Total Synthesis of the Rubrolone Aglycon

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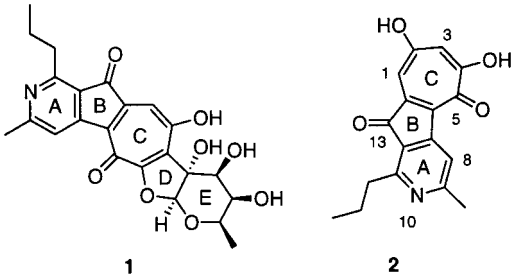
Abstract: A total synthesis of the rubrolone aglycon is detailed and is based on two key Diels−Alder reactions. The AB ring system incorporating a tetrasubstituted pyridine was assembled, enlisting the rare 4π participation of an *O*-alkyl α,β-unsaturated oxime in an intramolecular [4 + 2] cycloaddition reaction (70%). The C-ring oxygenated tropolone was introduced through a room-temperature, exo selective [4 + 2] cycloaddition of a cyclopropenone ketal (97%) followed by in situ generation of a norcaradiene and room-temperature electrocyclic rearrangement to a cycloheptatrienone ketal appropriately substituted for hydrolysis directly to a 2,4-dihydroxycycloheptatrienone.

Rubrolone (**1**),[1] a red tropoloalkaloid isolated from *Streptomyces enchinoruber*, was identified in a single-crystal X-ray structure determination and shown to possess the unique azuleno[2,3-*c*]pyridine-2,5,13-trione aglycon **2** characteristic of a class of structurally related agents (Figure 1).[2,3] To date, only a single total synthesis of the rubrolone aglycon has been reported[4] despite this unique structure. As part of the exploration of the Diels−Alder reactions of azadienes[5−11] and the thermal cycloaddition reactions of cyclopropenone ketals,[12−19] their respective potential for introduction of the AB and C rings of rubrolone have been examined.[3b,20] Herein we describe the realization of a total synthesis, based on these two unusual Diels−Alder reactions, of the rubrolone aglycon **2**. Key to the approach was the implementation of a rare 4π participation of an *O*-alkyl α,β-unsaturated oxime in an intramolecular Diels−Alder reaction for construction of the tetrasubstituted pyridine with assemblage of the AB ring system (Scheme 1, **11** → **12**) and the Diels−Alder reaction of the cyclopropenone ketal **17** with the highly oxygenated diene **16** as a prelude to C-ring tropolone introduction. Conversion of the [4 + 2] cycloadduct **18** to the norcaradiene **29**, in situ low-temperature electrocyclic rearrangement to a cycloheptatrienone ketal and tautomerization was anticipated to provide a fully oxygenated precursor to the rubrolone aglycon **2**. Inherent in the design of the tropolone annulation was the incorporation of three oxygen substituents in the diene−dienophile reaction partners, permitting the direct preparation of a 2,4-dihydroxycycloheptatrienone in a process complementary to those we have detailed in total syntheses of grandirubrine/imerubrine and colchicine based on the [4 + 2] and [3 + 4] cycloaddition reactions of cyclopropenone ketals, respectively.[12−15]



1 **2**

Figure 1.

Synthesis of the Rubrolone AB Ring System: 4π Participation of an *O*-Alkyl α,β-Unsaturated Oxime in an Intramolecular Diels−Alder Reaction. The AB ring system **12** was prepared by an approach we previously disclosed[3b] (Scheme 2). Condensation of aldehyde **3**[21] with 1-lithio-1-pentyne provided **4** (90%). Protection of the secondary alcohol as the

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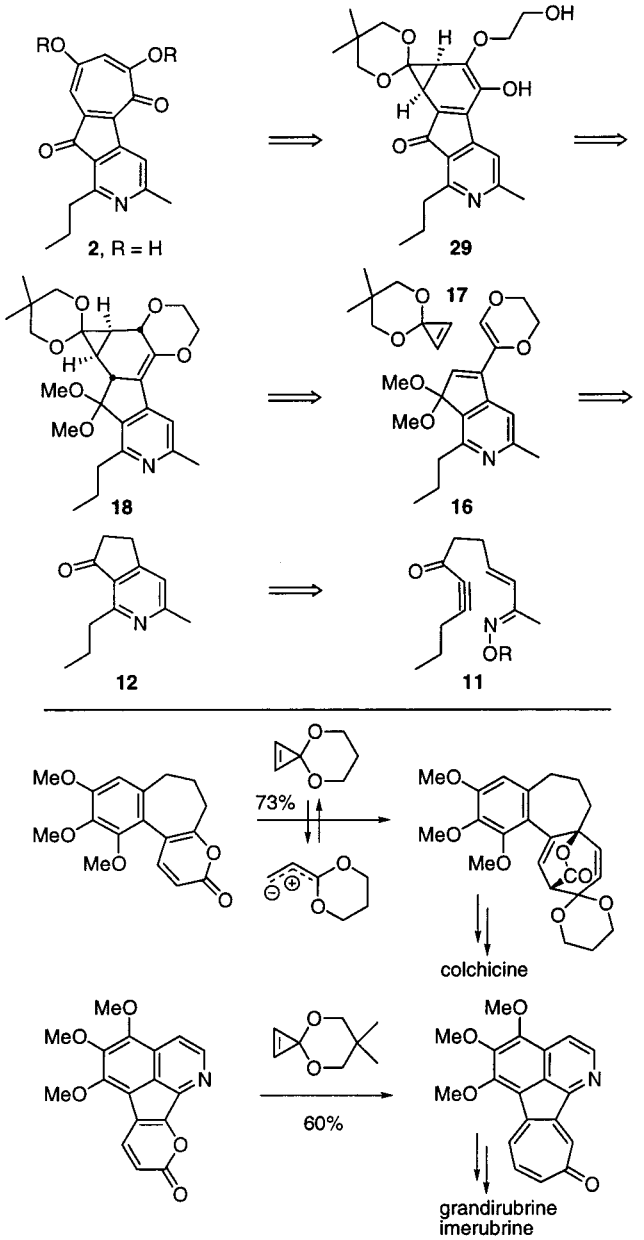
Scheme 1



Scheme 2

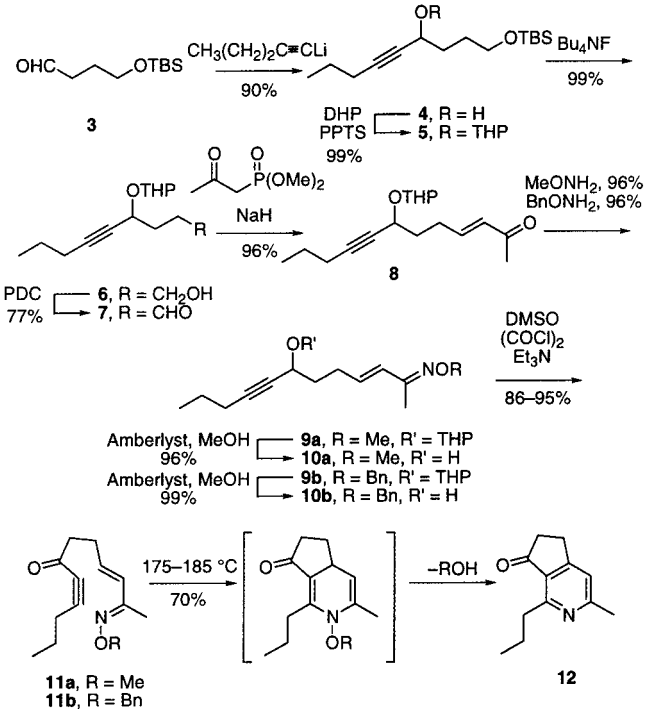


Table 1

substrate	R	solvent	temperature (°C)	time (h)	yield **12** (%)
11a	Me	triisopropylbenzene	185	24	53
11a	Me	triisopropylbenzene	175	36	70
11b	Bn	toluene	110−140	72	no reaction
11b	Bn	triisopropylbenzene	180	18	54
11b	Bn	triisopropylbenzene	185	36	70
11b	Bn	triisopropylbenzene	185	48	58

THP ether **5** (DHP, PPTS, CH_2Cl_2, 99%) followed by removal of the OTBS ether (Bu_4NF, THF, 99%) and PDC oxidation of the primary alcohol **6** (77%) provided aldehyde **7**. Treatment of **7** with dimethyl (2-oxopropyl)phosphonate provided the key intermediate **8** in 96% yield. Condensation of **8** with *O*-methyl hydroxylamine hydrochloride (pyridine, 96%) followed by removal of the THP-protecting group of **9a** (Amberlyst, MeOH, 96%) provided **10a**. Subsequent Swern oxidation of **10a** afforded **11a** (86%), which provided the initial *O*-alkyl α,*β*-unsaturated oxime for study. Similarly, treatment of **8** with *O*-benzyl hydroxylamine hydrochloride provided **9b** (96%). Removal of the THP-protecting group of **9b** (99%) followed by Swern oxidation of **10b** (95%) provided **11b**, an additional oxime for study.

Table 1 summarizes representative results obtained from a study of the intramolecular [4 + 2] cycloaddition of **11**. No reaction was found to occur at temperatures lower than 140 °C, and a productive rate of reaction was observed at 170−200 °C (triisopropylbenzene, bp 233−236 °C). The elimination of methanol (**11a**) or benzyl alcohol (**11b**) with formal oxidation of the initial cycloadduct to the corresponding pyridine was found to occur under the reaction conditions to provide **12** directly in 70% yield. Precedent for this Diels−Alder reaction may be found in the use of α,*β*-unsaturated *N*,*N*-dimethylhydrazones in intermolecular[9] and intramolecular[22] [4 + 2] cycloaddition reactions, even though the general reported failure of α,*β*-unsaturated oxime cycloadditions suggested that their use may not prove viable.[9] Since our initial disclosure,[3b] additional examples of such reactions have been disclosed.[23,24] Thus, the observation that the *O*-alkyl α,*β*-unsaturated oximes **11** participate as effective 4π components of an intramolecular Diels−Alder reaction with an electron-deficient dienophile indicate that the introduction of an alkoxy electron-donating substituent (OR) on the nitrogen atom of the inherently electron-deficient 1-aza-1,3-butadiene system, like the dimethylamino group of the unsaturated dimethylhydrazones (NMe_2), may be sufficient to promote its participation in a normal, $HOMO_{diene}$-controlled Diels−Alder reaction.

Synthesis of the Rubrolone Aglycon: [4 + 2] Cycloaddition of a Cyclopropenone Ketal. In a prior study, we demonstrated that the 1,4-addition of 2-bromoinden-1-one with

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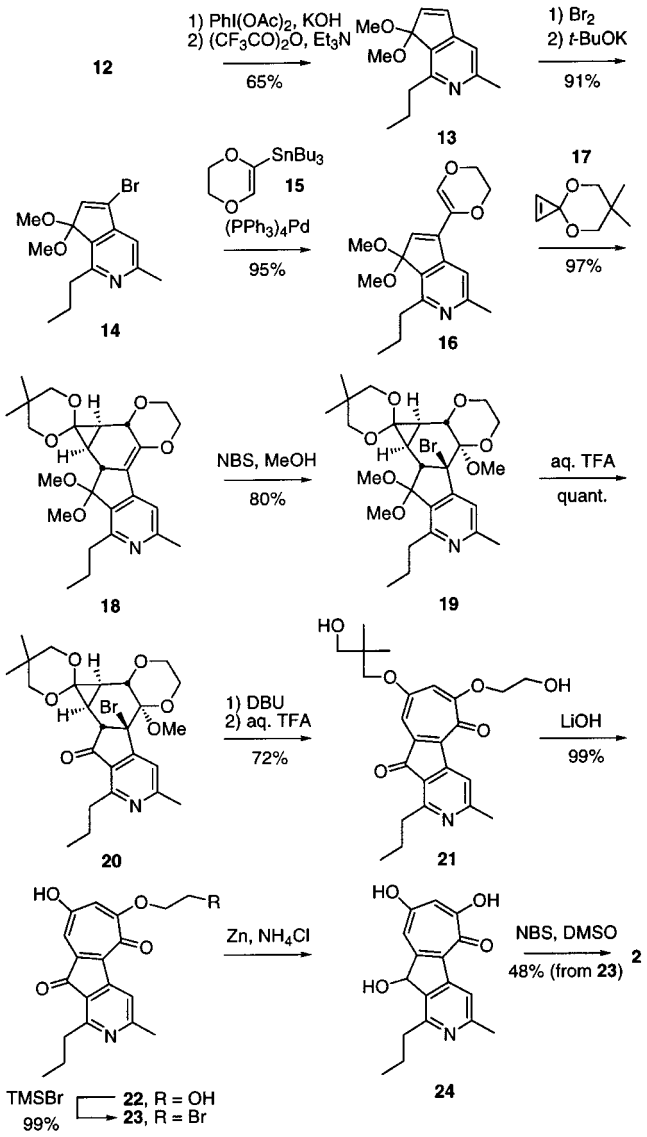
Scheme 3



the higher-order cyanocuprate[25] prepared from 2-lithio-1,4-dioxene was followed by the elimination of HBr to provide the corresponding diene which could serve as a suitably functionalized substrate for a Diels−Alder approach to rubrolone C-ring introduction.[20] However, all attempts to extend this approach to the preparation of **16** from **12** failed to afford the desired diene. Nonetheless, the diene **16** was obtained by Stille coupling of **14** with **15** which is formally equivalent to such a conjugate addition. Thus, C6 hydroxylation of **12** with $PhI(OAc)_2$[27] (KOH, MeOH), under conditions that provide the corresponding α-hydroxy dimethyl ketal in a reaction that first generates the α-iodoso intermediate and is followed by the formation of the alkoxy epoxide and ring opening of the epoxide with a MeOH trap, followed by elimination of water ($(CF_3CO)_2O$, Et_3N, 65%) gave **13**, Scheme 3.

Bromination of **13** (Br_2, CH_2Cl_2) and subsequent elimination of HBr (*t*-BuOK, DMF, 91% for two steps) selectively afforded **14** which is derived from an E2 elimination with removal of the most acidic and sterically most accessible hydrogen. Stille coupling of **14** with **15**[26] cleanly provided the diene **16** in superb yield upon treatment with $(Ph_3P)_4Pd$ (DMF-THF 1:4, 95%). No coupling product was observed when Pd(II) catalysts such as bis(benzonitrile)palladium dichloride were used, and a mixture of DMF−THF (1:4) as solvent gave **16** in high yield while the use of DMF or THF individually resulted in decreased yields.

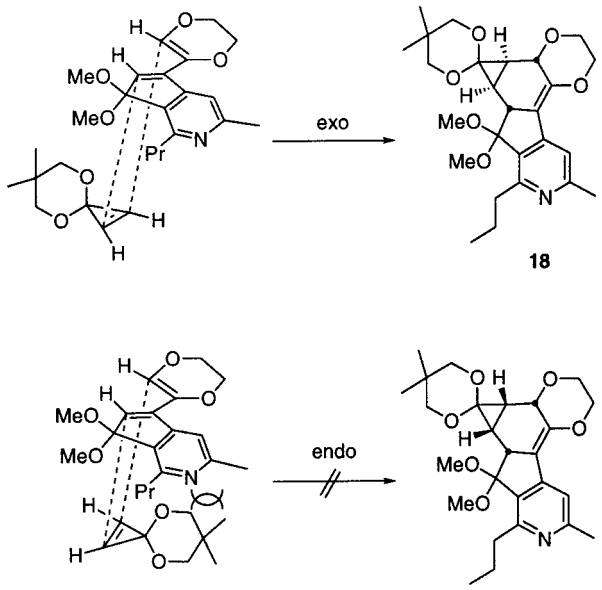


Figure 2.

The key Diels−Alder reaction of **16** with the cyclopropenone ketal **17**[28] was conducted at room temperature and was complete within 45 min, providing the single cycloadduct **18** in 97% yield. The success of this rapid and unusually effective [4 + 2] cycloaddition reaction may be attributed to the combined use of a reactive electron-rich diene and the strained dienophile **17**. The [4 + 2] cycloaddition reaction provided a single diastereomer, which could be purified by simple crystallization from EtOAc/hexanes. Single-crystal X-ray structure analysis[29] revealed that **18** was the anticipated cycloadduct shown in Supporting Information Figure 1a derived from exclusive cycloaddition through the less sterically encumbered exo transition state[14,15] (Figure 2).

Treatment of **18** with NBS−MeOH provided **19** in 80% yield as a single diastereomer, the structure of which was established by single-crystal X-ray structure analysis.[29] The stereochemical outcome indicates that the initial reaction of **18** with NBS proceeded selectively on the less hindered face (Supporting Information Figure 1b). Selective deprotection of dimethyl ketal was accomplished by brief treatment with aqueous TFA (CH_2Cl_2, quant.) to give ketone **20**. Elimination of HBr from **20** was effected by mild treatment with DBU, and was followed by acid-catalyzed hydrolysis of the mixed ketal (90% aqueous TFA, CH_2Cl_2, 72% for two steps) to provide **21**. In light of the number of potentially competitive reactions, this transformation proceeded smoothly and cleanly to **21**. Base treatment of the corresponding bromohydrin, derived from the reaction of the [4 + 2] cycloadduct **18** with NBS−H_2O, failed to give the analogous elimination product and resulted instead in the formation of the remarkable and stable epoxide **25** (Scheme 4)

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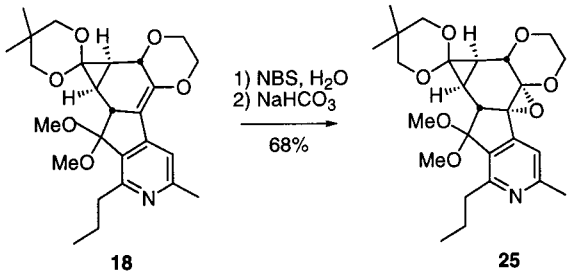
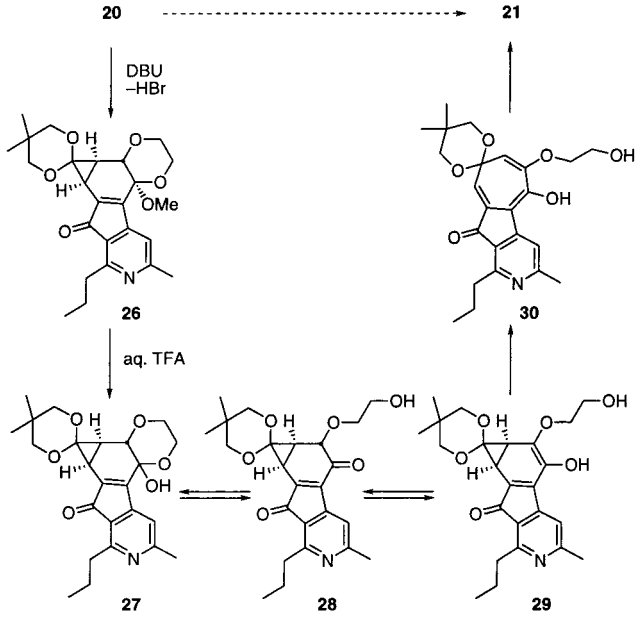
(29) The author has deposited the atomic coordinates for these structures with the Cambridge Crystallographic Data Centre, and these are allocated the deposition numbers (**18**: CCDC 147871, **25**: CCDC 147872, **19**: CCDC 147873). The coordinates may be obtained upon request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1 EZ, UK.

Scheme 4



Scheme 5



whose structure was established by X-ray analysis[29] (Supporting Information Figure 1c). Although not extensively investigated, treatment of either **19** or **25** with base under various conditions (*t*-BuOK, KOH, or DBU) gave no evidence of desired elimination product. Thus, ketone activation for elimination of HBr from **20** was required, and the subsequent formation of the cycloheptatrienone derivative **21** is derived from a reaction sequence that proceeds by mixed ketal hydrolysis (**26** → **27**), enolization with norcaradiene generation (**28** → **29**), electrocyclic rearrangement to the cycloheptatrienone ketal (**29** → **30**), and tautomerization to **21** (Scheme 5).

Subjection of **21** to hydrolysis (LiOH, THF−MeOH−H_2O 3:1:1, 99%) led to clean monodeprotection with selective generation of **22**. The remaining 2-hydroxyethyl ether of **22** could not be removed by either vigorous acid or base-catalyzed hydrolysis and was removed in a two-step sequence involving conversion of the alcohol to the primary bromide **23** (TMSBr, MeCN, 99%)[30] followed by reductive cleavage of the 2-bromoethyl ether (Zn, NH_4Cl, EtOH). Under these conditions, the benzylic ketone is also reduced, leading to the generation of **24**. Without purification or optimization, this crude alcohol was oxidized (NBS, DMSO) to provide **2** in 48% yield (two steps from **23**) completing the preparation of the rubrolone aglycon.

Experimental Section

2-Methyl-5-oxo-4-propyl-6,7-dihydro-*5H*-cyclopenta[*c*]pyridine (12). A solution of **11a**[31] (298 mg, 1.58 mmol) in triisopropylbenzene (35 mL) was stirred under Ar at 185 °C for 36 h. The reaction mixture was purified directly by column chromatography (SiO_2, 2 × 30 cm, 30% EtOAc−hexane) to give **12**[31] (132 mg, 70%) as white needles: mp 56−57 °C (EtOAc−hexane).

5,5-Dimethoxy-2-methyl-4-propyl-*5H*-cyclopenta[*c*]pyridine (13). A solution of **12** (1.30 g, 6.87 mmol) in MeOH (70 mL) was treated with KOH (3.85 g, 68.7 mmol) and $PhI(OAc)_2$ (4.43 g, 13.7 mmol), and the reaction mixture was stirred at 0 °C for 3 h. The reaction mixture was diluted with Et_2O (500 mL), and the mixture was washed with saturated aqueous NaCl (300 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was taken up in CH_2Cl_2 (70 mL) and treated with trifluoroacetic anhydride (1.94 mL, 13.7 mmol) and Et_3N (4.77 mL, 34.4 mmol), and the reaction mixture was stirred at 25 °C for 24 h. The reaction mixture was diluted with CH_2Cl_2 (200 mL), and the organic phase was washed with saturated aqueous $NaHCO_3$ (200 mL) and saturated aqueous NaCl (100 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography (SiO_2, 5 × 15 cm, 1% Et_3N and 20% EtOAc−hexane) afforded **13**[31] (1.04 g, 65%) as a light tan syrup.

7-Bromo-5,5-dimethoxy-2-methyl-4-propyl-*5H*-cyclopenta[*c*]pyridine (14). A solution of **13** (60 mg, 0.25 mmol) in CH_2Cl_2 (2.5 mL) was treated with Br_2 (79 mg, 0.5 mmol), and the reaction mixture was stirred at 0 °C for 2 h. The volatiles were removed in vacuo. The residue in DMF (2.5 mL) was treated with *t*-BuOK (1.0 M solution in THF, 0.75 mL, 0.75 mmol), and the reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was diluted with EtOAc (10 mL), and the organic phase was washed with H_2O (10 mL) and saturated aqueous NaCl (10 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography (SiO_2, 1 × 6 cm, 1% Et_3N and 20% EtOAc−hexane) afforded **14**[31] (71 mg, 91%) as a light tan syrup.

7-(1,4-Dioxen-2-yl)-5,5-dimethoxy-2-methyl-4-propyl-*5H*-cyclopenta[*c*]pyridine (16). A solution of **14** (53 mg, 0.17 mmol) and **15**[26] (76 mg, 0.20 mmol) in DMF−THF (1:4, 1.7 mL) was treated with $(Ph_3P)_4Pd$ (209 mg, 0.19 mmol), and the reaction mixture was stirred at 50 °C for 2 h. The reaction mixture was diluted with EtOAc (20 mL), and the mixture was washed with H_2O (20 mL) and saturated aqueous NaCl (10 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography (SiO_2, 1 × 8 cm, 1% Et_3N and 20% EtOAc−hexane) afforded **16**[31] (51 mg, 95%) as a light tan syrup.

Cycloadduct 18. Compound **16** (350 mg, 1.10 mmol) was treated with **17**[28] (403 mg, 2.88 mmol) at 25 °C for 45 min. Crystallization of the mixture from EtOAc−hexane afforded **18**[31] (420 mg, 84%) as colorless prisms. The filtrate was concentrated in vacuo, and flash chromatography of the mother liquors (SiO_2, 1 × 5 cm, 1% Et_3N and 33% EtOAc−hexane) afforded additional **18** (66 mg, 13%; 97% total) as a white solid: mp 164−166 °C (EtOAc−hexane).

Compound 19. A solution of **18** (280 mg, 0.61 mmol) in MeOH−THF (1:1, 5 mL) was treated with NBS (163 mg, 0.92 mmol), and the reaction mixture was stirred at 0 °C for 10 min before aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ (50 mL) were added. The reaction mixture was extracted with EtOAc (3 × 50 mL), and the organic layers were washed with saturated aqueous NaCl (30 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Crystallization of the residue from EtOAc−hexane afforded **19**[31] (280 mg, 80%) as colorless prisms: mp 153−155 °C (EtOAc−hexane).

Compound 20. A solution of **19** (100 mg, 0.17 mmol) in 20 mL of CH_2Cl_2 was treated with 90% aqueous TFA (500 μL), and the reaction mixture was stirred at 25 °C for 10 min before saturated aqueous $NaHCO_3$ (30 mL) was added. The mixture was extracted with CH_2Cl_2 (50 mL), and the organic layer was washed with saturated aqueous NaCl (30 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to afford **20**[31] (88 mg, quantative) as a colorless oil which was used without further purification.

2-[(2,2-Dimethyl-3-hydroxypropyl)oxy]-5,13-dioxo-9-methyl-11-propyl-4-[(2-hydroxyethyl)oxy]azuleno[2,3-*c*]pyridine (21). A solution of **20** (88 mg, 0.17 mmol) in 2 mL of CH_2Cl_2 was treated with DBU (31 μL, 2.0 mmol), and the reaction mixture was stirred at 0 °C for 10 min. The mixture was diluted with CH_2Cl_2 (20 mL), and the

(30) Treatment of **24** with NBS and PPh_3 gave only a trace of **25**, whereas NBS/PBu_3 effectively provided **25** although it was difficult to isolate free of reaction byproducts. Bates, H. A.; Farina, J.; Tong, M. *J. Org. Chem.* **1986**, *51*, 2637.

(31) Full details of the preparation and characterization of **4**−**11** and full characterization data for **12**−**14**, **16**, **18**−**23**, and **2** are provided in the Supporting Information.

organic layer was washed with saturated aqueous NaCl (10 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. A solution of the residue in 2 mL of CH_2Cl_2 was treated with 90% aqueous TFA (200 μL), and the reaction mixture was stirred at 25 °C for 1 h before addition of saturated aqueous $NaHCO_3$ (30 mL). The mixture was extracted with $CHCl_3$ (30 mL), and the organic layer was washed with saturated aqueous NaCl (10 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography (SiO_2, 1 × 4 cm, 2% MeOH−$CHCl_3$) afforded **21**[31] (52 mg, 72%) as a yellow powder.

5,13-Dioxo-2-hydroxy-9-methyl-11-propyl-4-[(2-hydroxyethyl)-oxy]azuleno[2,3-*c*]pyridine (22). A suspension of **21** (21.3 mg, 0.05 mmol) in 2 mL of THF−MeOH−H_2O(3:1:1) was treated with LiOH·H_2O (10.5 mg, 0.25 mmol), and the reaction mixture was stirred at 50 °C for 2 h. The mixture was cooled to 0 °C, and the THF was removed under a stream of N_2. The yellow precipitate was collected by filtration to afford **22**[31] (17.0 mg, 99%) as a yellow powder.

5,13-Dioxo-2-hydroxy-9-methyl-11-propyl-4-[(2-bromoethyl)oxy]-azuleno[2,3-*c*]pyridine (23). A suspension of **22** (4.0 mg, 0.012 mmol) in 2 mL of CH_3CN was treated with TMSBr (23 μL, 0.18 mmol), and the reaction mixture was warmed at reflux for 3 h. The mixture was cooled and washed with hexane (3 × 4 mL), and the CH_3CN layer was concentrated in vacuo to afforded **23**[31] (4.9 mg, quantitative) as a yellow solid sufficiently pure to use directly in the next reaction.

Rubrolone Aglycon (2). A solution of **23** (2.0 mg, 4.9 μmol) in 1 mL of EtOH was treated with Zn (3.2 mg, 49.6 μmol) and NH_4Cl (2.7 mg, 49.6 μmol), and the reaction mixture was stirred at 60 °C for 3 h. The reaction mixture was filtered, and the filtrate was concentrated in vacuo. A solution of the residue containing **24** in 0.5 mL of DMSO was treated with NBS (5.5 mg, 24.5 μmol), and the reaction mixture was stirred at 25 °C for 1 h before H_2O was added. The reaction mixture was concentrated in vacuo. Flash chromatography (reverse phase, 1 × 4 cm, 20% H_2O−MeOH) afforded **2**[31] (0.7 mg, 48%) as an orange solid identical in all respects with properties reported for authentic material.[4]

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Supporting Information Available: Full experimental details and characterization for **4**−**11** and full characterization data for **12**−**14**, **16**, **18**−**23** and **2**, and Supporting Information Figure 1a−c (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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