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Reductive cyclization of ω-azido/nitrocarbonyl compounds by samarium iodide: a facile preparation of DNA-binding pyrrolo[2,1-*c*][1,4]benzodiazepine and its dimers†

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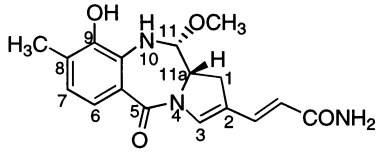
Abstract

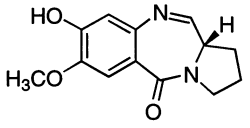
An efficient synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepines via reductive cyclization of ω-azido/nitrocarbonyl compounds employing samarium iodide is described. This methodology has also been extended for the preparation of DNA-crosslinking DC-81 dimers. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: reductive cyclization; pyrrolobenzodiazepines; DNA-binding; samarium iodide; DC-81 dimers.

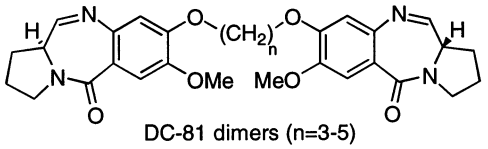
DNA-binding molecules are presently attracting interest due to their involvement in carcinogenesis and their use as antitumor agents and probes of DNA structure.[1] The pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) family of DNA-binding antitumor antibiotics (anthramycin) has been extensively studied as a potential source of antitumor agents and DNA probes.[2,3] The naturally occurring PBDs have been isolated from various *Streptomyces* species. It has been well established that they exert their biological activity through covalent binding to the exocyclic N2 of guanine in the minor groove of DNA.[4]



anthramycin



DC-81



DC-81 dimers (n=3-5)

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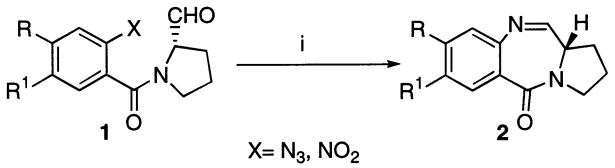
Many molecules based on the PBD ring system have been synthesized to improve upon their biological profile. In this search C-7 or C-8 linked dimers of PBD have been synthesized which are capable of sequence selective DNA-interstrand cross-linking.[5,6] For example, DC-81 dimers of this type are highly cytotoxic and very efficient sequence selective cross-linking agents.[7,8] Recently, new DNA-interstrand cross-linking, C-2 linked PBD dimers have also been synthesized.[9] Furthermore, hybrid molecules containing the PBD ring system have been recently reported with interesting minor groove DNA-binding properties.[10,11]

In view of the importance of these molecules we have been interested in the structural modifications of naturally occurring PBDs to improve their DNA-binding potential and sequence selectivity. We have also been involved in the development of new synthetic strategies for the PBD ring system.[12–15] In this endeavor, we wish to report a new approach of practical significance based on a reductive cyclization strategy for the PBD ring system and its dimers employing SmI_2.

The precursors, *N*-(2-azido/nitro-benzoyl)pyrrolidine-2-carboxaldehydes (**1**) were prepared by literature methods.[16] These upon reductive cyclization with SmI_2, afforded the desired PBD imines (**2**) in 70–72% yields.[17] It has been observed that reduction of either the azido or the nitro group does not have much effect on the yields of the desired product (**2**), except for the reductive cyclization of azido compounds that takes place in 1.5 h when compared to nitro compounds which is completed in 2 h (Scheme 1).

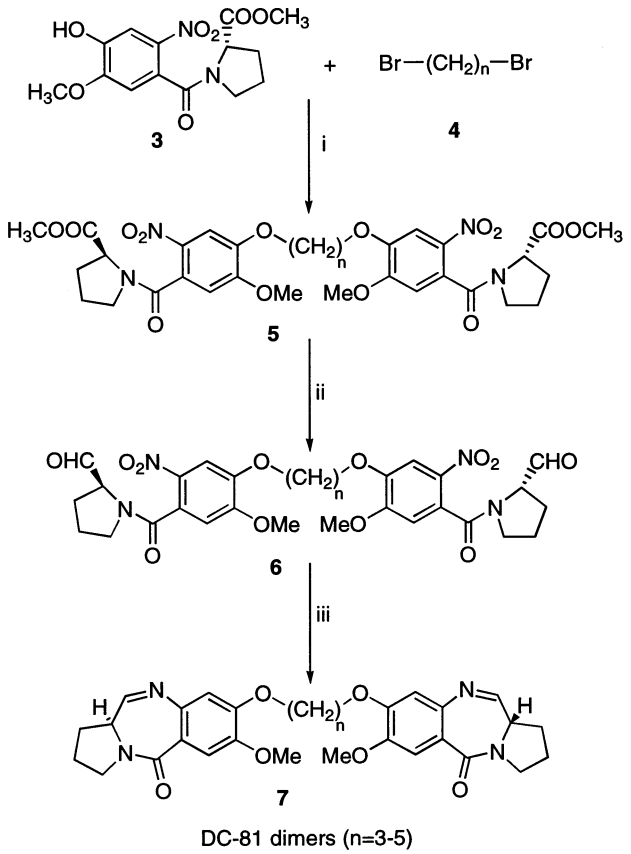


Scheme 1. (i) SmI_2, THF, rt, 1.5–2 h. (a) $R = R^1 = H$; (b) $R = H$, $R^1 = CH_3$; (c) $R = OH$, $R^1 = OCH_3$

This approach has also been extended to the synthesis of DC-81 dimers. The precursor, methyl-(2*S*)-(4-hydroxy-5-methoxy-2-nitrobenzoyl)pyrrolidine-2-carboxylate (**3**), was synthesized as described in the literature.[18] This was alkylated using the dibromoalkanes (**4**) to obtain the 4,4′-(alkane-α,ω-diyldioxy)bis[methyl-(2*S*)-*N*-(5-methoxy-2-nitrobenzoyl)pyrrolidine-2-carboxylates] (**5**).[19] There upon reduction with DIBAL-H gave the nitroaldehydes (**6**), which on reductive cyclization with SmI_2 afforded DSB-120 (**7**, n = 3) and other DC-81 dimers in 18–20% overall yields[20] (Scheme 2).

The significant feature of this method is that it addresses many of the difficulties encountered by the literature procedures, particularly solubility aspects after the dimerization process.[6,8] In the present method, the precursor **3** is synthesized in a facile manner and dimerized later, which leads to an improvement in the yield and ease of work up. Furthermore, this process avoids contamination by mercuric salts unlike the well-known ethanedithiol deprotective cyclization approach employing $HgCl_2$.

In summary, we have developed a new azido as well as nitro reductive cyclization route employing SmI_2 for the preparation of the PBD ring system, and extended this work to include dimers resulting not only in improved yields but also a facile synthetic sequence. This work will assist investigators in the preparation of similar biologically significant DNA-interactive dimers.



Scheme 2. (i) K_2CO_3, acetone, reflux, 36–48 h, 80–90%; (ii) DIBAL-H (4 equiv.), CH_2Cl_2, −78°C, 45 min, 72–78%; (iii) SmI_2, THF, 2 h, 55–63%

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17. Preparation of compound **2**: To a stirred 0.1 M solution of SmI_2 in THF (12.5 ml, 2.5 equiv.) was added dropwise a solution of **1** (122 mg, 0.5 mmol) in THF (5 ml) under a nitrogen atmosphere, at room temperature and the stirring was continued for 1.5 h. After completion of the reaction, as indicated by TLC (ethyl acetate), the solvent was evaporated, the mixture was dissolved in $CHCl_3$ and then it was washed with saturated K_2CO_3. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography using ethyl acetate–hexane (9:1) to obtain the pure imine (**2**) in good yields. Spectral data of compound **2a**: ^{1}H NMR: ($CDCl_3$) δ 1.90–2.36 (m, 4H), 3.52–3.92 (m, 3H), 7.28–7.56 (m, 3H), 7.78 (d, 1H, $J=4.6$ Hz), 8.05 (d, 1H, $J=5.2$ Hz); MS: m/z 200 (M^+, 100) 171, 160, 144, 120, 103, 83, 70.
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19. Preparation of compound **5**: To a stirred solution of 1,3-dibromopropane (202 mg, 1.0 mmol) in dry acetone (50 ml) was added anhydrous potassium carbonate (1.38 g, 10.0 mmol) and the monomer nitroester **3** (648 mg, 2.0 mmol). The reaction mixture was then heated under reflux for 48 h. After completion of the reaction, as indicated by TLC, using ethyl acetate–hexane as a solvent system, the potassium carbonate, was removed by filtration and the acetone evaporated under vacuum. The reaction mixture was purified by column chromatography using ethyl acetate–hexane (8:2) as eluent to afford pure dimer **5** in quantitative yields. Spectral data of compound **5**: ^{1}H NMR ($CDCl_3$): 1.90–2.12 (m, 2H), 2.22–2.46 (m, 8H), 3.50–3.65 (m, 4H), 3.70 (s, 6H), 3.82 (s, 6H), 4.18–4.34 (t, 4H), 4.50–4.82 (m, 2H), 6.80 (s, 2H), 7.32 (s, 2H); MS: m/z 689 (MH^+).
20. Preparation of DC-81 dimer (**7**): The dimeric nitroaldehyde (**6a**, 125 mg, 0.2 mmol) in THF (5 ml) was added slowly to a stirred 0.1 M solution of SmI_2 in THF (10 ml, 5 equiv.) at room temperature under a nitrogen atmosphere. The reaction was continued for 2 h and after completion of the reaction, the THF was evaporated under reduced pressure. This was dissolved in chloroform and washed with saturated K_2CO_3. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure, then purified by flash chromatography using $CHCl_3$:MeOH (9.5:0.5) as eluent to give the pure DC-81 dimer **7a** in 60% yield. Spectral data of compound **7a**: ^{1}H NMR ($CDCl_3$): δ 2.01–2.17 (m, 2H), 2.27–2.44 (m, 8H), 3.50–3.86 (m, 6H), 3.92 (s, 6H), 4.24–4.34 (m, 4H), 6.86 (s, 2H), 7.51 (s, 2H), 7.65 (d, 2H, $J=4.4$ Hz); FAB MS: m/z 533 (MH^+).