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Practical Syntheses of Proposed and Revised Manzacidin B and Their Congeners

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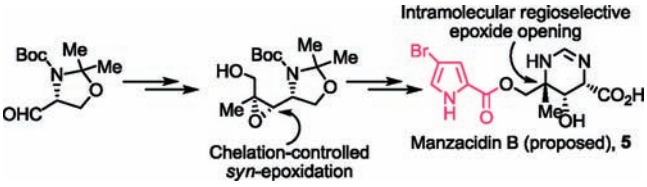
ABSTRACT



A concise and highly stereoselective total synthesis of manzacidin B and its congeners has been developed following chelation-controlled *syn*-epoxidation and Lewis acid catalyzed intramolecular regioselective epoxide ring opening to generate the quarternary amine center. Elaboration of the triol moiety to the target molecule was achieved in good overall yield, representing practical total syntheses of manzacidin B and its congeners. From the XRD, NMR, and analytical data, the correct structure of natural manzacidin B, (4*R*,5*R*,6*R*)-6, was confirmed.

Bromopyrrole alkaloids comprise a large and varied class of marine natural products possessing interesting and potentially useful pharmacological activities as α-adrenoreceptor blockers, seretonin antagonists, and actomyosin ATPase activators.[1] Manzacidins A, B, and C (**1**, **2**, **5**–**8**) belonging to an unprecedented class of bromopyrrole alkaloids (Figure 1) were isolated from the marine sponge *Hymeniacidon sp*. collected from Okinawa, Japan.[2a] Manzacidin D **4** was isolated from the coralline demosponge *Astrosclera willeyana* collected in Australia.[2b] *N*-Methyl manzacidin C **3** was isolated from the marine sponge *Axinella brevistyla* in Japan.[2c] These manzacidins exhibit similar biological activities to other bromopyrrole alkaloids. The paucity of natural material from marine sources has, however, resulted in only preliminary tests being carried out.

The constitution and relative stereochemistry of the manzacidins were elucidated *via* a combination of NMR, IR, and mass spectroscopic techniques. From a structural perspective, the manzacidins comprise a bromopyrrolecarboxylic acid and an unusual 3,4,5,6-tetrahydropyrimidine unit in which the two amino groups are attached to secondary and tertiary stereogenic carbon centers.

The natural scarcity and biological relevance of these materials have prompted many groups to pursue their total synthesis. Enantioselective syntheses of manzacidin A and C,[3−12] and a racemic synthesis of manzacidin D,[13] seem to

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be inapplicable to manzacidin B which contains an additional secondary alcohol moiety in the tetrahydropyrimidine core.

During the course of our work, the initially proposed stereochemistry of manzacidin B was revised by total synthesis *via* a chiral pool approach.[14a] In 2010, Ohfune and co-workers published a corrigendum stating that the diastereomers in their previous studies were incorrectly assigned leading to the revision of the stereochemistry of manzacidin B which is nothing but the enantiomer of the proposed stereochemistry of manzacidin B.[14b] To address the structural ambiguities of **5**, we chose to explore a stereoselective syntheses of manzacidin B (proposed) and its congeners to determine the relative configuration at each step and to confirm the absolute configuration of

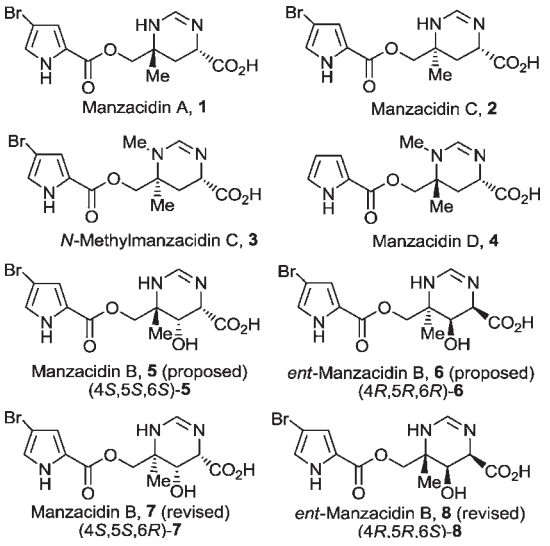
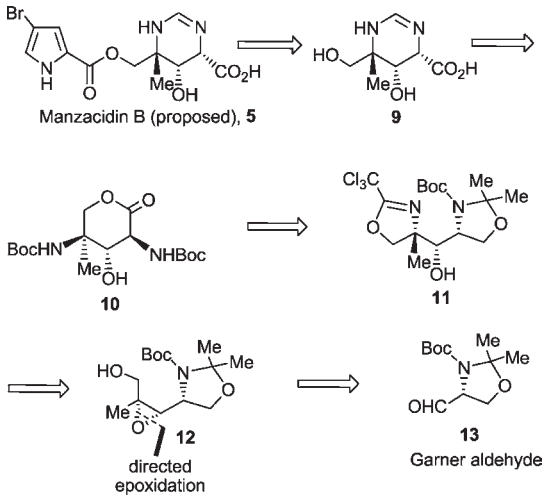


Figure 1. Structures of manzacidins and possible (6*S*)- and (6*R*)-diastereomers of manzacidin B.

manzacidin B. We report, herein, the concise and practical total syntheses of manzacidin B (proposed) **5**, *ent*-manzacidin B (proposed) **6**, manzacidin B (revised by Ohfune[14a]) **7**, and *ent*-manzacidin B (revised) **8**.

Scheme 1 summarizes key elements of the strategic plan to make manzacidin B and its congeners. The structural features of manzacidin B suggested the ester functionality as the strategic site for disconnection to give the known bromopyrrole moiety and the highly functionalized tetrahydropyrimidine core **9**. Compound **9** could be obtained from the lactone **10** using trimethyl orthoformate by following a similar strategy reported by Ohfune et al.[3] For the synthesis of the lactone **10**, which includes all three chiral centers present in the molecule, we devised a novel

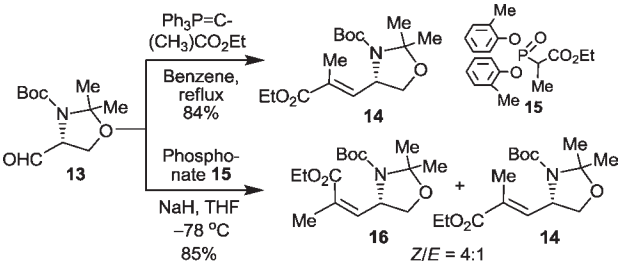
Scheme 1. Retrosynthetic Analysis



strategy combining a chelation-controlled epoxidation[15] of the allylic alcohol and an intramolecular regioselective epoxide opening with tricholoroacetimidate (Hatakeyama's protocol)[16] for the introduction of the tertiary amine. The allylic alcohol could be obtained from Garner's aldehyde (**13**) by a stereoselective Wittig–Horner olefination followed by reduction of the ester (Scheme 1).

We started our synthesis with (*R*)-Garner's aldehyde[17] (**13**), which on treatment with C-3 stable Wittig ylide[18] furnished the *E*-isomer **14**, exclusively, in 84% yield. Reaction with the phosphonate **15**[19] and NaH at −78 °C

Scheme 2. Synthesis of **14** and **16**



in THF for 4 h gave a mixture of conjugated esters in the ratio of 4:1 in favor of the desired *Z*-isomer **16** in 85% yield (Scheme 2).

Having synthesized the required conjugated ester **16**, we next turned our attention to constructing the *syn*

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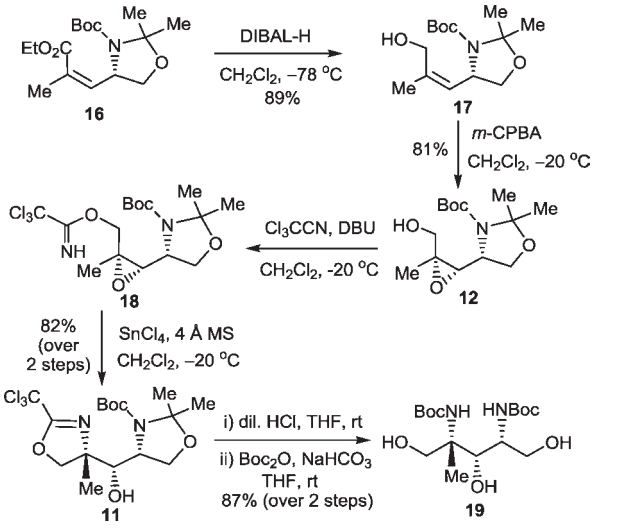
epoxide **12**, required for the introduction of a tertiary amine chiral center. Thus, unsaturated ester **16** was reduced to the corresponding allylic alcohol **18** with DIBAL-*H* at −78 °C in CH_2Cl_2. Chelation-controlled epoxidation[15] using 70% *m*-CPBA in CH_2Cl_2 at −20 °C afforded the epoxy alcohol **12** as a single isomer (Scheme 3).

Scheme 3. Synthesis of **19**



The expected stereoselectivity in this epoxidation was derived from chelation between the allylic alcohol and the carbamate carbonyl in the substrate with the perbenzoic acid (cooperative effect). This was confirmed at a later stage of the synthesis.

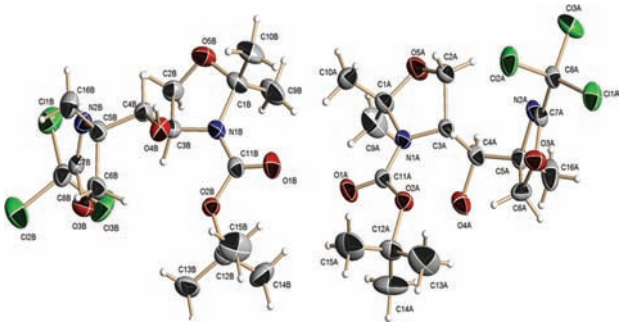
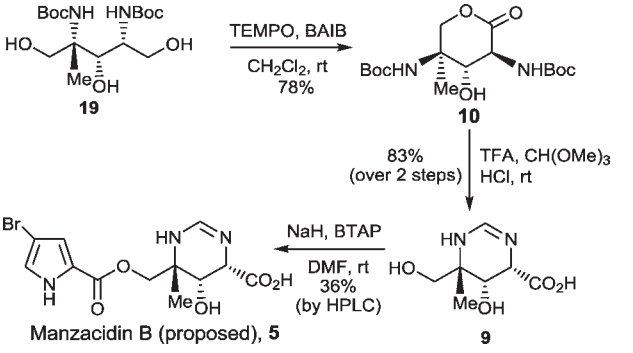


Figure 2. ORTEP diagram of compound **11**.

The epoxy alcohol **12** was converted to the imidate **18** using trichloroacetonitrile and DBU in CH_2Cl_2 at −20 °C which on opening with $SnCl_4$ at −20 °C furnished the desired oxazoline derivative **11** as a single product. The regioselectivity of the epoxide opening and the relative stereochemistry were unambiguously confirmed by the single crystal X-ray crystallographic analysis of the compound **11** (Figure 2).[20] The oxazoline **11** was next converted to the triol **20**, in two steps in the same pot, by treatment with 2 N HCl in THF to hydrolyze the oxazoline and the acetonide, neutralizing the reaction mixture with $NaHCO_3$ and then protecting both amine functionalities as their Boc derivative using di-*tert*-butyl dicarbonate (Scheme 3).

Scheme 4. Synthesis of Manzacidin B (proposed), **5**



Selective oxidation of the sterically less hindered primary alcohol in the presence of the secondary alcohol to the corresponding aldehyde employing bis-acetoxy iodobenzene (BAIB) as the co-oxidant and with catalytic TEMPO afforded lactone **10** in 78% yield (Scheme 4).[21] Construction of the tetrahydropyrimidine ring was accomplished by successive treatments with (i) TFA and (ii) methylorthoformate to give (4*S*,5*S*,6*S*)-**9** in 83% yield over two steps. Completion of the synthesis of originally proposed manzacidin B now required esterification of the bromopyrrolecarboxylate with **9**. This was accomplished by treatment of **9** with NaH and 4-bromo-2-trichloroacetylpyrrole (BTAP) at room temperature to afford **5** ($[\alpha]_D^{25}$ +41.1 (*c* 1.2, MeOH)). The spectral and analytical data (^1H, ^{13}C NMR, mass profile) of synthetic manzacidin B (proposed) **5** were identical to those of the natural and Ohfune's synthetic manzacidin B except for the sign of specific rotation. To confirm the absolute stereochemistry of manzacidin B, starting from ethyl-2-methyl-3-[3-(*tert*-butoxycarbonyl)-2,2-dimethyl-(4*R*)-oxazolidinyl]-prop-(2*Z*)-enoate (**16a**), the enantiomer of manzacidin B (proposed) **6** was synthesized, whose spectral (^1H, ^{13}C NMR, mass profile) and analytical data {$[\alpha]_D^{25}$ −40.7 (*c* 0.56, MeOH); lit.[14a] $[\alpha]_D^{25}$ −41.8 (*c* 1.04, MeOH)} were in good agreement with the reported values which further confirmed that the absolute stereochemistry of manzacidin B should be (4*R*,5*R*,6*R*)-**6** (Scheme 5).

Similarly, starting from ethyl-2-methyl-3-[3-(*tert*-butoxycarbonyl)-2,2-dimethyl-(4*S*)-oxazolidinyl]-prop-(2*E*)-enoate

(20) Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-853031 to CCDC-853036 (CCDC-853031 for **11**, CCDC-853032 for **12**, CCDC-853033 for **11b**, CCDC-853034 for **17a**, CCDC-853035 for **11a**, CCDC-853036 for **11c**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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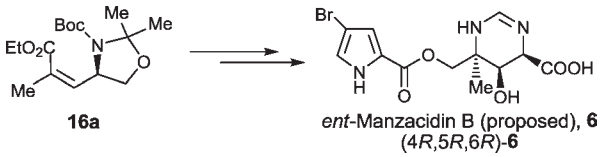
Scheme 5. Synthesis of ent Manzacidin B (proposed), **6**



(**14**) and ethyl-2-methyl-3-[3-(*tert*-butoxy carbonyl)-2,2-dimethyl-(4*R*)-oxazolidinyl]-prop-(2*E*)-en-oate, manzacidin B (revised by Ohfune[14a]) **7** and *ent*-manzacidin B (revised) **8** were synthesized with good overall yield.

In conclusion, we have achieved the total syntheses of manzacidin B (proposed) **5**, *ent*-manzacidin B (proposed) **6**, manzacidin B (revised by Ohfune) **7**, and *ent*-manzacidin B (revised) **8** in a highly stereoselective manner through chelation-controlled epoxidation and Hatakeyama's rearrangement of trichloroacetamidate to generate the quarternary amine center in short order with 20% overall yield in 8 steps starting from easily synthesizable Garner's aldehyde. This process allows for the alkene geometry in the allylic alcohol to dictate the configuration of the challenging tertiary amine stereocenter. Trivial protecting group manipulations and chemoselective oxidation/lactonization followed by tetrahydropyrimidine ring formation and esterification afforded the target molecule. The overall process is relatively concise; the route appears to be far more amenable to scale-up thus enabling preparation of significant quantities of the natural product and its congeners for further biological studies. By application of the same protocol, work in the total syntheses of manzacidin A and C is in progress in our laboratory and will be reported in due course.

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Supporting Information Available. Description of experimental procedures, and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.