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CARBOHYDRATE RESEARCH

Stereoselective synthesis of tetrahydrofurans and linear methyl enol-ethers from glycals [1]

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Abstract

The *O*-benzyl derivatives of 1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (D-glucal, **1**), 1,5-anhydro-2,6-dideoxy-L-*arabino*-hex-1-enitol (L-rhamnal, **7**), and 1,5-anhydro-2-deoxy-D-*lyxo*-hex-1-enitol (D-galactal, **9**), underwent stereoselectively a ring contraction by treatment with thallium(III) nitrate (TTN) in MeOH, giving respectively the dimethylacetal derivatives of 3,4,6-tri-*O*-benzyl-2,5-anhydro-D-mannose, 3,4-di-*O*-benzyl-6-deoxy-2,5-anhydro-L-mannose (**8**) and 3,4,6-tri-*O*-benzyl-2,5-anhydro-D-talose (**10**). Conversely, the protected glycals **1**, **7** and **9**, underwent the ring opening reaction by action of the TTN–$NaBH_4$ reagent in MeOH, providing the enantiomerically pure methyl enol-ethers 3,4,6-tri-*O*-benzyl-2-deoxy-1-*O*-methyl-D-*arabino*-hex-1-enitol, 3,4-di-*O*-benzyl-2,6-dideoxy-1-*O*-methyl-L-*arabino*-hex-1-enitol and 3,4,6-tri-*O*-benzyl-2-deoxy-1-*O*-methyl-D-*lyxo*-hex-1-enitol. The perbenzylated glycosyl-glycals, such as 3,6-di-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-*β*-D-glucopyranosyl)-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (cellobial) (**16**), 3,6-di-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-*β*-D-galactopyranosyl)-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (lactal) (**19**) and 3,4-di-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-*α*-D-galactopyranosyl)-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (melibial) (**22**), showed the same reactivity as the corresponding glycals by reaction with TTN in MeOH, resulting selectively in the ring contracted compounds at the glycal moiety. The reaction with TTN–$NaBH_4$ in MeOH, carried out on **16**, **19** and **22**, led to the formation of the open chain derivatives at the glycal site.

Keywords: Synthesis, tetrahydrofurans; Synthesis, linear methyl enol-ethers; Glycals; Glycosyl-glycals; Thallium(III) nitrate; 2,5-Anhydro sugars

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1. Introduction

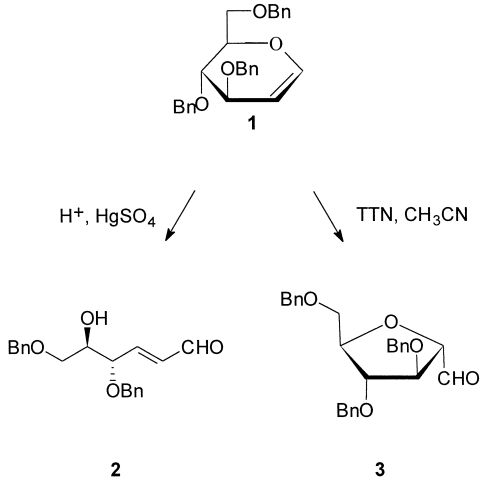
Electrophilic assistance to direct regio- and stereoselective transformations of carbohydrate derivatives into enantiomerically pure tetrahydrofurans is of synthetic value [1].

Ion-assisted transformations have been only occasionally described in the carbohydrate field, utilizing particularly mercury(II) sulfate in sulfuric acid [2] and thallium(III) nitrate, trihydrate [TTN, $Tl(NO_3)_3 \cdot 3\ H_2O$] [3]. Mercuric-ion-assisted acid hydrolysis of 1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (D-glucal) (**1**) resulted in the ring opening, providing the hydroxy-*trans*-enal **2** [2], losing one chiral centre. However treatment of **1** with TTN in acetonitrile gave a ring contracted product [3], the 2,5-anhydro-D-mannose derivative **3** (Scheme 1). The lack of a systematic study in this field prompted us to investigate this reaction with other glycals and disaccharide-derived glycals.

In this paper, we now report a general method that can lead either to the ring contraction or to the ring opening compounds with complete stereoselectivity.

2. Results and discussion

The perbenzylated glycals **1**, **7** and **9** [4] gave the highly substituted, enantiomerically pure tetrahydrofuran dimethylacetals **4**, **8** and **10** (Scheme 2) in high yields (90%) when treated with TTN in methanol at 35 °C for 8 h. According to the reaction mechanism of TTN, the stereochemical outcome observed during the ring contraction can be explained by a combination of stereoelectronic effects derived from the *cis* relationship between groups at C-3 and C-5 in the protected glycals, such as **1**, **7** and **9**; this steric hindrance could lead to a high stereoselectivity of the electrophilic attack of TTN at C-2, which occurs from the opposite side to the *cis* groups (Scheme 4).



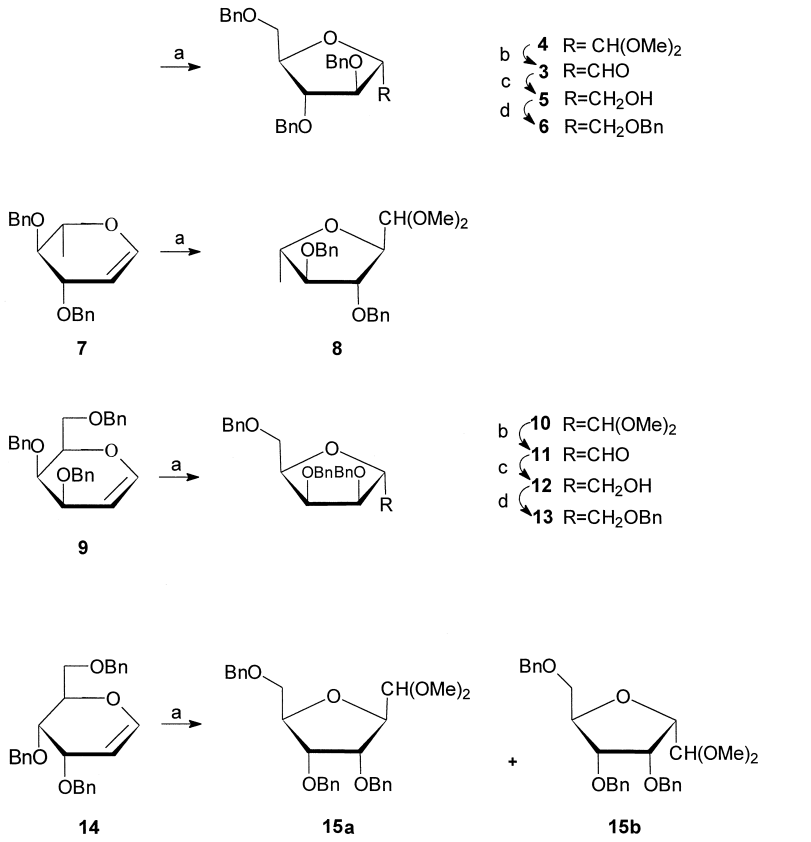
Scheme 1.

When the C-3 and C-5 substituents do not have the same relative orientation, the ring contraction did not prove to be a fully stereocontrolled process. The competing effect, which those groups could play during the rearrangement, was witnessed by an experiment that was carried out using the perbenzylated allal derivative (**14**) (Scheme 2). The treatment with TTN under the usual procedure led to the formation of two ring contracted products, epimers at C-1, almost in the same ratio. Their chemical shift values in ^{13}C NMR are in complete agreement with the structures proposed for **15a** and **15b**. The collected experimental data clearly show that the attack of TTN occurs from both sides at C-2 of **14** and that the C-3 and the C-5 substituents of the protected glycal **14** exert a competing, but not dominating effect on the stereochemical outcome of the molecular rearrangement.

Compounds **4** and **10** show a *trans* relationship between C-1 and C-2, C-1 and C-4 substituents, [4] (Scheme 2). Moreover, the dimethyl acetal derivative **4** was converted into the known perbenzylated 2,5-anhydro-D-mannitol (**6**) [3,7] by acid hydrolysis (**3**), reduction with sodium carohydride (**5**), and benzylation. The structure of the dimethyl acetal derivative **10** has been established following the previous sequence of reactions. Thus, **10** was converted into the corresponding perbenzylated 2,5-anhydro-D-talitol (**13**): its positive rotation ($[\alpha]_D$ +39.4° in $CHCl_3$) shows clearly that the C-2 and C-5 substituents must possess a *trans* relationship, since a *cis* stereochemistry would have led to a *meso* structure. Consequently, the rearranged compound **8** must possess the same stereochemical outcome, with *trans* relationships between C-1 and C-2, C-1 and C-4 substituents.

The acid hydrolysis of **4**, carried out with hydrochloric acid in acetone at 50 °C for 2 h, allowed to quantitatively hydrolyze the dimethyl acetal to the corresponding 3,4,6-tri-*O*-benzyl-2,5-anhydro-D-mannose **3**. The same reaction carried out on **10** afforded the aldehyde **11** (93%). All the compounds were pure as shown by their ^{13}C NMR data.

[4] For other stereocontrolled synthesis of *trans* 2,5-disubstituted tetrahydrofuran see Ref. [6].



a:TTN, MeOH; b:aq HCl, acetone; c:$NaBH_4$, MeOH; d:BnBr, NaH, THF; e:H_2SO_4, THF-H_2O

Scheme 2.

The ring contraction was successfully applied to the perbenzylated glycosyl-glycals **16**, **19** and **22** [5], treatment with TTN in methanol at 35 °C for 8 h leading stereospecifically to the formation of **17**, **20** and **23** in yields around 90% (Scheme 3). The structures were completely in agreement with the NMR data.

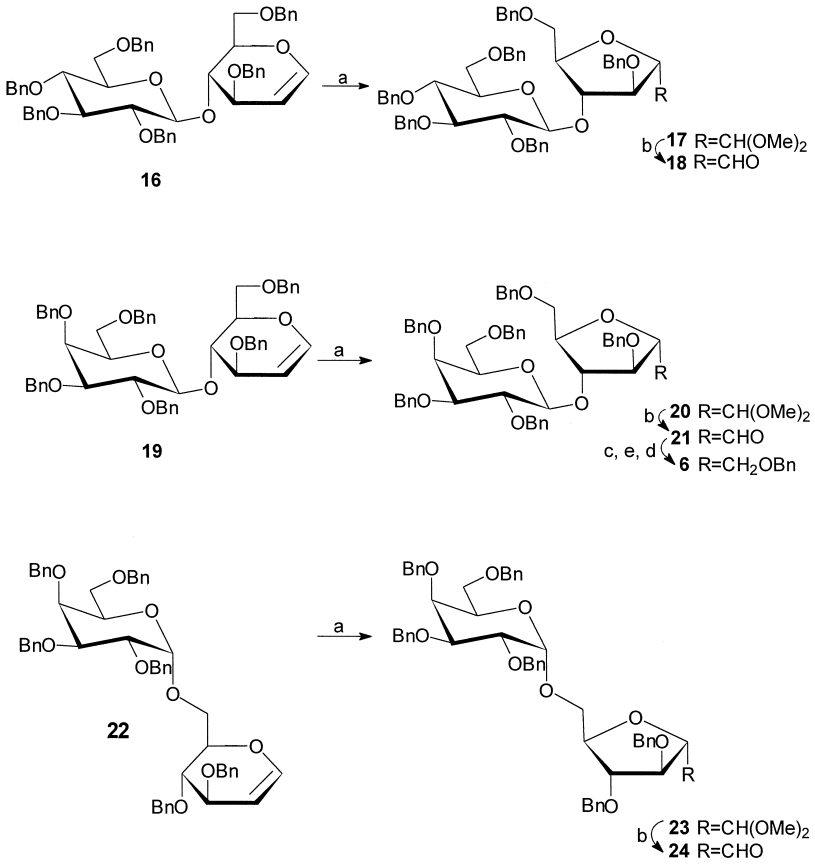
By analogy with compounds **4**, **8** and **10**, it was possible to remove easily the dimethylacetal groups also in **17**, **20** and **23** by treatment with hydrochloric acid in acetone at 50 °C for 2 h, with formation of the pure deprotected aldehydes **18**, **21** and **24** in good yields (90%).

The structure and the stereochemistry of the new compounds were established by chemical correlation involving reduction of the aldehyde **21** with sodium carohydride in methanol for 10 min, removal of the sugar moiety by 0.1 M H_2SO_4 in 1:1 tetrahydrofuran–water boiling solution for 1 h and then benzylation under the usual procedure which gave the pure and previously described **6**.

During the past few years, as a part of our continuing interest in the reactivity of glycals, we studied the reactivity of **1**, **7** and **9** under the action of TTN and sodium carohydride in methanol (1:4 molar ratio) [3]. In a typical experiment procedure, we reported that **1**, **7** and **9** in methanol were first allowed to react with TTN, then $NaBH_4$ was immediately added before the formation of the insoluble reduced TTN. All the reactions were strongly exothermic and practically instantaneous. Thus, the linear homochiral methoxy ethers **25**, **26** and **27** were isolated after chromatography on silica gel in a yield of 60% (Scheme 5). Yields are acceptable, since starting materials (35%) were recovered unchanged. It is interesting to note that all chiral centres have been conserved unlike the previous procedure for glycal derivatives ring opening by acids [2], which gave hydroxy-*trans*-enals like **2**, losing one chiral centre (Scheme 1).

The reaction mechanism can be explained through the initial formation of an intermediate from the protected D-glucal **1**, as previously described. The well-known reduction of Tl(III) to Tl(I) derivatives represents the key-step that makes the oxidative molecular rearrangement possible (Scheme 4) [3,6].

In the strong nucleophilic medium generated by

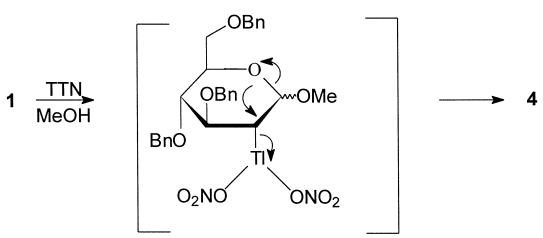


Scheme 3.

adding a large excess of sodium carohydride, the elimination from the initially formed intermediate of some Tl(III) cationic species could be favoured (Scheme 6). This elimination reaction gives rise to a competing process that could lead both to the formation of the ring opening product **25** and the starting tri-*O*-benzyl-D-glucal (**1**). Indeed, the cleavage of the cyclic enol-ether should form the opening products, such as **25** (route a), while the leaving of CH_3O^- group should generate the starting material (route b). It is worth noting that the ring contraction products were never observed under the above conditions, completely in agreement with the proposed reaction pathway. [5]

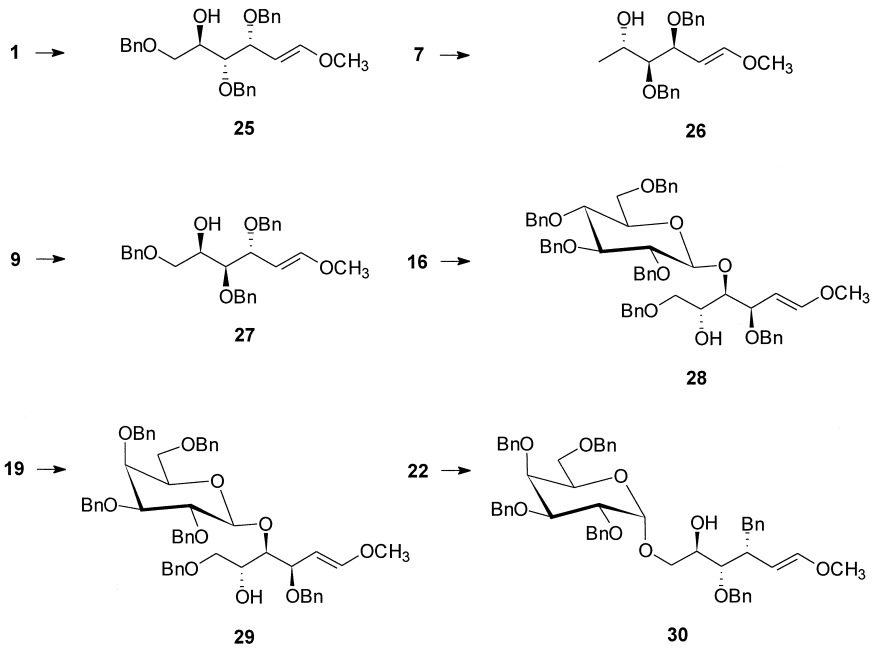
Owing to these promising results, we focused our attention on perbenzylated glycosyl-glycals, such as **16**, **19** and **22** [8]. All these compounds showed the same reactivity by treatment in 4:1 methanol–tetrahydrofuran mixture with TTN and sodium carohydride. The reactions gave stereospecifically the ring opening products **28**, **29** and **30** in 65% yield, without losing any chiral centre (Scheme 5). However, starting materials (30%) were recovered unchanged.

In order to show the flexibility and the utility of our findings in organic chemistry, we studied the TTN-promoted ring-transformations of cyclic enol-ethers, such as the protected aucubin **31** [9], a widespread iridoidic glycoside (Scheme 7). The *O*-benzyl ether derivative **31**, by reaction with TTN in methanol, underwent the usual stereoselective ring contraction, giving **32** in 94% yield, as shown by ^{13}C NMR data: [$CDCl_3$, δ] 106.8 (*C*-dimethylacetal).



Scheme 4.

[5] A parallel experiment carried out by adding MeONa to a hot solution of the glucal **1** and TTN in MeOH led to the formation of the product **25**, although in a low yield but without any ring contracted derivative.



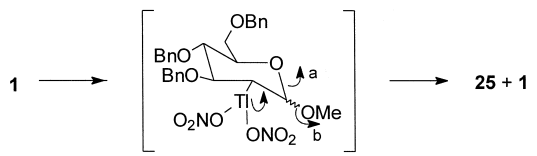
Scheme 5.

However, the ^{1}H NMR analysis did not allow to establish the stereochemistry at C-4, since both protons at C-4 and C-5 appeared as a complex and broad signal between δ 4.4–4.1.

On the other hand the reagent combination TTN–sodium carohydride on **31** lead to the formation of the ring opening compound [10] **33**, in 80% yield. The structure of **33** was completely in agreement with analytical and spectroscopic data, particularly the observed J (12.3 Hz) confirmed the *E*-configuration of the methyl enol-ether, as always previously described.

3. Experimental

General methods.—All moisture-sensitive reactions were performed under nitrogen using flamed or oven-dried glassware. Solvents were dried and distilled prior to use: tetrahydrofuran was distilled from sodium/benzophenone. Anhydrous diethyl ether and other common solvents were purchased and used as received. All other reagents were used as received.

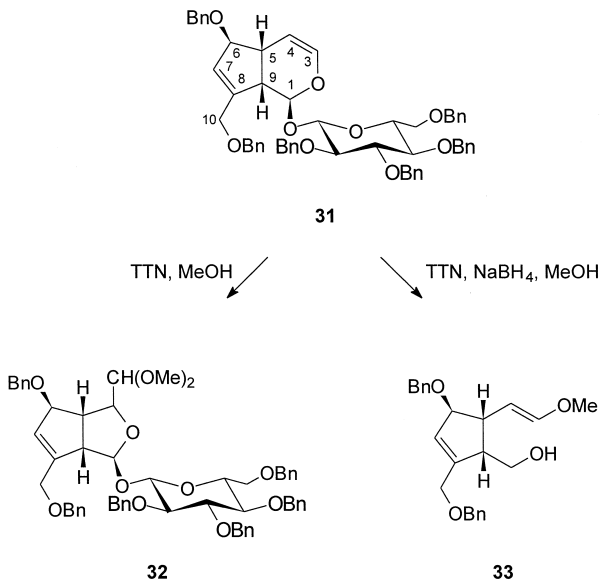


Scheme 6.

Reactions were monitored on Silica Gel 60-F_{254} (E. Merck) detection was performed using UV light (all *O*-benzyl derivatives) or H_2SO_4 (all glycal or glycosyl moiety). Chromatography was performed using Silica Gel 60 (230–400 mesh,) and eluted with the solvent mentioned.

^{1}H NMR spectra were recorded either at 200 or 300 MHz in $CDCl_3$ soln, and ^{13}C NMR were recorded either at 50.3 or 75.4 MHz in $CDCl_3$ soln.

As criteria of identity and degree of purity, TLC,



Scheme 7.

^{1}H NMR, ^{13}C NMR, and elemental analysis were used.

Starting materials.—Tri-*O*-benzyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (tri-*O*-benzyl-D-glucal) (**1**), di-*O*-benzyl-1,5-anhydro-2,6-dideoxy-L-*arabino*-hex-1-enitol (di-*O*-benzyl-L-rhamnal) (**7**) and tri-*O*-benzyl-1,5-anhydro-2-deoxy-D-*lyxo*-hex-1-enitol (tri-*O*-benzyl-D-galactal) (**9**) were prepared following standard procedures [4]. 3,6-Di-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-*β*-D-glucopyranosyl)-D-glucal (hexa-*O*-benzyl-cellobial) (**16**), 3,6-di-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-*β*-D-galactopyranosyl)-D-glucal (hexa-*O*-benzyl-lactal) (**19**) and 3,4-di-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-*α*-D-galactopyranosyl)-D-glucal (hexa-*O*-benzyl-melibial) (**22**) were prepared following standard procedures from the corresponding disaccharides [5]. Perbenzylated aucubin (**31**) was prepared according to the literature [5].

General procedure for reactions with TTN in MeOH.—A mixture of per-benzylated glycal (0.30 mmol) and TTN (0.90 mmol) in MeOH (15 mL) at 35 °C was stirred for 5 h, time after which no more starting material could be detected on TLC and insoluble $TLNO_3$ was precipitated. The mixture was diluted with diethyl-ether (100 mL) and the organic phase washed with saturated Na_2CO_3 (10 mL), water (until neutrality), brine (10 mL), followed by drying (Na_2SO_4) and concentration under reduced pressure. Chromatography on a column of silica gel with ether–hexane as the eluent afforded the required product.

*3,4,6-Tri-O-benzyl-2,5-anhydro-*D*-mannose dimethylacetal* (**4**). From 3,4,6-tri-*O*-benzyl-D-glucal (**1**) (100 mg, 0.24 mmol) and TTN (280 mg, 0.63 mmol) in MeOH (10 mL) at 35 °C: 109 mg (95%), colorless liquid; $[\alpha]_D$ +11° (in $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.27 (f, 1 H, H-5), 3.61 (d, 2 H *J* 5.7 Hz, CH_2OBn), 3.45 (s, 3 H, OMe), 3.42 (s, 3 H, OMe). ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 138.7, 138.5, 138.4, 128.8–128.1 (aromatic), 104.1 (C-1), 85.1, 85.0, 83.5, 82.5, 73.7, 72.0, [6] 70.1 (C-2,3,4,5,6 and CH_2–Ph), 55.8, 54.2 (2 OMe). Anal. Calcd for $C_{29}H_{34}O_6$: C, 72.78; H, 7.16. Found: C,72.90; H, 7.15.

*3,4-Di-*O*-benzyl-6-deoxy-2,5-anhydro-*L*-mannose dimethylacetal* (**8**). From 2,3-di-*O*-benzyl-D-rhamnal (**7**) (100 mg, 0.32 mmol): 114 mg (95%), colorless liquid; $[\alpha]_D$ −5.8° (in $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.42 (s, 3 H, OMe), 3.40 (s, 3 H, OMe), 1.28 (d, 3 H, *J* 6.4 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 138.7, 138.5, 129.1, 128.1 (aromatic), 104.3 (C-1), 89.6, 85.5, 82.7, 78.9, 72.2, 72.1 (C-2,3,4,5 and CH_2–Ph), 55.8, 54.1 (2 OMe), 19.2. Anal. Calcd for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.70; H, 7.60.

*3,4,6-Tri-O-benzyl-2,5-anhydro-*D*-talose dimethylacetal* (**10**). From 3,4,6-tri-*O*-benzyl-D-galactal (**9**) (150 mg, 0.36 mmol); 163 mg (95%), colorless liquid; $[\alpha]_D^{20}$ +10.0° (*c* 5.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.42 (s, 3 H, OMe), 3.39 (s, 3 H, OMe); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 138.9, 138.8, 138.7, 128.9–128.0 (aromatic), 105.3 (C-1), 81.8, 79.6, 78.6, 78.3, 73.7, 73.4, 72.5, 69.3 (C-2,3,4,5 and CH_2–Ph), 56.1, 55.5 (2 OMe). Anal. Calcd for $C_{29}H_{34}O_6$: C, 72.78; H, 7.16. Found: C, 72.60; H, 7.18.

*1,3,4,6-Tetra-O-benzyl-2,5-anhydro-*D*-mannitol* (**6**). The dimethylacetal **4** (230 mg, 0.48 mmol) was stirred with 20:1 acetone–concentrated HCl (10 mL) for 2 h at 50 °C, after which no more starting material could be detected on TLC. The mixture was diluted with diethyl ether (100 mL). The organic phase was washed with saturated Na_2CO_3 (10 mL), water (until neutrality), brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Then, the resulting crude aldehyde **3** (0.30 mmol) dissolved in MeOH (8 mL) was treated with $NaBH_4$ (40 mg) under stirring for 15 min, after which no more starting material could be detected on TLC with the formation of almost pure **5**. The mixture was neutralized by bubbling carbon dioxide and then diluted with diethyl ether (100 mL). The organic phase was washed with water and brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Sodium hydride (20 mg) was added to the refluxing soln of the crude **5** in dry tetrahydrofuran (10 mL). After 30 min, BnBr (0.05 mL, 0.42 mmol) was added. The mixture was heated under reflux for 5 h, after which no starting material could be detected on TLC. The mixture was diluted with diethyl ether and treated with MeOH to destroy the excess of NaH. The organic phase was washed with water and brine until neutrality, dried (Na_2SO_4), and evaporated under reduced pressure to give a pale yellow oil. Chromatography on a column of silica gel with hexane and then with 3:7 ether–hexane as the eluant afforded 214 mg of **6** (85% overall yield for the three steps, starting from **4**), identical to perbenzylated authentic 2,5-anhydro-D-mannitol (superimposable ^{1}H NMR and ^{13}C NMR spectra) [3].

*3,4,6-Tri-O-benzyl-2,5-anhydro-*D*-talose* (**11**). The

[6] This signal can be referred to a couple of carbon atoms.

conversion of **10** into aldehyde **11** was performed according to the procedure described for the preparation of **3** from **4**. Chromatography on a column of silica gel with 1:4 ether–hexane as the eluant afforded **11** (185 mg, 93%) as a colorless liquid; $[\alpha]_D^{20}$ +7.6° (*c* 5.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.60 (d, *J* 1.5 Hz, 1 H, CHO), 3.78 (d, *J* 6.6 Hz, 2 H, H-6). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 201.2 (C-1), 138.0, 137.8, 137.2, 128.6–127.7 (aromatic), 84.7, 80.3, 79.8, 77.4, 73.6, 73.5, 72.7, 68.7 (C-2,3,4,5,6 and CH_2–Ph). Anal. Calcd for $C_{27}H_{28}O_5$: C, 74.98; H, 6.53. Found: C, 74.85; H, 6.55.

*3,4,6-Tri-O-benzyl-2,5-anhydro-*D*-talitol* (**12**). The reduction of **11** (125 mg, 0.29 mmol) was performed according to the procedure described for the preparation of **5** from **3**. Chromatography on a column of silica gel with 1:4 ether–hexane as the eluant afforded **12** (124 mg, 98%) as a colorless oil: $[\alpha]_D^{20}$ +45.4° (*c* 3.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.71 (d, *J* 6.6 Hz, 2 H, H-6). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 138.8, 138.6, 138.3, 129.0–128.3 (aromatic), 80.5, 80.0, 79.4, 77.7, 73.9, 73.8, 73.2, 69.4 (C-2,3,4,5,6 and CH_2–Ph), 62.3 (C-1). Anal. Calcd for $C_{27}H_{30}O_5$: C, 74.63; H, 6.96. Found: C, 74.73; H, 6.95.

*1,3,4,6-Tetra-O-benzyl-2,5-anhydro-*D*-talitol* (**13**). The benzylation of **12** (100 mg, 0.23 mmol) was performed according to the procedure described for the conversion of **5** into **6**. Chromatography on column of silica gel with 1:4 ether–hexane as the eluant afforded **13** (116 mg, 96%) as a colorless oil: $[\alpha]_D^{20}$ +39.4° (*c* 5.0, $CHCl_3$). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 138.9, 138.8, [5] 138.4, 128.9–128.1 (aromatic), 80.0, 79.8, 79.5, 77.6, 73.8, [5] 73.7, 72.8, 70.4, 69.1 (C-1,2,3,4,5,6 and CH_2–Ph). Anal. Calcd for $C_{34}H_{36}O_5$: C, 77.84; H, 6.92. Found: C, 77.68; H, 6.94.

*3,4,6-Tri-*O*-benzyl-2,5-anhydro-*D*-allose-dimethylacetal* (**15a**) and 3,4,6-tri-*O*-benzyl-2,5-anhydro-D-*altrose-dimethylacetal* (**15b**). A stirred soln of **14** (390 mg, 0.94 mmol) in MeOH (25 mL) was treated with 1.66 g of TTN for 4 h. Following the same procedure for the working-up described for the ring contraction of **1** into **4**, the dimethylacetals **15a** (144 mg) and **15b** (126 mg) have been obtained as colorless oils. Compound **15a**: $[\alpha]_D^{20}$ +65° (*c* 12.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz); δ 4.3–4.15 (non-resolved broad signal, 3 H at C-5, C-2 and at C-dimethylacetal), 3.45 (OMe), 3.41 (OMe); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 138.2, 138.0, 137.9, 128.2, 127.6, 127.5 (aromatic), 104.8 (C-1), 83.2, 80.0, 78.1, 76.2, 73.2, 71.9, 71.3, 70.1 (C-2,3,4,5,6 and CH_2–Ph), 56.6, 55.1 (2 O–Me). Anal. Calcd for $C_{29}H_{34}O_6$: C, 72.78; H, 7.16. Found: C, 72.58; H, 7.22. Compound **15b**:$[\alpha]_D^{20}$ +58.5° (*c* 12.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.3–4.1 (non-resolved broad signal, 3 H at C-5, C-2 and at C-dimethylacetal), 3.43 (OMe), 3.38 (OMe); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 139.1, 138.1, 137.9, 128.9, 128.7, 128.3, 128.2, 128.0 (aromatic), 102.8 (C-1), 80.4, 80.1, 79.5, 74.2, 73.8, 73.2, 70.0 (C-2,3,4,5,6 and CH_2–Ph), 55.4, 53.4 (2 O-Me). Anal. Calcd for $C_{29}H_{34}O_6$: C, 72.78; H, 7.16. Found: C, 72.89; H, 7.34.

General procedure for the reaction of glycosyl-glycals with TTN in MeOH.—A solution of the glycosyl-glycal (0.40 mmol) in MeOH (15 mL) was stirred with TTN (1,2 mmol) at room temperature for 8 h, after which no more starting material could be detected on TLC. The mixture was diluted with diethyl ether (200 mL) and transferred in a separatory funnel. The organic phase was washed with saturated Na_2CO_3, water (until neutrality) and brine, then dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography on a column of silica gel with ether–hexane as the eluent gave the required product.

*3,6-Di-*O*-benzyl-4-*O*-(2,3,4,6-tetra-O-benzyl-β-*D*-glucopyranosyl)-2,5-anhydro-*D*-mannose dimethylacetal* (**17**). A solution of **16** (315 mg, 0.37 mmol) in MeOH (15 mL) was stirred with TTN 517 mg (1.16 mmol) at room temperature for 8 h, after which no more starting material could be detected on TLC. The mixture was diluted with diethyl ether (200 mL) and transferred in a separatory funnel. The organic phase, washed with Na_2CO_3, water until neutrality and brine, dried (Na_2SO_4) and concentrated under reduced pressure gave a colorless oil. Chromatography on a column of silica gel with 3:7 ether-hexane as the eluant gave **17** (308 mg, 90%) as a colorless oil; $[\alpha]_D^{20}$ +3.5° (*c* 4.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.42 (s, 3 H, OMe), 3.41 (s, 3 H, OMe).^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 139.2–138.7, 128.9–128.1 (aromatic), 104.0, 103.9 (2 C anomeric), 85.6[1], 85.1, 83.8, 83.5, 82.6, 78.0, 76.1, 75.3, 75.2[1], 73.9, 73.7, 71.9, 69.9, 69.1, 55.6, 54.1 (2 O–Me). Anal. Calcd for $C_{56}H_{62}O_{11}$: C, 73.82; H, 6.86. Found: C, 73.60; H 6.89.

*3,6-Di-O-benzyl-4-*O*-(2,3,4,6-tetra-O-benzyl-β-*D*-galactopyranosyl)-2,5-anhydro-*D*-mannose dimethylacetal* (**20**). The above procedure was followed with **19** (280 mg, 0.33 mmol), affording **20** (271 mg, 89%), as a colorless oil: $[\alpha]_D^{20}$ +3.3° (*c* 1.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.44 (s, 3 H, OMe), 3.42 (s, 3 H, OMe). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 139.3–138.3, 128.9–128.0 (aromatic), 104.0, 103.9

(2 C anomeric), 85.4, 85.2, 83.8, 83.3, 82.5, 79.7, 75.6, 75.0, 73.8, [6] 73.6, [6] 73.3, 71.9, 69.9, 68.8, 55.8, 54.0 (2 O–Me). Anal. Calcd for $C_{56}H_{62}O_{11}$: C, 73.82; H, 6.86. Found: C, 73.58; H 6.88.

3,4-Di-O-*benzyl-6*-O-*(2,3,4,6-tetra-O-benzyl-α*-D-*galactopyranosyl)-2,5-anhydro*-D-*mannose dimethylacetal* (**23**). From **22** (255 mg, 0.30 mmol); 241 mg (87%), colorless oil: $[\alpha]_D^{20}$ +42.2° (*c* 2.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.37 (s, 3 H, OMe), 3.34 (s, 3 H, OMe). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 139.1–138.1, 128.5–127.5 (aromatic), 103.7, 98.1 (2 C anomeric), 85.3, 84.9, 83.0, 81.9, 78.8, 76.5, 75.0, 74.7, 73.4, 72.9 [6], 72.9, 71.7, 71.6, 69.3, 68.7, 68.1, 55.1, 53.5 (2 O–Me). Anal. Calcd for $C_{56}H_{62}O_{11}$: C, 73.82; H, 6.86. Found: C,73.65; H, 6.88.

3,6-Di-O-benzyl-4-O-(2,3,4,6-tetra-O-benzyl-β-D-*glucopyranosyl)-2,5-anhydro*-D-*mannose* (**18**). The dimethylacetal **17** (175 mg, 0.19 mmol) was treated with 20:1 acetone–concd HCl (10 mL) under stirring at 50 °C for 2 h, after which no more starting material could be detected on TLC. The reaction mixture was diluted with diethyl ether (150 mL), washed with Na_2CO_3, water until neutrality and brine, dried with Na_2SO_4 and concentrated under reduced pressure. Chromatography on column of silica gel with 1:1 ether–hexane as the eluant gave **18** as an oil (148 mg, 90%): $[\alpha]_D^{20}$ +3.6° (*c* 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.62 (d, *J* 1 Hz, 1 H, CHO). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 201.4 (C-1), 138.5–137.4, 128.8–127.6 (aromatic), 103.1 (C-1′), 88.2, 85.4, 84.5, 84.4, 83.6, 82.0, 77.5, 75.6, 75.0, [6] 74.9, 73.5, 73.4, 71.9, 69.6, 68.7. Anal. Calcd for $C_{54}H_{56}O_{10}$: C, 74.98; H, 6.53. Found: C, 74.75; H, 6.56.

3,6-Di-O-benzyl-4-O-(2,3,4,6-tetra-O-benzyl-β-D-*galactopyranosyl)-2,5-anhydro*-D-*mannose* (**21**). From **20**, (185 mg, 0.20 mmol); 154 mg (89%), colorless oil; $[\alpha]_D^{20}$ +3.7° (*c* 8.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.61 (d, *J* 1 Hz, 1 H, CHO). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 202.2 (C-1), 139.1–137.9, 128.9–128.1 (aromatic), 103.4 (C-1′), 88.5, 85.8, 84.4, 83.5, 82.6, 79.5, 75.7, 74.9, 73.9, 73.7, 73.6, [6] 73.3, 72.3, 70.0, 68.9. Anal. Calcd for $C_{54}H_{56}O_{10}$: C, 74.98; H, 6.53. Found: C, 74.78; H, 6.55.

3,4-Di-O-benzyl-6-O-(2,3,4,6-tetra-O-benzyl-α-D-*galactopyranosyl)-2,5-anhydro*-D-*mannose* (**24**). From **23** (185 mg, 0.20 mmol); 149 mg (86%), colorless oil; $[\alpha]_D^{20}$ +42.0° (*c* 2.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.61 (d, *J* 1 Hz, 1 H, CHO). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 203.3 (C-1), 139.4–137.6, 129.1–127.9 (aromatic), 98.5 (C-1′), 87.9, 85.2, 83.9, 83.4, 79.3, 76.9, 75.4, 75.1, 73.8, 73.6, 73.4, 72.2, 71.8, 69.8, 69.3, 68.6. Anal. Calcd for $C_{54}H_{56}O_{10}$: C, 74.98; H, 6.53. Found: C, 74.98; H, 6.56.

3,4,6-Tri-O-*benzyl-2-deoxy-1*-O-*methyl*-D-arabino-*hex-1-enitol* (**25**). TTN (960 mg, 2.16 mmol) dissolved in MeOH (10 mL) was added to a stirred solution of (300 mg, 0.72 mmol) of glucal **1** in MeOH (30 mL). Immediately after, a large excess of $NaBH_4$ was added. After 5 min, the suspension, diluted with water was extracted then twice with ether (200 mL). Combined extracts were dried with Na_2SO_4, and evaporated to give a pale yellow oil. Chromatography on a column of silica gel with 1:4 ether–hexane as the eluant gave the starting glucal **1** (105 mg, 35%) and **25** (195 mg, 58%) as a colorless oil: $[\alpha]_D^{20}$ −21.8° C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.42 (d, $J_{1,2}$ 12.8 Hz, 1 H, H-1), 4.80 (dd, $J_{2,3}$ 9.5 Hz, 1 H, H-2), 3.92 (dd, $J_{3,4}$ 3.8 Hz, 1 H, H-3), 3.50 (s, 3 H, OMe), 2.96 (bs, 1 H, H-5). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 152.2 (C-1), 139.0, 138.7, [6] 128.9–128.2 (aromatic), 99.5 (C-2), 81.9, 77.8 (C-3 and C-4), 74.5 (C-5), 73.2, 71.5, 71.0, 69.8 (C-6 and CH_2–Ph), 56.3 (O–Me). Anal. Calcd for $C_{28}H_{32}O_5$: C, 74.98; H, 7.19. Found: C, 74.80; H, 7.22.

3,4-Di-O-benzyl-2,6-dideoxy-1-O-methyl-L-arabino-*hex-1-enitol* (**26**). From **7** (233 mg,0.75 mmol), affording **26** (142 mg, 60%) and the starting glycal **7** (77 mg, 33%), colorless oil; $[\alpha]_D^{20}$ +28° (*c*, 2.6, $CHCl_3$ ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.48 (d, $J_{1,2}$ 12.8 Hz, 1 H, H-1), 4.77 (dd, $J_{2,3}$ 9.5 Hz, 1 H, H-2), 3.55 (s, 3 H, OMe), 3.37 (t, $J_{3,4}$ 5.3 Hz, $J_{4,5}$ 5.3 Hz, 1 H, H-4), 1.13 (d, $J_{5,6}$ 6.3 Hz, 3 H, H-6). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 152.3 (C-1), 139.0, 138.5, 129.0–128.2 (aromatic), 98.9 (C-2), 84.6, 78.7 (C-3 and C-4), 74.4 (C-5), 69.7, 67.8 (2 CH_2–Ph), 56.3 (O–Me), 19.0 (C-6). Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.51; H, 7.67.

3,4,6-Tri-O-benzyl-2-deoxy-1-O-methyl-D-lyxo-*hex-1-enitol* (**27**). From **9** (250 mg, 0.60 mmol), affording **27** (159 mg, 59%) and the starting glycal **9** (85 mg, 34%), colorless oil: $[\alpha]_D^{20}$ −46.4° (*c*, 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.45 (d, $J_{1,2}$ 12.6 Hz, 1 H, H-1), 4.01–3.80 (m, 1 H, H-3), 3.55 (s, 3 H, OMe), 2.88 (m, 1 H, H-5). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 152.5 (C-1), 138.8, [7] 128.9–128.1 (aromatic), 100.0 (C-2), 81.1, 78.2 (C-3 and C-4), 74.4 (C-5), 73.7, 71.4, 70.3, 69.8 (C-6 and

[7] This signal can be referred to three carbon atoms.

CH_2–Ph), 56.4 (OMe). Anal. Calcd for $C_{28}H_{32}O_5$: C, 74.98; H, 7.19. Found: C, 74.82; H, 7.21.

*3,6-Di-O-benzyl-2-deoxy-4-O-(2,3,4,6-tetra-O-benzyl-β-*D*-glucopyranosyl)-1-*O*-methyl-*D*-arabino-hex-1-enitol* (**28**). From **16** (330 mg, 0.39 mmol), affording **28** and the starting glycal **16** (99 mg, 30%) (223 mg, 65%), colorless oil: $[\alpha]_D^{20}$ +5.5° (*c*, 4.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.55 (d, $J_{1,2}$ 12.8 Hz, 1 H, H-1), 3.53 (s, 3 H, OMe). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 152.3 (C-1), 139.2–138.8, 128.9–128.1 (aromatic), 103.9 (C-1′), 99.3 (C-2), 85.3, 82.5, 80.0, 78.2, [6] 76.0, 75.3, 75.2, [6] 73.8, 73.6, 71.3, 71.2, 69.9, 69.4, 56.2 (OMe). Anal. Calcd for $C_{55}H_{60}O_{10}$: C, 74.98; H, 6.86. Found: C, 74.71; H, 6.89.

*3,6-Di-O-benzyl-2-deoxy-4-O-(2,3,4,6-tetra-O-benzyl-β-galactopyranosyl)-1-*O*-methyl-*D*-arabino-hex-1-enitol* (**29**). From **19** (315 mg, 0.37 mmol), affording **29** (209 mg, 64%) and the starting glycal **19** (88 mg, 28%), colorless oil:; $[\alpha]_D^{20}$ +3.3° (*c*, 5.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.52 (d, 1 H, $J_{1,2}$ 12.8 Hz, H-1), 3.53 (s, 3 H, OMe). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 152.0 (C-1), 139.4–138.5, 129.0–128.0 (aromatic), 104.3 (C-1′), 99.3 (C-2), 82.9, 80.6, 79.8, 78.0, 75.5, 75.0, 74.0, 73.9, 73.5, 73.5, [5] 73.2, 71.2, [6] 69.8, 68.9, 56.1 (OMe). Anal. Calcd for $C_{55}H_{60}O_{10}$: C, 74.98; H, 6.86. Found: C, 74.82; H, 6.88.

*3,4-Di-O-benzyl-2-deoxy-6-O-(tetra-O-benzyl-α-galactopyranosyl)-1-O-methyl-*D*-arabino-hex-1-enitol* (**30**). From **22** (290 mg, 0.34 mmol), affording **30** (187 mg, 62%) and the starting glycal **22** (90 mg, 31%), colorless oil; $[\alpha]_D^{20}$ +52.9° (*c*, 2.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.45 (d, 1 H, $J_{1,2}$ 12.8 Hz, H-1), 3.51 (s, 3 H, OMe). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 152.0 (C-1), 139.2–138.5, 128.9–128.0 (aromatic), 99.8, 99.1 (C-2 and C-1′), 82.9, 79.3, 77.8, 76.9, 75.2, [6] 74.8, 73.9, 73.8, 73.1, 70.5, [6] 69.9, 69.8, 69.3, 56.2 (OMe). Anal. Calcd for $C_{55}H_{60}O_{10}$: C, 74.98; H, 6.86. Found: C, 74.80; H, 6.88.

*[1S,4S,5S,8S]-2-Bis(dimethoxymethyl)-4-O-(2,3,4,6-tetra-O-benzyl-β-*D*-glucopyranosyl)-6-benzyloxymethyl-8-benzyloxy-3-oxabicyclo[3.3.0]oct-6-ene* (**32**). The ring contraction of perbenzylated aucubin (**31**) (220 mg, 0.25 mmol) was performed according to the procedure described for the contraction of the glycal **1** to **4**. Chromatography on a column of silica gel with 3:7 ether–hexane as the eluant gave **32** (221 mg, 94%) as a colorless oil; ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 146.2 (C-7), 139.2–138.6, 128.9–128.1 (C-8 and aromatic), 106.8 (C-3), 101.2 (C-1′), 97.1 (C-1), 88.0, 85.5, 84.6, 82.3, 78.2, 76.1, 75.2, [7] 75.1, 73.8, 72.8, 71.2, 68.8, 68.1, 58.4 (C-9), 55.3, 54.2 (2 OMe), 49.8 (C-5). Anal. Calcd for $C_{59}H_{64}O_{11}$: C, 74.66; H, 6.80. Found: C, 74.52; H, 6.82.

[1S,4S,5S]-3-Benzyloxymethyl-4-hydroxymethyl-5[(E)-2′-(methoxyethenyl)]-O-benzylcyclopent-2-en-1-ol (**33**). The ring opening of perbenzylated aucubin (**31**) (220 mg, 0.25 mmol) was performed according to the procedure described for the opening of the glycal **1** to **25**. Chromatography on column of silica gel with 1:4 ether–hexane as the eluant gave **33** (75 mg, 80%) as a colorless oil; ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 149.6 (C-3), 144.5 (C-7), 139.2, 138.4, 132.8, 129.0–128.0 (C-8 and aromatic), 101.9 (C-4), 88.9 (C-6), 73.2, 72.1, 68.6 (C-10 and CH_2–Ph), 62.2 (C-1), 56.4, 52.7, 49.4. Anal. Calcd for $C_{55}H_{60}O_{10}$: C, 74.98; H, 6.86. Found: C, 75.76; H, 7.42.

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