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SYNTHESIS OF PINENYLSULFIDES FROM *cis*-VERBENOL

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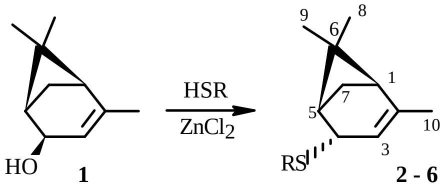
The reaction of cis-verbenol with thiols in the presence of $ZnCl_2$ occurred stereospecifically with substitution of the hydroxyl by a sulfide.

Key words: *cis*-verbenol, thiols, $ZnCl_2$ catalysis.

cis-Verbenol (**1**) contains a hydroxyl group in the α-position of the double bond and is interesting because of the possible involvement of both centers in reactions of this bicyclic monoterpenoid. The synthesis of *cis*-verbenol from α-pinene has been reported although data on its chemical behavior are limited to only condensation reactions with citral and olivetol [1, 2].

We previously studied electrophilic addition reactions of S-containing reagents to mono- and bicyclic monoterpenes in the presence of a Lewis acid [3-5]. Herein we describe the reaction of *cis*-verbenol prepared by us from *cis*-verbenone using $NaBH_4$ in the presence of $Ce(NO_3)_2\cdot 6H_2O$ [6] with various thiols such as ethanethiol, *iso*-propanethiol, octanethiol, and mercaptoacetic acid and its methyl ester [RSH, R = $–C_2H_5$, $–CH(CH_3)_2$, $–C_8H_{17}$, $–CH_2COOH$, $–CH_2COOCH_3$] using $ZnCl_2$ as a catalyst. The reaction was performed at room temperature in CH_2Cl_2 with catalytic amounts of $ZnCl_2$ using a three-fold excess of the mercaptan and was complete in 1-3 h, in each instance forming a single product (**2-6**) that was isolated by column chromatography (CC) over silica gel. The products were characterized by IR, PMR, and ^{13}C NMR spectroscopies and GC—MS.



2: R = CH_2CH_3; **3:** $CH(CH_3)_2$; **4:** R = $(CH_2)_7CH_3$
5: R = CH_2COOH; **6:** R = CH_2COOCH_3

The IR spectra of **2-6** lack the characteristic OH vibrational band that is present in the IR spectrum of starting *cis*-verbenol. However, the bands characteristic of a tri-substituted double bond at 840 and 1650 cm^{-1} persist. Singlets in the PMR spectra of **2-6** that correspond to protons of three CH_3 groups are found in the same regions as in the spectrum of *cis*-verbenol (0.8, 1.27, and 1.65 ppm). This indicates that the pinene structure of the starting terpene is retained.

The ^{13}C NMR spectra of **2-6** contain signals for the two C atoms of the double bond [116 (C-3) and 150 (C-2) ppm], the C atom of the HCS fragment [45 ppm (C-4)], the three C atoms of the methyls at 21-28 ppm, and the C atoms of the bicyclic framework and the thioalkyl group. The PMR spectrum of **3** has a triplet of doublets for the C-1 methine proton at 1.96 ppm ($J_{H\text{-}1—H\text{-}5}$ = 1.3, $J_{H\text{-}1—H\text{-}7\alpha}$ = 5.4, $J_{H\text{-}1—H\text{-}7\beta}$ = 11.3), multiplets for the C-5 (2.16 ppm) and double-bond (5.21 ppm, J = 1.5) protons, and two doublets with SSCC 1.6 and 1.8 Hz due to splitting by the two neighboring methine protons (H-1 and H-3) for the CH_3 on the double bond at 1.65 ppm.

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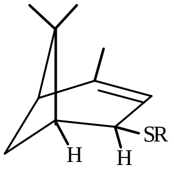
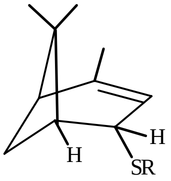
One pecularity of the PMR spectra of **2-6** is that the C-6 methylene protons are magnetically nonequivalent. One of the protons (H-7β) appears as a doublet at 1.2 ppm ($^2J = 9.1$) whereas the signal for H-7α "feels" the presence of the electron-accepting thioalkyl and shifts to weak field. These protons in the PMR spectrum of **3** appear as two doublets of doublets at 2.24 and 2.27 ppm with a vicinal coupling constant of 5.4 Hz due to coupling with C-6 (H-7α) and C-1.

Thus, the spectral data and the $[M]^+$ values in mass spectra of **2-6** lead to the conclusion that the reaction of *cis*-verbenol with thiols involved substitution of the OH by sulfide and not addition to the double bond.

The stereochemistry of the substitution of OH by sulfide, i.e., the stereoisomer (**A** or **B**) formed in the reactions, was determined by comparing PMR spectra of starting *cis*-verbenol and **3** with the literature data.



A



B

The signal for the C-4 methine proton in the PMR spectrum of *cis*-verbenol appears as a singlet at 4.5 ppm; in the spectrum of **3**, as a doublet of doublets at 3.48 ppm ($J_{H\text{-}4—H\text{-}5} = 2.7$, $J_{H\text{-}4—H\text{-}3} = 5.7$). By analogy with the literature values for SSCCs typical of protons in *cis*-positions of a ring in analogous systems (3-4 Hz) [7], it can be assumed that the vicinal constant of 2.7 Hz is due to coupling of the methine protons on C-4 and C-5 whereas the constant of 5.7 Hz is the result of coupling of the methine proton on the sulfide (H-4) and the proton of the double bond (H-3). Such SSCCs are characteristic of structure **B** with an *exo*-SR relative to the *gem*-dimethyl fragment. For structure **A**, the methine proton on the S atom would be located in the same region of the spectrum (3.5 ppm) as for stereoisomer **B**. However, the SSCC of an *exo*-proton H-4 with methine proton H-5 would differ markedly from the SSCC of the corresponding protons in *trans*-isomer **B** and would fall in the range 0-2 Hz.

Thus, the stereospecific formation of a single isomer in the reactions of *cis*-verbenol with thiols in the presence of $ZnCl_2$ indicates that the reaction occurs most probably by second-order nucleophilic substitution (S_N2). Steric hindrances created by the *gem*-dimethyl fragment cause the bulky complex reagent (thiol—catalyst) to approach from the side opposite to the leaving group with inversion of the configuration of the starting molecule and formation in each instance of a pinenylsulfide with an *exo*-thioalkyl group.

EXPERIMENTAL

PMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Unity (300 MHz) spectrometer with TMS internal standard. IR spectra were obtained for samples in vaseline oil on a 75-IR spectrometer; mass spectra, in a Turbo Mass Gold (Perkin—Elmer) GC—MS with a capillary column (30 m × 320 μm) and He carrier gas ($U_{He} = 1.2$ mL/min).

Synthesis of S-Containnig Derivatives of *cis*-Verbenol (2-6). *cis*-Verbenol (6.5 mmol) at room temperature was stirred and treated with the appropriate thiol (22 mmol) in CH_2Cl_2 (20 mL) and $ZnCl_2$ (0.2 g). After 1-3 h the reaction mixture was treated with water (200 mL) and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$. Solvent was removed. The adduct was purified by CC over silica gel (hexane), yield 65-70%, n_d**3** = 1.3670, n_d**4** = 1.3680.

2,6,6-Trimethyl-*trans*-4-(ethylthio)bicyclo[3.1.1]hept-2-ene (2). PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.88, 1.31 (6H, both s, H-8,9), 1.20 (1H, m, H-7β), 1.27 (3H, t, J = 7.5, H-12), 1.35 (1H, d, J = 9.0, H-7β), 1.64, 1.66 (3H, both d, J = 1.8, 1.9, H-10), 1.99 (1H, td, $J_{H\text{-}1—H\text{-}5} = 1.4$, $J_{H\text{-}1—H\text{-}7\alpha} = 5.7$, $J_{H\text{-}1—H\text{-}7\beta} = 10.9$, H-1), 2.28 (1H, m, H-5), 2.35, 2.38 (1H, both dd, J = 5.7, H-7α), 2.55 (2H, m, J = 7.5, H-11), 3.50 (1H, dd, $J_{H\text{-}4—H\text{-}5} = 2.6$, $J_{H\text{-}4—H\text{-}3} = 5.5$, H-4), 5.22 (1H, m, J = 1.5, H-3).

Mass spectrum (m/z, I_{rel}, %): 196 (5) $[M]^+$, 167 (22), 135 (15), 119 (40), 107 (18), 103 (28), 93 (100), 79 (13), 69 (67), 53 (18).

2,6,6-Trimethyl-*trans*-4-(isopropylthio)bicyclo[3.1.1]hept-2-ene (3). PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.86, 1.28 (6H, both s, H-8,9), 1.22, 1.26 (6H, both d, J = 6.7, H-12,13), 1.32 (1H, d, J = 9.1, H-7β), 1.64, 1.65 (3H, both d, J = 1.6, 1.8, H-10), 1.96 (1H, td, $J_{H\text{-}1—H\text{-}5} = 1.3$, $J_{H\text{-}1—H\text{-}7\alpha} = 5.4$, $J_{H\text{-}1—H\text{-}7\beta} = 11.3$, H-1), 2.16 (1H, m, H-5), 2.24, 2.27 (1H, both dd, J = 5.4, H-7α), 2.95 (2H, m, J = 6.7, H-11), 3.48 (1H, dd, $J_{H\text{-}4—H\text{-}5}$ = 2.7, $J_{H\text{-}4—H\text{-}3}$ = 5.7, H-4), 5.21 (1H, m, J = 1.5, H-3).

2,6,6-Trimethyl-*trans*-4-(octylthio)bicyclo[3.1.1]hept-2-ene (4). PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.75, 1.31 (6H, both s, H-8,9), 0.9 (3H, s, H-18), 1.62 (3H, s, J = 1.8, 1.9, H-10), 1.7-2.2 (4H, m, H-1,5,6), 3.2 (1H, s, H-4), 3.6 (14H, s, H-11-17), 5.1 (1H, s, H-3).

^{13}C NMR spectrum (75.43 MHz, $CDCl_3$): 150 (C-2), 116 (C-3), 49 (C-5), 48 (C-1), 46 (C-4), 33 (C-7), 32 (C-6), 30 (C-11-17), 27 (C-10), 23, 21 (C-8,9).

Mass spectrum (*m*/*z*, I_{rel}, %): 280 (2) $[M]^+$, 200 (10), 187 (12), 167 (14), 135 (16), 119 (40), 105 (12), 93 (100), 77 (13), 69 (64), 55 (12).

***trans*-4-Carboxymethylthio-2,6,6-trimethylbicyclo[3.1.1]hept-2-ene (5).** PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.8, 1.3 (6H, both s, H-8,9), 1.35 (1H, d, J = 9.1, H-7β), 1.62, 1.64 (3H, both d, J = 1.7, 1.8, H-10), 2.0-2.4 (3H, m, H-1,5, H-7α), 3.1 (2H, m, SCH_2), 3.5 (1H, m, H-4), 5.2 (1H, s, H-3), 11.1 (1H, s, COOH).

^{13}C NMR spectrum (75.43 MHz, $CDCl_3$): 177 (C=O), 147 (C-2), 117 (C-3), 49 (SCH_2), 48 (C-5), 47 (C-1), 46 (C-4), 33 (C-7), 29 (C-6), 27 (C-10), 23, 21 (C-8,9).

Methyl Ester of *S*-{*trans*-4′-(2,6,6-Trimethylbicyclo[3.1.1]hept-2-ene)yl}thioethanoic Acid (6). PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.79, 1.21 (6H, both s, H-8,9), 1.25 (1H, d, J = 9.6, H-7β), 1.60 (3H, s, H-10), 1.92 (1H, td, $J_{H\text{-}1—H\text{-}5}$ = 1.2, $J_{H\text{-}1—H\text{-}7\alpha}$ = 5.5, $J_{H\text{-}1—H\text{-}7\beta}$ = 10.4, H-1), 2.13 (1H, m, H-5), 2.18, 2.21 (1H, both d, J = 5.5, H-7α), 3.14 (2H, d, J = 7.4, SCH_2), 3.60 (3H, s, OCH_3), 5.22 (1H, s, H-3).

^{13}C NMR spectrum (75.43 MHz, $CDCl_3$): 170 (C=O), 150 (C-2), 118 (C-3), 53 (SCH_2), 48 (C-5), 47.5 (C-1), 46 (C-4), 33 (C-7), 29 (C-6), 27 (C-10), 23, 21 (C-8,9).

Mass spectrum (*m*/*z*, I_{rel}, %): 240 (1) $[M]^+$, 167 (20), 147 (22), 134 (50), 119 (70), 105 (25), 93 (100), 77 (55), 69 (68), 43 (98), 27 (31).

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