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A Concise Route to the Proposed Structure of Lydiamycin B, an Antimycobacterial Depsipeptide

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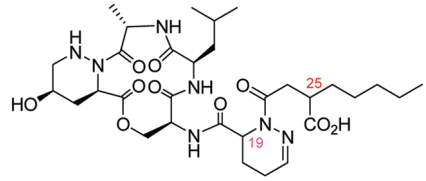
ABSTRACT

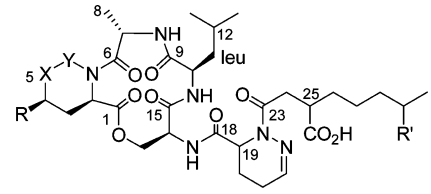


(19*S*,25*S*), (19*S*,25*R*), (19*R*,25*S*) and (19*R*,25*R*)-isomers

The total synthesis of four possible isomers with the proposed structure of antimycobacterial depsipeptide lydiamycin B is achieved. None of them shows identical NMR data with those reported for natural lydiamycin B, indicating that further structural revisions are required.

Lydiamycins A−D (**1**−**4**, Figure 1) are four cyclic depsipeptides that were isolated from the fermentation broth of *Streptomyces lydicus* (strain HKI0343) by Sattler et al.[1] The initial biological evaluation of these compounds revealed that the lydiamycins A−C could selectively inhibit *Mycobacterium smegmatis* SG 987, *M. Aurum* SB66, and *M. vaccae* IMET 10670 in a panel of Gram-positive and Gram-negative bacteria, yeasts, and fungi. Further studies on the antibiotic activity of lydiamycin A indicated that this compound is active against the standard and one multiresistant strain of *M. tuberculosis*. This result suggests that lydiamycin A might have an action mode different from that of available therapeutics like isoniazid, rifampicine, etambutol, and streptomycin.[1] Thus, total synthesis and subsequent SAR studies toward lydiamycins could be helpful for the discovery of novel antituberculosis drugs.[2]

Structurally, lydiamycins represent a novel class of small cyclodepsipeptides. Each of them contains two unusual amino acid residues, namely, Piz (piperazic acid building block) that is embodied in the cyclodepsipeptide part and dehydropiperazic acid that is connected with the 2-pentylsuccinic acid (PSA) moieties and the cyclodepsipeptide part.



lydiamycin A **1**: R = R' = H, X-Y = CH_2-NH
lydiamycin B **2**: R = OH, R' = H, X-Y = CH_2-NH
lydiamycin C **3**: R = R' = H, X-Y = CH=N
lydiamycin D **4**: R = H, R' = OH, X-Y = CH_2-NH

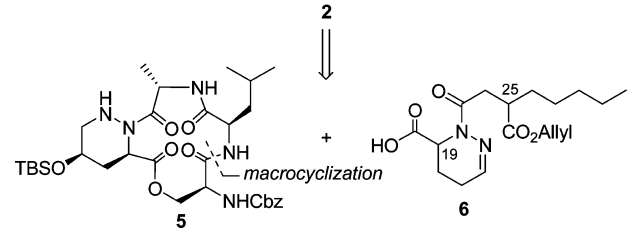


Figure 1. Proposed structures of lydiamycins A−D and the retrosynthetic analysis of lydiamycin B.

(1) Huang, X.; Roemer, E.; Sattler, I.; Moellmann, U.; Christner, A.; Grabley, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 3067.

(2) For a review on anti-tuberculosis drugs, see: Janin, Y. L. *Bioorg. Med. Chem.* **2007**, *15*, 2479.

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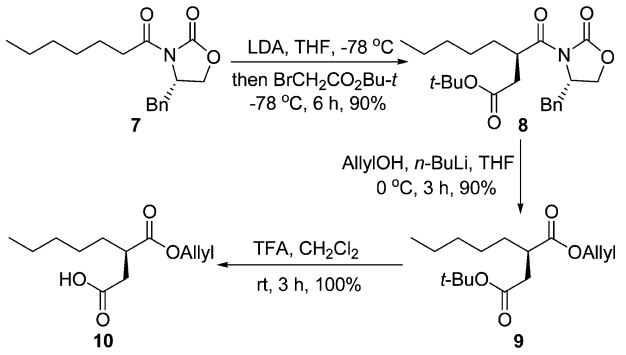
The stereochemistries of the dehydropiperazic acid unit and the PSA moieties have not been assigned via NMR experiments. The interesting biological activity and remaining structural questions prompted us to initiate a synthetic program toward these cyclodepsipeptides.[3] Herein, we wish to disclose our syntheses of four possible isomers with the proposed structure of lydiamycin B.

As illustrated in Figure 1, retrosynthetic analysis of lydiamycin B **2** led us to disconnect the peptide bond between L-Ser and the dehydropiperazic acid unit to provide macrocycle **5** and acid **6**. For the synthesis of **5**, we planned to carry out the macrocyclization at the D-Leu-L-Ser site. To establish the stereochemistry at C(19) and C(25), it was necessary to develop a diastereoselective approach for the assembly of the four possible isomers of **6**.

The required 2-*n*-pentyl succinic acid fragment **10** was prepared by applying an Evans' diastereoselective alkylation[4] as shown in Scheme 1, analogously to works in the Sankyo

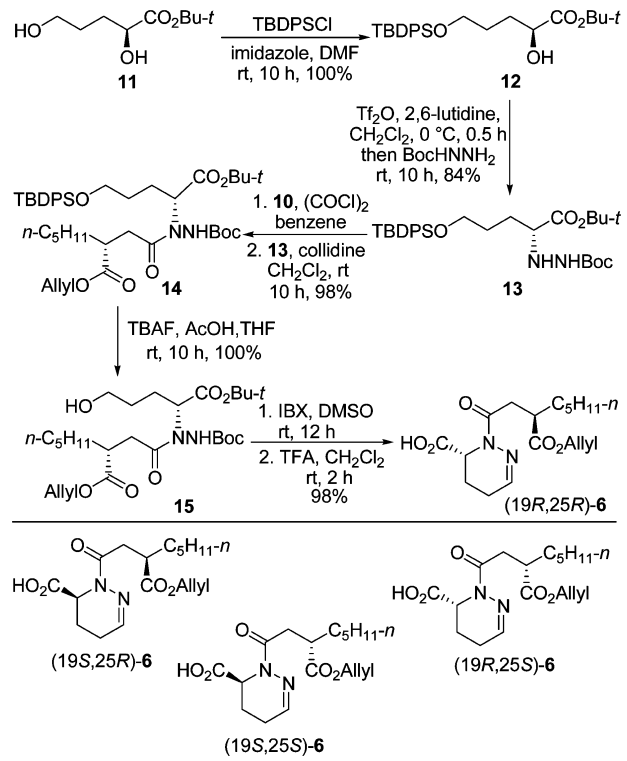
Scheme 1. Synthesis of the Acid **10**



group as part of their studies on the matlystatins.[5] The lithium enolate derived from *N*-acyl oxazolidinone **7** was reacted with *tert*-butyl bromoacetate to provide ester **8** in 90% yield. Removal of the chiral auxiliary using lithium allyloxide afforded allyl ester **9**, which was treated with TFA to form acid **10**.

As depicted in Scheme 2, our synthesis of the dehydropiperazic acid[6] fragment started from the known diol **11**.[6f]

Scheme 2. Synthesis of the Acids **6**



Selective protection of **11** as its TBDPS ether with TBDPSCl and imidazole afforded alcohol **12**. Sulfonylation of the hydroxyl group in **12** with triflic anhydride, followed by exposure of the resulting triflate to *tert*-butyl carbazate, provided hydrazide **13** in 84% yield.[7] Condensation of **13** with the acyl chloride generated from the acid **10** in the presence of 2,4,6-collidine gave the N-acylation product **14**. After removal of the TBDPS group in **14** with TBAF and AcOH to provide alcohol **15**, oxidation with IBX in DMSO solution[6j] was carried out. A mixture of aldehyde and cyclic hemiaminal was formed. Upon treatment of this mixture with TFA, deprotection and subsequent hydrazone formation occurred to deliver (19*R*,25*R*)-**6**. Following a similar procedure, the other three diastereomers were prepared.

The assembly of the cyclodepsipeptide part and its connection with the acids **6** is outlined in Scheme 3. Alcohol **17**, obtained from lactone **16** via a known procedure,[8−10] was converted into hydrazide **18** through its triflate in 88% yield. Condensation of **18** with an acyl chloride formed during the reaction of Cbz-L-Ala with 1-chloro-*N*,*N*-2-trimethyl-1-propen-1-amine[11] produced an amide, which was treated with TBAF and AcOH to provide dipeptide **19** in 95% yield over two steps. After conversion of alcohol **19**

(3) For our recent studies on the synthesis of cyclodepsipeptides, see: (a) Yu, S.; Pan, X.; Lin, X.; Ma, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 135. (b) Xie, W.; Zou, B.; Pei, D.; Ma, D. *Org. Lett.* **2005**, *7*, 2775. (c) Zou, B.; Long, K.; Ma, D. *Org. Lett.* **2005**, *7*, 4237. (d) Yu, S.; Pan, X.; Ma, D. *Chem.—Eur. J.* **2006**, *12*, 6572. (e) Ma, D.; Zou, B.; Cai, G.; Hu, X.; Liu, J. O. *Chem.—Eur. J.* **2006**, *12*, 7615. (f) Xie, W.; Ding, D.; Zi, W.; Li, G.; Ma, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 2844. (g) Tan, L.; Ma, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 3614, and ref 10.

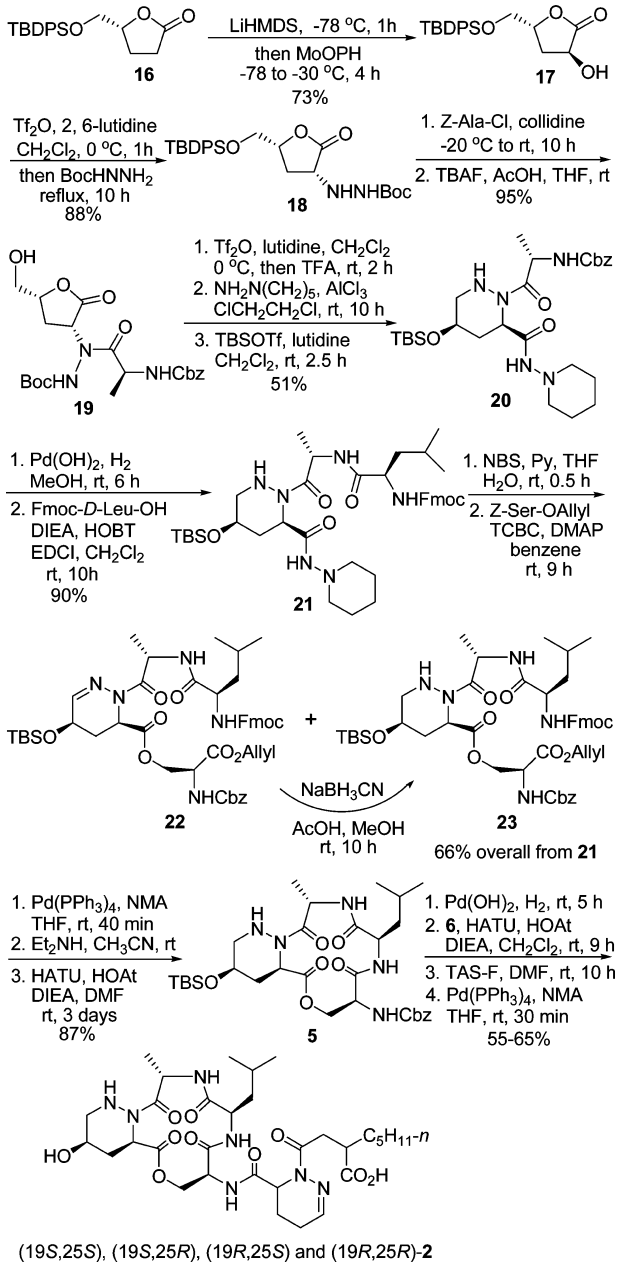
(4) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

(5) (a) Tamaki, K.; Ogita, T.; Tanzawa, K.; Sugimura, Y. *Tetrahedron Lett.* **1993**, *34*, 683. (b) Tamaki, K.; Kurihara, S.; Oikawa, T.; Tanzawa, K.; Sugimura, Y. *J. Antibiot.* **1994**, *47*, 1481.

(6) For previous studies on the asymmetric construction of the dehydropiperazic acid derivatives, see: (a) Nakamura, Y.; Shin, C.-G. *Chem. Lett.* **1991**, 1953. (b) Schmidt, U.; Riedl, B. *J. Chem. Soc., Chem. Commun.* **1992**, 1186. (c) Aspinall, I. H.; Cowley, P. M.; Mitchell, G.; Stoodley, R. J. *J. Chem. Soc., Chem. Commun.* **1993**, 1179. (d) Schmidt, U.; Riedl, B. *Synthesis* **1993**, 809. (e) Nakamura, Y.; Ito, A.; Shin, C.-G. *Bull. Chem. Soc. Jpn.* **1994**, 2151. (f) Schmidt, U.; Braun, C.; Sutoris, H. *Synthesis* **1996**, 223. (g) Ciufolini, M. A.; Xi, N. *Chem. Soc. Rev.* **1998**, *27*, 437. (h) Aspinall, I. H.; Cowley, P. M.; Mitchell, G.; Raynor, C. M.; Stoodley, R. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2591. (i) Ciufolini, M. A.; Valognes, D.; Xi, N. *Angew. Chem., Int. Ed.* **2000**, *39*, 2493. (j) Hannachi, J.-C.; Vidal, J.; Mulatier, J.-C.; Collet, A. *J. Org. Chem.* **2004**, *69*, 2367.

(7) Hoffmann, R. V.; Kim, H.-O. *Tetrahedron Lett.* **1990**, *31*, 2953.

Scheme 3. Completion of the Synthesis



into its triflate and deprotection with TFA, intramolecular N-alkylation occurred spontaneously to give a piperazide.[10] This intermediate was condensed with 1-aminopiperidine under the assistance of $AlCl_3$[12] and then silylated with TBSOTf and 2,6-lutidine to afford protected dipeptide **20** with 51% overall yield from **19**. Noteworthy is that using 1-aminopiperidine to protect the carboxylic acid moiety is essential in this case[13,14] because our initial attempts to protect this position with different ester groups led to exclusive diketopiperazine formation in the Cbz-deprotection step.

Hydrogenolysis of **20** followed by connection of the liberated amine with Fmoc-D-Leu provided tripeptide **21** in 90% yield. When removing the 1-aminopiperidine group with *N*-bromosuccinimide and pyridine in aqueous THF,[13] partial oxidation at the piperazic ring took place, and the resulting mixture was condensed with *Z*-Ser-OAllyl to furnish a mixture of esters **22** and **23** in a ratio of about 1:3. Since the hydrazone **22** could be transformed into **23** quantitatively via reduction with $NaBH_3CN$,[15] we were able to obtain **23** in 66% overall yield starting from **21**. Next, the allyl and the Fmoc protecting groups were cleaved with palladium chemistry and diethylamine treatment, respectively. The liberated amino acid was subjected to macrolactamization in the presence of HATU/HOAt/*i*-Pr_2NEt[16] in a diluted DMF solution to afford cyclization product **5** in 87% overall yield. Finally, deprotection of **5** via a $Pd(OH)_2$-catalyzed hydrogenolysis and subsequent coupling with each isomer of **6** produced the corresponding amides. These amides were sequentially treated with TAS-F and $Pd(Ph_3P)_4$/NMA to deliver four possible isomers of **2**. Unfortunately, none of them showed NMR data identical to those reported for natural lydiamycin B. It was observed that the major difference came from the proton signals of the C-8 position. All four isomers of **2** have a chemical shift of 1.27 ppm for these protons, whereas the reported one is 1.45 ppm. This observation implied that the stereochemistry of its surrounding amino acid residues might be misassigned.

In conclusion, we have developed a facile route to assemble all possible isomers of the proposed structure of lydiamycin B. However, the total synthesis showed that the original assignment of the structure was incorrect. Further investigations on elaborating more analogues to

(8) Hanessian, S.; Murray, P.; Sahoo, S. P. *Tetrahedron Lett.* **1985**, *26*, 5631.
(9) Taniguchi, M.; Koga, K.; Yamada, S. *Tetrahedron* **1974**, *30*, 3547.
(10) Li, W.; Gan, J.; Ma, D. *Angew. Chem., Int. Ed.* **2009**, *48*, 8891.
(11) Schmidt, U.; Kroner, M.; Beutler, U. *Synthesis* **1988**, 475.
(12) Lesimple, P.; Bigg, D. C. H. *Synthesis* **1991**, 306.
(13) Huang, S.-B.; Nelson, J. S.; Weller, D. D. *J. Org. Chem.* **1991**, *56*, 6007.
(14) For recent piperazic acid-containing natural products total syntheses that have used acyl hydrazide protection of the Piz 3-carboxyl to overcome problems with diketopiperazine formation, see: (a) Hale, K. J.; Cai, J. *Chem. Commun.* **1997**, 2319. (b) Hale, K. J.; Cai, J.; Williams, G. *Synlett* **1998**, 149. (c) Hale, K. J.; Lazarides, L. *Org. Lett.* **2002**, *4*, 1903. (d) Hale, K. J.; Manaviazar, S.; George, J. H.; Walters, M. A.; Dalby, S. M. *Org. Lett.* **2009**, *11*, 733. (e) Hale, K. J.; Manaviazar, S.; Lazarides, L.; George, J.; Walters, M. A.; Cai, J.; Delisser, V. M.; Bhatia, G. S.; Peak, S. A.; Dalby, S. M.; Lefranc, A.; Chen, Y.-N. P.; Wood, A. W.; Crowe, P.; Erwin, P.; El-Tanani, M. *Org. Lett.* **2009**, *11*, 737.
(15) Kopka, I. E. *Tetrahedron Lett.* **1990**, *31*, 4711.
(16) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397.
(17) For previous studies on the synthesis of γ-hydroxyl piperazic acid derivatives and the corresponding natural products from other groups, see: (a) Hassall, C. H.; Ramachandran, K. L. *Heterocycles* **1977**, *7*, 119. (b) Hale, K. J.; Jogiya, N.; Manaviazar, S. *Tetrahedron Lett.* **1998**, *39*, 7163. (c) Kamenecka, T. M.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 2993. (d) Kamenecka, T. M.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 2995. (e) Depew, K. M.; Kamenecka, T. M.; Danishefsky, S. J. *Tetrahedron Lett.* **2000**, *41*, 289. (f) Hale, K. J.; Hummersone, M. G.; Cai, J.; Manaviazar, S.; Bhatia, G. S.; Lennon, J. A.; Frigerio, M.; Delisser, V. M.; Chumnongsaksarp, A.; Jogiya, N.; Lemaitre, A. *Pure Appl. Chem.* **2000**, *72*, 1659. (g) Kamenecka, T. M.; Danishefsky, S. J. *Chem.—Eur. J.* **2001**, *7*, 41. (h) Ushiyama, R.; Yonezawa, Y.; Shin, C.-G. *Chem. Lett.* **2001**, *30*, 1172. (i) Makino, K.; Jiang, H.; Suzuki, T.; Hamada, Y. *Tetrahedron: Asymmetry* **2006**, *17*, 1644. (j) Kennedy, J. P.; Brogan, J. T.; Lindsley, C. W. *Tetrahedron Lett.* **2008**, *49*, 4116.

establish the real structure of this γ-hydroxy piperazic acid[17] containing natural products as well as exploring their SAR are in progress and will be reported in due course.

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Supporting Information Available: Experimental procedures and copies of ^{1}H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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