Pergamon

Tetrahedron Letters 41 (2000) 3489–3492

TETRAHEDRON LETTERS

Indole alkaloids by a chemoenzymatic approach: two convergent routes for the first enantioselective synthesis of (+)-20*R*-15,20-dihydrocleavamine

Bruno Danieli, Giordano Lesma,* Daniele Passarella and Alessandra Silvani

Dipartimento di Chimica Organica e Industriale, Università degli Studi di Milano, Centro CNR di Studio per le Sostanze Organiche Naturali, via Venezian 21-20133 Milano, Italy

Received 1 February 2000; accepted 7 March 2000

Abstract

A stereocontrolled total synthesis of the title compound is described, starting from enantiopure intermediates. Two alternative strategies have been developed to ensure the critical formation of the nine-membered ring of **3**.

Our continuing interest in the enantioselective synthesis of indole alkaloids by a chemoenzymatic approach[1] led us to explore the enzymatic desymmetrization of some *meso*-piperidine-3,5-dimethanols and their diacetates. By this method, the enantiopure, advanced derivatives **1** and **2** (Fig. 1) were provided in both enantiomeric forms and they are presently under investigation as potentially useful intermediates for the asymmetric synthesis of *Iboga* alkaloids possessing the tacaman or the *pseudo*-aspidosperma skeleton. In this communication we report the preliminary results of our study on the first enantioselective synthesis of (+)-20*R*-15,20-dihydrocleavamine **3**,[2] a tetracyclic alkaloid structurally related to 16-β-carbomethoxyvelbanamine, the indole 'upper half' of the antitumoral bisindole alkaloids occurring in *Catharantus roseus*, such as vinblastine and vincristine. Our plan for the construction of the dihydrocleavamine framework starting from **1** and **2**, was based upon two convergent strategies, as outlined in Fig. 1, wherein the construction of the central nine-membered C-ring plays a key role.

In the approach *a* (Fig. 1), we first planned the formation of the C(2)–C(16) bond of **3** (biogenetic numbering), by coupling tryptophol, in a Pictet–Spengler-like reaction, with a piperidine **A**, derived from **1**, bearing a masked aldehyde function. Then a N(4)→C(5) intramolecular alkylation would complete the construction of the C-ring. In this strategy, we decided to postpone the elaboration of the C(20) side chain of **3** until the later stages of the synthesis. In this way, the required chirality at C(20) and C(14) of **3** depended upon the stereogenic centres at C(3)-*R* and C(5)-*R* (piperidine numbering) of **1**, respectively.

* Corresponding author.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00404-4

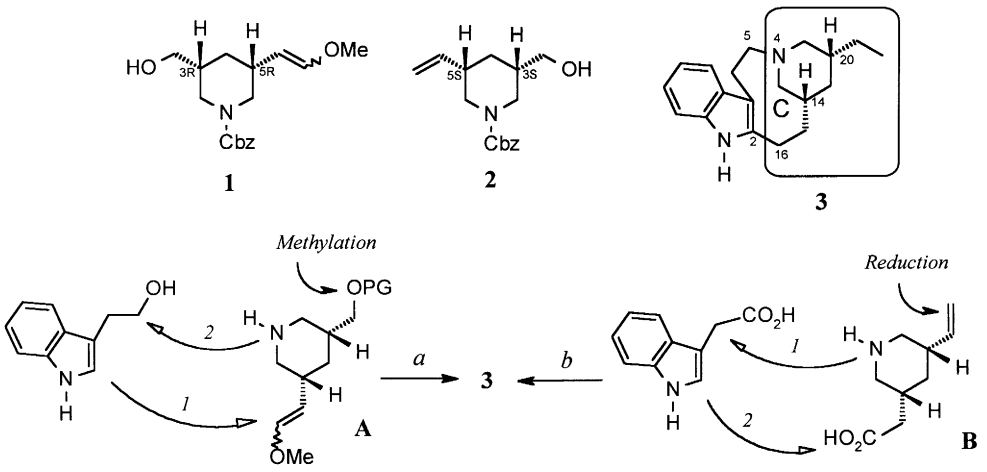
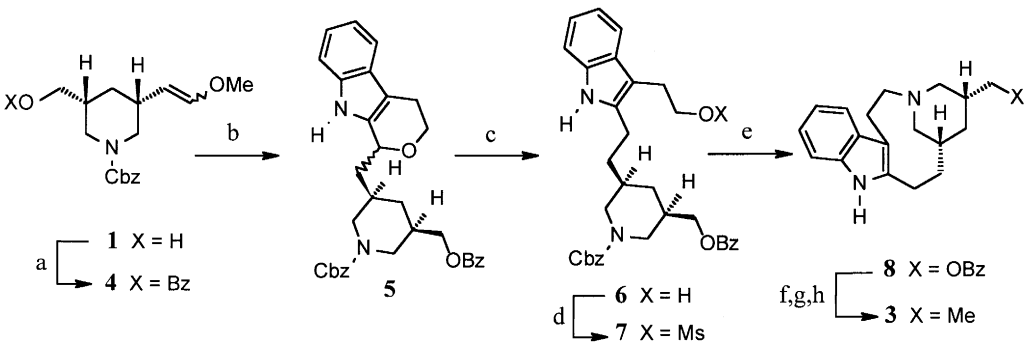


Fig. 1.

In a different approach (*b*, Fig. 1), the first stage of the synthesis would be the formation of the C(5)–N(4) bond of **3**, by coupling indoleacetic acid with a suitable piperidine **B**, derived from **2**. After elongation of the C(3) side-chain to a carboxymethylene group, an intramolecular Friedel–Crafts acylation with the formation of the C(2)–C(16) bond of **3** would afford the nine-membered ring. As a consequence of this sequence, the chirality at C(14) and C(20) of **3** results from that at positions C(3)-*S* and C(5)-*S* of **2**, respectively.

It should be noted that the overall strategy would allow the conversion of both the intermediates **1** and **2**, of opposite configuration at the stereogenic centres, into the same chiral product, by complementary modifications of the two different functional groups in the C(3) and C(5) side chains.

In the first synthetic pathway (Scheme 1) the fully protected piperidine **4** was initially prepared smoothly by benzoylation of **1**. Building on the precedent reported by Wilson et al.,[3] we then developed an efficient procedure for the installation of the indole unit which took advantage of the enol methyl ether function present in **4**. In the event, treatment of **4** with tryptophol in the presence of a catalytic amount of TFA and of 4 Å molecular sieves, cleanly generated the tricyclic indole derivative **5** in 74% yield, which was isolated as an inseparable 1:1 mixture of diastereoisomers.

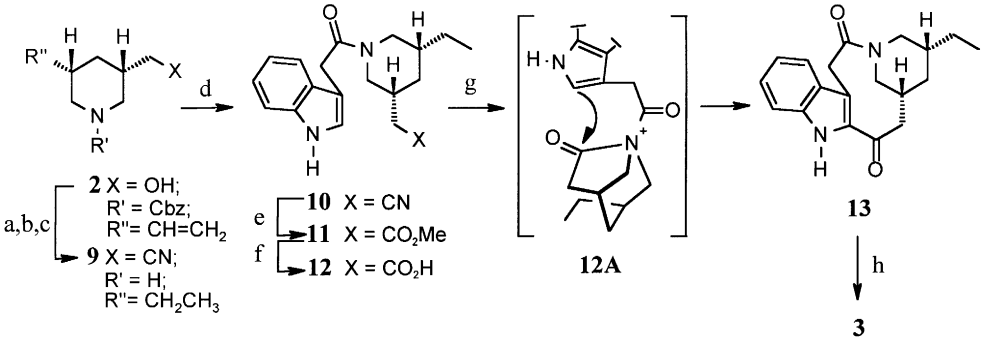


Scheme 1. *Reagents and conditions*: (a) BzCN, DIPEA, CH_2Cl_2, rt, 98%; (b) tryptophol, TFA (0.13 mol equiv.), 4 Å mol. sieves, CH_2Cl_2, rt, 45 h, 74%; (c) Et_3SiH, CF_3SO_3H, CH_2Cl_2, −50°C, 6 h, 44%; (d) MsCl, DIPEA, CH_2Cl_2, rt, 3 h, 98%; (e) H_2, 5% Pd(C), EtOAc, rt, 17 h, then chlorobenzene, DIPEA, reflux, 4 h, 28%; (f) NaOH, MeOH/H_2O, rt; (g) TsCl, DIPEA, CH_2Cl_2, rt, 6 h; (h) CuI, MeLi, Et_2O, −40°C, 62% from **8**

The ring opening to give the C(2)-substituted tryptophol derivative **6**, proved challenging. Most of the available methods for this reduction, based on the use of boron hydrides in acidic conditions [e.g. $NaBH_4$/TFA;[4] $NaBH_3CN/ZnI_2$;[5] $NaBH_4/PdCl_2$[6]], were also known to reduce indole systems to the corresponding 2,3-dihydroderivatives, and indeed when we examined a few of these procedures, they did not provide regioselective control in the reduction of **5**. Turning our attention to other reducing systems, the required **6** was finally accessed by the action of Et_3SiH/CF_3SO_3H, following the protocol described by Olah et al.[7] The reaction required 6 h at −50°C and provided **6** in 44% yield.

The final cyclization step required the conversion of the hydroxy group of **6** into a leaving group, followed by N(4)-deprotection and subsequent intramolecular nucleophilic displacement. Treatment of **6** with mesyl chloride gave the sensitive mesylate **7** in almost quantitative yield, which upon hydrogenation over 5% Pd(C) followed by heating in refluxing chlorobenzene, afforded the tetracyclic derivative **8**, albeit in only 28% yield. Finally, **8** was converted into (+)-20*R*-15,20-dihydrocleavamine **3**[8] as a single enantiomer ($[\alpha]_D$=130, *c* 0.1, $CHCl_3$; lit.[2] $[\alpha]_D$=133, *c* 0.078, $CHCl_3$), in 62% overall yield by a three-step sequence involving hydrolysis of benzoate, tosylation and displacement of the tosylate with lithium dimethylcuprate.

Evidently, the most notable difficulty of achieving our target resided in the formation of the nine-membered ring. Therefore, in our second synthetic approach (*b*, Fig. 1), we looked to an intramolecular acylation strategy, which was well precedented in the *Aspidosperma* alkaloid synthetic area,[9] although variable yields have been reported. It must be noted[9a] (Scheme 2) that the presence of the amidic piperidine nitrogen should play a key role for the success of this transformation. The tight coordination of N(4) with the transient acylium ion at C(16) would provide the 'activated' intermediate **12A**, and the consequent cyclization of a six-membered ring, so as to reduce the entropy of the system at the transition state.



Scheme 2. *Reagents and conditions*: (a) CBr_4, TPP, CH_2Cl_2, rt, 3 h, 88%; (b) Bu_4NCN, CH_2Cl_2, rt, 3 h, 85%; (c) H_2, 5% Pd(C), EtOH, 24 h, 80%; (d) indoleacetic acid, TEA, DPPA, acetonitrile, rt, 6 h, 81%; (e) HCl(g), MeOH, rt, 4 h, then H_2O, 93%; (f) NaOH, MeOH/H_2O, 50°C, 3 h, 81%; (g) PPE, $CHCl_3$, 60°C, 4 h, 32%; (h) LAH, dioxane reflux, 8 h, 42%

The cyanopiperidine **9** was readily prepared from the (3*S*,5*S*)-benzyl-3-(hydroxymethyl)-5-(ethenyl)-1-piperidinecarboxylate **2**, via the bromo derivative, according to the procedure described by Starks,[10] followed by hydrogenation. Upon treatment with indoleacetic acid in the presence of diphenylphosphoryl azide and Et_3N, **9** underwent smooth amidation to give the indolepiperidine **10**. In order to effect the subsequent cyclization, the nitrile **10** was first converted into the amido ester **11**, and then, upon hydrolysis with NaOH, into the amido acid **12**, in almost quantitative yield. In spite of the large variety of methods (e.g., PPA;[9a,b] Ph_3PO-Tf_2O;[11] PPSE;[12] $SnCl_4/CH_2Cl_2$) attempted to induce the crucial intramolecular Friedel–Craft acylation, only the protocol reported by Hanaoka et al.[9c] (PPE, $CHCl_3$, 60°C) succeeded in giving **13** in acceptable yields (32%). When treated with LAH[9] in refluxing dioxane,

the ketolactam **13** underwent clean reduction of both amide and carbonyl functions, furnishing the optically active (+)-20*R*-15,20-dihydrocleavamine **3** ($[\alpha]_D$=128, *c* 0.1, $CHCl_3$),[8] in 14% overall yield from **12**, identical in all respects to the natural compound.

The convergent strategies described herein provide possible solutions to the enantioselective construction of the unusual dihydrocleavamine tetracyclic framework, which is possible to achieve in both of the enantiomeric forms. Further efforts, aimed at improving the yields in the formation of the nine-membered ring, are currently underway.

Acknowledgements

This work was supported by Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST).

References

1. (a) Danieli, B.; Lesma, G.; Passarella, D.; Silvani, A. *J. Org. Chem.* **1998**, *63*, 3492–3496; (b) Danieli, B.; Lesma, G.; Passarella, D.; Silvani, A. *Current Organic Chemistry* **2000**, *4*, 111–141, and references cited therein.
2. Van Beek, T. A.; Verpoorte, R.; Baerheim Svendsen, A. *Tetrahedron* **1984**, *40*, 737–748.
3. Wilson, R. M.; Farr, R. A.; Burlett, D. J. *J. Org. Chem.* **1981**, *46*, 3293–3302.
4. Ketcha, D. M.; Lieurance, B. A.; Homan, D. F. *J. Org. Chem.* **1989**, *54*, 4350–4356.
5. Lau, C. K.; Dufresne, C.; Langer, P. C.; Pietre, S.; Scheigetz, J. *J. Org. Chem.* **1986**, *51*, 3038–3043.
6. Satoh, T.; Mitsuo, N.; Nishiki, M.; Nanba, K.; Suzuki, S. *Chemistry Lett.* **1981**, 1029–1030.
7. Olah, G. A.; Arvanaghi, M.; Ohannessian, L. *Synthesis* **1986**, 770–772.
8. The spectroscopic data of synthetic (+)-20*R*-15,20-dihydrocleavamine were in complete agreement with those reported in the literature.[2]
9. (a) Ziegler, F. E.; Kloek, J. A.; Zoretic, P. A. *J. Am. Chem. Soc.* **1969**, *91*, 2342–2346; (b) Ziegler, F. E.; Bennett, G. B. *J. Am. Chem. Soc.* **1973**, *95*, 7458–7464; (c) Hanaoka, M.; Imanishi, T.; Nakai, A.; Yagi, N. *Chem. Pharm. Bull.* **1981**, 901–903.
10. Starks, C. M. *J. Am. Chem. Soc.* **1971**, *93*, 195–199.
11. Hendrickson, J. B.; Hussoin, Md. S. *J. Org. Chem.* **1989**, *54*, 1144–1149.
12. Angelastro, R.; Marquat, A. L.; Podlogar, B. L.; Huber, E. W.; Demeter, D. A.; Poet, N. P.; Weintraub, H. J. R. *J. Org. Chem.* **1994**, *59*, 2092–2100.