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An Efficient Synthesis of Pyrrolo[2,1-*c*][1,4]benzodiazepine Antibiotics *via* Reductive Cyclization

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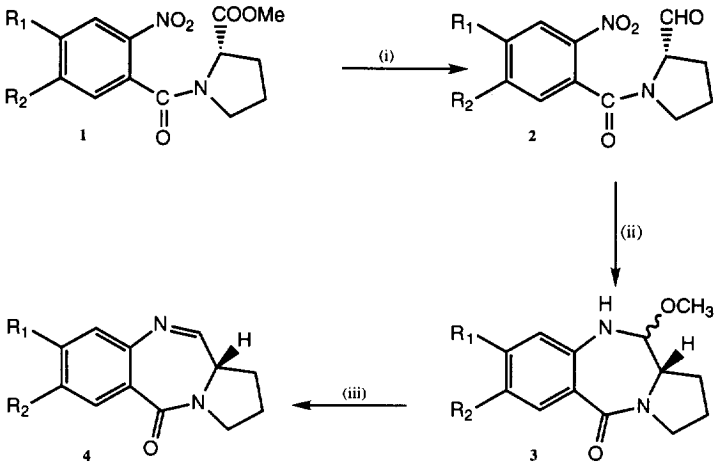
Abstract: A new and convenient one-pot synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) ring system has been achieved by a reductive cyclization employing N,N-dimethylhydrazine and $FeCl_3.6H_2O$ in good yields. © 1997 Elsevier Science Ltd.

The DNA-binding pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) class of compounds are produced by *Streptomyces* species which include anthramycin, tomaymycin, neothramycin and DC-81[1]. These molecules exert their biological activity by covalently binding to the N2 of guanine in the minor groove of DNA through the imine or imine equivalent functionality at N10-C11 of the PBD system and thus interferes with DNA function[2]. Most of these molecules interact with DNA in a sequence-selective manner and as such have potential as antitumour agents and gene targeted drugs[3].

In the last few years, various strategies have been proposed for the synthesis of these antibiotics and have met with varying degrees of success having different limitations[4,5]. It has been found that the introduction of the imine at N10-C11 position has usually given problems because of the reactivity of these functional groups.

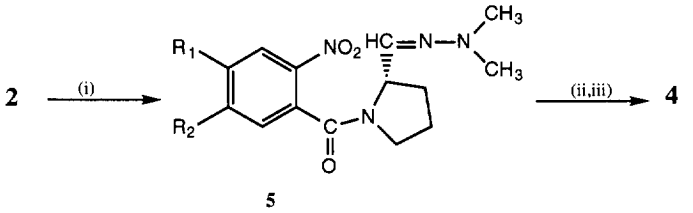
During the course of our studies in the design and synthesis of PBD analogues[6], it has occured to us to explore further efficient and convenient methodology towards the preparation of these DNA-interactive PBDs. Although hydrazine is well known for the reduction of aromatic nitro compounds[7], more recently N,N-dimethylhydrazine with ferric chloride hexahydrate ($FeCl_3.6H_2O$) has been described as a useful reducing agents. Based on this development, we envisioned a simultaneous reduction of aromatic nitro functionality and protection of the aldehydic group to offer a suitable precursor for the formation of the seven membered ring of the PBD by reductive cyclization reaction of the nitro aldehyde (**2**) with $FeCl_3.6H_2O$ and N,N-dimethyl hydrazine. To our surprise this reaction produced the methylether of the PBD carbinolamine (**3**) in one-pot, which features the present work. Our earlier studies on the reductive cyclization of acyclic nitroaldehydes in presence of iron-acetic acid (THF) yielded the PBD imines accompanied with undesired racemization at C11a position to some extent because of the acidic reaction conditions.[4k]



a) R_1=R_2=H ; b) R_1=OCH_2Ph, R_2=OCH_3; c) R_1=OH,R_2=OCH_3

Scheme 1: (i) DIBAL-H, CH_2Cl_2, -78° C, 45 min. (ii) $(CH_3)_2NNH_2$, $FeCl_3$-$6H_2O$, MeOH, 70° C, 6-8 h (iii) SiO_2, $CHCl_3$:MeOH (9.8:0.2)

The starting materials, methyl(2S)-N-(2-nitrobenzoyl)pyrrolidin-2-carboxylate esters (**1**) were prepared[5] from 2-nitrobenzoic acids through their acid chlorides on coupling with S-proline methylester hydrochloride. This upon reduction with DIBAL-H (2eq) gave the corresponding aldehyde [(2S)-N-(2-nitrobenzoyl)pyrrolidin-2-carboxaldehydes (**2a-d**)] in 55% yield. The reaction of **2** with $FeCl_3.6H_2O$ and N,N-dimethylhydrazine gave the corresponding methylethers of the PBD carbinolamine (**3a-d**) in good yields (82-85%). These have been converted to their imine forms (**4a-d**) by subjecting to column chromatography (silica gel, chloroform-methanol, 9.8:0.2)[10]. With a view to understand the mechanism of this reaction, **2** has been first converted to its hydrazone derivative **5** by the reaction with N,N-dimethylhydrazine. This upon reaction with ferric chloride N,N-dimethylhydrazine followed by column chromatography (silica gel) afforded



Scheme 2: (i) $(CH_3)_2NNH_2$,EtOH, Δh, 24h; (ii) $(CH_3)_2NNH_2$, $FeCl_3$-$6H_2O$,MeOH,70° C, (iii)SiO_2, $CHCl_3$:MeOH(9.8:0.2)

the PBD imine (**4**) in 50% yield. Thus illustrating the possibility of reductive and deprotective cyclization for the formation of the B-ring of the PBD in case of the one-pot reaction of **2**. However, the chances of an alternative possibility for the reductive cyclization of **2** can not be ruled out.

The procedure mentioned above has also been applied to the preparation of benzylated DC-81 (R_1= OCH_2Ph) and the natural product DC-81 (R_1= OH) demonstrates the generality of this method by the use of ferric chloride and N,N-dimethylhydrazine. Therefore, the present one-pot approach is a far more useful and convenient method for the preparation of natural and synthetic DNA binding PBD imines than the previously reported protocals.

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9. **Preparation of (2S)-N-(4-Hydroxy-5-methoxy-2-nitrobenzoyl)pyrrolidne-2-carboxaldhyde(2c)**: DIBAL-H solution (10.25 ml of a 1M solution in hexane, 15 mmol. 2.02 eq)

was added dropwise over a period of 10 min to a vigorously stirred solution of the methyl(2S)-N-(4-hydroxy-5-methoxy-2-nitrobenzoyl)pyrrolidine-2-carboxylate (**1c**) (1.390 g, 5 mmol, 1 eq) in anhydrous CH_2Cl_2 (50 ml) under dry nitrogen at -78°C (dry-ice / acetone bath). After the mixture was stirred for an additional 30 min excess reagent was decomposed by careful addition of methanol (20-30 ml) followed by 5% HCl (10 ml). The resulting mixture was allowed to warm to 0°C and the organic layer was then removed.The aqueous layer was extracted with CH_2Cl_2 (2x30 ml). The organic layers were combined, washed with brine and dried over $MgSO_4$. Finally, the solvent was evaporated in vacuum to afford the compound (**2c**) in 55% yield. Selected spectral data for **2c**: ^{1}H NMR ($CDCl_3$): δ 1.70-2.50 (m, 4H), 3.05-3.50 (m, 2H), 4.30-4.80 (m, 1H), 7.12-8.29 (m, 4H), 9.82 (d, 1H, 4.2 Hz).IR: ($CHCl_3$) 1730, 1640, 1530, 1478, 1340 cm-1. MS: m/e 248 ($M^{+}\cdot$, 30) 219, 200, 185, 171, 150, 104,76.

10. **General procedure for reductive cyclization** : To solution of nitroaldehyde (294 mg, 1 mmol) in methanol (10 ml) was added decolorizing charcoal (100 mg), $FeCl_3$-$6H_2O$ (10 mg, 0.04 mmol) and N,N-dimethylhydrazine (2.5 ml, 32.9 mmol). The reaction mixture was stirred at 70°C in an oil bath for 6-8h or until TLC showed the absence of starting material. After the completion of the reaction the mixture was cooled, filtered through a pad of celite and methanol was removed under vacuum to afford the crude PBD carbinolamine methylether **3** (65%). This upon subjecting to flash chromatography (silica gel, chloroform-methanol, 9.8:0.2) gave the imine form of the PBD **4** (50%). Selected spectral data for **4c**: ^{1}H NMR ($CDCl_3$): δ 1.89-2.02 (m,2H), 2.20-2.35 (m,2H), 3.33-3.90 (m,3H), 3.92 (s,1H), 6.90 (brs,1H), 7.49 (s,1H), 7.70 (d,1H, J= 6.2Hz); ^{13}C NMR ($CDCl_3$): δ 24.0, 28.9, 46.0, 52.3, 56.7, 110.1, 111.9, 118.2, 136.2, 139.8, 148.2, 163.2, 166.8; MS: m/e 246 ($M^{+}\cdot$, 100%).

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