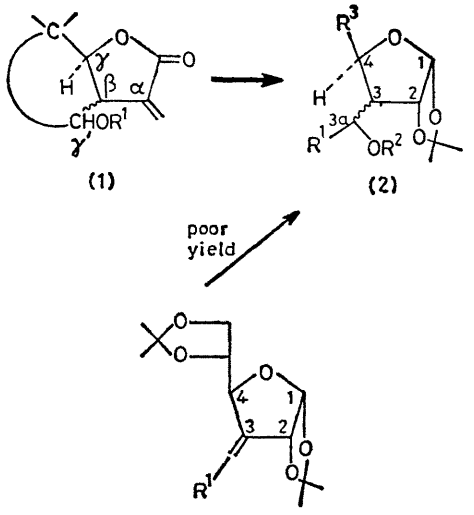
1,2-*O*-Isopropylidene Furanoses as Chiral Precursors for α-Methylene-γ-butyrolactones

By TIM FAT TAM and BERT FRASER-REID*
(*University of Waterloo, Waterloo, Ontario, Canada*, N2L 3G1)

Summary 1,2-*O*-isopropylidene furanose derivatives may be converted into *syn* or *anti* forms of the title lactones, *via* 2-*C*-methylene glycofuranosides which are hydrolysed under neutral conditions

THE α-methylene-γ-butyrolactone unit is a structural feature common to a large number of antineoplastic agents belonging to sesquiterpene families such as the germacranolides, elemanolides, eudemanolides, guaianolides, and pseudoguaianolides It has been suggested[1] that the

cytotoxic activity arises from the ability of the unsaturated lactone to alkylate cysteine residues *via* a Michael reaction and as a result of this hypothesis, the development of synthetic routes to this entity has commanded considerable attention.[2]

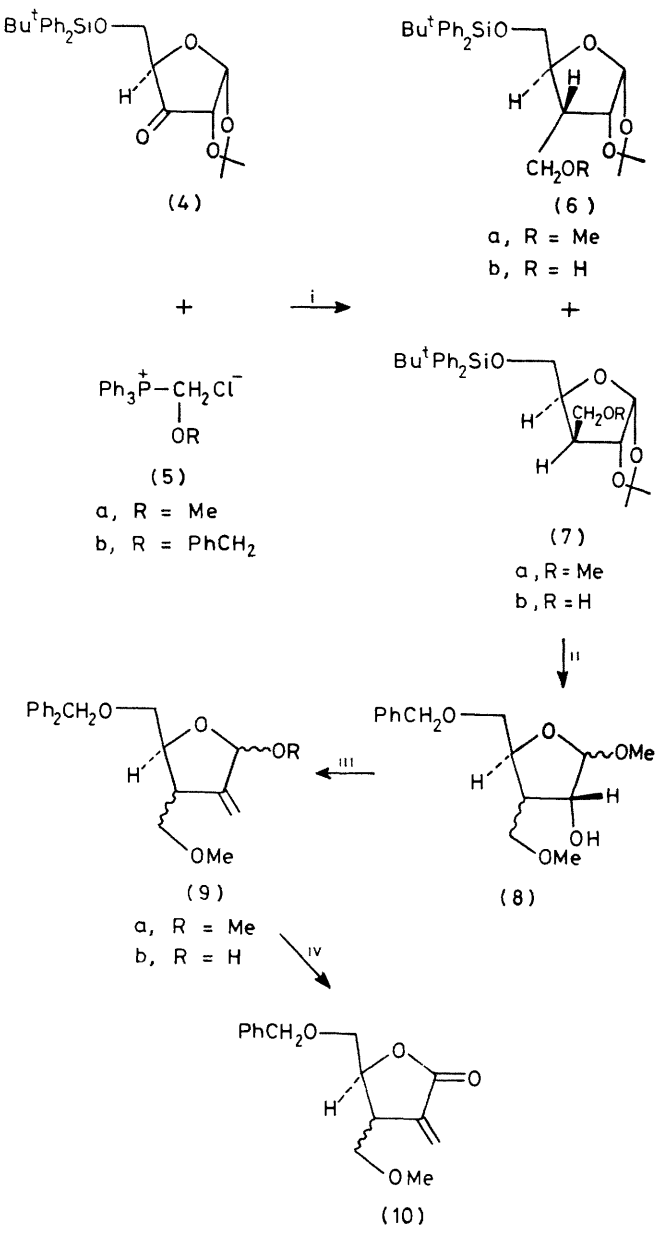


In connection with our work on the use of sugars as chiral synthons,[3] we were intrigued by the potential of furanoses as latent α-methylene-γ-butyrolactones, and particular interest arose from the fact that in most of these sesquiterpenes [*cf.* (**1**)], the absolute stereochemistry at the γ-position is congruent with that at C-4 of furanose derivatives such as (**2**). The configuration at the β-position may be *syn* as in helenanin[4] and confertin,[5] or *anti* as in vernolepin[6] or ciliarin.[7] We here outline a route from 1,2-*O*-isopropylidene furanoses that give the chiral *syn* and *anti* forms of α-methylene-γ-butyrolactones.

Another feature in may of these sesquiterpene lactones [*cf.* (**1**)] is the presence of an oxygen at the δ′-position,[4–7] which correlates with C-3a of (**2**). Such a derivative has been prepared by Rosenthal and co-workers by hydroboration–oxidation of the methylene precursor (**3a**); however loss of the acetonide(s) also occurred resulting in poor yields.[8] In our hands, the ethylidene analogue (**3**) fared even worse. The hydroboration route to these alcohols was therefore abandoned.

The ketone (**4**), prepared in 85% yield from 1,2-*O*-isopropylidene xylose [i, Bu^tPh_2SiCl; ii, Collins oxidation], was treated with the phosphorane derived from the methoxyphosphonium salt (**5a**), and the vinyl ether obtained (*ca.* 60%) was hydrogenated to afford (**6a**) and (**7a**) in 4:1 mixture. Similarly, the *O*-benzyl salt (**5b**) led to (**6b**) + (**7b**). The 5-OH protecting group of the *O*-methyl ethers (**6a**) + (**7a**) was changed to benzyl, and methanolysis led to the glycosidic mixture (**8**).

Oxidation with pyridinium chlorochromate gave an unstable ketone in 65% yield which was immediately treated with methylene triphenylphosphorane leading to the methylene glycoside (**9**).



Reagents: i, Bu^nLi, 1,2-dimethoxyethane (DME), then H_2, Pd–C, EtOH. ii, $Bu^n_4N^+F^-$, tetrahydrofuran (THF), 61%; $PhCH_2Br$, NaH, THF, $Bu^n_4N^+I^-$, 82%; 25% HCl–MeOH, 95%. iii, Pyridinium chlorochromate, CH_2Cl_2, 65%; $Ph_3P{=}CH_2$, DME, 45%; DME, H_2O (3:1), 87%. iv, Ag_2CO_3–Celite, benzene, 77%.

We now confronted a major concern of our synthetic plan, namely the fear that compound (**9a**), like analogous unsaturated glycosides, would go readily to furans upon treatment with acid.[9] Indeed we found that even dilute acetic acid caused immediate degradation at room temperature. However, our work with pyranosides had shown that hydrolysis of highly activated glycosides could be effected under neutral conditions.[3a,10] Accordingly, treatment of (**9a**) with refluxing dimethoxyethane-water (3:1)

for 2 h gave an 87% yield of the free glycose (**9b**) Oxidation with Fetizon's reagent[11] then led to a 77% yield of the lactone mixture (**10**) (M^+ calc 262·1203, found 262 1205)

Simplified α-methylene-γ-butyrolactones have been found to exhibit cytotoxicity,[12] and in view of this precedent (**10**) is being submitted for screening

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