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New Camphor Derivatives Functionalized at C^3 and C^{10}

N. S. Vostrikov, A. V. Abutkov, and M. S. Miftakhov

Institute of Organic Chemistry, Ufa Research Center, Russian Academy of Sciences, pr. Oktyabrya 71, Ufa, 450054 Bashkortostan, Russia
e-mail: bioreg@anrb.ru

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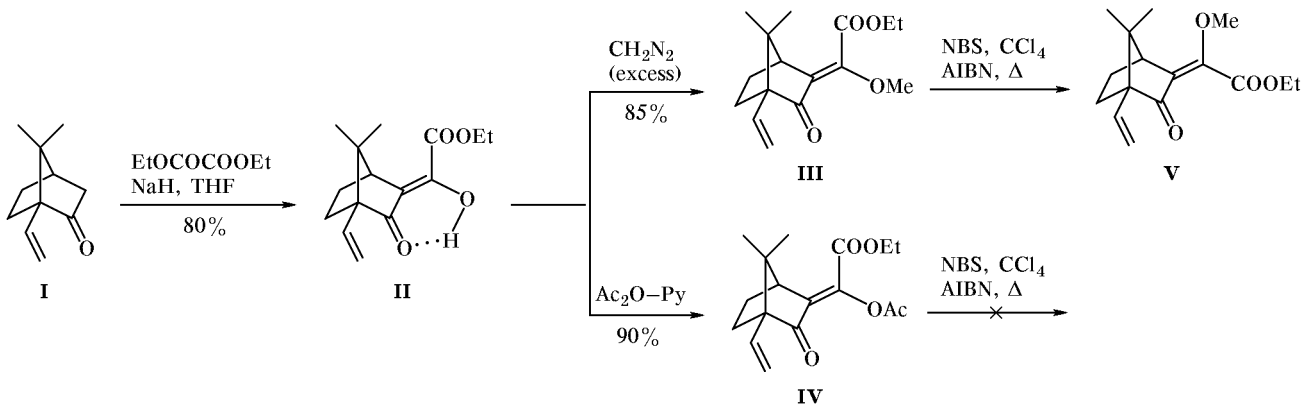
Abstract—Base-catalyzed condensation of 10-methylenecamphor with diethyl oxalate gave the corresponding (*Z*)-3-ethoxycarbonyl(hydroxy)methylene derivative which was converted into methyl ether and acetate. The *Z*-methyl ether undergoes isomerization into the *E*-methyl ether on treatment with *N*-bromosuccinimide in the presence of radical initiator [azobis(isobutyrodinitrile)]. (*Z*)-3-Ethoxycarbonyl(hydroxy)methylene-10-methylenecamphor smoothly reacts with *N*-bromosuccinimide to afford stereoisomeric 3-bromo derivatives.

Camphor derivatives are widely used in stereospecific syntheses of natural compounds [1–4]. Of particular interest is 10-methylenecamphor (**I**) which is readily available from *d*-10-camphorsulfonyl chloride [5]. 10-Methylenecamphor (**I**) is a key starting compound for the synthesis of taxoids developed by Paquette *et al.* [6, 7].

In continuation of our previous studies [8] on the synthesis of promising building blocks for taxoids on the basis of 10-methylenecamphor (**I**), the present communication reports on the transformation of **I** into new C^3-functionalized derivatives. Taking into account the ability of ketone **I** to undergo enolization in basic medium [9, 10], it was brought into reaction with diethyl oxalate in THF using sodium hydride as condensing agent. The reaction gave *Z*-enol **II** as the sole product. Its IR spectrum lacked hydroxy group absorption in the region 3000–3600 cm^{-1}, and the enol proton signal appeared in the ^1H NMR spectrum in an anomalously weak field. Presumably, stereoselective formation of *Z*-enol **II** is favored by additional stabilization of its structure due to intramolecular H bonding.

Z-Enol **II** readily reacted with excess diazomethane to give enol ether **III**. Treatment of compound **II** with a mixture of acetic anhydride and pyridine afforded enol acetate **IV** (Scheme 1). We also tried to effect further functionalization of these products at C^4 via allylic bromination using *N*-bromosuccinimide (NBS). However, acetate **IV** failed to react with NBS under conditions of radical initiation, whereas attempted bromination of ether **III** resulted in its isomerization into *E*-ether **V**. Only enol **II** rapidly reacted with NBS to give a mixture of stereoisomeric 3-bromo derivatives **VI** and **VII** at a ratio of 4:1 (Scheme 2).

Scheme 1.



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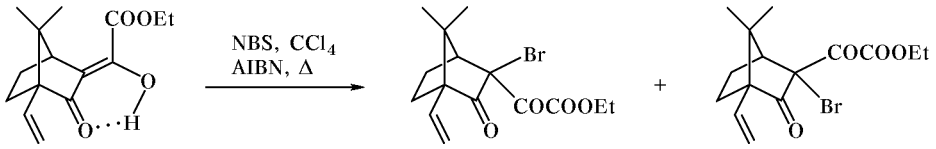
Scheme 2.



II **VI** **VII**

Isomeric enol ethers **III** and **IV** showed in the ^{1}H NMR spectra doublet signals from proton in the bridgehead position (4-H) at δ 3.13 (*Z*-**III**) and 2.87 ppm (*E*-**V**). The difference in the chemical shifts of 4-H between the isomers is explained by anisotropic effect of the ester group in **III** [11–13]. Isomeric bromoketones **VI** and **VII** can be distinguished by the signals of the *syn*-CH_3 group on C^7. In the spectrum of **VII** this signal is located in a weaker field (δ 1.3 ppm) as compared to compound **VI** (δ 1.05 ppm) due to deshielding by carbonyl groups of the *exo*-$COCO_2Et$ substituent. In the ^{13}C NMR spectrum of **VII** the signal from C^5 is displaced upfield (δ_C 20.16 ppm against δ_C 27.57 ppm for **VI**) due to influence of the *endo*-bromine atom.

EXPERIMENTAL

The IR spectra were obtained from thin films or Nujol mulls on a UR-20 spektrometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 instrument (at 300 MHz for ^{1}H and 75.47 MHz for ^{13}C) using $CDCl_3$ as solvent and TMS as internal reference. Thin-layer chromatography was performed on Silufol plates. The specific optical rotations were measured on a Perkin–Elmer instrument. The mass spectra (70 eV) were obtained on an MKh-1320 mass spectrometer with direct sample admission into the ion source; ion source temperature 60–90°C.

Ethyl (*Z*)-(1*S*,4*S*)-4-ethenyl-7,7-dimethyl-3-oxobicyclo[2.2.1]hept-2-ylidene(hydroxy)acetate (II). Sodium hydride, 0.61 g (12.18 mmol), was added under argon to a solution of 1 g (6.09 mmol) of ketone **I** and 1.65 ml (12.18 mmol) of diethyl oxalate in 50 ml of THF. The mixture was refluxed for 30 min, excess sodium hydride was decomposed by addition of hydrochloric acid, and the product was extracted into chloroform and purified by chromatography on silica gel. Yield 1.29 g (80%), oily substance, $[\alpha]_D^{20}$ = +120.95° (*c* = 0.1, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1640, 1700, 1740, 3100. ^{1}H NMR spectrum, δ, ppm: 0.83 s (3H, CH_3), 0.87 s (3H, CH_3), 1.30 t (3H, CH_3, *J* = 7.2 Hz), 1.43 m (2H, CH_2), 2.00–2.10 m (2H, CH_2), 3.25 d (1H, 1-H, *J* = 3.6 Hz), 4.23 q (2H, OCH_2, *J* = 7.2 Hz), 5.23 d.d (1H, *J* = 17.6, 1.3 Hz), 5.35 d.d (1H, *J* = 11.0, 1.3 Hz), 5.75 d.d (1H, *J* = 11.0, 17.6 Hz) ($CH{=}CH_2$). ^{13}C NMR spectrum, δ_C, ppm: 13.98 (CH_3), 18.52 (CH_3), 20.80 (CH_3), 26.43 (C^5), 26.75 (C^6), 48.43 (C^1), 50.21 (C^7), 61.77 (OCH_2), 64.08 (C^4), 119.67 and 130.70 ($CH{=}CH_2$), 122.71 (C^2), 148.18 ($C^{1'}$), 162.56 (CO_2), 212.55 (C^3).

Ethyl (*Z*)-(1*S*,4*S*)-4-ethenyl-7,7-dimethyl-3-oxobicyclo[2.2.1]hept-2-ylidene(methoxy)acetate (III). Enol **II**, 0.2 g (0.76 mmol), was dissolved in an ether solution of diazomethane (~3 equiv), the mixture was kept for 48 h at –10°C and evaporated, and the residue was purified by chromatography on silica gel. Yield 0.18 g (85%), oily substance. $[\alpha]_D^{20}$ = +91.69° (*c* = 0.1, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1640, 1660, 1740, 1750. ^{1}H NMR spectrum, δ, ppm: 0.90 (6H, $2CH_3$), 1.34 t (3H, CH_3, *J* = 7.2 Hz), 1.50 m (2H, CH_2), 2.00 m (2H, CH_2), 3.13 d (1H, 1-H, *J* = 4.0 Hz), 3.78 s (3H, OCH_3), 4.30 q (2H, OCH_2, *J* = 7.2 Hz), 5.25 d.d (1H, *J* = 17.6, 1.3 Hz), 5.38 d.d (1H, *J* = 11.0, 1.3 Hz), 5.84 d.d (1H, *J* = 11.0, 17.6 Hz) ($CH{=}CH_2$). ^{13}C NMR spectrum, δ_C, ppm: 14.19 (CH_3), 18.73 (CH_3), 20.95 (CH_3), 26.37 (C^5), 26.38 (C^6), 47.78 (C^7), 50.09 (C^1), 60.89 (OCH_3), 64.81 (C^4), 119.21 and 132.21 ($CH{=}CH_2$), 131.98 ($C^{1'}$), 146.39 (C^2), 163.80 (CO_2), 203.69 (C^3).

Ethyl acetoxy[(*Z*)-(1*S*,4*S*)-4-ethenyl-7,7-dimethyl-3-oxobicyclo[2.2.1]hept-2-ylidene]acetate (IV). A mixture of 0.2 g (0.76 mmol) of compound **II**, 0.07 ml (0.76 mmol) of acetic anhydride, and 0.07 ml (0.91 mmol) of pyridine was heated for 3 h. The mixture was then poured into ice water, acidified with 10% hydrochloric acid, and extracted with $CHCl_3$. The combined extracts were dried over Na_2SO_4, filtered, and evaporated, and the residue was purified by chromatography on silica gel. Yield 0.26 g (90%), oily substance, $[\alpha]_D^{20}$ = +19.71° (*c* = 0.1, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1644, 1668, 1714, 1728, 1736, 1772. ^{1}H NMR spectrum, δ, ppm: 0.90 (6H, $2CH_3$), 1.30 t (3H, CH_3, *J* = 7.1 Hz), 1.48–1.63 m (2H, CH_2), 2.00–2.20 m (2H, CH_2), 2.24 s (3H, CH_3), 3.54 d

(1H, 1-H, J = 7.1 Hz), 5.20 d.d (1H, J = 17.7, 1.4 Hz), 5.38 d.d (1H, J = 11.1, 1.4 Hz), 5.78 d.d (1H, J = 11.1, 17.7 Hz) ($CH{=}CH_2$). ^{13}C NMR spectrum, δ_C, ppm: 13.96 (CH_3), 18.37 (CH_3), 20.34 (CH_3), 20.98 (CH_3), 25.88 and 26.00 (C^5, C^6), 47.43 (C^7), 50.06 (C^4), 61.85 (OCH_2), 64.30 (C^1), 119.62 and 131.23 ($CH{=}CH_2$), 134.86 (C^3), 139.61 ($C^{1'}$), 162.33 (CO_2), 168.45 (C^2), 203.20 (C^2).

Ethyl (*E*)-(1*S*,4*S*)-4-ethenyl-7,7-dimethyl-3-oxobicyclo[2.2.1]hept-2-ylidene(methoxy)acetate (V). A solution of 0.2 g (0.72 mmol) of compound **III** and 0.16 g (0.9 mmol) of NBS in 20 ml of CCl_4 was refluxed for 30 min. It was then cooled, filtered, and evaporated. The residue was purified by chromatography on silica gel to obtain 0.1 g (50%) of compound **V** as an oily substance, $[\alpha]_D^{20}$ = +89.46° (c = 0.05, $CHCl_3$). ^1H NMR spectrum, δ, ppm: 0.88 s (3H, CH_3), 0.94 s (3H, CH_3), 1.33 t (3H, CH_3, J = 7.1 Hz), 1.50 m (2H, CH_2), 2.00 m (2H, CH_2), 2.87 d (1H, 1-H, J = 3.1 Hz), 3.73 s (3H, OCH_3), 4.35 q (2H, OCH_2, J = 7.1 Hz), 5.20 d.d (1H, J = 17.7, 1.6 Hz), 5.36 d.d (1H, J = 11.0, 1.6 Hz), 5.82 d.d (1H, J = 11.0, 17.7 Hz) ($CH{=}CH_2$). ^{13}C NMR spectrum, δ_C, ppm: 13.93 (CH_3), 18.73 (CH_3), 20.80 (CH_3), 26.09 and 26.61 (C^5, C^6), 46.92 (C^1), 48.56 (C^7), 57.18 (OCH_2), 119.13 and 132.09 ($CH{=}CH_2$), 149.51 (C^2), 163.40 ($C^{1'}$), 204.01 (C^3).

Ethyl (1*S*,2*S*,4*S*)-*exo*-2-bromo-4-ethenyl-7,7-dimethyl-3-oxobicyclo[2.2.1]hept-*endo*-2-yl(oxo)acetate (VI) and ethyl (1*S*,2*S*,4*S*)-*endo*-2-bromo-4-ethenyl-7,7-dimethyl-3-oxobicyclo[2.2.1]hept-*exo*-2-yl(oxo)acetate (VII). A solution of 0.2 g (0.76 mmol) of compound **II** and 0.17 g (0.95 mmol) of NBS in 20 ml of CCl_4 was refluxed for 30 min. It was then cooled, filtered, and evaporated, and the residue was separated by chromatography on silica gel to obtain 0.15 g (57%) of compound **VI** and 0.029 g (11%) of **VII**. Compound **VI**. IR spectrum, ν, cm^{-1}: 1648, 1720, 1732, 1748. ^1H NMR spectrum, δ, ppm: 0.9 s (3H, CH_3), 1.05 s (3H, CH_3), 1.35 t (3H, CH_3, J = 7.2 Hz), 1.65 m (1H) and 2.00–2.30 m (3H, $2CH_2$), 3.05 d (1H, 1-H, J = 3.8 Hz), 4.38 q (2H, OCH_2, J = 7.2 Hz), 5.30 d.d (1H, J = 17.6, 1.1 Hz), 5.44 d.d (1H, J = 11.0, 1.1 Hz), 5.83 d.d (1H, J = 17.6, 11.0 Hz) ($CH{=}CH_2$). ^{13}C NMR spectrum, δ_C, ppm: 13.96 (CH_3), 21.00 (CH_3), 22.07 (CH_3), 25.05 and 27.57 (C^5, C^6), 47.66 (C^7), 50.09 (C^1), 62.97 (OCH_2), 63.49 (C^4), 68.63 (C^2), 120.45 and 130.45 ($CH{=}CH_2$), 161.52 (CO_2), 184.77 ($C^{1'}$), 205.89 (C^3). Compound **VII**. IR spectrum, ν, cm^{-1}: 1648, 1720, 1732, 1748. ^1H NMR spectrum, δ, ppm: 0.98 s (3H, CH_3), 1.30 s (3H, CH_3), 1.38 t (3H, CH_3, J = 7.2 Hz), 1.60 m (1H), 2.00 d.t (1H, J = 1.7, 13.7 Hz), 2.20 m (2H, $2CH_2$), 3.03 d (1H, 1-H, J = 3.8 Hz), 4.35 q (2H, OCH_2, J = 7.2 Hz), 5.28 d.d (1H, J = 17.6, 1.1 Hz), 5.43 d.d (1H, J = 1.1, 11.0 Hz), 5.83 d.d (1H, J = 11.0, 17.6 Hz) ($CH{=}CH_2$).

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