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Synthesis and olfactory evaluation of the enantiomerically enriched forms of 7,11-epoxymegastigma-5(6)-en-9-one and 7,11-epoxymegastigma-5(6)-en-9-ols isomers, identified in *Passiflora edulis*

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Abstract—A study on the synthesis of the isomers of the natural C-13 norterpenoids derivatives 7,11-epoxymegastigma-5(6)-en-9-one and 7,11-epoxymegastigma-5(6)-en-9-ols is reported. The latter compounds were prepared from readily available racemic α-ionone and then resolved by mean of lipase-mediated acetylation. The obtained enantiomerically forms were evaluated for their odour properties.

1. Introduction

Many flavours occur in nature as a mixture of stereoisomers. The sensorial properties of these compounds are frequently related with their isomeric composition and several aspects of enantioselective perception of chiral odorants have been reported.[1] Therefore, the preparation of flavours and fragrances as pure stereoisomers has attracted much attention. In this context, we have been working on the enantioselective preparation of different natural norterpenoids compounds such as ionones[2] and irones[3] isomers.

We herein report on the synthesis and olfactory evaluation of the isomers of the C-13 norterpenoids derivatives 7,11-epoxymegastigma-5(6)-en-9-one and 7,11-epoxymegastigma-5(6)-en-9-ols. The latter compounds are unusual bicyclic ionone derivatives formally obtained by the oxidation of the C(11) carbon atom and ring closure between positions 7 and 11 of the ionone framework (Fig. 1). These were first described by Näf et al.[4] in 1977 as components of the volatiles of the purple-skinned passion fruit (*Passiflora edulis* Sims). In order to corroborate the structures, these compounds were prepared by chemical synthesis allowing structure **1** and the relative configuration of **2** to be assigned to the natural products. Afterwards, **1** was found by Kaiser[5] to be present in very high amounts in the headspace of the strong ionone floral smelling of the rare terrestrial orchid *Houlletia odoratissima* (Linden) and also in the scent of the orchidaceae *Gongora cruciformis* (Whitten and Bennett).[6] In all cases the paucity of the natural compounds and the lacking of enantiopure reference materials precluded the measurement of its enantiomeric composition. To the best of our knowledge, no enantioselective synthesis of compounds **1**–**3** has been reported to date. Herein we report on the preparation of compound **1**–**3** starting from readily available racemic α-ionone. The compounds were synthesized in racemic form and then were resolved by mean of lipase-mediated acetylation. The odour properties of the enantiomer-enriched forms were evaluated and described by expertise perfumers.

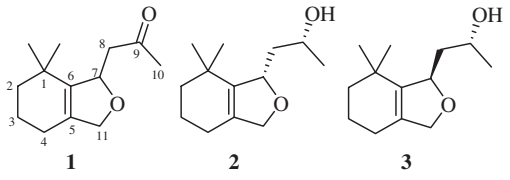

Figure 1.

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2. Results and discussion

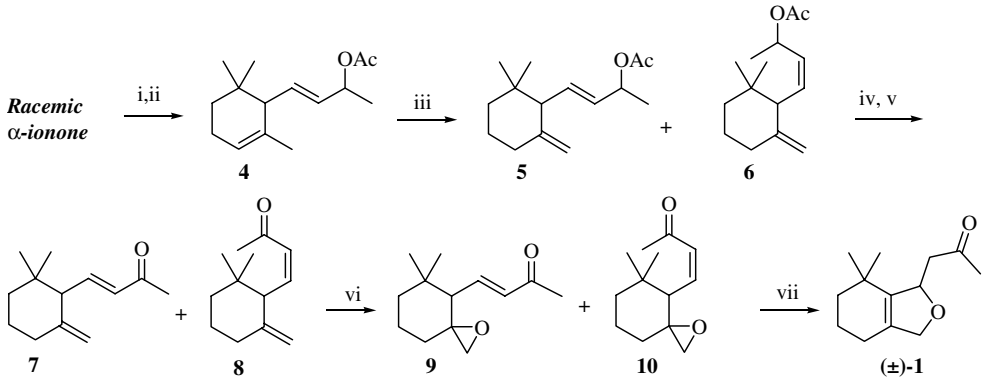
2.1. Preparation of racemic 7,11-epoxymegastigma-5(6)-en-9-one 1

As part of a program on the preparation of enantiopure odorants, we have previously shown the efficiency of lipase-mediated kinetic resolutions of racemic materials.[7] The latter approach has been successfully applied in the preparation of enantiomerically enriched ionone[2] and irone[3] isomers by mean of acetylation of racemic ionols and irols, respectively. Accordingly, we extended this flexible enzymic methodology to the resolution of 7,11-epoxymegastigma-5(6)-en-9-one derivative. Our study first needed a valuable amount of racemic starting materials. The previous preparation of **1** is based on the regioselective epoxidation of racemic γ-ionone followed by base-promoted isomerization. Racemic **1** was therefore obtained regioselectively in only two steps. In spite of these advantages, γ-ionone is not commercially available and should be prepared by synthesis.[8] Therefore, we amended this unfavourable aspect by some modification to the latter synthetic pathway. Our approach starts from the inexpensive and commercially available α-ionone (Scheme 1) that was reduced and converted in the α-ionol acetate **4**. According to a procedure we previously developed for γ-irone synthesis,[9] the latter compound was irradiated in quartz vessels, with high-pressure Hg lamps. By this mean, the *endo*-cyclic double bond of the α-ionol framework was isomerized to the *exo*-cyclic double bond of the γ-ionol derivatives. Acetate **4** was smoothly converted into a 2:1 mixture of γ-ionol acetate isomers **5** and **6**, respectively. The concomitant isomerization of the conjugated double bond does not effect the overall efficiency of the process since during the ring closure step, both regioisomers give **1**. Therefore, acetates **5** and **6** were not separated and were converted to γ-ionone isomers **7** and **8** by saponification of the acetate and oxidation. The epoxidation of the latter mixture with MCPBA afforded a mixture of four isomers with chemical structure **9** and **10**. According to Näf's procedure, the latter compounds were treated with sodium methylate in DMF to give 7,11-epoxymegastigma-5(6)-en-9-one **1** in a regioselective fashion.

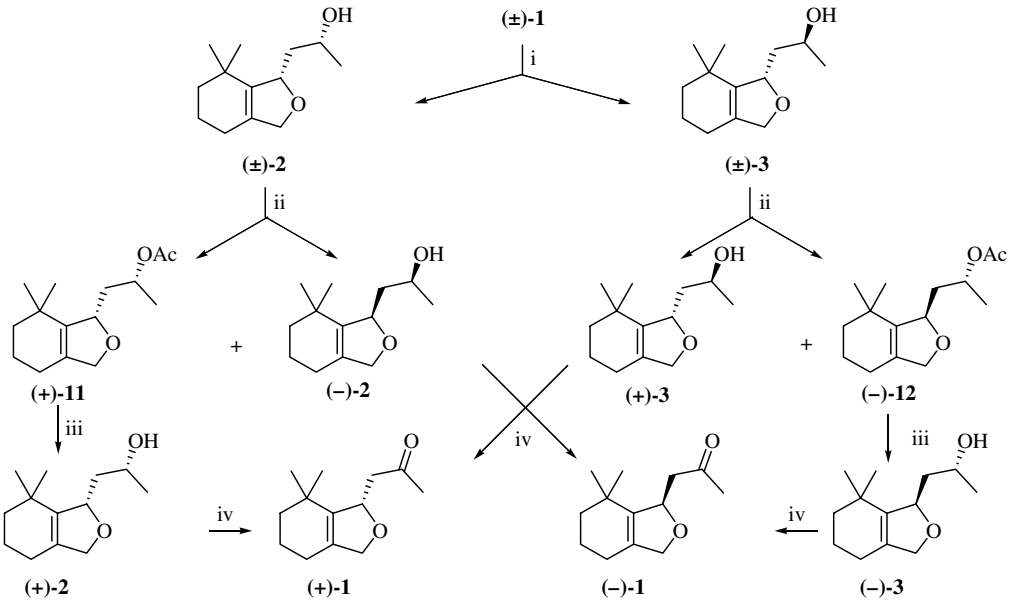
2.2. Lipase-mediated resolution of 7,11-epoxymegastigma-5(6)-en-9-ols 2 and 3

With an effective synthetic method to **1** in hand, the next step was the preparation and the resolution of alcohols **2** and **3**. The reduction of **1** with $NaBH_4$ in methanol gave a 70:30 mixture of diastereoisomers **2** and **3**, respectively. The latter was easily separated by chromatography and then submitted to lipase-mediated kinetic acetylation using vinyl acetate as an acyl donor and ^{t}BuOMe as solvent (Scheme 2). We selected lipase PS as catalyst since this enzyme gave the best performances in terms of enantioselectivity in the ionol and irol resolutions. Using the above-mentioned experimental conditions, (±)-**2** gave acetate (+)-**11** (97% ee) and unreacted alcohol (−)-**2** (97% ee), as well as (±)-**3** gave acetate (−)-**12** (99% ee) and unreacted alcohol (+)-**3** (90% ee). The latter compounds were separated by chromatography and acetates (+)-**11** and (−)-**12** were saponificated to give alcohols (+)-**2** and (−)-**3**, respectively. All the isomeric forms of epoxymegastigma-5(6)-en-9-ols **2** and **3** were therefore obtained. The enantiomeric forms of **1** were then prepared by $Py{\cdot}SO_3$ oxidation.[10] Transformation of (−)-**2** or (−)-**3** gave (−)-**1** whereas transformation of (+)-**2** or (+)-**3** gave (+)-**1**.

The assignment of the absolute configuration of these compounds needs further consideration. The chemical correlation with compounds of known stereochemistry was not possible due to the singularity of the latter structure and consequently the lack of data. The transformation of the isomeric forms of alcohols **2** and **3** into the corresponding *p*-bromobenzoate derivatives did not afford crystalline materials precluding the possibility of X-ray analysis. Therefore, we assigned the absolute configuration of the alcohols by a less rigorous method. We have previously demonstrated that lipase PS catalyses enantioselectively the acetylation of the alcohol with chemical structure relate to ionol[11] and dihydroionol.[12] This process affords invariably the corresponding (9*R*)-acetate. According to the latter finding, the stereochemistry of acetate (+)-**11** and (−)-**12** should be (7*S*,9*R*) and (7*R*,9*R*), respectively. Consequently, we assigned to compounds (+)-**1**, (−)-**1**, (−)-**2**, (+)-**2**, (+)-**3** and (−)-**3**



Scheme 1. Synthesis of racemic 7,11-epoxymegastigma-5(6)-en-9-one **1**. Reagents and conditions: (i) $NaBH_4$, MeOH; (ii) Ac_2O, Py; (iii) *hv*, ^{i}PrOH, xylene; (iv) KOH, MeOH; (v) MnO_2, $CHCl_3$; (vi) MCPBA, CH_2Cl_2; (vii) NaOMe, DMF.



Scheme 2. Lipase PS-mediated resolution of 7,11-epoxymegastigma-5(6)-en-9-one **1** and 7,11-epoxymegastigma-5(6)-en-9-ols **2** and **3**. Reagents and conditions: (i) $NaBH_4$, MeOH; (ii) lipase PS, vinyl acetate, *t*-butylmethylether; (iii) KOH, MeOH; (iv) $Py{\cdot}SO_3$, DMSO, Et_3N.

absolute configurations (7*S*), (7*R*), (7*R*,9*S*), (7*S*,9*R*), (7*S*,9*S*) and (7*R*,9*R*), respectively.

2.3. Olfactory evaluation

All the enantiomerically enriched forms of 7,11-epoxymegastigma-5(6)-en-9-one and 7,11-epoxymegastigma-5(6)-en-9-ols isomers were evaluated by qualified perfumers (Givaudan Schweiz AG). The results are shown in Table 1 and indicate some considerations. The evaluated compounds could be included in the class of floral odorants. In terms of intensity, there is not a great difference between the ketonic and alcoholic compounds: both ketone **1** and alcohols **2** and **3** are essentially weak. Otherwise, in terms of quality, the latter two classes of compounds show certain distinctions. Some differences in the odour features were anyway detected either between diastereoisomers or enantiomers.

3. Conclusions

The natural C-13 norterpenoids 7,11-epoxymegastigma-5(6)-en-9-one and 7,11-epoxymegastigma-5(6)-en-9-ols were prepared from the easily available racemic α-ionone. These racemic compounds were resolved for the first time by mean of lipase-mediated acetylation. The obtained enantiomerically enriched forms were evaluated and their odour properties described. The absolute configuration of the latter compounds were assigned.

4. Experimental

4.1. General

All solvents and reagents were purchased from suppliers and used without further purification. ^1H NMR spectra were recorded in a $CDCl_3$ solution at room temperature unless otherwise stated, on a Bruker AC-250 spectrometer (250 MHz ^1H). The chemical-shift scale is based on internal tetramethylsilane. IR spectra were recorded on a Perkin–Elmer 2000 FTIR spectrometer. Mass spectra were measured on a Finnigan-MAT TSQ 70 spectrometer. Melting points were measured on a Reichert melting-point apparatus, equipped with a Reichert microscope, and are uncorrected. Optical rotations were determined on a Propol automatic digital polarimeter. TLC analyses were performed on Merck Kieselgel 60 F_{254} plates. Microanalyses were determined on an analyzer *1106* from *Carlo Erba*. All the chromatographic separations were carried out on silica gel columns. Lipase PS from it Pseudomonas cepacia (Amano Pharmaceuticals Co., Japan) was employed. GC analyses:

Table 1. Olfactory evaluation of 7,11-epoxymegastigma-5(6)-en-9-one and 7,11-epoxymegastigma-5(6)-en-9-ols isomers

Compound	Odour description
(−)-**1**	Sweet, food-like, slightly vanillic note
(+)-**1**	Weak, somewhat floral-fruity, raspberry, ionone-like
(−)-**2**	Weak, floral-fruity, with a woody, cardboard-like nuance and some metallic facets
(+)-**2**	Weak, citric, acidic, slightly floral
(−)-**3**	Weak, citric, acidic, with a sweet floral touch
(+)-**3**	Weak, floral smell with technical, acidic component, a bit in the direction of rice wine

HP-6890 gas chromatograph; determined on a *HP-5* column (30 m × 0.32 mm; *Hewlett Packard*) with the following temp program 60° (1 min)–6°/min–150° (1 min)–12°/min–280° (5 min); t_R given in minutes. Chiral GC analyses: DANI-HT-86.10 gas chromatograph; enantiomeric excesses of compound **1** determined on a DACTBS BETA (MEGA, Italy)-Column with the following temp program 60° (3 min)–3°/min–180° (5 min); enantiomeric excesses of compound **2** determined by oxidation to compound **1** followed by chiral GC analyses; enantiomeric excesses of compound **3** determined on a CHIRASIL DEX CB-Column with the following temp program 40° (3 min)–1.5°/min–180° (5 min); t_R given in minutes.

4.2. Synthesis of racemic 7,11-epoxymegastigma-5(6)-en-9-one 1

A solution of α-ionone (40 g, 208 mmol) in methanol (200 cm^3) was cooled to 0 °C and treated under stirring with $NaBH_4$ (4 g, 106 mmol). After 2 h the reaction was diluted with water (500 cm^3), 5% HCl aq (200 cm^3) and extracted with ether (3 × 150 cm^3). The combined organic phases were washed with brine (100 cm^3), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was then treated with pyridine (50 cm^3) and Ac_2O (50 cm^3). When the acetylation was complete (6 h) the mixture was concentrated under reduced pressure and the residue was purified by chromatography (hexane→hexane/ethyl acetate 9:1) to afford pure ionol acetate **4** (44.9 g, 91%) as a 1:1 mixture of diastereoisomers (GC analysis: t_R 16.66 and 16.76).

A solution of **4** (42 g, 178 mmol) in isopropanol (250 cm^3) in the presence of xylene (50 cm^3) as the photosensitizer was irradiated in quartz vessels, in a Rayonet photochemical reactor equipped with 10 8-W high-pressure Hg lamps. The reaction was monitored by GC analysis and the irradiation interrupted until compound **4** became less than 5% of the mixture (20 days). The solution was then concentrated under reduced pressure to afford an oil that showed the following composition: compound **5** (59%, 1:1 mixture of diastereoisomers, t_R 17.06 and 17.14), compound **6** (29%, 1:1 mixture of diastereoisomers, t_R 16.45 and 16.56), compound **4** (4%, 1:1 mixture of diastereoisomers) and a mixture of unidentified compound (8%).

The above mentioned oil in methanol (100 cm^3) was treated with a solution of KOH (12 g, 214 mmol) in methanol (80 cm^3) stirring at rt until no more starting acetate was detected by TLC analysis. The mixture was diluted with water (300 cm^3) and extracted with diethyl ether (3 × 150 cm^3). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated. The residue was dissolved in $CHCl_3$ (200 cm^3) and treated with MnO_2 (30 g, 345 mmol) stirring at reflux for 6 h. The mixture was then cooled, filtered and the organic phase concentrated under reduced pressure to afford an oil (29.2 g) that showed the following composition (GC analysis): compound **7** (60%, t_R 16.28), compound **8** (26%, t_R 14.82), α-ionone (4%, t_R 16.06) and a mixture of unidentified compound (10%).

A solution of the above mentioned mixture (28 g) in CH_2Cl_2 (150 cm^3) was treated with MCPBA (28 g, 162 mmol) stirring at 0 °C until no more starting ionone was detected by TLC analysis (4 h). The MCBA was eliminated by filtration and the solution was washed in turn with saturated $NaHCO_3$ solution (100 cm^3) and 5% aq, Na_2SO_3 (150 cm^3). The organic layer was dried (Na_2SO_4), concentrated under reduced pressure and the residue was dissolved in dry DMF (100 cm^3). The obtained solution was treated with NaOMe (8 g, 148 mmol) stirring at rt for 3 h. After this time, the reaction was quenched by the addition of water (200 cm^3) and extraction with diethyl ether (3 × 100 cm^3). The organic phase was washed in turn with water (80 cm^3) and brine (100 cm^3), then dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography (hexane→hexane/ethyl acetate 7:3) to afford pure **1** (oil, 18.9 g, 72% two steps) (GC analysis: t_R 19.37, 98%). FT-IR (film) 1716, 1457, 1363, 1234, 1158, 1070, 1040, 1020, 914, 881; *m/z* (EI): 208 (M^+, 8), 193 (32), 165 (5), 151 (43), 150 (99), 135 (100), 123 (13), 107 (18), 95 (16), 91 (15), 81 (28), 69 (7), 55 (6); δ 1.04 (3H, s, *Me*–C(1)), 1.05 (3H, s *Me*–C(1)), 1.29–1.55 (2H, m), 1.65–1.78 (2H, m), 1.88–2.00 (2H, m) (C*H*$_2$(2), C*H*$_2$(3), C*H*$_2$(4)), 2.23 (3H, s, *Me*(10)), 2.60 (1H, dd, *J* 9.5 and 14.5, *H*–C(8)), 2.72 (1H, dd, *J* 3.4 and 14.5, *H*–C(8)), 4.37 (1H, dm, *J* 12 *H*–C(11)), 4.51 (1H, ddt, *J* 12, 5 and 1.2, *H*–C(11)), 5.21 (1H, m, *H*–C(7)). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.05; H, 9.70.

4.3. Synthesis of racemic 7,11-epoxymegastigma-5(6)-en-9-ols 2 and 10

A solution of compound **1** (16 g, 77 mmol) in methanol (80 cm^3) was cooled to 0 °C and treated under stirring with $NaBH_4$ (1.5 g, 40 mmol). After 2 h the reaction was diluted with water (150 cm^3), 5% HCl aq (50 cm^3) and extracted with ether (3 × 100 cm^3). The combined organic phases were washed with brine (100 cm^3), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography eluting with hexane/ethyl acetate (95:5→70:30) to afford pure **2** (first eluted diastereoisomer, oil, 10.2 g, 63%) (GC analysis: t_R 19.40, 99%). FT-IR (film) 3490, 1456, 1425, 1362, 1300, 1134, 1072, 1020, 947, 829; *m/z* (EI): 211 (M^++1, 2), 210 (M^+, 13), 192 (22), 177 (26), 163 (3), 152 (14), 151 (100), 135 (12), 133 (19), 123 (12), 109 (14), 107 (14), 95 (22), 81 (38), 69 (8), 67 (8), 55 (8); δ 1.03 (3H, s, *Me*–C(1)), 1.06 (3H, s *Me*–C(1)), 1.20 (3H, d, *J* 6.2 *Me*(10)), 1.30–1.57 (3H, m), 1.65–1.78 (2H, m), 1.82 (1H, dt, *J* 14 and 2.3) 1.88–2.02 (2H, m) (C*H*$_2$(2), C*H*$_2$(3), C*H*$_2$(4), C*H*$_2$(8)), 3.76 (1H, br s, O*H*), 4.00–4.15 (1H, m *H*–C(9)), 4.39 (1H, ddt, *J* 11.7, 2.6 and 1.1, *H*–C(11)), 4.54 (1H, ddt, *J* 11.7, 5.1 and 1.1, *H*–C(11)), 4.97 (1H, m, *H*–C(7)). Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.30; H, 10.50. The second eluted diastereoisomer was pure **3** (oil, 4.5 g, 28%), (GC analysis: t_R 19.29, 98%). FT-IR (film) 3431, 1457, 1363, 1128, 1065, 1020, 942, 843; *m/z* (EI): 211 (M^++1, 3), 210 (M^+, 16), 192 (24), 177 (32), 163 (4), 152 (15), 151 (100), 135 (18), 133 (18), 123 (13), 109 (16), 107 (16), 95 (24), 81 (40), 69 (8), 67

(7), 55 (8); δ 1.03 (3H, s, *Me*–C(1)), 1.04 (3H, s *Me*–C(1)), 1.21 (3H, d, *J* 6.3 *Me*(10)), 1.25–1.56 (2H, m), 1.64–1.79 (3H, m) 1.81–2.07 (3H, m) (CH_2(2), CH_2(3), CH_2(4) CH_2(8)), 3.20 (1H, br s, O*H*), 3.96–4.10 (1H, m *H*–C(9)), 4.39 (1H, ddt, *J* 11.7, 3.4 and 1.1, *H*–C(11)), 4.54 (1H, ddt, *J* 11.7, 5.3 and 1.1, *H*–C(11)), 5.12 (1H, m, *H*–C(7)). Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.35; H, 10.50.

4.4. Lipase PS-mediated resolution of the racemic substrates

4.4.1. General procedure. A mixture of the suitable racemic substrate (3 g, 14.3 mmol), lipase PS (1.5 g), vinyl acetate (5 cm^3) and ^{t}BuOMe (30 cm^3) was stirred at rt and the formation of the acetate monitored by TLC analysis. The reaction was stopped at about 50% conversion by filtration of the enzyme and evaporation of the solvent at reduced pressure. The residue was purified by chromatography eluting with hexane–ethyl acetate (95:5→70:30) to give the alcohol acetate and unreacted alcohol. The acetate was then dissolved in methanol (10 cm^3) and treated with KOH (1 g, 18 mmol) in methanol (10 cm^3) and stirring continued at rt until no more starting material was detected by TLC analysis. The mixture was diluted with water (60 cm^3) and extracted with diethyl ether (3 × 50 cm^3). The organic phase was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by chromatography and bulb-to-bulb distillation to give the enantiomeric form of the unreacted alcohol.

4.4.2. Resolution of racemic 2. Racemic **2** was resolved according to the general procedure to give acetate (+)-**11** (oil, 98% GC, t_R 21.33); bp (oven temp bulb-to-bulb distillation) 95–100 °C/0.02 mmHg; $[\alpha]_D^{20} = +77.1$ (*c* 2, $CHCl_3$); FT-IR (film) 1736, 1458, 1368, 1244, 1075, 1060, 1020, 955, 863; *m*/*z* (EI): 252 (M^+, 4), 209 (M^+−OAc, 1), 192 (76), 177 (88), 163 (9), 151 (100), 135 (48), 133 (21), 122 (16), 107 (20), 95 (21), 81 (39), 69 (16), 55 (8); δ 1.03 (3H, s, *Me*–C(1)), 1.07 (3H, s *Me*–C(1)), 1.31 (3H, d, *J* 6.3 *Me*(10)), 1.32–1.54 (2H, m), 1.64–1.78 (2H, m) 1.80–1.97 (4H, m) (CH_2(2), CH_2(3), CH_2(4) CH_2(8)), 2.02 (3H, s, OCO*Me*), 4.34 (1H, dm, *J* 11.7, *H*–C(11)), 4.51 (1H, dd, *J* 11.7 and 5.1, *H*–C(11)), 4.83 (1H, m, *H*–C(7)), 5.11 (1H, m, *H*–C(9)). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.45; H, 9.60. Alcohol (−)-**2** (oil, 97% GC); bp (oven temp bulb-to-bulb distillation) 90–95 °C/0.05 mmHg; $[\alpha]_D^{20} = -69.5$ (*c* 2, $CHCl_3$); ee = 97%, IR, ^{1}H NMR, MS: in accordance with that of (±)-**2**. Saponification of the acetate (+)-**11** gave pure (+)-**2** (oil, 98% GC), $[\alpha]_D^{20} = +72.5$ (*c* 2, $CHCl_3$); bp (oven temp bulb-to-bulb distillation) 90–95 °C/0.05 mmHg ee = 97%, IR, ^{1}H NMR, MS: in accordance with that of (±)-**2**.

4.4.3. Resolution of racemic 3. Racemic **3** was resolved according to the general procedure to give acetate (−)-**12** (oil, 98% GC, t_R 21.10); bp (oven temp bulb-to-bulb distillation) 95–100 °C/0.02 mmHg; $[\alpha]_D^{20} = -93.9$ (*c* 2, $CHCl_3$); ee >99%, FT-IR (film) 1735, 1457, 1372, 1243, 1136, 1063, 1021, 954, 860; *m*/*z* (EI): 252 (M^+, 2), 209 (M^+−OAc, 1), 192 (77), 177 (100), 163 (8), 151 (42), 135 (31), 133 (10), 121 (12), 107 (17), 95 (12), 81 (21), 69 (10), 55 (6); δ 1.05 (3H, s, *Me*–C(1)), 1.08 (3H, s *Me*–C(1)), 1.27 (3H, d, *J* 6.2 *Me*(10)), 1.29–1.60 (3H, m), 1.64–1.74 (2H, m) 1.85–2.07 (3H, m) (CH_2(2), CH_2(3), CH_2(4) CH_2(8)), 2.04 (3H, s, OCO*Me*), 4.34 (1H, dm, *J* 11.7, *H*–C(11)), 4.46 (1H, ddt, *J* 11.7, 4.8 and 1.3, *H*–C(11)), 4.81 (1H, m, *H*–C(7)), 5.15 (1H, m, *H*–C(9)). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.30; H, 9.55. Alcohol (+)-**3** (oil, 98% GC); bp (oven temp bulb-to-bulb distillation) 90–95 °C/0.05 mmHg; $[\alpha]_D^{20} = +55.2$ (*c* 2, $CHCl_3$); chiral GC (t_R 59.17) ee = 90%, IR, ^{1}H NMR, MS: in accordance with that of (±)-**3**. Saponification of the acetate (−)-**12** gave pure (−)-**3** (98% GC), $[\alpha]_D^{20} = -64.7$ (*c* 2, $CHCl_3$); bp (oven temp bulb-to-bulb distillation) 90–95 °C/0.05 mmHg; mp 42–44 °C; chiral GC (t_R 59.52) ee >99%, IR, ^{1}H NMR, MS: in accordance with that of (±)-**3**.

4.5. Preparation of (+)- and (−)-7,11-epoxymegastigma-5(6)-en-9-one 1

A solution of the pyridine–SO_3 complex (1.6 g, 10 mmol) in DMSO (10 cm^3) was added dropwise to a stirred mixture of alcohol (+)-**2** (1 g, 4.8 mmol), DMSO (15 cm^3) and triethylamine (5 cm^3, 36 mmol). The temperature was maintained below 30 °C and the reaction continued until no more starting alcohol was detected by TLC analysis (3 h). The mixture was then diluted with water (100 cm^3), acidified with 5% HCl aq (50 cm^3) and extracted with diethyl ether (3 × 50 cm^3). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (hexane→hexane/ethyl acetate 7:3) to afford pure (+)-**1** (oil, 0.93 g, 93%) (GC analysis: 98%); $[\alpha]_D^{20} = +158.2$ (*c* 2, $CHCl_3$); chiral GC (t_R 29.02) ee = 97%; IR, ^{1}H NMR, MS: in accordance with that of (±)-**1**.

The above described method was applied to the oxidation of the following alcohols:

(−)-**3** to give (−)-**1** (90%) $[\alpha]_D^{20} = -158.8$ (*c* 2, $CHCl_3$); chiral GC (t_R 29.64) ee >99%, IR, ^{1}H NMR, MS: in accordance with that of (±)-**1**.

(−)-**2** to give (−)-**1** (94%) $[\alpha]_D^{20} = -154.1$ (*c* 2, $CHCl_3$); chiral GC ee = 97%, IR, ^{1}H NMR, MS: in accordance with that of (±)-**1**.

(+)-**3** to give (+)-**1** (91%) $[\alpha]_D^{20} = +145.2$ (*c* 2, $CHCl_3$); chiral GC ee = 90%, IR, ^{1}H NMR, MS: in accordance with that of (±)-**1**.

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