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Synthesis and Absolute Structure of Manzacidin B

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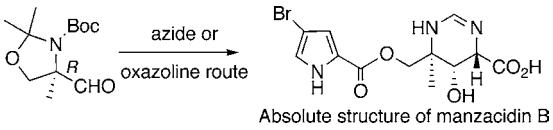
ABSTRACT



Four possible stereoisomers of manzacidin B were synthesized using stereochemically defined synthetic routes via the azide 7 and oxazoline 11 starting with the (*R*)-α-methyl Garner aldehyde 5. Comparisons of the spectroscopic data of the synthetic isomers 4a–d with those of the natural manzacidin B revised the proposed structure 3 to (4*S*,5*S*,6*R*)-4d.

Manzacidins A, B, and C, isolated from the Okinawan sponge *Hymeniacidon* sp. by Kobayashi et al. in 1991, possess a unique structure consisting of an ester-linked bromopyrrolecarboxylic acid and a 3,4,5,6-tetrahydropyrimidine ring in which one of the amino groups is attached to the C6 quaternary carbon center.[1,2] The relative and absolute structures of manzacidins A (**1**) and C (**2**) have been determined as the C6 isomers with the same 4*S* configuration by our previous total synthesis of both **1** and **2**.[3] Because of their unique structure and pharmacological profile, which includes α-adrenoceptor blockers, antagonists of serotonergic receptors, and actomyosin ATPase activators as in a class of bromopyrrole alkaloids,[4] manzacidins are intriguing target molecules. Although both manzacidin A and C have yielded to total synthesis,[5] no report has appeared for the synthesis of manzacidin B. The 4*S**,5*S**,6*S** stereochemistry **3** which corresponds to the 5α-hydroxylated form of **1** was originally assigned to manzacidin B on the basis of the similarity between the ^{1}H and ^{13}C NMR spectral data and those of manzacidin A.[1] However, it remained necessary to confirm its relative and absolute structure by its total synthesis. In this report, we describe the synthesis of four possible isomers (6*R*)-**4a**−**d** of manzacidin B (Figure 1) including an

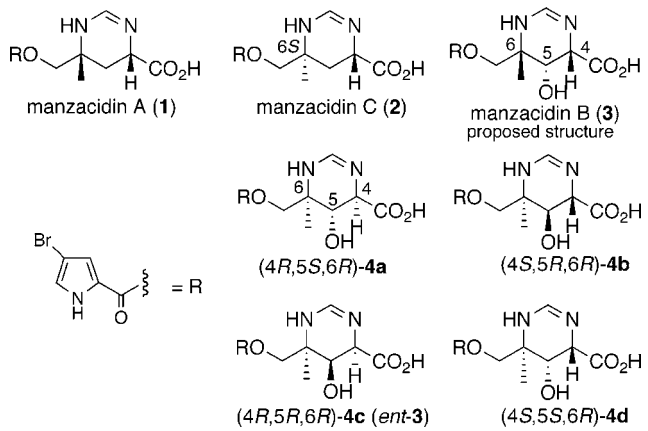


Figure 1. Structures of manzacidins and four possible (6*R*)-diastereomers of manzacidin B (**4a**−**d**).

(1) Kobayashi, J.; Kanda, F.; Ishibashi, M.; Shigemori, H. *J. Org. Chem.* **1991**, *56*, 4574−4576.

(2) Manzacidin D, the debromo N-1 methylated form of manzacidin C, was isolated from a fossil sponge. See: Jahn, T.; Konig, G. M.; Wright, A. D.; Worheide, G.; Reitner, J. *Tetrahedron Lett.* **1997**, *38*, 3883−3884.

(3) Namba, K.; Shinada, T.; Teramoto, T.; Ohfune, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10708−10709.

(4) Faulkner, D. J. *Nat. Prod. Rep.* **1998**, *15*, 113−158 and references therein.

(5) For the total synthesis of manzacidin A and/or C, see: (a) Wehn, P. M.; DuBois, J. *J. Am. Chem. Soc.* **2002**, *124*, 12950−12951. (b) Lanter, J. C.; Chen, H.; Zhang, X.; Sui, Z. *Org. Lett.* **2005**, *7*, 5905−5907. (c) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2174−2175. (d) Wang, L.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928−3930. For the synthesis of manzacidin D, see: Drouin, C.; Woo, J. C. S.; MacKay, D. B.; Lavigne, R. M. A. *Tetrahedron Lett.* **2004**, *45*, 7197−7199.

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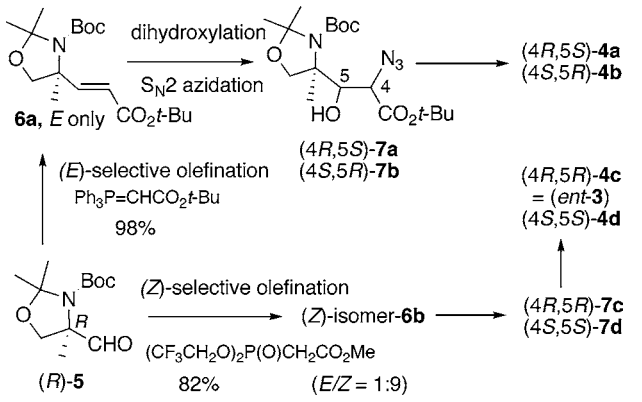
enantiomer of the proposed **3** by stereochemically unambiguous processes and the determination of its relative and absolute configuration to be (4*S*,5*S*,6*R*)-**4d**.

We envisioned that four diastereomers **4a**−**d** would be synthesized from the optically active (*R*)-α-methyl Garner aldehyde **5**[6,7] which is readily available in multigram quantities by an asymmetric Strecker synthesis from acetol.[8] After the *E*- or *Z*-selective olefination of **5**, the dihydroxylation of (*E*)-**6a** followed by S_N2 azidation[9] (azide route) would produce the azide alcohols (4*R*,5*S*)-**7a** and (4*S*,5*R*)-**7b**, and the same treatment with (*Z*)-**6b** would give (4*R*,5*R*)-**7c** and (4*S*,5*S*)-**7d**, respectively (Scheme 1). These isomers

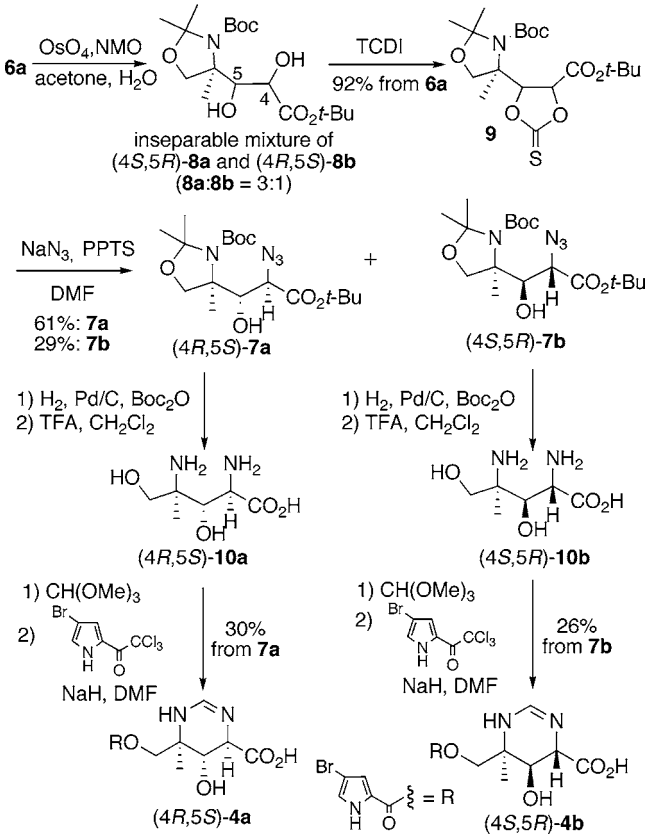
Scheme 1



can be converted to **4a**−**d**, respectively, using the same protocol previously employed for our synthesis of **1** and **2**.

The dihydroxylation of the *t*-butyl ester **6a** gave an inseparable mixture of the desired diols **8a**,**b** in a 3:1 ratio (Scheme 2).[10,11] The mixture was subjected to S_N2 azidation via the cyclic thionocarbonate **9** to give a separable mixture of azide alcohols (4*R*,5*S*)-**7a** (61%) and (4*S*,5*R*)-**7b** (29%). No epimerization at C4 of both **9** and **7a**,**b** under the azidation reaction was encountered using PPTS-*d* because no D atom was incorporated into **7a**,**b** and the recovered **9**. The major isomer **7a** was converted to the amino acid **10a** via the isolation of its *N*-Boc protected form followed by acidic treatment. The initial tetrahydropyrimidine formation and subsequent esterification were performed according to a slightly modified method reported by us[3,12] to give **4a** (30% from **7a** after HPLC purification). The minor isomer **7b** was

Scheme 2



converted to **4b** (28% from **7b**) in the same manner as that of **4a**. Both the ^1H and ^{13}C NMR data of **4a**,**b** were not identical to the reported spectra of natural manzacidin B indicating that the relative stereochemistry of manzacidin B is either (4*R*,5*R*,6*R*)-**4c** (*ent*-**3**) or (4*S*,5*S*,6*R*)-**4d**.

We next examined the synthesis of **4c**,**d** from (*Z*)-**6b** according to our initial plan. Dihydroxylation of (*Z*)-**6b** gave a 3:1 mixture of diols. However, subsequent treatment with 1,1′-thiocarbodiimidazole (TCDI) gave a 1:1 mixture of the *cis*- and *trans*-thionocarbonates, indicating that a substantial epimerization occurred at C4 under the reaction conditions. An undesired epimerization also occurred during the thionocarbonate formation even at low temperature or the substitution reaction conditions of the *cis*-thionocarbonate with an azide.

It has been reported that the aldol condensation of an isonitrile with an aldehyde in the presence of a metal catalyst gave a *trans*-oxazoline as the major product.[13] We envisioned that this method would produce a mixture of the desired *trans*-oxazolines **11a**,**b** (oxazoline route). To our delight, the reaction of an isonitrile with (*R*)-**5** in the presence of a catalytic amount of CuCl smoothly proceeded to give a mixture of the (4*R*,5*R*)- and (4*S*,5*S*)-*trans*-oxazolines **11a**,**b** (**11a**/**11b** = 7:1, 87%) (Scheme 3). Neither of the *cis*-isomers was detected. The exclusive formation of the *trans*-oxazolines

(6) Alia, M.; Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A.; Leperia, Y. *Tetrahedron* **1998**, *54*, 14963−14974.

(7) The addition of a dianion enolate derived from the Boc-glycine ester to **5** gave a mixture of four diastereomers. Although conversions of the mixture to **4a**−**d** were successfully performed, we did not deduce their relative structures by NMR experiments.

(8) (a) Moon, S.-H.; Ohfune, Y. *J. Am. Chem. Soc.* **1994**, *116*, 7405−7406. (b) Ohfune, Y.; Shinada, T. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1115−1129.

(9) Ko, S. Y. *J. Org. Chem.* **1995**, *60*, 6250−6251.

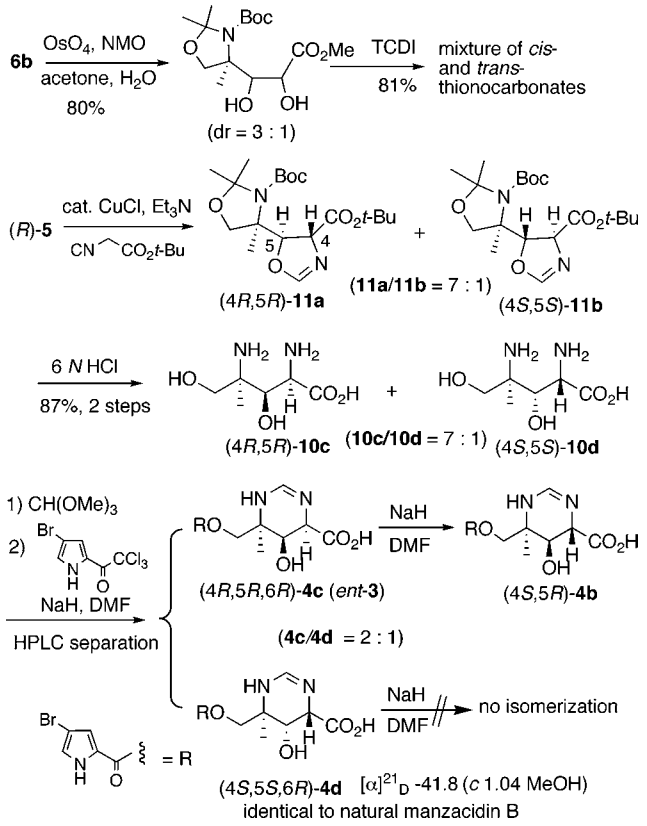
(10) Determination of the stereochemistry of the dihydroxylation products **8a**,**b**; see Supporting Information.

(11) A much higher 4*S*/4*R*-selectivity in the dihydroxylation reaction has been observed in a related system. See: Kawasaki, M.; Shinada, T.; Hamada, M.; Ohfune, Y. *Org. Lett.* **2005**, *7*, 4165−4167.

(12) See Supporting Information for the experimental details.

(13) (a) Togni, A.; Pastor, S. D. *Helv. Chim. Acta* **1989**, *72*, 1038−1041. (b) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405−6406.

Scheme 3



was ascertained by converting the mixture to amino acids **10c**,**d** (7:1, 100%) whose ^{1}H NMR spectra were apparently different from those of **10a**,**b**. Because the isomers possessing either the 4*R*,5*R* or 4*S*,5*S* configuration could not be determined at this stage, we decided to convert the mixture to **4c**,**d**. The initial amidination and subsequent esterification (2 equiv of NaH, DMF) of **10c**,**d** (7:1) gave a 2:1 mixture of **4c**,**d** together with the unexpected (4*S*,5*R*)-**4b**.[12,14] The decrease in the product ratio suggested that the C4 of the major isomer **4c** was epimerized to **4b** under the reaction conditions. In fact, after the HPLC separation of each isomer, the treatment of the major isomer **4c** with NaH/DMF allowed complete epimerization to **4b**, whereas **4d** remained unchanged.[15] These results clearly indicated that the structure of the major isomer **4c** derived from **11a** is (4*R*,5*R*,6*R*)-**4c** (*ent*-**3**), and the minor isomer **4d** possessed the 4*S*,5*S*,6*R* configuration. Comparisons of the ^{1}H and ^{13}C NMR spectra and the sign of the optical rotation of **4a**−**d** with those of the natural manzacidin B[1] clearly indicated that (4*S*,5*S*,6*R*)-**4d** is identical in all respects to the natural manzacidin B. Thus, the relative and absolute structure of manzacidin B is confirmed to be (4*S*,5*S*,6*R*)-**4d**, the C5 hydroxylated form of manzacidin C (**2**).

In summary, the stereochemically unambiguous syntheses of four diastereomers of manzacidin B revised the proposed relative structure of manzacidin B (**3**) to (4*S*,5*S*,6*R*)-**4d**. The syntheses of the four diastereomers were performed by the complementary use of the dihydroxylation/azide substitution route for **4a**,**b** and the isonitrile condensation route for **4c**,**d**. The latter route is shorter (four steps) and displays high *trans*-selectivity. Although the major isomer **11a** led to the formation of the *ent*-proposed structure of manzacidin B, we are currently investigating the stereochemical outcome of the isonitrile condensation which focuses on an inverse stereoselectivity for the efficient total synthesis of the natural manzacidin B (**4d**).

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Supporting Information Available: Experimental and characterization details of all new compounds, structure determination of the diols **8a**,**b**, and ^{1}H and ^{13}C NMR spectra of the natural and synthetic **4a**−**d** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) *β*-Elimination of the C5 hydroxy group was also observed as a side reaction.

(15) (4*R*,5*S*)-**4a** was not epimerized at C4 to (4*S*,5*S*)-**4d** under the same reaction conditions. The reason only **4c** was epimerized to **4b** is not clearly understood at this time.