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CYCLISATION OF ALLYL SILANES. FORMAL TOTAL SYNTHESIS OF (±)-MESEMBRINE

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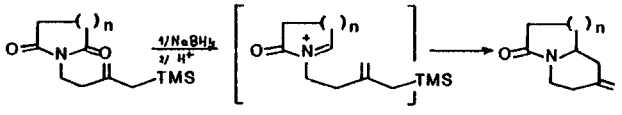
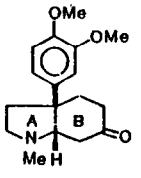
Abstract : The intramolecular reaction of an α-acyl iminium ion with an allyl silane occurs under non acidic conditions to afford the key intermediate 8 for the synthesis of (±)-mesembrine 1 in a stereospecific manner.

We recently reported a new approach to the synthesis of indolizidine and quinolizidine bicyclic systems[1] based upon the electrophilic reaction of α-acyl iminium ions with allyl silanes. An important feature of these cyclisations was the formation of an exocyclic double bond allowing further functionalisation of the heterocyclic ring (Scheme 1).



Scheme 1



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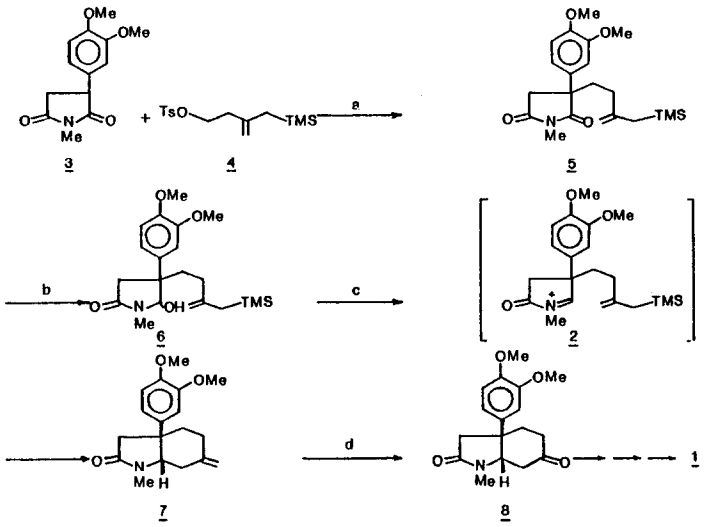
We wish, in the present communication, to describe the application of the above methodology towards an efficient stereospecific synthesis of (±)-mesembrine 1. The preparation of this alkaloid and its congeners is of considerable interest[2] due to the CNS activity of this class of compounds and to their structural similarity to the *Sceletium, Amaryllidaceae*[3] and even morphine type alkaloïds[4].

The key step in our strategy involves the intramolecular electrophilic cyclisation of the *in situ* generated α-acyl iminium intermediate 2 to give the B ring of 1. Examination of the Dreiding models showed that the geometry of side chain relative to the flat five membered ring of 2 should greatly favour the formation of *cis* fused ring as required in mesembrine 1.

Alkylation of the anion of 3 (NaH/DMSO ; DME, 50°C, 1 h) with the tosylate 4[6] led to the imide 5 (60 %)[7,8] exclusively (Scheme 2). The reduction of 5 using Speckamp's method[9] ($NaBH_4$, EtOH, HCl) proceeded with high regioselectivity affording the 2-hydroxy lactam 6 (60 %)[10] as a mixture of diastereomers[11].



a)NaH/DMSO,DME,b)$NaBH_4$,EtOH/H$^+$,c)MsCl,Et_3N,CH_2Cl_2,d)O_3,CH_2Cl_2-MeOH(1-1),Me_2S.

Scheme2

It was then expected that the treatment of 6 with CF_3CO_2H/CH_2Cl_2 would generate 2 which would in turn react with the allyl silane component to produce the olefin 7. However, under these conditions cyclisation was followed by the isomerisation of the exocyclic double bond to the more stable endocyclic position.

Non acidic conditions[12] were thus employed in order to avoid this undesirable isomerization process. It was found that, by treatment of 6 with $MsCl/Et_3N$ in CH_2Cl_2 at room temperature

overnight, the desired bicyclic olefin 7[13] was obtained in a stereospecific manner in 80 % yield (with respect to consumed starting material, 60 % conversion).

Ozonolysis[14] of 7 (O_3, CH_2Cl_2-MeOH (1-1), - 78°C, Me_2S) led to the keto lactam 8[15] in nearly quantitative yield. The spectral data for this compound were identical in all respects with previously reported literature data[2e]. The expected *cis* stereochemistry of compound 7 is thus confirmed.

In conclusion, the synthesis of 8 was realized in four steps (30 % overall yield) from the readily avalaible imide 3. Since the conversion of the intermediate 8 to (±)-1 has been reported to proceed in nearly quantitative yield, this approach constitutes a new formal synthesis of this alkaloid.

Acknowledgements

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6. Tosylate 4 was prepared from the corresponding alcohol[1] using standard conditions (TsCl, pyridine, overnight).

7. All NMR spectra were recorded at 60 MHz (^{1}H) and 15 MHz (^{13}C).

8. Imide 5 : oil, IR (film) : 1780, 1710 cm^{-1} ; ^{1}H NMR ($CDCl_3$) : δ 6.9 (m, 3H) ; 4.6 (s, 2H) ; 3.85 (s, 3H) ; 3.9 (s, 3H) ; 3.05 (s, 5H) ; 2.1 (m, 4H) ; 1.55 (s, 2H) ; 0.0 (s, 9H) ; ^{13}C NMR ($CDCl_3$) : δ 181.7 ; 176.9 ; 150.5 ; 149.8 ; 147.55 ; 133.9 ; 119.8 ; 112.5 ; 111.2 ; 108.9 ; 57.3 ; 52.6 ; 42.7 ; 39.8 ; 34.4 ; 28.3 ; 26.3 ; 0.0 ; Calc. for $C_{21}H_{31}NO_4$ Si 389.2014 ; found 389.2025.

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10. Hydroxylactam 6 : oil, IR (film) : 3350, 1710, 1685 cm^{-1} ; ^{1}H NMR ($CDCl_3$) : δ 6.9 (m, 3H) ; 6.2 (m, 1H) ; 5.2 (m, 1H) ; 4.6 (m, 2H) ; 3.9 (s, 6H) ; 2.9 (s, 5H) ; 1.3-2.1 (m, 4H) ; 1.5 (s, 2H) ; 0.0 (s, 9H).

11. The espected regiomer 6 (60 %) was obtained as a mixture of the two possible stereomers in a 9:1 ratio. They were identified by the multiplicity of the C<u>H</u>-OH signal and the presence of two N-<u>CH_3</u> singlets at 2.9 and 3.0 ppm in the ^{1}H NMR spectra. Both diastereomers were isolated by column chromatography and the spectral data of the major diastereomer is given in note 10. It is in agreement with these mentioned by J.B.P.A. Wijnberg and W.N. Speckamp (Tetrahedron, 1978, 34, 2579) for analogous products.
The other regiomer (corresponding to the reduction in 5 position of the imide group) was also isolated (20 %) as a mixture of diastereomers and identified by the multiplicity (broad multiplet) of the C<u>H</u>OH signal in ^{1}H NMR.

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13. Compound 7 : oil, IR (film) 1690 cm^{-1} ; ^{1}H NMR ($CDCl_3$) : δ 6.9 (m, 3H) ; 4.85 (s, 2H) ; 4.05 (t, 1H) ; 3.9 (s, 6H) ; 2.9 (s, 3H) ; 2.6 (m, 4H) ; 2.0 (m, 4H) ; ^{13}C NMR ($CDCl_3$) : δ 173.7 ; 118.4 ; 111.3 ; 110.7 ; 110.2 ; 64.4 ; 56.1 ; 56.0 ; 47.2 ; 35.0 ; 33.5 ; 29.7 ; 26.9 ; Calc. for $C_{18}H_{23}NO_3$: 301.1672 ; found : 301.1676.

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15. Compound 8 : oil, IR ($CHCl_3$) 1720, 1685 cm^{-1} ; ^{1}H NMR ($CDCl_3$) : δ 6.9 (m, 3H) ; 4.4 (t, 1H) ; 3.9 (s, 6H) ; 2.9 (m, 7H) ; 2.35 (m, 4H).

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