## One-Pot Synthesis of Enantiopure 3,4-Dihydroisocoumarins through Dynamic Reductive Kinetic Resolution Processes

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A straightforward chemoenzymatic synthesis of enantiopure 4-alkyl-3-methyl-3,4-dihydroisocoumarins through a ketoreductase-catalyzed onepot dynamic reductive kinetic resolution is reported. *E. coli*/ADH-A cells have shown outstanding diastereo- and enantioselectivity toward the bioreduction of a series of racemic ketones, with the use of anion exchange resins or triethylamine being compatible in the same aqueous reaction medium. The so-obtained enantiopure alcohols were subsequently cyclized in acid media affording the corresponding lactones in good to excellent conversions (72–96%) and excellent selectivities (dr  $\geq$ 99:1 and ee >99%).

Biocatalytic processes are well-established methodologies for the production of organic compounds under environmentally friendly conditions.<sup>1</sup> In fact, the potential of biotransformations for sustainable manufacturing has gained major attention because of the economic impact of enzymes for industrial applications.<sup>2</sup> From the group of asymmetric biocatalytic transformations, enzymatic kinetic resolutions (KRs) of racemic mixtures provide a straightforward access to enantiopure compounds. Unfortunately this approach is based on enantiomer separation where the maximum yield is limited to 50%,<sup>3</sup> although the development of elegant enzymatic dynamic kinetic resolutions (DKRs) has overcome this limitation. For instance hydrolases in combination with metal catalysts have allowed the synthesis of a wide variety of enantioenriched compounds from racemic amine or alcohols.<sup>4</sup> On the other hand, Baeyer–Villiger monooxygenases have efficiently catalyzed DKR processes for the formation of enantiopure esters.<sup>5</sup> However, DKR processes have been scarcely explored using alcohol dehydrogenases (ADHs).<sup>6</sup> Only some examples have been reported in the bioreduction of

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diketones<sup>7</sup> and racemic derivatives such as ketones,<sup>8</sup>  $\beta$ -keto esters,<sup>9</sup> or aldehydes.<sup>10</sup> In spite of the enzyme tridimensional structure, the generation in a single bio-transformation of multiple stereogenic centers has been scarcely reported and remains a challenging task.<sup>11</sup> In this context, it must be mentioned that DKR processes have been also recently defined as dynamic reductive kinetic resolution processes (DYRKR).<sup>12</sup>

Chiral heterocyclic compounds are widely found in biologically active natural products, and a great number of synthetic pharmacologically active molecules contain at least one heterocyclic ring. Therefore, the development of novel synthetic asymmetric methods for the preparation of enantiopure heterocyclic compounds is a highly appealing task for synthetic organic chemists. In particular, the asymmetric chemical synthesis of enantioenriched 3,4dihydroisocoumarin derivatives has attracted much attention in recent years,<sup>13</sup> due to its presence in many natural products that display a vast range of biological activities such as antibacterial, antifungal, antimalarial, or anticancer.<sup>14</sup>

Until now, different enzymatic transformations have been described for the asymmetric synthesis of 3-alkyl-3,4-dihydroisocoumarins, such as the oxidation of 2-alkyl-1-indanones using Baeyer–Villiger monooxigenases<sup>15</sup> or the ADH-catalyzed bioreduction of 2-(2-oxopropyl)benzonitriles.<sup>16</sup> However, as far as we know the chemoenzymatic synthesis of 3,4-dialkyl-3,4-dihydroisocumarines remains unexplored. Herein, we report an effective, simple one-pot synthesis of enantiopure 4-alkyl-3-methyl-3,4dihydroisocoumarins through DYRKR processes by a combination of an alcohol dehydrogenase (ADH-A from *Rhodococcus ruber*) and basic catalysis followed by intramolecular cyclization.

2-(3-Oxobutan-2-yl)benzonitrile (2a) was chosen as a model substrate because of its easy access through methylation of 2-(2-oxopropyl)benzonitrile (1a) with methyl iodide and sodium hydroxide under phase transfer catalysis conditions (Scheme 1). Trying to find suitable conditions for the dynamic process, KR and racemization

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experiments were independently conducted. As occurred with prochiral 2-(2-oxopropyl)-benzonitriles,<sup>14</sup> ADH-A from *Rhodococcus ruber* overexpressed in *E. coli* cells displayed outstanding activities in the bioreduction of racemic **2a**. For that reason this enzyme was chosen for studying the KR experiments in depth (Table 1).

Scheme 1. Chemical Synthesis and Kinetic Resolution of Ketone 2a Using *E. coli*/ADH-A Cells



Preliminary results showed that, after 24 h, E. coli/ADH-A was able to reduce 2a with 38% of conversion and high enantioselectivity (entry 1). The remaining ketone 2a was recovered in high ee (60%), showing that the enzyme reacts exclusively with the (S)-enantiomer. Different experiments were performed in order to obtain higher conversions. First, the influence of the enzyme loading was analyzed finding a slight improvement when using 15 mg (entry 2); unfortunately the use of higher amounts of the enzyme (25 mg, entry 3) did not provide better results. Interestingly, when the enzyme was added in portions, slightly better results were attained (entry 4) suggesting problems associated with the reversibility of the reaction or a possible inhibition effect by the product. To verify the correct hypotheses, additional 2-propanol and a hydrophobic solvent as hexane were used (entries 5 and 6). Any improvement of the conversion could be detected with higher amounts of 2-propanol discarding the problem of reversibility (entry 5). To our delight, the best conditions were obtained when using 5% of hexane as cosolvent (56% conversion, entry 6).

The addition of a hydrophobic cosolvent improved the process since the organic phase acts as a reservoir for the product and substrate, reducing its presence in the aqueous phase where the bioreduction takes place. To our surprise, conversion values and substrate ee did not fit with a classic KR model since **3a** was found in enantiopure form at conversion values higher than 50%. This unexpected behavior could be easily explained considering a partial racemization of the ketone caused by the acidity of the  $\alpha$ -hydrogen to the carbonyl group. Encouraged by this result, the racemization step has been deeply studied to develop an efficient DKR process.

Relative and absolute configurations were determined by NMR experiments (see Supporting Information (SI)).

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Table 1. Kinetic Resolution of  $(\pm)$ -Ketone 2a (20 mM) Catalyzed by ADH-A Using 2-Propanol as Cosubstrate (5% v/v), NADH as Cofactor in TRIS-HCl pH 7.5 Buffer at 250 rpm for 24 h

| entry    | ADH-A<br>(mg) | $\begin{array}{c} \operatorname{conv} \ (\%)^a \end{array}$ | ee 2a $(\%)^a$ | ee <b>3a</b><br>(%) <sup>b</sup> | dr <b>3a</b><br>(%) <sup>b</sup> |
|----------|---------------|---|----------------|----------------------------------|----------------------------------|
| 1        | 10            | 38  | 56             | >99                              | >99:1                            |
| <b>2</b> | 15            | 41  | 59             | >99                              | >99:1                            |
| 3        | 25            | 41  | 59             | >99                              | >99:1                            |
| 4        | $10+10^c$     | 44  | 64             | >99                              | >99:1                            |
| 5        | $15^d$        | 44  | 64             | >99                              | >99:1                            |
| 6        | $15^e$        | 56  | 90             | >99                              | >99:1                            |

<sup>*a*</sup> Conversions and enantiomeric excesses determined by chiral GC. <sup>*b*</sup> Enantiomeric excesses and diastereomeric ratio determined by chiral HPLC after derivatization to the 3,4-dihydroisocoumarin **4a** using an aq HCl concd solution. <sup>*c*</sup> Additional 10 mg were added after 12 h. <sup>*d*</sup> 2-Propanol was used for a total concentration of 10% v/v. <sup>*e*</sup> Biphasic media with 5% of hexane.

For the relative configuration, <sup>1</sup>H NMR NOESY experiments were performed showing space correlation between the two methyl groups in (+)-4a, confirming the *syn* disposition of the substituents. This correlates with the favored addition of the hydride by NADH to the carbonyl group through the less hindered face, disposing both groups on the same side. The absolute configuration was assigned preparing the Mosher's ester derivative, concluding that the absolute configuration was S,S (see SI for further details).

Racemization of the ketone was then investigated using enantioenriched alcohol (R)-2a obtained during KR studies (Table 2). First, KR conditions were attempted using TRIS-HCl buffer, 5% of 2-propanol as the cosubstrate, and 5% of hexane, with a slight loss of the optical purity (entry 1). Nevertheless, this racemization is not enough to perform a proper DKR where, at least, racemization has to be 10 times faster than the conversion of the slow-reacting enantiomer in the kinetic resolution. On the other hand, this slight decrease of ee may explain results observed in the KR optimization. Then, different additives were assayed to improve the kinetic of the racemization (entries 2-4). First, anion exchange resins were tested since they are efficient catalysts for the racemization of 1-aryl-1alkylacetones.<sup>17</sup> Satisfyingly, DOWEX MWA-1 afforded the ketone 2a in almost racemic form after 24 h in both aqueous and biphasic systems (entries 2 and 3). Bearing in mind the biphasic media where KR was optimized, we envisaged a plausible racemization in the hydrophobic phase so an organic base, triethylamine (Et<sub>3</sub>N), was tested, affording total racemization after 24 h (entry 4).

Once both KR and racemization were independently optimized, they were combined in a whole dynamic process (Table 3). First, the best conditions of both were brought together, using lyophilized *E. coli*/ADH-A cells, 5% of hexane, 2-propanol as the cosubstrate (5% v/v), triethylamine as the racemization system, and NADH as the cofactor in TRIS-HCl pH 7.5 buffer. After 44 h, 81% conversion was reached, obtaining (*S*,*S*)-**3a** as single

**Table 2.** Racemization of (*R*)-**2a** (20 mM) Using Different Additives, 2-Propanol as Cosubstrate (5% v/v) in TRIS-HCl pH 7.5 Buffer for 24 h at 30 °C and 250 rpm

| entry    | additive  | initial ee $\mathbf{2a} (\%)^a$ | final ee <b>2a</b> $(\%)^a$ |
|----------|---|---------------------------------|-----------------------------|
| 1        | 5% hexane (5% v/v)                                | 60                              | 54                          |
| <b>2</b> | DOWEX MWA-1 $^{b}$                                | 66                              | 6                           |
| 3        | hexane $(5\% \text{ v/v}) + \text{DOWEX MWA-1}^b$ | 57                              | 5                           |
| 4        | hexane (5% v/v) + Et <sub>3</sub> N (1% v/v)      | 63                              | 0                           |
|          |   | ,                               |                             |

<sup>*a*</sup> Enantiomeric excesses determined by chiral GC. <sup>*b*</sup> 12 mg of DOWEX MWA-1 were used.

diastereomer and in enantiopure form. However, substrate **2a** was obtained in 45% ee and longer reaction times do not improve the process significantly (entry 2). These results suggest that the racemization system is not completely effective for a total conversion into (S,S)-**3a**. Unfortunately, higher quantities of triethylamine led to enzyme inactivation (entries 3 and 4).

**Table 3.** Dynamic Reductive Kinetic Resolution of Ketone **2a**(20 mM) Using Different Racemization Systems



| entry    | racemization<br>system     | <i>t</i> (h) | ee <b>2a</b><br>(%) <sup>a</sup> | $conv$ $(\%)^a$ | ee <b>3a</b><br>(%) <sup>b</sup> | $\mathrm{dr}\mathbf{3a}\\(\%)^b$ |
|----------|----------------------------|--------------|----------------------------------|-----------------|----------------------------------|----------------------------------|
| 1        | Et <sub>3</sub> N (1% v/v) | 44           | 45                               | 81              | >99                              | >99:1                            |
| <b>2</b> | Et <sub>3</sub> N (1% v/v) | 72           | 45                               | 85              | >99                              | >99:1                            |
| 3        | Et <sub>3</sub> N (2% v/v) | 70           | 0                                | 77              | >99                              | >99:1                            |
| 4        | $Et_{3}N(3\% v/v)$         | 70           | 0                                | 45              | >99                              | >99:1                            |
| 5        | DOWEX MWA-1                | 24           | 81                               | 63              | >99                              | >99:1                            |
| 6        | DOWEX MWA-1                | 92           | 13                               | 86              | >99                              | >99:1                            |

<sup>*a*</sup> Enantiomeric excesses and conversions determined by chiral GC. <sup>*b*</sup> Enantiomeric excesses and diastereomeric ratio determined by chiral HPLC after derivatization to the corresponding 3,4-dihydroisocoumarins **4a** using an aq HCl concd solution.

Because of the good results previously obtained with the DOWEX MWA-1 anion exchange resin toward the racemization of ketone **2a** (entries 2 and 3, Table 2), this system was subjected to study. After 24 h, 63% conversion of enantiopure alcohol (*S*,*S*)-**3a** was reached, obtaining **2a** in 81% ee (entry 5). Satisfyingly, both the biocatalyst and racemization system remained active after long reaction times, leading to an efficient DYRKR with 86% conversion after 92 h (entry 6).

With the optimized conditions for the model substrate  $(\pm)$ -**2a**, the scope of the methodology was then examined. Ketones  $(\pm)$ -**2b**-**g** were prepared by alkylation of different 1-arylacetones **1b**-**g** in moderate to good yields.<sup>18</sup> In all cases, good to excellent conversions were reached after 72 h (Table 4), obtaining the enantiopure alcohols (*S*,*S*)-**3b**-**g**  with a perfect diastereomeric ratio. The presence of different substituents in the aromatic ring  $(\mathbf{R}^1)$  or in the chiral center  $(\mathbf{R}^2)$  does not affect the enzyme selectivity, demonstrating the scope of the methodology; albeit differences in conversions may be explained by the influence they have in the racemization rate.

Table 4. Dynamic Reductive Kinetic Resolution of Racemic Ketones 2a-g (20 mM) Using *E. coli*/ADH-A Cells as Biocatalysts



| entry | substrate     | $\mathbb{R}^1$ | $\mathbb{R}^2$ | $conv$ $(\%)^a$ | $ee \frac{3a-g}{(\%)^b}$ | $\frac{\mathrm{dr}\mathbf{3a}{-}\mathbf{g}}{(\%)^b}$ |
|-------|---------------|----------------|----------------|-----------------|--------------------------|--|
| 1     | 2a            | Н              | Me             | 93              | >99                      | >99:1  |
| 2     | <b>2b</b>     | 5-Me           | Me             | 72              | >99                      | >99:1  |
| 3     | 2c            | 4-Me           | Me             | 77              | >99                      | >99:1  |
| 4     | <b>2d</b>     | 5-OMe          | Me             | 93              | >99                      | 99:1   |
| 5     | $2\mathbf{e}$ | 4-F            | Me             | 95              | >99                      | 99:1   |
| 6     | <b>2f</b>     | Η              | $\mathbf{Et}$  | 87              | >99                      | >99:1  |
| 7     | $2\mathbf{g}$ | Н              | allyl          | 96              | >99                      | 99:1   |

<sup>*a*</sup> Conversion values determined by chiral GC. <sup>*b*</sup> Enantiomeric excesses determined by chiral HPLC after derivatization to the corresponding 3,4dihydroisocoumarins 4a-g using an aq HCl concd solution.

Finally, once the dynamic process was studied and optimized, we focused on the development of a one-pot methodology for the preparation of the target molecules in enantiopure form (Scheme 2). Reactions were initially

(19) General procedure for the one-pot synthesis of 4-alkyl-3-methylisochroman-1-ones 4a–g. To a solution containing rehydrated *E. coli/* ADH-A cells (425 mg/mmol, 128 mg) in TRIS-HCl 50 mM pH 7.5 buffer (0.02 M, 13.35 mL), isopropyl alcohol (5% v/v,  $750 \mu\text{L}$ ), hexane (5% v/v,  $750 \mu\text{L}$ ), Et<sub>3</sub>N (1% v/v,  $150 \mu\text{L}$ ), NADH (1 mM, 10.5 mg), and the corresponding ketone 2a–g (0.3 mmol) were succesively added. The reaction was shaken for 72 h and at 250 rpm, and then hydrochloric acid was added (37%, 0.02 M, 15 mL) and the mixture was shaken overnight at 30 °C. The reaction was centrifuged and extracted with EtOAc ( $3 \times 25 \text{ mL}$ ); organic layers were collected, dried over Na<sub>2</sub>SO<sub>4</sub>, and filtered; the solvent was evaporated under reduced pressure; and the crude was purified by flash chromatography ( $50\% \text{ Et}_2\text{O}/\text{Hexane}$ ) to afford the corresponding enantiopure lactones 4a–g in low to high isolated yields (24-86%).





performed using 15 mg of substrate and both racemization systems. At this scale, the Et<sub>3</sub>N system showed excellent reliability compared to the anion exchange resin where many phases are involved. Therefore, scale-ups (0.3 mmol) were performed using the Et<sub>3</sub>N-catalyzed racemization system at 30 °C and 250 rpm for 72 h.<sup>19</sup> Then, concd HCl was added and reactions were shaken for an additional 24 h, affording in all cases enantio- and diastereo-merically pure 4-alkyl-3-methyl-3,4-dihydroisocoumarins (*S*,*S*)-4a-g (24–86% overall isolated yields). The case of (*S*,*S*)-4e (R = 4-F) is noteworthy where the isolated yield is very low in comparison with the rest of substrates. In this case, the formation of the corresponding carboxylic acid is preferred, obtaining (*S*,*S*)-4e in poor yield (24%).

In summary, a straightforward method has been described for the transformation of a series of racemic ketones into benzofused lactones as single diastereomers and in enantiopure form. Remarkably, two new stereogenic centers were created starting from a prochiral ketone in a one-pot transformation by means of dynamic kinetic reductive resolution processes catalyzed by *E. coli*/ADH-A followed by an intramolecular cyclization reaction.

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**Supporting Information Available.** Experimental procedures and characterization data for all new compounds are included. This material is available free of charge via the Internet at http://pubs.acs.org.

<sup>(18)</sup> General procedure for the synthesis of racemic ketones 2a-g: Fry, A. J.; Bajanauskas, J. P. J. Org. Chem. 1978, 43, 3157. To a solution of the corresponding ketone 1a-g (1 mmol) in a biphasic mixture of CH<sub>2</sub>Cl<sub>2</sub> (500  $\mu$ L, 2 M) and NaOH (500  $\mu$ L, 2 M), tetrabutylammonium bisulfate (340 mg, 1 mmol) and the corresponding alkyl iodide (1.2 mmol) were added. The reaction mixture was stirred at 40 °C for 2 h until no starting material was detected by TLC analysis. The mixture was extracted afterwards with CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL); the organic layers were collected, dried over Na<sub>2</sub>SO<sub>4</sub>, and filtered; and the solvent was evaporated under reduced pressure. The crude was then purified by flash chromatography (50% Et<sub>2</sub>O/Hexane), affording the corresponding alkyl ketones 2a-g in moderate to good yields (57–78%).

The authors declare no competing financial interest.