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

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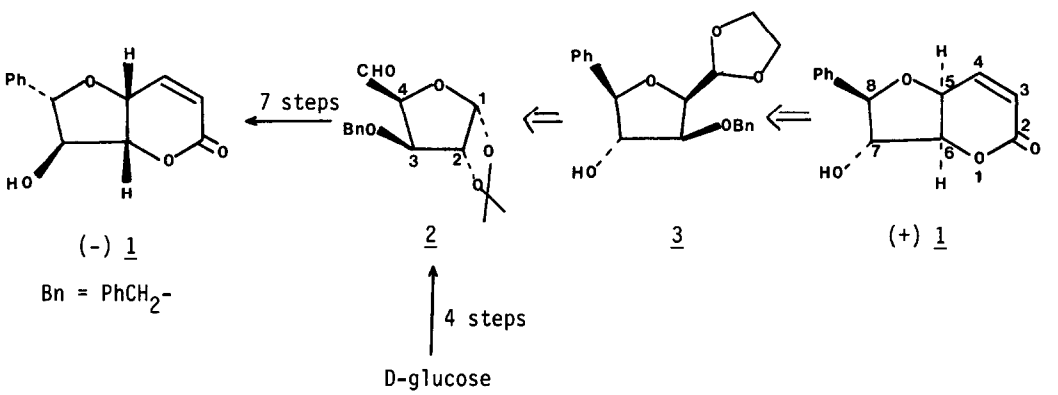
ABSTRACT : The first total synthesis of the antitumor (+) altholactone is described from D-Glucose.

In the preceding communication[1] we have described the synthesis of (-) altholactone 1, enantiomer of an antitumor pyrone isolated by LODER[2] and McLAUGHLIN[3] from different *Goniothalamus* species.

An enantiodivergent route to (+) 1 is now proposed from the readily available aldehyde 2[4] already used in the synthesis of (-) 1.



(-) 1 2 3 (+) 1

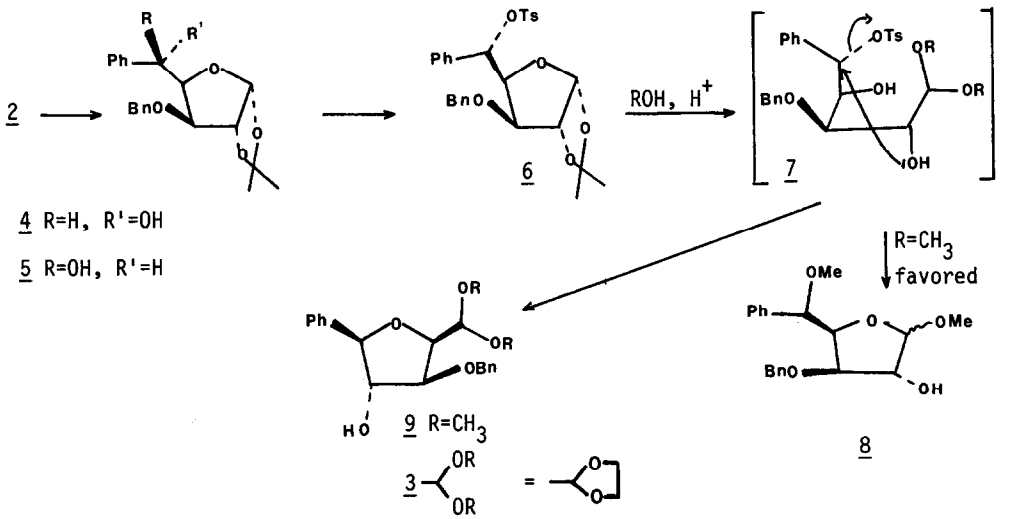
This compound has at C-2, C-3 and C-4 the absolute configurations required for (+) 1 (respectively at C-5, C-6 and C-7) and retrosynthetic analysis shows that preparation of the protected furano aldehyde 3 followed by pyrone ring closure should complete the synthesis of (+) 1. These two points will be successively discussed.

PREPARATION OF 3

Following Inch's procedure[5] condensation of Ph-MgBr (4.4 eq.) with aldehyde 2 in ether at 20°C for 2 h affords after SiO_2 filtration the expected alcohol 4 (73%)

arising from chelation-controlled addition and a trace of 5 (4%) in a diastereoisomeric ratio of 16 to 1.

Ring closure to the furan 3 is then expected to occur by internal displacement of tosylate 6[6] (m.p. 117-118°C, $[\alpha]_D$ =-12° ($CHCl_3$, c = 0.1) 86% yield from 5) after intermediate ketalisation to 7. This method first described by Ogawa[7] is generally carried out in methanolic HCl. However in this case, a complex mixture is obtained from which only pure α and β methyl furanosides 8 (The stereochemistry at the benzylic center cannot be secured on the basis of ^1H NMR) can be isolated. To obviate this intermolecular displacement of tosylate 7 which precludes the formation of 9, the reaction is carried out in benzene at reflux (1 hr) in presence of ethylene glycol (4 eq.) and a catalytic amount of paratoluene sulfonic acid to give 3[6] as an oil, $[\alpha]_D$ = + 11° ($CHCl_3$; c = 1.3) in 87% yield. The complete stereoselectivity of the internal displacement of benzylic tosylate 7 should be pointed out and the trans relationship between the aromatic ring and the neighbouring alcohol group is in agreement with the observed doublet (J = 4.8 Hz) for the benzylic proton (J = 5.5 Hz for the same proton in 1 vs J = 3 Hz for 8-epi 1, see preceding communication).



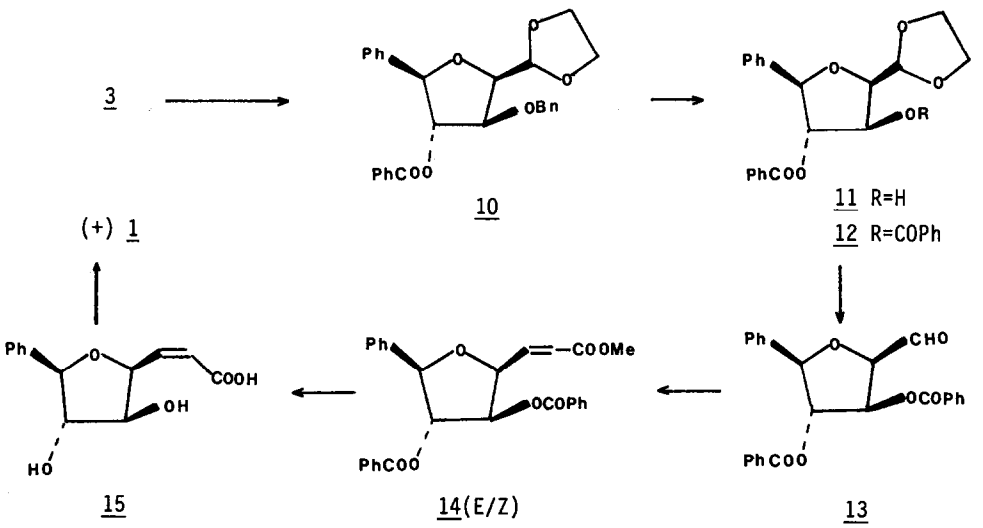
SYNTHESIS OF (+) 1

Conversion of 3 to a suitably protected aldehyde needed for a cis-Wittig olefination or Reformatsky reaction turns out to be difficult : this sequence requires a selective deprotection of a primary O-benzyl group in presence of a secundary one, protection of the two resulting hydroxyl functions with an acid stable protecting group and cleavage of the ethylene ketal. Selective hydrogenolysis of 3 proves to be synthetically useless under various conditions using different catalysts[8]. After several attempts we found that quantitative conversion of 3 to benzoate 10[6] (oil, $[\alpha]_D$ = + 44°, $CHCl_3$, c = 2) followed by treatment with 1.1 eq. of trimethylsilyl iodide (TMSI) in CH_2Cl_2 (-20°C to + 5°C) for 2 days affords the desired alcohol 11 as an oil ($[\alpha]_D$ = + 28°, $CHCl_3$, c = 0.1) in 58% yield together with starting material (15.5%)[9].

Benzoylation of 11 gives 12[6] (90%), m.p. 47-51°, $[\alpha]_D$ = - 49° ($CHCl_3$, c =

1.3),which is then hydrolyzed (CF_3COOH-H_2O (80-20), 20°C, 16 h) to aldehyde 13[6], oil (86%). This material is then submitted without purification to cis-Wittig olefination conditions[10] (Ph_3P = CH-COOMe (3 eq.), anhydrous methanol, 3 h, 20°C) to afford after column chromatography Z-14 (58%)[6] and the more polar E-14 (11%)[6]. Both compounds are easily characterized by ^1H NMR and particularly by ^3J between vinylic protons of 11 Hz for Z-14 and 16 Hz for E-14.

Alkaline hydrolysis of Z-14 (1 N NaOH, 20°C, 12 h) followed by acidification and continuous extraction with methylene chloride leads to the dihydroxy-acid 15[6] which is then converted without purification to (+) 1[6] (55% overall yield from Z-14) using CF_3COOH-CH_2Cl_2 (5/95, 20°C, 30 min). Our synthetic material exhibits similar m.p. 111-112°C (Litt.[2] = 75°C, [3] = 110°C), optical rotation in EtOH $[\alpha]_D$ = + 183° (Litt.[2] = + 188°, [3] = + 184.7°), TLC behaviour, IR and ^1H NMR spectra as does an authentic sample of (+) 1.



The first synthesis of the antitumor (+) altholactone 1 is thus completed in 14 steps from the D-glucose already used in the synthesis of (-) 1 (see preceding communication).

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