DOI: 10.1002/ejoc.200601080

First Enantioselective Synthesis and Absolute Stereochemistry Assignment of New Monoterpene Aldehyde-Esters from *Bupleurum gibraltaricum*

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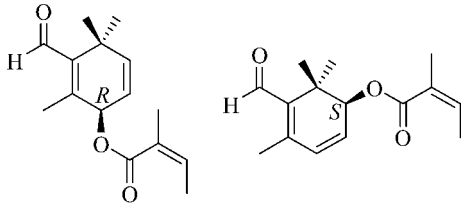
Keywords: Natural products / Terpene / Enantioselective synthesis / Absolute configuration determination

The first enantioselective synthesis of two new monoterpene aldehyde-esters from *Bupleurum gibraltaricum*, starting from an enantiopure building block, is described. The key step is a strictly controlled esterification to afford the somewhat unstable target compounds. The previously unknown absolute stereochemistries of these natural products have been established.

Introduction

Isoferulyl angelate [(–)-**1**] and the unnamed isomer (+)-**2** (Figure 1) are monoterpene aldehyde-esters isolated from the hexane extract of the leaves of *Bupleurum gibraltaricum* Lam (*B. verticale* Ortega),[1–3] a species whose distribution is restricted to southern Spain and northern Morocco.[4] The plant is used in folk medicine and its essential oil displays marked antiinflammatory activity.[5]

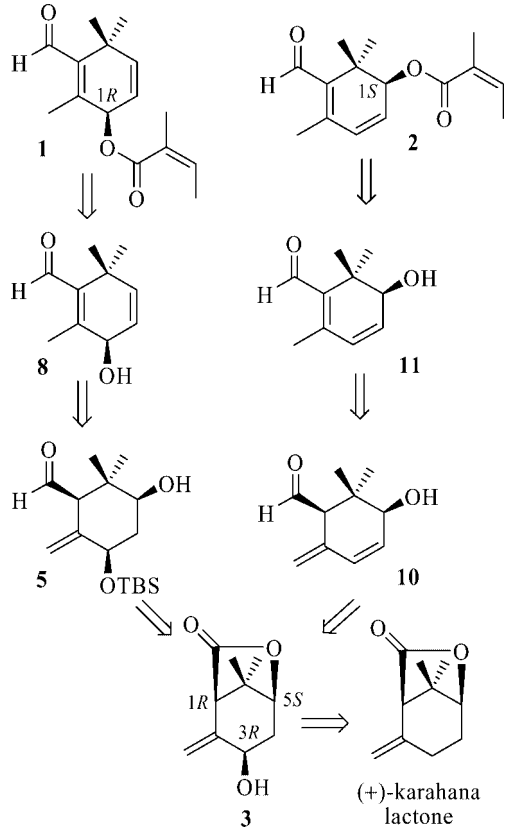


(–)-**1** (+)-**2**

Figure 1. Natural monoterpene aldehyde-esters (–)-**1** and (+)-**2** represented with their absolute stereochemistries as determined in this work.

The gross structures of (–)-**1** and (+)-**2** had been elucidated by spectroscopic analysis,[1,2,6] but during hexane extraction and identification it had been shown that these compounds were somewhat unstable and readily underwent elimination and rearrangement to give 2,3,6-trimethylbenzaldehyde.[2,3] This may explain why no synthesis of (–)-**1** or (+)-**2** had ever been disclosed until now, and also suggested that the success of such a venture could not be taken for granted at the outset.

Here we describe the first enantioselective syntheses of (–)-**1** and (+)-**2**, based on the retrosynthetic analysis depicted in Scheme 1 and starting from a common enantiopure building block for the introduction and determination of the absolute stereochemistry. The chiral information was already encoded in this starting building block, the 3*R* and 5*S* configurations in **3** corresponding to 1*R* in target molecule **1** and 1*S* in target compound **2**, respectively. We envisioned that the key conjugate hydroxyaldehydes **8** or **11**



Scheme 1. Retrosynthetic analysis of **1** and **2**.

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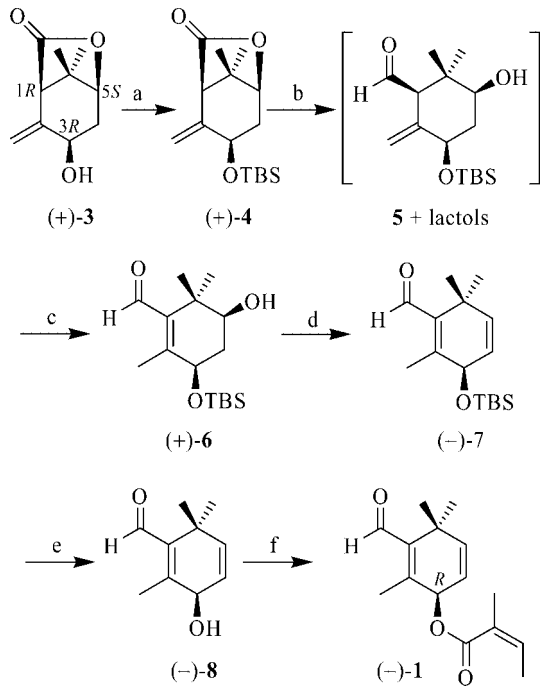
were traceable back to **5** or **10** through double-bond isomerization, with these in turn being obtainable through the partial reduction of the lactone group in **3**, subsequent to a functional group manipulation step. This methodology allowed us to establish the absolute stereochemistries of natural compounds **1** and **2** by comparison of the signs of their specific optical rotations with those of the synthetic samples.

Results and Discussion

The synthesis of the target compound (*R*)-**1** was achieved as presented in Scheme 2. The starting building block (1*R*,3*R*,5*S*)-3-hydroxy-8,8-dimethyl-2-methylene-6-oxabicylo[3.2.1]octan-7-one [(+)-**3**[7a]] was prepared in enantiomerically pure form from readily available (+)-karahana lactone (*ee* > 98%)[7b] through our previously reported stereocontroled Sharpless allylic hydroxylation.[8] Protection of the secondary alcohol in (+)-**3** by treatment with *tert*-butyldimethylsilyl chloride (TBSCl) and imidazole in DMF at room temperature[9] furnished the protected derivative (+)-**4** in 93% yield, while reduction of (+)-**4** with diisobutylaluminium hydride (DIBALH) in toluene at –80 °C provided a 4:1 mixture of aldehyde **5** and lactols (ratios based on ^{1}H NMR analysis). The crude product mixture was subjected to isomerization to the α,β-unsaturated aldehyde in the presence of MeONa (2 equiv.) in MeOH to afford (+)-**6** in 92% yield (two steps), and subsequent dehydration of (+)-**6** with trifluoromethanesulfonyl chloride (TfCl) and 4-(dimethylamino)pyridine (DMAP) in dichloromethane at 0 °C afforded olefin (–)-**7** in 79% yield.[10] At this stage, attempts to cleave the *tert*-butyldimethylsilyl ether in (–)-**7** under mildly acidic (PPTS/EtOH, AcOH/THF/H_2O, aq. HF/CH_3CN) or basic (nBu$_4$NF/THF) conditions failed.[11] This problem was associated with the lability of the bisallylic hydroxy group, which appeared to undergo facile decomposition to form a complex mixture of unidentified products, together with aromatization to 2,3,6-trimethylbenzaldehyde. Finally, desilylation of (–)-**7** was found to be best accomplished with HF·pyridine complex buffered in pyridine as solvent (*without* THF) by a modified literature procedure.[12] Under these conditions, the reaction proceeded uneventfully to deliver the desired product (–)-**8** in 95% yield.

Of the different methods developed for the preparation of angelate esters from alcohols,[13] the procedure of Greene and co-workers[13f] is by far the more effective. By this modified Yamaguchi esterification,[13c] under carefully controlled conditions (60 °C, 36 h) in order to balance the progress of the reaction and the moderate instability of the starting and final materials when subjected to even mild heat,[3] the alcohol (–)-**8** could be smoothly transformed into (–)-isoferulyl angelate [(–)-**1**] in a modest 41% yield but without *Z*/*E* isomerization. The spectroscopic data for our synthesized compound matched those reported for natural isoferulyl angelate,[1] and its optical rotation was comparable in magnitude and the identical in sign {$[\alpha]_D^{27}$ = –67.0 (*c* = 1.0, hexane)[3] $[\alpha]_D^{25}$ = –62.1 (*c* = 1.0, hexane)}, indicating the synthesis of the natural enantiomer. The high optical purity of (–)-**1** was established by chiral HPLC (Figure 2). The *R* configuration was therefore unambiguously assigned to natural isoferulyl angelate [(–)-**1**].



Scheme 2. a) TBSCl, imidazole, DMF, room temp., 93%. b) DIBALH, toluene, –78 °C. c) MeONa, MeOH, room temp., 92% (two steps). d) TfCl, DMAP, CH_2Cl_2, 0 °C, 79%. e) HF·py complex, py, room temp., 95%. f) Angelic acid, 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene, 2 h, room temp., then (–)-**8**, 60 °C, 36 h, 41%.

The synthesis of target compound (+)-**2** is summarized in Scheme 3. Early attempts to engage alcohol (+)-**3** in an elimination through treatment with TfCl and DMAP in dichloromethane as previously (see (–)-**7** above) proved sluggish at 0 °C, while raising the temperature resulted in degraded materials. Having failed to eliminate a triflate group unambiguously, we then turned to a methanesulfonyl (Ms) group. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) has been widely used for introduction of unsaturation through the elimination of sulfonic acids and reactions generally proceed under mild conditions without side reactions.[14] In our case, however, treatment of mesylate **9** with DBU in a typical procedure (equimolar base, benzene, 80 °C) afforded the desired product (+)-**10** only in a poor 22% yield, together with intractable materials. Fortunately, though, a change of the base to *t*BuOK and of the solvent to THF at room temperature cleanly provided the diene (+)-**10** in 60% overall yield (two steps). Reduction of (+)-**10** with DIBALH in toluene at –78 °C afforded a mixture of aldehyde **11** and the corresponding diastereomeric lactols (ratio 4:1, based on ^{1}H NMR analysis), and subsequent isomerization of the crude product mixture with MeONa (2 equiv.) in MeOH gave the α,β-unsaturated aldehyde (+)-**12** in 64% overall yield (two steps). On application of the Yamaguchi

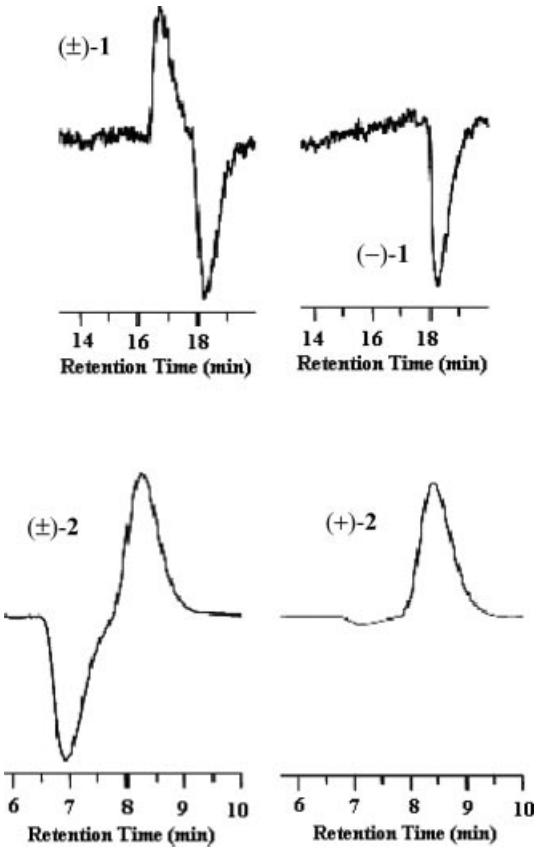
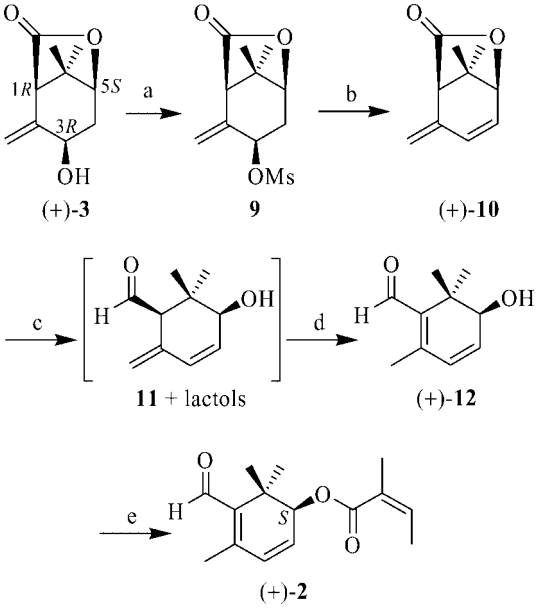


Figure 2. Chiral HPLC diagrams of (–)-**1**, (+)-**2** and the corresponding racemics.



Scheme 3. a) MsCl, NEt_3, CH_2Cl_2, room temp.. b) *t*BuOK, THF, room temp., 60% (two steps). c) DIBALH, toluene, –78 °C. d) MeONa, MeOH, room temp., 64% (two steps). e) Angelic acid, 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene, 2 h, room temp., then (+)-**12**, 60 °C, 36 h, 38%.

modified esterification procedure as applied with isoferulyl angelate (–)-**1**, completion of the synthesis of target compound (+)-**2** was accomplished in a modest 38% yield. The spectroscopic data for (+)-**2** prepared in this way were consistent with those reported in the literature for the natural product,[2] and the specific rotation was the same in sign, indicating the synthesis of the natural enantiomer. The high optical purity of (+)-**2** was confirmed by chiral HPLC (Figure 2). The *S* configuration was therefore assigned to natural (+)-**2**. In this case, however, the magnitude of the specific rotation of (+)-**2** {$[\alpha]_D^{25}$ = +401.8 (*c* = 1.0, $CHCl_3$)} disagreed with that given in the literature[2] {$[\alpha]_D^{27}$ = +194.2 (*c* = 1.0, $CHCl_3$)}. We suggest that this disagreement could be attributable to the presence of the levorotatory enantiomer in significant amounts in the biosynthesized natural compound, or that it may be an artefact of the extractive processes.

Conclusions

In conclusion, the first enantioselective synthesis of isoferulyl angelate [(–)-**1**] and the unnamed isomer (+)-**2** has been accomplished in concise and stereocontrolled fashion from a secured starting building block (+)-**3**, which allows unambiguous assignment of the absolute stereochemistry. By correlation with the signs of the specific rotations reported in the literature, the absolute stereochemistries of the natural products have thus been established as *R* for (–)-**1** and *S* for (+)-**2**.

Experimental Section

General Remarks: All air- and/or water-sensitive reactions were carried out under argon in dry, freshly distilled solvents with use of standard syringe & cannula/septa techniques. All corresponding glassware was oven-dried (80 °C) and/or carefully dried in line with a flameless heat gun. All solvents were distilled under argon: THF from a blue solution of sodium-benzophenone ketyl radical prior to use, and CH_2Cl_2, toluene and DMF from CaH_2. Routine monitoring of reactions was performed with Merck silica gel 60 F_{254} aluminium-supported TLC plates; spots were viewed by use of UV light and ethanolic acidic *p*-anisaldehyde solution or ethanolic phosphomolybdic solution, followed by heating. Purifications by means of column chromatography were performed on silica gel 60 (230–400 mesh) and with gradients of Et_2O/petroleum ether as eluent, unless otherwise stated. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or C_6D_6 solutions on a Bruker AM 300 spectrometer. Chemical shifts (δ) in ppm are reported with use of residual nondeuterated solvents[15] as internal reference. The analytical chiral HPLC experiments were performed on a unit composed of a Merck D-7000 system manager, Merck–Lachrom L-7100 pump, Merck–Lachrom L-7360 oven and on-line Jasco OR-1590 polarimeter. Hexane and *i*PrOH, HPLC grade, were degassed and filtered through a 0.45 mm membrane before use. The columns used were Chiralcel OD-H and Chiralcel OJ (250 × 4.6 mm) from Chiral Technologies Europe (Illkirch, France). Rt0 was determined by injection of tri-*tert*-butylbenzene. The sign given by the on-line polarimeter is the sign of the product in the solvent used for the chromatographic separation. Optical rotations were measured on a Per-

kin–Elmer 341 polarimeter. Microanalyses were performed at our university. Melting points are uncorrected. Infrared spectra were obtained as films or KBr pellets with a Perkin–Elmer 1600 FTIR spectrophotometer.

(1*R*,3*R*,5*S*)-3-Hydroxy-8,8-dimethyl-2-methylene-6-oxabicyclo-[3.2.1]octan-7-one [(+)-3]: Selenium dioxide (1.07 g, 9.6 mmol, 0.4 equiv.), *tert*-butyl hydroperoxide (70 wt.% in water, 9.64 mL, 96.3 mmol, 4.0 equiv.) and a catalytic amount of salicylic acid were added under argon to a stirred solution of (+)-karahana lactone (4.00 g, 24.1 mmol, 1.0 equiv.) in dry CH_2Cl_2 (250 mL). The reaction mixture was heated to reflux for 5 d, allowed to cool to room temperature, and Na_2SO_3 (24.3 g, 0.19 mol, 8.0 equiv.) and water (2 mL) were added. The mixture was stirred for a further 1 h, filtered through a pad of $MgSO_4$ and concentrated to give a solid residue. After purification by recrystallization from Et_2O/hexane, pure alcohol (+)-**3** (3.79 g, 85%) was obtained as white crystals. M.p. 155 °C. $[\alpha]_D^{25}$ = +145.0 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.17 (s, 1 H), 5.05 (s, 1 H), 4.40 (AB*M*X, d, *J* = 5.9 Hz, 1 H), 4.33 (ABM*X*, br. d, *J* = 3.7 Hz, 1 H), 2.73 (br. s, 1 H), 2.20 (*A*BMX, dd, *J* = 15.6, 3.7 Hz, 1 H), 2.06 (A*B*MX, ddd, *J* = 15.6, 5.9, 1.5 Hz, 1 H), 1.18 (s, 3 H), 0.92 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.8 (C), 143.8 (C), 117.0 (CH_2), 84.4 (CH), 67.9 (CH), 56.6 (CH), 42.9 (C), 32.8 (CH_2), 25.3 (CH_3), 20.1 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3443, 3087, 1762, 907 cm^{-1}. $C_{10}H_{14}O_3$ (182.22): calcd. C 65.92, H 7.74; found: C 65.59, H 7.71.

(1*S*,3*R*,5*S*)-3-(*tert*-Butyldimethylsilyloxy)-8,8-dimethyl-2-methylene-6-oxabicyclo[3.2.1]octan-7-one [(+)-4]: The alcohol (+)-**3** (1.00 g, 5.49 mmol, 1.0 equiv.) was dissolved in DMF (10 mL), imidazole (2.24 g, 32.9 mmol, 6.0 equiv.) and *tert*-butyldimethylsilyl chloride (2.90 g, 19.2 mmol, 3.5 equiv.) were added, and the mixture was stirred for 12 h at room temp. The solution was concentrated in vacuo and the residue was purified by column chromatography to give compound (+)-**4** (1.52 g, 93%) as a solid. Recrystallization from Et_2O/hexane afforded pure compound (+)-**4** as white crystals. M.p. 74 °C. $[\alpha]_D^{25}$ = +60.9 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.99 (s, 1 H), 4.94 (s, 1 H), 4.33 (br. d, *J* = 4.7 Hz, 1 H), 4.29–4.25 (m, 1 H), 2.68 (s, 1 H), 2.07–2.03 (m, 2 H), 1.19 (s, 3 H), 0.93 (s, 3 H), 0.85 (s, 9 H), 0.05 (s, 3 H), 0.01 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.9 (C), 143.8 (C), 115.2 (CH_2), 84.2 (CH), 68.6 (CH), 56.9 (CH), 43.3 (C), 34.5 (CH_2), 25.5 (CH_3), 25.4 (CH_3), 20.3 (CH_3), 17.8 (C), –4.7 (CH_3), –5.1 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 1783, 1647, 1259, 906 cm^{-1}. $C_{16}H_{28}O_3Si$ (296.48): calcd. C 64.82, H 9.52; found: C 64.59, H 9.54.

(3*R*,5*S*)-3-(*tert*-Butyldimethylsilyloxy)-5-hydroxy-2,6,6-trimethylcyclohex-1-enecarbaldehyde [(+)-6]: A portion (700 mg, 2.36 mmol, 1.0 equiv.) of (+)-**4** was dissolved in anhydrous toluene (25 mL) and a toluene solution of diisobutylaluminium hydride (1 M, 3.10 mL, 3.10 mmol, 1.3 equiv.) was added dropwise at –80 °C under argon. The reaction mixture was stirred for 45 min at this temperature, quenched with $Na_2SO_4 \cdot 10\,H_2O$ (3.10 g) and Celite (3.10 g), and allowed to warm to room temp. Filtration through a pad of $MgSO_4$ and concentration gave a mixture of lactols and aldehyde as a clear oil. These compounds were used for the next reaction without further purification. The crude mixture was dissolved in MeOH (25 mL) and a solution of MeONa (0.5 M in MeOH, 9.45 mL, 4.72 mmol, 2.0 equiv.) was added under argon. After the system had been stirred for 2 h at room temp., weakly acidic ion-exchange resin was added and the reaction mixture was filtered and concentrated. The residue was purified by chromatography to give (+)-**6** [650 mg, 92% yield from compound (+)-**4**]. $[\alpha]_D^{25}$ = +51.2 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.15 (s, 1 H), 4.17 (t, *J* = 4.9 Hz, 1 H), 3.46 (dd, *J* = 6.8, 2.8 Hz, 1 H), 2.11 (s, 3 H), 2.10–1.93 (m, 2 H), 1.27 (s, 3 H), 1.15 (s, 3 H), 0.91 (s, 9 H), 0.17 (s, 3 H), 0.15 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.9 (CH), 150.1 (C), 139.1 (C), 74.7 (CH), 71.0 (CH), 38.8 (C), 33.8 (CH_2), 25.7 (CH_3), 25.7 (CH_3), 22.0 (CH_3), 17.9 (C), 16.0 (CH_3), –4.3 (CH_3), –4.9 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3417, 1718, 1649, 1262 cm^{-1}. $C_{16}H_{30}O_3Si$ (298.50): calcd. C 64.38, H 10.13; found: C 64.60, H 10.15.

(*R*)-3-(*tert*-Butyldimethylsilyloxy)-2,6,6-trimethylcyclohexa-1,4-dienecarbaldehyde [(–)-7]: DMAP (737 mg, 6.03 mmol, 6.0 equiv.) and trifluoromethanesulfonyl chloride (268 μL, 2.51 mmol, 2.5 equiv.) were added at 0 °C to a stirred solution of alcohol (+)-**6** (300 mg, 1.01 mmol, 1.0 equiv.) in CH_2Cl_2 (25 mL). The cloudy mixture was stirred under argon at this temperature for 2 h and was then diluted with diethyl ether and poured into water. The resulting aqueous layer was extracted with diethyl ether, and the combined organic layers were washed with water and brine, dried with $MgSO_4$ and concentrated. Purification by column chromatography gave (–)-**7** (223 mg, 79%) as a clear oil. $[\alpha]_D^{25}$ = –38.7 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6): δ = 10.07 (s, 1 H), 5.49 (dd, *J* = 10.1, 3.1 Hz, 1 H), 5.39 (d, *J* = 10.1 Hz, 1 H), 4.27 (d, *J* = 3.1 Hz, 1 H), 1.83 (s, 3 H), 1.34 (s, 3 H), 1.31 (s, 3 H), 0.92 (s, 9 H), 0.01 (s, 6 H) ppm. ^{13}C NMR (75 MHz, C_6D_6): δ = 191.7 (CH), 151.3 (C), 140.2 (CH), 139.4 (C), 122.5 (CH), 68.8 (CH), 35.4 (C), 28.0 (CH_3), 27.1 (CH_3), 26.0 (3 CH_3), 18.3 (C), 15.0 (CH_3), –3.8 (CH_3), –4.2 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3031, 2715, 1705, 1630 cm^{-1}. $C_{16}H_{28}O_2Si$ (280.48): calcd. C 68.52, H 10.06; found: C 68.18, H 10.09.

(*R*)-3-Hydroxy-2,6,6-trimethylcyclohexa-1,4-dienecarbaldehyde [(–)-8]: HF·pyridine complex (70 wt.% HF, 4.0 mL) was carefully added at 0 °C under argon to a stirred solution of pyridine (6 mL) in a Teflon® round-bottomed flask. A solution of silyl ether (–)-**7** (200 mg, 0.71 mmol) in pyridine (4 mL) was slowly added, and the mixture was allowed to warm to room temp. After 2 h, the reaction mixture was concentrated in vacuo, and the residue was diluted in ether and poured into saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with diethyl ether, and the combined organic layers were washed with saturated aqueous $NaHCO_3$, water and brine, dried with $MgSO_4$ and concentrated. After purification by column chromatography, alcohol (–)-**8** (113 mg, 95%) was obtained as a clear oil. $[\alpha]_D^{25}$ = –8.7 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6): δ = 10.00 (s, 1 H), 5.51 (dd, *J* = 10.1, 3.4 Hz, 1 H), 5.36 (d, *J* = 10.1 Hz, 1 H), 4.07 (br. d, *J* = 3.4 Hz, 1 H), 1.87 (s, 3 H), 1.30 (s, 3 H), 1.25 (s, 3 H) ppm. ^{13}C NMR (75 MHz, C_6D_6): δ = 192.2 (CH), 152.0 (C), 140.7 (CH), 139.2 (C), 122.1 (CH), 67.5 (CH), 35.4 (C), 27.7 (CH_3), 27.4 (CH_3), 14.9 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3421, 3037, 2718, 1711, 1241 cm^{-1}. $C_{10}H_{14}O_2$ (166.22): calcd. C 72.26, H 8.49; found: C 71.99, H 8.45.

(*R*)-Isoferulyl Angelate [(*R*)-3-Formyl-2,4,4-trimethylcyclohexa-2,5-dienyl Angelate] [(–)-1]: 2,4,6-Trichlorobenzoyl chloride (658 μL, 4.21 mmol, 7.0 equiv.) and triethylamine (587 μL, 4.21 mmol, 7.0 equiv.) were added dropwise at 0 °C under argon to a stirred solution of angelic acid (422 mg, 4.21 mmol, 7.0 equiv.) in toluene (10 mL). The resulting mixture was stirred for 2 h at room temp., alcohol (–)-**8** (100 mg, 0.60 mmol) in toluene (2 mL) was then added, and the reaction mixture was stirred at 60 °C for 36 hours. After dilution with ether, filtration and concentration, the residue was purified by column chromatography to give natural angelate ester (–)-**1** (61 mg, 41%) as a clear oil. $[\alpha]_D^{25}$ = –67.0 (*c* = 1.0, hexane). ^{1}H NMR (300 MHz, C_6D_6): δ = 9.94 (s, 1 H), 5.81 (br. d, *J* = 3.3 Hz, 1 H), 5.70 (qq, *J* = 7.2, 1.5 Hz, 1 H), 5.63 (dd, *J* = 10.1, 3.3 Hz, 1 H), 5.40 (br. d, *J* = 10.1 Hz, 1 H), 1.93 (dq, *J* = 7.2, 1.5 Hz, 3 H), 1.80 (dq, *J* = 1.5, 1.5 Hz, 3 H), 1.64 (s, 3 H), 1.30 (s,

3 H), 1.24 (s, 3 H) ppm. ^{13}C NMR (75 MHz, C_6D_6): δ = 191.4 (CH), 167.2 (C), 147.0 (C), 142.8 (CH), 141.6 (C), 138.8 (CH), 127.8 (C), 118.4 (CH), 69.6 (CH), 35.5 (C), 27.4 (CH_3), 27.2 (CH_3), 20.7 (CH_3), 15.9 (CH_3), 14.7 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3037, 2719, 1733, 1712 cm^{-1}. $C_{15}H_{20}O_3$ (248.32): calcd. C 72.55, H 8.12; found: C 72.84, H 8.15.

(1*S*,3*R*,5*S*)-8,8-Dimethyl-2-methylene-7-oxo-6-oxabicyclo[3.2.1]-octan-3-yl Methanesulfonate (9): Methanesulfonyl chloride (637 μL, 8.23 mmol, 1.5 equiv.) and triethylamine (1.53 mL, 10.98 mmol) were added dropwise under argon at 0 °C to a stirred solution of alcohol (+)-**3** (1.00 g, 5.49 mmol, 1.0 equiv.) in CH_2Cl_2 (30 mL). The solution was allowed to warm to room temp. After 1 h, the mixture was poured into water, the resulting aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with water and brine, dried ($MgSO_4$) and filtered. Concentration of the organic layer gave the corresponding mesylate **9** (1.51 g) as a clear oil. This compound was used in the next step without any further purification.

(1*R*,5*S*)-8,8-Dimethyl-2-methylene-6-oxabicyclo[3.2.1]oct-3-en-7-one [(+)-10]: Dry *t*BuOK (1.35 g, 12.1 mmol, 2.2 equiv.) was carefully added in one portion to a stirred solution of the crude mesylate (1.51 g) in THF (50 mL). The mixture reaction was stirred for 2 h at room temp. under argon. After dilution with ether, the solution was poured into aqueous saturated NH_4Cl, and the aqueous layer was extracted with diethyl ether. The organic layers were combined, washed with water and brine, dried with $MgSO_4$, filtered and concentrated in vacuo. Recrystallization from Et_2O/hexane afforded the pure diene (+)-**10** (552 mg, 61% yield from (+)-**3**) as white needles. M.p. 95 °C. $[\alpha]_D^{25}$ = +385.1 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.27 (d, J = 9.2 Hz, 1 H), 6.12 (br. dd, J = 9.2, 5.6 Hz, 1 H), 5.18 (s, 1 H), 5.08 (s, 1 H), 4.32 (d, J = 5.6 Hz, 1 H), 2.99 (s, 1 H), 1.26 (s, 3 H), 1.06 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.4 (C), 137.7 (C), 132.2 (CH), 127.7 (CH), 117.6 (CH_2), 81.3 (CH), 58.6 (CH), 43.2 (C), 25.1 (CH_3), 19.5 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3067, 1781, 1654, 903 cm^{-1}. $C_{10}H_{12}O_2$ (164.20): calcd. C 73.15, H 7.37; found: C 72.81, H 7.33.

(*S*)-5-Hydroxy-2,6,6-trimethylcyclohexa-1,3-dienecarbaldehyde [(+)-12]: A portion (500 mg, 3.05 mmol, 1.0 equiv.) of diene (+)-**10** was dissolved in anhydrous toluene (30 mL), and a toluene solution of diisobutylaluminium hydride (1 M, 4.00 mL, 4.00 mmol, 1.3 equiv.) was added dropwise at –80 °C under argon. The reaction mixture was stirred for 45 min at this temperature, quenched with $Na_2SO_4 \cdot 10\,H_2O$ (4.0 g) and Celite (4.0 g), and allowed to warm to room temp. Filtration through a pad of $MgSO_4$ and concentration gave a mixture of lactols and aldehyde (1:4, 453 mg) as a clear oil. These compounds were used for the next reaction without any further purification. The crude mixture was dissolved in MeOH (30 mL) and a solution of MeONa (0.5 M in MeOH, 12.2 mL, 6.10 mmol, 2.0 equiv.) was added under argon. After the system had been stirred for 1 h at room temp., weakly acidic ion-exchange resin was added and the reaction mixture was filtered and concentrated. The residue was purified by chromatography to give (+)-**12** [324 mg, 64% yield from (+)-**10**] as a clear oil. $[\alpha]_D^{25}$ = +248.8 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.09 (s, 1 H), 6.21 (dd, J = 9.5, 4.1 Hz, 1 H), 5.93 (d, J = 9.5 Hz, 1 H), 3.85 (br. d, J = 4.1 Hz, 1 H), 2.15 (s, 3 H), 1.21 (s, 3 H), 1.15 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.1 (CH), 145.1 (C), 137.3 (C), 136.0 (CH), 130.0 (CH), 74.4 (CH), 38.3 (C), 24.0 (CH_3), 18.4 (CH_3), 17.7 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3426, 3049, 2731, 1708 cm^{-1}. $C_{10}H_{14}O_2$ (166.22): calcd. C 72.26, H 8.49; found: C 72.55, H 8.47.

(*S*)-5-Formyl-4,6,6-trimethylcyclohexa-2,4-dienyl Angelate [(+)-2]: 2,4,6-Trichlorobenzoyl chloride (658 μL, 4.21 mmol, 7.0 equiv.) and triethylamine (587 μL, 4.21 mmol, 1.0 equiv.) were added dropwise at 0 °C under argon to a stirred solution of angelic acid (422 mg, 4.21 mmol, 7.0 equiv.) in toluene (10 mL). The resulting mixture was stirred for 2 h at room temp., alcohol (+)-**12** (100 mg, 0.60 mmol, 1.0 equiv.) in toluene (2 mL) was then added, and the solution was stirred at 60 °C for 36 h. After dilution with ether, filtration and concentration, the residue was purified by column chromatography to give natural angelate ester (+)-**2** (57 mg, 38%) as an oil. $[\alpha]_D^{25}$ = +401.8 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.17 (s, 1 H), 6.24 (dd, J = 9.5, 4.4 Hz, 1 H), 6.06 (qq, J = 7.2, 1.5 Hz, 1 H), 6.05 (d, J = 9.5 Hz, 1 H), 5.10 (d, J = 4.4 Hz, 1 H), 2.21 (s, 3 H), 1.96 (dq, J = 7.2, 1.5 Hz, 3 H), 1.86 (dq, J = 1.5, 1.5 Hz, 3 H), 1.29 (s, 3 H), 1.20 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.5 (CH), 167.5 (C), 145.0 (C), 138.2 (CH), 137.4 (C), 132.0 (CH), 131.8 (CH), 127.8 (C), 75.7 (CH), 37.1 (C), 23.8 (CH_3), 20.5 (CH_3), 19.8 (CH_3), 17.6 (CH_3), 15.7 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 2736, 1751, 1716, 1649 cm^{-1}. $C_{15}H_{20}O_3$ (248.32): calcd. C 72.55, H 8.12; found: C 71.29, H 8.16.

Acknowledgments

P. B. thanks the Ministère de l'Education Nationale, de l'Enseignement Supérieur et de la Recherche for a Ph. D. grant. The authors are thankful to Dr. N. Vanthuyne (Stéréochimie dynamique et chiralité, Professor C. Roussel) for chiral HPLC analyses, and to P. Fournier for the English language revision of the manuscript.

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Received: December 13, 2006
Published Online: April 11, 2007

