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A systematic strategy for preparation of uncommon sugars through enzymatic resolution and ring-closing metathesis

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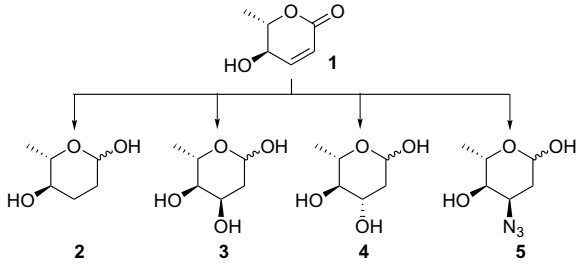
Abstract—A systematic synthetic strategy has been developed for producing uncommon sugars. This method involved kinetic resolution allylic alcohol followed by ring-closing-metathesis (RCM) to generate optical pure lactones as the common precursors. After further derivatization, four representative uncommon sugar units were successfully synthesized.

1. Introduction

Deoxysugars and their oligosaccharides are frequently found in the structure of bioactive drugs. Here, they play very important roles in the general mechanism of these drugs' action.[1] There have been continuing efforts on the synthesis of uncommon monosaccharides,[2] starting from either carbohydrates or noncarbohydrate precursors.[3] Traditionally uncommon sugars were synthesized through multistep transformations of relatively inexpensive common sugars. For example, L-vancosamine can be synthesized from methyl glucoside in 15 steps.[3b] One major disadvantage of this approach is the long reaction sequences for protection and deprotection manipulations. An alternative approach is using noncarbohydrate precursors. In this case, many chemists have come up with different synthetic approaches. For example, Nicolaou synthesized L-vancosamine starting from L-lactate in 11 steps,[4] while McDonald synthesized the same product by tungsten-catalyzed alkynol cycloisomerization in nine steps.[5] Recently, MacMillan's group developed a synthetic pathway for stereoselectively constructing sugar derivatives starting from β,γ-oxyalaldehydes.[6] However, all of these approaches to uncommon sugars from either carbohydrates or noncarbohydrate starting materials are 'target oriented', which means that the designed synthetic approach can only apply to one type of uncommon sugars. In 2002, Wang's group developed a strategy for generating six-membered β,γ-unsaturated lactones using ring-closing-metathesis (RCM).[7] These lactones could be conveniently converted to uncommon sugar derivatives. They are the common starting point for preparation of uncommon sugars, which means this method provides a 'convergent approach' to sugar derivatives. The major advantage of this synthetic strategy is that it provides a systematic synthesis pathway for producing desired uncommon sugar units. For instance, as shown in Scheme 1, four different uncommon sugar units could be synthesized starting from the same α,β-unsaturated lactone **1**. Unfortunately, the relatively high price of the starting materials limited the usage of this method for preparing large quantities of the desired uncommon sugars.

In order to address this drawback of the RCM strategy, we developed a new synthetic pathway by using a cheaper starting material, *trans*-4-phenyl-3-buten-2-one. This



Scheme 1.

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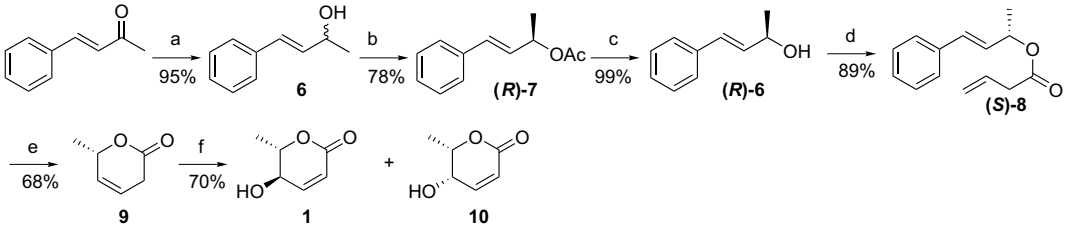
candidate ketone is readily available from commercial source at a very low price. In order to generate the optically pure form of the allylic alcohol, we utilized a novel enzymatic resolution developed by Park's group in 2000.[8] Reduction of this ketone, followed by an enzyme–metal catalytic resolution led to the desired allylic alcohol acetate in good yields with excellent optical purities (>97% ee).

2. Results and discussion

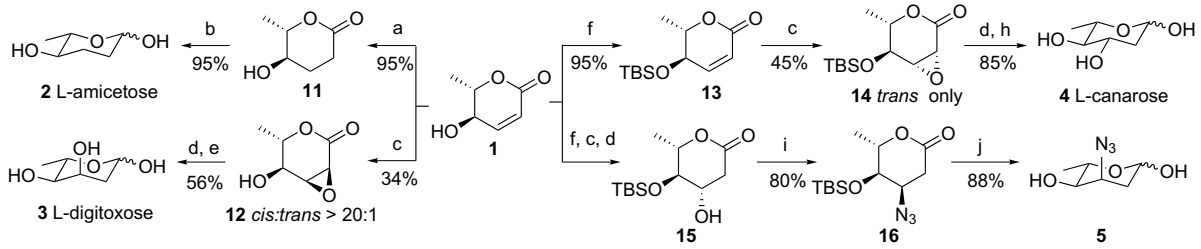
The commercially available *trans*-4-phenyl-3-buten-2-one was readily reduced by $NaBH_4$ in MeOH at 0 °C to give the racemic mixture of the allylic alcohol in >95% yield (Scheme 2). The enzyme–metal catalyzed reaction for dynamic kinetic resolution of the allylic alcohol was performed according to the published method.[8] Previous studies by Park's group indicated that the dichloro(*p*-cymene)-ruthenium(II) complex is an excellent racemization catalyst for dynamic kinetic resolution of allylic alcohol.[9] With the presence of isopropenyl acetate as an acyl donor, *trans*-4-phenyl-3-buten-2-ol (**6**) was converted to the corresponding acetate (*R*)-**7** by using commercially available dichloro(*p*-cymene)-ruthenium(II) dimmer and lipase (from *Pseudomonas cepacia*, immobilized on ceramic particles) as catalysts. It was found that triethylamine is crucial for this reaction. No reaction happened without adding Et_3N even after the reaction mixture was stirred at rt for 24 h. Beside the desired acetate, a saturated ketone was obtained as a side product (10%). Fortunately, the side product was easily removed by column chromatography. After reduction with DIBAL-H (2.0 equiv), alcohol (*R*)-**6** was obtained quantitatively in excellent optical purities (>97% ee).

The esterification was performed under Mitsunobu reaction conditions by adding diethylazodicarboxylate (DEAD) to a mixture of (*R*)-**6**, vinylacetic acid, and PPh_3 in CH_2Cl_2 at 0 °C. This led to the inversion of the chiral center to give (*S*)-ester **8** as a colorless oil in 89% yield (Scheme 3). For the other enantiomer (*R*)-**8**, it was prepared by esterification of vinylacetic acid and (*R*)-**6** using DCC and DMAP. The attempted esterification in acidic conditions failed, mainly due to the instability of the allylic alcohol under acidic conditions. When 2% H_2SO_4 or 5% camphor-10-sulfonic acid (CSA) was used as the catalyst, only the elimination product was observed. Compound (*S*)-**8** was subjected to ring-closing-metathesis under standard conditions using Grubb's second generation catalyst. However, the phenyl group at the terminal vinyl position did give negative effects to the RCM reaction. The reaction was sluggish and even with the presence of 5% catalyst the desired product was isolated in 68% yield after 3 days in refluxing CH_2Cl_2. The β,γ-unsaturated lactone **9** can then be transformed into the corresponding osmundalactones (**1** and **10**) by treatment with DMDO in acetone at pH = 8.5. Under these conditions, the epoxidation and the ring open of the epoxides happened subsequently, to give two osmundalactones, **1** and **10**, in 1.2:1 ratio. Compounds **1** and **10** both are desired products for us because they can be separated and used for synthesis of uncommon sugars individually. In order to clarify the synthetic pathway, only lactone **1** was used to explore the further derivatization steps. Four different types of deoxysugars were successfully prepared from compound **1** (Scheme 3).

After hydrogenation in the presence of Pd/C under H_2 atmosphere (25 psi), lactone **1** was transformed to γ-hydroxy lactone **11**. Subsequently, reduction with DIBAL-H, L-amicetose (**2**) was obtained in excellent yields. On the other hand, when lactone **1** was subjected to the epoxidation conditions (NaClO/pyridine), epoxide **12** was isolated in moderate yield.[12] Fortunately, these conditions enabled us to produce the epoxide compound **12**



Scheme 2. Reagents and conditions: (a) $NaBH_4$/MeOH, 0 °C; (b) lipase, Ru(II) complex, isopropenyl acetate, Et_3N/CH_2Cl_2; (c) DIBAL-H (2.0 equiv)/CH_2Cl_2; (d) vinylacetic acid, Ph_3P, DEAD; (e) Grubb's catalyst/CH_2Cl_2; (f) DMDO/acetone, PBS buffer, pH = 8.5.



Scheme 3. Reagents and conditions: (a) H_2, Pd/C; (b) DIBAL-H/CH_2Cl_2; (c) NaClO, pyridine; (d) $NaBH_4$, PhSeSePh, AcOH, ^{i}PrOH; (e) $NaBH_3CN$; (f) TBSCl, imidazole; (h) TBAF then $NaBH_3CN$; (i) DPPA, PPh_3, DEAD; (j) TBAF then DIBAL-H.

stereoselectively by giving the ratio of *cis trans* greater than 20:1. Compound **12** was then subjected to the selectively ring opening reaction with sodium phenylseleno(triisopropyloxy)borate ($NaBH_4$ and PhSeSePh in acetic acid). Finally, after reduction with $NaBH_3CN$, L-digitoxose (**3**) was obtained in 56% yield (over all yield of two reduction steps).[10]

In order to produce sugars with 3,4-*trans*-difunctionalities, a different strategy has to be taken. As shown in Scheme 3, lactone **1** was first protected as *tert*-butyldimethylsilyl ether. This bulky functional group helped to force the subsequent epoxidation to happen at the *anti*-face of the existing hydroxyl group. As a result, when compound **13** was treated with NaClO/pyridine, only *trans*-epoxide **14** was obtained.[12] Reductively opening the epoxide ring in **14** with sodium phenylseleno(triisopropyloxy)borate allowed the formation of 3,4-*trans*-dihydroxyl lactone. After it was treated with TBAF and $NaBH_3CN$ L-canarose (**4**) was obtained in very good yields. Through this strategy, 2,6-dideoxy sugars with 3,4-*trans*-difunctionalities were achieved, which largely expended the synthetic potential of the RCM methodology. (The previous strategy, RCM followed by asymmetric dihydroxylation, can only produce uncommon sugars with 3,4-*cis*-difunctionalities.[7])

Meanwhile, the stereoselective approach to 3-azido-2,3,6-trideoxy sugar was achieved by taking advantage of Mitsunobu reaction,[11] which was depicted in Scheme 3. Following the same procedure for preparation of the L-canarose (**4**), the precursor **15** was obtained. It was then treated with diphenylphosphoryl azide (DPPA) with the presence of DEAD and triphenylphosphine to give the azido-compound **16** in 80% yield. As a result, the azido-group was introduced inversely to afford the deoxysugar with 3,4-*cis*-difunctionalities (3,4-*cis*:3,4-*trans* >97:3 by NMR). Finally, compound **16** was successfully converted into the 3-azido-2,3,6-trideoxy sugar **5** after the treatment with TBAF and DIBAL-H subsequently.[12]

In summary, by utilizing the chemo-enzymatic synthetic pathway, we were able to generate the chiral allylic alcohols conveniently in large scale. In addition, starting from one osmundalactone, generated through RCM method, four different types of uncommon sugars were successfully prepared. Additional synthetic applications of the RCM methodology are currently undergoing in our laboratory.

Acknowledgements

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12. Spectroscopic data: Compound **5** was obtained as a mixture of α/β-anomers, selected data for β-anomer ^{1}H NMR (400 MHz, CD_3OD) δ 5.03 (dd, J = 9.0, 2.3 Hz, 1H), 4.10 (q, J = 3.5 Hz, 1H), 3.64 (dq, J = 9.2, 6.3 Hz, 1H), 3.41 (m, 1H), 2.14 (q, J = 14.0 Hz, 1H), 1.83 (m, 1H), 1.32 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 90.8, 69.7, 67.0, 63.1, 32.1, 15.3; $[\alpha]_D^{25} = -38$ (c = 1.0, MeOH-d_4); HRMS (EI) *m/z* calculated for $C_6H_{11}N_3O_3$ 173.0796, found 173.0801. Compound **8** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 7.5 Hz, 2H), 7.31 (t, J = 7.0 Hz, 2H), 7.23 (t, J = 7.0 Hz, 1H), 6.59 (d, J = 16.0 Hz, 1H), 6.17 (dd, J = 16.0, 7.0 Hz, 1H), 5.92 (m, 1H), 5.53 (quint, J = 7.0 Hz, 1H), 5.18 (m, 2H), 3.11 (dt, J = 7.8, 1.5 Hz, 2H), 1.40 (d,J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 136.3, 131.7, 130.4, 128.7, 128.6, 127.9, 126.6, 118.5, 71.3, 39.5, 20.4; HRMS (EI) *m/z* calculated for $C_{14}H_{16}O_2$ 216.1145, found 216.1146. Compound **12** ^{1}H NMR (400 MHz, CD_3OD) δ 4.37–4.32 (m, 1H), 3.86 (d, J = 9.0 Hz, 1H), 3.67 (d, J = 4.2 Hz, 1H), 3.62 (d, J = 4.2 Hz, 1H), 1.34 (d, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 167.6, 73.4, 71.1, 55.9, 50.5, 17.1; HRMS (ESI) *m/z* calculated for $C_6H_8O_4Na$ 167.0320 (M+Na$^+$), found 167.0324. Compound **14** ^{1}H NMR (400 MHz, CD_3OD) δ 4.48–4.42 (m, 1H), 3.92 (d, J = 9.2 Hz, 1H), 3.63 (d, J = 4.4 Hz, 1H), 3.54 (d, J = 4.4 Hz, 1H), 1.33 (d, J = 6.4 Hz, 3H), 0.93 (s, 9H), 0.18 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 166.7, 73.3, 71.0, 55.9, 50.7, 25.8, 18.3, −3.9, −4.5; HRMS (ESI) *m/z* calculated for $C_{12}H_{22}O_4SiNa$ 281.1185 (M+Na$^+$), found 281.1190.