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TETRAHEDRON: *ASYMMETRY*

# Novel stereocontrolled synthesis of the tricyclic lactone (1*R*,3*R*,6*R*,9*S*)-6,9-dimethyl-8-oxo-7-oxatricyclo[4.3.0.0$^{3,9}$]nonane

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**Abstract**

The stereocontrolled synthesis of (1*R*,3*R*,6*R*,9*S*)-6,9-dimethyl-8-oxo-7-oxatricyclo[4.3.0.0$^{3,9}$]nonane **1** from (*R*)-(−)-carvone has been accomplished by application of a 13-step sequence with 12% overall yield. The absolute stereochemistry of the unsaturated acid **8a** has been established by X-ray analysis of the chiral amide **8c**. 

## 1. Introduction

The tricyclic lactone (1*R*,3*R*,6*R*,9*S*)-6,9-dimethyl-8-oxo-7-oxatricyclo[4.3.0.0$^{3,9}$]nonane **1** has been used as a key intermediate in the preparation of several representatives of the pinane[1] and bergamotane[2] series; furthermore, this tricyclic derivative has been described as a valuable intermediate in the total synthesis of biologically active (+)-grandisol.[3]

The nitrite and hypobromite photolysis techniques for remote functionalization of unactivated carbon atoms have proved to be suitable methods for the introduction of substituents at C-9 in the pinane series, therefore such techniques have been successfully exercised to access the tricyclic structure present in **1** by Hortmann and Youngstrom[1] in their contribution to the synthesis of 9-substituted pinanes and by Gibson and Erman[2] in the preparation of *cis*-bergamotenes. A quite similar approach has been used in the total synthesis of (+)-grandisol, the male boll weevil pheromone, by Magnus and Hobbs.[3]

Very recently, the use of biochemical methods in the enantioselective synthesis of the α- and β- forms of the (*E*)-*endo*-bergamoten-12-oic acids **2** and **3** have been successfully applied by Mori et al.[4] These

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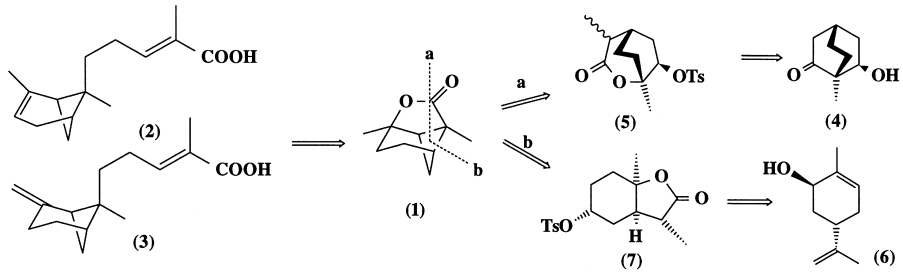



Fig. 1.

two sesquiterpenes have been isolated from the leaves of wild tomato (*Lycopersicon hirsutum*) and have been claimed to stimulate the oviposition behaviour of female gravid moths (*Heliothis zea*) whose larvae are major agricultural pests of tomatoes, corn and cotton.[5] Access to the tricyclic lactone **1** has been envisaged through the disconection (type a) depicted in Fig. 1. The enantiomerically pure form of the β-hydroxyketone **4** was obtained by yeast reduction of the prochiral diketone and has been used as a starting material to access the tosyloxy lactone **5** which then led to the tricyclic lactone **1** by internal tosylate displacement.

## 2. Results and discussion

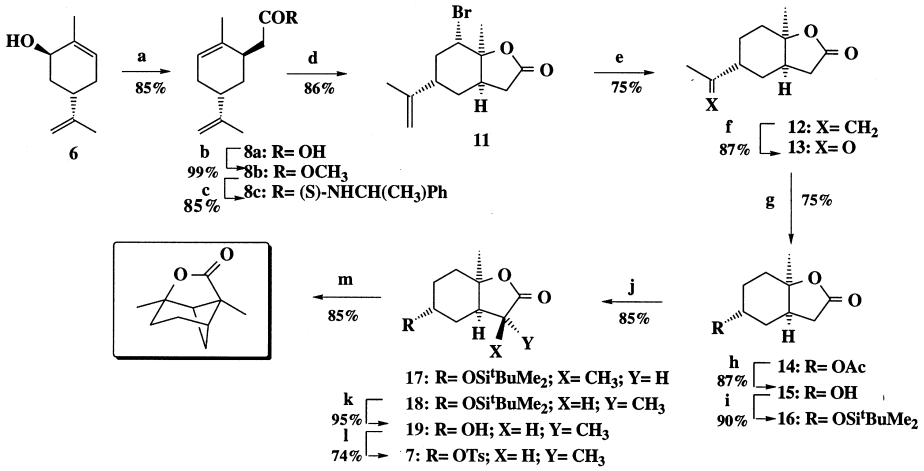
We became interested in the synthetic approach to the tricyclic lactone **1** outlined in Fig. 1 (type b of disconection) with the occasion of the total synthesis of (−)-ampullicin and (+)-isoampullicin, two sesquiterpene amides with growth regulating activity.[6] The target molecule was envisaged to be accessible from the tosyloxy lactone **7**, which can be easily prepared from (+)-*trans*-carveol **6**. The bicyclic lactone **12**, a valuable intermediate in the synthesis of **7** (Scheme 1), would be accessed via oxidative cyclization of the unsaturated acid **8a**, which in turn would be derived by the Johnson ortho ester Claisen rearrangement of the (+)-*trans*-carveol **6**.[7,8] The oxidative degradation of the isopropenyl chain present in **12** followed by trivial transformations would lead to **7** which would allow us to access **1** by intramolecular cyclization.

Enough evidence must be obtained for the stereocontrol in the crucial [3.3] sigmatropic Claisen rearrangement step[9] in order to ensure the enantioselectivity of our synthetic strategy. Treatment of (+)-*trans*-carveol **6** with ethyl orthoacetate and propionic acid followed by saponification of the crude ethyl ester led to the γ,δ-unsaturated acid **8a** with excellent yield. Treatment of **8a** with (*S*)-(−)-α-methylbenzylamine and DCC led exclusively to the chiral amide **8c** in 85% yield. The same sequence was performed on the (−)-*trans*-carveol **9**.[10] In this case the γ,δ-unsaturated acid **10a** was transformed into the amide **10c** as the single product by analogous treatment. Spectroscopic evidence was obtained to illustrate the diastereomeric relationship of both products **8c** and **10c** and to assess the enantiospecificity of the Claisen rearrangement in both cases.[11]

The absolute configuration of the chiral amide **8c** was unequivocally established by X-ray analysis (see Fig. 2) and hence the enantioselectivity of the process to access the lactone **1** was also ensured.[12]

With the unsaturated acid **8a** in our hands we continued our synthetic scheme to prepare the target molecule by application of a five-step sequence in 44% yield. Oxidative cyclization of **8a** by treatment with NBS led stereospecifically to the bromolactone **11** which was further reduced with tri-*n*-butyl hydride to afford the bicyclic lactone **12** with 65% yield.[13]

Ozonolysis of **12** followed by Baeyer–Villiger oxidation of the methyl ketone **13** yielded the acetate




**a**: i: $CH_3C(OEt)_3$ (7 equiv.), EtCOOH, 140 °C, 24 h.; ii: NaOH, $CH_3OH$, reflux; **b**: $CH_2N_2$ (ether); **c**: NHS, DCC and (-)-S-α-Methylbenzylamine, $CH_2Cl_2$, 1h. rt. ; **d**: NBS (1.1 equiv.), acetone, 0 °C, 1h. ; **e**: $nBu_3SnH$ (1.1 equiv.), AIBN, THF, 55 °C, 1h. ; **f**: $O_3$, $CH_2Cl_2$, -78 °C, $S(CH_3)_2$ 15h. ; **g**: mCPBA (5 equiv.), $NaHCO_3$ (5 equiv.), $CH_2Cl_2$, rt, 3 days; **h**: NaOMe (1.1 equiv.), MeOH, 0 °C, 45 min.; **i**: TBDMSCl (2.2 equiv.), imidazole (2.5 equiv.), DMF, rt, 1h.; **j**: LDA (1.1 equiv.), HMPA, -78 °C, THF, $CH_3I$.; **k**: $Bu_4N^+F^-$ (1.1 equiv.), THF, rt, 30 min.; **l**: TsCl (3 equiv.), pyr (3 equiv.), DMAP (cat.), $CH_2Cl_2$, rt, 15 h.; **m**: LDA (1.1 equiv.), HMPA (1.2 equiv.), -78 °C to rt.

Scheme 1.

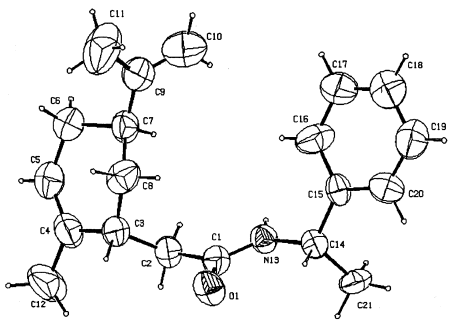



Fig. 2. ORTEP view of the X-ray crystal structure of **8c**. An arbitrary numbering system is given

**14** with 65% yield after flash chromatography. The alkaline methanolysis of the acetate **14** followed by protection of the hydroxy functionality present in **15** afforded the silyl ether **16** with 78% yield.[14]

Introduction of the methyl substituent was achieved by treatment of **16** with LDA in THF at −78°C followed by addition of HMPA and methyl iodide with 85% yield. As expected, the alkylation took place stereoselectively by the *exo* face leading to a mixture of the two methyl derivatives **17** and **18** in a 2:98 ratio.[15] Transformation of the major alkylated product **18** into the tosylate **7** was accomplished by *O*-silyl deprotection followed by treatment of the crude alcohol **19** with tosyl chloride under standard conditions to yield the tosyloxylactone **7** in 74% yield.

The intramolecular displacement of the tosylate took place successfully by treatment of **7** with LDA and HMPA in THF at −78°C leading to the tricyclic lactone **1** with 85% yield. The synthesized material had m.p. 36–38°C (light petroleum) [lit.[3] 37–38°C], the IR and $^1$H-NMR spectra were superimposable with those described for (1*R*,3*R*,6*R*,9*S*)-6,9-dimethyl-8-oxo-7-oxatricyclo[4.3.0.0$^{3,9}$]nonane[1,2]; furthermore, the enantioselectivity of the process has also been ensured by the specific rotation found for **1**: $[\alpha]_D^{24}$ +48.0 (c=1.3, $CHCl_3$) [lit.[3] $[\alpha]_D^{22}$ +49.7 (c=3%, $CHCl_3$)].

## 3. Experimental

All the reactions were carried out using dry solvents under a nitrogen or argon atmosphere. All the solvents and chemicals were commercially available and, unless otherwise indicated, were used as received. Tetrahydrofuran, diethyl ether and toluene were dried over sodium benzophenone ketyl. Methylene chloride was dried over $CaH_2$ under argon and kept over molecular sieves. Enantiomerically pure *trans*-carveols **6** and **9** were obtained following the Johnston procedure.[6,8] Optical rotations were determined on a digital Perkin–Elmer 241 polarimeter in a 1 dm cell. $^1$H-NMR and $^{13}$C-NMR spectra were measured in a Bruker WP-200-SY spectrometer operating at 200 MHz and 50.3 MHz respectively; chemical shifts are reported in ppm (δ), and the coupling constants are given in Hz. $^1$H-NMR spectra were referenced to either the residual proton in the deuterated solvent or TMS. $^{13}$C-NMR spectra were referenced to the chemical shifts of the deuterated solvent. The IR spectra were determined on a Bomen MB-100 FT-IR spectrophotometer as indicated in each case; the frequencies in the IR spectra are given in $cm^{-1}$. Mass spectra were recorded on a Kratos MS-25 instrument operating on either EI (70 eV) or FAB ionization (8 kV, using Xe and $(HOCH_2CH_2S)_2$ as matrix). Microanalyses were realized by Dr. Benigno Macías-Sánchez (Inorganic Chemistry Department, University of Salamanca) on a Perkin–Elmer 240-B analyzer. The X-ray analysis of compound **8c** was made by S. Bamidele Sanni and S. Garcia-Granda of the University of Oviedo.[12] Unless otherwise indicated, all the preparative chromatographies were performed with silica gel (40–63 mm) using the technique of flash chromatography.[16]

### *3.1. (1′R,5′R)-2-[2′-Methyl-5′-(2-propenyl)-2′-cyclohexen-1′-yl]-acetic acid **8a** and (1′R,5′R)-2-[2′-methyl-5′-(2-propenyl)-2′-cyclohexen-1′-yl]-acetic acid methyl ester **8b***

In a three-necked round-bottomed flask equipped with a distillation head were placed 15 g (0.1 mol) of (+)-*trans*-carveol **6** and 130 mL (0.7 mol) of triethyl orthoacetate. The mixture was stirred at 100°C for 2 h and then a few drops of propionic acid were added and the mixture was heated at 135°C and stirred for 15 h more, adding a drop of propionic acid when the distillation of ethanol ceased.

After cooling, the residue was diluted with ethyl acetate and the orthoester was hydrolyzed with 400 mL of 2 N HCl, then the aqueous phase was extracted with ethyl acetate, the combined organic phases were washed with saturated $NaHCO_3$ and brine, dried ($Na_2SO_4$) and evaporated at reduced pressure to give a crude material which was treated with 8.5 g (0.15 mol) of KOH in 60 mL of MeOH:$H_2O$ (3:1). After stirring at reflux for 2 h, the methanol was evaporated and the residue dissolved in water and extracted with ethyl acetate, then the aqueous phase was acidified (6 N HCl) and extracted again with ethyl acetate. The combined acid organic phases were washed with brine, dried ($Na_2SO_4$) and evaporated at reduced pressure to give the carboxylic acid **8a** (15.5 g, 75% yield), $[\alpha]_D$ −53.6 (c=2.71, $CHCl_3$). IR (film) $\nu_{max}$: 2920, 1709, 1645, 1412, 1294, 889 $cm^{-1}$. $^1$H NMR ($CDCl_3$): δ 1.69 (s, 3H), 1.73 (s, 3H), 1.8–2.7 (m, 6H), 2.34 (dd, 1H, *J*=16 Hz, *J*=12 Hz), 2.61 (dd, 1H, *J*=16 Hz, *J*=4 Hz), 4.71 (s, 2H), 5.48 (s, 1H), 10.8 (s, 1H) ppm. $^{13}$C NMR ($CDCl_3$): δ 20.67 (q), 21.59 (q), 30.89 (t), 32.29 (t), 37.71 (t), 35.84 (d); 35.86 (d), 108.83 (t), 123.22 (d), 134.53 (s), 149.17 (s), 179.63 (s) ppm. Analysis $C_{12}H_{18}O_2$ calc.: C, 74.19; H, 9.33; found: C, 74.12; H, 9.35.

Treatment of **8a** with an ethereal diazomethane solution yielded the methyl ester **8b** (15.6 g) which was purified by flash chromatography (hexane:ether=1:1). $[\alpha]_D$ −52.9 (c=1.08, $CHCl_3$). IR (film) $\nu_{max}$: 2922, 1738, 1645, 1437, 1258, 1169, 739 $cm^{-1}$. $^1$H NMR ($CDCl_3$): δ 1.67 (s, 3H), 1.70 (s, 3H), 1.8–2.2 (m, 6H), 2.25 (dd, 1H, *J*=16 Hz, *J*=11 Hz), 2.53 (dd, 1H, *J*=16 Hz, *J*=3. Hz), 3.66 (s, 3H), 4.69 (s, 2H), 5.43 (s, 1H) ppm. $^{13}$C NMR ($CDCl_3$): δ 20.70 (q), 21.64 (q), 30.91 (t), 32.30 (t), 37.69 (t), 35.83 (d),

36.06 (d), 51.37 (q), 108.72 (t), 122.99 (d), 134.85 (s), 149.41 (s), 173.45 (s) ppm. MS (FAB), *m/z* (%): 167.0 (21), 149.0 (100), 135.0 (9), 113.0 (20), 92.8 (19), 80.8 (20).

### 3.2. (1′S,5′S)-2-[2′-Methyl-5′-(2-propenyl)-2′-cyclohexen-1′-yl]-acetic acid **10a** and (1′S,5′S)-2-[2′-methyl-5′-(2-propenyl)-2′-cyclohexen-1′-yl]-acetic acid methyl ester **10b**

An identical procedure to that mentioned above for the transformation of **6** into **8a** and **8b** applied to (−)-*trans*-carveol **9** led to the carboxylic acid **10a** $[\alpha]_D$ +52.8 (c=0.3, $CHCl_3$) and the methyl ester **10b** $[\alpha]_D$ +51.9 (c=0.90, $CHCl_3$) with 76% and 80% yields, respectively. Both products exhibited identical spectroscopic properties to those exhibited by **8a** and **8b**. Analysis $C_{12}H_{18}O_2$ calc.: C, 74.19; H, 9.33; found: C, 74.13; H, 9.37.

### 3.3. (1′R,5′R,1′′S)-N-(1′′-Phenylethyl)-2-[2′-methyl-5′-(2-propenyl)-2′-cyclohexen-1′-yl]-acetamide **8c**

To a solution of *N*-hydroxysuccinimide (154 mg, 1.3 mmol) in 1 ml of dry dichloromethane were successively added a solution of carboxylic acid **8a** (217 mg, 1.1 mmol) in 2 ml of dichloromethane and dicyclohexylcarbodiimide (DCC) (277 mg, 1.3 mmol). The reaction mixture was stirred for 1 h at room temperature and (−)-*S*-α-methylbenzylamine (0.17 ml, 1.3 mmol) was added. The reaction mixture was stirred for 4 h at room temperature. The solvent was evaporated at reduced pressure and the crude residue was chromatographed on silica gel to yield 309 mg (93% yield) of the amide **8c**, m.p. 121–122°C (hexane), $[\alpha]_D$ −89.1 (c=1.5, $CHCl_3$). $^1$H-NMR ($CDCl_3$): δ 1.48 (d, *J*=7 Hz, 3H), 1.60 (s, 3H), 1.65 (s, 3H), 2.05 (dd, *J*=14 Hz, *J*=10 Hz, 2H), 2.50 (dd, *J*=14 Hz, *J*=4 Hz, 2H), 4.66 (s, 1H), 4.71 (s, 1H), 5.16 (quintet, *J*=7 Hz, 1H), 5.43 (s, 1H), 5.69 (d, *J*=7 Hz, 1H) ppm. $^{13}$C-NMR ($CDCl_3$): δ 20.5 (q), 21.6 (q) 21.7 (q), 30.8 (t), 31.9 (t), 35.9 (d), 36.2 (d), 40.3 (t), 48.5 (d), 108.6 (t), 122.5 (d), 125.9 (d), 126.9 (d), 128.4 (d), 135.4 (s), 143.3 (s), 159.2 (s), 171.2 (s) ppm. MS (EI), *m/z* (%): 297.20 (20), 254.15 (8), 163.10 (35), 150.09 (16), 133.10 (7), 119.08 (13), 105.07 (100), 91.05 (10), 79.05 (12).

#### 3.3.1. Crystal data

$C_{20}H_{27}NO$, $M_r$=297.43, monoclinic, space group $P2_1$, *a*=8.789(7) Å, *b*=9.717(4) Å, *c*=11.406(14) Å, β=108.84(5)°, *V*=921.9(14) Å$^3$, *Z*=2, $D_x$=1.07 Mg/m$^3$, $MoK_\alpha$ radiation (graphite-crystal monochromator, λ=0.71073 Å), μ=0.065 mm$^{-1}$, *F*(000)=324, *T*=294 K, final conventional *R*=0.065 and *wR*2=0.164, *S*=0.952 for 3247 'observed' reflections and 201 parameters.

#### 3.3.2. X-Ray experimental

A colourless crystal of the titled compound, approximately 0.30×0.20×0.33 mm, was used for the measurements at 293(2) K. The unit cell dimensions were determined from the angular settings of 25 reflections in the range 7≤θ≤12°. The space group was inferred to be $P2_1$ from systematic extinctions and the subsequent structure determination. The intensities of 4651 reflections in the range 1.89° to 24.97° in the range −10≤*h*≤9, −11≤*k*≤11, 0≤*l*≤13, were measured using the w−2θ scan technique with a scan angle of 1.5° and a variable scan rate with maximun scan time of 60 s per reflection. $MoK_\alpha$ radiation was used with a graphite-crystal monochromator on a Nonius CAD4 single-crystal diffractometer. The intensity of the primary beam was checked throughout the collection by monitoring three standard reflections every 60 min. On all reflections, profile analysis was performed.[17,18] Some double measured reflections were averaged, resulting in 4510 'unique' reflections of which 3247 were observed with $I>2\sigma(I)$. Lorentz polarization corrections were applied, and the data reduced to $F_o^2$.

The structure was solved by direct methods using the program SHELX86,[19] Isotropic least-squares refinement on $F^2$ using SHELXL93[20] converged at $R$=0.120. Additional empirical absorption corrections were applied at this stage, using the program XABS2.[21] The maximun and minimun corrections were 9.515 and 0.571 respectively. It was not possible to locate the H-atoms from the difference Fourier, and so all hydrogen atoms were geometrically placed and isotropically refined. Full matrix anisotropic least-squares treatment with SHELXL93, on all the positional parameters, but with the temperature factors for the H atoms fixed at 0.210 Å$^2$ converged at $R$=0.065 and $wR$=0.164, $S$=0.952 for the 3247 'observed' reflections and 614 variables. Since the Flack's parameters were not reliable, in order to establish the absolute configuration of the molecule, we calculated the average product of the calculated and observed Bijvoet difference,[22] and obtained a value of 0.541(128) on 639 Friedel pairs. The function minimized was $([\Sigma wF_o^2 - F_c^2)/\Sigma w(F_o^2)]^{1/2}$ where $w=1/[s^2(F_o^2)+0.1P)^2]$ with $s(F_o^2)$ from counting statistics and $P$=(Max $(F_o^2, o)+2\times F_c^2)/3$. The maximum shift-to-error ratio in the final full matrix least-squares cycle was 0.038 for the non-hydrogen atoms, while the highest and lowest peaks in the final difference Fourier calculated were 0.158 e/Å$^{-3}$ respectively. Atomic scattering factors were taken from International Tables for X-ray Crystallography (1976). Plots were made with the EUCLID package.[23] Geometrical calculations were made with PARST.[24] All calculations were made at the University of Oviedo at the Scientific Computer Centre and the X-ray group VAX-AXP computers. Further details concerning comments on the structure crystal data and structure refinements for ISOS, etc, can be obtained.[12]

### *3.4. (1′S,5′S,1′′S)-N-(1′′-Phenylethyl)-2-[2′-methyl-5′-(2-propenyl)-2′-cyclohexen-1′-yl]-acetamide* ***10c***

An identical procedure to that described above for **8a**, applied to the carboxylic acid **10a** led with 85% yield to the amide **10c**, m.p. 135–136°C (di-isopropyl ether); $[\alpha]_D$ +12.6 (c=1.5, $CHCl_3$). $^1$H-NMR ($CDCl_3$): δ 1.48 (d, $J$=7 Hz, 3H), 1.64 (s, 3H), 1.73 (s, 3H), 2.05 (dd, $J$=14 Hz, $J$=10 Hz, 2H), 2.49 (dd, $J$=14 Hz, $J$=4 Hz, 2H), 4.72 (s, 2H), 5.16 (quintet, $J$=7 Hz, 1H), 5.43 (s, 1H), 5.69 (d, $J$=7 Hz, 1H) ppm. $^{13}$C-NMR ($CDCl_3$): δ 20.6 (q), 21.6 (q), 21.7 (q), 30.9 (t), 32.2 (t), 36.1 (d), 36.3 (d), 40.4 (t), 48.7 (d), 108.7 (t) 122.6 (d), 126.1 (d), 127.1 (d), 128.5 (d), 135.6 (s), 143.4 (s), 149.3 (s), 171.2 (s) ppm. MS (EI), *m/z* (%): 297 (40), 163 (45), 105 (100).

### *3.5. (3a*R*,5*S*,7*S*,7a*S*)-7-Bromo-5-(2-propenyl)-7a-methyl-3a,4,5,6,7,7a-hexahydro-2(3*H*)-benzofuranone* ***11***

*N*-bromosuccinimide (4.21 g, 24 mmol) was added to a solution of carboxylic acid **10a** (3.55 g, 18 mmol) in 40 mL of acetone at 0°C. The reaction mixture was stirred at room temperature for 30 min. The solvent was evaporated and the residue was dissolved in ether, then poured into 100 mL of an aqueous solution of 10% $NaHSO_3$ and extracted with ether. The combined organic phases were washed with brine, dried ($Na_2SO_4$) and evaporated at reduced pressure. The solid residue was purified by flash chromatography (hexane:AcOEt=7:3) to yield 4.2 g (86%) of **11**, m.p. 78–80°C (hexane), $[\alpha]_D$ −7.6 (c=0.97, $CHCl_3$). IR ($CHCl_3$) $\nu_{max}$: 3470, 1769, 1645, 1458, 1385, 1121, 949, 719 cm$^{-1}$. $^1$H NMR ($CDCl_3$): δ 1.64 (s, 3H), 1.73 (s, 3H), 2.4–2.8 (m, 2H), 4.16 (dd, $J$=13.0 Hz, $J$=3.8 Hz, 1H), 4.74 (s, 1H), 4.79 (s, 1H) ppm. $^{13}$C NMR ($CDCl_3$) δ 20.8 (q), 21.5 (q), 28.7 (t), 33.0 (t), 39.5 (t), 40.4 (d), 43.1 (d), 56.3 (d), 85.9 (s), 110.6 (t), 146.1 (s), 174.4 (s) ppm. IR ($Cl_3CH$) $\nu_{max}$ 3470, 1769, 1645, 1458, 1385, 1121, 949, 719 cm$^{-1}$. MS (FAB), *m/z* (%): 272.8 (42), 193.0 (92), 153.6 (100), 104.8 (42).

### 3.6. (3aR,5R,7aR)-5-(2-Propenyl)-7a-methyl-3a,4,5,6,7,7a-hexahydro-2(3H)-benzofuranone **12**

Tributyltin hydride (15 ml) and a catalytic amount of AIBN were simultaneously added to a solution of **11** (1.02 g, 3.74 mmol) in 15 mL of anhydrous THF. The mixture was stirred under argon at 60°C until the reaction was finished (1.5 h). The reaction mixture was poured into an aqueous solution of 10% NaF, then extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($Na_2SO_4$) and evaporated at reduced pressure. The solid residue was purified by flash chromatography (hexane:AcOEt=7:3) to yield 690 mg (95%) of **12**, m.p. 53–55°C (hexane), $[\alpha]_D$ −25.6 (c=0.99, $CHCl_3$). IR ($CHCl_3$) $\nu_{max}$: 3059, 1765, 1645, 1456, 1267, 1094, 735 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 1.44 (s, 3H), 1.68 (s, 3H), 2.4–2.7 (m, 2H), 4.68 (s, 1H), 4.70 (t, 1H, *J*=1.5 Hz) ppm. $^{13}C$ NMR ($CDCl_3$): δ 24.0 (q), 24.6 (q), 27.2 (t), 29.2 (t), 33.3 (t), 34.2 (t), 38.1 (d), 41.1 (d), 84.3 (s), 109.1 (t), 147.7 (s), 175.14 (s) ppm. MS (FAB), *m/z* (%): 195.1 (100), 177.1 (11), 154.0 (54), 139.1 (35), 92.9 (18).

### 3.7. (3aR,5R,7aR)-5-Acetyl-7a-methyl-3a,4,5,6,7,7a-hexahydro-2(3H)-benzofuranone **13**

A solution of **12** (1.7 g, 9 mmol) in dichloromethane (60 mL) was cooled to −78°C. Ozone was bubbled through the solution until a blue color developed. After 15 min, the excess of ozone was removed with an $O_2$ purge, and dimethyl sulfide (3 ml) was added. The solution was allowed to warm to 20°C and stirred for 15 h. The solvent was removed under vacuum, and the residue partitioned between ether and saturated brine. The organic phase was dried, filtered and concentrated to give a crude product which was purified by flash chromatography (ether:AcOEt=1:1) to yield 1.64 g (93%) of **13**, m.p. 74–76°C (hexane:AcOEt), $[\alpha]_D$ −17.9 (c=0.99, $CHCl_3$). IR ($CHCl_3$) $\nu_{max}$: 3057, 2942, 1773, 1707, 1448, 1096, 945, 737 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 1.36 (s, 3H), 2.10 (s, 3H), 2.35–2.65 (m, 3H) ppm. $^{13}C$ NMR ($CDCl_3$): δ 23.8 (t), 24.5 (q), 26.5 (t), 27.9 (q), 32.8 (t), 34.1 (t), 39.4 (d), 44.4 (d), 84.1 (s), 175.3 (s), 209.8 (s) ppm. MS (FAB), *m/z* (%): 197.1 (100), 179.1 (37), 154.0 (73), 107.0 (42), 92.9 (11).

### 3.8. (3aR,5R,7aR)-5-Acetoxy-7a-methyl-3a,4,5,6,7,7a-hexahydro-2(3H)-benzofuranone **14**

3-Chloroperoxybenzoic acid (3.2 g, 18.3 mmol) and sodium bicarbonate (1.54 g 18.3 mmol) were added to a solution of methyl ketone **13** (1.8 g, 9.2 mmol) in 50 mL of dichloromethane. The mixture was stirred at room temperature for two days with eventual addition of one equivalent of each reactant. When the reaction finished, dichloromethane was added and the organic phase was washed with aqueous solutions of 10% $NaHSO_3$, 10% $NaHCO_3$ and brine. The organic phase was dried on $Na_2SO_4$ and evaporated at reduced pressure to lead to a solid residue (2.1 g), which was purified by flash chromatography (hexane:AcOEt=6:4) to yield 1.7 g (87%) of **14**, m.p. 64–66°C (hexane), $[\alpha]_D$ +3.7 (c=1.00, $CHCl_3$). IR ($CHCl_3$) $\nu_{max}$: 2945, 1778, 1732, 1381, 1250, 1101, 977 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 1.40 (s, 3H), 1.5–1.9 (m, 6H), 2.01 (s, 3H), 2.23–2.41 (m, 2H), 2.65–2.85 (dd, *J*=15.9 Hz, *J*=6.2 Hz; 1H), 4.93 (m, 1H) ppm. $^{13}C$ NMR ($CDCl_3$): δ 20.7 (q), 25.3 (q), 25.5 (t), 30.0 (t), 30.3 (t), 35.5 (t), 37.8 (d), 67.6 (d), 83.4 (s), 169.8 (s), 175.2 (s) ppm. MS (FAB) *m/z* (%): 213.1 (27), 153.1 (100), 108.7 (8), 92.9 (21), 78.5 (4).

### 3.9. (3aR,5R,7aR)-5-Hydroxy-7a-methyl-3a,4,5,6,7,7a-hexahydro-2(3H)-benzofuranone **15**

A solution of **14** (294.9 mg, 1.39 mmol) in 4 ml of methanol was added at 0°C to a solution of freshly prepared NaOMe (82.6 mg, 1.53 mmol) in 4 ml of methanol. The reaction mixture was stirred for 45 min and then the solvent was evaporated and the residue dissolved in water and extracted with ethyl acetate.

The combined organic layers were washed with brine, dried ($Na_2SO_4$) and evaporated under vacuum. The crude material was purified by flash chromatography (ether:AcOEt=1:1) to yield 69.7 mg (74%) of **15**, m.p. 111–113°C (hexane:AcOEt), $[\alpha]_D$ +2.1 (c=0.99, $CHCl_3$). IR ($CHCl_3$) $\nu_{max}$: 3453, 3057, 2938, 1759, 1265, 1094, 739 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 1.46 (s, 3H), 1.47–1.98 (m, 6H), 2.32 (dd, *J*=16.3 Hz, *J*=7 Hz, 1H), 2.43 (quintet, 1H, *J*=7 Hz), 2.72 (dd, *J*=16.3 Hz, *J*=7 Hz, 1H), 3.99 (m, 1H) ppm. $^{13}C$ NMR ($CDCl_3$): δ 25.6 (q), 29.4 (t), 30.4 (t), 34.5 (t), 35.9 (t), 38.3 (d), 65.1 (d), 84.3 (s), 175.9 (s) ppm. MS (FAB), *m/z* (%): 171.1 (100), 153.1 (65), 108.8 (35), 90.8 (62), 80.8 (15).

### *3.10. (3a*R,*5*R,*7a*R*)-5*-tert-*Butyldimethylsilyloxy-7a-methyl-3a,4,5,6,7,7a-hexahydro-2(3*H*)-benzofuranone **16***

To a solution of **15** (146.5 mg, 0.86 mmol) in 1 ml of dimethylformamide were successively added imidazol (146.4 mg, 2.15 mmol) and tertbutyldimethylsilyl chloride (168.8 mg, 1.12 mmol). The mixture was stirred for 1 h under an argon atmosphere and then 5 ml of an aqueous solution of $NH_4Cl$ were added. After extraction with AcOEt the combined organic layers were washed with brine, dried ($Na_2SO_4$) and evaporated at reduced pressure. The solid crude material was purified by flash chromatography (hexane:AcOEt=9:1) to yield 245 mg (100%) of **16**, m.p. 30–32°C (hexane), $[\alpha]_D$ +6.2 (c=1.01, $CHCl_3$). IR ($CHCl_3$) $\nu_{max}$: 2930, 2857, 1780, 1256, 1096, 1061, 1007, 837 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 0.04 (s, 6H), 0.87 (s, 9H), 1.39 (s, 3H), 1.15–2.05 (m, 6H), 2.21 (dd, *J*=17.0 Hz, *J*=4.2 Hz, 1H), 2.34–2.48 (m, 1H), 2.79 (dd, *J*=17.0 Hz, *J*=7.1 Hz, 1H), 3.99 (m, 1H) ppm. $^{13}C$ NMR ($CDCl_3$): δ −4.8 (q), −4.9 (q), 18.0 (s), 25.6 (q), 25.7 (q), 25.8 (q), 26.2 (q), 29.1 (t), 29.6 (t), 35.6 (t), 36.5 (t), 37.3 (d), 65.4 (d), 84.4 (s), 176.2 (s) ppm. MS (FAB), *m/z* (%): 285.1 (19), 227.1 (16), 153.1 (100), 92.9 (55), 74.7 (68).

### *3.11. (3*S,*3a*R,*5*R,*7a*R*)-5*-tert-*Butyldimethylsilyloxy-3,7a-dimethyl-3a,4,5,6,7,7a-hexahydro-2(3*H*)-benzofuranone **17** and (3*R,*3a*R,*5*R,*7a*R*)-5*-tert-*butyldimethylsilyloxy-3,7a-dimethyl-3a,4,5,6,7,7a-hexahydro-2(3*H*)-benzofuranone **18***

A solution of buthyllithium in hexane (1.9 mmol) was added dropwise to a solution of diisopropylamine (0.3 ml, 2 mmol) in 3 ml of anhydrous tetrahydrofuran at 0°C. The reaction was stirred for 1 h and then chilled to −78°C. A solution of **16** (260 mg, 1.3 mmol) in 3 ml of tetrahydrofuran was added dropwise and the reaction mixture was stirred for 1 h at the same temperature. Hexamethylphosphoramide (0.33 ml, 1.9 mmol) was then added, followed by freshly distilled methyl iodide (0.12 ml, 2 mmol) and the reaction mixture was allowed to warm up to room temperature by sudden withdrawal of the cold bath. The reaction was stirred for an additional 4 h at room temperature and then 5 ml of an aqueous saturated solution of ammonium chloride was added and the reaction was extracted with ethyl acetate. The combined organic layers were washed with brine, dried on $Na_2SO_4$ and evaporated at reduced pressure to afford a crude reaction product which was partitioned by flash chromatography. Elution with hexane:ethyl acetate (9:1) enabled the successive isolation of **17** (5 mg, 2%) and **18** (230 mg, 98%) which exhibited the following physical properties: **17**, $[\alpha]_D$ +8.2 (c=1.1, $CHCl_3$). $^1H$-NMR ($CDCl_3$): δ 0.04 (s, 6H), 0.9 (s, 9H), 1.1 (d, *J*=7 Hz, 3H), 1.4 (s, 3H), 1.5–2.1 (m, 6H), 2.4 (m, 1H), 3.1 (quintet, *J*=7 Hz, 1H), 4.1 (s, 1H) ppm. $^{13}C$ NMR ($CDCl_3$): δ −4.8 (q), −4.9 (q), 9.5 (q), 18.0 (s), 25.7 (q), 25.8 (q), 25.9 (q), 26.6 (q), 27.9 (t), 28.7 (t), 31.3 (t), 39.4 (d), 39.7 (d), 64.9 (d), 82.3 (s), 179.4 (s) ppm. Analysis $C_{16}H_{30}O_3Si$ calc.: C, 64.38; H, 10.13; found: C, 64.32; H, 10.16. **18**, m.p. 94–96°C; $[\alpha]_D$ +12.9 (c=1.1, $CHCl_3$). $^1H$-NMR ($CDCl_3$): δ 0.04 (s, 6H), 0.9 (s, 9H), 1.2 (d, *J*=7 Hz, 3H), 1.5 (s, 3H), 1.5–2.1 (m, 7H), 2.6 (quintet, *J*=7 Hz, 1H), 3.7 (m, 1H) ppm. $^{13}C$ NMR ($CDCl_3$): δ −4.7 (q), 4.8 (q),

13.7 (q), 18.0 (s), 24.6 (q), 25.6 (q), 25.7 (q), 25.8 (q), 32.2 (t), 33.0 (t), 33.6 (t), 38.9 (d), 49.9 (d), 66.7 (d), 82.3 (s), 177.8 (s) ppm. Analysis $C_{16}H_{30}O_3Si$ calc.: C, 64.38; H, 10.13; found: C, 64.30; H, 10.15.

### *3.12. (3*R*,3a*R*,5*R*,7a*R*)-5-Hydroxy-3,7a-dimethyl-3a,4,5,6,7,7a-hexahydro-2(3*H*)-benzofuranone **19***

Addition of $Bu_4NF \cdot H_2O$ (295 mg, 0.9 mmol) to a solution of **18** (254 mg, 0.9 mmol) in 10 ml of anhydrous tetrahydrofuran was followed by stirring of the reaction mixture for 30 min at room temperature. The organic solvent was evaporated at reduced pressure and the crude reaction product was chromatographed on silica gel. Elution with diethyl ether:AcOEt (1:1) followed by evaporation of the solvent afforded 157 mg (98%) of **19**, m.p. 117–119°C ($CHCl_3$), $[\alpha]_D$ +3.0 (c=0.8, $CHCl_3$). $^1$H-NMR ($CDCl_3$): δ 1.21 (d, *J*=7 Hz, 3H); 1.5 (s, 3H), 1.5–2.1 (m, 7H), 2.6 (quintet, *J*=7 Hz, 1H), 3.8 (m, 1H) ppm. $^{13}$C NMR ($CDCl_3$): δ 13.6 (q), 22.4 (q), 31.8 (t), 32.3 (t); 33.4 (t), 38.7 (d), 49.7 (d), 65.7 (d), 82.4 (s), 178.0 (s) ppm. MS (EI), *m/z* (%) 185.11 (1), 169.08 (9), 166.09 (43), 141.09 (24), 126.06 (54), 122.10 (100), 112.05 (20), 107.08 (65), 93.07 (46), 83.05 (56), 69.03 (35).

### *3.13. (3*R*,3a*R*,5*R*,7a*R*)-5-[(4-Methylbenzene)-1-sulfonyloxy]-3,7a-dimethyl-3a,4,5,6,7,7a-hexahydro-2(3*H*)-benzo furanone **7***

To a solution of **19** (154 mg, 0.8 mmol) in 5 ml of anhydrous dichloromethane, were successively added pyridine (0.3 ml), dimethylaminopyridine DMAP (25 mg) and tosyl chloride (333 mg). The reaction mixture was stirred overnight under an argon atmosphere at room temperature. An aqueous saturated sodium bicarbonate solution (5 ml) was added and the reaction was stirred for 1 h, extracted with dichloromethane and successively washed with 1 N HCl, sat. $NaHCO_3$ and brine solutions. The organic layer was dried on $Na_2SO_4$ and evaporated to afford a crude reaction mixture which was chromatographed on silica gel. Elution with hexane:AcOEt (7:3) followed by evaporation of the solvent afforded 220 mg (79%) of **7**, m.p. 157–159 (AcOEt), $[\alpha]_D$ +18.3 (c=1.0, $CHCl_3$). $^1$H-NMR ($CDCl_3$): δ 1.16 (d, *J*=7 Hz, 3H), 1.46 (s, 3H), 1.5–2.05 (m, 8H), 2.45 (s, 3H), 4.47–4.62 (m, 1H), 7.45 (d, *J*=8 Hz, 2H), 7.8 (d, *J*=8 Hz, 2H) ppm. $^{13}$C NMR ($CDCl_3$): δ 13.7 (q), 21.5 (q), 24.4 (q), 28.9 (t), 29.7 (t), 33.0 (t), 38.6 (d), 49.2 (d), 81.2 (s), 127.6 (d), 129.9 (d), 134.4 (s), 144.9 (s), 177.0 (s) ppm. MS (EI), *m/z* (%): 338.11 (5), 167.10 (85), 122.10 (90), 107.08 (45), 91.05 (100), 65.03 (22).

### *3.14. (1*R*,3*S*,6*R*,9*S*)-6,9-Dimethyl-8-oxo-7-oxatricyclo-[4.3.0.0$^{3,9}$]nonane **1***

A solution of buthyllithium in hexane (0.9 mmol) was added dropwise to a solution of diisopropylamine (0.13 ml, 0.95 mmol) in 3 ml of anhydrous tetrahydrofuran at 0°C. The reaction was stirred for 1 h and then chilled to −78°C. A solution of **7** (212 mg, 0.6 mmol) in 2 ml of tetrahydrofuran was added dropwise and the reaction mixture was stirred for 1 h at the same temperature. Hexamethylphosphoramide (0.15 ml) was then added and the reaction mixture was allowed to warm up to room temperature. The reaction was quenched by addition of 5 ml of an aqueous sat. ammonium chloride solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried on $Na_2SO_4$ and the solvent evaporated to afford 89 mg (85%) of **1**, m.p. 36–38°C (hexane), $[\alpha]_D$ +48.0 (c=1.3, $CHCl_3$). IR ($CHCl_3$): $\nu_{max}$ 2930, 1765, 1451, 1381, 1250, 1082, 926, 754 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) δ 1.36 (s, 3H); 1.46 (s, 3H), 1.68 (d, *J*=10 Hz, 1H), 1.9 (s, 4H), 2.21–2.43 (m, 3H) ppm. $^{13}$C NMR ($CDCl_3$) δ 16.4 (q), 23.1 (t), 23.3 (t), 29.8 (t), 24.9 (q), 42.5 (d), 49.9 (d), 52.0 (s), 87.9 (s), 178.9 (s) ppm. Analysis $C_{10}H_{14}O_2$ calc.: C, 72.26; H, 8.49; found: C, 72.21; H, 8.52.

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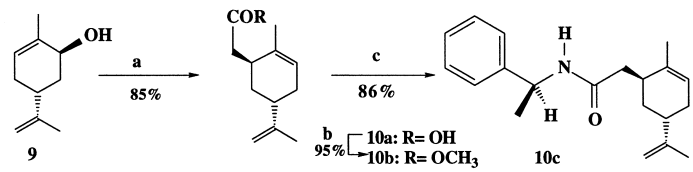
10. The enantiomerically pure amide **10c** has been obtained from (−)-*trans*-carveol **9** by application of a three-step sequence with 70% overall yield.




**a**: i: $CH_3C(OEt)_3$ (7 equiv.), EtCOOH, 140 °C; ii: NaOH, $CH_3OH$, reflux; **b**: $CH_2N_2$ (ether); **c**: NHS, DCC, (-)-S-α-Methylbenzylamine, $CH_2Cl_2$, 1h. rt.

11. No trace of the amide **10c** was found by $^1$H-NMR (400 MHz) analysis of the crude reaction product corresponding to the transformation of carboxylic acid **8a** into the amide **8c**. Analogously, no trace of the amide **8c** was found by $^1$H-NMR analysis of the crude reaction product corresponding to the transformation of carboxylic acid **10a** into the amide **10c**.
12. Correspondence regarding the X-ray crystallographic determination should be addressed to Prof. Dr. Santiago Garcia-Granda, Universidad de Oviedo, Spain.
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