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Short and stereoselective synthesis of manzacidins A and C, and their enantiomers

Kentaro Oe, Tetsuro Shinada *, Yasufumi Ohfune *

Graduate School of Science, Osaka City University, 3-3-138 Sugimoto, Sumiyoshi, Osaka 558-8585, Japan

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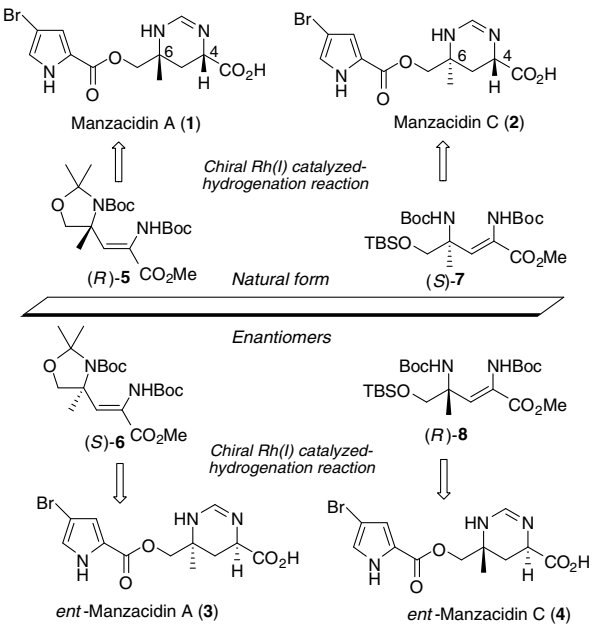
ABSTRACT

A short and stereoselective synthesis of manzacidins A and C, and their enantiomers was achieved via stereoselective hydrogenation reactions of dehydroamino acid esters **5**–**8** using a chiral Rh catalyst.

Manzacidin A (**1**) and manzacidin C (**2**), a novel class of 1,3-dehydropyrimidine alkaloids possessing a bromopyrrole ester unit, were isolated from the Okinawan sponge *Hymeniacidon* sp. by Kobayashi et al. in 1991 (Scheme 1).[1] Bromopyrrole alkaloids exhibit a diverse array of pharmacological activities represented by α-adrenoceptor blockers, antagonists of serotonergic receptors, or actomyosin ATPase activators.[2] In spite of their intriguing biological activities, the pharmacological evaluation of manzacidins A and C has not yet been undertaken due to the limited availability of these natural products. These facts together with the unique structural features of the manzacidins have attracted much attention as a synthetic target from the synthetic community. Many synthetic efforts focusing on the stereoselective construction of the 1,3-diamino stereogenic centers attached to the C4 methine and C6 quaternary carbon centers have been made since our first total synthesis in 2000.[3–5] We now report the short and stereoselective synthesis of manzacidins A (**1**) and C (**2**), and their enantiomers **3** and **4** via the diastereoselective hydrogenation reaction of optically active α,β-unsaturated esters **5–8** using a chiral [Rh(I)(COD)-Et-DuPHOS]$^{+}$OTf^{-} catalyst (Scheme 1).

The *N*-Boc dehydroamino acid esters **5**–**8**, and *N*-Cbz esters **15** and **16** were used in this study. These olefins were prepared from the chiral α-methylserine esters **9** and **10**, which were readily prepared on a multi-gram scale by the stereoselective Strecker synthesis of an acetol ester (Scheme 2).[5a,c,6] The dehydroamino acid esters



Scheme 1.

5, **6**, **15**, and **16** were synthesized by olefination reactions of the α-methyl Garner's aldehydes **11** and **12**[7,8] with the phosphonates **13** and **14**.[9] The TBS-protected derivatives **7** and **8** were prepared from

* Corresponding authors. Tel./fax: +81 6 6605 2570 (T.S.).
E-mail addresses: shinada@sci.osaka-cu.ac.jp (T. Shinada), ohfune@sci.osaka-cu.ac.jp (Y. Ohfune).

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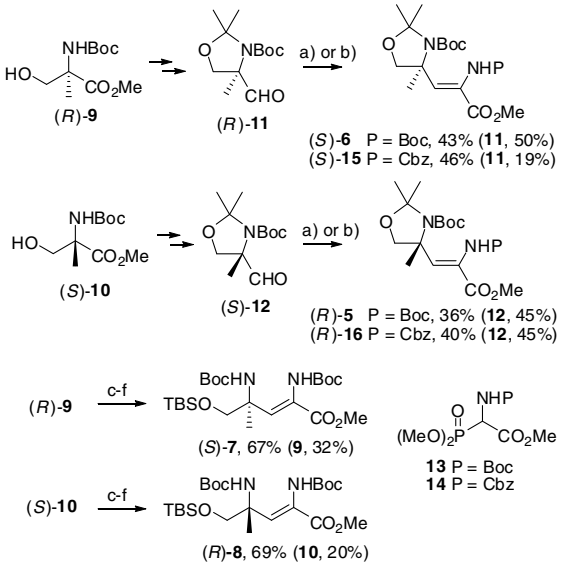
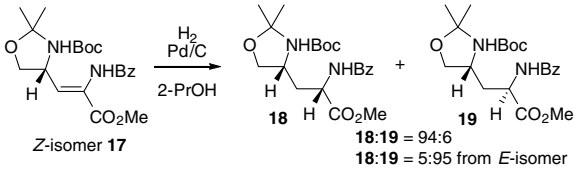


Scheme 2. Reagents and conditions: (a) **13** (3.0 equiv), DBU (3.0 equiv), CH_2Cl_2, 0 °C to rt, 22 h; (b) **14** (3.0 equiv), DBU (3.0 equiv), CH_2Cl_2, 0 °C to rt, 22 h; (c) TBSCl (2.0 equiv), imidazole (2.0 equiv), DMF, 0 °C to rt, 17 h; (d) $LiBH_4$ (4.0 equiv), MeOH (4.2 equiv), Et_2O, 0 °C, 1 h; (e) TEMPO (0.1 equiv), $PhI(OAc)_2$ (1.2 equiv), CH_2Cl_2, 0 °C to rt, 18 h; (f) **13** (3.0 equiv), DBU (3.0 equiv), CH_2Cl_2, 0 °C to rt, 22 h.

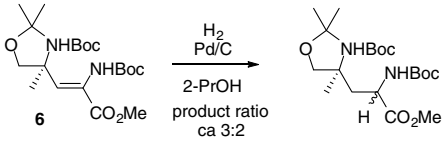
9 and **10** by a conventional silylation, reduction, oxidation, and olefination with **13** and **14**, respectively. These olefination reactions allowed the stereoselective formations of *Z*-isomers (>20:1). The conversion efficiency was satisfactory in terms of the yields based on the recovery of the starting materials (>80%).[10]

We were initially interested in the substrate-controlled hydrogenation reaction of **6** or **15**. Avenoza et al. reported the hydrogenation reaction of *Z*-**17** to give **18** in a stereoselective manner (**18**:**19** = 94:6 (Eq. 1)).[11] The inverse diastereoselectivity occurred when *E*-**17** was employed (**18**:**19** = 5:95). In view of the structural analogy of **17** with the α-methyl analogs **5** and **6**, we attempted the hydrogenation reactions of **6** prior to examining the chiral Rh catalyst-controlled hydrogenation reaction.



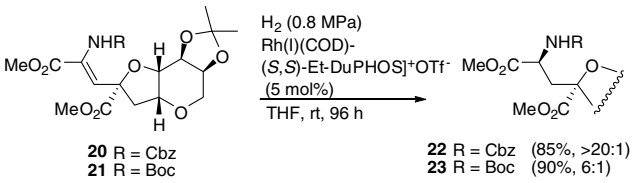
(1)

The *Z*-olefin **6** underwent a smooth hydrogenation reaction (Pd/C, H_2). However, the diastereoselectivity was found to be moderate (ca 3:2, (Eq. 2)). Although other hydrogenation reaction conditions [H_2, catalysts: Pd/Al_2O_3, Rh/Al_2O_3, PtO_2, $[Ir(COD)(Cy_3P)(Py)]PF_6$, solvents: MeOH, 2-PrOH, AcOEt] and the 1,4-reduction condition using Mg/MeOH were examined, the diastereoselectivities were not improved to a satisfactory level. The use of the *N*-Cbz-**15**, the *E*-isomers of **6,** and an acyclic dehydroamino acid **7** were not effective at all to give the corresponding reduced products in moderate selectivities. The more sterically congested nature of the quarternary amino carbon center of **6** would hamper the diastereoselective hydrogenation pathway.



(2)

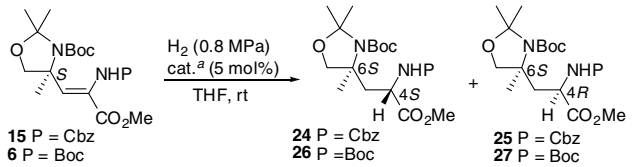
Based on the above results, we turned our attention to the chiral Rh catalyst-controlled hydrogenation reaction. Recently, Sasaki et al. reported the stereoselective reduction of a highly functionalized olefin with a chiral [Rh(I)(COD)-Et-DuPHOS]$^+$OTf$^-$ catalyst[12] during the synthesis of neodysiherbaine (Eq 3).[13] The *N*-Cbz derivative **20** was a superior substrate when compared to the *N*-Boc derivative **21**. In terms of the double asymmetric induction,[14] the combination of **20** and the (*S*,*S*)-[Rh(I)(COD)-Et-DuPHOS]$^+$OTf$^-$ catalyst was apparently the matched case to obtain the desired reduction product.



(3)

The *N*-Cbz-olefin **15** was used for the chiral [Rh(I)(COD)-Et-DuPHOS]$^+$OTf-catalyzed hydrogenation reaction (Scheme 3). The use of the (*S*,*S*)-Et-DuPHOS Rh catalyst resulted in the recovery of the starting olefin (entry 1). Switching the chiral catalyst to the (*R*,*R*)-Et-DuPHOS Rh catalyst allowed the hydrogenation reaction to give a 1:5 mixture of **24** and **25** (48 h, entry 2), in which the major (4*R*)-isomer **25** possessed the requisite (4*R*,6*S*)-stereochemistry of *ent*-manzacidin A. To improve the diastereoselectivity, the *N*-Boc olefin **6** was subjected to the same reduction conditions. The reduction with the (*R*,*R*)-Et-DuPHOS Rh catalyst proceeded in a highly stereoselective manner to give (4*R*,6*S*)-**27** (**26**:**27** = 1:13, entry 4). In contrast, the (*S*,*S*)-Et-DuPHOS Rh catalyst gave a 1:1 mixture of **26** and **27** (168 h, entry 3). These results indicated that the reaction of (*S*)-*N*-Boc **6** with the (*R*,*R*)-catalyst in the matched case of these hydrogenation reactions and the hydrogenation of (*R*)-**5** with the (*S*,*S*)-catalyst would afford (4*S*,6*R*)-**29** corresponding to manzacidin A (**1**).

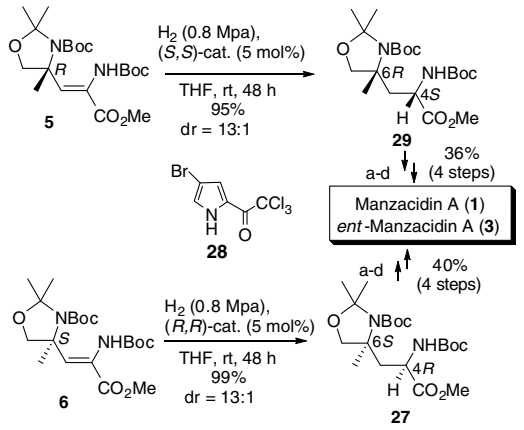
The treatment of (*R*)-**5** with the chiral (*S*,*S*)-Et-DuPHOS Rh catalyst gave **29** in a stereoselective manner (dr = 13:1, Scheme 4). (4*S*,6*R*)-**29** was converted to **1** by the following sequence of transformations:[3,15] (i) hydrolysis of the methyl ester, (ii) removal of the Boc groups, (iii) tetrahydropyrimidine ring formation, and (iv) esterification with **28**. Similarly, (4*R*,6*S*)-**27** derived from (*S*)-**6** was converted to *ent*-manzacidin A (**3**). The spectral data of the synthetic **1** were identical to those of the authentic data, confirming the stereochemical outcome of the chiral catalyst-controlled hydrogenation reactions of (*R*)-**5**. The spectral data of *ent*-manzacidin A (**3**) were identical to that of **1** except for the sign of the optical rotation. Thus, manzacidin A and its enantiomer were synthesized in 6 steps from the (*S*)-aldehyde **11** and (*R*)-aldehyde **12**, respectively.



Entry	Olefin	Catalyst	Time(h)	Yield	Product ratio
1	**15**	(*S*,*S*)	72	0[b]	---
2	**15**	(*R*,*R*)	48	96	**24**:**25** = 1:5[c,d]
3	**6**	(*S*,*S*)	168	76	**26**:**27** = 1:1
4	**6**	(*R*,*R*)	48	98	**26**:**27** = 1:13

[a]cat. [Rh(I)(COD)-Et-DuPHOS]$^+$OTf$^-$ [b] Recovery of **15**.
[c] Numbering system accords with those of the manzacidins.
[d] Product ratio was determined by the conversion to manzacidins.

Scheme 3.

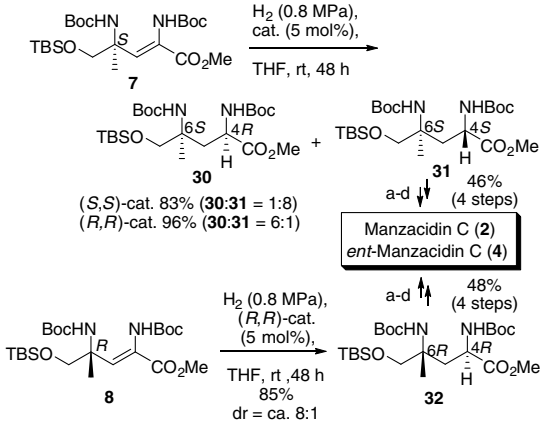


Scheme 4. Reagents and conditions: (a) 1 N NaOH, THF, 1 h; (b) TFA, CH_2Cl_2, 0 °C to rt, 30 min; (c) TFA, $CH(OMe)_3$, rt, 17 h; (d) **28**, (2.0 equiv), NaH (2.0 equiv), DMF, 0 °C to rt, 2 h.

Although the use of the cyclic unsaturated esters **5** and **6** was found to be the appropriate substrates to access manzacidin A (**1**) and its enantiomer **3**, these reductions forced limitations on the stereoselective synthesis of manzacidin C (**2**) and its enantiomer **4**. We assumed that the release of the ring strain to reduce the steric hindrance of the cyclic oxazolidine **5** could facilitate the reagent-controlled hydrogenation reaction. As expected, the reduction of the acyclic olefin **7** with the (*S*,*S*)-Rh catalyst smoothly proceeded to give (4*S*,6*S*)-**31** as the major product (**30**:**31** = 1:8). The diastereoselectivity was inverted to give (4*S*,6*S*)-**30** as the major product (**30**:**31** = 6:1) when the (*R*,*R*)-catalyst was employed. As a result, the use of the acyclic dehydroamino acid esters, attributed to the stereoselective formation of (4*S*,6*S*)-**31** was involved in the synthesis of manzacidin C (**2**). The (4*R*,6*R*)-**32** was prepared using the (*R*,*R*)-catalyst. The resulting (4*S*,6*S*)-**31** and its enantiomer (4*R*,6*R*)-**32** derived from **8** were converted into manzacidin C (**2**) and its enantiomer **4**, respectively, in a manner similar to the synthesis of manzacidin A (**1**) (Scheme 5).

Purification of the major stereoisomer of the manzacidins by recrystallization was initially not successful. Therefore, we examined the HPLC separation conditions and found that heptafluorobutyric acid (the lower chart) was the superior additive to trifluoroacetic acid (the upper chart) for the distinct separation of a mixture of the manzacidins (Fig. 1).

In summary, we have established a short and efficient synthetic route to access manzacidin A (**1**), manzacidin C (**2**), and their enantiomers **3** and **4** by the chiral catalyst-controlled hydrogenation reactions of the dehydroamino acid esters **5**–**8**. The improved HPLC purification protocol allows for ample of the enantiomerically pure manzacidins and their enantiomers for further evaluation of their biological activities.



Scheme 5. Reagents and conditions: (a) 1 N NaOH, THF, 0 °C, 1 h; (b) 6 N HCl, rt, 18 h; (c) TFA, $CH(OMe)_3$, rt, 17 h; (d) **28** (2.0 equiv), NaH (2.0 equiv), DMF, 0 °C to rt, 2 h.

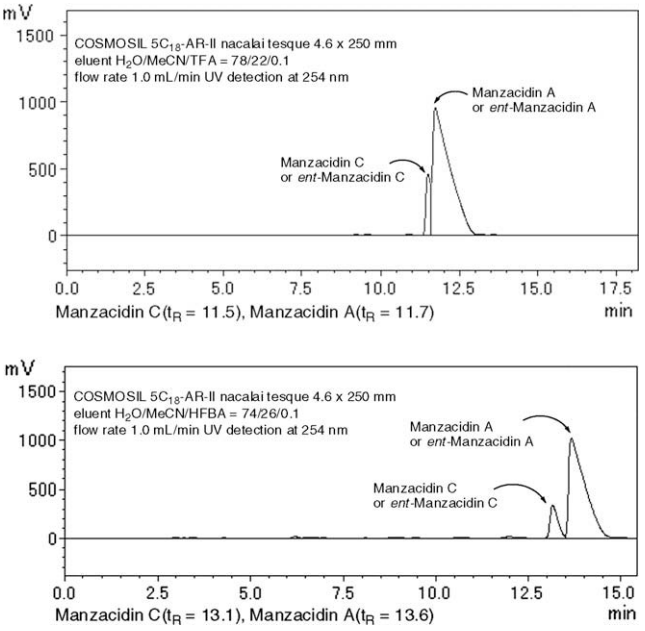


Figure 1. HPLC profiles of manzacidins.

Acknowledgments

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Supplementary data

Supplementary data (experimental details) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.074.

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