A new route for the synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepine antibiotics *via* oxidation of cyclic secondary amine

Ahmed Kamal* and N. Venugopal Rao

Indian Institute of Chemical Technology, Hyderabad 500 007, India

The synthesis of the imine-containing pyrrolo[2,1-*c*][1,4]benzodiazepine DNA-binding antitumour antibiotics was achieved by a new method of oxidation of cyclic secondary amines which does not endanger the stereochemical integrity of the C-11a position.

The pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) class of antitumour antibiotics is produced by various *streptomyces* species; well known members include anthramycin, tomaymycin and DC-81.[1] These compounds exert their biological activity by covalently binding to the N-2 of guanine in the minor groove of DNA, through the imine or imine equivalent functionality at N-10–C-11 of the PBD. This aminal linkage thus interferes with DNA function.[2] Although PBDs with either a secondary amine or amide functionality at N-10–C-11 are readily synthesized, the introduction of an imine or carbinolamine at this position is problematic due to the reactivity of these functional groups.

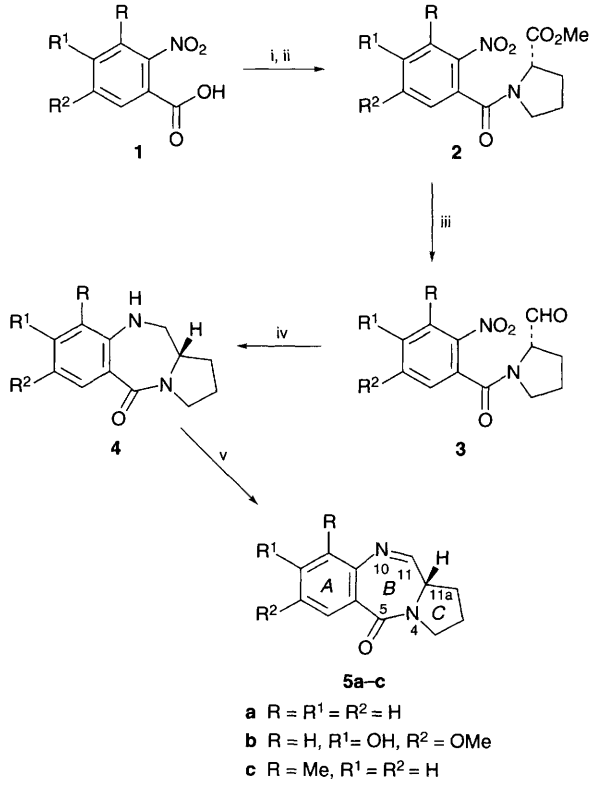
Various approaches to the synthesis of these antibiotics have been investigated, including hydride reduction of seven membered cyclic dilactams,[3] reductive cyclization acyclic nitro aldehydes,[4] reduction of cyclic iminothioethers,[3b,5] cyclization of amino acetals or thioacetals,[6] palladium catalysed carbonylation of *O*-haloanilides[7] and intramolecular aza-Wittig cyclization.[8] Most of the methods met with varying degrees of success, with each having different limitations,[9] one of the most successful methods being the deprotective cyclization of amino dithioacetals employing aqueous mercuric chloride to afford the desired PBD imine. Usually in this method, the isolation of the product results in lower yields due to the formation of excessive mercuric salts. One approach which has not been investigated is the oxidation of the cyclic secondary amine of the PBDs to form a N-10–C-11 imine. This approach has attracted us, as PBD secondary amines are readily prepared in high yield by a number of different methods including the reductive cyclization of *N*-(2-nitrobenzoyl)pyrrolidine-2-carboxaldehyde and the more recently developed palladium catalysed carbonylation reaction. Some recent attempts to oxidize the PBD amine by 'very active' MnO_2 have produced a fully unsaturated PBD system.[9]

We envisioned that the milder oxidation would be an excellent method for the desired conversion of PBD amines into imines. Useful oxidation procedures[10] of alcohols to yield ketones with Me_2SO activated by oxalyl chloride, trifluoroacetic anhydride, acetic anhydride or dicyclohexylcarbodiimide have been reported. While this work was in progress, some examples of the conversion of an amine into an imine by employing the activated Me_2SO reagent have also been reported.[11] We report herein the successful application of the activated Me_2SO reagent for the oxidation of the cyclic secondary amine to the corresponding PBD imines.

2-Nitrobenzoic acids **1** *via* their acid chlorides, on coupling with (*S*)-proline methylester hydrochloride gave the corresponding *N*-(2-nitrobenzoyl) proline esters **2**. This upon reduction with DIBAL-H and followed by reductive cyclization of the nitro aldehydes **3** in the presence of 10% Pd–C, provided the cyclic secondary amine precursors **4**. This upon oxidation† with activated Me_2SO afforded the desired PBD in the imine form **5** in 40–55% yield (Scheme 1).

This is the first report of the synthesis of imine-containing PBD antitumour antibiotics by the oxidation of a cyclic secondary amine. Employing this methodology, the natural product DC-81 **5b** has also been synthesized to illustrate the usefulness of this procedure. All biologically active PBDs possess the (*S*)-configuration at the chiral C-11a position which provides the molecule with a right handed twist when viewed from the *C*-ring towards the *A*-ring, thus providing the appropriate 3-dimentional shape for a snug fit within the minor groove of DNA. In this approach, in comparison to most successful methods,[6] the simultaneous cyclization with imine formation has been avoided. Therefore, in this investigation even the remote chance of racemization at C-11a position has been excluded and the desired stereochemistry is preserved.

In summary, the present method offers a versatile entry to the imine containing PBDs. Unlike the other successful methods, such as the reductive cyclization of amino dithioacetals, this method is devoid of protective and deprotective steps. Further, as this method involves a mild oxidative conversion of the cyclic secondary amine to the imine while almost fully retaining



Scheme 1 *Reagents and conditions*: i, $SOCl_2$, C_6H_6, 6 h; ii, Proline methylester hydrochloride, THF, Et_3N, 1 h; iii, DIBAL-H, CH_2Cl_2, −78 °C; iv, 10% Pd–C, H_2 (1.5 atm.), 6 h; v, Me_2SO, $(COCl)_2$, CH_2Cl_2, −50 °C, 3.5 h

the stereochemical integrity at the C-11a position, it seems to be an attractive approach for the synthesis of various naturally occurring PBDs and their synthetic analogues. The mechanistic details of the PBD imine formation and also the formation of some minor side-products will be discussed in due course.

Footnote

† *General procedure*: To Me_2SO (3 mmol) in dichloromethane (10 cm^3) was added oxalyl chloride (1.68 mmol) dropwise at −60 °C. The reaction mixture was stirred for 20 min at the same temperature. To this activated Me_2SO reaction mixture was added dropwise a solution of the cyclic secondary amine **4** (1.02 mmol) in dichloromethane (1 cm^3), the reaction mixture was stirred at −55 °C for 60 min and argon gas was bubbled into the reaction mixture at the same temperature for 30 min. Triethylamine (5 mmol) was added dropwise without raising the temperature above −50 °C. This was further stirred for 60 min, maintaining the same temperature. The reaction was monitored by TLC (EtOAc). On completion of the reaction it was diluted with dichloromethane (10 cm^3), then washed with water (2 × 50 cm^3) and brine solution, and then the organic phase was dried over anhydrous $MgSO_4$. This, upon evaporation at room temperature under vaccum, gave a residue, which was purified by flash silica gel chromatography (EtOAc–Hexane, 7 : 3) to afford the PBD imine **5** as a light yellow oil. **5a**, yield 40%; ^1H NMR (200 MHz, $CDCl_3$) δ 1.55–2.42 (4 H, m), 3.24–3.92 (3 H, m), 7.08–7.58 (3 H, m), 7.68 (1 H d, *J* 4,2 Hz), 8.02 (1 H d, *J* 5.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.2, 28.2, 49.4, 53.4, 121.4, 122.6, 122.9, 124.4, 129.2, 132.4, 158.4, 164.7; *m/z* 200 (M^+, 100%).

References

1 W. A. Remers, *Antitumour Antibiotics*, Wiley, 1988, pp. 28–92; D. E. Thurston, *Advances in the Study of Pyrrolo[2,1-c][1,4]benzodiazepine (PBD) Antitumour Antibiotics*, in *Molecular Aspects of Anticancer Drug-DNA Interactions*, ed. S. Neidle and M. J. Waring, Macmillan, 1993, vol. 1, pp. 54–88.

2 L. H. Hurley and D. R. Needham-van Devander, *Acc. Chem. Res.*, 1986, **19**, 230; L. H. Hurley, *J. Med. Chem.*, 1989, **32**, 2027; D. E. Thurston and A. S. Thompson, *Chem. Br.*, 1990, **26**, 767.

3 (*a*) W. Leimgruber, A. D. Batcho and R. C. Czajkowski, *J. Am. Chem. Soc.*, 1968, **90**, 5641; (*b*) T. Kaneko, H. Wong and T. W. Doyle, *Tetrahedron Lett.*, 1983, **24**, 5165; (*c*) J. W. Suggs, Y. S. Wang and K. S. Lee, *Tetrahedron Lett.*, 1985, **26**, 4871.

4 J. W. Lown and A. V. Joshua, *Biochem. Pharmacol.*, 1979, **28**, 2017; D. E. Thurston and D. R. Langley, *J. Org. Chem.*, 1986, **51**, 705; N. Langlois F. Favre and A. Rojas, *Tetrahedron Lett.*, 1993, **34**, 4635.

5 T. Kaneko, H. Wong, T. W. Doyle, W. C. Rose and W. T. Bradner, *J. Med. Chem.*, 1985, **28**, 388.

6 D. R. Langley and D. E. Thurston, *J. Org. Chem.*, 1987, **52**, 91; S. M. Courtney and D. E. Thurston *Tetrahedron Lett.*, 1993, **34**, 5327; D. S. Bose, G. B. Jones and D. E. Thurston, *Tetrahedron*, 1992, **48**, 751.

7 M. Mori, M. Kimura, Y. Uozumi and Y. Ban, *Tetrahedron Lett.*, 1985, **26**, 5947; M. Mori, Y. Uozumi and Y. Ban, *J. Chem. Soc., Chem. Commun.*, 1986, 841.

8 P. Molina, I. Diaz and A. Tarraga, *Tetrahedron*, 1995, **51**, 5617.

9 D. E. Thurston and D. S. Bose, *Chem. Rev.*, 1994, **94**, 433.

10 A. J. Mancuso and D. Swern, *Synthesis*, 1981, 165; T. T. Tidwell, *Synthesis*, 1990, 857.

11 Y. Jinbo, H. Kondo, M. Taguchi, F. Sakamoto and G. Tsukamoto, *J. Org. Chem.*, 1994, **59**, 6057; L. Gentilucci, Y. Grijzen, L. Thijs and B. Zwanenburg, *Tetrahedron Lett.*, 1995, **36**, 4665.

Received, 17th October 1995; Com. 5/06874F