

Tetrahedron Letters 39 (1998) 2119-2122

TETRAHEDRON LETTERS

A New Approach to the Synthesis of Functionalized Pyrido[2,3-b]indoles by Way of a Palladium-Catalyzed Ring Closing Reaction between the N-1 and C-9a Positions

Ahmed Abouabdellah and Robert H. Dodd*

Institut de Chimie des Substances Naturelles, Centre National de la Recherche Scientifique, 91198 Gif-sur-Yvette Cedex, France

Received 17 November 1997; accepted 6 January 1998

Abstract: The enolate of 4-N-(tert-butyloxycarbonyl)aminobutyro- γ -lactone 9 reacted with 2-bromo-1methylindole-3-carboxaldehyde in the presence of stannic chloride to give the product of aldol condensation 16. Deprotection and dehydration of the latter with trifluoroacetic acid and dimethyl sulfide followed by Pd₂(dba)₃-catalyzed ring closing of the product afforded the α -carboline 6 in good overall yield. © 1998 Elsevier Science Ltd. All rights reserved.

The recent discoveries of the first examples of naturally occurring products having a pyrido[2,3b]indole (or α -carboline) nucleus have stimulated considerable interest in the synthesis of substituted derivatives of this class of compounds. These natural products include the cytotoxic grossularines 1 and 2, isolated from the marine tunicate *Dendroda grossularia* (Stylidae)¹ as well as mescengricin (3), isolated from



Streptomyces griseoflavus, ² which protects neurons against L-glutamate toxicity. Moreover, synthetic α -carbolines have also been found to be of therapeutic interest as demonstrated by the 4-amino-3-carboxylate derivative 4,³ a modulator of the GABA_A receptor of the central nervous system.

With few exceptions, recent methodologies for the preparation of α -carbolines of general formula 5 can be divided into two major classes as a function of the starting materials and the bonds formed in the final ring closing steps. In the first, α -carboline synthesis proceeds from a 3-substituted-2-amino indole derivative or an equivalent, masked form of an amine e.g., an azide or carboxylate group (the latter being converted to an amine *via* a Curtius reaction). Generation of the α -carboline nucleus thus depends on formation of the N-1/C-2 bond



Fax : 01 69 07 72 47 - e-mail : Robert.Dodd@icsn.cnrs-gif.fr

(a) in the final step. This strategy was successfully applied to the synthesis of grossularines 1 and 2 and their analogues⁴ as well as of the CNS agent 4 and its analogues.⁵ In the second pathway, the B-ring is produced in the final step by formation of the N-9/C-9a bond (b) after cross-coupling of an appropriately substituted pyridine with an aniline derivative. This methodology has also been used in approaches to the synthesis of grossularines 1 and 2,⁶ as well as for the synthesis of unsubstituted α -carbolines.⁷

In this communication, we wish to present an alternative and unprecedented approach to the preparation of substituted α -carbolines (in the form of the fused butyrolactone derivative 6, Scheme 1) which relies on the formation of the N-1/C-9a bond (c) in the critical ring generating step. The α -carboline 6 is a highly interesting target since hydrolysis of the γ -lactone ring can be expected to provide two modifiable functional groups at C-2 and C-3 (hydroxymethyl and carboxylic acid, respectively). Moreover, because it has been shown that the C-4 position of 3-carboxycarbolines can be easily substituted by a variety of electrophilic reagents using the techniques of ortho-directed metalation,⁸ the target α -carboline constitutes a potentially versatile precursor to more complex derivatives.

As shown from a retrosynthetic analysis (Scheme 1), we hypothesized that reaction of the enolate of an N-protected β -aminobutyro- γ -lactone (I) with an indole-3-carboxaldehyde (II) would provide the coupled product III. Unmasking of the amine function would then allow formation of the α -carboline 6 either by an intramolecular conjugate addition to C-2 of the indole nucleus (for X = H) or, failing that, by a coupling reaction in the presence of a suitable activating group at C-2 (e.g., X = halogen).



Scheme 1

X= H. Halogen

Our starting material for the synthesis of 6 was thus 4-N-benzylaminobutyro- γ -lactone (8, Scheme 2). The latter was prepared in 50% yield by the Michael addition of benzylamine (1.1 eq) to 2[5H]-furanone (7) in methanol (0°C, 24 h).^{9,10} In order to insure that the N-blocking group of the amino lactone could be easily removed prior to the last step of our proposed synthesis of 6, the N-benzyl derivative 8 was transformed in one step and in 80% yield to the N-Boc derivative 9 by catalytic (palladium on carbon) hydrogenolysis for 3 h in ethyl acetate in the presence of di-*tert*-butyl dicarbonate (1.1 eq).



With compound 9 in hand, the aldol reaction with an indole-3-carboxaldehyde was then studied. Aldol reactions of butyrolactone enolates with a limited number of carbonyl derivatives have recently been reported.¹⁰ However, neither reactions of enolates of butyro- γ -lactones (of any type) with indole carboxaldehydes nor formation of the enolate of the N-Boc derivative 9 have been described. After considerable experimentation it was found that when 9 was treated with lithium hexamethyldisilazide (LiHMDS) (3 eq) in THF at -78°C and, after 2 h, with 1-methylindole-3-carboxaldehyde 10 (1.1 eq) and stannic chloride (1 eq, 4 h), the aldol product 11 was obtained in 60% yield¹¹ (Scheme 3). Much poorer yields (< 10%) were obtained in the absence of stannic chloride. Other Lewis acids were also less satisfactory (e.g., boron trifluoride etherate, titanium tetrachloride).



Our original intention was to attempt an intramolecular conjugate addition of the amine function of 11 (after deprotection) to the C-2 position of the indole nucleus. Such a reaction has been amply studied in the tryptophan area and gives rise to stable pyrrolo[2,3-b]indole species.¹² In order to facilitate this ring closing reaction, the secondary hydroxyl group of 11 was first oxidized to the ketone 12 (80%) using the Dess-Martin reagent (3.7 eq, 2 h) in dichloromethane at room temperature (Scheme 4). In addition to providing an



 α , β -unsaturated ketone motif susceptible to 1,4-addition by the amine group, it was hoped that the equilibrating enolic form of **12a**, i.e. **12b**, would, by virtue of hydrogen bonding with the lactone carbonyl function, orient the amine group for intramolecular attack at C-2 of the indole moiety. However, after removal of the Boc blocking group of **12** using a 3:1 mixture of dimethyl sulfide and trifluoroacetic acid (rt, 1 h), various attempts to cyclize the resulting amine **13** (obtained in 70% yield) under acidic or basic conditions led either to no reaction or to extensive decomposition of the starting material.

There has been much interest recently in the palladium-catalyzed coupling of aromatic halides with alkyl amines and this has now been developed into a synthetically useful, high yielding procedure for the preparation of aromatic amines.¹³ In view of our failure to achieve carbon-nitrogen bond formation using substrate 13, an obvious alternative was the incorporation of a halogen atom at C-2 of the indole moiety thereby allowing subsequent palladium-catalyzed coupling with the amine function. To this end, 2bromoindole-3-carboxaldehyde 14 was prepared 14 and then N-methylated using sodium hydride (1.2 eq) and methyl iodide (10 eq) in THF to give 15 (reflux, 4 h, 70%) (Scheme 5). The latter reacted cleanly with the enolate of butyrolactone 9 (prepared as before at -78°C using LiHMDS (3 eq) as base) in the presence of stannic chloride (1.1 eq, 4 h), affording the aldol product 16 in 57% yield as a mixture of diastereomers. Treatment of 16 with trifluoroacetic acid and dimethyl sulfide (1:3) for 1 h at rt resulted in simultaneous deprotection of the amine group and dehydration to provide 17 in 90% yield. The ¹H NMR spectrum of 17 pointed to the presence of a single geometrical isomer. When compound 17 was heated at 80°C in DMF for 48 h in the presence of sodium tert-butoxide (1.2 eq), Pd2(dba)3 (5 mole %) and BINAP (5 mole %),13 cyclization occurred to give the desired α -carboline 6¹⁵ in 51% yield after purification by chromatography on silica gel. That formation of 6 was indeed due to palladium-catalyzed coupling of the bromoindole moiety with the amine, rather than the result of nucleophilic aromatic substitution was shown by repeating the reaction in the absence of the palladium/BINAP couple. In this case, only starting material was recovered, even after prolonged heating.



In summary, this paper presents a novel methodology for the efficient synthesis of the α -carboline nucleus. The two key features of this synthesis are the aldol condensation of a 4-(Boc)aminobutyro- γ -lactone-derived enolate with an indole-3-carboxaldehyde followed by a palladium-catalyzed generation of the N-1/C-9a bond to give 6. By including substituents on the phenyl ring of the indole as well as on the butyro- γ -lactone moiety, access to a variety of analogues of 6 may be envisaged. This possibility, together with the chemical modification of the lactone ring of 6 is currently being pursued. Extension of this methodology to the synthesis of δ -carbolines will be reported elsewhere.

References and Notes

- 1. Moquin-Pattey, C.; Guyot, M. Tetrahedron 1989, 45, 3445-3450.
- 2. Kin, J.-S.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. Tetrahedron Lett. 1997, 38, 3431-3434.
- Bolton, D.; Forbes, I. T.; Hayward, C. J.; Piper, D. C.; Thomas, D. R.; Thompson, M.; Upton, N. Bioorg. Med. Chem. Lett. 1993, 3, 1941-1946.
- (a) Achab, S.; Guyot, M.; Potier, P. Tetrahedron Lett. 1995, 36, 2615-2618. (b) Choshi, T.; Yamada, S.; Sugino, E.; Kuwada, T.; Hibino, S. J. Org. Chem. 1995, 60, 5899-5904. (c) Molina, P.; Fresneda, P. M.; Sanz, M. Tetrahedron Lett. 1997, 38, 6909-6912.
- 5. Forbes, I. T.; Johnson, C. N.; Thompson, M. J. Chem. Soc., Perkin Trans. 1 1992, 275-281.
- 6. Achab, S.; Guyot, M.; Potier, P. Tetrahedron Lett. 1993, 34, 2127-2130.
- 7. Rocca, P.; Marsais, F.; Godard, A.; Queguiner, G. Tetrahedron 1993, 49, 49-64.
- (a) Papamicaël, C.; Dupas, G.; Bourguignon, J.; Queguiner, G. Tetrahedron Lett. 1994, 35, 4099-4102. (b) Mehta, A.; Dodd, R. H. J. Org. Chem. 1993, 58, 7587-7590.
- 9. de Lange, B.; van Bolhuis, F.; Feringa, B. L. Tetrahedron 1989, 45, 6799-6818.
- 10. Collis, M. P.; Perlmutter, P. Tetrahedron: Asymmetry 1996, 7, 2117-2134.
- 11. All new compounds gave spectroscopic and microanalytical data consistent with the assigned structures.
- (a) Hino, T.; Taniguchi, M. J. Am. Chem. Soc. 1978, 100, 5564-5565. (b) Sammes, P. G.; Weedon, A. C. J. Chem. Soc., Perkin Trans. 11979, 3048-3052. (c) Bourne, G. T.; Crich, D.; Davies, J. W.; Horwell, D. C. J. Chem. Soc., Perkin Trans. 11991, 1693-1699.
- 13. (a) Hartwig, J. F. Synlett. **1997**, 329-340. (b) Marcoux, J.-F.; Wagaw, S.; Buchwald, S. L. J. Org. Chem. **1997**, 62, 1568-1569 and references therein.
- 14. Gilchrist, T. L.; Kemmitt, P. D.; Germain, A. L. Tetrahedron 1997, 53, 4447-4456.
- Physical data for compound 6 : mp 210°C ; ¹H NMR (200 MHz, CDCl₃) δ 4.00 (s, 3H, CH₃), 5.42 (s, 2H, CH₂), 7.42 (t, 1H, J = 7.2 Hz, H-8), 7.47 (d, 1H, J = 8.2 Hz, H-6), 7.65 (t, 1H, J = 7.2 Hz, H-7), 8.15 (d, 1H, J = 7.8 Hz, H-9), 8.75 (s, 1H, H-10) ; ¹³C NMR (62.5 MHz, CDCl₃) δ 27.9, 69.9, 109.5, 110.9, 117.3, 120.0, 121.2, 121.3, 125.2, 128.0, 140.0, 155.2, 164.3, 170.3 ; CIMS m/z 239 (MH)⁺. Anal. Calcd for C₁₄H₁₀N₂O₂ : C, 70.58 ; H, 4.23 ; N, 11.76. Found : C, 70.26, H, 4.51 ; N, 11.43.