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Synthesis of unit-B of cryptophycin-24 via Sharpless asymmetric dihydroxylation

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ABSTRACT

A synthetic pathway for the synthesis of unit-B of cryptophycin-24 has been developed using Sharpless asymmetric dihydroxylation as the key step. This study shows that direct azidation of α-hydroxy acid ester using diphenylphosphoryl azide is beneficial to asymmetric synthesis of α-amino acid without the loss of chirality during the transformation.

The cryptophycins[1] are potent tumour selective cytotoxins, isolated from the blue green algae *Nostoc* sp. ATCC 53,789[2] and *Nostoc* sp. GSV 224.[3] The first representative of these depsipeptides, cryptophycin-1, was isolated from the blue-green algae *Nostoc* sp. ATCC 53789.[2] Several other cytotoxin analogues were also isolated from blue green algae belonging to Nostocaceae.[2,4] Structurally simpler cryptophycin, cryptophycin-24 was isolated from an Okinawan marine sponge, *Dysidea arnaria*.[5] Though cryptophycin-24 lacks a chlorine substituent on the aryl ring of the C-10 side chain and the methyl group at C_6 (Fig. 1), it was extremely potent against KB cells (ED50 = 5 pm).[5]

Retrosynthetically, cryptophycin-24 can be disconnected into four units (Fig. 1). The unit-B of cryptophycin can be derived from the commercially available α-amino acid, D-tyrosine.[6] However, few alternative pathways were also developed to synthesize the target amino-acid fragment. Maier developed a synthetic strategy for unit B via the asymmetric alkylation of a glycine imine in the presence of a cinchonine derived phase transfer catalyst (PTC).[7] Recently, Sewald developed another strategy for this unit based on the asymmetric hydrogenation in the presence of a chiral rhodium catalyst.[8] In this Letter, we are reporting a new synthetic strategy for unit-B of cryptophycin-24 using Sharpless asymmetric dihydroxylation as the key step. The retrosynthetic sequence is represented in Scheme 1.

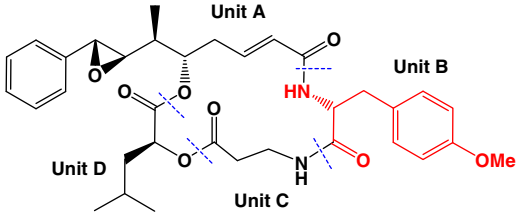

Figure 1. Structure of cryptophycin-24.

To realize the synthesis of unit B of cryptophycin-24, we have initiated the synthesis, using 4-methoxy cinnamic acid **1** as the starting material (Scheme 2). The acid was converted into methyl ester (2) in 87% yield using methanol and thionyl chloride ($SOCl_2$).[9] Ester **2** was then subjected to Sharpless asymmetric dihydroxylation procedure using $(DHQ)_2PHAL$ as the chiral ligand.[10] The corresponding diol **3** was obtained in 87% yield. The optical rotation of the compound was found to be +5.2° (c 1, EtOH) [Lit[11] +5.5° (c 1, EtOH)]. Hydrogenolysis of diol **3** using Pd/C and hydrogen gas in methanol[12] produced the corresponding alcohol **4** in 65% yield. The measured optical rotation of **4** was found to be +11.3° (c 1, $CHCl_3$). In the next step our strategy was to convert the alcohol functionality into azide.

Alcohol **4** was first transformed to the corresponding bromide **5** and then to the azido compound **6**. Bromination was carried out using CBr_4 in the presence of PPh_3.[13] The optical rotation of the bromo compound **5** was measured to be −3.6° (c 1, $CHCl_3$). Then

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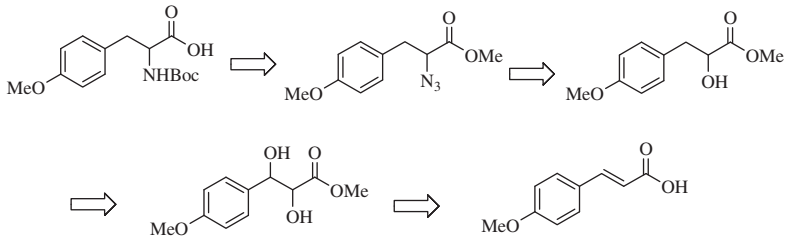
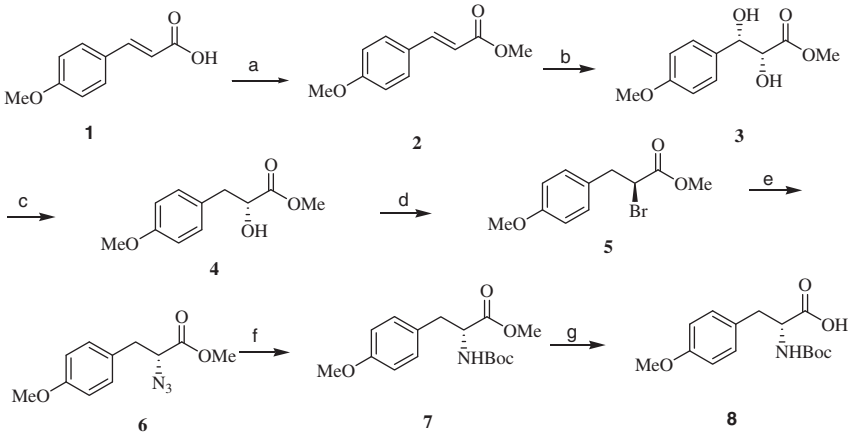


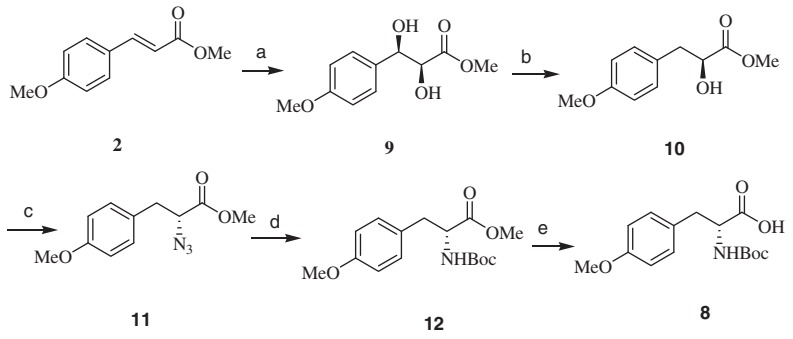
Scheme 1.



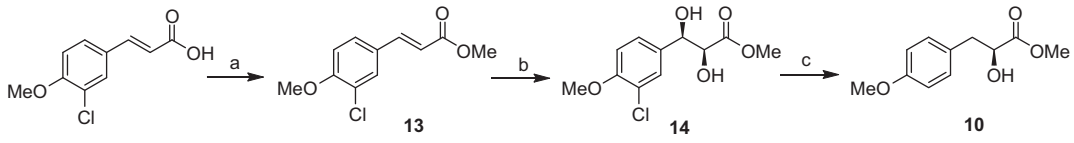
Scheme 2. Reagents and condition: (a) MeOH, $SOCl_2$, rt; (b) $K_2OsO_2(OH)_4$, $(DHQ)_2PHAL$, $MeSO_2NH_2$ ^tBuOH: H_2O (1:1), 0 °C; (c) Pd/C, H_2, MeOH; (d) CBr_4, TPP, dry DCM, rt; (e) NaN_3, DMF, rt; (f) H_2, EtOAc, Boc_2O; (g) K_2CO_3, H_2O, MeOH, rt.

the bromo ester **5** was converted into azide **6** using NaN_3 in dry DMF[14] {$[\alpha]_D^{26}$ = + 14.9° (c 1, $CHCl_3$)}. In the next step we converted the azide **6** into Boc-protected amino compound **7** through one pot synthesis.[15] The optical rotation of compound **7** [−16.1° (c 1, $CHCl_3$)] was found to be very low as compared to that reported in the literature [−58.4° (c 1, $CHCl_3$)].[16] This may be due to partial racemization of the product during bromination of the hydroxyl functionality of compound **4**, located at α-position to the ester functionality. Hence, we designed a new strategy to synthesize the target molecule. The new synthetic route is shown in Scheme 3.

Accordingly, we planned to synthesize the azido compound directly from monohydroxy compound **10** in one step. We have carried out the AD reaction of compound **2**, using $(DHQD)_2PHAL$ as the chiral ligand. The product was obtained with 89% yield with high optical purity. The measured optical rotation for the diol was found to be −5.6° (c 1, CH_2Cl_2) [Lit.[17] −5.8° (c 1, CH_2Cl_2)]. Thereafter compound **9** was subjected to hyderogenolysis by following the same method used previously to produce compound **10** with 67% yield. The optical rotation of the compound recorded to be −11.9° (c, 1, $CHCl_3$). In the next step we synthesized the azide **11** directly from **10** by using diphenylphosphoryl azide (DPPA).[18] The reaction was carried out by treating compound **10** with DPPA in the presence of DBU in THF under ice cool condition and continuing the reaction at room temperature for 24 h. The corresponding azide **11** was obtained in 75% yield and with high optical activity. The measured optical rotation this time was found to be +48.1° which is much better in comparison to the previous route (Scheme 2). Then we continued the synthesis to produce the Boc-protected α-amino acid ester **12** under hydrogenation condition. The present method resulted in improvement of the optical purity of compound **12** and the optical rotation was found to be −58.1° (c 1, $CHCl_3$). The enantiomeric excess of the product was analysed by using HPLC and found to be 99%. The amino ester was finally converted into corresponding amino acid **8** using K_2CO_3 in methanol[19] to yield the



Scheme 3. Reagents and condition: (a) $K_2OsO_2(OH)_4$, $(DHQD)_2PHAL$, $MeSO_2NH_2$ ^tBuOH: H_2O (1:1), 0 °C; (b) Pd/C, H_2, MeOH; (c) DPPA, DBU, dry THF, 0 °C; (d) H_2, EtOAc,Boc_2O; (e) K_2CO_3, H_2O, MeOH, rt.



Scheme 4. Reagents and condition: (a) $SOCl_2$, MeOH; (b) $K_2OsO_2(OH)_4$, $(DHQD)_2PHAL$, $MeSO_2NH_2$ ^tBuOH: H_2O (1:1), 0 °C; (c) Pd/C, H_2, MeOH.

product as a white solid. The optical rotation of the compound was found to be −26.9° (c 1, EtOH).

After getting success in the synthesis of unit B of cryptophycin-24, we made an attempt to synthesize unit B of other cryptophycins bearing a chloro substituent on the aromatic ring. The synthesis was started from methyl 3-(3-chloro-4-methoxyphenyl)acrylate (**13**), which was prepared from corresponding 3-chloro-4-methoxy cinnamic acid. Asymmetric dihydroxylation of ester **13** was performed using $(DHQD)_2PHAL$ ligand to produce the optically active diol **14** in 86% yield. However, the next step of hydrogenolysis of diol **14** resulted in the elimination of chlorine atom from the aromatic ring along with the hydrogenolysis of benzylic –OH functionality (Scheme 4). Product **10** was obtained in 65% yield. Since the hydrogenolysis step was unsuccessful, we did not proceed further.

In conclusion, we have developed a new asymmetric synthetic pathway for the synthesis of unit-B of cryptophycin-24 using Sharpless asymmetric dihydroxylation as the key step. Initial attempt to convert α-hydroxy acid ester into the corresponding α-amino acid ester via bromocompound was unsuccessful due to partial racemization of the product during bromination. However, direct azidation route was successful. This study shows that direct azidation using DPPA is beneficial for asymmetric synthesis of α-amino acid from α-hydroxy acid ester without the loss of chirality during the transformation. However, the present strategy is not suitable for the tyrosine-unit of other cryptophycins bearing a chloro-substituent on the aromatic ring.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.078.

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