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Inverse stereoselectivity in the nucleophilic attack on five-membered ring oxocarbenium ions. Application to the total synthesis of 7-*epi*-(+)-goniofufurone

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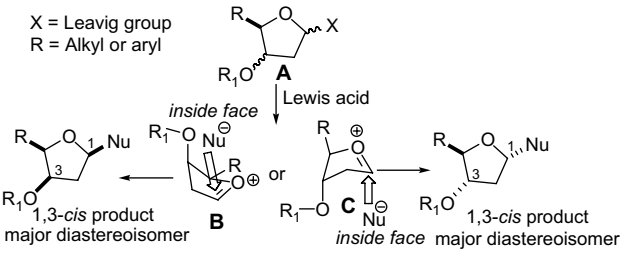
This work is dedicated to the memory of Pily

ABSTRACT

A highly stereoselective nucleophilic substitution at the anomeric position of 1,2-*O*-isopropylidene furanose derivatives was employed for the synthesis of 7-*epi*-(+)-goniofufurone and two of its stereoisomers. According to Woerpel's model, the stereoselectivity depends essentially on stereoelectronic factors that lead to a preferred nucleophilic attack on the *inside face* of the five-membered ring oxocarbenium ion in a folded conformation, whereby the stereochemical outcome generally is controlled by the substituent at the C3 position (OR group). Herein, we developed a strategy for a reverse stereoselective nucleophilic substitution, by placing an acetyl group at the C5 position of the *xylo*furanose ring, leading now to the nucleophilic approach on the *outside face* of the respective oxocarbenium ion. With this methodology, starting from diacetone-D-glucose derivative, we were able to achieve in seven steps the total synthesis of the powerful anti-tumor compound 7-*epi*-(+)-goniofufurone in a remarkable overall yield of 33%.

1. Introduction

The C-glycosylation reaction of carbohydrate-furanose derivatives has emerged as a useful technology for the construction of a number of biologically important compounds.[1] With exception of a limited number of examples where the S_N2-type mechanism is proposed,[2] this reaction follows a S_N1-type mechanism.[3] Furthermore, the reaction is frequently highly stereoselective.[4] Initially, steric interactions were invoked to explain the stereoselectivity for this reaction,[5] however, those considerations were insufficient to explain several highly stereoselective reactions.[4] Then, an elegant stereoelectronic model formulated by Woerpel appeared and the mechanistic situation became clearer.[6] This model that is also known as *the inside attack model* postulates that: the nucleophilic substitution at the anomeric position occurs via a S_N1-type mechanism, where the nucleophilic attack takes place preferentially on the inside face of a five-membered ring oxocarbenium ion having a folded conformation (**B** or **C**, Scheme 1). This reaction gives the 1,3-cis-product as major diastereoisomer. Additionally, according to this model, the preferential pseudo-axial orientation of the alkoxyl group at the C-3 position plays a key role for the preferential nucleophilic approach on the inside face of the oxocarbenium ion (**B** or **C**).[7]



Scheme 1. Woerpel's model for the C-glycosylation in furanose derivatives.

Having this model in mind, we recently applied the nucleophilic substitution reaction at the anomeric position of 1,2-*O*-isopropylidene-D-*xylo*furanose derivative **1** for the synthesis of goniofufurone diastereoisomers **2** and **3** (Scheme 2).[8,9] The nucleophilic substitution reaction afforded **4** as the major diastereoisomer, with the stereochemistry in accordance with the expected preferential nucleophilic attack on the inside face of the oxocarbenium ion **D** (Scheme 2).

2. Results and discussions

Continuing with our efforts on the synthesis of goniofufurone diastereoisomers, we decided to apply the above strategy to the stereoselective transformation of the *ribo*furanose derivative **7** to **8** (presumably expected as the major diastereoisomer), which could

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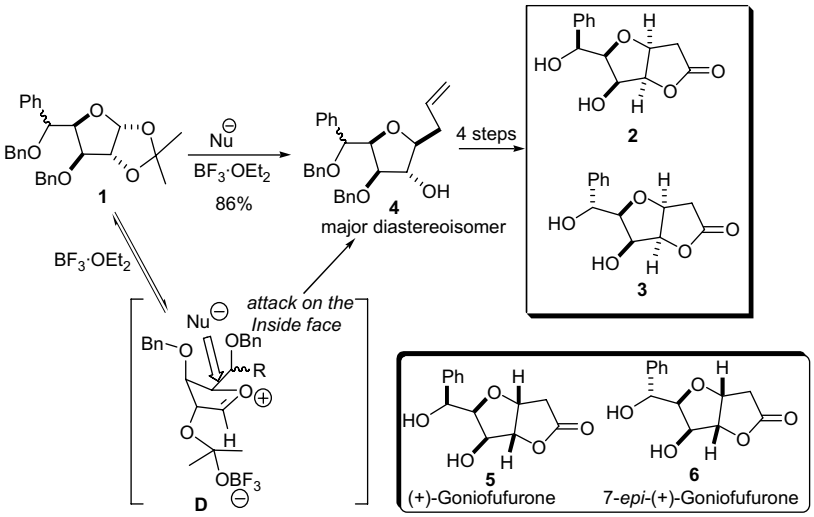
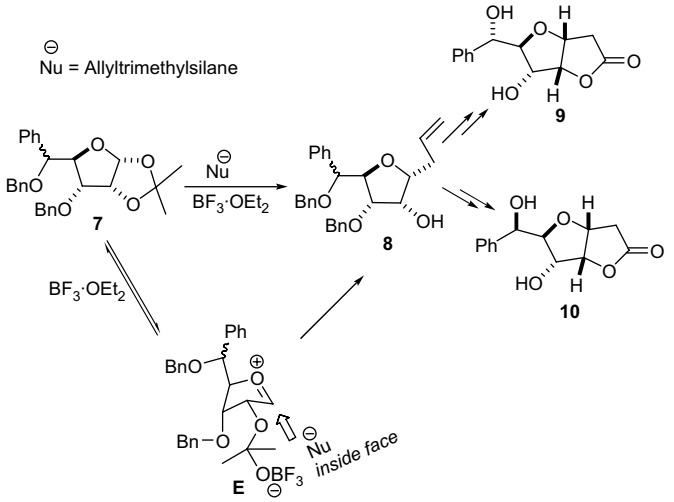


Scheme 2. Nucleophilic substitution of the *xylo*furanose derivative **1** for the synthesis of the goniofufurone diastereoisomers **2** and **3**.



Scheme 3. Synthetic strategy for the synthesis of goniofufurone diastereoisomers **9** and **10**.

then be converted into the goniofufurone diastereoisomers **9** and **10** (Scheme 3).

The *ribo*furanose derivatives **7a** and **7b** were obtained in two steps from diacetone-D-*allo*furanose **11**.[10] First, a sequential hydrolysis–oxidation–Grignard reagent addition (SHOGRA) procedure[11] was carried out whereupon the hydroxyl group was protected by treatment with benzylbromide and NaH (Scheme 4).

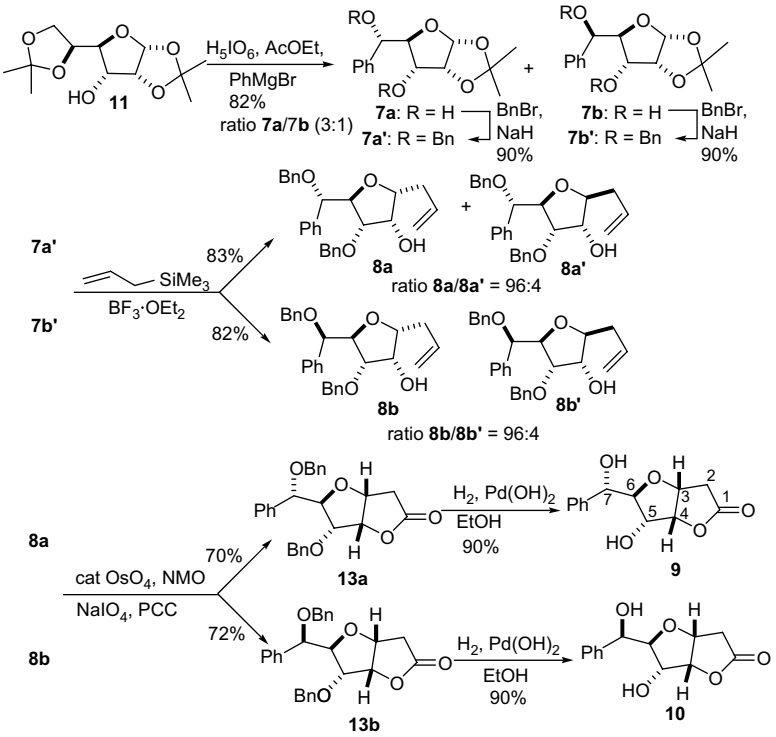
As expected, and in accordance with Woerpel's model, the treatment of **7a**′ and **7b**′ with allyltrimethylsilane in the presence of $BF_3{\cdot}OEt_2$ afforded **8a** and **8b** as the major diastereoisomers. The lactonization of **8a** and **8b** to **13a** and **13b** was achieved by a sequential dihydroxylation–dehomologation–oxidation procedure.[9] Finally a debenzylation of **13a** and **13b** with H_2 and $Pd(OH)_2$ afforded the goniofufurone diastereoisomers **9** and **10** (Scheme 4). The absolute stereochemistry of **10** was determined by comparison of its spectroscopic data.[12] Additionally, the stereochemistry of **9** was verified by single-crystal X-ray diffraction (Fig. 1).[13]

Having developed an accessible stereoselective route for the synthesis of the goniofufurone diastereoisomers **9** and **10**, we thought that it might be possible to prepare the naturally occurring goniofufurones **5** and **6** from **9** and **10** by inversion of the stereochemistry at the C5-OH group. Thus, we tried to selectively oxidize the C5-OH group with a number of oxidizing agents in order to stereoselectively reduce the formed carbonyl group. However, in all the cases the C7-OH group was always oxidized.[14] Changing the strategy, we reasoned that incorporating a temporal internal nucleophile in the *xylo*furanose derivative **14** could block the nucleophile approach on the favored *inside face* of the oxocarbenium ion **F**, inducing now a reverse nucleophilic attack to give **15** as the major diastereoisomer. Therefore, we concluded that an *O*-acetyl group at the C5 position (**14**) could provide the required internal nucleophile (Scheme 5).

It is important to mention that we chose to place the acetyl group at the C5 position rather than the C3 position, since a destabilizing effect of the acetyl or phosphate group at C3 on the cation center has been observed that inhibits the incorporation of an external nucleophile.[8,15]Additionally, another recent report has shown that an *O*-acetyl group participates effectively in the stereoselective nucleophilic addition to five-membered ring *N*-acyliminium ions to afford 5-substituted-2-pyrrolidinones.[16] With this new strategy in mind, we decided to apply it to the total synthesis of 7-*epi*-(+)-goniofufurone **6**,[17] which was recently found to be a more efficient cytotoxic agent against several neoplastic cell lines[18] than (+)-goniofufurone.

Compound **14** was stereoselectively obtained[19] in two steps from diacetone-D-glucose derivative **16** and then submitted to classical nucleophilic substitution conditions (vide supra). As planned, the nucleophilic substitution of **14** with allyltrimethylsilane and $BF_3{\cdot}OEt_2$ was highly stereoselective, affording the 1,3-trans-product **15** in high yield and as a single diastereoisomer (Scheme 6).

The completion of the synthesis of the 7-*epi*-(+)-goniofufurone is outlined in Scheme 6. The lactone **17** was prepared using the above sequential procedure (dihydroxylation–dehomologation–oxidation). The selective removal of the acetyl group was difficult to achieve, therefore, a basic hydrolysis protocol was applied, which led to lactone ring opening. However, the relactonization was achieved with DCC to give **18**. Finally, debenzylation with H_2 and $Pd(OH)_2$ afforded the 7-*epi*-(+)-goniofufurone in seven steps starting from diacetone-D-glucose derivative **16** in a remarkable overall yield of 33%.



Scheme 4. Synthesis of the goniofufurone diastereoisomers **9** and **10**.

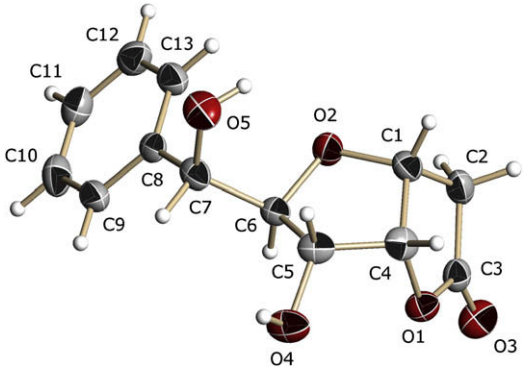


Figure 1. Perspective view of the molecular goniofufurone diastereoisomer **9**.

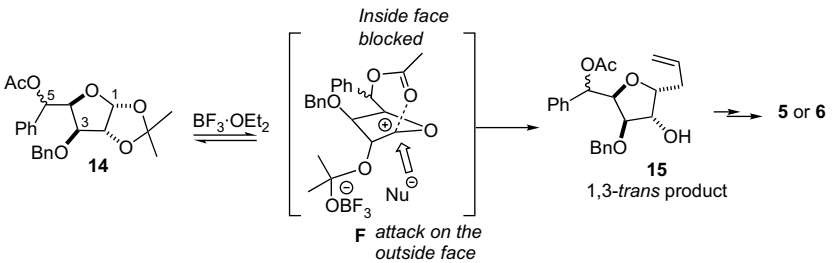
3. Conclusions

In conclusion, the success of the short and simple synthesis of the 7-*epi*-(+)-goniofufurone **6** and two of its diastereoisomers **9** and **10** depended on the development of a highly stereoselective nucleophilic substitution at the anomeric position of the *xylo*- and *ribo*furanose derivatives, and also on the adequate application of two sequential procedures. The above methodology is currently being used by our group in further syntheses of related biologically important compounds and will be reported soon.

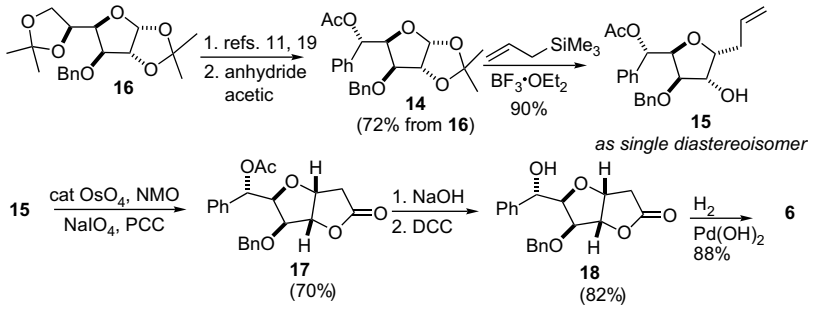
4. Experimental

4.1. General

The reagents were obtained from commercial sources and used without purification. The solvents were used as technical grade and freshly distilled prior use. NMR studies were carried out with 400 and 300 MHz spectrometers. TMS was used as internal reference for ^{1}H and ^{13}C NMR. Chemical shifts (δ) are stated in parts per



Scheme 5. Synthetic strategy for the synthesis of naturally occurring goniofufurones **5** or **6**.



Scheme 6. Synthesis of the 7-*epi*-(+)-goniofufurone **6**.

million (ppm). COSY, HSQC, and NOESY experiments have been carried out in order to assign the ^{1}H and ^{13}C spectra completely.

4.2. General protocol for the sequential hydrolysis–oxidation–Grignard reagent addition (SHOGRA) procedure[11]

A solution of diacetone-D-*allo*furanose **11** (0.8 mmol) and periodic acid (0.9 mmol) in 50 mL of dry ethyl acetate was stirred for 2 h, whereby a solid formed was separated by filtration. Evaporation under reduced pressured afforded a colorless syrup, which was dissolved in 10 mL of dry THF (Et_2O for the case of **16**[19]), and cooled to −30 °C. Then, phenyl magnesium bromide (21 mmol) was added and the reaction mixture was allowed to react for 6 h at the same temperature before adding a saturated solution of NH_4Cl (20 mL). The product was extracted with ethyl acetate (3×50 mL) and the solution dried over Na_2SO_4. The solution was evaporated under reduced pressure and the residue was purified by column chromatography.

4.3. (5*S*)-1,2-*O*-Isopropylidene-5-phenyl-α-D-*ribo*furanose (7a)

Yield 57%, mp=116–118 °C. $[\alpha]_D$ +25.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.36 (s, 3H), 1.55 (s, 3H), 2.26 (d, 1H, *J*=10.0 Hz), 2.60 (br, 1H), 3.99 (dd, 1H, *J*=3.6, 8.8 Hz), 4.08 (m, 1H), 4.58 (t, 1H, *J*=4.0 Hz), 4.81 (br, 1H), 5.82 (d, 1H, *J*=3.6 Hz), 7.36 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.6, 26.7, 71.8, 72.8, 78.7, 83.4, 103.9, 112.8, 126.5, 127.8, 128.3, 140.2. FABMS *m*/*z* (rel intensity) 267 ($[M+H]^+$, 18); FAB-HRMS *m*/*z* 267.1144 $[M+H]^+$ (calcd for $C_{14}H_{19}O_5$: 267.1145).

4.4. (5*R*)-1,2-*O*-Isopropylidene-5-phenyl-α-D-*ribo*furanose (7b)

Yield 25%, mp=130–132 °C. $[\alpha]_D$ +6.05 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35 (s, 3H), 1.55 (s, 3H), 4.03 (dd, 1H, *J*=4.0, 8.4 Hz), 4.06 (br, 1H), 4.56 (dd, 1H, *J*=4.0, 4.8 Hz), 4.98 (d, 1H, *J*=4.0 Hz), 5.78 (d, 1H, *J*=3.6 Hz), 7.37 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.9, 27.0, 71.6, 73.4, 79.4, 83.4, 103.9, 126.5, 128.2, 128.5, 128.3, 139.2. FABMS *m*/*z* (rel intensity) 267 ($[M+H]^+$, 22); FAB-HRMS *m*/*z* 267.1145 $[M+H]^+$ (calcd for $C_{14}H_{19}O_5$: 267.1145).

4.5. Typical hydroxyl group protection

To a suspension of corresponding 1,3-diol (1.5 mmol) and NaH (4.5 mmol) in dry THF (30 mL) was added dropwise benzylbromide (4.5 mmol) dissolved in THF (5 mL). The reaction mixture was allowed to react for 4 h at room temperature before adding 30 mL of water. The aqueous layer was extracted three times with CH_2Cl_2 (30 mL), the organic phase dried over Na_2SO_4, and concentrated in vacuo.

4.6. (5*S*)-3,5-Di-*O*-benzyl-1,2-*O*-isopropylidene-5-phenyl-α-D-*ribo*furanose (7a′)

Yield 90%, mp=84–86 °C. $[\alpha]_D$ +97.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.30 (s, 3H), 1.48 (s, 3H), 3.91 (dd, 1H, *J*=4.4, 8.8 Hz), 4.15 (d, 1H, *J*=12.4 Hz), 4.21 (dd, 1H, *J*=2.8, 8.8 Hz), 4.33 (d, 1H, *J*=11.7 Hz), 4.48 (d, 1H, *J*=3.2 Hz), 4.53 (m, 3H), 5.78 (d, 1H, *J*=3.6 Hz), 7.31 (m, 15H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.5, 26.7, 70.6, 72.0, 77.3, 77.8, 78.6, 81.8, 104.2, 112.7, 127.6, 127.8, 127.8, 128.0, 128.1, 128.2, 137.6, 137.8, 138.3. FABMS *m*/*z* (rel intensity) 447 ($[M+H]^+$, 14); FAB-HRMS *m*/*z* 447.2170 $[M+H]^+$ (calcd for $C_{28}H_{31}O_5$: 447.2172).

4.7. (5*R*)-3,5-Di-*O*-benzyl-1,2-*O*-isopropylidene-5-phenyl-α-D-*ribo*furanose (7b′)

Yield 90%, colorless oil. $[\alpha]_D$ +28.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.32 (s, 3H), 1.57 (s, 3H), 3.65 (dd, 1H, *J*=4.8, 8.4 Hz), 4.31 (d, 1H, *J*=12.0 Hz), 4.35 (d, 1H, *J*=12.0 Hz), 4.43 (m, 2H), 4.54 (m, 2H), 4.61 (d, 1H, *J*=12.0 Hz), 5.62 (d, 1H, *J*=3.6 Hz), 7.24 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.8, 27.1, 71.0, 71.8, 77.3, 77.6, 80.2, 82.1, 104.3, 113.0, 127.2, 127.6, 127.6, 127.9, 127.9, 128.0, 128.1, 128.1, 136.9, 137.3, 138.0. FABMS *m*/*z* (rel intensity) 447 ($[M+H]^+$, 22); FAB-HRMS *m*/*z* 447.2171 $[M+H]^+$ (calcd for $C_{28}H_{31}O_5$: 447.2172).

4.8. Typical acetylation reaction

To a solution of (5*S*)-1,2-*O*-isopropylidene-3-*O*-benzyl-5-phenyl-xylofuranose[19] in pyridine (2.5 mL) at 0 °C was added acetic anhydride (2.5 mL). The reaction mixture was allowed to react for 2 h at room temperature before adding dropwise an aqueous solution of HCl (1 N). After neutralization with HCl, it was extracted with EtOAc (3×50 mL), washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography.

4.9. (5*S*)-1,2-*O*-Isopropylidene-3-*O*-benzyl-5-phenyl-5-acetyl-α-D-*xylo*furanose (14)

Yield 92%, white solid, mp=121–123 °C. $[\alpha]_D$ +4.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.29 (s, 3H), 1.53 (s, 3H), 2.03 (s, 3H), 3.44 (d, 1H, *J*=4.4 Hz), 4.06 (d, 1H, *J*=15.6 Hz), 4.45 (m, 1H), 4.39 (d, 1H, *J*=15.6 Hz), 4.53 (d, 1H, *J*=4.0 Hz), 4.60 (d, 1H, *J*=4.4 Hz), 6.01 (d, 1H, *J*=5.2 Hz), 6.10 (d, 1H, *J*=12.0 Hz), 7.37 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.0, 26.2, 26.7, 72.2, 80.8, 81.2, 81.7, 105.1, 111.7, 127.5, 127.6, 127.9, 128.3, 128.4, 137.0, 138.2, 168.9. FABMS *m*/*z* (rel intensity) 399 ($[M+H]^+$, 20); FAB-HRMS *m*/*z* 399.1805 $[M+H]^+$ (calcd for $C_{23}H_{27}O_6$: 399.1808).

4.10. General procedure for the stereoselective substitution reaction of 1,2-*O*-isopropylidene-furanose derivatives

A solution of the corresponding 1,2-*O*-isopropylidene-furanose derivatives (2.0 mmol) in 50 mL of dry CH_2Cl_2 at 0 °C was treated with allyltrimethylsilane (4.0 mmol) and $BF_3{\cdot}OEt_2$ (4.0 mmol). The reaction mixture was warmed to room temperature and allowed to react for 4 h (20 h is necessary for compound **14**). The reaction mixture was treated with a saturated aqueous solution of $NaHCO_3$ (50 mL) and extracted with EtOAc (3×50 mL). The organic phase was dried with Na_2SO_4, concentrated in vacuo, and purified by column chromatography on silica gel.

4.11. (1′*S*,2*R*,3*R*,4*S*,5*R*)-2-Allyl-4-benzyloxy-5[(benzyloxy)-1′-phenyl-methyl]-tetrahydro-furan-3-ol (8a)

Yield 80%, white solid, mp=93–95 °C. $[\alpha]_D$ +23.0 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 2.41–2.49 (m, 2H), 3.75 (ddd, 1H, *J*=3.2, 7.2, 10.0 Hz), 3.87 (dd, 1H, *J*=3.6, 8.0 Hz), 4.00 (dd, 1H, *J*=4.8, 6.4 Hz), 4.22 (m, 3H), 4.33 (d, 1H *J*=11.2 Hz), 4.37 (d, 1H, *J*=4.8 Hz), 4.57 (d, 1H, *J*=11.2 Hz), 5.06 (m, 1H), 5.14 (m, 1H), 5.84 (m, 1H), 7.37 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.5, 70.2, 70.4, 72.4, 80.4, 80.7, 81.0, 83.1, 116.8, 127.0, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.2, 128.3, 128.4, 128.5, 128.6, 134.7, 137.1, 138.1, 138.2. FABMS *m*/*z* (rel intensity) 431 ($[M+H]^+$, 13); FAB-HRMS *m*/*z* 431.2223 $[M+H]^+$ (calcd for $C_{28}H_{31}O_4$: 431.2222).

4.12. (1′*R*,2*R*,3*R*,4*S*,5*R*)-2-Allyl-4-benzyloxy-5[(benzyloxy)-1′-phenyl-methyl]-tetrahydro-furan-3-ol (8b)

Yield 80%. $[\alpha]_D$ +90.4 (*c* 1.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 2.43 (m, 2H), 3.94 (ddd, 1H, *J*=4.4, 10.0, 13.6 Hz), 4.07 (m, 1H), 4.21 (m, 4H), 4.41 (d, 1H, *J*=16.4 Hz), 4.62 (m, 2H), 5.07 (m, 1H), 5.15 (m, 1H), 5.86 (m, 1H), 7.31 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 33.7, 70.6, 71.5, 72.1, 79.5, 81.6, 81.7, 84.5, 116.7, 127.0, 127.5, 127.6, 127.7, 127.9, 127.9, 128.3, 128.3, 128.4, 134.9, 137.0, 138.0, 138.3. FABMS *m*/*z* (rel intensity) 431 ($[M+H]^+$, 15); FAB-HRMS *m*/*z* 431.2225 $[M+H]^+$ (calcd for $C_{28}H_{31}O_4$: 431.2222).

4.13. (1′*S*,2*R*,3*R*,4*S*,5*R*)-2-Allyl-4-benzyloxy-5[(*O*-acetyl)-1′-phenyl-methyl]-tetrahydro-furan-3-ol (15)

Yield 90%. $[\alpha]_D$ +2.8 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 2.05 (s, 3H), 2.44 (m, 1H), 2.56 (m, 1H), 3.42 (dd, 1H, *J*=2.6, 4.4 Hz), 3.86 (m, 1H), 4.04 (dd, 1H, *J*=1.6, 2.8 Hz), 4.14 (d, 1H, *J*=11.2 Hz), 4.33 (d, 1H, *J*=11.2 Hz), 4.43 (dd, 1H, *J*=4.4, 8.4 Hz), 5.09 (br, 2H), 5.85 (m, 1H), 6.01 (d, 1H, *J*=8.0 Hz), 7.35 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.3, 38.0, 71.8, 75.3, 77.3, 82.1, 85.0, 85.6, 117.4, 127.5, 127.7, 127.8, 128.1, 128.2, 128.3, 134.2, 137.3, 137.5, 170.1. FABMS *m*/*z* (rel intensity) 383 ($[M+H]^+$, 12); FAB-HRMS *m*/*z* 383.1854 $[M+H]^+$ (calcd for $C_{23}H_{27}O_5$: 383.1858).

4.14. General procedure for the sequential dihydroxylation–dehomologation–PCC oxidation procedure

To a stirred solution of corresponding olefin (1.0 mmol) in 30 mL of a mixture of acetone/water (10:1) were added 4-methylmorpholine *N*-oxide (NMO, 2.0 mmol) and OsO_4 (0.08 mmol[20]). The reaction mixture was stirred for 2 h at room temperature before adding $NaIO_4$ (1.2 mmol) dissolved in 5 mL water. The reactions mixture was further stirred for 1 h at the same temperature. The solids formed were filtered off and the liquid mother solution was extracted with EtOAc (3×50 mL). The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was submitted to PCC (2 mmol) oxidation in CH_2Cl_2 for 4 h. The solids formed were filtered off and the liquid mother solution was evaporated under reduced pressure. The residue was purified by column chromatography.

4.15. (7*S*)-3,6-Anhydro-7,5-di-*O*-benzyl-2-deoxy-7-phenyl-D-*altro*-1,4-heptanolactone (13a)

Yield 70%. $[\alpha]_D$ +5.4 (*c* 0.8, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ: 2.64 (m, 2H), 4.15 (m, 2H), 4.18 (d, 1H, *J*=11.8 Hz), 4.35 (d, 1H, *J*=11.4 Hz), 4.41 (d, 1H, *J*=2.4 Hz), 4.55 (d, 1H, *J*=11.7 Hz), 4.57 (d, 1H, *J*=11.4 Hz), 4.8 (m, 2H), 7.35 (m, 15H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 36.5, 70.7, 72.6, 77.4, 78.9, 79.5, 81.0, 84.5, 127.5, 127.8, 127.9, 128.0, 128.1, 128.4, 137.1, 137.7, 137.8, 175.4. FABMS *m*/*z* (rel intensity) 431 ($[M+H]^+$, 11); FAB-HRMS *m*/*z* 431.1853 $[M+H]^+$ (calcd for $C_{27}H_{27}O_5$: 431.1858).

4.16. (7*R*)-3,6-Anhydro-7,5-di-*O*-benzyl-2-deoxy-7-phenyl-D-*altro*-1,4-heptanolactone (13b)

Yield 72%, mp=95–97 °C. $[\alpha]_D$ +12.8 (*c* 0.8, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 2.68 (m, 2H), 3.99 (t, 1H, *J*=4.8 Hz), 4.31 (m, 3H), 4.51 (m, 3H), 4.75 (dd, 1H, *J*=5.2, 8.8 Hz), 4.86 (t, 1H, *J*=5.2 Hz), 7.23 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 36.7, 71.3, 72.2, 77.6, 77.6, 81.2, 81.4, 86.0, 127.1, 127.5, 127.6, 127.7, 127.9, 128.1, 128.2, 128.3, 136.5, 136.8, 137.5, 175.1. FABMS *m*/*z* (rel intensity) 431 ($[M+H]^+$, 15); FAB-HRMS *m*/*z* 431.1859 $[M+H]^+$ (calcd for $C_{27}H_{27}O_5$: 431.1858).

4.17. (7*S*)-3,6-Anhydro-7-*O*-acetyl-5-*O*-benzyl-2-deoxy-7-phenyl-D-*ido*-heptono-1,4-lactone (17)

Yield 70%. $[\alpha]_D$ +18.8 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 2.05 (s, 3H), 2.74 (m, 2H), 3.72 (d, 1H, *J*=4.0 Hz), 4.25 (d, 1H, *J*=11.6 Hz), 4.33 (d, 1H, *J*=11.6 Hz), 4.48 (dd, 1H, *J*=4.0, 8.4 Hz), 4.79 (d, 1H, *J*=4.4 Hz), 5.07 (dt, 1H, *J*=4.4, 1.6 Hz), 6.04 (d, 1H, *J*=8.8 Hz), 7.32 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.2, 36.1, 72.8, 74.8, 77.6, 81.5, 82.7, 84.6, 127.7, 128.2, 128.5, 128.6, 128.7, 136.6, 136.7, 169.8, 175.2. FABMS *m*/*z* (rel intensity) 383 ($[M+H]^+$, 4), 323 ($[M+H-OAc]^+$, 34); FAB-HRMS *m*/*z* 323.1369 $[M+H-OAc]^+$ (calcd for $C_{20}H_{19}O_4$: 323.1383 $[M+H-OAc]^+$).

4.18. Procedure for removal of acetyl group

To a solution of **17** (0.2 g, 0.52 mmol) in methanol (2 mL) was added dropwise sodium hydroxide (1 mL, 1 M in water) at 0 °C. The reaction mixture was allowed to react for 5 min and rapidly was extracted with CH_2Cl_2 (3×15 mL), the organic phase was dried with Na_2SO_4, and the solvent was removed in vacuo. The residue was dissolved in 15 mL of CH_2Cl_2 and treated with DCC (0.109 g, 0.54 mmol) for 4 h at room temperature. The solids formed were filtered off and the liquid mother solution was evaporated under reduced pressure. The residue was purified by column chromatography with hexane/EtOAc (v/v=4:1).

4.19. (7*S*)-3,6-Anhydro-5-*O*-benzyl-2-deoxy-7-phenyl-D-*ido*-heptono-1,4-lactone (18)

Yield 82%, mp=146–148 °C; $[\alpha]_D$ +25.5 (*c* 0.5, $CHCl_3$); [lit.[18] mp=146–147 °C; $[\alpha]_D$ +39.9 (*c* 0.67, $CHCl_3$)]. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.70 (apparent d, 1H, *J*=4.0 Hz), 2.80 (apparent d, 1H, *J*=0.7 Hz), 3.90 (d, 1H, *J*=4.0 Hz), 4.23 (dd, 1H, *J*=6.4, 3.6 Hz), 4.42 (d, 1H, *J*=11.6 Hz), 4.53 (d, 1H, *J*=11.6 Hz), 4.88 (d, 1H, *J*=4.4 Hz), 5.02 (d, 1H, *J*=6.8 Hz), 5.08 (q, 1H, *J*=7.6 Hz), 7.33 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 35.9, 72.7, 72.8, 77.3, 81.9, 84.6, 85.1, 126.8, 127.7, 128.2, 128.3, 128.4, 128.6, 136.5, 139.6, 175.1. FABMS *m*/*z* (rel intensity) 323 ($[M-H_2O]^+$, 35); FAB-HRMS *m*/*z* 323.1286 $[M+H-H_2O]^+$ (calcd for $C_{20}H_{19}O_4$: 323.1283−H_2O).

4.20. General procedure for debenzylation reaction

Hydrogenolysis of the corresponding protected lactones (0.5 mmol) was carried out in methanol with 10% of $Pd(OH)_2$ (100 mg). It is important to mention that 100 psi is needed to accomplish the reactions with high yield.

4.21. (7*S*)-3,6-Anhydro-2-deoxy-7-phenyl-D-*altro*-1,4-heptanolactone (9)

Yield 90%, white solid, mp=121–123 °C. $[\alpha]_D$ +9.2 (*c* 1.0, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$,) δ: 2.69 (dd, 1H, *J*=1.6, 19.2 Hz), 2.79 (dd, 1H, *J*=6.0, 18.8 Hz), 3.97 (dd, 1H, *J*=3.2, 7.6 Hz), 4.37 (br, 1H), 4.80 (d, 1H, *J*=2.8 Hz), 4.87 (ddd, 1H, *J*=1.2, 4.8, 6.0 Hz), 4.95 (t, 1H, *J*=4.8 Hz), 7.35 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 37.0, 72.9, 73.1, 76.4, 82.8, 84.5, 126.3, 128.1, 128.4, 140.0, 174.5. FABMS *m*/*z* 251 ($[M+H]^+$, 5), 232 ($[M+H-H_2O]^+$, 14). Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.45; H, 5.82.

4.22. (7*R*)-3,6-Anhydro-2-deoxy-7-phenyl-D-*altro*-1,4-heptanolactone (10)[12]

Yield 90%. $[\alpha]_D$ +3.8 (*c* 0.6, $CHCl_3$) [lit.[18] $[\alpha]_D$ −32.4 (*c* 1.0, $CHCl_3$)]. ^{1}H NMR (400 MHz, $CDCl_3$, CD_3OD) δ: 2.75 (dd, 1H, *J*=1.2, 18.4 Hz), 2.76 (dd, 1H, *J*=6.0, 18.8 Hz), 4.03 (dd, 1H, *J*=4.4, 7.6 Hz), 4.21 (dd, 1H, *J*=4.4, 7.2 Hz), 4.78 (m, 2H), 4.91 (t, 1H, *J*=4.8 Hz), 7.33 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$, CD_3OD) δ: 37.0, 73.0, 74.1, 76.1, 83.6, 84.2, 126.4, 127.7, 128.0, 139.4, 175.7. FABMS *m*/*z* 251 ($[M+H]^+$, 9), 232 ($[M+H-H_2O]^+$, 14). Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.26; H, 5.70.

4.23. 7-*epi*-(+)-Goniofufurone (6)

Yield 88%, mp=200–203 °C. $[\alpha]_D$ +102 (*c* 0.5, EtOH) [lit.[18] mp=197–200 °C; $[\alpha]_D$ +108 (*c* 0.75, EtOH)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.72 (m, 2H), 4.20 (t, 1H, *J*=3.6 Hz), 4.36 (d, 1H, *J*=3.6 Hz), 4.87 (d, 1H, *J*=4.0 Hz), 5.07 (d, 1H, *J*=4.0 Hz), 5.11 (td, 1H, *J*=1.2, 5.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.6, 36.0, 72.6, 75.2, 83.1, 87.9, 126.5, 128.3, 128.6, 140.0, 175.0.

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