Total Synthesis of Granditropone, Grandirubrine, Imerubrine, and Isoimerubrine

Dale L. Boger* and Kanji Takahashi

Contribution from the Department of Chemistry, The Scripps Research Institute, 10666 North Torrey Pines Road, La Jolla, California 92037

Received September 5, 1995[⊗]

Abstract: Concise total syntheses of the naturally occurring tropoloisoquinolines grandirubrine (**1**), imerubrine (**2**), and isoimerubrine (**3**) are detailed. The regioselective total synthesis of grandirubrine (**1**) is based on the [4 + 2] cycloaddition reaction of the α-pyrone **44** with the cyclopropenone ketal **18**. Subsequent retro-Diels−Alder loss of CO_2, norcaradiene rearrangement to the cycloheptatrienone ketal, and ketal hydrolysis provided the tropone **7** (granditropone). Regioselective hydroxylation of granditropone (NH_2NH_2; KOH) provided grandirubrine (**1**) and *O*-methylation of **1** provided both imerubrine (**2**) and isoimerubrine (**3**).

Grandirubrine (**1**)[1] and imerubrine (**2**)[2] constitute the initial members of a rare class of naturally occurring tropoloisoquinolines[3] now including isoimerubrine (**3**),[4] pareirubrines A and B (**4** and **5**),[4] and pareitropone (**6**),[4] which are structurally similar to colchicine[5] and its naturally occurring congeners and biosynthetically related to the more common azafluoranthene alkaloids (Figure 1).[6−8] The tropolones **1**, **4**, and **5** each appear to exist preferentially in the 6-keto tautomer in solution, but both **4** and **5** preferentially crystallize in the alternative 5-keto tautomer shown in Figure 1. Despite their intriguing structures which for **2**,[2] **4**,[4] and **5**[4] were unambiguously established in single crystal X-ray structure determinations, their cytotoxic properties,[4] and their structural similarity to the mitotic inhibitor colchicine, little progress has been made on their synthesis. Only one recent total synthesis of grandirubrine and imerubrine has been reported[9] and few related efforts have been dislcosed.[10]

In an extension of our early efforts on the divergent total syntheses of the azafluoranthene alkaloids which resulted in the total syntheses of rufescine (**8**) and imeluteine (**10**),[8] herein we report the total syntheses of grandirubrine, imerubrine, and isoimerubrine which proceed through the intermediate tropone **7** (granditropone). The approach underscores the ease with which a single precursor may be utilized in the divergent preparation of related agents through implementation of a series of α-pyrone inverse electron demand Diels−Alder reactions (Scheme 1).[11,12]

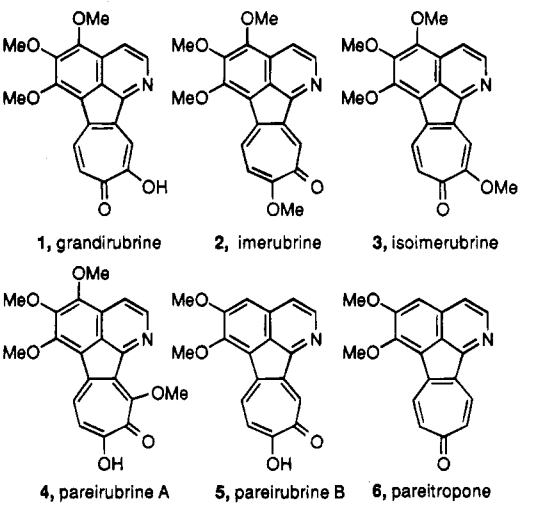


Figure 1.

In the initial development of the approach,[8] ring D introduction for construction of the azafluoranthene alkaloids was successfully realized through use of the electron-rich dienophiles, 1,1-dimethoxyethylene or 1,1,2-trimethoxyethylene, and the participation of the strained olefin of a cyclopropenone ketal[13] in a Diels−Alder reaction with the electron-deficient α-pyrone was expected to provide a direct introduction of the seven-membered tropone ring of the tropoloisoquinolines.[14−16] This cyclopropenone ketal [4 + 2] cycloaddition approach to a tropone annulation is complementary to its thermal [3 + 4] cycloaddition reaction that proceeds by a reversibly generated π-delocalized singlet vinylcarbene which we have utilized

[⊗] Abstract published in *Advance ACS Abstracts,* December 1, 1995.

(1) Menachery, M. D.; Cava, M. P. *Heterocycles* **1980**, *14*, 943.

(2) Silverton, J. V.; Kabuto, C.; Buck, K. T.; Cava, M. P. *J. Am. Chem. Soc.* **1977**, *99*, 6708.

(3) Buck, K. T. *Alkaloids (Academic Press)* **1984**, *23*, 301.

(4) Morita, H.; Matsumoto, K.; Takeya, K.; Itokawa, H.; Iitaka, Y. *Chem. Pharm. Bull.* **1993**, *41*, 1418. Morita, H.; Matsumoto, K.; Takeya, K.; Itokawa, H.; Iitaka, Y. *Chem. Lett.* **1993**, 339. Morita, H.; Matsumoto, K.; Takeya, K.; Itokawa, H. *Chem. Pharm. Bull.* **1993**, *41*, 1478. Morita, H.; Takeya, K.; Itokawa, H. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 597. Itokawa, H.; Matsumoto, K.; Morita, H.; Takeya, K. *Heterocycles* **1994**, *37*, 1025.

(5) Boye, O.; Brossi, A. *Alkaloids (Academic Press)* **1992**, *41*, 125.

(6) Cava, M. P.; Buck, K. T.; daRocha, A. I. *J. Am. Chem. Soc.* **1972**, *94*, 5931. Cava, M. P.; Buck, K. T.; Noguchi, I.; Srinivasan, M.; Rao, M. G.; daRocha, A. I. *Tetrahedron* **1975**, *31*, 1667. Klein, M. D.; Buck, K. T.; Cava, M. P.; Voet, D. *J. Am. Chem. Soc.* **1978**, *100*, 662. Menachery, M. D.; Cava, M. P. *J. Nat. Prod.* **1981**, *44*, 320. Morita, H.; Matumoto, K.; Takeya, K.; Itokawa, H. *Chem. Pharm. Bull.* **1993**, *41*, 1307.

(7) Menachery, M. D.; Cava, M. P. *Heterocycles* **1982**, *19*, 2255. Zhao, B.; Snieckus, V. *Tetrahedron Lett.* **1991**, *32*, 5277. Banwell, M. G.; Hamel, E.; Ireland, N. K.; Mackay, M. F.; Serelis, A. K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1905.

(8) Boger, D. L.; Brotherton, C. E. *J. Org. Chem.* **1984**, *49*, 4050.

(9) Imerubrine and grandirubrine: Banwell, M. G.; Hamel, E.; Ireland, N. K.; Mackay, M. F. *Heterocycles* **1994**, *39*, 205. Banwell, M. G.; Ireland, N. K. *J. Chem. Soc., Chem. Commun.* **1994**, 591.

(10) Approaches: Evans, D. A.; Hart, D. J.; Koelsch, P. M.; Cain, P. A. *Pure Appl. Chem.* **1979**, *51*, 1285. Banwell, M. G.; Bonadio, A.; Turner, K. A.; Ireland, N. K.; Mackay, M. F. *Aust. J. Chem.* **1993**, *46*, 325. Molina, P.; Garcia-Zafra, S.; Fresneda, P. M. *Synlett* **1995**, 43.

(11) Boger, D. L.; Mullican, M. D. *J. Org. Chem.* **1984**, *49*, 4033.

(12) Boger, D. L.; Patel, M. *Prog. Heterocycl. Chem.* **1981**, *1*, 30.

(13) Boger, D. L.; Brotherton-Pleiss, C. E. *Advances in Cycloaddition Chemistry*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, 1990; Vol. 2, pp 147−219.

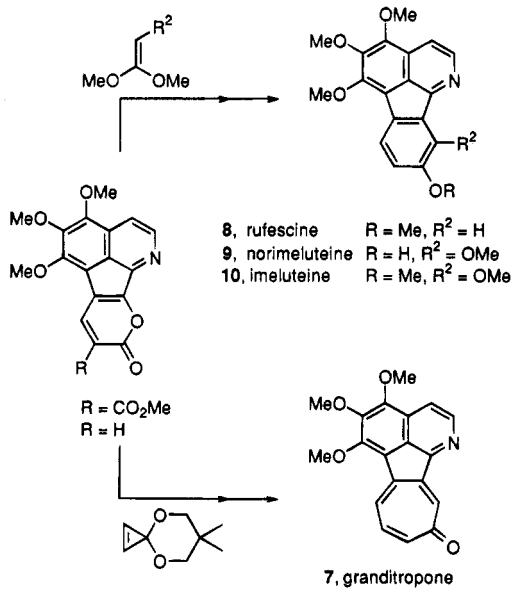
(14) Boger, D. L.; Brotherton, C. E. *Tetrahedron* **1986**, *42*, 2777.

(15) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1986**, *108*, 6695.

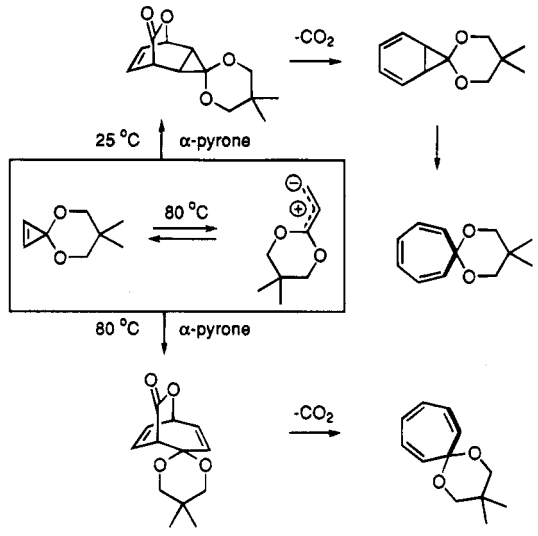
(16) Boger, D. L.; Zhu, Y. *J. Org. Chem.* **1994**, *59*, 3453.

0002-7863/95/1517-12452$09.00/0

Scheme 1



Scheme 2

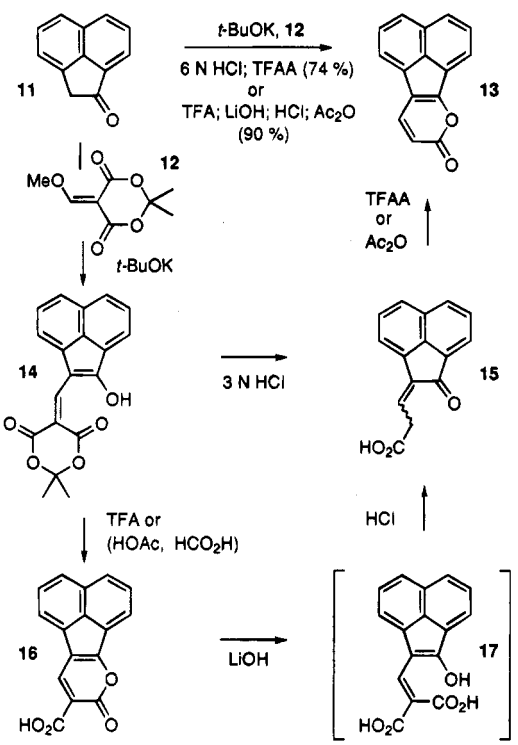


successfully in an approach to colchicine (Scheme 2).[17] In this latter work, the [3 + 4] cycloadduct was readily converted into the corresponding tropone while that of the corresponding [4 + 2] cycloadduct was not. Provided the Diels–Alder adduct could be effectively converted to the corresponding tropone, the tropone C5 carbonyl introduction with the [4 + 2] cycloaddition approach was anticipated to permit the regioselective tropolone introduction required of **1**–**3** while this would not appear as accessible to the more symmetrical C6 tropone derived from a [3 + 4] cycloaddition. Although the initial stages of this work culminating in the synthesis of the azafluoanthene alkaloids were completed nearly 10 years ago, the recent reports of useful levels of cytotoxic activity with the tropoloisoquinolines[4,5] and azafluoranthene alkaloids[6] provided the incentive for us to renew our efforts. In particular, the reported potent cytotoxic activity of the tropone **6** (pareitropone, $IC_{50} = 0.0008$ μg/mL, P388) relative to that of the naturally occurring tropolones (0.2–1 μg/mL) suggested that the intermediate granditropone (**7**) may prove more interesting than the natural products themselves.

Tropolone Annulation. Prior to implementing the [4 + 2] cycloaddition route to the tropone/tropolone annulation, we first

(17) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1986**, *108*, 6713. Boger, D. L.; Brotherton, C. E. *J. Org. Chem.* **1985**, *50*, 3425.

Scheme 3



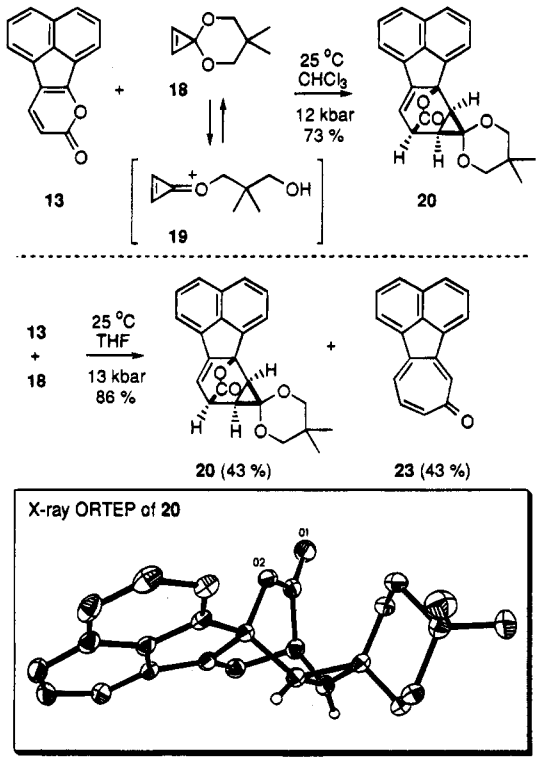
examined this process in detail with a readily available system closely related to the tropoloisoquinolone nucleus. Treatment of 1-acenaphthenone[18] (**11**) with 1.1 equiv of *t*-BuOK (*t*-BuOH–THF) followed by the addition of **12**[19] (1 equiv, 0 °C, 45 min) provided **14**, which was immediately treated with 6 N HCl (3 equiv, 25 °C, 12 h) without workup or isolation. Without purification, the resulting crude acid **15**[20] was treated with TFAA–CH_2Cl_2 (1:1, 25 °C, 14 h) to provide the α-pyrone **13** in 74% overall yield (Scheme 3). Although the intermediates could be isolated, purified, and characterized, some loss due to instability was experienced and the overall yields improved if the three steps were conducted without the intermediate isolations. Stoichiometric LDA could be employed in place of *t*-BuOK, but the overall conversions were lower and the isolation of **14** (65%) was more problematic. Alternatively, treatment of **14** with acid (TFA, HOAc, HCO_2H) under nonaqueous conditions led to the clean generation of **16**.[20] Hydrolysis of **16** (6 equiv of LiOH, THF–H_2O, 25 °C, 6 h) followed by 1 N HCl neutralization similarly provided **15**,[20] which upon treatment with Ac_2O (25 °C, 48 h, 88–90% overall) provided the α-pyrone **13**. Although this latter approach required more manipulations, the sequence could be effectively conducted without the intermediate isolations and provided **13** in superb overall yield (88–90% from **11**). While these two complementary approaches to **13** appear deceptively simple, the subjection of **14** or its derived products to a range of alternative reaction conditions resulted in their reversion back to **11** and they proved sensitive to air oxidation in the presence of traces

(18) PDC oxidation (2 equiv, CH_2Cl_2, 25 °C, 6 h, 77%) of commercially available 1-acenaphthenol (Aldrich) provided **11**.

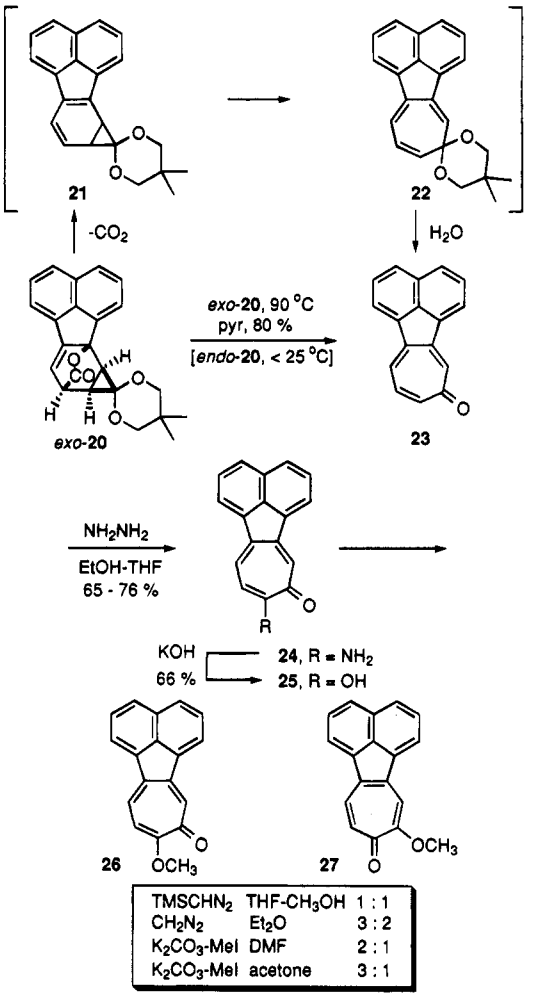
(19) Biblmayer, G. A.; Derflinger, G.; Derkosch, J.; Polansky, O. E. *Monatsh. Chem.* **1967**, *98*, 564.

(20) For **14**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.52 (1H, s), 8.13 (1H, d, J = 7.2 Hz), 8.09 (1H, d, J = 7.2 Hz), 7.73 (1H, d, J = 7.2 Hz), 7.72 (1H, d, J = 7.2 Hz), 7.63 (1H, t, J = 7.2 Hz), 7.56 (1H, t, J = 7.2 Hz), 3.52 (1H, s), 1.85 (6H, s). For **15**: ^{1}H NMR ($CDCl_3$ 250 MHz) δ 8.30–7.40 (6H, m), 7.22 (0.6H, t, J = 7.5 Hz), 7.03 (0.4H, t, J = 7.8 Hz), 4.24 (0.8H, d, J = 7.8 Hz), 3.84 (1.2H, d, J = 7.5 Hz). For **16**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.17 (1H, s), 8.24 (1H, d, J = 7.1 Hz), 8.22 (1H, d, J = 8.1 Hz), 7.99 (1H, d, J = 8.4 Hz), 7.97 (1H, d, J = 6.9 Hz), 7.82 (1H, dd, J = 7.1, 8.1 Hz), 7.73 (1H, dd, J = 6.9, 8.4 Hz).

Scheme 4



Scheme 5



of base. Moreover, while the former three-step synthesis of **13** from **11** proved satisfactory for this simple system, the latter approach proved more successful when applied to **1**–**3**.

The key Diels–Alder reaction of **13** with the cyclopropenone ketal **18**[21] proceeded well at room temperature under pressure-promoted reaction conditions (12 kbar, $CHCl_3$, 25 °C, 20 h, 73%) and cleanly provided exclusively the stable exo adduct **20** (Scheme 4). The adduct **20** was surprisingly stable to conventional chromatographic purification but losses were incurred during such purification. The stereochemistry of the Diels–Alder reaction was inferred from the typical thermal stability of the *exo* (≥100 °C) versus *endo* (<25 °C) adducts,[14,15] confirmed upon observation of the diagnostically small C4a-H/C5-H ^{1}H NMR coupling constant (J = 3.8 Hz; *exo* calcd J = 4.1 Hz, *endo* calcd J = 4.9 Hz), and unambiguously established in a single crystal X-ray structure determination (Scheme 4).[22] The [4 + 2] cycloaddition of **13** with the cyclopropenone ketal **18** proved surprisingly more effective in $CHCl_3$ than most other solvents, and the clean generation of the single *exo* adduct was unusual.[14,15,17] This potentially may be attributed to reaction through the cyclopropenium cation **19** with enhanced dipole, secondary orbital overlap, and stabilizing electrostatic interactions preferentially achieved through the exo transition state. Presumably trace acid in $CHCl_3$ serves as the adventious catalyst. Consistent with this interpretation, the comparable reaction in THF (13 kbar, 25 °C, 64 h) provided a 1:1 mixture of **20** and **23** (86%), albeit requiring longer reaction times and higher reaction pressures. In this reaction, the tropone **23** is derived from the thermally unstable endo [4 + 2] cycloadduct (<25 °C) that suffers retro-Diels–Alder loss of CO_2 and an ensuing electrocyclic rearrangment to the cycloheptatrienone ketal which was detected in the crude ^{1}H NMR. Subsequent hydrolysis of the labile ketal upon chromatographic purification provided **23**. The alternative thermal reaction of the cyclopropenone ketal **18** with **13** (75 °C, C_6H_6 or CH_3CN, 1–48 h), which would be expected to proceed through reversible π-delocalized singlet vinylcarbene generation and subsequent [3 + 4] cycloaddition,[14,17] provided only recovered **13** with no evidence of reaction.

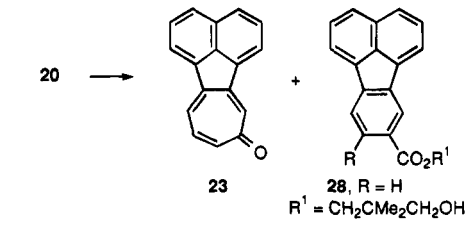
Thermal retro-Diels–Alder loss of CO_2 from *exo*-**20**, the ensuing low-temperature electrocyclic norcaradiene rearrangement,[23] and hydrolysis of the labile tropone ketal to provide **23** was effectively and directly accomplished upon warming at 90 °C (pyridine, 48 h, 80%) without detection of the intermediate diene **21** or tropone ketal **22** (Scheme 5). Presumably the labile ketal was hydrolyzed upon concentration and chromatographic assay or purification. The use of higher reaction temperatures (100–120 °C) led to progressively diminished conversions (65–41%), indicating further thermal consumption of the product.[17] Alternative attempts to employ more conventional solvents for the initial thermal loss of CO_2 proved more problematic. The reaction proved slower in both toluene (110 °C, 3 d) or xylene (135 °C, 24 h) and the generation of the product tropone **23** was accompanied by a variable but substantial amount of the benzoate ester **28**[24] (Scheme 6). Presumably, **28** is derived from adventious acid-catalyzed rearrangement of **20** or the norcaradiene **21** which is in equilibrium with the tropone ketal under

(21) Isaka, M.; Ejiri, S.; Nakamura, E. *Tetrahedron* **1992**, *48*, 2045. Boger, D. L.; Brotherton, C. E.; Georg, G. I. *Org. Synth.* **1987**, *65*, 32. Breslow, R.; Pecoraro, J.; Sugimoto, T. *Org. Synth.* **1977**, Collect. Vol. VI, 361. Butler, G. B.; Herring, K. H.; Lewis, P. L.; Sharpe, V. V.; Veazey, R. L. *J. Org. Chem.* **1977**, *42*, 679. Baucom, K. B.; Butler, G. B. *J. Org. Chem.* **1972**, *37*, 1730.

(22) The author has deposited the atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates may be obtained upon request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

(23) Maier, G. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 402.

Scheme 6



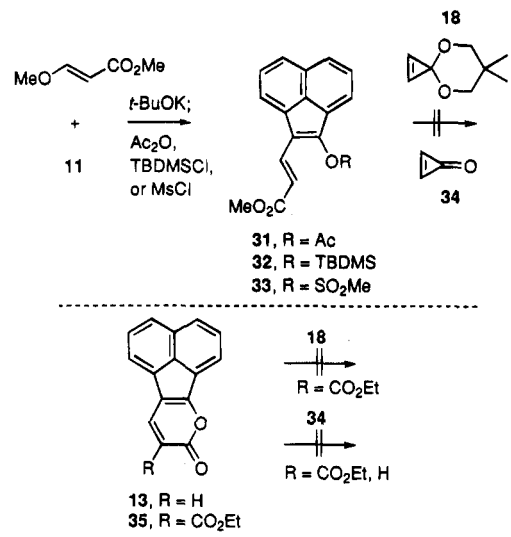
pyridine, 90 °C	80 %	-
xylene, 135 °C	30 %	28 %
HOAc, THF-H_2O, 25 °C	-	55 %
5 % HCl-THF (1:1), 25 °C	-	43 %
		29, R = CO_2CH_3
NaOMe, MeOH, 25 °C	-	39 % R¹ = $CH_2CMe_2CH_2OH$ + 32 % R¹ = CH_3

the reaction conditions. Consistent with this, the addition of base (Et_3N) to the reaction mixtures improved the **23**:**28** ratio and the use of pyridine as the reaction solvent surpressed its generation altogether. Deliberate acid treatment of **20** with HOAc−THF−H_2O (6:5:2, 25 °C, 72 h) or 5% aqueous HCl−THF (1:1, 25 °C, 4 h) did cleanly provide **28**[24] (43−55%). However, treatment of **20** with $NaOCH_3$ (25 °C, 24 h) also provided a mixture of the esters **29**[24] in better than 70% combined conversion presumably via methanolysis of the lactone, subsequent elimination of H_2O with generation of a norcaradiene and its similar rearrangement to **29** illustrating that this conversion may not be limited to acidic reaction conditions.

The final conversion of tropone **23** to the tropolone **25** proceeded uneventfully. Without optimization, treatment of **23** with hydrazine (THF−EtOH, 25 °C, 4 d, 65−76%) cleanly and regioselectively provided the 6-aminotropone **24** as the exclusive addition product (Scheme 5). Importantly, the isomeric 4-aminotropone was not detected under these reaction conditions, suggesting that the steric or electronic requirements for nucleophilic addition at C4 are more demanding.[25] Hydrolysis of **24** (2 N KOH−EtOH 1:1, 100 °C, 48 h, 66%) provided the tropolone **25**. Methylation of **25** under a variety of conditions provided a 3:1 to 1:1 mixture of *O*-methyl tropolones **26** and **27** in which **26** often predominated.

In the course of these studies, we also examined a number of alternatives to the **13** + **18** diene−dienophile combination. The dienes **31**−**33**,[26] readily prepared by addition of the potassium enolate of **11**[27] (1.1 equiv of *t*-BuOK, 0 °C, 30 min) to methyl 3-methoxyacylate (**30**) and subsequent *O*-acylation or silation, failed to react with the cyclopropenone ketal **18** or cyclopropenone (**34**)[13,21] under thermal or pressure-promoted reaction conditions (Scheme 7). Presumably, this may be attributed to preferential adoption of the unreactive transoid versus cisoid diene conformation. Similarly, the α-pyrone **35**[11] failed to react productively with **18** under thermal or pressure-promoted reaction conditions and both **35** and **13** failed to react productively with cyclopropenone. These observations proved instrumental in defining our approach to **1**−**3** detailed below.

Scheme 7



Total Synthesis of 1−3. The ketone **43**[8] was prepared from 5,6,7-trimethoxyisoquinoline (**36**)[28] as previously detailed with notable improvements (Scheme 8). First, the bromide **37** was prepared by low-temperature, acid-catalyzed bromination of **36** (1.4 equiv of NBS, cat. H_2SO_4, THF, 25 °C, 1 h, 80%)[8] rather than constructed from 2-bromo-3,4,5-trimethoxybenzyl bromide.[28] Trap of the aryllithium reagent derived from **37** with DMF provided the aldehyde **38** directly in good yields (61%), and in prior efforts, this was accomplished in three indirect steps ($CO(OCH_3)_2$, 83%; Dibal-H, MnO_2, 52%). In addition, the conversion of **39** to **41**[29] without intermediate purification of **40** provided **41** in higher overall conversions. Finally, the yield for hydrolysis and decarboxylation of **42** was improved by subsequent treatment with KOH which drives the reaction to completion and precluded the isolation of small amounts of the reaction intermediates.

Conversion of **43** to the α-pyrone **44** (52%) was accomplished by the five-step, one-pot sequence detailed for **13** without purification of the reaction intermediates. Treatment of **43** with *t*-BuOK (1.5 equiv, *t*-BuOH−THF) followed by the addition of **12** (1.5 equiv, 0 °C, 15 min) provided **45**. Treatment of **45** with TFA under nonaqueous conditions (25 °C, 14 h) led to clean generation of **46**. Hydrolysis of **46** (LiOH, H_2O, 0 °C, 15 min) followed by 1 N HCl neutralization and acid-catalyzed decarboxylation provided **48**, which upon treatment with Ac_2O (25 °C, 48 h, 52% overall) provided the α-pyrone **44** (Scheme 9). Notably, the hydrolysis of **46** conducted in THF−H_2O

(24) For **28**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.58 (1H, d, *J* = 1.5 Hz), 8.11 (1H, dd, *J* = 1.5, 7.9 Hz), 8.05 (2H, d, *J* = 6.9 Hz), 7.98 (1H, d, *J* = 7.9 Hz), 7.94 (1H, d, *J* = 8.2 Hz), 7.92 (1H, d, *J* = 8.2 Hz), 7.70 (2H, dd, *J* = 6.9, 8.2 Hz), 4.27 (2H, s), 3.44 (2H, s), 1.07 (6H, s). For **29** (R = COOMe, R¹ = $CH_2CMe_2CH_2OH$): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.31 (1H, s), 8.20 (1H, s), 8.05 (1H, d, *J* = 6.9 Hz), 8.04 (1H, d, *J* = 6.9 Hz), 7.96 (1H, d, *J* = 8.1 Hz), 7.95 (1H, d, *J* = 8.1 Hz), 7.70 (2H, dd, *J* = 6.9, 8.1 Hz), 4.21 (2H, s), 3.98 (3H, s), 3.39 (2H, s), 0.99 (6H, s). For **29** (R = COOMe, R¹ = Me): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.28 (2H, s), 8.06 (2H, d, *J* = 7.0 Hz), 7.97 (2H, d, *J* = 8.0 Hz), 7.73 (2H, dd, *J* = 7.0, 8.0 Hz), 3.97 (6H, s).

(25) When the reaction was conducted in THF alone without the EtOH cosolvent, **24** (76%) and the corresponding 4-aminotropone (17%) were produced. For 5-oxo-4-amino-9*H*-cycloheptatrieno[*a*]acenaphthylene: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02 (1H, d, *J* = 7.0 Hz), 7.97 (1H, d, *J* = 7.2 Hz), 7.93 (1H, d, *J* = 8.0 Hz), 7.89 (1H, d, *J* = 8.2 Hz), 7.70 (1H, dd, *J* = 7.2, 8.2 Hz), 7.69 (1H, dd, 7.0, 8.0 Hz), 7.61 (1H, dd, 1.0, 8.9 Hz), 7.40 (1H, dd, *J* = 8.9, 11.7 Hz), 7.27 (1H, dd, *J* = 1.0, 11.7 Hz), 6.72 (2H, br s).

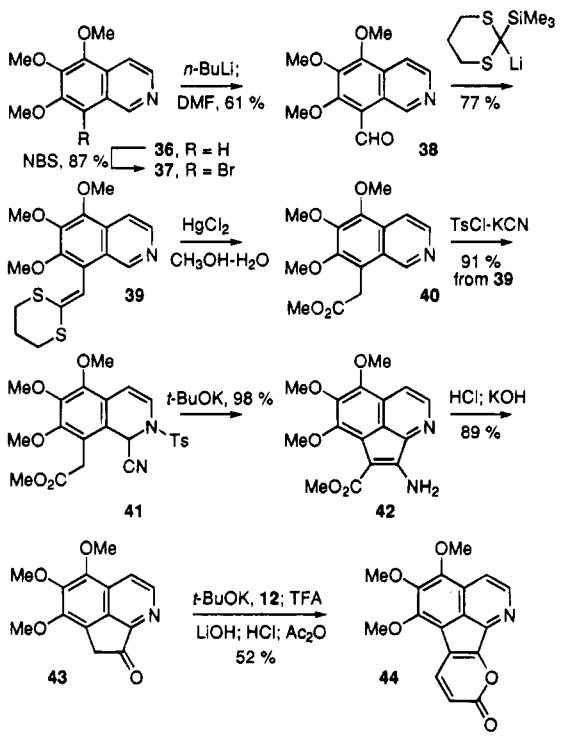
(26) For **31**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.94 (1H, d, *J* = 7.2 Hz), 7.87 (1H, dd, *J* = 0.8, 7.9 Hz), 7.82 (1H, d, *J* = 8.3 Hz), 7.81 (1H, d, *J* = 16.2 Hz), 7.70−7.50 (3H, m), 6.65 (1H, d, *J* = 16.2 Hz), 3.83 (3H, s), 2.50 (3H, s); IR (KBr) ν_{max} 1769, 1707, 1630, 1612, 1428, 1309, 1177, 1117, 821, 775 cm^{-1}. For **32**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.97 (1H, d, *J* = 16 Hz), 7.85 (1H, d, *J* = 8 Hz), 7.82 (1H, d, *J* = 7 Hz), 7.71 (1H, d, *J* = 8 Hz), 7.66 (1H, d, *J* = 7 Hz), 7.54 (1H, dd, *J* = 7, 8 Hz), 7.51 (1H, dd, *J* = 7, 8 Hz), 6.50 (1H, d, *J* = 16 Hz), 3.82 (3H, s), 1.13 (9H, s), 0.31 (6H, s). For **33**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.20 (1H, d, *J* = 8.1 Hz), 8.09 (1H, d, *J* = 8.5 Hz), 8.00 (1H, d, *J* = 7.3 Hz), 7.79 (1H, dd, *J* = 7.3, 8.1 Hz), 7.76 (1H, dd, *J* = 7.1, 8.5 Hz), 7.46 (1H, d, *J* = 15.8 Hz), 6.44 (1H, d, *J* = 15.8 Hz), 3.76 (3H, s), 3.19 (3H, s).

(27) The lithium enolate generated with LDA (1.4 equiv, −78 °C THF or THF−HMPA) was unreactive toward **30**.

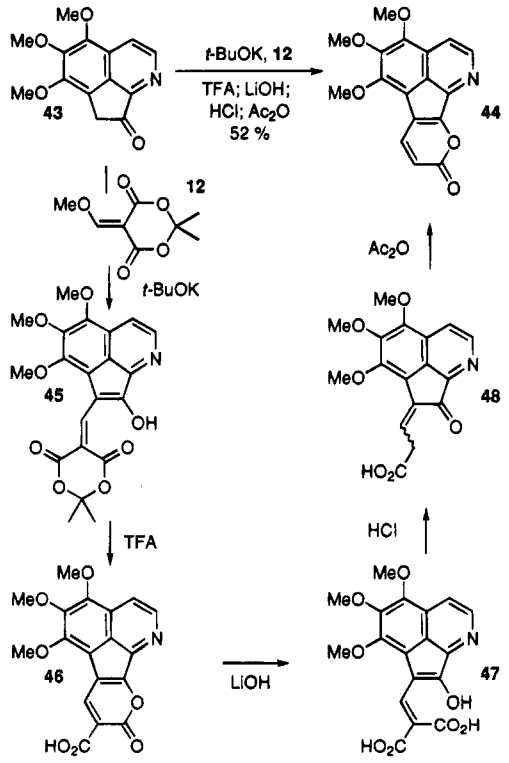
(28) Boger, D. L.; Brotherton, C. E.; Kelley, M. D. *Tetrahedron* **1981**, *37*, 3977.

(29) Boger, D. L.; Brotherton, C. E.; Panek, J. S.; Yohannes, D. *J. Org. Chem.* **1984**, *49*, 4056.

Scheme 8



Scheme 9



provided lower conversions (25–40%) due to its insolubility and was improved significantly by using H_2O alone as the reaction solvent.

The key Diels–Alder reaction of **44** with the cyclopropenone ketal **18** could be accomplished under a variety of conditions and in a range of solvents and, after purification, provided a mixture of the stable adduct *exo*-**49**, granditropone (**7**) derived from the thermally unstable *endo*-**49**, and small amounts of **50** (Scheme 10). The stereochemistry of *exo*-**49** could be inferred from the typical thermal stability of the *exo* (≥100 °C) versus *endo* (<25 °C) adducts[14,15] and their direct analogy to relative stability of the adducts derived from the Diels–Alder reactions leading to **20** and **23**, and was confirmed upon observation of the diagnostic C4a-H/C5-H ^{1}H NMR coupling constant (J = 4.0 Hz, *exo* calcd J = 4.1 Hz). Hydrolysis of the tropone ketal, derived from decarboxylation and electrocyclic rearrangement of *endo*-**49**, to provide **7** and rearrangement of *exo*-**49** to **50**[30] both were determined to occur upon chromatographic purification of the reaction mixture. Consequently, treatment of the crude Diels–Alder reaction mixture with 3.6 N HCl–EtOAc/THF to promote the conversion of *exo*-**49** to the corresponding tropone ketal followed by aqueous workup with concurrent tropone ketal hydrolysis provided **7** directly in yields as high as 40–60% accompanied by small amounts of **50** (10–20%) Scheme 11. In contrast to *exo*-**20**, which cleanly provided the tropone upon thermal decarboxylation (Scheme 6), *exo*-**49** provided **51**[30] presumably derived from rearrangement of the intermediate norcardiene under the reaction conditions. Moreover, in contrast to *exo*-**20**, which provided predominately rearrangement products upon acid treatment (Scheme 6), *exo*-**49** cleanly and predominately provided granditropone (**7**) upon aqueous acid treatment (Scheme 10).

The final conversions of granditropone (**7**) to **1**–**3** proved uneventful. Treatment of **7** with hydrazine (THF, 25 °C, 18 h, 78%) cleanly provided the C6-amine **52** with no trace of the isomeric C4-amine (Scheme 11). Hydrolysis of **52** (2 N KOH–CH_3OH 1:4, 85 °C, 30 h, 70%) cleanly provided grandirubrine (**1**) identical in all respects with the properties reported for authentic material.[1,2] Final *O*-methylation of **1** with $TMSCHN_2$ (THF–CH_3OH, 25 °C, 20 h, 72–76%) provided a 1:1 (2:1 CH_3OH–THF) to 2:1 (1:1 CH_3OH–THF) mixture of imerubrine (**2**) and isoimerubrine (**3**), which were readily separable by SiO_2 chromatography, and both proved identical in all respects with the properties reported[2–4] for authentic material.[31]

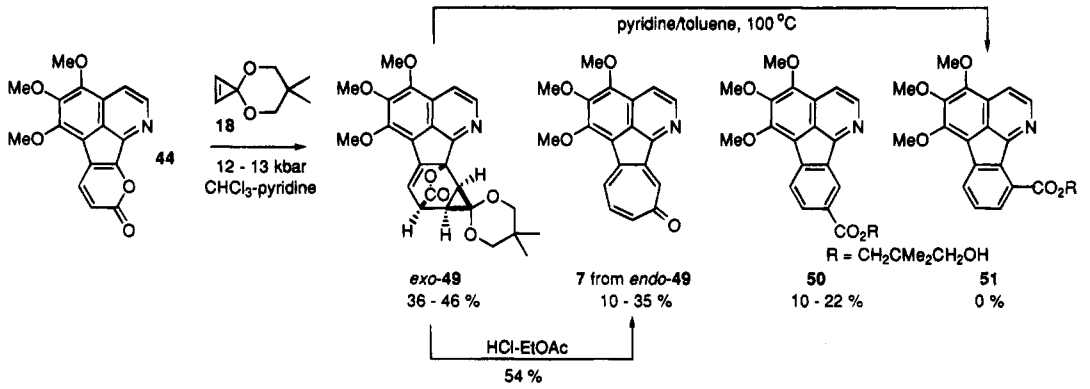
Experimental Section

4-Oxa-5-oxobenz[*a*]acenaphthylene (13). Method A. A solution of **11**[18] (3.0 g, 17.9 mmol) in 15 mL of anhydrous THF was added dropwise to a stirred solution of 20 mL of *t*-BuOK (1 M in *t*-BuOH, 20 mmol, 1.1 equiv) in 15 mL of THF at −78 °C under Ar, and the resulting dark purple solution was stirred for 30 min. The reaction mixture was allowed to warm to 0 °C, and **12**[19] (3.3 g, 17.9 mmol) was added. The red reaction mixture was stirred at 0 °C for 45 min, treated with 9 mL of 6 N HCl (3 × 17.9 mmol) at 25 °C overnight (12 h), poured onto H_2O, and extracted with CH_3OH–CH_2Cl_2 (1:9, 5 × 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The crude intermediate **15**, a yellow-orange solid, was dissolved in 5 mL of CH_2Cl_2 and 5 mL of $(CF_3CO)_2O$, and the reaction mixture was stirred at 25 °C overnight (14 h). Evaporation of the solvent and chromatography (SiO_2, 25% EtOAc–hexane) afforded 2.9 g (13.2 mmol, 74%) of pure **13** as a dark orange solid: mp 139–139.5 °C (EtOAc–hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90 (1H, dd, J = 0.4, 8.1 Hz), 7.85 (1H, br d, J = 6.9 Hz), 7.79 (1H, d, J = 9.4

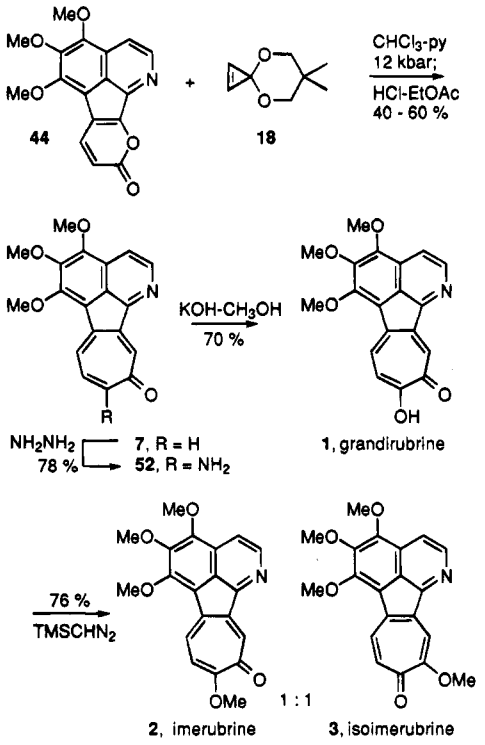
(30) For **50**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.73 (1H, d, J = 1.2 Hz), 8.65 (1H, d, J = 5.9 Hz), 8.17 (1H, dd, J = 1.2, 7.9 Hz), 8.02 (1H, d, J = 7.9 Hz), 7.69 (1H, d, J = 5.9 Hz), 4.23 (2H, s), 4.18 (3H, s), 4.14 (3H, s), 4.03 (3H, s), 3.50 (1H, br s), 3.40 (2H, br s), 1.03 (6H, s). For **51**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.61 (1H, d, J = 5.9 Hz), 8.09 (1H, dd, J = 1.2, 7.6 Hz), 7.70 (1H, d, J = 5.9 Hz), 7.54 (1H, dd, J = 1.2, 7.6 Hz), 7.48 (1H, t, J = 7.6 Hz), 4.32 (2H, s), 4.15 (3H, s), 4.11 (3H, s), 4.03 (3H, s), 3.47 (2H, br s), 3.35 (2H, br s), 0.97 (6H, s).

(31) L1210 cytotoxic testing results (IC_{50}) are provided in the supporting information. In contrast to the reported potent cytotoxic activity of pareitropone (**6**), IC_{50} = 0.0008 μg/mL (P388), the L1210 cytotoxic activities of granditropone (**7**, IC_{50} = 1 μg/mL) and **20** (IC_{50} = 16 μg/mL) proved comparable or less potent than those of the corresponding tropolones: **1** (0.2 μg/mL), **2** (4 μg/mL), **3** (1 μg/mL), and **25** (0.1 μg/mL). The most interesting observation was the equivalent cytotoxicities (IC_{50} = 0.1–0.2 μg/mL) of **25** and grandirubrine (**1**), indicating that the three methoxy substituents and the quinoline nitrogen of the natural products may not be essential to the observed properties.

Scheme 10



Scheme 11



Hz), 7.76 (1H, dd, J = 0.4, 8.2 Hz), 7.62 (1H, dd, J = 0.4, 6.9 Hz), 7.56 (1H, dd, J = 6.9, 8.1 Hz), 7.51 (1H, dd, J = 6.9, 8.2 Hz), 6.22 (1H, d, J = 9.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.1, 161.3, 138.7, 131.0, 130.8, 128.7, 128.6, 128.0, 127.3, 127.9, 126.5, 123.4, 121.9, 116.0, 111.4; IR (KBr) ν_{max} 3050, 1725, 1572, 1517, 1356, 1210, 1172, 1065, 1035, 820, 770 cm^{-1}; FABHRMS (NBA) *m/e* 221.0601 (M^+ + H, $C_{15}H_8O_2$ requires *m/e* 221.0603). Anal. Calcd for $C_{15}H_8O_2$: C, 81.81; H, 3.66. Found: C, 81.59; H, 3.64.

Method B. A solution of 1-acenaphthenone **11** (40 mg, 0.24 mmol) in 2 mL of anhydrous THF was added dropwise to a stirred solution of 0.26 mL of *t*-BuOK (1 M in *t*-BuOH, 0.26 mmol, 1.1 equiv) in 3 mL of THF at −78 °C under N_2, and the resulting dark purple solution was stirred for 30 min. The reaction mixture was allowed to warm to 0 °C, and **12** (45 mg, 0.24 mmol) was added. The red reaction mixture was stirred at 0 °C for 45 min before being quenched with the addition of saturated aqueous NH_4Cl (1 mL). The mixture was extracted with CH_3OH−$CHCl_3$ (1:9, 7 mL × 5). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The crude intermediate **14** was dissolved in 1 mL of CF_3COOH, and the reaction mixture was stirred at 25 °C for 14 h. After evaporation of CF_3COOH, the crude intermediate **16** was dissolved in 5 mL of THF. The mixture was treated with 1 mL of aqueous 1 N LiOH under N_2 for 6 h at 25 °C, then treated with 1 mL of aqueous 1 N HCl. The reaction mixture was extracted with CH_2Cl_2 (5 mL × 3), dried ($MgSO_4$), and concentrated in vacuo. The crude intermediate **15** was treated with 2 mL of Ac_2O at 25 °C for 48 h. Evaporation of the solvent and chromatography (SiO_2, 25% EtOAc−hexane) afforded **13** (46 mg, 0.21 mmol, 88%).

3b-Hydroxy-5-carboxyl-4-oxo-3b,3c,4a,5-tetrahydro-4*H*-cyclopropano[*f*]benz[*a*]acenaphthylene Lactone 2,2-Dimethyl-1,3-propylene Ketal (20). Method A. α-Pyrone **13** (20 mg, 0.09 mmol), cyclopropenone ketal **18**[21] (127 mg, 0.91 mmol, 10 equiv), and 0.2 mL of $CHCl_3$ were combined in a Teflon tube. The tube was sealed on both ends with brass clamps and placed under pressure (12 kbar)[32] for 20 h at 25 °C. Chromatography (SiO_2, 15% EtOAc−hexane eluent) afforded 23.9 mg (0.066 mmol, 73%) of **20** as a glassy material: mp 158−159 °C (dec, EtOAc−hexane, colorless prisms); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.88 (1H, dd, J = 0.6, 8.2 Hz), 7.80−7.77 (2H, m), 7.66 (1H, dd, J = 7.0, 8.2 Hz), 7.61−7.57 (2H, m), 6.88 (1H, d, J = 6.2 Hz), 3.99 (1H, ddd, J = 0.6, 3.8, 6.2 Hz), 3.83 (1H, d, J = 11.0 Hz), 3.75 (1H, d, J = 11.0 Hz), 3.57 (2H, s), 2.16 (1H, dd, J = 3.8, 10.5 Hz), 1.72 (1H, dd, J = 0.6, 10.5 Hz), 1.16 (3H, s), 1.04 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.2, 151.8, 139.3, 136.6, 132.0, 131.1, 128.3, 128.1, 126.4, 125.7, 121.0, 119.6, 118.7, 97.6, 86.1, 77.0, 76.2, 41.3, 31.8, 31.5, 30.5, 22.6, 22.1; IR (KBr) ν_{max} 2958, 2868, 1762, 1392, 1190, 1084, 997, 787 cm^{-1}.

A single crystal X-ray structure determination was conducted on **20** with colorless cubes grown from EtOAc−hexane.[22] Crystal data: $C_{23}H_{20}O_4$, MW = 360.4, monoclinic, space group *C2/c* (No. 15, $C_{2h}6$), a = 16.096(3) Å, b = 11.620(4) Å, c = 20.200(2) Å, β = 109.33(1)°, V = 3564(1) Å^3, F(000) = 1520, Z = 8, De = 1.343 mg/m^3, μ = 0.700 mm^{-1} (Cu Kα).

Method B. α-Pyrone **13** (20 mg, 0.091 mmol), cyclopropenone ketal **18** (38 mg, 0.27 mmol, 3 equiv), and 0.9 mL of THF were combined in Teflon tube. The tube was sealed on both ends with brass clamps and placed under pressure (12 kbar) for 64 h at 25 °C. Chromatography (SiO_2, 20−60% EtOAc−hexane eluent) afforded 14 mg (0.039 mmol, 43%) of **20** and 9 mg (0.039 mmol, 43%) of **23**.

5-Oxo-6-amino-5*H*-cycloheptatrieno[*a*]acenaphthylene (23). A solution of **20** (236 mg, 0.66 mmol) in 3 mL of pyridine was warmed at 90 °C with stirring for 2 d. The yellow reaction mixture was cooled to 25 °C and concentrated in vacuo. Chromatography (SiO_2, 5−40% EtOAc-CH_2Cl_2 gradient elution) afforded 120 mg (0.52 mmol, 80%) of **23** as a dark yellow wax: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.00 (1H, d, J = 8.2 Hz), 8.00 (1H, d, J = 7.2 Hz), 7.96 (1H, d, J = 8.2 Hz), 7.95 (1H, d, J = 7.0 Hz), 7.88 (1H, dd, J = 0.6, 2.8 Hz), 7.80−7.60 (3H, m), 7.30 (1H, dd, J = 8.4, 12.1 Hz), 7.16 (1H, ddd, J = 0.6, 2.8, 12.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 186.4, 146.7, 145.8, 140.6, 136.2, 136.1, 135.4, 134.8, 132.3, 130.3, 128.5, 128.4, 128.3, 127.5, 124.8, 119.9, 118.9; IR (KBr) ν_{max} 3422, 1642, 1560, 1444, 1221, 827, 772 cm^{-1}; FABHRMS (NBA) *m/e* 231.0814 (M^+ + H, $C_{17}H_{10}O$ requires *m/e* 231.0810).

5-Oxo-6-amino-5*H*-cycloheptatrieno[*a*]acenaphthylene (24). A solution of **23** (22 mg, 0.1 mmol) in 8 mL of THF−EtOH (1:1) was treated with 10 drops of hydrazine hydrate at 0 °C. The solution was allowed to warm to 25 °C and was stirred for 4 d before the reaction mixture was concentrated in vacuo. Chromatography (SiO_2, 75%

(32) The pressure-promoted Diels−Alder reactions were carried out in a AGP-10002 pressure generator manufactured by Leco Corp., Tem-Press Division, Bellefonte, PA 16823.

EtOAc–hexane) afforded 18 mg (0.73 mmol, 76%) of **24** as a red solid: mp 240–242 °C (CH_3OH–CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.04 (1H, d, J = 7.1 Hz), 8.00 (1H, s), 7.94 (1H, d, J = 8.2 Hz), 7.83 (1H, d, J = 10.1 Hz), 7.82 (1H, d, J = 7.0 Hz), 7.81 (1H, d, J = 8.1 Hz), 7.69 (1H, dd, J = 7.1, 8.1 Hz), 7.63 (1H, dd, J = 7.0, 8.2 Hz), 6.94 (1H, d, J = 10.1 Hz), 6.00 (2H, br s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.3, 155.8, 146.7, 138.2, 137.7, 134.7, 133.4, 130.1, 128.5, 128.4, 128.3, 127.6, 125.7, 123.4, 120.5, 117.7, 111.0; IR (KBr) ν_{max} 3414, 3294, 1595, 1491, 1460, 1424, 819, 769 cm^{-1}; FABHRMS (NBA) *m/e* 246.0925 (M^+ + H, $C_{17}H_{11}NO$ requires *m/e* 246.0919).

6-Oxo-5-hydroxy-6*H*-cycloheptatrieno[*a*]acenaphthylene (25). A solution of **24** (18 mg, 0.074 mmol) in 1:1 EtOH–2 N aqueous KOH (2 mL) was warmed at 100 °C under N_2 for 2 d. After cooling to 25 °C, the crude reaction mixture was diluted with CH_2Cl_2, acidified with 10% aqueous HCl, and extracted with CH_2Cl_2 (3 × 6 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 12 mg (0.049 mmol, 66%) of **25** as a purple solid: mp 259–260 °C (CH_3OH–CH_2Cl_2); ^1H NMR (DMSO-d_6, 400 MHz) δ 8.47 (1H, d, J = 7.0 Hz), 8.29 (1H, d, J = 10.7 Hz), 8.23 (1H, s), 8.23 (1H, d, J = 7.0 Hz), 8.16 (1H, d, J = 8.0 Hz), 8.04 (1H, d, J = 8.0 Hz), 7.90–7.70 (2H, m), 7.33 (1H, d, J = 10.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.9, 168.7, 147.1, 138.0, 137.2, 136.8, 132.4, 129.9, 129.4, 129.0, 128.7, 128.5, 127.3, 121.7, 119.8, 119.7, 119.0; IR (KBr) ν_{max} 3419, 3205, 1607, 1451, 1426, 1256, 818, 768 cm^{-1}; FABHRMS (NBA) *m/e* 247.0768 (M^+ + H, $C_{17}H_{10}O_2$ requires *m/e* 247.0759).

5-Oxo-6-methoxy-5*H*-cycloheptatrieno[*a*]acenaphthylene (26) and 6-Oxo-5-methoxy-6*H*-cycloheptatrieno[*a*]acenaphthylene (27). A solution of **25** (3.0 mg, 0.012 mmol) in 1 mL of CH_3OH–CH_2Cl_2 (1:1) was treated with excess diazomethane at 25 °C for 3 h before being concentrated in vacuo. Chromatography (SiO_2, 2% CH_3OH–CH_2Cl_2) afforded 1.0 mg (0.0038 mmol, 32%) of **26** and **27** as a mixture in a ratio of 3:2 determined by ^1H NMR.

A solution of **25** (2.0 mg, 0.008 mmol) in 1 mL of THF and 0.5 mL of CH_3OH was treated with trimethylsilyldiazomethane (0.2 mL of 1 M in hexane) at 25 °C for 4 d before being concentrated in vacuo. Chromatography (SiO_2, 2% CH_3OH–CH_2Cl_2) afforded 1.6 mg (0.0062 mmol, 77%) of a mixture of **26** and **27** in a ratio of 1:1 determined by ^1H NMR.

A mixture of **25** (2.0 mg, 0.008 mmol), K_2CO_3 (3.7 mg, 0.025 mmol), and CH_3I (0.2 mL) in 1 mL of acetone was warmed at reflux for 2 d. The reaction mixture was poured onto H_2O (2 mL) and extracted with CH_2Cl_2 (3 × 3 mL), dried ($MgSO_4$), and concentrated in vacuo. Chromatography (SiO_2, 2% CH_3OH–CH_2Cl_2) afforded 1.0 mg (0.0038 mmol, 43%) of a mixture of **26** and **27** in a ratio of 3:1 determined by ^1H NMR.

A mixture of **25** (2.0 mg, 0.008 mmol), K_2CO_3 (3.7 mg, 0.025 mmol), and CH_3I (0.5 mL) in 2 mL of DMF was stirred at 25 °C for 12 h. The reaction mixture was poured onto H_2O (2 mL) and extracted with CH_2Cl_2 (3 × 3 mL), dried ($MgSO_4$), and concentrated in vacuo. Chromatography (SiO_2, 2% CH_3OH–CH_2Cl_2) afforded 1.5 mg (0.0057 mmol, 72%) of a mixture of **26** and **27** in a ratio of 2:1 determined by ^1H NMR. For **26** and **27** (2:1) mixture: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.10 (0.5H, d, J = 7.0 Hz), 8.05 (1H, s), 8.02 (0.5H, d, J = 8.2 Hz), 8.01 (1H, d, J = 7.0 Hz), 8.00 (0.5H, d, J = 12 Hz), 7.99 (0.5H, d, J = 7.1 Hz), 7.98 (1H, d, J = 8.2 Hz), 7.94 (0.5 H, d, J = 8.2 Hz), 7.90 (2H, d, J = 7.6 Hz), 7.79 (1H, d, J = 10.0 Hz), 7.77–7.63 (3H, m), 7.60 (0.5H, s), 7.37 (0.5H, d, J = 12.0 Hz), 6.89 (1H, d, J = 10.0 Hz), 4.17 (1.5H, s), 4.03 (3H, s).

8-Bromo-5,6,7-trimethoxyisoquinoline (37). 5,6,7-Trimethoxyisoquinoline (**36**, 1.67 g, 7.6 mmol), NBS (1.43 g, 8.0 mmol, 1.05 equiv), and 3 drops of concentrated H_2SO_4 were combined in 75 mL of anhydrous THF, and the mixture was stirred under N_2 at 25 °C for 2 h. The reaction mixture was neutralized with the addition of 5% aqueous $NaHCO_3$, poured onto H_2O (50 mL), extracted with CH_2Cl_2 (3 × 60 mL), dried ($MgSO_4$), and concentrated in vacuo. Chromatography (SiO_2, 30% EtOAc–hexane) afforded 1.99 g (87%) of **37** as a white solid identical in all respects to authentic material:[28] mp 64–66 °C (lit. mp 64–67 °C).[28]

5,6,7-Trimethoxyisoquinoline-8-carboxaldehyde (38). A stirred solution of **37** (3.96 g, 13.3 mmol) in 66 mL of anhydrous Et_2O under Ar at 0 °C was treated with *n*-BuLi (5.85 mL of 2.5 M in hexane, 14.6 mmol, 1.1 equiv), and the reaction mixture was stirred at 0 °C for 30 min before the addition of DMF (5.15 mL, 66.5 mmol, 5 equiv). After the mixture was stirred for 30 min at 0 °C, H_2O was added, and the reaction mixture was allowed to warm to 25 °C. The mixture was poured onto H_2O and extracted with Et_2O (50 mL) and CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Chromatography (SiO_2, 30–70% EtOAc–hexane gradient elution) afforded 2.04 g (8.26 mmol, 61%) of **38** as a white solid identical in all respects to authentic material[8] (mp 92–92.5 °C, lit.[8] mp 92–92.5 °C) and 580 mg (2.65 mmol, 20%) of 5,6,7-trimethoxyisoquinoline (**36**).

8-((1,3-Dithiane-2-ylidene)methyl)-5,6,7-trimethoxyisoquinoline (39). A stirred solution of 2-(trimethylsilyl)-1,3-dithiane (5.97 g, 31.1 mmol, 1.3 equiv) in 40 mL of anhydrous THF at 0 °C under Ar was treated with *n*-BuLi (11.5 mL of 2.5 M in hexane, 28.7 mmol, 1.2 equiv). The reaction mixture was stirred at 0 °C for 15 min and allowed to cool to −78 °C before the dropwise addition of a solution of **38** (5.91 g, 23.9 mmol) in 20 mL of anhydrous THF. After stirring for 30 min, the reaction mixture was treated with H_2O, poured onto H_2O, and extracted with CH_2Cl_2 (2 × 80 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Chromatography (SiO_2, CH_2Cl_2–EtOAc–hexane (3:1:1)) afforded 9.29 g (26.6 mmol, 89%) of **39** as a pale yellow oil identical in all respects with authentic material.[8]

Methyl 2-(5,6,7-Trimethoxyisoquinolyl)acetate (40). A solution of **39** (9.29 g, 26.6 mmol) and $HgCl_2$ (15.9 g, 58.5 mmol, 2.2 equiv) in 1000 mL of 9:1 CH_3OH–H_2O was warmed at reflux under N_2 overnight. The white precipitate was filtered and washed with 9:1 CH_2Cl_2–CH_3OH. The combined filtrates were concentrated in vacuo. The residue was dissolved in CH_2Cl_2, washed with 5% aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated in vacuo to afford crude **40** identical to authentic material[8] which was used directly in the next reaction.

Methyl 2-(*N*-Tosyl-1-cyano-1,2-dihydro-5,6,7-trimethoxy-8-isoquinolyl)acetate (41). *p*-Toluenesulfonyl chloride (7.62 g, 39.3 mmol, 1.5 equiv) was added to a vigorously stirred solution of crude **40** (26.6 mmol) and KCN (5.19 g, 79.8 mmol, 3 equiv) in 500 mL of 1:1 CH_2Cl_2–H_2O, and the reaction mixture was stirred at 25 °C overnight. The reaction mixture was poured onto H_2O and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Chromatography (SiO_2, 20% EtOAc–hexane) afforded 10.4 g (24.3 mmol, 91%) of **41** as a colorless oil identical in all respects with authentic material.[8]

Methyl 8-Amino-4,5,6-trimethoxycyclopentadieno[2,1,5-*ij*]isoquinoline-7-carboxylate (42). A stirred solution of **41** (10.4 g, 24.3 mmol) in 250 mL of anhydrous THF under N_2 was treated with *t*-BuOK (73 mL of 1 M in *t*-BuOH, 73 mmol, 3 equiv). The resulting purple solution was stirred at 25 °C for 6 h before the addition of saturated aqueous NH_4Cl. The red mixture was poured onto saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Chromatography (SiO_2, CH_2Cl_2–EtOAc–hexane (1:1:1)) afforded 6.31 g (20.0 mmol, 82%; typically 80–98%) of **42** as a red crimson solid identical in all respects with authentic material (mp 145–146 °C, lit. mp 155–156 °C).[8]

8-Oxo-4,5,6-trimethoxycyclopenteno[1,2,3-*ij*]isoquinoline (43). A purple solution of **42** (118 mg, 0.37 mmol) in 10 mL of 9:1 dioxane–1 N aqueous HCl was warmed at 110 °C under N_2 with vigorous stirring for 10 min before 1 N aqueous KOH (1 mL) was added. The resulting mixture was stirred at 110 °C for 3 h. The yellow reaction mixture was cooled to 25 °C, poured onto 5% aqueous $NaHCO_3$, and extracted with EtOAc (3×). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Chromatography (SiO_2, 50% EtOAc–hexane) afforded 86 mg (0.33 mmol, 89%) of **43** identical in all respects with authentic material (mp 124 °C, lit. mp 124–125 °C).[8]

3-Aza-9,10,11-trimethoxy-4-oxa-5-oxobenz[*a*]acenaphthylene (44). A solution of **43** (80 mg, 0.31 mmol) in anhydrous THF (7 mL) was added dropwise to a stirred solution of *t*-BuOK (0.46 mL, 1 M in *t*-BuOH, 0.46 mmol, 1.5 equiv) in THF (3 mL) at −78 °C under N_2, and the resulting dark purple solution was stirred for 30 min. The reaction mixture was allowed to warm to 0 °C before **12** (86 mg, 0.46 mmol, 1.5 equiv) was added. The red reaction mixture was stirred at 0 °C for 15 min, quenched with the addition of saturated aqueous NH_4Cl (2 mL). The mixture was extracted with CH_3OH–$CHCl_3$ (1:9, 7 × 10 mL). The combined organic phases were dried ($MgSO_4$) and

concentrated in vacuo. The crude intermediate **45** was dissolved in CF_3COOH (4 mL), and the reaction mixture was stirred at 25 °C for 14 h. After evaporation of CF_3COOH, the crude intermediate **46** was dissolved in 20 mL of H_2O. The mixture was treated with 2 mL of 1 N aqueous LiOH under N_2 for 15 min at 0 °C before neutralization through addition of 2 mL of 1 N aqueous HCl. The reaction mixture was extracted with EtOAc (60 mL), washed with H_2O (3 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude intermediate **48** was treated with 4 mL of Ac_2O at 25 °C for 48 h. Evaporation of the solvent and chromatography (SiO_2, 20−40% EtOAc−hexane) afforded 50 mg of **44** (0.16 mmol, 52%). For **45**: ^1H NMR (CD_3OD, 400 MHz) δ 8.52 (1H, d, J = 5.6 Hz), 8.20 (1H, s), 7.83 (1H, d, J = 5.6 Hz), 4.06 (3H, s), 4.02 (3H, s), 3.84 (3H, s), 1.77 (6H, s). For **46**: ^1H NMR ($CDCl_3$, 400 MHz) δ 9.15 (1H, s), 8.88 (1H, d, J = 5.6 Hz), 7.95 (1H, d, J = 5.6 Hz), 4.27 (3H, s), 4.18 (3H, s), 4.00 (3H, s). For **44**: recrystallized from EtOAc−hexane, mp 179−180 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.66 (1H, d, J = 5.6 Hz), 7.91 (1H, d, J = 9.4 Hz), 7.71 (1H, d, J = 5.6 Hz), 6.31 (1H, d, J = 9.4 Hz), 4.15 (3H, s), 4.11 (3H, s), 3.99 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.0, 158.6, 153.6, 150.5, 150.3, 148.7, 145.8, 145.4, 139.5, 126.2, 118.7, 117.7, 116.1, 114.0, 62.2, 62.1, 61.4; IR (KBr) ν_{max} 3447, 2950, 1730, 1629, 1466, 1414, 1341, 1146, 1014 cm^{-1}. Anal. Calcd for $C_{17}H_{13}NO_5$: C, 65.59; H, 4.21; N, 4.50. Found: C, 65.46; H, 4.24; N, 4.54.

3-Aza-3b-hydroxy-5-carboxy-4-oxo-7,8,9-trimethoxy-3b,3c,4a,5-tetrahydro-4*H*-cyclopropano[*f*]benz[*a*]acenaphthylene Lactone 2,2-Dimethyl-1,3-propylene Ketal (49) and 3-Aza-9,10,11-trimethoxy-5-oxo-5*H*-cycloheptatrieno[*a*]acenaphthylene (7, Granditropone). α-Pyrone **44** (40 mg, 0.13 mmol), cyclopropenone ketal **18** (55 mg, 0.39 mmol, 3 equiv), pyridine (31 mg, 0.39 mmol, 3 equiv), and 1.3 mL of $CHCl_3$ were combined in Teflon tube. The tube was sealed on both ends with brass clamps and placed under pressure (12 kbar)[32] for 2.5 h at 25 °C. Chromatography (Al_2O_3, 10−100% EtOAc−hexane gradient elution) afforded 21 mg (0.047 mmol, 36%) of *exo*-**49**, 8.0 mg (0.024 mmol, 20%) of granditropone (**7**), and 5.0 mg (0.012 mmol, 10%) of **50**.[30] For *exo*-**49**: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.58 (1H, d, J = 6.0 Hz), 7.69 (1H, d, J = 6.0 Hz), 6.90 (1H, d, J = 6.1 Hz), 4.17 (1H, d, J = 10.8 Hz), 4.08 (3H, s), 4.03 (3H, s), 4.02 (3H, s), 4.00 (1H, dd, J = 4.0, 6.1 Hz), 3.76 (1H, dd, J = 1.8, 10.8 Hz), 3.65 (1H, d, J = 10.7 Hz), 3.54 (1H, dd, J = 1.8, 10.7 Hz), 2.22 (1H, dd, J = 4.0, 10.3 Hz), 1.69 (1H, d, J = 10.3 Hz), 1.23 (3H, s), 0.97 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.1, 158.7, 150.4, 149.5, 148.4, 147.4, 145.2, 130.1, 127.1, 122.1, 119.1, 114.2, 97.2, 85.7, 77.2, 77.2, 61.8, 61.5, 61.0, 41.7, 32.3, 30.8, 30.2, 23.3, 22.1; IR (KBr) ν_{max} 3447, 2948, 1768, 1536, 1559, 1411, 1364, 1084 cm^{-1}; FABHRMS (NBA) *m/e* 584.0667 (M^+ + H, $C_{25}H_{25}NO_7$ requires 584.0685).

For **7**: purple solid, mp 155−157 °C (EtOAc); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.66 (1H, d, J = 5.8 Hz), 8.12 (1H, dd, J = 0.8, 2.8 Hz), 7.97 (1H, dt, J = 8.5, 0.8 Hz), 7.75 (1H, d, J = 5.8 Hz), 7.24 (1H, dd, J = 8.5, 12.3 Hz), 7.07 (1H, ddd, J = 0.8, 2.8, 12.3 Hz), 4.15 (3H, s), 4.14 (3H, s), 4.04 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 186.8, 157.3, 152.0, 150.0, 145.5, 145.4, 143.4, 140.7, 135.7, 133.1, 128.0, 127.0, 126.2, 122.9, 121.4, 115.1, 61.9, 61.5, 61.3; IR (KBr) ν_{max} 3447, 2923, 1617, 1569, 1458, 1410, 1365, 1291, 1143, 1010 cm^{-1}; FABHRMS (NBA) *m/e* 322.1072 (M^+ + H, $C_{19}H_{15}NO_4$ requires 322.1079).

A solution of **49** (11.4 mg, 0.025 mmol) in 10 mL of THF was treated with 1 mL of 3.6 M HCl−EtOAc at 25 °C for 6 d. The reaction mixture was poured onto 20 mL of saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was dried ($MgSO_4$) and concentrated in vacuo. Chromatography (SiO_2, 25−80% EtOAc−hexane) afforded 2.7 mg (0.006 mmol, 24%) of recovered **49** and 3.3 mg (0.01 mmol, 41%, 54% based on recovered **49**) of **7**.

A solution of **44** (40 mg, 0.13 mmol), **18** (55 mg, 0.39 mmol, 3 equiv), and pyridine (31 mg, 0.39 mmol, 3 equiv) in $CHCl_3$ (1.3 mL) in a Teflon tube sealed with brass clamps was placed under 12 kbar pressure[32] for 2.5 h. Following depressurization and removal of the solvent in vacuo, the crude product was placed in 30 mL of THF and treated with 3.6 M HCl−EtOAc (3 mL). The resulting mixture was stirred at 25 °C for 4 d before being poured onto 20 mL of saturated aqueous $NaHCO_3$ and extracted with EtOAc (3 × 30 mL). The combined organic phase was dried ($MgSO_4$) and concentrated in vacuo. Chromatography (SiO_2, 25−80% EtOAc−hexane) afforded **7** (16−24 mg, 0.072 mmol, 40−60%) and **50** (5.0 mg, 0.012 mmol, 10%).

3-Aza-9,10,11-trimethoxy-5-oxo-6-amino-5*H*-cycloheptatrieno[*a*]-acenaphthylene (52). A solution of **7** (6.1 mg, 0.019 mmol) in 8 mL of THF was treated with 8 drops of hydrazine hydrate at 0 °C. The solution was allowed to warm to 25 °C and was stirred for 18 h. The reaction mixture was poured onto 5 mL of aqueous $NaHCO_3$, extracted with EtOAc (10 mL), and washed with saturated aqueous NaCl. The organic phase was dried (Na_2SO_4) and concentrated in vacuo. Chromatography (Al_2O_3, 75−100% EtOAc−hexane, 10−20% CH_3OH−CH_2Cl_2) afforded 5.0 mg (0.014 mmol, 78%) of **52** as a red glassy material: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.66 (1H, d, J = 5.8 Hz), 8.24 (1H, s), 8.07 (1H, d, J = 10.3 Hz), 7.72 (1H, d, J = 5.8 Hz), 6.90 (1H, d, J = 10.3 Hz), 4.11 (3H, s), 4.10 (3H, s), 4.04 (3H, s); IR (KBr) ν_{max} 3421, 2939, 1599, 1507, 1458, 1411, 1087, 1016, 976 cm^{-1}; FABHRMS (NBA) *m/e* 337.1173 (M^+ + H, $C_{19}H_{16}N_2O_4$ requires *m/e* 337.1188).

Grandirubrine (1). A solution of **52** (5.0 mg, 0.014 mmol) in 5 mL of CH_3OH and 1.6 mL of 2 N aqueous KOH was warmed at 85 °C under N_2 for 30 h. After cooling to 25 °C, the crude reaction mixture was diluted with 8 mL of H_2O, washed with CH_2Cl_2, acidified with the addition of 3.2 mL of 1 N aqueous HCl, and extracted with CH_2Cl_2 (3 × 4 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to afford 3.3 mg (0.0098 mmol, 70%) of **1**: mp 201−202 °C (lit.[4] mp 201−203 °C); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.73 (1H, d, J = 5.7 Hz), 8.42 (1H, s), 8.33 (1H, d, J = 10.6 Hz), 7.80 (1H, d, J = 5.7 Hz), 7.42 (1H, d, J = 10.6 Hz), 4.17 (3H, s), 4.14 (3H, s), 4.04 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.5, 167.7, 157.5, 152.4, 150.0, 149.8, 146.2, 145.6, 137.2, 131.3, 126.2, 124.4, 121.7, 120.2, 119.9, 115.8, 62.0, 61.5, 61.5; IR (KBr) ν_{max} 3442, 1617, 1559, 1458, 1406, 1261 cm^{-1}; FABHRMS (NBA) *m/e* 338.1080 (M^+ + H, $C_{19}H_{15}NO_5$ requires 338.1087).

Imerubrine (2) and Isoimerubrine (3). A solution of **1** (3.1 mg, 0.0092 mmol) in 3 mL of CH_3OH−THF (2:1) was treated with 0.5 mL of a solution containing $TMSCHN_2$ (2 M in hexane solution) at 25 °C for 20 h before being concentrated in vacuo. Chromatography (SiO_2, 60−100% EtOAc−hexane) afforded 1.32 mg (0.0038 mmol, 41%) of **2** and 1.11 mg (0.0032 mmol, 35%) of **3**. For **2**: R_f 0.24 (EtOAc); mp 181−183 °C (lit.[1,2] mp 183−185 °C); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.67 (1H, d, J = 5.7 Hz), 8.28 (1H, s), 8.05 (1H, d, J = 10 Hz), 7.74 (1H, d, J = 5.7 Hz), 6.86 (1H, d, J = 10 Hz), 4.14 (3H, s), 4.12 (3H, s), 4.04 (3H, s), 4.00 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.4, 164.1, 157.6, 151.1, 150.2, 148.8, 145.6, 145.3, 136.7, 128.4, 126.3, 126.2, 126.1, 121.9, 115.0, 112.0, 61.9, 61.4, 61.2, 56.4; FABHRMS (NBA) *m/e* 352.1241 (M^+ + H, $C_{20}H_{17}NO_5$ requires 352.1247).

For **3**: R_f 0.18 (EtOAc); mp 183−184 °C (lit.[4] mp 183−185 °C); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.72 (1H, d, J = 5.7 Hz), 8.27 (1H, d, J = 12.2 Hz), 7.90 (1H, s), 7.79 (1H, d, J = 5.7 Hz), 7.39 (1H, d, J = 12.2 Hz), 4.19 (3H, s), 4.17 (3H, s), 4.16 (3H, s), 4.01 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.2, 164.4, 158.5, 154.4, 151.3, 149.5, 145.2, 139.0, 136.9, 136.5, 132.5, 125.9, 121.3, 121.0, 115.8, 106.8, 62.2, 62.0, 61.5, 56.9; FABHRMS (NBA) *m/e* 352.1258 (M^+ + H, $C_{20}H_{17}NO_5$ requires 352.1247).

Acknowledgment. We gratefully acknowledge the financial support of the National Institutes of Health (CA 41986) and the sabbatical leave of K.T. sponsored by Ono Pharmaceuticals, Ltd. (1994−1995 Japan). We wish to thank Dr. Raj Chadha for the X-ray structure determination of **20** and Qing Jin, Brian Winter, and Professor Paul A. Kitos (Department of Biochemistry, University of Kansas) for the cytotoxicity testing (supporting information).

Supporting Information Available: The results of the cytotoxic evaluation (L1210) of **1−3**, **7**, **8**, **10**, **44**, **49**, **52**, **12**, **20**, and **23−25** (1 table) and details of the X-ray structure determination of **20** are provided (20 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA953030O