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New 2,10-Functionalized Camphor Derivatives

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Abstract—Synthetic routes to precursors of tricyclic camphor derivatives fused at the 2,10-positions, the corresponding halohydrins and dimethyl acetal, are discussed.

In continuation of our studies [1–3] aimed at searching for derivatives of keto olefin **I** [4], which can be suitable for intramolecular cyclizations (in particular, along the reaction sequence **I** → **IV** shown in Scheme 1), the present communication reports on our attempts to transform previously known triol **II** [5] into halohydrins **III**. The latter are considered to be precursors of the corresponding 5-hexynyl radicals which could give rise to the desired tricyclic compounds **IV** [6] via allowed version of intramolecular 5-*exo-dig* cyclization [7].

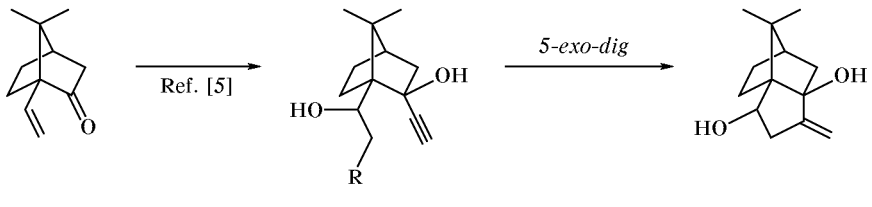
Triol **II** is an epimeric mixture with respect to $C^{1'}$ at a ratio of 3:1 (according to the ^{1}H NMR data), which cannot be separated by chromatography on silica gel [5]. Several methods were tried in order to differentiate vicinal hydroxy groups in the side chain of triol **II**. An attempt to obtain the corresponding mono-*p*-toluenesulfonate using 1.5 equiv of TsCl in pyridine at 20°C was unsuccessful, and unchanged initial triol **II** was recovered from the reaction mixture. The reaction with methanesulfonyl chloride resulted in fast and uncontrolled formation of epimeric tricyclic alcohols **V** which were oxidized to individual ketone **VI** by the Jones' reagent (Scheme 2). We also failed to obtain the corresponding 1′,2-carbonate by the action of 1,1′-carbonyldiimidazole on compound **II**. This reaction selectivily afforded 1′,2′-carbonate **VII** in high yield. Product **VII** can be converted back into initial triol **II** in a quantitative yield by treatment with 1 equiv of sodium hydride in THF. We also tried to effect regioselective transformation of benzylidene acetal **VIII** derived from **II** into bromine-containing benzoate **IX** with the aid of *N*-bromosuccinimide (NBS). However, the reaction was not selective, and it also involved the acetylene moiety.

The difficulties encountered while trying to obtain halohydrins **III** from triol **II** prompted us to search for synthetic routes to alternative structures related to **III** and **IV**. An example of such structures may be phenyl-substituted dimethyl acetal **XI** which was synthesized from ketone **I** in two steps as shown in Scheme 2. Compound **XI** can be used as a model for studying intramolecular electrophilic cyclizations according to Mukaiyama [9] with a view to built up tetracyclic system **XII**.

EXPERIMENTAL

The IR spectra were obtained on a UR-20 spectrometer from samples prepared as thin films or Nujol mulls. The ^{1}H and ^{13}C NMR spectra were measured

Scheme 1.



I **II, III** **IV**

II, R = OH; **III**, R = Hlg.

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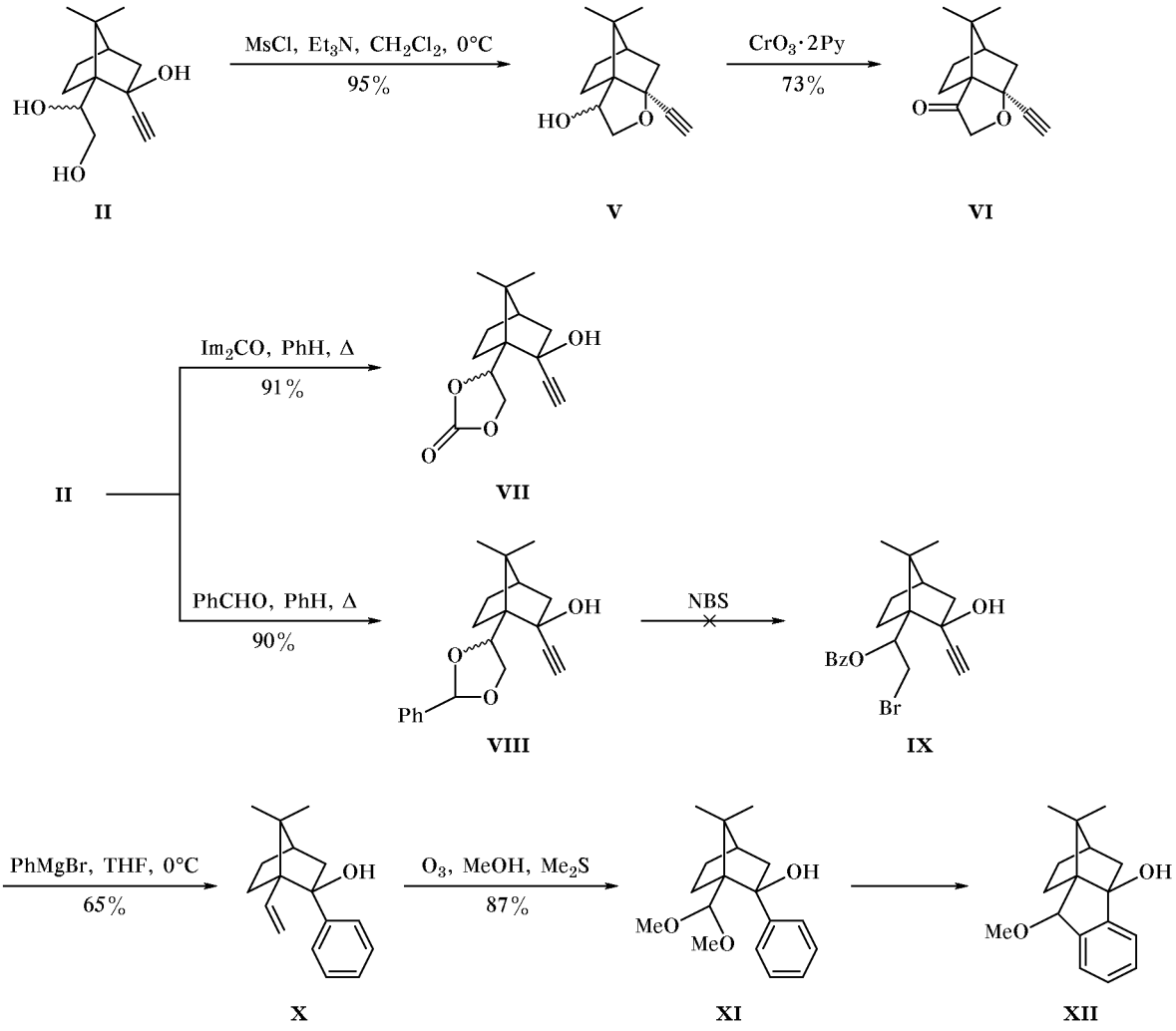
Scheme 2.



on a Bruker AM-300 instrument at 300 (^{1}H) and 75.47 MHz (^{13}C) from solutions in $CDCl_3$ containing tetramethylsilane as internal reference. Silufol plates were used for TLC analysis. The optical rotations were measured on a Perkin–Elmer polarimeter.

(1*R*,2*RS*,5*S*,7*R*)-5-Ethynyl-10,10-dimethyl-4-oxatricyclo[5.2.1.0^{1,5}]decan-2-ol (V). A solution of 0.38 ml (0.49 mmol) of methanesulfonyl chloride was added at 0°C to a solution of 100 mg (0.45 mmol) of triol **II** and 0.62 ml (4.46 mmol) of triethylamine in 10 ml of methylene chloride. The mixture was stirred for 15 min, and the solvent was evaporated. The residue was subjected to chromatographic purification on silica gel using hexane–ethyl acetate (7 : 3) as eluent to isolate 87 mg (95%) of crystalline compound **V**. R_f 0.43 (hexane–ethyl acetate, 1 : 1). mp 128–130°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.97 s (3H, CH_3); 1.05 s (3H, CH_3); 1.70–2.05 m (5H), 2.35–2.45 m (2H, CH_2); 2.62 s (1H, ≡CH); 3.10 br.s (1H, OH); 4.03 d.d (2H, CH_2O, *J* = 10.6, 2.8); 4.40 d.d [1H, CH(OH), *J* = 10.6, 2.8]. ^{13}C NMR spectrum, δ_C, ppm: 20.90 (CH_3), 21.25 (CH_3), 23.68 (C^6), 25.80 (C^5), 29.43 (C^3), 46.88 (C^4), 47.71 (C^7), 66.83 (C^1), 71.48 (C^{10}), 73.88 (C≡**C**H), 80.18 (C^2), 86.278(**C**≡CH).

(1*S*,5*S*,7*R*)-5-Ethynyl-10,10-dimethyl-4-oxatricyclo[5.2.1.0^{1,5}]decan-2-one (VI). A solution of Jones' reagent, 0.1 ml, was added to a solution of 100 mg (0.48 mmol) of epimeric alcohols **V** in 10 ml of acetone. The mixture was stirred for 1 h, and excess oxidant was decomposed with isopropyl alcohol. The solvent was evaporated, the residue was dissolved in 10 ml of water, and the product was extracted into ethyl acetate (3 × 10 ml). The extracts were combined, dried over $MgSO_4$, and evaporated, and the residue was purified by chromatography on

silica gel using hexane–ethyl acetate (10 : 1) as eluent to isolate 72 mg (73%) of compound **VI** as an oily substance. R_f 0.36 (hexane–ethyl acetate, 7 : 3). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.05 s (3H, CH_3), 1.29 s (3H, CH_3), 1.85–2.25 m (7H), 2.60 s (1H, ≡CH), 4.17 d (2H, CH_2O, *J* = 17.0). ^{13}C NMR spectrum, δ_C, ppm: 21.16 (CH_3), 21.20 (CH_3), 24.24 (C^6), 26.70 (C^5), 46.14 (C^4), 48.16 (C^3), 54.34 (C^7), 67.08 (C^1), 74.36 (C≡**C**H), 75.00 (CH_2O), 83.72 (C^2), 87.97 (**C**≡CH), 213.31 (C^{10}).

(4*RS*)-4-{(1*R*,2*S*,4*R*)-2-Ethynyl-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-yl}-1,3-dioxolan-2-one (VII). A solution of 100 mg (0.45 mmol) of triol **V** and 108 mg (0.67 mmol) of 1,1′-carbonyldiimidazole in 20 ml of benzene was heated for 3 h under reflux. The solvent was distilled off, and the residue was subjected to chromatographic purification on silica gel using hexane–ethyl acetate (10 : 1) as eluent to isolate 102 mg (91%) of compound **VII** as an oily substance. R_f 0.74 (hexane–ethyl acetate, 7 : 3). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.70–2.05 m (5H), 2.25–2.40 m (2H, CH_2), 2.65 s (1H, ≡CH), 2.80 br.s (1H, OH), 4.68 d.d (2H, CH_2O, *J* = 8.4, 14.6), 5.10 d (1H, CHO, *J* = 8.4). ^{13}C NMR spectrum, δ_C, ppm: 20.85 (CH_3), 22.56 (CH_3), 22.86 (C^6), 25.74 (C^5), 46.24 (C^4), 49.53 (C^3), 56.38 (C^7), 60.45 (C^1), 66.98 (CH_2O), 74.06 (C≡**C**H), 76.23 (C^{10}), 76.83 (C^2), 87.32 (**C**≡CH), 155.76 (CO_3).

(1*R*,2*S*,4*R*)-2-Ethynyl-7,7-dimethyl-1-[(4*RS*)-2-phenyl-1,3-dioxolan-4-yl]bicyclo[2.2.1]heptan-2-ol (VIII). A solution of 100 mg (0.45 mmol) of triol **V** and 0.05 ml (0.45 mmol) of benzaldehyde in 20 ml of benzene was heated for 1 h under reflux in a flask equipped with a Dean–Stark trap. The solvent was distilled off, and the residue was subjected to chromatographic purification on silica gel using hexane–ethyl acetate (10 : 1) as eluent to isolate 125 mg of compound **VIII** as an oily substance. R_f 0.68 (hexane–ethyl acetate, 7 : 3). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.12 s (3H, CH_3), 1.27 s (3H, CH_3), 1.70–2.10 m (5H), 2.20–2.40 m (2H, CH_2), 2.55 s (1H, ≡CH), 4.20 d.d (2H, CH_2O, *J* = 7.6, 15.4), 4.60 d.d (1H, CHO, *J* = 7.6, 15.4), 5.90 s (1H, PhC**H**), 7.20–7.60 m (5H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 21.31 (CH_3), 23.10 (CH_3), 24.66 (C^6), 26.19 (C^5), 46.53 (C^4), 49.41 (C^7), 56.43 (C^1), 67.26 (CH_2O), 74.98 (C≡**C**H), 75.86 (C^{10}), 76.65 (C^2), 88.09 (**C**≡CH), 102.94 (Ph**C**H), 126.10–139.04 (C_{arom}).

(1*R*,2*S*,4*R*)-7,7-Dimethyl-2-phenyl-1-vinylbicyclo[2.2.1]heptan-2-ol (X). A solution of 100 mg (0.61 mmol) of ketone **I** in 5 ml of diethyl ether was added dropwise with stirring to 0.58 ml of PhLi (as a 1.25 M solution in ether) in 10 ml of Et_2O. When the reaction was complete (TLC), the mixture was quenched with a saturated solution of NH_4Cl and extracted with diethyl ether. The extracts were dried over $MgSO_4$ and evaporated, and the residue was subjected to chromatographic purification on silica gel to isolate 96 mg (65%) of compound **X** as an oily substance. R_f 0.73 (hexane–ethyl acetate, 7 : 3). $[\alpha]_D^{20}$ = –4.1° (*c* = 0.01, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3530, 1730, 1635, 690. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.80 m (1H), 0.90 s (3H, CH_3), 1.25 m (1H), 1.40 s (3H, CH_3), 1.60 m (1H), 1.75 m (1H), 2.00 br.s (2H), 2.30 m (1H), 2.50 d (1H, *exo*-3-H, *J* = 18.3), 4.85 d.d (1H, H_2C=, *J* = 17.7, 2.1), 5.35 d.d (1H, H_2C=, *J* = 11.0, 2.1), 6.40 d.d (1H, HC=, *J* = 17.7, 11.0), 7.30–7.60 m (5H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 21.36 (CH_3); 21.80 (CH_3); 25.95 (C^5); 26.29 (C^6); 44.36 (C^3); 46.06 (C^4); 51.42 (C^7); 59.87 (C^1); 84.42 (C^2); 117.20 and 135.85 (CH=CH_2); 126.50, 126.91, 127.49, and 145.83 (C_{arom}).

1-Dimethoxymethyl-7,7-dimethyl-2-phenylbicyclo[2.2.1]heptan-2-ol (XI). Ozone was bubbled over a period of 1 min at a flow rate of 45 mmol/h through a solution of 100 mg (0.41 mmol) of olefin **X** in 50 ml MeOH, maintained at –78°C. The mixture was purged with argon, 0.12 ml (1.73 mmol) of dimethyl sulfide was added, and the mixture was allowed to warm up to room temperature, stirred for 3 h, and evaporated. The crude residue was purified by column chromatography on silica gel. Yield 104 mg (87%), R_f 0.85 (hexane–ethyl acetate, 7 : 3). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.95 s (3H, CH_3), 1.15 m (1H), 1.37 s (3H, CH_3), 1.40–1.50 m (1H), 1.60–1.70 m (2H), 2.05 d (1H, *exo*-3-H, *J* = 13.8), 2.15–2.25 m (1H), 3.30 s (6H, OCH_3), 4.12 s (1H, OH), 5.07 s (1H, OCHO), 7.00–7.40 m (5H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 23.16 (CH_3); 23.32 (CH_3); 26.17 (C^5); 26.92 (C^6); 46.42 (C^3); 47.11 (C^4); 51.38 (C^7); 57.11 (OCH_3); 58.84 (C^1); 59.93 (OCH_3); 83.82 (C^2); 110.96 (OCHO); 126.22, 126.98, 127.63, and 146.38 (C_{arom}).

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