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Vicinal Dibromo and Hydroxy(methoxy) Bromo Derivatives of (1*R*,4*R*)-7,7-Dimethyl-1-vinylnorbornan-2-one. Regio- and Stereoselectivity Aspects*

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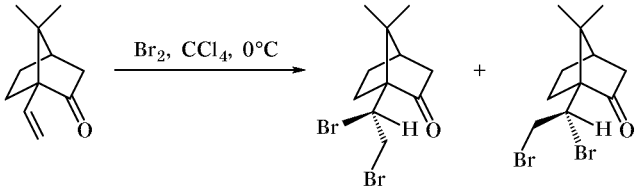
Abstract—Reactions of (1*R*,4*R*)-7,7-dimethyl-1-vinylnorbornan-2-one with bromine in carbon tetrachloride and with *N*-bromosuccinimide in methanol gave the corresponding $C^{1'}$-epimeric dibromo and methoxy bromo derivatives. Their structure was determined on the basis of spectral data.

Bromination of camphor yields its mono- (C^3, C^9, or C^{10}) and dibromo derivatives (C^3, C^{10} or C^9, C^{10}) which are widely used as chiral synthons for preparation of natural compounds [1–8]. In the present work we examined the possibility for selective synthesis of dibromo and bromo hydroxy derivatives of structurally related unsaturated ketone **I** [9] with participation of the exocyclic vinyl double bond.

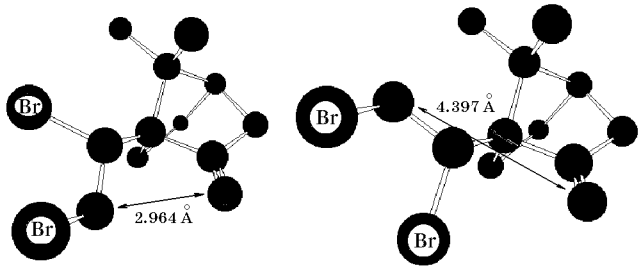
Treatment of compound **I** with an equimolar amount of bromine in carbon tetrachloride at 0°C led to formation of two isomeric dibromides **II** and **III** at a ratio of 2:1 (according to the ^{1}H NMR data); their overall yield was 82% (Scheme 1). When methylene chloride was used as solvent, the isomer ratio remained almost unchanged, but the yield was lower (72%). Compounds **II** and **III** were isolated in the pure state by column chromatography on silica gel.

The ^{1}H NMR spectra turned out to be very useful for assignment of structure of stereoisomeric dibromo derivatives **II** and **III**. Considerable differences were observed in the chemical shifts of the CH_2Br and CHBr protons. The CHBr signals appeared as doublets of doublets in a stronger field relative to the CH_2Br signal for one isomer, and in a weaker field, for the other. Obviously, this difference arises from the deshielding effect of the neighboring carbonyl group. Figure shows computer-simulated (Chem 3D software) steric structures of the low-energy conformers of compounds **II** and **III**. It is seen that the distance $C^{2'}$–O in isomer **II**, 2.964 Å, is much shorter than the corresponding distance in isomer **III**, 4.397 Å. Therefore, the $C^{2'}H_2$ protons in **II** fall into the area of anisotropic effect of the carbonyl group, and their signal is more downfield.

Scheme 1.



I **II** **III**



II **III**

Low-energy conformers of compounds **II** and **III**. Hydrogen atoms are not shown.

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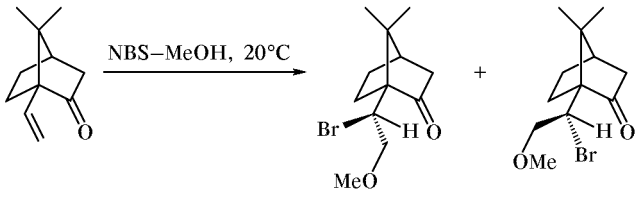
Unsaturated ketone **I** was also brought into bromohydroxylation reaction. However, under standard conditions (NBS, THF–H_2O) ketone **I** was rapidly transformed into a multicomponent mixture which was difficult to separate. The reaction was more selective when compound **I** was treated with NBS in anhydrous methanol. As a result, chromatographically pure major product was isolated in 60% yield. According to the spectral data (^{1}H NMR), the product was a mixture of epimers **IV** and **V** at a ratio of ~2 : 1 (Scheme 2). The signals were assigned to particular isomers **IV** and **V** on the basis of the spectral criteria discussed above for dibromides **II** and **III**.

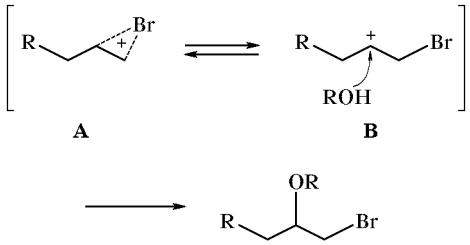
Scheme 2.



I **IV** **V**

The regioselectivity of bromomethoxylation of the double bond in **I** was somewhat surprising. Bromohydroxylation of terminal alkenes is known [10] to give predominantly primary bromo derivatives due to formation in the transition state of more stable acyclic bromomethyl cation **B** from cyclic bromonium cation **A** before nucleophilic attack (Scheme 3).

Scheme 3.

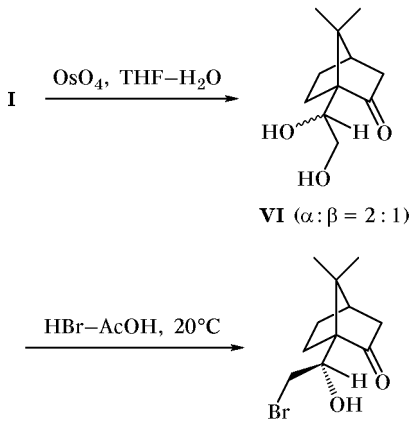


A **B**

In our case, the reaction does not follow Scheme 3, and secondary bromo derivatives **IV** and **V** are formed. The unusual regioselectivity can be explained in terms of steric control of the process. Stereodifferentiating properties of the camphor skeleton are well known, and numerous examples have been reported on the use of camphor derivatives as effective chiral auxiliaries [11–15]. Presumably, apical bromonium cation **A** can take up nucleophilic species only from the more accessible outer side. Insofar as the stage of generation of cation **A** is not completely stereoselective, two stereoisomeric cations **A** (α and β) can be formed, and the $C^{1'}$ center remains epimeric in the final products.

By bromination of stereoisomeric diols **VI** (which were described by us previously [16]) with HBr in acetic acid [17] we demonstrated the possibility for synthesizing bromo hydroxy derivatives regioisomeric to **IV** and **V**. As a result, pure compound **VII** was isolated (Scheme 4).

Scheme 4.



VII

The ^{1}H NMR spectrum of **VII** resembles those of α-bromo derivatives **III** and **V**. Likewise, the CH_2Br protons in **VII** suffer deshielding effect of the carbonyl group, and their signal appears in a weaker field relative to the C**H**OH signal.

Thus we have synthesized derivatives of ketone **I** via functionalization at the double bond and revealed spectral criteria for structure assignment of $C^{1'}$-epimeric camphor derivatives. The obtained products are promising for use in further syntheses.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrophotometer from samples prepared as thin films or dispersions in Nujol. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer at 300 MHz for ^{1}H and 75.47 MHz for ^{13}C using $CDCl_3$ as solvent and TMS as internal reference. Silica gel L 100/160 μm (Lachema) was used for column chromatography. Thin-layer chromatography was performed on Silufol plates. The optical rotations were measured on a Perkin–Elmer 241 MC instrument. The mass spectra (electron impact, 70 eV) were run on an MKh-1320 spectrometer; ion source temperature 80–90°C.

(1*S*,4*R*)-1-[(1*R*)-1,2-Dibromoethyl]-7,7-dimethylbicyclo[2.2.1]heptan-2-one (II) and (1*S*,4*R*)-1-[(1*S*)-1,2-dibromoethyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one (III). A solution of 98 mg (0.61 mmol) of bromine in 1 ml of carbon tetrachloride was added at 0°C over a period of 1 h to a solution of 100 mg (0.61 mmol) of unsaturated ketone **I** in 4 ml of CCl_4. The mixture was stirred for 30 min, warmed up to room temperature, and evaporated. The residue was purified by column chromatography on silica gel to isolate 107 mg (55%) of compound **II** and 53 mg (27%) of its epimer **III**.

Compound **II**. mp 107–109°C. R_f 0.69 (hexane–ethyl acetate, 7:3). $[\alpha]_D^{20}$ = +12.66° (*c* = 1.0, $CDCl_3$). IR spectrum, ν, cm^{-1}: 1750 (CO). ^1H NMR spectrum, δ, ppm: 1.05 s (3H, CH_3), 1.20 s (3H, CH_3), 1.38–1.48 m (1H, 5-H_{ax}), 1.64 m (1H, 6-H_{ax}), 1.90 d (1H, 3-H_{ax}, *J* = 18.5 Hz), 2.00–2.10 m (2H, 5-H_{eq}, 6-H_{eq}), 2.20 m (1H, 4-H), 2.43 d.t (1H, 3-H_{eq}, *J* = 4.0, 18.5 Hz), 3.67 d.d (1H, CHBr, *J* = 11.4, 10.3 Hz), 4.37 d.d, (1H, CH_2Br, *J* = 11.6, 11.4 Hz), 4.41 d.d (1H, CH_2Br, *J* = 11.6, 10.3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 20.68 q (CH_3), 22.89 q (CH_3), 24.94 t (C^5), 26.72 t (C^6), 37.11 t (CH_2Br), 43.03 t (C^3), 44.22 d (C^4), 49.99 s (C^7), 54.76 d (CHBr), 64.31 s (C^1), 214.42 s (CO). Found, %: C 41.25; H 5.19; Br 48.36. $C_{11}H_{16}Br_2O$. Calculated, %: C 40.77; H 4.98; Br 49.32.

Compound **III**. mp 99–102°C. R_f 0.64 (hexane–ethyl acetate, 7:3). $[\alpha]_D^{20}$ = –3.44° (*c* = 1.0, $CDCl_3$). IR spectrum, ν, cm^{-1}: 1755 (CO). ^1H NMR spectrum, δ, ppm: 1.13 s (6H, $2CH_3$), 1.40 m (1H, 5-H_{ax}), 1.65 m (1H, 6-H_{ax}), 1.90 d (1H, 3-H_{ax}, *J* = 18.5 Hz), 1.96–2.10 m (2H, 5-H_{eq}, 6-H_{eq}), 2.25 m (1H, 4-H), 2.50 d.t (1H, 3-H_{eq}, *J* = 4.0, 18.5 Hz), 3.91 d.d (1H, CH_2Br, *J* = 9.1, 9.2 Hz), 3.98 d.d (1H, CH_2Br, *J* = 9.2, 3.5 Hz), 4.30 d.d (1H, CHBr, *J* = 3.5, 9.1 Hz). ^{13}C NMR spectrum, δ_C, ppm: 20.72 q (CH_3), 23.43 q (CH_3), 26.39 t (C^5), 30.57 t (C^6), 36.36 t (CH_2Br), 43.16 t (C^3), 45.41 d (C^4), 49.02 s (C^7), 53.69 d (CHBr), 64.54 (C^1), 213.82 s (CO). Found, %: C 40.95; H 5.13; Br 49.07. $C_{11}H_{16}Br_2O$. Calculated, %: C 40.77; H 4.98; Br 49.32.

(1*S*,4*R*)-1-[(1*S*)-1-Bromo-2-methoxyethyl]-7,7-dimethylbicyclo[2.2.1]heptan-2-one (IV) and (1*S*,4*R*)-1-[(1*R*)-1-bromo-2-methoxyethyl]-7,7-dimethylbicyclo[2.2.1]heptan-2-one (V). *N*-Bromosuccinimide, 119 mg (0.67 mmol), was added to a solution of 100 mg (0.61 mmol) of ketone **I** in 10 ml of MeOH, and the mixture was stirred for 30 min. The solvent was distilled off, and the residue was subjected to chromatography on silica gel to obtain 112 mg (67%) of an oily mixture of epimers **IV** and **V**.

Compound **IV**. R_f 0.58 (hexane–ethyl acetate, 7:3). IR spectrum, ν, cm^{-1}: 1152, 1728. ^1H NMR spectrum, δ, ppm: 1.05 s (CH_3), 1.08 s (CH_3), 1.30 m (1H, 5-H_{ax}), 1.50 m (1H, 6-H_{ax}), 1.82 d (1H, 3-H_{ax}, *J* = 18.3 Hz), 1.90–2.00 m (2H, 5-H_{eq}, 6-H_{eq}), 2.20 m (1H, 4-H), 2.40 d.t (1H, 3-H_{eq}, *J* = 3.8, 18.3 Hz), 3.30 s (3H, OCH_3), 3.82 d.d (1H, CHBr, *J* = 10.1, 11.2 Hz), 4.22 d.d (1H, CH_2O, *J* = 11.2, 11.6 Hz), 4.30 d.d (1H, CH_2O, *J* = 11.6, 10.1 Hz). ^{13}C NMR spectrum, δ_C, ppm: 20.75 q (CH_3), 22.72 q (CH_3), 26.29 t (C^5), 30.05 t (C^6), 43.13 t (C^3), 45.28 d (C^4), 48.61 s (C^7), 51.42 q (OCH_3), 58.36 d (CHBr), 62.40 s (C^1), 74.69 t (CH_2O), 213.99 (CO). Found, %: C 52.51; H 7.01; Br 28.90. $C_{12}H_{19}BrO_2$. Calculated, %: C 52.38; H 6.96; Br 29.04.

Compound **V**. R_f 0.56 (hexane–ethyl acetate, 7:3). ^1H NMR spectrum, δ, ppm: 0.96 s (CH_3), 1.13 s (CH_3), 1.30 m (1H, 5-H_{ax}), 1.50 m (1H, 6-H_{ax}), 1.80 d (1H, 3-H_{ax}, *J* = 18.3 Hz), 1.90–2.00 m (2H, 5-H_{eq}, 6-H_{eq}), 2.20 m (1H, 4-H), 2.38 d.t (1H, 3-H_{eq}, *J* = 3.8, 18.3 Hz), 3.33 s (3H, OCH_3), 3.66 d.d (1H, CH_2O, *J* = 9.0, 9.2 Hz), 3.72 d.d (1H, CH_2O, *J* = 9.2, 3.4 Hz), 3.98 d.d (1H, CHBr, *J* = 9.0, 3.4 Hz). ^{13}C NMR spectrum, δ, ppm: 20.83 q (CH_3), 22.43 q (CH_3), 26.04 t (C^5), 26.65 t (C^6), 42.97 t (C^3), 44.36 d (C^4), 49.54 s (C^7), 53.72 q (OCH_3), 58.41 d (CHBr), 62.22 s (C^1), 74.95 t (CH_2O), 214.28 (CO).

(1*S*,4*R*)-1-[(1*R*)-2-Bromo-1-hydroxyethyl]-7,7-dimethylbicyclo[2.2.1]heptan-2-one (VII). A solution of 100 mg (0.51 mmol) of diol **V** in 1 ml of a 20% solution of HBr in AcOH was stirred for 30 min at 20°C. The solvent was distilled off, and the residue was purified by chromatography on silica gel to obtain 86 mg (65%) of pure crystalline product **VII**. mp 128–130°C. R_f 0.68 (hexane–ethyl acetate, 7:3). IR spectrum, ν, cm^{-1}: 1740, 3500. ^1H NMR spectrum, δ, ppm: 1.00 s (CH_3), 1.25 s (CH_3), 1.40 m (2H, 5-H_{ax}, 6-H_{ax}), 1.84 d (1H, 3-H_{ax}, *J* = 18.4 Hz), 1.96–2.20 m (3H, 4-H, 5-H_{eq}, 6-H_{eq}), 2.40 d.t (1H, 3-H_{eq}, *J* = 3.5, 8.4 Hz), 3.26 t (1H, CHO, *J* = 10.0 Hz), 4.07 d.d (1H, CH_2Br, *J* = 10.1, 10.0 Hz), 4.11 d.d (1H, CH_2Br, *J* = 10.1, 10.0 Hz). ^{13}C NMR spectrum, δ, ppm: 20.55 q (CH_3), 21.89 q (CH_3), 22.38 t (C^5), 26.65 t (C^6), 38.70 t (CH_2Br), 43.46 t (C^3), 43.95 d (C^4), 48.53 s (C^7), 63.72 s (C^1), 70.19 t (CHO), 217.54 (CO). Found, %: C 50.70; H 6.60; Br 30.98. $C_{11}H_{17}BrO_2$. Calculated, %: C 50.59; H 6.56; Br 30.60.

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