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Enantioselective Total Synthesis and Confirmation of the Absolute and Relative Stereochemistry of Streptorubin B

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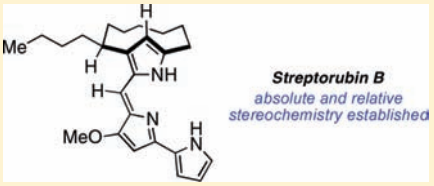
Supporting Information

ABSTRACT: The enantioselective total synthesis of the pyrrolophane natural product streptorubin B is described. Key steps in the concise route include the application of a one-pot enantioselective aldol cyclization/Wittig reaction and an anionic oxy-Cope rearrangement to forge the crucial 10-membered ring. Comparisons between CD spectra of synthetic and natural samples of streptorubin B coupled with X-ray crystallography allowed for the determination of the absolute stereochemistry of this natural product for the first time. These studies also provided unambiguous proof of the relative configuration between the butyl side chain and the bispyrrole subunit. Additional studies revealed a novel atropstereoselective Paal−Knorr pyrrole condensation and provided fundamental experimental insight into the barrier for atropisomerization of the natural product.



INTRODUCTION

The prodigiosin alkaloids have attracted widespread attention from both chemists and biologists because of their unique molecular architectures and the range of potentially useful biological activities they display.[1] For example, a prodigiosin-inspired medicinal chemistry program at Gemin X led to the development of a synthetic small-molecule Bcl inhibitor that is currently in phase I and II clinical trials for the treatment of a variety of cancers.[2] From a structural standpoint, streptorubin B (**1**)[3] and metacycloprodigiosin (**2**)[4] are especially notable because of their highly strained pyrrolophane cores, which are formed by oxidative ring closure from a common precursor, namely, the natural product undecylprodigiosin (**3**, Figure 1).[5] The more recently isolated congener prodigiosin R1 (**5**)[6] has a structure similar to that of **2** and provides an interesting link between these molecules and the related compound roseophilin (**6**),[7] while butylcycloheptylprodigiosin (**4**)[8,9] is a constitutional isomer of both **1** and **2**. In fact, the structural similarity between **1** and **4** led to significant confusion regarding the actual structures of these compounds. In 1975, Gerber and co-workers isolated a red pigment from *Streptomyces* sp. Y-42 and *Streptomyces abikoensis* to which they assigned the structure given by **4**.[8] Likewise, in 1985 the group of Floss assigned the structure **4** to a "pink pigment" they isolated from a strain of *Streptomyces coelicolor*.[9] Subsequent to these publications, in 1991 Weyland and co-workers reported the isolation of a pigment from an actinomycete (strain B 4358), which they showed to possess the pyrrolophane structure given by **1**.[3] They also went on to state that the assignment of **4** put forth earlier by Gerber (and presumably Floss also) should be revised in favor of **1**. Curiously, Gerber herself came to the same conclusion in 1978, although she did not elaborate on the reasons for this reassignment.[10] In 2005, Fürstner and co-workers reported the first synthesis of **4** and, on the basis of comparisons to the data collected by Floss, stated that **4** was in fact a natural product.[11] A second synthesis of **4** was reported in 2007 by Reeves, who came to the same conclusion as Fürstner.[12] These conclusions are confusing, given Floss' report that his data for the "pink pigment",[9] to which he assigned the structure **4**, "closely matched" that reported by Gerber, even though at that time she had already revised her assignment in favor of **1**. Furthermore, in 2008, Challis and co-workers reported that *S. coelicolor*, the organism from which Floss isolated his "pink pigment", produced **1**; they found no evidence for production of **4**.[5b]

The structure of streptorubin B (**1**) and its identity as a natural product are less questionable because of the full complement of NMR spectroscopic analyses conducted Weyland and co-workers in 1991[3] as well as those by Challis and workers in 2008.[5b] Key to the structural assignment was the presence of an upfield resonance at −1.55 ppm in the proton NMR spectrum that was attributed to one of the diastereotopic C4′ hydrogens (Weyland numbering), which suffers anisotropic shielding by the pyrrole nucleus as a result of the conformation of the strained 10-membered ring. Metacycloprodigiosin (**2**)[4] and prodigiosin R1 (**5**)[6] have similar proton resonances. While the structures of these two molecules have been confirmed through total synthesis,[11−13] there have been no reported syntheses of **1**, although the groups of Fürstner[13c] and Chang[14] have each prepared the pyrrole core. While the gross structure of **1** is not in doubt, several stereochemical issues remain. Weyland and co-workers noted that **1** possesses an element of planar stereochemistry;[3] that is, there are two potential atropdiastereomers of **1**, depending on the relative stereochemistry of the butyl side chain and the

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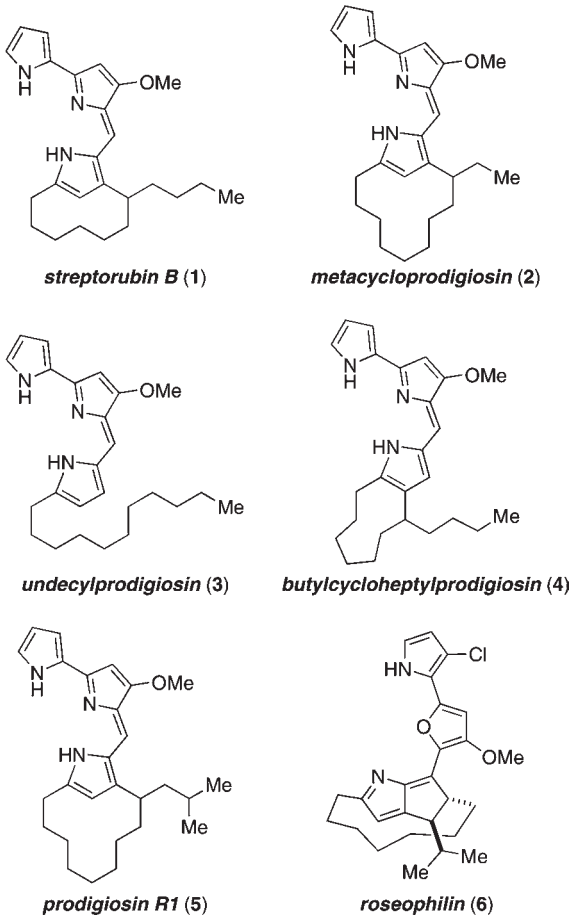


Figure 1. Some prodigiosin alkaloids and roseophilin.

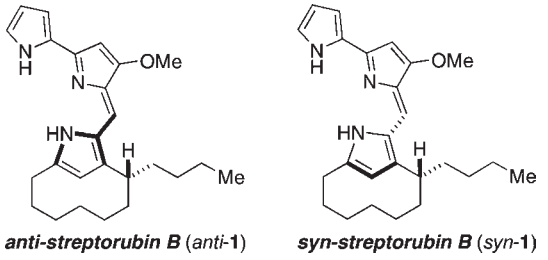


Figure 2. Atropisomerism within streptorubin B (**1**).

bispyrrole side arm (Figure 2). This stereochemical relationship has never been established. Additionally, the absolute configuration of **1** has not been established. In fact, at the outset of our work, the only compound of this family with known absolute stereochemisty was the related compound roseophilin (**6**). The independent synthetic efforts of the Tius and Boger groups[15] established that **6** possesses the absolute stereochemistry indicated in Figure 1. It was against this background that we initiated a synthesis of **1** with the goal of clarifying the structural ambiguities surrounding this fascinating molecule.

RESULTS AND DISCUSSION

Total Synthesis. In 2009, our research group completed the first enantioselective total synthesis of metacycloprodigiosin (**2**) and its relative, prodigiosin R1 (**5**).[13d] At the time of publication,

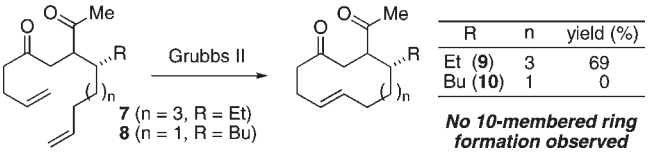
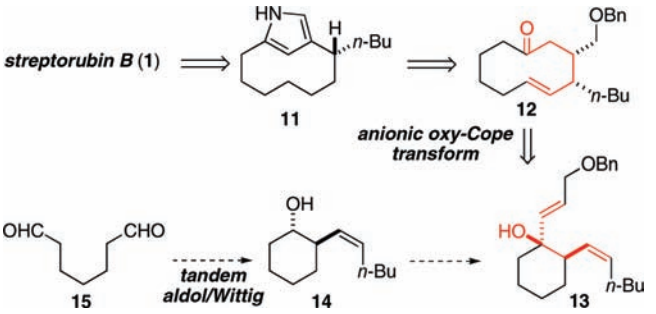


Figure 3. Failed RCM approach to the streptorubin B core.

Scheme 1. Synthesis Plan for Streptorubin B (1)



we were unable to confirm the absolute configuration of these natural products because of a lack of access to authentic samples. Subsequent to our publication, we were able to confirm the absolute configuration of natural **2** through comparison of the CD spectra recorded for our synthetic material and a natural sample isolated by Challis and co-workers.[16] The synthetic sample, which was *R*, matched the natural sample, thus establishing that natural metacycloprodigiosin possesses the *R* configuration for the side chain.

Wishing to also establish the stereochemistry of streptorubin B (**1**), we sought to apply the same strategy to its synthesis that had proven successful for **2**.[13d] Our total synthesis of **2** relied upon a ring-closing metathesis (RCM) reaction of diene **7** to produce the requisite 12-membered ring in 69% yield. In order to synthesize **1**, we prepared diene **8** by a route analogous to that which we used to prepare **7**. In contrast to what we found for 12-membered ring formation, diene **8** failed to undergo the desired ring closure (Figure 3). With the use of a variety of metathesis catalysts, the only isolated products were mixtures of dimeric species. Repositioning the alkene did not lead to any improvement. The failure of **8** to undergo efficient RCM is most likely a consequence of severe ring strain in the 10-membered product, and we therefore devised an alternative strategy.

Our revised synthesis plan for **1** (Scheme 1) entailed initial disconnection of the bispyrrole side arm of the natural product to generate the pyrrolophane core (**11**). Simplification of **11** by the Paal−Knorr pyrrole transform followed by some functional group interconversions led back to cyclodecanone **12**, which contains the full retron for the anionic oxy-Cope rearrangement.[17] Thus, the synthesis was simplified to devising a route to gain ready access to the functionalized cyclohexanol precursor **13**. To this end, we wished to employ a proline-catalyzed enantioselective desymmetrizing intramolecular aldol reaction on dialdehyde **15**[18] followed by an in situ Wittig reaction to form **14**, which could be easily converted to cyclohexanol **13**.

In 2003, List and co-workers reported the development of a proline-catalyzed enantioselective *exo*-enol-6-*exo*-trig aldol reaction as an effective means for desymmetrizing acyclic

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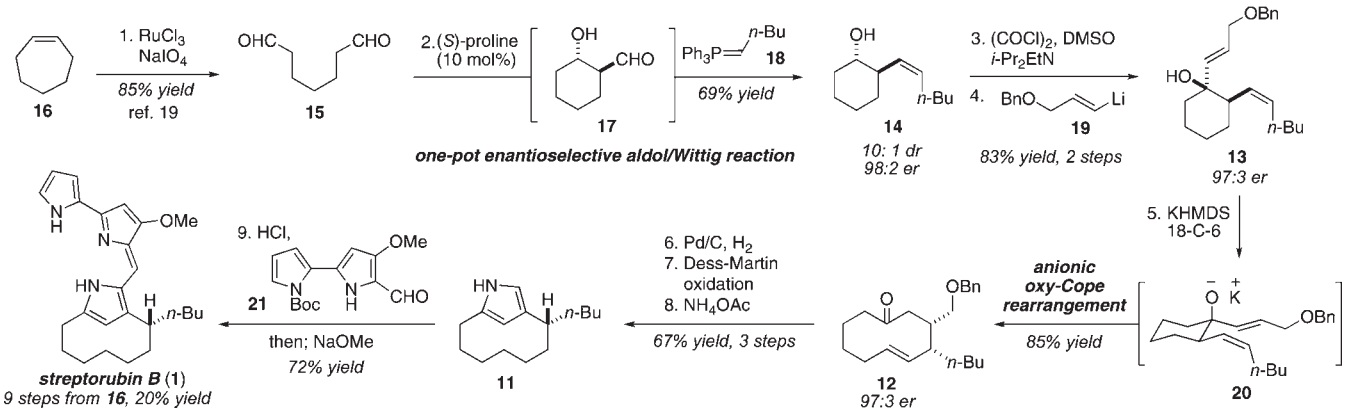
Scheme 2. Enantioselective Total Synthesis of Streptorubin B (1)



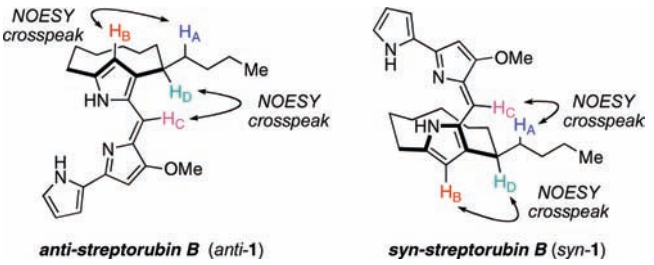


Figure 4. NOESY analysis of streptorubin B isomers.

dialdehydes.[18] In a footnote of the manuscript, the authors reported the use of an in situ Horner−Wadsworth−Emmons (HWE) reaction as a means of producing compounds with a chromophore for easy determination of enantiomeric excess by HPLC. We speculated that such a route employing a Wittig reaction rather than the HWE reaction might provide rapid access to the homoallylic alcohol (i.e., **14**) that we needed for our streptorubin B synthesis. Accordingly, we treated aldehyde **15**, which had been prepared in one step[19] from commercially available cycloheptene (**16**), with 10 mol % (*S*)-proline and upon consumption of the dialdehyde added ylide **18** to the reaction mixture (Scheme 2). In this way, the homoallylic alcohol **14** was obtained as the major diastereomer in 69% yield as a 98:2 mixture of enantiomers. Oxidation of **14** followed by addition of the vinyl anion **19**[20] gave **13**, the required precursor to the anionic oxy-Cope rearrangement, with an er of 97:3. Exposure of alcohol **13** to KHMDS and 18-crown-6 produced the desired 10-membered ring **12** in 85% yield. The enantiopurity of **12** was found to be 97:3 er, indicating a good level of stereochemical transfer during the oxy-Cope rearrangement. With **12** in hand, generation of the pyrrole core **11** proceeded smoothly following alkene reduction with concomitant benzyl ether cleavage, oxidation of the liberated alcohol to the aldehyde, and Paal−Knorr pyrrole synthesis (67% yield over three steps). Completion of the synthesis involved conducting an acid-promoted condensation between pyrrole **11** and aldehyde **21**,[21] which was followed by removal of the Boc group by basic methanolysis. Analysis of the bright-red material thus obtained revealed an approximately 10:1 mixture of two compounds in which the major compound did not match the natural product. Reexamination of this NMR sample after 10 days, however, revealed that this mixture had transformed almost completely to **1**. The synthetic material (as the HCl salt) was identical to the natural product as determined by ^{1}H and ^{13}C spectroscopy and mass spectrometry (MS).[22] Thus, streptorubin B (**1**) was prepared in nine steps from **16** in 20% overall yield.

Relative Stereochemistry of Streptorubin B and Key Intermediates. We were intrigued by the observation that the initially formed species of the final condensation step in the synthesis converted into the natural product upon standing. We speculated that the initially formed species was one atropdiastereomer of the natural product and that over time it isomerized into the other, presumably lower-energy atropisomer, which has the same structure as the natural product. Inspection of molecular models of the two possible atropisomers indicated that the lower-energy atropisomer should be *anti*-streptorubin B, in which the severe eclipsing interactions present within *syn*-streptorubin B are avoided. Analysis of the two possible atropdiastereomers, *anti*-**1** and *syn*-**1**, revealed that *anti*-**1** should display NOESY cross-peaks for H_A and H_B as well as H_C and H_D but lack H_A−H_C and H_B−H_D cross-peaks. The isomeric compound *syn*-**1** should display the opposite correlations. The NOESY data obtained, as shown in Figure 4, were fully consistent with the structure assigned as *anti*-**1**, where the two side arms effectively project from opposite faces of the 10-membered ring. An additional NOESY spectrum of the initially formed mixture resulting from condensation between **11** and **21** showed a clear H_B−H_D cross-peak, indicating that the initial adduct was indeed *syn*-**1**. From ^{1}H NMR spectroscopy, the equilibrium ratio of the anti and syn isomers is approximately 10:1 at room temperature, indicating that the anti isomer is thermodynamically favored by approximately 1.4 kcal mol^{-1}. By monitoring the change in the *syn*-**1**/*anti*-**1** ratio as a function of time at two temperatures, we determined the activation barrier for the conversion of *syn*-**1** into *anti*-**1** to be approximately 20.5 kcal mol^{-1}.[23] Thus, on the basis of these NMR spectroscopy studies, we established the relative stereochemistry of streptorubin B (**1**) for the first time. Unequivocal evidence was later obtained through X-ray crystallography (see below).

The question of why we initially observed a mixture of isomers favoring the unnatural atropisomer, *syn*-streptorubin B, during the final condensation step still remained unanswered, however. We hypothesized that perhaps the pyrrole precursor **11** existed as an atropisomer that favored the unnatural syn configuration, which would have led to the initial generation of *syn*-streptorubin

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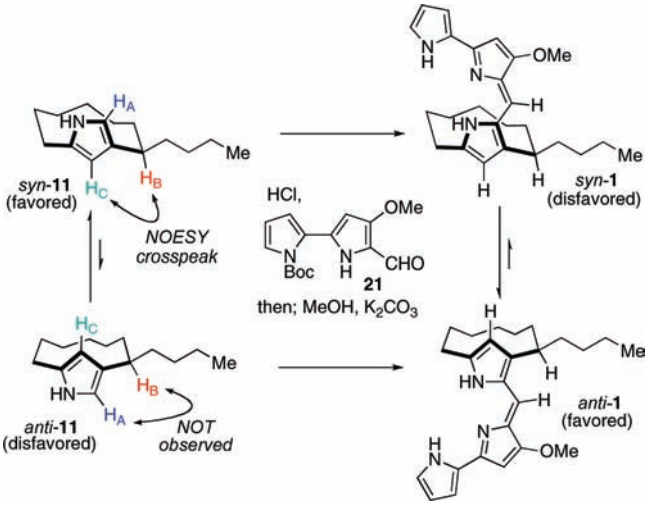
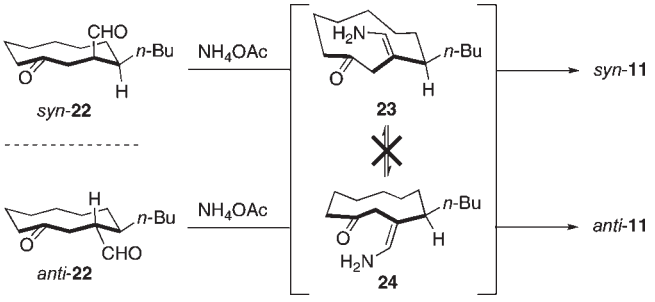
Scheme 3. Dissection of the Atropisomer Issue



Scheme 4. Atropselective Paal–Knorr Pyrrole Synthesis



B following condensation with bispyrrole **21** (Scheme 3). This higher-energy species would then have undergone conversion into the more stable anti isomer of the natural product. In fact, Fürstner and co-workers had prepared racemic pyrrole **11** as part of their work on **1** and noted in their manuscript[13c] that **11** displays an element of planar stereochemistry, although assignment of this stereochemistry and conversion of **11** into the natural product were not reported. They did, however, note that coalescence of pyrrole **11** could not be reached, indicating a barrier to rotation of greater than 17.5 kcal mol^{-1}. The NOESY experiment on pyrrole **11** conducted in our laboratories revealed that it exists predominantly as the unnatural isomer *syn*-**11** and that by ^{1}H NMR spectroscopy the ratio of *syn*-**11** to *anti*-**11** is approximately 10:1 when **11** is first synthesized. When as-synthesized **11** is left to stand over a period of 2 weeks or longer, the equilibrium ratio appears to be approximately 4:1 in favor of *syn*-**11**. Thus, a complete picture of this complex final condensation step has been revealed. When first synthesized, pyrrole **11** exists as a 10:1 mixture favoring the syn atropisomer, which upon condensation with **21** affords a 10:1 mixture of adducts favoring *syn*-**1**, which then isomerizes to the more stable compound, *anti*-**1**.[24]

Further analysis of pyrrole **11** and its immediate precursor, cyclodecanone *syn*-**22**, led us to speculate that perhaps the syn atropisomer of **11** was formed kinetically during the Paal–Knorr condensation (Scheme 4). If condensation of enamine **23** onto the endocyclic ketone occurs faster than bond rotation to form **24**, this might account for the selective (10:1) formation of *syn*-**11** (i.e., in a ratio greater than the equilibrium ratio, which we determined to be 4:1). We hypothesized that if this were the case, diastereomeric cyclodecanone *anti*-**22** would afford *anti*-**11** upon Paal–Knorr pyrrole synthesis via enamine **24**. Cyclodecanone *anti*-**22** was synthesized using a modified version of the route used to prepare *syn*-**22** (see the Supporting Information) and exposed to the conditions for pyrrole synthesis. Analysis of the pyrrole thus obtained revealed that the major isomer in this case was *anti*-**11**, indicating that the cyclodecanone precursors do not converge to the same intermediate upon condensation with ammonium acetate and that the intermediate enamines **23** and **24** do not readily interconvert under the reaction conditions. We did observe, however, that over the course of 10 days at room temperature, *anti*-**11** equilibrated to a 4:1 mixture favoring *syn*-**11**. Furthermore, we showed that condensation of *anti*-**11** with bispyrrole **21** directly afforded **1** as the favored atropisomer.

In hindsight, it was fortunate that the "unnatural" pyrrole isomer *syn*-**11** could be converted into the natural product through isomerization of the "unnatural" isomer of streptorubin B (i.e., *syn*-**1**) into streptorubin B. Had this final isomerization not occurred, however, completion of the total synthesis would still have been possible by taking advantage of a kinetically controlled Paal–Knorr pyrrole condensation of *anti*-**22** to generate *anti*-**11** and hence the correct atropisomer of **1**.

Absolute Configuration of Streptorubin B. As a final goal, we wished to establish the absolute stereochemistry of **1**, which necessitated that we first establish the absolute stereochemistry of our synthetic material. We had established the configuration of the initial aldol/Wittig reaction product **14** through Mosher ester analysis[25] but were mindful of the fact that the stereochemistry of the butyl side chain was set through the anionic oxy-Cope rearrangement. While it seemed entirely reasonable to expect the Cope product **12** to possess the stereochemistry indicated in Scheme 2 by way of the minimized chairlike transition state (i.e., **20**), we required stronger evidence. Fortunately, the solution to this issue came in the form of X-ray-quality crystals of the HCl salt of synthetic **1** itself (Figure 5A). Thus, through anomalous dispersion (Flack parameters of 0.04 for the indicated enantiomer and 0.87 for the opposite enantiomer)[26] we were able to unambiguously assign the configuration of our synthetic material as *R*, as predicted in our synthetic scheme (see Scheme 2). Additionally, this X-ray structure confirmed our NMR structural assignment that **1** exists as the anti atropdiastereomer (Figure 4). Comparisons between the CD spectra of a natural sample and our synthetic streptorubin B were somewhat surprising (Figure 5B). As shown in Figure 5B, the CD spectrum of the natural sample (blue) is the mirror image of the CD spectrum of synthetic (*R*)-streptorubin B (green), indicating that natural streptorubin B possesses an *S* configuration for the side chain (Figure 5C).[27] This stereochemistry is the opposite of that of metacycloprodigiosin (**2**) and is most likely a consequence of the conformation adopted by the linear side chain within the common biogenetic precursor, undecylprodigiosin (**3**), when it undergoes enzyme-mediated oxidative cyclization to produce either of the two natural products (i.e., streptorubin B or metacycloprodigiosin). We further confirmed this stereochemical assignment through preparation of the *S* enantiomer of streptorubin B (**1**) by using (*R*)-proline rather than (*S*)-proline during the one-pot aldol/Wittig reaction. This material displayed a CD spectrum (Figure 5B, red) identical in shape to that of the natural material.

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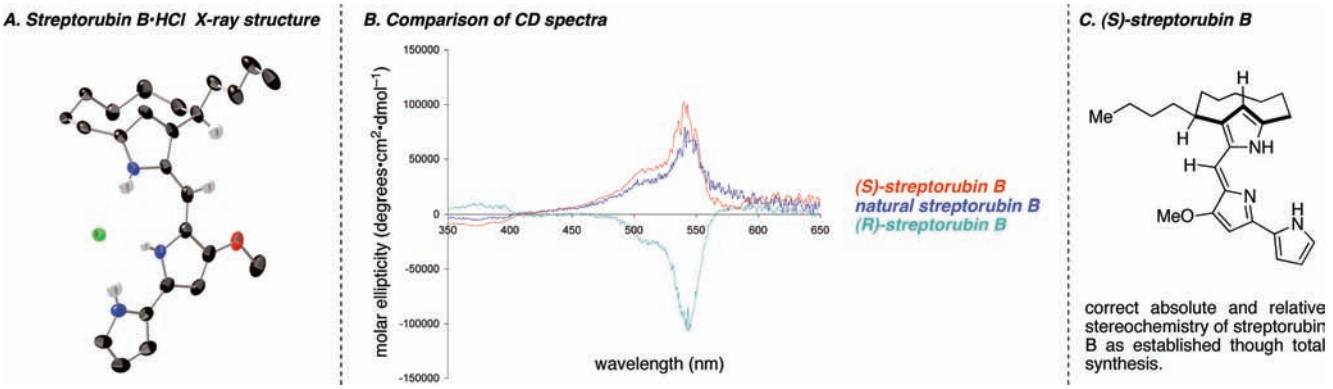

Figure 5. (A) X-ray structure of synthetic (*R*)-streptorubin B. (B) CD spectra. (C) Confirmed absolute and relative stereochemistry of streptorubin B.

CONCLUSIONS

The absolute and relative stereochemistry of streptorubin B (**1**) has been established through enantioselective total synthesis, providing definitive proof of the structure of this intriguing compound after decades of speculation. The concise synthesis made use of a novel one-pot enantioselective aldol/Wittig reaction to form a key homoallylic alcohol with high levels of enantiopurity. This powerful reaction, in combination with the anionic oxy-Cope rearrangement, proved to be pivotal for the construction of the strained 10-membered ring required for the synthesis. This straightforward procedure should prove useful in the enantioselective synthesis of other substituted 10-membered rings prevalent in many bioactive natural products. The complex question of atropstereoisomerism within **1** and its pyrrole precursor **11** was answered through a combination of NMR analysis and X-ray crystallography, while the absolute stereochemistry of **1** was determined through comparisons of CD spectra. Alongside our established enantioselective routes to the 12-membered pyrrolophane prodigiosins (i.e., metacycloprodigiosin and prodigiosin R1),[13d] the synthesis outlined herein for the 10-membered isomer (i.e., streptorubin B) will enable the ready preparation of these natural products (and analogues) for further biological evaluation.

ASSOCIATED CONTENT

Supporting Information. Complete ref 2b, detailed experimental procedures, spectral data for all compounds, and X-ray structure data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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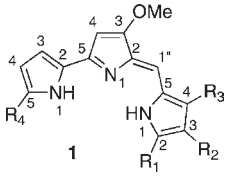

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(16) See the Supporting Information for CD spectra of synthetic material prepared as in ref 13d and the CD spectrum of natural metacycloprodigiosin kindly provided by Prof. Gregory Challis.

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(20) **19** was prepared from the corresponding iodide through lithium−halogen exchange (see the Supporting Information). The iodide was prepared using the protocol of Huang and Negishi (see: Huang, Z.; Negishi, E. *Org. Lett.* **2006**, *8*, 3675–3678).

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(22) Key compound data for synthetic **1**: IR (neat) 3436, 3371, 3019, 2937, 1764 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 12.70 (s, 1H), 12.66 (s, 1H), 12.58 (s, 1H), 7.22 (s, 1H), 7.21 (s, 1H), 7.11 (s, 1H), 6.90 (s, 1H), 6.51 (s, 1H), 6.34 (t, 1H, J = 2.7 Hz), 6.09 (s, 1H), 4.02 (s, 3H), 3.33 (m, 1H), 3.10 (m, 1H), 2.53 (dt, 1H, J = 12.3, 5.4 Hz), 1.96−1.68 (m, 5H), 1.55 (m, 2H), 1.37 (m, 5H), 1.24 (m, 3H), 1.14 (m, 2H), 0.91 (m, 5H), 0.78 (m, 1H), −1.55 (dt, 1H, J = 14.1, 8.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.4, 154.4, 150.6, 147.0, 126.7, 125.0, 122.4, 120.3, 116.8, 116.6, 112.5, 111.5, 92.8, 58.7, 38.9, 37.5, 31.7, 30.9, 30.4, 30.0, 29.1, 27.7, 25.4, 22.9, 14.2. HRMS (ESI) m/z: exact mass calcd for $C_{25}H_{33}N_3O$ $[M + H^+]$, 392.2696; found, 392.2700.

(23) See the Supporting Information for full details regarding the measurement and calculation of this activation energy.

(24) Because the isomers of pyrrole **11** do not interconvert rapidly at room temperature, the Curtin−Hammett principle need not be considered in order to rationalize this outcome. If the barrier for interconversion of the two pyrrole atropisomers were sufficiently low, one might have predicted that *anti*-**1** would be formed preferentially since the rate of condensation of *anti*-**11** with **21** is most likely significantly faster than that of *syn*-**11** with **21**. Since this interconversion does not occur rapidly under the reaction conditions, the product distribution reflects the ground-state stabilities of the two starting atropisomers. For further discussion of the Curtin−Hammett principle, see: Seeman, J. I. *Chem. Rev.* 1983, *83*, 83–134.

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(27) Challis and co-workers came to the same conclusion on the basis of their own studies of the biosynthesis of streptorubin B (private communication).