Total synthesis of bisabolane sesquiterpenoids, α-bisabol-1-one, curcumene, curcuphenol and elvirol: utility of catalytic enamine reaction in cyclohexenone synthesis

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Total syntheses of α-bisabol-1-one, curcumene, curcuphenol and elvirol have been accomplished via 1,4-conjugate addition of intact aldehydes to vinyl ketones followed by an intramolecular aldol condensation.

Introduction

A variety of bisabolane type natural products are widely distributed both in terrestrial as well as in marine organisms. In spite of their rather simple structures, some of them have characteristic biological activities (vide infra). These compounds are attractive synthetic targets especially to verify the usefulness of newly developed synthetic methodologies.

We previously reported the highly expedient nucleophilic reaction of intact aldehydes 1 mediated by diethylamino(trimethyl)silane (DEATMS) or diethylamine (DEA). The reaction enabled 1,4-conjugate addition to vinyl ketone 2 leading to 5-keto-aldehydes 4,[1,2] domino 1,4-conjugate addition—intramolecular substitution leading to formylcyclopropanecarboxylates 5[3] and self aldol condensation leading to α,β-unsaturated aldehydes 6[4] (Scheme 1). The reaction was proved to follow a

atography without aqueous work-up. In the case of 1,4-conjugate addition of intact aldehydes 1 to buten-3-one (MVK) 2, the reaction is completed with a catalytic amount of DEATMS or DEA in acetonitrile, which is another advantage. The product, 5-keto-aldehyde 4, is a versatile precursor of substituted cyclohexenone 7 via an intramolecular aldol cyclisation. In order to exemplify further utility of the reaction, we wish to report herein the total synthesis of several bisabolane sesquiterpenoids 8–12 (Fig. 1) starting from citronellal 13 as a chiral source.
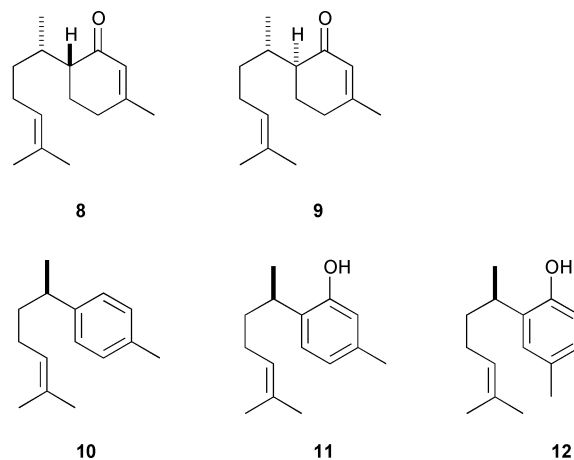

Fig. 1

catalytic enamine pathway as a catalytic amount of the diethylaminoenamine of aldehyde 1 promoted the reaction.[1] The reaction conditions were so mild that acid or base sensitive protecting groups such as tetrahydropyranyl ether, acetate or tert-butyldimethylsilyl ether survived. Moreover, it is very simple to isolate the products by distillation or column chrom-

Scheme 1

Results and discussion

Cyclohexenone 8 was first isolated from Stevia puypurea Pers[5a] and has been synthised by Jefferies et al.[6] Recently, both diastereomers 8 and 9 were found along with several other bisabolane type compounds from commercial Brazilian lantana oil obtained from Lantana camara L. (Verbenaceae).[5b]

Synthesis started from keto-aldehyde 14, obtained by DEATMS or DEA mediated conjugate addition of citronellal 13 to buten-3-one 2 (Scheme 2). Results of the conjugate addition are compiled in Table 1. As shown in entry 7, the keto-aldehyde 14 was prepared in 96% yield on a 0.1 M scale by simply refluxing a solution of citronellal 13 and buten-3-one 2 in the presence of 0.1 equiv. of DEATMS in

Table 1 1,4-Addition of citronellal **13** to buten-3-one **2**

Entry[a]	**13**/mmol	**2**/eq.	DEATMS/eq.	Conditions	Yield (%) **14**
1[b]	1	1.5	0.5	12 h, rt	13
2[c]	1	1.5	0.5	19 h, Reflux	81
3[d]	1	1.5	0.2	12 h, 80 °C	87
4[e]	1	1.5	0.2	4 h, 80 °C	70
5	5	4.0	0.2	20 h, Reflux	100
6	5	1.5	0.1	51 h, Reflux	92
7	100	1.5	0.1	48 h, Reflux	96

[a] Reaction was carried out with DEATMS in acetonitrile and worked up by Kugelrohr distillation unless otherwise indicated. [b] Reaction was carried out without solvent and worked up by MPLC (experimental procedure: see ref 1). [c] Reaction was worked up by MPLC (experimental procedure: see ref 1). [d] Reaction was carried out with DEA in toluene in a sealed tube and worked up by MPLC (experimental procedure: see ref 2). [e] Reaction was carried out with DEA in ionic liquid, [bmim]PF$_6$ and worked up by MPLC. The ionic liquid was recycled (detailed experimental procedure will be reported in due course).
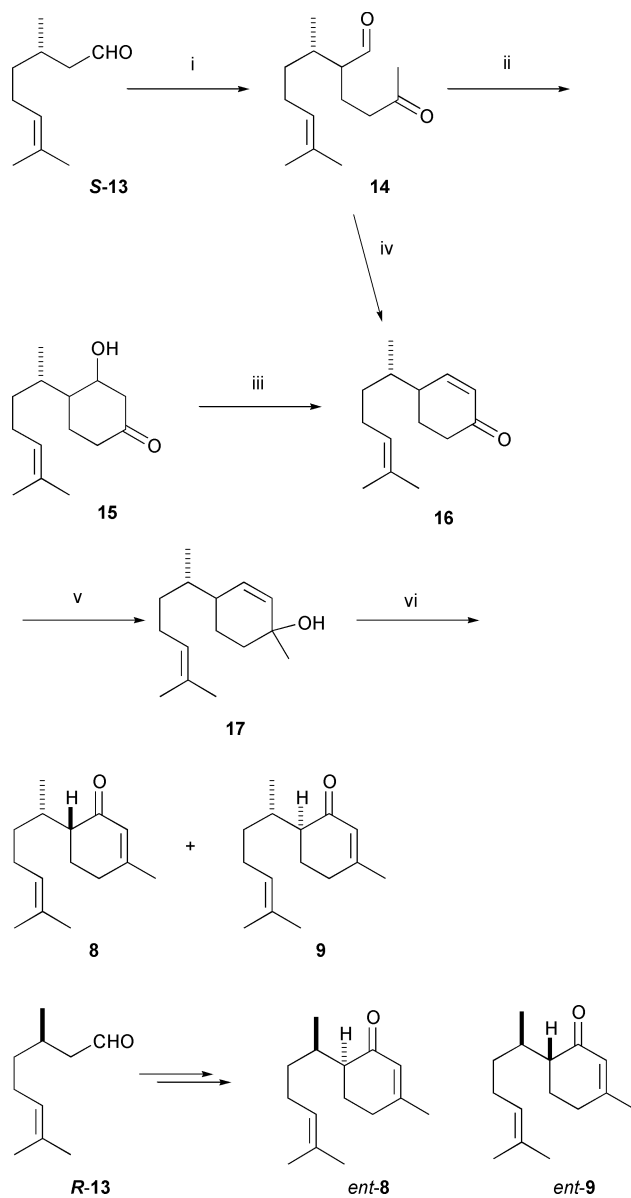

Scheme 2 *Reagents and conditions*: i, MVK, DEATMS (0.1 eq.), MeCN, reflux, 48 h, 96%; ii, TBAF, MeCN, 69%; iii, PTSA, benzene, 91%; iv, KOH, Bu$_4$NOH, THF, Et$_2$O, reflux, 4 h, 89%; v, MeLi, Et$_2$O, 96%; vi, PCC, CH$_2$Cl$_2$, 89%.

acetonitrile followed by evaporation of the solvent and subsequent Kugelrohr distillation. The reaction also proceeded with DEA (entries 3 and 4). The reaction in ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate [bmim]PF$_6$ (entry 4), did not require a sealed tube in spite of the highly volatile nature of DEA. The ionic liquid was recycled several times without the yields changing.

Intramolecular aldol condensation of the keto-aldehyde **14** was successful with TBAF in acetonitrile at room temperature to give hydroxy ketone **15** in 69% yield. Subsequent dehydration with a catalytic amount of PTSA gave a mixture of enone **16** in 91% yield along with a small amount of deconjugated enone. Alternatively, cyclisation of the keto-aldehyde **14** under phase transfer reaction conditions employing potassium hydroxide, tetrabutylammonium hydroxide in ether and THF, provided the enone **16**[6] directly in 89% yield as a mixture of diastereomers. Addition of methyllithium (MeLi) gave alcohol **17** in 96% yield. Oxidation of the alcohol **17** by PCC enabled oxidative rearrangement to provide enone in 89% yield as a mixture of diastereomers which were separated by MPLC to furnish natural enones **8** and **9**.

Enantiomeric enones, *ent*-**8** and *ent*-**9**, were also synthesized in the same way starting from (*R*)-citronellal *ent*-**13**.

Curcumene **10** is a constituent of *Curcuma aromatica*[7] and its total synthesis has been reported so far by several groups.[8] An attempt at aromatisation by dehydration of the alcohol **17** with PTSA in benzene followed by DDQ or chemical manganese dioxide (CMD)[9] oxidations resulted in the formation of complex mixtures. Then a phenylselanyl group was introduced to give selenide **18** in 84% yield by the reaction of the kinetic enolate of the enone *ent*-**16** generated by LDA with phenylselanyl chloride in the presence of HMPA (Scheme 3). Addition of
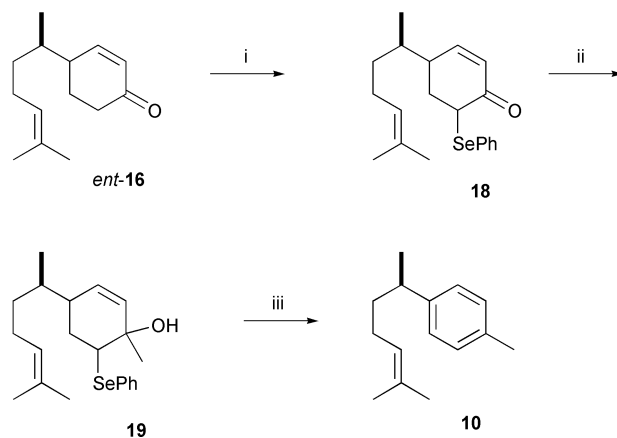
Scheme 3 *Reagents and conditions*: i, LDA, THF then PhSeCl, 84%; ii, MeLi, Et$_2$O, 77%; iii, PCC, CH$_2$Cl$_2$, 51%.

MeLi to the selenide **18** proceeded in 77% yield to give alcohol **19**. Though hydrogen peroxide oxidation of the alcohol **19** to **10** resulted in a low yield due to the very sensitive nature of the trisubstituted double bond, PCC oxidation furnished curcumene **10** in 51% yield by spontaneous elimination of benzeneselenenic acid and subsequent dehydration. Oxidative 1,3-migration of the hydroxy group of **19** was suppressed owing to facile elimination of benzeneselenenic acid. The overall yield from citronellal **13** was 28% in 6 steps, the shortest total synthesis in the highest yield of reported syntheses.

Curcuphenol **11** was isolated from the marine sponge *Didiscus flavus* and gorgonian *Pseudopterogorgia rigida*[10b] as well as from the terrestrial plant *Lasianthaea podocephala*.[10a] While the (*R*)-(−)-enantiomer **11** has antibacterial properties,[11b] the (*S*)-(+)-enantiomer **11** shows antitumor activity and has inhibitory activity against K-ATPase which transfers potassium ions into cells and sodium ions from cells.[8b] Several total syntheses of **11** have already appeared in the literature.[6,11] Though Jefferies *et al.*[6] illustrated aromatisation of the enones **8** and **9** by pyridinium perbromide leading to curcuphenol **11**, it was found that reproduction of the reported procedure was difficult. Dehydrogenation using sulfur gave curcuphenol **11** in only 8% yield with a large amount of enones **8** and **9** being recovered (Scheme 4). DDQ or CMD oxidation recovered the
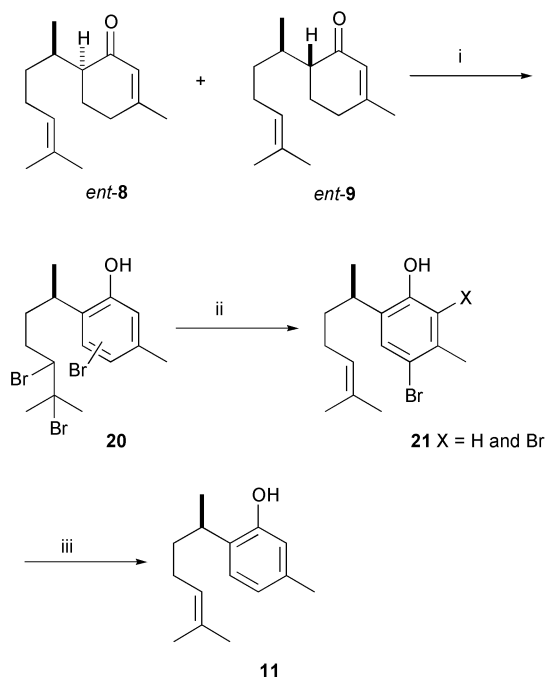
Scheme 4 *Reagents and conditions*: i, CuBr₂ MeCN; ii, Zn–AcOH, Et₂O; iii, *t*-BuLi, 44% in 3 steps.

starting enones completely. Other attempts to prepare enolic derivatives such as enol acetate or trimethylsilylenol ether also resulted in recovery of enones **8** and **9**. To this end, aromatisation of the enones **8** and **9** by cupric bromide[12] was investigated in order to furnish aromatic bromide **20**. The trisubstituted double bond was dibrominated due to its highly nucleophilic character. Fortunately, the trisubstituted double bond was regenerated by treatment of the bromide **20** with zinc in acetic acid to give phenol **21**. Finally, bromine atoms on the aromatic ring were removed by lithiation with *t*-BuLi to complete the synthesis of curcuphenol **11** in 44% overall yield from the enones **8** and **9**.

Elvirol **12** was isolated from *Elvira biflora* DC[13] and is known as a sesquiterpenoid which does not follow the isoprene rule. In addition to three syntheses of racemic **12**,[14a–c] Akita *et al.* described the first total synthesis[14d] of both enantiomers of **12** *via* enzymatic kinetic resolution as a key chirality generating step during the course of their synthetic study. Our synthesis was started by preparation of vinyl ketone **23** as a Michael acceptor (Scheme 5). Addition of vinylmagnesium bromide to (*R*)-citronellal **13** gave allyl alcohol **22** quantitatively. Oxidation of the alcohol **22** was investigated using various reagents and it was found that tetrapropylammonium perruthenate (TPAP) could be successfully employed to give vinyl ketone **23** which was used for further reaction without purification because of the volatility of the vinyl ketone **23**. Conjugate addition of propionaldehyde to the vinyl ketone **23** mediated by DEA afforded keto-aldehyde **24** in 48% overall yield in two steps. Reaction
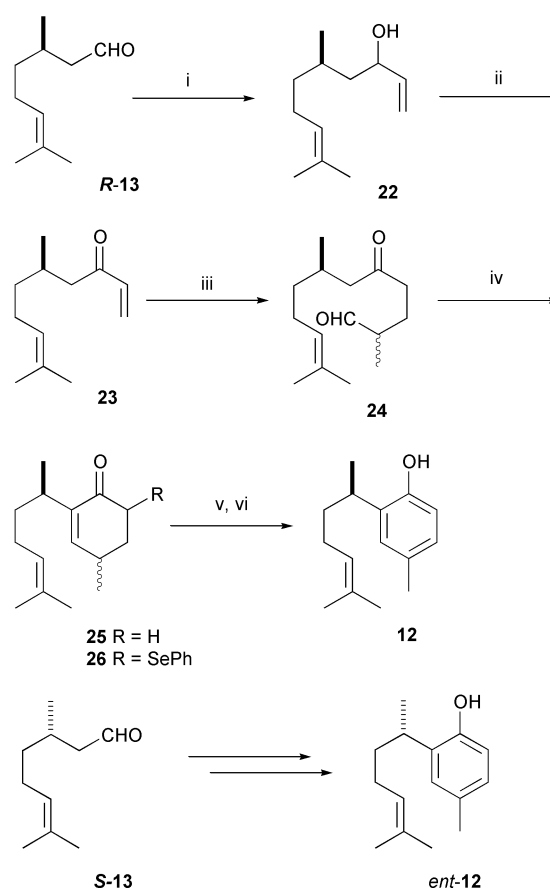
Scheme 5 *Reagents and conditions*: i, vinylmagnesium bromide, THF, 0 °C, quant.; ii, TPAP, NMO, CH₂Cl₂, 0 °C; iii, DEA, propionaldehyde, MeCN, sealed tube, 80 °C, 24 h, 48% in two steps; iv, 5% KOH, n-Bu₄NOH, THF, Et₂O, reflux, 95%; v, LDA, HMPA, THF, PhSeCl, 93%; vi, 30% H₂O₂, pyridine, CH₂Cl₂, 0 °C, 58%.

with DEATMS provided intractable materials contrary to our anticipation. Intramolecular aldol condensation under phase transfer reaction conditions gave enone **25** in 95% yield as a mixture of two diastereomers. Final aromatisation of the enone **25** *via* selenylation in 93% yield followed by oxidative elimination furnished elvirol **12** in 58% yield. Enantiomeric elvirol *ent*-**12** was also synthesized starting from (*S*)-citronellal **13**.

Spectral data of synthetic compounds **8**–**12** including values of optical rotations were completely identical with those of the natural products.

Thus, we have achieved total syntheses of both enantiomers of bisabolane sesquiterpenoids, α-bisabol-1-one **8**, its diastereomer **9**, curcumene **10**, curcuphenol **11** and elvirol **12** starting from citronellal as a chiral source. These syntheses demonstrate the utility of conjugate enamine addition of intact aldehydes to vinyl ketones catalysed by DEATMS or DEA. It is worthy of note that these syntheses have been accomplished in fewer steps with better overall yields without the use of any protecting groups.

Experimental

IR spectra were recorded on a Shimadzu FT/IR-4200 spectrophotometer for solutions in carbon tetrachloride unless otherwise indicated. ¹H-NMR spectra were obtained for solutions in deuteriochloroform with a Varian Gemini 200H (200 MHz) instrument with tetramethylsilane as internal standard. ¹³C-NMR spectra were obtained for solutions in deuteriochloroform with a Varian Gemini 200H (50 MHz) instrument with tetramethylsilane as internal standard. Specific rotations were measured (10^{-1}deg cm² g⁻¹) with a Horiba SEPA-200 spectrophotometer for solutions in chloroform. Medium-pressure liquid chromatographies (MPLC) were carried out on a JASCO

PRC-50 instrument with a silica gel packed column. Micro-analyses were carried out in the Instrumental Analysis Center for Chemistry, Tohoku University.

(3R)-3,7-Dimethyl-2-(3-oxobutyl)oct-6-enal *ent*-14

To a stirred solution of (R)-citronellal **13** (18 cm³, 100 mmol) in CH₃CN (400 cm³) was added MVK (12.5 cm³, 150 mmol) and DEATMS (1.9 cm³, 10 mmol) under a nitrogen atmosphere. After refluxing the solution for 48 h, excess MVK and CH₃CN were evaporated *in vacuo*. Kugelrohr distillation at 120–140 °C under 1.9 mmHg afforded the keto-aldehyde **14**[1] (21.62 g, 96%) as a mixture of 1 : 1 diastereomers; v_{max}/cm⁻¹ 2967, 2859, 2701, 1723 and 1163; δ_H (200 MHz) 0.89 (d, 1.5H, *J* 6.9 Hz), ‡ 0.99 (d, 1.5H, *J* 6.9 Hz), ‡ 1.60 (s, 3H), 1.69 (s, 3H), 2.10–1.08 (m, 7H), 2.13 (s, 3H), 2.65–2.26 (m, 3H), 5.68 (m, 1H), 9.60 (d, 0.5H, *J* 2.4 Hz)§ and 9.64 (d, 0.5H, *J* 2.9 Hz);§ δ_C (50 MHz) 16.9 (q), 17.6 (q), 19.7 (t), 25.5 (t), 25.6 (q), 29.9 (q), 32.2 (d), 32.3 (d), 33.8 (t), 41.4 (t), 56.2 (d), 123.8 (d), 131.9 (s) and 205.2 (s).

4-[(1R)-1,5-Dimethylhex-4-enyl]cyclohex-2-en-1-one 16

Method I. A mixture of the keto-aldehyde **14** (6.42 g, 28.6 mmol), aq. tetrabutylammonium hydroxide (5 cm³) and 5% aq. potassium hydroxide (220 cm³) in THF (62.5 cm³) and Et₂O (250 cm³) was heated at reflux for 4 h. The organic layer was extracted with ethyl acetate twice and washed with water and brine. Evaporation of the solvent followed by Kugelrohr distillation (120–140 °C, 1.9 mmHg) provided cyclohexenone **16**[6,8h,14b] (5.28 g, 89%).

Method II. (One pot synthesis from citronellal): a solution of (R)-citronellal **13** (75 µl, 0.4 mmol), MVK (85 µl, 1.0 mmol) and DEATMS (75 µl, 0.4 mmol) in CH₃CN (5 cm³) was refluxed for 20 h. After evaporation of the solvent *in vacuo*, to the residue in THF (10 cm³) and Et₂O (5 cm³) was added aq. 5% potassium hydroxide (5 cm³) and aq. tetrabutylammonium hydroxide (0.2 cm³) and the mixture was heated at reflux for 26 h. The organic layer was extracted with ethyl acetate twice, washed with water and brine, and dried over anhydrous sodium sulfate. After evaporation of the solvent followed by MPLC purification of the residue (eluent ethyl acetate–*n*-hexane = 1 : 20) gave the cyclohexenone **16** (66 mg, 89%); v_{max}/cm⁻¹ 2930, 1688, 1451 and 1381; δ_H (200 MHz) 0.89 (d, 1.5H, *J* 7.0 Hz), ‡ 0.93 (d, 1.5H, *J* 7.2 Hz), ‡ 1.61 (s, 3H), 1.69 (s, 3H), 1.12–2.60 (m, 11H), 5.10 (t, 1H, *J* 7.2 Hz), 6.02 (d, 1H, *J* 10.2 Hz) and 6.86 (m, 1H); anal. calc. for C₁₄H₂₂O: C, 81.50; H, 10.75; found: C, 81.42; H, 10.97%.

4-[(1R)-1,5-Dimethylhex-4-enyl]-1-methylcyclohex-2-en-1-ol 17

To a stirred solution of the enone **16** (104 mg, 0.5 mmol) in Et₂O (2 cm³) was added MeLi (1.5 cm³, 1.0 M in Et₂O, 1.5 mmol) at −78 °C under nitrogen atmosphere. After being stirred for 2.5 h, the reaction was quenched by addition of aq. ammonium chloride. The organic layer was extracted with ethyl acetate twice, washed with water and brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by column chromatography (eluent ethyl acetate–*n*-hexane = 1 : 15) provided more polar (85 mg, 76%) and less polar diastereomers **17**[6] (22 mg, 20%).

The more polar diastereomer of **17** had v_{max}/cm⁻¹ 3609, 3051, 2859, 1480 and 1377; δ_H (200 MHz) 0.86 (d, 1.5H, *J* 6.7 Hz), ‡ 0.82 (d, 1.5H, *J* 6.7 Hz), ‡ 1.28 (s, 3H), 1.60 (s, 3H), 1.69 (s, 3H), 1.20–2.20 (m, 11H), 5.10 (m, 1H) and 5.66 (m, 2H); anal. calc. for C₁₅H₂₆O: C, 81.02; H, 11.79; found: C, 80.75; H, 11.97%.

The less polar diastereomer of **17** had v_{max}/cm⁻¹ 3617, 3015, 2870, 1451 and 1377; δ_H (200 MHz) 0.84 (d, 1.5H, *J* 6.7 Hz), ‡

0.88 (d, 1.5H, *J* 6.7 Hz), ‡ 1.27 (s, 3H), 1.59 (s, 3H), 1.68 (s, 3H), 1.10–2.10 (m, 11H), 5.10 (m, 1H) and 5.66 (m, 2H); anal. calc. for C₁₅H₂₆O: C, 81.02; H, 11.79; found: C, 81.02; H, 12.19%.

(6R)-[(1R)-1,5-Dimethylhex-4-enyl]-3-methylcyclohex-2-en-1-one 8 and (6S)-[(1R)-1,5-dimethylhex-4-enyl]-3-methylcyclohex-2-en-1-one 9

To a stirred solution of the alcohol **17** (107 mg, 0.48 mmol) in CH₂Cl₂ (2 cm³) was added PCC (310 mg, 1.4 mmol) at 0 °C under a nitrogen atmosphere. After being stirred for 2.5 h at room temperature, the mixture was diluted with Et₂O. The organic layer was washed with aq. 5% sodium hydroxide, dilute hydrochloric acid, aq. sodium hydrogencarbonate and brine. Evaporation of the solvent followed by column chromatography of the residue (eluent ethyl acetate–*n*-hexane = 1 : 20) provided enones **8** and **9**[6] (107 mg, 89%) as a 1 : 1 mixture of diastereomers which was separated by MPLC.

The more polar diastereomer **9** was obtained in a 45% yield; v_{max}/cm⁻¹ 2965, 2857, 1672, 1443, 1379 and 1207; δ_H (200 MHz) 0.94 (d, 3H, *J* 6.8 Hz), 1.0–2.4 (m, 10H), 1.60 (s, 3H), 1.68 (s, 3H), 1.93 (s, 3H), 5.12 (m, 1H) and 5.84 (s, 1H); δ_C (50 MHz) 17.3 (q), 17.6 (q), 23.3 (t), 24.0 (q), 25.6 (q), 26.1 (t), 30.5 (t), 30.8 (d), 33.2 (t), 51.2 (d), 124.6 (d), 126.8 (d), 131.1 (s), 161.0 (s) and 201.0 (s).

The less polar diastereomer **8** was obtained in a 45% yield; $[a]_D^{24}$ −46.1 (*c* 3.1), lit.[5b] $[a]_D^{24}$ −37 (*c* 3.7); v_{max}/cm⁻¹ 2969, 2855, 1672, 1453, 1379 and 1290; δ_H (200 MHz) 0.79 (d, 3H, *J* 6.4 Hz), 1.2–2.5 (m, 10H), 1.59 (s, 3H), 1.68 (s, 3H), 1.93 (s, 3H), 5.10 (m, 1H) and 5.86 (s, 1H); δ_C (50 MHz) 15.5 (q), 17.6 (q), 22.3 (t), 24.1 (q), 25.7 (q), 25.9 (t), 30.2 (t), 30.8 (d), 34.6 (t), 49.8 (d), 124.4 (d), 127.0 (d), 131.3 (s), 161.2 (s) and 201.1 (s).

6-[(1S)-1,5-Dimethylhex-4-enyl]-3-methylcyclohex-2-en-1-one *ent*-8

Compounds *ent*-**8** and -**9** were both prepared in 27% overall yield from (S)-citronellal **13** according to the same procedure as the synthesis of **8**, *ent*-**8** had $[a]_D^{24}$ +37.1 (*c* 3.7), *ent*-**9** had $[a]_D^{24}$ −16.0 (*c* 3.7), lit.[6] $[a]_D^{24}$ −7.9 (*c* 3.7). Diastereomers **8** and **9** were separated by MPLC. Differences in optical rotational values might arise from a difference in the methods of separation, since **8** and **9** were separated by GLC in ref 6.

4-[(1S)-1,5-Dimethylhex-4-enyl]-6-(phenylselenamethyl)cyclohex-2-en-1-one 18

To a stirred solution of diisopropylamine (240 µl, 1.82 mmol) in THF (1.5 cm³) was added *n*-BuLi (1 cm³, 1.54 M in *n*-hexane, 1.54 mmol) at 0 °C under nitrogen. After being stirred for 15 min, HMPA (250 µl, 1.44 mmol) was added. The cyclohexenone *ent*-**16** (99 mg, 0.48 mmol) in THF (2 cm³) was added dropwise at −78 °C and the resulting solution was warmed to 0 °C over 1 h. To the solution at −78 °C was added a solution of phenyl-selanyl chloride (184 mg, 0.96 mmol) in THF (1.5 cm³). After being stirred for 5 min, the reaction was quenched by addition of aq. ammonium chloride. The organic layer was extracted with ethyl acetate twice, washed with water and brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent *in vacuo* followed by MPLC separation (eluent ethyl acetate–*n*-hexane = 2 : 7) gave selenide **18** (146 mg, 84%) along with recovered starting enone **16** (12 mg, 12%); v_{max}/cm⁻¹ 3075, 2967, 2957, 1678, 1453, 1383 and 1248; δ_H (200 MHz) 0.87 (d, 1.5H, *J* 5.7 Hz), ‡ 0.91 (d, 1.5H, *J* 5.7 Hz), ‡ 1.62 (s, 3H), 1.70 (m, 3H), 1.12–2.40 (m, 7H), 2.74 (m, 1H), 4.00 (t, 1H, *J* 3.5 Hz), 5.09 (t, 1H, *J* 7.2Hz), 6.01 (d, 1H, *J* 10.2 Hz), 6.88 (m, 1H), 7.28 (m, 3H) and 7.60 (m, 2H); anal. calc. for C₂₀H₂₆OSe: C, 66.47; H, 7.25; found: C, 66.19; H, 7.19%.

4-[(1S)-1,5-Dimethylhex-4-enyl]-1-methyl-6-(phenylselena-methyl)cyclohex-2-en-1-ol 19

To a stirred solution of the selenide **18** (64 mg, 0.18 mmol) in

‡ Total 3H.
§ Total 1H.

Et$_2$O (1.5 cm^3) was added MeLi (1.7 cm^3, 1.03 M solution in Et$_2$O, 1.8 mmol) at −78 °C under a nitrogen atmosphere. After being stirred for 5.5 h with gradual warming to 0 °C, the reaction was quenched by addition of aq. ammonium chloride. The organic layer was extracted with ethyl acetate twice, washed with water and brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by MPLC purification (eluent ethyl acetate–n-hexane = 1 : 10) provided more polar (23 mg, 34%) and less polar (30 mg, 43%) diastereomers of **19**.

The more polar diastereomer **19** had v_{max}/cm^{-1} 3568, 2967, 2859, 2368, 1581, 1478 and 1379; δ_H (200 MHz) 0.80 (d, 3H, J 6.8 Hz), 1.57 (s, 3H), 1.67 (s, 3H), 1.00–2.40 (m, 12H), 3.51 (dd, 1H, J 13.6, 3.3 Hz), 5.08 (t, 1H, J 7.1 Hz), 5.48 (d, 1H, J 10.3 Hz), 5.72 (dd, 1H, J 10.3, 2.6 Hz), 7.28 (m, 3H) and 7.60 (m, 2H).

The less polar diastereomer **19** had v_{max}/cm^{-1} 3568, 2967, 2859, 2368, 1581, 1478 and 1379; δ_H (200 MHz) 0.86 (d, 3H, J 6.8 Hz), 1.57 (s, 3H), 1.67 (s, 3H), 1.00–2.50 (m, 12H), 3.61 (dd, 1H, J 13.1, 3.7 Hz), 5.06 (t, 1H, J 7.1 Hz), 5.70 (d, 1H, J 10.0 Hz), 5.78 (dd, 1H, J 10.0, 2.2 Hz), 7.27 (m, 3H) and 7.61 (m, 2H); anal. calc. for C$_{21}$H$_{30}$OSe: C, 66.83; H, 8.01; found: C, 66.62; H, 8.23%.

4-[(1S)-1,5-Dimethylhex-4-enyl]-1-methylbenzene 10 (curcumene)

To a stirred slurry of PCC (138 mg, 0.64 mmol) in CH$_2$Cl$_2$ (1 cm^3) was added the alcohol **19** (121 mg, 0.32 mmol) in CH$_2$Cl$_2$ (1 cm^3) at 0 °C under a nitrogen atmosphere. After being stirred for 1.5 h, the mixture was diluted with Et$_2$O. The organic layer was washed with aq. 5% sodium hydroxide, dil. hydrochloric acid, aq. sodium hydrogencarbonate and brine. Evaporation of the solvent *in vacuo* followed by column chromatography of the residue (eluent n-hexane) afforded curcumene **10** (33 mg, 51%); $[a]_D^{23}$ −46.73 (c 0.95), lit.[8e] $[a]_D^{23}$ −46.2 (c 0.95); v_{max}/cm^{-1} 2926, 2368, 1514, 1453 and 1377; δ_H (200 MHz) 1.21 (d, 3H, J 6.9 Hz), 1.56 (br s, 3H), 1.67 (br s, 3H), 1.5–2.1 (m, 4H), 2.32 (s, 3H), 2.76 (sextet, 1H, J 6.9 Hz), 5.10 (m, 1H) and 7.08 (s, 4H); δ_C (50 MHz) 17.7 (s), 21.0 (q), 22.5 (q), 25.7 (q), 26.2 (t), 38.4 (t), 39.0 (d), 124.5 (d), 126.9 (d), 128.9 (d), 131.4 (s), 135.1 (s) and 144.6 (s).

2-[(1R)-4,5-Dibromo-1,5-dimethylhexyl]-4-bromo-5-methylphenol 20

A mixture of the enones **8** and **9** (122 mg, 0.576 mmol), CuBr$_2$ (1.033 g, 4.63 mmol) in acetonitrile (6 cm^3) was stirred at room temperature for 26 h. After removal of copper residue by filtration, the filtrate was diluted with ethyl acetate and the organic layer was washed with water and brine. Evaporation of the solvent gave a mixture of bromides **20** which was used for further reaction without purification.

Crude bromides **20** had δ_H (200 MHz) 1.25 (d, 3H, J 6.7 Hz), 1.50–2.20 (m, 4H, C8), 1.74 (s, 1.5H), 1.78 (s, 1.5H), 1.94 (s, 1.5H), 1.96 (s, 1.5H), 2.30 (s, 3H), 3.05 (m, 1H), 4.21 (t, 1H, J 10 Hz), 4.73 (s, 0.5H), 4.76 (s, 0.5H), 6.62 (s, 0.5H), 6.64 (s, 0.5H), 7.27 (s, 0.5H) and 7.28 (s, 0.5H).

2-[(1R)-1,5-Dimethylhex-4-enyl]-4-bromo-5-methylphenol 21

A mixture of the crude bromides **20** and zinc (195 mg, 2.98 mmol) in acetic acid (35 µl, 0.611 mmol) and ether (6.5 cm^3) was stirred at room temperature for 100 min. After filtration of excess Zn, the filtrate was diluted with ether and washed with water and brine. Evaporation of the solvent gave an inseparable mixture of bromides **21** which was used for further reaction without purification.

Crude bromide **21** had δ_H (200 MHz) 1.21 (d, 3H, J 7.0 Hz), 1.40–1.80 (m, 2H), 1.54 (s, 3H), 1.68 (s, 3H), 1.93 (q, 2H, J 7.1 Hz), 2.29 (s, 3H), 2.92 (sextet, 1H, J 7.0 Hz), 4.75 (s, 1H), 5.11 (t × sept, 1H, J 7.1, 1.3 Hz), 6.65 (s, 1H) and 7.24 (s, 1H).

2-[(1R)-1,5-Dimethylhex-4-enyl]-5-methylphenol 11 (Curcuphenol)

To a stirred solution of the mixture of crude bromides **21** in THF (6 cm^3) at 0 °C under nitrogen atmosphere was added t-BuLi (2.4 cm^3, 1.43 M solution in n-pentane, 3.4 mmol) and the resulting solution was warmed to room temperature. After being stirred for 1 h, the reaction was quenched by addition of aq. ammonium chloride. The organic layer was extracted with ethyl acetate four times. The combined organic layers were washed with water and brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent *in vacuo* followed by MPLC separation (eluent ethyl acetate–n-hexane = 1 : 5) gave curcuphenol **11** (53 mg, 44% from a mixture of enone **8** and **9** in 3 steps); $[a]_D^{20}$ −22.7 (c 1.67), lit.[11b] *ent*-**11** $[a]_D^{20}$ 24.8 (c 1.0); v_{max}/cm^{-1} 3613, 2926, 1514, 1453 and 1377; δ_H (200 MHz) 1.22 (d, 3H, J 7.1 Hz), 1.54 (s, 3H), 1.68 (s, 3H), 1.40–1.80 (m, 2H), 1.93 (q, 2H, J 7.2 Hz), 2.27 (s, 3H), 2.96 (sextet, 1H, J 7.1 Hz), 4.67 (s, 1H), 5.12 (t × sept, 1H, J 7.2, 1.1 Hz), 6.59 (s, 1H), 6.72 (d, 1H, J 7.5 Hz) and 7.03 (d, 1H, J 7.5 Hz); δ_C (50 MHz) 17.7 (q), 20.9 (q), 21.1 (q), 25.7 (q), 26.1 (t), 31.4 (d), 37.3 (t), 116.1 (d), 124.5 (d), 126.8 (d), 129.9 (s), 132.0 (s), 136.5 (s) and 152.8 (s); anal. calc. for C$_{15}$H$_{24}$O: C, 81.76; H, 10.98; found: C, 81.61; H, 11.15%.

(5R)-5,9-Dimethyldeca-1,8-dien-3-one 23

To a stirred solution of magnesium (267 mg, 11 mmol) in THF (1.0 cm^3) was added vinyl bromide (11 cm^3, 1.0 M solution in THF, 11 mmol) dropwise under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 2 h and then diluted with THF (10 cm^3). (R)-(+)-Citronellal **13** (0.95 cm^3, 5.24 mmol) was added slowly in an ice–water bath and then the solution was stirred at room temperature for 3 h. The reaction was quenched by addition of aq. ammonium chloride. The organic layer was extracted with ethyl acetate twice. The combined organic layers were washed with water and brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent *in vacuo* followed by column chromatography of the residue (eluent ethyl acetate–n-hexane = 1 : 10) provided allyl alcohol **22** (quant.) as a 1 : 1 mixture of diastereomers which was separated by MPLC.

The more polar diastereomer **22** had v_{max}/cm^{-1} 3622, 2964, 2855, 1456, 992 and 926; δ_H (200 MHz) 0.92 (d, J 6.6 Hz, 3H), 1.00–1.79 (m, 5H), 1.60 (s, 3H), 1.68 (d, J 1.1 Hz, 3H), 1.98 (m, 2H), 4.19 (q, J 6.7 Hz, 1H), 5.04–5.29 (m, 3H) and 5.84 (ddd, J 15.4, 10.3, 6.6 Hz, 1H); δ_C (50 MHz) 17.6 (q), 19.9 (q), 25.3 (t), 25.7 (q), 29.0 (d), 36.9 (t), 44.3 (t), 71.6 (d), 114.6 (t), 124.6 (d), 131.1 (s) and 141.4 (s).

The less polar diastereomer **22** had v_{max}/cm^{-1} 3623, 2928, 2855, 1453, 992 and 926; δ_H (200 MHz) 0.94 (d, J 6.6 Hz, 3H), 1.05–1.79 (m, 5H), 1.60 (s, 3H), 1.68 (s, 3H), 1.98 (m, 2H), 4.20 (m, 1H), 5.04–5.28 (m, 3H) and 5.88 (ddd, J 17.2, 10.3, 6.2 Hz, 1H); δ_C (50 MHz) 17.9 (q), 19.2 (q), 25.4 (t), 25.7 (q), 28.8 (d), 37.5 (t), 44.4 (t), 70.1 (d), 114.0 (t), 124.7 (d), 131.2 (s) and 141.8 (s); anal. calc. for C$_{12}$H$_{22}$O: C, 79.06; H, 12.16; found: C, 78.80; H, 12.24%.

To a stirred solution of a mixture of allyl alcohol **22** (182 mg, 1.00 mmol) and 4 Å molecular sieve powder (210 mg) in CH$_2$Cl$_2$ (10 cm^3) were added TPAP (71 mg, 0.20 mmol) and N-methylmorpholine N-oxide (356 mg, 3.03 mmol) at 0 °C under a nitrogen atmosphere. After being stirred for 2 h, the reaction mixture was diluted with ethyl acetate and filtered through a pad of Celite.

Evaporation of the solvent gave vinyl ketone **23** which was used for further reaction without purification due to its highly volatile nature.

(7R)-2,7,11-Trimethyl-5-oxododec-10-enal 24

A solution of crude vinyl ketone **23**, propionaldehyde (145 µl, 2.02 mmol) and DEA (52 µl, 0.5 mmol) in CH$_3$CN (2 cm^3) in a

sealed tube was heated at 80 °C for 24 h. Evaporation of the solvent *in vacuo* followed by MPLC separation (eluent ethyl acetate–*n*-hexane = 1: 3) gave keto-aldehyde **24** (115 mg, 48% from allyl alcohol **22** in 2 steps); v_{max}/cm^{-1} 2967, 2710, 1731, 1724, 1460, 1377, 1121 and 1047; δ_H (200 MHz) 0.89 (d, 3H, *J* 6.5 Hz), 1.12 (d, 3H, *J* 7.0 Hz), 1.10–2.50 (m, 12H), 1.60 (s, 3H), 1.68 (s, 3H), 5.04 (t × sept, 1H t, *J* 7.1, 1.4 Hz) and 9.60 (d, 1H, *J* 1.4 Hz); δ_C (50 MHz) 13.4 (q), 17.5 (q), 19.6 (q), 23.9 (t), 25.3 (t), 25.6 (q), 28.8 (d), 36.8 (t), 40.0 (t), 45.4 (d), 50.2 (t), 124.1 (d), 131.3 (s), 204.3 (d) and 209.8 (s).

2-[(1*R*)-1,5-Dimethylhex-4-enyl]-4-methylcyclohex-2-en-1-one 25

A mixture of the keto-aldehyde **24** (115 mg, 0.48 mmol), aq. tetrabutylammonium hydroxide (0.6 cm³) and 5% aq. potassium hydroxide (10 cm³) in THF (20 cm³) and Et₂O (10 cm³) was heated at reflux for 3 h. The organic layer was extracted with ethyl acetate twice and the combined organic layers were washed with water and brine. Evaporation of the solvent followed by MPLC separation (eluent ethyl acetate–*n*-hexane = 1 : 5) gave cyclohexenone **25** (101.3 mg, 95%); v_{max}/cm^{-1} 2963, 2932, 1678, 1456 and 1379; δ_H (200 MHz) 0.99 (d, 1.5H, *J* 7.0 Hz), 1.00 (d, 1.5H, *J* 7.0 Hz), 1.38 (d, 1.5H, *J* 7.1 Hz), 1.39 (d, 1.5H, *J* 7.1 Hz), 1.20–2.85 (m, 10H), 1.57 (s, 3H), 1.67 (s, 3H), 5.09 (m, 1H), 6.45 (s, 0.5H) and 6.46 (s, 0.5H); δ_C (50 MHz) 17.6 (q), 20.0 (q), 20.2 (q), 20.8 (q), 25.6 (q), 25.86 (t), 25.93 (t), 30.8 (d), 30.92 (t), 30.97 (t), 31.0 (d), 31.3 (d), 36.0 (t), 36.2 (t), 37.6 (t), 124.5 (d), 131.1 (s), 131.2 (s), 143.1 (s), 143.2 (s), 148.9 (d), 198.90 (s) and 198.99 (s); anal. calc. for C₁₅H₂₄O: C, 81.76; H, 10.98; found: C, 81.64; H, 11.29%.

2-[(1*R*)-1,5-Dimethylhex-4-enyl]-4-methylphenol 12 (Elvirol)

To a stirred solution of diisopropylamine (132.5 μl, 1.01 mmol) in THF (2 cm³) was added *n*-BuLi (0.56 cm³, 1.59 M in *n*-hexane, 0.89 mmol) at 0 °C under nitrogen. After being stirred for 15 min, HMPA (140 μl, 0.80 mmol) was added. The cyclohexenone **25** (84 mg, 0.38 mmol) in THF (2 cm³) was added dropwise at −78 °C and the resulting solution was warmed to 0 °C over 1 h. To the solution at −78 °C was added a solution of phenylselanyl chloride (158 mg, 0.82 mmol) in THF (2 cm³). After being stirred for 15 min, the reaction was quenched by addition of aq. ammonium chloride. The organic layer was extracted with ethyl acetate four times and the combined organic layers were washed with water and brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent *in vacuo* followed by MPLC separation (eluent ethyl acetate–*n*-hexane = 1 : 5) gave more polar (69 mg, 48%) and less polar (64 mg, 45%) diastereomers **26**.

The more polar diastereomer **26** had v_{max}/cm^{-1} 3061, 2965, 2930, 1672, 1456, 1379 and 1179; δ_H (200 MHz) 1.00 (d, 1.5H, *J* 6.9 Hz), 1.08 (d, 1.5H, *J* 7.1 Hz), 1.13 (d, 1.5H, *J* 7.1 Hz), 1.20–2.40 (m, 6H), 1.56 (s, 3H), 1.67 (s, 3H), 2.75 (m, 2H), 3.96 (t, 0.6H, *J* 3.6 Hz), 4.20 (dd, 0.4H, *J* 13.6, 4.9 Hz), 5.09 (m, 1H), 6.30 (s, 0.6H), 6.40 (s, 0.4H), 7.29 (m, 3H) and 7.59 (m, 2H); δ_C (50 MHz) 17.6 (q), 17.7 (q), 19.7 (q), 19.9 (q), 20.9 (q), 21.2 (q), 25.7 (q), 25.8 (q), 25.9 (t), 28.8 (d), 31.4 (d), 31.7 (d), 32.9 (d), 36.0 (t), 37.3 (t), 39.2 (t), 47.8 (d), 49.9 (d), 124.4 (d), 124.5 (d), 127.8 (d), 128.0 (d), 128.95 (d), 128.98 (d), 131.13 (s), 131.24 (s), 134.9 (d), 135.4 (d), 141.5 (s), 142.6 (s), 147.1 (d), 148.6 (d), 194.4 (s) and 195.9 (s).

The less polar diastereomer **26** had v_{max}/cm^{-1} 3075, 2965, 2930, 1674, 1453, 1379 and 1171; δ_H (200 MHz) 1.00 (d, 1.5H, *J* 6.9 Hz), 1.02 (d, 1.5H, *J* 6.9 Hz), 1.07 (d, 1.5H, *J* 7.1 Hz), 1.13 (d, 1.5H, *J* 7.1 Hz), 1.20–2.40 (m, 6H), 1.56 (s, 3H), 1.67 (s, 3H), 2.70 (m, 2H), 3.97 (t, 0.5H, *J* 3.5 Hz), 4.22 (dd, 0.5H, *J* 13.7, 4.9 Hz), 5.09 (m, 1H), 6.35 (s, 0.5H), 6.40 (s, 0.5H), 7.29 (m, 3H) and 7.59 (m, 2H); δ_C (50 MHz) 17.6 (q), 20.0 (q), 20.9 (q), 21.2 (q), 25.7 (q), 25.9 (t), 28.9 (d), 31.7 (d), 31.8 (d), 32.9 (d), 35.6 (t), 35.9 (t), 37.3 (t), 39.4 (t), 47.7 (d), 50.1 (d), 124.4 (d), 124.5

(d), 127.8 (d), 128.1 (d), 128.2 (d),128.95 (d), 129.00 (d), 131.2 (s), 131.3 (s), 134.9 (d), 135.5 (d), 141.3 (s), 142.6 (s), 147.1 (d), 148.6 (d), 194.4 (s) and 196.0 (s). anal. calc. for C₂₀H₂₈OSe: C, 67.19; H, 7.52; found: C, 67.32; H 7.41%.

To a solution of selenide **26** (69 mg, 0.18 mmol) in CH₂Cl₂ (4 cm³) was added pyridine (28 μl, 0.36 mmol) and 30% aq. hydrogen peroxide (31 μl, 0.27 mmol) at 0 °C. After being stirred for 2.5 h, the reaction was quenched by addition of aq. ammonium chloride and aq. sodium thiosulfate. The organic layer was extracted with ethyl acetate four times and the combined organic layers were washed with water and brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent *in vacuo* followed by MPLC separation (eluent ethyl acetate–*n*-hexane = 1 : 5) gave elvirol **12** (23 mg, 58%); $[\alpha]_D^{30}$ −35.6 (*c* 0.18), lit.[14a] $[\alpha]_D^{30}$ −37.2 (*c* 0.23); v_{max}/cm^{-1} 3615, 2965, 2924, 2859, 2361, 1501, 1452, 1377 and 1179; δ_H (200 MHz) 1.23 (d, 3H, *J* 7.0 Hz), 1.54 (s, 3H), 1.69 (s, 3H), 1.55–1.66 (m, 2H), 1.91 (dddd, 1H, *J* 14.0, 7.0, 7.0, 7.0 Hz), 1.96 (dddd, 1H, *J* 14.0, 7.0, 7.0, 7.0 Hz), 2.26 (s, 3H), 2.96 (sextet, 1H, *J* 7.0 Hz), 4.55 (s, 1H), 5.13 (t, 1H, *J* 7.0 Hz), 6.65 (d, 1H, *J* 7.9 Hz), 6.85 (ddd, 1H, *J* 7.9, 2.0, 1.1 Hz) and 6.94 (d, 1H, *J* 72.0 Hz); δ_C (50 MHz) 17.6 (q), 20.7 (q), 20.9 (q), 25.7 (q), 26.0 (t), 31.6 (d), 37.2 (t), 115.2 (d), 124.5 (d), 127.0 (d), 127.5 (d), 130.0 (s), 132.0 (s), 132.7 (d) and 150.7 (s).

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