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Total Synthesis of the *Strychnos* Alkaloid Tubotaiwine

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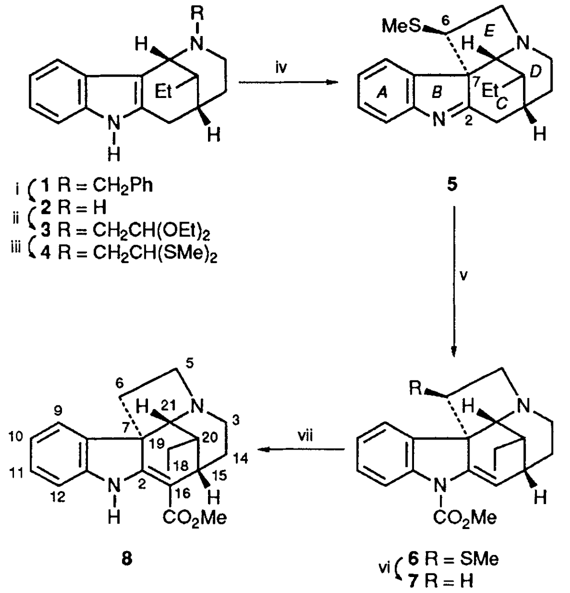
The total synthesis of racemic tubotaiwine **8** has been achieved from the tetracyclic intermediate **1**, the key steps being the construction of the C(7)-quaternary centre by cyclization of a thionium ion upon the indole 3-position and the introduction of the C(16)-methoxycarbonyl substituent by photochemical rearrangement of the *N*-methoxycarbonylenamine **7**.

Tubotaiwine **8** is a pentacyclic *Strychnos* alkaloid[1] having the Aspidospermatan skeleton,[2] *i.e.* with a C(7)–C(21) bond (biogenetic numbering)[3] and, accordingly, with the two-carbon [C(18)–C(19)] chain located at the bridge carbon.

We report herein a stereocontrolled total synthesis of (±)-tubotaiwine[4] taking advantage of the previously reported tetracycle **1**,[5] which possesses the correct relative stereochemistry at C(20). The two main problems to overcome in this synthesis were the elaboration of the five-membered *E* ring and the introduction of the C(16) methoxycarbonyl substituent.

The first problem was solved by using our previously reported[6] methodology for the synthesis of pentacyclic *Strychnos* alkaloids of the Strychnan type [*i.e.*, having a C(3)–C(7) bond]. The method is based on the closure of the pyrrolidine *E* ring in the last synthetic steps by formation of the crucial C(6)–C(7) bond by cyclization upon the indole 3-position from an appropriately *N*-substituted tetracyclic system embodying rings *ABCD* of the alkaloids. Thus, the tetracycle **1** (ethyl substituent equatorial with respect to the piperidine ring) was converted in three steps (50% overall yield) to the dithioacetal **4**,† which was cyclized by the way of a thionium ion generated by treatment with dimethyl(methylthio)sulphonium tetrafluoroborate (DMTSF)[7] (Scheme 1).

The resulting pentacyclic indolenine **5**‡ proved to be unstable, and readily decomposed in the presence of chlorinated solvents. The best yields (36%) were obtained when the cyclization was effected in acetonitrile solution, instead of



Scheme 1 *Reagents and conditions*: i, H_2, activated $Pd(OH)_2$, MeOH, 3 days; ii, $BrCH_2CH(OEt)_2$, anhydrous Na_2CO_3, dioxane, reflux, 17 h; iii, MeSH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C, 48 h; iv, $[Me_2SSMe]^+BF_4^-$, degassed MeCN, 0 °C, 2 h; v, NaH, $ClCO_2Me$, DME, reflux, 1 h; vi, Raney nickel (W-2), EtOH, reflux, 4 h; vii, hv, MeOH, 30 min

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† All new compounds reported herein exhibited IR and ^1H and ^{13}C NMR spectra in full accord with the assigned structures.

‡ Minor amounts of the C(6) epimer were detected by NMR spectroscopy.

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dichloromethane as is usual in similar DMTSF promoted cyclizations.[7]

The NMR data of this cyclized product, in particular the chemical shift for C-21 (δ 73.3) and C-14 (δ 34.5; absence of γ effect) clearly indicated that the relative configuration at C(20) had not changed after the cyclization step and, therefore, that epimerization at C(20) had not occurred, in contrast with what has been reported for some related pentacyclic indolenines (*e.g.* condyfoline).[8]

The direct introduction of the C(16) methoxycarbonyl substituent from the tetracycle **1**, by methoxycarbonylation of the *C,N*-dianion generated with the Schlosser base (BuLi, Bu^{t}OK),[9] was unsuccessful. For this reason, this substituent was introduced in a less straightforward, but efficient, manner from the indolenine **5**. Thus, treatment of **5** with sodium hydride and methyl chloroformate gave the *N*^{a}-methoxycarbonyl derivative **6**‡ in 50% yield. The most significant ^{1}H NMR (200 MHz) signal was a doublet at δ 5.91 due to the vinyl proton and a singlet (δ 3.93) for the methoxy group.§

The *N*-(methoxycarbonyl)enamine function present in **6** allowed us to effect both the chemoselective hydrogenolysis of the methylthio substituent without affecting the double bond at C(2) and a photochemical rearrangement to the vinylogous urethane moiety present in tubotaiwine. Thus, desulphurization of **6** using Raney nickel (W-2) in ethanol gave **7**¶ (64% yield), which was irradiated with a high-pressure mercury lamp to give (±)-tubotaiwine **8** in 20% yield. Our synthetic material **8** was identified as tubotaiwine by comparison of its ^{1}H NMR spectrum with that of the natural product.[10] The R_F values of **8** in several solvent mixtures were coincident with those of authentic samples of tubotaiwine.

This result confirms the relative configuration at C(20) in tubotaiwine, which, although recently established by NMR methods, has been a matter of controversy.[10,11]

We are grateful to Professor J. Schripsema (University of Leiden) for an authentic sample of natural tubotaiwine and a copy of its ^{1}H NMR spectrum. We also thank Professor G. Massiot (University of Reims) for a sample of tubotaiwine tartrate. Financial support from the DGICYT, Spain (project PB88-0316) is gratefully acknowledged. Thanks are also due to the Department d'Ensenyament (Generalitat de Catalunya) for a fellowship to one of us (J. G.).

Received, 17th January 1991; Com. 1/00247C

References

1 J. Bosch and J. Bonjoch, Pentacyclic *Strychnos* Indole Alkaloids, in *Studies in Natural Products Chemistry*, ed. Atta-ur-Rahman, Elsevier, Amsterdam, 1988, vol. 1, p. 31.

2 M. Lounasmaa and P. Somersalo, in The Condylocarpine Group of Indole Alkaloids, in *Progress in the Chemistry of Organic Natural Products*, eds. W. Herz, H. Grisebach, G. W. Kirby and Ch. Tamm, Springer Verlag, Wien, 1986, vol. 50, p. 27.

3 J. Le Men and W. I. Taylor, *Experientia*, 1965, **21**, 508.

4 For a previous total synthesis, see: B. A. Dadson and J. Harley-Mason, *Chem. Commun.*, 1969, 665.

5 J. Bonjoch, N. Casamitjana, J. Gràcia and J. Bosch, *Tetrahedron Lett.*, 1989, **30**, 5659.

6 M. Amat, A. Linares and J. Bosch, *J. Org. Chem.*, 1990, **55**, 6299.

7 M. Amat, M. Alvarez, J. Bonjoch, N. Casamitjana, J. Gràcia, R. Lavilla, X. Garcías and J. Bosch, *Tetrahedron Lett.*, 1990, **31**, 3453.

8 D. Schumann and H. Schmid, *Helv. Chim. Acta*, 1963, **46**, 1996.

9 S. Inagaki, Y. Nishizawa, T. Sugiura and H. Ishihara, *J. Chem. Soc., Perkin Trans. 1*, 1990, 179.

10 J. Schripsema, T. A. Van Beek, R. Verpoorte, C. Erkelens, P. Perera and C. Tibell, *J. Nat. Prod.*, 1987, **50**, 89.

11 M. Lounasmaa, A. Koskinen and J. O'Connell, *Helv. Chim. Acta*, 1986, **69**, 1343; Atta-ur-Rahman, K. A. Alvi and A. Muzaffar, *Planta Medica*, 1986, 325.

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§ The presence of a second, minor rotamer due to restricted rotation of the N^a–CO bond was observed by ^{1}H NMR.

¶ This compound gave satisfactory elemental (C, H, N) analyses. ^{13}C NMR (50.4 MHz, CDCl$_3$) δ 11.4 (C-18), 23.8 (C-19), 28.0 (C-14), 31.3 (C-15), 41.4 (C-20), 42.3 (C-6), 45.0 (C-3), 50.5 (C-7), 52.6 (OCH$_3$), 53.5 (C-5), 65.0 (C-21), 110.3 (C-12), 115.1 (C-16), 119.9 (C-9), 123.8 (C-10), 127.0 (C-11), 137.9 (C-8), 140.1 (C-13), 147.5 (C-2) and 153.1 (CO).