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# Doubly carbon-branched pentoses: synthesis of both enantiomers of 2,4-di-*C*-methyl arabinose and 2-deoxy-2,4-di-*C*-methyl arabinose using only acetonide protection

K. Victoria Booth [a], Sarah F. Jenkinson [a], Daniel Best [a], Fernando Fernández Nieto [b], Ramón J. Estévez [b], Mark R. Wormald [c], Alexander C. Weymouth-Wilson [d], George W. J. Fleet [a,*]

[a] Chemistry Research Laboratory, Department of Chemistry, University of Oxford, Mansfield Road, Oxford OX1 3TA, UK
[b] Departamento de Química Orgánica, Universidade de Santiago, 15782 Santiago de Compostela, Spain
[c] Glycobiology Institute, Department of Biochemistry, Oxford University, South Parks Road, Oxford OX1 3QU, UK
[d] Dextra Laboratories Ltd, The Science and Technology Centre, Whiteknights Road, Reading RG6 6BZ, UK

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ABSTRACT

An acetonide is the only protecting group used in the synthesis of both the enantiomers of 2,4-di-*C*-methyl arabinose and 2-deoxy-2,4-di-*C*-methyl arabinose via the enantiomeric 3-*C*-methyl-L-erythrono-lactone [from 2-*C*-methyl-D-ribono-lactone or D-ribose] and 3-*C*-methyl-D-erythronolactone [from D-tagatose or L-ribose]. NMR studies on unprotected *C*-methyl arabinoses show that methyl branching significantly affects the ratios of pyranose and furanose forms present in aqueous solution.



Although most carbohydrates have linear carbon chains, singly branched sugars with one methyl or hydroxymethyl branch are found in Nature, frequently as a component of a larger molecule.[1] For example, 3-*C*-methyl-D-mannose occurs in a polysaccharide of *Helicobacter pylori*;[2] the carbohydrate portion of apoptolidins, potential anti-cancer compounds, is essential for anti-tumor activity and contains a 3-*C*-methyl branched sugar.[3] Also 2-*C*-methyl-D-erythritol phosphate is an intermediate in the non-mevalonate biosynthesis of terpenes providing a strategy for the inhibition of the growth of many pathogens including mycobacteria such as tuberculosis.[4] Many recent papers have demonstrated the chemotherapeutic potential of 2′- and 4′-*C*-methyl nucleoside analogues,[5] particularly for the treatment of hepatitis C.[6] There have been very few studies on di-*C*-methyl carbohydrates, although the synthesis of bioactive 2′,4′-di-*C*-methyl nucleosides has recently been reported.[7]

The Kiliani[8] reaction of cyanide on monosaccharides is a very powerful and general method for access to C-branched sugars and polylols,[9] including all four of the diastereomeric ketohexoses[10] as well as the syntheses of C-3 branched sugars from C-2 branched sugars [such as hamamelose][11] and of β-sugar amino acids from unprotected Amadori ketoses.[12] Thus the protected deoxyribulose **3**, prepared by the addition of methylmagnesium bromide to the acetonide of D-erythronolactone **2** derived from arabinose **1**, reacts with cyanide to give the protected 1,5-lactone **4** with high diastereoselectivity (Scheme 1); reduction of **4** followed by deprotection gives 2-*C*-methyl-D-arabinose **5** which has been used in the synthesis of 2′-*C*-methyl nucleosides.[13] This Letter describes the preparation, by a similar strategy, of the two enantiomers of 2,4-di-*C*-methyl arabinoses **9D** and **9L** and of 2-deoxy-2,4-di-*C*-methyl-L-arabinose **11L** from the two enantiomers of the acetonides 3-*C*-methyl erythronolactones **7D** and **7L** via the 1,5-lactones **8D** and **8L**, respectively (Scheme 2). 2-deoxy-2,4-di-*C*-methyl-L-arabinose **11D** would be similarly accessible from **8D**. 2,4-Di-*C*-methyl-L-arabinose **9L** was efficiently synthesized from either D-glucose **6** or D-ribose **10D** whereas **9D** was obtained from either D-tagatose **12** or L-ribose **10L**. The only protection necessary for all the syntheses was an isopropylidene group. The effect of the introduction of carbon branching on the pyranose-furanose equilibrium forms of arabinose was studied by NMR.

3-*C*-Methyl-L-erythronolactone **7L**, the key intermediate for the synthesis of the 2,4-di-*C*-methylarabinoses **9L** and **11L**, was prepared from both D-glucose **6** and D-ribose **10D** (Scheme 3). D-Glucose **6** on reaction with dimethylamine in aqueous acetic acid, followed by treatment of the resulting Amadori ketose with calcium hydroxide, gave the branched lactone **13** in approximately 25% yield on a kilogram scale.[14] Acetonation of **13**, followed by reduction with lithium borohydride, gave the triol **14** in quantitative yield. Periodate oxidation of **14** formed the lactol **15L**, further oxidation of which using bromine water afforded the lactone **7L**[15,16] in an overall yield from **13** of 93%.

The L-lactone **7L** was also synthesized from D-ribose **10D** (Scheme 3). The branching hydroxymethyl group was introduced via a Ho crossed aldol reaction between the acetonide of ribose and formaldehyde to give the protected D-hamamelose **16D** in

* Corresponding author.
*E-mail address:* george.fleet@chem.ox.ac.uk (G.W.J. Fleet).

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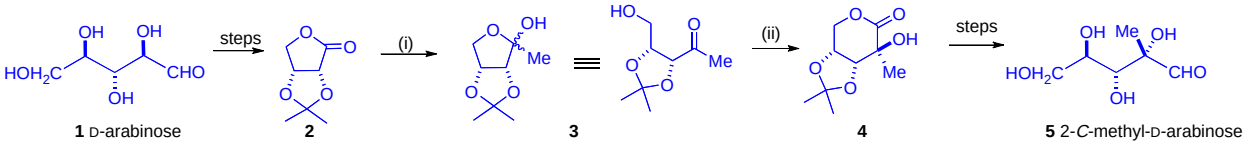
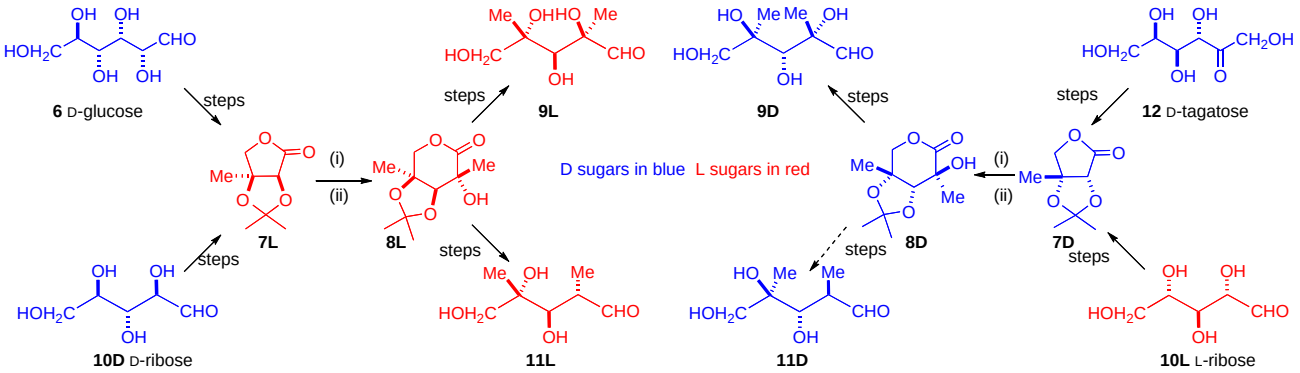
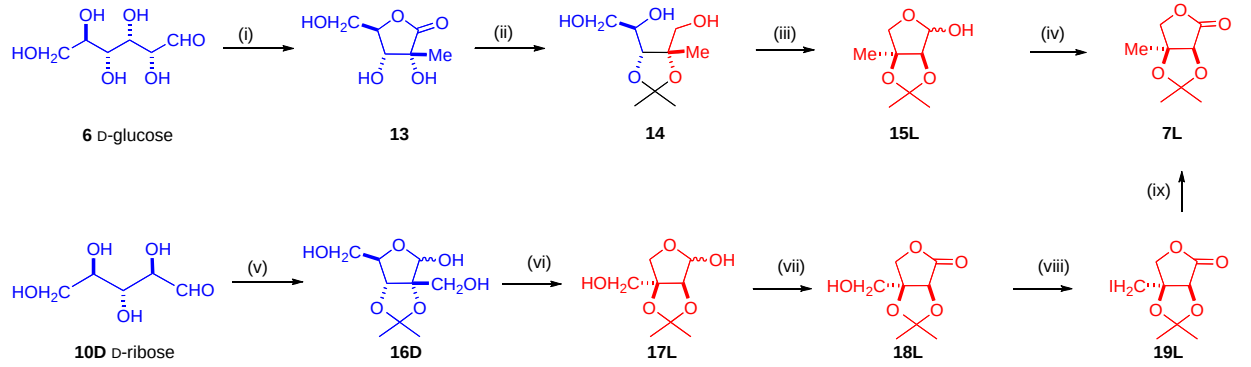



**Scheme 1.** Reagents: (i) MeMgBr; (ii) NaCN.




**Scheme 2.** Reagents: (i) MeMgBr; (ii) NaCN.




**Scheme 3.** Reagents and conditions: (i) $Me_2NH$, AcOH, $H_2O$; then $Ca(OH)_2$, $H_2O$, ~25%; (ii) $Me_2CO$, $CuSO_4$, cat. $H_2SO_4$, 16 h; then $LiBH_4$, THF, 1.5 h, 100% over two steps; (iii) $NaIO_4$, MeOH, $H_2O$, 45 min, 100%; (iv) $Br_2$, $BaCO_3$, $H_2O$, 0 °C to rt, 18 h, 93%;(v) $Me_2CO$, $CuSO_4$, cat. $H_2SO_4$; then $CH_2O$, $Na_2CO_3$, $H_2O$, 88%; (vi) $NaBH_4$, $H_2O$; then $NaIO_4$, AcOH, 94%; (vii) $Br_2$, $BaCO_3$, $H_2O$, 90%; (viii) $(CF_3SO_2)_2O$, pyridine, $CH_2Cl_2$, −30 °C; then $Bu_4NI$, DMF, 76%; (ix) Pd/C (10%), $H_2$, $Et_3N$, 85%.

88% yield as previously described.[17] Reduction of **16D** by sodium borohydride followed by sodium periodate oxidation afforded the protected L-apiose **17L** (94%) which on treatment with bromine water gave the L-apionolactone **18L** [mp 90–92 °C; $[\alpha]_D^{22}$ +70.5 (*c*, 0.95)[18]] in 90% yield. Esterification of the free alcohol in **18L** with triflic anhydride in dichloromethane in the presence of pyridine gave the corresponding triflate which on reaction with tetra-*n*-butylammonium iodide afforded the iodide **19L** [mp 60–62 °C; $[\alpha]_D^{18}$[18] +27.7 (*c*, 1.29)] in 76% yield. Hydrogenation of **19L** in the presence of palladium and triethylamine gave the 3-*C*-methyl lactone **7L**, identical to the material prepared from D-glucose **6**, in 85% yield [64% overall yield of **7L** from **16D**].

Reaction of the lactone **7L** with methylmagnesium bromide gave the protected 4-*C*-methyl deoxy-L-ribulose **20L** (87% yield). Treatment of **20L** with sodium cyanide resulted in a highly diastereoselective Kiliani reaction to give the arabinonolactone **8L**[19] in 77% yield together with a small amount (3%) of the epimeric ribonolactone **21L**.[20] The structure of **8L** was confirmed by X-ray crystal analysis.[21] The high yield of the protected lactone is due to lack of hydrolysis of the ketal protecting group in **8L** in comparison to the very easy hydrolysis of the mono-*C*-methyl analogue **4**.[14] 3,4-*O*-Isopropylidene-1,5-lactones invariably crystallize in a boat conformation;[22] the diastereoselectivity may be rationalized by less steric congestion in the *arabino* lactone **8L** [with a flagpole hydroxy group] than in the *ribo* epimer **21L** [with the larger flagpole methyl substituent]. DIBALH reduction of the lactone **8L** gave the protected lactol **22L** [mp 84–86 °C; $[\alpha]_D^{17}$ +26.6 (*c*, 0.60)] in 67% yield with 22% recovery of the starting material **8L**. Although removal of the isopropylidene protecting group in the lactone **8L** in good yield was not possible, the protected lactol **22L** with acid ion exchange resin, afforded the target di-*C*-methyl-L-arabinose **9L** [mp 132–134 °C; $[\alpha]_D^{17}$ +13.0 (*c*, 0.90 in MeOH)] in quantitative yield; **9L** crystallized as the hydrate of the α-pyranose form.[23]

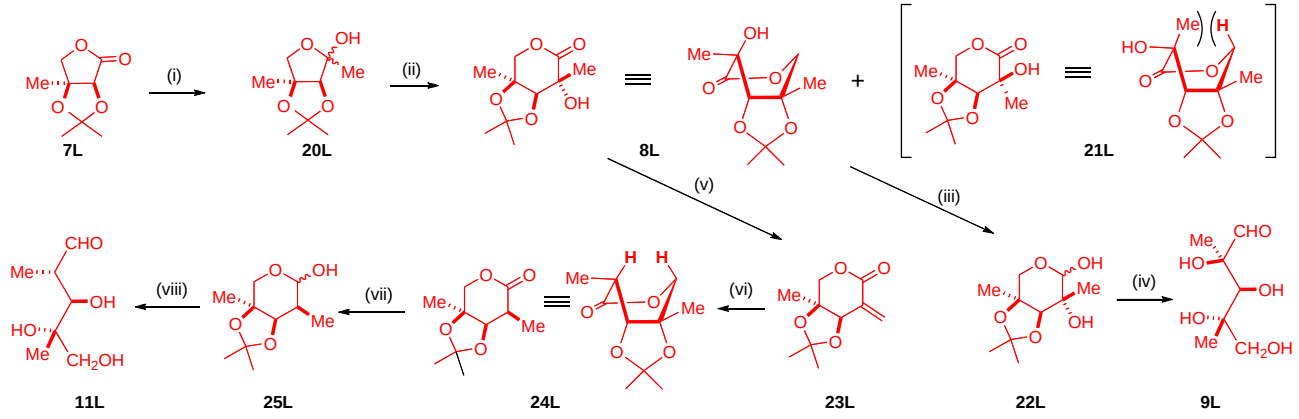
For the 2-deoxy sugar **11L**, the lactone **8L** was esterified with triflic anhydride and allowed to stand at room temperature; the unsaturated lactone **23L**[24] was formed as a stable crystalline solid in 63% yield. All attempts to base catalyze this elimination failed and gave complex mixtures. Hydrogenation of **23L** in the presence of palladium in ethanol gave a single *C*-methyl compound **24L**[25] in 72% yield; a significant nOe between C2H and C5H was strongly

suggestive of the production of the more stable *arabino* product **24L** even though this would require hydrogenation from the most hindered face. Reduction of **24L** by DIBALH gave the lactol **25L** [mp 76–79 °C; $[\alpha]_D^{25}$ −49.6 (*c*, 0.15)], which was crystallized as the β-pyranose anomer,[26] in 59% yield. Removal of the isopropylidene protecting group by acid ion exchange resin gave 2-deoxy-2,4-di-*C*-methyl-L-arabinose **11L** [oil, $[\alpha]_D^{22}$ −12.7 (*c*, 0.56 in MeCN)] in 82% yield.

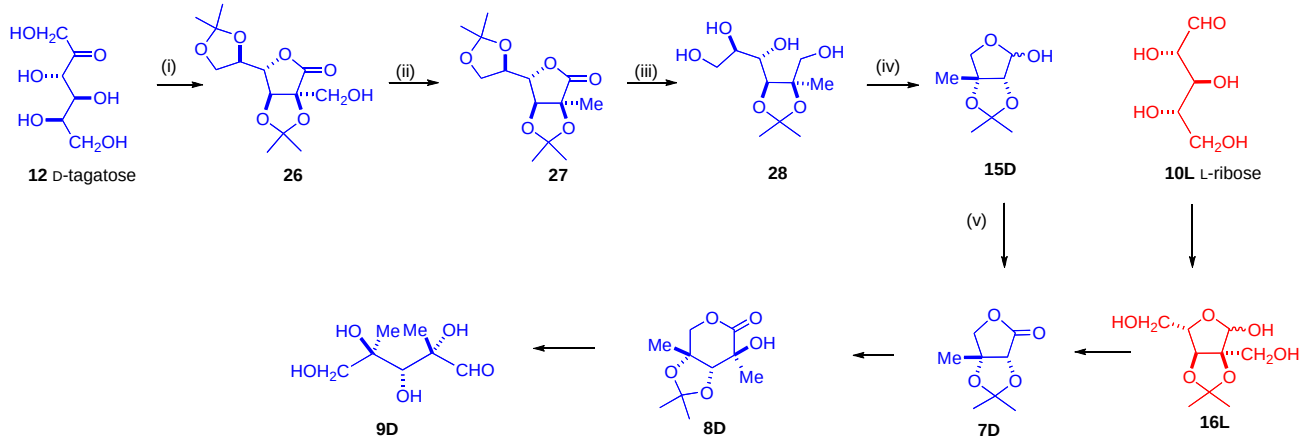
In the D-series the synthesis of 2,4-di-*C*-methyl-D-arabinose **9D** required D-erythronolactone **7D** which was prepared from both D-tagatose **12** and L-ribose **10L** (Scheme 5). Although the price of D-tagatose in the 2007–2008 Aldrich catalogue is £331.00 for 5 g,[27] it is now available cheaply in large quantities [around £5 per kg] by either chemical[28] or biotechnological[29] procedures and has been developed as a low calorie sweetener.[30] The potential of D-tagatose as a chiral building block is beginning to be recognized.[31] For example, D-tagatose **12** underwent an efficient Kiliani reaction to give a mixture of diastereomeric lactones which on treatment with acetone and acid resulted in the easy isolation of the diacetonide **26** in 51% yield. Appel reaction of the alcohol **26** with triphenylphosphine and iodine in the presence of imidazole afforded the corresponding iodide which on hydrogenation gave the 2-*C*-methyl branched lactone **27** in 92% yield.[32] Reduction of **27** with lithium borohydride in THF formed a diol from which the terminal acetonide was removed selectively by aqueous acetic acid to give the tetraol **28** [mp 81–82 °C; $[\alpha]_D^{25}$ +10.9 (*c*, 1.0)] in 90% yield. Sequential oxidation with periodate to **15D**[33] and then bromine water gave the lactone **7D** [mp 82–84 °C; $[\alpha]_D^{17}$ -106.6 (*c*, 1.34); $[\alpha]_D^{17}$ +101.6 (*c*, 0.80) for the enantiomer **7L**] in 90% yield [overall 75% yield from **26**]. The lactone **7D** was also prepared from L-ribose **10L**, via the protected hamamelose **16L**, by the same sequence of reactions described for the D-isomer in Scheme 3.

The lactone **7D** was then subjected to analogous reactions to those on **7L** to form the di-*C*-methyl D-arabinonolactone **8D** {mp 112–114 °C; $[\alpha]_D^{22}$ −139.4 (*c*, 1.20); for the enantiomer **8L**, $[\alpha]_D^{23}$ +131.8 (*c*, 1.50)}. DIBALH reduction followed by deprotection, as described for the L-enantiomer **8L** in Scheme 4, afforded the free di-*C*-methyl sugar **9D** {$[\alpha]_D^{22}$ −15.5 (*c*, 1.10 in MeOH); for the enantiomer **9L**, $[\alpha]_D^{17}$ +13.0 (*c*, 0.90 in MeOH)}.

Full NMR analyses[34] of 2-*C*-methyl-arabinose **5**, 2,4-di-*C*-methyl-arabinose **9**, and 2,4-di-*C*-methyl-2-deoxy-arabinose **11** were carried out in $D_2O$ to study the effect of introducing *C*-methyl groups on the equilibrium between pyranose and furanose forms, and between anomers; the 1D $^1H$ NMR spectra are shown in Figure 1, and the $^1H$ and $^{13}C$ assignments are given in Tables 1 and 2. For all compounds, the pyranose forms were identified by the HMBC peak between C1 and C5H/C5H′, and between C5 and C1H; the furanose forms were identified by the HMBC peak between C4 and C1H. There was no evidence of the open-chain keto form within the detection limit in any of the samples (<2%). The furanose




**Scheme 4.** Reagents and conditions: (i) MeMgBr, THF, −78 °C, 45 min, 87%; (ii) NaCN, $H_2O$, 77%; (iii) DIBALH, $CH_2Cl_2$, −78 °C, 1.5 h, 67%; (iv) Dowex® (50 W X8 $H^+$), $H_2O$, 90 °C, 1.5 h, 100%; (v) $(CF_3SO_2)_2O$, pyridine, $CH_2Cl_2$; then DMF, rt, 16 h, 63%; (vi) $H_2$, 20% Pd/C, EtOH, 72%; (vii) DIBALH, $CH_2Cl_2$, −78 °C, 59%; (viii) Dowex® (50 W X8 $H^+$), $H_2O$, 90 °C, 1.5 h, 82%.




**Scheme 5.** Reagents and conditions: (i) NaCN, $H_2O$; then $Me_2CO$, $H_2SO_4$, 51%; (ii) $Ph_3P$, $I_2$, imidazole, PhMe; then $H_2$, Pd/C, $Et_3N$, EtOH, 92%; (iii) $LiBH_4$, THF, 0 °C to rt, 16 h; then AcOH, $H_2O$, 16 h, 90%; (iv) $NaIO_4$, $H_2O$, rt, 4 h, 96%; (v) $Br_2$, $BaCO_3$, $H_2O$, 93%.

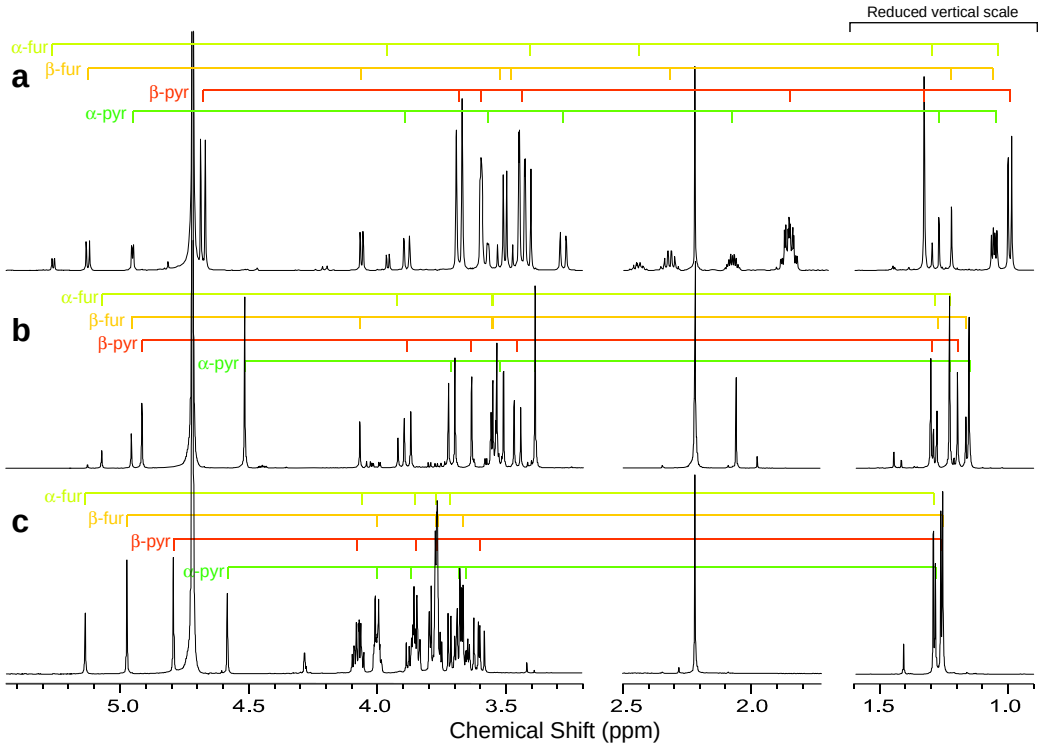



**Figure 1.** $^{1}$H NMR spectra of (a) 2,4-di-*C*-methyl-2-deoxy-arabinose **11L**, (b) 2,4-di-*C*-methyl-arabinose **9L**, and (c) 2-*C*-methyl-arabinose **5L**. The vertical scales of the methyl regions have been reduced. The peak at 2.22 ppm in each spectrum is acetone added as an internal standard.

β-anomers of all three sugars and the pyranose β-anomers of **5** and **9** could be identified by the strong C1H to C2CH$_3$ NOEs. The pyranose β-anomer of **11** could be identified by the large *trans*-diaxial coupling between C1H and C2H. The proportions of furanose and pyranose forms are shown in Figure 2 [shown for the L-enantiomers]. For the β-pyranose form of 2-*C*-methyl-arabinose **5**, the large $^{3}J_{HH}$ coupling between C4H and C5H′ indicates that these two protons are axial. This defines the ring conformation as $^{1}C_4$. For the α-pyranose form, the lack of a large coupling between C4H and either C5H or C5H′ indicates that C4H is equatorial and hence the ring is in the $^{4}C_1$ conformation. These conformations are those predicted on steric grounds, both having two axial and three equatorial substituents; however, in the α-form the axial substituents are on the same side of the ring, whilst in the β-form they are on the opposite sides, hence the α/β ratio is less than one.

**Table 1**
$^{13}$C chemical shifts of *C*-methyl-arabinoses (referenced to acetone at 30.90 ppm)

| | | C1 | C2 | C3 | C4 | C5 | C2*C* | C4*C* |
|---|---|---|---|---|---|---|---|---|
| *2-C-Methyl-arabinose* **5** | | | | | | | | |
| α-Fur | 21% | 103.16 | 81.02 | 77.81 | 84.79 | 62.4 | 15.98 | — |
| β-Fur | 30% | 100.71 | 78.54 | 76.36 | 81.91 | 63.23 | 18.04 | — |
| α-Pyr | 20% | 98.32 | 73.96 | 74.59 | 67.31 | 63.85 | 17.1 | — |
| β-Pyr | 29% | 95.95 | 73.24 | 73.66 | 65.82 | 63.61 | 20.97 | — |
| *2,4-Di-C-methyl-arabinose* **9** | | | | | | | | |
| α-Fur | 9% | 102.26 | 81.76 | 79.23 | 86.62 | 67.86 | 16.6 | 19.61 |
| β-Fur | 16% | 99.55 | 79.72 | 78.49 | 84.47 | 68.7 | 19.24 | 18.37 |
| α-Pyr | 46% | 99.34 | 75.05 | 78.52 | 72.23 | 71.82 | 13.7 | 22.39 |
| β-Pyr | 29% | 97.63 | 73.14 | 75.09 | 72.12 | 67.05 | 19.99 | 22.93 |
| *2,4-Di-C-methyl-2-deoxy-arabinose* **11** | | | | | | | | |
| α-Fur | 7% | 100.23 | 42.65 | 75.44 | 88.6 | 67.75 | 8.02 | 19.52 |
| β-Fur | 17% | 103.41 | 45.11 | 75.83 | 87.75 | 67.85 | 9.85 | 18.49 |
| α-Pyr | 15% | 95.36 | 36.11 | 75.66 | 69.69 | 63.27[a] | 12.01[a] | 22.55 |
| β-Pyr | 61% | 97.17 | 39.28 | 76.02 | 69.88 | 68.28 | 12.77 | 22.84 |

% ages were estimated from peak area in the $^{1}$H 1D spectrum.
[a] Broad peaks in the 1D spectrum.

For the β-pyranose form of 2,4-di-*C*-methyl-arabinose **9**, the relatively high chemical shift for C1H suggests that this proton is equatorial and the large difference between the chemical shifts of C5H and C5H′ implies that C1OH is axial, consistent with a $^{4}C_1$ ring conformation. For the α-pyranose form, the relatively low chemical shift for C1H indicates that this proton is axial, thus suggesting that the ring is also in the $^{4}C_1$ conformation. For the α-anomer, this conformation would be predicted on steric grounds, placing four of the six groups equatorial. For the β-anomer, both the $^{1}C_4$ and $^{4}C_1$ conformations place three groups axial and three equatorial.

The large $^{3}J_{HH}$ coupling between C1H and C2H indicates that these two protons are axial in the β-pyranose form of 2,4-di-*C*-methyl-2-deoxy-arabinose **11**. This defines the ring conformation as $^{1}C_4$, which maximizes the number of equatorial substituents relative to axial substituents. For the α-pyranose form, the relatively high chemical shift for C1H implies that this proton is equatorial and the large difference between the chemical shifts of C5H and C5H′ suggests that C1OH is axial. This implies that the ring conformation is also $^{1}C_4$, consistent with the identical $^{3}J_{HH}$ coupling between C2H and C3H and between C3H and C5H′. For the β-anomer, this conformation would be predicted on steric grounds, placing three of the five groups equatorial. For the α-anomer, steric arguments would favor the $^{4}C_1$ conformation rather than the $^{1}C_4$; however, the observed peak broadening may indicate some dynamic ring behavior. *C*-Methyl branching increases the proportion of furanose forms relative to pyranose forms compared to the parent arabinose **1**,[35] more so for the 2-*C*-methyl **5** than for the dimethyl **9** and **11** sugars (Fig. 2). The β-furanose form relative to α-furanose is stabilized by C2-methylation, **5**; C2,C4-dimethylation, **9** and **11**, stabilizes the β-anomer still further. This is as expected as both methyl groups are on the same side of the ring as C1OH in the α-anomer. For the pyranose forms, C-methylation causes more complex changes in ring conformation and stability. C2-Methylation does not alter the stable ring conformations of the α- and β-anomers relative to arabinose, but makes the β-ano-

**Table 2**
$^1$H chemical shifts (ppm) and 3-bond coupling constants (Hz) of *C*-methyl-arabinoses (referenced to acetone at 2.220 ppm)

| | | C1H | C2H | C3H | C4H | C5H | C5H′ | C2CH$_3$ | C4CH$_3$ |
|---|---|---|---|---|---|---|---|---|---|
| *2-C-Methyl-arabinose* **5** | | | | | | | | | |
| α-Fur | 21% | 5.137 | — | 3.853 ($J_{3,4}$ 5.8) | 4.068 | 3.773 ($J_{4,5}$ 3.6) | 3.708 ($J_{4,5'}$ 5.5) | 1.292 | — |
| β-Fur | 30% | 4.975 | — | 4.004 ($J_{3,4}$ 6.7) | 3.765 | 3.773 ($J_{4,5}$ 3.3) | 3.668 ($J_{4,5'}$ 6.5) | 1.256 | — |
| α-Pyr | 20% | 4.584 | — | 3.685 ($J_{3,4}$ 5.0) | 4.003 | 3.871 ($J_{4,5}$ 5.3) | 3.658 ($J_{4,5'}$ 3.1) | 1.285 | — |
| β-Pyr | 29% | 4.794 | — | 3.771 ($J_{3,4}$ 3.6) | 4.082 | 3.852 ($J_{4,5}$ 4.7) | 3.605 ($J_{4,5'}$ 8.5) | 1.263 | — |
| *2,4-Di-C-methyl-arabinose* **9** | | | | | | | | | |
| α-Fur | 9% | 5.074 | — | 3.921 | — | 3.55 | 3.55 | 1.292 | 1.23 |
| β-Fur | 16% | 4.958 | — | 4.069 | — | 3.56 | 3.56 | 1.279 | 1.166 |
| α-Pyr | 46% | 4.517 | — | 3.387 | — | 3.712 | 3.523 | 1.229 | 1.153 |
| β-Pyr | 29% | 4.917 | — | 3.634 | — | 3.884 | 3.456 | 1.303 | 1.199 |
| *2,4-Di-C-methyl-2-deoxy-arabinose* **11** | | | | | | | | | |
| α-Fur | 7% | 5.260 ($J_{1,2}$ 4.9) | 2.44 ($J_{2,3}$ 5.7) | 3.959 | — | 3.403 | 3.403 | 1.049 ($J_{2,Me}$ 7.2) | 1.296 |
| β-Fur | 17% | 5.126 ($J_{1,2}$ 6.5) | 2.317 ($J_{2,3}$ 5.7) | 4.06 | — | 3.522 | 3.484 | 1.057 ($J_{2,Me}$ 7.2) | 1.22 |
| α-Pyr | 15% | 4.952 ($J_{1,2}$ 3.3) | 2.073 ($J_{2,3}$ 2.6) | 3.57 | — | 3.886 | 3.276 | 1.05 ($J_{2,Me}$ 7.1) | 1.269 |
| β-Pyr | 61% | 4.679 ($J_{1,2}$ 8.8) | 1.852 ($J_{2,3}$ 2.6) | 3.596 | — | 3.68 | 3.437 | 0.993 ($J_{2,Me}$ 6.9) | 1.327 |

% ages were estimated from peak area in the $^1$H 1D spectrum.

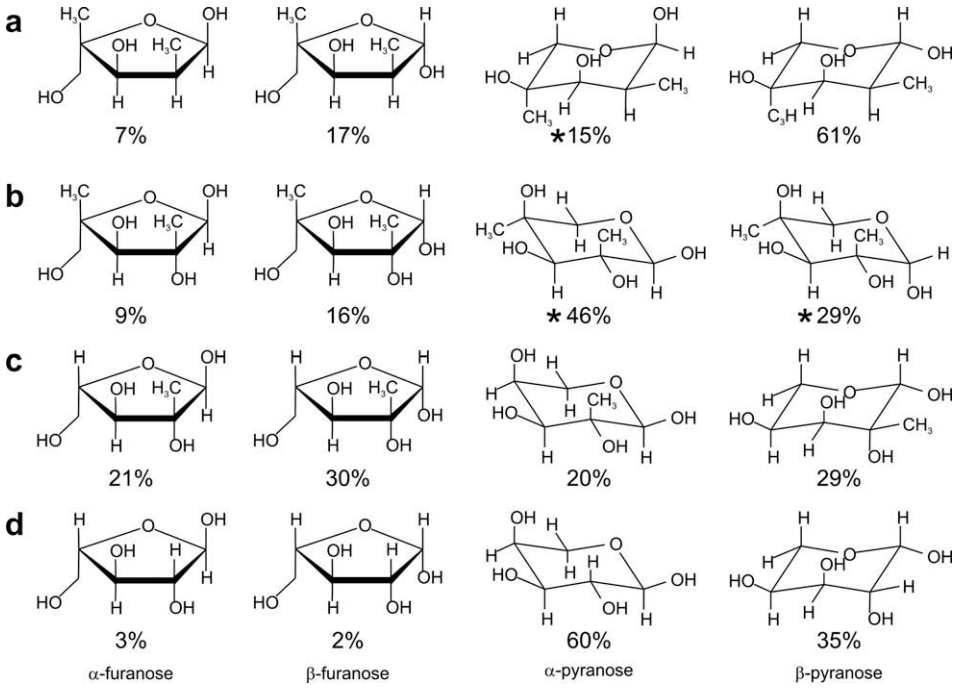



**Figure 2.** Ring conformations and relative populations for the α-pyr, β-pyr, α-fur, and β-fur forms of (a) **11L**, (b) **9L**, (c) **5L**, and (d) arabinose **1L**. * ring conformations not unambiguously determined by NMR.

mer more stable than the α-anomer. C2,C4-Dimethylation alters the ring conformation of the β-anomer relative to arabinose **1** and again increases its stability relative to the α-anomer, although the latter is still more stable. C2,C4-Dimethylation combined with loss of the C2-hydroxy group in **11** changes the ring conformation of the α-anomer and makes the β-anomer far more stable.

In summary, this Letter reports the first synthesis of unprotected di-*C*-methyl branched monosaccharides by an efficient Kiliani reaction on a branched deoxyketose. The effect of *C*-methyl branching on the ratios of pyranose to furanose anomers in arabinose has been studied.

## Acknowledgment

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## References and notes

1. (a) Daum, M.; Peintner, I.; Linnenbrink, A.; Frerich, A.; Weber, M.; Paululat, T.; Bechthold, A. *ChemBioChem* **2009**, *10*, 1073–1083; (b) Weymouth-Wilson, A. C. *Nat. Prod. Rep.* **1997**, *14*, 99–110; (c) Crimmins, M. T.; Christie, H. S.; Long, A.; Chaudhary, K. *Org. Lett.* **2009**, *11*, 831–834; (d) Carpenter, J.; Northrup, A. B.; Chung, D.; Wiener, J. J. M.; Kim, S. G.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 3568–3572.
2. Kocharova, N. A.; Knirel, Y. A.; Widmalm, G.; Jansson, P.; Moran, A. P. *Biochemistry* **2000**, *39*, 4755–4760.
3. (a) Wender, P. A.; Jankowski, O. D.; Tabet, E. A.; Seto, H. *Org. Lett.* **2003**, *5*, 2299–2302; (b) Wender, P. A.; Sukopp, M.; Longcore, K. *Org. Lett.* **2005**, *7*, 3025; (c) Wender, P. A.; Jankowski, O. D.; Longcore, K.; Tabet, E. A.; Seto, H.; Tomikawa, T. *Org. Lett.* **2006**, *8*, 589–592.
4. (a) Kuntz, L.; Tritsch, D.; Grosdemange-Billiard, C.; Hemmerlin, A.; Willem, A.; Bacht, T. J.; Rohmer, M. *Biochem. J.* **2005**, *386*, 127–135; (b) Giner, J. L.; Ferris, W. V.; Mullins, J. J. *J. Org. Chem.* **2002**, *67*, 4856–4859.
5. (a) Bio, M. M.; Xu, F.; Waters, M.; Williams, J. M.; Savary, K. A.; Cowden, C. J.; Yang, C.; Buck, C.; Song, Z. J.; Tschaen, D. M.; Volante, R. P.; Reamer, R. A.; Grabowski, E. J. J. *J. Org. Chem.* **2004**, *69*, 6257–6266; (b) Girardet, J.-L.; Gunic, E.; Esler, C.; Cieslak, D.; Pietrzkowski, Z.; Wang, G. *J. Med. Chem.* **2000**, *43*, 3704–

3713; (c) Maddaford, A.; Wainwright, P.; Glen, R.; Fisher, R.; Dragovich, P. S.; Gonzalez, J.; Kung, P. P.; Middleton, D. S.; Pryde, D. C.; Stephenson, P. S.; Sutton, S. C. *Synthesis* **2007**, 1378–1384.

6. (a) Eldrup, A. B.; Prhavc, M.; Brooks, J.; Bhat, B.; Prakash, T. P.; Song, Q.; Bera, S.; Bhat, N.; Dande, P.; Cook, P. D.; Bennett, C. F.; Carroll, S. S.; Ball, R. G.; Bosserman, M.; Burlein, C.; Colwell, L. F.; Fay, J. F.; Flores, O. A.; Getty, K.; LaFemina, R. L.; Leone, J.; MacCoss, M.; McMasters, D. R.; Tomassini, J. E.; Von Langen, D.; Wolanski, B.; Olsen, D. B. *J. Med. Chem.* **2004**, *47*, 5284–5297; (b) Pierra, C.; Benzaria, S.; Amador, A.; Moussa, A.; Mathieu, S.; Storer, R.; Gosselin, G. *Nucleosides, Nucleotides Nucleic Acids* **2005**, *24*, 767–770.
7. Maddaford, A.; Guyot, T.; Leese, D.; Glen, R.; Hart, J.; Zhang, X.; Fisher, R.; Middleton, D. S.; Doherty, C. L.; Smith, N. N.; Pryde, D. C.; Sutton, S. C. *Synlett* **2007**, 3149–3154.
8. (a) Hudson, C. S. *Adv. Carbohydr. Chem.* **1945**, *1*, 2–36; (b) Hudson, C. S. *J. Am. Chem. Soc.* **1951**, *73*, 4498–4499; (c) Pratt, J. W.; Richtmeyer, N. K.; Hudson, C. S. *J. Am. Chem. Soc.* **1953**, *75*, 4503–4505; (d) Bichard, C. J. F.; Wheatley, J. R.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1994**, *5*, 431–440; (e) Beacham, A. R.; Bruce, I.; Choi, S.; Doherty, O.; Fairbanks, A. J.; Fleet, G. W. J.; Skead, B. M.; Peach, J. M.; Saunders, J.; Watkin, D. J. *Tetrahedron: Asymmetry* **1991**, *2*, 883–900.
9. (a) Ferrier, R. J. *J. Chem. Soc.* **1962**, 3544–3549; (b) Kiliani, H. *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 3066–3072; (c) Kiliani, H. *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 221–227; (d) Kiliani, H. *Ber. Dtsch. Chem. Ges.* **1928**, *61*, 1155–1169; (e) Woods, R. J.; Neish, A. C. *Can. J. Chem.* **1953**, *31*, 471–475; Woods, R. J.; Neish, A. C. *Can. J. Chem.* **1954**, *32*, 404–414; Gorin, P. A. J.; Perlin, A. S. *Can. J. Chem.* **1956**, *36*, 480–485.
10. (a) Hotchkiss, D. J.; Soengas, R.; Simone, M. I.; van Ameijde, J.; Hunter, S.; Cowley, A. R.; Fleet, G. W. J. *Tetrahedron Lett.* **2004**, *45*, 9461–9464; (b) Soengas, R.; Izumori, K.; Simone, M. I.; Watkin, D. J.; Skytte, U. P.; Soetart, W.; Fleet, G. W. J. *Tetrahedron Lett.* **2005**, *46*, 5755–5759.
11. (a) Parker, S.; Watkin, D. J.; Simone, M. I.; Fleet, G. W. J. *Acta Crystallogr., Sect. E* **2006**, *62*, o3961–o3963; (b) Bream, R.; Watkin, D. J.; Soengas, R.; Eastwick-Field, V.; Fleet, G. W. J. *Acta Crystallogr., Sect. E* **2006**, *62*, o977–o979; (c) Simone, M.; Fleet, G. W. J.; Watkin, D. J. *Acta Crystallogr.* **2007**, *63*, o799–o801.
12. Jenkinson, S. F.; Hotchkiss, D. J.; Cowley, A. R.; Fleet, G. W. J.; Watkin, D. J. *Acta Crystallogr., Sect. E* **2008**, *64*, o294–o295.
13. Jenkinson, S. F.; Jones, N. A.; Moussa, A.; Stewart, A. J.; Heinz, T.; Fleet, G. W. J. *Tetrahedron Lett.* **2007**, *48*, 4441–4445.
14. (a) Hotchkiss, D. J.; Jenkinson, S. F.; Storer, R.; Heinz, T.; Fleet, G. W. J. *Tetrahedron Lett.* **2006**, *47*, 315–318; (b) Booth, K. V.; da Cruz, F. P.; Hotchkiss, D. J.; Jenkinson, S. F.; Jones, N. A.; Weymouth-Wilson, A. C.; Clarkson, R.; Heinz, T.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2008**, *19*, 2417–2424.
15. All NMR spectra and specific rotations were determined in $CHCl_3$ except where otherwise stated.
16. Selected data for 2,3-*O*-isopropylidene-3-*C*-methyl-L-erythrono-1,4-lactone **7L**: mp 82–84 °C; $[\alpha]_D^{17}$ +101.6 (*c*, 0.80); $\delta_H$: 1.40, 1.49 (2 × 3H, s, $CH_3$), 1.54 (3H, s, H3″), 4.15 (1H, d, H4, $J_{4,4'}$ 10.6), 4.44 (1H, d, H4′, $J_{4',4}$ 10.6), 4.46 (1H, s, H2); $\delta_C$: 21.9 (C3′), 27.7, 28.5 (C($CH_3$)$_2$), 75.6 (C4), 79.4 (C2), 83.5 (C3), 114.0 (*C*($CH_3$)$_2$), 174.7 (C=O).
17. (a) Ho, P. *Tetrahedron Lett.* **1978**, 1623–1626; (b) Ho, P.-T. *Can. J. Chem.* **1979**, *57*, 381–383; (c) Ho, P.-T. *Can. J. Chem.* **1985**, *63*, 2221–2224.
18. Best, D.; Jenkinson, S. F.; Watkin, D. J.; Booth, K. V.; Fleet, G. W. J. *Acta Crystallogr., Sect. E* **2007**, *63*, o1056–o1057.
19. Selected data for 2,4-di-*C*-methyl-3,4-*O*-isopropylidene-L-arabinono-1,5-lactone **8L**: mp 120–124 °C; $[\alpha]_D^{23}$ +131.8 (*c*, 1.50); $\delta_H$: 1.38, 1.40 (2 × 3H, s, C($CH_3$)$_2$), 1.43 (3H, s, H4′), 1.58 (3H, s, H2′), 2.81 (1H, s, OH), 4.01 (1H, s, H3), 4.13 (1H, d, H5, $J_{5,5'}$ 11.4), 4.62 (1H, d, H5′, $J_{5',5}$ 11.4); $\delta_C$: 23.0 (C2′), 24.7 (C4′), 26.7, 27.4 (C(*C*$H_3$)$_2$), 72.7 (C2), 74.1 (C5), 79.3 (C4), 84.7 (C3), 110.1 (*C*($CH_3$)$_2$), 171.5 (C=O).
20. Selected data for 2,4-di-*C*-methyl-3,4-*O*-isopropylidene-L-ribono-1,5-lactone **21L**: mp 62–64 °C; $[\alpha]_D^{22}$ +127.3 (*c*, 0.90); $\nu_{max}$ (thin film): 3463 (s, br s, OH), 1753 (s, C=O); $\delta_H$: 1.43 (6H, s, C($CH_3$)$_2$), 1.46 (3H, s, $CH_3$-4), 1.49 (3H, s, $CH_3$-4), 3.54 (1H, s, OH), 4.15 (1H, s, H3), 4.18–4.31 (2H, a-dd, H6, H6′, *J* 0.7, *J* 13.0); $\delta_C$: 19.8 ($CH_3$-2), 24.5 ($CH_3$-4), 26.5, 27.3 (C(*C*$H_3$)$_2$), 71.8 (C2), 73.9 (C5), 77.5 (C4), 85.7 (C3), 110.0 (*C*($CH_3$)$_2$), 174.1 (C=O).
21. Booth, K. V.; Watkin, D. J.; Jenkinson, S. F.; Fleet, G. W. J. *Acta Crystallogr., Sect. E* **2007**, *63*, o1128–o1130.
22. (a) Baird, P. D.; Dho, J. C.; Fleet, G. W. J.; Peach, J. M.; Prout, K.; Smith, P. W. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1785–1791; (b) Bruce, I.; Fleet, G. W. J.; Girdhar, A.; Haraldsson, M.; Peach, J. M.; Watkin, D. J. *Tetrahedron* **1990**, *46*, 19–32; (c) Punzo, F.; Watkin, D. J.; Jenkinson, S. F.; da Cruz, F. P.; Fleet, G. W. J. *Acta Crystallogr., Sect. E* **2005**, *61*, o511–o512; (d) Punzo, F.; Watkin, D. J.; Jenkinson, S. F.; da Cruz, F. P.; Fleet, G. W. J. *Acta Crystallogr., Sect. E* **2006**, *62*, o321–o323; (e) Booth, K. V.; Watkin, D. J.; Jenkinson, S. F.; Fleet, G. W. J. *Acta Crystallogr., Sect. E* **2007**, *63*, o1759–o1760.
23. Booth, K. V.; Jenkinson, S. F.; Watkin, D. J.; Fleet, G. W. J. *Acta Crystallogr., Sect. E* **2007**, *63*, o3592–o3593.
24. *Selected data for unsaturated lactone* **23L**: mp 68–69 °C; $[\alpha]_D^{21}$ +156.9 (*c*, 0.57); $\delta_H$: 1.42 (3H, s, $CH_3$-4), 1.44 (3H, s, C($CH_3$)$_2$), 1.46 (3H, s, C($CH_3$)$_2$), 3.82 (1H, d, H5, $J_{5,5'}$ 12.1), 4.18 (1H, d, H5′, $J_{5',5}$ 12.1), 4.60 (1H, s, H3), 5.87 (1H, s, H2′), 6.33 (1H, s, H2″); $\delta_C$: 22.6 ($CH_3$-4), 26.9, 27.6 C(*C*$H_3$)$_2$), 72.5 (C5), 79.3 (C4), 81.3 (C3), 110.9 (*C*($CH_3$)$_2$), 130.1 (C2′), 135.1 (C2), 167.0 (C1).
25. *Selected data for deoxylactone* **24L**; mp 117 °C; $[\alpha]_D^{21}$ +156.3 (*c*, 0.735); $\nu_{max}$ (thin film): 1745 (s, C=O); $\delta_H$ ($C_6D_6$, 400 MHz): 0.75 (3H, s, $CH_3$-4), 1.13 (3H, s, C($CH_3$)$_2$), 1.29 (3H, d, $CH_3$-2, $J_{CH3\text{-}2,2}$ 6.8), 1.38 (3H, s, C($CH_3$)$_2$), 1.71 (1H, dq, H2, $J_{2,3}$ 2.4, $J_{2,CH3\text{-}2}$ 6.8), 3.14 (1H, d, H5, $J_{5,5'}$ 12.5), 3.59 (1H, d, H3, $J_{3,2}$ 2.4), 3.79 (1H, d, H5″, $J_{5',5}$ 12.5). $\delta_C$ ($C_6D_6$, 100 MHz): 13.0 ($CH_3$-2), 22.5 ($CH_3$-4), 26.6, 27.3 (C(*C*$H_3$)$_2$), 38.0 (C2) 72.4 (C5), 79.3 (C4), 82.8 (C3), 109.6 (*C*($CH_3$)$_2$), 171.6 (C1).
26. Booth, K. V.; Jenkinson, S. F.; Fleet, G. W. J.; Watkin, D. J. *Acta Crystallogr., Sect. E* **2009**, *65*, o570.
27. Porwell, J. *Aldrich Handbook of Fine Chemicals*; 2007, p 2253.
28. (a) Beadle, J. R.; Saunders, J. P.; Wajda, T. J. Process for Manufacturing tagatose, US Patent 5078796, 1992.; (b) Beadle, J. R.; Saunders, J. P.; Wajda, T. J. From U.S. (1991), US 5002612 A 19910326; *Chem. Abs.* **1991**, *115*, 52172.
29. Granstrom, T. B.; Takata, G.; Tokuda, M.; Izumori, K. *J. Biosci. Bioeng.* **2004**, *97*, 89–94; Izumori, K. *Naturwissennshaften* **2002**, *89*, 120–124.
30. Skytte, U. P. *Cereal Foods World* **2002**, *47*, 224–227.
31. (a) Jones, N. A.; Jenkinson, S. F.; Soengas, R.; Fanefjord, M.; Wormald, M. R.; Dwek, R. A.; Kiran, G. P.; Devendar, R.; Takata, G.; Morimoto, K.; Izumori, K.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2007**, *18*, 774–786; (b) Yoshihara, A.; Haraguchi, S.; Gullapalli, P.; Rao, D.; Morimoto, K.; Takata, G.; Jones, N. A.; Jenkinson, S. F.; Wormald, M. R.; Dwek, R. A.; Fleet, G. W. J.; Izumori, K. *Tetrahedron: Asymmetry* **2008**, *19*, 739–745.
32. Jones, N. A.; Rao, D.; Yoshihara, A.; Gullapalli, P.; Morimoto, K.; Takata, G.; Hunter, S. J.; Wormald, M. R.; Dwek, R. A.; Izumori, K.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2008**, *19*, 1904–1918.
33. Other than specific rotation, the physical properties of all the enantiomers reported were identical.
34. NMR spectra for the *C*-methyl arabinoses **5**, **9**, and **11** were recorded on a Varian UnityINOVA 500 ($^1$H—500 MHz: $^{13}$C—125 MHz) spectrometer, in $D_2O$, with a probe temperature of 30 °C. Chemical shifts were measured relative to internal standards ($^1$H—acetone at 2.220 ppm: $^{13}$C—acetone at 30.9 ppm). Two-dimensional gradient COSY, HSQC, HMBC, and HSQC-TOCSY spectra were used to aid assignment of $^1$H and $^{13}$C spectra. ROESY spectra were recorded with a 400 ms mixing time. All chemical shifts ($\delta$) are quoted in ppm and coupling constants (*J*) in Hz.
35. (a) Zheng, R.; Wei, W.; Shi, Q. *J. Phys. Chem. A* **2009**, *113*, 157–164; (b) Angyal, S. J. *Adv. Carbohydr. Chem. Biochem.* **1984**, *42*, 15–68; (c) Angyal, S. J. *Adv. Carbohydr. Chem. Biochem.* **1991**, *49*, 19–35.