PERKIN 1 COMMUNICATION

Enantiopure synthesis of carbohydrates mediated by oxyselenenylation of 3,4-dihydro-2*H*-pyran

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Oxyselenenylation of 3,4-dihydro-2*H*-pyran with (*S*,*S*)-hydrobenzoin and subsequent stereoselective transformations afforded the enantiopure L- and D-arabinose while a disaccharide, 6-*O*-(β-D-arabinopyranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (13) was synthesized from 3,4-dihydro-2*H*-pyran by utilizing the same methodology.

Carbohydrates play key roles in many important biological processes, especially in molecular recognition for the transmission of biological information.[1] Increasing interest in carbohydrates due to biological significance has stimulated the development of a variety of synthetic methods for these compounds.[2] Recently, we reported the syntheses of enantiopure cyclitols from cyclohexene[3] utilizing iterative oxyselenenylation with a chiral alcohol such as (*S*,*S*)-hydrobenzoin (1,2-diphenylethane-1,2-diol). We have extended our oxyselenenylation methodology to 3,4-dihydro-2*H*-pyran, instead of cyclohexene, in an effort to develop a new route towards enantiopure carbohydrates. In fact, dihydropyrans and their derivatives were employed as precursors for racemic syntheses only of various carbohydrates a few decades ago.[4] In this paper, we demonstrate the syntheses of L- and D-arabinoses[5] and a disaccharide from dihydropyran utilizing our oxyselenenylation methodology.

Oxyselenenylation of 3,4-dihydro-2*H*-pyran was carried out with (*S*,*S*)-hydrobenzoin and PhSeCl in the presence of triethylamine to afford a 1.2:1 mixture of the (1*S*,2*R*)-oxyselenide **1** and its (1*R*,2*S*)-diastereomer in 71% yield (Scheme 1).[6] After separation from its diastereomer by column chromatography, the oxyselenide **1** was oxidized with $NaIO_4$, and subsequent elimination of the resulting selenoxide in CCl_4 cleanly provided the olefin **2** in almost quantitative yield. As described in our previous paper,[3] attempts were made to make the olefin **2** undergo the same intramolecular oxyselenenylation as in the case of cyclohexene. However, the bicyclic dioxane **3** could not be generated from the olefin **2**, in contrast to cyclohexene. To understand this unexpected result, we considered the transition state model for the intramolecular cyclization. The episelenonium ion, which would be the first intermediate, could possess either the conformation **A** or **B** as shown in Fig. 1. Conformation **A** containing the hydrobenzoin moiety in the pseudoaxial position would be more favorable due to the anomeric effect.[7] To achieve *trans*-1,2-diaxial opening[8] of the episelenonium ion, the hydroxy group should attack the C3 position in conformation **A**. It is, however, supposed that such cyclization leading to the seven-membered ring to produce a bicyclo[4.3.1]decane structure would be unfavorable.

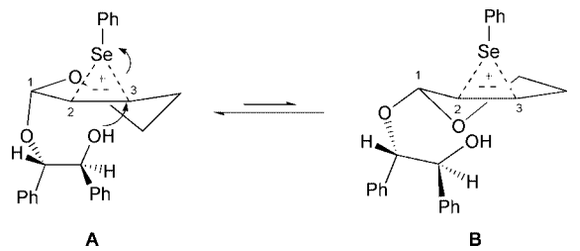
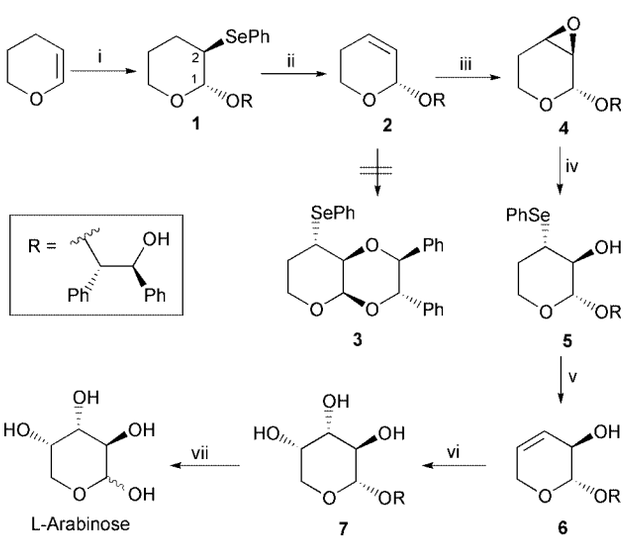


Fig. 1 Two half-chair conformations of the episelenonium ion generated from olefin **2**.

Alternatively, the olefin **2** was treated with dimethyldioxirane (DMD)[9] to give the *trans*-epoxide **4** almost exclusively in 75% yield.[10] Thus, complete diastereoselection was achieved by the directing effect of the bulky hydrobenzoin moiety in **2**. The ring opening of epoxide **4** by sodium phenyl selenide, prepared *in situ* from diphenyl diselenide and $NaBH_4$, yielded the hydroxyselenide **5**. Without isolation of **5**, when it was subjected to the conventional oxidation–elimination sequence with $NaIO_4$ and $NaHCO_3$, the allylic alcohol **6** was obtained as a single diastereomer. Complete regioselective opening of the epoxide ring in **4** with phenyl selenide could be explained again with the anomeric effect and the favorable diaxial opening of the epoxide ring. Dihydroxylation of **6** with OsO_4 and *N*-methylmorpholine *N*-oxide (NMO) occurred in the opposite direction from the C2-hydroxy group in dihydropyran to deliver the triol **7**.[11] Hydrogenolysis of **7** led to L-arabinose in high yield.[12] In the same manner, D-arabinose could be also synthesized starting with the (1*R*,2*S*)-diastereomer of **1**.

Further investigation was executed with a sugar-derived alcohol, instead of hydrobenzoin, to construct a disaccharide skeleton. With 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**8**) as a chiral alcohol partner, the oxyselenenylation of dihydropyran was carried out in a similar procedure to that with dihydropyran and (*S*,*S*)-hydrobenzoin to afforded a 1.2:1 mixture of the (1*R*,2*S*)-oxyselenide **9** and its (1*S*,2*R*)-diastereomer in 76% yield as shown in Scheme 2. The separ-



Scheme 1 *Reagents and conditions*: i, (*S*,*S*)-hydrobenzoin, PhSeCl, Et_3N, THF, room temp., 2 h, 38% of **1** and 33% of its (1*R*,2*R*)-diastereomer, then separation of the diastereomers by column chromatography; ii, $NaIO_4$, $NaHCO_3$, MeOH–H_2O, 60 °C, 1 h then CCl_4, reflux, 2 h, 99%; iii, DMD, acetone, room temp., 1 h, 75%. iv, PhSeSePh, $NaBH_4$, EtOH, reflux, 2 h; v, $NaIO_4$, $NaHCO_3$, MeOH–H_2O, 60 °C, 1 h, then CCl_4, reflux, 2 h, 64% in two steps; vi, OsO_4, NMO, acetone–H_2O, 50 °C, 4 h, 70%; vii, H_2, Pd/C, EtOH, 50 psi, rt, 12 h, 99%.

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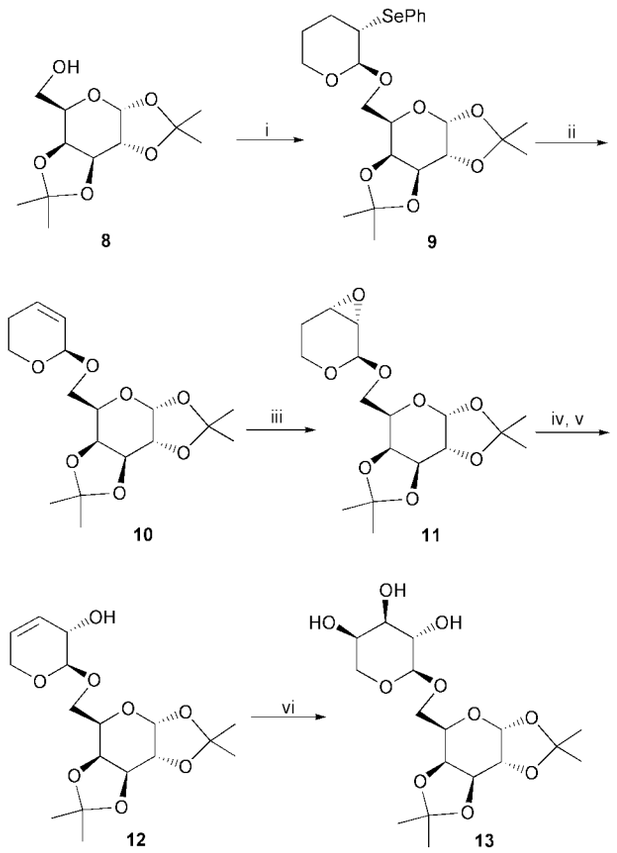

Scheme 2 *Reagents and conditions*: i, dihydropyran, PhSeCl, Et_3N, THF, rt, 2 h, 76% of a mixture of **9** and its diastereomer; ii, $NaIO_4$, $NaHCO_3$, MeOH–H_2O, 60 °C, 2 h then CCl_4, 60 °C, 2 h, 99% of a mixture of **10** and its diastereomer; iii, MCPBA, CH_2Cl_2, rt, 48 h, 68% of a mixture of **11** and its diastereomer; iv, PhSeSePh, $NaBH_4$, EtOH, reflux, 2 h; v, $NaIO_4$, $NaHCO_3$, MeOH–H_2O, 60 °C, 1 h then CCl_4, reflux, 2 h, 65% of a mixture of **12** and its diastereomer in two steps; vi, OsO_4, NMO, acetone–H_2O, 50 °C, 24 h, 45% of **13** and 38% of its diastereomers.

ation of not only **9** and its diastereomer but also two diastereomers in each step of the present reaction sequence shown in Scheme 2 could not be achieved until the final stage. The ratio of compound **9** and its diastereomer was, therefore, determined from the ^{1}H NMR spectrum of the diastereomeric mixture and confirmed by the ratio of the separable final products, **13** and its diastereomers. Oxidation–elimination of **9** and its diastereomer and the subsequent completely stereoselective epoxidation of the olefin **10** and its diastereomer afforded *trans*-epoxides, **11** and its diastereomer again in the ratio of 1.2 : 1. Dihydroxylation of allylic alcohols, **12** and its diastereomer, obtained from **11** and its stereoisomer, afforded a separable mixture of 6-*O*-(β-D-arabinopyranosyl)-1,2 : 3,4-di-*O*-isopropylidene-α-D-galactopyranose (**13**) and its diastereomers[13] in the ratio of 1.2 : 1 in 83% yield. The structure of compound **13** was determined by the comparison of its physical and spectroscopic data with those of the authentic **13**, which was prepared from D-arabinose.[14]

Consequently, this result exhibited that the present methodology could be applied for the synthesis of a variety of mono- and disaccharides by employing an appropriate chiral alcohol. Currently underway is asymmetric oxyselenenylation by using either a chiral selenium reagent or a chiral alcohol.

Experimental

(1*R*,2*S*)-Oxyselenide 1 and its diastereomer

To a solution of PhSeCl (2.31 g, 12.1 mmol) and 3,4-dihydro-2*H*-pyran (1.02 g, 12.1 mmol) in THF (50 cm^3) was added slowly a solution of (*S*,*S*)-hydrobenzoin (2.59 g, 12.1 mmol) and triethylamine (1.84 g, 18.2 mmol) in THF (7 cm^3) at room temperature. After stirring the reaction mixture at room temperature for further 2 h and workup, involving dilution with ether, washing with a saturated $NaHCO_3$ solution and with brine, drying over $MgSO_4$, removal of the solvent, and chromatographic purification (*n*-hexane–ethyl acetate, 6 : 1) of the resulting residue first gave (1*S*,2*R*)-oxyselenide **1** (2.14 g, 39%) (Found: C, 66.23; H, 5.83. $C_{25}H_{26}O_3Se$ requires C, 66.20; H, 5.78%); mp 98–99 °C; R_f 0.43 (silica gel, hexane–EtOAc = 3 : 1); $[\alpha]_D$ −48.3 (*c* 4.35 in $CHCl_3$); ν_{max} (NaCl)/cm^{-1} 3557; δ_H (500 MHz; $CDCl_3$; Me_4Si) 1.47–1.61 (3 H, m), 2.18–2.21 (1 H, m), 3.21–3.25 (1 H, m), 3.29–3.33 (1 H, m), 3.60–3.62 (1 H, m), 3.90 (1 H, s), 4.54 and 4.68 (2 H, ABq, *J* 7.9), 4.80 (1 H, d, *J* 6.5), 6.96–7.27 (13 H, m) and 7.63–7.64 (2 H, m); δ_C (125.8 MHz; $CDCl_3$; Me_4Si) 25.1, 28.7, 44.5, 44.8, 45.0, 64.4, 79.1, 87.3, 105.2, 127.1, 127.3, 127.4, 127.5, 127.7, 128.6, 129.1, 134.4, 138.9 and 139.2. Continued elution gave a diastereomer of **1**, (1*R*,2*S*)-oxyselenide (1.76 g, 32%) (Found: C, 66.22; H, 5.79. $C_{25}H_{26}O_3Se$ requires C, 66.20; H, 5.78%); R_f 0.33 (silica gel, hexane–EtOAc = 3 : 1); $[\alpha]_D$ +3.47 (*c* 2.1 in $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 1.57–1.70 (4 H, m), 2.18 (1 H, m), 3.35 (1 H, m), 3.44–3.47 (2 H, m), 3.91–3.93 (1 H, m), 4.46 (1 H, d, *J* 6.0), 4.67 and 4.70 (2 H, ABq, *J* 8.2), 7.02–7.26 (13 H, m) and 7.42–7.44 (2 H, m); δ_C (125.8 MHz; $CDCl_3$; Me_4Si) 24.9, 28.1, 43.7, 63.9, 78.1, 84.0, 99.8, 127.3, 127.5, 127.6, 127.8, 128.0, 128.2, 128.9, 134.3, 136.9 and 139.5.

6-*O*-(β-D-Arabinopyranosyl)-1,2 : 3,4-di-*O*-isopropylidene-α-D-galactopyranose (13)

To a solution of **12** (193 mg, 0.54 mmol) in acetone (10 cm^3) and water (2 cm^3), NMO (69 mg, 0.59 mmol) and osmium tetroxide (12.7 mg, 0.05 mmol) were added at room temperature and the reaction mixture was stirred at 50 °C for 24 h. After stirring the reaction mixture with $NaHSO_4$ (32 mg), it was partitioned between methylene chloride and water. The organic phase was dried and evaporated to dryness and the residue was chromatographed (chloroform–methanol, 8 : 1) to afford **13** (95 mg, 45%) and its diastereomers (81 mg, 38%). Compound **13** (Found: C, 52.05; H, 7.18. $C_{17}H_{28}O_{10}$ requires C, 52.03; H, 7.19%); mp 78–80 °C; R_f 0.50 (silica gel, $CHCl_3$–MeOH = 8 : 1); $[\alpha]_D$ −49.9 (c 0.75, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3444; δ_H (250 MHz; $CDCl_3$; Me_4Si) 1.33 (3 H, s), 1.35 (3 H, s), 1.46 (1 H, s), 1.53 (1 H, s), 2.30 (3 H, br s), 3.55–3.80 (4 H, m), 3.91–4.04 (3 H, m), 4.29–4.35 (3 H, m), 4.61 (1 H, d, *J* 7.8) and 5.54 (1 H, d, *J* 5.0).

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13 Although the dihydroxylation of **12** gave exclusively compound **13**, the dihydroxylation of the diastereomer of **12** afforded an inseparable mixture of diastereomers. Thus, the diastereomers of **13** were not completely characterized: R_f 0.44 (silica gel, $CHCl_3$–MeOH = 8 : 1).
14 Compound **13** was synthesized differently from authentic D-arabinose as follows: i) Ac_2O, 60% $HClO_4$; ii) P, Br_2, H_2O; iii) **8**, AgOTf, tetramethylurea, CH_2Cl_2; iv) NaOMe, MeOH.