Total Synthesis of the *Strychnos* Alkaloids (±)-Akuammicine and (±)-Norfluorocurarine from 3a-(*o*-Nitrophenyl)hexahydroindol-4-ones by Nickel(0)-Promoted Double Cyclization

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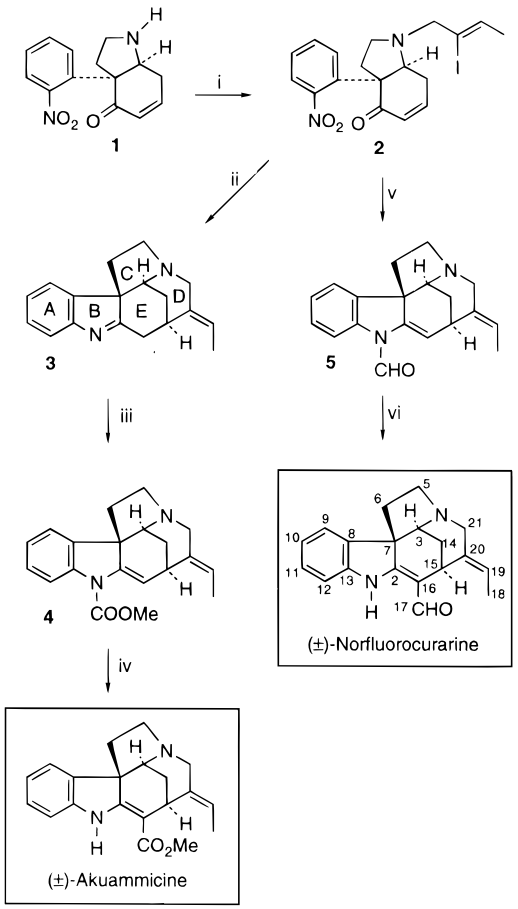
One of the most flexible approaches for the synthesis of *Strychnos* alkaloids[1] consists of the use of nonindolic starting materials, with elaboration of the indole moiety in the last synthetic steps from azapolycyclic intermediates with the appropriate functionality and stereochemistry. Efforts in this direction have culminated in the total synthesis of several pentacyclic *Strychnos* alkaloids[2,3] and in the first, and so far only, enantioselective total synthesis of Wieland−Gumlich aldehyde and strychnine.[4] In this context, we have recently reported the use of *cis*-3a-(*o*-nitrophenyl)hexahydroindol-4-ones as building blocks for assembling the pentacyclic ABCDE ring system of *Strychnos* alkaloids.[5] Treatment of vinyl halide **2** with nickel−bis(cyclooctadiene) [Ni(COD)$_2$][6] in the presence of lithium cyanide brought about both the closure of the piperidine ring (bond formed $C_{15}-C_{20}$)[7] and the reductive cyclization of the α-(*o*-nitrophenyl) ketone moiety to afford (40%) the norcuran type pentacycle (±)-dehydrotubifoline (**3**) in a single synthetic step.[5]

The synthesis of *Strychnos* alkaloids of the curan type requires the introduction of the oxidized one-carbon substituent (C-17) linked at C-16 in these alkaloids. Initially, this transformation was accomplished from the pentacyclic indolenine **3**. Thus, treatment of **3** with methyl chloroformate in the presence of NaH gave (36%)[8] the *N*-methoxycarbonyl derivative **4**, which was then photoisomerized (30%) to (±)-akuammicine (pseudo-akuammicine)[9] upon irradiation with a low-pressure mercury lamp.[10] Akuammicine was identified by comparison of its ^{1}H NMR (300 MHz) spectral data with those reported for the natural product.[11] The R_f values of our synthetic akuammicine in several solvent mixtures were also coincident with those of an authentic sample of the alkaloid[12] (Scheme 1).

Scheme 1[a]



[a] Key: (i) (*Z*)-BrCH$_2$CI=CHCH$_3$, anhyd K$_2$CO$_3$, CH$_3$CN, rt, 3h, 70%; (ii) Ni(COD)$_2$ (6.6 equiv), Et$_3$N, LiCN (10 equiv), 2.5:1 CH$_3$CN−DMF, rt, 2.5 h, 40%; (iii) ClCOOMe, NaH, DME, 60 °C, 4 h, 36%; (iv) *hν*, CH$_3$OH, 30%; (v) Ni(COD)$_2$ (6.6 equiv), Et$_3$N, LiCN (10 equiv), 2.5:1 CH$_3$CN−DMF, rt, 2.5 h, then (CH$_3$)$_2$N$^+$=CHCl Cl$^-$ (20 equiv), rt, 2 h, 15%; (vi) *hν*, CH$_3$OH, 15%.

A more straightforward method for the introduction of C-17 was the treatment of vinyl iodide **2** with Ni(COD)$_2$/LiCN, followed by trapping of the resulting intermediate with (chloromethylene)dimethyliminium chloride in a one-pot reaction. Under these conditions, the *N*-formyl derivative **5** was directly obtained in 15% yield from **2**. Probably, formylation occurs from a metalloenamine intermediate because dehydrotubifoline (**3**) was recovered unchanged after treatment with the above formylating agent (DMF, 80 °C, 15 h).[13]

Photoisomerization[14] of the *N*-formyl derivative **5** gave (±)-norfluorocurarine (vinervidine) in 15% yield,[15] the major product (69%) formed in this process being the

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(2) Bonjoch, J.; Solé, D.; Bosch, J. *J. Am. Chem. Soc.* **1993**, *115*, 2064−2065.

(3) Angle, S. R.; Fevig, J. M.; Knight, S. D.; Marquis, R. W., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 3966−3977.

(4) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1995**, *117*, 5776−5788.

(5) Bonjoch, J.; Solé, D.; Bosch, J. *J. Am. Chem. Soc.* **1995**, *117*, 11017−11018.

(6) For the use of Ni(COD)$_2$ in cyclizations of vinyl halides with alkenes, see: Solé, D.; Cancho, Y.; Llebaria, A.; Moretó, J. M.; Delgado, A. *J. Am. Chem. Soc.* **1994**, *116*, 12133−12134.

(7) The biogenetic numbering and ring labeling is used throughout this paper: Le Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508−510.

(8) All yields are after purification by chromatography. New compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, and/or microanalysis.

(9) (a) For the isolation of (±)-akuammicine, see: Edwards, P. N.; Smith, G. F. *Proc. Chem. Soc. (London)* **1960**, 215. (b) For previous syntheses of this racemic alkaloid, see: Kuehne, M. E.; Xu, F.; Brook, C. S. *J. Org. Chem.* **1994**, *59*, 7803−7806. See also ref 3.

(10) For the use of this photoisomerization in the synthesis of *Strychnos* alkaloids, see: (a) Amat, M.; Linares, A.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 6299−6312. (b) Gràcia, J.; Casamitjana, N.; Bonjoch, J.; Bosch, J. *J. Org. Chem.* **1994**, *59*, 3939−3951. For the use of this process in the construction of the anilinoacrylate moiety present in other groups of indole alkaloids, see: (c) Overman, L. E.; Sworin, M.; Burk, R. M. *J. Org. Chem.* **1983**, *48*, 2685−2690. (d) Wenkert, E.; Porter, B.; Simmons, D. P. *J. Org. Chem.* **1984**, *49*, 3733−3742.

(11) Hu, W.-L.; Zhu, J.-P.; Hesse, M. *Planta Med.* **1989**, *55*, 463−466. See also ref 9b.

(12) We are indebted to Professor Georges Massiot (University of Reims) for providing us with an authentic sample of natural akuammicine.

(13) Formylation (POCl$_3$, DMF, 50−60 °C) of dehydrotubifoline **3** to the *N*-formyl derivative **5** has been previously reported (no yield indicated): see ref 3.

(14) Lenz, G. R. *Synthesis* **1978**, 489−518.

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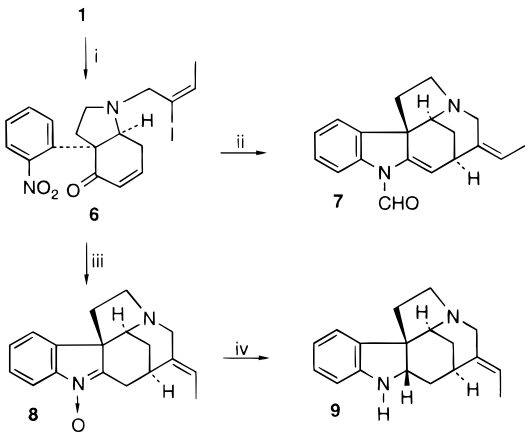
Scheme 2[a]



[a] Key: (i) (*E*)-$BrCH_2CI{=}CHCH_3$, anhyd K_2CO_3, CH_3CN, rt, 3h, 60%; (ii) $Ni(COD)_2$ (6.6 equiv), Et_3N, LiCN (10 equiv), 2.5:1 $CH_3CN-DMF$, rt, 2.5 h, then $(CH_3)_2N^+{=}CHCl\ Cl^-$ (20 equiv), rt, 2 h, 20%; (iii) $Ni(COD)_2$ (6.6 equiv), Et_3N, CH_3CN, rt, 2.5 h, 53%; (iv) $Ni(COD)_2$ (4 equiv), Et_3N, LiCN (8 equiv), 3.5:1 $CH_3CN-DMF$, rt, 2.5 h, 40%.

deformylated indolenine **3**. The ^1H NMR spectrum (300 MHz) of our synthetic (±)-norfluorocurarine was identical to that reported for the alkaloid.[16]

The potential and flexibility of this methodology for the construction of the pentacyclic curan skeleton was evident when the above one-pot treatment [$Ni(COD)_2$/LiCN/$Me_2N^+{=}CHCl\ Cl^-$] was applied to the (*E*)-vinyl iodide **6** to give the pentacyclic *N*-formylenamine **7** in 20% yield (Scheme 2). The constitution and relative configuration of **7** was unambiguously established from its ^1H and ^{13}C NMR data,[17] with the aid of 2D-NMR experiments and ROESY. These data are clearly different from those reported for bharhingine, an alkaloid isolated from *Rhazya stricta*,[18] for which the structure **7** had been proposed. So, a revised structure for the alkaloid is needed.[19]

However, when vinyl iodide **6** was treated with $Ni(COD)_2$ under the conditions satisfactorily used for the cyclization of **2** to **3** [$Ni(COD)_2$ (6.6 equiv), Et_3N, LiCN (10 equiv), 2.5:1 $CH_3CN-DMF$, rt, 2.5 h], a complex mixture was obtained instead of the expected pentacyclic indolenine. The crude reaction mixture (TLC) showed the clean formation of a new product, but after the workup a complex mixture was formed. In contrast, indicating that the above result is a consequence of the instability of the pentacyclic indolenine rather than to a failure of the cyclization, when the $Ni(COD)_2$-promoted double cyclization of **6** was performed in the absence of LiCN, the pentacyclic nitrone **8** was isolated in 53% yield. Under these conditions, not only the double cyclization [vinyl halide/alkene−α-(*o*-nitrophenyl) ketone] but also an alkene isomerization[20] to the natural *E* configuration for the ethylidene substituent[21] occurs in a single synthetic step in more than acceptable yield (53%). The formation of nitrone **8**, which was identical to that formed from **2** when the cyclization was carried out in the absence of lithium cyanide,[5] further illustrates the effect of LiCN in modulating the $Ni(COD)_2$-promoted reductive cyclization of α-(*o*-nitrophenyl) ketones either to the nitrone or the imine (indolenine) functionality. Interestingly, a further treatment of nitrone **8** with $Ni(COD)_2$ in the presence of LiCN afforded the pentacyclic indoline **9** (19,20-didehydrotubifolidine) in 40% yield.[22]

In conclusion, the $Ni(COD)_2$-promoted double cyclization of 3a-(*o*-nitrophenyl)hexahydroindol-4-ones constitutes a straightforward and flexible method for assembling the pentacyclic ABCDE ring system of *Strychnos* alkaloids that may be applicable to the synthesis of the most complex alkaloids of this group.

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Supporting Information Available: Experimental details for the preparation of all new compounds and copies of their ^1H and ^{13}C NMR spectra (18 pages).

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(15) (a) For the isolation of (±)-norfluorocurarine, see: Rakhimov, D. A.; Malikov, V. M.; Yusunov, C. Y. *Khim. Prir. Soedin* **1969**, *5*, 461−462; *Chem. Abstr.* **1970**, *72*, 67165n. (b) For the only previous synthesis of this racemic alkaloid, see: Crawley, G. C.; Harley-Mason J. *J. Chem. Soc., Chem. Commun.* **1971**, 685−686.

(16) Clivio, P.; Richard, B.; Deverre, J.-R.; Sevenet, T.; Zeches, M.; Le Men-Oliver, L. *Phytochemistry* **1991**, *30*, 3785−3792.

(17) Compound **7**: IR (film) 1685, 1656, 1462, and 1385 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) 1.43 (dm, 1H, J = 11.8 Hz, H-14), 1.64 (d, 3H, J = 7.7 Hz, H-18), 1.72 (ddd, 1H, J = 12.8, 6.9, 5.9 Hz, H-6), 2.12 (m, 1H, H-14), 2.75 (dt, 1H, J = 10.7, 6.6 Hz, H-6), 2.84−3.04 (m, 1H, H-5), 3.02 (dt, 1H, J = 11.2, 7 Hz, H-5), 3.13 (m, 1H, H-15), 3.18 (d, 1H, J = 14.6 Hz, H-21), 3.63 (d, 1H, J = 14.6 Hz, H-21), 4.03 (m, 1H, H-3), 5.49 (qd, 1H, J = 6.8, 1.2 Hz, H-19), 6.07 (dm, 2/3H, J = 6 Hz, H-16), 6.73 (broad, 1/3H, H-16), 7.18 (td, 1H, J = 7.5, 1.1 Hz, H-10), 7.28 (td, 1H, J = 7.7, 1.4 Hz, H-11), 7.39 (d, 1H, J = 7.7 Hz, H-9), 7.50 and 8.06 (2 broad, 1H, H-12), 8.92 and 9.26 (2 broad, 1H, H-17); ^{13}C NMR (acetone-d_6, 75 MHz, major rotamer) 13.0 (C-18), 29.1 (C-14), 36.2 (C-14), 41.8 (C-6), 46.7 (C-21), 53.4 (C-5), 54.2 (C-7), 59.7 (C-3), 114.4 (C-16), 116.3 (C-12), 120.3 (C-9), 121.4 (C-19), 125.7 (C-10), 128.2 (C-11), 137.0 (C-20), 141.3 (C-13), 146.2 (C-2), 157.8 (C-17); ^1H NMR ($CDCl_3$, 500 MHz) 1.50 (d, 1H, J = 8 Hz, H-14), 1.65 (d, 3H, J = 7 Hz, H-18), 1.96 (broad s, 1H, H-6), 2.21 (dt, 1H, J = 13.5, 3 Hz, H-14), 2.30 (broad s, 1H, H-6), 2.83 (broad s, 1H, H-5), 3.25 (broad s, 1H, H-15), 3.30−3.50 (m, 2H, H-5 and H-21), 3.75 (d, 1H, J = 15 Hz, H-21), 4.35 and 4.53 (2 broad s, 1H, H-3), 5.63 and 5.74 (2 broad s, 1H, H-19), 5.96 and 6.88 (2 broad s, 1H, H-16), 7.15 (t, 1H, J = 7.5 Hz, H-10), 7.26 (td, 1H, J = 7.5, 1 Hz, H-11), 7.34 (m, 1H, H-9), 7.30 and 8,07 (2 broad s, 1H, H-12), 8.83 and 9.09 (2 broad s, 1H, H-17); ^{13}C NMR ($CDCl_3$, 75 MHz, major rotamer) 13.1 (C-18), 28.1 (C-14), 34.2 (C-15), 40.4 (C-6), 46.0 (C-21), 52.6 (C-5), 53.3 (C-7), 58.9 (C-3), 114.1 (C-16), 116.2 (C-12), 120.4 (C-9), 125.3 (C-10 and C-19), 128.0 (C-11), 133.5 (C-8), 135.0 (C-20), 139.9 (C-13), 145.1(C-2), 156.7 (C-17); HRMS Calcd for $C_{19}H_{20}N_2O$ 292.1582, found 292.1577.

(18) Atta-ur-Rahman; Habib-ur-Rehman; Ahmad, Y.; Fatima, K.; Badar, Y. *Planta Med.* **1987**, *53*, 256−259.

(19) We thank Professor Atta-ur-Rahman for sending us detailed spectroscopic data of bharhingine.

(20) For alkene isomerizations in intramolecular palladium-catalyzed vinylations of olefins, see: (a) Owezarczyk, Z.; Lamaty, F.; Vawter, E. J.; Negishi, E. *J. Am. Chem. Soc.* **1992**, *114*, 10091−10092. (b) Rawal, V. H.; Michoud, C. *J. Org. Chem.* **1993**, *58*, 5583−5584.

(21) Bosch, J.; Bennasar, M. L. *Heterocycles* **1983**, *20*, 2471−2511.

(22) For a previous synthesis of 19,20-didehydrotubifolidine (**9**), see: Smith, G. F.; Wróbel, J. T. *J. Chem. Soc.* **1960**, 792−795.