Pergamon

Tetrahedron Letters 42 (2001) 1579–1582

TETRAHEDRON LETTERS

Simple syntheses of *N*-alkylated spermidine fragments and analogues of the spermine alkaloid kukoamine A

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Received 25 September 2000; revised 29 November 2000; accepted 14 December 2000

Abstract—Acylation of a variety of amines with succinimidyl *N*-trityl-β-alanyl-γ-aminobutyrate and *N*-trityl-γ-aminobutyryl-β-alaninate, readily obtained through coupling of succinimidyl *N*-trityl-β-alaninate with trimethylsilyl γ-aminobutyrate and of *N*-trityl-γ-aminobutyric acid with methyl β-alaninate, respectively, followed by $LiAlH_4$ reduction, produced *N*-monoalkylated spermidine fragments and analogues of the spermine alkaloid kukoamine A. The applicability of this methodology on the solid phase was also demonstrated. © 2001 Elsevier Science Ltd. All rights reserved.

Synthetic *N*-alkylated analogues and homologues of the naturally occurring linear polyamines (PAs) spermidine (SPD) and spermine (SPM) and natural or synthetic PA conjugates (PACs) show interesting biological properties and thus constitute attractive synthetic targets.[1] We have recently shown that a variety of PA analogues and analogues of the alkaloid kukoamine A (KukA) can be readily prepared, employing the *N*-triphenylmethyl (trityl, Trt)- or polymeric *o*-chlorotrityl (PCtr)-protected amino acids β-alanine (βAla) and γ-aminobutyric acid (γAba) in the form of the corresponding active esters (**1**–**3**, Fig. 1) with *N*-hydroxysuccinimide (HOSu) or 1-hydroxybenzotriazole (HOBt), to acylate suitable amino components, followed by $LiAlH_4$ reduction of the amides.[2] The required dihydrocaffeyl (Dhc) units were introduced in the SPM skeleton of KukA through the acyl chloride **4** (Dbc-Cl).[2b] Using a similar protocol, Nordlander et al. employed other derivatives of βAla and γAba to obtain *N*-polyalkylated SPDs.[3] We now wish to report on a simple fragment synthesis protocol which allows the efficient preparation of selectively *N*-alkylated SPDs and SPD analogues of KukA using active esters **1**–**3** and the dipeptide active esters **5**, **6** and **14** (Schemes 1 and 2).

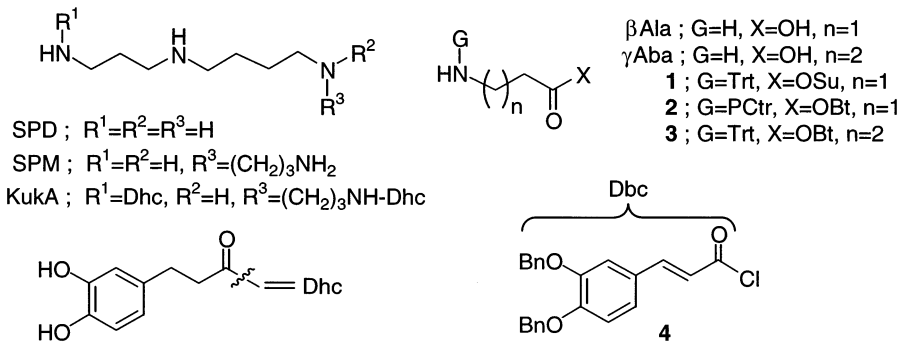

Figure 1. Structures of compounds used to prepare SPD and SPM analogues and conjugates.

Keywords: amino acids and derivatives; spermidine derivatives; fragment synthesis; solid-phase synthesis; protecting groups.
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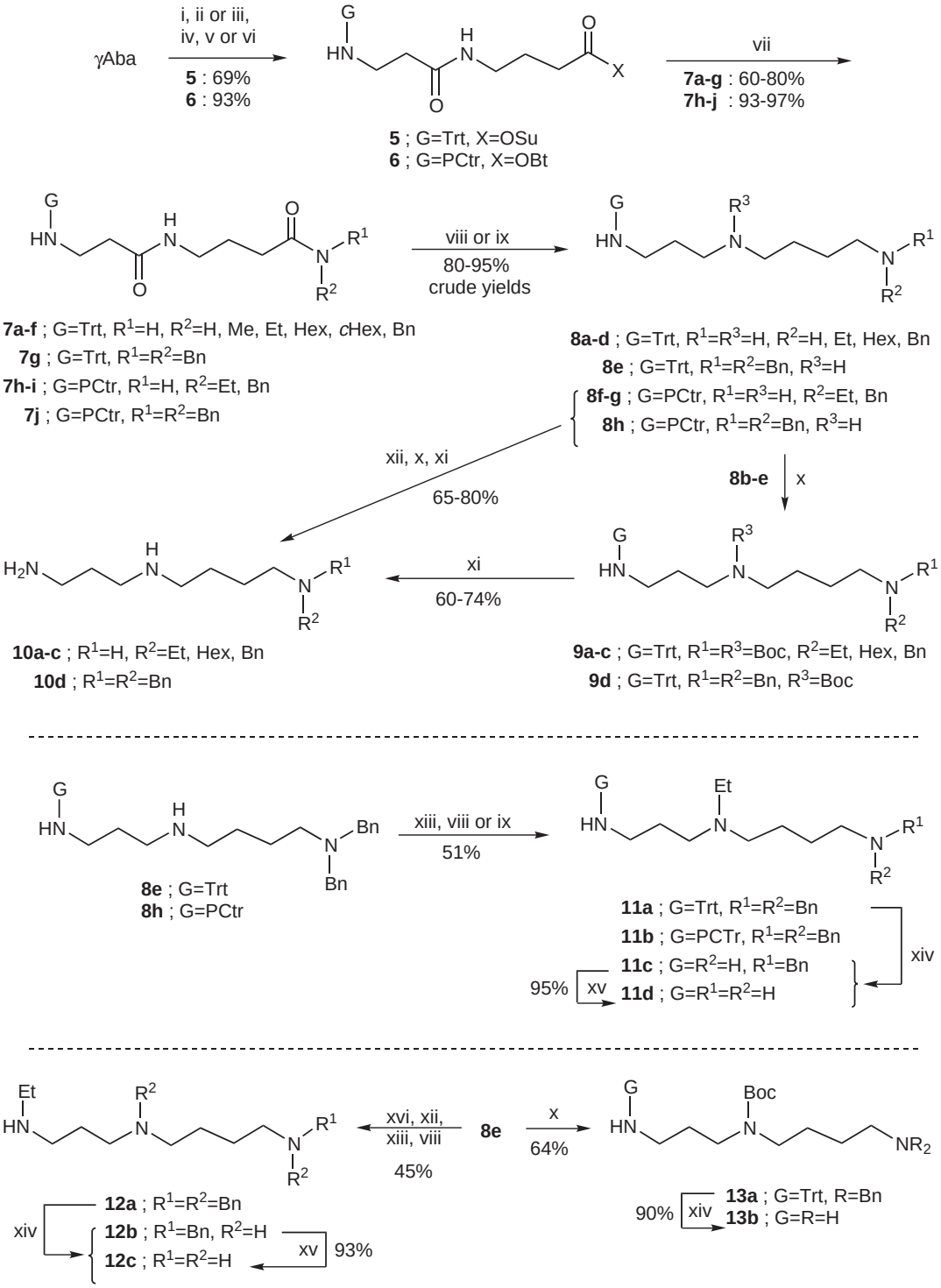
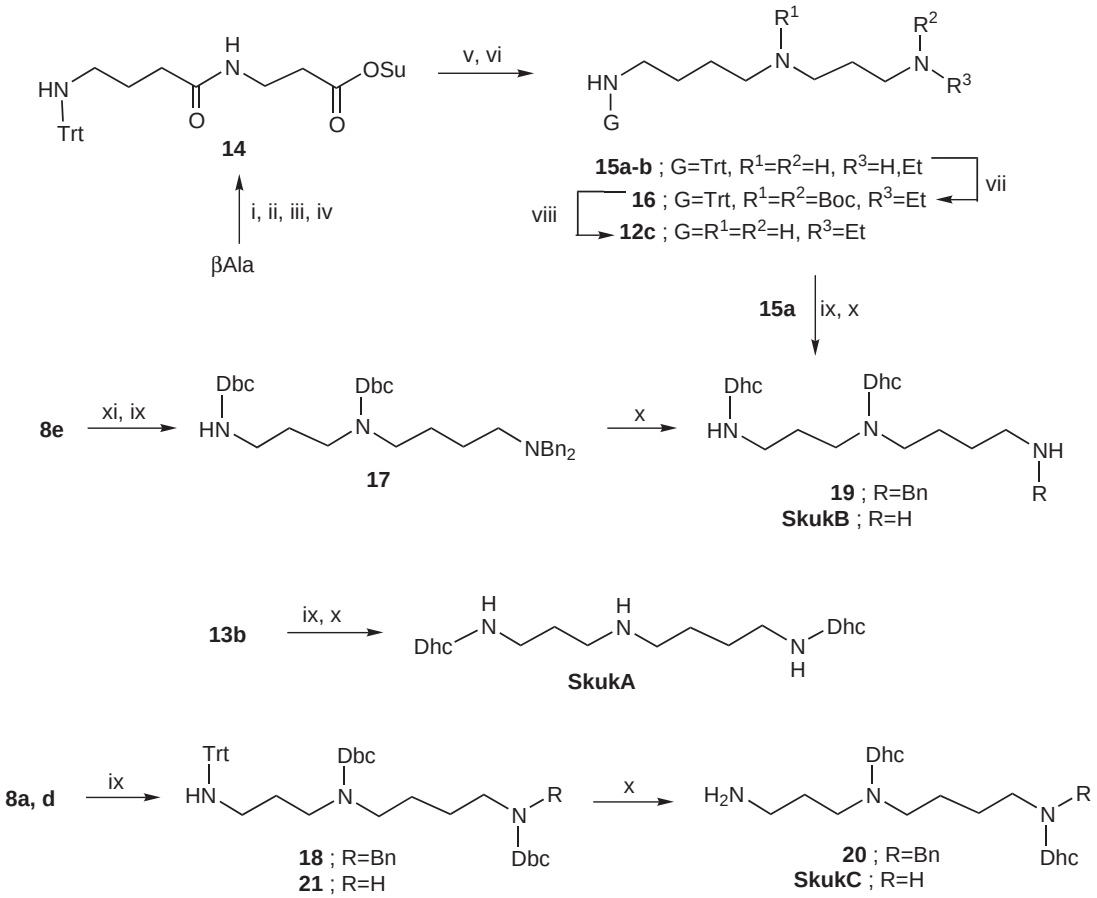
PII: S0040-4039(00)02308-X

Thus, acylation of the in situ generated TMS ester of γAba with either **1** or **2** and then methanolysis gave the dipeptide acids Trt- and PCtr-βAla-γAba-OH which, upon routine activation with HOSu or HOBt in the presence of DCC or diisopropylcarbodiimide (DIC), respectively, produced the corresponding isolable active



Scheme 1. Fragment synthesis of selectively *N*-alkylated SPDs. *Reagents and conditions*: (i) Me_3SiCl, CH_2Cl_2, 25°C, 10 min; (ii) **1**/Et_3N, 0–25°C, 20 min; (iii) **2**/Et_3N, 0, 10 min then 25°C, 6 h; (iv) MeOH; (v) DCC/HOSu, THF/DMF (3:1), 0°C, 1 h then 25°C, 12 h; (vi) DIC/HOBt–THF, 0°C, 1 h then 25°C, 12 h; (vii) R^1R^2NH/Et_3N, DMF (CH_2Cl_2 for resins **7i,j**), 0°C, 10 min then 25°C, 2 h (12 h for resins **7h–j**); (viii) $LiAlH_4$, THF, reflux 1–2 days; (ix) BH_3, THF, reflux, 1–2 days; (x) Boc_2O/Et_3N, $CHCl_3$, 0°C, 15 min then 25°C, 2 h; (xi) TFA/CH_2Cl_2 (1:1), 25°C, 30 min; (xii) TFA–CH_2Cl_2 (1:4), 25°C, 30 min; (xiii) Ac_2O/Et_3N, $CHCl_3$, 0°C, 15 min then 25°C, 1 h; (xiv) H_2/10% Pd–C, EtOAc/MeOH (1:1) then AcOH/MeOH/H_2O (1:1:0.05), 25°C, 1 day; (xv) H_2/20% $Pd(OH)_2$ on C, MeOH, 25°C, 1 day, 3 atm; (xvi) Bz-Cl/Et_3N, $CHCl_3$, 0°C, 15 min then 25°C, 1 h.



Scheme 2. Synthesis of N^1-alkylated SPDs and the KukA analogues SkukA–C. *Reagents and conditions*: (i) MeOH/$SOCl_2$, 0°C, 30 min then 25°C, 1 day, 97%; (ii) Trt-γAba/DCC/HOBt/Et_3N, DMF, 0°C, 30 min then 25°C, 1 day, 30%; (iii) 2N NaOH, MeOH, reflux, 30 min, 98%; (iv) DCC/HOSu, DMF, 0°C, 30 min then 25°C, 12 h, 97%; (v) R^1R^2NH/Et_3N, DMF, 0°C, 10 min then 25°C, 1 h, 55–65%; (vi) $LiAlH_4$, THF, reflux, 1–2 day, 58–82%; (vii) Boc_2O/Et_3N,$CHCl_3$, 0°C, 15 min then 25°C, 2 h, 92%; (viii) TFA/CH_2Cl_2 (1:1), 25°C, 1 h, 97%; (ix) Dbc-Cl (**4**)/Et_3N, CH_2Cl_2, 0°C, 30 min then 25°C, 1–3 h, 50–70%; (x) H_2/10% Pd–C, AcOH/MeOH/H_2O (1:1:0.05), 25°C, 3 h; (xi) TFA/DCM (1:4), 25°C, 30 min; (xii) 2N HCl in MeOH, 25°C, 12 h.

esters **5** and **6** (Scheme 1). Aminolysis of esters **5** and **6** with a variety of concentrated aqueous (aq.) amines, such as 30% NH_3, 40% $MeNH_2$ and 33% $EtNH_2$, or neat amines, such as hexylamine, cyclohexylamine, benzylamine and dibenzylamine, gave the corresponding crystalline amides **7a**–**g**[4] and the polymeric amides **7h**–**j**. Reduction of amides **7a**–**g** with $LiAlH_4$ and of **7h**–**j** with BH_3·THF produced the corresponding crude SPD derivatives **8a**–**h**.[5] Although compounds **8a**–**e** could be routinely purified by chromatography, pure N^8-alkylated SPDs (**10a**–**d**) were better obtained through routine Boc protection of crude compounds, producing compounds **9a**–**d**, followed by purification and complete deprotection with trifluoroacetic acid (TFA).

On the other hand, acetylation of **8e**, followed by reduction of the acetamide with either diisobutylaluminium hydride (DIBALH) or $LiAlH_4$ produced a mixture of the desired N^4-ethylated product **11a** and **8e** (**11a**:**8e** = 6:4), from which **11a** was obtained in pure form through chromatography. Similar results were obtained on the solid phase using **8h** as starting material and BH_3·THF to reduce the polymeric acetamide. Furthermore, benzoylation of **8e**, followed by sequential detritylation, acetylation and $LiAlH_4$ reduction, gave the intermediate **12a**. Complete deprotection of **11a** and **12a** could only be realized using Pearlman's catalyst at 3 atm of hydrogen pressure. On the contrary, compound **13a**, readily obtained from crude **8e** through *tert*-butoxycarbonylation, was readily hydrogenolyzed in the presence of 10% Pd–C producing N^4-Boc-SPD (**13b**). Compound **13b** is a useful intermediate in the synthesis of SPD conjugates.[5a,6] Alternatively, N^1-monoalkylated SPDs, such as N^1-Et-SPD (**12c**), were obtained using active ester **14** (Scheme 2) as key intermediate. Compound **14** was prepared through a four-step protocol involving esterification of H-βAla, followed by coupling with Trt-γAba, saponification and finally activation. Aminolysis of **14** with either 30% NH_3 or 40% $EtNH_2$, followed by $LiAlH_4$ reduction, produced the SPD derivatives **15a** and **b**. Compound **15b**, purified as the diBoc derivative **16**, gave pure **12c** upon deprotection with TFA.

Taking into consideration that the SPD analogue SkukA (Scheme 2) of the alkaloid KukA has similar antiparasitic properties with KukA,[7] we decided to

apply intermediates **8d**, **8e** and **13b** to the synthesis of the three isomers SkukA–C. Indeed, bisacylation of **13b** with Dbc-Cl (**4**), followed by hydrogenolysis and Boc group removal, produced SkukA in 55% overall yield. On the other hand, detritylation of **8e** with TFA, followed by bisacylation with **4**, produced the SkukB precursor **17**, whereas bisacylation of **8d** with **4** gave the SkukC precursor **18**. Hydrogenolyses of precursors **17** and **18**, under the conditions used to obtain N^4-Boc-SPD, produced N^8-Bn-SkukB **19** and -SkukC **20**, respectively, along with small amounts of the corresponding SkukB and SkukC. Finally, bisacylation of the alternative intermediates N^8-Trt-SPD **15a** and N^1-Trt-SPD **8a** with **4**, followed by hydrogenolysis, produced SkukB and SkukC, respectively, in ca. 60% overall yields.

In conclusion, the present methodology provides easy access to *N*-monoalkylated and *N*,*N*′-bisacylated SPDs. It can also be applied to the solid phase and is therefore amenable to combinatorial synthesis applications. Further applications of the new SPD derivatives **8a** and **e**, **13b** and **15a** in the synthesis of other medicinally interesting SPD conjugates are currently in progress.

Acknowledgements

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

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