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Simple Fragment Syntheses of All Four Isomers of the Spermine Alkaloid Kukoamine

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Abstract

All four isomers of the spermine alkaloid kukoamine were unambiguously prepared through diacylation with *O,O'*-dibenzylcaffeyl chloride of suitably protected (benzyl and/or trityl groups) spermine derivatives, assembled on solid and/or in liquid phase using β-alanine and γ-aminobutyric acid, followed by simultaneous *N*- and *O*- deprotection and double bond reduction using catalytic hydrogenation.

Keywords : amino acids and derivatives; polyamines; protecting groups; solid-phase synthesis

Kukoamine A (**1**) is a spermine alkaloid isolated from the dried root bark of *Lycium chinense* which shows hypotensive activity [1] and potent and selective inhibition of trypanothione reductase [2], whereas kukoamine B (**2**) has been recently isolated from the same source and characterized [3]. Two independent syntheses of **1** have been already disclosed [4,5]. We now wish to report a synthetic protocol which allows the preparation of all four regioisomers (**1-4**) of kukoamine. This protocol is based on a recently developed methodology which allows the synthesis of spermine (**5**), spermidine (**6**) and putrescine (**7**) derivatives using the triphenylmethyl (Trt), the 9-fluorenylmethoxycarbonyl (Fmoc) and the benzyl (Bn) groups for the selective protection of the amino functions [6]. The required dihydrocaffeic acid (**8**) derived moieties R for the present syntheses were projected to be introduced into the spermine derivatives **10-13**, bearing the Trt and Bn groups to block selectively two of the four amino functions, using the *O,O'*-dibenzylcaffeyl chloride (**9**). It was anticipated that simultaneous catalytic hydrogenation of the double bonds and hydrogenolysis of the benzyl-type protecting groups of the thus obtained fully protected unsaturated kukoamine derivatives **14-17** would lead to the corresponding kukoamines **1-4**.

Accordingly, stepwise assembly of the spermine skeleton was required. The readily available *N*-Trt and *N*-Fmoc-protected β-alanine (β-Ala) and γ-aminobutyric acid (GABA) as well as putrescine (**7**) were used to provide the N-C_3, N-C_4 and N-C_4-N synthons, respectively. The preparation of key-intermediates **10** and **12** for the synthesis of the corresponding kukoamine A (**1**) and C (**3**) has been already described and involves the assembly of the spermine skeleton through the diacylation of **7** with Trt-β-Ala, in the

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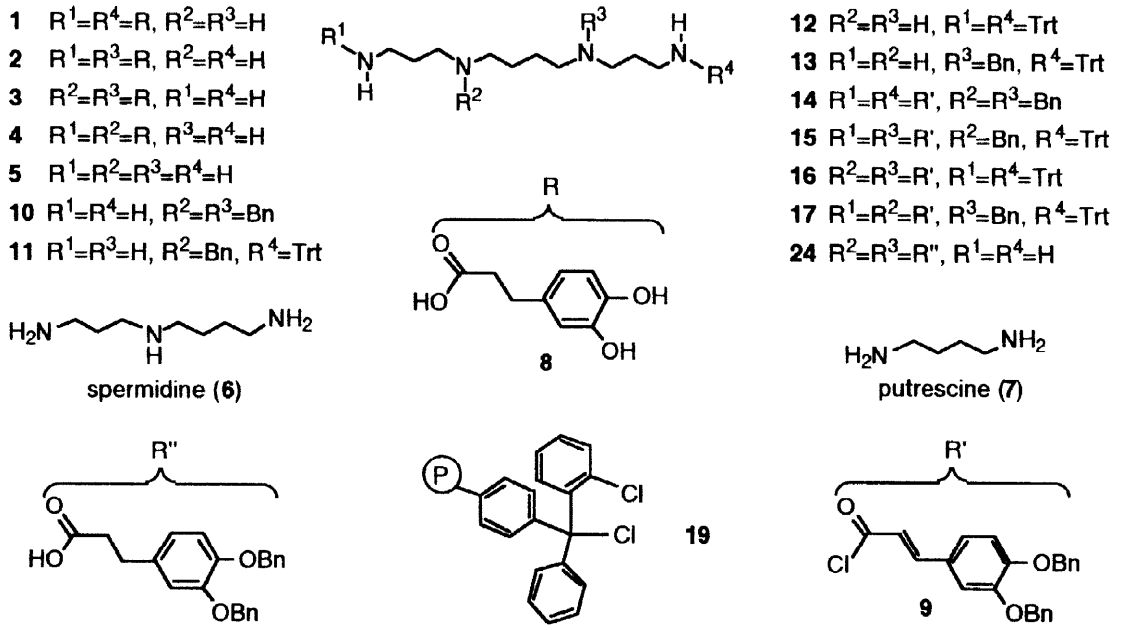
presence of *N,N'*-dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt) [6].[1,2] On the other hand, acyl chloride **9** was prepared in 72% overall yield through the Wittig reaction of the commercially available 3,4-dibenzyloxybenzaldehyde with methoxycarbonylmethylenetriphenylphosphorane, followed by saponification and treatment of the thus obtained unsaturated acid with thionyl chloride in refluxing benzene. Diacylation of **10** and **12** with acyl chloride **9**,[3] in the presence of triethylamine (TEA), proceeded uneventfully giving the bisamides **14** and **16**,[4] respectively in 75-80% yields. Finally, catalytic hydrogenation of bisamides **14** and **16**, in the presence of 10% Pd-C, initially in EtOAc/MeOH (1:1) and then in neat MeOH for 24 h at RT provided kukoamines A and C, respectively in 82-85% yields.[5]



Prompted by a recent report concerning the efficient solid phase synthesis of polyamine conjugates on a 2-chlorotrityl resin (PCTr) [9], we decided to investigate the preparation of kukoamines A and C on this solid support. For this purpose, the polymeric PCTr-Cl (**19**) [10] was used to anchor β-Ala on the solid support in the sameway used to attach amino acids on the trityl resin [11]. The resulting PCTr-β-Ala-OH (1.4 mmol β-Ala/g resin) was subsequently converted to the corresponding "active" ester **20** (Scheme 1) on treatment with 2.5 molar equivalents (eq) of HOBt and 2 molar eq of *N,N'*-diisopropylcarbodiimide (DIC) for 1 h at 0 °C and 5 h at RT. Coupling of **20**

[1] Improved yield (90%) and facilitation of the work-up procedure were secured in the present syntheses by using the isolable, crystalline, "active" ester **18**, readily obtained in 85% yield on reacting Trt-β-Ala with *N*-hydroxysuccinimide (HOSu) in the presence of DCC, for coupling Trt-β-Ala with **7**.

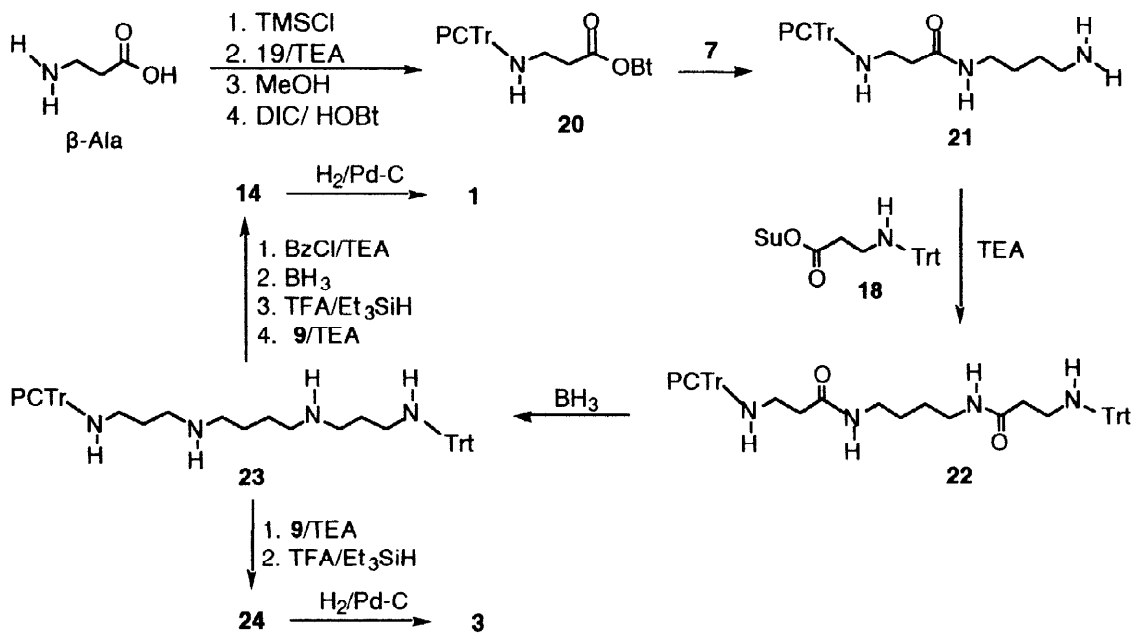
[2] Attempted direct tritylation of spermine to obtain **12** produced, under a variety of conditions, a complex mixture of *N*-tritylated spermine derivatives. However, direct protection of both primary amino functions of spermidine with the 4-methoxytrityl group has been reported [7].

[3] New compounds prepared in this work gave analytical and spectral data in agreement with the proposed structures.

[4] Direct amidation of polyamines with 1-hydroxypiperidinyl esters of dihydroxy aromatic acids with unprotected phenolic groups has been reported [8].

[5] The completion of hydrogenolysis was monitored by liquid secondary ion (LSI) mass spectroscopy.

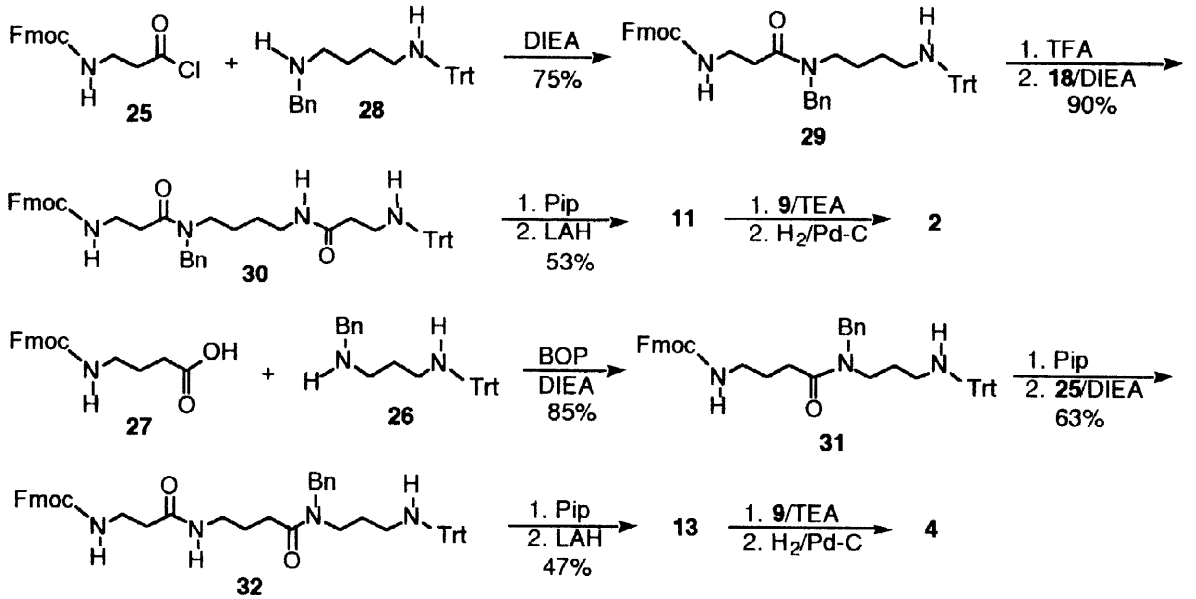
with 5 molar eq of **7** gave the spermidinamide derivative **21** which was then coupled to the "active" ester **18** affording the bisamide **22**. This was subsequently reduced with 5 molar excess of diborane (1M solution in THF) in refluxing THF for 2 d to give the polymeric spermine derivative **23**. Diacylation of **23** with 3 molar eq of the acyl chloride **9**, in the presence of 5 molar eq of TEA, for 2 h at 0 °C, followed by detritylation with 50% trifluoroacetic acid (TFA) and Et_3SiH (4:1) in dichloromethane (DCM) for 5 h at RT, provided the bisamide **24** in 65% overall yield. Catalytic hydrogenolysis of **24** in MeOH, as described above, finally led to kukoamine C. The precursor **14** to kukoamine A could also be readily obtained from **23**, in 63% overall yield, through N^4, N^9-dibenzoylation followed by BH_3 reduction, detritylation and finally diacylation with **9**.



Scheme 1

The synthesis of the other two key-intermediates **11** and **13** was effected using combinations of the β-Ala-derived acyl chloride **25**, the 1,3-diaminopropane derivative **26**, the GABA-derived acid **27** and the 1,4-diaminobutane derivative **28** (Scheme 2). The synthesis of **25** and **28** has been described [6]. On the other hand, routine treatment of GABA with FmocCl/$NaHCO_3$ produced the acid **27** in 85% yield whereas coupling of **18** with benzylamine, followed by LAH reduction, gave **26** in 76% overall yield. Acylation of **28** with **25**, in the presence of diisopropylethylamine (DIEA), gave amide **29** [6] in 75% yield. Detritylation of **29** with 20% TFA in DCM followed by further acylation with **18** provided the bisamide **30** which on routine Fmoc group removal with 20% piperidine (Pip) in DCM and LAH reduction afforded spermine derivative **11** in 48% yield. Spermine derivative **13** was obtained in 25% overall yield through the following sequence of reactions. Acylation of the 1,3-diaminopropane derivative **26** with acid **27** in the presence of the coupling agent benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) and DIEA produced the spermidinamide derivative **31** which upon Pip-mediated removal of the Fmoc group and acylation with chloride **25** gave the

bisamide **32**. The Fmoc group of **32** was then removed with Pip and the resulting compound was reduced with LAH to give **13**. Finally, diacylation of **11** and **13** with chloride **9**, followed by catalytic hydrogenation, produced the expected kukoamines B (**2**) and D (**4**) in 60-70% yields. The biological evaluation of the thus obtained kukoamines as potential hypotensive agents is now in progress and further applications of the presently developed methodology for the synthesis of other selectively modified spermine derivatives are under study.



Scheme 2

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