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A NEW REGIOSELECTIVE SYNTHESIS OF N^1- AND N^8-MONOACYLATED SPERMIDINES

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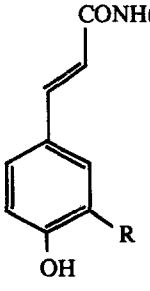
Abstract : N^1- and N^8-ferulylspermidine are obtained in three steps from the easily accessible intermediates **4a** and **4b**.

Biologically important polyamines like putrescine, spermidine and spermine have been isolated from bacteria, fungi, plants and mammalian cells often at high, up to millimolar concentration (1).

In higher plants, the presence of polyamines has been demonstrated and their role has been investigated, but it is only recently that the widespread nature of hydroxycinnamic acid amides of polyamines and their physiological significance has been discerned (2).

An efficient synthesis of monoacylated diamines (e.g. **1** and **2**) has been designed previously by one of us (3). The products obtained allowed for the first time a thorough investigation of some of their biological effects (4).



1 : R=H, N-*p*-coumarylputrescine
2 : R=OCH_3, N-ferulylputrescine

Since the putrescine conjugates **1** and **2** are generally accompanied in plants by the corresponding monoacylated spermidines (2), we set out to devise a scheme for the regioselective synthesis of N^1- and N^8-ferulylspermidine (we chose ferulic acid amides as our synthetic target since they contain two different oxygen substituents on the aromatic ring in addition to the cinnamic acid conjugated double bond).The fact that no reagent exists possessing Nature's discriminating capacity prompted several research groups to design synthetic routes towards monoacylated spermidines.

Although Bergeron's efforts (5) were essentially directed towards the synthesis of biologically important spermidine-derived siderophores, some intermediates prepared in the course of his work were also potentially useful starting material for monoacylation, but the rather harsh reduction conditions required for the hydrogenolysis of a N-benzyl group cannot be applied to double bond containing acids like ferulic acid. Much milder protection-deprotection sequences have been published by Das (6) and Ganem (7).

Our synthesis of N^1- and N^8-ferulylspermidine is based on the previously described key intermediates **4a** and **4b** (3a) which allowed us to prepare **6a** and **6b** in three steps. Addition of a 1.5 molar excess of **3a** and **3b** (benzylprotected ferulic acid and **3a** and **3b** were obtained in analogy to known methods (8) from commercially available products : vanilline and 1,3- or 1,4-dibromopropane, respectively) to a solution of ferulic acid chloride in anhydrous CH_2Cl_2 in the presence of triethylamine provides **4a** and **4b** in good yields (67 % and 86 %) after column chromatography (CH_2Cl_2/THF)(9). In contrast to earlier results (3a), our attempts to debenzylate **4a** and **4b** with CF_3COOH gave only poor yields. Finally, treatment of **4a** and **4b** with BF_3/C_2H_5SH(10) at r. t. led to the isolation of **5a** and **5b** in acceptable yields (60 % and 68 %), but this reaction must be carefully monitored by TLC in order to avoid the undesired 1,4-addition of C_2H_5SH to the cinnamoyl moiety of **5a** and **5b**.

Since 1,3- and 1,4-diamines are strong bases (pK_a = 10.94 and 11.15 respectively) and good nucleophiles, similar problems arising from 1,4-addition could be expected in the last step, but the reaction of **5a** and **5b** with an excess of the suitable diamines proceeded smoothly to afford crude **6a** and **6b** which could be purified by preparative HPLC [solvent : CH_2Cl_2/MeOH/NH_3conc. = 2:2:1 (6)] [isolated yields : 49 % (**6a**) and 68 % (**6b**)].

This reaction sequence offers a rapid access to a biologically important family of natural products under mild conditions. The combination of a wide variety of cinnamic acids derived from the phenylalanine metabolic pathway with the equally abundant natural (or modified) diamines should allow the regioselective synthesis of a great number of monoacylated polyamines which in turn should make possible the full assessment of their biological role (11).

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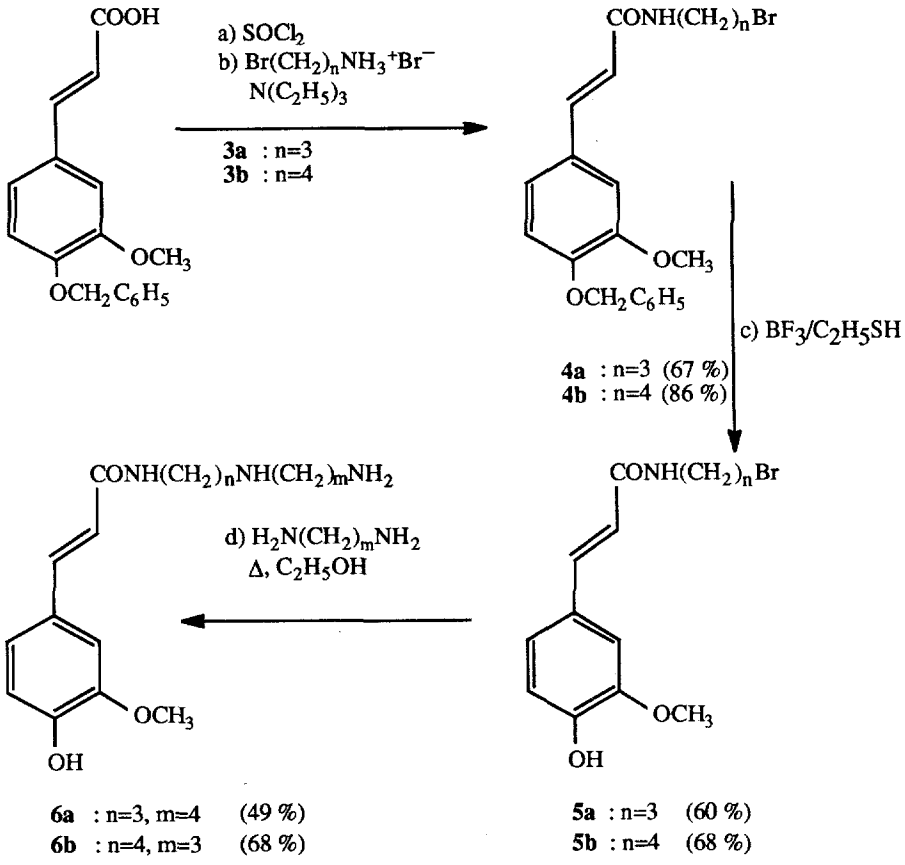

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9. Comparable yields of **4a** and **4b** are obtained *without* chromatographic purification by reacting 3-ferulylbenzisoxazolidine-2-thione with **3a** and **3b** in anhydrous THF in the presence of triethylamine :
M. Ueda, K.Seki and Y. Imai, *Synthesis*, 991 (1981).
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11. Yields have not been optimized. Some important and significant physical data of new compounds obtained are listed below. Their IR and UV spectra are in agreement with the proposed structures. The (*E*)-stereochemistry of the cinnamic acid double bonds was ascertained by the coupling constants (J_{HH}= 15-16 Hz) measured in the ^{1}H-NMR spectra.

4a : $C_{20}H_{22}BrNO_3$ Calc. % : C 59.57, H 5.50; found % : C 59.57, H 5.44. F = 108°-110°C; Mass spectrum (MS) : (CI/NH_3) M+1 at *m/z*: 404 (^{79}Br); NMR : ^{1}H ($CDCl_3$) : NH-C$\underline{H}_2$ and C$\underline{H}_2$-Br : 3.68 (4p, m); CH_2-C$\underline{H}_2$-CH_2 : 2.38 (2p, m).^{13}C ($CDCl_3$) : NH-$\underline{C}H_2$: 38.1, CH_2-$\underline{C}H_2$-CH_2 : 32.3 , $\underline{C}H_2$-Br : 31.1.
4b : $C_{21}H_{24}BrNO_3$ Calc. % : C 60.42, H 5.79; found % : C 60.50, H 5.75. F = 115°-117°C; Mass spectrum (MS) : (CI/NH_3) M+1 at *m/z*: 418 (^{79}Br); NMR : ^{1}H ($CDCl_3$) : NH-C$\underline{H}_2$ and C$\underline{H}_2$-Br : 3.40 (4p, m); CH_2-C$\underline{H}_2$-C$\underline{H}_2$-CH_2 : 1.80 (4p, m).^{13}C ($CDCl_3$) : NH-$\underline{C}H_2$: 38.8, $\underline{C}H_2$-Br :33.2, $\underline{C}H_2$-$\underline{C}H_2$: 30.1 and 28.4.
5a : $C_{13}H_{16}BrNO_3$ Calc. % : C 49.68, H 5.09, N 4.45; found % : C 49.51, H 5.25, N 4.31; Colourless oil; Mass spectrum (MS) : (EI) M^+ at *m/z*: 313 (^{79}Br); NMR : ^{1}H ($CDCl_3$) : NH-C$\underline{H}_2$ and C$\underline{H}_2$Br : 3.80 (4p, m); CH_2-C$\underline{H}_2$-CH_2 : 2.19 (2p, m).^{13}C ($CDCl_3$) : NH-$\underline{C}H_2$: 38.4, $\underline{C}H_2$-Br : 31.3, CH_2-$\underline{C}H_2$-CH_2 : 32.4.
5b : $C_{14}H_{18}BrNO_3$ Calc. % : C 51.37, H 5.54; found % : C 51.64, H 5.65. Colourless oil; Mass spectrum (MS) : (EI) M^+ at *m/z*: 327 (^{79}Br) ; NMR : ^{1}H ($CDCl_3$) : NH-C$\underline{H}_2$ and C$\underline{H}_2$-Br : 3.40 (4p, m); NH-CH_2-C$\underline{H}_2$: 1.85 (2p,m); C$\underline{H}_2$-CH_2-Br : 1.65 (2p, m). ^{13}C ($CDCl_3$) : NH-$\underline{C}H_2$: 38.9, $\underline{C}H_2$-Br : 33.5, -$\underline{C}H_2$-$\underline{C}H_2$-: 33.5 and 30.1.
6a : $C_{17}H_{27}N_3O_3$.Yellow oil. High resolution (peak matching) MS : Calc. 321.2054; found 321.2051; NMR : ^{1}H (CD_3OD) :CO- NH-C$\underline{H}_2$: 3.43 (2p, t); NH-C$\underline{H}_2$-CH_2-CH_2 :3.30 (2p, t); NH-C$\underline{H}_2$-$(CH_2)_3$ and NH_2-C$\underline{H}_2$: 3.00(4p, t); C$\underline{H}_2$-C$\underline{H}_2$: 1.95 (4p, m).^{13}C (CD_3OD) : CO-NH-CH_2-(42.1)-CH_2-(30.2)- CH_2- (38.3)- NH- CH_2-(38.3) - CH_2- (30.0)- CH_2- (27.7)-CH_2-(39.6)-NH_2.
6b : $C_{17}H_{27}N_3O_3$. Yellow oil. High resolution (peak matching) MS : Calc. 321.2054; found 321.2063; NMR : ^{1}H (CD_3OD) : NH-C$\underline{H}_2$: 2.65 (8p, m) ; CH_2-C$\underline{H}_2$-CH_2 : 1.58 (6p, m).^{13}C (CD_3OD) : CO-NH-CH_2-(40.4)-CH_2-(28.1)-CH_2-(27.1)-CH_2-(40.1)-NH-CH-(40.1)-CH_2-(30.4)-CH_2-(39.8)-NH_2.

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