Free radical reactions of carbohydrate derivatives in the synthesis of carbocyclic compounds

4.* Unusual cyclization of methyl 2-alkoxycarbonylmethylene-3,4-di-*O*-benzyl-6-bromo-6-deoxy-α-D-*ribo*-hexopyranoside and methyl 4-*O*-benzyl-6-bromo-3,6-dideoxy-2-methoxycarbonylmethylene-β-D-*erythro*-hexopyranoside

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The benzyloxy group at C(4) of the pyranose ring in 3,4-disubstituted and 3-deoxy carbohydrate derivatives affects the direction of intramolecular free-radical C(2)—C(6) cyclization. A possible mechanism of the formation of the tetrahydrofuran ring was proposed.

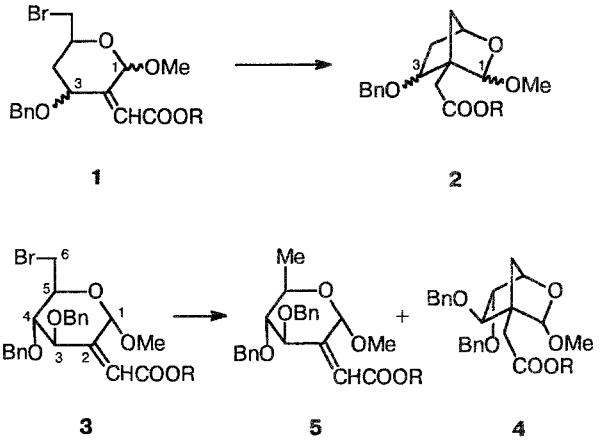
Key words: free radical reactions, carbohydrates, chiral cyclopentanes, chiral tetrahydrofurans.

It has been demonstrated in the previous works of this series[1,2] that the free-radical C(2)—C(6)-cyclization of the 4-deoxy derivatives **1** affords compounds of type **2** in a high yield, regardless of the configuration of the C(1) and C(3) centers; compounds **2** are key intermediates in the synthesis of chiral cyclopentanes. However, even for D-*arabino*-bromide (**3**), which bears a substituent at C(4), the reaction proceeds under more drastic conditions, and the yield of the cyclization product (**4**) is significantly lower than that of **2**, and a significant amount of the product of the direct reduction (**5**) is formed (Scheme 1**).[1]

In the present work, the preparation and cyclization of D-*ribo*-derivatives (**6** and **7**) (Scheme 2) is described. The cyclization unexpectedly afforded tetrahydrofuran derivatives **8** and **9**, which is probably related to the 1,5-migration of the hydrogen from the benzyl group at O(4) and the translocation of the radical[3,4] from C(6) to the benzyl group. The analogous cyclization of 3-deoxy derivative **10** (Scheme 3) gave the expected C(2)—C(6)-cyclization product **11**, which is similar to derivatives **8** and **9**, along with tetrahydrofuran **12**, in a ratio of 1:2, respectively.

Esters **6** and **7** (Scheme 2) were synthesized as follows: alcohol **13** prepared by the known procedure,[5]

Scheme 1



1 **2** **3** **5** **4**

after protection of its hydroxyl group with *p*-methoxybenzyl bromide, removal of the 4,6-*O*-benzylidene protection in ether **14** followed by tritylation of diol **15** and benzylation of ether **16** was transformed into ether **17**. Removal of the *O*-trityl group in the latter afforded alcohol **18** in good overall yield. The hydroxyl group in **18** was replaced by bromine by the action of triphenylphosphine and carbon tetrabromide in pyridine,[6] thus affording compound **19**.

Removal of the O—MPM group in **19** by ammonium cerium (IV) nitrate[7] gave the important intermediate bromide **20**. Finally, Swern oxidation[8] of **20** and the

* For Part 3, see Ref. 1.

** To make the spectral information comprehensible, the numbering of atoms in compounds **2**, **4**, **8**, **9**, **11**, **12**, **22**, **23**, and **26** is given as in the corresponing starting carbohydrates.

† Deceased.

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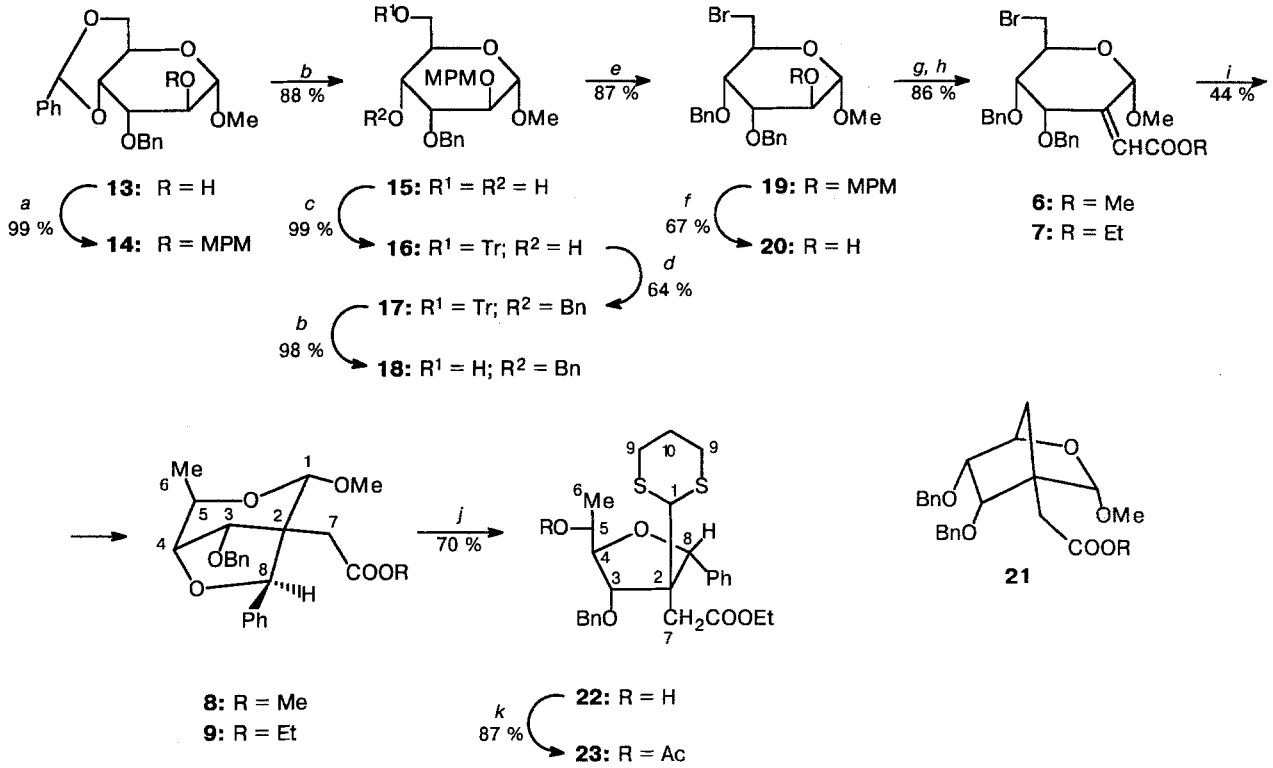
Scheme 2



Reagents and conditions: *a*. THF, NaH, MPMCl; *b*. THF, H_2O, CF_3COOH; *c*. Py, TrCl; *d*. DMSO, NaH, BnBr; *e*. Py, Ph_3P, CBr_4; *f*. CH_3CN, H_2O, CAN; *g*. CH_2Cl_2, −60 °C, $(COCl)_2$, DMSO, Et_3N, 1 *M* HCl; *h*. THF, $Ph_3PCHCOOR$; *i*. $PhCH_3$, Bu_3SnH, AIBN; *j*. CH_2Cl_2, $HS(CH_2)_3SH$, $ZnCl_2$, −30 °C; *k*. Py, Ac_2O.

reaction of the prepared ketone with the corresponding carbalkoxymethylenetriphenylphosphoranes afforded unsaturated esters **6** and **7**. The structures of all of the intermediate products were established by ^1H NMR.

The free-radical cyclization of esters **6** and **7** during tratment with tributyltin hydride gave **8** and **9** instead of the desired **21**. The striking difference between the ^1H and ^{13}C NMR spectra of the compounds obtained and those of D-*arabino*-analog[1] **4** indicated the unusual direction of the reaction. In the ^1H NMR spectra of compounds **8** and **9**, the CH_2 signals of one of the *O*-benzyl groups were absent, the number of aromatic protons was 10, the signal of an isolated proton was present in low field, and the signal of the C—Me group at 1.21 ppm had J = 6.5 Hz, which is characteristic for 6-deoxy sugars. Taking into account the structures of starting bromides **6** and **7**, one can assume that the methyl group is formed from CH_2Br. The ^1H NMR spectrum of **8** contains signals of the methoxyl group at C(1) (3.48 ppm) and of the methoxycarboxyl group (3.58 ppm), and the ^1H NMR spectrum of **9** contains the signals of the OEt group. This indicates that these centers are retained during the transformation of **6** and **7** into **8** and **9**. The presence of the characteristic doublets of the CH_2COOR protons at 2.32 and 2.07 ppm and the absence of the signal of the proton at C(2) allows one to conclude that the C(2) atom in **8** (**9**) is quaternary. However, the chemical shifts of these protons are rather high in comparison with those of analogs[1,2,7] of compound **21**.

In the ^{13}C NMR spectrum of **8**, only one signal at 71.55 ppm of the O—CH_2 group and five signals of the O—CH fragments are present, whereas there should be two and four signals, respectively, for the expected structure **21**. There is also a methyl group signal in the ^{13}C NMR spectrum of derivative **8**, the position of which (16.25 ppm) indicates its axial orientation.[9]

The nuclear Overhauser effect (NOE) data and the spectral characteristics of compounds **22** and **23** prepared by mercaptolysis of tetrahydrofuran **9** followed by acetylation, provide unequivocal confirmation of the structures of **8** and **9**.

Pre-irradiation of H(8) (δ 5.38 ppm) in **8** demonstrated its proximity to the protons of the phenyl groups (which made it possible to presume that it originates from one of the OCH_2Ph groups: either the one at C(3) or the one at C(4)). The H-8 proton is close to the

protons of the CH_2COOMe group (2.33 and 3.58 ppm, respectively) and to the H(4) or H(5) protons. Since the signals of the latter protons coincided, the question of the configuration of the C(8) center could not be unequivocally solved at this stage of the investigation. However, the absence of its interaction with H(3) allowed one to assume that the configuration of the C(8) center depicted in Scheme 2 is the most probable. Later, the configuration was established on the basis of the spectra of derivatives **22** and **23**.

Pre-irradiation of the H(1) proton (δ 5.00 ppm) is accompanied by a response of the protons of the methoxyl group at C(1) (which allows one to assign it unequivocally to H(1)) and by pronounced responses of the H(3) protons and the methyl group. In conjunction with the response of the H(3) and H(1) protons to the pre-irradiation of the methyl group, this fact suggests $^1C_4$-conformation of the pyranose ring, which is confirmed by small values of J for practically all of the ring protons of molecules **8** and **9**.

The experiment on pre-irradiation of one of the protons of the benzyl group (4.71 ppm) allowed us to make a very important conclusion. NOE was observed for one of the H(7) protons (2.08 ppm) and for the H(3) proton, but not for H(4). This phenomenon indicated unequivocally that the benzyloxy group is at C(3), therefore, the benzyloxy group at C(4) was involved in the cyclization, and the newly formed ring should be five-membered. The response of the H(3) proton to the pre-irradiation of the H(7) proton (2.57 ppm) was also an indication of this fact.

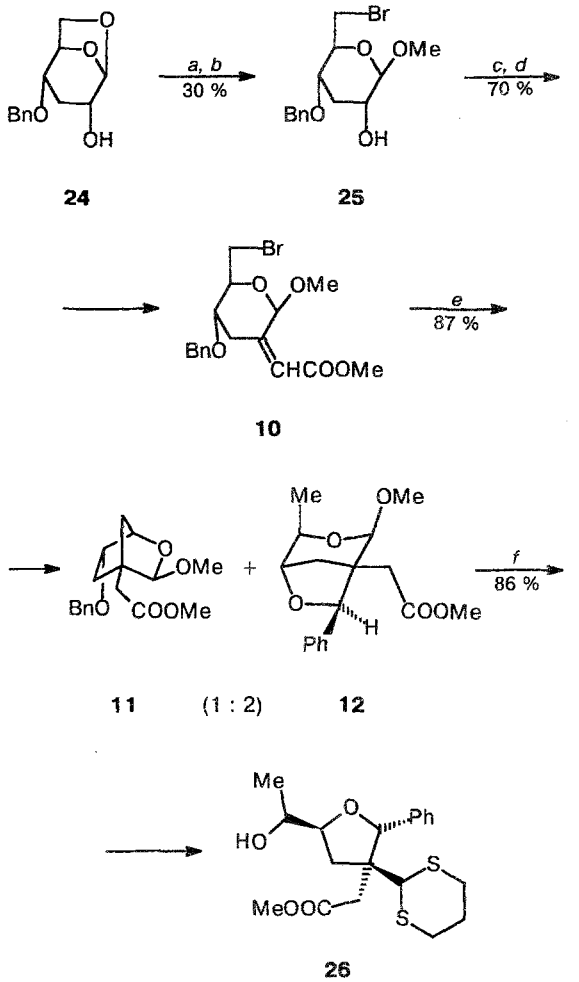
The opening of the glycoside cycle in **9** by 1,3-dimercaptopropane catalyzed by $ZnCl_2$ at −40 °C gave monocyclic derivative **22**. Acetate **23** was obtained by treatment of **22** with acetic anhydride in pyridine. Pre-irradiation of the H(8) proton both in compound **22** and in acetate **23** caused responses by H(5), H(6), and H(3); the latter of which is the most important. This allowed us to assign the configuration of the C(8) center in **22** and **23**, and, hence, in compounds **8** and **9**. Like in the case of compounds **8** and **9**, the pre-irradiation of one of the *O*-benzyl protons (4.90 or 4.93 ppm) in derivatives **22** and **23** caused a significant response by the H(1), H(3), and phenyl protons, giving additional confirmation of the presence of benzyloxy group at C(3).

Thus, the spectral data on compounds **8**—**23** allows one to establish their structures unequivocally.

The cyclization of the 3-deoxy analog of derivative **6**, *i.e.*, bromide **10**, obtained by four-step synthesis from alcohol **24** prepared according to the known procedure[10] (see Scheme 3) proceeds in a similar manner. However, the absence of the benzyloxy group at C(3) in **10** causes some changes in the course of the cyclization; a mixture of "normal" product **11** and tetrahydrofuran **12** in a ratio of 1 : 2 are the products.

All of the compounds have well-resolved and easily interpreted ^1H NMR spectra. Like in the previous case, the configuration of the C(8) center in compound **12**

Scheme 3

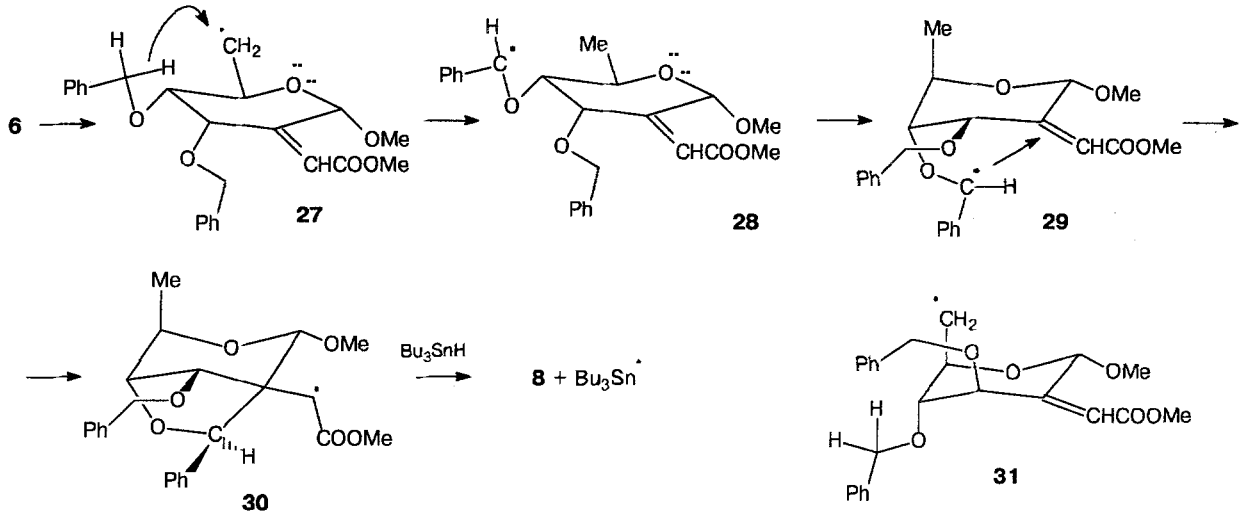


Reagents and conditions: *a*. MeOH + 5 % H_2SO_4; *b*. Ph_3P, CBr_4, Py; *c*. $(COCl)_2$, DMSO, CH_2Cl_2, −60 °C, Et_3N, 1 *M* HCl; *d*. $Ph_3PCHCOOMe$, THF; *e*. $PhCH_3$, AIBN, Bu_3SnH; *f*. CH_2Cl_2, $HS(CH_2)_3SH$, $ZnCl_2$, −30 °C.

was established by NOE for tetrahydrofuran **26** obtained by mercaptolysis of compound **12**. Pre-irradiation of the H(10) proton caused the effect only on the *ortho*-protons of the phenyl group, not on H(7,7'), whereas pre-irradiation of the H(1) proton caused responses by the H(9) and H(8) protons; this fact gave evidence for the configuration of the C(8) center in compounds **12** and **26**. Otherwise, the ^1H NMR spectra of compounds **11** and **12** are similar to the spectra of their analogs **8**, **22**, and **4** (see Ref. 1).

According to the available data, the anomalous course of the cyclization to afford tetrahydrofuran derivatives **8** and **9** may be explained as follows: in the intermediate radical **27** formed from bromide **6**, the action of Bu_3SnH causes a 1,5-hydrogen shift from the *O*-benzyl group at

Scheme 4



C(4). As the primary radical **27** is reduced, the more stable benzyl radical **28** is formed, and is stabilized by its conformational transformation into **29**. Subsequent attack on the unsaturated C(2) center leads to closure of the tetrahydrofuran ring, giving intermediate **30**, which is reduced by tributyltin hydride to derivative **8**. The tributyltin radical carries on the chain of transformations of bromide **6** into derivative **8**.

The 1,5-hydrogen shift in the radical reactions and the subsequent translocation of the radical are quite usual. Thus, Curran *et al.*[3,4] demonstrated that the similar shift was observed for the α-protons of benzyl derivatives, for acetals, and even for ethers. Other examples of the 1,5-hydrogen shift in free-radical reactions are also known.[11]

The reasons for these processes probably involve the interaction of the radical center and the unshared electron pairs of the neighboring oxygen atoms. Recently, in articles on the stereochemistry of radical centers in monosaccharide pyranose rings,[13,14] it was established that similar interactions were the most important factors, determining the conformation of the molecule. According to the published data, the disadvantage of the overlapping of the orbitals bearing unshared electrons with the orbitals bearing the unpaired electron of the radical center and the stabilization of the latter by conjugation with the σ-antibonding orbitals of the bonds in the β-position, significantly exceeds destabilization due to transition of the equatorial substituents to axial positions.

In the case of the cyclization of the *altro*-derivative in radical **27** (Scheme 4) the presented conformation seems the most probable, because the stabilization of the radical is achieved due to conjugation with the σ-antibonding orbitals of the C—H bonds of the benzyloxy group at C(4). The translocation of the radical from C(6) to the substituent at C(4) (with the formation of radical **28**) may occur as a result of the known stability of the benzyl radicals, and also as a result of the removal of the radical center from the unshared electron pairs of the exocyclic oxygen atom. The subsequent conformational transformation of the molecule, which affords radical **29** and gives additional possibilities for the stabilization of the radical due to conjugation with the π-orbitals of the multiple bond, becomes possible due to free rotation of the benzyloxy group around two σ-bonds. The capture of the unpaired electron by the multiple bond results in formation of radical **30**, and the reaction of the latter with tributyltin hydride affords furan derivatives, which are the final products of the cyclization.

It is interesting to note that during cyclization of *gluco*-analog[1] **3**, which differs from **6** only in the configuration of the C(3) center, the formation of the tetrahydrofuran derivative of type **8** was not observed. This can be explained by the fact that the radicals generated from the *gluco*-derivative are sterically hindered from taking the boat conformation due to the difference in the configuration at C(3) (*cf.* **27** and **31**). The substituent at C(4) in radical **31** is remote from the radical center, impeding the translocation of the radical and subsequent transformations, thus forming the tetrahydrofuran ring.

The data presented in this article demonstrate that monosaccaride derivatives may be one of the most favorable subjects for the investigation of the mechanism of intramolecular free-radical reactions due to their structural peculiarities.[12] The influence of other factors and, first, the effect of the C(3) and C(4) configurations, as well as the character of the substituents at C(3) and C(4) in bromides of type **6**, are the subjects of our further investigations.

Experimental

Melting points were measured on a heating stage in capillaries and are uncorrected. Specific rotations were measured with a Jasco DIP-360 polarimeter in chloroform. The ^{1}H NMR spectra were registered with a Bruker WM-250 spectrometer in $CDCl_3$. Signals in the proton spectra were assigned by homonuclear decoupling in the differential mode.

The reactions were monitored and the purity of the isolated compounds was determined by TLC on Kieselgel 60 silica gel plates. Chromatograms were sprayed with 5% H_2SO_4 in MeOH followed by heating to *ca.* 200 °C. Separation of the reaction mixtures was performed by column chromatography on Silpearl 60 silica gel (25—40 μm) in a benzene—ether eluent. The solvents for the reactions were distilled under argon over appropriate drying agents (CaH_2, $LiAlH_4$).

During free-radical cyclizations the solutions were evacuated to remove dissolved oxygen until a solvent began to boil and then the reactor was filled with argon.

Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-*p*-methoxybenzyl-α-D-*altro*-hexopyranoside (14). An 80 % suspension of NaH (0.8 g, 26.8 mmol) was added to a solution of alcohol **13** (5 g, 13.4 mmol) in anhydrous THF (50 mL), and the mixture was stirred until dissolution of NaH for *ca.* 4 h. Then MPMCl (3.2 g, 20.4 mmol; 2.7 mL) was added and the mixture was refluxed for 28 h with a reflux condenser (TLC control). The residual NaH was neutralized with dry ice, the precipitate of salts was filtered off through a SiO_2 layer, the solids were washed with $CHCl_3$ (50 mL), the filtrates were combined, and the solvent was removed. The syrup obtained was purified by chromatography on SiO_2 in a benzene—THF gradient. **14** (6.58 g, 99 %) was obtained as a syrup; $[\alpha]_D$ +10.92° (c 1.0, $CHCl_3$). ^{1}H NMR (δ, *J*/Hz): 4.68 (s, 1 H, H(1)); 3.70 (d, 1 H, H(2), $J_{2,3}$ = 3); 3.96 (t, 1 H, H(3), $J_{3,4}$ = 3); 4.05 (dd, 1 H, H(4), $J_{4,5}$ = 9); 4.42—3.62 (m, 3 H, H(5), H(6), H(6')); 5.62 (s, 1 H, H acetal); 4.85 and 4.75 (2 H, CH_2Ph, AB spin system, *J* = 13); 4.48 (s, 2 H, CH_2MPM); 3.45 (s, 3 H, OMe—C(1)); 3.84 (s, 3 H, OMe (MPM)); and 7.30 (m, 5 H, C_6H_5).

Methyl 3-*O*-benzyl-2-*O*-*p*-methoxybenzyl-α-D-*altro*-hexopyranoside (15). Compound **14** (6.58 g, *ca.* 13.4 mmol) was dissolved in a mixture of CF_3COOH (8 mL), H_2O (8 mL), and THF (16 mL). The mixture was kept at *ca.* 20 °C for 3.5 days, then it was neutralized with sodium bicarbonate, the product was washed from the precipitate of salts with chloroform (5×50 mL), and the solvent was removed. The residue was chromatographed on SiO_2 in a benzene—THF gradient. **15** (4.6 g, 88 %) was obtained as a syrup, $[\alpha]_D$ +65.5° (c 1.0, $CHCl_3$).

Methyl 3-*O*-benzyl-2-*O*-*p*-methoxybenzyl-6-*O*-trityl-α-D-*altro*-hexopyranoside (16). A solution of diol **15** (4.6 g, 11.4 mmol) in anhydrous pyridine (70 mL) was placed in a dry flask. Then TrCl (3.4 g, *ca.* 12 mmol) was added and the mixture was kept at *ca.* 20 °C for 3 days. The reaction mixture was poured into water (150 mL) and extracted with chloroform (2×150 mL); the organic layer was washed with H_2O (2×50 mL), then with HCl (1 *M*) to acidic reaction, H_2O (1×50 mL), saturated aqueous $NaHCO_3$ (1×50 mL), and H_2O (1×50 mL); the solution was dried over Na_2SO_4, and the solvent was removed. **16** (7.5 g, 99 %) was obtained as a syrup.

Methyl 3,4-di-*O*-benzyl-2-*O*-*p*-methoxybenzyl-α-D-*altro*-hexopyranoside (17). Trityl derivative **16** (7.5 g, 11 mmol) was added to a solution of an 80 % NaH suspension (0.7 g, 22 mmol) in DMSO (70 mL). The mixture was stirred for 30 min. Then BnBr (2.33 g, 22 mmol, 1.62 mL) was added and the mixture was stirred at 80 °C for 3 h. It then was neutralized with dry ice, diluted with chloroform (50 mL) and the salts were filtered off. After removal of the solvent the residue was purified by chromatography on SiO_2 in a benzene—THF gradient. **17** (5.2 g, 64 %) was obtained as a syrup.

Methyl 3,4-di-*O*-benzyl-2-*O*-*p*-methoxybenzyl-α-D-*altro*-hexopyranoside (18). A solution of **17** (5.2 g, 7.06 mmol) in a mixture of CF_3COOH (6 mL), H_2O (6 mL), and THF (15 mL) was kept at 20 °C for 3 days. Then the mixture was neutralized with sodium bicarbonate, and the product was washed from the precipitated salts with chloroform (5×50 mL). The solvent was removed. After removal of the solvent the residue was purified by chromatography on SiO_2 in a benzene—THF gradient. Product **18** (3.5 g, 98 %) was obtained as a syrup; $[\alpha]_D$ +70.08° (c 1.0, $CHCl_3$); m.p. = 92 °C. ^{1}H NMR (δ, *J*/Hz): 4.61 (s, 1 H, H(1)); 3.69 (dd, 1 H, H(2), J_1 = 1.5, J_2 = 3); 3.75 (m, 2 H, H(3), H(4)); 4.15 (m, 1 H, H(5)); 3.86 (dd, 1 H, H(6), $J_{5,6}$ = 3.5, $J_{6,6'}$ = 12); 3.77 (dd, 1 H, H(6'), $J_{5,6'}$ = 3); 1.80 (br.s, 1 H, OH); 3.48 (s, 3 H, OMe at C(1)); 3.85 (s, 3 H, OMe (MPM)); 4.34 and 4.44 (2 H, CH_2Ph, AB spin system, *J* = 12); 4.45 and 4.52 (2 H, CH_2Ph, AB spin system, *J* = 12); 4.54 and 4.67 (2 H, CH_2MPM, AB spin system, *J* = 13); and 7.30 (m, 14 H, C_6H_5)

Methyl 3,4-di-*O*-benzyl-6-bromo-6-deoxy-2-*O*-*p*-methoxybenzyl-α-D-*altro*-hexopyranoside (19). Ph_3P (2 g, *ca.* 7.5 mmol) was added to a solution of **18** (3,6 g, 7.3 mmol) in anhydrous pyridine (30 mL) and, after dissolution, CBr_4 (2.5 g, 7.5 mmol) was added. The mixture warmed up and turned dark. The reaction mixture was kept at 20 °C for 1 h and diluted with a hexane—ether (1 : 1) mixture (50 mL). Triphenylphosphine oxide was removed by filtration through a SiO_2 layer, the silica gel was washed with a 1 : 1 hexane—ether mixture, (100 mL). The filtrate was washed with 1 *M* HCl to acidic reaction, then with saturated NaCl, and saturated $NaHCO_3$, and dried over Na_2SO_4. The solvent was removed. Bromide **19** (3.5 g, 87 %) was obtained as a syrup; $[\alpha]_D$ +80.12° (c 1.0, $CHCl_3$). ^{1}H NMR (δ, *J*/Hz): 4.71 (s, 1 H, H(1)); 3.70 (dd, 1 H, H(2), $J_{1,2}$ = 1, $J_{2,3}$ = 3.5); 3.75 (m, 2 H, H(3), H(4)); 4.31 (m, 1 H, H(5) $J_{5,6}$ = 3, $J_{5,6'}$ = 7); 3.76 (dd, 1 H, H(6), $J_{6,6'}$ = 11); 3.58 (dd, 1 H, H(6')); 3.44 (s, 3 H, OMe at C(1)); 3.83 (s, 3 H, OMe (MPM)); 4.40 and 4.48 (2 H, CH_2Ph, AB spin system, *J* = 12.5); 4.65 and 4.37 (2 H, CH_2Ph, AB spin system, *J* = 12); 4.52 and 4.47 (both s, 2 H, CH_2MPM); and 6.80—7.40 (m, 14 H, C_6H_5)

Methyl 3,4-di-*O*-benzyl-6-bromo-6-deoxy-α-D-*altro*-hexopyranoside (20). Starting MPM-ether **19** (1.5 g, 2.7 mmol) was dissolved in acetonitrile (5 mL), and $(NH_4)_2Ce(NO_3)_6$ (2.5 g, 5.5 mmol) in acetonitrile (5 mL) and water (1.5 mL) was added at stirring. The mixture was stirred for 4 h, diluted with saturated NaCl (20 mL), and extracted with chloroform (2×50 mL). The solvent was removed. The residue was chromatographed on silica gel in a benzene—THF gradient. Monohydroxy derivative **20** (816 mg, 67 %) was obtained, $[\alpha]_D$ +80.65° (c 1.0, $CHCl_3$). ^{1}H NMR (δ, *J*/Hz): 4.65 (s, 1 H, H(1)); 4.05 (m, 1 H, H(2)); 3.84 (t, 1 H, H(3), $J_{2,3}$ = $J_{3,4}$ = 3.5); 3.79 (dd, 1 H, H(4), $J_{4,5}$ = 8); 4.31 (m, 1 H, H(5) $J_{5,6}$ = 3.5, $J_{5,6'}$ = 6); 3.68 (dd, 1 H, H(6), $J_{6,6'}$ = 12); 3.59 (dd, 1 H, H(6')); 1.98 (d, 1 H, OH, $J_{2,OH}$ = 5); 3.45 (s, 3 H, OMe at C(1)); 4.46 and 4.58 (2 H, CH_2Ph, AB spin system, *J* = 13); 4.64 and 4.74 (2 H, CH_2Ph, AB spin system, *J* = 13); and 7.30 (m, 10 H, C_6H_5).

Methyl 3,4-di-*O*-benzyl-6-bromo-6-deoxy-2-methoxycarbonylmethylene-α-D-*ribo*-hexopyranoside (6). Oxalyl chloride (0.2 g, 1.5 mmol, 0.2 mL) was dissolved in anhydrous CH_2Cl_2 (2 mL) and the solution was cooled in a flow of Ar to

−60 °C (dry ice—acetone bath). A solution of anhydrous DMSO (0.23 g, 3 mmol, 0.23 mL) in anhydrous CH_2Cl_2 (0.5 mL) was added dropwise to the reaction mixture over a period of 5 min. The mixture was stirred at −60 °C for 10 min. Then a solution of **20** (0.4 g, 0.92 mmol) in anhydrous CH_2Cl_2 (1.5 mL) was added dropwise for 5 min, and the mixture was stirred at −60 °C for of 30 min. Triethylamine (0.6 g, *ca.* 6 mmol, 0.9 mL) was added to the reaction mixture and, after 5 min, 1 *M* HCl (7.5 mL) was added. The mixture was warmed with stirring to *ca.* 20 °C, the reaction product was extracted with chloroform, the organic layer was separated and washed with saturated NaCl, then with saturated $NaHCO_3$, dried over Na_2SO_4, and the solvent was removed. The residue was dissolved in 5 mL of anhydrous THF, Ph_3P=CHCOOMe (0.7 g, *ca.* 2 mmol) was added, and the reaction mixture was refluxed with a reflux condenser for 1.5 h. The solvent was removed and the residue was chromatographed on silica gel (benzene was used as the eluent). Product **6** (348 mg, 86 %) was obtained as a syrup.

Methyl 3,4-di-*O*-benzyl-6-bromo-6-deoxy-2-ethoxycarbonylmethylene-α-D-*ribo*-hexopyranoside (7), was prepared in a similar way using Ph_3P=CHCOOEt in the Wittig reaction. Since inseparable mixtures of *cis*- and *trans*-isomers were formed in the course of the reactions, the ^1H NMR spectra of the unsaturated derivatives were inconclusive.

(1*S*,2*S*,4*R*,5*S*,7*R*,8*S*)-8-benzyloxy-4-methyl-2-methoxy-1-methoxycarbonylmethyl-7-phenyl-3,6-dioxabicyclo[3.2.1]octane (8). A solution of **6** (0.19 g, *ca.* 0.37 mmol) in anhydrous toluene (20 mL) was placed in a dry flask. The flask was evacuated until toluene began to boil intensely, the flask was filled with argon. Then, a solution of AIBN (10 mg, 0.06 mmol) and Bu_3SnH (0.2 g, 0.6 mmol, 165 μL) in anhydrous toluene (20 mL) (also evacuated) was added dropwise to a refluxed solution of **5** in a stream of Ar over a period of 2 h. The solution was refluxed for additional 30 min, and the solvent was removed. The syrup obtained was chromatographed on silica gel in a benzene—hexane (2 : 1)—ether gradient. Compound **8** (71 mg, *ca.* 44 %, the substance was partially lost during chromatography) was obtained as a syrup, $[\alpha]_D$ +13.13° (c 1.0, $CHCl_3$). ^{13}C NMR (δ): 101.0 (C(1)); 54.2 (C(2)); 79.0 (C(3)); 80.0 (C(4)); 74.9 (C(5)); 16.2 (C(6)); 31.1 (C(7)); 81.2 (C(8)); 71.5 (CH_2Ph); 51.3 (OMe at C(1)); 56.8 (COO<u>Me</u>); 172.5 (CO); 139.8, 128.4—127.4 (Ph); ^1H NMR (δ, *J*/Hz): 5.00 (s, 1 H, H(1)); 4.35 (s, 1 H, H(3)); 4.29 (d, 1 H, H(4), $J_{4,5}$ = 2.5); 4.28 (dq, 1 H, H(5), $J_{5,6}$ = 6.5); 1.21 (d, 3 H, H(6)); 2.32 and 2.07 (2 H, H(7), H(7'), AB spin system, J_{gem} = 17); 5.38 (s, 1 H, H(8)); 3.48 (s, 3 H, OMe at C(1)); 3.58 (s, 3 H, COOMe); 4.56 and 4.71 (d, 2 H, CH_2Ph, J_{gem} = 12); and 7.25 (m, 10 H, C_6H_5).

(1*S*,2*S*,4*R*,5*S*,7*R*,8*S*)-8-benzyloxy-4-methyl-2-methoxy-1-ethoxycarbonylmethyl-7-phenyl-3,6-dioxabicyclo[3.2.1]octane (9) was prepared from **7** analogously. ^1H NMR (δ, *J*/Hz): 5.02 (s, 1 H, H(1)); 4.35 (s, 1 H, H(3)); 4.29 (d, 1 H, H(4), $J_{4,5}$ = 2.5); 4.26 (d.q, 1 H, H(5), $J_{5,6}$ = 7); 1.21 (d, 3 H, H(6)); 2.30 and 2.06 (2 H, H(7), H(7'), AB spin system, J_{gem} = 17); 5.38 (s, 1 H, H(8)); 3.50 (s, 3 H, OMe); 4.03 (dq, 2 H, <u>CH_2</u>CH_3, $J_{CH2,CH3}$ = 7.5, *J* = 1.5); 1.18 (t, 3 H, CH_2<u>CH_3</u>); 4.56 and 4.71 (2 H, CH_2Ph, AB spin system, J_{gem} = 12); and 7.20 (m, 10 H, C_6H_5).

(2*R*,3*S*,4*S*,5*R*)-4-benzyloxy-5-(1-*R*-hydroxyethyl)-3-(1,3-dithian-2-yl)-3-ethoxycarbonylmethyl-2-phenyltetrahydrofuran (22). 1,3-Propanedithiol (20 mg, 0.17 mmol, 20 μL) was added to a solution of **10** (35 mg, 0.11 mmol) in CH_2Cl_2 (1 mL) and the mixture was cooled to −30 °C. $ZnCl_2$ (18 mg, 0.13 mmol) fused and powdered immediately prior to use was added. The reaction mixture was stirred for 1 h, neutralized with sodium bicarbonate, and warmed to *ca.* 20 °C. The precipitate was filtered off and washed with benzene, the filtrate was evaporated, and the residue was chromatographed on SiO_2 in a benzene—THF gradient. **22** (38 mg, 70 %) was obtained as a syrup, $[\alpha]_D$ 20.1° (c 1.0; $CHCl_3$). ^1H NMR (δ, *J*/Hz): 5.45 (s, 1 H, H(1)); 4.76 (d, 1 H, H(3), $J_{3,4}$ = 6); 3.97 (m, 2 H, H(4), H(5)); 1.29 (d, 3 H, H(6), $J_{5,6}$ = 6); 2.97 and 2.57 (2 H, H(7), H(7'), AB spin system, J_{gem} = 17); 5.48 (s, 1 H, H(8)); 2.90—3.15 (m, 4 H, H(9)); 1.90—2.20 (m, 2 H, H(10)); 3.58 (m, 2 H, O<u>CH_2</u>CH_3); 1.03 (t, 3 H, OCH_2<u>CH_3</u>); 4.90 and 4.68 (2 H, CH_2Ph, AB spin system, J_{gem} = 11); and 7.25 (m, 10 H, C_6H_5).

(2*R*,3*S*,4*S*,5*R*)-5-(1-*R*-acetoxyethyl)-4-benzyloxy-3-(1,3-dithian-2-yl)-1-phenyl-3-ethoxycarbonylmethyltetrahydrofuran (23). Ac_2O (0.5 mL) in anhydrous pyridine (1 mL) was added to a solution of **22** (38 mg, *ca.* 0.08 mmol). The mixture was kept overnight, cooled to 0 °C, then MeOH (1 mL) was added. The solution was allowed to warm to *ca.* 20 °C, then it was diluted with chloroform (30 mL) and washed with 1 *M* HCl (2×50 mL), H_2O (50 mL), saturated $NaHCO_3$ (50 mL), and dried over Na_2SO_4. The solvent was removed. The residue was chromatographed on SiO_2 in a benzene—THF gradient. Compound **23** (35 mg, 87 %) was obtained as a syrup. ^1H NMR (δ, *J*/Hz): 5.44 (s, 1 H, H(1)); 4.66 (d, 1 H, H(3), $J_{3,4}$ = 6.5); 4.10 (dd, 1 H, H(4), $J_{4,5}$ = 5); 5.08 (dq, 1 H, H(5), $J_{5,6}$ = 6.5); 1.35 (d, 3 H, H(6)); 2.97 and 2.56 (2 H, H(7), H(7'), AB spin system, J_{gem} = 17); 5.50 (s, 1 H, H(8)); 2.90—3.17 (m, 4 H, H(9)); 1.90—2.25 (m, 2 H, H(10)); 4.90 and 4.68 (2 H, CH_2Ph, AB spin system, J_{gem} = 11); 3.55 (m, 2 H, O<u>CH_2</u>CH_3); 1.03 (t, 3 H, OCH_2<u>CH_3</u>); 2.12 (s, 3 H, CO<u>CH_3</u>); and 7.25 (m, 10 H, C_6H_5).

Methyl 4-*O*-benzyl-6-bromo-3,6-deoxy-β-D-*erythro*-hexopyranoside (25). Starting 1,6-anhydro derivative **24** (1.5 g, 6.3 mmol) was dissolved in 5% (v/v) methanolic H_2SO_4 (30 mL) and the solution was refluxed for 6 h with a reflux condenser. The acid was neutralized with sodium bicarbonate, the mixture was diluted with chloroform (50 mL), and the precipitated salts were removed by filtration through a silica gel layer. The solids were washed with chloroform (50 mL), the solvent was removed, and the residue was dissolved in anhydrous pyridine (30 mL). Triphenylphosphine (1.7 g, 6.5 mmol) was added, and, after its dissolution, CBr_4 (2 g, 6.3 mmol) was added. The mixture was kept at *ca.* 20 °C for 1.5 h and then diluted with a hexane—ether (1 : 1) mixture (50 mL). Triphenylphosphine oxide was removed by filtration through a silica gel layer, and the solids were washed with a hexane—ether (1 : 1) mixture (50 mL). The filtrates were washed with 1 *M* HCl to acidic reaction, then with saturated NaCl and saturated $NaHCO_3$, and dried over Na_2SO_4. The solvent was removed. A mixture of α- and β-bromides (1 : 1) (1.2 g, 60 %) was obtained as a syrup. The mixture was separated by column chromatography on silica gel in a benzene—ether gradient. β-Bromide **25** (*ca.* 600 mg) $[\alpha]_D$ +123.4° (c 1.0, $CHCl_3$) and α-bromide (*ca.* 600 mg) $[\alpha]_D$ +106.02° (c 1.0, $CHCl_3$) were obtained. ^1H NMR (δ, *J*/Hz): 4.72 (d, 1 H, H(1), $J_{1,2}$ = 2.5); 3.41 (m, 1 H, H(2)); 2.39 (dt, 1 H, H(3e), $J_{3,3'}$ = 11, $J_{2,3e}$ = $J_{3e,4}$ = 5); 1.69 (q, 1 H, H(3a), $J_{3a,2}$ = 11, $J_{3a,4}$ = 11); 3.66—3.86 (m, 2 H, H(4), H(5)); 3.57 (dd, 1 H, H(6), $J_{6,6'}$ = 11, $J_{5,6}$ = 6); 3.72 (d, 1 H, H(6')); 4.65 (d, 1 H, OH, $J_{2,OH}$ = 2); 3.44 (s, 3 H, OMe at C(1)); 4.65 and 4.47 (2 H, CH_2Ph, AB spin system, *J* = 11.5); and 7.30 (m, 5 H, C_6H_5).

Methyl 4-*O*-benzyl-6-bromo-3,6-deoxy-2-methoxycarbonylmethylene-β-D-*erythro*-hexopyranoside (10) was prepared analogously to **6** from **25** (400 mg), DMSO (0.39 mL),

$(COCl)_2$ (0.24 mL), Et_3N (2.1 mL), 1 *M* HCl (21 mL), and Ph_3P=CHCOOMe (0.7 g). Compound **8** (420 mg, 70 %) was obtained as a syrup. Since an inseparable mixture of *cis*- and *trans*-isomers was formed, the ^1H NMR spectra of the products were inconclusive.

(1*R*,3*R*,4*R*,6*S*)-6-benzyloxy-3-methoxy-4-methoxycarbonylmethyl-2-oxabicyclo[2.2.1]heptane (11) and **(1*R*,2*R*,4*R*,5*S*,7*R*)-2-methoxy-1-methoxycarbonylmethyl-4-methyl-7-phenyl-3,6-dioxabicyclo[3.2.1]octane (12)** were prepared analogously to **9** from **8** (400 mg), Bu_3SnH (400 μL), and AIBN (25 mg). A mixture of **11** and **12** (267 mg) (58 % and 29 %, respectively) was obtained. Compounds **12** (55 mg) and **11** (12 mg) were obtained in pure form by column chromatography on silica gel (benzene—hexane (1 : 1)—ether gradient). **11**: $[\alpha]_D$ −116.60° (c 0.5, $CHCl_3$). ^1H NMR (δ, *J*/Hz): 4.70 (s, 1 H, H(1)); 1.42 (dt, 1 H, H(3e), $J_{3,3'}$ = 13.5, $J_{3e,4}$ = 2); 1.94 (m, 2 H, H(3a), H(6)); 3.85 (ddd, 1 H, H(4), $J_{4,5}$ = 4, $J_{4,3a}$ = 9.5); 4.36 (dd, 1 H, H(5), $J_{5,6}$ = 2); 1.40 (d, 1 H, H(6), $J_{6,6'}$ = 10); 2.72 and 2.54 (2 H, H(7), H(7'), AB spin system, $J_{7,7'}$ = 16); 3.42 (s, 3 H, OMe at C(1)); 3.68 (s, 3 H, COOMe); 4.54 (2 H, CH_2Ph, AB spin system, *J* = 12); 7.30 (m, 5 H, C_6H_5). **12**: $[\alpha]_D$ 78.10° (c 1, $CHCl_3$). ^1H NMR (δ, *J*/Hz): 4.80 (s, 1 H, H(1)); 2.22 (d, 1 H, H(3e), $J_{3,3'}$ = 12); 1.85 (ddd, 1 H, H(3a), $J_{3a,4}$ = 6, $J_{3a,5}$ = 1.5); 4.22 (dd, 1 H, H(4), $J_{4,5}$ = 2.5); 4.14 (dq, 1 H, H(5), $J_{5,6}$ = 7); 1.12 (d, 3 H, H(6)); 2.35 and 1.25 (2 H, H(7), H(7'), AB spin system, $J_{7,7'}$ = 15.5); 5.25 (s, 1 H, H(8)); 3.42 (s, 3 H, OMe at C(1)); 3.58 (s, 3 H, COOMe); and 7.30 (m, 5 H, C_6H_5).

(2*R*,3*R*,5*S*)-5-(1-*R*-hydroxyethyl)-3-(1,3-dithian-2-yl)-3-methoxycarbonylmethyl-2-phenyltetrahydrofuran (26) was prepared analogously to **22** from **12** (55 mg, 0.19 mmol), 1,3-propanedithiol (38 μL, 0.38 mmol), and $ZnCl_2$ (100 mg). Compound **26** (63 mg, 86 %) was obtained as a syrup; $[\alpha]_D$ 21.20° (c 1, $CHCl_3$). ^1H NMR (δ, *J*/Hz): 4.89 (s, 1 H, H(1)); 2.60 (dd, 1 H, H(3), $J_{3,3'}$ = 13, $J_{3,4}$ = 10); 2.12 (dd, 1 H, H(3'), $J_{3',4}$ = 6.5); 4.08 (d.d.d, 1 H, H(4)); 3.96 (dq, 1 H, H(5), $J_{5,6}$ = 6.5); 1.11 (d, 3 H, H(6)); 2.39 and 2.27 (2 H, H(7), H(7'), AB spin system, $J_{7,7'}$ = 17); 5.34 (s, 1 H, H(8)); 2.85 (m, 4 H, H(9)); 2.09 and 1.85 (m, 3 H, H(10), OH); 3.30 (s, 3 H, COOMe); 7.30 (m, 5 H, C_6H_5). NOE: interaction of H(8) with the *ortho*-protons and the absence of interaction with H(7), H(7').

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