Chemistry of Natural Compounds and Bioorganic Chemistry

Free-radical reactions of carbohydrate derivatives in the synthesis of carbocyclic compounds. 2*. Conversion of 3-methoxy-4-methoxycarbonylmethyl-2-oxabicyclo[2.2.1]heptanes into the corresponding cyclopentane derivatives**

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The decisive influence of the carboxyl group on the methanolysis of 3-methoxy-4-methoxycarbonylmethyl-2-oxabicyclo[2.2.1.]heptanes was proved experimentally, and several routes of conversion of the latter to the corresponding cyclopentanes were found.

Key words: free-radical reactions, carbohydrates, chiral cyclopentanes.

The possibility in principle of the synthesis of type **1** chiral carbocyclic compounds (Scheme 1) by intramolecular free-radical C(2)—C(6)-cyclization of monosaccharide derivatives was demonstrated in the previous report of this series.[1] It was noted also that unlike 2-oxabicyclopentanes,[2] compound **1** undergoes no transformation into cyclopentane **3** by methanolysis even in the presence of a 20 % H_2SO_4 solution. Under these conditions transesterification of the carboxyl group and anomerization of the C(1) center take place and derivative **4** forms in 40 % yield. This was established by the comparison of the ^1H NMR spectra of compounds **4** and **5*****; the former were reported previously[1] and the latter was obtained in this work.

Thus, the difficulty of conversion of 2-oxabicycloheptanes **1** into type **3** derivatives impedes the synthesis of chiral cyclopentanes from monosaccharides by the strategy offered previously.[1] This behavior of derivative **1** under methanolysis conditions may be caused by the stabilizing influence of the ethoxycarbonylmethyl group on the carbocation at C(1) formed in methanolysis. This stabilizing effect blocks pyranose ring opening and hinders the final formation of cyclopentane **3**. To prove this assumption and to solve the problem of the transition from type **1** 2-oxabicycloheptanes to the corresponding cyclopentanes we undertook the study of several routes, which provided the subject of this work.

The most logical confirmation of the negative effect of the carboxyl group on the methanolysis of a type **1** compound is the transformation of derivative **5** *via* alcohol **7** into the mixture of methylglycosides **8**. We obtained the ester **5** by cyclization of unsaturated bromide **6** by a modified method[1] using preliminary degasification of the solutions and filling of the appara-

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***Carbon atoms are numbered according to carbohydrate nomenclature for the convenience of discussion of the spectra.

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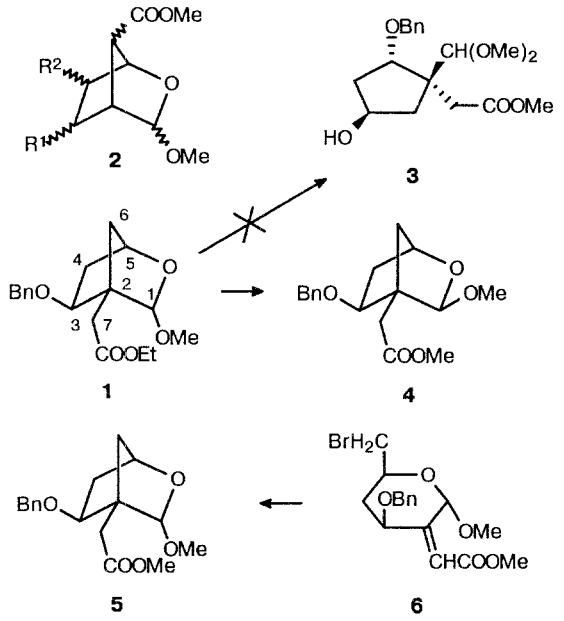
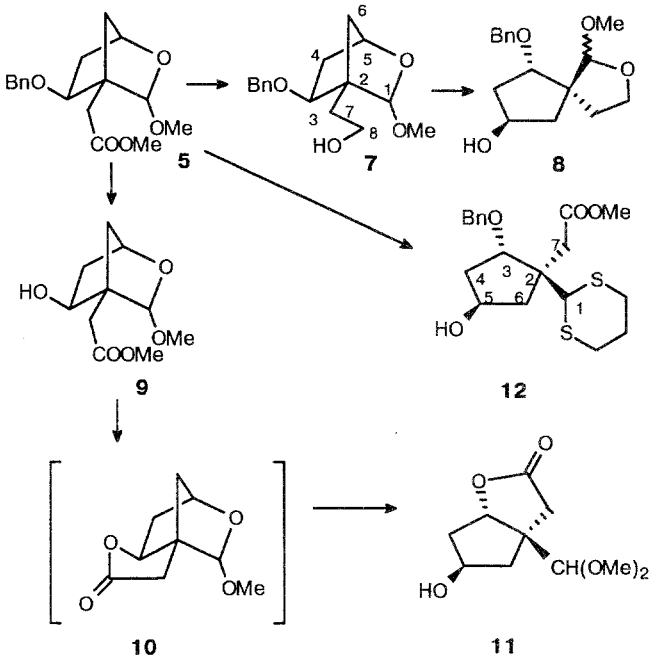
Scheme 1



Scheme 2



tus with argon. The reduction of ester **5** with $LiAlH_4$ in THF proceeds almost quantitatively. The subsequent methanolysis of alcohol **7** proceeds very smoothly to afford the mixture of methylglycosides **8** in 77 % yield.

Alcohol **9** was obtained through the debenzylation of ester **5** by refluxing in methanol with Raney Ni. The analysis of the molecular model of the alcohol **9** allows one to suppose that during its methanolysis, lactone **10** could be formed at first, the carboxyl group becoming "blocked" and no longer stabilizing the carbocation at C(1) formed at the initial stage of pyranoside methanolysis. In fact, the methanolysis of alcohol **9** afforded cyclopentane **11** in 73 % yield. The ^1H NMR spectrum and the specific rotation of this substance proved it to be identical to the one described earlier.[1]

Finally, the acetolysis of compound **1** was shown in a previous report[1] to be inefficient and to afford cyclopentane **11** after methanolysis in 36 % yield only. In the present work we carried out the mercaptolysis of derivative **5** at low temperatures with $ZnCl_2$ as the calalyst[3] and found that it proceeds smoothly and leads to compound **12** (65 %), in which all protective groups and the degree of oxidation of all functions are retained.

Thus, the controlling influence of the carboxyl group at C(2) on the methanolysis of derivatives like **5** is confirmed experimentally and some routes of the conversion of the latter into the corresponding cyclopentanes are found. The most general of them are, apparently, carboxyl group reduction with subsequent methanolysis of the intermediate alcohol, as well as mercaptolysis with $ZnCl_2$ as the catalyst at low temperatures. The removal of the benzyl protection and the methanolysis of intermediate **9** can probably be used to obtain chiral cyclopentanes only in the case of substances with an equatorial hydroxyl group at C(3).

Experimental

Melting points were measured using an electrically heated block in a capillary and are uncorrected. Specific rotation was measured with a Jasco DIP-360 polarimeter in chloroform. ^1H NMR spectra were recorded on a Brucker WM-250 in $CDCl_3$. The assignment of the signals was made using homonuclear double resonance techniques in differential variants.

The course of the reaction and the purity of the isolated substances were monitored by TLC on Kieselgel 60. Thin-layer chromatograms were visualized by treatment with a 5 % H_2SO_4 solution in MeOH and heating to ~200 °C. The reactive mixtures were separated by column chromatography on Silpearl (25—40 μm) in benzene—ether. The solvents were distilled in an argon atmosphere over a suitable drying agent (CaH_2, $LiAlH_4$).

To remove the dissolved oxygen before free-radical cyclization the solutions were evacuated until intense ebullition of the solvent and the apparatus was filled with argon.

(1*S*, 2*S*, 3*S*, 5*S*)-5-Benzyloxy-3-methoxy-4-methoxycarbonylmethyl-2-oxabicyclo[2.2.1]heptane (5). A solution of AIBN (50 mg, 0.3 mmol) and tributyltin hydride (680 mg, 2.34 mmol) in 20 mL of absolute benzene was added dropwise to a boiling solution of methyl 3-*O*-benzyl-6-bromo-2-

carbomethoxymethylidene-4,6-dideoxy-α-D-treohexopyranoside **6**[1] (600 mg, 1.56 mmol) in 50 mL of absolute benzene in an argon stream for 3 h. The mixture was refluxed for 20 min, benzene was evaporated and the residue was subjected to gradient chromatography on SiO_2 (benzene—THF). Yield 450 mg (95 %), syrup, $[\alpha]_D$ = +65.4 ° (*c* 1.0; $CHCl_3$). ^{1}H NMR (δ, ppm, *J*, Hz): 4.89 (c, 1 H, H-1); 4.07 (dt, 1 H, H-3, $J_{3,4e}$ = 6.5; $J_1 = J_2$ = 1.5); 1.64 (dt, 1 H, H-4a, $J_{4,4}$ = 13.5; $J_1 = J_2$ = 2.5); 2.20 (ddd, 1 H, H-4e, $J_{4e,6}$ = 2.5); 4.36 (t, 1 H, H-5, $J_{5,4a} = J_{5,4e}$ = 2.5); 2.10 (d, 1 H, H-6, $J_{6,6'}$ = 10); 1.93 (ddd, 1 H, H-6, J_1 = 2; J_2 = 3.5); 2.78 and 2.71 (d, 2 H, H-7,7', AB-system, J_{gem} = 14); 4.42 and 4.53 (d, 2 H, CH_2Ph, AB-system, J_{gem} = 11.5); 3.38 (c, 3 H, OMe at C(1)); 3.61 (c, 3 H, COOMe); 7.30 (m, 5 H, $OCH_2C_6H_5$ at C(3)).

β-Anomer **4**:[1] 4.58 (c, 1 H, H-1); 3.86 (dd, 1 H, H-3, $J_{3,4a}$ = 2.5; $J_{3,4e}$ = 6.5); 1.57 (dt, 1 H, H-4a, $J_{4,4}$ = 13; $J_1 = J_2$ = 2.5); 2.07 (ddd, 1 H, H-4e, $J_{4e,6}$ = 2.5); 4.38 (dd, 1 H, H-5, J_1 = 2.0; J_2 = 3.0); 1.70 (d, 1 H, H-6, $J_{6,6'}$ = 10); 1.79 (dt, 1 H, H-6', $J_1 = J_2$ = 2.5); 2.78 and 2.95 (m, 2 H, H-7,7', AB-system, J_{gem} = 16.5); 4.34 and 4.51 (d, 2 H, CH_2Ph, AB-system, J_{gem} = 11.5); 3.35 (c, 3 H, OMe at C(1)); 3.62 (c, 3 H, COOMe); 7.30 (m, 5 H, $OCH_2C_6H_5$ at C(3)).

(1*S*, 3*S*, 4*S*, 5*S*)-5-Benzyloxy-4-(β-hydroxyethyl)-3-methoxy-2-oxabicyclo[2.2.1]heptane (7). Compound **5** (100 mg, 0.33 mmol) was dissolved in 2 mL of absolute THF, $LiAlH_4$ (13 mg, 0.33 mmol) was added and the mixture was refluxed for 1 h . The mixture was cooled, decomposed carefully with water, filtered, and the residue was washed with chloroform. The filtrate was evaporated and chromatographed on SiO_2 in a benzene—THF gradient. Yield 85 mg (93 %), syrup, $[\alpha]_D$ = −15.0 ° (*c* 1.0; $CHCl_3$). ^{1} NMR: (δ, ppm, *J*, Hz): 4.78 (c, 1 H, H-1); 4.13 (dt, 1 H, H-3, $J_{3,4e}$ = 6.5; $J_1 = J_2$ = 1.5); 1.66 (dt, 1 H, H-4a, $J_{4,4'}$ = 13.5; $J_{4a,5} = J_1$ = 2.5); 2.21 (ddd, 1 H, H-4e, $J_{4e,6'}$ = 2.5); 4.37 (t, 1 H, H-5, *J* = 2.5): 1.97 (d, 1 H, H-6, $J_{6,6'}$ = 10); 1.75 (ddd, 1 H, H-6', J_1 = 4); 2.17 and 2.11 (t, 2 H, H-7, H-7', $J_{7,7'}$ = 15, $J_{7,8} = J_{7,8'}$ = 5); 4.54 and 4.37 (d, 2 H, CH_2Ph, AB-system, J_{gem} = 12); 3.12 (dd, 1 H, OH, $J_{OH,H-8}$ = 4.5; $J_{OH,\ H-8'}$ = 8); 3.70 (m, 2 H, H-8, H-8'); 3.42 (c, 3 H, OMe at C(1)); 7.30 (m, 5 H, $OCH_2C_6H_5$).

(1*RS*, 5*S*, 6*S*, 8*S*)-6-Benzyloxy-8-hydroxy-1-methoxy-2-oxaspiro[4.4]nonane (8). Derivative **7** (85 mg, 0.3 mmol) was dissolved in 1 mL of a 5 % H_2SO_4 solution in MeOH and refluxed for 1 h, then neutralized with sodium bicarbonate, evaporated and chromatographed on SiO_2 in a benzene—THF gradient. Yield 64 mg (77 %), syrup. ^{1}H NMR (δ, ppm, *J*, Hz): 4.71 (c, 1 H, H-1); 4.54 (d, 1 H, H-1, *J* = 1.5); 4.41 and 4.56 (d, 2 H, CH_2Ph, AB-system, J_{gem} = 12); 3.35 (c, 3 H, OMe at C(1)); 3.32 (c, 3 H, OMe at C(1)); 4.22-3.76 (m, 4 H, H-3, H-5, H-8, H-8'); 2.50—1.60 (m, 6 H, H-4, H-4', H-6, H-6', H-7, H-7'); 7.30 (m, 5 H, $OCH_2C_6H_5$).

(1*S*, 2*S*, 3*S*, 5*S*)-5-Hydroxy-3-methoxy-4-methoxycarbonylmethyl-2-oxabicyclo[2.2.1]heptane (9). Raney Ni (1.5 g) was added to a solution of **5** (210 mg, 1 mmol) and the mixture was refluxed with intense stirring for 30 min. Then 5 mL of acetone was added, the mixture stirred for 5 min and filtered, and the precipitate was washed with 10 mL of acetone. The filtrate was evaporated, and the residue was chromatographed on SiO_2 in a benzene—THF gradient. Yield: 140 mg (95 %), syrup, $[\alpha_D]$ = 29.62 ° (*c* 1.0; $CHCl_3$). ^{1}NMR (δ, ppm, *J*, Hz): 4.81 (c, 1 H, H-1); 4.36 (dt, 1 H, H-3, $J_{3,4e}$ = 7.5; $J_1 = J_2$ = 2); 1.48 (dt, 1 H, H-4a, $J_{4,4'}$ = 14.5; $J_1 = J_2$ =2.5); 2.26 (ddd, 1 H, H-4e, *J* = 2.5); 4.29 (t, 1 H, H-5, $J_1 = J_2$ = 2.5); 1.65 (d, 1 H, H-6, $J_{6,6'}$ = 10); 1.72 (ddd, 1 H, H-6', J_1 = 2; J_2 = 4); 2.72 and 2.54 (d, 2 H, H-7, H-7', AB-system, J_{gem} = 13.5); 3.32 (c, 3 H, OMe at C-1), 3.66 (c, 3 H, COOMe).

(1*S*, 5*S*, 7*S*)-7-Hydroxy-5-dimethoxymethyl-2-oxabicyclo[3.3.0]octane-3-one (11). A solution of **9** (70 mg, 0.33 mmol) in 2 mL of a 2.5 % H_2SO_4 solution in methanol was refluxed for 20 min, then cooled and neutralized with sodium bicarbonate. The mixture was extracted with chloroform (2×5 mL), evaporated, and chromotographed on SiO_2 in a benzene—THF gradient. Yield 51 mg (73 %), syrup, $[\alpha_D]$ = −6.4° (*c* 1.0; $CHCl_3$)[1]: $[\alpha_D]$ = −6.7° (*c* 1.0; $CHCl_3$)]. The ^{1}H NMR spectrum is identical to the one described previously.[1]

(1*S*, 2*S*, 4*S*)-2-Benzyloxy-1-(1,3-dithian-2-yl)-4-hydroxy-1-(methoxycarbonylmethyl)cyclopentane (12). 1,3-Dithiopropane (87 mg, 0.8 mmol) was added to a solution of **5** (161 mg, 0.51 mmol) in 1 mL of CH_2Cl_2, and the mixture was cooled to −60°C. $ZnCl_2$ (82 mg, 0.1 mmol) was added, and the mixture was stirred for 1 h, neutralized by sodium bicarbonate, heated to room temperature, filtered, and the precipitate was washed with benzene. The filtrate was evaporated, and the residue was chromatographed on SiO_2 in a benzene—THF gradient. Yield 125 mg (65 %), syrup, $[\alpha_D]$ = +13.1° (*c* 1.0; $CHCl_3$). ^{1}H NMR (δ, ppm, *J*, Hz): 4.84 (c, 1 H, H-1): 4.36—4.43 (m, 2 H, H-3, H-5); 1.80—2.20 (m, 6 H, H-7, H-7', AB-system, J_{gem} = 17); 4.52 and 4.47 (d, 2 H, CH_2Ph, AB-system, J_{gem} = 11.5); 2.90 (m, 4 H, H-8, H-8, H-8', H-8'); 3,48 (c, 3 H, COOMe); 7.30 (m, 5 H, $OCH_2C_6H_5$).

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