from experiments conducted in oil baths.

These experiments demonstrate that the reaction rates for the esterification under microwave irradiation are not different from the rates observed under conventional heating and support the conclusions of earlier workers.[7,8]

Experimental Section

NMR spectroscopy was performed at 90 MHz. GC analysis was carried out on an instrument fitted with a QS BP5 capillary column 25 m in length. Helium was used as the carrier gas at a flow rate of 2.0 mL/min. The oven was maintained at 50 °C for 2 min and was then heated at 10 °C/min to a final temperature of 280 °C. The final temperature was held for 10 min.

Esterification of 2,4,6-Trimethylbenzoic Acid with *i*-PrOH under Conventional Conditions. An *i*-PrOH solution containing 2,4,6-trimethylbenzoic acid (0.28 M), TsOH (0.19 M), and 2-methylnaphthalene (0.050 M) was prepared. Samples of this solution (5 mL) were sealed in thick-walled glass tubes and were placed in an oil bath thermostatted at the appropriate temperature. The tubes were withdrawn at intervals and were cooled and opened. Pyridine (0.25 mL) was added to a small sample of the reaction mixture (0.5 mL) and the solution was diluted by addition of dichloromethane (2 mL). This was then analyzed by GC: the t_R of the various peaks were 11.22 (2-methylnaphthalene), 13.06 (2,4,6-trimethylbenzoic acid), and 13.68 min (isopropyl 2,4,6-trimethylbenzoate).

Esterification of 2,4,6-Trimethylbenzoic Acid with *i*-PrOH in the Microwave Reactor. *i*-PrOH solutions (75 mL) containing 2,4,6-trimethylbenzoic acid (0.28 M), TsOH (0.19 M), and 2-methylnaphthalene (0.050 M) were prepared and added to the PFA Teflon/PTFE reaction vessel. The microwave power was applied and the solution temperature was raised to the desired level. The temperature was monitored throughout the experiment by a Luxtron fluoroptic thermometer probe located in the reaction vessel. Thermal homogeneity was maintained by magnetic stirring. After the appropriate time, the microwave power was either reduced or turned off to allow the reaction solution to cool. The vessel was then opened and the contents were analyzed by GC as described above.

Acknowledgment. We thank Kodak (Australasia) Pty Ltd. for financial support and F. Vyskoc for technical assistance.

Registry No. 2,4,6-Trimethylbenzoic acid, 480-63-7; 2-propanol, 67-63-0; isopropyl 2,4,6-trimethylbenzoate, 41589-61-1.

Synthesis of CBI-PDE-I-Dimer, the Benzannelated Analogue of CC-1065

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A practical synthesis of CBI (2), utilizing inexpensive starting materials, was developed and applied to the synthesis of benzannelated analogs of CC-1065, in particular CBI-PDE-I-dimer (13) and CBI-bis-indole (17). While a Sharpless asymmetric dihydroxylation reaction proved effective at providing optically active intermediates, a more classical resolution procedure was used to prepare materials of higher optical purity. A novel cyclization employing a six-membered-ring intermediate (12) was employed to construct the cyclopropyl ring in CBI. Like CC-1065, CBI-PDE-I-dimer appears to cause delayed toxicity in mice.

CC-1065 (1), an extremely potent antitumor antibiotic,[1] exhibits a number of interesting biological effects,[2] including the production of delayed deaths in mice at microgram per kilogram doses.[3] Subsequent investigation of this fascinating natural product revealed that the delayed lethality of the compound resulted when the carbon skeleton of PDE-1-dimer (the right-hand portion of the molecule) was attached to CPI, the left-hand alkylating segment.[4] Structurally simplified CPI derivatives were shown not only to be free of this detrimental toxicity, but also to be much more active than CC-1065, and one such compound has since entered clinical testing.[5] To better understand the structural features of CC-1065 responsible for its biological effects, we have had an interest in preparing compounds containing an altered CPI moiety, including the benzannelated derivative CBI (2). The synthesis of CBI was first reported by Boger who has also reported the preparation of a number of interesting CBI analogues.[6] Cava has also reported the preparation of a protected CBI derivative.[7] Herein we describe an alternative synthesis of CBI and its application to the preparation of CBI-PDE-I-dimer (13). Unlike previous routes

(1) (a) Hanka, L. J.; Dietz, A.; Gerpheide, S. A.; Kuentzel, S. L.; Martin, D. G. *J. Antibiot.* **1978**, *31*, 1211–1117. (b) Martin, D. G.; Chidester, C. G.; Duchamp, D. J.; Mizsak, S. A. *J. Antibiot.* **1980**, *33*, 902–903. (c) Chidester, C. G.; Krueger, W. C.; Mizsak, S. A.; Duchamp, D. J.; Martin, D. G. *J. Am. Chem. Soc.* **1981**, *103*, 7629–7635. (d) Reynolds, V. L.; McGovren, J. P.; Hurley, L. H. *J. Antibiot.* **1986**, *39*, 319–334. (e) Hurley, L. H.; Needham-VanDevanter, D. R. *Acc. Chem. Res.* **1986**, *19*, 203–237.

(2) (a) Hurley, L. H.; Reynolds, V. L.; Swenson, D. H.; Petzold, G. L.; Scahill, T. A. *Science* **1984**, *226*, 843–844. (b) Reynold, V. L.; Molineux, I. J.; Kaplan, D. J.; Swenson, D. H.; Hurley, L. H. *Biochemistry* **1985**, *24*, 6228–6237. (c) Hurley, L. H.; Lee, C. S.; McGovren, J. P.; Warpehoski, M. A.; Mitchell, M. A.; Kelly, R. C.; Aristoff, P. A. *Biochemistry* **1988**, *27*, 3886–3892. (d) Warpehoski, M. A.; Hurley, L. H. *Chem. Res. Toxicol.* **1988**, *1*, 315–333. (e) Warpehoski, M. A. *Drugs of the Future* **1991**, *16*, 131–141.

(3) McGovren, J. P.; Clarke, G. L.; Pratt, E. A.; DeKoning, T. F. *J. Antibiot.* **1984**, *37*, 63–70.

(4) Warpehoski, M. A.; Bradford, V. S. *Tetrahedron Lett.* **1988**, *29*, 131–134.

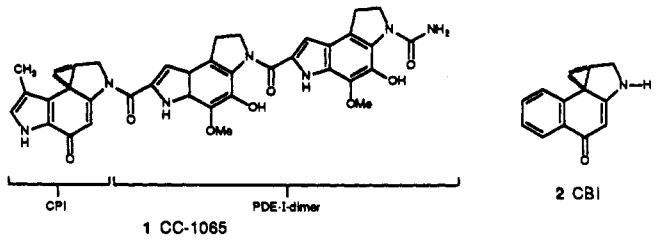
(5) (a) Warpehoski, M. A. *Tetrahedron Lett.* **1986**, *27*, 4103–4106. (b) Warpehoski, M. A.; Gebhard, I.; Kelly, R. C.; Kreuger, W. C.; Li, L. H.; McGovren, J. P.; Prairie, M. D.; Wicnienski, N.; Wierenga, W. *J. Med. Chem.* **1988**, *31*, 590–603. (c) Kelly, R. C.; Gebhard, I.; Wicnienski, N.; Aristoff, P. A.; Johnson, P. D.; Martin, D. G. *J. Am. Chem. Soc.* **1987**, *109*, 6837–6838. (d) Li, L. H.; Kelly, R. C.; Warpehoski, M. A.; McGovren, J. P.; Gebhard, I.; DeKoning, T. F. *Inv. New Drugs* **1991**, *9*, 137–148.

(6) (a) Boger, D. L.; Ishizaki, T.; Wysocki, R. J.; Munk, S. A.; Kitos, P. A.; Suntornwat, O. *J. Am. Chem. Soc.* **1989**, *111*, 6461–6463. (b) Boger, D. L.; Ishizaki, T. *Tetrahedron Lett.* **1990**, *31*, 793–796. (c) Boger, D. L.; Ishizaki, T.; Kitos, P. A.; Suntornwat, O. *J. Org. Chem.* **1990**, *55*, 5823–5832. (d) Boger, D. L.; Ishizaki, T.; Zarrinmayeh, H.; Kitos, P. A.; Suntornwat, O. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 55–58. (e) Boger, D. L.; Ishizaki, T.; Sakya, S. M.; Munk, S. A.; Kitos, P. A.; Jir, Q.; Besterman, J. M. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 115–120. (f) Boger, D. L.; Yun, W.; Teegarden, B. R. *J. Org. Chem.* **1992**, *57*, 2873–2876.

(7) Drost, K. J.; Cava, M. P. *J. Org. Chem.* **1991**, *56*, 2240–2241.

0022-3263/92/1957-6234$03.00/0

to CBI, this synthesis utilizes very inexpensive starting materials and does not involve the isolation of any unstable intermediates. The strategy also differs from that of previous syntheses of CBI and CPI[8] in that in the final ring-forming step, a six-membered-ring precursor (12) is employed.[9]



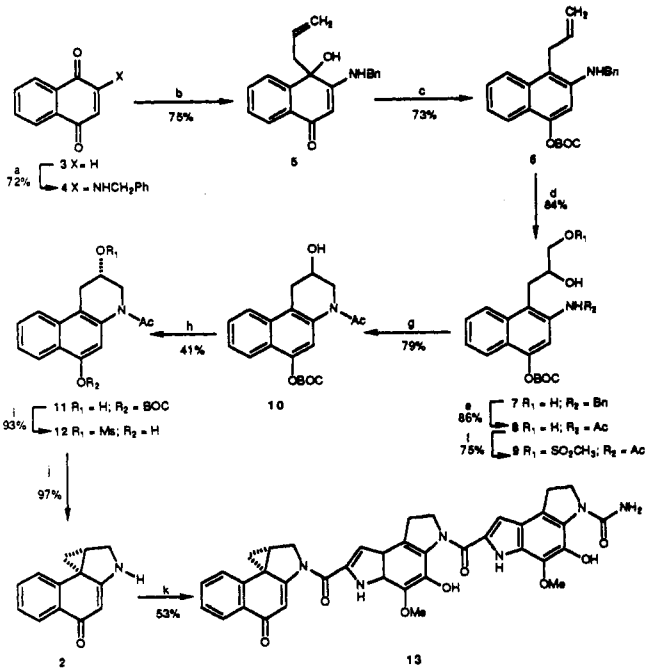
1 CC-1065

2 CBI

Reaction of commercially available 1,4-naphthalenedione (3) with benzylamine cleanly gave the crystalline enamide 4 in 72% yield (Scheme I). Upon treatment of 4 with 2 equiv of allylmagnesium bromide (the first equivalent to deprotonate the amine and deactivate the carbonyl group at C-4), crystalline allyl alcohol 5 was produced. A number of attempts were made to reduce and aromatize 5 with hydride reducing agents including lithium aluminum hydride (with or without aluminum chloride), sodium borohydride, diisobutylaluminum hydride, and triethylsilane/trifluoroacetic acid. However, the vinylogous amide was resistant to these attempts and starting material was usually recovered. This system was also resistant to zinc in acetic acid. While compound 5 itself proved difficult to reduce directly, possibly due to the amine proton, reaction of 5 initially with several equivalents of BOC anhydride followed by immediate treatment of the crude product with sodium dithionite served not only to reduce to the desired naphthalene ring system but also provided the protected phenol 6 (40% overall yield from 3). Osmium-catalyzed dihydroxylation[10] of 6 furnished the racemic diol 7 in 84% yield.

We also investigated the synthesis of 7, in optically active form, utilizing Sharpless asymmetric dihydroxylation protocols.[11] Reaction using the *p*-chlorobenzoate ester of dihydroquinidone (DHQD) also gave an excellent yield of 14, but in rather low optical purity (Table I). Use of the phenanthranyl ether of DHQD (PHN-DHQD) as the chiral ligand and $K_3Fe(CN)_6$ as the reoxidant for the catalytic osmylation at 0 °C afforded in 60% yield a 1:1 mixture of diol 14 and imine 16 each in 70% optical purity. While these isomers could be separated, this was not necessary as each compound could be converted to the same aromatic amine 15 upon catalytic hydrogenation. Another ligand that is reported to give excellent enantioselectivity for terminal olefins, the 9-*o*-(4′-methyl-2′-quinolyl) ether of DHQD[12], MEK-DHQD, was not as good for our substrate (44% ee) and gave lower yields of the desired diol. Surprisingly, dihydroxylation of 6 using the recently reported procedures and the AD-mix formulation of the phthalazine class of ligands[12b] resulted in only a 19% yield of 7 (after

Scheme I[a]

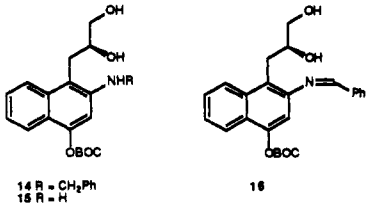


[a] Key: (a) $PhCH_2NH_2$, DMF. (b) 2 equiv $CH_2{=}CHCH_2MgBr$, THF. (c) (i) 2.5 equiv $(t\text{-}BuO_2C)_2O$, CH_3CN; (ii) $Na_2S_2O_4$, H_2O, EtOAc. (d) 0.25 equiv OsO_4, *N*-methylmorpholine *N*-oxide, acetone, H_2O. (e) (i) HCO_2H, Pd/C, MeOH. (ii) Ac_2O, pyridine; (iii) K_2CO_3, MeOH, H_2O. (f) 1 equiv MsCl, pyridine, 0 °C. (g) (i) 1 equiv Me_3SiCl, pyridine; (ii) 1.2 equiv NaH, THF; (iii) K_2CO_3, MeOH. (h) (i) (*R*)-*O*-acetylmandelic acid, EDC, CH_2Cl_2; (ii) K_2CO_3, MeOH. (i) (i) MsCl, Et_3N, CH_2Cl_2; (ii) TFA, CH_2Cl_2. (j) 3 equiv NaH, THF. (k) (i) HCl, EtOAc; (ii) PDE-I-dimer acid, EDC, DMF; (iii) Et_3N, CH_3CN, H_2O.

Table I. Results of Catalytic Asymmetric Dihydroxylation of 6

catalyst	*T*, °C	% yield of 14	% yield of 16	% of ee
DHQD *p*-chlorobenzoate	25	81	0	7
PHN-DHQD	25	80	0	40
PHN-DHQD	0	30	30	70
MEK-DHQD	0	46	10	44
MEK-DHQ	0	46	trace	33
AD-Mix α	0	19	0	0

48 h at 0 °C and 24 h at 25 °C) and 62% of recovered 6 with no enantiomeric enrichment of 7.



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Although this procedure afforded optically enriched materials, operationally it proved simpler to carry on racemic 7 and resort to resolution of a later stage intermediate (vide infra) in order to obtain compounds of high

(8) (a) Wierenga, W. *J. Am. Chem. Soc.* **1981**, *103*, 5621–5623. (b) For a review see: Rawal, V. H.; Jones, R. J.; Cava, M. P. *Heterocycles* **1987**, *25*, 701–728.

(9) The duocarmycin series of antitumor antibiotics contain two members, duocarmycin B_1 and C_1, which also incorporate a six-member ring, which may be derived from ring opening of the corresponding cyclopropyl derivative. (See Ogawa, T.; Ichimura, M.; Katsumata, T.; Morimoto, M.; Takahashi, K. *J. Antibiot.* **1989**, *42*, 1299–1301.) Although presumably these compounds can cyclize in vitro or in vivo to the cyclopropyl-containing duocarmycin A, this has not yet been demonstrated nor has this reaction been demonstrated chemically in the published literature.

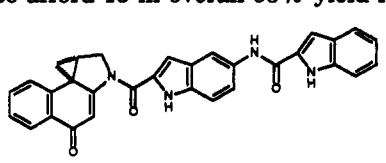
(10) VanRheenen, V.; Kelly, R. C.; Cha, D. F. *Tetrahedron Lett.* **1976**, 1973.

(11) (a) Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968–1970. (b) Kwong, H.-L.; Sorato, C.; Ogino, Y.; Chen, H.; Sharpless, K. B. *Tetrahedron Lett.* **1990**, *31*, 2999–3002.

(12) (a) Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, *56*, 4585–4588. (b) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768–2771.

enantiomeric purity. Thus, compound 7 was converted to the acetylated intermediate 8 employing catalytic transfer hydrogenation to debenzylate the protected amine, and then was treated with 1 equiv of methanesulfonyl chloride to give the primary mesylate 9. Temporary protection of the secondary alcohol in 9 with trimethylsilyl chloride, treatment with sodium hydride, and hydrolytic workup furnished key alcohol 10 in overall 50% yield from diol 7. A basic procedure (methanolic potassium carbonate) was used to hydrolyze the silyl group as acidic workups led to small amounts of hydrolysis of the phenol protecting group. Resolution of 10 utilizing mandelic acid[6] furnished two diastereomers readily separated by column chromatography; subsequent hydrolysis afforded compound 11 in greater than 99% optical purity.[13] Activation of the alcohol as its mesylate and BOC protecting group removal using trifluoroacetic acid furnished the cyclization precursor 12 in 93% yield. Compound 12 readily formed the cyclopropyl ring upon treatment with sodium hydride. Under the conditions of the reaction the acetate protecting group was also hydrolyzed, presumably by adventitious water, such that a 97% yield of CBI (2) was realized from mesylate 12.[14]

CBI itself can be readily converted into a number of interesting analogs. For example, treatment of 2 with 2 equiv of sodium hydride followed by 1 equiv of the imidazolide of 5-[(1*H*-indol-2-yl-carbonyl)amino]-1*H*-indole-2-carboxylic acid,[5] afforded the previously prepared[6f] CBI-bis-indole derivative 17 in 59% yield. To prepare the more elaborate PDE-I-dimer analog 13, it was necessary to first solvolyze CBI to give intermediate 18[6] which was immediately coupled with PDE-I-dimer acid[15] and cyclized in an analogous manner to the preparation of CC-1065[5c] to afford 13 in overall 53% yield from CBI.



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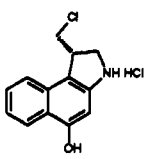

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A number of these CBI derivatives exhibit interesting biological properties. For example, when tested side by side with the corresponding CPI derivative,[5a] compound 17 was half as potent in vitro but equipotent in vivo as an antitumor agent.[16] In side-by-side testing, the CBI derivative 13 appeared to be roughly equipotent in vitro but about half as potent in vivo as CC-1065. Perhaps most fascinating is that unlike simplified analogs, such as compound 17, compound 13, albeit less potent than CC-1065, produced a delayed lethality pattern similar to the natural product.[17] Additional chemical and biological studies of CBI analogs will be reported in due course.

Experimental Section

General Methods. Microanalyses and infrared and mass spectra were obtained by the Physical and Analytical Chemistry Unit of The Upjohn Company. Melting points were obtained on a Mettler FP62 melting point apparatus and are uncorrected. UV spectra were recorded on a Beckman DU7500. HPLC was conducted on a Perkin-Elmer Series 4 chromatograph or a Waters 600E chromatograph equipped with an ISCO V[4] detector. NMR spectra were recorded on a Bruker Aspect 3000 300-MHz NMR spectrometer, and chemical shifts are reported in ppm (parts per million) on the δ scale relative to internal tetramethylsilane. Coupling constants are reported in hertz. Specific rotations were obtained on a Perkin-Elmer 241 polarimeter. All reactions were carried out under a nitrogen atmosphere unless otherwise noted in glassware that was oven-dried. Flash chromatography refers to the method of Still and utilized silica gel 60 (Merck, particle size 0.04–0.063). Solvents were reagent grade, distilled from glass (Burdick and Jackson or Mallinkrodt). Dry tetrahydrofuran (THF) refers to THF distilled from benzophenone ketyl. Reagents were used as purchased.

2-(Benzylamino)-1,4-naphthalenedione (4). A solution of 1,4-napthalenedione (3, 10.0 g, 63.2 mmol) in 100 mL of DMF open to the air was treated with benzylamine (15 mL, 137 mmol) and stirred at room temperature for 18 h. The mixture was diluted with 700 mL of water and extracted with ethyl acetate (3 × 200 mL), and the combined organic layers were washed with 100 mL of brine, dried (sodium sulfate), and concentrated in vacuo. The resulting black oil from two identical reactions was combined and crystallized from ethanol to give 4 (23.9 g, 72%) in two crops: mp 160–161 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 8.1 (m, 2 H), 7.2 (m, 2 H), 7.4 (m, 5 H), 6.21 (bs, 1 H), 5.78 (s, 1 H), 4.38 (d, 2 H, J = 5.7); ^{13}C NMR ($CDCl_3$, 300 MHz, ppm) 46.77, 101.74, 126.18, 126.25, 127.61, 128.10, 128.98, 130.46, 132.03, 133.51, 134.73, 135.85, 147.68, 181.83, 183.03; IR (mull) ν_{max} 3334, 1681, 1604, 1598, 1593, 1563, 1504, 1360, 1260, 728 cm^{-1}; EIMS m/e (relative intensity) 263 (M^+, 76), 262 (40), 246 (59), 91 (100). Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.54; H, 4.97; N, 5.32. Found: C, 77.34; H, 5.05; N, 5.25.

1-Hydroxy-1-allyl-2-(benzylamino)-1,4-dihydronaphthalen-4-one (5). A solution of 4 (3.0 g, 11.4 mmol) in 50 mL of dry THF at 5 °C was treated dropwise with allylmagnesium bromide (1.0 M in diethyl ether, 25 mL). The resulting yellow suspension was stirred an additional 1 h at 5 °C, quenched with 300 mL of saturated aqueous ammonium chloride, extracted with methylene chloride (2 × 100 mL), dried (sodium sulfate), concentrated in vacuo, and crystallized from ethyl acetate, ethanol, and hexane (6:1:2) to give 5 (2.6 g, 75%) in two crops: mp 182–183 °C; ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) 7.71 (t, 1 H, J = 6.0 Hz), 7.62 (d, 1 H, J = 6.6 Hz), 7.52 (d, 1 H, J = 7.5 Hz), 7.36 (t, 1 H, J = 6.6 Hz), 7.0–7.2 (m, 6 H), 6.16 (s, 1 H), 4.9–5.1 (m, including a 1 H singlet at 4.90, 2 H), 4.55 (dd, 1 H, J = 2.1 and 9.9 Hz), 4.45 (dd, 1 H, J = 2.1 and 17.1 Hz), 4.26 (dd, 1 H, J = 6.3 and 16.3 Hz), 4.15 (dd, 1 H, J = 6.3 and 16.3), 2.57 (dd, 1 H, J = 7.2 and 13.2 Hz), 2.41 (dd, 1 H, J = 7.2 and 13.2 Hz); ^{13}C NMR (DMSO-d_6, 300 MHz, ppm) 45.47, 50.40, 72.04, 95.21, 118.42, 124.13, 125.56, 127.05, 127.20, 128.42, 130.75, 131.80, 131.85, 138.54, 144.71, 166.07, 180.38; IR (mull) ν_{max} 3287, 1613, 1599, 1555, 1535, 1452, 1442, 1375, 1290, 1063, 735 cm^{-1}; EIMS m/e (relative intensity) 305 (M^+, 16), 214 (41), 91 (100). Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.46; H, 6.21; N, 4.51.

1-Allyl-2-(benzylamino)-4-[[(*tert*-butyloxy)carbonyl]oxy]naphthalene (6). A solution of 5 (10.0 g, 32.7 mmol) in 300 mL of acetonitrile was treated with di-*tert*-butyl dicarbonate (18 g, 83 mmol) and 4-(dimethylamino)pyridine (500 mg, 4 mmol) and then stirred 18 h at room temperature. The solution was diluted with 300 mL of ethyl acetate and washed with water and brine, and the layers were separated. The organic layer was concentrated in vacuo to approximately 100 mL, diluted with 100

(13) The optical purity was determined by a ChiralCel column (4.6 mm × 25 cm) eluting with 10% 2-propanol in hexane at 1 mL/min monitored at 255 nM. R_f 11.6 min for 11; R_f 16.7 min for the enantiomer of 11.

(14) Compound 2 had identical physical characteristics, including rotation, as that previously reported by D. L. Boger (ref 6c).

(15) Martin, D. G.; Mizak, S. A.; Krueger, W. C. *J. Antibiot.* **1985**, *38*, 746–752.

(16) For example, against L1210 leukemia administered intraperitoneally to mice, compound 17 at an intravenous dose of 100 μg/kg exhibited a 67% increase in the lifespan relative to control mice, whereas the corresponding CPI derivative, U-71184 (ref 5a), exhibited an 83% increase in lifespan at the same dose. Both compounds were acutely toxic to the mice at 200 μg/kg iv.

(17) When administered intravenously to mice, compound 13 was acutely toxic at 400 μg/kg, whereas CC-1065 was acutely toxic at 100 μg/mkg. Delayed deaths starting at about day 40 occurred with compound 13 at 200 μg/kg and 50 μg/kg with CC-1065. Interestingly, the enantiomer of compound 13, like the enantiomer of CC-1065 (ref 18), was as acutely toxic as 13 but did not produce any deaths in mice when administered below the acutely toxic dose.

(18) Hurley, L. H.; Warpehoski, M. A.; Lee, C.-S.; McGovren, J. P.; Scahill, T. A.; Kelly, R. C.; Mitchell, M. A.; Wicnienski, N.; Gebhard, I.; Johnson, P. D.; Bradford, V. S. *J. Am. Chem. Soc.* **1990**, *112*, 4633–4649.

mL of water, and thoroughly degassed with nitrogen. Sodium dithionite (36 g, 210 mmol) was added, and the mixture was stirred 24 h at room temperature. The layers were separated, and the organic layer was washed with water and brine, dried (sodium sulfate), concentrated in vacuo, and flash chromatographed eluting with 10% ethyl acetate in hexane to give **6** (9.3 g, 73%) as a pale yellow oil which crystallized upon standing in the refrigerator: mp 108–109 °C (hexane); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 7.81 (d, 2 H, J = 9.0), 7.3–7.5 (m, 7 H), 6.95 (s, 1 H), 6.0 (m, 1 H), 5.05 (d, 1 H, J = 10.2), 4.96 (d, 1 H, J = 17.4), 4.45 (d, 2 H, J = 4.7), 4.27 (bs, 1 H), 3.66 (d, 2 H, J = 5.4), 1.57 (s, 9 H); ^{13}C NMR ($CDCl_3$, 300 MHz, ppm) 27.67, 30.13, 48.35, 83.37, 106.85, 112.19, 115.78, 120.87, 121.51, 122.12, 122.48, 126.90, 127.27, 127.35, 128.67, 133.94, 134.79, 139.20, 143.48, 146.85, 152.06; IR (mull) ν_{max} 3458, 1752, 1627, 1453, 1371, 1294, 1269, 1253, 1161, 1147, 1130, 766 cm^{-1}; EIMS m/e (relative intensity) 389 (M^+, 26), 333 (10), 289 (100), 198 (67), 181 (15), 91 (73), 57 (100); EIHRMS m/e 389.1999 ($C_{25}H_{27}NO_3$ requires 389.1991). Anal. Calcd for $C_{25}H_{27}NO_3$: C, 77.09; H, 7.03; N, 3.58. Found: C, 77.14; H, 7.03; N, 3.58.

1,2-Dihydroxy-3-[2-(benzylamino)-4-[[(*tert*-butyloxy)carbonyl]oxy]naphthalen-1-yl]propane (7). A solution of **6** (2.5 g, 6.4 mmol) and 4-methylmorpholine N-oxide (1.8 g, 15.3 mmol) in 4:1 acetone/water (80 mL) was treated with osmium tetraoxide (4% in water, 1.6 mL, 0.25 mmol) and stirred 18 h at room temperature in the dark. Sodium sulfite (400 mg) was added and the reaction stirred an additional 1 h at which time the solution was diluted with 300 mL of 1:1 water/brine and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried (sodium sulfate), concentrated in vacuo, and flash chromatographed, eluting with 20% ethyl acetate in hexane to give **7** (2.3 g, 84%) as a tan foam: ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 7.8 (m, 2 H), 7.3–7.5 (m, 8 H), 6.93 (s, 1 H), 4.42 (s, 2 H), 4.0 (m, 1 H), 3.68 (dd, 1 H, J = 3.3 and 11.4), 3.47 (dd, 1 H, J = 5.4 and 11.4), 3.11 (m, 2 H), 2.5 (bs, 1 H), 2.3 (bs, 1 H), 1.56 (s, 9 H); ^{13}C NMR ($CDCl_3$, 300 MHz, ppm) 27.65, 29.55, 48.47, 65.45, 72.31, 83.63, 107.21, 111.74, 120.88, 121.60, 122.16, 127.00, 127.20, 127.37, 128.62, 134.18, 139.12, 144.65, 146.88, 152.09; IR (mull) ν_{max} 3374, 1758, 1628, 1605, 1455, 1370, 1271, 1252, 1148, 1133, 1100 cm^{-1}; EIMS m/e (relative intensity) 423 (M^+, 14), 323 (26), 262 (64), 172 (22), 91 (61), 57 (100); EIHRMS m/e 423.2046 ($C_{25}H_{29}NO_5$ requires 423.2060). Anal. Calcd for $C_{25}H_{29}NO_5$: C, 70.89; H, 6.90; N, 3.20. Found: C, 70.49; H, 6.86; N, 3.20.

(2*S*)-1,2-Dihydroxy-3-[2-(benzylamino)-4-[[(*tert*-butyloxy)carbonyl]oxy]naphthalen-1-yl]propane (14). A mixture of hydroquinidine 9-phenanthryl ether (250 mg, 0.5 mmol), potassium ferricyanide (1.35 g, 4.1 mmol), and potassium carbonate (560 mg, 4.06 mmol) in 1:1 *tert*-butyl alcohol/water (20 mL) was treated with osmium tetraoxide (200 μL, 4% in *tert*-butyl alcohol). The resulting solution was cooled to 0 °C. **6** (500 mg, 1.3 mmol) was added, and the solution was stirred for 18 h at 0 °C, then treated with sodium sulfite (2 g), and stirred 30 min. The two phases were diluted with water and extracted with methylene chloride (3 × 50 mL). The combined organics were dried (sodium sulfate), concentrated in vacuo, and flash chromatographed, eluting with 40% ethyl acetate in hexane to give recovered **6** (75 mg, 15%), **14** (160 mg, 30%), and **15** (160 mg, 30%). The ee of **14** and **15** was determined by converting them to **2** (vide infra) and analyzing by chiral phase HPLC. **15** could be converted to **8** by the same procedure as used to convert **14** to **8**. Chiral phase HPLC of the resulting **2** (ChiralCel OD, 4.6 mm × 25 cm), 10% 2-propanol in hexane, 1 mL/min, monitored at 255 nm, R_f = 18.1 (15%) and 21.3 (85%) $[\alpha]^{23}_D$ = −232° (c = 0.71, MeOH), 70% ee [lit.[6c] $[\alpha]^{23}_D$ = −334° (c = 0.033, MeOH)].

1,2-Dihydroxy-3-[2-(aminoacetyl)-4-[[(*tert*-butyloxy)carbonyl]oxy]naphthalen-1-yl]propane (8). A solution of **7** (5.8 g, 13.7 mmol) in 100 mL of 10% formic acid in methanol was treated with 10% palladium on charcoal (600 mg) and stirred at room temperature for 30 min. The mixture was filtered through Celite and the filter cake washed with ethyl acetate. The combined organics were washed with water, bicarbonate, and brine, dried (sodium sulfate), and concentrated in vacuo. The resulting oil was dissolved in 30 mL of acetic anhydride, treated with pyridine (2 mL), stirred for 1 h, cooled to 5 °C, treated with 30 mL of cold methanol, allowed to stir for 1 h at ambient temperature, diluted with ethyl acetate (100 mL), and washed with water, bicarbonate, and brine, and the organic layer was concentrated in vacuo to give an oil. The resulting oil was dissolved in methanol (50 mL) and treated with 1 N aqueous potassium carbonate (20 mL), stirred for 30 min, then diluted with water (200 mL), extracted with methylene chloride, dried (sodium sulfate), concentrated in vacuo, and flash chromatographed eluting with 7% methanol in methylene chloride to give **8** (4.4 g, 86%) as a tan foam. An analytical sample was crystallized from ethyl acetate/hexane: mp 139–141 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 9.31 (bs, 1 H), 7.9 (m, including 1 H singlet at 7.88, 2 H), 7.77 (m, 1 H), 7.45 (m, 2 H), 2.8–3.8 (m, 7 H), 2.22 (s, 3 H), 1.59 (s, 9 H); ^{13}C NMR ($CDCl_3$, 300 MHz, ppm) 23.77, 27.54, 29.66, 65.06, 72.45, 83.95, 115.47, 121.45, 122.48, 122.75, 124.86, 126.32, 126.87, 132.95, 134.05, 145.31, 152.15, 169.44; IR (mull) ν_{max} 3362, 3284, 1762, 1674, 1607, 1512, 1459, 1379, 1371, 1306, 1277, 1267, 1251, 1147, 1115 cm^{-1}; EIMS m/e (relative intensity) 375 (M^+, 1), 331 (3), 275 (21), 215 (55), 172 (62), 57 (71), 44 (100), 41 (100); FABHRMS (M + H) m/e 376.1706 ($C_{20}H_{25}NO_6$ requires 376.1706). Anal. Calcd for $C_{20}H_{25}NO_6$: C, 63.98; H, 6.71; N, 3.73. Found: C, 63.83; H, 6.89; N, 3.65.

1-[(Methylsulfonyl)oxy]-2-hydroxy-3-[2-(benzylamino)-4-[[(*tert*-butyloxy)carbonyl]oxy]naphthalen-1-yl]propane (9). A solution of **8** (2.0 g, 5.3 mmol) and 4-(dimethylamino)-pyridine (50 mg, 0.4 mmol) in pyridine (50 mL) at 5 °C was treated dropwise over 5 min with methanesulfonyl chloride (0.45 mL, 5.8 mmol) and stirred 18 h at 5 °C. The solution was then diluted with water (200 mL) and extracted with methylene chloride (3 × 50 mL). The combined organic layers were washed with water and brine, dried (sodium sulfate), concentrated in vacuo, and flash chromatographed, eluting with 40% ethyl acetate in hexane to give **9** (1.72 g, 71%, 75% based on recovered **8**) as a white foam: ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 8.93 (s, 1 H), 7.95 (m, 1 H), 7.80 (s, 1 H), 7.75 (m, 1 H), 7.5 (m, 2 H), 4.3 (m, 3 H), 3.2 (d, 1 H, J = 13.0 Hz), 2.9–3.1 (m, including 3 H singlet at 3.05, 5 H), 2.17 (s, 3 H), 1.59 (s, 9 H); IR (mull) ν_{max} 3319, 1759, 1669, 1505, 1460, 1372, 1356, 1277, 1252, 1175, 1149, 1114, 964 cm^{-1}; FABMS m/e (relative intensity) 454 (M + H, 5), 398 (14), 353 (9), 172 (23), 57 (100), 41 (31); FABHRMS m/e + H 454.1536 ($C_{21}H_{28}NO_8S$ requires 454.1513).

3-Acetyl-2-hydroxy-5-[[(*tert*-butyloxy)carbonyl]oxy]-1,2,3,4-tetrahydro-4*H*-benzo[*f*]quinoline (10). A solution of **9** (840 mg, 1.8 mmol) in pyridine (10 mL) at room temperature was treated dropwise with trimethylsilyl chloride (0.29 mL, 2.3 mmol), stirred 30 min, diluted with water (100 mL), extracted with methylene chloride (3 × 50 mL), dried (sodium sulfate), and concentrated in vacuo to give 960 mg of a white foam [^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 8.66 (bs, 1 H), 7.96 (d, 1 H, J = 7.8), 7.95 (s, 1 H), 7.87 (d, 1 H, J = 7.8), 7.5 (m, 2 H), 4.33 (m, 3 H), 3.4 (m, 1 H), 3.1 (m, including 3 H singlet, 4 H), 2.22 (s, 3 H), 1.57 (s, 9 H), −0.19 (s, 9 H)]. The foam was dissolved in dry THF (5 mL) and added dropwise over 5 min to a solution of sodium hydride (50% in mineral oil, 100 mg, 2.1 mmol) in dry tetrahydrofuran (20 mL) at 5 °C. The resulting solution was stirred at ambient temperature for 1 h, then quenched with water, diluted with ethyl acetate (100 mL), and washed with water. The organic layer was concentrated in vacuo and the residue dissolved in methanol (25 mL), treated with 1 N potassium carbonate (5 mL), stirred 30 min, diluted with water, extracted with methylene chloride, dried (sodium sulfate), concentrated in vacuo, and flash chromatographed, eluting with 50% ethyl acetate in hexane to give **10** (510 mg, 79%) as a white solid: mp 243–244 °C; ^{1}H NMR (acetone-d_6, 300 MHz, ppm) 8.0 (d, 1 H, J = 8.4), 7.9 (d, 1 H, J = 8.1), 7.5 (m, 3 H), 4.42 (m, 1 H), 3.8–4.0 (m, 2 H), 3.48 (dd, 1 H, J = 6.0 and 17.7), 3.05 (dd, 1 H, J = 4.8 and 17.7), 2.9 (m, 1 H), 2.30 (s, 3 H), 1.57 (s, 9 H); ^{13}C NMR (DMSO-d_6, 300 MHz ppm) 23.11, 27.12, 32.57, 63.04, 83.43, 116.55, 120.77, 123.34, 123.88, 125.79, 127.06, 132.28, 135.49, 143.50, 151.26, 170.13; IR (mull) ν_{max} 3455, 1758, 1643, 1635, 1410, 1379, 1276, 1266, 1250, 1220, 1158, 1141, 1087, 762 cm^{-1}; EIMS m/e (relative intensity) 357 (M^+, 7), 257 (85), 215 (79), 196 (18), 57 (100); EIHRMS m/e 357.1577 ($C_{20}H_{23}NO_5$ requires 357.1576). Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 66.87; H, 6.57; N, 3.87.

3-Acetyl-2-hydroxy-5-[[(*tert*-butyloxy)carbonyl]oxy]-1,2,3,4-tetrahydrobenzo[*f*]quinoline, (*R*)-(−)-*O*-Acetylmandelate Ester. A solution of (±)-**10** (450 mg, 1.27 mmol), *R*-(−)-*O*-acetylmandelic acid (366 mg, 1.89 mmol), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (410 mg, 2.2

mmol), and 4-(dimethylamino)pyridine (5 mg) in methylene chloride (20 mL) was stirred at room temperature for 1 h. The solution was flash chromatographed, eluting with 40% ethyl acetate in hexane to give two fractions (420 and 220 mg) enriched in the diastereomeric esters. Each fraction was chromatographed separately, using a Waters 600E HPLC with two 25 × 100 RCM 10-μ silica gel columns eluting at 10 mL/min with 30% ethyl acetate in hexane, monitored at 255 nm coupled to an ISCO FOXY fraction collector in the peak detection mode. The separated diastereomers were collected from each chromatography to give (2*R*,2′*R*)-**10**, mandelate ester (300 mg, 45%) and (2*S*,2′*R*)-**10**, mandelate ester (280 mg, 42%). HPLC analysis of the separated diastereomers indicated that each diastereomer was >99% diastereomerically pure (ChiralCel, 4.6 mm × 25 cm, 1 mL/min, 10% 2-propanol in hexane, monitored at 260 nm).

(2*R*,2′*R*)-10, mandelate ester: R_f = 13.1 min (normal phase), R_f = 32.9 min (chiral phase), white foam, $[\alpha]^{23}_D$ = +26.1° (*c* = 0.465, methanol); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 7.2–8.0 (m, 10 H), 5.83 (s, 1 H), 5.5 (m, 1 H), 4.1 (m, 1 H), 3.7 (m, 1 H), 3.48 (dd, 1 H, *J* = 6.0 and 17.9), 3.25 (dd, 1 H, *J* = 3.3 and 17.9), 2.18 (s, 3 H), 2.05 (bs, 3 H), 1.59 (s, 9 H); IR (mull) ψ_{max} 1757, 1672, 1372, 1275, 1269, 1250, 1228, 1207, 1176, 1161, 1141 cm^{-1}; FABMS *m/e* (relative intensity) 534 (M + H, 7), 478 (14), 433 (10), 374 (12), 239 (48), 196 (81), 57 (100); FABHRMS *m/e* 534.2126 (M + H) ($C_{30}H_{32}NO_8$ requires 534.2128).

(2*S*,2′*R*)-10, mandelate ester (11, mandelate ester): R_f = 17.0 min (normal phase), R_f = 32.9 min (chiral phase), white foam, $[\alpha]^{23}_D$ = −80.2° (*c* = 0.475, methanol); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 7.2–8.0 (m, 10 H), 5.83 (s, 1 H), 5.5 (m, 1 H), 4.1 (m, 1 H), 3.8 (m, 1 H), 3.32 (dd, 1 H, *J* = 6.0 and 17.9), 3.06 (d, 1 H, *J* = 12.0), 2.26 (s, 3 H), 2.09 (s, 3 H), 1.59 (s, 9 H); IR (mull) ψ_{max} 1755, 1671, 1373, 1269, 1250, 1225, 1141 cm^{-1}; FABMS *m/e* (relative intensity) 534 (M^+ + H, 11), 478 (10), 433 (12), 374 (12), 332 (21), 239 (42), 196 (72), 57 (100); FABHRMS *m/e* 534.2152 (M + H) ($C_{30}H_{32}NO_8$ requires 534.2128).

(+)-(2*R*)-3-Acetyl-2-hydroxy-5-[[(*tert*-butyloxy)carbonyl]oxy]-1,2,3,4-tetrahydrobenzo[*f*]quinoline (11). A solution of 11 mandelate ester (250 mg, 0.47 mmol) in methanol (10 mL) was treated with 1 N aqueous potassium carbonate (2 mL), stirred 30 min at room temperature, diluted with ethyl acetate (100 mL), and washed with water and brine, dried (sodium sulfate), concentrated in vacuo, and flash chromatographed, eluting with 50% ethyl acetate in methylene chloride to give 11 (165 mg, 98%) as a white solid with spectroscopic characteristics identical with those of the racemic material, **10**: $[\alpha]^{23}_D$ = −39.0° (*c* = 0.445, methanol), $[\alpha]^{23}_D$ = −47.8° (*c* = 0.753, methylene chloride). Chiral HPLC (ChiralCel OD, 4.6 mm × 25 cm), 10% 2-propanol in hexane, 1 mL/min, monitored at 255 nm, R_f = 11.6 for (+)-(2*R*)-**10** (*ent*-**11**) and R_f = 16.7 for (−)-(2*S*)-**10** (**11**).

***ent*-11**: $[\alpha]^{23}_D$ = +39.1° (*c* = 0.445, methanol), $[\alpha]^{23}_D$ = +48.3° (*c* = 0.933, methylene chloride).

(−)-(2*S*)-3-Acetyl-2-[(methylsulfonyl)oxy]-5-hydroxy-1,2,3,4-tetrahydrobenzo[*f*]quinoline (12). A solution of 11 (150 mg, 0.42 mmol) in methylene chloride (5 mL) at 5 °C was treated with triethyl amine (100 μL, 0.72 mmol) and methanesulfonyl chloride (40 μL, 0.51 mmol) then stirred at ambient temperature for 1 h. The reaction solution was washed with water, dried (sodium sulfate), and flash chromatographed, eluting with 30% ethyl acetate in methylene chloride to give the mesylate (170 mg, 93%) as a white foam: ^{1}H NMR (acetone-d_6, 300 MHz, ppm) 7.99 (d, 1 H, *J* = 7.8), 7.93 (d, 1 H, *J* = 7.8), 7.5–7.7 (m, 3 H), 5.47 (m, 1 H), 4.4 (m, 1 H), 3.92 (dd, 1 H, *J* = 2.7 and 13.5), 3.66 (dd, 1 H, *J* = 6.0 and 18.0), 3.42 (dd, 1 H, *J* = 3.6 and 18.3), 3.24 (s, 3 H), 2.32 (s, 3 H), 1.57 (s, 9 H); ^{13}C NMR (acetone-d_6, 300 MHz, ppm) 23.29, 27.75, 31.36, 38.33, 75.15, 84.09, 117.47, 122.25, 124.06, 125.65, 126.80, 128.21, 133.41, 136.73, 145.81, 152.57, 170.96; IR (mull) ψ_{max} 1759, 1669, 1465, 1406, 1371, 1335, 1277, 1270, 1251, 1175, 1142 cm^{-1}; EIMS *m/e* (relative intensity) 335 (32), 293 (18), 239 (34), 197 (69), 196 (100), 57 (80); FABHRMS *m/e* 436.1411 ($C_{21}H_{25}NO_7S$ requires 436.1430), $[\alpha]^{23}_D$ = −87.0° (*c* = 0.47, methanol). The mesylate (150 mg, 0.34 mmol) was dissolved in methylene chloride (7 mL) at 5 °C and treated with trifluoroacetic acid (2 mL) and then stirred 2 h at ambient temperature. The solution was diluted with methylene chloride, washed with water, dried (sodium sulfate), and concentrated in vacuo to give **12** (115 mg, 100%): ^{1}H NMR (acetone-d_6, 300 MHz, ppm) 8.25 (d, 1 H, *J* = 7.8), 7.89 (d, 1 H, *J* = 7.8), 7.59 (t, 1 H, *J* = 7.1), 7.47 (t, 1 H, *J* = 7.1), 7.1 (bs, 1 H), 5.4 (m, 1 H), 4.35 (m, 1 H), 3.92 (dd, 1 H, *J* = 3.1 and 11.1), 3.59 (dd, 1 H, *J* = 6.3 and 12.3), 3.30 (dd, 1 H, *J* = 4.2 and 12.3), 3.24 (s, 3 H), 2.93 (s, 1 H), 2.28 (s, 3 H); IR (mull) ν_{max} 3141, 1622, 1596, 1454, 1450, 1422, 1398, 1377, 1362, 1353, 1347, 1332, 1174, 964, 901, 758 cm^{-1}; EIMS *m/e* (relative intensity) 335 (M^+, 4), 239 (50), 197 (80), 196 (100), 168 (27), 44 (68); FABHRMS *m/e* 335.0817 ($C_{16}H_{17}NO_5S$ requires 335.0827); $[\alpha]^{23}_D$ = −98.8° (*c* = 0.400, methanol).

***ent*-12**: FABHRMS *m/e* 336.0921 M + H_1 ($C_{16}H_{17}NO_5S$ + H_1 requires 336.0906); $[\alpha]^{23}_D$ = +99.8° (*c* = 0.475, methanol).

(+)-(8b*R*,9a*S*)-1,2,9,9a-Tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one [2, (+)-CBI]. A solution of **12** (35 mg, 0.10 mmol) in THF (4 mL) was added dropwise to sodium hydride (50% in mineral oil, 15 mg, 0.3 mmol) in tetrahydrofuran (2 mL) at 5 °C and then stirred at ambient temperature for 6 h. The solution was then diluted with water and extracted with ethyl acetate (3 × 20 mL), and the combined organics were dried (sodium sulfate), concentrated in vacuo, and flash chromatographed, eluting with 60% acetone in hexane to give **2** (20 mg, 97%) as a pale yellow solid: $[\alpha]^{23}_D$ = +335° (*c* = 0.200, MeOH) [lit.[6c] $[\alpha]^{23}_D$ = +332° (*c* = 0.052, MeOH)]. Compound **2** had spectroscopic characteristics that were identical with the published data: ^{1}H NMR ($CDCl_3$, 300 MHz, ppm), 8.21 (d, 1 H, *J* = 7.8), 7.3–7.4 (m, 2 H), 6.82 (d, 1 H, *J* = 7.5), 5.75 (s, 1 H), 5.40 (bs, 1 H), 3.84 (ddd, 1 H, *J* = 1, 4.5, and 10.5), 3.65 (d, 1 H, *J* = 10.5), 2.84 (m, 1 H), 1.58 (dd, 1 H, *J* = 3.9 and 7.8), 1.41 (t, 1 H, *J* = 4.5); UV (316) nm (ϵ = 11 200, THF); EIMS *m/e* (relative intensity) 197 (M^+, 100), 180 (32), 168 (44), 154 (14), 139 (21), 83 (20); EIHRMS *m/e* 197.0841 ($C_{13}H_{11}NO$ requires 197.0841).

Chiral phase HPLC (ChiralCel 4.5 mm × 25 mm, 10% 2-propanol in hexane, 1 mL/min, monitored at 254 nm): R_f = 18.1 min, >99% ee (<1% *ent*-**2**; R_f = 21.3 min).

2-[[5-[(1*H*-Indol-2-ylcarbonyl)amino]-1*H*-indol-2-yl]carbonyl]-(+)-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one, (+)-CBI-Bis-indole (17). A solution of 5-[(1*H*-indol-2-ylcarbonyl)amino]-1*H*-indole-2-carboxylic acid (100 mg, 0.29 mmol) in DMF (2 mL) was treated with 1,1′-carbonyldiimidazole (55 mg, 0.34 mmol), stirred 18 h at room temperature and then at 40 °C for 1 h, and diluted with water (20 mL), and the resulting yellow solid was collected by filtration. The filter cake was washed with water and dried in vacuo to give the imidazolide (102 mg, 95%): ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) 12.32 (s, 1 H), 11.75 (s, 1 H), 10.26 (s, 1 H), 8.57 (s, 1 H), 8.31 (s, 1 H), 7.94 (s, 1 H), 7.5–7.8 (m, 6 H), 7.2 (m, 2 H), 7.07 (t, 1 H, 7.8); ^{13}C NMR (DMSO-d_6, 300 MHz, ppm) 103.45, 111.79, 112.27, 112.68, 113.17, 118.30, 119.77, 121.48, 121.56, 123.53, 126.64, 126.99, 127.60, 130.20, 131.61, 132.35, 135.40, 136.65, 137.86, 158.26, 159.53; FABMS *m/e* (relative intensity) 369 (M^+, 96), 302 (28), 226 (57), 158 (100), 144 (74); FABHRMS *m/e* 369.1236 ($C_{21}H_{15}N_5O_2$ requires 369.1236). A suspension of sodium hydride (50% in mineral oil washed with hexane, 2 mg, 0.04 mmol) in DMF (1 mL) at 5 °C was treated with a solution of **2** (4 mg, 0.02 mmol) in DMF (0.5 mL), stirred 30 min, then treated with the imidazolide (vide supra, 9 mg, 0.025 mmol) in DMF (1 mL), stirred 4 h at 5 °C, diluted with ethyl acetate (50 mL), washed with water, dried (sodium sulfate), and concentrated in vacuo, adsorbing the crude material on Celite (1 g). The Celite mixture was placed on top of a column of silica gel and flash chromatographed, eluting with 10% DMF in toluene to give **17** (6 mg, 59%): ^{1}H NMR (DMF-d_7, 300 MHz, ppm) 11.82 (s, 1 H), 11.75 (s, 1 H), 10.30 (s, 1 H), 8.39 (bs, 1 H), 8.04 (d, 1 H, *J* = 9.0), 7.4–7.7 (m, 7 H), 7.3 (m, 3 H), 7.10 (d, 1 H, *J* = 7.2), 7.05 (s, 1 H), 4.74 (dd, 1 H, *J* = 4.8 and 10.2), 4.60 (d, 1 H, *J* = 10.2), 3.3 (m, 1 H), 1.81 (t, 1 H, *J* = 4.0), 1.78 (apparent dd, 1 H, *J* = 4.0 and 5.5); UV (1% DMF in methanol) 314 nm (ϵ = 45 200), 338 nm (ϵ = 46 100); MS *m/e* (relative intensity), 499 (M^+ + H, 12), 376 (40), 320 (67), 275 (42), 198 (41), 172 (38); FABHRMS *m/e* 499.1773 (M^+ + H), ($C_{31}H_{23}N_4O_3$ requires 499.1770); $[\alpha]^{23}_D$ = +87.7 (*c* = 0.180, DMF).

(+)-(8bR,9aS)-3-(PDE-I-dimer)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (13). Anhydrous hydrochloric acid was introduced via a teflon tube extending below the surface of a solution of **2** (10 mg, 0.051 mmol) in ethyl acetate (2 mL) for 30 min at room temperature. The resulting yellow solution of **18** was concentrated in vacuo, dissolved in dimethylformamide (1 mL) and treated with PDE-I-dimer (26 mg, 0.049 mmol) and

1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (12 mg, 0.06 mmol) then stirred at room temperature for 4 h, quenched with water (0.5 mL), and diluted with 20% dimethylformamide in toluene (15 mL). The aqueous layer was separated, Celite (1 g) was added to the organic layer, and the mixture was concentrated in vacuo. The resulting Celite mixture was placed on top of a column of silica gel and flash chromatographed, eluting with 10% dimethylformamide in toluene to give a yellow powder (21 mg, 56%): ^{1}H NMR (DMF-d_7, 300 MHz, ppm) 13.05 (s, 1 H), 11.40 (s, 1 H), 11.34 (s, 1 H), 11.10 (s, 1 H), 8.34 (s, 1 H), 8.23 (d, 1 H, J = 8.1), 7.92 (d, 1 H, J = 8.4), 7.69 (s, 1 H), 7.40 (t, 1 H, J = 8.1), 7.40 (t, 1 H, J = 8.1), 7.24 (s, 1 H), 7.20 (s, 1 H), 6.98 (bs, 2 H), 4.82 (t, 2 H, J = 8.7), 4.70 (d, 1 H, J = 8.7), 3.8–4.3 (m, partially obscured by residual water, including 4.22, t, J = 8.7; 4.1, dd, J = 1.8 and 8.7; 3.99, s, 3 H; 3.93, s, 3 H), 3.46 (t, 1 H, J = 9.3), 3.36 (t, 1 H, J = 9.3); UV (1% DMF in methanol) 358 nm (ϵ = 53 400); FABMS m/e (relative intensity) 737 (M + H_2, 0.5), 736 (M + H_1, 0.4), 279 (15), 202 (50), 177 (17), 167 (13), 135 (17), 118 (21), 103 (22), 91 (100); FABHRMS, the spectra was too weak for a peak match; $[\alpha]^{23}_D$ = +54.9° (c = 0.133, DMF). A portion of this yellow powder (14 mg, 0.019 mmol) was dissolved in acetonitrile/water/triethylamine (3:1:1, 10 mL), stirred at room temperature for 1 h, diluted with ethyl acetate (50 mL), washed with water (3 × 20 mL), dried (sodium sulfate), concentrated in vacuo, adsorbing the crude material on Celite (1 g), and flash chromatographed, eluting with 20% DMF in toluene to give **13** (12 mg, 94%) as a yellowish brown solid: ^{1}H NMR (DMF-d_7, 300 MHz, ppm) 13.08 (s, 1 H), 11.64 (s, 1 H), 11.37 (s, 1 H), 11.22 (s, 1 H), 8.10 (d, 1 H, J = 7.8), 7.62 (t, 1 H, J = 8.7), 7.47 (t, 1 H, J = 8.7), 7.29 (s, 1 H), 7.28 (d, 1 H, J = 7.8), 7.20 (s, 1 H), 7.00 (s, 2 H), 6.93 (s, 1 H), 4.80 (t, 2 H, J = 10.2), 4.68 (dd, 1 H, J = 6.0 and 10.2), 4.54 (d, 1 H, J = 10.2), 4.22 (t, 2 H, J = 10.2), 3.97 (s, 3 H), 3.93 (s, 3 H), 3.3–3.5 (m, 5 H), 1.82 (d, 2 H, J = 6.2); UV (1% DMF in methanol) 367 nm (ϵ = 32 100); FABMS m/e (relative intensity) 701 (M + H, 4), 504 (4), 436 (4), 411 (6), 274 (6), 198 (17), 73 (100); FABHRMS m/e 701.2399 (M + H) ($C_{38}H_{33}N_6O_8$ requires 701.2360); $[\alpha]^{23}_D$ = +37.3° (c = 0.166, DMF).

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Supplementary Material Available: Copies of ^{1}H NMR spectra (10 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Synthesis of Hypusine and Other Polyamines Using Dibenzyltriazones for Amino Protection

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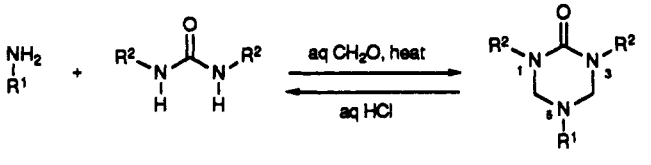
The use of 1,3-dibenzyl-5-substituted-hexahydro-2-oxo-1,3,5-triazine ("dibenzyltriazone") as a protecting group for primary amino is described. Optimized conditions for formation and hydrolysis of dibenzyltriazones, as well as a variety of transformations (reduction, oxidation, hydroxyl modification, C–C bond formation) compatible with this protecting group, are presented. N-Protected amino aldehydes such as **46**, **47**, and **94** are particularly valuable building blocks, as demonstrated by the syntheses of hypusine (**86**), deoxyhypusine (**85**), spermidine (**74**), and two unsaturated spermidine analogues **81** and **84**.

The synthesis of polyfunctional amino acids, amino alcohols, and polyamines typically requires the use of an amino protecting group so that functional group manipulations can be carried out at other sites.[1] Whereas commonly used protecting groups like benzyloxycarbonyl (Z), *tert*-butoxycarbonyl (BOC), or phthaloyl are suitable in many cases, we have encountered some applications where interfering side reactions involving the NH of –NHBOC or –NHZ, or the C=O of phthaloyl, rule out their use. To address the need for a simple amino protecting group that blocks both NH positions, and does not contain an electrophilic carbonyl or nucleophilic nitrogen, we have explored the chemistry of 1,3,5-tri-*N*-substituted hexahydro-2-oxo-1,3,5-triazines ("triazones"), **3**.[2-4] Triazones **3** may be formed from a primary amine **1**, an *N*,*N*′-disubstituted urea **2**, and aqueous formaldehyde, and are hydrolyzed by aqueous hydrochloric acid at room temperature. At higher temperature, mild acid (pH ~3–5) causes hydrolysis if an amine is added as a formaldehyde scavenger. Triazones also show good compatibility with a variety of functional group conversions and carbon–carbon bond forming reactions. In this paper, we describe (1) our progress optimizing triazone formation and hydrolysis, (2) the synthesis and properties of some triazone-containing polyfunctional building blocks, and (3) the use of triazones for the synthesis of the mysterious triamino hydroxy acid hypusine (**86**), its formal biosynthetic precursor 6-deoxyhypusine (**85**), and some unsaturated spermidines **81** and **84** designed to help elucidate hypusine biosynthesis.



Optimization of Triazone Formation. Although the earlier studies[2] indicated that triazones **3** could serve as useful amino protecting groups, the quandary of choosing

(1) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley and Sons: New York, 1991; pp 309–405. (b) Kunz, H.; Waldmann, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, Chapter 3.1, pp 635–645.

(2) Knapp, S.; Hale, J. J.; Bastos, M.; Gibson, F. S. *Tetrahedron Lett.* **1990**, *31*, 2109.

(3) Petersen, H. *Synthesis* **1973**, 243.

(4) (a) Larsen, B. R.; Nicolaisen, F. M.; Nielsen, J. T. *J. Mol. Struct.* **1976**, *32*, 247. (b) Hardies, D. E.; Krass, D. K. U.S. Patent 4150220, 1979; *Chem. Abstr.* **1979**, *91*, P57062e. (c) Hardies, D. E. U.S. Patent 4152516, 1979; *Chem. Abstr.* **1979**, *91*, P57063f.

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