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Enantiospecific total synthesis of both enantiomers of laurene by a chemical diastereoselection/lipase-catalyzed kinetic resolution sequence

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Abstract

A short and efficient enantiospecific total synthesis of natural (+)-laurene and its enantiomer is described. The methodology was developed by employing a stereoselective H-ene reaction of an isocyclic allyltrimethylsilane with paraformaldehyde, followed by a lipase-mediated kinetic resolution of the racemic key intermediate.

1. Introduction

The sesquiterpene hydrocarbon laurene was first isolated as the (+)-enantiomer **1** from *Laurencia glandulifera* and subsequently found in several other Laurencia species (Fig. 1).[1–3] Its carbon framework is suitable for the construction of similar biologically important compounds.[4,5] Despite the relatively simple substitution pattern on the cyclopentane skeleton, the *cis*-1,2 relationship of the secondary methyl group with the *p*-tolyl group has made both the stereoselective[6,7] and enantioselective[8,9] synthesis of this product difficult.

(+)-laurene (+)-**1** (-)-laurene (-)-**1**

Figure 1.

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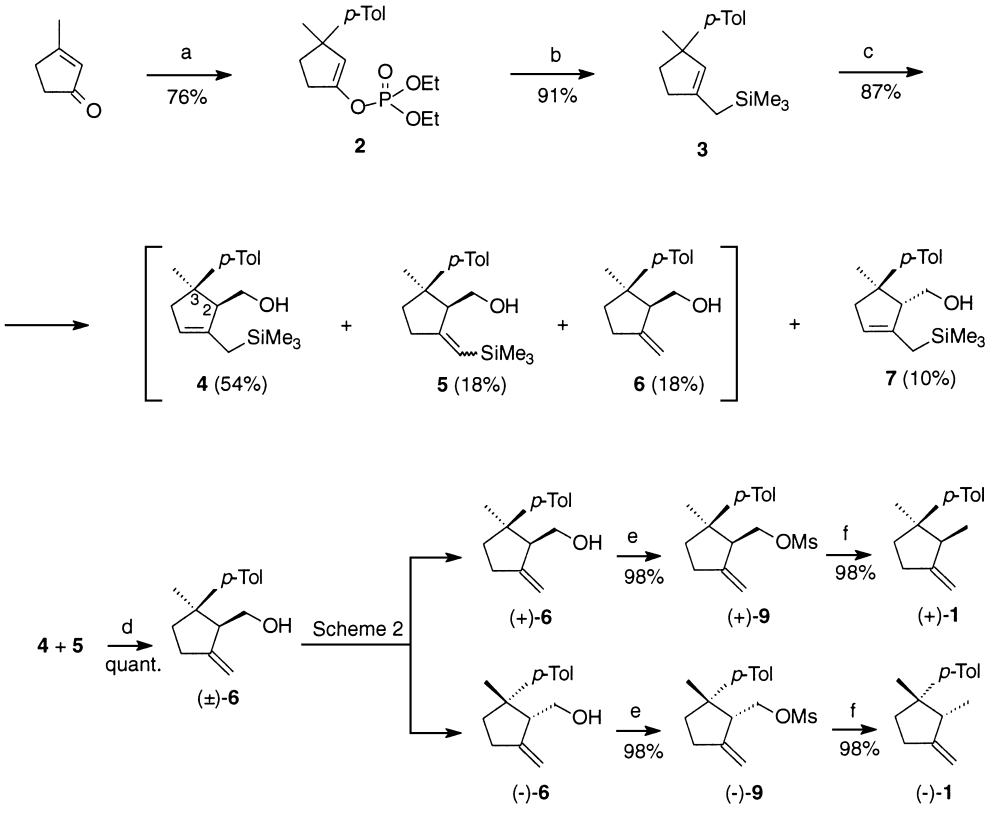
In this paper, we report the first enantiospecific synthesis of both enantiomers of laurene. Our approach is based upon the stereoselective H-ene reaction between an isocyclic allyltrimethylsilane and paraformaldehyde,[10] followed by an enzymatic kinetic resolution of the key racemate. Our methodology is described in Scheme 1.



Scheme 1. Reagents: (a) *p*-TolylMgBr, CuBr·DMS 25%, THF, −5°C then $ClPO(OEt)_2$, HMPA, rt; (b) $ClMgCH_2SiMe_3$, $Ni(acac)_2$ 10%, THF, reflux; (c) $(CH_2O)_n$, Me_2AlCl, MS 4 Å, CH_2Cl_2, −10°C; (d) MeOH, 1 equiv. HCl (35%), rt; (e) MsCl, py, rt; (f) $LiAlH_4$, Et_2O, reflux

2. Results and discussion

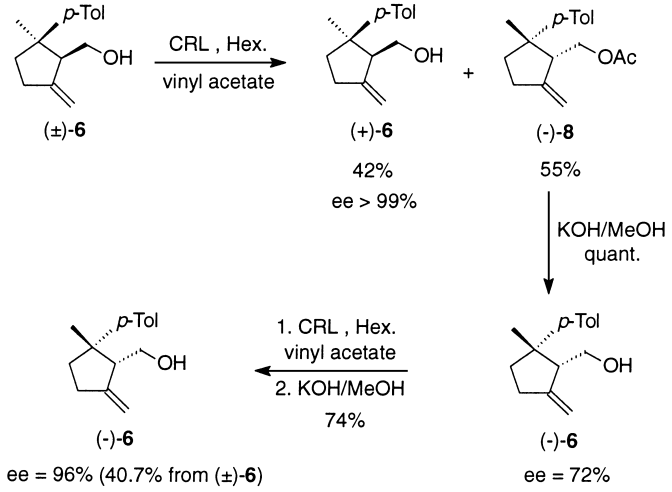
The commercially available 3-methyl-cyclopent-2-en-1-one was converted into the cyclic diethyl enol phosphate **2** in 76% yield by the CuBr·DMS-catalyzed 1,4-addition of *p*-tolyl magnesium bromide, followed by quenching with diethylchlorophosphate in hexamethylphosphoric triamide.[11,12]

The nickel acetylacetonate-catalyzed reaction of **2** with (trimethylsilyl)methylmagnesium chloride gave trimethyl[(3-methyl-3-*p*-tolyl-cyclopent-1-enyl)methyl]silane **3** in 91% yield.[12] The Me_2AlCl-induced H-ene reaction of **3** with paraformaldehyde in the presence of 4 Å molecular sieves (zeolite) furnished, in 87% overall yield, a mixture of three main products (**4**+**5**+**6**) and small amounts (9:1) of a fourth (**7**).

In view of the elucidation of their different structures, the mixture of products was submitted to silica gel column chromatography and the different components readily separated and analyzed. In the ^{13}C NMR spectra, regioisomers **4**, **5** and **7** were identified by the chemical shifts of the quaternary sp^2-

hybridized carbons which differed highly.[13] Those of the allylic isomers **4** (δ=143.5) and **7** (δ=148.4) gave more upfield signals than that of the vinylic isomer **5** (δ=161.5). The stereoselectivity was assessed by comparing the chemical shift of the hydroxymethyl group in the ^{1}H NMR spectra. When the hydroxymethyl and *p*-tolyl substituents are oriented *syn*-like in **4**, **5** or **6**, an upfield shift for the hydroxymethyl AB system is observed relative to the *anti*-orientation as in **7**.[14]

NOESY experiments on the major compound **4** have corroborated this observation. The NOESY plots were characterized by strong cross-peaks between H-2 and Me-3 as well as between the C*H*$_2$OH protons and the *ortho*-positioned protons of the *p*-tolyl group (Scheme 1). So **4**, **5** and **6** had the carbon stereostructure of laurene, and **7** (which could be conveniently discarded by column chromatography) had that of *epi*-laurene. Remarkably, treatment of the mixture (**4**+**5**) with 1 equiv. of HCl (35%) in MeOH provided, without any further isomerization of the exocyclic double bond, the alcohol **6** as the only product in 78% overall yield based on **3**. Treatment of **6** with vinyl acetate:hexane (1:5) in the presence of *Candida rugosa* lipase for 5 days gave the results outlined in Scheme 2.[15–17]



Scheme 2.

Enantiomeric excess (ee) was determined by the ratio of the peak areas obtained by GC separation using a chiral phase (see Section 3). The enantiomers of the alcohol were perfectly separated. However, those of the acetate did not separate. Accordingly, the enantiomeric purity of the acetate was determined after hydrolysis to the corresponding alcohol. So, acetate (−)-**8**, readily separated from unreacted alcohol (+)-**6** (ee >99%) by silica gel column chromatography, was quantitatively hydrolyzed with 3 M KOH/MeOH. The resulting alcohol, (−)-**6** (ee 72%), was resubjected to enzymatic transesterification to provide, after a new hydrolysis, (−)-**6** in 74% yield and an enantiopurity enhancement to 96%. The overall production of (+)-**6** and (−)-**6** from racemic **6** was 42% and 40.7%, respectively. Treatment of alcohol (+)-**6** with an excess of MsCl in pyridine afforded the corresponding mesylate (+)-**9**, which was then reduced with $LiAlH_4$ in refluxing Et_2O to (+)-laurene **1** (96% overall yield from (+)-**6**). The known absolute configuration of natural (+)-laurene[8,9] correlated with the absolute configurations of alcohol (+)-**6** and mesylate (+)-**9**. The same sequence applied to alcohol (−)-**6** provided unnatural (−)-laurene.

In summary, we have developed a short and efficient enantiospecific synthesis of both enantiomers of laurene in very high enantiomeric excess via a stereoselective H-ene reaction and an asymmetric enzymatic transesterification. Following this sequence, the natural enantiomer (+)-laurene is available in an overall yield of 22% and in >99% ee, whereas (−)-laurene is available in an overall yield of 21% and 96% ee.

3. Experimental

3.1. General procedures

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on Bruker AM-400 or Bruker AM-200 spectrometers (Bruker AM-400 for NOESY experiments). Infrared spectra were obtained as films using a Perkin–Elmer 257 infrared spectrophotometer. Routine monitoring of reactions was performed using Merck 60F 254 silica gel, aluminum-supported TLC plates. Column chromatography was performed using silica gel 60 (230–400 mesh) and pentane/ether (gradients) as eluent unless otherwise stated. GC analyses were carried out on a Chrompack 9001 using a WCOT fused silica column (25 m×0.32 mm i.d.; CP-Wax-52 CB stationary phase; N_2 carrier gas: 50 kPa). Enantiomeric excess determinations were carried out using a MEGADEX DETTBSβ fused silica column (30 m×0.25 mm i.d.; N_2 carrier gas: 70 kPa). Optical rotations were measured on a Perkin–Elmer 341 polarimeter. CRL (*Candida rugosa* lipase; EC 3.1.1.3, Type VII, lyophilized, 746 U/mg) was purchased from Sigma. Microanalyses were performed on a Technicon CHN analyzer at our University. Solutions were dried over magnesium sulfate and evaporated in a rotary evaporator under reduced pressure.

3.2. Diethyl[3-methyl-3-p-tolyl-cyclopent-1-en-1-yl]phosphoric triester **2**

p-Tolylmagnesium bromide was prepared in the standard fashion from Mg turnings and *p*-bromotoluene in refluxing dry THF.

To a stirred suspension of cuprous bromide–dimethylsulfide complex (3.47 g, 16.9 mmol) and 3-methyl-cyclopent-2-en-1-one (6.50 g, 67.7 mmol) in dry THF (150 ml) at −5°C was added dropwise *p*-tolylMgBr (1.5 M in THF, 90 ml, 135 mmol) under an Ar atmosphere. The reaction mixture was stirred for 2 h at this temperature, and then a mixture of $ClPO(OEt)_2$ (20.2 ml, 135 mmol) and HMPA (23.4 ml, 135 mmol) in THF (50 ml) was added dropwise. The solution temperature was allowed to rise to rt, stirred for 15 h and then poured into a saturated aqueous NH_4Cl/NH_4OH solution (400 ml) and extracted with ether (3×100 ml). The organic layers were combined, washed with 100 ml of brine, dried, and evaporated. The oily residue was subjected to rapid column chromatography on silica gel (pentane:ether, 30:70) to afford 16.7 g (76%) of **2**. IR (neat): ν 3030, 1645, 1280, 1040, 960 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.22 (d, *J*=8.1 Hz, 2H), 7.11 (d, *J*=8.1 Hz, 2H), 5.45 (br s, 1H), 4.20 (q, *J*=7.1 Hz, 4H), 2.72–2.48 (m, 2H), 2.32 (s, 3H), 2.20–1.98 (m, 2H), 1.45 (s, 3H), 1.37 (t, *J*=7.1 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 149.1 (d, *J*=−8.1 Hz), 146.6, 135.1, 128.7, 125.3, 117.8 (d, *J*=5.0 Hz), 64.2 (d, *J*=−6.0 Hz), 48.6, 38.7, 31.1 (d, *J*=5.0 Hz), 28.5, 20.7, 15.9 (d, *J*=6.7 Hz). Anal. calcd for $C_{17}H_{25}O_4P$: C, 62.95; H, 7.77. Found: C, 63.26; H, 7.80.

3.3. Trimethyl[(3-methyl-3-p-tolyl-cyclopent-1-en-1-yl)methyl]silane **3**

To a stirred solution of enol phosphate **2** (4.00 g, 12.3 mmol) and $Ni(acac)_2$ (474 mg, 1.84 mmol) in THF (80 ml) was added dropwise a 1 M ether solution of (trimethylsilyl)methyl magnesium chloride (36.9 ml, 36.9 mmol) and the mixture was refluxed for 2 h. The reaction was cooled and quenched with 70 ml of a 20% aqueous NH_4Cl solution and stirred for 45 min. After extractive workup with ether (3×100 ml), the organic layers were combined, washed with 50 ml of brine, dried, and evaporated. Purification by chromatography on silica gel (pentane) afforded 2.89 g (91%) of **3**. IR (neat): ν 3020, 1640, 1250, 850 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.25 (d, *J*=7.9 Hz, 2H), 7.11 (d, *J*=7.9 Hz, 2H), 5.28 (s, 1H), 2.32 (s, 3H), 2.51–2.17 (m partially overlapped, 2H), 2.15–1.91 (m, 2H), 1.62 (s, 2H), 1.39 (s, 3H), 0.06

(s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 148.1, 140.7, 134.7, 131.1, 128.7, 125.8, 52.2, 41.8, 36.9, 28.3, 21.4, 20.9, −1.2. Anal. calcd for $C_{17}H_{26}Si$: C, 79.00; H, 10.14. Found: C, 78.76; H, 10.12.

3.4. Reaction of **3** with paraformaldehyde

To a slurry of isocyclic allylsilane **3** (2.20 g, 8.51 mmol), powdered 4 Å molecular sieves and paraformaldehyde (280 mg, 9.36 mmol) in 25 ml of CH_2Cl_2 at −10°C was added dropwise 17.0 ml of Me_2AlCl (1 M in hexanes, 17.0 mmol). The reaction was monitored by TLC. After stirring for 1 h, the reaction reached completion. It was then poured into 50 ml of $NaHCO_3$ saturated ice-water and extracted with 2×50 ml of Et_2O. The collected organic extracts were washed with brine, dried and concentrated. The mixture was then subjected to careful silica gel column chromatography which allowed successive separation of pure **4** (1.15 g, 47%), **5** (383 mg, 15.6%), **7** (213 mg, 8.7%) and **6** (287 mg, 15.6%).

4: IR (neat): ν 3380, 3020, 1640, 1240, 850 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.28 (d, *J*=8.0 Hz, 2H), 7.15 (d, *J*=8.0 Hz, 2H), 5.42 (s, 1H), 3.42 (m, 2H), 3.08 (br d, *J*=15.3 Hz, 1H), 2.43 (br s, 1H), 2.34 (s, 3H), 2.15 (dd, *J*=15.3 and 1.9 Hz, 1H), 1.70 and 1.46 (AB, *J*=−13.6 Hz, 2H), 1.43 (s, 3H), 0.09 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 143.5, 140.6, 135.2, 129.0, 126.7, 122.7, 62.3, 61.7, 48.6, 43.4, 32.4, 20.8, 19.9, −1.1. Anal. calcd for $C_{18}H_{28}OSi$: C, 74.94; H, 9.78. Found: C, 75.16; H, 9.81.

5: IR (neat): ν 3360, 3020, 1620, 1250, 840 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.17 (m, 4H), 5.61 (s, 1H), 3.45–3.29 (m, 1H), 3.14–2.98 (m, 1H), 2.96–2.82 (m, 1H), 2.70–2.53 (m, 2H), 2.50–2.22 (m partially overlapped, 1H), 2.33 (s, 3H), 1.84–1.67 (m, 1H), 1.22 (s, 3H), 0.17 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 161.5, 143.4, 135.4, 129.1, 126.5, 124.8, 62.6, 57.1, 48.3, 32.3, 32.0, 30.7, 20.9, 0.4. Anal. calcd for $C_{18}H_{28}OSi$: C, 74.94; H, 9.78. Found: C, 74.64; H, 9.75.

7: IR (neat): ν 3350, 3020, 1645, 1245, 840 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.26 (d, *J*=8.1 Hz, 2H), 7.10 (d, *J*=8.1 Hz, 2H), 5.45 (s, 1H), 3.85 (m, 2H), 2.78 and 2.40 (AB, *J*=−16.4 Hz, 2H), 2.61 (br s, 1H), 2.31 (s, 3H), 1.64 and 1.39 (AB, *J*=−13.7 Hz, 2H), 1.50 (s, 3H), −0.14 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 148.4, 139.7, 134.8, 128.7, 125.8, 123.5, 62.1, 61.1, 47.6, 47.0, 23.3, 20.7, 19.6, −1.4. Anal. calcd for $C_{18}H_{28}OSi$: C, 74.94; H, 9.78. Found: C, 75.29; H, 9.74.

6: IR (neat): ν 3350, 3040, 1650, 1040, 890, 815 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.16 (s, 4H), 5.12 (br s, 2H), 3.33 and 2.97 (ABX, *J*=−10.5, 10.5 and 5.2 Hz, 2H), 2.75–2.51 (m, 3H), 2.44–2.20 (m partially overlapped, 1H), 2.33 (s, 3H), 1.81 (dt, *J*=11.8 and 5.9 Hz, 1H), 1.29 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 153.0, 143.2, 135.3, 129.0, 126.7, 109.4, 61.9, 58.2, 48.0, 33.7, 30.5, 28.6, 20.8. Anal. calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 82.98; H, 9.35.

3.5. 2-Hydroxymethyl-3-methyl-1-methylidene-3-p-tolyl-cyclopentane **6**

To a stirred mixture of **4** and **5** (1.53 g, 5.33 mmol) in 30 ml of MeOH was added dropwise 0.5 ml of 35% HCl (~1 equiv.) at rt. TLC monitoring showed the total disappearance of **4** and **5** after 1 h. To this mixture was then added 30 ml of CH_2Cl_2, the reaction mixture was poured into a saturated aqueous $NaHCO_3$ solution (40 ml) and extracted with CH_2Cl_2 (3×30 ml). The organic layers were combined, dried and evaporated to afford a residue from which **6** (1.15 g, quant.) was obtained pure after rapid chromatography (gradient pentane/ether).

3.6. General procedure for lipase-catalyzed acylation of (±)-**6**

A mixture of (±)-**6** (1.00 g, 4.63 mmol), vinyl acetate (5 ml) and lipase CR (2.0 g) in 25 ml of hexane was magnetically stirred at rt and the reaction progress monitored by GC on a chiral column. After 3 days

the reaction became very slow. So the mixture was filtered, 2.0 g of lipase CR was added and the slurry stirred until the desired conversion was achieved. After two more days, GC chromatography showed that the remaining alcohol was enantiopure. The reaction was stopped by filtration. Removal of the solvent followed by separation on a silica gel column yielded 420 mg (42%) of pure (+)-(2*S*,3*R*)-**6**, $[\alpha]_D^{20}$=+66.1 (*c* 1.0, $CHCl_3$), and 662 mg (55%) of acetate (−)-**8**; (+)-**6**: ^{1}H and ^{13}C NMR spectra were identical to those of (±)-**6**.

(−)-**8**: IR (neat): ν 3030, 1730, 1650, 1250, 1040, 890, 810 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.15 (m, 4H), 5.03 (br s, 2H), 3.86 (m, 2H), 3.28 (br t, *J*=6.8 Hz, 1H), 2.70–2.51 (m, 2H), 2.48–2.24 (m partially overlapped, 1H), 2.33 (s, 3H), 1.96 (s, 3H), 2.00–1.70 (m partially overlapped, 1H), 1.32 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.8, 151.9, 143.0, 135.3, 128.9, 126.5, 109.1, 64.7, 54.3, 48.1, 34.4, 30.2, 28.8, 20.8. Anal. calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.34; H, 8.62.

Compound (−)-**8** was treated with 3 M KOH (1 ml) in 10 ml of MeOH for 2 h at rt. The solution was diluted with 20 ml of cold water, 20 ml of CH_2Cl_2 and neutralized with 1 M HCl. The aqueous layer was extracted with CH_2Cl_2 (2×20 ml), and the recombined organic phases were dried, filtered and concentrated to afford (−)-**6** (550 mg, quant.) with 72% ee.

Alcohol (−)-**6** was resubjected to lipase-catalyzed acylation as in the previously described conditions. After 2 days, GC analysis showed that the remaining alcohol was near racemic. The reaction was stopped by filtration. Removal of the solvent followed by separation on a silica gel column yielded 490 mg (74%) of acetate (−)-**8**. Treatment of (−)-**8** as previously described gave (−)-(2*R*,3*S*)-**6** (407 mg, quant.) with 96% ee and 40.7% overall yield from (±)-**6**; $[\alpha]_D^{20}$=−63.4 (*c* 1.0, $CHCl_3$); (−)-**6**: ^{1}H and ^{13}C NMR spectra were identical to those of (±)-**6**.

*3.7. (+)-(2*S,*3*R*)-2-[(Methanesulfonyl)-oxy]methyl-3-methyl-1-methylidene-3-*p*-tolyl-cyclopentane (+)-**9***

To a solution of (+)-**6** (216 mg, 1 mmol) in 10 ml of dry pyridine was added dropwise methanesulfonyl chloride (126 mg, 1.1 mmol) under an Ar atmosphere. The solution was stirred at rt for 1 h, then poured onto 100 ml of cold water and extracted with CH_2Cl_2 (3×20 ml). The combined organic extracts were washed with water (5×20 ml), dried, filtered, and concentrated in vacuo (0.02 mmHg). Rapid silica gel column chromatography afforded (+)-(2*S*,3*R*)-**9** (288 mg, 98%); $[\alpha]_D^{20}$=+22.8 (*c* 1.0, $CHCl_3$). IR (neat): ν 3020, 1655, 1350, 1175, 950, 900, 820, 730 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.16 (s, 4H), 5.14 (br s, 2H), 3.96 and 3.76 (ABX, *J*=−9.7, 8.2 and 4.7 Hz, 2H), 2.90–2.78 (m, 1H), 2.70 (s, 3H), 2.68–2.52 (m, 2H), 2.32 (s, 3H), 2.43–2.22 (m partially overlapped, 1H), 1.86 (dt, *J*=12.2 and 6.1 Hz, 1H), 1.32 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 150.6, 142.5, 135.7, 129.2, 126.5, 110.4, 70.9, 54.3, 48.3, 36.7, 34.6, 30.4, 28.9, 20.8. Anal. calcd for $C_{16}H_{22}O_3S$: C, 65.28; H, 7.53. Found: C, 65.65; H, 7.50.

*3.8. (−)-(2*R,*3*S*)-2-[(Methanesulfonyl)-oxy]methyl-3-methyl-1-methylidene-3-*p*-tolyl-cyclopentane (−)-**9***

The same procedure applied to (−)-**6** afforded (−)-(2*R*,3*S*)-**9**, $[\alpha]_D^{20}$=−21.8 (*c* 1.0, $CHCl_3$); ^{1}H and ^{13}C NMR spectra were identical to those of (+)-**9**.

*3.9. (+)-(2*S,*3*R*)-2,3-Dimethyl-1-methylidene-3-*p*-tolyl-cyclopentane: (+)-laurene (+)-**1***

A mixture of mesylate (+)-**9** (200 mg, 0.68 mmol) and $LiAlH_4$ (25 mg, 0.68 mmol) in 10 ml of dry ether was refluxed for 0.5 h. After cooling in an ice bath, Celite (0.7 g), $Na_2SO_4 \cdot 10H_2O$ (0.7 g), and 0.5

ml of 10% NaOH were added. After 30 min the reaction mixture was filtered through a pad of $MgSO_4$ and concentrated to give 133 mg (98%) of pure laurene (+)-(2*S*,3*R*)-**1**; $[\alpha]_D^{20}$=+37.9 (*c* 1.0, EtOH). IR (neat): ν 3060, 1380, 1280, 1020, 880, 815 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.13 (s, 4H), 4.90 (br s, 2H), 2.78–2.47 (m, 3H), 2.34 (s, 3H), 2.35–2.16 (m, 1H), 1.82 (dt, *J*=12.6 and 6.3 Hz, 1H), 1.30 (s, 3H), 0.73 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 157.5, 144.6, 135.0, 128.6, 126.9, 105.6, 50.4, 49.0, 34.6, 29.6, 29.1, 20.9, 17.2. Anal. calcd for $C_{15}H_{20}$: C, 89.94; H, 10.06. Found: C, 89.69; H, 10.09.

*3.10. (−)-(2*R,3S*)-2,3-Dimethyl-1-methylidene-3-*p*-tolyl-cyclopentane: (−)-laurene (−)-**1***

The same procedure applied to (−)-**9** afforded (−)-(2*R*,3*S*)-**1**, $[\alpha]_D^{20}$=−36.6 (*c* 1.0, EtOH); ^1H and ^{13}C NMR spectra were identical to those of (+)-**1**.

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