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Elimination of Butylcycloheptylprodigiosin as a Known Natural Product Inspired by an Evolutionary Hypothesis for Cyclic Prodigiosin Biosynthesis

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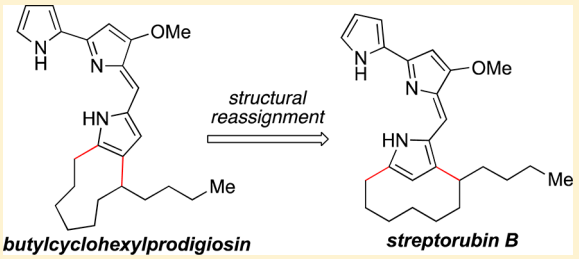
Supporting Information

ABSTRACT: The cyclic prodigiosins are an important family of bioactive natural products that continue to be the subject of numerous structural, synthetic, and biosynthetic studies. In particular, the structural assignments of the isomeric cyclic prodigiosins butylcycloheptylprodigiosin (BCHP) and streptorubin B have been the cause of significant confusion. Herein, we report detailed studies regarding the electron impact (EI) mass spectra of synthetic BCHP and streptorubin B that have allowed us to distinguish the two compounds in the absence of quality historical isolation NMR data. On the basis of these fragmentation differences, the status of BCHP as a natural product is challenged. The proposed mechanism of fragmentation is supported by the EI mass spectra of synthetic pentyl-chain analogues of BCHP and streptorubin B, X-ray crystallography, and DFT calculations. Elimination of BCHP from the prodigiosin family supports a proposed evolutionary hypothesis for the surprising biosynthesis of cyclic prodigiosins.



The prodigiosins are a family of bacterially produced natural products that possess a defining tripyrrolic core.[1] This tripyrrolic core is believed to be responsible for the wide range of interesting properties that the prodigiosins display, such as anion transport, radical generation, cation binding, and protein binding.[2] These physical properties are further responsible for the potentially useful biological activities that the prodigiosins display, including immunosuppressive, anticancer, and antiparasitic activities.[3] A prodigiosin-inspired medicinal chemistry program at Gemin X led to the development of a synthetic small-molecule pro-apoptotic factor that is currently in multiple phase I and II clinical trials for the treatment of a variety of cancers.[4]

Bacteria biosynthesize pyrrolophane prodigiosins such as streptorubin B (**2**) and metacycloprodigiosin (**3**) through a Rieske-oxygenase (RedG or McpG)-mediated radical cyclization from a common linear precursor, undecylprodigiosin (UDP, **1**).[5] These oxidative cyclizations are remarkable given the high degree of strain present within the products, leading us to speculate about the impact of the structural differences between UDP (**1**) and its cyclized products (i.e., **2** and **3**). We hypothesized that the evolutionary purpose of this additional cyclization step may be due to advantageous enforcement of the geometry necessary for anion or cation binding (Figure 2).

For the pyrrolophanes streptorubin B (**2**) and metacycloprodigiosin (**3**) cyclization introduces a source of conformational bias that is not present within UDP (**1**), which should lead to a predisposition for anion or cation binding (i.e., A vs B, Figure 2).[6] In fact, each cyclic prodigiosin so far discovered has possessed this conserved structural characteristic, introduced by either cyclization to C4 of the C-ring pyrrole or to C5 of the distal A-ring pyrrole (Figure 3).[7]

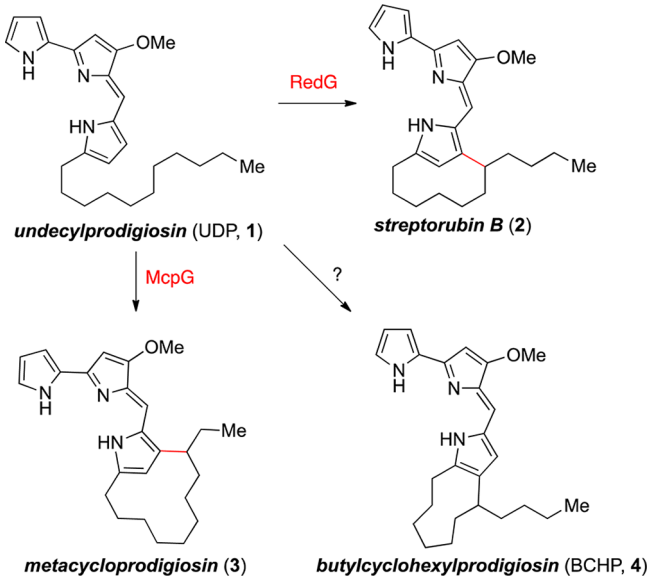


Figure 1. Biosynthesis of cyclic prodigiosins.

Therefore, the appearance of butylcycloheptylprodigiosin (BCHP, **4**) as an apparent natural product is intriguing, as this molecule would not appear to provide a significant conforma-

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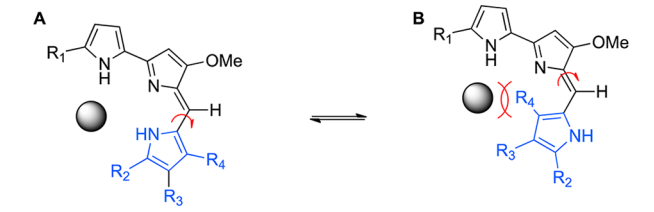


Figure 2. Enforced conformations of cyclic prodigiosins.

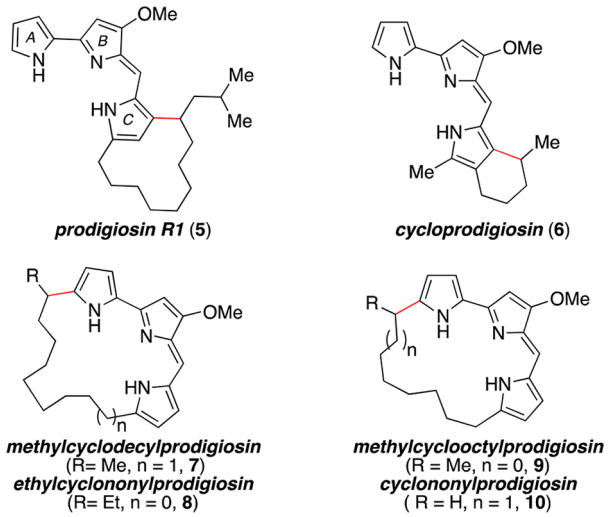


Figure 3. Conserved structural trends for cyclic prodigiosins.

tional (and, hence, evolutionary) advantage over its likely linear progenitor, (i.e., UDP, **1**). Among all known cyclic prodigiosin structures, BCHP (**4**) stands alone in this respect, which led us to reconsider its assignment as an actual natural product.

Historically, there has been some significant confusion as to whether BCHP is a natural product or not. The structure **4** was first proposed for a pink pigment isolated from *Streptomyces* sp. Y-42 and *S. rubrireticuli* by Gerber in 1975,[8] but she reassigned the structure of this compound to that of **2** (i.e., streptorubin B) in 1978.[9] In 1985, Floss and co-workers assigned the structure **4** to a pink pigment they isolated from *Streptomyces coelicolor* A3(2).[10] Given that Gerber had reassigned the structure of the pink pigment she isolated from **4** to **2**, there was some doubt regarding the actual structure of Floss's pink pigment. To provide insight into this quandry, Fürstner and co-workers synthesized BCHP (**4**) in 2005 and concluded that BCHP (**4**) was a natural product distinct from streptorubin B (**2**).[11] They came to this conclusion based on comparisons between their NMR data and that of the authentic pigment, despite commenting that the authentic spectrum was not entirely pure. Reeves supported this conclusion in his 2007 article.[12] Following these synthetic studies, Challis and co-workers reported the isolation of a cyclic prodigiosin from *S. coelicolor* M511 [a prototrophic derivative of *S. coelicolor* A3(2) lacking plasmids and the ability to produce actinorhodin] and identified it as streptorubin B (**2**), not BCHP (**4**).[13] The findings by Challis are at odds with the report by Floss and the subsequent confirmation of the BCHP structure by both Fürstner and Reeves. However, given that the organism Challis and co-workers studied was not exactly the same as the one Floss isolated the pink pigment from, there still remains room for doubt regarding the formulation of a definitive statement as to whether BCHP (**4**) is a natural product or not.

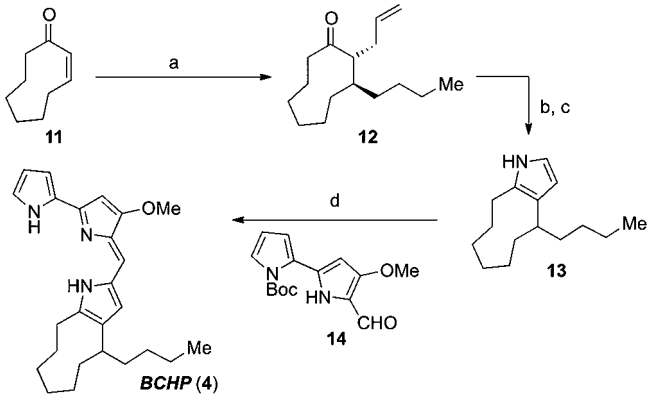
Because of our own interests in the synthesis, structure, and biosynthesis of the cyclic prodigiosins,[14] and in light of our evolutionary hypothesis (see above), we were motivated to reinvestigate the BCHP/streptorubin B question. The results of our structural investigations into BCHP (**4**) and its relationship to streptorubin B (**2**) are reported herein.

RESULTS AND DISCUSSION

As part of our interest in the synthesis of prodigiosins, we had previously completed an enatioselective total synthesis of streptorubin B (**2**).[14b] Curiously, we observed that the EI mass spectrum of streptorubin B (**2**) matched the EI mass spectrum of the pink pigment isolated by Floss (i.e., BCHP, **4**).[15] While streptorubin B (**2**) and BCHP (**4**) bear some structural resemblance to one another, it seemed unlikely to us that they would have identical fragmentation patterns. We suspected that the strained *meta*-fusion of the pyrrolophane core of streptorubin B (**2**) would provide a characteristic fragmentation pattern that would be distinct from the *ortho*-linked pyrrole core of BCHP (**4**) and that perhaps a detailed analysis of mass spectra of the two compounds might finally answer the BCHP/streptorubin B question for good.

First, we sought to design a short synthesis of BCHP (**4**) that would quickly provide us with the material we needed. Previously, our research group had synthesized the pyrrolophane prodigiosins metacycloprodigiosin (**3**), prodigiosin R1 (**5**), and streptorubin B (**2**),[14] and due to the ease with which we were able to prepare **2** using a late-stage "biomimetic" condensation,[16] we sought to employ a similar strategy in the preparation of BCHP. Our synthesis was initiated with a one-pot conjugate-addition/Tsuji–Trost allylation[17] on cyclononen-2-one (**11**) to afford compound **12** as a single diastereomer (Scheme 1). Subjecting the resulting alkene (i.e., **12**) to Lemieux–Johnson oxidation[18] conditions afforded a 1,4-dicarbonyl, which underwent smooth Paal–Knorr condensation[19] with ammonium acetate to provide *ortho*-substituted pyrrole **13**. A one-step condensation/deprotection sequence between pyrrole **13** and bispyrrole-aldehyde **14**[20] cleanly afforded the desired compound **4** as either the free base

Scheme 1. Synthesis of BCHP (5)



[a]Reagents and conditions: *n*-BuMgCl, CuBr·DMS (20 mol %), −40 °C; then allylBr, $Pd(PPh_3)_4$ (10 mol %), 85%. [b]OsO_4 (3 mol %), $NaIO_4$, EtOAc/H_2O, 73%. [c]NH_4OAc, MeOH, reflux 98%. [d]HCl, **14**; then NaOMe, MeOH, 80%.

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or the hydrochloride salt depending on isolation conditions (four steps from **11**, 49% overall yield).

NMR spectroscopic data (^{1}H NMR, ^{13}C NMR) of **4** were identical to those reported by both Fürstner[11] and Reeves[12] for synthetic BCHP (**4**), but there were discrepancies between our ^{1}H NMR data and that of the ^{1}H NMR spectrum of the authentic pigment.[15] Although the spectrum of synthetic BCHP (**4**) and the authentic spectrum had some similar features, comparisons to streptorubin B (**2**) were likewise similar. On the basis of NMR data alone, and in contrast to previous findings,[11,12] we do not believe a definitive conclusion can be made as to whether BCHP is a natural product or not.

While the NMR data were not convincing, the electron impact (EI) mass spectra of synthetic BCHP (**4**) and streptorubin B (**2**) were, as we had hoped, characteristically distinct.[21] Direct probe of the HCl salts of BCHP and streptorubin B revealed idiosyncratic differences in the % abundance of early fragments from the parent ion $[M]^{+\bullet}$, *m*/*z* 391 (expanded section shown in Figure 4).

We noted a reproducible (n = 5) pattern of the relative abundance between the *m*/*z* 376 $[M - CH_3]^+$, *m*/*z* 348 $[M - C_3H_7]^+$, and *m*/*z* 334 $[M - C_4H_9]^+$ ions. Most striking was the change in relative abundance of the ions from the loss of propyl and butyl for each molecule. For BCHP (**4**), $[M - C_3H_7]^+$ and $[M - C_4H_9]^+$ were 9% and 41%, respectively. In contrast, for streptorubin B (**2**) $[M - C_3H_7]^+$ and $[M - C_4H_9]^+$ were 25% and 13%, respectively. Thus, BCHP (**4**) undergoes more favorable loss of butyl relative to propyl, while for streptorubin B (**2**) the opposite is true. The EI mass spectra reported for the pink pigments isolated by both Gerber[8] and Floss[10] display the same characteristic relative abundance of these key fragment ions in 70 eV EI-MS as streptorubin B (**2**) and not BCHP (**4**). Thus, in light of these data we concluded that the pink pigment isolated by Floss was in fact streptorubin B (**2**) and not BCHP (**4**). On the basis of this information we conclude that butylcycloheptylprodigiosin (**4**) is, at this time, not a known natural product.

We were curious as to why the relative abundances of the peaks corresponding to the loss of propyl and butyl were so different between streptorubin B (**2**) and BCHP (**4**). These two compounds are constitutional isomers wherein the point of attachment of the undecyl-hydrocarbon chain to the pyrrole differs: *ortho* for BCHP (**4**) and *meta* for streptorubin B (**2**). This seemingly trivial difference has dramatic effects on the corresponding structures, however. Specifically, the strained *meta*-cyclophane nature of streptorubin B's 10-membered ring leads to significant distortion of the σ-bonds attached to the pyrrole nucleus. An X-ray structure we obtained of **2**·HCl revealed substantial pyramidalization of the pyrrole carbons attached to the *meta*-bridge (between 21° and 24° from planarity) (see Figure 5).[14b,22] Such deformation is not present within the X-ray structure of **4**·HCl that we were also able to obtain, since the nine-membered ring is *ortho*-fused and does not suffer the additional strain that *meta*-fusion engenders.[22]

On the basis of this structural analysis, we hypothesized that cleavage of the *meta* carbon−carbon bond adjacent to the butyl side chain within streptorubin B (**2**) would be more favorable during fragmentation of the molecular ion (i.e., **15**) under EI conditions for mass spectrometry (Figure 6). Following this logic, we rationalized the higher abundance of *m*/*z* 348 $[M - C_3H_7]^+$ (i.e., **16** or **17**) relative to *m*/*z* 334 $[M - C_4H_9]^+$ (i.e., **18**). Loss of propyl from $[M]^{+\bullet}$ **15**, shown in Figure 6, with concomitant rupture of the cyclophane ring leads to fragment **16** or **17**, which due to strain release should be kinetically more favorable than the corresponding loss of butyl to form **18** from $[M]^{+\bullet}$ **15**′. In contrast to streptorubin B (**2**), BCHP (**4**) undergoes a more favorable loss of butyl from $[M]^{+\bullet}$ **19**′ to

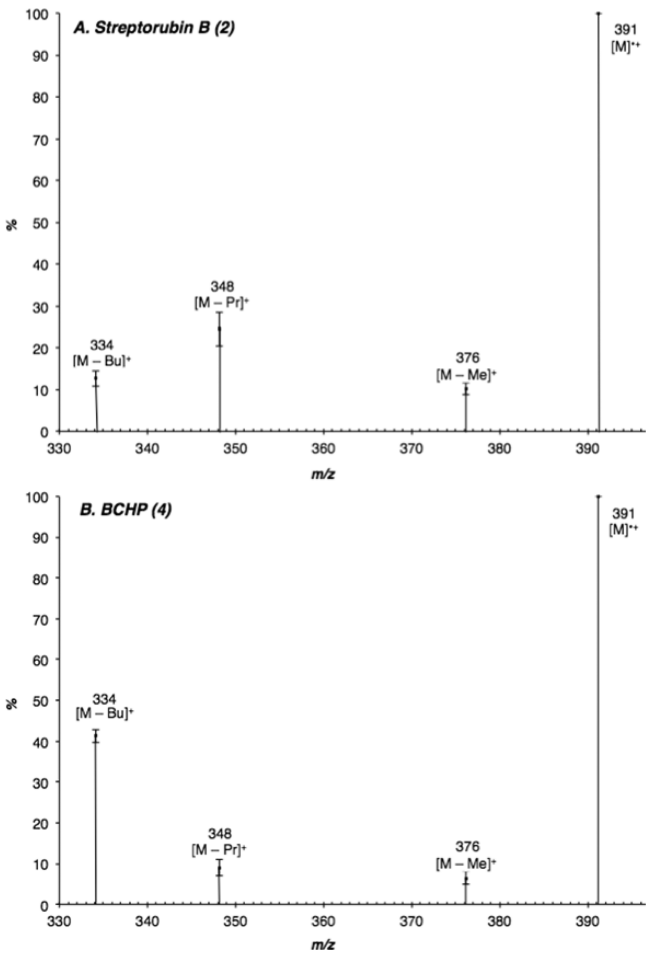

Figure 4. Higher molecular weight fragments within electron impact mass spectra of (A) streptorubin B (**2**) and (B) BCHP (**4**). Error bars show one standard deviation of measured value from five separate runs.

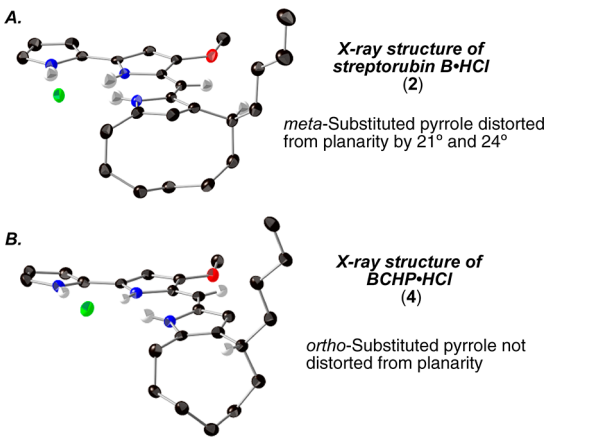

Figure 5. (A) X-ray crystal structure of streptorubin B·HCl (**2**). (B) X-ray crystal structure of BCHP·HCl (**4**).

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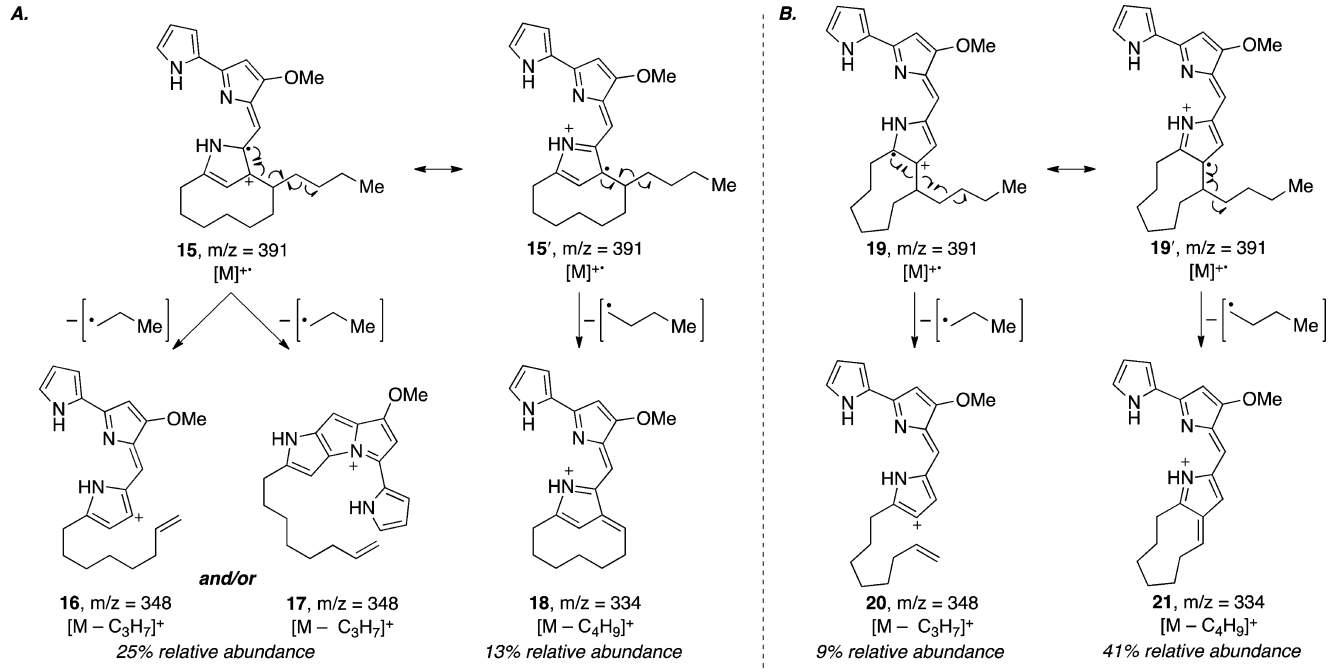

Figure 6. Mechanistic hypothesis for electron impact mass spectrometry fragmentations: (A) streptorubin B; (B) BCHP.

generate fragment **21**. The driving force for scission of the *ortho*-linked nine-membered ring within **4** is reduced relative to **2**, and therefore loss of propyl to produce **20** occurs with lower frequency.

We provided evidence that these ions in the EI mass spectra are derived specifically from fragmentation of the aliphatic side chains by synthesizing pentyl homologues of streptorubin B and BCHP, namely, STRB-5C (**22**) and PCHP (**23**).[23] For each pentyl homologue we observed the same trend of fragmentation patterns using EI mass spectrometry as we had seen for the butyl series (Figure 4).

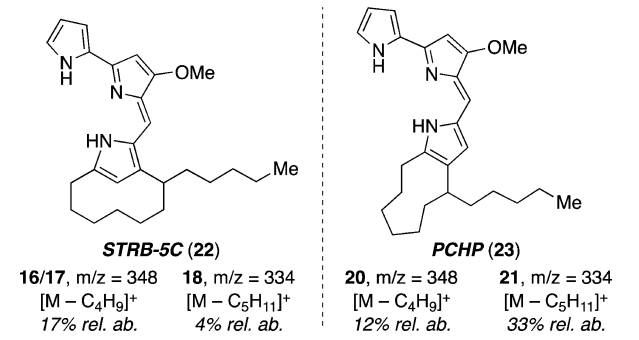

Figure 7. Relevant EI fragmentation data for the pentyl homologues of streptorubin B and BCHP, STRB-5C (**16**) and PCHP (**17**).

Loss of butyl was now favored for the streptorubin B homologue **22** (i.e., to form **16**/**17**), while loss of pentyl was favored for the BCHP homologue **23** (i.e., to form **21**).

Density functional theory (DFT) calculations were conducted to gain some insight into the stability of these proposed molecular fragments. Structure optimizations using Q-Chem[24] at the B3LYP/6-31+G* level of theory provided the relative energies shown in Figure 5. As expected, the ground-state energy minimizations indicated that streptorubin B (**2**) was higher in energy than BCHP (**4**), most likely due to the aforementioned ring strain induced by the *meta*-bridge. This energy difference is reflected in the relative energies of the radical-cation molecular ions for each compound (i.e., **15**/**15′** and **19**/**19′**). Loss of butyl from each molecular ion produces fragments **18** and **21** through a process that is endothermic by 52 and 57 kcal·mol^{-1}, respectively. The corresponding fragmentations of each molecular ion to generate ring-opened ions **16** and **20** were calculated as being endothermic by 98 and 131 kcal·mol^{-1}, respectively. For the case of BCHP (**4**), the thermodynamic difference in energy between **20** and **21** is reflected in the observed relative abundances of each ion in the EI mass spectrum. For streptorubin B (**2**), however, the energy difference between the corresponding fragments (i.e., **16** and **18**) is not reflected in their relative abundance. We considered the cyclized structure **17** in our analysis, which intuitively appeared to be a better candidate fragment than the sp^2-cation **16**. Indeed, energy minimization of **17** showed it was significantly more stable than both **16** and **18** and was only 27 kcal·mol^{-1} higher in energy than the molecular ion **15**/**15′**. The analogous cyclized structure cannot form from BCHP (**4**) due to geometric constraints, and it is therefore tempting to conclude that the higher abundance of the *m*/*z* 348 ion in the mass spectrum of streptorubin B (**2**) is due to the formation of stable fragment **17**. We conclude that a combination of this thermodynamic driving force, coupled to the facile kinetic scission of the strained *meta*-pyrrolophane ring system within streptorubin B (**2**), accounts for the observed fragmentation patterns.

CONCLUSIONS

Our studies into the structural assignment of BCHP (**4**) were motivated by a proposed evolutionary hypothesis for the biosynthesis of the cyclic prodigiosins. These studies, which involved detailed mass spectral analysis of BCHP (**4**) and streptorubin B (**2**), have concluded that BCHP (**4**) was not the compound isolated from *S. coelicolor* A3(2) by Floss in 1985. This species was in fact streptorubin B (**2**), as indicated by

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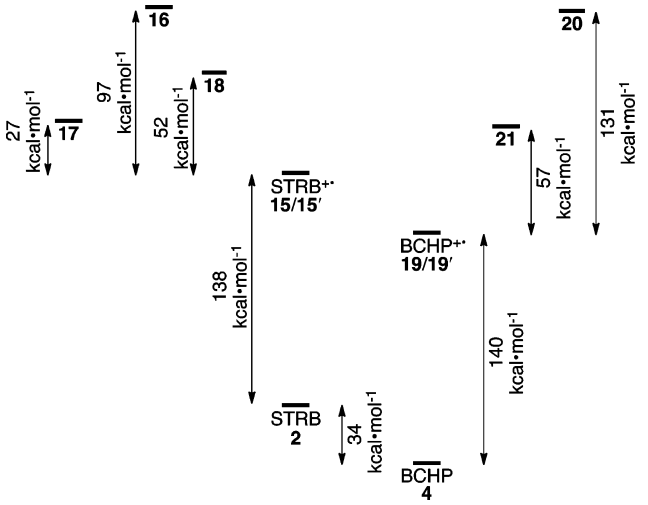

Figure 8. Relative energies of fragments calculated using Q-Chem (B3LYP/6-31+G* level). Energies for **16**, **17**, **18**, **20**, and **21** include the lost neutral radical fragment (i.e., Pr· or Bu·).

identical EI-MS fragmentation patterns, a finding that supports the 2008 isolation study by Challis and co-workers.[25] If BCHP (**4**) was a natural product produced by *S. coelicolor* A3(2), there should be a second Rieske-oxygenase encoded within its genome that is analogous to the recently determined sequence that encodes the conversion of undecylprodigiosin (**1**) into streptorubin B (**2**), i.e., *redG*.[5,25] No such homologous sequence has been found within *S. coelicolor* A3(2).[26] Furthermore, constitutive expression of *redG* in an engineered mutant of *S. veneuzelae* (a bacteria that does not contain the prodigiosin gene cluster) converts undecylprodigiosin (**1**) into streptorubin B (**2**) with no evidence of BCHP (**4**) production.[5] The combination of our mass spectral comparisons with this genetic and biochemical data provides overwhelming evidence that BCHP (**4**) is not a natural product produced by *S. coelicolor*. Further studies of these fascinating molecules will hopefully provide insights into the as yet unanswered questions surrounding their tightly regulated biosynthesis and their possible evolutionary purpose. Studies regarding the difference in anion- and cation-binding properties of the naturally occurring cyclic vs acyclic prodigiosins, which are ongoing in our laboratories, will shine light on these questions. The results of these studies will be reported in due course.

EXPERIMENTAL SECTION

General Experimental Procedures. All reactions were carried out under a nitrogen atmosphere in flame-dried glassware with magnetic stirring unless otherwise stated. THF and CH_2Cl_2 were purified by passage through a bed of activated alumina. Reagents were purified prior to use unless otherwise stated. Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230−400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and anisaldehyde followed by heating. Film infrared spectra were recorded using a BioRad Excalibur and a BioRad FTS-60. Diamond infrared spectra were recorded using a Thermo Mattson ATR. ^{1}H NMR spectra were recorded on a Bruker Advance III 500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm) or tetramethylsilane (0.00 ppm). Two-dimensional NMR experiments were run on a Bruker Advance III 500 (500 MHz). Data are reported as follows: app = apparent, obs = obscured, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = hextet, sep = septet, o = octet, m = multiplet, br = broad; integration; coupling constant(s) in Hz. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker Advance III 500 (125 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.00 ppm). Mass spectral data were obtained on an Agilent 6210 time-of-flight LC/MS and a Waters GC-TOF Premier high-resolution time-of-flight MS with an EI source.

A. Synthesis of *ortho*-Butylcycloheptylprodigiosin. *trans-2-Allyl-3-(n-butyl)cyclononanone (**12**).* To a stirred suspension of CuBr·DMS (30 mg, 0.14 mmol) in THF (3 mL) at −40 °C was added *n*-BuMgCl (1.5 M in THF, 528 μL, 1.1 equiv). The suspension was stirred for 10 min before cyclonon-2-enone (100 mg, 0.72 mmol) was added dropwise in THF (1.5 mL). The solution became homogeneous and bright yellow before turning heterogeneous and black upon complete addition. After 45 min freshly distilled allyl bromide (182 μL, 2.16 mmol) was quickly added, followed by addition of solid $Pd(PPh_3)_4$ (83 mg, 0.07 mmol). The mixture was allowed to warm to room temperature and stir for an additional 6 h. The solution was quenched with aqueous AcOH (2 mL) and diluted with Et_2O (3 mL). The organic phase was separated, and the aqueous layer extracted with Et_2O (3 × 5 mL). The organic layers were combined, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (20% EtOAc in hexanes, silica gel) to afford the title compound (145 mg, 85%). IR (neat) 2955, 2929, 2873, 1703, 1476, 1356, 995, 914; ^{1}H NMR (500 MHz, $CDCl_3$) 5.59 (dddd, 1H, *J* = 17.1, 10.0, 8.1, 6.1 Hz), 4.92 (dd, 1H, *J* = 17.1, 1.1 Hz), 4.88 (dd, 1H, *J* = 10.0, 1.1 Hz), 2.47 (m, 2H), 2.29 (m, 1H), 2.14 (m, 2H), 1.82 (m, 1H), 1.62 (m, 1H), 1.54 (m, 1H), 1.48−1.16 (m, 14H), 0.83 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 218.6, 136.2, 116.7, 57.9, 42.5 (br), 39.2, 35.7, 32.4, 28.4, 27.3, 24.0, 23.5, 23.4, 23.0, 22.9, 14.1; HRMS (EI^+) exact mass calcd for $C_{16}H_{28}O$ [M^+] 236.2140, found 236.2148.

*trans-2-(Acetaldehyde)-3-(n-butyl)cyclononanone (**24**).* To a stirred solution of allylcyclononanone **6** (38 mg, 0.16 mmol) in EtOAc (0.75 mL) were added $NaIO_4$ (76 mg, 0.35 mmol), OsO_4 (2.5 wt % in *t*-BuOH, 204 mg, 0.016 mmol), and H_2O (0.75 mL). The solution was stirred vigorously overnight before being partitioned between Et_2O (3 mL) and brine (3 mL). The organic layer was separated, and the aqueous layer extracted with Et_2O (3 × 3 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (20% EtOAc in hexanes, silica gel) to afford the title compound (28 mg, 73%). IR (neat) 2932, 2872, 2721, 1723, 1702, 1467, 1382, 1240, 1043; ^{1}H NMR (500 MHz, $CDCl_3$) 9.69 (s, 1H0, 2.98 (m, 2H0, 2.79 (ddd, 1H, *J* = 14.8, 7.3, 5.6 Hz), 2.68 (m, 1H), 2.56 (m, 1H), 1.80 (m, 2H), 1.70 (m, 1H), 1.59 (m, 1H), 1.53−1.16 (m, 14H), 0.88 (t, 3H, *J* = 8.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 201.2, 50.4, 46.8, 45.7, 40.9, 33.3, 31.6, 28.2, 27.3, 26.5, 25.2, 24.7, 23.6, 22.9, 22.6, 14.1; HRMS ($APPI^+$) exact mass calcd for $C_{15}H_{28}O_2$ [M + H^+] 239.2010, found 239.2010.

*3-(n-Butyl)-ortho-cyclononylpyrrole (**13**).* To a solution of dicarbonyl **24** (65 mg, 0.273 mmol) in dry MeOH (3 mL) was added azeotropically dried NH_4OAc (210 mg, 2.73 mmol). The solution was refluxed (65 °C) for 30 min before being cooled to room temperature and diluted with hexanes (7 mL). The solution was directly subjected to flash column chromatography (20% EtOAc in hexanes, silica gel) to afford the title compound as a clear oil (59 mg, 98%). IR (neat) 3377, 2923, 2853, 1686, 1457, 1082; ^{1}H NMR (500 MHz, $CDCl_3$) 7.65 (br s, 1H), 6.65 (t, 1H, *J* = 2.66 Hz), 5.96 (t, 1H, *J* = 2.8 Hz), 2.70 (m, 1H), 2.66 (m, 2H), 1.87 (m, 1H), 1.66−1.28 (m, 14H), 1.03 (m, 1H), 0.89 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 129.6, 122.8, 115.0, 106.2, 37.16, 36.7, 35.8, 30.5, 27.7, 27.3, 27.0, 26.9, 23.4, 22.9, 14.2; HRMS ($APPI^+$) exact mass calcd for $C_{15}H_{26}N$ [M + H^+] 220.2060, found 220.2067.

*ortho-Butylcycloheptylprodigiosin (BCHP, **4**).* To a solution of pyrrole **14** (7.5 mg, 0.34 mmol) and bispyrrole aldehyde **8**[20] (12 mg, 1.2 equiv) in MeOH (1 mL) was added dry HCl in MeOH (1 M, 34 μL, 1 equiv, freshly prepared from AcCl and MeOH) at 0 °C. The solution immediately turned a deep red color and was allowed to stir for 1 h 15 min. A suspension of NaOMe (36 mg) in MeOH (0.66 mL)

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was then added, causing the solution to turn dark orange. The reaction was monitored by LCMS, and after 1 h, the solution was poured into ether (10 mL), washed with brine (5 mL), and dried over Na_2SO_4. The organic phase was concentrated in vacuo, and the residue was purified by flash column chromatography (gradient: 5% to 20% EtOAc in hexanes with 2% NEt_3, silica gel) to afford the title compound as a dark orange solid (10.6 mg, 80%). IR (neat) 3112, 2922, 2853, 1624, 1555, 1467, 1378, 1346, 1287, 1233; ^{1}H NMR (500 MHz, CD_2Cl_2) 6.73 (s, 1H), 6.61 (s, 1H), 6.59 (s, 1H), 6.25 (s, 1H), 6.09 (t, 1H, J = 2.7 Hz), 6.01 (s, 1H), 3.88 (s, 3H), 2.46 (m, 1H), 2.16 (br s, 2H), 1.56 (m, 1H), 1.48−1.40 (m, 4H), 1.23 (m, 2H), 1.18−1.04 (m, 7H), 0.75 (t, 3H, J = 7.6 Hz), 0.66 (br m, 1H); ^{13}C NMR (125 MHz, CD_2Cl_2) 169.4, 159.8, 143.2, 138.8, 129.1, 128.3, 128.1, 122.5, 118.9, 116.5, 112.6, 110.5, 95.9, 58.9, 38.1, 37.0, 36.0, 30.6, 28.2, 28.1, 27.6 (2), 23.3, 23.1, 14.2; HRMS (ESI$^+$) exact mass calcd for $C_{25}H_{34}N_3O$ [M + H$^+$] 392.2696, found 392.2703.

The HCl salt of **4** was obtained using the same procedure but by purifying the product by silica gel chromatography under different conditions (gradient: $CHCl_3$ to 1% MeOH/$CHCl_3$, silica gel) (11 mg of **4**·HCl from 6 mg of **7**, 95%). IR (neat) 3156, 2953, 2869, 1632, 1602, 1572, 1346, 1268, 1115, 962; ^{1}H NMR (500 MHz, $CDCl_3$) 12.80 (s, 1H), 12.63 (s, 2H), 7.25 (s, 1H), 7.00 (s, 1H), 6.94 (s, 1H), 6.65 (d, 1H, J = 3 Hz), 6.37 (s, 1H), 6.10 (s, 1H), 4.03 (s, 3H), 3.35 (m, 1H), 2.76 (m, 2H), 2.15 (m, 1H), 1.71 (m, 2H), 1.63−1.58 (m, 4H), 1.45−1.38 (m, 4H), 1.30−1.22 (m, 4H), 1.14 (m, 1H), 0.88 (t, 3H, J = 7.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 165.9, 153.0, 147.8, 132.5, 127.1, 126.6, 125.8, 122.4, 120.8, 117.2, 116.2, 111.8, 92.9, 58.6, 37.0, 36.6, 35.9, 30.1, 27.3, 27.1, 26.9, 26.6, 23.6, 22.7, 14.1.

B. Synthesis of Streptorubin B-5C (STRB-5C). *trans-2-((Z)-Hept-1-enyl)cyclohexanol (**25**).* To a solution of heptanedial (0.26 g, 2 mmol) in dichloromethane (20 mL) was added (*rac*)-proline (23 mg, 0.2 mmol) at room temperature. The heterogeneous mixture was stirred for 15 h, after which the solution became clear and homogeneous. To a heterogeneous solution of hexyltriphenylphosphonium bromide (1.11 g, 2.6 mmol) in THF (20 mL) at 0 °C was added sodium hexamethyldisilazane (2.6 mL, 2.6 mmol, 1 M in THF), upon which the solution turned bright orange. The ylide solution was allowed to stir for 1 h 20 min prior to addition of aldehyde solution via cannula at 0 °C, upon which the solution turned cloudy and white. After 3 h, the reaction mixture was quenched with saturated NH_4Cl (20 mL), and the ether layer separated. The aqueous/halogenated layers were extracted with Et_2O (3 × 20 mL), washed with brine (60 mL), and dried with $NaSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% Et_2O in hexanes, silica gel) to afford the title compound as a 5:1 mixture of diastereomers (260 mg, 66%). IR (neat) 3430, 2998, 2927, 2856, 1449, 1076 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63−5.55 (dt, J = 11.2, 7.4 Hz, 1H), 5.21−5.12 (ddt, J = 11.3, 9.8, 1.6 Hz, 1H), 3.24−3.15 (m, 1H), 2.28−2.17 (dtd, J = 12.9, 9.8, 3.7 Hz, 1H), 2.14−1.98 (m, 4H), 1.86−1.81 (d, J = 1.9 Hz, 1H), 1.81−1.74 (dt, J = 8.1, 2.7 Hz, 1H), 1.69−1.56 (m, 4H), 1.45−1.19 (m, 13H), 1.19−1.07 (tdd, J = 13.3, 11.3, 3.6 Hz, 1H), 0.92−0.85 (t, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.47, 131.55, 73.83, 44.85, 33.48, 31.51, 31.45, 29.62, 27.79, 25.26, 24.85, 22.58, 14.08; HRMS (TOF EI$^+$) exact mass calcd for $C_{13}H_{24}O$ [M$^+$] 196.1827, found 196.1812.

*(Z)-2-(Hept-1-enyl)cyclohexanone (**26**).* To a solution of freshly distilled oxalyl chloride (75 μL, 0.86 mmol) in DCM (3 mL) at −78 °C was added dropwise DMSO (70 μL, 0.99 mmol). The solution was stirred for 5 min, after which a solution of secondary alcohol **25** (140 mg, 0.71 mmol) in DCM (3 mL) was added. The solution was stirred for 20 min, followed by addition of *i*-Pr_2NEt (0.618 mL, 3.55 mmol) dropwise. The solution was stirred for 10 min before being warmed to 0 °C in an ice bath. The solution was further stirred at 0 °C for 30 min, then poured into H_2O (15 mL). The organic phase was collected, and the aqueous layer extracted with DCM (2 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash chromatography (10% EtOAc in hexanes, silica gel) afforded the title compound (92 mg, 67%): IR (neat) 2930, 2859, 1712, 1449, 1340, 1310, 1126 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.61−5.48 (m, 2H), 3.33−3.21 (dddd, J = 10.7, 7.7, 5.6, 1.2 Hz, 1H), 2.52−2.38 (dtd, J = 13.8, 4.3, 1.3 Hz, 1H), 2.38−2.25 (dddd, J = 14.1, 12.9, 7.1, 4.3 Hz, 1H), 2.11−1.82 (m, 5H), 1.82−1.56 (m, 3H), 1.46−1.18 (m, 7H), 0.95−0.83 (t, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.52, 132.38, 126.38, 77.29, 77.23, 77.03, 76.78, 49.43, 41.77, 34.94, 31.49, 29.22, 27.75, 27.57, 24.44, 22.56, 14.07; HRMS (ESI) exact mass calcd for $C_{13}H_{23}O$ [M + H$^+$] 195.1743, found 195.1752.

*trans-1-((E)-3-(Benzyloxy)prop-1-enyl)-2-((Z)-hept-1-enyl)-cyclohexanol (**27**).* To a solution of (*E*)-1-benzyloxy-3-iodo-2-propene[27] (96 mg, 0.35 mmol) in Et_2O (4.5 mL) at −78 °C was added a solution of *n*-BuLi in hexanes (135 μL, 2.52 M). The mixture was allowed to stir for 1 min prior to addition of ketone **26** (40 mg, 0.20 mmol) in Et_2O (1.5 mL) at −78 °C. The reaction mixture was allowed to stir for 30 min before being warmed to 0 °C and quenched with saturated NH_4Cl solution (2 mL). The organic layer was separated, and the aqueous layer extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by flash chromatography (5−10% EtOAc in hexanes) afforded the title compound (49 mg, 72%): IR (neat) 3476, 3010, 2929, 2855, 1452, 1359, 1114, 1068, 973, 909 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.31 (m, 4H), 7.30−7.27 (dt, J = 6.2, 3.0 Hz, 1H), 5.77−5.71 (d, J = 2.5 Hz, 2H), 5.44−5.37 (dd, J = 11.1, 7.1 Hz, 1H), 5.35−5.26 (m, 1H), 4.51−4.44 (m, 2H), 4.04−3.96 (m, 2H), 2.40−2.25 (ddd, J = 11.4, 9.7, 4.2 Hz, 1H), 2.04−1.89 (m, 2H), 1.78−1.41 (m, 7H), 1.35−1.20 (m, 7H), 0.94−0.80 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.16, 138.40, 130.98, 129.65, 128.41, 128.36, 127.77, 127.75, 127.56, 123.70, 73.07, 71.79, 70.49, 43.55, 38.04, 31.59, 29.42, 28.46, 27.78, 25.22, 22.62, 21.34, 14.12; HRMS (ESI) exact mass calcd for $NaC_{23}H_{34}O_2$ [M + Na$^+$] 365.2451, found 365.2447.

*trans-(E)-3-(Benzyloxymethyl)-4-pentylcyclodec-5-enone (**28**).* To a stirring suspension of KH (12 mg, 0.3 mmol) in Et_2O (4 mL) at 0 °C was added hexamethyldisilazane (63 μL, 0.3 mmol). The suspension was stirred for 30 min at room temperature prior to addition into a stirring solution of allylic alcohol **27** (50 mg, 0.15 mmol) and 18-crown-6 ether (79 mg, 0.3 mmol) in Et_2O (5 mL) at 0 °C. The resulting yellow solution was stirred for 18 h at room temperature. The reaction was quenched with saturated NH_4Cl solution (1 mL) and poured into H_2O (5 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (3−15% EtOAc in hexanes) afforded the title compound (23 mg, 49%): IR (neat) 2928, 2857, 1704, 1496, 1361, 1090, 736 cm^{-1} (*note: NMR spectra were significantly obscured, presumably due to alkene anisotropy*); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29−7.25 (m, 4H), 7.24−7.20 (td, J = 5.2, 4.1, 2.5 Hz, 1H), 5.44−4.96 (m, 2H), 4.55−4.40 (m, 2H), 3.64−3.22 (m, 2H), 2.44−2.09 (m, 5H), 2.00−1.77 (m, 2H), 1.72−1.55 (m, 1H), 1.45−1.11 (m, 8H), 1.07−0.92 (m, 1H), 0.92−0.68 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.37, 127.67, 33.45, 22.70, 14.16; HRMS (ESI) exact mass calcd for $NaC_{23}H_{34}O_2$ [M + Na$^+$] 365.2451, found 365.2443.

*trans-3-(Hydroxymethyl)-4-pentylcyclodecanone (**29**).* To a solution of cyclodecanone **28** (23 mg, 0.07 mmol) in dry MeOH (3 mL) was added 10% Pd/C (7 mg). The flask was purged with H_2, and the solution allowed to stir under a balloon of H_2 at room temperature for 19 h and recharged with an additional 5 mg of 10% Pd/C. After an additional 18 h the solution was filtered through Celite, eluting with 25 mL of ethyl acetate, and concentrated in vacuo. Purification by flash chromatography (20% EtOAc in hexanes) afforded the title compound (15 mg, 85%): IR (neat) 3417, 2925, 2857, 1698, 1469, 1045 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74−3.66 (dd, J = 10.4, 4.5 Hz, 1H), 3.55−3.46 (t, J = 9.8 Hz, 1H), 2.93−2.82 (m, 1H), 2.61−2.50 (ddd, J = 14.2, 10.4, 3.5 Hz, 1H), 2.50−2.41 (ddd, J = 15.1, 7.6, 3.8 Hz, 1H), 2.41−2.31 (tt, J = 13.8, 4.3 Hz, 2H), 2.10−1.96 (m, 1H), 1.95−1.85 (d, J = 6.6 Hz, 1H), 1.76−1.57 (m, 2H), 1.57−1.47 (m, 2H), 1.46−1.14 (m, 14H), 0.92 − 0.82 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.86, 77.29, 77.24, 77.04, 76.78, 64.55, 43.44, 41.83, 40.96, 36.33, 32.13, 31.71, 28.51, 27.67, 25.58, 25.52, 24.27, 23.99,

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22.69, 14.14; HRMS (ESI) exact mass calcd for $NaC_{16}H_{30}O_2$ [M + Na^+], 277.2138, found 277.2138.

*trans-9-Oxo-2-pentylcyclodecanecarbaldehyde (**30**).* To a solution of keto-alcohol **29** (10 mg, 0.04 mmol) in DCM (2 mL) was added Dess−Martin periodinane (25 mg, 0.06 mmol). The solution was allowed to stir for 30 min under a N_2 atmosphere. The solution was diluted in ether and concentrated to a small volume in vacuo. The residue was taken up in ether and washed with 1:1 0.5 M $Na_2S_2O_3$/saturated $NaHCO_3$ (10 mL), H_2O (10 mL), and brine (10 mL). The aqueous layers were back-extracted with EtOAc (3 × 5 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography (20% EtOAc in hexanes, silica gel) afforded the title compound (10 mg, 99%): IR (neat) 2926, 2859, 2708, 1723, 1703, 1467 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.75−9.72 (s, 1H), 3.21−3.13 (dt, J = 9.7, 3.6 Hz, 1H), 2.91−2.80 (dd, J = 16.2, 9.8 Hz, 1H), 2.69−2.61 (dd, J = 16.2, 3.4 Hz, 1H), 2.59−2.46 (dtdt, J = 15.3, 11.7, 7.6, 3.9 Hz, 2H), 2.18−2.08 (tt, J = 8.2, 3.2 Hz, 1H), 2.08−1.94 (m, 1H), 1.77−1.66 (m, 1H), 1.56−1.20 (m, 16H), 0.92−0.79 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.24, 203.62, 52.02, 43.11, 37.15, 35.60, 32.01, 31.92, 28.77, 27.45, 26.18, 25.19, 23.80, 23.45, 22.59, 14.08; HRMS (ESI) exact mass calcd for $NaC_{16}H_{28}O_2$ [M + Na^+], 275.1982, found 275.1991.

*2-Pentyl-10-azabicyclo[7.2.1]dodeca-1(11),9(12)-diene (**31**).* To a solution of dicarbonyl **30** (6 mg, 0.024 mmol) in anhydrous methanol (1 mL) was added dry NH_4OAc (18 mg, 0.24 mmol). The stirred solution was heated at reflux at 65 °C for 40 min under N_2 and cooled to room temperature. The reaction mixture was concentrated and subjected to flash chromatography (10% ethyl acetate in hexanes, silica gel) to afford the title compound (6 mg, 99%): ^1H NMR (500 MHz, $CDCl_3$) δ 7.81−7.56 (s, 1H), 6.46−6.39 (t, J = 1.9 Hz, 1H), 6.24−6.16 (dd, J = 2.6, 1.5 Hz, 1H), 2.69−2.58 (m, 1H), 2.50−2.34 (m, 2H), 1.79−1.59 (m, 4H), 1.53−1.36 (m, 2H), 1.34−1.23 (m, 7H), 0.92−0.85 (m, 6H), 0.76−0.63 (tdd, J = 14.0, 9.4, 6.1 Hz, 1H), 0.56−0.44 (dt, J = 12.8, 10.8 Hz, 1H), −1.80 to −2.05 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.54, 130.02, 114.64, 111.67, 41.73, 41.25, 33.78, 32.55, 32.25, 30.02, 29.79, 29.38, 27.73, 26.71, 22.74, 14.19; HRMS (ESI) exact mass calcd for $C_{16}H_{28}N$ [M + H^+], 234.2216, found 234.2218.

*Streptorubin B-5C·HCl (**22**).* To pyrrole **31** (4.3 mg, 0.018 mmol) and bispyrrole aldehyde **8**[20] (6.4 mg, 0.022 mmol) under N_2 atmosphere was added anhydrous MeOH (0.4 mL). To the stirred solution in a water bath (18 °C) was added a solution of HCl in MeOH (18 μL, 1 M, freshly generated from AcCl in MeOH) dropwise, upon which the solution turned a brilliant red. The solution was stirred for 1 h 15 min before addition of NaOMe in MeOH (25 μL, 25 wt % solution), upon which the solution turned a dark brown. After 45 min the reaction mixture was poured into Et_2O (5 mL) and washed with H_2O (5 mL). The aqueous layer was extracted with Et_2O (3 × 5 mL), and the combined organic layers were dried with Na_2SO_4. Two iterations of column chromatography (15−20% EtOAc in hexanes, then $CHCl_3$ to 3% MeOH/$CHCl_3$, silica gel) afforded the natural product as the HCl salt, as a ca. 1:1 mixture of atropisomers, which upon mild heating in $CHCl_3$ in a closed vessel equilibrated to a single atropisomer (7 mg, 90%). IR (neat) 3151, 2928, 2858, 1599, 1543, 1516, 1255 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 12.73−12.68 (s, 1H), 12.67−12.62 (s, 1H), 12.61−12.53 (s, 1H), 7.26−7.18 (td, J = 2.7, 1.3 Hz, 1H), 7.14−7.10 (s, 1H), 6.93−6.87 (m, 1H), 6.53−6.49 (d, J = 1.8 Hz, 1H), 6.37−6.30 (dt, J = 4.3, 2.4 Hz, 1H), 6.13−6.07 (d, J = 1.9 Hz, 1H), 4.05−3.97 (s, 3H), 3.37−3.28 (ddd, J = 12.9, 4.9, 2.4 Hz, 1H), 3.14−3.06 (ddt, J = 8.1, 5.6, 2.7 Hz, 1H), 2.59−2.49 (td, J = 12.3, 5.5 Hz, 1H), 1.96−1.89 (m, 1H), 1.87−1.68 (m, 3H), 1.56 − 1.51 (m, 1H), 1.41−1.30 (m, 7H), 1.29−1.22 (d, J = 6.7 Hz, 4H), 1.21−1.08 (m, 3H), 0.97−0.73 (m, 8H), −1.48 to −1.60 (dt, J = 15.7, 8.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.38, 154.68, 150.62, 146.99, 126.66, 125.02, 122.37, 120.28, 116.74, 116.54, 112.54, 111.54, 92.71, 77.29, 77.24, 77.03, 76.78, 58.65, 38.92, 37.48, 32.10, 31.64, 31.24, 29.98, 29.72, 29.14, 27.91, 27.72, 25.45, 22.66, 14.13; HRMS (TOF EI^+) exact mass calcd for $C_{25}H_{33}N_3O$ [M^+], 405.2991, found 405.2748.

C. Synthesis of Pentylcycloheptylprodigiosin (PCHP). *trans-2-Allyl-3-(n-pentyl)cyclononanone (**32**).* To a stirred suspension of CuBr·DMS (14 mg, 0.07 mmol) in THF (3 mL) at −40 °C was added *n*-PentMgBr (2.0 M in hexanes, 400 μL, 1.1 equiv). The suspension was stirred for 10 min before cyclonon-2-enone (100 mg, 0.72 mmol) was added dropwise in THF (1.5 mL). The solution became homogeneous and bright yellow before turning heterogeneous and black upon complete addition. After 1 h, freshly distilled allyl bromide (183 μL, 2.16 mmol) was quickly added, turning the reaction mixture purple. After 10 min, a solution of $Pd(PPh_3)_4$ (173 mg, 0.15 mmol) in THF (7 mL) was added, turning the reaction a yellow-brown color. The reaction was then warmed to room temperature and allowed to stir for an additional 3 h. The solution was quenched with aqueous AcOH (2 mL) and diluted with Et_2O (10 mL). The organic phase was separated, and the aqueous layer extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (3% EtOAc in hexanes, silica gel) to afford the title compound (167 mg, 93%). IR (neat) 2922, 1703, 1640, 1475, 1169, 1038, 914 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.76−5.56 (dddd, J = 16.4, 10.1, 8.1, 6.0 Hz, 1H), 5.05−4.96 (dq, J = 17.0, 1.5 Hz, 1H), 4.96−4.92 (dd, J = 10.1, 1.5 Hz, 1H), 2.62−2.46 (tdd, J = 10.5, 8.0, 3.7 Hz, 2H), 2.43−2.31 (dddd, J = 13.9, 5.8, 3.8, 1.8 Hz, 1H), 2.28−2.12 (m, 2H), 1.92−1.80 (m, 1H), 1.76−1.65 (ddt, J = 11.0, 7.7, 3.8 Hz, 1H), 1.63−1.56 (m, 2H), 1.55−1.11 (m, 16H), 0.96−0.81 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 218.50, 136.01, 116.47, 57.74, 39.18, 35.44, 32.67, 32.20, 27.27, 25.92, 24.07, 23.49, 23.39, 22.91, 22.68, 14.13; HRMS (ESI^+) exact mass calcd for $C_{17}H_{31}O$ [M + $H]^+$ 251.2369, found 251.2373.

*trans-2-(Acetaldehyde)-3-(n-pentyl)cyclononanone (**33**).* To a stirred solution of allylcyclononanone **32** (50 mg, 0.20 mmol) in EtOAc (1 mL) were added $NaIO_4$ (94 mg, 0.44 mmol), OsO_4 (2.5 wt % in *t*-BuOH, 250 μL, 0.02 mmol), and H_2O (1 mL). The solution was allowed to stir vigorously overnight before being partitioned between Et_2O (3 mL) and brine (3 mL). The organic layer was separated, and the aqueous layer extracted with Et_2O (3 × 3 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (10% EtOAc in hexanes, silica gel) to afford the title compound (35 mg, 69%). IR (neat) 2926, 2857, 2720, 1722, 1701, 1465, 1381, 1222, 1121, 1043 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.74−9.63 (s, 1H), 3.06−2.91 (m, 2H), 2.85−2.73 (m, 1H), 2.73−2.52 (m, 2H), 1.85−1.78 (m, 2H), 1.75−1.67 (m, 1H), 1.63−1.57 (tt, J = 11.3, 5.0 Hz, 1H), 1.54−1.15 (m, 15H), 0.91−0.86 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 218.92, 201.18, 50.44, 46.79, 45.80, 40.99, 33.57, 32.11, 27.27, 26.51, 25.67, 25.18, 24.62, 23.57, 22.65, 14.11; HRMS (ESI^+) exact mass calcd for $NaC_{16}H_{28}O_2$ [M + Na^+] 275.1982, found 275.1987.

*3-(n-Pentyl)-ortho-cyclononylpyrrole (**34**).* To a solution of dicarbonyl **33** (20 mg, 0.08 mmol) in dry MeOH (1 mL) was added azeotropically dried NH_4OAc (61 mg, 0.8 mmol). The solution was refluxed (65 °C) for 30 min before being cooled to RT and diluted with hexanes (3 mL). The solution was directly subjected to flash column chromatography (20% EtOAc in hexanes, silica gel) to afford the title compound (15 mg, 80%). IR (neat) 3478, 2283, 2922, 2852, 1458 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72−7.57 (s, 1H), 6.65−6.61 (t, J = 2.7 Hz, 1H), 5.96−5.91 (t, J = 2.8 Hz, 1H), 2.74−2.65 (tdd, J = 11.2, 6.1, 2.7 Hz, 1H), 2.65−2.60 (m, 2H), 1.90−1.79 (m, 1H), 1.64−1.23 (m, 17H), 1.08−0.93 (dtdd, J = 16.6, 10.8, 4.8, 2.7 Hz, 1H), 0.90−0.82 (t, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 129.62, 122.90, 115.03, 106.15, 37.15, 37.07, 35.92, 32.22, 27.98, 27.75, 27.38, 27.03, 26.89, 23.45, 22.70, 14.22; HRMS (ESI^+) exact mass calcd for $C_{16}H_{28}N$ [M + H^+] 234.2216, found 234.2218.

*Pentylcycloheptylprodigiosin·HCl (PCHP, **23**).* To a solution of pyrrole **34** (7.6 mg, 0.033 mmol) and bispyrrole aldehyde **8**[20] (12 mg, 0.04 mmol) in MeOH (1 mL) was added dry HCl in MeOH (1 M, 33 μL, 1 equiv, freshly prepared from AcCl and MeOH) at 0 °C. The solution immediately turned a deep red color and was allowed to stir for 90 min. A solution of NaOMe (0.066 mL, 25%) was then added, causing the solution to turn dark orange. After 1 h, the solution was

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poured into ether (10 mL) and extracted in ether (10 × 10 mL) until the aqueous layer was colorless. The combined extracts were washed with brine (10 mL) and dried over Na_2SO_4. The organic phase was concentrated in vacuo, and the residue was purified by flash column chromatography (gradient: $CHCl_3$ to 1% MeOH/$CHCl_3$, silica gel) to give the product as the hydrochloride salt (14 mg, 96%). IR (neat) 3155, 3131, 3102, 3057, 2924, 2853, 1629, 1604, 1545, 1507,1367, 1232, 1139 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 12.82−12.64 (s, 1H), 12.61−12.39 (s, 2H), 7.17−7.11 (m, 1H), 6.93−6.88 (s, 1H), 6.86−6.82 (dt, J = 3.2, 1.7 Hz, 1H), 6.60−6.50 (d, J = 2.7 Hz, 1H), 6.32−6.23 (dt, J = 4.0, 1.9 Hz, 1H), 6.05−5.97 (d, J = 1.8 Hz, 1H), 4.01−3.87 (s, 3H), 3.34−3.19 (m, 1H), 2.76−2.57 (dddd, J = 19.0, 11.7, 8.7, 3.6 Hz, 2H), 2.15−1.97 (dpd, J = 11.9, 6.0, 3.8, 3.2 Hz, 1H), 1.72−1.57 (m, 2H), 1.56−1.43 (m, 4H), 1.41−1.26 (m, 4H), 1.25−1.10 (m, 6H), 1.11−0.98 (m, 1H), 0.81−0.77 (t, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.78, 152.97, 147.71, 132.42, 126.97, 126.60, 125.71, 122.26, 120.78, 117.03, 116.08, 111.72, 92.85, 58.75, 37.00, 36.88, 35.96, 31.97, 27.64, 27.27, 27.11, 26.89, 26.63, 23.68, 22.65, 14.15; HRMS (TOF EI$^+$) exact mass calcd for $C_{26}H_{35}N_3O$ [M^+] 405.2780, found 405.2798.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H and ^{13}C NMR spectra for all new compounds, plus cif files for **2**·HCl and **4**·HCl. ^1H NMR spectra and EI mass spectra of synthetic BCHP (**4**) and streptorubin B (**2**) and copies of the corresponding data for the pigment isolated by Floss. DFT data for calculations depicted in Figure 8. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

†The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. B. T. Jones and D. X. Hu contributed equally.

Notes

The authors declare no competing financial interest.

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