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Synthesis of Pyrrolo[2,1-*c*][1,4]benzodiazepine Antibiotics via Azido Reductive Cyclization with HMDST

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Abstract: A new facile synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) ring system has been achieved by reductive cyclization of the azide employing hexamethyldisilathiane (HMDST). The parent unsubstituted PBD and the natural product DC-81 have also been prepared in good overall yields.

There is presently considerable interest in DNA-binding ligands such as the pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs) as potential antitumour agents and gene targeted drugs.[1] The PBD class of antitumour antibiotics are produced biosynthetically by various *Streptomyces* species: well known members include anthramycin, tomaymycin and DC-81. Their antitumour activity is due to covalent binding in the minor groove of DNA through nucleophilic attack of the N2 of a guanine base on the electrophilic C11 position of the PBD. This aminal linkage thus interferes with DNA function.[2]

Although PBDs with either a secondary amine or amide functionality at N10-C11 are readily synthesized whereas the introduction of an imine or carbinolamine is usually problematic. Various approaches[3] to the synthesis of these antibiotics have been investigated over the past few years which met with varying degrees of success, having different limitations.[4] One of the most successful methods is the deprotective cyclization of amino dithioacetals employing mercuric chloride in aqueous acetonitrile to afford the desired PBD imine. However, in this method too, the isolation of the product results in lower yields by the formation of excessive amounts of mercuric salts.

Our interest in the design and synthesis of PBD analogues[5] has led us to develop an improved synthetic methodology for the DNA-interactive PBDs. We envisaged a modified approach based on the formation of the seven membered ring through an azido reductive cyclization process. This allows cyclization of the diazepine ring to take place under extremely mild reaction conditions and involves a simple and rapid work-up procedure.

Initially, the PBD dilactams were prepared by the azido reductive cyclization process to study the scope of this reaction. The starting materials methyl (2S)-N-(2-nitrobenzoyl)pyrrolidine-2-carboxylate esters (**1**), were prepared[4] from 2-nitrobenzoic acids through their acid chlorides on coupling with S-proline methyl ester hydrochloride. The reaction of **1** with NaN_3 in HMPA gave the azido derivatives **2**[6] which upon reduction

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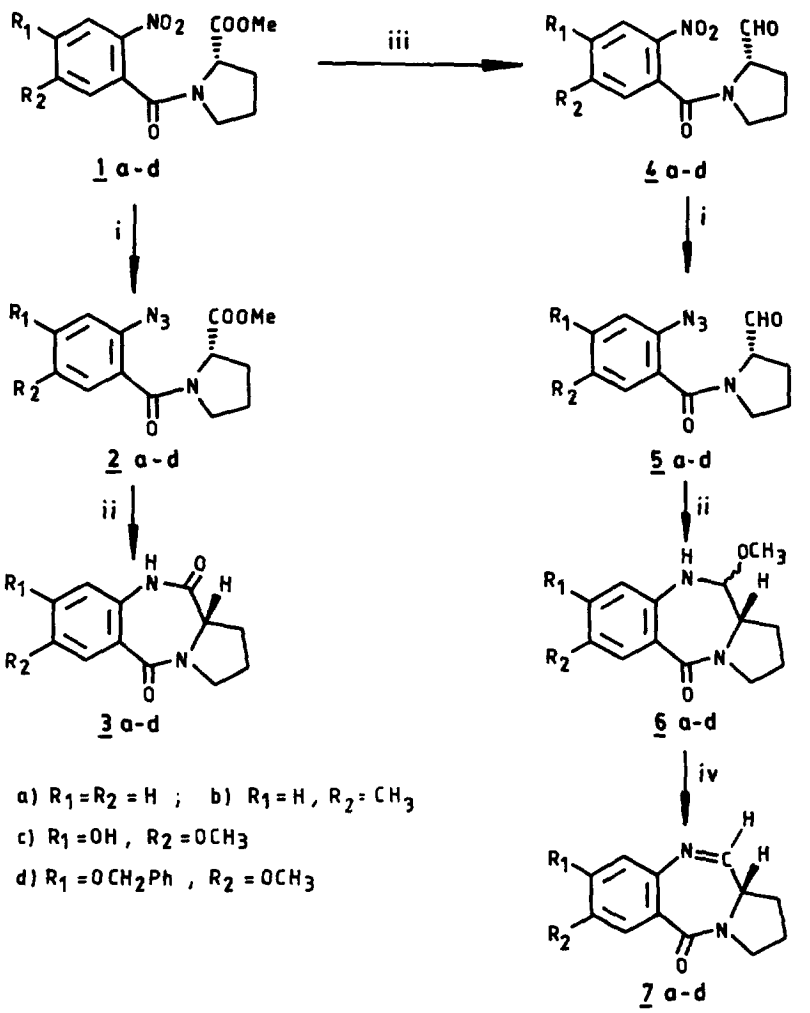

Reagents : i) NaN_3 / HMPA / RT / 6-8h , ii) HMDST / MeOH / RT / 4-5h
iii) DIBAL-H / CH_2Cl_2 / -78°C / 45 min. , iv) SiO_2 / $CHCl_3$: MeOH (9.8:0.2)

with hexamethyldisilathiane (HMDST) in methanol gave the PBD dilactam (**3a-d**) in good yields.[7] In view of these positive results the PBD imine precursor was prepared by the reduction of **1** with DIBAL-H to give the corresponding (2S)-N-(2-nitrobenzoyl)pyrolidine-2-carboxaldehydes (**4**). These upon subsequent reaction with NaN_3 in HMPA followed by reduction with HMDST in methanol gave the desired PBD imino methylethers **6**. These methyl ethers (**6a-d**) have been converted to their imine forms (**7a-d**) by subjecting to column chromatography (silica, chloroform-methanol, 9.8:0.2).[7]

The possible mechanism of the azide reduction may involve initial nucleophilic attack of the HMDST sulfur atom at the terminal azido nitrogen, followed by methanol desilylation of the ensuing azide-HMDST complex as described recently.[8] There also exists a possibility that hydrogen sulfide may be generated from HMDST in methanol. To assertain this aspect we have also carried out this reduction directly by passing hydrogen sulfide gas under the usual reductive conditions. It has been observed that some reduction did occur along with a large number of secondary products, thus posing problems for the isolation of the desired reduced product. As such HMDST is more suitable for this reductive cyclization rather than using hydrogen sulfide.

The usefulness of this procedure has been illustrated by employing this methodology for the synthesis of the natural product DC-81 (**7c**). All biologically active PBDs possess the (S)-configuration at the chiral C11a position which provides the molecule with a right-handed twist when viewed from the C-ring towards the A-ring, thus providing the appropriate three dimensional shape for a snug fit within the minor groove of DNA. There are studies[3d] and also our observation[5d] that in acidic conditions for the cyclization step of the diazepine ring formation through the amino aldehydes can lead to recemization at the C11a position of the product. Therefore, the present approach which is carried out under mild conditions could be safe for the retention of steriochemical integrity at C11a and may not effect the DNA binding potential of the PBD imine.

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6. **Typical procedure for the synthesis of Azides from nitrocompounds using HMPA:** A solution of nitro esters **1** (500mg, 1.85mmol) or nitroaldehydes **4** (244mg, 1.85 mmol) and sodium azide (247 mg, 3.80 mmol) in HMPA (15 ml) was stirred at room temperature for 6-8 h. The reaction mixture was poured on to water and then extracted several times with ether. Evaporation of the combined ether extract gave the crude azides in 90-95% yield, which was further purified by column chromatography on silica gel. Selected spectral data for **2a** ^{1}H NMR ($CDCl_3$) : δ 1.80-2-41 (m,4H), 3.20-3.49 (m,2H), 3.92 (s,3H), 4.67 (dd,1H, J=7.2, 4.2Hz), 7.34-7.6 (m,3H), 8.10 (d,1H, J=8.2 Hz); IR ($CHCl_3$): 1740, 1635, 1575, 1530, 1240, 1175, 1045, 855, 790cm^{-1} ; MS: m/e 274 ($m^{+\cdot}$ 2). **4a**: ^{1}H NMR ($CDCl_3$) : δ 1.90-2.39 (m,4H), 3.32 (t,2H, J=7.0Hz), 4.74 (t,1H, J=7.2Hz), 7.50-7.98 (m.3H), 8.29 (d,1H, J=6.2Hz), 9.87 (d,1H, J=4.2Hz); IR ($CHCl_3$) : 1730, 1625, 1575, 1346, 850, 790, 765 cm^{-1}; MS: m/e 244 ($m^{+\cdot}$ 4).

7. **General procedure for the azide reduction with HMDST**: A solution of azidoesters **2** or azidoaldehydes **5** (1mmol) in methanol (10ml) was treated with 2-3 equivalents of HMDST and then stirred at room temperature for about 4-5h or until TLC showed the absence of the starting material. The mixture was diluted with dichloromethane washed with saturated $NaHCO_3$ solution, dried and evaporated. Purification of the crude material by column chromatography on silica gel using chloroform and methanol (9.8:0.2) as eluent gave the pure compound **7**, in case of **5** as starting material. Selected spectral data for **3a**: ^{1}H NMR ($CDCl_3$) : δ 1.90-2.56 (m,4H), 3.30-3.52 (m,2H), 4.10 (d,1H, J=5.2Hz), 7.08 (d,1H, J=6.2Hz), 7.21 (d,1H, J=7.2Hz), 7.57 (m,1H), 8.10 (dd,1H, J=6.1,7.9Hz). 10.20 (s,1H, exchanges with D_2O) ; IR ($CHCl_3$) : 3440, 3260, 2930, 1675, 1625, 1580, 1490, 1375, 1240, 1095, 965, 760cm^{-1}; MS: m/e 232 ($m^{+\cdot}$ 2). **7a**: ^{1}H NMR ($CDCl_3$) : δ 1.56-2.48 (m,4H), 3.20-3.89 (m,3H), 7.10-7.59 (m.3H), 7.66 (d,1H, J=4.2Hz), 8.02 (d,1H, J=5.8 Hz) ; IR ($CHCl_3$) : 3300, 2975, 2875, 1615, 1570, 1480, 1240, 1165, 860, 830cm^{-1}: MS: m/e 200 ($M^{+\cdot}$ 100).

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