Enantiospecific Synthesis of Both Enantiomers of 2-Benzyloxydihydropyran-3-ones from Arabinose

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Abstract: Approaches to the enantioselective synthesis of the useful building blocks (2*R*)- and (2*S*)-2-benzyloxy-2(*H*)-pyran-3(6*H*)-one (**12** and **17**, respectively) are described. The most direct and highly yielding route for the synthesis of **12** was based on the 'one-pot' preparation of benzyl 2-*O*-acetyl-arabinopyranoside 3,4-thionocarbonates (**7** and **14**) from benzyl β-L- or β-D-arabinopyranosides (**1** and **13**). Trimethylphosphite-promoted olefination, followed by O-deacetylation and oxidation gave the optically pure enantiomeric enones **12** and **17** in about 50% overall yield.

Key words: enones, carbohydrates, stereoselective synthesis, chiral pool, olefination

Sugar enones (dihydropyranones) constitute a versatile category of carbohydrate compounds possessing synthetic utility.[1] The usefulness of sugar enones as chiral building blocks relies upon the fact that they posses olefinic and carbonyl unsaturations to which a number of well-established reactions may be applied.[2] In addition, because of the chiral environment generated by the remaining stereocenters, reactions to the enone system are usually highly diastereoselective.[2,3] Even though, the use of alkyl 3-enopyranosid-2-uloses as precursors of chiral molecules is somewhat limited as their synthesis from common monosaccharides requires several protection-deprotection steps with the consequent lowering of the yield.[4] We have overcome such a difficulty in the preparation of 2-alkoxypyran-3-ones derived from hexoses, via the corresponding 2-acyloxyglycal derivatives.[5] These compounds undergo a double allylic rearrangement by the tin(IV) chloride-promoted glycosylation to give optically pure 4-en-3-one derivatives in good yields. However, the same procedure applied to 2-acetoxyglycals derived from pentoses, led to dihydropyranones having enantiomeric excesses (ee) lower than 90%, unless a chiral alcohol is employed for the glycosylation.[6] In this case, a rather difficult separation of diastereoisomers by column chromatography was required. The sugar enones derived from pentoses proved to be excellent dienophiles in Diels–Alder reactions with butadienes[6] and cyclic dienes.[7,8] They have also been employed as Michael acceptors of thiols in the synthesis of glycosides of 3-deoxy-4-thiopyranosid-2-ulose and 3-deoxy-4-thiopentopyranosides.[9] In view of the synthetic usefulness of the chiral dihydropyranones derived from pentoses, we describe here direct approaches to the enantiospecific synthesis of both enantiomers of 2-benzyloxy-2(*H*)-pyran-3(6*H*)-one starting from L- and D-arabinose.

Benzyl β-L-arabinopyranoside (**1**) was readily prepared by Fischer glycosylation of L-arabinose. The conversion of the C-3,4 diol system of **1** into a double bond, via a disulfonyl derivative, required the selective protection of HO-2 (Scheme 1). For this reason, compound **1** was treated with acetone under acidic conditions to give the 3,4-*O*-isopropylidene derivative **2**, which was acetylated under standard conditions. Removal of the isopropylidene group of the resulting **3** with trifluoroacetic acid afforded the crystalline 2-*O*-acetyl derivative **4**, in about 84% yield from **1**. The 3,4-di-*O*-*p*-toluenesulfonylation (tosylation) of **4** was accomplished with a relatively good yield (72%) after a long reaction time (3 days). In fact, tosylation of methyl 2-*O*-benzoyl-β-L-arabinopyranoside with an excess of tosyl chloride gave 46% of the 3,4-di-*O*-tosyl derivative.[10] In contrast, the methylsulfonylation (mesylation) shoud be more readily accomplished.[11] As expected, the mesylation of **4** took place in a shorter time than the tosylation and the yield of the dimesylate **6** was higher (90%).

The conversion of the disulfonic ester derivatives **5** and **6** into a double bond was effected with a large excess of sodium iodide and zinc dust in refluxing DMF.[12,13] Thus, the ditosylate **5** led to the 3,4-unsaturated derivative **7**, which appeared, accompanied by the O-deacetylation product **8**. As the allylic alcohol **8** was the immediate precursor of the pyran-2-one, in further preparations the crude mixture of enopyranosides **7** and **8** was treated with methanolic sodium methoxide to give **8** as a single product. The same sequence applied to **6** led also to **8**, but the yield was around 10–15% lower than that obtained from **5**.

As an alternative method for the conversion of the vicinal diol system of **4** into an alkene, the Corey–Winter olefin synthesis was attempted.[14] Thus, compound **4** was treated with 1,1′-thiocarbonyldiimidazole to afford the thionocarbonate **9**. Desulfuration of the 1,3-dioxolane-2-thione ring with trimethylphosphite at 150 °C led to the expected alkene derivative **7**. For the successful conversion of **9** into **7** freshly distilled, anhydrous trimethylphosphite was required; as otherwise complicating byproduct formation (the orthoformate **11**) was observed.[15]

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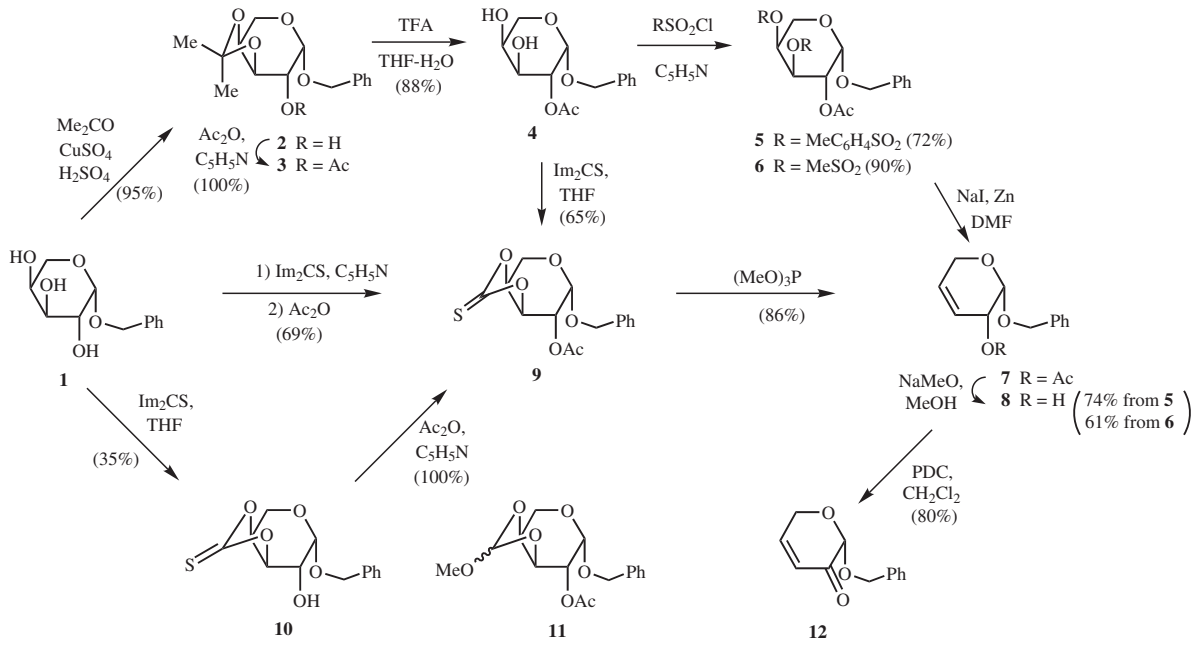


Scheme 1

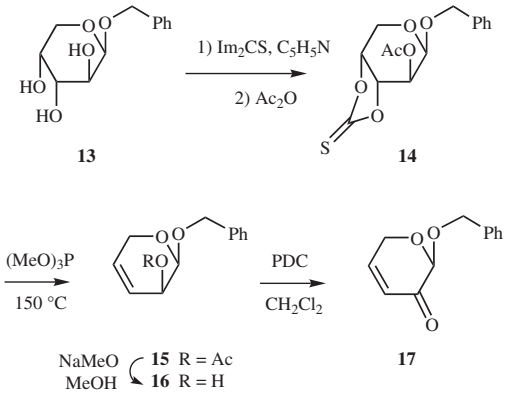
In order to avoid the protection-deprotection steps from **1** to **4**, we explored the possibility of preparing the 3,4-thionocarbonate directly from **1**. The relative orientation of HO-3 in **1** (*cis* to HO-4 and *trans* to HO-2) seems to be favorable for such a substitution. Therefore, compound **1** was treated with an excess of 1,1′-thiocarbonyldiimidazole and the reaction conditions were optimized. When conducted in either THF or acetonitrile, the reaction led to low yields (30–40%) of the expected thionocarbonate **10**. Furthermore, in contrast with **9**, the desulfurization of **10** with trimethylphosphite led to decomposition of the starting material. For this reason, compound **1** was directly converted into **9** by formation of the 3,4-thionocarbonate followed by in situ acetylation of HO-2. Pyridine proved to be a good solvent for both reactions, and **9** was obtained in approximately 70% yield from **1**. Subsequent desulfuration of **9** with trimethylphosphite afforded **7**, which was quantitatively O-deacetylated to give the allylic alcohol **8**.

The oxidation of **8** with activated manganese(IV) oxide[16] afforded the dihydropyranone **12** in low yield (ca. 40%). The success of such an oxidation critically depends on the method of preparation of the oxidant, and it is also sensitive to structural features of the starting alcohol.[16] Thus, similar to the alcohol function of **8**, the HO-3 of allal derivatives was resistant towards oxidation with MnO_2; whereas the HO-3 of glucal derivatives, which has the opposite configuration, was readily oxidized.[17] Noteworthy, compound **8** possesses, as the allal derivatives, the same stereochemical relationship between the HO group to be oxidized and the vicinal substituents. The crowding around the hydroxyl function could be the cause of the lower reactivity of these two compounds compared with that of glucal. Oxidation of **8** with pyridinium dichromate[18] (PDC) gave a better result. Although the reaction occurred slowly and required successive additions of the oxidant, the enone **12** was obtained in 80% yield. Thus, the route that involves the formation of the thionocarbonate **9** from **1**, its elimination to **8**, followed by oxidation, afforded satisfactorily the enone **12** in 47% overall yield.

On the other hand, the previous sequence applied to benzyl β-D-arabinopyranoside (**13**)[19] led to the dihydropyranone **17** in 52% overall yield (Scheme 2). The target enones **12** and **17** showed the same spectra as those described for the same products having ee >86%,[6] and their absolute values of optical rotation were higher. To confirm the enantiopurity of **12** and **17**, ^{1}H NMR studies were conducted using ytterbium tris[3-(heptafluoropropylhydroxy-methylene)-(+)-camphorate] as a chiral shift reagent.[20] The spectrum of **12**, recorded after successive additions of the lanthanide, showed a symmetric singlet for H-2, and no splitting for the signals of the other protons. Upon addition of **17** to the solution, lower field satellite signals appeared for the singlet of H-2, and for the signals corresponding to H-4, 5, 6 and 6′. The same experiments applied to **17** ensure the enantiomeric purity of both dihydropyranones **12** and **17** (ee >98%).

In conclusion, we describe here an efficient synthesis of enantiomerically pure (2*R*)- and (2*S*)-2-benzyloxy-2(*H*)-pyran-3(6*H*)-one (**12** and **17**) starting from benzyl β-L-arabinopyranoside (**1**) or its enantiomer **13**, respectively.

As **1** or **13** could be readily converted into the thionocarbonate derivatives **9** or **14**, selective protection and deprotection steps of the hydroxyl groups of **1** or **13** were avoided. The following desulfuration (olefination) and oxidation reactions were high yielding, and afforded **12** and **17** in 47% and 52% overall yield, respectively. These



Scheme 2

dihydropyranones may be employed for the synthesis of optically pure carbocyclic systems,[6–8] and highly modified 4-thiosugars.[9] The synthesis of **12** and **17** constitute also an additional example of the conversion of carbohydrate raw materials into enantiopure building blocks, in line with recent efforts on this aspect.[2b,21] Furthermore, the pyranone system has been found in natural products as, for example, in the D-glucose-derived antibiotic cortalcerone.[22]

Melting points were determined with a Fisher-Johns apparatus and are uncorrected. Analytical TLC was performed on Silica Gel 60 F254 (Merck) aluminum supported plates (layer thickness 0.2 mm) with solvent systems given in the text. Visualization of the spots was effected by exposure to UV light and charring with a solution of 5% H_2SO_4 in EtOH, containing 0.5% *p*-anisaldehyde. Column chromatography was carried out with Silica Gel 60 (230–400 mesh, Merck). Optical rotations were measured with a Perkin-Elmer 343 digital polarimeter, for solutions in $CHCl_3$. Nuclear magnetic resonance (NMR) spectra were recorded with a Bruker AC 200 or with a Bruker AMX 500 instruments, in $CDCl_3$ solutions using TMS as an internal standard. When necessary, the signals from the ^{13}C NMR spectra were assigned by DEPT experiments.

Benzyl β-L-Arabinopyranoside (1)

Compound **1** was prepared from L-arabinose following the procedure of Fletcher[19] for the D-enantiomer. The crude product was prutified by two successive recrystallizations from EtOH.

Mp: 170 °C (Lit.[19] 172–173 °C); $[\alpha]_D^{20}$ +212 (*c* 0.4, H_2O) {$[\alpha]_D$ –209 (*c* 0.4, H_2O) for the enanatiomer}.

Benzyl 3,4-*O*-Isopropylidene-β-L-arabinopyranoside (2)

To a stirred suspension of **1** (5.00 g, 20.83 mmol) and anhyd $CuSO_4$ (15.0 g) in anhyd acetone (200 mL) was added concentrated H_2SO_4 (0.25 mL) and the stirring was continued for 18 h. The mixture was treated as described by Fletcher[19] and the resulting syrup crystallized from hexane–Et_2O (3:1) to afford **2** (3.75 g, 64.3%). Flash chromatography (hexane–EtOAc, 8:1) of the residue obtained upon concentration of the mother liquors led to a second crop of crystals of **2** (1.79 g, overall yield 95.0%).

Mp: 56–57 °C (Lit.[19] 55–58 °C); $[\alpha]_D^{20}$ +210 (*c* 1.0 EtOH) {$[\alpha]_D^{20}$ –209 for the enantiomer}.

^1H NMR ($CDCl_3$): δ = 7.35 (m, 5 H, C_6H_5), 4.93 (d, 1 H, $J_{1,2}$ = 3.6 Hz, H-1), 4.79, 4.55 (2 d, 2 H, *J* = 11.7 Hz, PhCH_2), 4.21 (m, 2 H, H-3,4), 4.02 (dd, 1 H, $J_{4,5}$ = 2.2 Hz, $J_{5,5'}$ = 13.2 Hz, H-5), 3.92 (dd, 1 H, $J_{4,5'}$ = 1.2 Hz, H-5′), 3.80 (dd, 1 H, $J_{2,3}$ = 5.8 Hz, H-2), 1.56, 1.36 [2 s, 6 H, (CH_3)$_2$C].

^{13}C NMR ($CDCl_3$): δ = 136.9, 128.6, 128.2, 128.0 (C-Ar), 109.2 (Me$_2$*C*), 96.9 (C-1), 75.9, 72.9 (C-3,4), 70.0 (C-2), 69.7 (Ph*C*H$_2$), 59.8 (C-5), 27.9, 25.9 [(*C*H$_3$)$_2$C].

Benzyl 2-*O*-Acetyl-3,4-di-*O*-isopropylidene-β-L-arabinopyranoside (3)

To a solution of **2** (3.25 g, 11.61 mmol) in anhyd pyridine (3.0 mL) was added Ac_2O (3.0 mL) and the mixture was stirred overnight at r.t. The solvent was coevaporated with toluene to afford quantitatively syrupy **3** (3.74 g, 100%). The NMR spectra of this product showed that the compound was pure enough for use in the next step. Purification of a small mass of crude **3** by column chromatography (hexane–EtOAc, 19:1) afforded an analytical sample of **3**.

$[\alpha]_D^{20}$ +241.2 (*c* = 1.0, $CHCl_3$).

^1H NMR ($CDCl_3$): δ = 7.32 (m, 5 H, C_6H_5), 4.99 (d, 1 H, $J_{1,2}$ = 3.5 Hz, H-1), 4.91 (dd, 1 H, $J_{2,3}$ = 8.1 Hz, H-2), 4.73, 4.50 (2 d, 2 H, *J* = 12.2 Hz, PhCH_2), 4.37 (dd, 1 H, $J_{3,4}$ = 5.6 Hz, H-3), 4.26 (dt, 1 H, $J_{4,5}$ = $J_{4,5'}$ = 1.9 Hz, H-4), 4.01 (m, 2 H, H-5,5′), 2.08 (s, 3 H, CH_3CO), 1.54, 1.46 [2 s, 6 H, (CH_3)$_2$C].

^{13}C NMR ($CDCl_3$): δ = 170.5 (*C*O), 137.1, 128.5, 128.0, 127.6 (C-Ar), 109.4 (Me$_2$*C*), 95.2 (C-1), 73.6, 72.9, 72.2 (C-2,3,4), 69.5 (Ph*C*H$_2$), 58.8 (C-5), 28.0, 26.3 [(*C*H$_3$)$_2$C], 20.9 (*C*H$_3$CO).

Anal. Calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.39; H, 6.85.

Benzyl 2-*O*-Acetyl-β-L-arabinopyranoside (4)

To a stirred solution of crude **3** (3.85 g, 11.96 mmol) in THF–water (4:1, 45 mL) at 0 °C was added TFA (2.0 mL). The solution was allowed to warm to r.t. and the stirring was continued for 2 h. The solvent was removed at 50 °C under reduced pressure. The residue was dissolved in water (30 mL), neutralized with aq NH_3 and the solution extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to afford crystalline **4** (2.96 g, 87.8%).

Mp: 101 °C (hexane–Et_2O); $[\alpha]_D^{20}$ +239.6 (*c* 1.0, $CHCl_3$).

^1H NMR ($CDCl_3$): δ = 7.34 (m, 5 H, C_6H_5), 5.05 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-1), 5.01 (dd, 1 H, $J_{2,3}$ = 10.0 Hz, H-2), 4.72, 4.51 (2 d, 2 H, *J* = 12.3 Hz, PhCH_2), 4.07 (dd, 1 H, $J_{3,4}$ = 3.5 Hz, H-3), 3.99 (m, 1 H, H-4), 3.91 (dd, 1 H, $J_{4,5}$ = 1.3 Hz, $J_{5,5'}$ = 12.6 Hz, H-5), 3.74 (dd, 1 H, $J_{4,5'}$ = 2.0 Hz, H-5′), 2.09 (s, 3 H, CH_3CO)

^{13}C NMR ($CDCl_3$): δ = 171.6 (Me*C*O), 137.2, 128.4, 127.8, 127.6 (C-Ar), 95.7 (C-1), 71.6, 69.4 (2 C), 67.7 (C-2,3,4 and Ph*C*H$_2$), 62.4 (C-5), 20.9 (*C*H$_3$CO).

Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C, 59.56; H, 6.46.

Benzyl 2-*O*-Acetyl-3,4-di-*O*-*p*-tolylsulfonyl-β-L-arabinopyranoside (5)

To a stirred solution of the diol **4** (2.24 g, 7.94 mmol) in anhyd pyridine (10 mL) at 0 °C, was slowly added *p*-TsCl (5.49 g, 28.8 mmol). The mixture was stirred at r.t. for 3 d, when TLC (hexane–EtOAc, 2:1) showed a major product having R_f 0.52. After the addition of MeOH (10 mL) the mixture was stirred for 1 h and concentrated. Two successive additions of toluene and subsequent evaporations of the solvent led to a syrup. Purification by column chromatography (hexane–EtOAc, 3:1) afforded **5** (3.37 g, 71.9%).

Mp: 120 °C (EtOH); $[\alpha]_D^{20}$ +172.2 (*c* 1.0, $CHCl_3$).

^1H NMR ($CDCl_3$): δ = 7.78, 7.73 (2 d, 4 H, *J* = 8.3 Hz, C_6H_4Me), 7.23–7.33 (m, 9 H, C_6H_4Me and C_6H_5), 5.05 (d, 1 H, $J_{1,2}$ = 3.2 Hz, H-1), 5.02 (m, 2 H, H-3,4), 4.95 (dd, 1 H, $J_{2,3}$ = 10.5 Hz, H-2), 4.68, 4.46 (2 d, 2 H, *J* = 12.3 Hz, PhCH_2O), 3.92 (br d, 1 H, $J_{5,5'}$ = 13.3

Hz, H-5), 3.88 (br d, 1 H, H-5′), 2.47, 2.45 (2 s, 6 H, 2 × CH_3Ar), 1.76 (s, 3 H, CH_3CO).

^{13}C NMR ($CDCl_3$): δ = 169.5 (CO), 145.1, 136.6, 133.1, 129.9, 129.7, 128.4, 128.0, 127.9, 127.6 (C-Ar), 95.4 (C-1), 77.0, 72.9, 67.5 (C-2,3,4), 69.7 (Ph*C*H_2O), 60.6 (C-5), 21.7, 21.6 (*C*H_3Ar), 20.2 (*C*H_3CO).

Anal. Calcd for $C_{28}H_{30}O_{10}S_2$: C, 56.94; H, 5.12; S, 10.86. Found: C, 57.00; H, 5.20; S, 10.91.

Benzyl 2-*O*-Acetyl-3,4-di-*O*-methylsulfonyl-β-L-arabinopyranoside (6)

A solution of **5** (0.15 g, 0.53 mmol) in anhyd pyridine (2 mL) was cooled to 0 °C, and MsCl (0.10 mL, 1.28 mmol) was slowly added. The mixture was stirred at r.t. for 24 h, and then treated as described for the tosylation. The residue was subjected to flash column chromatography (hexane–EtOAc, 5:1) to give syrupy **6** (0.21 g, 90.1%).

$[\alpha]_D^{20}$ +172.0 (*c* 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 7.35 (m, 5 H, C_6H_5), 5.17 (d, 1 H, $J_{1,2}$ = 2.8 Hz, H-1), 5.13–5.11 (m, 3 H, H-2,3,4), 4.73, 4.54 (2 d, 2 H, *J* = 12.3 Hz, PhCH_2O), 4.00 (br d, 1 H, $J_{5,5'}$ = 13.4 Hz, H-5), 3.94 (dd, 1 H, $J_{4,5'}$ = 1.8 Hz, H-5′), 3.11, 3.15 (2 s, 6 H, 2 × CH_3SO_3), 2.04 (s, 3 H, CH_3CO)

^{13}C NMR ($CDCl_3$): δ = 169.5 (CO), 136.3, 128.6, 128.3, 128.0 (C-Ar), 95.4 (C-1), 77.0, 73.1, 67.7 (C-2,3,4), 70.0 (Ph*C*H_2O), 61.0 (C-5), 38.7, 38.5 (CH_3SO_3), 20.6 (*C*H_3CO).

Anal. Calcd for $C_{16}H_{22}O_{10}S_2$: C, 43.83; H, 5.06; S, 14.63. Found: C, 44.11; H, 5.18; S, 14.48.

Benzyl 2-*O*-Acetyl-3,4-dideoxy-α-D-*glycero*-pent-3-enopyranoside (7) and Benzyl 3,4-Dideoxy-α-D-*glycero*-pent-3-enopyranoside (8)

A vigorously stirred mixture of **5** (0.93 g, 1.57 mmol), NaI (11.5 g, 77 mmol), zinc dust (5.54 g, 85 mmol) and DMF (21 mL) was boiled for 2.5 h under reflux. The mixture was cooled to r.t., water (20 mL) was added and the suspension was filtered. The residue was washed successively with water (50 mL) and CH_2Cl_2 (3 × 50 mL). The liquids were extracted with CH_2Cl_2 (3 × 50 mL) and the extract dried ($MgSO_4$) and concentrated to a syrup, which showed by TLC (hexane–EtOAc, 2:1) two main spots (R_f 0.64 and 0.49). Column chromatography (hexane–EtOAc, 12:1) led first to the expected product **7** (0.21 g, 53.7%) and the following fractions of the column (R_f 0.49) gave the allylic alcohol **8** (65 mg, 20.0%).

Alternatively, compound **8** was obtained upon treatment of the crude mixture of enopyranosides **7** and **8**, prepared from **5** (0.93 g, 1.57 mmol), with NaOMe in MeOH (5 × 10^{-3} M, 10 mL). When TLC (hexane–EtOAc, 2:1) showed complete conversion of **7** into **8** (1.5 h), the reaction mixture was neutralized with Dowex 50W (H^+) resin, filtered and concentrated. Column chromatography led to pure **8** (0.24 g, 73.9% from **5**).

The last procedure when applied to the dimesylate **6** (0.23 g, 0.52 mmol), led to the enopyranoside **8** (66 mg, 61.1%).

7

$[\alpha]_D^{20}$ +132.3 (*c* = 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 7.33 (m, 5 H, C_6H_5), 5.95 (br dq, 1 H, $J_{3,4}$ = 10.5 Hz, $J_{2,3}$ = $J_{3,5}$ = $J_{3,5'}$ = 2.5 Hz, H-3), 5.69 (br dq, 1 H, $J_{3,4}$ = 10.5 Hz, $J_{2,4}$ = $J_{4,5}$ = $J_{4,5'}$ = 2.5 Hz, H-4), 5.30 (m, 1 H, H-2), 5.08 (d, 1 H, $J_{1,2}$ = 3.8 Hz, H-1), 4.83, 4.63 (2 d, 2 H, *J* = 12.3 Hz, PhCH_2O), 4.27 (dq, 1 H, $J_{2,5}$ = 2.5 Hz, $J_{5,5'}$ = 16.9 Hz, H-5), 4.09 (dq, 1 H, $J_{2,5'}$ = 2.5 Hz, H-5′), 2.08 (s, 3 H, CH_3CO).

^{13}C NMR ($CDCl_3$): δ = 170.4 (CO), 137.3, 129.2, 128.3, 127.8 (C-Ar), 127.7, 121.7 (C-3,4), 93.6 (C-1), 69.7 (Ph*C*H_2O), 66.2 (C-2), 60.4 (C-5), 20.9 (*C*H_3CO).

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.50; H, 6.60.

8

Mp 69 °C (hexane); $[\alpha]_D^{20}$ +129.2 (*c* 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$–D_2O): δ = 7.36 (m, 5 H, C_6H_5), 5.81, 5.73 (2 m, 2 H, H-3,4), 4.97 (d, 1 H, $J_{1,2}$ = 4.0 Hz, H-1), 4.86, 4.64 (2 d, 2 H, *J* = 11.8 Hz, PhCH_2O), 4.19 (m, 2 H, H-2,5), 4.04 (ddd, 1 H, *J* = 2.9, 4.9, 17.3 Hz, H-5′).

^{13}C NMR ($CDCl_3$): δ = 137.2, 128.5, 128.0 (C-Ar), 127.0, 126.1 (C-3,4), 95.8 (C-1) 69.9 (Ph*C*H_2O), 64.1 (C-2), 60.2 (C-5).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.13; H, 6.82.

Benzyl 2-*O*-Acetyl-β-L-arabinopyranoside 3,4-Thionocarbonate (9)

a) Synthesis of 9 from 4

To a stirred solution of **4** (0.40 g, 1,42 mmol) in THF (5 mL) was added 1,1′-thiocarbonyldiimidazole (0.54 g, 3.03 mmol). The mixture was stirred at r.t. for 20 h, when TLC (hexane–EtOAc, 2:1) showed a main spot having R_f 0.52. The solvent was evaporated and the residue purified by flash chromatography (hexane–EtOAc, 4:1) to afford **9** (0.30 g, 65.3%).

Mp 123 °C (MeOH); $[\alpha]_D^{20}$ +238.3 (*c* 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 7.38–7.28 (m, 5 H, C_6H_5), 5.15 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-1), 5.09 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 7.4 Hz, H-3), 4.93 (m, 2 H, H-2,4), 4.72, 4.53 (2 d, 2 H, *J* = 12.1 Hz, PhCH_2O), 4.20 (br d, 1 H, $J_{4,5}$ < 1 Hz, $J_{5,5'}$ = 14.3 Hz, H-5), 4.03 (dd, 1 H, $J_{4,5'}$ = 2.9 Hz, H-5′), 2.08 (s, 3 H, CH_3CO).

^{13}C NMR($CDCl_3$): δ = 190.3 (CS), 169.6 (CO), 136.2, 128.6, 128.4, 127.8 (C-Ar), 94.0 (C-1), 79.3, 77.9 (C-3,4), 70.3 (Ph*C*H_2O), 69.8 (C-2), 57.0 (C-5), 20.6 (*C*H_3CO).

Anal. Calcd for $C_{15}H_{16}O_6S$: C, 55.55; H, 4.97; S, 9.89. Found: C, 55.62; H, 4.95; S, 9.99.

b) Synthesis of 9 from 1

A solution of **1** (1.50 g, 6.25 mmol) and 1,1′-thiocarbonyldiimidazole (1.5 g) in pyridine (15 mL) was heated to 80 °C under nitrogen, in a thick-walled sealed tube. Three successive 0.5 g portions of 1,1′-thiocarbonyldiimidazole were added every 10 h (total 3.0 g, 16.83 mmol). After an additional 10 h of heating (total 40 h) TLC revealed a main spot having the same movility as **10**. The mixture was cooled to 0 °C, and upon addition of Ac_2O (8 mL) was stirred overnight at r.t. The solution, which showed by TLC (hexane–EtOAc, 2:1) a main spot of R_f 0.52, was diluted with MeOH and concentrated. The syrup was chromatographed (hexane–EtOAc, 6:1) to give **9**, which crystallized from MeOH. Compound **9** (1.40 g, 69.1%) had the same properties as the product described in **a**).

Benzyl β-L-Arabinopyranoside 3,4-Thionocarbonate (10)

Compound **1** (0.80 g, 3.33 mmol) was treated with 1,1′-thiocarbonyldiimidazole under the conditions described for the preparation of **9** from **4**, affording **10** (0.33 g, 35.1%). Syrupy **10** (R_f 0.42, hexane–EtOAc, 1.5:1) crystallized upon standing and it was recrystallized from *i*-PrOH–hexane.

Mp 94 °C; $[\alpha]_D^{20}$ +172.1 (*c* = 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$–D_2O): δ = 7.36–7.34 (m, 5 H, C_6H_5), 5.04 (dd, 1 H, $J_{2,3}$ = 5.6, $J_{3,4}$ = 7.7 Hz, H-3), 4.96 (dd, 1 H, $J_{4,5}$ = 2.0 Hz, $J_{4,5'}$ = 0.9 Hz, H-4), 4.94 (d, 1 H, $J_{1,2}$ = 4.1 Hz, H-1), 4.81, 4.61 (2 d, 2 H, *J* = 11.6 Hz, PhCH_2O), 4.09 (dd, 1 H, $J_{5,5'}$ = 14.0 Hz, H-5), 4.02 (dd, 1 H, H-5′), 3.99 (dd, 1 H, H-2).

^{13}C NMR ($CDCl_3$): δ = 190.8 (CS), 136.2, 128.7, 128.5, 128.2 (C-Ar), 94.2 (C-1), 79.2, 79.0 (C-3,4), 70.1 (Ph*C*H_2O), 65.7 (C-2), 58.7 (C-5).

Anal. Calcd for $C_{13}H_{14}O_5S$: C, 55.31; H, 5.00; S, 11.36. Found: C, 55.26; H, 4.96; S, 11.46.

Synthesis of 7 and 8 from 9

Compound **9** (345 mg, 1.06 mmol) was dissolved in commercial (97%) trimethylphosphite (2 mL). Nitrogen was flushed through the solution and the tube was sealed and heated in a sand bath to 150 °C for 10 h. The solution was cooled and poured into sat. aq $NaHCO_3$ (20 mL) and stirred vigorously for 1 h. The mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined extracts were dried ($MgSO_4$) and concentrated. Column chromatography (hexane–EtOAc, 12:1) of the residue afforded the compound having R_f 0.64 (hexane–EtOAc, 2:1) identified as **7** (185 mg, 70.1%).

A byproduct was isolated from next fractions of the column (R_f 0.45). This product was characterized as benzyl 2-*O*-acetyl-3,4-(methylorthoformyl)-β-L-arabinopyranoside (**11**, 65 mg, 18.8%) on the basis of its spectral data.

^{1}H NMR ($CDCl_3$): δ = 7.36-7.30 (m, 5 H, C_6H_5), 5.81 (s, 1 H, HCO_3), 5.00 (d, 1 H, $J_{1,2}$ = 3.4 Hz, H-1), 4.80 (dd, 1 H, $J_{2,3}$ = 8.0 Hz, H-2), 4.72, 4.50 (2 d, 2 H, J = 12.2 Hz, PhCH_2O), 4.54 (dd, 1 H, $J_{3,4}$ = 5.7 Hz, H-3), 4.36 (dd, 1 H, $J_{4,5'}$ = 2.7 Hz, H-4), 4.05 (d, 1 H, $J_{4,5}$ < 1 Hz, $J_{5,5'}$ = 13.4 Hz, H-5eq), 3.99 (dd, 1 H, H-5′ax), 3.36 (s, 3 H, CH_3O), 2.07 (s, 3 H, CH_3CO).

^{13}C NMR ($CDCl_3$): δ = 170.4 (CH_3*C*O), 136.9, 128.5, 128.0, 127.6 (C-Ar), 115.6 (HCO_3), 94.8 (C-1), 73.5, 72.4, 71.6, 69.7 (C-2, 3, 4, Ph*C*H_2O), 58.3 (C-5), 52.2 (CH_3O), 20.8 (*C*H_3CO_2).

The same reaction conducted with freshly distilled trimethylphosphite led to 86.0% yield of **7**, and **11** was detected by TLC as a faint spot.

Compound **7** (0.40 g, 1.61 mmol) was deacetylated with NaOMe in MeOH (10 mL), as described above, to afford alcohol **8** (0.33 g) almost quantitatively.

(2*R*)-2-Benzyloxy-2*H*-pyran-3(6*H*)-one (12)

Compound **8** (315 mg, 1.53 mmol) was dissolved in anhyd CH_2Cl_2 (35 mL) and PDC (0.52 g) was added. The mixture was vigorously stirred for 15 h, when TLC (hexane–EtOAc, 2:1) showed a main spot having R_f 0.52 and some starting **8** (R_f 0.39) remaining. Two successive portions of PDC (0.15 g) were added, with stirring, over a period of 5 h. When no remaining **8** was detected by TLC (10 h), the mixture was filtered through a silica gel pad (CH_2Cl_2). Concentration of the eluant and further purification by flash chromatography (hexane–EtOAc, 10:1) afforded pure **12** (250 mg, 80.1%).

$[\alpha]_D^{20}$ +247.4 (*c* 1.2, $CHCl_3$).

^{1}H and ^{13}C NMR spectra identical as those described previously for the product having ee >86%.[6]

Oxidation of allylic alcohol **8** (150 mg, 0.73 mmol) with freshly prepared, activated MnO_2[23] (0.65 g) in Et_2O gave, after chromatographic purification, oily **12** (60 mg, 40.4%).

$[\alpha]_D^{20}$ +245.2 (*c* 1.0, $CHCl_3$).

Benzyl 2-*O*-Acetyl-β-D-arabinopyranoside 3,4-Thionocarbonate (14)

The one-pot procedure for the synthesis of **9** from **1**, applied to **13** (3.00 g, 12.5 mmol), afforded **14** (3.02 g, 74.6%).

Mp: 121–122 °C (MeOH); $[\alpha]_D^{20}$ –234.7 (*c* 1.0, $CHCl_3$).

Benzyl 2-*O*-Acetyl-3,4-dideoxy-α-L-*glycero*-pent-3-enopyranoside (15)

Heating compound **14** (1.86 g, 5.76 mmol) in freshly distilled trimethylphosphite (6 mL), under the conditions described for **9**, led to the enopyranoside **15** (1.28 g, 89.6%).

$[\alpha]_D^{20}$ –131.4 (*c* 2.1, $CHCl_3$).

Benzyl 3,4-Dideoxy-α-L-*glycero*-pent-3-enopyranoside (16)

NaOMe deacetylation of **15** (0.83 g, 3.36 mmol) gave **16** (0.69, 99.7%).

Mp 68 °C; $[\alpha]_D^{20}$ –132.3 (*c* 1.0, $CHCl_3$).

(2*S*)-2-Benzyloxy-2*H*-pyran-3(6*H*)-one (17)

Oxidation of **16** (0.63 g, 3.06 mmol) with PDC (1.61 g), as described for **8**, afforded **17** (0.49 g, 78.5%).

$[\alpha]_D^{20}$ –248.4 (*c* 1.4, $CHCl_3$).

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