Facile Synthesis of Monoacetylated Spermidines, Illustrating Selective Deacetylation and Application of a Common Precursor

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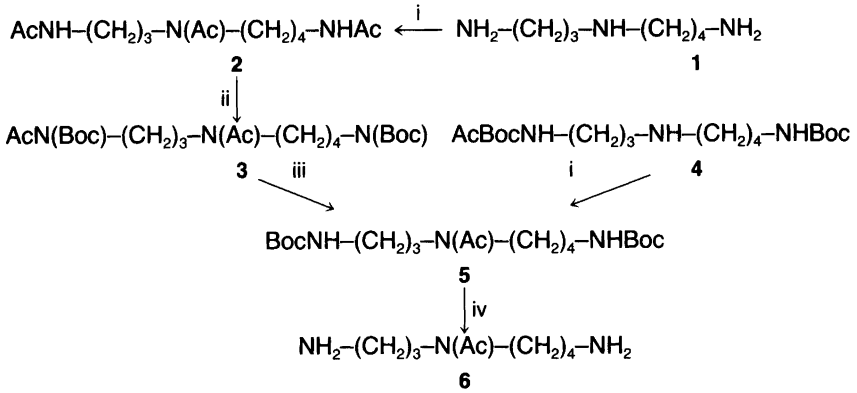
The synthesis of all three monoacetylated spermidines is reported. N^4-Acetylspermidine was obtained in four steps from spermidine via the triacetylated intermediate by selective deacetylation after exhaustive *t*-butoxycarbonylation as well as directly from a previously described protected precursor. N^1-Acetylspermidine and N^8-acetylspermidine were both obtained in four simple protection/deprotection steps from a common, selectively protected compound, thus illustrating the versatility of the latter.

In continuation of our previous work on selective protection of mixed primary–secondary amines[1] and, in particular, its applications in the spermidine field,[2] we have now designed unequivocal routes to all three monoacetylated spermidines. These substances are of importance as metabolites and excretory products.[3] Their preparations also provide illustrative examples, in the case of compound **6** of the use of acetyl as *N*-protecting group[4] in the presence of another *N*-acetyl function, and in the cases of compounds **11** and **15** of the versatility of a selectively protected precursor (**7**) previously prepared.[2]

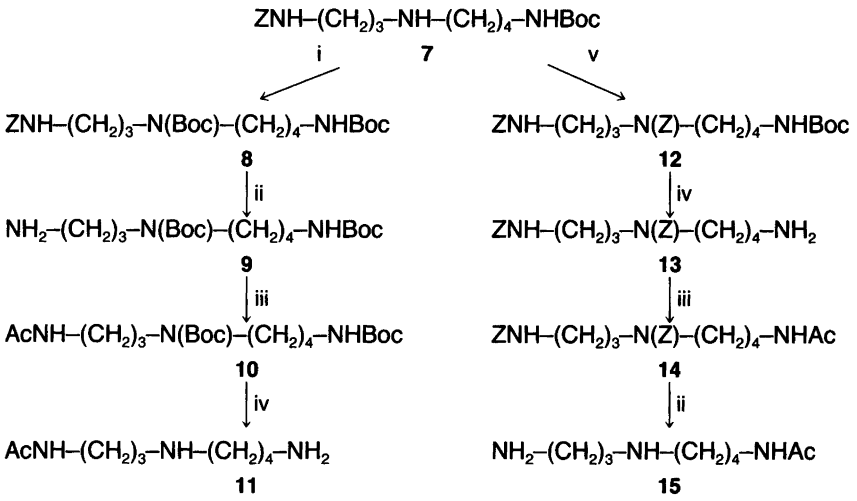
Synthesis of N^4*-acetylspermidine* (**6**). The synthetic scheme leading to this compound is outlined in Scheme 1.

Thus, spermidine was first converted into triacetylspermidine (**2**). Both aqueous and non-aqueous conditions were attempted in this step with essentially the same result. The product was exhaustively *t*-butoxycarbonylated (*t*-butoxycarbonyl = Boc) using Boc_2O and 4-dimethylaminopyridine (DMAP) to give **3**. This reaction turned out to be unusually sluggish and required several additions of fresh Boc_2O to go to completion. The following key step, the selective deacetylation of **3** to give the Boc-protected 4-monoacetylated intermediate **5**, was accomplished cleanly in 85 % yield by tetramethylguanidine (TMG)-mediated methanolysis. The product was identical with one obtained directly by acetylation of N^1,N^8-Boc_2-spermidine (**4**).[1,5–7] Finally the Boc-groups were removed by acidolysis to give N^4-acetylspermidine (**6**) which was characterized as its oxalate salt.

Synthesis of N^1*-acetylspermidine* (**11**) *and* N^8*-acetylspermidine* (**15**). The synthetic scheme leading to these compounds is outlined in Scheme 2.



Scheme 1. Reagents: i, Ac_2O; ii, Boc_2O, DMAP; iii, TMG, MeOH; iv, HCl in dioxane.



Scheme 2. Reagents: i, Boc_2O; ii, H_2/Pd; iii, Ac_2O; iv, HCl in dioxane; v, benzotriazol-1-yl benzyl carbonate or Z_2O.

The starting material for our syntheses of N^1-acetylspermidine (**11**) and N^8-acetylspermidine (**15**) was in both cases N^1 - benzyloxycarbonyl - N^8 - *t* - butoxycarbonylspermidine (N^1-Z-N^8-Boc-spermidine).[2,8] This compound can be prepared in five simple steps from spermidine via Ganem's simply generated spermidine–formaldehyde adduct.[9,10] The orthogonality of the Z and Boc groups which was the basis of much work in the field of peptide synthesis made the ensuing four steps rather straightforward: protection at N^4 provided derivatives **8** and **12**, respectively, which were selectively deprotected at N^1 in the former and at N^8 in the latter to give compounds **9** and **13**. Acetylation of these furnished **10** and **14** which in their turn on deprotection unequivocally provided the title compounds **11** and **15**.

Attempted synthesis of N^1-*Boc*-N^8-*Z-spermidine.* As this spermidine derivative, if available, would be an alternative to **7** for the preparation of **11** and **15**, its synthesis was attempted. Using the new reagent, Z–CN,[11] which acylates only primary amino groups, we tried to make (*not* described in the Experimental Section) N^1,N^4-methylene-N^8-Z-spermidine from Ganem's monocyclic spermidine derivative.[9,10] Our attempts have so far only afforded the desired compound in a very modest yield after a laborious work-up. This outcome was presumably due to partial ring opening, as according to TLC, Ganem's compound seemed to be unstable in the presence of cyanide ion as tested by tetraethylammonium cyanide. Strict proof of this has, however, not been obtained so far. Nevertheless, in the synthesis of a simple model compound using Z–CN no problems with respect to the selectivity of primary amino groups were encountered.

Discussion

From the principal point of view, Scheme 1 merits a few comments. Although we have shown earlier that acetamides as well as many other amides and urethanes can be exhaustively *t*-butoxycarbonylated and cleaved,[12–14] up to now we have applied only the benzyloxycarbonyl group for temporary protection of all amino functions in mixed primary–secondary (poly)amines.[2] Presumably, the *p*-nitrobenzyloxycarbonyl protecting group can also be used for this purpose.[2] This work, however, demonstrates that acetyl is also applicable. Moreover, the selective cleavage of acetyl from the primary amino groups in the presence of such on the secondary group of the spermidine derivative **3** allows acetylation to be performed already as the first step of the synthetic sequence. The subsequent introduction of the Boc-groups serves to labilize the two terminal acetyl groups rather than to protect the amide.[12]

Compound **7** was previously elaborated exploiting the orthogonal Boc–Z set of amino-protecting groups and Scheme 2 illustrates its versatility for synthetic purposes. Thus, for the synthesis of **11** an additional Boc group is introduced at N^4, whereas for **15** a new Z group is attached at this position. Selective deprotection followed by acetylation of the sole liberated, free amino function and final removal of both Boc and Z groups, respectively, completed the syntheses of compounds **11** and **15**. Their physical data agreed with those earlier reported.

Experimental

All melting points were recorded on a Gallenkamp apparatus and are uncorrected. All solvents applied as reaction media were of analytical grade and dried for several days over molecular sieves (4 A). The spermidine used in this work was obtained from Fluka AG (purum quality). TLC analyses were performed on 0.25 mm thick, precoated silica plates (Merck DC-Fertigplatten Kieselgel 60 F_{254}), eluting with (A), (B) CH_2Cl_2–MeOH (4:1), (20:1), (C) CH_2Cl_2–acetone–HOAc (5:5:1), (D) diethyl ether, (E), (F) CH_2Cl_2–acetone (2:1), (9:1), (G) $CHCl_3$–MeOH–aq. 25 % NH_3 (2:2:1), (H) diethyl ether–light petroleum (3:1), (K) EtOAc–acetone–HOAc–water (5:3:1:1) and (L) CH_2Cl_2–

MeOH–HOAc (18:2:1). Spots were visualized by inspection under UV light at 254 nm or, after brief heating, by exposure to Cl_2 followed by dicarboxidine spray (violet–blue spots). NMR spectra were routinely recorded in $CDCl_3$ on a Jeol FX90Q instrument at 90 MHz (^1H) or 22.5 MHz (^{13}C). Chemical shifts are generally given with tetramethylsilane as an internal standard but for spectra recorded in D_2O, they refer to $Me_3SiCH_2CH_2CH_2SO_3Na$. Elemental analyses of selected derivatives were carried out by *Mikro Kemi AB,* Uppsala, Sweden.

N^1,N^4,N^8-*Ac_3-spermidine* (**2**): *Procedure A.* Spermidine (1.12 g, 7.7 mmol) was dissolved in 1 M NaOH (20 ml) and, after being cooled in ice–water, simultaneously treated dropwise, with stirring, with Ac_2O (3.17 g, 31.0 mmol) and 1 M NaOH (80 ml) and then left for several hours. The solution was saturated with NaCl and extracted with $CHCl_3$ (4 × 50 ml). The extract was dried ($MgSO_4$) and evaporated to afford 1.63 g (78 %) of a colourless oil which was chromatographed on silica with CH_2Cl_2–MeOH (4:1), yielding 1.36 g (65 %) of compound **2** as a pale yellow oil, homogeneous by TLC (A, C), chromatographically identical with that obtained in the next paragraph.

Procedure B. An ice-cooled solution of spermidine (1.00 g, 6.88 mmol) and TEA (2.16 g, 21.3 mmol) in CH_2Cl_2 (10 ml) was treated dropwise with Ac_2O (2.18 g, 21.3 mmol) and then stirred overnight at room temperature. The solvent was evaporated and the colourless residue was chromatographed as described above to afford 1.37 g (73 %) of compound **2** as a pale yellow oil, essentially pure by TLC (A, C). δ_H ca. 6.98 and 6.40 (2 broad signals, ca. 2 H, amide NH), 3.07–3.46 (m, 8 H, CH_2N), 2.10 and 2.07 [2 signals, 3 H, –N(CH_3CO)–], 1.98 (s, 6 H, CH_3CONH), 1.49–1.87 (m, 6 H, CCH_2C). δ_C 171.0 and 170.5 (CO), 48.4, 46.7, 45.2, 42.5, 38.7, 36.9 and 36.1 (CH_2N), 29.0, 27.7, 27.4, 27.0, 26.5, 25.9, 24.8, 23.3, 23.1, 23.0, 21.4 (other C).

N^1,N^4,N^8-*Ac_3-N^1,N^8-Boc_2-spermidine* (**3**). A solution of **2** (0.787 g, 2.90 mmol) and DMAP (71 mg, 0.58 mmol) in CH_3CN (10 ml) was treated with Boc_2O (1.40 g, 6.40 mmol) in one portion and stirred at r.t. After 4 h, TLC (A) showed that more than 50 % of the starting material remained. Additional Boc_2O was added in six portions (1 equiv. each) at intervals over 5 days. TLC (A) still showed some remaining starting material and two other major spots. The reaction mixture was therefore evaporated to dryness and the residue was again dissolved in CH_3CN (10 ml) and a new batch of Boc_2O (1 equiv.) and DMAP (0.1 equiv.) was added. The reaction was left overnight. This procedure was repeated once more until TLC (A) of the reaction mixture showed one major spot. The solvent was evaporated *in vacuo* and the dark, brown residue partitioned between 1 M $KHSO_4$ (50 ml) and ether (100 ml). The solution was again extracted with ether (2 × 25 ml) and the combined organic layers were washed in turn with 1 M $KHSO_4$, 1 M $NaHCO_3$ and saturated NaCl (2 × 50 ml each). The yellowish extract was dried ($MgSO_4$) and evaporated. The brown residue was chromatographed on silica using CH_2Cl_2–acetone (9:1) to afford 932 mg (68 %) of **3**, pure by TLC (A, D). δ_H 3.68 [t, 4 H, CH_2N(Ac)Boc], 3.14–3.40 (m, 4 H, CH_2NAcCH_2), 2.46 [s, 6 H, CH_3CO(Boc)N], 2.07 (s, 3 H, N(CH_3CO), 1.25–1.73 (m) and 1.54 [s, together ca. 24 H, CCH_2C + $C(CH_3)_3$]. δ_C 172.9 (Boc$NCOCH_3$), 170.1 and 170.0 (CH_3CON), 153.0 and 152.8 (CO, Boc), 83.5, 83.3, 83.1 and 83.0 [$OC(CH_3)_3$], 48.2, 46.3, 45.2, 43.8, 43.6, 43.0, 42.1 and 41.7 (CH_2N), 28.1 [$C(CH_3)_3$], 26.9, 26.1, 25.9, 25.0, 21.5 (other C).

N^4-*Ac*-N^1,N^8-*Boc_2-spermidine* (**5**). *Procedure A: Acetylation of compound* **4**. A solution of Ac_2O (123 mg, 1.20 mmol) in CH_2Cl_2 (5 ml) was added to a cooled solution of **4** (345 mg, 1.00 mmol) and TEA (152 mg, 1.50 mmol) in CH_2Cl_2 (10 ml) and the reaction was stirred for 4 h. The solvent was evaporated *in vacuo* and the remaining colourless residue partitioned between 1 M $KHSO_4$ (10 ml) and ether (25 ml). After further extraction with ether (25 ml), the combined organic layers were washed in turn with 1 M $KHSO_4$, 1 M $NaHCO_3$ and saturated NaCl (2 × 20 ml each) and dried ($MgSO_4$). The extract was evaporated to dryness to afford a colourless oil which by column chromatography (silica; CH_2Cl_2–acetone 2:1) furnished 288 mg (74 %) of **5** as a pale yellow oil, homogeneous by TLC (B, E). δ_H ca. 5.4 and 4.7 (2 br signals, ca. 2 H, amide NH), 3.04–3.52 (m, 8 H, CH_2N), 2.09 and 2.08 (2 signals, 3 H, CH_3CON), 1.50–1.73 (m) and 1.44 [s, together 24 H, CCH_2C + $C(CH_3)_3$]. δ_C 170.8 and 170.2 (CO, Ac), 156.1 and 156.0 (CO, Boc), 79.4 and 78.9 [$C(CH_3)_3$], 48.3, 46.4, 45.3, 42.4, 40.0 and 37.4 (CH_2N), 28.4 [$C(CH_3)_3$], 29.7, 28.0, 27.6, 26.0, 25.0 and 21.4 (other C).

Procedure B: Methanolysis of **3** *in the presence of catalytic amounts of TMG.* Compound **3** (547 mg, 1.2 mmol) was dissolved in dry methanol (10 ml) and treated with TMG (30 mg, 0.26 mmol) with stirring at r.t. for 4 h. The reaction mixture was evaporated *in vacuo,* worked up as under Procedure A and chromatographed (silica; CH_2Cl_2–acetone 2:1) to afford 395 mg (88 %) of compound **5**. ^1H and ^{13}C NMR spectra were in agreement with the data given under Method A.

N^4-*Ac-spermidine oxalate* (**6**). – Compound **5** (324 mg, 0.84 mmol) was treated with 2.29 M HCl in dioxane (2 ml) with stirring at r.t. for 3 h. Most of the solvent was evaporated *in vacuo* and the sticky residue was taken up in ether (20 ml) and evaporated twice. It was then dissolved in distilled water (40 ml) and extracted with ether (3 × 20 ml). The aqueous layer was flushed with N_2 and lyophilized to afford 202 mg (92 %) of a sticky white residue, nearly pure by TLC (G). This was converted into its oxalate salt by the loading of a portion (100 mg), dissolved in water, onto a QAE-Sephadex A-25 column (oxalate form) and eluting

with distilled water to afford 111 mg of a white residue after lyophilization. Recrystallization from water–ethanol (1:20, 25 ml) gave a white solid, pure by HPLC (did not contain **11** or **15** in detectable amounts), m.p. 187.5–188.5 °C. δ_H (D_2O) 3.27–3.55 [m, 4 H, $CH_2N(Ac)CH_2$], 2.82–3.13 (m, 4 H, CH_2NH_2), 2.14 and 2.13 (2 signals, 3 H, CH_3CON), 1.54–2.08 (m, 6 H, CCH_2C). δ_C 177.2, 176.7 and 176.0 (CO), 51.0, 48.7, 47.9, 45.0, 41.8 and 39.5 (CH_2N), 28.5, 27.6, 27.5, 26.8, 26.4, 23.3 and 23.1 (other C). (Found: C 46.1; H 8.0; N 14.7. $C_9H_{21}N_3O \cdot C_2H_2O_4 \cdot 1/2H_2O$ requires C 46.1; H 8.45; N 14.7 %).

N^1-*Z*-N^4,N^8-*Boc_2-spermidine* (**8**). To an ice-cold solution of **7** (1.90 g, 5.01 mmol) in CH_2Cl_2 (10 ml) was added dropwise a solution of Boc_2O (1.15 g, 5.26 mmol) in dry CH_2Cl_2 (10 ml). The colourless reaction mixture was stirred for 30 min in ice and overnight at r.t. The solvent was evaporated and the residue was partitioned between 1 M $KHSO_4$ (100 ml) and ether (500 ml). The extract was washed in turn with aq. 1 M $KHSO_4$, $NaHCO_3$, saturated NaCl (2 × 100 ml each), dried ($MgSO_4$) and evaporated to afford 3.0 g of a pale yellow oil. Column chromatography (silica; ether–light petroleum 3:1) furnished 2.10 g (87 %) of **8**, homogeneous by TLC (F, H). δ_H 7.34 (s, 5 H, arom. H), 5.10 (s, 2 H, CH_2Ph), ca. 5.70 and 4.60 (2 broad signals, ca. 2 H, amide NH), 3.08–3.32 [m, 8 H, $CH_2N(Boc)$, CH_2NHZ], 1.51–1.78 (m) and 1.44 [s, together 24 H, CCH_2C + $C(CH_3)_3$]. δ_C 156.4 and 155.9 (CO), 136.6, 128.4 and 128.0 (arom. C), 79.7 and 79.2 [$OC(CH_3)_3$], 66.4 (OCH_2Ph), 46.6 and 43.7 [$CH_2N(Boc)CH_2$], 40.2 and 37.8 (CH_2NHBoc, CH_2NHZ), 28.4 [$C(CH_3)_3$], 27.4 and 25.6 (CCH_2C).

N^4,N^8-*Boc_2-spermidine* (**9**). Compound **8** (1.90 g, 3.96 mmol) was hydrogenolyzed as outlined in Ref. 8 to give 1.35 g (98 %) of **9** as a colourless oil, essentially pure by TLC (K, L). δ_H ca. 4.60 (br signal, ca. 1 H, amide NH), 3.09–3.46 [m, 6 H, CH_2NHBoc, $CH_2N(Boc)CH_2$], 2.69 (t, 2 H, CH_2NH_2), 1.53–1.71 (m), 1.45 and 1.44 [2 signals, together 26 H, CCH_2C, $C(CH_3)_3$ + NH_2]. δ_C 156.0 and 155.7 (CO), 79.4 and 79.1 [$OC(CH_3)_3$], 46.5, 44.2, 40.3 and 39.3 (CH_2N), 32.3, 27.5 and 25.7 (CCH_2C), 28.5 [$C(CH_3)_3$].

N^1-*Ac*-N^4,N^8-*Boc_2-spermidine* (**10**). A solution of **9** (1.22 g, 3.53 mmol) was treated and the product purified in a manner similar to that described for **5** (Procedure A): yield 1.30 g (95 %) of **10** obtained as an oil. δ_H ca. 6.75 and 4.60 (br signal, amide NH), 3.02–3.33 (m, 8 H, CH_2N), 1.98 (s, 3 H, CH_3CON), 1.53–1.72 (m) and 1.46 and 1.44 [2 signals, together ca. 24 H, CCH_2C + $C(CH_3)_3$]. δ_C 170.2 (CO, Ac), 156.0 (CO, Boc), 79.8 and 79.2 [$OC(CH_3)_3$], 46.6, 44.1, 40.1 and 35.9 (CH_2N), 28.4 [$C(CH_3)_3$], 27.7, 27.5 and 25.6 (CCH_2C), 23.4 (CH_3CON).

N^1-*Ac-spermidine dihydrochloride* (**11**). Compound **10** (539 mg, 1.39 mmol) was treated and the product purified in a manner similar to that described for **6**: yield 350 mg (97 %); pure by HPLC (did not contain **6** or **15** in detectable amounts); m.p. 191–193 °C (EtOH) (lit.,[15,16] 173–178 or 189–191 °C). δ_H(D_2O) 3.28 (t, 2 H, *J* 6.7 Hz, CH_2NHAc), 2.98–3.15 (m, 6 H, CH_2N), 2.00 (s, 3 H, CH_3CO), 1.74–1.88 (m, 6 H, CCH_2C). δ_C 177.2 (CO), 49.6, 47.7, 41.4 and 38.7 (CH_2N), 28.2, 26.6 and 25.4 (CCH_2C), 24.5 (CH_3CON). (Found: C 41.3; H 8.8; N 15.9. $C_9H_{21}N_3O \cdot 2HCl$ requires C 41.54; H 8.91; N 16.15 %).

N^8-*Boc*-N^1,N^4-Z_2-*spermidine* (**12**). To a stirred suspension of benzotriazol-1-yl benzyl carbonate[17] (1.30 g, 4.82 mmol) in dry CH_3CN (40 ml) was added a solution of **7** (1.18 g, 4.77 mmol) in the same solvent (30 ml). The clear solution obtained was left overnight and then evaporated to dryness. The residue was partitioned between 1 M $KHSO_4$ (150 ml) and ether (500 ml) and the organic phase was washed with $KHSO_4$, 1 M $NaHCO_3$ and satd. NaCl (2 × 150 ml each) and finally dried ($MgSO_4$). Evaporation furnished 2.36 g (96 %) of crude product which was chromatographed (silica; ether–light petroleum 3:1) to give 2.04 g (83 %) of **12** as a pale yellow oil, pure by TLC (D, H). δ_H 7.33 and 7.32 (2 signals, 10 H, arom. H), 5.11 and 5.08 (2 × s, 4 H, CH_2Ph), 3.04–3.38 (m, 8 H, CH_2N), 1.51–1.76 (m) and 1.43 [s, together 15 H, CCH_2C + $C(CH_3)_3$]. δ_C 156.4 and 155.9 (CO), 136.6, 128.5, 128.4 and 128.0 (arom. C), 79.2 [$OC(CH_3)_3$], 67.1 and 66.5 (CH_2Ph), 46.5, 44.1, 40.1 and 37.6 (CH_2N), 28.4 [$C(CH_3)_3$], 28.2, 27.4 and 25.6 (CCH_2C). This compound was also prepared in 88 % yield after chromatography on a 1 mmol scale using Z_2O.[18]

N^1,N^4-Z_2-*spermidine* (**13**). Compound **12** (1.84 g, 3.58 mmol) was treated with 2.29 M HCl in dioxane (15 ml) and stirred at r.t. for 3 h. The solvent was evaporated off and the white residue was treated with 30 % K_2CO_3 (40 ml) and extracted with $CHCl_3$ (5 × 100 ml). The combined organic layers were dried (Na_2SO_4) and evaporated to afford 1.42 g (96 %) of **13** as a pale yellow oil, nearly pure by TLC (K, L). δ_H 7.34 and 7.33 (2 × s, 10 H, arom. H), ca. 5.60 (1 br signal, ca. 1 H, amide NH), 5.11 and 5.08 (2 × s, 4 H, CH_2Ph), 3.05–3.39 (m, 6 H, CH_2NZH, CH_2NZCH_2), 2.66 (t, 2 H, CH_2NH_2), 1.25–1.84 (m, 8 H, CCH_2C + NH_2). δ_C 156.4 (CO), 136.6, 128.5, 128.4, 128.0 and 127.9 (arom. C), 67.1 and 66.5 (CH_2Ph), 46.8, 44.1, 41.7 and 37.7 (CH_2N), 30.7, 28.1 and 25.8 (CCH_2C).

N^8-*Ac*-N^1,N^4-Z_2-*spermidine* (**14**). A solution of **13** (1.18 g, 2.85 mmol) was treated and the product purified in a manner similar to that described for **5** to give 1.10 g (85 %) of **14** as an oil. δ_H 7.33 (s, 10 H, arom. H), ca. 6.00 and 5.60 (2 br signals, ca. 2 H, amide NH), 5.11 and 5.08 (2 × s, 4 H, CH_2Ph), 3.05–3.37 (m, 8 H, CH_2NZ, CH_2NAc), 1.92 (s, 3 H, CH_3CON), 1.33–1.77 (m, 6 H, CCH_2C). δ_C 170.2 (CO, Ac), 156.5 (CO, Z), 136.5, 128.6, 128.4, 128.0 and 127.9 (arom. C), 67.2 and 66.5 (CH_2Ph), 46.5, 44.3, 39.0 and 37.9 (CH_2N), 28.4, 26.7 and 25.7 (CCH_2C), 23.2 (CH_3CON).

N^8-*Ac-spermidine dihydrochloride* (**15**). A solution of **14** (497 mg, 1.09 mmol) was treated in a manner similar to that described for **9**, to give the free amine (200 mg, 98 %) as a colourless oil which was converted into its dihydrochloride salt with an excess of HCl in dioxane to afford 250 mg (90 %) of **15** pure by HPLC (did not contain **6** or **11** in detectable amounts); m.p. 202–203 °C (from EtOH) (lit.,[15,16] 204–205.5 or 203.5–205 °C). δ_H (D_2O) 3.01–3.24 (m, 8 H, CH_2N), 1.91–2.26 (m, 2 H, CCH_2C), 1.98 (s, 3 H, CH_3CO), 1.53–1.77 (m, 4 H, CCH_2CH_2C). δ_C 176.1 (CO), 49.8, 46.9, 41.1 and 39.1 (CH_2N), 28.0, 26.3 and 25.5 (CCH_2C), 24.4 (CH_3CON). (Found: C 40.8; H 8.8; N 15.6. $C_9H_{21}N_3O \cdot 2HCl$ requires C 41.54; H 8.91; N 16.15 %).

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