Synthesis of Cyclopropanated Dimethyl Mercaptal Sulfoxide Pyranoses from Epoxytriflate Pyranosides and Methyl Methylthiomethyl Sulfoxide

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The reaction of 4-O-triflyl-2,3-anhydropyranosides with methyl methylthiomethyl sulfoxide in the presence of n-ButLi or NaH affords 3,4-cyclopropanated pyranoses via triflate substitution and subsequent intramolecular epoxide opening.

1. Introduction

Stereo specifically cyclopropanated sugar derivatives are not only interesting from their biological point of view, but they can also serve as templates for the synthesis of natural products using the chiron approach [1]. The previous successes in the synthesis of a number of cyclopropanated sugar derivatives via displacement of the triflyl group [2] promoted us to investigate a similar reaction with a carbanion derived from methyl methylthiomethyl sulfoxide [3] for the synthesis of 2,3-cyclopropanated dimethyl mercaptal sulfoxide sugars.

2. Results and Discussion

For the reaction of benzyl 2,3-anhydro-4-O-triflyl-α-D-ribofuranoside (2) and benzyl 2,3-anhydro-4-O-triflyl-β-L-ribofuranoside (3) with methyl methylthiomethyl sulfoxide (1), two types of procedures were employed: a) After treating 1 with NaH (3–4 equivalents) at 0 °C in THF, a pre-cooled solution of 2 and 3 respectively, in THF was added dropwise using a double-ended needle and the resulting mixture was stirred for several hrs at 0 °C and gradually warmed to room temperature (Method A). b) 2 and 3 respectively, dissolved in a THF/HMPA 5:1 mixture, were subjected to react with 3–4 equivalents of the carbanion, formed by the addition of n-ButLi to 1 (Method B). In each case, a diastereomeric mixture of the cyclopropanated sugar derivatives 4 and 5 were obtained from 2 and 3 respectively, in a 1:1 ratio in 70% and 71% total yield (Scheme 1). As observed in similar cases [2], apparently the formed substitution products 2a and 3a are further alkylated by the trans-oriented oxirane ring. In fact, all attempts to isolate 2a and 3a failed. The products 4 and 5 were isolated by column chromatography and the diasteriomeric mixtures separated by plate chromatography using a 1:2 mixture of methylene chloride and ethyl acetate. The two different conformations $^1\!H_1$ and $^1\!H_6$ can be safely assigned to the compounds 4a, 4b and 5a, 5b based on the chemical shifts of H-1 and the H$_{1,2}$ coupling constants. In the case of compounds 4a and 4b, H-1 resonates at $\delta = 4.80$ and 4.82 ppm, while in the case of 5a and 5b the chemical shifts are $\delta = 4.14$ and 4.18 ppm. The coupling constants $J_{1,2} = 4.2$ and 4.3 Hz in 4a and 4b respectively, indicate the equatorial axial relationship between H-1 and 2, suggesting a $^3\!H_1$ conformation for these compounds. In 5a and 5b, the coupling constants $J_{1,2} = 7.2$ and 7.3 Hz respectively, give evidence for the diaxial orientation of H-1 with H-2, and therefore the adoption of a $^3\!H_6$ conformation has to be assumed.

Regarding the conversion of methyl dimethyl mercaptal sulfoxide compounds to cyclic ketones by different hydrolysis conditions, reported in the literature [4], we tried to hydrolyze the cyclopropanated products into cyclopropanone derivatives, however without any positive results. When 4 was subjected to hydrolysis with cupric chloride dihydrate in 1,2-dimethoxyethane [3b] at room temperature for several hours, also no reaction took place, but when it was refluxed for 5 min, a new
product appeared with the rest of starting material. After continuation of the reaction for another 5 min, the formation of further 5 decomposition products was observed. Therefore, the reaction was repeated again and stopped after 5 min. The product, separated from the starting material on TLC plates using 10% methanol in ethyl acetate was identified to be benzyl 3,4-dideoxy-4-C-formyl-β-D-erythro-pent-3-enopyranoside (6). 6 is probably formed via a cyclopropanone intermediate, followed by rearrangement, shows one downfield singlet at $\delta = 9.35$ in the $^1$H NMR spectrum indicating the presence of the aldehyde group which is also confirmed by the downfield signal at $\delta = 190.3$ ppm in $^{13}$C NMR spectrum. One more downfield singlet at $\delta = 6.58$ ppm in the $^1$H-NMR and two signals at $\delta = 177.0$ and 145.4 ppm in the $^{13}$C NMR spectrum confirm the presence of the olefinic hydrogen and carbon atoms, respectively.

### 3. Experimental

Melting points: Büchi 501 capillary melting point apparatus.- $^1$H and $^{13}$C NMR: Bruker AC 250 in CDCl$_3$.- MS: Varian MAT 711.- Elemental analyses: Perkin-Elmer elemental analyser, model 240.- Optical rotations: Zeiss Polarimeter, model LEP AZ.- Column chromatography: Merck silica gel 60 (70–230 mesh).- Thin-layer chromatography: Merck precoated silica gel plates (F$_{254}$).- All the solvents used were purified by distillation: THF was distilled from sodium and benzophenone and HMPA from calcium hydride under nitrogen.
**General methods for the synthesis of cyclopropanated sugar derivatives**

**Method A:** 0.17 ml (4 equivalent, 1.7 mmol) methyl methylthiomethyl sulfoxide was treated with 67.72 mg (4 eq., 1.7 mmol) NaH (60% dispersion in oil) suspension in THF (5 ml) at 0°C under N₂. After further stirring of the reaction mixture at the same temperature for 20 min, the reaction mixture was warmed to room temperature and stirred for 4–5 hr. After completion of the reaction (TLC analysis), the reaction mixture was decomposed with 5 mmol) of 2 and 3 respectively, dissolved in THF (5 ml) was added and the reaction mixture gradually warmed to room temperature and stirred for 4–5 hr. After cooling the reaction mixture in oil suspension in THF (5 ml) at 0°C under N₂. After further stirring of the reaction mixture for 1 hr the resulting mixture was quenched by adding a saturated ammonium chloride solution and worked up as described in method A.

**Method B:** To a solution of 0.17 ml (4 equivalent, 1.7 mmol) methyl methylthiomethyl sulfoxide was treated with 67.72 mg (4 eq., 1.7 mmol) NaH (60% dispersion in oil) suspension in THF (5 ml) at 0°C under N₂. 4.82 (d, 1H, J = 4.3 Hz, H-1), 4.79 (d, 1H, J = 11.7 Hz, H-2), 3.45 (bs, 1H, OCH₂Ph), 2.4 (s, 3H, SCH₃), 2.16 (t, 1H, J = 11.7 Hz, H-5'), 4.34 (dd, 1H, J = 12.7 Hz, H-5'), 4.20 (dd, 1H, J = 12.5, 4.2 Hz, H-5'). 3.50 (dd, 1H, J = 4.1 Hz, H-2), 3.45 (bs, 1H, OCH₂Ph), 2.72 (s, 3H, SOCH₃), 2.4 (s, 3H, SCH₂), 2.16 (t, 1H, J = 1.5 Hz, H-3), 1.95 (d, 1H, J = 12.8 Hz, H-4). -¹³C NMR (63 MHz, CDCl₃): δ = 137.5, 128.6–128.0 (Ar-C), 93.8 (C-1), 70.0 (OCH₂Ph), 62.7 (C-2), 35.2 (C-7), 24.3 (C-3), 16.1 (C-4), 14.4 (SCH₃). - MS(FD): m/z = 328 (M⁺).

C₁₅H₂₀O₄S₂ (328.45)
- Calcd C 54.85 H 6.14 S 19.52%.
- Found C 55.18 H 6.04 S 19.81%.

**Benzyl 3,4-di-oxoy-(C-dimethyl mercaptal sulfoxide)-methylene-α-D-arabinopyranoside (5)**

**Isomer 5a:** Yield: 49 mg (35.5%) oil. -¹H NMR (250 MHz, CDCl₃): δ = 7.33–7.25 (m, 5H, Ar-H), 4.81 (d, 1H, J = 11.6 Hz, OCH₂Ph), 4.63 (d, 1H, J = 12.9 Hz, H-5'), 4.46 (d, 1H, J = 11.6 Hz, OCH₂Ph), 4.20 (dd, 1H, J = 12.9, 4.3 Hz, H-5'), 4.14 (d, 1H, J = 7.2 Hz, H-1), 3.42 (dd, 1H, J = 7.3, 1.8 Hz, H-2), 2.78 (bs, 1H, OCH₂Ph), 2.35 (s, 3H, SCH₂), 1.95 (dd, 1H, J = 9.6, 2.0 Hz, H-3), 1.82 (dd, 1H, J = 9.7, 3.8 Hz, H-4). -¹³C NMR (63 MHz, CDCl₃): δ = 136.8, 128.6–128.2 (Ar-C), 101.8 (C-1), 70.6 (OCH₂Ph), 65.0 (C-2), 63.0 (C-5), 49.0 (C-6), 36.4 (C-7), 34.8 (C-3), 27.3 (C-4), 17.48 (C-8). - MS(FD): m/z = 328 (M⁺).

**Isomer 5b:** Yield: 49 mg (35.5%) oil. -¹H NMR (250 MHz, CDCl₃): δ = 7.33–7.23 (m, 5H, Ar-H), 4.84 (d, 1H, J = 11.7 Hz, OCH₂Ph), 4.50 (d, 1H, J = 11.7 Hz, OCH₂Ph), 4.18 (d, 1H, J = 7.3 Hz, H-1), 4.14 (dd, 1H, J = 10.8, 2.7 Hz, H-5'), 4.20 (d, 1H, J = 12.4 Hz, H-5), 3.70 (dd, 1H, J = 7.3, 2.1 Hz, H-2, D₂O exchange), 3.30 (bs, 1H, OH), 2.54 (s, 3H, SOCH₃), 2.21 (s, 3H, SCH₂), 1.96 (m, 1H, J = 10.2 Hz, J = 2.2 Hz, H-4), 1.82 (dd, 1H, J = 10.6, 4.2 Hz, H-3). -¹³C NMR (63 MHz, CDCl₃): δ = 137.1, 128.8–128.0 (Ar-C), 101.5 (C-1), 70.6 (OCH₂Ph), 65.7 (C-2), 61.9 (C-5), 48.0 (C-6), 38.7 (C-7), 36.1 (C-3), 26.5 (C-4), 17.2 (SCH₂) - MS(FD): m/z = 328 (M⁺).

C₁₅H₂₁O₄S₂ (328.45)
- Calcd C 54.85 H 6.14 S 19.52%.
- Found C 54.84 H 6.47 S 19.90%.

**Benzyl 3,4-di-oxoy-(C-dimethyl mercaptal sulfoxide)-methylene-α-D-arabinopyranoside (6)**

150 mg (0.46 mmol) 4 and 77.84 mg (1 equivalent, 0.46 mmol) CuCl₂ were refluxed in 5 ml 1,2-dimethoxyethane for 5 min. After cooling the reaction mixture, the solvent was evaporated in vacuo and the product separated from the starting
material on TLC plates using the solvent system 10% methanol/ethyl acetate. Yield: 10%, oil. $^1$H NMR (250 MHz, CDCl$_3$): $\delta = 9.35$ (s, 1H, CHO), 7.30–7.25 (m, 5H, Ar H), 6.58 (bs, 1H, H-3), 5.30 (d, 1H, $J = 4.0$ Hz, H-1), 4.75 (d, 1H, $J = 11.7$ Hz, OCH$_2$Ph), 4.60 (d, 1H, $J = 12.6$ Hz, H-5), 4.53 (d, 1H, $J = 11.6$ Hz, OCH$_2$Ph), 4.35 (m, 1H, H-5'), 4.24 (dd, 1H, $J = 4.8$, 2.7 Hz, H-2). $^{13}$C NMR (63 MHz, CDCl$_3$): $\delta = 190.3$ (CHO), 177.0 (C-4), 145.4 (C-3), 128.7–128.2 (Ar-C), 95.0 (C-1), 70.3 (OCH$_2$Ph), 64.8 (C-2), 57.4 (C-5).

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