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A TOTAL SYNTHESIS OF THE NATURALLY OCCURRING PYRROLO[2,3-d]PYRIMIDINE NUCLEOSIDE, MYCALISINE A

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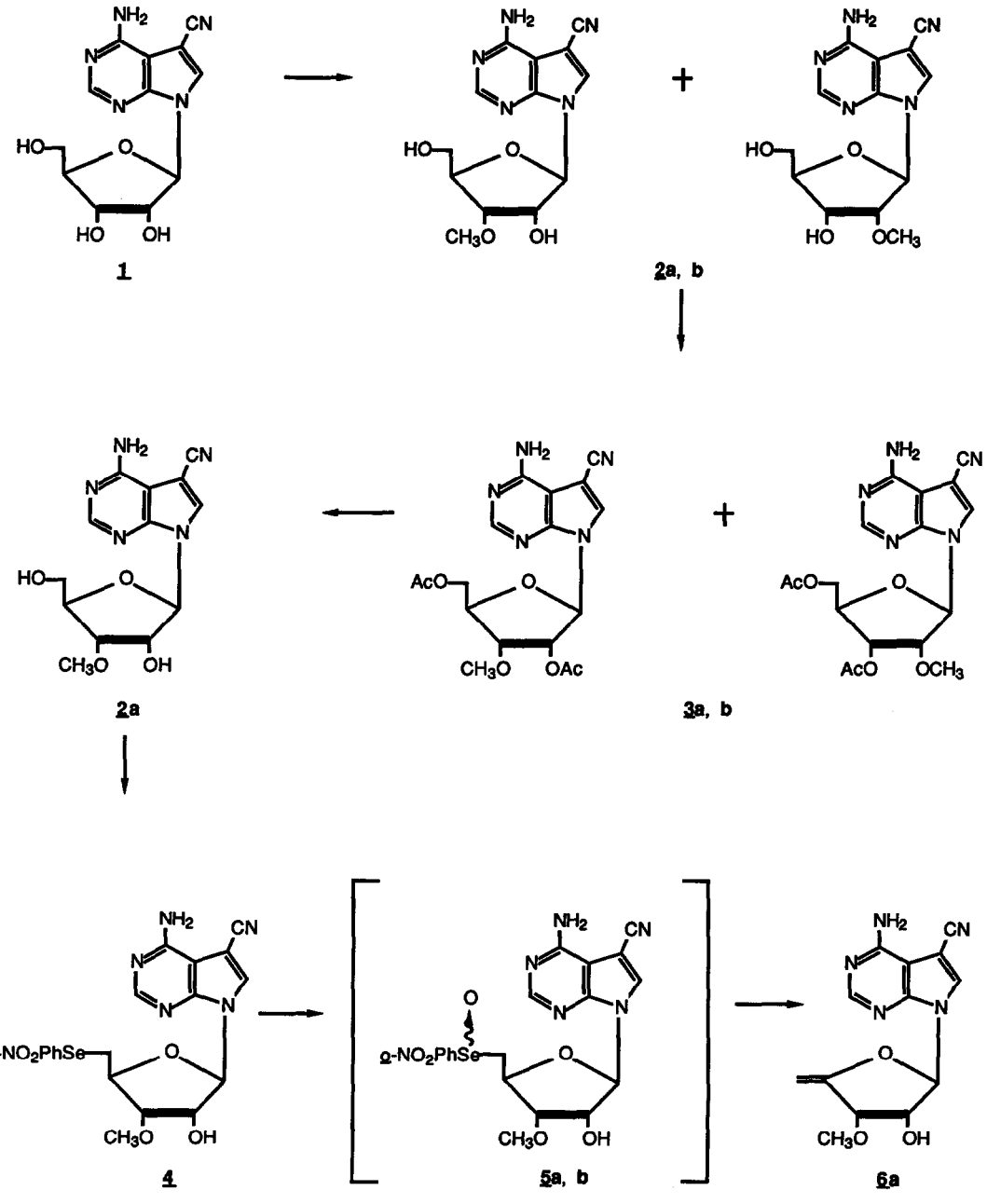
Abstract: The first total synthesis of mycalisine A, a pyrrolo[2,3-d]pyrimidine nucleoside, was accomplished by a multi-step synthesis from toyocamycin.

A search for bioactive marine metabolites has resulted in the isolation of an unusual compound from a lipophilic extract of a marine sponge mycale sp.[1] This compound, mycalisine A, was found to inhibit the cell division of fertilized starfish eggs. Additional studies established that mycalisine A was a pyrrolo[2,3-d]pyrimidine nucleoside with unsaturation between the 4' and 5'-positions of the ribose moiety.[1] A number of structurally related pyrrolo[2,3-d]pyrimidine nucleosides have been previously isolated from naturally occurring sources[2], as well as prepared[3] by synthetic procedures. These pyrrolo[2,3-d]pyrimidine nucleosides have exhibited some very interesting biological and chemotherapeutic activities[4,5]. This prompted us to initiate a study designed to provide the first total synthesis of mycalisine A.

After the evaluation of several retrosynthetic approaches for the synthesis of mycalisine A, we elected to use an approach where the nucleoside antibiotic toyocamycin was our starting material. Toyocamycin (1) was methylated[6] with diazomethane and a catalytic amount of $SnCl_2$. The solid which was isolated from the reaction mixture proved to be a mixture of the 2'-O-methyl and 3'-O-methyl isomers (2a,b). That the actual site of methylation was on an oxygen of the carbohydrate moiety in both isomers, was determined by the chemical shifts observed for the methyl protons in the ^1H NMR (δ 3.31 and 3.38). This assignment was supported by the UV spectrum of 2a,b which was essentially unchanged in comparison to the UV spectrum of toyocamycin. Integration of the peaks corresponding to the anomeric protons revealed a 60:40 ratio of regioisomers. In contrast to a previous report,[7] we could not improve on the regioselectivity of the methylation by using different Lewis acids. Separation of the regioisomers was not achieved by silica gel chromatography, reverse phase HPLC, or by recrystallization from a number of solvents. The use of a Dowex ion-exchange column was also excluded because of the known lability of the nitrile group of toyocamycin to these specific conditions.[8]



MYCALISINE A

The separation of regioisomers was achieved by acetylating the mixture (2a,b) with acetic anhydride and a catalytic amount of DMAP to afford the acetylated mixture 3a,b, as determined by ^{1}H NMR. A single recrystallization of the mixture from toluene afforded a solid, 90% of which appeared to be a single isomer as judged by TLC. This enriched solid was deblocked using methanolic ammonia. A single regioisomer of 2 was isolated,[9] after recrystallization of the crude product from MeOH. This isomer was identified as the desired 3'-O-methyl isomer (2a) on the basis of the intense B+30 peak in the mass spectra. This peak has been shown to be characteristic of the 3'-O-methyl regioisomer of purine and purine-like ribosides.[6,10]

Unsaturation at the 4',5' position of 3'-O-methyltoyocamycin (2a) was accomplished using a modification of a literature procedure.[11] Treatment of 2a with 3 equivalents each of o-nitrophenylselenocyanate[12] and tributyl phosphine afforded the desired[9] 5'-selenide derivative 4. The site of attachment for the o-nitrophenylselenide group was shown to be at the 5' position by ^{1}H NMR analysis of the 5' methylene protons. In the ^{1}H NMR spectrum of 2a, the peaks corresponding to the 5' methylene protons were observed as a multiplet centered at δ 3.6. Upon conversion to the selenide 4, these protons appeared as a doublet which was centered upfield at δ 3.4.

The selenide 4 was then oxidized to afford the presumed epimeric selenoxides 5a,b using an excess of a $NaIO_4$ in water-THF solution. After evaporation of the solvent, the crude reaction concentrate was suspended in pyridine and the excess $NaIO_4$ was removed by filtration. The filtrate was treated with one equivalent of Et_3N and heated at 50°C for 5 hours. Removal of the solvent and column chromatography of the resulting residue afforded a white crystalline solid, 35.4% yield from 4. The 270 MHz ^{1}H NMR, UV, and mass spectral data obtained for this compound[13] was essentially identical to that reported[1] for mycalisine A (6).

In conclusion, we have developed a total synthesis of the naturally occurring pyrrolo [2,3-d]pyrimidine nucleoside mycalisine A.

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9. 2a, mp 161-163°C; 4 mp 191.5-193°C. Satisfactory elemental analyses (C,H,N), ^1H NMR, UV, IR, and mass spectra were obtained for all new compounds.

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13. ^1H NMR (DMSO-d_6): δ 8.49 (s, 1H, H-2), 8.23 (s, 1H, H-6), 6.95 (brs, 2H, $-NH_2$), 6.30 (d, 1H, H-1'), 5.77 (d, 1H, 2' -OH), 4.87 (m, 1H, H-2'), 4.42 (d, 1H, H-5'), 4.29 (d, 1H, H-5'),4.21(d, 1H, H-3'), 3.39 (s, 3H, $-OCH_3$); mass spectrum m/z 288 (MH^+), 160, 272, 202, 188; UV λ_{max} nm (ε x 10^4); (pH 7) 278, 230, 208; (pH 1) 272, 232, 205; (pH 11) 278, 232; IR (KBr pellet) ν (cm^{-1}) 3480, 3230, 3120, 2140, 1745, 1665, 1600, 1580; m.p. 184.5-186°C; Anal. (C, H, N).

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