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Functionalization of the Allyl Fragment in (+)-δ-Cadinol

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Abstract—Epoxidation, bromination, and iodination of the double bond in (+)-δ-cadinol under various conditions are accompanied by formation of 1,4- or 1,5-epoxy derivatives. By contrast, vicinal hydroxylation gives rise to "normal" products. Intramolecular cyclization of the resulting vicinal diols was studied.

(+)-δ-Cadinol (**I**) is a sesquiterpene alcohol which was isolated for the first time in 1922 from *Torreya nucifera Sieb et Zucc. (Taxaceae)* leafs and was later found in some other conifers [1]. This compound is present in a relatively large concentration in the *Pinus sibirica* R. Mayr oleoresin [2, 3]. Among other sources, *Clitocybe illudens* fungi must be noted; some their strains produce crystalline (+)-δ-cadinol directly at the mycelium surface [4].

The identification of (+)-δ-cadinol included ozonolysis of the double bond and such transformations as hydrochlorination, hydroboration–oxidation, vicinal hydroxylation with OsO_4 and epoxidation with peroxyacids; mild dehydration of (+)-δ-cadinol afforded α-murolene [1, 3, 5, 6]. The formation of an oxygen bridge in the hydroboration–oxidation product gave a strong support to the *cis*-junction of the bicycic system. This conclusion was repeatedly confirmed by the subsequent studies [7–11]. As concerns the stereochemistry of reactions involving (+)-δ-cadinol, it was noted [5] that their result is controlled by the substrate structure, i.e., attack by a reagent occurs preferentially from the less hindered β-side.

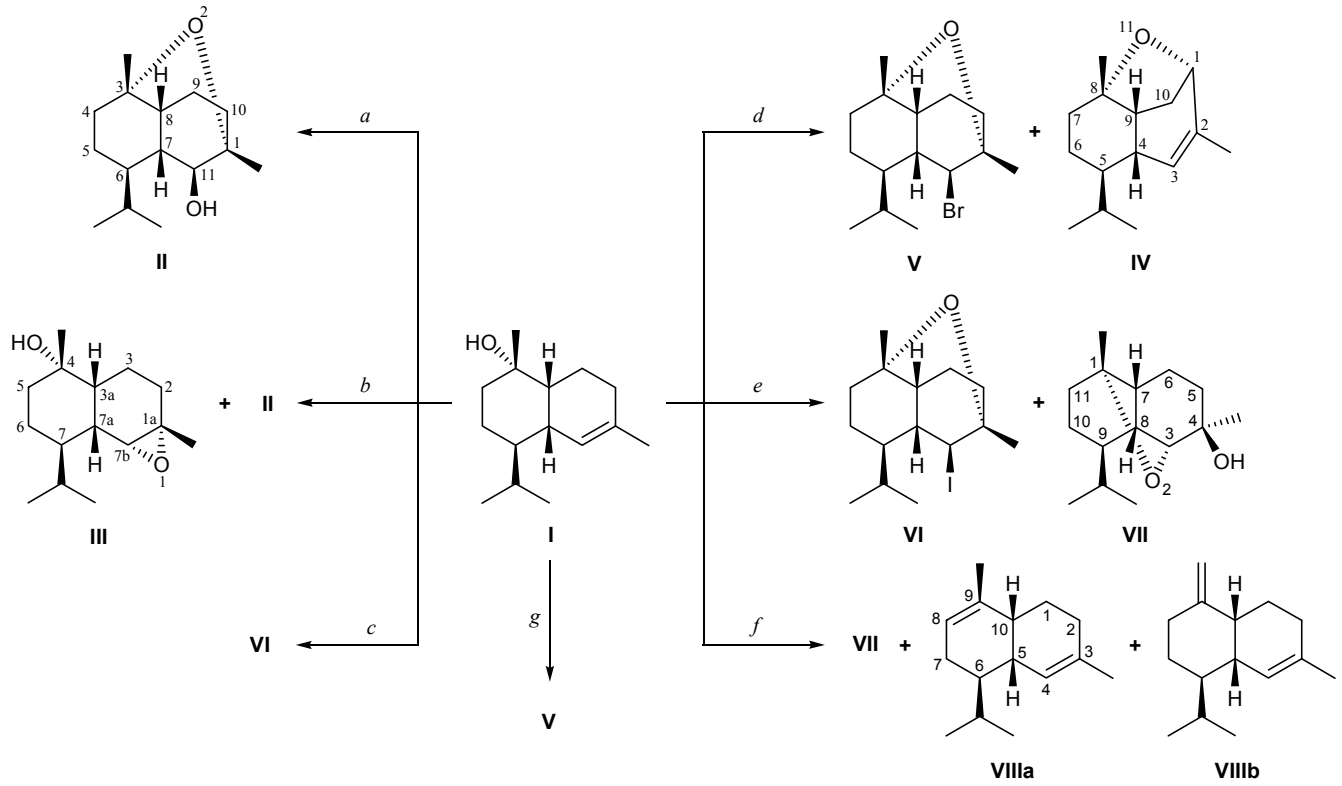
However, the results of some experiments need to be refined, specifically the formation of fused oxepanes or the complete inactivity of the α-epimeric oxirane toward $LiAlH_4$ [5]. One more anomalous finding, the absence of an aldehyde group in the ozonolysis product [5, 6], is likely to be the result of spontaneous aldol condensation at the stage of reduction of the ozonide [12, 13].

With the goal of refining some results of previous studies, as well as of establishing a relation between the (+)-δ-cadinol structure and the mode of transformation of the double bond therein, this compound was brought into epoxidation, bromination (including allylic bromination), iodination, hydroboration–oxidation, and vicinal hydroxylation; some reactions of the products thus formed were also examined.

Allylic oxidation of (+)-δ-cadinol (**I**) with H_2O_2 in the presence of SeO_2 [14] gave tricyclic 1,5-epoxy alcohol **II** in 71% yield. No other oxidation products were detected. The structure of compound **II** was determined on the basis of its ^1H and ^{13}C NMR spectra. In the ^1H NMR spectrum, the 11-H signal characteristically appeared as a broadened singlet at δ 3.42 ppm, indicating equatorial orientation of that proton and ~90° torsion angle $HC^7C^{11}H$. The C^7 and C^3 atoms are characterized by very similar chemical shifts and signal characters in the ^{13}C NMR spectrum (δ_C 72.41 and 72.91 ppm), in keeping with the assumed symmetric arrangement of these atoms in the molecule.

Most probably, this result is explained by intramolecular opening of intermediate β-epimeric oxirane and replacement at the tertiary carbon atom, which fixes the **A** ring in a conformation close to *B*1 with a rigid equatorial orientation of the methyl group; the equilibrium shifts toward conformer with axial orientation of the isopropyl group. In the ^{13}C NMR spectrum of the product, the chemical shifts of the methyl carbon atoms in the isopropyl group are very similar, δ_C 22.20

Scheme 1.



Reagents and conditions: *a*: SeO_2–*t*-BuOH, H_2O_2; *b*: *m*-$ClC_6H_4CO_3H$, $CHCl_3$; *c*: I_2, H^+, THF; *d*: Bz_2O_2, NBS, CCl_4, reflux; *e*: I_2, $CHCl_3$, pyridine; *f*: I_2, OH^-, THF; *g*: NBS, CCl_4, reflux, or Br_2, THF, or Br_2, $CHCl_3$, pyridine.

and 21.26 ppm, in contrast to the corresponding values for initial (+)-δ-cadinol (Δδ 6.2 ppm) [8]. Thus, the new asymmetric centers C^1 and C^{11} have absolute *S* configuration. This is consistent with the known data on preferential attack by nucleophile in acid medium at the more substituted oxirane carbon atom [15].

Epoxidation of the double bond in (+)-δ-cadinol with *m*-chloroperoxybenzoic acid resulted in formation of two products, α-epimeric oxirane **III** and (contrary to [5]) 1,5-epoxy alcohol **II**. This means that the process is accompanied by rearrangement of β-epimeric oxirane to pyran derivative, 1,5-epoxy alcohol **II**, which is inert with respect to $LiAlH_4$.

Allylic bromination of compound **I** with *N*-bromosuccinimide, initiated by benzoyl peroxide, afforded 1,4-epoxy derivative **IV** and 1,5-epoxy bromide **V** in 10 and 76% yield, respectively. In the ^1H NMR spectrum of **V**, the 11-H proton (δ 3.76 ppm) shows coupling with 7-H ($J \approx 2.5$ Hz), indicating axial orientation of the bromine atom. Here, the methyl group is equatorial, which reduces 1,2-interaction with the bromine atom. Interaction of the bromine atom with the isopropyl group favors axial orientation of the latter: the methyl carbon chemical shifts are δ_C 22.17 and 21.12 ppm; i.e., the conformations of the bicyclic systems of 1,5-epoxy bromide **V** and 1,5-epoxy alcohol **II** are similar. Therefore, the absolute configuration of the new asymmetric centers is also 1*S*,11*S*.

Presumably, 1,5-epoxy bromide **V** is formed following initially the Ad_E2 pattern, and the final stage is intramolecular nucleophilic substitution in bromonium cation (as in the oxidation with H_2O_2–SeO_2). In fact, the use of "red" NBS or Br_2 gives 96% of **V**. The structure of compound **IV** corresponds to product of allylic bromination followed by intramolecular nucleophilic substitution. Its physical and spectral properties were identical to those of the known 1,4-epoxy derivative [16].

Like electrophilic bromination, molecular iodine adds to (+)-δ-cadinol in the presence of acetic acid to give 1,5-epoxy iodide **VI**; in alkaline medium, three products are obtained: 1,4-epoxy alcohol **VII** and isomeric (+)-α- and (+)-γ-murolenes **VIIIa** and **VIIIb** (ratio **VII**:**VIII** = 1:1). The most characteristic signal in the ^1H NMR spectrum of **VII** is that from the 3-H proton, which appears as a singlet at δ 3.60 ppm. This

indicates that the torsion angle between the C^3–H bond and the neighboring C–H bond approaches 90°; therefore, the C^3–H bond is equatorial. The 4-Me signal in the ^{13}C NMR spectrum is displaced upfield (δ_C 21.93 ppm) due to 1,2-*syn* interaction with the oxirane oxygen atom. β-Orientation of the hydroxy group in **VII** is confirmed by the fact that this compound is formed by cyclization of triol **XII**.

The result of iodination in alkaline medium may be interpreted in terms of intramolecular nucleophilic substitution at the secondary carbon atom at the stage of formation of iodonium cation and subsequent replacement of iodine at the tertiary carbon atom by hydroxy group. Under these conditions, murolenes **VIII** are formed via iodine-catalyzed dehydration of alcohols, which is a well-known process.

Our attempt to effect bromination of (+)-δ-cadinol under analogous conditions with a view to estimate the effect of the halogen nature was unsuccessful: the mixture underwent tarring. We succeeded in effecting the bromination and iodination under similar conditions with the use of pyridine as a base. The bromination gave 1,5-epoxy bromide **V**, while the iodination products were 1,5- and 1,4-epoxy derivatives **VI** and **VII** (48 and 43%, respectively). Presumably, these results are explained by high nucleofugality of iodine, which makes other factors insignificant; the reaction leads to formation of a statistical mixture of **VI** and **VII**. Probably, a tricyclic system analogous to 1,4-epoxy derivative **VII** is generated by brosylation of the hydroboration–oxidation product [5]. Tosylation of diol **IX** obtained in such a way, gave compound **X** which was identical to that synthesized previously [5].

Thus we can presume that functionalization of the double bond in (+)-δ-cadinol (**I**), which involves formation of tricyclic ether intermediates, is completed by intramolecular cyclization through oxygen atom. However, the oxidation of (+)-δ-cadinol according to Wagner afforded only triol **XII** and dihydroxy ketone **XI** (product of more profound oxidation) at a ratio of 1:3 in an overall yield of 95% (Scheme 2). In the ^1H NMR spectrum of **XII**, the coupling constant between the 8a-H and 1-H protons is 8.0 Hz; therefore, both these protons are oriented axially and, correspondingly, one of the vicinal hydroxy group is equatorial, and the other is axial.

The orientations of the methyl and hydroxy groups on C^2 were confirmed by calculations of the ^{13}C NMR spectra using additivity schemes. The calculated chemical shift of C^2 (δ_C 72.60 ppm) almost coincides with the experimental value (δ_C 72.03 ppm) only when the hydroxy group on C^1 and the methyl group on C^2 both are equatorial. The chemical shift of the 2-Me carbon, δ_C 25.83 ppm suggests equatorial orientation of the 2-methyl group. In the ^{13}C NMR spectra of compounds **IX** and **X** where the methyl group is axial, the corresponding chemical shifts range from 21 to 22 ppm [17]. Thus, *syn* addition of $KMnO_4$, as well as of OsO_4 [6], occurs from the less sterically hindered β-side, leading to triol **XII** with equatorial and axial vicinal hydroxy groups.

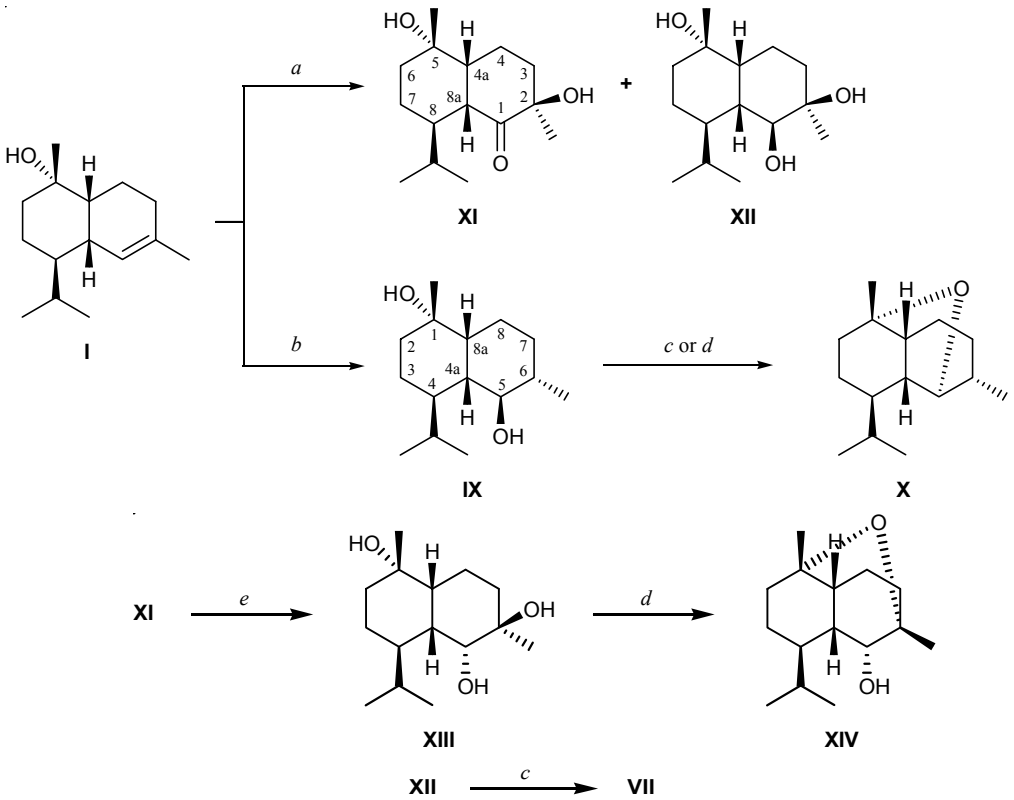
We failed to effect cyclization of triol **XII** by heating in boiling benzene in the presence of *p*-toluenesulfonic acid; on the other hand, treatment of **XII** with *p*-toluenesulfonyl chloride in pyridine gave a product which was identical to 1,4-epoxy alcohol **VII**. Most probably, intramolecular substitution in triol **XII** is hampered, apart from steric factors, by electronic effect of the neighboring hydroxy group [18]. This effect is likely to operate as well at the stage of formation of cyclic ether intermediate in the oxidation with $KMnO_4$. In this case, replacement of the hydroxy group by a good nucleofuge favors anchimeric assistance to substitution by the tertiary hydroxy group. Presumably, an analogous effect of the neighboring group (methyl) is observed in the formation of 1,4-epoxy derivative **X** [19].

Reduction of the carbonyl group in dihydroxy ketone **XI** with $NaBH_4$ gave triol **XIII** as a single diastereoisomer which is epimeric to **XII** with respect to C^1. The stereoselectivity of this process is likely to originate from both steric factor and chelate control by the nearby 5α-hydroxy group; as a result, β-attack by hydride ion on the carbonyl group becomes the only possible.

The structure of triols **XII** and **XIII** was proved by spectral methods. In the ^1H NMR spectrum of triol **XII**, the 1-H signal appears as a doublet at δ 3.85 ppm ($J_{1,8a}$ = 8.0 Hz), indicating a large torsion angle, whereas the corresponding signal from the lα-epimer is a doublet of doublets at δ 3.20 ppm (J = 3.1 and 1.4 Hz), i.e., the torsion angle considerably decreases due to α-orientation of the hydroxy group. Comparison of the chemical shifts of 1-H in triols **XII** (δ 3.85 ppm) and **XIII** (δ 3.20 ppm) shows that this proton in the former is arranged *trans* with respect to the hydroxy group on C^2, while in the latter it is oriented *cis*.

The *trans*-diaxial orientation of the hydroxy groups on C^5 and C^2 in **XIII** is the most favorable for "axial attack" [17], so that 1,5-epoxy alcohol **XIV** is slowly

Scheme 2.



Reagents and conditions: *a*: $KMnO_4$, OH^-, *t*-BuOH; *b*: (1) $MaBH_4/BF_3 \cdot Et_2O$, THF; (2) H_2O_2, OH^-; *c*: *p*-TsCl, pyridine; *d*: H^+, benzene, reflux; *e*: $NaBH_4$, EtOH.

formed even on storage of compound **XIII**. Heating of triol **XIII** in benzene in the presence of *p*-toluenesulfonic acid gives 64% of 1,5-epoxy alcohol **XIV**.

Comparison of the ^1H NMR parameters of 1,5-epoxy alcohol **XIV** with those of compounds **II** and **III** suggests a considerable effect of the hydroxy group attached to C^{11} on the molecular conformation. The coupling constant $J_{6,7}$ increases to 13.0 Hz, indicating that the 6-H and 7-H protons are oriented axially and that the isopropyl group is equatorial. The coupling constant $J_{7,11}$ is small, which counts in favor of the *gauche* arrangement of the respective protons and equatorial orientation of the α-hydroxy group on C^{11}. Just the latter is responsible for nonequivalence of the methyl carbon atoms in the isopropyl group, δ_C 21.57 and 14.99 ppm.

We can conclude that intramolecular cyclization of (+)-δ-cadinol with formation of 1,4- and 1,5-epoxy bridges becomes possible when functionalization of the double bond and the allylic C^3 atom gives rise to β-oriented intermediates.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer at 300 and 75.47 MHz, respectively, using chloroform-*d* as solvent. The proton and carbon signals of compounds **II**, **IV**–**VII**, **VIIIa**, **IX**, **X**, **XIII**, and **XIV** were assigned on the basis of the ^{13}C–^1H and ^1H–^1H correlation spectra. The optical rotations were measured on a Perkin–Elmer-141 spectropolarimeter. The physical constants and analytical data of the synthesized compounds are given in table. (+)-δ-Cadinol had mp 137.8°C, $[\alpha]_D^{20}$ = +100.3° (*c* = 1.0, $CHCl_3$).

(1*S*,3*S*,6*R*,7*R*,8*R*,11*S*)-6-Isopropyl-1,3-dimethyl-2-oxatricyclo[5.3.1.$0^{3,8}$]undecan-11-ol (II). R_f = 0.4 (petroleum ether–ethyl acetate, 4:1). To a solution of 0.2 g (0.9 mmol) of (+)-δ-cadinol (**I**) in 4 ml of *t*-BuOH containing a catalytic amount of SeO_2, we added dropwise at 40°C 0.11 ml (1.08 mmol) of 30% hydrogen peroxide, and the mixture was kept at a temperature not exceeding 50°C. When the initial compound disappeared (TLC), the mixture was diluted

Melting points, specific optical rotations, and elemental analyses of compounds **II**–**XIV**

Comp. no.	mp, °C	Found, %		Formula	Calculated, %		$[\alpha]_D^{20}$, deg (c = 1.0, $CHCl_3$)
		C	H		C	H	
II		75.23	10.52	$C_{15}H_{26}O_2$	75.58	10.99	+54.5
III	115–116[a]	75.49	11.10	$C_{15}H_{26}O_2$	75.58	10.99	–42.2
IV	–	81.64	10.96	$C_{15}H_{24}O$	81.76	10.96	–58.0
V[b]	100[c]	60.12	8.71	$C_{15}H_{25}BrO$	59.80	8.36	–31.12
VI[d]	–	57.71	7.17	$C_{15}H_{25}IO$	57.73	7.24	–25.7
VII	–	75.64	10.90	$C_{15}H_{26}O_2$	75.58	10.99	–21.5
VIIIa/VIIIb[e]	–	88.49	11.65	$C_{15}H_{24}$	88.16	11.84	+52.5
IX	132–133	75.17	11.72	$C_{15}H_{28}O_2$	75.00	11.67	+5.5
X		80.91	11.64	$C_{15}H_{26}O$	81.08	11.71	–44.0
XI	77–79[a]	71.04	10.51	$C_{15}H_{26}O_3$	70.83	10.30	+1.5
XII	103	70.13	11.19	$C_{15}H_{28}O_3$	70.27	11.01	+23.8
XIII		70.25	10.97	$C_{15}H_{28}O_3$	70.27	11.01	–7.07
XIV		76.05	10.75	$C_{15}H_{25}O_2$	75.95	10.55	

[a] From diethyl ether.
[b] Found Br, %: 26.23. Calculated Br, %: 26.52.
[c] From pentane–diethyl ether.
[d] Found I, %: 36.42. Calculated I, %: 36.44.
[e] A mixture of compounds **VIIIa** and **VIIIb** at a ratio of 12 : 13.

with a saturated solution of NH_4Cl (5 ml), the organic phase was separated, the aqueous phase was extracted with ethyl acetate (3×5 ml), the extracts were combined with the organic phase and dried over $MgSO_4$, and the solvent was distilled off. The residue was purified by chromatography. Yield 0.15 g (71%). ^{1}H NMR spectrum, δ, ppm: 0.93 d (3H, CH_3, J = 6.7 Hz), 0.94 d (3H, CH_3, J = 6.7 Hz), 1.13 m (6-H), 1.17 s (3H, 1-CH_3), 1.20 s (3H, 3-CH_3), 1.22–1.39 m (3H, C^4H_2, 9-H_{eq}), 1.40–1.56 m (3H, 8-H, 5-H_{eq}, 10-H_{eq}), 1.68 d.sept (1H, Me_2**C**H, J = 10.0, 6.7 Hz), 1.72–1.92 m (3H, 7-H, 5-H_{ax}, 10-H_{ax}), 1.97 m (1H, 9-H_{ax}), 3.42 br.s (1H, 11-H). ^{13}C NMR spectrum, δ_C, ppm: 20.29 (C^5), 21.22 (C^9), 21.26 (CH_3), 22.20 (CH_3), 24.49 (1-CH_3), 25.54 (C^{10}), 25.86 (**C**Me_2), 27.86 (3-CH_3), 32.13 (C^8), 34.36 (C^4), 45.41 (C^6), 46.24 (C^7), 72.41 (C^1), 72.91 (C^3), 77.79 (C^{11}).

(1*S*,3*S*,6*R*,7*R*,8*R*,11*S*)-6-Isopropyl-1,3-dimethyl-2-oxatricyclo[5.3.1.0^{3,8}]undecan-11-ol (II) and (1a*S*,3a*R*,4*S*,7*R*,7a*R*,7b*R*)-1-isopropyl-1a,4-dimethylperhydronaphtho[1,2-*b*]oxiran-4-ol (III). To a solution of 0.1 g (0.5 mmol) of (+)-δ-cadinol (**I**) in 5 ml of $CHCl_3$ we added 0.13 g (0.8 mmol) of *m*-chloroperoxybenzoic acid. The mixture was stirred until the initial compound disappeared (TLC). The mixture was treated with a saturated solution of $NaHCO_3$ to pH 7, washed with water (3×5 ml), and extracted with ethyl acetate (3×5 ml). The extracts were combined and dried over $MgSO_4$, the solvent was distilled off, and the residue was subjected to chromatography to isolate 0.04 g (58%) of compound **II** and 0.02 g (40%) of epoxy derivative **III**, R_f = 0.35 (petroleum ether–ethyl acetate, 4:1). ^{1}H NMR spectrum, δ, ppm: 0.88 d (3H, CH_3, J = 7.0 Hz), 0.97 d (3H, CH_3, J = 7.0 Hz), 1.0–1.25 m (2H, 7-H, 6-H), 1.27 s (3H, 1a-CH_3), 1.33 s (3H, 4-CH_3), 1.31–1.50 m (3H, 6-H, C^5H_2), 1.50–1.57 m (1H, 2-H), 1.57–1.7 m (3H, 2-H, 3-H, 7-H), 2.02–2.10 m (2H, 3-H, 7a-H), 2.11 d.sept (1H, Me_2C**H**, J = 3.0, 7.0 Hz), 3.05 d (1H, 7b-H, J = 5.4 Hz). ^{13}C NMR spectrum, δ_C, ppm: 15.93 (CH_3), 16.46 (C^6), 20.76 (C^3), 21.75 (CH_3), 23.29 (1a-CH_3), 27.35 (**C**Me_2), 27.78 (4-CH_3), 31.63 (C^2), 35.07 (C^5), 35.12 (C^{7a}), 38.44 (C^{3a}), 45.60 (C^7), 59.52 (C^{1a}), 62.61 (C^{7b}), 72.15 (C^4).

(1*S*,4*S*,5*R*,8*S*,9*R*)-6-Isopropyl-2,8-dimethyl-11-oxatricyclo[6.2.1.0^{4,9}]undec-2-ene (IV) and (1*S*,3*S*,6*R*,7*R*,8*R*,11*S*)-11-bromo-6-isopropyl-1,3-dimethyl-2-oxatricyclo[5.3.1.0^{3,8}]undecane (V). *a.* A solution of 0.1 g (0.5 mmol) of (+)-δ-cadinol (**I**) in 5 ml of CCl_4 containing a catalytic amount of benzoyl peroxide was heated to the boiling point, and 0.08 g (0.45 mmol) of freshly recrystallized *N*-bromosuccinimide was added. When the reaction was complete (TLC), the mixture was filtered, the solvent was distilled off from the filtrate, and the residue was subjected to chromatography on silica gel to isolate

0.01 g (10%) of 1,4-epoxy derivative **IV** [16] and 0.1 g (76%) of 1,5-epoxy bromide **V**, R_f = 0.4 (petroleum ether–ethyl acetate, 3:1). ^{1}H NMR spectrum, δ, ppm: 0.88 d (3H, CH_3, J = 6.7 Hz), 0.92 d (3H, CH_3, J = 6.7 Hz), 1.10 s (3H, 3-CH_3), 1.12 m (1H, 6-H), 1.20 s (3H, 1-CH_3), 1.28–1.35 m (2H, C^4H_2), 1.40 m (1H, 8-H), 1.45–1.55 m (2H, 5-H_{eq}, 9-H_{eq}), 1.49–1.65 m (2H, Me_2C**H**, 10-H_{eq}), 1.78 t.t (1H, 5-H_{ax}, J = 14.2, 5.2 Hz), 1.96 d.d.d.d (1H, 9-H_{ax}, J = 13.2, 11.1, 4.7, 2.1 Hz), 2.10 d.d.d (1H, 10-H_{ax}, J = 11.6, 11.1, 2.0 Hz), 2.41 d.t (1H, 7-H, $J_{7,8}$ = 4.6, 2.3 Hz), 3.76 d.d (1H, 11-H, J = 2.5, 2.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 19.30 (C^5), 20.79 (C^9), 21.12 (CH_3), 22.17 (CH_3), 25.84 (**C**CH_3), 25.89 (1-CH_3), 26.75 (C^{10}), 27.27 (3-CH_3), 31.29 (C^4), 32.97 (C^8), 44.27 (C^6), 48.24 (C^7), 59.17 (C^{11}), 73.10 (C^3), 73.55 (C^1).

(1*S*,3*S*,6*R*,7*R*,8*R*,11*S*)-11-Bromo-6-isopropyl-1,3-dimethyl-2-oxatricyclo[5.3.1.0^{3,8}]undecane (V). *b*. To a solution of 0.1 g (0.5 mmol) of (+)-δ-cadinol (**I**) in 5 ml CCl_4 we added 0.16 g (0.9 mmol) of "red" NBS, and the mixture was heated under reflux until the reaction was complete (TLC). The mixture was filtered, the solvent was distilled off from the filtrate, and the residue was purified by chromatography on silica gel. Yield 0.13 g (96%).

c. To a solution of 0.2 g (1 mmol) of (+)-δ-cadinol (**I**) in 10 ml of chloroform, containing 0.08 g (1 mmol) of pyridine, we added at –10°C 0.16 g (1 mmol) of bromine, and the mixture was stirred until the reaction was complete (TLC). The mixture was treated with 3 ml of a 1% solution of sodium hydroxide and extracted with ethyl acetate (3×10 ml). The combined extracts were dried over $MgSO_4$ and evaporated, and the residue was purified by chromatography on silica gel. Yield 0.3 g (73%).

(1*R*,3*S*,6*R*,7*R*,8*R*,11*S*)-11-Iodo-6-isopropyl-1,3-dimethyl-2-oxatricyclo[5.3.1.0^{3,8}]undecane (VI). To a solution of 0.2 g (1 mmol) of (+)-δ-cadinol (**I**) in 3 ml of THF we added under stirring 0.3 ml of acetic acid and 0.2 g (0.9 mmol) of iodine. When the reaction was complete (TLC), the mixture was washed with 10 ml of a saturated solution of $Na_2S_2O_3$ and extracted with ethyl acetate (3×10 ml). The extract was dried over $MgSO_4$, the solvent was distilled off, and the residue was purified by chromatography. Yield 0.16 g (69%), R_f = 0.3 (petroleum ether–ethyl acetate, 3:1). ^{1}H NMR spectrum, δ, ppm: 0.82 d (3H, CH_3, J = 6.6 Hz), 0.90 d (3H, CH_3, J = 6.6 Hz), 1.10 s (3H, 3-CH_3), 1.05–1.15 m (1H, 6-H), 1.24 s (3H, 1-CH_3), 1.20–1.37 m (3H, 8-H, C^4H_2), 1.45 m (1H, 5-H_{eq}), 1.49–1.60 m (2H, 9-H_{eq}, Me_2C**H**), 1.69 d.d.d (1H, 10-H_{eq}, J = 11.0, 7.7, 2.0 Hz), 1.84 t.t (1H, 5-H_{ax}, J = 14.1, 5.1 Hz), 2.0 d.d.d.d (1H, 9-H_{ax}, J = 13.1, 11.0, 4.6, 2.0 Hz), 2.21 d.t (1H, 10-H_{ax}, J = 11.0, 11.0, 2.0 Hz), 2.61 br.s (1H, 7-H), 3.9 t (1H, 11-H, J = 2.7 Hz). ^{13}C NMR spectrum, δ_C, ppm: 18.84 (C^5), 20.71 (C^9), 21.09 (CH_3), 22.16 (CH_3), 25.74 (Me_2**C**), 27.0 (3-CH_3), 27.26 (1-CH_3), 28.35 (C^{10}), 32.32 (C^8), 34.42 (C^4), 39.55 (C^{11}), 44.59 (C^6), 50.33 (C^7), 73.02 (C^7), 73.79 (C^3).

(1*S*,3*R*,4*R*,7*R*,8*R*,9*R*)-9-Isopropyl-1,4-dimethyl-2-oxatricyclo[5.4.0.0^{3,8}]undecan-4-ol (VII), (4*R*,4a*S*,8a*R*)-3,4,4a,7,8,8a-hexahydro-4-isopropyl-1,6-dimethylnaphthalene (VIIIa), and (4*R*,4a*R*,8a*R*)-1,2,3,4,4a,7,8,8a-octahydro-4-isopropyl-6-methyl-1-methylenenaphthalene (VIIIb). To a solution of 0.1 g (0.5 mmol) of (+)-δ-cadinol (**I**) in 5 ml of THF, containing 0.3 ml of a 10% aqueous solution of KOH, we added at room temperature 0.10 g (0.5 mmol) of iodine. The mixture was stirred at 20°C until the reaction was complete (TLC), washed with 10 ml of a saturated solution of $Na_2S_2O_3$, and extracted with ethyl acetate (3×10 ml), the combined extracts were dried over $MgSO_4$ and evaporated, and the residue was subjected to chromatography on silica gel to isolate 0.04 g (67%) of epoxy alcohol **VII** and 0.01 g (25%) of a mixture of (+)-α-murolene (**VIIIa**) and (+)-γ-murolene (**VIIIb**).

Compound **VII**. R_f = 0.32 (petroleum ether–ethyl acetate, 3:1). ^{1}H NMR spectrum, δ, ppm: 0.93 d (6H, $2CH_3$, J = 6.4 Hz), 1.18 m (1H, 9-H), 1.24 s (3H, 1-CH_3), 1.25 s (3H, 4-CH_3), 1.34 d.d (1H, 5-H_{eq}, J = 13.7, 6.3 Hz), 1.39–1.45 m (2H, $C^{11}H_2$), 1.50 m (1H, 10-H, ^2J = 14.7 Hz), 1.53–1.62 m [2H, C**H**$(CH_3)_2$, 6-H], 1.71–1.82 m (3H, 10-H, 6-H, 7-H), 1.84 t.d (1H, 5-H_{ax}, J = 13.7, 6.8 Hz), 2.6 d (1H, 8-H, $J_{7,8}$ = 3.4 Hz), 3.6 br.s (1H, 3-H). ^{13}C NMR spectrum, δ_C, ppm: 20.92 (CH_3), 21.54 (CH_3), 21.93 (4-CH_3), 22.40 (C^{10}), 24.40 (C^6), 28.20 (**C**Me_2), 28.86 (1-CH_3), 33.11 (C^5), 36.27 (C^{11}), 41.02 (C^7), 43.13 (C^8), 44.15 (C^9), 73.24 (C^4), 82.87 (C^7), 87.66 (C^3).

Compound **VIIIa**. R_f = 0.81 (petroleum ether–ethyl acetate, 3:1). ^{1}H NMR spectrum, δ, ppm: 0.72 d (3H, CH_3, J = 6.8 Hz), 0.87 d (3H, CH_3, J = 6.8 Hz), 1.45 d.d.d.d (1H, 6-H, J = 3.0, 4.5, 10.0, 14.2 Hz), 1.70 s (3H, CH_3), 1.72 s (3H, CH_3), 1.79–1.89 m (4H, C^7H_2, C^1H_2), 1.95–2.05 m (5H, C^2H_2, 10-H, Me_2C**H**, 5-H), 5.42 m (1H, 8-H), 5.48 d.q (1H, 4-H, J = 2.6, 1.3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 15.77 (CH_3), 21.34 (CH_3), 21.66 (CH_3), 23.91 (CH_3), 24.46 (C^1),

24.63 (C^7), 26.57 (Me_2**C**), 30.47 (C^2), 36.65 (C^5), 39.08 (C^{10}), 40.98 (C^6), 121.45 (C^8), 124.14 (C^4), 134.39 (C^3), 136.39 (C^9).

Compound **VIIIb**. R_f = 0.8 (petroleum ether–ethyl acetate, 3:1). ^{13}C NMR spectrum, δ_C, ppm: 14.11 (CH_3), 21.1 (CH_3), 21.9 (CH_3), 22.67 (C^7), 28.10 (Me_2**C**), 29.34 (C^7), 31.92 (C^2), 32.2 (C^8), 36.5 (C^5), 39.42 (C^{10}), 41.80 (C^6), 112.38 (CH_2=), 124.14 (C^4), 125.2 (C^9), 135.30 (C^3).

(1*R*,3*S*,6*R*,7*R*,8*R*,11*S*)-11-Iodo-6-isopropyl-1,3-dimethyl-2-oxatricyclo[5.3.1.0^{3,8}]undecane (VI) and (1*S*,3*R*,4*R*,7*R*,8*R*,9*R*)-9-isopropyl-1,4-dimethyl-2-oxatricyclo[5.4.0.0^{3,8}]undecan-4-ol (VII). To a solution of 0.16 g (0.7 mmol) of (+)-δ-cadinol (**I**) in 5 ml of chloroform, containing 0.06 ml (0.8 mmol) of pyridine, we added 0.2 g (0.8 mmol) of iodine, and the mixture was stirred for 30 min at room temperature. When the reaction was complete (TLC), the mixture was evaporated, and the residue was subjected to chromatography on silica gel to isolate 0.1 g (48%) of 1,5-epoxy iodide **VI** and 0.7 g (43%) of 1,4-epoxy alcohol **VII**.

(1*S*,4*R*,4a*R*,5*R*,6*S*,8a*R*)-4-Isopropyl-1,6-dimethylperhydronaphthalene-1,5-diol (IX). To a solution of 0.4 g (1.8 mmol) of (+)-δ-cadinol (**I**) and 0.03 g (0.8 mmol) of $NaBH_4$ in 10 ml of THF we added 0.04 g (0.3 mmol) of boron trifluoride–ether complex, and the mixture was stirred for 2 h at room temperature. Water, 1.5 ml, and a 1:1 mixture of a 3 N solution of NaOH and a 30% solution of H_2O_2 (1.6 ml) were added, and the mixture was stirred for an additional 1.5 h and extracted with diethyl ether (3×10 ml). The extract was washed with 10 ml of a saturated solution of NaCl, dried over $MgSO_4$, and evaporated, and the residue was purified by chromatography on silica gel. Yield 0.3 g (75%). ^1H NMR spectrum, δ, ppm: 0.90 d (3H, CH_3, J = 6.5 Hz), 0.92 d (3H, CH_3, J = 6.5 Hz), 1.05 d (3H, 6-CH_3, J = 6.2 Hz), 1.25 s (3H, 1-CH_3), 1.25 m (1H, 2-H), 1.40 m (1H, 3-H), 1.45 m (3H, C^7H_2, 2-H), 1.50 m (1H, 6-H), 1.55 m (2H, 8a-H, 8-H), 1.60 m (2H, 4a-H, 4-H), 1.65 m [1H, C**H**$(CH_3)_2$], 1.70 m (1H, 3-H), 1.95 m (1H, 8-H), 3.63 t (1H, 5-H, $J_{5,6}$ = 8.7, $J_{5,4a}$ = 8.7 Hz). ^{13}C NMR spectrum, δ_C, ppm: 18.93 (6-CH_3), 19.25 (C^3), 20.31 (CH_3), 21.83 (CH_3), 24.93 (C^8), 26.06 (**C**Me_2), 30.04 (1-CH_3), 30.48 (C^7), 36.54 (C^2), 39.18 (C^{8a}), 40.03 (C^4, C^{4a}), 45.48 (C^6), 73.0 (C^7), 73.67 (C^5).

(1*R*,3*S*,4*S*,7*R*,8*R*,9*R*)-9-Isopropyl-1,4-dimethyl-2-oxatricyclo[5.4.0.0^{3,8}]undecane (X). *a.* A solution of 0.15 g (0.6 mmol) of diol **IX** and 0.24 g (1.3 mmol) of *p*-toluenesulfonyl chloride in 3 ml of pyridine was stirred at room temperature until the initial compound disappeared (TLC). The mixture was diluted with 3 ml of water and extracted with ethyl acetate (3×5 ml), the extract was dried over $MgSO_4$ and evaporated, and the residue was subjected to chromatography on silica gel. Yield 0.13 g (96%). ^1H NMR spectrum, δ, ppm: 0.85 d (6H, 2CH_3, J = 6.5 Hz), 0.90 d (3H, 4-CH_3, J = 6.2 Hz), 1.20 m (1H, 9-H), 1.25 s (3H, 1-CH_3), 1.30 m (1H, 6-H), 1.40 m (2H, $C^{11}H_2$), 1.45 m (2H, C^5H_2), 1.50 m (1H, 10-H), 1.55 d [1H, C**H**$(CH_3)_2$, J = 6.5 Hz], 1.55 m (1H, 7-H), 1.67 m (1H, 8-H), 1.82 m (1H, 6-H), 1.85 m (2H, 4-H, 10-H), 3.7 br.s (1H, 3-H). ^{13}C NMR spectrum, δ_C, ppm: 19.71 (CH_3), 20.40 (1-CH_3), 20.80 (CH_3), 22.22 (C^{10}), 22.22 (4-CH_3), 27.14 (C^5), 27.56 (C^6), 27.90 (CMe_2), 36.49 (C^{11}), 37.34 (C^7), 41.32 (C^8), 44.73 (C^9), 50.41 (C^4), 82.56 (C^1), 85.76 (C^3).

b. A solution of 0.1 g (0.4 mmol) of diol **IX** in 10 ml of benzene, containing a catalytic amount of *p*-toluenesulfonic acid, was heated under reflux until the initial compound disappeared (TLC). The mixture was washed with water (3×5 ml), dried over $MgSO_4$, and evaporated, and the residue was purified by chromatography on silica gel. Yield 0.07 g.

(2*S*,4a*R*,5*S*,8*R*,8a*R*)-2,5-Dihydroxy-8-isopropyl-2,5-dimethylperhydronaphthalen-1-one (XI) and (1*S*,2*R*,4a*R*,5*S*,8*R*,8a*R*)-8-isopropyl-2,5-dimethylperhydronaphthalene-1,2,5-triol (XII). A solution of 0.2 g (1 mmol) of (+)-δ-cadinol (**I**) in 10 ml of *t*-BuOH was cooled to 0°C, and a solution of 0.28 g (1.49 mmol) of $KMnO_4$ in 30 ml of H_2O, cooled to 0°C, was added. The mixture was stirred for 15 min at 0°C, 16 ml of a 10% aqueous solution of $NaHCO_3$ was added, and the mixture was extracted with ethyl acetate (3×10 ml). The extract was dried over $MgSO_4$ and evaporated, and the residue was subjected to chromatography to isolate 0.12 g (36.5%) of dihydroxy ketone **XI** and 0.07 g (34.6%) of triol **XII**.

Compound **XI**. R_f = 0.35 (petroleum ether–ethyl acetate, 5:1). ^1H NMR spectrum, δ, ppm: 0.79 d (3H, CH_3, J = 6.2 Hz), 0.82 d (3H, CH_3, J = 6.2 Hz), 1.12 t.d (1H, 8-H, J = 3.9, $J_{8,8a}$ = 8.9 Hz), 1.18 s (3H, CH_3), 1.31 s (3H, CH_3), 1.35–1.60 m (4H, CH_2, C^7H_2), 1.65 m [1H, C**H**$(CH_3)_2$], 1.70–1.85 m (3H, C^3H_2, 4-H), 1.90 m (1H, 4-H), 2.15 d.t (1H, 4a-H, $J_{4a,4}$ = 11.9, $J_{4a,8a}$ = 3.9 Hz), 2.75 d.d (1H, 8a-H, $J_{8a,8}$ = 8.9, $J_{8a,4a}$ = 3.9 Hz). ^{13}C NMR spectrum, δ_C, ppm: 15.42 (CH_3), 19.60 (C^4), 21.03 (C^7), 21.18 (CH_3), 25.37 (2-CH_3), 27.56 (**C**Me_2), 28.03 (5-CH_3), 34.98 (C^6), 39.17 (C^{4a}),

40.48 (C^3), 49.62 (C^8), 52.84 (C^{8a}), 71.13 (C^5), 75.91 (C^2), 215.20 (C^1).

Compound **XII**. R_f = 0.18 (petroleum ether–ethyl acetate, 5:1). ^{1}H NMR spectrum, δ, ppm: 0.87 d (3H, CH_3, J = 6.6 Hz), 0.92 d (3H, CH_3, J = 6.6 Hz), 1.26 s (3H, 1-CH_3), 1.28 s (3H, 6-CH_3), 1.20–1.40 m (3H, 8-H, C^6H_2), 1.5–1.65 m [4H, C**H**$(CH_3)_2$, 4-H, 7-H, 3-H], 1.65–1.85 m (3H, 8a-H, 4a-H, 7-H), 1.87–2.0 m (2H, 4-H, 3-H), 3.85 d (1H, 1-H, J = 8.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 18.99 (C^7), 20.11 (C^4), 21.20 (CH_3), 21.82 (CH_3), 25.83 (2-CH_3), 27.32 (**C**Me_2), 29.67 (5-CH_3), 35.41 (C^3), 36.65 (C^6), 39.27 (C^{4a}), 40.37 (C^8), 41.33 (C^{8a}), 72.03 (C^2), 73.03 (C^5), 73.19 (C^7).

Cyclization of triol XII to 1,4-epoxy alcohol VII. The reaction was carried out according to the procedure described above for the synthesis of compound **X** (method *a*). Yield of **VII** 73%.

(1*R*,2*R*,4a*R*,5*S*,8*R*,8a*R*)-8-Isopropyl-1,2,5-dimethylperhydronaphthalene-1,2,5-triol (XIII). To a solution of 0.1 g (0.4 mmol) of dihydroxy ketone **XI** in 10 ml of ethanol we added under stirring a solution of 0.21 g (0.57 mmol) of $NaBH_4$ in 3 ml of EtOH. When the reaction was complete (TLC), 2 ml of acetone and 10 ml of a saturated solution of sodium chloride were added, the mixture was extracted with ethyl acetate (3×10 ml), the extracts were dried over $MgSO_4$ and evaporated, and the residue was purified by chromatography. Yield 0.06 g (64%), R_f = 0.16 (petroleum ether–ethyl acetate, 5:1). ^{1}H NMR spectrum, δ, ppm: 0.85 d (3H, CH_3, J = 6.6 Hz), 0.90 d (3H, CH_3, J = 6.6 Hz), 1.19 s (3H, 2-CH_3), 1.19 m (1H, 8-H), 1.20 s (3H, 5-CH_3), 1.29 m (1H, 3-H), 1.40 m (2H, C^6H_2), 1.49 m (1H, 4-H), 1.57 t.d (1H, 4a-H, $J_{4a,4}$ = 6.7, $J_{4a,8a}$ = 6.7, $J_{4a,4}$ = 1.7 Hz), 1.60 d.sept [1H, C**H**$(CH_3)_2$, J = 6.6, 2.5 Hz], 1.67 d.d.d.d (1H, 7-H$_{ax}$, J_{gem} = 13.0, J = 10.4, 6.4, 3.9 Hz), 1.88 m (1H, 7-H), 1.94 m (1H, 3-H), 2.05 d.d.d.d (1H, 4-H$_{ax}$, $J_{4a,4a}$ = 1.7, J_{gem} = 11.5, J = 11.5, 3.4 Hz), 2.35 d.d.d (1H, 8a-H, $J_{8a,4a}$ = 6.7, $J_{8a,8}$ = 2.0, $J_{8a,1}$ = 3.1 Hz), 3.2 d.d (1H, 1-H, $J_{1,8}$ = 1.4, $J_{1,8a}$ = 3.1 Hz). ^{13}C NMR spectrum, δ_C, ppm: 20.17 (C^7), 20.81 (CH_3), 21.17 (C^4), 22.22 (CH_3), 28.19 (2-CH_3), 28.86 (**C**Me_2), 29.15 (5-CH_3), 31.30 (C^3), 35.72 (C^{8a}), 37.49 (C^6), 37.95 (C^{4a}), 44.65 (C^8), 71.61 (C^2), 72.88 (C^5), 79.42 (C^7).

(1*S*,3*S*,6*R*,7*R*,8*R*,11*R*)-6-Isopropyl-1,3-dimethyl-2-oxatricyclo[5.3.1.0^{3,8}]undecan-11-ol (XIV). Compound **XIV** was synthesized from triol **XIII** following the procedure described above for epoxy derivative **X** (method *b*). Yield 64%. R_f = 0.36 (petroleum ether–ethyl acetate, 5:1). ^{1}H NMR spectrum, δ, ppm: 0.80 d (3H, CH_3, J = 6.9 Hz), 0.92 d (3H, CH_3, J = 6.9 Hz), 1.13 q.d (1H, 5-H$_{ax}$, J = 13.1, 4.5 Hz), 1.27 s (3H, CH_3), 1.28 s (3H, CH_3), 1.38 m (1H, 9-H), 1.48 m (1H, 6-H), 1.50 m (2H, C^4H_2), 1.57 m (1H, 5-H), 1.70 m (2H, $C^{10}H_2$), 1.76 m (1H, 9-H), 1.92 d.d.d (1H, 8-H, J = 12.7, 3.8, 3.4 Hz), 2.02 d.sept [1H, C**H**$(CH_3)_2$, J = 6.9, 3.5 Hz], 2.11 d.d.d (1H, 7-H, $J_{6,7}$ = 13.0, $J_{7,8}$ = 3.8, 2.0 Hz), 3.38 d (1H, 11-H, J = 2.0 Hz). ^{13}C NMR spectrum, δ, ppm: 14.99 (CH_3), 19.44 (C^9), 21.57 (CH_3), 21.94 (C^5), 23.97 (1-CH_3), 26.92 (3-CH_3), 27.82 (**C**Me_2), 34.84 (C^4), 36.22 (C^{10}), 37.34 (C^6), 38.31 (C^7), 43.11 (C^8), 72.19 (C^3), 78.38 (C^{11}), 78.47 (C^1).

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