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

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Abstract — Reaction of tryptamine with (±)-(1R*,5S*,8R*)-1-(methoxy-methyl)-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). These alkaloids are of interest because of their structural complexity and their pharmacological and medicinal properties. This communication describes a short route to C(20)-substituted analogs of these pentacyclic indole alkaloids.

Our approach was based on a route to perhydroisoquinolines developed during the course of studies directed toward the manzamine family of alkaloids. Thus, we had previously reported that lactones of type (3) could be prepared from benzoic acid using a reductive alkylolation-halolactonization-allylation sequence, and that such lactones could be converted to perhydroisoquinolines 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 analogs 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-benzylypyrrolidine (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 ¹H-NMR spectroscopy. For example, the proximity of H₅α and H₁₇β to H₃ in 17 and the proximity of H₅α and H₁₅ to H₃ 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
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

1. This paper is dedicated to Dr. Bernhard Witkop on the occasion of his 80th birthday, and we thank his chemical home, the National Institutes of Health, for their support of this research.
8. Typical Johnson-Lemieux oxidation conditions gave 12 in only 30% yield.

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