

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

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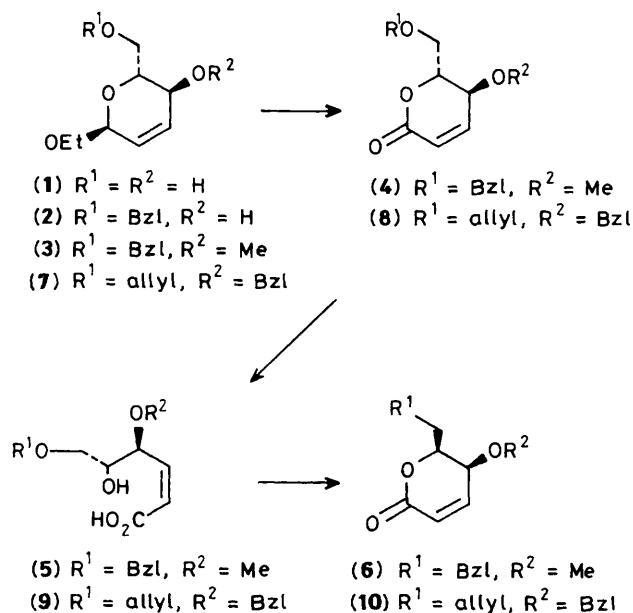
A new synthesis of 2,3-dideoxy-L-threo-hex-2-enono-1,5-lactones, starting from D-glucose, is described.

There are numerous natural products containing an  $\alpha,\beta$ -unsaturated  $\delta$ -lactone structure.<sup>1</sup> Frequently the configuration at C-5 of their lactone ring corresponds with that of a hexopyranoside of the L-series.<sup>1d</sup> The enantiospecific synthesis of L-lactones [e.g. (C)] could eventually lead to the syntheses of biologically important<sup>2</sup> L-sugars, and we report a direct, versatile method using D-glucose. We assumed that application of Mitsunobu's procedure<sup>3,4</sup> 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.

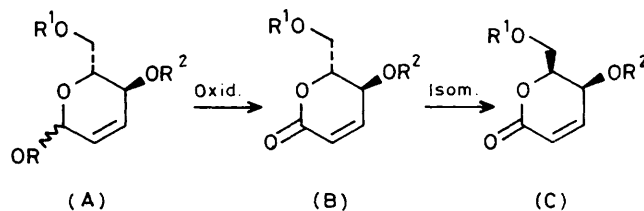
Compounds of type (A) ( $R = OEt$ )<sup>†</sup> were easily prepared using Ferrier's method.<sup>5</sup> Thus, the diol (1) (see Scheme 2) was obtained by treatment of tri-O-acetyl-D-glucal with  $BF_3 \cdot Et_2O$  in EtOH, and subsequent methanolysis (MeOH, NaOMe cat.).

Benzoylation of (1) ( $BzI$ Br,  $Bu^4_4NBr$ ) following selective activation of the primary hydroxy group with dibutyltin oxide,<sup>6</sup> afforded the 6-O-benzyl derivative (2) (87%). The 4-OH group was methylated ( $NaH$ ,  $MeI$ ) (88%) and compound (3) was oxidized<sup>7</sup> ( $m-ClC_6H_4CO_3H$ ,  $BF_3 \cdot Et_2O$ ) to the corresponding lactone (4) (82%) [ $\delta$  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<sup>3,4</sup> ( $Ph_3P$ , diethyl azodicarboxylate) led to the C-5

epimeric lactone (6) in 69% overall yield for the last two steps<sup>‡</sup> [ $\delta$  6.11 (d, H-2) and 6.97 (dd, H-3)]. The same conditions were successfully applied<sup>§</sup> to compound (7); compounds (8) (78%), (9), and (10) were obtained (59%, last two steps).<sup>¶</sup>



Scheme 2.  $Bzl = PhCH_2$ .



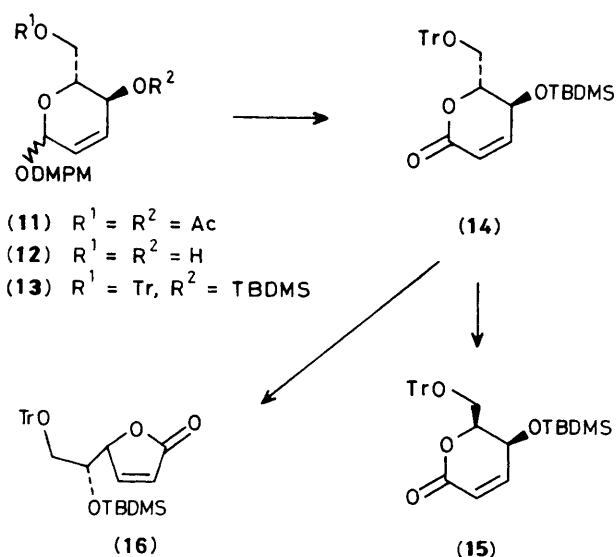
Scheme 1

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

<sup>‡</sup> (6):  $[\alpha]_D^{20} +210^\circ$  (c 0.3,  $CHCl_3$ );  $^1H$  n.m.r. (200 MHz):  $\delta$  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).

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

<sup>¶</sup> (10):  $[\alpha]_D^{20} +70^\circ$  (c 0.3,  $CHCl_3$ ), m.p. 133–135  $^\circ C$ ;  $^1H$  n.m.r. (200 MHz):  $\delta$  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<sub>3</sub>C; TBDMS = Bu<sup>t</sup>Me<sub>2</sub>Si; DMPM = 3,4-(MeO)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>.

Unfortunately, protecting groups such as triphenylmethyl (Tr) and *t*-butyldimethylsilyl (TBDMS) did not survive<sup>8</sup> 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*-triacyl-*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<sub>2</sub>CO<sub>3</sub>) gave the corresponding diol (12), which was selectively tritylated at C-6 [TrCl, 4-dimethylaminopyridine (DMAP), Et<sub>3</sub>N] (81%) and finally silylated at C-4 (TBDMSCl, DMAP, Et<sub>3</sub>N) (91%) to afford (13).

\*\* Treatment of ethyl 4-*O*-benzyl-6-*O*-trityl-2,3-dideoxy-α-*D*-erythro-hex-2-enopyranoside with BF<sub>3</sub>·Et<sub>2</sub>O and *m*-ClC<sub>6</sub>H<sub>4</sub>CO<sub>3</sub>H led to extensive decomposition.

Lactonization of (13) was achieved in two steps. The DMPM-group was removed using 2,3-dichloro-5,6-dicyano-benzoquinone (DDQ),<sup>9</sup> and the intermediate hemiacetal was oxidized with pyridinium dichromate (PDC)<sup>10</sup> 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 <sup>1</sup>H 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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