# Stereoselective Syntheses of 2,4:5,6-Di-*O*-isopropylidene-1-*C*-phenyl-D-*glycero*-D-*ido*-hexitol and 2,4:5,6-Di-*O*-isopropylidene-1-*C*-phenyl-D-*glycero*-D-*gulo*-hexitol from D-*glycero*-D-*gulo*-Heptono-γ-lactone. X-Ray Structure of 1-*O*-Acetyl-2,4:5,6-di-*O*-isopropylidene-1-*C*-phenyl-D-*glycero*-D-*ido*-hexitol

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D-*glycero*-D-*gulo*-Heptonolactone has been converted by three consecutive reactions (acetonation, reduction and glycol cleavage reaction) into 2,4:5,6-di-*O*-isopropylidene-D-glucose which with phenylmagnesium bromide gave preponderantly 2,4:5,6-di-*O*-isopropylidene-1-*C*-phenyl-D-*glycero*-D-*ido*-hexitol **5**. 2,4:5,6-Di-*O*-isopropylidene-1-*C*-phenyl-D-*glycero*-D-*gulo*-hexitol **6** has been obtained from **5** *via* an oxidation–reduction sequence. The structure of **5** has been confirmed by X-ray crystallographic analysis of its 1-*O*-acetyl-derivative **12**.

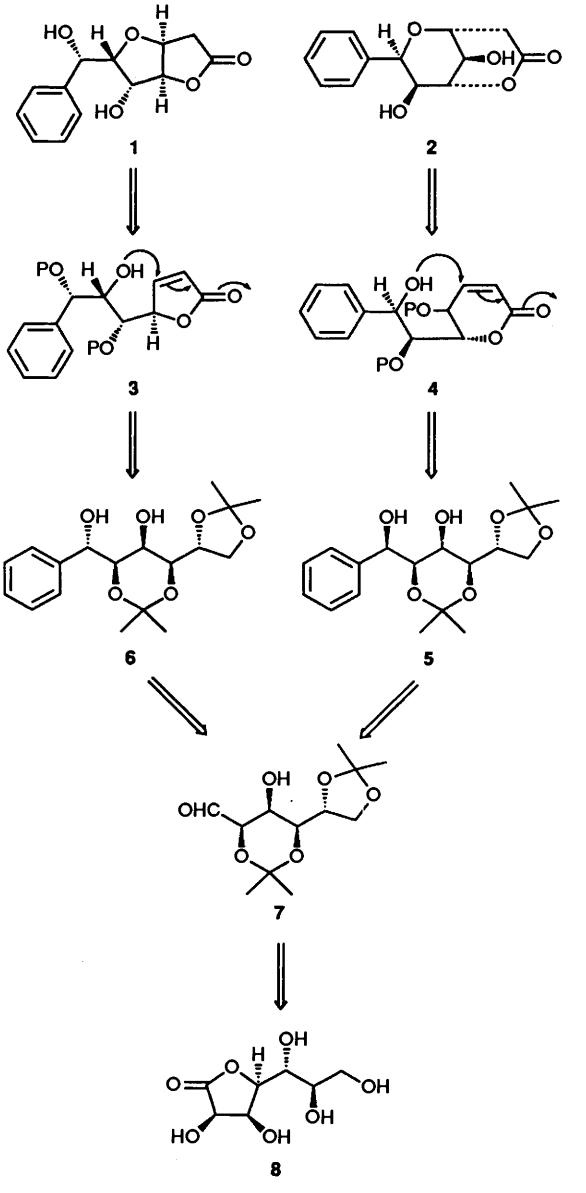
Recently, two novel styryl-lactones, goniofufurone **1** and goniopypyrone **2**, which are cytotoxic to human tumour cells, have been isolated from ethanolic extracts of the stem bark of *Goniothalamus giganteus* Hook. f., Thomas (Annonaceae).[1] The structures and the relative configurations of **1** and **2**, which represent unusual natural skeletons, were confirmed by X-ray crystallographic analysis.[1]

Retrosynthetic analysis of compounds **1** and **2** shows that the *C*-glycosyl lactone part of the molecules can be constructed *via* an intramolecular Michael protocol[2] of **3** and **4** (Scheme 1). Further disconnection of **3** and **4** indicates that they can be derived from the key intermediates **5** and **6** *via* sequential selective hydrolysis, glycol cleavage reaction, and Wittig reaction. The differentially protected compounds **5** and **6**, which are epimeric at the benzylic position, can be obtained from 2,4:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose **7** *via* a steric or chelate-controlled addition of a suitable phenyl carbanion synthon. The aldehyde **7** is then readily accessible from D-*glycero*-D-*gulo*-heptonolactone **8**.

As part of our long-term programme in the syntheses of heavily oxygenated lactones as potential antitumour agents from carbohydrates, we recently reported the enantiospecific synthesis of a related cytotoxic styryl-lactone, (+)-altholactone, from D-gulonolactone.[3] We also described an unambiguous synthesis of the (6*R*,7*S*)-diastereoisomer of the antitumour antibiotic asperlin from D-glucose.[4] The present paper reports, starting from abundant and readily affordable D-*glycero*-D-*gulo*-heptonolactone **8**, the stereoselective syntheses of **5** and **6** which are the key intermediates for the fabrication of goniofufurone **1** and goniopypyrone **2**.

## Results and Discussion

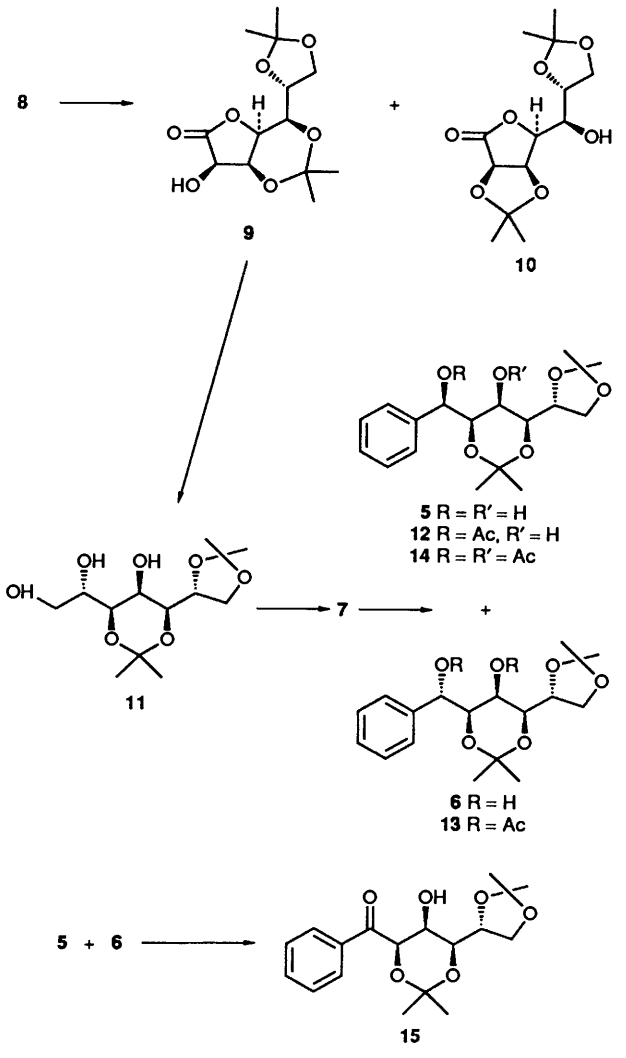
The route to 2,4:5,6-di-*O*-isopropylidene-1-*C*-phenyl-D-*glycero*-D-*ido*-hexitol **5** is shown in Scheme 2. The aforementioned retrosynthetic analysis has already indicated that initially, the *aldehydo*-D-glucose **7** with the 2,4:5,6-blocking pattern is required. Amongst the several routes considered, the one starting from D-*glycero*-D-*gulo*-heptonolactone **8** seems most expedient and convenient. Thus the reaction sequence from **8** to **7** was undertaken and follows that developed by Brimacombe and Tucker[5] with some modification. Isopropylidenation of **8** with acetone in the presence of phosphoric acid and anhydrous zinc chloride at room temperature gave cleanly 3,5:6,7-di-*O*-isopropylidene-D-*glycero*-D-*gulo*-heptonolactone **9** in 66% yield




Scheme 1

**Table 1** Reaction of compound **7** with PhMgBr, PhCuCNMgBr or PhLi

| Entry | Reagent | Temp. (° C) | Solvent | Yield (%) | Ratio **5**:**6** |
|---|---|---|---|---|---|
| 1 | PhMgBr | 70 | THF | 73 | 6.0:1 |
| 2 | PhMgBr | 0 | THF | 74 | 8.0:1 |
| 3 | PhMgBr | 0 | $Et_2O$ | 65 | 3.7:1 |
| 4 | PhCuCNMgBr | 0 | THF | 70 | 6.2:1 |
| 5 | PhLi | 0 | THF | 45 | 2.0:1 |
| 6 | PhLi | −78 | THF | 48 | 2.2:1 |
| 7 | PhLi | 0 | $Et_2O$ | 47 | 3.3:1 |
| 8 | PhLi | −78 | $Et_2O$ | 48 | 5.6:1 |




**Scheme 2**

**Table 2** Atomic co-ordinates ( × $10^4$) for compound **12**

| Atom | *x* | *y* | *z* |
|---|---|---|---|
| O(1) | 5 475(3) | 5 608(2) | 1 598(1) |
| O(2) | 7 635(3) | 7 591(2) | 1 911(1) |
| O(3) | 6 022(3) | 10 197(2) | 1 611(1) |
| O(4) | 9 395(3) | 9 539(2) | 1 785(1) |
| O(5) | 8 478(3) | 11 718(3) | 707(1) |
| O(6) | 11 021(3) | 12 496(3) | 734(1) |
| O(7) | 3 846(4) | 5 729(3) | 2 262(1) |
| C(1) | 5 242(4) | 7 131(3) | 1 478(1) |
| C(2) | 6 918(4) | 7 741(3) | 1 427(1) |
| C(3) | 6 995(4) | 9 346(3) | 1 287(1) |
| C(4) | 8 744(4) | 9 819(3) | 1 299(1) |
| C(5) | 8 990(4) | 11 412(4) | 1 205(1) |
| C(6) | 10 744(5) | 11 923(4) | 1 214(1) |
| C(7) | 4 714(4) | 5 044(4) | 1 992(1) |
| C(8) | 5 085(6) | 3 496(4) | 2 052(2) |
| C(9) | 9 261(4) | 8 052(4) | 1 944(1) |
| C(10) | 10 381(5) | 7 071(5) | 1 656(2) |
| C(11) | 9 651(5) | 8 092(5) | 2 494(1) |
| C(12) | 9 494(4) | 12 811(4) | 520(4) |
| C(13) | 8 899(7) | 14 285(4) | 677(2) |
| C(14) | 9 648(6) | 12 663(5) | −38(1) |
| C(1′) | 4 237(4) | 7 226(3) | 1 008(1) |
| C(2′) | 3 493(4) | 8 536(4) | 888(1) |
| C(3′) | 2 533(5) | 8 628(5) | 464(1) |
| C(4′) | 2 316(5) | 7 447(5) | 157(2) |
| C(5′) | 3 063(6) | 6 164(5) | 271(2) |
| C(6′) | 4 008(5) | 6 051(4) | 693(1) |
| H(3) | 6 413 | 10 161 | 1 939 |

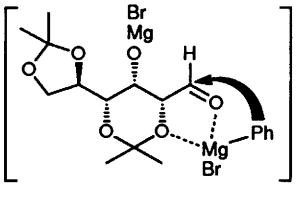



**Fig. 1** Transition state for the addition reaction of PhMgBr to **7** to give **5**

together with a small amount (7%) of the unwanted 2,3:6,7-diacetonide **10**. Sodium borohydride reduction of **9** in methanol from 0 °C to room temperature gave the triol **11** in 98% yield. Glycol cleavage reaction of **11** with sodium metaperiodate in aqueous dioxane at room temperature afforded the aldehyde **7** in essentially quantitative yield. The nucleophilic addition reaction of phenylmagnesium bromide and of phenyllithium with the aldehyde **7** under various conditions was then studied. Examination of the transition state for the addition reaction according to either the open chain or the cyclic (chelate) model[6] indicates that the major product would be **5** in either case. The results given in Table 1 demonstrate that our prediction is correct. The best stereoselectivity was achieved using phenylmagnesium bromide in tetrahydrofuran (THF) at 0 °C (Entry 2). Presumably the reaction proceeded through an α-chelate transition state (5-membered chelate ring) with the nucleophile attacking at the β-face of the carbonyl group as shown in Fig. 1. This rationalisation is consistent with Still's finding that Grignard reagents in THF solutions generally prefer α-chelation.[7] The resulting reaction mixture containing **5** and **6** proved difficult to separate at this stage. Thus acetylation of the mixture (**5** + **6**) with acetic anhydride in dichloromethane containing *N*,*N*′-dimethylaminopyridine (DMAP) furnished, after chromatography, the monoacetate **12** and diacetate **13** in 69 and 8.6% yields respectively.

The stereochemistry of the newly formed alcohol in **5** was confirmed by X-ray structure analysis of **12** (Fig. 2, and Tables 2 and 3) which also indicated the existence of an intermolecular hydrogen bond between 3-OH and the carbonyl oxygen of the acetyl group. As illustrated in Fig. 3, the molecules related by the $2_1$ axis form a hydrogen-bonded zigzag chain in the

direction of the *b* axis and the resulting crystal structure is built of thick layers which match the (100) family of planes.

Deacetylation of the monoacetate **12** with a catalytic amount of sodium methoxide in methanol provided the desired 2,4:5,6-di-*O*-isopropylidene-1-*C*-phenyl-D-*glycero*-D-*ido*-hexitol **5** in a quantitative yield. This diol **5** was characterised as the diacetate **14**.

On the other hand, the preparation of 2,4:5,6-di-*O*-isopropylidene-1-*C*-phenyl-D-*glycero*-D-*gulo*-hexitol **6** is also shown in Scheme 2. Thus selective oxidation of the benzylic alcohol in the Grignard reaction mixture (**5** + **6**) with pyridinium chlorochromate (PCC) in dichloromethane at room temperature gave the corresponding ketone **15** in 61% yield. The reduction of the carbonyl group in **15** with sodium borohydride or diisobutylaluminium hydride (DIBAL-H) was then investigated. As shown by the data in Table 4, $NaBH_4$–$CeCl_3 \cdot 7H_2O$ reduction[8] in MeOH at −78 °C (Entry 4) gives very high stereoselectivity for the diol **6**. The stereochemical outcome of this reduction may be rationalised by considering the chair-like transition state illustrated in Fig. 4 which involves an intramolecular transfer of hydride. The alternate transition state which would lead to **5** is destabilised by the 1,3-diaxial interaction between the OMe and the phenyl group. In the same manner as mentioned previously for the diol **5**, pure compound **6** was obtained by acetylation of the reduction reaction mixture followed by chromatography and deacetylation.

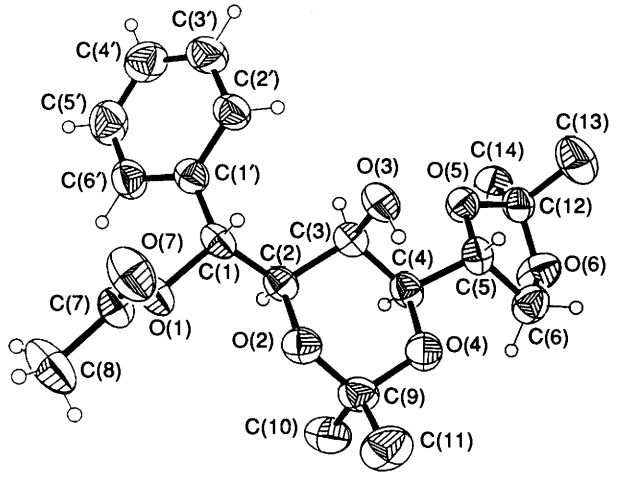



Fig. 2 Perspective view of the molecular structure of **12** with atom labelling. The thermal ellipsoids are drawn at the 50% probability level.

It is noteworthy that the stereochemistry of the reduction of **15** was reversed with DIBAl-H, giving the diol **5** as the major product (Table 4, Entry 1). In this case, the reaction was believed to proceed through a six-membered chelated transition state (Fig. 5) whereby the external hydride approached the carbonyl group from the less hindered β-face.

In summary, we have synthesised stereoselectively, from D-*glycero*-D-*gulo*-heptonolactone **8**, 2,4:5,6-di-*O*-isopropylidene-1-*C*-phenyl-D-*glycero*-D-*ido*-hexitol **5** and 2,4:5,6-di-*O*-isopropylidene-1-*C*-phenyl-D-*glycero*-D-*gulo*-hexitol **6** which are the key intermediates for the syntheses of antitumour agents

**Table 3** Bond lengths (Å), bond angles and torsion angles (°)

| | | | |
|---|---|---|---|
| O(1)–C(1) | 1.455(4) | O(1)–C(7) | 1.337(4) |
| O(2)–C(2) | 1.435(4) | O(2)–C(9) | 1.423(4) |
| O(3)–C(3) | 1.425(4) | O(4)–C(4) | 1.434(4) |
| O(4)–C(9) | 1.442(4) | O(5)–C(5) | 1.428(4) |
| O(5)–C(12) | 1.410(4) | O(6)–C(6) | 1.409(4) |
| O(6)–C(12) | 1.426(4) | O(7)–C(7) | 1.201(4) |
| O(3)–H(3) | 0.937 | | |
| | | | |
| C(1)–C(2) | 1.513(5) | C(1)–C(1') | 1.517(4) |
| C(2)–C(3) | 1.531(4) | C(3)–C(4) | 1.522(5) |
| C(4)–C(5) | 1.506(5) | C(5)–C(6) | 1.537(5) |
| C(7)–C(8) | 1.470(5) | C(9)–C(10) | 1.512(5) |
| C(9)–C(11) | 1.509(5) | C(12)–C(13) | 1.508(5) |
| C(12)–C(14) | 1.507(5) | C(1')–C(2') | 1.397(5) |
| C(1')–C(6') | 1.386(5) | C(2')–C(3') | 1.392(5) |
| C(3')–C(4') | 1.377(6) | C(4')–C(5') | 1.373(6) |
| C(5')–C(6') | 1.382(6) | | |
| | | | |
| O(1)–C(1)–C(2) | 104.9(3) | O(1)–C(1)–C(1') | 108.3(2) |
| O(2)–C(2)–C(1) | 105.5(2) | O(2)–C(2)–C(3) | 107.3(2) |
| O(3)–C(3)–C(2) | 111.1(2) | O(3)–C(3)–C(4) | 112.0(3) |
| O(4)–C(4)–C(3) | 109.3(2) | O(4)–C(4)–C(5) | 106.1(3) |
| O(5)–C(5)–C(4) | 107.9(3) | O(5)–C(5)–C(6) | 103.8(3) |
| O(6)–C(6)–C(5) | 104.9(3) | O(1)–C(7)–O(7) | 123.7(3) |
| O(1)–C(7)–C(8) | 111.3(3) | O(7)–C(7)–C(8) | 125.0(3) |
| O(2)–C(9)–O(4) | 109.9(3) | O(2)–C(9)–C(10) | 112.2(3) |
| O(4)–C(9)–C(10) | 111.8(3) | O(2)–C(9)–C(11) | 105.8(3) |
| O(4)–C(9)–C(11) | 104.4(3) | O(5)–C(12)–O(6) | 104.4(3) |
| O(5)–C(12)–C(13) | 110.5(3) | O(6)–C(12)–C(13) | 111.5(3) |
| O(5)–C(12)–C(14) | 109.8(3) | O(6)–C(12)–C(14) | 107.7(3) |

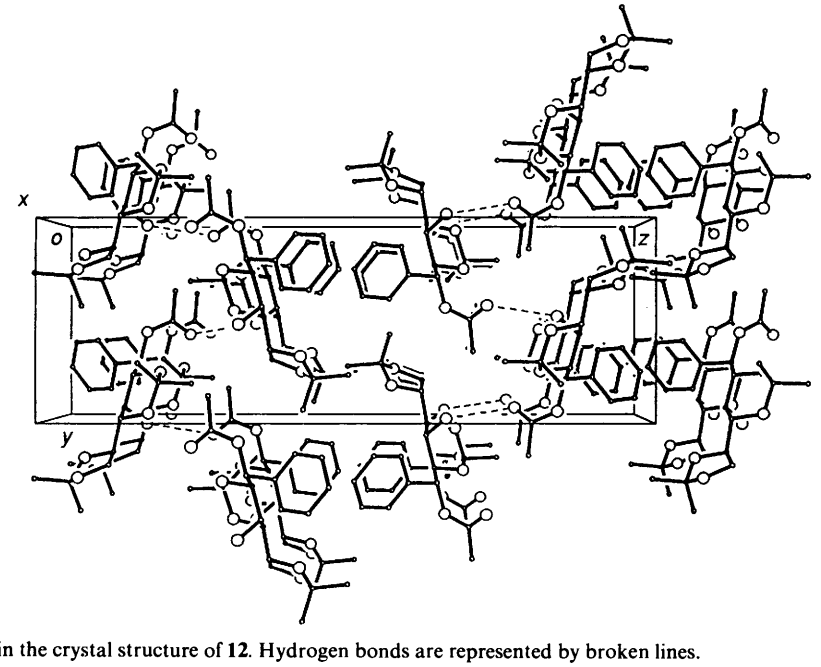



Fig. 3 Molecular packing in the crystal structure of **12**. Hydrogen bonds are represented by broken lines.

**Table 3** *continued*

| | | | |
|---|---|---|---|
| C(1)–O(1)–C(7) | 119.2(3) | C(2)–O(2)–C(9) | 115.1(2) |
| C(4)–O(4)–C(9) | 114.3(2) | C(5)–O(5)–C(12) | 107.0(3) |
| C(6)–O(6)–C(12) | 107.3(3) | C(2)–C(1)–C(1′) | 114.4(3) |
| C(1)–C(2)–C(3) | 115.0(3) | C(2)–C(3)–C(4) | 108.2(3) |
| C(3)–C(4)–C(5) | 114.0(3) | C(4)–C(5)–C(6) | 115.3(3) |
| C(10)–C(9)–C(11) | 112.3(3) | C(13)–C(12)–C(14) | 112.7(3) |
| C(1)–C(1′)–C(2′) | 119.1(3) | C(1)–C(1′)–C(6′) | 122.4(3) |
| C(2′)–C(1′)–C(6′) | 118.5(3) | C(1′)–C(2′)–C(3′) | 119.7(3) |
| C(2′)–C(3′)–C(4′) | 120.9(4) | C(3′)–C(4′)–C(5′) | 119.4(4) |
| C(4′)–C(5′)–C(6′) | 120.3(4) | C(1′)–C(6′)–C(5′) | 121.1(3) |
| Intermolecular hydrogen bonding | | | |
| O(7)···H(3)[a] | 2.215(8) | O(3)–H(3)···O(7)[a] | 149.7(5) |
| Selected torsion angles | | | |
| C(2)–C(1)–O(1)–C(7) | 128.8 | C(2)–C(1)–C(1′)–C(2′) | −80.2 |
| C(1′)–C(1)–C(2)–C(3) | 60.1 | C(1)–C(2)–C(3)–C(4) | 174.8 |
| C(2)–C(3)–C(4)–O(4) | −57.2 | C(3)–C(4)–O(4)–C(9) | 56.4 |
| C(4)–O(4)–C(9)–O(2) | −54.1 | O(4)–C(9)–O(2)–C(2) | 56.4 |
| C(9)–O(2)–C(2)–C(3) | −59.4 | O(2)–C(2)–C(3)–C(4) | 57.7 |
| C(2)–C(3)–C(4)–C(5) | −175.7 | O(3)–C(3)–C(4)–C(5) | −52.9 |
| C(3)–C(4)–C(5)–C(6) | −179.9 | C(4)–C(5)–C(6)–O(6) | 119.6 |
| C(5)–C(6)–O(6)–C(12) | 19.6 | C(6)–O(6)–C(12)–O(5) | −34.2 |
| O(6)–C(12)–O(5)–C(5) | 35.4 | C(12)–O(5)–C(5)–C(6) | −24.8 |

Symmetry transformation: *a* $(1-x, \frac{1}{2}+y, \frac{1}{2}-z)$

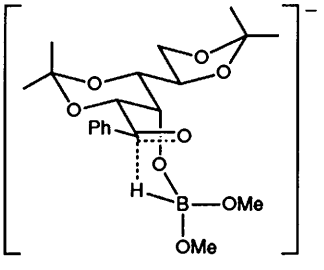



**Fig. 4** Transition state involved in the reduction of ketone **15** by $CeCl_3$–$NaBH_4$ to yield **6**

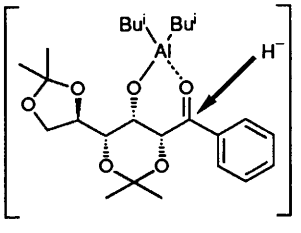



**Fig. 5** Transition state involved in the reduction of ketone **15** by DIBAL-H to give **5**

goniofufurone **1** and goniopypyrone **2**. The research in this direction is in progress.

## Experimental

M.p.s were recorded on a Peichert apparatus and are uncorrected. $^1$H NMR spectra were recorded on a Brucker WM250 spectrometer at 250 MHz using deuteriochloroform as solvent unless otherwise stated and chemical shift positions were in $\delta_H$(ppm) downfield from internal tetramethylsilane, coupling constants ($J$ values) are given in Hz. IR spectra were recorded on a Nicolet 20SXC Fourier Transform spectrometer. Mass spectra were recorded on a VG Micromass 7070F instrument. Optical rotations were measured on a JASCO DIP-300 polarimeter using ethyl acetate as solvent unless otherwise stated; $[\alpha]_D$ values are recorded in $10^{-1}$ deg cm$^2$ g$^{-1}$. Elemental analyses were carried out at Shanghai Institute of Organic Chemistry, Academic Sinica, China. TLC was performed on aluminium percoated with silica gel $60F_{254}$, and compounds were visualised with a spray of 5% w/v dodecamolybdophosphoric acid in ethanol and subsequent heating. Flash chromatography was performed on silica gel (230–400 mesh). THF was distilled from sodium and benzophenone under nitrogen. Pyridine and ether were distilled from calcium hydride.

*Preparation of* 2,4:5,6-*Di*-O-*isopropylidene*-D-*glucose* **7**.—A modification of the literature method[5] for the preparation of 2,4:5,6-di-*O*-isopropylidene-D-glucose **7** was followed.

3,5:6,7-*Di*-O-*isopropylidene*-D-*glycero*-D-gulo-*heptono*-γ-*lactone* **9** *and* 2,3:6,7-*Di*-O-*isopropylidene*-D-glycero-D-gulo-*heptono*-γ-*lactone* **10**.—A suspension of dry D-*glycero*-D-*gulo*-heptonolactone **8** (40 g, 0.19 mol), anhydrous zinc chloride (26 g, 0.19 mol) and phosphoric acid (2.0 g, 88% v/v) in dry acetone (1000 cm$^3$) was stirred at room temperature for 24 h. Inorganic salts were precipitated by the addition of a solution of sodium hydroxide (15 g, 0.19 mol) in water (20 cm$^3$). The resulting suspension was filtered through a bed of Celite. Removal of acetone gave a syrup which was partitioned between water (100 ml) and chloroform (250 cm$^3$). The aqueous layer was further extracted with chloroform (2 × 100 cm$^3$). The combined organic extracts were dried ($MgSO_4$) and filtered. The filtrate was concentrated to approximately 200 cm$^3$ and hexane was added in small portions until precipitation of the *diacetonide* **9**. The white solid was collected and recrystallized from chloroform and hexane (1:5 v/v) to give the *diacetonide* **9** (36 g, 66%) as colourless needles, m.p. 154–155 °C (lit.,[5] m.p. 153–154 °C); $R_f$ 0.30 (ether); $[\alpha]_D$ −84.9 (*c* 1.06) {lit.,[5] $[\alpha]_D$ −76 (*c* 2, chloroform)}; $\nu_{max}$/cm$^{-1}$ 3458 (OH) and 1789 (γ-lactone); $\delta_H$ 1.36 (3 H, s, Me), 1.41 (3 H, s, Me), 144 (3 H, s, Me), 1.50 (3 H, s, Me), 2.95 (1 H, d, *J* 10.0, 2-OH), 3.84 (1 H, dd, *J* 8.5 and 2.0, 5-H), 3.93 (1 H, dd, *J* 8.9 and 4.0, 7-Ha), 4.11 (1 H, dd, *J* 8.9 and 6.2, 7-Hb), 4.32 (1 H, ddd, *J* 8.5, 6.2 and 4.0, 6-H), 4.34 (1 H, dd, *J* 2.2 and 2.0, 4-H), 4.50 (1 H, dd, *J* 10.0 and 4.1, 2-H) and 4.62 (1 H, dd, *J* 4.1 and 2.2, 3-H).

The combined mother liquors were concentrated and recrystallized twice from ethanol and ether to give 2,3:6,7-*diacetonide* **10** (3.4 g, 7.0%) as a white solid, m.p. 170–171 °C (lit.,[5] m.p. 169–170°); $R_f$ 0.66 (ether); $[\alpha]_D$ −72.1 (*c* 1.17) {lit.,[5] $[\alpha]_D$ −70 (*c* 1, chloroform)} $\nu_{max}$/cm$^{-1}$ 3408 (OH) and 1763 (γ-lactone); $\delta_H$ 1.36 (3 H, s, Me), 1.41 (3 H, s, Me), 1.43 (3 H, s, Me), 1.51 (3 H, s, Me), 3.94 (1 H, dd, *J* 3.6 and 3.4, 4-H), 4.06–4.18 (3 H, m, 6-H and 7-H), 4.65 (1 H, dd, *J* 3.4 and 3.4, 5-H), 4.87 (1 H, d, *J* 5.3, 2-H) and 4.97 (1 H, dd, *J* 5.3 and 3.6, 3-H).

1,2:3,5-*Di*-O-*isopropylidene*-D-glycero-L-gulo-*heptitol* **11**.—

**Table 4** Reduction of ketone **15** by DIBAL-H or $NaBH_4$

| Entry | Reagent | Solvent | Temp. (°C) | Yield (%) | **5**:**6** |
|---|---|---|---|---|---|
| 1 | DIBAL-H | THF | −78 | 43 | 7:1 |
| 2 | $NaBH_4$ | MeOH | 0 | 74 | 1:1 |
| 3 | $NaBH_4$–$CeCl_3$·$7H_2O$ | MeOH | 0 | 60 | 1:5 |
| 4 | $NaBH_4$–$CeCl_3$·$7H_2O$ | MeOH | −78 | 70 | 1:19 |

A solution of the diacetonide **9** (10 g, 34 mmol) in methanol (50 $cm^3$) was treated with a solution of sodium borohydride (4.0 g, 0.10 mol) in water (20 $cm^3$) at 0 °C. The temperature was allowed to reach room temperature during 12 h. The solution was then neutralised with a few drops of acetic acid and the solvents were removed under reduced pressure. Chloroform (50 $cm^3$) was added to the residue and the resulting mixture was filtered through a bed of Celite. The filtrate was dried ($MgSO_4$) and filtered. Removal of solvent yielded the *triol* **11** (9.9 g, 98%) as a white solid, m.p. 70–71 °C (lit.,[5] m.p. 67–68 °C); $R_f$ 0.29 (ethyl acetate); $[\alpha]_D$ −10.1 (*c* 0.89) {lit.,[5] $[\alpha]_D$ −6 (*c* 2, water)}; $\nu_{max}/cm^{-1}$ 3407 and 3414 (OH); $\delta_H$ 3.5–4.3 (9 H, m), 1.35 (3 H, s, Me), 1.41 (3 H, s, Me), 1.48 (3 H, s, Me) and 1.50 (3 H, s, Me).

2,4:5,6-*Di*-O-*isopropylidene*-D-*glucose* **7**.—A solution of the triol **11** (5.0 g, 17 mmol) in dioxane (40 $cm^3$) was treated with a solution of sodium metaperiodate (3.8 g, 17 mmol) in water (10 $cm^3$) and then stirred for 3 h at room temperature. The white precipitate was filtered and the filtrate was concentrated under reduced pressure. The residue was then extracted with chloroform (3 × 40 $cm^3$). Concentration of the dried ($MgSO_4$) extracts afforded the *aldehyde* **7** as a white solid (4.5 g, 100%), $R_f$ 0.42 (ethyl acetate). This compound was used in the next step without further purification.

*Stereoselective Synthesis of* 2,4:5,6-*Di*-O-*isopropylidene*-1-C-*phenyl*-D-glycero-D-ido-*hexitol* **5** and 2,4:5,6-*Di*-O-*isopropylidene*-1-C-*phenyl*-D-glycero-D-gulo-*hexitol* **6**.—*Method A*. In a typical reaction, a solution of the aldehyde **7** (5.0 g. 19 mmol) in dry THF (50 $cm^3$) was stirred at 0 °C under nitrogen while a solution of 1.7 mol $dm^{-3}$ phenylmagnesium bromide (50 $cm^3$, 86 mmol) freshly prepared from bromobenzene and magnesium in THF was added dropwise during 1 h. The mixture was then boiled for a further 2 h and quenched with cold, saturated aqueous ammonium chloride (20 $cm^3$). The mixture was filtered through Celite and the filtrate concentrated. The residue was then extracted with chloroform (3 × 30 $cm^3$) and the combined extracts were dried ($MgSO_4$) and filtered. Solvent removal gave a mixture of the diastereoisomers **5** and **6** as a yellow syrup. Fractionation of the syrup by flash chromatography [ethyl acetate–hexane (1:1, v/v)] yielded the mixture (**5**:**6**, *ca.* 8:1) as a white solid (4.8 g, 74%); $R_f$ 0.12 for **5** and $R_f$ 0.10 for **6** [chloroform–ethanol (98:2, v/v)]. Pure **5** or **6** was obtained by the hydrolysis of 1-O-acetyl-2,4:5,6-di-O-isopropylidene-1-C-phenyl-D-*glycero*-D-*ido*-hexitol **12** or 1,3-di-O-acetyl-2,4:5,6-di-O-isopropylidene-1-C-phenyl-D-*glycero*-D-*gulo*-hexitol **13** respectively as shown below.

Likewise, the Grignard reaction was performed in dry ether and the ratio of the mixture (4.2 g, 65%) was 3.7:1 (**5**:**6**).

*Method B*. A solution of 1.0 mol $dm^{-3}$ organocopper(I) Grignard reagent (PhCuCNMgBr) (9.0 $cm^3$, 9.0 mmol) freshly prepared from phenylmagnesium bromide (1.0 mol $dm^{-3}$, 9.0 $cm^3$) and copper(I) cyanide (0.80 g, 9.0 mmol) in THF was added to a solution of the aldehyde **7** (0.78 g, 3.0 mmol) at 0 °C. The reaction mixture was heated at 40 °C for a further 2 h and quenched with cold, saturated ammonium chloride (5 $cm^3$). The mixture was extracted and separated as described in Method A. A mixture of diastereoisomers (**5**:**6**, *ca.* 6.2:1) was obtained as a white solid (0.71 g, 70%).

*Method C*. A solution of phenyllithium (7.2 mmol, 10 $cm^3$) freshly prepared from phenyl bromide and lithium metal in THF was added to a solution of the aldehyde **7** (0.62 g, 2.4 mmol) at 0 °C. The mixture was stirred at 0 °C for a further 4 h and quenched with cold, saturated aqueous ammonium chloride (5 $cm^3$). The mixture was extracted and separated as described in Method A. A mixture of diastereoisomers (**5**:**6**, *ca.* 2.0:1) was obtained as a white solid (0.41 g, 45%). The same reaction was proceeded in dry ether and the ratio of the mixture (0.43 g, 47%) was 3.3:1 (**5**:**6**).

*Method D*. A solution of phenyllithium (7.2 mmol, 10 $cm^3$) freshly prepared in THF was added dropwise to a solution of the aldehyde **7** cooled in a solid $CO_2$ bath (−78 °C). The reaction mixture was stirred for a further 8 h and warmed to room temperature. The mixture was quenched with cold, saturated aqueous ammonium chloride (5 $cm^3$) and separated as described in Method A. A mixture of diastereoisomers (**5**:**6**, *ca.* 2.2:1) was obtained as a white solid (0.44 g, 48%). Likewise, the same reaction proceeded in dry ether and the ratio of diastereoisomers (0.44 g, 48%) was 5.6:1 (**5**:**6**). In all the above experiments, the ratios were determined by $^1H$ NMR spectral analyses.

*Acetylation of the Mixture of* 2,4:5,6-*Di*-O-*isopropylidene*-1-C-*phenyl*-D-glycero-D-ido-*hexitol* **5** *and* 2,4:5,6-*Di*-O-*isopropylidene*-1-C-*phenyl*-D-glycero-D-gulo-*hexitol* **6**.—*Method A*. A solution containing a catalytic amount of DMAP in dry pyridine (4.0 $cm^3$) was added to the mixture **5** (4.0 g, 12 mmol) in dry dichloromethane (10 $cm^3$). The reaction was cooled to 0 °C and acetic anhydride (5.0 $cm^3$, 45 mmol) added. The reaction mixture was allowed to warm to room temp. for 12 h and quenched with saturated aqueous sodium hydrogen carbonate (5.0 $cm^3$). The mixture was extracted with dichloromethane (3 × 20 $cm^3$), dried ($MgSO_4$) and filtered. Concentration of the filtrate under reduced pressure followed by flash chromatography [ethyl acetate–hexane (1:4 v/v)] afforded two pure compounds, the more polar compound, 1-O-acetyl-2,4:5,6-di-O-isopropylidene-1-C-phenyl-D-*glycero*-D-*ido*-hexitol **12**, was a white solid (3.1 g, 69%), m.p. 136–137 °C; $R_f$ 0.26 [ethyl acetate–hexane (1:4 v/v)]; $[\alpha]_D$ −27.7 (*c* 0.94); $\nu_{max}/cm^{-1}$ 3479 (OH) and 1740 (ester C=O); *m/z* (EI) 365 (2.6%, $M^+$ − Me); $\delta_H$ 1.28 (3 H, s, Me), 1.44 (3 H, s, Me), 1.46 (3 H, s, Me), 1.62 (3 H, s, Me). 2.06 (3 H, s, Ac), 2.42 (1 H, d, *J* 12.0, 3-OH), 3.09 (1 H, ddd, *J* 1.0, 1.1, 12.0, 3-H), 3.54 (1 H, dd, *J* 1.1, 8.2, 4-H), 3.79 (1 H, dd, *J* 5.1, 8.5, 6-$H_b$), 4.01 (1 H, dd, *J* 1.0, 9.0, 2-H), 4.03 (1 H, dd, *J* 6.3, 8.5, 6-$H_a$), 6.01 (1 H, d, *J* 9.0, 1-H) and 7.34–7.45 (5 H, m, Ph) (Found: C, 62.7; H, 7.3. $C_{20}H_{28}O_7$ requires C, 63.1; H, 7.4%).

The less polar compound, 1,3-di-O-acetyl-2,4:5,6-di-O-isopropylidene-1-C-phenyl-D-*glycero*-D-*gulo*-hexitol **13**, was also a white solid (0.39 g, 8.6%), m.p. 88–89 °C; $R_f$ 0.32 [ethyl acetate–hexane (1:4 v/v)]; $[\alpha]_D$ −8.0 (*c* 0.85); $\nu_{max}/cm^{-1}$ 1747 (ester C=O); *m/z* (EI) 407 (10.6%, $M^+$ − Me); $\delta_H$ 1.28 (3 H, s, Me), 1.32 (3 H, s, Me), 1.44 (3 H, s, Me), 1.59 (3 H, s, Me), 2.04 (3 H, s, Ac), 2.15 (3 H, s, Ac), 3.87–4.02 (4 H, m), 4.26 (1 H, dd, *J* 1.2, 9.5, 2-H), 5.32 (1 H, dd, *J* 0.5, 1.2, 3-H), 5.63 (1 H, d, *J* 9.5, 1-H) and 7.28–7.36 (5 H, m, Ph) (Found: C, 62.2; H, 7.2. $C_{22}H_{30}O_8$ requires C, 62.5; H, 7.2%).

*Method B*. A solution of the diol **5** (1.0 g, 3.0 mmol) in dry dichloromethane (5.0 $cm^3$) was added dropwise to a solution of pyridine (5.0 $cm^3$) and acetyl chloride (2.0 $cm^3$) in dichloromethane cooled in an ice–water bath. The reaction was allowed to warm to room temperature for 12 h and then quenched with saturated aqueous sodium hydrogen carbonate (3.0 $cm^3$). The mixture was extracted with dichloromethane (3 × 10 $cm^3$), dried ($MgSO_4$) and filtered. Concentration of the filtrate was followed by flash chromatography [ethyl acetate–hexane (1:4 v/v)] yielded 1,3-di-O-acetyl-2,4:5,6-di-O-isopropylidene-1-C-phenyl-D-*glycero*-D-*ido*-hexitol **14** (0.65 g, 58%) as a white solid, m.p. 117–118 °C; $R_f$ 0.28 [ethyl acetate–hexane (1:4 v/v)]; $[\alpha]_D$ −43.5 (*c* 1.0); $\nu_{max}/cm^{-1}$ 1743 (ester C=O); $\delta_H$ 1.24 (3 H, s, Me), 1.33 (3 H, s, Me), 1.48 (3 H, s, Me), 1.49 (3 H, s, Me), 2.03 (3 H, s, Ac), 2.10 (3 H, s, Ac), 3.83–3.87 (4 H, m), 4.28 (1 H, dd, *J* 1.4, 8.1, 2-H), 4.58 (1 H, dd, *J* 0.5, 1.2, 3-H), 5.78 (1 H, d, *J* 8.1, 1-H) and 7.28–7.35 (5 H, m, Ph); *m/z* (EI) 407 (15.2%, $M^+$ − Me) (Found: C, 62.2; H, 7.1. $C_{22}H_{30}O_8$ requires C, 62.5; H, 7.2%).

2,4:5,6-*Di*-O-*isopropylidene*-1-C-*phenyl*-D-glycero-D-ido-*hexitol* **5**.—A solution of compound **12** (1.0 g, 2.6 mmol) in methanol (10 $cm^3$) was hydrolysed with a catalytic amount of sodium methoxide at room temperature for 1 h. The mixture was passed through a pad of silica gel. Evaporation of the filtrate yielded the *hexitol* **5** (0.89 g, 100%) as a white solid, m.p. 82–83 °C; $R_f$ 0.12 [chloroform–ethanol (98:2 v/v)]; $[\alpha]_D$ −5.3 (*c* 1.2); $\nu_{max}/cm^{-1}$ 3471 (OH); $\delta_H$ 1.29 (6 H, s, 2 × Me), 1.48 (3 H, s, Me), 1.49 (3 H, s, Me), 2.41 (1 H, d, *J* 11.3, 3-OH), 2.93 (1 H, s, 1-OH), 3.27 (1 H, ddd, *J* 1.1, 1.2, 11.3, 3-H), 3.53 (1 H, dd, *J* 1.2, 8.5, 4-H), 3.76 (1 H, dd, *J* 1.1, 8.2, 2-H), 3.79 (1 H, dd, *J* 8.6, 5.2, 6-$H_b$), 4.05 (1 H, dd, *J* 6.4, 8.5, 6-$H_a$), 4.18 (1 H, ddd, *J* 5.2, 6.2, 8.1, 5-H), 4.92 (1 H, d, *J* 8.3, 1-H) and 7.32–7.51 (5 H, m, Ph); *m/z* (EI) 323 (3.6%, $M^+$ − Me) (Found, C, 63.9; H, 7.9. $C_{18}H_{26}O_6$ requires C, 63.9; H, 7.7%).

2,4:5,6-*Di*-O-*isopropylidene*-1-C-*phenyl*-D-glycero-D-gulo-*hexitol* **6**.—A solution of compound **13** (0.50 g, 1.2 mmol) in methanol (5.0 $cm^3$) was hydrolysed with a catalytic amount of sodium methoxide at room temperature for 1 h. The mixture was passed through a pad of silica gel. Concentration of the filtrate yielded the *hexitol* **6** (0.40 g, 100%) as a white solid, m.p. 149–150 °C; $R_f$ 0.10 [chloroform–ethanol (98:2 v/v)]; $[\alpha]_D$ +10.2° (*c* 1.1); $\nu_{max}/cm^{-1}$ 3468 (OH); $\delta_H$ 1.30 (3 H, s, Me), 1.35 (3 H, s, Me), 1.37 (3 H, s, Me), 1.40 (3 H, s, Me), 3.05 (1 H, d, *J* 7.8, 3-OH), 3.22 (1 H, d, *J* 5.5, 1-OH), 3.60 (1 H, dd, *J* 1.3, 8.1, 4-H), 3.85 (1 H, dd, *J* 0.9, 4.9, 2-H), 3.87 (1 H, ddd, *J* 0.9, 1.3, 7.8, 3-H), 3.88 (1 H, dd, *J* 4.8, 8.5, 6-$H_b$), 4.10 (1 H, dd, *J* 6.4, 8.6, 6-$H_a$), 4.26 (1 H, ddd, *J* 4.8, 6.2, 8.1, 5-H), 4.90 (1 H, dd, *J* 5.6, 5.0, 1-H) and 7.30–7.43 (5 H, m, Ph); *m/z* (EI) 323 (3.3%, $M^+$ − Me) (Found: C, 63.6; H, 7.7. $C_{18}H_{26}O_6$ requires C, 63.9; H, 7.7%).

2,4:5,6-*Di*-O-*isopropylidene*-1-C-*phenyl*-D-gluco-*hex*-1-*ulose* **15**.—Pyridinium chlorochromate (0.64 g, 2.96 mmol) was added in one portion to a stirred solution of the mixture (**5** + **6**) (0.50 g, 1.48 mmol) in dry dichloromethane (20 $cm^3$) containing powdered 4 Å molecular sieve (0.5 g) at room temperature. After the mixture had been stirred at room temperature for 3 h, Celite (1.0 g) and diethyl ether (100 $cm^3$) were added and the whole stirred at room temperature for a further 15 min; it was then filtered through a bed of silica gel topped with Celite. Evaporation of the filtrate under reduced pressure gave crude **15** as a yellow solid. Further purification by flash chromatography [ethyl acetate–hexane (1:2 v/v)] afforded the *ketone* **15** as a white solid. Recrystallization of the solid from diethyl ether–hexane afforded the *title compound* **15** (0.30 g, 61%) as colourless needles, m.p. 201–202 °C; $R_f$ 0.38 [ethyl acetate–hexane (1:2 v/v)]; $[\alpha]_D$ +9.6° (*c* 0.73); $\nu_{max}/cm^{-1}$ 3450 (OH) and 1655 (conjugated C=O); *m/z* (EI) 231 (7.52%, $M^+ - C_6H_5C{=}O$) and 105 (100%, $C_6H_5C{=}O^+$); $\delta_H$ 1.30–1.60 (12 H, 4s, 4 × $CH_3$), 2.73 (1 H, d, *J* 9.2, 3-OH), 3.84 (1 H, dd, *J* 1.2, 8.1, 4-H), 3.91 (1 H, dd, *J* 4.7, 8.7, 6-H), 4.07 (1 H, ddd, *J* 1.2, 1.3, 9.2, 3-H), 4.09 (1 H, dd, *J* 6.2, 8.7, 6-H), 4.29 (1 H, ddd, *J* 4.7, 6.2, 8.1, 5-H), 5.22 (1 H, d, *J* 1.3, 2-H) and 7.40–8.00 (5 H, m, Ph); (Found: C, 63.9; H, 7.0. $C_{18}H_{24}O_6$ requires C, 64.3; H, 7.1).

*Stereoselective Reduction of the Ketone* **15**.—*Method A*. In a typical reaction, cerium trichloride heptahydrate (2.8 g, 7.6 mmol) was added to a stirred solution of the ketone **15** (1.3 g, 3.8 mmol) in methanol (200 $cm^3$) at room temperature. The solution was cooled in a solid $CO_2$–acetone bath and then sodium borohydride (0.15 g, 3.8 mmol) was added to it. After 15 min, the mixture was quenched with a few drops of acetic acid and its temperature allowed to rise gradually to room temperature. The methanol was removed under reduced pressure and the residue extracted with chloroform (100 $cm^3$). The extract was dried ($MgSO_4$), filtered and evaporated to give a mixture of diastereoisomers (**5**:**6**, *ca.* 1:19) as a white solid (0.90 g, 70%). The ratio of diastereoisomers was determined by $^1H$ NMR spectral analysis.

*Method B*. Sodium borohydride (8 mg, 0.21 mmol) was added to a stirred solution of the ketone **15** (70 mg, 0.21 mmol) in methanol (10 $cm^3$) at 0 °C, and after 15 min a few drops of acetic acid were added to quench the reaction. The methanol was removed under reduced pressure and the residue extracted with chloroform (20 $cm^3$). The extract was dried ($MgSO_4$) and filtered and the filtrate was concentrated to give a mixture of diastereoisomers (**5**:**6** *ca.* 1:1) as a white solid (52 mg, 74%). The ratio was estimated by TLC.

*Method C*. Cerium trichloride heptahydrate (11 mg, 0.030 mmol) was added to a stirred solution of the ketone **15** (5 mg, 0.015 mmol) in methanol (10 $cm^3$) at room temperature. The mixture was cooled to 0 °C and sodium borohydride (0.6 mg, 0.016 mmol) was added to it. After the mixture had been stirred for 15 min, the reaction was quenched with a few drops of acetic acid; the temperature of the mixture was then allowed to rise gradually to room temperature. The methanol was removed and the residue was extracted with chloroform (20 $cm^3$). The resulting mixture was dried ($MgSO_4$) and filtered, and the filtrate evaporated to give a mixture of diastereoisomers (**5**:**6**, *ca.* 1:5) as a white solid (3 mg, 60%). The ratio of diastereoisomers was estimated by TLC.

*Method D*. DIBAL-H in toluene (1.0 dm $mol^{-1}$; 0.12 $cm^3$, 0.12 mmol) was added to a solution of the ketone **15** (10 mg, 0.03 mmol) in THF (10 $cm^3$) at −78 °C. After the mixture had been stirred for 15 min, a few drops of acetic acid were added to it to quench the reaction. The temperature of the mixture was then allowed to rise to room temperature when the solvent was removed under reduced pressure. The residue was extracted with chloroform (20 $cm^3$) and the extract dried ($MgSO_4$) and filtered. Evaporation of the filtrate gave a mixture of diastereoisomers (**5**:**6**, *ca.* 7:1) as a white solid (4.3 mg, 43%). The ratio of diastereoisomers was also estimated by TLC.

*X-Ray Crystallographic Analysis of* 1-O-*Acetyl*-2,4:5,6-*di*-O-*isopropylidene*-1-C-*phenyl*-D-glycero-D-ido-*hexitol* **12**.—Crystals of good quality were obtained as transparent plates by recrystallization from ether–hexane. The density of the crystals was determined by flotation in $CCl_4$–hexane.

*Crystal data*. $C_{20}H_{28}O_7$, $M$ = 380.48, colourless plates, orthorhombic, space group $P2_12_12_1$ (No. 19); $a$ = 8.337 (2), $b$ = 9.232 (2), $c$ = 26.793 (4) Å, $Z$ = 4, $D_c$ = 1.23 g $cm^{-3}$, $D_m$ = 1.15 g $cm^{-3}$, $F$ (000) = 816, Mo-K$\alpha$ radiation ($\lambda$ = 0.710 73 Å), $\mu$(Mo-K$\alpha$) = 12.89 $cm^{-1}$.

X-Ray data collection, structure solution and refinement. Intensities (2707 unique reflections; $2\theta_{max.}$ = 55°) collected on a Nicolet R3m/V diffractometer were processed with the profile-fitting procedure of Diamond[9] and corrected for absorption using $\varphi$-scan data.[10] A total of 1976 reflections with $I > 3\sigma(I)$ were considered to be observed and used in the structure analysis. The structure was solved by direct phase determination and refined with anisotropic temperature factors for all non-hydrogen atoms. The hydrogen atom of the hydroxy group was located from a difference map, and the other hydrogen atoms in the molecule were generated geometrically (C–H bond fixed at 0.96 Å). All hydrogen atoms were assigned the same isotropic temperature factor of $U$ = 0.08 $Å^2$. Final $R$ and $R_w$ are 0.043 and 0.058, respectively, with $w = [\sigma^2|F_o| + 0.0002|F^2]^{-1}$. Computations were performed using the SHELTXL-PLUS program package[11] on a DEC Micro VAX-II computer. Analytical expressions of neutral-atom scattering factors were used, and anomalous dispersion corrections were incorporated.[12] The final positional parameters and equivalent isotropic thermal parameters are listed in Table 2. Selected bond lengths and angles involving non-hydrogen atoms are presented in Table 3

while torsion angles involving skeletal atoms of the two isopropylidene rings are also given.*

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* *Supplementary data available:* (see Instructions for Authors, section 5.6.3, in the January issue). Tables of data collection and processing parameters, thermal parameters and H-atom co-ordinates have been deposited at the Cambrige Crystallographic Data Centre.

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