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Dynamic reductive kinetic resolution of benzyl ketones using alcohol dehydrogenases and anion exchange resins

Daniel Méndez-Sánchez,[a] Juan Mangas-Sánchez,[a,b] Eduardo Busto,[a,c] Vicente Gotor[a] and Vicente Gotor-Fernández[a]*

[a] Organic and Inorganic Chemistry Department, Biotechnology Institute of Asturias (IUBA), University of Oviedo, Avenida Julián Clavería s/n 33006 Oviedo (Spain)
Phone number: +34985103454; fax number: +34985103446; e-mail address: vicgotfer@uniovi.es
[b] Department of Biotechnology, University of Lund, PO Box 124, SE-221 00 Lund, (Sweden)
[c] Organic Chemistry Department I, Faculty of Chemistry, Complutense University of Madrid, 28040-Madrid (Spain)

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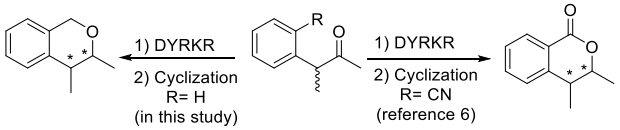
Abstract. Dynamic reductive kinetic resolutions of racemic 3-aryl-alkanones have been performed by the proper combination of an alcohol dehydrogenase and a basic anionic resin. The best results were found for the bioreduction with the alcohol dehydrogenase type A from *Rhodococcus ruber* DSM 44541 overexpressed in *Escherichia coli* (*E. coli*/ADH-A) and the commercially available evo-1.1.200, while the Amberlite IRA-440 C and the DOWEX-MWA-1 resins allowed efficient *in situ* racemizations. Reaction conditions were optimized in terms of enzyme source and loading, type and amount of resin, pH, temperature and reaction times, obtaining a series of (*R,R*)-substituted propan-2-ols with good conversions and both diastero- and stereoselectivity. As a proof of concept, the subsequent intramolecular cyclization of a selected propan-2-ol substrate afforded a valuable isochroman heterocycle without any loss of the optical purity.

Keywords: Alcohol dehydrogenases; Dynamic processes; Dynamic reductive kinetic resolutions; Ion exchange resins; Ketones

Introduction

Dynamic kinetic resolutions (DKRs) provide significant advantages in synthetic chemistry leading to enantiopure compounds in theoretically maximum 100% yield.[1] In this context, the use of enzymes has been extensively explored for the selective modification of one enantiomer while the unreacted substrate enantiomer is racemized using either biological or chemocatalysts, or even through a spontaneous process. Thus, the DKRs of racemic alcohols, amines and their derivatives have been achieved with excellent selectivity levels mainly using hydrolases.[2] Redox enzymes have also been presented along recent years as ideal catalysts for the development of dynamic processes.[3] In this context, alcohol dehydrogenases are valuable tools for the selective bioreduction of ketones, obtaining valuable alcohols with one or multiple stereocenters.[4] Consequently, the racemization of the untouched stereocenter is possible, enabling the generation of multiple stereocenters in a single reaction. This epimerizable stereocenter is normally located in the adjacent position of the carbonyl group, bearing an acidic proton that facilitates the racemization, leading to the development of the so-called dynamic reductive kinetic resolutions (DYRKRs).[5]

In our continuous efforts to develop efficient one-pot transformations for the design of dynamic processes using redox enzymes, the synthesis of a series of racemic 3-aryl-alkan-2-ones was performed, to later explore the combination of ADHs under basic conditions for the development of DYRKRs.[6] This chemoenzymatic strategy provides access to enantioenriched alcohols, immediate precursors of enantio- and diastereomerically pure 3,4-dihydroisocoumarines by intramolecular cyclization processes (Scheme 1). Herein, we wish to expand the synthetic possibilities of this methodology using different benzyl ketones as starting materials, in order to obtain new families of privileged heterocyclic structures such as isochromanes,[7] through a chemoenzymatic and asymmetric strategy. Isochromanes represent an interesting family of compounds due to their cytotoxicity properties and high value as building blocks or more complex structures.

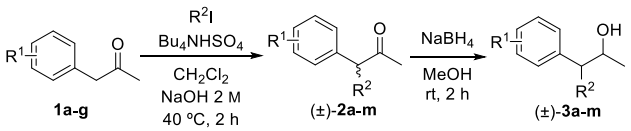


Scheme 1. Synthesis of different heterocyclic scaffolds from benzyl ketones in a sequential dynamic bioreduction and intramolecular cyclization.

Results and Discussion

A series of racemic α-substituted benzyl ketones **2a-m** were prepared by reacting the prochiral ketones **1a-g** with alkyl iodides in the presence of equimolecular amounts of tetrabutylammonium bisulfate (Table 1). Based on the commercial availability of benzyl ketones, different pattern substitutions were considered for the aromatic ring such as methoxy, hydroxy, nitro or fluoro rests in *orto* and *para* position (entries 1-7), but also a broad selection of alkyl iodides were tested from linear aliphatic reagents (methyl, ethyl, propyl, allyl and butyl chains, entries 1-7, 8, 9, 10 and 11) to cyclohexyl (entry 12) and benzyl (entry 13). After 2 h at 40 ºC, the corresponding alkylated ketones **2a-m** were obtained with moderate to high yields after an extraction and a column chromatography purification (30-84%). Then, in order to find suitable conditions for the measurement of conversion and enantiomeric excess values for the bioreduction processes, the chemical reduction of the so-obtained benzyl ketones was performed by reaction with sodium borohydride in methanol, yielding the alcohols **3a-m** in very high yields (90-99%). The anti-configurations were favoured in all cases (up to 13:87 diastereomeric ratio syn:anti).

Table 1. Synthesis of ketones **2a-m** through alkylation reaction of **1a-g** with alkyl iodides, and subsequent chemical reduction towards the formation of racemic alcohols **3a-m**.



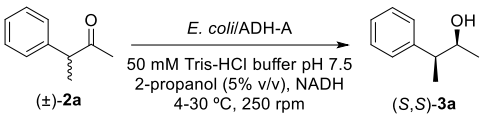
Entry	**3**	R^1	R^2	**2a-m** (%)[a]	**3a-m** (%)[a,b]
1	**3a**	H	Me	67	93 (20:80)
2	**3b**	4-OMe	Me	60	96 (16:84)
3	**3c**	4-OH	Me	45	93 (14:86)
4	**3d**	4-NO_2	Me	67	96 (23:77)
5	**3e**	2-OMe	Me	55	99 (13:87)
6	**3f**	2-Me	Me	55	90 (13:87)
7	**3g**	2-F	Me	84	97 (16:84)
8	**3h**	H	Et	56	97 (19:81)
9	**3i**	H	*n*-Pr	49	98 (15:85)
10	**3j**	H	Allyl	54	98 (21:79)
11	**3k**	H	*n*-Bu	60	95 (14:86)
12	**3l**	H	Cy	30	90
13	**3m**	H	Bn	40	96

[a] Isolated yields (See further details in the experimental section).

[b] Diastereomeric ratios syn:anti measured by GC analysis appear in parentheses (see Supporting Information for further details). No data are reported for **3l** and **3m** as adequate analytical were not found for the determination of the *dr*.

The less substituted substrate from this series, 3-phenylbutan-2-one (**2a**) was chosen as model substrate for the development of bioreduction processes. Initially, KR and racemization experiments were independently conducted trying to find adequate conditions aiming the later combinations of both processes in order to explore and compare the possibilities of DYRKR with previous benzyl ketones,[6] but now lacking of a cyano group in the C-2′ position (Table 2). Based on our previous findings, the *Rhodococcus ruber* DSM 44541 overexpressed in *Escherichia coli* (*E. coli*/ADH-A),[8] was used considering its potential for the bioreduction of those benzyl ketones.[6] Surprisingly, high conversion values and then poor diasteroselectivities were found after 24 h at 30 ºC using either 5 or 15 mg of enzyme loading (entries 1 and 2). This is in contrast with the moderate conversion associated to an excelent enantio- and diastereoselectivity found for the C-2 substituted ketone namely 2-(3-oxobutan-2-yl)benzonitrile (41% conversion, >99:<1 *dr*).[6]

Table 2. Bioreduction of ketone **2a** using *E. coli*/ADH-A in a Tris-HCl buffer pH 7.5 at 250 rpm.



Entry	T (ºC)	t	ADH-A (mg)	*c* (%)[a]	*dr*[b]
1	30	24 h	15	96	53:47
2	30	24 h	5	98	53:47
3	30	5 min	15	19	91:9
4	30	10 min	15	41	87:13
5	30	20 min	15	52	82:18
6	30	40 min	15	70	70:30
7	30	1 h	15	75	63:37
8	30	2 h	15	88	54:46
9	30	5 min	5	12	93:7
10	30	10 min	5	21	91:9
11	30	20 min	5	30	89:11
12	30	40 min	5	49	82:18
13	4	5 min	5	8	90:10
14	4	10 min	5	12	90:10
15	4	20 min	5	16	90:10
16	4	40 min	5	20	90:10
17	4	1 h	5	26	90:10
18	4	2 h	5	41	89:11
19	4	4 h	5	53	83:17
20	4	6 h	5	64	76:24

[a] Conversion values measured by GC analysis (see Supporting Information for further details)

[b] Diastereomeric ratios syn:anti measured by GC analysis (see Supporting Information for further details)

A series of experiments were carried out to understand the reaction outcome, considering shorter reaction times for a selectivity improvement. As it can be seen the use of 15 mg (entries 3-8) or 5 mg of enzyme (entries 9-12) at 4 (entries 13-20) or 30 ºC (entries 3-12), led to good selectivity values at short

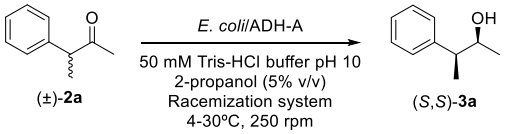
reaction times (up to 83:17 *dr*) for conversion values closed to 50% (entries 5, 12 and 19). Reducing the bioreduction kinetics would allow a good DYRKR always that a highly faster racemization kinetic could be achieved (see enantiomeric excess of ketone **2a** in the Supporting information for the reaction at 4 ºC). In contrast with the non enzymatic bioreduction performed with $NaBH_4$, now the formation of the syn-diastereomer was favoured. In all cases the (*S*,*S*)-alcohol was identified as the major diasteroisomer by HPLC analysis.

Next, conditions for the dynamic process were implemented based on the presence of an acidic α-hydrogen next to the carbonyl group. On one hand, the addition of a hydrophobic co-solvent such as hexane was tested in the presence of triethylamine as basic catalyst for the racemization. The organic solvent acts as a reservoir for both product and substrate, reducing their presence in the aqueous phase where the bioreduction occurs, thus favouring the solubilization of the substrate and avoiding the enzyme inhibition at high substrate concentrations. On the other hand, the use of an anion exchange resin was considered due to the good racemization obtained in the development of dynamic Baeyer-Villiger oxidation of racemic benzyl ketones catalyzed by Baeyer-Villiger monooxygenases.[10] Identical results were achieved using the DOWEX-MWA-1 and the Amberlite IRA-440C (data not shown) in comparison with the previous kinetic resolution experiments (Table 2). Aiming for a higher racemization rate, the dynamic process was tested at higher pHs (9-10). Unfortunately, only a slight racemization was found when using the IRA-440C resin at pH 9 (data not shown). For that reason, the reactions at pH 10 were immediately analyzed in depth (Table 3).

Partial racemization was observed with the triethylamine/hexane and the DOWEX systems at 4 ºC (entries 1-3). Nevertheless, the racemization of the remaining ketone was more pronounced with the IRA-440C as occurred at pH 9, but now in a higher extent (entry 4). Unfortunately the enzyme was highly inactivated in these conditions, either at a higher enzyme loading (entry 5). For that reason, a higher loading of *E.coli*/ADH-A was considered through two different strategies: by using a higher reaction temperature and adding the enzyme in one portion (entry 6) or stepwise addition of the ADH-A (entries 7 and 8), affording in the latter a 27% conversion at 4 ºC and a 84% conversion at 30 ºC with a good selectivity after 3 days. It must be mentioned that the addition of an external nicotinamide cofactor was not required for the correct action of the *E.coli*/ADH-A.[8c]

At this point, DYRKR experiments were conducted over a series of benzyl ketones **2b**-**m**. The bioreduction experiments were performed at 30 ºC in a Tris-HCl buffer pH 10 using the IRA-440C or the DOWEX-MWA-1 resin, and adding in all cases the ADH-A in portions over 3 or 4 days. Data are depicted in Table 4. As occurred with the formation of alcohol **3a**, the diastereoisomers syn-(*S*,*S*)-**3b**-**m** were obtained in all cases as major compounds and with a perfect enantiomeric excess. In all cases, the resins and the ADH were compatible with the pattern substitution, only observing some side reactions for the IRA-440C resin and the 3-(4'-nitrophenyl)butan-2-one (**2d**), affecting the enantiomeric excess of the resulting alcohol (entry 8).

Table 3. DYRKR of racemic ketone **2a** using *E. coli*/ADH-A in a 50 mM Tris-HCl buffer pH 10 at 250 rpm, and subsequent intramolecular cyclization catalysed by anhydrous $ZnCl_2$.



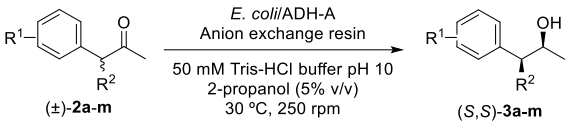
Entry	ADH-A (mg)	Racemization system	t (h)	T (ºC)	*c* (%)[a]	*ee* **2a** (%)[a]	*dr* **3a**[b]
1	5	-----	24	4	63	86	80:20
2	5	Et_3N/Hexane	24	4	59	60	85:15
3	5	DOWEX-MWA-1	24	4	58	72	83:17
4	5	IRA-440C	24	4	11	6	95:5
5	15	IRA-440C	24	4	15	10	94:6
6	15	IRA-440C	24	30	43	6	88:12
7	5+5+5[c]	IRA-440C	72	4	27	22	95:5
8	5+5+5[c]	IRA-440C	72	30	84	23	88:12

[a] Conversion values measured by GC (see Supporting Information for further details)

[b] Enantiomeric excess values and diastereomeric ratios syn:anti measured by HPLC (see Supporting Information for further details).

[c] 5 mg of ADH-A added at 24 and 48 h of reaction.

Table 4. DYRKR of racemic ketones **2a-m** using *E. coli*/ADH-A in a 50 mM Tris-HCl buffer pH 10 at 250 rpm.



Entry	**2a-m**	**R¹**	**R²**	ADH-A (mg)[a]	Resin	t (h)	*c* (%)[b]	*ee* **3a-m** (%)[c]	*dr* **3a-m**[c]
1	**2a**	H	Me	5+5+5	IRA-440C	72	84	>99	88:12
2	**2a**	H	Me	5+5+5	DOWEX-MWA-1	72	94	>99	70:30
3	**2b**	4-OMe	Me	5+5+5	IRA-440C	72	34	>99	91:9
4	**2b**	4-OMe	Me	5+5+5	DOWEX-MWA-1	72	79	>99	82:18
5	**2c**	4-OH	Me	5+5+5	IRA-440C	72	47	>99	69:31
6	**2c**	4-OH	Me	5+5+5	DOWEX-MWA-1	72	38	>99	86:14
7	**2d**	4-NO_2	Me	5+5+5	IRA-440C	72	67	10	95:5
8	**2d**	4-NO_2	Me	5+5+5	DOWEX-MWA-1	72	91	>99	95:5
9	**2e**	2-OMe	Me	5+5+5	IRA-440C	72	4	>99	>99: <1
10	**2e**	2-OMe	Me	5+5+5	DOWEX-MWA-1	72	52	>99	>99: <1
11	**2f**	2-Me	Me	5+5+5	IRA-440C	72	14	>99	>99: <1
12	**2f**	2-Me	Me	5+5+5	DOWEX-MWA-1	72	36	>99	>99: <1
13	**2g**	2-F	Me	5+5+5	IRA-440C	72	24	>99	97:3
14	**2g**	2-F	Me	5+5+5	DOWEX-MWA-1	72	90	>99	96:4
15	**2h**	H	Et	5+5+5	IRA-440C	72	67	>99	95:5
16	**2h**	H	Et	5+5+5+5	IRA-440C	96	83	>99	89:11
17	**2h**	H	Et	10+10+10	IRA-440C	72	83	>99	79:21
18	**2h**	H	Et	5+5+5	DOWEX-MWA-1	72	87	>99	68:32
19	**2i**	H	*n*-Pr	5+5+5	IRA-440C	72	51	>99	96:4
20	**2i**	H	*n*-Pr	5+5+5	DOWEX-MWA-1	72	86	>99	65:35
21	**2j**	H	Allyl	5+5+5	IRA-440C	72	74	>99	92:8
22	**2j**	H	Allyl	5+5+5+5	IRA-440C	96	89	>99	76:24
23	**2j**	H	Allyl	10+10+10	IRA-440C	72	92	>99	72:28
24	**2k**	H	*n*-Bu	5+5+5	IRA-440C	72	25	>99	76:24
25	**2k**	H	*n*-Bu	5+5+5	DOWEX-MWA-1	72	86	>99	57:43
26	**2l**	H	Cy	5+5+5	IRA-440C	72	<3	n.d.	n.d.
27	**2m**	H	Bn	5+5+5	IRA-440C	72	18	n.d.	n.d.

[a] Five or ten mg of ADH-A were added at the starting of the reaction and then five or ten every 24 h.

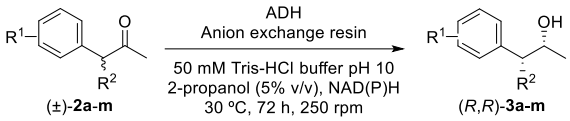
[b] Conversion values measured by GC (see Supporting Information for further details)

[c] Enantiomeric excess values and diastereomeric ratios syn:anti measured by HPLC (see Supporting Information for further details). n.d.: not determined.

Excellent enantio- and diastereoselectivities were found for the C-2 substituted 3-arylbutan-2-ones (**2e-g**, entries 9-14). For the IRA-440C resin, the bioreduction of ketones with alkyl chains longer than butan-2-ones (R^2 different than the methyl group) led to a significant decrease of the reactivity (entries 15, 19, 21, 24, 26 and 27), requiring of the addition of higher enzyme loadings and longer reaction times to reach high conversions into the corresponding alcohols (entries 16, 17, 22 and 23). On the contrary, the use of DOWEX-MWA-1 provided better conversion values (86-87% for **2h**, **2i** and **2k**, entries 18, 20 and 25) although modest diastereomeric ratios were found in these cases.

Encouraged by the excellent selectivities attained with the ADH-A, other alcohol dehydrogenases such as commercially available *Lactobacillus brevis* (LBADH) and evo-1.1.200 were tested, enzymes that usually act with an opposite *anti-Prelog* selectivity in comparison with the ADH-A.[9] Thus, their compatibility with the racemization systems (IRA-440C and DOWEX-MWA-1 anion resins) was investigated for the development of efficient DYRKR experiments (Table 5). Firstly, control experiments in the absence of resin and the use of LBADH and evo-1.1.200 were studied in the bioreduction of 3-phenylbutan-2-one (**2a**) to explore the compatibility of these two ADHs with the anion exchange resins (entries 1-6), finding a considerable inhibition when using the Amberlite IRA-440C, while the combination of DOWEX-MWA-1 with the evo-1.1.200 provided a 72% conversion into the syn-alcohol (*R*,*R*)-**3a** with excellent enantioselectivity and good diastereoselectivity (entry 6). Then, the racemic ketones **2b-n** were subjected to the DYRKR using the same catalytic system, affording the corresponding (*R*,*R*)-**3b-m** with moderate to good conversions and every high selectivities for most of the cases (entries 7-18).

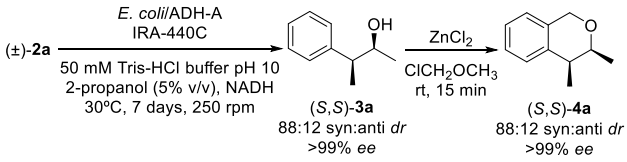
Table 5. DYRKR of racemic ketones **2a**-**m** using *anti-Prelog* ADHs in a 50 mM Tris-HCl buffer pH 10 at 250 rpm.



Entry	**2a-m**	R^1	R^2	ADH[a]	Resin	*c* (%)[b]	*ee* **3a-m** (%)[c]	*dr* **3a-m**[c]
1	**2a**	H	Me	LBADH	-----	47	>99	95:5
2	**2a**	H	Me	LBADH	IRA-440C	2	>99	n.d.
3	**2a**	H	Me	LBADH	DOWEX-MWA-1	14	>99	97:3
4	**2a**	H	Me	evo-1.1.200	-----	59	>99	80:20
5	**2a**	H	Me	evo-1.1.200	IRA-440C	14	>99	97:3
6	**2a**	H	Me	evo-1.1.200	DOWEX-MWA-1	72	>99	80:20
7	**2b**	4-OMe	Me	evo-1.1.200	DOWEX-MWA-1	85	>99	85:15
8	**2c**	4-OH	Me	evo-1.1.200	DOWEX-MWA-1	30	>99	87:13
9	**2d**	4-NO_2	Me	evo-1.1.200	DOWEX-MWA-1	96	>99	>99: <1
10	**2e**	2-OMe	Me	evo-1.1.200	DOWEX-MWA-1	22	>99	>99: <1
11	**2f**	2-Me	Me	evo-1.1.200	DOWEX-MWA-1	16	>99	>99: <1
12	**2g**	2-F	Me	evo-1.1.200	DOWEX-MWA-1	78	>99	>99: <1
13	**2h**	H	Et	evo-1.1.200	DOWEX-MWA-1	71	>99	96:4
14	**2i**	H	*n*-Pr	evo-1.1.200	DOWEX-MWA-1	65	>99	97:3
15	**2j**	H	Allyl	evo-1.1.200	DOWEX-MWA-1	21	>99	91:9
16	**2k**	H	*n*-Bu	evo-1.1.200	DOWEX-MWA-1	82	>99	98:2
17	**2l**	H	Cy	evo-1.1.200	DOWEX-MWA-1	<3	n.d.	n.d.
18	**2m**	H	Bn	evo-1.1.200	DOWEX-MWA-1	27	n.d.	n.d.

[a] Three units of enzyme were added at the starting of the reaction and every 24 h (total 9 units of enzyme).
[b] Conversion values measured by GC (see Supporting Information for further details)
[c] Enantiomeric excess values and diastereomeric ratios syn:anti measured by HPLC (see Supporting Information for further details). n.d.: not determined.

Finally, this chemoenzymatic strategy was applied to the synthesis of a representative member of the isochroman family. The bioreduction reaction of racemic ketone **2a** was scaled-up from an eppendorf tube to a 1 mmol scale at 30 ºC, developing later the intramolecular cyclization of the resulting optically active alcohol (*S*,*S*)-**3a** (Scheme 2). A sequential addition of the enzyme and the presence of external cofactor from the beginning was required, observing a slower reaction rate in comparison with the bioprocess in an eppendorf tube. Nevertheless, after 7 days and the addition of 100 mg of enzyme every 24 h, the alcohol (*S*,*S*)-**3a** was obtained with 77% conversion (55% isolated yield) and a 88:12 syn:anti diastereomeric ratio. Subsequent intramolecular cyclization catalyzed by anhydrous zinc chloride in methoxymethyl chloride, led to the desired isochroman (*S*,*S*)-**4a** in 42% isolated yield and without any loss of the optical purity (see Supporting Information).



Scheme 2. Chemoenzymatic strategy for the synthesis of 3,4-dimethylisochroman by a dynamic bioreduction followed by intramolecular cyclization.

Conclusion

In summary, the chemical synthesis of a series of benzyl ketones was developed by reaction of 1-aryl-propan-2-ones with alkyl halides, to later explore their DYRKR using alcohol dehydrogenases and anion exchange resins. After optimization of the bioreduction and racemization steps, the dynamic processes were performed, affording optically active alcohols in good conversions, diastereo- and stereoselectivities. Remarkably, the creation of two stereogenic centers was possible starting from structuraly simple racemic ketones.

The applicability of these valuable compounds was demonstrated through the development of a chemoenzymatic strategy based on the stereocontrolled bioreduction of 3-phenylbutan-2-one under basic conditions, followed by intramolecular cyclization of the resulting optically active alcohol. Thus, (*S*,*S*)-3,4-dimethylisochroman was obtained as a representative member of this family of oxygenated heterocycles.

Experimental Section

ADH from *Lactobacillus brevis* (LBADH, 300 U/mL), was obtained from Codexis Inc. ADH evo-1.1.200 (0.42 U/mg) was purchased from Evocatal GmbH. ADH-A from *Rhodococcus ruber* was overexpressed in *E. coli* BL21 cells and later lyophilized.[8] The Amberlite IRA-440 C and the DOWEX-MWA-1 anion exchange resins were purchased from Sigma-Aldrich.

General procedure for the synthesis of racemic ketones 2a-m.[11] To a solution of the corresponding ketone **1a-g** (1 mmol) in a biphasic mixture composed of CH_2Cl_2 (500 μL) and an aqueous NaOH 2 M solution (500 μL), tetrabutylammonium bisulfate (340 mg, 1 mmol) and the corresponding alkyl iodide (1.2 mmol) were added. The reaction mixture was stirred at 40 ºC for 2 h until no starting material was detected by TLC analysis. The mixture was extracted afterwards with CH_2Cl_2 (3 x 10 mL), combining the organic layers that were dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The resulting reaction crude was purified by column chromatography on silica gel (20-50% Et_2O/Hexane), affording the corresponding alkyl ketones **2a-m** (30-84%).

3-Phenylbutan-2-one (2a). Colourless oil (67%). R_f (50% Et_2O/Hexane): 0.48. IR (NaCl): 3061, 2954, 1713, 1484, 1242 and 967 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.39 (d, $^3J_{HH}$= 7.0 Hz, 3H), 2.04 (s, 3H), 3.74 (q, $^3J_{HH}$= 7.0 Hz, 1H), 6.83-7.75 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 17.2 (CH_3), 28.3 (CH_3), 53.7 (CH), 127.1 (CH), 127.8 (2CH), 128.9 (2CH), 140.6 (C), 208.8 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{10}H_{12}NaO)^+$ $(M+Na)^+$: 171.07858 found 171.07864.

3-(4'-Methoxyphenyl)butan-2-one (2b). Colourless oil (60%). R_f (50% Et_2O/Hexane): 0.43. IR (NaCl): 3045, 2978, 1716, 1367, 1200 and 1083 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.34 (d, $^3J_{HH}$= 7.0 Hz, 3H), 2.01 (s, 3H), 3.67 (q, $^3J_{HH}$= 7.0 Hz, 1H), 3.76 (s, 3H), 6.85 (d, $^3J_{HH}$= 8.6 Hz, 2H), 7.11 (d, $^3J_{HH}$= 8.7 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 17.0 (CH_3), 27.9 (CH_3), 52.5 (CH), 54.9 (CH_3), 114.1 (2CH), 128.6 (2CH), 132.4 (C), 158.6 (C), 208.8 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{11}H_{14}NaO_2)^+$ $(M+Na)^+$: 201.08915 found 201.0892.

3-(4'-Hydroxyphenyl)butan-2-one (2c). Yellow oil (45%). R_f (50% Et_2O/Hexane): 0.59. IR (NaCl): 3361, 3056, 2944, 1710, 1489, 1075, and 796 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.38 (d, $^3J_{HH}$ = 7.0 Hz, 3H), 2.07 (s, 3H), 3.70 (q, $^3J_{HH}$ = 7.0 Hz, 1H), 6.82 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 7.10 (d, $^3J_{HH}$ = 8.4 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 17.6 (CH_3), 28.6 (CH_3), 53.3 (CH), 116.2 (CH), 129.4 (CH), 132.9 (C), 155.3 (C), 210.3 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{10}H_{12}NaO)^+$ $(M+Na)^+$: 187.07350 found 187.07344.

3-(4'-Nitrophenyl)butan-2-one (2d). Yellow solid (67%). R_f (50% Et_2O/Hexane): 0.60. IR (NaCl): 3061, 2954, 1720, 1537, 1359 and 800 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.46 (d, $^3J_{HH}$ = 4.6 Hz, 3H), 2.12 (s, 3H), 3.92 (q, $^3J_{HH}$ = 7.0 Hz, 1H), 7.42 (d, $^3J_{HH}$ = 8.8 Hz, 2H), 8.22 (d, $^3J_{HH}$ = 8.8 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8 (CH_3), 29.1 (CH_3), 53.8 (CH), 124.5 (2CH), 129.2 (2CH), 148.2 (CH), 162.7 (C), 207.4 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{10}H_{11}NNaO_3)^+$ $(M+Na)^+$: 216.06366 found 216.06358.

3-(2'-Methoxyphenyl)butan-2-one (2e). Yellow oil (55%). R_f (50% Et_2O/Hexane): 0.68. IR (NaCl): 3031, 2924, 1722, 1055 and 739 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.37 (d, $^3J_{HH}$ = 7.0 Hz, 3H), 2.04 (s, 3H), 3.85 (s, 3H), 4.07 (q, $^3J_{HH}$ = 7.0 Hz, 1H), 6.89-6.98 (m, 2H), 7.14 (dd, $^3J_{HH}$ = 7.5 Hz; $^4J_{HH}$ = 1.8 Hz, 1H), 7.23-7.29 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 16.1 (CH_3), 28.5 (CH_3), 47.3 (CH), 55.7 (CH_3), 111.7 (CH), 121.4 (CH), 128.6 (CH), 130.0 (C), 157.1 (C), 210.1 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{11}H_{14}NaO_2)^+$ $(M+Na)^+$: 201.08915 found 201.08923.

3-(2'-Methyphenyl)butan-2-one (2f). Yellow oil (55%). R_f (50% Et_2O/Hexane): 0.68. IR (NaCl): 3058, 2951, 1708, 1490, 1222 and 742 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.37 (d, $^3J_{HH}$ = 6.9 Hz, 3H), 2.02 (s, 3H), 2.40 (s, 3H), 3.95 (q, $^3J_{HH}$ = 6.9 Hz 1H), 7.05-7.09 (m, 1H), 7.16-7.22 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 17.0 (CH_3), 20.1 (CH_3), 28.7 (CH_3), 50.2 (CH), 127.1 (CH), 127.3 (CH), 127.4 (CH), 131.2 (CH), 139.5 (C), 209.6 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{11}H_{14}NaO)^+$ $(M+Na)^+$: 185.09423 found 185.09418.

3-(2'-Fluorophenyl)butan-2-one (2g). Colourless oil (84%). R_f (50% Et_2O/Hexane): 0.58. IR (NaCl): 3029, 2924, 1718, 1484, 1237 and 750 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.42 (d, $^3J_{HH}$ = 7.0 Hz, 3H), 2.11 (s, 3H), 4.08 (q, $^3J_{HH}$ = 7.0 Hz, 1H), 7.07-7.29 (m, 4H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 16.0 (CH_3), 28.4 (CH_3), 45.9 (CH), 115.5 (d, $^2J_{CF}$ = 22.4 Hz, CH), 124.6 (CH, d, $^4J_{CF}$ = 3.3 Hz), 128.8 (d, $^3J_{CF}$ = 7.5 Hz, CH), *129.1* (d, $^3J_{CF}$ = 4.9 Hz, CH,), 162.1 (d, $^1J_{CF}$ = 244.6 Hz, C), 207.9 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{10}H_{11}FNaO)^+$ $(M+Na)^+$: 189.06916 found 189.06922.

3-Phenylpentan-2-one (2h). Yellow oil (56%). R_f (50% Et_2O/Hexane): 0.69. IR (NaCl): 3027, 2933, 1712, 1493, 759 and 701 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 0.86 (t, $^3J_{HH}$ = 7.4 Hz, 3H), 1.69-1.78 (m, 1H), 2.04-2.14 (m, 3H), 2.07 (s, 3H), 3.54 (t, $^3J_{HH}$ = 7.4 Hz, 2H), 7.22-7.35 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 12.0 (CH_3), 24.9 (CH_2), 29.0 (CH_3), 61.5 (CH), 127.2 (CH), 128.3 (CH), 128.9 (CH), 139.0 (C), 208.6 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{11}H_{14}NaO)^+$ $(M+Na)^+$: 185.09423 found 185.09427.

3-Phenylhexan-2-one (2i). Colorless oil (49%). R_f (50% Et_2O/Hexane): 0.70. IR (NaCl): 3060, 2957, 1715, 1491, 1161, 746 and 701 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 0.90 (t, $^3J_{HH}$ = 7.3 Hz, 3H), 1.15-1.27 (m, 2H) 1.63-1.76 (m, 1H), 1.96-2.08 (m, 1H), 2.07 (s, 3H), 3.63 (t, $^3J_{HH}$ = 7.4 Hz, 1H), 7.21-7.37 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.4 (CH_3), 21.0 (CH_2), 29.4 (CH_3), 34.3 (CH_2), 60.0 (CH), 127.5 (CH), 128.6 (CH), 129.2 (CH), 139.5 (C), 209.0 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{12}H_{16}NaO)^+$ $(M+Na)^+$: 199.10988 found 199.10991.

3-Phenylhex-5-en-2-one (2j). Yellow oil (54%). R_f (50% Et_2O/Hexane): 0.71. IR (NaCl): 3063, 2977, 1716, 1641, 1161, 749 and 700 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 2.07, (s, 3H), 2.40-2.50 (m, 1H), 2.77-2.86 (m, 1H), 3.71 (t, $^3J_{HH}$ = 7.5 Hz, 1H), 4.94-5.06 (m, 2H), 5.62-5.75 (m, 2H), 7.21-7.38 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 29.5 (CH_3), 36.5 (CH_2), 59.8 (CH), 116.9 (CH_2), 127.7 (CH), 128.7 (CH), 129.3 (CH), 136.1 (CH), 138.7 (C), 208.0 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{12}H_{14}NaO)^+$ $(M+Na)^+$: 197.09423 found 197.09421.

3-Phenylheptan-2-one (2k). Yellow oil (60%). R_f (50% Et_2O/Hexane): 0.70. IR (NaCl): 3056, 2977, 1710, 1355, 1117, 731 and 698 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 0.86 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.10-1.35 (m, 4H), 1.62-1.77 (m, 2H), 2.06 (s, 3H), 3.61 (t, $^3J_{HH}$ = 7.4 Hz, 3H), 7.21-7.38 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.3 (CH_3), 22.7 (CH_2), 29.4 (CH_3), 30.0 (CH_2), 31.9 (CH_2), 60.2 (CH), 127.5 (CH), 128.6 (CH), 129.2 (CH), 139.5 (C), 209.0 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{13}H_{18}NaO)^+$ $(M+Na)^+$: 213.12553 found 213.12558.

1-Cyclohexyl-1-phenylpropan-2-one (2l). Yellow oil (30%). R_f (50% Et_2O/Hexane): 0.69. IR (NaCl): 3061, 2964, 1719, 1355, 732 and 696 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 0.68-0.81 (m, 1H), 0.91-1.04 (m, 1H), 1.11-1.21 (m, 2H), 1.25-1.40 (m, 2H), 1.60-1.75 (m, 3H), 1.79-1.89 (m, 1H), 2.10 (s, 3H), 2.05-2.19 (m, 1H), 3.42 (d, $^3J_{HH}$ = 10.4 Hz 1H), 7.22-7.38 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 26.1 (CH_2), 26.4 (CH_2), 30.4 (CH_3), 30.5 (CH_2), 32.2 (CH_2), 39.5 (CH), 66.5 (CH), 127.1 (CH), 128.7 (CH), 128.8 (CH), 137.5 (C), 208.8 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{15}H_{20}NaO)^+$ $(M+Na)^+$: 239.14118 found 239.14113.

3,4-Diphenylbutan-2-one (2m). Yellow oil (40%). R_f (50% Et_2O/Hexane): 0.63. IR (NaCl): 3058, 2958, 1735 and 696 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 2.06 (s, 3H), 2.93 (dd, $^2J_{HH}$ = 13.8 Hz, $^3J_{HH}$ = 7.4 Hz 1H), 3.46 (dd, $^3J_{HH}$ = 13.8 Hz, $^2J_{HH}$ = 7.4 Hz 1H), 3.95 (t, $^3J_{HH}$ = 7.4 Hz, 1H), 7.05-7.09 (m, 2H), 7.17-7.24 (m, 4H), 7.29-7.36 (m,

3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 29.9 (CH_2), 38.7 (CH_2), 61.9 (CH), 126.5 (CH), 127.8 (CH), 128.6 (CH), 128.7 (CH), 129.3 (CH), 129.4 (CH), 138.9 (C), 140.1 (C), 208.8 (C). HRMS (ESI$^+$, *m/z*): calcd for $(C_{16}H_{16}NaO)^+$ $(M+Na)^+$: 247.10988 found 247.11001.

General procedure for the synthesis of racemic alcohols 3a-m. To a solution of racemic ketones **2a-m** (1 mmol) in dry MeOH (10 mL), sodium borohydride (38 mg, 1 mmol) was carefully added under nitrogen atmosphere. The mixture was stirred for 2 h until no starting material was detected by TLC analysis (50% Et_2O/Hexane). The reaction was quenched afterwards with H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The resulting reaction crude was purified by column chromatography on silica gel (50% Et_2O/Hexane), affording the corresponding racemic alcohols **3a-m** (90-99%).

3-Phenylbutan-2-ol (3a). Colourless oil (93%). R_f (50% Et_2O/Hexane): 0.32. Diastereomeric ratio for (±)-**3a** (*syn:anti*): 20:80. IR (NaCl): 3373, 3065, 2969, 1472, 1374 and 935 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.10 (d, $^3J_{HH}$= 6.3 Hz, 3H, *syn*), 1.24 (d, $^3J_{HH}$= 6.2 Hz, 3H, *anti*), 1.28 (d, $^3J_{HH}$= 7.0 Hz, 3H, *anti*), 1.34 (d, $^3J_{HH}$= 7.1 Hz, 3H, *syn*), 1.56 (br s, 1H, *syn+anti*), 2.44-3.29 (m, 1H, *syn+anti*), 3.49-4.30 (m, 1H, *syn+anti*), 6.86-7.68 (m, 5H, *syn+anti*). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 16.0 (CH_3, *syn*), 17.8 (CH_3, *anti*), 20.5 (CH_3, *anti*), 21.0 (CH_3, *syn*), 47.1 (CH, *syn*), 47.9 (CH, *anti*), 72.3 (CH, *syn+anti*), 126.4 (CH, *syn*), 126.7 (CH, *anti*), 127.8 (2CH, *syn*), 128.0 (2CH, *anti*), 128.3 (2CH, *syn*), 128.5 (2CH, *anti*), 143.5 (C, *anti*), 144.2 (C, *syn*). HRMS (ESI$^+$, *m/z*): calcd for $(C_{10}H_{14}NaO)^+$ $(M+Na)^+$: 173.0397 found 173.0390.

3-(4'-Methoxyphenyl)butan-2-ol (3b). Colourless oil (96%). R_f (50% Et_2O/Hexane): 0.28. Diastereomeric ratio for (±)-**3b** (*syn:anti*): 16:84. IR (NaCl): 3390, 3045, 2967, 1477, 1267 and 990 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.07 (d, $^3J_{HH}$= 6.3 Hz, 3H, *syn*), 1.21 (d, $^3J_{HH}$= 6.2 Hz, 3H, *anti*), 1.24 (d, $^3J_{HH}$= 7.1 Hz, 3H, *anti*), 1.29 (d, $^3J_{HH}$= 7.1 Hz, 3H, *syn*), 1.50 (br s, 1H, *syn+anti*), 2.52-2.78 (m, 1H, *syn+anti*), 3.63-3.95 (m, 4H, *syn+anti*), 6.77-6.97 (m, 2H, *syn+anti*), 7.06-7.20 (m, 2H, *syn+anti*). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 16.2 (CH_3, *syn*), 18.0 (CH_3, *anti*), 20.6 (CH_3, *anti*), 20.9 (CH, *syn*), 46.2 (CH, *syn*), 47.1 (CH, *anti*), 55.3 (CH_3, *syn+anti*), 72.4 (CH, *syn+anti*), 113.8 (2CH, syn), 114.0 (2CH, *anti*), 128.7 (CH, *syn*), 129.0 (CH, *anti*), 135.3 (C, *anti*),136.1 (C, *syn*), 158.0 (C, *syn*), 158.2 (C, *anti*). HRMS (ESI$^+$, *m/z*): calcd for $(C_{11}H_{16}NaO_2)^+$ $(M+Na)^+$: 203.1043 found 203.1053.

3-(4'-Hydroxybutan-2-yl)phenol (3c). Colourless oil (93%). R_f (50% Et_2O/Hexane): 0.39. Diastereomeric ratio for (±)-**3c** (*syn:anti*): 14:86. IR (NaCl): 3361, 3056, 2944, 1488, 1076, and 797 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.24-1.32 (m, 6H, *anti+syn*), 1.50 (br s, 1H, *anti+syn*), 2.59-2.75 (m, 1H, *syn+anti*), 3.77-3.89 (m, 1H, *syn+anti*), 6.78-6.82 (m, 2H, *syn+anti*), 7.09-7.13 (m, 2H, *syn+anti*). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 16.4 (CH_3, *syn*), 18.4 (CH_3, *anti*), 20.1 (CH_3, *syn+anti*), 47.5 (CH_3, *syn+anti*), 73.1 (CH, *syn+anti*), 115.9 (2CH, *syn+anti*), 129.5 (2CH, *syn+anti*), 135.6 (C, *syn+anti*), 155.0 (C, *syn+anti*). HRMS (ESI$^+$, *m/z*): calcd for $(C_{10}H_{14}NaO_2)^+$ $(M+Na)^+$: 189.08915 found 189.08920.

3-(4'-Nitrophenyl)butan-2-ol (3d). Colourless oil (96%). R_f (50% Et_2O/Hexane): 0.53. Diastereomeric ratio for (±)-**3d** (*syn:anti*): 23:77. IR (NaCl): 3360, 3055, 2969, 1473, 1374, 1222 and 860 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.11 (d, $^3J_{HH}$= 6.3 Hz, 3H, *syn*), 1.23 (d, $^3J_{HH}$= 6.2 Hz, 3H, *anti*), 1.33 (d, $^3J_{HH}$= 7.1 Hz, 3H, *anti*), 1.37 (d, $^3J_{HH}$= 7.0 Hz, 3H, *syn*), 1.50 (br s, 1H, *syn+anti*), 2.80-2.92 (m, 1H, *syn+anti*), 3.93-3.99 (m, 1H, *syn+anti*), 7.38-7.45 (m, 2H, *syn+anti*), 8.16-8.20 (m, 2H, *syn+anti*). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.6 (CH_3, *syn*), 17.7 (CH_3, *anti*), 21.2 (CH_3, *anti*), 21.3 (CH_3, *syn*), 47.1 (CH, *syn*), 47.5 (CH, *anti*), 71.8 (CH, *syn), 71.9* (CH, *anti*), 123.6 (2CH, *syn+anti*), 128.7 (2CH, *syn*), 129.0 (2CH, *anti*), 146.7 (C, *syn+anti*), 151.8 (C, *syn+anti*). HRMS (ESI$^+$, *m/z*): calcd for $(C_{10}H_{13}NNaO_3)^+$ $(M+Na)^+$: 218.07931 found 218.07928.

3-(2'-Methoxyphenyl)butan-2-ol (3e). Yellow oil (99%). R_f (50% Et_2O/Hexane): 0.47. Diastereomeric ratio for (±)-**3f** (*syn:anti*): 13:87. IR (NaCl): 3390, 3045, 2967, 1477, 1267 and 742 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ, , 1.12 (d, *J* = 6.3 Hz, 3H, *syn*), 1.22 (d, *J* = 6.2 Hz, 3H, *anti*), 1.26 (d, *J* = 7.2 Hz, 3H, *anti*), 1.30 (d, *J* = 7.2 Hz, 3H, *syn*), 1.86 (brs, 1H, *syn+anti*), 3.21-3.33 (m, 1H, syn+*anti*), 3.85 (s, 3H, *syn+anti*) 3.92-4.01 (m, 1H, *syn+anti*), 6.89-7.00 (m, 2H, *syn+anti*), 7.19-7.26 (m, 2H, *syn+anti*). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.2 (CH_3, *syn*), 17.1 (CH_3, *anti*), 21.0 (CH_3, *syn*), 21.1 (CH_3, *anti*),39.8 (CH, *syn*), 40.8 (CH, *anti*), 55.8 (CH, *anti+syn*), 111.0 (CH, *syn*), 111.1 (CH, *anti*), 121.1 (CH, *syn*), 121.3 (CH, *anti*), 127.6 (CH, *syn*), 127.8 (CH, *anti*), 128.6 (*anti+syn*), 132.1 (C, *syn*), 132.3 (C, *anti*), 157.4 (C, *syn*), 157.8 (C, *anti*). HRMS (ESI$^+$, *m/z*): calcd for $(C_{11}H_{16}NaO_2)^+$ $(M+Na)^+$: 203.10480 found 203.10487.

3-(2'-Methylphenyl)butan-2-ol (3f). Colourless oil (90%). R_f (50% Et_2O/Hexane): 0.47. Diastereomeric ratio for (±)-**3g** (*syn:anti*): 13:87. IR (NaCl): 3203, 2951, 1490, 1222, 1035 and 742 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.14 (d, $^3J_{HH}$ = 6.3 Hz, 3H, *syn*), 1.22 (d, $^3J_{HH}$ = 7.0 Hz, 3H, *anti*), 1.30 (d, $^3J_{HH}$= 6.1 Hz, 3H, syn+*anti*), 1.69 (br s, 1H, *syn+anti*), 2.36 (s, 3H, *syn*) 2.39 (s, 3H, *anti*), 2.91-3.24 (m, 1H, syn+*anti*), 3.92-3.96 (m, 1H, *syn+anti*), 7.13-7.30 (m, 4H, *syn+anti*): ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 18.3 (CH_3, *syn+anti*), 20.3 (CH_3, *syn+anti*), 20.9 (CH_3, *syn+anti*), 40.0 (CH, *syn+anti*), 72.7 (CH, *syn+anti*), 126.2 (CH, *syn+anti*), 126.6 (CH, *syn+anti),* 126.9 (CH, *syn+anti*), 137.2 (C, *syn+anti*), 142.5 (C, *syn+anti*). HRMS (ESI$^+$, *m/z*): calcd for $(C_{11}H_{16}NaO)^+$ $(M+Na)^+$: 187.10988 found 187.10978.

3-(2'-Fluorophenyl)butan-2-ol (3g). Colourless oil (97%). R_f (50% Et_2O/Hexane): 0.51. Diastereomeric ratio for (±)-**3h** (*syn:anti*): 16:84. IR (NaCl): 3350, 2920, 1489, 1237 and 752 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ ^{1}H NMR (300 MHz, $CDCl_3$) δ, , 1.14 (d, *J* = 6.3 Hz, 3H, *syn*), 1.23 (d, *J* = 6.2 Hz, 3H,*anti*), 1.31 (d, *J* = 7.2 Hz, 3H, *anti*), 1.36 (d, *J* = 7.1 Hz, 3H, *syn*), 1.55 (brs, 1H, *syn+anti*), 3.09-3.18 (m, 1H, syn+*anti*), 3.95-4.03 (m, 1H, *syn+anti*), 7.03-7.34 (m, 4H, *syn+anti*). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.1 (CH_3, *syn*), 16.8 (CH_3, *anti*), 20.8 (CH_3, *anti*), 21.1 (CH_3, *syn*) 40.0 (CH, *syn*), 40.3 (CH, *anti*), 71.3 (CH, *anti*), 71.4 (CH, syn) 115.5 (d, $^2J_{CF}$ = 23.2 Hz, CH, *syn+anti*), 124.2 (CH, d, $^4J_{CF}$ = 3.2 Hz *syn+anti*), 127.9 (d, $^3J_{CF}$ = 8.4 Hz, CH, *syn+anti*), *129.1* (d, $^3J_{CF}$ = 4.9 Hz, CH, *syn+anti*), 130.3 (C, *syn+anti*), 161.1 (d, $^1J_{CF}$ = 244.6 Hz, C, *syn+anti*). HRMS (ESI$^+$, *m/z*): calcd for $(C_{10}H_{13}FNaO)^+$ $(M+Na)^+$: 191.19779 found 191.19786.

3-Phenylpentan-2-ol (3h). Colourless oil (97%). R_f (50% Et_2O/Hexane): 0.57. Diastereomeric ratio for (±)-**3i** (*syn:anti*): 19:81. 3227, 1493, 1050, 740 and 703 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 0.78 (t, $^3J_{HH}$ = 7.4 Hz, 3H, *syn+anti*), 1.23 (d, $^3J_{HH}$= 6.2 Hz, 3H, syn+*anti*), 1.37 (br s, 1H, *syn+anti*), 1.61-1.71 (m, 1H, syn+*anti*), 1.76-1.86 (m, 1H, *syn+anti*), 2.39-2.47 (m, 1H, *syn+anti*), 3.90-3.99 (m, 1H, *syn+anti*), 7.22-7.29 (m, 3H, *syn+anti*), 7.33-7.38 (m, 2H, *syn+anti*). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 12.6 (CH_3, *syn+anti*), 21.5 (CH_3, *syn+anti*), 25.2 (CH_2, *syn+anti*), 56.4 (CH, *syn+anti*), 71.5 (CH, *syn+anti*), 127.1 (CH, *syn+anti*), 128.9 (CH, *syn+anti), 129.3* (CH, *syn+anti*), 141.7 (C, *syn+anti*). HRMS (ESI$^+$, *m/z*): calcd for $(C_{11}H_{16}NaO)^+$ $(M+Na)^+$: 187.10988 found 187.10993.

3-Phenylhexan-2-ol (3i). Yellow oil (98%). R_f (50% Et_2O/Hexane): 0.60. Diastereomeric ratio for (±)-**3j** (*syn:anti*): 15:85. IR (NaCl): 3350, 2957, 1487, 1051, 748 and 703 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 0.85 (t, $^3J_{HH}$ = 7.3 Hz, 3H, *syn+anti*), 1.10-1.20 (m, 2H, *syn+anti*), 1.23 (d, $^3J_{HH}$= 6.2 Hz, 3H, syn+*anti*), 1.37 (br s, 1H, *syn+anti*), 1.61-1.71 (m, 1H, syn+*anti*), 1.76-1.86 (m, 1H,

syn+anti), 2.50-2.57 (m, 1H, *syn+anti*), 3.90-3.99 (m, 1H, *syn+anti*), 7.22-7.29 (m, 3H, *syn+anti*), 7.33-7.38 (m, 2H, *syn+anti*). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.5 (CH_3, *syn+anti*), 21.1 (CH_2, *syn+anti*), 21.5 (CH_3, *syn+anti*), 33.7 (CH_2, *syn)*, 34.5 (CH_2, *anti)*, 54.0 (CH, *syn*), 54.2 (CH, *anti*), 71.7 (CH, *anti*), 72.2 (CH, *syn*), 126.8 (CH, *syn*), 127.1 (CH, *anti)*, 128.7 (CH, *syn*), 128.9 (CH, *anti), 129.2* (CH, *syn+anti*), 142.0 (C, *syn+anti*). HRMS (ESI$^+$, *m/z*): calcd for $(C_{12}H_{18}NaO)^+$ $(M+Na)^+$: 201.12553 found 201.12556.

3-Phenyl-hex-5-en-2-ol (3j). Yellow oil (98%). R_f (50% Et_2O/Hexane): 0.48. IR (NaCl): 3323, 2977, 1641, 1161, 760 and 702 cm^{-1}. Diastereomeric ratio for (±)-**3k** (*syn:anti*): 21:79 ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.07, (d, $^3J_{HH}$ = 6.3 Hz, 3H, *syn*), 1.21, (d, $^3J_{HH}$ = 6.3 Hz, 3H, *anti*) 1.53 (brs, 1H), 2.46-2.69 (m, 2H, *syn+anti*), 3.98-4.02 (m, 1H, *syn+anti*), 4.92-5.06 (m, 2H, *syn+anti*), 5.59-5.70 (m, 1H, *syn+anti*), 7.17-7.38 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.5 (CH_3, *syn+anti*), 35.9 (CH_2, *syn*), 36.8 (CH_2, *anti*), 53.8 (CH, *anti*), 53.9 (CH, *syn*), 70.4 (CH, *anti*), 70.5 (CH, *syn*), 116.3 (CH_2,*syn*), 116.6 (CH_2, *anti*), 127.0 (CH, *syn*), 127.2 (CH, *anti*), 128.8 (CH, *syn*), 128.9 (CH, *anti*), 129.0 (CH, *syn*) 129.4 (CH, *anti*), 137.0 (CH, *anti*), 137.4 (CH, *syn*), 141.1 (C); HRMS (ESI$^+$, *m/z*): calcd for $(C_{12}H_{16}NaO)^+$ $(M+Na)^+$: 199.10988 found 199.10991.

3-Phenylheptan-2-ol (3k). Colourless oil (95%). R_f (50% Et_2O/Hexane): 0.62. Diastereomeric ratio for (±)-**3l** (*syn:anti*): 14:86. IR (NaCl): 3366, 2917, 1399, 1061, 743 and 700 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 0.85 (t, $^3J_{HH}$ = 7.2 Hz, 3H, *syn+anti*), 1.04-1.18 (m, 2H, syn+*anti*), 1.23 (d, $^3J_{HH}$= 6.3 Hz, 3H, syn+*anti*), 1.26-1.34 (m, 2H, syn+*anti*) 1.45 (br s, 1H, *syn+anti*), 1.64-1.76 (m, 2H, syn+*anti*), 2.48-2.55 (m, 1H, *syn+anti*), 3.89-3.97 (m, 1H, *syn+anti*), 7.22-7.29 (m, 3H, *syn+anti*), 7.33-7.41 (m, 2H, *syn+anti*). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.3 (CH_3, *syn+anti*), 21.5 (CH_3, *syn+anti*), 23.1 (CH_2, *syn+anti*), 30.1 (CH_2, *syn+anti)*, 32.0 (CH_2, *syn+anti)*, 54.5 (CH, *syn+anti*), 71.7 (CH, *syn+anti*), 127.1 (CH, *syn+anti*), 128.7 (CH, *syn+anti*), 129.2 (CH, *syn+anti)*, 142.0 (C, *syn+anti*). HRMS (ESI$^+$, *m/z*): calcd for $(C_{13}H_{20}NaO)^+$ $(M+Na)^+$: 215.14118 found 215.14109.

1-Cyclohexyl-1-phenylpropan-2-ol (3l). Yellow oil (90%). R_f (50% Et_2O/Hexane): 0.55. IR (NaCl): 3389, 2964, 1352, 729 and 695 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 0.78-2.05 (m, 10H), 1.08 (d, $^3J_{HH}$ = 6.3 Hz, 3H), 2.27 (dd, $^3J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 5.1 Hz, 1H), 4.30-4.38 (m, 1H), 7.20-7.35 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.5 (CH_3), 26.5 (CH_2), 26.6 (CH_2), 30.8 (CH_2), 31.9 (CH_2) 59.3 (CH), 66.6 (CH), 126.8 (CH), 128.5 (CH), 130.2 (CH), 140.5 (C). HRMS (ESI$^+$, *m/z*): calcd for $(C_{15}H_{22}NaO)^+$ $(M+Na)^+$: 241.15683 found 241.15868.

3,4-Diphenylbutan-2-ol (3m). Yellow oil (96%). R_f (50% Et_2O/Hexane): 0.50. IR (NaCl): 3395, 2961, 1352, 729, 699 and 695 cm^{-1}cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.22 (d, $^3J_{HH}$ = 6.3 Hz, 3H), 1.41 (brs, 1H),2.84-3.02 (m, 2H), 3.22 (dd, $^2J_{HH}$ = 13.3 Hz, $^3J_{HH}$ = 6.5 Hz, 1H), 4.02-4.06 (m, 1H), 7.10-7.36 (m, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.0 (CH_3), 39.0 (CH_2), 55.7 (CH), 69.9 (CH), 126.3 (CH), 127.2 (CH), 128.6 (CH), 128.8 (CH), 129.5 (CH), 129.6 (CH), 140.8 (C), 141.0 (C). HRMS (ESI$^+$, *m/z*): calcd for $(C_{16}H_{18}NaO)^+$ $(M+Na)^+$: 249.12553 found 249.12558.

General procedure for the kinetic resolution of racemic ketones 2a using *E. coli*/ ADH-A. *E. coli*/ADH-A cells (15 mg) were rehydrated in an eppendorf tube with a 50 mM Tris-HCl buffer (500 µL) at different pHs. The mixture was shaken at 250 rpm for 30 min and after this time the corresponding ketone **2a** (0.01 mmol), 2-propanol (25 µL), hexane (25 µL) and a 10 mM solution of NADH in the corresponding Tris-HCl buffer (50 µL) were successively added. The reaction was shaken at 250 rpm and 30 ºC, measuring the conversion values by GC analysis.

General procedure for the dynamic reductive kinetic resolution of racemic ketones 2a-m using *E. coli*/ADH-A. In an eppendorf tube containing rehydrated *E. coli*/ADH-A cells (5 or 10 mg) in a 50 mM Tris-HCl buffer (500 µL) at different pHs, the corresponding ketone **2a-m** (0.01 mmol), 2-propanol (25 µL), IRA-440C resin (12 mg) or DOWEX-MWA-1 resin (12 mg) were successively added. The reaction was shaken at 250 rpm and 30 ºC, adding additional enzyme (5 or 10 mg) every 24 h. The conversion values into the corresponding alcohols (*S*,*S*)-**3a-m** were measured by GC analysis, and their optical purity by HPLC analysis.

Scale-up dynamic reductive kinetic resolution of racemic ketones 2a using *E. coli*/ ADH-A. To a solution containing rehydrated *E. coli*/ADH-A cells (100 mg/mmol, 100 mg) in a 50 mM Tris-HCl buffer pH 10 (0.05 M, 19 mL), 2-propanol (5% v/v, 1 mL), IRA-440C resin (100 mg), NADH (1 mM, 14 mg) and the racemic ketone **2a** (1 mmol) were successively added. The reaction was shaken for 24 h and 250 rpm. Then, additional *E. coli*/ADH-A cells (100 mg) were added every 24 h during 7 days. The process was monitored by GC analysis. After seven days, the mixture was centrifuged and extracted with EtOAc (3 x 15 mL). Organic layers were combined, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The resulting reaction crude was purified by column chromatography on silica gel (50% Et_2O/Hexane), affording the corresponding optically active (*S*,*S*)-alcohol **3a**. $[\alpha]^{20}_D$ +8.7 (c 1, $CHCl_3$), >99% *ee* (diastereomeric ratio syn:anti 88:12).

General procedure for the dynamic reductive kinetic resolution of racemic ketones 2a-m using evo.1.1.200 ADH. To a solution of the corresponding ketone **2a-m** (0.01 mmol) in a Tris-HCl buffer (325 µL) at different pHs in an eppendorf tube, 2-propanol (25 µL), IRA-440C resin (12 mg) or DOWEX-MWA-1 resin (12 mg), a 10 mM $MgCl_2$ solution (50 µL), a 10 mM NADH solution (50 µL) and a stock evo-1.1.200 solution (3 U every 24 h) were successively added. The mixture was shaken at 250 rpm and 30 ºC for 72 h. After this time, the reaction was extracted with EtOAc (3 x 0.5 mL). Organic layers were collected, dried over Na_2SO_4 and filtered, measuring the conversions values into the corresponding alcohols (*R*,*R*)-**3a-m** by GC analysis, and their optical purity by HPLC analysis.

General procedure for the dynamic reductive kinetic resolution of racemic ketones 2a-m using ADH from *Lactobacillus brevis*. To a solution of the corresponding ketone **2a-m** (0.01 mmol) in a 50 mM Tris-HCl buffer (336 µL) at different pHs in an eppendorf tube, 2-propanol (32 µL), IRA-440C resin (12 mg) or DOWEX-MWA-1 resin (12 mg), a 10 mM $MgCl_2$ solution (50 µL), a 10 mM NADPH solution (60 µL) and a LBADH solution (3 U every 24 h) were successively added. The mixture was shaken at 250 rpm and 30 ºC for 72 h. After this time, the reaction was extracted with EtOAc (3 x 0.5 mL). Organic layers were collected, dried over Na_2SO_4, filtered, measuring the conversions values into the corresponding alcohols (*R*,*R*)-**3a-m** by GC analysis, and their optical purity by HPLC analysis.

General procedure for the cyclization of alcohol 3a. To a solution of the alcohol racemic or (*S*,*S*)-**3a** (100 mg, 0.74 mmol) in methoxymethyl chloride (1.64 mL, 19 mmol), anhydrous $ZnCl_2$ (43 mg, 0.32 mmol) was added at room temperature under nitrogen atmosphere. The mixture was stirred for 15 min until no starting material was detected by TLC analysis (50% Et_2O/Hexane). The reaction was quenched afterwards with H_2O (10 mL) at 0 ºC and extracted with Et_2O (3 x 10 mL). Organic layers were collected, dried over Na_2SO_4, filtered, and the solvent evaporated under reduced pressure. The reaction crude was finally purified by column chromatography on silica gel (5% Et_2O/Hexane), affording the 3,4-dimethylisochroman (**4a**) as a colorless oil (53 mg, 44%). R_f (5% Et_2O/Hexane): 0.22. Diastereomeric ratio for (±)-**4a** syn:anti 88:12. IR

(NaCl): 3068, 2978, 1616, 1380, 1035 and 809 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.24 (d, $^3J_{HH}$= 7.1 Hz, 3H, *syn*), 1.31 (d, $^3J_{HH}$= 6.9 Hz, 3H, *anti*), 1.32 (d, $^3J_{HH}$= 6.4 Hz, 3H, *syn*), 1.40 (d, $^3J_{HH}$= 6.2 Hz, 3H, *anti*), 2.57-2.83 (m, 1H, *syn*+*anti*), 3.53 (dq, $^3J_{HH}$= 8.7, 6.1 Hz, 1H, *anti*), 3.92 (qd, $^3J_{HH}$= 6.4, 2.8 Hz, 1H, *syn*), 4.82 (s, 3H, *anti*), 4.87 (s, 3H, *syn*), 6.97-7.04 (m, 1H, *syn*+*anti*), 7.13-7.34 (m, 3H, *syn*+*anti*). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 16.3 (CH_3, *syn*), 17.6 (CH_3, *anti*), 18.1 (CH_3, *syn*), 19.7 (CH_3, *anti*), 36.6 (CH, *syn*), 38.0 (CH, *anti*), 67.5 (CH_2, *anti*), 68.4 (CH_2, *syn*), 72.8 (CH, *syn*), 77.0 (CH, *anti*), 123.9 (CH, *anti*), 124.0 (CH, *syn*), 125.7 (CH, *anti*), 126.0 (CH, *syn*), 126.4 (CH, *syn*), 126.7 (CH, *anti*), 127.2 (CH, *anti*), 128.8 (CH, *syn*), 134.0 (C, *syn*), 134.3 (C, *anti*), 138.1 (C, *anti*), 140.6 (C, *syn*). HRMS (ESI^+, *m/z*): calcd for $(C_{11}H_{14}NaO)^+$ $(M+Na)^+$: 185.0937 found 185.0943. $[\alpha]^{20}_D$ +85.8 (*c* 1, $CHCl_3$), >99% *ee* for the (*S*,*S*)-diasteroisomer (diastereomeric ratio syn:anti 88:12).

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Dynamic reductive kinetic resolution of benzyl ketones using alcohol dehydrogenases and anion exchange resins

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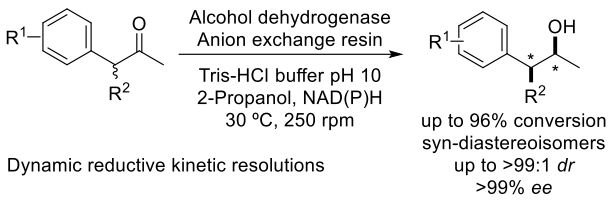
Daniel Méndez-Sánchez, Juan Mangas-Sánchez, Eduardo Busto, Vicente Gotor and Vicente Gotor-Fernández*



Dynamic reductive kinetic resolutions