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Studies toward the total synthesis of phalarine: a survey of some biomimetic possibilities

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Abstract—Biomimetically inspired oxidative coupling strategies toward the total synthesis of phalarine (**1**) are described.

Upon assaying the perennial grass *P. coerulescens* for alkaloid content, Colegate and co-workers identified an alkaloid termed phalarine (**1**). Its structure, as determined through intensive NMR studies, encompasses a novel furanobisindole framework featuring a unique propeller-like motif.[1] However, at the moment, its absolute configuration remains to be established. The proposed biosynthetic pathway, suggested in Figure 1, involves oxidative coupling of a tetrahydro-β-carboline (**2**) with an oxygenated gramine subunit (**3**). Intrigued by the unusual structure of **1**, we sought to accomplish a total synthesis of phalarine through a strategy that would draw inspiration from the proposed biosynthetic pathway. We describe herein our efforts toward this goal.

In principle, coupling of a species derivable from oxidation of a phenol (cf. **4**) with a tetrahydro-β-carboline (**5**) nucleophile could potentially lead to formation of two regioisomeric adducts (cf. **8** and **9**).[2] Of course, the natural bias of a 2,3-bis-unsubstituted indole is to undergo initial electrophilic attack at the β-carbon (C_3).[3] In the case of phalarine, we suppose that the active 'nucleophile' is the tetrahydro-β-carboline (**5**). Here again, it would be assumed, on the basis of precedent, that the initial electrophilic event would also occur at the β-carbon of **5**. If this be so, reaching phalarine would require initial C–O bond formation at C_3. However, if initial bond formation in the electrophilic sense is that through a putative aryloxenium ion, for which ample precedence exists, it would involve reversal of the normative indole type behavior with initial C–C bond formation at the α-carbon of **5** (cf. **6**). Alternatively, as noted in Figure 2 (path a), one could well imagine C–C bond formation at the β-carbon of **5** followed by rearrangement, perhaps through a spirocyclohexadienone and a subsequent unraveling event to phalarine (**1**).

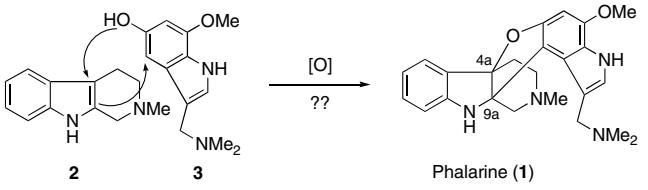

Figure 1. Proposed biosynthesis of phalarine (**1**).

Hence, we sought at the synthesis level to evaluate such issues of regioselectivity in the context of what seemed to be a representative key oxidative coupling protocol. Thus, treatment of **11** with PIFA, followed by addition of tetrahydro-β-carboline (**10**) provided cycloadduct **12**.[4] Its structure was tentatively assigned through spectroscopic analyses and subsequently confirmed through X-ray analysis on a crystalline sample (Scheme 1).[5] As seen from the structure of **12**, our attempts to create a form of umpolung characteristic of the indole ring system in **10** had proven to be unsuccessful.[6]

As an alternative approach, we considered the possibility of creating a potentially useful intermediate by first oxidizing the tetrahydro-β-carboline unit in a Witkop type process.[7,8] Accordingly, indole **10** was oxidized

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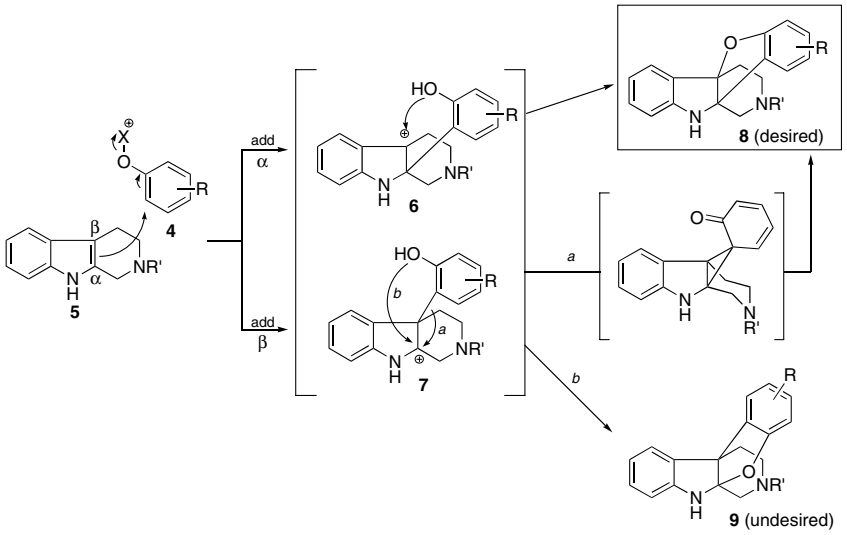
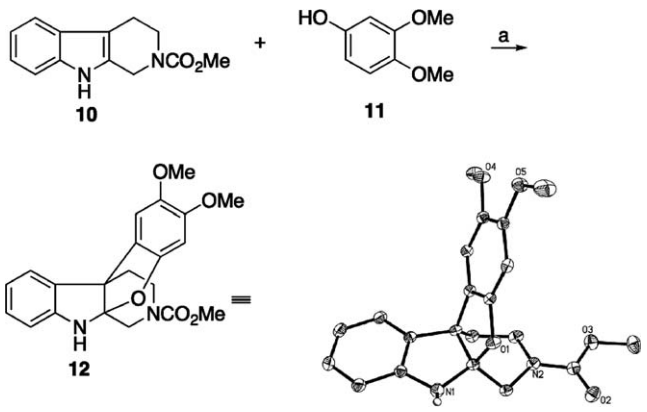
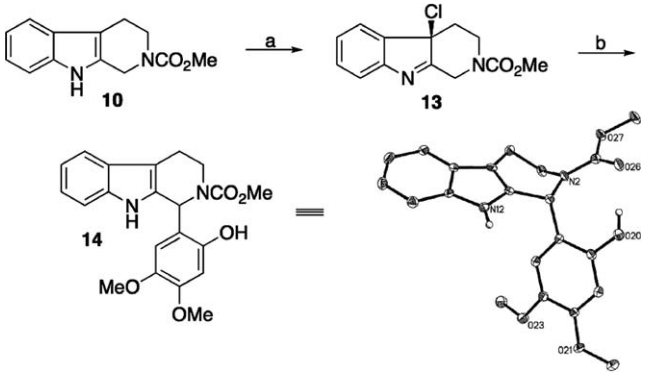


Figure 2. Regiochemical issues in the oxidative coupling reaction.



Scheme 1. Reagents and conditions: (a) PIFA, CH_3CN.



Scheme 2. Reagents and conditions: (a) *t*-BuOCl, CH_2Cl_2; (b) **11**, CSA, benzene.

with *t*-butyl hypochlorite to afford chloroindolenine **13**, possessing the requisite electrophilic β-carbon (Scheme 2).[9] Upon treatment of **13** with phenol **11** in refluxing benzene and catalytic camphorsulfonic acid, a novel product was formed. Although the NMR spectrum of the isolated product was not in accord with the spectrum expected of cycloadduct corresponding to **12**, we were unable to elucidate its structure. Fortunately, suitable crystals were obtained. Through X-ray crystallographic analysis, we were able to unambiguously assign the structure of the complex product as **14**, still another non-phalarine type isomer.[10]

In attempting to account for this intriguing result, two mechanistic types present themselves (Fig. 3). In principle, **13** could conceivably undergo an imine to bis-enamine transformation, as shown (cf. **13**→**15**, path a).[11] This tautomerization would be followed by S_N2' attack by **11**. Alternatively, one could imagine that the substrate would undergo solvolysis at the β-carbon of the carboline in the desired sense. This step would be followed by imine to bis-enamine tautomerization to intermediate **16** (path b).[12] The latter would undergo [3,3] sigmatropic rearrangement, providing the observed adduct **14**. Definitive support of either hypothesis was not obtained, although it is well to note that tautomerization of a structure such as **13** to generate a bis-enamine double bond is not without precedent in the traditional chemistry of tetrahydrocarbazoles.[12]

In summary, two conceptually related biomimetic coupling strategies to gain access to the furanobisindole core of phalarine (**1**) were studied. Interesting chemistry ensued, though not in the desired sense. Oxidation of the phenolic subunit with a hypervalent iodide species led in the end to formation of the non-phalarine regioisomeric core system (cf. **10** → **12**). Alternatively, reaction of the oxidized form of the tetrahydro-β-carboline fragment (**13**) with the phenolic moiety provided the mechanistically intriguing structural isomer, **14**. We emphasize, however, that the trends exhibited in our findings certainly should not be construed as invalidating the arching biosynthetic hypothesis of Figure 1. Enzymatically mediated processes may be regulated by special circumstances, not readily translatable to the laboratory setting. Efforts to accomplish the total synthesis of phalarine (**1**) by taking account of the issues described herein are continuing in earnest in our laboratory.

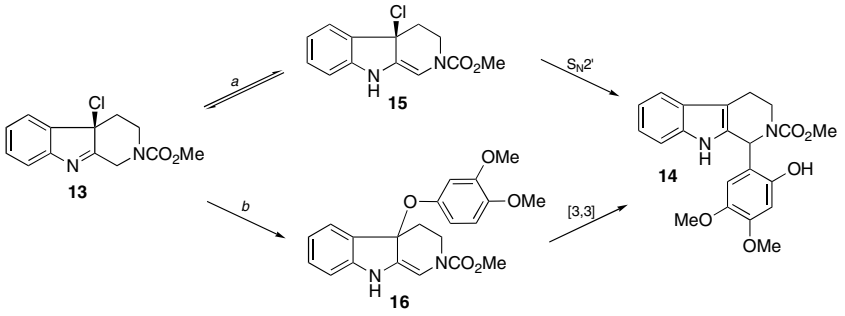


Figure 3. Possible mechanisms to account for formation of **14**.

Acknowledgements

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1. Anderton, N.; Cockrum, P. A.; Colegate, S. M.; Edgar, J. A.; Flower, K.; Gardner, D.; Willing, R. I. *Phytochemistry* **1999**, *51*, 153–157.
2. Although our current supposition is initial C–C bond formation between either the α or β carbon of the indole ring in **5** and the *ortho* carbon in **4**, another conceivable pathway is direct S_N2 displacement centered at the oxygen atom, in the phenoxenium-like intermediate. Support of such a pathway can be found in the work of Abramovitch and Okamoto, individually. These works suggest that C–O, as opposed to C–C bond formation depends on the mode of generation of the presumed phenoxenium intermediate. See, Abramovitch, R. A.; Alvernhe, G.; Bartnik, R.; Dassanayake, N. L.; Inbasekaran, M. N.; Kato, S. *J. Am. Chem. Soc.* **1981**, *103*, 4558–4565; Endo, Y.; Shudo, K.; Okamoto, T. *J. Am. Chem. Soc.* **1982**, *104*, 6393–6397.
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4. Burgett, A. W.; Li, Q.; Wei, Q.; Harran, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4961–4966.
5. CCDC 601434 contains the supplementary crystallographic data for compound **12**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
6. Attempts to change the order of addition of reagents did not affect the outcome of the reaction.
7. (a) Witkop, B.; Patrick, J. B. *J. Am. Chem. Soc.* **1953**, *75*, 2572–2576; See, (b) Buchi, G.; Manning, R. E. *J. Am. Chem. Soc.* **1966**, *88*, 2532–2535, and references therein.
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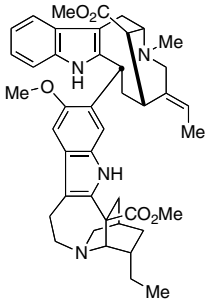
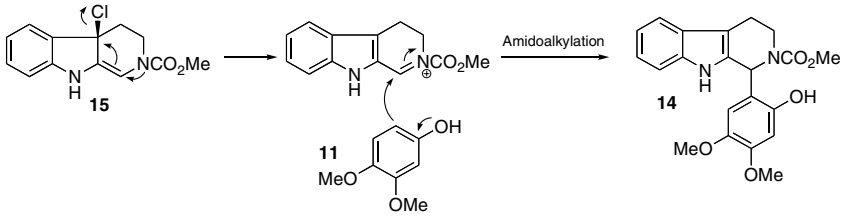


9. Kuehne, M. E.; Roland, D. M.; Hafter, R. *J. Org. Chem.* **1978**, *43*, 3705–3710.
10. CCDC 602220 contains the supplementary crystallographic data for compound **14**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
11. A possible pathway to **14** through which bis-enamine **15** could proceed is via an *N*-acyliminium intermediate (see below), whose formation can be accounted for by elimination of chloride ion through participation of the carbamate nitrogen. Such an intermediate upon α-amidoalkylation with phenol **11**, would provide compound **14**. See, Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367–4416.



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