in 58% efficiency (90% yield based on consumed starting material) by treatment of **18a** with excess *o*-nitrophenyl selenocyanate and $NaBH_4$ (EtOH, 23 °C, 20 h).[14] Oxidation of **19a** (*m*-chloroperoxybenzoic acid, -70 °C, CH_2Cl_2) followed by addition of Me_2S and Et_3N and simple warming to room temperature provided (±)-meloscine (**2**) in 81% yield as a colorless solid, mp 220-222 °C (Et_2O). Spectral (500-MHz ^1H NMR, ^{13}C NMR) properties of this material were consistent with those reported[2,15] and synthetic (±)-**2** was indistinguishable (by TLC comparisons) from an authentic sample of (+)-meloscine kindly provided by Professor J. Lévy. Repetition of this sequence with the minor pentacyclic diastereomer **16b** afforded (±)-epimeloscine (**3**)[2,15] in 43% overall yield from **16b**.

In summary, the *first* total syntheses of the structurally unusual *Melodinus* alkaloids, (±)-meloscine and (±)-epimeloscine, were accomplished by a highly stereocontrolled sequence. These syntheses provide further demonstration of the utility of tandem cationic aza-Cope rearrangement-Mannich cyclization reactions as key elements of alkaloid synthesis design.[1]

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Supplementary Material Available: Experimental procedures for preparing **10** and **16** as well as full characterization data for **7** and **10-19** (12 pages). Ordering information is given on any current masthead page.

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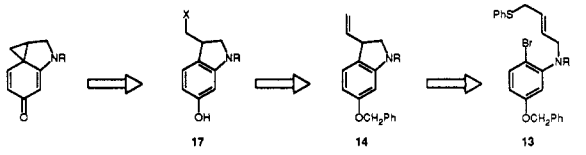
Total Synthesis of (±)-*N*-(Phenylsulfonyl)- and (±)-*N*-(*tert*-Butyloxycarbonyl)-CI, (±)-CI-CDPI$_1$, and (±)-CI-CDPI$_2$: CC-1065 Functional Analogues Incorporating the Parent 1,2,7,7a-Tetrahydrocycloprop[1,2-*c*]indol-4-one (CI) Left-Hand Subunit

Summary: The total synthesis of (±)-*N*-(phenylsulfonyl)- and (±)-*N*-(*tert*-butyloxycarbonyl)-1,2,7,7a-tetrahydrocycloprop[1,2-*c*]indol-4-one [(±)-*N*-(phenylsulfonyl)-CI (**7**) and (±)-*N*-BOC-CI (**8**)] and its incorporation into the total synthesis of (±)-CI-CDPI$_1$ (**5**) and (±)-CI-CDPI$_2$ (**6**), minimum potent pharmacophores of the antitumor antibiotic CC-1065, are detailed.

Sir: (+)-CC-1065 (**1**, NSC-298223)[1] possesses exceptionally potent in vitro cytotoxic activity, broad spectrum antimicrobial activity, and confirmed in vivo antitumor activity. The site and mechanism of the (+)-CC-1065 antitumor activity has been related to its irreversible, covalent alkylation of sequence-selective B-DNA minor groove sites [5′-d(A/GNTTA)-3′ and 5′-d(AAAAA)-3′] and proceeds by acid-catalyzed, 3′-adenine N-3 alkylation of the electrophilic cyclopropane present in the left-hand subunit (CPI) of (+)-CC-1065.[2] In contrast to initial conclusions,[2-4] recent investigations have demonstrated that the sequence-selective DNA binding properties and antitumor activity of (+)-CC-1065 are embodied in the CPI left-hand subunit albeit at a substantially reduced potency (ca. 10000×).[5] Thus, the definition of the structural and functional features of the CC-1065 CPI left-hand subunit that contribute to its sequence-selective B-DNA minor groove binding properties, cytotoxic activity, and intrinsic antitumor activity has become important to the understanding of the properties of the agents.[6-9] Herein we detail the total synthesis of *N*-(phenylsulfonyl)- and *N*-(*tert*-butyloxycarbonyl)-1,2,7,7a-tetrahydrocycloprop[1,2-*c*]indol-4-one [*N*-(phenylsulfonyl)-CI (**7**) and *N*-BOC-CI (**8**)] constituting stable derivatives of the parent spirocyclic cyclopropylcyclohexadienone ring system of the CC-1065 left-hand subunit,[10] describe initial studies of their comparative properties versus the stable N^2-(phenylsulfonyl)-CPI (**3**) and N^2-BOC-CPI (**4**), and detail the incorporation of this parent CI left-hand subunit into the total synthesis of two functional analogues of CC-1065: (±)-CI-CDPI$_1$ (**5**) and (±)-CI-CDPI$_2$ (**6**),[11] constituting

Scheme I



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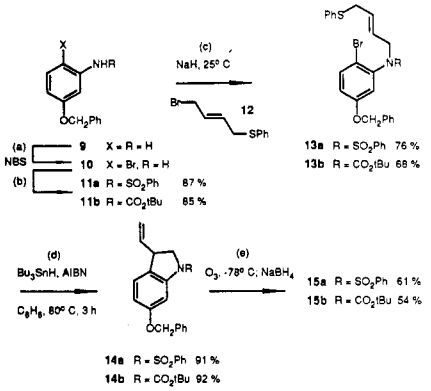
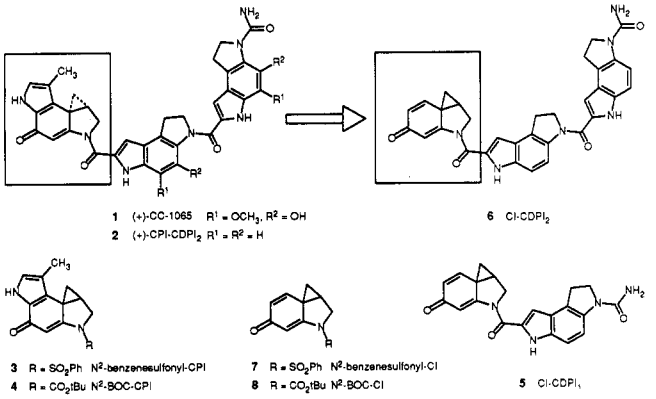
Scheme II[a]



[a] (a) 1.1 equiv of *N*-bromosuccinimide, catalytic H_2SO_4, THF, −78 °C, 10 h, 42%. (b) For R = SO_2Ph, 1.2 equiv of $PhSO_2Cl$, 4.7 equiv of pyridine, THF, 66 °C, 40 h, 87%; for R = CO_2tBu, 6.3 equiv of $(BOC)_2O$, dioxane, 105 °C, 10 h, 85%. (c) For R = SO_2Ph, 1.5 equiv of NaH, 1.4 equiv of **12**, DMF, 25 °C, 2 h, 76%; for R = CO_2tBu, 1.05 equiv of NaH, 1.1 equiv of **12**, THF–DMF (9:1), 25 °C, 3 h, 68%. (d) For R = SO_2Ph, 2.2 equiv of Bu_3SnH, 0.1 equiv of AIBN, benzene, 80 °C, 2 h, 92%; for R = CO_2tBu, 2.1 equiv of Bu_3SnH, 0.1 equiv of AIBN, benzene, 80 °C, 3 h, 91%. (e) For R = SO_2Ph, ozone, ethanol–CH_2Cl_2 (1:1), −78 °C, 8 min; 4.0 equiv of $NaBH_4$, ethanol–H_2O (1:1), −78 °C to 24 °C, 9 h, 61%; for R = CO_2tBu, ozone, ethanol, −78 °C, 3 min; 4.2 equiv of $NaBH_4$, ethanol–H_2O (1:1), −78 °C to 24 °C, 4 h, 54%.

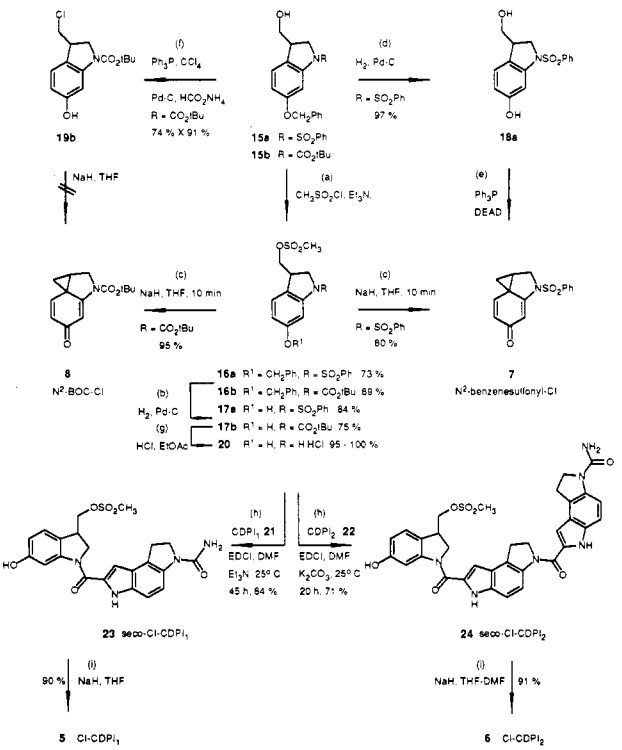
minimum potent pharmacophores of the naturally occurring agent. The potentially prohibitive electrophilic reactivity of the CI derivatives **5**–**8** and the recognition that



the intact parent CI bearing a free amine would not be expected to couple productively with activated carboxylic acids[4,6] including $CDPI_1$ and $CDPI_2$ require that the final step in their preparation constitute the introduction of the activated cyclopropane. Consequently, the total synthesis of the CI derivatives was based on a final intramolecular alkylation (Winstein Ar-3′ alkylation)[12] of an appropriately C-3 functionalized 3-methyl-6-hydroxyindoline (**17**), which in turn was anticipated to be derived indirectly from 3-vinyl-6-(benzyloxy)indoline (**14**), the product of a self-terminating 5-*exo*-*trig* aryl radical-alkene cyclization (**13** → **14**) in an overall approach complementary to that disclosed in our total synthesis of CC-1065[7] (Scheme I).

Alkylation of the sodium salts derived from *N*-(phenylsulfonyl)- and *N*-(*tert*-butyloxycarbonyl)-2-bromo-5-benzyloxyaniline (**11a,b**) with phenyl 4-bromo-2-butenyl sulfide (**12**) provided **13a,b**, the immediate precursors for implementation of self-terminating 5-*exo*-*trig* aryl radical-alkene cyclizations (Scheme II).[13,14] The 5-*exo*-*trig* aryl

Scheme III[a]



[a] (a) For R = SO_2Ph, 1.6 equiv of CH_3SO_2Cl, 2.0 equiv of Et_3N, CH_2Cl_2, 0 °C, 1 h, 73%; for R = CO_2tBu, 1.6 equiv of CH_3SO_2Cl, 2.0 equiv of Et_3N, CH_2Cl_2, 0 °C, 25 min, 89%. (b) For R = SO_2Ph, 1 atm of hydrogen, 0.6 wt equiv 10% Pd/C, THF, 24 °C, 9 h, 84%; for R = CO_2tBu, 1 atm of hydrogen, 0.35 wt equiv 10% Pd/C, THF, 24 °C, 7 h, 75%. (c) For R = SO_2Ph, 3.1 equiv of NaH, THF, 24 °C, 10 min, 80%; for R = CO_2tBu, 4.5 equiv of NaH, THF, 24 °C, 10 min, 95%. (d) 1 atm of hydrogen, 2.5 wt equiv 5% Pd/C, THF, 24 °C, 20 h, 97%. (e) 1.5 equiv of Ph_3P, 1.3 equiv of DEAD, THF, 24 °C, 11 h, see text. (f) (1) 1.4 equiv of Ph_3P, CCl_4, 75 °C, 16 h, 74%; (2) 25% aqueous HCO_2NH_4–THF (1:10), 0.4 wt equiv 10% Pd/C, 24 °C, 12 h, 91%. (g) 3.0 M HCl–EtOAc, 24 °C, 10 min, 95–100%. (h) For **23**, 2.7 equiv of EDCI, 1.6 equiv of **20**, 3.7 equiv of Et_3N, DMF, 24 °C, 45 h, 84%; for **24**, 2.9 equiv of EDCI, 1.0 equiv of **20**, 5.0 equiv of K_2CO_3, DMF, 24 °C, 20 h, 71%. (i) For **5**, 1.5 equiv, NaH, THF, 24 °C, 25 min, 90%; for **6**, 1.5 equiv, NaH, 2:1 THF–DMF, 24 °C, 25 min, 91%.

radical-alkene cyclizations of **13a,b** were effected by treatment with tri-*n*-butyltin hydride (2.1 equiv, 0.1 equiv AIBN, benzene, 80 °C) under conditions described by Ueno and co-workers[13] and afforded the *N*-(phenylsulfonyl)- and *N*-(*tert*-butyloxycarbonyl)-6-(benzyloxy)-3-vinylindoline (**14a,b**). Oxidative cleavage of the carbon–carbon double bond under carefully controlled conditions for ozonolysis followed by direct sodium borohydride reduction of the crude ozonide provided *N*-(phenylsulfonyl)- and *N*-(*tert*-butyloxycarbonyl)-6-(benzyloxy)-3-(hydroxymethyl)indoline (**15a,b**).

Activation of the primary alcohol toward intramolecular alkylation through methanesulfonate formation (2.0 equiv of Et_3N, 1.6 equiv of CH_3SO_2Cl, 0 °C), catalytic hydrogenolysis (H_2/10% Pd–C cat.) of the benzyl ether, which proved to proceed without competitive hydrogenolysis of the methanesulfonate, followed by intramolecular Ar-3′ alkylation promoted by the treatment of **17a,b** with sodium hydride (10 min, THF, 24 °C) provided *N*-(phenylsulfonyl)- and *N*-(*tert*-butyloxycarbonyl)-CI (**7** and **8**) (Scheme III). Initial attempts to promote the intramo-

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Table I

agent	7	8	3	4	5	6
UV λ_{max}, nm (ϵ)	287 (9000)[a]	294 (14000)[a]	344 (–)[b]	344 (12000)[b]	321 (15000)[a]	328 (35000)[a]
	260 (10000)	258 (21000)	275 (–)	278 (17000)	300 (14000)	304 (32000)
					268 (14000)	278 (25000)
IR C=O (cm^{-1})	1612	1618, 1704	1616	1570, 1725[b]	1602, 1658	1611, 1636
$t_{1/2}$[c] pH = 7	15 s	30 s	stable	stable	≤15 s	≤15 s
pH = 3	–	–	64 h[b]	38.5 h[b]	–	–
IC_{50} (μg/mL)[d]						
L1210[e]	3.6 (0.2)	9.0 (0.2)	0.9[b]	0.1	0.008 (0.03)	0.05–0.0004 (0.006)

[a] Solvent = THF for 7 and 8, DMF for 5 and 6. [b] Taken from ref 4; UV solvent = 10% H_2O–CH_3OH (3), CH_3OH (4). [c] Half-life ($t_{1/2}$) in 50% H_2O–THF for 7 and 8 and 50% H_2O–DMF for 5 and 6 at pH = 7; and 50% THF–buffer at pH = 3 as monitored by UV. Buffer is 4:1:20 (v/v) 0.1 M citric acid, 0.2 M Na_2HPO_4, and water, respectively. [d] IC_{50} = inhibitory concentration for 50% cell growth relative to untreated controls. The value in parentheses refers to the *O*-methanesulfonate seco agents **17a**, **17b**, **23**, and **24**, respectively. [e] L1210 mouse lymphocytic leukemia cell culture. The comparative IC_{50} for (+)-1 and (+)-2 are 1.1×10^{-5} and 1.2×10^{-5} μg/mL, respectively.[7]

lecular Winstein Ar-3′ alkylation directly on alcohol **18a** employing the in situ alcohol activation and intramolecular alkylation conditions introduced by Mitsunobu (triphenylphosphine, diethyl azodicarboxylate, THF, 24 °C)[15] provided *N*-(phenylsulfonyl)-CI (**7**) although the reactivity of **7** precluded attempts to preparatively separate it from the reaction byproducts. Additional, early attempts to promote the closure of **19b** possessing a less reactive chloride leaving group failed to provide **8** and afforded recovered **19b**. Although **7** proved too reactive toward nucleophilic addition to survive purification by conventional chromatographic methods (SiO_2), **8** proved marginally stable to conventional chromatographic purification.[16] Both have proven to be more stable than might be anticipated, presumably the consequence of vinylogous imide stabilization of the cyclohexadienone structure.[17] Table I details a preliminary evaluation of the properties and stability of the CI (**7**, **8**) versus CPI (**3**, **4**) agents. In contrast to the CPI system,[4] *N*-BOC-CI proved more stable than *N*-(phenylsulfonyl)-CI.

The incorporation of the parent CI left-hand subunit into two functional analogues of CC-1065, CI-$CDPI_1$ (**5**) and CI-$CDPI_2$ (**6**), is detailed in Scheme III. Treatment of **17b** with anhydrous hydrochloric acid (3 N HCl, EtOAc, 24 °C, 10 min) afforded the unstable indoline hydrochloride **20**, which was coupled directly with CDPI[11] [**21**, 3-carbamoyl-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-carboxylic acid] and CDPI dimer[11] [$CDPI_2$, **22**] in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (2.7–2.9 equiv of EDCI, DMF, 24 °C) to afford **23** (84%) and **24** (71%), respectively. Final Ar-3′ alkylative ring closure of **23** and **24** (1.5 equiv of NaH, 25 min, 24 °C) provided CI-$CDPI_1$ (**5**, 90%) and CI-$CDPI_2$ (**6**, 91%).[16]

Evidence for the covalent interaction of the stable seco agents **23** and **24** with DNA was obtained from the thermally induced strand cleavage of double-stranded DNA after exposure to the agents (autofootprinting).[5] Autofootprinting was carried out with use of a 5′-end labeled fragment of SV40 (b.p. 4210-4359) cloned into the Sma 1 site of the M13 polylinker region [agent:DNA incubation at 4 °C, 24 h; 90 °C, 30 min], and the observed sites of covalent alkylation and their relative intensity (sequence specificity) have proven *identical* for **23**, **24**, and (+)-CC-1065 (**1**), Figure 1 (supplementary material).[18] The comparable in vitro cytotoxic activity of the CI and CPI derivatives, the surprisingly robust cytotoxic activity of the CI derivatives despite their limited stability, the stability of the precursor seco agents (**17a,b**, **23**, and **24**, Table I), and their capability to serve as stable in vitro/in vivo precursors of the reactive CI agents, the comparable potentiation of the CI effects with its incorporation into the agents CI-$CDPI_1$ and CI-$CDPI_2$ like that observed with CPI, and the *identical* sequence-selective covalent alkylation of DNA exhibited by **23**, **24**, and (+)-CC-1065 suggest that the agents are acting by a comparable mechanism. Thus, the agents **5**–**8** bearing the reactive, parent 1,2,7,7a-tetrahydrocycloprop[1,2-*c*]indol-4-one (CI) subunit of the left-hand CPI segment of CC-1065 embody the fundamental, minimum structural features of the agents responsible for the observed properties. Further studies on the agents **5**–**8** and their biologically active, stable precursor agents **17a,b**, **23**, and **24** are in progress and will be reported in due course.

Acknowledgment. This work was assisted through the financial support of the National Institutes of Health (Grant CA 41986) and the Alfred P. Sloan Foundation. We thank Dr. B. J. Invergo and Dr. M. Yasuda for early experimental contributions to this work, Professor P. A. Kitos and Sandra Collins Thompson (University of Kansas) for preliminary in vitro cytotoxicity testing (L1210, B16), and Professor M. Bina and Dr. S. A. Munk for preliminary autofootprinting results.

Supplementary Material Available: A detailed experimental for the preparation of **12**, full physical and spectroscopic characterization of **9**–**19**, **23**–**24**, and **5**–**8**, the ^1H NMR spectra (300 MHz) of **7**–**8**, and a figure illustrating the comparative footprinting of **24** and (+)-CC-1065 (12 pages). Ordering information is given on any current masthead page.

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(16) Although **7** and **8** could be clearly visualized by TLC (SiO_2, R_f = 0.30, 60% EtOAc–hexane), attempts to isolate **7** by chromatography (alumina, florisil, silica gel, or silica gel deactivated with 0.1–1.0% triethylamine or acetone) led to decomposition. However, **8**, despite degradation on alumina and florisil, could be isolated by silica gel chromatography, albeit with 10–25% recovery. In view of these difficulties, we found it most convenient to isolate the agents by filtration of the reaction mixture to remove inorganic salts (CH_3SO_3Na) and in vacuo concentration of the filtrate in a foil-wrapped flask submerged in a water bath maintained at 15–20 °C. The agents **5**–**8** isolated by this procedure were found to be homogeneous by TLC and ^1H NMR (supplementary material), stable to storage as solids, and stable in most anhydrous aprotic solvents carefully freed of adventitious acid.

(17) Preliminary studies [MOPAC; AM1, MNDO] had suggested that the CI system (N^2-acetyl-CI) should be more susceptible to nucleophilic ring opening of the activated cyclopropane than CPI derivatives [e.g., N^2-acetyl-CPI, $\Delta\Delta H°$ for the N-3 addition of adenine = 8.8 (AM1) and 9.0 (MNDO) kcal]. Full details of this study and its relationship to the sequence-selective B-DNA binding properties of the CI derivatives will be described in a full account of this work.

(18) Munk, S. A.; Bina, M.; Boger, D. L. Unpublished observations. Full details of this study will be described in a full account of this work.

(19) National Institutes of Health research career development award recipient, 1983–1988 (CA 01134). Alfred P. Sloan Research Fellow, 1985–1989.