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Use of lipase-catalyzed kinetic resolution for the enantioselective approach toward sesquiterpenes containing quaternary centers: the cuparane family

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Abstract—The enzymatic kinetic resolution of a suitable hydroxylated precursor of the deoxygenated molecule **3**, a key intermediate in a synthesis of the cuparane skeleton, was investigated by screening a range of lipases for enantioselective transesterification with vinyl acetate. CAL-B proved to be the best lipase, affording both enantiomers in high enantiomeric excess (>98% ee). Single-crystal X-ray diffraction analysis enabled assignment of the absolute configuration and the enantiospecificity of the tested lipases.

1. Introduction

A number of natural aromatic sesquiterpenes contain 1-aryl-1,2,2-trimethylcyclopentane (e.g. Cuparene **1**, Fig. 1) or 2-aryl-1,2-dimethyl-1-acetoxymethylcyclopentane (e.g. Tochuinyl acetate **2**, Fig. 1) ring systems which involve two adjacent quaternary carbon centers.[1] The stereoselective synthesis of molecules of this type has been a challenge for numerous synthetic chemists, owing to the difficulty associated with the construction of these two adjacent quaternary centers in the cyclopentane ring. The reported syntheses of **1** or **2**, whether racemic or non-racemic, employ diverse methodologies.[2–4]

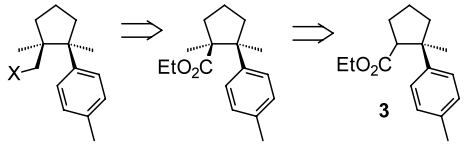

Figure 1.

Some of the developed racemic strategies involved the stereoselective alkylation of the target molecule **3** (Fig. 1) in which the quaternary aromatic stereocenter has been already constructed.[2a,4] Lipases have been frequently used as efficient biocatalysts for the asymmetric synthesis of numerous organic compounds.[5] Their greatest advantages are that they do not require any expensive or labile cofactors nor sophisticated recycling technology.

We report herein a study towards the enantioselective synthesis of the target molecule **3** and its enantiomer based upon a lipase-assisted kinetic resolution. Our methodology is depicted in Scheme 1.

2. Results and discussion

The $Ni(acac)_2$-catalyzed 1,4-addition of di-*p*-tolylzinc[6] to the readily available[7] ethyl 2-methyl-4-oxocyclopent-2-enecarboxylate furnished stereoselectively the keto ester (±)-**4** in 91% yield via the approach of the reagent from the unhindered face. $NaBH_4$–$CeCl_3$ Luche reduction[8] of (±)-**4** afforded the single diastereoisomer (±)-**5** in 93% yield. The relative configuration of the three stereocenters in (±)-**5** was assigned using ^1H NMR NOESY experiments (Fig. 2). The four aromatic

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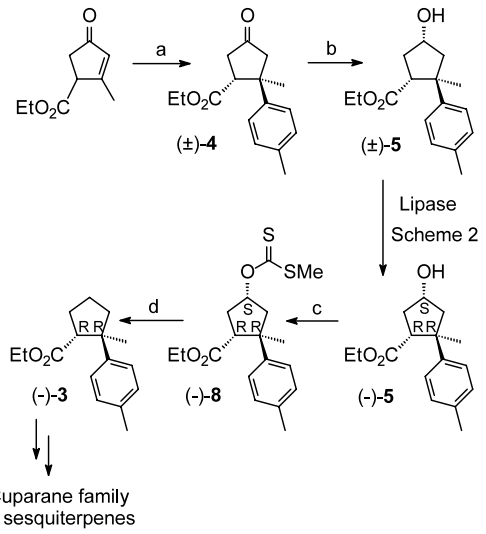


Scheme 1. *Reagents and conditions*: (a) $(p\text{-tol})_2Zn$, $Ni(acac)_2$, Et_2O/THF, rt, 91%; (b) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, EtOH, 93%; (c) NaH, CS_2, MeI, THF, 98%; (d) Bu_3SnH, AIBN, toluene, 96%.

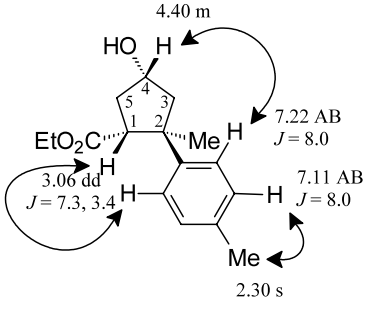


Figure 2. High-field ^1H NMR analysis and NOESY correlations of (±)-**5**.

protons of the *p*-tolyl substituent resonated as two AB systems at $\delta_H = 7.11$ and 7.22 ppm ($J = 8.0$ Hz) and a NOESY correlation among the Me-(C_6H_4), which resonated at $\delta_H = 2.30$ ppm, and the pair at $\delta_H = 7.11$ ppm showed the vicinal proximities of these protons.

On the other hand, strong NOESY correlations between the other pair of aromatic protons at $\delta_H = 7.22$ ppm and H–C(4) and H–C(1) which resonated at $\delta_H =$ 4.40 and 3.06 ppm established the *cis* spatial orientation of these protons and the *p*-tolyl group. In addition, the stereochemistry was secured by the X-ray structural analysis of the crystalline derivative (–)-**7** (vide infra).

With (±)-**5** in hand, screening experiments were made using five commercially available lipases. The resolution procedure is as follows: a mixture of (±)-**5** (50 mg), lipase (50 mg) and vinyl acetate (3 mL) was stirred at room temperature. The reaction progress was monitored by removing aliquots from the supernatant and analyzing directly by both TLC and capillary GC (see Section 4). The reaction was stopped at the conversion rate indicated in Table 1. The outcome of the screening test indicates that with *Candida antartica* (CAL-B, entry 5), the lipase-mediated acylation was fast (the conversion reached ca. 50% in 5 h) and the molecular recognition for the enantiomers of the substrate was high, both for the product (92% ee) and the remaining substrate (91% ee).

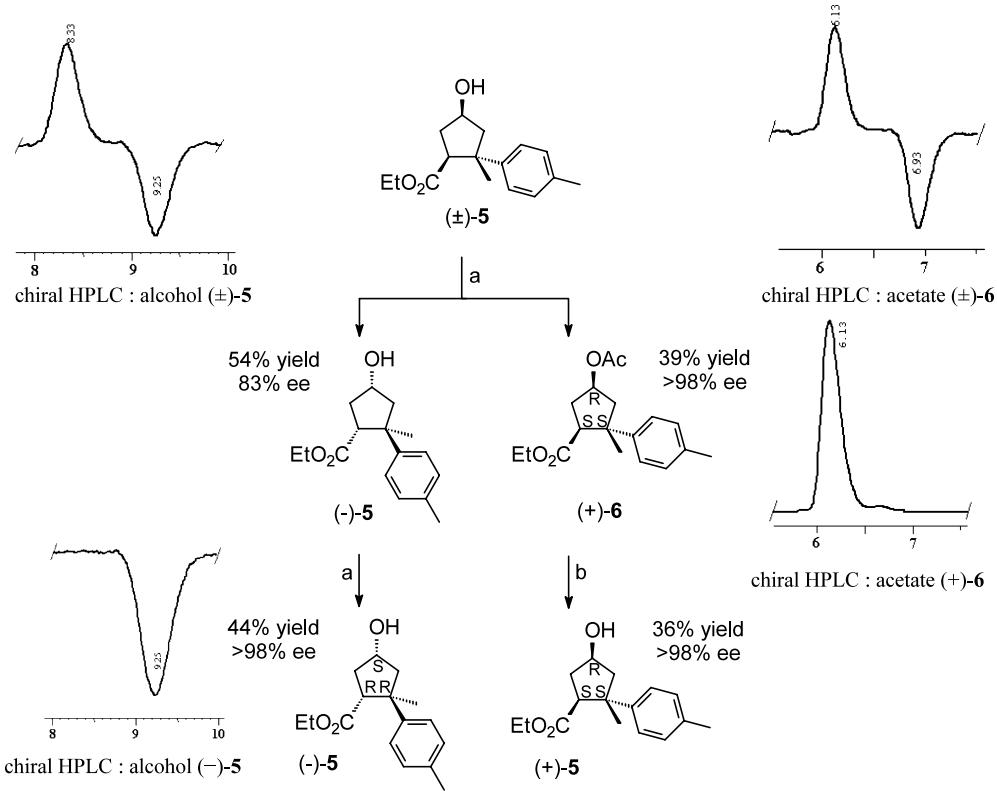
Consequently, in order to improve the results, large-scale enzymatic resolution was performed using that lipase and gave the results outlined in Scheme 2. After 3 h at rt (ca. 40% conversion), the active enzyme was recovered for reuse by filtration. Concentration of the filtrate and column chromatography afforded a 54% yield of the nonreactive alcohol (–)-**5** (83% ee) and a 39% yield of the acetate (+)-**6** (>98% ee). Acetate (+)-**6** was hydrolyzed with Na_2CO_3/MeOH to afford alcohol (+)-**5** in 92% yield (>98% ee, 36% overall yield from racemic **5**). The remaining alcohol (–)-**5** was resubjected in the same conditions to enzymatic transesterification using the recovered lipase. The progress of the reaction was monitored by chiral HPLC until one enantiomer of the starting material was completely consumed. After 4 h, (–)-**5** was obtained in 44% overall yield and >98% ee. To establish the enantiomeric specificity of *Candida antartica* lipase (CAL-B) and, in the same time, to confirm the relative configuration of substituents in substrate (±)-**5**, the absolute configuration of alcohol (–)-**5** was determined as follows. The crystalline ester (–)-**7** was synthesized using (1*S*,4*R*)-camphanic chloride[9] as a chiral auxiliary and submitted to X-ray crystallography. The 3D ORTEP diagram of (–)-**7** fully supported the structure assigned on the basis of NMR methods (Fig. 3).

Finally, Barton–McCombie deoxygenation[10] of (–)-**5** proceeded by way of xanthate (–)-**8,** which was reduced

Table 1. Lipases screening performed on (±)-**5**

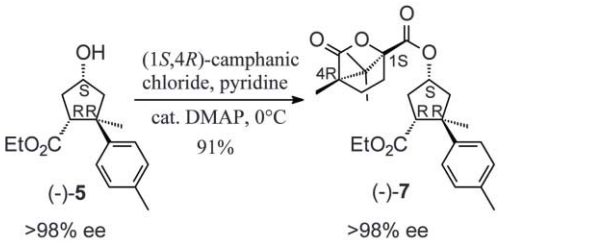
Entry	Lipase	Reaction time	Conversion (%)[a]	Remaining alcohol ee (%)[b]	Produced acetate ee (%)[b]	Lipase[c] specificity
1	PPL	3 days	0	/	/	/
2	CRL	8 days	39	10	23	*S*
3	RML	6 days	34	34	83	*R*
4	PFL	2 days	50	71	74	*R*
5	CAL-B	5 h	50	91	92	*R*

[a] Measured by GC on a capillary column (CP-Wax-52).
[b] Measured by chiral HPLC (Chiralcel OD-H) after isolation by column chromatography.
[c] Assigned by comparison with the t_R of the established (–)-**5** using chiral HPLC chromatogram.



Scheme 2. *Reagents and conditions*: (a) CAL-B, vinyl acetate; (b) Na_2CO_3, MeOH, rt, 91%.

smoothly with tri-*n*-butyltin hydride to provide the target molecule (−)-**3** in an overall yield of 94% for the two steps. Starting from alcohol (+)-**5**, this sequence allowed the synthesis of the enantiomer (+)-**3**.



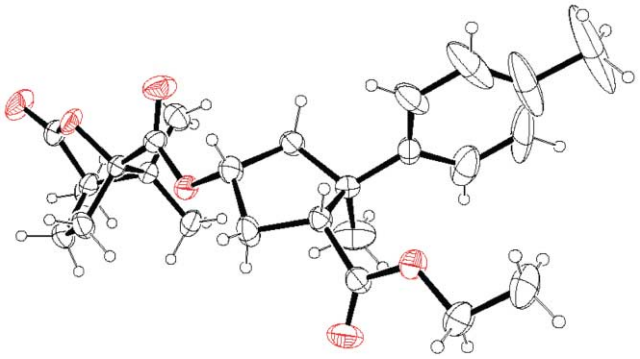


Figure 3. Synthesis and ORTEP view of (−)-**7** (the ellipsoids are drawn at the 30% probability level).

3. Conclusion

In conclusion, we have achieved an enantioselective synthesis of the target molecule (−)-**3** and its enantiomer. For this purpose, CAL-B has proven to be a very efficient and selective catalyst for the resolution of the intermediate (±)-**5** by transesterification with vinyl acetate. Studies on the application of this methodology to the enantioselective total synthesis of natural products in the field of cuparane and herbertane families are underway and will be reported in due course.

4. Experimental

4.1. General

Lipase from *Candida rugosa* type VII (CRL) was purchased from Sigma (S^t Quentin Fallavier, France). Lipase from porcine pancreas (PPL) was purchased from Fluka (Buchs, Switzerland). Lipase AK (from *Pseudomonas fluorescens*, PFL) was gift from Amano Pharmaceutical (Nagoya, Japan). Novozyme 435 (from *Candida antartica B* lipase, CAL-B) and Lipozyme RM IM (from *Rhizomucor miehei* lipase, RML) were gifts from Novo Nordisk A/S (Bagsværd, Denmark). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Bruker AM-300 spectrometer (Bruker AM-400 spectrophotometer for NOESY experiments). Infrared spectra were obtained as films or KBr pellets using a Perkin–Elmer 1600 FT-IR spectrophotometer. Routine monitoring of reactions was performed using Merck

silica gel 60 F_{254}, aluminum supported TLC plates. Column chromatography was performed with silica gel 60 (230–400 mesh) and gradients pentane/ether 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 commercial column from Daiser: CHIRALCEL OD-H® (250×4.6 mm; 10 μm) with hexane/*i*PrOH (98:2 v/v) and a flow rate of 1 mL/min. Specific rotations were recorded on a Perkin–Elmer 341 polarimeter. Microanalyses were performed on a ThermoFinnigan EA 1112 analyzer at our University. Melting points were uncorrected and determined by using a Büchi Totolli apparatus. Unless otherwise stated, the solutions were dried over magnesium sulfate and evaporated in a rotary evaporator under reduced pressure.

4.2. Compounds

4.2.1. 2-Methyl-4-oxo-2-*p*-tolyl-cyclopentanecarboxylic acid ethyl ester, 4. To a 1 M $ZnCl_2$ solution in ether (27.5 mL, 27.5 mmol) at 5°C under argon atmosphere was added dropwise a 1 M *p*-tolylMgBr solution in ether (55 mL, 55 mmol). The mixture was allowed to warm to rt and stirred for 1 h to produce the ditolylzinc reagent. To a stirred suspension of ethyl 2-methyl-4-oxocyclopent-2-enecarboxylate (1.00 g, 5.95 mmol) and $Ni(acac)_2$ (240 mg, 0.93 mmol) in THF (30 mL) was added dropwise the freshly prepared ditolylzinc reagent at 5°C, and the mixture was allowed to rise to rt. After 15 h the solution was poured into a NH_4Cl saturated aqueous solution, and extracted with ether. The organic layers were combined, washed with brine, dried, and evaporated. The oily residue was subjected to rapid column chromatography to afford 1.41 g (91%) of **4**. IR (film): 3095, 3059, 1741, 1183. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=7.26$ and 7.15 (AB, 4H, $J=8.3$ Hz), 4.16 (m, 2H), 3.38 (dd, 1H, $J=8.0$, 6.0 Hz), 2.82 and 2.58 (AB, 2H, $J=17.9$ Hz), 2.65 and 2.36 (ABX, 2H, $J=18.2$, 8.4, 5.9 Hz), 2.33 (s, 3H), 1.45 (s, 3H), 1.22 (t, 3H, $J=7.0$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=215.4$, 173.1, 142.9, 136.4, 129.3×2, 125.6×2, 60.8, 51.8, 51.7, 46.0, 40.0, 24.4, 20.8, 14.2. Anal. calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.59; H, 7.76.

4.2.2. 4-Hydroxy-2-methyl-2-*p*-tolyl-cyclopentane-carboxylic acid ethyl ester, 5. A solution of ketone **4** (0.90 g, 3.46 mmol) and $CeCl_3{\cdot}7H_2O$ (1.56 g, 4.19 mmol) in absolute EtOH (60 mL) was stirred at rt for 1 h. The solution was cooled to −90°C and treated with $NaBH_4$ (330 mg, 8.72 mmol) in four portions. The reaction mixture was stirred for an additional 3 h before being concentrated under reduced pressure to provide a residue which was partitioned between 100 mL of water and 100 mL of CH_2Cl_2. After separation, the aqueous layer was extracted with CH_2Cl_2 (2×50 mL) and the combined extracts were dried with $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on column to afford 0.84 g (93%) of pure alcohol **5**. IR (film): 3417, 3095, 3052, 1736, 1181. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=7.22$ and 7.11 (AB, 4H, $J=8.0$ Hz), 4.40 (m, 1H), 4.20 (m, 2H), 3.06 (dd, 1H, $J=7.3$, 3.4 Hz), 2.76 (dd, 1H, $J=14.3$, 7.1 Hz), 2.30 (s, 3H), 2.03 (quin, 1H, $J=7.3$ Hz), 1.91 (dt, 1H, $J=14.4$, 2.8 Hz), 1.85 (dd, 1H, $J=14.4$, 5.0 Hz), 1.38 (s, 3H), 1.29 (t, 3H, $J=7.1$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=176.6$, 145.3, 135.7, 129.0×2, 125.6×2, 72.4, 60.8, 54.7, 50.6, 48.8, 38.0, 27.1, 20.8, 14.3. Anal. calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 72.97; H, 8.47.

4.3. General procedure for lipases screening acylation of (±)-5

To a solution of (±)-**5** (50 mg) in vinyl acetate (3 mL) was added the lipase (50 mg). The mixture was stirred magnetically in a hermetically stoppered one-neck flask. The course of the reaction was monitored by GC and TLC. After the period indicated in Table 1, the reaction mixture was filtered through a pad of Celite, and the cake was washed with dry Et_2O. The filtrate was concentrated in vacuo to give an oil which was chromatographed on column. Acetate **6** (the first eluted compound) and alcohol **5** were separated and analyzed on the chiral HPLC column. Results of the lipase-mediated acylations are reported in Table 1.

4.4. Lipase-catalyzed acylation of (±)-5

A mixture of (±)-**5** (1.80 g, 6.87 mmol) and CAL-B (300 mg) in 10 mL of vinyl acetate was magnetically stirred at rt and the reaction progress monitored by GC. After 3 h and 40% conversion, a chiral HPLC analysis showed that the formed acetate (+)-**6** had a >98% ee. At this stage, the reaction was stopped by filtration. Removal of the solvent followed by separation on column yielded 972 mg (54%) of unreacted (−)-**5** (83% ee) and 815 mg (39%) of the formed acetate (+)-**6** (>98% ee). Compound (+)-**6**: $[\alpha]_D^{25}=+50.6$ (*c* 1.0, $CHCl_3$). IR (film): 3094, 3052, 1739, 1185. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=7.28$ and 7.12 (AB, 4H, $J=8.1$ Hz), 5.20 (tt, 2H, $J=7.8$, 5.5 Hz), 4.12 (m, 2H), 3.13 (t, 1H, $J=8.5$ Hz), 2.54 (dd, 1H, $J=14.0$, 7.6 Hz), 2.43 (dt, 1H, $J=14.1$, 8.1 Hz), 2.32–2.20 (m, 1H), 2.31 (s, 3H), 2.05 (s, 3H), 2.00 (dd, 1H, $J=14.1$, 5.1 Hz), 1.40 (s, 3H), 1.19 (t, 3H, $J=7.2$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=173.5$, 170.9, 144.9, 135.6, 128.9×2, 125.6×2, 73.6, 60.3, 53.1, 48.2, 46.9, 34.8, 24.9, 21.2, 20.8, 14.2.

Acetate (+)-**6** (815 mg, 2.68 mmol) was treated with Na_2CO_3 (876 mg, 8.26 mmol) in 20 mL of MeOH for 12 h at rt. An excess of NH_4Cl (1.71 g, 32.0 mmol) was added, and the reaction mixture was concentrated to remove MeOH, diluted with CH_2Cl_2, filtered and concentrated. Purification by column chromatography gave 648 mg (91%) of (+)-**5** as an oil. Ee >98%, $[\alpha]_D^{25}=+93.1$ (*c* 1.0, $CHCl_3$). The ^{1}H and ^{13}C NMR data were identical with those reported for (±)-**5**.

The nonreactive alcohol (−)-**5** (ee=83%) was resubjected in the same conditions to lipase-catalyzed acylation using the recovered active enzyme and the progress of the reaction was monitored by chiral HPLC. After 4 h, HPLC analysis showed that one enantiomer of the alcohol was completely consumed.

The reaction was stopped by filtration. Removal of the solvent followed by column chromatography yielded 792 mg of alcohol (−)-**5** (44% overall yield from (±)-**5**). Ee >98%, $[\alpha]_D^{25} = -93.3$ (*c* 1.0, $CHCl_3$). The ^1H and ^{13}C NMR data were identical with those reported for (±)-**5**.

4.5. (1*S*,4*R*,1′*S*,3′*R*,4′*R*)-4,7,7-Trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane-1-carboxylic acid 4′-ethoxy-carbonyl-3′-methyl-3′-*p*-tolyl-1′-cyclopentyl ester, (−)-7

To a solution of (−)-5 (100 mg, 0.382 mmol) and DMAP (10 mg) in pyridine (4 mL) at 0°C under argon atmosphere was added (−)-(1*S*,4*R*)-camphanic acid chloride (Fluka, 116 mg, 0.535 mmol). The cooling bath was removed, and the solution was stirred at rt. The reaction was monitored by TLC and was completed within 4 h. The mixture was diluted with CH_2Cl_2 and was sequentially washed with water, 1N HCl (until pH 2), saturated $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture was subjected to column chromatography and afforded the camphanate derivative (−)-**7** (153 mg, 91%). Crystallization of (−)-**7** from petroleum ether/ether afforded white crystals. Mp: 73°C. $[\alpha]_D^{25} = -27.5$ (*c* 1.0, $CHCl_3$). IR (neat): 3084, 1785, 1741, 1174. ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.28$ and 7.13 (AB, 4H, $J = 8.1$ Hz), 4.10 (m, 2H), 5.33 (tt, 1H, $J = 7.8$, 5.5 Hz), 3.16 (t, 1H, $J = 8.5$ Hz), 2.59 (dd, 1H, $J = 14.1$, 7.5 Hz), 2.54–2.37 (m, 2H), 2.35–2.22 (m, 1H), 2.32 (s, 3H), 2.13–1.83 (m, 3H), 1.68 (ddd, 1H, $J = 13.2$, 9.2, 4.1 Hz), 1.41 (s, 3H), 1.18 (t, 3H, $J = 7.1$ Hz), 1.11 (s, 3H), 1.07 (s, 3H), 0.99 (s, 3H). Anal. calcd for $C_{26}H_{34}O_6$: C, 70.56; H, 7.74. Found: C, 70.49; H, 7.71.

Diffraction analysis of (−)-7 ($C_{26}H_{34}O_6$, M = 442.53): The colorless single crystals were analyzed at 293 K with a Brucker Nonius Kappa-CCD automated four circle diffractometer using graphite-monochromated Mo-*K*α radiation ($\lambda = 0.71073$ Å). Crystal data: monoclinic, space group $P2_1$, $a = 13.303(1)$ Å, $b = 6.311(3)$ Å, $c = 15.918$ (1) Å, $\beta = 111.141(4)°$, $V = 1246.4(1)$ Å^3, $Z = 2$, $D_x = 1.179$ g/cm^3, $F(000) = 476$, and μ(Mo-*K*α) = 0.83 cm^{-1}. 289 parameters were refined on F^2 using 2667 reflections (Shelxl: Sheldrick, G. M. *SHELXL-97*, *Program for Crystal Structure Refinement*; University of Göttingen, Göttingen, Germany, 1997) to final indices R [$F^2 > 4\sigma(F^2)$] = 0.0663, wR [$w = 1/[\sigma^2(F_o^2) + (0.101P)^2 + 0.294P$ where $P = (F_o^2 + 2F_c^2)/3$] = 0.192. CCDC 209352 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at http://www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk].

4.6. (1*R*,2*R*,4*S*)-2-Methyl-4-methylsulfanylthiocarboxy-oxy-2-*p*-tolyl-cyclopentanecarboxylic acid ethyl ester, (−)-8

To a suspension of sodium hydride (73 mg, 1.52 mmol, 50% dispersion) in 10 mL of THF at 0°C was added alcohol (−)-**5** (200 mg, 0.76 mmol). After the mixture was stirred for 30 min at 0°C, carbon disulfide (231 mg, 184 μL, 3.04 mmol) and iodomethane (864 mg, 379 μL, 6.08 mmol) was added. The resulting mixture was stirred for another 1 h, carefully poured into ice, and extracted with ether. The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to an oily residue, which was column chromatographed to provide 262 mg (98%) of xanthate (−)-**8**. $[\alpha]_D^{25} = -37.7$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.31$ and 7.14 (AB, 4H, $J = 8.1$ Hz), 5.88 (tt, 1H, $J = 7.8$, 5.3 Hz), 4.12 (m, 2H), 3.18 (t, 1H, $J = 8.7$ Hz), 2.66 (dd, 1H, $J = 14.3$, 7.5 Hz), 2.57 (s, 3H), 2.53–2.44 (m, 2H), 2.33 (s, 3H), 2.19 (dd, 1H, $J = 14.3$, 4.3 Hz), 1.43 (s, 3H), 1.19 (t, 3H, $J = 7.2$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 215.1$, 173.2, 144.5, 135.8, 129.0×2, 125.6×2, 83.2, 60.4, 53.1, 48.5, 46.7, 34.6, 24.6, 20.8, 18.9, 14.2. Anal. calcd for $C_{18}H_{24}O_3S_2$: C, 61.33; H, 6.86; S, 18.19. Found: C, 61.49; H, 6.84; S, 18.09.

4.7. (1*R*,2*R*)-2-Methyl-2-*p*-tolyl-cyclopentanecarboxylic acid ethyl ester, (−)-3

To a solution of xanthate (120 mg, 0.341 mmol) and AIBN (10 mg) in toluene (3 mL) was added tri-*n*-butyltin hydride (172 mg, 157 μL, 0.591 mmol), and the reaction mixture heated under reflux for 40 min, cooled, and concentrated in vacuo. The resulting oily residue was chromatographed on column to provide 80 mg (96%) of (−)-**3**. $[\alpha]_D^{25} = -98.0$ (*c* 1.0, $CHCl_3$). IR (film): 3091, 3043, 1742, 1163. ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.31$ and 7.12 (AB, 4H, $J = 8.1$ Hz), 4.11 (m, 2H), 3.07 (t, 1H, $J = 7.9$ Hz), 2.32 (s, 3H), 2.26–2.05 (m, 2H), 2.00–1.71 (m, 4H), 1.30 (s, 3H), 1.19 (t, 3H, $J = 7.2$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 174.8$, 146.1, 135.2, 128.8×2, 125.8×2, 59.9, 54.5, 49.6, 41.5, 28.1, 24.3, 22.9, 20.8, 14.2. Anal. calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.87; H, 8.98.

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