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Thermal Rearrangement of Enantioenriched α-Hydroxy Imines -II. Formal Synthesis of (-)-Perhydrohistrionicotoxin.

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Abstract : Synthesis of (+)-1-benzyl-1-azaspiro[5.5]undecan-7-one 6 from α -ketol 1, via a 1,2-suprafacial chirality transfer, is described.

In the preceding paper¹, we have shown that thermal rearrangement of enantioenriched α -allyl and α -trimethylsilylpropargyl α -hydroxy imines proceeded with a complete 1,2-transfer of chirality. However, it still remained to determine the sense of chirality of the newly created stereogenic center formed in the transposition.

In this communication, we answer unambiguously this question via a correlative asymmetric synthesis involving an iminium ion-vinylsilane cyclization as a key step. Moreover, 1-benzyl-1-azaspiro[5.5]undecan-7one $6^{2,3}$ implicated in the correlation is a precursor of (-)-perhydrohistrionicotoxin 8^4 obtained via its depentyl derivative 7, a significant neurophysiological tool to study the mechanism of action of cholinergic agonists in the neuromuscular system⁵.

Firstly, enantioenriched α -ketol 1 (>96% ee), obtained as described in the preceding paper, was converted to the N-benzyl imine 2⁶ which was in turn heated at diglyme reflux for 2h to provide α -amino ketone 3 in 84% yield [[α]_D-86 (c 1.93, CHCl₃)] (Scheme 1).



As a prelude to cyclization, semi-hydrogenation of 3 was performed in the presence of Pd/BaSO4 and quinoline to give stereochemically pure Z-vinylsilane $4^7 [\alpha]_D - 54$ (c2.27,CHCl3) in 67% yield (Scheme 2). Then, cyclization⁸ was efficiently accomplished by treatment of 4 with an excess of paraformaldehyde at 70°C in acetonitrile in the presence of 1 equiv. of camphorsulfonic acid to afford the spirotetrahydropyridine 5^9 in 73% yield [$[\alpha]_D + 11$ (c 1.88, CHCl3)]. Finally, hydrogenation of the double bond of 5 was successfully realized, without affecting the N-benzyl group, in the presence of Adams' catalyst to provide (+)-6 in 54% yield

[$[\alpha]_D$ + 15 (c 2.06, CHCl₃)] identical in all respects with a sample¹⁰ obtained from (-)-2-cyano-6-oxazolo piperidine^{2c}.



Scheme 2

The sense of chirality of the spiropiperidine 6 demonstrates that the rearrangement of α -hydroxy imine 2 proceeds by a 1,2-suprafacial shift providing α -amino ketone 3 which is consequently heterofacial¹¹ with respect to the starting α -ketol 1.

In conclusion, the asymmetric synthesis of 6, an advanced intermediate of the synthesis of (-)perhydrohistrionicotoxin 8, described herein, highlights the power and great synthetic value of the rearrangement of α -hydroxy imines. Other applications of this rearrangement are underway in our laboratories.

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