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A Formal Total Synthesis of (±)-Ferruginine by Pd-catalyzed Intramolecular Aminocarbonylation.

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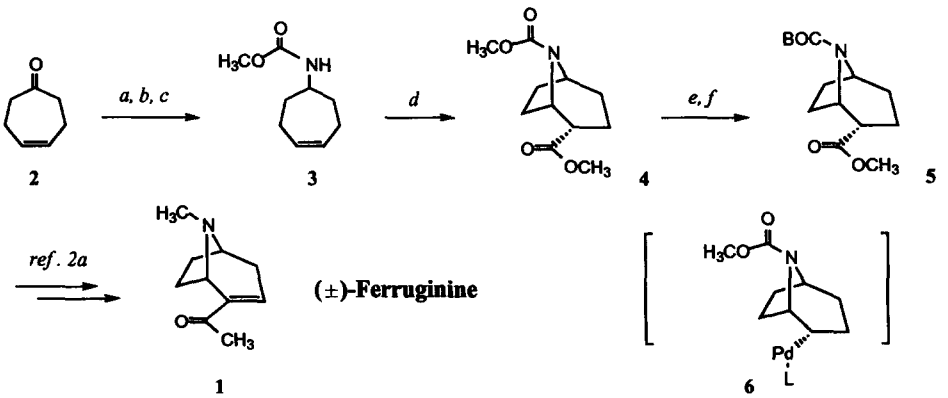
Abstract: A practical and efficient synthetic route to the neuroactive alkaloid ferruginine has been developed. 8-Azabicyclo[3.2.1]octane skeleton **4** was prepared in one step by intramolecular aminocarbonylation of **3** catalyzed by palladium. © 1997 Elsevier Science Ltd.

Ferruginine **1**,[1] one of the tropane alkaloids, has been isolated from *Darlingiana ferruginea* and *D. darlingiana* and a number of its synthetic approaches[2] have been reported due to its unusual structure and its interesting biological activity. As part of a program to develop general methods for the synthesis of azabicyclic compounds related to anatoxin-a[3] and epibatidine[4] analogues, we have previously reported the intramolecular aminocyclization using various electrophiles.[5] Herein we would like to report a practical and efficient route to (±)-ferruginine starting from 4-cycloheptenone (**2**),[6] easily prepared by the known synthetic methodology. The key step in our approach consists of an intramolecular aminocarbonylation of 5-(N-methoxycarbonylamino)cycloheptene (**3**) catalyzed by palladium to form the desired bicyclic ring skeleton.

Since the intramolecular aminocarbonylation has been proved to be an efficient method for constructing biologically important alkaloids and related compounds, there are many examples of the cyclization of unsaturated amine compounds.[7]



Scheme I

Reagents and Conditions: a) NH_2OH·HCl (1.60 eq), Na_2CO_3(1.06 eq), MeOH, reflux, 85%; b) LAH (4.00 eq), THF, reflux, 89%; c) methyl chloroformate (1.70 eq), CH_2Cl_2, 0℃, 39%; d) $PdCl_2$ (0.10 eq), $CuCl_2$ (3.00 eq), CO (1 atm), MeOH, r.t., 49%; e) 30% HBr-HOAc (1.05 eq), r.t.; f) $(BOC)_2O$, dioxane, r.t., 69% from **4**.

However, the intramolecular aminocarbonylation has never been applied to the synthesis of tropane alkaloids so far. Therefore, we tried to synthesize the tropane alkaloid, ferruginine, using intramolecular aminocarbonylation.

5-(N-methoxycarbonylamino)cycloheptene (**3**), was prepared from the known compound 4-cycloheptenone (**2**). Namely, 4-cycloheptenone (**2**) was treated with hydroxylamine to afford its corresponding oxime, which was reduced with lithium aluminum hydride and the amine was protected with methyl chloroformate to give the desired carbamate **3** in 30% overall yield in three steps.

Palladium(II) chloride, in the presence of copper(II) chloride as an oxidant, catalyzed the intramolecular aminocarbonylation of **3** in methanol under 1 atm atmosphere of carbon monoxide to give bicyclic methyl ester **4**[8] as a single product in 49% yield. **4** was converted to the known compound **5** by deprotection with 30% HBr-HOAc and protection with $(BOC)_2O$ in 69% overall yield (**Scheme I**). Structure of bicycle **5** was confirmed by comparison with spectroscopic data in the literature,[2a] in which the stereochemistry of the ester group was assigned trans to the nitrogen. Therefore, the intramolecular aminocarbonylation proceeded through the intermediate **6**, and then the CO insertion occurred to the Pd-C bond. In this process, structural rigidity of bicyclic ring system might induce the high stereoselectivity.

The conversion of **5** to (±)-**1** has been earlier reported by Rapoport group.[2a]

In summary, 8-azabicyclo[3.2.1]octane skeleton **4** was prepared by intramolecular aminocarbonylation of **3** catalyzed by palladium and **5** had previously been transformed into ferruginine, thus completing the formal total synthesis.

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8. Spectral data for **4** : ^{1}H NMR (300 MHz, $CDCl_3$), δ (rotamers): 1.50-2.08 (m, 8H), 2.71 (br, 1H), 3.68 (s, 3H), 3.72 (s, 3H), 4.31 (br, 1H), 4.46 (br, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$), δ (rotamers): 19.3, 25.8, 28.0, 29.6, 45.1, 51.6, 52.2, 53.4, 55.0, 153.8, 173.3; I.R. (neat) (cm^{-1}): 1732, 1702, 1449; MS (m/z): 227 (16, M^+), 196 (7), 168 (18), 140 (18), 126 (100), 108 (8), 93 (11).

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