Enantiospecific First Total Synthesis of *ent*-Allothapsenol

A. Srikrishna,* K. Mahesh

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560012, India
Fax +91(80)3600683; E-Mail: askiisc@gmail.com

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Dedicated to Professor A. J. Rao on the occasion of his 70th birthday

Abstract: The enantiospecific first total synthesis of the enantiomer of the irregular sesquiterpene from *Ligusticumgrayi* allothapsenol, starting from the readily available monoterpene (*R*)-carvone, is described, which confirmed the assumed absolute configuration of the natural product.

Key words: allothapsane, enantiospecific synthesis, irregular sesquiterpenes, carvone

Allothapsenol (**1**) is one of the 17 irregular sesquiterpenes recently isolated[1] by Cool and co-workers from the root oil of *Ligusticumgrayi*, which belongs to the Apiaceae family and grows in Cascade mountains of California, Nevada, Oregon, and Washington. The Apiaceae family is known to be a rich source of novel natural products, particularly, several sesqui- and diterpenoids containing irregular carbon frameworks. The roots of the plant *Ligusticumgrayi* were used by native Americans for medicinal purposes. The structure of allothapsenol (**1**, Figure 1) was assigned on the basis of spectroscopic data, in particular the 1D and 2D NMR, and the absolute configuration was tentatively assigned in analogy to that of thapsanes, such as **2**, isolated from *Thapsia villosa*.[2]

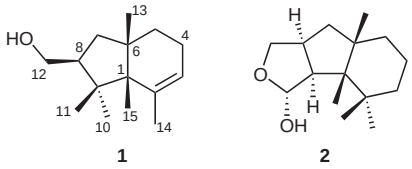

Figure 1

The sterically crowded framework containing three contiguous all-carbon quaternary centers made the allothapsanes attractive synthetic targets. So far there is no report in the literature on the synthesis, either in racemic or enantiopure form, of any allothapsane. In continuation of our interest in the chiral-pool-based enantiospecific synthesis of natural products starting from the readily available monoterpenes,[3] we have initiated the synthesis of the irregular *Ligusticumgrayi* sesquiterpenes, and herein we report the enantiospecific first total synthesis of the enantiomer of allothapsenol (**1**), which also confirmed the absolute configuration of the natural allothapsenol.

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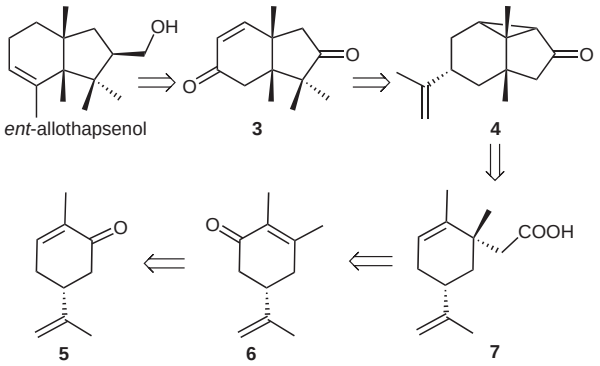
It was contemplated (Scheme 1) that the synthesis of allothapsenol (**1**) could be accomplished via the hydrindanedione (**3**).The tricyclic ketone **4** containing two vicinal all-carbon quaternary carbon atoms, a key intermediate used in the synthesis of valerane sesquiterpenes,[4] was considered as the ideal precursor for the synthesis of **3**, via degradation of the isopropenyl group followed by cyclopropane ring cleavage. The ketone **4** could readily be prepared from the monoterpene carvone (**5**) via 3-methylcarvone (**6**) and the γ,δ-unsaturated acid **7**.



Scheme 1

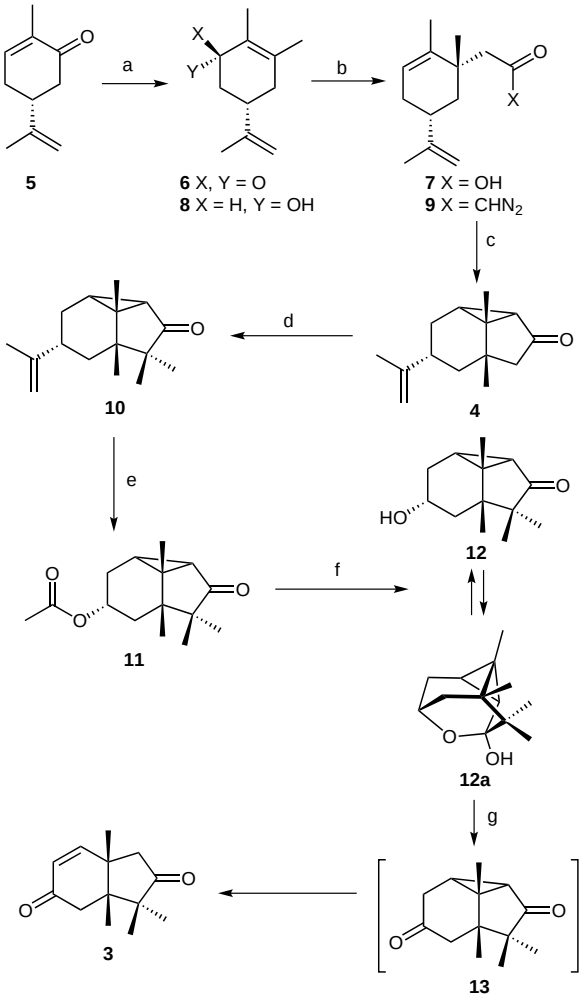
The synthetic sequence starting from (*R*)-carvone (**5**) is depicted in Scheme 2 and Scheme 3. To begin with (*R*)-carvone (**5**) has been transformed into (*S*)-3-methylcarvone (**6**) via an alkylative 1,3-enone transposition strategy,[5] which was then transformed into the γ,δ-unsaturated acid **7** via Johnson's orthoester Claisen rearrangement of the alcohol **8**. The requisite key intermediate of the sequence, the tricyclic ketone **4** was regio- and stereospecifically obtained from the acid **7** via the anhydrous copper sulfate catalysed intramolecular cyclopropanation of the diazo ketone **9**. The third quaternary carbon atom was created by a one-step dialkylation of the tricyclic ketone **4** with sodium hydride and methyl iodide in THF to furnish the alkylated ketone **10** in 78% yield, whose structure was established from its spectral data.[6] Next, degradation of the isopropenyl into a ketone group was addressed by employing a one-step ozonation–Criegee rearrangement.[7] Thus, ozonation of the tricyclic ketone **10** in dichloromethane–methanol (4:1) at low temperature, followed by treatment of the resultant methoxy hydroperoxide with acetic anhydride and triethylamine in refluxing benzene furnished the tricyclic keto acetate **11** in 43% yield.[8] Hydrolysis of the acetate with potassium carbonate in meth-

anol transformed the tricyclic keto acetate **11** into the hydroxy ketone **12** in 86% yield, which was found to exist (>85%) as the hemiacetal **12a**. Oxidation of the hydroxy group in **12** with pyridinium chlorochromate (PCC) and silica gel in dichloromethane at room temperature, followed by treatment with *p*-toluenesulfonic acid (PTSA) furnished the bicyclic enedione **3** in 86% yield, via cleavage of the cyclopropane ring (or uncaging) in the resultant tricyclic dione **13**, whose structure was established from its spectral data in particular the IR, ^{1}H NMR, and ^{13}C NMR.[6]

To avoid regiochemical problems in subsequent reactions (Scheme 3), the cyclopentanone in the enedione **3** was protected as its ethylene ketal by treating with 1.2 equivalents of ethanediol in the presence of a catalytic amount of 4-toluenesulfonic acid (PTSA) in refluxing benzene under Dean–Stark conditions to furnish the keto ketal **14** in 76% yield, in a regioselective manner. Kinetic alkylation of the enone **14** with lithium hexamethyldisilazide (LiHMDS) and methyl iodide furnished the norallothapsane derivative **15** in 68% yield, in a highly stereoselective manner as it is both kinetic and thermodynamically preferred. The stereochemistry of the secondary methyl group was assigned on the basis of the approach of the electrophile from the less hindered face of the bicyclic system as one face is blocked by the methyl group on the C-9 carbon atom of the bicyclic system.

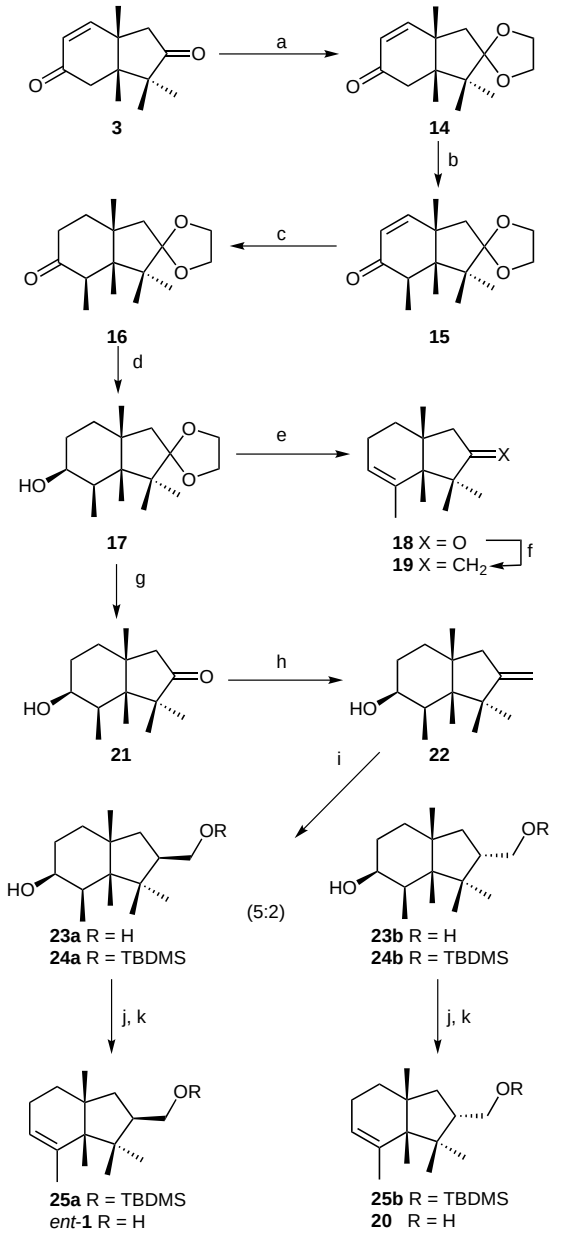
Hydrogenation of the enone **15** in ethyl acetate using 10% palladium over carbon as the catalyst at one atmospheric pressure of hydrogen furnished the saturated ketone **16** in near quantitative yield. Reduction of the ketone **16** with lithium aluminum hydride (LAH) in diethyl ether generated the secondary alcohol **17** in 82% yield, in a highly stereoselective manner. The stereochemistry of the alcohol in **17** was assigned based on the ^{1}H NMR spectrum (broad singlet due to C*H*OH established the axial orientation of the hydroxy group), and was confirmed by its facile dehydration as it is axial orientated and hence nicely suited for a facile E_2 elimination. It was contemplated to dehydrate the secondary alcohol in **17** via elimination of the corresponding mesylate. Treatment of the alcohol **17** with methanesulfonyl chloride and pyridine followed by work-up directly furnished the norallothapsenone **18** in 70% yield, in a highly regioselective manner via formation as well as elimination of the mesylate and hydrolysis of the ketal moiety. Since the conventional Wittig reaction of the ketone **18** was found to be inefficient, Yan's protocol[9] was employed. Thus, treatment of the norketone **18** with magnesium, dichloromethane, and titanium tetrachloride in THF furnished allothapsa-2,8(12)-diene (**19**) in 71% yield, whose structure was established from its ^{1}H NMR and ^{13}C NMR spectral data.[6]

Since regioselective hydroboration of the *exo*-methylene in the diene **19** under a variety of conditions was found to be inefficient, and also bulky dialkylboranes are expected to generate the *endo*-hydroxymethyl group leading to epi-allothapsenol (**20**), the sequence was modified, and it was considered that the primary hydroxy group may be introduced prior to the generation of the trisubstituted olefin. Thus, hydrolysis of the ketal group in **17** generated the hydroxy ketone **21**. Treatment of the hydroxy ketone **21** with magnesium, dichloromethane, and titanium tetrachloride furnished allothaps-8(12)-en-3-ol (**22**) in 58% yield. Reaction of allothapsenol **22** with an excess of in situ generated borane–THF followed by oxidation with alkaline hydrogen peroxide, as expected, furnished a 5:2 mixture of the *exo*-**23a** and *endo*-**23b** diols in 74% yield, which were separated by column chromatography on silica gel. The stereochemistry of the hydroxymethyl group in **23a** and **23b** were tentatively assigned and was confirmed by the conversion of the major isomer into *ent*-allothapsenol (**1**). In order to avoid a regiochemical problem, the primary alcohol in **23a** was protected as its TBDMS ether by treating with one equivalent of *tert*-butyldimethylsilyl chloride and imidazole in the presence of a catalytic amount of 4-*N*,*N*-dimethylpyridine (DMAP) to furnish



Scheme 2 *Reagents and conditions*: (a)[4] i. MeMgI, Et_2O; ii. PCC, silica gel, CH_2Cl_2; iii. LAH, Et_2O; (b)[4] i. $MeC(OEt)_3$, EtCOOH, temp; ii. NaOH, MeOH, H_2O; iii. $(COCl)_2$, C_6H_6; iv. CH_2N_2, Et_2O; (c)[4] anhyd $CuSO_4$, *c*-C_6H_{12}; (d) NaH, THF, MeI, r.t., 18 h, 78%; (e) i. O_3/O_2, CH_2Cl_2–MeOH (4:1), $NaHCO_3$; –70 °C; ii. Ac_2O, Et_3N, DMAP, C_6H_6, reflux, 6 h; 43%; (f) K_2CO_3, MeOH, r.t., 6 h, 86%; (g) i. PCC, silica gel, CH_2Cl_2, r.t., 8 h; PTSA, CH_2Cl_2, 1 h; 86%.

the ether **24a**. Dehydration of the secondary alcohol in **24a** was effected by reacting with methanesulfonyl chloride and pyridine to furnish allothapsenyl TBDMS ether **25a**, which on deprotection with tetrabutylammonium fluoride (TBAF) generated *ent*-allothapsenol (**1**). In a similar manner, the minor diol **24b** was transformed into epi-allothapsenol **20**. Structures of *ent*-**1** and **20** were assigned on the basis of the spectral data. Synthetic *ent*-allothapsenol (**1**) exhibited ^{1}H NMR and ^{13}C NMR spectral data[6] in C_6D_6 identical to that of natural allothapsenol (**1**), whereas the sign of the optical rotation was found to be opposite to that natural product, confirming the assigned absolute configuration of the natural product.



Scheme 3 *Reagents and conditions*: (a) $(CH_2OH)_2$, PTSA, C_6H_6, reflux (Dean–Stark), 6 h, 76%; (b) LiHMDS, THF, –70 °C; MeI, r.t., 8 h, 68%; (c) H_2 (1 atm), 10% Pd/C, EtOAc, 1 h, 98%; (d) LAH, Et_2O, 0 °C to r.t., 1 h, 82%; (e) MsCl, pyridine, CH_2Cl_2, 0 °C, 1 h, 70%; (f) Mg, CH_2Cl_2, $TiCl_4$, THF, r.t., 1 h, 71%; (g) 3 M HCl, THF, r.t., 1 h, 81%; (h) Mg, CH_2Cl_2, $TiCl_4$, THF, r.t., 1 h, 58%; (i) i. $NaBH_4$, BF_3?OEt_2, THF, 0 °C to r.t., 1 h; ii. 3 N NaOH, 30% H_2O_2, r.t., 1 h; 74%; (j) TBDMSCl, imidazole, DMAP, CH_2Cl_2, **24a** 82%; **24b** 87%; (k) i. MsCl, pyridine, CH_2Cl_2, 0 °C, 1 h; ii. TBAF, THF, r.t., 3 h, 75%.

In conclusion, we have developed the enantiospecific first total synthesis of the enantiomers of allothapsa-2,8(12)-diene (**19**) and allothapsenol (**1**), starting from the readily available monoterpene (*R*)-carvone. A combination of the Criegee rearrangement and the regiospecific cyclopropane ring cleavage were conveniently employed for the generation of the key intermediate of the sequence.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(6) Yields refer to isolated and chromatographically pure compounds. All the compounds exhibited spectral data [IR, HRMS, ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz)] consistent with their structures.
Selected Spectral Data for (1*R*,2*R*,4*R*,6*R*,9*S*)-4-Isopropenyl-1,6,7,7-tetramethyltricyclo[4.3.0.0^{2,9}]-nonan-8-one (10): $[\alpha]_D^{23}$ +116.9 (*c* 3.7, $CHCl_3$). IR (neat): ν_{max}= 1721 (C=O), 1381, 1017, 885 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.65 (1 H, s) and 4.58 (1 H, s) [C=C*H*$_2$], 2.10–1.95 (2 H, m), 1.87 (1 H, d, *J*= 10.1 Hz), 1.69 (3 H, s, olefinic CH_3), 1.75–1.25 (3 H, m), 1.28 (3 H, s), 1.17 (3 H, s), 1.06 (3 H, s) and 0.81 (3 H, s) [4 × *t*-CH_3], 0.68 (1 H, td, *J* = 14.0, 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 217.5 (C=O), 148.6 (*C*=CH$_2$), 108.9 (C=*C*H$_2$), 58.3 (C, C-7), 40.3 (C), 39.4 (CH), 38.5 (CH), 38.1 (CH_2), 30.1 (CH), 28.9 (C),

26.3 (CH_3), 24.7 (CH_2), 24.1 (CH_3), 21.3 (CH_3), 19.9 (CH_3), 18.6 (CH_3). HRMS: *m/z* calcd for $C_{16}H_{24}O$ [M + Na]: 255.1725; found: 255.1726.

(1*R*,6*S*)-1,6,9,9-Tetramethylbicyclo[4.3.0]non-4-ene-3,8-dione (3): $[\alpha]_D^{23}$ –35.5 (*c* 2.4, $CHCl_3$). IR (neat): ν_{max} = 1737 (C=O), 1683 (C=O), 1458, 1390, 1379, 1267, 1117, 1087, 785 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$ + CCl_4): δ = 6.66 (1 H, d, *J* = 10.1 Hz, H-5), 5.98 (1 H, d, *J* = 10.1 Hz, H-4), 2.63 (1 H, d, *J* = 19.2 Hz), 2.47 (1 H, d, *J* = 16.4 Hz), 2.46 (1 H, d, *J* = 19.2 Hz), 2.29 (1 H, d, *J* = 16.4 Hz), 1.34 (3 H, s), 1.10 (3 H, s), 1.06 (3 H, s), 1.01 (3 H, s) [4 × *t*-CH_3]. ^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ = 219.9 (C, C-8), 198.8 (C, C-3), 156.8 (CH, C-5), 126.5 (CH, C-4), 53.3 (C), 48.6 (CH_2), 47.8 (C), 45.0 (CH_2), 41.1 (C), 25.3 (CH_3), 22.8 (CH_3), 22.6 (CH_3), 19.5 (CH_3). HRMS: *m/z* calcd for $C_{13}H_{18}O_2$ [M + Na]: 229.1204; found: 229.1206.

(1*R*,2*R*,3*S*,6*R*)-3-Hydroxy-1,2,6,9,9-pentamethylbicyclo-[4.3.0]nonan-8-one (21): $[\alpha]_D^{22}$ –54.4 (*c* 4.0, $CHCl_3$). IR (neat): ν_{max} = 3510 (OH), 1719 (C=O), 1381, 1246, 1227, 963 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.84 (1 H, br s, C*H*OH), 2.66 (1 H, d, *J* = 17.6 Hz, H-7A), 1.95 (1 H, ddd, *J* = 14.2, 9.3, 7.5 Hz), 1.86 (1 H, d *J* = 17.6 Hz, H-7B), 1.74–1.68 (2 H, m), 1.60 (1 H, br s), 1.33–1.28 (1 H, m), 1.10–1.05 (15 H, m, 4 × *t*-CH_3 and *s*-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 224.4 (C, C=O), 72.0 (CH, C-3), 54.1 (C), 48.3 (C), 47.9 (CH_2), 40.1 (C), 38.1 (CH), 29.2 (CH_2), 28.4 (CH_2), 28.1 (CH_3), 26.1 (CH_3), 25.9 (CH_3), 15.9 (CH_3), 15.2 (CH_3). HRMS: *m/z* calcd for $C_{14}H_{24}O_2Na$ [M + Na]: 247.1674; found: 247.1672.

(1*R*,6*R*)-1,2,6,9,9-Pentamethyl-8-methylenebicyclo-[4.3.0]non-2-ene [Allothapsa-2,8(12)-diene (19)]: $[\alpha]_D^{22}$ –11.5 (*c* 1.1, $CHCl_3$). IR (neat): ν_{max} = 3069, 1648, 1377, 1075, 879 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.40 (1 H, br s, H-3), 4.84 (1 H, d, *J* = 2.2. Hz) and 4.79 (1 H, d, *J* = 2.3 Hz), 2.57 (1 H, dt, *J* = 15.6, 2.2 Hz) and 2.04 (1 H, d, *J* = 15.6 Hz) [H-7], 2.15–1.98 (1 H, m), 1.95–1.80 (1 H, m), 1.80–1.65 (1 H, m), 1.66 (3 H, s, vinylic CH_3), 1.15–1.00 (1 H, m), 1.12 (3 H, s), 1.11 (3 H, s), 0.99 (3 H, s) and 0.90 (3 H, s) [4 × *t*-CH_3]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.9 (C, C-8), 137.1 (C, C-2), 121.7 (CH, C-3), 104.6 (CH_2, C=*C*H_2), 51.4 (C, C-1), 47.2 (CH_2), 46.7 (C), 41.2 (C), 32.3 (CH_2), 31.5 (CH_3), 30.3 (CH_3), 22.1 (2 C, CH_3 and CH_2), 21.5 (CH_3), 19.2 (CH_3). MS: *m/z* (%) = 204 (100) [M^+], 189 (12), 166 (22), 135 (18), 121 (100).

(1*R*,6*R*,*8S*)-1,2,6,9,9-Pentamethylbicyclo[4.3.0]nona-2-ene-8-methanol [8-Epiallothapsenol (20)]: $[\alpha]_D^{22}$ –5.4 (*c* 0.4, $CHCl_3$). IR (neat): ν_{max} = 3338 (OH), 1545, 1377, 1083, 1067, 1018, 818, 669 cm^{-1}. ^1H NMR (400 MHz, C_6D_6): δ = 5.46 (1 H, br s, olefinic H), 3.51 (1 H, dd, *J* = 10.2, 5.8 Hz), 3.23 (1 H, dd, *J*= 10.2, 7.9 Hz), 2.13–1.76 (2 H, m), 1.74–1.68 (2 H, m), 1.67 (3 H, s, vinylic CH_3), 1.33–1.30 (2 H, m), 1.23 (1 H, dd, *J*= 13.3, 9.8 Hz), 1.06 (3 H, s), 0.93 (3 H, s) 0.90 (3 H, s), 0.86 (3 H, s) [4 × *t*-CH_3]. ^{13}C NMR (100 MHz, C_6D_6): δ = 138.7 (C, C-2), 124.2 (CH, C-3), 64.9 (CH_2, CH_2OH), 53.6 (C), 49.2 (CH), 46.2 (C), 44.9 (CH_2), 42.0 (C), 38.9 (CH_2), 28.4 (CH_3), 25.9 (CH_3), 23.2 (CH_2), 22.7 (CH_3), 21.8 (CH_3), 20.4 (CH_3).

(1*R*,6*R*,*8R*)-1,2,6,9,9-Pentamethylbicyclo[4.3.0]nona-2-ene-8-methanol [*ent*-Allothapsenol (*ent*-1)]: $[\alpha]_D^{22}$ –28.5 (*c* 0.3, $CHCl_3$). IR (neat): ν_{max} = 3342 (OH), 1376, 1074, 1017, 817 cm^{-1}. ^1H NMR (400 MHz, C_6D_6): δ = 5.42 (1 H, br s, olefinic H), 3.45 (1 H, dd, *J* = 10.4, 7.0 Hz), 3.26 (1 H, dd, *J* = 10.3, 6.7 Hz), 2.10–1.75 (4 H, m), 1.61 (3 H, s, vinylic CH_3), 1.40 (1 H, br s), 1.35 (1 H, dd, *J* = 12.5, 5.3 Hz), 1.25 (1 H, t, *J* = 12.7 Hz), 1.12 (3 H, s), 0.96 (3 H, s), 0.86 (3 H, s), 0.85 (3 H, s) [4 × *t*-CH_3]. ^{13}C NMR (100 MHz, C_6D_6): δ = 137.7 (C, C-2), 122.2 (CH, C-3), 64.6 (CH_2, CH_2OH), 52.5 (C), 50.7 (CH), 44.2 (C), 42.8 (CH_2), 42.5 (C), 33.6 (CH_3), 32.9 (CH_2), 23.5 (CH_3), 23.3 (CH_3), 22.7 (CH_2), 21.7 (CH_3), 20.1 (CH_3).

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(8) In addition to the acetate **11**, ca. 10% of the ene-dione **3** was also obtained.

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