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A New Solution for the Construction of the Piperidine Ring of *Strychnos* Alkaloids from 3a-(*o*-Nitrophenyl)hexahydroindol-4-ones. Total Syntheses of (±)-Tubifolidine, (±)-Dihydroakuammicine, and (±)-Akuammicine

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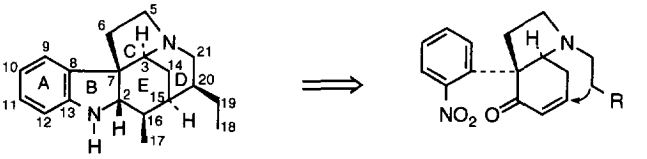
Abstract: Alkylation of *cis*-3a-(*o*-nitrophenyl)hexahydroindol-4-one **1** with 1-iodo-4-(trimethylsilyl)-2-butyne followed by BF_3·Et_2O-promoted cyclization of the resulting propargylic silane **2** afforded the tricyclic vinylidene ketone **3**, which was further converted to the *Strychnos* alkaloids tubifolidine, 19,20-dihydroakuammicine, and akuammicine.

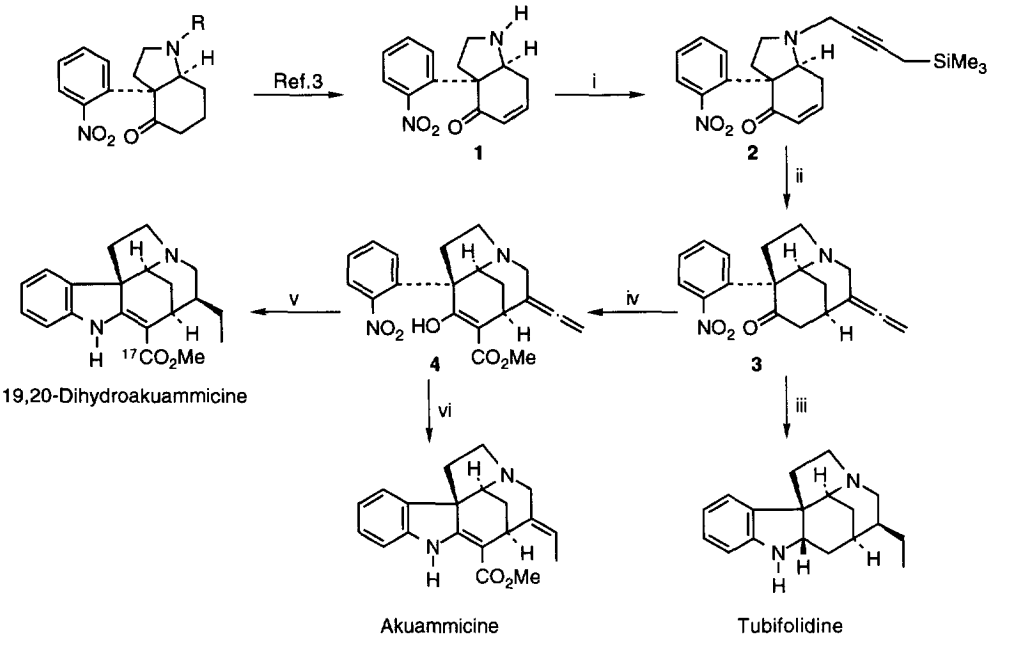
cis-3a-(*o*-Nitrophenyl)octahydroindol-4-ones[1] have proved to be useful building blocks for assembling the pentacyclic ABCDE ring system of *Strychnos* alkaloids.[2] After generation of an enone functionality,[3] closure of the bridged piperidine D ring (bond formed C_{15}-C_{20})[4] has been accomplished either by an intramolecular Michael addition[3] or by nickel(0)-promoted cyclization of a vinyl halide.[5,6] Subsequent or concomitant reductive cyclization of the α-(*o*-nitrophenyl) ketone moiety completes the pentacyclic *Strychnos* system.



Curan skeleton

In this letter we present an alternative procedure for the formation of the crucial C_{15}-C_{20} bond of *Strychnos* alkaloids from 3a-(*o*-nitrophenyl)hexahydroindol-4-one **1**. It is based on the intramolecular conjugate addition of a propargylic silane to the α,β-unsaturated ketone moiety (Scheme 1).[7]

Thus, alkylation of *cis*-3a-arylhexahydroindol-4-one **1**[3] with 1-iodo-4-(trimethylsilyl)-2-butyne[8] led to the propargylic silane **2**, which, upon treatment with BF_3·Et_2O, underwent a smooth cyclization to give the key tricyclic ketone **3**[9] in 55% overall yield.[10] This cyclization constitutes the first application of this



Scheme 1. *Reagents and Conditions*: (i) $ICH_2C{\equiv}CCH_2SiMe_3$, K_2CO_3, butanone, 80 °C, 5 h, 65%. (ii) $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 20 h, 84%. (iii) H_2, 10% Pd/C, Na_2CO_3, MeOH, 18h, 60%. (iv) LDA (2.5 equiv), HMPA (5 equiv), anhyd THF, -78 °C, then $NCCO_2Me$, rt, 30%. (v) H_2, 10% Pd/C, Na_2CO_3, MeOH, 18h, 57%. (vi) HCl, then H_2, 10% Pd/C, MeOH, 100 psi, 1h 15 min, 38%.

methodology of ring closure to the elaboration of a 2-azabicyclo[3.3.1]nonane nucleus.[11] Catalytic hydrogenation of a methanolic solution of **3** in the presence of Pd on charcoal brought about both the reductive cyclization of the α-(*o*-nitrophenyl) ketone moiety and the stereoselective reduction of the vinylidene side chain to give (±)-tubifolidine[12,13] in 60% yield. The use of PtO_2 as the catalyst was less efficient from the synthetic standpoint, and the best result (48% yield of isolated tubifolidine) was obtained operating from **3**·hydrochloride using ethyl acetate as the solvent.[14]

For the synthesis of the *Strychnos* alkaloids with the curan skeleton, which bear an oxidized one-carbon substituent (C-17) linked at C-16, the tricyclic ketone **3** was treated with LDA and then with methyl cyanoformate[15] to give β-keto ester **4**[16] in 30% yield (not optimized).[17] Catalytic hydrogenation of **4** in the presence of Pd on charcoal gave (±)-19,20-dihydroakuammicine in 57% yield.[12,18] Interestingly, when the above hydrogenation was carried out from **4**·hydrochloride for a short time, a 3:1 mixture of (±)-akuammicine (pseudoakuammicine)[19,20] and (±)-19,20-dihydroakuammicine was obtained in 50% yield.

The above results not only provide new solutions for the construction of the piperidine ring of *Strychnos* alkaloids from 3a-(*o*-nitrophenyl)hexahydroindol-4-ones but also further illustrate the usefulness of the strategy for indole alkaloid synthesis based on the elaboration of the indole ring in a late synthetic stage.[21] The C-20 vinylidene side chain of **3** might be further elaborated into the variety of functionalized two-carbon substituents present at C-20 in *Strychnos* alkaloids.

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9. **3**: ^{1}H NMR ($CDCl_3$, 200 MHz) 2.26-2.38 (m, 3H), 2.68 (d, 2H, J = 4 Hz), 2.92-3.10 (m, 4H), 3.25 (m, 1H), 3.62 (dt, 1H, J = 14, 2.4 Hz), 3.95 (broad s, 1H), 4.75 (dd, 2H, J = 4.9, 2.4 Hz), 7.38-7.55 (m, 4H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 25.4 (C-14), 31.8 (C-15), 38.9 (C-6), 46.5 (C-16), 49.7 (C-21), 54.9 (C-5), 62.2 (C-7), 65.0 (C-3), 76.1 (C-18), 99.8 (C-20), 125.1 (C-12), 127.9 (C-11), 129.1 (C-9), 132.0 (C-10), 133.8 (C-8), 150.9 (C-13), 203.5 (C-19), 210.1 (C-2); IR (film) 1950, 1699, 1532, 1366 cm^{-1}; HRMS Calcd for $C_{18}H_{18}N_2O_3$ 310.1325, found 310.1317.
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14. The complete reduction (PtO_2) of the α-(*o*-nitrophenyl) ketone moiety of **3** was slower in ethanolic solution and, after longer reaction times (≈ 40h), N_a-ethyltubifolidine was isolated as the major product (20%).
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16. **4**: ^{1}H NMR ($CDCl_3$, 300 MHz) 2.07 (t, 2H, *J* = 3.2 Hz, H-14), 2.43 (ddd, 1H, *J* = 15.2, 7.6, 3.5 Hz, H-6), 2.71 (dt, 1H, *J* = 14.8, 7.4 Hz, H-6), 2.96 (ddd, 1H, *J* = 11.8, 7.6, 3.5 Hz, H-5), 3.16 (dt, 1H, *J* = 13, 4 Hz, H-21), 3.15-3.27 (m, 1H, H-5), 3.55 (d, 1H, *J* = 13.4 Hz, H-21), 3.62 (broad s, 1H, H-15), 3.83 (s, 3H, OCH_3), 3.91 (broad s, 1H, H-3), 4.70 (dd, 1H, *J* = 11.1, 3 Hz, H-18), 4.75 (dd, 1H, *J* = 11.1, 3 Hz, H-18), 7.30-7.45 (m, 2H), 7.45-7.55 (m, 2H), 12.6 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 75.4 MHz) 24.1 (C-14), 30.5 (C-15), 36.4 (C-6), 48.3 (C-21), 52.0 (OMe), 54.8 (C-5), 55.3 (C-7), 65.2 (C-3), 75.2 (C-18), 97.1 (C-20), 102.5 (C-16), 124.8 (C-12), 127.8 (C-11), 131.1 (C-9), 132.0 (C-10), 133.6 (C-8), 150.9 (C-13), 172.2 (C-2), 172.8 (C-17), 203.2 (C-19); IR (film) 1650, 1611, 1530, 1363, 1246 cm^{-1}.
17. The corresponding *O*-acylated product was formed in ≈ 5% yield in some runs. Unreacted starting ketone was recovered to a considerable extent (30%).
18. For the only previous synthesis of 19,20-dihydroakuammicine, see reference 12.
19. Akuammicine was identified by comparison of its ^{1}H NMR (300 MHz) spectral data with those reported for the natural product: (a) Hu, W.-L.; Zhu, J.-P.; Hesse, M. *Planta Med.* **1989**, *55*, 463-466. (b) Kuehne, M.E.; Xu, F.; Brook, C.S. *J. Org. Chem.* **1994**, *59*, 7803-7806. The R_f values of our synthetic akuammicine in several solvent mixtures were also coincident with those of an authentic sample of the alkaloid kindly provided by Professor Georges Massiot (University of Reims).
20. For previous syntheses of this racemic alkaloid, see references 5b, 15, and 19b.
21. Knight, S.D.; Overman, L.E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1995**, *117*, 5776-5788. See also references 3, 5, and 15.

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