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Syntheses of a prenylbisabolane diterpene, a natural insecticide from *Croton linearis*, and of the bisabolane sesquiterpenes (−)-delobanone and (−)-*epi*-delobanone

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Abstract—An enantioselective first total synthesis of a constituent of *Croton linearis*, the (−)-7-hydroxy-3,10-prenylbisaboladien-2-one **1**, is described as well as the syntheses of the 7-hydroxy-3,10-bisaboladien-2-ones (−)-*epi*-delobanone (**14a**) and (−)-delobanone (**14b**). The model compounds, 7-hydroxy-11-nor-methyl-3-bisabolen-2-one (**8a**), and 11,15-nor-dimethyl-7-hydroxy-3-bisabolen-2-one (**8b**), were successfully prepared by opening of the protected carvone epoxide derivative **6** with the appropriate organocuprates. An alternative approach was used for compounds **1** and **14**. Thus, these were obtained from homogeranyllithium or homoprenyl Grignard reagent, which reacted successfully with a masked nor-carvone, ketone **11**, prepared in four steps from (*R*)-carvone.

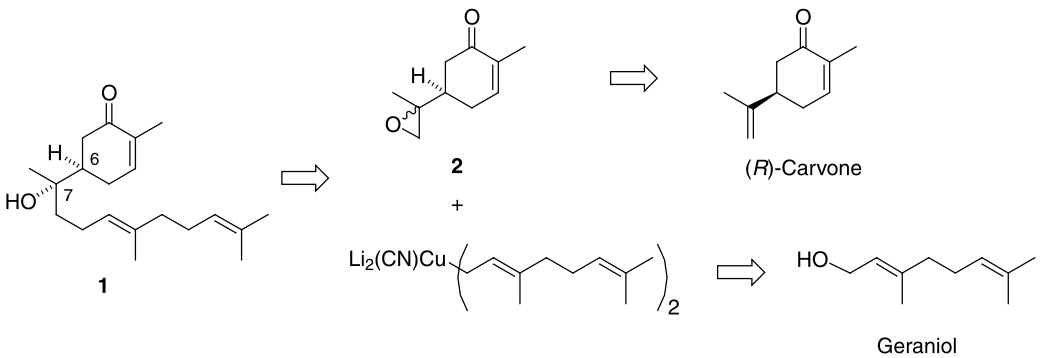
1. Introduction

In connection with a project aiming at developing methods of controlling some forest pest insects, we were interested in the preparation of heavier analogues of the monoterpene carvone. One analogue that appeared especially interesting was the naturally occurring prenylbisabolane diterpene **1**, a constituent of the Jamaican plant *Croton linearis* (Jacq.), exhibiting insecticidal properties.[1] The proposed structure of **1** relied on NMR-data (Scheme 1, drawn with the proposed configuration at C-6, C-7, using the bisabolane numbering system).[1]

Originally, we wanted to develop a biomimetic synthetic approach to this natural product. This approach consisted of a disconnection leading to *R*-carvone and geraniol as starting materials (Scheme 1). This synthetic strategy relied on the regioselective preparation of ketoepoxide **2**, which could then hopefully be opened with a 'higher order' geranylcyanocuprate.[2,3] To our knowledge, no synthesis of a prenylbisabolane has yet been reported.

2. Results and discussion

In order to evaluate the potential of such a synthetic strategy, we first prepared some model compounds (Scheme 2). Regioselective epoxidation at the electron-rich double bond of *R*-carvone with *m*-CPBA yielded the known epoxycarvone **2**,[4] as a 2/3 mixture of diastereomers. Not



Scheme 1.

Keywords: isoprenoids; natural products; insecticides.

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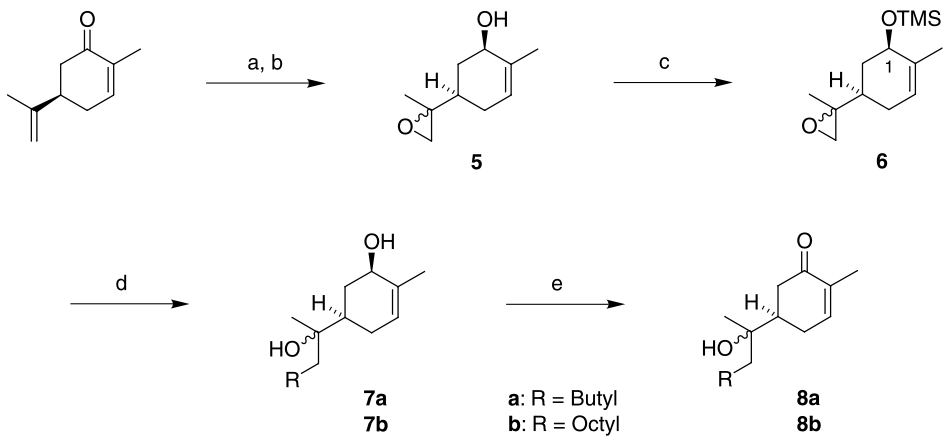


Scheme 2. *Reagents and conditions* (yields): (a) *m*-CPBA, CH_2Cl_2, 0°C (90%), Ref 4; (b) $NaBH_4$, sucrose, H_2O, rt; (c) TMSCl, Et_3N, DMF, rt (84% from **2**, >90% 1*R* isomer); (d) for **7a**: (1) BuLi, CuI (cat.), THF, −72 to 0°C, (2) TsOH (cat.), MeOH, rt (76% over two steps); for **7b**: (1) OctylMgBr, CuI (cat.), THF, −30°C to rt, (2) TsOH (cat.), MeOH, rt (74% over two steps); (e) MnO_2, CH_2Cl_2, rt (~60%, 1/1 mixture of diastereomers in both cases).

unexpectedly, addition of a lower order organocuprate (Bu_2CuLi) to the epoxycarvone **2**, furnished the undesired 1,4-addition product. In order to ensure a chemoselective nucleophilic attack on the epoxide moiety rather than on the conjugated double bond, it was therefore necessary to mask the ketone. Reduction of epoxycarvone **2** to the corresponding allylic alcohol, followed by silyl protection to give the TMS ether **6**, appeared to be an attractive strategy. However, the selective 1,2-reduction of the α,β-unsaturated ketone **2** and the subsequent silylation of the allylic alcohol were not as straightforward as we had anticipated.

It is well-known that reduction of α,β-unsaturated carbonyl compounds with $NaBH_4$ in methanol results in significant amounts of the saturated alcohol due to 1,4-addition, followed by reduction of the keto group ultimately giving a mixture of the saturated and the allylic alcohols. Other reagents were, therefore explored. Attempted selective 1,2-reduction of epoxycarvone **6** with lithium tri-*tert*-butoxyaluminum hydride, $(t\text{-BuO})_3LiAlH$, was unsuccessful. One way to suppress the saturation of the conjugated double bond is to use the Luche reduction ($CeCl_3$, MeOH).[5] Indeed, in our hands this resulted in a chemoselective 1,2-reduction. Unfortunately, however, this was accompanied by an intramolecular Lewis acid catalyzed cyclization to yield a mixture of the known, and previously synthesized, [3.2.1]-oxabicyclooctane monoterpenes(+)-bottrospicatol (**3**), and (+)-*iso*-bottrospicatol (**4**), shown in Fig. 1.[6]

Sucrose has rather recently been used as a 'reactant transfer' agent in aqueous $NaBH_4$ reductions, causing highly selective 1,2-reductions of α,β-unsaturated aldehydes and ketones.[7] When we applied this method to the epoxycarvone **2**, the unstable allylic alcohol, the epoxycarveol **5**, was obtained (Scheme 2) along with only a minute amount (<2%) of the undesired saturated epoxyalcohol. The

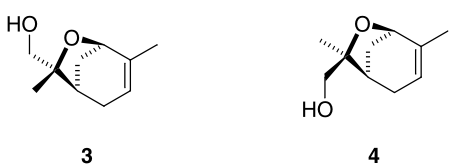
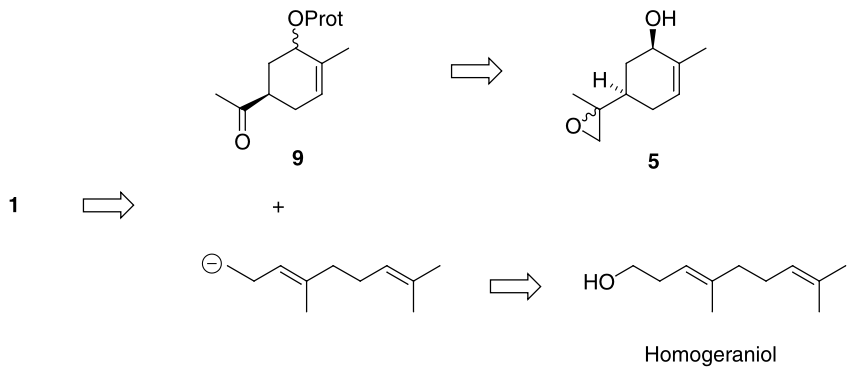


Figure 1. Bottrospicatol monoterpenes.

reduction was also highly stereoselective (>90% *anti* addition). The propensity of the epoxycarveol **5** to undergo cyclization to the bottrospicatols **3** and **4** made us directly protect the alcohol **5** as the TMS ether **6**.

Our plan was to make the TMS ether epoxide **6** react with prenyl- or geranylcuprates either as Gilman-cuprates,[8] (R_2CuLi), or as higher-order cyanocuprates,[9] ($R_2Cu(CN)Li_2$). To evaluate the potential of such an approach, we studied the reactions of the TMS ether epoxide **6** with some alkyl cuprates prepared from butyllithium and octylmagnesium bromide. TMS ether epoxide **6** was successfully reacted with Gilman cuprates, as well as with higher order cyanocuprates ($R_2Cu(CN)Li_2$). The cuprates were prepared either from butyllithium or octylmagnesium bromide. When the epoxide **6** was treated with these cuprates, it yielded the alcohols **7a** or **7b**, respectively, after removal of the TMS-group (Scheme 2). Each of these alcohols was obtained as a mixture of diastereomers, which was not separated. Manganese dioxide oxidation of **7a** and **7b** furnished the model compounds **8a** and **8b**, respectively, each as a mixture of diastereomers. If pure diastereomers should be required, separation of the precursor diols **7** should be possible.

Having established that the strategy proposed for the preparation of the model substances was successful, we turned to the preparation of the target diterpene **1**. First, we tried to explore the potential of the Grignard reagent prepared from commercially available geranyl bromide. This Grignard reagent had been used successfully in a Li_2CuCl_4 catalyzed coupling reaction with 2-bromo-1,4-dimethoxybenzene.[10] However, all our attempts to make the TMS ether epoxide **6** react with the cuprate of geranylmagnesium bromide were unsuccessful. The reason for this might be intramolecular cyclization of the Grignard reagent, which in turn suffered from steric hindrance.[11] If this reaction had been successful, we had expected problems concerning the retention of the *trans* geometry of the allylic double bond.[12] Some efforts have been made to get a better understanding of allylic cuprates in general and to improve their reactivity in a reliable way.[13] There is, however, still a lack of general guidelines for the successful preparation and reaction of complex allylic cuprates. Higher order allylic



Scheme 3.

cyanocuprates can be prepared from geranyl chloride and Rieke copper.[14] We chose, however, not to use that method,[14] because this method can be expected to lead to a certain extent of γ-attack by the cuprate on the terminal epoxide group. Instead, a survey of the literature led us to focus on the preparation of allyl cuprates from the corresponding allyl stannanes.[15] This approach has earlier been used successfully in total syntheses.[3] The higher order cyanocuprate derived from prenyltributylstannane has been used successfully in ring-opening of epoxides,[15a] and geranyltributylstannane, required in this case, has been prepared from geraniol with retained *E*-stereochemistry of the γ-double bond.[16]

In our hands, the higher order geranylcyanocuprate prepared from geranyltributylstannane failed to react with the TMS ether epoxide **6**. Instead, the latter was recovered unchanged. In order to investigate whether other allylic cuprates would react with the epoxide **6**, we also prepared prenyltributylstannane and used it as a starting material for the preparation of a higher order cyanocuprate,[15a] which was subsequently added to the epoxide **6**. However, no trace of the desired silylated precursor of **7** (R=prenyl) was detected. Instead unchanged epoxide **6** was the only compound obtained, despite certain reaction characteristics, such as color changes having been observed. These unsuccessful attempts to make the epoxide **6** react with allylic cuprates led us to abandon the 10C+10C disconnection strategy for the synthesis of the prenylbisabolane **1** (Scheme 1).

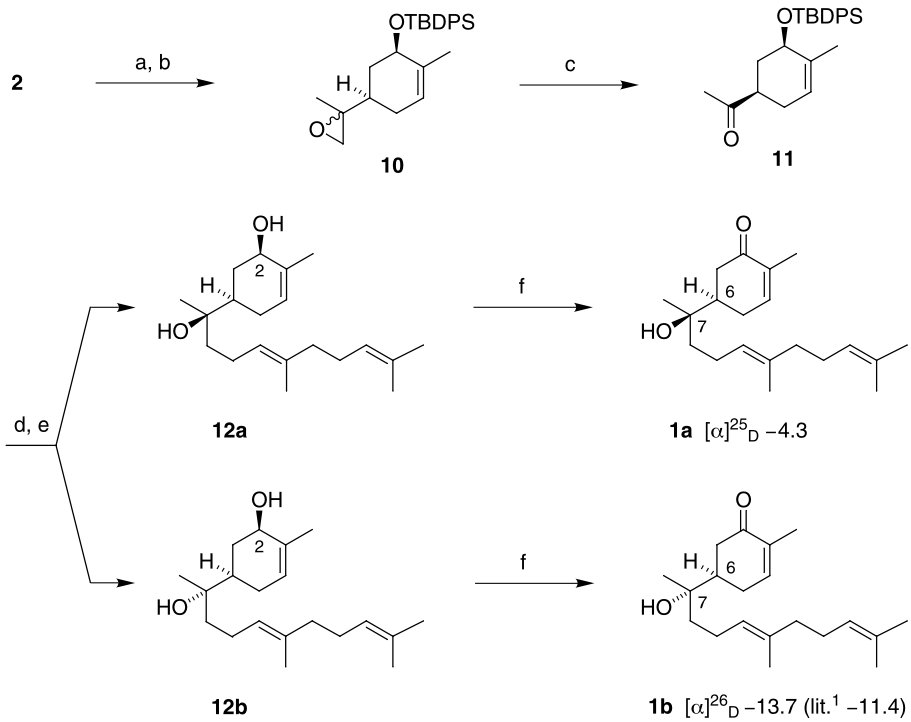
A second retrosynthetic strategy was then considered, leading to a C9- and a C11-building block (Scheme 3). The C9-building block would be derived from carvone after removal of one carbon atom, whereas the C11-building block would be a homoallylic metal reagent derived from a homogeranyl halide. The reaction sequence projected (Scheme 4) involved a cleavage by periodic acid of a silyl protected form of epoxycarveol **5** to give the norterpene ketone **9** (Scheme 3). For that reason, it was necessary to increase the stability of the silyl protecting group so that it could withstand the acidic conditions used during the oxidative cleavage of the epoxide.

The *tert*-butyldimethylsilyl ether (TBDMS ether) of epoxycarveol **5** was first investigated. However, the epoxide cleavage reaction only gave about 50% yield, due to deprotection of the alcohol under the acidic conditions.[17]

We then decided to test the protection of the alcohol group of epoxycarveol **5** as the *tert*-butyldiphenylsilyl ether (TBDPS ether) **10**. It soon became clear that our initial reaction conditions, which worked well for the preparation of the TMS ether **6** (DMF, Et_3N), were not the appropriate ones for efficient formation of the other two silyl ethers. When these, initial, conditions (Scheme 2) were used, the overall yields of silylated ethers of **5** from carvone were 84% (TMS), 65% (TBDMS) and 51% (TBDPS). The reason for the decrease of the yield was an unwanted formation of the silyl ethers of the diastereomeric bottrospicatols, **3** and **4** (Fig. 1). An additional complication was the fact that the latter products were difficult to separate from the desired silylated ethers of **5**. A change of reaction conditions (CH_2Cl_2, imidazole, DMAP) gave a more satisfactory yield (73% from carvone) of the TBDPS ether epoxide **10**. Subsequent oxidative periodic acid cleavage of this epoxide furnished the norterpene silyloxyketone **11** as the dominating stereoisomer (*syn* vs *anti*=94/6) in 60% overall yield starting from carvone.

Homogeraniol was prepared in more than 99% *E*-selectivity by the excellent procedure described by Kocieński et al.[18,19] Thus, 4,5-dihydrofuran-2-yllithium was alkylated with homoprenyl iodide, followed by Ni^0-catalyzed ring opening with methylmagnesium bromide.[18] Homogeraniol was then converted to the corresponding bromide, which was used in an attempt to prepare the Grignard reagent. Probably side reactions, such as Wurtz coupling of the Grignard reagent with the bromide or β-elimination of homogeranyl bromide induced by the Grignard reagent,[20] interfered with the desired reaction of the Grignard reagent with ketone **11**. Thus only a trace of the desired product, diol **12**, could be detected after deprotection. An alternative choice of the required nucleophile was the lithium reagent. Such reagents are readily available from iodoalkanes via a lithium–iodine exchange using *tert*-butyllithium at −78°C.[21] Using this method, we converted homogeranyl iodide to homogeranyllithium which was reacted with the ketone **11** to give a diastereomeric mixture of the coupling product desired,[22] the silyl ether protected precursor of **12**, in 95% crude yield, containing the complete carbon backbone of the target molecule **1**.

Desilylation of this product, followed by chromatographic separation of the diols obtained gave two 90/10 mixtures of one (2*R*,6*R*,7*R* or *S*?)-isomer **12a** together with its (2*S*,6*R*,7*R* or *S*?)-diastereomer, respectively, followed by a



Scheme 4. *Reagents and conditions* (yields): (a) $NaBH_4$, sucrose, H_2O, rt; (b) TBDPSCl, imidazole, DMAP, CH_2Cl_2, rt (73% over two steps); (c) $HIO_4{\cdot}2H_2O$, Et_2O, THF (82%, 94/6 *syn*/*anti* ratio); (d) homogeranyllithium, Et_2O, then **11**, Et_2O, −78 to −10°C; (e) TBAF, THF, (80% over two steps), separation (**12a** vs **12b**, 3/2); (f) MnO_2, CH_2Cl_2, rt (89% for **1a**, 76% for **1b**).

similar mixture of another (2*R*,6*R*,7*S* or *R*?)-isomer **12b** together with its (2*S*,6*R*,7*S* or *R*?)-diastereomer (bisabolane numbering system).

For the determination of the relative configuration of C-7, bearing the tertiary hydroxyl groups in the two purified stereoisomers of **12** (Scheme 4), derivatives with a bridging moiety between the oxygens would be useful. The structures of such rigid bicyclic diastereomeric compounds probably could be determinated by NMR. Some diols can form cyclic silyl-bridged derivatives if they are reacted with dialkylsilyl reagents.[23] Using this method, we prepared the diastereomeric [4.3.1] bicyclic silyl derivatives **13** from the separated diols **12a** and **12b** by silylation with di-*tert*-butylsilyl ditriflate. From NOE measurements (see Fig. 2) it was unambiguously clear that compounds **13a** and **13b** had the

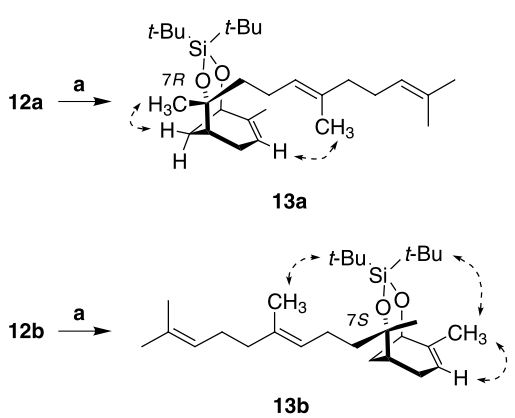
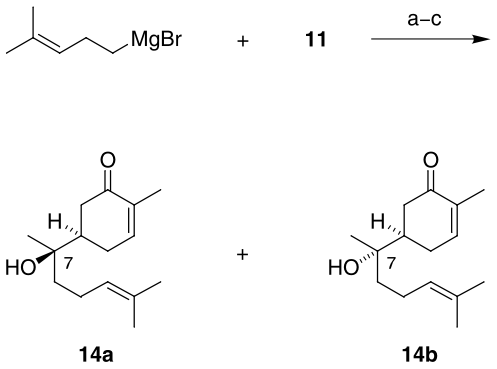


Figure 2. Significant NOE's of the bicyclic di-*tert*-Bu-silyl derivatives, **13a** and **13b** prepared from diols **12a** and **12b**, respectively. Reaction conditions: (a) $(t\text{-Bu})_2Si(OTf)_2$, 2,6-lutidine, CH_2Cl_2, 0°C.

structures shown in Fig. 2. This established the relative configuration at the stereogenic C-7. The absolute configuration of the starting carvone was *R*. Hence, compound **12a** was the (2*R*,6*R*,7*R*)-isomer, and **12b** was the (2*R*,6*R*,7*S*)-isomer as shown (Scheme 4). The 3/2 ratio of the diols, **12a** vs **12b**, formed from the homogeranyllithium addition after deprotection, was that expected according to Cram's rule.

Manganese dioxide oxidation of the two separated 90/10-mixtures (of (2*R*)- and (2*S*)-isomers) of **12** from above furnished the pure (6*R*,7*R*)- and (6*R*,7*S*)-diastereomers of hydroxyketones **1a** and **1b**, respectively. The spectral properties of both diastereomers were virtually identical with those of the naturally occurring compound from *C. linearis*.[1] Although only some of the NMR-shifts observed for the natural product differed slightly from those obtained from the synthetic (6*R*,7*R*)-diastereomer **1a**, the optical rotations were significantly different. Both of the synthetic compounds **1a** and **1b** were 98% enantiomerically pure as judged by gas chromatography using a chiral stationary phase (Supelco® β-dex 120). The natural product has $[\alpha]_D^{25}=-11.4$.[1] The synthetic isomers **1a** and **1b** had $[\alpha]_D^{25}=-4.3$ and $[\alpha]_D^{26}=-13.7$, respectively, which strongly indicated that **1b** was identical with the natural product. Furthermore, the ^1H NMR spectrum registered for the natural product was compared with those of the synthetic isomers **1a** and **1b**. Whereas an incomplete match was observed for **1a**, the spectrum of **1b** matched that of the natural product establishing that the structure originally suggested,[1] namely **1b**, actually was correct.

In order to accomplish the synthesis of the diastereomeric delobanones, we made homoprenylmagnesium bromide and the ketone **11** react (Scheme 5)



Scheme 5. *Reagents and conditions* (yields): (a) Et_2O, 0°C to rt; (b) TBAF, THF, (21% over two steps), separation (7*R* vs. 7*S*, 1/1); (c) MnO_2, CH_2Cl_2, rt.

to give (−)-7-*epi*-delobanone (**14a**) and (−)-delobanone (**14b**) (bisabolane numbering system), after deprotection, chromatographic separation of the diastereomeric products and subsequent MnO_2 oxidation in the same manner as described (Scheme 4) above. The enantiomer of compound **14b**, (+)-delobanone, has been isolated from the root of *Lindera triloba*, and the structure has been unambiguously proven by NMR studies.[24] Both (+)-7-*epi*-delobanone (**14a**) and (+)-delobanone (**14b**) have been synthesized before.[25] Our method appeared to offer better control of the number of products formed, and of their stereochemical purity. The Grignard reaction used by us (Scheme 5) was not as clean and efficient, however, as the organolithium method used for the homogeranyl elongation, described above (Scheme 4).

3. Conclusion

In conclusion, we have explored the utility of alkyl and allylic cuprates, regarding regioselectivity, functional group compatibility and reactivity. We have made a regioselective transformation of carvone to silyl ether protected carveol epoxides and further transformed these to analogues of carvone. With this strategy we prepared the two separated (−)-diastereomers (**1a** and **1b**) of the prenylbisabolane diterpene **1**, and the two separated (−)-diastereomers of the sesquiterpene delobanone (**14a** and **14b**).

4. Experimental

4.1. General

Commercially available chemicals were used as received. The ee of *R*-carvone was 98.0%. Dry THF and Et_2O were obtained by distillation under argon from potassium benzophenone ketyl and from $LiAlH_4$, respectively. The boiling points were not corrected. ^1H (250.13 MHz) and ^{13}C (62.9 MHz) NMR spectra were obtained with a sample temperature of 25°C, using $CDCl_3$ as solvent (unless otherwise stated) and TMS as internal reference. Mass spectroscopy was carried out using a GC–MS (ion trap detector) in EI or CI (CH_3CN as chemical ionization gas) mode. Optical rotation values were measured with a 1 dm cell. Mikrokemi AB, Uppsala, Sweden, carried out the elemental analyses.

4.2. Synthesis of model compounds 8a and 8b

4.2.1. (1*R*/*S*,5*R*)-2-Methyl-5-[(2*R*/*S*)-2-methyloxiran-2-yl]-1-[(trimethylsilyl)oxy]cyclohex-2-ene (6). Epoxycarvone **2** was prepared according to the published procedure.[4] Complementary data of **2**: bp 90–92°C/0.7 mbar; ^{13}C NMR δ 198.9, 198.8, 144.1, 143.9, 135.7, 135.6, 58.0, 57.9, 53.0, 52.4, 41.4, 40.8, 40.4, 40.0, 27.9, 27.8, 19.1, 18.4, 15.7 (2C); MS (CI) *m*/*z* (rel. int.) 167 ($M+H^+$, 10), 149 (40), 109 (100). Other data were in agreement with those in the literature.[26] The epoxycarvone **2** (5.25 g, 31.6 mmol) was stirred in an aqueous solution of sucrose (0.8 M, 375 mL), whereupon $NaBH_4$ (96%, 2.31 g, 58.7 mmol) was added in portions over a 5 min period. The mixture was stirred for 1 h at rt and then extracted with Et_2O. The combined organic phases were dried over Na_2SO_4, filtered and Et_3N (2 drops) was added. Concentration in vacuo resulted in epoxycarveol **5** as a yellow unstable oil (5.55 g), which was used in the next step without further purification. Data of the crude mixture of major (1*R*) isomers: ^1H NMR (MeOD (*d*-4)) δ 5.44 (m, 1H), 4.09 (m, 1H), 2.67 (d, J=4.7 Hz, 1H), 2.54–2.58 (2×d, J=4.8 Hz, 1H), 1.87–2.15 (m, 3H), 1.71 (s, br, 3H), 1.32–1.65 (m, 2H), 1.26 (s, 3H of one diast.), (1.26 (s, 3H of other diast.)); ^{13}C NMR (MeOD (*d*-4)) δ 138.5, 138.4, 123.7, 123.6, 71.1, 71.0, 60.2, 60.1, 54.2, 53.6, 41.5, 40.8, 36.1 (2C), 28.8, 28.6, 19.4, 19.3, 18.7, 18.1. The crude epoxycarveol **5** (5.52 g) from above was stirred in DMF (90 mL), and Et_3N (6.54 g, 64.7 mmol, distilled from CaH_2) was added, followed by TMSCl (5.15 g, 47.4 mmol) in DMF (26 mL). After stirring for 1.5 h at rt, water was added and the resulting mixture was extracted with Et_2O and dried over Na_2SO_4. After filtration and concentration, the resulting oil was purified using MPLC (200 g silica gel, with a gradient of EtOAc/cyclohexane (0/1→2/3) as eluent). The title compound (6.35 g, 84% over two steps) was isolated as a slightly yellowish oil, consisting of a mixture of diastereomers (~95% purity, of which >90% (1*R*)-*syn*-diastereomers (GC, EC-1 column, FID)), which was subjected to the next step without further purification. IR (neat, KBr) 2960, 1455, 1350, 1250, 1100, 1065, 905, 840 cm^{-1}. Other data of the mixture of the two major (1*R*)-*syn*-isomers: ^1H NMR δ 5.45 (m, 1H), 4.19 (m, 1H), 2.54–2.65 (m, 2H), 1.89–2.10 (m, 3H), 1.66 (d, br, J=1.6 Hz, 3H), 1.47–1.53 (m, 2H), 1.27 (s, 3H of one diast.), (1.26 (s, 3H of other diast.)), 0.15 (s, 9H); ^{13}C NMR δ 137.0, 136.9, 123.0, 122.7, 70.9, 70.7, 58.9, 58.7, 53.6, 52.6, 40.3, 39.3, 35.6, 35.4, 27.9, 27.7, 19.5, 19.4, 18.6, 17.5, 0.3 (6C); MS (EI) *m*/*z* (rel. int.) 240 (M^+, 5), 223 (15), 209 (35), 181 (60), 151 (10), 93 (35), 73 (100); MS (CI) *m*/*z* (rel. int.) 241 ($M+H^+$, 4), 223 (5), 183 (20), 151 (50), 93 (100).

4.2.2. (6*R*,7*R*/*S*)-7-Hydroxy-11-nor-methyl-3-bisabolen-2-one (8a). Dry THF (5 mL) was added to CuI (0.34 g, 1.8 mmol) under argon. The stirred mixture was cooled to −72°C (bath temperature) and a solution of BuLi in hexanes (12 mL, 1.6 M, 19 mmol) was added dropwise during a 5 min period. After 5 min additional stirring, the epoxysilyl ether **6** (3.45 g, 14.4 mmol) was added dropwise. The mixture was allowed to reach 0°C during 2.5 h and NH_4Cl

(aq, sat.) was added. The resulting mixture was extracted with Et_2O. The combined organic phases were washed with water, followed by brine. Drying (Na_2SO_4), filtration and evaporation of the solvents afforded (2*R*/*S*,6*R*,7*R*/*S*)-7-hydroxy-11-nor-methyl-2-[(trimethylsilyl)oxy]-3-bisabolene (3.59 g) as a slightly yellowish oil, which was subjected to the next step without further purification. Data of the crude mixture of major (−OTMS=2*R*) isomers: ^{1}H NMR δ 5.50 (m, 1H), 4.21 (m, 1H), 1.85–2.02 (m, 2H), 1.69 (s, br, 3H), 1.20–1.58 (m, 10H), 1.16, (s, 3H of one diast.), (1.12 (s, 3H of other diast.)), 0.89–0.99 (m, 4H), 0.18 (s, 9H); ^{13}C NMR δ 136.6, 136.3, 123.8, 123.6, 73.8, 73.7, 71.4 (2C), 42.3, 41.7, 40.3, 39.3, 34.4, 33.8, 32.5 (2C), 27.1, 26.2, 24.3, 23.4, 23.2, 22.9, 22.7 (2C), 19.5 (2C), 14.1 (2C), 0.3 (6C); MS (EI) *m*/*z* (rel. int.) 298 (M^+, 5), 280 (30), 265 (10), 209 (50), 181 (100), 137 (35). The crude monosilylated diol (3.59 g) from above was stirred in MeOH (60 mL) with TsOH (0.17 g, 1.0 mmol) at rt. After 15 h the MeOH was evaporated and the resulting oil was purified using flash chromatography (80 g silica gel, EtOAc/cyclohexane (3/7) as eluent), affording the diol **7a** (2.47 g, 76% over two steps) as a slightly yellowish viscous oil, which was a mixture of diastereomers. This mixture was subjected to the next synthetic step without further purification. Oven temperature 200°C/0.85 mbar (Kugelrohr distillation); IR (neat, KBr) 3385, 2930, 2850, 1450, 1375 cm^{-1}. Other data of the mixture of the major (2*R*)-*syn*-isomers: ^{1}H NMR δ 5.49 (m, 1H), 4.17 (m, 1H), 1.88–2.26 (m, 3H), 1.76 (s, br, 3H), 1.20–1.55 (m, 10H), 1.15 (s, 3H of one diast.), (1.12 (s, 3H of other diast.)), 0.89 (t, *J*=7 Hz, 3H); ^{13}C NMR δ 136.6, 136.4, 123.9, 123.7, 74.0, 73.9, 71.0 (2C), 42.0, 41.8, 40.2, 39.7, 34.3, 33.8, 32.5, 32.4, 27.0, 26.3, 24.3, 23.6, 23.3, 23.0, 22.7 (2C), 18.9, 18.8, 14.1 (2C); MS (EI) *m*/*z* (rel. int.) 227 ($M+H^+$, 2), 193 (10), 137 (55), 115 (35), 109 (45), 93 (90), 79 (100). The diol **7a** (0.85 g, 3.8 mmol) was stirred in a mixture of CH_2Cl_2 (10 mL) and MnO_2 (90%, 5.0 g, 52 mmol, dried at 140°C, stored in a desiccator before use) at rt for 2.5 days. The mixture was filtered through a pad of celite, which was rinsed with CH_2Cl_2. The solvent was evaporated, and the resulting oil was purified using MPLC (15 g silica gel, with a gradient of EtOAc/cyclohexane (0/1→2/3) as eluent). This resulted in the title compound (0.51 g, 61%) as a slightly yellowish viscous oil, which was a ~1/1 mixture of diastereomers: oven temperature 175°C/0.6 mbar (Kugelrohr distillation); IR (neat, KBr) 3465, 2935, 2870, 1660, 1450, 1370 cm^{-1}; ^{1}H NMR δ 6.77 (m, 1H), 2.57 (m, 1H), 2.05–2.43 (m, 4H), 1.78 (m, 3H), 1.40–1.54 (m, 2H), 1.20–1.40 (m, 6H), 1.17 (s, 3H of one diast.), (1.16 (s, 3H of other diast.)), 0.89 (t, *J*=7 Hz, 3H); ^{13}C NMR δ 200.5, 200.3, 145.4, 145.1, 135.2 (2C), 73.3 (2Cs), 44.0, 43.9, 40.2, 40.0, 39.5, 39.0, 32.4 (2C), 27.1, 26.7, 24.2, 24.1, 23.3, 23.2, 22.6 (2C), 15.6 (2C), 14.0 (2C); MS (EI, one of the isomers, the other similar) *m*/*z* (rel. int.) 207 (M^+−OH, 5), 153 (10), 135 (10), 115 (40), 110 (100), 95 (70). Anal. Calcd for $C_{14}H_{24}O_2$: C, 75.0; H, 10.8. Found: C, 74.6; H, 10.8.

4.2.3. (6*R*,7*R*/*S*)-11,15-nor-Dimethyl-7-hydroxy-3-bisabolen-2-one (8b). Dry Et_2O (31 mL) was added to activated magnesium turnings (2.7 g, 0.11 mol) under argon. 1-Bromooctane (15 g, 78 mmol, dried over K_2CO_3, distilled before use) was added dropwise under gentle reflux. After refluxing for 15 min the resulting Grignard reagent was added dropwise to CuI (1.1 g, 5.8 mmol) in dry THF (77 mL) at −30°C under Ar, followed by addition of the epoxysilyl ether **6** (10 g, 42 mmol). The resulting mixture was stirred over a period of 15 h while allowed to reach rt. NH_4Cl (aq, sat.) was added and the resulting mixture was extracted with Et_2O. Drying (Na_2SO_4), filtration and evaporation of the ether afforded (2*R*/*S*,6*R*,7*R*/*S*)-11,15-nor-dimethyl-7-hydroxy-2-[(trimethylsilyl)oxy]-3-bisabolen (15.3 g) as a slightly yellowish oil. This oil was subjected to the next step without further purification. Thus the crude monosilylated diol was deprotected using the procedure described for **7a** (see Section 4.2.2). This afforded the diol **7b** as a mixture of diastereomers, which was subjected to the next step without further purification. MnO_2 oxidation of the diol **7b** using the same procedure as that described for the oxidation of **7a** (see Section 4.2.2.), resulted in the title compound as a slightly yellowish viscous oil and as a ~1/1 mixture of diastereomers: oven temperature 220°C/0.4 mbar (Kugelrohr distillation); IR (neat, KBr) 3470, 2925, 2855, 1665, 1455, 1370 cm^{-1}; ^{1}H NMR δ 6.77 (m, 1H), 2.56 (m, 1H), 2.05–2.43 (m, 4H), 1.76 (d, br, *J*=1.0 Hz, 3H), 1.40–1.54 (m, 2H), 1.18–1.38 (m, 16H), 1.16 (s, 3H of one diast.), (1.15 (s, 3H of other diast.)), 0.88 (t, *J*=7 Hz, 3H); ^{13}C NMR δ 200.6, 200.5, 145.6, 145.3, 135.1 (2C), 73.1 (2C), 44.1, 44.0, 40.2, 40.0, 39.5, 39.0, 31.9 (2C), 30.3 (2C), 29.6 (4C), 29.3 (2C), 27.2, 26.7, 24.1 (2C), 23.6 (2C), 22.7 (2C), 15.6 (2C), 14.1 (2C); MS (EI, one of the isomers, the other similar) *m*/*z* (rel. int.) 281 ($M+H^+$, 3) 264 (5), 171 (20), 153 (5), 135 (5), 110 (100), 95 (45). Anal. Calcd for $C_{18}H_{32}O_2$: C, 77.1; H, 11.5. Found: C, 77.0; H, 11.6.

4.3. Synthesis of prenylbisabolanes: 1a, 1b and bisabolanes: 14a, 14b

4.3.1. (1*R*)-1-[(3*R*/*S*)-3-{(*tert*-Butyldiphenylsilyl)oxy}-4-methylcyclohex-4-enyl]ethanone (11). A mixture of epoxycarveol isomers **5** (1.58 g), prepared as described for **6** (see Section 4.2.1.), was dissolved in CH_2Cl_2 (40 mL), and imidazole (1.34 g, 19.7 mmol) was added, followed by DMAP (0.30 g, 2.45 mmol) and TBDPSCl (2.88 g, 10.5 mmol). The mixture was stirred at rt for 19 h, water was added and the resulting mixture was extracted with CH_2Cl_2. The organic phase was washed with brine and dried over Na_2SO_4 and the solvent was evaporated. The resulting oil was purified using flash chromatography (205 g silica gel, with EtOAc/cyclohexane (400 mL, 1/39 followed by 800 mL, 1/19) as eluent) affording the epoxysilyl ether **10** (2.76 g, 73%), as a 93/7 mixture of the *syn*–*anti* diastereomers (GC, EC-1 column, FID) as a colorless viscous oil. $[\alpha]_D^{24}=-40.8$ (*c* 0.98, $CHCl_3$); IR (neat, KBr) 3070, 3045, 2930, 2855, 1425, 1110, 1060, 740, 700 cm^{-1}. Other data for the mixture of major (1*R*)-*syn*-isomers: ^{1}H NMR δ 7.65–7.75 (m, 4H), 7.33–7.46 (m, 6H), 5.39 (m, 1H), 4.25 (m, 1H), 2.38–2.47 (m, 2H), 1.80–1.93 (m, 2H), 1.65–1.75 (m, 3H), 1.46–1.26 (m, 3H), 1.11 (s, 3H of one diast.), (1.10 (s, 3H of other diast.)), 1.07 (s, 9H); MS (EI) *m*/*z* (rel. int.) 407 ($M+H^+$, 2), 389 (5), 349 (100), 271 (30), 255 (50), 199 (85), 151 (5), 133 (35), 93 (40); MS (CI) *m*/*z* (rel. int.) 407 ($M+H^+$, 5), 151 (100), 133 (50), 93 (95). Periodic acid, $HIO_4{\cdot}2H_2O$ (3.27 g, 14.3 mmol) was dissolved in THF (110 mL) and stirred at 0°C (bath temperature). The epoxysilyl ether **10** (4.88 g, 12.0 mmol)

from above, dissolved in Et_2O (25 mL) was added, and the mixture was stirred for 1 h at 0°C to give a milky white solution, to which $NaHCO_3$ (50 mL, aq, sat.) was added. After stirring for an additional 15 min, the mixture was filtered through a pad of celite, which was rinsed with Et_2O. The filtrate was extracted with Et_2O and the combined organic phases were washed with water, $Na_2S_2O_3$ (5% aq), brine and dried over $MgSO_4$. Concentration in vacuo afforded an oil, which was purified using flash chromatography (150 g silica gel, with Et_2O/pentane (300 mL, 1/19 followed by 600 mL, 1/9) as eluent). This afforded the title compound (3.86 g, 82%) as a 94/6 mixture of the (3*R*)-*syn*- and (3*S*)-*anti*-diastereomers (GC, EC-1 column, FID) and as a colorless viscous oil. $[\alpha]_D^{23}=-85.4$ (*c* 1.06, $CHCl_3$); IR (neat, KBr) 3070, 3045, 2930, 2855, 1715, 1425, 1110, 1060, 740, 700 cm^{-1}. Other data of the major (3*R*)-*syn*-isomer: ^1H NMR δ 7.67–7.75 (m, 4H), 7.33–7.47 (m, 6H), 5.40 (m, 1H), 4.29 (m, 1H), 2.38 (m, 1H), 2.00–2.21 (m, 2H), 1.93 (s, 3H), 1.88 (m, 1H), 1.72 (d, br, *J*=1.3 Hz, 3H), 1.56 (ddd, *J*=12.4, 12.4, 9.8 Hz, 1H), 1.07 (s, 9H); ^{13}C NMR δ 210.0, 137.5, 136.1 (2C), 136.0 (2C), 134.5, 133.7, 129.7, 129.6, 127.6 (2C), 127.5 (2C), 121.9, 71.8, 47.0, 34.8, 27.6, 27.1 (3C), 27.0, 20.2, 19.5; MS (EI) *m/z* (rel. int.) 392 (M^+, 1), 335 (100), 199 (35), 139 (10), 119 (25), 77 (15); MS (CI) *m/z* (rel. int.) 393 ($M+H^+$, 1), 137 (100). Anal. Calcd for $C_{25}H_{32}O_2Si$: C, 76.5; H, 8.2. Found: C, 76.9; H, 8.3.

4.3.2. (3*E*)-4,8-Dimethylnona-3,7-dien-1-ol (homogeraniol). This was prepared according to the published procedure.[18] The crude intermediate 5-(4-methylpent-3-enyl)-2,3-dihydrofuran was used directly in the following step without further purification. Thus homogeraniol was obtained in 70% total yield with more than 99% isomeric purity (GC, EC-1 column, FID). Complementary data: ^{13}C NMR δ 139.0, 131.7, 124.1, 119.9, 62.4, 39.8, 31.5, 26.6, 25.7, 17.7, 16.2; MS (EI) *m/z* (rel. int.) 125 (60), 109 (10), 95 (15), 81 (35), 69 (100); MS (CI) *m/z* (rel. int.) 169 ($M+H^+$, 25), 151 (55), 125 (50), 109 (25), 95 (100), 81 (30), 69 (20).

4.3.3. (6*E*)-9-Bromo-2,6-dimethylnona-2,6-diene (homogeranyl bromide). This compound was prepared according to the published procedure in 90% yield.[27] Complementary data: bp 93–94°C/4 mbar; IR (neat, KBr) 2965, 2925, 1440, 1375, 1265, 1205, 1110 cm^{-1}; ^1H NMR δ 5.05–5.17 (m, 2H), 3.34 (t, *J*=7.3 Hz, 2H), 2.57 (dt, *J*=7.2, 7.0 Hz, 2H), 1.97–2.12 (m, 4H), 1.68 (d, br, *J*=1.0 Hz, 3H), 1.63 (s, 3H), 1.60 (s, 3H); ^{13}C NMR δ 138.6, 131.6, 124.0, 120.9, 39.6, 32.8, 31.7, 26.5, 25.7, 17.7, 16.3; MS (EI) *m/z* (rel. int.) 231 ($M+H^+$, 5), 229 (4), 217 (10), 215 (10), 189 (50), 187 (50), 123 (30), 109 (10), 95 (40), 81 (30), 69 (100).

4.3.4. (6*E*)-9-Iodo-2,6-dimethylnona-2,6-diene (homogeranyl iodide). Homogeranyl bromide (4.59 g, 19.9 mmol) was added dropwise to a mixture of NaI (7.64 g, 51.0 mmol) in acetone (40 mL, dried over K_2CO_3 before use). The mixture was stirred at rt for 4 h whereupon the milky white suspension was concentrated in vacuo. Water was added, and the mixture was extracted with Et_2O. The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated off to leave an oil which on distillation gave the title iodide (5.16 g, 93%) as a colorless oil: bp 65–67°C/0.4 mbar; ^1H NMR δ 5.06–5.14 (m, 2H), 3.11 (t, *J*=7.4 Hz, 2H), 2.58 (dt, *J*=7.4, 7.2 Hz, 2H), 1.97–2.12 (m, 4H), 1.68 (d, br, *J*=1.1 Hz, 3H), 1.61 (2×s, 2×3H); ^{13}C NMR δ 138.1, 131.6, 124.1, 123.0, 39.6, 32.4, 26.5, 25.7, 17.7, 16.3, 6.1; MS (EI) *m/z* (rel. int.) 278 (M^+, 2), 235 (20), 151 (10), 123 (35), 109 (10), 95 (50), 81 (30), 69 (100). Other data were in agreement with those described earlier.[18a]

4.3.5. (2*R*/*S*,6*R*,7*R*)-7-Hydroxy-3,10-prenylbisabola-dien-2-ol (12a) and (2*R*/*S*,6*R*,7*S*)-7-hydroxy-3,10-prenyl-bisaboladien-2-ol (12b). Homogeranyl iodide (2.34 g, 8.34 mmol, stored over K_2CO_3, 3 Å molecular sieves) in dry Et_2O (50 mL, degassed with argon) under argon was stirred at −78°C (bath temperature). *t*-BuLi (10.3 mL, 1.7 M in pentane, 17.5 mmol) was added dropwise. After the temperature had slowly been raised to −35°C during 1.5 h, the mixture was cooled to −78°C and the ketone **11** (2.53 g, 6.44 mmol) in dry Et_2O (25 mL) was added dropwise. The temperature was slowly raised to −35°C during a 2.5 h period and NH_4Cl (aq, sat.) and Et_2O were added. The organic phase was separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with brine, dried over Na_2SO_4 and the solvents were evaporated. The resulting oil was filtered through a plug of silica gel using EtOAc/cyclohexane (1/9 followed by 1/4) as eluent. This afforded (2*R*/*S*,6*R*,7*R*/*S*)-2-[(*tert*-butyldiphenylsilyl)-oxy]-7-hydroxy-3,10-prenylbisaboladien (3.32 g) as a colorless viscous oil and as a 3/2 mixture of diastereomers (regarding epimers at the exocyclic hydroxyl group). This mixture was used in the following step without further purification. Data of the crude mixture of major (−OTBDPS=2*R*) isomers: ^1H NMR δ 7.66–7.75 (m, 4H), 7.32–7.45 (m, 6H), 5.42 (m, 1H), 4.98–5.13 (m, 2H), 4.28 (m, 1H), 1.71–2.12 (m, 15H), 1.68 (s, br, 3H), 1.60 (s, br, 3H) 1.54 (s, br, 3H), 1.18–1.32 (m, 2H), 1.08 (s, 9H), 1.08 (s, 3H of one diast.), (1.07 (s, 3H of other diast.)); MS (EI) *m/z* (rel. int.) 545 ($M+H^+$, 1), 450 (5), 433 (5), 375 (15), 347 (20), 199 (55), 177 (100), 135 (25), 121 (55), 107 (25), 93 (50), 85 (30); MS (CI) *m/z* (rel. int.) 177 (100), 85 (15). Tetrabutylammonium fluoride, TBAF (15 mL, 1.0 M in THF, 15 mmol), was added to the diastereomeric mixture of the monosilylated diols from above (2.98 g, 5.47 mmol) in THF (50 mL) at 0°C (bath temperature). After stirring at rt overnight, the main part of the solvent was evaporated off and water was added. The mixture was extracted with Et_2O and the combined organic phases were washed with $NaHCO_3$ (aq, sat.), brine, dried over Na_2SO_4 and concentrated. The resulting oil was purified using MPLC (70 g silica gel, with a gradient of EtOAc/cyclohexane (0/1→3/2) as eluent). At first, this furnished the diol **12a** (0.75 g), then a mixture of diastereomers (0.21 g, ~1/1) and at last the diol **12b** (0.45 g) all as colorless viscous oils (80% yield over two steps).

Data of **12a**: R_f 0.40 (EtOAc/cyclohexane (3/2) as eluent); $[\alpha]_D^{24}=+0.48$ (*c* 0.84, MeOH); IR (neat, KBr) 3375, 2965, 2920, 1450, 1375, 1105, 1035 cm^{-1}. Other data of the major (2*R*)-isomer: ^1H NMR δ 5.50 (m, 1H), 5.04–5.18 (m, 2H), 4.17 (m, 1H), 1.88–2.20 (m, 10H), 1.76 (s, br, 3H), 1.68 (d, br, *J*=0.8 Hz, 3H), 1.62 (s, br, 3H), 1.60 (s, br, 3H), 1.48–1.58 (m, 2H), 1.35 (m, 1H), 1.17 (s, 3H); ^{13}C NMR δ 136.3,

135.6, 131.5, 124.2 (2C), 123.9, 74.1, 71.0, 42.3, 39.7, 39.4, 34.4, 26.7, 26.3, 25.7, 24.0, 22.3, 18.9, 17.7, 16.0; MS (EI) *m/z* (rel. int.) 307 ($M+H^+$, 1), 289 (5), 270 (15), 255 (10), 195 (5), 177 (40), 135 (30), 121 (45), 109 (50), 93 (95), 79 (70), 69 (100), 55 (25); MS (CI) *m/z* (rel. int.) 289 (M^+-OH, 5), 271 (5), 215 (10), 195 (20), 177 (100), 119 (15), 109 (10), 95 (15). Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.4; H, 11.2. Found: C, 78.1; H, 11.3.

Data of **12b**: R_f 0.32 (EtOAc/cyclohexane (3/2) as eluent); $[\alpha]_D^{24}=+14.8$ (*c* 0.79, MeOH). Other data of the major, (2*R*)-isomer: ^{1}H NMR δ 5.47 (m, 1H), 5.04–5.17 (m, 2H), 4.18 (m, 1H), 2.25 (m, 1H), 1.78–2.16 (m, 9H), 1.76 (s, br, 3H), 1.68 (d, br, *J*=1.0 Hz, 3H), 1.62 (s, br, 3H), 1.60 (s, br, 3H), 1.48–1.59 (m, 2H), 1.35 (m, 1H), 1.13 (s, 3H); ^{13}C NMR δ 136.6, 135.6, 131.5, 124.2 (2C), 123.7, 74.0, 71.1, 42.1, 39.9, 39.7, 33.8, 27.1, 26.7, 25.7, 23.4, 22.1, 18.8, 17.7, 16.0.

4.3.6. (6*R*,7*R*)-Hydroxy-3,10-prenylbisaboladien-2-one (1a). The diol **12a** (0.27 g, 0.88 mmol) was stirred in a mixture of CH_2Cl_2 (11 mL) and MnO_2 (2.26 g, 23 mmol, 90%, dried at 140°C, stored in desiccator before use) at rt for 2 h. The mixture was filtered through a pad of celite, concentrated, and the resulting oil was purified using flash chromatography (8 g silica gel, EtOAc/cyclohexane (3/7) as eluent). This gave the title compound **1a** (0.24 g, 89%), as a slightly yellowish viscous oil: R_f 0.52 (EtOAc/cyclohexane (3/2) as eluent); oven temperature 215°C/0.3 mbar (Kugelrohr distillation); $[\alpha]_D^{25}=-4.3$ (*c* 1.01, $CHCl_3$); IR (neat, KBr) 3460, 2970, 2925, 1660, 1450, 1375, 1110 cm^{-1}; ^{1}H NMR δ 6.78 (m, 1H), 5.04–5.17 (m, 2H), 2.39–2.61 (m, 2H), 1.94–2.35 (m, 9H), 1.78 (m, 3H), 1.68 (d, br, *J*=0.9 Hz, 3H), 1.62 (s, br, 3H), 1.60 (s, br, 3H), 1.47–1.59 (m, 3H), 1.17 (s, 3H); ^{13}C NMR δ 200.2, 145.3, 136.0, 135.2, 131.6, 124.2, 123.8, 73.4, 44.3, 39.7 (2C), 39.6, 26.7, 26.6, 25.7, 23.9, 22.2, 17.7, 16.1, 15.6; MS (EI) *m/z* (rel. int.) 304 (M^+, 1), 287 (5), 269 (5), 195 (10), 177 (55), 135 (35), 121 (50), 110 (90), 109 (100), 108 (15), 107 (40), 95 (50), 81 (50), 69 (65), 55 (15); MS (CI) *m/z* (rel. int.) 305 ($M+H^+$, 10), 287 (75), 269 (100), 177 (80), 135 (50), 109 (45). Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.9; H, 10.6. Found: C, 78.6; H, 10.6.

4.3.7. (6*R*,7*S*)-Hydroxy-3,10-prenylbisaboladien-2-one (1b). Similar treatment (see Section 4.3.6.) of the diol **12b** furnished the title compound **1b**, as a slightly yellowish viscous oil: R_f 0.54 (EtOAc/cyclohexane (3/2) as eluent); $[\alpha]_D^{26}=-13.7$ (*c* 0.76, $CHCl_3$), lit.[1] $[\alpha]_D^{25}=-11.37$ (*c* 1, $CHCl_3$); ^{1}H NMR δ 6.75 (m, 1H), 5.04–5.17 (m, 2H), 2.63 (m, 1H), 1.93–2.45 (m, 10H), 1.78 (m, 3H), 1.68 (d, br, *J*=0.9 Hz, 3H), 1.62 (s, br, 3H), 1.60 (s, br, 3H), 1.47–1.58 (m, 3H), 1.19 (s, 3H); ^{13}C NMR δ 200.4, 145.0, 136.0, 135.3, 131.6, 124.2, 123.8, 73.3, 44.4, 39.7, 39.5, 39.0, 27.2, 26.6, 25.7, 24.0, 22.2, 17.7, 16.1, 15.6; MS (EI) *m/z* (rel. int.) 304 (M^+, 5), 287 (5), 269 (5), 195 (10), 177 (50), 135 (35), 121 (50), 110 (100), 109 (95), 108 (20), 107 (40), 95 (65), 81 (60), 69 (90), 55 (20); MS (CI) *m/z* (rel. int.) 305 ($M+H^+$, 10), 287 (70), 269 (80), 177 (100), 135 (75), 109 (65). Quadrupol MS (HP 5973) data were very similar to the MS data reported for the natural product for both isomers.[1]

4.3.8. [4.3.1] Bicyclic bis(*tert*-butyl)silyl derivative (13b). 2,6-Lutidine (98 mg, 0.91 mmol) followed by $(t\text{-Bu})_2Si(OTf)_2$ (0.11 mL, 0.30 mmol) were added to a stirred solution of the diol **12b** (36 mg, 0.12 mmol) in CH_2Cl_2 (1.1 mL) at 0°C (bath temperature) under argon. The solution was stirred at rt for 2 h, $NaHCO_3$ (5% aq) was added and the mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The resulting oil was purified by chromatography (Et_2O/pentane (1/13) as eluent). This gave the silyl derivative **13b** (32 mg, ~60%) as a viscous oil: R_f 0.77 (EtOAc/cyclohexane (3/2) as eluent); ^{1}H NMR (acetone (*d*-6)) δ 5.41 (m, 1H), 5.06–5.19 (m, 2H), 4.56 (m, 1H), 2.50 (dddd, *J*=11.9, 5.5, 2, 2 Hz, 1H), 1.83–2.14 (m, 9H), 1.78 (s, br, 3H), 1.66 (s, br, 3H), 1.61 (s, br, 3H), 1.59 (s, br, 3H), 1.42–1.51 (m, 2H), 1.33 (m, 1H), 1.08 (s, 3H), 1.07 (s, 9H), 1.04 (s, 9H).

4.3.9. [4.3.1] Bicyclic bis(*tert*-butyl)silyl derivative (13a). Similar treatment (see Section 4.3.8.) of the diol **12a** furnished the title silyl derivative **13a**: R_f 0.72 (EtOAc/cyclohexane (3/2) as eluent); ^{1}H NMR (acetone (*d*-6)) δ 5.42 (m, 1H), 5.06–5.21 (m, 2H), 4.57 (m, 1H), 2.39 (dddd, *J*=11.8, 5.5, 2, 2 Hz, 1H), 1.89–2.26 (m, 9H), 1.78 (d, br, *J*=1.2 Hz, 3H), 1.66 (d, br, *J*=0.7 Hz, 3H), 1.61 (s, br, 3H), 1.59 (s, br, 3H), 1.42–1.52 (m, 2H), 1.32 (m, 1H), 1.11 (s, 3H), 1.07 (s, 9H), 1.02 (s, 9H).

4.3.10. (6*R*,7*R*)-7-Hydroxy-3,10-bisaboladien-2-one (14a), (−)-7-*epi*-delobanone and (6*R*,7*S*)-7-hydroxy-3,10-bisaboladien-2-one (14b), (−)-delobanone. Dry Et_2O (5 mL) was added to activated magnesium turnings (0.15 g, 6.2 mmol) under argon. 5-Bromo-2-methylpent-2-ene (1.0 g, 6.1 mmol) was added dropwise under gentle reflux. After refluxing for 15 min the mixture was cooled to 0°C (bath temperature) and the ketone **11** (1.8 g, 4.6 mmol) in dry Et_2O (10 mL) was added dropwise. The resulting mixture was stirred at rt for 2.5 h, followed by addition of NH_4Cl (aq, sat.), and the mixture was extracted with Et_2O. The combined organic phases were washed water, brine and dried over $MgSO_4$ and the solvents were evaporated. The resulting oil was filtered through a plug of silica gel using EtOAc/cyclohexane (1/9 followed by 1/4) as eluent. This gave (2*R*/*S*,6*R*,7*R*/*S*)-2-[(*tert*-butyldiphenylsilyl)oxy]-7-hydroxy-3,10-bisaboladiene (1.1 g) as a colorless viscous oil. This mixture of diastereomers was taken to the next step without further purification. Data of the crude mixture of major (−OTBDPS=2*R*) isomers: δ 7.65–7.75 (m, 4H), 7.30–7.44 (m, 6H), 5.41 (m, 1H), 5.01 (m, 1H), 4.28 (m, 1H), 1.50–2.12 (m, 10H), 1.67 (s, br, 3H), 1.54 (s, br, 3H), 1.14–1.36 (m, 3H), 1.08 (s, 9H+3H of one diast.), (1.08 (s, 3H of other diast.)); MS (EI) *m/z* (rel. int.) 477 (M^+, 2), 337 (80), 259 (20), 199 (100), 181 (15), 139 (35), 121 (75), 93 (55), 77 (35); MS (CI) *m/z* (rel. int.) 139 (95), 121 (35), 95 (100). The mixture of diastereomers of the crude monosilylated diols from above was desilylated as described for (2*R*/*S*,6*R*,7*R*/*S*)-2-[(*tert*-butyldiphenyl-silyl)-oxy]-7-hydroxy-3,10-prenylbisaboladiene (see Section 4.3.5.). MPLC (70 g silica gel, with a gradient of EtOAc/cyclohexane (0/1→3/2) as eluent) first furnished (2*R*/*S*,6*R*,7*R*)-7-hydroxy-3,10-bisaboladien-2-ol (0.10 g), then a mixture of diastereomers (0.02 g), and at last (2*R*/*S*,6*R*,7*S*)-7-hydroxy-3,10-bisaboladien-2-ol (0.11 g), both as colorless viscous oils (21% yield over two steps).

Data of the (2*R*/*S*,6*R*,7*R*)-isomer: R_f 0.34 (EtOAc/cyclohexane (3/2) as eluent); $[\alpha]_D^{23}$=+2.4 (*c* 0.78, MeOH); IR (neat, KBr) 3375, 2970, 2920, 1450, 1375, 1110, 1035 cm^{-1}. Other data of the major, (2*R*)-isomer: δ 5.50 (m, 1H), 5.13 (m, 1H), 4.17 (m, 1H), 1.86–2.22 (m, 6H), 1.76 (s, br, 3H), 1.69 (d, br, *J*=0.8 Hz, 3H), 1.62 (s, br, 3H), 1.48–1.58 (m, 3H), 1.35 (m, 1H), 1.17 (s, 3H); ^{13}C NMR δ 136.3, 132.0, 124.3, 123.9, 74.0, 71.0, 42.3, 39.4, 34.4, 26.3, 25.7, 24.0, 22.4, 18.9, 17.7; MS (EI) *m*/*z* (rel. int.) 238 (M^+, 1), 221 (5), 202 (25), 187 (15), 135 (10), 127 (50), 119 (20), 109 (100), 94 (55), 79 (60), 69 (45), 55 (30); MS (CI) *m*/*z* (rel. int.) 221 (M^+–OH, 5), 203 (55), 147 (10), 127 (100), 119 (10), 109 (10), 95 (5).

Data of the (2*R*/*S*,6*R*,7*S*)-isomer: R_f 0.26 (EtOAc/cyclohexane (3/2) as eluent); $[\alpha]_D^{24}$=+6.0 (*c* 0.78, MeOH). Other data of the major (2*R*)-isomer: ^{1}H NMR δ 5.47 (m, 1H), 5.12 (m, 1H), 4.17 (m, 1H), 2.25 (m, 1H), 1.85–2.11 (m, 5H), 1.76 (s, br, 3H), 1.69 (d, br, *J*=0.9 Hz, 3H), 1.62 (s, br, 3H),. 1.47–1.55 (m, 3H), 1.35 (m, 1H), 1.13 (s, 3H); ^{13}C NMR δ 136.6, 132.0, 124.3, 123.7, 73.9, 71.1, 42.1, 39.9, 33.8, 27.1, 25.7, 23.4, 22.1, 18.8, 17.7; MS (EI) and (CI) similar to the 7*R* isomer.

The diols (2*R*/*S*,6*R*,7*R*)-7-hydroxy-3,10-bisaboladien-2-ol and (2*R*/*S*,6*R*,7*S*)-7-hydroxy-3,10-bisaboladien-2-ol were oxidized separately using the procedure described for **12a** (see Section 4.3.6.). This afforded (−)-7-*epi*-delobanone (**14a**) and (−)-delobanone (**14b**).

4.3.11. (−)-7-*epi*-Delobanone (14a). R_f 0.50 (EtOAc/cyclohexane (3/2) as eluent); $[\alpha]_D^{23}$=−7.0 (*c* 0.63, dioxane), lit.[25] $[\alpha]_D^{22}$=+10.6 of slightly impure *ent*-**14a**; ^{1}H NMR δ 6.78 (m, 1H), 5.12 (m, 1H), 2.38–2.60 (m, 2H), 1.99–2.34 (m, 5H), 1.78 (m, 3H), 1.69 (d, br, *J*=1.0 Hz, 3H), 1.62 (s, br, 3H), 1.49–1.57 (m, 3H), 1.17 (s, 3H); ^{13}C NMR δ 200.2, 145.3, 135.2, 132.4, 123.9, 73.4, 44.2, 39.7, 39.6, 26.7, 25.7, 23.9, 22.3, 17.7, 15.6; MS (EI) *m*/*z* (rel. int.) 237 (M+H^+, 1), 219 (25), 201 (5), 135 (5), 110 (60), 109 (100), 95 (25), 81 (15), 69 (25), 55 (10); MS (CI) *m*/*z* (rel. int.) 237 (M+H^+, 5), 219 (100), 201 (25), 135 (5), 95 (5).

4.3.12. (−)-Delobanone (14b). R_f 0.52 (EtOAc/cyclohexane (3/2) as eluent); $[\alpha]_D^{24}$=−11.4 (*c* 0.69, dioxane), lit.[24] $[\alpha]_D^{23}$=+10.2 (*c* 0.998, dioxane) of *ent*-**14b**; IR (neat, KBr) 3460, 2970, 2925, 1660, 1450, 1375, 1110 cm^{-1}; ^{1}H NMR δ 6.76 (m, 1H), 5.11 (m, 1H), 2.62 (m, 1H), 1.99–2.37 (m, 6H), 1.78 (m, 3H), 1.69 (d, br, *J*=1.0 Hz, 3H), 1.62 (s, br, 3H), 1.48–1.56 (m, 3H), 1.18 (s, 3H); ^{13}C NMR δ 200.4, 145.0, 135.3, 132.3, 123.9, 73.3, 44.4, 39.5, 39.0, 27.2, 25.7, 24.0, 22.3, 17.7, 15.6; MS (EI) *m*/*z* (rel. int.) 237 (M+H^+, 1), 219 (5), 135 (5), 110 (70), 109 (100), 95 (35), 81 (20), 69 (35), 55 (10); MS (CI) *m*/*z* (rel. int.) 237 (M+H^+, 1), 219 (100), 201 (60), 135 (15), 123 (30), 95 (20).

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