

# Unexpected bromination reaction of isosteviol methyl ester with bromoalkanes

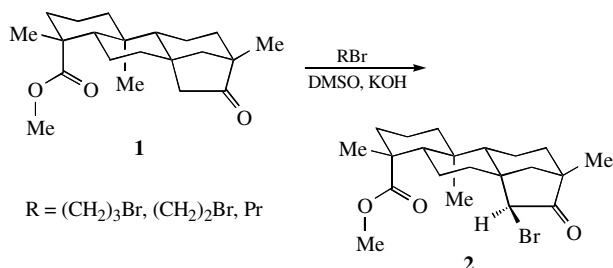
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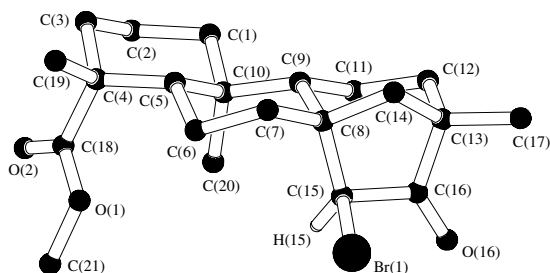
10.1070/MC2003v013n05ABEH001782

The reactions of isosteviol methyl ester **1** with 1,3-dibromopropane, 1,2-dibromoethane and 1-bromopropane give rise to 15-bromoisosteviol methyl ester **2**.

We found that the interaction of isosteviol methyl ester<sup>1</sup> **1** with an excess of 1,3-dibromopropane, 1,2-dibromoethane or 1-bromopropane in a DMSO solution in the presence of KOH under reflux gives rise to earlier unknown 15-bromoisosteviol methyl ester **2**.<sup>†</sup>



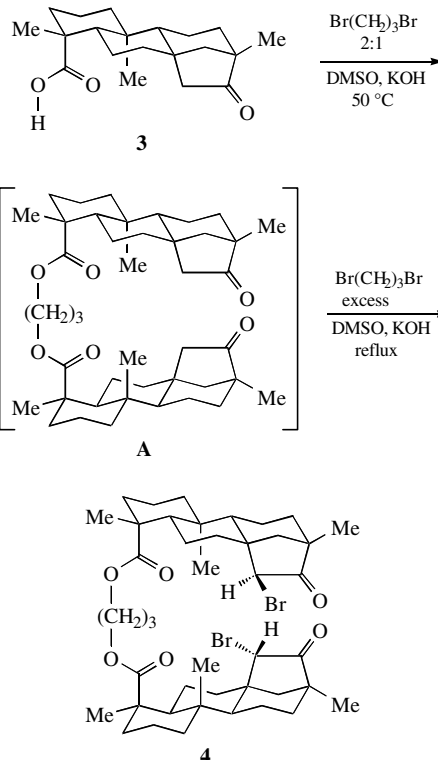
NMR data indicate that only one of two possible stereoisomers, namely, compound **2**, was formed in the reaction mixture. The doublet of doublets corresponding to either of protons of the  $\text{CH}_2$  group at  $\text{C}^{15}$  at 2.6 ppm disappeared and only one doublet corresponding to the proton of the  $\text{CHBr}$  moiety at 4.5 ppm was observed. According to X-ray single crystal diffraction,<sup>‡</sup> product **2** is 15-bromoisosteviol methyl ester having (*R*)- $\text{C}^4$ , (*S*)- $\text{C}^5$ , (*R*)- $\text{C}^8$ , (*S*)- $\text{C}^9$ , (*S*)- $\text{C}^{10}$ , (*S*)- $\text{C}^{13}$  and (*S*)- $\text{C}^{15}$  carbon atoms. The structure of compound **2** was determined by X-ray single crystal diffraction,<sup>‡</sup> and the molecular structure of compound **2** is shown in Figure 1. Thus, the bromoalkanes used under these reaction conditions act as bromination agents and introduce bromine at the  $\alpha$ -position with respect to the



**Figure 1** Molecular structure of compound **2**. Only the H atom at  $\text{C}^{15}$  is shown.

<sup>†</sup> Isosteviol methyl ester **1** (0.2 g, 0.6 mmol) was put in a suspension of KOH (0.06 g) in DMSO (3 ml); 1,3-dibromopropane (0.25 ml, 4.4 mmol) was added to a stirred mixture, and the mixture was boiled for 20 min. Then, it was poured into water and extracted with diethyl ether. The extract was washed with water, dried and evaporated. The crystals of **2** (0.23 g, 92%, mp 197–200 °C) were obtained.  $[\alpha]_D^{26} -17.9^\circ$  (*c* 0.78,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.73 (s, 3H, 10-Me), 1.09 (s, 3H, 13-Me), 1.20 (s, 3H, 4-Me), 3.65 (s, 3H,  $\text{COOMe}$ ), 4.48 (d, 1H,  $\text{CHBr}$ ,  $^4J_{\text{HH}}$  2.5 Hz). IR (mineral oil,  $\nu/\text{cm}^{-1}$ ): 1730 ( $\text{MeOC=O}$ ), 1750 ( $\text{C=O}$  ketone), 510, 560 ( $\text{C-Br}$ ). Found (%): C, 61.30; H, 10.17; Br, 18.74. Calc. for  $\text{C}_{21}\text{H}_{31}\text{O}_3\text{Br}$  (%): C, 61.31; H, 10.01; Br, 19.42.

<sup>‡</sup> X-ray data collected on an Enraf–Nonius CAD4 four-circle diffractometer will be published elsewhere. NMR spectra were recorded on a Bruker MSL instrument (250 MHz). The IR spectra were measured on an UR-20 spectrometer.

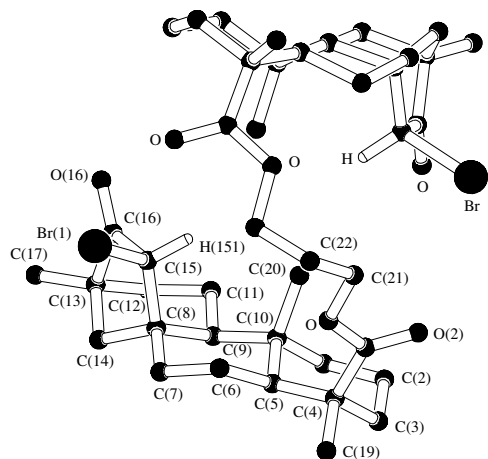


carbonyl group. To the best of our knowledge, these bromoalkanes did not exhibit such properties earlier.

If we used isosteviol<sup>2</sup> **3** in the reaction with 1,3-dibromopropane and step-by-step enlarged an amount of 1,3-dibromopropane in the reaction mixture, first, the alkylation reaction of isosteviol carboxylic groups took place with formation of 1,3-bis(iso-stevioxyloxy)propane **A**. Then, the bromination reaction at the  $\text{C}^{15}$  position of both isosteviol residues gave rise to 1,3-bis-(15-bromoisostevioxyloxy)propane **4**.<sup>§</sup> The structure of **4** was determined by X-ray single crystal diffraction<sup>‡</sup> (Figure 2).

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<sup>§</sup> Isosteviol **3** (0.5 g, 1.6 mmol) was dissolved in a suspension of KOH (0.16 g) in DMSO (7 ml) with stirring. 1,3-Dibromopropane (0.08 ml, 1.4 mmol) was added, and the mixture was heated for 6 h; then, an excess of 1,3-dibromopropane (1.25 ml, 8.9 mmol) was added, and the mixture was boiled for 20 min, poured into water and extracted with diethyl ether. The extract was washed with water, dried and evaporated. The residue was chromatographed on silica gel and eluted with chloroform–light petroleum (1:1) to give crystals of **4** (0.34 g, 52%), mp 188–190 °C.  $[\alpha]_D^{20} -12^\circ$  (*c* 0.74,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.75 (s, 6H, 10-Me), 1.10 (s, 6H, 13-Me), 1.21 (s, 6H, 4-Me), 4.16 (m, 4H,  $\text{COOCH}_2$ ), 4.48 (d, 2H,  $\text{CHBr}$ ,  $^4J_{\text{HH}}$  2.5 Hz). IR (mineral oil,  $\nu/\text{cm}^{-1}$ ): 1148, 1175, 1722 ( $\text{COO}$ ), 1745 ( $\text{C=O}$ ).



**Figure 2** Molecular structure of compound **4**. Only the H atoms at C<sup>15</sup> are shown.

## References

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