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PAPER

Efficient synthesis of the anticancer β-elemene and other bioactive elemanes from sustainable germacrone†

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Highly efficient preparations of anticancer β-elemene and other bioactive elemanes were carried out using the natural product germacrone as a renewable starting material. The syntheses were achieved in only 3–5 steps with excellent overall yields (43–54%). An enantioselective approach to these molecules is also described

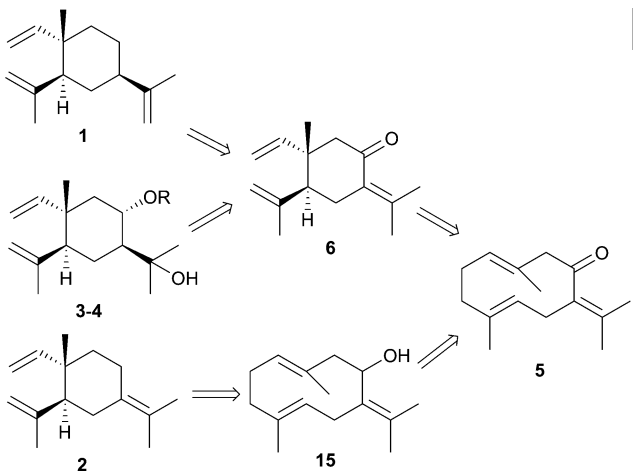
Introduction

The sesquiterpenes β-elemene (**1**) and γ-elemene (**2**) are usually minor components of the essential oils of numerous plants.[1] Compound **1** is a potent antitumor agent[2] which has a selective inhibitory effect on cerebrovascular endothelial cells and has given excellent results as an antitumor agent in the treatment of brain tumors and suppresses the growth of brain metastasis from lung cancer. It induces apoptosis, limits cellular differentiation and inhibits of neoplastic metastasis proving to be a good candidate for use in chemotherapy in the treatment of neoplasms in the lung, colon, stomach, brain *etc*.[3] Some formulations for pharmacological uses containing **1** or **1** plus small quantities of **2**, have been patented[3] and some more polar derivatives with enhanced activity have also recently been described,[3,4] and are now in application for clinical studies in the United States.[5] 8α-Hydroxy-β-elemene (**3**) and 8α-acetoxy-β-elemene (**4**) are sesquiterpenes isolated from *Juniperus* species[6] featuring antifungal activity against eczema fungi and also insecticidal activity.[7]

Concerning the preparation of these four natural elemanes, several multistep syntheses of **1** and **2** have been reported[1a,8] or patented.[4b] However, the synthesis of **3** and **4** has still not been reported, despite the interesting properties attributable to these compounds.

In the field of the synthesis of potent bioactive natural products, it should be remarked that the efficiency of synthetic approaches including the use of renewable starting material is generally far ahead of the current capabilities of chemical total synthesis. For instance, tonnes of 10-deacetyl baccatin III are produced by the needles of *Taxus baccata* yew tree as a renewable starting material for the commercial semi-synthesis of taxol,[9] in contrast with the few milligrams available from the total synthesis, and only after significant effort. In this sense we believe that structure and functionality of germacrone (**5**), found as the major component in the oils of *Baccharis latifolia*[10] and *Geranium macrorrhizum*[11] may well serve as a versatile building block for the efficient preparation of a wide variety of bioactive molecules.[12]

In this context, and given the increasing interest of the aforementioned elemanes, we describe in this paper a convenient methodology for the semisynthesis of the elemanes **1–4** using **5** as starting material (Scheme 1).



Scheme 1 Retrosynthetic analysis for the compounds **1–4**.

Results and discussion

The retrosynthetic planning to **1–4** includes as key step a Cope rearrangement of the germacrane skeleton to provide the elemane skeleton present in the target molecules as the key step (Scheme 1).

Some years ago, our research group described a Pd-promoted rearrangement of germacranolides to either elemanolides or eudesmanolides, depending on the experimental conditions.[13]

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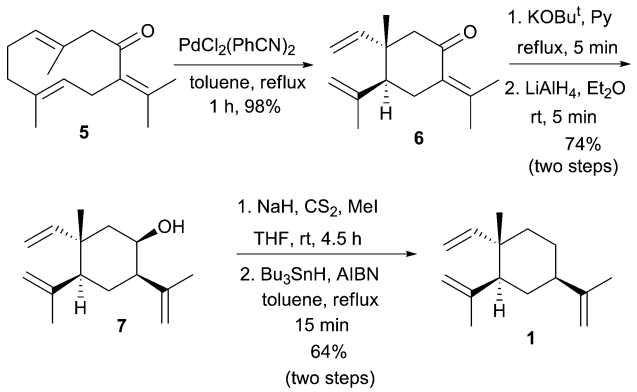
† Electronic supplementary information (ESI) available: COSY, HSQC, HMBC and NOE diff. data of epoxide **13**, and NMR spectra of new intermediates and final products. See DOI: 10.1039/c0ob00467g

Table 1 Pd(II) catalyzed Cope rearrangement of germacrone (**5**)

Method	Conditions	Yield of **6** (%)
A	Toluene, rt, Pd(II) (0.2 equiv), 5 h.	82
B	Toluene, reflux, Pd(II) (0.2 equiv), 60 min.	98
C	Toluene, reflux, Pd(II) (0.04 equiv), 6.5 h.	72

Based in this precedent, we started this work by subjecting germacrone (**5**), isolated in multigram scale from the essential oil of *Geranium macrorrhizum* or *Baccharis latifolia*, to Pd(II)-catalyzed Cope rearrangement under different experimental conditions. The results of this study are summarized in Table 1, method B featuring the best conditions where the yield obtained of elemenone (**6**) was nearly quantitative (98%).[14]

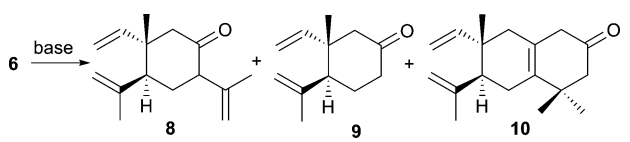
Once we had elemenone (**6**) in our hands, the following steps towards the synthesis of **1** supposed the deconjugation of the α,β-carbonyl system, and then the reduction of the carbonyl group to give **7**, which after the corresponding deoxygenation would produce **1** (Scheme 2).



Scheme 2 Synthesis of β-elemene (**1**) from germacrone (**5**).

To achieve the desired deconjugation, enone **6** was treated with different bases. The results obtained (Table 2) showed that no alteration of the starting material was observed with hard bases (protonation of the kinetic enolate), and only by using KOBu^t in pyridine at reflux[15] **6** afforded, after 2.5 h, the deconjugated ketone **8** and by-products **9–10**. Compound **9** was the result of a retroaldolic condensation which also produced acetone,[16] whereas ketone **10** was produced after a Robinson annulation between **6** and the acetone previously formed.

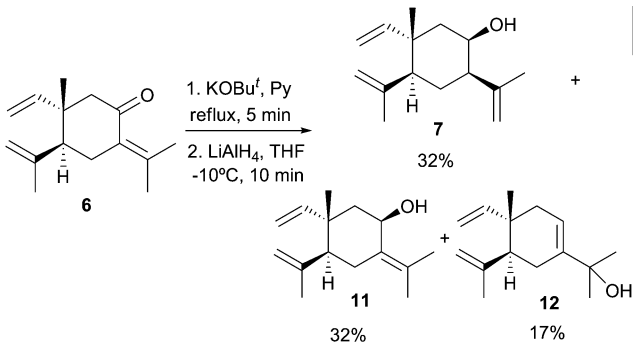
Table 2 Deconjugation of **6** with different bases



Base	Temp. (°C)	Time (h)	**8**	**9**	**10**
LDA/HMPA	–78	24	—	—	—
NaH	rt	1[a]	—	—	—
KOBu^t/Py	reflux	2.5	40	22	5

[a] Decomposition of **6** was observed after long reaction times.

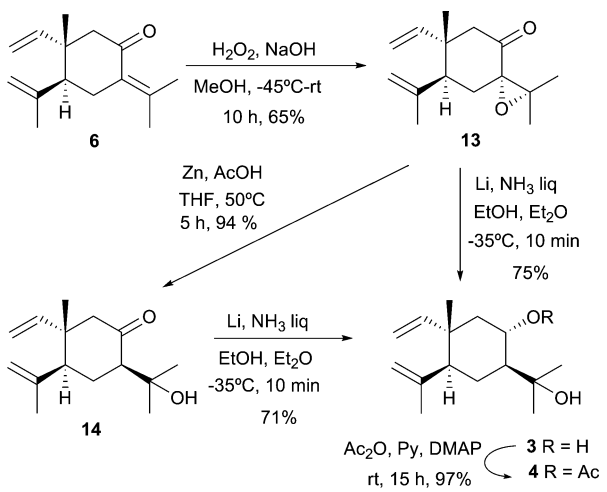
Since compound **8** proved to be unstable, the deconjugation reaction was repeated under the same conditions but shortening the reaction time significantly (5 min *versus* 2.5 h), and then, the thus-obtained resulting crude reaction was quickly reduced with $LiAlH_4$. Under these conditions, the desired alcohol **7** was obtained in 32% yield, together with its isomers **11**[17] (32%) and **12**[18] (17%) (Scheme 3). In the ^1H NMR spectrum of 7, H-8 appears as a broad singlet, which determines the β orientation of the hydroxyl group.



Scheme 3 Deconjugation of **6** with KOBu^t/Py followed by fast LAH reduction.

In order to increase the yield of these two steps, the $LiAlH_4$ reduction was carried out before the work-up of the deconjugation reaction, however the reduction was slow and the yield of **7** was only 10%. Gratifyingly, ketone reduction could be carried out efficiently if KOBu^t is removed from the crude by Et_2O–H_2O partitioning, and the dried ether phase is added to a suspension of $LiAlH_4$ in ether. Alcohol **7** was thus obtained with an acceptable yield of 74%. Barton–McCombie deoxygenation[19] of **7** yielded (±)-β-elemene (**1**) (Scheme 2) with a yield of 64%. MS, ^1H and ^{13}C NMR of our synthetic β-elemene coincide completely with those of the natural product.[8c]

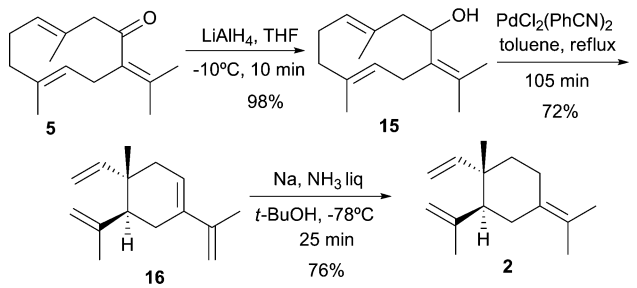
Once the synthesis of β-elemene (**1**) was achieved, we decided to focus our efforts to the synthesis of its congeners 8α-hydroxy-β-elemene (**3**) and 8α-acetoxy-β-elemene (**4**) (Scheme 4). Thus, selective epoxidation of the double bond 7,11 of elemenone was carried out diastereoeselectively with the hydroperoxide anion to



Scheme 4 Synthesis of **3–4** from **6**.

obtain the α-epoxide **13** with a yield of 65%, together with a 28% of the β-isomer (**13b**). The nOe effect observed between H-13 and H-6 and H-14 suggested that the stereochemistry of epoxy group in **13** is that depicted in Scheme 4. Epoxide **13**, was then treated with Zn/AcOH. In this process, the zinc enolate intermediate evolves to the most stable keto-alcohol, that is compound **14**,[20] where the 2-hydroxypropyl moiety is disposed equatorially. Reduction of **14** with lithium in liquid ammonia–EtOH led with total stereoselectivity to the most stable equatorial hydroxyl group, yielding (±)-8α-hydroxy-β-elemol (**3**) (71%). The efficiency of this synthesis could be improved by treating epoxyketone **13** with excess of lithium in liquid ammonia, a reagent that proved to achieve the required double reduction to afford **3** in one single step with a 75% yield. This transformation also permitted the confirmation of the stereochemistry previously assigned to epoxide **13**. Standard acetylation of **3** gave (±)-8α-acetoxy-β-elemol (**4**) (97%). The spectroscopic data of both synthetic products were identical to those of the authentic natural samples.[6]

Finally, γ-elemene (**2**) was synthesized as depicted in Scheme 5. This approach included as key step the 1,4 reduction of the diene intermediate **16**, a process which permitted the suitable location for the tetrasubstituted double bond. Starting again from germacrone, germacrol (**15**)[21] was obtained almost quantitatively after $LiAlH_4$ reduction.



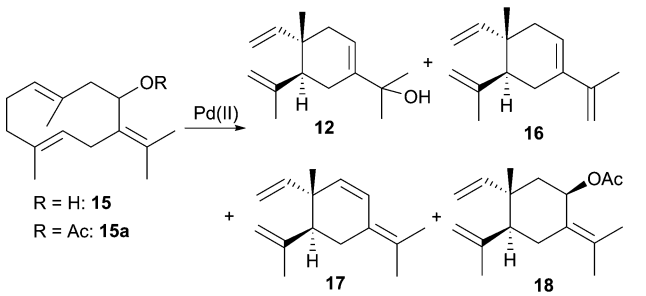
Scheme 5 Synthesis of γ-elemene (**2**) from **5**.

At this point, Pd catalyzed Cope rearrangement of **15** and of its acetate **15a** was studied under different conditions by varying the temperature, reaction time and the Pd(II) loading (Table 3).

Thus for compound **15**, when this transformation was performed at room temperature, compound **12** turned out to be the major compound, as result of an allylic rearrangement of the C8 hydroxyl group at C11 in addition to the Cope rearrangement. Fortunately, heating the reaction media led to the target diene **16**. Considerable experimentation was needed to find the best conditions for this transformation (method E, Table 3). In the case of compound **15a**, similar results were obtained, although at room temperature the major reaction product was acetate **18**, whereas at refluxing toluene the major compound turned out to be elemene **16**. This data indicates that the Cope rearrangement is previous to the loss of the acetate moiety. Finally, reduction of **16** with sodium in liquid ammonia yielded uneventfully (±)-γ-elemene (**2**). MS, ^1H and ^{13}C NMR of our synthetic coincide completely with those of the natural product.

Once an efficient methodology to the racemic syntheses of bioactive elemanes had been established, an enantioselective approach was envisaged *via* the use of chiral Pd(II) catalysts

Table 3 Cope rearrangement of germacrol (**15**) and its acetate **15a**



Method[a]	Conditions[b]	12[c]	16[c]	17[c]	18[c]
A	rt, Pd^{II} (0.2 equiv), 15 min	19	—	—	—
B	rt, Pd^{II} (0.2 equiv), 60 min	36	19	5	—
C	rt, Pd^{II} (0.05 equiv), 1.5 h	12	—	—	—
D	rt, Pd^{II} (0.05 equiv), 6 h	31	15	4	—
E	reflux, Pd^{II} (0.2 eq.), 105 min	—	72	19	—
F	rt., Pd^{II} (0.2 eq.), 15 min	16[d]	—	—	72[d]
G	rt., Pd^{II} (0.2 equiv), 6 h	27[d]	14	—	45[d]
H	reflux, Pd^{II} (0.2 equiv), 120 min	—	73	18	—

[a] Methods A–E used for **15** and methods F–H used for **15a**. [b] All reactions were realized in toluene. [c] Isolated yields (%). [d] Yields (%) calculated after NMR crude analysis due to the instability of **18**

to achieve asymmetrically the key Cope rearrangement of the germacrane skeleton. In this context, the Pd(II) catalyst known as COP-Cl (**I**) (Fig. 1) was the catalyst of choice due to the good yields and high enantiomeric purities described for the [3.3]-sigmatropic rearrangement of prochiral allylic imidates into higher value chiral allylic amides and amines when mediated by this Pd(II) species.[22] Unfortunately when germacrone was made to react with COP-Cl, no alteration of the starting material was observed, even after increasing the temperature and reaction times. Then, we decided to prepare enantioselectively a derivative of germacrone, with the hope the introduced asymmetry would be reflected in the product of the Pd(II)-catalyzed Cope rearrangement. In this context, and being sensitive to the advantages of the organocatalysis research with its potential for savings in cost, time and energy, easier

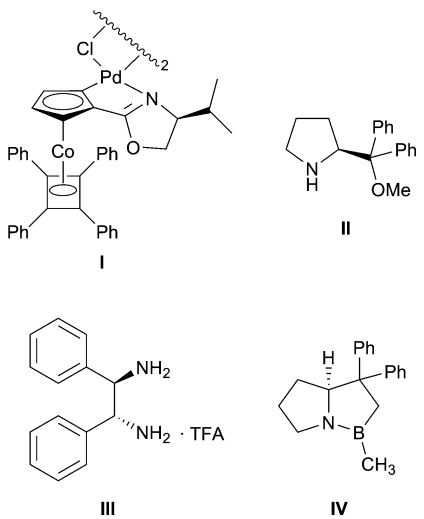
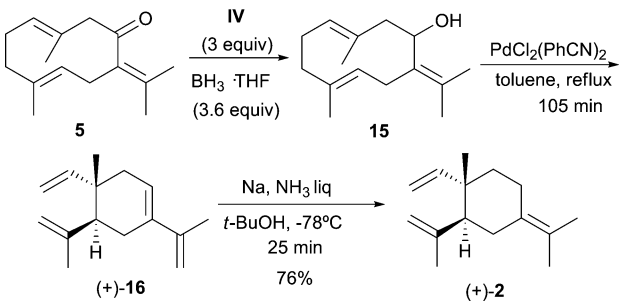


Fig. 1 Catalysts employed in the asymmetric approach to the target elemenes.

experimental procedures and reduction in chemical waste, we decided to explore the asymmetric epoxidation of the enone present in germacrone *via* iminium catalysis, using either the diarylprolinol ether derivative **II**[23] or and the diamine salt **III**[24] in the presence of H_2O_2. Unfortunately, no satisfactory results were obtained when these epoxidation were tested under different experimental conditions, with the starting material remaining unaltered in most of cases.

We next shifted our efforts to check the enantioselective reduction of germacrone to germacrol[25] using the chiral 2-methyl-CBS-oxazaborolidine catalyst **IV**. When performing this reaction under usually reported experimental conditions,[26] it was observed that low transformations were obtained by using the 1 equiv of **IV** and 1.2 equiv of borane and only a 15% of germacrol[27] together with a 72% of starting material were obtained. When the quantities of **IV** and borane were increased up to 3 and 3.6 equiv respectively, moderate yields of germacrol were produced (52%, together with 30% of starting germacrone). When the acetate derivative of the thus-obtained germacrol was heated at reflux for 2 h with 0.2 equiv of Pd(II) (Method H, Table 3), 72% of **16**, together with 19% of **17**[28] were obtained. Treatment of tetraene **16** with sodium in liquid ammonia afforded (+)-γ-elemene (**2**), which showed an optical rotation value of +3.5°. Comparison of this datum with that of the natural product[29] permitted us to establish that our synthetic (+)-**2** showed an enantiomeric excess of 75% (Scheme 6). It was thus proved that an enantioselective version of our protocol for the asymmetric preparation of bioactive elemenes is viable.



Scheme 6 Enantioselective approach to (+)-γ-elemene (**2**).

Conclusions

In this work the natural product germacrone (**5**), obtained from the essential oils of *Baccharis latifolia* or *Geranium macrorrhizum*, is used for first time as a starting material in the synthesis of bioactive elemanes. Thus, the racemic synthesis of antitumor β-elemene (**1**) and γ-elemene (**2**) and that of the antifungal 8α-hydroxy-β-elemene (**3**) and 8α-acetoxy-β-elemene (**4**) has been achieved by a process entailing just a few steps (3–5) and featuring high overall yields (43–53%.). These results show that semisyntheses using an easily available renewable starting material constitute a advantageous alternative to total syntheses in the preparation of products of interest. Moreover, this method can be easily adapted for asymmetric synthesis, *via* CBS asymmetric reduction of germacrone to chiral germacrol.

Experimental

General details

IR spectra were recorded on a Mattson Satellite FTIR spectrometer. NMR spectra were performed with a Varian Direct-Drive 400 (^{1}H 400 MHz/^{13}C 100 MHz) and 500 (^{1}H 500 MHz/^{13}C 125 MHz) spectrometers. High-resolution MS were determined on an Autospec-Q VG-Analytical (FISONS) mass spectrometer. HPLC with RI detection was used. Semi-preparative HPLC separations were carried out on a column (5 μm silica, 10 × 250 mm) at a flow rate of 2.0 cm^3 min^{-1} in an Agilent Series 1100 instrument. All air- and water-sensitive reactions were performed in flasks flame-dried under a positive flow of argon and conducted under an argon atmosphere. The solvents used were purified according to standard literature techniques and stored under argon.

Isolation of germacrone (5) from essential oil of *Geranium macrorrhizum*

The essential oil (5 g) was chromatographed over silica gel column (hexane/*t*-butylmethylether, 98 : 2) to obtain **5**[30] (2.7 g, 54%) as a crystalline solid. Crystals mp 53–54 °C (from hexane).

Cope rearrangement of germacrone (5). Preparation of elemenone (6)

Germacrone (**5**, 105 mg, 0.48 mmol) and $PdCl_2(PhCN)_2$ (37 mg, 0.2 equiv) were dissolved in dry toluene (6 cm^3), under argon. The solution was heated at reflux under stirring for 60 min. After cooling at room temperature, the mixture was filtered through silica gel and the layer was washed with *t*-butylmethylether. The solvent was concentrated *in vacuo* yielding a crude product which was chromatographed over a silica gel column (hexane : *t*-butylmethylether, 95 : 5) to obtain **6** (86 mg, 98%).[14]

Elemenone (6). δ_C(125 MHz; $CDCl_3$; Me_4Si) 19.1 (CH_3, C-14), 22.6 (CH_3, C-15), 23.4 (CH_3, C-13) 24.8 (CH_3, C-14), 32.0 (CH_2, C-6), 41.9 (C, C-10), 50.7.3 (CH, C-5), 54.1 (CH_2, C-9), 111.3 (CH_2, C-2), 113.0 (CH_2, C-3), 130.8 (C, C-7), 144.0 (C, C-11), 146.4 (C, C-4), 146.8 (CH, C-1), and 202.7 (C, C-8).

Deconjugation of 6 with KOBu^t/Py. Preparation of compound 7

Method A. KOBu^t (78 mg, 0.66 mmol) was added to a solution of **6** (97 mg, 0.44 mmol) in pyridine (2.5 cm^3). The mixture was heated at reflux under stirring for 2.5 h. After cooling at room temperature, the mixture was diluted with *t*-butylmethylether and washed with 2 N HCl solution, saturated aqueous $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* yielding a crude product which was chromatographed over a silica gel column (hexane : *t*-butylmethylether, 95 : 5) to obtain **8** (39 mg, 40%), **9** (17 mg, 22%)[16] and **10** (6 mg, 5%).

(6*S*,7*S*)-3,4,5,6,7,8-Hexahydro-4,4,7-trimethyl-6-isopropenyl-7-vinylnaphthalen-2(1*H*)-one (10). Yellow syrup. IR ν_{max}(film)/cm^{-1} 2963, 2926, 2876, 1714, 1667, 1455, 1416, 1374, 1304, 1260, 1076, 1035, 911, 895 and 803; δ_H(500 MHz; $CDCl_3$; Me_4Si) 0.99 (3 H, s, 15-H)[a], 1.02 (3 H, s, 14-H)[a], 1.08 (3 H, s, 13-H)[a], 1.66–1.80 (3 H, m, 5β-H, 8α-H, 8β-H), 1.75 (3 H,

s, 16-H), 2.02–2.21 (4 H, m, 3α-H, 3β-H, 5α-H, 6α-H), 2.36 (1 H, d, *J* 13.3, 1α-H), 2.42 (1 H, d, *J* 13.3, 1β-H), 4.73 (1 H, s, 11a-H), 4.85 (1 H, s, 11b-H), 4.93 (1 H, d, *J* 10.6, 10a-H), 4.94 (1 H, d, *J* 17.2, 10b-H) and 5.80 (1 H, dd, *J* 10.6 and 17.2, 9-H) ([a]Signals with the same letter are exchangeable); δ_C(125 MHz; $CDCl_3$; Me_4Si) 19.4 (CH_3, C-16), 24.8 (CH_3, C-15)[a], 27.2 (CH_3, C-13)[a], 27.5 (CH_3, C-14)[a], 28.4 (CH_2, C-5), 38.7 (C, C-4), 39.3 (CH, C-7), 43.1 (CH_2, C-8), 45.1 (CH_2, C-1), 49.3 (CH, C-6), 55.1 (CH_2, C-3), 110.8 (CH_2, C-10), 112.4 (CH_2, C-11), 123.2 (C, C-4a), 135.2 (C, C-8a), 147.7 (C, C-12), 147.8 (CH, C-9) and 210.5 (C, C-2) ([a]Signals with the same letter are exchangeable); *m/z* (HRMS(FAB)) 281.1881 (M + Na. $C_{18}H_{26}ONa$ requires 281.1882)

Method B. This method is similar to the method A but the reaction time was 5 min. $LiAlH_4$ (93 mg) was added to a cold (–10 °C) solution of the crude product (411 mg) in dry THF (15 cm^3) under argon and vigorous stirring. After 10 min the reaction was stopped by successive addition of water (2 drops), 6 N NaOH solution (2 drops) and water (6 drops). The mixture was worked up as usual to give a crude product which was chromatographed over silica gel column (hexane : *t*-butylmethylether, 70 : 30) to obtain alcohols **7** (325 mg, 32%), **11** (322 mg, 32%) and **12** (171 mg, 17%).[18]

(5*S*,7*R*,8*R*,10*S*)-Elema-1,3,11-trien-8-ol (7). Colorless syrup. IR ν_{max}(film)/cm^{-1} 3551, 3479, 3083, 2966, 2926, 2870, 1712, 1642, 1446, 1376, 1260, 1151, 1059, 1027, 1005 and 964; δ_H(500 MHz; $CDCl_3$; Me_4Si) 1.12 (3 H, s, 14-H), 1.29 (1 H, m, 6α-H), 1.41 (1 H, br s, OH), 1.53 (1 H, dd, *J* 3.2 and 14.5, 9α-H), 1.67 (3 H, br s, 13-H), 1.73 (3 H, br s, 15-H), 1.73 (1 H, dd, *J* 2.9 and 14.4, 9β-H), 1.95–2.07 (3 H, m, 5α-H, 7α-H, 6β-H), 3.96 (1 H, br s, 8α-H), 4.58 (1 H, br s, 3a-H), 4.77 (1 H, br s, 3b-H), 4.80 (1 H, br s, 12a-H), 4.83 (1 H, dd, *J* 1.1 and 17.8, 2a-H), 4.84 (1 H, dd, *J* 1.1 and 10.5, 2b-H), 4.93 (1 H, br s, 12b-H) and 5.72 (1 H, dd, *J* 10.4 and 17.8, 1-H) ([a]Signals with the same letter are exchangeable); δ_C(125 MHz; $CDCl_3$; Me_4Si) 19.5 (CH_3, C-14), 22.8 (CH_3, C-13), 24.8 (CH_3, C-15), 26.2 (CH_2, C-6), 39.9 (C, C-10), 44.7 (CH_2, C-9), 49.7 (CH, C-7), 53.3 (CH, C-5), 66.6 (CH, C-8), 110.5 (CH_2, C-2), 111.9 (CH_2, C-12), 112.7 (CH_2, C-3), 146.9 (C, C-4), 147.5 (C, C-11) and 150.7 (CH, C-1); *m/z* (HRMS(FAB)) 243.1727 (M + Na. $C_{15}H_{24}ONa$ requires 243.1725).

(5*S*,10*R*)-Elema-1,3,7(11)-trien-8β-ol (11). Colorless syrup. IR ν_{max}(film)/cm^{-1} 3334, 3080, 2965, 2917, 2727, 1636, 1447, 1373, 1261, 1098, 1051, 1018, 905, 889 and 802; δ_H(400 MHz; $CDCl_3$; Me_4Si) 0.92 (3 H, s, 14-H), 1.56 (1 H, br s, OH), 1.67 (1 H, dd, *J* 3.9 and 14.6, 9a-H), 1.69 (3 H, s, 12-H)[a], 1.72 (3 H, s, 15-H), 1.79 (3 H, s, 13-H)[a], 1.87 (1 H, dd, *J* 3.8 and 14.6, 9b-H), 2.31 (1 H, dd, *J* 7.9 and 14.9, 6α-H), 2.43–2.50 (1 H, m, H-6β), 2.52 (1 H, dd, *J* 4.6 and 7.8, 5-H), 4.69 (1 H, br s, 3a-H), 4.74 (1 H, t, *J* 3.8, 8-H), 4.79 (1 H, br s, 3b-H), 4.96 (1 H, d, *J* 10.8, 2a-H), 5.04 (1 H, d, *J* 17.6, 2b-H) and 6.26 (1 H, dd, *J* 10.8 and 17.6, 1-H) ([a]Signals with the same letter are exchangeable); δ_C(100 MHz; $CDCl_3$; Me_4Si) 20.2 (CH_3, C-12)[a], 20.7 (CH_3, C-13)[a], 23.9 (CH_3, C-14), 25.1 (CH_3, C-15), 28.1 (CH_2, C-6), 38.1 (C, C-10), 43.7 (CH_2, C-9), 48.1 (CH, C-5), 67.5 (CH, C-8), 110.1 (CH_2, C-2), 112.1 (CH_2, C-3), 128.7 (C, C-11), 131.5 (C, C-7), 148.2 (C, C-4) and 151.1 (CH, C-1) ([a]Signals with the same letter are exchangeable); *m/z* (HRMS(FAB)) 243.1726 (M + Na. $C_{15}H_{24}ONa$ requires 243.1725).

(5*S*,10*S*)-Elema-1,4,7-trien-11-ol (12). Colorless syrup. IR ν_{max}(film)/cm^{-1} 3381, 3081, 2971, 2905, 2833, 1637, 1455, 1435, 1373, 1136, 1035, 1002, 908, 890 and 816; δ_H(500 MHz; $CDCl_3$; Me_4Si) 0.97 (3 H, s, 14-H), 1.32 (3 H, s, 12-H)[a], 1.34 (3 H, s, 13-H)[a], 1.74 (3 H, s, 15-H), 1.86 (1 H, dd, *J* 4.0 and 17.3, 9α-H), 2.13-2.32 (4 H, m, 5α-H, 2 H-6, 9β-H), 4.73 (1 H, bs, 3a-H), 4.84 (1 H, bs, 3b-H), 4.92 (1 H, d, *J* 10.7, 2a-H), 4.95 (1H, d, *J* 17.5, 2b-H), 5.70 (1 H, m, 8-H), 5.81 (1H, dd, *J* 10.7 and 17.5, 1-H) ([a]Signals with the same letter are exchangeable); δ_C(100 MHz; $CDCl_3$; Me_4Si) 19.1 (CH_3, C-15), 24.7 (CH_3, C-14), 28.3 (CH_2, C-6), 29.2 (2 CH_3, C-12, C-13), 38.2 (C, C-10), 38.6 (CH_2, C-9), 49.2 (CH, C-5), 73.0 (C, C-11), 110.6 (CH_2, C-3), 112.3 (CH_2, C-2), 117.3 (CH, C-8), 143.0 (C, C-7), 147.9 (C, C-4) and 148.4 (CH, C-1).

Method C. $KOBu^t$ (250 mg, 2.12 mmol) was added to a solution of **6** (303 mg, 1.416 mmol) in dry pyridine (6 cm^3) under argon and the mixture was refluxed for 5 min. After cooling at 0 °C it was diluted with dry Et_2O (10 cm^3) and was rapidly washed with water, dried over anhydrous Na_2SO_4 and filtered. This solution was added to a suspension of $LiAlH_4$ (566 mg, 14.16 mmol) in dry Et_2O, under argon and vigorous stirring. After 5 min at room temperature, the reaction was stopped by successive addition of water (2 drops), 6 N NaOH solution (2 drops) and water (6 drops). The mixture was worked up as usual to give a crude product, which was chromatographed over silica gel column to give **7** (hexane/*t*-butylmethylether, 70 : 30, 225 mg, 74%).

Deoxygenation of 7. Preparation of β-elemene (1)

A solution of **7** (94 mg, 0.43 mmol) and carbon disulfide (154 μL, 4.0 equiv) in THF (5 cm^3) was added to suspension of sodium hydride (86 mg, 1.2 equiv, 60% dispersion) in THF (3 cm^3) at 0 °C. The mixture was stirred at room temperature for 90 min and iodomethane (214 μL, 8.0 equiv) was added at 0 °C. The mixture was stirred at room temperature for 3 h, diluted with *t*-butylmethylether, and carefully poured into water. After extraction with *t*-butylmethylether, the combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. A solution of tri-n-butyltin hydride (198 μL, 2 equiv) and AIBN (3 mg, 0.1 equiv) in dry and strictly deoxygenated toluene (8 cm^3) was added dropwise (10 cm^3 h^{-1}) to a solution of crude product in dry and strictly deoxygenated toluene (8 cm^3), under argon and heated at reflux. 15 min after the addition had finished, the solvent was concentrated *in vacuo* and the crude product was chromatographed over silica gel column (hexane) to obtain **1** (56 mg, 64%).[8c]

β-Elemene (1). Colorless syrup. IR ν_{max}(film)/cm^{-1} 2955, 2925, 2855, 1643, 1454, 1375, 1260, 1093, 1025, 948, 908 and 809; δ_H(500 MHz; $CDCl_3$; Me_4Si) 0.94 (3 H, s, 14-H), 1.14–1.60 (6 H, m, 6-H, 8-H, 9-H), 1.64 (3 H, s, 13-H), 1.68 (3 H, s, 15-H), 1.84–1.98 (2 H, m, 5α-H, 7α-H), 4.52 (1 H, br s, 3a-H), 4.63 (1 H, br s, 3b-H), 4.65 (1 H, br s, 12a-H), 4.75 (1 H, br s, 12b-H), 4.83 (1 H, d, *J* 10.9, 2a-H), 4.84 (1 H, d, *J* 17.5, 2b-H) and 5.76 (1 H, dd, *J* 10.9, 17.5, 1-H) ([a]Signals with the same letter are exchangeable); δ_C(125 MHz; $CDCl_3$; Me_4Si) 16.9 (CH_3, C-14), 21.2 (CH_3, C-13), 24.9 (CH_3, C-15), 27.0 (CH_2, C-8), 33.1 (CH_2, C-6), 40.0 (C, C-10), 40.1 (CH_2, C-9), 45.9 (CH, C-7), 53.0 (CH, C-5), 108.4 (CH_2, C-12), 110.0 (CH_2, C-2), 112.3 (CH_2, C-3), 148.0 (C, C-4), 150.5 (CH, C-1) and 150.6 (C, C-11).

Epoxidation of elemenone (6) with H_2O_2/OH^-

2 N NaOH solution (3 cm^3) and 30% H_2O_2 (9.1 cm^3) were successively added to a solution of **6** (1031 mg, 4.73 mmol) in MeOH (150 cm^3) at –45 °C. The mixture was vigorously stirred for 7 h and was then kept at room temperature for 2 h. The mixture was diluted with *t*-butylmethylether (150 cm^3), washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford a crude product, which was chromatographed over silica gel column to obtain the epoxides **13** (hexane/*t*-butylmethylether, 90 : 10, 719 mg, 65%) and **19** (hexane/*t*-butylmethylether, 80 : 20, 314 mg, 28%).

(5*S*,7*R*,10*S*)-7,11-Epoxyelema-1,3-dien-8-one (13). Colorless syrup. IR ν_{max}(film)/cm^{-1} 3084, 3001, 2966, 2927, 2732, 1722, 1641, 1453, 1433, 1377, 1273, 1123, 1063, 1002, 914 and 809; δ_H(500 MHz; $CDCl_3$; Me_4Si) 1.08 (3 H, s, 14-H), 1.27 (3 H, s, 12-H), 1.35 (3 H, s, 13-H), 1.83 (3 H, s, 15-H), 2.10 (2 H, d, *J* 6.1, 6-H), 2.47 (1 H, t, *J* 6.2, 5α-H), 2.49 (1 H, d, *J* 14.5, 9a-H), 2.70 (1 H, d, *J* 14.5, 9b-H), 4.76 (1 H, br s, 3a-H), 5.00 (1 H, br s, 3b-H), 5.03 (1 H, d, *J* 17.5, 2a-H), 5.04 (1 H, d, *J* 10.7, 2b-H) and 5.80 (1 H, dd, *J* 10.7 and 17.4, 1-H); δ_C(125 MHz; $CDCl_3$; Me_4Si) 20.1 (CH_3, C-12)[a], 21.0 (CH_3, C-13)[a], 23.0 (CH_3, C-14), 26.0 (CH_3, C-15), 32.2 (CH_2, C-6), 43.9 (C, C-10), 49.4 (CH, C-5), 50.9 (CH_2, C-9), 65.9 (C, C-11), 68.3 (C, C-7), 113.3 (CH_2, C-3), 113.4 (CH_2, C-2), 145.9 (C, C-4), 146.5 (CH, C-1) and 206.7 (C, C-8) ([a]Signals with the same letter are exchangeable); *m*/*z* (HRMS(FAB)) 257.1519 (M + Na $C_{15}H_{22}O_2Na$ requires 257.1517).

(5*S*,7*S*,10*S*)-7,11-Epoxyelema-1,3-dien-8-one (13b). Colorless syrup. IR ν_{max}(film)/cm^{-1} 3087, 2961, 2925, 1719, 1641, 1451, 1376, 1275, 1117, 1059, 923, 912, 889, 820 and 750; δ_H(500 MHz; $CDCl_3$; Me_4Si) 1.08 (3 H, s, 14-H), 1.22 (3 H, s, 12-H), 1.43 (3 H, s, 13-H), 1.76 (3 H, s, 15-H), 1.79 (1 H, dd, *J* 3.3 and 14.2, 6α-H), 2.31 (1 H, d, *J* 13.5, 9a-H), 2.38 (1 H, d, *J* 13.7, 9b-H), 2.39 (1 H, t, *J* 14.0, 6β-H), 2.53 (1 H, dd, *J* 3.3 and 13.8, 5α-H), 4.71 (1 H, br s, 3a-H), 4.94 (1 H, d, *J* 17.3, 2a-H), 4.95 (1 H, t, *J* 1.4, 3b-H), 5.01 (1 H, d, *J* 10.7, 2b-H), and 5.84 (1 H, dd, *J* 10.7 and 17.3, 1-H); δ_C(125 MHz; $CDCl_3$; Me_4Si) 17.6 (CH_3, C-14), 19.7 (CH_3, C-13), 19.8 (CH_3, C-12), 24.7 (CH_3, C-15), 32.4 (CH_2, C-6), 44.1 (C, C-10), 51.6 (CH, C-5), 55.2 (CH_2, C-9), 63.8 (C, C-11), 69.9 (C, C-7), 111.9 (CH_2, C-2), 114.3 (CH_2, C-3), 145.5 (C, C-4), 146.2 (CH, C-1) and 205.8 (C, C-8); *m*/*z* (HRMS(FAB)) 257.1515 (M + Na $C_{15}H_{22}O_2Na$ requires 257.1517).

Reduction of 13 with Zn/AcOH

Glacial acetic acid (13.25 cm^3) and zinc dust (1.3 g, 9 equiv) were added to a solution of **13** (514 mg, 2.20 mmol) in THF (13.25 cm^3). The mixture was heated at 50 °C and vigorously stirred for 5 h. It was then diluted with *t*-butylmethylether (100 cm^3), washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* yielding a crude product, which was chromatographed over a silica gel column (hexane : *t*-butylmethylether, 80 : 20) to obtain **14** (483 mg, 94%).

(5*S*,7*R*,10*S*)-11-Hydroxyelema-1,3-dien-8-one (14). Colorless syrup. IR ν_{max}(film)/cm^{-1} 3525, 3082, 2968, 2878, 1696, 1640, 1445, 1377, 1278, 1210, 1155, 1060, 1026, 1003, 913 and 897; δ_H(500 MHz; $CDCl_3$; Me_4Si) 0.96 (3 H, s, 14-H), 1.24 (6 H, s, 12-H, 13-H), 1.76 (3 H, s, 15-H), 1.92 (1 H, q, *J* 13.1, 6β-H), 1.98–2.04 (1 H, m, 6α-H), 2.08 (1 H, d, *J* 12.9, 9a-H), 2.45–2.52 (3 H, m, 5α-H, 7α-H, 9b-H), 3.82 (1 H, br s, OH), 4.69 (1 H, br s, 3a-H), 4.90 (1 H, d, *J* 17.4, 2a-H), 4.93 (1 H, br s, 3b-H), 4.97 (1 H, d, *J* 10.7, 2b-H) and 5.82 (1 H, dd, *J* 10.7 and 17.4, 1-H); δ_C(125 MHz; $CDCl_3$; Me_4Si) 17.5 (CH_3, C-15), 25.1 (CH_3, C-14), 25.8 (CH_3, C-12)[a], 28.8 (CH_3, C-13)[a], 31.0 (CH_2, C-6), 45.0 (C, C-10), 52.1 (CH, C-5), 55.2 (CH_2, C-9), 59.1 (CH, C-7), 71.4 (C, C-11), 111.5 (CH_2, C-3), 113.8 (CH_2, C-2), 145.5 (C, C-4), 146.6 (CH, C-1) and 214.2 (C, C-8) ([a]Signals with the same letter are exchangeable); *m*/*z* (HRMS(FAB)) 237.1856 (M + Na $C_{15}H_{25}O_2Na$ requires 237.1854).

Preparation of 8α-hydroxyelemol (3). Method A

A solution of **14** (440 mg, 1.86 mmol) in a (1 : 1) mixture of diethylether : absolute ethanol (40 cm^3) and lithium (17 mg) were successively added to a cold (–35 °C) stirred liquid ammonia (120 cm^3) under argon. After 10 min, the mixture was kept at room temperature and the excess of ammonia evaporated. The residue obtained was extracted with *t*-butylmethylether, concentrated *in vacuo* and the crude product was chromatographed over silica gel column (hexane : *t*-butylmethylether, 50 : 50) to obtain **3**[6a,31] (315 mg, 71%).

8α-Hydroxyelemol (3). White solid, mp 108 °C (from hexane–*t*-butylmethylether). IR ν_{max}(film)/cm^{-1} 3300, 3082, 2971, 2939, 2873, 1640, 1464, 1443, 1377, 1276, 1169, 1050, 1030, 968, 907 and 893; δ_H(500 MHz; $CDCl_3$; Me_4Si) 0.94 (3 H, s, 14-H), 1.18 (3 H, s, 12-H), 1.23 (3 H, s, 13-H), 1.28 (1 H, q, *J* 13.2, 6β-H), 1.43–1.48 (3 H, m, 6α-H, 7α-H, 9α-H), 1.63 (1 H, dd, *J* 4.3, 12.5, 9β-H), 1.64 (3 H, s, 15-H), 1.96 (1 H, dd, *J* 3.1, 12.8, 5α-H), 3.26 (2 H, br s, 2 OH), 3.92 (1 H, dt, *J* 4.3, 10.0, 8β-H), 4.52 (1 H, br s, 3a-H), 4.77 (1 H, br s, 3b-H), 4.85 (1 H, dd, *J* 1.1, 10.7, 2a-H), 4.86 (1 H, dd, *J* 1.1, 17.7, 2b-H) and 5.72 (1 H, dd, *J* 10.7, 17.7, 1-H); δ_C(125 MHz; $CDCl_3$; Me_4Si) 18.0 (CH_3, C-14), 24.1 (CH_3, C-12), 24.9 (CH_3, C-15), 29.4 (CH_2, C-6), 30.2 (CH_3, C-13), 41.2 (C, C-10), 48.5 (CH_2, C-9), 52.5 (CH, C-7), 54.3 (CH, C-5), 69.4 (CH, C-8), 75.3 (C, C-11), 110.7 (CH_2, C-3), 112.7 (CH_2, C-2), 146.8 (CH, C-4) and 149.0 (C, C-1).

Method B. This method is similar to method A, but the starting material was **13** (97 mg, 0.41 mmol). 8α-hydroxyelemol (**3**) was obtained with a yield of 75% (74 mg).

Acetylation of 3. Preparation of 8α-acetoxyelemol (4)

Acetic anhydride (2 cm^3) and 4-dimethylaminopyridine (5 mg) were added to solution of **3** (27 mg, 11.34 mmol) in pyridine (2 cm^3). The mixture was kept at room temperature for 15 h and then was worked up as usual to give a crude product which was chromatographed over silica gel column (hexane : *t*-butylmethylether, 60 : 40) to obtain **4**[6] (31 mg, 97%).

8α-Acetoxyelemol (4). Colorless syrup. IR ν_{max}(film)/cm^{-1} 3451, 3082, 2971, 2936, 2875, 1731, 1639, 1465, 1443, 1376, 1246, 1165, 1128, 1025, 968, 910 and 895; δ_H(500 MHz; $CDCl_3$; Me_4Si) 1.01 (3 H, s, 14-H), 1.13 (3 H, s, 12-H)[a], 1.14 (3 H, s, 13-H)[a], 1.41 (1 H, q, *J* 12.8, 6β-H), 1.64 (3 H, br s, 15-H), 1.64–1.75 (4 H, m, 6α-H, 7α-H, 9α-H), 1.71 (1 H, dd, *J* 4.0, 12.5, 9β-H), 1.97 (1 H, dd, *J* 3.2, 13.1, 5α-H), 1.99 (3 H, s, $OCOCH_3$), 4.54 (1 H, br s,

3a-H), 4.79 (1 H, t, *J* 1.5, 3b-H), 4.84 (1 H, d, *J* 17.4, 2a-H-), 4.86 (1 H, d, *J* 10.7, 2b-H), 5.01 (1 H, dt, *J* 4.2, 11.0, 8β-H) and 5.70 (1 H, dd, *J* 10.7, 17.4, 1-H); δ_C(125 MHz; $CDCl_3$; Me_4Si) 17.7 (CH_3, C-14), 21.9 (CH_3, CH_3CO), 24.8 (CH_3, C-15), 26.4 (CH_3, C-12), 28.7 (CH_3, C-13), 29.3 (CH_2, C-6), 41.3 (C, C-10), 45.0 (CH_2, C-9), 52.3 (CH, C-5)[a], 52.4 (CH, C-7)[a], 72.9 (C, C-11)[b], 73.0 (CH, C-8)[b], 111.0 (CH_2, C-3), 113.0 (CH_2, C-2), 146.4 (C, C-4), 148.5 (CH, C-1) and 169.9 (C, CH_3CO) ([a]Signals with the same letter are exchangeable).

Cope rearrangement of germacrol (15)

Germacrol (**15**, 150 mg, 0.67 mmol) and $PdCl_2(PhCN)_2$ (52 mg, 0.14 mmol, 0.2 equiv) were dissolved in dry toluene (9 cm^3), under argon. The solution was heated at reflux under stirring for 105 min. After cooling at room temperature, the mixture was filtered through silica gel and the layer was washed with a 3 : 1 mixture of hexane : *t*-butylmethylether. The solvent was concentrated *in vacuo* yielding a crude product which was chromatographed over 20% $AgNO_3$-silica gel column to obtain the hydrocarbons **16** (hexane : *t*-butylmethylether, 90 : 10, 99 mg, 72%) and (5*S*,10*R*)-elema-1,3,7(11),8-tetraene (**17**)[28] (hexane : *t*-butylmethyl ether, 95 : 5, 26 mg, 19%).

When this reaction is carried out at room temperature for 15 min, a mixture of **12** and **18** in an approximate ratio of 1 : 4.5, respectively (NMR crude analysis).

(5*S*,10*R*)-Elema-1,3,7(11)-trien-8β-yl acetate (18). δ_H(400 MHz; $CDCl_3$; Me_4Si) 1.18 (3 H, s), 1.58 (1 H, dd, *J* 3.5 and 14.2), 1.68–1.80 (3 H, m), 1.70 (3 H, s), 1.73 (3 H, s), 1.77 (3 H, s), 1.97 (1 H, t, *J* 7.1), 2.02 (3 H, s), 2.39 (1 H, d, *J* 7.8), 4.67 (1 H, br s), 4.86–4.91 (3 H, m), 5.72 (1 H, d, *J* 10.5 and 17.6) and 5.88 (1 H, t, *J* 3.2).

(5*S*,10*S*)-Elema-1,3,7,11(12)-tetraene (16). Colorless syrup. IR ν_{max}(film)/cm^{-1} 3081, 2967, 2901, 1638, 1608, 1437, 1372, 1000, 884 and 816; δ_H(400 MHz; $CDCl_3$; Me_4Si) 0.98 (3 H, s, 14-H), 1.75 (3 H, s, 15-H), 1.90 (3 H, s, 13-H), 2.20–2.35 (5 H, m, 5-H, 6-H, 9-H), 4.74 (1 H, br s, 3a-H), 4.85 (2 H, br s, 3b-H, 12a-H), 4.90 (1 H, d, *J* 10.5, 2a-H), 4.92 (1 H, d, *J* 17.5, 2b-H), 4.95 (1 H, br s, 12b-H), 5.80 (1 H, m, 8-H), 5.85 (1 H, dd, *J* 10.5 and 17.5, 1-H); δ_C(100 MHz; $CDCl_3$; Me_4Si) 18.5 (CH_3, C-15)[a], 20.6 (CH_3, C-13)[a], 24.7 (CH_3, C-14), 29.2 (CH_2, C-6), 38.2 (C, C-10), 39.6 (CH_2, C-9), 49.1 (CH, C-5), 109.9 (CH_2, C-3), 110.4 (CH_2, C-2), 112.2 (CH_2, C-12), 122.9 (CH, C-8), 135.7 (C, C-7), 143.1 (C, C-11), 147.7 (C, C-4) and 148.1 (CH, C-1) ([a]Signals with the same letter are exchangeable).

Reduction of 16 with Na/liq NH_3. Preparation of γ-elemene (2)

A solution of **16** (1000 mg, 4.95 mmol) in dry THF (80 cm^3) was added to a cold (–78 °C) stirred solution of sodium (494 mg, 21.48 mmol) in liquid ammonia (50 cm^3). The mixture was stirred for 25 min, then treated with *t*-BuOH (10 cm^3) and allowed to stir for an additional 5 min. The excess of ammonia was then removed at room temperature. The residue was dissolved in hexane (50 cm^3) and the organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* yielding a crude product, which was chromatographed over 20% $AgNO_3$-silica gel column (hexane : *t*-butylmethylether, 80 : 20), and the obtained mixture was subjected to HPLC (hexane) to yield **2** (768 mg, 76%).

γ-Elemene (2). Colorless syrup, HPLC (hexane, R_t = 8.7 min). IR ν_{max}(film)/cm^{-1} 3081, 2966, 2917, 2855, 1637, 1450, 1373, 1260, 1096, 1004, 908 and 889; δ_H(500 MHz; $CDCl_3$; Me_4Si) 1.06 (3 H, s, 14-H), 1.40–1.44 (2 H, m, 9-H), 1.66 (3 H, s, 12-H)[a], 1.67 (3 H, s, 13-H)[a], 1.72 (3 H, s, 15-H)[a], 1.90–1.99 (1 H, m, 8β-H), 1.96 (1 H, dd, *J* 3.4 and 12.8, 5α-H), 2.08 (1 H, t, *J* 13.5, 6β-H), 2.43 (1 H, dq, *J* 2.0 and 13.9, 6α-H), 2.50 (1 H, dsextuplet, *J* 2.0 and 14.2, 8α-H), 4.63 (1 H, br s, 3a-H), 4.83 (1 H, d, *J* 1.6, 3b-H), 4.89 (1 H, dd, *J* 1.3 and 10.8, 2a-H), 4.91 (1 H, dd, *J* 1.2 and 17.6, 2b-H) and 5.79 (1H, dd, *J* 10.8 and 17.6, 1-H) ([a]Signals with the same letter are exchangeable); δ_C(125 MHz; $CDCl_3$; Me_4Si) 17.1 (CH_3, C-15)[a], 20.1 (CH_3, C-13)[a], 20.2 (CH_3, C-12)[a], 24.9 (CH_3, C-14), 25.6 (CH_2, C-8), 31.5 (CH_2, C-6), 40.1 (C, C-10), 40.2 (CH_2, C-9), 53.2 (CH, C-5), 110.1 (CH_2, C-2), 112.0 (CH_2, C-3), 121.1 (CH_3, C-7), 131.1 (C, C-11), 148.1 (C, C-4) and 150.1 (CH, C-1) ([a]Signals with the same letter are exchangeable).

Reduction of 5 with (*S*)-2-methyl-CBS-oxazaborolidine (IV)

A solution of **5** (80 mg, 0.37 mmol) in anhydrous THF (1.80 cm^3) was added slowly (1–2 h) over an ice-cooled solution of **IV** (1 M in toluene, 1.10 cm^3) and borane:THF complex (1 M in THF, 1.32 cm^3), under argon. The mixture was vigorously stirred at 0 °C for 2 h. After water was added and was extracted with *t*-butylmethylether. The organic phase was washed with 2 N NaOH solution, 2 N HCl solution, saturated aqueous $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* yielding a crude product which was chromatographed over silica gel column (hexane : *t*-butylmethylether, 4 : 1) to obtain of **15** (42 mg, 52%) and recovering 24 mg of starting material.

(+)-(5*S*,10*S*)-Elema-1,3,7,11(12)-tetraene (16). $[\alpha]_D$ +4.1 (*c* 1, $CHCl_3$).

(+)-γ-Elemene (2). $[\alpha]_D$ +3.5 (*c* 1, $CHCl_3$), in literature $[\alpha]_D$ +3.93 (*c* 1, $CHCl_3$).[29]

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Notes and references

1 (*a*) A. M. Adio, *Tetrahedron*, 2009, **65**, 5145–5159; W. M. Bandaranayake, *Phytochemistry*, 1980, **19**, 255–257; (*b*) V. Sykora, V. Herout and F. Sorm, *Chem. Listy*, 1955, **49**, 942–943; (*c*) G. V. Pigulevskii and A. V. Borovkov, *Zhurnal Obshchei Khimii*, 1962, **32**, 3106.

2 (*a*) B. G. Choi, E. Y. Kwak, B. H. Chung, W. J. Cho and S. H. Cheon, *Arch. Pharmacal Res.*, 1999, **22**, 575–578; (*b*) J. Zhao, Q. Q. Li, B. Zou,

G. Wang, X. K. Li, E. Jee, C. F. Cuff, L. Huang, E. Reed and K. Gardner, *Int. J. Oncology*, 2007, **31**, 241–252.
3 W. Hua and S. Cai, *Zhongyaocai*, 2006, **29**, 93–97; J. Zhou, *Faming Zhuanli Shenqing Gongkai Shuomingshu*, 2007 A 20070822.
4 L. Huang, *US Pat.*, WO 2006016912, 2006.
5 R. Zhang, A. Tian, X. Shi, H. Yu and L. Chen, *Int. Immunopharmacol.*, 2010, **10**, 738–743.
6 (*a*) J. De Pascual Teresa, A. San Feliciano, T. Egido and A. F. Barrero, *An. Quim.*, 1977, **73**, 151–152; (*b*) A. San Feliciano, M. Medarde, J. L. López, J. M. Miguel del Corral, P. Puebla and A. F. Barrero, *Phytochemistry*, 1988, **27**, 2241–2248.
7 D. E. Wedge, N. Tabanca, B. J. Sampson, C. Werle, B. Demirci, K. H. C. Baser, P. Nan, J. Duan and Z. Liu, *Nat. Prod. Commun.*, 2009, **4**, 123–127.
8 (*a*) J. E. McMurry and P. Kocovsky, *Tetrahedron Lett.*, 1985, **26**, 2171–2172; (*b*) E. J. Corey, B. E. Roberts and B. R. Dixon, *J. Am. Chem. Soc.*, 1995, **117**, 193–196; (*c*) D. Kim, J. Lee, J. Chang and S. Kim, *Tetrahedron*, 2001, **57**, 1247–1252.
9 J. N. Denis, A. E. Greene, D. Guenard, F. Gueritte-Voegelein, L. Mangatal and P. Potier, *J. Am. Chem. Soc.*, 1988, **110**, 5917–5919.
10 (*a*) I. Loayza, D. Abujder, R. Aranda, J. Jakupovic, G. Collin, H. Deslauriers and F. Jean, *Phytochemistry*, 1995, **38**, 381–389; (*b*) I. Loayza, G. Collin, M. Gagnon and E. Dellacassa, *Revista Italiana*, 1993, **4**, 728–736.
11 (*a*) I. Ognyanov and D. Ivanov, *Perfumery and Essential Oil Record*, 1958, **49**, 617; (*b*) I. Ognyanov and D. Ivanov, *Recent Developments in the Chemistry of Natural Carbon Compounds*, 1967, **2**, 47–62; (*c*) J. Chalchat, S. D. Petrovic, Z. A. Maksimovic and M. S. Gorunovic, *J. Essent. Oil Res.*, 2002, **14**, 333–335.
12 A. F. BArrero, M. M. Herrador, J. L. López Pérez, J. F. Arteaga and J. Catalán, *Org. Lett.*, 2009, **11**, 4782–4785.
13 A. F. Barrero, J. E. Oltra and M. Alvarez, *Tetrahedron Lett.*, 1998, **39**, 1401–1404.
14 G. Majetich, P. A. Grieco and M. Nishizawa, *J. Org. Chem.*, 1977, **42**, 2327–2329.
15 A. K. Colter and R. E. Miller, Jr., *J. Org. Chem.*, 1971, **36**, 1898–1903.
16 D. Friedrich and F. Bohlmann, *Tetrahedron*, 1988, **44**, 1369–1392.
17 K. Takeda, I. Horibe and H. Minato, *J. Chem. Soc., Perkin Trans. 1*, 1973, 2212–2220.
18 H. R. Fransen and H. M. Buck, *J. Chem. Soc., Chem. Commun.*, 1982, 786–787.
19 D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1574–1585.
20 M. Kato, M. Watanabe, B. Vogler, B. Z. Awen, Y. Masuda, Y. Tooyama and A. Yoshikoshi, *J. Org. Chem.*, 1991, **56**, 7071–7076.
21 W. J. G. M. Peijnenburg, G. J. M. Dormans and H. M. Buck, *Tetrahedron*, 1988, **44**, 2339–2350.
22 L. E. Overman, C. E. Owen, M. M. Pavan and C. J. Richards, *Org. Lett.*, 2003, **5**, 1809–1812.
23 C. Palomo and A. Mielgo, *Angew. Chem., Int. Ed.*, 2006, **45**, 7876–7880.
24 X. Wang, C. M. Reisenger and B. List, *J. Am. Chem. Soc.*, 2008, **130**, 6070–6071.
25 The asymmetric reduction of germacrone to germacrol was reported by Hill *et al.* using the LAH-quinine reagent, although with variable results. These authors also achieved separation of a mixture of diastereomeric 1-menthoxy acetates derived from racemic germacrol: R. K. Hill, M. G. Fracheboud, S. Sawada, R. M. Carlson and S.-J. Yan, *Tetrahedron Lett.*, 1978, 945–948.
26 The quantity of CBS catalyst usually varies between 0.05 and 0.2 equiv, see: E. J. Corey and C. J. Helal, *Angew. Chem., Int. Ed.*, 1998, **37**, 1986–2012, however, in certain cases, higher loadings (up to 2 equiv) were needed, see: E. J. Corey and B. E. Roberts, *J. Am. Chem. Soc.*, 1997, **119**, 12425–12431.
27 Having taken into consideration the relative complexity in the study of the asymmetry of germacrol (this compound was reported to exist as a mixture of diastereomers with the asymmetric carbon and the ring as elements of asymmetry, see ref. 25), the relative unstability of germacrol and of its acetate, together with the fact that the CBS reduction of α,β-enones with exocyclic double bonds has not been extensively studied,[26] we decided to explore the stereochemical outcome of this reduction by comparing the optical rotation values of the elemenes obtained form the thus-obtained germacrol with those of the natural compounds.
28 C. Zdero, F. Bohlmann, R. M. King and H. Robinson, *Phytochemistry*, 1986, **25**, 2841–2855.
29 J. H. Gough and M. D. Sutherland, *Aust. J. Chem.*, 1964, **17**, 1270–1281.
30 T. Takahashi, K. Kitamura, H. Nemoto and J. Tsuji, *Tetrahedron Lett.*, 1983, **24**, 3489–3492.
31 R. Mata, A. Navarrete, L. Alvarez, R. Pereda-Miranda, G. Delgado and A. Romo de Vivar, *Phytochemistry*, 1986, **26**, 191–193.