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Assessing the absolute configuration of (7*S*,8*R*)-(−)-epoxyjasmone

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ABSTRACT

The absolute configuration of *cis*-epoxyjasmone (−)-**2**, isolated from *Trichosporum cutaneum* CCT 1903 whole cells, has been unambiguously established as (7*S*,8*R*), $[\alpha]_D^{20}$ −29.0° (*c* 1.3, $CHCl_3$), by a new two step method, using a regioselective epoxide opening as the key step followed by Mosher acid derivatization.

1. Introduction

Epoxides are key intermediates directly associated to the biological activity of many synthetic drugs and natural products, their versatility is highly appreciated in the pharmaceutical industry as they react with nucleophiles, electrophiles, acids and bases. These intermediates are commonly used in the synthesis of β-blockers, anti-obesity and anti-HIV drugs such as triptolide, epothilones, cryptophycin A, laulimalide, epoxy isoprostane, phospholipids, among others [1–4]. Consequently there is a high demand for methods to access epoxides or vicinal diols in high enantiomeric purity either applying chemo-catalytic [5–10] or biocatalytic methods [3,11–13].

The odoriferous properties of *cis*-jasmone and derivatives make these constituents highly valuable in the flavor and fragrance industry for their floral and woody notes in essential oils [14–16]. Thus new *cis*-jasmone derivatives are appreciated and the epoxidation may be an elegant way to introduce new functionalities and chirality.

In a previous communication [17] we reported the enantioselective epoxidation of *cis*-jasmone **1**, a fragrant compound, by *Trichosporum cutaneum* CCT 1903 whole cells producing 7,8-epoxyjasmone (−)-**2** (92% ee). The absolute configuration of (−)-**2**, however, was not easily assessed due to the lack of convenient and general methods to obtain 1,2-disubstituted epoxides in the presence of a carbonyl group.

The present paper reports the unambiguous determination of the absolute configuration of (7*S*,8*R*)-(−)-epoxyjasmone obtained by biotransformation (Scheme 1).

2. Experimental

2.1. Materials and methods

^{1}H NMR spectra were recorded with Inova 500 (499.88 MHz) or Varian Gemini 300 (300.07 MHz) spectrometers. ^{13}C NMR spectra were obtained with Inova 500 (125.70 MHz) or Varian Gemini 300 (75.45 MHz) spectrometers. $CDCl_3$ was used as solvent, with Me_4Si (TMS) as internal standard and chemical shifts (δ) are reported in parts per million. Coupling constants (*J*) are given in Hertz. Thin-layer chromatography (TLC) was performed using precoated plates (Aluminum foil, silica gel 60 F_{254} Merck, 0.25 mm) and compound visualization was obtained by using *p*-anisaldehyde/sulfuric acid followed by heating (approximately 120 °C). Merck 60 silica gel (230–400 mesh) was used in column chromatography. Reactions were monitored by GC–MS using a HP-5890 chromatograph with a HP-5970 MS detector and helium as the carrier gas. The fused silica capillary column used was a J&W Scientific DB-5 (30 m × 0.25 mm × 0.25 m). Optical rotation was measured in $CHCl_3$ using J-702 Jeol polarimeter (589.3 nm). The specific optical rotation for (7*S*,8*R*)-(−)-epoxyjasmone (−)-**2** was $[\alpha]_D^{20}$ −29.0° (*c*. 1.3, $CHCl_3$).

2.2. Chemicals

Compound (−)-**2** was isolated as previously reported [17]. *cis*-Jasmone, *m*-chloroperoxybenzoic acid, trimethyl *ortho*-acetate, pyridinium *p*-toluene sulfonate, (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, (±)-1,2-epoxydecane and solvents are commercially available and were used without purification.

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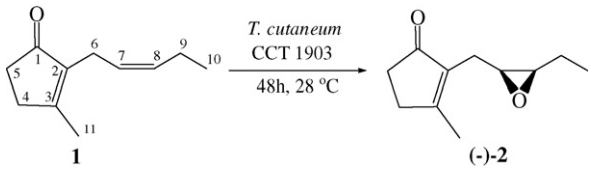


Scheme 1. Bioconversion of *cis*-jasmone **1** into (7*S*,8*R*)-epoxyjasmone (−)-**2** by *T. cutaneum* CCT 1903 whole cells (13% isolated yield).

2.3. Syntheses

2.3.1. Synthesis of (±)-7,8-epoxyjasmone (±)-*2*

To a solution of *m*-chloroperoxybenzoic acid (53 mg, 0.31 mmol) in CH_2Cl_2 (1 mL) at 0 °C, a solution of *cis*-jasmone (50.4 mg, 0.31 mmol) in CH_2Cl_2 (0.3 mL) was added dropwise. The resulting solution was then stirred for 12 h at room temperature. CH_2Cl_2 (20 mL) was added to the reaction mixture and the organic layer was washed with $NaHCO_3$ saturated aqueous solution (2× 20 mL), $NaHSO_3$ (2× 20 mL) and H_2O (2× 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography using CH_2Cl_2 as eluent to yield the desired epoxide (±)-**2** as yellow oil (41.3 mg, 0.23 mmol, 74%). (±)-7,8-Epoxyjasmone (±)-**2**: ($C_{11}H_{16}O_2$) GC–MS (R_T = 9.7 min), (EI, 70 eV) *m*/*z* (rel. inten.): 180 ($M^{\bullet+}$, 8), 165 (26), 122 (46), 110 (64), 109 (32), 107 (19), 95(26), 79 (100) 67 (31) 41 (28). ^{1}H NMR (499.88 MHz, $CDCl_3$) δ 3.04 (1H, m, H-7), 2.88 (1H, m, H-8), 2.60–2.27 (6H, m, H-6, H-5, H-4), 2.12 (3H, s, H-11), 1.64 (2H, m, H-9), 1.06 (3H, t, *J* 7.5 Hz, H-10). ^{13}C NMR (125.69 MHz, $CDCl_3$) δ 209.2 (C-1), 172.6 (C-3), 136.8 (C-2), 58.6 (C-8), 55.7 (C-7), 34.2 (C-4), 31.9 (C-5), 22.0 (C-6), 21.2 (C-9), 17.6 (C-11), 10.6 (C-10).

2.3.2. Synthesis of (±)-7-hydroxy-8-methoxyjasmone (±)-3 and (±)-8-hydroxy-7-methoxyjasmone (±)-*4*

A solution of (±)-7,8-epoxyjasmone (±)-2 (50.0 mg, 0.278 mmol), pyridinium *p*-toluene sulfonate (1.97 mg, 7.87 mmol) and trimethyl *ortho*-acetate (0.272 mL, 2.128 mmol) in anhydrous methanol (2.0 mL) was refluxed under argon for 18 h and then diluted with Et_2O. The organic layer was washed with a 1:1 mixture of 5% sodium hydroxide and saturated brine solution, then water and saturated brine solution and dried over $MgSO_4$. The solvent was evaporated under reduced pressure yielding a yellow oil (22.4 mg). The GC–MS analysis revealed the presence of two regioisomers in a 4:1 ratio (analytical conditions: from 50 °C to 290 °C at 20 °C min^{-1}; $T_{inj.}$ = 240 °C, 1 mL min^{-1} flow rate, split 50). Purification by silica gel chromatography, eluted with hexane with increasing amounts of ethyl acetate produced a mixture of (±)-7-hydroxy-8-methoxyjasmone (±)-**3** and (±)-8-hydroxy-7-methoxyjasmone (±)-**4** (10.2 mg, 0.048 mmol, 17%). (±)-7-Hydroxy-8-methoxyjasmone (±)-**3**: ($C_{12}H_{20}O_3$) GC–MS (EI, 70 eV) *m*/*z* (rel. inten.): 212 ($M^{\bullet+}$, absent), 180 (11), 139 (100), 110 (36), 73 (18), 41 (12). R_T = 8.6 min. ^{1}H NMR (499.88 MHz, $CDCl_3$) δ 3.70 (1H, ddd, *J* 9.3, 4.8, 3.2 Hz, H-7), 3.42 (3H, s, OCH_3), 3.01 (1H, dt, *J* 6.5, 4.8 Hz, H-8), 2.56 (2H, m, H-5), 2.45 (1H, dd, *J* 14.0, 3.2 Hz, H-6), 2.41 (2H, t, *J* 4.5 Hz, H-4), 2.33 (1H, dd, *J* 14.0, 9.3 Hz, H-6), 2.11 (3H, s, H-11), 1.75–1.50 (2H, m, H-9), 0.95 (3H, t, *J* 7.4 Hz, H-10). ^{13}C NMR (125.69 MHz, $CDCl_3$) δ 210.9 (C-1), 172.9 (C-3), 138.0 (C-2), 84.8 (C-8), 71.0 (C-7), 58.0 (–OCH_3), 34.2 (C-4), 32.0 (C-5), 27.6 (C-6), 22.2 (C-9), 17.5 (C-11), 9.7 (C-10). (±)-8-Hydroxy-7-methoxyjasmone (±)-**4**: ($C_{12}H_{20}O_3$) GC–MS (EI, 70 eV) (R_T = 8.4 min) *m*/*z* (rel. inten.): 212 ($M^{\bullet+}$, absent), 194 (5), 179 (8), 154 (26), 153 (100), 139 (26), 110 (33), 41 (10). ^{1}H NMR (499.88 MHz, $CDCl_3$) δ 3.41 (3H, s, OCH_3), 3.17 (2H, m, H-7 and H-8), 2.56 (2H, m, H-5), 2.49 (2H, m, H-6), 2.41 (2H, t, *J* 4.5 Hz, H-4), 2.13 (3H, s, H-11), 1.75–1.50 (2H, m, H-9), 0.94 (3H, t, *J* 7.4 Hz, H-10). ^{13}C NMR (125.69 MHz, $CDCl_3$) δ 210.9 (C-1), 172.9 (C-3), 138.0 (C-2), 81.5 (C-7), 73.7 (C-8), 58.6 (–OCH_3), 34.2 (C-4), 31.9 (C-5), 26.6 (C-9), 24.2 (C-6), 17.5 (C-11), 10.4 (C-10).

2.3.3. Synthesis of 7-hydroxy-8-methoxyjasmone 3 and 8-hydroxy-7-methoxyjasmone *4*

After the procedure described above the reaction of (7*S*,8*R*)-(−)-epoxyjasmone (−)-**2** (50.0 mg, 0.278 mmol), obtained by biotransformation, was performed in the presence of trimethyl *ortho*-acetate (0.272 mL, 2.128 mmol) and pyridinium *p*-toluene sulfonate (1.97 mg, 7.87 mmol) for 18 h affording a mixture of **3** and **4** (8.4 mg, 0.04 mmol, 14%). 7-Hydroxy-8-methoxyjasmone **3**: ($C_{12}H_{20}O_3$) GC–MS (R_T = 8.6 min) (EI, 70 eV) *m*/*z* (rel. inten.): 212 ($M^{\bullet+}$, absent), 180 (11), 139 (100), 110 (36), 73 (20), 41 (12). ^{1}H NMR (300,06 MHz, $CDCl_3$) δ 3.70 (1H, ddd, *J* 9.3, 4.8, 3.2 Hz, H-7), 3.42 (3H, s, OCH_3), 3.01 (1H, dt, *J* 6.5, 4.8 Hz, H-8), 2.56 (2H, m, H-5), 2.45 (1H, dd, *J* 14.0, 3.2 Hz, H-6), 2.41 (2H, t, *J* 4.5 Hz, H-4), 2.33 (1H, dd, *J* 14.0, 9.3 Hz, H-6), 2.11 (3H, s, H-11), 1.75-1.50 (2H, m, H-9), 0.96 (3H, t, *J* 7.4 Hz, H-10). ^{13}C NMR (75.45 MHz, $CDCl_3$) δ 210.8 (C-1), 172.9 (C-3), 138.0 (C-2), 84.7 (C-8), 71.0 (C-7), 58.0 (–OCH_3), 34.2 (C-4), 32.0 (C-5), 27.6 (C-6), 22.2 (C-9), 17.5 (C-11), 9.7 (C-10). 8-Hydroxy-7-methoxyjasmone 4: ($C_{12}H_{20}O_3$) GC–MS (EI, 70 eV) (R_T = 8.4 min) *m*/*z* (rel. inten.): 212 ($M^{\bullet+}$, absent), 194 (6), 179 (9), 154 (26), 153 (100), 139 (24), 110 (34), 41 (9). ^{1}H NMR (300.06 MHz, $CDCl_3$) δ 3.41 (3H, s, OCH_3), 3.17 (2H, m, H-7 and H-8), 2.56 (2H, m, H-5), 2.49 (2H, m, H-6), 2.41 (2H, t, *J* 4.5 Hz, H-4), 2.13 (3H, s, H-11), 1.75–1.50 (2H, m, H-9), 0.95 (3H, t, *J* 7.4 Hz, H-10). ^{13}C NMR (75.45 MHz, $CDCl_3$) δ 210.9 (C-1), 172.9 (C-3), 138.0 (C-2), 81.5 (C-7), 73.7 (C-8), 58.6 (–OCH_3), 34.2 (C-4), 31.9 (C-5), 26.6 (C-9), 24.3 (C-6), 17.5 (C-11), 10.4 (C-10).

2.3.4. Synthesis of Mosher esters *5a* and *5b* derivatives of (±)-7-hydroxy-8-methoxyjasmone (±)-*3*

To a racemic mixture of (±)-7-hydroxy-8-methoxyjasmone (±)-**3** and (±)-8-hydroxy-7-methoxyjasmone (±)-**4** (7.6 mg, 0.036 mmol) in CH_2Cl_2 (0.3 mL) at 0 °C were sequentially added (*S*)-methoxy-(trifluoromethyl)phenylacetic acid (12.6 mg, 0.053 mmol), 4-dimethylaminopyridine (catalytic amount) and 1,3-dicyclohexylcarbodiimide (10.9 mg, 0.053 mmol). The solution was stirred for 48 h under N_2 atmosphere and purified by silica gel column chromatography eluted with hexane:EtOAc, increasing the polarity from 10 to 25% of EtOAc. The solvent was removed under vacuum to give the (*S*)-Mosher esters **5a** and **5b** (11.5 mg, 0.027 mmol, 75%). The GC–MS analysis were conducted as follows: from 100 °C to 290 °C (20′) at 20 °C min^{-1}, $T_{inj.}$ = 200 °C, 1 mL min^{-1} flow rate, split 50. (*S*)-Mosher ester of (7*S*)-hydroxy-(8*S*)-methoxyjasmone **5a**: ($C_{22}H_{27}F_3O_5$) GC–MS (R_T = 9.6 min) (EI, 70 eV) *m*/*z* (rel. inten.): 428 ($M^{\bullet+}$, absent), 396 (10), 194 (15), 189 (100), 163 (18), 139 (16), 123 (30), 105 (20), 73 (48). ^{1}H NMR (499.88 MHz, $CDCl_3$) δ 7.62–7.34 (5H, m, Ph-C(2′)), 5.47–5.43 (1H, m, H-7), 3.51 (3H, s, H_3CO-C2′), 3.44 (3H, s, H_3CO-C8), 3.29–3.25 (1H, m, H-8), 2.62–2.46 (2H, m, H-6), 2.52–2.44 (2H, m, H-5), 2.29 (2H, t, *J* 4.5 Hz, H-4), 1.79 (3H, s, H-11), 1.64–1.53 (2H, m, H-9), 0.98 (3H, t, *J* 7.5 Hz, H-10). ^{13}C NMR (125.69 MHz, $CDCl_3$) δ 210.1 (C-1), 174.4 (C-3), 166.2 (C-1′), 158.5 (C-3′), 135.4 (C-2), 131.6, 129.7, 128.6, 127.5 (Ph-C2′), 122.2 (C-2′), 82.4 (C-8), 74.1 (C-7), 57.7 (H_3CO-C8), 55.4 (H_3CO-C2′), 34.0 (C-4), 31.7 (C-5), 23.3 (C-6), 22.2 (C-9), 17.0 (C-11), 9.7 (C-10). (*S*)-Mosher ester of (7*R*)-hydroxy-(8*R*)-methoxyjasmone **5b**: ($C_{22}H_{27}F_3O_5$) GC–MS (R_T = 9.8 min) (EI, 70 eV) *m*/*z* (rel. inten.): 428 ($M^{\bullet+}$, absent), 319 (49), 194 (40), 189 (87), 179 (41), 153 (100), 105 (19), 101 (19), 77 (13). ^{1}H NMR (499.88 MHz, $CDCl_3$) δ 7.62–7.34 (5H, m, Ph-C(2′)), 5.47–5.43 (1H, m, H-7), 3.51 (3H, s, H_3CO-C(2′)), 3.40 (3H, s, H_3CO-C(8)), 3.22–3.19 (1H, m, H-8), 2.62–2.46 (2H, m, H-6), 2.52–2.44 (2H, m, H-5), 2.41–2.39 (2H, m, H-4), 2.01 (3H, s, H-11), 1.52–1.35 (2H, m, H-9), 0.91 (3H, t, *J* 7.5 Hz, H-10). ^{13}C NMR (125.69 MHz, $CDCl_3$) δ 210.1 (C-1), 174.4 (C-3), 169.4 (C-1′), 158.3 (C-3′), 135.8 (C-2), 131.6,

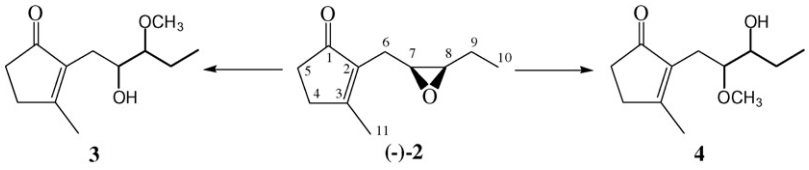


Fig. 1. Regioselective opening epoxide.

129.7, 128.6, 127.5 (Ph-C2′), 124.2 (C-2′), 82.2 (C-8), 74.3 (C-7), 58.0 (H_3CO-C8), 55.4 (H_3CO-C2′), 34.1 (C-4), 31.9 (C-5), 22.0 (C-9), 17.2 (C-11), 9.8 (C-10).

*2.3.5. Synthesis of the (S)-MTPA ester **5a** derivative of 7-hydroxy-8-methoxyjasmone **3***

Treatment of the mixture of 7-hydroxy-8-methoxyjasmone **3** and 8-hydroxy-7-methoxyjasmone **4** with (*S*)-(−)-methoxy-(trifluoromethyl)phenylacetic acid was conducted as described above yielding the (*S*)-Mosher ester **5a** (11.5 mg, 0.027 mmol, 75%). (*S*)-Mosher ester of (7*S*)-hydroxy-(8*S*)-methoxyjasmone **5a**: ($C_{22}H_{27}F_3O_5$) GC–MS (R_T = 9.6 min) (EI, 70 eV) *m*/*z* (rel. inten.): 428 ($M^{\bullet+}$, absent), 396 (10), 194 (15), 189 (100), 163 (18), 139 (16), 123 (30), 105 (20), 73 (48). ^{1}H NMR (499.88 MHz, $CDCl_3$) δ 7.64–7.35 (5H, m, Ph-C(2′)), 5.48–5.44 (1H, m, H-7), 3.53 (3H, s, H_3CO-C2′), 3.44 (3H, s, H_3CO-C8), 3.28–3.24 (1H, m, H-8), 2.52–2.42 (4H, m, H-6 and H-5), 2.24 (2H, t, *J* 4.5 Hz, H-4), 1.79 (3H, s, H-11), 1.62–1.52 (2H, m, H-9), 0.98 (3H, t, *J* 7.5 Hz, H-10). ^{13}C NMR (125.69 MHz, $CDCl_3$) δ 208.6 (C-1), 173.0 (C-3), 166.1 (C-1′), 135.4 (C-2), 132.3, 129.5, 128.2, 127.3 (Ph-C2′) 122.0 (C-2′), 82.4 (C-8), 74.1 (C-7), 57.7 (H_3CO-C(8)), 55.4 (H_3CO-C(2′)), 34.0 (C-4), 31.5 (C-5), 23.3 (C-6), 22.2 (C-9), 17.0 (C-11), 9.7 (C-10).

*2.3.6. Synthesis of (±)-1-hydroxy-2-methoxydecane (±)-**7** and (±)-1-methoxy-2-hydroxydecane (±)-**8***

(±)-1,2-Epoxydecane, (±)-6, (50.1 mg, 0.32 mmol), pyridinium *p*-toluene sulfonate (2.3 mg, 9.06 μmol) and the trimethyl *ortho*-acetate (0.31 mL, 2.45 mmol) in anhydrous methanol (2 mL) were mixed and stirred at room temperature under an Ar atmosphere for 48 h. The mixture was purified on silica gel chromatography, packed in hexane and eluted with a gradient of Hexane:AcOEt (19:1, then 9:1). The mixture of diastereoisomers (±)-**7** and (±)-**8** was obtained in 4:1 molar ratio with 21% yield. (±)-1-Hydroxy-2-methoxydecane (±)-**7**: ($C_{11}H_{24}O_2$, MW 188.31 g mol^{-1}) ^{13}C NMR (75.45 MHz, $CDCl_3$) δ 81.6 (C-2), 64.0 (C-1), 57.0 (OCH_3), 31.8, 30.3, 29.8, 29.5, 29.2, 25.3, 22.6 (C3-C-9), 14.1 (C-10). (±)-1-Methoxy-2-hydroxydecane (±)-**8**: ($C_{11}H_{24}O_2$, MW 188.31 g mol^{-1}) ^{13}C NMR (75.45 MHz, $CDCl_3$) δ 74.0 (C-1), 69.5 (C-2), 57.0 (OCH_3), 14.1 (C-10).

3. Results and discussion

To establish the absolute configuration of the epoxy derivative (−)-**2** of *cis*-jasmone, we proposed transforming (−)-**2** into a compound containing one single free hydroxyl (**3** or **4**, Fig. 1), which after derivatization with Mosher's reagent (α-methoxy-α-(trifluoromethyl)phenylacetic acid, MTPA), would give access to the absolute stereochemistry of this hydroxyl containing carbon by NMR [18–20]. Consequently the configuration of the adjacent chiral carbon would be assessed using the relative configuration of the epoxide in (−)-**2**.

A survey of the literature [21–23] indicated that there are several natural enzymes acting on carbon–carbon double bond epoxidation, indicating that oxidation by cytochrome P-450 and methane monooxygenase, among others, proceeds in a stereospecific way with configuration retention of the *cis*- or *trans*-alkene stereochemistry during the biological epoxidation. However, enzymes display various degrees of stereospecificity, thus the stereochemistry of the epoxyjasmone (−)-**2** from *cis*-jasmone **1** was determined as *cis* by the presence of a double doublet at δ 3.01 (H-7) and a triple doublet at δ 2.84 (H-8) with a coupling constant of ca. 4.5 Hz in the ^{1}H NMR spectrum [17].[1] Comparison with a synthetic standard further confirmed the *cis* stereochemistry of the epoxide ring. Thus *T. cutaneum* monooxygenase stereospecifically oxidizes *cis*-jasmone to *cis*-epoxyjasmone (−)-**2** (over 99% de).

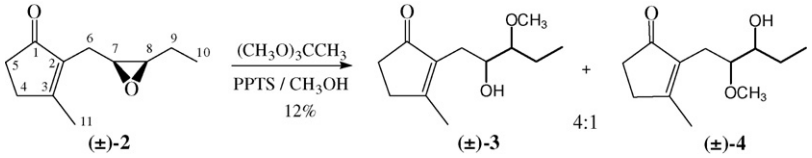
Accessing the absolute configuration of carbons seven and eight demanded a S_N2 or S_N2-like regioselective ring opening of epoxide (−)-**2** into **3** or **4** (Fig. 1). This was challenging and a literature investigation [24–29] pointed to few regioselective methods for 1,2-dialkylsubstituted epoxide ring opening and these were either restricted to epoxides attached to rings or required the application of epoxide hydrolases. The methodologies were further restricted by the presence of the α,β-unsaturated carbonyl group imposing the introduction of an additional step involving the carbonyl protection.

In an attempt to promote carbonyl group protection while avoiding thio groups that are laborious to remove, we first reacted (±)-**2** (obtained by treating *cis*-jasmone with *m*-chloroperoxybenzoic acid [30]) with trimethyl *ortho*-acetate in the presence of pyridinium *p*-toluene sulfonate (PPTS) and a regioselective ring opening instead of the carbonyl protection was observed (Scheme 2).

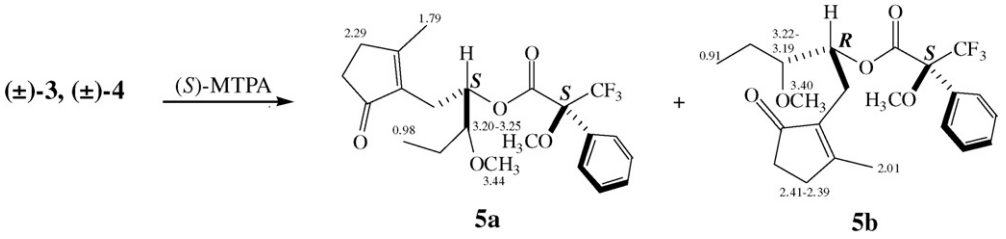
Both regioisomers were characterized by 2D NMR spectrum (^{1}H, ^{13}C HSQC) using the four methines with chemical shifts of methoxy and hydroxyl bearing carbons. The most intense signals δ_C 71.0 (δ_H 3.70) and δ_C 84.8 (δ_H 3.01) were assigned to C-7 and C-8 of (±)-**3**, respectively and the less intense δ_C 73.7 (δ_H 3.20–3.14) and δ_C 81.5 (δ_H 3.20–3.14) were assigned to C-7 and C-8 of (±)-**4**, respectively. Methines at δ_C 84.5 and 81.5 were assigned to carbons bearing methoxy groups, which have a recognized larger alfa effect than OH [31]. The identification of the methoxy group position at C-8 of (±)-**3** (major regioisomer) took into consideration the H-8 correlations with H-7 (δ_H 3.70) and H-9 (δ_H 1.75–1.50 two hydrogens) in the ^{1}H,^{1}H gCOSY spectrum. Finally a cross peak between H-9 and H-9′ with the methyl hydrogens (H-10) provided an unequivocal proof of the C-7 to C-10 connectivities for isomer (±)-**3**. With the unambiguous assignment of all hydrogens and carbons, the isomer ratio, (±)-**3**:(±)-**4**, was determined as 4:1.

This stereoselective epoxy ring opening provided a practical entry to determine the absolute configuration of epoxyjasmone(−)-**2**. Theoretically, the Mosher reaction of an optically pure compound will result in a single Mosher ester derivative. Therefore, esterification of the racemic mixture of (±)-**3** and (±)-**4** with (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (Mosher acid) afforded two mono-ester derivatives in approximately 1:1 ratio. NMR analyses (^{1}H and ^{13}C, DEPT 135° and 90°, ^{1}H,^{1}H gCOSY, ^{1}H,^{13}C HSQC) showed that Mosher's esters **5a** and **5b** were obtained from (±)-**3** (Scheme 3). The assignment of C-7 configuration in **5a** and **5b** was based on the (*S*)-MTPA phenyl group anisotropic effect

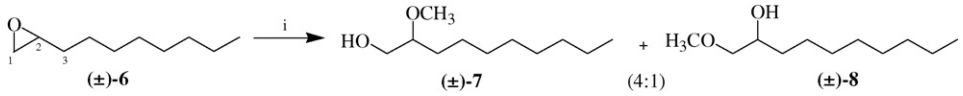
[1] Hydrogen and carbon numbering of **2**–**5** were adopted in accordance with *cis*-jasmone (**1**).



Scheme 2. Synthesis of (±)-7-hydroxy-8-methoxyjasmone, (±)-**3** and (±)-8-hydroxy-7-methoxy-jasmone, (±)-**4** by epoxyjasmone regioselective ring opening.



Scheme 3. Conformational models for the (*S*)-MTPA esters of compounds **5a** and **5b**.



Scheme 4. Synthesis of (±)-1-hydroxy-2-methoxydecane (±)-**7** and (±)-1-methoxy-2-hydroxydecane (±)-**8**. *Reagents and conditions*: (i) $(CH_3O)_3CCH_3$, PPTS, anhydrous CH_3OH, rt.

on the alcohol substituents, according to the well-established conformational models [18–20]. ^{1}H NMR analysis showed that H-1 to H-6 are shielded in isomer **5a** (7*S*) relative to those in isomer 5**b** (7*R*) and H-8 to H-10 are shielded in **5b** compared to those in **5a**.

The same protocol (trimethyl *ortho*-acetate/PPTS epoxy ring opening followed by (*S*)-Mosher acid derivatization) was applied to the *cis*-epoxyjasmone (−)-**2**, obtained by biotransformation of *cis*-jasmone **1** using *T. cutaneum* CCT 1903 whole cells. In this case, a single Mosher ester (**5a**) derivative was observed. The ^{1}H and ^{13}C NMR spectra analysis revealed that the configuration of the predominant enantiomer was 7*S*, corresponding to the levorotatory isomer, as revealed by optical rotation (−)-**2**. Consequently *T. cutaneum* oxidation of the *cis*-jasmone **1** produced *cis* (7*S*,8*R*)-(−)-epoxyjasmone (−)-**2**.

It is important to point out that the enantiomeric excess determined by ^{1}H NMR spectrum signal amplitude using the methoxy group of the Mosher derivative was 75% ee, lower than the 92% ee determined by chiral GC, indicating that some spontaneous epoxy opening by trimethyl *ortho*-acetate and PPTS occurred, thus not recommending this methodology for simultaneous assessment of the enantiomeric excess and absolute configuration.

To investigate whether this regioselective ring opening would occur in terminal epoxides we applied the same protocol to (±)-1,2-epoxydecane, (±)-**6**, and a regioselective opening was once again observed (Scheme 4). The products (±)-**7** and (±)-**8** were characterized by ^{1}H and ^{13}C NMR (DEPT 135° and 90°) and a more deshielded carbinolic carbon was observed for (±)-1-hydroxy-2-methoxydecane (±)-**7** assigned to the presence of a methoxy group in C-2 [32,33].

It was thus concluded that for terminal epoxides the ring opening is regioselective and S_N2 like as observed for the 1,2-dissubstituted epoxides. Consequently the method could be used to establish the absolute configuration of epoxides, keeping in mind that for terminal epoxides the absolute configuration can also be assessed by ^{1}H NMR using Riguera's protocol on the mandelic acid derivatives [34]. This method will be tested on a wider range of epoxides to observe the method limitations.

4. Conclusion

In summary, we have demonstrated that trimethyl *ortho*-acetate and PPTS in association with Mosher derivatization represent a versatile method to determine the absolute configuration of *cis* (7*S*,8*R*)-(−)-epoxyjasmone (−)-**2** due to a regioselective epoxide opening. We anticipate that this method could be extended to a variety of other structures including terminal epoxides.

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