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A Concise Synthesis of the *Erythrina* Alkaloid 3–Demethoxyerythratidinone via Combined Rhodium Catalysis

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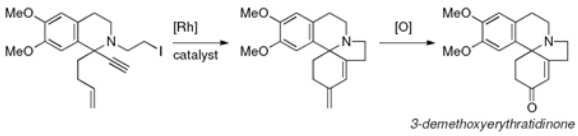
Abstract



The total synthesis of the erythrina alkaloid 3–demethoxyerythratidinone has been achieved via a strategy based on combined rhodium catalysis. The catalytic tandem cyclization effected by the interplay of alkynyl and vinylidene rhodium species allows for efficient access to the A and B rings of the tetracyclic erythrinane skeleton in a single step. The synthesis also features rapid preparation of the requisite precursor for the double ring closure and thus has been completed in only 7 total steps in 41% overall yield.

Erythrinanes (**1**) and homoerythrinanes (**2**) are a large class of structurally diverse natural products isolated from tropical and subtropical plants of the *Erythrina* genus that have long been used for various indigenous medicines (Figure 1).1 These plant-derived alkaloids exhibit a wide range of pharmacological effects such as hypotensive, sedative, hypnotic, anticonvulsive, CNS depressing, and curare-like properties. Structurally, four rings are fused with the A/C spiro juncture to constitute the distinctive 6–5–6–n and 6–5–7–n skeletons with considerable structural variance in the D ring. Thus, not surprisingly, this unique molecular architecture along with interesting biological activities of erythrina alkaloids has stimulated a number of chemical synthesis investigations.2

Among the synthetic efforts toward erythrina alkaloids, notable are the approaches involving synthesis of more than one ring via sequential or tandem cyclization that facilitates rapid access to the archetypal tetracyclic core.3 However, rarely have these strategies been explored for simultaneous construction of the A and B rings despite the fact that the 6-5 fused system constitutes a “conserved subunit” for all members of erythrina alkaloids.4 Thus, it would be of potentially broad interest to develop synthetic routes that are amenable for both the erythrinane and homoerythrinane series. Herein, we report a concise total synthesis of 3-demethoxyerythratidinone (**3**),5,6 in which a combined rhodium(I) catalysis enables tandem annulation of the A and B rings of the erythrinane skeleton and thus greatly simplifies the synthesis.7

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Our synthetic plan arose from the notion that diene **4** possessing the essential framework of the target **3** might be readily accessed from enyne **6** via a catalytic domino process involving a transition metal unsaturated carbene (vinylidene, e.g. **5**) complex as an intermediate (Scheme 1). Based on our recent studies on combined rhodium catalysis,8 it was envisioned that **6** could be mobilized to undergo C–C bond formations at both the α- and β-positions of its alkyne moiety, thus establishing the A/B ring system in one step. In this scenario, a single catalyst would have to mediate the two distinct bond-forming events, the β-alkylation and enyne cycloisomerization. The requisite haloenyne **6** for the double ring closure was then anticipated to be easily assembled from the three commercially available building blocks, **7, 8** and **9**, in a straightforward manner without extensive engineering.

With the plan to evaluate the tandem A/B approach, our studies commenced with the construction of the C and D rings (Scheme 2). Thus, homoveratrylamine (**7**) was first acylated with pentenoyl chloride (**8**), and the resulting amide was subjected to Bischler–Napieralski conditions to afford isoquinoline **10** in quantitative yield.9 For the introduction of the requisite halide and alkyne groups, a sequence involving *N*-alkylation and iminium addition was carried out. Thus, treatment of isoquinoline **10** with the silyl protected iodoethanol **9a** followed by addition of an ethynyl Grignard reagent to *N*–alkyliminium ion **11a** provided the desired propargyl amine **12a** in high yield.10 After removal of the TBDPS group, the resultant alcohol **12b** was then converted into iodide **6a**, thereby procuring the key haloenyne intermediate **6** (X = I) of our synthesis. Alternatively, it was found that this sequence could be more efficiently performed by using 2-iodoethanol (**9b**), with which *N*-alkylation of **10** led to the formation of the cyclic ammonium salt **13** from the incipient iminium isomer **11b**.11 The alkynylation of **13** appeared to involve a Grignard addition reaction to an iminium salt of type **11** (R = MgBr) arising from the cyclic *N*,*O*-ketal **14**,12 which could be isolated under basic conditions. Through this protecting group-free route, homoveratrylamine (**7**) was expediently advanced to alcohol **12b** in 4 stages with only one purification step.

With iodoenyne **6a** in hand, we set out to examine the possibility of effecting its double ring closure by rhodium catalysis (Scheme 3). When iodide **6a** was subjected to the standard conditions derived from our previous study,8 the tandem cyclization did occur to generate the desired tetracyclic diene **4**, but only in 36% yield. In contrast to our previous experience where the reaction times ranged from 6 to 24 h, **6a** was completely consumed within 1 h. The formation of diene **15**, the simple cycloisomerization product without β-alkylation, was not detected (Figure 2). In addition, a rapid decomposition process seemed to be operative independent of the desired product formation, a problem not encountered before.

In light of these observations, a series of control experiments were carried out to identify the side reaction pathway. These tests revealed that the loss of **6a** was due almost exclusively to its reaction with triethylamine that gave the quaternary ammonium salt **16**, whereas **6a** was unaffected by other reaction components. Indeed, clean conversion of **6a** to **16** in quantitative yield was observed when it was heated at 85 °C for 2 h in the presence of 3 equivalents of triethylamine. 13 This *N*-alkylation was found to take place to a significant degree even at a low reaction temperature in either DMF or CH_3CN (ca. 50% at 25 °C in 1 h).

The serious setback faced in initial studies prompted us to probe a range of parameters affecting the outcome of the key cyclization. Our focus was first placed on the base effect because of the unexpected detrimental role played by triethylamine in the reaction of **6a**. However, a set of screening experiments varying the nature as well as amount of the base did not lead to amelioration, with the highest yield still resulting from the reaction employing triethylamine. 14 Given that the rapid *N*-alkylation was mainly responsible for

the low yield of **4**, attempts were made to reduce the rate of this substitution process (Table 1). Although a maximum yield of 39% was obtained from the reaction of bromide **6b**, substrates with a poor leaving group, **6c** (X = Cl) and **6d** (X = OTs), in general, gave rise to inferior results (entry 1 vs entries 2-5). On the other hand, significant improvement came from the solvent screening, which revealed THF to be more efficient than CH_3CN or DMF (entries 6-8). Thus, the cyclization reaction of **6a** in THF could afford **4** in 70% yield. These results formed a stark contrast to our previous findings, in which the use of THF solvent did not induce β–alkylation but instead rendered only the simple cycloisomerization product such as **15** at room temperature. It would seem that although the rates of formation of **4** and **16** were both decelerated in THF (entries 1 and 2 vs entries 6-8), the intermolecular *N*-alkylation producing the undesired **16** was slowed down much more than the intramolecular β-alkylation en route to the desired **4**. This solvent effect might be a consequence of differential product solvation in entropic origin: in a relatively nonpolar medium as THF vis-à-vis CH_3CN and DMF, the biomolecular *N*–alkylation process forming the ammonium salt **16** involves a higher degree of charge development in the transition state and thus is disfavored.

With the tetracyclic framework established through the catalytic tandem cyclization, the final stage of the total synthesis entailed excision of the methylene unit from **4** (Scheme 4). The single-pot oxidation combining osmium-catalyzed dihydroxylation and periodate-mediated glycol cleavage was thus performed on diene **4** to furnish 3-demethoxyerythratidinone (**3**), whose spectroscopic data matched the literature values in all aspects.

In summary, we have accomplished a total synthesis of 3-demethoxyerythratidinone based on a tandem strategy emanating from the combined rhodium catalysis. In this approach, the A/B ring system of the erythrinane skeleton is constructed in one step mediated by a single catalyst. Also notable is the rapid assembly of the key intermediate from simple commercial materials in a highly convergent manner. These features allow the synthesis to be completed in only 7 total steps with an overall yield of 41%. Our work represents the first example of an application of the C–C bond-forming metal vinylidene catalysis to natural product synthesis, wherein an alkynyl group catalytically undergoes novel β-alkylation and formal C–H insertion in tandem to effect double ring closure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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11. Interestingly, the reaction employing 1,2-diiodoethane did not result in a similar *N*-alkylation, but instead led to iodinium-induced cyclization of the alkenylimine to give an iodoiminium salt. See Supporting Information.
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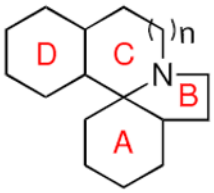
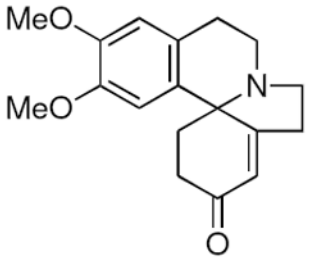
13. Resubjection of **16** to the rhodium-catalyzed tandem cyclization conditions resulted only in the recovery of the starting material.
14. See Supporting Information for the detailed results of the base screening experiments.

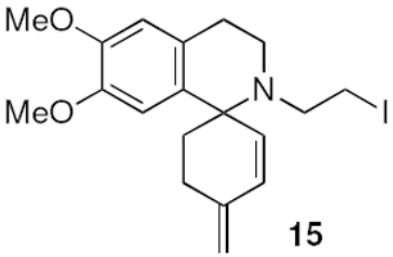


skeleton of erythrinane (**1**, n = 1) and homoerythrinane (**2**, n = 2)



3-demethoxyerythratidinone (**3**)

Figure 1.
Erythrina Alkaloids



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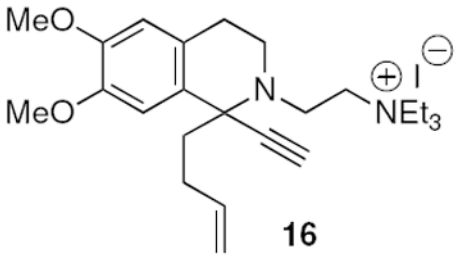

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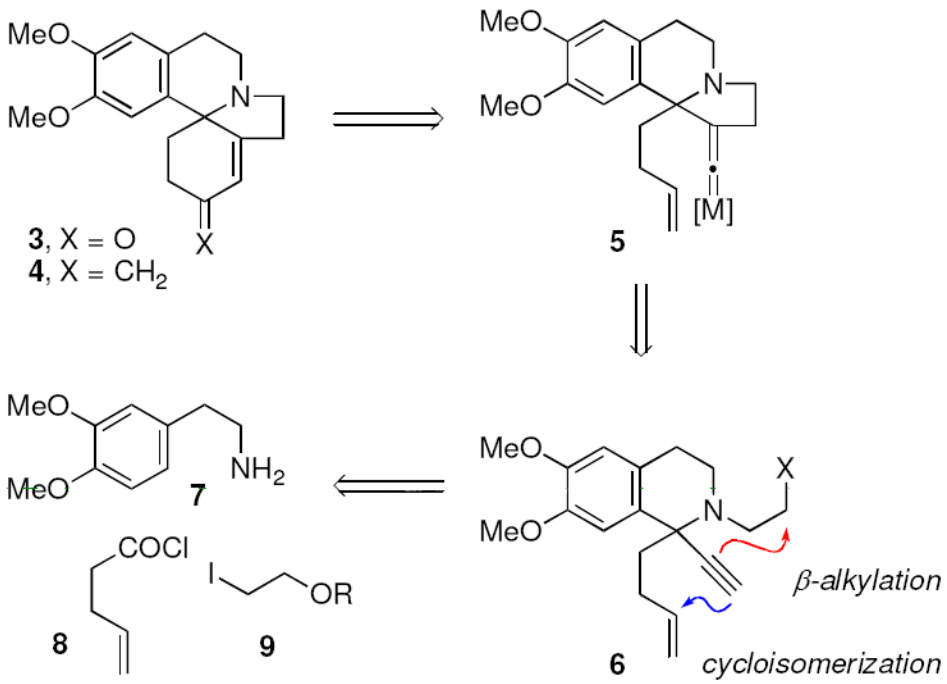
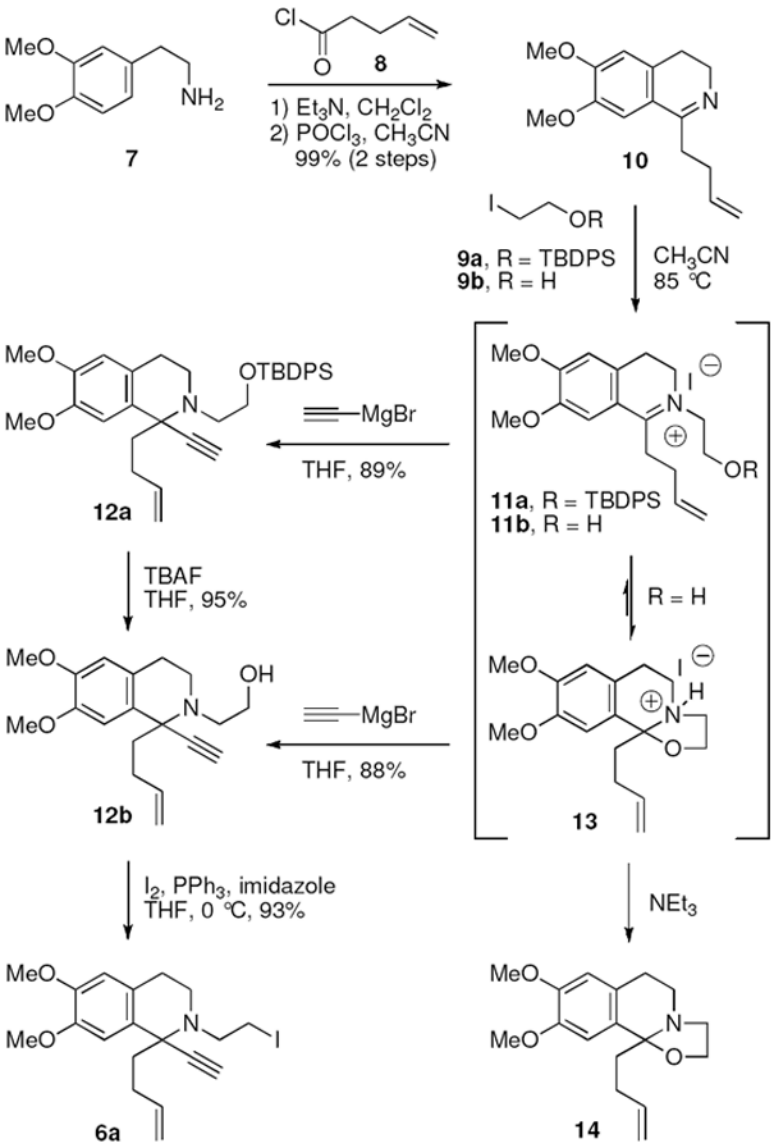
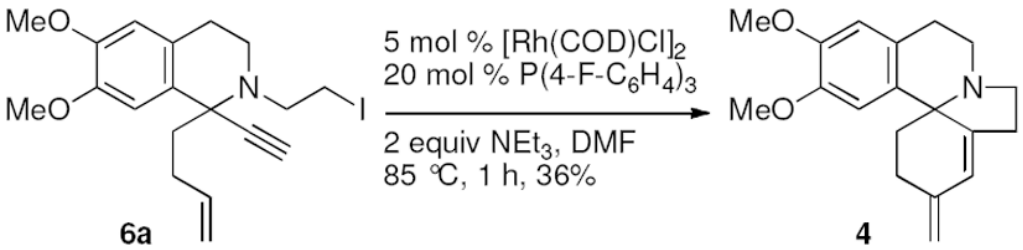
Figure 2.
Possible Byproducts



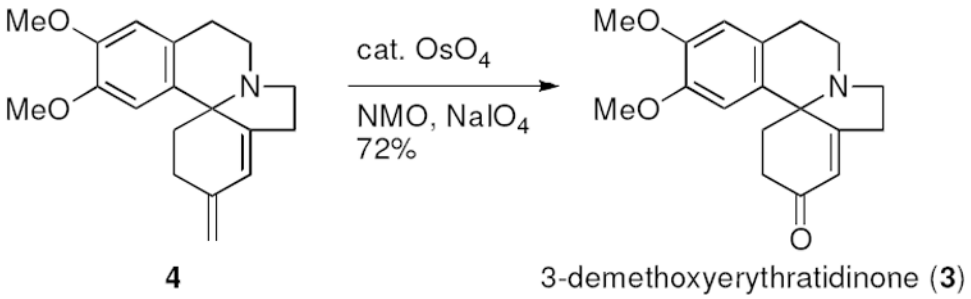
Scheme 1.
Retrosynthetic Analysis



Scheme 2.
Synthesis of Iodoenyne **6a**



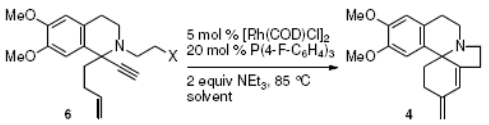
Scheme 3.
Rhodium-Catalyzed Tandem Cyclization of **6a**



Scheme 4.
Completion of the Total Synthesis of **3**

Table 1

Leaving Group and Solvent Effects[a]



entry	reactant	X	solvent	time	yield[b]
1	**6a**	I	DMF	1 h	36%
2	**6a**	I	CH_3CN	1 h	29%
3	**6b**	Br	CH_3CN	1 h	39%
4	**6c**	Cl	CH_3CN	1 h	9%[c]
5	**6d**	OTs	CH_3CN	1 h	11%
6	**6b**	Br	THF	14 h	49%
7[d]	**6b**	Br	THF	8 h	47%
8	**6a**	**I**	**THF**	**12 h**	**70%**

[a] All reactions were performed with 0.20 mmol of halide **6**, 0.40 mmol of Et_3N, 0.01 mmol of $[Rh(COD)Cl]_2$, and 0.04 mmol of $P(4–F–C_6H_4)_3$ at 85 °C in the solvent indicated (0.1 M).

[b] Isolated yield.

[c] Unreacted **6c** was recovered in 20%.

[d] The reaction was carried out in the presence of 0.02 mmol of tetrabutylammonium iodide.