the conversion was much slower (20 h) and other unidentified products were formed. TLC comparison with an authentic sample of (-)-koumine showed an identical R_f; $[\alpha]_D^{24}$ +218° (c 0.200, EtOH); IR ($CHCl_3$) 3050-2850, 1700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.63 (1 H, d, J = 7.6 Hz), 7.57 (1 H, d, J = 7.4 Hz), 7.38 (1 H, td, J = 7.6, 1.2 Hz), 7.27 (1 H, td, J = 7.4, 1.1 Hz), 5.04 (1 H, ddd, J = 3.6, 2.4, 1.1 Hz), 4.85 (1 H, dd, J = 17.5, 1.2 Hz), 4.81 (1 H, dd, J = 11.2, 1.2 Hz), 4.70 (1 H, dd, J = 17.5, 11.2 Hz), 4.28 (1 H, dd, J = 12.0, 4.4 Hz), 3.64 (1 H, d, J = 12.0 Hz), 3.19 (1 H, d, J = 11.4 Hz), 3.12 (1 H, d, J = 11.4 Hz), 2.84-2.81 (2 H, m), 2.63 (3 H, s), 2.63 (1 H, dt, J = 14.7, 3.8 Hz), 2.42 (1 H, dt, J = 14.3, 1.9 Hz), 2.38 (1 H, dd, J = 14.3, 3.3 Hz), 2.36 (br d, J = 11.7 Hz), 1.90 (1 H, dt, J = 14.7, 2.1 Hz); EIMS (m/e) 306 (M^+, base), 293, 281, 243, 231, 219, 193, 181, 169, 163, 192, 151, 143, 131, 119, 113, 100, 93, 69; HRMS m/e calcd for $C_{20}H_{22}N_2O$ 306.1734, found 306.1734.

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Synthesis of *N*-(Phenylsulfonyl)-CI, *N*-((*tert*-Butyloxy)carbonyl)-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

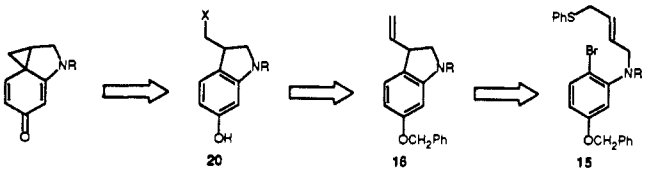
Dale L. Boger,*[1a] Ronald J. Wysocki, Jr., and Takayoshi Ishizaki[1b]

Contribution from the Department of Chemistry, Purdue University, West Lafayette, Indiana 47907. *Received January 11, 1990*

Abstract: Full details of the synthesis of *N*-(phenylsulfonyl)- and *N*-((*tert*-butyloxy)carbonyl)-1,2,7,7a-tetrahydrocycloprop[1,2-*c*]indol-4-one [*N*-(phenylsulfonyl)-CI (**9**) and *N*-BOC-CI (**10**)] constituting stable derivatives of the parent cyclopropylcyclohexadienone ring system of the CC-1065 left-hand subunit are described. The resolution of an immediate CI synthetic precursor, (+)- and (-)-**17b**, and the incorporation of (±)-, (+)-, and (-)-**17b** into the synthesis of racemic and optically active CI-CDPI$_1$ (**7**) and CI-CDPI$_2$ (**8**) are detailed.

(+)-CC-1065 (**1**, NSC-298223), an antitumor-antibiotic isolated from cultures of *Streptomyces zelensis*,[2] possesses exceptionally potent in vitro cytotoxic activity, broad spectrum antimicrobial activity, and confirmed in vivo antitumor activity. In a series of extensive investigations, the site and mechanism of the (+)-CC-1065 antitumor activity have 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′] that has been demonstrated to proceed by 3′-adenine *N*-3 alkylation of the electrophilic spiro[2.5]octa-4,7-dien-6-one present in the left-hand segment (CPI) of (+)-CC-1065.[3] In contrast to conclusions drawn from early efforts,[2-4] recent investigations have suggested that the sequence-selective DNA binding properties as well as the intrinsic antitumor activity of (+)-CC-1065 may be embodied in the CPI left-hand segment albeit with substantially reduced potency (ca. 10000×).[5] However, the additional observations of the distinct and indistinguishable cytotoxic potency of the enantiomeric pairs of agents, (+)-CC-1065 (**1**)/*ent*-(-)-CC-1065 (**2**)[6] and (+)-CPI-CDPI$_2$ (**3**)/(-)-CPI-CDPI$_2$ (**4**),[7,8] the contrasting observation of the lack of potent cytotoxic activity exhibited by simplified[4] and aborted[9] agents bearing the enantiomeric CPI left-hand subunit, the demonstrated A-T rich noncovalent DNA binding selectivity of simplified agents including CDPI$_3$ methyl ester,[10] and the recent results of direct comparative footprinting studies of a series of structurally related agents[5,9] have suggested that the CC-1065 central and right-hand segments may simply potentiate[5] *and/or* alter[9] the DNA binding properties of the class of agents bearing the intact CPI left-hand subunit. Consequently, 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 ac-

Scheme I



†The numbering system used for the parent CI is not that given in the *Ring Systems Handbook*. For consistency with related work, the numbering sequence follows that used for CPI in the *Ring Systems Handbook*.

(1) (a) National Institutes of Health research career development award recipient, 1983-1988 (CA 01134). Alfred P. Sloan Foundation research fellow, 1985-1989. (b) On sabbatical from Kyorin Pharmaceutical Co., Ltd., Tochigi, Japan.

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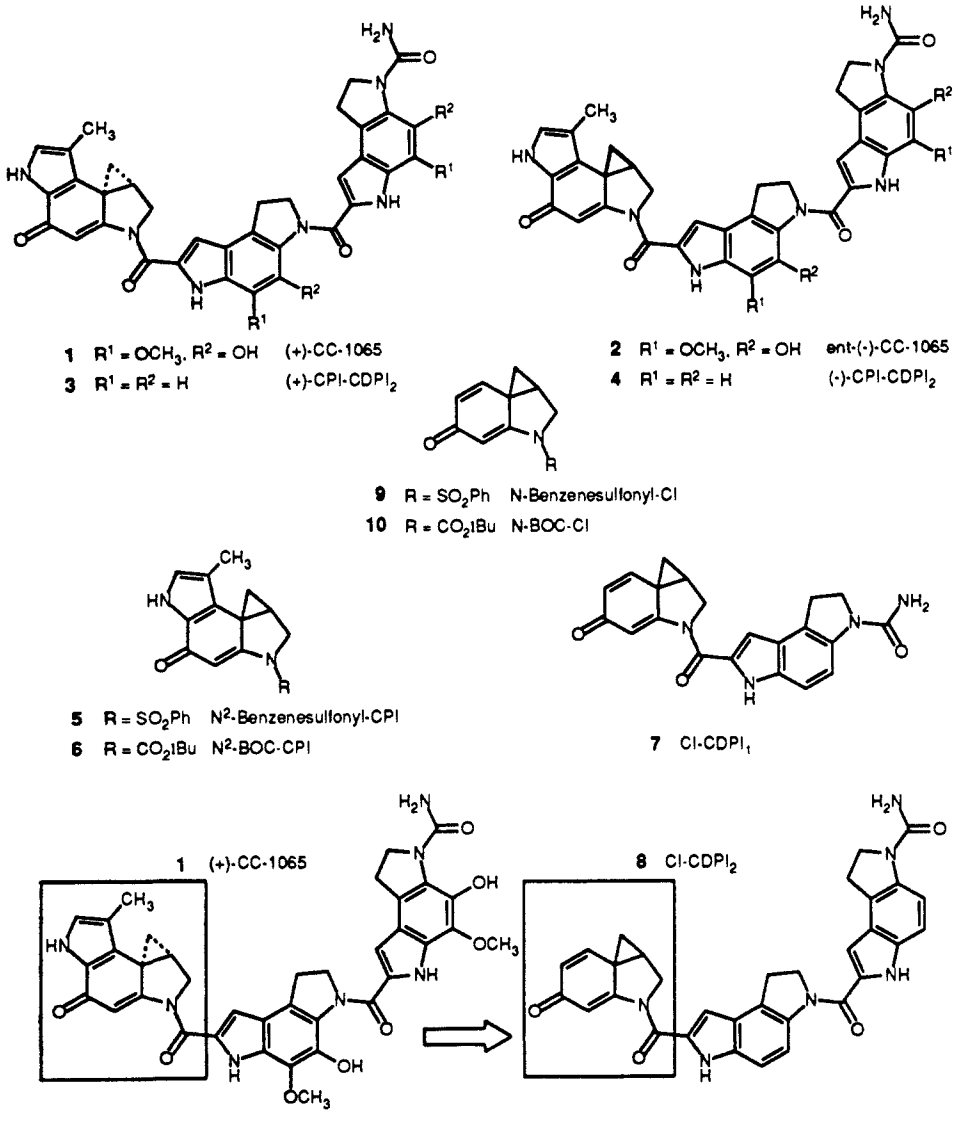

Figure 1.

tivity, and intrinsic antitumor activity has become important to the understanding of the properties of the agents. In efforts directed toward this end, herein we provide full details[11] of the synthesis of *N*-(phenylsulfonyl)- and *N*-(*tert*-butyloxycarbonyl)-1,2,7,7a-tetrahydrocycloprop[1,2-*c*]indol-4-one [*N*-(phenylsulfonyl)-CI (**9**) and *N*-BOC-CI (**10**)] constituting stable derivatives of the parent ring system of the CC-1065 left-hand segment. The resolution of an immediate CI precursor and the incorporation of the parent CI left-hand subunit into racemic and optically active functional analogues of CC-1065, CI-CDPI$_1$ (**7**) and CI-CDPI$_2$ (**8**), are described.

The potentially prohibitive reactivity of the CI derivatives **7–10** along with the recognition that preformed CI would not be expected to couple productively with activated carboxylic acids including CDPI$_1$ (3-carbamoyl-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]-indole-7-carboxylic acid)[12] and CDPI$_2$ (CDPI-dimer)[12] suggested that the final step in their preparation be the introduction of the activated cyclopropane. Consequently, the approach employed in the total synthesis of the CI agents was based on a final intramolecular Winstein Ar-3′ alkylation[13] of an appropriately C-3 functionalized 3-methyl-6-hydroxyindoline **20** (Scheme I). This in turn was anticipated to be derived indirectly from 3-vinyl-6-benzyloxyindoline **16**, the product of a self-terminating 5-*exo-trig* aryl radical–alkene cyclization (**15** → **16**) in an overall approach complementary to that disclosed in a total synthesis of CC-1065.[7]

Synthesis of *N*-(Phenylsulfonyl)-CI. In recent reports we have detailed the utility of both a 5-*exo-dig* aryl radical–alkyne cyclization and a self-terminating 5-*exo-trig* aryl radical–alkene cyclization[14-16] for the indirect preparation of functionalized

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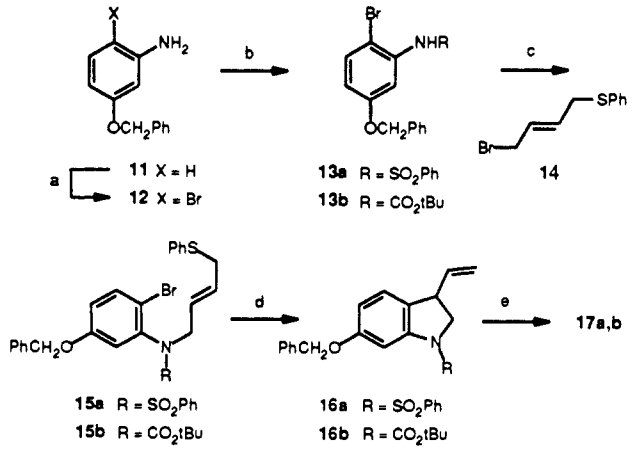
Scheme II[a]



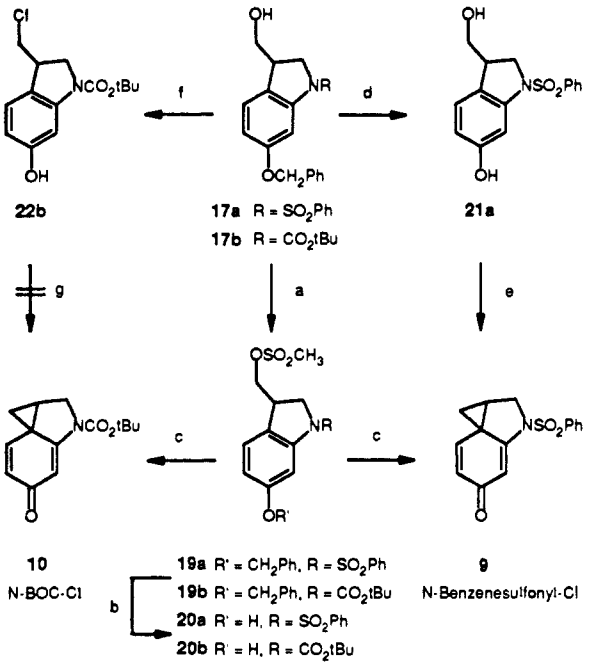
[a] 1.0 equiv of *N*-bromosuccinimide, catalytic H_2SO_4, THF, −78 °C, 1 h, 60%. [b] For R = SO_2Ph: 1.2 equiv of $PhSO_2Cl$, 4.7 equiv of pyridine, THF, 66 °C, 40 h, 87%. For R = CO_2tBu: 6.3 equiv of $(tBuOCO)_2O$, dioxane, 105 °C, 10 h, 85%. [c] For R = SO_2Ph: 1.5 equiv of NaH, 1.4 equiv of **14**, DMF, 24 °C, 2 h, 76%. For R = CO_2tBu: 1.0 equiv of NaH, 1.1 equiv of **14**, THF–DMF (9:1), 24 °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 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 to 24 °C, 4 h, 54%.

3-(hydroxymethyl)indolines. The implementation of the former proved most expedient for introduction of the 3-(hydroxymethyl)pyrroline C ring found in the CPI left-hand segment of CC-1065 and structurally related agents[7,9] in spite of the problematic 3-methyleneindoline to 3-methylindole isomerization that precludes purification of such intermediates by standard chromatographic techniques. Our use of this approach in the preparation of the CPI-based agents may be attributed to the competitive oxidation of indoles with the oxidative cleavage of the vinyl carbon–carbon double bond required for implementation of the self-terminating 5-*exo-trig* aryl–alkene cyclization.[7] Herein we detail the successful implementation of the self-terminating 5-*exo-trig* aryl radical–alkene cyclization in the preparation of the CI agents.

The implementation of the self-terminating aryl radical–alkene cyclization for use in the preparation of the 6-(benzyloxy)-3-(hydroxymethyl)indolines **17** is detailed in Scheme II. Low-temperature, acid-catalyzed bromination[17] of 3-(benzyloxy)aniline (**11**) employing *N*-bromosuccinimide (1.0 equiv, catalytic H_2SO_4, −78 °C) provided 5-(benzyloxy)-2-bromoaniline (**12**).[18] Treatment of **12** with phenylsulfonyl chloride followed by N-alkylation of the sodium salt of the benzenesulfonamide **13a** with (*E*)-1-bromo-4-(phenylthio)-2-butene[7b,15] (**14**) afforded **15a**. The self-terminating 5-*exo-trig* aryl radical–alkene cyclization[15] was effected by treatment of **15a** with tri-*n*-butyltin hydride (2.1 equiv) in the presence of a catalytic amount of 2,2′-azobis(2-methylpropionitrile) (AIBN, 0.1 equiv, benzene, 2 h) at 80 °C and provided 3-vinylindoline **16a** in 92% yield.[19] Careful ozonolysis of **16a** in a solution of dichloromethane–ethanol (1:1) at −78 °C followed by direct reduction of the crude ozonide[20] (4.0 equiv $NaBH_4$, 1:1 ethanol–H_2O, −78 to 24 °C, 9 h, 61%) cleanly provided 3-(hydroxymethyl)indoline **17a**. Initial attempts to effect this oxidative olefin cleavage with introduction of ozone at 0 °C followed by sodium borohydride reduction provided the desired 3-(hydroxymethyl)indoline **17a** as the sole organic extractable product in a modest 20% yield, and the use of an indicator dye, Sudan Red,[21a] or a solution of sodium iodide in acetic acid (iodine-discharge trap)[21b] to monitor the ozone consumption was found to be insufficient for determining the endpoint consumption of **16a**.[22]

It was anticipated that direct Ar-3′ cyclization of **21a** to **9** could be achieved by Mitsunobu[23] activation and intramolecular alkylation as implemented in a synthesis of the left-hand CPI subunit

Scheme III[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 of 10% Pd–C, THF, 24 °C, 9 h, 84%. For R = CO_2tBu: 1 atm of hydrogen, 0.35 wt equiv of 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 of 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 of 10% Pd–C, 24 °C, 12 h, 91%. [g] NaH, THF or DMF, 24 °C, 0–8 h, no reaction.

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(18) A study of this reaction revealed that higher yields of **12** (55–60% on a 5-g scale) may be obtained by freshly generating 3-(benzyloxy)aniline (**11**) through O-benzylation of 3-acetamidophenol (1.0 equiv of NaH, 1.05 equiv of benzyl bromide, THF, 66 °C, 8 h) followed by *N*-deacetylation (9.0 equiv of KOH, absolute ethanol, 24 °C, 8 h) rather than employing commercial material.

(19) Increasing the amount of initiator AIBN (0.2 to 0.25 equiv) was found to shorten the reaction times from 2 h to 0.5 h without altering the yield.

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(22) Subjection of **16a** to the conditions of the Johnson–Lemieux oxidation (catalytic OsO_4, 3.0 equiv of $NaIO_4$, 3:1 acetone–H_2O) served only to consume starting material without productively affording characterizable products. Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.

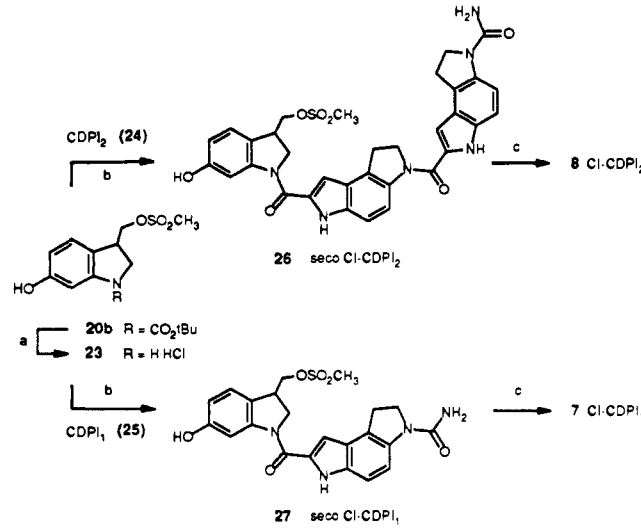
(23) Mitsunobu, O. *Synthesis* **1981**, 1.

of CC-1065.[24] Catalytic hydrogenolysis (1 atm of H_2, 5% Pd–C catalyst, THF, 24 °C) effected cleavage of the benzyl ether protecting group and cleanly provided **21a** in 97% yield (Scheme III). Treatment of **21a** with 1.5 equiv of triphenylphosphine and 1.3 equiv of diethyl azodicarboxylate in tetrahydrofuran (24 °C, 11 h) afforded a clean conversion to *N*-(phenylsulfonyl)-CI (**9**) as judged by ^{1}H NMR. Although this product was clearly visualized by thin-layer chromatography (R_f = 0.3, 60% ethyl acetate–hexane), repeated attempts to isolate *N*-(phenylsulfonyl)-CI (**9**) free from the Mitsunobu reaction byproducts by column chromatography (alumina, florisil, silica gel or silical gel deactivated with 0.1 to 1.0% triethylamine or acetone) led to decomposition of the agent. Consequently, activation of the primary alcohol **17a** toward intramolecular alkylation through methanesulfonate formation[25] (1.6 equiv of CH_3SO_2Cl, 2.0 equiv of Et_3N, CH_2Cl_2, 0 °C, 73%) and subsequent *O*-benzyl ether deprotection by catalytic hydrogenolysis (1 atm of H_2, 10% Pd–C catalyst, THF, 24 °C, 84%) provided **20a**. Completion of the synthesis required the use of a nonnucleophilic, insoluble base to effect the intramolecular Ar-3′ alkylation thereby avoiding the difficulties of separating the CI agent from soluble reaction byproducts. Addition of a tetrahydrofuran solution of **20a** to a suspension of mineral oil-free sodium hydride (3.1 equiv) in tetrahydrofuran (24 °C, 10 min) provided *N*-(phenylsulfonyl)-CI (**9**) homogeneous by thin-layer chromatography. Removal of the insoluble materials (CH_3SO_3Na, NaH) followed by removal of the tetrahydrofuran in vacuo in a base-treated, oven-dried flask shielded from light submerged in a water bath maintained at 15–20 °C afforded **9** in 80% yield and homogeneous by ^{1}H NMR. Initial studies employing potassium carbonate (5.0 equiv) failed to promote spirocyclization and only resulted in unchanged recovered starting material.

Synthesis of *N*-((*tert*-Butyloxy)carbonyl)-CI. Treatment of 5-(benzyloxy)-2-bromoaniline with di-*tert*-butyl dicarbonate (6.3 equiv of dioxane, 105 °C, 10 h, 85%) provided **13b**. Lower reaction temperatures (<100 °C) surprisingly led to little or no reaction, and the use of a catalytic amount of 4-(dimethylamino)pyridine (DMAP, 0.1 equiv) provided competitive formation of bisacylated product (Scheme II). *N*-Alkylation of **13b** with (*E*)-1-bromo-4-(phenylthio)-2-butene (**14**) followed by implementation of the self-terminating 5-*exo*-*trig* aryl radical–alkene cyclization (2.1 equiv of Bu_3SnH, 0.1 equiv of AIBN, benzene, 80 °C, 3 h, 91%) afforded 3-vinylindoline **16b** in excellent yield.[19] Oxidative cleavage of the carbon–carbon double bond under carefully controlled reaction conditions for ozonolysis (ozone, ethanol, −78 °C, 3 min) and direct sodium borohydride reduction of the crude ozonide[20] afforded 1-((*tert*-butyloxy)carbonyl)-6-(benzyloxy)-3-(hydroxymethyl)indoline (**17b**).

In initial attempts to promote the spirocyclization in the preparation of *N*-BOC-CI, substrates bearing a chloride leaving group were investigated.[3,11] Direct conversion of alcohol **17b** to the primary chloride was accomplished with 1.4 equiv of triphenylphosphine–carbon tetrachloride[26] (75 °C, 16 h, 74%) (Scheme III). The *O*-benzyl ether was cleaved selectively by two-phase, catalytic transfer hydrogenolysis with 10% palladium-on-carbon catalyst and 25% aqueous ammonium formate[27] as the hydrogen donor without the observation of competitive hydrogenolysis of the primary chloride. Unsuccessful attempts to promote the Ar-3′ closure of **22b** with sodium hydride (1.5 equiv, THF or DMF, 24 °C, >8 h) served only to provide a quantitative recovery of starting material. Consequently, methanesulfonate[25] formation (1.6 equiv of CH_3SO_2Cl, 2.0 equiv of Et_3N, CH_2Cl_2, 0 °C, 25 min, 89%) afforded **19b** followed by *O*-debenzylation through catalytic hydrogenolysis provided **20b**. Competitive methanesulfonate hydrogenolysis[28] to afford *N*-((*tert*-butyloxy)-carbonyl)-6-hydroxy-3-methylindoline as a reaction byproduct was observed but could be avoided by using a minimum amount of fresh, activated 10% palladium-on-carbon catalyst (0.35 wt equiv). Under such conditions, this reaction did require longer reaction times (7–30 h) for complete O-debenzylation and clean **20b** could be obtained in 75% yield. Analogous to the final step for the preparation of *N*-(phenylsulfonyl)-CI, treatment of **20b** with sodium hydride (4.5 equiv, THF, 24 °C, 10 min) provided *N*-BOC-CI (**10**, 95%). In contrast to **9**, *N*-BOC-CI (**10**) could be purified by silica gel chromatography albeit with degradation and in 25%–65% recovery,[29] and like **9** it suffered complete degradation on alumina and florisil. Consequently the isolation of substantial quantities of pure *N*-BOC-CI was accomplished best following the protocol developed for the isolation of *N*-(phenylsulfonyl)-CI.

Scheme IV[a]



[a] 3.0 M HCl–EtOAc, 24 °C, 10 min, 95–100%. [b] For **27**: 2.7 equiv of EDCI, 1.6 equiv of **23**, 3.7 equiv of Et_3N, DMF, 23 °C, 45 h, 84%. For **26**: 2.9 equiv of EDCI, 1.0 equiv of **23**, 5.0 equiv of K_2CO_3, DMF, 24 °C, 20 h, 71%. [c] For **7**: 1.5 equiv of NaH, THF, 24 °C, 25 min, 90%. For **8**: 1.4 equiv of NaH, THF–DMF (2:1), 24 °C, 25 min, 91%.

Synthesis of CI-CDPI$_1$ (7) and CI-CDPI$_2$ (8). Removal of the *N*-((*tert*-butyloxy)carbonyl) protecting group of *seco*-*N*-BOC-CI (**20b**, 3.0 *M* HCl-EtOAc, 24 °C, 10 min) followed by immediate coupling of the unstable indoline hydrochloride **23**[30] directly with $CDPI_1$ (**25**)[12] in the presence of 1-[(3-dimethylamino)propyl]-3-ethylcarbodiimide (EDCI, 2.7 equiv, 3.7 equiv of Et_3N, DMF, 23 °C, 45 h) afforded *seco*-CI-$CDPI_1$ (**27**, 84%) (Scheme IV). Shorter reaction times led to reduced yields of **27**, and the use of sodium bicarbonate or potassium carbonate as base failed to promote the coupling of the agents. The final Ar-3′ spirocyclization was effected by treatment of **27** with sodium hydride (1.5 equiv, THF, 24 °C) and afforded CI-$CDPI_1$ (**7**) in 90% isolated yield. In a similar manner, CI-$CDPI_2$ (**8**) was prepared by coupling the unstable indoline hydrochloride **23**[30] with $CDPI_2$[12] (**24**, 2.9 equiv of EDCI, 5.0 equiv of K_2CO_3, DMF, 24 °C, 20 h, 71%) followed by intramolecular alkylation effected by treatment of **26** with sodium hydride (1.4 equiv, THF–DMF (2:1), 24 °C, 25 min, 91%).

For comparative evaluation purposes, the agents **29**, **32–35** were prepared and constitute agents that cannot undergo Winstein Ar-3′ alkylation with closure to the parent CI agents (Scheme V).

(+)- and (−)-20b: Resolution of a CI Precursor. Reaction of 6-(benzyloxy)-1-((*tert*-butyloxy)carbonyl)-3-(hydroxymethyl)-indoline (**17b**) with (*R*)-(−)-*O*-acetylmandelic acid (1.5 equiv, 1.8

(24) Magnus, P. D.; Gallagher, T.; Schultz, J.; Or, Y.-S.; Ananthanarayan, T. P. *J. Am. Chem. Soc.* **1987**, *109*, 2706. Magnus, P. D.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1984**, 289. Magnus, P. D.; Or, Y.-S. *J. Chem. Soc., Chem. Commun.* **1983**, 26.
(25) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.
(26) Hooz, J.; Gilani, S. S. H. *Can. J. Chem.* **1968**, *46*, 86.
(27) Ram, S.; Ehrenkaufer, R. E. *Synthesis* **1988**, 91. Bieg, T.; Szeja, W. *Synthesis* **1985**, 76.

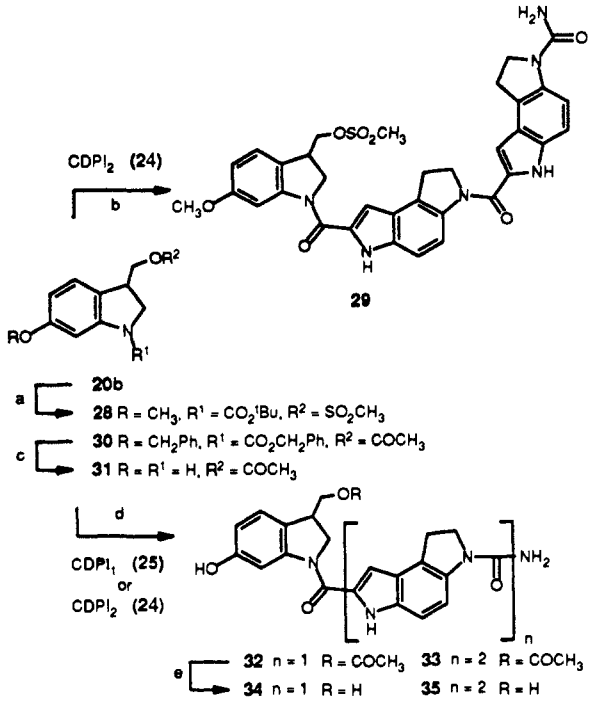
(28) Although direct hydrogenolysis of the primary mesylate may provide this product, it may be derived through intramolecular cyclization to **10** followed by hydrogenation of the activated cyclopropane.
(29) For related observations, see ref 11c.
(30) Indoline hydrochloride **23** immediately discolors upon exposure to air.

Table I. Comparative Properties of the CI- and CPI-Based Agents

	BOC-CI (**10**)	$PhSO_2$-CI (**9**)	BOC-CPI (**6**)	$PhSO_2$-CPI (**5**)
UV, λ_{max}, nm (ϵ)	294 (14000)[a] 258 (21000)	287 (9000)[a] 260 (10000)	344 (12000)[b,c] 278 (17000)	344[c,d] 275
IR(C=O), cm^{-1}	1618, 1705	1612	1570, 1725[c]	1616
$t_{1/2}$, pH = 7[e]	5.24 h		stable[c]	stable[c]
$t_{1/2}$, pH = 3 (rel)	35 s (0.0003)	≤15 s (≤0.0001)	36.7 h (1)[c]	64 h (1.8)[c]
	CI-$CDPI_1$ (**7**)	CI-$CDPI_2$ (**8**)	CC-1065 (**1**)	CPI-$CDPI_2$ (**3**)
UV λ_{max}, nm (ϵ)	321 (15000)[f] 300 (14000) 268 (14000)	328 (35000)[f] 304 (32000) 278 (25000)	364 (49100)[c,g] 258 (31200) 236 (36100)	355 (34000)[b,h] 318 (40000)
IR(C=O), cm^{-1}	1602, 1658	1611, 1636	1634, 1577	1635, 1605, 1576
$t_{1/2}$, pH = 7			stable	stable
$t_{1/2}$, pH = 3	≤15 s	≤15 s		

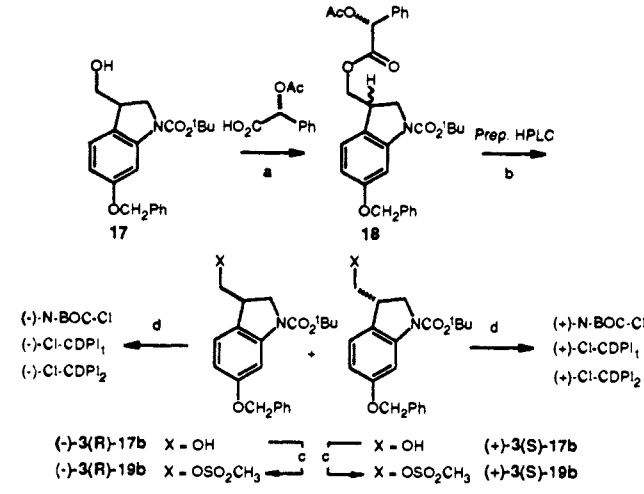
[a] THF. [b] CH_3OH. [c] Taken from ref 4, solvolysis data for CH_3SO_2-CPI vs **5**. [d] 10% H_2O-CH_3OH. [e] Half-life ($t_{1/2}$) in 50% H_2O-THF (**9**), 50% H_2O-CH_3OH (**1**, **3**, **5**, **6**, **10**), 50% H_2O-DMF (**7**, **8**), pH = 7; 50% buffer-CH_3OH, pH = 3 for **5**, **6**, and **10**. Buffer is 4:1:20 (v:v:v) 0.1 M citric acid, 0.2 M Na_2HPO_4, and water, respectively. [f] DMF. [g] Dioxane. [h] Taken from ref 8.

Scheme V[a]



[a] CH_2N_2, CH_2Cl_2-Et_2O, 25 °C, 90%. [b] 3.0 M HCl-EtOAc, 24 °C, 10 min, 100%; 3.0 equiv of EDCI, 1.0 equiv of **24**, DMF, 23 °C, 24 h, 60%. [c] 1 atm of hydrogen, 0.16 wt equiv of 10% Pd-C, THF, 22 °C, 13 h, 70%. [d] For **32**: 1.01 equiv of **25**, 3 equiv of EDCI, THF, 22 °C, 48 h, 60%. For **33**: 0.88 equiv of **24**, 3 equiv of EDCI, 22 °C, 8.5 h, 44%. [e] For **34**: 5 equiv of LiOH, THF-MeOH-H_2O (3:2:1), 22 °C, 3 h, 94%. For **35**: 3 equiv of LiOH, THF-MeOH-H_2O (3:2:1), 22 °C, 1 h, 90%.

Scheme VI[a]



[a] 1.5 equiv of $PhC^RH(OAc)CO_2H$, 1.8 equiv of EDCI, 0.1 equiv of DMAP, CH_2Cl_2, 23 °C, 9 h, 92%; HPLC separation, 86% recovery. [b] 4.0 equiv of LiOH, THF-H_2O (4:1), 23 °C, 4 h, 75-78%. [c] See Scheme III. [d] See Scheme IV.

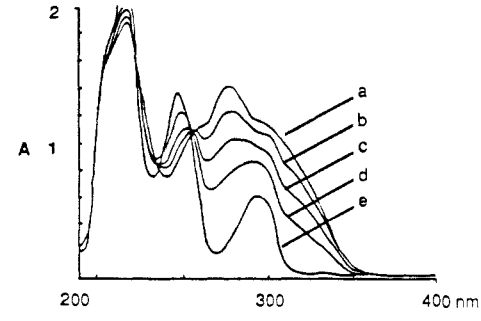


Figure 2. UV spectra of *N*-BOC-CI (**10**) in aqueous solution (pH = 7) at (a) 0, (b) 1, (c) 3, (d) 6, and (e) 43 h after mixing.

equiv of EDCI, 0.1 equiv of DMAP) in dichloromethane cleanly provided the diastereomeric esters **18** (92%) (Scheme VI). Normal phase preparative HPLC separation of **18** (10 mm × 25 cm column, 10 μm SiO_2, 3.2 mL/min flow rate, 8.4% tetrahydrofuran-hexane eluant) afforded the purified diasteromeric esters, α = 1.08. This procedure routinely provided both 3(*S*),2′(*R*)-**18** and 3(*R*),2′(*R*)-**18** of ≥99% diastereomeric purity as determined by HPLC and ^1H NMR analysis of the separated diastereomers.[31,32] Base-promoted hydrolysis (4.0 equiv of LiOH, THF-H_2O 4:1, 23 °C) provided the enantiomeric 3-(hydroxymethyl)-indolines (+)-**17b** and (-)-**17b** in 78% and 75% yield, respectively. Independent conversion of (+)-**17b** and (-)-**17b** to the corresponding primary methanesulfonates (1.6 equiv of CH_3SO_2Cl, 2.0 equiv of Et_3N, CH_2Cl_2, 0 °C) followed by catalytic hydrogenolysis (1 atm of H_2, 10% Pd-C catalyst, THF, 24 °C) afforded (+)-*seco*-*N*-((*tert*-butyloxy)carbonyl)-CI [(+)-**20b**] and (-)-*seco*-*N*-((*tert*-butyloxy)carbonyl)-CI [(-)-**20b**], respectively. Incorporation of (+)-**20b** and (-)-**20b** into (+)- and (-)-BOC-CI [(+)- and (-)-**10**], (+)- and (-)-CI-$CDPI_2$ [(+)- and (-)-**8**], and (+)- and (-)-CI-$CDPI_1$ [(+)- and (-)-**7**] followed the protocol presented in Scheme VI.

(31) The tentative assignment of the absolute configurations is based on the consistent observation of the selective, more potent cytotoxic activity of (+)-**20b**, (+)-**7**, and (+)-**8** and their seco precursors to which the 1(*S*) absolute configuration (natural configuration of (+)-CC-1065) was assigned. Differences in the DNA binding properties of (-)-CI-$CDPI_1$ versus (+)-CI-$CDPI_1$ and (+)-CC-1065 are in agreement with this assignment of absolute configuration and provide strong, albeit not unambiguous, confirmation of the assignment. For the unambiguous assignment of the absolute configuration of (+)-CC-1065, see: Martin, D. G.; Kelly, R. C.; Watt, W.; Wicnienski, N.; Mizsak, S. A.; Nielsen, J. W.; Prairie, M. D. *J. Org. Chem.* **1988**, *53*, 4610.

(32) HPLC separation and analysis was performed on an Alltech 10-μm SiO_2 chromatography column (10 mm × 25 cm) and the effluant was monitored at 280 nm.

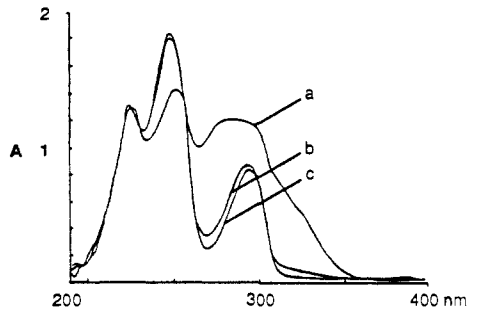


Figure 3. UV spectra of *N*-BOC-CI (**10**) in aqueous buffer (pH = 3) at (a) 15, (b) 120, and (c) 300 s after mixing.

Studies of the Solvolytic Reactivity of the CI Derivatives. Previous investigations have shown that acid-catalyzed solvolysis of N^2-substituted derivatives of the CPI segment of CC-1065 correlated with capabilities for DNA alkylation of the agents (**5** or **6**, R = COR > R = CO_2R > R = H) and was attributed to the extent and site of substrate protonation.[4a] Thus, it has been suggested that the electronic nature of the N^2-substituent of CPI[4a] and its inherent reactivity[11b] may have an influence on the agents DNA covalent alkylation properties. In our studies, the CI subunit proved sufficiently stable in a neutral aqueous solution to accurately measure the solvolysis rate of the agents.[33] The CI derivatives undergo rapid reaction upon dilution of a stock solution of the agent with water (**7–9** > **10**) as indicated by the disappearance of the long-wavelength absorption band of the CI chromophore (287–304 nm) by UV spectroscopy. The half-life of **10**, the most stable of the CI agents studied, proved to be 5.24 h (pH = 7, $k = 3.67 \pm 0.02 \times 10^{-5}$ s^{-1}) and 35 s (pH = 3, $k = 1.98 \pm 0.06 \times 10^{-2}$ s^{-1}) (Table I and Figures 2 and 3). These results correlate well with the original work of Winstein and Baird[13a,b] in which the parent spiro[2.5]octa-1,4-dien-3-one undergoes rapid solvolysis of the cyclopropyl ring under basic, neutral, and acidic aqueous conditions. In contrast, CPI derivatives exhibit no significant decomposition in aqueous solutions at pH 5 to 7 over a 2-week period although solvolytic reactivity was evident at pH 3 (**10** 3650 × **6**). The UV spectra of the CI agents **7–10** were distinct from those of the precursor *seco*-CI agents with the presence of the intense CI chromophore (287–304 nm). The chromatographic properties and UV spectra of the solvolyzed agents were similar, if not identical, with those of the *seco*-CI agents and are consistent with the previous observations that the solvolysis products result from methanol and water addition to the less hindered cyclopropane carbon of the cyclopropylcyclohexadienone system.[4a] These results, in conjunction with the results of computational studies,[34–37] suggest a small productive vinylogous imide stabilization of the parent CI system.

The results of the preliminary in vitro cytotoxic evaluation of the CI-based agents are summarized in Table II (supplementary material). These results are striking in that *both* enantiomers of the CI-based agents exhibit comparable cytotoxic potency that has proven comparable in potency to many clinically employed agents[3] even though the agents' half-life in aqueous solution is limited. These results, the comparable cytotoxic activity of the stable seco agents **20**, **26**, and **27**, and the demonstration of the comparable DNA covalent alkylation sequence selectivity of (±)-*N*-BOC-CI (**10**) and (+)-N^2-BOC-CPI (**6**)/(+)-N^2-acetyl-CPI that proceeds with a profile that is easily distinguished from that of (+)-CC-1065 (**1**),[9] the related CPI-based agents [(+)-CPI-$CDPI_1$ and (+)-CPI-$CDPI_2$ (**3**)], and the CI-based agents [(+)-CI-$CDPI_1$ (**7**), and (+)-CI-$CDPI_2$ (**8**)] will necessarily be presented elsewhere.

Experimental Section[38]

5-(Benzyloxy)-2-bromoaniline (12). A solution of 3-(benzyloxy)-aniline (**11**, 6.90 g, 34.7 mmol) in tetrahydrofuran (100 mL) cooled in an acetone–dry ice bath was treated with three drops of concentrated sulfuric acid and stirred for 5 min. The cold reaction mixture was treated with *N*-bromosuccinimide (6.3 g, 34.7 mmol, 1.0 equiv) in 1-g portions over 30 min and stirred for 1 h. Sodium carbonate (1 g) was added, and the reaction mixture was warmed to room temperature. Tetrahydrofuran was removed in vacuo, the residue was taken up into ethyl ether (200 mL) and washed with water (3 × 100 mL) and saturated aqueous sodium chloride (1 × 200 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 3 × (5 cm × 17 cm), 15–20% ethyl acetate–hexane eluant) afforded 5-(benzyloxy)-2-bromoaniline (**12**, 5.78 g, 9.64 g theoretical, 60%) as a tan solid. An analytical sample of **12** was prepared by recrystallization from benzene–hexane to give tan needles: mp 76–77 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 7.40 (m, 5 H, $OCH_2C_6H_5$), 7.27 (d, 1 H, J = 8.5 Hz, C3-H), 6.40 (d, 1 H, J = 2.7 Hz, C6-H), 6.29 (dd, 1 H, J = 8.5, 2.7 Hz, C4-H), 5.00 (s, 2 H, $OCH_2C_6H_5$), 4.05 (br s, 2 H, NH_2); IR (melt) ν_{max} 3481, 3386, 3033, 2943, 2933, 1608, 1518, 1489, 1453, 1426, 1290, 1267, 1194, 1008, 822, 798, 734, 693 cm^{-1}; EIMS, *m/e* (rel intensity) 279/277 (M^+, 4/4), 91 (base); CIMS (isobutane), *m/e* (rel intensity) 280/278 (M + H^+, base/base); EIHRMS, *m/e* 277.0105 ($C_{13}H_{12}NOBr$ requires 277.0102).

Anal. Calcd for $C_{13}H_{12}NOBr$: C, 56.14; H, 4.35; N, 5.04; Br, 28.73. Found: C, 56.53; H, 4.24; N, 4.71; Br, 28.85.

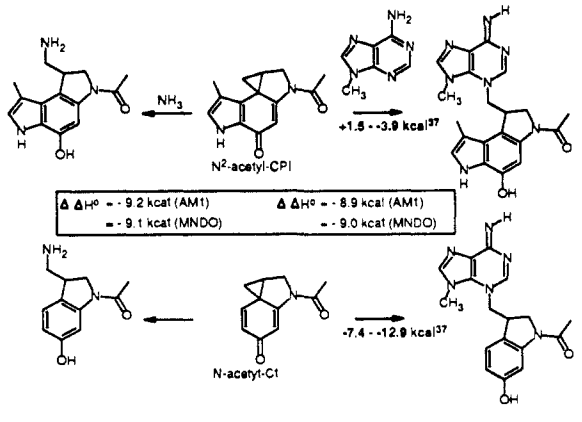
Continued elution afforded 5-(benzyloxy)-2,4-dibromoaniline (772 mg) and 3-(benzyloxy)-4-bromoaniline (3.02 g). **5-(Benzyloxy)-2,4-dibromoaniline**: tan solid, mp 86–87 °C (ethyl acetate–hexane); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 7.53 (s, 1 H, C3-H), 7.45 (m, 5 H, $OCH_2C_6H_5$), 6.34 (s, 1 H, C6-H), 5.05 (s, 2 H, $OCH_2C_6H_5$), 4.88 (br s, 2 H, NH_2); ^{13}C NMR ($CDCl_3$, 50 MHz, ppm) 155.3 (C-5), 144.4 (benzyl C-1), 136.4 (C-1), 135.6 (C-3), 128.8 (benzyl C-2), 128.1 (benzyl C-4), 127.0 (benzyl C-3), 101.6 (C-6), 100.0 (C-2 and C-4), 70.8 ($OCH_2C_6H_5$); IR (KBr) ν_{max} 3451, 3365, 3064, 2909, 2864, 1612, 1581, 1567, 1497, 1484, 1462, 1410, 1376, 1275, 1230, 1199, 1034, 1026, 877, 815, 737 cm^{-1}; EIMS *m/e* (rel intensity) 359/357/355 (M^+, 3/6/3), 276 (1), 91 (base); CIMS (isobutane), *m/e* (rel intensity) 360/358/356 (M + H^+, 45/base/56); EIHRMS, *m/e* 354.9211 ($C_{13}H_{11}NOBr_2$ requires 354.9207).

Anal. Calcd for $C_{13}H_{11}NOBr_2$: C, 43.73; H, 3.11; N, 3.94; Br, 44.76. Found: C, 43.63; H, 3.17; N, 3.94; Br, 44.50.

3-(Benzyloxy)-4-bromoaniline: light tan solid, mp 68–69 °C (ethyl acetate–hexane); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 7.33 (m, 5 H,

(33) In initial studies, we (R.J.W.) reported the observation of significantly shorter half-lives of **10** and related agents (pH = 7, t = 30 s) that we now attribute to a trace amount of base present in the samples evaluated.

(34) A summary of the computational studies (AM1,[35] MNDO[36]) is provided in the supplementary material.[37]



(35) AM1: Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

(36) MNDO: Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899.

(37) This estimation includes a correction for errors inherent in the computational methods that is derived through comparison of the experimental versus calculated heat of reaction ($\Delta H°$) derived from the heats of formation (ΔH_f, MOPAC; AM1 and MNDO) for the addition of ammonia to cyclopropane as taken from ref 35.

	c-C_3H_6 + NH_3 → $CH_3CH_2CH_2NH_2$			
ΔH_f, kcal				
exp	12.7	−11.0		−16.8
AM1	17.8	−7.3		−22.1
error	+5.1	+3.7	(−14.1)	−5.3
MNDO	11.2	−6.4		−18.2
error	−1.5	+4.6	(−4.5)	−1.4

(38) General experimental details are provided in supplementary material.

$OCH_2C_6H_5$), 7.16 (d, 1 H, J = 8.4 Hz, C5-H), 6.15 (d, 1 H, J = 2.4 Hz, C2-H), 6.08 (dd, 1 H, J = 8.4, 2.4 Hz, C6-H), 4.94 (s, 2 H, $OCH_2C_6H_5$), 3.51 (br s, 2 H, NH_2); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) 155.6 (C-3), 147.2 (benzyl C-1), 136.6 (C-1), 133.4 (C-5), 128.5 (benzyl C-2), 127.8 (benzyl C-4), 126.9 (benzyl C-3), 108.9 (C-6), 101.3 (C-2), 99.9 (C-4), 70.3 ($OCH_2C_6H_5$); IR (KBr) ν_{max} 3432, 3356, 3032, 2871, 1617, 1590, 1496, 1486, 1437, 1320, 1032, 1009, 914, 825, 737 cm^{-1}; EIMS, m/e (rel intensity) 279/277 (M^+, 4/5), 198 (3), 91 (base); ClMS (isobutane), m/e 280/278 (M + H^+, 90/base); ElHRMS, m/e 277.0100 ($C_{13}H_{12}NOBr$ requires 277.0102).

N-(Phenylsulfonyl)-5-(benzyloxy)-2-bromoaniline (13a). A stirred solution of 5-(benzyloxy)-2-bromoaniline (**12**, 740 mg, 2.7 mmol) in tetrahydrofuran (10 mL) was treated with phenylsulfonyl chloride (567 mg, 3.2 mmol, 1.2 equiv) and pyridine (1 mL, 12.4 mmol, 4.7 equiv), and the reaction mixture was warmed at reflux under nitrogen. After 40 h the mixture was cooled to room temperature, diluted with ether (90 mL), washed with 5% aqueous hydrochloric acid (2 × 30 mL), saturated aqueous sodium bicarbonate (1 × 30 mL), and saturated aqueous sodium chloride (1 × 40 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 3 × 12 cm, 11% ethyl acetate–hexane eluant) provided **13a** (970 mg, 1.10 g theoretical, 87%) as a white solid: mp 114–116 °C (benzene); ^1H NMR ($CDCl_3$, 300 MHz, ppm) 7.68 (d, 2 H, J = 7.9 Hz, phenylsulfonyl C2-H), 7.53 (t, 1 H, J = 7.9 Hz, phenylsulfonyl C4-H), 7.42 (m, 7 H, $OCH_2C_6H_5$ and phenylsulfonyl C3-H), 7.26 (d, 1 H, J = 8.5 Hz, C3-H), 7.24 (d, 1 H, J = 2.2 Hz, C6-H), 6.93 (s, 1 H, NH), 6.62 (dd, 1 H, J = 8.5, 2.2 Hz, C4-H), 5.06 (s, 2 H, $OCH_2C_6H_5$); IR (KBr) ν_{max} 3259, 3085, 1593, 1484, 1446, 1392, 1370, 1332, 1300, 1262, 1235, 1164, 1120, 1091, 1043, 1018, 963, 889, 847, 811, 754, 737, 723, 697, 648 cm^{-1}; EIMS, m/e (rel intensity) 419/417 (M^+, 2/2), 91 (base); ClMS (isobutane), m/e (rel intensity) 420/418 (M + H^+, base/96); ElHRMS, m/e 417.0014 ($C_{19}H_{16}NO_3BrS$ requires 417.0034).

Anal. Calcd for $C_{19}H_{16}NO_3BrS$: C, 54.60; H, 3.86; N, 3.35; Br, 19.16; S, 7.66. Found: C, 54.81; H, 3.70; N, 3.51; Br, 19.27; S, 7.58.

5-(Benzyloxy)-2-bromo-N-((*tert*-butyloxy)carbonyl)aniline (13b). A stirred solution of 5-(benzyloxy)-2-bromoaniline (**12**, 1.9 g, 6.9 mmol) in dioxane (24 mL) was treated with di-*tert*-butyl dicarbonate (9.5 g, 43.5 mmol, 6.3 equiv) and warmed at 105 °C for 10 h under nitrogen, cooled to room temperature, and concentrated in vacuo. Flash chromatography (SiO_2, 3.0 × 12.5 cm, hexane eluant) and crystallization from ethyl acetate–hexane afforded **13b** (2.23 g, 2.61 g theoretical, 85%) as white flakes: mp 82–83 °C; ^1H NMR ($CDCl_3$, 300 MHz, ppm) 7.97 (d, 1 H, J = 2.6 Hz, C6-H), 7.40 (m, 5 H, $OCH_2C_6H_5$), 7.38 (d, 1 H, J = 8.8 Hz, C3-H), 7.00 (s, 1 H, NH), 6.54 (dd, 1 H, J = 8.8, 2.6 Hz, C4-H), 5.05 (s, 2 H, $OCH_2C_6H_5$), 1.52 (s, 9 H, $OC(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) 158.7 (e, C-5), 152.2 (e, C=O), 136.9 (e, C-1), 136.5 (e, benzyl C-1), 132.3 (o, C-3), 128.5 (o, benzyl C-3), 127.9 (o, benzyl C-4), 127.6 (benzyl C-2), 110.8 (o, C-4), 105.9 (o, C-6), 102.7 (e, C-2), 81.0 (e, $OC(CH_3)_3$), 69.9 (e, $OCH_2C_6H_5$), 28.2 (o, $OC(CH_3)_3$); IR (melt) ν_{max} 3419, 3130, 2980, 2934, 2875, 1734, 1591, 1519, 1475, 1455, 1427, 1388, 1367, 1285, 1252, 1216, 1120, 1065, 1008, 849 cm^{-1}; EIMS, m/e (rel intensity) 379/377 (M^+, 2/2), 332 (2), 91 (base), 57 (94); ClMS (isobutane), m/e (rel intensity) 380/378 (M + H^+, 4/4), 324/322 (base/98), 322 (98); ElHRMS, m/e 377.0630 ($C_{18}H_{20}NO_3Br$ requires 377.0627).

Anal. Calcd for $C_{18}H_{20}NO_3Br$: C, 57.15; H, 5.35; N, 3.70; Br, 21.12. Found: C, 56.95; H, 5.66; N, 3.61; Br, 21.34.

(*E*)-1-Bromo-4-(phenylthio)-2-butene (14). A suspension of sodium hydride (1.35 g of 60% in oil, 33.8 mmol, 1.2 equiv) washed with pentane (3 × 20 mL) in tetrahydrofuran (100 mL) was treated with thiophenol 3.22 g, 29 mmol) and stirred at 0 °C under nitrogen for 30 min. The freshly generated sodium thiophenoxide suspension was transferred to a jacketed addition funnel and added slowly to an ice-cold solution of 1,4-dibromo-2-butene (Aldrich, 10 g, 47 mmol, 1.5 equiv) in tetrahydrofuran (250 mL). The resulting suspension was allowed to warm to room temperature with stirring over 4 h. The reaction mixture was filtered through Celite, and the filtrate was treated with water (100 mL) and separated. The organic layer was washed with saturated aqueous potassium carbonate (2 × 100 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 2 × (5 cm × 17 cm), 0–2% ether–hexane eluant) afforded **14** (2.6 g, 7.1 g theoretical, 37%) as a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz, ppm) 7.37–7.15 (m, 5 H, SC_6H_5), 5.89–5.69 (m, 2 H, CH=CH), 3.88 (d, 2 H, J = 7.0 Hz, $BrCH_2$), 3.52 (d, 2 H, J = 7.0 Hz, SCH_2); IR (neat) ν_{max} 3057, 3034, 2959, 1653, 1583, 1480, 1438, 1419, 1314, 1204, 1091, 1069, 1049, 1025, 999, 962, 889, 739 cm^{-1}; CIMS (isobutane), m/e (rel intensity) 245/243 (M + H^+, 3/3), 163 (base); ElHRMS, m/e 241.9778 ($C_{10}H_{11}BrS$ requires 241.9765).

N-(Phenylsulfonyl)-2-bromo-5-(benzyloxy)-N-(4-(phenylthio)-2-buten-1-yl)aniline (15a). A solution of *N*-(phenylsulfonyl)-5-(benzyloxy)-2-bromoaniline (**13a**, 595 mg, 1.4 mmol) in dry *N*,*N*-dimethylformamide (12 mL) was treated with sodium hydride (85 mg of 60% in oil, 2.1 mmol, 1.5 equiv) and stirred at 24 °C under nitrogen for 15 min. After effervescence ceased, (*E*)-1-bromo-4-(phenylthio)-2-butene (**14**, 470 mg, 1.9 mmol, 1.4 equiv) was added to the reaction mixture and the resulting reaction mixture was stirred at 24 °C for 2 h. The mixture was treated with saturated aqueous sodium chloride (4 mL), diluted with ether (30 mL), and separated. The ether layer was washed with water (3 × 10 mL) and saturated aqueous sodium chloride (1 × 20 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 5 × 14 cm, 12% ethyl acetate–hexane eluant) afforded **15a** (630 mg, 824 mg theoretical, 76%) as a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz, ppm) 7.75 (d, 2 H, J = 7.3 Hz, phenylsulfonyl C2-H), 7.59 (t, 1 H, J = 7.3 Hz, phenylsulfonyl C4-H), 7.48 (t, 2 H, J = 7.3 Hz, phenylsulfonyl C3-H), 7.40 (m, 10 H, SC_6H_5 and $OCH_2C_6H_5$), 7.24 (d, 1 H, J = 8.5 Hz, C3-H), 6.82 (dd, 1 H, J = 8.5, 3.0 Hz, C4-H), 6.65 (d, 1 H, J = 3.0 Hz, C6-H), 5.61–5.44 (m, 2 H, CH_2CH=$CHCH_2$), 4.93 (ABq, 2 H, J_{AB} = 19.0 Hz, $OCH_2C_6H_5$), 4.10 (br dd, 2 H, J = 10.0, 9.0 Hz, NCH_2), 3.38 (d, 2 H, J = 6.5 Hz, SCH_2); IR (neat) ν_{max} 3065, 3034, 2924, 2867, 1591, 1571, 1497, 1478, 1454, 1447, 1439, 1352, 1333, 1237, 1167, 911, 736, 690 cm^{-1}; EIMS, m/e (rel intensity) 472 (8), 391 (7), 91 (base); CIMS (isobutane), m/e (rel intensity) 582/580 (M + H^+, base/98), 472 (21), 382/380 (48/48), 163 (99), 143 (50); EIHRMS, m/e 579.0531 ($C_{29}H_{26}NO_3BrS_2$ requires 579.0537).

5-(Benzyloxy)-2-bromo-N-((*tert*-butyloxy)carbonyl)-N-(4-(phenylthio)-2-buten-1-yl)aniline (15b). A solution of 4-(benzyloxy)-2-bromo-*N*-((*tert*-butyloxy)carbonyl)aniline (**13b**, 830 mg, 2.2 mmol) in tetrahydrofuran (18 mL) and *N*,*N*-dimethylformamide (2 mL) was treated with sodium hydride (92 mg of 60% in oil, 2.3 mmol, 1.05 equiv) under nitrogen and stirred until effervescence ceased. (*E*)-1-Bromo-4-(phenylthio)-2-butene (**14**, 600 mg, 2.5 mmol, 1.12 equiv) was added neat to the reaction mixture and the resulting reaction mixture was stirred at room temperature for 3 h. The reaction mixture was treated with saturated aqueous sodium chloride (5 mL), diluted with ether (20 mL), and separated. The organic layer was washed with water (3 × 10 mL) and saturated aqueous sodium chloride (1 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 4.0 × 17 cm, 7% ethyl acetate–hexane eluant) afforded **15b** (810 mg, 1.20 g theoretical, 68%) as a pale orange oil: ^1H NMR ($CDCl_3$, 300 MHz, ppm) 7.45–7.10 (m, 10 H, SC_6H_5 and $OCH_2C_6H_5$), 6.80 (m, 2 H, C3-H and C4-H), 6.70 (br s, 1 H, C6-H), 5.66–5.58 (m, 2 H, CH_2CH=$CHCH_2$), 5.01 (s, 2 H, $OCH_2C_6H_5$), 4.33 (dd, 1 H, J = 15.0, 6.0 Hz, $NCHH$), 3.78 (dd, 1 H, J = 15.0, 6.0 Hz, $NCHH$), 3.48 (d, 2 H, J = 6.0 Hz, SCH_2), 1.34 (s, 9 H, $OC(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) 157.9 (e, C-5), 153.6 (e, C=O), 141.3 (e, thiophenyl C-1), 136.1 (o, benzyl C-1 and C-1), 132.8 (o, CH=CH), 129.2 to 125.9 (all o, benzyl C-2, benzyl C-3, benzyl C-4, thiophenyl C-2, thiophenyl C-3, thiophenyl C-4), 116.9 (o, C-4), 115.2 (o, C-6), 114.3 (e, C-2), 80.0 (e, $OC(CH_3)_3$), 70.0 (e, $OCH_2C_6H_5$), 50.4 (e, NCH_2), 35.4 (e, SCH_2), 28.0 (o, $OC(CH_3)_3$); IR (neat) ν_{max} 3060, 3033, 2976, 2931, 1702, 1650, 1591, 1573, 1479, 1454, 1439, 1383, 1366, 1315, 1356, 1238, 1160, 1025, 1014, 737 cm^{-1}; EIMS, m/e (rel intensity) 367 (17), 91 (base), 57 (59); CIMS (isobutane), m/e (rel intensity) 540 (M + H^+, 5), 486 (96), 484 (base), 376 (9), 374 (9); CIHRMS (isobutane), m/e 540.1200 ($C_{28}H_{30}NO_3BrS$ + H^+ requires 540.1208).

6-(Benzyloxy)-1-(phenylsulfonyl)-3-vinylindoline (16a). A stirred solution of *N*-(phenylsulfonyl)-2-bromo-5-(benzyloxy)-*N*-(4-(phenylthio)-2-buten-1-yl)aniline (**15a**, 630 mg, 1.1 mmol) in dry benzene (30 mL) was treated with tri-*n*-butyltin hydride (703 mg, 2.4 mmol, 2.2 equiv) and a catalytic amount of 2,2′-azobis(2-methylpropionitrile) (AIBN, 18 mg, 0.11 mmol, 0.1 equiv). The reaction mixture was warmed at reflux under nitrogen for 2 h and cooled to room temperature. Benzene was removed in vacuo, and the oily residue was taken up in acetonitrile (20 mL) and washed with hexane (1 × 10 mL). The acetonitrile phase was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (SiO_2, 3.5 × 12 cm, 12% ethyl acetate–hexane eluant) and recrystallization from benzene provided **16a** (390 mg, 426 mg theoretical, 92%) as a white crystalline solid: mp 115–116 °C; ^1H NMR ($CDCl_3$, 300 MHz, ppm) 7.65 (d, 2 H, J = 7.5 Hz, phenylsulfonyl C2-H), 7.54–7.37 (m, 8 H, $OCH_2C_6H_5$, phenylsulfonyl C3-H and phenylsulfonyl C4-H), 7.34 (d, 1 H, J = 2.3 Hz, C7-H), 7.07 (d, 1 H, J = 8.5 Hz, C4-H), 6.64 (dd, 1 H, J = 8.5, 2.3 Hz, C5-H), 5.46 (ddd, 1 H, J = 17.0, 10.0, 8.2 Hz, $CHCH$=CH_2), 5.12 (s, 2 H, $OCH_2C_6H_5$), 5.01 (apparent d, 1 H, J = 17.0 Hz, *cis*-CH=CHH), 4.99 (apparent d, 1 H, J = 10.0 Hz, *trans*-CH=CHH), 4.15 (dd, 1 H, J = 10.0, 9.0, Hz, C2-HH), 3.66 (apparent q, 1 H, J = 8.1 Hz, C2-HH), 3.57 (ddd, 1 H, J = 10.0, 8.2, 8.1 Hz, C3-H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) 159.7 (e, indoline C-6), 143.2 (e, phenylsulfonyl C-1), 138.3 (o, CH=CH_2), 137.5 (e, benzyl C-1), 137.2 (e, indoline C-7a), 133.7 (o, phenylsulfonyl C-4), 129.2 (o, phenylsulfonyl C-3), 128.5 (o, benzyl C-3), 128.0 (o,

benzyl C-2), 127.8 (o, phenylsulfonyl C-2), 126.5 (e, indoline C-3a), 117.3 (e, CH=CH_2), 111.7 (o, indoline C-5), 102.7 (o, indoline C-7), 70.7 (e, $OCH_2C_6H_5$), 56.8 (e, indoline, C-2), 44.6 (o, indoline C-3); IR (KBr) ν_{max} 3084, 2966, 2899, 1642, 1616, 1592, 1497, 1449, 1435, 1385, 1358, 1328, 1291, 1269, 1196, 1171, 1107, 1091, 747, 685, 599 cm^{-1}; EIMS, *m/e* (rel intensity) 391 (M^+, 3), 250 (6), 91 (base); CIMS (isobutane); *m/e* (rel intensity) 392 (M + H^+, base); EIHRMS, *m/e* 391.1242 ($C_{23}H_{23}NO_3S$ requires 391.1242).

Anal. Calcd for $C_{23}H_{23}NO_3S$: C, 70.56; H, 5.41; N, 3.58; S, 8.19. Found: C, 70.87; H, 5.51; N, 3.65; S, 7.98.

6-(Benzyloxy)-1-((*tert*-butyloxy)carbonyl)-3-vinylindoline (16b). A stirred solution of 5-(benzyloxy)-2-bromo-*N*-((*tert*-butyloxy)-carbonyl)-*N*-(4-(phenylthio)-2-buten-1-yl)aniline (**15b**, 355 mg, 0.66 mmol), tri-*n*-butyltin hydride (400 mg, 1.37 mmol, 2.1 equiv), and a catalytic amount of 2,2'-azobis(2-methylpropionitrile) (AIBN, 12 mg, 0.07 mmol, 0.11 equiv) in benzene (7 mL) was warmed at reflux under nitrogen for 3 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The oily residue was taken up in acetonitrile (10 mL) and washed with hexane (3 × 5 mL). The acetonitrile phase was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (SiO_2, 3.0 × 15 cm, 6% ethyl acetate–hexane eluant) provided **16b** (210 mg, 231 mg theoretical, 91%) as a pale yellow oil: ^1H NMR ($CDCl_3$, 300 MHz, ppm) 7.60 (br s, 1 H, C7-H), 7.40 (m, 5 H, $OCH_2C_6H_5$), 6.95 (d, 1 H, *J* = 8.1 Hz, C4-H), 6.58 (dd, 1 H, *J* = 8.1, 1.8 Hz, C5-H), 5.81 (ddd, 1 H, *J* = 17.0, 10.0, 8.2 Hz, CHC*H*=CH_2), 5.17 (dm, 1 H, *J* = 17.0 Hz, *cis*-CH=CH*H*), 5.11 (dm, 1 H, *J* = 10.0 Hz, *trans*-CH=CH*H*), 5.06 (s, 2 H, $OCH_2C_6H_5$), 4.19 (dd, 1 H, *J* = 10.0, 9.0 Hz, C2-*H*H), 3.88 (apparent q, 1 H, C2-H*H*), 3.69 (m, 1 H, C3-H), 1.56 (s, 9 H, $OC(CH_3)_3$); IR (neat) ν_{max} 3066, 3033, 2977, 2931, 1704, 1639, 1611, 1597, 1498, 1454, 1445, 1392, 1369, 1336, 1323, 1282, 1252, 1193, 1169, 1139, 1041, 1027, 917, 735 cm^{-1}; EIMS, *m/e* (rel intensity) 351 (M^+, 9), 295 (20), 91 (base), 57 (55); CIMS (isobutane), *m/e* (rel intensity) 352 (M + H^+, 25), 296 (base); EIHRMS, *m/e* 351.1830 ($C_{22}H_{25}NO_3$ requires 351.1835).

Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99. Found: C, 74.92; H, 7.54, N, 4.08.

6-(Benzyloxy)-3-(hydroxymethyl)-1-(phenylsulfonyl)indoline (17a). A solution of 6-(benzyloxy)-1-(phenylsulfonyl)-3-vinylindoline (**16a**, 272 mg, 0.7 mmol) in absolute ethanol (4 mL) and dichloromethane (4 mL) was cooled in an acetone–dry ice bath. A stream of ozone/oxygen was bubbled into the reaction mixture through a fitted gas inlet for 8 min, and immediately afterward a 50% aqueous ethanol solution (10 mL) of sodium borohydride (107 mg, 2.8 mmol, 4 mol equiv) was added and the reaction mixture was allowed to slowly warm to room temperature. After 9 h, the solvent was removed in vacuo and the residue was treated with water (10 mL) and extracted with ether (3 × 20 mL). The combined ether layers were washed with saturated aqueous sodium chloride (1 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 3 × 12 cm, 55% ethyl acetate–hexane eluant) provided **17a** (107 mg, 175 mg theoretical, 61%) as a white foam: ^1H NMR ($CDCl_3$, 300 MHz, ppm) 7.67 (d, 2 H, *J* = 7.9 Hz, phenylsulfonyl C2-H), 7.66 (t, 1 H, *J* = 7.9 Hz, phenylsulfonyl C4-H), 7.50 (t, 2 H, *J* = 7.9 Hz, phenylsulfonyl C3-H), 7.42 (m, 5 H, $OCH_2C_6H_5$), 7.34 (d, 1 H, *J* = 2.7 Hz, C7-H), 6.99 (d, 1 H, *J* = 8.1 Hz, C4-H), 6.62 (dd, 1 H, *J* = 8.1, 2.7 Hz, C5-H), 5.17 (s, 2 H, $OCH_2C_6H_5$), 3.96 (dd, 1 H, *J* = 11.0, 9.0 Hz, C2-*H*H), 3.86 (dd, 1 H, *J* = 11.0, 5.0 Hz, C2-H*H*), 3.50 (dd, 1 H, *J* = 10.5, 5.0 Hz, HOC*H*H), 3.35 (dd, 1 H, *J* = 10.5, 7.0 Hz, HOCH*H*), 3.26 (m, 1 H, C3-H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) 159.8 (e, indoline C-6), 143.7 (e, phenylsulfonyl C-1), 137.4 (e, benzyl C-1), 137.0 (e, indoline C-7a), 133.8 (o, phenylsulfonyl C-4), 129.2 (o, phenylsulfonyl C-3), 128.5 (o, benzyl C-3), 128.0 (o, benzyl C-2), 127.7 (o, phenylsulfonyl C-2), 126.0 (o, benzyl C-4), 125.9 (o, indoline C-4), 124.6 (e, indoline C-3a), 111.4 (o, indoline C-5), 102.6 (o, indoline C-7), 70.7 (e, $OCH_2C_6H_5$), 65.3 (e, CH_2CHCH_2OH), 54.1 (e, indoline C-2), 42.4 (o, indoline C-3); IR (neat) ν_{max} 3540, 3090, 3064, 3032, 3006, 2934, 1612, 1592, 1492, 1446, 1352, 1310, 1282, 1168, 1106, 1028, 690 cm^{-1}; EIMS, *m/e* (rel intensity) 395 (M^+, 11), 364 (17), 91 (base); CIMS (isobutane), *m/e* (rel intensity) 396 (M + H^+, base), 255 (24); EIHRMS, *m/e* 395.1185 ($C_{22}H_{21}NO_4S$ requires 395.1191).

6-(Benzyloxy)-1-((*tert*-butyloxy)carbonyl)-3-(hydroxymethyl)indoline (17b). A stream of ozone/oxygen was bubbled through a −78 °C solution of 6-(benzyloxy)-1-((*tert*-butyloxy)carbonyl)-3-vinylindoline (**16b**, 210 mg, 0.60 mmol) in absolute ethanol (50 mL) for 3 min. The reaction mixture was then treated immediately with a 50% aqueous ethanol solution (10 mL) of sodium borohydride (95 mg, 2.5 mmol, 4.2 mol equiv) and was warmed to room temperature over 4 h. The reaction mixture was concentrated in vacuo, treated with water (10 mL), and extracted with ethyl acetate (3 × 10 mL). The combined ethyl acetate layers were washed with saturated aqueous sodium chloride (1 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 2.0 × 15 cm, 22% ethyl acetate–hexane eluant) provided **17b** (115 mg, 212 mg theoretical, 54%) as a pale yellow oil: ^1H NMR ($CDCl_3$, 470 MHz, ppm) 7.70 (br s, 1 H, C7-H), 7.40 (m, 5 H, $OCH_2C_6H_5$), 7.07 (d, 1 H, *J* = 8.0 Hz, C4-H), 6.57 (dd, 1 H, *J* = 8.0, 2.0 Hz, C5-H), 5.06 (s, 2 H, $OCH_2C_6H_5$), 4.07 (dd, 1 H, *J* = 11.0, 10.0 Hz, C2-*H*H), 3.91 (dd, 1 H, *J* = 11.0, 5.0 Hz, C2-H*H*), 3.75 (m, 2 H, CH_2OH), 3.44 (m, 1 H, C3-H), 1.56 (s, 9 H, $OC(CH_3)_3$); IR (neat) ν_{max} 3423, 2975, 2932, 1701, 1611, 1499, 1395, 1368, 1324, 1251, 1168, 1142, 1026 cm^{-1}; EIMS, *m/e* (rel intensity) 355 (M^+, 4), 299 (8), 268 (18), 91 (base), 57 (80); CIMS (isobutane), *m/e* (rel intensity) 356 (M + H^+, base); EIHRMS, *m/e* 355.1784 ($C_{21}H_{25}NO_4$ requires 355.1784).

6-(Benzyloxy)-1-((*tert*-butyloxy)carbonyl)-3-(hydroxymethyl)indoline, *R*-(−)-*O*-Acetylmandelic Ester (18) [3*S*,2'*R*-18 and 3*R*,2'*R*-18].[31] A solution of 6-(benzyloxy)-1-((*tert*-butyloxy)carbonyl)-3-(hydroxymethyl)indoline (**17b**, 29 mg, 0.082 mmol) in dichloromethane (2 mL) was treated with *R*-(−)-*O*-acetylmandelic acid (23 mg, 0.118 mmol, 1.5 equiv), 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (EDCI, 28 mg, 0.146 mmol, 1.8 equiv), and a catalytic amount of 4-(dimethylamino)pyridine (DMAP, 1.0 mg, 0.008 mmol, 0.1 equiv). The reaction mixture was stirred at 23 °C for 9 h and concentrated in vacuo. Flash chromatography (SiO_2, 2 × 9 cm, 70% ethyl acetate–hexane) afforded 3*R*,2'*R*-**18** and 3*S*,2'*R*-**18** as a 1:1 mixture (40 mg, 43.4 mg theoretical, 92%) as a pale yellow oil. The mixture was resolved by preparative HPLC.[32] A solution of **18** (50 mg in 0.3 mL of dichloromethane) was chromatographed on an Alltech 10 mm × 25 cm column packed with 10 μm SiO_2 with 8.4% tetrahydrofuran–hexane eluant at a flow rate of 3.2 mL/min. The effluant was monitored at 280 nm and the diastereomeric esters 3*R*,2'*R*-**18** and 3*S*,2'*R*-**18** were eluted with retention times of 24.0 and 25.8 min, respectively. The separated diastereomers were collected, and the solvent was removed in vacuo to afford 3*R*,2'*R*-**18** (R_T = 24.0 min, 22 mg) and 3*S*,2'*R*-**18** (R_T = 25.8 min, 21 mg) with a total 86% recovery. HPLC and ^1H NMR (300 MHz) analyses of the separated diastereomers indicated that both diastereomers were ≥99% pure.

3*R*,2'*R*-18: R_T = 24.0 min, pale yellow oil; $[\alpha]^{25}_D$ −71° (*c* = 1, dichloromethane); ^1H NMR ($CDCl_3$, 300 MHz, ppm) 7.64 (br s, 1 H, C7-H), 7.45–7.31 (m, 10 H, C_6H_5), 6.86 (d, 1 H, *J* = 8.0 Hz, C4-H), 6.46 (dd, 1 H, *J* = 8.0, 2.0 Hz, C5-H), 5.93 (s, 1 H, $CH_3CO_2CHC_6H_5$), 5.04 (s, 2 H, $OCH_2C_6H_5$), 4.27 (dd, 1 H, *J* = 11.0, 6.0 Hz, C2-*H*H), 4.10 (dd, 1 H, *J* = 11.0 8.5 Hz, C2-H*H*), 3.89 (m, 1 H, CHC*H*HOCO), 3.70 (m, 1 H, CHCH*H*OCO), 3.49 (m, 1 H, C3-H), 2.20 (s, 3 H, $COCH_3$), 1.55 (s, 9 H, $OC(CH_3)_3$); IR (neat) ν_{max} 3066, 2978, 1744, 1701, 1612, 1499, 1455, 1395, 1370, 1233, 1174, 1081, 1028, 756, 697 cm^{-1}.

3*S*,2'*R*-18: R_T = 25.8 min, pale yellow oil; $[\alpha]^{25}_D$ −12.4° (*c* = 1, dichloromethane); ^1H NMR ($CDCl_3$, 300 MHz, ppm) 7.60 (br s, 1 H, C7-H), 7.44–7.30 (m, 10 H, C_6H_5), 6.83 (d, 1 H, *J* = 8.0 Hz, C4-H), 6.48 (dd, 1 H, *J* = 8.0, 2.0 Hz, C5-H), 5.91 (s, 1 H, $CH_3CO_2CHC_6H_5$), 5.04 (s, 2 H, $OCH_2C_6H_5$), 4.21 (apparent t, 2 H, *J* = 9.0 Hz, C2-H_2), 3.97 (m, 1 H, CHC*H*HOCO), 3.66 (m, 1 H, CHCH*H*OCO), 3.52 (m, 1 H, C3-H), 2.18 (s, 3 H, $COCH_3$), 1.55 (s, 9 H, $OC(CH_3)_3$); IR (neat) ν_{max} 3066, 2967, 2925, 1744, 1701, 1617, 1499, 1455, 1395, 1234, 1174, 1027, 739, 696 cm^{-1}.

Mixture: EIMS, *m/e* (rel intensity) 531 (M^+, 2), 281 (17), (91) (base), 57 (89); CIMS (isobutane), *m/e* (rel intensity) 532 (M + H^+, 5), 488 (4), 476 (base), 432 (94), 416 (27); CIHRMS, *m/e* 532.2340 ($C_{31}H_{33}NO_7$ + H^+ requires 532.2335).

(−)-(3*R*)-6-(Benzyloxy)-1-((*tert*-butyloxy)carbonyl)-3-(hydroxymethyl)indoline [(−)-17b]. A solution of 3*R*,2'*R*-**18** (R_T = 24.0 min, 21 mg, 0.04 mmol) in tetrahydrofuran (1 mL) and water (0.25 mL) was treated with lithium hydroxide monohydrate (6.6 mg, 0.16 mmol, 4 equiv) and stirred at room temperature for 4 h. The reaction mixture was diluted with water (10 mL) and extracted with ether (3 × 10 mL). The combined ether layers were washed with aqueous sodium chloride (1 × 20 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 1 × 12 cm, 46% ethyl acetate–hexane eluant) afforded (−)-(3*R*)-6-(benzyloxy)-1-((*tert*-butyloxy)carbonyl)-3-(hydroxymethyl)indoline (10.5 mg, 14 mg theoretical, 75%) as a colorless oil with spectroscopic characteristics identical with racemic material: $[\alpha]^{25}_D$ = −25.1° (*c* = 0.5, dichloromethane).

(+)-(3*S*)-6-(Benzyloxy)-1-((*tert*-butyloxy)carbonyl)-3-(hydroxymethyl)indoline [(+)-17b]. A solution of 3*S*,2'*R*-**18** (R_T = 25.8 min, 19 mg, 0.036 mmol) in tetrahydrofuran (1 mL) and water (0.25 mL) was treated with lithium hydroxide monohydrate (6 mg, 0.143 mmol, 4 equiv) and stirred at room temperature for 8 h. The reaction mixture was diluted with water (10 mL) and extracted with ether (3 × 10 mL). The combined ether layers were washed with saturated aqueous sodium chloride (1 × 20 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 1 × 5 cm, 50% ethyl acetate–hexane eluant) afforded (+)-(3*S*)-6-(benzyloxy)-1-((*tert*-butyloxy)carbonyl)-3-(hydroxymethyl)indoline ((+)-**17b**, 10 mg, 12.8 mg theoretical, 78%) as a

colorless oil with spectroscopic characteristics identical with racemic material: $[\alpha]^{25}_D$ = +25.0° (c = 0.4, dichloromethane).

6-(Benzyloxy)-3-(((methanesulfonyl)oxy)methyl)-1-(phenylsulfonyl)indoline (19a). A vigorously stirred ice-cooled solution of 6-(benzyloxy)-3-(hydroxymethyl)-1-(phenylsulfonyl)indoline (**17a**, 165 mg, 0.42 mmol) and triethylamine (0.12 mL, 87 mg, 0.86 mmol, 2.0 equiv) in dichloromethane (5 mL) was treated with methanesulfonyl chloride (0.05 mL, 74 mg, 0.65 mmol, 1.6 equiv) under argon and stirred for 1 h. The reaction mixture was diluted with dichloromethane (10 mL), washed with water (3 × 15 mL) and saturated aqueous sodium bicarbonate (2 × 10 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 12 cm, 26% ethyl acetate–hexane eluant) afforded **19a** (145 mg, 198 mg theoretical, 73%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 470 MHz, ppm) 7.67 (d, 2 H, J = 7.6 Hz, phenylsulfonyl C2-H), 7.56 (t, 1 H, J = 7.6 Hz, phenylsulfonyl C4-H), 7.47 (t, 2 H, J = 7.6 Hz, phenylsulfonyl C3-H), 7.40 (m, 5 H, $OCH_2C_6H_5$), 7.34 (d, 1 H, J = 2.0 Hz, C7-H), 7.01 (d, 1 H, J = 8.4 Hz, C4-H), 6.64 (dd, 1 H, J = 10.0, 6.0 Hz, C5-H), 4.05 (dd, 1 H, J = 10.0, 5.5 Hz, O_2SOCHH), 3.96 (dd, 1 H, J = 11.0, 9.0 Hz, C2-H*H*), 3.88 (dd, 1 H, J = 11.0, 4.0 Hz, C2-H*H*), 3.78 (dd, 1 H, J = 10.0, 9.0 Hz, O_2SOCHH), 3.49 (m, 1 H, C3-H), 2.87 (s, 3 H, OSO_2CH_3); IR (neat) ν_{max} 3066, 3032, 2939, 2872, 1612, 1594, 1498, 1469, 1454, 1447, 1358, 1311, 1286, 1171, 1109, 1092, 1065, 1025, 958, 799, 743, 690 cm^{-1}; EIMS, *m/e* (rel intensity) 473 (M^+, 0.1), 91 (base); CIMS (isobutane), *m/e* (rel intensity) 474 (M + H^+, 61), 378 (base), 288 (20), 236 (42); EIHRMS, *m/e* 473.0966 ($C_{23}H_{23}NO_6S_2$ requires 473.0967).

6-(Benzyloxy)-1-((*tert*-butyloxy)carbonyl)-3-(((methanesulfonyl)oxy)methyl)indoline (19b). A vigorously stirred solution of 6-(benzyloxy)-1-((*tert*-butyloxy)carbonyl)-3-(hydroxymethyl)indoline (**17b**, 115 mg, 0.32 mmol) and triethylamine (65 mg, 0.65 mmol, 2.0 equiv) in dichloromethane (4 mL) cooled in an ice–methanol bath was treated with methanesulfonyl chloride (59 mg, 0.52 mmol, 1.6 equiv) under nitrogen. After 25 min, the reaction mixture was treated with saturated aqueous sodium bicarbonate (5 mL) and separated. The aqueous layer was extracted with dichloromethane (3 × 10 mL), and the combined dichloromethane layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (SiO_2, 2.0 × 15 cm, 29% ethyl acetate–hexane eluant) provided **19b** (123 mg, 139 mg theoretical, 89%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 7.65 (br s, 1 H, C7-H), 7.40 (m, 5 H, $OCH_2C_6H_5$), 7.08 (d, 1 H, J = 8.2 Hz, C4-H), 6.58 (dd, 1 H, J = 8.2, 2.0 Hz, C5-H), 5.06 (s, 2 H, $OCH_2C_6H_5$), 4.32 (dd, 1 H, J = 10.0, 6.0 Hz, O_2SOCHH), 4.17 (dd, 1 H, J = 11.0, 9.0 Hz, C2-H*H*), 4.10 (apparent t, 1 H, J = 10.0 Hz, O_2SOCHH), 3.89 (dd, 1 H, J = 11.0, 4.5 Hz, C2-H*H*), 3.66 (m, 1 H, C3-H), 2.95 (s, 3 H, OSO_2CH_3), 1.56 (s, 9 H, $OC(CH_3)_3$); IR (neat) ν_{max} 3059, 2974, 2932, 1701, 1612, 1500, 1454, 1396, 1356, 1284, 1254, 1174, 1143, 1025, 955, 738 cm^{-1}; EIMS, *m/e* (rel intensity) 239 (9), 91 (base); CIMS (isobutane), *m/e* (rel intensity) 434 (M + H^+, 4), 378 (80), 240 (base), 150 (16), 97 (27); EIHRMS, *m/e* 433.1551 ($C_{22}H_{27}NO_6S$ requires 433.1559).

(−)-**3*R*-19b**: $[\alpha]^{25}_D$ = −31.8° (c = 0.49, dichloromethane).

(+)-**3*S*-19b**: $[\alpha]^{25}_D$ = +31.7° (c = 0.29, dichloromethane).

6-Hydroxy-3-(((methanesulfonyl)oxy)methyl)-1-(phenylsulfonyl)indoline (20a). A vigorously stirred suspension of 6-(benzyloxy)-3-(((methanesulfonyl)oxy)methyl)-1-(phenylsulfonyl)indoline (**19a**, 144 mg, 0.30 mmol) and 10% palladium on carbon (89 mg, 0.6 wt equiv) in tetrahydrofuran (4 mL) was placed under a hydrogen atmosphere (1 atm) at room temperature for 9 h. The reaction mixture was filtered through Celite and the Celite pad was washed with ethyl acetate (3 × 5 mL). The combined washings and filtrate were concentrated in vacuo. Flash chromatography (SiO_2, 52% ethyl acetate–hexane eluant) afforded **20a** (97 mg, 116 mg theoretical, 84%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 470 MHz, ppm) 7.84 (d, 2 H, J = 7.8 Hz, phenylsulfonyl C2-H), 7.60 (t, 1 H, J = 7.8 Hz, phenylsulfonyl C4-H), 7.49 (t, 2 H, J = 7.8 Hz, phenylsulfonyl C3-H), 7.25 (d, 1 H, J = 2.1 Hz, C7-H), 6.98 (d, 1 H, J = 8.2 Hz, C4-H), 6.51 (dd, 1 H, J = 8.2, 2.1 Hz, C5-H), 5.76 (s, 1 H, OH), 4.07 (dd, 1 H, J = 10.0, 5.5 Hz, O_2SOCHH), 3.98 (dd, 1 H, J = 11.0, 10.0 Hz, C2-H*H*), 3.88 (dd, 1 H, J = 11.0, 4.2 Hz, C2-H*H*), 3.77 (dd, 1 H, J = 10.0, 9.0 Hz, O_2SOCHH), 3.47 (m, 1 H, C3-H), 2.90 (s, 3 H, OSO_2CH_3); IR (neat) ν_{max} 3450, 3067, 3032, 2967, 2940, 1606, 1500, 1448, 1363, 1330, 1291, 1107, 758, 725 cm^{-1}; EIMS, *m/e* (rel intensity) 274 (2), 151 (12), 111 (89), 65 (92), 47 (base); CIMS (isobutane), *m/e* (rel intensity) 384 (M + H^+, 15), 288 (13), 247 (68), 143 (base) 97 (96); EIHRMS, *m/e* 383.0496 ($C_{16}H_{17}NO_6S_2$ requires 383.0496).

1-((*tert*-Butyloxy)carbonyl)-6-hydroxy-3-(((methanesulfonyl)oxy)methyl)indoline (20b). A stirred suspension of 6-(benzyloxy)-1-((*tert*-butyloxy)carbonyl)-3-(((methanesulfonyl)oxy)methyl)indoline (**19b**, 113 mg, 0.26 mmol) and 10% palladium on carbon (40 mg, 0.35 wt equiv) in tetrahydrofuran (4 mL) was placed under a hydrogen atmosphere (1 atm) and stirred at room temperature for 7 h. The suspension was filtered through Celite and the Celite cake was washed with ethyl acetate (20 mL). The combined filtrate and washings were concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 11 cm, 25% ethyl acetate–hexane eluant) provided **20b** (67 mg, 89 mg theoretical, 75%) as a white foam: ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 7.44 (br s, 1 H, C7-H), 7.06 (d, 1 H, J = 8.2 Hz, C4-H), 6.46 (dd, 1 H, J = 8.2, 1.9 Hz, C5-H), 4.86 (br s, 1 H, OH), 4.34 (dd, 1 H, J = 10.0, 5.0 Hz, O_2SOCHH), 4.18 (dd, 1 H, J = 10.0, 8.0 Hz, O_2SOCHH), 4.08 (dd, 1 H, J = 11.0, 10.0 Hz, C2-H*H*), 3.86 (dd, 1 H, J = 11.0, 4.5 Hz, C2-H*H*), 3.64 (m, 1 H, C3-H), 2.96 (s, 3 H, OSO_2CH_3), 1.56 (s, 9 H, $OC(CH_3)_3$); IR (neat) ν_{max} 3372, 2979, 2935, 1701, 1617, 1502, 1465, 1406, 1369, 1300, 1254, 1169, 954, 733 cm^{-1}; EIMS, *m/e* (rel intensity) 343 (M^+, 1), 287 (1), 173 (3), 56 (base); CIMS (isobutane), *m/e* (rel intensity) 344 (M + H^+, 4), 288 (66), 80 (base); EIHRMS, *m/e* 343.1091 ($C_{15}H_{21}NO_6S$ requires 343.1089).

(−)-**3*R*-20b**: $[\alpha]^{25}_D$ −48.9° (c = 0.19, dichloromethane).

(+)-**3*S*-20b**: $[\alpha]^{25}_D$ +48.4° (c = 0.06, dichloromethane).

1-((*tert*-Butyloxy)carbonyl)-6-hydroxy-3-methylindoline: yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 7.44 (br s, 1 H, C7-H), 6.95 (d, 1 H, J = 8.0 Hz, C4-H), 6.46 (dd, 1 H, J = 8.0, 2.0 Hz, C5-H), 4.14 (apparent t, 1 H, J = 9.7 Hz, C2-H*H*), 3.49 (m, 1 H, C2-H*H*), 3.33 (m, 1 H, C3-H), 1.55 (s, 9 H, $OC(CH_3)_3$), 1.27 (d, 3 H, J = 7.0 Hz, $CHCH_3$); IR (neat) ν_{max} 3387, 2965, 2929, 1704, 1619, 1459, 1307, 1163, 1045, 1007, 902, 855, 809, 765 cm^{-1}; EIMS, *m/e* (rel intensity) 249 (M^+, 3), 193 (12), 178 (16), 146 (10), 134 (27), 57 (base); CIMS (isobutane), *m/e* (rel intensity) 250 (M + H^+, 27), 194 (base), 150 (20); EIHRMS, *m/e* 249.1360 ($C_{14}H_{19}NO_3$ requires 249.1364).

6-Hydroxy-3-(hydroxymethyl)-1-(phenylsulfonyl)indoline (21a). A vigorously stirred suspension of 6-(benzyloxy)-3-(hydroxymethyl)-1-(phenylsulfonyl)indoline (**17a**, 120 mg, 0.30 mmol) and 5% palladium on carbon (270 mg, 2.5 wt equiv) in tetrahydrofuran (10 mL) was placed under a hydrogen atmosphere (1 atm) at room temperature. After 20 h, the reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo. Flash chromatography (SiO_2, 2.0 × 10 cm, 20% ether–dichloromethane eluant) afforded **21a** (90 mg, 93 mg theoretical, 97%) as a white foam: ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) 9.48 (s, 1 H, phenol OH), 7.83 (d, 2 H, J = 7.4 Hz, phenylsulfonyl C2-H), 7.70 (t, 1 H, J = 7.4 Hz, phenylsulfonyl C4-H), 7.62 (t, 2 H, J = 7.4 Hz, phenylsulfonyl C3-H), 7.03 (s, 1 H, C7-H), 6.97 (d, 1 H, J = 8.1 Hz, C4-H), 6.41 (d, 1 H, J = 8.1 Hz, C5-H), 4.86 (br s, 1 H, CH_2OH), 3.94 (dd, 1 H, J = 10.0, 9.0 Hz, C2-H*H*), 3.82 (dd, 1 H, J = 10.0, 5.0 Hz, C2-H*H*), 3.38 (m, obscured by water, HOC*H*H), 3.14 (m, 1 H, C3-H), 3.04 (apparent t, 1 H, J = 9.0 Hz, HOCHH); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 7.82 (d, 2 H, J = 7.5 Hz, phenylsulfonyl C2-H), 7.60 (t, 1 H, J = 7.5 Hz, phenylsulfonyl C4-H), 7.47 (t, 2 H, J = 7.5 Hz, phenylsulfonyl C3-H), 7.22 (d, 1 H, J = 2.3 Hz, C7-H), 6.97 (d, 1 H, J = 8.1 Hz, C4-H), 6.48 (dd, 1 H, J = 8.1, 2.3 Hz, C5-H), 3.99 (dd, 1 H, J = 11.0, 9.0 Hz, C2-H*H*), 3.88 (dd, 1 H, J = 11.0, 6.0 Hz, C2-H*H*), 3.52 (dd, 1 H, J = 10.0, 5.0 Hz, HOC*H*H), 3.37 (dd, 1 H, J = 10.0, 7.0 Hz, HOCH*H*), 3.26 (m, 1 H, C3-H); IR (neat) ν_{max} 3500, 3384, 3069, 2937, 2887, 1611, 1500, 1459, 1363, 1317, 1278, 1220, 1113, 1077, 1031, 717, 689 cm^{-1}; EIMS, *m/e* (rel intensity) 305 (M^+, 43), 274 (91), 133 (28), 77 (base); CIMS (isobutane), *m/e* (rel intensity) 306 (M + H^+, base), 288 (26); EIHRMS, *m/e* 305.0723 ($C_{15}H_{15}NO_4S$ requires 305.0722).

1-((*tert*-Butyloxy)carbonyl)-3-(chloromethyl)-6-hydroxyindoline (22b). A suspension of 6-(benzyloxy)-1-((*tert*-butyloxy)carbonyl)-3-(hydroxymethyl)indoline (**17b**, 40 mg, 0.11 mmol) and triphenylphosphine (41 mg, 0.16 mmol, 1.4 equiv) in carbon tetrachloride (1 mL) under nitrogen was warmed at 75 °C for 16 h. The reaction mixture was cooled to room temperature. Flash chromatography (SiO_2, 1.0 × 10 cm, dichloromethane eluant) afforded the chloride (31 mg, 42 mg theoretical, 74%) as a white foam: mp 157–158 °C (CH_2Cl_2–hexane); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 7.65 (br s, 1 H, C7-H), 7.38 (m, 5 H, $OCH_2C_6H_5$), 7.07 (d, 1 H, J = 8.2 Hz, C4-H), 6.58 (dd, 1 H, J = 8.2, 2.2 Hz, C5-H), 5.06 (s, 2 H, $OCH_2C_6H_5$), 4.11 (dd, 1 H, J = 11.0, 10.0 Hz, C2-H*H*), 3.93 (dd, 1 H, J = 11.0, 4.0 Hz, C2-H*H*), 3.71 (dd, 1 H, J = 10.0, 4.0 Hz, ClC*H*H), 3.69 (m, 1 H, C3-H), 3.50 (dd, 1 H, J = 10.0, 9.0 Hz, ClCH*H*), 1.57 (s, 9 H, $OC(CH_3)_3$); IR (neat) ν_{max} 2983, 2974, 2932, 1701, 1595, 1507, 1448, 1400, 1369, 1178, 863, 669 cm^{-1}; EIMS, *m/e* (rel intensity) 375/373 (M^+, 10/31), 319/317 (12/40), 97 (88), 57 (base); CIMS (isobutane), *m/e* (rel intensity) 376/374 (M + H^+, 2/5), 320/318 (29/base); EIHRMS, *m/e* 373.1442 ($C_{21}H_{24}NO_3Cl$ requires 373.1444).

A vigorously stirred suspension of 6-(benzyloxy)-1-((*tert*-butyloxy)carbonyl)-3-(chloromethyl)indoline (29 mg, 0.08 mmol) and 10% palladium on carbon (12 mg, 0.41 wt equiv) in tetrahydrofuran (2 mL) was treated with 25% aqueous ammonium formate (0.2 mL) under nitrogen. After 12 h, the reaction mixture was filtered through Celite and the Celite cake was washed with ethyl acetate (5 × 1 mL). The combined

filtrate and washings were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (SiO_2, 2.0 × 10 cm, 17% ethyl acetate–hexane eluant) afforded **22b** (20 mg, 22 mg theoretical, 91%) as a white foam: mp 174–175 °C dec (ether); ^1H NMR ($CDCl_3$, 300 MHz, ppm) 7.44 (br s, 1 H, C7-H), 7.03 (d, 1 H, J = 8.1 Hz, C4-H), 6.46 (dd, 1 H, J = 8.1, 1.1 Hz, C5-H), 5.50 (br s, 1 H, OH), 4.10 (dd, 1 H, J = 11.0, 9.0 Hz, C2-H*H*), 3.91 (dd, 1 H, J = 11.0, 3.0 Hz, C2-H*H*), 3.71 (dd, 1 H, J = 10.0, 4.0 Hz, ClC*H*H), 3.59 (m, 1 H, C3-H), 3.50 (dd, 1 H, J = 10.0, 9.0 Hz, ClCH*H*), 1.56 (s, 9 H, $OC(CH_3)_3$); IR (KBr) ν_{max} 3390, 2975, 1684, 1611, 1500, 1453, 1418, 1394, 1370, 1350, 1269, 1173, 1144, 1039, 846 cm^{-1}; ElMS, m/e (rel intensity) 283 (M^+, 2), 277 (11), 178 (31), 57 (base); ClMS (isobutane), m/e (rel intensity) 284 (M + H^+, 2), 230 (32), 228 (base); ElHRMS, m/e 283.0977 ($C_{14}H_{18}NO_3Cl$ requires 283.0975).

***N*-(Phenylsulfonyl)-1,2,7,7a-tetrahydrocycloprop[1,2-*c*]indol-4-one (9).** Sodium hydride (12 mg of 60% in oil, 0.40 mmol, 3.1 equiv) was washed with pentane (3 × 1 mL) and suspended in tetrahydrofuran (3 mL) under argon. A solution of 6-hydroxy-3-(((methanesulfonyl)oxy)-methyl)-1-(phenylsulfonyl)indoline (**20a**, 50 mg, 0.13 mmol) in tetrahydrofuran (1 mL) was slowly added to the suspension of sodium hydride and the resulting solution was stirred at 24 °C (10 min). The reaction mixture was filtered, and the tetrahydrofuran was removed in vacuo shielding the flask from light and maintaining the water bath temperature between 15 and 20 °C to afford **9** (30 mg, 37.6 mg theoretical, 80%) as a tan solid: mp 215 °C dec; ^1H NMR ($CDCl_3$, 300 MHz, ppm) 7.91 (d, 2 H, J = 7.5 Hz, phenylsulfonyl C2-H), 7.67 (t, 1 H, J = 7.5 Hz, phenylsulfonyl C4-H), 7.57 (t, 2 H, J = 7.5 Hz, phenylsulfonyl C3-H), 6.53 (d, 1 H, J = 1.5 Hz, C3-H), 6.44 (d, 1 H, J = 9.7 Hz, C6-H), 6.34 (dd, 1 H, J = 9.7, 1.5 Hz, C5-H), 4.05 (d, 1 H, J = 10.0 Hz, C1-*H*H), 3.94 (dd, 1 H, J = 10.0, 5.0 Hz, C1-H*H*), 2.48 (dt, 1 H, J = 7.7, 5.0 Hz, C7a-H), 1.60 (dd, 1 H, J = 7.7, 4.6 Hz, C7-*H*H), 1.09 (t, 1 H, J = 4.6 Hz, C7-H*H*); IR (neat) ν_{max} 2924, 2854, 1612, 1496, 1447, 1357, 1282, 1168, 1091, 724, 688, 598, 565 cm^{-1}; UV (tetrahydrofuran) 287 (ϵ 9000), 260 nm (ϵ 10000); ElMS, m/e (rel intensity) 146 (40), 77 (base), 57 (81); ClMS (isobutane), m/e (rel intensity) 288 (M + H^+, 12), 184 (22), 143 (base); ElHRMS, m/e 287.0616 ($C_{15}H_{13}NO_3S$ requires 287.0616).

***N*-((*tert*-Butyloxy)carbonyl)-1,2,7,7a-tetrahydrocycloprop[1,2-*c*]indol-4-one (10).** Sodium hydride (10 mg of 60% in oil, 0.25 mmol, 4.5 equiv) was washed with pentane (3 × 1 mL) and suspended in tetrahydrofuran (0.2 mL) under argon. A solution of 1-((*tert*-butyloxy)-carbonyl)-6-hydroxy-3-(((methanesulfonyl)oxy)methyl)indoline (**20b**, 19 mg, 0.055 mmol) in tetrahydrofuran (0.5 mL) was slowly added to the sodium hydride suspension and stirred at 24 °C (10 min). The reaction mixture was filtered and tetrahydrofuran was removed in vacuo, shielding the flask from light and maintaining the water bath temperature between 15 and 20 °C, to afford **10** (12.9 mg, 13.7 mg theoretical, 95%) as a white foam: ^1H NMR ($CDCl_3$, 300 MHz, ppm) 6.58 (br s, 1 H, C3-H), 6.50 (d, 1 H, J = 9.6 Hz, C6-H), 6.38 (dd, 1 H, J = 9.6, 1.0 Hz, C5-H), 3.92 (m, 2 H, C1-H), 2.50 (dt, 1 H, J = 7.7, 5.0 Hz, C7a-H), 1.68 (dd, 1 H, J = 7.7, 4.6 Hz, C7-*H*H), 1.56 (s, 9 H, $OC(CH_3)_3$), 1.35 (t, 1 H, J = 4.6 Hz, C7-H*H*); IR (KBr) ν_{max} 2965, 2925, 1705, 1618, 1498, 1457, 1398, 1364, 1324, 1264, 1231, 1171, 1144, 1044, 1024, 984, 917, 864, 804, 770, 730 cm^{-1}; UV (tetrahydrofuran) 294 (ϵ 14000), 258 nm (ϵ 21000); ElMS, m/e (rel intensity) 247 (1), 191 (11), 57 (base); ClMS (isobutane), m/e (rel intensity) 248 (M + H^+, 7), 210 (base), 192 (55); ClHRMS (isobutane), m/e 248.1256 ($C_{14}H_{17}NO_3$ + H^+ requires 248.1286).

Flash chromatography of pure **10** (10 mg; SiO_2, 1 × 5 cm, 60% ethyl acetate–hexane eluant) afforded **10** (6.5–2.5 mg, 65–25% recovery), indicating partial decomposition on the column.

***seco*-Cl-CDPI$_1$ (27).** A suspension of 1-((*tert*-butyloxy)carbonyl)-6-hydroxy-3-(((methanesulfonyl)oxy)methyl)indoline (**20b**, 40 mg, 0.12 mmol) in 3.0 M hydrogen chloride in ethyl acetate (1 mL) was stirred at 23 °C under nitrogen (10 min) and concentrated in vacuo to afford **23** (31 mg, 32.6 mg theoretical, 95%) as a tan solid. The hydrochloride salt **23** (0.11 mmol, 1.6 equiv) was taken up in *N*,*N*-dimethylformamide (1.0 mL) and treated with 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (EDCI, 36 mg, 0.19 mmol, 2.7 equiv), CDPI$_1$ (**25**, 17 mg, 0.07 mmol), and triethylamine (0.03 mL, 0.21 mmol, 3.1 equiv) under argon. The reaction mixture was stirred at 23 °C (45 h). The reaction suspension was concentrated under a positive pressure of nitrogen. The dry paste was washed with water (12 × 3 mL), 1.0 M aqueous hydrochloric acid (3 × 3 mL), and water (2 × 3 mL) and dried under vacuum. Flash chromatography of the brown solid (SiO_2, 1 × 8 cm, 0–30% *N*,*N*-dimethylformamide–toluene eluant) afforded *seco*-Cl-CDPI$_1$ (**27**, 28 mg, 33 mg theoretical, 84%) as a light tan solid: mp >245 °C; ^1H NMR (DMSO-d_6, 300 MHz, ppm) 11.58 (br s, 1 H, pyrrolo-N*H*), 9.47 (s, 1 H, OH), 7.98 (d, 1 H, J = 9.0 Hz, C4′-H), 7.71 (d, 1 H, J = 2.2 Hz, C7-H), 7.21 (d, 1 H, J = 9.0 Hz, C5′-H), 7.20 (d, 1 H, J = 8.1 Hz, C4-H), 6.94 (s, 1 H, C1′-H), 6.50 (dd, 1 H, J = 8.1, 2.2 Hz, C5-H), 6.09 (s, 2 H, NH_2), 4.67 (apparent t, 1 H, J = 8.6 Hz, O_2SOCHH), 4.37 (m, 3 H, C2-H_2 and O_2SOCHH), 3.97 (t, 2 H, J = 8.6 Hz, C7′-H_2), 3.79 (m, 1 H, C3-H), 3.28 (t, obscured by H_2O, J = 8.0 Hz, C8′-H_2), 3.15 (s, 3 H, OSO_2CH_3); IR (KBr) ν_{max} 3424, 2933, 2925, 1638, 1624, 1580, 1506, 1499, 1460, 1421, 1383, 1347, 1173, 810 cm^{-1}; FABMS (dithiothreitol/dithioerythritol), m/e 471 (M + H^+); FABMS (3-nitrobenzyl alcohol), m/e 471 (M + H^+), 470 (M^+); FABHRMS (3-nitrobenzyl alcohol), m/e 471.1354 ($C_{22}H_{22}N_4O_6S$ + H^+ requires 471.1338); HPLC (0.1 mg of **27**/0.01 mL of DMF, solvent = THF, flow rate = 3.3 mL/min, R_T = 12.2 min) purity >98%.

(−)-3*R*-**27**: $[\alpha]^{25}_D$ −64° (c = 0.025, *N*,*N*-dimethylformamide).

(+)-3*S*-**27**: $[\alpha]^{25}_D$ +64° (c = 0.025, *N*,*N*-dimethylformamide).

Cl-CDPI$_1$ (7). A suspension of *seco*-Cl-CDPI$_1$ (**27**, 9.0 mg, 0.019 mmol) in tetrahydrofuran (0.2 mL) was treated with oil-free sodium hydride (0.6 mg, 0.025 mmol, 1.3 equiv) and stirred at 24 °C. After 25 min the reaction mixture was concentrated in vacuo. The resulting solid was dissolved in *N*,*N*-dimethylformamide (5 mL), treated with tetrahydrofuran (45 mL), and filtered. Concentration of the filtrate afforded Cl-CDPI$_1$ (**7**, 6.5 mg, 7.2 mg theoretical, 90%) as a light tan solid: mp 236 °C dec; ^1H NMR (DMSO-d_6, 300 MHz, ppm) 7.62 (d, 1 H, J = 8.5 Hz, C4′-H), 7.09 (d, 1 H, J = 8.5 Hz, C5′-H), 6.83 (d, 1 H, J = 9.5 Hz, C6-H), 6.73 (s, 1 H, C1′-H), 6.64 (s, 1 H, C3-H), 6.20 (d, 1 H, J = 9.5 Hz, C5-H), 5.87 (s, 2 H, NH_2), 4.93 (br d, 1 H, J = 11.0 Hz, C1-*H*H), 4.45 (dd, 1 H, J = 11.0, 5.0 Hz, C1-H*H*), 3.88 (t, 2 H, J = 8.5 Hz, C7′-H_2), 3.43 (m, obscured by H_2O, C7a-H), 3.11 (t, 2 H, J = 8.5 Hz, C8′-H_2), 2.80 (apparent q, 1 H, J = 6.0 Hz, C7-*H*H), 1.86 (m, 1 H, C7-H*H*); IR (KBr) ν_{max} 3407, 3373, 2951, 1658, 1602, 1506, 1475, 1437, 1366, 1205, 1053, 1027, 1007, 880 cm^{-1}; UV (*N*,*N*-dimethylformamide) 321 (ϵ 15000), 300 (ϵ 14000), 268 nm (ϵ 14000); negative FABMS (triethanolamine), m/e 373 (M − H^+); negative FABHRMS (triethanolamine), m/e 373.1307 ($C_{21}H_{18}N_4O_3$ − H^+ requires 373.1302); HPLC (0.5 mg of **7**/0.01 mL of DMF, solvent = THF, flow rate = 3.1 mL/min, R_t = 11.8 min) purity ≥95%.

(−)-**7**: $[\alpha]^{25}_D$ −24.1° (c = 0.08, *N*,*N*-dimethylformamide).

(+)-**7**: $[\alpha]^{25}_D$ +24.6° (c = 0.06, *N*,*N*-dimethylformamide).

***seco*-Cl-CDPI$_2$ (26).** A solution of 1-((*tert*-butyloxy)carbonyl)-6-hydroxy-3-(((methylsulfonyl)oxy)methyl)indoline (**20b**, 70 mg, 0.20 mmol) in 3.0 M hydrogen chloride in ethyl acetate (3.0 mL) was stirred at 24 °C (20 min). The reaction mixture was concentrated in vacuo to afford 6-hydroxy-3-(((methanesulfonyl)oxy)methyl)indoline hydrochloride (**23**, 55 mg, 57 mg theoretical, 96%) as a tan solid. The hydrochloride salt **23** (0.20 mmol, 1.3 equiv) was taken up in *N*,*N*-dimethylformamide (2 mL), cooled in an ice bath, and treated with 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide (EDCI, 82 mg, 0.43 mmol, 2.7 equiv), CDPI$_2$ (**24**, 68 mg, 0.16 mmol), and anhydrous potassium carbonate (110 mg, 0.80 mmol, 5.0 equiv). The reaction mixture was warmed slowly to room temperature, and after 20 h the reaction mixture was concentrated under vacuum. The solid residue was washed with water (9 × 5 mL), 5% aqueous hydrochloric acid (3 × 5 mL), and water (2 × 5 mL) and dried under vacuum. Flash chromatography (SiO_2, 2.0 × 12.0 cm, 0–50% *N*,*N*-dimethylformamide–toluene eluant) afforded *seco*-Cl-CDPI$_2$ (**26**, 74 mg, 104 mg theoretical, 71%) as a light tan solid: mp >245 °C; ^1H NMR (DMSO-d_6, 300 MHz, ppm) 11.80 (br s, 1 H, pyrrolo-N*H*), 11.55 (br s, 1 H, pyrrolo-N*H*), 9.50 (s, 1 H, OH), 8.27 (d, 1 H, J = 8.9 Hz, C4′-H), 7.97 (d, 1 H, J = 8.9 Hz, C4″-H), 7.70 (br s, 1 H, C7-H), 7.36 (d, 1 H, J = 8.9 Hz, C5′-H), 7.24 (d, 1 H, J = 8.9 Hz, C5″-H), 7.22 (d, 1 H, J = 8.4 Hz, C4-H), 7.10 (s, 1 H, C1′-H), 6.96 (s, 1 H, C1″-H), 6.50 (dd, 1 H, J = 8.4, 2.1 Hz, C7-H), 6.10 (s, 2 H, NH_2), 4.75 (dd, 1 H, J = 10.0, 9.0 Hz, O_2SOCHH), 4.70 (dd, 1 H, J = 10.0, 5.0 Hz, O_2SOCHH), 4.63 (t, 2 H, J = 8.0 Hz, C7′-H_2), 4.38 (m, 2 H, C2-H_2), 4.00 (t, 2 H, J = 8.0 Hz, C7″-H_2), 3.80 (m, 1 H, C3-H), 3.39 (t, 2 H, J = 8.0 Hz, C8′-H_2), 3.28 (t, 2 H, J = 8.0 Hz, C8″-H_2), 3.15 (s, 3 H, OSO_2CH_3); IR (KBr) ν_{max} 3416, 2962, 2925, 2888, 2851, 1655, 1496, 1441, 1385, 1262, 1119 cm^{-1}; FABMS (dithiothreitol/dithioerythritol), m/e 655 (M + H^+); FABMS (3-nitrobenzyl alcohol), m/e 655 (M + H^+); FABHRMS (3-nitrobenzyl alcohol), m/e 655.1960 ($C_{33}H_{30}N_6O_7S$ + H^+ requires 655.1977); HPLC (1 mg of **26**/0.01 mL of DMF, solvent = DMF, flow rate = 3.3 mL/min, R_t = 11.2 min) purity ≥98%.

(−)-3*R*-**26**: $[\alpha]^{25}_D$ −28° (c = 0.025, *N*,*N*-dimethylformamide).

(+)-3*S*-**26**: $[\alpha]^{25}_D$ +27.5° (c = 0.04, *N*,*N*-dimethylformamide).

Cl-CDPI$_2$ (8). A stirred suspension of *seco*-Cl-CDPI$_2$ (**26**, 3.9 mg, 5.9 μmol) in *N*,*N*-dimethylformamide (0.05 mL) and tetrahydrofuran (0.10 mL) was treated with sodium hydride (0.20 mg, 8.3 μmol, 1.4 equiv) under argon and stirred at 24 °C for 25 min. The reaction mixture was diluted with *N*,*N*-dimethylformamide (0.5 mL), filtered, washed with cyclohexane (2 × 0.4 mL), and concentrated under vacuum to afford Cl-CDPI$_2$ (**8**, 3.0 mg, 3.3 mg theoretical, 91%) as a tan solid: mp >245 °C; ^1H NMR (DMSO-d_6, 300 MHz, ppm) 11.62 (s, 1 H, pyrrolo-N*H*), 11.58 (s, 1 H, pyrrolo-N*H*), 8.27 (d, 1 H, J = 8.5 Hz,

C4'-H), 8.00 (d, 1 H, J = 8.5 Hz, C4''-H), 7.38 (d, 1 H, J = 8.5 Hz, C5'-H), 7.24 (d, 1 H, J = 8.5 Hz, C5''-H), 7.22 (d, 1 H, J = 9.0 Hz, C6-H), 7.14 (s, 1 H, C1'-H), 6.99 (s, 1 H, C3-H), 6.95 (s, 1 H, C1''-H), 6.45 (d, 1 H, J = 9.0 Hz, C5-H), 6.17 (s, 2 H, NH_2), 4.66 (m, 2 H, C1-H_2), 4.12 (t, 2 H, J = 8.5 Hz, C7'-H_2), 4.09 (t, 2 H, J = 8.5 Hz, C7''-H), 3.43 (t, 2 H, J = 8.5 Hz, C8'-H_2), 3.58 (apparent t, 1 H, J = 6.0 Hz, C7''-H), 3.29 (t, obscured by H_2O, J = 8.5 Hz, C8''-H_2), 2.27 (m, 1 H, C7-*H*H), 1.92 (m, 1 H, C7-H*H*); IR (KBr) ν_{max} 3416, 2959, 2928, 2854, 1636, 1611, 1580, 1507, 1503, 1431, 1403, 1364, 1285, 1113 cm^{-1}; UV (*N*,*N*-dimethylformamide) 328 (ϵ 35 000), 304 (ϵ 32 000), 278 nm (ϵ 25 000); positive FABMS (triethanolamine), m/e 559 ($M + H^+$); negative FABMS (triethanolamine), m/e 557 ($M - H^+$); FABHRMS (triethanolamine), m/e 559.2091 ($C_{32}H_{26}N_6O_4 + H^+$ requires 559.2096); HPLC (0.5 mg of **8**/0.01 mL of DMF, solvent = THF, flow rate = 3.1 mL/min, R_t = 14 min) purity ≥95%.

(−)-**8**: $[\alpha]^{25}_D$ −19.6° (c = 0.046, *N*,*N*-dimethylformamide).

(+)-**8**: $[\alpha]^{25}_D$ +19.5° (c = 0.041, *N*,*N*-dimethylformamide).

Aqueous Solvolytic Reactivity of CI Agents 7-10. Stock solutions (25-100 μL, 2.0 mM concentration) of the agents in *N*,*N*-dimethylformamide (**1**, **3**), tetrahydrofuran (**6**), or dioxane (**10**) were diluted with a 1:1 mixture of methanol and water (pH 7) or a mixture of 1:1 methanol and aqueous buffer (pH 3) to prepare the solvolysis solution (30-100 μM). In selected instances, an aqueous *N*,*N*-dimethylformamide solution (**7**, **8**) or aqueous tetrahydrofuran solution (**9**) was used as solvolysis solvent instead of aqueous methanol (2.5 μM). The buffer contained 4:1:20 (volumes) of 0.1 M aqueous citric acid, 0.2 M aqueous Na_2HPO_4, and water, respectively. The UV spectrum of each solution was recorded immediately after mixing with water or aqueous buffer, the control and aqueous solutions were stoppered, protected from light, and allowed to stand at room temperature. The UV spectrum of each solution was recorded periodically (every 15 s for **10**, pH = 3) until no further change was detectable in the spectra. The residual absorbance at the long-wavelength absorbance (352 nm for **6**, 280 nm for **10**) was subtracted from the measured absorbances. Linear regression analysis ($r > 0.998$) of the linear plots of log (A/A_0) versus time revealed solvolysis rate constants of 3.67 ± 0.02 × 10^{-5} s^{-1} (pH = 7, $t_{1/2}$ = 5.24 h) and 1.98 ± 0.06 × 10^{-2} s^{-1} (pH = 3, $t_{1/2}$ = 35 sec) for **10**. The spent reaction mixture from the acidic or neutral solvolysis of **10** was extracted with ethyl acetate and analyzed by thin-layer chromatography (TLC). Two major products were detectable on TLC (50% hexane/tetrahydrofuran), which presumably correspond to the water and methanol addition products, respectively.

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Supplementary Material Available: General experimental details, details of the preparation and/or diagnostic characterization of **28**, **29**, and **31-35**, details of computational studies (ref 34), and a summary of the in vitro cytotoxic activity of the agents (Table II) (9 pages). Ordering information is given on a current masthead page.

Oxygen Scrambling and Stereochemistry during the Trifluoroethanolysis of Optically Active 2-Butyl 4-Bromobenzenesulfonate

Paul E. Dietze* and Marek Wojciechowski

Contribution from the Department of Chemistry and Biochemistry, University of Maryland Baltimore County, Baltimore, Maryland 21228. *Received October 27, 1989. Revised Manuscript Received March 5, 1990*

Abstract: It is shown that during the trifluoroethanolysis of 2-butyl 4-bromobenzenesulfonate, containing ^{18}O in the nonbridging oxygens, scrambling of the oxygen label occurs. When enantiomerically enriched 2-butyl 4-bromobenzenesulfonate is subjected to the same solvolysis conditions, racemization of the starting ester is not observed. Therefore if an ion-pair intermediate is involved in the trifluoroethanolysis reaction, the ion pair has a sufficient lifetime to permit rotation of the anion leading to oxygen scrambling. However, rotation of the cation, which would lead to racemization, does not occur. The possibility that the oxygen scrambling may be a concerted reaction and not involve an ion-pair intermediate is discussed.

Although the mechanism of substitution at carbon centers has been studied extensively, there is still disagreement concerning the existence of intermediates in the solvolysis of simple secondary carbon centers. The solvolysis of simple secondary carbon compounds is generally thought to proceed by a stepwise mechanism that involves the formation of an intermediate ion pair.[1-7] The observation that oxygen isotope scrambling occurs in the substrate during solvolysis of benzenesulfonate[7-15] and carboxylate esters[16] is usually interpreted according to a mechanism that involves an ion-pair intermediate and is often cited as evidence for the existence of an ion-pair intermediate.[7,9-11,16] Isotope scrambling in benzenesulfonate esters according to an ion-pair mechanism presumably involves formation of a carbocation-benzenesulfonate ion pair, with sufficient lifetime to allow rotation of the benzenesulfonate anion followed by collapse of the ion pair to regenerate covalently bonded sulfonate ester as depicted in Scheme I and by the solid line of Figure 1.

Recent results have led to the suggestion that the solvolysis of simple secondary carbon compounds may actually be one-step

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