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An intramolecular Schmidt reaction strategy for the synthesis of a methyl analogue of crispine A

Ponminor Senthil Kumar, Ajoy Kapat, Sundarababu Baskaran *

Department of Chemistry, Indian Institute of Technology Madras, Chennai 600 036, India

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Abstract

A convenient approach for the synthesis of a methyl analogue of crispine A, a potent anticancer agent, through intramolecular Schmidt reaction of azido-ketone **6** is described.

Medicinal plants and herbs represent a huge source of novel biologically active natural products. In particular, constituents of plants used in traditional medicine are attractive candidates for the discovery of new lead drug molecules. *Carduus crispus*, a popular invasive plant occurring in Asia and Europe, has been used as Chinese folk medicine for the treatment of colds, stomach ache, and rheumatism. In 2002, a new indolizidine alkaloid known as crispine A (**1**), was isolated from *C. crispus*, which was found to exhibit superior antitumor activity against SKOV3, KB and HeLa human cancer lines.[1] As a result of its potent antitumor activity, various synthetic methods have been developed for the synthesis of crispine A (**1**).[2]

Interestingly, Schell and Smith reported the first synthesis of crispine A (**1**), even before its isolation, using a novel *N*-chloramine rearrangement reaction.[2f] To understand the structure activity relationship (SAR) as well as to improve the efficacy of this novel anticancer agent, a flexible approach for the synthesis of various analogues of crispine A (**1**) is much sought after (Fig. 1). One of the most efficient methods for the construction of the indolizidine framework is based on intramolecular Schmidt reaction of azides.[3,4] Pearson and Aube have exploited the synthetic potential

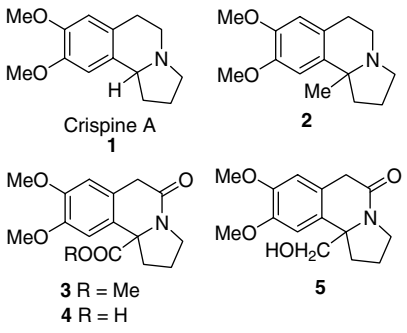

Fig. 1. Crispine A and its analogues.

of this intramolecular Schmidt reaction for the synthesis of numerous indolizidine alkaloids.[4] Recently, we reported a novel approach for the construction of the indolizidine skeleton using epoxide initiated cationic cyclization of an azide which was further exploited in the stereo- and enantioselective synthesis of indolizidines 167B and 209D.[5]

In this Letter, we report the synthesis of the methyl analogue of crispine A **2** via intramolecular Schmidt reaction of azido-ketone **6**. Key intermediate **6** can be readily synthesized from β-ketoester **7** as shown in Scheme 1. β-Ketoester **7**, prepared as described in the literature[6] was protected as the corresponding ethylene ketal **8** in moderate yield. Alkylation of ethylene ketal **8** with 1-chloro-3-iodopropane, followed by azidation and subsequent hydrolysis

* Corresponding author. Tel.: +91 44 2257 4218; fax: +91 44 2257 0545.
E-mail address: sbhaskar@iitm.ac.in (S. Baskaran).

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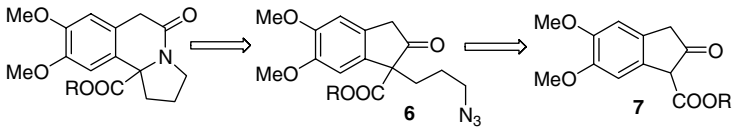
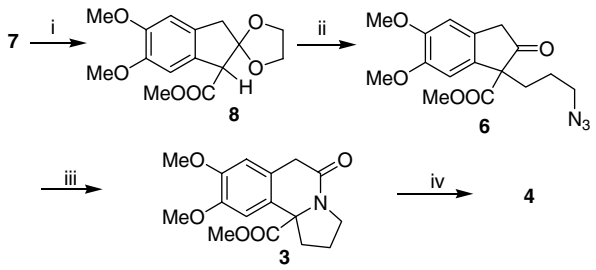


Scheme 1. Retrosynthetic analysis of crispine A analogues.



Scheme 2. Intramolecular Schmidt cyclization of azido-ketone **6**. Reagents and conditions: (i) ethylene glycol, PTSA, $HC(OEt)_3$, dry DCM, rt, 3 d, 53%, (ii) (a) 1-chloro-3-iodopropane, NaH, dry DMF, 0 °C to rt, 30 min, 70%; (b) NaN_3, DMF, 60 °C, 24 h, 83%; (c) DOWEX®50WX8H$^+$, MeOH, reflux, 20 h, 81%; (iii) triflic acid, dry DCM, −5 to 0 °C, 15 min, 54%; (iv) LiOH, dioxane/water (3:1), rt, 5 h, 68%.

gave the corresponding azido-ketone **6** in 48% overall yield (Scheme 2). Finally, the intramolecular Schmidt reaction of azido-ketone **6** was successfully achieved using TfOH at −5 to 0 °C and the resultant cyclized product **3** was isolated in 54% yield, (Scheme 2). The structure of cyclized product **3** was unambiguously established by single crystal X-ray analysis on the corresponding acid **4** (Fig. 2).[7]

After achieving the construction of the indolizidine skeleton via intramolecular Schmidt reaction, our next objective was to convert ester **3** to the methyl analogue of crispine A (**2**).[8]

Consequently, ester **3** on reduction with LAH gave the corresponding alcohol **5** in 70% yield. Mesylation of hydroxymethyl-lactam **5** with mesyl chloride, followed by reduction with LAH in the presence of concd H_2SO_4[2a] afforded the desired methyl analogue of crispine A (**2**) in good yield (Scheme 3). Spectral data of compound **2** were in complete agreement with the reported values.[8a]

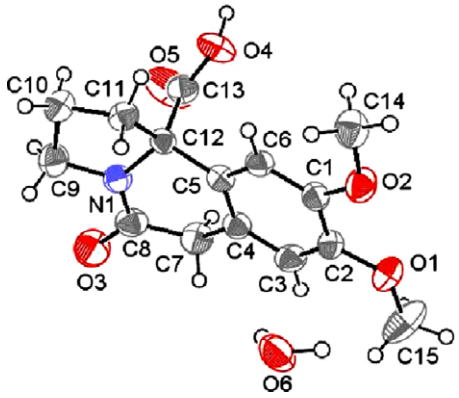
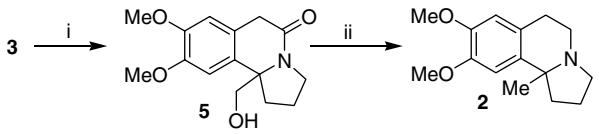


Fig. 2. ORTEP diagram of acid **4**.



Scheme 3. Synthesis of the methyl analogue of crispine A **2**. Reagents and conditions: (i) LAH, dry THF, 0 °C, rt, 8 h, 70%, (ii) (a) MsCl, Et_3N, dry DCM, 0 °C to rt, 6 h, 93%; (b) LAH, concd H_2SO_4, dry THF, 0 °C to rt, 80%.

In conclusion, we have achieved successfully the synthesis of a methyl analogue of crispine A (**2**) via intramolecular Schmidt reaction of azido-ketone **6**. The structure of the cyclized indolizidine derivative **3** was unambiguously established by single crystal X-ray analysis. Functionalized alcohol **5** can be further exploited in the synthesis of a library of anticancer analogues of crispine A.[9]

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.12.040.

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7. *X-ray crystallographic analysis for compound* **4**: $C_{15}H_{19}NO_6$, MW = 309.31, orthorhombic, $P2_12_12_1$, $a = 10.3243(9)$, $b = 10.6834(10)$, $c = 13.6598(12)$ Å, $V = 1506.7(2)$ Å3, $Z = 4$, $D_{calcd} = 1.364$ mg m^{-3}, $F(000) = 656$, $T = 298$ K, colorless needles, $0.25 \times 0.22 \times 0.22$ mm, 19,002 reflections collected ($R_{int} = 0.0738$), 3594 unique. All measurements were carried out on a Bruker axs (Kappa Apex2) equipped with graphite monochromatic Mo Kα radiation. Structure refinements by full-matrix least-squares methods on F^2. Programs: SHELXS and SHELXL [Bruker axs (Kappa Apex2)]. Crystallographic details have been deposited at the Cambridge Crystallographic Data Centre (deposition number CCDC 663178).
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9. *Spectral data for selected compounds*: Compound **8**. IR (neat): 2957, 2836, 1728, 1508, 1466, 1257, 1180, 1031, 857, 572 cm^{-1}; ^{1}H NMR [400 MHz, $CDCl_3$] δ 6.77 (s, 1H), 6.74 (s, 1H), 4.01–4.11 (m, 5H), 3.86 (s, 3H), 3.84 (s, 3H), 3.73 (s, 3H), 3.43 (d, $J = 16$ Hz, 1H), 3.06 (d, $J = 16$ Hz, 1H); ^{13}C NMR [100 MHz, $CDCl_3$] δ 171.02, 149.44, 148.54, 132.34, 129.44, 117.911, 108.39, 107.79, 65.45, 64.55, 59.39, 56.05, 55.98, 52.06, 42.99; MS (ESI) $C_{15}H_{18}O_6$ $(M+Na)^+$ 317. Compound **6**. IR (neat): 2913, 2095, 1728, 1613, 1494, 1454, 1286, 1164, 1032, 763 cm^{-1}; ^{1}H NMR [400 MHz, $CDCl_3$] δ 6.87 (s, 1H), 6.76 (s, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.76 (d, $J = 22.4$ Hz, 1H), 3.65 (s, 3H), 3.44 (d, $J = 22.4$ Hz, 1H), 3.24–3.16 (m, 2H), 2.28–2.21 (m, 2H), 1.31–1.26 (m, 2H); ^{13}C NMR [100 MHz, $CDCl_3$] δ 212.20, 170.87, 149.95, 145.59, 131.60, 129.15, 107.77, 106.47, 64.60, 56.19, 56.05, 52.84, 51.15, 43.42, 31.03, 23.70; HRMS (ESI) calcd for $C_{16}H_{19}N_3O_5$ $(M+H)^+$: 334.1326; found: 334.1329. Compound **3**. IR (neat): 2953, 1731, 1650, 1518, 1433, 1411, 1254, 1217, 1133, 805, 628 cm^{-1}; ^{1}H NMR [400 MHz, $CDCl_3$] δ 6.77 (s, 1H), 6.55 (s, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.70 (d, $J = 19.2$ Hz, 1H), 3.59 (s, 3H), 3.58–3.56 (m, 1H) 3.41 (d, $J = 18.8$ Hz, 1H), 3.05–3.02 (m, 1H), 2.05–1.97 (m, 2H), 1.88–1.81 (m, 2H); ^{13}C NMR [100 MHz, $CDCl_3$] δ 172.15, 168.19, 149.41, 148.13, 126.05, 125.10, 110.0, 108.66 71.60, 56.23, 56.02, 53.14, 44.77, 37.63, 36.23, 21.50; HRMS (ESI) calcd for $C_{16}H_{19}NO_5$ $(M+H)^+$: 306.134; found: 306.1350. Compound **5**. IR (neat): 3385, 2940, 1618, 1514, 1452, 1298, 1214, 1065, 765 cm^{-1}; ^{1}H NMR [400 MHz, $CDCl_3$] δ 6.67 (s, 1H), 6.64 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.78 (d, $J = 19.2$ Hz, 1H), 3.73–3.59 (m, 4H), 3.43 (d, $J = 19.2$ Hz, 1H), 2.55–2.54 (m, 1H), 2.11–2.04 (m, 4H); ^{13}C NMR [100 MHz, $CDCl_3$] δ 168.52, 148.74, 147.94, 129.45, 124.90, 110.26, 108.46, 69.33, 67.95, 56.25, 56.04, 44.97, 37.51, 33.88, 14.19; MS (ESI) $C_{15}H_{19}NO_4$ $(M+H)^+$ 278.