Oxidative dearomatization in the synthesis of erythrina, oxindole and hexahydropyrrolo[2,3-*b*]indole skeletons†

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New synthetic strategies leading to highly functional erythrina, oxindole and pyrrolidinoindoline skeletons have been developed and an efficient formal syntheses of (±)-demethoxyerythratidinone reported.

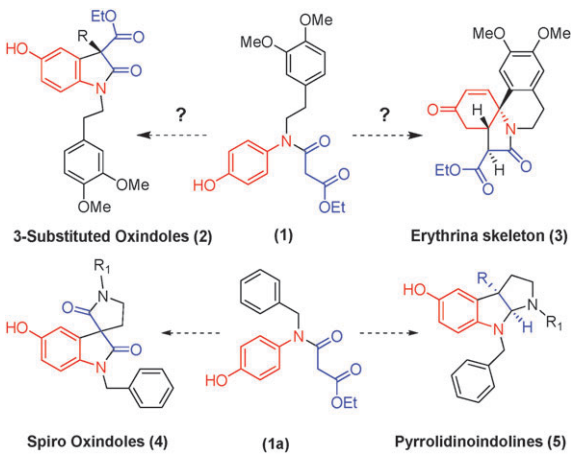
Over the past two years, our laboratory has been involved in a research program concerned with the synthesis of bioactive alkaloids. We are especially interested in developing a general and flexible strategy towards the synthesis of natural product-like compounds with erythrina, oxindole and pyrrolidino-indoline ring systems. Recently we reported a process towards the synthesis of spiro-cyclohexyldienonyl β-lactams from amide derivatives of 4-aminophenol, with a new oxidative formation of a carbon–carbon bond being the key feature.[1] The potential of 4-aminophenol derived amides as a building block for the synthesis of more complex alkaloid structures was not fully explored in our previous research. We envisaged that the same phenolic amide derivative might be used as a starting material in the synthesis of stereochemically and skeletally different frameworks such as highly functional erythrina, oxindole and hexahydropyrrolo[2,3-*b*]indole ring systems through an oxidative dearomatization strategy. Herein, we report our results for the synthesis of erythrina and oxindole skeletons from the same phenolic amide (**1**, see Scheme 1), and spiro-oxindole and hexahydropyrrolo[2,3-*b*]-indole ring systems from the same phenolic amide (**1a**). A formal syntheses of (±)-demethoxyerythratidinone based on our new method is also presented in this communication.

We began our research by treatment of 4-aminophenol, a commercially cheap starting material (Aldrich 1kg/$157USD), with homoveratroyl chloride.[2] The product, amide **8**, was then converted to amine by a reduction with lithium aluminium hydride. By treatment of amine **9** with ethyl 3-chloro-3-oxopropanoate, the amide (**1**) was obtained in 50% yield over three steps. The oxidative dearomatization process was then conducted by treatment of amide **1** with iodobenzene diacetate (IBD) in methanol. The tandem process, involving an oxidative dearomatization followed by an intramolecular Michael addition, led to cyclohexenone **10** (see Scheme 2). Without further purification, compound **10** was then treated with allyl bromide in THF in the presence of potassium carbonate at 70 °C (oil bath). To our pleasure, alkylation as well as aromatization occurred, and afforded oxindole **11a** in good yield. To the best of our knowledge, there have been no reports of this kind of transformation as exemplified by the sequential alkylation and re-aromatization of intermediate **10** under basic condition.[3] It is noteworthy that a complex mixture was produced when strong bases such as sodium hydride or potassium *tert*-butoxide were used.

To get further insight of this process, a number of oxindoles were then synthesized and the results are summarized in Table 1. In comparison with our previous procedure,[3] this method is more flexible and efficient, and could also be applied to the synthesis of oxindoles with acid sensitive functionalities (Table 1, **11d**).

Based on this new method, we then initiated the synthesis of spirooxindole and pyrrolidinoindoline related skeletons, with the aim of creating diverse core structures for medicinal chemistry. Amide **1a** was converted to compound **12** (53% yield over two steps) by an oxidative dearomatization–conjugate addition with IBD in methanol followed by an alkylation with *tert*-butyl-2-iodoethyl carbamate [4] in the presence of potassium carbonate. Methylation of phenol **12** with dimethyl sulfate resulted in compound **13** in 88% yield.

With intermediate **13** in hand, we decided to remove the protecting group (Boc) and conduct a lactamization. To our surprise, treatment of carbamate **13** with HCl followed by potassium carbonate in methanol under nitrogen resulted in an unprecedented rearrangement, with oxindole **14** being obtained (Scheme 3). In the presence of oxygen, however, this process could lead directly to the formation of 3-hydroxy-oxindole **15** in high yield (see Scheme 4).



Scheme 1 Speculation for the synthesis of erythrina, oxindole and pyrrolidinoindoline skeletons.

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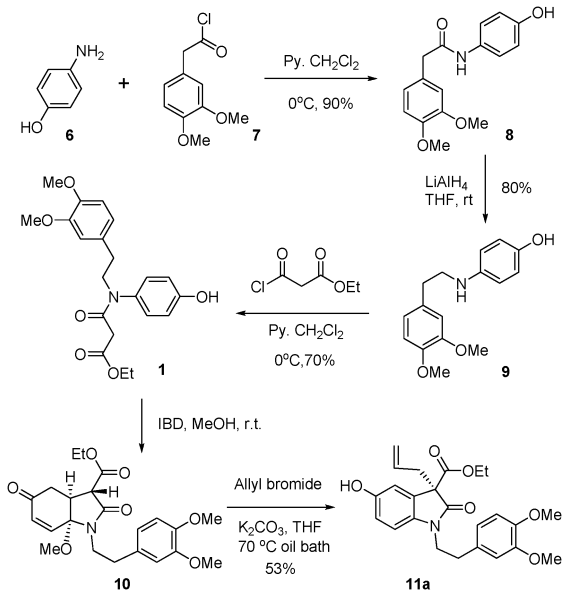
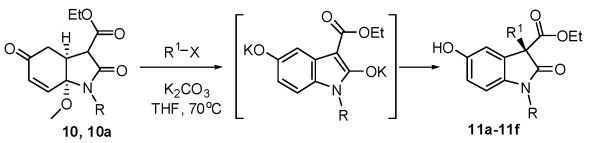
† Electronic supplementary information (ESI) available: ^{1}H NMR, ^{13}C NMR spectra of all key intermediates and experimental details. See DOI: 10.1039/c001465f

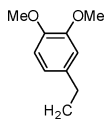
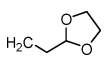
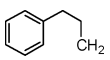


Scheme 2 Synthesis of oxyindole with a full carbon quaternary center.

Table 1 Oxindoles prepared under basic conditions[a]



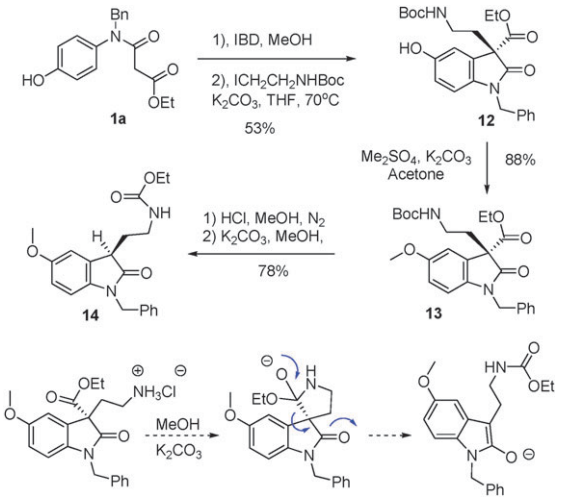
10, 10a — 11a-11f

Substrate	R	Product	R^1	Yield (%)
10		**11a**	Allyl	52.6
		11b	CH_2Ph	48.0
		11c	*i*-Bu	46.9
10a	CH_2Ph	**11d**		51.3
		11e		54.8
		11f	*n*-Bu	36.8

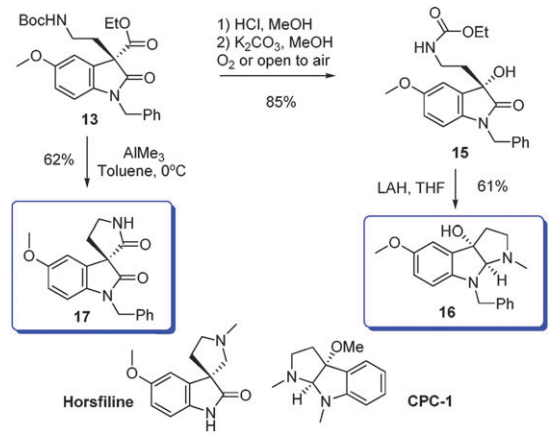
[a] *Reaction conditions*: see ESI†. [b] Yields represent isolated yields over two steps (average of two runs).

After rearrangement, oxidation of the enolate intermediate led to the formation of 3-hydoxyloxindole **15**. Reduction of **15** with lithium aluminium hydride afforded a C-3a hydroxy-pyrrolidinoindoline (**16**) in 61% yield (Scheme 5). It is noteworthy that compound **16** is a mimic of the natural alkaloid CPC-1.[5] The spirooxindole **17**, might be used as an advanced precursor for the total synthesis of horsfiline,[6] was obtained by treatment of compound **13** with trimethyl aluminium in toluene.

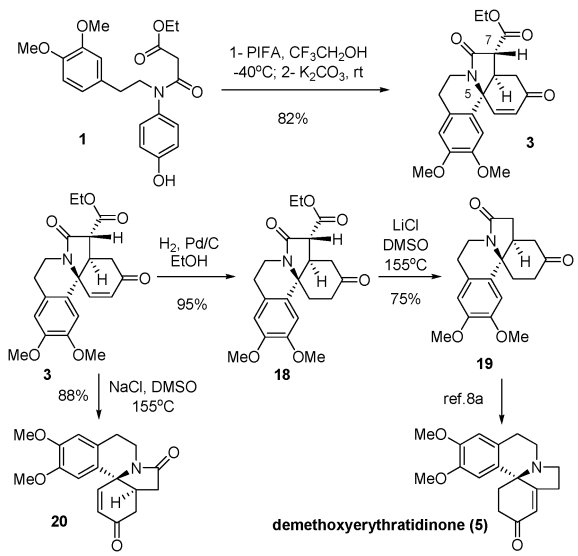
Having successfully established the new method for the synthesis of core structures for horsfoline and CPC-1, we then turned our attention to the construction of a highly functional erythrina skeleton from amide **1**. The initial oxidative dearomatization was carried out in dichloromethane, using IBD as an oxidant. This reaction conditions unfortunately led to a complex mixture. We then tried the oxidation with IBD in



Scheme 3 Rearrangement of oxindole **13**.



Scheme 4 Synthesis of spiro-oxindole and pyrrolidinoindoline related skeletons.



Scheme 5 Synthesis of erythrina alkaloid.

trifluoroethanol at −40 °C.[7] To our delight, we were able to access the desire product in 15% yield. Finally, an optimized "one pot" procedure was established, the erythrina type compound (**3**) was obtained in 82% isolated yield after an oxidative carbon–carbon coupling (PIFA) followed by a Michael addition (K_2CO_3) in trifluoroethanol (Scheme 5).[8] Only one diastereomer was isolated in this sequential step and the relative stereochemistry, shown in Scheme 5, was established by a NOE experiment.

This cyclization established the tricyclic ring system and provided a highly functional Erythrina skeleton in an efficient way (four steps for Erythrina derivative **3**). Compound **3** was further manipulated, hydrogenation followed by decarboxylation, to a known intermediate for the synthesis of natural erythrina alkaloid (±)-demethoxyerythratidinone (Scheme 5), thus furnished a formal synthesis.[9]

In conclusion, we have explored in this research new approaches towards the synthesis of structurally diverse molecules starting from phenolic amide derivatives (**1**, **1a**). With an oxidative dearomatization as the key step, we have developed a practical, efficient and flexible method for the synthesis of oxindoles, hexahydropyrrolo[2,3-*b*]indole ring and erythrina skeletons. We also disclosed an interesting rearrangement in this research for the first time. Based on the new methodology, we have completed a formal synthesis of natural demethoxyerythratidinone. The highly functional erythrina and pyrrolidinoindoline derivatives generated in this research could be used not only as intermediates for the synthesis of natural alkaloids, but also as building blocks in the synthesis of natural product-like compounds for the interests of medicinal chemistry.

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Notes and references

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2 The homoveratroyl chloride was generated by treatment of homoveratric acid with oxalic chloride in dichloromethane in the presence of DMF, for examples, see: C. D. Gilmore, K. M. Allan and B. M. Stoltz, *J. Am. Chem. Soc.*, 2008, **130**, 1558.
3 Although we have reported a procedure leading to oxindoles with a quaternary carbon center, introduction of an alkyl substituent to the α-position of the two carbonyl groups in amide (**1**, or **1a**) before conducting the oxidative dearomatization is obviously a drawback and decreases the flexibility of the method (see ref. 1).
4 *tert*-Butyl-2-iodoethylcarbamate was prepared by following a literature procedure: C. Hunter, R. F. W. Jackson and H. K. Rami, *J. Chem. Soc., Perkin Trans. 1*, 2000, 219.
5 M. Kitajima, I. Mori, K. Arai, N. Kogure and H. Takayama, *Tetrahedron Lett.*, 2006, **47**, 3199.
6 A similar intermediate has been used for the synthesis of horsfiline, see: B. M. Trost and M. K. Brennan, *Org. Lett.*, 2006, **8**, 2027.
7 Oxidative coupling with IBD or PIFA in trifluoroethanol at −40 °C was well documented in Kita's synthesis of maritidine and Node's synthesis of galanthamine. See (*a*) Y. Kita, T. Takada, M. Gyoten, H. Tohma, M. H. Zenk and J. Eichhorn, *J. Org. Chem.*, 1996, **61**, 5857; (*b*) S. Kodama, Y. Hamashima, K. Nishida and M. Node, *Angew. Chem., Int. Ed.*, 2004, **43**, 2659.
8 Characteristic NMR peaks for compound **3** are a doublet signal (J = 11.7 Hz) at 3.38 ppm (proton signal at C7 position) in the ^{1}H NMR spectrum and a quaternary carbon resonance at 59.5 ppm (carbon signal at C5 position) in the ^{13}C NMR spectrum.
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