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Chiral *exo*-Alkylidenecyclopentanes from (1*S*,4*R*)-7,7-Dimethyl-1-vinylbicyclo[2.2.1]heptan-2-one

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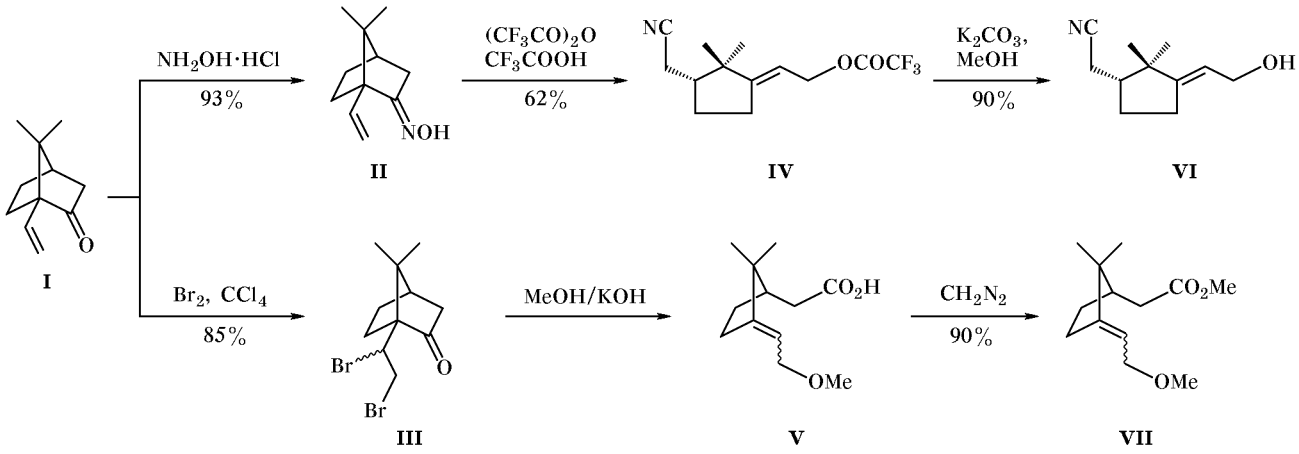
Abstract—(1*S*,4*R*)-7,7-Dimethyl-1-vinylbicyclo[2.2.1]heptan-2-one oxime in the system $(CF_3CO)_2O$–CF_3COOH and (1*S*,4*R*)-1-(1,2-dibromoethyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one in the system MeONa–MeOH undergo fragmentation to give *exo*-alkylidenecyclopentane derivatives, (4*R*)-4-cyanomethyl-5,5-dimethyl-1-[(1*E*)-trifluoroacetoxyethylidene]cyclopentane and isomeric (4*R*)-4-carboxymethyl-1-[(1*ZE*)-2-methoxyethylidene]-5,5-dimethylcyclopentanes, respectively. The trifluoroacetate derivative undergoes unusual rearrangement, yielding an equilibrium mixture of two isomers with endo- and exocyclic double bond.

Despite its obvious synthetic potential, norbornane ketoolefin **I**, which is obtainable from *d*-camphorsulfonic acid [1], has received a limited application in target-oriented syntheses of natural compounds [2]. It was used as a starting chiral compound in the synthesis of taxoids, which was extensively developed in the recent years [3–5]. In continuation of our studies [6–8] on new derivatives of compound **I** of synthetic interest, in the present work we examined its partial ring-opening reactions. As substrates we selected readily accessible derivatives of enone **I**, oxime **II** and dibromide **III**, the latter being a ~2:1 mixture of (1′*R*)- and (1′*S*)-diastereoisomers [9]. As expected, treatment of oxime **II** with trifluoroacetic acid in trifluoroacetic anhydride (Beckmann rearrangement) and of dibromide **III** with alkali resulted in their smooth transformation into monocyclic compounds **IV** and **V** which were converted into alcohol **VI** and methyl ester **VII**, respectively (Scheme 1). The fragmentation of oxime **II** was stereoselective, while from stereoisomeric mixture **III** we obtained product **V** with a different isomeric composition, $E:Z \approx 6:4$. The isomer structure of **V** was determined on the basis of the ^{13}C NMR spectra, where the strongest difference was observed for the resonance signals from the C^2 atom of the cyclopentane ring. In the spectrum of *Z*-**V**, the C^2 signal is located at δ_C 33.46 ppm, while the corresponding signal of *E*-**V** appears in a stronger

Scheme 1.



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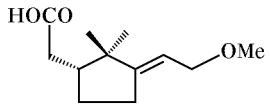
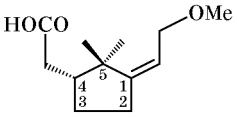
field, δ_C 26.99 ppm, for steric reasons. The C^2 signal in the spectrum of structurally related compound **IV** is located at δ_C 26.57 ppm, indicating *E* configuration of the exocyclic double bond therein.



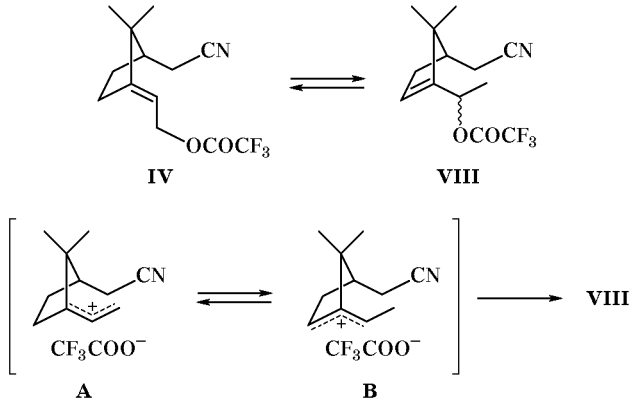
E-**V**



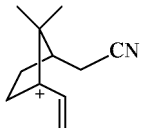
Z-**V**

On storage of purified samples of **IV** we observed slow formation of a new substance **VIII** until equilibrium established at an isomer ratio of ~1:1. This unusual rearrangement is likely to involve ion pairs **A** and **B** (Scheme 2). Compound **VIII** is also a mixture of diastereoisomers, one of which prevailing. We did not determine the confguration of the new chiral center in **VIII**.

Scheme 2.



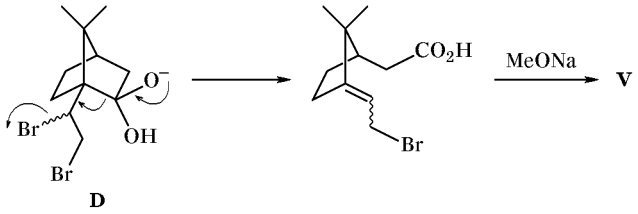
The above two reactions are interesting from the synthetic viewpoint. The fragmentation of oxime **II** involves intermediate formation of cation **C** which is stabilized via S_N2' capture of an external nucleophile (CF_3COOH).



C

The transformation **III** → **V** can formally be regarded as oxidative fragmentation occurring without participation of an oxidant. Its result may be interpreted in terms of the Grob fragmentation [10, 11] with formation of ion **D** from compound **III** via attack by hydroxide ion on the carbonyl group (Scheme 3).

Scheme 3.



EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer from samples prepared as thin films or dispersed in Nujol. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300 MHz for ^1H and 75.47 MHz for ^{13}C) in $CDCl_3$ with TMS as internal reference. Silica gel L 100/160 μm (Lachema) was used for column chromatography. TLC analysis 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 mass spectrometer (ion source temperature 80–90°C).

(*E*,1*S*,4*R*)-7,7-Dimethyl-1-vinylbicyclo[2.2.1]-hepten-2-one oxime (II). To a solution of 100 mg (0.61 mmol) of ketone **I** in 5 ml of EtOH we added 222 mg (3.19 mmol) of hydroxylamine hydrochloride and a solution of 313 mg (7.82 mmol) of NaOH in 1 ml of water. The mixture was heated for 3 h under reflux, cooled to room temperature, and neutralized with a 10% solution of H_2SO_4. The alcohol was distilled off under reduced pressure, and the aqueous phase was extracted with ethyl acetate (3 × 5 ml). The combined extracts were dried over $MgSO_4$ and evaporated, and the residue was purified by column chromatography on silica gel using petroleum ether–ethyl acetate (10:1) as eluent. Yield 100 mg (92%). mp 86–88°C, R_f 0.40 (hexane–EtOAc, 7:3), $[\alpha]_D^{20}$ = –77.3° (*c* = 1.0, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3625, 1665, 945. ^1H NMR spectrum, δ, ppm: 0.82 s (3H, CH_3), 0.87 s (3H, CH_3), 1.20–1.30 m (2H), 1.50 m (1H), 1.80–2.20 m (4H), 2.60 d (1H, *exo*-3-H, *J* = 17.5 Hz), 5.15 d (1H, *J* = 17.6 Hz) and 5.30 d (1H, CH_2=, *J* = 10.8 Hz), 5.90 d.d (1H, =CH, *J* = 10.8, 17.6 Hz), 8.50 br.s (OH). ^{13}C NMR spectrum, δ_C, ppm: 18.79 (CH_3), 19.73 (CH_3), 26.99 (C^5), 27.84 (C^6), 33.30 (C^3), 44.15 (C^4), 49.89 s (C^7), 58.13 (C^1), 117.69 and 133.78 (CH=CH_2), 168.86 (C^2). Found, %: C 73.1; H 9.39; N 8.0. $C_{11}H_{17}NO$. Calculated, %: C 73.70; H 9.56; N 7.81.

(4*R*)-4-Cyanomethyl-5,5-dimethyl-1-[(1*E*)-trifluoroacetoxyethylidene]cyclopentane (IV). To a solution of 100 mg (0.56 mmol) of oxime **II** in 2 ml

of dry methylene chloride we added at 0°C 200 mg (0.95 mmol) of trifluoroacetic anhydride, the mixture was stirred for 2 h, 64 mg (0.56 mmol) of trifluoroacetic acid was added, and the mixture was stirred for 2 h. The solution was evaporated, the residue was treated with a saturated solution of $NaHCO_3$, the aqueous phase was extracted with ethyl acetate (3 × 10 ml), and the extract was dried over $MgSO_4$ and evaporated. The residue was subjected to column chromatography on silica gel using petroleum ether–ethyl acetate (10 : 1) as eluent to isolate 95 mg (62%) of compound **IV** as an oily substance. R_f 0.38 (hexane–EtOAc, 7 : 3), $[\alpha]_D^{20}$ = +6.9° (*c* = 1.0, $CDCl_3$). IR spectrum, ν, cm^{-1}: 1784, 2248. ^1H NMR spectrum, δ, ppm: 0.88 s (3H, CH_3), 1.15 s (3H, CH_3), 1.50–1.65 m (2H), 1.90–2.60 m (5H), 4.80 d (2H, CH_2O, *J* = 7.1 Hz), 5.40 m (1H). ^{13}C NMR spectrum, δ_C, ppm: 17.63 (C**H**$_2$CN), 27.76 (2CH_3), 26.57 (C^2), 27.96 (C^3), 44.54 (C^5), 46.13 (C^4), 65.57 (CH_2O), 114.50 q (CF_3, *J* = 283.5 Hz), 119.20 (CN), 119.93 (=CH), 157.30 q (C=O, *J* = 54.4 Hz), 159.64 (C^1). Found, %: C 56.90; H 5.90; N 4.81. $C_{13}H_{16}F_3NO_2$. Calculated, %: C 56.72; H 5.86; N 5.09.

(4*R*)-4-Carboxymethyl-1-[(1*Z*,*E*)-2-methoxyethylidene]-5,5-dimethylcyclopentane (V) (mixture of isomers). To a solution of 200 mg (0.62 mmol) of dibromide **III** [9] in 3 ml of methanol we added 200 mg (3.57 mmol) of potassium hydroxide. The mixture was heated for 4 h under reflux, cooled to 0°C, neutralized with 10% sulfuric acid, and evaporated under reduced pressure. The residue was extracted with ethyl acetate (3 × 10 ml), the combined extracts were dried over $MgSO_4$ and evaporated, and the residue was subjected to column chromatography on silica gel using petroleum ether–ethyl acetate (10 : 1) as eluent. Yield 55 mg (46%), oily substance, *E*,*Z*-isomer ratio 6 : 4 (^1H NMR data). R_f 0.34 (hexane–EtOAc, 7 : 3), $[\alpha]_D^{20}$ = +17.7° (*c* = 1.0, $CDCl_3$). IR spectrum, cm^{-1}: 1720, 1730. ^1H NMR spectrum, δ, ppm: isomer *Z*-**V**: 0.82 s (3H, CH_3), 1.08 s (3H, CH_3), 1.25–1.40 m (2H), 1.80–2.45 m (5H), 3.23 s (3H, OMe), 3.85 d.d (2H, CH_2O, *J* = 6.8, 1.0 Hz), 5.30 m (1H, HC=): isomer *E*-**V**: 0.92 s (3H, CH_3), 1.20 s (3H, CH_3), 1.20–1.40 m (2H), 1.80–2.45 m (5H), 3.26 s (3H, OMe), 4.03 d.d (2H, CH_2O, *J* = 6.7, 1.0 Hz), 5.30 m (1H, HC=). ^{13}C NMR spectrum, δ_C, ppm: isomer *Z*-**V**: 22.70 (CH_3), 25.88 (CH_3), 26.51 (C^2), 28.02 (C^3), 33.97 (C**H**$_2$CO$_2$H), 43.53 (C^5), 46.15 (C^4), 56.47 (OMe), 69.35 (CH_2O), 116.86 (HC=), 154.86 (C^1), 173.94 (CO_2); isomer *E*-**V**; 21.14 (CH_3), 25.96 (CH_3), 29.09 (C^3), 32.98 (C^2), 33.54 (C**H**$_2$CO$_2$H), 42.51 (C^5), 48.67 (C^4), 56.78 (OMe), 67.96 (CH_2O), 115.77 (HC=), 152.72 (C^1), 173.94 (CO_2). Found, %: C 68.30; H 8.40. $C_{12}H_{20}O_3$. Calculated, %: C 68.54; H 8.63.

(4*R*)-4-Cyanomethyl-1-[(1*E*)-2-hydroxyethylidene]-5,5-dimethylcyclopentane (VI). To a solution of 192 mg (0.70 mmol) of compound **IV** in 2 ml of methanol we added 145 mg (1.05 mmol) of K_2CO_3, the mixture was stirred for 15 min and evaporated, the residue was washed with a saturated solution of $NaHCO_3$, the aqueous phase was extracted with ethyl acetate (3 × 10 ml), and the extract was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel using petroleum ether–ethyl acetate (10 : 1) as eluent. Yield 115 mg (91%), oily substance. R_f 0.37 (hexane–EtOAc, 1 : 1), $[\alpha]_D^{20}$ = +13° (*c* = 1.0, $CDCl_3$). IR spectrum, cm^{-1}: 2248, 3376. ^1H NMR spectrum, δ, ppm: 0.85 s (3H, CH_3), 1.10 s (3H, CH_3), 1.50 m (1H), 1.90 m (1H), 2.00–2.50 m (5H), 2.90 br.s (OH), 4.10 m (2H, CH_2O), 5.40 m (1H, HC=). ^{13}C NMR spectrum, δ_C, ppm: 17.65 (**C**H$_2$CN), 22.87 (2CN_3), 26.23 (C^2), 26.64 (C^3), 43.93 (C^5), 46.16 (C^4), 60.15 (CH_2O), 118.97 (HC=), 119.41 (CH), 153.15 (C^1). Found, %: C 73.90; H 9.83; N 7.32. $C_{11}H_{17}NO$. Calculated, %: C 73.70; H 9.56; N 7.81.

(4*R*)-4-Methoxycarbonylmethyl-1-[(1*E*,*Z*)-2-methoxyethylidene]-5,5-dimethylcyclopentane (VII) (mixture of isomers) was obtained by treatment of isomeric acids **V** with diazomethane in a mixture of methanol with diethyl ether. Yield 90%, *E* : *Z*-isomer ratio ~3 : 1 (^1H NMR data), oily liquid, R_f 0.75 (hexane–EtOAc, 5 : 1), $[\alpha]_D^{20}$ = +9.5° (*c* = 1.0, $CDCl_3$). IR spectrum, cm^{-1}: 1740. ^1H NMR spectrum, δ, ppm: isomer *E*-**VII**: 0.78 s (3H, CH_3), 1.03 s (3H, CH_3), 1.20–1.40 m (2H), 1.80–2.40 m (5H), 3.26 s (3H, OMe), 3.62 s (3H, OMe), 3.86 d (2H, CH_2O, *J* = 6.7 Hz), 5.30 m (1H, HC=); isomer *Z*-**VII**: 0.90 s (3H, CH_3), 1.18 s (3H, CH_3), 1.20–1.40 m (2H), 1.80–2.40 m (5H), 3.30 s (3H, OMe), 3.63 s (3H, OMe), 4.00 d.t (2H, CH_2O, *J* = 6.9, 1.7 Hz), 5.30 m (1H, HC=). ^{13}C NMR spectrum, δ_C, ppm: isomer *E*-**VII**: 24.40 (CH_3), 26.78 (CH_3), 26.99 (C^2), 28.34 (C^3), 34.73 (**C**HCO$_2$Me), 44.06 (C^5), 46.28 (C^4), 51.48 (OMe), 57.77 (OMe), 70.07 (CH_2O), 115.74 (HC=), 155.52 (C′), 173.92 (CO_2); isomer *Z*-**VII**: 22.08 (CH_3), 26.52 (CH_3), 28.98 (C^3), 33.46 (C^2), 34.34 (**C**H$_2$CO$_2$Me), 43.01 (C^5), 48.85 (C^4), 51.48 (OMe), 57.96 (OMe), 70.07 (CH_2O), 118.55 (HC=), 153.78 (C^1), 173.92 (CO_2). Found, %: C 69.00; H 9.72. $C_{13}H_{22}O_3$. Calculated, %: C 69.20; H 9.63.

(4*R*)-4-Cyanomethyl-5,5-dimethyl-1-[(1*R*,*S*)-1-trifluoroacetoxyethyl]cyclopentene (VIII) was formed on storage in a refrigerator of samples of compound **IV** purified by column chromatography on silica gel.

The spectra were obtained for a mixture of compounds **IV** and **VIII** at a ratio of 6:5, which was formed after storage for a week at 0°C. According to the ^{1}H NMR data, the stereoisomeric composition of product **VIII** was ~5:1 (determined from the intensities of somewhat different doublet signals from the side-chain methyl protons). ^{1}H NMR spectrum, δ, ppm: 0.95 s (3H, CH_3), 1.10 s (3H, CH_3), 1.52 d (3H, CH_3, J = 6.6 Hz), 1.90–2.60 m (5H), 5.50 m (1H, CHO, J = 7.1 Hz), 5.80 m (1H, HC=). ^{13}C NMR spectrum, δ_C, ppm: 17.65 and 17.76 (**C**H_2CN), 20.11 (CH_3), 20.25 (CH_3), 25.80 (CH_3), 25.88 (CH_3), 35.30 (C^3), 46.71 and 46.30 (C^4), 46.91 and 46.77 (C^5), 71.81 and 71.32 (CHO), 114.55 q (CF_3, J = 283.5 Hz), 119.17 and 118.95 (CN), 125.41 and 127.12 (C^2), 149.44 and 148.80 (C^1), 156.40 q (**C**OCF_3, J = 42.5 Hz).

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