# Chemoenzymatic Approach to Optically Active 4-Hydroxy-5-alkylcyclopent-2-en-1-one Derivatives: An Application of a Combined Circular Dichroism Spectroscopy and DFT Calculations to Assignment of Absolute Configuration

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*ABSTRACT* A series of representative optically active derivatives of 4-hydroxy-5-alkylcyclopent-2-en-1-one were prepared from the respective 2-furyl methyl carbinols via the Piancatelli rearrangement followed by the enzymatic kinetic resolution of racemates. Applicability of chiroptical methods (experimental and calculated electronic circular dichroism [ECD] and vibrational circular dichroism [VCD] spectra) to determine the absolute configuration of both stereogenic centers in 4-hydroxy-5-methylcyclopent-2-en-1-one was demonstrated. It was also demonstrated that the concurrent application of ECD and VCD spectroscopy can be used for the determination of the configuration of two stereogenic centers. *Chirality 26:300–306, 2014.* © 2014 Wiley Periodicals, Inc.

*KEY WORDS:* chiral cyclopentenones; Piancatelli rearrangement; kinetic resolution; *Candida antarctica* lipase; density functional theory; electronic circular dichroism; vibrational circular dichroism

## INTRODUCTION

Diverse optically active cyclopentenone derivatives are required as starting materials in the natural product synthesis, most notably prostaglandins and terpenoids.[1–3] In this context a great deal of attention was devoted to the preparation and chemoenzymatic kinetic resolution of racemic 4-hydroxy-2-alkylcyclopent-2-en-1-one derivatives (**1**, Fig. 1). Several representatives of this group of compounds have been successfully resolved using various lipases and acylating reagents.[4–9] However, to the best of our knowledge no reports on the preparation of closely related optically active 4-hydroxy-5-alkylcyclopent-2-en-1-ones (**2**, Fig. 1), are available in the literature. One could expect that the application of enzyme-mediated acylation to hydroxy-enones **2** would be methodologically more demanding due to their propensity to isomerization[10] into **1** and their possible epimerization at C-5.

The determination of absolute configuration of products of kinetic resolution of **2** with two stereogenic centers could be considered as a challenge by itself. Although the preference of lipases to catalyze acylation of (*R*)-enantiomers of aliphatic secondary alcohols has been established, the application of the empirical rules to cyclic alcohols requires a caution.[11–13] In the given case, it was anticipated that the determination of absolute configuration (AC) of the resolution products will be achieved employing a set of modern chiroptical methods.

We now present the results of our studies on the preparation and kinetic resolution of racemic hydroxy enones **4a–4c** (Scheme 1), and on the determination of the AC of the resolved representative compound **4a** applying combination of electronic (ECD) and vibrational circular dichroism (VCD) spectroscopy. Such a combined approach has been made possible due to the recent progress in ab initio simulation of the CD spectra and availability of commercial instruments dedicated to the VCD spectroscopy. Currently, the application of multiple (usually not less than two) chiroptical techniques is recommended by many authors since it greatly enhances the confidence level of stereochemical assignment.[14] Moreover, a combination of theoretical and experimental studies enhances the prospects for the safe use of chiroptical spectroscopy since it enables the direct mutual verification of the results.



## MATERIALS AND METHODS

### *Synthesis*

Melting points were determined on a hot-stage apparatus and are uncorrected. Optical rotations were measured on a Jasco P-2000 polarimeter using 1 mL capacity cell (10 cm path length) in $CHCl_3$. Nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ solutions on a Varian (Palo Alto CA) VNMRS spectrometer for $^1H$ at 500 MHz/$^{13}C$ at 125 MHz, Varian Mercury 400 for $^1H$ at 400 MHz/$^{13}C$ at 100 MHz, or Varian Gemini $^1H$ at 200 MHz and $^{13}C$ at 50 MHz. Chemical shifts are quoted using δ scale and taking the solvent signal as the internal standard ($CHCl_3$, $^1H$ NMR 7.26 ppm; $CDCl_3$, $^{13}C$ NMR 77.00 ppm). High-performance liquid chromatography (HPLC) analyses were conducted using a Daicel (Tokyo, Japan) Chiralcel AD-H or OD-H columns, flow 1 mL/min, on a Knauer (Germany) analytical instrument equipped with a UV detector (220 nm). Column chromatography was performed on Merck silica gel 60, 230–400 mesh and thin-layer chromatography (TLC) on aluminum sheets, Merck 60F 254. Organic extracts were dried over anhydrous $Na_2SO_4$ and solvents were evaporated using a rotary evaporator. Sigma-Aldrich (St. Louis, MO) lipase from *Candida antarctica* (recombinant expressed in *Aspargilus niger*) on acrylic resin was used and is further referred to as lipase. Kinetic resolution experiments were carried out at ambient

Contract grant sponsor: National Science Centre
Contract grant number: UMO-2011/01/B/ST5/00827.
Contract grant sponsor: Interdisciplinary Center for Mathematical and Computational Modeling (ICM) of the University of Warsaw
Contract grant number: G50-5.
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Received for publication 28 November 2013; Accepted 27 February 2014
DOI: 10.1002/chir.22322
Published online 1 May 2014 in Wiley Online Library (wileyonlinelibrary.com).

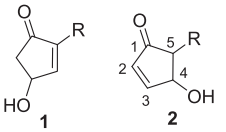
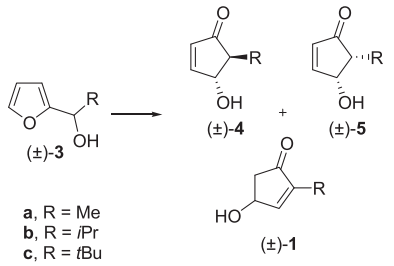


**Fig. 1.** Chiral hydroxycyclopentenones.



**Scheme 1.** Synthesis of hydroxy-cyclopentenone derivatives.

temperature using a rotary shaker. Isopropenyl acetate was used as purchased (Aldrich). Triethylamine was distilled prior to the use.

### *Spectroscopy*

The UV spectra were measured using a Jasco V-670 spectrometer in acetonitrile solutions. The ECD spectra were recorded between 185 and 400 nm at room temperature with a Jasco J-815 spectrometer in acetonitrile solutions. The solutions with concentrations of 0.00143 mol·L were examined in cells with a pathlength of 0.1 or 1 cm. The IR and VCD spectra were measured on a Chiral*IR-2X* (DualPEM) spectrometer (BioTools, Jupiter, FL). Spectra were obtained using the following two conditions: (a) for measurements in the 1650–1050 $cm^{-1}$ region (fingerprint region, FP) 19.02 mg of sample was dissolved in 120 μL of $CD_3CN$ (~1.30 M) and the spectrum was collected for 3.3 h (10,204 scans); (b) for measurements in the 1800–1650 $cm^{-1}$ region (carbonyl region, CO) 1.57 mg of sample was dissolved in 120 μL of $CD_3CN$ (~0.117 M) and spectrum was collected for 7 h (21,504 scans). In both cases the photoelastic modulators (PEM) were set to 1400 $cm^{-1}$ and the spectral resolution was 4 $cm^{-1}$. A demountable cuvette SL-4 Heavy Duty (ICL) with $BaF_2$ windows (each 6.5 mm thick) with 102 μm Teflon spacer was used and rotation 11 rpm was applied. Baseline correction was performed with the spectra of $CD_3CN$ using the same measurement setup, cuvette, and time acquisition as for solution of sample.

### *Computation*

All possible diastereoisomers of 4-hydroxy-5-methylcyclopent-2-en-1-one were the subject of conformational analysis. The molecular mechanics-based conformational search program HyperChem08[15] was used for conducting the preliminary conformational search. The identified conformers were subsequently subjected to the quantum chemical geometry optimization using B3LYP density functional and 6-31G(d) basis set. The optimized geometries at the B3LYP/6-31G(d) level were subjected to further geometry optimizations at the B3LYP/TZVP level with PCM model for acetonitrile solvent. For all Density Functional Theory (DFT) calculations, Gaussian 09[16] was used. Populations were calculated based on ΔG, assuming Boltzmann statistics at 298.15 K.

The UV, IR, ECD, and VCD spectra were computed for the fully optimized geometries using B3LYP functional and TZVP basis sets with the PCM model for acetonitrile solvent. The UV and ECD spectra were simulated from the first 15 singlet singlet electronic transitions by applying Gaussian band shapes with 0.35 eV exponential half bandwidth at 1/e peak height using the program SpecDis v. 1.53.[17] The rotatory strengths were calculated using both the length and the velocity representations. The differences between the length and the velocity calculated values of the rotatory strengths were quite small and for this reason, only the velocity rotatory strengths were taken into further consideration. The ECD and UV spectra were simulated by overlapping Gaussian functions for each transition according to the procedure described by Diedrich and Grimme.[18] The populations of conformers derived from the Gibbs free energies were used to obtain the population-weighted ECD spectra.

The IR and VCD spectra were simulated with Lorentzian band shapes of 6 $cm^{-1}$ half-width at half-peak height. Populations of conformers derived from Gibbs free energies were used to obtain the population-weighted VCD spectra.

The computed ECD and VCD spectra (the UV and IR spectra as well) were determined as the sum of the individual conformer spectra, each one weighted by the fractional equilibrium population of the corresponding conformer.

**(±)-*trans*-4-Hydroxy-5-methylcyclopent-2-en-1-one [(±)-4a], (±)-*cis*-4-hydroxy-5-methylcyclopent-2-en-1-one [(±)-5a] and (±)-4-hydroxy-2-methylcyclopent-2-en-1-one [(±)-1a].** (a) Distilled water (1 L) was placed in a 2 L round-bottomed flask equipped with a reflux condenser and a magnetic stirring device. Water was stirred, brought to boiling, and then (±)-**3a** (10 g, 89.25 mmol) was added. The addition was repeated 3 more times every 20 min (40 g in total). The mixture was heated for additional 3 h and allowed to cool to ambient temperature. The aqueous solution was decanted from polymeric material and was washed with a mixture of hexane and *tert*-butyl methyl ether (MTBE) (1:1, 2 × 40 mL). The organic extract was discarded. The aqueous solution was subsequently salted out with NaCl and extracted with EtOAc (450 mL and then 4 × 300 mL). The combined extracts were dried and the solvent was removed on a rotary evaporator. The residue (20.5 g) was distilled under reduced pressure collecting a fraction with bp 82–84°C/2 mm Hg. Product (16.3 g, 41% yield) composition was estimated by HPLC analysis as: (±)-**4a** (91%), (±)-**5a** (4%), (±)-**1a** (3%) and (±)-**3a** (2%). Column chromatography of the above described product [2 g of mixture, 200 g of silica gel, 1% acetone in methyl-*tert*-butyl ether (1.2 L)] gave 550 mg of (±)-**4a** free from (±)-**5a**; all our attempts to isolate sample of pure (±)-**5a** failed.

(±)-**4a**, $^1$H NMR (500 MHz):7.50 (dd, $J$ = 5.8, 2.2 Hz, 1H), 6.21 (dd, $J$ = 5.8, 1.3 Hz, 1H), 4.57 (dd, $J$ = 3.6, 2.4 Hz, 1H), 2.27 (dq, $J$ = 2.6, 7.4 Hz, 1H), 1.25 (d, $J$ = 7.4 Hz, 3H). $^{13}$C NMR (125 MHz): 208.1, 161.4, 134.0, 78.4, 50.5, 12.5; in agreement with reported data.[9]

(±)-**5a** (from the mixture):$^1$H NMR (500 MHz): 7.55 (dd, $J$ = 5.8, 2.5 Hz, 1H), 6.21 (dd, $J$ = 5.8, 1.3 Hz, 1H), 5.04-4.97 (m, 1H), 2.52 (dq, $J$ = 6.1, 7.7 Hz, 1H), 1.14 (d, $J$ = 7.7 Hz, 3H).

(b) Distilled water (67 mL), dioxane (134 mL) and (±)-**3a** (7.509 g) were placed in a thick-wall ampoule equipped with a magnetic stirring bar. The ampoule was sealed and immersed in an oil bath preheated to 160°C (placed behind a protective shield), and the mixture was vigorously stirred for 18 h. After cooling, the mixture was transferred into a flask and concentrated using rotary evaporator to a residual volume of ca. 40 mL. The solution was decanted from an oily polymer into a separatory funnel containing TBME (2 mL) and hexane (4 mL). The content of the separatory funnel was vigorously agitated and allowed to settle. The organic layer was separated, washed with water previously used for washing the ampoule and the flask (4 mL), and discarded. The combined aqueous solution was extracted with EtOAc (30 mL and then 4 × 20 mL). The combined organic extracts were dried and the solvent was evaporated. The crude product thus obtained (6.542 g) was distilled using a Kugelrohr apparatus at 140°C/1.7 mm Hg to give the product (5.820 g, 78% yield) consisting of (±)-**4a**, (±)-**5a** and (±)-**1a** in a ratio of 87:10:3 by $^1$H NMR.

(c) Acetone (60 mL), distilled water (2.5 mL, 139 mmol), **2** (1.547 g, 13.8 mmol), and $ZnCl_2$ (1.194 g, 8.8 mmol) were placed in a thick-wall ampoule equipped with a magnetic stirring bar. The ampoule was sealed and immersed in an oil bath preheated to 70°C (placed behind a protective shield), and the mixture was stirred for 8 d. After cooling, the mixture was transferred into a flask and the solvent was evaporated. The water-soluble residue was transferred using 10% aq $Na_2SO_4$ (30 mL) into a separatory funnel containing MTBE (2 mL) and hexane (2 mL) (the polymeric material remaining in the ampoule was discarded). The mixture was agitated and allowed to settle and the organic layer was

separated and discarded. The aqueous layer was extracted with EtOAc (1 × 30 mL and then 4 × 20 mL). The organic extracts were combined and the solvent was evaporated. The crude product (1.02 g) was purified by column chromatography on silica gel [20 g, hexane:EtOAc, 7:3 (200 mL) and then 4:6 (200 mL)] to give mixture of (±)-**4a** and (±)-**5a**, 97:3 by $^1$H NMR (775 mg, 50% yield).

**2-Furyl isopropyl carbinol [(±)-3b].** A stirred solution of isopropylmagnesium bromide, prepared from magnesium turnings (21.9 g; 0.90 mol) and 2-bromopropane (97.6 g; 0.80 mol; 74.5 mL) in $Et_2O$ (600 mL) was cooled to –78°C (a thick suspension has formed). Furfural (48.0 g; 0.5 mol, 41.5 mL) in $Et_2O$ (200 mL) was then added dropwise over ~1 h, maintaining the temperature below -60°C. The mixture was stirred at –78°C for an additional 15 min and allowed to warm to room temperature. Sat. aq. $NH_4Cl$ (170 mL) was carefully added. The mixture was briefly stirred and left to settle. The organic layer was decanted from a semisolid mass and the residue was washed with $Et_2O$ (1 × 100 mL; 2 × 50 mL). The combined ethereal solutions were dried ($Na_2SO_4$) and the solvent was evaporated. The residue was distilled at 76°C/10 mmHg to give (±)-**3b**: (oil; 36.6 g, 51 % yield, >99% pure by $^1$H NMR): $^1$H NMR (400 MHz) 7.36 (dd, $J$ = 2.0, 0.8 Hz, 1H), 6.33 (dd, $J$ = 3.2, 2.0 Hz, 1H), 6.22 (dd, $J$ = 3.2, 0.8 Hz, 1H), 4.37 (dd, $J$ = 6.8, 5.1 Hz, 1H), 2.10 (oct, $J$ = 6.8 Hz, 1H), 1.88 (d, 5.1 Hz, 1H, OH), 1.02 (d, $J$ = 6.8 Hz, 3H), 0.86 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz) 156.1, 141.7, 110.0, 106.5, 73.5, 33.3, 18.7 and 18.2; in agreement with reported data.[19,20]

Product of the analogous reaction carried out at room temperature was contaminated with ~5% of (2-furyl)methanol.

**(±)-*trans*-4-Hydroxy-5-isopropylcyclopent-2-en-1-one [(±)-4b].** A mixture of **3b** (970 mg; 6.9 mmol), PPTS (100 mg), and distilled water (31 mL) was heated at the reflux for 3.5 h. After cooling, the solution was decanted from the polymeric material and the residue was washed with water (2 mL). The combined aqueous solution was washed with MTBE (2 × 2.5 mL), saturated with NaCl, and extracted with AcOEt (1 × 12 mL; 3 × 6 mL). The organic extracts were combined and solvent was evaporated. The residue was purified by column chromatography on silica gel (10 g, hexane:AcOEt, 6:4) to give (±)-**4b** containing ~1% of **5b** (406 mg, 42% yield): $^1$H NMR (400 MHz) 7.51 (dd, $J$ = 5.6, 2.4 Hz, 1H), 6.16 (dd, $J$ = 5.6, 1.2 Hz, 1H), 4.80-4.79 (m, 1H), 2.39 (brs, 1H, OH), 2.32-2.24 (m, 1H), 2.19 (dd, $J$ = 4.4, 2.4 Hz, 1H), 1.09 (d, $J$ = 6.8 Hz, 3H), 0.83 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz): 208.2, 162.2, 134.9, 72.8, 60.8, 27.1, 20.7 and 20.2, in agreement with reported data.[7,21,22]

An analogous experiment carried out over an extended reaction time afforded (±)-**4b** contaminated with a side product to which the structure of (±)-**5b** was tentatively assigned, $^1$H NMR (400 MHz) (from the mixture) 7.57 (dd, $J$ = 5.6, 2.4 Hz, 1H), 6.20 (dd, $J$ = 5.6, 1.2 Hz, 1H), 5.03-5.00 (m, 1H).

**(±)-2-Furyl *tert*-butyl carbinol [(±)-3c].** Dry THF (63 mL) and furan (10.71 g; 0.16 mol; 1.25 equiv) were placed, under argon, in a 250 mL round-bottomed flask. The stirred mixture was cooled to –78°C and *n*-butyllithium (2.32 M in hexane, 54 mL, 0.13 mol; 1 equiv) was added dropwise maintaining the temperature below –65°C. After completed addition, the mixture was allowed to warm to 0°C (a white cloudy precipitate appeared). Thus prepared furyllithium slurry was cooled to –78°C. In parallel, a solution of pivaloyl chloride (19.58 g; 0.16 mol; 20 mL; 1.3 equiv) in dry THF (63 mL), under argon, was prepared and cooled to –78°C. The furyllithium slurry was then added dropwise via a cannula the cold pivaloyl chloride solution maintaining the temperature below –65°C. After the addition was completed (~1 h) the mixture was allowed to warm to room temperature and the solvent was evaporated. The residue was taken up in hexane (100 mL) and washed consecutively with a mixture of sat. aq. $NaHCO_3$ and water (1:1, 100 mL) and water (100 mL). The organic solution was then dried and the solvent was evaporated. The residue was distilled collecting fraction 88–92°C/14 mmHg to give the intermediary *tert*-butyl 2-furyl ketone (13.0 g, 68% yield from *n*-BuLi). The latter product (13.0 g) was dissolved in MeOH (250 mL) and the solution was cooled to 10°C. The solid $NaBH_4$ (9.75 g) was then added in portions to a stirred solution maintaining the temperature below 20°C. After the addition was completed, the mixture was stirred for an additional 1 h at room temperature and then the bulk of the solvent was evaporated. The residue was diluted with water (400 mL) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine, dried, and the solvent was evaporated. The residue was distilled collecting fraction with bp 79–82°C/12 mmHg to give carbinol (±)-**3c** (8.85 g, 69% yield from the ketone): $^1$H NMR (200 MHz) 7.35 (dd, $J$ = 2.0, 1.0 Hz, 1H), 6.33 (ddd, $J$ = 3.2, 1.8, 0.2 Hz, 1H), 6.21 (ddd, $J$ = 3.2, 0.6, 0.4 Hz, 1H), 3.09 (d, $J$ = 5.0 Hz, 1H), 1.95 (d, $J$ = 5.0 Hz, 1H), 0.96 (s, 9H); $^{13}$C NMR (50 MHz) 155.7, 141.3, 109.9, 107.0, 76.4, 35.8, 25.8 in agreement with reported data.[23]

**(±)-5-*tert*-Butyl-4-hydroxycyclopent-2-en-1-one [(±)-4c].** Carbinol (±)-**3c** (2.5 g) was added portionwise to distilled water (250 mL) heated under reflux and stirred. The mixture was maintained at the reflux temperature for 24 h, cooled, and the solution was decanted from a polymeric material. The residue was washed with water (15 mL) and the combined aqueous solution was washed with MTBE-hexane (1:2, 10 mL). Organic washings were discarded. Aqueous solution was saturated with NaCl and extracted with EtOAc (100 mL and then 3 × 50 mL). The combined organic extracts were dried and the solvent was evaporated. The residue was distilled (Kügelrohr apparatus) at 150°C/2.5 mmHg to give (±)-**4c**, as s colorless oil, solidifying on standing, (1.93 g, 77% yield), An analytical sample was recrystallized from hexane: mp 40–41°C, $^1$H NMR (400 MHz) 7.46 (dd, $J$ = 6.0, 2.4 Hz, 1H), 6.12 (dd, $J$ = 5.6, 1.2 Hz, 1H), 4.80 (s, 1H), 2.25 (brs, 1H, OH), 2.00 (d, $J$ = 2.4 Hz, 1H), 1.06 (s, 9H); $^{13}$C NMR (100 MHz) 207.5, 160.9, 135.4, 74.0, 64.0, 32.7, 27.8. Anal. Calcd. for $C_9H_{14}O_2$ (MW 154.21): C, 70.10; H, 9.15; found: C, 69.97, H, 9.03%.

**Kinetic resolution of (±)-4a.** Isopropenyl acetate (1.52 mL, 13.79 mmol, 3 equiv.) and *Candida antarctica* lipase (5.75 mg, 5% w/w) were consecutively added to a solution of (±)-**4a** (515 mg, 4.60 mmol; 99% pure by $^1$H NMR) in MTBE (15.5 mL) shaken at room temperature (rt). The reaction was conducted until the residual alcohol reached ~95% enantiomeric excess (ee) (30 h). The solid was then filtered off and the filtrate was evaporated. The residue was purified by column chromatography on silica gel (9 g, hexane:EtOAc, 9:1 (150 mL) and then 6:4 (125 mL) to give consecutively: (1) (4*R*,5*S*)-**6a**, (oil, 548.4 mg, 28% ee, 77% yield), (2) (4*S*, 5*R*)-**4a,** (oil, 107.2 mg, 99% ee, 21% yield), $[\alpha]_D^{23}$ = +95.9 (c = 1.29, $CHCl_3$); ECD ($\Delta\varepsilon$, $\lambda_{max}$): -12.9 (197 nm), +19.3 (221.5 nm), -2.2 (329.6 nm). HPLC, AD-H column, *n*-hexane:isopropanol, 90:10; the following $t_R$ were recorded: (4*R*,5*S*)-**6a**, 6.3 min, its enantiomer 6.0 min; (4*S*,5*R*)-**4a**, 7.5 min, its enantiomer 8.1 min.

The separate analogous experiment, using the distilled rearrangement product (2 g), isopropenyl acetate (5.89 mL, 53.6 mmol), lipase (100 mg, 5% w/w) and in MTBE (60 mL) afforded: (1) acetate fraction, 1.693 g (65%) and (2) alcohol fraction 0.667 g (35%) consisting of: (4*S*,5*R*)-**4a**, 90% and ca. 10% of isomers (by HPLC).

**Kinetic resolution of (±)-4b.** Isopropenyl acetate (217 mg; 2.17 mmol; 238 μL) and *Candida antarctica* lipase, (15.2 mg, 15% w/w) were consecutively added to a solution of (±)-**4b** (99% pure by $^1$H NMR, 101.3 mg, 9.72 mmol) in MTBE (2.3 mL) shaken at rt. The progress of reaction was monitored by HPLC. After 46 h the solid was filtered off and the solvent was evaporated. The residue was purified by column chromatography on silica gel (2 g, hexane) to give: (1) (4*R*,5*S*)-**6b** (oil, 54.4 mg, 96% ee, 41% yield), (2) (4*S*,5*R*)-**4b** (oil, 46.4 mg, (99% ee, 46% yield); $[\alpha]_D^{23}$ = +65.2 (c = 2.18, $CHCl_3$). Retention times, OJ-H column, *n*-hexane: isopropanol, 98:2): (4*R*,5*S*)-**6b** - 9.5 min, its enantiomer - 11.5 min; (4*S*,5*R*)-**4b** - 22.7 min, its enantiomer - 26.0 min.

**Kinetic resolution of (±)-4c.** Isopropenyl acetate (202 mg; 0.22 mL, 2.02 mmol) and *Candida antarctica* lipase (41 mg; 50% w/w) were added to a solution of (±)-**4c** (104 mg, 0.68 mmol) in MTBE (2 mL). The progress of reaction was monitored by HPLC. After 71 h the solid was filtered off and the solvent was evaporated. The residue was purified by column chromatography on silica gel (3 g, hexane–isopropanol, 90:10 and then 70:30) to give: (1) (4*R*,5*S*)-**6c** (oil, 69 mg, >95% ee, 52% yield), (2) (4*S*,5*R*)-**4c** (oil, 50 mg, 98% ee, 48% yield) $[\alpha]_D^{22}$ + 96.3 (c = 2.51, $CHCl_3$). HPLC, OJ-H column, *n*-hexane:isopropanol, 96:4 the following $t_R$ were recorded: (4*R*,5*S*)-**6c** - 6.7 min, its enantiomer - 7.5 min; (4*S*,5*R*)-**4c** - 12.4 min, its enantiomer - 14.6 min.

**TABLE 1. Rearrangement of 2-furyl alkyl carbinols**

| | Substrate | Conditions | Product composition[a] (%) (by $^1$H NMR) | Yield (%, distilled product) |
|---|---|---|---|---|
| 1 | (±)-**3a** | Water, reflux, 4 h | (±)-**4a** (91),[b] (±)-**5a** (4), (±)-**1a** (3), (±)-**3a** (2) | 41 |
| 2 | (±)-**3a** | Water-dioxane, 1:2, 160°, 18 h | (±)-**4a** (87), (±)-**5a** (10), (±)-**1a** (3) | 78 |
| 3 | (±)-**3a** | $ZnCl_2$, aq acetone, 70°, 8 days | (±)-**4a** (97), (±)-**5a** (3) | 50 |
| 4 | (±)-**3b** | Water, PPTS, reflux, 3.5 h | (±)-**4b** (99), (±)-**5b** (1) | 42 |
| 5 | (±)-**3c** | Water, reflux 24 h | (±)-**4c**[c] | 77 |

[a]Distilled products.
[b]The product of 99% purity was prepared by column chromatography.
[c]The product was purified by crystallization.

## RESULTS AND DISCUSSION

### *Synthesis*

The carbinol (±)-**3a** (Scheme 1) was prepared by $NaBH_4$–MeOH reduction of 2-acylfuran following the reported procedure.[24] For the preparation of carbinols (±)-**3b**[7,25] and (±)-**3c**[23] with purity over 99%, some modifications of the reported procedures proved necessary: (±)-**3b** was prepared in reaction of isopropylmagnesium bromide and furfural in diethyl ether at –78°C [at higher temperatures (2-furyl)methanol was formed as a by-product], (±)-**3c** was obtained by coupling of 2-lithiofuran with pivalic chloride followed by $NaBH_4$ reduction of the intermediate 2-furyl *tert*-butyl ketone.

The preparation of 4-hydroxy-5-alkylcyclopent-2-en-1-ones from respective 2-furyl alkyl carbinols via the Piancatelli rearrangement is well documented.[26,27] The challenge of the present work was to prepare the *trans*-isomers (±)-**4a–4c**, free of the accompanying isomerization and rearrangement byproducts. Since the starting carbinols are available at low cost, we focused on the development of operationally convenient procedures with the yield of product being of secondary importance.

Heating of (±)-**3a** in water[28,29] (1 g/100 mL) until the starting material was consumed afforded (±)-**4a** contaminated with the double bond migration product (±)-**1a** and the difficult to remove isomer to which the structure (±)-**5a** was assigned (5–10%). It was convenient to carry out the reaction until ~60% of the carbinol (±)-**3a** was consumed and then remove the remaining starting material by distillation. In this way (±)-**4a**, contaminated with (±)-**5a**, (±)-**1a**[9] and some unchanged (±)-**3a**, was prepared (Table 1, entry 1). A sample of (±)-**4a** with purity over 99% was prepared by column chromatography. Other examined methods of affecting the rearrangements of (±)-**3a** such as heating in aqueous dioxane at 160°C, or in acetone (or dioxane) in the presence of zinc chloride[6,7,30] similarly afforded mixtures of isomers (Table 1, entries 2 and 3).

The rearrangement of the isopropyl derivative (±)-**3b** in boiling water afforded (±)-**4b** contaminated with 5–10% (±)-**5b**. Addition of catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) and reduction of the reaction time resulted in (±)-**4b** contaminated with ~1% of (±)-**5b** (Table 1, entry 4). Rearrangement of (±)-**3c** was markedly slower affording crystalline (±)-**4c**, which was purified by recrystallization (Table 1, entry 5). The results are compiled in Table 1.

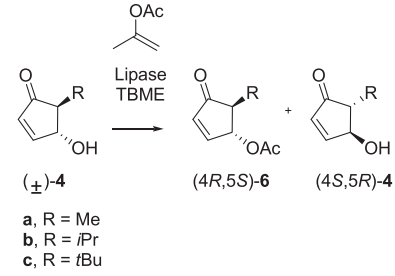
### *Kinetic Resolution*

Irreversible trans-esterification of alcohols was conducted using the immobilized *Candida antarctica* lipase (Sigma-Aldrich) and an excess of isopropenyl acetate.[31,32] The reactions were carried out in *tert*-butyl methyl ether (MTBE) at ambient temperature using a rotary shaker. The composition of the mixture was determined by HPLC equipped with a Daicel Chiralcel AD-H or OJ-H column and a UV detector. The results are presented in Scheme 2 and Table 2.

### *Determination of Absolute Configuration of 4a*

To determine the absolute configuration of alcohol obtained as described above by the kinetic optical resolution of (±)-**4** a simultaneous use of experimental and theoretical ECD and VCD spectroscopy was applied. Nowadays, such a combined approach of more than one chiroptical method is widely recognized as leading to confident assignment of absolute configuration.[14] Moreover, the comparison of experimental and theoretical circular dichroism spectra has already proven efficient and reliable for the assignment of the absolute configuration of various chiral organic molecules.[33–36]

A fundamental prerequisite for the computational calculation of CD spectra is the knowledge of all CD-relevant conformational species of the respective molecule. In our case, the conformational analysis performed within the 5 kcal/mol energy window revealed three conformers for each diastereoisomer. These conformers were in fact rotamers of hydroxy




**Scheme 2.** Kinetic resolution of rac-2-alkyl-4-hydroxycyclopent-2-en-1-ones using *Candida antarctica* lipase.

**TABLE 2. Kinetic optical resolution of alcohols (±)-4 according to Scheme 2**

| Substrate | Lipase w/w% | Time (h) | Acetate, yield (%),[a] ee (4*R*,5*S*)-**6** | Residual alcohol yield (%)[a], ee (4*S*,5*R*)-**4** |
|---|---|---|---|---|
| (±)-**4a** | 5 | 30 | 77, 28 | 21, 99 |
| (±)-**4a**[b] | 5 | 30 | 65, 32 | 35, 90[b] |
| (±)-**4b** | 15 | 32 | 41, 96 | 47, 99 |
| (±)-**4c** | 50 | 71 | 52, >95 | 48, 98 |

[a]Isolated yields.
[b]The product containing ~10% of isomers (by HPLC).

group at carbon C-4. Attempts to obtain the ring conformers by manually changing ring torsion C3-C4-C5-C1 followed by the time-dependent density functional theory (TD-DFT) optimization was fruitless, indicating the restricted conformational freedom for the ring. In *cis*-diastereoisomers, i.e., (4*R*,5*R*) and (4*S*,5*S*), the five-membered ring is almost planar, whereas in the case of *trans*-diastereoisomers, i.e., (4*R*,5*S*) and (4*S*,5*R*), it is slightly skewed. Based on the increasing free Gibbs energy, the distribution of conformers of *cis*-diastereoisomers was 0.72, 0.23, and 0.05, respectively, and the distribution for one of *trans*-diastereoisomers was 0.57, 0.26, and 0.17, respectively. The relative electronic free energies with corresponding fractional populations for the DFT conformers of all diastereoisomers and the geometric parameters reported in Tables 1 and 2, respectively, can be found in Supplemental Information section.

From a set of four isomers only two diastereoisomers [(4*S*,5*R*)-**4a** and (4*S*,5*S*)-**5a**] were selected for further structural analysis. The structures of all conformers of **4a** and **5a** found within the 5 kcal/mol energy window are shown in Fig. 2. The molar ratio of conformers in conformational equilibrium recalculated at a higher level of theory (B3LYP/TZVP/PCM) using Gibbs free energy were found to be 0.34, 0.34, 0.32 for (4*S*,5*R*)-**4a** and 0.37, 0.39, 0.24 for (4*S*,5*S*)-**5a**. In the subsequent calculations of the chiroptical properties the above population molar ratios of conformers were taken into account.

In the Boltzmann-averaged ECD spectra comprising, by definition, the sum of contributions from all populated

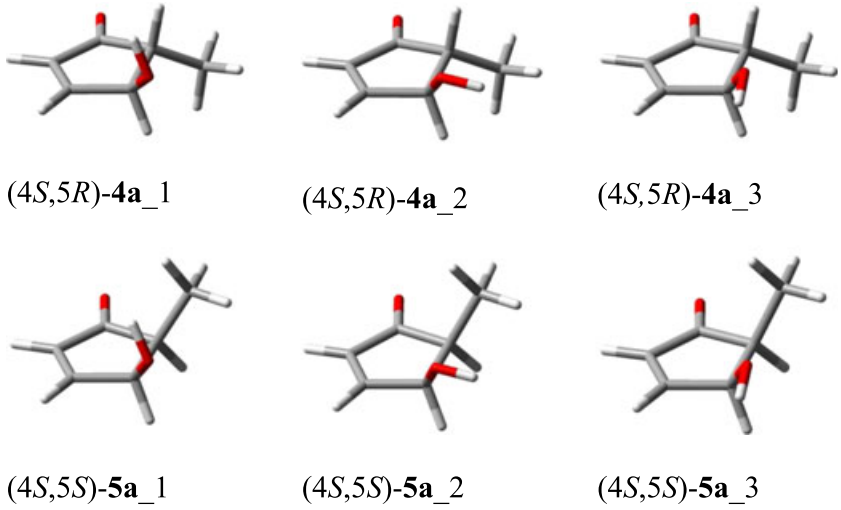



**Fig. 2.** B3LYP/TZVP/PCM ($CH_3CN$) structures of conformers (rotamers) of (4*S*,5*R*)-**4a** (top) and (4*S*,5*S*)-**5a** (bottom).

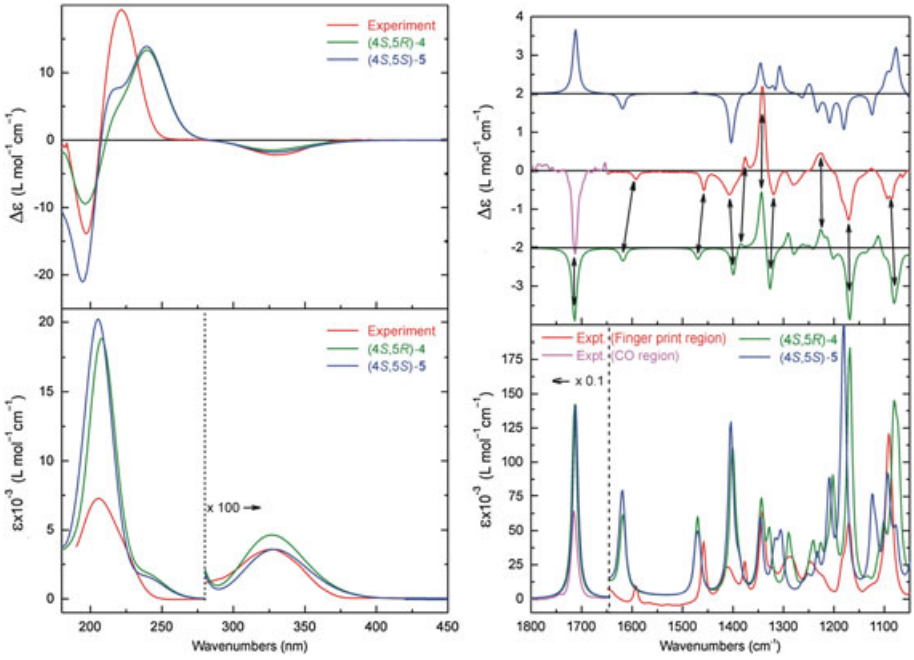



**Fig. 3.** Comparison of experimental spectra to the conformationally averaged B3LYP/TZVP/PCM spectra of (4*S*,5*S*)-**5a** and (4*S*,5*R*)-**4a**; left: ECD (top) and UV (bottom); right: VCD (top) and IR (bottom).

conformers, three ECD bands in the 190–400 nm spectral range are visible (Fig. 3, left). The simulated spectra show a very satisfactory agreement between experiment and theory, especially in the range of nπ* enone transition, i.e., at around 330 nm. Since for both diastereoisomers the absolute configuration at C-4 carbon atom was arbitrarily chosen as the *S*, this result unambiguously identifies the AC in **4a** as 4*S*. This further means that the ECD is mainly governed by the AC at C-4.

Based on the presented ECD results, however, the proper assignment of the absolute configuration of the methyl group at C-5 was not unequivocal. Both diastereoisomers under study exhibit quite good consistency of the simulated spectra with the experimental spectrum throughout the whole spectral range. Although the calculated spectrum of (4*S*,5*R*) diastereoisomer, in particular in the 220 nm region, shows a better compatibility with the experiment, even then the ECD spectrum is not uniquely conclusive for the confident assignment of absolute configuration at C-5. The comparison of experimental and simulated VCD spectra for both diastereoisomers should bring the solution to this problem.

In Fig. 3, right, the averaged B3LYP/TZVP/PCM VCD spectra of both (4*S*,5*R*) and (4*S*,5*S*) diastereoisomers are compared with the experimental VCD spectrum of optical resolution product of (±)-**4a**. As can be seen in Fig. 3, only for the diastereoisomer (4*S*,5*R*) is there a sufficiently good correlation for relatively large number of bands in experimental and simulated VCD spectrum to conclude that the AC at C-5 can be assigned with confidence. First of all, the most striking evidence provides the band at 1713 $cm^{-1}$ corresponding to the stretching modes of the carbonyl group. In the simulated spectra, the sign of this band is consistent with the sign of the experimental spectrum only for diastereoisomer (4*S*,5*R*), whereas for diastereoisomer (4*S*,5*S*) it is of opposite sign. Similar signs, shapes, and intensity conformity occurs also for peaks at 1458 ($CH_3$ out of phase bending), 1375 ($CH_3$ in phase bending), 1342 (*cis* H–C = C–H rocking), 1319 (C-4–H and C-5–H bending), 1225 (C-4–H and O–H in phase bending), 1171 (C-5–CO–C-2 out of phase stretching), and 1094-1084 $cm^{-1}$ (ring in phase stretching and C-4–O stretching) for the same (4*S*,5*R*) diastereoisomer. On this basis, the assignment of absolute configuration can be regarded as definitive.

## CONCLUSION

In conclusion, a costs-efficient synthesis of potentially useful optically active cyclopent-2-en-1-one derivatives: (4*S*,5*R*)-**4a**, (4*S*,5*R*)-**4b**, and (4*S*,5*R*)-**4c** was developed. The synthesis involves the Piancatelli rearrangement of the respective alkyl 2-furyl carbinols and an enzyme-mediated kinetic optical resolution of racemates. The absolute configuration of (4*S*,5*R*)-**4a** was assigned by comparative analysis of the theoretical chiroptical properties of this compound and its isomers and actual experimental measurements. ECD allowed unambiguous assignment of configuration at C-4 carbon atom giving only an indication of the absolute configuration at C-5. The VCD spectrum distinguished the diastereoisomers and allowed to assign the (*R*) configuration at C-5. The present study demonstrated that for the examined compounds a rapidly developing VCD method complements the ECD spectroscopy, thus enabling a reliable and unambiguous assignment of the AC at both stereogenic centers simultaneously.

## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.

## LITERATURE CITED


1. Collins PW, Djuric SW. Synthesis of therapeutically useful prostaglandin and prostacyclin analogs. Chem Rev 1993;93:1533–1564.
2. Das S, Chandrasekhar S, Yadav JS, Gree R. Recent developments in the synthesis of prostaglandins and analogues. Chem Rev 2007;107:3286–3337.
3. Roche SP, Aitken DJ. Chemistry of 4-hydroxy-2-cyclopentenone derivatives. Eur J Org Chem 2010:5339–5358.
4. Babiak KA, Ng JS, Dygos JH, Weyker CL, Wang Y-F, Wong CH. Lipase-catalyzed irreversible transesterification using enol esters: resolution of prostaglandin synthons 4-hydroxy-2-alkyl-2-cyclopentenones and inversion of the 4S enantiomer to the 4R enantiomer. J Org Chem 1990;55:3377–3381.
5. Tanis SP, Robinson ED, McMills MC, Watt W. Furans in synthesis. 11. Total synthesis of (±)-and (-)-fastigilin C. J Am Chem Soc 1992; 114:8349–8362.
6. Rodríguez A, Nomen M, Spur BW, Godfroid J-J. An efficient asymmetric synthesis of prostaglandin E1. Eur J Org Chem 1999;1999:2655–2662.
7. Csákÿ AG, Mba M, Plumet J. Enantioselective synthesis of gamma,delta-disubstituted beta- hydroxy delta-lactones from furans: Synthesis of (+)-prelactone B and its C-4 epimer. Synlett 2003;:2092–2094.
8. Csákÿ AG, Mba M, Plumet J. Asymmetric synthesis of cyclopentenones with benzylic alpha- quaternary carbon stereogenic centres from furans. Tetrahedron-Asymmetry 2004;15(4):647–652.
9. Michalak K, Wicha J. An enantioselective total synthetic approach to (+)-heptemerone G and (+)-guanacastepene A from 2-furyl methyl carbinol. Synlett 2013;24:1387–1390.
10. Stork G, Kowalski C, Garcia G. Route to prostaglandins via a general synthesis of 4-hydroxycyclopentenones. J Am Chem Soc 1975;97: 3258–3260.
11. Jing Q, Kazlauskas RJ. Determination of absolute configuration of secondary alcohols using lipase-catalyzed kinetic resolutions. Chirality 2008;20:724–735.
12. Ferreira HV, Rocha LC, Severino RP, Porto ALM. Syntheses of enantiopure aliphatic secondary alcohols and acetates by bioresolution with lipase B from Candida antarctica. Molecules 2012;17:8955–8967.
13. Chen BS, Hanefeld U. Enantioselective preparation of (R) and (S)-3-hydroxycyclopentanone by kinetic resolution. J Mol Catal B: Enzym 2013;85–86:239–242.
14. Polavarapu PL. Why is it important to simultaneously use more than one chiroptical spectroscopic method for determining the structures of chiral molecules? Chirality 2008;20:664–672.
15. HyperChemProfesional 8.0. Gainesville, FL: Hypercube, Inc.
16. Frisch MJ, Trucks GW, Schlegel HB, et al. Gaussian 09, Revision A.02. Wallingford CT: Gaussian, Inc.; 2009.
17. Bruhn T, Schaumlöffel A, Hemberger Y, Bringmann G. SpecDis version 1.53. Germany: University of Wuerzburg; 2012.
18. Diedrich C, Grimme S. Systematic investigation of modern quantum chemical methods to predict electronic circular dichroism spectra. J Phys Chem A 2003;107:2524–25391.
19. Hatano M, Mizuno T, Ishihara K. Catalytic enantioselective synthesis of sterically demanding alcohols using di(2[degree]-alkyl)zinc prepared by the refined Charette's method. J Chem Soc Chem Commun 2010;46:5443–5445.
20. Martin-Matute B, Nevado C, Cárdenas DJ, Echavarren AM. Intramolecular reactions of alkynes with furans and electron rich arenes catalyzed by PtCl2: The role of platinum carbenes as intermediates. J Am Chem Soc 2003;125:5757–5766.
21. Li CC, Wang CH, Liang B, Zhang XH, Deng LJ, Liang S, Chen JH, Wu YD, Yang Z. Synthetic study of 1,3-butadiene-based IMDA approach to construct a [5-7-6] tricyclic core and its application to the total synthesis of C8-epi-guanacastepene O. J Org Chem 2006;71:6892–6897.
22. West FG, Gunawardena GU. Pseudocine substitution of 4-(mesyloxy)-2-cyclopentenones: an efficient route to 2,4-disubstituted 2-cyclopentenones. J Org Chem 1993;58:2402–2406.
23. Jung ME, Gervay J. gem-Dialkyl effect in the intramolecular Diels-Alder reaction of 2-furfuryl methyl fumarates: the reactive rotamer effect, the

enthalpic basis for acceleration, and evidence for a polar transition state. J Am Chem Soc 1991;113:224–232.

24. Coombs TC, Lee MD, Wong H, Armstrong M, Cheng B, Chen W, Moretto AF, Liebeskind LS. Practical, scalable, high-throughput approaches to Î·3-pyranyl and Î·3-pyridinyl organometallic enantiomeric scaffolds using the Achmatowicz reaction. J Org Chem 2008;73: 882–888.
25. Peters FN, Fischer R. The preparation and properties of some new furan derivatives 1. J Am Chem Soc 1930;52:2079–2082.
26. Piancatelli G, Scettri A, Barbadoro S. A useful preparation of 4-substituted 5-hydroxy-3-oxocyclopentene. Tetrahedron Lett 1976:3555–3558.
27. Scettri A, Piancatelli G, D'Auria M, David G. General route and mechanism of the rearrangement of the 4-substituted 5-hydroxy-3-oxocyclopentenes into the 2-substituted analogs. Tetrahedron 1979;35:135–138.
28. D'Auria M. A new simple procedure for the isomerization of 2- furylcarbinols to cyclopentenones. Heterocycles 2000;52:185–194.
29. Saito K, Yamachika H. Process for producing 3-oxocyclopentenes. USA patent US4356326, 1982.
30. Piancatelli G, Scettri A, David G, D'Auria M. A new synthesis of 3-oxocyclopentenes. Tetrahedron 1978;34:2775–2778.
31. Ohtani T, Nakatsukasa H, Kamezawa M, Tachibana H, Naoshima Y. Enantioselectivity of Candida antarctica lipase for some synthetic substrates including aliphatic secondary alcohols. J Mol Catal B-Enzym 1998;4:53–60.
32. Ahmed M, Kelly T, Ghanem A. Applications of enzymatic and non-enzymatic methods to access enantiomerically pure compounds using kinetic resolution and racemisation. Tetrahedron 2012;68:6781–6802.
33. Kołodziejska R, Górecki M, Frelek J, Dramiski M. Enantioselective enzymatic desymmetrization of the prochiral pyrimidine acyclonucleoside. Tetrahedron: Asymmetry 2012;23:683–689.
34. Polavarapu PL, Frelek J, Woźnica M. Determination of the absolute configurations using electronic and vibrational circular dichroism measurements and quantum chemical calculations. Tetrahedron: Asymmetry 2011;22:1720–1724.
35. Krohn K, Kouam SF, Kuigoua GM, Hussain H, Cludius-Brandt S, Florke U, Kurtan T, Pescitelli G, Di Bari L, Draeger S, Schulz B. Xanthones and oxepino[2,3-b]chromones from three endophytic fungi. Chem Eur J 2009;15:12121–12132.
36. Di Bari L, Pescitelli G, Salvadori P, Rovini M, Anzini M, Cappelli A, Vomero S. Synthesis, resolution, and absolute configuration of two novel and selective cyclooxygenase-2 inhibitors based on the 1,5-diarylpyrrole structure. Tetrahedron: Asymmetry 2006;17:3430–3436.