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TOTAL SYNTHESIS OF (-) ALTHOLACTONE (GONIOTHALENOL) FROM D-GLUCOSE

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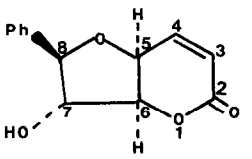
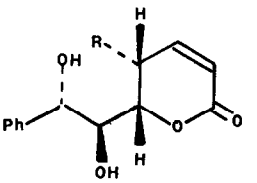
ABSTRACT : A ten steps total synthesis of (-) altholactone, enantiomer of an antitumor pyrone isolated from *Goniothalamus* species, is described starting from D-glucose.

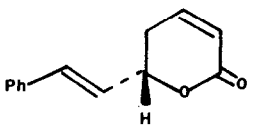
(+) Altholactone 1 has been isolated in 1977 by LODER *et al.*[1] from an unknown *Polyalthea* species. This substance is characterized by a cis-fused tetrahydrofurano-2 pyrone structure proposed on the basis of spectral data and chemical derivatization. Recently, McLAUGHLIN *et al.*[2] have extracted 1 (structure confirmed by X-Ray analysis) from the stem bark of *Goniothalamus giganteus* Annonceæ and subsequently shown that it is cytotoxic *in vitro* (BS, 9 KB) and active *in vivo* against P 388 leukemia.



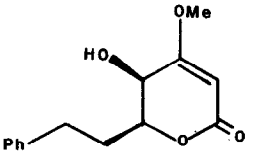
(+) 1 Altholactone
(Goniothalenol)



2 R = H Goniodiol
3 R = OH Goniotriol



4 Goniothalamin



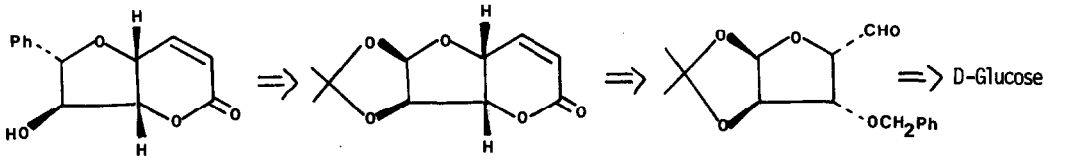
5 Dihydrokawain-5 ol

It is worthy of note that other bioactive pyrones with the opposite 6S configuration have been isolated from other *Goniothalamus* species : goniothalamin 4[3] and the more oxygenated goniodiol 2 and goniotriol 3[4] (this latter compound may be considered as a non cyclized form of (-) altholactone).

The 6R configuration of (+) altholactone is however found in related pyrones such as dihydrokawainol-5[5], olguin[6], asperlin[7] and analogues[8].

The interesting biological activities demonstrated by most of these pyrones (with either a 6R or a 6S configuration) justify that we propose two enantiodivergent syntheses of (+) and (-) altholactone from D-glucose[9].

Retrosynthetic analysis of (-) 1 shows that the requested 5R, 6S and 7S configurations may be obtained from a carbohydrate (i.e. respectively C-4, C-3 and C-2 of D-glucose) and that construction of the pyrone ring from 6 to give 11 followed by arylation at C-8 should give (-) 1.



(-) 1 11 6

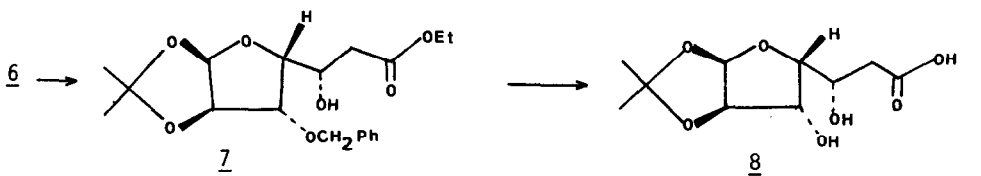
These two points will be discussed successively.

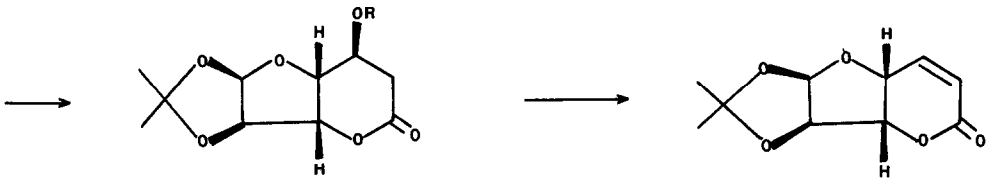
PREPARATION OF PYRONE 11

Reformatsky condensation of the readily available 6[10] with ethyl bromoacetate affords a major oily compound 7, $[\alpha]_D$ = -22° ($CHCl_3$, c = 2), 85% isolated yield[11] which is thought to result from the favored chelation-controlled addition of the zinc enolate[10,12]. Base catalyzed hydrolysis of ester 7 followed by hydrogenolysis (H_2,Pd/C, ethyl acetate) gives 8[11], m.p. 142°C (85%) which is then converted to lactone 9 (1.2 eq. dicyclohexylcarbodiimide, pyridine) and to acetate 10, m.p. 85-86°C, $[\alpha]_D$ = + 22° ($CHCl_3$, c = 1.2), (Ac_2O, pyridine, 78% from 8)[11].

The axial orientation of the acetoxy group, confirming the previous assumption about the relative stereochemistry of 7, is demonstrated by the presence of a doublet (J H-4/H-5 = 2.2 Hz) of triplets (J H-5/H-6 = 8.8 Hz) at δ = 5.32 ppm for H-4.

Finally, the requested pyrone 11, m.p. 70-71°C, $[\alpha]_D$ = + 33° (c = 1.5, $CHCl_3$)[11] is obtained from 10 on treatment with 1.1 eq. of diazabicyclounḍecene (DBU) in CH_2Cl_2 at room temperature (87%).





9 R = H
10 R = $COCH_3$

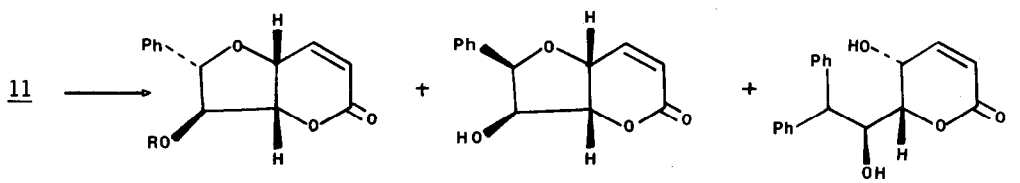
11

ARYLATION OF PYRONE 11

The conversion of pyrone 11 to (-) altholactone 1 may be considered as analogous to the synthesis of C-aryl nucleosides from carbohydrates. Although many activating groups and reaction conditions have been reported to promote the formation and arylation of the intermediate onium ion[13], we anticipated that anhydrous HF will catalyze both ketal cleavage and arylation of 11 to 1. As a matter of fact treatment of 11 with 40 eq. of benzene in HF at 0°C for 10 min. affords three compounds :

. (-) 1 (48%) whose TLC behaviour, IR, ^{1}H and ^{13}C NMR spectra are identical with those of (+) 1[1,2]. This oily synthetic material, $[\alpha]_D$ = - 166° (c = 0.5, EtOH) appears to retain even after Florisil chromatography[14] trace amounts of impurities (not detected by NMR and TLC) which preclude crystallization ($F_{Litt.}$ = 75°C, $[\alpha]_D$ = + 188° (EtOH)[1] and $F_{Litt.}$ = 110°C, $[\alpha]_D$ = + 184.7° (EtOH)[2] for (+) 1). Acetylation of this sample affords quantitatively 14, m.p. 141°C, $[\alpha]_D$ = - 200° (EtOH, c = 1) whose physical (m.p. 142°C) and spectral data[11] are similar to those reported by LODER[1] except for the sign of optical rotation ($[\alpha]_D$ = + 208°C, (EtOH, c = 1)).

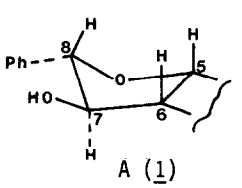
. 12 (18%), m.p. 190-192°C, $[\alpha]_D$ = 266° (EtOH, c = 0.5)[11]. This material must be, on the basis of MS and NMR data, epimeric at C-8 with 1. The observed coupling constant J H-7/H-8 is however smaller for 12 than for 1 (see Table) in contrast with the usual respective values for cis and trans ^{3}J in five membered rings[14]. This may be explained by the occurrence of conformations A for 1 and B for 12 which both exhibit dihedral angles in agreement with the experimental ^{3}J values (see Table).



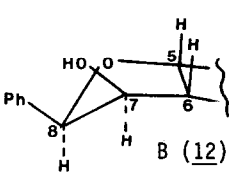
(-) 1 R = H
14 R = $COCH_3$

12

13



A (1)



B (12)

Table ^{3}J (Hz)

	1	12
H_5-H_6	5	5
H_6-H_7	2	0
H_7-H_8	5.5	3.5

. 13 (3%), m.p. 201-202°C, $[\alpha]_D$ = + 53° (EtOH, c = 0.5)[11].

This minor compound results from diarylation as shown by MS and NMR spectra.

As expected (-) 1 resulting from arylation anti to the C-7/OH is favored over 12 (2.7 ratio) and under these conditions diarylation is minimized[15]. This result holds promise for HF-catalyzed arylation of suitably protected carbohydrates to C-nucleosides.

In conclusion, (-) altholactone 1 has been prepared in 10 steps from D-glucose using an efficient HF catalyzed arylation as the last step. The antitumor activity of these new pyrones will be reported later.

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