JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

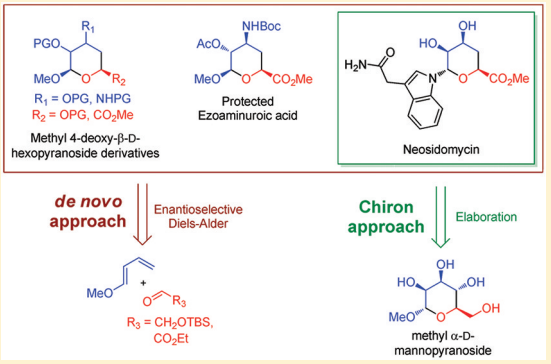
Enantioselective de Novo Synthesis of 4-Deoxy-D-hexopyranoses via Hetero-Diels–Alder Cycloadditions: Total Synthesis of Ezoaminuroic Acid and Neosidomycin

Denis Giguère, Julien Martel, Tze Chieh Shiao, and René Roy*

Pharmaqam, Department of Chemistry, Université du Québec à Montréal, P.O. Box 8888, Succ. Centre-Ville Montréal, Québec, Canada H3C 3P8

Supporting Information

ABSTRACT: The de novo synthesis of carbohydrates constitutes an important aspect of organic chemistry, and its application toward deoxy sugars is particularly noteworthy in targeting biologically active compounds. The enantioselective preparation of 4-deoxy-D-*ribo*-, 4-deoxy-D-*lyxo*-, and 4-deoxy-D-*xylo*-hexopyranosides, along with their uronate counterparts has been successfully accomplished using hetero-Diels–Alder reactions as the key step. Jacobsen chromium(III) catalyst and a titanium–binaphthol complex have been used to successfully catalyze diene and aldehyde cycloadditions, leading to optically active dihydropyran templates. 6-Hydroxydesosamine, orthogonally protected ezoaminuroic acid, and neosidomycin were synthesized using a comparative study. Also, a novel chiron approach to 4-deoxy-*lyxo*-hexopyranosiduronic acid methyl ester derivatives was efficiently accomplished starting from readily accessible starting materials. This work represents a systematic and comprehensive study toward a de novo synthesis of 4-deoxy-hexopyranoses via enantioselective hetero-Diels–Alder reactions.



INTRODUCTION

Over the past decade, there has been a large expansion in the understanding of the importance of carbohydrates in biology. The rate of these discoveries is somewhat dependent on medicinal chemists to provide unnatural sugar analogues having attractive and novel biological properties. Deoxy-hexoses are of particular interest, and the preparation of this family of compounds from achiral starting materials has attracted attention and stands out as a challenge to asymmetric catalysis.[1,2]

4-Deoxy-hexopyranose motifs (shown in blue) are present in several natural products as shown in Figure 1. Erythromycin A1 (**1**) is an antibiotic macrolide within a family of diverse molecular architectures. Its desosamine moiety, presented in blue, is in part responsible for the potent antibacterial activity of **1**.[3] Moreover, nikkomycin B (**2**), ezomycin A_2 (**3**), and ezomycin B_2 (**4**) are secondary metabolite members of the peptidyl nucleoside family and possess antimicrobial and antifungal properties.[4] These three natural products are composed of a nucleobase and a central 4-deoxy-hexopyranose (named ezoaminuroic acid for compounds **3** and **4**). Furthermore, metabolites **5**–**8** have been isolated from bacterial strains and represent rare examples of sugars linked to an indole moiety through a nitrogen atom.[5] This family of compounds possesses appealing antiviral or antibacterial activity against various bacterium strains.[5b,c]

The natural abundance of 4-deoxy-hexopyranoses is relatively limited in comparison to their 2-deoxy counterparts. Consequently, modest interest and methods have been developed toward the de novo synthesis of these medically relevant compounds. The most common approach toward the synthesis of 4-deoxy-hexopyranoses consists of selective protection of the natural hexopyranose hydroxyl groups followed by deoxygenation of the residual free 4-hydroxyl group or elimination to form 4,5-unsaturated derivatives.[6] Other approaches involve enzymatic synthesis (using microbial oxidation,[7] transketolase,[8] aldolase,[9] or *Saccharomyces cerevisiae*[10]), Diels–Alder reactions (1,3-diene with a carbonyl compound,[11] oxa-diene with electron-rich dienophile[12] or using the naked approach[13]), and other methods (from benzyl glycidyl ether[14] or using Sharpless asymmetric dihydroxylation[15]).

Most methods are long, require stoichiometric amounts of reagents, give racemic products, or do not provide access to various carbohydrate configurations (D, L, *ribo*, *lyxo*, *xylo*, ...). Thus, the use of a catalytic enantioselective hetero-Diels–Alder (HDA) reaction could be most efficient toward the synthesis of 4-deoxy-hexopyranose derivatives. This report describes the use of Jacobsen tridentate chromium catalyst and a binaphthol–titanium complex for catalytic enantioselective HDA reactions toward 4-deoxy-hexopyranoses.

For several decades, asymmetric catalysis has constituted an important aspect of organic synthesis toward the preparation of biologically active compounds. Moreover, the asymmetric HDA

Received: August 23, 2011
Published: October 25, 2011

   dx.doi.org/10.1021/jo201673w | J. Org. Chem. 2011, 76, 9687–9698

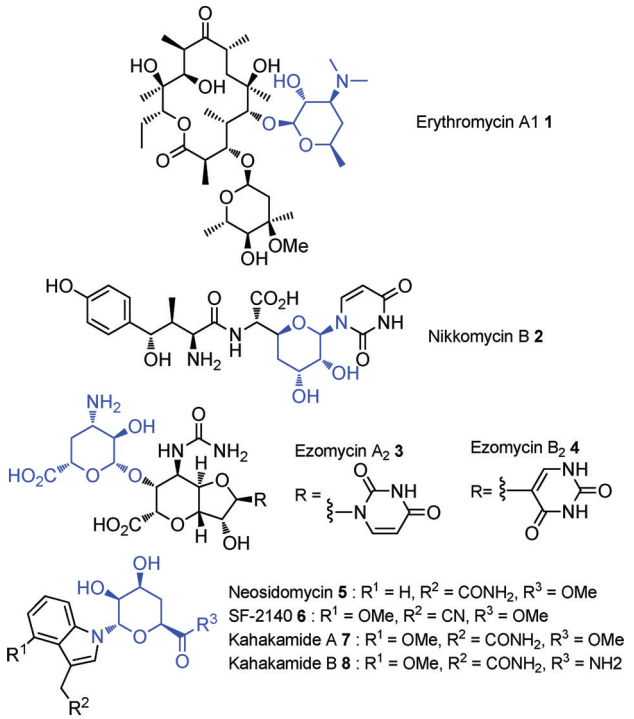


Figure 1. 4-Deoxy-hexopyranose motifs (shown in blue) present in various natural products **1**–**8**.

reaction is highly powerful for the construction of optically active heterocycles, the starting point of many natural or unnatural products with a wide range of biological activities.[16] The high regio- and stereoselectivity during the course of the catalyzed HDA, along with the creation of up to four new stereocenters, renders this methodology very attractive to construct various targets having similar structures. Finally, chiral catalysts allow the use of mild reaction conditions in an atom-economical fashion as compared to the use of chiral auxiliaries.

Figure 2 presents the synthetic plan for the construction of various 4-deoxy-D-hexopyranoses. Reaction of inactivated

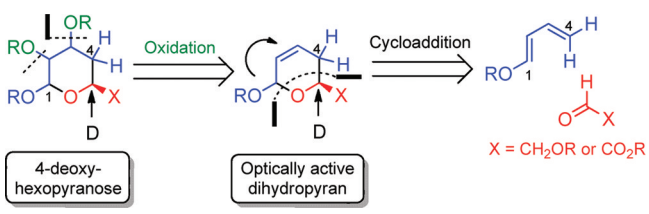


Figure 2. Synthetic plan for the construction of various 4-deoxy-D-hexopyranoses.

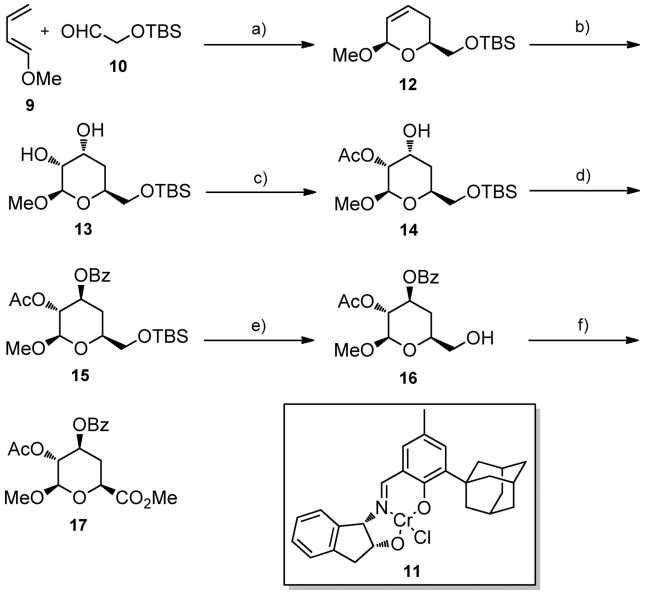
carbonyl compounds with a non-nucleophilic diene would provide a direct route to enantiomerically enriched dihydropyran derivatives from simple achiral starting materials.[17] Therefore, the choice of catalyst is crucial and allows the installation of a C-5 chiral center, fixing the D configuration of the sugar moiety. The choice of starting dienophile is also essential, allowing direct access to the uronic acid scaffold after the HDA reaction. Moreover, the anomeric configuration could direct the stereochemical outcome of the dihydropyran double-bond functionalization. This key strategy was used because of the easy access of chiral complexes, the high enantio- and diastereomeric excesses, and finally the simple experimental protocol, allowing scalable pyran templates.

As part of an ongoing research program aimed at the synthesis and biological evaluation of deoxy-hexopyranoses, novel approaches are needed.[18] To the best of our knowledge, there is no preparation of an enantioenriched 4-deoxy-sugar using as the key step an asymmetric HDA cycloaddition catalyzed by a chiral complex. We wish to report the preparation of 4-deoxy-D-*ribo*, 4-deoxy-D-*xylo*, and 4-deoxy-D-*lyxo*-hexopyranosides along with their methyl uronate counterparts. The key step for their synthesis is based on asymmetric HDA cycloadditions catalyzed by Jacobsen tridentate chromium(III) catalyst and a binaphthol–titanium complex. The synthesis of 6-hydroxydesosamine, protected ezoaminuroic acid, and neosidomycin was also achieved in high overall yield. Moreover, a new chiron approach to neosidomycin was also developed, starting from methyl α-D-mannopyranoside. Finally, a comparative study was used in order to determine the most efficient route for the preparation of various 4-deoxy-hexopyranoses.

RESULTS AND DISCUSSION

In order to achieve the rapid preparation of 4-deoxy-D-hexopyranoses, a robust synthetic strategy allowing its large-scale preparation was needed. The syntheses were initiated with the highly enantio- and diastereoselective HDA between 1-methoxybutadiene **9** and (*tert*-butyldimethylsilyloxy)-acetaldehyde **10** catalyzed by 1.5 mol % of Jacobsen chiral tridentate chromium(III) catalyst **11**[19] to provide **12** (Scheme

Scheme 1. Synthesis of Methyl 4-Deoxy-β-D-*ribo*-hexopyranoside 13, Methyl 4-Deoxy-β-D-*xylo*-hexopyranoside 15, and Methyl 4-Deoxy-β-D-*xylo*-hexopyranosiduronic Acid Methyl Ester 17[a]



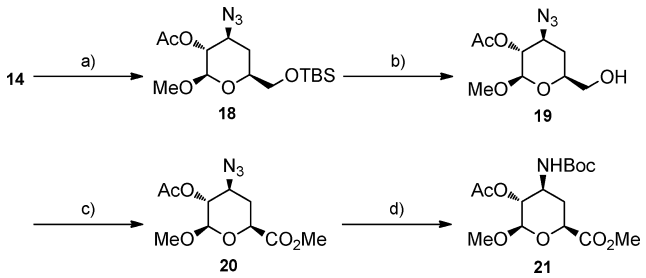
[a]Reagents and conditions: (a) **10**, **11** (1.5 mol %), 4 Å molecular sieves, then **9**, 0–24 °C, 16 h, 89%, ee >99%, de >99%; (b) OsO_4, NMO, acetone/water, 24 °C, 16 h, 70%; (c) Ac_2O, DMAP, pyridine, CH_2Cl_2, 24 °C, 50 min, 77%; (d) benzoic acid, PPh_3, DIAD, toluene, 24 °C, 50 min, 82%; (e) TBAF, THF, 24 °C, 30 min, 94%; (f) (i) TEMPO, BAIB, CH_2Cl_2/water, 24 °C, 45 min, (ii) K_2CO_3, MeI, CH_3CN, 24 °C, 16 h, 60%.

dx.doi.org/10.1021/jo201673w | J. Org. Chem. 2011, 76, 9687–9698

1). Dihydropyran **12** (89% yield, ee >99%, de >99%) possesses two chiral centers, thereby fixing C-1 with a β configuration and C-5 establishing the D series of the newly formed carbohydrate core. Catalytic diastereoselective dihydroxylation of dihydropyran **12** with 6 mol % of osmium tetroxide (from the less hindered face) afforded methyl 4-deoxy-β-D-*ribo*-hexopyranoside **13** in 70% yield. Furthermore, the *xylo* configuration could be easily achieved following a two-step procedure. Selective acetylation of the equatorial (O-2) hydroxyl group (77% yield),[20] followed by a Mitsunobu treatment, resulted in the inversion of the C-3 stereocenter (82% yield) using benzoic acid. Compound **15** constitutes an orthogonally protected methyl 4-deoxy-β-D-glucopyranoside that was synthesized in only four steps. Methyl 4-deoxy-β-D-*xylo*-hexopyranoside **15** was further transformed into its uronic acid derivative by unmasking the primary hydroxyl group using TBAF (94%), followed by a TEMPO/BAIB oxidation allowing formation of the uronic acid. Its methyl ester was formed after treatment with MeI under basic conditions, thus providing methyl 4-deoxy-β-D-*xylo*-hexopyranosiduronic acid methyl ester **17** in 60% yield over two steps.[21]

Being able to control the oxidation level at C-6 of the carbohydrate moiety, we focused our attention on the preparation of ezoaminuroic acid (present in compounds **3** and **4**; Figure 1). The synthesis was initiated by a modified Mitsunobu procedure on pyran **14**, allowing formation of the corresponding azido sugar with inversion of configuration in 92% yield (Scheme 2). The silyl ether of **18** was cleaved to

Scheme 2. First-Generation Synthesis of Protected Ezoaminuroic Acid 21 from Pyran 14[a]

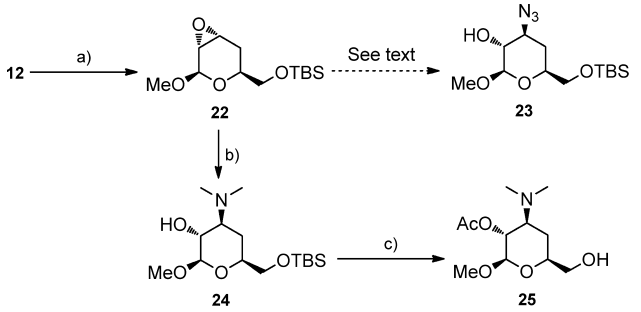


[a]Reagents and conditions: (a) DPPA, PPh_3, DIAD, THF, 0–24 °C, then 50 °C, 16 h, 92%; (b) TBAF, THF, 24 °C, 30 min, 93%; (c) (i) TEMPO, BAIB, CH_2Cl_2/water, 24 °C, 45 min, (ii) K_2CO_3, MeI, CH_3CN, 24 °C, 16 h, 57%; (d) Pd/C, H_2, EtOAc, 24 °C, 3 h, then Boc_2O, Et_3N, 24 °C, 16 h, 92%.

provide **19** in 93% yield, which was transformed into its methyl ester using the above procedure (TEMPO/BAIB, then K_2CO_3, MeI) in 57% over two steps. Finally, reduction of the azido group using a catalytic amount of Pd/C was followed by in situ Boc protection, providing amino sugar **21** in 92% yield over two steps.

Additionally, 3-amino derivatives were obtained by epoxide opening of 4-deoxyanhydropyranoside. Toward this goal, epoxidation of dihydropyran **12** with *m*CPBA afforded the anhydro derivative **22** in 70% yield as the sole diastereoisomer (Scheme 3). Epoxide opening with NaN_3 failed or gave poor regioselectivities and yields under standard or chelating conditions.[22] Decomposition was predominant, and opening at C-2 was important, in accord with previously described epoxide opening on similar systems.[23] On the other hand, regiochemical epoxide opening could be successfully achieved

Scheme 3. Epoxide Opening toward Desosamine Derivative 25[a]

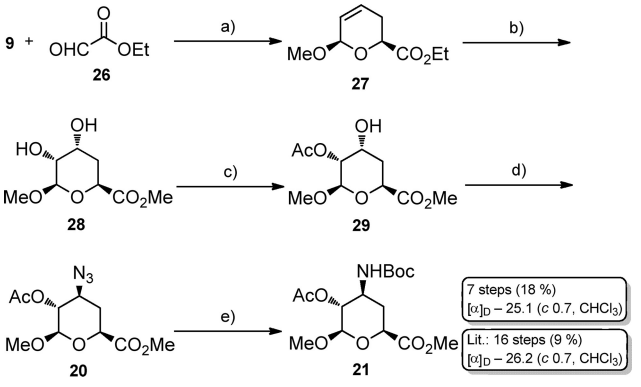


[a]Reagents and conditions: (a) *m*CPBA, CH_2Cl_2, 24 °C, 16 h, 70%; (b) dimethylamine (33% in EtOH), 24 °C, 3 days, 85%; (c) (i) Ac_2O, pyridine, 24 °C, 3 h, quantitative, (ii) TBAF, THF, 24 °C, 30 min, 81%.

using a different amine-based nucleophile. When dimethylamine (33% in EtOH) was stirred for 3 days at 24 °C, compound **24** was isolated in 85% yield. C-3 opening product was the only detected regioisomer, in accord with the Fürst–Plattner rule, providing an equatorially substituted product. Compound **24** could be transformed into methyl 2-acetyl-6-hydroxy-β-D-desosamine through protecting group manipulation. Compound **25** was isolated in 81% yield over two steps and represents a valuable antibiotic when joined to various ketolides.[24]

Fully protected ezoaminuroic acid **21** was alternatively synthesized starting from ethyl glyoxylate **26** used as dienophile partner (Scheme 4). This modification allowed formation of a

Scheme 4. Second-Generation Synthesis of Protected Ezoaminuroic Acid 21 Using HDA Catalyzed by a Binaphthol–Titanium Complex as a Key Step[a]



[a]Reagents and conditions: (a) (−)-(*S*)-BINOL (20 mol %), Ti(O-*i*-Pr)$_4$ (10 mol %), CH_2Cl_2, 40 °C, 1 h, then **26** and **9**, −30 to 24 °C, 2.5 h, 61%, ee 95%, de >95%; (b) (i) OsO_4, NMO, acetone/water, 24 °C, 16 h, (ii) NaOMe, MeOH, 24 °C, 2 h, 64%; (c) Ac_2O, DMAP, pyridine, CH_2Cl_2, 24 °C, 50 min, 70%; (d) DPPA, PPh_3, DIAD, THF, 0–24 °C, then 50 °C, 16 h, 73%; (e) Pd/C, H_2, EtOAc, 24 °C, 3 h, then Boc_2O, Et_3N, 24 °C, 16 h, 92%.

fully oxidized dihydropyran at the C-6 position while still having a D configuration at C-5. Jacobsen chiral tridentate chromium(III) catalyst **11** gave poor yields and diastereo- and enantiomeric excesses when used to catalyze the reaction between diene **9** and *n*-butyl glyoxylate.[25] As an alternative, a binaphthol–titanium complex, developed by the group of

dx.doi.org/10.1021/jo201673w | J. Org. Chem. 2011, 76, 9687–9698

Mikami, was used next.[26] The HDA reaction between 1-methoxybutadiene **9** and ethyl glyoxylate **26** catalyzed by a 2:1 molar ratio of (−)-(*S*)-1,1′-binaphthol (20 mol %) and Ti(O-*i*-Pr)$_4$ (10 mol %) provided dihydropyran **27** in 61% yield in high diastereo- and enantiomeric excesses.[27] Catalytic dihydroxylation (6 mol %) followed by methyl ester synthesis provided compound **28** in 64% yield over two steps. Finally, monoacetylation and a modified Mitsunobu reaction, as previously described, gave compound **20**. Boc protection of the reduced azido group afforded the known protected ezoaminuroic acid intermediate.[28] The most efficient synthesis of **21** was described by the Datta group (**21**: 16 steps (9% global yield) starting from (*R*)-glycidol).[20] Using the present strategy, compound **21** was prepared in only seven steps and 18% yield from pyran **27**.

In order to expand the use of this strategy for the synthesis of 4-deoxy-D-hexopyranose-containing natural products, we next focused on the preparation of neosidomycin **5** (Figure 1). This natural product was isolated in 1979 from *Streptomyces hygroscopicus* by the Furuta group.[5c] There are three other members of this family of indole-*N*-glycosyls (**6**−**8**, Figure 1),[5a,b] and these molecules possess antibacterial or antiviral activities. Only one synthesis of neosidomycin **5** has been previously described (as an inseparable anomeric mixture of products), and the chiron approach was used for the preparation of the carbohydrate moiety.[29] Our retrosynthetic analysis shows that compound **5** could be made by coupling of a glycosyl donor with indole **30** (Figure 3). The glycosyl donor

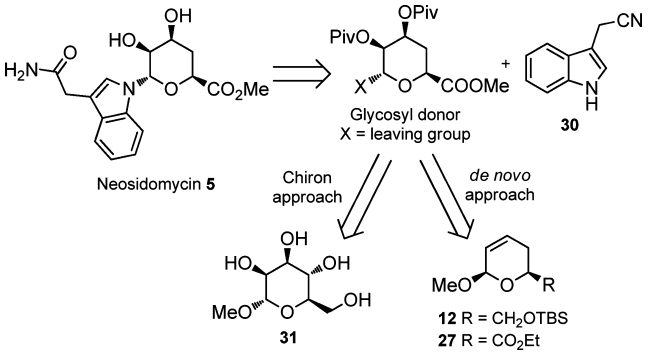


Figure 3. Retrosynthetic analysis of neosidomycin **5**.

could be obtained from methyl α-D-mannopyranoside **31** using a new chiron approach or from pyran **12** and **27** using a de novo approach.

First of all, Wightman's synthesis of neosidomycin **5** relied on O-4 deoxygenation of an orthogonally protected mannoside, followed by oxidation at the C-6 position.[6g,29] In opposition, we believe the synthesis could be shortened by first oxidizing C-6 followed by O-4 deoxygenation of a suitable mannoside derivative.

Hence, the synthesis of various glycosyl donors using the chiron approach was initiated with compound **32** readily available from methyl α-D-mannopyranoside **31** following a known three-step sequence (Scheme 5).[30] Removal of the O-4 hydroxyl group was achieved in a classical manner through formation of thiocarbonyl **33** in 63% yield, followed by a radical deoxygenation using AIBN and Bu_3SnH in 62% yield. The derivative methyl 4-deoxy-β-D-*lyxo*-uronate **34** was deprotected under acidic conditions (**35**)[31] and suitably protected with PivCl in 91% yield, affording the known compound **36**.[29]

An improved procedure for the synthesis of this compound relied on the acetonide deprotection of compound **32** followed by trimethylacetyl protection, affording compound **37** in 86% yield over two steps. Then, DBU-induced elimination provided the unsaturated ester **38** in quantitative yield.[31] Catalytic hydrogenation of the double bond leads to ester **36** in 97% yield as the sole diastereoisomer, as judged by the ^{1}H NMR spectrum of the crude reaction mixture. Finally, acetolysis of compound **36** furnished the inseparable anomeric acetate in a 6:1 α:β ratio, which was recrystallized in pentane, affording pure α-anomer **39** in 67% yield. The α configuration was determined by direct NMR coupling of the anomeric proton and carbon (91.3 ppm, $^1J_{C-H}$ = 177.8 Hz).[32] This compound was previously described by the Wightman group (**39**: nine steps, 20% yield),[29] and our strategy (**39**: eight steps, 26% yield) represents a slightly improved synthesis using a new chiron approach, both methods from methyl α-D-mannopyranoside **31**. Finally, the preparation of a halogenated glycosyl donor was achieved by treating compound **39** in a mixture of HBr 33% in acetic acid, affording the unstable α-bromo compound **40** in quantitative yield.

The preparation of glycosyl donor **39** could be shortened again, but using a different approach. Compound **39** was made using a de novo methodology as described below.

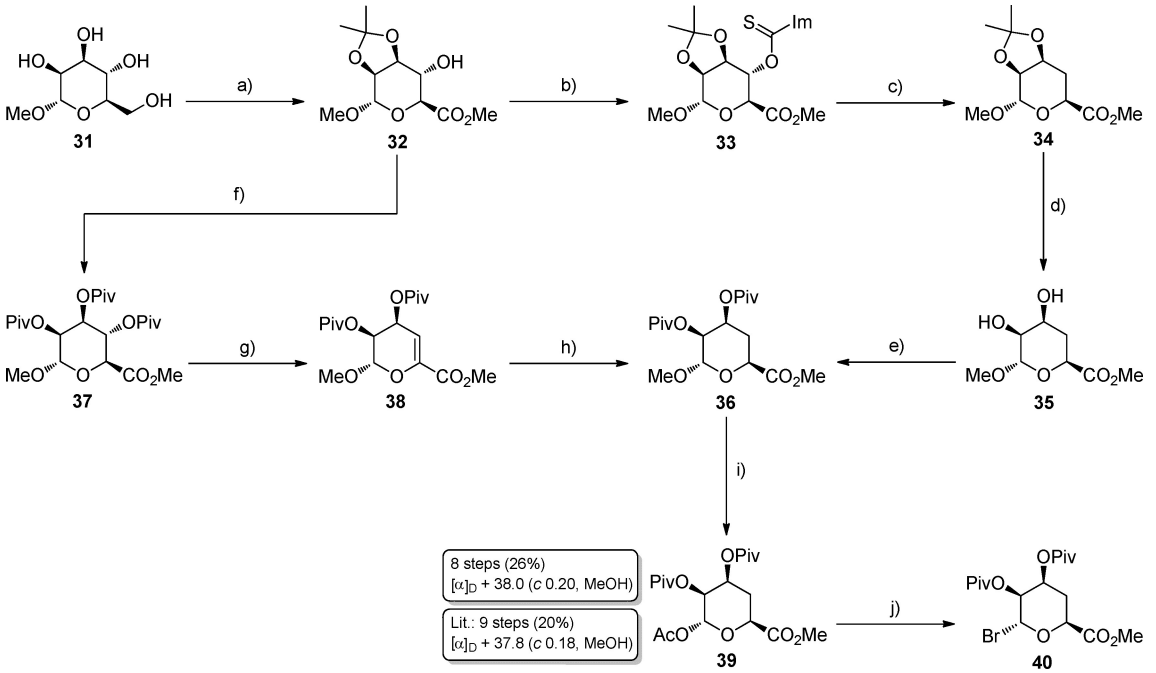
In order to achieve the preparation of 4-deoxy-*lyxo*-D-hexopyranoside derivatives, dihydroxylation of pyran **12** must occur on the β face.[33] Consequently, compound **12** was treated with PPTS in *i*-PrOH, allowing formation of pure α-anomer **41** in nearly quantitative yield (Scheme 6). Catalytic dihydroxylation using osmium tetroxide occurred on the less hindered β-face of pyran **41**, allowing access to diol **42** in 86% yield as the only diastereoisomer. The hydroxyl group's configuration of **42** was determined by NOE experiments. Synthesis of the glycosyl donor **39** was easily accomplished in a four-step manner: (i) diol protection with excess trimethylacetyl chloride in pyridine (55% yield), (ii) primary hydroxyl group deprotection using TBAF (70% yield), (iii) TEMPO oxidation, followed by treatment with excess of MeI and K_2CO_3 (66% over 2 steps), and finally (iv) acetolysis of the isopropyl group, allowing formation of **39** as the only anomer after recrystallization in pentane (70% yield).

The second-generation synthesis of glycosyl donor **39** proceeded via a similar strategy (Scheme 7). Anomerization of pyran **27** successfully provided compound **46** in 89% yield, allowing a diastereoselective osmium-catalyzed (6 mol %) dihydroxylation to give diol **47** in 67% yield after treatment with methanolic sodium methoxide. The previously synthesized compound **39** was accessible after hydroxyl group protection using PivCl in pyridine in 83% yield, followed by acetolysis in 70% yield.

With glycosyl donors **39** and **40** in hand, we explored the challenging coupling with 3-cyanomethylindole **30**, providing α-indole-*N*-glycosyl **48** (Scheme 8).[34] Previous studies related to this crucial step were carried out using a glycosyl chloride (as glycosyl donor) treated with the sodium salt of 3-cyanomethylindole.[29] A 6:1 ratio of diastereoisomers was obtained in favor of the α anomer, but in a low 44% yield (it is worth noting that only the β isomer was isolated for the synthesis of SF-2140). Our initial attempts to accomplish this coupling using brominated compound **40** following classical methods[35] failed; at best, only trace amounts of the desired product were obtained. Following extensive experimentation, it was found that pretreatment of $BF_3{\cdot}OEt_2$ with glycosyl donor

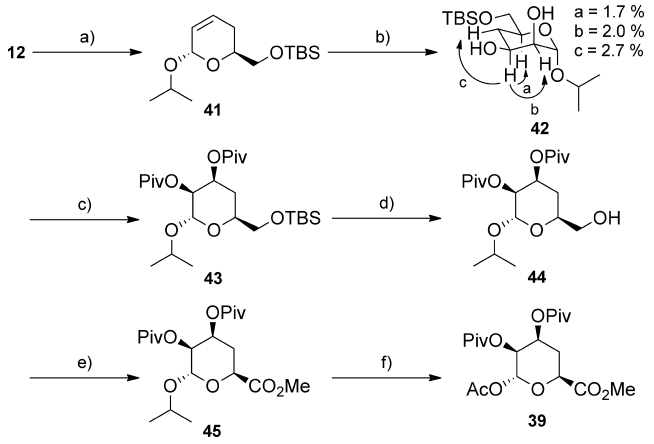
dx.doi.org/10.1021/jo201673w | J. Org. Chem. 2011, 76, 9687−9698

Scheme 5. New Chiron Approach to Glycosyl Donors 39 and 40[a]



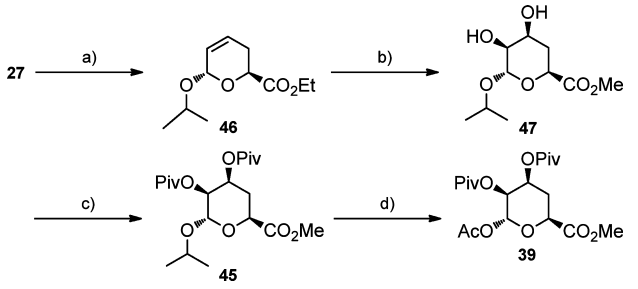
[a]Reagents and conditions: (a) ref 31, three steps, 53%; (b) TCDI, DMAP, CH_2Cl_2, 24 °C, 48 h, 63%; (c) AIBN, Bu_3SnH, toluene, 110 °C, 1 h, 62%; (d) $AcOH/H_2O$, 60 °C, 6 h, 75%; (e) PivCl, DMAP, pyridine, 60 °C, 16 h, 91%; (f) (i) $AcOH/H_2O$, 60 °C, 6 h, (ii) PivCl, DMAP, pyridine, 60 °C, 16 h, 86%; (g) DBU, CH_2Cl_2, 0−24 °C, 16 h., quantitative; (h) Pd/C, H_2, EtOAc, 24 °C, 16 h, 95%; (i) $Ac_2O/AcOH/H_2SO_4$, 24 °C, 16 h, 67%; (j) 33% HBr/AcOH, CH_2Cl_2, 24 °C, 1 h, quantitative.

Scheme 6. First-Generation de Novo Synthesis of Glycosyl Donor 39[a]



[a]Reagents and conditions: (a) PPTS, *i*-PrOH, 24 °C, 24 h, 99%; (b) OsO_4, NMO, acetone/water, 24 °C, 16 h, 86%; (c) PivCl, DMAP, pyridine, 60 °C, 16 h, 55%; (d) TBAF, THF, 24 °C, 30 min, 70%; (e) (i) TEMPO, BAIB, CH_2Cl_2/water, 24 °C, 45 min, (ii) K_2CO_3, MeI, CH_3CN, 24 °C, 16 h, 66%; (f) $Ac_2O/AcOH/H_2SO_4$, 24 °C, 16 h, 70%.

Scheme 7. Second-Generation Synthesis of Glycosyl Donor 39[a]



[a]Reagents and conditions: (a) PPTS, *i*-PrOH, 24 °C, 24 h, 89%; (b) (i) OsO_4, NMO, acetone/water, 24 °C, 16 h, (ii) NaOMe, MeOH, 24 °C, 2 h, 67%; (c) PivCl, DMAP, pyridine, 60 °C, 16 h, 83%; (d) $Ac_2O/AcOH/H_2SO_4$, 24 °C, 16 h, 70%.

39 (4 h), followed by addition of 3-cyanomethylindole **30** provided α-indole-*N*-glycosyl **48** in 78% yield as the only anomer, as judged by the ^{1}H NMR of the crude reaction mixture.

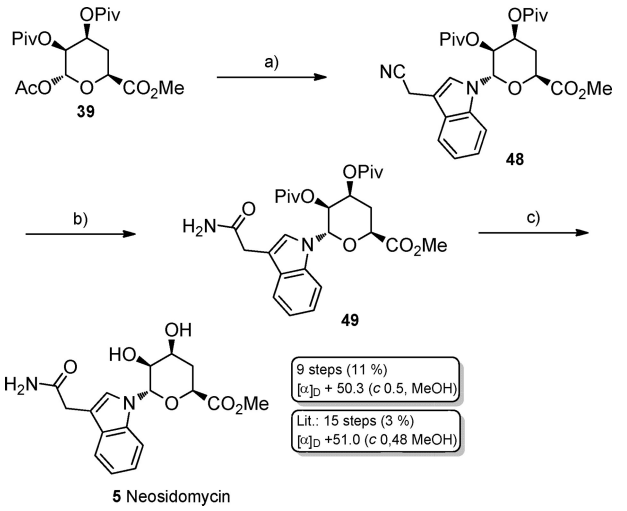
With this demanding coupling successfully achieved, completion of the total synthesis was accomplished by amide formation using hydrated nickel acetate in 67% yield (Scheme 8). Deprotection of compound **49** using classical methods were ineffective,[36] and after careful experimentation, the use of a 1 M solution of sodium methoxide in methanol provided neosidomycin **5** after 4 days, in 35% yield, 97% based on recovered starting material. The physical properties of synthetic **5** (i.e., ^{1}H NMR spectrum, mass spectral data, melting point, and optical rotation)[37] matched those reported for the natural substance.[5c,29] It is worth noting that the Wightman synthesis of neosidomycin (**5**: 15 steps (3% yield) from methyl α-D-mannopyranoside **31**) provided compound **5** along with the inseparable β anomer. Consequently, this synthesis represents the first selective synthesis of neosidomycin in nine steps (11% yield) from pyran **27**.

CONCLUSION

In conclusion, the enantioselective preparations of various 4-deoxy-D-hexopyranosyl derivatives have been successfully accomplished. Both Jacobsen chromium(III) catalyst and a

dx.doi.org/10.1021/jo201673w | J. Org. Chem. 2011, 76, 9687−9698

Scheme 8. Final Stage for the Synthesis of Neosidomycin 5[a]



[a]Reagents and conditions: (a) **39**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0−24 °C, 4 ., then **30**, 24 °C, 16 h, 78%; (b) $Ni(OAc)_2{\cdot}4H_2O$, AcOH, 118 °C, 20 h, 67%; (c) NaOMe, MeOH, 24 °C, 4 days, 35% (97% brsm).

titanium−binaphthol complex catalyzed the formation of dihydropyrans as a key methodology. Few synthetic steps were required to access 4-deoxy-D-*ribo*-, 4-deoxy-D-*lyxo*-, and 4-deoxy-D-*xylo*-hexopyranosides, along with their uronic acid counterparts. 6-Hydroxydesosamine, orthogonally protected ezoaminuroic acid, and neosidomycin were synthesized using a de novo approach. Moreover, a novel chiron approach to 4-deoxy-*lyxo*-hexopyranosiduronic acid methyl ester derivatives was accomplished starting from methyl α-D-mannopyranoside. The efficiency of the above strategy could provide access to other members of the α-indole-*N*-glycosyl metabolites. Finally, the synthetic approach described herein is quite general and, by using chiral catalyst *ent*-**11**, it should be possible to access several 4-deoxy-hexopyranosyl derivatives with an L configuration.

EXPERIMENTAL SECTION

General Considerations. All reactions in organic media were performed in standard oven-dried glassware under an inert atmosphere of nitrogen using freshly distilled solvents. CH_2Cl_2 was distilled from CaH_2 and DMF from ninhydrin and kept over molecular sieves. THF was distilled from Na/benzophenone immediately before use. All reagents were used as supplied without prior purification unless otherwise stated. The evolution of the reaction was monitored by analytical thin-layer chromatography using silica gel 60 F_{254} precoated plates, and compounds were visualized by 254 nm light, a mixture of iodine and silica gel, and/or a molybdenum−cerium solution (100 mL of H_2SO_4, 900 mL of H_2O, 25 g of $(NH_4)_6Mo_7O_{24}H_2O$, 10 g of $Ce(SO_4)_2$) and subsequent development by gentle warming with a heat gun. Purifications by flash column chromatography were performed using flash silica gel (60 Å, 40−63 μm) with the indicated eluent.

^1H NMR and ^{13}C NMR spectra were recorded at 300 or 600 MHz and 75 or 150 MHz, respectively. All NMR spectra were measured at 25 °C in the indicated deuterated solvents. Proton and carbon chemical shifts (δ) are reported in ppm, and coupling constants (*J*) are reported in hertz (Hz). The resonance multiplicities in the ^1H NMR spectra are described as "s" (singlet), "d" (doublet), "t" (triplet), and "m" (multiplet), and broad resonances are indicated by "br". The residual protic solvent of $CDCl_3$ (^1H, δ 7.27 ppm; ^{13}C, δ 77.0 ppm (central resonance of the triplet)), $CO(CD_3)_2$ (^1H, δ 2.05 ppm; ^{13}C, δ 29.84 ppm), and MeOD-d_4 (^1H, δ 3.34 ppm; ^{13}C, δ 49.9 ppm) were used as the internal references in the ^1H and ^{13}C NMR spectra. 2D Homonuclear correlation $^1H-^1H$ COSY experiments were used to confirm NMR peak assignments. Optical rotations were measured on a polarimeter at the indicated temperature (±2 °C) in the stated solvent. Fourier transform infrared (FTIR) spectra were measured on neat NaCl. The absorptions are given in wavenumbers (cm^{-1}). The enantiomeric excesses of the HDA reactions were determined with an HPLC with a chiral column DNBPG (covalent) Chiral 5 μm, Standard Analytical 4.6 × 250 mm, coupled with a UV detector (UV−vis 229 nm). Melting points are uncorrected. Accurate mass measurements (HRMS) were performed on a LC-MSD-TOF instrument in positive electrospray mode. Either protonated molecular ions $[M + nH]^{n+}$ or sodium adducts $[M + Na]^+$ were used for empirical formula confirmation.

(2*R*,6*S*)-6-(*tert*-Butyldimethylsilyloxymethyl)-2-methoxy-2,5-dihydropyran (12). Compound **9** (240 μL, 2.37 mmol) was added dropwise to a mixture of compound **10** (360 μL, 2.13 mmol), Cr(III) catalyst **11** (160 mg, 16.0 μmol), and 4 Å molecular sieves (20.0 mg) at 0 °C. The mixture was stirred for 1 h at 0 °C and 16 h at 24 °C. Kugelrohr distillation of the reaction mixture allowed isolation of compound **12** (491 mg, 89%) as a colorless oil. The enantiomeric excess (>99%) was determined with a GC using chiral column DNBPG ((covalent) Chiral 5 μm, Standard Analytical 4.6 × 250 mm, elution gradient MeOH:CH_3CN (5% H_2O), (0.05% TFA) (1:4) → MeOH:CH_3CN (5% H_2O), (0.05% TFA) (1:1), 1 mL/min, 30 °C, t_r **12** 4.2 min, t_r *ent*-**12** 5.2 min). **12**: R_f 0.37 (EtOAc:hexanes, 1:5); $[\alpha]_D$ = −55.1° (*c* = 1.1 in $CHCl_3$), lit.[19a] (*ent*-**12**) $[\alpha]_D$ = +55.3° (*c* = 1.1 in $CDCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.85 (s, 9H), 2.00−2.04 (m, 2H), 3.41 (s, 3H), 3.60 (dd, *J* = 6.5, 10.2 Hz, 1H), 3.70 (dd, *J* = 5.5, 10.3 Hz, 1H), 3.80 (q, *J* = 5.9 Hz, 1H), 4.95−4.96 (m, 1H), 5.57−5.61 (m, 1H), 5.88−5.94 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 128.2, 126.7, 97.4, 72.3, 65.2, 54.9, 26.5, 25.7 (3×), 18.1, −5.4, −5.5 ppm; HRMS *m*/*z* calcd for $C_{13}H_{26}O_3Si$ $[M + Na]^+$ 281.1543, found 281.1541.

Methyl 6-*O*-(*tert*-Butyldimethylsilyloxy)-4-deoxy-β-D-*ribo*-hexopyranoside (13). To a solution of compound **12** (252 mg, 0.974 mmol) in an acetone/water mixture (4:1, 9.7 mL, 0.1 M) were added NMO (285 mg, 2.43 mmol) and OsO_4 (4% in water, 370 μL, 0.0580 mmol). The solution was stirred at 24 °C for 16 h, and 10% aqueous $NaHSO_3$ (5 mL) was added; this mixture was stirred for 5 min and diluted with EtOAc (10 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (5 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 1:1) affording compound **13** (200 mg, 70%) as a colorless oil. **13**: R_f 0.21 (EtOAc:hexanes, 1:1); $[\alpha]_D$ = −47.1° (*c* = 0.7 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.86 (s, 9H), 1.56−1.47 (m, 1H), 1.86−1.90 (m, 1H), 3.14 (s, 1H), 3.33−3.36 (m, 1H), 3.49 (s, 1H), 3.54−3.59 (m, 1H), 3.65−3.70 (m, 1H), 3.88−3.93 (m, 1H), 4.16 (s, 1H), 4.49 ppm (d, *J* = 7.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 101.3, 71.6, 71.1, 67.3, 65.6, 56.6, 33.5, 25.7 (3×), 18.2, −5.4 ppm (2×); IR (NaCl) ν 3420 cm^{-1}; HRMS *m*/*z* calcd for $C_{13}H_{28}O_5Si$ $[M + Na]^+$ 315.1603, found 315.1602.

Methyl 2-*O*-Acetyl-6-*O*-(*tert*-butyldimethylsilyloxy)-4-deoxy-β-D-*ribo*-hexopyranoside (14). To a solution of compound **13** (200 mg, 0.685 mmol) in CH_2Cl_2 (6.8 mL, 0.10 M) were added pyridine (10 μL, 0.11 mmol), DMAP (10 mg), and Ac_2O (64 μL, 0.68 mmol). The mixture was stirred for 50 min at 24 °C, and water (5 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (1 × 10 mL) and then brine (1 × 10 mL). The organic solution was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 2:1) affording compound **14** (176 mg, 77%) as a colorless oil. **14**: R_f 0.67 (EtOAc:hexanes, 2:1); $[\alpha]_D$ = −61.7° (*c* = 0.9 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.85 (s, 9H), 1.57−1.65 (m, 1H), 1.83−1.89 (m, 1H), 2.09 (s, 3H), 2.49 (br s, 1H), 3.43 (s, 3H), 3.49−3.56 (m, 1H), 3.65−3.70 (m, 1H), 3.91−3.98 (m, 1H), 4.23 (br s, 1H), 4.61−4.69 ppm

dx.doi.org/10.1021/jo201673w | J. Org. Chem. 2011, 76, 9687−9698

(m, 2H); NMR ^{13}C (75 MHz, $CDCl_3$) δ 169.8, 98.8, 73.0, 70.8, 66.2, 65.4, 56.2, 33.7, 25.7 (3×), 20.9, 18.2, −5.4 ppm (2×); IR (NaCl) ν 3484, 1741 cm^{-1}; HRMS m/z calcd for $C_{15}H_{30}O_6Si$ $[M + Na]^+$ 357.1708, found 357.1704.

Methyl 2-*O*-Acetyl-3-*O*-benzoyl-6-*O*-(*tert*-butyldimethylsilyloxy)-4-deoxy-β-D-*xylo*-hexopyranoside (15). To a solution of compound **14** (37 mg, 0.11 mmol) in toluene (1 mL, 0.1 M) were added benzoic acid (16 mg, 0.13 mmol) and PPh_3 (57 mg, 0.218 mmol). Then, DIAD (45 μL, 0.22 mmol) was added dropwise at 24 °C and the mixture was stirred for 40 min at 24 °C. Ten milliliters of EtOAc was added to the reaction mixture, and the organic mixture was washed with saturated aqueous NH_4Cl (2 × 2 mL) and brine (2 × 2 mL). The organic solution was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified using flash column chromatography (silica gel, hexanes:EtOAc, 4:1) affording compound **15** (39 mg, 82%) as a colorless oil. **15**: R_f 0.55 (hexanes:EtOAc, 1:1); $[\alpha]_D$ = +15.6° (c = 1.0 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.89 (s, 9H), 1.57−1.68 (m, 1H), 2.00 (s, 3H), 2.32−3.49 (m, 1H), 3.52 (s, 3H), 3.64−3.79 (m, 2H), 3.80−3.83 (m, 1H), 4.40 (d, J = 7.9 Hz, 1H), 5.05−5.08 (m, 1H), 5.11−5.23 (m, 1H), 7.44 (t, J = 7.7 Hz, 2H), 7.54−7.59 (m, 1H), 8.00 ppm (d, J = 7.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 165.9, 133.2, 129.7 (2×), 129.6, 128.4 (2×), 101.8, 72.3 (2×), 72.0, 65.3, 56.6, 33.0, 25.8 (3×), 20.8, 18.3, −5.4 ppm (2×); IR (NaCl) ν 1751, 1724 cm^{-1}; HRMS m/z calcd for $C_{22}H_{34}O_7Si$ $[M + Na]^+$ 461.1971, found 461.1960.

Methyl 2-*O*-Acetyl-3-*O*-benzoyl-4-deoxy-β-D-*xylo*-hexopyranoside (16). To a solution of compound **15** (75 mg, 0.171 mmol) in THF (1.7 mL, 0.10 M) was added TBAF (1 M in THF, 0.342 mL, 0.342 mmol). The solution was stirred for 30 min at 24 °C and then concentrated under reduced pressure and purified by flash column chromatography (silica gel, hexanes:EtOAc, 1:1), affording compound **16** (52 mg, 94%) as a colorless oil. **16**: R_f 0.19 (EtOAc:hexanes, 1:1); $[\alpha]_D$ = +23.4° (c = 0.7 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.67−1.79 (m, 1H), 2.00 (s, 3H), 2.09−2.28 (m, 2H), 3.54 (s, 3H), 3.58−3.77 (m, 3H), 4.44 (d, J = 7.9 Hz), 5.06−5.12 (m, 1H), 5.16−5.24 (m, 1H), 7.43 (t, J = 7.4 Hz, 2H), 7.53−7.59 (m, 1H), 7.98 ppm (d, J = 7.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 165.9, 133.3, 129.7 (2×), 129.4, 128.5 (2×), 128.5, 101.9, 72.1, 71.7, 64.7, 56.9, 32.1, 20.8 ppm; IR (NaCl) ν 3407, 1750, 1717 cm^{-1}; HRMS m/z calcd for $C_{16}H_{20}O_7$ $[M + Na]^+$ 347.1106, found 347.1101.

Methyl 2-*O*-Acetyl-3-*O*-benzoyl-4-deoxy-β-D-*xylo*-hexopyranosiduronic Acid Methyl Ester (17). Step 1: to a solution of compound **16** (79 mg, 0.24 mmol) in a CH_2Cl_2/water mixture (3/1, 4.9 mL, 0.050 M) were added TEMPO (7.6 mg, 0.049 mmol) and BAIB (195 mg, 0.608 mmol). The mixture was stirred for 45 min at 24 °C, and 10 mL of aqueous Na_2SO_3 (1 M) was added followed by aqueous HCl (1 M) until pH 2. The mixture was extracted with CH_2Cl_2 (3 × 5 mL) and EtOAc (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Crude acid was used for the next step without further purification. Step 2: the crude acid was dissolved in acetonitrile (4 mL), and K_2CO_3 (40 mg, 0.27 mmol) was added followed by MeI (0.61 mL, 9.72 mmol). The mixture was stirred at 24 °C for 16 h, and then filtered and purified using flash column chromatography (silica gel, hexanes:EtOAc, 1:1), affording compound **17** (52 mg, 60%) as a white solid. **17**: R_f 0.34 (EtOAc:hexanes, 1:2); mp 97−98 °C (EtOAc/hexanes); $[\alpha]_D$ = +22.6° (c = 1.1 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.89−1.96 (m, 1H), 2.00 (s, 3H), 2.62−2.68 (m, 1H), 3.56 (s, 3H), 3.78 (s, 3H), 4.24 (dd, J = 2.2, 11.8 Hz), 4.46 (d, J = 7.4 Hz, 1H), 5.11−5.25 (m, 2H), 7.43 (t, J = 7.7 Hz, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.99 ppm (d, J = 7.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 169.1, 165.7, 133.4, 129.7 (3×), 128.5 (2×), 101.9, 71.6, 71.1, 70.3, 57.0, 52.5, 33.0, 20.7 ppm; IR (KBr) ν 1749, 1734, 1718 cm^{-1}; HRMS m/z calcd for $C_{17}H_{20}O_8$ $[M + Na]^+$ 375.1055, found 375.1050.

Methyl 2-*O*-Acetyl-3-azido-6-*O*-(*tert*-butyldimethylsilyloxy)-3,4-dideoxy-β-D-*xylo*-hexopyranoside (18). To a solution of compound **14** (77 mg, 0.23 mmol) in THF (7.6 mL, 0.030 M) at 0 °C were added DIAD (63 μL, 0.32 mmol), PPh_3 (80 mg, 0.32 mmol), and DPPA (70 μL, 0.32 mmol) dropwise. The reaction was warmed to 24 °C and then heated to 50 °C for 16 h. After this time, the solution was concentrated under reduced pressure and purified using flash column chromatography (silica gel, hexanes:EtOAc, 3:1), affording compound **18** (76 mg, 92%) as a yellow oil. **18**: R_f 0.68 (EtOAc:hexanes, 1:2); $[\alpha]_D$ = −43.4° (c = 1.1 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 9H), 0.88 (s, 6H), 1.40−1.52 (m, 1H), 2.05−2.14 (m, 4H), 3.45 (s, 3H), 3.48−3.62 (m, 3H), 3.69−3.78 (m, 1H), 4.27 (d, J = 7.9 Hz, 1H), 4.77 ppm (dd, J = 9.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 101.8, 73.2, 72.9, 65.1, 60.1, 56.4, 32.8, 25.7 (3×), 20.8, 18.2, −5.4 ppm (2×); IR (NaCl) ν 2100, 1751 cm^{-1}; HRMS m/z calcd for $C_{15}H_{29}N_3O_5Si$ $[M + Na]^+$ 382.1773, found 382.1775.

Methyl 2-*O*-Acetyl-3-azido-3,4-dideoxy-β-D-*xylo*-hexopyranoside (19). The same procedure was used as for the synthesis of compound **16**. Compound **19** was purified by flash column chromatography (silica gel, hexanes:EtOAc, 1:1) and was isolated as a colorless oil (93%). **19**: R_f 0.21 (EtOAc:hexanes, 1:1); $[\alpha]_D$ = −8.3° (c = 2.1 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.55−1.67 (m, 1H), 1.95−2.09 (m, 1H), 2.13 (s, 3H), 3.49 (s, 3H), 3.53−3.74 (m, 5H), 4.32 (d, J = 7.7 Hz, 1H), 4.75−4.81 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 101.9, 73.0, 72.8, 64.6, 59.9, 56.8, 31.9, 20.8 ppm; IR (NaCl) ν 3436, 2100, 1743 cm^{-1}; HRMS m/z calcd for $C_9H_{15}N_3O_5$ $[M + Na]^+$ 268.0908, found 268.0905.

Methyl 2-*O*-Acetyl-3-azido-3,4-dideoxy-β-D-*xylo*-hexopyranosiduronic Acid Methyl Ester (20). From **19**: using the same procedure as for the synthesis of compound **17** (57%). From **29**: using the same procedure as for the synthesis of compound **18**. Compound **20** was purified using flash column chromatography (silica gel, hexanes:EtOAc, 1:1) and was isolated as a white solid (73%). **20**: R_f 0.52 (EtOAc:hexanes, 1:1); mp 112−113 °C (EtOAc/hexanes); $[\alpha]_D$ = −13.9° (c = 1.5 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.75−1.88 (m, 1H), 2.13 (s, 3H), 2.34−2.41 (m, 1H), 3.51 (s, 3H), 3.52−3.67 (m, 1H), 3.79 (s, 3H), 4.14 (dd, J = 2.2, 11.8 Hz, 1H), 4.34 (d, J = 7.7 Hz, 1H), 4.83 ppm (dd, J = 2.2, 7.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 169.0, 101.9, 72.5, 70.9, 59.5, 56.9, 52.6, 32.9, 20.8 ppm; IR (KBr) ν 2106, 1753, 1739 cm^{-1}; HRMS m/z calcd for $C_{10}H_{15}N_3O_6$ $[M + Na]^+$ 296.0856, found 296.0863.

Methyl 2-*O*-Acetyl-3-(*tert*-butoxycarbonylamino)-3,4-dideoxy-β-D-*xylo*-hexopyranosiduronic Acid Methyl Ester (21). To a solution of compound **20** (21 mg, 0.075 mmol) in dried EtOAc (5 mL) was added 10% Pd/C (5 mg). The mixture was stirred under a H_2 atmosphere at 24 °C for 3 h. Boc_2O (49 mg, 0.23 mmol) and Et_3N (10 μL) were added to the mixture, and the reaction mixture was stirred under nitrogen at 24 °C for 16 h. After this time, the mixture was filtered and the organic solution was concentrated under reduced pressure and purified using flash column chromatography (silica gel, hexanes:EtOAc, 3:2), affording compound **21** (24 mg, 92%) as white crystals. **21**: R_f 0.45 (EtOAc:hexanes, 1:1); mp 156−157 °C (EtOAc/hexanes), (lit.[20] mp 158−160 °C); $[\alpha]_D$ = −25.1° (c = 0.65 in $CHCl_3$), (lit.[20] $[\alpha]_D$ = −26.2° (c = 0.65 in $CHCl_3$)); ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (s, 9H), 1.59−1.72 (m, 1H), 2.09 (s, 3H), 2.40−2.47 (br d, J = 13.18 Hz, 1H), 3.52 (s, 3H), 3.77 (s, 3H), 3.83−4.10 (br s, 1H), 4.14 (dd, J = 2.2, 11.5 Hz, 1H), 4.39 (d, J = 7.4 Hz, 1H), 4.63 (dd, J = 2.7, 7.4 Hz, 1H), 4.75 ppm (d, J = 8.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 169.6, 155.2, 102.2, 79.9, 72.6, 71.3, 57.0, 52.4, 50.5, 34.4, 28.2 (3×), 20.8 ppm; IR (KBr) ν 3362, 1741, 1689 cm^{-1}; HRMS m/z calcd for $C_{15}H_{25}NO_8$ $[M + Na]^+$ 370.1477, found 370.1487.

Methyl 2,3-Anhydro-6-*O*-(*tert*-butyldimethylsilyloxy)-4-deoxy-β-D-*ribo*-hexopyranoside (22). To a solution of compound **12** (298 mg, 1.15 mmol) in CH_2Cl_2 (11.5 mL, 0.1 M) was added purified *m*CPBA (775 mg, 3.46 mmol) at 0 °C. The mixture was stirred at 24 °C for 16 h, and saturated aqueous $NaHCO_3$ (10 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 8:1), affording compound **22** (221 mg, 70%) as a colorless oil. **22**: R_f 0.43 (hexanes:EtOAc, 6:1); $[\alpha]_D$ = −58.9° (c = 0.9 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.88 (s, 9H), 1.69−1.82 (m,

dx.doi.org/10.1021/jo201673w | J. Org. Chem. 2011, 76, 9687−9698

1H), 2.03−2.09 (m, 1H), 3.13 (d, J = 4.0 Hz, 1H), 3.36−3.37 (m, 1H), 3.54 (m, 3H), 3.57−3.59 (m, 1H), 3.60−3.68 (m, 2H), 4.70 ppm (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 98.9, 67.5, 65.7, 56.6, 53.4, 51.1, 27.1, 25.8, 18.3 (3×), −5.3 ppm (2×); IR (NaCl) ν 2928, 1096, 837 cm^{-1}; HRMS m/z calcd for $C_{13}H_{26}O_4Si$ $[M + Na]^+$ 297.1493, found 297.1492.

Methyl 6-*O*-(*tert*-Butyldimethylsilyloxy)-3,4-dideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranoside (24). Compound **22** (193 mg, 0.703 mmol) was dissolved in a commercial solution of dimethylamine (33% in ethanol, 7 mL, 0.1 M), and the mixture was stirred at 24 °C for 3 days. The mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography (silica gel, CH_2Cl_2:MeOH, 10:1), affording compound **24** (191 mg, 85%) as a colorless oil. **24**: R_f 0.26 (MeOH:CH_2Cl_2, 9:1); $[\alpha]_D$ = −11.5° (c = 0.57 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.90 (s, 9H), 1.17−1.29 (m, 1H), 1.78−1.84 (m, 1H), 2.30 (s, 6H), 2.51−2.60 (m, 1H), 2.84 (br s, 1H), 3.22 (dd, J = 7.5, 7.4 Hz, 1H), 3.55 (s, 3H), 3.45−3.61 (m, 2H), 3.76 (dd, J = 5.2, 5.5 Hz, 1H), 4.20 ppm (d, J = 7.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.9, 74.1, 70.1, 65.9, 65.1, 56.6, 40.3 (2×), 25.8 (3×), 23.5, 18.3, −5.3 ppm (2×); IR (NaCl) ν 2929, 1653, 1096 cm^{-1}; HRMS m/z calcd for $C_{15}H_{33}NO_4Si$ $[M + H]^+$ 320.2252, found 320.2258.

Methyl 2-*O*-Acetyl-6-*O*-(*tert*-butyldimethylsilyloxy)-3,4-dideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranoside (24-OAc). To a solution of compound **24** (134 mg, 0.432 mmol) in pyridine (15 mL) was added Ac_2O (7 mL). The mixture was stirred for 3 h at 24 °C, and water (20 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (1 × 10 mL) and brine (1 × 10 mL). The organic solution was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, CH_2Cl_2:MeOH, 20:1), affording compound **24-OAc** (156 mg, quantitative) as a colorless oil. **24-OAc**: R_f 0.37 (MeOH:CH_2Cl_2, 9:1); $[\alpha]_D$ = −20.3° (c = 1.2 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.89 (s, 9H), 1.26−1.41 (m, 1H), 1.83−1.89 (m, 1H), 2.08 (s, 3H), 2.28 (s, 6H), 2.74−2.83 (m, 1H), 3.46 (s, 3H), 3.43−3.53 (m, 1H), 3.57−3.62 (m, 1H), 3.74−3.79 (m, 1H), 4.24 (d, J = 7.4 Hz, 1H), 4.82 ppm (dd, J = 7.4, 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 103.1, 73.8, 70.8, 65.8, 62.9, 56.4, 40.5 (2×), 29.7, 25.8 (3×), 21.3, 18.3, −5.3 ppm (2×); IR (NaCl) ν 1749 cm^{-1}; HRMS m/z calcd for $C_{17}H_{35}NO_5Si$ $[M + H]^+$ 362.2357, found 362.2365.

Methyl 2-*O*-Acetyl-3,4-dideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranoside (25). To a solution of **24-OAc** (137 mg, 0.381 mmol) in THF (3.8 mL, 0.10 M) was added TBAF (1 M in THF, 0.763 mL, 0.763 mmol). The solution was stirred for 30 min at 24 °C and then concentrated under reduced pressure and purified by flash column chromatography (silica gel, CH_2Cl_2:MeOH, 10:1), affording compound **25** (76 mg, 81%) as a yellow oil. **25**: R_f 0.22 (MeOH:CH_2Cl_2, 9:1); $[\alpha]_D$ = −3.7° (c = 1.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40−1.69 (m, 1H), 1.73−1.75 (m, 1H), 2.07 (s, 3H), 2.25 (s, 6H), 2.75−2.85 (m, 1H), 3.13 (br s, 1H), 3.46 (s, 3H), 3.49−3.58 (m, 1H), 3.60−3.71 (m, 2H), 4.26 (d, J = 7.7 Hz, 1H), 4.78 ppm (dd, J = 7.4, 7.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 103.2, 73.7, 70.6, 65.1, 62.7, 56.7, 40.4 (2×), 24.6, 21.2 ppm; IR (NaCl) ν 3024, 1653, 1215, 1091, 776 cm^{-1}; HRMS m/z calcd for $C_{11}H_{21}NO_5$ $[M + H]^+$ 248.1493, found 248.1495.

(2*S*,6*R*)-3,6-Dihydro-6-methoxy-2*H*-pyran-2-carboxylic Acid Ethyl Ester (27). To a solution of (−)-(*S*)-BINOL (214 mg, 0.750 mmol) in CH_2Cl_2 (1 mL) was added a solution of Ti(O-*i*-Pr)$_4$ (106 mg, 0.375 mmol) in CH_2Cl_2 (0.5 mL). The mixture was heated under reflux for 1 h and cooled to to −30 °C. Freshly distilled ethyl glyoxylate **26** (382 mg, 3.75 mmol), dissolved in CH_2Cl_2 (0.5 mL), was added, followed by 1-methoxy-1,3-butadiene **9** (252 mg, 3.00 mmol) dissolved in CH_2Cl_2 (0.5 mL). The mixture was stirred for 2.5 h at −30 °C and then warmed to 24 °C. Aqueous saturated $NaHCO_3$ (20 mL) was added, and the aqueous layer was extracted with ether (5 × 30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. ^{1}H NMR of the crude product revealed presence of only one diastereoisomer. The residue was purified using flash column chromatography (silica gel, hexanes:Et_2O, 8:1), affording compound **27** (341 mg, 61%), isolated as a colorless oil. The optical purity (95%) was determined using a HPLC with a chiral column DNBPG ((covalent) Chiral 5 μm, Standard Analytical 4.6 × 250 mm, gradient of elution: MeOH:CH_3CN (5% H_2O), (0.05% TFA) (1:8) → MeOH:CH_3CN (5% H_2O), (0.05% TFA) (1:1), 1 mL/min, 30 °C, t_r **27** 12.4 min, t_r *ent*-**27** 12.9 min). **27**: R_f 0.29 (EtOAc:hexanes 1:4); $[\alpha]_D$ = −45.1° (c = 1.0 in $CHCl_3$), lit.[27] $[\alpha]_D$ = +45.6° (c = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 1H), 2.24−2.35 (m, 1H), 2.39−2.50 (m, 1H), 3.45 (s, 3H), 4.12−4.26 (m, 2H), 4.34 (dd, J = 5.2, 6.5 Hz, 1H), 4.98−5.00 (m, 1H), 5.64 (dq, J = 2.0, 10.3 Hz, 1H), 5.96−6.02 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 127.6, 125.9, 97.0, 69.4, 61.0, 55.4, 25.9, 14.0 ppm; HRMS m/z calcd for $C_9H_{14}O_4$ $[M + Na]^+$ 209.0784, found 209.0788.

Methyl 4-Deoxy-β-D-*ribo*-hexopyranosiduronic Acid Methyl Ester (28). To a solution of compound **27** (89 mg, 0.515 mmol) in an acetone/water mixture (4:1, 5 mL, 0.1 M) were added NMO (150 mg, 1.29 mmol) and OsO_4 (4% in water, 0.196 mL). The resulting solution was stirred at 24 °C for 16 h. A 10% aqueous solution of $NaHSO_3$ (5 mL) was added, the mixture was stirred for 5 min, and EtOAc (10 mL) was added. The mixture was extracted with EtOAc (5 × 10 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and comcentrated under reduced pressure. The residue was purified using flash column chromatography (hexanes:EtOAc 4:1), affording a yellow oil that was dissolved in MeOH (5 mL). A solution of 1 M NaOMe in MeOH was added until pH 9, and the mixture was stirred for 2 h. Acidic resin (IR-120) was added until pH 7, and the mixture was filtered, concentrated under reduced pressure, and purified using flash column chromatography (silica gel, hexanes:EtOAc, 4:1), affording compound **28** (68 mg, 64%) as a colorless oil. **28**: R_f 0.18 (EtOAc:hexanes, 4:1); $[\alpha]_D$ = −4.0° (c = 1.7 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.56 (d, J = 7.7 Hz, 1H), 4.50 (dd, J = 2.5, 11.5 Hz, 1H), 4.22 (br s, 1H), 3.76 (s, 3H), 3.54 (s, 3H), 3.48−3.44 (m, 1H), 3.14 (bs s, 1H), 3.05 (bs s, 1H), 2.22−2.15 (m, 1H), 1.91−1.81 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 101.6, 70.9, 69.5, 66.7, 57.2, 52.2, 33.9 ppm; IR (NaCl) ν 3234, 2937, 1735, 1094 cm^{-1}; HRMS m/z calcd for $C_8H_{14}O_6$ $[M + Na]^+$ 229.0683, found 229.0680.

Methyl 2-*O*-Acetyl-4-deoxy-β-D-*ribo*-hexopyranosiduronic Acid Methyl Ester (29). The same procedure was used as for the preparation of compound **14**. Compound **29** was purified using flash column chromatography (silica gel, hexanes:EtOAc, 3:1) and was isolated as a colorless oil (70%). **29**: R_f 0.45 (EtOAc:hexanes, 3:1); $[\alpha]_D$ = −1.9° (c = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00−2.07 (m, 1H), 2.12 (s, 3H), 2.11−2.19 (m, 1H), 2.46 (br s, 1H), 3.48 (s, 3H), 3.75 (s, 3H), 4.31 (br s, 1H), 4.52 (dd, J = 3.2, 9.4 Hz, 1H), 4.74−4.75 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 169.9, 99.5, 72.0, 69.3, 64.8, 56.9, 52.2, 33.1, 21.0 ppm; IR (NaCl) ν 3433, 3021, 1743, 1216, 1094, 775 cm^{-1}; HRMS m/z calcd for $C_{10}H_{16}O_7$ $[M + Na]^+$ 271.0788, found 271.0791.

Methyl 2,3-*O*-Isopropylidene-4-*O*-thiocarbonylimidazoyle-α-D-mannopyranosiduronic Acid Methyl Ester (33). To a solution of compound **32**[30] (817 mg, 3.12 mmol) in CH_2Cl_2 (31 mL, 0.10 M) were added thiocarbonyl diimidazole (1.85 g, 9.34 mmol) and DMAP (380 mg, 3.12 mmol). The mixture was stirred for 48 h at 24 °C and then concentrated under reduced pressure and purified using flash column chromatography (silica gel, hexanes:EtOAc, 3:2), affording compound **33** (731 mg, 63%) as a yellow oil. **33**: R_f 0.23 (EtOAc:hexanes, 1:1); $[\alpha]_D$ = +9.3° (c = 4.3 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 3H), 1.42 (s, 3H), 3.33 (s, 3H), 3.51 (s, 3H), 4.07 (d, J = 5.1 Hz, 1H), 4.27 (d, J = 8.9 Hz, 1H), 4.33−4.37 (m, 1H), 4.95 (s, 1H), 5.86−5.91 (m, 1H), 6.88 (br s, 1H), 7.49 (br s, 1H), 8.19 ppm (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.9, 167.4, 136.6, 130.5, 117.8, 110.3, 98.2, 77.2, 74.7, 74.0, 66.4, 55.6, 52.6, 26.9, 25.7 ppm; IR (NaCl) ν 2937, 1750, 1399 cm^{-1}; HRMS m/z calcd for $C_{15}H_{20}N_2O_7S$ $[M + H]^+$ 373.1064, found 373.1070.

Methyl 2,3-*O*-Isopropylidene-4-deoxy-α-D-*lyxo*-hexopyranosiduronic Acid Methyl Ester (34). To a solution of compound **33**

dx.doi.org/10.1021/jo201673w | J. Org. Chem. 2011, 76, 9687−9698

(727 mg, 1.95 mmol) in toluene (19 mL, 0.10 M) were added Bu_3SnH (10.34 mL, 39.02 mmol) and AIBN (64 mg, 0.39 mmol). The mixture was stirred under reflux for 1 h and then concentrated under reduced pressure. To this residue was added acetonitrile (20 mL) and hexanes (20 mL). The acetonitrile layer was washed with hexanes (2 × 15 mL), concentrated under reduced pressure, and purified using flash column chromatography (silica gel, hexanes:EtOAc, 2:1), affording compound **34** (298 mg, 62%) as a colorless oil. **34**: R_f 0.66 (EtOAc:hexanes, 2:1); $[\alpha]_D$ = +37.0° (*c* = 1.6 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (s, 3H), 1.45 (s, 3H), 2.02−2.12 (m, 1H), 2.29 (dt, *J* = 5.0, 19.0 Hz, 1H), 3.42 (s, 3H), 3.75 (s, 3H), 3.94 (dd, *J* = 1.4, 6.2 Hz, 1H), 4.29 (dd, *J* = 5.1, 7.4 Hz, 1H), 4.36 (dd, *J* = 6.6, 11.6 Hz, 1H), 4.91 ppm (d, *J* = 1.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 109.4, 99.1, 73.2, 69.8, 66.1, 55.7, 52.2, 28.8, 27.0, 25.5 ppm; IR (NaCl) ν 2938, 1734, 1559, 1090 cm^{-1}; HRMS *m*/*z* calcd for $C_{11}H_{18}O_6$ $[M + Na]^+$ 269.0996, found 269.0997.

Methyl 4-Deoxy-α-D-*lyxo*-hexopyranosiduronic Acid Methyl Ester (35). Compound **34** (250 mg, 1.02 mmol) was dissolved in a mixture of AcOH/H_2O (10 mL, 3/2, 0.10 M) and heated at 60 °C for 6 h. The solution was concentrated under reduced pressure and purified using flash column chromatography (silica gel, hexanes:EtOAc, 1:2), affording compound **35**[31] (157 mg, 75%) as a colorless oil. **35**: R_f 0.18 (EtOAc:hexanes, 2:1); $[\alpha]_D$ = +38.1° (*c* = 3.4 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78−1.92 (m, 1H), 1.98−2.03 (m, 1H), 3.37 (s, 3H), 3.64−3.52 (m, 3H), 3.74 (s, 3H), 3.95−3.99 (m, 1H), 4.29 (dd, *J* = 2.6, 11.3 Hz, 1H), 4.84 ppm (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 101.5, 68.6, 67.3, 65.2, 55.4, 52.3, 31.0 ppm; IR (NaCl) ν 3370, 2922, 1734, 1098 cm^{-1}; HRMS *m*/*z* calcd for $C_8H_{14}O_6$ $[M + Na]^+$ 229.0683, found 229.0683.

Methyl 4-Deoxy-2,3-di-*O*-pivaloyl-α-D-*lyxo*-hexopyranosiduronic Acid Methyl Ester (36). From **35**: to a solution of compound **35** (140 mg, 0.679 mmol) in pyridine (6.8 mL, 0.10 M) were added PivCl (0.418 mL, 3.40 mmol) dropwise followed by DMAP (2 mg). The mixture was stirred at 60 °C for 16 h and then cooled to 24 °C. EtOAc (15 mL) was added, and the mixture was washed with aqueous 1 M HCl (3 × 10 mL), saturated aqueous $NaHCO_3$ (3 × 10 mL), and brine (3 × 10 mL). The organic solution was dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified using flash column chromatography (hexanes:EtOAc, 5:1), affording compound **36** (231 mg, 91%) as a colorless oil. From **38**: to a solution of compound **38** (112 mg, 0.302 mmol) in EtOAc (6 mL, 0.05 M) was added 10% Pd/C (11 mg), and the mixture was stirred under an H_2 atmosphere for 16 h at 24 °C. The mixture was filtered over Celite, concentrated under reduced pressure, and purified using flash column chromatography (silica gel, hexanes:EtOAc, 5:1), affording compound **36** (107 mg, 95%). **36**: R_f 0.23 (EtOAc:hexanes, 1:5); $[\alpha]_D$ = +34.7° (*c* = 1.8 in $CHCl_3$), (lit.[29] $[\alpha]_D$ = +33.7° (*c* = 1.8 in MeOH)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.14 (s, 9H), 1.86−1.98 (m, 1H), 2.08−2.12 (m, 1H), 3.32 (s, 3H), 3.70 (s, 3H), 4.35−4.39 (m, 1H), 4.74 (br s, 1H), 4.95 (br s, 1H), 5.14−5.19 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 177.0, 170.3, 99.4, 67.1, 67.0, 66.1, 55.4, 52.3, 38.8, 38.5, 27.0, 26.9 ppm (6×); IR (NaCl) ν 2960, 1762, 1734, 1482, 1133 cm^{-1}; HRMS *m*/*z* calcd for $C_{18}H_{30}O_8$ $[M + Na]^+$ 397.1833, found 397.1838.

Methyl 2,3,4-Tri-*O*-pivaloyl-α-D-mannopyranosiduronic Acid Methyl Ester (37). To a solution of methyl α-D-mannopyranosiduronic acid methyl ester[38] (933 mg, 4.20 mmol) in pyridine (42 mL, 0.10 M) were added PivCl (10.3 mL, 84.0 mmol) dropwise followed by DMAP (10 mg). The mixture was stirred at 60 °C for 16 h and then cooled to 24 °C. EtOAc (50 mL) was added, and the solution was washed with aqueous 1 M HCl (3 × 30 mL), saturated aqueous $NaHCO_3$ (3 × 30 mL), and brine (3 × 30 mL). The organic solution was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc, 4:1) afforded compound **37** (1.714 g, 86%) as a colorless oil. **37**: R_f 0.73 (EtOAc:hexanes, 1:1); $[\alpha]_D$ = +20.7° (*c* = 7.3 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 3H), 1.13 (s, 3H), 1.23 (s, 3H), 3.43 (m, 3H), 3.72 (s, 3H), 4.27−4.30 (m, 1H), 4.76 (d, *J* = 2.0 Hz, 1H), 5.18 (t, *J* = 2.1 Hz, 1H), 5.39−5.42 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 176.8, 176.7, 168.2, 98.8, 69.7, 68.8, 68.3, 66.6, 55.8, 52.6, 38.6 (3×), 27.0−26.9 ppm (9×); IR (NaCl) ν 2972, 1742, 113 cm^{-1}; HRMS *m*/*z* calcd for $C_{23}H_{38}O_{10}$ $[M + Na]^+$ 497.2357, found 497.2361.

Methyl 4-Deoxy-2,3-di-*O*-pivaloyl-L-*erythro*-hex-4-enopyranosiduronic Acid Methyl Ester (38). To a solution of compound **37** (137 mg, 0.289 mmol) in CH_2Cl_2 (2.8 mL, 0.10 M) was added DBU (66 μL, 0.44 mmol) at 0 °C. The mixture was stirred for 16 h at 24 °C and then washed with saturated aqueous NH_4Cl (3 × 2 mL) and water (3 × 2 mL). The organic solution was dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified using flash column chromatography (silica gel, hexanes:EtOAc, 5:1), affording compound **38** (112 mg, quantitative) as a colorless oil. **38**: R_f 0.28 (EtOAc:hexanes, 1:5); $[\alpha]_D$ = +113.4° (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.44 (s, 9H), 3.75 (s, 9H), 4.99 (d, *J* = 2.7 Hz, 1H), 5.14 (br s, 1H), 5.56 (t, *J* = 2.4 Hz, 1H), 5.91 ppm (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 177.1, 162.0, 141.2, 108.9, 99.1, 64.0, 63.5, 56.5, 52.4, 38.7 (2×), 26.9 ppm (6×); IR (NaCl) ν 2972, 1740, 1734, 1481 cm^{-1}; HRMS *m*/*z* calcd for $C_{18}H_{28}O_8$ $[M + Na]^+$ 395.1676, found 395.1683.

1-*O*-Acetyl-4-deoxy-2,3-di-*O*-pivaloyl-α-D-*lyxo*-hexopyranosyluronic Acid Methyl Ester (39). From **36**: compound **36** (80 mg, 0.21 mmol) was dissolved in a Ac_2O/AcOH/H_2SO_4 mixture (1 mL, 35/15/1 v/v, 0.2 M) and stirred at 24 °C for 16 h. CH_2Cl_2 (10 mL) was added, and the mixture was washed with saturated aqueous $NaHCO_3$ (3 × 5 mL) and water (3 × 5 mL). The organic solution was dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified using flash column chromatography (silica gel, hexanes:EtOAc, 3:1). Anomeric acetate was isolated (71 mg, 83%) as a 6:1 mixture (α:β) as an amorphous yellow solid. This mixture was recrystallized in pentane, affording compound **39** (57 mg, 67%) as white crystals. From **45**: using the same procedure as described above (70%). **39**: R_f 0.13 (EtOAc:hexanes, 1:4); mp 104−105 °C (pentane), (lit.[29] mp 104−105 °C); $[\alpha]_D$ = +38.0° (*c* = 0.2 in MeOH) (lit.[29] $[\alpha]_D$ = +37.8° (*c* = 0.18 in MeOH)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (s, 9H), 1.26 (s, 9H), 2.14 (s, 3H), 2.22−2.24 (m, 1H), 2.26−2.29 (m, 1H), 3.80 (s, 3H), 4.55 (dd, *J* = 3.1, 11.6 Hz, 1H), 5.10 (t, *J* = 2.4 Hz, 1H), 5.31−5.37 (m, 1H), 6.21 ppm (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 176.9, 169.6, 168.0, 91.3 ($^1J_{C\text{-}1/H\text{-}1}$ (*J* = 177.8 Hz)), 69.3, 66.1, 66.0, 52.6, 38.9, 38.7, 28.5, 27.1−27.0 (6×), 20.8 ppm; IR (KBr) ν 2972, 1735, 1140 cm^{-1}; HRMS *m*/*z* calcd for $C_{19}H_{30}O_9$ $[M + Na]^+$ 425.1782, found 425.1786.

1-Bromo-1,4-dideoxy-2,3-di-*O*-pivaloyl-α-D-*lyxo*-hexopyranosyluronic Acid Methyl Ester (40). To a solution of compound **39** (144 mg, 0.358 mmol) in CH_2Cl_2 (3.5 mL, 0.10 M) was added a commercial solution of HBr 33% in acetic acid (3.5 mL), and the mixture was stirred for 1 h at 24 °C. The mixture was poured into a beaker containing saturated aqueous $NaHCO_3$ (10 mL). The organic solution was washed with saturated aqueous $NaHCO_3$ (3 × 10 mL) and brine (3 × 10 mL) and then dried over Na_2SO_4, filtered, and concentrated under reduced pressure, affording compound **40** (152 mg, quantitative) as white needles. **40**: R_f 0.46 (EtOAc:hexanes, 1:5); mp 93−94 °C (EtOAc/hexanes); $[\alpha]_D$ = +113.7° (*c* = 0.8 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (s, 9H), 1.25 (s, 9H), 2.04−2.17 (m, 1H), 2.35−2.40 (m, 1H), 3.82 (s, 3H), 4.69 (dd, *J* = 2.3, 12.4 Hz, 1H), 5.28 (br s, 1H), 5.64−5.72 (m, 1H), 6.40 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 176.8, 168.7, 84.2, 70.9, 69.5, 65.1, 52.7, 39.0, 38.7, 28.5, 27.1−27.0 ppm (6×); IR (KBr) ν 2968, 1771, 1735, 1138 cm^{-1}; HRMS *m*/*z* calcd for $C_{17}H_{27}BrO_7$ $[M + Na]^+$ 445.0832, found 445.0840.

(2*S*,6*S*)-6-(*tert*-Butyldimethylsilyloxy)-2-isopropoxy-2,5-dihydropyran (41). To a solution of compound **12** (114 mg, 0.441 mmol) in *i*-PrOH (4.4 mL, 0.10 M) was added PPTS (11 mg, 0.044 mmol). The mixture was stirred for 24 h at 24 °C and then concentrated under reduced pressure and purified using flash column chromatography (silica gel, hexanes:EtOAc, 7:1), affording compound **41** (125 mg, 99%) as a colorless oil. **41**: R_f 0.82 (EtOAc:hexanes, 1:1); $[\alpha]_D$ = −24.1° (*c* = 1.1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.85 (s, 9H), 1.12 (d, *J* = 6.2 Hz, 3H), 1.19 (d, *J* = 6.2 Hz, 3H), 1.91−2.03 (m, 2H), 3.55−3.69 (m, 2H), 3.95−4.03 (m, 2H), 5.05 (br s, 1H), 5.64−5.69 (m, 1H), 5.93−5.98 ppm (m, 1H); ^{13}C

dx.doi.org/10.1021/jo201673w | J. Org. Chem. 2011, 76, 9687−9698

NMR (75 MHz, $CDCl_3$) δ 128.3, 126.0, 92.7, 69.1, 67.0, 66.1, 26.9, 25.9 (3×), 23.8, 21.8, 18.4, −5.3 ppm (2×); IR (NaCl) ν 2954, 1403, 1130 cm^{-1}; HRMS m/z calcd for $C_{15}H_{30}O_3Si$ $[M + Na]^+$ 309.1856, found 309.1859.

Isopropyl 6-*O*-(*tert*-Butyldimethylsilyloxy)-4-deoxy-α-D-*lyxo*-hexopyranoside (42). The same procedure was used as for the preparation of compound **13**. Compound **42** was purified using flash column chromatography (silica gel, hexanes:EtOAc, 1:1) as a colorless oil (86%). **42**: R_f 0.33 (EtOAc:hexanes, 1:1); $[\alpha]_D$ = +25.1° (c = 1.1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.89 (s, 9H), 1.13 (d, J = 6.1 Hz, 3H), 1.19 (d, J = 6.3 Hz, 3H), 1.45−1.57 (m, 1H), 1.75−1.81 (m, 1H), 2.51 (br s, 1H), 3.58 (dd, J = 4.9, 10.6 Hz, 1H), 3.65−3.71 (m, 2H), 3.79−3.87 (m, 1H), 3.88−3.96 (m, 1H), 3.96−4.03 (m, 1H), 4.96 ppm (d, J = 1.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 98.1 ($^1J_{C\text{-}1,H\text{-}1}$ (J = 168.3 Hz)), 69.7, 68.9, 68.7, 66.0, 65.7, 31.1, 25.9 (3×), 23.2, 21.2, 18.3, −5.3, −5.4 ppm; IR (NaCl) ν 3490, 1745 cm^{-1}; HRMS m/z calcd for $C_{15}H_{32}O_5Si$ $[M + Na]^+$ 343.1911, found 343.1913.

Isopropyl 6-*O*-(*tert*-Butyldimethylsilyloxy)-4-deoxy-2,3-di-*O*-pivaloyl-α-D-*lyxo*-hexopyranoside (43). The same procedure was used as for the preparation of compound **36**. Compound **43** was purified using flash column chromatography (silica gel, hexanes:Et_2O, 9:1) and isolated as a colorless oil (55%). **43**: R_f 0.62 (EtOAc:hexanes, 1:1); $[\alpha]_D$ = +29.9° (c = 2.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.87 (s, 9H), 1.12 (s, 9H), 1.22 (s, 9H), 1.17−1.24 (m, 6H), 1.72−1.78 (m, 2H), 3.58−3.71 (m, 2H), 3.84−3.99 (m, 2H), 4.88−4.89 (m, 1H), 4.94−4.95 (m, 1H), 5.22−5.29 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 177.3, 96.3, 69.4, 68.8, 68.4, 67.2, 65.9, 38.8, 38.6, 28.2, 27.1 (3×), 26.9 (3×), 26.4, 25.8 (3×), 23.2, 21.3, −5.4 ppm (2×); IR (NaCl) ν 2960, 1735, 1140, 838 cm^{-1}; HRMS m/z calcd for $C_{25}H_{48}O_7Si$ $[M + Na]^+$ 511.3062, found 511.3065.

Isopropyl 4-Deoxy-2,3-di-*O*-pivaloyl-α-D-*lyxo*-hexopyranoside (44). The same procedure was used as for the synthesis of compound **16**. Compound **44** was purified using flash column chromatography (silica gel, hexanes:EtOAc, 3:1) and isolated as a colorless oil (70%). **44**: R_f 0.22 (EtOAc:hexanes, 1:3); $[\alpha]_D$ = +28.4° (c = 2.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (s, 9H), 1.14−1.20 (m, 6H), 1.23 (s, 9H), 1.70−1.76 (m, 1H), 1.81−1.93 (m, 1H), 2.06 (br s, 1H), 3.53−3.59 (m, 1H), 3.66−3.70 (m, 1H), 3.84−3.93 (m, 1H), 3.98−4.05 (m, 1H), 4.90 (s, 1H), 4.96 (br s 1H), 5.25−5.31 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 177.3, 96.2, 69.7, 68.4, 68.3, 66.9, 65.3, 38.9, 38.6, 27.5, 27.1 (3×), 27.0 (3×), 23.2, 21.4 ppm; IR (NaCl) ν 3510, 2974, 1734, 1482, 1149 cm^{-1}; HRMS m/z calcd for $C_{19}H_{34}O_7$ $[M + Na]^+$ 397.2197, found 397.2194.

Isopropyl 4-Deoxy-2,3-di-*O*-pivaloyl-α-D-*lyxo*-hexopyranosiduronic Acid Methyl Ester (45). From **44**: using the same procedure as for the synthesis of compound **17**. Compound **45** was purified using flash column chromatography (silica gel, hexanes:EtOAc, 5:1) and isolated as a yellow oil (66%). From **47**: using the same procedure as for the synthesis of compound **36** (83%). **45**: R_f 0.51 (EtOAc:hexanes, 1:3); $[\alpha]_D$ = +39.4° (c = 1.7 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18−1.23 (m, 6H), 1.16 (s, 9H), 1.25 (s, 9H), 1.96−2.08 (m, 1H), 2.19−2.26 (m, 1H), 3.80 (s, 3H), 3.92−4.00 (m, 1H), 4.53 (dd, J = 2.8, 11.8 Hz, 1H), 4.98−4.99 (m, 1H), 5.06 (d, J = 2.0 Hz, 1H), 5.28−5.35 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 177.2, 170.7, 96.5, 70.4, 68.0, 67.1, 66.4, 52.3, 38.9, 38.6, 28.8, 27.1 (3×), 27.0 (3×), 23.2, 21.1 ppm; IR (NaCl) ν 3510, 2974, 1734, 1132 cm^{-1}; HRMS m/z calcd for $C_{20}H_{34}O_8$ $[M + Na]^+$ 425.2146, found 425.2149.

Isopropyl 4-Deoxy-α-D-*lyxo*-hexopyranosiduronic Acid Methyl Ester (47). To a solution of compound **46**[39] (90 mg, 0.42 mmol) in an acetone/water mixture (4:1, 4.2 mL, 0.10 M) were added NMO (122 mg, 1.04 mmol) and OsO_4 (4% in water, 16 μL, 0.025 mmol). The resulting solution was stirred at 24 °C for 16 h, and then 10% aqueous $NaHSO_3$ (5 mL) was added and the mixture was stirred for 5 min. The mixture was extracted with EtOAc (5 × 10 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified using flash column chromatography (silica gel, hexanes:EtOAc 1:1) and then dissolved in MeOH (4.2 mL, 0.10 M). A 1 M solution of NaOMe in MeOH was added until pH 9, and the mixture was stirred for 2 h at 24 °C. Acidic resin (IR-120) was added until pH 7, and the mixture was filtered and concentrated under reduced pressure. The residue was purified using flash column chromatography (silica gel, hexanes:EtOAc, 1:1), affording compound **47** (66 mg, 67%) as a colorless oil. **47**: R_f 0.19 (EtOAc:hexanes, 2:1); $[\alpha]_D$ = +12.2° (c = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (d, J = 6.0 Hz, 3H), 1.25 (d, J = 6.2 Hz, 3H), 1.89−1.91 (m, 1H), 2.04−2.09 (m, 1H), 2.76 (br s, 1H), 3.59−3.73 (m, 2H), 3.80 (s, 3H), 3.82−4.01 (m, 3H), 5.10 ppm (d, J = 1.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 98.3, 69.9, 69.3, 68.7, 67.4, 52.4, 34.3, 23.2, 21.4 ppm; HRMS m/z calcd for $C_{10}H_{18}O_6$ $[M + Na]^+$ 257.0996, found 257.1001.

1-[3-(Cyanomethyl)indol-1-yl]-1,4-dideoxy-2,3-di-*O*-pivaloyl-α-D-*lyxo*-hexopyranosyluronic Acid Methyl Ester (48). To a solution of **39** (41 mg, 0.097 mmol) in CH_2Cl_2 (0.9 mL, 0.1 M) at 0 °C was added $BF_3{\cdot}OEt_2$ (240 μL, 0.194 mmol). The mixture was stirred for 4 h while being warmed to 24 °C. Compound **30** (61 mg, 0.39 mmol) in CH_2Cl_2 (0.2 mL) was added, and the mixture was stirred for 16 h at 24 °C. CH_2Cl_2 (10 mL) was added, and the mixture was washed with saturated aqueous $NaHCO_3$ (3 × 5 mL), water (3 × 5 mL), and brine (3 × 5 mL). The organic solution was dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified using flash column chromatography (silica gel, hexanes:EtOAc, 4:1), affording compound **48** (38 mg, 78%) as a colorless amorphous solid. **48**: R_f 0.28 (EtOAc:hexanes, 1:2); $[\alpha]_D$ = +19.8° (c = 0.6 in $CHCl_3$), (lit.[29] $[\alpha]_D$ = +18.7° (c 0.48, MeOH)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (s, 9H), 1.27 (s, 9H), 2.53−2.57 (m, 2H), 3.78 (s, 3H), 3.89 (s, 3H), 4.66 (dd, J = 2.3, 6.5 Hz, 1H), 5.40 (dd, J = 2.9, 9.7 Hz, 1H), 5.68−5.71 (m, 1H), 6.58 (d, J = 9.7 Hz, 1H), 7.19−7.25 (m, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.72 ppm (d, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 176.7, 171.5, 137.4, 126.7, 123.5 (2×), 122.3, 121.0 (2×), 118.4 (2×), 110.2, 70.6, 69.0, 67.2, 52.4, 38.9, 38.6, 31.2, 27.0 (3×), 26.9 (3×), 14.3 ppm; IR (NaCl) ν 2972, 1740, 1465, 1150 cm^{-1}; HRMS m/z calcd for $C_{27}H_{34}N_2O_7$ $[M + Na]^+$ 521.2258, found 521.2249.

1-[3-(Carbamoylmethyl)indol-1-yl]-1,4-dideoxy-2,3-di-*O*-pivaloyl-α-D-*lyxo*-hexopyranosyluronic Acid Methyl Ester (49). To a solution of compound **48** (27 mg, 0.054 mmol) in AcOH (2.7 mL, 0.020 M) was added $Ni(OAc)_2{\cdot}4H_2O$ (80 mg, 0.32 mmol). The mixture was stirred under reflux for 20 h and then cooled to 24 °C. $CHCl_3$ (5 mL) was added, and the solution was washed with saturated aqueous $NaHCO_3$ (2 × 1 mL), dried over Na_2SO_4, filtered, and purified using flash column chromatography (silica gel, EtOAc), affording compound **49** (19 mg, 67%) as a light brown solid. **49**: R_f 0.42 (EtOAc); mp 55−56 °C (EtOAc/hexanes); $[\alpha]_D$ = +0.6° (c = 0.9 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.72 (s, 9H), 1.28 (s, 9H), 2.47−2.64 (m, 2H), 3.69 (s, 2H), 3.89 (s, 3H), 4.69 (d, J = 6.4 Hz, 1H), 5.36 (dd, J = 2.7, 9.5 Hz, 1H), 5.48 (br s, 1H), 5.65 (d, J = 2.9 Hz, 1H), 5.85 (br s, 1H), 6.55 (d, J = 9.5 Hz, 1H), 7.15−7.22 (m, 2H), 7.30 (t, J = 7 Hz, 1H), 7.53−7.59 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 176.6, 173.8, 171.4, 137.2, 127.4, 123.1, 123.0, 120.7 (2×), 118.9 (2×), 109.6, 70.5, 69.6, 67.1, 52.3, 38.9, 38.4, 31.2, 29.6, 27.0 (3×), 26.4 ppm (3×); IR (KBr) ν 2960, 2923, 1740, 1735, 1154, 1110 cm^{-1}; HRMS m/z calcd for $C_{27}H_{36}N_2O_8$ $[M + Na]^+$ 539.2364, found 539.2365.

1-[3-(Carbamoylmethyl)indol-1-yl]-1,4-dideoxy-α-D-*lyxo*-hexopyranosyluronic Acid Methyl Ester (Neosidomycin, 5). To a solution of compound **49** (40 mg, 0.077 mmol) in MeOH (0.77 mL, 0.10 M) was added a 1 M solution of NaOMe in MeOH until pH 9. The mixture was stirred at 24 °C for 4 days, and then acidic resin (IR-120) was added until pH 7. The mixture was filtered, concentrated under reduced pressure, and purified using flash column chromatography (silica gel, CH_2Cl_2:MeOH, 9:1), affording 25 mg of starting material **49** and neosidomycin **5** (9 mg, 35%), isolated as an amorphous brown solid (97% brsm). **5**: R_f 0.29 (MeOH:CH_2Cl_2, 1:9); mp 92−95 °C (EtOH), (lit. mp 93−103 °C); $[\alpha]_D$ = +50.3° (c = 0.5 in MeOH), (lit.[5c] $[\alpha]_D$ = +51.0° (c = 0.48 in MeOH)); ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 2.26−2.30 (m, 1H), 2.50 (dd, J = 3.2, 14.0 Hz, 1H), 2.78 (br s, 2H, D_2O exchangeable), 3.58 (s, 2H), 3.75 (s, 3H), 4.18−4.16 (m, 1H), 4.29 (br s, 1H), 4.44 (d, J = 6.9 Hz, 1H), 6.15 (br

s, 1H, D_2O exchangeable), 6.42 (d, J = 9.2 Hz, 1H), 6.58 (br s, 1H, D_2O exchangeable), 7.07 (t, J = 7.5 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H), 7.43 (s, 1H), 7.56 (d, J = 7.7 Hz, 1H), 7.78 ppm (d, J = 8.2 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 177.7, 174.3, 139.1, 129.6, 125.2, 123.2, 121.1, 119.5, 111.9, 110.9, 79.9, 71.4, 70.5, 69.0, 52.4, 35.0, 33.3 ppm; IR (KBr) ν 2960, 2923, 1740, 1735, 1154, 1110 cm^{-1}; HRMS m/z calcd for $C_{17}H_{20}N_2O_6$ $[M + Na]^+$ 371.1214, found 371.1216.

■ ASSOCIATED CONTENT

Supporting Information

Text giving additional experimental details and figures giving ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*roy.rene@uqam.ca

■ ACKNOWLEDGMENTS

This work was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC) for a Canadian Research Chair in Therapeutic Chemistry to R.R. We are also grateful to the FQRNT (Québec) for a postgraduate and postdoctoral fellowship to D.G. Isabelle Rhéault (Plateforme analytique pour molécules organiques, UQÀM) is acknowledged for high-resolution mass spectra, along with Stephen Hanessian from Université de Montréal for helpful discussions.

■ REFERENCES

(1) For reviews on the de novo synthesis of carbohydrates: (a) Vogel, P.; Robina, I. In *Glycoscience*; Vol. 2, Fraser-Reid, B., Tatsuta, K, Thiem, J., Eds.; Springer: Berlin, 2001; pp 1023−1174. (b) Hudlicky, T.; Entwistle, D. A.; Pitzer, K. K.; Thorpe, A. *Chem. Rev.* **1996**, *96*, 1195−1220. (c) Schmidt, R. R. *Pure Appl. Chem.* **1987**, *59*, 415−424. (d) Jurczak, J. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Dekker: New York, 1997; pp 595−614. (e) Zamojski, A. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Dekker: New York, 1997; pp 615−636. (f) Ager, D. J.; East, M. B. *Tetrahedron* **1993**, *49*, 5683−5765. (g) Ager, D. J.; East, M. B. *Tetrahedron* **1992**, *48*, 2803−2894. (h) Fang, J.-M.; Lin, C. H.; Bradshaw, C. W.; Wong, C.-H. *J. Chem. Soc., Perkin Trans. 1* **1995**, *8*, 967−978. (i) Limbach, M. *Chem. Biodiv.* **2005**, *2*, 825−836. (j) Roush, W. R., Ed. *Trends in Synthetic Carbohydrate Chemistry*; American Chemical Society: Washington, DC, 1989; Vol. *386*, pp 242−277. (k) Yu, X.; O'Doherty, G. A. *ACS Symp. Ser.* **2008**, *990*, 3−28. (l) Mlynarski, J.; Gut, B. *Chem. Soc. Rev.* **2012**, DOI: 10.1039/C1CS15144D.

(2) For reviews on the de novo synthesis of deoxy-carbohydrates: (a) Hanessian, S. *Carbohydr. Chem.* **1966**, *21*, 143−207. (b) De Lederkremer, R. M.; Marino, C. *Adv. Carbohydr. Chem. Biochem.* **2007**, *61*, 143−216. (c) Kirschning, A.; Jesberg, M.; Schoning, K.-U. *Synthesis* **2001**, 507−540. (d) Zamojski, A.; Banaszek, A.; Grynkiewicz, G. *Adv. Carb. Chem. Biochem.* **1982**, *40*, 1−129. (e) McGarvey, G. J.; Kimura, M.; Oh, T.; Williams, M. J. *J. Carbohydr. Chem.* **1984**, *3*, 125−188.

(3) (a) Ritter, T. K.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2001**, *40*, 3508−3533. (b) Wong, C.-H.; Bryan, M. C.; Nyffeler, P. T.; Liu, H.; Chapman, E. *Pure Appl. Chem.* **2003**, *75*, 179−186.

(4) (a) Isono, K. J. *Antibiotics* **1988**, *41*, 1711−1739. (b) Isono, K. *Pharmacol. Ther.* **1991**, *52*, 269−286.

(5) (a) Schumacher, R. W.; Harrigan, B. L.; Davidson, B. S. *Tetrahedron Lett.* **2001**, *42*, 5133−5135. (b) Ito, T.; Ohba, K.; Koyama, M.; Sezaki, M.; Tohymaya, H.; Shomura, T.; Fukuyasa, H.; Kazuno, Y.; Niwa, T.; Kojima, M.; Niida, T. *J. Antibiot.* **1984**, *8*, 931−934. (c) Furuta, R.; Naruto, S.; Tamura, A.; Yokogawa, K. *Tetrahedron Lett.* **1979**, *19*, 1701−1704.

(6) For selected examples: (a) Inanaga, J.; Katsuki, J.; Yamaguchi, M. *Chem. Lett.* **1991**, 1025. (b) Withers, S. C.; Percival, M. D.; Street, I. P. *Carbohydr. Res.* **1989**, *187*, 43−66. (c) Patroni, J. J.; Stick, R. V.; Engelhardt, L. M.; White, A. H. *Aust. J. Chem.* **1986**, *39*, 699−711. (d) Barette, E. P.; Goodman, L. *J. Org. Chem.* **1984**, *49*, 176−178. (e) Barton, D. H.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574−1585. (f) Hedgley, J.; Meresz, O.; Overend, W. G. *J. Chem. Soc. C* **1967**, 888−894. (g) Rasmussen, J. R. *J. Org. Chem.* **1980**, *45*, 2725−2727. (h) Blattner, R.; Ferrier, R. J.; Tyler, P. C. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1535−1539.

(7) (a) Haylock, C. H.; Slesser, K. N. *Can. J. Biochem.* **1973**, *51*, 969−971. (b) Kucar, S.; Zemek, J.; Zamocky, J. *Chem. Zvesti* **1982**, *36*, 241−244.

(8) (a) Guérard, C.; Alphand, V.; Archelas, A.; Demuynck, C.; Hecquet, L.; Furstoss, R.; Bolte, J. *Eur. J. Org. Chem.* **1999**, 3399−3402. (b) André, C.; Guérard, C.; Hecquet, L.; Demuynck, C.; Bolte, J. *J. Mol. Catal. B* **1998**, *5*, 113−118.

(9) Miura, T.; Kajimoto, T. *Chirality* **2001**, *13*, 577−580.

(10) Fronza, G.; Fuganti, C.; Grasselli, P.; Servi, S. *J. Org. Chem.* **1987**, *52*, 2086−2089.

(11) (a) Danishefsky, S. J.; Kerwin, J. F. Jr.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358−360. (b) Danishefsky, S. J.; Kato, N.; Askin, D.; Kerwin, J. F. Jr. *J. Am. Chem. Soc.* **1982**, *104*, 360−362. (c) Danishefsky, S. J.; Kerwin, J. F. Jr. *J. Org. Chem.* **1982**, *47*, 1597−1598. (d) Kubler, D. G. *J. Org. Chem.* **1962**, *27*, 1435−1436. (e) Konowal, A.; Jurczak, J.; Zamojski, A. *Rocz. Chem.* **1968**, *42*, 2045−2059. (f) Shavrygina, O. A.; Makin, S. M. *Zh. Org. Khim.* **1966**, *2*, 1354−1357. (g) Shavrygina, O. A.; Jablonovskaya, S. D.; Makin, S. M. *Zh. Org. Khim.* **1969**, *5*, 775−778. (h) Zamojski, A.; Konowal, A.; Jurcak, J. *Rocz. Chem.* **1970**, *44*, 1981−1986. (i) Banaszek, A.; Zamojski, A. *Rocz. Chem.* **1971**, *45*, 391−403. (j) Konowal, A.; Zamojski, A. *Rocz. Chem.* **1971**, *45*, 859−868. (k) Srivastava, R. M.; Brown, R. K. *Can. J. Chem.* **1971**, *49*, 1339−1342. (l) Murray, T. P.; Singh, U. P.; Brown, R. K. *Can. J. Chem.* **1971**, *49*, 2132−2138. (m) Hu, Y.-J.; Huang, X.-D.; Yao, Z.-J.; Wu, Y.-L. *J. Org. Chem.* **1998**, *63*, 2456−2461.

(12) Boger, D. L.; Robarge, K. D. *J. Org. Chem.* **1988**, *53*, 5793−5796.

(13) Fattori, D.; De Guchteneere, E.; Vogel, P. *Tetrahedron Lett.* **1989**, *30*, 7415−7418.

(14) Caputo, R.; De Nisco, M.; Festa, P.; Guaragna, A.; Palumbo, G.; Pedatella, S. *J. Org. Chem.* **2004**, *69*, 7033−7037.

(15) (a) Ahmed, M. Md.; Berry, B. P.; Hunter, T. J.; Tomcik, D. J.; O'Doherty, G. A. *Org. Lett.* **2005**, *7*, 745−748. (b) Ahmed, M. Md.; O'Doherty, G. A. *Carbohydr. Res.* **2006**, *341*, 1505−1521.

(16) (a) Pellissier, H. *Tetrahedron* **2009**, *65*, 2839−2877. (b) Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558−3588. (c) Marco, A. J.; Carda, M.; Murga, J.; Falomir, E. *Tetrahedron* **2007**, *63*, 2929−2958.

(17) Taylor, M. S.; Jacobsen, E. N. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5368−5373.

(18) (a) Chabre, Y. M.; Giguère, D.; Blanchard, B.; Rodrigue, J.; Rocheleau, S.; Neault, M.; Rauthu, S.; Papadopoulos, A.; Arnold, A. A.; Imberty, A.; Roy, R. *Chem. Eur. J.* **2011**, *17*, 6545−6562. (b) Giguère, D.; Bonin, M.-A.; Cloutier, P.; St-Pierre, C.; Sato, S.; Roy, R. *Bioorg. Med. Chem.* **2008**, *16*, 7811−7823. (c) Giguère, D.; Patnam, R.; Bellefleur, M.-A.; St-Pierre, C.; Sato, S.; Roy, R. *Chem. Commun.* **2006**, 2379−2381.

(19) (a) Chavez, D. E.; Jacobsen, E. N.; Grabowski, E. J. J.; Kubryk, M. *Org. Synth.* **2002**, *82*, 34−39. (b) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398−2400. (c) Gademann, K.; Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3059−3061.

(20) Khalaf, J. K.; Datta, A. *J. Org. Chem.* **2005**, *70*, 6937−6940.

(21) The uronic moiety of **17** is present in some bacteria: Itoh, T.; Hashimoto, W.; Mikami, B.; Murata, K. *J. Biol. Chem.* **2006**, *281*, 29807−29816.

(22) Martin, A.; Païs, M.; Monneret, C. *Carbohydr. Res.* **1983**, *113*, 189−201.

(23) Crotti, P.; Di Bussolo, V.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron* **2002**, *58*, 6069−6091.
(24) (a) Liang, C.-H.; Yao, S.; Chiu, Y.-H.; Leung, P. Y.; Robert, N.; Seddon, J.; Sears, P.; Hwang, C.-K.; Ichikawa, Y.; Romero, A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1307−1310. (b) Romero, A.; Liang, C.-H.; Chiu, Y.-H.; Yao, S.; Duffield, J.; Sucheck, S. J.; Marby, K.; Rabuka, D.; Leung, P. Y.; Shue, Y.-K.; Ichikawa, Y.; Hwang, C.-K. *Tetrahedron Lett.* **2005**, *46*, 1483−1487.
(25) Kwiatkowski, P.; Asztemborska, M.; Jurczak, J. *Synlett* **2004**, 1755−1758.
(26) (a) Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem. Soc.* **1994**, *116*, 2812−2820. (b) Keck, G. E.; Li, X. Y.; Krishamurthy, D. *J. Org. Chem.* **1995**, *60*, 5998−5999.
(27) Quitschalle, M.; Christmann, M.; Bhatt, U.; Kalesse, M. *Tetrahedron Lett.* **2001**, *42*, 1263−1265.
(28) (a) Tietze, L. F.; Hartfiel, U. *Tetrahedron Lett.* **1990**, *31*, 1697−1700. (b) Knapp, S.; Jaramillo, C.; Freeman, B. *J. Org. Chem.* **1994**, *59*, 4800−4804. (c) Knapp, S.; Levorse, A. T.; Potenza, J. A. *J. Org. Chem.* **1988**, *53*, 4773−4779.
(29) (a) Buchanan, J. G.; Stoddart, J.; Wightman, R. H. *J. Chem. Soc., Chem. Commun.* **1989**, 823−824. (b) Buchanan, J. G.; Stoddart, J.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1417−1426.
(30) (a) Evans, M. E. *Carbohydr. Res.* **1977**, *54*, 105−114. (b) Becher, J.; Seidel, I.; Plass, W.; Klemm, D. *Tetrahedron* **2006**, *62*, 5675−5681.
(31) Stanford, D.; Stachulski, A. V. *Tetrahedron Lett.* **2007**, *48*, 2361−2364.
(32) Bock, K.; Pedersen, C. *J. Chem. Soc., Perkin Trans. 2* **1974**, *3*, 293−297.
(33) Attemp to use Sharpless asymmetric dihydroxylation failed. This result is consistent with earlier observations: Sharpless, B. K.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768−2771.
(34) See the Supporting Information for a complete account of this coupling optimization.
(35) (a) Kazimierczuk, Z.; Cottam, H. B.; Revankar, G. R.; Robins, R. K. *J. Am. Chem. Soc.* **1984**, *106*, 6379−6382. (b) Marminon, C.; Pierré, A.; Pfeiffer, B.; Pérez, V.; Léonce, S.; Joubert, A.; Bailly, C.; Renard, P.; Hickman, J.; Prudhomme, M. *J. Med. Chem.* **2003**, *46*, 609−622. (c) Schwarz, B.; Hofmann, T. *J. Agric. Food Chem.* **2007**, *55*, 1405−1410.
(36) (a) Mori, K.; Tominaga, M.; Takigawa, T.; Matsui, M. *Synthesis* **1973**, 790−791. (b) Herzig, J. *J. Org. Chem.* **1986**, *51*, 727−730. (c) Pérez, M. G.; Maier, M. S. *Tetrahedron Lett.* **1995**, *36*, 3311−3314. (d) Van Boeckel, C. A. A.; Van Boom, J. H. *Tetrahedron Lett.* **1979**, *37*, 3561−3564.
(37) No ^{13}C NMR data are provided in the isolation publication[5c] or in the Wightman synthesis publications.[29]
(38) Gorin, P. A. J.; Mazurek, M. *Can. J. Chem.* **1975**, *53*, 1212−1223.
(39) Christmann, M.; Bhatt, U.; Quitschalle, M.; Claus, E.; Kalesse, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4364−4366.