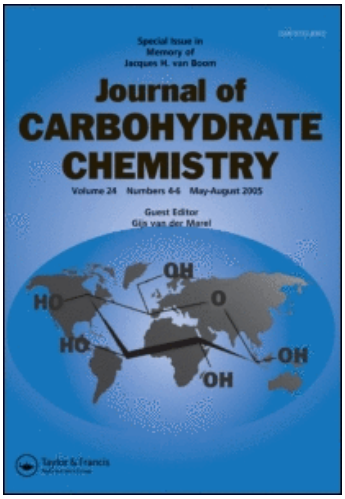

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SOME UNEXPECTED RESULTS IN DONDONI'S ONE-CARBON HOMOLOGATION PROCEDURE[1]

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SOME UNEXPECTED RESULTS IN DONDONI'S ONE-CARBON HOMOLOGATION PROCEDURE[1]

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ABSTRACT

The formation of the unexpected secondary products (**3** and **9**) during Dondoni's one-carbon homologation of 6-deoxy-6-iodo-2,3:4,5-bis-*O*-isopropylidene-D-glucose (**1**) are described.

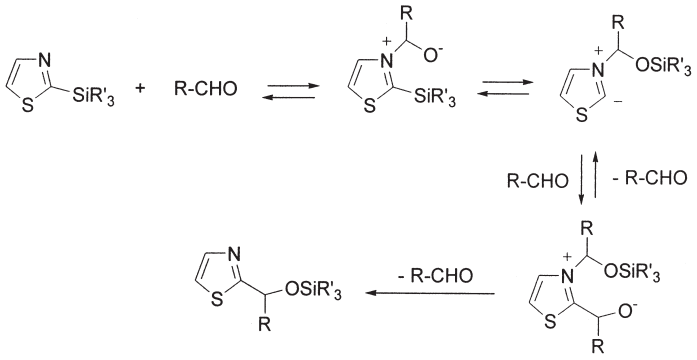
INTRODUCTION

Dondoni's one-carbon homologation procedure is one of the most successful protocols described to date for the homologation of aldehydes.[2] The mild and simple experimental conditions enhance the interest and synthetic potential of this efficient and reproducible process. In addition, the highly *anti*-stereoselective[3] asymmetric induction applied to α-alkoxy aldehydes has been used in a number of synthetic approaches for the preparation of enantiomerically pure products.[4] The mechanism of this useful transformation has been discussed by Dondoni and coworkers (Scheme 1).[5]

Very recently we wished to carry out a one-carbon homologation of 6-deoxy-6-iodo-2,3:4,5-bis-*O*-isopropylidene-D-glucose (**1**) and we chose Dondoni's method.[2] In this communication we describe in full the unexpected, secondary products obtained in a three-step protocol for the addition of 2-trimethylsilylthiazole (2-TST) to the aldehyde carbonyl of **1**.[6]

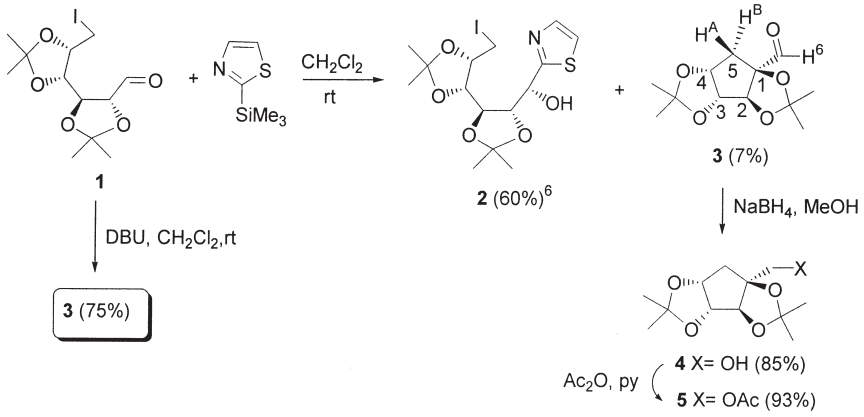
RESULTS AND DISCUSSION

Aldehyde **1** has been prepared in enantiomerically pure form and multigram quantities from commercially available D-glucose diethyl dithioacetal.[7] The reac-

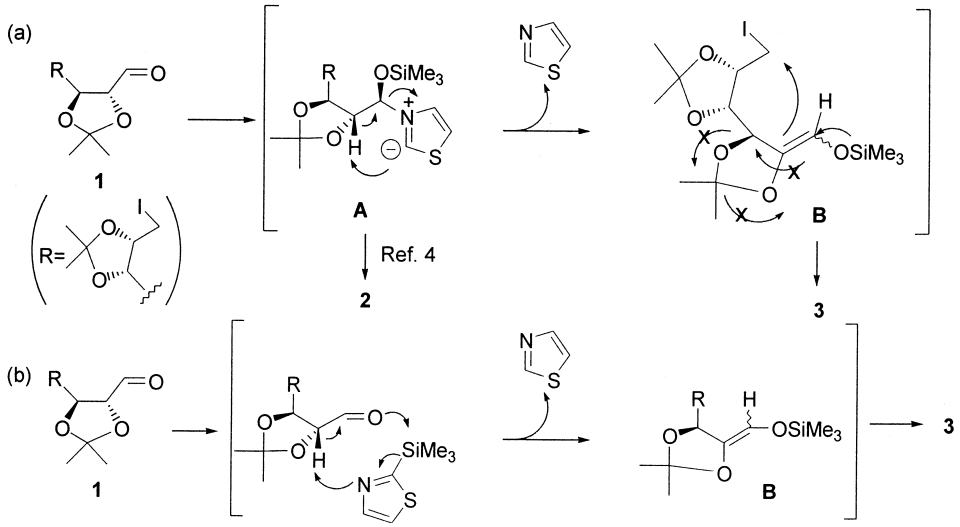


Scheme 1. Proposed mechanism for the 2-TST coupling with aldehydes (ref. 5).

tion of this compound with 2-TST under standard conditions[3] afforded the expected 6-deoxy-6-iodo-2,3:4,5-bis-*O*-isopropylidene-1-(1′,3′-thiazol-2′-yl)-D-*glycero*-D-gulose (2, 60%),[7] and a secondary product (3a*R*,3b*S*,6a*R*,7a*R*)-tetrahydro-2,2,5,5-tetramethyl-6a*H*-cyclopenta[1,2-d:3,4-d′]bis[1,3]dioxole-6a-carboxaldehyde (**3**) in 7% yield (Scheme 2). The structure of the latter product was firmly established after inspection of the analytical and spectroscopic data. In the ^{1}H NMR spectrum of **3** we observed a singlet aldehydic proton at 9.73 ppm (198.4 ppm for H—*C*O in the ^{13}C NMR spectrum) and two significant protons at 2.50 ppm (dd, $J_{5A,5B}$ = 15.2 Hz, $J_{4,5bB}$ = 2.9 Hz, 1 H, H5B) and 2.17 ppm (dd, $J_{5A,5B}$ = 15.2 Hz, $J_{4,5A}$ = 6.2 Hz, 1 H, H5A) (C5: 39.9 ppm) forming the AB part of an ABX system with a proton at 4.91 ppm (td, $J_{4,5B}$ = 2.9 Hz, $J_{4,5A}$ = 6.2 Hz, 1 H, H4). In the IR spectrum of **3** no carbonyl band absorption was observed, the carbonyl function being in the hydrated form. The absolute configuration at C1 was easily assigned as *R* by NOE experiments. These data along with the elemental analysis and the MS spectral results clearly pointed out that product **3** contained a cy-



Scheme 2. Reaction of 2-TST with α-alkoxy aldehyde 1.



Scheme 3. Possible mechanisms for the intramolecular alkylation of α-alkoxy aldehyde 1.

clopentane ring system resulting from the intramolecular α-alkylation of the α-alkoxy aldehyde **1**. Additional proof of structure was obtained upon reduction of compound **3** with sodium borohydride to give alcohol **4**, which was then acetylated to yield product **5** (Scheme 2).

Finally, we tested the direct alkylation of compound **1** with DBU (1.1 equiv) as base, under the same experimental conditions (Scheme 3). Very interestingly, a rapid reaction ensued (1 h) giving cleanly compound **3** in 75% isolated yield after flash chromatography.

It is noteworthy that compounds **3**–**5** are densely functionalized, chiral cyclopentane derivatives with some of the structural and functional moieties present in carbocyclic nucleosides[8] and glycosidase inhibitors such as trehazolin aglycon (Figure 1).[9]

The present reactivity was completely unexpected and unprecedented. As it is well known, base-mediated alkylation of aldehydes is hampered by crotonization or polymerization due to aldol condensation-like competitive reactions. A series of aldehyde derivatives (imines, hydrazones, oximes or enamines) have been

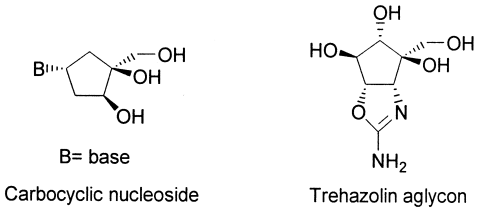


Figure 1.

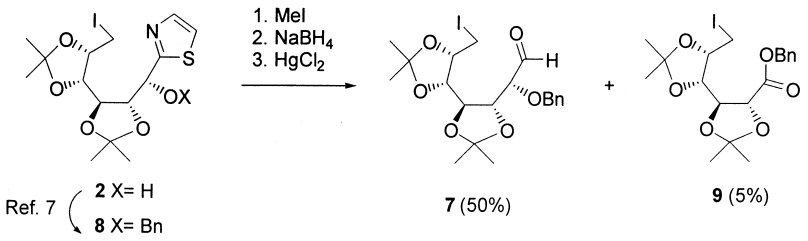
used for this purpose,[10] whereas a literature search for α-alkylation of α-alkoxy aldehydes gave a limited number of examples.[11] In addition, a recent synthesis of chiral α-alkyl, α-trifluoromethyl α-alkoxy aldehydes used an indirect approach from ketones,[12a] and an elegant synthesis of spirocyclopentenenones from α-alkoxy aldehydes in furanose templates was only possible through enamine intermediates.[12b] This is in sharp contrast with the α-alkoxy ketones which have proved to be excellent intermediates for aldol reactions *via* the enol borinates.[13]

In Scheme 3 we show two possible mechanisms to explain these results: (a) An intramolecular mechanism, where the presumed intermediate **A**, after proton abstraction gives the trimethylsilyl enol ether **B**, the real precursor for the intramolecular alkylation. Note that intermediate **A** can also yield the major product (**2**) in this reaction,[14] and (b) Alternatively, the intermolecular 2-TST mediated abstraction of the α-proton in compound **1** could also afford the reactive intermediate **B** leading to compound **3**.

In any case β-elimination in intermediate **B** (Scheme 3) was not observed. This is really exceptional, considering the experimental conditions used (room temperature with 2-TST as the only reagent in the medium) compared with the necessary controlled conditions [low temperature reaction (−78°C), LDA as base, cosolvents such as HMPT or DMPU, and highly reactive alkylating agents] for the intermolecular alkylation of tartaric acid derivatives described by Seebach.[15] In the present case, the stability of the enolate may also be due to the rigid acetonide skeleton which precludes the optimal geometrical arrangement for β-elimination to take place.[15]

In summary, we have reported the first example of an intramolecular alkylation of an ε-iodo α-alkoxy aldehyde, by using basic, extremely simple and mild reaction conditions. These results open the way for new exciting synthetic ventures directed to the important, synthetic intermolecular alkylation of chiral α-heteroatom *O* or *N*-substituted aldehydes, as a new strategy for the synthesis of enantiomerically pure molecules containing quaternary centers.[16]

Continuing with Dondoni's protocol for the synthesis of aldehyde **7** from intermediate **2** (Scheme 4), we first *O*-benzylated the free alcohol **2** to give compound **8**,[7] and then submitted it to sequential reactions[2] with methyl iodide, sodium borohydride and mercuric chloride to give the desired product **7**, in 50% yield, and compound **9**, in 5% overall yield from product **8** (Scheme 4).



Scheme 4. Synthesis of compounds 7 and 9 from intermediate 8.

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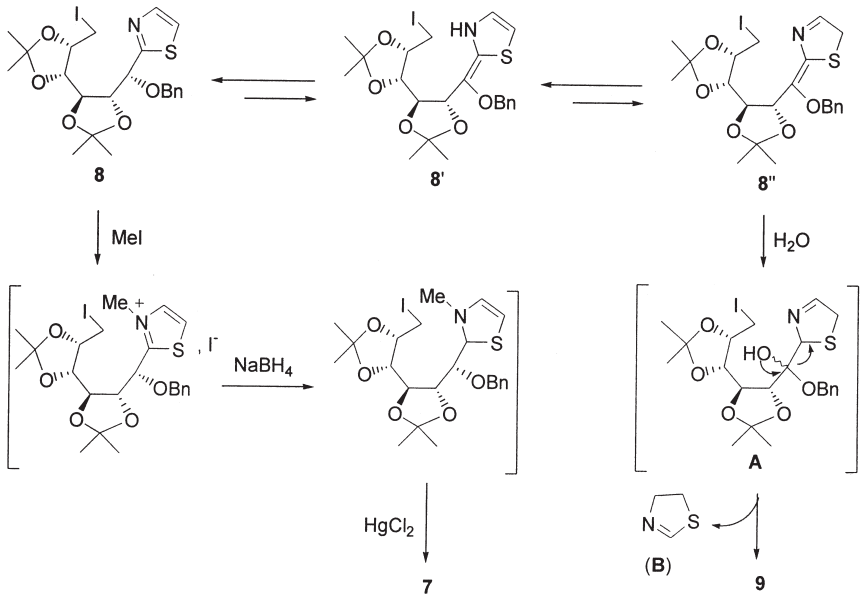
The unexpected compound **9** was an extremely unstable product, and no reliable elemental analysis of the product could be obtained. However, the spectroscopic data strongly supported this structure. The IR spectrum of **9** contained a strong carbonyl ester band at 1760 cm^{-1}. In the ^{1}H NMR spectrum of compound **9** we could assign the same protons, with similar chemical shifts, as those bonded to carbons C3-C8, in compounds **7** or **8**: the iodide atom and the two isopropylidene groups were still present, but the thiazole nucleus was absent. The phenyl*methyl* protons were more shifted in compound **9** (ca. 0.6 ppm) than in the precursor 8.[7] These IR and ^{1}H NMR data were supported in the ^{13}C NMR spectrum plus the results from a DEPT experiment;[9] a signal at 170.4 ppm was assigned to the ester carbonyl group, and the methylene carbon bearing the iodide appeared at 1.4 ppm. Finally, the mass spectrum of **9** showed an intense peak at *m/z* 461, suggesting that the structure of compound **9** corresponded to the benzylic ester of the oxidized form of aldehyde **1** (Scheme 2).

Looking very carefully at the three steps protocol for Dondoni's homologation of product **8**, we could see that this secondary product was already present in the first step of the protocol, the reaction with methyl iodide, and that it survived untouched the mild and quick reduction with sodium borohydride and the mercuric mediated deprotection of the masked aldehyde. To the best of our knowledge a similar product has not been documented in the reported Dondoni's systematic application of this method.[2] In fact, it is difficult to rationalize the formation of this molecule in the reaction with methyl iodide until formation of the quaternary salt!

In Scheme 5 we show a mechanism that we tentatively propose for the formation of ester **9**. Obviously, the equilibrium between **8** and **8″** is displaced to the



Scheme 5. Possible mechanism for the formation of compound 9 from intermediate 8.

left, to the most stable aromatic "imine" **8**. However, we think that enamine **8″** may react with small traces of water to give intermediate **A**, affording ester **9** after elimination of thiazolidine **B**.

In summary, in this report we have described the successful homologation of aldehyde **1** to aldehyde **7** using Dondoni's method, showing also the formation of some secondary, unexpected products (**3** and **9**) in this protocol. These results enhance the generality of the method, but also point out the possible formation of secondary products when designing synthetic schemes using this methodology.

EXPERIMENTAL

General Methods. Reactions were monitored by TLC using precoated silica gel aluminium plates containing a fluorescent indicator (Merck, 5539). Detection was done by UV (254 nm) followed by charring with sulfuric-acetic acid spray, 1% aqueous potassium permanganate solution or 0.5% phosphomolybdic acid in 95% EtOH. Anhydrous Na_2SO_4 was used to dry organic solutions during work-ups and the removal of solvents was carried out under vacuum with a rotary evaporator. Flash column chromatography was performed using silica gel 60 (230–400 mesh, Merck) and hexane/ ethyl acetate mixtures as eluent unless otherwise stated. ^{1}H spectra were recorded with a Varian VXR-300(400)S spectrometer, using tetramethylsilane as internal standard and ^{13} C NMR spectra were recorded with a Bruker WP-200-SY.

(3a*R*,3b*S*,6a*R*,7a*R*)-Tetrahydro-2,2,5,5-tetramethyl-6a*H*-cyclopenta[1,2-d:3,4-d′]bis[1,3]dioxole-6a-carboxaldehyde (3). *Method (A).* Compound **1** (197 mg, 0.53 mmol) dissolved in dry methylene chloride (1 mL) was treated with 2-TST (0.094 mL, 0.58 mmol, 1.1 equiv) at 0°C, under argon. The reaction mixture was warmed and stirred at room temperature for 18 h. The solvent was removed, and the residue was treated with Bu_4NF (0.53 mL, 1.1 M in THF) until desilylation was complete. The solvent was evaporated, the residue diluted with water and extracted with methylene chloride several times. The organic layer was dried, filtered and concentrated. Flash chromatography (hexane/ethyl acetate 10%) gave compounds **2**[7] (141.4 mg, 60%) and **3** (9.3 mg, 7%). *Method (B).* Aldehyde **1** (104.4 mg, 0.28 mmol) was dissolved in dry CH_2Cl_2 (1 mL, 0.3 M), cooled at 0 °C and treated with DBU (0.05 mL, 0.31 mmol, 1.1 equiv). The mixture was stirred and warmed at rt for 1 h. The solvent was removed and the crude product was submitted to chromatography (hexane/ethyl acetate, 9/1) to give compound **3** (51 mg, 75%): oil; $[\alpha]_D^{25}$ − 2 (*c* 0.7, $CHCl_3$); IR (film) *v* 3470, 2986, 2942, 1744, 1644, 1376, 1254, 1166, 1060 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 (s, 1 H, CHO), 4.91 (td, $J_{4,5B}$= $J_{4,3}$= 6.2 Hz, $J_{4,5A}$= 2.9 Hz, 1 H, H4), 4.63 (d, $J_{3,4}$= 6.2 Hz, 1 H, H3), 4.61 (s, 1 H, H2), 2.50 (dd, $J_{5A,5B}$= 15.2 Hz, $J_{4,5A}$= 2.9 Hz, 1 H, H5A), 2.17 (dd, $J_{5A,5B}$= 15.2 Hz, $J_{4,5B}$= 6.2 Hz, 1 H, H5B), 1.52, 1.46, 1.38, 1.31 [4 s, 12 H, 2 × $OC(CH_3)_2O$]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.4 (CHO), 113.5,

111.1 [2 × O*C*$(CH_3)_2$O], 97.3 (C1), 86.6, 83.6 (C2, C3), 81.2 (C4), 39.9 (C5), 27.5, 26.7, 25.9, 24.7 [2 × OC(*C*$H_3)_2$O]; MS (70 eV) *m/z* 243 ($M+1^+$, 19), 227 (M^+-15, 64), 43 (100).

Anal. Calcd for $C_{12}H_{18}O_5$ (242.27): C, 52.94; H, 7.49. Found: C, 52.75; H, 7.38.

(3a*R*,3b*S*,6a*R*,7a*R*)-Tetrahydro-2,2,5,5-tetramethyl-6a*H*-cyclopenta[1,2-d:3,4-d′]bis[1,3]dioxole-6a-methanol (4). To a solution of compound **3** (84.9 mg, 0.35 mmol) in methanol (2.1 mL, 0.17 M), cooled at 0°C, sodium borohydride (20 mg, 0.52 mmol, 1.5 equiv) was added, and the mixture was warmed at rt and stirred for 30 min. Acetone (0.5 mL) was added and the solvents removed by evaporation. The crude product was diluted with methylene chloride, washed with brine, dried and filtered. The solvent was evaporated and the residue was submitted to chromatography (hexane/ethyl acetate, 4/1) to give alcohol **4** (73 mg, 85%): oil; $[\alpha]_D^{25}$ − 13 (*c* 0.47, $CHCl_3$); IR (film) *v* 3468, 2986, 2944, 1380, 1210, 1168, 1058 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.81 (ddd, $J_{3,4}$= 5.9 Hz, $J_{4,5A}$= 4.0 Hz, $J_{4,5B}$= 2.9 Hz, 1 H, H4), 4.62 (d, $J_{3,4}$= 5.9 Hz, 1 H, H3), 4.40 (s, 1 H, H2), 3.78 (dd, $J_{1'A,1'B}$= 12.1 Hz, $J_{1'A,OH}$= 4.9 Hz, 1 H, H1′A), 3.69 (dd, $J_{1'A,1'B}$= 12.1 Hz, $J_{1'B,OH}$= 8.2 Hz, 1 H, H1′B), 2.18 (dd, $J_{1'B,OH}$= 8.2 Hz, $J_{1'A,OH}$= 4.9 Hz, 1 H, OH), 2.16 (d, $J_{5A,4}$= 4.0 Hz, 1 H, H5A), 2.10 (d, $J_{5B,4}$= 2.9 Hz, 1 H, H5B), 1.48, 1.46, 1.37, 1.29 [4 s, 12 H, 2 × OC$(CH_3)_2$O]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 110.8, 109.8 [2 × O*C*$(CH_3)_2$O], 92.1, (C1), 84.7 (C2), 82.3 (C3), 80.2 (C4), 65.0 (C1′), 41.2 (C5), 28.1, 26.4, 26.0, 23.6 [2 × OC(*C*$H_3)_2$O]; MS (70 eV) *m/z* 229 (M-15^+, 100), 213 (4), 155 (10), 111 (56), 99 (17), 43 (74).

Anal. Calcd for $C_{12}H_{20}O_5$ (244.29): C, 59.00; H, 8.25. Found: C, 59.15; H, 8.36.

(3a*R*,3b*S*,6a*R*,7a*R*)-Tetrahydro-2,2,5,5-tetramethyl-6a*H*-cyclopenta[1,2-d:3,4-d′]bis[1,3]dioxole-6a-methyl Acetate (5). Alcohol **4** (32 mg, 0.13 mmol) was treated with a mixture of acetic anhydride/pyridine (1 mL, 1/1) at rt overnight. The solvent was evaporated and the crude product was submitted to chromatography (hexane/ethyl acetate, 83/17) to give acetate 5 (35 mg, 93%): oil; $[\alpha]_D^{25}$ − 4 (*c* 0.51, $CHCl_3$); IR (film) *v* 2989, 2938, 1747, 1382, 1211, 1169, 1062 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.79 (dt, $J_{3,4}$= $J_{4,5B}$= 5.6 Hz, $J_{4,5A}$= 1.5 Hz, , 1 H, H4), 4.59 (d, $J_{3,4}$= 5.7 Hz, 1 H, H3), 4.37/4.15 (2 d, *J*= 12.1 Hz, 2 H, 2 H1′), 4.32 (s, 1 H, H2), 2.17 (br d, $J_{5A,5B}$= 15.0 Hz, 1 H, H5A), 2.09 (s, 3 H, $OCOCH_3$), 2.07 (dd, $J_{5A,5B}$= 15.0 Hz, $J_{5B,4}$= 5.6 Hz, 1 H, H5B), 1.44 (s, 6 H), 1.37, 1.29 [3 s, 12 H, 2 × OC$(CH_3)_2$O]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1 (O*C*OCH_3), 111.2, 109.9 [2 × O*C*$(CH_3)_2$O], 89.9, (C1), 85.0 (C2), 82.2 (C3), 80.2 (C4), 65.8 (C1′), 41.5 (C5), 27.9, 26.0 (2 C), 23.6 [2 × OC(*C*$H_3)_2$O], 20.9 (OCO*C*H_3); MS (70 eV) *m/z* 286 (M, 1), 271 (M-15^+, 72), 228 (8), 171 (10), 153 (34), 111 (66), 81 (33), 59 (20), 43 (100).

Anal. Calcd for $C_{14}H_{22}O_6$ (286.32): C, 58.73; H, 7.74. Found: C, 58.65; H, 7.63.

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2-*O*-Benzyl-7-deoxy-7-iodo-3,4:5,6-bis-*O*-isopropylidene-D-*glycero*-D-*gulo*-heptose (7) and Benzyl 6-deoxy-6-iodo-2,3:4,5-bis-*O*-isopropylidene-D-gluconoate (9). Product **8**[7] (930 mg, 1.7 mmol) was dissolved in acetonitrile (10 mL) and the solution treated with methyl iodide (0.53 mL, 9.5 mmol, 15 equiv) at 80 °C (bath temperature) for 24 h in a sealed tube. The reaction was cooled, the solvent evaporated and the residue was dissolved in methanol (10 mL), cooled at 0°C and treated with sodium borohydride (96.7 mg, 2.55 mmol, 1.5 equiv) under vigorous stirring for 30 min. Acetone was then added to destroy the excess of reagent, the solvent was evaporated in vacuo, and the crude product was dissolved in methylene chloride, washed with brine, dried, filtered, and the solvent was evaporated. The residue was dissolved in acetonitrile (1 mL) and to this solution, a solution of mercuric chloride (562 mg, 2.04 mmol, 1.2 equiv) in a mixture of acetonitrile/water (7.4 mL, 4/1) was slowly added. The mixture was stirred at rt for 15 min. The suspension was filtered over celite, which was washed with ethyl acetate. The organic layer was washed with brine, dried, filtered, concentrated and the residue was submitted to chromatography (hexane/ethyl acetate, 84/16) to give compounds **7** (420 mg, 50%) and **9** (30 mg, 5%).

7: oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.71 (d, $J_{1,2}$= 2.1 Hz, 1 H, H-1), 7.36/7.27 (m, 5 H, $OCH_2C_6H_5$), 4.76/4.60 (AB system, J= 11.7 Hz, 2 H, $OCH_2C_6H_5$), 4.54 (q, $J_{5,6}$= $J_{6,7}$= $J_{6,7'}$= 7.0 Hz, 1 H, H-6), 4.32 (dd, $J_{3,4}$= 7.9 Hz, $J_{2,3}$= 5.9 Hz, 1 H, H-3), 4.13 (q, $J_{4,5}$= 10.4 Hz, $J_{3,4}$= 7.9 Hz, 1 H, H-4), 4.12 (dd, $J_{4,5}$= 10.4 Hz, $J_{5,6}$= 7.0 Hz, 1 H, H-5), 3.88 (dd, $J_{2,3}$= 5.9 Hz, $J_{1,2}$= 2.1 Hz 1 H, H-2), 3.37−3.34 (m, 2 H, 2 H-7), 1.50, 1.43, 1.37, 1.35 [4 s, 2 × $OC(CH_3)_2O$].

Anal. Calcd for $C_{20}H_{27}IO_6$ (490.33): C, 48.99; H, 5.55. Found: C, 48.76; H, 5.67.

9: oil; $[\alpha]_D^{25}$ − 21 (*c* 0.34, $CHCl_3$); IR (film) υ 2987, 2936, 1760, 1498, 1456, 1381, 1214, 1100, 1062 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.32 (m, 5 H, $CO_2CH_2C_6H_5$), 5.26/5.23 (2 d, J= 12.1 Hz, 2 H, $CO_2CH_2C_6H_5$), 4.57 (d, $J_{2,3}$= 8.1 Hz, 1 H, H2), 4.53 (q, $J_{5,6A}$= $J_{5,6B}$= $J_{5B,4}$= 7.0 Hz, 1 H, H5), 4.33 (dd, $J_{3,4}$= 1.5 Hz, $J_{4,5}$= 6.7 Hz, 1 H, H4), 4.25 (dd, $J_{3,4}$= 1.5 Hz, $J_{3,2}$= 8.0 Hz, 1 H, H3), 3.39 (dd, $J_{6A,6B}$= 10.1 Hz, $J_{6A,5}$= 6.7 Hz, 1 H, H6A), 3.33 (dd, $J_{6A,6B}$= 10.1 Hz, $J_{6B,5}$ = 7.7 Hz, 1 H, H5B), 1.49, 1.48 1.42, 1.36 [3 s, 12 H, 2 × $OC(CH_3)_2O$]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4 ($CO_2CH_2C_6H_5$), 135.3−128.5 ($CO_2CH_2C_6H_5$), 111.9, 109.6 [2 × $OC(CH_3)_2O$], 77.8, (C5), 76.8 (C3), 75.7 (C2), 75.2 (C4), 67.1 ($CO_2CH_2C_6H_5$), 26.8, 26.6, 25.9, 25.5 [2 × $OC(CH_3)_2O$], 1.4 (C6); MS (70 eV) *m/z* 461 (M-15$^+$, 63), 283 (17), 235 (38), 183 (18), 91 (100).

HRMS: *m/z* Calcd for $C_{19}H_{25}IO_6$: 476.0695. Found: 476.0643.

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