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CHEMISTRY

A Novel Approach to Key Synthons in the Synthesis of Eleuthosides

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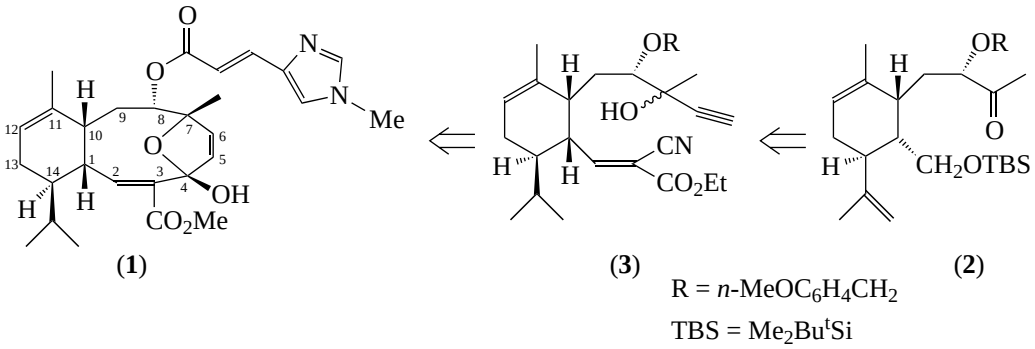
Diterpene metabolites of soft corals, forming the group of eleuthosides, are currently considered to be a novel class of promising anticancer agents [1–3]. In activity and mechanism of action, these derivatives of 4,7-oxaeunicellane are similar to pharmaceuticals of the Taxol group [4]. The importance of the synthesis of eleuthosides is indicated, in particular, by the fact that strong schools of synthetic chemists are involved in solving this problem [5, 6].

According to [5], the synthesis of one important eleuthoside, sarcodictyin (**A1**), implies the use of compound **2**, followed by its transformation into key synthon **3**. Ketodiol **2** is prepared from (+)-carvone in fifteen stages.



Scheme 1.

A search for precursors whose structure would serve to reduce the pathway toward the key synthons used in the synthesis of eleuthosides led us to sesquiterpenes of the muurolane series. These compounds have an appropriate stereochemistry and could be isolated from oleoresin of Siberian stone pine *Pinus sibirica* R. Mayr. [7, 8]. One of these compounds, (+)-δ-cadinol (**4**), attracted our attention, and we accomplished a number of its transformations.

The oxidation of (+)-δ-cadinol by SeO_2–Ac_2O at 70°C resulted in epimeric acetates **5a** and **5b** and oxide **6** in 42, 32, and 13% yields, respectively. Acetate **5a** and oxide **6** were further converted into compounds structurally related to synthons **2** and **3**. Hydrolysis of acetate **5a** and benzylation of resultant diol **7** led to monobenzyl ether **7a**, whose ozonolysis in a methanol solution produced mixed acetal **8** in 75% yield containing structural elements of synthon **2**.

Using the transformation of oxide **6** as an example, we demonstrated the possibility of important reactions in the route from compound **2** to synthon **3**, such as ethynylation of the keto group and condensation of the formyl group with ethyl cyanoacetate. We showed that the ozonolysis of oxide **6** in a methanol solution resulted in ketoacetal **9** in roughly 100% yield. The ethynylation of the latter (HC≡CMgBr, THF) gave a mixture of the diastereomeric acetylenic alcohols **10a** and **10b** in a 7 : 1 ratio (yield 61%). It might be supposed that the high diastereoselectivity of the reaction is due to the chelate control over the reaction of the organomagnesium compound accomplished by the oxygen-containing functional groups of the molecule of ketoacetal **9**. Condensation of isomer **10a** with $NCCH_2CO_2Et$ in the presence of β-alanine following the procedure in [5] allowed us to obtain cyanoester **11** containing all structural elements necessary for the synthesis of diterpenoids of the 4,7-oxaeunicellane series.

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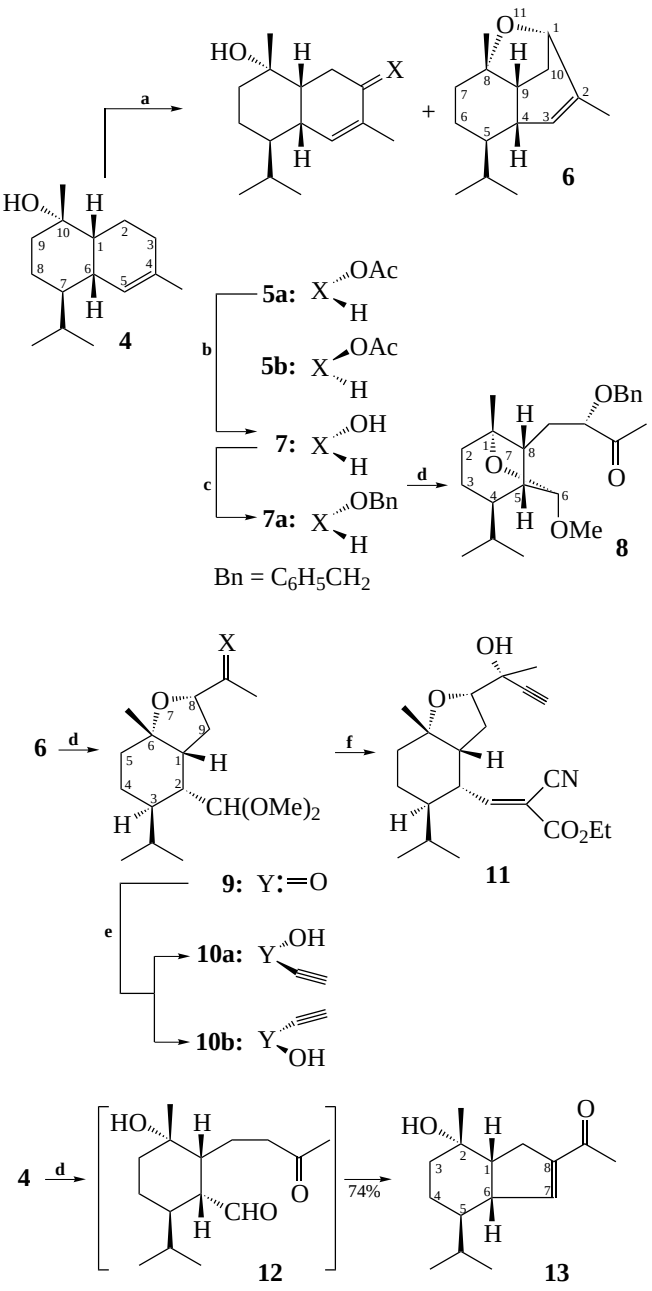
We obtained another promising synthon through the ozonolysis of (+)-δ-cadinol **4**. The reaction proceeds as intramolecular cyclization of intermediate ketoaldehyde **12** and leads to unsaturated hydroxyketone **13**. It is easy to see that the controllable cleavage of the double bond in the molecule of ketone **13** makes it possible to prepare compounds with the desired arrangement of oxygen-containing functional groups.



Reagents and conditions. a: SeO_2–Ac_2O, 70°C; **b**: MeONa–MeOH; **c**: BnCl, DMSO, 20°C; **d**: O_3, MeOH, –78°C, Me_2S; **e**: HC≡CMgBr, THF, 0°C; **f**: $NCCH_2CO_2Et$, β-alanine, EtOH.

Scheme 2.

Thus, the oxidative transformations of (+)-δ-cadinol, the sesquiterpene component of oleoresin of Siberian stone pine, are proposed as a novel approach to convenient preparation of synthons used in the synthesis of anticancer metabolites of the eleuthoside series.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on a Bruker AM 300 spectrometer operating at 300.13 MHz for ^1H and at 75.47 MHz for ^{13}C. Signal assignment was made on the basis of C–H correlation (CH corr.). Mass spectra were obtained on an MX-1320 spectrometer (EI, 70 eV); optical rotation angles were measured on a Perkin-Elmer 141 polarimeter. Initial (+)-δ-cadinol was isolated from a neutral fraction of oleoresin of Siberian stone pine, mp 137.8°C, $[\alpha]_D^{20}$ +100.3° (*c* 1.0, $CHCl_3$).

(1*R*,3*S*,6*S*,7*R*,10*S*)-3-Acetyloxy-7-isopropyl-4,10-dimethylbicyclo[4.4.0]dec-4-en-10-ol (5a), mp 134–136°C, $[\alpha]_D^{26}$ +138.1° (*c* 1.0, $CHCl_3$). ^1H NMR (δ, ppm, *J*, Hz): 0.81 (d, 3H, CH_3, *J* = 6.9), 0.88 (d, 3H, CH_3, *J* = 6.9), 1.10 (m, 1H, H^{ax}-8), 1.30 (m, 1H, H-7), 1.30 (s, 1H, CH_3), 1.50 (m, 3H, H^{eq}-8 and CH_2-9), 1.68 (s, 3H, CH_3), 1.72 (dd, 1H, H^{ax}-2, J_{2-3}^{ax} = 9.2, J_{gem} = 14.9), 1.83 (m, 1H, H-1), 1.94 (dqq, 1H, $Me_2C\underline{H}$, J_{Me_2CH-7} = 3.4, J_{Me_2CH-Me} = 6.9), 2.05–2.18 (m, 2H, H^{eq}-2, H-6), 2.10 (s, 3H, CH_3), 5.30 (dd, 1H, H-3, J_{3-2}^{eq} = 4.6, J_{3-2}^{ax} = 9.2), 5.82 (d, 1H, H-5, J_{5-6} = 5.6). ^{13}C NMR (δ, ppm): 15.25 (CH_3), 20.70 (CH_3), 21.29 (C-8), 21.41 (CH_3), 21.52 (CH_3), 25.33 (C-2), 27.82 (CH_3), 26.73 ($Me_2\underline{C}$), 34.93 (C-9), 36.63 (C-6), 40.09 (C-1), 42.54 (C-7), 70.34 (C-3), 71.68 (C-10), 131.17 (C-5), 131.66 (C-4), 170.76 (C=O).

For $C_{17}H_{28}O_3$ anal. calcd. (%): C, 72.82; H, 10.06.
Found (%): C, 72.68; H, 10.19.

(1*S*,4*R*,5*R*,8*S*,9*R*)-5-Isopropyl-2,8-dimethyl-11-oxatricyclo[6.2.1.0^{4,9}]undec-2-ene (6), oil, $[\alpha]_D^{26}$ –58.0° (*c* 1.0, $CHCl_3$). ^1H NMR (δ, ppm, *J*, Hz): 0.83 (d, 3H, CH_3, *J* = 6.5), 0.86 (d, 3H, CH_3, *J* = 6.5), 1.02 (m, 1H, H-5), 1.08 (s, 3H, CH_3), 1.28 (m, 1H, H^{ax}-6), 1.40 (m, 1H, H^{ax}-7), 1.53 (m, 1H, H^{eq}-6), 1.62 (m, 2H, H^{ax}-10, $Me_2C\underline{H}$), 1.65 (d, 3H, CH_3, J_{Me-3} = 1.7), 1.72 (m, 1H, H^{eq}-7), 1.90 (ddd, 1H, H-9, J_{9-10}^{eq} = 5.0, J_{9-4} = 5.4, and J_{9-10}^{ax} = 8.0), 2.25 (ddd, 1H, H^{eq}-10, J_{10-9}^{eq} = 5.0, J_{10-1}^{eq} = 5.4, and J_{gem} = 10.8), 2.50 (m, 1H, H-4), 3.94 (d, 1H, H-1, J_{1-10}^{eq} = 5.4), 4.88 (m, 1H, H-3). ^{13}C NMR (δ, ppm): 19.33 (C-6), 20.83 ($2CH_3$), 20.92 (CH_3), 25.42 ($Me_2\underline{C}$), 30.19 (CH_3), 30.51 (C-7), 35.42 (C-10), 38.50 (C-9), 38.90 (C-4), 44.98 (C-5), 76.58 (C-1), 81.60 (C-8), 127.26 (C-3), 140.19 (C-2). MS (EI) (*m*/*z*, I_{rel}, %): 220 (M^+, 25).

For $C_{15}H_{24}O$ anal. calcd. (%): C, 81.76; H, 10.96.
Found (%): C, 81.64; H, 10.86.

(1*R*,3*S*,6*S*,7*R*,10*S*)-7-Isopropyl-4,10-dimethylbicyclo[4.4.0]dec-4-ene-3,10-diol (7), mp 102–103°C, $[\alpha]_D^{26}$ +49.1° (*c* 1.0, $CHCl_3$). ^1H NMR (δ, ppm, *J*, Hz): 0.81 (d, 3H, CH_3, *J* = 7.0), 0.88 (d, 3H, CH_3, *J* = 7.0), 1.20 (m, 1H, H^{ax}-9), 1.25 (s, 3H, CH_3), 1.37 (m, 1H, H-7), 1.50 (m, 3H, CH_2-8, H^{eq}-9), 1.67 (dd, 1H, H^{eq}-2, J_{gem} = 9.5, J_{2-3}^{eq} = 5.0, J_{2-1}^{eq} not determined), 1.73 (m, 1H, H-1), 1.75 (s, 3H, CH_3), 1.88 (dqq, 1H, $Me_2C\underline{H}$, J_{Me_2CH-7} = 4.5, J_{Me_2CH-Me} = 7.0), 2.05 (m, 1H, H-6, J_{6-5} = 5.0), 2.24 (dd, 1H, H^{ax}-2, J_{gem} = 9.5, J_{2-3}^{ax} = 7.5), 2.30 (br s, 1H, OH), 2.56 (br s, 1H, OH), 4.03 (dd, 1H, H-3, J_{3-2}^{eq} = 5.0, J_{3-2}^{ax} = 7.5), 5.54 (qd, 1H, H-5, $J_{5\text{-Me}}$ = 1.5, J_{5-6} = 5.0). ^{13}C NMR (δ, ppm): 16.22 (CH_3), 19.62 (CH_3), 21.15 (C-8), 21.70 (CH_3), 26.47 ($Me_2\underline{C}$), 27.74 (CH_3), 29.80 (C-2), 35.13 (C-9), 37.18 (C-6), 43.32 (C-7), 44.40 (C-1), 70.72 (C-3), 72.07 (C-10), 128.37 (C-5), 137.29 (C-4).

For $C_{15}H_6O_2$ anal. calcd. (%): C, 75.58; H, 10.99.

Found (%): C, 75.78; H, 11.19.

(1*R*,3*S*,6*S*,7*R*,10*S*)-3-Benzyloxy-7-isopropyl-4,10-dimethylbicyclo[4.4.0]dec-4-en-10-ol (7a), mp 97–99°C, $[\alpha]_D^{22}$ +54.6° (*c* 1.0, $CHCl_3$). ^1H NMR (δ, ppm, *J*, Hz): 0.82 (d, 3H, CH_3, *J* = 6.9), 0.90 (d, 3H, CH_3, *J* = 6.9), 1.15 (ddd, 1H, H-8, *J* = 3.4, *J* = 4.0, and *J* = 11.2), 1.28 (s, 3H, CH_3), 1.48 (m, 1H, H-7, *J* = 3.0), 1.50 (m, 3H, CH_2-9, H-8), 1.68 (m, 1H, H-1), 1.78 (s, 3H, CH_3), 1.98 (dqq, 1H, $Me_2C\underline{H}$, *J* = 3.0, *J* = 6.9), 2.05 (m, 1H, H-6), 2.30 (m, 1H, H-2, *J* = 10.0), 2.46 (ddd, 1H, H-2, *J* = 1.0, *J* = 6.3, *J* = 10.0), 3.96 (dd, 1H, H-3, *J* = 6.3, *J* = 8.4), 4.51 (d, 1H, $OC\underline{H}_2Ph$, *J* = 11.5), 4.70 (dd, 1H, $OC\underline{H}_2Ph$, *J* = 11.5, *J* = 10.4), 5.67 (d, 1H, H-5, *J* = 5.4), 7.38 (m, 5H, Ph). ^{13}C NMR (δ, ppm): 15.24 (CH_3), 19.76 (CH_3), 21.32 (C-8), 21.46 (CH_3), 24.80 (C-2), 26.32 (CH_3), 27.68 ($\underline{C}Me_2$), 35.06 (C-9), 36.88 (C-6), 43.68 (C-7), 44.10 (C-1), 70.42 ($O\underline{C}H_2Ph$), 71.83 (C-10), 78.22 (C-3), 128.80 (C-5), 135.48 (C-4), 127.35, 127.66, 128.33, 138.69 (Ph).

For $C_{22}H_{32}O_2$ anal. calcd. (%): C, 80.44; H, 9.82.

Found (%): C, 80.79; H, 9.60.

[1*S*,4*R*,5*R*,6*S*,8*R*(2'*S*)]-8-(2'-Benzyloxy-3'-oxobutyl)-4-isopropyl-1-methyl-6-methoxy-7-oxabicyclo-[3.2.1]octane (8), oil, $[\alpha]_D^{20}$ –55.0° (*c*, 1.0, $CHCl_3$). ^1H NMR (δ, ppm, *J*, Hz): 0.80 (d, 3H, CH_3, *J* = 6.8), 0.87 (d, 3H, CH_3, *J* = 6.8), 1.18 (s, 3H, CH_3), 1.25 (m, 1H, H-4), 1.35–1.45 (m, 3H, CH_2-2 and H-8), 1.50–1.62 (m, 3H, $Me_2C\underline{H}$, CH_2-3), 1.75 (ddd, 1H, CH_2-1', *J* = 2.6, *J* = 9.6, and *J* = 11.0), 2.05 (ddd, 1H, CH_2-1', *J* = 3.8, *J* = 9.9, and *J* = 11), 2.12 (s, 3H, CH_3), 2.40 (d, 1H, H-5, *J* = 3.4), 3.30 (s, 3H, OCH_3), 3.92 (dd, 1H, H-2', *J* = 2.6, *J* = 9.9), 4.30 (d, 1H, $OC\underline{H}_2Ph$, *J* = 10.8), 4.53 (d, 1H, $OC\underline{H}_2Ph$, *J* = 10.8), 4.70 (s, 1H, H-6), 7.30 (m, 5H, Ph). ^{13}C NMR (δ, ppm): 20.65 (CH_3), 22.03 (CH_3), 22.18 (CH_3), 22.29 (C-3), 25.45 (CH_3), 27.61 ($\underline{C}Me_2$), 30.60 (C-2), 36.65 (C-1'), 40.28 (C-4), 43.35 (C-5), 48.03 (C-8), 54.71 (OMe), 72.02 ($O\underline{C}H_2Ph$), 83.29 (C-2'), 86.22 (C-1), 109.22 (C-6), 127.84, 127.95, 128.02, 128.20, 128.37, 137.57 (Ph), 204.32 (C=O).

For $C_{23}H_{34}O_4$ anal. calcd. (%): C, 73.76; H, 9.15.

Found (%): C, 73.53; H, 9.24.

(1*R*,2*R*,3*R*,6*S*,8*S*)-8-Acetyl-3-isopropyl-6-methyl-2-dimethoxymethyl-7-oxabicyclo[4.3.0]nonane (9), oil, $[\alpha]_D^{26}$ +19.4° (*c* 1.0, $CHCl_3$). ^1H NMR (δ, ppm, *J*, Hz): 0.72 (d, 3H, CH_3, *J* = 7.0), 0.83 (d, 3H, CH_3, *J* = 7.0), 1.08–1.20 (m, 3H, CH), 1.25 (s, 3H, CH_3), 1.38 (m, 1H, CH), 1.43–1.58 (m, 3H, CH), 1.78 (m, 2H, CH_2), 2.12 (s, 3H, CH_3), 2.20 (m, 1H, CH), 3.33 (s, 6H, OCH_3), 4.23 (d, 1H, $C\underline{H}(OMe)_2$, *J* = 3.5), 4.35 (m, 1H, H-8). ^{13}C NMR (δ, ppm): 15.14 (CH_3), 21.55 (CH_3), 21.81 (C-4), 24.55 (CH_3), 26.18 (CH_3), 26.23 ($\underline{C}Me_2$), 32.06 (C-9), 34.55 (C-5), 37.47 (C-1), 39.95 (C-2), 44.34 (C-3), 56.08 (OCH_3), 56.47 (OCH_3), 82.61 (C-8), 83.48 (C-6), 107.09 ($\underline{C}(OMe)_2$), 210.94 (C=O).

For $C_{17}H_{30}O_4$ anal. calcd. (%): C, 68.45; H, 10.07.

Found (%): C, 68.74; H, 9.81.

MS (EI) (*m*/*z* (I_{rel}, %): 298 $[M]^+$ (37).

[1*R*,2*R*,3*R*,6*S*,8*S*,(2'*R*)]-8-(2'-Hydroxybut-3'-yn-2'-yl)-3-isopropyl-6-methyl-2-dimethoxymethyl-7-oxabicyclo[4.3.0]nonane (10a). ^1H NMR (δ, ppm, *J*, Hz): 0.78 (d, 3H, CH_3, *J* = 6.7), 0.92 (d, 3H, CH_3, *J* = 6.7), 0.95 (m, 1H, H^{ax}-4), 1.28 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.50–1.62 (m, 4H, H-2, CH_2-5, H^{eq}-4), 1.80–1.93 (m, 4H, $Me_2C\underline{H}$, CH_2-9, H-1), 2.22 (dddd, 1H, H-3, J_{3-4}^{eq} = 6.4, $J_{3\text{-}Me_2CH}$ = 6.4, J_{3-4}^{ax} = 12.0, J_{3-2} = 12.0), 4.03 (dd, 1H, H-8, J_{8-9}^{a} = 5.4, J_{8-9}^{b} = 10.5), 4.30 (d, $C\underline{H}(OMe)_2$, $J_{(MeO)_2CH-2}$ = 3.6). ^{13}C NMR (δ, ppm): 15.75 (CH_3), 21.67 (CH_3), 21.84 (C-4), 25.0 (CH_3), 26.46 ($\underline{C}Me_2$), 29.35 (C-9), 35.89 (C-5), 37.90 (C-3), 39.98 (C-2), 44.46 (C-1), 56.05 (OCH_3), 56.25 (OCH_3), 67.69 (HC≡), 71.03 (C-6), 82.32 (COH), 84.55 (C-8), 86.93 (C≡), 107.53 ($\underline{C}(OMe)_2$).

[1*R*,2*S*,3*R*,6*S*,8*S*(2'*R*)]-8-(2'-Hydroxybut-3'-yn-2'-yl)-3-isopropyl-6-methyl-2-(2''-cyano-2''-ethoxycarbonylethenyl)-7-oxabicyclo[4.3.0]nonane (11), $[\alpha]_D^{20}$ +50.6° (*c* 1.0, $CHCl_3$). ^1H NMR (δ, ppm, *J*, Hz): 0.78 (d, 3H, CH_3, *J* = 6.8), 0.92 (d, 3H, CH_3, *J* = 6.8), 1.10 (m, 1H, H^{ax}-4), 1.30 (m, 1H, H^{eq}-4), 1.39 (t, 3H, $C\underline{H}_3CH_2O$, *J* = 7.2), 1.44 (s, 6H, CH_3), 1.55–1.76 (m, 4H, CH_2-5, $Me_2C\underline{H}$, H-3), 2.10 (m, 3H, CH_2-9, H-1), 2.50 (s, 1H, ≡CH), 2.60 (br s, 1H, OH), 3.0 (ddd, 1H, H-2, J_{2-1} = 4.5, $J_{2\text{-}CH=}$ = 11.0, J_{2-3} = 11.0), 4.02 (dd, 1H, H-8, J_{8-9}^{a} = 5.8, J_{8-9}^{b} = 10.3), 4.33 (q, 2H, OCH_2, J_{CH_2-Me} = 6.1), 7.51 (d, 1H, CH=, $J_{=CH-2}$ = 11.0). ^{13}C

NMR (δ, ppm): 14.18 (CH_3), 15.66 (CH_3), 21.40 (CH_3), 21.70 (C-4), 25.33 (CH_3), 25.62 (Me_2C), 27.50 (CH_3), 29.74 (C-9), 35.76 (C-5), 41.40 (C-3), 42.87 (C-2), 48.77 (C-1), 62.76 (OCH_2), 67.76 (≡CH), 71.82 (C-6), 82.04 (COH), 84.45 (C-8), 86.80 (–C≡), 109.78 (=C(CN)), 113.50 (CN), 161.1 (C=O), 165.9 (HC=).

For $C_{22}H_{31}NO_4$ anal. calcd. (%): C, 70.75; H, 8.37; N, 3.75.

Found (%): C, 70.33; H, 8.58; N, 3.29.

(1*R*,2*S*,5*R*,6*S*)-8-Acetyl-5-isopropyl-2-methylbicyclo[4.3.0]non-7-en-2-ol (13), mp 51.7°C, $[\alpha]_D^{20}$ + 36.4° (*c*, 1.0, $CHCl_3$). ^{1}H NMR (δ, ppm, *J*, Hz): 0.80 (d, 3H, CH_3, *J* = 6.9), 0.88 (d, 3H, CH_3, *J* = 6.9), 1.10 (m, 1H, H^{ax}-4), 1.25 (s, 3H, CH_3), 1.17–1.32 (m, 2H, H^{eq}-4, H^{ax}-3), 1.48–1.72 (m, 4H, H^{eq}-3, H-5, H^a-9, $Me_2C\underline{H}$), 2.25 (s, 3H, CH_3), 2.20–2.43 (m, 2H, H-1, H^b-9), 2.50 (dd, 1H, H-6, J_{6-1} = 6.5, J_{6-5} = 13.5), 6.89 (br s, 1H, H-7). ^{13}C NMR (δ, ppm): 14.0 (CH_3), 21.41 (CH_3), 21.81 (C-4), 26.19 (CH_3), 28.36 (CMe_2), 28.62 (CH_3), 30.04 (C-3), 35.33(C-9), 45.02 (C-5), 47.02 (C-1), 50.69 (C-6), 71.43 (C-2), 144.59 (C-8), 149.07 (C-7), 197.54 (C=O).

For $C_{15}H_{24}O_2$ anal. calcd. (%): C, 76.23; H, 10.24. Found (%): C, 76.58; H, 10.44.

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