

## SYNTHESIS OF R-LAUDANOSINE AND 9-R-O-METHYLFLAVINANTINE BY ASYMMETRIC ALKYLATION

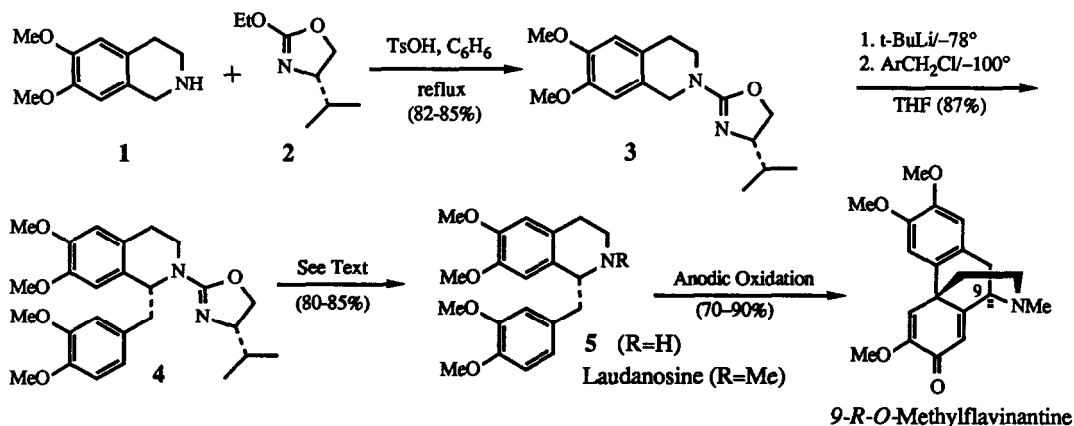
Robert E. Gawley\* and Gregory A. Smith

Department of Chemistry, University of Miami, Coral Gables, Florida 33124, USA

Isoquinoline alkaloids are ubiquitous in nature and the types of biological activity exhibited by members of the class are nearly as varied as the structures themselves.<sup>1</sup> Additionally, certain of the benzyloisoquinolines are the synthetic and biosynthetic precursors of the morphine alkaloids. The importance of these compounds has inspired considerable effort in their synthesis.<sup>2</sup> Many of the more important recent efforts have been in the synthesis of the natural products in enantiomerically pure form.<sup>3</sup> This Letter details the asymmetric synthesis of the unnatural enantiomer of the benzyloisoquinoline alkaloid laudanosine, a minor constituent of opium, and the first asymmetric synthesis of the morphinandienone *O*-methylflavinantine (*synonyms*: *O*-methylpalladine, sebiferine), which occurs in nature as both the racemate and as either enantiomer, depending on the source.<sup>4</sup> The latter compound is of interest both for its possession of the morphine carbon skeleton, and for its possible analgesic and antitussive effects.<sup>5</sup> The key step is our recently reported asymmetric alkylation of aminooxazolines.<sup>6</sup>

For the target alkaloids, 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, **1**, was required, and was prepared in 92% yield by Pictet-Spengler cyclization of the commercially available (Aldrich) 3,4-dimethoxyphenyl ethyl amine. Condensation of **1** with ethoxoxazoline **2** afforded isoquinolyloxazoline **3** in 82-85% yield. Lithiation (*tert*-butyllithium,  $-78^{\circ}$ ) and alkylation with a solution of 3,4-dimethoxybenzyl chloride at  $-100^{\circ}$  afforded **4** in 94% diastereomeric excess (32:1 selectivity) and 87% yield. Hydrazinolysis of **4** afforded norlaudanosine **5** as a glass (96% yield). Pirkle analysis of the corresponding  $\alpha$ -naphthamide indicates the major enantiomer to be *R*, confirming the stereochemical assignment made initially by analogy with the model systems.<sup>7</sup>

The laudanosine synthesis may be completed in either of two ways. Formylation of **5** with acetic formic anhydride and lithium aluminum hydride reduction gave the product in 71% yield. Serendipitously, we learned



that the aminooxazoline 4 can be converted to laudanosine by *the same sequence*. In other words, acetic formic anhydride cleaves the oxazoline and formylates the nitrogen in one step. This unusual transformation is the synthetic equivalent of a hydrolysis followed by a formylation, but is remarkable in that it is done under anhydrous conditions. Moreover, the nucleophile which effects opening of the usually robust oxazoline is the usually non-nucleophilic acetate ion. Presumably the oxazoline nitrogen is first formylated, but previous attempts to facilitate ring-opening in these systems using a strategy of prior quaternization of nitrogen were met with failure. In a model system (*i.e.*, 3), *N*-formyl-6,7-dimethoxytetrahydroisoquinoline is obtained in 85% yield after chromatography. Laudanosine is obtained in two steps and 80–85% overall yield from 4.

The electrochemical oxidative cyclization of laudanosine to *O*-methylflavinantine was first reported by Miller in 1971,<sup>8</sup> and has become a popular method for the non-phenolic oxidative cyclization of benzyloisoquinoline alkaloids.<sup>9</sup> For the conversion of laudanosine to *O*-methylflavinantine, we used the procedure of Kametani,<sup>10</sup> as recommended by Miller.<sup>11</sup> Thus, the asymmetric alkylation of aminooxazolines now affords routine access to morphinanes of high enantiomeric purity.

**Acknowledgements:** We are grateful to Professors L. Echevoyen and A. Kaifer, and Mr. J. Nieves for their assistance with the electrochemical experiment. This work was supported in part by the National Science Foundation (CHE-8210586).

#### Footnotes

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(Received in USA 9 September 1987)