A Facile Synthesis of (–)-Cucurbitine

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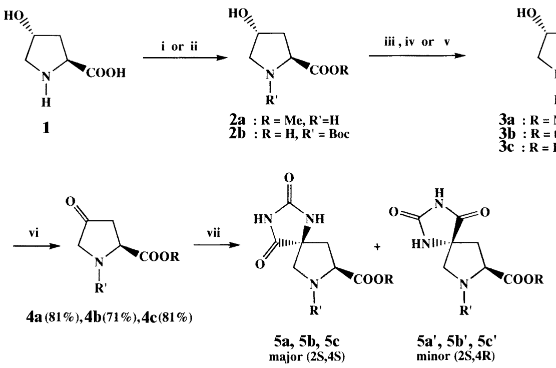
In recent years, there has been much interest in structurally unique pyrrolidines, which were isolated from natural sources and could be utilized as common synthetic subunits of products with biological activity.[1] In the course of our work related to the synthesis of a series of novel quinolone antibiotics[2] having a pyrrolidine moiety at the 7-position, we searched for the pyrrolidine derivatives, bearing a chiral amino acid function at C-3 position, which could be substituted at C-7 position of the quinolone nucleus.

(–)-Cucurbitine, bearing the α-amino acid function at the C-3 position in the pyrrolidine ring, has been isolated from the seeds of several species of cucurbitaceaes, and has been known to inhibit the growth of the immature *Schistosomas japonicum*.[3] However, only two asymmetric syntheses[4c,4e] of cucurbitine are found in the literature[4] despite of its interesting biological activity and useful synthetic precursor of pyrrolidine-bearing compounds. We here report a practical stereoselective synthesis of cucurbitine using a *trans*-4-hydroxy-L-proline as a chiral template. *trans*-4-Hydroxy-L-proline was widely used as a starting material in natural product synthesis and its conversion to 4-oxoprolinate has been well established in literature.[5] Our synthetic strategy was the preparation of the diastereoselective spirohydantoin of 4-oxoprolinate by the Bucherer-Berg reaction, followed by the selective decarboxylation of proline unit as shown on Schemes 1 and 2.

In order to find the most suitable spirohydantoin candidate as a precursor of cucurbitine, several spirohydantoin derivatives were prepared with analysis of the diastereoselectivity. Thus, *N*-benzylproline **3a** was obtained through protection of the carboxyl group of **1** to methyl ester with $SOCl_2$ in MeOH, and the amino group with Boc_2O (in 70% from **1**). Treatment of **1** with Boc_2O, followed by esterification with benzyl bromide in the presence of TBAB afforded hydroxyproline **3c** in 70% yield. Hydroxyproline **3b** was easily obtained by treatment of **2b** with 2 equiv of dimethylformamide dineopentylacetal and 8 equiv of *t*-BuOH in 80% yield. The Swern oxidation of hydroxyprolines (**3a, 3b** and **3c**) afforded the corresponding oxoprolines (**4a, 4b** and **4c**) in 71-81% yields. In previous papers, Tanaka *et al.* reported that a diastereoselective Bucherer-Bergs reaction of oxoproline **4a** provided a diastereomeric mixture of spirohydantoins **5a** and **5a'** with a ratio of 75 : 25 in which the absolute stereochemistry was established by NMR studies.[5b]



Scheme 1. Reagents and yields: i) **2a**: MeOH, $SOCl_2$, 70, 6 h, 90%, ii) **2b**: TEA, $(Boc)_2O$, 25 °C, 24 h, 93%, iii) **3a**: BnCl, TEA, 45 °C, 6 h, 78%, iv) **3b**: N,N-Dimethylformamid dineopentyl acetal, *t*-BuOH, anhydrous Benzene, 80%, v) **3c**: TBAB, BnBr, 50% CH_2Cl_2, 45 °C, 24 h, 70%, vi) $(COCl)_2$, DMSO, TEA, vii) **5a**: KCN, $(NH_4)_2CO_3$, 55-60, 50% MeOH, 24 h; **5b** and **5c**: KCN, $(NH_4)_2CO_3$, 55-60, 50% DMF, 24 h.

In our case, the Bucherer-Bergs reaction of oxoproline **4a** (2 equiv of KCN, 4 equiv of $(NH_4)_2CO_3$, 50% MeOH, 60 °C, 24 h) afforded 79% of the desired **5a** and **5a'** as a diastereomeric mixture in a ratio of 74 : 26. Especially, the major diastereomer **5a** was readily separated by recrystallization (ether/hexane/EtOAc = 1 : 3 : 1) from a viscous mixture after aqueous work-up. The remaining residue after a chromatographic separation on silica gel ($CHCl_3$/MeOH = 50 : 1) afforded the minor isomer **5a'**, which was solidified on standing at room temperature. The Bucherer-Bergs reaction of oxoprolines **3b** and **3c** bearing N-Boc group in 50% DMF (55-60 °C, 24 h) was carried out to give a mixture of **5b** and **5b'** (65%, 94 : 6 after chromatographic separation) and a mixture of **5c** and **5c'** (68%, 90 : 10). The high diastereoselectivity of the reaction reflected the formation of the thermodynamically stable intermediate proposed by Edward and Jitransgri.[6]

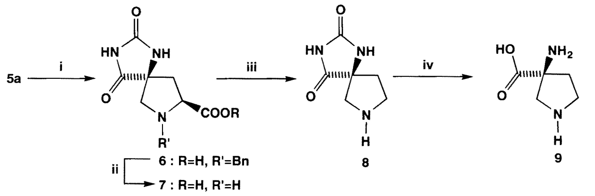
In order to achieve the synthesis of (–)-cucurbitine, we considered the use of **5a** due to the easy separation of the major diastereomer by recrystallization in relatively high yield. Decarboxylation of the pyrrolidine ring and the completion of the synthesis were then addressed (Scheme 2).

It is known that α-amino acids undergo decarboxylation in

Table 1. Diastereomeric ratio of spirphydantoins (**5**)

Starting material	Diastereomeric ratio[a] major : minor	Combined yield (%)
4a	74[b] : 26	79
4b	94 : 6	65
4c	90 : 10	68

[a]determined after chromatographic separation on silica gel. [b]isolated by recrystallization.



Scheme 2. Reagents and yields: i) 2N NaOH, 70% 1,4-dioxane, 25 °C, 24 h, 73%, ii) Pd/C, H2, acetic acid, 25 °C, 24 h, 88%, iii) Cyclohexanol, 2-cyclohexenone, 165 °C, 3 h, 65%, iv) 6N HCl 100 °C, 24 h, 60%.

the presence of a catalytic amount of 2-cyclohexen-1-one in cyclohexanol.[7] We first attempted the model reaction of decarboxylation using spirohydantoin derivatives by employing the method of Hashimoto *et al.* It is noteworthy that attempted decarboxylation of N-benzyl or N-Boc protected prolines resulted in the recovery of the starting materials. This result indicates that free amino and carboxylic groups of α-amino acid chains are essential for decarboxylation. Thus, methyl prolinate **5a** was treated with 2 N NaOH in dioxane to provide an acid **6** (73%) and the subsequent hydrogenolysis of **6** (10% Pd/C, H_2, 25 °C) then afforded a spiroproline **7** in 88% yield. Decarboxylation of **7** was then successfully accomplished by heating the mixture in the presence of 0.1 mol% of 2-cyclohexen-1-one in cyclohexanol for 24 h, followed by the addition of saturated HCl in ether to afford the pyrrolidine HCl salt **8** (65%).[8] Finally, hydrolysis of **8** with 6N HCl for 24 h provided the synthetic (–)-cucurbitine (60% after ion chromatography on Dowex 50W × 8), whose spectroscopic and physical properties agreed in all respects with the data (^{1}H NMR, IR, $[\alpha]_D$, HRMS) reported in the literature[3,4] for the natural and synthetic products.

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8. Data for **8**: mp 239 °C (dec); IR (KBr) ν_{max} 3304, 1780, 1724 cm^{-1}; 400 MHz-^{1}H NMR (CD_3OD) δ 3.51(d, J = 12.8 Hz, 1H), 3.42 (m, 2H), 3.32 (d, J = 12.8 Hz, 1H), 2.39 (m, 1H), 2.20 (m, 1H); 100 MHz-^{13}C NMR (CD_3OD) δ 176.2, 157.3, 66.8, 51.8, 45.5, 35.2.