Pergamon

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

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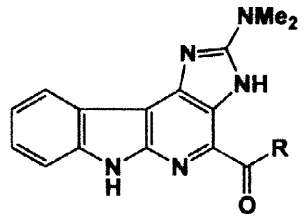
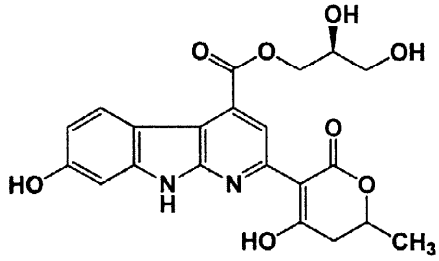
Received 17 November 1997; accepted 6 January 1998

Abstract *: The enolate of 4-N-(tert-butyloxycarbonyl)aminobutyro-γ-lactone* ***9*** *reacted with 2-bromo-1-methylindole-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* $Pd_2(dba)_3$ *-catalyzed ring closing of the product afforded the α-carboline* ***6*** *in good overall yield.*

The recent discoveries of the first examples of naturally occurring products having a pyrido[2,3-b]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



1 R= 3-indolyl
2 R= *p*-hydroxyphenyl



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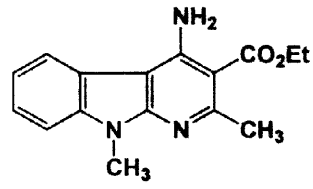

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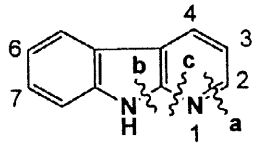
Streptomyces griseoflavus,[2] which protects neurons against L-glutamate toxicity. Moreover, synthetic α-carbolines have also been found to be of therapeutic interest as demonstrated by the 4-amino-3-carboxylate derivative **4**,[3] a modulator of the $GABA_A$ receptor of the central nervous system.

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



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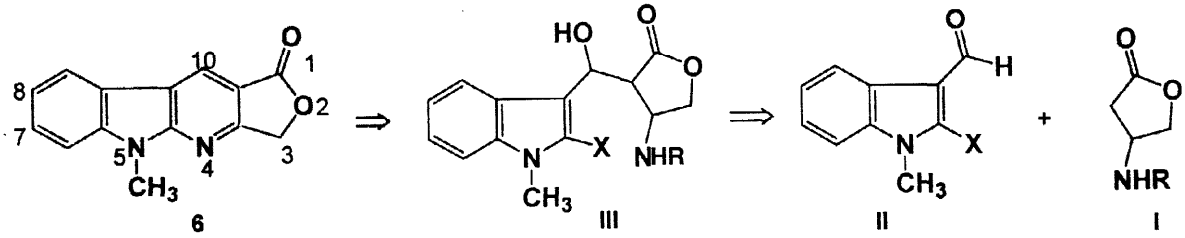
0040-4039/98/$19.00
PII: S0040-4039(98)00065-3

(*a*) in the final step. This strategy was successfully applied to the synthesis of grossularines **1** and **2** and their analogues[4] 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]

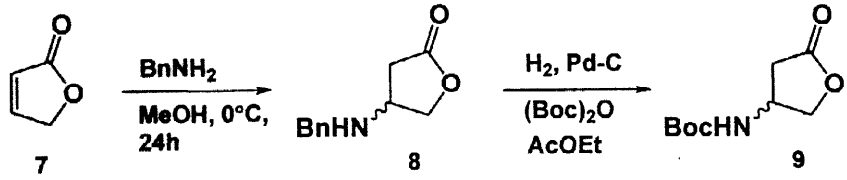
In this communication, we wish to present an alternative and unprecedented approach to the preparation of substituted α-carbolines (in the form of the fused butyrolactone derivative **6**, Scheme 1) which relies on the formation of the N-1/C-9a bond (*c*) in the critical ring generating step. The α-carboline **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).



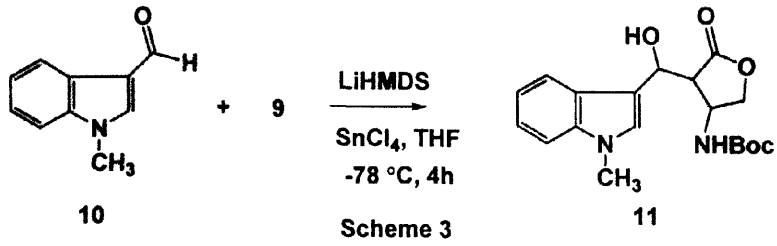
Scheme 1

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).



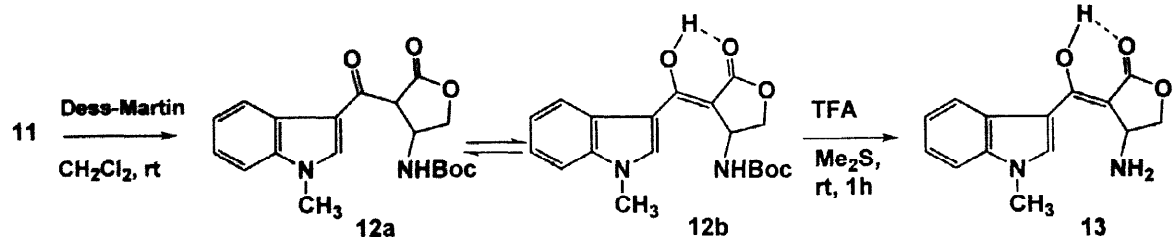
Scheme 2

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% yield[11] (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).



Scheme 3

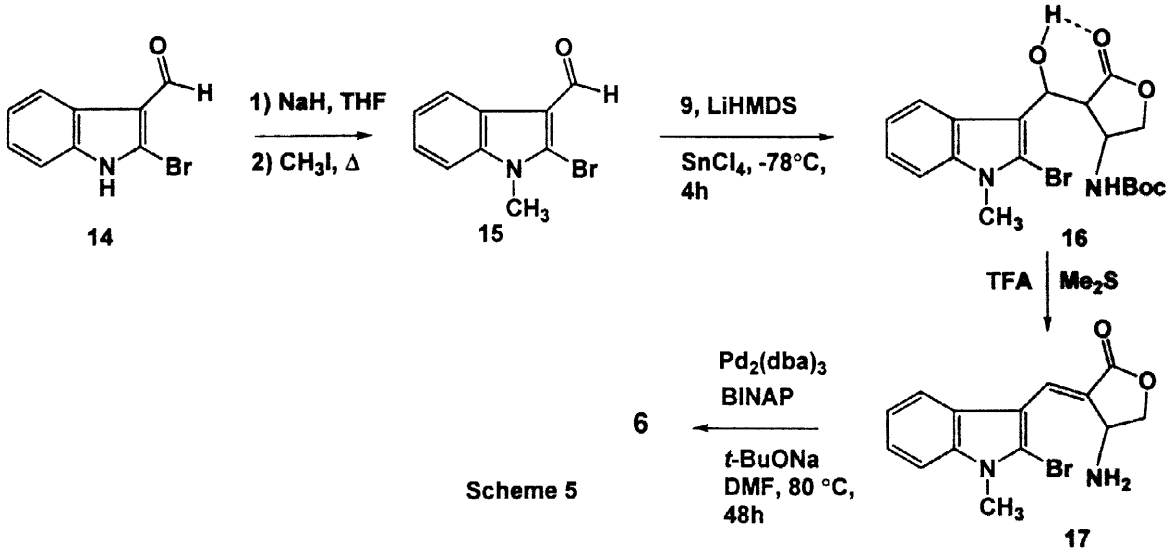
Our original intention was to attempt an intramolecular conjugate addition of the amine function of **11** (after deprotection) to the C-2 position of the indole nucleus. Such a reaction has been amply studied in the tryptophan area and gives rise to stable pyrrolo[2,3-b]indole species.[12] In order 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



Scheme 4

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, 2-bromoindole-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 ^{1}H 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), $Pd_2(dba)_3$ (5 mole %) and BINAP (5 mole %),[13] cyclization occurred to give the desired α-carboline **6**[15] 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.



Scheme 5

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.

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15. Physical data for compound **6** : mp 210°C ; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.00 (s, 3H, CH_3), 5.42 (s, 2H, CH_2), 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) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) 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 $C_{14}H_{10}N_2O_2$: C, 70.58 ; H, 4.23 ; N, 11.76. Found : C, 70.26, H, 4.51 ; N, 11.43.