Carbohydrate Research, 151 (1986) 379–389
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

APPLICATION OF A RADICAL REACTION TO THE SYNTHESIS OF L-IDURONIC ACID DERIVATIVES FROM D-GLUCURONIC ACID ANALOGUES*†

TAKU CHIBA AND PIERRE SINAŸ‡
Laboratoire de Biochimie Structurale, U.A. 499, U.F.R. de Sciences Fondamentales et Appliquées, B.P. 6759, 45067 Orléans Cédex 2 (France)

(Received January 22nd, 1986; accepted for publication, February 21st, 1986)

ABSTRACT

Commercially available D-glucofuranurono-6,3-lactone was transformed into the known, crystalline methyl (5*R*)-1,2,3,4-tetra-*O*-acetyl-5-*C*-bromo-β-D-glucopyranuronate (**3**) in three steps. Reduction with tributyltin hydride gave crystalline methyl 1,2,3,4-tetra-*O*-acetyl-α-L-idopyranuronate (**4**) in ~30% yield, together with the crystalline methyl 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranuronate (**1**, 63.5%) which may be separated and converted back by Ferrier's photobromination into **3**. This procedure provides the first practical and expeditious conversion of D-glucuronic acid into L-iduronic acid by epimerization. Acetate **4** was converted in quantitative yield into methyl (2,3,4-tri-*O*-acetyl-α-L-idopyranosyl bromide)-uronate (**22**), and then into methyl 3,4-di-*O*-acetyl-β-L-idopyranuronate 1,2-(methyl orthoester) (**23**), which are useful compounds for glycosylation reactions. Various β-D-glucuronic acid derivatives have been epimerized to α-L-iduronic acid analogues by this novel procedure.

INTRODUCTION

L-Iduronic acid is a typical component of mammalian dermatan sulfate, heparan sulfate, and heparin[2]. The presence of iduronic acid as a constituent of dermatan sulfate was first reported by Hoffman *et al.*, and then by Cifonelli *et al.*[3], but the unambiguous chemical identification of L-iduronic acid was made by Stoffyn and Jeanloz[4], who described the isolation from dermatan sulfate of crystalline 2,3,4-tri-*O*-acetyl-1,6-anhydro-β-L-idopyranose, identified by comparison with the synthetic compound. It was unequivocally established later that L-iduronic acid is an important constituent of heparin from various sources[5]. Within the framework of a program of chemical synthesis of heparin fragments[6], we required various L-idopyranosyluronic acid derivatives. A synthetic route based on practical isomer-

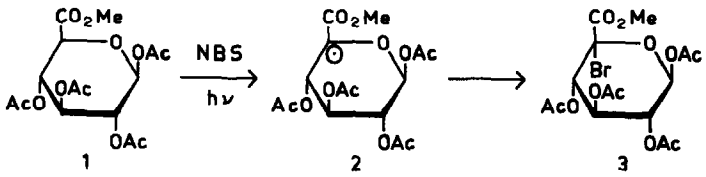
*Dedicated to Roger W. Jeanloz.
†Part of this work has been presented; see ref. 1.
‡To whom enquiries should be sent.

0008-6215/86/$ 03.50

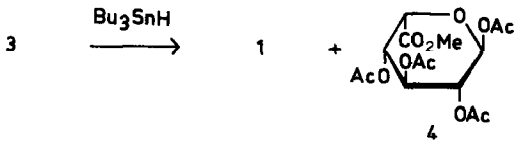
ization at C-5 of an appropriate D-glucopyranosyluronic acid derivative would be attractive, because of the availability of the former. An early claim[7] to have readily achieved this epimerization in aqueous alkali was later shown to be invalid by two groups[8]. The epimerization of 2-*O*-(4-*O*-methyl-α-D-glucopyranosyluronic acid)-D-xylitol promoted by aqueous sodium hydroxide gave the corresponding L-iduronic acid derivative in low yield, the major product arising by β-elimination[9]. More recently. Baggett and Smithson[10] prepared, in limited yields, derivatives of L-iduronic acid by epimerization of D-glucuronic acid derivatives that were constrained to adopt a conformation having C-6 in axial disposition, so that the L-iduronic acid derivatives would be thermodynamically more stable. The yields were decreased by decomposition, probably through β-elimination. Thus methyl 3,5-*O*-benzylidene-1,2-*O*-isopropylidene-α-D-glucofuranuronate, prepared in two steps from the commercially available D-glucofuranurono-6,3-lactone, was epimerized to the crystalline L-*ido* analogue in 33% yield. A limitation of this interesting procedure is that the L-*ido* analogue is not directly usable as glycosylating agent. We now demonstrate that such an epimerization can be cleanly achieved without β-elimination by way of a radical at C-5.

RESULTS AND DISCUSSION

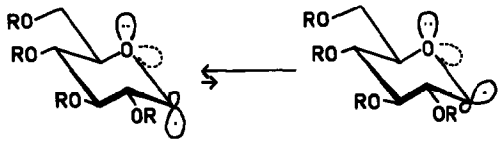
Radical brominations α to ester carbonyl groups are known with simple compounds[11] and Ferrier's group extended this reaction[12] to light-induced *N*-bromosuccinimide bromination at C-5 of methyl 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranuronate (**1**) to give methyl (5*R*)-1,2,3,4-tetra-*O*-acetyl-5-*C*-bromo-β-D-glucopyranuronate (**3**) crystalline in 68% yield. The abstraction of H-5 leading to the bromo derivative **3** is a homolytic process, with the methoxycarbonyl group at C-5 providing stabilization of radical **2** at C-5.



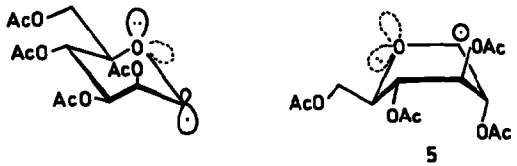
Reaction of bromide **3** with tributyltin hydride for 2 min or 30 min on a multigram scale in boiling dry toluene gave methyl 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranuronate (**1**) in ~63% yield and methyl 1,2,3,4-tetra-*O*-acetyl-α-L-idopyranuronate (**4**) in ~27% yield. These two crystalline derivatives were separated by chromatography on a column of silica gel.



The reaction of either β- or α-D-glucopyranosyl halides with tributyltin hydride has previously been explained by postulating the formation of an intermediate, bent σ-radical which then mainly reacts by *cis* addition to afford an axially substituted product[13]. This stereoselectivity was originally explained[14] by the occurrence of two rapidly interconverting σ-radicals:



Because of interaction with the non-bonding electron pair on the ring oxygen atom, the axial σ-radical should be more stable[14,15] and more nucleophilic[16] than the corresponding equatorial σ-radical. Although this anomeric effect of radicals explains the excellent diastereoselectivity observed in the reaction of 2-deoxy-*arabino*-hexopyranosyl radicals[15b], it does not completely explain the more limited selectivity — from 98:2 to 78:22 — observed for glucopyranosyl σ-radicals. Dobbs *et al.*[17] have observed a favored conformation in open-chain radicals of the type ROCHCHR'OR" in which the half-occupied orbital and the β-CO bond have a coplanar arrangement. This may be explained in terms of a SOMO/LUMO interaction. Such a radical-stabilizing effect by a coplanar β-CO bond has also apparently been observed in glycosyl radicals[18]: e.s.r. spectra show that the D-mannosyl radical adopts exclusively the $^4C_1$ chair conformation, whereas the D-glucosyl radical **5** adopts the $B_{2,5}$ conformation. According to Giese *et al.*[18], the stabilizing interaction between the half-occupied orbital at the radical center and the σ* orbital of C–OR bond overcompensation for the repulsive interactions in the transition from the $^4C_1$ chair to the $B_{2,5}$ boat conformations.



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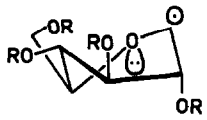
As the $^1S_5$ conformer as a lower energy (~0.9 kcal.mol^{-1}) from than the $B_{2,5}$ conformer[19] is in agreement with the e.s.r. spectrum, and offers a better coplanar arrangement between the half-occupied orbital and both the β-CO bond and the non-bonding electron-pair on the ring oxygen atom, we suggest that it may be favored over $B_{2,5}$ as a possible conformer for **5**.

The radical **2** may be planar, as the tendency of the ring oxygen atom to induce bending is outweighed by the tendency of the methyloxycarbonyl group to induce coplanarity and thereby maximize delocalization of the unpaired electron[20]. Attack of this radical from the bottom face provides compound **1**, which adopts the

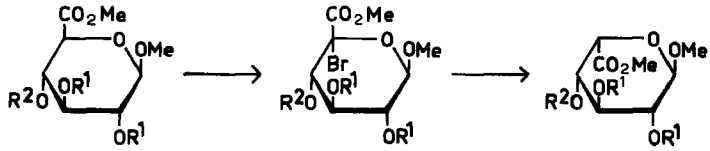


$^1S_5$

$^4C_1$ conformation. Kinetic attack from the upper side provides compound **4**, which has been shown to adopt in solution the $^1C_4$ conformation where the incoming hydrogen presents a coplanar arrangement with the β-CO bond at C-4.

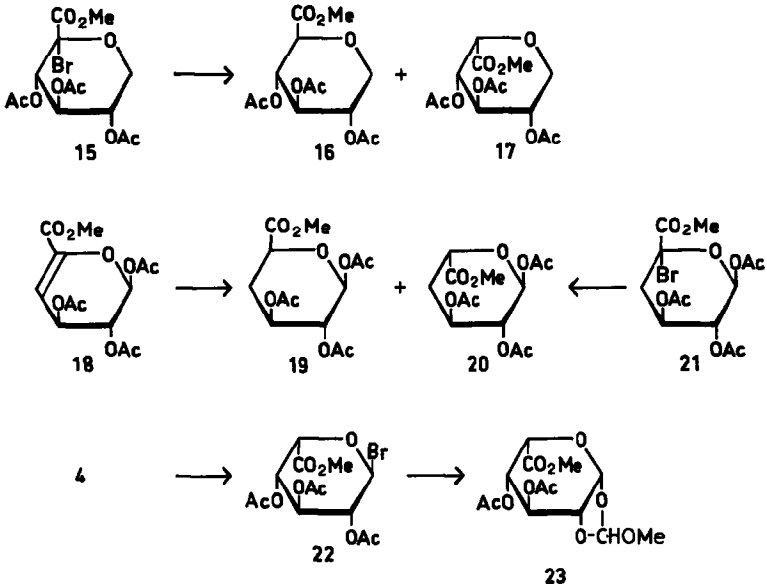
In order to study the influence of the various substituents on the steric outcome of this reaction, several derivatives of D-glucuronic acid were prepared, photobrominated, and then reduced with tributyltin hydride. Methyl (methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosid)uronate[21] (**6**) was photobrominated under a lamp in the presence of *N*-bromosuccinimide and benzoyl peroxide to give the crystalline bromide **9** in 46% yield. Reduction of **9** with tributyltin hydride gave compound **6** in 44.5% yield and the L-*ido* analogue (**12**) in 38% yield. This reaction offers an expeditious synthesis of methyl α-glycosides of L-iduronic acid derivatives. Similarly, methyl (methyl 2,3,4-tri-*O*-methyl-β-D-glucopyranosid)uronate[22] (**7**) was photobrominated to give bromide **10**, which was reduced to give compound **7** in 42% yield and the L-*ido* analogue **13** in 35% yield. The replacement of acetyl by methyl groups has thus practically no influence on the D-*gluco*:L-*ido* ratio observed upon reduction by tributyltin hydride. Methyl (methyl 4-*O*-acetyl-2,3-di-*O*-methyl-β-D-glucopyranosid)uronate[22] (**8**) was similarly photobrominated to give bromide **11** which was reduced to give compound **8** in 44% yield and the L-*ido* analogue **14** in 37% yield. The magnitude of the β-effect is thus about the same for a 4-*O*-methyl or a 4-*O*-acetyl group. Finally, methyl tri-*O*-acetyl-α-L-*xylo*-hexulopyranosyl-uronate bromide[12] (**15**) was reduced to give methyl 3,4,5-tri-*O*-acetyl-2,6-anhydro-L-gulonate (**16**) in 44% yield and methyl 3,4,5-tri-*O*-acetyl-2,6-anhydro-L-idonate (**17**) in 34% yield.

In order to confirm the critical role of the β-CO bond on the steric outcome of the reaction, deoxygenation of position 4 was performed. Methyl 1,2,3-tri-*O*-acetyl-4-deoxy-α-L-*threo*-hex-4-enopyranuronate[23] (**18**) was hydrogenated in the presence of Pd/C to give a mixture of methyl 1,2,3-tri-*O*-acetyl-4-deoxy-β-D-*xylo*-hexopyranuronate (**19**) and methyl 1,2,3-tri-*O*-acetyl-4-deoxy-α-L-*arabino*-hexo-



6 $R^1=R^2=Ac$	9 $R^1=R^2=Ac$	12 $R^1=R^2=Ac$
7 $R^1=R^2=Me$	10 $R^1=R^2=Me$	13 $R^1=R^2=Me$
8 $R^1=Me, R^2=Ac$	11 $R^1=Me, R^2=Ac$	14 $R^1=Me, R^2=Ac$

pyranuronate (**20**). Photobromination of **19** gave the unstable bromide **21**, which was reduced with tributyltin hydride to give a mixture **19** and **20** in the ratio of 17:1. This dramatic shift towards a D-*gluco* derivative after deoxygenation at C-4 is a strong argument in favor of the critical role played by the β-effect. When the derivative **4** was submitted to photobromination, the bromide **3** was obtained as the only isolable product. The radical **2** cannot be brominated from the upper (β) side because of the strong steric interaction with the anomeric acetate. In a similar manner, Blattner *et al.*[23] have shown that photobromination of penta-*O*-acetyl-α-D-idopyranose involves abstraction of an axial hydrogen atom and leads to a radical that ring-inverts prior to bromination. This reaction cannot be applied to a benzylated molecule, as benzyl ethers are photobrominated. A similar reaction has been attempted[24] on 1,6-anhydro-2,3-di-*O*-benzoyl-4-*O*-(methyl 2,3,4-tri-*O*-benzoyl-5-*C*-bromo-β-D-glucopyranosyluronate)-β-D-glucopyranose using neat triphenyltin hydride, but the reductive replacement of the bromine atom occurred with configurational retention and a D-glucosyluronate-containing disaccharide was obtained.



Interestingly, when methyl (5*R*)-1,2,3-tri-*O*-acetyl-5-*C*-bromo-4-deoxy-β-D-*xylo*-hexopyranuronate (**21**) was treated with zinc dust in dry acetic acid, the L-*ido* compound **20** was obtained as the major isomer. In accordance with the concept of steric control of ketonization of enols[25], kinetic protonation of the exo-enolic moiety favors an exo (equatorial) approach. Additional positive influence of electronic factors may also increase the stereoselectivity[26]. Expectedly, the application of this reaction to bromo compounds **3**, **9**, **10**, and **11** led to elimination.

The synthesis of **4** in four steps from commercially available D-gluco-

furanurono-6,3-lactone is expeditious and can be used readily to prepare multigram amounts. Radical chemistry solves the long-standing problem of the practical epimerization of a D-glucopyranosyluronic acid derivative into its L-*ido* analogue without concomitant extensive β-elimination. Finally, compound **4** was routinely converted into the bromide **22**, and then into orthoester **23**, which are potential glycosylating agents. The use of **22** for the synthesis of α-L-iduronic acid-containing disaccharides has been achieved[27] and will be described elsewhere.

EXPERIMENTAL

General methods. — Melting points were determined in capillary tubes with a Büchi apparatus and are uncorrected. Optical rotations were measured at 22–25° with a Perkin–Elmer Model 141 polarimeter. ^{1}H-N.m.r. spectra were recorded with a Perkin–Elmer R-32 (90 MHz) or Bruker CXP (300.13 MHz) instrument for solutions in $CDCl_3$ (internal Me_4Si). The purity of products was determined by t.l.c. on Silica Gel 60F 254 (Merck) with detection by charring with sulfuric acid. Column chromatography was performed on Silica Gel 60 (Merck, 63–200 μm) which was used without pretreatment, with 1 g of the mixture to be separated per 30 g of adsorbent. The bulb used for irradiation was a standard, transparent Mazda, 240 V, 150 W. Two bulbs were used for multigram experiments. Elemental analyses were performed by the Service Central de Micro-Analyse du Centre National de la Recherche Scientifique (Vernaison, France).

*Methyl 1,2,3,4-tetra-*O*-acetyl-β-*D*-glucopyranuronate* (**1**) *and -α-*L*-idopyranuronate* (**4**). — Tributyltin hydride (23.6 mL) was added to a solution of methyl (5*R*)-1,2,3,4-tetra-*O*-acetyl-5-*C*-bromo-β-D-glucopyranuronate (**3**) (29.8 g) in dry toluene (340 mL) and the mixture was boiled under reflux for 30 min. 1-Bromobutane (23.6 mL) was then added and the mixture was boiled for a further 30 min, cooled to room temperature, and evaporated. Elution of the residue from a column of Silica Gel Merck 60H (Jobin–Yvon chromatospac Prep) with hexane, (3 L), and then successively with 3:1 (500 mL), 2:1 (500 mL), and 1:3 (500 mL) hexane–ethyl acetate gave first compound **1** (15.64 g, 63.5%), m.p. 177–178° (from ethanol); lit.[28] m.p. 176.5–178° (from ethanol).

Next eluted was methyl 1,2,3,4-tetra-*O*-acetyl-α-L-idopyranuronate (**4**) (6.80 g, 27.6%), m.p. 118–119° (from ethanol), $[\alpha]_D$ −88° (*c* 1.00, chloroform); ^{1}H-n.m.r. data: (300 MHz, C_6D_6): δ 6.69 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 5.58 (t, 1 H, $J_{2,3} = J_{3,4} = 5.0$ Hz, H-3), 5.44 (dd, 1 H, $J_{3,4}$ 5.0, $J_{4,5}$ 3.5 Hz, H-4), 5.18 (dd, 1 H, $J_{1,2}$ 3.5, $J_{2,3}$ 5.0 Hz, H-2), 4.89 (d, 1 H, $J_{4,5}$ 3.5 Hz, H-5), 3.27 (s, 3 H, CO_2Me), 1.63, 1.57, and 1.49 (3 s, 12 H, Ac); (300 MHz, $CDCl_3$): δ 6.29 (d, 1 H, $J_{1,2}$ 2.5 Hz, H-1), 5.18 (dd, 1 H, $J_{3,4}$ 4.5, $J_{4,5}$ 2.4 Hz, H-4), 5.17 (ddd, 1 H, $J_{1,3}$ 1.0, $J_{2,3} = J_{3,4} =$ 4.5 Hz, H-3), 4.88 (d, 1 H, $J_{4,5}$ 2.4 Hz, H-5), 4.86 (ddd, 1 H, $J_{1,2}$ 2.5, $J_{2,3}$ 4.5, $J_{2,4}$ 1.0 Hz, H-2), 3.80 (3 H, s, CO_2Me), 2.13, 2.12, 2.11, and 2.08 (4 s, 12 H, Ac).

Anal. Calc. for $C_{15}H_{20}O_{11}$: C, 47.88; H, 5.36. Found: C, 47.89; H, 5.59.

This reaction was performed on various amounts of starting material **3**: 110 mg (2 min), 12 g (10 min), 14 g (20 min). Identical yields were observed.

*Methyl [methyl (5*R*)-2,3,4-tri-*O*-acetyl-5-*C*-bromo-β-*D*-glucopyranosid]uro-*

nate (**9**). — A suspension of methyl (methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosid)uronate (**6**, 1 g), *N*-bromosuccinimide (613 mg) and benzoyl peroxide (90 mg) in dry carbon tetrachloride (40 mL) was boiled under reflux with stirring and under a lamp. After 2 h, a further addition of *N*-bromosuccinimide (153 mg) and benzoyl peroxide (23 mg) was made and the mixture refluxed for 30 min. The mixture was cooled, filtered, and evaporated. The residue was eluted from a column of silica gel with 1:1 hexane–ethyl acetate containing 0.1% of triethylamine, to give **9** (567 mg, 46.2%), m.p. 122–124° (dec.) (from ethanol), $[\alpha]_D$ −160° (*c* 1.00, chloroform); ^{1}H-n.m.r. data (90 MHz, $CDCl_3$): δ 5.39 (dd, 1 H, $J_{2,3}$ 7.3, $J_{3,4}$ 9.0 Hz, H-3), 5.26 (d, 1 H, $J_{3,4}$ 9.0 Hz, H-4), 5.07 (d, 1 H, $J_{1,2}$ 7.3 Hz, H-1), 5.03 (t, 1 H, $J_{1,2} = J_{2,3}$ = 7.3 Hz, H-2), 3.81 (s, 3 H, CO_2Me), 3.52 (s, 3 H, OMe), 2.06, 2.04, and 1.98 (3 s, 9 H, Ac).

Anal. Calc. for $C_{14}H_{19}BrO_{10}$: C, 39.36; H, 4.48. Found: C, 39.32; H, 4.42.

Methyl [methyl (5R)-5-C-bromo-2,3,4-tri-O-methyl-β-D-glucopyranosid]uronate (**10**). — A suspension of methyl (methyl 2,3,4-tri-*O*-methyl-β-D-glucopyranosid)uronate (**7**, 84 mg), *N*-bromosuccinimide (68 mg), and benzoyl peroxide (10 mg) in dry carbon tetrachloride (3.4 mL) was boiled under reflux for 30 min with stirring and under a lamp. After 30 min, a further addition of *N*-bromosuccinimide (17 mg) and benzoyl peroxide (3 mg) was made and the mixture refluxed for 20 min. The previously described isolation gave amorphous **10** (49.8 mg, 45.6%), $[\alpha]_D$ −117.5° (*c* 0.48, chloroform); ^{1}H-n.m.r. data (90 MHz, $CDCl_3$): δ 4.78 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 3.89 (s, 3 H, CO_2Me), 3.68, 3.60, and 3.58 (3 s, 12 H, OMe).

As this compound is very unstable, a correct elemental analysis was not obtained.

Methyl [methyl (5R)-5-O-acetyl-5-C-bromo-2,3-di-O-methyl-β-D-glucopyranosid]uronate (**11**). — A suspension of methyl (methyl 4-*O*-acetyl-2,3-di-*O*-methyl-β-D-glucopyranosid)uronate (**8**, 152 mg), *N*-bromosuccinimide (120 mg), and benzoyl peroxide (16 mg) in dry carbon tetrachloride (4 mL) was boiled under reflux for 30 min with stirring and under a lamp. The previously described isolation gave **11** (88.3 mg, 46%), m.p. 97–98° (from ethanol), $[\alpha]_D$ −188.5° (*c* 1.04, chloroform); ^{1}H-n.m.r. data (90 MHz, $CDCl_3$): δ 5.07 (d, 1 H, $J_{3,4}$ 9.0 Hz, H-4), 4.76 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 3.77 (s, 3 H, CO_2Me), 3.55, 3.51 (2 s, 9 H, OMe), 3.40 (dd, 1 H, $J_{1,2}$ 8.0, $J_{2,3}$ 9.0 Hz, H-2), and 2.10 (s, 3 H, Ac).

Anal. Calc. for $C_{12}H_{19}BrO_8$: C, 38.83; H, 5.16. Found: C, 38.98; H, 4.96.

Methyl (methyl 2,3,4-tri-O-acetyl-α-L-idopyranosid)uronate (**12**). — Methyl [methyl (5*R*)-2,3,4-tri-*O*-acetyl-5-*C*-bromo-β-D-glucopyranosid]uronate (**9**, 100 mg) was treated as previously described for the reduction of **3** to give first methyl (methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosid)uronate (**6**) (36.3 mg, 44.5%), m.p. 151–152° (from ethanol); lit.[23] m.p. 151–152°.

Next eluted was compound **12** (31.2 mg, 38.3%), $[\alpha]_D$ −56.5° (*c* 1.12, chloroform); ^{1}H-n.m.r. data (300 MHz, $CDCl_3$): δ 5.13 (ddd, 1 H, $J_{2,4}$ 1.0, $J_{3,4}$ = 3.6, $J_{4,5}$ 2.6 Hz, H-4), 5.06 (six lines, 1 H, $J_{1,3}$ 1.0, $J_{2,3} = J_{3,4}$ 3.6 Hz, H-3), 4.91 (dd, 1 H, $J_{1,2}$ 1.8, $J_{1,3}$ 1.0 Hz, H-1), 4.83 (d, 1 H, $J_{4,5}$ 2.6 Hz, H-5), 4.79 (ddd, 1 H, $J_{1,2}$ 1.8, $J_{2,3}$ 3.6, $J_{2,4}$ 1.0 Hz, H-2), 3.80 (s, 3 H, CO_2Me), 3.44 (s, 3 H, OMe), 2.11, 2.09, and 2.08 (3 s, 9 H, Ac).

Anal. Calc. for $C_{14}H_{20}O_{10}$: C, 48.28; H, 5.79. Found: C, 48.14; H, 5.71.

*Methyl (methyl 2,3,4-tri-*O*-methyl-α-*L*-idopyranosid)uronate* (**13**). — Methyl [methyl (5*R*)-5-*C*-bromo-2,3,4-tri-*O*-methyl-β-D-glucopyranosid]uronate (**10**, 50 mg) was treated as previously described, except that the reflux was maintained for 10 min, to give first methyl (methyl 2,3,4-tri-*O*-methyl-β-D-glucopyranosid)-uronate (**7**, 16 mg, 41.7%), m.p. 54–55°; lit.[24] m.p. 52–53° (from petroleum ether).

Next eluted was compound **13** (13.3 mg, 34.6%), $[\alpha]_D$ −54° (*c*, 0.30, chloroform); ^{1}H-n.m.r. data (300 MHz, $CDCl_3$): δ 4.87 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.63 (d, 1 H, $J_{4,5}$ 3.5 Hz, H-5), 3.80 (s, 3 H, CO_2Me), 3.55, 3.49, 3.47, and 3.45 (4 s, 12 H, OMe).

Anal. Calc. for $C_{11}H_{20}O_7$: C, 49.99; H, 7.63. Found: C, 49.80; H, 7.66.

*Methyl (methyl 4-*O*-acetyl-2,3-di-*O*-methyl-α-*L*-idopyranosid)uronate* (**14**). — Methyl [methyl (5*R*)-4-*O*-acetyl-5-*C*-bromo-2,3-di-*O*-methyl-β-D-glucopyranosid]-uronate (**11**, 21 mg) was treated as previously described to give first methyl (methyl 4-*O*-acetyl-2,3-di-*O*-methyl-β-D-glucopyranosid)uronate (**8**) (7.2 mg, 43.6%), m.p. 97–99° (from ethanol); lit.[24] m.p. 97–99° (from ethanol).

Next eluted was compound **14** (6.0 mg, 36.4%), $[\alpha]_D$ −83° (*c* 1.30, chloroform); ^{1}H-n.m.r. data (300 MHz, $CDCl_3$): δ 5.17 (dd, 1 H, $J_{3,4}$ 3.9, $J_{4,5}$ 3.0 Hz, H-4), 4.92 (d, 1 H, $J_{1,2}$ 2.5 Hz, H-1), 4.77 (d, 1 H, $J_{4,5}$ 3.0 Hz, H-5), 3.77 (s, 3 H, CO_2Me), 3.61 (six lines, 1 H, $J_{1,3}$ 0.7 Hz, $J_{2,3} = J_{3,4} = 3.9$ Hz, H-3), 3.55, 3.48, 3.43 (3 s, 9 H, OMe), 3.20 (ddd, 1 H, $J_{1,2}$ 2.5, $J_{1,3}$ 0.7, $J_{2,3}$ 3.9 Hz, H-2), and 2.06 (s, 3 H, Ac).

Anal. Calc. for $C_{12}H_{20}O_8$: C, 49.31; H, 6.90. Found: C, 49.09; H, 7.10.

*Methyl 3,4,5-tri-*O*-acetyl-2,6-anhydro-*L*-idonate* (**17**). — Methyl tri-*O*-acetyl-α-L-*xylo*-hexulopyranosyluronate bromide (**15**, 76 mg) was treated for 10 min as previously described to give first methyl 3,4,5-tri-*O*-acetyl-2,6-anhydro-L-gulonate (**16**) (25.4 mg, 43.6%), m.p. 114–115°; lit.[11] 116–117° (from ethanol).

Next eluted was compound **17** (20.8 mg, 34.2%), $[\alpha]_D$ +8° (*c* 1.63, chloroform); ^{1}H-n.m.r. data (90 MHz): δ 5.40–5.05 (m, 2 H, H-3 and H-4), 4.75 (m, 1 H, H-5), 4.47 (d, 1 H, $J_{2,3}$ 2.3 Hz, H-2), 4.25 (dd, 1 H, $J_{5,6e}$ 2.0, $J_{6a,6e}$ 13.3 Hz, H-6*e*), 3.90 (dd, 1 H, $J_{5,6a}$ 2.3, $J_{6a,6e}$ 13.3 Hz, H-6*a*), 3.80 (s, 3 H, CO_2Me), 2.17, 2.13, and 2.11 (3 s, 9 H, Ac).

Anal. Calc. for $C_{13}H_{18}O_9$: C, 49.06; H, 5.70. Found: C, 48.99; H, 5.53.

*Methyl 1,2,3-tri-*O*-acetyl-4-deoxy-β-*D*-xylo-hexopyranuronate* (**19**) *and methyl 1,2,3-tri-*O*-acetyl-4-deoxy-α-*L*-arabino-hexopyranuronate* (**20**). — (*a*) A solution of methyl 1,2,3-tri-*O*-acetyl-4-deoxy-α-L-*threo*-hex-4-enopyranuronate (**18**, 214 mg) in methanol (7 mL) was hydrogenated in the presence of 10% Pd/C (50 mg) for 1.5 h, filtered, and evaporated. The residue was eluted from a column of silica gel with hexane–ethyl acetate (from 3:1 to 1:1) to give first pure, amorphous compound **19** (61.9 mg, 29%), $[\alpha]_D$ +0.5° (*c* 0.75, chloroform); ^{1}H-n.m.r. data (90 MHz): δ 5.74 (d, 1 H, $J_{1,2}$ 7.3 Hz, H-1), 5.25–5.00 (m, 2 H, H-2 and H-3), 4.33 (dd, 1 H, $J_{4a,5}$ 11.3, $J_{4e,5}$ 2.7 Hz, H-5), 3.80 (s, 3 H, CO_2Me), 2.50 (m, 1 H, H-4*e*), 2.13, 2.07 (2 s, 9 H, Ac), and 1.90 (m, 1 H, H-4*a*).

Anal. Calc. for $C_{13}H_{18}O_9$: C, 49.06; H, 5.70. Found: C, 49.30; H, 5.71.

Next eluted was a mixture of **19** and **20** (111.7 mg, 52%), and finally a small amount of pure, amorphous **20** (4.2 mg, 2%), $[\alpha]_D$ −29.5° (*c* 0.85, chloroform); ^{1}H-n.m.r. data (90 MHz): δ 6.16 (broad s, 1 H, H-1), 5.08 (m, 1 H, H-3), 4.95–4.65 (m, 2 H, H-2 and H-5), 3.82 (s, 1 H, CO_2Me), 3.75 (m, 1 H, H-4*e*), 2.25 (m, 1 H, H-4*a*), and 2.15 (s, 9 H, Ac).

Anal. Found: C, 48.70; H, 5.60.

(*b*) Methyl (5*R*)-1,2,3-tri-*O*-acetyl-5-*C*-bromo-4-deoxy-β-D-*xylo*-hexopyranuronate (**21**, 27 mg) was reduced with tributyltin hydride as previously described to give a mixture of **19** and **20**. The ratio **19**:**20** (^{1}H-n.m.r., 300 MHz) was ~17:1.

(*c*) A suspension of methyl (5*R*)-1,2,3-tri-*O*-acetyl-5-*C*-bromo-4-deoxy-β-D-*xylo*-hexopyranuronate (**21**, 63 mg) and zinc dust (206 mg) in dry acetic acid (8 mL) was stirred for 12 h at room temperature. The mixture was diluted with dichloromethane (50 mL), washed with water, aqueous saturated sodium hydrogencarbonate, and water, dried ($MgSO_4$), and evaporated to give a mixture of **19** and **20** (61%). The ratio **19**:**20** was ~5:6.

*Methyl (5R)-1,2,3-tri-*O*-acetyl-5-*C*-bromo-4-deoxy-β-*D*-xylo-hexopyranuronate* (**21**). — A suspension of methyl 1,2,3-tri-*O*-acetyl-4-deoxy-β-D-*xylo*-hexopyranuronate (**19**, 116 mg), *N*-bromosuccinimide (78 mg), and benzoyl peroxide (12 mg) in dry carbon tetrachloride (4.6 mL) was boiled under reflux for 20 min with stirring and under a lamp. The previously described isolation gave amorphous **21** (67.5 mg, 47%), $[\alpha]_D$ −97° (*c* 1.55, chloroform); ^{1}H-n.m.r. data (90 MHz): δ 6.25 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 5.57 (ddd, 1 H, $J_{2,3}$ 9.3, $J_{3,4a}$ 10.7, $J_{3,4e}$ 5.0 Hz, H-3), 5.15 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-2), 3.92 (3 H, s, CO_2Me), 3.07 (dd, 1 H, $J_{3,4e}$ 5.0, $J_{4a,4e}$ 14.0 Hz, H-4*e*), 2.31 (dd, 1 H, $J_{3,4a}$ 10.7, $J_{4a,4e}$ 14.0 Hz, H-4*a*), 2.17, 2.12, and 2.08 (3 s, 9 H, Ac).

This compound is very unstable and was immediately reduced. In consequence, no correct elemental analysis was obtained.

*Photobromination of methyl 1,2,3,4-tetra-*O*-acetyl-α-L-idopyranuronate.* — A suspension of methyl 1,2,3,4-tetra-*O*-acetyl-α-L-idopyranuronate (**4**, 30 mg), *N*-bromosuccinimide (17 mg), and benzoyl peroxide (3 mg) in dry carbon tetrachloride (1.2 mL) was boiled under reflux for 1.5 h with stirring and under a lamp. The previously described isolation gave **3** (22.9 mg, 63%), and unreacted starting material **4** (4.5 mg, 15%).

*Methyl (2,3,4-tri-*O*-acetyl-α-L-idopyranosyl bromide)uronate* (**22**). — A solution of methyl 1,2,3,4-tetra-*O*-acetyl-α-L-idopyranuronate (**4**, 100 mg) in 30% HBr solution in acetic acid (1 mL) was stirred for 4 h at room temperature. The mixture was diluted with chloroform (30 mL), poured into ice-cold water (50 mL), and stirred for 10 min. The organic layer was separated, washed with ice-cold water, aqueous saturated sodium hydrogencarbonate and ice-cold water, dried ($MgSO_4$), and evaporated. The unstable bromide **22** (101.9 mg, 97%) was immediately used for the next reaction; $[\alpha]_D$ −131° (*c* 1.03, chloroform); ^{1}H-n.m.r. data (90 MHz): δ 6.42 (s, 1 H, H-1), 5.35–4.80 (m, 4 H, H-2, H-3, H-4, and H-5), 3,80 (s, 3 H, CO_2Me), 2.18, 2.11, and 2.08 (3 s, 9 H, Ac).

Methyl 3,4-di-O-acetyl-β-L-idopyranuronate 1,2-(methyl orthoacetate) (**23**). — A solution of bromide **22** (232 mg) in dry dichloromethane (5 mL) containing 2,4,6-trimethylpyridine (0.4 mL) and methanol (0.25 mL) was stirred for 24 h at room temperature. The mixture was diluted with dichloromethane (100 mL), washed with aqueous saturated sodium hydrogencarbonate, water, dried ($MgSO_4$), and evaporated. Elution of the residue from a column of silica gel with 10:1 chloroform–acetone containing 0.5% of triethylamine gave the amorphous orthoacetate **23** (157.6 mg, 77.4%), $[\alpha]_D$ −48° (*c* 1.05, chloroform); ^{1}H-n.m.r. data (90 MHz): δ 5.53 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), 5.40 (dd, 1 H, $J_{2,3}$ 2.0, $J_{3,4}$ 2.7 Hz, H-3), 5.07 (dd, 1 H, $J_{3,4}$ 2.7, $J_{4,5}$ 1.3 Hz, H-4), 4.44 (d, 1 H, $J_{4,5}$ 1.3 Hz, H-5), 4.02 (m, 1 H, H-2), 3.77 (s, 3 H, CO_2Me), 3.28 (s, 3 H, OMe), 2.17, 2.08 (2 s, 6 H, Ac), and 1.79 (s, 3 H, C-Me).

Anal. Calc. for $C_{14}H_{20}O_{10}$: C, 48.28; H, 5.79. Found: C, 48.62; H, 5.70.

ACKNOWLEDGMENTS

The authors thank Drs. Jean-Marie Beau and Jean-Claude Jacquinet for helpful discussions, and the Institut Choay for generous financial support.

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