A Short and Efficient Total Synthesis of (+)-Ferruginine Using the CN(*R,S*) Method

Isabelle Gauthier, Jacques Royer,* and Henri-Philippe Husson*

Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette, France

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(+)-Ferruginine ((+)-**1a**), a potent neurotoxin containing an 8-azabicyclo[3.2.1]octane ring system, was isolated from the arboreal species *Darlingiana ferruginea*[1] and *D. darlingiana*.[2] Its biological activity has not been fully studied, unlike its unnatural (−) enantiomer which has been prepared from cocaine.[1] (−)-Ferruginine ((−)-**1a**) and (−)-norferruginine ((−)-**1b**) were found to be good agonists for the nicotinic acetylcholine receptor (nAchR) although they appear to be only 2.7×10^{-3} and 1.2×10^{-3} times as potent, respectively, as (+)-anatoxin a (Figure 1).[3]

Due to the intense interest in its potent nicotinic agonist activity, several syntheses of ferruginine have been reported, mainly as a racemate,[4] but two asymmetric syntheses of the (+)-enantiomer have also appeared recently in the literature.[5] Campbell *et al.* first reported a racemic synthesis from cocaine,[4a] then Davies *et al.* reported the preparation of racemic material *via* the reaction of vinylcarbenoids with *N*-(alkoxycarbonyl)-pyrroles.[4b,c] Synthesis of racemic ferruginine has also been described by Pd-catalyzed intramolecular aminocarbonylation.[4d] More recently Rigby *et al.* achieved the first asymmetric synthesis of (+)-ferruginine by metal-promoted [$6\pi + 2\pi$] cycloaddition of azepines followed by ring contraction.[5a] In a more classical approach, Rapoport *et al.* reported an asymmetric synthesis *via* intramolecular cyclization of an iminium ion derived from L-pyroglutamic acid,[5b] leading to (+)-ferruginine in 15 steps and 1% yield.

We undertook an asymmetric synthesis of (+)-ferruginine **1a** based on a similar bond disconnection strategy, but starting from 2-cyano-5-oxazolopyrrolidine **2** which we designed, some years ago, for the preparation of α- (and α′-) substituted pyrrolidine derivatives.[6,7a]

2-Cyano-5-oxazolopyrrolidine **2**, easily prepared in one step from phenylglycinol, dimethoxytetrahydrofuran, and potassium cyanide,[6] appeared as an ideal starting material for the construction of the 8-azabicyclo[3.2.1]octane skeleton since it possesses two potential iminium systems permitting substitutions α and α′ to the nitrogen atom.

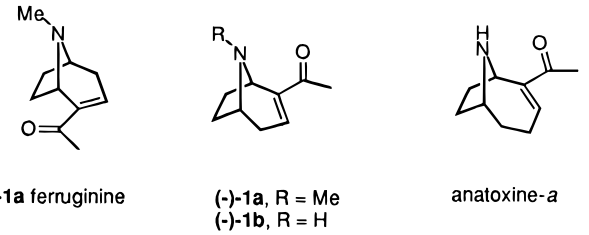
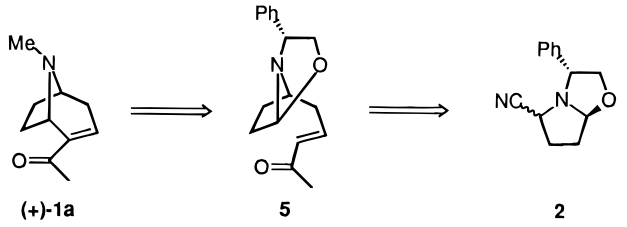


Figure 1.

Scheme 1



It can thus be considered as a chiral nonracemic equivalent of the pyrrolinium salts involved in the biosynthesis of tropane alkaloids.[8a,b] According to the CN(*R,S*) method,[7b] it is possible to introduce at will a 2-pentanone chain in an *R* or an *S* absolute configuration. Mannich type cyclization onto the oxazolidine ring of such a compound might be possible, but the creation of the double bond would require several tedious steps using standard methods.[5b] Our intention was to take advantage of a compound of type **5** (Scheme 1) already containing a double bond and which could also cyclize to a tropane system.

The cyclization of an α,β-unsaturated ketone onto an acyliminium ion, reported by Speckamp[9] for the synthesis of elaeokanine B, appeared an attractive means of achieving our objective. The synthesis of the required pyrrolidine **5** is described in Scheme 2.

The anion of 2-cyano-5-oxazolopyrrolidine **2** was alkylated with bromoacetaldehyde diethyl acetal in the presence of HMPA to afford **3** as a diastereomeric mixture in 86% yield.[10] Decyanation of **3** was achieved using Li/NH_3,[7] to give compound **4** in 66% yield as a single stereomer. Previous studies from this laboratory have shown this reduction step to be completely stereoselective and to furnish pyrrolidine **4** with the 2*R* configuration.[7,10] Careful cleavage of the acetal function of compound **4** with dilute hydrochloric acid was effected without opening the oxazolidine, to furnish the aldehyde which was not isolated but immediately converted into the *trans* enone **5** by treatment with dimethyl (2-oxopropyl)phosphonate under Horner−Wadsworth−Emmons conditions[11] (iPr_2NEt, LiCl, MeCN) in 86% overall yield. Cyclization of **5** to the bicyclic enone **6** was then carried out using the experimental conditions described by Speckamp, *i.e.*, by treatment with hydrogen chloride gas in methanol at −50 °C.[9] The desired tropane **6** was thus obtained in 66% yield, accompanied by the chlorinated

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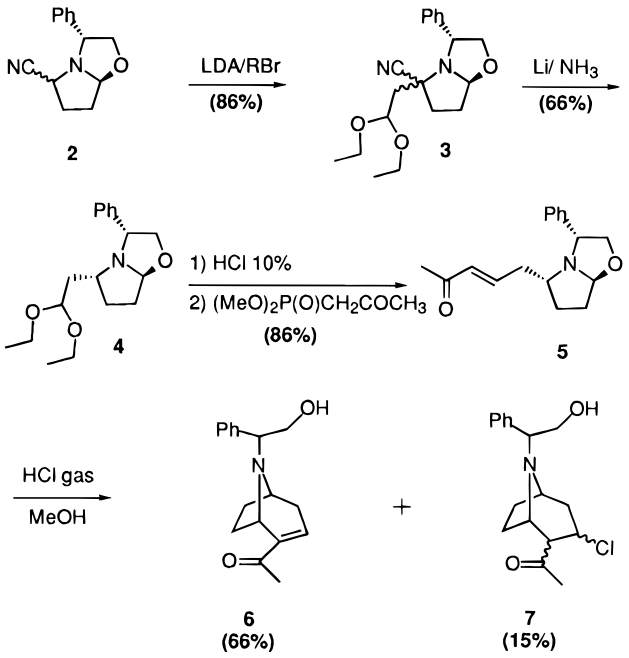
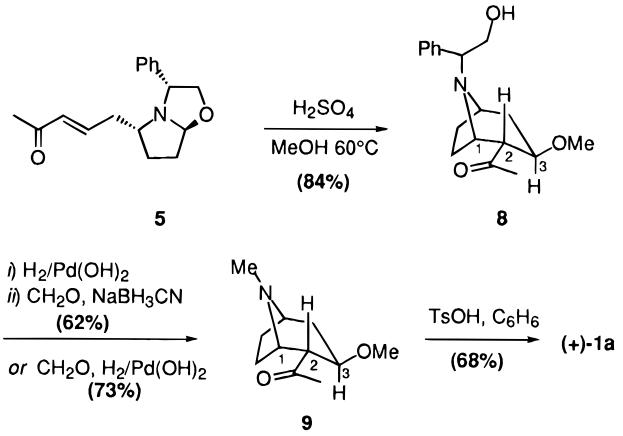
Scheme 2



product **7** in 15% yield. The latter could be transformed easily into **6**.[9a] Removal of the chiral appendage to afford the corresponding free amine was usually carried out under hydrogenolytic conditions; the presence of the enone function of **6**, however, precluded this method. *N*-Debenzylation using a chloroformate[12] (ethyl, vinyl, (trimethylsilyl)ethyl, or benzyl chloroformate) or dissolving metal conditions (Li/NH_3)[13] could not be achieved, even after the protection of the keto group of **6** using Noyori's reagent.[14]

We therefore decided to examine the possibilities of preparing a related compound in which the double bond was protected. Product **7** was a potential candidate, but unfortunately it underwent elimination too quickly to give **6**, and the presence of the chlorine atom was also incompatible with hydrogenolytic conditions. We thus decided to use the more stable methoxy group and repeated the iminium ion cyclization by treatment of **5** (Scheme 3) with sulfuric acid in methanol (15 h, 60 °C). Under these conditions compound **8** was obtained in 84%

Scheme 3



yield. This transformation was totally stereoselective: only one stereomer was found in the crude mixture as proved by ^1H and ^{13}C NMR and chromatographic analyses. The configuration of this compound was deduced from ^1H NMR: the diagnostic proton H-2 exhibited coupling constants of 10.1 and 2.5 Hz with H-3 and H-1, respectively, which clearly indicated that H-2 and H-3 occupy axial positions. Hydrogenolysis (H_2, $Pd(OH)_2/C$) of the *N*-benzylic bond of **8** afforded the free amine (TLC analysis), not isolated but immediately converted into **9** in the presence of CH_2O, $NaCNBH_3$ (62% yield for the two steps).[4c] Alternatively, treatment of **8** with aqueous formaldehyde under hydrogenation conditions (H_2, $Pd(OH)_2/C$) gave the *N*-methyl derivative **9** in an improved 73% yield. Elimination of methanol was achieved by treatment of compound **9** with *p*-toluenesulfonic acid in benzene at 80 °C[15] to give (+)-ferruginine in 68% yield ($[\alpha]_D = +36$ ($CHCl_3$, *c* 0.27); lit.[1] $[\alpha]_D = +37$ ($CHCl_3$)).

In conclusion, we have performed a new, short, and efficient synthesis of (+)-ferruginine in seven steps and 20% overall yield, starting from a versatile chiral nonracemic starting material, *via* the intramolecular cyclization of an α,β-unsaturated ketone onto a potential iminium system. Such a stereospecific intramolecular cyclization should allow easy access to a range of analogues. This strategy, starting from commercially available material, compares favorably to previously described synthetic routes.

Supporting Information Available: Experimental procedures and ^1H NMR and ^{13}C NMR spectra of all new compounds (17 pages).

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