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SYNTHESIS OF (–)-TROLLINE, (–)-CRISPINE A AND (–)-CRISPINE E

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Abstract – Biologically active 1-subsutituted tetrahydroisoquinoline alkaloids, (–)-trolline, (–)-crispine A, and (–)-crispine E were synthesized using a chiral isoquinolinecarbaldehyde as a key material. The aldehyde was readily obtained from a 1-cyanoisoquinoline, and subjected to a Horner-Wadsworth-Emmons reaction. The chiral tetrahydroisoquinoline derivative thus obtained was used for the synthesis of the optically active isoquinoline alkaloids.

INTRODUCTION

Tetrahydroisoquinoline alkaloids have been selected as synthetic targets due to their various physiological activities and structural properties.[1] We have studied asymmetric synthetic approach of 1-substituted isoquinoline alkaloids to elucidate their biological roles.[2] Trolline (**1**) is an isoquinoline alkaloid isolated from the ethanol extract of the flowers of *Trollius chinensis* by Cai and co-workers in 2004.[3] The alkaloid has pyrrolo[2,1-*a*]isoquinolin-3-one core structure (Figure 1) and exhibits antibacterial activity against respiratory bacteria such as *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Klebsiella pneumoniae*, as well as antiviral activity against influenza virus A and B. Crispine A (**2**) and E (**3**) were isolated from *Carduus crispus* by Zhao and co-workers in 2002.[4] These alkaloids showed cytotoxic activity against SKOV3, KB and HeLa human cancer cell lines. Crispine A has pyrrolo[2,1-*a*]isoquinoline core and synthetic approaches have been reported recently by several groups.[5] Crispine E is an isoquinoline alkaloid having a guanidinyl group (Figure 1).

We have reported an asymmetric synthetic strategy for the preparation of pyrrolo[2,1-*a*]isoquinoline core using chiral auxiliaries.[6] In the process, however, vigorous conditions were needed for the elimination of chiral auxiliaries, and we thought that a catalytic synthesis would be advantageous strategy to asymmetric procedure. Especially, metal free organocatalytic asymmetric synthesis was thought to be a powerful method to prepare natural products.[7] Thus we studied organocatalytic addition of a carbon unit at C-1 of isoquinoline, and Jacobsen's thiourea-containing catalyst[8] was found to be efficient for asymmetric

This paper is dedicated to Professor Dr. Ekkehard Winterfeldt on the occasion of his 75th birthday.

Strecker reaction to the 6,7-dimethoxy-3,4-dihydroisoquinoline.[2(b)] We envisioned that a lot of 1-substituted isoquinoline alkaloids could be prepared from the chiral 1-cyanoisoquinoline. In this paper, we describe the application of the chiral 1-cyano-6,7-dimethoxyisoquinoline to synthesis of 1-substituted isoquinoline alkaloids.

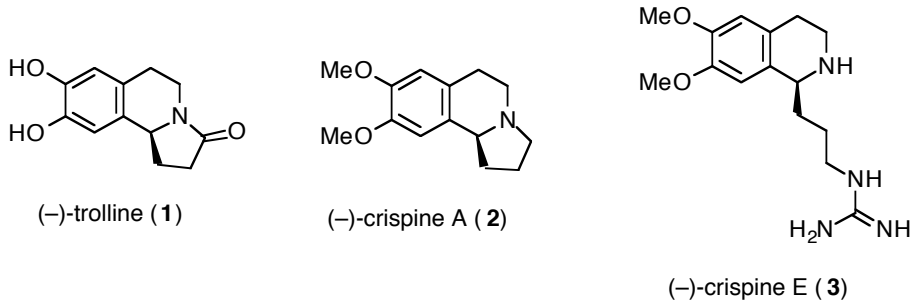
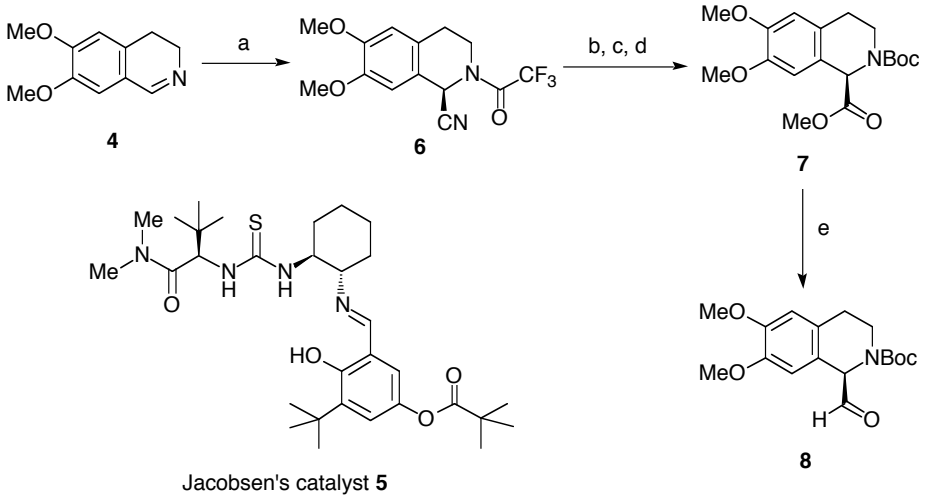


Figure 1. Structures of (–)-trolline (**1**), (–)-crispine A (**2**), and (–)-crispine E (**3**).

RESULTS AND DISCUSSION

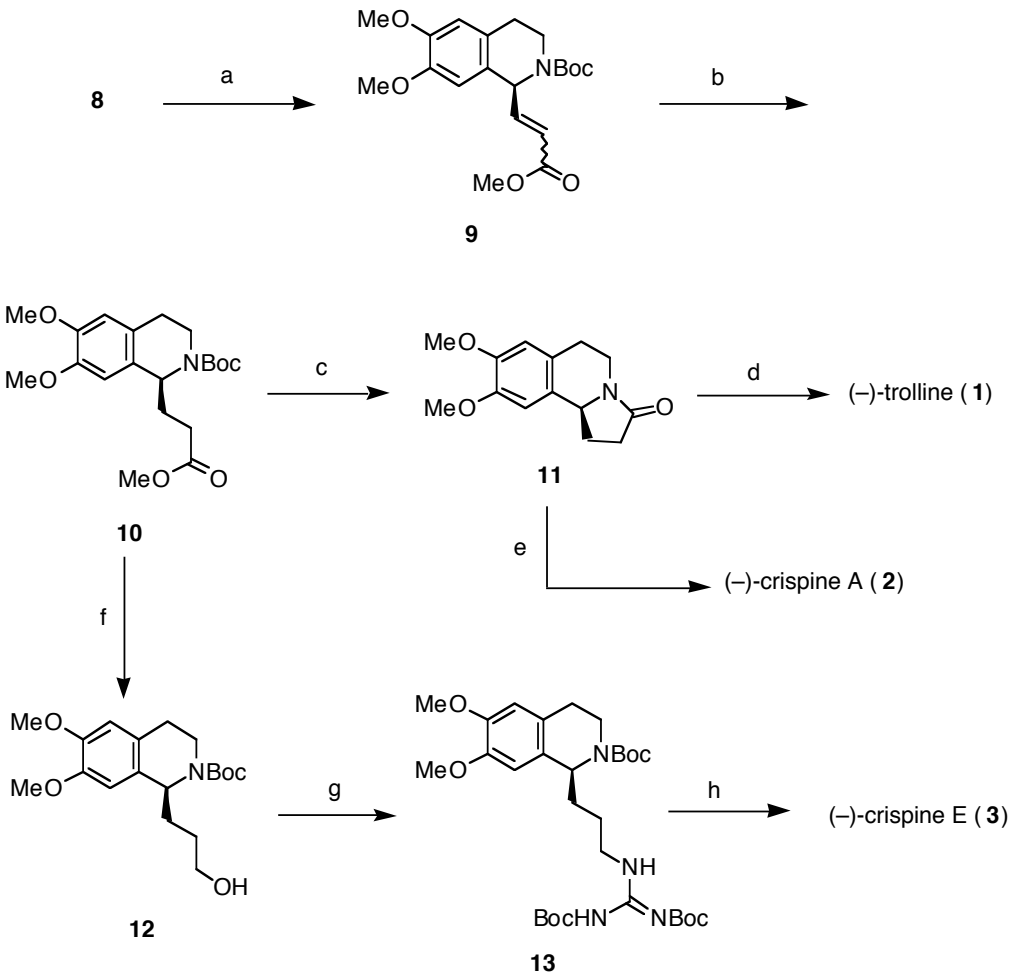
The first step of our study was to obtain a key compound **8** for a nucleophilic addition reaction. 2-*tert*-Butyl 1-methyl 6,7-dimethoxy-3,4-dihydro-1*H*-isoquinoline-1,2-dicarboxylate (**7**) was prepared from 6,7-dimethoxy-3,4-dihydroisoquinoline (**4**) in four steps as previously described.[8] The Strecker reaction of **4** was succeeded in high yield (86%) and high enantioselective excess (95% ee) with Jacobsen's thiourea containing organocatalyst **5**. The conversion of compound **7** to aldehyde **8** was efficiently accomplished by reduction with DIBAL-H in 92% yield.



Scheme 1. (a) HCN (1.5 equiv), Jacobsen's catalyst **5** (0.05 equiv), toluene, –70 °C, 40 h, then trifluoroacetic anhydride (4.0 equiv), –60 °C, 2 h, 86%, 95% ee; (b) H_2SO_4/H_2O (1/1, v/v), rt, 40 h; (c) H_2SO_4/MeOH (1/5, v/v), reflux, 4 h, 72% (2 steps); (d) $(Boc)_2O$ (2.0 equiv), CH_2Cl_2, rt, 30 min, 99%; (e) DIBAL-H (3.0 equiv), CH_2Cl_2, –78 °C, 30 min, 92%.

The aldehyde **8** was subjected to nucleophilic addition of a carbanion of trimethyl phosphonoacetate which was formed by the treatment with NaH to furnish the corresponding α,β-unsaturated ester **9** in high

yield (95%). Our first attempt under the Horner-Wadsworth-Emmons reaction using excess amount of NaH to trimethyl phosphonoacetate gave an undesired epimerized compound. To circumvent this problem, less amount of NaH than trimethyl phosphonoacetate was used. Reduction of unsaturated ester **9** to saturated ester **10** was accomplished readily by hydrogenation under an atmosphere of H_2 in the presence of Pd on carbon. The Boc group was deprotected by treatment with TMSOTf followed by Et_3N to obtain a pyrrolo[2,1-*a*]isoquinolin-3-one **11**. The use of TFA for the deprotection gave unsatisfactory results. The compound **11** was converted to trolline (**1**)[9] by demethylation with BBr_3, and converted to crispine A (**2**)[10] by reduction with $LiAlH_4$. Next, we turned to preparation of alcohol **12**. The methyl ester group of **10** was reduced with $LiAlH_4$ at room temperature to obtain **12**. A guanidinyl derivative **13** was readily obtained under Mitsunobu condition in 93% yield. The final step, removal of the Boc groups of **13** with TMSOTf, led to crispine E (**3**)[11] in 86% yield.



Scheme 2. (a) trimethyl phosphonoacetate (5 equiv), NaH (ca. 4 equiv), benzene, rt, 1 h, 95%; (b) H_2, 10% Pd/C, MeOH, rt, 12 h, 93%; (c) TMSOTf (2 equiv), CH_2Cl_2, rt, 30 min, then Et_3N (4 equiv), rt, 72 h, 99%; (d) BBr_3 (5 equiv), CH_2Cl_2, –20 °C, 24 h, 92%; (e) $LiAlH_4$ (5 equiv), THF, reflux, 2 h, 92%; (f) $LiAlH_4$ (5 equiv), THF, rt, 1 h, 97%; (g) PPh_3 (5 equiv), DEAD (5 equiv), 1,3-bis(*tert*-butoxycarbonyl)guanidine (2 equiv), toluene, rt, 8 h, 95%; (h) TMSOTf (5 equiv), CH_2Cl_2, rt, 1 h, 86%.

In conclusion, we described the application of the chiral isoquinolinecarbaldehyde derived from 1-cyanoisoquinoline to the synthesis of 1-subsutituted isoquinoline alkaloids. The Horner-Wadsworth-Emmons reaction afforded a useful intermediate **9** in good yield. Thus, the natural products, (–)-trolline, (–)-crispine A, and (–)-crispine E were synthesized.

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9. **(–)-Trolline (1)**: $[\alpha]^{25}_{D}$ –172.0 (*c* 1.0, MeOH). lit.,[3] $[\alpha]^{20}_{D}$ –197 (*c* 0.8, MeOH); ^{1}H NMR (DMSO-d_6) δ 6.50 (s, 1 H), 6.49 (s, 1 H), 4.56 (t, 1 H, *J* = 7.7 Hz), 3.97-3.91 (m, 1 H), 2.91-2.86 (m, 1 H), 2.61-2.48 (m, 3 H), 2.43-2.34 (m, 1 H), 2.23-2.17 (m, 1 H), 1.62-1.52 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 172.03, 144.15, 143.98, 128.36, 123.65, 115.36, 111.64, 55.56, 36.61, 31.24, 27.37, 27.29.
10. **(–)-Crispine A (2)**: $[\alpha]^{25}_{D}$ –95.4 (*c* 1.0, MeOH). lit.,[4] $[\alpha]^{25}_{D}$ +91.0 (MeOH), *R* enantiomer; ^{1}H NMR ($CDCl_3$) δ 6.61 (s, 1 H), 6.57 (s, 1 H), 3.849 (s, 3 H), 3.847 (s, 3 H), 3.48 (t, 1 H, *J* = 8.1 Hz), 3.20-3.15 (m, 1 H), 3.10-2.98 (m, 2 H), 2.77-2.58 (m, 3 H), 2.37-2.30 (m, 1 H), 1.97-1.85 (m, 2 H), 1.84-1.69 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 147.38, 147.27, 130.67, 126.11, 111.33, 108.87, 62.85 55.99, 55.88, 53.12, 48.28, 30.54, 27.89, 22.23.
11. **(–)-Crispine E (3)**: $[\alpha]^{25}_{D}$ –72.3 (*c* 0.3, MeOH); ^{1}H NMR (DMSO-d_6) δ 6.82 (s, 1 H), 6.72 (s, 1 H), 4.26-4.19 (m, 1 H), 3.74 (s, 3 H), 3.71 (s, 3 H), 3.31-3.25 (m, 1 H), 3.16 (br s, 2 H), 3.09-3.02 (m, 1 H), 2.92-2.85 (m, 1 H), 2.80-2.73 (m, 1 H), 2.02-1.97 (m, 1 H), 1.90-1.85 (m, 1 H), 1.70-1.65 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 157.04, 147.78, 147.43, 126.30, 124.96, 111.83, 109.96, 55.83, 55.46, 53.64, 40.35, 31.08, 27.83, 25.63, 24.72.