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Preparation of Spiroindolines as Potential Intermediates in *Aspidosperma* Alkaloid Synthesis

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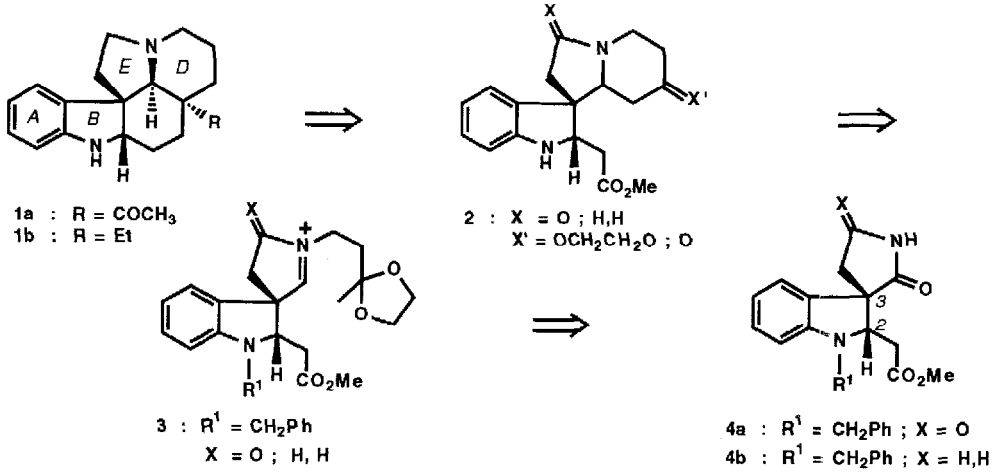
Abstract : *The photocyclization of enaminoester **5a** gave indoline **8** which was used in the synthesis of tricyclic spiro compound **4a**.*

In previous work, we have described the synthesis of *Aspidosperma* alkaloids, such as 19-oxo-aspidospermidine **1a**,[1] through an [ABC] → [ABCE] → [ABCED] sequential ring construction based on the photochemical conversion of arylenaminones into hexahydrocarbazol-4-ones.[2] The success of this methodology led us to consider an alternative route in which the tetracyclic spiro compounds **2**,[3a] that constitute the key intermediates of pentacyclic alkaloids **1**, are accessible by an intramolecular Mannich cyclization of a suitable acyliminium acetal **3** (X = O) related to our general procedure (Scheme 1).[3b] A very close strategy, using allylsilanes, has been recently reported in the context of the preparation of the *Aspidosperma* framework.[4]

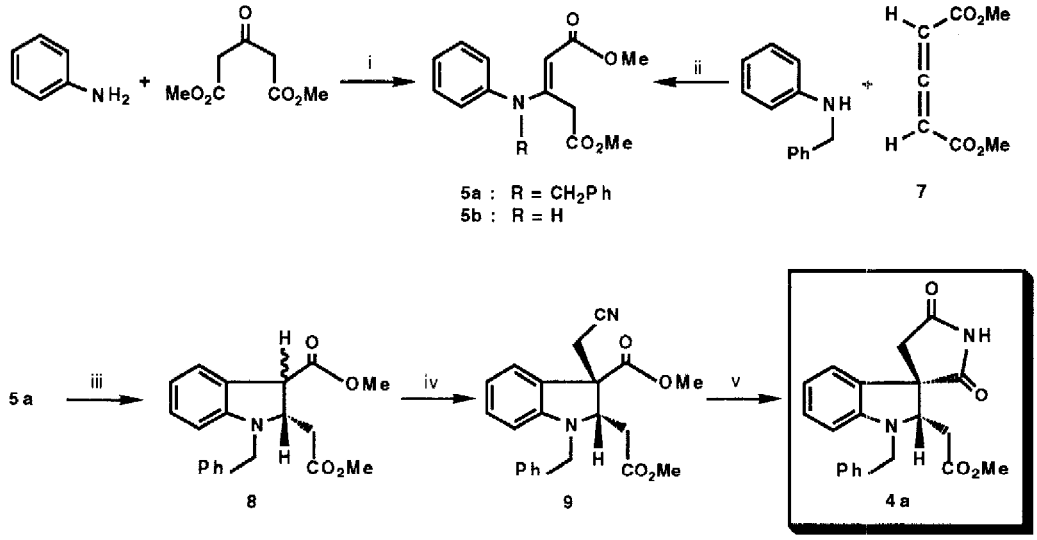


Scheme 1

In the present work we report the synthesis of spiroindoline **4a** with the natural relative stereochemistry, *i.e. cis* ,[5] essential for the synthetic usefullness of our approach to prepare natural compounds. The synthesis of **4a** was envisaged through photocyclization of enaminoesters **5**, whose preparation was first assayed by direct condensation[6] of the suitable aniline with 1,3-dimethylacetone dicarboxylate.

Nevertheless, while **5b** (Z/E mixture) was obtained in high yield, this procedure only furnished **5a**[7] in very poor yield, leading mainly to amide **6**.[8] On the other hand, the alkylation of **5b** led exclusively to a complex mixture where no desired *N*-alkylated **5a** was found. Alternatively, **5a**[9] was obtained as a single isomer by condensation[10] of *N*-benzylaniline with dimethyl 2,3-pentanedienedioate **7**[11] in 85% yield.

Irradiation of **5b** turned out to be unsuccessfull leading only to the corresponding Z isomer.[12] However, photocyclization of **5a** led to indoline **8**[13] as a 9 : 1 mixture of *cis* : *trans* diastereomers in excellent yield.[14] Alkylation of the crude mixture with iodoacetonitrile furnished the expected 3,3-disubstituted compound **9**[15] together with *N*-benzyl-3-methyl indole carboxylate **10**,[16] the latter resulting from a retro-Michael reaction. Structure and relative configuration[5] of **9** were inferred from ^{1}H and ^{13}C NMR analyses and ROE experiments.[17] Finally, treatment of **9** with basic hydrogen peroxide[18] furnished the target compound **4**[19] in 20% yield (80 % on transformed product) (Scheme 2).



Reagents and conditions : i) APTS, C_6H_6, Δ, Dean-Stark, 12h ; ii) MeOH, r.t., 8h, 85% ; iii) hν (Pyrex, 400W), C_6H_6 : MeOH (1 : 1), 45min., 95%; iv) LDA, 1.1 eq., -60°C then ICH_2CN, r.t., 58% ; v) H_2O_2 / OH^- / $Bu_4N^+HSO_4^-$, CH_2Cl_2, r.t, 24h, 20%.

Scheme 2

Further applications of this methodology to the total synthesis of dihydroindole alkaloids are in progress.

Acknowledgements

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References and notes

1 - Dufour, M. ; Gramain, J.-C. ; Husson, H.-P. ; Sinibaldi, M.-E. ; Troin, Y. *J. Org. Chem.* **1990**, *55*, 5483 and references cited therein.

2 - (a) Gramain, J.-C. ; Husson, H.-P. ; Troin, Y. *Tetrahedron Lett.* **1985**, *26*, 2323.
(b) Gramain, J.-C. ; Husson, H.-P. ; Troin, Y. *J. Heterocyclic Chem.* **1988**, *25*, 201.

3 - (a) The synthesis of related tetracyclic spiroindolines lacking the acetate chain at the C-2 position has been recently reported : Rubiralta, M. ; Diez, A., Vila ; C. *Tetrahedron Lett.* **1990**, *31*, 3779.
(b) For intramolecular Mannich cyclization, see : Rubiralta, M. ; Diez, A. ; Bosch, J. ; Solans, X. *J. Org.Chem.* **1989**, *54*, 5591 and references cited therein.

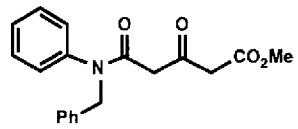
4 - Mittendorf, J. ; Hiemstra, H. ; Speckamp, W.N. *Tetrahedron* **1990**, *46*, 4049.

5 - *cis* Stereochemistry is referred to the case where H-C_2 and the methylene group on C_3 have a *cis* relationship.

6 - Melillo, D.G. ; Cvetovich, R.J. ; Ryan, K.M. ; Sletziwger, M. *J. Org. Chem.* **1986**, *51*, 1498.

7 - All new compounds gave satisfactory spectral data and elemental analysis.

8 - Formation of **6** can be attributed to the use of a secondary amine instead of a primary one, whose largerer steric hindrance promotes the reaction to occur preferentially upon the ester group.



6

9 - **5a** : m.p. 90-91°C (ether); IR ($CHCl_3$) ν_{max} 1738, 1685, 1602 cm^{-1} ; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.60 (s, 3H) ; 3.65 (s, 3H) ; 3.92 (s, 2H) ; 4.85 (s, 2H) ; 5.10 (s, 1H) ; 7.15-7.40 (m, 10H) ; ^{13}C NMR ($CDCl_3$) δ 36.0, 50.4, 52.0, 57.3, 90.6, 126.8, 127.3, 127.5, 128.0, 128.7, 129.7, 136.4, 144.9, 155.8, 169.0, 170.3 ; UV (EtOH) λ_{max} 289 nm.

10 - Nixon, N.S. ; Sheimann, F. *J. Chem. Research. (M).***1984**, 3401.

11 - Bryson, T.A. ; Dolak, T.M. *Org. Syn.* **1978**, *57*, 62.

12 - (a) Similar isomerization was recently described : see ref. 6
(b) For some photocyclizations with N-H compounds see : Schultz, A.G. ; Sha, C.K. *Tetrahedron* **1980**, *36*, 1757 and references cited therein.

13 - *cis*-**8** (major isomer): oil ; IR (CCl_4) ν_{max} 1748, 1602 cm^{-1} ; IR ($CHCl_3$) ν_{max} 1740, 1735, 1602 cm^{-1} ^1H NMR ($CDCl_3$, 300 MHz) δ 2.60-3.10 (m, 2H) ; 3.68 and 3.75 (2s, 3H each, OCH_3) ; 4.28 and 4.45 (2d, J_{AB} = 16 Hz, 1H each, CH_2Ph) ; 4.25-4.35 (m, 1H, H-C_2) ; 4.43 (d, J = 9 Hz, 1H, H-C_3) ; 6.50 (d, J = 8 Hz, 1H, H-C_7) ; 6.75 (t, J = 8 Hz, 1H, H-C_5) ; 7.15 (t, J = 8Hz, 1H, H-C_6) ; 7.20 (d, J = 8 Hz, 1H, H-C_4) ; 7.30-7.50 (m, 5H, ArH) ; ^{13}C NMR ($CDCl_3$) δ 34.2 ($\underline{C}H_2CO$), 49.7 (C_3), 51.2 ($\underline{C}H_2Ph$), 51.6 (OCH_3), 51.8 (OCH_3), 62.7 (C_2), 108.0 (C_7), 118.4 (C_5), 124.5 (C_4), 126.0 (C_{3a}), 127.0 (C_{ortho}), 128.6 (C_{meta}), 129.0 (C_6), 138.1 (C_{ipso}), 152.1 (C_{7a}), 171.6 and 171.9 (C=0).

trans-**8** : oil ; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.60-2.90 (m, 2H) ; 3.65 and 3.85 (2s, 3H each, OCH_3) ; 4.20 (d, J = 7 Hz, 1H, H-C_3) ; 4.38 and 4.51 (2d, J_{AB} = 16 Hz, 1H each, CH_2Ph) ; 4.45-4.53 (m, 1H, H-C_2) ; 6.40 (d, J = 8 Hz, 1H, H-C_7) ; 6.75 (t, J = 8 Hz, 1H, H-C_5) ; 7.10 (t, J = 8 Hz, 1H, H-C_6) ; 7.20-7.40 (m, 6H, H C_4 and ArH) ; ^{13}C NMR ($CDCl_3$) δ 38.6 ($\underline{C}H_2CO$), 51.7 (OCH_3), 51.8 (CH_2Ph), 52.4 (C_3 and OCH_3), 63.6 (C_2), 107.7 (C_7), 118.1 (C_5), 124.6 (C_4), 125.2 (C_{3a}), 127.1 (C_{ortho}), 128.6 (C_{meta}), 129.0 (C_6), 138.4 (C_{ipso}), 151.3 (C_{7a}), 171.2 and 172.1 (C=O).

14 - The relative stereochemistry assignment of the major isomer as *cis*-**8** was carried out by the magnitude of coupling constant between H-C_2 and H-C_3 (J = 9 Hz) in its ^{1}H NMR spectrum and by the existence of shielding effect (Δδ = 3-4 ppm) upon $\underline{C}H_2CO$ and C_3 by steric effect in its ^{13}C NMR spectrum.

15 - **9** : oil ; IR (CCl_4) ν_{max} 2250, 1745, 1740 cm^{-1} ; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.70-2.80 (m, 2H) ; 2.95 (d, J = 15.5 Hz, 1H, C$\underline{H}$-CN) ; 3.15 (d, J = 15.5 Hz, 1H, C$\underline{H}$-CN) ; 3.62 (s, 3H, OCH_3) ; 3.78 (s, 3H, OCH_3) ; 4.20 (dd, J = 6.3 and 8 Hz, 1H, H-C_2) ; 4.32 (d, J = 16 Hz, 1H, N-C$\underline{H}$Ph) ; 4.48 (d, J = 16 Hz, 1H, N-C$\underline{H}$Ph) ; 6.50 (d, J = 8 Hz, 1H) ; 6.80 (t, J = 8 Hz, 1H) ; 7.15 (t, J = 8 Hz, 1H) ; 7.17 (d, J = 8 Hz, 1H) ; ^{13}C NMR ($CDCl_3$) δ 26.8, 35.2, 51.2, 51.9, 52.9, 56.6, 68.2, 108.2, 117.2, 118.8, 123.9, 127.1, 127.5, 128.8, 130.2, 137.8, 150.9, 171.0, 171.3.

16 - **10** : m.p. 69-70°C (ether) ; IR (CCl_4) ν_{max} 1715 cm^{-1} ; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.90 (s, 3H, OCH_3) ; 5.30 (s, 2H, CH_2Ph) ; 7.10 (d, J = 8 Hz, 1H) ; 7.20-7.40 (m, 7H) ; 7.90 (s, 1H) ; 8.3 (d, J = 8 Hz, 1H) ; ^{13}C NMR ($CDCl_3$) δ 50.7, 50.9, 107.5, 110.3, 120.7, 122.0, 122.9, 127.1, 128.1, 128.9, 134.5, 135.9, 136.7, 165.4.

17 - (a) Correlation between H-C_2 and the methylene group on C_3 was observed in a ROE spectrum at 300 MHz. For structure determination by ROE experiments : see Bothner-By, A.A. ; Stephens, R.L. ; Lee, J.-M. ; Warren, C.D. ; Jeanloz, R.W. *J. Am. Chem. Soc.*, **1984**, *106*, 811.
(b) We thank Dr. G. Massiot and Dr. C. Lavaud for ROE experiments.

18 - Cacchi, A., Misiti, D. ; Latorre, F. *Synthesis* **1980**, 243.

19 - **4a** : foam ; IR (CCl_4) ν_{max} 3420, 1770, 1740, 1602 cm^{-1} ; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.90 (dd, J = 3.7 and 16.5 Hz, 1H, C$\underline{H}$COOCH$_3$) ; 3.12 (d, J = 18 Hz, 1H, C$\underline{H}$CONH) ; 3.20 (dd, J = 10.5 and 16.5 Hz, 1H, C$\underline{H}$COOCH$_3$) ; 3.22 (d, J = 18 Hz, 1H, C$\underline{H}$CONH) ; 3.63 (s, 3H, OCH_3) ; 4.09 (dd, J = 3.7 and 10.5 Hz, 1H, H-C_2) ; 4.28 (d, J = 16.5 Hz, 1H, N-C$\underline{H}$Ph) ; 4.45 (d, J = 16.5 Hz, 1H, N-C$\underline{H}$Ph) ; 6.50 (d, J = 8Hz, 1H) ; 6.75 (t, J = 8Hz, 1H) ; 7.02 (d, J = 8 Hz, 1H) ; 7.15 (t, J = 8 Hz, 1H) ; 7.30-7.40 (m, 5H) ; 8.05 (m, 1H exchange with D_2O, NH) ; ^{13}C NMR ($CDCl_3$) δ 34.2, 46.3, 51.4, 52.0, 56.4, 69.1, 108.3, 119.1, 122.2, 127.1, 127.6, 128.9, 129.5, 130.0, 137.6, 151.1, 172.1, 175.3, 177.1.

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