Total Synthesis and Absolute Structure of Manzacidin A and C

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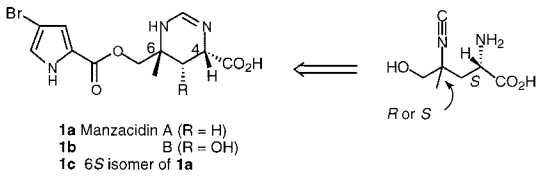
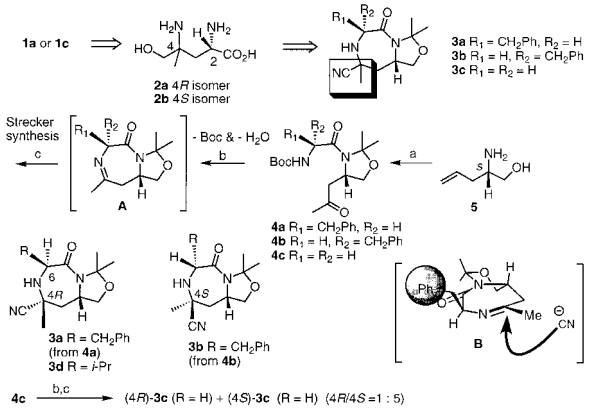
A number of bromopyrrole alkaloids have been found from marine sponges which are known to exhibit pharmacologically useful activities such as α-adrenoceptor blockers, antagonists of serotonergic receptor, actomyosin ATPase activators, etc.[1] Recently, Kobayashi et al. have isolated a novel class of the alkaloids, manzacidin A−C (**1a**−**1c**),[2] from an Okinawan sponge *Hymeniacidon* sp.[3] which 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 C4 quarternary carbon center.[4] Although manzacidins exhibit similar biological activities to those of other bromopyrrole alkaloids, only preliminary tests have been carried out, owing to the extremely small amount of samples available from marine sources.[2] In the following, we describe highly stereoselective synthesis of both natural manzacidin A (**1a**) and C (**1c**), which unambiguously assigned their absolute structures to be (4*S*,6*R*)-**1a** and (4*S*,6*S*)-**1c**.



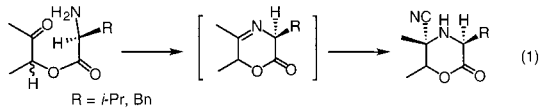
1a Manzacidin A (R = H)
1b B (R = OH)
1c 6*S* isomer of **1a**

The stereochemical relationship between **1a** and **1c** has been proposed as either the C4 or the C6 diastereomer. We presumed that their C4 configuration would be the same *S* by considering a plausible biosynthetic pathway which involves (*R*)- or (*S*)-isonitrile intermediate as often seen in the structure of marine natural products.[5] Thus, diastereoselective construction of (2*S*,4*R*)- and (2*S*,4*S*)-diamines, **2a** and **2b**, would lead to **1a** and **1c**, respectively (Scheme 1). This route relies on a stereoselective construction of the amino nitrile **3** by the Strecker synthesis of the amino ketone **4**. However, an asymmetric version of the Strecker synthesis using an amide is unknown, and the stereochemistry of a cyanide addition to the imine **A** is unpredictable in this case because its C2 chiral center also affects the facial selectivity, while in our previous work the nitrile addition to a six-membered ketimine intermediate occurred from the sterically less demanding α-face (eq 1).[6]

Scheme 1



[a] (a) (1) Et_3N, Boc-L-Phe-OSu, THF−MeOH (7:1), 0 °C, 2 h; (2) *p*-TsOH, 2,2-dimethoxypropane, toluene, reflux, 2 h; (3) 0.1 equiv $PdCl_2$, 1 equiv CuCl, O_2, DMF−H_2O (7:1), rt, 12 h (66% from **5**). (b) TMSOTf, 2,6-lutidine, CH_2Cl_2, rt, 30 min. (c) TMSCN, $ZnCl_2$, 2-PrOH, rt, 18 h (81% from **3a**, 87% from **3b**, and 48% from **3c**).



To examine the stereochemical outcome of the nitrile addition to the imine **A**, we prepared three types of Strecker precursors having Boc-L-phenylalanyl amide **4a**, its D-Phe isomer **4b**, and Boc-glycyl amide **4c**, respectively, from (2*S*)-allylglycinol **5** readily available from L-allylglycine or Boc-L-aspartate (Scheme 1).[7] After chemoselective removal of the Boc group of **4a** with TMSOTf/2,6-lutidine,[8] the resulting amine was treated with trimethylsilylnitrile (TMSCN) to produce in 81% yield the amino nitrile (4*R*)-**3a** as a single diastereomer.[9] The D-Phe isomer **4b** afforded (4*S*)-**3b** (87%), exclusively. These results clearly indicated that in each case the nitrile addition to the imine occurred from the opposite side of the C6 benzyl group, for example, B,[10] similar to the six-membered case (vide supra). On the other hand, the glycyl amide **4c** gave a 1:5 mixture of (4*R*)-**3c** and (4*S*)-**3c**, indicating that the cyanide preferentially attacks from the sterically less hindered β-face when the C6 substituent is absent. Thus, not only was the stereochemical outcome of the amino nitrile formation clearly understood, but also the desired amino nitriles **3a** and **3b**, which correspond to the stereochemistry of **1a** and **1c**, were obtained, respectively, with excellent stereocontrol.

We next examined the conversion of **3a** into (2*S*,4*R*)-**2a**. This process requires initial oxidation of **3a** to the imino ketone **6**,

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

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

(3) Several bromopyrrole alkaloids have been isolated from Himeniacidon Sponge: Kobayashi, J.; Inaba, K.; Tsuda, M. *Tetrahedron* **1997**, 46, 16679−16682 and references therein.

(4) Recently, manzacidin D structurally related to **1** has been isolated from "Living Fossil" sponge: Jahn, T.; König, G. M.; Wright, A. D.; Wörheide, G.; Reitner, J. *Tetrahedron Lett*. **1997**, *38*, 3883−3884.

(5) Isonitrile-containing marine natural products, see: (a) Wright, A. D.; König, G. M.; Angerhofer, C. K.; Greenidge, P.; Linden, A.; Desqueyroux-Faundez, R. *J. Nat. Prod*. **1996**, *59*, 710−716. (b) Kobayashi, J.; Tsuda, M.; Nemoto, A.; Tanaka, Y.; Yazawa, K.; Mikami, Y. *J. Nat. Prod*. **1997**, *60*, 719−720.

(6) (a) Moon, S.-H.; Ohfune, Y. *J. Am. Chem. Soc.* **1994**, *116*, 7405−7406. (b) Ohfune, Y.; Moon, S.-H.; Horikawa, M. *Pure Appl. Chem*. **1996**, *68*, 645−648. (c) Horikawa, M.; Nakajima, T.; Ohfune, Y. *Synlett* **1997**, 253−254. (d) Ohfune, Y.; Nanba, K.; Takada, I.; Kan, T.; Horikawa, M.; Nakajima. T. *Chirality* **1997**, *9*, 459−462. (e) Ohfune, Y.; Horikawa, M. *J. Synth. Org. Chem. Jpn.* **1997**, *55*, 982−993.

(7) Ouerfelli, O.; Ishida, M.; Shinozaki, H.; Nakanishi, K.; Ohfune, Y. *Synlett* **1993**, 409−410.

(8) (a) Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 870−876. (b) Shimamoto, K.; Ohfune, Y. *J. Med. Chem*. **1996**, *39*, 407−423.

(9) The structure of **3a** was determined by comparison of its ^{1}H NMR data with those of the iso-propyl derivative **3d** whose structure has been confirmed by X-ray crystallographic analysis, see: Supporting Information.

(10) Although it is difficult to elucidate the conformation of the seven-membered ring ketimine intermediate **B**, this was proposed as depicted in Scheme 1 by means of the ^{1}H NMR data of **3a** and the X-ray structure of **3d**. Boatlike conformation of a six-membered ring ketimine has been reported, see: Schulz, G.; Steglich, W. *Chem. Ber.* **1977**, *110*, 3615−3623. The high stereoselectivity in the addition of a cyanide ion would be due to steric as well as stereoelectronic reasons. It is noted that the nitrile group of the addition product **3** locates in axial which has an antiperiplanar relationship with the neighboring amino lone pair providing stereoelectronic stabilization to the axial orientation of the nitrile group.

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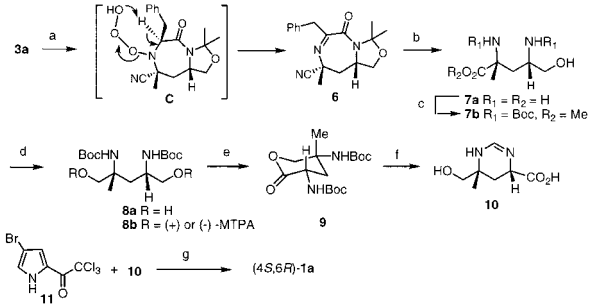
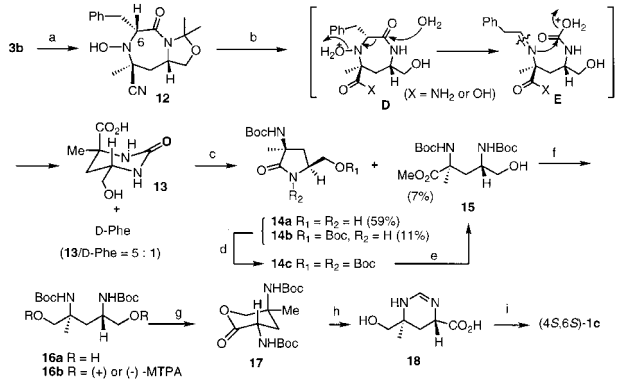
Scheme 2



[a] (a) O_3, MeOH, −78 °C, 20 min (94%). (b) concd HCl, 0 °C, 8 h, rt, 15 h, and 100 °C, 18 h. (c) (1) Boc_2O, $NaHCO_3$, dioxane−H_2O (1:1), rt, 12 h; (2) $Me_4NOH-5H_2O$, Boc_2O, CH_3CN, rt, 15 h; (3) CH_2N_2, Et_2O (70% from **6**). (d) $LiAlH_4$, Et_2O, 0 °C, 2 h (81%). (e) PDC, CH_2Cl_2, rt, 15 h (55%). (f) TFA, CH_2Cl_2, rt, 30 min, then $CH(OMe)_3$, catalytic amount of concd HCl, reflux, 4 h (91%). (g) 2 equiv NaH, DMF, rt, 4 h (100%).

where *t*-BuOCl/Et_3N is often employed,[6] and subsequent hydrolytic removal of the phenylalanyl group. However, not only this reagent system but also other combinations of oxidants and bases were unsuccessful,[11] resulting in almost all cases in recovery of the starting material due probably to steric reasons as well as the low acidity of the C6 hydrogen. Fortunately, we found that the oxidation with ozone was quite effective for this conversion to give in 94% yield the desired imino ketone **6**. We presumed that the reaction proceeded via **C** since ozone is a small molecule compared to other oxidants and has a bidentate chemical characteristic acting as an internal base after oxidation of the nitrogen (Scheme 2). On treatment with concentrated HCl, **6** underwent removal of the phenylpyruvic acid and simultaneous hydrolysis of the nitrile group to afford diaminocarboxylic acid **7a**, which without purification, was converted into protected ester **7b**. This was reduced to diol **8a**,[12] whose oxidation with PDC occurred from the sterically less hindered hydroxymethyl group to give **9**. Construction of the tetrahydropyrimidine ring was performed by successive treatments with (1) TFA and (2) methyl orthoformate to give **10** (91%). Completion of the synthesis now required esterification of the bromopyrrolecarboxylate with **10**. This was accomplished by means of trichloroacetylbromopyrrole **11**[13] to give **1a** ($[\alpha]^{27}_D$ −22.4 (*c* 0.52, MeOH)).[14] Synthetic **1a** was identical in all respects (^{1}H and ^{13}C NMR, HRMS, and HPLC profile) including the sign of specific rotation with natural **1a** (lit.[2] $[\alpha]^{27}_D$ −28 (*c* 0.67, MeOH)). Thus, the absolute structure of natural (−)-**1a** was unambiguously assigned to (4*S*,6*R*)-**1a**.

Scheme 3



[a] (a) 0.1 equiv $MeReO_3$, urea−H_2O_2, 40 °C, 15 min (87%). (b) concd HCl, 85 °C, 15 h (76%). (c) (1) 10% H_2SO_4, 120 °C, 40 h; (2) Boc_2O, 3 equiv $NaHCO_3$, dioxane/H_2O (1:1), rt, 14 h; (3) $Me_4NOH-5H_2O$, Boc_2O, CH_3CN, rt, 14 h; (4) CH_2N_2, AcOEt (79% from **13**: 1**4a**/**14b**/**15** = 6:1:1). (d) Boc_2O, Et_3N, DMAP, THF (80% from **14a** and 63% from **14b**). (e) (1) 2.5 equiv 0.3 *N* NaOH, MeOH, rt, 24 h; (2) CH_2N_2, Et_2O (78% from **14c**). (f) $LiAlH_4$, Et_2O, 0 °C, 2 h (61%). (g) PDC, CH_2Cl_2, rt, 15 h (62%). (h) TFA, CH_2Cl_2, rt, 30 min, then $CH(OMe)_3$, catalytic amount of concd HCl, reflux, 3 h (79%). (i) **11**, 2 equiv NaH, DMF, rt, 4 h (68%).

The successful synthesis of **1a** led us to examine the synthesis of **1c** from the (4*S*)-amino nitrile **3b**. We again faced difficulty upon oxidative removal of the D-Phe moiety of **3b** which did not produce desired imine (4*S*)-**6** even by ozone. With an expectation that **12** would give (4*S*)-**6**, **3b** was converted into hydroxylamine **12** by trioxorhenium oxidation.[15] Teatment of **12** with a base did not give (4*S*)-**6**, but with concentrated HCl it produced unexpectedly cyclic urea **13** (76%). D-Phe was a byproduct (**13**/D-Phe = 5:1).[16] We propose that the carbon−carbon fragmentation between C6 and C7 of the protonated hydroxylamine **D** occurred to give **E** which re-cyclized to **13** (Scheme 3). Treatment of the urea **13** with 10% H_2SO_4 gave a mixture of hydrolyzed products which, upon protection, afforded a mixture of **14a** (59%), **14b** (11%), and **15** (7%). Both the pyrrolidines **14a** and **14b** were converted into **15** in three steps, respectively. The ester **15** was reduced to diol **16a** whose conversion into **1c** was successfully performed in the same manner as that of **1a** from **9a**. Synthetic **1c** showed completely identical spectral data with those of reported.[2] The sign of specific rotation of synthetic **1c** ($[\alpha]^{28}_D$ +89.0 (*c* 0.73, MeOH))[17] was also the same plus as that reported for (+)-**1c** (lit.[2] $[\alpha]^{27}_D$ +37 (*c* 0.23, MeOH)). Thus, both natural (−)-**1a** and (+)-**1c** were found to possess the same 4*S* configuration.

In summary, we have synthesized both natural (−)-**1a** and (+)-**1c** via a Strecker synthesis of amino ketones **4a** and **4b**, respectively. Not only was sufficient synthetic material (14 steps, 14% overall for **1a**, and 15 steps, 3.5% for **1c**) obtained to permit further pharmacological studies on these alkaloids, but also the present route enables the synthesis of the enantiomers or diastereomers of **1** using the combination of (*R*)-**5** with D- or L-Phe. Furthermore, general applications of the methods employed for the oxidation of the amino nitriles **3a** and **3b** are currently being investigated.

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Supporting Information Available: Full experimentals and characterization of the compounds **1a**, **1c**, **2**−**18** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Treatment of **3a** with *t*-BuOCl gave the corresponding N−Cl derivative. However, subsequent dehydrochlorination did not proceed at all using the following bases: DBU, DMAP, (*i*-Pr)$_2$NEt, DABCO, KHMDS, NaH, *t*-BuOK, and $AgBF_4$. The combinations of other oxidants and bases were not successful: PhIO, $CuBr_2$/*t*-BuOLi, PhSeBr/H_2O_2, and Swern oxidation.

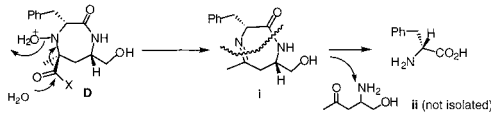
(12) Optical purity of the diols **8a** and **16a** was ascertained to be >95% ee by converting them into the corresponding bis-(+)- or (−)-MTPA ester **8b** and **16b**, respectively, see: Supporting Information.

(13) Synthesis of 2-trichloroacetylpyrrole, see: (a) Bailey, D. M.; Johnson, R. E.; Albertson, N. F. *Org. Synth.* **1971**, *51*, 100−102. (b) Bailey, D. M.; Johnson, R. E. *J. Med. Chem.* **1973**, *16*, 1300−1302.

(14) The synthetic **1a** showed a smaller $[\alpha]_D$ value than the reported one although the optical purity (>95% ee) of synthetic **1a** had been confirmed using the diol **8a**.[12] The $[\alpha]_D$ value of synthetic **1a** using other solvent: $[\alpha]^{27}_D$ −19.7 (*c* 0.65, CH_3CN/0.1 *N* HCl = 1:1).

(15) Trioxorhenium oxidation of an amine, see: Goti, A.; Nannelli, L. *Tetrahedron Lett.* **1996**, *37*, 6025−6028.

(16) We propose that D-Phe was eliminated from **D** via the imine **i** although the amino ketone **ii** could not be isolated from the reaction mixture due probably to its subsequent decomposition.



(17) The $[\alpha]_D$ value of synthetic **1c** was much larger than the reported value in this case.[12,14] The $[\alpha]_D$ value of synthetic **1c** using another solvent: $[\alpha]^{23}_D$ +75.8 (*c* 0.5, CH_3CN/0.1 *N* HCl = 1:1). Since only a small amount of **1c** was isolated from the sponge, the discrepancy of the $[\alpha]_D$ value between synthetic and natural **1c** would be due to contamination of an impure material in natural **1c** which was inseparable even by repeated HPLC purification. In fact, unidentifiable impure material is observed in the ^{1}H NMR spectra of natural **1c**, see: Supporting Information.[2]