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Tandem aza-Michael/spiro-ring closure sequence: access to a versatile scaffold and total synthesis of (±)-coerulescine

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ABSTRACT

The total synthesis of the alkaloid (±)-coerulescine is presented. The key step of this approach is an efficient tandem aza-Michael initiated ring closure (aza-MIRC) process between ethoxymethylene-oxindole and benzyl(2-bromoethyl)carbamate. The potency of the aza-MIRC reaction was first tested onto less challenging Michael acceptors and led in good yields to the corresponding *N*-Cbz α-alkoxy-β-gem-disubstituted pyrrolidines. The resulting *N*-acyliminium precursor obtained from ethoxymethylidene-oxindole was efficiently converted in four steps, including 2 deprotections, into the targeted (±)-coerulescine.

The simplest members of the spirooxindole family are coerulescine (**1**) and horsfiline (**2**) isolated respectively from the blue canary grass *Phalaris coerulescens*, and the roots of the Malaysian tree *Horsfieldia superba* (Fig. 1).[1] Another tricyclic member elacomine (**3**),[2] substituted in the 4′ position, exhibits anti-tumor activity. Moreover, tetra- and pentacyclic spirooxindole alkaloids such as rhynchophylline (**5**)[3] and spirotryprostatins A (**6**) and B (**7**)[4] are well known for their interest as a neuroprotective agent or anticancer agents, respectively. In fact, the spiro[oxindole-3,3′-pyrrolidine] ring system is among the most interesting scaffold since it is found in many relevant biologically active compounds. For example, synthetic MI-219 (**4**) is a highly selective inhibitor of the MDM2–P53 interactions making it an efficient anti-cancer agent.[5]

Furthermore, the formation of the spiro junction remains a stimulating synthetic challenge for chemists. These observations explain why numerous approaches were developed over the years[6] including our own results for the access to unprecedented spirooxindole cores.[7] We wish to report herein our recent findings regarding the total synthesis of (±)-coerulescine (**1**). The key step for this sequence is an efficient aza-MIRC (Michael initiated ring closure) process between 3-ethoxymethylene-oxindole **8**[9] and benzyl(2-bromoethyl)carbamate **9** developed by our group.[8]

The retrosynthetic pathway envisioned for this total synthesis is presented in Scheme 1. The requisite original key substrate (±)-**10**[10] bearing orthogonally protected nitrogen atoms would be obtained by an aza-MIRC sequence between **9** and Michael acceptor

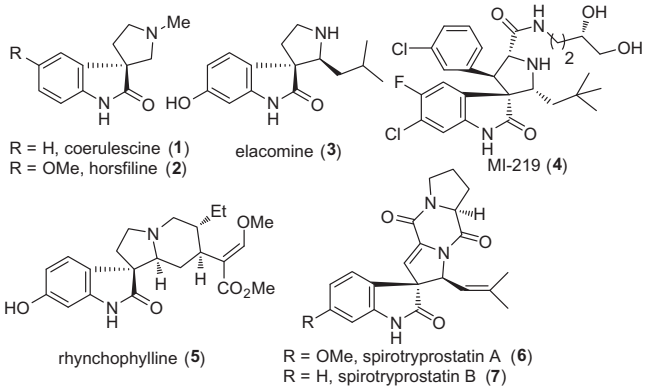

Figure 1. Representative spirooxindoles.

8. Starting from compound (±)-**10**, selective reduction, via *N*-acyliminium ion chemistry, deprotections, and methylation of the resulting amine should lead to the desired (±)-coerulescine (**1**). This retrosynthetic pathway implied to use benzyl(2-bromoethyl)carbamate **9** as a partner for the spiro-ring closure.

Indeed, the key step of the synthesis was the tandem reaction between benzyl(2-bromoethyl)carbamate **9** and an oxindole derived Michael acceptor. As mentioned above, this reaction is known with α-bromoacetamides but investigated for the first time using compound **9** as the starting material.[7,8] The challenge of this step was the possible competitive formation of *N*-Cbz aziridine

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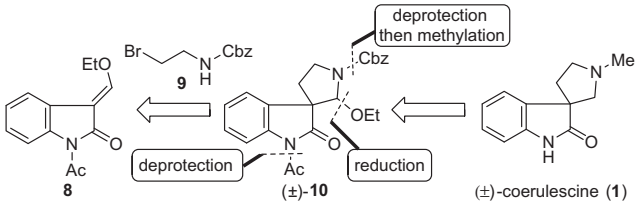
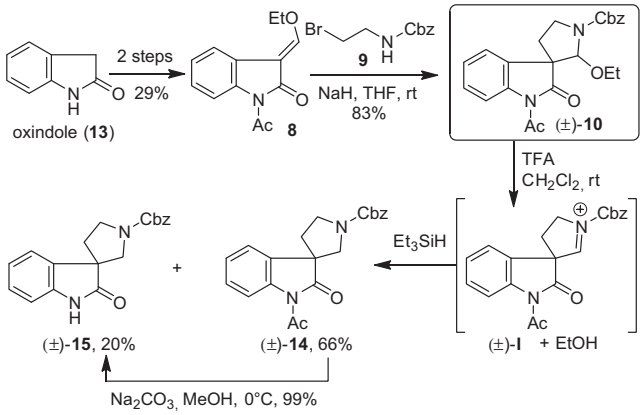


Scheme 1. Retrosynthetic analysis.

resulting from the intramolecular cyclization of N-protected 2-bromoethanamine **9**.[11] For this reason, the first attempts of the tandem reaction were performed with more conventional Michael acceptors **11** in Table 1.[12] Thankfully, the process proved to be highly efficient leading in moderate to good yield to the expected *N*-Cbz α-alkoxypyrrolidines **12**. For instance, commercially available Michael acceptors **11a**–**d** led to the formation of the corresponding pyrrolidine systems **12a** and **d** in good yields ranking from 64% to 84% (Table 1, entries 1–4). Diphenylketone derived Michael acceptor **11e** furnished the desired cyclic compound in an acceptable 57% yield (Table 1, entry 5). The reaction was also efficient with the acceptor **11f** bearing a bulky phenylsulfone moiety, giving a high 98% yield (Table 1, entry 6).

Next we turned our attention to the application of this tandem process to the total synthesis of (±)-coerulescine (**1**). Oxindole (**13**) was first converted into the Michael acceptor **8** by using classical procedures (Scheme 2).[13] The tandem reaction furnished in 83% yield the desired tricyclic spiro-product (±)-**10**. Reduction of the resulting α-ethoxy-pyrrolidine was performed via *N*-acyliminium ion (±)-**I** generated in situ upon acidic treatment (e.g., excess of TFA in DCM at rt) using triethylsilane as the reducing agent. We obtained a 3:1 mixture of (±)-**14** together with the deacylated compound (±)-**15** in an overall 86% yield. This deprotection can be rationalized by the addition of EtOH produced during the process onto the acyl group. Product (±)-**14** was easily and quantitatively converted into (±)-**15** in the presence of sodium carbonate in methanol.[14]

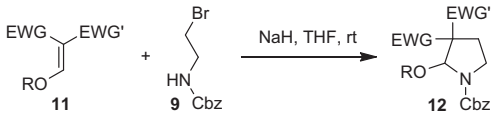


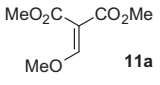
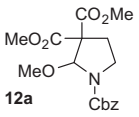
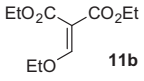
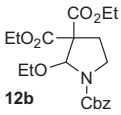
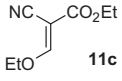
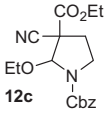
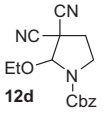
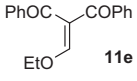
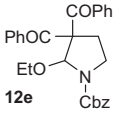
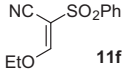
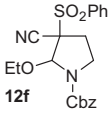
Scheme 2. Access to *N*-Cbz spiro[oxindole-3,3′-pyrrolidine] ring system (±)-**15**.

Interestingly, the *N*-Cbz-spiro-system (±)-**15** was afterward isolated in three steps and 71% yield starting from **8** without any intermediate purification (Scheme 3). The carboxybenzyl group was then quantitatively removed by hydrogenation in the presence of a catalytic amount of Pd/C in methanol. The resulting tricyclic product (±)-**16**[15] was converted in 38% yield to (±)-coerulescine (**1**) by methylation of the secondary amine with dimethyl sulfate in acetonitrile. The ^{1}H NMR spectral data are in accordance with those reported in the literature.[16] It is important to note that the conversion of coerulescine (**1**) into horsfiline (**2**) was previously published.[17]

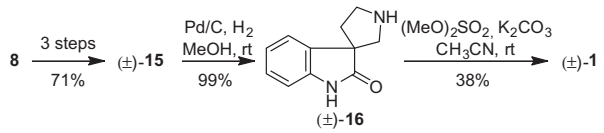
In summary, we have demonstrated the efficiency of benzyl(2-bromoethyl)carbamate to access *N*-Cbz α-ethoxy-pyrrolidines **12** (Table 1). For the total synthesis of coerulescine (**1**), the key precursor (±)-**10**, bearing orthogonally protected nitrogen atoms, was readily obtained in good yield employing an aza-MIRC methodology. An application to the straightforward total synthesis of (±)-coerulescine (**1**) in seven steps and 8% overall yield starting from oxindole (**13**) has been achieved. The reactivity of *N*-Cbz α-ethoxy-pyrrolidines **12** thus obtained by our tandem process in the *N*-acyliminium ion chemistry is currently studied. Moreover, the promising spiro-template (±)-**10** is a key intermediate for the synthesis of a wide library of spirooxindole derivatives by the way of nucleophilic addition onto the *N*-acyliminium ion (±)-**I**. This reactivity is also already under investigation and will be published in due course.

Table 1
Tandem reaction between benzyl(2-bromoethyl)carbamate **9** and Michael acceptors **11**[a]



Entry	11	12	Yield[b] (%)
1	 **11a**	 **12a**	84
2	 **11b**	 **12b**	80
3	 **11c**	 **12c**	64[c]
4	 **11d**	 **12d**	81
5	 **11e**	 **12e**	57
6	 **11f**	 **12f**	98[c]

[a] Reaction conditions: benzyl(2-bromoethyl)carbamate **9** (0.5 mmol), Michael acceptors **11** (0.5 mmol), NaH (0.6 mmol), THF (2.5 mL).
[b] Isolated yields.
[c] dr >95:5 determined by ^{1}H NMR analysis of the crude mixture.



Scheme 3. Synthesis of (±)-coerulescine (**1**).

Acknowledgments

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11. A solution of benzyl(2-bromoethyl)carbamate **9** (129 mg, 0.5 mmol) and NaH (60% in mineral oil, 24 mg, 0.6 mmol) in THF (2.5 mL) was stirred at rt for 7 h. ^{1}H NMR of the crude mixture showed the presence of **9** together with *N*-Cbz aziridine in a ratio of 45:55. The ^{1}H NMR spectral data of *N*-Cbz aziridine is in accordance with the literature: Moore, E. G.; Xu, J.; Jocher, C. J.; Corneillie, T. M.; Raymond, K. N. *Inorg. Chem.* **2010**, *49*, 9928–9939; Access to *N*-Cbz aziridine starting from tosylate derivative, see: Žinić, M.; Alihodžić, S.; Škarić, V. *J. Chem. Soc., Perkin Trans. 1* **1993**, 21–26; For the use of *N*-substituted aziridines in the alkylative cyclization of 1,3-dimethylindole catalyzed by $Sc(OTf)_3$ and TMSCl for the formation of eserine-like alkaloids, see: Nakagawa, M.; Kawahara, M. *Org. Lett.* **2000**, *2*, 953–955.
12. *General procedure:* To a solution of benzyl(2-bromoethyl)carbamate **9** (129 mg, 0.5 mmol) and the corresponding Michael acceptor **11** (0.5 mmol) in THF (2.5 mL) at 0 °C, was added NaH (60% in mineral oil, 24 mg, 0.6 mmol) portion by portion. The ice bath was removed and the reaction mixture was stirred for 3 h to 3 days (monitored by TLC), was then poured into a saturated NH_4Cl solution, and extracted with ethyl acetate (2 × 25 mL). The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture was purified by flash chromatography (cyclohexane/EtOAc: 20/80). 1-Benzyl 3,3-dimethyl 2-methoxypyrrolidine-1,3,3-tricarboxylate (**12a**): 84% as a white solid. mp 67–69 °C. IR (neat) 1737, 1705, 1396, 1275, 1246, 1108, 1071, 970, 954, 754, 702 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) of a mixture of two rotamers (55:45), δ (ppm): 2.29–2.38 (m, 1H), 2.33 (dt, *J* = 13.2, 6.6 Hz, 1H), 2.72–2.86 (m, 1H), 2.68–2.91 (m, 1H), 3.29 and 3.46 (s, 3H), 3.32–3.43 (m, 1H), 3.52–3.61 (m, 1H), 3.56 (dd, *J* = 18.1 and 9.1 Hz, 1H), 3.70 and 3.71 (s, 3H), 3.74 and 3.76 (s, 3H), 5.11–5.25 (m, 2H), 5.05–5.33 (m, 2H), 5.62 (d, *J* = 15 Hz, 1H), 5.61 (d, *J* = 15.1 Hz, 1H), 7.32–7.39 (m, 5H), 7.28–7.47 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) of a mixture of two rotamers (55:45), δ (ppm): 28.4, 29.3, 43.8, 43.9, 52.9, 53.2, 56.9, 57.6, 63.9, 64.7, 67.3, 67.7, 90.4, 90.9, 127.9, 128.2, 128.3, 128.7, 136.4, 136.5, 154.9, 155.6, 166.9, 167.1, 169.2. HRMS (ESI, $C_{17}H_{21}NO_7$: $[M+Na]^+$): calcd 374.1216, found: 374.1206.
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14. Sodium carbonate (21 mg, 0.2 mmol) was added in one portion to a solution of acylated product (±)-**14** (364 mg, 1.0 mmol) in MeOH (10 mL) at 0 °C. The mixture was stirred at this temperature for 20 min, poured into brine (20 mL), and extracted with ethyl acetate (3 × 30 mL). The combined organic phase was dried over $MgSO_4$, filtered and, concentrated in vacuo. The crude mixture was purified by flash chromatography (cyclohexane/EtOAc: 50/50). (±)-Benzyl 2-oxospiro[indoline-3,3′-pyrrolidine]-1′-carboxylate (**15**): 99% as colorless oil. IR (neat) 3229, 1698, 1677, 1416, 1121, 747, 695 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) of a mixture of two rotamers (55:45), δ (ppm): 9.05 (d, *J* = 17.2 Hz, 1H), 7.42–6.93 (m, 8H), 5.29–5.08 (m, 2H), 3.94–3.64 (m, 4H), 2.48–4.38 (m, 1H), 2.17–2.51 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) of a mixture of two rotamers (55:45), δ (ppm): 180.9, 180.7, 155.4, 140.8, 140.7, 137.2, 137.0, 133.0, 132.7, 128.9, 128.9, 128.4, 128.3, 128.2, 123.4, 123.1, 110.5, 67.1, 54.3, 54.0, 53.2, 52.3, 45.7, 45.2, 36.2, 35.3. HRMS (ESI, $C_{17}H_{18}N_2O_3$: $[M+Na]^+$): calcd 345.1210, found: 345.1212.
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