Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 3499–3501
Tetrahedron Letters

Selective reduction of aromatic azides with hexamethyldisilathiane: synthesis of new 2-azidopyrrolo[2,1-*c*][1,4]benzodiazepines

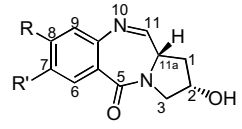
Ahmed Kamal,* K. Laxma Reddy, G. Suresh Kumar Reddy and B. S. Narayan Reddy†

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India

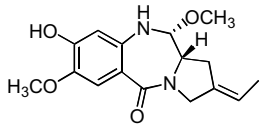
Received 6 January 2004; revised 10 February 2004; accepted 27 February 2004

Abstract—2-Azidopyrrolobenzodiazepines have been synthesized via cyclization of ω-azidocarbonyl compounds employing hexamethyldisilathiane by selectively reducing the aryl azido functionality.

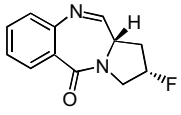
Pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs) a group of potent naturally occurring antitumour antibiotics from various *Streptomyces* species are of considerable interest due to their potential as antitumour agents, gene regulators and DNA probes.[1] Well known members of this group include abbeymycin (**1a**), chicamycin A and B (**1b**), anthramycin, tomaymycin (**2**), neothramycin A and B, sibiromycin and DC-81.[2] The cytotoxicity and antitumour activity of these agents are attributed to their property of sequence selective covalent binding to the N2 of guanine in the minor groove of duplex DNA via an acid-labile aminal bond to the electrophilic imine at the N10–C11 position. The (*S*)-configuration at the chiral C11a-position provides the PBD structure with the necessary right handed twist to fit snugly within the minor groove of DNA spanning three base pairs with a preference for the Pu–G–Pu sequence.[3] The PBDs are being used in the development of gene targeting agents with the potential to down-regulate genes of therapeutic interest. The major problems encountered in the synthesis of PBDs are the installation of the sensitive N10-C11 imine or carbinolamine functionality and racemization at the C11a position. In recent years, a number of hybrid molecules containing the PBD ring system have been synthesized to improve the DNA binding ability and sequence selectivity.[4,5] We have been interested in the structural modifications of the PBD ring system and the development of new synthetic strategies.[6] In continuation of these efforts, we would like to report an efficient synthesis of a novel 2-azidopyrrolobenzodiazepine to probe its DNA sequence selective binding ability and cytotoxicity.



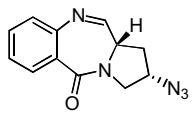
R = R' = H; Abbeymycin (**1a**)
R = OH, R' = OCH_3 ; Chicamycin B (**1b**)



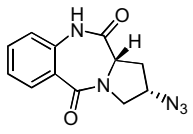
Tomaymycin (**2**)



3



4



5

It is well known in the literature that C-ring hydroxy substitution plays an important role in the biological activity of PBDs, examples being naturally occurring PBDs such as chicamycin A and B (**1b**),[7a] neothramycin A and B[7b] and abbeymycin (**1a**).[7c] According to SAR

Keywords: Pyrrolobenzodiazepines; Reductive cyclization; Antitumour agents.

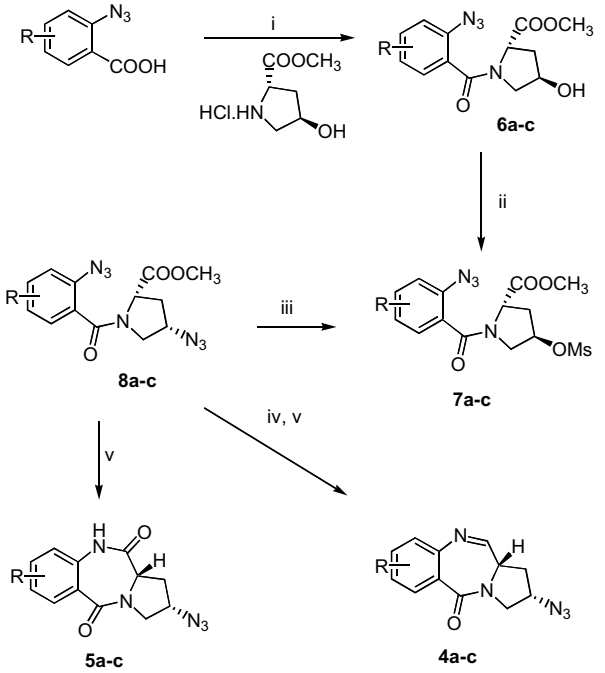
* Corresponding author. Tel.: +91-40-27193157; fax: +91-40-271931-89; e-mail addresses: ahmedkamal@iict.ap.nic.in, ahmedkamal@iict.res.in

† Present address: Department of Medicinal Chemistry, University of Kansas, Lawrence, KS 66045, USA.

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.02.148

studies, C2 *exo* and *endo* unsaturation enhances the DNA binding affinity and cytotoxicity of this class of compounds, for example, tomaymycin.[8] Thurston and co-workers have reported the synthesis of C2/C2′-unsaturated DC-81 analogues and their dimers (SJG-136), which demonstrates the importance of C2/C2′-*exo*-unsaturation in enhancing DNA-binding affinity and cytotoxicity.[9] Recently, the effect of fluorination at the C2-position of the PBD ring system (e.g., **3**) on the biological activity particularly DNA binding potential has been investigated.[10] In view of the importance of C-ring substitution,[11] we have developed an efficient synthetic pathway for the introduction of an azido group at the C2-position in the PBD molecule. In the literature, there are some reports on the synthesis of pyrrolobenzodiazepines employing an intramolecular aza-Wittig approach using triphenylphosphine or tributylphosphine.[12] In our synthetic route we have employed a mild and selective reducing agent, $(CH_3)_3SiSSi(CH_3)_3$ [hexamethyldisilathiane (HMDST)] which is in continuation of our earlier studies on the reductive cyclization of azides.[13] Our previous attempts to reduce the azido functionality by triphenylphosphine produced products that could not be isolated, probably because of the reduction of both the aryl and alkyl azido functionalities, whereas, C-2 azido substituted PBD amidines[14] and dilactams[15] have been prepared by azidation of mesyl or tosyl ethers of the cyclic PBD amidine or dilactams. There are no reports on the synthesis of imine containing 2-azido PBDs.

Compounds **4** and **5** were synthesized according to the routes outlined in Scheme 1. 2-Azidobenzoic acids were coupled with *trans*-4-hydroxy-L-proline methyl ester to give the corresponding azidoesters **6**. The hydroxy group of the proline moiety was activated as its mesyl ether **7** by treatment with MsCl and triethylamine and the mesylates treated with NaN_3 in DMF to afford the bis-azides **8**, which were reduced with HMDST in MeOH to give the 2-azido PBD-5,11-diones **5** quantitatively. The ester functionality of the bis-azides **8** was also reduced with DIBAL-H at −78 °C to give the corresponding azidoaldehydes without detectable racemization, which were reacted further with HMDST in MeOH at room temperature, to afford the 2-azido PBD imines **4** in good yields[16] (Table 1).



Scheme 1. Reagents and conditions: (i) $SOCl_2$, triethylamine, DMF, C_6H_6 (ii) MsCl, triethylamine, CH_2Cl_2 (iii) NaN_3, DMF, 50 °C, (iv) DIBAL-H, CH_2Cl_2, −78 °C (v) HMDST, MeOH, rt, 4 h.

Table 1. Yields and molecular ions observed for PBD analogues **4a–c** and **5a–c**

Entry	R	Yields (%)[a]	EIMS
4a	H	69	241
4b	7-OMe, 8-OMe	65	301
4c	7-OMe, 8-OBn	62	377
5a	H	74	257
5b	7-OMe, 8-OMe	68	317
5c	7-OMe, 8-OBn	65	393

[a] Overall yields.

In summary, a mild, efficient and selective reduction of an aromatic azido functionality in the presence of alkyl azides employing HMDST has been developed and used to prepare 2-azido PBDs in good yields. The anticancer activity and DNA binding affinity studies of these compounds will be published in due course.

Acknowledgements

K.L.R. and G.S.K.R. are grateful to CSIR (New Delhi) for the award of Senior Research Fellowships.

References and notes

1. (a) Hurley, L. H. *J. Antibiot.* **1977**, *30*, 349; (b) Hurley, L. H. *J. Med. Chem.* **1989**, *32*, 2027; (c) Thurston, D. E.; Thompson, A. S. *Chem. Ber.* **1990**, *26*, 767.
2. (a) Thurston, D. E.; Bose, D. S. *Chem. Rev.* **1994**, *94*, 433; (b) Kamal, A.; Rao, M. V.; Laxman, N.; Ramesh, G.; Reddy, G. S. K. *Curr. Med. Chem. Anti-cancer Agents* **2002**, *2*, 215.
3. (a) Thurston, D. E. In *Molecular Aspects of Anticancer Drug DNA Interactions*; Neidle, D., Waring, M. J., Eds.; Macmillan: London, 1993; p 54; (b) Tender, M. D.; Korman, S. *Nature* **1963**, *199*, 501; (c) Hurley, L. H.; Petrusek, R. L. *Nature* **1979**, *282*, 529.
4. (a) Kamal, A.; Rao, M. V.; Reddy, B. S. N. *Khim. Getoroski Soedenin. (Chem. Heterocycl. Compd.)* **1998**, *12*, 1588; (b) Baraldi, P. G.; Balboni, G.; Cacciari, B.; Guiotto, A.; Manfridini, S.; Romagnoli, R.; Spalluto, G.; Thurston, D. E.; Howard, P. W.; Bianchi, N.; Rutigliano, C.; Mischiati, C.; Gambari, R. *J. Med. Chem.* **1999**, *42*, 5131; (c) Damayanthi, Y.; Reddy, B. S. P.; Lown, J. W. *J. Org. Chem.* **1999**, *64*, 290.

5. (a) Kamal, A.; Ramesh, G.; Laxman, N.; Ramulu, P.; Srinivas, O.; Kondapi, A. K.; Neelima; Srinivas, V. B.; Nagarajaram, H. A. *J. Med. Chem.* **2002**, *45*, 4679; (b) Kamal, A.; Ramesh, G.; Ramulu, P.; Srinivas, O.; Rehana, T.; Sheelu, G. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3451; (c) Kamal, A.; Ramulu, P.; Srinivas, O.; Ramesh, G. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3517; (d) Kamal, A.; Srinivas, O.; Ramulu, P.; Ramesh, G.; Kumar, P. P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3577; (e) Kamal, A.; Ramulu, P.; Srinivas, O.; Ramesh, G. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3955; (f) Kamal, A.; Ramesh, G.; Srinivas, O.; Ramulu, P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 471.
6. (a) Kamal, A.; Reddy, K. L.; Devaiah, V.; Reddy, G. S. K. *Tetrahedron Lett.* **2003**, *44*, 4741; (b) Kamal, A.; Reddy, P. S. M. M.; Reddy, D. R. *Tetrahedron Lett.* **2003**, *44*, 2857; (c) Kamal, A.; Reddy, G. S. K.; Reddy, K. L.; Raghavan, S. *Tetrahedron Lett.* **2002**, *43*, 2103; (d) Kamal, A.; Reddy, G. S. K.; Raghavan, S. *Bioorg. Med. Chem. Lett.* **2001**, 387.
7. (a) Konishi, M.; Ohkuma, H.; Naruse, N.; Kaqaguchi, H. *J. Antibiot.* **1984**, *37*, 200; (b) Takeuchi, T.; Miyanoto, M.; Ishizuka, M.; Naganawa, H.; Kondo, S.; Hamada, M.; Umezawa, H. *J. Antibiot.* **1976**, *29*, 93; (c) Hochlowski, J. E.; Andres, W. W.; Theriault, R. J.; Jackson, M.; MeAlpine, J. B. *J. Antibiot.* **1987**, *40*, 145.
8. Arima, K.; Kohsaka, M.; Tamura, G.; Imanaka, H.; Sakai, H. *J. Antibiot.* **1972**, *25*, 437.
9. (a) Gregson, S. J.; Howard, P. W.; Hartley, J. A.; Brooks, A. A.; Adams, L. J.; Jenkins, T. C.; Kelland, L. R.; Thurston, D. E. *J. Med. Chem.* **2001**, *44*, 737; (b) Gregson, S. J.; Howard, P. W.; Corcoran, K. E.; Barcella, S.; Yasin, M. M.; Hurst, A. A.; Jenkins, T. C.; Kelland, L. R.; Thurston, D. E. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1845; (c) Gregson, S. J.; Howard, P. W.; Barcella, S.; Nakamaya, A.; Jenkins, T. C.; Kelland, L. R.; Thurston, D. E. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1949.
10. O'Neil, I. A.; Thompson, S.; Kalindjian, S. B.; Jenkins, T. C. *Tetrahedron. Lett.* **2003**, *44*, 7809.
11. (a) Cooper, N.; Hagan, D. R.; Tiberghien, A.; Ademefun, T.; Matthews, C. S.; Howard, P. W.; Thurston, D. E. *Chem. Commun.* **2002**, 1764; (b) Kang, G. D.; Howard, P. W.; Thurston, D. E. *Chem. Commun.* **2003**, 1688.
12. (a) Molina, P.; Diaz, I.; Tarraga, A. *Tetrahedron* **1995**, *51*, 5617; (b) Eguchi, S.; Yamashita, K.; Matsushita, Y.; Kakehi, A. *J. Org. Chem.* **1995**, *60*, 4006; (c) O'Neil, A.; Murray, C. L.; Hunter, R. C.; Kalindjian, B.; Jenkins, T. C. *Synlett* **1997**, 75.
13. Kamal, A.; Reddy, B. S. P.; Reddy, B. S. N. *Tetrahedron Lett.* **1996**, *37*, 6803.
14. Gillard, A.-C.; Rault, S. *J. Heterocycl. Chem.* **1997**, *34*, 1185.
15. Gillard, A.-C.; Alkhader, M.; Rault, S. *Heterocycl. Commun.* **1996**, *2*, 409.
16. Synthesis of **5a**: A solution of ester **8** (0.5 g, 1.59 mmol) in methanol (10 mL) was treated with 2–3 equiv of HMDST and then stirred at room temperature for about 4 h or until TLC showed the absence of the starting material. The mixture was diluted with dichloromethane, washed with saturated $NaHCO_3$ solution, dried and concentrated under reduced pressure. Purification of the crude product was carried out by column chromatography on silica gel using ethyl acetate and hexane (8:2) as eluents (2*S*,11*aS*)-2-azido-1,2,3,10,11,11*a*-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepine-5,11-dione **5a**: $[\alpha]_D^{32}$ +596 (*c* 1, MeOH); ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.25–2.40 (m, 1H), 3.00–3.10 (m, 1H), 3.60–3.70 (m, 1H), 3.80–3.95 (dd, $J = 6.2$ Hz, $J = 13.7$ Hz, 1H), 4.05–4.15 (m, 1H), 4.25–4.35 (m, 1H), 7.10–7.20 (m, 2H), 7.40–7.45 (m, 1H), 7.90 (d, $J = 10.3$ Hz, 1H), 10.20 (s, 1H); EIMS: m/z 257 $[M]^{+\cdot}$; HRMS: 257.0912 (calculated), 258.0917 (observed); IR: ν_{max}/cm^{-1} 2933, 2107, 1689, 1617, 1451, 1383, 1213, 1046, 750; mp: 217–220 °C.

Synthesis of **4a**: A solution of the azidoaldehyde (0.5 g, 1.75 mmol) in methanol (10 mL) was treated with 2–3 equiv of HMDST and then stirred at room temperature for about 4 h or until TLC showed the absence of starting material. The mixture was diluted with dichloromethane, washed with saturated $NaHCO_3$ solution, dried and concentrated under reduced pressure. Purification of the crude product was carried out by column chromatography on silica gel using ethyl acetate as eluent (2*S*,11a*S*)-2-azido-1,2,3,11*a*-tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5-one **4a**: $[\alpha]_D^{32}$ −138 (*c* 0.5, MeOH); ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.20–2.30 (m, 1H), 3.20–3.30 (m, 1H), 3.50–3.60 (m, 1H), 3.90–4.00 (m, 2H), 4.25– 4.30 (m, 1H), 6.75–6.80 (m, 1H), 6.90–7.00 (m, 1H), 7.15–7. 25 (m, 2H), 7.60 (d, $J = 6$ Hz, 1H); EIMS: m/z 241 $[M]^{+\cdot}$; HRMS: 241.0963 (calculated), 241.0966 (observed); IR: ν_{max}/cm^{-1} 3311, 2103, 1618, 1448, 1211, 1145, 638; mp: 101–104 °C.