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The Revised Structure, Total Synthesis, and Absolute Configuration of Streptophenazine A

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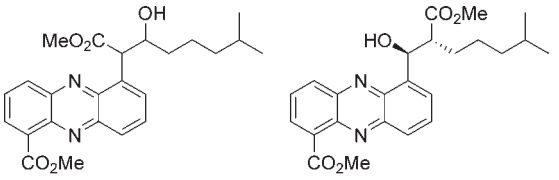
ABSTRACT

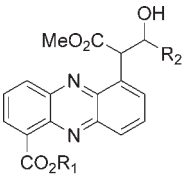


1
Proposed Structure of Streptophenazine A

(−)-17b
Revised Structure of Streptophenazine A

A total synthesis of both diastereomers of the originally proposed structure for streptophenazine A (1) has been achieved. However, both synthetic compounds are different from the natural product. Re-examination of NMR data reported for streptophenazine A and a concise total synthesis of both diastereomers of 17 (17a and 17b) led to the structural revision of streptophenazine A to 17b. Asymmetric synthesis of (−)-streptophenazine A was also conducted, and its absolute configuration was determined to be 1′*S*,2′*R*.

Phenazine derivatives, such as saphenamycin[1] as well as esmeraldin A and B,[2] are a potential source of antibiotics. Several novel phenazine analogues, streptophenazines A−H (**1**−**8**), have been recently isolated by Mitova and co-workers from cultures of marine *Streptomyces* sp. strain HB202 (Figure 1), some of which have shown moderate antibacterial activities.[3] The structures of streptophenazines A−H were elucidated by spectroscopic methods; however, the stereochemistry of the side chain was not determined. We are interested in these novel phenazine analogues and report herein the first total synthesis, the



1–**2** and **4**–**8**: R_1 = Me
3: R_1 = H

1: R_2 = -$(CH_2)_3CHMe_2$;
2: R_2 = -$(CH_2)_5Me$;
3: R_2 = -$(CH_2)_3CHMe_2$;
4: R_2 = -$CH_2CH_2CHMe_2$;
5: R_2 = -$(CH_2)_3Me$;
6: R_2 = -$(CH_2)_4CHMe_2$;
7: R_2 = -$(CH_2)_3CHMeEt$;
8: R_2 = -$(CH_2)_3C(OH)Me_2$

Figure 1. Proposed structures of streptophenazines A−H (**1**−**8**).

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(1) (a) Kitahara, M.; Nakamura, H.; Matsuda, Y.; Hamada, M.; Naganawa, H.; Maeda, K.; Umezawa, H.; Itaka, Y. *J. Antibiot.* **1982**, *35*, 1412–1414. (b) Geiger, A.; Keller-Schierlein, W.; Brandl, M.; Zahner, H. *J. Antibiot.* **1988**, *41*, 1542–1551. (c) Laursen, J. B.; Jorgensen, C. G.; Nielsen, J. *Bioorg. Med. Chem.* **2003**, *11*, 723–731.

(2) (a) Keller-Schierlein, W.; Geiger, A.; Zaehner, H.; Brandl, M. *Helv. Chim. Acta* **1988**, *71*, 2058–2070. (b) Van't Land, C. W.; Mocek, U.; Floss, H. G. *J. Org. Chem.* **1993**, *58*, 6576–6582.

(3) Mitova, M. I.; Lang, G.; Wiese, J.; Imhoff, J. F. *J. Nat. Prod.* **2008**, *71*, 824–827.

(4) (a) Rewcastle, G. W.; Denny, W. A.; Baguley, B. C. *J. Med. Chem.* **1987**, *30*, 843–851. (b) Petersen, L.; Jensen, K. J.; Nielsen, J. *Synthesis* **1999**, 1763–1766.

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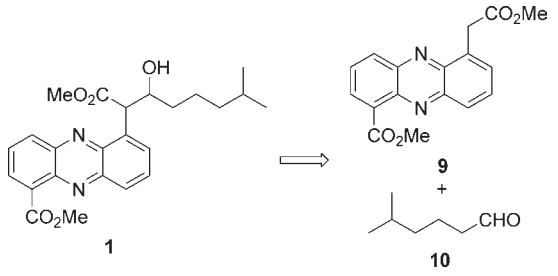
revised structure, and absolute configuration of streptophenazine A.

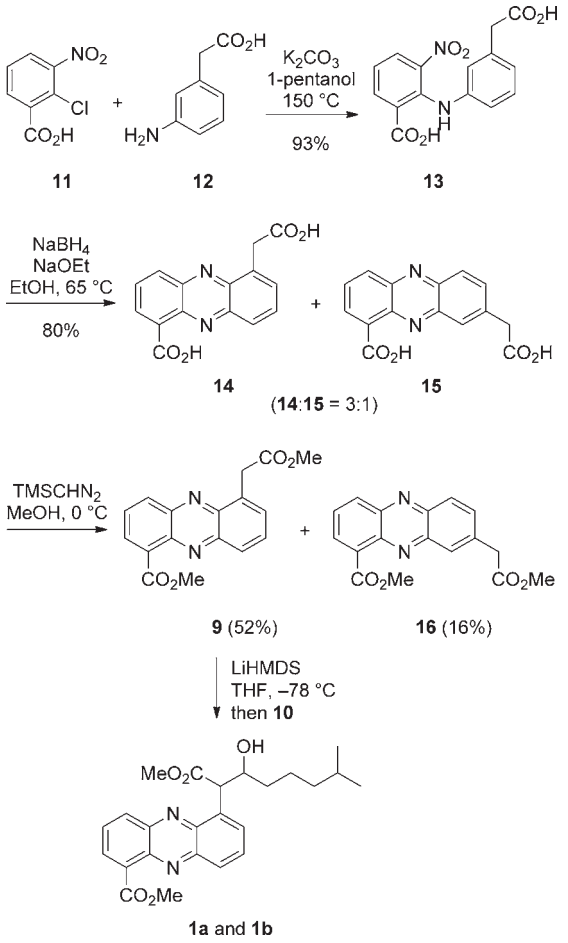
As shown in Scheme 1, the key step in our synthesis is an aldol reaction, which couples ester **9** with aldehyde **10** to generate both diastereomers of **1** in a concise manner.

Scheme 1. Retrosynthetic Analysis



The synthesis of the target **1** started from commercially available chloride **11** and aniline **12** (Scheme 2). Reaction of **11** with aniline **12** in the presence of potassium carbonate provided amine **13** in excellent yield. Reductive cyclization of **13** gave the desired acid **14** and a minor regioisomer **15** in a ratio of 3:1.[4] The mixture of acids **14** and **15** were converted to the corresponding methyl esters **9** and **16**, which are separable by silica gel chromatography. Treatment of ester **9** with lithium bis(trimethylsilyl)amide (LiHMDS), followed by coupling of the resulting enolate with aldehyde **10**,[5] afforded a 1:1 mixture of the two diastereomers (**1a** and **1b**) of the proposed structure of streptophenazine A. The individual diastereomers **1a** and **1b** were isolated by semipreparative HPLC on a C18 column.

Scheme 2. Synthesis of the Proposed Structure **1**



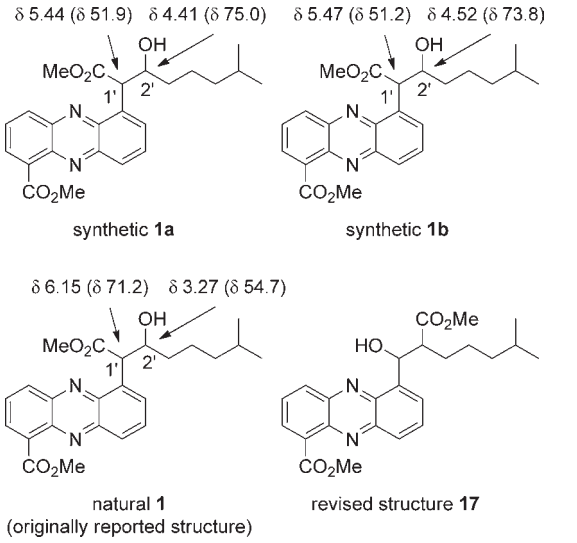


Figure 2. ^{1}H and ^{13}C NMR data of synthetic **1a**, **1b**, and the naturally occurring streptophenazine A. The revised structure **17**.

The structures of diastereomers **1a** and **1b** were confirmed by HRMS, ^{1}H, ^{13}C, 2D COSY, HSQC, and HMBC NMR analyses. Unexpectedly, the ^{1}H and ^{13}C NMR data of both **1a** and **1b** were different from those reported for naturally occurring streptophenazine A. In particular, the chemical shifts of H-1′ and H-2′ in the ^{1}H NMR spectra were quite different (Figure 2). For the natural product **1**, the chemical shifts of H-1′ and H-2′ were reported to be δ 6.15 and δ 3.27, respectively. However, these protons for synthetic **1a** were observed at δ 5.44 and δ 4.41, respectively, and for synthetic **1b** the signals were observed at δ 5.47 and δ 4.52, respectively. Likewise, significant chemical shift differences for the corresponding C-1′ and C-2′ in the ^{13}C NMR spectra were also observed (Figure 2). For the natural product **1**, the chemical shifts for C-1′ and C-2′ were reported at δ 71.2 and δ 54.7, whereas, in the synthetic samples, these carbon signals were found at δ 51.9 and δ 75.0 for **1a** and at δ 51.2 and δ 73.8 for **1b**, respectively.

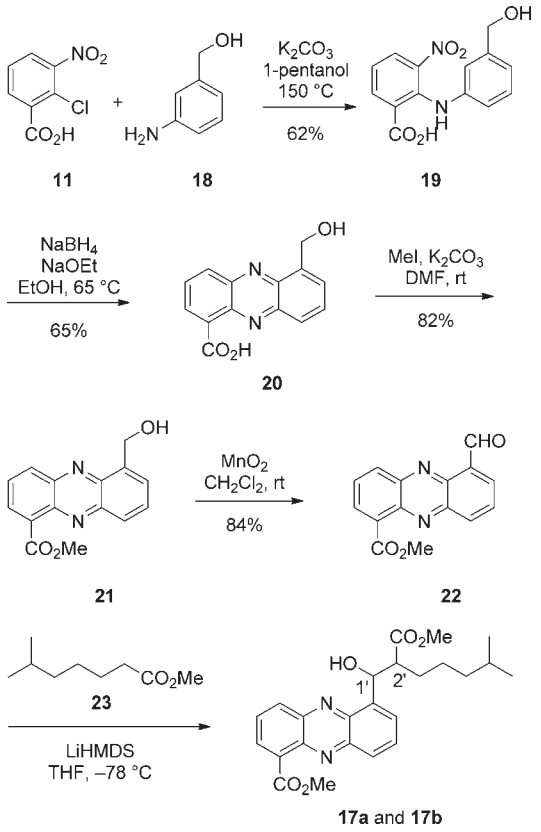
Comparison of the ^{1}H and ^{13}C NMR data originally reported for the natural product **1** (i.e., the chemical shifts for H-1′, H-2′, C-1′, and C-2′) with those of the synthetic

(5) Graham, S. M.; Prestwich, G. D. *J. Org. Chem.* **1994**, *59*, 2956–2966.

(6) (a) Nakamura, S.; Yagishita, K.; Umezawa, H. *J. Antibiot.* **1961**, *14*, 108–110. (b) Yagishita, K. *J. Antibiot.* **1960**, *13*, 83–96.

compounds **1a** and **1b** established that the original structural assignment for streptophenazine A was incorrect. It seemed more plausible that the actual structure should be revised to structure **17** (Figure 2). Based on these results, we set out to confirm our hypothesis by total synthesis of the revised structure **17**.

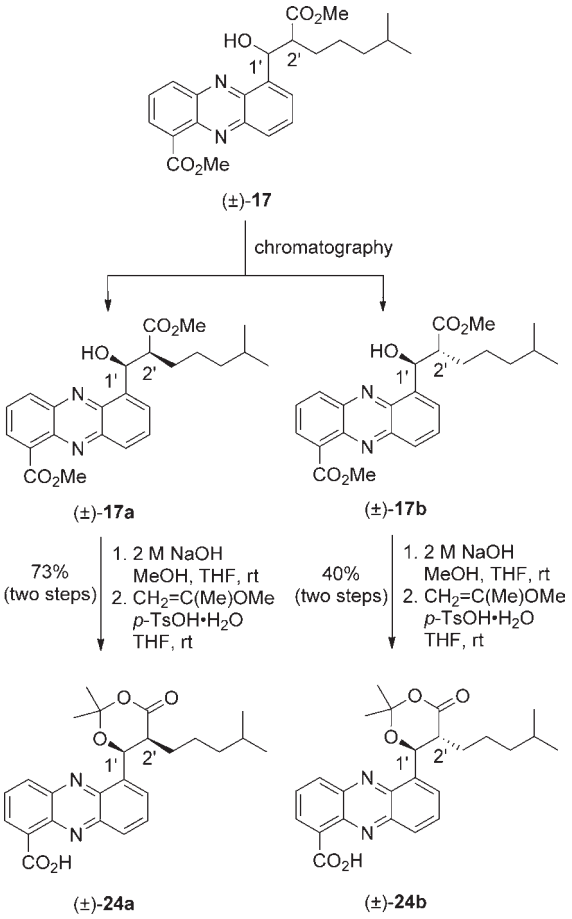
Scheme 3. Synthesis of the Revised Structure **17**



The total synthesis of the revised structure **17** employing an aldol reaction as the key step is shown in Scheme 3. Utilizing the same strategy from Scheme 2, the known alcohol **21**[6] was prepared in three steps. Coupling of chloride **11** with aniline **18** in the presence of potassium carbonate afforded compound **19** smoothly. Reductive cyclization of **19** with sodium borohydride and sodium ethoxide in ethanol provided the desired regioisomer **20**[6] exclusively. Treatment of acid **20** with methyl iodide using potassium carbonate as base yielded the compound **21**, mp 189–192 °C (lit.[6] 189 °C). Oxidation of alcohol **21** with activated manganese(IV) oxide furnished aldehyde **22** in good yield. Aldol reaction of aldehyde **22** with methyl ester **23**[7] provided two separable diastereomers **17a** and **17b** in a ratio of 3:2.

The structures of **17a** and **17b** were assigned on the basis of HRMS, ^{1}H, ^{13}C, 2D COSY, HSQC, and HMBC NMR analyses. Both ^{1}H and ^{13}C NMR data of **17b** in CD_3OD are identical with those reported for naturally occurring streptophenazine A. To confirm the hydroxyl group is located on 1′-position, ^{1}H NMR of **17b** was recorded in $CDCl_3$, in which the hydroxyl was observed at δ 5.07 (d, J = 10.0 Hz) and the H-1′ was observed at δ 5.57 (dd, J = 10.0, 7.5 Hz). The coupling correlation between the hydoxyl and H-1′ was observed and confirmed by a 2D COSY NMR experiment[8] in $CDCl_3$. Therefore, the originally proposed structure for streptophenazine A was revised to **17**, although the stereochemistry of the side chain was still unknown at that point.

Scheme 4. Relative Configuration of (±)-**17a** and (±)-**17b**



In order to determine the relative configuration of the side chain of **17a** and **17b**, both racemic diastereomers were transformed into cyclic compounds **24a** and **24b** in two steps, hydrolysis and cyclization (Scheme 4). As expected, a significant difference in the proton coupling constant $J_{1'\text{-}2'}$ between **24a** and **24b** was observed by ^{1}H NMR ($J_{1'\text{-}2'}$ = 2.5 Hz for **24a** and $J_{1'\text{-}2'}$ = 10.5 Hz for **24b**). In 1D

(7) Dickschat, J. S.; Helmke, E.; Schulz, S. *Chem. Biodiversity* **2005**, *2*, 318–353.

(8) See Supporting Information.

(9) The ee values were determined by chiral HPLC analyses on a chiral column.

(10) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392–393.

(11) Chavan, S. P.; Pasupathy, K.; Shivasankar, K. *Synth. Commun.* **2004**, *34*, 397–404.

(12) Yokokawa, F.; Shioiri, T. *J. Org. Chem.* **1998**, *63*, 8638–8639.

NOE studies, a strong NOE between H-1′ and H-2′ was recorded for **24a**, whereas no NOE between H-1′ and H-2′ was observed for **24b** (Figure 3). The diagnostic NOE difference between **24a** and **24b** supported the assignment of the relative stereochemistry for both compounds and their precursors (**17a** and **17b**).

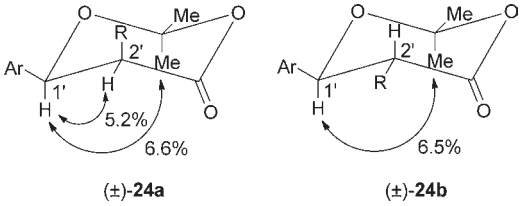


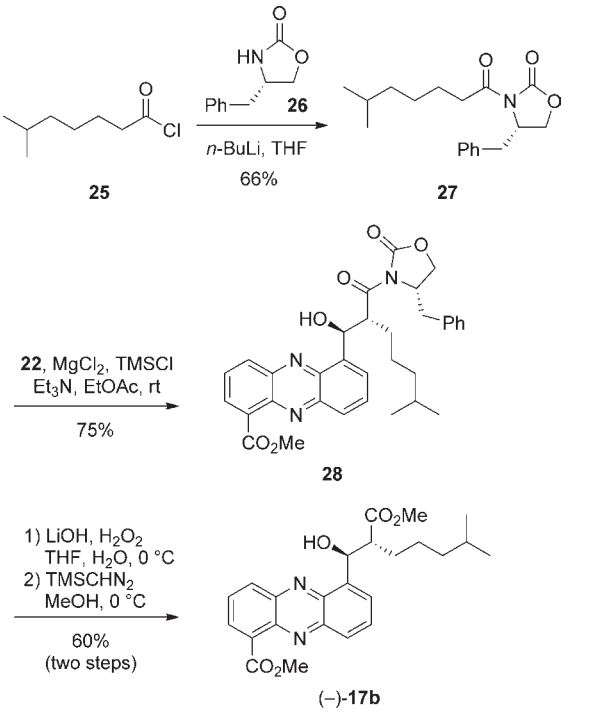
Figure 3. Key NOE correlations of (±)-**24a** and (±)-**24b**.

Chiral HPLC resolution of (±)-**17b** was performed on a chiral column to provide (+)-**17b** $\{[\alpha]^{20}_D = +47.5°$ (*c* 1.2, MeOH, >99% ee[9])$\}$ and (−)-**17b** $\{[\alpha]^{20}_D = -45.0°$ (*c* 1.2, MeOH, >99% ee[9])$\}$. The optical rotation of (−)-**17b** is in agreement with that reported for streptophenazine A in the literature.[3]

Asymmetric synthesis of (−)-**17b** was conducted utilizing asymmetric aldol reaction[10] as the key step (Scheme 5). Reaction of acid chloride **25**[11] with (*S*)-4-benzyloxazolidin-2-one (**26**) provided **27** smoothly. Asymmetric aldol reaction of oxazolidinone **27** with aldehyde **22** afforded exclusively the desired *anti*-adduct **28**. Oxidative hydrolysis of **28** with lithium hydroxide in the presence of hydrogen peroxide,[12] followed by treatment of the resulting acid with (trimethylsilyl)diazomethane gave (−)-**17b**, $[\alpha]_D^{20}$ −48.4° (*c* 1.0, CH_3OH). The optical rotation and ^1H, ^{13}C NMR data of (−)-**17b** are in agreement with those of naturally occurring streptophenazine A.[3] Therefore, the absolute configuration of (−)-**17b** was determined to be 1′*S*,2′*R*.

In conclusion, we have achieved the first total synthesis of (−)-streptophenazine A, leading to the structural revision of streptophenazine A to structure **17b**. The absolute

Scheme 5. Asymmetric Synthesis of (−)-**17b**



configuration of (−)-streptophenazine A was determined to be 1′*S*,2′*R*. Utilizing the same strategy described in Scheme 5, asymmetric synthesis of streptophenazines B and E has also been carried out.[8]

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Supporting Information Available. Asymmetric synthesis of streptophenazines B and E, X-ray crystallographic data, Experimental procedures, NMR spectra for **1**, **9**, **13**−**17**, **19**−**22**, **27**, and **28**. This material is available free of charge via the Internet at http://pubs.acs.org.