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Enzymatic kinetic resolution of a functionalized 4-hydroxy-cyclopentenone: synthesis of the key intermediates in the total synthesis of isoprostanes

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Abstract—The enzymatic kinetic resolution of racemic alcohol 4-hydroxy-cyclopentenone **1** was investigated using four different lipases for enantioselective transacetylation, as well as for enantioselective hydrolysis, leading to the pure (*R*)- and (*S*)-enantiomers **2** and **3**.

1. Introduction

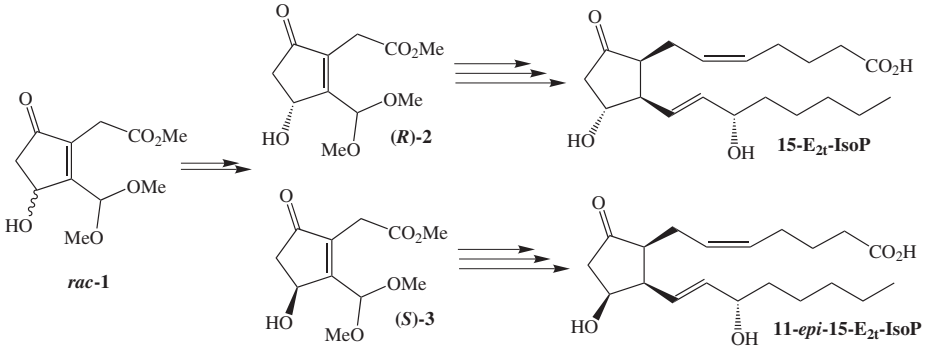
Lipases are extensively used for the synthesis of enantiomerically pure compounds via resolution of racemic mixtures.[1] These enzymes possess broad substrate specificity, generally high regio- and enantioselectivity and in many cases perform under mild conditions. Recently, Rodriguez and Spur used an enzymatic kinetic resolution for the synthesis of the E type I phytoprostanes.[2]

As a consequence, and in connection with our program directed towards the synthesis of isoprostanes, we were interested by accessing the two pure 4-hydroxy-cyclopentenones **2** and **3** which are important building blocks for the total synthesis of isoprostanes and analogues (Scheme 1).[3]

2. Results and discussion

2.1. Preparation of 4-hydroxy-cyclopentenone 1

The preparation of racemic 4-hydroxy-cyclopentenone **1**, depicted in Scheme 2, was achieved with the



Scheme 1.

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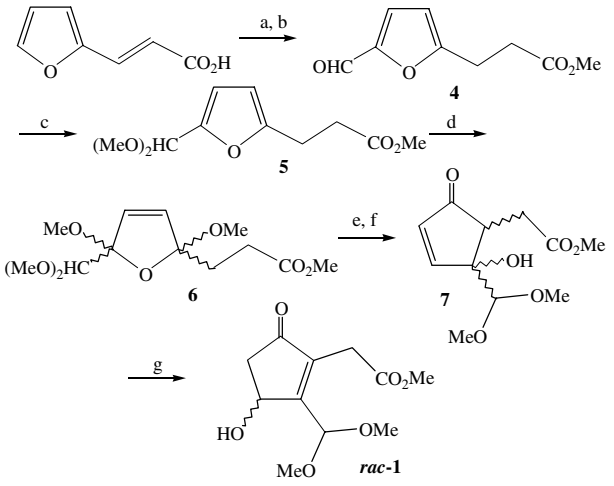


Scheme 2. Reagents and conditions: (a) MeOH, H_2SO_4, reflux, followed by H_2, Pd–C 10%, 80%; (b) $POCl_3$, DMF, 92%; (c) $HC(OMe)_3$, APTS, TsOH, 73%; (d) Br_2, MeOH, Na_2CO_3; (e) citric acid, Na_2HPO_4, dioxane; (f) Na_2HPO_4; (g) chloral hydrate, Et_3N, EtOAc, reflux.

commercially available *trans*-3-(2-furyl)acrylic acid as starting material, using the Freïmanis procedure.[4]

The first step was a Pd-catalyzed reduction under hydrogen atmosphere, followed by a Vilsmeyer reaction for the introduction of the formyl group at C5, which was protected in the presence of methyl orthoformate. Electrophilic addition with $MeOH/Br_2$ under basic conditions to the furan **5**, afforded bis-acetal **6**, which underwent an 'aldol-type' cyclization under acidic hydrolysis and basic treatment leading to the 3-hydroxy-cyclopentenone **7**. Finally, migration of the hydroxy group and double bond with chloral under basic conditions led to the racemic 4-hydroxy-cyclopentenone **1** in 28% yield after five steps. It is worth noting that all these reactions were achieved in multi-gram scale, up to 50 gram and afforded at least 20 g of *rac*-**1**.

2.2. Enzymatic kinetic resolution of 4-hydroxy-cyclopentenone *rac*-1

Our first attempt was to screen a range of lipases for enantioselective transacetylation of the racemic alcohol **1** (Table 1). We have used four well-known different lipases with the best results being obtained with the *Candida antarctica* lipase B (CAL-B). All the enzymes investigated preferentially converted the (*R*)-enantiomer of *rac*-**1**, in agreement with the literature.[5]

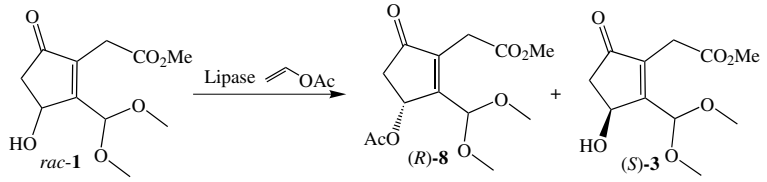
Using CAL-B, we were also interested in finding the best conditions and investigated the effect of the solvent (hexane), time of reaction and finally the amount of CAL-B (Table 1). The results are shown in Table 1, and the highest conversion obtained, was by using 0.2 equiv of CAL-B, in hexane at room temperature for 20 h. Under these conditions, we obtained 45.4% of acetate (*R*)-**8** and 48.5% of alcohol (*S*)-**3**.

It is worth noting that during the resolution process, the reaction was monitored by HPLC using a chiral stationary phase (Chiralcel OD column). This process enables us to control the degree of conversion. Typical chromatograms are shown in Figure 1.

2.3. Enzymatic hydrolysis

We also used the CAL-B for the enzymatic hydrolysis of (*R*)-acetate **8** to reach the enantiomerically pure (*R*)-alcohol **2** (Scheme 3). In a typical experiment for the enzymatic hydrolysis, the (*R*)-acetate **8** was dissolved in acetonitrile, at which point the phosphate buffer (0.1 M, pH = 7) was added and the mixture was stirred at room temperature in the presence of the enzyme (0.8 mass equivalent). The progress of the reaction

Table 1. Enzyme-catalyzed transesterification of *rac*-**1** with vinyl acetate



Enzyme	% of Enzyme w/w (equiv)	Solvent	Time (h)	Conversion (%) (*R*)-**8**	Conversion (%) (*S*)-**3**
PPL	1	—	168	10	
Amano F-AP15	1	—	72	—	—
Amano F-AP15	1	Hexane	72	—	—
Amano PS	1	—	72	45.4	45
Amano PS	1	Hexane	72	43.7	36.8
CAL-B	1	—	72	40.2	38.9
CAL-B	1	—	48	45.4	45
CAL-B	1	Hexane	40	36.7	45.3
CAL-B	1	Hexane	48	41.9	43
CAL-B	0.5	Hexane	48	43	43
CAL-B	0.2	Hexane	20	45.4	48.5

PPL: porcine pancreatic lipase; CAL-B: *Candida antarctica* lipase B.

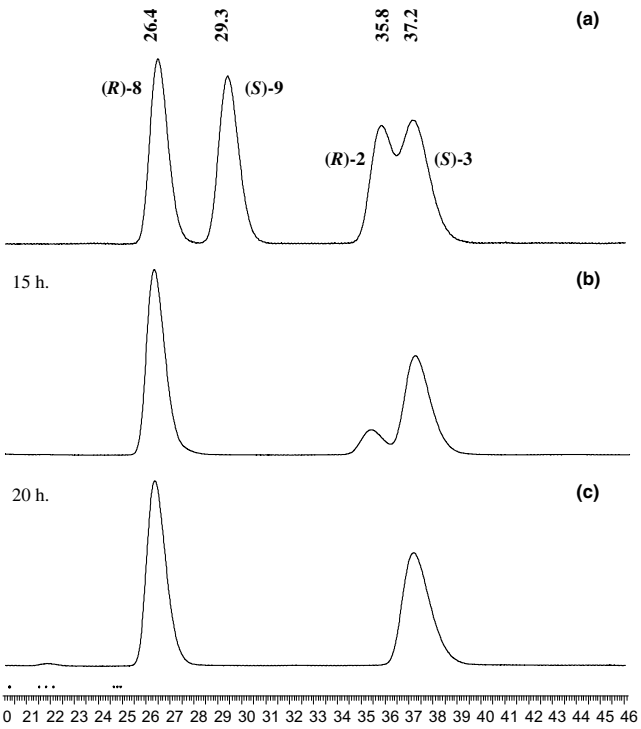
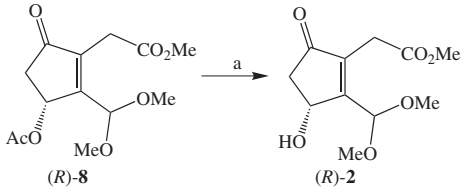


Figure 1. (a) Chromatogram of a racemic mixture of acetates **8**, **9** and alcohols **2**, **3**. (b) and (c) Chromatograms of the kinetic resolution of *rac*-**1** by CAL-B after 15 h (b) and 20 h (c). Column: Chiralcel OD, 25 cm × 4.6 mm. Mobile phase: 97/3 hexane/*i*-PrOH. Flow rate: 0.7 mL/min. Detection : 210 nm.

monitored by TLC and the enantiomerically pure (*R*)-alcohol **2** obtained in 98% yield.



Scheme 3. Reagents and conditions: (a) CAL-B, CH_3CN, phosphate buffer (0.1 M) pH = 7.

2.4. Comparison of the specific rotations of 2 and 3, and 8 and 9

Acetate **9** was obtained from alcohol **3** with $(Ac)_2O$ in Et_2O in the presence of DMAP in 74% yield.

The physicochemical properties of the enantiomerically pure alcohol (*R*)-**2** and acetate (*R*)-**8** were identical to those of (*S*)-**3** and (*S*)-**9**, respectively, except for the sign of the specific rotation, as shown in Table 2.

2.5. Determination of the ee

The ee of alcohol (*S*)-**3** (94%) and (*R*)-**2** (94%) was determined by ^{19}F NMR spectra analysis of the corresponding Mosher esters (Fig. 2).[6] We also confirmed these ee by ^1H NMR experiments (data not shown).

Table 2. $[\alpha]_D^{20}$ (c 1×10^{-2}, MeOH) for alcohols **2** and **3** and acetates **8** and **9**

(*R*)-**2**	+0.21	−0.21	(*S*)-**3**
(*R*)-**8**	−0.05	+0.05	(*S*)-**9**

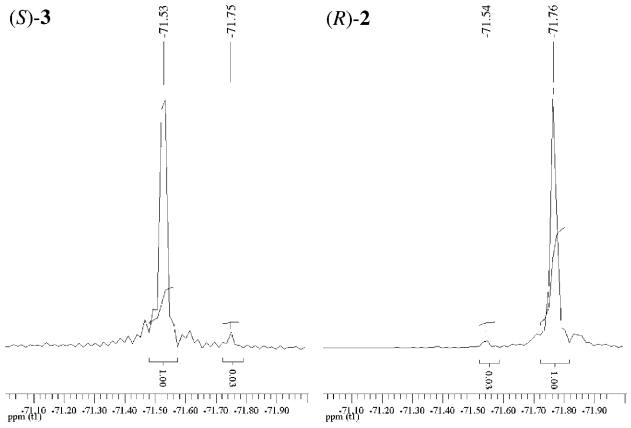


Figure 2. ^{19}F NMR spectra of alcohols (*S*)-**3** and (*R*)-**2**.

3. Conclusion

In conclusion, we have developed an efficient asymmetric synthesis of the two enantiomerically pure hydroxycyclopentenones (*R*)-**2** and (*S*)-**3**. The extension of this methodology towards the synthesis of new isoprostanes will be reported in due course.

Acknowledgments

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