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Simple Total Syntheses of *N*-Substituted Polyamine Derivatives Using *N*-Tritylamino Acids[1]

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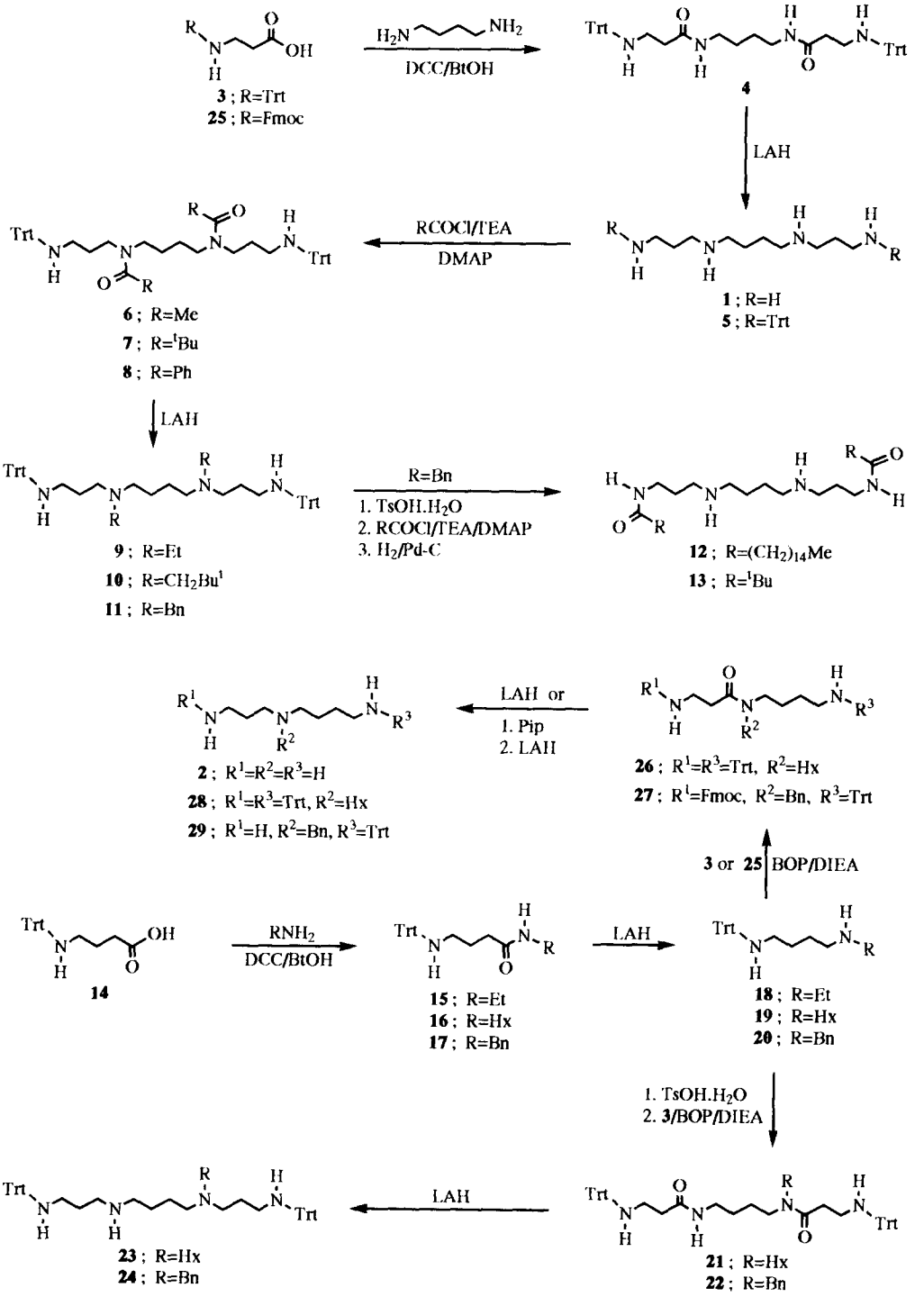
Abstract : A general methodology for the total synthesis of *N*-alkyl- and acylpolyamine derivatives is described which is based on the coupling of suitable *N*-tritylamino acids with amines followed by lithium aluminium hydride reduction of the thus obtained amides.

Polyamines, such as spermine (**1**) and spermidine (**2**), are interesting natural products which are involved in a variety of very important biological functions.[2] Moreover, polyamine surrogates with amino acids such as tyrosine[3] or arginine,[4] isolated from spiders, exhibit potent inhibition of mammalian neurotransmitter receptors. Various synthetic protocols have been devised which allow the preparation of polyamine analogs selectivily modified at their amino functions. These protocols involve either the selective protection of the amino functions of polyamines with groups such as methylene, tosyl (Ts), tert-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz) and phthalyl (Phth),[5] and most recently metal cations[6] and the 4-azidobenzyloxcarbonyl group,[7] or the assembly of the polyamine sceleton from suitably protected amino components using reactions such as the reductive alkylation,[8] the Michael addition on acrylonitrile,[2,9] acylation followed by lithium aluminium hydride (LAH) reduction,[10] and the alkylation of sulfonylamides[11] or more recently triflyl amides using the Mitsunobu reaction.[12] We now wish to report our preliminary results on the development of a general methodology which allows easy access to mono- and di-*N*- alkyl- and acylated spermine derivatives using readily available *N*-tritylamino acids as building blocks.

Key-features in our approach are (a) the use of the bulky triphenymethyl (trityl, Trt) group and the readily removed by hydrogenolysis benzyl group for blocking the desired amino functions and (b) the LAH-mediated reduction of amides, derived from the condensation of suitable *N*-tritylamino acids with a series of amines. The Trt group was chosen for *N*-protection because it is compatible with complex metal


3 ; R=Trt
25 ; R=Fmoc
DCC/BtOH
4
LAH
RCOCl/TEA
DMAP
1 ; R=H
5 ; R=Trt
6 ; R=Me
7 ; R=tBu
8 ; R=Ph
LAH
R=Bn
1. TsOH.H2O
2. RCOCl/TEA/DMAP
3. H2/Pd-C
9 ; R=Et
10 ; R=CH2tBu
11 ; R=Bn
12 ; R=(CH2)14Me
13 ; R=tBu
LAH or
1. Pip
2. LAH
2 ; R1=R2=R3=H
28 ; R1=R3=Trt, R2=Hx
29 ; R1=H, R2=Bn, R3=Trt
26 ; R1=R3=Trt, R2=Hx
27 ; R1=Fmoc, R2=Bn, R3=Trt
3 or 25 BOP/DIEA
14
RNH2
DCC/BtOH
15 ; R=Et
16 ; R=Hx
17 ; R=Bn
LAH
18 ; R=Et
19 ; R=Hx
20 ; R=Bn
1. TsOH.H2O
2. 3/BOP/DIEA
LAH
23 ; R=Hx
24 ; R=Bn
21 ; R=Hx
22 ; R=Bn

hydrides[13] and confers high lipophilicity to intermediates, thus facilitating work-up and purification procedures involving flash column chromatography (FCC).

Thus, *N*- tritylation[14] of the commercially available β-alanine produced crystalline Trt-β-Ala (**3**) in 88% yield. Coupling of **3** with putrescine (1,4-diaminobutane) in DMF for 24 h at RT, in the presence of *N,N'*-dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (BtOH) produced a 82% yield of crystalline bisamide **4**, which upon LAH reduction for 10 h in refluxing THF, produced a 57% yield of N^1,N^{12}-ditritylspermine (**5**). This compound was shown to be a versatile intermediate for the production of a variety of dialkyl- and acylspermine derivatives. Thus, reaction of **5** with a variety of acyl chlorides, e.g. acetyl, pivaloyl and benzoyl chloride, in the presence of triethylamine (TEA) and 4-dimethylamino-pyridine (DMAP) in $CHCl_3$ for 30 min at 0 °C and 2 h at RT, produced the diacylated spermine derivatives **6-8** in 75-85% yields, which could be unexceptionally reduced with LAH in refluxing THF for 1-2 d to the corresponding dialkylated spermine derivatives **9-11** in 62-70% yields. In particular, derivative **11** is valuable for the synthesis of terminally disubstituted spermine derivatives. Thus, detritylation of **11** with $TsOH.H_2O$ in refluxing isopropanol, followed by acylation with e.g. palmitoyl and pivaloyl chlorides, in the presence of TEA and DMAP, and finally catalytic hydrogenolysis of the derived amides using 10% Pd-C in glacial AcOH for 6 h at RT, readily produced the terminally diacylated spermine analogs **12** and **13**, respectively in 64-75% yields.

This methodology could be also applied in the synthesis of mono-*N*-functionalized spermine derivatives. Thus, *N*-tritylation of the also commercially available γ-aminobutyric acid (GABA) produced a 85% yield of crystalline Trt-GABA (**14**), which upon condensation with a variety of amines, e.g. ethyl, hexyl(Hx) and benzylamine, in the presence of DCC and BtOH in DMF, for 3 h at 0 °C and 24 h at RT, produced the corresponding crystalline amides **15-17** in 72-90% yields. LAH reduction of these amides for 1-2 d at refluxing THF, produced the *N*-tritylated putrescine derivatives **18-20** respectively, in 65-80% yields. Detritylation of e.g. **19** and **20** with $TsOH.H_2O$ in refluxing isopropanol for 4 h produced the corresponding tosylates which upon coupling with Trt-β-Ala, in the presence of either the coupling agent benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP)[15] and diiso-propylethylamine (DIEA) or cheaper, but it takes longer reaction times, with DCC/BtOH, gave the bisamides **21** and **22**, respectively in 68-74% yields. Finally, LAH reduction of these compounds produced the corresponding spermine derivatives **23** and **24**, in 65-70% yields.

Furthermore, putrescine derivatives **18-20** are interesting intermediates in the assembly also of the spermidine skeleton. Thus, condensation of Trt-β-Ala with e.g. **19**, in the presence of BOP and DIEA, produced the amide **26** in 89% yield, which upon LAH reduction gave unexceptionally the spermidine derivative **28** in 77% yield. On the other hand, *N*-9-fluorenylmethoxycarbonyl(Fmoc)ation[16] of β-alanine produced crystalline Fmoc-β-Ala (**25**) in 85% yield. This was further routinely activated by $SOCl_2$ in refluxing benzene and the resulting crystalline acyl chloride was used to acylate, in 75% yield, the putrescine derivative **20** in the presence of DIEA. The thus obtained amide **27** was selectively deprotected with 20% piperidine (Pip) in CH_2Cl_2 and the resulting product was reduced with LAH to give the partially protected spermidine derivative **29** in 64% yield. Preliminary experiments on the detritylation of the above prepared spermine and spermidine derivatives showed that the Trt group can

be efficiently removed with $TsOH.H_2O$ in refluxing isopropanol, or with catalytic hydrogenolysis with 10% Pd-C in glacial $AcOH/H_2O$ (9:1), or 20% trifluoroacetic acid in CH_2Cl_2. Further applications of the presently described methodology as well as biological assessment of detritylated spermine and spermidine derivatives are now in progress.

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