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SYNTHESIS OF (±)DI-O-METHYL-12-OXOCURVULARIN+

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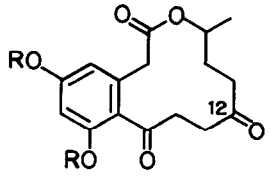
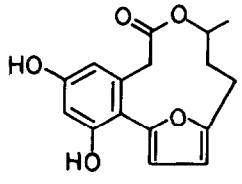
Abstract: Synthesis of (±)di-O-methyl-12-oxocurvularin (**1a**) has been described.

Recently Yamamura and coworkers[1] have reported the isolation of several curvularin type metabolites from the mycelium of the hybrid strain ME0005 derived from Penicillium citreo-veride B. Their stereostructures have been determined on the basis of chemical evidence and spectral data. Although curvularin[2] was first isolated in 1956 from the curvularia species, curvularin-type metabolites have not been found in the mycelium of P. citreo-viride B. Of the known curvularins, only 12-oxocurvularin (**1**) and citerofuran (**2**) have shown attractive physiological properties. They also possess an unusual oxygen function at C_{12} position in their structures.



1 , R=H
1a, R=CH_3



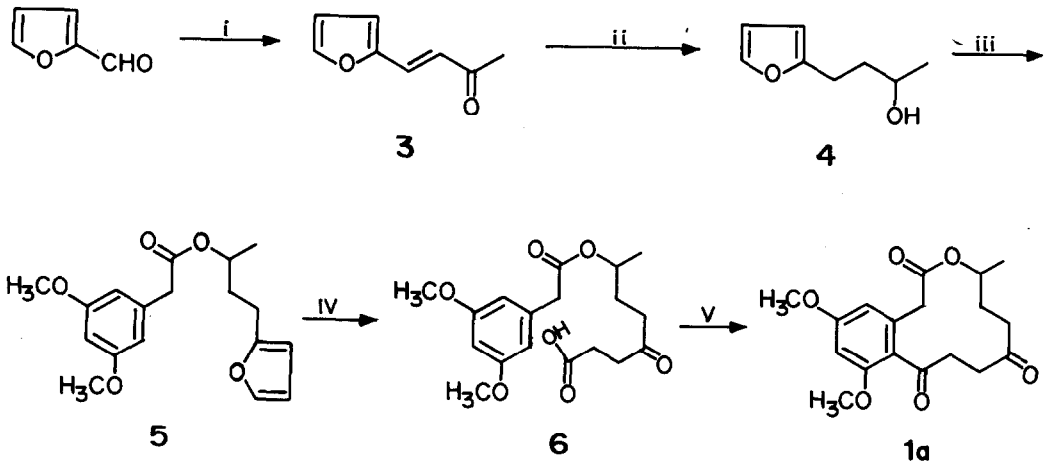
2

Several syntheses of curvularin have been reported.[3] However, 12-oxocurvularin (**1**) has not been synthesised so far. It has been shown[1a] that 12-oxocurvularin on treatment with CsOH in benzene gets readily converted into citerofuran (**2**).

As a continuation of our work on the synthesis of macrolides,[4] we now describe the first and a short synthesis of (±)di-O-methyl-12-oxocurvularin (**1a**). The 4-(2-furyl) -3-buten-2-one (**3**) prepared by condensation of 2- furfural with acetone in presence of sodium hydroxide, was reduced with LAH in THF to give 4-(2-furyl)-butan-2-ol (**4**)[5] in 81% yield (Scheme). Reaction of **4** with 3,5-dimethoxyphenylacetyl chloride[3a] in benzene in presence of pyridine afforded the ester **5** in 75% yield. Oxidative ring cleavage of the 2-substituted furan **5** with Jones reagent gave the keto acid **6** (67%), which on intramolecular acylation in a mxiture of TFA-TFAA afforded di-O-methyl-12-oxocurvularin (**1a**)[6] in 16% yield.

+ NCL Communication No. 5076

SCHEME



Reagents: i) Acetone, cat.NaOH; ii) LAH in THF, 0°C; iii) 3,5-Dimethoxyphenylacetyl chloride in benzene and pyridine; iv) Jones reagent, 0°C, v) TFA-TFAA (1:5) r.t. 4 h.

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6. (±)Di-O-methyl-12-oxocurvularin **1a**: semisolid; MS(M^+) m/z 334; IR (Neat): 1745, 1730 and 1610 cm^{-1} ; UV (MeOH, λ max): 220, 275 and 300 nm; ^{1}H-NMR (90 MHz, $CDCl_3$): δ 1.17 (3H, d, J=6.2Hz), 1.72-2.1 (2H, m), 2.1-2.75 (4H, m), 3.0 (2H, m), 3.60 (2H, bs), 3.71 (3H, s), 3.80 (3H, s), 4.92 (1H, m), 6.28 (1H, d, J=2.2Hz) and 6.4 (1H, d, J=2.2Hz).

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