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Chiral 1,4-Dicarbonyl-2,3-*O*-Isopropylidene Derivatives. Rapid Racemization on Standing

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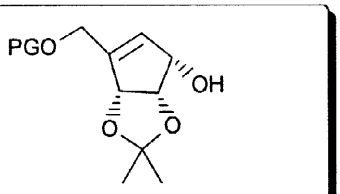
Abstract 1,4-Dicarbonyl-2,3-chiral derivatives are useful synthetic precursors for the preparation of carbocyclic rings but, in many cases, losses of optical purity have been reported. 1-Deoxy-3,4-*O*-isopropylidene-6-*O*-trityl-D-*erythro*-hexo-2,5-diulose and 1-deoxy-3,4-*O*-isopropylidene-6-*O*-(*tert*-butyldiphenylsilyl)-D-*erythro*-hexo-2,5-diulose were synthesized from D-ribono-1,4-lactone. These compounds were selected to study the epimerizability of 2,3-*O*-isopropylidene-1,4-dicarbonyl derivatives. It was found that both compounds smoothly epimerize and partially racemize on standing.

Keywords: Carbohydrates; Nucleosides; Racemization; Epimerization

INTRODUCTION

Carbohydrates are an important chiral source for the preparation of enantiomerically pure compounds [1,2]. Of special interest is the synthesis of carbocyclic rings for being advanced precursors of carbanucleosides, compounds in which the furanosic oxygen has been replaced by a methylene group, giving rise to a new family of nucleoside analogues [3,4]. As normal nucleosides, these compounds exhibit a wide range of biological properties with the advantage that they are not recognized by phosphorylases and hydrolases that cleave the glycosidic bond [5,6]. The availability of optically pure carbocyclic nucleosides is crucial to evaluate their biological action, mainly as antiviral and antitumor agents. The



1, PG = Bn
2, PG = MOM
3, PG = Ph_2tBuSi

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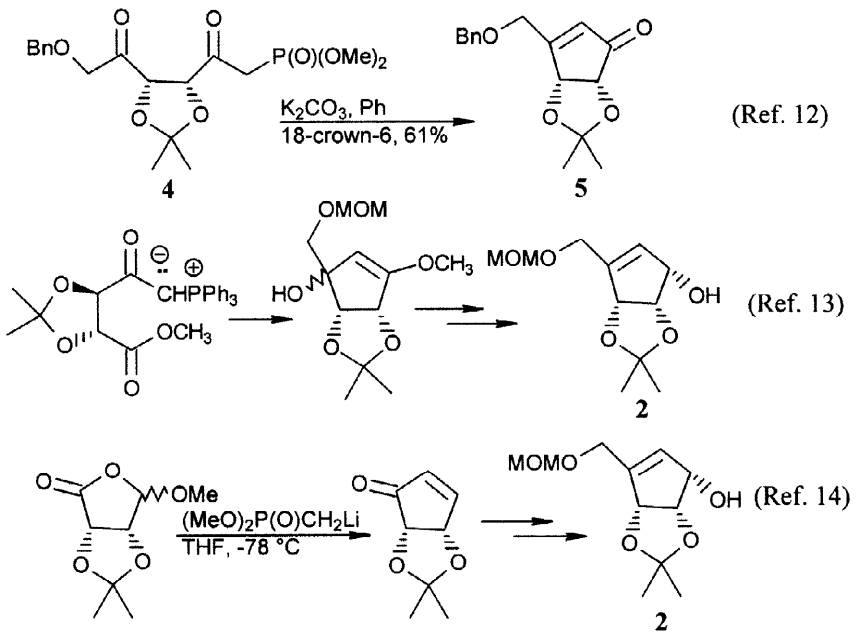
skalemic synthesis of these drugs is always performed with an enantiomeric excess of the pseudosugar precursor due to the fact that the most efficient and elegant ways to couple the heterocyclic base onto the carbocyclic ring proceed *via* S_N2 reactions (convergent approach) [3,4,7-11].

Scheme 1



Cyclopentenols **1-3** and closely related compounds have been widely employed as advanced precursors for the synthesis of several representative members of carbanucleosides including the neplanocin family [12-16]. The preparation of these pseudosugar moieties always involves an intramolecular Wittig reaction from a 1,4-diketo derivative which, in turn, is usually prepared from aldonolactones whose use as chiral starting materials has been reviewed [17-19]. The observed loss of optical purity may be attributed to the basic conditions of the Wittig-type reaction. Thus, partial racemization was observed when 1,4-diketo derivative **4** was transformed into the respective cyclopentenone **5** (Scheme 1) [12]. In this case, the product could be enriched in the desired enantiomer by fractionated crystallization [12]. On the other hand, an independent group was unable to obtain **5** in skalemic form, suggesting an optical purity close to 50% [20]. Moreover, the optical rotation value for cyclopentenol **2** differs significantly when this product is prepared from (*R,R*)-monomethyl tartrate ($[\alpha]_D$ +36.8) [13] or from D-ribose ($[\alpha]_D$ +46) [14]. A strict measurement of the enantiomeric excess of some intermediate has not been carried out in any case [12-16]. In contrast, only comparison of the optical rotation of the target compound neplanocin A [12-16] with the original reported value [21] has been covered [12-16]. For the

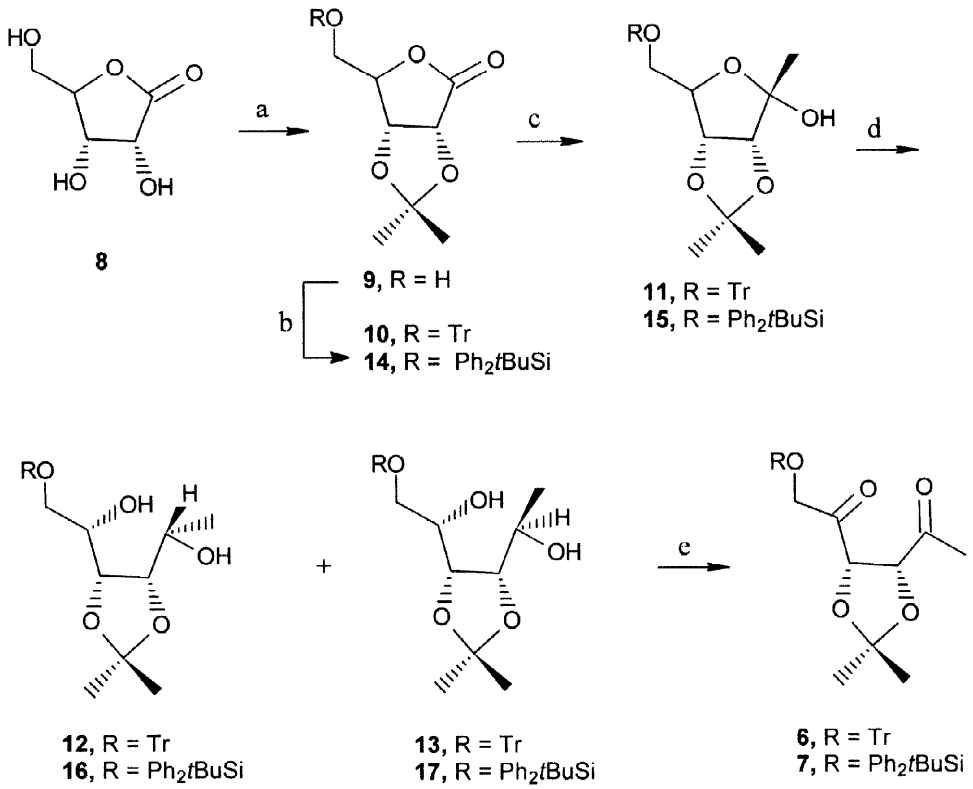
above reasons, it was considered worthwhile to study whether 1,4-chiral diketo derivatives undergo racemization, not only under basic media but also on standing. Consequently, compounds **6** and **7** were selected as target molecules since they are closely related to the advanced precursors of carbocyclic pseudosugars. The aim of introducing the isopropylidene group into the molecule was to prevent enol formation.

RESULTS AND DISCUSSION

Compounds **6** and **7** were prepared starting from D-ribono-1,4-lactone (**8**). Compound **8** was transformed into isopropylidene derivative **9** in very good yield by treatment with hydrochloric acid and acetone [22]. Lactone **9** was protected as the trityl ether derivative **10** by reaction with trityl chloride in pyridine [23]. Treatment of **10** with methyllithium at low temperature [24] led stereospecifically to lactol **11** in excellent yield. The stereochemistry of this product may be explained considering that the nucleophilic attack, modulated by the presence of the isopropylidene group, takes place from the less hindered β-face of the molecule. It is worthy to point out that only one equivalent of the organometallic reagent coupled with compound **10**; i.e., formation of the tertiary alcohol by the attack of two molecules of methyllithium was not observed. Two approaches were considered in order to obtain the target compound: (a) ring-opening of the lactol group to the corresponding 4-hydroxy carbonyl compound followed by oxidation of the resulting alcohol, or (b) reduction of the lactol to the respective diol derivative followed by oxidation of both functionalities to the diketo compound. In spite of having been described [12], the former alternative did not work properly because hydrolysis of lactol **11** was not complete, giving rise to equilibrium between the open chain and lactol. In the second approach, **11** reacted with sodium borohydride [25] to give a diastereomeric mixture of diols **12** and **13** favoring the *altro* derivative in a 2:1 ratio. In this case, the stereochemical course of the reaction was controlled by hydride attack induced by van der Waals interactions between the isopropylidene group and the incoming nucleophile. Diols **12** and **13** could be readily separated by column chromatography. Swern oxidation [26] of either diol derivative led to the desired target molecule **6** in almost theoretical yield. Attempts to oxidize diols **12** and **13** with pyridinium chlorochromate (PCC) [27] or pyridinium dichromate (PDC) [28] were not satisfactory, not only in terms of the yields but also in the formation of several side products. Using a similar synthetic approach compound **7** was successfully prepared protecting the primary alcohol with a *tert*-butyldiphenyl silyl group [29-30] instead of a trityl unit. Thus, compound **9** reacted with *tert*-butylcholorodiphenylsilane in *N,N*-dimethylformamide in the presence of imidazole to give silyl

derivative **14**. Treatment of **14** with methyllithium at low temperature gave lactol **15**, which, on reaction with sodium borohydride, afforded a diastereomeric mixture of diol **16** and **17** in a comparable ratio to that observed for the trityl derivative. The overall yield was also similar to that observed for the trityl compound. As was the case of trityl derivatives, this isomeric mixture could be separated by column chromatography. In separate experiments, Swern oxidation of each diol led the target molecule **7**.

Scheme 2

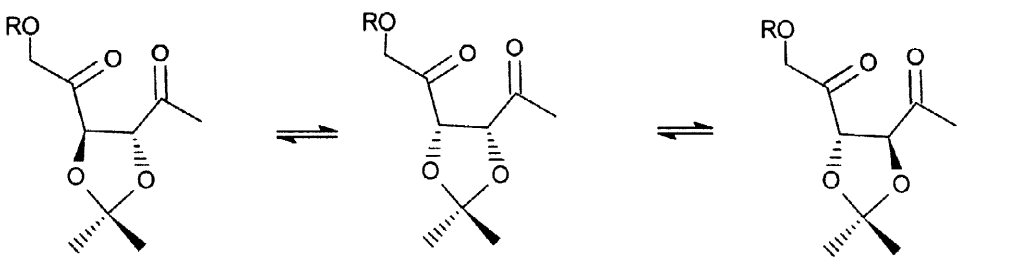


Reagents and Conditions: a) Me_2CO, HCl (c), r.t., 18 h, 81%; b) TrCl, py, r.t., 3 d, 51% for **10**, $Ph_2tBuSiCl$, Im, DMF, r.t. 16 h, 73% for **14**; c) MeLi, THF, -78 °C, 2 h, 91% for **11**, 93% for **15**; d) $NaBH_4$, THF, r.t. overnight, 25% for **12**, 54% for 13, 28% for **16**, 56% for **17**; e) i. $(ClCO)_2$, Cl_2CH_2, DMSO, -70 °C, 15 min, ii. TEA, -70 °C → r.t., 99% for **6**, 95% for **7**.

As predicted, the diketo *erythro* derivative **6** smoothly isomerized to the *threo* compound **18** on standing (Scheme 3). This transformation was somewhat capricious due to the variable degree of conversion observed. In chloroform solution, 30% epimerization of crude **6** was noticed after 3 days at 5 °C as a nonseparable epimeric mixture, perhaps due to the presence of a residual amount of hydrochloric acid that catalyzes epimerization. On the other hand, purification of crude **6** by column chromatography on silica gel gave rise to a mixture of the D- or L- *threo* derivatives (compounds **D-18** and **L-18**, respectively) in an undetermined ratio. It is important to

notice that compound **6** epimerized in the absence of solvent, as a simple oil on standing. This behavior can be clearly observed by analysis of the nuclear magnetic resonance spectra. Thus, the typical signals for compound **6**, two coupled doublets, centered at 3.93 ppm and 4.09 ppm, respectively, for H-6 moved downfield to a singlet at 4.16 ppm, while the *AB* system corresponding to the H-3 and H-4, centered at 4.77 ppm, shifted upfield to a coupled doublet centered at 4.51 ppm and 4.60 ppm, respectively. Diketo derivative **7** also exhibited an epimerization reaction similar to that of **6**. The corresponding nuclear magnetic resonance data reveals similar shifts in the proton spectrum. Thus, if the same representative signals as compound **6** are compared, the coupled protons corresponding to H-6 occur as two doublets centered at 4.32 ppm and 4.50 ppm, respectively; both of these signals move slightly downfield to 4.40 and 4.58 ppm. The doublets of the vicinal hydrogen atoms H-3 and H-4, centered at 4.83 and 4.98 ppm, shift to higher fields as an *AB* system centered at 4.58 ppm (Scheme 3) after epimerization. It is worth noting that NMR data for **6** and **7** are in agreement for an *erythro* stereochemistry with respect to the isopropylidene group. The geminal coupling constants corresponding to H-6 (close to 18 Hz for both compounds) are diagnostic as can be observed for closely related compounds [12]. However, the respective signals of H-6 for the *threo* derivatives **18** and **19** are observed as a broad singlet (probably an *AB* system) and a distorted *AB* system, respectively.

Scheme 3



L-**18**, R = Tr
L-**19**, R = Ph_2tBuSi

6, R = Tr
7, R = Ph_2tBuSi

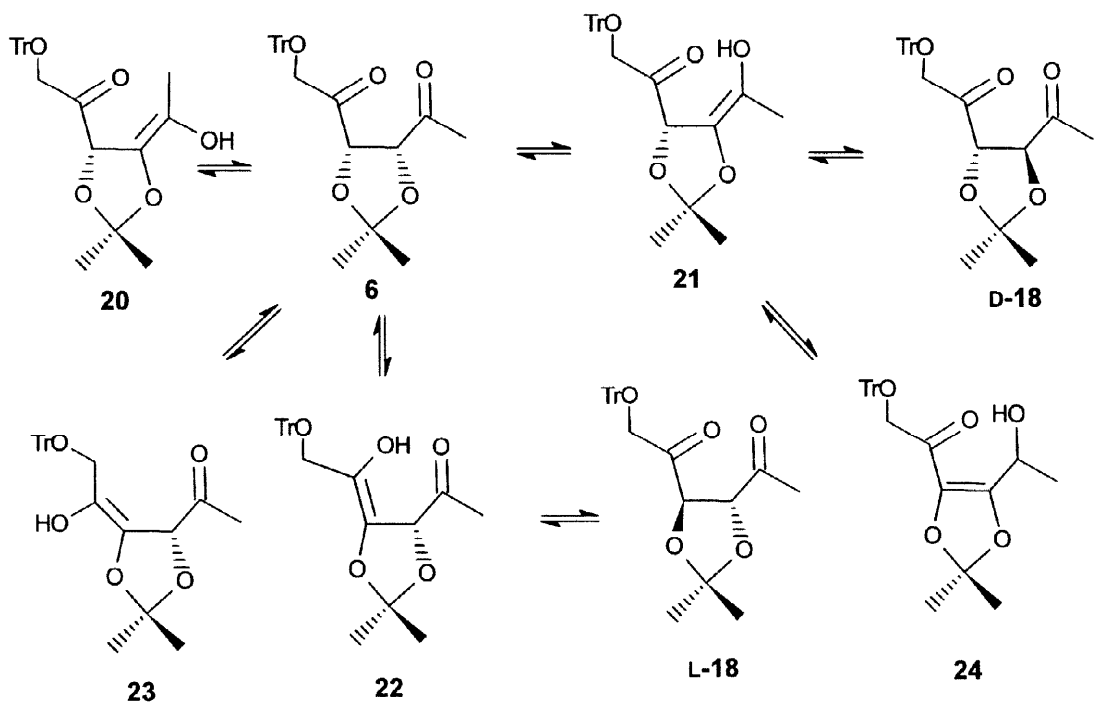
D-**18**, R = Tr
D-**19**, R = Ph_2tBuSi

In order to rationalize the propensity for racemization of **6**, the heat of formation values for all intermediates (Scheme 4) involved in this process were calculated. Molecular modeling studies [31,32] on these species would provide an estimation of the energy for the transition states to form enolic species that finally lead to the D or L series of the respective *threo* derivatives (compounds **D-18** and **L-18**, respectively). Consequently, the heat of formation for the lowest-energy conformer of **6** was −105.1 kcal/mol, while the calculated value for **D-18** were

very close, namely -102.3 kcal/mol. Two different enol intermediates may be postulated to epimerize C-3 forming the D-*threo* series, the Z enol (**20**) and the E enol (**21**). Surprisingly, the heats of formation for the lowest-energy conformers of these enols were not so high as expected, bearing in mind the exocyclic doble bond. The calculated enthalpy values were –96.3 and –96.9 kcal/mol, respectively. The epimerization *via* the E-enol **22** seems to be the preferred route for this transformation. The minimized-energy conformer of enol **22** presented a heat of formation of –100.9 kcal/mol. On the other hand, the corresponding calculated value for the Z-enol **23** was –97.0 kcal/mol. Surprisingly, the calculated heat of formation for the α,β-unsaturated ketone **24** (-96.5 kcal/mol) was close to the values of the other intermediates. Considering all the lowest-energy conformers for the species involved in the epimerization process, especially **6**, **D-18** and **22**, there is good reason to believe that the activation energy for the respective transition state in the course of enolization should be sufficiently low to smoothly produce the epimeric product (Scheme 4).

It is worth pointing out that when **7** (including the isomeric mixture **D/L-19**) was treated with sodium borohydride in tetrahydrofuran, diol **16** was recovered but with a significant loss of optical purity (close to 35%), clearly indicating the racemization course discussed. The epimeric diol **17** was not detected in this reduction. The more polar diols (**25** and **26**; see Experimental Section) that were produced under these reaction conditions were not further characterized.

Scheme 4



It can be concluded that 1,4-diketo-2,3-chiral compounds are important precursors to prepare different carbocyclic rings but the tendency to isomerize under different reaction conditions as well as on standing limits their use as optically pure starting materials.

EXPERIMENTAL SECTION

Unless otherwise noted, chemicals were commercially available and used without further purification. Air and/or moisture sensitive reactions were carried out under a dry nitrogen atmosphere in flame dried glassware. Solvents were distilled before use. Pyridine was distilled from calcium hydride and stored over KOH pellets, dimethyl sulfoxide was distilled from calcium hydride and stored over freshly activated 3 Å molecular sieves, and tetrahydrofuran was distilled from sodium benzophenone ketyl.

Nuclear magnetic resonance spectra were recorded using a Bruker AC-200 and a Bruker AM-500 spectrometers. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane. The ^{1}H-NMR spectra are referenced with respect to the residual $CHCl_3$ proton of the solvent $CDCl_3$ at 7.26 ppm. ^{13}C-NMR spectra were fully decoupled and are referenced to the middle peak of the solvent $CDCl_3$ at 77.0 ppm.

Melting points were determined using a Fisher-Johns apparatus and are uncorrected. IR spectra were recorded using a Nicolet Magna 550 spectrometer.

Low-resolution mass spectra were obtained on a VG TRIO 2 instrument at 70 eV (direct inlet). Positive ion fast-atom-bombardment mass spectra (FABMS) were obtained on a VG ZAB BEqQ spectrometer at an accelerating voltage of 8 kV and a resolution of 1000. NOBA was used as the sample matrix, and ionization was effected by a beam of cesium atoms.

Column chromatography separations were run using E. Merck silica gel (Kieselgel 60, 230-400 mesh). Analytical thin layer chromatography was performed employing 0.2 mm coated commercial silica gel plates (E. Merck, DC-Plaskitkfolien, Kieselgel 60 F_{254}) and was visualized by 254 nm UV or by immersion into an ethanolic solution of 5% H_2SO_4.

Elemental analyses were performed by UMYMFOR (Facultad de Ciencias Exactas y Naturales-CONICET). The results were within ± 0.4% of the theoretical values except where otherwise stated.

2,3-*O*-Isopropylidene-D-1,4-ribonolactone (9).

A solution of 1,4 D-ribonolactone (compound **8**; 4.00 g, 27.0 mmol) in acetone (160 mL) was treated with concentrated hydrochloric acid (1.6 mL). The reaction mixture was stirred at room

temperature for 18 h. The mixture was partitioned between a saturated aqueous solution of sodium bicarbonate (200 mL) and methylene chloride (150 mL). The aqueous phase was extracted with methylene chloride (3 x 100 mL). The combined organic layers were washed with brine (2 x 200 mL), dried ($MgSO_4$), and the solvent was evaporated to afford 4.125 g (81% yield) of pure compound **9** as a white solid that was used in the next step without further purification: mp 138-139 °C. Lit. [22] mp 138-139 °C; $[\alpha]_D$ -128.2° (*c* 0.35, MeOH). Lit. [22] $[\alpha]_D$ -65.7° (*c* 2.13, pyridine); ^1H NMR ($CDCl_3$) δ 1.38 (s, 3 H, C*Me*), 1.47 (s, 3 H, C*Me*), 2.63 (m, 1 H, -O*H*), 3.79 (ddd, J = 12.2, 5.5, 1.7 Hz, 1 H, H-5_a), 3.99 (ddd, J = 12.2, 5.2, 2.3 Hz, 1 H, H-5_b), 4.62 (t, J = 2.0 Hz, 1 H, H-4), 4.77 (d, J = 5.6 Hz, 1 H-3), 4.83 (d, J = 5.6 Hz, 1 H, H-2).

2,3-*O*-Isopropylidene-5-*O*-trityl-D-1,4-ribonolactone (10).

To a solution of compound **9** (2.20 g, 11.7 mmol) in pyridine (10 mL) was added trityl chloride (3.6 g, 12.9 mmol). The reaction mixture was stirred at room temperature for 3 days. The mixture was filtered and the white precipitate was washed with cold pyridine. The organic layer was evaporated and the residue was purified by column chromatography (silica gel) eluting with hexane-EtOAc (9:1) to afford 2.566 g (51% yield) of a white solid: mp 115-116 °C; $[\alpha]_D$ +5.0 (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) 3059, 2990, 2938, 1788, 1728, 1491, 1219, 1178,1082, 1001, 846, 706; ^1H NMR ($CDCl_3$) δ 1.33 (s, 3 H, C*Me*), 1.47 (s, 3 H, C*Me*), 3.09 (dd, J = 10.7, 1.7 Hz, 1 H, H-5_a), 3.72 (dd, J = 10.7, 2.6 Hz, 1 H, H-5_b), 4.43 (d, J = 5.6 Hz, 1 H, H-3), 4.58 (t, J = 2.0 Hz, 1 H, H-4), 4.97 (d, J = 5.6 Hz, 1 H, H-2); ^{13}C NMR ($CDCl_3$) δ 25.6, 26.8, 62.9, 75.8, 81.4, 113.2, 127.4, 128.1, 128.5, 142.9; MS (*m/z*, relative intensity) 430 (M^+, 25), 353 (22), 258 (15), 243 (100), 165 (59).

1-Deoxy-3,4-*O*-isopropylidene-6-*O*-trityl-α-D-psicofuranose (11).

To a solution of compound **10** (3.25 g, 7.55 mmol) in anhydrous tetrahydrofuran (60 mL) cooled at –78° C under nitrogen atmosphere was added 2.0 M methyllithium (9.5 mL, 17.2 mmol) dropwise over a period of 15 min. The reaction mixture was stirred at –78 °C for 2 h. then a saturated aqueous solution of ammonium chloride was added (40 mL). The mixture was allowed to warm to room temperature and was partitioned between brine (200 mL) and methylene chloride (70 mL). The aqueous phase was extracted with methylene chloride (3 x 70 mL). The combine organic layers were dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) employing hexane-EtOAc (9:1) as eluent to afford 3.050 g (91% yield) of pure compound **11** as a white solid: mp 55-57 °C; $[\alpha]_D$ +10.4° (*c* 0.13, $CHCl_3$); IR (KBr, cm^{-1}) 3422, 2988, 2938, 1491, 1450, 1375, 1211, 1157, 1072, 874, 704; ^1H NMR ($CDCl_3$) δ 1.34 (s, 3 H, C*Me*), 1.49 (s, 3 H, C*Me*), 1.51 (s, 3 H, H-1), 3.38 (d,

J = 3.9 Hz, 2 H, H-6), 4.25 (dt, J = 3.8, 1.6 Hz, 1 H, H-5), 4.50 (d, J = 5.9 Hz, 1 H, H-3), 4.81 (dd, J = 5.9, 1.5 Hz, 1 H, H-4), 7.14-7.48 (m, 15 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 22.00, 25.3, 26.7, 65.3, 82.5, 85.0, 87.1, 106.9, 112.5, 127.4, 128.0, 128.7, 142.9; MS (*m/z*, relative intensity) 446 (M^+, 1), 243 (100).

1-Deoxy-3,4-*O*-isopropylidene-6-*O*-trityl-D-allose (12) and 1-Deoxy-3,4-*O*-isopropylidene-6-*O*-trityl-D-altrose (13).

A solution of lactol **11** (2.40 g, 5.38 mmol) in tetrahydrofuran (100 mL) was treated with sodium borohydride (2.65 g, 70 mmol). The reaction mixture was stirred at room temperature overnight then water (150 mL) was added. The mixture was extracted with methylene chloride (3 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with hexane-EtOAc (7:3) to afford 600 mg (25% yield) of compound **12** as a white solid and 1.296 g (54% yield) of compound **13** as a colorless oil:

Compound **12**: mp 155-156 °C; $[\alpha]_D$ + 41.8° (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) 3219, 2984, 2933, 2870, 1450, 1380, 1221, 1074, 913, 880, 779, 712, 642; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.23 (s, 3 H, C*Me*), 1.28 (s, 3 H, *Me*), 1.30 (d, J = 6.0 Hz, 3 H, H-1), 3.17 (s, 1 H, -O*H*), 3.28 (dd, J = 9.9, 7.3 Hz, 1 H, H-6_a), 3.51 (dd, J = 9.9, 2.8 Hz, 1 H, H-6_b), 3.87 (ddd, J = 9.8, 7.5, 2.8, 1 H, H-5), 3.90 (dd, J = 9.1, 5.2 Hz, 1 H, H-3), 3.97 (dq, J = 9.1, 6.0 Hz, H-2), 4.05 (dd, J = 9.8, 5.2 Hz, 1 H, H-4), 7.20-7.46 (m, 15 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 20.3, 25.5, 28.0, 65.1, 65.2, 77.4, 82.5, 87.2, 108.5, 127.2, 127.9, 128.6, 143.7; MS (*m/z*, relative intensity) 433 (M^+-15, 0.2), 390 (0.5), 371 (1), 243 (100), 183 (10), 165 (38). Anal. Calcd. for $C_{28}H_{32}O_5$: C 74.98, H 7.19. Found C 75.06, H 7.34.

Compound **13**: $[\alpha]_D$ -1.5° (*c* 1.7, $CHCl_3$); IR (film, cm^{-1}) 3335, 3086, 3032, 2986, 2936, 1489, 1447, 1381, 1217, 1157, 1065, 1032, 889, 760, 700, 638; ^1H NMR ($CDCl_3$) δ 1.27 (d, J = 6.4 Hz, 3 H, H-1), 1.33 (s, 3 H, C*Me*), 1.36 (s, 3 H, C*Me*), 2.51 (d, J = 5.6 Hz, 1 H, -O*H*), 2.83 (br s, 1 H, -O*H*), 3.29 (dd, J = 9.5, 5.6 Hz, 1 H, H-6_a), 3.42 (dd, J = 9.7, 2.6 Hz, 1 H, H-6_b), 3.95-4.07 (m, 4 H, H-2, H-3, H-4 and H-5), 7.19-7.46 (m, 15 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 20.7, 25.2, 27.4, 65.1, 68.8, 77.0, 81.0, 87.0, 108.0, 127.1, 127.9, 128.6, 143.8; MS (*m/z*, relative intensity) 260 (7), 243 (2), 231 (4), 183 (23) 105 (43), 59 (89), 43 (100). Anal. Calcd. for $C_{28}H_{32}O_5$: C 74.98, H 7.19. Found C 75.02, H 7.37.

1-Deoxy-3,4-*O*-isopropylidene-6-*O*-trityl-D-*erythro*-hexo-2,5-diulose (6).

To a solution of oxalyl chloride (100 μL, 1 mmol) in anhydrous methylene chloride (10 mL) cooled at –70° C under nitrogen atmosphere was added dimethyl sulfoxide (170 μL). The mixture

was stirred 5 min. then diol **13** (224 mg, 0.5 mmol) in methylene chloride (5 mL) was added and the reaction was stirred for 15 min. Triethylamine (0.7 mL) was then added and the mixture was stirred for an additional 5 min. The mixture was allowed to warm to room temperature and water (30 mL) was added. The aqueous phase was reextracted with methylene chloride (30 mL). The combined organic layers were washed with brine (3 x 50 mL), dried ($MgSO_4$), and the solvent was evaporated to afford 220 mg (99% yield) of crude compound **6** as a colorless oil: $[\alpha]_D$ -0.0 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.35 (s, 3 H, C*Me*), 1.43 (s, 3 H, C*Me*), 2.22 (s, 3 H, H-1), 3.93 (d, *J* = 17.4 Hz, 1 H, H-6_a), 4.09 (d, *J* = 17.4 Hz, 1 H, H-6_b), 4.77 (m *AB*, *J* = 9.2 Hz, 2 H, H-3 and H-4), 7.20-7.49 (m, 15 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 25.4, 26.7, 68.7, 80.1, 82.2, 87.8, 111.5, 127.3, 128.0, 128.6, 143.1, 202.6, 206.1. The use of alcohol **12** as substrate led to the same diketo compound with similar yields.

2,3-*O*-Isopropylidene-5-*O*-(*tert*-butyldiphenylsilyl)-D-1,4-ribonolactone (14).

To a solution of lactone **9** (3.90 g, 20.7 mmol) in anhydrous dimethylformanide (10 mL) was added imidazole (3.10 g, 45.5 mmol) and *tert*-butyldiphenyl chlorosilane (6.30 g, 22.9 mmol) and the reaction mixture was stirred at room temperature overnight. The mixture was partitioned between water (100 mL) and methylene chloride (100 mL). The aqueous phase was reextracted with methylene chloride (100 mL), and the combined organic layers were washed with brine (5 x 100 mL), dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography eluting with hexane-EtOAc (19:1) to give 6.45 g (73% yield) of pure compound **14** as a white solid: mp 72-73 °C; $[\alpha]_D$ -6.2° (*c* 1.5, $CDCl_3$); IR (film, cm^{-1}) 3073, 2959, 28690, 1790, 1472, 1429, 1377, 1179, 1113, 980, 943, 824, 704, 505; ^1H NMR ($CDCl_3$) δ 1.07 (s, 3 H, SiC*Me*$_3$), 1.42 (s, 3 H, C*Me*), 1.50 (s, 3 H, C*Me*), 3.79 (dd, *J* = 11.6, 1.5 Hz, 1 H, H-5_a), 3.94 (dd, *J* = 11.5, 2.3 Hz, 1 H, H-5_b), 4.60 (t, *J* = 1.8 Hz, 1 H, H-4), 4.77 (d, *J* = 5.6 Hz, 1 H, H-3), 4.83 (d, *J* = 5.7 Hz, 1 H, H-2), 7.37-7.49 (m, 6 H, aromatic protons), 7.62-7.68 (m, 4 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 19.0, 25.5, 26.7, 63.5, 75.7, 78.3, 82.2, 113.0, 127.9, 130.1, 131.5, 132.3, 135.3, 135.5, 174.0.

1-Deoxy-3,4-*O*-isopropylidene-6-*O*-(*tert*-butyldiphenylsilyl)-α-D-psicofuranose (15).

A solution of compound **14** (2.050 g, 4.81 mmol) in anhydrous tetrahydrofuran (60 mL) cooled at –78 °C under nitrogen atmosphere was treated with 2.0 M methyllithium (6.0 mL). The reaction mixture was stirred at -78 °C for 2 h. The mixture was quenched as depicted for **10**. The residue was purified by column chromatography (silica gel) employing toluene-EtOAc (19:1) as eluent to yield 1.985 g (93% yield) of pure compound **15** as a colorless oil: $[\alpha]_D$ -9.2° (*c* 0.5, $CDCl_3$); IR (film, cm^{-1}) 3412, 3073, 2943, 2858, 1474, 1427, 1375, 1206, 1070, 929, 824, 705,

609. 496; ^{1}H NMR ($CDCl_3$) δ 1.09 (s, 9 H, SiC*Me*$_3$), 1.33 (s, 3 H, H-1), 1.48 (s, 3 H, C*Me*), 1.54 (s, 3 H, C*Me*), 3.66 (dd, *J* = 11.3, 2.9 Hz, 1 H, H-6$_a$), 3.84 (dd, *J* = 11.3, 2.8 Hz, 1 H, H-6$_b$), 4.18 (m, 1 H, H-5), 4.51 (d, *J* = 5.9 Hz, 1 H, H-3), 4.65 (s, 1 H, -O*H*), 4.82 (dd, *J* = 5.9, 1.3 Hz, 1 H, H-4), 7.36-7.50 (m, 6 H, aromatic protons), 7.63-7.70 (m, 4 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 19.1, 21.5, 25.2, 26.9, 65.7, 82.1, 86.0, 87.6, 106.7, 112.4, 114.8, 127.7, 128.0, 128.0, 130.2, 130.3, 135.6, 135.8. Anal. Calcd. for $C_{25}H_{34}O_5Si$: C 67.84, H 7.74. Found C 67.66, H 7.96.

1-Deoxy-3,4-*O*-isopropylidene-6-*O*-(*tert*-butyldiphenylsilyl)-D-allose (16) and 1-Deoxy-3,4-*O*-isopropylidene-6-*O*-(*tert*-butyldiphenylsilyl)-D-altrose (17).

A solution of lactol **15** (2.10 g, 4.74 mmol) in tetrahydrofuran (100 mL) was treated with sodium borohydride (1.50 g, 39.6 mmol). The reaction mixture was stirred at room temperature for 3 h then quenched as depicted for compounds **12** and **13**. The residue was purified by column chromatography (silica gel) eluting with toluene-EtOAc (9:1) to afford 590 mg of compound **16** (28% yield) as a white solid and 1.18 g (56% yield) of pure diol **17** as a colorless oil.

Compound **16**: R_f 0.43 (toluene-EtOAc, 4:1); mp 121 °C; $[\alpha]_D$ +34.9° (*c* 0.3, $CHCl_3$); IR (film, cm^{-1}) 3356, 2984, 2932, 2854, 1440, 1381, 1134, 1221, 1134, 1115, 1009, 966, 870, 826, 760, 713; ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 9 H, SiC*Me*$_3$), 1.20 (s, 3 H, C*Me*), 1.27 (s, 3 H, C*Me*), 1.31 (d, *J* = 5.6 Hz, 3 H, H-1), 3.41 (br s, 1 H, -O*H*), 3.70-4.11 (m, 6 H, H-2, H-3, H-4, H-5 and H-6), 4.15 (br s, 1 H, -O*H*), 7.37-7.41 (m, 6 H, aromatic protons), 7.63-7.70 (m, 4 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 19.2, 20.2, 25.4, 26.8, 27.9, 65.3, 69.7, 77.2, 82.4, 108.4, 127.9, 129.9, 132.8, 132.9, 135.4, 135.5; MS (*m/z*, relative intensity) 429 (M^+-15, 1); 329 (21), 241 (17), 199 (47), 193 (14), 181 (21), 163 (31), 59 (58), 43 (100). Anal. Calcd. for $C_{25}H_{36}O_5Si$: C 67.53, H 8.16. Found C 67.56, H 8.22.

Compound **17**: R_f 0.25 (toluene-EtOAc, 4:1); $[\alpha]_D$ -3.9° (*c* 1.7, $CHCl_3$); IR (film, cm^{-1}) 3439, 3073, 2932, 2858, 1480, 1371, 1217, 1111, 1059, 1007, 878, 824, 702, 615, 505; ^{1}H NMR ($CDCl_3$) δ 1.07 (s, 3 H, SiC*Me*$_3$), 1.29 (d, *J* = 6.4 Hz, 3 H, H-1), 1.32 (s, 3 H, C*Me*), 1.35 (s, 3 H, C*Me*), 2.48 (d, *J* = 6.2 Hz, 1 H, -O*H*), 2.89 (d, *J* = 4.4 Hz, 1 H, -O*H*), 3.77 (dd, *J* = 10.2, 5.2 Hz, 1 H, H-6$_a$), 3.89 (dd, *J* = 10.2, 2.6 Hz, 1 H, H-6$_b$), 3.98-4.20 (m, 4 H, H-2, H-3, H-4 and H-5), 7.25-7.44 (m, 6 H, aromatic protons), 7.64-7.70 (m, 4 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 19.3, 20.7, 25.1, 26.9, 27.4, 65.2, 65.5, 69.4, 76.4, 81.0, 108.1, 127.8, 127.8, 129.8, 133.0, 135.5, 135.5; MS (*m/z*, relative intensity) 429 (M^+-15, 1), 329 (27), 251 (19), 199 (75), 193 (27), 181 (28), 163 (46), 135 (36), 59 (74), 43 (100).

1-Deoxy-3,4-*O*-isopropylidene-6-*O*-(*tert*-butyldiphenylsilyl)-D-*erythro*-hexo-2,5-diulose (7).

To a solution of oxalyl chloride (0.7 mL, 70 mmol) in anhydrous methylene chloride (20 mL)

cooled at –70° C under nitrogen atmosphere was added dimethyl sulfoxide (1.2 mL). The mixture was stirred for 5 min at -70 °C then diol **17** (1.550 g, 3.5 mmol) in methylene chloride (10 mL) was added and the reaction mixture was stirred for 15 min. Triethylamine (4.9 mL) was then added and the mixture was stirred for an additional 5 min. The reaction was worked up as described for **6**, affording compound **7** in 95% yield: IR (film, cm^{-1}) 3073, 2959, 2932, 2858, 1739, 1724, 1474, 1427, 1113, 822, 702, 621; ^1H NMR ($CDCl_3$) δ 1.09 (s, 9 H, SiC*Me*$_3$), 1.39 (s, 3 H, C*Me*), 1.48 (s, 3 H, C*Me*), 2.23 (s, 3 H, H-1), 4.32 (d, J = 17.9 Hz, 1 H, H-6_a), 4.50 (d, J = 17.9 Hz, 1 H, H-6_b), 4.83 (d, J = 7.0 Hz, 1 H, H-3), 4.98 (d, J = 7.1 Hz, 1 H, H-4), 7.35-7.44 (m, 6 H, aromatic protons), 7.62-7.70 (m, 4 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 19.2, 25.4, 26.8, 68.7, 79.8, 82.2, 110.2, 127.7, 127.9, 130.0, 135.5; MS (*m/z*, relative intensity) 427 (0.4), 367 (1), 327 (3); 309 (5), 267 (6), 241 (16), 199 (54), 83 (41), 43 (100).

(±)-1-Deoxy-3,4-*O*-isopropylidene-6-*O*-(*tert*-butyldiphenylsilyl)-allose ((±)-16).

A solution of compound **7** (70 mg, 0.16 mmol) in tetrahydrofuran (10 mL) was treated with sodium borohydride. The reaction mixture was stirred for 3 h. After the usual workup, the residue was purified by column chromatography (silica gel) eluting with toluene-EtOAc (9:1) to afford 25 mg of partially racemized **16**, 20 mg of diol **25**, and 15 mg of diol **26**. The less polar product presented the same spectroscopic properties than **16** with the exception that the optical rotation value suffered a substantial value reduction: Compound **16**: R_f 0.47 (toluene-EtOAc, 9:1); $[\alpha]_D$ +22.7° (*c* 0.5, $CHCl_3$). Compound **25**: R_f 0.42 (toluene-EtOAc, 9:1); ^1H NMR ($CDCl_3$) δ 1.06 (s, 9 H), 1.27 (d, J = 6.2 Hz, 3 H), 1.34 (s, 3 H), 1.43 (s, 3 H), 2.86 (d, J = 6.5 Hz, 1 H), 3.02 (d, J = 3.8 Hz, 1 H), 3.72-3.79 (m, 2 H), 4.00-4.17 (m, 2 H), 4.28 (dd, J = 5.9, 1.5 Hz, 1 H), 7.35-7.44 (m, 6 H), 7.65-7.69 (m, 4 H); MS (*m/z*, relative intensity) 429 (M^+-15, 2), 329 (3), 251 (18), 199 (54), 163 (38), 59 (67), 43 (100). Compound **26**: R_f 0.37 (toluene-EtOAc, 9:1); ^1H NMR ($CDCl_3$) δ 1.06 (s, 9 H), 1.27 (d, J = 6.3 Hz, 3 H), 1.38 (s, 3 H), 1.53 (s, 3 H), 3.73 (dd, J = 9.5, 2.0 Hz, 1 H), 3.81 (d, J = 9.5 Hz, 1 H), 4.00 (m, 2 H), 4.32 (dd, J = 7.1, 1.2 Hz, 1 H), 7.34-7.44 (m, 6 H), 7.64-7.68 (m, 4 H); MS (*m/z*, relative intensity) 429 (M^+-15, 2), 411(2), 329 (6), 251 (73), 199 (81), 193 (40), 163 (50) 59 (72), 43 (100).

1-Deoxy-3,4-*O*-isopropylidene-6-*O*-trityl-D-*threo*-hexo-2,5-diulose (18).

Compound **6** isomerized partially to the *threo* derivative on standing: ^1H NMR ($CDCl_3$) δ 1.25 (s, 3 H, C*Me*), 1.34 (s, 3 H, C*Me*), 2.24 (s, 3 H, H-1), 4.16 (br s, 2 H, H-6), 4.51 (d, J = 5.5 Hz, 1 H, H-3), 4.60 (d, J = 5.5 Hz, 1 H, H-4), 7.14-7.49 (m, 15 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 26.0, 26.1, 67.8, 79.6, 80.1, 87.1, 127.3, 128.0, 128.7, 143.2.

1-Deoxy-3,4-*O*-isopropylidene-6-*O*-(*tert*-butyldiphenylsilyl)-*threo*-hexo-2,5-diulose (19).

Compound **7** partially epimerized to compound **19** on standing: IR (film, cm^{-1}) 3072, 3049, 2690, 2934, 2858, 1792, 1734, 1645, 1589, 1427, 1383, 1113, 862, 824, 743, 702, 611; ^1H NMR ($CDCl_3$) δ 1.10 (s, 9 H, SiC*Me*$_3$), 1.24 (s, 3 H, C*Me*), 1.33 (s, 3 H, C*Me*), 2.23 (s, 3 H, H-1), 4.40 (d, J = 5.8 Hz, 1 H, H-3), 4.58 (d, J = 5.6 Hz, 1 H, H-4), 4.58 (m *AB*, 2 H, H-6), 7.35-7.44 (m, 6 H, aromatic protons), 7.59-7.69 (m, 4 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 19.27, 25.96, 26.57, 67.73, 79.31, 81.63, 112.58, 127.67, 127.80, 129.91, 132.71, 134.78, 135.60; FABMS (*m/z*, relative intensity) 479 (M^+ + K, 100).

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