# PERHYDROISOQUINOLINE SYNTHESIS: C(20)-SUBSTITUTED ANALOGS OF YOHIMBINE-TYPE ALKALOIDS

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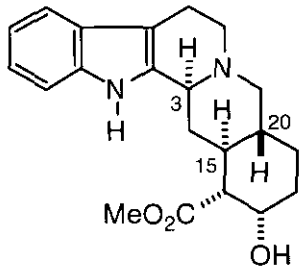
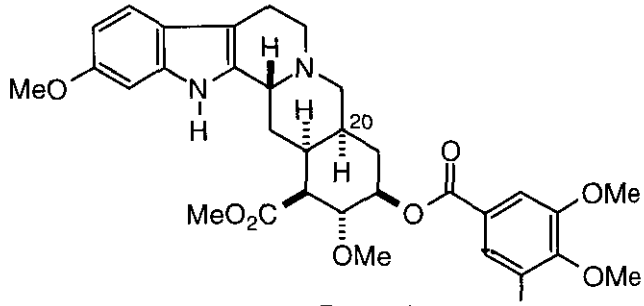
**Abstract** – Reaction of tryptamine with (±)-(1*R**,5*S**,8*R**)-1-(methoxymethyl)-7-oxo-6-oxabicyclo[3.2.1]oct-2-ene-8-acetaldehyde (**12**) provides a new entry to pentacyclic derivatives of yohimbine-type alkaloids.

Yohimbine (**1**) and reserpine (**2**) are members of a large family of natural products known as yohimbine-type alkaloids (Figure 1).[1,2] These alkaloids are of interest because of their structural complexity and their pharmacological and medicinal properties.[2] This communication describes a short route to C(20)-substituted analogs of these pentacyclic indole alkaloids.

**Figure 1**




**1** Yohimbine




**2** Reserpine

Our approach was based on a route to perhydroisoquinolines developed during the course of studies directed toward the manzamine family of alkaloids.[3] Thus, we had previously reported that lactones of type (**3**) could be prepared from benzoic acid using a reductive alkylation-halolactonization-allylation sequence, and that such lactones could be converted to perhydroisoqinolines of type (**5**) upon sequential reaction with an amine, cleavage of the

terminal olefin, and reduction of the resulting carbinol lactam (**4**) (Scheme 1). We imagined that if tryptamine was used as the amine, and if an intramolecular electrophilic aromatic substitution reaction could replace carbinol lactam reduction, this sequence might offer an efficient route to C(20)-substituted anologs of yohimbine-type alkaloids.

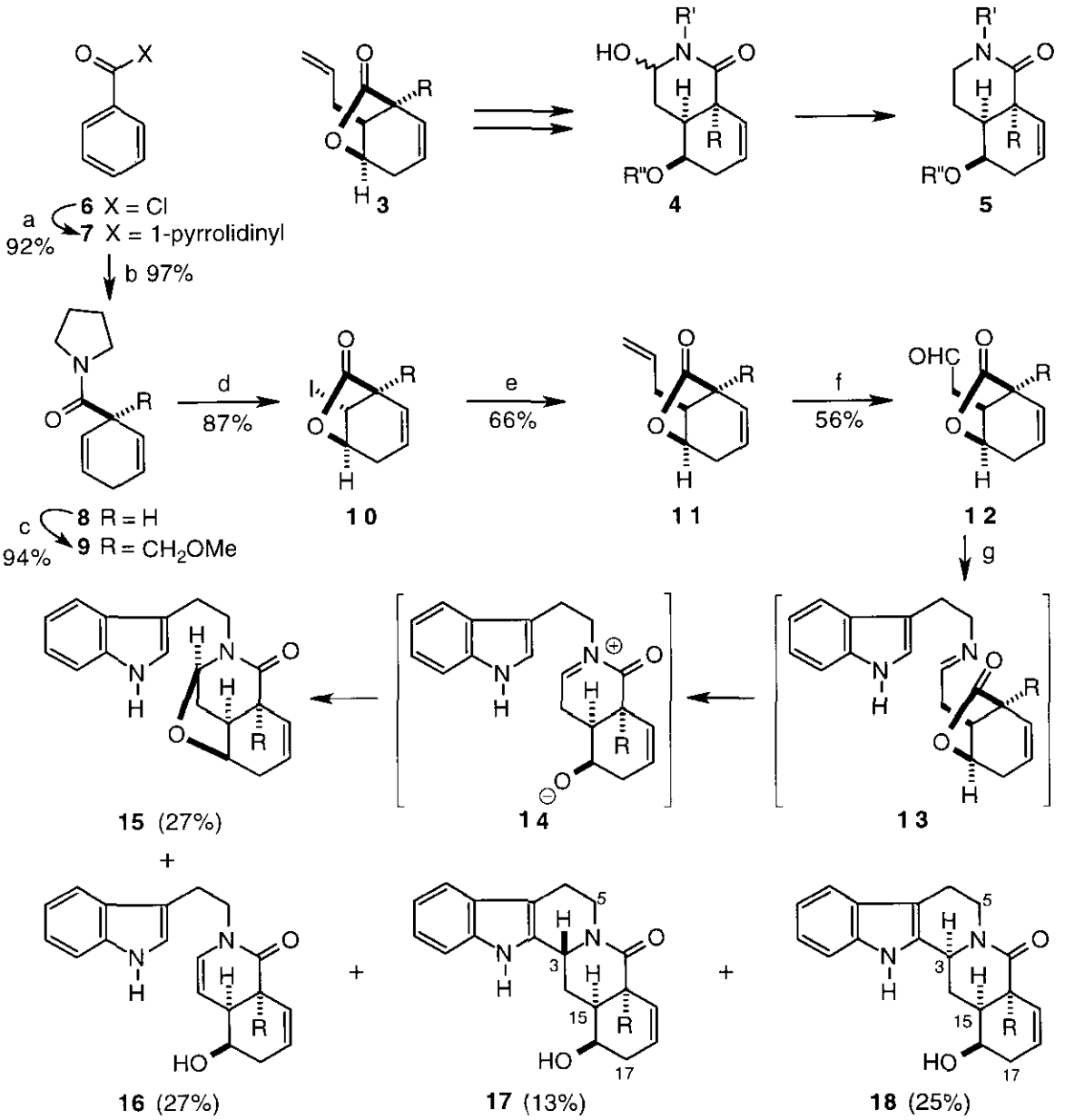
To test this idea, lactone (**11**) was prepared as outlined in Scheme 1. Treatment of benzoyl chloride (**6**) with pyrrolidine in aqueous sodium hydroxide gave *N*-benzoylpyrrolidine (**7**) (mp 61-63 °C) in 92% yield.[4] Dissolving metal reduction of **7** gave amide (**8**) in 97% yield.[5] Deprotonation of **8** with lithium diisopropylamide and treatment of the resulting enolate with chloromethyl methyl ether delivered amide (**9**) (mp 58-60 °C) in 94% yield. Treatment of **9** with iodine in aqueous tetrahydrofuran afforded iodo lactone (**10**) (mp 81.5-84.3 °C) in 87% yield. Keck allylation of **10** completed the synthesis of lactone (**11**).[6]

In light of previous studies, we were surprised to find that treatment of **11** with tryptamine under a variety of conditions resulted in low yields of the desired amide. It was presumed that steric hindrance was responsible for these troubles and thus, we decided to examine a strategy that involved intramolecular delivery of the nitrogen nucleophile to the lactone carbonyl group. This strategy required selective cleavage of the terminal olefin of **11**, a task that was accomplished using AD-mix-β in aqueous *tert*-butanol at 5 °C for 48 h, followed by periodate cleavage of the resulting diol.[7] This afforded aldehyde (**12**) (mp 50.2-51.5 °C) in 56% yield.[8,9]

Inspired by Cook's work on Pictet-Spengler reactions in aprotic media,[10] aldehyde (**12**) was warmed with tryptamine in toluene under reflux with removal of water using a Dean-Stark trap. This gave a good yield of four separable products: *N,O*-acetal (**15**) (27%), enamide (**16**) (27%), and pentacycles (**17**) [mp 250 °C (dec )] and (**18**) [mp 198.5 °C (dec )] in 13% and 25% yields, respectively. The stereochemical assignments for **17** and **18** were based on $^1$H-NMR spectroscopy. For example, the proximity of $H_{5\beta}$ and $H_{17\beta}$ to $H_3$ in **17** and the proximity of $H_{5\alpha}$ and $H_{15}$ to $H_3$ in **18** was established using difference nOe experiments.

We imagine that **15-18** result from initial Schiff base formation (**12**→**13**) followed by intramolecular attack on the lactone carbonyl group to afford *N*-acyliminium ion (**14**). Nucleophilic attack of the alkoxide on the iminium ion would give **15**, proton transfer from the iminium ion to the alkoxide would afford **16**, and electrophilic aromatic substitution reactions would provide both **17** and **18**. It is notable that **15-18** were stable in toluene at reflux, an indication that the product ratio reflects the kinetic partitioning of **14** to products. Although the

## SCHEME 1




(a) Pyrrolidine, NaOH, $H_2O$ (b) K, $NH_3$, THF, *t*-BuOH (c) LDA, THF; $MeOCH_2Cl$ (d) $I_2$, THF-$H_2O$ (e) allyltributylstannane, AIBN, PhH, Δ (f) AD-mix-β, $H_2O$, *t*-BuOH; $NaIO_4$ (g) tryptamine, toluene, Δ

reaction of tryptamine with **12** under these neutral conditions gave a mixture, treatment of this material with trifluoroacetic acid (1 h at 25 °C) gave **17** and **18** as the only isolable products in 18% and 36% overall yields, respectively, from **12**. Whereas the independent behavior of

enamide (**16**) in TFA was not examined, it was shown that treatment of *N,O*-acetal (**15**) with TFA provided a 1:7 mixture of **17** and **18**, respectively, in 62% yield.

In summary, a short route to C(20)-substituted analogs of yohimbine-type alkaloids has been developed. We note, however, that direct application of this strategy to C(20)-unsubstituted compounds is problematic at the stage of selective cleavage of the terminal olefin. Studies that address this problem are underway.

## REFERENCES AND NOTES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