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Synthesis of Enantiomerically Pure 4-Hydroxy-2-cyclopentenones

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ABSTRACT: Conversion of furfuryl alcohol to 4-hydroxy-2-cyclopentenone was studied in a microreactor channel of 0.5 mm diameter and 1.5 m length. Addition of 1 M *N*-methylpyrrolidinone as a cosolvent significantly reduces the polymeric material normally formed during the reaction in purely aqueous solution. The reaction follows pseudo-first-order kinetics at constant pressure (200 bar) with the values of $\Delta H^{\ddagger} = 18 \pm 2$ kcal/mol and $\Delta S^{\ddagger} = -38 \pm 3$ cal/mol/K. At 240 °C, 200 bar pressure, and residence time of 1.5 min, the product is obtained with 98% conversion and is isolated as a stable *O*-phenylacetyl derivative in 80% yield. This racemic mixture was resolved into enantiomerically pure forms by kinetic resolution with penicillin G acylase (E.C.3.5.1.11) immobilized on epoxy-activated polymer in 90−92% theoretical yield and >99% ee.

INTRODUCTION

The synthesis of enantiomerically pure 4-hydroxy-2-cyclopentenone **1** is a matter of great interest to organic chemists because of its interesting features of possessing three different functional groups in a small cyclopentyl molecule. It is possible to use this molecule as a building block for synthesis of a variety of natural products. For example (*R*)- and (*S*)-4-hydroxy-2-cyclopentenones are used in synthesis of prostaglandins, prostacyclins, thromboxane, and nucleosides.[1−4] Preparation of enantiomerically pure forms of **1** can be performed in a variety of ways.[5,6] Recently, an interesting methodology of kinetic resolution of *O*-Boc derivative has been reported by Reiser and co-workers. Here, palladium-catalyzed allylation was performed with various nucleophiles using Trost's ligand in excellent enantiomeric purity and yield.[5] Earlier, we reported the resolution of the racemic **1** via penicillin G acylase-catalyzed hydrolysis of its phenylacetyl derivative[6] wherein the required racemic **1** was prepared by known literature procedure of acid-catalyzed rearrangement of furfuryl alcohol (FA) in water.[7−11] However, the yields were low (40−50%) and required long reaction period (2 days). Besides, the reaction was accompanied by formation of dark brown polymeric material which was difficult to remove. Reiser and co-workers have demonstrated that the same reaction can be performed in a microreactor in 87% yield (GC purity 97%) with shorter reaction periods.[12] However, the reaction has been performed at only one temperature (240 °C), flow rate (2 mL/min), and pressure (1000 psi). The worldwide interest in multigram synthesis of **1** prompted us to study this interesting methodology in more detail with varying temperature, flow rates, and pressure and optimize reaction conditions. Herein, we report our studies in conversion of furfuryl alcohol to **1** in a microreactor (Scheme 1) coupled with an enzymatic resolution process.

RESULTS AND DISCUSSION

Microreactor. We have investigated the rearrangement of FA into **1** in a microreactor similar to that described by Reiser and co-workers.[12] The reaction chamber consisted of a standard HPLC stainless steel tube of 0.5 mm diameter and 1.5 m length (total volume 296 μL). The tubing was connected to a single HPLC pump, and a solution of FA was pumped through the reactor attached to a back-pressure regulating device. The reactor chamber was placed in a GC oven for temperature control.

Use of *N*-Methylpyrrolidinone as a Cosolvent in the Reaction. One major problem associated with conversion of FA to **1** in a microreactor is the side reaction in which a dark brown polymeric material is formed which blocks the capillary tubing. To overcome this problem, Reiser and co-workers have employed a second pump which injects toluene in the reaction mixture. Such two-pump microreactor systems are well-known,[13−15] but they are cumbersome since it is necessary to study different rates of mixing for optimal conditions. It is desirable to simplify the procedure and to reduce the formation of polymeric product itself. Mechanistically, the formation of **4** has been proposed to proceed through protonation and dehydration of FA to **2** followed by deprotonation and hydration of **4** to **5** which then cyclizes to give **1** (Scheme 2).[12]

The mechanism of formation of polymeric side product is complex but has been shown to involve formation of carbocationic species via protonation of furfuryl alcohol.[16] Both of these reactions involve charged and highly polar species. Addition of a water-miscible organic cosolvent would be expected to decrease the solvent polarity and slow down the reactions.[17] We have examined the effects of addition of water-miscible organic cosolvent on conversion of FA to **1**. We envisaged that the organic cosolvent would help in reducing polymer formation as well as keep the polymer in solution (if formed) and prevent the blocking of microreactor tubing.

After examining solvents such as DMSO, formamide, and DMF, we selected *N*-methylpyrrolidinone (NMP) as a cosolvent of choice because of its relatively low toxicity (LD_{50} oral, 4 mg/kg, rat), high boiling point (202 °C), and good capacity to dissolve the brown polymer. To optimize its concentration in the reaction mixture, a solution of furfuryl alcohol (0.4 M) in water containing NMP (0.5−5 M) and acetic acid (0.03 M) was passed through the microreactor channel with feed rate of 0.2 mL/min at 200 °C and 200 bar

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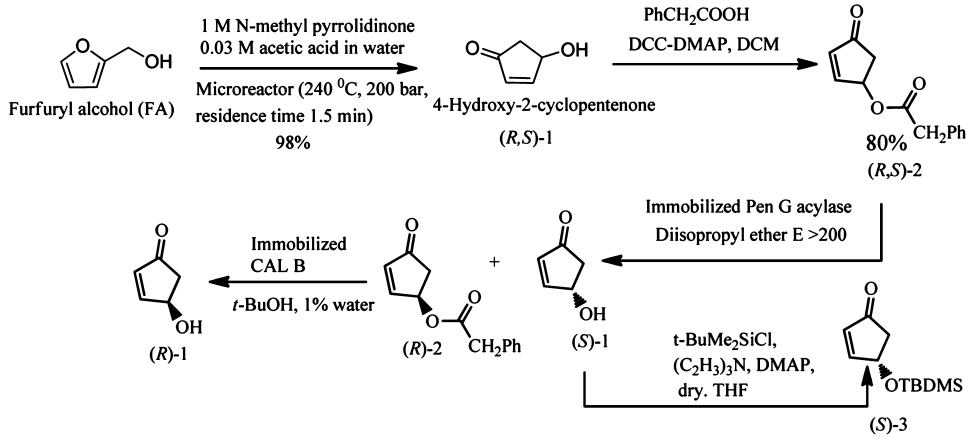
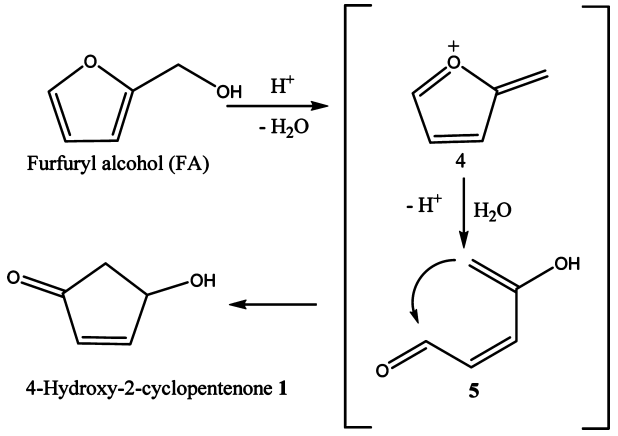
Scheme 1. Preparation of 4-Hydroxy-2-cyclopentenone



Scheme 2. Acid-Catalyzed Rearrangement of Furfuryl Alcohol (FA) to 4-Hydroxy-2-cyclopentenone 1



pressure. Steady-state samples were analyzed by HPLC to determine the conversion. In aqueous solution without NMP, 90% conversion was achieved as reported,[12] but the reaction was accompanied with polymer formation that blocked the tubing and no amount of washing with different solvents could remove the block. On addition of NMP, the conversion decreased with increasing NMP concentration (Figure 1), but interestingly, formation of polymer was also suppressed substantially as seen from the color of the product stream. An optimum was reached at 1 M NMP concentration (10% v/v) where polymer formation was negligible but conversion was 80%. Thus further experiments were performed in solutions containing 1 M NMP.

Effect of Flow Rate on Conversion. A series of experiments were performed to investigate the effect of flow rate on reactor performance. For each experiment, a solution of FA in water containing 0.03 M acetic acid was pumped through the microreactor at various flow rates for 1 h. At steady state, the overall conversion increased as the flow rate decreased (average residence time, τ, increased) (Figure 1b).

The conversion of FA to **1** is essentially a pseudo-first-order reaction (although the mechanism of rearrangement and conversion is a complex multistep process), and the microreactor described above is basically a tubular reactor. At steady state, the product formation in a tubular reactor is described by eq 1:

$$k\tau = -\ln(1 - X) \quad (1)$$

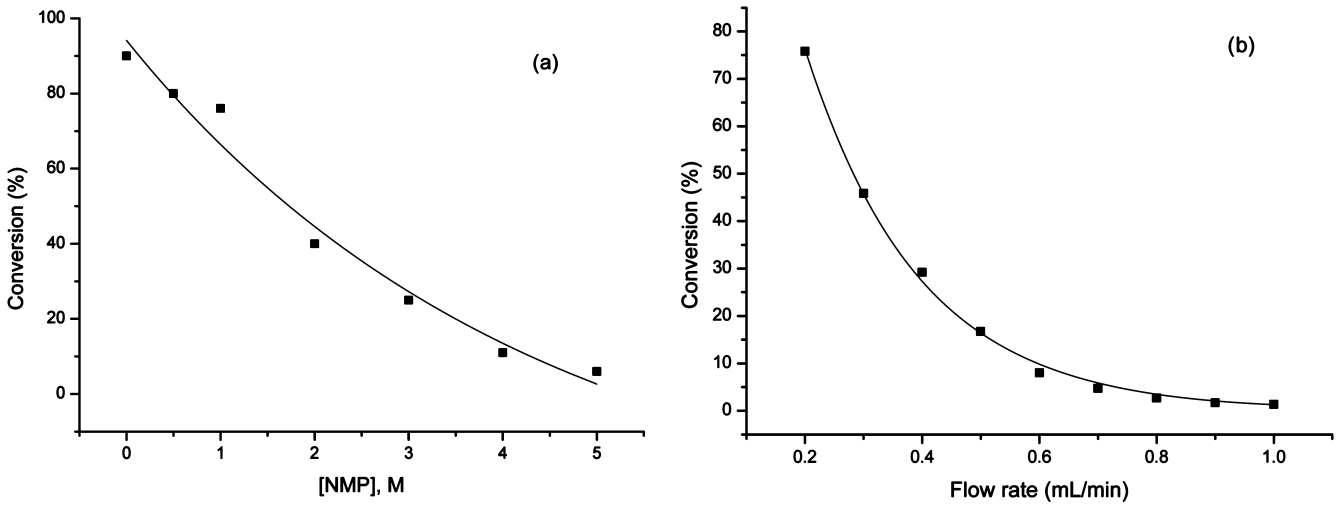


Figure 1. Conversion of furfuryl alcohol (FA) to **1**. Temp = 200 °C. Pressure = 200 bar. Reactor volume = 0.29 mL. [FA] = 0.4 M. (a) Effect of NMP concentration in reaction mixture. Flow rate 0.2 mL/min. (b) Effect of flow rate on conversion, [NMP] = 1 M.

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where τ is residence time defined as τ = reactor volume/flow rate; X is the mole fraction of the product, and k is the pseudo-first-order rate constant.[18]

A performance curve was constructed from the steady-state conversion at different flow rates ranging from 30 to 1000 μL/min. The plot of τ versus mole fraction of product, $[X]$, followed an exponential curve expected for a pseudo-first-order reaction.

Effect of FA Concentration. Since it is desirable to conduct reactions at high concentrations for a high space−time yield and reduce the cost of product isolation, experiments were conducted at different concentrations of FA. On increasing FA concentration in the inlet stream, the product concentration in the outlet stream increased linearly up to 0.4 M at a fixed τ. However, the observed pseudo-first-order rate constants, k_{obsd}, were unchanged within ±5%, supporting the assumption that conversion of FA to **1** is essentially a unimolecular reaction.

Beyond FA concentration of 0.4 M, formation of side products could be detected in HPLC analysis along with distinct formation of yellow polymeric material. This type of behavior has been observed earlier for this reaction in stirred tank reactors.[19] This is most probably due to the fact that the conversion of FA to **1** occurs via an intramolecular rearrangement. Chances of formation of side products through intermolecular reactions would increase with increasing FA concentration in solution. Thus to minimize formation of side products, FA concentration in feed was fixed at 0.4 M for further studies.

Effect of Temperature. Conversion of FA to **1** as a function of τ was studied at different temperatures ranging from 150 to 240 °C at constant pressure (200 bar) and FA concentration (0.4 M). The conversion increased with increasing temperature and residence time. For example, residence times required for 50% conversion were 7.5 min, 2.5 min, and 46 s, and 9 s at 150, 175, 200, and 240 °C, respectively. The pseudo-first-order rate constants, k_{obsd}, determined from the values of conversion versus residence time gave the values of 0.094, 0.268, 0.906, and 4.87 min^{-1} at 150, 175, 200, and 240 °C, respectively, and provided the activation parameters $\Delta H^{\ddagger}$ = 18 ± 1.4 kcal/mol and $\Delta S^{\ddagger}$ = −38 ± 3 cal/mol/K. These values are in accordance with those generally observed for unimolecular reactions in water near neutral pH.[20−22]

Effect of Pressure on Conversion. In contrast to conventional benchtop reactions at near-atmospheric pressure, conversion of FA into **1** in the microreactor at constant temperature and flow rate was significantly dependent on pressure. The product formation was negligible at pressure less than 50 bar but increased in a sigmoidal fashion with increase in pressure up to 200 bar (Figure 2). Due to lack of thermodynamic data on NMP−water mixtures at high temperature and pressures, we have not attempted to calculate the isochoric activation parameters and analyze our data in more detail.

Optimized Method for Preparation of 1. On the basis of our studies described above, we have carried out the transformation of FA to **1** in the following manner. The solution of furfuryl alcohol in water (0.4 M) containing NMP (1 M) and acetic acid (0.03 M) was passed through the microreactor channel with a feed rate of 0.2 mL/min at 240 °C and 200 bar pressure. Here, collection and storage of the product stream was still problematic due to its tendency to polymerize even in cold and under N_2 atmosphere. The problem was solved by collecting the product stream in a two-necked round-bottom flask containing NMP (10 mL) that was maintained at 60 °C and also connected to a vacuum pump which removed water present in the product stream. This ensured the prevention of product polymerization. The product stream after 11 h reaction was collected. For immediate use, NMP was removed under reduced pressure at 80 °C (10 mmHg). The residual product was obtained in almost quantitative yield with HPLC purity of 98%. For long-term storage and enzymatic resolution of enantiomers, the product stream in NMP was directly converted to its phenylacetate derivative **2** using dicyclohexylcarbodiimide (DCC) in 81% yield.

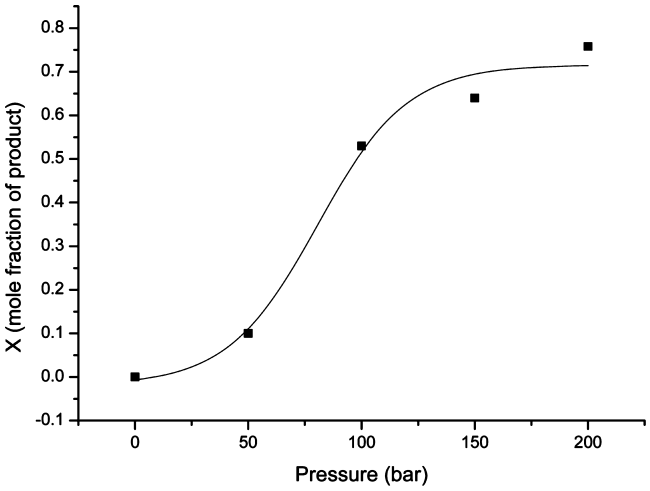

Figure 2. Effect of pressure on conversion. Temperature = 200 °C. Flow rate = 0.2 mL/min. Reactor volume = 0.29 mL. [FA] = 0.4 M, [NMP] = 1 M.

Enzymatic Resolution of 2. The *O*-phenylacetyl ester **2** was resolved via enantioselective hydrolysis with immobilized penicillin G acylase in diisopropyl ether. At the end of the reaction, the reaction mixture contained an equimolar mixture of (*S*)-**1** and (*R*)-**2** with >99% ee. Usually, such a mixture can be easily separated by reaction with a 1,2-dicarboxylic acid anhydride such as succinic anhydride to obtain a half ester which can be extracted into sodium carbonate solution. Unfortunately, this strategy failed in the present case because the unprotected hydroxy compound was vulnerable to polymerization in the presence of alkali. The problem was solved by converting (*S*)-**1** to its TBDMS derivative (*S*)-**3** and separating it from (*R*)-**2** by column chromatography. Both of the products were obtained in 45−46% yield (90−92% theoretical) and >99% ee.

Deprotection. The phenylacetyl protecting group of (*R*)-**2** was easily removed with immobilized lipase B from *Candida antarctica* (CAL B) in 95% yield (Scheme 1). The hydrolytic reaction was quite efficient but unfortunately did not exhibit enantioselectivity. The deprotection of TBDMS is conveniently performed by stirring (*S*)-**3** with tetrabutylammonium fluoride (TBAF) in THF.[9]

■ CONCLUSIONS

Present work demonstrates efficient synthesis of 4-hydroxy-2-cyclopentenone from furfuryl alcohol in a microreactor. Formation of polymeric material which tends to block the microreactor tubing can be suppressed by using 1 M *N*-methylpyrrolidinone as a cosolvent. The product is obtained

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with 98% conversion and is isolated as a stable *O*-phenylacetyl derivative in 80% yield based on the furfuryl alcohol used for transformation. When commercially available immobilized penicillin G acylase is employed, kinetic resolution can be performed to obtain both (*R*)- and (*S*)-enantiomers with high enantiomeric excess (>99%) and high yields. The immobilized enzyme works well in suspension of diisopropyl ether and can be recycled several times.

EXPERIMENTAL SECTION

General. HPLC analysis was carried out on Varian Pro Star HPLC unit. All other reagents and solvents used were of analytical grade obtained from Hi Media and Qualigens, India. SS tube of 0.5 mm diameter was obtained from M/s Swagelok, Germany. HPLC pump LC-10AT (Shimadzu, Japan) was used for pumping. The reactor chamber was placed in a Shimadzu GC oven model GC-2010 for temperature control. Immobilized CAL B (Addzyme CAL B 10 P, activity 1000 tributyrin units/g) was a generous gift from M/s Advanced Enzyme Technologies Ltd., Mumbai, India. The enzyme penicillin G acylase immobilized on a polymeric support with an average particle size of 150 μm (200 units/g, wet) was a generous gift from M/s KDL Biotech Limited, Savroli, India.

Conversion of Furfuryl Alcohol to 4-Hydroxy-2-cyclopentenone 1. A solution of furfuryl alcohol in water (39.2 g/L, 0.4 M) containing NMP (100 g/L, 1 M) and acetic acid (210 mg/L, 0.03M) was passed through the microreactor channel of 0.5 mm diameter and 1.5 m length with a feed rate of 0.2 mL/min at 240 °C and 200 bar pressure. The product stream was collected in a two-necked round-bottom flask containing NMP (10 mL) that was maintained at 60 °C and also connected to a vacuum pump (50 mmHg pressure). At intervals of 1 h, the pumping of reactants was stopped for 10 min; the inlet valve to the round-bottom flask was closed, and vacuum pump was switched on to remove water from the product stream. After 11 h reaction, a solution of product in NMP was obtained (29 g). For immediate use, NMP was removed from this solution by further decreasing the pressure to 10 mmHg and increasing the temperature to 80 °C. The product obtained as a pale yellow residue (5.1 g, 98% yield, 98% HPLC purity) was collected.

For long-term storage and enzymatic resolution, the product in NMP was directly converted to its phenylacetate derivative **2** without isolation.

(±)-4-Oxocyclopent-2-enyl 2-Phenylacetate 2. The solution of (±)-4-hydroxycyclopent-2-en-1-one **1** (28 mL product solution in NMP containing 4.9 g, 50 mmol) was diluted with dichloromethane (100 mL). Phenylacetic acid (7.4 g, 55 mmol) and 4-*N*,*N*-dimethylaminopyridine (DMAP, 0.6 g, 0.5 mmol) were added, and the solution was cooled in an ice bath. A solution of dicyclohexylcarbodiimide (DCC, 10.2 g, 50 mmol) in DCM (50 mL) was added to the reaction mixture, and after being stirred for 20 min, the ice bath was removed. The dark brown reaction mixture was stirred for 3 h at room temperature and filtered. The filtrate was washed with hydrochloric acid (0.5 N, 2 × 10 mL) and then with sodium carbonate solution (10%, 2 × 10 mL). The organic layer was then dried over anhydrous magnesium sulfate and evaporated on a rotavapor. The dark brown residue was extracted with diisopropyl ether. Removal of the solvent gave 4-oxocyclopent-2-enyl 2-phenylacetate as a pale yellow low melting powder (8.7 g, 81%). Mp 55−56.2 °C. ^{1}H NMR ($CDCl_3$): δ 7.51 (dd, 1H, *J*= 5.6, 4.8 Hz), 7.29−7.22 (m, 5H), 6.3 (d, IH, *J* = 6 Hz), 5.8 (m, 1H), 3.6 (s, 2H), 2.8 (dd, 1H, *J* = 6.0, 18.1 Hz), 2.28 (dd, 1H, *J* = 2.3, 18.8 Hz). ^{13}C NMR ($CDCl_3$): δ 204.5, 170.7, 158.6, 136.8, 133.1, 128.9, 128.4, 127.0, 72.1, 40.8, 40.6. IR (neat): ν_{max} 2937, 1724, 1660 cm^{-1}. MS (ESI) *m*/*e* 217 (M + 1). HRMS [ESI, (M + H)$^+$]: *m*/*z* calcd for $C_{13}H_{13}O_3$ 217.0864; found 217.0859.

Enzymatic Reaction. Polymer beads bearing penicillin G acylase (10 g, 2000 units, water content 67% w/w determined by Karl Fischer titration) were washed with phosphate buffer (0.05 M, pH 7.5) several times to remove the preservatives and dried by tapping with a filter paper. The moist polymer beads were taken in a glass kettle (250 mL), and Celite (3 g) and substrate solution (5 g, 23 mmol) in diisopropyl ether (100 mL) were added and the contents were stirred mechanically at 100 rpm using an overhead stirrer. The reaction was found to be inhibited by product when enantiomeric excess of the unreacted ester reached 40% (24 h). At this stage, the enzyme was removed, washed with diisopropyl ether (2 × 25 mL), and the washings were combined with the reaction mixture. The reaction mixture was then concentrated on a rotavapor to 100 mL, and fresh enzyme (10 g) and Celite (3 g) were added and stirring was continued. After one more repetition with fresh enzyme, the reaction was complete (ee of the unreacted ester reached >99%) in 3 days. The reaction mixture was separated from the enzyme and dried over anhydrous magnesium sulfate (caution: it is important that the reaction mixture is free of water for the preparation of TBDMS derivative), and the solvent was removed by rotary evaporation. The residue consisted of an equimolar mixture of (*S*)-**1** and the unhydrolyzed (*R*)-**2**.

Product Separation. The residue obtained as described above was dissolved in dry THF (50 mL) and cooled in ice. Et_3N (5.7 mL, 0.039 mol) and DMAP (300 mg, 0.25 mmol) were added. A solution of *tert*-butyldimethylsilyl chloride (TBDMS) (4.6 g, 30 mmol) in dry THF (20 mL) was added dropwise over 20 min under nitrogen atmosphere. The mixture was stirred for 30 min in cold and then allowed to warm to room temperature. After stirring for 3 h, the solvent was removed on a rotavapor, distilled water (50 mL) was added to the residue, and the product was extracted in ethylacetate (3 × 25 mL). The combined organic fractions were dried over anhydrous Mg_2SO_4 and concentrated in vacuum. The resulting mixture of products (*R*)-**2** and (*S*)-**3** was transferred to the top of the silica gel column and the TBDMS derivative was eluted with hexane/ethylacetate (95:5). The phenylacetyl derivative remaining on the column was eluted with ethylacetate. On removal of the solvents, **3** was obtained as a pale brown oil (4.8 g) while **2** was obtained as a pale yellow solid (2.3 g). Both of the products were obtained in 45−46% yield (90−92% theoretical) and >99% ee. The *O*-protected products were stable and could be stored in a refrigerator for months.

HPLC Analysis. The rearrangement of furfuryl alcohol was followed by reverse-phase HPLC column RP-8 (250 × 4.6 mm), Merck KGa, Germany. Mobile phase 30% MeOH/water; flow rate 0.5 mL/min; detection wavelength 230 nm. Retention times: 4-hydroxy-2-cyclopentenone **1**, 6.9 min; *N*-methylpyrrolidinone (NMP), 8.4 min; furfuryl alcohol (FA), 10.4 min. NMP served as the internal standard.

Enzymatic hydrolysis of phenylacetyl derivative **2** was followed by reverse-phase HPLC column C-8 (250 × 5 mm), Chrompack, The Netherlands. Mobile phase, 50% MeOH/water containing 0.1% perchloric acid; flow rate, 0.7 mL/min; detection wavelength, 230 nm. Retention times: 4-hydroxy-2-

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cyclopentenone, 5 min; 4-oxocyclopent-2-enyl 2-phenylacetate, 16.3 min; phenylacetic acid, 10.65 min.

Determination of Enantiomeric Purity. Enantiomeric purity of unreacted **2** was determined directly as the *O*-phenylacetyl derivative, while that of the product alcohol **1** was determined after its derivatization to an acetate derivative.[6] Analysis was carried out on Chiralcel AD-H column (250 × 5 mm), Daicel Chemical Industries, Japan. Mobile phase, 3% 2-propanol in hexane; flow rate, 0.5 mL/min; detection wavelength, 220 nm. Retention times: (*S*)-**2**, 18.7; (*R*)-**2**, 23.2 min; (*R*)-4-oxocyclopent-2-enyl acetate, 14.8; (*S*)-4-oxocyclopent-2-enyl acetate, 16.6 min.

Deprotection of (*R*)-2. A solution of (*R*)-**2** (2.2 g in 25 mL of *tert*-BuOH containing 250 μL of water) was stirred with immobilized CAL B (50 mg, 50 units) for 10 h at room temperature. The reaction was followed by HPLC. On completion of the reaction, the enzyme was filtered and washed with *tert*-BuOH (2 × 5 mL). The combined washings were evaporated, and the residue was stirred with cyclohexane (2 × 5 mL) to remove phenylacetic acid formed during deprotection. Compound **1** was obtained as a pale yellow liquid (0.93 g, 93%, >98% pure by HPLC).

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Harre, M.; Raddatz, P.; Walenta, R.; Winterfeldt, E. *Angew. Chem.* **1982**, *94*, 496−508.
(2) Das, S.; Chandrasekhar, S.; Yadav, J. S.; Grée, R. *Chem. Rev.* **2007**, *107*, 3286−3337.
(3) Perry, N. B.; Albertson, G. D.; Blunt, J. W.; Cole, A. L. J.; Munro, M. H. G.; Walker, J. R. L. *Planta Med.* **1991**, *57*, 129−131.
(4) Roche, S. P.; Aitken, D. J. *Eur. J. Org. Chem.* **2010**, 5339−5358.
(5) Ulbrich, K.; Kreitmeier, P.; Vilaivan, T.; Reiser, O. *J. Org. Chem.* **2013**, *78*, 4202−4206.
(6) Kumaraguru, T.; Fadnavis, N. W. *Tetrahedron: Asymmetry* **2012**, *23*, 775−779.
(7) Piancatelli, G.; D'Auria, M.; D'Onofrio, F. *Synthesis* **1994**, 867−889.
(8) Ghorpade, S. R.; Bastawade, K. B.; Gokhale, D. V.; Shinde, P. D.; Mahajan, V. A.; Kalkote, U. R.; Ravindranathan, T. *Tetrahedron: Asymmetry* **1999**, *10*, 4115−4122.
(9) Curran, T. T.; Hay, D. A.; Koegel, C. P. *Tetrahedron* **1997**, *53*, 1983−2004.
(10) Demir, A. S.; Sesenoglu, O. *Tetrahedron: Asymmetry* **2002**, *13*, 667−670.
(11) Byrne, A. O.; Murray, C.; Keegan, D.; Palacio, C.; Evans, P.; Morgan, B. S. *Org. Biomol. Chem.* **2010**, *8*, 539−545.
(12) Ulbrich, K.; Kreitmeier, P.; Reiser, O. *Synlett* **2010**, *13*, 2037−2040.
(13) Mason, B. P.; Price, K. E.; Steinbacher, J. L.; Bogdan, A. R.; McQuade, D. T. *Chem. Rev.* **2007**, *107*, 2300−2318.
(14) Ehrfeld, W.; Hessel, V.; Löwe, H. *Microreactors: New Technology for Modern Chemistry*; Wiley-VCH Verlag GmbH: Weinheim, Germany, 2000.
(15) Wirth, T., Ed. *Microreactors in Organic Synthesis and Catalysis*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2008.
(16) Bertarione, S.; Bonino, F.; Cesano, F.; Damin, A.; Scarano, D.; Zecchina, A. *J. Phys. Chem. B* **2008**, *112*, 2580−2589.
(17) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751−2772.
(18) Gavhane, K. A. *Chemical Reaction Engineering 1*, 11th ed.; Nirali Prakashan: Pune, India, 2010; Chapter 2, pp 2.39−2.40.
(19) Watson, T. J. N.; Curran, T. T.; Hay, D. A.; Shah, R. S.; Wenstrup, D. L.; Webster, M. E. *Org. Process Res. Dev.* **1998**, *2*, 357−365.
(20) Blandamer, M. J. *Adv. Phys. Org. Chem.* **1977**, *14*, 202−352.
(21) Frank, F. A., Ed. *Comprehensive Treaties*; Plenum Press: New York, 1973; Vol. *2*, Chapter 1, pp 1−48.
(22) Frank, F. A., Ed. *Comprehensive Treaties*; Plenum Press: New York, 1975; Vol. *4*, Chapter 1, pp 1−93.