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CONCISE APPROACH TO THE AROMATIC YOHIMBOID AND PROTOBERBERINE ALKALOIDS VIA INTRAMOLECULAR DIELS-ALDER REACTIONS

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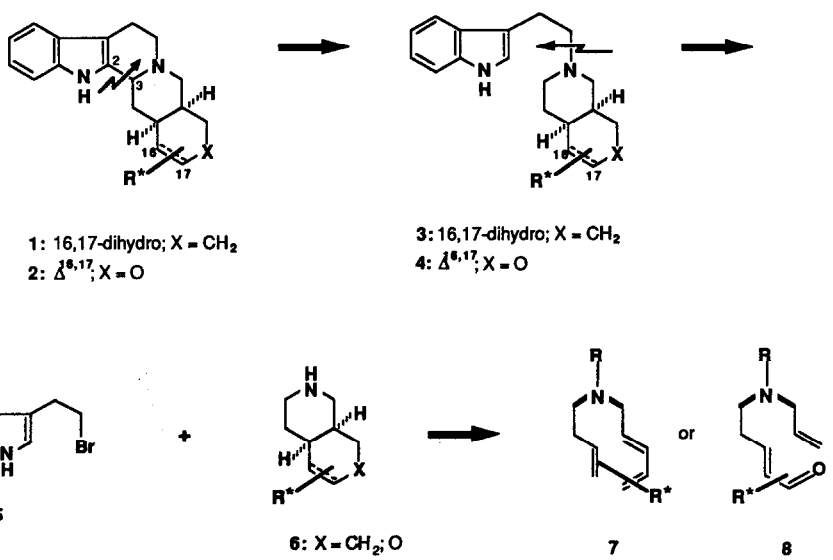
Abstract. The aromatic yohimboid indole alkaloid oxogambirtannine (**9**) was synthesized in high yield via the intramolecular [4 + 2] cycloaddition/dehydrogenation of the substituted ß-carboline **13**, which was readily accessed by the reaction of **10** with the acid chloride **11** in the presence of the diene **12**. In a similar manner the prototypical protoberberine skeleton **20** was rapidly constructed upon cyclization of the substituted isoquinoline **17**.

Intramolecular [4 + 2] cycloaddition reactions have already been successfully exploited in this laboratory[2,3] as the key steps in the syntheses of several pharmacologically active monoterpenoid indole alkaloids.[4] The general approach that has been employed in these syntheses is depicted in a retrosynthetic format in Scheme 1 for the generalized yohimboid alkaloid **1** and the heteroyohimboid alkaloid **2**, wherein R* collectively represents the substituents and functional groups on the E ring. In each of these syntheses, the pentacyclic ring systems of the targeted alkaloids were elaborated from the *seco*-derivatives **3** and **4** by an oxidative cyclization that was induced by mercuric ion. The intermediates **3** and **4** were constructed by coupling the tryptophyl moiety **5** with the intact D/E ring subunits **6**, which were accessed via the intramolecular cycloadditions of trienes such as **7** and **8**.

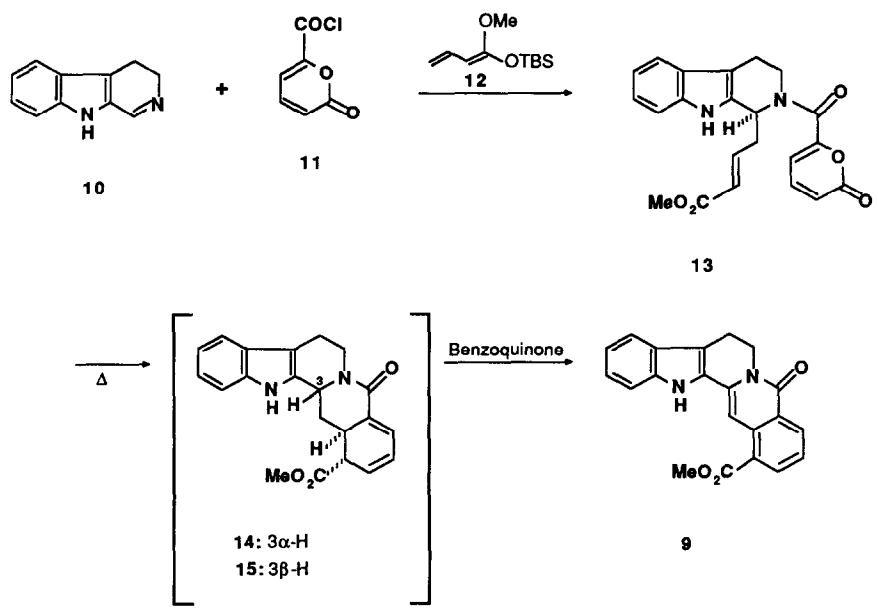
Scheme 1



There is, however, a significant problem inherent in the application of this strategy to the syntheses of the pentacyclic indole alkaloids. Namely, there is typically a relatively low degree of regioselectivity in the oxidation of the tertiary amines **3** and **4** at C(3) to generate intermediate $\Delta^{3,4}$-iminium salts that will cyclize to the desired ring systems **1** and **2** rather than the corresponding inside derivatives. Consequently, we sought to design an alternative approach that would not suffer this design flaw. One attractive plan that evolved to redress this issue featured the formation of the D/E rings via the intramolecular Diels-Alder reaction of a precursor in which the ABC rings were in place *prior* to the crucial cycloaddition. Indeed, this new strategy was recently reduced to practice and was exploited for the total syntheses of representative members of the heteroyohimboid and corynantheioid families.[3] We now disclose the practical extension of this concept as evidenced by its implementation in an extraordinarily facile synthesis of the indole alkaloid oxogambirtannine (**9**), one of several yohimboid constituents isolated from the Rubiacea *Uncaria gambier* Roxb.[5,6] The applicability of this strategic device to the syntheses of selected isoquinoline alkaloids was also convincingly evidenced with the successful elaboration of **20**, which constitutes the basic architectural framework characteristic of the protoberberines.[7]

The key feature of this novel synthetic approach to oxogambirtannine (**9**) (Scheme 2) entails the facile nucleophilic addition of a vinyl ketene silyl acetal[8] to an *N*-acyliminium[9] salt derived from the known 3,4-dihydro-β-carboline[10] (**10**), a construction which then sets the stage for the [4+2] cycloaddition to the elaboration of the pentacyclic ring system. The requisite 3-substituted β-carboline **13** was prepared in 86% yield by the reaction of the 1,1-dioxygenated butadiene **12** (2 equiv) with the carboline **10** in the presence of 2-pyrone-6-carbonyl chloride (**11**)[11] (1.1 equiv) [THF; -78 °C (1 h) → RT (2 h)].[12] The preferential reactivity of vinyl ketene silyl acetals at the γ-position is known,[3,8] and no products derived from reaction at the α-position were isolated. Thermolysis of the triene **13** in refluxing mesitylene in the presence of benzoquinone (2 equiv) for 48 h delivered oxogambirtannine (**9**) (m.p. 206 - 206.5 °C; lit.[5] 205 °C) in 91% yield. Although a mixture (1:2) of the intermediate dienes **14** and **15** could be obtained

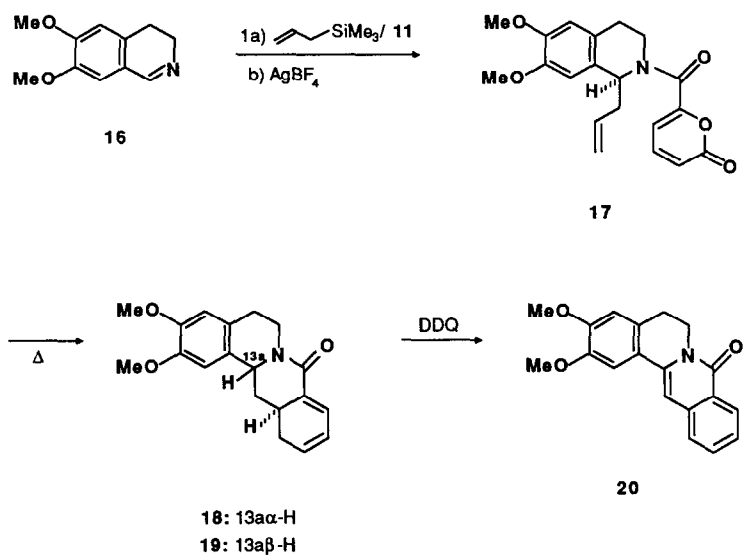
Scheme 2



when this reaction was conducted in the absence of benzoquinone, the combined yield of **14** and **15** was low, and their isolation by chromatography proved somewhat tedious owing to the presence of E ring double bond isomers together with the corresponding E ring oxidized derivative and variable amounts of **9**.

In a closely related sequence of reactions, the substituted isoquinoline **17** (Scheme 3) was obtained in 64% yield by the prior admixing of the 3,4-dihydroisoquinoline **16**,[13] allylsilane[14] (2 equiv) and **11** (1.1 equiv) [CH_2Cl_2, 0 °C (1h)] followed by treatment of the resulting mixture with $AgBF_4$ [CH_2Cl_2, 0 °C (1 h) → RT (12 h)]. Subsequent thermolysis of **17** [mesitylene, 220 °C (6 h); 90%] gave a mixture (1:7) of the isomeric cycloadducts **18** and **19**,[12] oxidation of which with DDQ [CH_2Cl_2, 0 °C (30 min)] delivered the known[15] protoberberine derivative **20** (m.p. 187-188 °C; lit.[15a] 189-190 °C) in 76% overall yield from **17**.

Scheme 3



18: 13aα-H
19: 13aβ-H

The further extensions of this fundamental plan to the efficacious total syntheses of other alkaloids of the indole and protoberberine families are currently in progress and will be disclosed in due course.

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