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A Short Step Synthesis of AV-toxin D

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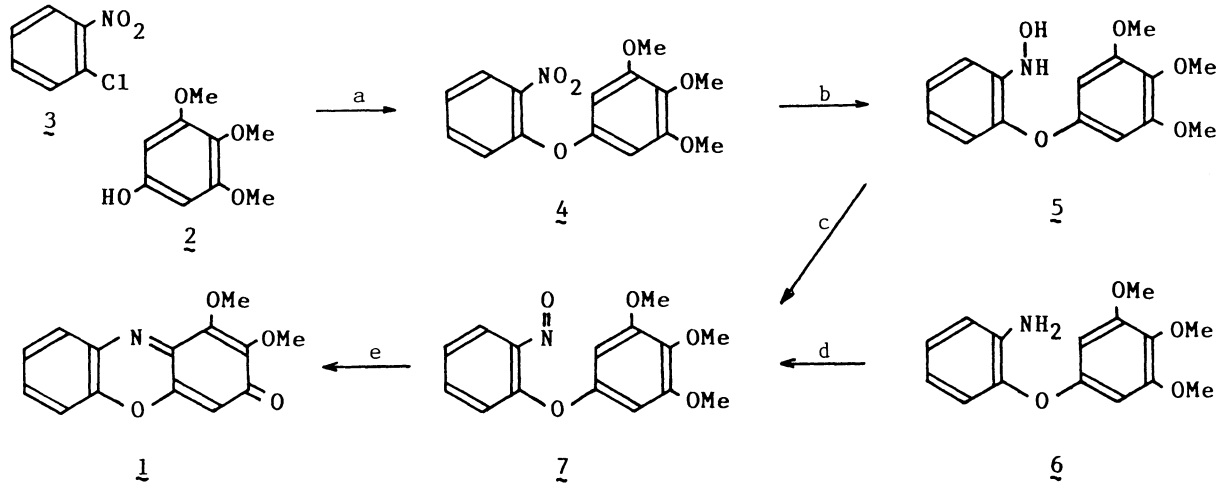
AV-toxin D(1) is the most active phytotoxic component among AV-toxins isolated from the cultural medium of Acrospermum viticola which cause the zonate leave spot disease, and is the sole natural product having methoxy groups on phenoxazone skeleton. By using the nitrene annulation reaction, we succeeded in the short step synthesis of 1.

AV-toxins are the phytotoxins which were produced by Acrospermum viticola Ikata causing the zonate leaf spot disease against the leaves of mulberry, and AV-D(1), one of AV-toxins, was shown to be the most active component by Nohara who isolated these toxins and determined the structures of them.[1] Our interests were stimulated by the facts that AV-D(1) is the sole natural occurring compound which has the methoxy groups on the phenoxazone skeleton being the fundamental structure of actinomycins. Nevertheless actinomycins are well-used drug in cancer chemotherapy, the general synthetic methods for these series of componds have not yet been well established. In earlier time, the derivatives of these compounds were prepared by oxidative couplings of o-aminophenols,[2] but this method is inadequate for syntheses of phenoxazones having different substituents on A and C ring. Recently, Bird reported the striking scheme that could overcome the above disadvantage point.[3] Although the Bird's method is excellent, the requirement of the phenolic hydroxy groups on C-3 possition seems to limit its applicable region. Thus, we improved the above method and synthesized AV-D(1) to scrutinize the bioactivities of this compound.

3,4,5-Trimethoxyphenol(2) and o-chloronitrobenzene(3) were chosen as the starting materials, because both of them are commercially available. At first, the pottasium salt of 2 and 3 were heated at 130 °C for 2 hours to give o-nitrophenyl trimethoxyphenyl ether(4) in 92% yield. Nextly, the annulation on the nitrogen atom should be done. As this type of the reaction, Cadogan's method[4] are well-known in which the cyclization occurs via nitrene produced by deoxygenation of nitroso or nitro group. However, on applying this reaction to the o-nitrophenyl phenyl ether, it was reported that the aminotetroxyphosphite was obtained instead of the expected phenoxazine.[5] Thus, the nitro group in 4 had to be transformed to the nitroso group, as follows. Ether(4) was reduced with zinc powder in the presence of ammonium chloride at 50 °C for 2 hours to give o-hydroxyaminophenyl trimethoxy-

phenyl ether(5) and o-aminophenyl trimethoxyphenyl ether(6) in 34% and 49% yield, respectively. Hydroxyamine(5) and amine(6) were oxidized with sodium bichromate and m-CPBA, individually. The obtained o-nitrosophenyl trimethoxyphenyl ether(7) were reacted with triethyl phosphite, according to the Cadogan's method. Due to the instability of the resulting compound which was assumed to be trimethoxyphenoxazine, the treatment with silica gel afforded the expected compound AV-D(1) in 20% yield from 7. Despite the low yield, this is the first case that Cadogan's nitrene annulation reaction was applied to synthesize the phenoxazine derivatives. The spectral data of synthesized AV-D completely coincided with those of the authentic sample.



a:EtOK, b:Zn/NH_4Cl, c:$Na_2Cr_2O_7$, d:m-CPBA, e:$P(OEt)_3$, SiO_2

Fig.1. Synthetic route of AV-D.

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