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Total Synthesis of (+)-Indolizidine 195 B and (+)-Monomorine

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Abstract: The total synthesis of (+)-Indolizidine 195 B and (+)-Monomorine is described. The formation of the chiral centers was stereocontrolled by chiral sulfoxides.

Indolizidine alkaloids offer attractive targets for synthesis because of their exotic provenance, scarcity and marked biological activity¹. The Colombian poison-frog *Dendrobates histrionicus* contains a variety of indolizidine alkaloids : compound 195 B, (+)-(3S, 5S, 9S)-3-n-butyl-5-methyl indolizidine 1, was isolated in 1986² and several syntheses have been reported³. (+)-Monomorine **2** was identified as the trail-laying pheromone of the Pharaoh ant, *Monomorium pharaonis* L^4 and its synthesis deeply investigated⁵. Compounds **1** and **2** are epimers at C-3.



The synthetic strategy we developed is based on the formation of the enantiomerically pure 2,6-disubstituted-piperidine intermediate 9 which, by adding the appropriate substituent, will afford by ring closure the indolizidine skeleton, a different approach with respect

to the literature reports^{3,5} in which the bicyclic structure was built up from a chiral 2,5-disubstituted pyrrolidine.

We have already reported the synthesis of piperidine alkaloids⁶. The 2,6-disubstituted piperidine ring was made from chiral 1,5-diols readily obtained from β -ketosulfoxides. In the present paper, the synthetic approach to 9 was different : the first chiral center was created from the β -ketosulfoxide 3 while the second one was obtained by reductive cyclization of the amino-ketone derived from 8 (Scheme I).

Scheme I



a) $(CH_2OH)_2$, TsOH, PhH, Δ , 12h, 83%; b) (R) methyl p-tolylsulfoxide, LDA, THF, 84%; c) ZnCl₂, DIBAL, THF, 95%, (de>95%); d) TBSCl, imid., DMF, 97%; e) Ac₂O, AcONa, Δ , 96%; f) LiAlH₄, PhCH₃, -35°C, 75%; g) MEMCl, i-Pr₂NEt, CH₂Cl₂, 91%; h) TBAF, THF, rt, quant. yield; i) MsCl, Et₃N, CH₂Cl₂, 0°C, 1h; j) N₃Na, DMF, 80°C, 90% for the 2 steps; k) TsOH, acetone, rt, 2 days, 98%; l) 10% Pd/C, MeOH, H₂; m) CBzCl, 20% K₂CO₃, CH₂Cl₂, 0°C, 1h, 74% for the 2 steps; n) Raney Ni, MeOH, 83%; o) 1. MsCl, Et₃N, 2. NaN₃, DMF, 80°C, overnight, 97% overall yield; p) TBAF, THF, quant. yield; q) MsCl, Et₃N, CH₂Cl₂, 0°C, 1h; r) 10% Pd/C, MeOH, H₂; s) K₂CO₃, CHCl₃, rt, 4 days; t) CBzCl, 20% K₂CO₃, CH₂Cl₂, 0°C, 1h, 66% yield for the 4 steps.

(+)-(R)- β -ketosulfoxide **3** was obtained in 84% yield by reaction of the carbanion of (+)-(R) methyl p-tolylsulfoxide⁷ in THF with protected ethyl 4-acetyl butyrate. Following our previous results⁸, stereoselective reduction of the carbonyl of **3** with ZnCl₂/DIBAL afforded (+) (R,R)- β -hydroxysulfoxide **4** in 95% yield (de > 95%, only one diastereomer was observed by ¹H NMR⁹). After protecting the hydroxyl group, the compound **5** was submitted to a Pummerer rearrangement followed by reduction of the Pummerer intermediate with LiAlH₄ in toluene¹⁰. The compound **7** was then, after deprotection, transformed into the corresponding mesylate which was displaced with sodium azide in 90% overall yield. The carbonyl of **8** was deprotected and the product cyclized under reducing conditions (10% Pd/C) giving a crude product which was transformed into the pure corresponding benzyl carbamate **9** in 74% overall yield¹¹. The stereochemistry of the reduction of the

imino intermediate was controlled by the chiral center α to nitrogen.

The stereochemistry of 9 was confirmed by an independant synthesis : the trihydroxysulfoxide 10, prepared by a method already published⁶, was desulfurized with Raney Ni and the free OH was displaced by sodium azide *via* the mesylate. Removal of the TBS group gave the compound 11. Mesylation, reduction of the azide and cyclization followed by the formation of the corresponding benzyl carbamate yielded a product identical in all respects with 9.

The piperidine 9 was deprotected with TiCl₄, the hydroxyl group oxidized to the corresponding aldehyde which was finally condensed with the appropriate ketophosphonate¹² (Scheme II). The Wittig adduct 13 was cyclized under reducing conditions to give a 1.8/1 mixture¹³ of compounds 2 and 1 which were easily separated by chromatography on aluminium oxide (ether / hexane : 1/6). Compounds 1 and 2 showed all the characteristics described in literature^{3,5}.



 $(MeO)_2P(0)CH_2C(0)n-Bu, rt, 18h, 72\%$ yield for the 2 steps; d) 10% Pd/C, MeOH, rt, overnight, 72%; e) chromatography on aluminium oxide (ether / hexane:1/ 6).

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References and notes

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- 9) ¹H NMR (200 MHz, CDCl₃): δ : 1.29 (s, 3H, Me), 1.54-1.64 (m, 6H, H-3, H-4, H-5), 2.42 (s, 3H, Me), 2.75 (dd, A part of ABX, 1H, J=13Hz and 2.5Hz, H-1), 2.95 (dd, B part of ABX, 1H, J=13 and 9Hz, H-1), 3.86-3.95 (m, 5H, OCH₂CH₂O, OH), 4.27 (m, 1H, H-2), 7.33, 7.54 (2d, 4H, J=8.2Hz, arom.H).
- 10) Reduction with LiAlH₄ in ether or THF led to a TBS exchange between the secondary to the primary OH.
- 11) ¹H NMR (200 MHz, CDCl₃) : δ : 1.10 (d, 3H, J=6.9Hz, Me), 1.41-1.81 (m, 6H, H-3, H-4, H-5), 3.35 (s, 3H, OMe), 3.49-3.62 (m, 6H, OCH₂CH₂O, H-8), 4.34 (m, 2H, H-2, H-6), 4.67 (s, 2H, OCH₂O), 5.12 (s, 2H, COOCH₂Ph), 7.32 (m, 5H, arom.H). ¹³C NMR (CDCl₃) : δ : 13.7, 20.3, 24.8, 29.7, 45.7, 49.5, 58.8, 66.6, 66.7, 67.9, 71.6, 127.6, 127.7, 128.2, 136.8, 155.6.
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- 13) In all the reported syntheses^{3,5}, a similar stereoselectivity was observed during the formation of the bicyclic indolizidine.

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