Pergamon

Tetrahedron Letters, Vol. 37, No. 1, pp. 111-114, 1996

0040-4039/96 $15.00 + 0.00

0040-4039(95)02086-1

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

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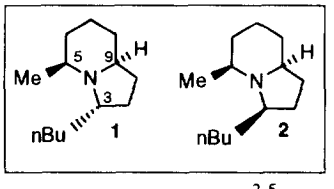
Abstract: The total synthesis of (+)-Indolizidine 195 B and (+)-Monomorine is described. The formation of the chiral centers was stereocontrolled by chiral sulfoxides.

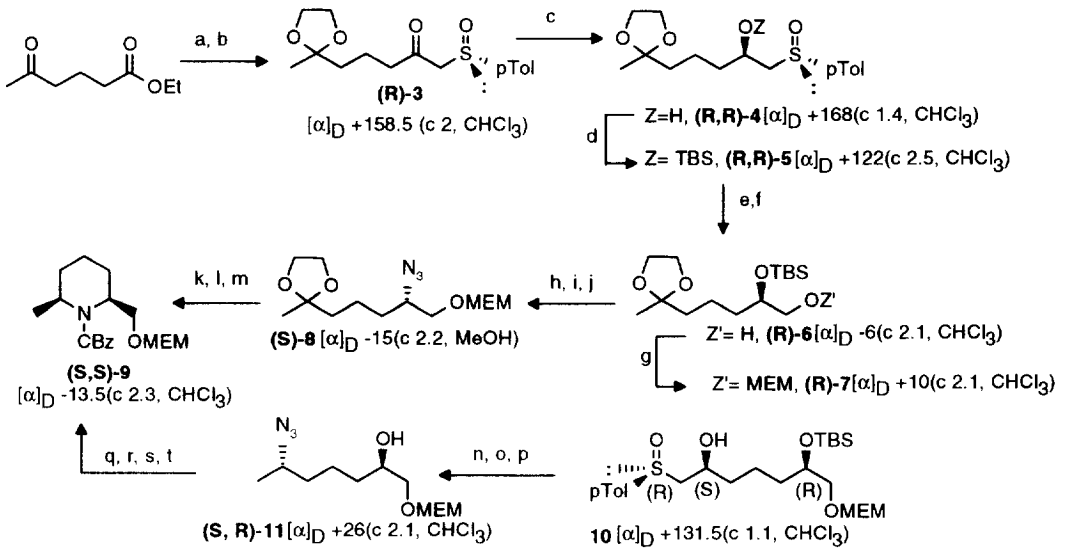
Indolizidine alkaloids offer attractive targets for synthesis because of their exotic provenance, scarcity and marked biological activity[1]. The Colombian poison-frog *Dendrobates histrionicus* contains a variety of indolizidine alkaloids : compound 195 B, (+)-(3S, 5S, 9S)-3-n-butyl-5-methyl indolizidine **1**, was isolated in 1986[2] and several syntheses have been reported[3]. (+)-Monomorine **2** was identified as the trail-laying pheromone of the Pharaoh ant, *Monomorium pharaonis L*[4] and its synthesis deeply investigated[5]. 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 alkaloids[6]. 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**) $ZnCl_2$, DIBAL, THF, 95%, (de>95%); **d**) TBSCl, imid., DMF, 97%; **e**) Ac_2O, AcONa, Δ, 96%; **f**) $LiAlH_4$, $PhCH_3$, -35°C, 75%; **g**) MEMCl, i-Pr_2NEt, CH_2Cl_2, 91%; **h**) TBAF, THF, rt, quant. yield; **i**) MsCl, Et_3N, CH_2Cl_2, 0°C, 1h; **j**) N_3Na, DMF, 80°C, 90% for the 2 steps; **k**) TsOH, acetone, rt, 2 days, 98%; **l**) 10% Pd/C, MeOH, H_2; **m**) CBzCl, 20% K_2CO_3, CH_2Cl_2, 0°C, 1h, 74% for the 2 steps; **n**) Raney Ni, MeOH, 83%; **o**) 1. MsCl, Et_3N, 2. NaN_3, DMF, 80°C, overnight, 97% overall yield; **p**) TBAF, THF, quant. yield; **q**) MsCl, Et_3N, CH_2Cl_2, 0°C, 1h; **r**) 10% Pd/C, MeOH, H_2; **s**) K_2CO_3, $CHCl_3$, rt, 4 days; **t**) CBzCl, 20% K_2CO_3, CH_2Cl_2, 0°C, 1h, 66% yield for the 4 steps.

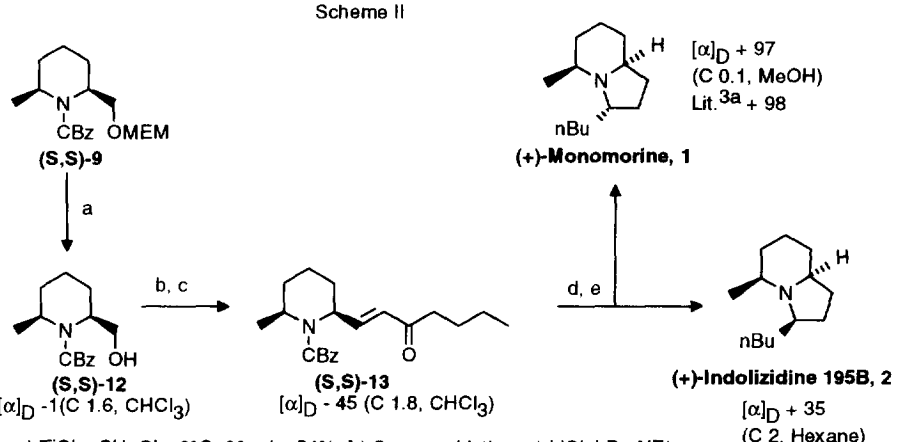
(+)-(R)-β-ketosulfoxide **3** was obtained in 84% yield by reaction of the carbanion of (+)-(R) methyl p-tolylsulfoxide[7] in THF with protected ethyl 4-acetyl butyrate. Following our previous results[8], stereoselective reduction of the carbonyl of **3** with $ZnCl_2$/DIBAL afforded (+) (R,R)-β-hydroxysulfoxide **4** in 95% yield (de > 95%, only one diastereomer was observed by ^1H NMR[9]).

After protecting the hydroxyl group, the compound **5** was submitted to a Pummerer rearrangement followed by reduction of the Pummerer intermediate with $LiAlH_4$ in toluene[10]. 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 yield[11]. 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 published[6], 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 $TiCl_4$, the hydroxyl group oxidized to the corresponding aldehyde which was finally condensed with the appropriate ketophosphonate[12] (Scheme II). The Wittig adduct **13** was cyclized under reducing conditions to give a 1.8/1 mixture[13] 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].

Scheme II



a) $TiCl_4$, CH_2Cl_2, 0°C, 30 min, 54%; **b)** Swern oxidation; **c)** LiCl, i-Pr_2NEt, $(MeO)_2P(0)CH_2C(0)$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)..

Acknowledgments : Dr. Guo-Hua Chu thanks CNRS for a one year associate position.

References and notes

† On leave from the Institute Materia Medica, Chinese Academy of Sciences, Shanghai, China.

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9) ^{1}H NMR (200 MHz, $CDCl_3$) : 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, OCH_2CH_2O, OH), 4.27 (m, 1H, H-2), 7.33, 7.54 (2d, 4H, J=8.2Hz, arom.H).

10) Reduction with $LiAlH_4$ in ether or THF led to a TBS exchange between the secondary to the primary OH.

11) ^{1}H NMR (200 MHz, $CDCl_3$) : 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, OCH_2CH_2O, H-8), 4.34 (m, 2H, H-2, H-6), 4.67 (s, 2H, OCH_2O), 5.12 (s, 2H, $COOCH_2Ph$), 7.32 (m, 5H, arom.H). ^{13}C NMR ($CDCl_3$) : 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.

(*Received in UK* 29 *September* 1995; *revised* 23 *October* 1995; *accepted* 3 *November* 1995)