Stereocontrol at 'Off-template' Sites in 1,2-*O*-Isopropylidene Glycofuranoses

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Hydrogenation of the double bond at C(5) of diester (**12**) occurs exclusively from the *si-si* face provided that a bulky substituent is present at C(3) in *cis* relationship to the olefinic side chain.

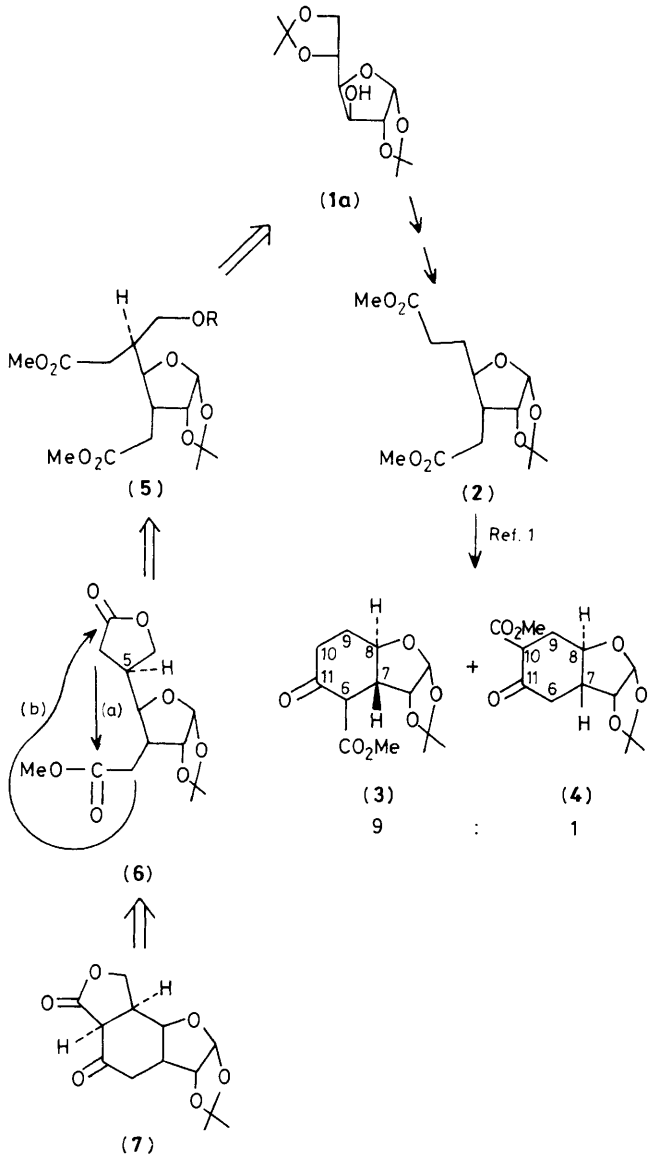
A research programme in our laboratory is concerned with the use of 'diacetone glucose' (**1a**) as a latent α-methylene lactone in the synthesis of sesquiterpene lactones.[1] We reported recently that the Dieckmann cyclization of diester (**2**) gave a 9:1 mixture of the regioisomers (**3**) and (**4**). From the sesquiterpene numbering shown in Scheme 1 it is evident that the minor product (**4**) would be more compatible with most sesquiterpene skeleta since (i) C(10) is activated for elaboration of the A ring and (ii) the methoxycarbonyl group would represent the ubiquitous C(10) angular Me group. The desired regioselectivity would be ensured with the lactonic ester (**6**) since pathway (a) is much preferred to (b) which would involve a tetrahedral intermediate containing an impossible *trans*-fused [3.2.1] bicyclic system. To this regiocontrolling constraint, a tandem stereocontrolling factor could be added if the C(5) stereocentre of (**6**) were of (*S*) configuration, for the *cis*-fused 6–5 system (**7**) would then be favoured overwhelmingly *vis a vis* its *trans*-counterpart. This analysis ultimately requires stereocontrol at C(5) of (**5**) which, being an 'off-template' site, is not readily achieved.[2] We report here on success in using this objective to form (**7**) as well as in the formation of an unrelated system reported in the following communication.[3]

According to the plan in Scheme 1, the C(3) and C(5) centres of 'diacetone glucose' (**1a**) are to be equipped with two-carbon side chains, and it would be easier to deal with C(3) first since (**8**) is a known compound[4] (Scheme 2). However, hydrogenation of (**9**), obtained as the only geometric isomer, gave a *ca.* 3:2 mixture of (**5**) and its 5-epimer.

The alternative sequence was therefore examined beginning with benzoate (**1b**) from which ketone (**10**) was obtained by routine transformations. Wittig reaction in acetonitrile afforded the geometric isomers (**11**) and (**12**) in the ratios of 5:1 (n.m.r. spectroscopic estimation). However, with dimethylsulphoxide (DMSO), (**11**) was obtained exclusively. The configurational assignments were based on the fact that upon desilylation of the mixture, the minor component [(**12**)] formed the butenolide (**13**).

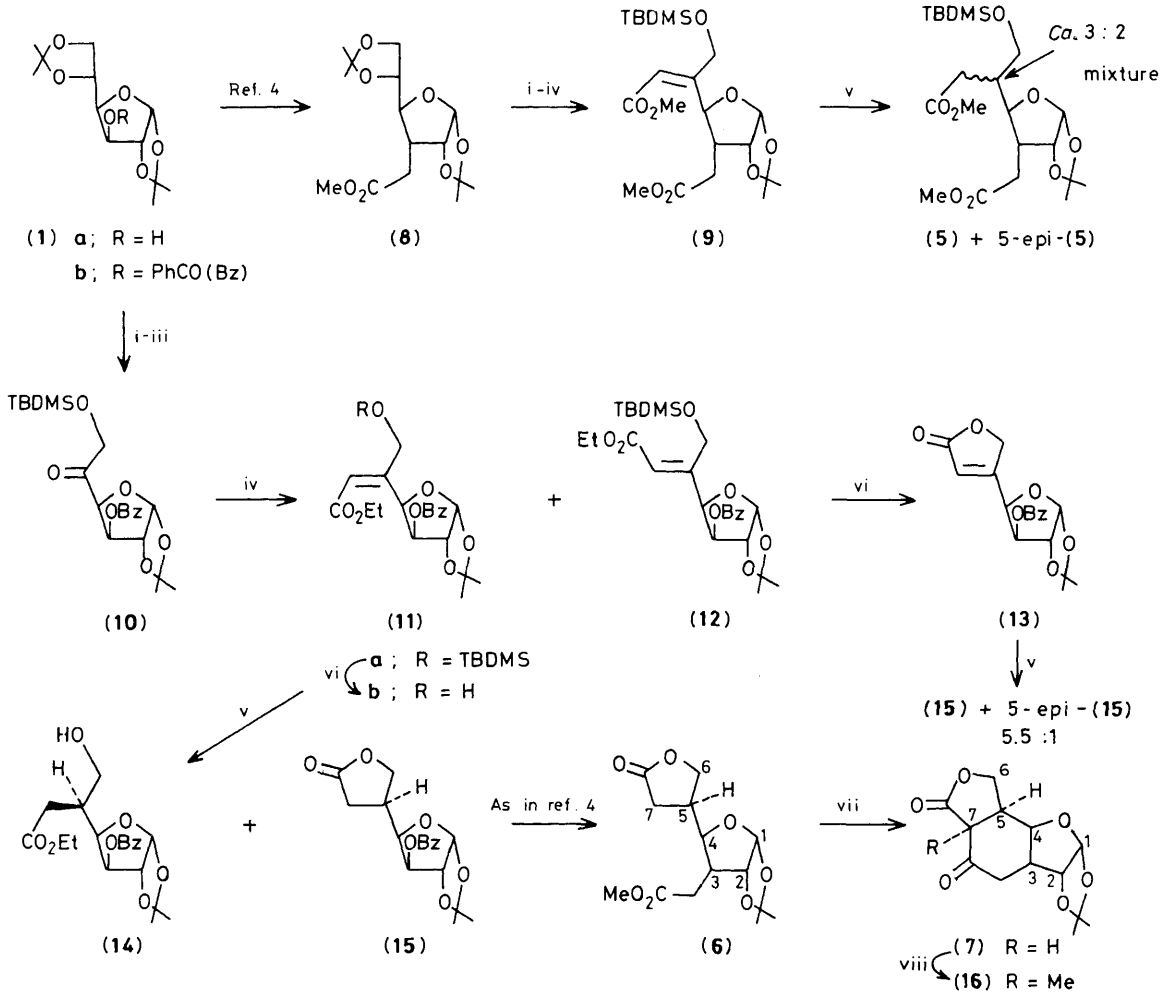
Surprisingly, attempts to hydrogenate the silylated compounds (**11a**) and (**12**), using palladium and platinum at varying pressures of hydrogen, were unsuccessful. However, upon desilylation, hydrogenation of (**11b**) over platinum proceeded smoothly to give a mixture of (**14**) and (**15**). Treatment of this mixture with a catalytic amount of toluene-*p*-sulphonic acid afforded pure (**15**). In contrast, desilylation of (**12**) yielded the butenolide (**13**) directly which, upon hydrogenation, furnished a mixture of (**15**) and its 5-epimer in a ratio of 5.5:1.

The high stereoselectivity in the hydrogenation of (**11**) [in comparison with (**9**) or (**13**)] can be rationalized on the grounds that the rotamer shown in Scheme 2 is distinctly favoured since the methoxycarbonyl group is 'away' from the furan ring. In this conformation, the bulky benzoate ester group shields the *si-si* face of (**11**) thereby forcing hydrogenation to yield the (*S*) configuration at C(5) of (**14**). The results suggest that this conformational bias does not exist in the butenolide (**13**).



Scheme 1

The furano-lactone (**15**) obtained as indicated in Scheme 2 was then processed to give the desired lactonic ester (**6**), cyclization of which afforded keto-lactone (**7**) in 91% yield. The structure of (**7**) was apparent from the ^{1}H n.m.r. parameters for H(7) (δ 3.47, $J_{5,7}$ 6.4 Hz) and H(4) (δ 4.08, $J_{3,4}$ 11.6, $J_{4,5}$ 6.8 Hz). Alkylation of (**7**) proceeded very smoothly at room temperature in 15 min to give (**16**) in which the H(4) ^{1}H n.m.r. parameters were again consistent with the *cis*-ring junction (δ 3.97, $J_{3,4}$ 11.0, $J_{4,5}$ 7.5 Hz).



Scheme 2. i, H_3O^+; ii, Bu^tMe_2SiCl (TBDMSCl); iii, pyridinium dichromate; iv, Ph_3PCHCO_2Et; v, H_2; vi, Bu^n_4NF; vii, Bu^tOK, PhH; viii, Bu^tOK–DMSO–MeI.

The structure of (**16**) was further confirmed by an *X*-ray analysis.

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