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Tetrahedron 63 (2007) 9705–9711

A divergent strategy for constructing a sugar library containing 2,6-dideoxy sugars and uncommon sugars with 4-substitution

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Received 28 May 2007; revised 5 July 2007; accepted 7 July 2007
Available online 13 July 2007

Abstract—A practical strategy has been developed for delivering 2,6-dideoxy sugars and uncommon sugars with 4-substitution. This strategy employed Ferrier rearrangement reaction and $BF_3 \cdot OEt_2$-induced peroxidation to construct key intermediates 2,3-unsaturated glycosides and α,β-unsaturated lactones from peracetyl rhamnal. After further derivatization, four uncommon sugars with 4-substitution and eight uncommon sugar units with 3,4-disubstitution were successfully synthesized.

1. Introduction

Uncommon sugars are derived from common sugars (e.g., D-glucose) by replacement of at least one hydroxyl group or hydrogen atom with another functional group. They are present in numerous biologically intriguing natural products and have received special attention, due to the increased recognition of their vital roles in the biological function of many natural products. The function of the uncommon sugar moieties ranges from affecting the pharmacokinetics of the drug to directly interacting with cellular targets like proteins, RNA and DNA.[1] They add important features to the shape and the stereoelectronic properties of a molecule and often play an essential role in the biological activities of many natural product drugs. Areas in which their significance has been well-established include cellular adhesion and cell–cell recognition, fertilization, protein folding, neurobiology, xenotransplantation and target recognition in the immune response.[2] By analyzing various glycosylated natural products and drugs, it was found that the majority of uncommon sugars are 2,6-dideoxy sugars (uncommon sugars with 3,4-disubstitution) and 2,3,6-trideoxy sugars (uncommon sugars with 4-substitution) (e.g., daunorubicin and landomycin, Fig. 1).

Many efforts have been focused on the total synthesis of uncommon monosaccharides because of their biological importance in natural products.[3] Generally, uncommon sugars were synthesized through multistep transformations of relatively economical common sugars. For instance, starting from methyl glucoside, L-vancosamine was synthesized in 15 steps.[4] An alternative strategy is to start from non-carbohydrate precursors. In this case, many researchers have come up with different synthetic approaches. For example, Nicolaou's group synthesized L-vancosamine starting from L-lactate in 11 steps,[5a] while McDonald and Cutchins synthesized the same aminosugar by tungsten-catalyzed alkynol cycloisomerization in nine steps.[5b] MacMillan's group developed a synthetic pathway for stereoselectively constructing sugar derivatives starting from β,γ-oxyalaldehydes.[6] O'Doherty's group synthesized sugar derivatives starting from furan alcohols.[7] Wang's group developed a systematic strategy for the synthesis of uncommon sugars via ring-closing metathesis (RCM).[8] In Wang's strategy, the intermediates six-membered β,γ-unsaturated lactones generated from RCM could be directly converted to cis-3,4-difunctional uncommon sugar derivatives through asymmetric dihydroxylation followed by reduction.[8a] These intermediates could also be converted to α,β-unsaturated lactones, which could be further modified to various uncommon sugars.[8b] Wang's strategy provided a synthetic pathway to produce uncommon sugars systematically and revealed the importance of α,β-unsaturated lactones in uncommon sugar synthesis. However, the relatively high price of the chiral starting materials and the Grubb's catalysts, and the very dilute conditions required by RCM reaction are the main hurdles for this method to be utilized in large scale synthesis. In order to address these drawbacks of the RCM strategy, Wang's group developed a practical method for the syntheses of α,β-unsaturated lactones starting from furanaldehyde in six steps.[9]

It has been indicated that structural modifications of sugar moieties in some pharmaceuticals may enhance their pharmacological profile.[10] Lack of uncommon sugar sources is

Keywords: Uncommon sugars; Synthesis; Peracetyl rhamnal.
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doi:10.1016/j.tet.2007.07.019

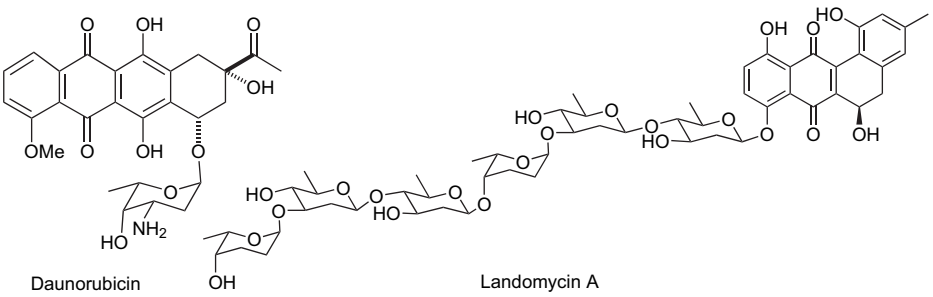


Figure 1. Structure of daunorubicin and landomycin A.

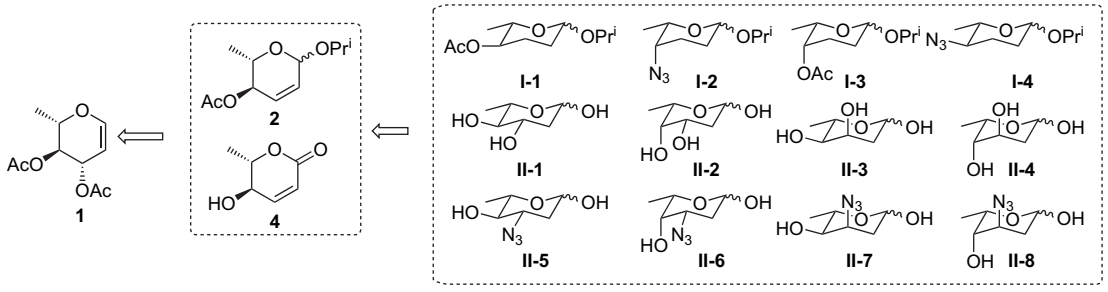
the major disadvantage in the development of glycosylated drugs. In our research, we plan to construct a diverse uncommon sugar library to facilitate the systematic structure–activity relationship investigation of the potential anticancer drugs. Therefore, it is necessary to develop a divergent and practical method to deliver various uncommon sugars.

Herein, we present our strategy (Scheme 1) to produce uncommon sugars by employing Ferrier rearrangement reaction and $BF_3 \cdot OEt_2$-induced peroxidation[11] to construct key intermediates 2,3-unsaturated glycoside (**2**) and α,β-unsaturated lactone (**4**) from 3,4-di-*O*-acetyl-L-rhamnal (**1**). This method is economic and practical for large scale manipulations. Following this strategy, the corresponding D-series of uncommon sugars can also be produced from 3,4-di-*O*-acetyl-D-rhamnal (D-**1**), which could be readily prepared from glucal.[12] To demonstrate that this strategy is practicable, four L-uncommon sugars with 4-substitution (**I-1–4**) and eight L-uncommon sugars with 3,4-disubstitution (**II-1–8**) were synthesized starting from 3,4-di-*O*-acetyl-L-rhamnal (**1**) in 2–9 steps.

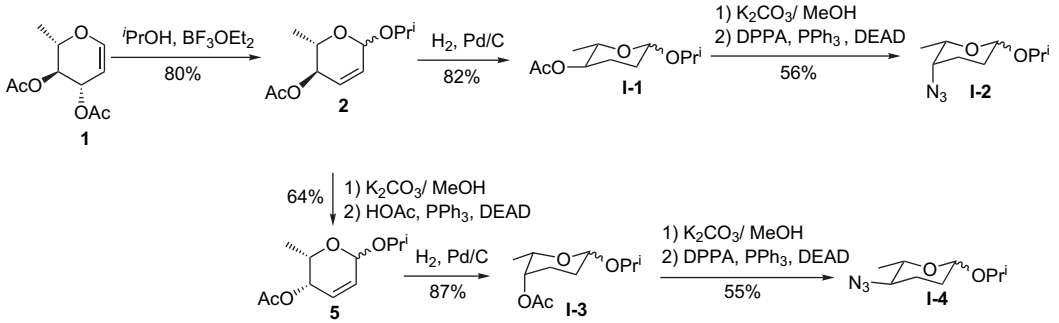
Most recently, we have reported a communication for the preparation of 3-azido-2,3,6-trideoxy-L-hexoses (**II-5–8**) from peracetyl rhamnal **1**.[13] Here, we present our more detailed results on the preparation of uncommon sugar units with 4-substitution (**I-1–4**, Scheme 2) and 2,6-dideoxy sugars (**II-1–4**, Scheme 3).

2. Results and discussion

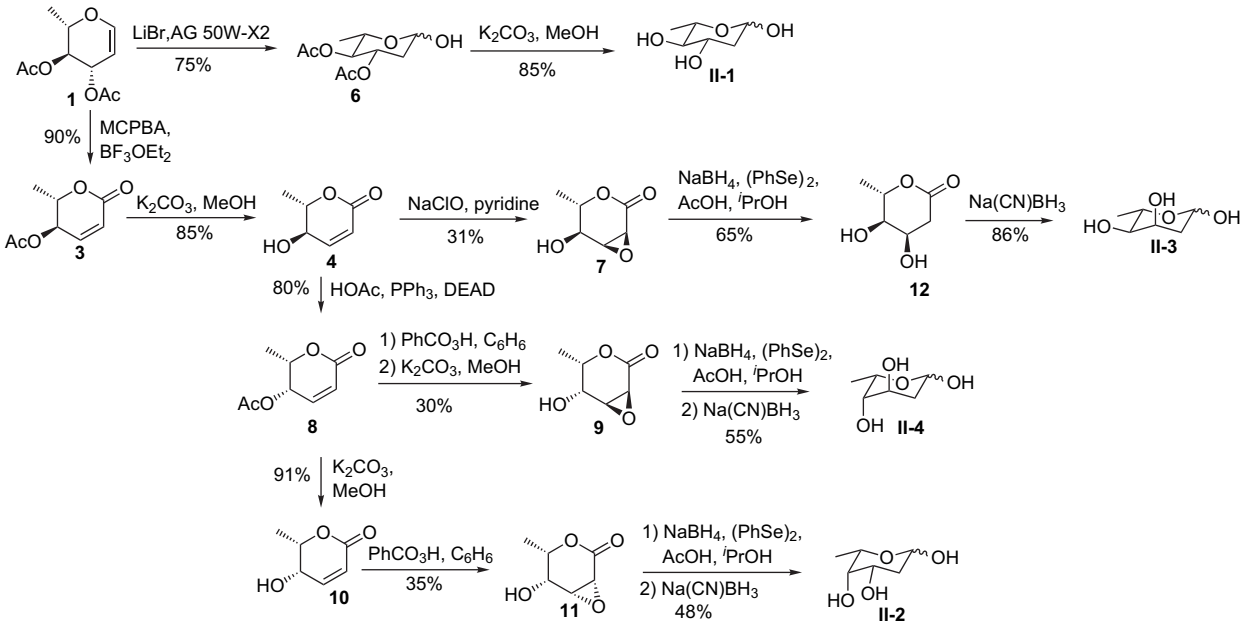
We began our synthetic route with the Ferrier reaction of **1** and isopropanol in the presence of $BF_3 \cdot OEt_2$ in dichloromethane at 0 °C for 1.5 h. The key intermediate **2** was obtained as an anomeric mixture (α/β>10:3 by NMR) in 80% yield. Isopropanol was selected because the isopropoxy group on the resulted uncommon sugars (**I-1–4**) is relatively reactive. These isopropyl glycosides could be directly used as glycosyl donors or readily converted to other more active donors such as thioglycosides.[14] The compound **4**, which is another key intermediate for uncommon sugars with 3,4-disubstitution, was obtained by the deacetylation of lactone **3**, which



Scheme 1. The strategy to deliver uncommon sugars from peracetyl rhamnal.



Scheme 2. Synthesis of uncommon sugars with 4-functionality.



Scheme 3. Synthesis of 2,6-dideoxy sugars.

was generated via the reaction of glycal **1** with *m*-chloroperbenzoic acid (*m*-CPBA) and $BF_3 \cdot OEt_2$ in dichloromethane at −20 °C in 90% yield.

With large quantity of these two key intermediates in hand, we turned our attention to the transformation of these intermediates to the uncommon sugars. As outlined in Schemes 2 and 3, starting from unsaturated glycoside **2** and unsaturated lactone **4**, eight different L-uncommon sugars (**I-1**–**4**, **II-1**–**4**) were successfully synthesized. Due to the importance of aminosugar moiety in natural products (e.g., daunorubicin), we strategically incorporated azido group in our uncommon sugars, since the azido group can be an excellent masking group for amino group and can be amplified to diversified drug-resembling moieties (e.g., triazole ring).

As shown in Scheme 2, the uncommon sugars **I-1**–**4** were obtained by derivatization of the unsaturated glycoside **2** resulted from the Ferrier reaction of glycal **1**. Hydrogenation of glycoside **2** in the presence of Pd/C under H_2 atmosphere (30 psi) provided uncommon sugar **I-1**. Conversion of **I-1** to azido sugar **I-2** was done by deacetylation with K_2CO_3 in methanol, followed by Mitsunobu reaction[15] in a total of 56% yield.

Glycoside **2** was deacetylated with K_2CO_3 in methanol, subsequently treated with HOAc in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine in THF at room temperature to give the glycoside **5** in 64% yield from two steps. Following the same procedures for the preparation of the uncommon sugar **I-1** and azido sugar **I-2**, the uncommon sugars **I-3** and **I-4** were obtained from the unsaturated glycoside **5** with good yield.

The synthetic pathway of 2,6-dideoxy sugars (**II-1**–**4**) is outlined in Scheme 3. Glycal **1** was treated with water in the presence of lithium bromide and AG 50W-X2 cation exchange resin[16] to give 3,4-di-*O*-acetyl-L-rhamnose **6** as a mixture of α- and β-anomer, in a α/β ratio of 2:1, in 75% yield. Deacetylation of **6** with K_2CO_3 in methanol produced the 2,6-dideoxy sugar L-canarose **II-1** in excellent yield.

The treatment of osmundalactone **4** with NaClO in pyridine gave *syn*-epoxide **7** as the major product with the ratio of cis/trans greater than 20:1 in 31% yield. Reductive opening of epoxide ring of **7** with sodium phenylseleno(triisopropyloxy)-borate ($NaBH_4$ and PhSeSePh in acetic acid)[17] allowed the formation of 3,4-*trans*-dihydroxyl lactone. Further reduction of the lactone with $Na(CN)BH_3$ furnished L-digitoxose (**II-3**) in 56% yield from two steps.

In order to synthesize the uncommon sugar L-boivinose **II-4**, the lactone **4** was firstly converted to another lactone **8** by reaction with HOAc in the presence of DEAD and triphenylphosphine as shown in Scheme 3. Epoxidation of **8** following the procedure for the preparation of epoxide **7** did not work well. However, $PhCO_3H$ worked well for the conversion in benzene at 0 °C. Epoxidation of **8** using peroxybenzoic acid proceeded stereoselectively from the less hindered face of the molecule to afford the *anti*-epoxide as the major product with the ratio of trans/cis greater than 5:1. After removal of the acetyl group, the epoxide **9** was obtained in 30% yield from two steps. Finally, following the same procedure for the preparation of D-digitoxose (**II-3**) from epoxide **7**, L-boivinose (**II-4**) was obtained in 55% yield from **9**.

Meanwhile, the stereoselective approach to uncommon sugar L-oliose **II-2** was also achieved from lactone **8**. Deacetylation of **8** with K_2CO_3 in methanol gave another lactone **10** in excellent yield. Following the procedure for epoxidation of lactone **8**, lactone **10** was epoxidized to epoxide **11** in 35% yield. Following the same procedure for the preparation of the D-digitoxose (**II-3**) from epoxide

7, the epoxide **11** was reduced to L-oliose **II-2** in 48% yield from two steps.

3. Conclusion

In conclusion, we have demonstrated a concise and feasible route to uncommon sugars. By employing the Ferrier reaction and $BF_3\cdot OEt_2$-induced peroxidation, we were able to generate the 2,3-unsaturated glycosides and α,β-unsaturated lactones in large scale. The efficiency of our diversity-orientated synthesis was exemplified by the successful synthesis of L-uncommon sugars. Combination of our previous work,[13] four L-uncommon sugars with 4-substitution (**I-1**–**4**), four 2,6-dideoxy-L-sugars (**II-1**–**4**) and four 3-azido-2,3,6-trideoxy-L-sugars (**II-5**–**8**) were delivered starting from peracetyl L-rhamnal in 2–9 steps. Following the procedures presented in Schemes 2 and 3, the corresponding D-series of uncommon sugars could be prepared from 3,4-di-*O*-acetyl-D-rhamnal. The syntheses of D-deoxy sugars are currently undergoing in our laboratory.

4. Experimental section

4.1. General remarks

All solvents were of reagent grade materials purified by standard methods. All reagents were obtained from commercial sources and used without further purification. The commercial AG 50W-X2 (H^+ form, moisture) resin was treated as follows: the commercial resin (5 g) was washed with water (3×15 mL) until the filtrate was colourless and then with reagent grade acetonitrile (10×10 mL). It was then dried over phosphorus pentoxide under vacuum to give dry resin (1 g). The reactions, unless stated otherwise, were all carried out under a positive pressure of argon and were monitored by TLC on silica gel 60 F_{254} (0.25 mm, E. Merck). Column chromatography was performed on silica gel 60 (230–400 mesh). The ratio between silica gel and crude product ranged from 100 to 50:1 (w/w). ^1H and ^{13}C NMR spectra were recorded on Bruker AC-400 NMR spectrometer in solutions of $CDCl_3$ or CD_3OD using tetramethylsilane as the internal standard, δ values are given in parts per million and coupling constants (J) in hertz. Infrared absorption spectra were recorded as neat films. The mass spectra and high-resolution mass spectra were collected at the Zhengzhou University Campus Instrumentation Center.

4.2. Synthesis of isopropanyl 3-*O*-acetyl-2,3,6-trideoxy-L-*erythro*-hex-2-enopyranoside, 2

3,4-Di-*O*-acetyl-L-rhamnal **1** (21.5 g, 0.1 mol) and isopropanol (0.15 mol) were dissolved in dry dichloromethane (100 mL) and boron trifluoride–ether (5 mL) was added at 0 °C. Stirring was continued at 0 °C for 1.5 h. TLC showed that the glycal disappeared. After neutralization with saturated $NaHCO_3$, the reaction mixture was extracted with dichloromethane, and the organic layer was dried over $MgSO_4$, then purified with silica gel chromatography (cyclohexane/EtOAc 15:1) to give the product (17.2 g, 80% yield) as a colourless viscous liquid. It was a mixture of α- and β-isomer (α/β>10:3). Since both the isomers were able to be used for next reactions, they were not separated. HRMS m/z calculated for $C_{11}H_{18}O_4Na$ 237.1097 ($M+Na^+$), found 237.1099.

4.3. Synthesis of (5*R*,6*S*)-5-acetoxy-5,6-dihydro-6-methylpyran-2-one, 3

A solution of *m*-CPBA (11 mmol) in dry CH_2Cl_2 (30 mL) was added dropwise to a stirred solution of the glycal **1** (2.0 g, 9.3 mmol) in CH_2Cl_2 (30 mL) at −20 °C. Subsequently, $BF_3\cdot OEt_2$ (0.5 mL, 4 mmol) was added dropwise and the mixture was stirred at −20 °C for 1 h. Then the reaction was quenched by the addition of saturated $NaHCO_3$ (70 mL) containing $Na_2S_2O_3$ (40 mg). The mixture was extracted with CH_2Cl_2 and the combined organic layer was dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by chromatography on silica gel (hexanes/EtOAc 6:1) to give pure product (1.33 g, 90%). ^1H NMR (400 MHz, $CDCl_3$) δ 6.75 (dd, 1H, J=9.9, 3.2 Hz), 6.07 (dd, 1H, J=9.9, 1.5 Hz), 5.27–5.21 (m, 1H), 4.59 (quint, 1H, J=6.6 Hz), 2.10 (s, 3H), 1.39 (d, 3H, J=6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 143.1, 123.0, 76.6, 67.9, 21.0, 18.5; HRMS m/z calculated for $C_8H_{10}O_4$ 170.0579 (M^+), found 170.0580.

4.4. Synthesis of (5*R*,6*S*)-5,6-dihydro-5-hydroxy-6-methylpyran-2-one, 4

A solution of the L-*erythro*-enelactone **3** (1.30 g, 7.65 mmol) and K_2CO_3 (0.5 g) in dry MeOH (20 mL) was stirred overnight. After removal of the solvent under reduced pressure, the crude product was purified by chromatography on silica gel (hexanes/EtOAc 1:1) to give pure product (85%). ^1H NMR (400 MHz, $CDCl_3$) δ 6.86 (dd, 1H, J=10.0, 2.0 Hz), 5.94 (dd, 1H, J=9.5, 1.5 Hz), 4.39–4.34 (m, 1H), 4.23 (d, 1H, J=9.0 Hz), 3.26 (br, 1H), 1.46 (d, 3H, J=6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 149.9, 120.4, 79.5, 67.7, 18.3; HRMS calculated for $C_6H_8O_3$ 128.0473 (M^+), found 128.0475.

4.5. Synthesis of isopropanyl 3-*O*-acetyl-2,3,6-trideoxy-L-*threo*-hex-2-enopyranoside, 5

A suspension of the glycoside **2** (1.64 g, 7.66 mmol) and K_2CO_3 (0.5 g) in dry MeOH (20 mL) was stirred for 15 h. The solvent was removed in vacuo to give the crude product, which was purified by silica gel column chromatography (cyclohexane/EtOAc 10:1) to give the deacetylated compound (1.14 g, 85% yield). The compound obtained above (1.14 g, 6.5 mmol), AcOH (0.4 g, ca. 6.5 mmol) and triphenylphosphine (1.71 g, 6.5 mmol) were dissolved in dry THF (10 mL) and cooled to 0 °C. Diethyl azodicarboxylate (1.14 g, ca. 6.5 mmol) in dry THF (3 mL) was added dropwise to the resulted solution at 0 °C. The reaction mixture was stirred for 15 h and solvent was removed in vacuo, diethyl ether (25 mL) was added to the residue and the insoluble part was filtered off. After removal of solvent, the crude product was purified by column chromatography (cyclohexane/EtOAc 16:1) to give **5** (1.05 g, 64% yield from **2**) as a colourless viscous liquid. It was a mixture of α- and β-isomer. Since both the isomers were able to be used for next reaction, they were not separated. HRMS m/z

calculated for $C_{11}H_{18}O_4Na$ 237.1097 (M+Na$^+$), found 237.1089.

4.6. Preparation of 2-deoxy-3,4-di-*O*-acetyl-L-rhamnopyranose, 6

AG 50W-X2 resin (0.3 g) and water (0.6 mL) were added to a solution of 3,4-di-*O*-acetyl-L-rhamnal (0.4 g, 1.87 mmol) and lithium bromide hydrate (0.5 g) in acetonitrile (15 mL). The mixture was stirred at room temperature for 15 min. The reaction mixture was filtered, neutralized with triethylamine and evaporated to dryness. The residue was dissolved in dichloromethane and washed with water, ice-cold 1 M hydrochloric acid and saturated sodium bicarbonate solution. The colourless solid (α/β=2:1) of compound **6** (325 mg, 75% yield) was obtained after purification on a column of silica gel using ethyl acetate/hexane (1:3) as eluent. ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.24 (d, J=3.4 Hz, H-1α), 5.27–5.21 (m, H-3α), 4.92–4.86 (m, H-3β), 4.80 (dd, J=1.9, 9.4 Hz, H-1β), 4.63 (t, J=9.6 Hz, H-4), 4.05–3.98 (m, H-5α), 3.43 (m, H-5β), 2.29–2.25 (m, H-2β_{eq}), 2.16–2.12 (m, H-2α_{eq}), 1.75–1.70 (m, H-2β_{ax}), 1.60 (m, H-2α_{ax}), 1.11 (d, J=6.2 Hz, H-6β), 1.05 (d, J=6.2 Hz, H-6α).

4.7. Synthesis of (3*S*,4*S*,5*R*,6*S*)-3,4-epoxy-5-hydroxy-6-methylpyran-2-one, 7

Lactone **4** (200 mg, 1.56 mmol) and pyridine (30 mL) were placed in a 100 mL round bottom flask. After cooled to -10 °C, NaOCl solution (10–13%, 3 mL, 4 equiv) was added into the flask in 10 min. The resulted mixture was allowed to stir at -10 °C for 1 h. The reaction was quenched by the addition of saturated NH_4Cl. The mixture was extracted with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by chromatography on silica gel (hexanes/EtOAc 2:1) to give pure product (70 mg, 31%). ^{1}H NMR (400 MHz, CD_3OD) δ 4.36–4.30 (m, 1H), 3.79 (d, 1H, J=9.0 Hz), 3.65 (d, 1H, J=4.2 Hz), 3.62 (d, 1H, J=4.2 Hz), 1.34 (d, 3H, J=6.3 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 167.5, 73.4, 55.9, 50.4, 17.0. MS ES$^+$ m/z 167 (M+Na); HRMS m/z calculated for $C_6H_8O_4Na$ 167.0320 (M$^+$), found 167.0329.

4.8. Synthesis of (5*S*,6*S*)-5-acetoxy-5,6-dihydro-6-methylpyran-2-one, 8

Diethyl azodicarboxylate (1.140 g, ca. 6.5 mmol) in dry THF (2 mL) was added dropwise to the solution of **4** (0.832 g, 6.5 mmol) obtained above, AcOH (4.0 g, ca. 65 mmol) and triphenylphosphine (17.10 g, 65 mmol) in dry THF (100 mL) at 0 °C. The reaction mixture was stirred for 15 h and solvent was removed in vacuo, diethyl ether (50 mL) was added to the residue and the insoluble part was filtered off. After removal of solvent, the crude product was purified by silica gel column chromatography (hexanes/EtOAc 6:1) to give **8** (0.884 g, 80%) as a colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (dd, 1H, J=9.9, 2.2 Hz), 5.97 (dd, 1H, J=9.9, 1.8 Hz), 4.38–4.30 (m, 1H), 4.25–4.19 (m, 1H), 2.11 (s, 3H), 1.47 (d, 3H, J=6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 140.8, 122.9, 76.6, 67.9, 20.9, 18.4; HRMS m/z calculated for $C_8H_{10}O_4$ 170.0579 (M$^+$), found 170.0575.

4.9. Synthesis of (5*S*,6*S*)-5,6-dihydro-5-hydroxy-6-methylpyran-2-one, 10

A solution of **8** (600 mg, 3.53 mmol) and K_2CO_3 (0.2 g) in dry MeOH (20 mL) was stirred overnight and solvent was removed in vacuo. Silica gel column chromatography (hexanes/EtOAc 1:1) of the crude product yielded **10** (411 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (dd, 1H, J=9.8, 5.8 Hz), 6.10 (d, 1H, J=9.8 Hz), 4.52 (qd, J=6.8 Hz, 2.8 Hz), 4.10–3.98 (m, 1H), 1.47 (d, 3H, J=6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 148.9, 120.4, 79.6, 67.6, 18.0; HRMS m/z calculated for $C_6H_8O_3$ 128.0473 (M$^+$), found 128.0480.

4.10. Synthesis of isopropanyl 4-*O*-acetyl amicetoside, I-1

2,3-Unsaturated glycoside **2** (920 mg, 4.3 mmol) was dissolved in EtOAc (30 mL), palladium catalyst (10% Pd/C, 200 mg) was added and the reaction mixture was hydrogenated at 30 psi overnight. Then, it was filtered through a Celite bed, washed with EtOAc and the filtrate was concentrated under low pressure to give pure product (763 mg, 82%) as a mixture of α- and β-anomer (α/β=5:2), which could not be separated by silica gel chromatography. The spectroscopic data of the mixture: ^{1}H NMR (250 MHz, CD_3OD) δ 4.83 (d, 1H, J=2.5 Hz, H$_\alpha$-1), 4.49–4.38 (m, 1.4H, H$_\alpha$-4, H$_\beta$-1), 3.91–3.78 (m, 2.4H, H$_\alpha$-5, H$_\beta$-4, H$_\alpha$-secondary proton on isopropyl), 3.33–3.28 (m, 0.8H, H$_\beta$-5, H$_\beta$-secondary proton on isopropyl), 2.13–1.31 (m, 9.8H, H-2, H-3, OAc), 1.20–1.04 (m, 12.6H, Me); HRMS m/z calculated for $C_{11}H_{20}O_4Na$ 239.1253 (M+Na$^+$), found 239.1256.

4.11. Synthesis of isopropanyl 4-azido-4-deoxy rhodinoside, I-2

A solution of **I-1** (212 mg, 0.98 mmol) and K_2CO_3 (0.1 g) in dry MeOH (10 mL) was stirred overnight and solvent was removed in vacuo. Silica gel column chromatography (hexanes/EtOAc 3:1) of the crude product yielded the deacetylated glycoside (145 mg, 85%). To a solution of the glycoside (145 mg, 0.83 mmol) and Ph_3P (655 mg, 2.50 mmol) in THF (10 mL) was slowly added DEAD (0.40 mL, 2.50 mmol) at 0 °C. After 3–5 min, diphenylphosphorylazide (DPPA, 0.54 mL, 2.50 mmol) was added by dropwise and the resulting solution was allowed to slowly warm up to room temperature and stirred overnight. The reaction mixture was then concentrated to a small volume via an atmospheric pressure distillation by means of a short path apparatus fitted with a 15 cm Vigreux column and then chromatographed on a silica gel column with a 0–20% Et_2O in pentane gradient to afford the product (110 mg, 56% yield from **I-1**) as a light-yellow oil. The data of IR, ^{1}H and ^{13}C NMR were identical with those reported in literature.[8b]

4.12. Synthesis of isopropanyl 4-*O*-acetyl rhodinoside, I-3

Following the same procedure described for **I-1**, the glycoside **I-3** was obtained from **5** as a colourless oil (α/β=5:1). Selected data for α anomer: ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.95 (d, 1H, J=2.8 Hz, H-1), 4.80 (br, 1H, H-4), 4.08–4.01 (quint, 1H, J=6.6 Hz, H-5), 3.95–3.83 (sept, 1H, J=6.2 Hz, H-secondary proton on isopropyl), 2.21 (s, 3H), 2.07–1.21 (m, 4H), 1.21 (d, 3H, J=6.3 Hz), 1.13 (d, 3H,

J=6.0 Hz), 1.09 (d, 3H, J=6.6 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.1, 94.4, 68.1, 65.1, 59.8, 24.3, 23.0, 22.7, 21.3, 21.1, 17.8; HRMS m/z calculated for $C_{11}H_{20}O_4Na$ 239.1253 ($M+Na^+$), found 239.1254.

4.13. Synthesis of isopropanyl 4-azido-4-deoxy amicetoside, I-4

Following the same procedure described for **I-2**, compound **I-4** was obtained from **I-3** as a mixture of α- and β-anomer (55%). The parent ion was not observed by HRMS, due to the decomposition of this compound under the analysis conditions. IR (neat, cm^{-1}) 2950, 2110 (N_3 group), 1270, 1050; selected data for α anomer: ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.85 (d, 1H, J=2.4 Hz), 4.02–3.96 (qd, 1H, J= 8.9, 6.3 Hz), 3.86–3.76 (sept, J=6.1 Hz, 1H), 3.37 (m, 1H), 2.09 (m, 1H), 1.84 (m, 2H), 1.48 (m, 1H), 1.13 (d, J= 6.1 Hz, 6H), 1.06 (d, J=6.3 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 94.2, 67.6, 63.0, 59.8, 24.2, 23.0, 22.6, 21.2, 17.6.

4.14. Synthesis of L-canarose, II-1

A solution of **6** (232 mg, 1.0 mmol) and K_2CO_3 (0.1 g) in dry MeOH (10 mL) was stirred overnight and solvent was removed in vacuo. Silica gel column chromatography ($EtOH/CH_2Cl_2$ 1:10) of the crude product yielded **II-1** (126 mg, 85%). Selected data for β-anomer: ^{1}H NMR (250 MHz, D_2O) δ 4.97 (d, 1H, J=9.7 Hz), 3.49–3.43 (m, 1H), 3.21 (qd, 1H, J=9.1, 6.2 Hz), 2.81 (t, 1H, J=9.1 Hz), 2.05–2.01 (m, 1H), 1.29–1.25 (m, 1H), 1.04 (d, 3H, J=6.2 Hz); ^{13}C NMR (63 MHz, D_2O) δ 92.6, 77.5, 68.5, 68.4, 40.6, 17.8. MS ES$^+$ m/z 149 $(M+H)^+$.

4.15. Synthesis of L-oliose, II-2

Following the procedures described for epoxidation of **8** with peroxybenzoic acid, the lactone **10** was epoxidized to **11** in approximately 35% yield with a little unseparated contaminant. MS ES$^+$ m/z 145 $(M+H)^+$. The epoxide **11** was reduced following the procedures described for **II-3** from **7** to give the sugar L-oliose **II-2** as a syrup (mixture of α- and β-anomer) in 48% yield. Selected data for α anomer: ^{1}H NMR (500 MHz, D_2O) δ 5.22 (br, 1H), 4.15 (qd, 1H, J=7.0, 2.0 Hz), 4.07 (dd, 1H, J=6.5, 3.0 Hz), 3.68 (d, 1H, J=7.0 Hz), 1.83–1.81 (dd, 2H, J=18.0, 2.0 Hz), 1.20 (d, 3H, J=7.0 Hz); ^{13}C NMR (125 MHz, D_2O) δ 92.5, 70.9, 67.2, 65.5, 32.4, 16.8. MS ES$^+$ m/z 149 $(M+H)^+$.

4.16. Synthesis of (4*R*,5*S*,6*S*)-dihydroxy-6-methyl-tetrahydropyran-2-one, 12, and L-digitoxose, II-3

To a stirred solution of PhSeSePh (1000 mg, 3.20 mmol) in isopropanol (18 mL) was added in batches $NaBH_4$ (245 mg, 6.30 mmol) at room temperature. After 8 min, AcOH (63 μL, 1.05 mmol) was added into the mixture. The resulting mixture was stirred for additional 10 min. Then a solution of the epoxy lactone **7** (150 mg, 1.04 mmol) in isopropanol (10 mL) was added to the mixture at 0 °C. The reaction was monitored via TLC (EtOAc/MeOH 5:2). The mixture was stirred at 0 °C for 1 h and subsequently diluted with EtOAc. The organic solution was washed with brine and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave a residue that was purified by silica gel chromatography using EtOAc and methanol as the mobile phase to give the pure compound **12** (99 mg, 65%). ^{1}H NMR (500 MHz, CD_3OD) δ 4.46 (dt, 1H, J=6.9, 2.0 Hz), 4.18 (dd, 1H, J=3.6, 1.8 Hz), 3.90 (dq, 1H, J=6.9, 2.5 Hz), 2.91 (dd, 1H, J=18.0, 6.6 Hz), 2.35 (dd, 1H, J=18.0, 2.5 Hz), 1.25 (d, 3H, J=6.6 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 167.5, 91.0, 69.3, 67.0, 37.9, 18.4; HRMS m/z calculated for $C_6H_{10}O_4$ 146.0579 (M^+), found 146.0586.

Dihydroxylated lactone **12** (99 mg, 0.68 mmol) and AcOH/AcONa (1.0 M, 25 mL) were added in a 50 mL round bottom flask. $Na(CN)BH_3$ (3.5 equiv) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was then lyophilized and subjected to silica gel column chromatography (CH_2Cl_2/EtOH 8:1) to give the sugar L-digitoxose **II-3** (87 mg, 86%), mixture of α- and β-anomer. Selected data for α anomer: ^{1}H NMR (400 MHz, D_2O) δ 5.24 (t, 1H, J=2.5 Hz), 4.28 (ddd, 1H, J=4.0, 2.5, 2.0 Hz), 3.96 (qd, 1H, J=7.5, 3.0 Hz), 3.68 (dd, 1H, J=17.0, 7.0 Hz), 2.02–2.00 (dd, 1H, J=18.0, 2.0 Hz), 1.15 (d, 3H, J=6.5 Hz); ^{13}C NMR (100 MHz, D_2O) δ 91.0, 69.9, 67.2, 64.5, 32.0, 17.0. MS ES$^+$ m/z 171 $(M+Na)^+$.

4.17. Synthesis of L-boivinose, II-4

A solution of the lactone **8** (727 mg, 4.28 mmol) in benzene (10 mL) and perbenzoic acid in benzene (0.48 M, 10 mL) was cooled to 0 °C, mixed and kept at 0 °C. At intervals, aliquot portions were removed from the reaction solution in order to follow the rate of consumption of the peracid. After 30 h, the solution was washed with saturated K_2CO_3 solution twice and dried, and the solution was removed under reduced pressure. The residue was dissolved in methanol (10 mL) and K_2CO_3 (0.2 g) was added to the solution above. The resulting mixture was stirred overnight and the solvent was removed under reduced pressure. The crude product was purified by chromatography on silica gel (hexanes/EtOAc 2:1) to give the epoxide **9** (185 mg, ~30%) with a little unseparated contaminant. MS ES$^+$ m/z 167 $(M+Na)^+$.

Following the procedures described for **II-3** from **7**, the compound **9** obtained above was treated to give the sugar L-boivinose **II-4** (105 mg, 55%) as a mixture of α- and β-anomer. Selected data for β-anomer: ^{1}H NMR (250 MHz, D_2O) δ 4.80 (dd, 1H, J=9.8, 3.0 Hz), 3.66 (quint, 1H, J=6.2 Hz), 3.59 (m, 1H), 2.95–2.89 (m, 1H), 1.69–1.55 (m, 1H), 1.42–1.36 (m, 1H), 1.02 (d, 3H, J=6.2 Hz); ^{13}C NMR (63 MHz, D_2O) δ 92.6, 69.5, 69.4, 68.9, 34.7, 16.8. MS ES$^+$ m/z 149 $(M+H)^+$.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (20672031) and a fund from the Program for New Century Excellent Talents in University of Henan Province (2006-HACET-06) to G.Z.

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