Pergamon

Tetrahedron Letters 43 (2002) 2597–2600

TETRAHEDRON LETTERS

Simple syntheses of the polyamine alkaloid tenuilobine and analogues using selectively *N*-tritylated polyamines and dicarboxylic acids as bridging elements

Stratos Vassis,[a] Ioannis Govaris,[a] Katerina Voyagi,[a] Petros Mamos[b] and Dionissios Papaioannou[a,*]

[a]*Department of Chemistry, University of Patras, GR-265 00 Patras, Greece*
[b]*Department of Medicine, University of Patras, GR-265 00 Patras, Greece*

Received 6 November 2001; revised 7 February 2002; accepted 12 February 2002

Abstract—Selectively *N*-tritylated spermidine and spermine derivatives and the monophenacyl ester of 1,16-hexadecanedioic acid (Hda) were used to obtain the polyamine alkaloid tenuilobine and its fully reduced analogue. Other symmetric or side-chain-shortened tenuilobine analogues were readily obtained by using Hda or its dichloride or succinic anhydride to bridge the polyamine moieties.

In the preceding letter we have shown that cyclic polyamines (PAs) can be readily obtained from suitable *N*-tritylated PAs and cyclic anhydrides, such as succinic anhydride. We now wish to report an extension of this protocol to accommodate the synthesis of asymmetric (cross-conjugated) and symmetric polyamine conjugates and their reduced analogues.[1] We were interested in these compounds because the alkaloid tenuilobine (**1**) is the first natural polyamine conjugate (PAC) incorporating both spermine (SPM) and spermidine (SPD),[2] whereas a recent publication reported that certain symmetrical SPD and norspermidine dimers are high affinity PA transport inhibitors.[3] Symmetric PA dimers with dicarboxylic acids have been already synthesized using the corresponding dichlorides and linear triamines, such as **2**–**5** (Fig. 1), selectively protected at their primary amino functions with either the phthalyl (Phth)[4] or the trityl (Trt) group.[3,5] On the other hand,

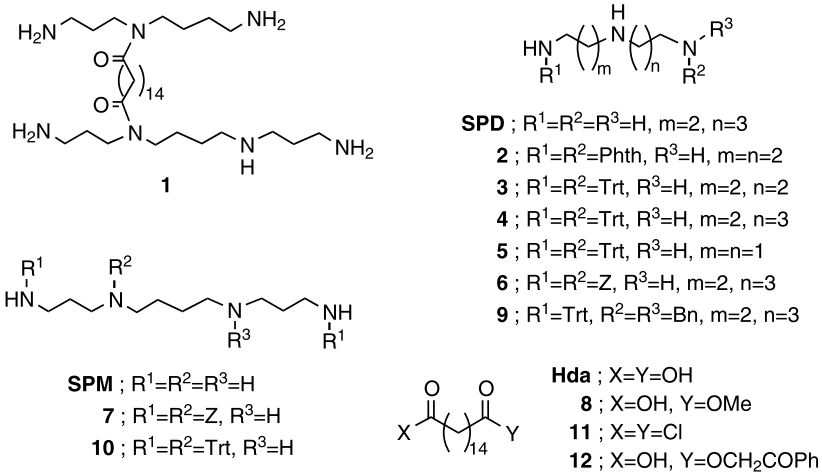


Figure 1. Structures of compounds encountered in the present work.

Keywords: dicarboxylic acids; cyclic anhydrides; polyamine conjugates; spermine; spermidine; tenuilobine; protecting groups.
* Corresponding author. E-mail: d.a.papaioannou@chemistry.upatras.gr

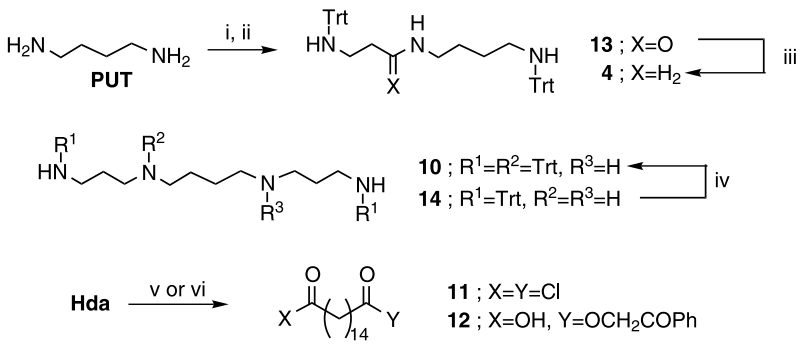
0040-4039/02/$ - see front matter
PII: S0040-4039(02)00338-6

Hesse et al. used the di-benzyloxycarbonyl (*Z*)-protected SPD (**6**), Z_3-SPM (**7**) and the monomethyl ester **8** of 1,16-hexadecanedioic acid (Hda) to assemble tenuilobine.[6] Ester **8** was obtained from the corresponding ω-hydroxyacid through a two-step sequence whereas all the aforementioned, selectively protected, PAs were obtained through selective protection of the primary amino functions of the parent PAs. For our synthetic purposes, we used the SPD derivatives **4**[3] or **9**[7] and the novel SPM derivative **10** for the introduction of the PA moieties and cyclic anhydrides, such as succinic anhydride, or longer chain dicarboxylic acids, such as Hda, or their corresponding dichlorides, e.g. **11**, or the monophenacyl esters, e.g. **12**, for bridging the PA moieties.

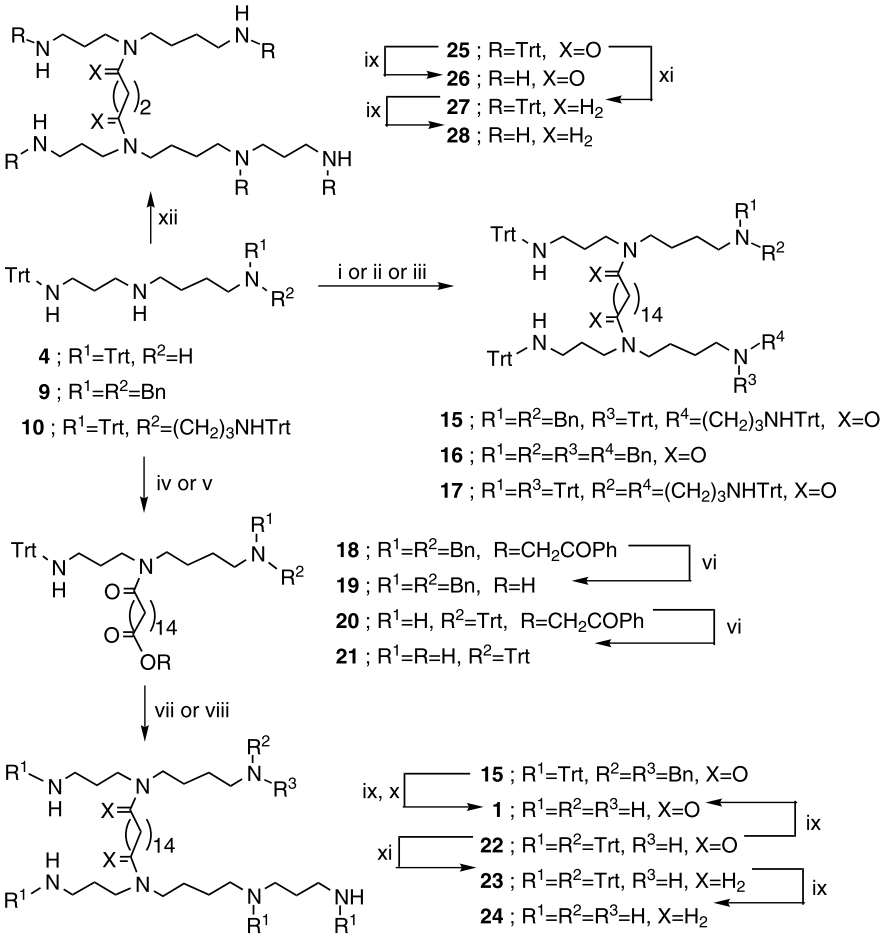
For the needs of this project, the SPD derivative **4** was obtained in 47% overall yield through selective monotritylation of a 5-fold excess of putrescine (PUT) with TrtCl, followed by acylation of the primary amino function with Trt-Ala-OSu[8] and finally reduction of the amide **13** thus obtained (Scheme 1) with $LiAlH_4$. On the other hand, the SPM derivative **10** was readily secured in 55% yield through monotritylation of N^1,N^{12}-Trt_2-SPM (**14**)[8,9] with 1 equiv. TrtCl, followed by routine flash column chromatography purification. Similarly, the ester **12** was obtained in 65% yield through monoesterification of the commercially available Hda with 1 equiv. phenacyl bromide in the presence of $^iPr_2NEt$, also followed by flash column chromatography purification.[10] The choice of the phenacyl group was based on its well-known property to be readily removable under conditions (PhSNa) which do not affect the highly hydrophobic Trt group, whereas following the esterification (by TLC) and the subsequent purification of the monoester from the diester which was also formed and unreacted dicarboxylic acid was greatly facilitated by the presence of its lipophilic PhCO-chromophore. Finally, the required dichloride **11** was simply obtained in 95% yield by treating the commercially available acid Hda with $SOCl_2$ at reflux in PhH.

Condensation of equimolar amounts of the PA derivatives **9** and **10** and the acid Hda in the presence of 2 molar equiv. of the condensing agent bromotripyrrolidinophosphonium hexafluorophosphate (PyBrOP) and 5 equiv. of $^iPr_2NEt$ produced a mixture of the fully protected tenuilobine **15** and the symmetric analogues **16** and **17** in the ratio of 1.5:1:1 (Scheme 2), which were readily separated by flash column chromatography. The SPD dimer **16** was simply prepared in 45% yield by reacting 2 equiv. of SPD derivative **9** with 1 equiv. of the dichloride **11** in the presence of Et_3N, whereas the SPM dimer **17** was obtained in 57% yield by reacting 2 equiv. of SPM derivative **10** with 1 equiv. of acid Hda in the presence of 2 equiv. of PyBrOP and 5 equiv. of $^iPr_2NEt$. On the other hand, the tenuilobine derivative **15** was assembled in 25% overall yield using the following three-step sequence. PyBrOP-mediated coupling of SPD derivative **9** with ester **12** gave the intermediate **18** in 60% yield. The phenacyl group was then selectively removed with NaSPh and the acid **19** thus obtained was coupled to **10**, also in the presence of PyBrOP, to give **15**. The formal synthesis of tenuilobine (**1**) was completed in 67% yield by routine detritylation of **15** using a solution of CF_3CO_2H in CH_2Cl_2 (1:2), followed by hydrogenolysis at ambient temperature and 3 atm of H_2 pressure in the presence of Perlman's catalyst to remove both benzyl (Bn) groups.[7] The synthesis of tenuilobine was further simplified by using the alternative SPD derivative **4** to introduce the SPD skeleton into the molecule. Thus, PyBrOP-mediated coupling of **4** with ester **12** gave the intermediate ester **20** in 70% yield. The phenacyl group was then split off with NaSPh to give acid **21** in 57% yield. Coupling of the latter to **10**, also in the presence of PyBrOP, gave the fully protected tenuilobine **22** in 68% yield. Complete detritylation with CF_3CO_2H in CH_2Cl_2 produced tenuilobine in 98% yield as its corresponding pentatrifluoroacetate salt. It should be noted that $LiAlH_4$ reduction of the bisamide **22** in refluxing THF gave the branched PA derivative **23** in 86% yield,[11,12] which upon detritylation with CF_3CO_2H in CH_2Cl_2 gave the fully reduced tenuilobine analogue **24** in 96% yield.

Furthermore, side-chain-shortened tenuilobine analogues can be simply assembled in one-pot reactions using commercially available cyclic anhydrides as exem-



Scheme 1. Synthesis of key-intermediates for the assembly of PACs. *Reagents and conditions*: (i) TrtCl, CH_2Cl_2, 0°C, 2 h; (ii) Trt-βAla-OSu/Et_3N, DMF, 0°C, 30 min then 25°C, 1 h, 73%; (iii) $LiAlH_4$, THF, reflux 2 day, 65%; (iv) TrtCl/Et_3N, CH_2Cl_2, 0°C, 1 h then 25°C, 1 day, FCC (EtOAc), 55%; (v) $SOCl_2$, PhH, reflux, 2 h, 95%; (vi) $PhCOCH_2Br$/$^iPr_2NEt$, DMF, 25°C, 1 day, FCC ($CHCl_3$/MeOH = 98:2), 65%.



Scheme 2. Synthesis of symmetric and asymmetric PACs. *Reagents and conditions*: (i) [**9**+**10**+**Hda**]/PyBrOP/$^{i}Pr_2NEt$, DMF, 0°C, 30 min then 25°C, 3 h; (ii) [**9**]/**11**/Et_3N, CH_2Cl_2, 0°C, 30 min then 25°C, 3 h, FCC (PhMe/EtOAc = 8:2), 45%; (iii) [**10**+**Hda**]/PyBrOP/$^{i}Pr_2NEt$, DMF, 25°C, 1 day, FCC (PhMe/EtOAc = 95:5 then 9:1), 57%; (iv) [**9**+**12**]/PyBrOP/$^{i}Pr_2NEt$, DMF, 0°C, 30 min then 25°C, 3 h, FCC (PhMe/EtOAc = 95:5 then 9:1), 60%; (v) [**4**+**12**]/PyBrOP/Et_3N, $CHCl_3$, 0°C, 30 min then 25°C, 24 h, FCC (PhMe/EtOAc = 95:5 then 9:1), 70%; (vi) PhSH/NaH (55%)/imidazole (cat.), DMF, 25°C, 2–3 days, FCC (PhMe/EtOAc = 7:3), 60% (**19**) and 57% (**21**); (vii) [**10**+**19**]/PyBrOP/$^{i}Pr_2NEt$, CH_2Cl_2, 0°C, 30 min then 25°C, 3 h, FCC (PhMe/EtOAc = 5:95), 70%; (viii) [**10**+**21**]/PyBrOP/$^{i}Pr_2NEt$, CH_2Cl_2, 0°C, 30 min then 25°C, 1 day, FCC (PhMe/EtOAc = 9:1), 68%; (ix) CF_3CO_2H/CH_2Cl_2 (1:2), 25°C, 2 h, 94–98%; (x) 20% $Pd(OH)_2$-C, H_2 (3 atm), MeOH, 25°C, 2 days, 71%; (xi) $LiAlH_4$, THF, reflux, 1 day, 86% (**23**), 50% (**27**) following FCC ($CHCl_3$/MeOH = 98:2); (xii) [**10**+succinic anhydride]/Et_3N, CH_2Cl_2, 0°C, 30 min then **4** and PyBrOP, 25°C, 1 h, FCC (PhMe/EtOAc = 9:1), 60%.

plified herein with succinic anhydride. Thus, treatment of **10** with an equimolar amount of succinic anhydride in the presence of Et_3N for 30 min at 0°C, followed by the sequential addition of equimolar amounts of **4** and PyBrOP and stirring for a further 1 h at 25°C provided the bisamide **25** in 60% yield. From this, the tenuilobine analogue **26** was obtained in 95% yield by detritylation, whereas its reduced analogue **28** was obtained in 48% overall yield via $LiAlH_4$-mediated reduction of bisamide **25**, followed by routine detritylation of the PA derivative **27** thus obtained. Recently, syntheses of other novel tenuilobine analogues, incorporating aromatic carboxylic acids, have been disclosed.[13]

In conclusion, the present methodology provides easy access to cross-conjugated and symmetric PA conjugates and reduced analogues using readily available *N*-tritylated PAs and cyclic anhydrides or longer-chain linear dicarboxylic acids or their corresponding monophenacyl esters. Further applications of this synthetic protocol and the biological evaluation of the final products currently described as potential polyamine transport inhibitors are presently under investigation.

Acknowledgements

The European Commission and the Greek Ministry of Education are gratefully acknowledged for financial support in the form of a fellowship (S.V.) and consumables.

References

1. For recent reviews on PAs and PACs, see: (a) Blagbrough, I. S.; Carrington, S.; Geall, A. J. *Pharm. Sci.* **1997**, *3*, 223–233; (b) Schulz, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 314–326; (c) Karigiannis, G.; Papaioannou, D. *Eur. J. Org. Chem.* **2000**, 1841–1863; (d) Kuksa, V.; Buchan, R.; Kong Thoo Lin, P. *Synthesis* **2000**, 1189–1207.
2. Doll, M. K.-H.; Guggisberg, A.; Hesse, M. *Heterocycles* **1996**, *42*, 319–324.
3. Covassin, L.; Desjardins, M.; Charest-Gaudreault, R.; Audette, M.; Bonneau, M.-J.; Poulin, R. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1709–1714.
4. Sosnovsky, G.; Lukszo, J. *Z. Naturforsch.* **1986**, *41b*, 122–129.
5. Zang, E.; Sadler, P. J. *Synth. Commun.* **1997**, *27*, 3145–3150. See also Ref. 11b.
6. Doll, M. K.-H.; Guggisberg, A.; Hesse, M. *Helv. Chim. Acta* **1996**, *79*, 541–547.
7. Vassis, S.; Karigiannis, G.; Balayiannis, G.; Militsopoulou, M.; Mamos, P.; Francis, G. W.; Papaioannou, D. *Tetrahedron Lett.* **2001**, *42*, 1562–1579.
8. Karigiannis, G.; Mamos, P.; Balayiannis, G.; Katsoulis, I.; Papaioannou, D. *Tetrahedron Lett.* **1998**, *39*, 5117–5120.
9. Krakowiak, K. E.; Bradshaw, J. S. *Synth. Commun.* **1998**, *28*, 3451–3459.
10. The structures of new compounds were determined by IR, ESI-MS, NMR and microanalysis. Yields of the reactions described herein are not optimized. For the sake of brevity, flash column chromatography is abbreviated as FCC in the captions to schemes.
11. For recent references to the reduction of polyamides by $LiAlH_4$ or diborane en route to the synthesis of linear and cyclic polyamines, see: (a) Aston, K. W.; Henke, S. L.; Modak, A. S.; Riley, D. P.; Sample, K. R.; Weiss, R. H.; Neumann, W. L. *Tetrahedron Lett.* **1994**, *35*, 3687–3690; (b) Zang, E.; Sadler, J. *Synthesis* **1997**, 410–412; (c) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Tetrahedron* **1999**, *55*, 335–344; (d) Wang, F.; Manku, S.; Hall, D. G. *Org. Lett.* **2000**, *2*, 1581–1583; (e) Acharya, A. N.; Ostresh, J. M.; Houghten, R. A. *Tetrahedron* **2001**, *57*, 9911–9914; (f) Achmatowicz, M.; Jursczak, J. *Tetrahedron: Asymmetry* **2001**, *12*, 111–119; (g) Achmatowicz, M.; Jursczak, J. *Tetrahedron: Asymmetry* **2001**, *12*, 487–495; (h) Manku, S.; Laplante, C.; Kopac, D.; Chan, T.; Hall, D. G. *J. Org. Chem.* **2001**, *66*, 874–885. For the reduction of sensitive amides to amines Raney nickel-mediated desulfurization of the corresponding thioamides may be used: Blagbrough, I. S.; Moya, E. *Tetrahedron Lett.* **1994**, *35*, 2057–2060.
12. A variety of unsymmetrical PACs have been synthesized using the alternative reductive alkylation approach for the assembly of their PA skeleton. For examples see: (a) Geall, A. J.; Blagbrough, I. S. *Tetrahedron Lett.* **1998**, *39*, 443–446; (b) Carrington, S.; Renault, J.; Tomasi, S.; Corbel, J.-C.; Uriac, P.; Blagbrough, I. S. *J. Chem. Soc., Chem. Commun.* **1999**, 1341–1342; (c) Blagbrough, I. S.; Geall, A. J.; David, S. A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1959–1962; (d) Geall, A. J.; Blagbrough, I. S. *Tetrahedron* **2000**, *56*, 2449–2460.
13. Popaj, K.; Guggisberg, A.; Hesse, M. *Helv. Chim. Acta* **2000**, *83*, 3021–3024.