http://dx.doi.org/10.5012/bkcs.2012.33.6.1821

Intramolecular Allylation to Coerulescine and a New Route to Formal Synthesis of Horsfiline

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Received February 7, 2012, Accepted March 3, 2012

Key Words : Coerulescine, Horsfiline, Spirooxindole, Intramolecular allylation

The 3,3'-pyrrolidinyl-spirooxindole alkaloids featuring quaternary center constitute a fascinating molecular architecture and pharmacological properties such as anticancer activities,[1] contraceptive activities,[2] and antimigraine activity.[3] Coerulescine **1** and horsfiline **2**, the simplest molecules of this subfamily, also attracted synthetic chemists to develop imaginative approaches toward their synthesis.[4] The structurally similar esermethole **3** possesses methyl group at the quaternary center instead of spiro ring (Figure 1). Coerulescine **1** was isolated from the blue canary grass *Phalaris coerulescens*,[5] and horsfiline **2** was first isolated from the Malaysian medical plant *Horsfieldia superba* in 1991 by Bodo and co-workers.[6]

As an extension of our synthetic study on the alkaloid containing a quarternary center,[7] we also wanted to develop a practical way of establishing the center ensuring the synthesis of coerulescine and horsfiline. In this approach, we hoped to apply Tsuji allylation,[8] which has been known to proceed under mild and neutral condition, however, not applied in the synthesis of those compounds. In this communication, we describe a concise route to coerluescine **1** by applying Tsuji allylation and the following cyclization under reductive amination condition, and want to suggest a concise synthetic pathway for the compounds.

For the synthetic study, we prepared the allyl enol carbonate precursor **5** in 80% yield using a general reaction condition for carbonate formation from the intermediate **4** obtained *via* a known reaction.[9] Tsuji allylation would afford allylic aldehyde **6**, however, which has been assumed to be readily deformylated. Therefore, after we treated **5** with $Pd_2(dba)_3$ and PPh_3 in THF, prompt filtration and concentration was followed by reduction of the crude product under $NaBH_4$ in MeOH at 0 °C. The careful and rapid two step process afforded compound **7**[10] in 60% yield. Spontaneous

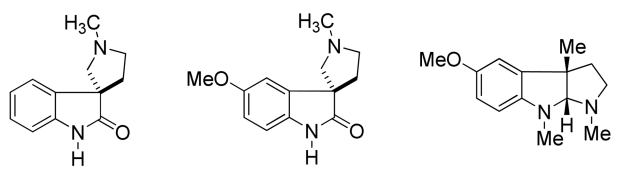
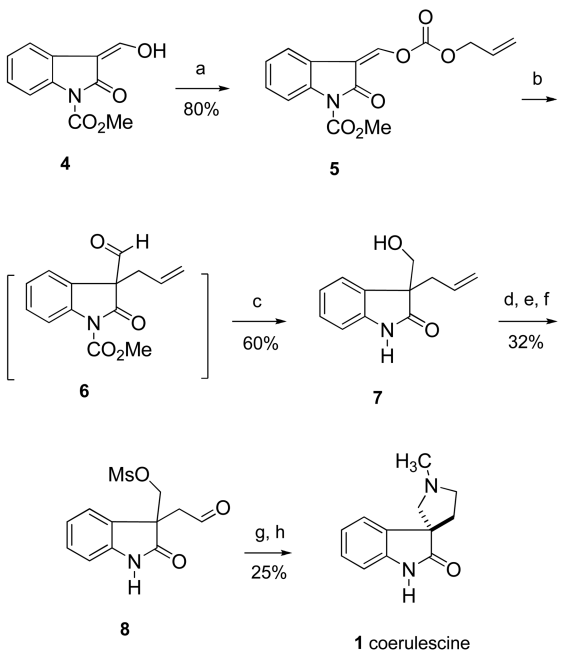


Figure 1



Scheme 1. Reagents and conditions (a) allyl chloroformate, $NaHCO_3$, DMF (b) $Pd_2(dba)_3$, Ph_3P, THF (c) $NaBH_4$, LiCl, THF-EtOH (d) MsCl, TEA, CH_2Cl_2 (e) OsO_4, NMO, CH_2Cl_2 (f) $Pb(OAc)_4$ (g) $MeNH_2$, $MgSO_4$, THF (h) $NaBH_4$, EtOH.

deprotection of methyl carbamate group on nitrogen was detectedin the two steps. Mesylation of **7** was followed by oxidative cleavage of the allylic double bond to aldehyde **8** using OsO_4 and $Pb(OAc)_4$ in 32% yield in 2 steps. The final transformation of **8** to coerulescine **1** was carried out *via* sequential treatment with $MeNH_2$ and $NaBH_4$ to ensue reducutive amination and the following cyclization in 25%. The spectral data of **1** were identical to those published.

In summary, we have shown a concise way to 3,3'-pyrrolidinyl-spirooxindole alkaloid by applying the combination of Tsuji allylation and reducutive amination allowing the following cyclization, achieving a formal synthesis of horsfiline. Though this synthesis provided a racemic mixture of the natural product precursor, Tsuji allylation step is potentially the process for providing enantioselection. Further study of asymmetric induction of the step and application to enantioselective synthesis of the related alkaloids including

coerulescine is under way.

Acknowledgments. This work was supported by the Korea Research Foundation Grant funded by Korean Government (MOEHRD, Basic Research Promotion Fund) (KRF-2008-313-C00461), and we appreciate Center for Research Facilities, CNU for the permission to NMR.

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10. **7**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.40 (1H, bs), 2.56-2.72 (2H, *m*), 3.76 (1H, *d*, *J* = 10.9 Hz), 3.90 (1H, *d*, *J* = 10.9 Hz), 4.93 (1H, *d*, *J* = 10.9 Hz), 5.02 (1H, *d*, *J* = 17.1 Hz), 5.37-5.50 (1H, *m*), 6.86 (1H, *d*, *J* = 7.77 Hz), 7.09 (1H, *t*, *J* = 7.49 Hz), 7.24 (1H, *d*, *J* = 7.30 Hz), 7.31 (1H, *t*, *J* = 7.77 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.7, 141.1, 137.3, 129.8, 127.8, 127.8, 124.8, 116.4, 115.2, 68.6, 65.2, 40.4; (MS (EI) *m/z* 203 (M^+).