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Carbohydrate Research 342 (2007) 2695–2704
Carbohydrate RESEARCH

On the synthesis of the 2,6-dideoxysugar L-digitoxose

Shannon C. Timmons[a] and David L. Jakeman[b,*]

[a]Department of Chemistry, Dalhousie University, Halifax, Nova Scotia, Canada B3H 4J3
[b]College of Pharmacy, Dalhousie University, 5968 College Street, Halifax, Nova Scotia, Canada B3H 3J5

Received 20 June 2007; received in revised form 24 September 2007; accepted 28 September 2007
Available online 5 October 2007

Abstract—As deoxysugars are integral components of many natural products, the development of efficient chemical and enzymatic routes to prepare these compounds is of particular interest. Herein, we report a comparison of several synthetic methodologies used to prepare protected derivatives of the 2,6-dideoxysugar L-digitoxose. A novel, stereoselective synthetic route to efficiently access methyl 4-*O*-*tert*-butyldimethylsilyl-2,6-dideoxy-3-*O*-trimethylsilyl-α-L-*ribo*-hexopyranoside in 35% yield over nine facile steps is described.

Keywords: L-Digitoxose; 2,6-Dideoxysugars; Glycosylation; Natural products

1. Introduction

Natural products continue to serve as reliable scaffolds for drug discovery and development.[1] Interestingly, many therapeutically relevant natural products are glycosylated and it is widely acknowledged that carbohydrate functionalities are often critical in conferring bioactivity,[2–4] with the most common biologically relevant sugar residues being 2,6-dideoxyhexoses and 2,3(4),6-trideoxysugars.[5] The functional role of deoxysugar residues varies greatly between biomolecules and remains ambiguous in many cases, due in part to the diverse expanse of chemical space accessed by glycosides.[6] Thus, a clear understanding of the biological implications of natural product glycosylation has significantly lagged behind that of proteins and nucleic acids[7] and the potential of carbohydrate-based therapeutic agents remains largely under-explored.[8] As this research area is expanding, there is a renewed interest in the efficient chemical and enzymatic synthesis of deoxysugars of medicinal value, as well as the total and semi-synthesis of carbohydrate-containing natural products.

The 2,6-dideoxysugar L-digitoxose (**2**) is of particular interest in our laboratory because it is the single carbohydrate component of the structurally unique angucycline jadomycin B (**1**) (Fig. 1).[9,10] L-Digitoxose (**2**) is also a component of numerous other bacterial secondary metabolites including polyketide-derived antitumor antibiotics[11,12] and antifungal antibiotics.[13] Interestingly, D-digitoxose (**3**) is also a well-known constituent of cardiac[14] and plant-derived[15,16] steroidal glycosides.

With respect to L-digitoxose, a number of chemical syntheses based on significantly different strategies have been described.[17–22] Several of these routes rely on chiral non-carbohydrate precursors and stereoselective

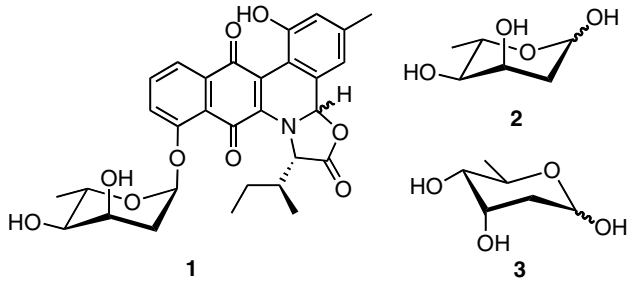


Figure 1. Structures of jadomycin B (**1**), L-digitoxose (**2**), and D-digitoxose (**3**).

* Corresponding author. Tel.: +1 902 494 7159; fax: +1 902 494 1396; e-mail: david.jakeman@dal.ca

0008-6215/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2007.09.012

reactions,[17–19] which often necessitate numerous diastereomeric chromatographic separations and result in low overall yields.[18,19] Other syntheses of L-digitoxose originate from monosaccharide precursors,[20–22] but typically involve a large number of synthetic steps and result in similarly low overall yields.[20,21] Of the synthetic routes previously described, the methodology of Brimacombe and co-workers was first investigated to prepare L-digitoxose due to its reasonable number of synthetic steps (six) and its commercially available monosaccharide origin (L-rhamnose).[22]

2. Results and discussion

2.1. Synthesis of L-digitoxose: method of Brimacombe

The key step in the synthetic strategy of Brimacombe and co-workers for preparing L-digitoxose involves the reaction of fully protected α-L-rhamnopyranoside **4a** or **4b** with *n*-butyllithium (*n*-BuLi) at <−30 °C in THF (Fig. 2).[22] This elimination reaction, first described by Klemer and Rodemeyer in 1974,[23] is based on the preferential abstraction of the quasi-axial hydrogen atom attached to C-3 of the carbohydrate ring.[24] In the hands of Brimacombe and co-workers, reaction of **4a** and **4b** with 6 equiv of *n*-BuLi successfully produced desired 2-deoxy-3-ketosugars **5a** and **5b** in 41% and 38% yields, respectively, after careful silica gel chromatography.[22] In addition to these rhamnopyranosides, 4-*O*-methyl-protected α-L-rhamnopyranoside **4c** was also previously used by Horton and co-workers to prepare 2-deoxy-3-ketosugar **5c** in 40% yield upon reaction with *n*-BuLi at <−30 °C in THF.[25] Interestingly, 4-hydroxyl and 4-*O*-benzyl derivatives produced only complex mixtures of products under the aforementioned reaction conditions.[25]

In light of these results, α-L-rhamnopyranosides **4a**, **4b**, and **4c** were prepared as previously reported[22,25] to test the efficacy of the Klemer–Rodemeyer elimination reaction in synthesizing 2-deoxy-3-ketosugars **5a**, **5b**, and **5c**, respectively, under various reaction conditions. Initial experiments were conducted using 4-*O*-MEM-protected derivative **4a** under similar reaction conditions to those described by Brimacombe and co-workers[22] and, in our experience, the highest isolated yield of 2-deoxy-3-ketosugar **5a** achieved was 22% (Table 1, entry 1). The use of smaller C-4 protecting groups, as in the case of 4-*O*-MOM- and 4-*O*-methyl-protected derivatives **4b** and **4c**, with 6 equiv of *n*-BuLi resulted in similarly low yields of **5b** and **5c**, 16% and 19%, respectively, after silica gel chromatography (Table 1, entries 2–3). Using **4c**, many attempts were made to improve the yield of the desired 2-deoxy-3-ketosugar by varying the number of equivalents of *n*-BuLi (frequently titrated with 2,5-dimethoxybenzyl alcohol as an indicator[26]), the internal temperature of the reaction mixture, and the reaction time (Table 1, entries 4–7) with little success.

These disappointingly low yields prompted a careful analysis of the ^{1}H NMR spectra of crude reaction mixtures. Surprisingly, this analysis revealed that only one diastereomer of **4a**, **4b**, and **4c** had primarily reacted after reaction times of 1–3 h under various reaction conditions, which were equal to or longer than the 30 min reaction time reported by Horton[25] with **4c**, as well as

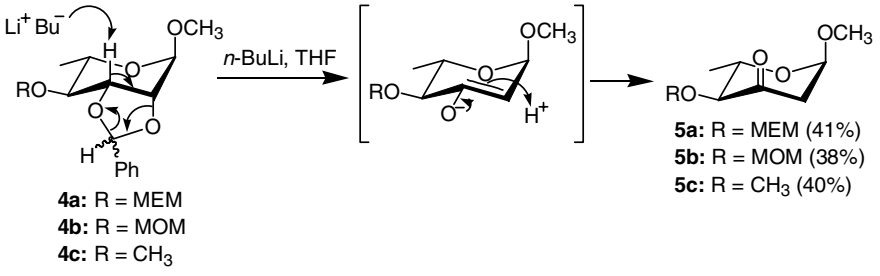


Figure 2. Mechanism of the Klemer–Rodemeyer elimination reaction with results reported by Brimacombe[22] and Horton.[25]

Table 1. Selected results from varying conditions of Klemer–Rodemeyer elimination reaction with **4a**, **4b**, and **4c**

Entry	4-*O*-R group (compound)	Equiv of *n*-BuLi	Temperature (°C)	Time (h)	Isolated yield (%) (product)
1	MEM (**4a**)	6	−40 to −30	1	22 (**5a**)
2	MOM (**4b**)	6	−40 to −30	1	16 (**5b**)
3	CH_3 (**4c**)	6	−40 to −30	1	19 (**5c**)
4	CH_3 (**4c**)	3	−40 to −30	3	23 (**5c**)
5	CH_3 (**4c**)	3	−75 to −65	20	5 (**5c**)
6	CH_3 (**4c**)	6	−75 to −65	20	No desired product
7	CH_3 (**4c**)	3	−10 to 0	1	No desired product

the 1 h reaction time reported by Brimacombe[22] with **4a** and **4b**. Through one-dimensional nuclear Overhauser effect (NOE) NMR experiments, using **4c** as a model, it was determined that the *exo* diastereomer reacted significantly faster than the *endo* diastereomer (Fig. 3). Given the 3:2 *exo*:*endo* diastereomeric ratio of **4a**, **4b**, and **4c**, these NMR results were useful in rationalizing the low yields described in Table 1.

Of particular interest with respect to these observations are the conformational studies of Nánasi and co-workers on methyl 2,3-*O*-benzylidene-α-L-rhamnopyranoside, as well as 4-*O*-acetyl and 4-*O*-benzyl derivatives.[27] Their NMR spectroscopy-based investigations revealed that significant conformational differences exist in the pyranoside and 1,3-dioxolane rings of *exo* and *endo* diastereomers of the three aforementioned α-L-rhamnopyranosides. With respect to pyranoside rings, $^{3}J_{\text{H-2,H-3}}$ values were consistently larger for *endo* diastereomers as compared to *exo* diastereomers, suggesting that the corresponding dihedral angles are smaller in the case of *endo* diastereomers. Moreover, the coupling constant between the acetal carbon atom and quasi-axial proton H-3, which is also dependent on dihedral angle,[28] was consistently larger for *exo* diastereomers of these α-L-rhamnopyranosides. This indicates that the C–O–C–H dihedral angle between the acetal carbon atom and H-3 must be greater in the *exo* diastereomers as compared to the *endo* diastereomers. These conformational observations may provide insight into the differential reactivity of *exo* and *endo* diastereomers of α-L-rhamnopyranosides **4a**, **4b**, and **4c**, as the synthetic utility of this reaction has been linked to the conformational rigidity of the monosaccharide ring.[24]

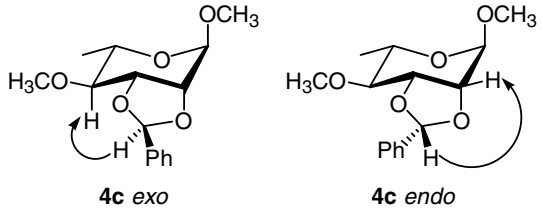


Figure 3. *exo* and *endo* Diastereomers of **4c** (arrows indicate strong 1D NOE interactions).

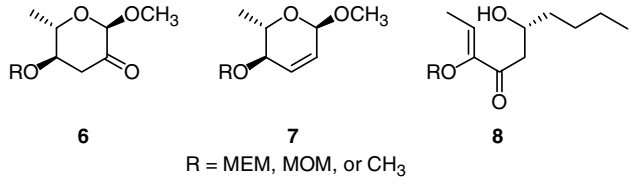
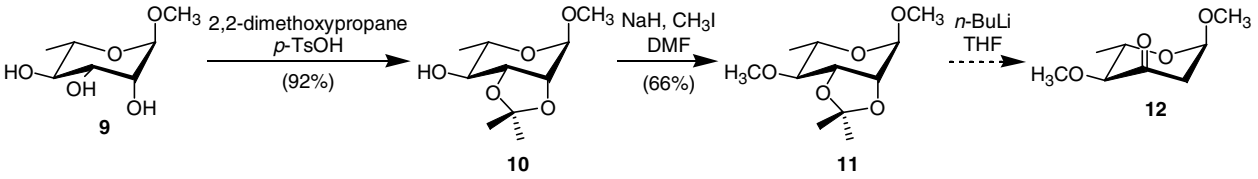


Figure 4. Identified Klemer–Rodemeyer elimination reaction byproducts.

In addition to establishing the lower reactivity of *endo* diastereomers, careful analysis of both ^{1}H NMR spectra of crude reaction mixtures and chromatographically separated products facilitated the identification of several Klemer–Rodemeyer elimination reaction byproducts (Fig. 4). The first byproduct, 3-deoxy-2-ketosugar **6**, was observed in only trace quantities in the ^{1}H NMR spectra of several crude reaction mixtures and is attributed to proton abstraction from C-2 of the carbohydrate ring.[24] Secondly, a significant quantity of alkene **7** was frequently identified and chromatographically isolated from crude reaction mixtures. Byproduct **7** is attributed to abstraction of the benzylic proton, H-2 in the 1,3-dioxolane ring, in lieu of H-3 in the carbohydrate ring.[24] In addition to these two expected byproducts, a third compound (**8**), also frequently observed in significant quantity, was chromatographically separated and characterized from numerous Klemer–Rodemeyer reaction mixtures. Byproduct **8** appears to result from two additional reactions of *n*-BuLi with desired 2-deoxy-3-ketosugars **5a**, **5b**, and **5c**. One reaction presumably involves an S_N2 attack of *n*-BuLi at the anomeric center, displacing the methoxy substituent, while the second reaction seemingly involves the abstraction of H-4, resulting in ring opening and the formation of **8**.

In an attempt to address the diastereoselectivity issues associated with benzylidene acetal-protected α-L-rhamnopyranosides **4a**, **4b**, and **4c**, an isopropylidene acetal was installed to protect the C-2 and C-3 hydroxyls of methyl-α-L-rhamnopyranoside. Although largely unprecedented in a Klemer–Rodemeyer reaction, an isopropylidene acetal-protected α-L-rhamnopyranoside was desirable for two reasons: (i) C-2 of the 1,3-dioxolane ring would no longer be chiral, eliminating diastereoselectivity issues; and, (ii) there would be no proton attached to C-2 of the 1,3-dioxolane ring, eliminating the possibility of a byproduct resulting from the abstraction of the benzylic proton. To facilitate this proposed Klemer–Rodemeyer reaction, isopropylidene-protected α-L-rhamnopyranoside **11** was prepared from **9**[25]



Scheme 1. Proposed synthesis of 2-deoxy-3-ketosugar **12**.

according to the isopropylidene installation method of Lipták and co-workers[29] and the methylation conditions of Brimacombe[30] (Scheme 1). The Klemer–Rodemeyer elimination reaction was first attempted with **11** at −50 to −40 °C using 5 equiv of *n*-BuLi, but after 2 h a significant quantity of starting material remained and no 2-deoxy-3-ketosugar **12** was formed as determined by analysis of the ^{1}H NMR spectrum of the crude reaction mixture. Warmer reaction temperatures (−10 to 0 °C) and lower equivalents of *n*-BuLi (2.5) facilitated the reaction of **11**, but only complex mixtures of products were obtained and no 2-deoxy-3-ketosugar **12** was observed in the ^{1}H NMR spectra of crude reaction mixtures.

Interestingly, the conformation of methyl 4-*O*-acetyl-2,3-*O*-isopropylidene-α-L-rhamnopyranoside has also been studied by Nánasi and co-workers using NMR spectroscopy.[27] In terms of the pyranose ring, the conformation of this compound was found to be similar to the *exo* diastereomers of benzylidene acetal-protected α-L-rhamnopyranosides, however; with respect to the 1,3-dioxolane ring, this isopropylidene acetal-protected α-L-rhamnopyranoside possessed a conformation similar to the *endo* diastereomers of benzylidene acetal-protected α-L-rhamnopyranosides.

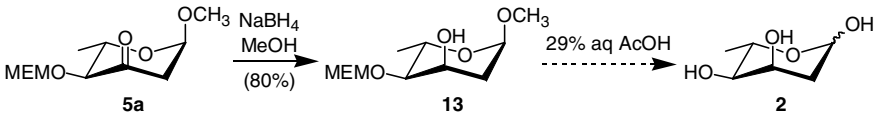
The lack of success obtained using **11**, as well as the nucleophilic role of *n*-BuLi in byproduct formation, motivated us to explore the use of different bases. Although the majority of Klemer–Rodemeyer elimination reactions published to date report the use of *n*-BuLi,[22–25,31,32] one procedure has been described using *sec*-butyllithium (*s*-BuLi) as a base.[33] Thus, 4-*O*-methyl- and 4-*O*-MEM-protected α-L-rhamnopyranosides **4c** and **4a** were used in Klemer–Rodemeyer reactions with various bases in attempts to improve the yields of 2-deoxy-3-ketosugars **5c** and **5a**, respectively (Table 2). Reaction of **4c** with lithium diisopropylamide (LDA) remained sluggish at successively higher temperatures, producing only a 6% yield of 2-deoxy-3-ketosugar **5c** after 4 h at −30 to 0 °C with 2 equiv of base (Table 2, entries 1–2). Longer reaction times using **4c** and LDA resulted in degradation, as no desired product was isolated after 23 h at −40 to 20 °C with 4 equiv of base (Table 2, entry 3). Similarly poor results were obtained using *tert*-butyllithium (*t*-BuLi), which produced a yield of only 5% after 3 h at −50 to −25 °C with 2 equiv of base (Table 2, entry 4). Interestingly, the use of *s*-BuLi as an alternative base provided an essential mixture of strong basicity and steric hindrance, limiting byproducts resulting from nucleophilic attack of the base. Specifically, reaction of **4a** with 3 equiv of *s*-BuLi at −50 to −35 °C for 4 h resulted in a significantly improved 71% yield of 2-deoxy-3-ketosugar **5a** after silica gel chromatography (Table 2, entry 5). Consistent with aforementioned stereochemical observations, NMR analysis of crude reaction mixtures revealed that the *exo* diastereomer of **4a** reacted fastest when *s*-BuLi was used as the base.

With a viable synthetic route to 2-deoxy-3-ketosugar **5a** in hand, a sodium borohydride reduction was attempted to prepare **13** (Scheme 2). This reaction proceeded stereoselectively, as reported by Brimacombe and co-workers,[22] resulting in a C3–OH axial:equatorial ratio of 10:1 and an 80% yield of **13** after silica gel chromatography. This high level of stereoselectivity presumably results from sodium borohydride attack via an equatorial trajectory, avoiding an energetically unfavorable 1,3-diaxial interaction with the axial methoxy group located at the anomeric center.[34,35]

We next chose to deprotect 2,6-dideoxysugar **13** to facilitate the conversion of **2** into a glycosyl donor suitable for sugar nucleotide synthesis with the aim of using this substrate to confirm the in vitro activity of the glycosyltransferase involved in jadomycin B biosynthesis. Deprotection of **13** using 29% aq acetic acid under gentle reflux for 2 h, as reported by Brimacombe and co-workers,[22] was unsuccessful. Interestingly, NMR and MS analysis of the reaction product revealed that, although the anomeric methoxy group had been removed under the aforementioned conditions, the 4-*O*-MEM ether functionality was still intact (Scheme 2). Higher concentrations of aq acetic acid and longer

Table 2. Selected Klemer–Rodemeyer elimination reactions results with different bases

Entry	4-*O*-R group (compound)	Base (equiv)	Temperature (°C)	Time (h)	Isolated yield (%) (product)
1	CH_3 (**4c**)	LDA (2)	−50 to −25	3	4 (**5c**)
2	CH_3 (**4c**)	LDA (2)	−30 to 0	4	6 (**5c**)
3	CH_3 (**4c**)	LDA (4)	−40 to 20	23	No desired product
4	CH_3 (**4c**)	*t*-BuLi (2)	−50 to −25	3	5 (**5c**)
5	MEM (**4a**)	*s*-BuLi (3)	−50 to −35	4	71 (**5a**)



Scheme 2. Sodium borohydride reduction of **5a** and deprotection of **13**.

reaction times unfortunately resulted in the complete degradation of this 2,6-dideoxysugar derivative.

In summary, the importance of the base in Klemer–Rodemeyer elimination reactions involving conformationally flexible monosaccharides has been demonstrated. The regioselectivity of this elimination reaction is also dependent on the type and steric bulk of the C-4 protecting group,[36] complicating the selection of another suitable C-4 protecting group. Thus, efforts were re-directed toward the design and execution of an alternative synthetic route to access L-digitoxose, or a protected derivative thereof, which could be used directly in the coupling of an L-digitoxosyl halide with a phosphate or nucleoside 5′-diphosphate, as previously demonstrated in the synthesis of other 2,6-dideoxysugar nucleotides.[37,38]

2.2. Synthesis of L-digitoxose: a second approach

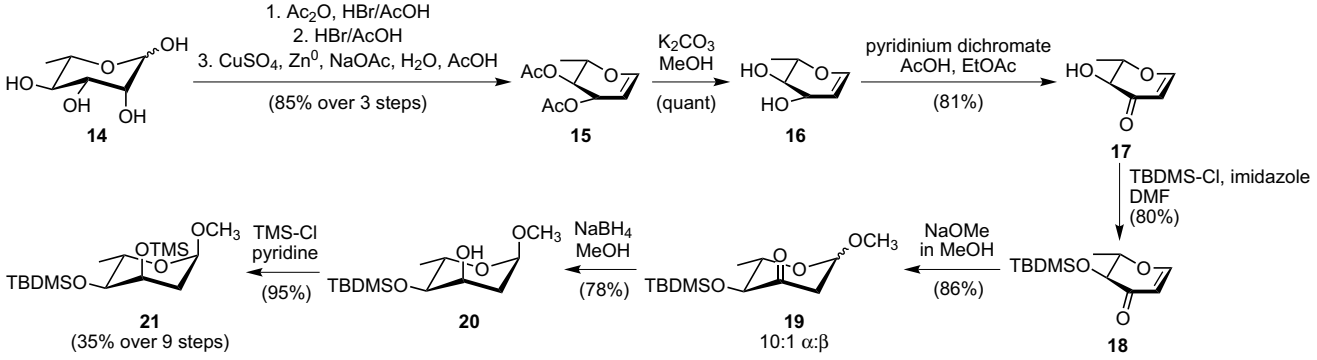
Given the previous success of the stereoselective sodium borohydride reduction of **5a**, a new synthetic plan was devised to synthesize L-digitoxose, which included the preparation of a 2-deoxy-3-ketosugar via a different route. This new strategy also originated from L-rhamnose and involved the use of a glycal (Scheme 3).[39]

The first step in this synthetic route involved the preparation of 3,4-di-*O*-acetyl-6-deoxy-L-glucal (**15**) from L-rhamnose (**14**) using a one-pot, three-step procedure originally developed by Koreeda and co-workers.[40] Following a facile purification using a silica gel plug, **15** was isolated in 85% yield over three steps in only 8 h.

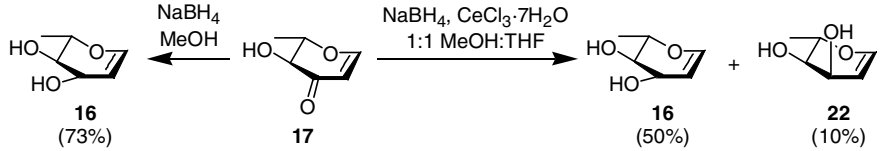
Deacetylation of **15** using potassium carbonate in methanol was accomplished using a procedure similar to the one previously described by van Heerden and co-workers.[41] The original procedure involved the use of 0.008 equiv of potassium carbonate and a reaction time of 24 h at room temperature, however, by increasing the equivalents of potassium carbonate 5-fold to 0.04, the reaction time was decreased to only 3 h at room temperature. Following a simple filtration through a silica gel plug, crystalline 6-deoxy-L-glucal (**16**) was obtained in quantitative yield.

Regioselective oxidation of **16** was accomplished using pyridinium dichromate as previously reported by Czernecki and co-workers.[42] In our experience, precipitation of the resulting Cr(III) species using toluene proved tedious and largely ineffective. Alternatively, the reaction mixture was passed successively through two short silica gel plugs, which effectively bound the green Cr(III) species, facilitating an efficient purification of enulose **17** and affording crystals of **17** in 81% yield.

In attempts to streamline the proposed synthetic strategy, the sodium borohydride reduction of enulose **17** was investigated (Scheme 4). Using conditions previously described for the preparation of **13** from 2-deoxy-3-ketosugar **5a**,[22] reduction with sodium borohydride provided only an inefficient route back to 6-deoxy-L-glucal (**16**). Interestingly, Luche reduction conditions,[43] which include a lanthanide salt such as $CeCl_3{\cdot}7H_2O$ in addition to sodium borohydride, sometimes result in stereoselectivities opposite to reductions involving sodium borohydride alone.[44] The high regio- and stereoselectivity associated with Luche-type reductions was first noted by Danishefsky[45] and is postulated to result from the coordination of $CeCl_3$, a Lewis acid, with the carbonyl group, essentially blocking one face of the molecule.[46] In the case of enulose **17**, Luche-type reduction did result in a difference in stereoselectivity, but the



Scheme 3. Novel synthesis of silyl-protected L-digitoxose derivative **21**.



Scheme 4. Reduction of enulose **17** under various reaction conditions.

5:1 ratio of 6-deoxy-L-glucal (**16**):L-digitoxal (**22**) was very unfavorable.

To facilitate the efficient reduction of the 3-keto-functionality of **17** to an axial hydroxyl group, access to a 2-deoxy-3-ketosugar analogous to those previously described (**5a**, **5b**, and **5c**) was required. This transformation was accomplished in two steps. The remaining free hydroxyl group of enulose **17** was first protected with a *tert*-butyldimethylsilyl (TBDMS),[47] which afforded TBDMS-protected enulose **18** in 80% yield. A TBDMS protecting group was chosen to protect enulose **17** because of its well-documented, non-acidic ease of removal using tetra-*n*-butylammonium fluoride (Bu_4NF),[47,48] as well as its stability to reaction conditions in forthcoming synthetic steps.

To prepare 2-deoxy-3-ketosugar **19** from **18**, a simple procedure involving sodium methoxide in methanol was employed, which afforded **19** in 86% yield as a 10:1 α:β mixture of diastereomers.[35] This diastereomeric mixture was used directly in the next synthetic step without any further purification.

Reduction of **19** with sodium borohydride[22] provided straightforward, stereoselective access to a 2,6-dideoxysugar containing an axially configured C-3 hydroxyl group (**20**). Interestingly, diastereomeric mixture **19** (10:1 α:β) was reduced to a crude 2,6-dideoxysugar mixture with a C3–OH axial:equatorial ratio of 10:1, demonstrating the importance of the axial anomeric methoxy substituent in conferring diastereoselectivity. Following silica gel chromatography, **20** was isolated in 78% yield.

Lastly, the remaining C-3 hydroxyl group was protected with a trimethylsilyl (TMS) group,[49] which afforded fully protected L-digitoxose derivative **21** in 95% yield. The 3-*O*-TMS functionality was chosen as a protecting group at this last step in the synthetic strategy because it could be easily removed under the same conditions as the 4-*O*-TBDMS group with Bu_4NF after **21** is coupled with a nucleoside 5′-diphosphate in due course.

3. Conclusions

In conclusion, the yields of Klemer–Rodemeyer elimination reactions can potentially be improved through the use of *s*-BuLi as a base, although careful monitoring of reaction temperature and time is critical and regioselectivity is often determined only on a case by case basis. Higher predictability can be established for conformationally rigid carbohydrates (e.g., monosaccharides containing two benzylidene acetals) as compared to carbohydrates with more conformational flexibility (e.g., monosaccharides containing a single benzylidene acetal).[24] The utility of this reaction with conformationally rigid monosaccharides has previously been demonstrated in the large-scale (20 g) synthesis of the bioactive 2,6-dideoxysugar L-daunosamine[31] and related sugars.[32] Although the deprotection of the 4-*O*-MEM ether was problematic, this work illustrates the potential use of the Klemer–Rodemeyer elimination reaction with *s*-BuLi and conformationally flexible monosaccharides.

A novel synthetic route was also developed to provide efficient access to silyl-protected L-digitoxose derivative **21** in 35% overall yield over nine steps. The benefits of this route over other methods previously described to prepare this 2,6-dideoxysugar include the ease and speed of synthetic steps as well as the high degree of regio- and stereoselectivity achieved in key transformations. This synthetic strategy could potentially be extended for use in the synthesis of other 2,6-dideoxy- and 2-deoxysugars where a change in stereochemistry at C-3, as compared to the starting glycal, is desired.

4. Experimental

4.1. General methods

With the exclusion of certain solvents, chemicals were purchased commercially and used without further purification unless otherwise specified. Anhydrous CH_2Cl_2 and THF were dried and purified via filtration through alumina using an Innovative Technology solvent purification system. All other solvents were reagent grade unless otherwise noted. Analytical thin-layer chromatography was performed on glass-backed TLC plates pre-coated with silica gel (SiliCycle™, 250 μm) and compounds were detected by UV absorbance (254 nm) and/or by spraying with a $KMnO_4$ visualization solution (3 g $KMnO_4$, 20 g K_2CO_3, 5 mL of 5% w/v aq NaOH, 300 mL H_2O). Automated normal-phase silica gel chromatography was performed using a Biotage SP1™ flash chromatography system. Normal-phase silica gel benchtop chromatography was performed using SiliCycle™ 230–400 mesh ultra pure silica. Melting points were measured in open capillary tubes using a Gallenkamp melting point apparatus and are reported uncorrected. Nuclear magnetic resonance experiments were conducted using a Bruker AVANCE 500 MHz spectrometer. 1D NOE NMR experiments were performed using a mixing time of 750 ms. Chemical shifts are reported in parts per million (ppm) relative to a tetramethylsilane internal standard at 0.00 ppm for samples in $CDCl_3$, while spectra recorded in D_2O were referenced to the solvent peak at 4.79 ppm and externally to 2,2-dimethyl-2-silapentane-5-sulfonate (DSS). High-resolution EI-MS measurements were obtained using a DuPont CEC 21-110B double-focusing magnetic sector instrument and high-resolution ESI-MS measurements were obtained using a Bruker Daltonics micrOTOF instrument.

4.2. General procedure for the synthesis of 2-deoxy-3-ketosugars 5a, 5b, and 5c

A diastereomeric mixture of α-L-rhamnopyranoside acetals (**4a**, **4b**, or **4c**; *exo*:*endo* = 3:2) was dissolved in anhydrous THF under a nitrogen atmosphere in a two-necked round-bottomed flask fitted with a thermometer. The reaction mixture was cooled in a dry ice-acetone bath to the desired reaction temperature and the desired base (*n*-BuLi or *s*-BuLi) was added dropwise. Upon reaction completion, as determined by TLC, the reaction mixture was allowed to warm to −10 °C before pouring into an ice-water mixture containing 10% w/v NH_4Cl. The resulting aqueous solution was extracted with equal volumes of CH_2Cl_2 (thrice) and the combined organic extracts were then extracted with an equal volume of H_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude product as a yellow syrup. See Tables 1 and 2 for specific reaction conditions and corresponding yields.

4.2.1. Methyl 2,6-dideoxy-4-*O*-(2-methoxyethoxy)-methyl-α-L-*erythro*-hexopyranosid-3-ulose (5a). Compound **5a** was prepared as described above starting from 0.354 g (1.00 mmol) of **4a**. Purification via benchtop silica gel chromatography (isocratic 35:65 EtOAc:hexanes) afforded **5a** as a colorless syrup: $R_f = 0.21$ (35:65 EtOAc:hexanes); ^{1}H NMR spectral data matched that reported.[22]

4.2.2. Methyl 2,6-dideoxy-4-*O*-methoxymethyl-α-L-*erythro*-hexopyranosid-3-ulose (5b). Compound **5b** was prepared as described above starting from 0.266 g (1.00 mmol) of **4b**. Purification via benchtop silica gel chromatography (isocratic 22:78 EtOAc:hexanes) afforded **5b** as a colorless syrup: $R_f = 0.45$, (35:65 EtOAc:hexanes); ^{1}H NMR spectral data matched that reported.[22]

4.2.3. Methyl 2,6-dideoxy-4-*O*-methyl-α-L-*erythro*-hexopyranosid-3-ulose (5c). Compound **5c** was prepared as described above starting from 0.253 g (1.00 mmol) of **4c**. Purification via benchtop silica gel chromatography (isocratic 10:90 EtOAc:hexanes) afforded **5c** as a colorless syrup: $R_f = 0.17$ (10:90 EtOAc:hexanes); ^{1}H NMR spectral data matched that reported.[25]

4.2.4. Methyl 2,3,6-trideoxy-4-*O*-(2-methoxyethoxy)-methyl-α-L-*erythro*-hex-2-enopyranoside (7). This compound was isolated as a byproduct from several Klemer–Rodemeyer elimination reactions in which **4a** was used as a starting material to prepare **5a**. Similar byproducts were also observed in the crude ^{1}H NMR spectra of analogous reactions aimed at preparing 2-deoxy-3-ketosugars **5b** and **5c**. Compound **7** was a colorless syrup: $R_f = 0.38$ (35:65 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$): δ 6.03 (br d, 1H, $J_{2,3} = 10.0$ Hz, H-3), 5.74 (ddd, 1H, $J_{2,4} = 0.5$ Hz, $J_{1,2} = 2.5$ Hz, H-2), 4.86 (d, 1H, $J_{H,H} = 7.0$ Hz, OCH_2O), 4.81 (m, 1H, H-1), 4.77 (d, 1H, OCH_2O), 3.88–3.54 (m, 6H, H-4, H-5, OCH_2CH_2O), 3.42 (s, 3H, OCH_3), 3.39 (s, 3H, OCH_3), 1.30 (d, 3H, $J_{5,6} = 5.5$ Hz, H_3-6); ^{13}C NMR ($CDCl_3$): δ 131.7 (C-3), 126.6 (C-2), 95.5 (C-1), 95.1 (OCH_2O), 75.5, 71.8, 67.3, 66.0 (C-4, C-5, OCH_2CH_2O), 59.2 (OCH_3), 55.7 (OCH_3), 18.3 (C-6); HRMS (ESI^+) *m*/*z*: calcd for $C_{11}H_{20}O_5Na$, 255.1203; found, 255.1181.

4.2.5. (6*R*)-6-Hydroxy-3-methoxy-dec-2-en-4-one (8). This compound was isolated as a byproduct from several Klemer–Rodemeyer elimination reactions in which **4c** was used as a starting material to prepare **5c**. Similar byproducts were also observed in the crude ^{1}H NMR spectra of analogous reactions aimed at preparing 2-deoxy-3-ketosugars **5a** and **5b**. Compound **8** was a colorless syrup: $R_f = 0.27$ (20:80 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$): δ 6.29 (q, 1H, $J_{1,2} = 7.0$ Hz, H-2), 4.07 (m, 1H, H-6), 3.66 (s, 3H, OCH_3), 3.09 (br s, 1H, O*H*), 2.80 (dd, 1H, $J_{5a,6} = 2.5$ Hz, $J_{5a,5b} = 17.5$ Hz, H-5a), 2.66 (dd, 1H, $J_{5b,6} = 9.0$ Hz, H-5b), 1.84 (d, 3H, H_3-1), 1.57–1.22 (m, 6H, $CH_2CH_2CH_2$), 0.91 (t, 3H, $J_{H,H} = 5.0$ Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$): δ 198.5 (C=O), 154.9 (C-3), 124.8 (C-2), 67.9 (C-6), 60.0 (OCH_3), 44.4 (C-5), 36.3 (CH_2), 27.7 (CH_2), 22.6 (CH_2), 14.0 (CH_2CH_3), 11.4 (C-1); HRMS (EI^+) *m*/*z*: calcd for $C_{11}H_{20}O_3$, 200.1412; found, 200.1408.

4.3. Methyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside (10)

This compound was prepared using a procedure described by Lipták and co-workers.[29] Starting from 6.39 g (35.9 mmol) of **9**, compound **10** was isolated in 92% yield (7.20 g, 33.0 mmol) as a pale yellow syrup: $R_f = 0.43$ (6:3:1 CH_2Cl_2:EtOAc:EtOH); ^{1}H NMR ($CDCl_3$): δ 4.86 (br s, 1H, H-1), 4.14–4.00 (m, 2H, H-2, H-3), 3.58 (m, 1H, H-5), 3.36 (s, 3H, OCH_3), 3.31 (m, 1H, H-4), 1.51 (s, 3H, $C(CH_3)_2$), 1.34 (s, 3H, $C(CH_3)_2$), 1.28 (d, 3H, $J_{5,6} = 6.6$ Hz, H_3-6).

4.4. Methyl 2,3-*O*-isopropylidene-4-*O*-methyl-α-L-rhamnopyranoside (11)

This compound was prepared using a procedure described by Brimacombe.[30] Starting from 2.75 g (12.6 mmol) of **10**, compound **11** was isolated in 66% yield (1.93 g, 8.32 mmol) following benchtop silica gel chromatography (isocratic 10:90 EtOAc:hexanes) as a colorless syrup: $R_f = 0.78$ (35:65 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$): δ 4.83 (br s, 1H, H-1), 4.14–4.08 (m, 2H, H-2, H-3), 3.57 (m, 1H, H-5), 3.53 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 2.96 (dd, 1H, $J_{3,4} = 9.6$ Hz,

$J_{4,5} = 6.3$ Hz, H-4), 1.54 (s, 3H, C(CH_3)$_2$), 1.35 (s, 3H, C(CH_3)$_2$), 1.28 (d, 3H, $J_{5,6} = 6.3$ Hz, H_3-6); HRMS (ESI^+) *m/z*: calcd for $C_{11}H_{20}O_5Na$, 255.1203; found, 255.1185.

4.5. Methyl 2,6-dideoxy-4-*O*-(2-methoxyethoxy)methyl-α-L-*ribo*-hexopyranoside (13)

This compound was prepared using a procedure described by Brimacombe and co-workers.[22] Starting from 0.560 g (2.26 mmol) of **5a**, compound **13** was isolated in 80% yield (0.453 g, 1.81 mmol) following benchtop silica gel chromatography (isocratic 75:25 EtOAc:hexanes) as a pale yellow syrup: $R_f = 0.22$ (75:25 EtOAc:hexanes); ^{1}H NMR spectral data matched that reported.[22]

4.6. Di-*O*-acetyl-6-deoxy-L-glucal (15)

This compound was prepared using a procedure described by Koreeda and co-workers[40] except that the bromination reaction was complete as determined by TLC after 1.5 h and was not stirred overnight as previously reported.[40] Starting from 5.00 g (27.4 mmol) of **14**, compound **15** was isolated in 85% yield (4.99 g, 23.3 mmol) over three steps following purification using a short silica gel plug in a scintillated funnel (isocratic 10:90 EtOAc:hexanes) as a colorless syrup: $R_f = 0.60$ (25:75 EtOAc:hexanes); ^{1}H and ^{13}C NMR spectral data matched that reported.[41]

4.7. 6-Deoxy-L-glucal (16)

This compound was prepared using a procedure described by van Heerden and co-workers[41] except that the number of equivalents of potassium carbonate was increased 5-fold to significantly reduce the reaction time to 3 h. Vigorous stirring was also necessary. Starting from 2.84 g (13.3 mmol) of **15**, compound **16** was isolated in quantitative yield (1.73 g, 13.3 mmol) following filtration through a short silica gel plug in a scintillated funnel (isocratic HPLC grade MeOH), which afforded white crystals: mp 73–74 °C, lit.[42] 72–73 °C; $R_f = 0.36$ (100% EtOAc); ^{1}H NMR ($CDCl_3$): δ 6.31 (dd, 1H, $J_{1,2} = 6.0$ Hz, $J_{1,3} = 1.5$ Hz, H-1), 4.69 (dd, 1H, $J_{2,3} = 2.0$ Hz, H-2), 4.21 (ddd, 1H, $J_{3,4} = 7.5$ Hz, H-3), 3.84 (dq, 1H, $J_{4,5} = 10.0$ Hz, $J_{5,6} = 6.0$ Hz, H-5), 3.40 (dd, 1H, H-4), 1.38 (d, 3H, H_3-6); ^{13}C NMR ($CDCl_3$): δ 144.8 (C-1), 102.7 (C-2), 75.2 (C-4), 74.5 (C-5), 70.2 (C-3), 17.1 (C-6).

4.8. 1,5-Anhydro-2,6-dideoxy-L-*erythro*-hex-1-en-3-ulose (17)

This compound was prepared using a procedure described by Czernecki and co-workers[42] except that the reaction mixture was filtered through two short silica gel plugs in scintillated funnels (washing with HPLC grade EtOAc), to remove the Cr(III) species instead of precipitating with toluene as previously reported.[42] Starting from 2.74 g (21.1 mmol) of **16**, compound **17** was isolated in 81% yield (2.19 g, 17.1 mmol) as white crystals: mp 87–88 °C, lit.[42] 92–93 °C, lit.[50] 86 °C; $R_f = 0.77$ (100% EtOAc); ^{13}C NMR (125 MHz, $CDCl_3$): δ 194.2 (*C*=O), 164.7 (C-1), 103.5 (C-2), 80.0 (C-5), 72.8 (C-4), 18.0 (C-6). ^{1}H NMR spectral data matched that reported.[50]

4.9. 1,5-Anhydro-4-*O*-*tert*-butyldimethylsilyl-2,6-dideoxy-L-*erythro*-hex-1-en-3-ulose (18)

1,5-Anhydro-2,6-dideoxy-L-*erythro*-hex-1-en-3-ulose (**17**) (1.54 g, 12.0 mmol) was dissolved in anhydrous DMF (15 mL) in a round-bottomed flask under a nitrogen atmosphere. Imidazole (2.05 g, 30.1 mmol) and *tert*-butyldimethylsilyl chloride (2.17 g, 14.4 mmol) were added and the reaction mixture was stirred for 19 h at rt, after which time TLC analysis revealed the complete consumption of **17**. The reaction mixture was diluted with EtOAc (50 mL) and extracted with H_2O (3×50 mL). After drying the organic extracts over Na_2SO_4 and concentration under reduced pressure, TBDMS-protected derivative **18** was obtained in 80% yield (2.33 g, 9.61 mmol) as a colorless syrup: $R_f = 0.38$ (10:90 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$): δ 7.29 (d, 1H, $J_{1,2} = 6.0$ Hz, H-1), 5.35 (d, 1H, H-2), 4.32 (dq, 1H, $J_{4,5} = 11.5$ Hz, $J_{5,6} = 6.0$ Hz, H-5), 4.02 (d, 1H, H-4), 1.52 (d, 3H, H_3-6), 0.95 (s, 9H, C(CH_3)$_3$), 0.24 (s, 3H, Si(CH_3)$_2$), 0.12 (s, 3H, Si(CH_3)$_2$); ^{13}C NMR ($CDCl_3$): δ 193.7 (*C*=O), 162.3 (C-1), 105.0 (C-2), 80.2 (C-5), 75.3 (C-4), 26.0 (C(*C*H_3)$_3$), 25.83 (C(*C*H_3)$_3$), 25.80 (C(*C*H_3)$_3$), 18.7 (*C*(CH$_3$)$_3$), 18.2 (C-6), −3.9 (Si(*C*H_3)$_2$), −5.4 (Si(*C*H_3)$_2$); HRMS (ESI^+) *m/z*: calcd for $C_{12}H_{22}O_3SiNa$, 265.1230; found, 265.1220.

4.10. Methyl 4-*O*-*tert*-butyldimethylsilyl-2,6-dideoxy-α/β-L-*erythro*-hexopyranosid-3-ulose (19)

1,5-Anhydro-4-*O*-*tert*-butyldimethylsilyl-2,6-dideoxy-L-*erythro*-hex-1-en-3-ulose (**18**) (85 mg, 0.35 mmol) was dissolved in 0.01 M NaOMe in MeOH (7.1 mL) and the resulting reaction mixture was stirred for 1 h at rt, after which time TLC analysis revealed the complete consumption of **18**. The reaction mixture was neutralized to pH 7 using Amberlite® IR-120 (H^+) ion exchange resin (free acid form), filtered, and concentrated under reduced pressure to afford **19** in 86% yield (81 mg, 0.30 mmol) in an α:β ratio of 10:1 as a pale yellow syrup: $R_f = 0.35$, 0.27 (10:90 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$): δ α diastereomer: 5.06 (br d, 1H, $J_{1,2ax} = 4.5$ Hz, H-1), 3.96 (dq, 1H, $J_{4,5} = 9.5$ Hz,

$J_{5,6} = 6.5$ Hz, H-5), 3.88 (d, 1H, H-4), 3.36 (s, 3H, OCH_3), 2.75 (dd, 1H, $J_{2ax,2eq} = 14.0$ Hz, H-2ax), 2.61 (br d, 1H, H-2eq), 1.44 (d, 3H, H_3-6), 0.95 (s, 9H, C(CH_3)$_3$), 0.20 (s, 3H, Si(CH_3)$_2$), 0.06 (s, 3H, Si(CH_3)$_2$), β diastereomer: 4.59 (dd, 1H, $J_{1,2a} = 9.5$ Hz, $J_{1,2e} = 2.5$ Hz, H-1); ^{13}C NMR ($CDCl_3$): δ α diastereomer: 203.4 (*C*=O), 99.6 (C-1), 80.5 (C-4), 70.7 (C-5), 54.8 (O*C*H$_3$), 46.5 (C-2), 25.94 (C(*C*H$_3$)$_3$), 25.93 (C(*C*H$_3$)$_3$), 25.91 (C(*C*H$_3$)$_3$), 19.2 (C-6), 18.7 (*C*(CH$_3$)$_3$), −4.1 (Si(*C*H$_3$)$_2$), −5.4 (Si(*C*H$_3$)$_2$); HRMS (ESI^+) *m*/*z*: calcd for $C_{13}H_{26}O_4SiNa$, 297.1493; found, 297.1488.

4.11. Methyl 4-*O*-*tert*-butyldimethylsilyl-2,6-dideoxy-α-L-*ribo*-hexopyranoside (20)

Methyl 4-*O*-*tert*-butyldimethylsilyl-2,6-dideoxy-α/β-L-*erythro*-hexopyranosid-3-ulose (**19**) (1.78 g, 6.49 mmol) was dissolved in HPLC grade MeOH (72 mL) in a round-bottomed flask. $NaBH_4$ (2.33 g, 61.7 mmol) was added in small portions and the reaction mixture was stirred for 1 h at rt, after which time TLC analysis revealed the complete consumption of **19**. The reaction mixture was concentrated under reduced pressure, re-dissolved in CH_2Cl_2 (50 mL), and washed with H_2O (25 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to yield crude **20** as a pale yellow syrup, which was purified via automated silica gel chromatography using the following gradient: 5:95 A:B (10 CV), linear gradient to 10:90 A:B (5 CV), 10:90 A:B (2 CV) where A = EtOAc and B = hexanes. Following chromatography diastereomerically pure **20** was obtained in 78% yield (1.40 g, 5.06 mmol) as a colorless syrup: $R_f = 0.16$ (10:90 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$): δ 4.70 (br d, 1H, $J_{1,2ax} = 4.0$ Hz, H-1), 3.96 (dq, 1H, $J_{4,5} = 9.5$ Hz, $J_{5,6} = 6.0$ Hz, H-5), 3.91 (m, 1H, H-3), 3.36 (s, 3H, OCH_3), 3.32 (dd, 1H, $J_{3,4} = 3.0$ Hz, H-4), 3.05 (d, 1H, $J_{3,OH} = 5.5$ Hz, O*H*), 2.14 (dd, 1H, $J_{2ax,2eq} = 15.0$ Hz, $J_{2eq,3} = 3.0$ Hz, H-2eq), 1.88 (dt, 1H, $J_{2ax,3} = 3.5$ Hz, H-2ax), 1.24 (d, 3H, H_3-6), 0.92 (s, 9H, C(CH_3)$_3$), 0.11 (s, 3H, Si(CH_3)$_2$), 0.10 (s, 3H, Si(CH_3)$_2$); ^{13}C NMR ($CDCl_3$): δ 98.2 (C-1), 74.8 (C-4), 67.8 (C-3), 63.2 (C-5), 55.3 (O*C*H$_3$), 35.4 (C-2), 25.94 (C(*C*H$_3$)$_3$), 25.93 (C(*C*H$_3$)$_3$), 25.92 (C(*C*H$_3$)$_3$), 18.3 (C-6), 18.2 (*C*(CH$_3$)$_3$), −4.1 (Si(*C*H$_3$)$_2$), −4.5 (Si(*C*H$_3$)$_2$); HRMS (ESI^+) *m*/*z*: calcd for $C_{13}H_{28}O_4SiNa$, 299.1649; found, 299.1638.

4.12. Methyl 4-*O*-*tert*-butyldimethylsilyl-2,6-dideoxy-3-*O*-trimethylsilyl-α-L-*ribo*-hexopyranoside (21)

Methyl 4-*O*-*tert*-butyldimethylsilyl-2,6-dideoxy-α-L-*ribo*-hexopyranoside (**20**) (460 mg, 1.66 mmol) was dissolved in anhydrous pyridine (8 mL) in a round-bottomed flask under a nitrogen atmosphere and cooled to 0–5 °C in an ice-water bath. Trimethylsilyl chloride (320 μL, 2.49 mmol) was added dropwise and the reaction mixture was stirred for 1 h at 0–5 °C, after which time TLC analysis revealed the complete consumption of **20**. The reaction mixture was diluted with hexanes (50 mL) and washed with H_2O (5 × 20 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford **21** in 95% yield (549 mg, 1.57 mmol) as a colorless syrup: $R_f = 0.50$ (10:90 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$): δ 4.62 (dd, 1H, $J_{1,2ax} = 4.0$ Hz, $J_{1,2eq} = 3.5$ Hz, H-1), 4.08 (dq, 1H, $J_{4,5} = 10.0$ Hz, $J_{5,6} = 6.5$ Hz, H-5), 3.94 (m, 1H, H-3), 3.32 (dd, 1H, $J_{3,4} = 3.0$ Hz, H-4), 3.31 (s, 3H, OCH_3), 1.97 (ddd, 1H, $J_{2ax,2eq} = 14.0$ Hz, $J_{2eq,3} = 5.0$ Hz, H-2eq), 1.78 (dt, 1H, $J_{2ax,3} = 4.0$ Hz, H-2ax), 1.19 (d, 3H, H_3-6), 0.90 (s, 9H, C(CH_3)$_3$), 0.12 (s, 9H, Si(CH_3)$_3$), 0.07 (s, 3H, Si(CH_3)$_2$), 0.06 (s, 3H, Si(CH_3)$_2$); ^{13}C NMR ($CDCl_3$): δ 97.9 (C-1), 74.9 (C-4), 68.1 (C-3), 65.9 (C-5), 55.1 (O*C*H$_3$), 36.5 (C-2), 26.08 (C(*C*H$_3$)$_3$), 26.07 (C(*C*H$_3$)$_3$), 26.06 (C(*C*H$_3$)$_3$), 18.33 (*C*(CH$_3$)$_3$), 18.31 (*C*(CH$_3$)$_3$), 18.27 (C-6), 0.66 (Si(*C*H$_3$)$_3$), 0.65 (Si(*C*H$_3$)$_3$), 0.64 (Si(*C*H$_3$)$_3$), −3.8 (Si(*C*H$_3$)$_2$), −4.6 (Si(*C*H$_3$)$_2$); HRMS (EI^+) *m*/*z*: calcd for $C_{16}H_{36}O_4Si_2$, 348.2152; found, 348.2151.

Acknowledgments

This work was supported by grants from the Canadian Institutes of Health Research and the Nova Scotia Health Research Foundation. We thank Professor T. Bruce Grindley (Department of Chemistry, Dalhousie University) for helpful discussions.

Supplementary data

Supplementary data (NMR spectra of compounds **5a**–**c**, **7**–**8**, **10**–**11**, **13**, and **15**–**21**) associated with this article can be found, in the online version, at doi:10.1016/j.carres.2007.09.012.

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