Reactions of 1,6-anhydro-3,4-dideoxy-2-*O*-methyl-β-D-*threo*-hex-3-enopyranose with thiols and methanol

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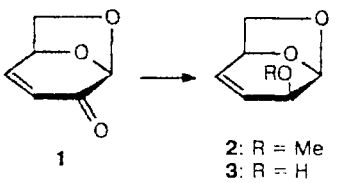
Thiolysis and methanolysis of 1,6-anhydro-3,4-dideoxy-2-*O*-methyl-β-D-*threo*-hex-3-enopyranose yield anomeric thio- and methyl glycosides, respectively, and an acyclic product (in the reaction with EtSH).

Key words: hex-3-enopyranose, anomers, thiols, allylic carbocations, substitution.

Some aspects of the use of levoglucosenone (**1**) as the chiral matrix in the synthesis were considered in Refs. 1 and 2. With the aim of transforming **1** into new acyclic chiral synthons with a *cis* double bond,[3] in this work we studied possible pathways of the ring cleavage in 2-*O*-methyl-1,6-anhydro-3,4-dideoxy-β-D-*threo*-hex-3-enopyranose (**2**), which are initiated by HCl or $BF_3 \cdot Et_2O$[4] and occur under the action of some *O*- and *S*-nucleophiles, in particular, MeOH, $HSCH_2CH_2SH$, or EtSH.

The initial ether **2** was obtained by methylation of 1,6-anhydro-3,4-dideoxy-β-D-*threo*-hex-3-enopyranose (**3**)[5] with MeI in the presence of KOH in DMSO[6] in a yield of 90%. Storage of ether **2** in a methanolic solution of HCl at 0 °C for 24 h gave an anomeric mixture of methyl glycosides **4** and **5** in a ratio of 7 : 1 in a total yield of 63% (Scheme 1). Individual anomer **4** was isolated by chromatography. The anomeric configurations were assigned based on the data of ^1H and ^{13}C NMR spectroscopy, nuclear Overhauser effect (NOE) experiments, and MM2 calculations.

Scheme 1



1 **2**: R = Me **3**: R = H

The main difference between isomers **4** and **5** is that in the ^{13}C NMR spectrum of the major isomer **4**, the signals of the C(2) and C(1) atoms are shifted upfield, which may be explained by "1,2-*cis* interaction",[7,8] whereas the signal of the H(1) atom in the ^1H NMR spectrum is shifted downfield. This allows the assignment of a β-anomeric configuration to isomer **4**. Taking into account a probable anomeric effect,[9] β-anomer **4** and α-anomer **5** exist in the ^1H_O and $^OH_1$ conformations, respectively. Calculations by the MM2 method suggested that the dihedral H(1)—C(1)—C(2)—H(2) angles for β-anomer **4** and α-anomer **5** are ~90° and ~70°, respectively, which is consistent with the patterns of the signals of H(1) (broadened singlet for **4** and the doublet ($^3J_{1,2}$ ~3) for **5**[10]).

The NOE experiments also confirmed this assignment: irradiation of the proton at the C(1) atom in 1,2-*cis*-isomer **4** increases the intensities of the signals of protons at C(2) and of both methoxyl groups (the distance between the C(1)—H and the C(2)—OMe proton is 2.5 Å). Excitation of C(1)—H in isomer **5** increases the intensities of the C(2)—H and C(1)—OMe signals, whereas NOE for the C(2)—OMe protons is not observed because the C(2)—OMe fragment is far removed from the irradiated C(1)—H group (~4.5 Å).

Reaction of **2** with thiols proceeds readily in the presence of $BF_3 \cdot Et_2O$. A reaction with $HSCH_2CH_2SH$ yields a mixture of thioglycosides **6** and **7** (Scheme 2), which is difficult to separate, in a ratio of 3 : 1 (^1H NMR) in good yield. The structures of **6** and **7** were established by comparing their NMR spectra with the spectra of compounds **4** and **5**. The reaction of **2** with more nucleophilic thiol EtSH yields a mixture of several compounds, which are difficult to separate. Based on the spectral data, the structure of the acyclic compound (**8**) was assigned to the major product. With the aim of identifying other components of the mixture, the reaction of ether **2** with EtSH was stopped at the initial stage by adding Et_3N. According to the spectral data, the product obtained was a mixture of three compounds, namely, acyclic trithio derivative **8** (50%) and anomeric thioglycosides **9** and **10** in a ratio of 2 : 3, whose NMR spectra are similar to those of **6** and **7**. The total yield of compounds **8**—**10** was higher than 95%. According to the ^{13}C NMR data, the repeated storage of the purified

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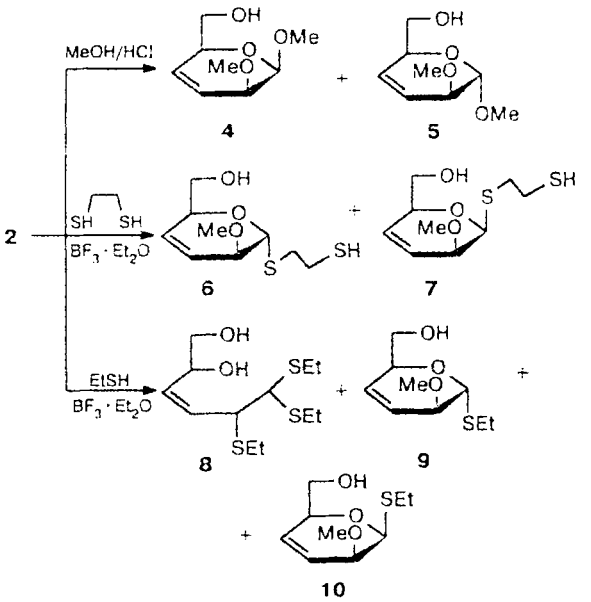
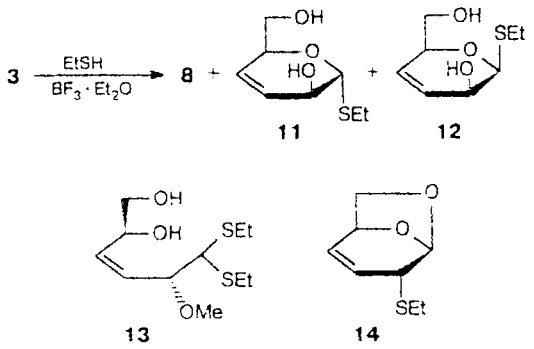
mixture of **8**—**10** in EtSH in the presence of $BF_3 \cdot Et_2O$ at 0°C for 48 h afforded only an equilibrium mixture of anomeric compounds **9** and **10** with a somewhat increased proportion of β-anomer **10**. We succeeded in isolating anomer **10** in the pure form. No other changes in the composition of the mixture were observed.

Scheme 2

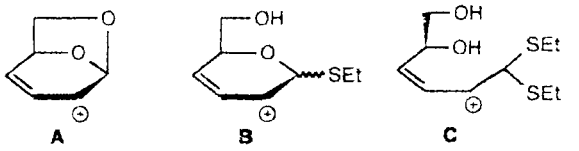


We also studied thiolysis of alcohol **3** under conditions of the ring cleavage of ether **2** (Scheme 3). As expected, trithio derivative **8** and anomeric thioglycosides **11** and **12** (in a ratio of 2 : 1, 51%) were formed in good yield (88%).

Scheme 3



In the reactions of ether **2** under study, the transformation of **2** into trithio derivative **8** is of prime interest. This transformation is absolutely regio- and stereospecific. The replacement of the OMe group at the C(2) atom in compound **2** by the SEt group is not accompanied by the allylic rearrangement, which is confirmed by the data of ^1H NMR and COSY for compound **8** ($J_{1,2}$ = 5.7 Hz). It is difficult to establish unambiguously a configuration of the C(2) center* based on the available data. The assignment was made considering possible chemical pathways of formation of **8**. Apparently, transformation of **2** into **8** occurs by the S_Ni mechanism through allylic carbocationic intermediates, which can be generated either directly from ether **2** or from products of successive cleavage of the rings (*i.e.*, compounds **9**, **10**, and **13**). These carbocations are represented below by structures **A**, **B**, and **C**, respectively.



First, the acyclic carbocation **C** should be excluded from consideration. If the key stage of the replacement of the OMe group by the SEt group proceeded through formation of **13** *via* the acyclic carbocation **C**, the subsequent attack of thiol could not be stereoselective due to the absence of significant stereodifferentiating factors. In general, one of carbocations (**B**), which is stabilized by the S atom of the vicinal SEt group (which acts also as a stereocontrolling factor), could give more clear results because in this case, attack of the external nucleophile EtSH on the carbocationic center **B** would proceed from the side of the molecule opposite to the SEt substituent. However, as mentioned above, direct conversion of compounds **9**, **10** → **8** does not occur.

Therefore, carbocation **A** seems to be the most probable intermediate responsible for the stereochemical result of the reaction. An alternative C(4) carbocation, the product of the allylic rearrangement, is not formed.** Oxygen atoms of the acetal fragment stabilize the C(2) carbenium center in **A**, and its 1,6-anhydro bridge provides an efficient face differentiation of the direction of nucleophilic attack from the α-side of the molecule.[1] We failed to isolate compound **14**, which is an intermediate along the **2** → **A** → **8** pathway. Apparently, in this case, generation of carbocation **A** is the rate-determining step, which is followed by fast steps of complete ring cleavage and thioacetalization. Simultaneously, the concurrent process **2** → **9**, **10** occurs. We attribute the

* For simplicity of discussion, the atomic numbering scheme is given analogous to that of compound **2**.

** In the case of acid-catalyzed thermal decomposition of levoglucosan, the initially formed C(3)-carbocation undergoes 1,2-hydride shift to form C(2)-hydroxycarbenium ion, which is more stable than the alternative C(4)-ion.[11]

exceptional regio- and stereoselectivity of formation of **8** to the above-mentioned factors, although it is known that most of analogous reactions of allylic electrophiles are nonselective and hard to control.

Experimental

The ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer operating at 300 and 75.47 MHz, respectively; Me_4Si was used as the internal standard; $CDCl_3$ was used as the solvent. The NOE and COSY H,H experiments were carried out according to routine procedures using the standard Bruker software. Molecular mechanics calculations were performed using the program, which implements the MM2 method[12,13] according to Ref. 13. TLC was carried out on Silufol plates (Czech Republic). The mass spectra were measured on a MKh-1320 instrument (EI, 70 eV); the temperature of the ionization chamber was 50—90 °C. The optical rotation was measured on a Perkin-Elmer 141 polarimeter.

1,6-Anhydro-3,4-dideoxy-2-*O*-methyl-β-D-*threo*-hex-3-enopyranose (2). Powdered KOH (3.5 g) was added to a solution of alcohol **3** [5] (2.0 g) in DMSO (30 mL). The mixture was stirred for 1 h, and then MeI (4.4 g) was added dropwise. The mixture was stirred for 30 min and poured into cold water (100 mL). The product was extracted with ethyl acetate (3×50 mL). The combined extracts were dried over $MgSO_4$ and concentrated. The residue was chromatographed on SiO_2 to give compound **2** (2.0 g, 90%), R_f 0.36 (ethyl acetate), $[\alpha]_D^{20}$ −41.7° (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$), δ: 3.49 (s, 3 H, CH_3), 3.80 (dddd, 1 H, $H_a(6)$, J =6.5, 4.1, 1.2, and 1.1 Hz), 4.00 (d, 1 H, $H_b(6)$, J = 6.5 Hz), 4.11 (m, 1 H, H(2)), 4.67 (dd, 1 H, H(5), J = 4.1 and 4.2 Hz), 5.67 (dd, 1 H, H(1), J = 2.4 and 2.2 Hz), 5.79 (ddd, 1 H, H(3), J = 10.0, 2.4 and 2.2 Hz), 6.14 (dddd, 1 H, H(4), J = 10.0, 4.2, 1.4, and 1.1 Hz). ^{13}C NMR ($CDCl_3$) δ: 56.88 (CH_3), 71.53 (C(2), C(6)), 77.92 C(5), 99.91 C(1), 125.91 C(4), 130.98 C(3).

Methyl 3,4-dideoxy-2-*O*-methyl-β-D-*threo*-hex-3-enopyranoside (4) and its α-anomer (5). AcCl (4.5 mL) was added to anhydrous methanol (90 mL) at 0 °C. Ether **2** (0.9 g) was dissolved in the resulting mixture, and the mixture was stirred at ~20 °C for 24 h. The reaction mixture was neutralized with a saturated aqueous solution of $NaHCO_3$. Methanol was evaporated, and the residue was extracted with $CHCl_3$ (3×50 mL). The combined extracts were dried over $MgSO_4$ and evaporated. The residue was chromatographed on SiO_2 to give β-anomer **4** (0.26 g) and a mixture of anomers **4** and **5** (0.5 g). Anomer **4**. $[\alpha]_D^{20}$ +18.5° (*c* 0.08, $CHCl_3$). ^1H NMR δ: 3.43 (s, 3 H, OCH_3), 3.50 (s, 3 H, OCH_3), 3.52 (m, 1 H, H(2)), 3.65 (dd, 1 H, $H_a(6)$, J = 5.9 and 11.4 Hz), 3.70 (dd, 1 H, $H_b(6)$, J = 3.4 and 11.4 Hz), 4.30 (m, 1 H, H(5)), 4.85 (s, 1 H, H(1)), 5.90—6.10 (m, 2 H, CH=CH). ^{13}C NMR, δ: 55.71 and 56.41 (2 OMe), 64.33 C(6), 68.69 C(2), 72.04 C(5), 98.91 C(1), 123.16 and 130.51 (CH=CH).

Anomer **5** (the spectra were recorded for a mixture of **4+5**). ^1H NMR, δ: 3.50 (s, 3 H, OCH_3), 3.59 (s, 3 H, OCH_3), 4.70 (d, 1 H, H(1), J = 2.8 Hz), 5.85—6.05 (m, 2 H, CH=CH). ^{13}C NMR δ: 56.76 (OMe), 57.45 (OMe), 64.85 C(6), 71.99 C(2), 75.01 C(5), 99.51 C(1), 125.76 and 129.55 (CH=CH).

Reactions of enopyranoses 2 and 3 with thiols (general procedure). $BF_3 \cdot Et_2O$ (0.03 mol) was added to a mixture of enopyranose (0.03 mol) and the corresponding thiol (0.15 mol) at 0°C. The mixture was stirred for 2 h, and then Et_3N (0.05 mol) was added. The solution was evaporated, and the residue was chromatographed on a column with SiO_2.

2-Mercaptoethyl 3,4-dideoxy-2-*O*-methyl-1-thio-α-D-*threo*-hex-3-enopyranoside (6) and its β-anomer (7) were obtained in a total yield of 75%. Anomer **6**, $[\alpha]_D^{21}$ +48.0° (*c* 1.0, $CHCl_3$). ^1H NMR, δ: 1.78 (t, 1 H, SH, J = 8.2 Hz), 2.60—3.00 (m, 4 H, 2 SCH_2), 3.39 (s, 3 H, OCH_3), 3.60—3.75 (m, 3 H, H(2), 2 H (6)), 4.20 (m, 1 H, H(5)), 4.75 (d, 1 H, H(1), J = 2.4 Hz), 5.90—6.10 (m, 2 H, CH=CH). ^{13}C NMR, δ: 25.34 (SCH_2), 35.36 (SCH_2), 56.76 (CH_3), 64.44 C(6), 71.92 C(5), 76.93 C(2), 84.95 C(1), 125.25 and 131.25 (CH=CH).

Anomer **7**. ^1H NMR, δ: 1.70 (t, 1 H, SH, J = 8.0 Hz), 2.70—3.00 (m, 4 H, 2 SCH_2), 3.36 (s, 3H, OCH_3), 3.50—3.75 (m, 3 H, H(2), 2 H(6)), 4.40 (m, 1 H, H(5)), 5.33 (s, 1 H, H(1)), 5.90—6.10 (m, 2 H, CH=CH). ^{13}C NMR, δ: 24.99 (SCH_2), 34.98 (SCH_2), 56.30 (CH_3), 63.98 C(6), 68.75 C(2), 73.01 C(5), 81.66 C(1), 123.43 and 130.96 (CH=CH).

(*Z*)-5(*R*),6,6-Tri(ethylthio)hex-3-ene-1,2(*S*)-diol (8). $[\alpha]_D^{20}$ +94.3° (*c* 1.0, $CHCl_3$). ^1H NMR δ: 1.20 (t, 3 H, CH_3, J = 7.0 Hz), 1.21 (t, 6 H, 2 CH_3, J = 7.0 Hz), 2.51 (q, 2 H, SCH_2, J = 7.3 Hz), 2.60—2.72 (m, 4 H, 2 SCH_2), 3.47 (dd, 1 H, $H_a(6)$, J = 11.3 and 7.8 Hz), 3.65 (dd, 1 H, $H_b(6)$, J = 11.3 and 3.4 Hz), 3.90 (d, 1 H, H(1), J = 5.7 Hz), 4.01 (dd, 1 H, H(2), J = 5.7 and 9.6 Hz), 4.40 (ddd, 1 H, H(5), J = 7.7, 3.4, and 7.8 Hz), 5.54 (dd, 1 H, H(4), J = 11.9 and 7.7 Hz), 5.61 (dd, 1 H, H(3), J = 11.9 and 9.6 Hz). ^{13}C NMR, δ: 14.22 (CH_3), 14.28 (CH_3), 14.45 (CH_3), 25.49 (SCH_2), 25.58 (SCH_2), 25.68 (SCH_2), 48.04 C(2), 55.46 C(1), 66.13 C(6), 68.66 C(5), 130.02 and 131.08 (CH=CH). Mass spectrum (EI), m/z (I_{rel} (%)): 296 $[M]^+$(1), 235 $[M-SEt]^+$ (4), 175 $[M-SEt-C_2H_4S]^+$ (3), 173 $[M-SEt-HSEt]^+$ (4), 143 $[M-CH(SEt)_2-H_2O]^+$ (4), 135 $[CH(SEt)_2]^+$ (100), 106 $[135-C_2H_5]^+$ (7), 75 $[135-C_2H_4S]^+$ (15).

Ethyl-2-*O*-methyl-3,4-dideoxy-1-thio-α-D-*threo*-hex-3-enopyranoside (9). ^1H NMR (obtained for a mixture of **9+10**), δ: 1.35 (t, 3 H, CH_3, J = 7.4 Hz), 2.65 (q, 2 H, SCH_2, J = 7.4 Hz), 3.36 (s, 3 H, OCH_3), 3.56—3.72 (m, 3 H, H(2), 2 H(6)), 4.18 (m, 1 H, H(5)), 4.72 (d, 1 H, H(1), J = 2.4 Hz), 5.85—5.95 (m, 2 H, CH=CH). ^{13}C NMR, δ: 15.12 (CH_3), 25.11 (SCH_2), 56.81 (OCH_3), 64.65 C(6), 72.19 C(5), 76.91 C(2), 84.41 C(1), 125.68 and 131.26 (CH=CH).

Ethyl 3,4-dideoxy-2-*O*-methyl-1-thio-β-D-*threo*-hex-3-enopyranoside (10), $[\alpha]_D^{18}$ +315.7° (*s*, 1.0, $CHCl_3$). ^1H NMR, δ: 1.34 (t, 3 H, CH_3, J = 7.4 Hz), 2.60—2.70 (m, 2 H, SCH_2), 3.42 (s, 3 H, OCH_3), 3.56 (m, 1 H, H(2)), 3.70—3.85 (m, 2 H, 2 H(6)), 4.46 (m, 1 H, H(5)), 5.40 (s, 1 H, H(1)), 5.90—6.10 (m, 2 H, CH=CH). ^{13}C NMR, δ: 15.03 (CH_3), 25.00 (SCH_2), 56.30 (OCH_3), 64.19 C(6), 68.58 C(2), 73.36 C(5), 81.12 C(1), 123.75 and 130.97 (CH=CH).

Ethyl 3,4-dideoxy-1-thio-α-D-*threo*-hex-3-enopyranoside (11) and its β-anomer (12). After chromatography, the total yield of a mixture of **8+11+12** was 88%, the yield of **11+12** was 51%. Anomer **11**. ^1H NMR, δ: 1.26 (t, 3 H, CH_3, J = 7.4 Hz), 2.70 (m, 2 H, SCH_2, J = 7.4 Hz), 3.65 (dd, 1 H, $H_a(6)$, J = 12.0 and 4.4 Hz), 3.78—3.98 (m, 4 H, $H_b(6)$, H(2), OH(6), OH(2)), 4.20 (m, 1 H, H(5)), 4.72 (s, 1 H, H(1)), 5.80—5.88 and 6.05—6.15 (both m, 2 H, CH=CH). ^{13}C NMR, δ: 15.17 (CH_3), 24.87 (SCH_2), 64.02 C(6), 64.56 C(5), 76.96 C(2), 85.45 C(1), 128.94 and 129.87 (CH=CH).

Anomer **12**. ^1H NMR, δ: 1.27 (t, 3 H, CH_3, J = 7.4 Hz), 2.65 (q, 2 H, SCH_2, J = 7.4 Hz), 3.75 (dd, 1 H, $H_a(6)$, J = 11.8 and 3.6 Hz), 3.78—3.98 (m, 4 H, $H_b(6)$, H(2), OH(6), OH(2)), 4.42 (m, 2 H, H(5)), 5.25 (s, 1 H, H(1)), 5.80—5.88

and 6.05—6.15 (both m, 2 H, CH=CH). ^{13}C NMR, δ: 15.11 (CH_3), 25.02 (SCH_2), 63.63 C(6), 64.79 C(5), 68.77 C(2), 84.78 C(1), 126.63 and 129.92 (CH=CH).

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