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Efficient synthesis of β-hydroxy sulfides by microwave-promoted ring opening in (+)-3-carene *trans*-epoxide with sodium thiolates

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Reaction of (+)-3-carene *trans*-epoxide with sodium thiolates in methanolic solution in a microwave oven at 140 °C for 35–40 min affords corresponding (1*S*,3*S*,4*S*,6*R*)-4-sulfanylcaran-3-ols in 75–95% yields.

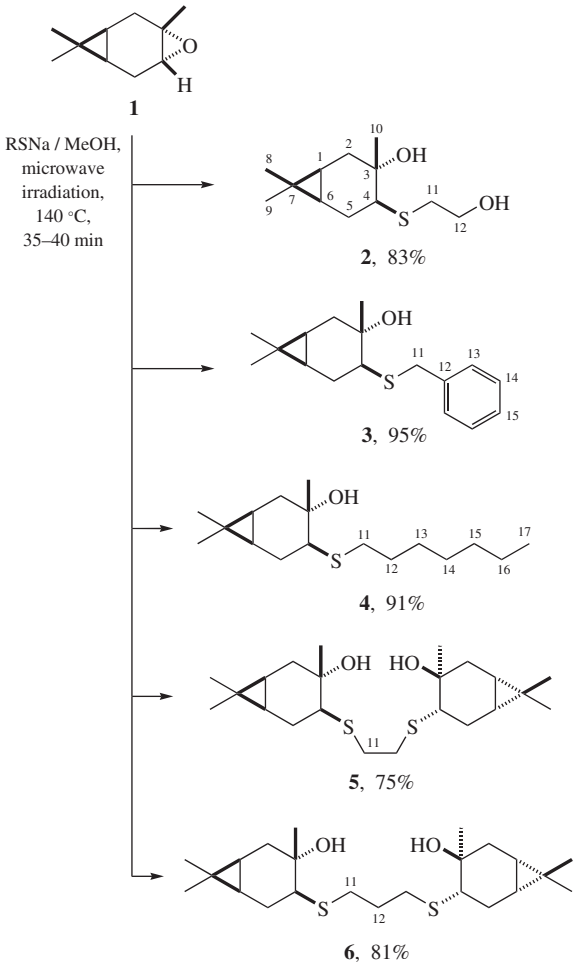
β-Hydroxyalkyl sulfides are very important organic compounds which can be used as starting material in syntheses of cyclic sulfides,[1] allylic alcohols,[2] benzoxathiepin derivatives,[3] benzothiazepines,[4] keto thiones,[5] leucotrienes,[6] *etc*. Moreover, β-hydroxyalkyl sulfides are utilized as S,O-ligands in asymmetric synthesis.[7] The main strategy for their preparation includes ring opening of epoxides with S-nucleophiles using heterogeneous or homogeneous catalysts like liquid proton acids or Lewis acids,[8] solid Lewis acids,[9] and bases[10] in usual organic solvents,[8–10] in water,[11] in perfluorinated alcohols,[12] or without solvents.[13] Syntheses of chiral β-hydroxyalkyl sulfides are carried out either from chiral epoxides or chiral thiols,[6,7] or from achiral precursors in the presence of chiral auxiliary.[14] Microwave irradiation is known to promote many organic reactions, including synthesis of the simplest β-hydroxyalkyl sulfides.[9,11]

Many naturally occurring terpenes like 3-carene, limonene, and α- and β-pinenes are considered as primary source of chirality in enantioselective syntheses and can be easily transformed to the corresponding labile epoxides. 3-Carene-derived *trans*-epoxide **1** is important and popular model for adopting different synthetic schemes to terpene series. Epoxide **1** was studied in reactions with thiophenol in ethanol,[15] with isothiuronium salts,[16,17] and thiourea,[18] with thiols in ethanol[19] and in DMSO.[20] The corresponding β-hydroxycaranyl sulfides were the main products in all the cases, although the procedures were sophisticated and prolonged (5–50 h) and provided moderate yields of the products even when 10-fold excess of a thiol was used.[20]

Here we report a plain and practical means for the preparation of β-hydroxycaranyl sulfides by treatment of *trans*-epoxide **1** with sodium thiolates under microwave irradiation.

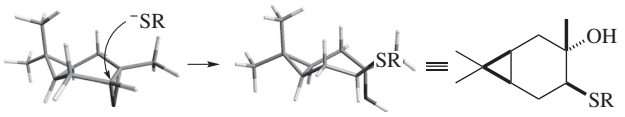
The reaction of *trans*-epoxide **1** with sodium thiolates was carried out in a Single-Mode Microwave reactor Discover™ System S-Class (CEM corp., USA) using a special 15 ml sealed reaction vessel. According to TLC the period of 35–40 min is sufficient for the reaction completion providing the desired sulfides **2**–**6** in very good preparative yields (Scheme 1).†

High resolution mass spectrometry of all the compounds synthesized gave the correct molecular formula, whereas IR spectra detected formation of the hydroxyl group. Analysis of high-field 2D ^{1}H–^{1}H and ^{13}C–^{1}H-correlation NMR spectra of the products **2**,‡ **3**,§ **4**,§ **5**,¶ and **6**†† showed that in all the compounds the carane carbon frame has the same set of heteroatomic functions attached and the same configurations of the asymmetric carbons C(3) and C(4). Configuration of the benzylthio derivative **3** had been established earlier.[17] In our hands, the benzylthio derivative prepared *via* benzylthiuronium salt[17] is identical (IR, NMR) to that syn-



Scheme 1 (The numbering scheme is given for NMR interpretation only).

† *Typical synthetic procedure.* Sodium (5–10 mmol) was dissolved in a solution of thiol (1 equiv.) in MeOH (5–10 ml). The resulting mixture was kept at room temperature for 30 min and then added to *trans*-epoxide **1** (1 equiv.). The reaction mixture was subjected to MW-irradiation at 140 °C for 35–40 min. The solvent was distilled off, the residue was treated with Bu^{t}OMe (20 ml) and water (20 ml). The organic layer was separated, the aqueous phase was extracted with Bu^{t}OMe (2×20 ml). The combined organic extract was dried (Na_2SO_4) and concentrated *in vacuo* to leave the crude product (90–99%) as viscous yellowish oil which was then purified by column chromatography (SiO_2, hexane–EtOAc) to afford the target compound **2** (83% yield), **3** (95%), **4** (91%), **5** (75%), or **6** (81%).



Scheme 2

thesized by the microwave-assisted method newly developed. So, all the derivatives **2**–**6** (Scheme 1) have the same 1*S*,4*S*,3*S*,6*R*-configuration, the derivatives of 1,2-dithioethane (**5**) and 1,3-dithiopropane (**6**) being C_2-symmetrical.

The reaction of *trans*-epoxide **1** with sodium thiolates proceeds as typical S_N2 epoxide ring cleavage in boat-like conformation of six-membered carbocycle with nucleophilic attack at the less substituted carbon C(4) with inversion of configuration of the carbon C(4) and retention of configuration at C(3) (Scheme 2). Due to *trans*-disposition of the two heteroatomic functions at the carbons C(3) and C(4), the six-membered carbocycle in products **2**–**6** exists as more or less distorted boat conformation (see vicinal couplings in ^{1}H NMR spectra), degree of the distortion being dependent on the nature of the sulfur-containing substituent at the carbon C(4).

‡ *(1S,3S,4S,6R)-4-(2-Hydroxyethylthio)caran-3-ol* **2**: yield 83%, colourless oil, $[\alpha]_{589}^{29}$ +77 (*c* 0.90, $CHCl_3$). IR (*c* 2%, $CHCl_3$, ν_{max}/cm^{-1}): 3594, 3582. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.64 (ddd, 1H, H-1, *J* 9.0, 8.0 and 7.1 Hz), 0.73 (ddd, 1H, H-6, *J* 9.0, 7.8 and 7.6 Hz), 0.91 (ddd, 1H, $H_{pro\text{-}R}$-5, *J* 14.5, 11.2 and 7.6 Hz), 0.93 (s, 3H, H-8 or H-9), 0.98 (s, 3H, H-8 or H-9), 1.07 (dd, 1H, $H_{pro\text{-}R}$-2, *J* 15.3 and 7.1 Hz), 1.11 (s, 3H, H-10), 1.83 (dd, 1H, $H_{pro\text{-}S}$-2, *J* 15.3 and 8.0 Hz), 2.05 (ddd, 1H, $H_{pro\text{-}S}$-5, *J* 14.5, 7.8 and 4.7 Hz), 2.66 (ddd, 1H, H-4, *J* 11.2 and 4.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.1 (C^8, $^1J_{CH}$ 3×124 Hz, $^{2,3}J_{CH}$ 3×4 Hz), 17.8 (C^1 or C^6), 18.4 (C^7), 22.9 (C^1 or C^6), 26.4 (C^5), 26.8 (C^{10}, $^{2,3}J_{CH}$ 3, 3 and 2 Hz), 28.1 (C^9), 33.2 (C^2, $^1J_{CH}$ 2×125 Hz), 35.3 (C^{11}, $^1J_{CH}$ 2×138 Hz, $^{2,3}J_{CH}$ 2×3 Hz), 53.6 (C^4, $^1J_{CH}$ 142 Hz), 61.0 (C^{12}, $^1J_{CH}$ 2×144 Hz, $^{2,3}J_{CH}$ 2×3 Hz). MS, *m*/*z* (%): 230.1338 (11, [M]$^+$, calc. for $[C_{12}H_{22}O_2S]^+$: 230.1335), 187 (81), 185 (45), 152 (30), 137 (30), 134 (23), 126 (32), 119 (40), 109 (54), 107 (25), 93 (48), 83 (68), 71 (32), 67 (42), 55 (26).

§ For characteristics of compounds **3** and **4**, see Online Supplementary Materials.

¶ *1,2-Bis[(1S,3S,4S,6R)-3-hydroxycaran-4-ylthio]ethane* **5**: yield 75%, colourless oil, $[\alpha]_{589}^{23}$ +90 (*c* 1.59, $CHCl_3$). IR (*c* 2% in $CHCl_3$, ν_{max}/cm^{-1}): 3579, 1134. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.65–0.80 (m, 4H, H-1 and H-6), 0.96 (s, 6H, H-8 or H-9), 1.02 (s, 6H, H-8 or H-9), 1.14 (ddd, 2H, $H_{pro\text{-}R}$-5, *J* 14.7, 9.9 and 5.7 Hz), 1.22 (s, 6H, H-10), 1.30 (dd, 2H, $H_{pro\text{-}R}$-2, *J* 15.2 and 6.6 Hz), 1.95 (dd, 2H, $H_{pro\text{-}S}$-2, *J* 15.2 and 7.9 Hz), 2.21 (ddd, 2H, $H_{pro\text{-}S}$-5, *J* 14.6, 8.0 and 5.8 Hz), 2.45 (br. s, 2H, OH), 2.64 (m, 4H, H-11), 2.70 (dd, 2H, H-4, *J* 9.5 and 5.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.73 (C^8), 17.93 (C^5), 18.39 (C^6), 22.2 (C^1), 25.97 (C^7), 28.37 (C^9), 28.71 (C^{10}), 33.46 (C^2), 34.20 (C^{11}), 51.93 (C^4), 71.54 (C^3). MS, *m*/*z* (%): 398.2312 (1, [M]$^+$, calc. for $[C_{22}H_{38}O_2S_2]^+$: 398.2308), 245 (17), 213 (97), 195 (21), 185 (31), 167 (19), 153 (29), 135 (100), 127 (15), 119 (21), 109 (32), 93 (90), 81 (17), 67 (17).

†† *1,3-Bis[(1S,3S,4S,6R)-3-hydroxycaran-4-ylthio]propane* **6**: yield 81%, colourless oil, $[\alpha]_{589}^{29}$ +99 (*c* 1.37, $CHCl_3$). IR (*c* 2% in $CHCl_3$, ν_{max}/cm^{-1}): 3586. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.65–0.80 (m, 4H, H-1 and H-6), 0.96 (s, 6H, H-8 or H-9), 0.99 (s, 6H, H-8 or H-9), 1.11 (dddd, 2H, $H_{pro\text{-}R}$-5, *J* 14.5, 9.7 and 6.3 Hz), 1.19 (s, 6H, H-10), 1.24 (dd, 2H, $H_{pro\text{-}R}$-2, *J* 15.0 and 6.3 Hz), 1.86 (t, 4H, H-12, *J* 7.1 Hz), 1.92 (dd, 2H, $H_{pro\text{-}S}$-2, *J* 15.0 and 8.6 Hz), 2.20 (ddd, 2H, $H_{pro\text{-}S}$-5, *J* 14.5, 7.9 and 5.2 Hz), 2.45 (br. s, 2H, OH), 2.64 (m, 4H, H-11), 2.67 (dd, 2H, H-4, *J* 9.8 and 5.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.01 (C^8), 18.90 (C^6), 19.01 (C^5), 22.50 (C^1), 26.66 (C^7), 27.70 (C^9), 28.90 (C^{10}), 30.12 (C^{12}), 32.01 (C^2), 33.45 (C^{11}), 53.95 (C^4), 73.03 (C^3). MS, *m*/*z* (%): 412.2450 (12, [M]$^+$, calc. for $[C_{23}H_{40}O_2S_2]^+$: 412.2464), 259 (100), 241 (22), 185 (22), 153 (21), 135 (75), 109 (32), 107 (23), 106 (23), 95 (30), 93 (66), 81 (20), 71 (24), 67 (24), 43 (24), 43 (68), 41 (25).

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2011.07.006.

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