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Simple syntheses of cyclic polyamines using selectively *N*-tritylated polyamines and succinic anhydride

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Abstract—Treatment of selectively *N*-tritylated spermidine and spermine derivatives with succinic anhydride, followed by PyBrOP-mediated intramolecular amide bond formation and $LiAlH_4$ reduction, allows for an easy and general entry to cyclic polyamine derivatives.

Linear polyamines (PAs), like spermidine (SPD, **1**) and spermine (SPM, **2**) and conjugates (PACs) are widely distributed in living organisms and are associated with interesting biological functions. A variety of open-chain, branched and cyclic PA analogues and PACs have been synthesized in order to determine structure–activity relationships and identify lead compounds for the development of PA-based pharmaceuticals.[1] We have shown that the PA skeleton of *N*-alkylated PAs and PACs of the alkaloid kukoamine A (KukA, **3**) type can be assembled simply using the *N*-hydroxysuccinimide (HOSu) or 1-hydroxybenzotriazole (HOBt) active esters (**4** and **5**, Fig. 1) of the *N*-triphenylmethyl (trityl, Trt)-protected amino acids β-alanine (Ala) and γ-aminobutyric acid (γAba) to acylate suitable amino components, followed by $LiAlH_4$ reduction of the amides.[2–4] We now wish to report on a simple synthetic protocol which allows the preparation of cyclic PAs (CPAs) of variable ring-sizes using selectively *N*-tritylated SPM and SPD derivatives, such as N^1,N^{12}-Trt_2-SPM (**6**),[2a] N^4-Trt-SPD (**7**) and N^1-Trt-SPD (**8**)[2c] and cyclic anhydrides, such as succinic anhydride, to bridge intramolecularly the polyamine moieties.

Thus, reaction of the SPM derivative **6** with an equimolar amount of succinic anhydride produced a 55% yield of the anticipated acid **9** (Scheme 1), which precipitated out from the solution of the reactants in CH_2Cl_2. Small amounts of unreacted **6** and some diacylated derivative **10** remained in the reaction solution. The condensing agent, bromotripyrrolidinophosphonium hexafluorophosphate (PyBrOP), was then chosen to bring about the required intramolecular amide bond formation. Indeed, dropwise addition, over 5 h, of a solution of **9** and $^iPr_2NEt$ in $CHCl_3$ to a solution of PyBrOP, also in $CHCl_3$, and then stirring at ambient temperature for an

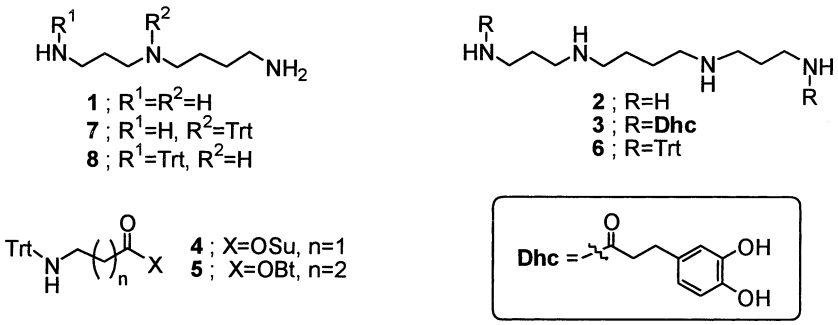

Figure 1. Structures of compounds encountered in this work.

Keywords: spermine; spermidine; cyclic anhydride; cyclic polyamine; trityl group.

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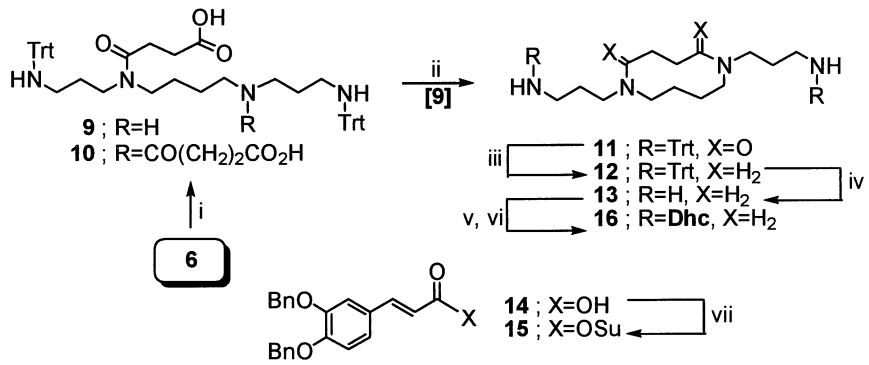
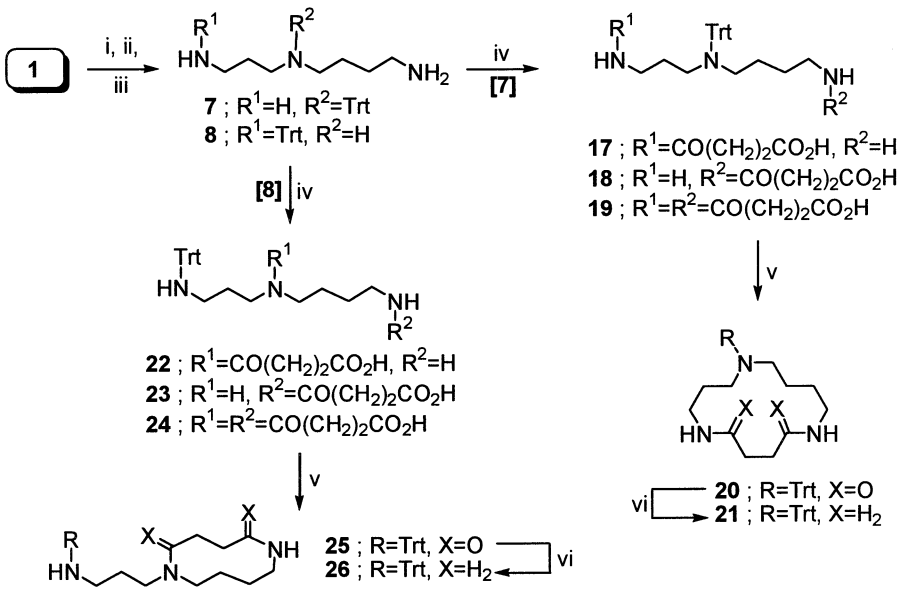


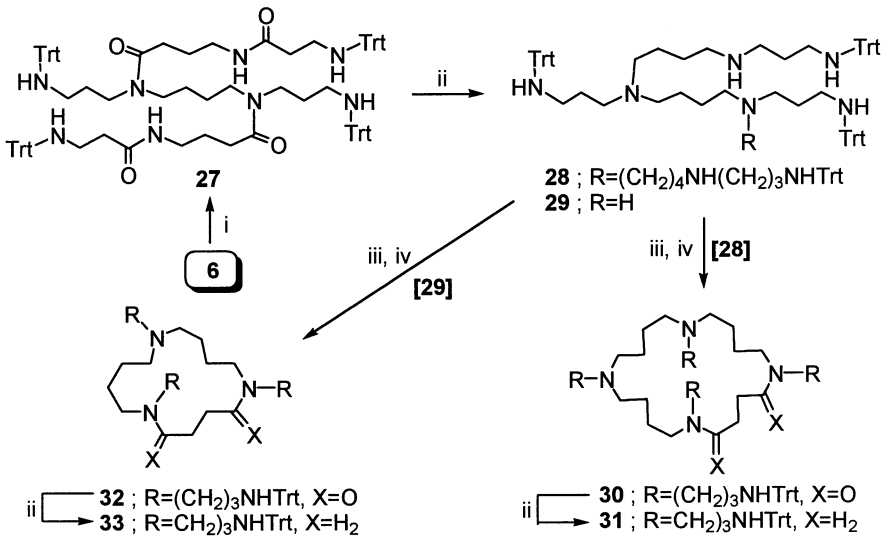
Scheme 1. Synthesis of cyclic SPM and KukA analogues. *Reagents and conditions*: (i) succinic anhydride, CH_2Cl_2, 0°C, 1 h then 25°C, 1 day, 55%; (ii) PyBrOP/^{i}Pr$_2$NEt, $CHCl_3$, 25°C, 2 days, FCC ($CHCl_3$/MeOH = 8:2), 57%; (iii) $LiAlH_4$, THF, reflux 5 h, 78%; (iv) CF_3CO_2H/CH_2Cl_2 (1:4), 25°C, 30 min; (v) **15**/Et_3N, DMF, 0°C, 30 min then 25°C, 24 h, FCC ($CHCl_3$/MeOH/conc. NH_3 (9:1:0.1), 47%; (vi) H_2 (1 atm)/10% Pd–C, AcOH/MeOH/H_2O (5:4:0.2), 25°C, 4 h, then 2N HCl in MeOH, 89%; (vii) HOSu/*N*,*N*′-dicyclohexylcarbodiimide, THF/DMF (3:1), 0°C, 1 h then 25°C, 2 days, 72%.

additional 2 days produced bislactam **11** in 57% yield following routine purification by flash column chromatography.[5] Subsequently, the amide functions were readily reduced with $LiAlH_4$ in refluxing THF to give the cyclic SPM derivative **12** in 78% yield. The Trt-groups were then cleaved off with a 20% trifluoroacetic acid solution in CH_2Cl_2. The SPM analogue **13** thus obtained could be readily converted to the novel conformationally restricted KukA analogue **16** in 42% overall yield through double acylation with the isolable active ester **15** followed by catalytic hydrogenolysis.[2b] Ester **15** was readily obtained in 72% yield upon condensing acid **14**[2b] with HOSu in the presence of *N*,*N*′-dicyclohexylcarbodiimide.[6] It should be noted that syntheses of several cyclic SPD and SPM analogues or other PAs have been reported using the alkylation of suitable tosylamides[7,8] or amine nucleophiles[9] as the ring-forming reaction.

The suitability of this protocol for the preparation of other CPAs was tested with the preparation of the SPD derived heterocycles **21** and **26** (Scheme 2). The preparation of these CPAs required the availability of the selectively monotritylated SPD derivatives **7** and **8**, respectively. For the needs of this project, derivative **8**[2c] was obtained in a 40% overall yield by selective monoacylation of a ten-fold excess of 1,4-diaminobutane with the active ester **4**, followed by $LiAlH_4$ reduction. On the other hand, derivative **7** was readily obtained in 64% yield through selective bistrifluoroacetylation of SPD at the primary amino functions[10] followed by N^4-tritylation and alkaline



Scheme 2. Synthesis of cyclic SPDs. *Reagents and conditions*: (i) CF_3CO_2Et/H_2O, MeCN, reflux, 12 h, 92%; (ii) TrtCl/^{i}Pr$_2$NEt, DMF, 0°C, 30 min then 25°C, 1 h, FCC (PhMe/EtOAc = 8:2), 91%; (iii) K_2CO_3, H_2O/MeOH, reflux, 90 min, FCC ($CHCl_3$/MeOH/conc. NH_3 = 8:2:0.2), 77%; (iv) succinic anhydride, CH_2Cl_2, 0°C, 1 h then 25°C, 1 day, FCC ($CHCl_3$/MeOH/conc. NH_3 = 7:3:0.3), 38% (**17**+**18**) and 50% (**22**+**23**); (v) PyBrOP/^{i}Pr$_2$NEt, $CHCl_3$, 25°C, 2 days, 56% (**20**) and FCC ($CHCl_3$/MeOH = 95:5), 50% (25); (vi) $LiAlH_4$, THF, reflux, 2 days, FCC ($CHCl_3$/MeOH/conc. NH_3 = 8:2:0.2), 44% (**21**) and 35% (**26**).



Scheme 3. Synthesis of the cyclic octa-amine **31** and hexa-amine **33**. *Reagents and conditions*: (i) Trt-Ala-γ-Aba-OSu/$^{i}Pr_2NEt$, DMF, 25°C, 1 day, FCC (EtOAc), 70%; (ii) $LiAlH_4$, THF, reflux, 2–3 days, FCC: (a) ($CHCl_3$/MeOH/conc. NH_3 = 9:1:0.1), 56% (**28**) and 23% (**29**), (b) ($CHCl_3$/MeOH/conc. NH_3 = 9:1:0.1), 70% (**31**) and (c) ($CHCl_3$/MeOH = 9:1), 65% (**33**); (iii) succinic anhydride, $CHCl_3$, 0°C, 1 h then 25°C, 1 day, FCC ($CHCl_3$/MeOH/conc. NH_3 = 8:2:0.2), 77% [**28**] and 68% [**29**]; (iv) PyBrOP/$^{i}Pr_2NEt$, $CHCl_3$, 25°C, 1–2 days, FCC ($CHCl_3$/MeOH/conc. NH_3 = 8:2:0.2), 70% (**30**) and 72% (**32**).

hydrolysis. Treatment of intermediates **7** and **8** with succinic anhydride produced the expected mixtures of regioisomers **17**, **18** and **22**, **23** which were readily separated in 38 and 50% yields by flash column chromatography from unreacted starting materials and diacylated byproducts **19** and **24**, respectively. Although, separation of these regioisomers (e.g. of **17** and **18**) was also possible, the mixtures were used as such in the next cyclization step. Indeed, PyBrOP-mediated cyclization of these intermediates produced unexceptionally, the corresponding cyclic bisamides **20** and **25** in 56 and 50% yields, respectively. From these amides, the projected cyclic SPD derivatives **21** and **26** were obtained in 44 and 35% yields, respectively, upon $LiAlH_4$ reduction.

This methodology was extended to accommodate even more complex polyamine molecules, as exemplified by the preparation of the cyclic octa-amine **31** and hexa-amine **33** (Scheme 3). Thus, bisacylation of **6** by the isolable active ester Trt-Ala-γAba-OSu[2c] produced the tetra-amide **27** in 70% yield. $LiAlH_4$ reduction of **27** gave a mixture of the expected branched octa-amine **28** (56% yield) and the hexa-amine **29** (23%) together with **6** and the alcohol Trt-$NH(CH_2)_3NH(CH_2)_4OH$. The last three components were obviously produced through a $LiAlH_4$-mediated mono- and dideacylation of **27**.[11] However, the octa-amine **28** and the hexa-amine **29** could be separated by flash column chromatography and when first treated with succinic anhydride and then subjected to PyBrOP-mediated cyclization gave the corresponding bislactams **30** and **32** in 54 and 49% yields. Finally, $LiAlH_4$-mediated reduction of these produced, unexceptionally, the cyclic octa-amine (**31**) and hexa-amine (**33**) derivatives in 70 and 65% yields, respectively.

In conclusion, the present methodology provides easy access to cyclic polyamines of variable ring-sizes using simple and readily available *N*-tritylated polyamines and cyclic anhydrides. Further applications of this protocol in the synthesis of other medicinally interesting cyclic polyamine analogues and conjugates are currently under investigation.

Acknowledgements

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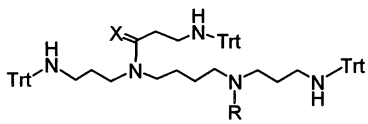
11. We have also encountered this side-reaction with tertiary polyamine amides on $LiAlH_4$ reductions of N^4-acyl, N^1-Trt-N^8,N^8-Bn_2-SPDs (see Ref. 2c) and of the bisamide **34**. The latter is readily obtained in 70% yield through bisacylation of **6** with active ester **4**, in the presence of Et_3N in DMF, for 45 min at 0°C and 15 h at 25°C and finally purification with flash column chromatography (PhMe/EtOAc = 9:1). Thus, reduction of **34** in refluxing THF for 12 h produced a mixture (by ESI–MS) of the anticipated hexa-amine **35**, the penta-amine **36**, the SPM derivative **6** and $TrtNH(CH_2)_3OH$, from which **35** was readily recovered in 50% yield through flash column chromatography ($CHCl_3$/MeOH = 9:1).



34 ; R=$CO(CH_2)_2NHTrt$, X=O
35 ; R=$(CH_2)_3NHTrt$, X=H_2
36 ; R=H, X=H_2