A Straightforward Synthesis of L-Lactones from D-Glucose. A Simple Entry into L-Sugars

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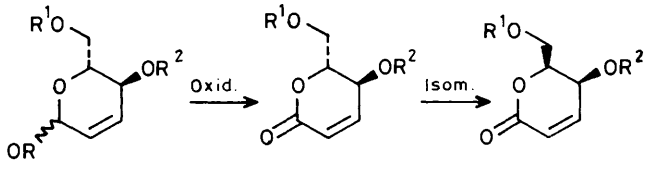
A new synthesis of 2,3-dideoxy-L-*threo*-hex-2-enono-1,5-lactones, starting from D-glucose, is described.

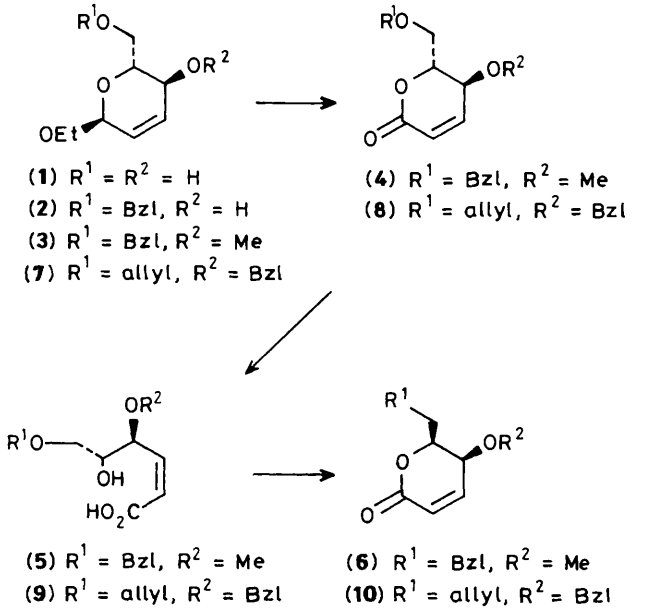
There are numerous natural products containing an α,β-unsaturated δ-lactone structure.[1] Frequently the configuration at C-5 of their lactone ring corresponds with that of a hexopyranoside of the L-series.[1d] The enantiospecific synthesis of L-lactones [*e.g.* (C)] could eventually lead to the syntheses of biologically important[2] L-sugars, and we report a direct, versatile method using D-glucose. We assumed that application of Mitsunobu's procedure[3,4] to the hydroxy-acid derived from a lactone such as (B) would lead to inversion of configuration at C-5 and to the formation of an L-lactone of type (C). The general approach is shown in Scheme 1.

Compounds of type (A) (R = OEt)† were easily prepared using Ferrier's method.[5] Thus, the diol (**1**) (see Scheme 2) was obtained by treatment of tri-*O*-acetyl-D-glucal with $BF_3{\cdot}Et_2O$ in EtOH, and subsequent methanolysis (MeOH, NaOMe cat.).

Benzylation of (**1**) (BzlBr, $Bu^n{}_4NBr$) following selective activation of the primary hydroxy group with dibutyltin oxide,[6] afforded the 6-*O*-benzyl derivative (**2**) (87%). The 4-OH group was methylated (NaH, MeI) (88%) and compound (**3**) was oxidized[7] (*m*-$ClC_6H_4CO_3H$, $BF_3{\cdot}Et_2O$) to the corresponding lactone (**4**) (82%) [δ 5.91 (1H, dd, *J* 10.0 and 1.7 Hz, H-2) and 6.82 (1H, dd, *J* 10.0 and 2.4 Hz, H-3)]. Basic hydrolysis of (**4**), to the corresponding hydroxy-acid (**5**) (1 M LiOH), and epimerization at C-5 under Mitsunobu's conditions[3,4] (Ph_3P, diethyl azodicarboxylate) led to the C-5 epimeric lactone (**6**) in 69% overall yield for the last two steps‡ [δ 6.11 (d, H-2) and 6.97 (dd, H-3)]. The same conditions were successfully applied§ to compound (**7**); compounds (**8**) (78%), (**9**), and (**10**) were obtained (59%, last two steps).¶



Scheme 1



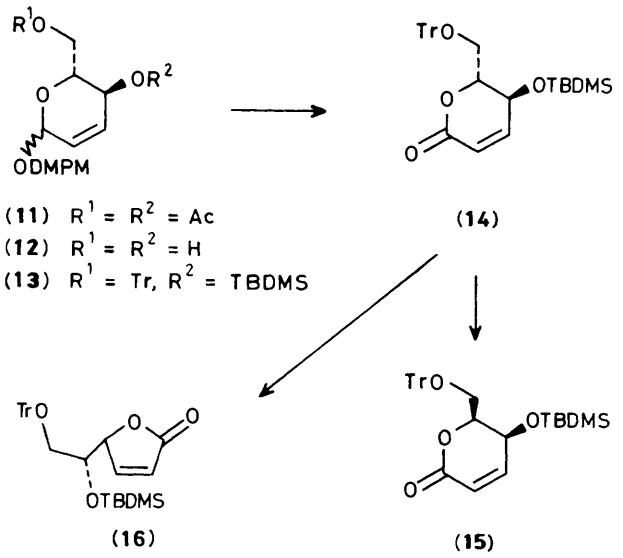
Scheme 2. Bzl = $PhCH_2$·

† Satisfactory analytical and/or spectroscopic data were obtained for all new compounds.

‡ (**6**): $[\alpha]_D^{20}$ +210° (*c* 0.3, $CHCl_3$); ^1H n.m.r. (200 MHz): δ 3.71 (1H, dd, *J* 9.8 and 6.8 Hz, H-6), 3.83 (1H, dd, *J* 9.8 and 6.8 Hz, H-6), 3.86 (1H, dd, *J* 5.4 and 3.2 Hz, H-4), 4.50 (1H, dt, *J* 6.8 and 3.2 Hz, H-5), 6.11 (1H, d, *J* 9.8 Hz, H-2), and 6.97 (1H, dd, *J* 9.8 and 5.4 Hz, H-3).

§ The C-6 *O*-allyl group was selectively introduced using dibutyltin oxide activation, as in the previous case; treatment with NaH and BzlBr gave the 4-*O*-benzyl derivative in 85 and 75% yields, respectively, for the compound corresponding to (**2**) and for (**7**).

¶ (**10**): $[\alpha]_D^{20}$ +70° (*c* 0.3, $CHCl_3$), m.p. 133—135 °C; ^1H n.m.r. (200 MHz): δ 3.33 (1H, dd, *J* 10.0 and 6.1 Hz, H-6), 3.61 (1H, dd, *J* 10.0 and 6.1 Hz, H-6), 5.88 (1H, d, *J* 9.9 Hz, H-2), and 6.78 (1H, dd, *J* 9.9 and 1.7 Hz, H-3).



Scheme 3. Tr = Ph_3C; TBDMS = Bu^tMe_2Si; DMPM = $3,4\text{-}(MeO)_2C_6H_3CH_2$.

Unfortunately, protecting groups such as triphenylmethyl (Tr) and t-butyldimethylsilyl (TBDMS) did not survive[8] this oxidation step.**

We thought that the use of a milder oxidation method would permit the use of these more labile groups, and so compounds of type (A) [R = 3,4-dimethoxyphenylmethanol (DMPM)] could be prepared by heating *O*-triacetyl-D-glucal with the corresponding alcohol at 180 °C, in the absence of catalyst.

Thus compound (**11**) (see Scheme 3) was obtained using 3,4-dimethoxyphenylmethanol (82% yield). Basic hydrolysis (K_2CO_3) gave the corresponding diol (**12**), which was selectively tritylated at C-6 [TrCl, 4-dimethylaminopyridine (DMAP), Et_3N] (81%) and finally silylated at C-4 (TBDMSCl, DMAP, Et_3N) (91%) to afford (**13**).

** Treatment of ethyl 4-*O*-benzyl-6-*O*-trityl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside with $BF_3{\cdot}Et_2O$ and *m*-$ClC_6H_4CO_3H$ led to extensive decomposition.

Lactonization of (**13**) was achieved in two steps. The DMPM-group was removed using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ),[9] and the intermediate hemiacetal was oxidized with pyridinium dichromate (PDC)[10] in the presence of 3 Å molecular sieves to give the lactone (**14**) in 81% overall yield. Treatment of compound (**14**) under the foregoing hydrolysis and Mitsunobu's epimerization conditions gave the two new lactones (**15**) and (**16**) (1.75 : 1). The α,β-unsaturated γ-lactone ring of (**16**) was supported by ^1H n.m.r. and i.r. data.

Therefore, although the use of DMPM acetals such as (**11**) allows lactones such as (**14**) to be prepared under mild conditions, the migration (partial or total) that takes place during the hydrolysis, preceding Mitsunobu's epimerization, precludes the use of the TBDMS group in this procedure.

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