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Total synthesis of the antitumor active pyrrolo[2,1-*a*]isoquinoline alkaloid (±)-crispine A

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Abstract—Addition of a propargyl Grignard reagent to 3,4-dihydro-6,7-dimethoxyisoquinoline, silver(I)-promoted oxidative cyclization, and chemoselective hydrogenation of the pyrrole ring provide a simple three-step route to the antitumor active pyrrolo[2,1-*a*]isoquinoline alkaloid (±)-crispine A.

Extracts of the plant *Carduus crispus* have been applied in Chinese folk medicine for the treatment of cold, stomach ache, and rheumatism. Moreover, a screening test revealed that the extracts inhibit the growth of some human cancer lines in vitro and show a significant cytotoxic activity.[1] Recent phytochemical studies on *C. crispus* by Zhao and co-workers led to the isolation of the two pyrrolo[2,1-*a*]isoquinoline alkaloids crispine A (**1**) and crispine B (**2**) along with three bicyclic isoquinoline alkaloids (Fig. 1).[1]

Crispine A (**1**) was already obtained by synthesis prior to its isolation as a natural product.[2,3] 1,2,3,5,6,10b-Hexahydropyrrolo[2,1-*a*]isoquinoline (**3**), the parent framework of crispine A (**1**), is a known degradation product of the alkaloid norsecurinone[4] and has been prepared previously using different synthetic strategies.[4–9] Compound **3** is an α_2-adrenoreceptor antagonist[10] and its 5-phenyl derivatives exhibit antidepressant-like activity.[11]

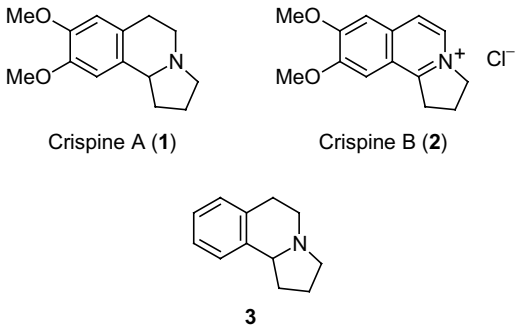

Figure 1. Pyrrolo[2,1-*a*]isoquinoline alkaloids of *C. crispus* and parent framework.

We envisaged a short and direct total synthesis of crispine A (**1**) by using a novel pyrrole synthesis recently developed in our laboratories.[12] Since the simple pyrrole annulation at 3,4-dihydroisoquinoline (**4a**)[13] has already been shown,[12a] we focused initially on the synthesis of the unsubstituted parent compound **3** (Scheme 1). A closer inspection of the product resulting from the Lewis acid promoted addition of 3-trimethylsilylpropargylmagnesium bromide to **4a** revealed that the allene **6a** was formed as a by-product (11% yield) along with the propargyl derivative **5a** (80% yield). The silver(I)-promoted oxidative cyclization of the homopropargylamine **5a** in dichloromethane at room temperature afforded after 14 h 5,6-dihydropyrrolo[2,1-*a*]isoquinoline **7a** in 72% yield.[12a] The 5,6-dihydropyrrolo[2,1-*a*]isoquinoline ring system has been obtained previously using alternative procedures.[14] Treatment of the allenyl derivative **6a** with silver acetate under the same set of reaction conditions led only to recovery of starting material. However, reaction of the allene **6a** with silver acetate in acetone at reflux for 14 h provided the annulated pyrrole **7a** in 56% yield. Chemoselective hydrogenation of the pyrrole ring[15] with 5% rhodium on activated charcoal in methanol/acetic acid (1:1) afforded 1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline (**3**) in 91% yield. The spectroscopic data of compound **3**[16] are in agreement with those described in the literature.[4–9]

Keywords: Total synthesis; Alkaloids; Pyrroles; Hydrogenation.
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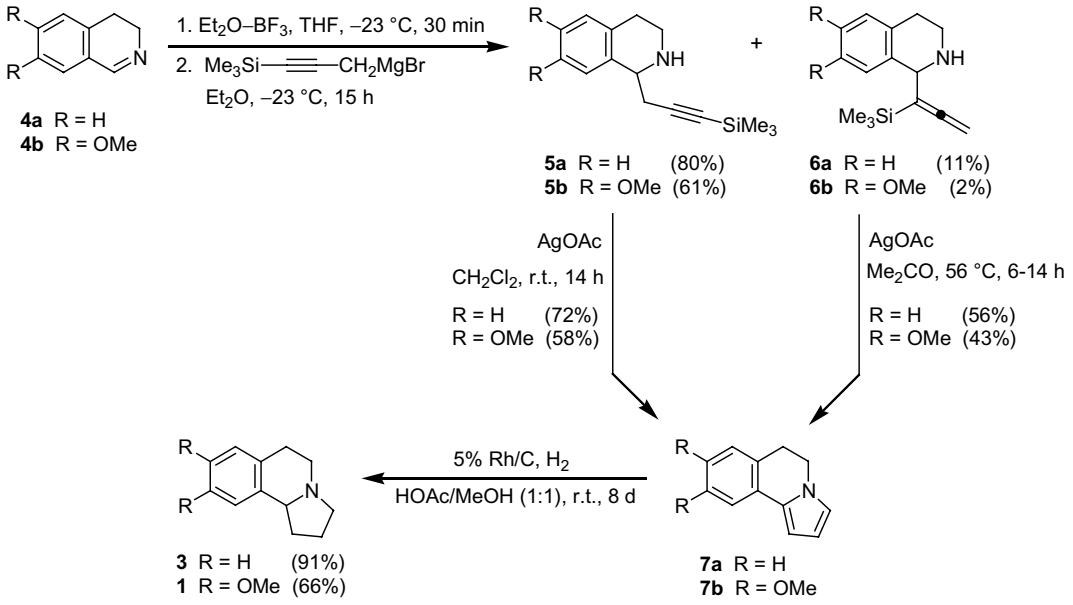

Scheme 1. Synthesis of (±)-crispine A (**1**) and the parent compound, 1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline (**3**).

3,4-Dihydro-6,7-dimethoxyisoquinoline (**4b**) is readily available by Bischler–Napieralski cyclization of *N*-formyl-3,4-dimethoxyphenylethylamine (80–90% yield on a 25 g scale).[17] The boron trifluoride promoted addition of 3-trimethylsilylpropargylmagnesium bromide to **4b** afforded the propargyl compound **5b** (61% yield) and the allene **6b** (2% yield). The silver(I)-promoted oxidative cyclization of **5b** using our standard conditions provided 5,6-dihydro-8,9-dimethoxypyrrolo[2,1-*a*]-isoquinoline (**7b**) in 58% yield.[18] As found previously for compound **6a**, the oxidative cyclization of the allenyl derivative **6b** did not proceed at room temperature. The conversion of **6b** to the pyrrolo[2,1-*a*]isoquinoline **7b** with silver acetate in acetone at reflux for 6 h afforded the desired product in 43% yield. Finally, chemoselective hydrogenation of the pyrrole ring provided (±)-crispine A (1,2,3,5,6,10b-hexahydro-8,9-dimethoxypyrrolo[2,1-*a*] isoquinoline) (**1**). All spectroscopic data of our synthetic crispine A (**1**)[19] are in full agreement with those reported for the natural product.[1] The catalytic dehydrogenation of (±)-crispine A (**1**) (10% Pd/C, C_6H_6, 80 °C, 12 h) leads back to compound **7b** (88% yield).

In conclusion, the present three-step route provides the antitumor active pyrrolo[2,1-*a*]isoquinoline alkaloid (±)-crispine A (**1**) in 24% overall yield and the biologically active 1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline (**3**) in 58% overall yield. Our approach can be easily applied to the preparation of a wide range of synthetic analogues for structure–activity studies. Investigations in this direction are currently ongoing.

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16. 1,2,3,5,6,10b-Hexahydropyrrolo[2,1-*a*]isoquinoline (**3**): light yellow oil. IR (ATR): ν = 2922, 2872, 2783, 1578, 1493, 1452, 1377, 1351, 1325, 1285, 1255, 1218, 1182, 1162, 1136, 1116, 1082, 1040, 1013, 932, 913, 740 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.71–1.78 (m, 1H), 1.82–1.98 (m, 2H), 2.37 (m, 1H), 2.62 (q, J = 8.1 Hz, 1H), 2.70 (ddd, J = 14.8, 10.1, 4.7 Hz, 1H), 2.84 (dt, J = 16.6, 4.0 Hz, 1H), 3.04–3.12 (m, 2H), 3.14–3.20 (m, 1H), 3.53 (t, J = 8.3 Hz, 1H), 7.06–7.16 (m, 4H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ 22.22 (CH_2), 28.31 (CH_2), 30.40 (CH_2), 48.24 (CH_2), 53.25 (CH_2), 63.04 (CH), 125.69 (CH), 125.84 (CH), 126.05 (CH), 128.41 (CH), 134.01 (C), 138.51 (C). MS (EI): *m*/*z* (%) = 173 (46) [M^+], 172 (100), 170 (11), 145 (36), 117 (18). HRMS: *m*/*z* calcd for $C_{12}H_{15}N$ [M^+]: 173.1204; found: 173.1206.
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18. 5,6-Dihydro-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline (**7b**): light yellow crystals; mp: 110–112 °C. IR (ATR): ν = 2935, 1611, 1553, 1506, 1464, 1441, 1333, 1266, 1226, 1210, 1166, 1131, 1073, 1050, 1015, 859, 791, 711 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.99 (t, J = 6.6 Hz, 2H), 3.88 (s, 3H), 3.91 (s, 3H), 4.05 (t, J = 6.6 Hz, 2H), 6.19 (br s, 1H), 6.38 (br d, J = 2.3 Hz, 1H), 6.64 (br s, 1H), 6.69 (s, 1H), 7.01 (s, 1H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 29.05 (CH_2), 44.25 (CH_2), 56.00 (CH_3), 56.01 (CH_3), 102.22 (CH), 105.91 (CH), 108.30 (CH), 111.29 (CH), 120.36 (CH), 122.57 (C), 122.75 (C), 129.91 (C), 147.20 (C), 148.22 (C). MS (EI): *m*/*z* (%) = 229 (100) [M^+], 214 (46), 186 (19), 185 (6), 171 (7). HRMS: *m*/*z* calcd for $C_{14}H_{15}NO_2$ [M^+]: 229.1103; found: 229.1105. Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.37; H, 6.88; N, 6.05.
19. (±)-Crispine A (**1**): colorless crystals; mp 76–78 °C. IR (ATR): ν = 2921, 2801, 1607, 1517, 1466, 1409, 1376, 1359, 1323, 1312, 1250, 1228, 1211, 1198, 1159, 1135, 1111, 1086, 1012, 850, 811, 762, 721 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.71 (m, 1H), 1.86 (m, 1H), 1.92 (m, 1H), 2.31 (m, 1H), 2.55 (br q, J = 8.5 Hz, 1H), 2.63 (dt, J = 4.6, 10.8 Hz, 1H), 2.72 (br dt, J = 16.4, 3.5 Hz, 1H), 3.01 (m, 1H), 3.07 (dt, J = 3.7, 8.7 Hz, 1H), 3.17 (ddd, J = 11.3, 6.2, 2.9 Hz, 1H), 3.41 (br t, J = 8.0 Hz, 1H), 3.83 (s, 3H), 3.84 (s, 3H), 6.56 (s, 1H), 6.60 (s, 1H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ 22.21 (CH_2), 28.03 (CH_2), 30.47 (CH_2), 48.35 (CH_2), 53.14 (CH_2), 55.87 (CH_3), 55.98 (CH_3), 62.94 (CH), 108.81 (CH), 111.30 (CH), 126.20 (C), 130.94 (C), 147.19 (C), 147.31 (C). MS (EI): *m*/*z* (%) = 233 (63) [M^+], 232 (100), 218 (6), 216 (7), 205 (49), 190 (28), 177 (5). HRMS: *m*/*z* calcd for $C_{14}H_{19}NO_2$ [M^+]: 233.1416; found: 233.1391.