Pergamon

Tetrahedron Letters, Vol. 35, No. 38, pp. 7123-7126, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01474-4

Short Formal Syntheses of Indole Alkaloids of the Uleine and *Strychnos* Groups

Mercedes Amat, Swargam Sathyanarayana, Sabine Hadida, and Joan Bosch

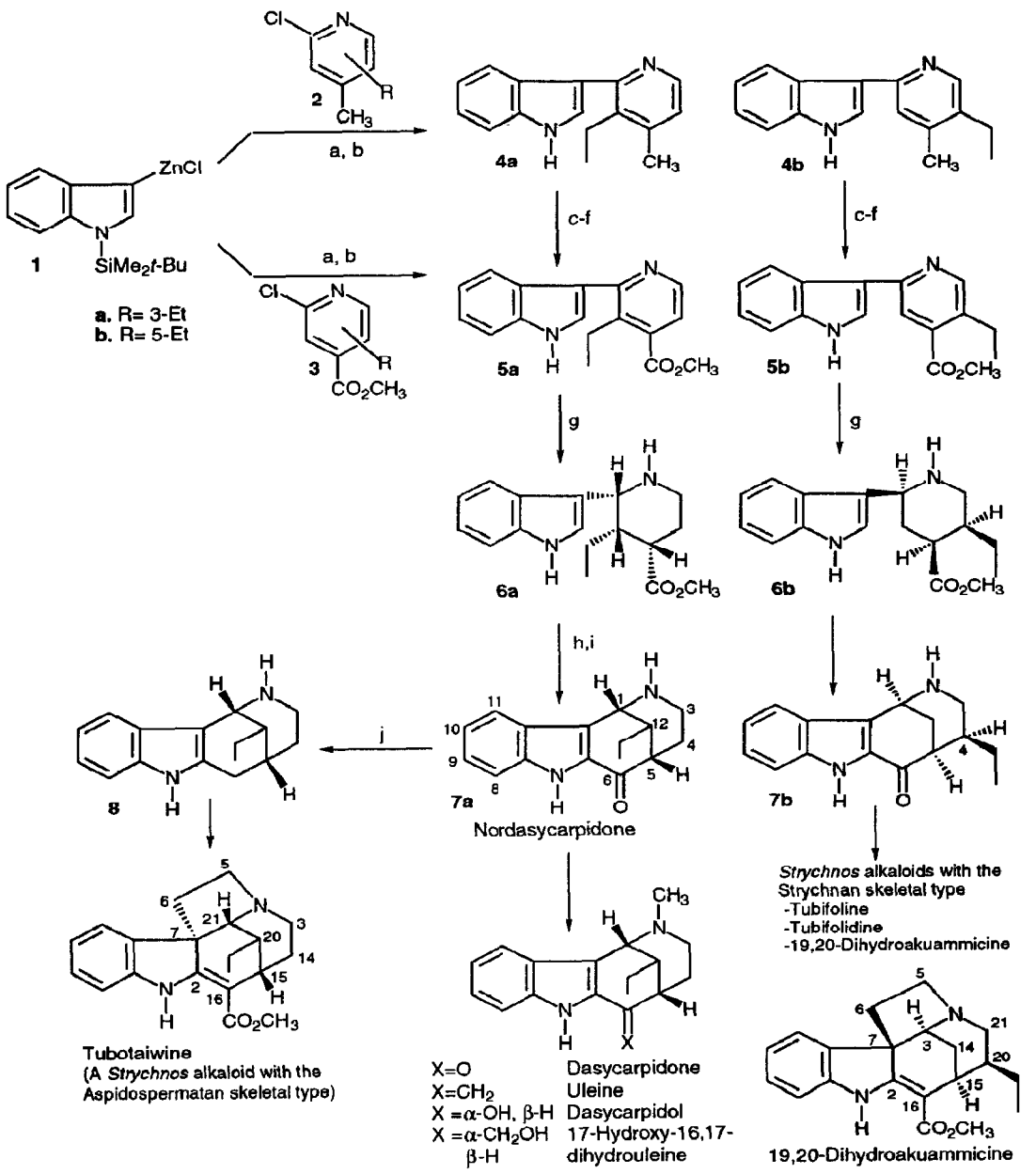
Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona,
08028-Barcelona, Spain

Abstract: The formal synthesis of uleine-type (dasycarpidone, dasycarpidol, uleine, and 17-hydroxy-16,17-dihydrouleine) and *Strychnos* alkaloids belonging to both the Strychnan (tubifoline, tubifolidine, and 19,20-dihydroakuammicine) and Aspidospermatan (tubotaiwine) skeletal types from 3-(2-pyridyl)indoles is described.

The 3-(2-piperidyl)indole moiety is present in a large number of indole alkaloids belonging to different skeletal types such as Strychnan, Aspidospermatan, and Plumeran, as well as in the alkaloids of the uleine group.[1] In a previous work we have reported a simple, efficient, and general method for the synthesis of 3-(2-pyridyl)indoles[2] based on the palladium(0)-catalyzed cross-coupling of 1-(*tert*-butyldimethylsilyl)-3-indolylzinc chloride (**1**) with 2-halopyridines.[3] For instance, heteroarylation of **1** with a nearly equimolecular mixture of 2-chloro-3-(and 5-)ethyl-4-methylpyridines, **2a** and **2b** respectively, followed by deprotection of the indole nitrogen, afforded (88% overall yield) the corresponding 3-(2-pyridyl)indoles **4a** and **4b**, which could be easily separated by column chromatography.

We illustrate here the potential of this method for the synthesis of indole alkaloids. Thus, compound **4a** was converted to ester **5a** in 59% overall yield through a four-step sequence consisting in the protection of the indole nucleus as an N-benzenesulfonyl derivative, oxidation of the methyl substituent with SeO_2 in pyridine, deprotection of the indole nitrogen, and, finally, esterification with methanol. All attempts to directly oxidize the methyl substituent of **4a**, without protection of the indole ring, were unsuccessful. Similarly, the 5-ethyl isomer **4b** was converted to the ester **5b** in 61% overall yield. Moreover, esters **5a** and **5b** were prepared in a more straightforward manner by Pd(0)-catalyzed heteroarylation of the indolylzinc derivative **1** with a mixture of methyl 2-chloro-3-(and 5-)ethylpyridine-4-carboxylates[4] **3a** and **3b**, followed by desilylation with a catalytic amount of *p*-TsOH in ethanol. In this manner, esters **5a** and **5b** were obtained in 85% yield as a 1:1 mixture and were easily separated by column chromatography.

Catalytic hydrogenation of pyridine **5b** hydrochloride stereoselectively afforded the all-*cis*-piperidine **6b**[5] in 65% yield. A mixture of this piperidine and other stereoisomers had been previously cyclized[6] to tetracycle **7b** (and the corresponding C-4 epimer) and then converted[7] to the *Strychnos* alkaloids with the Strychnan skeletal type, tubifoline, tubifolidine, and 19,20-dihydroakuammicine.



(a) $Cl_2Pd(Ph_3P)_2$, DIBAH, reflux; (b) *p*-TsOH, EtOH, reflux; (c) $ClSO_2C_6H_5$, Bu_4NHSO_4, aqueous NaOH, C_6H_6, r.t. ; (d) SeO_2, pyridine, 95°C; (e) aqueous NaOH, EtOH, reflux; (f) MeOH, H_2SO_4, r.t. ; (g) HCl, MeOH and then H_2, PtO_2; (h) $Ba(OH)_2$, dioxane, reflux; (i) PPA, 85-90°C; (j) $LiAlH_4$, dioxane, reflux.

Similarly, pyridine **5a** hydrochloride was hydrogenated following the conditions reported by Kametani[8] to stereoselectively give the all-*cis*-piperidine **6a**[5] in 60% yield. Alkaline hydrolysis of ester **6a** followed by cyclization of the resulting piperidine-4-carboxylic acid with PPA led to (±)-nordasycarpidone[8,9] (**7a**) in 36% yield. Taking into account previous correlations,[8,10] this constitutes a formal total synthesis of the alkaloids dasycarpidone, dasycarpidol, uleine, and 17-hydroxy-16,17-dihydrouleine as well as a notable improvement with regard to previous syntheses for the alkaloids of the uleine group.

Finally, $LiAlH_4$ reduction of (±)-nordasycarpidone (**7a**) gave tetracycle **8**, from which we have recently reported the synthesis of tubotaiwine,[11] a *Strychnos* alkaloid with the Aspidospermatan skeletal type.

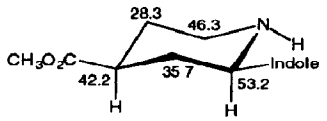
In summary, from 3-(2-pyridyl)indoles **4** and **5** we have reported formal total syntheses of alkaloids of the uleine and *Strychnos* groups, the latter with either the Strychnan or Aspidospermatan skeletal types.

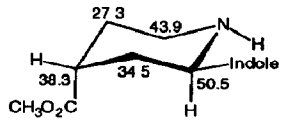
Acknowledgement

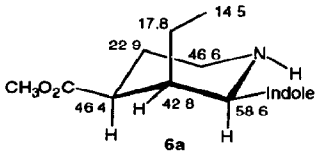
Financial support from the "Direcección General de Investigación Científica y Técnica", Spain (project PB91-0800) and the "Comissionat per a Universitats i Recerca", Generalitat de Catalunya (project GRQ93-1.059) is gratefully acknowledged. S. S. thanks the "Comisión Interministerial de Ciencia y Tecnología", Spain, for providing a postdoctoral fellowship.

References and Notes

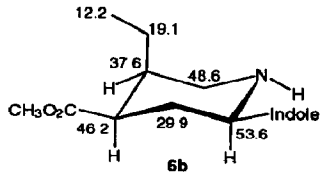
1. Kisakürek, M. V.; Leeuwenberg, A. J. M.; Hesse, M. In *Alkaloids: Chemical and Biological Perspectives* Pelletier, S. W., Ed.; Chapter 5, John Wiley & Sons, 1983, New York.
2. Amat, M.; Hadida, S.; Bosch, J. *Tetrahedron Lett.* **1994**, *35*, 793.
3. For other similar approaches, see: a) Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1994**, *35*, 2405. b) Sakamoto, T.; Kondo, Y.; Takazawa, N.; Yamanaka, H. *Tetrahedron Lett.* **1993**, *34*, 5955.
4. a) 2-Chloropyridines **3a** and **3b** were prepared as a nearly equimolecular mixture in 67% yield by treatment of methyl 3-ethyl-4-pyridinecarboxylate *N*-oxide[4b] with $POCl_3$. b) Kametani, T.; Suzuki, T. *J. Org. Chem.* **1971**, *36*, 1291.
5. The stereochemical assignment of all-*cis*-piperidines **6a** and **6b** was effected by comparison of their ^{13}C-NMR data with the data of the *cis* and *trans* isomers of methyl 2-(3-indolyl)-4-piperidinecarboxylate.







6a



6b

The chemical shifts of the piperidine carbons are in agreement with a *cis* relationship between the indolyl and methoxycarbonyl substituents. Furthermore, the signals corresponding to C-5 in **6a** and to C-3 in **6b** are shifted upfield due to the steric effect of the axial ethyl substituent.

6a: ^{1}H-NMR ($CDCl_3$) 0.30 (t, *J*= 7.5 Hz, 3H, CH_3CH_2); 1.20 and 1.50 (2m, 2H, CH_2CH_3); 1.70-2.00 (cs, 3H, H-5_{ax}, H-5_{eq}, and NH); 2.36 (m, 1H, H-3_{eq}); 2.78-2.89 (cs, 2H, H-4_{ax} and H-6_{ax}); 3.27 (ddd, *J*= 12.0, 4.3 and 2.3 Hz, 1H, H-6_{eq}); 3.69 (s, 3H, CH_3O); 4.20 (d, *J*= 2.5 Hz, 1H, H-2_{ax}); 7.10-7.25 (m, 3H, H-2', H-5', and H-6'); 7.38 (dm, *J*= 7.0 Hz, 1H, H-7'); 7.68 (dm, *J*= 6.6 Hz, 1H, H-4'); 8,18 (bs, 1H, NH).

6b: ^{1}H-NMR ($CDCl_3$) 0.94 (t, *J*= 7.5 Hz, 3H, CH_3CH_2); 1.20 and 1.75 (2m, 2H, CH_2CH_3); 1.83-2.10 (cs, 4H, H-3_{ax}, H-3_{eq}, H-5_{eq}, and NH); 2.81 (m, 1H, H-4_{ax}); 2.93 (dd, *J*= 12.5 and 1.8 Hz, 1H, H-6_{ax}); 3.25 (dd, *J*= 12.5 and 1.8 Hz, 1H, H-6_{eq}); 3.69 (s, 3H, OCH_3); 3.96 (dd, *J*= 10.0 and 4.4 Hz, 1H, H-2_{ax}); 7.00-7.20 (cs, 3H, H-2', H-5', and H-6'); 7.30 (dm, *J*= 7.0 Hz, 1H, H-7'); 7.70 (dm, *J*= 6.6 Hz, 1H, H-4'); 8.32 (bs, 1H, NH).

6. Bosch, J.; Rubiralta, M.; Domingo, A.; Bolós, J.; Linares, A.; Minguillón, C.; Amat, M.; Bonjoch, J. *J. Org. Chem.* **1985**, *50*, 1516.
7. Amat, M.; Linares, A.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 6299.
8. Kametani, T.; Suzuki, T. *Chem. Pharm. Bull.* **1971**, *19*, 1424.
9. Minor amounts (9% yield) of the C-12 epimer were also isolated: ^{1}H-NMR ($CDCl_3$) 1.04 (t, *J*= 7.3 Hz, 3H, CH_3CH_2); 1.60 (dm, *J*= 13.5 Hz, 1H, H-4_{eq}); 1.82 and 2.10 (2m, 2H, CH_2CH_3); 1.90-2.05 (m, 1H, H-4_{ax}); 2.25 (m, 1H, H-12); 2.60-2.80 (m, 3H, 2H-3 and H-5); 4.88 (bs, 1H, H-1); 7.16 (t, *J*= 7.2 Hz, 1H, H-10); 7.37 (t, *J*= 7.5 Hz, 1H, H-9); 7.50 (d, *J*= 8.4 Hz, 1H, H-8); 7.72 (d, *J*= 8.1 Hz, 1H, H-11); 10.42 (bs, 1H, H-7). ^{13}C-NMR ($CDCl_3$) 11.6 (CH_3CH_2); 23.1 (CH_2CH_3); 23.3 (C-4); 37.1 (C-3); 44.6 (C-12); 45.9 (C-5); 47.3 (C-1); 113.0 (C-8); 120.7 (C-10); 121.0 (C-11); 124.1 (C-11b); 126.9 (C-9); 128.0 (C-11a); 133.4 (C-6a); 138.8 (C-7a); 195.4 (C=O).
10. a) Gràcia, J.; Casamitjana, N.; Bonjoch, J.; Bosch, J. *J. Org. Chem.* **1994**, *59*, 000. b) Blechert, S. *Liebigs Ann. Chem.* **1985**, 2073. c) Borris, R. P.; Lankin, D. C.; Cordell, G. A. *J. Nat. Prod.* **1983**, *46*, 206. d) Jackson, A.; Wilson, N. D. V.; Gaskell, A. J.; Joule, J. A. *J. Chem. Soc. (C)* **1969**, 2738. e) Joule, J. A.; Ohashi, M.; Gilbert, B.; Djerassi, C. *Tetrahedron* **1965**, *21*, 1717.
11. Gràcia, J.; Bonjoch, J.; Casamitjana, N.; Amat, M.; Bosch, J. *J. Chem. Soc., Chem. Commun.* **1991**, 614.

(*Received in UK* 6 *July* 1994; *revised* 26 *July* 1994; *accepted* 29 *July* 1994)