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Synthesis of Isovalerenenol, a Sesquiterpene Alcohol Isolated from a Soft Coral and the Stability of Related Hydrindanone Derivatives

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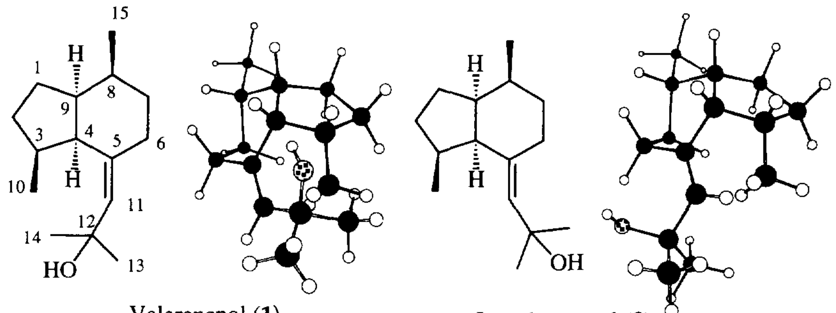
Abstract: Isovalerenenol (**2**) was synthesized using intramolecular aldol and hydrogenation reactions of the corresponding hydrindenone derivative. This hydrogenation afforded exclusively one desired product, while the other isomer gave several products, whose structures were determined by spectroscopic methods as well as base treatments. The introduction of α,β-unsaturated aldehyde was accomplished by the Grignard reaction using vinyl magnesium bromide and oxidative allyl alcohol rearrangement. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

Valerenenol (**1**) and isovalerenenol (**2**) have an *ent*-valerenane type skeleton and were isolated from a soft coral by Kitagawa and his coworkers.[1] Their structures were established by spectroscopic as well as chemical degradation to the *cis*-hydrindanone, whose hydrazone derivative was determined by X-ray crystallography.[1] The molecule is sterically crowded due to two secondary methyl groups which are oriented inside the *cis*-hydrindanone molecule (Fig. 1). Thus the most crucial step is to construct the *cis*-hydrindanone skeleton with two methyl groups oriented toward the β face. Furthermore, as revealed by Kitagawa *et al.*, *cis*-hydrindanone **6c** easily isomerized into the *trans*-derivative **6t** by base treatment.[1] It is very important not to use the basic conditions after construction of the *cis*-hydrindanone system. To the best of our knowledge, there has been no report concerning the total synthesis of these natural products so far. This is presumably due to the above mentioned problems. Honda *et al.* reported a synthesis of *epi*-isovalerenenol by application



Valerenenol (**1**) Isovalerenenol (**2**)

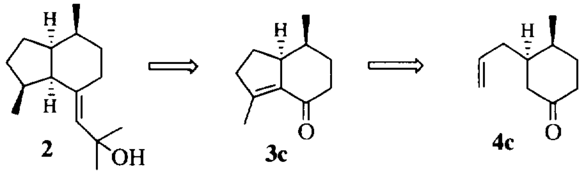
Figure 1. Structures of valerenenol (**1**) and isovalerenenol (**2**).

of their diazoketone methodology,[2] but the final isomerization of the juncture proton failed. In this system, the *trans* fused ketone is much stabler than the *cis* ketone. Therefore, we first planned to construct a *cis*-hydrindanone system using the Diels-Alder reaction between 2-cyclopenten-1-one and the diene derivative. However, the yield of this reaction was very poor. We then used the Sakurai reaction to 4-methylcyclohex-2-en-1-one (**5**) to yield **4**. We now wish to describe the details of the total synthesis of isovalerenenol (**2**) and also the results of the isomerization reaction of hydrindanone derivatives obtained in this work.

RESULTS AND DISCUSSION

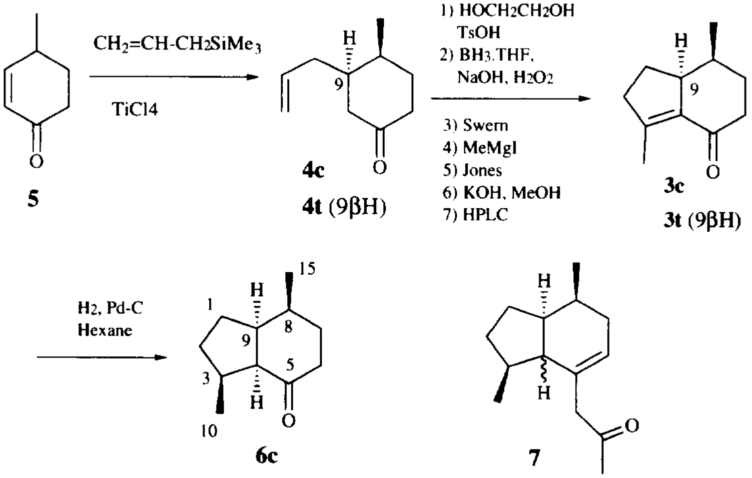
Synthetic Plan

The 1,4-addition followed by the intramolecular aldol condensation provides hydrindenone **3c**. The *cis*-fused hydrindane system can be prepared by hydrogenation of hydrindenone **3c**, because production of the hydrindanone system usually results in a *cis* system due to the kinetically controlled reaction. The final C4 unit will be introduced by the Grignard and allylic rearrangement reactions.


2 **3c** **4c**

Synthesis

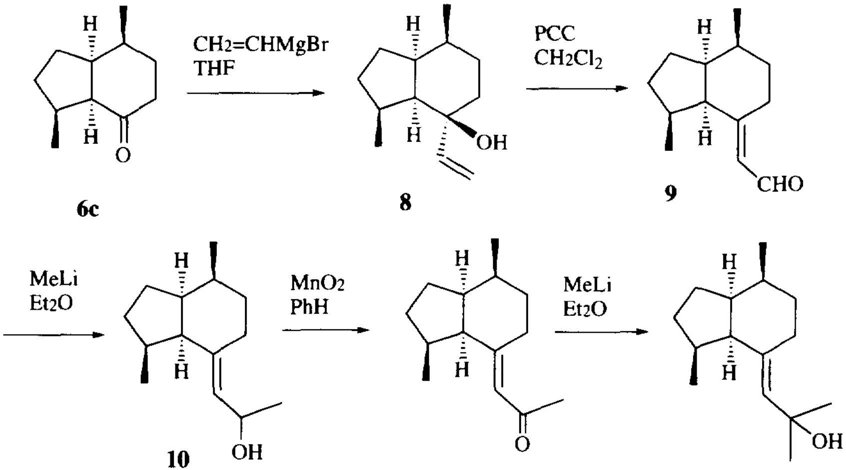
The Sakurai reaction of allyltrimethylsilane with 4-methylcyclohex-2-en-1-one (**5**) was reported by Heathcock *et al.* to yield more of the *cis* product **4c** than the *trans* ketone **4t**.[3,4] Thus allylation followed by ketalization and hydroboration-oxidation afforded a mixture of alcohols. Swern oxidation to the aldehyde, methylation, and again oxidation with Jones reagent gave a diketone with deprotection of the ketal group at the same time. Base-catalyzed intramolecular aldol cyclization (KOH) of the diketone smoothly proceeded, and a mixture of hydrindenones **3c** and **3t** was obtained in good yield. The separation of this mixture was



5 **4c** **4t** (9βH) **3c** **3t** (9βH) **6c** **7**

accomplished by HPLC. The assignment of each product was carried out by an independent synthesis.[5] In fact, hydrogenation of the major hydrindenone **3c** in the presence of Pd-C in hexane afforded a single product **6c**, which was identical with that reported by Kitagawa *et al.* as an ozonolysis product of the natural compounds.[1] Thus we succeeded in a synthesis of the *cis* hydrindanone **6c** with two methyl groups correctly oriented inside the molecule.

The next problem is to attach a 4-carbon unit at the position of the carbonyl group. It is very important that we should avoid the basic conditions because of the instability of the *cis*-hydrindanone system. We first attempted the Grignard reaction using methallyl chloride followed by ozonolysis and dehydration. However, the isolated product was trisubstituted olefin **7**. The next approach using the Wittig-Horner olefination using dimethyl cyanomethylphosphonate proceeded smoothly. However, isomerization of the double bond into the deconjugated *endo* position occurred on methylation and hydrolysis of the cyano group to afford **7**. The olefinic proton of **7** appeared at δ 5.76 as a broad doublet, which indicated that the double bond was not at the desired position but instead isomerized into the endo position.[6]



6c **8** **9**

10 **11** isovalerenenol (**2**)

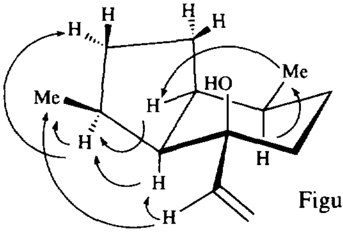


Figure 2. NOEs for **8**.

Hydrindanone **6c** was treated with vinylmagnesium bromide very carefully to afford an alkylated product with several minor products. The major one was analyzed by 600 MHz NMR spectroscopy and its structure was unambiguously established as **8**. Because NOEs were detected as shown in Fig 2., the conformation of this molecule was also established. If this compound had an isomerized *trans*-system, the NOEs shown by the arrows could have not been observed. The juncture of the *cis*-hydrindanone did not isomerize into the *trans*-system under Grignard conditions.

Alcohol **8** was then treated with PCC in CH$_2$Cl$_2$.[7] Although the yield was not so high, the reaction was slow, and most of the starting material was recovered; the main product was the desired aldehyde **9**. In this reaction, we could not detect the geometric isomer. The only product was the more stable E isomer. Methylation of aldehyde **9**, followed by MnO$_2$ oxidation, yielded ketone **11**. Swern oxidation of the intermediate alcohol **10** gave only a poor yield of the ketone; instead mostly decomposition occurred. The final methylation was accomplished by MeLi to afford isovalerenenol (**2**). The MS, IR, ^{1}H NMR and ^{13}C NMR spectra were identical with those of the natural product.[1]

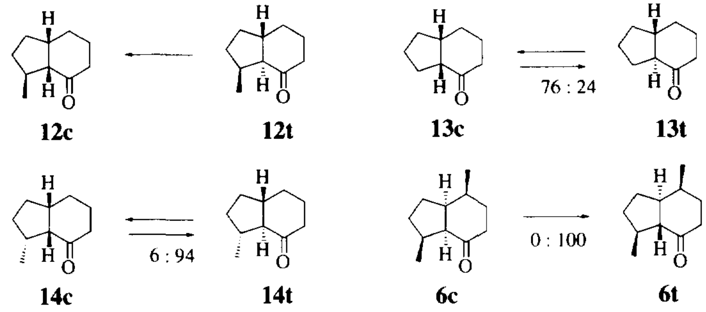
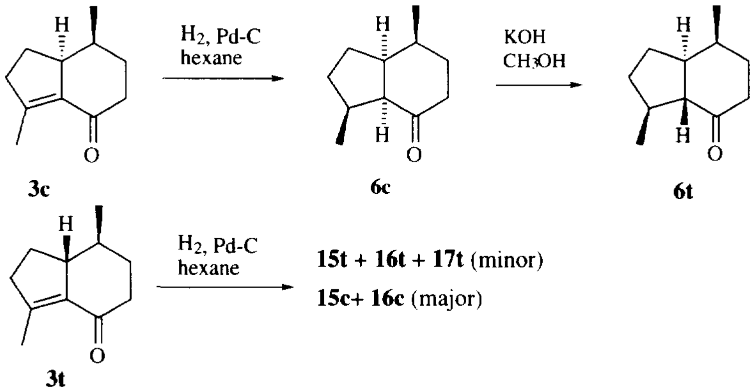
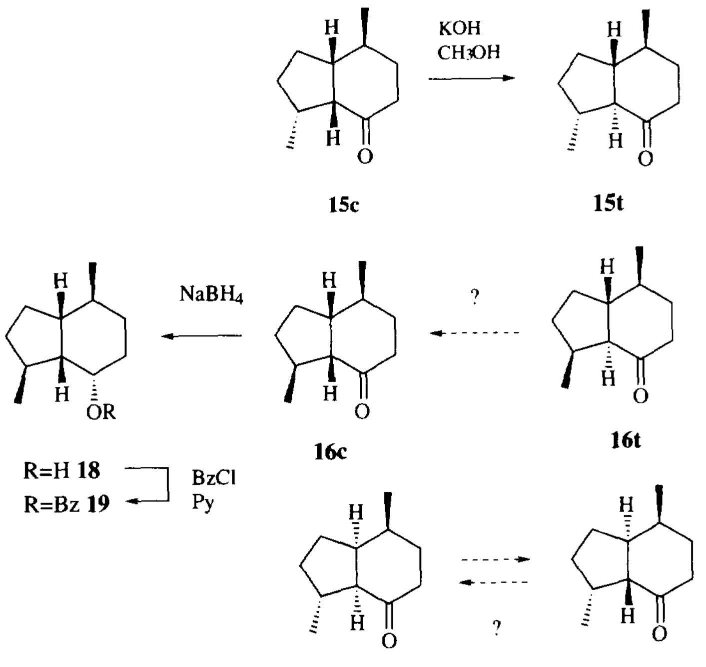


Figure 3. Relative ratio of hydrindanone derivatives.

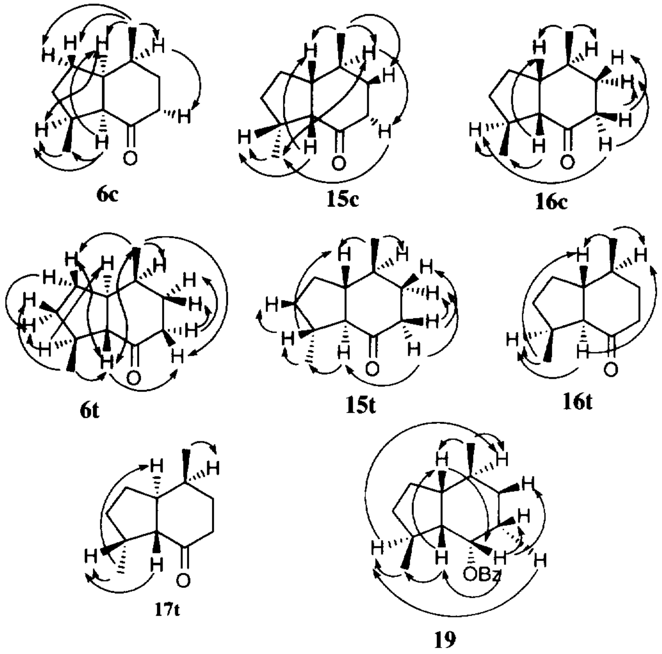
It is generally believed that in the hydrindanone systems, *cis* isomers are stabler than *trans* isomers. However, there are many cases where the *trans* isomer is stabler. Several examples were noted in Fig.3.[8] The product ratios under basic isomerization conditions were described. In the case of our hydrindanone **6c**, the *trans* isomer **6t** was stabler than **6c** upon treatment with K$_2$CO$_3$ in MeOH at 60°C overnight. The *cis* isomer **6c** completely disappeared and instead the *trans* isomer **6t** was obtained. Compounds **12c** and **13c** are stabler than the correspomding *trans* isomers, while **14t** and **6t** are stabler than *cis* isomers.



The isomeric hydrindenone **3t**, which cannot be used for the synthesis, was hydrogenated under similar conditions. Five products were isolated (**15t**, **15c**, **16t**, **16c**, and **17t**), among which two (**15c** and **16c**) were major and the three (**15t**, **16t**, and **17t**) were minor, which were separable by HPLC. None of them was identical with **6c** or **6t**. All five of these were analyzed by 600 MHz NMR spectroscopy. The NOEs detected for seven isomers **6c**, **6t**, **15c**, **15t**, **16c**, **16t**, and **17t** are shown in Fig. 4. Therefore, the stereochemistries of these compounds were determined. Compound **15c** was isomerized into **15t** very cleanly under basic conditions (K_2CO_3 in MeOH). Compound **16c** did not undergo isomerization, but instead the starting material was recovered completely. We failed to see if compounds **16t** and **17t** isomerized into **16c** and **17c** due to the minute quantity of the sample. In order to establish the structure of ketone **16c**, it was reduced with $NaBH_4$ to yield a sole product **18**. This alcohol **18** was converted into a benzoate **19**. Although the benzoate did not crystallize, its structure was established as **19** by the NOEs (Fig. 4). We isolated 7 isomers out of 8 possible hydrindanones of this type. The structures of these isomers were assigned as shown in the formulae. The NMR spectra of those of the *trans* derivatives were similar to each other, while those of the *cis*-isomers were similar to each other but not to those of the *trans*-isomers. The primary products in the hydrogenation were presumably **15c** and **16t**, which isomerized into **15t** and **16c** under the reaction conditions. There is still the possibility that the double bond in compound **3t** isomerized into the C-4 and C-9 positions followed by hydrogenation. However, the course to produce compound **17t** is not clear at this stage.



15c **15t** **16c** **16t** **17c** **17t**



6c **15c** **16c**

6t **15t** **16t**

17t **19**

Figure 4. The NOEs detected for hydrindanone isomers **6c**, **6t**, **15c**, **15t**, **16c**, **16t**, and **17t**, and benzoate **19**.

Table 1. Steric energy, population, and heat of formation for hydrindanones **6** and **12** - **17**.

Compound	Steric energy[a]	Population[b]	Heat of formation[c]
12c	19.8	59.3	-65.9
12t	21.5	98.0	-63.7
13c	19.4	49.4	-60.4
13t	18.9	99.1	-61.1
14c	19.8	56.1	-65.8
14t	19.4	99.2	-66.5
15c	22.5	61.7	-69.8
15t	19.9	99.5	-71.7
16c	20.4	90.8	-71.0
16t	22.1	98.8	-69.1
17c	21.5	91.4	-70.3
17t	24.5	86.4	-66.9
6c	22. 8	87.5	-68.1
6t	22.5	93.4	-70.1

[a] data for the most stable conformer calculated by CONFLEX (kcal/mol).

[b] data for the most stable conformer calculated by CONFLEX (%).

[c] caluculated by MOPAC6 for the most stable conformer calculated by CONFLEX (kcal/mol).

These results suggest that the isomer having the *cis* stereochemistry concerning the methyl group at C-3 and the hydrogen at C-4 is stable. The steric energy and the population of the most stable conformer for these hydrindanones were calculated by MM2 using CONFLEX.[9] The heat of formation for the most stable conformer was then calculated by MOPAC6. The results were shown in Table 1. The stabilities of *cis-trans* isomers are dependent upon the orientation of substituents. However, only in the case of **13** were the results from isomarization and calculation not consistent, which must be reinvestigated. Thus the relative stabilities of these types of hydrindanones must be very carefully considered either by isomerization experiments or by calculations.

In conclusion, we succeeded in the total synthesis of isovalerenenol (**2**) for the first time using hydrogenation of *cis*-hydrindenone **3c** into *cis*-hydrindanone **6c** and also oxidative allylic rearrangement of vinylic alcohol **8**. Seven isomers of the 3,8-dimethylhydrindan-5-ones were isolated and the stability was investigated by base-catalyzed isomerizations and MM2 calculations.

EXPERIMENTAL

General. IR spectra were measured on a Shimadzu IR-408 or a JASCO FT/IR-5300 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM FX90Q, a JEOL JNM GX400, a Varian Unity 200, or a Unity 600 spectrometer. Mass spectra were measured on a JEOL JMS HX-100 or AX-500 spectrometer. A Chemcopak Nucleosil 50-5 (10 X 250 mm) or Develosil 60-10 (20 X 250 mm) column was used for HPLC (JASCO pump system). Silica gel 60 for column chromatography was purchased from Merck.

***Preparation of 3-allyl-4-methylcyclohexanone* (4).** To a stirred solution of 4-methyl-cyclohex-2-ene-1-one (**5**) (3.10 g, 28.2 mmol) in dry CH_2Cl_2 (270 m*l*) was added $TiCl_4$ (3.6 m*l*, 32.8 mmol) at -78°C. After stirring for 5 min., a solution of allyltrimethylsilane (6.6 m*l*, 41.5 mmol) in dry CH_2Cl_2 (12 m*l*) was added into the mixture over 45 min. The mixture was further stirred for 45 min and then water (66 m*l*) was added over 10 min. The temperature of the reaction was raised to rt and held until the color disappeared. The organic phase was separated, washed with water and brine, and dried over $MgSO_4$. The solvent was evaporated to afford a residue (2.9 g), which was purified by silica gel column chromatography (hexane-EtOAc, 0 to 8 %) to afford **4** (2.3 g, 54%); oil; IR (FT-film) 1725, 1650 cm^{-1}; *m/z* 152 (M$^+$), 137, 123, 111, 95, 83, 69, 55 and 41 (base); δ_H (200 MHz; $CDCl_3$) 1.04 (3 H, d, *J* 7.0 Hz), 5.00, 5.06, 5.09 (each br s) and 5.73 (1 H, m); δ_C (50 MHz; $CDCl_3$) (major peaks only) 13.3 (q), 31.1 (d), 31.5 (t), 35.8 (t), 38.0 (t), 41.4 (d), 43.5 (t), 116.4 (t), 136.1 (d) and 211.4 (s); HRMS (GC-EI) Found *m/z* 152.1212. $C_{10}H_{16}O$ requires 152.1202.

***Preparation of enone* 3c.** A mixture of ketone **4** (5.4 g, 35.7 mmol), benzene (300 m*l*), ethylene glycol (3.0 m*l*, 53.8 mmol), and TsOH (686.2 mg, 3.61 mmol) was heated under reflux for 16 h. The mixture was washed with saturated aq. $NaHCO_3$ and brine, dried over $MgSO_4$, and was evaporated to give a ketal (6.6 g, 95%); oil; FTIR (film) 1650 cm^{-1}; *m/z* (GC-EI) 196 (M$^+$), 181, 155, 139, 127, 111, 99 (base), 95, 86, 79, 67, 55 and 41; δ_H (200 MHz; $CDCl_3$) 0.85 (d, *J* 6.9 Hz), 0.94 (d, *J* 5.6 Hz), 3.93 (8 H, m), 5.01 (4 H, m) and 5.74 (2 H, m); HRMS (GC-EI) Found *m/z* 196.1447. $C_{12}H_{20}O_2$ requires 196.1463.

A solution of the ketal (6.3 g, 32.3 mmol) in dry THF (30 m*l*) was treated with BH_3•THF (48.75 m*l*, 48.75 mmol) at rt for 1.4 h. Water (12 m*l*) was added slowly and aq. NaOH (3 mol/*l*) solution (36 m*l*) was added at once. Then 30% H_2O_2 (11.0 m*l*, 97.0 mmol) was added to maintain the temperature of the mixture at 30 to 50°C, and the mixture was stirred for 1 h. Aqueous $Na_2S_2O_3$ (3 mol/*l*, *ca.* 20 m*l*) was added and the solvent was evaporated to give a residue, which was extracted with ether. The organic phase was washed with water and brine, dried over $MgSO_4$, and evaporated to afford an alcohol (6.5 g, 95%); FTIR (film) 3425 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 0.84 (d, *J* 7.0 Hz), 0.95 (d, *J* 7.1 Hz), 3.61 (2 H, t, *J* 6.5 Hz) and 3.93 (3 H, s).

To a stirred solution of oxalyl chloride (2 m*l*, 22.9 mmol) in dry CH_2Cl_2 (50 m*l*) was added a solution of dimethylsulfoxide (3.5 m*l*, 49.3 mmol) in dry CH_2Cl_2 (10 m*l*) at -50 to -60°C under Ar atmosphere. After stirring for 2 min., a solution of the alcohol (4.2 g, 19.6 mmol) in dry CH_2Cl_2 (20 m*l*) was added into the mixture during 5 min. After stirring for 5 min., triethylamine (15 m*l*, 107.6 mmol) was added and kept stirring for 15 min. Water (100 m*l*) was added and the organic phase was washed with water and brine, dried over $MgSO_4$, and was evaporated to afford an aldehyde (4.0 g, 96%); δ_H (200 MHz; $CDCl_3$) 0.86 (d, *J* 7.0 Hz), 0.95 (d, *J* 5.7 Hz) and 9.78 (1 H, t, *J* 1.8 Hz).

The aldehyde (6.3 g, 29.7 mmol) was methylated with methylmagnesium iodide prepared from Mg (2.9 g, 119.7 mmol) and methyl iodide (7.4 m*l*, 118.9 mmol) in dry ether (180 m*l*) at room temperature. The mixture was stirred for 2.4 h., and then saturated aq. NH_4Cl was added slowly. The organic phase was separated, washed with water and brine, dried over $MgSO_4$, and was evaporated to afford an alcohol (6.12 g, 90%); δ_H (200 MHz; $CDCl_3$) 0.84 (d, *J* 7.0 Hz), 0.92 (br d, *J* 5.6 Hz), 1.13 (d, *J* 6.2 Hz), 3.76 (1 H, m) and 3.93 (4 H, s).

A solution of the alcohol (441.8 mg, 1.94 mmol) in acetone (12 m*l*) was treated with Jones reagent (2.5 m*l*, 20 mmol) at 0°C for 1 h. 2-Propanol was added until the color of the mixture turned from orange to green. Water was added and the solvent was evaporated to give a residue, which was extracted with ether. The ethereal solution was washed with water, saturated aq. $NaHCO_3$, and brine, dried over $MgSO_4$, and was evaporated to afford a diketone (336.6 mg, 95%); δ_H (200 MHz; $CDCl_3$) 1.04 (3 H, d, *J* 7.0 Hz), 1.05 (3 H, d, *J* 5.5 Hz) and 2.14 (3 H, s).

A solution of the diketone (3.8 g, 20.9 mmol) in 5% KOH in MeOH (100 m*l*) was heated at *ca.* 50°C for 2.3 h. Water was added and the solvent was evaporated to give a residue, which was extracted with ether. The ethereal solution was washed with water and brine, dried over $MgSO_4$, and evaporated to afford a residue (4.1 g), which was separated by silica gel column chromatography (hexane-EtOAc, 0 to 7%) followed by HPLC (Develosil 60-10, 30X250 mm) (hexane-EtOAc, 9:1) to give *cis*-enone **3c** (771.9 mg, 22.5%) and *trans*-enone **3t** (491.7 mg, 14.4%).

3c: oil; FTIR (film) 1690, 1630 cm^{-1}; *m/z* (GC-EI) 164 (M^+) (base), 149, 136, 122, 108, 93, 79, 65 and 55; δ_H (400 MHz; $CDCl_3$) 0.88 (3H, d, *J* 7.1 Hz), 2.09 (3H, d, *J* 1.0 Hz) and 3.12 (1 H, m); d_C (100 MHz; $CDCl_3$) 12.4 (q), 16.5 (q), 26.1 (t), 29.7 (d), 31.0 (t), 36.0 (t), 38.7 (t), 50.5 (t), 133.2 (s), 154.6 (s) and 200.6 (s); HRMS (GC-EI) Found *m/z* 164.1196. $C_{11}H_{16}O$ requires 164.1202.

3t: oil; FTIR (film) 1695, 1637 cm^{-1}; *m/z* (GC-EI) 164 (M^+) (base), 149, 136, 122, 108, 93, 79, 65 and 55; δ_H (400 MHz; $CDCl_3$) 0.99 (3H, d, *J* 6.1 Hz) and 2.07 (3H, br s); d_C (100 MHz; $CDCl_3$) 15.9 (q), 19.1 (q), 30.0 (t), 32.7 (t), 38.0 (d), 38.1 (t), 40.8 (t), 53.7 (d), 134.5 (s), 152.8 (s) and 199.8 (s); HRMS (GC-EI) Found *m/z* 164.1189. $C_{11}H_{16}O$ requires 164.1202.

***Hydrogenation of cis-enone* 3c.** A solution of *cis*-enone **3c** (715.3 mg, 4.36 mmol) in hexane (18 m*l*) was stirred under a hydrogen atmosphere in the presence of 10% Pd-C (70 mg) at rt overnight. Filtration and evaporation of the solvent afforded hydrindanone **6c** (724 mg, quant.) after a short silica gel column; oil; FTIR (film) 1730 cm^{-1}; *m/z* (GC-EI) 166 (M^+), 151, 137, 124, 111 (base), 95, 81, 69, 55 and 41; d_H (200 MHz; $CDCl_3$) 0.94 (3 H, d, *J* 6.8 Hz), 1.19 (3 H, d, *J* 7.0 Hz), 2.62 (1 H, t, *J* 8.0 Hz); δ_H (600 MHz; C_6D_6) 0.69 (3H, d, *J* 6.8 Hz, 15), 1.22 (1 H, dddd, *J* 11.2, 5.8, 5.8 and 2.0 Hz, 1α), 1.30 (1 H, m, 1β), 1.32 (2 H, m, 7), 1.42 (3 H, d, *J* 7.1 Hz, 10), 1.53 (1 H, m, 2α), 1.60 (1 H, m, 2β), 1.69 (1 H, m, 8α), 1.75 (1 H, m, 3α), 1.93 (1 H, tdd, *J* 13.0, 6.9 and 1.2 Hz, 6α), 1.99 (1 H, m, 9α), 2.05 (1 H, ddd, *J* 13.0, 4.3 and 3.1 Hz, 6β) and 2.16 (1 H, t, *J* 6.5 Hz, 4α); δ_C (50 MHz; $CDCl_3$) 16.1 (q), 19.0 (q), 23.0 (t), 29.6 (t), 30.7 (t), 31.9 (d), 38.0 (d), 42.1 (t), 48.7 (d), 56.2 (d) and 214.9 (s); δ_C (150 MHz, C_6D_6) 16.3 (q, 10), 19.0 (q, 15), 22.7 (t, 1), 30.2 (t, 7), 30.3 (t, 2), 32.0 (d, 8), 38.3 (d, 3), 42.4 (t, 6), 49.5 (d, 9), 56.1 (d, 4) and 211.9 (s, 5); HRMS (GC-EI) Found *m/z* 166.1392. $C_{11}H_{18}O$ requires 166.1358.

***Base treatment of cis-hydrindanone* 6c.** A solution of *cis*-hydrindanone **6c** (31.2 mg, 0.19 mmol) in dry MeOH (10 m*l*) was treated with K_2CO_3 (30.7 mg, 0.22 mmol) at *ca* 80°C for 19.5 h. The solvent was evaporated and the residue was extracted with ether. The ethereal solution was washed with hydrochloric acid (1 mol/*l*) and brine, dried over $MgSO_4$, and was evaporated to afford a residue, which was purified by silica gel column chromatography (hexane-EtOAc; 0 to 10%) to give *trans*-hydrindanone **6t** (15.4 mg, 49%); oil; FTIR (film) 1725 cm^{-1}; *m/z* (GC-EI) 166 (M^+), 151, 133, 124, 109 (base), 95, 81, 67, 55 and 41; δ_H (200 MHz, $CDCl_3$) 1.03 (3 H, d, *J* 6.3 Hz), 1.08 (3 H, d, *J* 7.0 Hz); δ_H (600 MHz; C_6D_6) 0.70 (3H, d, *J* 7.1 Hz, 15), 1.02 (1H, m, 2β), 1.13 (3H, d, *J* 6.6 Hz, 10), 1.23 (1H, td, *J* 11.3 and 3.4 Hz, 1β), 1.29 (1H, dtd, *J* 11.3, 6.8 and 3.4 Hz, 1α), 1.41 (1 H, m, 7β), 1.50 (1 H, m, 7α), 1.55 (1 H, m, 2α), 1.65 (1 H, m, 8α), 1.68 (1 H, m, 2α), 1.72 (1 H, dd, *J* 13.6 and 9.4 Hz, 4β), 1.94 (1 H, td, *J* 13.8 and 6.3 Hz, 6β), 2.06 (1 H, ddd, *J* 13.8, 4.9 and 2.4 Hz, 6α) and 2.29 (1 H, m, 3α); δ_C (50 MHz; $CDCl_3$) 11.4 (q), 20.6 (q), 27.0 (t), 29.4 (d), 30.9 (t), 31.6 (d), 35.0 (t), 37.8 (t), 52.5 (d), 57.7 (d) and 212.0 (s); δ_C (150MHz, C_6D_6) 11.1 (q, 15), 20.7 (q, 10), 27.1 (t, 1), 29.4 (d, 8), 31.0 (t, 2), 32.1 (d, 3), 34.8 (d, 7), 37.6 (t, 6), 52.1 (d, 9), 57.5 (d, 4) and 209.0 (s, 5); HRMS (GC-EI) Found *m/z* 166.1360. $C_{11}H_{18}O$ requires 166.1358.

***Grignard reaction of cis-hydrindanone* 6c.** A solution of *cis*-hydrindanone **6c** (726.2 mg, 4.37 mmol) in dry THF (20 m*l*) was added to a stirred solution of vinylmagnesium bromide in THF (1.01 mol/*l*, 22.5 m*l*, 22.7 mmol) at 0°C. The mixture was stirred at room temperature for 2.3 h. and saturated aq. NH_4Cl was added slowly. The solvent was evaporated to give a residue, which was extracted with ether. The ethereal solution was washed with water and brine, dried over $MgSO_4$, and was evaporated to afford a residue. The residue was purified by silica gel column chromatography (hexane-EtOAc, 0 to 2 %) followed by HPLC (Nucleosil 50-5, 10X250 mm) (hexane-EtOAc, 99:1) to give an alcohol **8** (604.8 mg, 71%); oil; FTIR (film) 3530, 1645 cm^{-1}; *m/z* (GC-EI) 194 (M^+), 179, 161, 147, 137, 122 (base), 111, 95, 81, 69, 55 and 41; δ_H (200 MHz, $CDCl_3$) 0.91 (3 H, d, *J* 6.7 Hz), 1.06 (3 H, d, *J* 7.2 Hz), 4.97 (1 H, dd, *J* 10.7 and 1.2 Hz), 5.15 (1 H, dd, *J* 17.3, 1.2 Hz), 6.00 (1 H, dd, *J* 17.3, 10.7 Hz); δ_H (600 MHz, C_6D_6) 0.92 (3H, d, *J* 6.8 Hz, 15), 1.08 (1 H, m, 7β), 1.18 (3 H, d, *J* 7.3 Hz, 10), 1.20 (1 H, m, 6a), 1.26 (1 H, td, *J* 13.2 and 3.7 Hz, 6b), 1.43 (1 H, dd, *J* 17.3 and 6.6 Hz, 4α), 1.49 (2 H, m, 1a and 7α), 1.57 (1 H, m, 8α), 1.64 (1 H, m, 2β), 1.78 (1 H, m, 1b), 1.81 (1 H, m, 2α), 1.88 (1 H, m, 9α), 2.06 (1 H, m, 3α), 4.90 (1 H, dd, *J* 10.7 and 1.0 Hz, 12a), 5.06 (1 H, dd, *J* 17.3 and 1.0 Hz, 12b), 5.82 (1 H, dd, *J* 17.3 and 10.7 Hz, 11); δ_C (50 MHz, C_6D_6) 18.8 (q) , 23.9 (q), 24.3 (t), 32.9 (d), 39.9 (d), 42.4 (t), 46.4 (d), 50.2 (d), 75.0 (s), 110.2 (t) and 150.0 (d); HRMS (GC-EI) Found *m/z* 194.1661. $C_{13}H_{22}O$ requires 194.1670.

***PCC oxidation of alcohol* 8.** A solution of the alcohol **8** (289.5 mg, 1.49 mmol) in dry CH_2Cl_2 (20 m*l*) was treated with PCC (1.7 g, 7.5 mmol) in the presence of molecular sieves 4A (powder, 163 mg) at room temperature for 8 h. Ether (*ca.* 50 m*l*) was added and the mixture was passed through a short silica gel column (elution with ether). The eluate was washed with hydrochloric acid (1 mol/*l*) and brine, dried over $MgSO_4$, and was evaporated to give a residue. The residue was separated by silica gel column chromatography (hexane-EtOAc, 0 to 5%) to afford an aldehyde **9** (47.6 mg, 16.6 %) and recovered **8** (117.1 mg, 40.4%).

9: oil; FTIR (film) 1725, 1680, 1635 cm^{-1}; m/z (GC-EI) 192 (M^+), 191, 177, 163, 148 (base), 135, 133, 121, 107, 91, 79, 67, 55, 53 and 41; δ_H (200 MHz, $CDCl_3$) 0.70 (3H, d, *J* 6.2 Hz), 0.71 (3 H, d, *J* 6.2 Hz), 2.34 (1 H, t, *J* 9.0 Hz), 2.55 (1 H, dt, *J* 16.0 and 8.0 Hz), 5.90 (1 H, d, J 7.8 Hz), 9.94 (1H, d, *J* 7.8 Hz); δ_C (50 MH, C_6D_6) 16.5 (q), 19.8 (q), 23.9 (t), 26.0 (t), 27.5 (t), 30.2 (d), 33.6 (t), 39.9 (d), 46.1 (d), 53.1 (d), 129.5 (d), 189.0 (d) and 205.8 (s); HRMS (GC-EI) Found *m/z* 192.1525. $C_{13}H_{20}O$ requires 192.1514.

***Preparation of enone* 11.** Methyl lithium (1.08 mol/*l*, 0.8 m*l*, 0.86 mmol) was added into a solution of the aldehyde **9** (51.9 mg, 0.27 mmol) in ether (5 m*l*) at room temperature. The mixture was stirred for 50 min. and water (10 m*l*) was added. The organic phase was washed with water and brine, dried over $MgSO_4$, and was evaporated to afford an alcohol **10** (54.3 mg, 97%); FTIR (film) 3420 cm^{-1}; δ_H (200MHz, C_6D_6) 2.52 (1 H, m), 4.94 (1 H, m), 5.29 (1 H, t, *J* 9.0 Hz); m/z (GC-EI) 208 (M^+), 190, 175, 161, 150, 135 (base), 121,107, 93, 81, 67, 59, 55 and 43.

A solution of the alcohol **10** (54.3 mg, 0.26 mmol) in dry benzene (10 m*l*) was treated with MnO_2 (986.5 mg, 11.4 mmol) at room temperature for 4.4 h under Ar. The mixture was filtered through Celite and the eluate was evaporated to afford a residue. The residue was purified by silica gel column chromatography (hexane-EtOAc, 0 to 3%) to give an enone **11** (19.7 mg, 37.0%); oil; FTIR (film) 1695 and 1600 cm^{-1}; m/z (GC-EI) 206 (M^+), 191, 177, 164, 151 (base), 133, 121, 107, 93, 81, 67, 55 and 43; δ_H (200 MHz, C_6D_6) 0.74 (3 H, d, *J* 6.7 Hz), 0.77 (3 H, d, *J* 7.2 Hz), 1.91 (3 H, s), 3.58 (1 H, dt, *J* 17.6 and 8.8 Hz), 5.84 (1H, br s); δ_C (50 MHz, C_6D_6) 16.6 (q), 19.8 (q), 24.6 (t), 26.5 (t), 28.6 (t), 30.6 (d), 31.7 (q), 34.2 (t), 40.7 (d), 45.1 (d), 52.6 (d), 125.5 (d), 162.2 (s) and 196.3 (s); HRMS (GC-EI) Found *m/z* 206.1667. $C_{14}H_{22}O$ requires 206.1670.

***Synthesis of isovalerenenol* (2).** Methyl lithium (1.08 mol/*l*, 0.02 m*l*, 0.02 mmol) was added into a solution of the enone **11** (2.8 mg) in dry ether (0.7 m*l*) at room temperature . The mixture was stirred for 25 min. and water (10 m*l*) was added. The organic phase was washed with water and brine, dried over $MgSO_4$, and was evaporated to afford a residue, which was passed through a short column of silica gel to give isovalerenenol (**2**) (2.4 mg, 80%); FTIR (film) 3420, 1665 cm^{-1}; *m/z* (GC-EI) 222 (M^+), 204, 189, 161, 149 (base), 135, 122, 107, 95, 85, 81, 71, 59, 55 and 43; δ_H (400 MHz, $CDCl_3$) 0.86 (3 H, d, *J* 6.6 Hz), 0.90 (3 H, d, *J* 7.1 Hz), 1.37 (6 H, s), 2.54 (1 H, t, *J* 8.2 Hz), 2.82 (1 H, ddd, *J* 14.9, 9.3 and 5.8 Hz) and 5.36 (1 H, s); δ_H (200 MHz, C_6D_6) 0.86 (3 H, d, *J* 6.8 Hz), 0.96 (3 H, d, *J* 7.0 Hz), 1.30 (6 H, s), 2.48 (1 H, t, *J* 8.4 Hz), 2.96 (1 H, ddd, *J* 15.1, 9.3 and 5.5 Hz) and 5.34 (1 H, s); δ_H (400 MHz, C_5D_5N) 0.82 (3 H, d, *J* 6.8 Hz), 0.97 (3 H, d, *J* 7.1 Hz), 1.59 (6 H, s) , 2.59 (1 H, t, *J* 8.4 Hz), 3.22 (1 H, ddd, *J* 14.9, 9.3 and 5.6 Hz) and 5.62 (1 H, s); δ_C (100 MHz, $CDCl_3$) 16.8, 20.1, 24.1, 25.3, 27.3, 30.1, 31.4, 31.8, 33.7, 39.6, 45.4, 52.9, 71.0, 134.1 and 140.6; δ_C (100 MHz, C_5D_5N) 17.0, 20.4, 24.3, 25.4, 27.7, 30.4, 32.0, 32.6, 33.9, 40.0, 45.7, 53.2, 70.1, 136.1 and 138.6.

***Hydrogenation of trans-enone* 3t.** A solution of the *trans*-enone **3t** (277.6 mg, 1.69 mmol) in hexane (5 m*l*) was treated with hydrogen in the presence of 10%Pd-C (20 mg) at room temperature overnight. The mixture was filtered and the eluate was evaporated to afford a residue, which was purified by HPLC (Nucleosil 50-5, 10X250 mm) (hexane-EtOAc, 95:5) to give **15t** (7.5 mg, 2.7%), **17t** (2.6 mg, 0.9%), **16t** (3.0 mg, 1.1%), **16c** (40.2 mg, 14.3%), and **15c** (76.0 mg, 27%).

15t : oil; FTIR (film) 1725 cm^{-1}; *m/z* (GC-EI) 166 (M^+), 151, 124, 109 (base), 95, 81, 67, 55 and 41; δ_H (600 MHz, C_6D_6) 0.69 (3 H, d, *J* 6.6 Hz, 15), 0.99 (1 H, m, 9β), 1.00 (1 H, m, 1α, and 7β), 1.01 (1 H, m, 2α), 1.11 (3 H, d, *J* 6.6 Hz, 10), 1.13 (1 H, m, 8α), 1.46 (1 H, t, *J* 11.1 Hz, 4α), 1.51 (1 H, m, 1β), 1.53 (1 H, m, 7α), 1.67 (1 H, m, 2β), 1.88 (1 H, tdd, *J* 13.7, 6.6 and 1.3 Hz, 6α), 2.19 (1 H, ddd, *J* 13.7, 4.7 and 2.1 Hz, 6β), 2.26 (1 H, m, 3β); δ_C (150 MHz, C_6D_6) 19.1 (q, 15), 20.5 (q, 10), 29.4 (t, 1), 30.9 (t, 2), 32.6 (d, 3), 36.6 (t, 7), 37.5 (d, 8), 41.8 (t, 6), 55.0 (d, 9), 62.9 (d, 4) and 208.8 (s, 5); HRMS (GC-EI) Found *m/z* 166.1366. $C_{11}H_{18}O$ requires 166.1358.

17t : oil; FTIR (film) 1720 cm^{-1}; *m/z* (GC-EI) 166 (M^+), 151, 124 (base), 109, 95, 81, 67, 55 and 41; δ_H (600 MHz, C_6D_6) 0.71 (3 H, d, *J* 6.8 Hz, 15), 0.90 (3 H, d, *J* 7.1 Hz, 10), 1.27 (1 H, m, 9α), 1.67 (1 H, m, 8α), 1.83 (1 H, m, 4β), and 2.85 (1 H, m, 3β); HRMS (GC-EI) Found *m/z* 166.1369. $C_{11}H_{18}O$ requires 166.1358.

16t : oil; FTIR (film) 1725 cm^{-1}; *m/z* (GC-EI) 166 (M^+), 151, 124, 109 (base), 95, 81, 67, 55 and 41; δ_H (200 MHz, $CDCl_3$) 0.91 (3 H, d, *J* 6.7 Hz) and 0.94 (3 H, d, *J* 5.7 Hz); δ_H (600 MHz, C_6D_6) 0.74 (3 H, d, *J* 6.3 Hz, 15), 1.01 (1 H, m, 8α), 1.19 (3 H, d, *J* 7.1 Hz, 10), 1.27 (1 H, m), 1.34 (1 H, m, 9β), 1.46 (1 H, m), 1.59 (1 H, dd, *J* 6.0, 1.4 Hz, 4α), 1.83 (1 H, ddd, *J* 14.6, 6.3 and 1.2 Hz), 2.18 (1 H, ddd, *J* 14.8, 4.6 and 2.1 Hz) and 2.32 (1 H, m, 3α); δ_C (100 MHz, $CDCl_3$) 17.7, 19.6, 28.7, 31.1, 32.0, 35.5, 37.7, 41.9, 48.6, 58.9 and 211.4; HRMS (GC-EI) Found *m/z* 166.1364. $C_{11}H_{18}O$ requires 166.1358.

16c : oil; FTIR (film) 1715 cm^{-1}; *m/z* (GC-EI) 166 (M^+), 151, 133, 124 (base), 111, 95, 81, 67, 55 and 41; δ_H (200 MHz, $CDCl_3$) 0.97 (3 H, d, *J* 6.1 Hz), 1.01 (3H, d, *J* 6.5 Hz) and 0.90-2.48 (12 H, m); δ_H (600 MHz, C_6D_6) 0.68 (3 H, d, *J* 6.3 Hz, 15), 0.91 (1 H, m, 2α), 0.95 (1 H, m, 8α), 1.02 (3 H, d, *J* 6.3 Hz, 10), 1.06 (1 H, qd, *J* 12.5 and 5.3 Hz, 7b), 1.12 (1 H, m, 1α), 1.37 (1 H, ddt, *J* 12.5, 9.3 and 3.2 Hz, 7α), 1.53 (1 H, m, 1β), 1.58 (1 H, m, 9β), 1.68 (1 H, dtd, *J* 12.2, 7.9 and 4.1 Hz, 2β), 1.93 (1 H, t, *J* 8.9 Hz, 4β), 2.03 (1 H, ddd, *J* 15.9, 12.5 and 6.3 Hz, 6α), 2.06 (1 H, m, 3α), 2.13 (1 H, dddd, *J* 15.9, 5.3, 3.1 and 1.2 Hz, 6β); δ_C (50 MHz, $CDCl_3$) 19.6 (q), 19.9 (q), 30.4 (t), 33.3 (t), 33.5 (t), 34.1 (d), 37.1 (d), 38.7 (t), 49.9 (d), 60.5 (d) and 214.9 (s); δ_C (150 MHz, C_6D_6) 19.8 (q, 15), 20.0 (q, 10), 30.7 (t, 1), 33.0 (t, 7), 33.6 (t, 2), 34.2 (d, 8), 36.8 (d, 3), 38.6 (d, 6), 49.6 (t, 9), 60.0 (d, 4) and 211.5 (s, 5); HRMS (GC-EI) Found *m/z* 166.1357. $C_{11}H_{18}O$ requires 166.1358.

15c : oil; FTIR (film) 1720 cm^{-1}; *m/z* (GC-EI) 166 (M$^+$) (base), 151, 137, 124, 111, 93, 81, 67, 55 and 41; δ_H (200 MHz, $CDCl_3$) 0.91 (3 H, d, *J* 7.2 Hz), 1.01 (3 H, d, *J* 6.0 Hz) and 2.69 (1 H, dd, *J* 8.1 Hz); δ_H(600 MHz, C_6D_6) 0.72 (3 H, d, *J* 6.1 Hz, 15), 0.82 (3 H, d, *J* 7.1 Hz, 10), 0.95 (1 H, m, 8α), 0.99 (1 H, dtd, *J* 13.0, 11.2 and 4.6 Hz, 7β), 1.20 (1 H, dtd, *J* 12.1, 7.3 and 4.7 Hz, 2α), 1.31 (1 H, m, 1α), 1.36 (1 H, m, 7α), 1.44 (1 H, m, 2β), 1.46 (1 H, m, 9β), 1.55 (1 H, dtd, *J* 12.7, 8.0 and 5.1 Hz, 1β), 1.77 (1 H, ddd, *J* 16.8, 12.9 and 5.9 Hz, 6α), 2.30 (1 H, m, 6β), 2.34 (1 H, m, 3β) and 2.50 (1 H, t, *J* 9.0 Hz, 4β); δ_C (50 MHz, $CDCl_3$) 17.8 (q), 20.6 (q), 30.6 (t), 32.3 (t), 33.2 (t), 36.5 (d), 37.6 (d), 42.3 (t), 47.0 (d), 55.0 (d), 215.6 (s); δ_C (100 MHz, C_6D_6) 17.8 (q, 10), 20.7 (q, 15), 30.7 (t, 1), 32.3 (t, 7), 33.1 (t, 2), 36.5 (d, 8), 37.7 (d, 3), 42.1 (t, 6), 47.1 (d, 9), 54.8 (d, 4) and 212.0 (s, 5); HRMS (EI, GC) Found *m/z* 166.1356. $C_{11}H_{18}O$ requires 166.1358.

***Reduction of ketone* 16c.** To a stirred solution of the ketone **16c** (19.4 mg , 0.12 mmol) in MeOH (1.3 m*l*) was added $NaBH_4$ (20 mg) and the mixture was stirred for 35 min at room temperature under Ar. The mixture was extracted with ether and the ethereal solution was washed with brine, dried over $MgSO_4$, and was evaporated to afford a residue, which was purified using a short silica gel column to give an alcohol **18** (18.9 mg, 96%); FTIR (film) 3425 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.83 (3 H, d, *J* 5.9 Hz), 1.11 (3 H, d, *J* 6.3 Hz) and 4.00 (1 H, dt, *J* 10.7 and 4.8 Hz); δ_H (200 MHz, C_6D_6) 0.75 (3 H, d, *J* 5.6 Hz), 1.21 (3 H, d, *J* 6.4 Hz) and 3.72 (1 H, dt, *J* 10.5 and 5.2 Hz); δ_C (50 MHz, $CDCl_3$) 20.3 (q), 23.5 (q), 28.4 (t), 30.4 (t), 30.7 (d), 31.2 (d), 32.7 (t), 33.1 (t), 49.0 (d), 53.7 (d) and 72.7 (d).

***Benzoylation of alcohol* 18.** To a solution of the alcohol **18** (34.9 mg, 0.21 mmol) in dry CH_2Cl_2 (2 m*l*) was added *p*-bromobenzoyl chloride (251.8 mg, 1.15 mmol), triethylamine (0.15 m*l*, 1.08 mmol), and dimethylaminopyridine (14 mg, 0.11 mmol). The mixture was stirred for 13.3 h at room temperature under Ar. Water was added and the mixture was stirred for 1.2 h. The organic phase was washed with water, saturated aq. $NaHCO_3$, hydrochloric acid (1 mol/*l*), and brine, dried over $MgSO_4$, and was evaporated to afford a residue. The residue was purified by silica gel column chromatography (hexane-EtOAc, 0 to 10 %) to give a benzoate **19** (48.9 mg, 67%); oil; FTIR (film) 1730 cm^{-1}; *m/z* (GC:CI-CH_4) 353, 351 (M+1)$^+$, 335, 243, 241, 231, 229, 203, 201, 185, 183, 151 (base), 135, 109, 95 and 81; δ_H (200 MHz, $CDCl_3$) 0.88 (3 H, d, *J* 5.9 Hz), 1.00 (3 H, d, *J* 6.4 Hz), 5.33 (1 H, dt, *J* 10.5 and 5.2 Hz), 7.57 (2 H, d, *J* 8.8 Hz) and 7.90 (2 H, d, *J* 8.8 Hz); δ_H (600 MHz, C_6D_6) 0.72 (3 H, d, *J* 6.3 Hz, 15), 0.83 (1 H, m, 7β), 0.92 (1 H, m, 8α), 1.04 (3 H, d, *J* 6.6 Hz, 10), 1.10 (1 H, m, 2β), 1.34 (1 H, m, 9β), 1.39 (1 H, dddd, *J* 12.6, 8.6, 3.7 and 1.5 Hz, 1α), 1.43 (1 H, m, 7α), 1.46 (1 H, m, 1β), 1.57 (1 H, qd, *J* 12.2 and 3.7 Hz, 6α), 1.71 (1 H, dq, *J* 12.2 and 5.1 Hz, 1β), 1.87 (1 H, dq, *J* 12.9 and 9.1 Hz, 2α), 1.93 (1 H, dt, *J* 10.4 and 5.1 Hz, 4β), 2.10 (1 H, m, 3α), 5.39 (1 H, dt, *J* 12.2 and 5.1 Hz, 5β), 7.18 (2 H, d, *J* 8.4 Hz, arom) and 7.85 (2 H, d, *J* 8.4 Hz, arom); δ_C (50 MHz, $CDCl_3$) 20.2 (q), 22.4 (q), 26.9 (t), 28.4 (t), 31.2 (d), 31.4 (d), 32.7 (2C, t), 49.0 (d), 50.2 (d), 76.0 (d), 127.7 (s), 129.8 (s), 131.1 (2C, d), 131.6 (2C, d) and 165.4 (s); δ_C (150 MHz, C_6D_6) 20.2 (q, C-15), 22.6 (q, C-10) , 27.1 (t, C-6), 28.5 (t, C-1), 31.3 (d, C-8), 31.6 (d, C-3), 32.8 (t, C-7), 32.9 (t, C-2), 49.0 (d, C-9), 50.3 (d, C-4), 75.8 (d, C-5), 128.3 (s), 130.3 (s), 131.3 (2C, d), 131.9 (2C, d) and 165.1 (s); HRMS (GC:CI-CH_4) Found *m/z* 351.0952 (M+1). $C_{18}H_{24}O_2Br$ requires 351.0960.

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REFERENCES AND NOTES

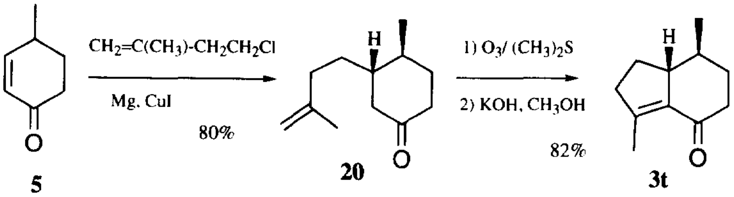
1 Kobayashi, M.; Yasuzawa, T.; Kyogoku, Y.; Kido M.; Kitagawa, I. *Chem. Pharm. Bull.*, **1982**, *30*, 3431-3434.

2 Honda, T.; Ishige, H.; Tsubuki, M.; Naito K.; Suzuki, Y. *J. Chem. Soc., Perkin Trans. 1*, **1991**, 954-955; Honda, T.; Ishige, H.; Tsubuki, M.; Naito K.;Suzuki, Y. *Chem. Pharm. Bull.*, **1991**, *39*, 1641-1643.

3 Blumenkopf, T. A.; Heathcock, C. H. *J. Am. Chem. Soc.*, **1983**, *105*, 2354-2358.

4 Numbering following the natural products[1] were used throughout the work.

5 The authentic *trans* hydrindanone **3t** was prepared in three steps from **5**. The 1,4-addition of 4-chloro-2-methyl-1-butene to **5** in the presence of CuI afforded *trans* product **20** in 80% yield. Ozonolysis and aldol cyclization gave **3t** in 82% yield.



6 Because the product had a double bond between C-5 and C-6, the stereochemistry at C-4 was not determined.

7 Majetich, G.; Condon, S.; Hull, K.; Ahmad, S. *Tetrahedron Lett.*, **1989**, *30*, 1033-1036.

8 Cicero, B. L.; Weisbuch F.; Dana, G. *J. Org. Chem.*, **1981**, *46*, 914-919 (1981); Peterson, P. E.; Leffew, R. L. B.; Jensen, B. L. *J. Org. Chem.*, **1986**, *51*, 1948-1954; House, H. O.; Rasmusson, G. H. *J. Org. Chem.*, **1963**, *28*, 31-34.

9 CONFLEX Ver. 3.45, by H. Goto and E. Ôsawa, Department of Knowledge-Based Information Engineering, Toyohashi University of Technology, Toyohashi 441, Japan; Goto, H.; Ôsawa, E. *Tetrahedron Lett.*, **1992**, *33*, 1343-4346; Goto, H.; Ôsawa, E. *J. Chem. Soc., Perkin Trans 2*, **1993**, 187-198.

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