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TOTAL SYNTHESIS OF PROTECTED FORM OF FUNGI METABOLITE CORTALCERONE

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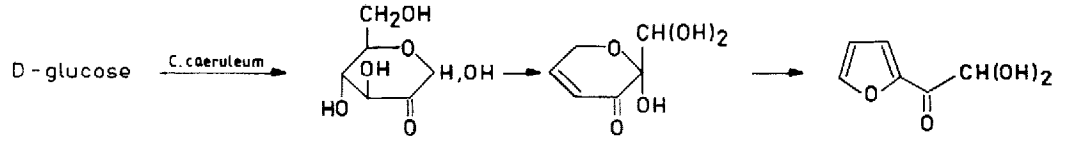
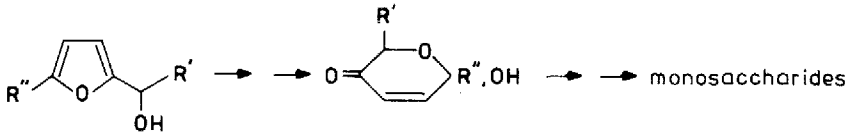
Abstract: Synthesis of methyl 4,5-dideoxy-D,L-hex-4-enos-2-ulopyranosid-3-ulose ethylene acetal, derivative of first natural sugar with dihydropyranone moiety, from 5-acetoxymethylfurfural is described.

Lignicolous fungus Corticium caeruleum transforms D-glucose into the antibacterial compound named cortalcerone and identified as 4,5-dideoxy-D,L-hex-4-enos-2-ulopyranos-3--ulose hydrate (2)[1a,b]. It has been also shown that this biotransformation is specific for D-glucose[1c,d], proceeds in two steps with D-glucosone (1) as the intermediate[1d,h] and occurs also in other macrofungi[1e,g]. Upon treatment with acid cortalcerone gives 2-furyl-glyoxal hydrate (3)[1a].



1 2 3

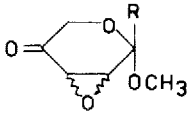
An unusual structure of 2 comprising three consecutive carbonyl groups in addition to the double bond, a moiety which to our knowledge has not been encountered before in natural products, makes cortalcerone an interesting target of the synthesis. Its easy degradation to 3 suggested an approach based on the general method of monosaccharides synthesis from furans 4[2]:



4 5

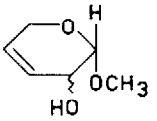
Since cortalcerone has a regioisomeric α,β-unsaturated carbonyl system to the one present in ulose 5, its synthesis required an efficient method of the dihydropyran functions transposition, i.e. 9 ⟶ 19 (Scheme). An attempt to carry it without reduction of the 5-keto group failed. Reacting keto-epoxide 22 with hydrazine and acetic acid according to

the known procedure[3] gave no identifiable product, though a model compound 21 under these conditions afforded the expected allylic alcohol 23[4] albeit with only 15% yield.



21 R=H

22 R= 



23

On the other hand an alternate approach, entailing reduction of carbonyl group and utilizing 1,3-transposition of an allylic alcohol via an intermediate selenoxide[5] worked smoothly.

As a starting furan compound the readily available 5-acetoxymethylfurfural was used. After protection of formyl group and deacetylation, resulting alcohol 7 was oxidized with m-chloroperbenzoic acid[6] to give pyranosid-5-ulose 8[7]. Methylation of the latter and reduction of resulting methyl glycoside 9 with DIBAL gave epimeric alcohols 10 and 11 in the 4.4:1 ratio[8]. Alcohol 10 was reacted with o-nitrophenyl selenocyanate in the presence of tributylphosphine to give with inversion of configuration at C-5 selenide 14. Oxidation of the latter with 30% H_2O_2 in CH_2Cl_2/pyr. proceeded with concomitant elimination and rearrangement to give cleanly albeit with moderate yield alcohol 15. In the same fasfion 17 was obtained from 11. Oxidation of alcohol 15 or 17 with MnO_2 afforded in each case cortalcerone derivative 19 as a sole product. In fact for the synthetic purposes 10 and 11 need not be separated and all reactions could be performed on the mixture.

Treatment of 19 with an acid gave 2-furylglyoxal ethylene acetal (20).

The stereochemistry of acetates 12 and 13 as well as 16 and 18 could not be deduced unequivocally from their ^{1}H NMR spectra[9]. Values of vicinal and allylic coupling constants for 12 and 13 showed that for both compounds prevailed conformation with pseudoequatorial H-5. Since due to the quaternary C-2 the other set of vicinal couplings is missing, it precluded the assignment of the relative configuration of dihydropyran ring substituents. The reported stereochemistry for all obtained compounds is based on the configuration established for 16 by the X-ray single crystal diffraction method (Figure)[10] and the steric relation in the series 10 ⟶ 14 ⟶ 15 and 11 ⟶ 17, which stems from the method of their preparation.

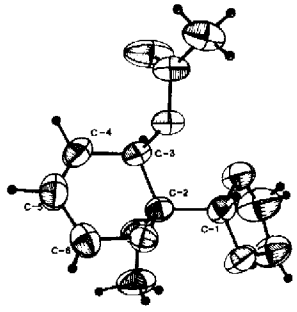
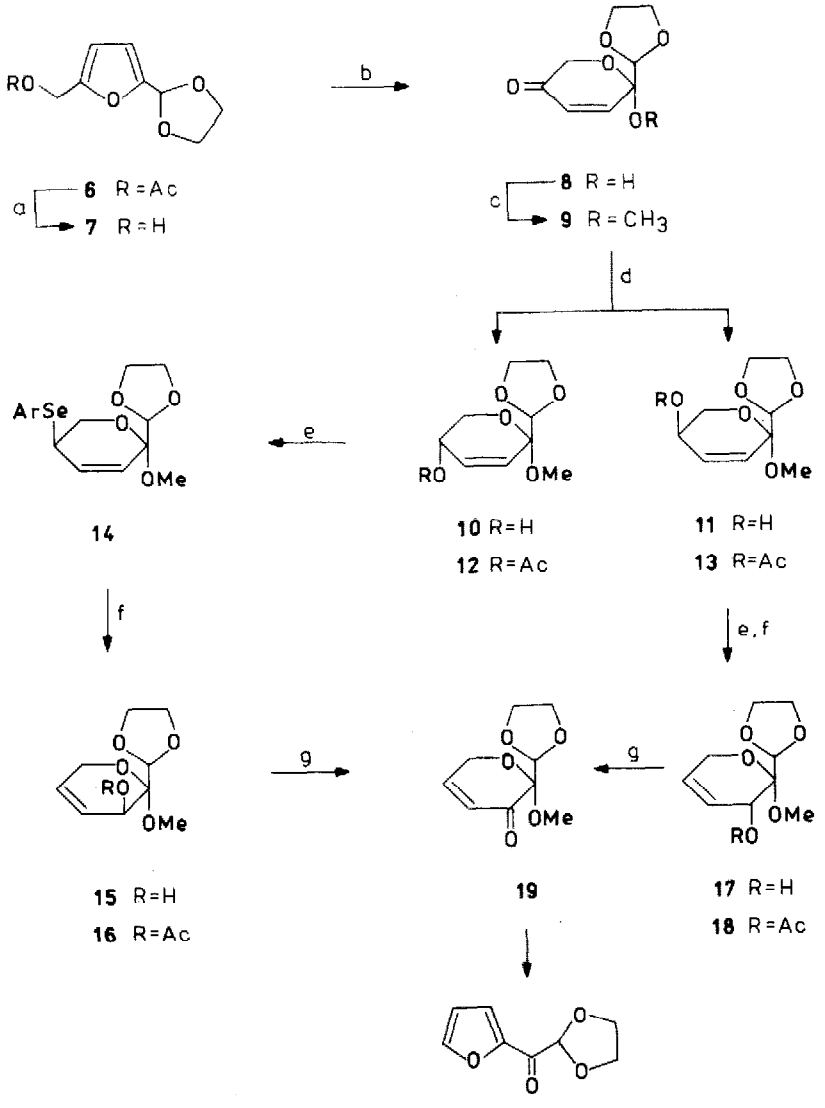


Figure. ORTEP drawing of 16

Scheme



Ar = o-NO_2Ph

(a) MeONa, MeOH; (b) m-ClPBA; (c) MeI, Ag_2O; (d) DIBAL, THF, -78°C; (e) o-NO_2PhSeCN, Bu_3P, THF, r.t.; (f) 30% H_2O_2, CH_2Cl_2/pyr., r.t.; (g) MnO_2, CH_2Cl_2

References and notes

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7. All new compounds described herein have been characterized by ^{1}H NMR, IR and either high resolution mass spectroscopy or combustion analysis.
8. Reduction of 9 with LAH (ether, r.t.) gave alcohols 10 and 11 in the 1:1 ratio.
9. Selected ^{1}H NMR data:

   12 (270 MHz, $CDCl_3$) δ : 6.24 (dd, 1H, $J_{3,4}$ = 11.03, $J_{4,5}$ = 4.00 Hz, H-4); 5.83 (dd, 1H, $J_{3,5}$ = 1.2 Hz, H-3); 5.15 (m, 1H, H-5); 4.23 (dd, 1H, $J_{6,6'}$ = 12.06, $J_{5,6}$ = 4.22, H-6); 3.86 (dd, 1H, $J_{5,6'}$ = 5.22 Hz, H-6').

   13 (270 MHz, $CDCl_3$) δ : 6.19 (ddd, 1H, $J_{3,4}$ = 10.18, $J_{4,5}$ = 4.77, $J_{4,6'}$ = 1.01 Hz, H-4); 5.98 (dd, 1H, $J_{3,5}$ = 0.85 Hz, H-3); 5.05 (m, 1H, H-5); 4.12 (dd, 1H, $J_{6,6'}$ = 12.52, $J_{5,6}$ = 3.43 Hz, H-6').

   16 (270 MHz, $CDCl_3$) δ : 6.05 (ddd, 1H, $J_{4,5}$ = 10.50, $J_{5,6}$ = 2.95, $J_{5,6'}$ = 1.8 Hz, H-5); 5.94 (dddd, 1H, $J_{3,4}$ = 5.02, $J_{4,6}$ = 2.1, $J_{4,6'}$ = 2.1 Hz, H-4); 5.10 (bdd, 1H, $J_{3,6}$ 0.4, $J_{3,6'}$ = 1.8 Hz, H-3); 4.37 (dddd, 1H, $J_{6,6'}$ = 17.30 Hz, H-6); 4.24 (dddd, 1H, H-6').

   18 (500 MHz, $CDCl_3$) δ : 5.89 (apparent ddt, 1H, $J_{4,5}$ = 10.50, J = 2.81, 2xJ = 2.26 Hz, H-4 or H-5); 5.82 (m, 1H, H-3); 5.55 (apparent dq, 1H, 3xJ = 2.19, H-5 or H-4); 4.23 - 4.14 (m, 2H, $J_{6,6'}$ = 16.81 Hz, H-6, H-6').

   19 (300 MHz, $CDCl_3$) δ : 7.05 (ddd, 1H, $J_{4,5}$ = 10.53, $J_{5,6}$ = 2.35, $J_{5,6'}$ = 3.38 Hz, H-5); 6.14 (ddd, 1H, $J_{4,6}$ = 2.24, $J_{4,6'}$ = 1.91 Hz, H-4); 5.37 (s, 1H, H-1); 4.58 (ddd, 1H, $J_{6,6'}$ = 19.36 Hz, H-6); 4.49 (ddd, 1H, H-6'); 4.11 - 3.86 (m, 4H, $\underset{O}{\overset{}{CH_2}}-\underset{O}{\overset{}{CH_2}}$); 3.50 (s, 3H, OCH_3).
10. The full details of X-ray analysis will be published separately.

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