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Facile and Efficient Synthesis of the Dimers of DC-81 Antitumour Antibiotics

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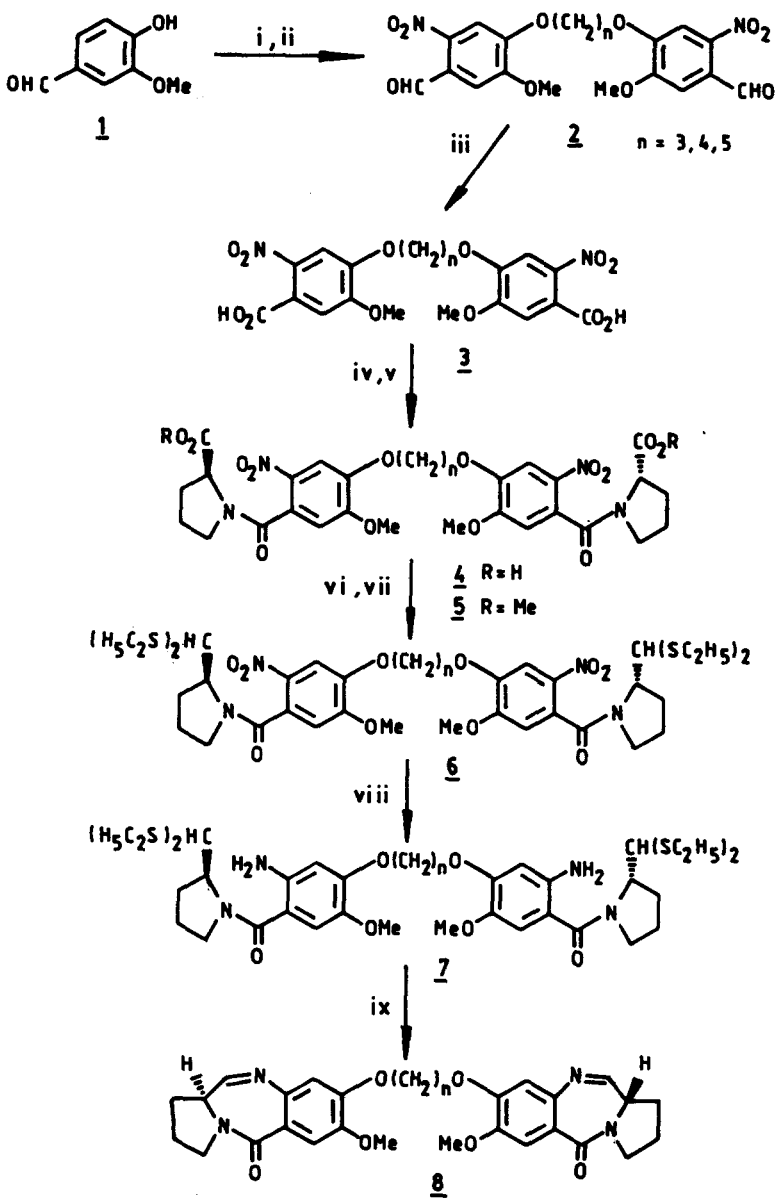
Abstract : We report an improved, economical and versatile route to the dimers of DC-81 anti-tumour antibiotics. Particularly, the protection and deprotection steps in its synthesis and in the preparation of its precursors have been avoided. There is a significant improvement in the overall yields.

There is a growing interest in pyrrolo[2,1-c][1,4]benzodiazepine (PBD) ring system compounds in the area of molecular recognition. They can recognize and bind to specific sequences of DNA and have potential as therapeutic agents in the treatment of certain genetic disorders including some cancers[1]. They exert their biological activity by reacting covalently in the minor groove of DNA to form an aminal linkage between the electrophilic carbinolamine present at the C-11 position and the N-2 of gaunine[2,3]. The preferred bonding sequence involving 5'-PuGPu motifs. Based on the molecular modelling studies C8-linked dimers of two PBD units of the natural product DC-81 were recently designed and synthesized[4-6] for better cytotoxic potency and sequence specificity. This along with our interest in the modified PBD analogues[7] has inspired us to develop a more versatile and improved synthetic methodology for preparation of irreversible interstrand cross-linking agents[8]. Recently, the synthetic aspects of the DNA-interactive PBD's have been reviewed extensively[9].

We envisaged a modified approach for the nitroacid precursor of the dimer. In the literature[5], vanillic acid has been dimerized with diiodo alkanes to obtain the dimer acid and which resisted the usual nitration reactions, owing to the insoluble nature of the dimer acids[5]. For this reason, the dimer acid was converted to its methyl ester followed by nitration. Further, the normal hydrolysis of the nitro methyl esters gave demethylated nitro acids of **3**. Therefore, the required compounds **3** have been claimed to be obtained under mild hydrolytic conditions.

However, in our methodology we prepared the dimer of the cheaper starting material vanillin (**1**) instead of vanillic acid. During dimerization of **1** there was very little monoalkylation product formed using either the dibromo or the diiodo alkanes[5]. Most importantly, the nitration of vanillin dimers was extremely successful unlike the vanillic acid dimers. As a result the steps of conversion of acid to its ester and later its hydrolysis after the nitration have been eliminated which in turn reduces the number of steps, and as well improves the yields.



i) Br-$(CH_2)_n$-Br, (n=3,4,5), K_2CO_3, dry acetone, reflux, 48 h, 75-85%; ii) $SnCl_4$-HNO_3, CH_2Cl_2, -25°C, 5 min.; iii) $NaClO_2$, HSO_3NH_2, THF/H_2O (9:1); iv) $SOCl_2$, C_6H_6, 3h, (2S)-proline, THF, Et_3N, H_2O, 1 h; v) $SOCl_2$, C_6H_6, CH_3OH; vi) DIBAL-H, CH_2Cl_2, -78°C, 1 h; vii) TMSi-Cl, EtSH, CH_2Cl_2, 30°C, 24 h; viii) 10% Pd/C, MeOH, 1 h; ix) $HgCl_2$, HgO, THF/CH_3CN-H_2O, 8 h.

Thus 1 was dimerized with dibromo- or diiodo-alkanes followed by the nitration with $SnCl_4$-HNO_3 to obtain the nitroaldehyde dimers 2[10]. These aldehydes upon oxidation with $NaClO_2$ by a modified literature procedure[11] gave the required nitroacids 3 in good yields[12] (78-84%).

The nitro acids 3 were converted to their acid chlorides by thionyl chloride in dry benzene and coupled to S-proline to give compounds 4. These were esterified with methanol to give the dimers of 5[13]. Reduction to the aldehydes with DIBAL-H was followed by protection to the diethyl thioacetals 6[13]. Here as well, the preparation of pyrrolidine-2-carboxaldehyde diethyl thioacetal and diprotection steps by N-CBZ protection has been avoided. Thus the nitro thioacetals 6 were reduced by 10% Pd/C to the amino thioacetals 7[13]. Finally, reductive cyclization with $HgCl_2$-HgO affords the DSB-120 (8: n=3) and other DC-81 dimers 8 in 22-25% overall yields[13].

In summary, we developed a modified route to the dimers of DC-81 that results in significantly improved yields and a shorter synthetic sequence. This has been accomplished by employing more commercially viable vanillin as the starting material which further reduced the additional steps of esterification and desterification of the vanillic acid. The overall route results in yields that are more than twice to that reported via the previously employed route. This will assist investigators in the preparation of other important dimers of this class.

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10. Compounds **2** were purified by recrystallization (EtOAc/hexane) **2** (n=3), ^{1}H NMR (200 MHz, $CDCl_3$-d_6-DMSO) : 2.10-2.35 (t, 2H), 3.90 (s, 6H), 4.20-4.35 (t, 4H), 7.31 (s, 2H), 7.45 (s, 2H), 10.35 (s, 2H).

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12. Compounds **3** were purified by dissolving them in saturated $NaHCO_3$ solution and reprecipitation of the filtrate with HCl. **3** (n=3) ^{1}H NMR (200 MHz, $CDCl_3$+d_6-DMSO): δ 2.30-2.45 (t, 2H), 3.90 (s, 6H), 4.25-4.40 (t, 4H), 7.20 (s, 2H), 7.50 (s, 2H), 13.50-14.20 (broad, 2H).

13. Compounds **5, 6, 7** and **8** were purified by flash chromatography over SiO_2 (**5**, EtOAc; **6**, EtOAc:Hexane, 4:6; **7**, EtOAc:Hexane, 7:3; **8**, $CHCl_3$:MeOH, 9.5:0.5). ^{1}H NMR (200 MHz, $CDCl_3$): **5** (n=3): δ 1.90-2.10 (m, 2H), 2.20-2.45 (m, 8H), 3.50-3.66 (m, 4H), 3.70 (s, 6H), 3.80 (s, 6H), 4.18-4.35 (t, 4H), 4.50-4.80 (m, 2H), 6.80 (s, 2H), 7.30 (s, 2H); **6** (n=3): δ 1.15-1.40 (m, 12H), 1.55-1.80 (m, 2H), 1.82-2.05 (m, 4H), 2.15-2.42 (m, 4H), 2.59-2.88 (q, 8H), 3.18-3.31 (m, 4H), 3.85 (s, 6H), 4.18-4.20 (t, 4H), 4.62-4.78 (m, 2H), 4.82 (d, 2H), 6.80 (s, 2H), 7.68 (s, 2H); **7** (n=3): δ 1.15-1.30 (m, 12H), 1.60-1.75 (m, 2H), 1.80-2.00 (m, 4H), 2.10-2.35 (m, 4H), 2.56-2.78 (q, 8H), 3.50-3.65 (m, 6H), 3.75 (s, 6H), 4.10-4.23 (t, 4H), 4.55-4.65 (m, 4H), 6.25 (s, 2H), 6.75 (s, 2H); **8** (n=3): δ 1.95-2.15 (m, 4H), 2.25-2.50 (m, 6H), 3.45-3.85 (m, 6H), 3.89 (s, 6H), 4.15-4.28 (t, 4H), 6.78 (s, 2H), 7.42 (s, 2H), 7.60 (d, 2H, J=4.2 Hz).

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