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Total Synthesis of Desferrisalmycin B

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Abstract: The first total synthesis of a naturally occurring siderophore antibiotic, desferrisalmycin B, is described, and the configuration of the unknown stereocenter is assigned. The synthesis features a synthetic strategy of constructing the novel amino-heptopyranoside component by stereoselective dihydroxylation followed by a Bose-modified Mitsunobu reaction. Through this convergent approach, other members of salmycins should also be synthetically accessible.

Introduction

Siderophores are functionally defined as low molecular mass molecules which acquire iron(III) from the environment and transport it into microorganisms.[1] Because of the significant roles they play in the active transport of physiologically essential iron(III) through microbe cell membranes, it is not surprising that siderophore-drug conjugates are attracting more and more attention from both medicinal chemists and clinical researchers as novel drug delivery systems in the war against microbial infections, especially in an era of widespread emergence of multidrug-resistant (MDR) strains.[2] There have been three families of compounds identified as natural siderophore-drug conjugates, including ferrimycin, albomycin, and salmycin.[3] Among these, salmycin B (**1b**, Figure 1) was isolated from the fermentation broth of *Streptomyces violaceus* DSM 8286 in 1995 by Vértesy and co-workers.[3c] Salmycin B, along with other congeners (A, C, and D, **1a**, **1c**, and **1d**, respectively, Figure 1), shows potent antibacterial activity against both *Staphylococci* and *Streptococci*, including resistant strains of these pathogens.[3c]

The structure of salmycin B incorporates the known siderophore, danoxamine,[4] and an unusual amino-disaccharide, which contains a D-*arabino*-hexopyranos-2-ulose and a 6-deoxy-6-(methylamino)-D-*gluco*-heptopyranose. The unique and complex architecture of this compound, in conjunction with its potential therapeutic significance, stimulated our synthesis of desferri-

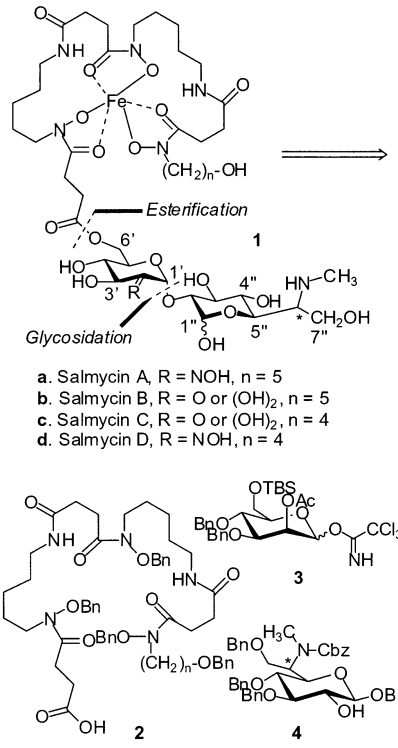

Figure 1. Salmycin and retrosynthetic analysis.

salmycin B. Although most of the stereochemical information for this compound has been revealed on the basis of extensive NMR spectroscopic experiments and degradation studies, the stereochemistry of C-6″ at the heptopyranose remained unknown.[3c] Thus, the syntheses of both stereoisomers of desferrisalmycin B also provided an opportunity to unambiguously assign this configuration.

Results and Discussion

The conspicuous structural features of salmycin B led us to a retrosynthetic analysis disconnecting this compound into three major parts as shown in Figure 1. The protected siderophore

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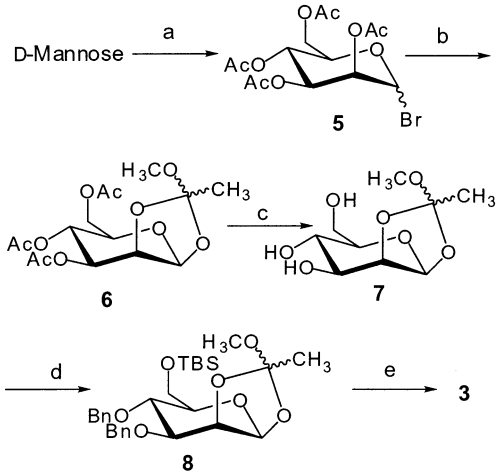
(1) (a) Neilands, J. B. *J. Biol. Chem.* **1995**, *270*, 26723. (b) Matzanke, B. F.; Muller-Matzanke, G.; Raymond, K. N. In *Iron Carriers and Iron Proteins*; Loehr, T. M., Ed.; VCH: New York, 1989; Chapter 1.
(2) (a) Miller, M. J.; Malouin, F. *Acc. Chem. Res.* **1993**, *26*, 241. (b) Roosenberg, J. M., II; Lin, Y.-M.; Lu, Y.; Miller, M. J. *Curr. Med. Chem.* **2000**, *9*, 159. (c) Braun, V.; Braun, M. *Curr. Opin. Microbiol.* **2002**, *5*, 194.
(3) (a) Benz, G.; Schröder, T.; Kurz, J.; Wünsche, C.; Karl, W.; Steffens, G.; Pfitzner, J.; Schmidt, D. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 527. (b) Bickel, H.; Gauman, E.; Nussberger, G.; Reusser, P.; Vischer, E.; Vosser, W.; Wettstein, A.; Azhner, H. *Helv. Chim. Acta* **1960**, *43*, 2105. (c) Vértesy, L.; Aretz, W.; Fehlhaber, H.-W.; Koger, H. *Helv. Chim. Acta* **1995**, *78*, 46.
(4) Huber, P.; Leuenberger, H.; Keller-Schierlein, W.-K. *Helv. Chim. Acta* **1986**, *69*, 231.

Scheme 1 [a]

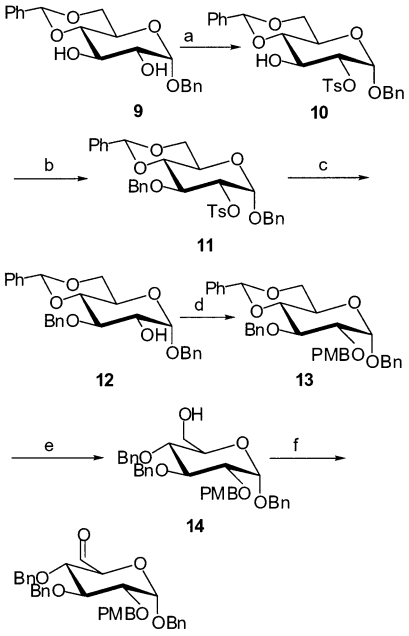


[a] Reagents and conditions: (a) (i) Ac_2O, I_2, rt; (ii) HBr/AcOH, CH_2Cl_2, rt; (b) CH_3OH, 2,6-lutidine, rt; (c) K_2CO_3, CH_3OH, rt; (d) (i) TBSCl, imidazole, DMF, rt; BnBr, NaH, DMF, rt, 67% for six steps; (e) (i) Dowex resin (50 × 8-400), 95% EtOH, rt; (ii) CCl_3CN, DBU, CH_2Cl_2, rt, 60% for two steps.

component **2** ($n = 5$) has been synthesized in this group.[5] We envisioned that hexapyranoside **3** and heptopyranoside **4** could be conjoined through a stereoselective trichloroacetimidate glycosidation.[6] Hexapyranose **3** was readily prepared through the following sequence (Scheme 1). Starting from D-mannose, peracetylation, anomeric bromination, and cyclization gave rise to ortho ester **6**,[7,8] which was deacetylated to generate compound **7**. The primary hydroxyl group of triol **7** was selectively protected as a *tert*-butyldimethylsilyl (TBS) ether followed by benzyl protection of the remaining hydroxyl groups to furnish suitably protected ortho ester **8**. Thus, by modifying the procedure described by Ley et al.,[9] multigram quantities of compound **8** could be easily accessed from D-mannose without purification of the intermediates. The ortho ester was then hydrolyzed upon exposure to Dowex resin (50 × 8-400) without jeopardizing the acid-sensitive TBS group.[10] Treatment of the resulting crude material with CCl_3CN and DBU finalized the preparation of trichloroacetimidate **3**.[11]

Having developed a viable route for the preparation of hexapyranose unit **3**, we then attended to the synthesis of the properly protected heptopyranoside **4**. Our synthetic plan called for the assembly of aldehyde **15**, which would serve as a platform for incorporation of the required additional carbon atom and introducing an amino group at C-6 through one of several possible approaches. To access this key intermediate, we took advantage of the stannylene-mediated regioselective protection to differentiate the 2,3-hydroxyl of benzyl α-glucoside derivative **9** as depicted in Scheme 2. Multigram quantities of benzylidene **9** can be readily prepared in high enantiomeric purity from D-glucose by modifying Ogawa's procedure.[12] After the formation of a 2,3-stannylene intermediate of compound **9** (not isolated), a tosyl group was selectively introduced to temporarily

Scheme 2 [a]



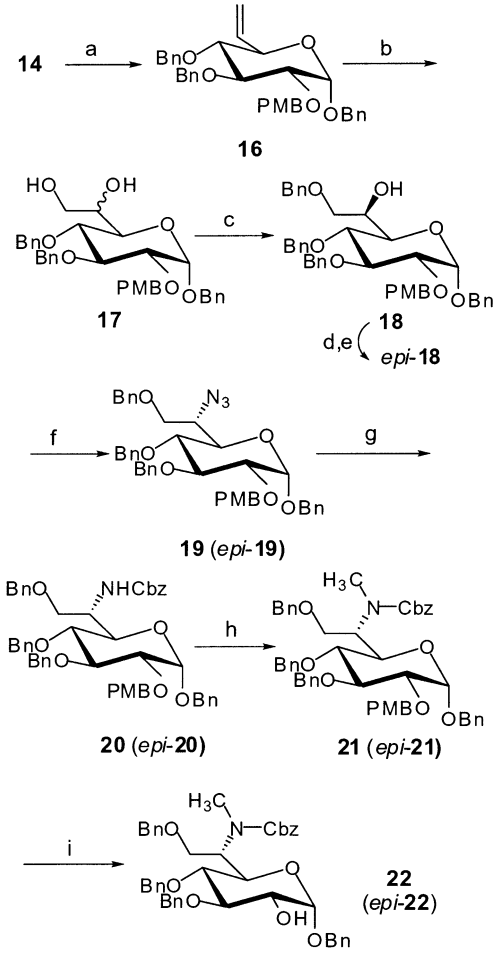
[a] Reagents and conditions: (a) Bu_2SnO, Tol/CH_3OH, reflux; TsCl, TEA, Tol, rt, 89%; (b) BnBr, $Ba(OH)_2$, BaO, DMF, rt, 88%; (c) $NaBH_4$, DMSO, 140 °C, 82%; (d) PMBCl, TBAB, NaH, DMF, rt, 94%; (e) BH_3·THF, Bu_2BOTf, 0 °C, 88%; (f) $(CO)_2Cl_2$, DMSO, CH_2Cl_2, −78 °C; NEt_3 −78 °C to rt.

mask the 2-hydroxyl group.[13] Benzylation of the remaining alcohol proceeded uneventfully to provide compound **11**. In the following step, discharge of the tosyl group in compound **11** by $NaBH_4$ reduction at elevated temperature regenerated the 2-hydroxyl group.[14] This transformation was sensitive to the concentration of the reaction, and diluted conditions were critical for achieving a reproducibly high yield. Subsequent PMB-protection of alcohol **12** was followed by the opening of the benzylidene ring through a Lewis acid-promoted regioselective borane reduction to expose the C-6 hydroxyl group with concomitant protection of the C-4 hydroxyl group.[15] Swern oxidation of primary alcohol **14** then successfully generated aldehyde **15** which was not purified due to the instability of this compound.[16]

With aldehyde **15** in hand, several strategies including a Strecker reaction,[17] the formation of an aziridine,[18] aminohy-

(5) Roosenberg, J. M., II; Miller, M. J. *J. Org. Chem.* **2000**, *65*, 4833.
(6) Schmidt, R. R.; Jung, K.-H. *Prep. Carbohydr. Chemistry* **1996**, 283.
(7) Katha, K. P. R.; Field, R. A. *Tetrahedron* **1997**, *53*, 11753.
(8) Meldal, M.; Franzyk, H.; Paulsen, H.; Brock, K. *J. Chem. Soc., Perkin Trans. 1* **1995**, *22*, 2883.
(9) Baeschlin, D. K.; Green, L. G.; Hahn, M. G.; Hinzen, B.; Ince, S. J.; Ley, S. V. *Tetrahedron: Asymmetry* **2000**, *11*, 173.
(10) Liu, C. M.; Waren, C. D.; Jeanloz, R. W. *Carbohydr. Res.* **1985**, *136*, 273.
(11) Lubineau, A.; Bonnaffé, D. *Eur. J. Org. Chem.* **1999**, 2523.
(12) (a) Ogawa, T.; Kaburagi, T. *Carbohydr. Res.* **1982**, *103*, 53. (b) Ho, W. H.; Wong, H. N. C.; Laurence, N.; Destrade, C.; Nguyen, H. T.; Noel, I. *Tetrahedron* **1995**, *51*, 7373.
(13) Grindley, T. B.; Thangarasa, R. *Can. J. Chem.* **1990**, *68*, 1007. Although the regioselective benzyl protection of 2-hydroxyl of compound **9** was reported in ref 12a, under similar conditions, PMB-protection led to a roughly 1:1 mixture of the two possible isomers. The 2-hydroxyl group of compound **9** can also be selectively acetylated. However, the following benzylation led to a complex mixture due to the acetyl migration.
(14) Pozsay, V.; Dubois, E. P.; Pannell, L. *J. Org. Chem.* **1997**, *62*, 2832.
(15) Jiang, L.; Chan, T. *Tetrahedron Lett.* **1998**, *39*, 355.
(16) Leeuwenburgh, M. A.; Kalker, C.; Duynstee, H. I.; Overkleeft, H. S.; van der Marcel, G. A.; van Boom, J. H. *Tetrahedron* **1999**, *55*, 8253.
(17) (a) Czernecki, S.; Valery, J.-M. *Carbohydr. Res.* **1988**, *184*, 121. (b) Arndt, H.; Polborn, K.; Koert, U. *Tetrahedron Lett.* **1997**, *38*, 3879. (c) Brown, H. C.; Garg, C. P. *J. Am. Chem. Soc.* **1964**, *86*, 1085. After the Strecker reaction of aldehyde **15** with KCN/CH_3NH_2 hydrochloride and the subsequent protection of the amino group with a Boc group, the nitrile could not be reduced to the corresponding aldehyde under various conditions.
(18) (a) Hashimoto, H.; Asano, K.; Fujii, F.; Yoshimura, J. *Carbohydr. Res.* **1982**, *104*, 87. (b) Effenberger, F.; Stelzer, U. *Tetrahedron: Asymmetry* **1995**, *6*, 283. The aziridine was prepared in less than 10% yield from the cyanohydrin of aldehyde **15** due to the reductive cleavage of the mesylate by LAH. The Lewis acid-mediated aziridine opening by benzyl alcohol also failed.

Scheme 3 [a]



[a] Reagents and conditions: (a) Swern oxidation; CH_3PPh_3Br, NaHMDS, THF, 0 °C to rt, 80% for two steps; (b) OsO_4, NMO, acetone/H_2O, 0 °C to rt, 92%; (c) Bu_2SnO, Tol/MeOH, reflux; BnBr, Tol, 85 °C, 81%; (d) DEAD, Ph_3P, *p*-nitrobenzoic acid, THF, rt, 89%; (e) K_2CO_3, MeOH, rt, 96%; (f) DEAD, PPh_3, DPPA, THF, 0 °C to rt, 89%; (g) (i) Ph_3P, H_2O/THF, reflux; (ii) CbzCl, TEA, CH_2Cl_2, 0 °C to rt, 65% for two steps; (h) CH_3I, NaH, DMF, rt, 94%; (i) DDQ, CH_2Cl_2/H_2O, rt, 90%.

droxylation of related olefin **16**,[19] and addition of organometallic phenyldimethylsilylmethyl reagents[20] were attempted to achieve the required one-carbon atom chain extension and install the methyl amino functionality at C-6. However, for various reasons, none of the above approaches proved feasible with our substrates. The ultimate solution to this problem relied on the dihydroxylation of olefin **16** followed by introduction of an amino group at C-6 (Scheme 3). Toward this end, a consecutive Swern oxidation and Wittig olefination were conducted on compound **14** to afford olefin **16** in high yield.[16] Treatment of olefin **16** with OsO_4 (5 mol %) and NMO at room temperature furnished diol **17** as an inseparable 5:1 mixture of two diastereomers.[21] The attempts to enhance this stereochemical bias by using a stoichiometric amount of osmium reagent or an asymmetric method (AD-mix-α)[22] provided little improvement. However, decreasing the reaction temperature to 0 °C improved the ratio to 8:1. These selectivities fall into the normal range observed with monosubstituted allylic alcohols and derivatives.[23] Stannylene-mediated regioselective protection of compound **17** successfully installed a benzyl group on the primary hydroxyl group.[24] We were glad to note that the major diastereomer could be separated at this stage by column chromatography to deliver compound **18** in an enantiomerically pure form. As the minor isomer could not be cleanly separated and both epimers were desirable, compound ***epi*-18** was prepared by inverting the stereochemistry of the C-6 of compound **18** through a Mitsunobu reaction followed by removal of the *p*-nitrobenzoate.[25] Both of these epimers were carried out through the rest of the reaction sequence separately.

To establish the absolute stereochemistry at C-6 in compound **18**, correlation studies were conducted. Hydrogenolysis of compound **18** removed the PMB and benzyl groups to afford the corresponding heptose. This product was found to possess the same optical rotation and melting point as D-*glycero*-D-*gluco*-heptose.[26] Thus, the configuration of the new stereogenic center was unambiguously assigned as *R*. The *anti*-selectivity of the osmylation (with respect to the pyranose ring-oxygen atom) was in good agreement with Kishi's empirical rule for predicting the stereoselectivity of the dihydroxylation of allylic alcohols and derivatives.[27]

To install the required methylamino group at C-6, the mesylate of alcohol **18** was prepared and subjected to a nucleophilic substitution by methylamine. However, the corresponding mesylate was unreactive toward methylamine. Gratifyingly, azide was able to be successfully introduced as an amino group equivalent through a Bose-modified Mitsunobu reaction, and the desired compound **19** was obtained in good yield.[28] Subsequent reduction of the azido group followed by Cbz protection then furnished compound **20**.[29] Finally, *N*-methylation and PMB deprotection completed the assembly of heptopyranoside **22** (Scheme 3).

The stage was now set for the stereoselective glycosidation between components **3** and **22**. The TMSOTf-mediated glycosidic bond formation proceeded smoothly to provide disaccharide **23** in excellent yield (Scheme 4). The α-configuration of the new bond was unambiguously proven by C−H coupling constants from NMR analyses.[30] After the removal of the acetyl

(19) (a) Li, G.; Angert, H. H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2813. (b) Tao, B.; Schlingloff, T. B.; Sharpless, K. B. *Tetrahedron Lett.* **1998**, *39*, 2507. Both the conversion (~30%) and the regioselectivity (1:1.6) of the aminohydroxylation reaction were poor. An extensive assay of the available ligands showed that they had little effect on the distribution of regioisomers, while in the absence of any ligand the reaction was very sluggish. The best result was obtained by employing $(DHQ)_2AQN$ as the ligand which provided a mixture in a ratio of 1.6 to 1 favoring the desired product.

(20) (a) van Delft, F.; de Kort, M.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron: Asymmetry* **1994**, *5*, 2261. (b) Matsumoto, T.; Kobayashi, Y.; Takemoto, Y.; Ito, Y.; Kamijo, T.; Harada, H.; Terashima, S. *Tetrahedron Lett.* **1990**, *31*, 4175. The addition of organometallic phenyldimethylsilylmethyl reagents (magnesium or cerium) to aldehyde **15** or aldimine prepared from **15** and methylamine failed to generate the desired products.

(21) MacManus, D. A.; Grabowska, U.; Biggadike, K.; Bird, M. I.; Davies, S.; Vulfson, E. N.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 295.

(22) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(23) Cha, J. K.; Kim, N.-S. *Chem. Rev.* **1995**, *95*, 1761.

(24) Castro-Palomino, A.; Tsvetkov, Y. E.; Schmidt, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 5438.

(25) Ghosh, A. K.; Lei, H. *J. Org. Chem.* **2000**, *65*, 4779.

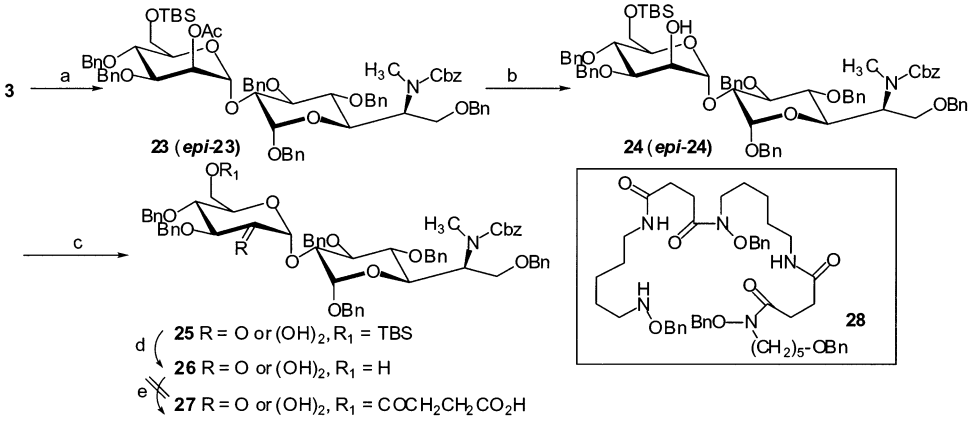
(26) (a) Brimacombe, J. S.; Kabir, N.; Abul, K. M. S. *Carbohydr. Res.* **1986**, *150*, 35. L,D-isomer: mp 195−196 °C, $[\alpha]_D = +52.0°$ (*c* 1.9, H_2O). (b) Begbie, R.; Richtmyer, N. K. *Carbohydr. Res.* **1966**, *2*, 272. D,D-isomer: mp 156−157 °C, $[\alpha]_D = +46.2°$ (*c* 2.4, H_2O). The synthetic sample: mp 154−155 °C, $[\alpha]_D = +46.9°$ (*c* 0.8, H_2O).

(27) (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943. (b) Christ, W. J.; Cha, J. K.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3947. (c) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247.

(28) Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, *19*, 1977.

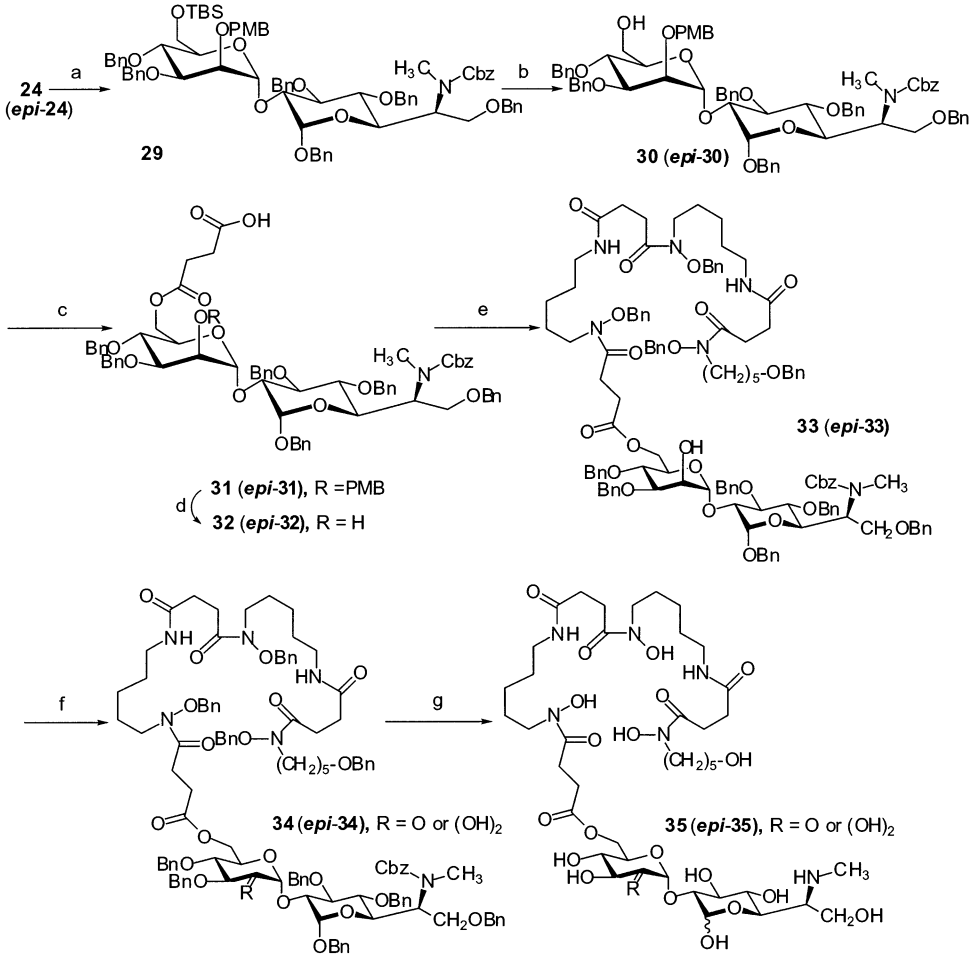
(29) Gololobov, Y. G.; Zhmurova, I. N.; Kasukhin, L. F. *Tetrahedron* **1981**, *37*, 437.

Scheme 4 [a]



[a] Reagents and conditions: (a) **22** (***epi*-22**), TMSOTf, CH_2Cl_2, 0 °C to rt, 88%; (b) K_2CO_3, MeOH, rt, 94%; (c) $(CO)_2Cl_2$, DMSO, CH_2Cl_2; TEA, −78 °C to rt, 91%; (d) 80% aqueous AcOH, rt, 83%; (e) SA, DMAP, Py, 80 °C.

Scheme 5 [a]



[a] Reagents and conditions: (a) PMBCl, NaH, DMF, rt, 54%; (b) 80% aqueous AcOH, rt, 86%; (c) SA, Py, DMAP 80 °C to rt, 88%; (d) DDQ, CH_2Cl_2/H_2O, rt, 74%; (e) **28**, EDC, HOAt, DMF, 0 °C to rt, 91%; (f) $(CO)_2Cl_2$, DMSO, CH_2Cl_2; TEA, −78 °C to rt, 98%; (g) H_2, Pd black, $HClO_4$, rt, 35%.

group from disaccharide **23**, a Swern oxidation was performed to generate ketone **25** that exists as a mixture of the ketone and the corresponding hydrate. Although compound **26** was obtained by the cleavage of the TBS group from **25**, it was found that the union of compound **26** and protected danoxamine **2**[5] could not be accomplished. Various methods including Mitsunobu reactions,[31] DCC/DMAP coupling reactions,[32] and Mukaiyama's reagent[33] all failed to effect the formation of the desired ester bond.

(30) In mannose, the α-anomers usually give a C−H coupling constant of greater than 170 Hz, whereas the β-anomers usually give C−H couplings of less than 160 Hz. The nondecoupled ^{13}C NMR of compound **23** indicated that the newly formed resonance was at 94.48 ppm with a coupling constant of 170.35 Hz.

(31) McKee, J. A. Ph.D. Thesis, University of Notre Dame, 1991.
(32) Kim, H.; Kim, I. J.; Danishefsky, S. J. *J. Am. Chem. Soc*. **2001**, *123*, 35.
(33) Tennant-Eyles, R. J.; Fairbanks, A. J. *Tetrahedron: Asymmetry* **1999**, *10*, 391.

Finally, we decided to switch the roles of two coupling partners by acylating the disaccharide with succinic anhydride (SA) and connecting the resulting carboxylic acid to danoxamine precursor **28**[5] to circumvent the problematic esterification step. However, our attempts to prepare compound **27** were not successful possibly due to the presence of the hydrated ketone.[34]

After further consideration, we decided to postpone the oxidation until after the coupling reaction with the siderophore. Because the eventual removal of the acetyl group in compound **23** was not compatible with the danoxamine-disaccharide ester linkage[35] and the selective acylation of the primary alcohol in the presence of a secondary hydroxyl group by succinic anhydride could not be implemented, the 2′-hydroxyl group was protected as a PMB ether to provide compound **29** (Scheme 5). Surprisingly, this seemingly straightforward transformation only proceeded with modest efficiency due to the complication of a facile silyl group migration under reaction conditions. With compound **29** in hand, the silyl group was removed by treatment with aqueous acetic acid, which was followed by acylation with succinic anhydride and PMB deprotection to afford acid **32**.[36] Although we did not expect the secondary alcohol to interfere with the hydroxamate formation, we were pleased to find that acid **32** turned out to be an ideal coupling partner with compound **28**, and conjugate **33** was obtained in excellent yield. The following Swern oxidation also progressed extremely well to afford compound **34**. The endgame global deprotection by hydrogenolysis, however, was not trivial. Most of the common methods led to incomplete conversion or decomposition. After an extensive investigation of different catalysts and conditions, we finally discovered that a combination of Pd black and catalytic perchloric acid was the reagent of choice to effect this transformation. By employing these conditions, we obtained compound **35** whose structure was supported by NMR (^{1}H and ^{13}C), IR, and MS analyses (Scheme 5). In a similar fashion, ***epi*-35** was prepared from compound ***epi*-18**.

Through comparison of the NMR spectra of the authentic sample[3c] with those of our synthetic material, compound ***epi*-35** was identified as the natural desferrisalmycin B. On the basis of these facts, the heptopyranose component of salmycin B has a D-*glycero*-D-*gluco* configuration.

Conclusion

The first total synthesis of desferrisalmycin B was accomplished. The synthesis provided a platform from which the easy entry to other compounds in this family could be achieved. By preparation of both epimers of desferrisalmycin B and subsequent comparison with the authentic sample, the stereochemistry of the unknown chiral center was determined. Our work in this area will significantly advance the understanding of the siderophore drug delivery systems and facilitate the design of more effective siderophore-drug conjugates in the future.

Acknowledgment. This research was supported by a grant from the NIH (AI 30988). L.D. thanks the Reilly and Albany Molecular fellowships. The authors are grateful to Donald R. Schifferl and Dr. Jaroslav Zajicek for assistance with NMR experiments and Dr. William C. Boggess Jr. and Nonka Sevova for performing MS analyses. We extend our gratitude to Ms. Maureen Metcalf for her help in the preparation of this manuscript. We gratefully acknowledge Dr. László Vértesy at Aventis Pharma Deutschland GmbH for providing copies of NMR spectra of authentic desferrisalmycin B.

Supporting Information Available: Detailed experimental procedures and characterization data for compounds **3**, **8**, **9**, and all new compounds as well as ^{1}H NMR of the authentic sample (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA028386W

(34) Bessodes, M.; Dubertret, C.; Jasin, G.; Scherman, D. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1393. Alternatively, the *E*-oxime was prepared as a protected carbonyl compound (Barili, P. L.; Berti, G.; D'Andrea, F.; Di Bussolo, V. *Carbohydr. Res.* **1996**, *290*, 17). This also provided an easy entry to salmycin A. Unfortunately, although the silyl ether deprotection and acylation could be conducted without incident to afford the desired acid, the final coupling reaction with compound **28** failed to afford the desired product.

(35) The siderophore conjugate was prepared with the 2′-hydroxyl group protected with an acetyl group. However, deacetylation caused the simultaneous cleavage of the ester linkage.

(36) Although the coupling reaction of acid **31** and compound **28** afforded the desired conjugate, this compound was too sensitive to survive the DDQ-mediated PMB deprotection.