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Inhibition of Intramolecular Reactions of (+)-δ-Cadinol

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Abstract—(+)-δ-Cadinol is smoothly acetylated with isopropenyl acetate to form the corresponding acetate which is difficultly hydrolyzable in the presence of bases; unlike initial (+)-δ-cadinol, the acetylation product gives no 1,4- and 1,5-epoxy derivatives as by-products in the allylic oxidation and epoxidation reactions.

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It is known that functionalization of the allyl fragment in (+)-δ-cadinol (**I**) is accompanied by side formation of 1,4- and 1,5-epoxy derivatives [1, 2]. Presumably, these side reactions can be avoided by blocking the hydroxy group in (+)-δ-cadinol, which may be difficult taking into account that this group is attached to a tertiary carbon atom. An effective technique for protection of hydroxy group via conversion into trimethylsilyl ether is unsuitable, for the latter readily undergoes hydrolysis under the conditions of such functionalizations.

We tried to solve the above problem by protecting the tertiary hydroxy group in (+)-δ-cadinol via treatment with isopropenyl acetate. The efficiency of the acetylation strongly depended on the purity of initial isopropenyl acetate. The reaction with commercial isopropenyl acetate gave acetate **II** in 24 h and was accompanied by migration of the double C=C bond with formation of isomer **III** as by-product (Scheme 1). By treatment of compound **I** with freshly prepared isopropenyl acetate [3] we succeeded in obtaining acetate **II** with quantitative yield in 15 min. We then examined the ability of the acetate moiety in **II** to undergo hydrolysis, migration, or elimination. For this purpose, compound **II** was treated with a solution of sodium hydroxide in aqueous ethanol. Under these conditions, acetate **II** remained unchanged for a few hours; after 15 h, it was hydrolyzed by 50%; and the conversion of **II** was 30% on treatment with methanolic sodium methoxide. Presumably, the acetoxy group in molecule **II** is stabilized due to its position at a tertiary carbon atom, as well as due to *cis*-junction of the six-membered rings.

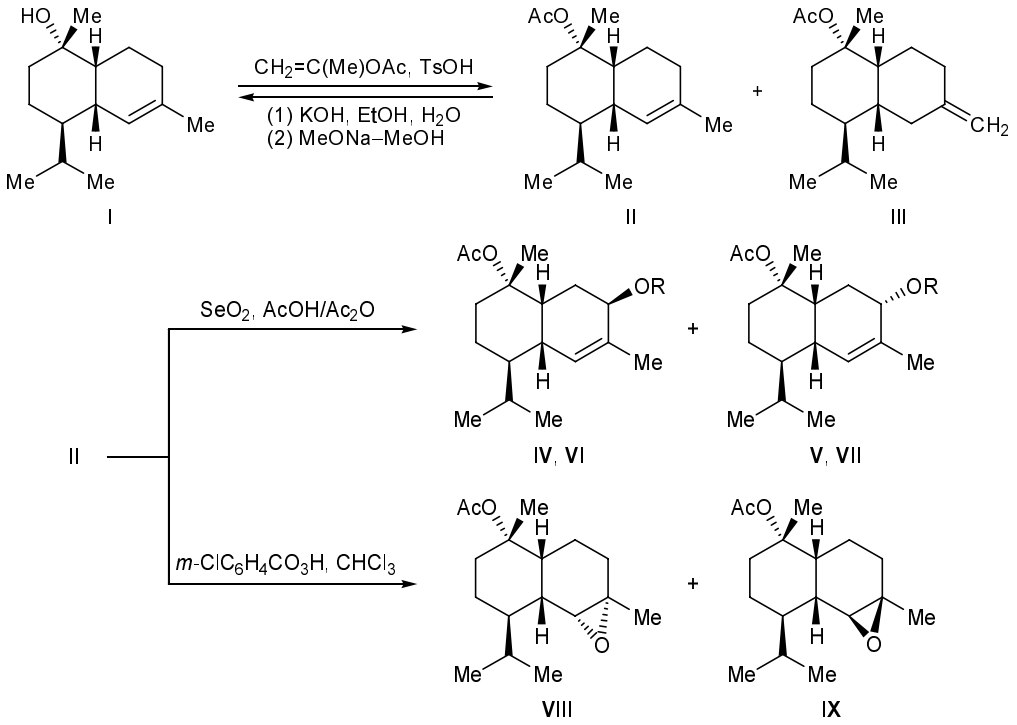
Allylic oxidation of acetate **II** with the system SeO_2–AcOH/Ac_2O, followed by treatment of the resulting mixture of epimeric acetates and alcohols [4, 5] with a solution of sodium hydroxide in aqueous ethanol, resulted in the formation of a mixture of epimeric hydroxy acetates **VI** and **VII** (Scheme 2). 1,4-Epoxy derivative **X** was obtained in 62% yield only when mixture **VI**/**VII** was heated in boiling benzene in the presence of *p*-toluenesulfonic acid [1]. Diastereoisomeric epoxy derivatives **VIII** and **IX** were synthesized by oxidation of acetate **II** at the double bond with *m*-chloroperoxybenzoic acid. In no case intramolecular oxa cyclization products were detected.

We can conclude that effective protection of the tertiary hydroxy group in (+)-δ-cadinol by acetylation with isopropenyl acetate makes it possible to avoid side intramolecular processes typical of functionalization of parent (+)-δ-cadinol.

EXPERIMENTAL

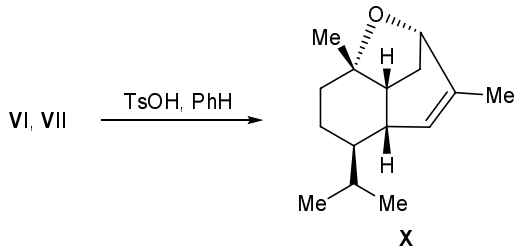
The ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer at 300 MHz for ^1H and 75.47 MHz for ^{13}C. The melting points were measured on a Kofler S 30A/G melting point apparatus (DDR). Analytical thin-layer chromatography was performed on Sorbfil PTSKh-AF-A plates (manufactured by

Scheme 1.



IV, **V**, R = Ac; **VI**, **VII**, R = H.

Scheme 2.



Sorbpolimer Ltd., Krasnodar). The optical rotations were measured on a Perkin–Elmer 141 polarimeter.

(+)-δ-Cadinol with mp 137.8°C and $[\alpha]_D^{20}$ = +100.3° (*c* = 1.0, $CHCl_3$) was used.

Acetylation of (+)-δ-cadinol. *a*. A catalytic amount of *p*-toluenesulfonic acid was added to a solution of 0.100 g (0.45 mmol) of (+)-δ-cadinol (**I**) in 1 ml of isopropenyl acetate (from Lancaster), the mixture was stirred for 24 h, excess isopropenyl acetate was distilled off, and the residue was subjected to chromatography on silica gel to isolate 0.077 g (65%) of acetoxy derivative **II** and 0.27 g (23%) of by-product **III**.

b. A catalytic amount of *p*-toluenesulfonic acid was added to a solution of 0.100 g (0.45 mmol) of (+)-δ-cadinol (**I**) in 1 ml of freshly prepared isopropenyl acetate [3], the mixture was stirred for 15 min, excess isopropenyl acetate was distilled off, and the residue was subjected to chromatography on silica gel to isolate 0.108 g (90.7%) of compound **II**.

(1*R*,4*R*,4a*S*,8a*R*)-4-Isopropyl-1,6-dimethyl-1,2,3,-4,4a,7,8,8a-octahydronaphthalen-1-yl acetate (II). R_f 0.65 (hexane–EtOAc, 10:1), $[\alpha]_D^{26}$ = +56.20° (*c* = 1.0, CH_3Cl). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.80 d (3H, CH_3, *J* = 6.9 Hz), 0.88 d (3H, CH_3, *J* = 6.9 Hz), 1.10 m (1H, CH), 1.3–1.53 m (5H, CH, CH_2), 1.58 s (3H, CH_3), 1.63 s (3H, CH_3), 1.95 m (5H, CH, CH_2), 1.98 s (3H, CH_3), 2.33 m (1H, CH), 5.50 d (1H, 7-H, *J* = 5.5 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 15.28 (CH_3), 19.21 (C^3), 20.77 (C^7), 21.59 (CH_3), 22.43 (1-CH_3), 23.10 (CH_3), 23.57 (6-CH_3), 26.57 (**C**Me_2), 31.06 (C^8), 32.65 (C^2), 36.36 (C^{4a}), 44.08 (C^4), 85.27 (C^1), 124.3 (C^5), 134.29 (C^6), 170.21 (**C**OCH_3). Found, %: C 77.23; H 10.64. $C_{17}H_{28}O_2$. Calculated, %: C 77.22; H 10.67.

(1*R*,4*R*,4a*R*,8a*R*)-4-Isopropyl-1-methyl-6-methylidenedecahydronaphthalen-1-yl acetate (III). R_f 0.89 (hexane–EtOAc, 10:1). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.82 d (3H, CH_3, J = 6.9 Hz), 0.88 d (3H, CH_3, J = 6.9 Hz), 1.02 m (1H, CH), 1.28–1.50 m (3H, CH, CH_2), 1.58–1.62 m (2H, CH, CH_2), 1.68 s (3H, CH_3), 1.83 m (2H, CH_2), 1.78–1.86 m (5H, CH, CH_2), 1.97 s (3H, CH_3), 2.34 m (1H, CH), 4.63 d (1H, C=CH_2, J = 2.1 Hz), 4.78 d.d (1H, C=CH_2, J = 2.1, 1.6 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 15.07 (CH_3), 22.37 (CH_3), 22.56 (CH_3), 22.67 (C^3), 23.35 (CH_3), 25.92 (C^8), 28.42 (C^7), 27.11 (C^{4a}), 38.92 (C^5), 41.24 (C^2), 46.53 (C^{8a}), 55.13 (C^4), 84.81 (C^1), 112.42 (=CH_2), 147.30 (C^6), 170.31 (C=O). Found, %: C 77.19; H 10.66. $C_{17}H_{28}O_2$. Calculated, %: C 77.22; H 10.67.

Hydrolysis of acetoxycadinol II. *a*. Compound **II**, 0.100 g (0.45 mmol), was added to a solution of 0.20 g of sodium hydroxide in 3 ml of a 2:1 ethanol–water mixture. After 15 h, the mixture was neutralized with 5% hydrochloric acid, and the alcohol was distilled off on a rotary evaporator. The residue was extracted with ethyl acetate (3×3 ml), the extracts were combined, washed with a saturated solution of sodium chloride (3×3 ml), and dried over $MgSO_4$, the solvent was distilled off, and the residue was subjected to chromatography to isolate 0.042 g (50%) of (+)-δ-cadinol (**I**) and 0.027 g (27%) of acetoxycadinol **II**.

b. Compound **II**, 0.100 g (0.45 mmol), was dissolved in 3 ml of methanol, and a solution of 0.025 g (0.05 mmol) of sodium methoxide in 5 ml of methanol was added. When the reaction was complete (TLC), the mixture was neutralized with 3% hydrochloric acid, methanol was distilled off under reduced pressure, and the products were extracted from the residue into ethyl acetate (3×5 ml). The extracts were combined, dried over $MgSO_4$, and evaporated, and the residue was separated by chromatography to isolate 0.025 g (30%) of (+)-δ-cadinol (**I**) and 0.062 g (62%) of acetoxycadinol **II**.

(1*R*,4*R*,4a*S*,7*R*,8a*R*)- and (1*R*,4*R*,4a*S*,7*S*,8a*R*)-7-Hydroxy-4-isopropyl-1,6-dimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-yl acetates (VI/VII). Selenium dioxide, 0.05 g (0.45 mmol), was added to a solution of 0.130 g (0.49 mmol) of acetoxycadinol **II** in a mixture of 1 ml of acetic acid and 0.3 ml of acetic anhydride. When the reaction was complete (TLC), ethyl acetate was added, and the mixture was poured onto ice. The mixture was filtered, and the filtrate was extracted with ethyl acetate (3×2 ml). The extracts were combined, washed with water (3×10 ml), and dried over $MgSO_4$. The solvent was distilled off, the residue was subjected to hydrolysis as described above (method *a*), and the products were isolated by chromatography. Yield 0.097 g (71%), **VI**:**VII** ratio 1:2. The (7*R*)-diastereoisomer was isolated as individual substance.

(7*R*)-Diastereoisomer. R_f 0.25 (hexane–EtOAc, 3:1), mp 147°C, $[\alpha]_D^{26}$ = +4° (c = 1.0, $CHCl_3$). ^{1}H NMR spectrum (CD_2Cl_2), δ, ppm: 0.80 d (3H, CH_3, J = 6.9 Hz), 0.86 d (3H, CH_3, J = 6.9 Hz), 1.08–1.25 m (2H, CH, CH_2), 1.37–1.53 m (1H, CH_2), 1.57 s (3H, CH_3), 1.58–1.67 m (4H, CH, CH_2), 1.74 d.d (3H, CH_3, J = 1.4, 1.3 Hz), 1.80–1.94 m (2H, CH, CH_2), 1.95 s (3H, CH_3), 2.02 m (1H, CH), 2.51 m (1H, 8a-H, J = 13.6 Hz), 3.88 d.d (1H, 7-H, J = 4.3, 1.3 Hz), 5.69 d.d (1H, 5-H, J = 5.8, 1.4 Hz). ^{13}C NMR spectrum (CD_2Cl_2), δ_C, ppm: 15.39 (CH_3), 20.90 (C^3), 21.08 (CH_3), 21.57 (CH_3), 22.55 (CH_3), 23.15 (CH_3), 27.26 (**C**HMe_2), 29.0 (C^8), 32.84 (C^2), 36.87 (C^{4a}), 37.22 (C^{8a}), 42.94 (C^4), 68.50 (C^7), 84.62 (C^1), 128.59 (C^5), 135.43 (C^6), 170.46 (C=O). Found, %: C 72.78; H 10.04. $C_{17}H_{28}O_2$. Calculated, %: C 72.82; H 10.06.

(7*S*)-Diastereoisomer [from (7*R*/7*S*)-epimer mixture]. R_f 0.32 (hexane–EtOAc, 3:1). ^{1}H NMR spectrum (CD_2Cl_2), δ, ppm: 0.79 d (3H, CH_3, J = 6.9 Hz), 0.88 d (3H, CH_3, J = 6.9 Hz), 1.52 s (3H, CH_3), 1.69 s (3H, CH_3), 1.95 s (3H, CH_3), 2.43 m (1H, CH_2), 3.88 d.d (1H, 7-H, J = 4.5, 1.7 Hz), 5.59 d.d (1H, 5-H, J = 5.7, 1.5 Hz). ^{13}C NMR spectrum (CD_2Cl_2), δ_C, ppm: 19.28 (CH_3), 20.87 (CH_3), 21.30 (CH_3), 21.50 (C^3), 22.54 (CH_3), 26.97 (**C**HMe_2), 29.92 (C^8), 32.81 (C^2), 36.83 (C^{4a}), 37.17 (C^{8a}), 41.79 (C^4), 71.68 (C^7), 84.27 (C^1), 128.03 (C^5), 137.21 (C^6), 170.40 (C=O).

(1a*S*,3a*R*,4*S*,7*R*,7a*R*,7b*R*)- and (1a*R*,3a*R*,4*S*,7*R*,-7a*R*,7b*S*)-7-Isopropyl-1a,4-dimethyldecahydronaphtho[1,2-*b*]oxiran-4-yl acetates (VIII/IX). *m*-Chloroperoxybenzoic acid, 0.285 g (1.6 mmol), was added to a solution of 0.140 g (0.53 mmol) of acetoxycadinol **II** in 2 ml of chloroform. When the reaction was complete (TLC), 2 ml of water was added to the mixture, and the products were extracted into chloroform (3×3 ml). The extracts were combined, washed with a 2% solution of sodium hydrogen carbonate and a solution of sodium chloride, and dried over $MgSO_4$. The solvent was distilled off on a rotary evaporator, and the residue was subjected by chromatography on silica gel to isolate 0.097 g (65.5%) of a mixture of epimeric epoxy derivatives **VIII** and **IX** at a ratio of 3:2. The (1a*S*,7b*R*)-diastereoisomer was isolated as individual substance.

(1a*S*,7b*R*)-Diastereoisomer VIII. R_f 0.33 (hexane–EtOAc, 10:1), $[\alpha]_D^{26}$ = +10.88° (*c* = 1.0, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.85 d (3H, CH_3, *J* = 6.9 Hz), 0.96 d (3H, CH_3, *J* = 6.9 Hz), 1.10–1.25 m (4H, 7-H, 6-H, 5-H), 1.31 s (3H, 1a-CH_3), 1.43–1.52 m (1H, 2-H), 1.54 s (3H, CH_3), 1.60–1.77 m (3H, 2-H, 3-H, 7-H), 1.98 s (3H, CH_3), 1.80–2.08 m (2H, 3-H, 7a-H), 2.08 m (1H, Me_2C**H**), 2.18 m (1H, 5-H), 3.04 d (1H, 7b-H, *J* = 5.6 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 15.53 (CH_3), 16.79 (C^6), 19.72 (C^3), 21.52 (CH_3), 22.37 (CH_3), 22.58 (CH_3), 23.07 (**C**HMe_2), 27.29 (4-CH_3), 31.64 (C^2), 32.36 (C^5), 34.42 (C^{7a}), 37.87 (C^{3a}), 42.48 (C^7), 59.38 (C^{1a}), 62.17 (C^{7b}), 84.56 (C^4), 170.26 (C=O). Found, %: C 72.74; H 10.11. $C_{17}H_{28}O_3$. Calculated, %: C 72.82; H 10.06.

(1a*R*,7b*S*)-Diastereoisomer IX [from (1a*S*,7b*R*)/(1a*R*,7b*S*)-epimer mixture]. R_f 0.20 (hexane–EtOAc, 10:1). ^{1}H NMR spectrum (CD_2Cl_2), δ, ppm: 0.83 d (3H, CH_3, *J* = 6.9 Hz), 0.92 d (3H, CH_3, *J* = 6.9 Hz), 1.12–1.20 m (4H, CH, CH_2), 1.22 s (3H, CH_3), 1.22–1.47 m (2H, CH, CH_2), 1.49 s (3H, CH_3), 1.50–1.98 m (3H, CH), 1.92 s (3H, CH_3CO), 1.98–2.13 m (3H, CH, CH_2), 2.94 d (1H, 7b-H, *J* = 5.6 Hz). ^{13}C NMR spectrum (CD_2Cl_2), δ_C, ppm: 15.30 (CH_3), 17.47 (C^6), 21.31 (C^3), 21.70 (CH_3), 22.51 (CH_3), 23.25 (CH_3), 27.55 (**C**HMe_2), 28.24 (CH_3), 31.68 (C^2), 35.78 (C^5), 38.29 (C^{7a}), 38.61 (C^3), 43.00 (C^7), 58.13 (C^{1a}), 62.75 (C^{7b}), 84.83 (C^4), 170.41 (C=O).

(1*S*,4*S*,5*R*,8*S*,9*R*)-5-Isopropyl-2,8-dimethyl-11-oxatricyclo[6.2.1.0^{4,9}]undec-2-ene (X) was synthesized by the procedure described in [1]. Yield 62%.

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