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AN APPROACH TO THE SYNTHESIS OF OPTICALLY ACTIVE TRICHOTHECENES FROM TRI-O-ACETYL-D-GLUCAL [1]

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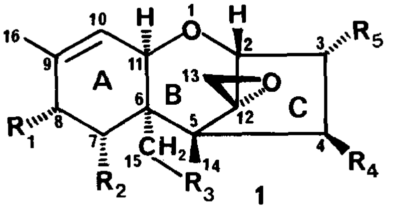
Summary : A chiral synthesis of the B-C ring system of trichothecenes from tri-O-acetyl-D-glucal by using a photochemical cycloaddition of acetylene to the unsaturated ketone 7, followed by acid-catalyzed rearrangement, is described .

The trichothecenes 1, e.g.1a form one of the most diverse families of mycotoxins and are produced by numerous species of *Trichoderma*, *Myrothecium*, *Strachybotrys* and *Cephalosporium* [2] .



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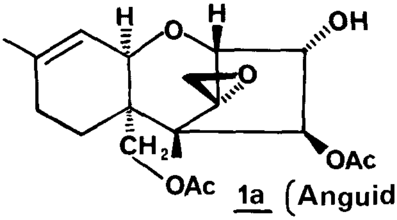


1a (Anguidin)

As trichothecenes exhibit a broad range of biological activities, especially anticancer activity, depending on the respective functional groups present on the tricyclic backbone [3], many synthetic studies of these compounds have been actively pursued .

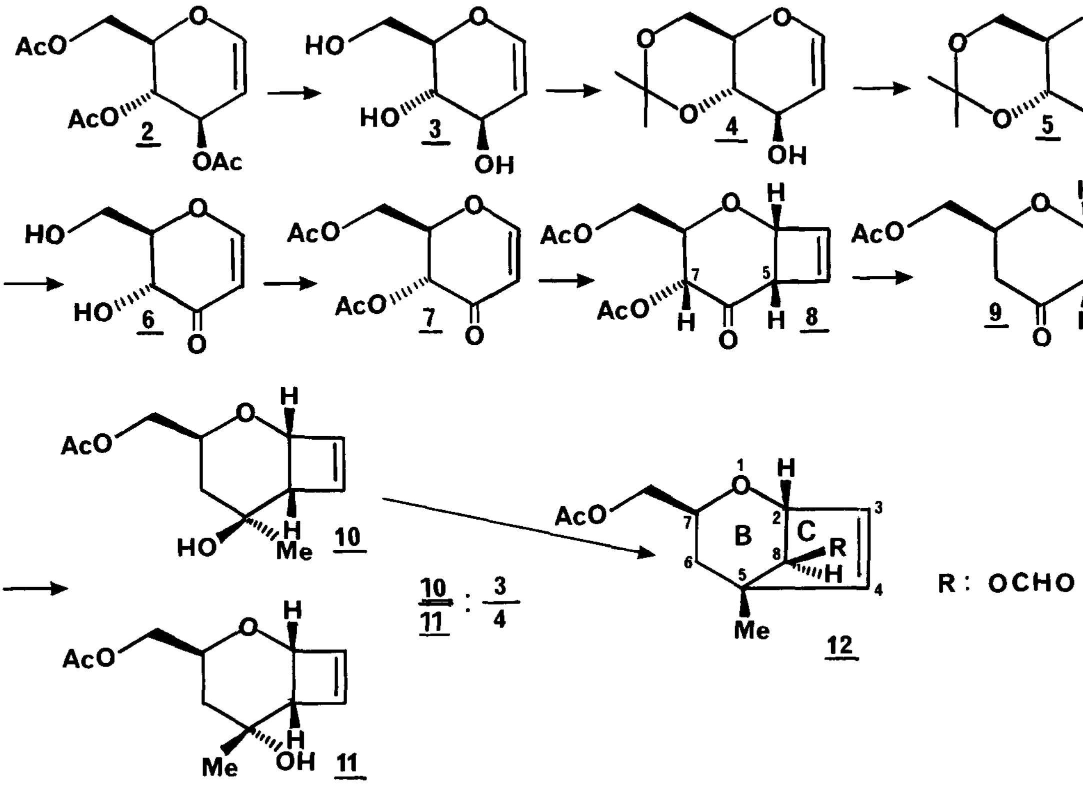
The approaches of the synthesis of trichothecenes can be divided into four groups according to the strategy employed to assemble the tricyclic skeleton : a) the "bridging approach" [4] b) the "B-ring expansion approach" [5] c) the "biomimetic approach"[6] d) addition of an A-ring unit to a fully functionalized C-ring unit followed by an intramolecular cyclization providing the B-ring [7].

In this communication, we wish to report a new synthetic pathway from tri-O-acetyl-D-glucal 2, an inexpensive, commercially available compound leading to the construction of chiral B-C rings 12 of trichothecenes 1 with the right absolute configuration .

The synthesis of 12 is outlined in scheme I [8] . The diacetoxy ketone 7 was prepared following a modification of the general procedure of FRASER REID [9] . Thus, 2 was transformed into D-glucal 3 by treatment with a suspension of sodium carbonate in methanol . Crude 3 was allowed to react with 2,2-dimethoxypropane in DMF with a catalytic amount of p-TsOH . The acetonide 4 was obtained in 44 % yield from 2 . Oxidation of alcohol 4 with 1.5 equiv. of pyridinium dichromate (P.D.C.) in DMF [10] at r.t. followed by filtration of the crude product in DMF on silica gel using ether as eluent followed by recrystallisation (pentane-ether) provided the crystalline ketone 5, m.p. 104°-105°C in 90 % yield . Removal of the acetonide protecting group of 5 with p-TsOH, 1 H_2O (0.30 mg of p-TsOH, 1 H_2O/mg of 5) in acetone (1 mg of 5/0.1 ml acetone) at r.t. gave 6 which was not isolated . Direct acetylation of the crude product with 3 equiv. Ac_2O in pyridine at r.t. gave 7 in 90 % yield . Photocycloaddition of acetylene (Hanau T.Q. 150 high pressure lamp with a Pyrex filter, $\lambda > 295$ nm) [11] to 7 using acetone as solvent at - 20°C provided 8 in 50 % yield . Deacetoxylation of 8 with lithium dimethyl cuprate [12] in ether at - 30°C afforded 9 in 60 % yield [13] . Treatment of 9 with 3 equiv. methyl lithium in ether at 0°C gave alcohols 10 and 11 (10 : 11 = 3 : 4) in 70 % yield [13] . Finally, treatment of 10 with formic acid at r.t. led to 12 in 80 % yield .

The α-stereochemistry of the cyclobutene ring in 8 was proved by the presence of a W.^4J coupling constant between proton on C-$_5$ and β-proton on C-$_7$ ($^4J_{H\text{-}5|H\text{-}7}$ = 1.2 Hz) by decoupling experiment on H-$_5$ (fig. 1) .

Scheme I



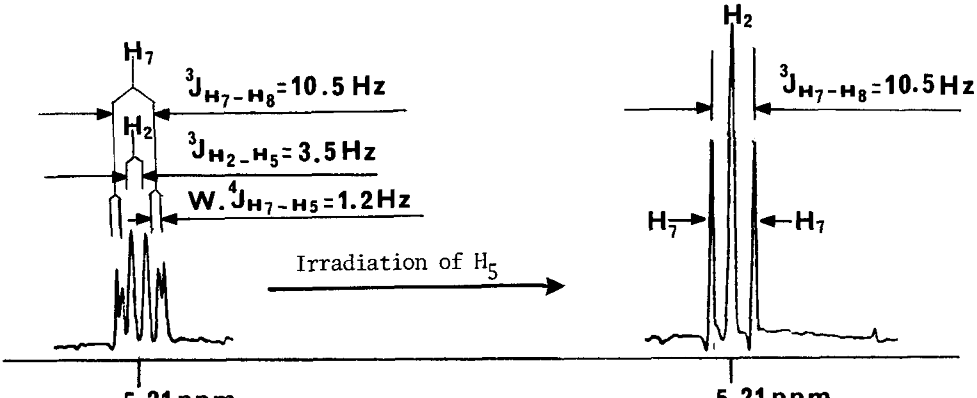
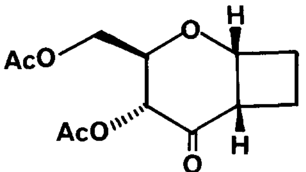


Fig. 1



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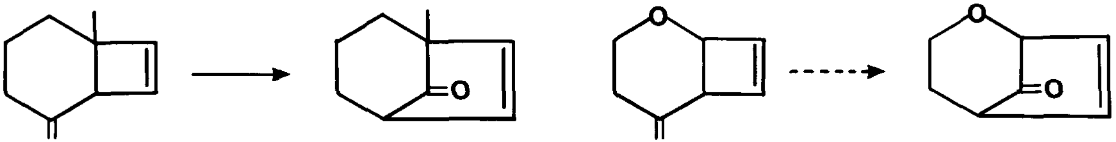
On the other hand, the OCD (optical circular dichroism) of 13, the hydrogenated compound of 8 is in agreement with the stereochemistry ($\Delta\varepsilon$ = - 0.102) . The ^{1}H NMR spectrum (200 MHz-$CDCl_3$) of 12 showed signals for two olefinic protons H-$_3$ and H-$_4$ at 6.03 ppm and 6.18 ppm and appeared as a quartet and a doublet respectively with $^3J_{\text{H-}_3|\text{H-}_4}$ = 6 Hz ; $^3J_{\text{H-}_3|\text{H-}_2}$ = 3 Hz; $^3J_{\text{H-}_4|\text{H-}_3}$ = 6 Hz . This $^3J_{\text{H-}_3|\text{H-}_4}$ = 6 Hz is compatible with the coupling constant of olefinic protons in an cyclopentene ring [14] . The singlet signal at 8.23 ppm is assigned to the formate proton on C-$_8$. Proton H-$_8$ appeared as a doublet at 4.58 ppm with $^3J_{\text{H-}_8|\text{H-}_2}$ = 5 Hz ; for this reason, we conclude that the stereochemistry of H-$_8$ is α [15] .

Although we could duplicate the rearrangement of 14 into 15 under CARGILL's conditions [17] or in the presence of BF_3-Et_2O, our oxygenated substrates 8 and 9 led to entirely different results which will be published elsewhere . Solvolysis of the tertiary alcohol 10 was in our hands, the only successful pathway .



14 **15** **16** **17**

To our knowledge, no rearrangement of bicyclic ketones such as 16 into 17 has ever been described so far .

Study of the elaboration of A ring in 12 is in progress in our laboratory .

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