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Stereochemical Elucidation of Streptorubin B

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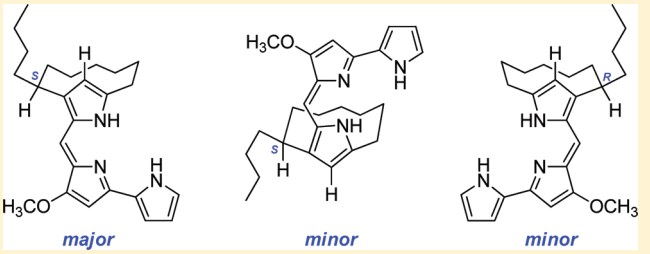
Supporting Information

ABSTRACT: Streptorubin B is a structurally remarkable member of the prodiginine group of antibiotics produced by several actinobacteria, including the model organism *Streptomyces coelicolor* A3(2). Transannular strain within the pyrrolophane structure of this molecule causes restricted rotation that gives rise to the possibility of (diastereomeric) atropisomers. Neither the relative nor the absolute stereochemistry of streptorubin B is known. NOESY NMR experiments were used to define the relative stereochemistry of the major atropisomer of streptorubin B·HCl in solution as anti. We exploited this finding together with our knowledge of streptorubin B biosynthesis in *S. coelicolor* to determine the absolute stereochemistry of the anti atropisomer. 2-Undecylpyrrole stereoselectively labeled with deuterium at C-4′ was synthesized and fed to a mutant of *S. coelicolor*, which was unable to produce streptorubin B because it was blocked in 2-undecylpyrrole biosynthesis, and in which the genes responsible for the last two steps of streptorubin B biosynthesis were overexpressed. ^{1}H and ^{2}H NMR analysis of the stereoselectively deuterium-labeled streptorubin B·HCl produced by this mutasynthesis strategy allowed us to assign the absolute stereochemistry of the major (anti) atropisomer as 7′*S*. HPLC analyses of streptorubin B isolated from *S. coelicolor* on a homochiral stationary phase and comparisons with streptorubin B derived from an enantioselective synthesis showed that the natural product consists of an approximately 88:7:5 mixture of the (7′*S*, *anti*), (7′*S*, *syn*), and (7′*R*, *anti*) stereoisomers.



INTRODUCTION

The prodiginines are a structurally remarkable group of 4-methoxypyrrolyldipyrromethene antibiotics produced by a wide variety of bacteria, in particular *Streptomyces* and related actinobacteria.[1] Members of this family include undecylprodigiosin (**1**) and its cyclic derivatives streptorubin B (**2**) and metacycloprodigiosin (**3**) as well as the cometabolites prodigiosin R1 (**4**) and roseophilin (**5**), which appear to derive from a common precursor (Figure 1).[2−6] There has been much recent interest in the prodiginines arising from the broad range of biological activities displayed by these antibiotics.[1] In particular, GX-15-070, a synthetic analogue of metacycloprodigiosin and streptorubin B, is currently in phase 1 and 2 oncology trials.[7]

There has been confusion in the literature regarding the structure of streptorubin B **2**. Gerber and co-workers reported the isolation of a prodiginine pigment from two *Streptomyces* species in 1975, to which they assigned the structure **6** (Figure 1; a regioisomer of streptorubin B).[8] Three years later, the structure of this pigment was revised by Gerber to **2**, although the reasons for this are not clear.[9] In 1985, Floss and co-workers reported the isolation of a carbocyclic derivative of **1** to which they also tentatively assigned the structure **6**.[10] Subsequently, Laatsch and co-workers isolated a carbocyclic prodiginine pigment from an unidentified actinomycete, which they convincingly identified as **2** on the basis of extensive NMR data.[3] As suggested by Gerber, they proposed that the structure **6** should be revised to **2**, i.e., that the carbocyclic undecylprodigiosin derivatives isolated from the four different actinomycetes are all the same compound, namely, streptorubin B. In 2005, Fürstner and co-workers reignited the controversy surrounding the structure of the carbocyclic undecylprodigiosin derivative produced by *S. coelicolor*. They completed a total synthesis of structure **6** and, by comparison with the NMR data reported by Floss and co-workers, concluded that this is identical to the carbocyclic undecylprodigiosin derivative produced by *S. coelicolor*.[11] However, in the course of biosynthetic studies, we recently isolated the carbocyclic undecylprodigiosin derivative produced by *S. coelicolor* and showed conclusively by an extensive array of 1D and 2D NMR experiments that this compound is **2**.[12] Thus, to summarize, there is no convincing evidence that compound **6** is a natural product, whereas **2** has been unambiguously identified as the carbocyclic undecylprodigiosin derivative produced by two different actinomycetes.[3,12]

Laatsch and co-workers recognized that the pyrrolophane structure of streptorubin B **2** possesses considerable conformational stability.[3] This causes one of the protons attached to C-4′ to sit directly within the anisotropy cone of pyrrole C, resulting in a remarkable chemical shift of −1.54 ppm for this proton in the ^{1}H NMR spectrum of **2**. The other proton attached to C-4′ lies

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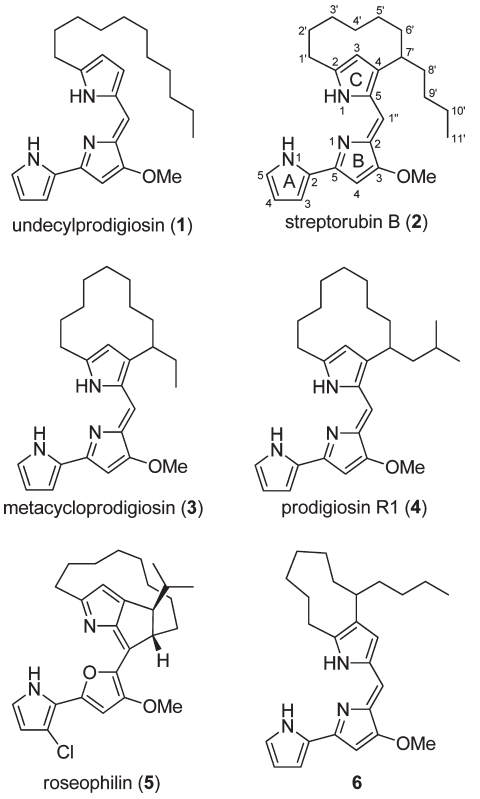

Figure 1. Structures of some of the prodiginine alkaloids **1**−**5** produced by actinomycetes and the incorrect structure **6** originally proposed for streptorubin B (**2**).

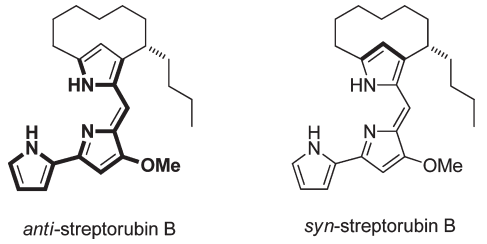

Figure 2. Structures of the anti and syn atropisomeric diastereomers of streptorubin B that arise from restricted rotation about the C-1′—C-2$_C$ and C-7′—C-4$_C$ bonds.

outside the anisotropy cone, and as a result, it has a "typical" methylene chemical shift of 1.16 ppm. The conformational stability of the streptorubin B pyrrolophane implies some intriguing stereochemical features. Thus, in addition to the conventional stereocenter at C-7′, restricted rotation about the C-7′—C-4$_C$ and C-1′—C-2$_C$ bonds arising from the strained ansa-bridged 10-membered carbocycle in **2** results in an axial stereochemical element. As a consequence, streptorubin B has the potential to exist as atropisomeric diastereomers in which the *n*-butyl group attached to C-7′ is either syn or anti to rings A and B (Figure 2). However, these stereochemical features have not been investigated further, and both the relative and absolute stereochemistry of streptorubin B remain unknown.

Undecylprodigiosin **1** and streptorubin B **2** are biosynthesized in *S. coelicolor* from the common intermediates 4-methoxy-2,2′-bipyrrole-5-carboxaldehyde (MBC, **7**) and 2-undecylpyrrole (**8**).[12,13] MBC is assembled from one unit each of L-proline, /BQNL-serine, *S*-adenosyl-L-methionine, and malonyl-CoA, whereas **8** is assembled from one unit of acetyl-CoA, six units of malonyl-CoA, and a unit of glycine.[14,15] Both pathways involve the first-discovered examples of polyketide chain termination catalyzed by α-oxamine synthase domains within polyketide synthases[15] (a fact which was overlooked in a recent review of the subject of chain-release mechanisms in polyketide biosynthesis[16]). The condensation of **7** and **8** to form **1** is catalyzed by the putative ATP-dependent multienzyme RedH, and **1** undergoes oxidative cyclization catalyzed by the Rieske oxygenase-like enzyme RedG to form **2** (Figure 3).[17,18] Mutants in which MBC biosynthetic genes are deleted do not produce prodiginines and thus accumulate **8**.[13] Prodiginine production is restored in such mutants by feeding them with synthetic MBC, and analogues of **1** can be produced by "mutasynthesis" (feeding the mutants with chemically synthesized analogues of MBC).[13,17] Similarly, mutants lacking 2-undecylpyrrole biosynthetic genes cannot produce prodiginines, and the production of both **1** and streptorubin B **2** can be restored by feeding the mutants with synthetic **8**.[12]

Here we report the elucidation of the relative stereochemistry of the major solution configuration of the hydrochloride salt of streptorubin B **2** using nuclear Overhauser effect spectroscopy (NOESY) NMR experiments. We also report the exploitation of the remarkable chemical shift difference between the diastereotopic protons attached to C-4′ of **2** to assign the absolute stereochemistry of the major isomer via mutasynthetic production of **2** stereoselectively deuterium-labeled at C-4′ coupled with ^{1}H and ^{2}H NMR analysis. The deuterium-labeled **2** was produced by stereoselective synthesis of deuterium-labeled **8**, which was then fed to mutants of *S. coelicolor* blocked in 2-undecylpyrrole biosynthesis. HPLC comparisons of natural streptorubin B with chemically synthesized (7′*S*)-, (7′*R*)-, and (7′*RS*)-streptorubin B on a homochiral stationary phase showed that **2** isolated from *S. coelicolor* consists of the (7′*S*, *anti*), (7′*S*), and (7′*R*, *syn*) isomers in an approximately 88:7:5 ratio.

RESULTS AND DISCUSSION

Relative Stereochemistry of the Major Diastereomer of Streptorubin B·HCl in Solution. NOESY NMR analysis of streptorubin B·HCl (**9**) purified from *S. coelicolor* M511 established the relative stereochemical relationship of C-1″ and the *n*-butyl group attached to C-7′ in the major species present in solution (Figure 4). Correlations between the protons attached to C-7′ and C-1″ and those attached to C-8′ and C-3$_C$ indicated that C-1″ and the *n*-butyl group attached to C-7′ have an anti stereochemical relationship. The presence of a signal at −1.48 ppm in the ^{1}H NMR spectrum of **9** having ∼5% of the intensity of the signal at −1.54 ppm indicated that a second, minor diastereomer (presumably the syn diastereomer) is also present. The NOESY data also established that the relative stereochemical relationship between the proton with a chemical shift of −1.54 ppm attached to C-4′ and the C-7′ stereocenter is *pro-R*, *S* in the major diastereomer.

The configurations of the C-5$_C$—C-1″, C-1″—C-2$_B$, and C-5$_B$—C-2$_A$ bonds were likewise deduced from the NOESY data. Correlations between the protons attached to C-7′ and C-1″, those attached to C-1″ and the methoxy group at C-3$_B$, and those attached to C-4$_B$ and C-3$_A$ indicated that the C-5$_C$—C-1″, C-1″—C-2$_B$ and C-5$_B$—C-2$_A$ bonds all have the *Z* or

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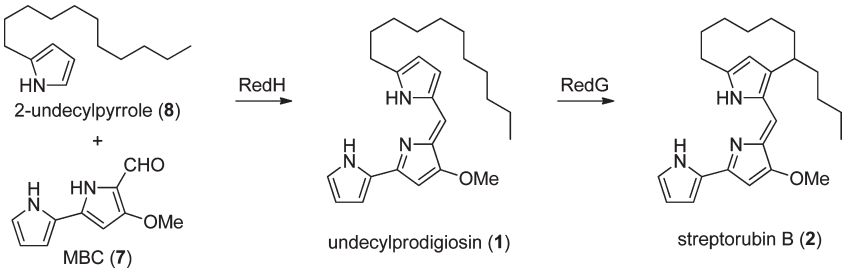

Figure 3. Pathway for the biosynthesis of undecylprodigiosin (**1**) and streptorubin B (**2**) in *S. coelicolor* A3(2). RedH catalyzes the condensation of 2-undecylpyrrole (**8**) and 4-methoxy-2,2′-bipyrrole-5-carboxaldehyde (MBC, **7**) to form **1**, which undergoes oxidative carbocyclization catalyzed by RedG to form **2**.

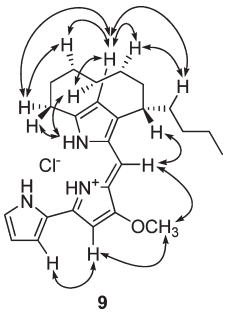

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Figure 4. Key correlations observed in the NOESY NMR spectrum of streptorubin B·HCl (**9**) isolated from *S. coelicolor* M511 that establish the relative stereochemistry of the major isomer in solution.

S-*cis* configurations. These configurations place the three nitrogen atoms in streptorubin B·HCl in close proximity, and as a consequence, strong repulsion between the protons attached to each of these atoms would be expected. We hypothesized that this repulsion is overcome by coordination of the chloride ion by the three protons (Figure 4). This supposition, along with our relative stereochemical assignments for streptorubin B·HCl **9**, were confirmed by subsequent X-ray crystallographic analysis of synthetic (7′*R*)-streptorubin B·HCl.[19]

Mutasynthesis of Streptorubin B Stereoselectively Deuterium-Labeled at C-4′. Our mutasynthesis approach for elucidation of the absolute stereochemistry of streptorubin B **2** required 2-undecylpyrrole **8** stereoselectively deuterium-labeled at C-4′. [4′-^{2}H](4′*R*)-2-undecylpyrrole [(4′*R*)-**10**] was synthesized from the known epoxy ester **11**[20] in six steps (Scheme 1). Regiospecific opening of the epoxide in **11** with the cuprate derived from *n*-hexyllithium and copper cyanide yielded (4*R*)-γ-butyrolactone (4*R*)-**12**,[21] which upon treatment with excess trimethylsilyl iodide followed by methanol afforded iodo ester (4*S*)-**13**.[22] The stereochemical purity of the iodo ester was confirmed by converting it back to (4*R*)-**12** using aqueous sodium hydroxide and then performing HPLC analysis on a homochiral stationary phase (see the Supporting Information). Reaction of (4*S*)-**13** with sodium borodeuteride gave the deuterated ester **14**, which was assumed to result predominantly from S_N2 displacement of iodide with deuteride and, as a consequence, to be enriched in the 4*R* enantiomer.[23] Hydrolysis of (4*R*)-**14** yielded the corresponding acid (4*R*)-**15**, which was converted to (4′*R*)-**10** using a previously reported procedure.[12]

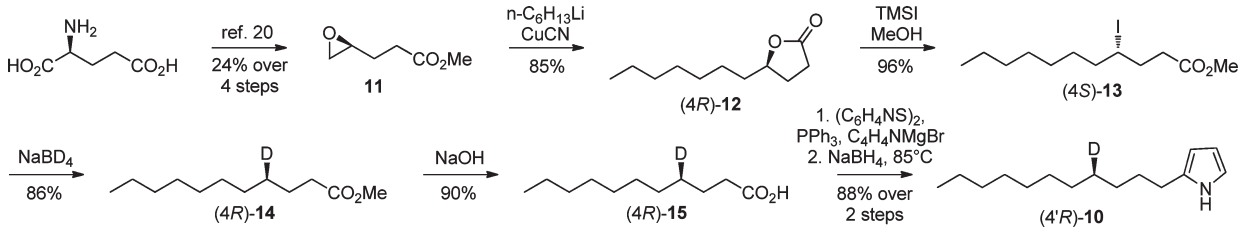
[4′-^{2}H](4′*S*)-2-undecylpyrrole [(4′*S*)-**10**] was synthesized from γ-butyrolactone (4*R*)-**12** in seven steps (Scheme 2). Reaction of (4*R*)-**12** with the hydrochloride salt of dimethylamine and trimethylaluminum afforded hydroxyamide **16**,[24] which upon treatment with tosyl chloride and pyridine gave the (4*S*)-γ-butyrolactone (4*S*)-**12**. (4′*S*)-**10** was synthesized from this lactone using chemistry identical to that used for the synthesis of (4′*R*)-**10** from (4*R*)-**12**.

Feeding 2-undecylpyrrole **8** to a *redL* mutant of *S. coelicolor* M511 (blocked in 2-undecylpyrrole biosynthesis) restores production of undecylprodigiosin **1** and streptorubin B **2**.[12] However, the amount of **2** relative to **1** produced in the experiment is low, making it difficult to purify sufficient **2** for NMR spectroscopic analysis. Thus, we investigated the effect of expressing additional copies of the genes encoding the enzymes that catalyze condensation of MBC **7** and 2-undecylpyrrole **8** to form undecylprodigiosin **1** (RedH)[17] and the oxidative carbocyclization of undecylprodigisin **1** to afford streptorubin B **2** (RedG)[18] in *trans* under the control of the strong constitutive *ermE** promoter in *S. coelicolor* M511. Expression of *redG* alone did not significantly affect the **1**/**2** ratio. In contrast, expression of *redHG* resulted in a significant increase in the amount of **2** produced relative to the amount of **1** produced, providing further evidence for the formation of a RedH−RedG complex.[18] Similarly, overexpression of *redHG* in the *redL* mutant of *S. coelicolor* M511[12] to create *S. coelicolor* W116 resulted in significantly higher production levels of **2** relative to **1** upon feeding with **8**, facilitating the isolation of sufficient quantities of **2** from the experiment for NMR spectroscopic analysis.

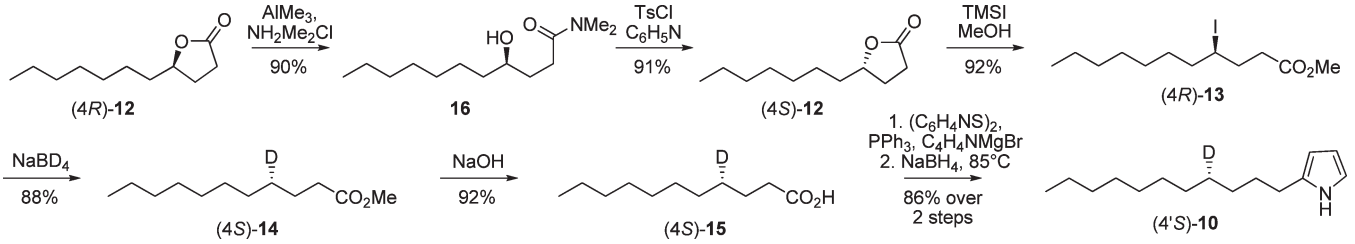
LC−MS analyses of mycelia extracts of *S. coelicolor* W116 to which (4′*S*)-**10** or (4′*R*)-**10** had been separately fed indicated that **2** bearing a single deuterium label was produced in both cases. The deuterium-labeled **2** afforded by each of these experiments was purified from the extracts by a combination of alumina chromatography and semipreparative HPLC.

Absolute and Relative Stereochemical Assignment of Streptorubin B. ^{1}H and ^{2}H NMR spectroscopic analysis of deuterium-labeled streptorubin B·HCl (**17**) isolated from the mutasynthesis experiment using (4′*S*)-**10** indicated that ∼70% of the deuterium label occupied the endo position at C-4′ (with the deuterium atom sitting directly above the π electrons of ring C) and ∼30% of the deuterium label was in the exo position (see the Supporting Information). In contrast, **17** isolated from the mutasynthesis experiment with (4′*R*)-**10** contained ∼30% label in the endo position and ∼70% label in the exo position of C-4′ (see the Supporting Information). Our discovery that *anti*-streptorubin B·HCl is the major diastereomer in solution coupled with the finding that the proton with a chemical shift of −1.54 ppm attached to C-4′ and the C-7′ stereocenter in this

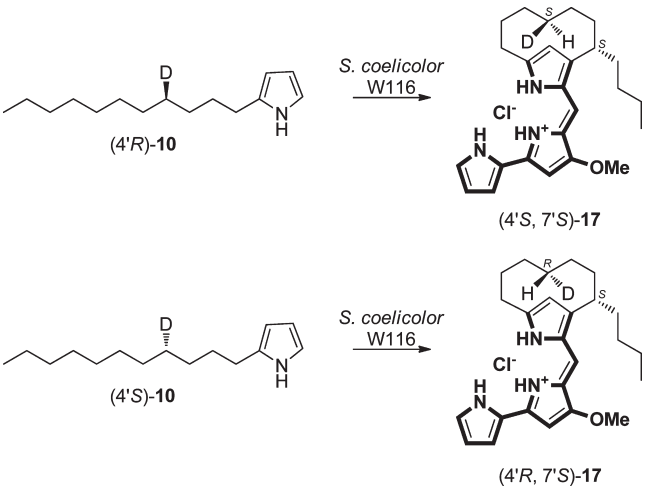
Scheme 1. Synthesis of [4′-^{2}H](4′*R*)-2-Undecylpyrrole [(4′*R*)-10]



Scheme 2. Synthesis of [4′-^{2}H](4′*S*)-2-Undecylpyrrole [(4′*S*)-10]



Scheme 3. Relative and Absolute Stereochemistry Assigned to the Stereoselectively Deuterium-Labeled Streptorubin B Derivatives 17 Produced by Mutasynthesis



diastereomer have a *pro-R, S* relative stereochemical relationship allowed us to use the results of the deuterium labeling experiments to assign the absolute stereochemistry of C-7′ as *S* in the predominant enantiomer of streptorubin B produced by *S. coelicolor* (Scheme 3).

The observation that the labeling of streptorubin B in the mutasynthesis experiments appears merely to be stereoselective rather than stereospecific intrigued us. This could be explained simply by partial racemization during conversion of the enantiomerically pure iodides (4*S*)-**13** and (4*R*)-**13** to the corresponding deuterated esters (4*R*)-**14** and (4*S*)-**14**, which may have resulted from the displacement of iodide with deuteride via an S_N1 mechanism in addition to the predominant S_N2 pathway. However, this observation could also result if the natural product were a mixture of enantiomers and/or contained *syn*-streptorubin B as a minor diastereomer alongside the major anti diastereomer (as indicated by the ^{1}H NMR spectroscopic analysis of **17**). Thus, we analyzed streptorubin B·HCl **9** isolated from *S. coelicolor* using HPLC on a homochiral stationary phase, monitoring the absorbance at 470 nm (the λ_{max} for the free base of the 4-methoxypyrrolyldipyrromethene core structure of streptorubin B, which was produced from the hydrochloride salt under the HPLC conditions) (Figure 5). Comparisons with authentic standards of (7′*R*)-, (7′*S*)-, and (7′*RS*)-streptorubin B[19] identified the compound with a retention time of ~9.5 min as (7′*S, anti*)-streptorubin B and the compound with a retention time of ~34.5 min as (7′*R, anti*)-streptorubin B (Figure 5). The compound with a retention time of ~13.5 min was also found in the synthetic sample of (7′*S*)-streptorubin B. We hypothesized that this is (7′*S, syn*)-streptorubin B, which can be derived from (7′*S, anti*)-streptorubin B by rotation about the C-1′—C-2$_C$ and C-4$_C$—C-7′ bonds. To test this hypothesis, we collected the compound with a retention time of ~9.5 min and reanalyzed it using HPLC both immediately and after allowing the compound to stand for 7 days at room temperature. While none of the compound with a retention time of ~13.5 min was detected in the sample that was reanalyzed immediately after collection, this compound was detected in the sample that was reanalyzed after 7 days. These findings are consistent with the hypothesis that the compound with a retention time of ~13.5 min is (7′*S, syn*)-streptorubin B and that it results from (7′*S, anti*)-streptorubin B via slow rotation about the C-1′—C-2$_C$ and C-4$_C$ — C-7′ bonds.[25] This hypothesis was corroborated by the findings of Thomson and co-workers,[19] who showed that in the synthesis of streptorubin B, the syn diastereomer is initially formed but isomerizes to the anti diastereomer upon standing. Thus, the stereoselective rather than stereospecific labeling of streptorubin B in the mutasynthesis experiments results from the fact that natural streptorubin B contains small amounts of (7′ *R, anti*)-streptorubin B and (7′ *S, syn*)-streptorubin B in addition to (7′ *S, anti*)-streptorubin B as well as from some erosion of stereochemical purity during the predominantly S_N2 displacement of iodide with deuteride in (4*S*)-**13** and (4*R*)-**13**.[26]

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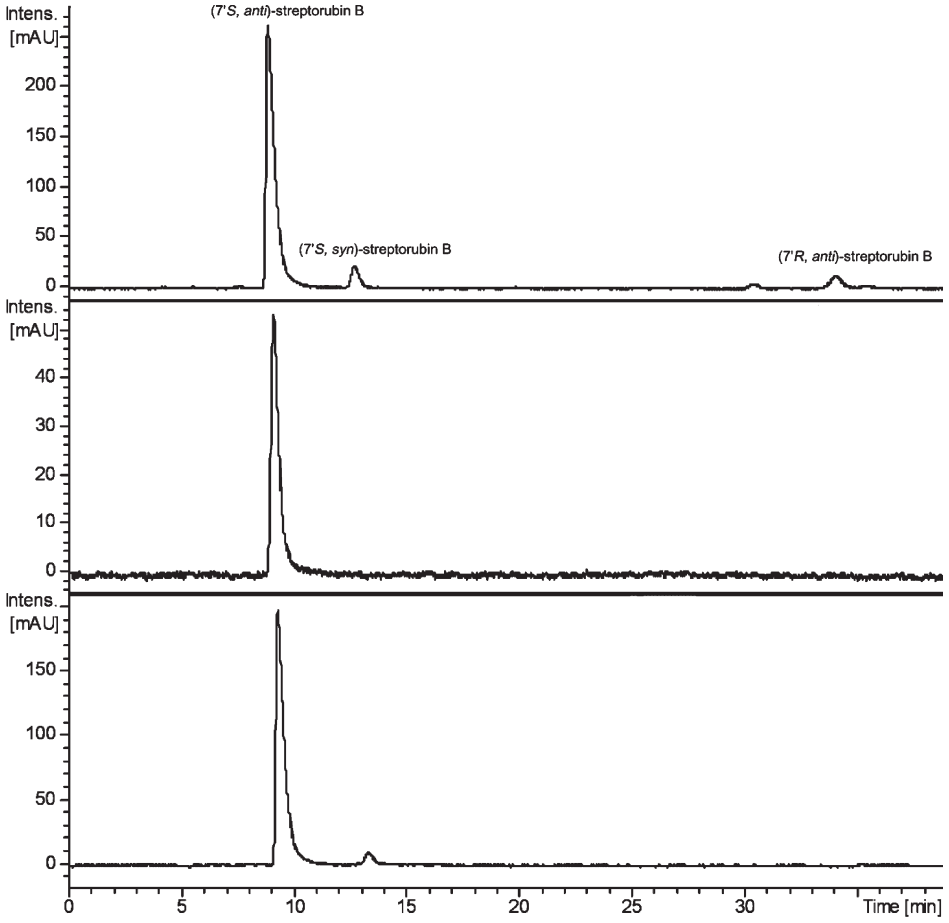

Figure 5. Chromatograms from HPLC analyses on a homochiral stationary phase of streptorubin B isolated from *S. coelicolor* M511 (top trace), the compound with a retention time of ~9.5 min analyzed immediately after collection (middle trace), and that compound analyzed after it was allowed to stand for 7 days at room temperature (bottom trace).

CONCLUSION

We have used a combination of NOESY NMR spectroscopy, mutasynthesis of stereoselectively deuterium-labeled streptorubin B derivatives, and HPLC analyses on a homochiral stationary phase to show that natural streptorubin B isolated from *S. coelicolor* M511 consists of a mixture of three stereoisomers, among which the (7′*S*, *anti*) isomer predominates. The (7′*S*, *syn*) atropisomer, which is a minor component of the mixture, can arise from the major stereoisomer by rotation about the C-1′—C-2_C and C-4_C—C-7′ bonds. Intriguingly, the (7′*R*, *anti*) enantiomer of the major stereoisomer is also a minor component of the mixture, indicating that the RedG-catalyzed oxidative carbocyclization of undecylprodigiosin to form streptorubin B[18] proceeds with incomplete stereocontrol. This could arise either from (1) the formation of a radical or cation intermediate by stereospecific hydrogen/hydride extraction at C-7′ that can on occasion undergo rotation about the C-6′—C-7′ bond prior to cyclization onto pyrrole ring C to generate the minor 7′*R* isomer or (2) as a result of incomplete stereocontrol during oxidation at C-7′ to generate stereoisomeric intermediates that undergo cyclization to form enantiomeric products. Discrimination between these mechanistic possibilities could be achieved by mutasynthesis experiments using 2-undecylpyrrole that is stereospecifically labeled at C-7′.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, chromatograms from HPLC analyses of (4*R*)- and (4*S*)-**12** on a homochiral stationary phase, ^{1}H and ^{2}H NMR spectra for deuterium-labeled **17** isolated from the mutasynthesis experiments, and complete ref . This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) (7′*R*, *syn*)-streptorubin B (retention time ≈ 10 minutes) could be detected in the samples of synthetic (7′*RS*) and (7′*R*)-streptorubin B (see the Supporting Information). It was not detectable in the sample of streptorubin B isolated from *S. coelicolor* because it constitutes only ∼0.5% of the mixture [the anti/syn ratio is ∼88:7 and only ∼5% of (7′*R*, *anti*)-streptorubin B is present in the natural product].
(26) This erosion of stereochemical purity could presumably be overcome, in principle, by using a more reactive source of deuteride, such as $LiAlD_4$, which should promote the S_N2 reaction and ensure that a greater proportion of the displacement proceeds with inversion. However, $LiAlD_4$ would also reduce the ester in **13** to the corresponding alkoxide, which would be expected to displace iodide in an intramolecular reaction to form the corresponding tetrahydrofuran. Thus, a different synthetic approach for the stereospecific deuterium-labeling of 2-undecylpyrrole at C-4′ would be required.