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SYNTHESIS OF CYTOTOXIC SPERMIDINE METABOLITES FROM THE SOFT CORAL SINULARIA BRONGERSMAI[1]

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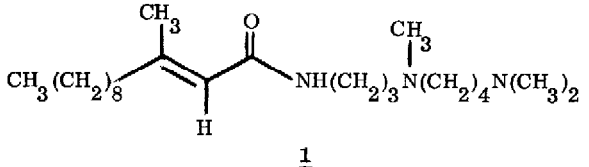
Summary: Two unusual cytotoxic agents, the first spermidine derivatives from marine organisms, have been synthesized directly from the parent polyamine using new methodology.

The biogenic amines putrescine, spermine and spermidine are widely distributed throughout the plant and animal kingdom.[3] A number of such bases and their derivatives play key biochemical roles and possess interesting pharmacological properties, but only recently have polyamine conjugates been discovered in the marine world. Last year, Schmitz and co-workers reported the isolation of trimethylated spermidine amides 1 and 2 from the coral reef coelenterate Sinularia brongersmai.[4] Extracts of this soft coral exhibited cytotoxic properties and careful fractionation identified 1 and 2 as the active compounds. Here we describe a practical synthetic route to these natural products based on new methodology we have been developing for regiospecific polyamine transformations.[1,5] One unusual aspect worth noting in our scheme is the dual purpose served by an hexahydropyrimidine ring both as a protecting group and as a latent N-methyl function.



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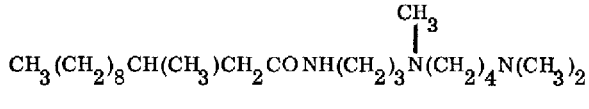

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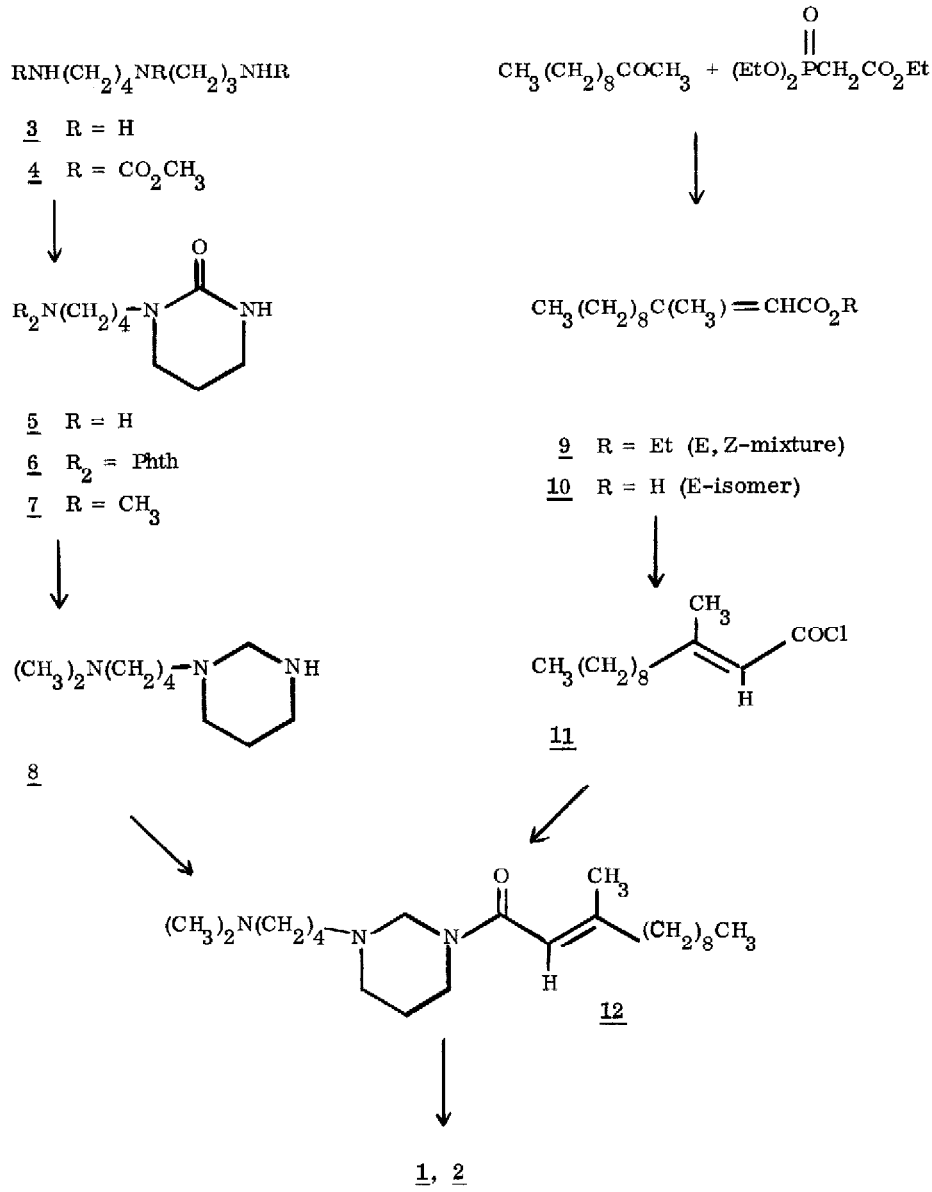
The 1,3-disposition of N^1 and N^2 in spermidine 3 makes possible[5] a number of strain-free cyclic, six-center derivatives which form selectively in preference to seven-membered structures


RNH(CH2)4NR(CH2)3NHR
3 R = H
4 R = CO2CH3
R2N(CH2)4-N NH
O
5 R = H
6 R2 = Phth
7 R = CH3
(CH3)2N(CH2)4-N NH
8
CH3(CH2)8COCH3 + (EtO)2PCH2CO2Et
O
CH3(CH2)8C(CH3)=CHCO2R
9 R = Et (E, Z-mixture)
10 R = H (E-isomer)
CH3(CH2)8
CH3
COCl
H
11
(CH3)2N(CH2)4-N N
O
CH3
(CH2)8CH3
H
12
1, 2

between N^3 and N^2. Thus exhaustive acylation of 3 [CH_3OCOCl, $CHCl_3/H_2O$/NaOH, rt] followed by partial hydrolysis of 4 [$Ba(OH)_2/H_2O$, reflux] produced urea 5 in 92% overall yield [mp 44-45°C; NMR δ ($CDCl_3$) 5.05 (broad s, 1H, urea NH), 3.3 (m, 6H), 2.7 (t, 2H, J=7 Hz, CH_2NH_2), 1.92 (q, 2H, J=6 Hz), 1.4-1.75 (m, 6H); IR λ_{max} ($CHCl_3$) 2.87, 6.10μm]. The structure of this substance was unambiguously confirmed by comparison of its phthalimide derivative 6 [mp 179.5-180.5°C; mass spectrum m/e 301 (M^+), 113 (base)][6] with an authentic sample made from trimethylene urea and N-(4-bromobutyl)phthalimide. Eschweiler-Clarke methylation of 5 (2.2 equiv formalin solution/88% HCO_2H) formed 7 [80%; NMR δ 5.00 (s, 1H, NH), 3.13-3.56 (m, 6H, N-CH_2-), 2.20 (s, 6H, NMe_2), 2.20-2.40 (m, 2H), 1.70-2.06 (m, 2H), 1.33-1.70 (m, 4H); IR λ_{max} (film) 2.87, 6.10, 6.15μm].[6,7] Upon reduction with $LiAlH_4$[8] (1.1 mole-equiv), urea 7 was transformed into hexahydropyrimidine 8 [57%; bp 175-177°C (0.2 torr); NMR δ 3.40 (s, 2H, -NCH_2N-)] thus setting the stage for a regioselective acylation at N^1.

The requisite fatty acid component was synthesized as follows.

Condensation of 2-undecanone with triethylphosphonoacetate by the Horner-Emmons method[9] produced a 3:1 E:Z mixture of ethyl 3-methyl-2-dodecenoates 9 as judged by the expected[10] difference in chemical shifts for the C-3 methyl resonances [δ ($CDCl_3$) 2.16 (d, J=1.5 Hz, E-isomer), 1.88 (d, J=1.5 Hz, Z-isomer)]. After saponification (10% NaOH, CH_3OH-H_2O, reflux), the desired E-acid 10 readily crystallized from the mixture [mp 36-37°C (petroleum ether)][6] and was smoothly converted to its acid chloride 11 by thionyl chloride in 67% yield.

In a two-phase CH_2Cl_2-aqueous Na_2CO_3 system, "protected" spermidine 8 reacted with 1.1 equiv of 11 to afford amide 12 as a colorless oil possessing all the requisite carbons of the natural products [82% after prep TLC, R_f 0.73 in 99:1 CH_3OH-NH_4OH; NMR δ 5.68 (broad s, 1H, vinyl), 4.20 and 4.06 (two broad s, 2H, -NCH_2N-), 3.32-3.66 (m, 2H, -CCH_2N-), 1.90-2.50 (broad m, 6H, -CCH_2C-), 2.20 (s, 6H, NMe_2), 1.83 (d, 3H, J=0.5 Hz, -C=C-CH_3); IR λ_{max} 6.10μ; m/e 379 (M^+), 184 (base)]. Geminal diamines typically exhibit reactivity characteristic *of their corresponding imine forms,*[1,5,11] *and hexahydropyrimidine 12 behaved accordingly.* Reductive cleavage of 12 occurred regiospecifically upon heating in formic acid and produced nearly

pure 1 in 96% yield.[12] Preparative layer chromatography provided a pure sample of 1 (83%, R_f 0.67 in 99:1 CH_3OH-NH_4OH) whose IR, NMR and mass spectra agreed in every respect with the published data for the natural product as it occurs admixed with 2 [for pure 1: NMR δ ($CDCl_3$) 6.83 (broad, 1H, NH), 5.53 (broad s, 1H, vinyl), 3.36 (q, 2H, J=5 Hz, $-NHCH_2-$), 2.20 (s, 9H, N-methyls), 2.14 (s, 3H, vinyl methyl); IR λ_{max} (film) 3.05, 6.01, 6.12 mμ; m/e 381 (M^+), 366, 295, 252, 195]. Catalytic hydrogenation of 1 (Pd/C, ethyl acetate) quantitatively furnished the saturated amide 2, and spectra of pure, naturally occurring 2 (kindly provided by Professor F. J. Schmitz) were superimposable with those of our synthetic sample. Thus the two cytotoxic polyamine derivatives are now readily available in 15% overall yield from spermidine.

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