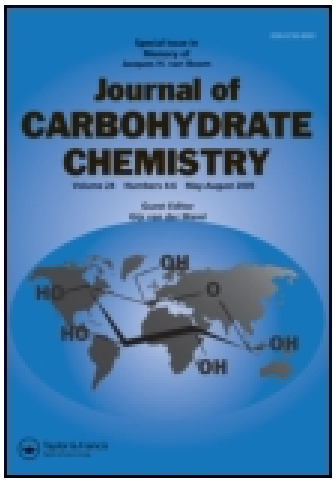

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A NEW APPROACH TO ISOLEVOGLUCOSENONE VIA THE 2,3-SIGMATROPIC REARRANGEMENT OF AN ALLYLIC SELENIDE

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ABSTRACT

A convenient method is described for the synthesis of isolevoglucosenone **5**, via allylic selenide **3**, and its rearrangement to allylic alcohol **4**, followed by oxidation with manganese oxide. Isolevoglucosenone **5**, is produced in 62% overall yield.

INTRODUCTION

Levoglucosenone **1**[1–4] and its isomer isolevoglucosenone **5**[5–9] (Figure 1), are excellent chiral precursors for the functionalization and introduction of biologically important functional groups such as thio- azido- fluoro, fluoromethyl etc. The bicyclic rigidity of **1** and **5** allows for the stereoselective functionalization of the ring system. An efficient and economically feasible method to synthesize isolevoglucosenone is a desirable goal in carbohydrate chemistry.

As part of our continuing studies on thiodisaccharides,[10,11] we required a convenient, quick, and efficient way to produce both enones **1** and **5** for their further stereoselective conversion into *S*-thiodisaccharides[10–12] and *C*-disaccharides.[13] Exist-

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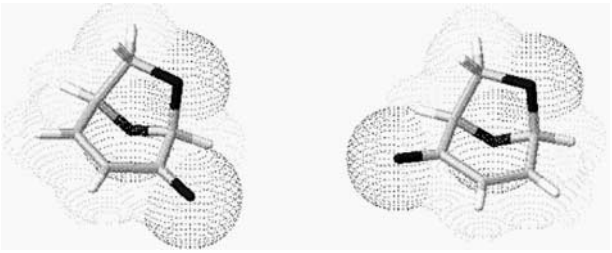


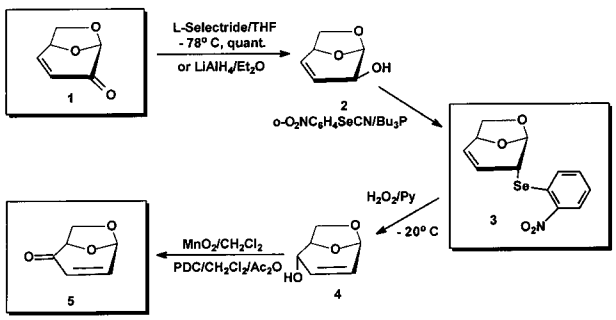
Figure 1. Bicyclic rigidity of levoglucosenone **1** and isolevoglucosenone **5**. Molecular models generated by ACD ChemSketch 4.0, 3D (http://www.acdlabs.com).

ing methods of preparing isolevoglucosenone require multiple steps, and are labor intensive.[5,6] Köll and coworkers[5] reported the first chemical synthesis of enone **5** in six steps.

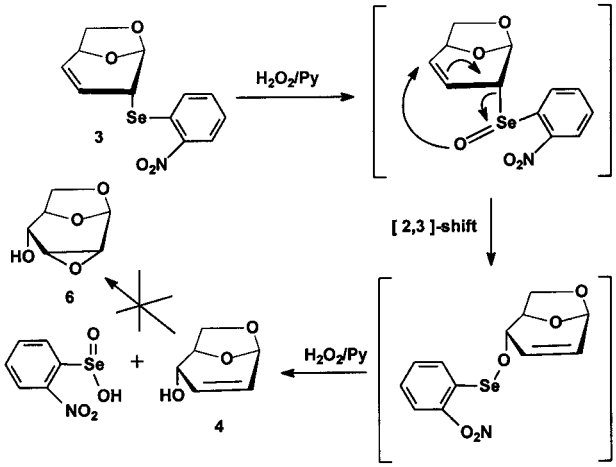
The second synthetic approach, reported by Furneaux and coworkers,[6] also started from levoglucosenone **1** and produced isomeric enone **5** in low yield over seven steps. The general methodology, developed by Horton and Roski[7] for the synthesis of **5** is based on the rearrangement of 3-mesyl-D-glucofuranose, but requires anhydrous reaction conditions and an excess of the catalyst. A new approach to **5** from non-carbohydrate precursor 2-vinylfuran via an Achmatowicz rearrangement[8] was reported by Ogasawara.[9] Recently, we developed a direct route to enone **5** from D-glucal through the 2,3-allylic alcohol **4**.[12] In this paper we report a new and convenient approach for direct conversion of levoglucosenone **1** into its isomeric isolevoglucosenone **5** in 62% overall yield.

RESULTS AND DISCUSSION

Our strategy for the functionalization of C-2 of levoglucosenone **1**, required a stereoselective reduction, followed by the selenium mediated functionalization and oxidation of the allylic selenide. The practical synthesis of **5** is as follows (Scheme 1): the carbonyl group of **1** was reduced with L-Selectride® in THF at −78 °C according to the literature methodology[19] or alternatively with lithium aluminum hydride in ethyl ether to give allylic alcohol **2** in 70% yield as a crystalline derivative, mp 53–54 °C.



Scheme 1.



Scheme 2.

The hydroxy group of **2** was further functionalized by utilizing a combination of the selenium reagent [20] *o*-nitrophenylselenocyanate/tributyl phosphine [21] in a tetrahydrofuran solution with the formation of allylic selenate **3** in 94% yield. The oxidative elimination reaction of the *o*-nitrobenzeneselenyl group with hydrogen peroxide in pyridine at −20 °C for 2 h produced the 1,3 rearranged allylic alcohol **4** in 89% yield (Scheme 1).

The oxidation of **3** with a stoichiometric amount of hydrogen peroxide performed at low temperature (preferably at −20 °C) produced the allylic alcohol **4** in good yield (68%) along with the formation of *o*-nitrobenzeneselenenic acid *o*-$NO_2C_6H_4SeOH$ easily separated from the reaction mixture. The stoichiometric amount of hydrogen peroxide is critical as the *o*-nitrobenzeneselenenic acid formed by further oxidation will be converted to *o*-nitro-benzeneseleninic acid, *o*-$NO_2C_6H_4Se(O)OH$, which is known to catalyze the epoxidation of allylic alcohols. [14] In the oxidation of **3**, described above, the formation of the epoxide **6** [14] was not observed.

The [2,3]-sigmatropic shift leading to rearrangement of the allylic selenide via the intermediate selenoxide during hydrogen peroxide oxidation is presumably catalysed by evolved *o*-nitrophenylseleninic acid, as described by Kametani et. al. [14]

The mechanism of this sigmatropic rearrangement [15] is shown in Scheme 2. This key-step results in double bond transposition and introduction of allylic functionality at C-4 of isolevoglucosenone. To our knowledge, this is the first example of a [2.3]-sigmatropic rearrangement of a functionalized carbohydrate selenide.

The 2,3-allylic alcohol **4**, prepared by this method was identical to the product synthesized by the Oberdorfer procedure. [16,17]

Oxidation of allylic alcohol **4** was performed with manganese oxide [18] in dichloromethane solution to produce the enone **5** in high 89% yield. Alternatively, oxidation of **4** with pyridinium dichromate (PDC) in dichloromethane/acetic anhydride solution produced enone **5** in comparable yield (88%) but required purification by column chromatography to remove residual colloidal chromium complex. In summary, isolevoglucosenone was synthesized in four efficient steps from levoglucosenone, using a sigmatropic rearrangement of an allylic selenoxide as the key step.

EXPERIMENTAL

General Methods. Unless otherwise noted, starting materials were obtained from commercial suppliers and used without purification. Organic extracts were dried with $MgSO_4$ and concentrated with a rotary evaporator under reduced pressure (aspirator). Flash column chromatography was carried out with Silica Gel 60 (70-213 mesh, Merck No. 7734). Thin-layer chromatography (TLC) was performed with Merck F-254 TLC plates. All melting points were uncorrected and were measured in open capillary tubes. Optical rotations were measured with a Jasco DIP-370 polarimeter. ^{1}H NMR spectra were recorded at 250 MHz and ^{13}C NMR spectra at 50 MHz, with TMS as an internal standard on a Bruker DPX250 spectrometer. Levoglucosenone was produced according to the convenient published methodology[4,5] and 1,6-anhydro-3,4-dideoxy-β-D-*threo*-hex-3-enopyranose[2] was prepared according to the method of Shafizadeh et al.[1]

1,6-Anhydro-3,4-dideoxy-2-*Se*-(*o*-nitrobenzyl)-β-D-*erythro*-hex-3-enopyran-ose (3). A solution of **2** (0.72 g, 5.6 mmol) in 15 mL of dry THF containing *o*-nitrobenzeneselenylcyanate, (1.28 g, 5.6 mmol) under nitrogen was treated dropwise with tri-*n*-butylphosphine (300 mg, 1.48 mmol) at room temperature. After the reaction was stirred for 30 min the solvent was removed in vacuo. Column chromatography of the residue on silica gel using hexane–ether (3:1) gave 1.72 g (94%) of *o*-nitrophenylselenide **3**, crystallized as white–yellow crystals mp 160–161.5 °C, 94%, $R_f = 0.52$ (EtOAc), $[\alpha]_D$ −238° (*c* 1.0 $CHCl_3$), ^{1}H NMR ($CDCl_3$): δ 3.72–3.84 (2H, m H-6 and H-6′), 4.85–4-82 (1H, m, H-5), 5.0 (1H, d, J = 4.0 Hz, H-2), 5.69 (1H, br, H-1), 5.9 (1H, ddd, J = 9.8, 4.0, 2.0 Hz, H-3), 6.38 ddd (1H, J = 9.5, 4.8, 1.1 Hz, H-4), 8.24–8.32 (4H, m, aromatic H). ^{13}C NMR: ($CDCl_3$) δ 65.10 (C-2), 118.68, 125.90, 127.4–128.6 (CH-arom), 137.8–138.8 (C-arom), 99.36 (C-1), 71.85 (C-5), 130.24 (C-4), 66.0 (C-6), 132.56 (C-3). HRMS $(M)^+$ *m*/*z*: Calcd for $C_{12}H_{11}NO_4Se$: 312.9853. Found: 312.6195.

Anal. Calcd for $C_{12}H_{11}NO_4Se$: C, 46.17; H, 3.55; N, 4.49. Found: C, 46.56, H, 3.53, N, 4.55.

1,6-Anhydro-2,3-dideoxy-β-D-*erythro*-hex-2-enopyranose (4). To a cooled solution of **3** (1.25 g, 3.9 mmol) in dry pyridine (35 mL), a solution of 32 wt.% water solution of hydrogen peroxide 25 mL was added dropwise at −20 °C. The resulting solution was warmed to ambient temperature and stirred for 4 h. The solution was added to saturated aqueous sodium hydrogen carbonate (100 mL) and the mixture was extracted with chloroform (3×30 mL). The organic layer was washed with water, dried ($MgSO_4$), and concentrated to a yellow oil. Column chromatography on silica gel with hexane/ethyl acetate (5:1) as eluant yielded compound **4** (0.45 g in 89% yield) which crystallized (mp 61–62 °C) upon refrigeration. Compound **4** was independently prepared by the Oberdorfer[16,17] method. $R_f = 0.59$ (EtOAc), mp 60–61.5 °C, Lit. 58–59 °C,[16] $[\alpha]_D$ +318° (*c* 1.0 $CHCl_3$), $[\alpha]_D$ +318° (*c* 1.0 $CHCl_3$): for NMR data see (16, 17). For ^{13}C NMR see (17).

1,6-Anhydro-2,3-dideoxy-β-D-glycero-hex-2-enopyranos-4-ulose (5) (Isolevoglucosenone). (a) A mixture of the crude allylic alcohol **4** (2.56 g, 20 mmol) was dissolved in dry chloroform or dichloromethane (300 mL) and manganese dioxide (MnO_2), (29 g, 334 mmol) was stirred at room temperature for 6 h. After filtration,

the mixture was concentrated to a syrup and the crude product was purified by flash chromatography with 5:1, *n*-pentane-Et_2O, to give enone **5**, (2.25 g, 89%) as a pale yellow oil.

(b) The crude allylic alcohol **4** (2.56 g, 20 mmol) was dissolved in dichloromethane (30 mL). Pyridinium dichromate (PDC), (9.63 g, 25.6 mmol) was added to the mixture while stirring at room temperature for 40 h. Filtration through a column of silica/sand/Celite and concentration afforded a brown syrup (1.5 g, 59.5%) which was purified by flash chromatography using 5:1, *n*-pentane-Et_2O, to produce the enone **5**, as a pale yellow oil (2.22 g, 88%).

Enone **5** could be obtained as an analytically pure colorless syrup after a second chromatographic purification using 5:1, *n*-pentane-Et_2O. ($[\alpha]_D + 319.6$ o (*c* 1.0 $CHCl_3$) lit. $[\alpha]_D + 321°$ (*c* 1.1 $CHCl_3$).[9] The ^1H NMR and ^{13}C NMR spectra of **5** were identical with those published in the literature.[5–9]

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