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# FIRST TOTAL SYNTHESIS OF CRISPINE B BY NITRO ALDOL AND THE BISCHLER-NAPIERALSKI REACTION†

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**Abstract** – A pyrrolo[2,1-*a*]isoquinoline alkaloid, crispine B, was firstly synthesized in 55% overall yield from 3,4-dimethoxyaldehyde *via* five steps by employing nitro-aldol reaction and the Bischler-Napieralski reaction.

## INTRODUCTION

We have been involved in the total synthesis of biologically active multi-substituted tetrahydroisoquinoline alkaloids by utilizing the high nucleophilicity of carbanions generated at the α-nitric position,[1] such as nitro-aldol reaction or conjugate addition of the anions to α,β-unsaturated esters. In our previous studies, α- (**1**) , β- (**2**) and γ-lycoranes (**3**), which are deoxygenated skeletons of amaryllidaceae tetrahydroisoquinoline alkaloid lycorine (**4**), were successfully synthesized[2,3] by the strategy mentioned above, chemoselective conjugate addition of aryllithium to a nitroalkene and subsequent stereoselective intramolecular nitro-Michael cyclization being employed.[4]

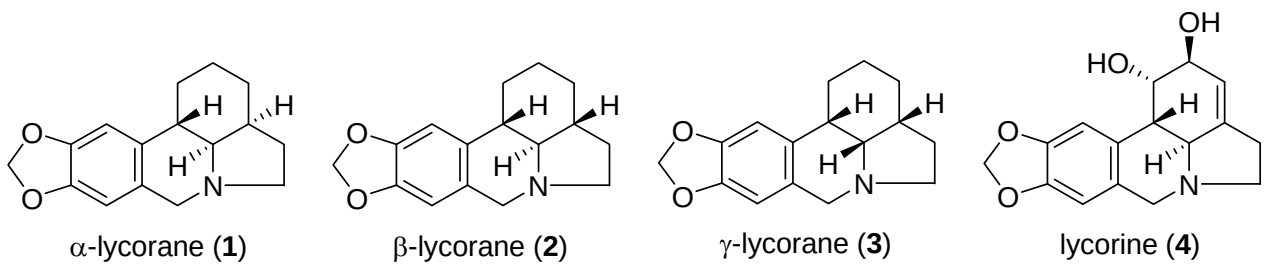



Figure 1. Lycoranes and lycorine

† This paper is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.

Recently, another pyrroloisoquinoline type of alkaloids, such as crispine A (**5**) and B (**6**), have been isolated as bioactive constituents from a Chinese fork medicine *Carduus crispus L*. which has been used for the treatment of cold, stomachache and rheumatism.[5] Significant cytotoxic activities[6,7] of these compounds on some human-cancer cell line have also been reported. Of these two bioactive alkaloids, enantioselective total syntheses of **5** were accomplished by several groups,[7-16] but compound **6** has still been left unsynthesized so far.

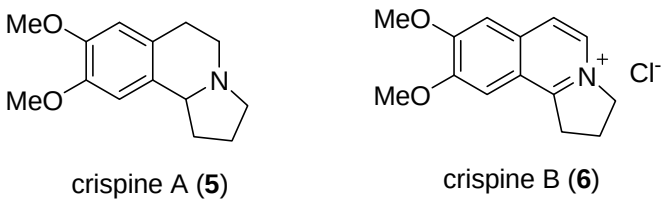
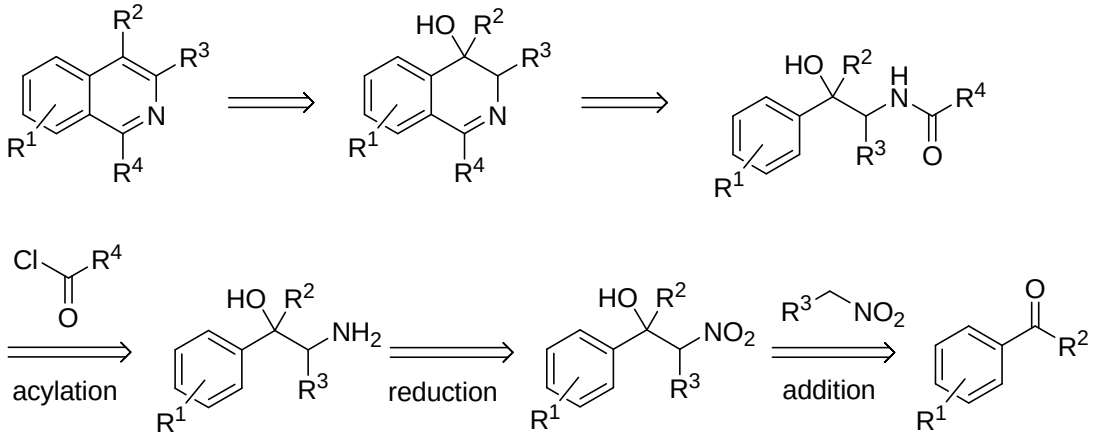



**Figure 1.** Crispine A and B

As a part of our continuing study on the synthesis of multi-substituted tetrahydroisoquinoline alkaloids, we describe herein the facile first total synthesis of crispine B (**6**) by applying our general strategy, as is shown in Scheme 1, for the synthesis of such kind of alkaloids. In the present study, the target compound **6** was synthesized in 55% overall yield in five steps by using 3,4-dimethoxybenzaldehyde (**7**, $R^1$ = (-OMe)$_2$, $R^2$ = H), nitromethane (**8**, $R^3$ = H) and 4-chlorobutyric acid (**9**, $R^4$ = -$CH_2CH_2CH_2Cl$) as substrates.

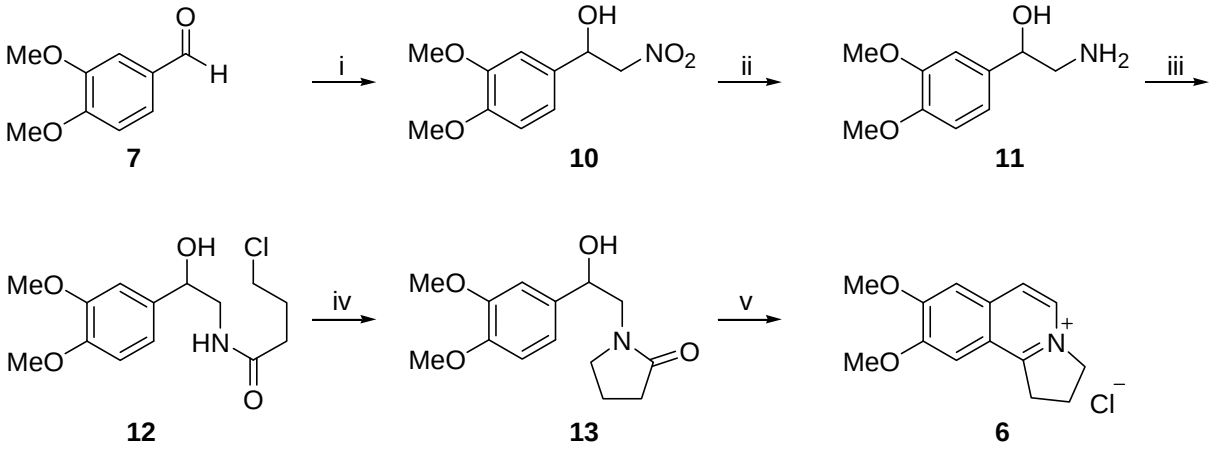



**Scheme 1.** General retrosynthetic pathway for multi-substituted isoquinolines or tetrahydroisoquinoline

## RESULTS AND DISCUSSION

As for the Henry reaction of the first step, we employed the simple and practical method recently developed by Oriyama and co-workers.[17] Thus, in the presence of MS4A, treatment of 3,4-dimethoxy-

benzaldehyde (**7**) with nitromethane (**8**) in DMSO for 24 h at room temperature afforded 1-(3,4-dimethoxyphenyl)-2-nitroethanol (**10**) in 86% yield (Scheme 2). Palladium catalyzed reduction of the nitro group of **10** with hydrogen gave 2-amino-1-(3,4-dimethoxyphenyl)ethanol (**11**), which was then treated, without purification, with 4-chlorobutyloyl chloride (**9**) in the presence of triethylamine at 0 °C to give the desired *N*-acylated product, 4-chloro-*N*-[2-(3,4-dimethoxyphenyl)-2-hydroxyethyl]-butyramide **12** in 93% yield from **10**. Intramolecular cyclization reaction of **12** with sodium hydride in DMF for 3 h at 0 °C afforded 1-[2-(3,4-dimethoxyphenyl)-2-hydroxyethyl]pyrrolidin-2-one (**13**) in 85% yield. The Bischler-Napieralski reaction[9,18-20] of **13** and dehydration reaction with phosphoryl chloride in toluene under reflux for 3.5 h gave crispine B (**6**) in 81% yield. Spectroscopic data and the melting point of the synthetic crispine B (**6**) were in good accordance with those reported.[6]




**Scheme 2.** Reagents and conditions: i $MeNO_2$ (**8**), MS4A, DMSO, rt, 24 h, 86%; ii $H_2$, Pd-C, EtOH, rt, 2 h; iii $Cl(CH_2)_3COCl$ (**9**), TEA, $CHCl_3$, 0 °C, 2 h, 93% (2 steps), iv NaH, DMF, 0 °C, 3 h, 85%; v $POCl_3$, toluene, reflux, 3.5 h, 81%

Thus, facile total synthesis of crispine B (**6**) was accomplished in 55% overall yield from 3,4-dimethoxyaldehyde *via* five steps. Synthesis of other multi-substituted tetrahydroisoquinoline alkaloids by employing the general strategy shown in Scheme 1 is in progress.

## EXPERIMENTAL

Column chromatography was effected over Fuji Silysia Chemical silica gel BW-200. NMR spectra (400 MHz $^1H$, 100 MHz $^{13}C$) were measured in $CDCl_3$ on a JEOL AL-400 spectrometer using tetramethylsilane as an internal standard unless otherwise noted. Chemical shifts ($\delta$) and coupling constants ($J$) are given in ppm and Hz, respectively. IR spectra were measured on a Shimadzu IR-455 spectrometer, and wavenumbers of maximum absorption peaks are presented in $cm^{-1}$. MS spectra were measured on a JEOL tandem MStaion JMS-700 spectrometer. All melting points were taken on a hot

stage apparatus and are uncorrected. Combined organic extracts were dried over anhydrous sodium sulfate prior to evaporation.

**1-(3,4-Dimethoxyphenyl)-2-nitroethanol (10).** To a solution of 3,4-dimethoxybenzaldehyde (**7**, 4.99 g, 30 mmol) in DMSO (180 mL) were added powdered MS4A (6.0 g) and nitromethane (8.06 mL, 150 mmol) under argon atmosphere. After stirring at rt for 24 h, the reaction mixture was quenched with phosphate buffer (pH 7, 50 mL), and extracted with EtOAc (100 mL x 3). Combined organic layers were washed successively with water (20 mL x 3) and brine (20 mL), and dried. Concentration and column chromatography (hexane : EtOAc = 4 : 1) of the residue afforded **10** as a pale yellow solid (5.81 g, 86%); mp 91–92 °C (lit.,[21] 92–93.5 °C (from benzene–petroleum ether)). $^1$H NMR $\delta$: 3.89 (3H, s), 3.89 (3H, s), 4.50 (1H, dd, $J$ = 3.2, 13.2), 4.62 (1H, dd, $J$ = 10.0, 13.2), 4.10 (1H, ddd, $J$ = 3.2, 6.4, 9.6), 6.86−6.94 (3H, m). $^{13}$C NMR $\delta$: 55.8, 55.8, 70.8, 81.2, 108.8, 111.2, 118.2 (C x 2), 130.7, 149.2. IR ($CHCl_3$): 3422, 2939, 2839, 1558, 1458, 1420, 1377, 1238, 1142, 1076, 1026. FAB-MS *m/z*: 228 $[M+H]^+$.

**4-Chloro-*N*-[2-(3,4-dimethoxyphenyl)-2-hydroxyethyl]butyramide (12).** To a solution of **10** (1.14 g, 5.02 mmol) in MeOH (10 mL), palladium on carbon (500 mg) was added, and the reaction mixture was stirred at rt for 2 h under hydrogen atmosphere. Then the mixture was filtrated, and concentration of the filtrate afforded crude **11** as a colorless oil. The resulting oil was then dissolved in $CHCl_3$ (10 mL), and to the solution triethylamine (1.0 mL, 6.9 mmol) and 4-chlorobutyric chloride (0.60 mL, 5.5 mmol) were added under ice-cooling. After stirring for 2 h at 0 °C, the reaction mixture was washed successively with 10% hydrochloric acid (10 mL x 2), saturated $NaHCO_3$ aq (10 mL x 2) and brine (10 mL). The organic layer was dried and concentrated. Column chromatography (hexane : EtOAc = 4 : 1) of the residue afforded **12** as a pale yellow oil (1.409 g, 93%, 2 steps). **11**: $^1$H NMR $\delta$: 2.90–3.12 (2H, m), 3.76 (3H, s), 3.78 (3H, s), 4.81 (1H, brs), 5.29 (3H, brs), 6.70 (1H, d, $J$ = 8.4), 6.79 (1H, d, $J$ = 8.4), 6.89 (1H, s). $^{13}$C NMR $\delta$: 47.7, 55.7, 55.7, 71.8, 109.1, 110.9, 117.9, 133.9, 148.4, 148.8. **12**: $^1$H NMR $\delta$: 2.08 (2H, tt, $J$ = 6.2, 7.0), 2.36 (2H, t, $J$ = 7.0), 3.33 (1H, ddd, $J$ = 5.2, 8.0, 14.0), 3.56 (2H, t, $J$ = 6.2), 3.64 (1H, ddd, $J$ = 3.2, 6.8, 14.0), 3.88 (3H, s), 3.89 (3H, s), 4.76 (1H, dd, $J$ = 3.2, 8.0), 6.22 (1H, brs), 6.82 (1H, d, $J$ = 8.0), 6.87 (1H, d, $J$ = 8.0), 6.91 (1H, s). $^{13}$C NMR $\delta$: 28.0, 33.0, 44.3, 47.3, 55.8, 55.9, 73.1, 108.9, 111.0, 117.9, 134.3, 148.5, 149.0, 172.9. IR ($CHCl_3$): 3345, 2940, 1647, 1597, 1516, 1466, 1261, 1219. FAB-MS *m/z*: 302 $[M+H]^+$. HR-FAB-MS *m/z*: Calcd for $C_{14}H_{21}ClNO_4$: 302.1159. Found 302.1165.

**1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]pyrrolidin-2-one (13).** To a suspension of sodium

hydride (160 mg, 4.0 mmol) in dry DMF (40 mL), a solution of **12** (1.0 g, 3.3 mmol) in dry DMF (10 mL) was added dropwise at 0 °C. After stirring for 2 h at 0 °C, the reaction was quenched with saturated ammonium chloride aq (20 mL), and the resulting mixture was extracted with EtOAc (20 mL x 3). Combined organic extracts were washed successively with water (20 mL x 3) and brine (20 mL), and dried. Concentration and column chromatography (hexane : EtOAc = 2 : 1) of the residue afforded **13** as a colorless solid (995 mg, 85%). For analytical purpose a small portion was recrystallized from hexane–EtOAc to give colorless crystals; mp 90–92 °C (lit.,[22] 90-91 °C). $^1$H NMR: $\delta$: 1.99 (2H, m), 2.42 (2H, t, $J$ = 7.4 Hz), 3.26 (1H, ddd, $J$ = 6.8, 7.6, 9.6 Hz), 3.36 (1H, ddd, $J$ = 6.8, 7.2, 9.6 Hz), 3.50 (1H, dd, $J$ = 4.0, 14.4 Hz) , 3.56 (1H, dd, $J$ = 7.2, 14.0 Hz), 3.88 (3H, s), 3.90 (3H, s), 4.00 (1H, brs), 4.92 (1H, brs), 6.84 (1H, d, $J$ = 8.0 Hz), 6.89 (1H, d, $J$ = 8.0 Hz), 6.96 (1H, s). $^{13}$C NMR $\delta$: 18.4, 30.8, 49.5, 51.9, 55.9 (C x 2), 72.9, 108.9, 110.9, 118.0, 134.7, 148.5, 149.1, 177.1. IR ($CHCl_3$): 3333, 1666, 1516, 1466, 1261, 1219. FAB-MS *m/z*: 266 $[M+H]^+$.

**Crispine B (6).** To a refluxing solution of **13** (143 mg, 0.54 mmol) in dry-toluene (3 mL), phosphoryl chloride (1.2 mL, 1.29 mmol) was added, and the resulting mixture was stirred under reflux for 3.5 h. Concentration and column chromatography afforded **6** as a colorless solid (116 mg, 81%). Analytical sample of **6** was obtained as colorless crystals by recrystallization from $CHCl_3$–hexane; mp 212–214 °C (lit.,[6] 213–215 °C). $^1$H NMR (MeOH-$d_4$): $\delta$: 2.63 (2H, tt, $J$ = 7.6, 8.0 Hz), 3.89 (2H, t, $J$ = 8.0 Hz), 4.08 (3H, s), 4.10 (3H, s), 4.91 (2H, t, $J$ = 7.6 Hz), 7.57 (1H, s), 7.65 (1H, s), 8.07 (1H, d, $J$ = 6.8 Hz), 8.36 (1H, d, $J$ = 6.8 Hz). $^{13}$C NMR $\delta$: 22.0, 32.5, 57.2, 57.4, 60.2, 106.5, 107.4, 122.4, 123.8, 130.9, 137.0, 154.7, 159.1, 159.7. IR (Nujol): 2943, 2855, 1458, 1377. FAB-MS *m/z*: 230 $[M\text{-}Cl^-]^+$.

## ACKNOWLEDGEMENTS

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