = 	1.18	2% EtOAc–98% CH_2Cl_2
5 R = SO_2Ph, R' = 	1.00	2% EtOAc–98% CH_2Cl_2
6 R = $CO_2{}^tBu$, R' = 	1.09	2% EtOAc–98% CH_2Cl_2
7 R = SO_2Ph, R' = 	1.00	5% EtOAc–95% CH_2Cl_2
8 R = $CO_2{}^tBu$, R' = 	1.16	2.5% EtOAc–97.5% CH_2Cl_2
9 R = SO_2Ph, R' = 	1.23	2.5% EtOAc–97.5% CH_2Cl_2

[a] 4.6 mm × 25 cm column, 5 μm SiO_2, 1.5 mL/min flow rate, 280 nm detection. [b] (Retention time of slower eluting compound)/(retention time of faster eluting compound).

(resolution).[12] Thus, reaction of the optically active carboxylic acids (*R*)-(−)-O-acetylmandelic acid, (−)-menthoxyacetic acid, and *N*-BOC-L-tryptophan[8a] with (±)-**2** and (±)-**3** (EDCI, DMAP, CH_2Cl_2, 23 °C) afforded the diastereomeric esters **4–7** (Table I) and reaction of (±)-**2** and (±)-**3** with (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate[13] (toluene, 90–100 °C) provided the diastereomeric carbamates **8** and **9** (Table I). The results of normal-phase HPLC analysis of diastereomers **4–9** are presented in Table I. The advantages afforded with the use of an optically active carboxylic acid as the resolving agent (i.e., ease of ester formation and subsequent hydrolysis), the technical preference for performing the resolution subsequent to the removal of the indoline *N*-phenylsulfonyl protecting group, and the relative α values (Table I) led to the selection of ester **4** as the substrate for preparative chromatographic separation. Normal-phase preparative HPLC separation of **4** (10 mm × 25 cm column, 10 μm SiO_2, 3.5 mL/min flow rate, 2% EtOAc–98% CH_2Cl_2 eluant) afforded the purified diastereomeric esters.[14] Base-promoted hydrolysis (LiOH, $THF/CH_3OH/H_2O$ 3:2:1, 23 °C) of (1*R*,2′*R*)-**4** and (1*S*,2′*R*)-**4** provided the enantiomeric alcohols (+)-(1*R*)-**2** and (−)-(1*S*)-**2**, respectively, in 76% and 83% recovery from (±)-**2**. Independent conversion of (+)-**2** and (−)-**2** to the corresponding *primary* chlorides (Ph_3P, CCl_4)[15] afforded (+)-(1*R*)-**10** ($[\alpha]^{23}_D$ +18.8° (*c* 0.82, $CHCl_3$)) and (−)-(1*S*)-**10** ($[\alpha]^{23}_D$ −16.1° (*c* 0.69, $CHCl_3$)),[14] respectively, constituting the resolved substrates for incorporation into the synthesis of (−)- and (+)-CPI-$CDPI_2$ [(−)- and (+)-**14**].

Sequential removal of the benzyl ether (HCO_2NH_4, THF/H_2O 4:1, 10% Pd/C, 30 min, 23 °C, 100%) and the *t*-BOC protecting groups (3 N HCl–EtOAc, 30 min, 23 °C) of (+)-(1*R*)-**10** and (−)-(1*S*)-**10** following the conditions described by Kelly and co-workers[9] afforded the unstable indoline hydrochlorides **11**, which were coupled directly with CDPI dimer (**12**)[16] in the presence of EDCI (DMF, $NaHCO_3$, 23 °C, 20–24 h) to provide (1*R*)-**13** and (1*S*)-**13**, respectively, in excellent conversion. Final spirocyclization (Wierenga–Kelly Winstein Ar-3′ alkylation)[9] was effected by treatment of (1*R*)-**13** and (1*S*)-**13** with 1:1:1 $Et_3N/H_2O/CH_3CN$[9] (23 °C, 4 h) and afforded (−)-CPI-$CDPI_2$ ((−)-**14**, $[\alpha]^{25}_{578}$ −74° (*c* 0.17, DMF)) and (+)-CPI-$CDPI_2$[17] ((+)-**14**, $[\alpha]^{25}_{578}$ +65° (*c* 0.11, DMF))[14] in 50% overall yields from **12** (Scheme I).

Unlike the simplified CC-1065 analogues bearing modified central and right-hand subunits, e.g., U-71,184/U-71,185, (+)-CPI-$CDPI_2$ and (−)-CPI-$CDPI_2$ display equipotent cytotoxic activity[17] which has proven indistinguishable from (+)-CC-1065 and *ent*-(−)-CC-1065.[9,11]

Experimental Section[18]

(1*RS*,2′*R*)-4. A solution of (±)-**2** (67.5 mg, 0.165 mmol) and (*R*)-(−)-*O*-acetylmandelic acid (49 mg, 0.25 mmol, 1.5 equiv) in 1.1 mL of dry methylene chloride was treated with EDCI (52 mg, 0.27 mmol, 1.67 equiv) and DMAP (ca. 2 mg, catalytic) at 23 °C under nitrogen and the reaction mixture was stirred for 1 h (23 °C). Chromatography (0.5 × 15 cm SiO_2, CH_2Cl_2) afforded (1*RS*,2′*R*)-**4** (95 mg, 96.5 mg theoretical yield, 98%) as a colorless oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 8.08 (br s, 1 H, NH), 7.60 (br s, 1 H, C4-H), 7.25–7.15 (m, 10 H, ArH), 6.89 (s, 1 H, C7-H), 5.96 and 5.95 (two s, 1 H each, PhC*H*(OAc)CO), 5.18 (s, 2 H, PhCH_2), 4.6–4.4 (m, 2 H, CH_2O), 3.9–3.6 (m, 3 H, C1-H and C2-H), 2.42 and 2.39 (two d, 3 H each, *J* = 0.9 Hz, ArCH_3), 2.23 and 2.20 (two s, 3 H each, COCH_3), 1.57 and 1.56 (two s, 9 H each, CO_2-*t*-Bu); IR (neat) ν_{max} 3355, 1746, 1690, 1588, 1501, 1455, 1421, 1401, 1372, 1346, 1320, 1232, 1203, 1173, 1141, 1085, 1050, 1029, 939, 896, 735, 697 cm^{-1}; EIMS, *m/e* (relative intensity) 584 (M^+, 30), 528 (22), 484 (31), 321 (24), 277 (34), 243 (53), 199 (67), 185 (12), 171 (16), 107 (29), 91 (base); CIMS (isobutane), *m/e* (relative intensity) 585 (M^+ + H, 26), 529 (base), 485 (56), 471 (19), 391 (10), 291 (26), 195 (29), 135 (34); HRMS, *m/e* 584.2523 ($C_{34}H_{36}N_2O_7$ requires 584.2523).

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(14) HPLC analysis of the separated diastereomers showed that the faster eluting diastereomer (corresponding to unnatural (+)-(1*R*)-**2**) was ≥99% pure and the slower eluting diastereomer (corresponding to natural (−)-(1*S*)-**2**) was 93% diastereomerically pure. Using these values, the specific rotations of optically pure (−)-(1*S*)-**10** and (+)-**14** are calculated to be $[\alpha]^{23}_D$ −18.7° (*c* 0.69, $CHCl_3$) and $[\alpha]^{25}_{578}$ +75.6° (*c* 0.11, DMF), respectively.

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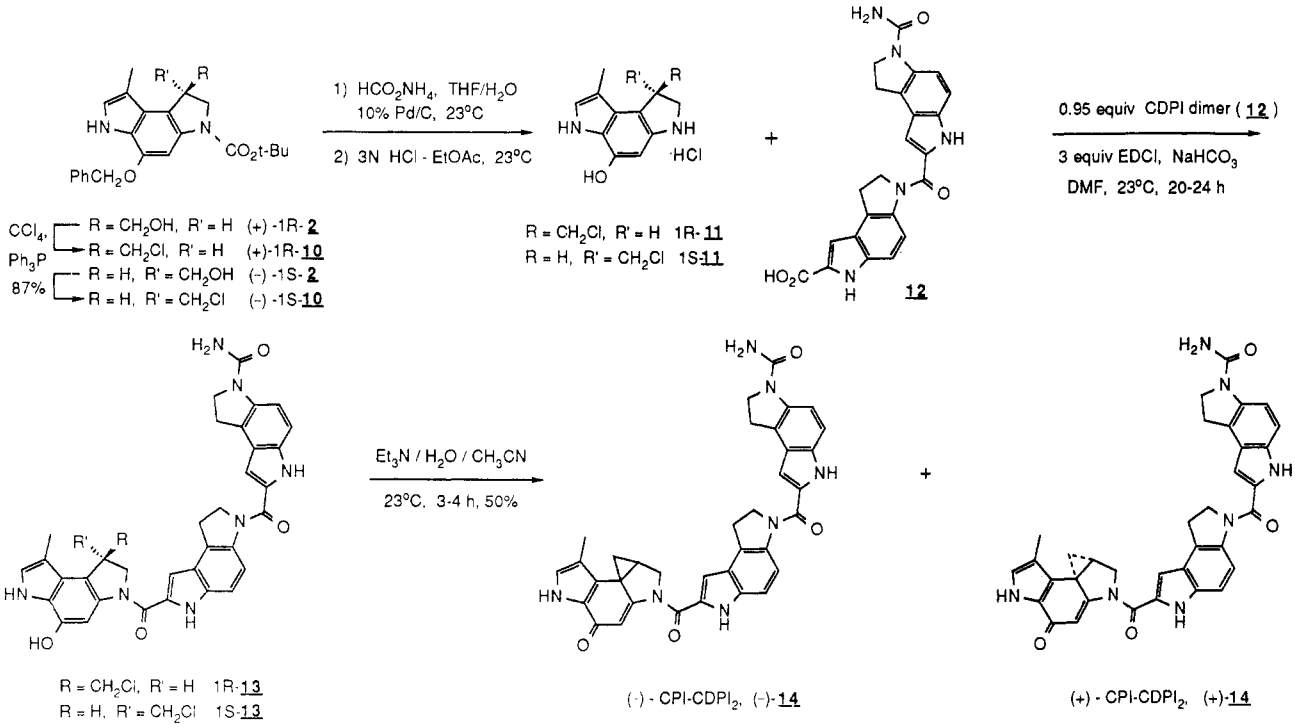
(17) (±)-CPI-$CDPI_2$: ^1H NMR (DMSO-d_6, 200 MHz) δ 11.85 (s, 1 H, NH), 11.54 (br s, 2 H, NH), 8.28 (d, 1 H, *J* = 9.3 Hz), 7.97 (d, 1 H, *J* = 8.8 Hz), 7.36 (d, 1 H, *J* = 9.3 Hz), 7.22 (d, 1 H, *J* = 8.8 Hz), 7.14 (s, 1 H), 6.96 (d, 1 H, *J* = 0.7 Hz), 6.88 (d, 1 H, *J* = 1.7 Hz), 6.67 (s, 1 H), 6.10 (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, 1143, 1120, 803, 758, 697, 667 cm^{-1}; FABMS (dithiothreitol/dithioerythritol), *m/e* 612 (M^+ + H). In a preliminary comparative evaluation, (+)-CPI-$CDPI_2$ and (−)-CPI-$CDPI_2$ have exhibited essentially equipotent in vitro cytotoxic activity (P388 leukemia: ID_{50} = 1.2×10^{-5} μg/mL and 3.9×10^{-6} μg/mL; L1210: ID_{50} = 1.3×10^{-5} μg/mL and 1.3×10^{-5} μg/mL; B16: ID_{50} = 11×10^{-5} μg/mL and 1.3×10^{-5} μg/mL; respectively).

(18) Proton nuclear magnetic resonance spectra (^1H NMR) were recorded on a Varian XL-200 or General Electric QE-300 spectrometer and chemical shifts are reported in parts per million relative to internal tetramethylsilane (δ 0.00). Infrared spectra (IR) were recorded on a Perkin-Elmer 1800 Fourier transform spectrometer. Electron-impact mass spectra (EIMS) and chemical-ionization mass spectra (CIMS) were recorded on a Finnegan 4000 spectrometer. High-resolution mass spectra (HRMS) and fast atom bombardment mass spectra (FABMS) were recorded on a Kratos MS-50 spectrometer. Optical rotations were measured on a Perkin-Elmer Model 1210 polarimeter. High-performance liquid chromatography (HPLC) was performed on a Gilson Model 302 dual pump chromatograph equipped with a ISCO V^4 absorbance detector. The 10 mm × 25 cm preparative SiO_2 chromatography column was purchased from Altech Associates. (*R*)- (−)-O-Acetylmandelic acid and 1-[3-(dimethylamino)-3-propyl]-3-ethylcarbodiimide hydrochloride (EDCI) were purchased from Aldrich Chemical Co.

Scheme I



Preparative HPLC Separation of (1*R*,2′*R*)-4 and (1*S*,2′*R*)-4. A solution of (1*RS*,2′*R*)-4 (95 mg in 0.5 mL of CH_2Cl_2) was subjected to chromatography on an Altech 10 mm × 25 cm column packed with 10 μm SiO_2 using 2% EtOAc–98% CH_2Cl_2 eluant at a flow rate of 3.5 mL/min. The effluant was monitored at 280 nm and the diastereomeric esters (1*R*,2′*R*)-4 and (1*S*,2′*R*)-4 eluted with retention times of 15.3 min and 17.2 min, respectively. The separated diastereomers were collected and the solvent was removed in vacuo to afford (1*R*,2′*R*)-4 and (1*S*,2′*R*)-4 (90% recovery). HPLC analysis of the separated diastereomers showed that the faster eluting diastereomer ((1*R*,2′*R*)-4) was ≥99% pure and the slower eluting diastereomer ((1*S*,2′*R*)-4) was 93% diastereomerically pure. This procedure routinely afforded (1*R*,2′*S*)-4 of ≥99% diastereomeric purity and (1*S*,2′*S*)-4 of 93–98% diastereomeric purity.

(1*R*,2′*R*)-4: $[\alpha]^{23}_D$ −22.8° (*c* 1.29, CH_2Cl_2); $[\alpha]^{23}_{578}$ −24.3° (*c* 1.29, CH_2Cl_2).

(1*S*,2′*R*)-4: $[\alpha]^{23}_D$ −43.8° (*c* 1.17, CH_2Cl_2, 95% optically pure), calcd $[\alpha]^{23}_D$ −46.1° (*c* 1.17, CH_2Cl_2); $[\alpha]^{23}_{578}$ −45.4° (*c* 1.17, CH_2Cl_2, 95% optically pure), calcd $[\alpha]^{23}_{578}$ −47.8° (*c* 1.17, CH_2Cl_2).

5-(Benzyloxy)-3-((*tert*-butyloxy)carbonyl)-1-(hydroxymethyl)-8-methyl-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole (2). The diastereomeric esters (1*R*,2′*R*)-4 (≥99% diastereomerically pure) and (1*S*,2′*R*)-4 (98% diastereomerically pure) were independently subjected to lithium hydroxide promoted ester hydrolysis by treatment of a solution of the ester in 0.5 mL of THF/CH_3OH (3:2) with a solution of aqueous lithium hydroxide (0.1 mL of 4.0 N, 0.4 mmol, 5 equiv). The reaction mixtures were stirred 3 h at 20 °C. The solvents were removed in vacuo and the residues were chromatographed (0.5 × 10 cm SiO_2, 0–10% EtOAc–CH_2Cl_2 gradient elution) to afford (+)-(1*R*)-**2** (25.8 mg, 76% from (±)-**2**) and (−)-(1*S*)-**2** (27.9 mg, 83% from (±)-**2**) as colorless oils. ^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, PhC*H*$_2$O), 4.3–3.65 (m, 6 H, C1-H, C2-H, C*H*$_2$OH and CH_2OH), 2.41 (s, 3 H, CH_3), 1.59 (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 (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*)-2: $[\alpha]^{23}_D$ +7.0° (*c* 0.63, CH_2Cl_2).

(−)-(1*S*)-2: $[\alpha]^{23}_D$ −7.1° (*c* 0.74, CH_2Cl_2).

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Supplementary Material Available: Spectroscopic characterization of **3**, **10**, and **13** (2 pages). Ordering information is given on any current masthead page.

Formation of 9,10-Diphenylanthracene Radical Cation from Friedel–Crafts Alkylation Reactions. Absence of the Triphenylsilyl Radical

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In our continued interest in ESR studies of triphenylmethyl radicals,[1] we noticed that although the triphenylmetal radicals of group IV elements (M = C, Si, Ge, Sn)[2] have been well studied, the ESR spectrum of $Ph_3Si^•$ in solution has not been reported.[3] We demonstrate that well-resolved ESR spectra recorded from mixtures of

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