(from acetone); IR (Nujol) 3320, 2600, 1686, 1640, 1578, 1535, 1296, 1260 cm^{-1}; ^1H NMR (300 MHz, Me_2SO-d_6) δ 12.26 (1 H, s), 11.68 (1 H, br s), 7.04 (1 H, d, J = 2 Hz), 4.22 (2 H, t, J = 8 Hz), 3.83 (3 H, s), 3.80 (3 H, s), 3.21 (2 H, t, J = 8 Hz), 2.29 (3 H, s); MS, m/e calcd for $C_{15}H_{16}O_5N_2$ M^+ 304.1059, found 304.1056.

An exactly comparable procedure carried out on **54** (208 mg, 0.472 mM) gave **56**: 93 mg, 68%; mp 221–222 °C (dec) (from acetone); IR (Nujol) 3300, 1694, 1632 cm^{-1}; ^1H NMR (300 MHz, Me_2SO-d_6) δ 12.93 (1 H, s), 11.49 (1 H, br s), 6.96 (1 H, d, J = 2 Hz), 6.89 (2 H, b), 4.00 (2 H, t, J = 8 Hz), 3.82 (3 H, s), 3.79 (3 H, s), 3.20 (2 H, t, J = 8 Hz); MS, m/e calcd for $C_{14}H_{15}N_3O_5$ M^+ 305.1011, found 305.1008.

PDE I (2) and PDE II (3). A solution of **56** (14.3 mg, 46.9 μM) in 0.01 N KOH (21 mL degassed) was allowed to stand at 20 °C for 31.5 h. The solution was acidified with 2 N HCl (15 mL) and brine (7 mL) and extracted with EtOAc (10 × 5 mL). The dried (Na_2SO_4) extract was evaporated in vacuo to give a tan solid, which was crystallized from MeOH to give **2**: 3 mg; mp 230–233 °C; IR (Nujol) 3450, 3340, 3200, 1662, 1634, 1335, 1298, 1261, 1088 cm^{-1}; UV (in water) 251, 308 nm (ϵ 40 000, 15 000), (in 0.01 N NaOH) 236, 254 (shoulder), 338 nm (ϵ 35 000, 24 000); ^1H NMR (300 MHz, $CDCl_3$) δ 12.83 (1 H, s), 11.26 (1 H, br s), 6.87 (3 H, b), 3.99 (2 H, t, J = 9.0 Hz), 3.77 (3 H, s), 3.19 (2 H, t, J = 9.0 Hz).

To a stirred suspension of the ester **55** (13.1 mg, 45.2 μM) in EtOH (0.5 mL degassed) containing $Na_2S_2O_5$ (25 mg) was added INKOH (0.5 mL degassed). After 11.5 h at 20 °C, 2 N HCL (1 mL)/brine (1 mL) and EtOAc (2 mL) were added. The aqueous phase was extracted with EtOAc (4 × 2 mL), washed with brine (2 mL), dried (Na_2SO_4), and evaporated to give crude **3** (8.0 mg). Purification by chromatography over Celite eluting with EtOAc, then $CHCl_3$, and finally MeOH gave **3**: 2 mg; mp slow dec at ca. 180 °C; IR (Nujol) 3280, 2500–3700, 1663, 1640, 1600, 1565 cm^{-1}; UV (in water) 265, 324 nm (ϵ 55 000, 40 000), (in 0.01 N NaOH) 262, 333 nm (ϵ 21 000, 7000); ^1H NMR (300 MHz, $CDCl_3$) δ 12.19 (1 H, s), 11.46 (1 H, br s), 6.95 (1 H, br s), 4.20 (2 H, t, J = 8.1 Hz), 3.77 (3 H, s), 3.19 (2 H, t, J = 8 Hz), 2.28 (3 H, s).

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Supplementary Material Available: Experimental and characterization details for **11**, **12**, **13**, **38**, and **39** (2 pages). Ordering information is given on any current masthead page.

Diels–Alder Reactions of Heterocyclic Azadienes: Total Synthesis of PDE I, PDE II, and PDE I Dimer Methyl Ester

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Abstract: Full details of the total synthesis of PDE I (**2**) and PDE II (**3**), two 3′,5′-cAMP phosphodiesterase inhibitors possessing the identical, functionalized 1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole structure constituting the central and right-hand segments of the potent antitumor antibiotic CC-1065 (**1**), are described. The linkage of two 1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole units in the preparation of PDE-I dimer methyl ester (**4**) is detailed and constitutes the preparation of the fully assembled central and right-hand segments of CC-1065.

CC-1065 (**1**, NSC-298223), an antitumor antibiotic isolated from *Streptomyces zelensis*,[2] initially identified by spectroscopic methods[3a] and confirmed by single-crystal X-ray structural analysis,[3b] has been shown to possess exceptional, potent in vitro cytotoxic activity,[4] antimicrobial activity,[2] and confirmed, potent in vivo antitumor activity.[2] Recent studies have shown that CC-1065 binds to double-stranded B-DNA in an initial, high-affinity, five base pair sequence-specific (A/GNTTA or AAAAA), nonintercalative fashion along the minor groove[5] and subsequently forms an irreversible, covalent adduct.[6] The covalent alkylation of DNA has been shown to proceed by N-3 adenine alkylation of the 4,4-spirocyclopropylcyclohexa-2,5-dienone (spirobicyclo-[5.2.0]octa-2,5-dien-4-one) unit present in the left-hand segment of CC-1065.[6] Consequently, the mechanism of CC-1065 cytotoxicity has been proposed to be derived from the overstabilization of the DNA helix and the inhibition of the normal unwinding and melting process necessary for DNA synthesis.[5] The binding specificity and cytotoxic potency associated with this agent may be attributed to two complementary structural features: the repeating, identical 1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole units constituting the central and right-hand segments of CC-1065 appear to be responsible for the high-affinity, sequence-specific

(1) (a) National Institutes of Health research career development award recipient, 1983–1988 (CA 00898/01134). Alfred P. Sloan research fellowship recipient, 1985–1989. (b) National Institutes of Health predoctoral trainee, 1984–1985 (GM 07775). David Ross Fellow, Purdue University, 1986–1987.

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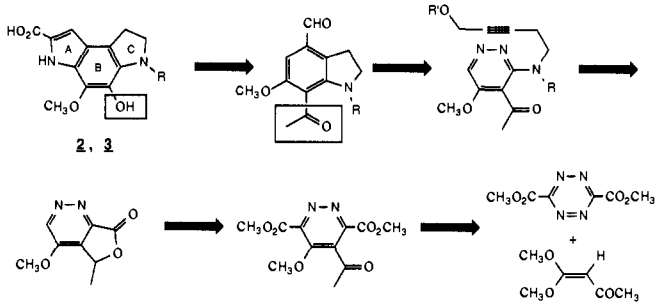
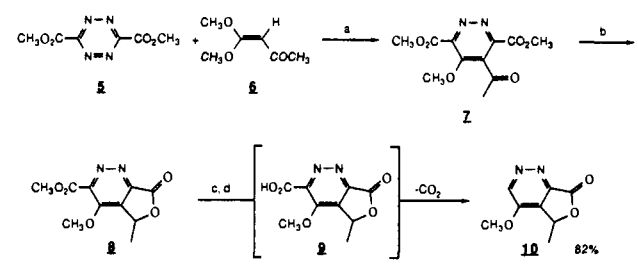
Scheme I



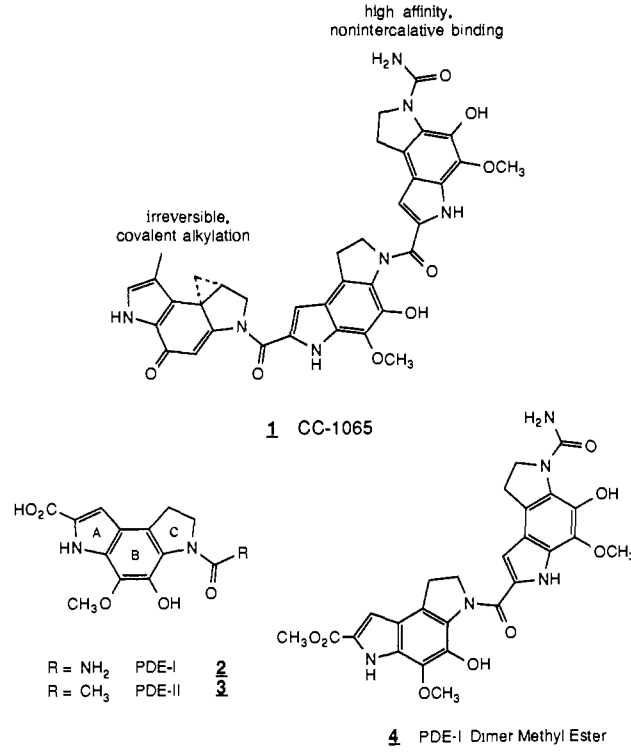
Scheme II[a]



[a] (a) **5**/**6** (1:1.5), dioxane, 60 °C, 21.5 h, 70%. (b) 1.25 equiv of $NaBH_4$, THF, 10 equiv of H_2O, −23 °C, 1 h, 82%. (c) 2.1 equiv of LiOH, THF/MeOH/H_2O (3:1:1), 23 °C, 1 h. (d) Aqueous HCl, pH 1, 23 °C, 4.5 h, 82% from **8**.

B-DNA minor groove binding,[5] and the 4,4-spirocyclopropylcyclohexa-2,5-dienone unit present in the left-hand segment of CC-1065 functions as a selective, reactive alkylating agent effectively delivered to double-stranded DNA.[6] The irreversible, covalent alkylation of the 4,4-spirocyclopropylcyclohexa-2,5-dienone unit was postulated[5,6] to be selective for the natural 3b*R*,4a*S* enantiomer and has received experimental verification with the observation of the selective antitumor potency and DNA alkylation of the 3b*R*,4a*S* vs. 3b*S*,4a*R* pair of CC-1065 analogues U-71 184/U-71 185.[7] In addition, CC-1065 displays a characteristic, delayed hepatotoxicity which is fatal in mice,[8] thus limiting the potential clinical usefulness of the agent. This latter observation has stimulated the search for potential methods of effectively separating the cytotoxic and hepatotoxic properties associated with the administration of CC-1065.[7,9,10]

PDE I (**2**) and PDE II (**3**), two 3′,5′-cAMP phosphodiesterase inhibitors isolated from *Streptomyces* strain MD769-C6,[11] whose structures were determined by single-crystal X-ray analysis[12] and concurrently confirmed by total synthesis,[13] possess the identical 1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole structure constituting the central and right-hand segments of CC-1065.[14,15] Herein, we provide full details of our initial efforts[14c] on the total synthesis of CC-1065, which have resulted in the total synthesis of PDE I (**2**) and PDE II (**3**) as well as the first report of the linkage of two 1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole units in the preparation of PDE I dimer methyl ester (**4**).



1 CC-1065

R = NH_2 PDE-I **2**
R = CH_3 PDE-II **3**

4 PDE-I Dimer Methyl Ester

The approach to PDE I and PDE II is based on the application of two heterocyclic azadiene Diels–Alder reactions[16] in the successful implementation of a 1,2,4,5-tetrazine → 1,2-diazine → indoline strategy[17,18] for the construction of the BC indoline component of the 1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole skeleton, Scheme I. The PDE I/II BC indoline ring system was assembled by implementation of an intramolecular Diels–Alder reaction of an alkyne 1,2-diazine[18,20] which in turn was derived from the

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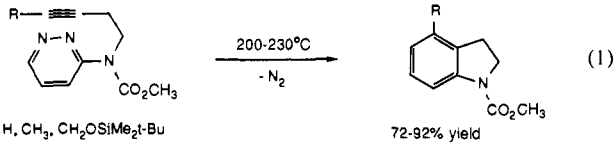
product of the inverse electron demand Diels–Alder reaction of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate[17,19] with 4,4-dimethoxybut-3-en-2-one. Subsequent introduction of the 1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole A ring system was achieved by application of the Hemetsberger–Rees styryl azide thermolysis for indole-2-carboxylate formation.[21] A late, apparently indirect, introduction of the C-4 phenolic hydroxyl group permitted the effective differentiation of the PDE I/II, C-4/C-5 oxygen substituents and was achieved by the application of a newly developed, Lewis acid catalyzed benzylic hydroperoxide rearrangement.[22] A C-4 acetyl group, which served as the required functionality to permit the C-4 hydroxyl introduction, also served as the necessary functionality to provide an effective differentiation of the C-3/C-6 methoxycarbonyl groups present in the initial 1,2-diazine Diels–Alder cycloadduct. This differentiation, which was achieved by reduction–lactonization, was accompanied by the observation of a room temperature, acid-catalyzed decarboxylation of a 4-methoxy-1,2-diazine-3-carboxylic acid.

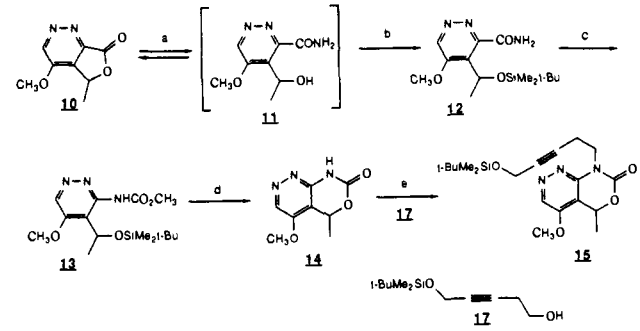
Inverse Electron Demand Diels–Alder Reaction of Dimethyl 1,2,4,5-Tetrazine-3,6-dicarboxylate: 1,2-Diazine Synthesis. In a preliminary study,[18] the feasibility of constructing the PDE I/II BC indoline ring system of the 1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole skeleton employing an intramolecular Diels–Alder reaction of an alkyne 1,2-diazine, eq 1, as well as the suitability of the Hemetsberger–Rees styryl azide thermolysis[21] for PDE I/II A ring introduction had been examined and established. It was anticipated that the alkyne 1,2-diazine required for implementation in the total synthesis of PDE I/II and CC-1065 would be derived from the product of a Diels–Alder reaction of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**5**)[19] with a dienophile possessing suitable functionality for regiospecific introduction of the PDE I/II C-4/C-5 selectively protected *o*-catechol *and* which would permit the differentiation of the 1,2-diazine C-3/C-6 carboxylates. Treatment of **5** with the electron-rich dienophile 4,4-dimethoxybut-3-en-2-one (**6**)[23] provided dimethyl 5-acetyl-4-methoxy-1,2-diazine-3,6-dicarboxylate (**7**, dioxane, 60 °C, 21.5 h, 70%; 101 °C, 3 h, 71%),[17a] Scheme II. The methyl ketone of **7** was expected to provide a method for differentiation of the 1,2-diazine C-3/C-6 methoxycarbonyl groups and to provide the necessary functionality for the late, regiospecific introduction of the C-4 phenolic hydroxyl group present in PDE I/II and CC-1065. Reduction of the methyl ketone **7** was accomplished by using sodium borohydride in tetrahydrofuran containing water (10 equiv) and afforded the lactone **8** directly, thus providing an effective differentiation of the C-3/C-6 methoxycarbonyl groups. Carefully controlled, low reaction temperatures as well as the use of stoichiometric reducing agent were found to be necessary to prevent a competing, subsequent reduction of the electron-deficient 1,2-diazine ring.



(1)

Initial attempts to promote the simple hydrolysis of the remaining C-3 methoxycarbonyl group of **8** failed to provide the expected carboxylic acid **9** upon aqueous acid workup. Moreover, upon extended exposure of the hydrolysis reaction mixture to aqueous acid, the lactone **10**, derived from decarboxylation of the C-3 carboxylic acid, was isolated as the sole organic extractable product, Scheme II. Optimization of this unexpectedly facile room temperature, acid-catalyzed decarboxylation[24] by carefully controlling the conditions for initial ester hydrolysis (2.1 vs. 2.5 equiv of LiOH) and optimization of the aqueous acid concentration and reaction time afforded the lactone **10** in 82% isolated yield from **8**, after purification by recrystallization. The use of excess lithium hydroxide in the ester hydrolysis step appears to promote a subsequent, competing O-demethylation and/or nucleophilic displacement of the 1,2-diazine C-4 methoxy group. The unanticipated room temperature decarboxylation of **9** appears to be general for 4-alkoxy-1,2-diazine-3-carboxylic acids[25] and may result from C-3 ipso protonation facilitated by the presence of the C-4 *o*-methoxy group. The two-step sequence of reduction/lactonization followed by hydrolysis and room temperature decarboxylation provided **10** and completed differentiation of the C-3/C-6 methoxycarbonyl groups present in **7**.

Scheme III[a]



[a] (a) NH_3, CH_3OH, 25 °C, 1 h. (b) *t*-$BuMe_2SiCl$, imidazole, DMF, 25 °C, 63% from **10** (28% recovered **10**). (c) 1.25 equiv of MeOBr, 4 equiv of $NaOCH_3$, MeOH, −43 to 0 °C, 30 min; 60 °C, 30 min. (d) Aqueous H_2SO_4, pH 1, 25 °C, 12 h, 91% from 12. (e) 1.4 equiv of **17**, 1.4 equiv of Ph_3P, 1.4 equiv of $EtO_2CN{=}NCO_2Et$, THF, 22 °C, 24 h, 61% (35% **16**).

Initial efforts directed at the introduction of a 1,2-diazine C-3 amino group, which necessarily preceded attempts to construct the PDE I/II BC indoline ring system, focused on methods for effecting a one-step oxidative hydrolysis of the lactone **10** to the corresponding keto acid **10b** and the potential of subsequently implementing a Curtius rearrangement of the free carboxylic acid, eq 2. Methods examined to convert **10** to the alcohol–acid **10a** (R = OH) and subsequently oxidize the resulting *secondary*, benzylic alcohol (aqueous $NaOH/KMnO_4$; aqueous $NaOH/Ag_2O$;[26] aqueous NaOH and then PDC/pyridine;[27] $NaOBr$[28]) failed to provide the keto acid **10b** and afforded only recovered lactone **10**.[29] Similar efforts at the direct introduction of the 1,2-diazine C-3 amino functionality employing methods for effecting the Curtius rearrangement of the alcohol–acid **10a** (R = OH) proved unsuccessful. Treatment of the lactone **10** with hydrazine in ethanol followed by low-temperature oxidation of the resulting hydrazide (**10a**, $R = NHNH_2$) with nitrogen dioxide in methylene chloride and thermolysis of the resulting acyl azide (**10a**, $R = N_3$) in benzene[30] failed to provide the Curtius product and afforded recovered lactone **10**. Similarly, hydrolysis of **10** with lithium hydroxide followed by direct treatment of the lithium salt of the alcohol–acid (**10a**, R = OLi) with diphenyl phosphorazidate [$(PhO)_2P(O)N_3$] according to the conditions described by Shioiri and Yamada[31] likewise failed to provide the Curtius

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(25) The room temperature decarboxylation of 4-(benzyloxy)-1,2-diazine-3,6-dicarboxylic acid (C-3 carboxylic acid) slowly occurs at 25 °C (12–24 h) in aqueous HCl and appears to be accelerated by the presence of Li^+ salts. In contrast, C-6 decarboxylation in the same system occurs at 110 °C (xylene, 15 min): Boger, D. L.; Coleman, R. S., unpublished observations.

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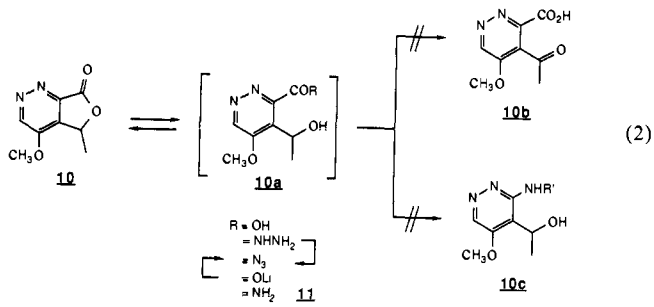
(28) Adjangba, M. S.; Barnes, E. P. D.; Ikonne, J. V. *Ghana J. Sci.* **1969**, *9*, 91.

(29) Attempted benzylic bromination of **10** (NBS or Br_2, AIBN, CCl_4, $h\nu$ or heat) failed to afford the brominated product. For use of this procedure in the bromination of γ-lactones, see: Koten, I. A.; Sauer, R. J. *Org. Synth. Collect. Vol. V* **1969**, 145. Harland, P. A.; Hodge, P. *Synthesis* **1983**, 419.

(30) Bonjouklian, R.; Ganem, B. *Tetrahedron Lett.* **1977**, 2835. Edwards, O. E.; Ho, P.-T. *Can. J. Chem.* **1977**, *55*, 371. Fischer, H. O. L.; Dangschat, G. *Chem. Ber.* **1932**, *65*, 1009.

rearrangement product and afforded only starting lactone **10**. In all cases the reclosure of the alcohol–acid (**10a**, R = OH) or the intermediate acyl azide (**10a**, R = N_3) to the lactone **10** precluded Curtius product formation.



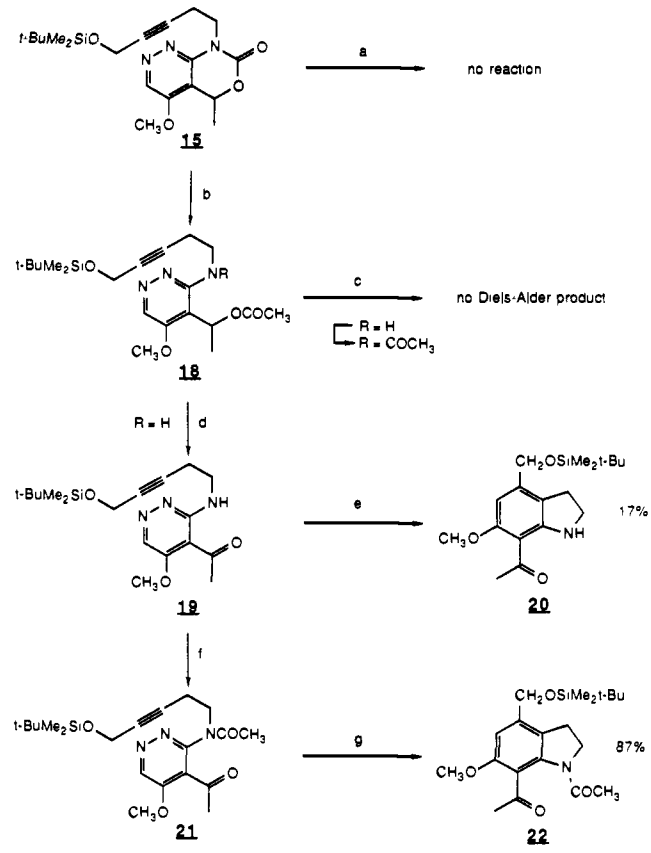
(2)

Treatment of lactone **10** with 25% methanolic ammonia afforded the unstable amide **11**, Scheme III. Although the hydroxy amide **11** could be isolated, relactonization to **10** again precluded its use under conditions required of a subsequent Hofmann rearrangement. Protection of the *secondary* alcohol of **11** (*tert*-butyldimethylsilyl chloride, imidazole, DMF)[32] afforded the stable, crystalline *tert*-butyldimethylsilyl ether **12** (65–50%) along with recovered **10** (25–40%). The ease with which **12** and **10** could be separated by chromatography permitted the recovery and recycling of the lactone **10** through this two-step sequence. Treatment of the amide **12** with in situ generated methyl hypobromite (MeOBr) and sodium methoxide in methanol at −43 °C *followed by warming at 60 °C afforded* the *N*-carbomethoxy 3-amino-1,2-diazine **13**. The use of this modified Hofmann rearrangement[33] employing the low-temperature generation of the thermally unstable methyl hypobromite and the subsequent base-catalyzed, thermal (60 °C) rearrangement of the intermediate *N*-bromoamide proved to be an excellent method for 1,2-diazine C-3 amine introduction. Subsequent deprotection of the *tert*-butyldimethylsilyl ether of **13** (*n*-Bu_4NF or aqueous acid)[32] was accompanied by the closure of the intermediate hydroxycarbamate to **14**. Optimization of the Hofmann rearrangement with the subsequent in situ deprotection of the *tert*-butyldimethylsilyl ether of **13** by exposure to aqueous sulfuric acid afforded 5,8-dihydro-7*H*-pyridazino[3,4-*d*][1,3]oxazin-7-one **14** directly in 91% isolated overall yield from the *O*-*tert*-butyldimethylsilyl amide **12**.

Intramolecular Diels–Alder Reactions of Alkyne 1,2-Diazines: PDE I/II BC Indoline Ring Construction. Introduction of the functionalized alkyne side chain necessary for the intramolecular alkyne 1,2-diazine Diels–Alder reaction[18] was accomplished employing the monoprotected pentynediol 5-((*tert*-butyldimethylsilyl)oxy)-3-pentyn-1-ol (**17**), and alkylation conditions developed by Mitsunobu,[34,35] and afforded the desired alkylated oxazinone **15** (61%) accompanied by 1,2-diazine N-2 alkylated material (**16**, 35%)[36] which were separated readily by silica gel chromatography, Scheme III.

Alkyne 1,2-diazine **15** proved reluctant to undergo the desired intramolecular Diels–Alder reaction necessary for BC indoline ring construction, Scheme IV. Under the thermal conditions

Scheme IV[a]



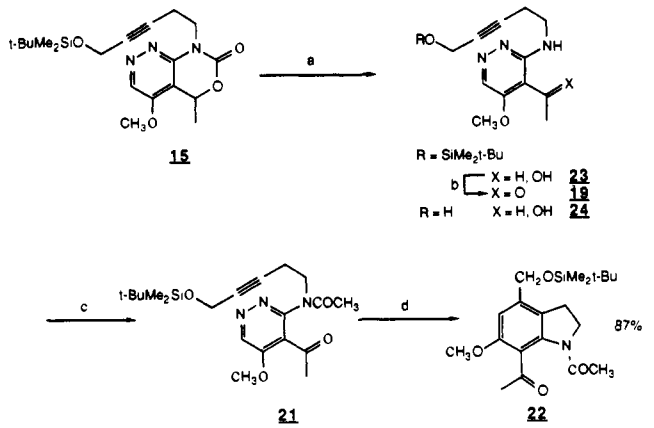
[a] (a) 200–230 °C, TIPB, 18 h. (b) 1.05 equiv of MeLi, THF, −78 to 0 °C, 1 h, 53–64% for **18**, R = H. (c) 175–230 °C, TIPB, 6–18 h. (d) NH_3, CH_3OH, 25 °C, 1–3 h; MnO_2, CH_2Cl_2, 24 h, 72%. (e) 200–230 °C, TIPB, 14–18 h, 17%. (f) Neat Ac_2O, 10 equiv of NaOAc, 120 °C, 1.5 h, 96%. (g) 230 °C, TIPB, 16–18 h, 87%.

examined (200–230 °C, 1,3,5-triisopropylbenzene), no evidence for indoline formation was observed, and 1,2-diazine starting material was recovered unchanged. As might be expected, this unreactivity arises from the stereochemical constraint of the alkyne side chain imposed by the 5,8-dihydro-7*H*-pyridazino[3,4-*d*]-[1,3]oxazin-7-one system of **15**, which prevents the alkyne from assuming the required conformation for Diels–Alder reaction with the 1,2-diazine azadiene system. Therefore, the intramolecular Diels–Alder reaction was examined by using systems in which the alkyne side chain was not constrained.[18]

Addition of nucleophiles (e.g., MeLi, MeMgBr) to the *N*-alkyloxazinone system (e.g., **15**) was anticipated to lead to ring-opened *N*-acyl hydroxy amide derivatives, and the comparable reaction of 1,4-dimethyl-1,4-dihydro-2*H*-benz[1,3]oxazin-2-one[38] with methyllithium cleanly afforded the expected *N*-acetyl hydroxy amide.[39] In contrast, subjection of **15** to identical reaction conditions afforded the *O*-acetyl amine **18**[39] (R = H, 65%), Scheme IV. As a consequence of the electron-deficient character of the 1,2-diazine ring system, the collapse of the tetrahedral intermediate produced by addition of methyllithium to the carbamate carbonyl of **15** occurs with loss of the 1,2-diazine stabilized amine anion vs. the anticipated alkoxide anion. Upon thermolysis, alkyne 1,2-diazine **18** (R = H) as well as *N*-acetyl alkyne 1,2-diazine **18** (R = $COCH_3$) failed to provide the indoline intramolecular Diels–Alder product despite the slow consumption of starting material, Scheme IV. In part, this was attributed to the thermal instability of the benzylic acetate present in both starting material and product. Removal of the *O*-acetate group of **18**

(31) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151. Ninomiya, K.; Shiorii, T.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203.
(32) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(33) Radlick, P.; Brown, L. R. *Synthesis* **1974**, 290.
(34) Mitsunobu, O. *Synthesis* **1981**, 1. Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679.
(35) Use of methods for direct N-alkylation was unsuccessful. In related efforts, attempts to alkylate derivatives of 3-chloro-6-amino-1,2-diazines (*N*-benzyl and *N*-carbomethoxy) utilizing homopropargylic alkylating agents (e.g., 3-pentynyl iodide and 3-pentynyl tosylate) under standard conditions (NaH, THF/DMF, 25 °C, 1–24 h) resulted only in consumption of alkylating agent with no evidence of N-alkylation.[18]
(36) The Mitsunobu alkylations of 3-amino-1,2-diazines proceed to afford varying ratios of desired C-3 amino-alkylated product and the N-2 1,2-diazine ring-alkylated product: see ref 18.
(37) Details of efforts to effect the Mitsunobu alkylation of 3-amino-1,2-diazines related to **14** with 3-butyn-1-ol are provided in the supplementary material.
(38) Prepared from 2′-aminoacetophenone by the sequence (a) $ClCO_2CH_3$, K_2CO_3, THF, 25 °C, 24 h; (b) $NaBH_4$, THF–H_2O, 25 °C, 12 h; and (c) NaH, CH_3I, THF, 25 °C, 12 h to afford **16**.
(39) Spectral characterizations of these compounds are provided in the supplementary material.

Scheme V[a]

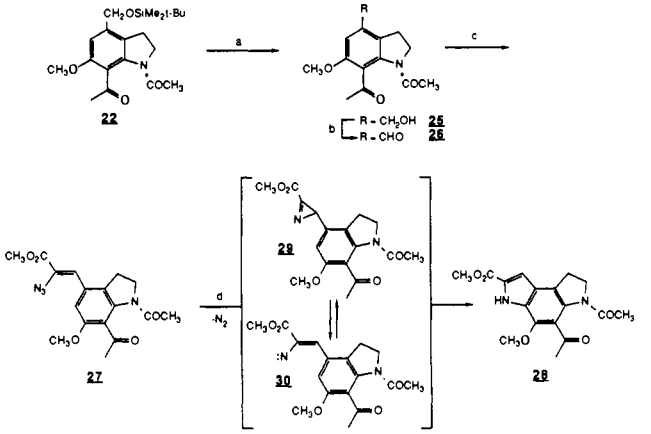


[a] (a) 2 equiv of KOH, 1 equiv of *t*-BuOK, ether, 0 °C, 0.5 h. (b) 10 wt equiv of MnO_2, CH_2Cl_2, 22 °C, 24–36 h, 79% from **15**. (c) Neat Ac_2O, 10 equiv of NaOAc, 120 °C, 2.2 h, 96%. (d) 230 °C, TIPB, argon, 18 h, 87%.

(NH_3, MeOH) followed by oxidation (MnO_2, CH_2Cl_2) of the resulting alcohol afforded the 4-acetyl-3-(alkylamino)-5-methoxy-1,2-diazine **19** (72% overall from **18**, R = H). Subjection of **19** to the conditions previously employed for intramolecular alkyne 1,2-diazine Diels–Alder reaction (200–230 °C, 1,3,5-triisopropylbenzene, 14–18 h) afforded the indoline **20**,[40] albeit in modest yield (17%). Shorter reaction times and lower reaction temperatures resulted in increased recovery of unreacted alkyne 1,2-diazine **19** with no significant change in the isolated yield of the **20**. Consequently, it appeared as if a subsequent, thermal consumption of **20** was effectively competing with the intramolecular cycloaddition of **19**. Consistent with this observation, acetylation of the nonnucleophilic, nonbasic amine **19**[41] (Ac_2O, NaOAc, 120 °C, 96%) cleanly afforded the *N*-acetyl amide **21**, and subjection of **21** to Diels–Alder conditions (230 °C, 1,3,5-triisopropylbenzene, 18 h) provided the indoline **22** in 87% yield (optimized).

With the success of this Diels–Alder reaction secured, attention focused on developing an alternative, more direct route to the *N*-acetyl amide **21**. Although standard aqueous lithium hydroxide promoted hydrolysis of **15** afforded mixtures of desired product **23**, starting material, and the O-desilyl hydrolysis product **24**,[42] Scheme V, the treatment of the oxazinone **15** with anhydrous potassium hydroxide in ether at 0 °C following the conditions described by Gassman[43] afforded **23** (94–100%) with no trace of O-desilylation competing with the exhaustive carbamate hydrolysis. Without purification, oxidation of the crude amino alcohol **23** (MnO_2) provided **19** (79% overall yield from **15**), Scheme V. Acetylation of **19** under the conditions described beforehand (Ac_2O, NaOAc, 120 °C) provided **21** (96%), and thermolysis of **21** afforded the indoline **22** (87% optimized yield), completing the construction of the BC indoline ring system of the 1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole subunits of PDE I/II and CC-1065.

Scheme VI[a]



[a] (a) $HOAc/H_2O/THF$ (3:1:1), 22 °C, 12–18 h. (b) 10 wt equiv of MnO_2, CH_2Cl_2, 22 °C, 18 h, 74% from **22**. (c) 10 equiv of $N_3CH_2CO_2CH_3$, 8 equiv of NaOMe, MeOH, −23 to 0 °C, 1 h. (d) Xylene, 0.05 M, N_2, reflux, 5 h, 65% from **26**; see Table I.

Table I. Thermolysis of Azidocinnamate **27**: Preparation of **28** and Introduction of PDE I/II Indole 2-Carboxylate A Ring

temp, °C	time	yield, %
140	20 min	27
140	2 h	49
140	3 h	55
140	4 h	59
140	5 h	65

Styryl Azide Thermolysis: Indole-2-carboxylate A Ring Introduction. The introduction of the PDE I and PDE II A ring was achieved with the use of methodology introduced and developed by Hemetsberger and Rees.[21] Preparation of the indoline-4-carboxaldehyde **26** required for condensation with methyl azidoacetate and indole-2-carboxylate preparation was achieved by deprotection of the *tert*-butyldimethylsilyl ether of **22** (3:1:1, AcOH:H_2O:THF),[32] Scheme VI, affording a near quantitative yield of the free benzylic alcohol **25**. Subsequent oxidation of **25** (MnO_2) provided the aldehyde **26** (74% overall yield). Condensation of **26** with methyl azidoacetate[44] (10 equiv) with sodium methoxide (8 equiv) in methanol (0 °C) afforded the azidocinnamate **27** in greater than 95% crude yield. Without purification, this homogeneous, unstable intermediate cyclized upon thermolysis in refluxing xylenes under nitrogen and afforded the 1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-carboxylate **28** in 65% overall yield from aldehyde **26**. This reaction proceeds with the thermal generation of the intermediate 2*H*-azirine **29**,[21,45] Scheme VI. The slow step in the generation of the indole-2-carboxylate **28** appears to be the aryl CH insertion reaction of the nitrene intermediate **30**, and disappearance (TLC, SiO_2) of the starting azidocinnamate **27** (15–30 min, 140 °C) does not correspond with the temporal appearance of **28**, Table I. The rapid thermolytic generation of the intermediate 2*H*-azirine **29** (15–30 min, 140 °C) precedes product formation (5 h, 140 °C) and serves as an intermediate, reversible source of the reactive nitrene **30** in the thermal conversion of the azidocinnamate **27** to the corresponding indole-2-carboxylate **28**.

Benzylic Hydroperoxide Rearrangement: C-4 Phenolic Hydroxyl Group Introduction. Total Synthesis of PDE I and PDE II. The original strategy for the introduction of the C-4 phenolic hydroxyl group of PDE I and PDE II relied on a Baeyer–Villiger oxidation of the existing C-4 methyl ketone of **22**, **28**, or related intermediates. The combination of steric and electronic features of hindered, electron-rich substrates, e.g., **22** and **28**, which slow or

(40) **20**: ^1H NMR ($CDCl_3$, 80 MHz, ppm) 7.3 (br s, 1 H, NH), 6.16 (s, 1 H, C5-H), 4.57 (s, 2 H, CH_2O), 3.83 (s, 3 H, OCH_3), 3.72 (t, 2 H, J = 8.3 Hz, NCH_2CH_2), 2.85 (t, 2 H, J = 8.3 Hz, NCH_2CH_2), 2.55 (s, 3 H, $COCH_3$), 0.95 (s, 9 H, $SiCMe_3$), 0.11 (s, 6 H, $SiMe_2$); EIMS, *m/e* (relative intensity) 335 (M^+, 27), 278 (2), 202 (base), 189 (10), 174 (2), 160 (11), 130 (5), 75 (11).

(41) Acylation of **19** with methyl chloroformate under standard conditions (K_2CO_3, DMAP, THF, 23 °C) failed to provide the corresponding methyl carbamate. Acylation of **19** with acetic anhydride (neat Ac_2O, *i*-Pr_2EtN, DMAP, 100 °C; neat Ac_2O, 100 °C) afforded **21** in modest yields (25%) while *N*-acetylimidazole (THF, 60 °C), pentafluorophenyl acetate (DMF, 80 °C), and neat acetic anhydride/pyridine (10 equiv, 25 °C) failed to react with **19**. Use of anhydrous sodium acetate (10 equiv) in neat acetic anhydride (120 °C) provided **21** in excellent yields (82–96%).

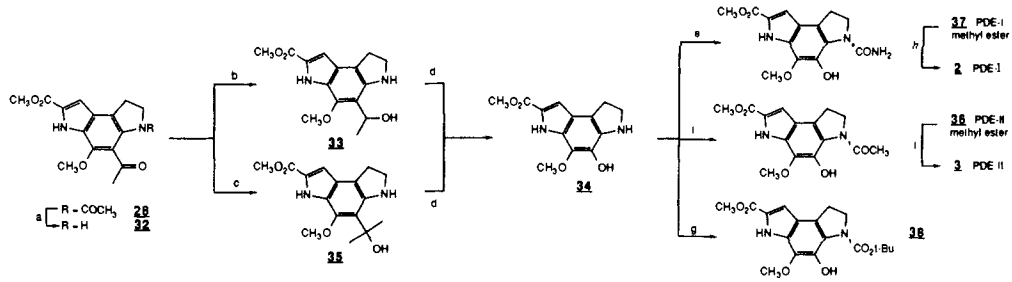
(42) **24**: ^1H NMR ($CDCl_3$, 80 MHz, ppm) 8.34 (s, 1 H, C6-H), 6.8 (br m, 1 H, NH), 5.48 (q, 1 H, J = 6.7 Hz, $CHCH_3$), 4.21 (t, 2 H, J = 2.1 Hz, OCH_2), 3.87 (s, 3 H, OCH_3), 3.68 (t, 2 H, J = 6 Hz, NCH_2CH_2), 2.0–2.7 (br m, 4 H, NCH_2CH_2 and two OH), 1.45 (d, 3 H, J = 6.7 Hz, $CHCH_3$).

(43) Gassman, P. G.; Hodgson, P. K. G.; Balchunis, R. J. *J. Am. Chem. Soc.* **1976**, *98*, 1275. Gassman, P. G.; Schenk, W. N. *J. Org. Chem.* **1977**, *42*, 918.

(44) Forster, M. O.; Fierz, H. E. *J. Chem. Soc.* **1908**, *93*, 72.

(45) Hassner, A.; Wiegand, N. H.; Gottlieb, H. E. *J. Org. Chem.* **1986**, *51*, 3176. Knittle, D. *Synthesis* **1985**, 186. Hickey, D. M. B.; Moody, C. J.; Rees, C. W. *J. Chem. Soc., Chem. Commun.* **1982**, 1419.

Scheme VII[a]



[a] (a) Anhydrous HCl, MeOH, 70 °C, 12 h, 85%. (b) Excess $NaBH_4$, MeOH, 22 °C, 15 min, 78%. (c) 4 equiv of MeMgCl, THF, 0–22 °C, 20 min, 76%. (d) See Table II. (e) 5 equiv of trimethylsilyl isocyanate, CH_2Cl_2, catalytic DMAP, 21–23 °C, 12 h. (f) 10 equiv of Ac_2O, excess NaOAc, THF, 23–24 °C, 4 h. (g) 5 equiv of di-*tert*-butyl dicarbonate, THF, 23 °C, 6 h. (h) 10 equiv of LiOH, THF/MeOH/H_2O, 50 °C, 1 h, 96%. (i) 20 equiv of LiOH, THF/MeOH/H_2O, 50 °C, 45 min, 70%.

preclude the formation of an initial tetrahedral peracyl hemiketal, could not be addressed effectively by using standard or recent variants of the peracid Baeyer–Villiger oxidation.[46-50] Under vigorous reaction conditions, substrates bearing sensitive functionality or groups susceptible to oxidation underwent secondary oxidation reactions of the substrate at the expense of the desired Baeyer–Villiger oxidation.[22,51] The difficulty in effecting a Baeyer–Villiger oxidation for the introduction of the PDE I/II C-4 phenolic hydroxyl group led to an examination of appropriate alternatives for phenol introduction from acyl aromatic precursors. The benzylic hydroperoxide rearrangement[22,52] proved to be an excellent, complementary alternative to the Baeyer–Villiger oxidation and provided the required transformation that led to the successful completion of the total synthesis of PDE I and PDE II.

In preliminary studies[22] with derivatives of 7-acetylindoline it was found that the free indoline NH was required for substrate participation in the Lewis acid catalyzed benzylic hydroperoxide rearrangement. Consequently, the *N*-acetyl group of **28** was removed by treatment with anhydrous methanolic hydrochloric acid, Scheme VII. Because of the relative ease with which the alcohol **33** could be prepared from **32** ($NaBH_4$, MeOH, 23 °C), initial efforts at implementation of the benzylic hydroperoxide rearrangement were directed at use of this *secondary* benzylic alcohol. Treatment of **33** with a mixture of $BF_3{\cdot}Et_2O$ and 90% H_2O_2 (2:1 mole:mole complex)[53] in methylene chloride followed by selective N-acetylation of the readily oxidized, free indoline phenol **34** (Ac_2O, NaOAc, THF, 23 °C) provided PDE II methyl ester (**36**), consistent with expectations albeit in disappointing yield, Table II.

Therefore, attention was directed necessarily toward the preparation of the *tertiary* alcohol **35** with the expectation that the enhanced reactivity of the *tertiary* alcohol **35** vs. the *secondary* alcohol **33** would provide improved yields of the rearrangement product.[22,52] Addition of methylcerium dichloride ($MeCeCl_2$)[54] to ketone **32** (THF, −65 °C) afforded the *tertiary* alcohol **35** in moderate yield, with substantial amounts of recovered starting material observed. The addition of methylmagnesium chloride (MeMgCl) to **32** at room temperature (THF) proved surprisingly selective, and *tertiary* alcohol **35** could be isolated in 76% yield after purification by flash chromatography with only trace amounts of ester addition products detected, Scheme VII. The observed selectivity in the conversion of **32** to **35** may be attributed to coordination of the Grignard reagent with the indoline nitrogen followed by delivery of the methyl nucleophile to the proximal C-4 acetyl group.

Table II. Lewis Acid Catalyzed Benzylic Hydroperoxide Rearrangement of *Secondary* and *Tertiary* Alcohols **33** and **35**

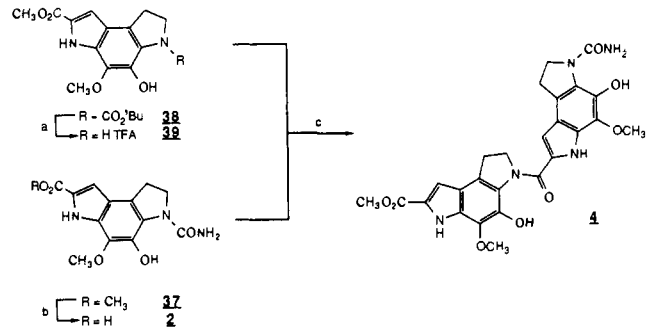
substrate	equiv of H_2O_2[a]	equiv of $BF_3{\cdot}Et_2O$[a]	time[b]	acylation[c]	product	yield, %
33	5.0	10.0	1 h	B	**36**	<10
35	5.0	10.0	30 min	B	**36**	0
35	2.5	5.0	10 min	B	**36**	27
35	1.5	6.0	7 min	B	**36**	63[d]
35	2.5	7.5	7 min	C	**38**	35
35	1.5	6.0	5 min	C	**38**	46
35	1.5	6.0	5 min	A	**37**	41
35	1.5	6.0	7 min	A	**37**	64[d]
35	1.4	5.6	8 min	A	**37**	81[d]

[a] Preformed reagent was prepared by addition of 90% H_2O_2 to $BF_3{\cdot}Et_2O$ at 0 °C immediately prior to use. See ref 53. [b] All reactions were conducted at 21–23 °C in CH_2Cl_2 as detailed in the Experimental Section. [c] A = trimethylsilyl isocyanate; B = acetic anhydride; C = di-*tert*-butyl dicarbonate. [d] The preformed $H_2O_2/BF_3{\cdot}Et_2O$ reagent was stirred 30–45 min at 0 °C prior to use.

Subjection of the *tertiary* alcohol **35** to the previously defined[22] conditions for Lewis acid catalyzed benzylic hydroperoxide rearrangement (5 equiv of H_2O_2, 10 equiv of $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0.5 h, 23 °C) led to the rapid, complete consumption of the substrate **35** without the isolation of **34** (or **36**, after acetylation). Conducting this reaction with a reduction of the number of equivalents of oxidant and Lewis acid catalyst (2.5 equiv of H_2O_2, 5 equiv of $BF_3{\cdot}Et_2O$, 23 °C, 10 min) afforded PDE II methyl ester (**36**), after acetylation, in moderate yield (27%), Scheme VII. Further optimization of the Lewis acid catalyzed hydroperoxide rearrangement by continuing to reduce the number of equivalents of hydrogen peroxide while maintaining the concentration of Lewis acid improved the conversion to the phenolic product **34**. Immediate, subsequent N-acylation of the crude, unstable free indoline phenol **34** with trimethylsilyl isocyanate or acetic anhydride afforded PDE I methyl ester (**37**) and PDE II methyl ester (**36**), respectively, in good overall yields, Scheme VII and Table II. PDE I methyl ester (**37**) and PDE II methyl ester (**36**) each proved identical in all comparable respects (^1H NMR, IR, EIMS, HRMS, TLC) with the methyl esters of authentic and synthetic PDE I and PDE II.[55] Acylation of crude **34** with di-*tert*-butyl

(46) Trifluoroperacetic acid: Emmons, W. D.; Lucas, G. B. *J. Am. Chem. Soc.* **1955**, *77*, 2287. Wetter, H. *Helv. Chim. Acta* **1981**, *64*, 761.
(47) 3,5-Dinitroperbenzoic acid: Rastetter, W. H.; Richard, T. J.; Lewis, M. D. *J. Org. Chem.* **1978**, *43*, 3163.
(48) Permonophosphoric acid: Ogata, Y.; Tomizawa, K.; Ikeda, T. *J. Org. Chem.* **1978**, *43*, 2417.
(49) *o*-Alkoxypercarbonic acids: Tsunokawa, Y.; Iwasaki, S.; Okuda, S. *Tetrahedron Lett.* **1982**, *23*, 2113; *Chem. Pharm. Bull.* **1983**, *31*, 4578.
(50) Acidic hydrogen peroxide: Matsumoto, M.; Kobayashi, H.; Hotta, Y. *J. Org. Chem.* **1984**, *49*, 4740.
(51) A summary of representative efforts is provided in the supplementary material.
(52) (a) Anderson, G. H.; Smith, J. G. *Can. J. Chem.* **1968**, *46*, 1553, 1561. (b) Kharasch, M. S.; Fono, A.; Nudenberg, W.; Poshkus, A. C. *J. Org. Chem.* **1950**, *15*, 775. (c) Deno, N. C.; Billups, W. E.; Kramer, K. E.; Lastomirsky, R. R. *J. Org. Chem.* **1970**, *35*, 3080. (d) Hawkins, E. G. E. *Organic Peroxides*; Van Nostrand: New York, 1961. (e) Davies, A. G. *Organic Peroxides*; Butterworths: London, 1961. (f) Lee, J. B.; Uff, B. C. *Q. Rev., Chem. Soc.* **1967**, *21*, 449. (g) For application of a hydroperoxide rearrangement in the total synthesis of triumferol, see: Kusumi, T.; Chang, C. C.; Wheeler, M.; Kubo, I.; Nakanishi, K.; Naoki, H. *Tetrahedron Lett.* **1981**, *22*, 3451. (h) For application of a hydroperoxide rearrangement in the synthesis of 4-hydroxypyrazoles, see: Albrand, M.; Gelin, S. *Synthesis* **1983**, 1030.
(53) McClure, J. D.; Williams, P. H. *J. Org. Chem.* **1962**, *27*, 24.
(54) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233.

Scheme VIII[a]



[a](a) Trifluoroacetic acid, 23 °C, 1 h. (b) 10 equiv of LiOH, THF/MeOH/H_2O, 50 °C, 1 h, 96%. (c) **2**/**39** (1:1), 3.0 equiv of Et_3N, 2.0 equiv of EDCI, 23 °C, 18 h, 66% overall from **2**/**38**.

dicarbonate afforded **38**, Scheme VII and Table II. Aging the preformed reagent prepared by the addition of 90% hydrogen peroxide (1 equiv) to neat boron trifluoride etherate (4 equiv) at 0 °C for 30–45 min prior to use resulted in a significant improvement in the quality and conversion (percent yield) of the Lewis acid catalyzed benzylic hydroperoxide rearrangement of **35**, Table II. It is remarkable that the basic, readily oxidized substrate **35** and indoline phenol product **34** withstand the strong oxidizing conditions of the hydroperoxide rearrangement. This may be attributed to the Lewis acid coordination/protection of the free amine under the oxidizing conditions of the rearrangement.

Conversion of the methyl esters of **37** and **36** to the corresponding carboxylic acids was accomplished by lithium hydroxide promoted ester hydrolysis (10–20 equiv of LiOH, THF/MeOH/H_2O, 50 °C) and afforded PDE I (**2**, 96%) and PDE II (**3**, 70%), respectively, identical in all comparable respects (^{1}H NMR, IR, TLC) with authentic and synthetic PDE I and PDE II.[56]

Coupling of 1,2-Dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-carboxylate Units: Synthesis of PDE I Dimer Methyl Ester. At the onset of the investigation of methods to promote the central amide bond formation and coupling of monomeric 1,2-dihydro-3*H*-pyrrolo-[3,2-*e*]indole subunits suitable for use in the coupling of the central and right-hand segments of CC-1065, it was not evident whether the terminal *N*-carbamoyl functionality or the acidic C-4 phenol would interfere with the direct coupling of the appropriate CC-1065 subunits. In addition, efforts to effect the desired coupling were hampered by the insoluble nature of the monomeric 1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole subunits. Consequently, both direct and indirect approaches to providing PDE I dimer methyl ester were examined, first employing the readily available 4,5-didesoxy 3-carbamoyl 1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-carboxylate system (CDPI).[57] The use of the carboxyl activating reagents bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl)[58] and 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (EDCI)[59] were found to be successful in promoting both the desired direct and indirect coupling of the CDPI subunits.[57]

The unstable indoline **34** required as the nucleophilic component of the desired coupling reaction, Scheme VIII, was prepared from **38** (trifluoroacetic acid, 1 h, 23 °C) immediately prior to use and was used directly as the trifluoroacetate salt **39**. Treatment of an equimolar mixture of PDE I (**2**) and the trifluoroacetate salt **39** in tetrahydrofuran with excess triethylamine (3 equiv) followed by 2.0 equiv of 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (23 °C, 18 h) afforded PDE I dimer methyl ester (**4**) in 66% isolated yield, identical in all respects (^{1}H NMR, IR) with an authentic comparison sample.[60] The organic-insoluble, water-insoluble nature of PDE I dimer methyl ester (**4**) coupled with the use of the water-soluble carbodiimide reagent (EDCI) provided a technically convenient method for conducting the reaction in which the purification of **4** required simple centrifugation of an aqueous reaction workup.

Table III. Sodium Borohydride Reduction of Ketone **7**

equiv of $NaBH_4$	temp, °C	time	yield of **8**, %
1.25	25	1 h	48
1.25	0	25 min	67
1.25	−23	1 h	82

The total syntheses of PDE I, PDE II, and PDE I dimer methyl ester are summarized in Scheme IX. Extensions of the work detailed herein to the preparation of the left-hand segment of CC-1065 and its incorporation into the total synthesis of CC-1065 are in progress, as are efforts on the preparation of structurally related agents.[57]

Experimental Section[61]

Dimethyl 5-Acetyl-4-methoxy-1,2-diazine-3,6-dicarboxylate (7). A mixture of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate[19] (**5**, 14.6 g, 74 mmol) and 4,4-dimethoxybut-3-en-2-one[23] (**6**, 14.4 g, 110 mmol, 1.5 equiv) in 250 mL of dry dioxane was warmed with stirring at 60 °C under N_2 (21.5 h). The solvent was removed in vacuo, and the residue was dissolved in CH_2Cl_2 and filtered through a short column of silica gel (5 × 20 cm, ether). The ether eluant was evaporated in vacuo. Flash chromatography (5 × 30 cm, 80–100% ether–hexane gradient elution) afforded **7** (13.9 g, 19.8 g theoretical, 70%) as a yellow, crystalline solid: mp 76–77.5 °C (MeOH, white needles); ^{1}H NMR ($CDCl_3$, 80 MHz, ppm) 4.09 (s, 3 H, OCH_3), 4.04 (s, 3 H, OCH_3), 4.0( ) (s, 3 H, OCH_3), 2.60 (s, 3 H, $ArCOCH_3$); ^{13}C NMR ($CDCl_3$, 20 MHz, ppm) 194.8 (s), 163.9 (s), 163.6 (s), 154.0 (s), 148.6 (s), 148.5 (s), 134.0 (s), 62.2 (q), 53.5 (q, two carbons), 32.1 (q); IR (KBr) ν_{max} 2960, 1743, 1729, 1715, 1538, 1447, 1394, 1305, 1277, 1221, 1066 cm^{-1}; EIMS, *m/e* (relative intensity) 268 (M^+, 7), 253 (2), 238 (19), 210 (17), 195 (14), 181 (5), 167 (9), 151 (12), 109 (22), 43 (base); HRMS, *m/e* 268.0693 ($C_{11}H_{12}N_2O_6$ requires 268.0695).

Anal. Calcd for $C_{11}H_{12}N_2O_6$: C, 49.26; H, 4.51; N, 10.44. Found: C, 48.88; H, 4.38; N, 10.30.

This procedure routinely afforded 7 (71–55%) from **5** and **6** (5–74-mmol scale).

5,7-Dihydro-7*H*-3-(methoxycarbonyl)-4-methoxy-5-methyl-7-oxofuro[3,4-*e*]pyridazine (8). A solution of **7** (13.9 g, 51.8 mmol) in 150 mL of THF under N_2 was cooled to −23 °C (dry ice/CCl_4), and sodium borohydride (0.65 g, 68.7 mmol, 1.3 hydride equiv) was added. Water (9.3 mL, 10 equiv) was added dropwise over 5 min, and the reaction mixture was stirred at this temperature for 70 min (cf. Table III). Aqueous HCl (5%) was added carefully to destroy the excess sodium borohydride, and the reaction mixture was allowed to warm to room temperature. The resulting reaction mixture was diluted with 100 mL of saturated aqueous NaCl and extracted with CH_2Cl_2 (2 × 200 mL). The combined extracts were dried ($MgSO_4$), and the solvent was removed in vacuo. Flash chromatography (5 × 30 cm, 50–70% EtOAc–hexane gradient elution) afforded **8** (8.46 g, 12.3 g theoretical, 69%) as a light-yellow, crystalline solid: mp 116.5–117.5 °C (EtOAc–hexane, white needles); ^{1}H NMR ($CDCl_3$, 80 MHz, ppm) 5.73 (q, 1 H, J = 7 Hz, CH_3CH), 4.14 (s, 3 H, OCH_3), 4.09 (s, 3 H, OCH_3), 1.75 (d, 3 H, J = 7 Hz, CH_3CH); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) 164.9 (s), 164.1 (s), 152.8 (s), 149.5 (s), 146.6 (s), 135.0 (s), 75.2 (d), 60.4 (q), 53.6 (q), 19.8 (q); IR (KBr) ν_{max} 2960, 1794, 1740, 1590, 1559, 1456, 1395, 1375, 1341, 1281, 1219, 1140, 1045, 920 cm^{-1}; EIMS, *m/e* (relative intensity)

(55) Comparison was based on published spectral data,[11] on copies of ^{1}H NMR and IR spectra (PDE I and PDE II methyl esters derived from naturally occurring material) supplied by Professor H. Umezawa, and by direct comparison of ^{1}H NMR ($CDCl_3$, 200 MHz) and SiO_2 TLC comparison (2.5% MeOH–$CHCl_3$, EtOAc, Et_2O solvent systems) with PDE I and PDE II methyl esters prepared by diazomethane esterification[11] of authentic, synthetic samples of PDE I and PDE II generously provided by Professor C. W. Rees.

(56) Comparison was based on published spectral data,[11] on copies of ^{1}H NMR and IR spectra (natural PDE I and PDE II) supplied by Professor H. Umezawa, and by direct SiO_2 TLC comparison (20% EtOH–EtOAc, 25% MeOH–$CHCl_3$ solvent systems) with authentic, synthetic samples of PDE I and PDE II generously provided by Professor C. W. Rees.

(57) Boger, D. L.; Coleman, R. S.; Invergo, B. J. *J. Org. Chem.*, in press.

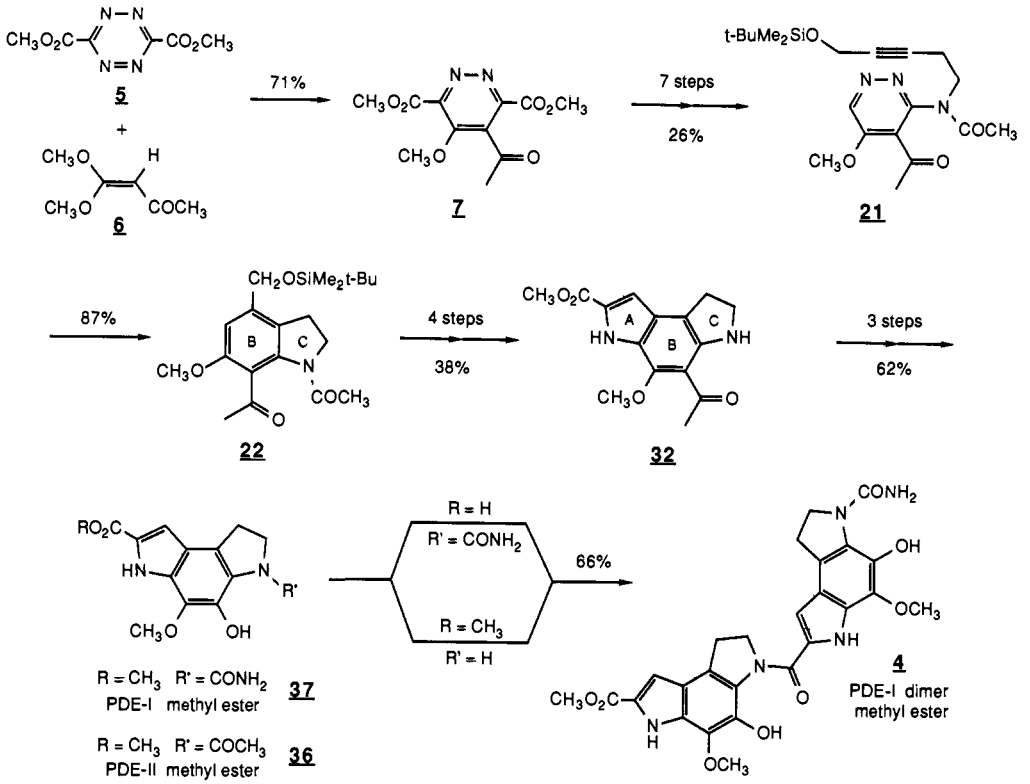
(58) Diago-Meseguer, J.; Palomo-Coll, A. L.; Fernandez-Lizarbe, J. R.; Zugaza-Bilbao, A. Z. *Synthesis* **1980**, 547.

(59) Dhaon, M. K.; Olsen, R. K.; Ramasamy, K. *J. Org. Chem.* **1982**, *47*, 1962.

(60) Comparison was based on direct comparison of ^{1}H NMR (Me_2SO-d_6, 200 MHz) and IR spectra of synthetic PDE I dimer methyl ester and a sample of PDE I dimer methyl ester derived from natural CC-1065 (Martin, D. G.; Mizsak, S. A.; Krueger, W. C. *J. Antibiot.* **1985**, *38*, 746) and kindly supplied by the Upjohn Company.

(61) General experimental details are provided in the supplementary material.

Scheme IX



239 ($M^+ + H$, 6), 238 (M^+, 5) 223 (1), 207 (7), 180 (10), 165 (4), 152 (9), 135 (9), 124 (75), 107 (16), 94 (46), 81 (30), 66 (62), 59 (base), 53 (21), 43 (83); CIMS (isobutane), *m/e* 239 ($M^+ + H$); HRMS, *m/e* 238.0594 ($C_{10}H_{10}N_2O_5$ requires 238.0589).

Anal. Calcd for $C_{10}H_{10}N_2O_5$: C, 50.42; H, 4.23; N, 11.76. Found: C, 50.33; H, 4.15; N, 11.96.

This procedure consistently provided **8** (82–69%) from **7** (2.9–51.8-mmol scale).

5,7-Dihydro-7*H*-4-methoxy-5-methyl-7-oxofuro[3,4-*e*]pyridazine (10). Lithium hydroxide monohydrate (1.62 g, 38.7 mmol, 2.1 equiv) was added to a solution of **8** (4.38 g, 18.4 mmol) in 75 mL of THF/MeOH/H_2O (3:1:1) at 23 °C. The reaction mixture was stirred for 1 h (23 °C) before 4.0 mL of concentrated HCl (48 mmol) was added carefully, initiating the mild, slow evolution of gas (CO_2). After the reaction mixture was stirred an additional 4.5 h (23 °C), the solvent was removed in vacuo, and the residue was diluted with 50 mL of water and extracted with CH_2Cl_2 (5 × 75 mL). The organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give crude **10** as white solid. Recrystallization from EtOAc–hexane (1:1, 400 mL) afforded **10** (2.71 g, 3.31 g theoretical, 82%) as a white crystalline solid: mp 145–150 °C dec (EtOAc, white needles); ^1H NMR ($CDCl_3$, 80 MHz, ppm) 9.15 (s, 1 H, C6–H), 5.64 (q, 1 H, J = 7 Hz, CH_3CH), 4.16 (s, 3 H, OCH_3), 1.71 (d, 3 H, J = 7 Hz, CH_3CH); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) 165.9 (s), 153.4 (s), 148.5 (s), 138.9 (d), 133.7 (s), 74.7 (d), 56.8 (q); IR (KBr) ν_{max} 3082, 2997, 2949, 1777, 1601, 1576, 1478, 1437, 1360, 1310, 1223, 1146, 1080, 1051, 1017, 938 cm^{-1}; EIMS, *m/e* (relative intensity) 180 (M^+, base), 165 (64), 137 (16), 110 (14), 94 (38), 82 (59), 66 (59); HRMS, *m/e* 180.0526 ($C_8H_8N_2O_3$ requires 180.0535).

Anal. Calcd for $C_8H_8N_2O_3$: C, 53.33; H, 4.48; N, 15.55. Found: C, 53.48; H, 4.30; N, 15.34.

5-Methoxy-4-(1-((*tert*-butyldimethylsilyl)oxy)ethyl)-1,2-diazine-3-carboxamide (12). A solution of NH_3 in MeOH (ca. 25%, prepared at 0 °C; 5 mL) was added to **10** (99.4 mg, 0.55 mmol) and sealed in a vial. The reaction mixture was allowed to warm to 23 °C with stirring. The solid **10** dissolved after 5–10 min, and the reaction mixture was stirred for 1 h (23 °C). The solvent was evaporated with a stream of N_2 (bath temperature < 25 °C) and then in vacuo (5–10 min, <0.1 mmHg) to afford **11** as an unstable white, crystalline solid. Compound **11** was treated with a solution of *t*-$BuMe_2SiCl$ (0.85 mmol) and imidazole (1.8 mmol) in DMF (1.7 mL), and the resulting reaction mixture was allowed to stir at 23 °C (6–12 h). The reaction mixture was poured onto 20 mL of water and was extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was allowed to stand at 23 °C for 12–24 h to allow conversion of small amounts of *N*-silyl, *O*-silyl material to **12**. Chromatography (PCTLC, 1 mm SiO_2, EtOAc) afforded recovered **10** (28 mg, 28%) and **12** (107.2 mg, 171.3 mg theoretical, 63%) as a white solid: mp 171–172 °C (EtOAc–hexane, white plates); ^1H NMR ($CDCl_3$, 80 MHz, ppm) 8.99 (s, 1 H, C6-H), 7.4 (br s, 1 H, NH), 5.92 (q, 1 H, J = 6.5 Hz, CH_3CH), 5.8 (br s, 1 H, NH), 4.03 (s, 3 H, OCH_3), 1.59 (d, 3 H, J = 6.5 Hz, CH_3CH), 0.82 (s, 9 H, $SiCMe_3$), 0.01 (s, 3 H, SiMe), –0.13 (s, 3 H, SiMe); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) 167.4 (s), 156.5 (s), 151.5 (s), 139.4 (d), 132.0 (s), 63.9 (s), 56.1 (q), 25.6 (q), 22.3 (q), 17.9 (s), –5.06 (q); IR (KBr) ν_{max} 3395, 3324, 3206, 2953, 2930, 2859, 1698, 1657, 1559, 1474, 1320, 1306, 1254, 1098, 1053, 963, 839, 776 cm^{-1}; EIMS, *m/e* (relative intensity) 311 (M^+, 1), 296 (3), 279 (1), 254 (base), 237 (6), 209 (4), 195 (2), 180 (4), 163 (3), 124 (4), 74 (92); HRMS, *m/e* 311.1644 ($C_{14}H_{25}N_3O_3Si$ requires 311.1665).

This procedure routinely afforded **12** (65–50%) from **10** (1.0–2.5-mmol scale; 25–40% recovered **10**).

5,8-Dihydro-7*H*-4-methoxy-5-methyl-7-oxopyridazino[3,4-*d*][1,3]oxazine (14). A solution of Br_2 in carbon tetrachloride (1.07 mL of 4.0 M, 4.3 mmol, 1.25 equiv) was added dropwise (10 min) to a cooled (–43 °C, dry ice/acetonitrile) solution of NaOMe (13.7 mmol, 4 equiv) in MeOH (7.5 mL) under N_2.[33] After 5 min the amide **12** (1.07 g, 3.43 mmol) was added as a solid, and the reaction mixture was slowly allowed to warm to room temperature (0.5 h). The reaction mixture then was warmed at 60 °C (0.5 h), cooled to room temperature, and diluted with 25 mL of water. [Unstable *N*-carbomethoxyamino-1,2-diazine **13** could be isolated at this stage by extraction (CH_2Cl_2) and chromatography (PCTLC, 1 mm SiO_2, EtOAc): ^1H NMR ($CDCl_3$, 80 MHz, ppm) 9.1 (br s, 1 H, NH), 8.77 (s, 1 H, C6-H), 5.44 (q, 1 H, J = 6.6 Hz, $CHCH_3$), 3.98 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 1.41 (d, 3 H, J = 6.6 Hz, $CHCH_3$), 0.90 (s, 9 H, $SiCMe_3$), 0.13 (s, 3 H, $SiCH_3$), 0.01 (s, 3 H, $SiCH_3$)]. The pH was adjusted to ca. 1 by the addition of concentrated H_2SO_4, and the mixture was allowed to stir at 21 °C (12 h). The reaction mixture was poured onto 100 mL of water, and solid $NaHCO_3$ was added until the mixture was basic (pH ca. 8–9). Exhaustive extraction with CH_2Cl_2 (10 × 60 mL), drying the combined extracts ($MgSO_4$), and removal of the solvent in vacuo gave crude **14** as a white solid. Trituration with absolute EtOH (10 mL, 5 mL) afforded **14** (607 mg, 670 mg theoretical, 91%) as a white solid: mp 225 °C dec (MeOH, white plates); ^1H NMR ($CDCl_3$, 80 MHz, ppm) 8.78 (s, 1 H, C6-H), 5.70 (q, 1 H, J = 7 Hz, CH_3CH), 4.05 (s, 3 H, OCH_3), 1.62 (d, 3 H, J = 7 Hz, CH_3CH); IR (KBr) ν_{max} 3108, 3026, 2994, 2952, 2930, 1730, 1607, 1589, 1466, 1383, 1341, 1263, 1239, 1146, 1078 cm^{-1}; EIMS, *m/e* (relative intensity) 195 (M^+, 53), 180 (32), 152 (15), 123 (12), 108 (54), 94 (17), 80 (55), 66 (base); HRMS, *m/e* 195.0625 ($C_8H_9N_3O_3$ requires 195.0644).

This five-reaction, one-flask sequence consistently provided **14** (91–74%) from **12** (0.3–4.8-mmol scale).

8-(5-((*tert*-Butyldimethylsilyl)oxy)-3-pentynyl)-5,8-dihydro-7*H*-4-methoxy-5-methyl-7-oxopyridazino[3,4-*d*][1,3]oxazine (15). A slurry of **14** (682 mg, 3.49 mmol), triphenylphosphine (1.28 g, 4.9 mmol, 1.4 equiv), and 5-((*tert*-butyldimethylsilyl)oxy)-3-pentyn-1-ol[62] (**17**, 1.07 g, 4.9 mmol, 1.4 equiv) in 13 mL of dry THF was cooled to 0 °C under N_2, and diethyl azodicarboxylate (0.77 mL, 4.9 mmol, 1.4 equiv) was added dropwise over 5 min.[34] The reaction mixture was allowed to warm to room temperature (22 °C) and was stirred for 24 h (22 °C) before the solvent was removed in vacuo. The residual oil was dissolved in 10 mL of ether, and a seed crystal of triphenylphosphine oxide ($Ph_3P{=}O$) was added. The reaction mixture was allowed to stand at room temperature for several hours before the precipitated $Ph_3P{=}O$ was removed by filtration. The filtrate was evaporated in vacuo to afford a yellow oil. MPLC (1.5 × 50 cm, 50–80%, EtOAc–hexane gradient elution) afforded **15** (816 mg, 1.37 g theoretical, 60%) as a viscous, light-yellow oil: ^{1}H NMR ($CDCl_3$, 80 MHz, ppm) 8.80 (s, 1 H, C3-H), 5.62 (q, 1 H, J = 7 Hz, CH_3CH), 4.45 (td, 2 H, J = 7, 2 Hz, NCH_2), 4.23 (t, 2 H, J = 2.2 Hz, OCH_2), 4.04 (s, 3 H, OCH_3), 2.73 (m, 2 H, NCH_2CH_2), 1.59 (d, 3 H, J = 7 Hz, CH_3CH), 0.88 (s, 9 H, $SiCMe_3$), 0.08 (s, 6 H, $SiMe_2$); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) 152.3 (s), 150.8 (s), 150.2 (s), 135.6 (d), 109.9 (s), 81.31 (s), 80.33 (s), 69.0 (d), 56.6 (q), 51.7 (t), 41.3 (t), 25.7 (q), 20.1 (q), 18.2 (s), 17.6 (t), $SiMe_2$ not observed (upfield from Me_4Si); IR (neat) ν_{max} 2955, 2930, 2896, 2857, 1734, 1599, 1408, 1381, 1329, 1258, 1088, 837 cm^{-1}; CIMS (isobutane), m/e (relative intensity) 392 (M^+ + H, base), 348 (27); HRMS, m/e 391.1924 ($C_{19}H_{29}N_3O_4Si$ requires 391.1927).

This procedure routinely afforded **15** (61–56%) from **14** (2.0–12.2 mmol scale).

Further elution with a more polar solvent system (10% EtOH–EtOAc) afforded the 1,2-diazine N-2-alkylated product **16** (35%) as a light-brown solid: ^{1}H NMR ($CDCl_3$, 80 MHz, ppm) 7.95 (s, 1 H, C6-H), 5.45 (q, 1 H, J = 6 Hz, $CHCH_3$), 4.47 (t, 2H, J = 7 Hz, NCH_2CH_2), 4.20 (t, 2 H, J = 2 Hz, OCH_2), 4.04 (s, 3 H, OCH_3), 2.80 (m, 2 H, NCH_2CH_2), 1.49 (d, 3 H, J = 6 Hz, $CHCH_3$), 0.89 (s, 9 H, $SiCMe_3$), 0.09 (s, 6 H, $SiMe_2$).

4-(1-Hydroxyethyl)-5-methoxy-3-((5-((*tert*-butyldimethylsilyl)oxy)-3-pentynyl)amino)-1,2-diazine (23). A slurry of potassium hydroxide (KOH) and potassium *tert*-butoxide (*t*-BuOK) in ether[43] was prepared by adding water (18.5 μL, 1.03 mmol, 2 equiv) to a slurry of solid *t*-BuOK (175 mg, 1.56 mmol, 3 equiv) in 3 mL of dry ether at 0 °C. The mixture was stirred for 5 min (0 °C) and then was added (via 17-gal cannula) to a cooled (0 °C) solution of **15** (204 mg, 0.52 mmol) in 5.6 mL of dry ether. The reaction mixture was stirred vigorously for 20 min (0 °C) before it was poured onto 20 mL of saturated aqueous NH_4Cl solution. The mixture was extracted with EtOAc (4 × 30 mL), and the combined extracts were dried (Na_2SO_4). Removal of the solvent in vacuo afforded **23** (190 mg, 190 mg theoretical, 100%) as a light-yellow oil. This material, which proved unstable to chromatographic purification, was homogeneous by TLC (EtOAc) and was used without further purification: ^{1}H NMR ($CDCl_3$, 80 MHz, ppm) 8.39 (s, 1 H, C6-H), 6.7 (br m, 1 H, NH), 5.45 (q, 1 H, J = 7 Hz, CH_3CH), 4.26 (t, 2 H, J = 2 Hz, OCH_2), 3.88 (s, 3 H, OCH_3), 3.5–4.0 (br m, 2 H, NCH_2), 2.6 (br m, 2 H, NCH_2CH_2), 1.45 (d, 3 H, J = 7 Hz, CH_3CH), 0.88 (s, 9 H, $SiCMe_3$), 0.09 (s, 6 H, $SiMe_2$); CIMS (isobutane), m/e 366 (M^+ + H).

This procedure consistently provided **23** (100–94%) from **15** (0.5–4.5-mmol scale).

4-Acetyl-5-methoxy-3-((5-((*tert*-butyldimethylsilyl)oxy)-3-pentynyl)-amino)-1,2-diazine (19). A solution of crude **23** (193 mg, 0.528 mmol) in 6 mL of dry CH_2Cl_2 was cooled to 0 °C under N_2, and activated manganese dioxide (MnO_2, 2 g) was added slowly over 1 min. The slurry was allowed to warm to 23 °C and was stirred under N_2 (24 h). An additional portion of MnO_2 (0.5 g) was added and stirring continued at 23 °C (12 h). The MnO_2 was removed by filtration through Celite (EtOAc wash, 4 × 50 mL). The filtrate was evaporated in vacuo and the residual oil passed through a short column of silica gel (0.5 × 30 cm, EtOAc) to afford pure **19** (149.6 mg, 189 mg theoretical, 79% from **15**) as a yellow oil: ^{1}H NMR ($CDCl_3$, 80 MHz, ppm) 8.60 (s, 1 H, C6-H), 8.4–8.7 (br s, 1 H, NH) 4.32 (t, 2 H, J = 2 Hz, OCH_2), 4.05 (s, 3 H, OCH_3), 3.81 (apparent q, 2 H, J = 6 Hz, $NHCH_2CH_2$), 2.60 (s, 3 H, $COCH_3$), 2.4–2.7 (m, 2 H, NCH_2CH_2), 0.90 (s, 3 H, $SiCMe_3$), 0.11 (s, 6 H, $SiMe_2$); IR (neat) ν_{max} 3326, 2930, 2857, 1647, 1601, 1559, 1528, 1464, 1362, 1246, 1196, 1179, 1136, 1076, 837, 779 cm^{-1}; EIMS, m/e (relative intensity) 364 (M^+ + H, 3), 363 (M^+, 3), 321 (19), 306 (base), 292 (17), 276 (4), 265 (9), 232 (23), 224 (6), 218 (19), 207 (5), 191 (39), 180 (54), 162 (23), 152 (17), 138 (12), 124 (8), 109 (30), 96 (18), 75 (75); CIMS (isobutane), m/e 364 (M^+ + H); HRMS, m/e 364.2056 ($C_{18}H_{29}N_3O_3Si$ + H requires 364.2056).

This two-step sequence consistently provided **19** (79–62%) from **15** (0.5–4.5-mmol scale).

4-Acetyl-5-methoxy-3-((5-((*tert*-butyldimethylsilyl)oxy)-3-pentynyl)-*N*-acetylamino)-1,2-diazine (21). Anhydrous sodium acetate (NaOAc, 1.8 g, 21.9 mmol, 10 equiv) was added to a solution of **19** (790 mg, 2.17 mmol) in 43 mL of distilled acetic anhydride (Ac_2O), and the slurry was warmed under N_2 at 120 °C (2.2 h). The reaction mixture was cooled, and the Ac_2O was removed in vacuo. The residue was slurried in CH_2Cl_2, and the insoluble NaOAc was removed by filtration. The filtrate was concentrated in vacuo. Flash chromatography (SiO_2, 2 × 20 cm, 50–75% EtOAc–hexane gradient elution) afforded **21** (849 mg, 880 mg theoretical, 96%) as a light-brown solid: mp 124.5–125.5 °C (EtOAc–hexane, white needles); ^{1}H NMR ($CDCl_3$, 80 MHz, ppm) 9.05 (s, 1 H, C6-H), 4.25 (t, 2 H, J = 2 Hz, OCH_2), 3.7–4.1 (br m, 2 H, NCH_2CH_2), 4.07 (s, 3 H, OCH_3), 2.4–2.8 (br m, 2 H, NCH_2CH_2), 2.53 (s, 3 H, $ArCOCH_3$), 2.1 (br s, 3 H, $NCOCH_3$), 0.89 (s, 9 H, $SiCMe_3$), 0.09 (s, 6 H, $SiMe_2$); IR (neat) ν_{max} 2953, 2928, 2857, 1707, 1674, 1549, 1462, 1399, 1360, 1333, 1314, 1250, 1174, 1076, 1063, 837 cm^{-1}; EIMS, m/e (relative intensity) 406 (M^+ + H, 1), 390 (1), 362 (3), 348 (20), 321 (3), 306 (14), 232 (2), 225 (8), 180 (26), 169 (19), 162 (4), 152 (2), 138 (3), 109 (7); CIMS (isobutane), m/e (relative intensity) 406 (M^+ + H, base), 364 (53); HRMS, m/e 406.2170 ($C_{20}H_{31}N_3O_4Si$ + H requires 406.2162).

This procedure consistently provided **21** (96–82%) from **19** (0.5–2.2-mmol scale).

1-Acetyl-7-acetyl-6-methoxy-4-(((*tert*-butyldimethylsilyl)oxy)-methyl)indoline (22). A mixture of **21** (339 mg, 0.836 mmol) and 10 mL of 1,3,5-triisopropylbenzene (TIPB) was warmed under argon in a 20 mL of resealable glass tube[63] to effect solution, and the homogeneous reaction mixture was warmed at 230 °C (±5 °C) for 18 h. The reaction mixture was cooled and was placed on a silica gel column (3 × 12 cm, packed in hexane). The column was eluted first with hexane (200 mL) to remove TIPB and then with EtOAc (200 mL). The EtOAc effluent was collected, and the solvent was removed in vacuo. Chromatography (PCTLC, 1 mm SiO_2, 50–100% EtOAc–hexane gradient elution) afforded **22** (273.2 mg, 315.5 mg theoretical, 87%) as a light-brown solid: mp 121–122 °C (Et_2O–hexane, white plates); ^{1}H NMR ($CDCl_3$, 470 MHz, ppm) 6.75 (s, 1 H, C5-H), 4.62 (s, 2 H, OCH_2), 4.10 (t, 2 H, J = 8 Hz, NCH_2CH_2), 3.82 (s, 3 H, OCH_3), 2.98 (t, 2 H, J = 8 Hz, NCH_2CH_2), 2.65 (s, 3 H, $ArCOCH_3$), 2.19 (s, 3 H, $NCOCH_3$), 0.95 (s, 9 H, $SiCMe_3$), 0.11 (s, 6 H, $SiMe_2$); ^{13}C NMR ($CDCl_3$, 50 MHz, ppm) 201.1 (s), 167.5 (s), 156.0 (s), 138.0 (s), 137.6 (s), 121.9 (s), 120.2 (s), 104.5 (d), 62.6 (t), 55.8 (q), 49.8 (t), 31.7 (q), 26.1 (t), 25.7 (q), 23.5 (q), 18.1 (s), −5.5 (q); IR (neat) ν_{max} 2953, 2930, 2855, 1696, 1672, 1462, 1420, 1399, 1360, 1343, 1323, 1252, 1144, 1086, 839 cm^{-1}; EIMS, m/e (relative intensity) 377 (M^+, 5), 362 (7), 335 (8), 278 (5), 244 (3), 231 (4), 228 (3), 226 (3), 202 (base), 189 (9), 174 (3), 170 (4), 160 (13), 139 (3), 132 (3), 117 (4), 75 (16), 73 (10), 57 (9), 43 (32); HRMS, m/e 377.2030 ($C_{20}H_{31}NO_4Si$ requires 377.2022).

Anal. Calcd for $C_{20}H_{31}NO_4Si$: C, 63.62; H, 8.28; N, 3.71. Found: C, 63.37; H, 8.45; N, 3.63.

This procedure consistently afforded **22** (87–74%) from **21** (0.5–1.2-mmol scale).

1-Acetyl-7-acetyl-6-methoxyindoline-4-carboxaldehyde (26). A mixture of $AcOH/H_2O/THF$[32] (3:1:1, 20 mL) was added to **22** (898 mg, 2.38 mmol), and the resulting solution was stirred at 24 °C (24 h). The solvents were removed in vacuo, and the residue was mixed with 20 mL of saturated aqueous NaCl. Solid K_2CO_3 was carefully added until the aqueous mixture was basic (pH ca. 9–10). The mixture was extracted with EtOAc (4 × 50 mL), and the combined extracts were dried ($MgSO_4$). Removal of the solvent in vacuo afforded crude **25** (599 mg, 626 mg theoretical, 96%): ^{1}H NMR ($CDCl_3$, 200 MHz, ppm) 6.71 (s, 1 H, C5-H), 4.60 (s, 2 H, OCH_2), 4.08 (t, 2 H, J = 8 Hz, NCH_2CH_2), 3.81 (s, 3 H, OCH_3), 3.02 (t, 2 H, J = 8 Hz, NCH_2CH_2), 2.63 (s, 3 H, $ArCOCH_3$), 2.17 (s, 3 H, $NCOCH_3$), 2.02 (br s, 1 H, OH).

This procedure consistently provided **25** (100–96%) from **22** (0.35–2.4-mmol scale).

The crude alcohol **25** (599 mg) was dissolved in 22 mL of dry CH_2Cl_2, and the solution was cooled to 0 °C under N_2. Activated MnO_2 (6.5 g) was added in one portion. The slurry was allowed to warm to 24 °C and

(62) This alcohol was prepared by alkylation of the lithium acetylide of 1-((*tert*-butyldimethylsilyl)oxy)-2-propyne (*n*-BuLi, THF, −78–0 °C) with ethylene oxide (THF, 0–23 °C, 3–6 h) and was characterized: see the supplementary material.

(63) (a) The reaction was performed in a thick-walled glass tube internally threaded on one end and sealed under argon with a solid, threaded Teflon plug. The reaction vessel was fabricated from a chromatography column purchased from Ace Glass Company. These vessels are currently commercially available from Ace Glass Company. (b) Careful exclusion of oxygen from the reaction vessel and the use of carefully purified alkyne 1,2-diazine noticeably affected the mass recovery and appearance of the Diels–Alder reactions.

was stirred under N_2 (23 h). The reaction mixture was filtered through Celite (EtOAc wash, 200 mL), and the filtrate was concentrated in vacuo. Flash chromatography (2 × 20 cm SiO_2, 75–100% EtOAc–hexane gradient elution) afforded **26** (403 mg, 621 mg theoretical, 65%) as a yellow foam: ^1H NMR ($CDCl_3$, 200 MHz, ppm) 10.06 (s, 1 H, CHO), 7.05 (s, 1 H, C5-H), 4.17 (t, 2 H, J = 8 Hz, NCH_2CH_2), 3.89 (s, 3 H, OCH_3), 3.45 (t, 2 H, J = 8 Hz, NCH_2CH_2), 2.66 (s, 3 H, $ArCOCH_3$), 2.22 (s, 3 H, $NCOCH_3$); ^{13}C NMR ($CDCl_3$, 50 MHz, ppm) 199.8 (s), 191.0 (d), 167.9 (s), 156.5 (s), 139.1 (s), 131.5 (s), 128.4 (s), 125.8 (s), 107.9 (d), 56.2 (q), 50.0 (t), 31.6 (q), 27.3 (t), 23.6 (q); IR (KBr) ν_{max} 2996, 2971, 2936, 2900, 2862, 1693, 1674, 1606, 1586, 1478, 1464, 1424, 1405, 1357, 1333, 1290, 1260, 1245, 1207, 1192, 1150, 1142, 1094, 1067, 1047, 1035, 1010, 972, 904, 834, 802, 765, 667, 602 cm^{-1}; EIMS, m/e (relative intensity) 261 (M^+, 11), 246 (2), 219 (base), 204 (13), 190 (4), 176 (11), 148 (36), 133 (10), 117 (7), 104 (5), 84 (11), 43 (72); CIMS (isobutane), m/e 262 (M^+ + H); HRMS, m/e 261.1009 ($C_{14}H_{15}NO_4$ requires 261.1001).

This two-step sequence consistently provided **26** (69–64%) from **22** (0.35–2.4-mmol scale).

Methyl 3,4-Diacetyl-1,2-dihydro-3*H*-5-methoxypyrrolo[3,2-*e*]indole-7-carboxylate (28). A slurry of **26** (403 mg, 1.54 mmol) and methyl azidoacetate[44] (1.53 mL, 15.4 mmol, 10 equiv) in 10 mL of dry MeOH was cooled to −23 °C (dry ice/CCl_4) under N_2, and a solution of NaOMe in MeOH (2.82 mL of 4.37 M soln, 12.3 mmol, 8 equiv) was added dropwise over 2–3 min.[21] The reaction mixture was warmed to 0 °C (ice/H_2O) and was allowed to stir for an additional 1.25 h (0 °C). The reaction mixture was poured onto 100 mL of saturated aqueous NaCl, and the mixture was extracted into EtOAc (3 × 50 mL). The combined extracts were dried (Na_2SO_4), and the solvent was removed in vacuo to afford **27** (540 mg, 552 mg theoretical, 98%) as an unstable, yellow crystalline solid: ^1H NMR ($CDCl_3$, 200 MHz, ppm) 7.50 (s, 1 H, C=CH), 6.80 (s, 1 H, C5-H), 4.11 (t, 2 H, J = 8 Hz, NCH_2CH_2), 3.93 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 3.13 (t, 2 H, J = 8 Hz, NCH_2CH_2), 2.65 (s, 3 H, $ArCOCH_3$), 2.20 (s, 3 H, $NCOCH_3$). Compound **27** was slurried in 30 mL of xylenes, and the mixture was warmed at reflux under N_2 (**27** dissolved as the reaction mixture was warmed). After 5 h at reflux (cf. Table I) the reaction mixture was cooled, and the xylenes were removed in vacuo. Flash chromatography (2 × 16 cm SiO_2, 75–100% EtOAc–hexane gradient elution) afforded **28** (320 mg, 509 mg theoretical, 65% from **26**) as a light-brown solid: mp 237–239 °C dec; ^1H NMR ($CDCl_3$, 200 MHz, ppm) 9.01 (br s, 1 H, NH), 7.10 (d, 1 H, J = 1.6 Hz, C8-H), 4.23 (t, 2 H, J = 8 Hz, NCH_2CH_2), 3.97 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 3.28 (t, 2 H, J = 8 Hz, NCH_2CH_2), 2.75 (s, 3 H, $ArCOCH_3$), 2.23 (s, 3 H, $NCOCH_3$); IR (KBr) ν_{max} 3137, 3116, 2992, 2945, 2931, 1713, 1700, 1639, 1536, 1499, 1443, 1423, 1406, 1374, 1356, 1317, 1290, 1269, 1231, 1196, 1151, 1127, 1099, 1053, 1044, 1005, 969, 919, 844, 788, 772, 698, 661 cm^{-1}; EIMS, m/e (relative intensity) 330 (M^+, 14), 315 (1), 288 (20), 256 (40), 241 (4), 228 (7), 213 (7), 43 (base); CIMS (isobutane), m/e (relative intensity) 331 (M^+ + H, base), 317 (2), 289 (13); HRMS, m/e 330.1219 ($C_{17}H_{18}N_2O_5$ requires 330.1215).

Methyl 4-Acetyl-1,2-dihydro-3*H*-5-methoxypyrrolo[3,2-*e*]indole-7-carboxylate (32). Acetyl chloride (0.86 mL, 12.2 mmol) was added dropwise (2–3 min) to a cooled (0 °C) slurry of **28** (201 mg, 0.608 mmol) in 6 mL of dry MeOH in a 20-mL resealable tube.[63a] The vessel was sealed, and the reaction mixture was allowed to warm to 23 °C (0.5 h) and then was warmed at 70 °C (bath temperature) with stirring (15 h). The reaction mixture was cooled and poured onto 100 mL of 10% aqueous Na_2CO_3. The mixture was extracted with CH_2Cl_2 (3 × 100 mL), the combined extracts were dried (Na_2SO_4), and the solvent was removed in vacuo. Flash chromatography (2 × 15 cm, 35–50% EtOAc–hexane gradient elution) afforded **32** (136.7 mg, 175.3 mg theoretical, 78%) as an orange, crystalline solid: mp 172–175 °C; ^1H NMR ($CDCl_3$, 80 MHz, ppm) 8.6 (br s, 1 H, pyrrole NH), 6.93 (d, 1 H, J = 2.2 Hz, C8-H), 3.95 (s, 6 H, two OCH_3), 3.72 (t, 2 H, J = 8 Hz, NCH_2CH_2), 3.11 (t, 2 H, J = 8 Hz, NCH_2CH_2), 2.69 (s, 3 H, $ArCOCH_3$); ^{13}C NMR ($CDCl_3$, 50 MHz, ppm) 200.0 (s), 162.0 (s), 148.1 (s), 146.2 (s), 131.2 (s), 129.8 (s), 125.2 (s), 113.3 (s), 105.5 (d), 62.3 (q), 52.1 (q), 47.4 (t), 31.7 (q), 27.7 (t); IR (KBr) ν_{max} 3411, 3379, 3339, 3277, 2949, 2882, 2850, 1722, 1632, 1578, 1533, 1489, 1435, 1364, 1313, 1284, 1268, 1243, 1212, 1141, 1101, 1075, 1003, 973, 811, 779, 754, 689, 616 cm^{-1}; EIMS, m/e (relative intensity) 288 (M^+, 86), 256 (base), 241 (16), 228 (18), 213 (17); CIMS (isobutane), m/e 289 (M^+ + H); HRMS, m/e 288.1109 ($C_{15}H_{16}N_2O_4$ requires 288.1110).

This procedure consistently provided **32** (85–67%) from **28** (0.03–0.6-mmol scale).

Methyl 1,2-Dihydro-3*H*-4-(1-hydroxyethyl)-5-methoxypyrrolo[3,2-*e*]indole-7-carboxylate (33). A slurry of **32** (3.2 mg, 11.1 μmol) in 150 μL of dry MeOH was treated with sodium borohydride (ca. 1 mg). The reaction mixture was stirred 10 min at 22 °C before 5% aqueous HCl (three drops) was added. The reaction mixture was diluted with 1 mL of 10% aqueous Na_2CO_3 and was extracted with EtOAc (3 × 1 mL). The combined extracts were dried (Na_2SO_4), and the solvent was removed in vacuo. Chromatography (PCTLC, 1 mm SiO_2, EtOAc) afforded **33** (2.5 mg, 3.2 mg theoretical, 78%) as a yellow solid: ^1H NMR ($CDCl_3$, 200 MHz, ppm) 8.85 (br s, 1 H, NH), 7.00 (d, 1 H, J = 2.1 Hz, C8-H), 5.48 (q, 1 H, J = 6.6 Hz, $CHCH_3$), 3.94 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 3.5–3.8 (m, 2 H, NCH_2CH_2), 3.14 (t, 2 H, J = 7 Hz, NCH_2CH_2), 1.61 (d, 3 H, J = 6.6 Hz, $CHCH_3$); IR (KBr) ν_{max} 3421, 3355, 3234, 2981, 2938, 2874, 2839, 1720, 1631, 1589, 1528, 1440, 1350, 1332, 1309, 1281, 1263, 1231, 1205, 1127, 1096, 1074, 1002, 963, 938, 875, 815, 760 cm^{-1}; EIMS, m/e (relative intensity) 290 (M^+, 60), 272 (27), 258 (4), 240 (base), 225 (8), 212 (6), 197 (6); CIMS (isobutane), m/e (relative intensity) 291 (M^+ + H, base), 273 (41); HRMS, m/e 290.1259 ($C_{15}H_{18}N_2O_4$ requires 290.1266).

Methyl 1,2-Dihydro-3*H*-4-(2-hydroxy-2-propyl)-5-methoxypyrrolo[3,2-*e*]indole-7-carboxylate (35). A solution of methylmagnesium chloride (0.23 mL, 3.1 M in THF, 0.73 mmol, 4 equiv) was added dropwise (1 min) to a solution of **32** (52.4 mg, 0.182 mmol) in 2.1 mL of dry THF at 0 °C. The reaction mixture was allowed to warm to 22 °C and was stirred 20 min (22 °C) when water (2 mL) was added. The reaction mixture was poured onto 10 mL of saturated aqueous $NaHCO_3$ and was extracted with EtOAc (3 × 20 mL). The combined extracts were dried (Na_2SO_4) and the solvent was removed in vacuo to afford a yellow-orange solid. Flash chromatography (1 × 17 cm SiO_2, 50–75% EtOAc–hexane gradient elution) afforded **35** (42.0 mg, 55.4 mg theoretical, 76%) as a yellow, crystalline solid: ^1H NMR ($CDCl_3$, 200 MHz, ppm) 8.7 (br s, 1 H, NH), 6.99 (d, 1 H, J = 2.2 Hz, C8-H), 3.93 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 3.62 (t, 2 H, J = 8.5 Hz, NCH_2CH_2), 3.11 (t, 2 H, J = 8.5 Hz, NCH_2CH_2), 1.76 (s, 6 H, CMe_2); IR (KBr) ν_{max} 3430, 3352, 3224, 2958, 2857, 1717, 1632, 1585, 1528, 1440, 1419, 1338, 1317, 1301, 1266, 1235, 1207, 1143, 1127, 1093, 1016, 882, 761, 741 cm^{-1}; EIMS, m/e (relative intensity) 304 (M^+, 59), 286 (54), 271 (3), 254 (base), 239 (9), 226 (8), 211 (11); HRMS m/e 304.1420 ($C_{16}H_{20}N_2O_4$ requires 304.1423).

Methyl 3-Acetyl-1,2-dihydro-3*H*-4-hydroxy-5-methoxypyrrolo[3,2-*e*]indole-7-carboxylate (36, PDE II Methyl Ester). Hydrogen peroxide (90%, 50 μL, 1.8 mmol) was added to $BF_3{\cdot}Et_2O$ (0.88 mL, 1.01 g, 7.1 mmol) at 0 °C, and the homogeneous mixture was stirred for 30–45 min (0 °C).

A slurry of **35** (5.6 mg, 18.4 μmol) in 0.2 mL of dry CH_2Cl_2 at 23 °C was treated with the above reagent (14.5 μL, 27 μmol H_2O_2, 1.5 equiv) and the two-phase mixture vigorously stirred for 7 min (23 °C). Saturated, aqueous Na_2SO_3 (0.5 mL) was added, and the reaction mixture was stirred 5 min (23 °C) when water (1 mL) was added and the mixture was extracted with EtOAc (4 × 2 mL). The combined extracts were dried (Na_2SO_4), and the solvent was removed in vacuo to afford crude **34** as a brown oil. The crude indoline **34** was dissolved in 0.2 mL of dry THF at 23 °C, and anhydrous NaOAc (15 mg, 0.18 mmol, 10 equiv) was added followed by Ac_2O (17 μL, 18.4 mg, 0.18 mmol). The reaction mixture was stirred 15 h (23 °C). Flash chromatography (0.7 × 10 cm SiO_2, 30–60% EtOAc–hexane) afforded **36** (3.5 mg, 5.6 mg theoretical, 63%) as a white, crystalline solid, identical in all comparable respects with authentic PDE II methyl ester:[55] ^1H NMR ($CDCl_3$, 200 MHz, ppm) 12.01 (s, 1 H, OH), 8.82 (br s, 1 H, NH), 7.03 (d, 1 H, J = 2.3 Hz, C8-H), 4.19 (t, 2 H, J = 8 Hz, NCH_2CH_2), 4.02 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 3.29 (t, 2 H, J = 8 Hz, NCH_2CH_2), 2.35 (s, 3 H, $NCOCH_3$); IR (KBr) ν_{max} 3418, 3325, 2956, 2922, 2853, 2833, 1686, 1642, 1613, 1579, 1535, 1513, 1452, 1438, 1349, 1331, 1295, 1260, 1217, 1195, 1166, 1147, 1117, 1096, 1023, 995, 948, 933, 896, 814, 772, 747, 690, 680, 615, 584, 534 cm^{-1}; EIMS, m/e (relative intensity) 304 (M^+, 60), 289 (1), 273 (3), 272 (6), 263 (3), 262 (26), 261 (5), 247 (11), 231 (13), 230 (base), 229 (11), 215 (16), 214 (6), 202 (7), 187 (9); CIMS (isobutane), m/e (relative intensity) 305 (M^+ + H, base), 275 (3), 262 (2), 177 (6); HRMS, m/e 304.1060 ($C_{15}H_{16}N_2O_5$ requires 304.1059).

Methyl 3-Carbamoyl-1,2-dihydro-3*H*-4-hydroxy-5-methoxypyrrolo[3,2-*e*]indole-7-carboxylate (37, PDE I Methyl Ester). Following the procedure for the preparation of **36**, a solution of **35** (12.8 mg, 42.0 μmol) in 0.4 mL of dry CH_2Cl_2 was treated with a preformed mixture of 90% H_2O_2 and $BF_3{\cdot}Et_2O$ (31 μL, 1:4 molar ratio, 59 μmol H_2O_2, 1.4 equiv) at 23 °C (8 min). The crude product **34** was dissolved in 0.3 mL of dry CH_2Cl_2, and trimethylsilyl isocyanate (33 μL, 85%, 0.21 mmol, 5 equiv) was added followed by a catalytic amount of 4-(dimethylamino)pyridine. The reaction mixture was stirred 18 h (23 °C). Flash chromatography (6 × 120 mm SiO_2, 50–70% EtOAc–hexane gradient elution) afforded **37** (10.4 mg, 12.8 mg theoretical, 81%) as a light-brown, crystalline solid, identical in all comparable respects with authentic PDE I methyl ester:[55] ^1H NMR ($CDCl_3$, 200 MHz, ppm) 12.10 (s, 1 H, OH), 8.8 (br s, 1 H, NH), 7.00 (d, 1 H, J = 2.2 Hz, C8-H), 4.79 (br s, 2 H, $CONH_2$), 4.08 (t, 2 H, J = 8 Hz, NCH_2CH_2), 4.02 (s, 3 H, OCH_3), 3.92 (s, 3 H,

OCH_3), 3.33 (t, 2 H, J = 8 Hz, NCH_2CH_2); IR (KBr) ν_{max} 3505, 3423, 3371, 2922, 2851, 1692, 1632, 1481, 1433, 1337, 1301, 1262, 1226, 1196, 1083, 994, 952, 768, 745 cm^{-1}; EIMS, m/e (relative intensity) 305 (M^+, 33), 288 (5), 268 (3), 262 (59), 247 (5), 247 (5), 230 (base), 215 (21), 202 (11), 187 (15); CIMS (isobutane), m/e 306 (M^+ + H, base), 263 (12); HRMS, m/e 305.1003 ($C_{14}H_{15}N_3O_5$ requires 305.1012).

Methyl 3-((*tert*-Butyloxy)carbonyl)-1,2-dihydro-3*H*-4-hydroxy-5-methoxypyrrolo[3,2-*e*]indole-7-carboxylate (38). Following the procedure for the preparation of **36**, a solution of **35** (3.5 mg, 11.5 μmol) in 0.11 mL of dry CH_2Cl_2 was treated with a preformed mixture of 90% H_2O_2 and $BF_3{\cdot}Et_2O$ (9.1 μL, 1:4 molar ratio, 17 μmol of H_2O_2, 1.5 equiv) at 23 °C (5 min). The crude product **34** was dissolved in 0.15 mL of dry THF and di-*tert*-butyl dicarbonate (5.4 μL, 23.5 μmol, 2 equiv) and the reaction mixture stirred 6 h (23 °C). Flash chromatography (5 × 70 mm SiO_2, 10% EtOAc–hexane) afforded **38** (1.9 mg, 4.2 mg theoretical, 46%) as a light-yellow, crystalline solid: ^1H NMR ($CDCl_3$, 200 MHz, ppm) 11.54 (s, 1 H, OH), 8.2 (br s, 1 H, NH), 7.00 (d, 1 H, J = 2.2 Hz, C8-H), 4.10 (t, 2 H, J = 8 Hz, NCH_2CH_2), 4.02 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 3.17 (t, 2 H, J = 8 Hz, NCH_2CH_2), 1.56 (s, 9 H, CMe_3); IR (KBr) ν_{max} 3396, 3328, 2976, 1696, 1654, 1450, 1433, 1334, 1301, 1263, 1166, 1148, 1104, 881, 813, 766, 740 cm^{-1}; EIMS, m/e (relative intensity) 362 (M^+, 13), 306 (72), 288 (3), 274 (3), 262 (24), 247 (4), 230 (base), 215 (9), 202 (7); CIMS (isobutane), m/e 363 (M^+ + H, 40), 307 (base), 263 (6); HRMS, m/e 362.1468 ($C_{18}H_{22}N_2O_6$ requires 362.1478).

3-Carbamoyl-1,2-dihydro-3*H*-4-hydroxy-5-methoxypyrrolo[3,2-*e*]indole-7-carboxylic Acid (2, PDE I). An aqueous solution of LiOH (50 μL, 4 M, 0.2 mmol, 10 equiv) was added to a slurry of **37** (6.1 mg, 20 μmol) in 0.15 mL of THF/MeOH/H_2O (3:2:1). The resulting homogeneous reaction mixture was warmed at 50 °C (1 h). The reaction mixture was diluted with 1 mL of saturated, aqueous NaCl, and 10% aqueous HCl (five drops) was added. The reaction mixture was extracted with EtOAc (20 × 2 mL), the combined extracts were dried (Na_2SO_4), and the solvent was removed in vacuo to afford **2** (5.6 mg, 5.8 mg theoretical, 96%) as a light-brown solid, homogeneous by SiO_2 TLC and identical in all comparable respects with authentic PDE I:[56] ^1H NMR (Me_2SO-d_6, 200 MHz, ppm) 12.81 (s, 1 H, OH), 11.25 (s, 1 H, NH), 6.88 (s, 1 H, C8-H), 6.85 (s, 2 H, $CONH_2$), 4.00 (t, 2 H, J = 8 Hz, NCH_2CH_2), 3.77 (s, 3 H, OCH_3), 3.19 (t, 2 H, J = 8 Hz, NCH_2CH_2); IR (KBr) ν_{max} 3384, 3223, 2944, 2506, 1673, 1641, 1511, 1442, 1297, 1267, 1228, 1195, 1095, 751 cm^{-1}.

3-Acetyl-1,2-dihydro-3*H*-4-hydroxy-5-methoxypyrrolo[3,2-*e*]indole-7-carboxylic Acid (3, PDE II). An aqueous solution of LiOH (20 μL, 4 M, 80 μmol, 20 equiv) was added to a slurry of **36** (1.2 mg, 3.95 μmol) in 80 μL of THF/MeOH/H_2O (3:2:1). The resulting homogeneous reaction mixture was warmed at 50 °C (45 min). The reaction mixture was diluted with 1 mL of saturated, aqueous NaCl, and 10% aqueous HCl (two drops) was added. The reaction mixture was extracted with EtOAc (4 × 2 mL), the combined extracts were dried (Na_2SO_4), and the solvent was removed in vacuo to afford crude **3**. Chromatography (5 × 10 mm SiO_2, 20% EtOH–EtOAc) afforded pure **3** (0.8 mg, 1.15 mg theoretical, 70%) as a light-brown solid, identical in all comparable respects with authentic PDE II:[56] ^1H NMR (Me_2SO-d_6, 200 MHz, ppm) 12.01 (s, 1 H, OH), 10.80 (br s, 1 H, NH), 6.73 (d, 1 H, J = 0.6 Hz, C8-H), 4.21 (t, 2 H, J = 8 Hz, NCH_2CH_2), 3.79 (s, 3 H, OCH_3), 3.20 (t, 2 H, J = 8 Hz, NCH_2CH_2), 2.28 (s, 3 H, $NCOCH_3$); IR (KBr) ν_{max} 3424, 3287, 2924, 2853, 1671, 1640, 1603, 1571, 1523, 1464, 1385, 1331, 1290, 1245, 1191, 1098, 1026, 803, 782, 748 cm^{-1}.

PDE I Dimer Methyl Ester (4). Trifluoroacetic acid (0.2 mL) was added to **38** (6.0 mg, 16.5 μmol), and the reaction mixture was stirred at 23 °C (1 h). The trifluoroacetic acid was removed in vacuo to afford crude **39** as a brown oil. A suspension of PDE I (**2**, 4.6 mg, 15.8 μmol) and crude **39** in 0.15 mL of dry THF was treated sequentially with triethylamine (6.6 μL, 47 mmol, 3 equiv) and 1-((3-dimethylamino)-propyl)-3-ethylcarbodiimide hydrochloride (EDCI, 6.4 mg, 33.4 μmol, 2 equiv). The reaction mixture was stirred at 23 °C (18 h), and the THF was removed by using a stream of N_2. The residual solid was slurried in 1 mL of water containing one drop of 10% aqueous HCl. The solid was collected by centrifugation and was washed with water (2 × 1 mL). Drying the solid in vacuo afforded pure **4** (5.6 mg, 8.5 mg theoretical, 66%) as a grey-green solid, identical in all comparable respects with authentic PDE I dimer methyl ester:[60] ^1H NMR (Me_2SO-d_6, 200 MHz, ppm) 12.91 (s, 1 H), 11.78 (s, 1 H), 11.32 (s, 1 H), 11.03 (s, 1 H), 7.10 (d, 1 H, J = 1.4 Hz, ArH), 7.04 (d, 1 H, J = 0.5 Hz, ArH), 6.89 (br s, 2 H, $CONH_2$), 4.66 (t, 2 H, J = 7.8 Hz, NCH_2CH_2), 4.03 (t, 2 H, J = 8.5 Hz, NCH_2CH_2), 3.85 (s, 6 H, two OCH_3), 3.81 (s, 3 H, OCH_3), 3.1–3.4 (m, 4 H, two NCH_2CH_2, partially obscured by H_2O resonance); IR (KBr) ν_{max} 3468, 3334, 2926, 2853, 1700, 1641, 1561, 1524, 1489, 1444, 1421, 1379, 1338, 1314, 1260, 1178, 999, 961, 771, 749 cm^{-1}; FABMS (dithiothreitol/dithioerythritol), m/e 536 (M^+, H).

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Supplementary Material Available: General experimental details, details of the efforts to effect the Mitsunobu alkylation of 3-amino-1,2-diazines related to **14**, representative efforts on the Baeyer–Villiger oxidation of **22**, and spectral characterizations of compounds **17** and **18** are provided (5 pages). Ordering information is given on any current masthead page.