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Total synthesis of TMS-*ent*-bisabolangelone☆

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ABSTRACT

The absolute configuration of bisabolangelone has been established by an eleven step total synthesis of the corresponding TMS protected antipode starting from (R)-(+)-pulegone. Comparison of the TMS-derivatives by GC on a chiral column, allowed us to assign the absolute configuration of the synthetic compound and thus of the corresponding natural product. The latter has been confirmed by the Mosher's ester analysis of the known secondary carbinol derivative.

1. Introduction

Bisabolangelone **1**[1] (Angelikoreanol, Ligustilone[2]), a bisabolane-type sesquiterpene[3] present in *Angelica* species[4] known for their therapeutic values,[5] belongs to a very small family of related compounds with a poly-hydroxylated perhydro-benzofuran core and a rare conjugated exo-cyclic enol-ether moiety (Fig. 1). Bisabolangelone was found together with Osterivolones A-C[6] in *Angelica koreana.* Liginvolones A-D[7] were found in *Ligusticum involucratum,* and Ashitabaol A[8] in *Angelica keiskei.* Bisabolangelone is known for a variety of biological activities such as anti-microbial,[9] insecticidal,[10] anti-feeding,[11] and many pharmacological[12] properties such as: neuroprotective, anti-tumor, antioxidant and anti-inflammatory. It has been identified as an anti-melanogenesis factor,[13] and derivatives[14] are investigated as pharmaceutical drug candidates. Unfortunately, a broad evaluation is hampered by its limited availability. Isolation from natural sources is cumbersome, and the total syntheses[15,16] disclosed so far, were lengthy and delivered the target molecule in racemic form and low yield. In order to enable a broader evaluation, we focused our attention on the development of a practical synthesis. Although further efforts are required to achieve our goal, we considered worth publishing our first results about the synthesis of TMS-*ent*-bisabolangelone, which enabled us to assign the absolute configuration of (+)-bisabolangelone, which was ambiguous considering the corresponding CAS number,[17] and those of related derivatives.

2. Results and discussion

Among potential routes considered for the total synthesis of bisabolangelone **1** (considering the abs. config. assigned to CAS:30557-81-4), we focused our approach on the perhydro-benzofuran intermediate **6b** and the precursor (*R*)-5-methylcyclohexenone **3b**, readily available from (*R*)-(+)-pulegone (Scheme 1).

In order to develop the chemistry considered to build our target molecule, we used the hemi-acetal **4a** (Scheme 2a) reported by Saimoto et al.,[18] as a model substrate. The latter is formed by an oxa-Michael addition of 1,3-dihydroxy-acetone **2a** (DHA) with

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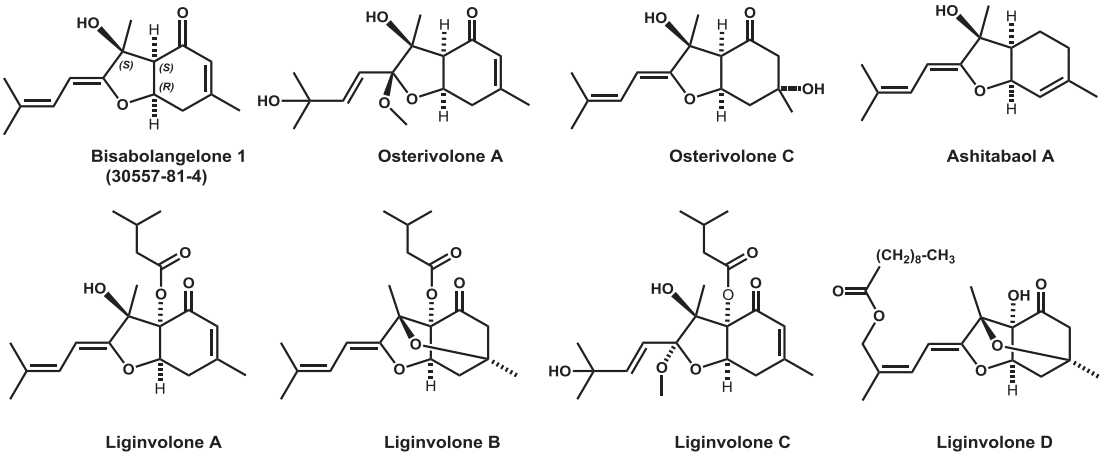
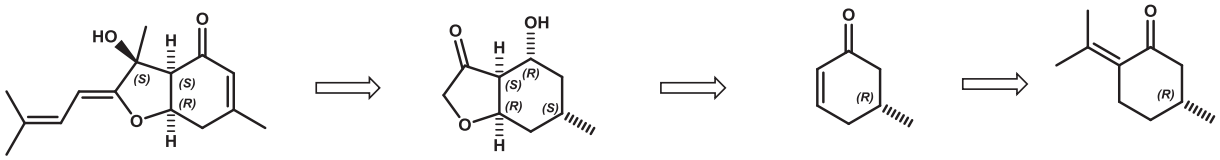
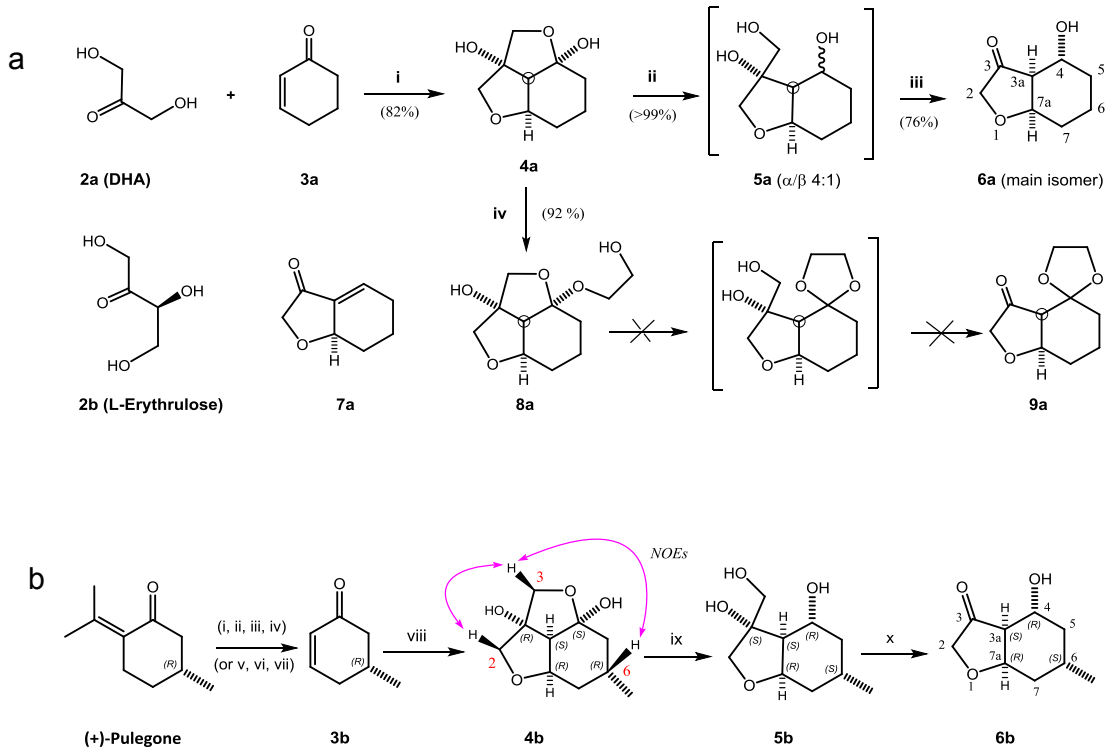


Fig. 1. Related bisabolane sesquiterpenes (stereochemistry drawn according to SciFinder).



Scheme 1. Retrosynthetic analysis.



Scheme 2. a. *Reagents and conditions*: (i) 1 eq. dihydroxyacetone (dimer), 0.05 eq. NaOH, water, 0–20 °C, 20h (82%); (ii) 1 eq. $NaBH_4$, water, 0 °C, 2h (>99%); (iii) 2 eq. $NaIO_4$, water, 0–20 °C, 5 h (76%); (iv) $HOCH_2CH_2OH$, MsOH, 20 °C, 0.5 h (92%). b. *Reagents and conditions*: (i) 2 eq. H_2O_2, 0.2 eq. LiOH, methanol/water 20 °C, 20h, (100%); (ii) 1.2 eq. NaSPh, Me-THF 60 °C, 15 h (81%); (iii) 1 eq. $NaBO_3$, AcOH, 20 °C, 2 h (93%); (iv) excess $CaCO_3$, tetraglyme 140 °C, 50 mbar, cold trap, (91%); (v) aq. H_2SO_4, trimethylcetylammonium chloride (90%); (vi) Br_2, water, acetic acid (100%); (vii) MgO, *n*-butylpyrrolidone, 120 °C (57%, ee > 99%); (viii) dihydroxyacetone (dimer, 0.5 eq), NaOH (0.1 eq), water, 0 °C, 20h; (ix) $NaBH_4$ (1 eq) water, 0 °C, 4h; (x) $NaIO_4$ (2 eq) water, 0–20 °C, 15 h (91% from **3b**, α/β 15:85).

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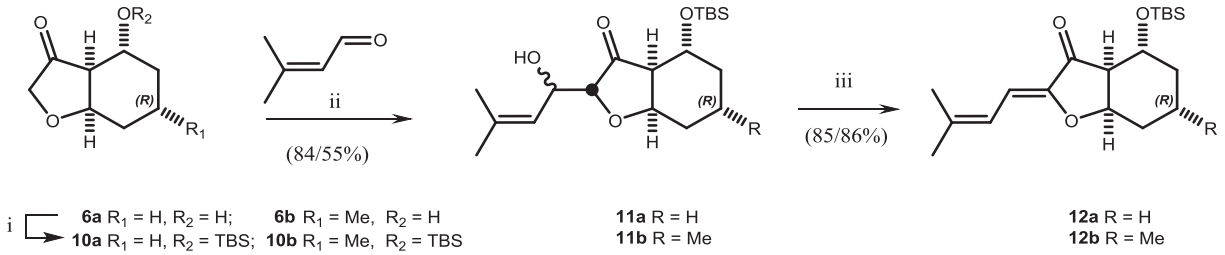


Scheme 3. *Reagents and conditions*: (i) TBS-triflate, imidazole, THF, rt (99%); (ii) LDA (1.1 eq), prenal (1.2 eq), THF -78 °C (84% for **11a** and 55% for **11b**); (iii) Trifluoroacetic anhydride (3 eq), Et_3N (6 eq). DMAP (0.1 eq), DCM, 35h, rt (85% for **12a** and 86% for **12b**).

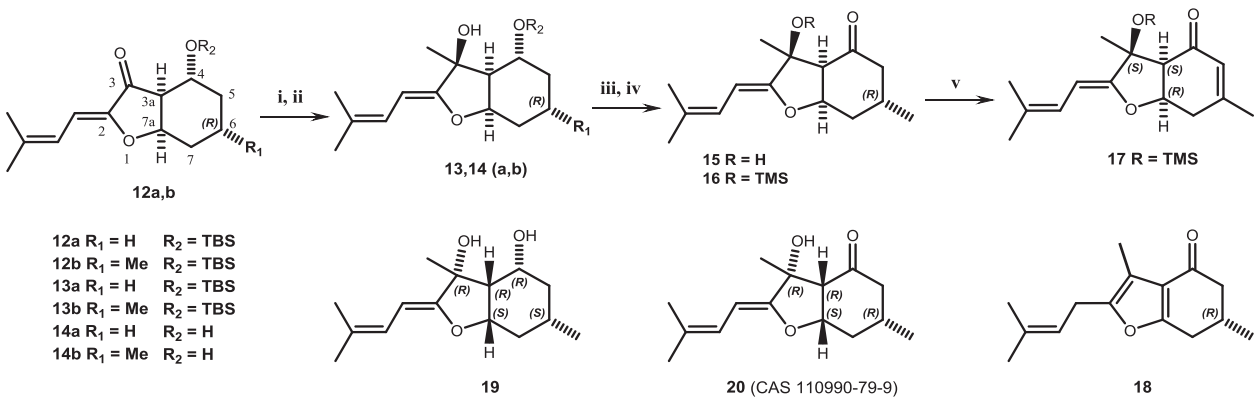
unsaturated carbonyls, such as cyclohexenone **3a**, and might be extended to organo catalyzed enantioselective approaches.[19] We found that compound **4a** can be readily converted to compound **5a** by reduction with $NaBH_4$ in water,[20] and to 4-hydroxy-perhydro-benzofuran-3-one **6a** by a subsequent treatment with sodium periodate. Conversely, the dioxolane **9a**,[16] could not be obtained from **4a** and ethylene glycol under acidic conditions, despite the facile formation of the mixed acetal **8a**, emphasizing the stability of the *intra* molecular hemi-acetal bond. It is noteworthy that **6a** can equally be obtained by using (L)-(+)-erythrulose **2b** instead of DHA.[21]

Under optimized conditions, a *one-pot* telescoped reaction, which consist in stirring an alkaline solution of cyclohexenone and DHA at 0 °C in water until full conversion, neutralizing the solution with acetic acid, adding sodium borohydride, neutralizing again with acetic acid and adding sodium periodate, provided after an extractive work up, the compound **6a** as the main product in ~62% yield, together with minor amounts of the corresponding C-4 epimer and the dehydrated by-product **7a**.[22] Although each epimer can be obtained in pure form by chromatographic purification, this opportunity is of limited interest, since the hydroxyl group of the minor isomer, which is anti-periplanar to the hydrogen on carbon-3a, is quite labile and prone to elimination.

With the method to synthesize **6a** in place, we turned our attention to compound **6b** required for the synthesis of bisabolangelone (Scheme 2b). The latter can be obtained in ~80% yield by a telescoped sequence starting from 5-methyl-cyclohexenone **3b**, which can be obtained in enantiomerically pure form from (*R*)-(+)-pulegone by known methods.[23,24] The relative configuration of the stereogenic centers in the intermediate **4b** obtained this way, was established by proton NMR investigations. In particular, by NOESY correlations between the axial hydrogens on carbons 2, 3, and carbon 6, which abs. config. (*R*) is derived from pulegone. The absolute configuration, was confirmed by the anomalous X-ray diffractions analysis of the corresponding crystalline acetate (section 4.6). Notable is, that the corresponding enantiomer, can be obtained from (*S*)-5-methyl-cyclohexenone accessible by known methods,[25] in particular from (*S*)-5-methyl-cyclohexanone, available by resolution of the racemic mixture with cholic acid (guest/host inclusion with >90% ee) according to Bertolasi et al.[26]

With the central core in place, we followed our goal to synthesize bisabolangelone, taking advantage of the methodologies established, reducing however the number of protecting groups to a strict minimum. We tried therefore, to introduce the prenyl side chain by an aldol reaction directly on the unprotected hydroxy-ketone **6a**/**6b**, expecting high selectivity[27] and enhanced stability. Unfortunately, this approach failed due to by-products formation by retro-aldol reaction and homo-coupling. Consequently, we introduced the TBS protecting group on the labile hydroxyl. To our delight, TBS-triflate reacted preferentially with the main isomer, providing compounds **10a**/**10b** in pure form by simple silica gel filtration in about 80% isolated yield from **3a/3b** (ee >96% for **10b**). The introduction of the prenyl side chain was performed in analogy to Cossy et al.,[16] by deprotonation with LDA at low temperature, and subsequent addition of senecialdehyde, providing compounds **11a**/**11b** as a mixture of diastereomers in 84% and 55% yield respectively. Subsequent treatment with trifluoroacetic anhydride, DMAP and triethylamine, provided the desired compounds **12a**/**12b** in 85–86% yield[28] (Scheme 3).

With the diene structural feature in place, introduction of the methyl group in position 3, was achieved stereoselectively with methyl-magnesium bromide in the presence of anhydrous



Scheme 4. *Reagents and conditions*: (i) $CeCl_3$ (1.5 eq), MeMgBr (3 eq), THF 0 °C (52% for **13b**); (ii) tetrabutylammonium fluoride (3 eq), THF, rt (90%); (iii) TPAP/NMO, CH_2Cl_2, 4 Å molecular sieves (50%); (iv) TMS-Cl, TMS-imidazole, imidazole, DMF (>99%); (v) LDA, *N-tert*-butylbenzenesulfinimidoyl chloride, THF -78 °C (20%).

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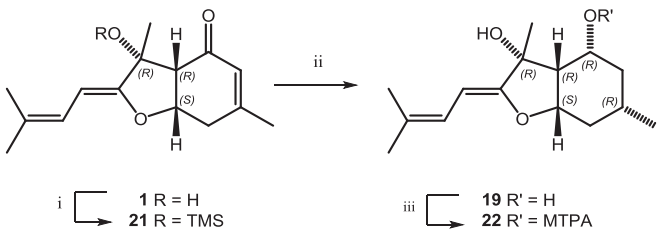
cerium chloride, providing **13a**/**13b** in 52% yield (Scheme 4). The TBS protecting group, was smoothly removed with tetrabutylammonium fluoride, providing the corresponding diols **14a**/**14b** in >90% yield. Selective oxidation of **14b** by means of the Ley-Griffith method (TPAP/NMO),[29] provided ketone **15** in 50% isolated yield, while other methods such as TEMPO/bleach, Saegusa-Ito, failed. The modest yield is mainly due to the facile dehydration of ketone **15**, since compound **18** forms readily under slightly acidic conditions. Notably, compound **14b** and ketone **15** are diastereomers of 5,6-dihydro-bisabolangelol **19**[30] and 5,6-dihydro-bisabolangelone **20**[31] respectively, both derivatives of the natural product **1**, distinguishable by their physical and spectroscopic properties.

After silylation of the labile hydroxyl group (>99% yield with TMS-imidazole, imidazole and cat. amounts of TMS-Cl in DMF),[32] formation of the enone **17** succeeded under the remarkable Mukaiyama-Matsuo conditions[33] (generation of the lithium enolate with LDA and quench with *N-tert*-butylbenzenesulfinimidoyl chloride at −78 °C). However, the conversion was low (20% yield), likely due to the poor quality of the hygroscopic reagent. The identity of compound **17** obtained in this way was ascertained by NMR/MS signals and comparison with an authentic sample of TMS-bisabolangelone **21**.[34] Moreover, GC on a chiral column[35] (Fig. 2), showed that compound **17** did not match with the TMS derivative of natural bisabolangelone, but was superimposable with one of the two peaks of the corresponding racemate obtained by synthesis from rac. 5-methylcyclohexenone. According to these results, compound **17** is the enantiomer of the derivative **21**. We can therefore conclude, that the absolute configuration of the natural product (+)-bisabolangelone is: **3R, 3aR, and 7aS**.

2.1. Material and conditions

GC apparatus HP6890, FID detector, 1.5 mL/min hydrogen flow, 1 μL injection, split 1:10. Column HYDRODEX-γ-TBDAc (25 m × 0.25 mm) at 140 °C isotherm. Sample 1: racemic TMS-bisabolangelone obtained by synthesis from 5-methyl-cyclohexenone; Sample 2: mixture of racemic TMS-bisabolangelone and compound **17**; Sample 3: mixture of compound **17** (chiral) and (+)-TMS-bisabolangelone **21** (from natural source); Sample 4: (+)-TMS-bisabolangelone **21**; Sample 5: compound **17** (chiral); Sample 6: mixture of racemic TMS-bisabolangelone and (+)-TMS-bisabolangelone **21**.

In order to confirm our finding, we performed the advanced Mosher-Kusumi analysis[36] of the MTPA esters **22**(*R*) and **22**(*S*), of the secondary carbinol **19**,[30,31] obtained by reduction of natural (+)-bisabolangelone **1**, with sodium borohydride (Scheme 5, Fig. 3).



Scheme 5. *Reagents and conditions*: (i) TMS-imidazole, Imidazole, TMS-Cl, DMF, 1h, RT (99%); (ii) 1.5 eq. $NaBH_4$, MeOH, 4h, 0 °C (32%); (iii) MTPA-Cl (*R*/*S*) pyridine, rt (99%).

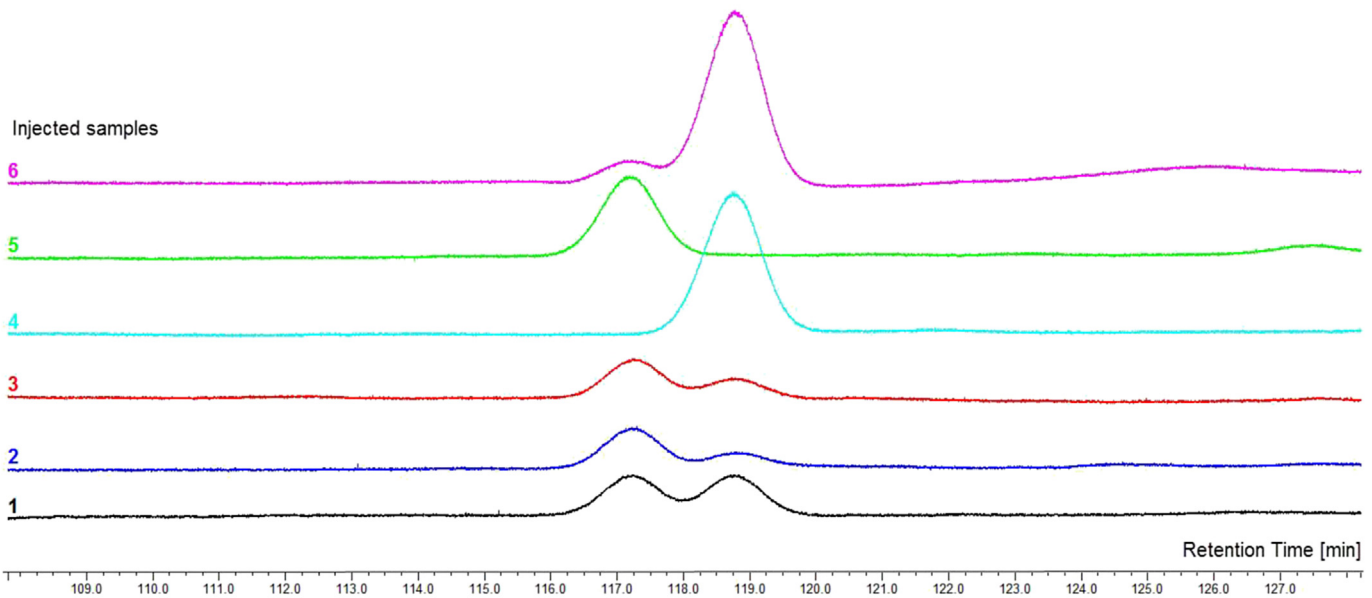


Fig. 2. GC overlays.

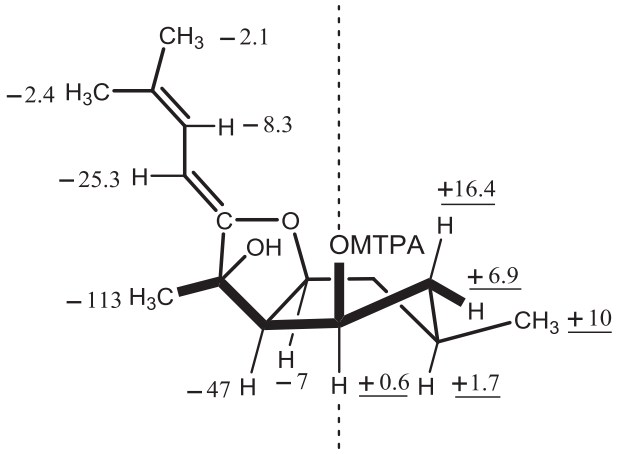


Fig. 3. Drawing of the MTPA-esters **22**. Δδ = $^{\delta}$(*S*)-MTPA-**22**(*S*) - $^{\delta}$(*R*)-MTPA-**22**(*R*).

3. Conclusion

In the present work, we describe the total synthesis of enantiomerically pure TMS-*ent*-bisabolangelone in eleven steps and ~2% overall yield, starting from (*R*)-5-methyl-cyclohexenone obtained from (*R*)-(+)-pulegone (Scheme 6). The synthesis relies on the stereoselective and straightforward access to the central perhydrobenzofuran core, which allowed us to establish without ambiguity the absolute configuration of the natural product, confirmed by the MTPA-ester analysis of a known derivative. Despite additional improvements to the prior art, further effort will be devoted to synthesize (+)-bisabolangelone in an efficient and practical manner.

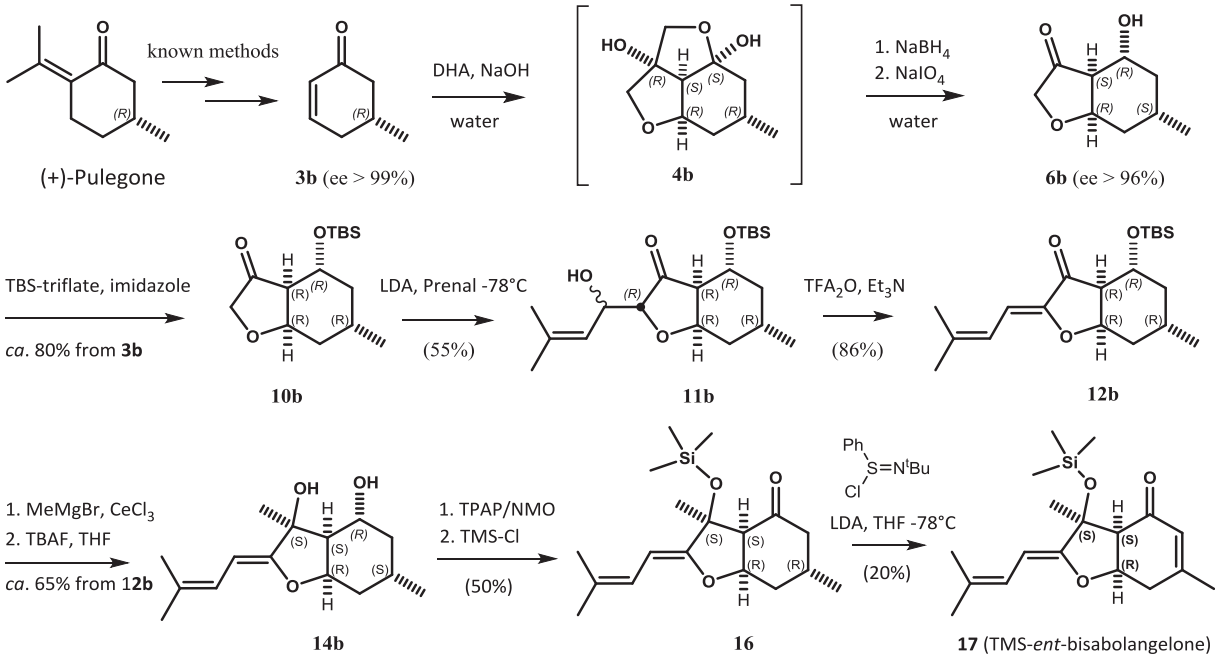
4. Experimental part

4.1. General methods

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Reactions were monitored by thin-layer chromatography (TLC) on silica gel coated glass plates (0.25 mm thickness, 60F-254, E. Merck). Chromatograms were visualized by fluorescence quenching with UV light at 254 nm or by staining with vanillin/sulfuric acid/ethanol solution. ^{1}H and ^{13}C NMR spectra were recorded in deuterated solvents on Bruker DPX-300, AV-400 and 600 spectrometers. Chemical shifts (δ ppm) are relative to the solvent used. ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, q = quartet, m = multiplet), coupling constants in hertz (Hz). Molecular mass (LC/Ms-ToF), were obtained on a Bruker maXis. LC-method: 1% acetonitrile +0.1% HCOOH to 99% acetonitrile +0.1% HCOOH within 4 min, flow rate 0.4 mL/min, UV detector at 210 nm. Temperature 30 °C. Optical rotations were measured on an Autopol® V PLUS polarimeter (Rudolph Research Analytical). Gas chromatography (GC) was performed on HP6850 with a HP-5 capillary column (phenyl methyl siloxane 30 m × 320 × 0.25), and a time program beginning with 1 min at 80 °C, followed by a 12 min ramp to 280 °C, column flow: 2 mL helium/min. Chiral GC analysis of 3-methyl-cyclohexanone, 5-methyl-cyclohex-2-enone and TMS-(*ent*)-bisabolangelone were performed on a GC apparatus HP6890 with a FID detector, on a HYDRODEX-γ-TBDAc column (25 m × 0.25 mm) at 100 °C isotherm (140 °C for TMS-bisabolangelone), 1.5 mL/min hydrogen flow, 1 μL injection, split 1:10. Monoisotopic mass were calculated with ChemCalc.[37]

4.2. (R)-3-methylcyclohexanone[38]

Practical (*R*)-(+)-pulegone (250 g, 1.64 mol, 92% from ABCR, $[\alpha]_D^{20}$ +22.3° neat) was added dropwise at 80 °C to a well stirred solution of sulfuric acid (552 g, 5.63 mol), water (1.2 L) and cetylpyridinium chloride (5.0 g, 14.7 mmol) in a 3 L double-jacketed vessel equipped with an overhead stirrer. After 15 h, the reaction mixture was cooled to 25 °C and phases were separated. The organic phase was washed with brine (20 mL) and neutralized with $NaHCO_3$. After drying with $MgSO_4$, the crude brownish oil (184 g)



Scheme 6. Synthesis overview of TMS-*ent*-bisabolangelone.

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was purified by distillation under reduced pressure (52 °C, 5.6 mbar) providing a colorless liquid (110 g, 96% purity by GC). Additional 43 g were obtained from the aqueous phase (via steam distillation) increasing the overall yield to 90%.

$[\alpha]_D^{20}$ +12.1° (neat), lit.[39] +12.7° (neat). Enantiomeric purity >99% (according to GC on a HYDRODEX-γ-TBDAc column, 100 °C isotherm, RT: 6.7 min for *R* and 6.3 min for *S*). ^{1}H NMR (400 MHz, Chloroform-d) δ ppm 2.40–2.29 (m, 2H), 2.22 (dddd, *J* = 14.1, 12.4, 6.2, 1.4 Hz, 1H), 2.08–2.00 (m, 1H), 1.97 (dd, *J* = 13.4, 1.3 Hz, 1H), 1.94–1.80 (m, 2H), 1.65 (dtdd, *J* = 13.5, 12.1, 4.8, 3.5 Hz, 1H), 1.32 (dddd, *J* = 13.3, 12.0, 10.4, 3.6 Hz, 1H), 1.00 (d, *J* = 6.3 Hz, 3H).

4.3. (5R)-2-bromo-5-methylcyclohexanone (isomeric mixture)

Bromine (157 g, 980 mmol) was added dropwise at 5 °C to a stirred solution of (*R*)-3-methylcyclohexanone (100 g, 892 mmol) in water (400 mL) and acetic acid (10 g). During the addition, the color of the solution changed from colorless to orange and later to red. After full addition, the temperature was raised to 18 °C within 1 h and stirring was continued overnight. After that time, the organic layer was separated, and the aqueous phase extracted with dichloromethane (DCM, 2 × 50 mL). The combined organic layers were washed with a diluted solution of sodium bisulfite (20 mL, 5%), $NaHCO_3$ (2 × 30 mL), and water (30 mL). The organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure, leaving a purple liquid (180 g) as a mixture of isomers (32:14:19:32 according to GC). The latter was used as is in the next step without further purification.

4.4. (R)-5-methylcyclohex-2-enone (**3b**)

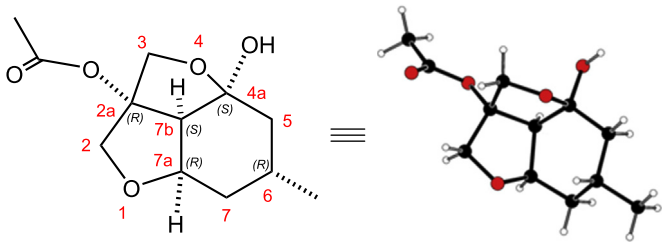
The isomeric mixture of (5*R*)-2-bromo-5-methylcyclohexanone (82.3 g, 0.43 mol) diluted in *N*-methyl-pyrrolidone (NMP, 55 mL), was added dropwise at 110 °C to a stirred suspension of MgO (27.0 g, 0.67 mol) in NMP (200 mL). After 50 min stirring, the crude product was isolated by distillation under reduced pressure (5 mbar, jacket 120 °C). The clear distillate (80 g) is a mixture of desired product **3b**, 3-methyl isomer and NMP, with a ratio of 33:18:49. (57% yield by NMR quantification with 1,3,5-trimethoxybenzene as internal standard and >99% ee according to GC on a HYDRODEX-γ-TBDAc column, 100 °C isotherm, RT: 10.4 min for *R* and 10.0 min for *S*). Further purification can be performed by fractionate distillation under reduced pressure or by column chromatography (eluent: methyl acetate/pentane 1:9).

4.5. (2aR,4aS,6R,7aR,7bS)-6-Methyltetrahydro-2H-furo[4,3,2-cd][1]benzofuran-2a,4a(3H,5H)-diol (**4b**)

Sodium hydroxide (1.2 g, 30% solution, 9.4 mmol) was added at 0–2 °C to a solution of dihydroxy-acetone dimer (DHA, 8.5 g, 47 mmol), water (440 mL) and (*R*)-5-methylcyclohex-2-enone **3b** (10.3 g, 94 mmol according to NMR quantification). After 15 h at 0–2 °C (pH occasionally adjusted to 10–11 with NaOH), the temperature was allowed to rise to RT. Once TLC analysis (EtOAc/MeOH 90/10, stained with vanillin/sulfuric acid in ethanol) showed full conversion, acetic acid (about 0.5 mL) was added to set the pH to 5–6. The solution was evaporated to dryness (jacked 35 °C), and the crude oil was purified by silica gel chromatography (160 g). Elution with EtOAc/MeOH gradient 95/5 to 50/50, provided **4b** in pure form (16.5 g, 88% isolated yield). The stereochemistry has been established by proton NMR, thanks to NOE correlations between the axial proton on carbon 2, 3 and carbon 6 (which configuration is *R*, as it is the case for (+)-pulegone).

$[\alpha]_D^{20}$ +8.33° (*c* 1.9, MeOH); HRMS calcd for $C_{11}H_{17}O_6$ $[M+HCOO]^-$ 245.10251, found 245.10306; IR: 3390 ν(OH) 2953, 2929, 2871 ν(CH aliph.) 1458, 1441 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6), δ ppm 5.55 (s, 1H) 5.30 (s, 1H) 4.10–4.06 (m, 1H) 3.96 (dd, J_1 = 8.5 Hz – J_2 = 2.4 Hz, 1H) 3.88 (d, *J* = 8.7 Hz, 1H) 3.79 (d, *J* = 8.5 Hz, 1H) 3.46 (dd, J_1 = 8.7 Hz – J_2 = 2.4 Hz, 1H) 2.06 (d, *J* = 6.9 Hz, 1H) 1.86 (dd, J_1 = 13.7 Hz – J_2 = 2.5 Hz, 1H) 1.77 (dd, J_1 = 14.2 Hz – J_2 = 2.5 Hz, 1H) 1.74–1.67 (m, 1H) 1.17–1.06 (m, 2H) 0.82 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6), ppm 104.36, 87.68, 79.12, 78.00, 77.04, 57.10, 44.39, 36.48, 22.59, 21.44.

4.6. (2aR,4aS,6R,7aR,7bS)-4a-Hydroxy-6-methylhexahydro-2H-furo[4,3,2-cd][1]benzofuran-2a(3H)-yl acetate



A solution of hemiacetal **4b** (2.0 g), THF (20 mL), pyridine (3.1 g 4 eq.), dimethylaminopyridine (DMAP, 0.06 g, 0.05 eq.) and acetic anhydride (3.0 g, 3 eq.) was stirred overnight at RT. Next day, TLC (heptane/MTBE, 50/50) showed full conversion. The reaction was diluted with ethyl acetate (50 mL) and quenched with water (50 mL). After phase split and wash with sat. $NaHCO_3$, the org. phase was dried over Na_2SO_4 and concentrated to dryness. The crude solid was purified by column chromatography on silica gel (eluent heptane/MTBE 100/0 to 30/70) leaving 1.6 g of pure acetate which was crystallized from ethyl acetate/heptane providing crystals suitable for X-ray analysis (fig. above). X-ray parameters, temperature: 100(2)°K, wavelength: 1.54178 Å, crystal system: monoclinic, unit cell dimensions, a = 17.818(9) Å (α = 90°), b = 16.961(9) Å (β = 107.080(16)°), c = 8.195(4) Å (γ = 90°), volume 2367(2) $Å^3$, theta range for data collection: 3.68–66.58°, reflections collected: 24150, refinement method: full-matrix least-squares on F2, goodness-of-fit on F2: 1.059, final R indices [I > 2sigma(I)], R1 = 0.0286, w*R*2 = 0.0736, R indices (all data), R1 = 0.0288, w*R*2 = 0.0737. Absolute structure parameter 0.02(10), largest diff. peak and hole 0.180 and −0.252 e.$Å^{-3}$.

$[\alpha]_D^{20}$ +3.57° (*c* 2, MeOH); mp 151–152 °C; HRMS calcd for $C_{12}H_{18}O_5Na$ $[M+Na]^+$ 265.10519, found 265.10472; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.96 (d, *J* = 6.78 Hz, 3 H) 1.26 (ddd, *J* = 14.68, 12.17, 3.51 Hz, 1 H) 1.37 (dd, *J* = 13.43, 12.42 Hz, 1 H) 1.60 (s, 2 H) 1.91–2.02 (m, 1 H) 2.02–2.09 (m, 1 H) 2.13 (s, 3 H) 2.72 (d, *J* = 6.78 Hz, 1 H) 3.02 (s, 1 H) 3.70 (ddd, *J* = 9.54, 2.76, 0.70 Hz, 1 H) 4.22 (ddd, *J* = 6.65, 3.89, 2.26 Hz, 1 H) 4.27 (dd, *J* = 9.64, 2.76 Hz, 1 H) 4.38 (d, *J* = 9.64 Hz, 1 H) 4.51 (d, *J* = 9.54 Hz, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 171.14, 104.87, 93.12, 78.39, 77.90, 77.36, 76.36, 55.01, 44.24, 36.50, 22.96, 21.42, 21.13.

4.7. (3S,3aS,4R,6S,7aR)-3-(hydroxymethyl)-6-methyloctahydrobenzofuran-3,4-diol (**5b**)

Sodium borohydride (0.43 g) was added portionwise at 0 °C to an aq. solution of compound **4b** (prepared from 1.2 g (*R*)-5-methylcyclohex-2-enone and DHA, and neutralisation with acetic acid). After 3 h stirring at 0–2 °C and full conversion according to NMR and TLC, acetic acid (about 1 g) was added to destroy the excess of reagent. The resulting mixture was concentrated to

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dryness leaving 2.3 g of a yellowish residue. The latter was purified by silica gel chromatography (150 g), eluted with ethyl acetate/methanol 90/10, providing compound **5b** (1.6 g, 74%) as a colorless solid.

$[\alpha]_D^{20}$ −8.17° (*c* 2.6, MeOH); HRMS calcd for $C_{11}H_{19}O_6$ $[M+HCOO]^-$ 247.11816, found 247.11876; ^{1}H NMR (600 MHz, DMSO-d_6) ppm: 5.01 (s, 1H) 4.67 (s, 1H) 4.65 (s, 1H) 4.31–4.27 (m, 1H) 3.70 (d, J = 9.4 Hz, 1H) 3.62 (d, J = 11.6 Hz, 1H) 3.48–3.44 (m, 2H) 3.31–3.27 (m, 1H) 1.82–1.76 (m, 1H) 1.74–1.70 (m, 1H) 1.60–1.51 (m, 2H) 1.03 (td, 1H) 0.85 (d, J = 6.6 Hz, 3H) 0.84–0.77 (m, 1H); ^{13}C NMR (151 MHz, DMSO-d_6), ppm: 77.69, 75.25, 69.80, 66.79, 64.94, 54.76, 43.05, 36.34, 24.95, 21.73.

4.8. (3aS,4R,6S,7aR)-4-hydroxy-6-methyl-hexahydro-benzofuran-3(2H)-one (**6b** and minor isomer)

A solution of (*R*)-5-methylcyclohex-2-enone (5.7 g, 25.4 mmol), DHA (4.6 g, 50.8 mmol) and NaOH (0.2 g, 0.1 eq) in water (250 mL), was hold ca. 20 h at 0 °C. After full conversion according to NMR, acetic acid (0.25 mL) was added, followed by $NaBH_4$ (0.97 g). Again, after 4 h stirring at 0 °C and full conversion according to NMR, acetic acid (3.5 mL) was added to destroy the excess of reagent. Then after neutralisation with NaOH (4 mL 10% solution, pH 7), sodium periodate (3.9 g) was added portionwise in such a way to keep the temperature between 15–25 °C. After 15 h at 20 °C and full conversion according to NMR and TLC, the solid formed was removed by filtration, and washed with ethyl acetate (50 mL). After phase split, and three additional extraction with ethyl acetate (30 mL each), the organic phase was evaporated to dryness leaving 7.9 g of a viscous oil (91% yield, as an 85:15 mixture of diastereomers). An aliquot (0.7 g) was submitted to a silica gel chromatography (75 g SiO_2, eluent heptane/MTBE: 50/50), providing the two isomers of compound **6b** in pure form.

Main isomer (4*R*-epimer): 0.56 g, crystalline solid (needle shaped) mp 80–82 °C; $[\alpha]_D^{20}$ +6.46° (*c* 1.9, MeOH); HRMS calcd for $C_9H_{14}O_3Na$ $[M+Na]^+$ 193.0840, found 193.085; ^{1}H NMR (600 MHz, DMSO-d_6) ppm: 4.86 (s, 1H) 4.25 (dd, J = 3.4 Hz, 1H) 4.16 (d, J = 16.9 Hz, 1H) 3.76 (d, J = 16.9 Hz, 1H) 3.53–3.46 (m, 1H) 2.00 (dd, J_1 = 9.7 Hz, J_2 = 4.3 Hz, 1H) 1.87–1.82 (m, 1H) 1.79–1.75 (m, 1H) 1.75–1.66 (m, 1H) 1.20 (td, J_1 = 14.6 Hz, J_2 = 12.2 Hz, J_3 = 3.7 Hz, 1H) 0.93 (q, J = 11.8 Hz, 1H) 0.90 (d, J = 6.6 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6), ppm: 214.5, 77.66, 70.70, 65.55, 53.99, 42.67, 35.33, 25.57, 21.77.

Minor isomer (4*S*-epimer): 57 mg (gel) $[\alpha]_D^{20}$ +68.09° (*c* 2.4, methanol). ^{1}H NMR (400 MHz, D_2O) ppm: 0.81 (t, J = 7.53 Hz, 1H) 0.87 (d, J = 6.53 Hz, 3H) 1.14–1.20 (m, 1H) 1.21–1.38 (m, 1H) 1.39–1.48 (m, 1H) 1.73–1.81 (m, 1H) 2.46 (t, J = 5.27 Hz, 1H) 3.51 (t, J = 6.65 Hz, 1H) 3.87 (d, J = 17.32 Hz, 1H) 3.97 (d, J = 17.57 Hz, 1H) 4.21–4.26 (m, 1H) 4.35–4.40 (m, 1H).

4.9. (3aR,4R,6R,7aR)-4-((tert-butyldimethylsilyl)oxy)-6-methylhexahydrobenzofuran-3(2H)-one (**10b**)

Tert-butyldimethylsilyl-trifluoromethane-sulfonate (19.3 g, 73 mmol, 1.1 eq.) was added dropwise at 0 °C to a crude mixture of compound **6b** (11.3 g, isomeric ratio 85:15, 66 mmol of **6b**) anhydrous THF (120 mL) and imidazole (11.3 g, 165 mmol, 2.5 eq.). After 2 h at 0 °C, sodium bicarbonate (50 mL, 10% solution) was added and the mixture was partially concentrated under reduced pressure to remove the THF. The resulting mixture was extracted with ethyl acetate (3 × 150 mL) and the combined organic layers were washed with water (2 × 50 mL), dried over sodium sulfate and concentrated under reduced pressure, leaving 35 g of an orange oil. The latter was purified through a pad of silica gel (200 g) eluted with heptane/ethyl acetate 8:2, providing 12.8 g of **10b** as a colorless oil (about 80% overall yield from **3b**, ee > 96% according to GC on a 25 m HYDRODEX-β-TBDMS column, gradient: 80–200 °C in 60 min. RT: 40.7 min for **10b** and 41.8 min for the enantiomer).

$[\alpha]_D^{20}$ −11.5 (*c* 2, acetonitrile); HRMS calcd for $C_{15}H_{29}O_3Si$ $[MH]^+$ 285.18859; found 285.18850. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.02 (d, J = 2.01 Hz, 6 H) 0.89 (s, 9 H) 0.98 (d, J = 6.53 Hz, 3 H) 1.08 (ddd, J = 13.00, 12.50, 11.30 Hz, 1 H) 1.26 (ddd, J = 15.30, 12.00, 3.00 Hz, 1 H) 1.80–1.95 (m, 2 H) 1.96–2.07 (m, 1 H) 2.15 (dd, J = 9.29, 4.27 Hz, 1 H) 3.77 (ddd, J = 11.11, 9.10, 4.14 Hz, 1 H) 3.85 (d, J = 17.07 Hz, 1 H) 4.18 (d, J = 17.32 Hz, 1 H) 4.26–4.32 (m, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm −4.98, −4.69, 17.75, 21.70, 25.50, 25.60, 35.49, 42.75, 54.76, 67.69, 71.16, 78.26, 213.59.

4.10. (2R,3aR,4R,6R,7aR)-4-((tert-butyldimethylsilyl)oxy)-2-(1-hydroxy-3-methylbut-2-en-1-yl)-6-methyl-hexahydrobenzofuran-3(2H)-one (**11b**)

Compound **10b** (3.0 g) in anhydrous THF (6 mL) was added dropwise at −78 °C to a solution of LDA (prepared with 1.7 g diisopropylamine in 30 mL THF and 7.4 mL n-butyl-lithium 1.6 M in hexane). After 10 min at −78 °C, freshly distilled senecialdehyde (1.4 mL) diluted in THF (5 mL) was added dropwise within 10 min, in such a way to keep the temperature below −75 °C. After 20 min stirring, acetic acid (16.7 g, 5% in water) was added rapidly, and the solution was allowed to warm to RT. After removal of the THF by distillation under reduced pressure and extraction with MTBE (3 × 50 mL), purification of the crude oil by column chromatography (120 g SiO_2, eluent heptane/ethyl acetate 95:5, 750 mL, then 90:10, 750 mL) left 2.0 g of a clear colorless oil (55% as a 1:1 isomeric mixture).

HRMS calcd for $C_{20}H_{33}O_3Si$ $[MH-(H_2O-H_2)]^+$ 349.2198, found 349.2577; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.01 (m, 6 H) 0.86–0.88 (m, 9 H) 0.96 (dd, J = 6.53, 2.26 Hz, 3 H) 0.98–1.13 (m, 1 H) 1.17–1.33 (m, 2 H) 1.69 (dd, J = 11.30, 1.00 Hz, 3 H) 1.73 (s, 3 H) 1.77–1.91 (m, 1 H) 1.93–2.09 (m, 1 H) 2.17–2.24 (m, 1 H) 3.69–3.79 (m, 1 H) 3.97–4.01 and 4.06–4.10 (m, 1 H) 4.44–4.50 and 4.69–4.76 (m, 1 H) 4.57–4.64 (m, 1 H) 5.30 [(dt, J = 9.03, 1.38 Hz) + 5.39 (ddt, J = 9.10, 2.82, 1.32, 1.32 Hz), 1 H].

4.11. (3aR,4R,6R,7aR,Z)-4-((tert-butyldimethylsilyl)oxy)-6-methyl-2-(3-methylbut-2-en-1-ylidene)-hexahydro-benzofuran-3(2H)-one (**12b**)

A solution of trifluoroacetic anhydride (3.8 mL, 26.9 mmol, 3 eq.) in dichloromethane (30 mL) was added dropwise within 1 h at 0 °C to a solution of compound **11b** (3.3 g, 8.9 mmol, 1 eq.), dichloromethane (60 mL), triethylamine (7.5 mL, 53.7 mmol, 6 eq.) and DMAP (109 mg, 0.9 mmol, 0.1 eq.). The mixture was heated to 24 °C and stirred for 38 h. After full conversion according to GC, $NaHCO_3$ (50 mL) and MTBE (30 mL) was added, and the layers were separated. The organic layer was washed with distilled water (2 × 50 mL) and concentrated under vacuum. The crude oil was purified through a pad of silica gel, eluted with heptane/ethyl acetate 8:2, providing **12b** (2.8 g, 86%) as a yellowish oil.

HRMS calcd for $C_{20}H_{35}O_3Si$ $[MH]^+$ 351.2355, found 351.2354; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.00 (s, 3 H) 0.03 (s, 3 H) 0.88–0.90 (m, 9 H) 0.99 (d, J = 6.50 Hz, 3 H) 1.05–1.16 (m, 2 H) 1.30–1.40 (m, 2 H) 1.86 (dd, J = 13.30, 1.00 Hz, 6 H) 2.13 (ddt, J = 15.03, 3.61, 1.98, 1.98 Hz, 1 H) 2.36 (dd, J = 8.53, 5.02 Hz, 1 H) 3.71 (ddd, J = 10.48, 8.60, 4.27 Hz, 1 H) 4.53 (ddd, J = 5.33, 3.45, 2.51 Hz, 1 H) 6.12 (dq, J = 12.05, 1.25 Hz, 1 H) 6.27 (d, J = 12.05 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$) ppm: −4.72, −4.62, 17.98, 18.84, 21.86, 25.80, 25.87, 26.64,

31.89, 35.56, 42.15, 54.21, 69.01, 78.45, 103.34, 118.41, 142.91, 199.23.

4.12. (3S,3aR,4R,6R,7aR,Z)-4-((tert-butyldimethylsilyl)oxy)-3,6-dimethyl-2-(3-methylbut-2-en-1-ylidene)-octahydrobenzofuran-3-ol (**13b**)

Methylmagnesium-bromide (5.7 mL, 1.6 M in Et_2O, 17.1 mmol, 3 eq.) was added dropwise at 0 °C to a slurry of compound **12b** (2 g, 5.7 mmol, 1 eq.) and cerium chloride (2.1 g, 17.1 mmol, 1.5 eq. weighted in a glove box under an inert and dry atmosphere) in anhydrous tetrahydrofuran (80 mL) previously stirred 1 h at RT before being cooled to 0 °C. After 45 min and full conversion according to GC and TLC, the reaction was quenched by addition of a 10% solution of $NaHCO_3$ (30 mL). THF was removed under vacuum and the aqueous residue was extracted with MTBE (3 × 100 mL). The combined organic layers were washed with distilled water (2 × 30 mL) and concentrated under vacuum, leaving 2.1 g of a yellowish oil which was purified by flash chromatography on silica gel (75 g) eluted with heptane/ethyl acetate 95:5, providing 1.5 g (72%) of a pale yellow oil.

$[\alpha]_D^{20}$ −1.57 (*c* 1, acetonitrile); HRMS calcd for $C_{20}H_{35}O_3Si$ [M-CH3]$^+$ 351.2355, found 351.2360; ^{1}H NMR (400 MHz, BENZENE-d6) δ ppm 0.02 (d, *J* = 2.76 Hz, 6 H) 0.78 (s, 9 H) 0.86 (d, *J* = 6.78 Hz, 3 H) 0.91 (q, *J* = 12.00 Hz, 1 H) 1.01–1.10 (m, 1 H) 1.36 (br s, 3 H) 1.47 (s, 1 H) 1.63 (br s, 3 H) 1.66 (dd, *J* = 9.28, 4.26 Hz, 1 H) 1.68 (s, 3 H) 1.73–1.81 (m, 1 H) 2.00 (ddt, *J* = 14.81, 3.83, 1.98, 1.98 Hz, 1 H) 3.86 (ddd, *J* = 11.80, 9.29, 4.27 Hz, 1 H) 4.02 (s, 1 H) 4.28–4.33 (m, 1 H) 5.29 (d, *J* = 11.54 Hz, 1 H) 5.92 (ddt, *J* = 11.45, 2.73, 1.32, 1.32 Hz, 1 H). ^{13}C NMR (101 MHz, BENZENE-d6) δ ppm −4.55, −2.92, 17.73, 17.85, 21.44, 25.18, 25.65, 25.80, 29.02, 36.28, 42.45, 54.19, 70.97, 77.81, 79.40, 94.20, 119.56, 128.58,160.35.

4.13. (3S,3aS,4R,6S,7aR,Z)-3,6-dimethyl-2-(3-methylbut-2-en-1-ylidene)octahydrobenzofuran-3,4-diol (**14b**)

Tetra-n-butylammonium fluoride (2.9 mL, 1 M in THF, 1.2 eq.) was added to a solution of compound **13b** (0.9 g, 1 eq.) in anhydrous THF (50 mL) at 0 °C under an inert atmosphere. After 30 min stirring at 0 °C, $NaHCO_3$ (30 mL, 10% solution) was added. THF was removed by distillation under reduced pressure, and the aqueous residue extracted with MTBE (2 × 100 mL). The combined organic layers were washed with water (2 × 20 mL) and concentrated under vacuum to afford 1.4 g of a brownish oil, which was purified by column chromatography, eluted with heptane/ethyl acetate 8:2 to 6:4 providing 0.5 g (90%) of a colorless solid.

$[\alpha]_D^{20}$ −28 (*c* 0.5, acetonitrile); mp 84–85 °C; HRMS calcd for $C_{15}H_{25}O_3$ [MH]$^+$ 253.1803, found 253.1797; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.86 (m, 1H) 0.97 (d, *J* = 6.53 Hz, 3 H) 1.00 (q, *J* = 12 Hz, 1 H) 1.18 (m, 1 H) 1.52 (s, 3 H) 1.73 (d, *J* = 0.75 Hz, 3 H) 1.76 (dd, *J* = 9.28, 4.26 Hz, 1 H) 1.78 (s, 3 H) 1.87 (m, 1 H) 2.13 (m, 1 H) 2.84 (s, 1 H) 3.09 (s, 1 H) 3.77 (dddd, *J* = 11.80, 9.30, 4.30, 1.20 Hz, 1 H) 4.38 (m, 1 H) 5.32 (d, *J* = 11.29 Hz, 1 H) 6.01 (ddt, *J* = 11.23, 2.82, 1.38, 1.38 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 18.20, 21.61, 25.27, 25.97, 28.42, 36.46, 40.55, 54.54, 68.61, 78.58, 80.77, 93.57, 117.85, 131.18, 159.87.

4.14. (3S,3aS,6R,7aR,Z)-3-hydroxy-3,6-dimethyl-2-(3-methylbut-2-en-1-ylidene)hexahydro-benzo-furan-4(2H)-one (**15**)

A solution of compound **14b** (100 mg, 2 mmol) in acetonitrile (1 mL) was added to a suspension of tetra-n-propylammonium perruthenate (TPAP, 28 mg, 0.08 mmol), *N*-Methyl-morpholine *N*-oxide (NMO, 93 mg, 0.8 mmol) and 4 Å powdered molecular sieves (0.4 g) in dichloromethane (5 mL) stirred under an inert atmosphere. After 1 h and full conversion according to GC and TLC, the suspension was filtered through a pad of silica gel, eluted with ethyl acetate and concentrated under vacuum, providing 50 mg (50%) of compound **15** as a yellowish solid.

$[\alpha]_D^{20}$ +28 (*c* 0.25, acetonitrile); mp 99–100 °C; HRMS calc for $C_{15}H_{22}O_3Na$ [M+Na]$^+$ 273.1466, found 273.1461; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.06 (d, *J* = 6.53 Hz, 3 H) 1.46 (d, *J* = 0.75 Hz, 3 H) 1.66 (ddd, *J* = 14.62, 11.11, 3.64 Hz, 1 H) 1.72 (d, *J* = 0.75 Hz, 3 H) 1.78 (s, 3 H) 2.01–2.09 (m, 1 H) 2.19–2.28 (m, 1 H) 2.28–2.36 (m, 1 H) 2.42 (ddd, *J* = 13.43, 3.39, 2.01 Hz, 1 H) 2.55 (d, *J* = 5.27 Hz, 1 H) 4.77 (dt, *J* = 5.08, 3.48 Hz, 1 H) 5.34 (d, *J* = 0.75 Hz, 1 H) 5.40 (d, *J* = 11.54 Hz, 1 H) 5.97 (ddt, *J* = 11.45, 2.79, 1.29, 1.29 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 18.19, 21.50, 26.00, 27.58, 28.39, 36.12, 50.19, 55.92, 77.23, 78.87, 93.66, 109.98, 117.83, 131.63, 213.85.

4.15. (3S,3aS,6R,7aR,Z)-3,6-dimethyl-2-(3-methylbut-2-en-1-ylidene)-3-((trimethylsilyl)oxy)hexahydro -benzofuran-4(2H)-one (**16**)

1-(Trimethylsilyl)imidazole (0.07 mL) and TMS-Chloride (4 μL) was added to a solution of compound **15** (4 mg**)** and imidazole (18.3 mg) in dimethylformamide (0.7 mL). After 1 h stirring at RT, and full conversion (TLC, LC/MS), the solution was diluted with ethyl acetate (10 mL) and treated with sat. sodium bicarbonate (10 mL). After phase split, the org. phase was diluted with n-heptane (5 mL) and washed with water (2 × 10 mL). Concentration to dryness, left 5 mg (>99%) of a colorless residue which crystallized on the recipient walls.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.03 (s, 9 H) 0.90 (d, *J* = 7.28 Hz, 3 H) 1.67 (d, *J* = 0.75 Hz, 3 H) 1.75 (s, 3 H) 1.92 (br dd, *J* = 13.30, 6.02 Hz, 1 H) 2.02–2.11 (m, 2 H) 2.33 (br d, *J* = 3.51 Hz, 1 H) 2.46 (dd, *J* = 16.44, 5.40 Hz, 1 H) 2.64 (d, *J* = 8.78 Hz, 1 H) 4.67 (td, *J* = 8.91, 6.27 Hz, 1 H) 5.23 (d, *J* = 11.0 Hz, 1 H) 5.97 (dm, *J* = 11.0 Hz, 1 H).

4.16. (3S,3aS,7aR,Z)-3,6-dimethyl-2-(3-methylbut-2-en-1-ylidene)-3-((trimethylsilyl)oxy)-3,3a,7,7a-tetrahydro-benzofuran-4(2H)-one (TMS-ent-bisabolangelone, **17**)

A solution of compound **16** (5 mg, 1 eq.) in anhydrous THF (0.5 mL) was added dropwise at −78 °C to a solution of LDA, prepared by addition of nBuLi (1 M in hexane, 2.2 eq.) to a solution of diisopropylamine (2.4 eq.) in anhydrous THF (0.5 mL) at 0 °C under argon. After 10 min stiring at −78 °C, a solution of *N-tert*-butylbenzenesulfinimidoyl chloride (3 eq.) in anhydrous THF (0.5 mL) was added dropwise and the mixture kept stirring for 50 min at −78 °C. The reaction was quenched by addition of a saturated solution of NH_4Cl and ethyl acetate. The layers were separated, washed with water and concentrated under vacuum. LC/MS, GC and TLC showed that only 20% conversion took place. The crude residue was passed through a pad of silica gel (0.5 g), eluted with heptane/ethyl acetate 8:2. Despite poor separation of the excess of reagent, LC/MS, GC and NMR (same retention time and NMR signals as (+)-TMS-bisabolangelone **21** described *ibid*) led to the conclusion that the desired enone **17** has been formed. Unfortunately, unsufficient material was available for full characterisation, but, GC on a chiral columns HYDRODEX-γ-TBDAc and LIPODEX E, allowed us to attribute compound **17** and (+)-TMS-bisabolangelone (section 4.19) to one distinct peak of a racemic sample, obtained by synthesis from rac. 5-methylcyclohexenone.

4.17. (R)-3,6-dimethyl-2-(3-methylbut-2-en-1-yl)-6,7-dihydrobenzofuran-4(5H)-one (**18**)

Trimethylsilyl-chloride (0.35 mL, 3 eq.) was added at 0 °C to a suspension of compound **16** (230 mg, 1 eq.) imidazole (187 mg, 3

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eq.) and DMF (0.3 mL) in acetonitrile (5 mL) under an inert atmosphere of argon. The mixture was stirred 1 h at 0 °C and 3 h at RT, and quenched subsequently by addition of a saturated solution of $NaHCO_3$ (5 mL). Acetonitrile was removed by distillation under reduced pressure and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with water (2 × 10 mL) and concentrated under vacuum. The crude oil was purified over a pad of silica gel, eluted with heptane/ethyl acetate 1:1, providing 75 mg (35%) of compound **18** as yellowish oil, which solidified on standing.

HRMS calcd for $C_{15}H_{21}O_2$ $[MH]^+$ 233.1541, found: 233.1536; ^1H NMR (600 MHz, $CDCl_3$) δ ppm 1.15 (d, J = 6.60 Hz, 3 H) 1.72 (d, J = 7.34 Hz, 6 H) 2.14 (s, 3H) 2.15–2.23 (m, 1 H) 2.35–2.43 (m, 1H) 2.44–2.52 (m, 2 H) 2.88 (dd, J = 16.69, 4.95 Hz, 1 H) 3.25 (br d, J = 7.34 Hz, 2 H) 5.20–5.26 (m, 1 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 8.65, 17.61, 20.95, 24.54, 25.50, 30.69, 31.44, 46.63, 112.04, 119,29, 120.52, 133,51, 150.39, 165.02, 195.22.

4.18. Isolation of bisabolangelone from Angelica silvestris L.

Fruits, leaves and roots from *Angelica silvestris,* were harvested August 1st, 2014, along the Rhine river banks between Basel's border and Huningue's pedestrian bridge in France. 400 g fresh seeds (fruits) were dried in a vacuum oven at 40 °C and 50 mbar during 3 days, leaving about 123 g of dry material. This substrate was subsequently powdered with a kitchen mixer to yield a fine brownish powder. 100 g seed powder, suspended in 500 g acetonitrile (HPLC grade), was submitted to ultra-sonication at 20–30 °C and alternate stirring for 6 h. The solid was separated by filtration, and submitted to a second extraction with 250 g acetonitrile. After a second round of sonication, the clear green filtrate was extracted twice with 200 g heptane fractions. Both layers were concentrated separately leaving: 3.6 g of an oily residue for the heptane fraction which contains little bisabolangelone, and 7.6 g for the acetonitrile fraction which contains about 25% bisabolangelone (HPLC A%). The solid residue from acetonitrile was subsequently dissolved in 50 mL MTBE, and aged at 5 °C for 48 h. After this time the solid formed was collected leaving 1.58 g of crude bisabolangelone (70% content). The later was dissolved in 5 g methanol under reflux, filtered for clarity and let crystallize at RT. The solid formed was collected by filtration, washed with cold methanol and dried under vacuum, leaving 0.44 g colorless crystals of bisabolangelone (>98% purity by HPLC A%).

Spectral data's were consistent with those previously reported.[1] LC/MS $[MH]^+$ 249; UV max. 248 nm, $[\alpha]_D^{20}$ +148 (*c* 1, acetonitrile), $[\alpha]_D^{20}$ +85 (*c* 1, $CHCl_3$), lit.[31] $[\alpha]_D^{20}$ +111 (*c* 1.1, $CHCl_3$). The discrepancies between the opt. rotations in chloroform may be explained by the rapid decomposition of bisabolangelone in this solvent. The content of bisabolangelone has been determined by HPLC in different parts of the plant (table below). Equipment: Agilent 1200, column: Waters Acquity BEH Phenyl, particle size: 1.7 μm, length: 50 mm internal diameter: 2.1 mm, column temperature: 45 °C; mobile phase A: water/acetonitrile/TFA: 95/5/0.05 (v), B: water/acetonitrile/TFA: 5/95/0.05 (v). Gradient: T_0 5% B, $T_{0.75}$ 5% B, $T_{4.75}$ 60% B, $T_{5.75}$ 95% B, $T_{6.51}$ 5% B, $T_{7.50}$ 5% B. Flow rate: 0.6 mL/min. Run time: 7.5 min. Injection volume: 1 μl. Detection: UV, wavelength 220 nm. Sample preparation: 1 g dry powdered material (seeds, stem pieces, leaves and roots) were subjected to ultra-sonication with 10 mL THF for 5 min. 1 mL supernatant was transferred in an HPLC vial, and injected as it. Quantification was made by comparison with a reference solution of bisabolangelone in acetonitrile (5.6 mg in 5 mL, inj. 1 μL, RT 4.3 min).

Material	Bisabolangelone (area %)	Bisabolangelone (weight %)
Seeds	2.4	1.4
Stem	3.17	0.02
Leaves	14.7	0.3
Roots	8.6	0.06

4.19. (3R,3aR,7aS,Z)-3,6-dimethyl-2-(3-methylbut-2-en-1-ylidene)-3-((trimethylsilyl)oxy)-3,3a,7,7a -tetra-hydrobenzofuran-4(2H)-one, (+)-TMS-bisabolangelone (**21**)

Bisabolangelone (10 mg) and imidazole (5 mg) were dissolved in dimethylformamide (1 mL). TMS-imidazole (0.1 mL) and TMS-Cl (0.01 mL) were added subsequently at RT. After 30 min stirring LC/MS, GC and TLC showed full conversion. After dilution with ethyl acetate, quench with water (10 mL), phase split, wash with sat. $NaHCO_3$ and brine (5 mL each), provided after concentrated to dryness 12 mg (93%) of a yellowish oil which crystallized from heptane.

Mp 95–96 °C, $[\alpha]_D^{20}$ +82.5 (*c* 1, acetonitrile); HRMS calcd for $C_{18}H_{28}NaO_3Si$ $[M+Na]^+$ 343.1705, found 343.1698; ^1H NMR (400 MHz, BENZENE-d_6) δ ppm 0.07 (s, 9 H) 1.35 (s, 3 H) 1.68 (d, J = 3.26 Hz, 6 H) 1.74 (s, 3 H) 2.18 (dd, J = 17.57, 7.53 Hz, 1 H) 2.43 (d, J = 8.78 Hz, 1 H) 2.56 (ddt, J = 17.47, 8.63, 1.25, 1.25 Hz, 1 H) 4.39 (q, J = 8.20 Hz, 1 H) 5.44 (d, J = 11.04 Hz, 1 H) 5.91 (s, 1H) 6.52 (dm, J = 11.46 Hz, 1 H). ^{13}C NMR (151 MHz, BENZENE-d_6) δ ppm 1.75, 2.32, 18.45, 24.07, 25.03, 26.53, 36.87, 57.23, 77.72, 81.35, 96.35, 119.85, 131.75, 157.32, 158.51, 194.25.

4.20. Chiral GC conditions

GC apparatus HP6890, injector 260 °C, detector 200 °C, H_2 flow 1.5 mL min, pressure 0.52 bar, mode: split 1:10, injection 1 μl. Column HYDRODEX-γ-TBDAc (Macherey-Nagel), 25 m × 0.25 mm, temperature program: 140 °C for 130 min then 200 °C within 12 min. Diluted samples (ca. 0.1% in MTBE) of compound **17**, racemic mixture (obtained by synthesis starting with rac. 5-methyl-cyclohexenone) and TMS-bisabolangelone **21**, were injected single or mixed accordingly to check the increase of the corresponding peak.

4.21. (3R,3aR,4R,6S,7aS,Z)-3,6-dimethyl-2-(3-methylbut-2-en-1-ylidene)octa-hydrobenzofuran-3,4-diol, 5,6-dihydro-bisabolangelol (**19**)

Sodium borohydride (80 mg) was added in small portions within 30 min to a cold solution (0 °C) of bisabolangelone (250 mg) dissolved in anhydrous methanol (15 mL). After 3 h, the reaction was over according to HPLC (one peak) and TLC (two spots). After acidification with acetic acid and work up with MTBE/$NaHCO_3$, we got after concentration to dryness 200 mg of a residue which was purified by column chromatography (10 g SiO_2, eluent Heptane/MTBE 3:2), providing 31 mg (12%) of a less polar compound (amorphous solid) which correspond to the 1,2-reduction product (obtained by Chen et al.[30] as the main product) and 81 mg (32%) of compound **19** obtained as a colorless solid.

HRMS calcd for $C_{15}H_{25}O_3$ $[MH]^+$ 253.1803, found 253.1797, calcd for $C_{15}H_{24}NaO_3$ $[M+Na]^+$ 275.1623, found 275.1618; mp 142–143 °C (lit.[30] 140–142 °C, lit.[31] 135–137 °C). Notice, the opt. rotation could not be measured with accuracy. The value: −11.6° obtained, is not reliable due to the fast decomposition of the substrate in chloroform. Lit.[31] $[\alpha]_D^{20}$ -3.7 (*c* 1, $CHCl_3$). ^1H NMR (600 MHz, DMSO-d_6) δ ppm 0.89 (br d, J = 6.05 Hz, 3 H) 1.28–1.43 (m, 2 H) 1.50

(s, 3 H) 1.51–1.62 (m, 2 H) 1.64 (s, 3 H) 1.69 (br d, J = 5.14 Hz, 1 H) 1.72 (s, 3 H) 2.18 (br t, J = 6.97 Hz, 1 H) 3.92 (dq, J = 11.39, 5.74 Hz, 1 H) 4.29 (dt, J = 10.09, 6.97 Hz, 1 H) 4.47 (br d, J = 5.69 Hz, 1 H) 4.49 (s, 1 H) 5.14 (d, J = 11.19 Hz, 1 H) 5.91 (br d, J = 11.37 Hz, 1 H) ^{13}C NMR (151 MHz, DMSO-d_6) δ ppm 18.19, 22.28, 26.13, 29.11, 37.89, 40.16, 49.54, 68.97, 79.74, 92.91, 119.72.

(m, 2 H) 2.31 (t, J = 7.03 Hz, 1 H) 3.21 (d, J = 1.51 Hz, 1 H) 3.63 (s, 3 H) 4.35–4.45 (m, 1 H) 5.23 (d, J = 11.29 Hz, 1 H) 5.41 (dt, J = 11.54, 5.77 Hz, 1 H) 6.00 (br dd, J = 11.29, 1.25 Hz, 1 H) 7.35–7.42 (m, 3 H) 7.52–7.59 (m, 2 H) ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 18.14, 21.52, 25.99, 26.34, 26.98, 28.51, 35.86, 37.18, 47.29, 55.68, 74.61, 78.23, 79.21, 94.94, 118.14, 127.03, 128.37, 129.57, 132.05, 160.26, 165.91.

NMR signals (HSQC) of tetrahydrobisabolangelol **19** and the corresponding MTPA-esters **22** (*R* and *S*)

Sample	**19**		(*R*)-MTPA-ester, **22**-(*R*)			(*S*)-MTPA-ester, **22**-(*S*)			Δ δ $^{S-R}$
Position	^{1}H NMR	^{13}C NMR[30]	^{1}H NMR δ ppm/Hz		^{13}C NMR	^{1}H NMR δ ppm/Hz		^{13}C NMR	Hz
6-CH3	0.99 ppm	21.8 ppm	0.97	388.8	21.09 ppm	1.00	398.8	21.14 ppm	+10.0
7-H	1.35								
5/7 ax	1.42		1.46	563.2	36.76	1.44	579.6	36.98	+16.4
6-H	1.50	26.0	1.50	600.1	25.89	1.50	601.8	26.40	+1.7
5/7 eq	1.86	37.5	1.92	764.9	36.35	1.93	771.8	36.91	+6.9
5-H eq	1.95								
3-CH3	1.64	30.6	1.37	548.5	29.24	1.09	435.6	28.04	−113
19-CH3	1.73	18.2	1.69	677.7	17.34	1.68	675.3	16.60	−2.4
18-CH3	1.79	26.1	1.78	711.4	25.89	1.77	709.3	25.89	−2.1
4-OH	2.04								
3-OH	2.07		3.22			3.22			
3a-H	2.46	48.8	2.43	971.0	47.27	2.31	924.0	47.08	−47.0
7a-H	4.41	79.1	4.42	1768.5	79.01	4.40	1762.0	78.87	−7.0
CH=	5.34	94.5	5.29	2118.3	95.11	5.23	2093.0	94.64	−25.3
4-H	4.14	70.4	5.41	2165.4	74.53	5.41	2166.0	73.99	+0.6
CH=	6.06	118.3	6.02	2410.6	119.5	6.00	2402.3	117.80	−8.3
O-CH3			3.50	1401.8	55.31	3.63	1451.4	55.27	
Ar. para			7.39	2957.6	128.92	7.30	2409.7	123.55	
Ar. ortho			7.41	2963.5	128.93	7.39	2963.4	128.55	
Ar.ortho			7.52	3007.9	127.21	7.56	3007.9	126.88	

*4.22. (3R,3aS,4R,6R,7aS,Z)-3-hydroxy-3,6-dimethyl-2-(3-methylbut-2-en-1-ylidene)octahydro-benzofuran-4-yl (R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate, (R)-MTPA ester **22**(R)*

(*S*)-MTPA-Cl (20 μL) was added to 7 mg diol **19** dissolved in 0.5 mL pyridine. The clear yellowish solution was kept at RT for 8 h. After that time, HPLC showed full conversion. The solution was quenched with diluted sodium bicarbonate solution (5 mL, 10%) and extracted with MTBE (10 mL). After a second wash with water, the org. phase was concentrated to dryness leaving about 12 mg of the corresponding ester, which was used for HSQC-NMR investigations (caution: the *S*-Mosher acid chloride gives rise to the *R*-Mosher ester, since there is a change in relative priority: CF3 is lower than COCl but higher than COOR. The product was purified afterwards by flash chromatography (1 g SiO2, eluent MTBE/Heptane 2:8) providing 9 mg of a waxy solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.97 (d, J = 6.02 Hz, 3 H) 1.37 (s, 3 H) 1.39–1.52 (m, 3 H) 1.70 (s, 3 H) 1.78 (s, 3 H) 1.87–1.96 (m, 2 H) 2.43 (t, J = 7.03 Hz, 1 H) 3.21 (d, J = 1.25 Hz, 1 H) 3.51 (s, 3 H) 4.42 (dt, J = 10.50, 6.60 Hz, 1 H) 5.29 (d, J = 11.04 Hz, 1 H) 5.41 (quin, J = 5.70 Hz, 1 H) 6.02 (br dd, J = 11.17, 1.13 Hz, 1 H) 7.36–7.48 (m, 3 H) 7.48–7.57 (m, 2 H) ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 18.17, 21.49, 26.01, 26.17, 29.16, 35.38, 37.06, 47.46, 55.29, 74.83, 78.24, 79.21, 95.30, 118.22, 127.54, 128.63, 129.82, 131.84, 132.01, 159.99, 165.88.

*4.23. (3R,3aS,4R,6R,7aS,Z)-3-hydroxy-3,6-dimethyl-2-(3-methylbut-2-en-1-ylidene)octahydro-benzo-furan-4-yl (S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate, (S)-MTPA ester **22**-(S)*

22-(*S*) was obtained under the same conditions as **22**-(*R*) with (*R*)-MTPA-chloride (Notice, **22**-(*S*) and (*R*) have different retention time by HPLC).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.00 (d, J = 6.00 Hz, 3 H) 1.09 (d, J = 1.00 Hz, 3 H) 1.37–1.55 (m, 3 H) 1.68 (s, 3 H) 1.77 (s, 3 H) 1.89–1.97

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24. The synthesis of (R)-5-methyl-cyclohexenone has been addressed intensively in our lab., without major breakthrough. None of the route described so far, are suitable for scale up. Organocatalysis require high loading of expensive catalyst. Use of a cheap chiral auxiliary (menthol) to build on an advanced intermediate already used by Myers[a] and Collet[b] is lengthy and resolution by crystallization tricky. Lipase desymetrisation of meso-cyclohexandiol was attractive, but access to the required diol is not easy and isolation of the pure cis isomer failed. Finally we developed the well-known chemistry based on the retro aldol reaction of (R)-(+)-pulegone followed by bromination/elimination. Since practical pulegone (92% according to the suppliers COA) can be purchased for a fairly low price (400 USD for 500 g by ACROS) or manufactured in one steps from the very cheap (-)-iso-pulegol, we believe that this route is the most attractive, especially when sodium bromate/HBr is used instead of elemental bromine. By this way we manufactured (R)-5-methyl-cychlohexenone in three steps in about 40% overall yield. The isomeric mixture of 3-methyl and 5-methylcyclohexenones formed can be separated by fractional distillation or column chromatography if required. In our case, due to different reactivity, the crude mixture was suitable for our one-pot synthesis of compound 6b and subsequent protection to yield compound 10b. (a) Myers AG, Tom NJ, Fraley ME, Cohen SB, Madar DJ. A convergent synthetic route to (+)-Dynemicin A and analogs of wide structural variability. *J Am Chem Soc*. 1997;119:6072–6094;
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35. The analysis was performed on a chiral column HYDRODEX-γ-TBDAc, isotherm at 140 °C (RT: 117.2 and 118.8 min) and LIPODEX E, isotherm at 180 °C (inversed retention times at 34.2 and 34.6 min).
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