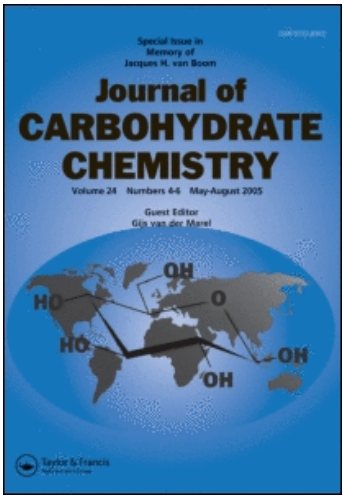


Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

A Concise Synthesis of (±) Ketodeoxyheptulosonic Acid Derivatives Via Aqueous Hetero Diels Alder Reaction and NBS Mediated Dibromination

André Lubineau[a]; Yves Queneau[a]
[a] Laboratoire de Chimie Organique Multifonctionnelle CNRS, URA n°462, Institut de Chimie Moléculaire d'Orsay Université Paris-Sud, Orsay Cédex, France

To cite this Article Lubineau, André and Queneau, Yves(1995) 'A Concise Synthesis of (±) Ketodeoxyheptulosonic Acid Derivatives Via Aqueous Hetero Diels Alder Reaction and NBS Mediated Dibromination', Journal of Carbohydrate Chemistry, 14: 9, 1295 — 1306
To link to this Article: DOI: 10.1080/07328309508005412
URL: http://dx.doi.org/10.1080/07328309508005412

J. CARBOHYDRATE CHEMISTRY, 14(9), 1295-1306 (1995)

A CONCISE SYNTHESIS OF (±) KETODEOXYHEPTULOSONIC ACID DERIVATIVES VIA AQUEOUS HETERO DIELS ALDER REACTION AND NBS MEDIATED DIBROMINATION

André Lubineau and Yves Queneau*,[1]

Laboratoire de Chimie Organique Multifonctionnelle
CNRS, URA n°462
Institut de Chimie Moléculaire d'Orsay
Université Paris-Sud, Bât. 420
91405 Orsay Cédex, France

Received April 4, 1995 - Final Form July 17, 1995

ABSTRACT

Cycloaddition of sodium glyoxylate, in water, onto penta-2,4-dienol provided 2-deoxyheptulosonic acid derivatives. Activation of the anomeric carbon was achieved through NBS mediated C-2-C-3 dibromination.

INTRODUCTION

Ulosonic acids have attracted much attention in recent years as the scope of their biological importance widens constantly.[2] For example, *N*-acetylneuraminic acid, present in cell surface glycoproteins, has been found to play an essential role in cellular recognition and adhesion phenomena.[3] This compound and other members of the same family, such as DAH, KDO or KDN, have been chosen as targets by synthetic chemists.[2,4] The seven carbon-atom analog in this series, DAH (3-deoxy-D-*arabino*-2-heptulosonic acid), was only found in plants, appearing as a key intermediate in the shikimate pathway that controls aromatic amino acid biosynthesis from glucose.[5,6]

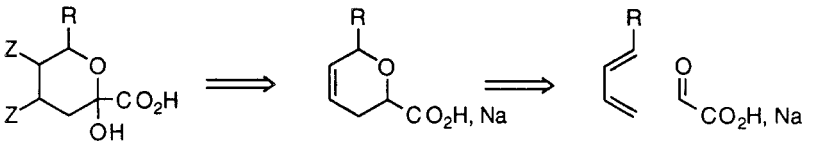
In the past years, we have been concerned with the total synthesis of such carbohydrates,[4d] based on the retrosynthetic analysis depicted in Scheme 1, namely an aqueous hetero Diels Alder[7] reaction of glyoxylic acid with an appropriate conjugated diene, producing 2,6-disubstituted dihydropyrans, and further functionalization at C-2, C-4 and C-5.

We report herein the application of this methodology in a new synthesis of racemic 2-heptulosonic acid derivatives starting from (*E*)-penta-2,4-dienol and sodium glyoxylate. The oxidation of 2-deoxy-2-ulosonates, that was performed via enolate chemistry in the KDO synthesis recently reported by one of us,[4d] is here achieved by reaction with *N*-bromosuccinimide, which appeared to be an interesting alternative for producing the desired activated 2-ulosonic acid derivatives.

RESULTS AND DISCUSSION

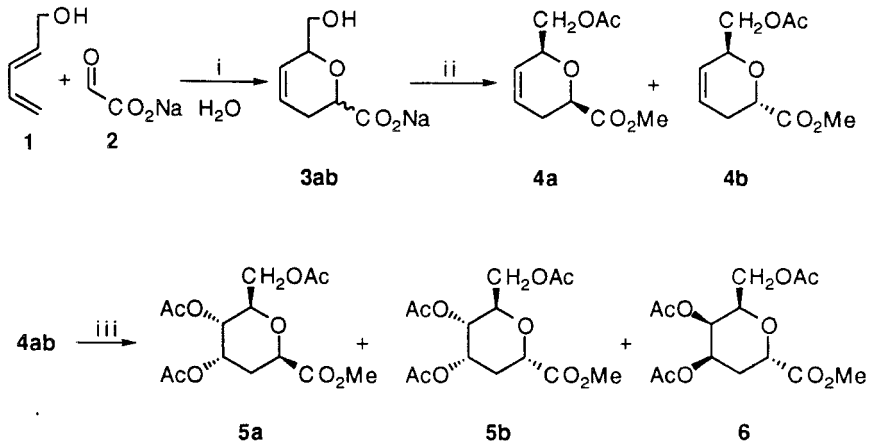
Cyloaddition of (*E*)-penta-2,4-dienol (**1**) with sodium glyoxylate (**2**) in water led to adducts **3ab** that were directly protected as acetylated methyl esters **4ab** (as a 1.5:1 mixture in favor of pseudo-axial ester exo **4b**), by treatment with iodomethane in dimethylformamide followed by acetylation with acetic anhydride in pyridine (Scheme 2). A 71% yield of **4ab** was obtained, comparable with the result obtained from a protected diene and an alkyl glyoxylate.[8] The protecting step of the diene and the somewhat tedious preparation of the alkyl glyoxylate could thus be avoided. Catalytic osmylation of the mixture of dihydropyrans **4ab** and further acetylation gave triacetates **5a**, **5b** and **6** (29:44:27) in 71% yield from **4ab**. Major products **5ab** arise, as anticipated, from an attack of oxidant *anti* to the pyranosic oxygen atom and substituent in position 6, while **6** is the result of an attack *anti* to the carboxymethyl group of **4b**.

In order to generalize the methodology used to prepare KDO, some enolate mediated oxidations were attempted. In this case, enolates bearing benzyl protective groups, useful for strongly basic reaction conditions, led to only limited success upon direct oxygenation.[9] We thought that an alternative for achieving such an oxidation could be the use of a radical reaction. Indeed, it has been shown that reaction of NBS or bromine with carbohydrates is useful for functionalizing sugars having a carboxy substituent (as in glucuronic acid), or simpler sugars.[10] This strategy has been also employed in syntheses of unsaturated carbohydrates,[11] in a new



R = -(CHOH)$_n$-CH$_2$OH, Z = OH, NHAc...

Scheme 1

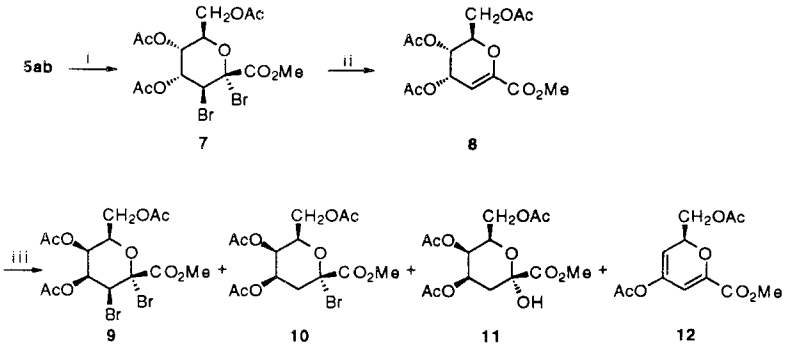


i. H_2O, 100 C, 2 d; ii. MeI, DMF, r.t., 1 d, then Ac_2O, Py, r.t., 15 h, 71% from **1**; iii. cat. OsO_4-NMO, Me_2CO-H_2O-r.t. 6 h, 71%.

Scheme 2

preparation of iduronic acid,[12] in the generation of anomeric gem-dihalogenosugars,[13] and in an approach to oxetan and furan nucleosides.[14]

We therefore studied the outcome of the reaction of esters **5ab** with *N*-bromosuccinimide in refluxing carbon tetrachloride. The first attempt was made using a nearly equimolar amount of both reactants; a new product, more polar (probably the anomeric bromide), appeared but could not be isolated, because it disappeared before all the starting ester was consumed. Two new less polar compounds were formed, which could be isolated in low yield. The first one (the less polar) appeared to be dibromide **7** and the



i. excess NBS, CCl_4, reflux, 19 h, **7**: 86%. ii. Bu_3SnH, benzene, reflux, 0.5 h, 90%. iii. excess NBS, CCl_4, reflux, 91% (39:24:14:23).

Scheme 3

second, UV active, the unsaturated ester **8** (Scheme 3).[15] We finally found that upon treating **5ab** with excess of *N*-bromosuccinimide for a longer time (producing bromine), **8** was slowly brominated, generating dibromide **7** in 86% isolated yield. Tributyltin hydride mediated bromine elimination of **7** gave back unsaturated ester **8** in 90% yield. A large shift for the H-5 NMR signal, a small H-3-H-4 coupling constant and the fact that dibromide **7** is produced from unsaturated ester **8**, are consistent with the trans diaxial configuration for the bromine atoms.[16]

Since we had in hand a small amount of isomer **6**, we looked at its reaction with NBS under the same conditions in order to evaluate the importance of the orientation of substituents at positions 4 and 5. A mixture of four products was obtained, for which proton NMR spectra were consistent with structures **9** to **12**.[17] H-3-H-4 coupling constant in dibromide **9** ascertained the axial stereochemistry of the bromine atom at C-3. Compound **12** accumulated upon prolonged reaction time, indicating that elimination of the C-5 acetate function occurred faster than dibromination of the C-2-C-3 double bond.

Dibromides like **7** have been shown to serve as useful glycosyl donors in Koenigs-Knorr type reactions, since blocking the 3-axial position prevents the competitive elimination, often observed during glycosylation reactions of 2-ulosonic ester halides.[18] Methyl glycosides **13** and **14** were thus prepared under mercury salts catalysis,[19] as well as the 3-deoxy-*ribo*-2-heptulosonic

acid methyl esters methyl glycosides **15** and **16** after tributyltin hydride reduction (Scheme 4). The results from a proton NMR study of **15** and **16** allowed us to propose the stereochemistry at the anomeric carbon for these glycosides. It is based on the general observation that in numerous α- and β-3-deoxy-2-ulosonic acid glycosides, the anomer which has both equatorial H-3 and carboxy group in equatorial position, is the one for which equatorial H-3 is shifted downfield (ca. 0.2 ppm).[20]

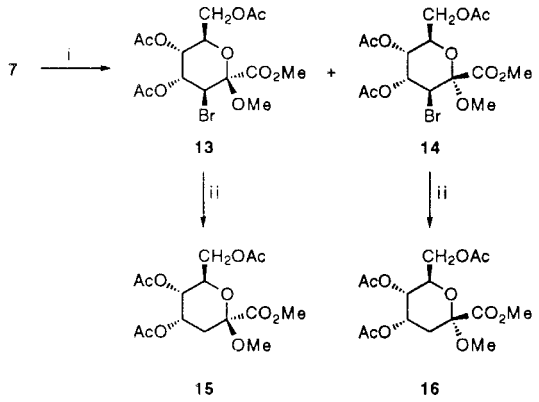
The racemic 4-epi-DAH acetylated esters **15** and **16** were thus obtained. Preparation of these compounds allowed us to evaluate the feasability of the oxidation step at C-2 using the alternative radical pathway instead of the oxidation of an enolate. Application of this reaction on higher members in this series is being pursued.

CONCLUSION

In this study, through the preparation of model compounds **13** to **16**, we show that the combination of the aqueous hetero Diels Alder cycloaddition of commercially available sodium glyoxylate, and a radical dibromination as anomeric functionality elaboration, provides concise access to activated 2-ulosonic esters. Furthermore, the use of simple and convenient acetyl protecting groups accomodate all steps of this straightforward process.

EXPERIMENTAL

General. NMR spectra were recorded with Brüker AM 250 and AC 200 and 250 spectrometers. Chemical shifts are given in ppm downfield from internal tetramethylsilane; signal multiplicity is indicated as follows: s for singlet, d for doublet, t for triplet, q for quadruplet, m for multiplet and br for broad. IR spectra were recorded using a Brüker FT instrument. Flash-chromatography was performed using 6-35μ silica gel (60) purchased from S.D.S. company. TLC was run using Merck 60 F254 plates, and visualized first with UV light and second by heating after alcoholic sulfuric or phosphomolybdic acid treatment. Melting points were measured on a Reichert apparatus and are uncorrected. Elementary analyses were performed at the Service Central de Microanalyse du C.N.R.S.



i. MeOH, $Hg(CN)_2$-$HgCl_2$, CH_2Cl_2, 40 °C, 2.5 d, 85% (1:1). ii. Bu_3SnH-AIBN, benzene, reflux, 2 h, 85%.

Scheme 4

Methyl 7-*O*-Acetyl-2,3,4,5-tetradeoxy-D,L-*glycero*-2-hept-4-enulosonate (4ab). (*E*)-Penta-2,4-dienol (168 mg, 2 mmol) and sodium glyoxylate monohydrate (1.14 g, 10 mmol) were heated in water (4 mL) at 100 °C for 2 days. After TLC (7:3 1-propanol-water) indicated total disappearance of the starting alcohol, the mixture was cooled to room temperature and the solvent was evaporated. The residue was dissolved in DMF (2 mL) and iodomethane (2 mL, excess) was added. After 1 day of stirring at room temperature, the mixture was concentrated to dryness, and the residue was treated with a 1:1 (vol) mixture of pyridine and acetic anhydride (10 mL) and left overnight at room temperature. After coevaporation several times with toluene, the residue was dissolved in CH_2Cl_2 (10 mL) and washed with water (2 x 10 mL) and brine (10 mL). The organic layer was then dried ($MgSO_4$), filtered, and concentrated. Subsequent flash chromatography (1:3 ethyl acetate-hexane) of the residue allowed us to isolate ester **4ab** (304 mg, 71%). ^1H NMR ($CDCl_3$, 250 MHz) δ 2.09 (s, 3 H, Ac), 2.37-2.50 (m, 2 H, $H_{3,3}$), 3.77, 3.78 (2 s, 3 H, CO_2Me), 4.01-4.34, 4.40-4.56, 4.60-4.75 (3 m, 4 H, $H_{2,6,7,7}$), 5.61-5.73 (m, 1 H, H_5), 5.91-6.06 (m, 1 H, H_4). ^{13}C NMR ($CDCl_3$, 62 MHz) δ 20.47, 26.55, 27.44, 51.74, 64.58, 65.56, 68.49, 70.44, 72.18, 73.15, 124.67, 125.03, 125.44, 125.66, 170.43, 170.71, 171.52. IR (neat, cm^{-1}) 2955.2, 1744.1, 1727.9, 1440.9, 1370.0, 1232.2, 1107.4, 1042.1.

Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59; O, 37.74. Found: C, 55.76; H, 6.67; O, 37.52.

Methyl 4,5,7-Tri-*O*-acetyl-2,3-dideoxy-D,L-*ribo* and *lyxo*-2-heptulosonate (5ab and 6). To a solution of compound **4ab** (90 mg, 0.42 mmol), *N*-methyl morpholine *N*-oxide (100 mg, 0.74 mmol) in a 8:1 (vol.) acetone-water mixture (5 mL), was added OsO_4 (0.05 M in *t*-BuOH, 1 mL). The mixture was stirred with nitrogen sparging at room temperature during 6 h. While cooling the flask with cold water because of exothermicity, excess oxidant was quenched by addition of sat. aqueous $NaHSO_3$ (10 mL) and further stirring for 15 min. The mixture was then extracted with CH_2Cl_2 (4 x 20 mL) and the combined organic layer was concentrated under reduced pressure. The residue was treated with a 1:1 (vol.) mixture of acetic anhydride and pyridine (5 mL) and left overnight at room temperature. Coevaporation with toluene and flash chromatography of the residue (1:2 ethyl acetate-hexane) allowed for isolation of triacetates **5ab+6** (100 mg, 71%) as a 29:44:26 mixture (^{1}H NMR). Further purification allowed isolation of pure **6** as the less polar product. Further elution gave **5ab**. Major ester **5b** (axial) crystallized from a CH_2Cl_2-Et_2O-hexane mixture: mp 109 C. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.03, 2.06, 2.13 (3 s, 9 H, 3 Ac), 2.24 (ddd, 1 H, J = 14, 6, 3 Hz, H_{3ax}), 2.44 (ddd, 1 H, J = 14, 3.5, 1.5, H_{3eq}), 3.77 (s, 3 H, CO_2Me), 4.22 (d, 1 H, J = 12, 2 Hz, H_7), 4.33 (d, 1 H, J = 12, 4 Hz, H_7), 4.48 (dd, 1 H, J = 6, 1.5 Hz, H_2), 4.54 (ddd, 1 H, J = 10, 4, 2 Hz, H_6), 4.88 (dd, 1 H, J = 10, 3 Hz, H_5), 5.40 (br q, 1 H , J = 3 Hz, H_4). ^{13}C NMR ($CDCl_3$, 62 MHz) δ 20.56, 20.64, 30.58, 51.92, 62.59, 66.37, 66.78, 68.13, 69.24, 169.35, 169.53, 170.64, 171.52. IR (neat, cm^{-1}) 2972.1, 2444.5, 1734.6, 1376.4, 1231.8, 1055.4.

Anal. Calcd for $C_{14}H_{20}O_9$: C, 50.60; H, 6.07, O, 43.33. Found: C, 51.02; H, 6.37; O, 42.61.

Data for **6**. mp 69.5-70 °C (Et_2O-hexane). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.01, 2.08, 2.14 (3 s, 9 H, 3 Ac), 2.05-2.45 (m, 2 H, $H_{3ax, 3eq}$), 3.80 (s, 3 H, CO_2Me), 4.03-4.20 (m, 2 H, $H_{7,7}$), 4.34 (ddd, 1 H, J = 7, 5, 1.5 Hz, H_6), 4.69 (dd, 1 H, J = 6, 2 Hz, H_2), 4.99 (ddd, 1 H, J = 11, 4, 2 Hz, H_4), 5.28-5.33 (m, 1 H, H_5). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.21, 20.30, 26.11, 51.99, 61.89, 65.92, 66.33, 70.66, 71.53, 169.40, 169.73, 170.02, 170.76. IR (neat, cm^{-1}).

Anal. Calcd for $C_{14}H_{20}O_9$: C, 50.60; H, 6.07; O, 43.33. Found: C, 50,82; H, 6.08; O, 43.22.

Methyl 4,5,7-Tri-*O*-acetyl-2,3-dideoxy-2,3-dibromo-α-D,L-*altro*-2-heptulosonate (7). To a solution of **5ab** (530 mg, 1,58 mmol) in refluxing

carbon tetrachloride (50 mL) was added in one portion *N*-bromosuccinimide (1.13 g, 6.34 mmol). After 19 h, the mixture was cooled to room temperature and the unsoluble succinimides were filtered off. Evaporation of the solvent and flash-chromatography of the residue (1:3 ethyl acetate-hexane) gave **7** (665 mg, 86%) as a white solid that could be recrystallized (mp 125 °C)from a CH_2Cl_2-Et_2O-hexane mixture. ^1H NMR ($CDCl_3$, 250 MHz) δ 2.07, 2.11, 2.23 (3 s, 9 H, 3 Ac), 3.91 (s, 3 H, CO_2Me), 4.30 (d, 1 H, J = 12.5, 2 Hz, H_7), 4.47 (d, 1 H, J = 12.5, 4 Hz, H_7), 4.65 (ddd, 1 H, J = 10, 4, 2 Hz, H_6), 4.97 (d, 1 H, J = 2.5 Hz, H_3), 5.45 (t, 1 H, J = 2.5 Hz, H_4), 5.61 (dd, 1 H, J = 10, 2.5 Hz, H_5). ^{13}C NMR ($CDCl_3$, 62 MHz) δ 20.43, 20.59, 20.98, 47.15, 53.56, 61.12, 62.01, 69.25, 71.38, 88.34, 164.46, 168.95, 169.49, 170.51. IR (neat, cm^{-1}) 2957.7, 1756.6, 1441.0, 1370.8, 1234.0, 1107.8, 1071.3.

Anal. Calcd for $C_{14}H_{18}Br_2O_9$: C, 34.31; H, 3.70; Br, 32.61; O, 29.38. Found: C, 34.61; H, 3.91; Br, 32.72; O, 29.08.

Methyl 4,5,7-Tri-*O*-acetyl-2,3-dideoxy-D,L-*ribo*-hept-2-en-2-ulosonate (8). A solution of **7** (123 mg, 0.25 mmol) and tributyltin hydride (73 mg, 0.26 mmol) in benzene (5 mL) was heated under reflux during 30 min. After cooling to room temperature and evaporation of the solvent, flash-chromatography of the residue (1:2 ethyl acetate-hexane) provided **8** (74 mg, 90%). ^1H NMR ($CDCl_3$, 250 MHz) δ 1.98, 2.03, 2.07 (3 s, 9 H, 3 Ac), 3.77 (s, 3 H, CO_2Me), 4.21-4.45 (m, 3 H, $H_{6,7,7}$), 5.11 (dd, 1 H, J = 9.5, 3.5 Hz, H_5), 5.52 (dd, 1 H, J = 7.5, 3.5 Hz, H_4), 6.00 (d, 1 H , J = 7.5 Hz, H_3). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.40, 20.54, 20.67, 52.53, 61.35, 61.95, 65.33, 71.86, 105.05, 146.49, 161.67, 169.15, 169.82, 170.42. IR (neat, cm^{-1}) 2958.0, 1739.8, 1652.9, 1439.7, 1373.6, 1227.0, 1124.2, 1081.3, 1017.7.

Anal. Calcd for $C_{14}H_{18}O_9$: C, 50.91; H, 5.49; O, 43.60. Found: C, 50.01; H, 5.69; O, 44.42.

Methyl (Methyl 4,5,7-tri-*O*-acetyl-3-bromo-3-deoxy-D,L-*altro*-2-heptulopyranosid)onate [13 (β) and 14 (α)]. A solution of **7** (490 mg, 1 mmol), mercuric cyanide (126 mg, 0.5 mmol), mercuric bromide (360 mg, 1 mmol) and methanol (0.6 mL, 15 mmol) in CH_2Cl_2 (10 mL) was heated under reflux for 2.5 days. After cooling to room temperature, the mixture was washed with brine (2 x 50 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. Flash chromatography of the residue (1:2 ethyl acetate-hexane) gave in order of elution glycosides **13** (β, 175 mg, 40%) and **14** (α, 200 mg, 45%). Data for **13**: ^1H NMR ($CDCl_3$, 250 MHz) δ 2.06, 2.09, 2.13 (3 s, 9 H, 3 Ac), 3.40 (s, 3 H, Me), 3.87 (s, 3 H, CO_2Me), 4.28

(d, 1 H, J = 11, 4 Hz, H_7), 4.35 (d, 1 H, J = 11, 3 Hz, H_7), 4.42-4.52 (m, 1 H, H_6), 4.64 (d, 1 H, J = 4 Hz, H_3), 5.50-5.58 (m, 2 H, $H_{4,5}$). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.33, 20.47, 48.00, 52.12, 52.62, 62.00, 63.70, 69.22, 70.40, 96.66, 166.24, 168.42, 169.11, 170.40. IR (neat, cm^{-1}) 2955.9, 2842.8, 2257.4, 1761.7, 1751.0, 1739.7, 1734.1, 1436.5, 1373.8, 1225.3, 1107.1, 1032.3.

Anal. Calcd for $C_{15}H_{21}BrO_{10}$: C, 40.83; H, 4.80; O, 36.21. Found: C, 40.75; H, 4.61; O, 35.98.

Data for **14**: mp 132 C (CH_2Cl_2-Et_2O-hexane). ^1H NMR ($CDCl_3$, 200 MHz) δ 2.03, 2.11, 2.14 (3 s, 9 H, 3 Ac), 3.28 (s, 3 H, Me), 3.83 (s, 3 H, CO_2Me), 4.25-4.41 (m, 4 H, $H_{3,6,7,7}$), 5.40-5.50 (m, 2 H, $H_{4,5}$). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.36, 20.53, 45.19, 52.03, 52.66, 62.28, 62.59, 66.29, 69.82, 99.53, 165.70, 169.00, 169.68, 170.47. IR (neat, cm^{-1}) 2956.8, 2838.4, 2257.3, 1751.1, 1734.2, 1436.7, 1373.7, 1228,7, 1161.8, 1109.4, 1039.8.

Anal. Calcd for $C_{15}H_{21}BrO_{10}$: C, 40.83; H, 4.80; Br, 18.11; O, 36.21. Found: C, 40.78; H, 4.68; Br, 17.41; O: 36.21.

Methyl (Methyl 4,5,7-tri-*O*-acetyl-3-deoxy-β-D,L-*ribo*-2-heptulopyranosid)onate (15). A solution of glycoside **13** (200 mg, 0.45 mmol), and tributyltin hydride (0.183 mL, 0.68 mmol) in benzene (10 mL) was heated at reflux with a few mg of AIBN during 2 h. The mixture was cooled to room temperature, concentrated to dryness, and purified by flash chromatography (1:3, ethyl acetate-hexane) to give 3-deoxyglycoside **15** (139 mg, 85%). ^1H NMR ($CDCl_3$, 200 MHz) δ 2.02, 2.03, 2.12 (m and 3 s, 10 H, 3 Ac, H_{3ax}), 2.58 (dd, 1 H, J 14, 5 Hz, H_{3eq}), 3.30 (s, 3 H, Me), 3.84 (s, 3 H, CO_2Me), 4.22-4.39 (m, 2 H, $H_{7,7}$), 4.48 (dt, 1 H, J = 8, 4, H_6), 4.98 (dd, 1 H, J = 8, 2.5 Hz, H_5), 5.44 (dd, 1 H, J = 5, 2.5 Hz, H_4). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.58, 35.54, 51.53, 52.30, 62.53, 66.06, 66.49, 70.26, 97.80, 168.53, 169.24, 169.61, 170.62. IR (neat, cm^{-1}) 2920.0, 2848.8, 1739.9, 1456.9, 1373.9, 1219.9.

Anal. Calcd for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12; O, 44.16. Found: C, 49.67; H, 6.31; O, 44.37.

Methyl (Methyl 4,5,7-tri-*O*-acetyl-3-deoxy-α-D,L-*ribo*-2-heptulopyranosid)onate (16). Following the same procedure as for preparing **15**, compound **16** was obtained from glycoside **14**. ^1H NMR ($CDCl_3$, 250 MHz) δ 2.04, 2.10, 2.12 (3 s, 9 H, 3 Ac), 2.09 (dd, 1 H, J = 15, 6 Hz, H_{3ax}), 2.41 (dd, 1 H, J = 15, 3 Hz, H_{3eq}), 3.30 (s, 3 H, Me), 3.82 (s, 3 H, CO_2Me), 4.18-4.40 (m, 3 H, $H_{6,7,7}$), 4.96 (dd, 1 H, J = 9.5, 3 Hz, H_5), 5.37 (m, 1 H, H_4). ^{13}C NMR ($CDCl_3$, 62 MHz) δ 20.57, 20.70, 20.98, 35.23, 51.04, 52.72, 62.52,

65.80, 66.29, 97.77, 168.10, 169.48, 170.40, 170.73. IR (neat, cm^{-1}) 3059.0, 2955.7, 2848.4, 1743.0, 1652.8, 1436.7, 1370.7, 1229.7, 1167.4, 1100.4, 1064.8.

Anal. Calcd for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12; O, 44.16. Found: C, 49.37; H, 5.92; O, 43.14.

ACKNOWLEDGEMENTS

We thank C.N.R.S. and Université de Paris-Sud for financial support.

REFERENCES AND NOTES

1. Present address: Unité Mixte CNRS - Béghin-Say "Sucrochimie" (UMR 143). *c/o* Eridania Béghin-Say. CEI. B.P. 2132, 69603 Villeurbanne cedex, France.
2. R. Schauer, *Adv. Carbohydr. Chem. Biochem.*, **40**, 131 (1982); A. Hasegawa and M. Kiso, K. Ikeda and K. Achiwa, H. Ogura, E. Zbiral, and R. Schauer, *Carbohydrates Synthetic Methods and Applications in Medicinal Chemistry*, H. Ogura, A. Hasegawa and T. Suami, Eds.; VCH: Weinheim, 1991, pp 243-354.
3. K. Furukawa and A. Kubota, *ibid.*, pp 369-384; C.-T. Yuen, K. Bezouska, J. O'Brien, M. Stoll, R. Lemoine, A. Lubineau, M. Kiso, A. Hasegawa, N. J. Bockovich, K. C. Nicolaou and T. Feizi, *J. Biol. Chem.*, **269**, 1595 (1994).
4. See also the following reports and references therein: a) S. J. Danishefsky, M. P. DeNinno and S.-H. Chen, *J. Am. Chem. Soc.*, **110**, 3929 (1988); b) W. Frick, T. Krülle and R. R. Schmidt, *Liebigs Ann. Chem.*, 435 (1991); c) T.-H. Chan and C.-J. Li, *J. Chem. Soc., Chem. Commun.*, 747 (1992); d) A. Lubineau, J. Augé and N. Lubin, *Tetrahedron*, **49**, 4639 (1993); e) A. Dondoni, A. Marra and P. Merino, *J. Am. Chem. Soc.*, **116**, 3324 (1994); f) J. W. Cornforth, M. E. Firth and A. Gottschalk, *Biochem. J.*, **68**, 57 (1958); g) R. Kuhn and G. Baschang, *Liebigs Ann. Chem.*, **659**, 156 (1962); h) L. Benzing-Nguyen and M. B. Perry, *J. Org. Chem.*, **43**, 551 (1978); i) S. J. Danishefsky and M. P. DeNinno, *J. Org. Chem.*, **51**, 2615 (1986); j) F. Baumberger and A. Vasella, *Helv. Chim. Acta*, **69**, 1205 (1986); k) R. Julina, I. Müller, A. Vasella and R. Wyler, *Carbohydr. Res.*, **164**, 415 (1987); l) R. Csuk, M. Hugener and A. Vasella, *Helv. Chim. Acta*, **71**, 609 (1988); m) C. Augé, S. David, C. Gautheron, A. Malleron and B. Cavayé, *New J. Chem.*, **12**, 733 (1988).
5. B. Ganem, *Tetrahedron*, **34**, 3353 (1978); E. Haslam, *Shikimic Acid. Metabolism and Metabolites*; Wiley: New York, 1993.
6. For syntheses of 2-heptulosonic acid derivatives, see: D. B. Sprinson, J. Rothschild, M. Sprecher, *J. Biol. Chem.*, **238**, 3170 (1963); V. N. Nigam, *Can. J. Biochem.*, **42**, 1561 (1964); K. M. Herrmann and M. D. Poling, *J. Biol. Chem.*, **250**, 6817 (1975); F. Trigalo, M. Level, L. Szabo, *J. Chem. Soc., Perkin Trans. 1*, 600 (1975); J. W. Frost and J. R. Knowles, *Biochemistry*, **23**, 4465 (1984); D. Crich and T. J. Ritchie, *J.*

Chem. Soc., Chem. Commun., 985 (1988); P. A. M. van der Klein, E. E. J. de Nooy, G. A. van der Marel and J. H. van Boom, *Synthesis*, 348 (1991).

7. A. Lubineau, J. Augé and N. Lubin, *Tetrahedron Lett.*, **32**, 7529 (1991); A. Lubineau, J. Augé, E. Grand and N. Lubin, *Tetrahedron*, **50**, 10265 (1994); A. Lubineau, J. Augé and Y. Queneau, *Synthesis*, 741 (1994).
8. Cycloaddition of 5-benzyloxy-(*E*)-penta-1,3-diene and butyl glyoxylate was described in ref. 3d.
9. Potassium enolate of the 4,5-*O*-isopropylidene-7-*O*-benzyl analog of **5ab** was oxidized with *N*-phenylsulfonyl-phenyloxaziridine in 34% yield; overoxidation due to ring opening of intermediate 2-alcoholate was circumvented in the KDO case (ref. 3d) by using diphenyl disulfide.
10. L. Somsák and R. J. Ferrier, *Adv. Carbohydr. Chem. Biochem.*, **49**, 37 (1991).
11. R. J. Ferrier and R. H. Furneaux, *J. Chem. Soc., Perkin Trans. 1*, 1993 (1977); *ibid.*, 1996 (1977); R. Blattner and R. J. Ferrier, *ibid.*, 1523 (1980); R. J. Ferrier and P. C. Tyler, *ibid.*, 1528 (1980); R. Blattner, R. J. Ferrier and P. C. Tyler, *ibid.*, 1535 (1980).
12. T. Chiba and P. Sinaÿ, *Carbohydr. Res.*, **151**, 379 (1986).
13. G. Descotes in *Carbohydrates Synthetic Methods and Applications in Medicinal Chemistry*, H. Ogura, A. Hasegawa and T. Suami, Eds.; VCH: Weinheim, 1991, pp 89-96; H.-G. Korth, J.-P. Praly, L. Somsák and R. Sustmann, *Chem. Ber.*, **123**, 1155 (1990).
14. S. Choi, D. R. Witty, G. W. J. Fleet, P. L. Myers, R. Storer, C. J. Wallis, D. Watkin and L. Pearce, *Tetrahedron Lett.*, **32**, 3569 (1991).
15. Direct α,β–dibromination of α-alkoxy-α-alkyl carbonyl compounds has already been observed in the benzodioxan and bezodioxazin series; see: G. Farina and G. Zecchi, *Synthesis*, 755 (1977); G. Coudert, G. Guillaumet and B. Loubinoux, *Tetrahedron Lett.*, **19**, 1059 (1978); G. Guillaumet, B. Loubinoux and G. Coudert, *ibid.*, **19**, 2287 (1978). For an example of overoxidation with NCS see: A. R. Maguire, M. E. Murphy, M. Schaeffer and G. Ferguson, *Tetrahedron Lett.*, **36**, 467 (1995).
16. K. Okamoto, T. Kondo and T. Goto, *Bull. Chem. Soc. Jpn.*, **60**, 631 (1987).
17. ^{1}H NMR ($CDCl_3$, 250 MHz) for **9**: δ 2.07, 2.13, 2.16 (3 s, 9 H, 3 Ac), 3.94 (s, 3 H, CO_2Me), 4.29 (d, 1 H, J = 11, 6 Hz, H_7), 4.40 (d, 1 H, J = 11, 6 Hz, H_7), 4.63 (dt, 1 H, J = 2, 6 Hz, H_6), 4.89 (dd, 1 H, J = 4, 0.5 Hz, H_3), 5.49 (ddd, 1 H, J = 4, 2, 0.5 Hz, H_5), 5.73 (t, 1 H , J = 4 Hz, H_4). **10**: δ 2.02, 2.08, 2.13 (3 s, 9 H, 3 Ac), 2.40 (dd, 1 H, J = 13, 10 Hz, H_{3ax}), 2.69 (dd, 1 H, J = 13, 4 Hz, H_{3eq}), 3.93 (s, 3 H, CO_2Me), 4.13-4.33 (m, 1 H, $H_{7,7}$), 4.47 (t, 1 H, J = 6 Hz, H_6), 5.42 (m, 2 H, $H_{4,5}$). **11**: δ 1.92 (ddd, 1 H, J = 12, 4, 1 Hz, H_{3ax}), 2.01, 2.05, 2.17 (3 s, 9 H, 3 Ac), 2.47 (brt, 1 H, J = 12 Hz, H_{3eq}), 3.88 (s, 3 H, CO_2Me), 4.03-4.18 (m, 3 H, $H_{7,7}$, OH), 4.44 (dt, 1 H, J = 6, 1 Hz, H_6), 5.31-5.41 (m, 2 H, $H_{4,5}$). **12**: δ 2.10, 2.20 (2 s, 6 H, 2 Ac), 3.93 (s, 3 H, CO_2Me), 4.37 (d, 1 H, J = 12, 4 Hz, H_7), 4.51 (d, 1 H, J = 12, 6 Hz, H_7), 4.90 (dt, 1 H, J = 6, 4 Hz, H_6), 5.61 (d, 1 H, J = 4 Hz, H_5), 6.21 (s, 1 H, H_3).

18. K. Okamoto, T. Kondo and T. Goto, *Tetrahedron,* **43**, 5909 (1987).
19. M. Nakamura, S. Fujita and H. Ogura, *Chem. Pharm. Bull.*, **41**, 21 (1993).
20. J. F. G. Vliegenthart, L. Dorland, H. van Halbeek and J. Haverkamp, *Cell Biology Monographs*, Vol. 10, p 127 (1982).