Pergamon

Tetrahedron Letters 41 (2000) 1099–1102

TETRAHEDRON LETTERS

# Solid-phase synthesis of polyamines using a Dde-linker: philanthotoxin-4.3.3 via an on-resin Mitsunobu reaction

Siri Ram Chhabra, Azra N. Khan and Barrie W. Bycroft *

*School of Pharmaceutical Sciences, University of Nottingham, University Park, Nottingham NG7 2RD, UK*

Received 30 September 1999; accepted 29 November 1999

**Abstract**

A Dde linker/solid-phase procedure for the stepwise construction of polyamines is illustrated with the synthesis of philanthotoxin-4.3.3. Resin-bound 4-aza-1,7-heptanediamine was $N^4$-protected and $N^7$-activated in a single operation with 2-nitrobenzenesulphonyl chloride. Alkylation with *N*-Fmoc-4-aminobutanol under Mitsunobu conditions completed the polyamine backbone. Deprotection of the sulphonamide groups was readily achieved with thiolates in DMF at room temperature. 

*Keywords:* solid-phase synthesis; polyamines; Mitsunobu reaction; Dde-linker.

In the preceding paper,[1] we described a further application of our Dde-based primary amine linker to the synthesis of polyamines and illustrated the procedure with the synthesis of polyamine derivative philanthotoxin-3.4.3 (PhTX-3.4.3) **1** and the structural isomer PhTX-3.3.4 **2**. Philanthotoxins and other naturally occurring polyamine toxins, as well as their synthetic analogues, are valuable investigative tools in neuropharmacology and show some promise as lead entities for the development of therapeutic agents.[2–5]

The synthesis of **1** was readily achieved starting with spermine but the polyamine backbone of **2** was constructed by two successive rounds of reductive alkylation of resin bound 1,4-butanediamine with *N*-Fmoc-3-aminopropanal.† We sought, by a similar procedure, to synthesise the remaining analogue PhTX-4.3.3 **3** in order to complete the series, and further demonstrate the flexibility of the approach.

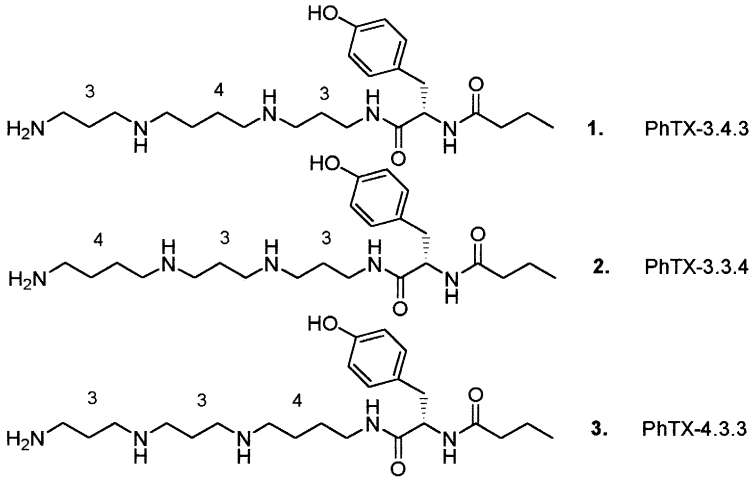
* Corresponding author. Tel: +44 115 9515101; fax: +44 115 9515049; e-mail: barrie.bycroft@nottingham.ac.uk (B. W. Bycroft)

† **Abbreviations:** Amino acids and peptides follow the IUPAC-IUB nomenclature where applicable (*Eur. J. Biochem.* **1984**, 9-37); Boc, *t*-butoxycarbonyl; *t*Bu, *tert*-butyl; DCM, dichloromethane, DEAD, diethyl azodicarboxylate; DIEA, *N*,*N*-diisopropylethylamine; DMF, *N*,*N*-dimethylformamide; ES-MS, electrospray mass spectrometry; Fmoc, 9-fluorenylmethoxycarbonyl; HOBt, 1-hydroxybenzotriazole; Nbs, 2-nitrobenzenesulfonyl; RPHPLC, reverse phase high performance liquid chromatography; TBTU, *O*-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate; THF, tetrahydrofuran; TFA, trifluoroacetic acid; TIPS, triisopropylsilane.

0040-4039/00/$ - see front matter 
*PII:* S0040-4039(99)02239-X

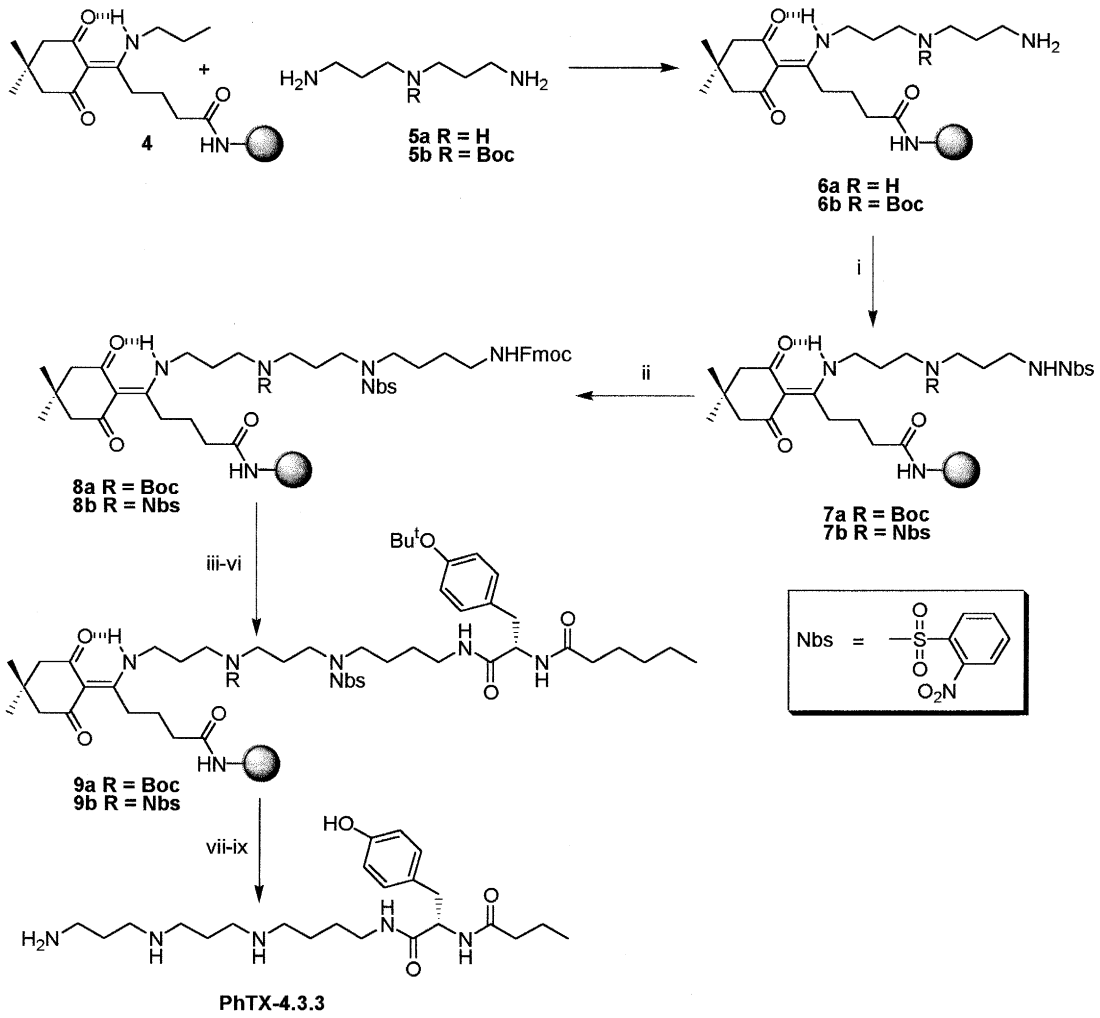
Although a solution phase synthesis of this naturally occurring toxin has been described,[6] no solid phase methods have been reported.

We envisaged that the reductive alkylations would be straightforward and the approach would involve anchoring 1,3-propanediamine to the solid support followed by stepwise elongation of the polyamine with *N*-Fmoc-3-aminopropanal and *N*-Fmoc-4-aminobutanal. The first step, as anticipated from the previous work, proceeded smoothly but implementing the latter was thwarted by our inability to achieve a convenient synthesis of *N*-Fmoc-4-aminobutanal. Neither reduction of the corresponding acid nor the oxidation of the corresponding alcohol led to clean products. Since similar difficulties were experienced with the corresponding $C_5$ analogues, we assumed that a predisposition for both these aldehydes to undergo intramolecular cyclisation to hemiaminal derivatives and subsequently to other products might be the reason. Rather than pursue this line of investigation for introducing $C_4$ and $C_5$ units into polyamines, we decided to explore the alternative possibility of using the readily available Fmoc-amino alcohols for on-resin *N*-alkylation via a Mitsunobu type reaction.




Generally this procedure requires that the primary amine is converted into a derivative in which the NH is strongly acidic.[7] This can be achieved through the formation of toluenesulfonamide,[8] trifluoroacetamide,[9] trifluoromethanesulfonamide[10] and 2,2,5,7,8-pentamethylchroman-6-sulfonyl (pmc)[11] derivatives but the conditions required for their deprotection render them unsuitable for our solid-phase approach. However, Fukuyama et al.[12] have recently reported that 2- and 4-nitrobenzenesulfonamide derivatives can be conveniently prepared, and following alkylation, efficiently deprotected at room temperature under neutral conditions using sodium thiophenolate in DMF.[13] These conditions have been recently employed for the synthesis of *N*-methyl amino acids[14] and the site-specific *N*-alkylation of peptides on solid-phase.[14,15]

We have now successfully completed the synthesis of PhTX-4.3.3 using 2-nitrobenzenesulfonyl derivatives by the two routes summarised in Scheme 1. Either the triamine **5a** or its $N^4$-Boc derivative **5b**[16] was directly ligated onto the Dde-linker **4**[17] to afford **6a** and **6b** respectively, or alternatively built up on the resin via reductive alkylation of bound 1,3-propanediamine with *N*-Fmoc-3-aminopropanal in the manner previously described.[1] The primary amine groups of both reacted with 2-nitrobenzenesulfonyl chloride in the presence of DIEA to give **7a** or **7b**, respectively. It is noteworthy that in the process $N^4$ in **6a** is also sulfonylated and thereby protected with a 2-Nbs group. Alkylation of **7a** and **7b** with excess of *N*-Fmoc-4-aminobutanol[18] in the presence of triphenylphosphine and diethyl azodicarboxylate completed the polyamine backbones **8a** or **8b**. Fmoc loading assays at this stage indicated resin




Scheme 1. Reagents and conditions. (i) 2-NbsCl (4 equiv.), DIEA (6 equiv.) in THF, 5 h; (ii) FmocNH$(CH_2)_4$OH (10 equiv.), $Ph_3P$ (5 equiv.), DEAD (5 equiv.) in dry THF, 20 h; (iii) 20% v/v piperidine in DMF, 10 min; (iv) Fmoc-Tyr(*t*Bu)-OH/TBTU/HOBt/DIEA, 4 h; (v) 20% v/v piperidine in DMF, 10 min; (vi) *n*-butyric acid/TBTU/HOBt/DIEA, 4 h; (vii) 50% TFA in DCM/TIPS/$H_2O$, 3 h; (viii) 1 M NaSPh in DMF (2×1 ml) per 100 mg of resin 2×1 h; (ix) 10% v/v *n*-propylamine in DMF, 6×30 min

substitutions of approximately 80%. Removal of the Fmoc group and successive acylations with activated Fmoc-Tyr(O*t*Bu)-OH and *n*-butyric acid gave the resin-bound protected toxin **9a** or **9b**. Both acylation steps were monitored by TNBS test and the efficiency of the first acylation step was also determined by a Fmoc loading assay. After removal of the Boc and *t*Bu groups by acidolysis with 50% TFA in DCM, the deprotection of the Nbs group was achieved by exposing the resin to 1 M solution of PhSNa in DMF. Finally cleavage from the support in both cases, using 10% v/v *n*-propylamine in DMF, afforded PhTX-4.3.3 as an oil in 75% overall yield and with excellent purity as determined by a single peak eluting at 12.3 min in RPHPLC analysis.[19] The isolated product gave satisfactory ES-MS, *m/z* 436 (M+H, $C_{23}H_{41}N_5O_3$ requires *m/z* 435) and appropriate spectral data.

In conclusion, Mitsunobu alkylation complements the reductive alkylation procedure reported previously but importantly allows the convenient introduction of $C_4$ and $C_5$ units into polyamines. These

protocols can now be exploited, either individually or together for the elaboration of a polyamine backbone of any sequence. Furthermore the high yield obtained further demonstrates the stability of Dde-linker not only towards acid, base and reductive alkylation but also to the reagents employed for Mitsunobu alkylation. In addition, the compatibility of the linker with the introduction and deprotection of the 2-Nbs group adds another level of protective orthogonality and thus further extends the utility of this linker.

## Acknowledgements

We thank the Commonwealth Scholarship Commission, UK for a research studentship to A. N. Khan.

## References

1. Chhabra, S. R.; Khan, A. N.; Bycroft, B. W. *Tetrahedron Lett*. **2000**, *41*, 1095–1098.
2. Goodnow, R.; Konno, K.; Niwa, M.; Kallimopoulos, T.; Buknownik, R.; Lenares, D.; Nakanishi, K. *Tetrahedron* **1990**, *46*, 3267–3286.
3. Piek, T. *Am. Chem. Soc. Symp. Series* **1993**, *524*. 233–238.
4. Blagbrough, I. S.; Usherwood, P. N. R. *Proc. Roy. Soc. Edin*. **1992**, *99B*, 67–81.
5. Eldefrawi, A. T.; Elderfrawi, E. E.; Konno, K.; Mansour, N. A.; Nakanishi, K.; Oltz, E.; Usherwood, P. N. R. *Proc. Natl. Acad. Sci. USA* **1988**, *85*, 4910–4913.
6. A solution phase synthesis of PhTX-4.3.3 has been reported via cyanoethylation of the mono protected 1,4-butanediamine followed by $LiAlH_4$ reduction of the nitrile group. The remaining $C_3$ unit was added by reductive alkylation with Boc-aminopropanal. (Kalivretenos, A. G.; Nakanishi, K. *J. Org. Chem*. **1993**, *58*, 6596–6608).
7. (a) Mitsunobu, O. *Synthesis* **1981**, 1–28; (b) Hughes, D. L. *Org. React*. **1992**, *42*, 335– 656.
8. Henry, J. R.; Marcin, L. R.; Mcintosh, M. C.; Scola, P. M.; Harris Jr., G. D.; Weinreb, S. M. *Tetrahedron Lett*. **1989**, *30*, 5709–5712.
9. Tsunoda, T.; Otsuka, J.; Yamaniya, Y.; Ito, S. *Chem. Lett*. **1994**, 539–542.
10. Edwards, M. L.; Stemerick, D. M.; McCarthy, J. R. *Tetrahedron* **1994**, *50*, 5579–5590.
11. Wisniewski, K.; Kolodziejczk, A. S. *Tetrahedron Lett*. **1997**, *38*, 483–486.
12. Fukuyama, T.; Jow, C.-K.; Chueng, M. *Tetrahedron Lett*. **1995**, *36*, 6373–6376.
13. Yang, L.; Chiu, K. *Tetrahedron Lett*. **1997**, *38*, 7307–7310.
14. Reichwein, J. F.; Liskamp, M. J. *Tetrahedron Lett*. **1998**, *39*, 1243–1246.
15. Miller, S. C.; Scanlan, T. S. *J. Am. Chem. Soc*. **1997**, *119*, 2301–2302.
16. Prepared from 4-aza-1,7-heptanediamine via transient Dde-protection of the terminal amines by the procedure reported for the preparation of $N^4$, $N^9$-bis-Boc spermine (see preceding paper).
17. Chhabra, S. R.; Khan, A. N.; Bycroft, B. W. *Tetrahedron Lett*. **1998**, *39*, 3585–3588.
18. In the second approach, when $N^4$is 2-Nbs protected, inexpensive *N*-Boc-4-aminobutanol can be used instead of the *N*-Fmoc derivative.
19. RPHPLC conditions — see preceding paper.