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Synthesis of a Ring Fragment of 9α,11α-Thiathromboxane A_2. Procedure for Bond C^1–C^2 Cleavage in Monosaccharides by an Example of D-Glucose 2-Deoxy-3-mesyl Derivative

R. V. Bikbulatov, R. R. Akhmetvallev, F. A. Akbutina, L. V. Spirikhin, and M. S. Miftakhov

Institute of Organic Chemistry, Ufa Scientific Center, Russian Academy of Sciences, Ufa, Russia

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Abstract—4-C-Allyl-1-S-acetyl-2,4-dideoxy-3-*O*-mesyl-6-*O*-methoxymethyl-1-sulfanyl-α,β-D-arabinohexopyranoside treated with $(Me_3Si)_2NNa$ in benzene at room temperature affords a bicyclic product resulting from intramolecular cyclization, and at treatment with a system MeONa–MeOH at heating suffers fragmentation furnishing (2*S*,3*S*)-1-methoxymethyloxy-3-vinyl-5-hexen-2-ol.

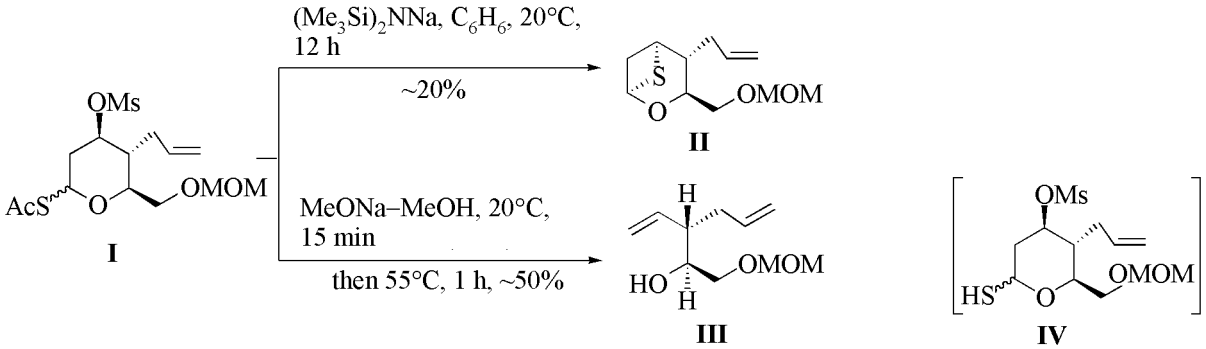
In attempt to perform intramolecular cyclization of anomeric (3 : 2) glucose thioacylals (**I**) by treatment with MeONa in MeOH aiming at preparation compound **II** as a model of the 9α,11α-thiathromboxane A_2 [1, 2] we obtained a remarkable fragmentation product, diol **III**. This transformation occurred stepwise. First the acetylthioester function of **I** readily hydrolyzed at room temperature providing sulfanylpyran (**IV**) that at heating to ~50°C gradually transformed into dienol **III**. Compound **III** has been detected by TLC, and it can be separated as individual substance.

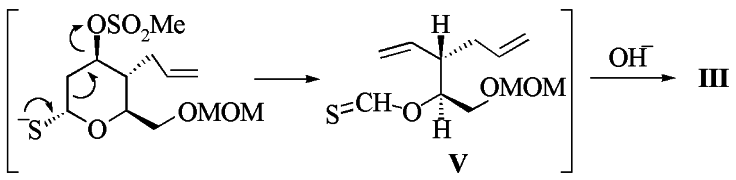
Note that without heating of the mixture (20°C, 12 h) only trace amounts of products originating from fragmentation (**III**) and cyclization (**II**) were detected.

We succeeded in preparation of compound **II** in a moderate yield at the use sodium hexamethyldisilazide in benzene to effect the thietane ring closure. The reaction was carried out at room temperature till complete consumption of the initial compound (TLC monitoring). When *t*-BuOK in THF was attempted as a cyclization agent for compound **I** we observed only significant tarring and formation of dienol **III** in a small yield.

In the reactions described alongside the demonstrated possibility to build up the ring fragment of the 9α,11α-thiathromboxane A_2 also conversion I → III is obviously interesting from the synthetic viewpoint.

The conversion discovered may be classed as a new thia version of Grob fragmentation [3, 4] whose driving force is a formation of thioformal function in intermediate **V** facilitated by ejection of a leaving mesyl group.





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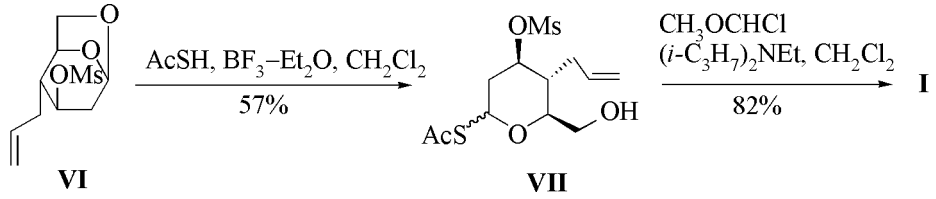
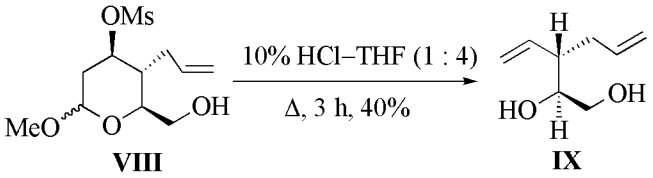


It should be mentioned in conclusion that a transformation similar to **I**→**III** we already observed before: Anomeric methyl-3-*O*-mesylglycosides **VIII** at heating in a mixture aqueous HCl–THF also furnished fragmentation product **IX** [5]. These results indicate a certain general trend in the cleavage of the C^1–C^2 bond in 2-deoxy-3-*O*-mesyl derivatives of glycosides. This process can be applied in synthesis to building chiral blocks resembling compound **III**.



EXPERIMENTAL

IR spectra were recorded on spectrophotometers UR-20 and Specord M-80 from films or mulls in mineral oil. ^{1}H and ^{13}C NMR spectra were registered on spectrometer Bruker AM-300 at operating frequencies 300 and 75.47 MHz respectively from solutions in $CDCl_3$. TLC was performed on Silufol UV 254:366, visualizing of spots was carried out by iodine vapor, calcination, or treating the plates with solution of anisaldehyde and sulfuric acid in ethanol at the ratio 1:0.5:10 followed by heating to 120–150°C. The optical rotation was measured on Perkin Elmer 141 instrument.

4-C-Allyl-1-S-acetyl-2,4-dideoxy-3-*O*-mesyl-6-*O*-methoxymethyl-1-sulfanyl-α,β-D-arabino-hexopyranoside (I). To a solution of 0.2 g (0.62 mmol) of compound **VII** in 5 ml of anhydrous CH_2Cl_2 at room temperature while stirring was added 0.6 ml (0.8 mmol) of methoxymethyl chloride and 1.1 ml (0.8 mmol) of diisopropylethylamine. The reaction mixture was stirred for 2 h, then washed in succession with cold water and saturated NaCl solution, dried on $MgSO_4$, and evaporated. The residue was subjected to column chromatography on silica gel (eluent ethyl acetate–hexane, 1:2) to isolate 0.19 g (82%) of anomeric 3:2 mixture of oily compound **I**. ^{1}H NMR spectrum, δ, ppm: 1.95– 2.10 m (2H), 2.20–2.40 m (3H), 2.31 (2.36) s (3H, $COCH_3$), 3.01 (3.03) s (3H, SO_2CH_3), 3.32 s (3H, OCH_3), 3.60–3.80 m (3H, H^5, $2H^6$), 4.60 s (OCH_2O), 4.80 m (1H, H^3), 5.10–5.20 m (2H, CH_2=), 5.80 m (1H, CH=), 6.09 m (1H, H^1). ^{13}C NMR spectrum, δ, ppm: 30.10 (30.42) (CH_2), 30.51 (31.19) ($COCH_3$), 37.97 (C^2), 38.94 (SO_2CH_3), 39.89 (40.45) (C^4), 55.38 (OCH_3), 66.73 (66.78) (C^6), 74.12 (76.14) (C^1), 76.66 (78.14) (C^5), 78.42 (78.62) (C^3), 96.57 (OCH_2O), 118.72 (118.80) (CH_2=), 132.64 (132.69) (CH=), 192.39 (192.54) (CO).

(1*R*,3*S*,4*R*,5*R*)-4-Allyl-3-methoxymethoxymethyl-2-oxa-6-thiabicyclo[3.1.1]heptane (II). To a stirred solution of 0.2 g (0.54 mmol) of compound **I** in 1 ml of benzene at room temperature under argon atmosphere was added 0.11 g (0.6 mmol) of sodium hexamethyldisilazide. After 10 h 5 ml of water was added to the reaction mixture, the products were extracted into dichloromethane (3×5 ml), the combined organic extracts were dried on $MgSO_4$, evaporated, the residue was subjected to column chromatography on silica gel deactivated with triethylamine (eluent ethyl acetate–hexane, 1:2) to yield 50 mg (20%) of oily compound **II**. $[\alpha]_D^{20}$ +220° (*c* 1.0, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm: 2.10 d (1H, H^{7B}, *J* 10 Hz), 2.20–2.30 m (3H, CH_2, H^4), 3.38 s (3H, OCH_3), 3.42 d.t (1H, H^5, *J* 1 and 5 Hz), 3.53 d.d.d (1H, H^{7A}, *J* 5 and 10 Hz), 3.72 d.d (1H, OCH_2, *J* 5 and 11 Hz), 4.38 m (1H, H^3), 4.68 d (1H, *J* 6.4 Hz) and 4.70 d (1H, *J* 6.4 Hz) (OCH_2O), 5.00–5.10 m (2H, CH_2=), 5.38 d.d (1H, H^1, *J* 3 and 5 Hz,), 5.70–5.85 m (1H, CH=). ^{13}C NMR spectrum, δ, ppm: 35.84 (CH_2), 42.86 (C^7), 46.99 (C^4), 47.19 (C^5), 55.25 (OCH_3), 66.34 (CH_2O), 76.36 (C^3), 85.98 (C^1), 96.58 (OCH_2O), 117.47 (CH_2=), 135.25 (CH=).

(2*S*,3*S*)-1-Methoxymethyloxy-3-vinyl-5-hexen-2-ol (III). To a stirred solution of 0.2 g (0.54 mmol) of compound **I** in 1 ml of MeOH at room temperature was added a solution of 30 mg (0.6 mmol) of MeONa in 0.5 ml of MeOH. In 15 min the reaction mixture was heated to 55°C, and the stirring was continued for about 1 h more. To the reaction mixture 5 ml of water was added, and the reaction product was extracted into dichloromethane (3×5 ml). The combined organic extracts were dried on $MgSO_4$, the solvent

was evaporated, and the residue was subjected to column chromatography on silica gel (eluent ethyl acetate–hexane, 1 : 8) to isolate 50 mg (50%) of oily dienol **III**. $[\alpha]_D^{20}$ +15° (*c* 1.0, $CHCl_3$). ^1H NMR spectrum, δ, ppm: 2.20–2.35 m (3H, CH_2, CH), 3.40 s (OCH_3), 3.48 d.d (1H, H^{1B}, *J* 8 and 10 Hz), 3.63 d.d (1H, H^{1A}, *J* 3 and 10 Hz), 3.79 m (H^2), 4.66 s (OCH_2O), 5.00–5.20 m (4H, $2CH_2$=), 5.77 m (2H, 2CH=). ^{13}C NMR spectrum, δ, ppm: 35.64 (C^4), 46.61 (C^3), 55.41 (OCH_3), 71.45 (C^1), 71.72 (C^2), 97.02 (OCH_2O), 116.26, 117.30 (C^6, CH_2=), 136.47, 137.60 (C^5, CH=).

4-C-Allyl-1-S-acetyl-2,4-dideoxy-3-*O*-mesyl-1-sulfanyl-α,β-D-arabino-hexopyranoside (VII). To a mixture of 0.5 g (2.02 mmol) of mesylate **VI** [5] and 0.3 g (4 mmol) of ethanethioic acid at room temperature was added 0.18 g (2.02 mmol) of $BF_3 \cdot Et_2O$. The mixture was stirred for 4 h, then 0.5 g (5 mmol) of Et_3N was added, and the reaction product was extracted into dichloromethane (3 × 5 ml). The combined organic extracts were dried on $MgSO_4$, the solvent was evaporated, and the residue was subjected to column chromatography on silica gel (eluent ethyl acetate–hexane, 1 : 1). We isolated 0.37 g (57%) of α,β-anomeric (3 : 2) mixture of oily compound **VII**. ^1H NMR spectrum, δ, ppm: 1.90–2.10 m (2H), 2.20–2.40 m (4H), 2.33 (2.36) s (3H, $COCH_3$), 3.04 (3.06) s (3H, SO_2CH_3), 3.60–3.80 m (3H, H^5, $2H^6$), 4.78 m (1H, H^3), 5.10–5.20 m (2H, CH_2=), 5.77 m (1H, CH=), 6.08 d.d (1H, H^1, *J* 2 and 5 Hz). ^{13}C NMR spectrum, δ, ppm: 30.19 (30.71) (CH_2), 30.62 (31.26) ($COCH_3$), 37.55 (37.90) (C^2), 38.97 (SO_2CH_3), 40.07 (40.41) (C^4), 62.19 (62.48) (C^6), 75.16 (76.26) (C^1), 76.66 (78.03) (C^5), 78.16 (79.79) (C^3), 118.72 (118.80) (CH_2=), 132.84 (132.97) (CH=), 192.52 (193.01) (CO).

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