FREE RADICAL REACTIONS OF CARBOHYDRATE DERIVATIVES IN THE SYNTHESIS OF CARBOCYCLIC COMPOUNDS. 1. INTRAMOLECULAR C_2—C_6 CYCLIZATION OF MONOSACCHARIDES — A NEW ROUTE TO SUBSTITUTED CYCLOPENTANES

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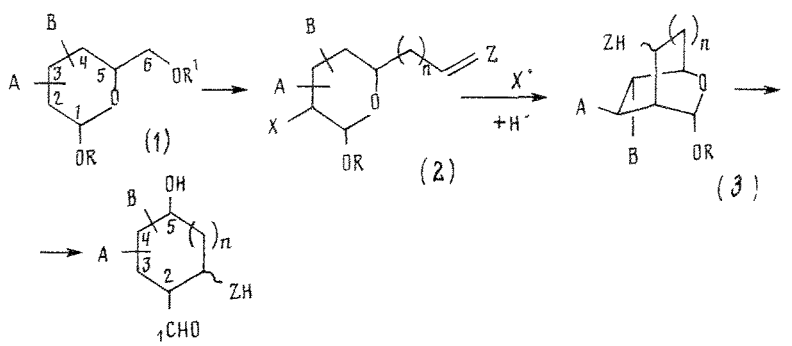
The feasibility of adopting a new approach to the preparation of chiral carbocyclic compounds has been demonstrated by experiment. Synthesis was achieved by way of intramolecular free radical C_2—C_6 cyclization of carbohydrate derivatives, which produced compounds with quaternary C_2 carbon atom having a strictly defined configuration.

Keywords: *free radical reactions, carbohydrates, carbocyclic compounds, cyclopentanes, cyclization, monosaccharides.*

In recent years considerable progress has been made in the use of free radical intermediates in precision organic chemistry [1]. Since carbohydrates and their derivatives are widely used in the stereochemically directed syntheses of natural compounds of almost limitless structural complexity (see [2, 3], for example), the application to this particular field of free radical reactions that proceed very rapidly, in the absence of strong acids or bases, has tremendous potential, particularly in obtaining carbocyclic compounds.

Most of the work on intramolecular cyclization via free radicals [4] has been based on acyclic derivatives and high stereoselectivity has been achieved in isolated instances. When applied to carbohydrates, this approach employs the C^1 center as the aldehyde component, on which a chosen method is used to build a multiple bond (acceptor radical), and bases itself on the creation of a free radical center at C_5.

In an alternative strategy proposed by Fraser-Reid and coworkers [5], the free radical center is generated at C_2 in the pyranose ring, and the multiple bond is formed at the C_6 (or C_7) atom (Scheme 1).



n = 0 (**4**), cyclopentanes; n = 1 (**5**), cyclohexanes.

Each of these approaches produces structurally unique cyclopentane or cyclohexane derivatives, which form the basis of many natural compounds. But even taken together they cannot cover the synthesis of such a wide diversity of compounds. This is what makes the development of other alternatives using free radical cyclization of carbohydrate derivatives to produce fundamentally new carbocyclic compounds of particular interest.

In the current work a new approach is presented for synthesizing chiral carbocyclic compounds by means of intramolecular free radical cyclization of carbohydrate derivatives, in which the exocyclic double bond is situated at C_2, and the radical center at C_6 or C_7 (Scheme 2).

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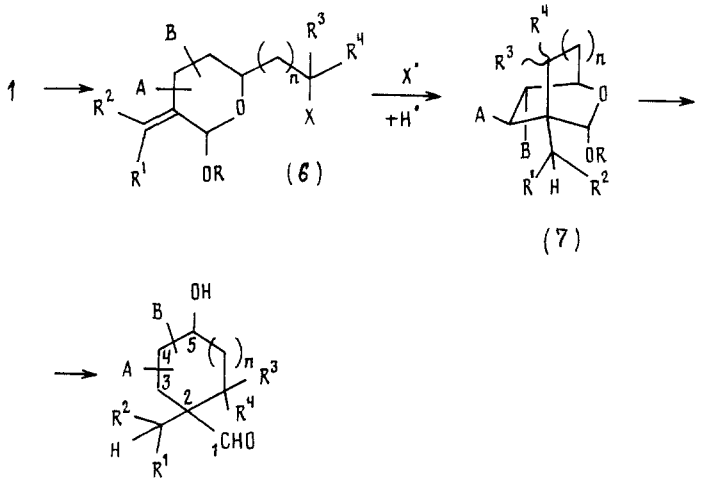


n = 0 (**8**), cyclopentanes; n = 1 (**9**), cyclohexanes.

Despite the apparent similarity of the two latter approaches, significant differences exist between them, namely the specific structural features of the compounds taking part in the cyclization reaction (**2** or **6**), and the ensuing possibility of obtaining chiral carbocyclic compounds (**4, 5** or **8, 9**) that differ in substitution type.

We synthesized a specific representative of the type **6** derivatives, which could be used to study the feasibility of free radical cyclization, from the readily available levoglucosan derivative **10** in nine stages (Scheme 3); this yielded the requisite 6-desoxy-6-bromide having an exocyclic double bond (**20**).

It is worth noting that we achieved a significant improvement in the synthesis of the starting epoxide **10** (at the stage where 1,6:3,4-dianhydro-2-O-tosyl-β-*D*-galactopyranose undergoes reduction) by using $LiAlH_4$ in THF instead of Raney nickel or lithium aluminohydride in Et_2O (see [6, 7]). Under these circumstances the yield of 1,6-anhydro-4-desoxy-2-O-tosyl-β-*D*-xylopyranose reached 80% and contamination from the manno-configuration product was kept to a minimum; all intermediate products in the synthesis of **10** proved to be crystalline.

The opening of epoxide **10** by sodium benzylate, which occurs exclusively at C_3, produced alcohol **11** in 79% yield. Methanolysis of the latter yielded a mixture of methyl-α- and β-*D*-glycosides **12**, which were separated chromatographically via acetates **13**. α-Anomer **12** was used in the basic scheme to simplify spectral information (see scheme below).

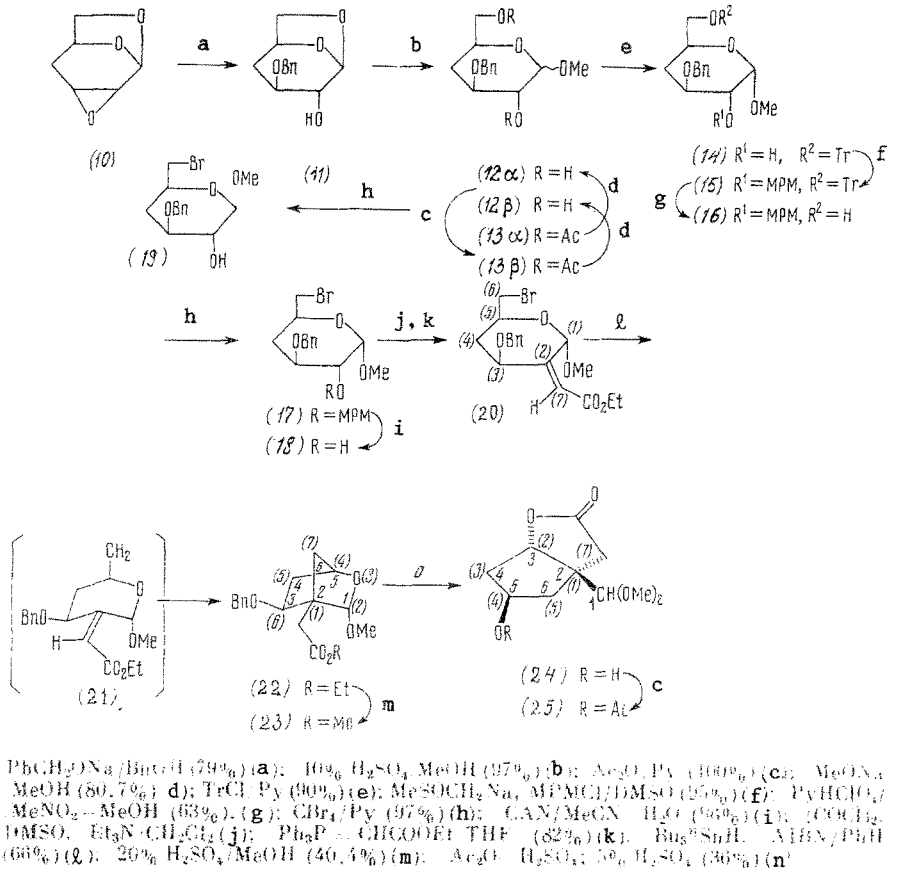
Tritylation of the latter, protection of the hydroxyl group at C_2in derivative **14**, and removal of the trityl group in **15** produced alcohol **16** in high total yield. This compound can be used to obtain type **20** derivatives with a modified C_6 center. Replacement of the primary hydroxyl group in **16** by bromine [8] yielded bromide **17**, for which removal of the *p*-methoxybenzyl (MPM) protective group by cerium (**4**) ammonium nitrate [9] produced an important intermediate — bromide **18**. The same compound was obtained by a shorter route under the same conditions from the diol (**12**-α) (the β-isomer **19** was obtained in a similar way).

Finally, oxidation of alcohol **18** using the Swern method [10] and subsequent reaction between the intermediate ketone and carbethoxymethylenetriphenylphosphorane produced exclusively the *E*-isomer **20** in 82% yield. The nuclear Overhauser effect (~2%) between the C_7 proton and a benzyl group (CH_2) proton suggested that the double bond was an *E*-configuration.

Cyclization of compound **20** in the presence of tributyltin hydride and 2,2′-azobisisobutyronitrile under high dilution conditions in boiling benzene (or toluene) afforded the bicyclooxaheptane (**22**) in 66% yield. The structure of compound **22** can be deduced by comparing its PMR spectrum with that of bromide **20**. Thus, the C_1 proton singlet in the spectrum of derivative **22** shifted into the strong field region, appearing at 4.92 ppm (6.42 pm for **20**); the H_7 proton signal disappeared, to be replaced at 2.70 and 2.78 ppm by the two geminal proton signals with characteristic coupling constant of 14.5 Hz. Finally, the C_6 proton signals in the PMR spectrum of derivative **22**, as was to be expected, shifted by an appreciable amount into the strong field region, appearing at 2.0 and 1.93 ppm (3.43 and 3.38 ppm for **20**). The signals for the other protons and their multiplets in the spectrum of compound **22** fell within expected limits.

Analysis of molecular models showed that the cyclization of bromide **20** probably proceeds through intermediate **21**, whose formation can be accounted for by simple rotation of the substituents about the C_4—C_5 bond. This rotation is probably facilitated

by the absence of a substituent at C_4 and the flattening of the ring in the region of the C_1—C_3 atoms due to the presence of the exomethylene bond.*



The quoted reaction sequence was also investigated using as an example bromide **19**, whose anomeric center has the β-configuration. As it turned out, however, oxidation of this alcohol at C_2 and the subsequent Wittig reaction led to incomplete epimerization of the C_1 center and produced an anomeric mixture (~1:1) of type **20** derivatives, which went on to react by cyclization, yielding an anomeric mixture of derivatives **22**. Thus, it is possible to make use of an anomeric mixture of methylglycosides (**12**) in preparative syntheses. The successful free radical cyclization of bromides **20** and **19** showed that chiral cyclopentanes can be synthesized using the strategy that we have proposed.

Unexpected difficulties arose during an attempt to methanolyze compound **22** so as to obtain chiral cyclopentane (**24**). Prolonged boiling of compound **22** in 5-10% H_2SO_4 solutions in MeOH only shifted the reaction very slightly toward formation of the corresponding cyclopentane. A similar result was obtained using 20% H_2SO_4 in MeOH (24 h, 25°C); boiling of the solution produced considerable resinification. The only difference between compound **22** and the type **3** intermediate, which is readily methanolyzed [5], is the ethoxycarbonylmethylene fragment at C_2. Clearly, protonation of the ester group in **22** is the main obstacle to its methanolysis, ester **23** being the principal product.

The transition from the bicyclooxaheptane system (**22**) to the cycloheptanone (**24**) was accomplished by acetolysis and subsequent methanolysis, compound **24** being formed in moderate yield (36%). Acetylation of alcohol **24** afforded acetate **25**, whose structure was corroborated by PMR spectral data. For example, the presence of the dimethoxyacetal group was suggested by the three singlets at 4.25 (CH), 3.52 and 3.54 ppm (OMe). The two multiplets at 4.81 and 5.21 ppm pointed to there being two CH protons in the vicinity of the hydroxyl groups. The presence of the lactone grouping was confirmed by the two doublets at 2.35 and 2.93 ppm. The position and multiplicity of the remaining protons of compound **25** came within expected limits. Synthesized derivative **25** could be used to obtain modified prostaglandins having geminal side-chain configuration, which are known to be antagonists of natural compounds [13].

*The conformation of free radicals in cyclic systems in general and in carbohydrates in particular is more complex than might be logically assumed by analogy with the conformations of normal carbocyclic compounds. As the recent research of Giese and coworkers has shown (see [1, 11, 12], for example), radical intermediates of cyclic sugar derivatives can assume the most unexpected conformations, even energetically unfavorable ones (most or all the substituents becoming axial).

In summary, one of the virtues of the proposed new approach to the synthesis of chiral carbocyclic compounds is the possibility of obtaining derivatives with a quaternary C_2 carbon atom of rigidly defined configuration. In view of the diversity and variety of possible A, B, and R^1—R^4 substituents, it is to be hoped that the configuration of the C_6 atom and, more importantly, the configuration of the exocyclic carbon atom bearing the R^1 and R^2 substituents might be controlled to some extent.

The free radical cyclization of other intermediates obtained from diols **12** and alcohol **16** are the subject of further research by the authors.

EXPERIMENTAL

Melting points were measured in a capillary in an electrically heated unit, without correction of the results. Specific rotation was measured in chloroform on a Jasco DIP-360 polarimeter. PMR spectra were taken in $CDCl_3$ on a Bruker WM-250 instrument. Signals in the proton spectra were referenced using the differential variant homonuclear double resonance method.

The reaction course and the purity of isolated substances were monitored using TLC on Kieselgel 60 silica gel plates. Spots were developed by spraying the plates with a 5% solution of H_2SO_4 in MeOH and then heating to ~200°C.

Reaction mixtures were separated using column chromatography on Silpearl 60 silica gel (25-40 μm) in benzene—ester (ethyl acetate) systems.

Solvents used in the reactions were distilled in an argon atmosphere over a suitable drying agent (CaH_2, $LiAlH_4$).

1,6-Anhydro-3-O-benzyl-4-desoxy-β-*D*-xylo-hexopyranose (11). A sample of 9.6 g (a 55% suspension in oil) (0.2 *M*) of NaH was added in small amounts with vigorous stirring to 70 ml of freshly distilled benzyl alcohol. After the NaH had completely dissolved, 12.8 g (0.1 *M*) of epoxide **10** in 50 ml of dry benzene was added to the mixture, which was boiled until **10** had disappeared (1.5-2 h, TLC monitoring). The mixture was cooled, diluted with 50 ml of benzene, neutralized with solid CO_2, and diluted with 100 ml of water; the organic layer was separated off and washed with a saturated NaCl solution (2 × 100 ml). The aqueous layer was extracted thoroughly with $CHCl_3$ (TLC control). After boiling down the combined organic extracts, the benzyl alcohol was evaporated off in vacuum and the residue was chromatographed. Yield 18.6 g (79%), mp 80-81°C (benzene—hexane), $[\alpha]_D^{25}$ −22.4° (C 1.0). PMR spectrum (δ, ppm, *J*, Hz): 5.43 s (1H, H^1); 3.68 br.s (1H, H^2); 4.50 d.d (1H, H^3, $J_{3,4} = 4$, $J_{3,4'} = 6$); 1.80 d (1H, H^{4e}, $J_{4,4} = 15$); 2.27 m (2H, H^{4a}, OH); 3.58 d.d.d (1H, H^5, $J_{5,6} = 5$, $J_{5,4} = J_{5,4'} = 1.5$); 4.24 d (1H, H^{6exo}, $J_{6,6} = 6.5$); 3.75 d.d.d (1H, H^{6endo}, $J = 1.5$); 4.62 d and 4.53 d (2H, OCH_2Ph at C^3, $J_{gem} = 12$, AB system); 7.30 m (5H, OCH_2Ph at O^3).

Methyl-3-O-benzyl-4-desoxy-α,β-*D*-xylo-hexopyranosides (12)-α,β- and (13)-α,β. A solution of 10 g (42 mmoles) of alcohol **11** in 100 ml of 10% H_2SO_4 in MeOH was boiled for 2 h, cooled, neutralized with $NaHCO_3$, and evaporated to dryness. The solid residue was extracted with $CHCl_3$, which was then evaporated off. Yield of **12**-α,β 11.0 g (97%). The diol mixture **12**-α,β was acetylated in 50 ml of a pyridine—Ac_2O (1:1) mixture (15 h, 25°C), carefully decomposed with MeOH, and evaporated; the residue was then chromatographed. Yield of **13**-α 9.47 g (63.5%), syrup, $[\alpha]_D^{25}$ +112.1° (*C* 1.0). Yield of **13**-β 2.57 g (17.2%), syrup, $[\alpha]_D^{25}$ +20.2° (*C* 1.0). Acetates **13**-α,β were deacetylated with MeONa in MeOH with quantitative yield. **12**-α, syrup, $[\alpha]_D^{26}$ +106.0° (*C* 0.7); **12**-β, mp 108-109°C (benzene—hexane), $[\alpha]_D^{26}$ +2.1° (*C* 1.0). PMR spectrum of **13**-α (δ, ppm, *J*, Hz): 4.92 d (1H, H^1, $J_{1,2} = 3.5$); 4.85 d.d (1H, H^2, $J_{2,3} = 10$); 3.95 m (2H, H^3, H^5); 2.10 m (7H, $OCOCH_3$ at C^2 and C^6, H^{4e}); 1.57 q (1H, H^{4a}, $J_{4,4} = 11.5$, $J_{4a,3} = J_{4a,5} = 12$); 4.14 m (2H, H^6, H^6); 4.58 d and 4.64 d (2H, OCH_2Ph at C^3, AB system, $J_{gem} = 12$); 3.38 s (3H, OMe); 7.30 m (5H, OCH_2Ph at C^3). PMR spectrum of **13**-β (δ, ppm, *J*, Hz): 4.23 d (1H, H^1, $J_{1,2} = 8$); 4.87 d.d (1H, H^2, $J_{2,3} = 9.5$); 3.60 m (2H, H^3, H^5); 2.10 m (7H, $OCOCH_3$ at C^2 and C^6, H^{4e}); 1.55 q (1H, H^{4a}, $J_{4a,3} = J_{4a,5} = 12$, $J_{4,4} = 11.5$); 4.14 m (2H, H^6, H^6); 4.48 d and 4.63 d (2H, OCH_2Ph at C^3, AB system, $J_{gem} = 12$); 3.45 s (3H, OMe); 7.30 m (5H, OCH_2Ph at C^3).

Methyl-3-O-benzyl-4-desoxy-6-O-trityl-α-*D*-xylo-hexopyranoside (14). To a solution of 13.4 g (50 mmoles) of **12**-α in 100 ml of dry pyridine were added 27.8 g (100 mmoles) of trityl chloride; after the mixture had been kept at 25°C for 72 h, it was poured into water and extracted with $CHCl_3$ (5 × 100 ml). The organic layer was washed with water, 1 *M* HCl, water, saturated $NaHCO_3$, and NaCl; it was then evaporated and the residue was chromatographed. Yield 23 g (90%), mp 123-124°C (hexane—benzene), $[\alpha]_D^{27}$ +53.5° (*C* 0.32).

Methyl-3-O-benzyl-4-desoxy-2-O-*p*-methoxybenzyl(MPM)-6-O-trityl-α-*D*-xylo-hexopyranoside (15). A sample of 12 g (25.5 mmoles) of compound **14** was added to a solution of 1 g (33 mmoles) of NaH in 50 ml of DMSO and the mixture stirred for 1.5 h. To this was added dropwise 5.65 g (36 mmoles, 5 ml) of *p*-methoxybenzylchloride, the mixture being stirred for a further 12 h. It was then diluted with saturated NaCl and extracted with benzene. The solution was evaporated and the residue was chromatographed. Yield 14.8 g (95%), mp 90-91°C (hexane—$CHCl_3$) $[\alpha]_D^{27}$ +11.7° (*C* 1.0).

Methyl-3-O-benzyl-4-desoxy-2-O-*p*-methoxybenzyl-α-*D*-xylo-hexopyranoside (16). A solution of 12 g (20 mmoles) of derivative **15**, 2.87 g of pyridinium perchlorate in 35 ml of $MeNO_2$ and 100 ml of abs. MeOH was boiled for 30 min. After

the solvents had been evaporated, the residue was dissolved in $CHCl_3$, washed with saturated NaCl, evaporated, and chromatographed. Yield 4.7 g (63%), syrup, $[\alpha]_D^{27}$ +34.2° (*C* 1.0). PMR spectrum (δ, ppm, *J*, Hz): 4.62 d (1H, H^1, $J_{1,2}$ = 3.5); 3.44 d.d (1H, H^2, $J_{2,3}$ = 9.5); 3.95 d.d.d (1H, H^3, $J_{3,4e}$ = 5, $J_{3,4a}$ = 11.5), 1.99 d.d.d (^1H, H^{4e}, $J_{4,4}$ = 13, $J_{4e,5}$ = 2); 1.47 q (1H, H^{4a}, $J_{4a,5}$ = 9.5); 3.61 m (1H, H^5); 3.55 m (2H, H^6, H^6); 2.14 s (1H, OH); 4.63 d and 4.68 d, 4.77 d and 4.79 d (4H, AB system, OCH_2Ph at C^3, $OCH_2C_6H_4OMe$-*p* at C^2, J_{gem} = 12); 3.37 s (3H, OMe at C^1); 3.60 s (3H, MeO at $OCH_2C_6H_4OMe$-*p* at C^2); 7.30 m (9H, $C_6H_5CH_2O$ at C^3, $MeOC_6H_4CH_2O$ at C^2).

Methyl-3-O-benzyl-6-bromo-5,6-didesoxy-2-O-*p*-methoxybenzyl-α-*D*-xylo-hexopyranoside (17). A sample of 1.5 g (4.03 mmoles) of alcohol **16** and 1.155 g (5 mmoles) of triphenylphosphine were dissolved in 25 ml of abs. pyridine; to the solution was added 1.66 g (5 mmoles) of CBr_4. After keeping the mixture at 25°C for 1 h, it was diluted with an ether—hexane mixture (50 × 50 ml) and filtered through a silica gel bed, the adsorbent having been washed with the same solvent mixture (100 ml); it was then evaporated and the residue was chromatographed. Yield 1.7 g (97%), syrup, $[\alpha]_D^{25}$ +32.3° (*C* 1.0). PMR spectrum (δ, ppm, *J*, Hz): 4.62 d (1H, H^1, $J_{1,2}$ = 3.5); 3.45 d.d (1H, H^2, $J_{2,3}$ = 10); 3.93 m (2H, H^3, H^5, $J_{3,4a}$ = 12, $J_{3,4e}$ = 5); 2.16 d.d.d (1H, H^{4e}, $J_{4,4}$ = 13, $J_{4e,5}$ = 2.5); 1.47 q (1H, H^{4a}, $J_{4a,5}$ = 12); 3.35 m (2H, H^6, H^6); 4.62 d, 4.68 d, 4.78 d, 4.79 d (AH, OCH_2Ar at C^2 and C^3, AB system, J_{gem} = 12); 3.40 s (3H, OMe at C^1); 3.82 s (3H, MeO in $OCH_2C_6H_4OMe$-*p* at C^2); 7.30 m (9H, $C_6H_5CH_2O$ at C^3); *p*-$MeOC_6H_4CH_2O$ at C^2).

Methyl-3-O-benzyl-6-bromo-4,6-didesoxy-α-*D*-xylo-hexopyranoside (18). a. A sample of 1.05 g (2.57 mmoles) of cerium ammonium nitrate was dissolved in 5 ml of a CH_3CN—H_2O mixture (5:1), then 0.848 g (1.88 mmoles) of bromide **17** in 4 ml of CH_3CN were added to the solution. After stirring for 1 h, another 1.05 g (2.57 mmoles) of the reagent was added. After further stirring for 0.5 h, the mixture was diluted with 100 ml of $CHCl_3$, washed with saturated NaCl, and evaporated; the residue was then chromatographed. Yield 0.6 g (98%), mp 81-82°C ($CHCl_3$—hexane), $[\alpha]_D^{30}$ —110.7° (*C* 1.0). PMR spectrum (δ, ppm, *J*, Hz): 4.62 d (1H, H^1, $J_{1,2}$ = 4); 3.12 m (1H, H^2); 3.73 d.d.d (1H, H^3, $J_{2,3}$ = 9.5, $J_{3,4a}$ = 11, $J_{3,4e}$ = 5); 2.16 d.d.d (1H, H^{4e}, $J_{4,4}$ = 12.5, $J_{4e,5}$ = 2.5); 1.42 q (1H, H^{4a}, $J_{4a,5}$ = 11); 3.91 d.d.d.d (1H, H^5, $J_{5,6}$ = $J_{5,6'}$ = 6); 3.38 m (2H, H^6, H^6); 2.55 s (1H, OH); 4.68 d and 4.63 d (2H, OCH_2Ph at C^3, AB system, J_{gem} = 12); 3.43 s (3H, OMe at C^1); 7.30 m (5H, $OCH_2C_6H_5$ at C^1).

b. A sample of 3.5 g (13 mmoles) of diol **12**-α and 3.40 g (13 mmoles) of triphenylphosphine were dissolved in 15 ml of dry pyridine; to this was added 4.40 g (13 mmoles) of CBr_4 and the mixture kept at 25°C for 5 h. This was diluted with 50 ml of dry THF, filtered through a silica gel bed, washed with dry THF (3 × 50 ml), and evaporated; the residue was then chromatographed. Yield 3.16 g (74%).

Methyl-3-O-benzyl-6-bromo-4,6-didesoxy-β-*D*-xylo-hexopyranoside (19). A sample of 1.66 g (5 mmoles) of CBr_4 was added to a solution of 1 g (3.7 mmoles) of diol **12**-β and 1.155 g (5 mmoles) of triphenylphosphine in 15 ml of dry pyridine; then the mixture was kept at 25°C for 1.5 h. This was diluted with a hexane—ether mixture (1:1, 100 ml) and filtered through a silica gel bed; the precipitate was washed with ether, the filtrate was evaporated, and the residue was then chromatographed. Yield 0.99 g (80.5%), syrup, $[\alpha]_D^{26}$ +58.2° (*C* 1.0). PMR spectrum (δ, ppm, *J*, Hz): 4.19 d (1H, H^1, $J_{1,2}$ = 7.5); 3.44 d.d (1H, H^2, $J_{2,3}$ = 9); 2.58 s (1H, OH); 3.54 d.d.d (1H, H^3, $J_{3,4e}$ = 7, $J_{3,4a}$ = 11); 2.28 d.d.d (1H, H^{4e}, $J_{4,4}$ = 12.5, $J_{4e,5}$= 2); 1.45 d.d.d (1H, H^{4a}, $J_{4a,5}$ = 11); 3.64 d.d.d.d (1H, H^5, $J_{5,6}$ = $J_{5,6'}$ = 5.5); 3.38 d.d (1H, H^6, $J_{6,6}$ = 10.5); 3.47 d.d (1H, H^6); 4.73 d and 4.66 d (2H, $OCH_2C_6H_5$ at C^3, AB system, J_{gem} = 11.5); 3.58 s (3H, OMe at C^1); 7.30 m (5H, $OCH_2C_6H_5$ at C^3).

Methyl-3-O-benzyl-6-bromo-4,6-didesoxy-2-carbethoxymethylidene-α-*D*-threohexopyranoside (20). A sample of 2.3 g (7 mmoles) of alcohol **18** was oxidized using the Swern method [8] in the presence of 2.18 g (2 ml, 28 mmoles) of DMSO, 1.64 g (1.17 ml, 14 mmoles) of $(COCl)_2$, and 5.05 g (7 ml, 50 mmoles) of triethylamine. The resulting ketone was boiled without purification with 4.87 g (14 mmoles) of carbethoxymethylidenetriphenylphosphorane in 25 ml of dry THF for 1 h, diluted with a hexane—ether mixture (1:1, 50 ml) and filtered through a silica gel bed. The precipitate was washed with the same mixture, the filtrate was evaporated, then the residue was chromatographed. Yield 2.30 g (82%), syrup, $[\alpha]_D^{26}$ +18.7° (*C* 1.0). PMR spectrum (δ, ppm, *J*, Hz): 6.42 s (1H, H^1); 6.15 d (1H, H^7, $J_{3,7}$ = 2); 4.44 d.d.d (1H, H^3, $J_{3,4a}$ = 13, $J_{3,4e}$ = 6.5); 2.36 d.d.d (1H, H^{4e}, $J_{4,4}$ = 13, $J_{4e,5}$ = 2.5); 1.59 d.d.d (1H, H^{4a}, $J_{4a,5}$ = 13); 4.13 m (1H, H^5); 3.42 d.d (1H, H^6, $J_{6,6}$ = 10.5, $J_{5,6}$ = 7.5); 3.38 d.d (1H, $H^{6'}$, $J_{5,6}$ = 5); 3.48 s (3H, OMe at C^1); 4.90 q (2H, $\underline{OCH_2}CH_3$, J_{CH_2,CH_3} = 7); 1.30 t (3H, $OCH_2\underline{CH_3}$); 4.62 d, 4.68 d (2H, OCH_2Ph at C^3, AB system, J_{gem} = 12); 7.30 m (5H, $\underline{OCH_2Ph}$ at C^3). Nuclear Overhauser effect: [H^7], [H at 4.62 ppm for the OCH_2Ph group] = 2%, absent for H^1.

Similar processing of alcohol **19** yielded a mixture of methyl-α,β-*D* glycosides (**20**) (89%). PMR spectrum of β-*D*-isomer **20** (δ, ppm, *J*, Hz): 5.98 d (1H, H^1, $J_{1,7}$ = 1.5); 6.12 t (1H, H^7, $J_{3,7}$ = 1.5); 4.09-4.25 m (5H, H^3, H^3, $H^{5'}$, OCH_2CH_3-α,β); 2.46 d.d.d (1H, H^{4e}, $J_{4,4}$ = 13, $J_{4e,3}$ = 4, $J_{4e,5}$ = 6); 1.95 d.d.d (1H, H^{4a}, $J_{3,4a}$ = 9, $J_{4a,5}$ = 10.5); 3.69 d.d (1H, H^6, $J_{6,6}$ = 9.5, $J_{6,5}$ = 6); 3.55 d.d (1H, H^6, $J_{5,6}$ = 7.5); 3.58 s (3H, OMe-β at C^1); 1.3 t (3H, $OCH_2\underline{CH_3}$-α,β); 4.64 d, 4.59

d (2H, OCH_2Ph at C^3, AB system, J_{gem} = 8); 7.30 m (5H, $OCH_2\underline{Ph}$ at C^3).

(1*S*, 2*S*, 4*S*, 6*S*)-2-Methoxy-6-benzylhydroxy-1-ethoxycarbonylmethylene-3-oxabicyclo[2,2,1]heptane (22). To a boiling solution of 2.0 g (5 mmoles) of bromide **20** in 75 ml of dry benzene was added dropwise over 5 h a solution of 2.43 g (8.3 mmoles) of tributyl tin hydride and 150 mg (10% molar) AIBN in 50 ml of dry benzene. After the reagents had been added together, the mixture was boiled for 1 h and evaporated; the residue was then chromatographed. Yield 1.06 g (66%), syrup, $[\alpha]_D^{27}$ +90.2° (*C* 1.0). PMR spectrum (δ, ppm, *J*, Hz): 4.90 s (1H, H^1); 4.35 t (1H, H^3, $J_{3,4a} = J_{3,4e}$ = 2.5); 2.20 d.d.d (1H, H^{4e}, $J_{4,4}$ = 13.5; $J_{4e,5}$ = 6.5); 1.62 t.d (1H, H^{4a}, $J_{4a,5}$ = 2.5); 4.08 m (1H, H^5); 2.0 d (1H, H^6, $J_{5,6}$ = 10); 1.93 d (1H, $H^{6'}$); 2.78 d, 2.70 d (2H, H^7, $H^{7'}$, AB system, J_{gem} = 14.5); 4.53 d, 4.43 d (2H, OCH_2Ph at C^3, AB system, J_{gem} = 11.5); 3.38 s (3H, OMe at C^1); 4.08 q (2H, OCH_2CH_3, J_{CH_2,CH_3} = 7.5); 1.24 t (3H, $OCH_2\underline{CH_3}$); 7.30 m (5H, $OCH_2\underline{Ph}$ at C^3).

Using a similar method a mixture of anomers **20** yielded a mixture of anomers **22** (82%). PMR spectrum of **22-β** (δ, ppm, *J*, Hz): 4.59 s (1H, H^1); 4.38 m (1H, H^3); 2.07 d.d.d.d (1H, $J_{4,4}$ = 15, $J_{4e,5}$ = 2.5, *J* = 8.5, *J* = 1.5); 1.63 d.d.d (1H, H^{4a}, *J* = 9, *J* = 3); 3.86 d.d.d (1H, H^5, $J_{5,6}$ = 6.5, *J* = 1); 1.79 d.d.d.d (1H, H^6, $J_{6,6}$ = 10, *J* = 1, *J* = 2.5, *J* = 2.5); 1.69 d (1H, $H^{6'}$); 4.52 d, 4.34 d (2H, OCH_2Ph at C^3, AB system, J_{gem} = 11.5); 2.94 d, 2.76 d (2H, H^7, $H^{7'}$, AB system, J_{gem} = 16.5); 4.09 q (2H, OCH_2CH_3, J_{CH_2,CH_3} = 7); 1.24 t (3H, OCH_2CH_3); 3.34 s (CH, OMe at C^1); 7.30 m (5H, CH_2Ph at C^3).

Methanolysis of Bicyclooxaheptane (22). A solution of 1.977 g (6.17 mmoles) of derivative **22** in 10 ml of 20% H_2SO_4 was kept at 25°C for 24 h, then boiled for 1 h. The solution was cooled, diluted with 50 ml of $CHCl_3$, washed with water and saturated $NaHCO_3$ and NaCl solutions, and evaporated; the residue was then chromatographed. Yield of ester (**23**) 0.758 g (40.4%). PMR spectrum (δ, ppm, *J*, Hz): 4.58 s (1H, H^1); 4.38 m (1H, H^3); 1.57 d.t (1H, H^{4a}, $J_{4,4}$ = 13, $J_{4a,5}$ = 2.5); 2.07 d.d.d (1H, H^{4e}, $J_{4e,5}$ = 6.5, *J* = 2.5); 3.86 d.d (1H, H^5); 1.70 d (1H, H^6, $J_{6,6}$ = 10); 1.79 d.t (1H, $H^{6'}$, *J* = 2.5); 2.76 d, 2.94 d (2H, H^7, $H^{7'}$, AB system, J_{gem} = 16.5); 4.34 d, 4.52 d (2H, OCH_2Ph at C^3, AB system, J_{gem} = 11); 3.62 s (3H, $COOCH_3$); 3.34 s (3H, MeO at C^1); 7.30 m (5H, $OCH_2\underline{Ph}$ at C^3).

(1*S*, 2*S*, 4*S*)-1-Dimethoxymethyl-2,4-dihydroxy-1-carboxymethylenecyclopentane, lactone (24). To a solution of 0.371 g (1.16 mmoles) of derivative **22** in 3 ml of Ac_2O was added 0.1 ml of H_2SO_4. This was kept at 25°C for 1 h, cooled to 0°C, decomposed with water, and extracted with $CHCl_3$. The solution was then washed with water and saturated $NaHCO_3$ and NaCl, dried, and evaporated. The residue was dissolved in 5 ml of 5% H_2SO_4 in MeOH and boiled for 1 h. This solution was cooled, diluted with $CHCl_3$, then washed with water and saturated $NaHCO_3$ and NaCl. After drying and evaporation, the residue was chromatographed. Yield 88 mg (36%), syrup, $[\alpha]_D^{26}$ −6.7° (*C* 1.0). PMR spectrum (δ, ppm, *J*, Hz): 4.29 s (1H, H^1); 4.84 d.d (1H, H^3, $J_{3,4}$ = 6.5, $J_{3,4'}$ = 3); 2.16 d.d.d.d (1H, H^4, $J_{4,4}$ = 14, *J* = 1.5, *J* = 3, *J* = 6); 1.98 m (3H, H^4, H^6, $H^{6'}$); 4.38 m (1H, H^5); 2.87 d, 2.31 d (2H, H^7, H^7, AB system, J_{gem} = 18); 3.54 s (6H, OMe at C^1).

Diacetoxy-lactone (25). The substance from the previous experiment was acetylated with an Ac_2O—pyridine mixture (1:1, 3 ml) at 25°C for 24 h. The mixture was decomposed with MeOH and evaporated, then the residue was chromatographed. Quantitative yield, syrup, $[\alpha]_D^{27}$ −26.2° (*C* 1.0). PMR spectrum (δ, ppm, *J*, Hz): 4.25 s (1H, H^1); 4.81 d.d (1H, H^3, $J_{3,4}$ = 2, $J_{3,4'}$ = 6.5); 2.11 d.d.d (1H, H^4, $J_{4,4}$ = 13, $J_{4,5}$ = 1.5); 1.98 d.d.d (1H, $H^{4'}$, $J_{4,5}$ = 8); 5.21 m (1H, H^5, $J_{5,6}$ = 6.5, $J_{5,6'}$ = 8.5); 2.37 d.d.d.d (1H, H^6, $J_{6,6}$ = 14.5, *J* = 3.5, *J* = 3.5); 1.97 d.d.d (1H, $H^{6'}$, *J* = 6); 2.31 d, 2.95 d (2H, H^7, H^7, AB system, J_{gem} = 18); 2.05 s (3H, $OCOCH_3$); 3.52 s, 3.54 s (6H, OMe at C^1).

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