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Chemoenzymatic synthesis of chiral unsymmetrical benzoin esters

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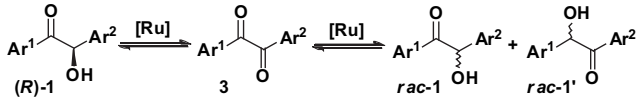
ABSTRACT

A chemoenzymatic Dynamic Kinetic Resolution (DKR) of unsymmetrical benzoins ($Ar^1 \neq Ar^2$) has been carried out, by using *Pseudomonas stutzeri* lipase stereorecognition pattern. After studying this lipase behaviour, a high preference towards acylation of those benzoins containing substituents in the phenyl ring rather than in the benzoyl moiety was observed. This fact allowed the development of the DKR process of this kind of substrates, avoiding the accumulation of secondary products derived from the in situ racemization mediated by Shvo's catalyst action, and allowing the synthesis of enantiopure unsymmetrical benzoins acetates (not previously described) in very good yields (60–95%) and excellent enantiomeric excess values (always >99%).

1. Introduction

Enantiomerically pure benzoins (1,2-diaryl-2-hydroxyethanone structures) are important building blocks in organic and pharmaceutical chemistry due to their wide versatility.[1] These compounds are involved in the synthesis of many natural products, drugs and heterocycles.[2–6] Different chemical strategies, as well as biomimetic organocatalytic routes and biocatalytic methodologies, have been developed for the synthesis of these kind of compounds,[1] such as the asymmetric carboligation of aromatic aldehydes catalyzed by thiamine diphosphate (ThDP) enzymes,[7,8] the asymmetric microbial monoreduction of the correspondent diketone,[9–11] or the dynamic kinetic resolution (DKR) of racemic mixtures.[12,13] However, only scarce examples can be found in literature describing the synthesis of chiral unsymmetrical benzoins (also called *crossed* benzoins), containing two different aromatic moieties at both sides of the acyloin core, generally obtained via a crossed condensation of different aromatic aldehydes. Linghu et al. obtained chiral silyl-ether protected benzoin adducts in a metallophosphites-catalyzed asymmetric crossed benzoin reaction;[14] Blay et al. described the synthesis of enantioenriched unsymmetrical benzoins from (*S*)-mandelic acid enolate and aromatic aldehydes[15] and Dünkelman et al. carried out the first enzyme catalyzed asymmetric crossed benzoin condensation.[16]

In the last decade, lipase-transition metal combo-catalyzed DKR of secondary alcohols has become a very useful tool for the production of pure enantiomers.[17–19] By using this approach, a lipase-catalyzed enantioselective transesterification is combined in situ with the action of a metal catalyst (commonly ruthenium catalyst), which racemizes the starting material. However this methodology has not been applied to the resolution of unsymmetrical benzoins, as the formation of an intermediate diketone, mediated by the oxidizing action of the ruthenium catalyst, would furnish the rearrangement of the substrate, so that two possible compounds could be obtained (Scheme 1).



Scheme 1. Possible mixture of racemic compounds produced by the action of a ruthenium catalyst over a chiral unsymmetrical benzoin.

To avoid this drawback, DKRs of other type of α-hydroxyketones have been carried out by masking the carbonyl group with other functionalities.[20] These tricky alternatives cannot be applied to benzoins, because of the great size of the substrates, which would be too bulky for common lipases recognition. In fact, during the synthesis of unsymmetrical benzoins, an intermediate containing the carbonyl group protected by a dithiane function was synthesized (**5**, Scheme 2). If racemic **5** could be resolved by the lipase, in a further step the enantiopure dithiane so obtained could be

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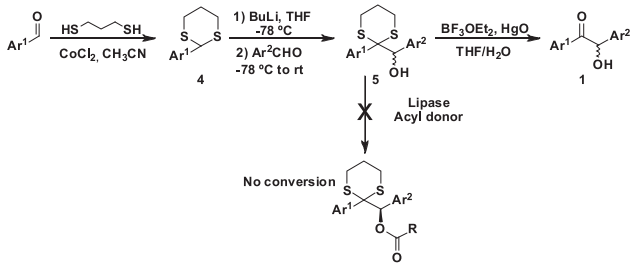
hydrolyzed, affording the desired chiral acylated α-hydroxyketone. Thus, (*rac*)-**5** was tested as substrate of the lipase transesterification process, but no conversion was detected in the enzymatic reaction.

In this work we present the application of a lipase-Shvo's catalyst mediated DKR of unsymmetrical benzoins, based on the study of the lipase stereorecognition. To the best of our knowledge, Lipase TL® (lipase from *Pseudomonas stutzeri*) is the only lipase able to carry out the kinetic resolution of benzoins by a transesterification process, reaching maximum conversions and enantiomeric excesses.[3,12,21]



Scheme 2. Synthesis of unsymmetrical benzoins.

Although the broad substrate specificity of lipases is well known and their use is widespread in asymmetric synthesis,[22,23] the knowledge of the factors, which determine the stereospecificity is still limited. In the case of *P. stutzeri* lipase, at present only experimental data can contribute to elucidate its selectivity towards benzoin type compounds, because the 3D structure of this lipase is not known. According to the *S*-stereobias described for this lipase upon benzoin acylation[3,12,21] the keto group of benzoins could influence the lipase–substrate recognition (as suggested previously by Bäckvall's group for other racemic hydroxyketones resolved by lipase B from *Candida antarctica*[24,25]), forcing the benzoyl residue (larger than phenyl) to be placed in the medium-size recognition pocket of the enzyme, in an apparent contradiction with the well known Kazlauskas' rule.[26] Thus, according to this empirical rule, the increase of the size of the substituent at the phenyl ring at other side of the carbinol (Ar^2 in *rac*-**1**, Scheme 1), theoretically recognized in the large stereospecific pocket, would improve the enantioselectivity of the reaction and the lipase could differ between compounds *rac*-**1** and *rac*-**1′** (Scheme 1). In this way, Lipase TL® should show higher preference towards the stereoselective esterification of those benzoins containing no substituents at the aromatic ring of the benzoyl moiety (Ar^1 in *rac*-**1**, Scheme 1).

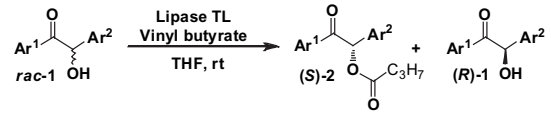
2. Results and discussion

To verify our theory, several racemic unsymmetrical benzoins were synthesized following the methodology shown in Scheme 2. Benzaldehyde and other different substituted aromatic aldehydes were coupled, to afford the substrates required for studying Lipase TL® catalytic behaviour (Table 1).

Substrates **1a**–**d** were chosen because of the different size of the substituent at the aromatic rings, in order to study the ability of the lipase to distinguish between a benzoin and its 'crossed analogue' (**1a**,**b** and **1c**,**d**). Rotticci et al. described that steric interactions are not the only important factors in lipase–substrate recognition, but others (such as the presence of halogen atoms) can also modify lipase selectivity.[27] Thus, substrates **1e**–**h** were also included in these experiments.

The enzymatic kinetic resolution of compounds **1a**–**h** was carried out in THF at room temperature, employing vinyl butyrate as acyl donor and the reaction progress was monitored by HPLC in order to calculate the initial rate of the enzymatic process.

Table 1
Kinetic resolution (KR) of unsymmetrical benzoins[a]



1a: Ar^1= Phenyl; Ar^2= *p*-Isopropylphenyl
1b: Ar^1= *p*-Isopropylphenyl; Ar^2= Phenyl
1c: Ar^1= Phenyl; Ar^2= *p*-Ethoxyphenyl
1d: Ar^1= *p*-Ethoxyphenyl; Ar^2= Phenyl
1e: Ar^1= Phenyl; Ar^2= *p*-Chlorophenyl
1f: Ar^1= *p*-Chlorophenyl; Ar^2= Phenyl
1g: Ar^1= Phenyl; Ar^2= 3,4-Dichlorophenyl
1h: Ar^1= 3,4-Dichlorophenyl; Ar^2= Phenyl

Substrate	Conv. (%) 4 h	Conv. (%) 24 h	ee_p (%)	V_0 (μmol prod./min)
1a	>49	>49	>99	$(5.7\pm0.8)10^{-1}$
1b	15	40	>99	$(4.6\pm0.9)10^{-2}$
1c	47	>49	>99	$(3.5\pm0.1)10^{-1}$
1d	25	>49	>99	$(9.0\pm0.5)10^{-2}$
1e	45	>49	>99	$(3.5\pm0.1)10^{-1}$
1f	30	>49	>99	$(1.70\pm0.1)10^{-1}$
1g	>49	>49	>99	$(5.5\pm0.5)10^{-1}$
1h	>49	>49	>99	$(4.6\pm0.1)10^{-1}$

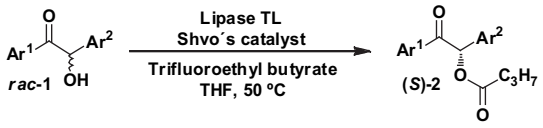
[a] Reaction conditions: 0.1 mmol of substrate, 20 mg of Lipase TL®, 0.6 mmol of vinyl butyrate in 1 mL of THF at room temperature. Different samples were taken in order to monitor the reaction by HPLC analysis.

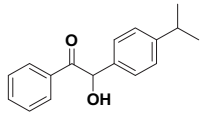
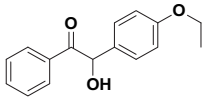
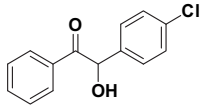
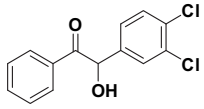
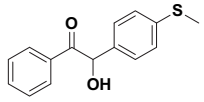
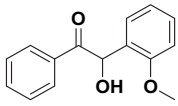
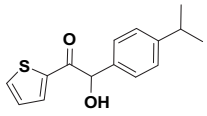
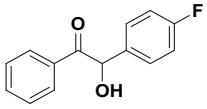
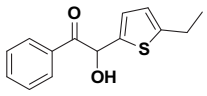
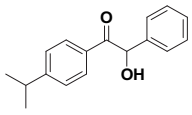
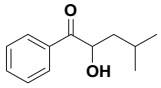
As can be seen in Table 1, although in most cases maximum conversions were reached after 24 h, the initial rate of the transesterification process highly decreased if the substituents were placed on the benzoyl moiety, especially in the case of the bulkier groups (**1a**,**b** comparison and **1c**,**d** comparison). V_0 was higher if the chlorine-substituted ring was located adjacent to the hydroxyl function, but this effect was not that appreciable. Furthermore, the incorporation of two atoms of chlorine on any phenyl ring seemed to favour lipase activity, independently of their placement at the benzoyl or the phenyl moieties. In all cases high conversions and excellent enantiomeric excess values were obtained, and in this way enantiomerically pure butyrated products were easily isolated and purified by silica column chromatography and the optical rotations were measured. The absolute configurations were assigned to be *S* according to a correlation of the positive optical rotations values of these compounds with data from literature.[12,28]

These results are in accordance with the thesis exposed above: Lipase TL® can accommodate the benzoyl residue in the medium-size pocket, displaying higher catalytic activities if the substituted aromatic ring is that one closer to the hydroxyl function, as this will be placed in the large pocket.

On the basis of these observations, we decided to carry out the DKR of **1a** (Table 2, entry 1), employing similar reaction conditions to those previously described by our group.[12] We had previously studied the combination of the Shvo's catalyst and lipase from *P. stutzeri* in the resolution of symmetrical benzoins, developing a three-step DKR in order to avoid lipase deactivation at 50 °C. Thus, in a sequential process, a first rapid KR of (*R*,*S*)-**1a** was performed in 1 h at 50 °C, until approximately 30% conversion was reached. Then, the mixture was filtered and the THF and the remnant acyl donor were evaporated. It is well known that the acetaldehyde produced from vinyl esters during the KR can interfere with the ruthenium catalyst action. Thus, vinyl butyrate was replaced by another acyl donor, trifluoroethyl butyrate, which would not hamper the racemization catalysis, although the transesterification process would be slower. The solid (a mixture of remnant **1a** and (*S*)-**2a**) was redissolved in freshly distilled THF and the DKR was started by addition of a new amount of fresh lipase, Shvo's catalyst and trifluoroethyl butyrate as acyl donor. After 24 h at 50 °C complete conversion was reached, and only optically active (*S*)-**2a** and traces of the correspondent dicarbonyl intermediate were detected by

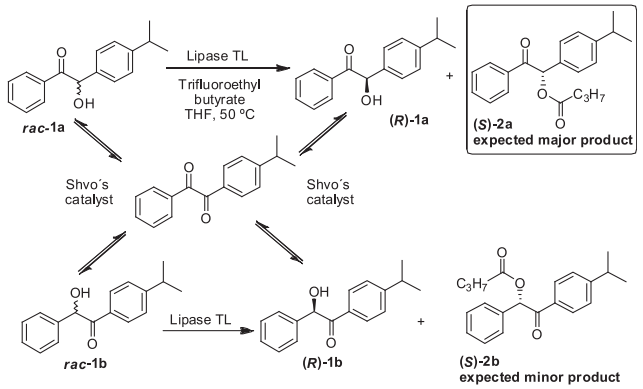
Table 2
Chemoenzymatic DKR of different unsymmetrical benzoins[a]



Entry	Substrate		Conversion[b] (%)	Product ee[b] (%)
1	**1a**		94	(*S*)-**2a** >99
2	**1c**		95	(*S*)-**2c** >99
3	**1e**		79	(*S*)-**2e** >99
4	**1g**		56	(*S*)-**2g** >99
5	**1i**		63	(*S*)-**2i** >99
6	**1j**		61	(*S*)-**2j** >99
7	**1k**		93	(*S*)-**2k** >99
8	**1l**		80	(*S*)-**2l** >99
9	**1m**		89	(*R*)-**2m** >99
10	**1b**		50	(*S*)-**2b**[c] >99
11	**1n**		94	(*S*)-**2n** >99

[a] Reaction conditions: first KR step: 0.2 mmol of substrate, Lipase TL (10 mg/mL) and 1.2 mmol of vinyl butyrate in 2 mL THF at 50 °C. Second DKR step: product of first step and remnant substrate, Lipase TL (20 mg/mL), 0.005 mmol of Shvo's catalyst and 1.2 mmol of trifluoroethyl butyrate in THF at 50 °C under argon.
[b] Determined by HPLC equipped with a chiral column (Chiralcel OD-H or Chiralpak AD).
[c] Traces of product (*S*)-**2a** were also detected.

HPLC analysis. Although during the process compound **1b** could be formed because of the ruthenium catalyst action, lipase preference regarding (*S*)-**1a** would displace the reaction equilibrium towards the acylation of this enantiomer (Scheme 3).



Scheme 3. Dynamic kinetic resolution process.

To study the scope of the reaction, different unsymmetrical benzoins were resolved under the same conditions described above (Table 2), leading to the desired butyrates in excellent optical purity in each case. DKR products were purified and, based on the data from the optical rotation measurements, absolute configurations were assigned to be *S*, with the exception of the product (*R*)-**2m** (Table 2, entry 9). The stereorecognition is similar to the other substrates, but the absolute configuration differs because of the priority of the sulfur atom.

In the case of substrates **1c**, **k** and **m** (Table 2, entries 2, 7 and 9), as well as for **1a**, high conversions and enantiomeric excesses were achieved. As expected, these results show a clear preference of Lipase TL® towards compounds containing the substituent in the phenyl moiety rather than in the benzoyl one, as no traces of the butyrates of the 'opposite unsymmetrical' benzoins were detected.

Monohalogenated substrates (**1e** and **l**, Table 2, entries 3 and 8, respectively) led to only moderate conversions, although excellent enantiomeric excess values were maintained. In both cases the correspondent butyrates (*S*)-**2e** and (*S*)-**2l** were detected, but a great amount of the dicarbonyl intermediate was accumulated in the medium. However, conversion achieved from the dihalogenated substrate **1g** (Table 2, entry 4) was considerably low, and not only the desired butyrate (*S*)-**2g** was detected in 56%, but also 5% of the crossed analogue butyrate (*S*)-**2h** could be found, as well as a great amount of the dicarbonyl intermediate. As we have observed before, this lipase displays similar activity towards the transesterification of compounds **1g** and **h** (Table 1). As this last compound can be also formed during the DKR process, the presence of the butyrated product (*S*)-**2h** could be also expected.

Different attempts to increase the moderate yields reached with substrates **1i** and **j** (Table 2, entries 5 and 6) were carried out, such as the addition of an extra amount of fresh lipase, although only small improvements were obtained. The methylthio substituent (**1i**) and the change in the substitution position from *para*- to *ortho*-methoxy may interfere in the lipase–substrate recognition.

In order to verify the resolution of compounds containing a substituted benzoyl moiety, the DKR of substrate **1b** was tested (Table 2, entry 10). The first KR was stopped after 4 h and then the ruthenium catalyst, as well as fresh lipase, THF and trifluoroethyl butyrate were added. In this case, after 24 h, just near 50% conversion had been reached. Compound *rac*-**1b** was accumulated in the medium, showing that the Shvo's catalyst was working properly but the lipase action was considerably lower than in the other cases. Furthermore, traces of *rac*-**1a** were also detected, as well as the corresponding acylated product (*S*)-**2a**.

As a last attempt to study the applicability of this process, a similar acyloin, synthesized from benzaldehyde and an aliphatic aldehyde, was included in our investigation (compound **1n**, Table 2, entry 11). Firstly the KR of **1n** was carried out, reaching conversion higher than 49% in 18 h at room temperature. After having checked that it was possible to resolve this racemic mixture employing Lipase TL® as biocatalyst, **1n** was employed as substrate of the DKR, following the same methodology employed before. In this case, although it was necessary to increase the reaction time until 48 h, only the ester formed by the transesterification of the hydroxyl group closer to the isobutyl group was detected, reaching 94% conversion and 99% enantiomeric excess.

3. Conclusion

In summary, optically pure unsymmetrical benzoins esters have been obtained through a chemoenzymatic DKR process, taking into account the lipase–substrate recognition. The lipase would accommodate the benzoyl moiety in the medium-size pocket; thus, the increase of the dimensions difference of the substituents at both sides of the hydroxyl group, by the introduction of a bulky substituent on the aryl moiety next to the alcohol function, enhances the lipase preference towards these last substrates, allowing the synthesis of chiral unsymmetrical benzoin esters in high yields and enantiomeric purity.

4. Experimental section

4.1. General

Lipase from *P. stutzeri* (Lipase TL®) was purchased from Meito and Sangyo. Shvo's catalyst was purchased from Strem Chemicals. All other reagents were obtained from Sigma–Aldrich and used as received. NMR spectra were recorded on a Bruker AC-250. Chemical shifts (δ) are reported in parts per million (ppm) relative to $CHCl_3$ (^{1}H: δ 7.27 ppm) and $CDCl_3$ (^{13}C: δ 77.0 ppm). All enzymatic reactions were monitored by HPLC (Chiralcel OD-H; Chiralpak AD) employing the previously prepared racemic alcohols and esters as references. Column chromatography purifications were conducted on silica gel 60 (40–63 μm). TLC was carried out on aluminium sheets precoated with silica gel; the spots were visualized under UV light (λ=254 nm).

4.2. Typical procedure for benzoins synthesis: synthesis of 1-(4-ethoxyphenyl)-2-hydroxy-2-phenylethanone [(*R*,*S*)-1d]

*4.2.1. Synthesis of 2-(4-ethoxyphenyl)-1,3-dithiane (**4a**)*[29]. 4-Ethoxybenzaldehyde (695 μL, 5 mmol) was dissolved in acetonitrile (15 mL) and 1,3-propanedithiol (602 μL, 6 mmol) and $CoCl_2$ (30 mg, 0.23 mmol) were added to the flask. The mixture was stirred at room temperature and after 15 h the solvent was evaporated under reduced pressure and the product was purified by column chromatography on silica gel (CH_2Cl_2) yielding 1.130 g (4.7 mmol) of a white solid (94% yield). Anal. Calcd for $C_{12}H_{16}OS_2$: C, 59.96; H, 6.71; S, 26.68. Found: C, 59.90; H, 6.67; S, 26.58. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.33 (t, 3H, *J*=7.05 Hz), 1.73–1.94 (m, 1H), 2.07–2.15 (m, 1H), 2.73–3.08 (m, 4H), 3.94 (c, 2H, *J*=7.05 Hz), 5.06 (s, 1H), 6.77 (d, 2H, *J*=8.02 Hz), 7.31 (d, 2H, *J*=8.02 Hz). ^{13}C NMR (63 MHz, $CDCl_3$): δ 14.8, 25.0, 32.2, 50.7, 63.4, 114.6, 128.8, 131.0, 158.9.

*4.2.2. Synthesis of 2-(4-isopropylphenyl)-1,3-dithiane (**4b**).* White solid (1.110 g, 93% yield). Anal. Calcd for $C_{13}H_{18}S_2$: C, 65.49; H, 7.61; S, 26.90. Found: C, 65.35; H, 7.58; S, 26.85. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.26 (d, 6H, *J*=6.95 Hz), 1.86–2.06 (m, 1H), 2.13–2.26 (m, 1H), 2.82–3.18 (m, 5H), 5.18 (s, 1H), 7.22 (d, 2H, *J*=8.22 Hz), 7.41 (d,

2H, J=8.22 Hz). ^{13}C NMR (63 MHz, $CDCl_3$): δ 23.8, 25.1, 32.1, 33.8, 51.2, 126.7, 127.6, 136.3, 149.1.

*4.2.3. Synthesis of 2-(4-chlorophenyl)-1,3-dithiane (**4c**).* White solid (1.095 g, 95% yield). Anal. Calcd for $C_{10}H_{11}ClS_2$: C, 52.04; H, 4.80; S, 27.79. Found: C, 51.95; H, 4.78; S, 27.70. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.75–1.93 (m, 1H), 2.05–2.19 (m, 1H), 2.79–3.06 (m, 4H), 5.05 (s, 41H), 7.21–7.27 (m, 2H), 7.31–7.38 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.9, 31.9, 50.5, 128.9, 129.1, 134.1, 137.6.

*4.2.4. Synthesis of 2-(3,4-dichlorophenyl)-1,3-dithiane (**4d**).* White solid (1.260 g, 95% yield). Anal. Calcd for $C_{10}H_{10}Cl_2S_2$: C, 45.29; H, 3.80; S, 24.18. Found: C, 45.22; H, 3.81; S, 24.15. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.84–2.04 (m, 1H), 2.12–2.28 (m, 1H), 2.87–3.16 (m, 4H), 5.12 (s, 1H), 7.31–7.37 (m, 1H), 7.41–7.46 (m, 1H), 7.61 (d, 1H, J=2.11 Hz). ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.8, 31.8, 49.9, 127.2, 129.9, 130.6, 132.4, 132.7, 139.2.

*4.2.5. Synthesis of 2-(thiophen-2-yl)-1,3-dithiane (**4e**).* White solid (930 mg, 92% yield). Anal. Calcd for $C_8H_{10}S_3$: C, 47.48; H, 4.98; S, 47.54. Found: C, 47.30; H, 4.96; S, 47.45. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.79–1.99 (m, 1H), 2.05–2.13 (m, 1H), 2.78–3.00 (m, 4H), 5.33 (s, 1H), 6.89 (dd, 1H, J=3.59, 5.16 Hz), 7.09 (dd, 1H, J=1.30, 3.59 Hz), 7.20 (dd, 1H, J=1.30, 5.16 Hz). ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.9, 30.9, 44.6, 125.6, 126.2, 126.7, 142.5.

*4.2.6. Synthesis of (2-(4-ethoxyphenyl)-1,3-dithian-2-yl)(phenyl) methanol [(R,S)-**5d**]*[9]. Compound **4a** (510 mg, 2.12 mmol) was dissolved in 5 mL of anhydrous THF and *n*-BuLi (1.39 mL, 2.22 mmol) was added drop wise. The mixture was stirred at −78 °C under argon during 1 h and then benzaldehyde (280 μL, 2.75 mmol) was added. The reaction was left to warm to room temperature and stirred for 5 h. The reaction was quenched by the addition of NH_4Cl 0.5 M (5 mL) and the organic phase was collected and dried over Na_2SO_4. The solution was filtered and the solvent evaporated. The product was purified by column chromatography (SiO_2, CH_2Cl_2), to afford (*R,S*)-**5d** as a white solid (550 mg. 1.59 mmol, 75% yield). Anal. Calcd for $C_{19}H_{22}O_2S_2$: C, 65.86; H, 6.40; S, 18.51. Found: C, 65.00; H, 6.05; S, 18.15. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.31 (t, 3H, J=7.02 Hz), 1.74–1.73 (m, 2H), 2.52–2.64 (m, 4H), 3.92 (c, 2H, J=7.02 Hz), 4.85 (s, 1H), 6.68 (d, 2H, J=8.89 Hz), 6.76 (d, 2H, J=9.08 Hz), 6.98–7.11 (m, 3H), 7.43 (d, 2H, J=8.89 Hz). ^{13}C NMR (63 MHz, $CDCl_3$): δ 15.2, 25.2, 27.3, 27.6, 63.8, 66.4, 81.5, 114.2, 126.3, 127.4, 128.4, 128.6, 128.8, 129.2, 132.3, 137.7, 158.7.

*4.2.7. Synthesis of (4-isopropylphenyl)(2-phenyl-1,3-dithian-2-yl) methanol [(R,S)-**5a**].* White solid (621 mg, 85% yield). Anal. Calcd for $C_{20}H_{24}OS_2$: C, 69.72; H, 7.02; S, 18.61. Found: C, 69.26; H, 6.25; S, 18.12. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.22(d, 6H, J=6.87 Hz), 1.88–2.00 (m, 2H), 2.65–2.76 (m, 4H), 2.78–2.92 (m, 1H), 5.00 (s, 1H), 6.82 (d, 2H, J=7.82 Hz), 7.03 (d, 2H, J=7.82 Hz), 7.30–7.38 (m, 3H), 7.68–7.78 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.3, 25.3, 27.5, 27.8, 34.3, 66.9, 81.5, 125.6, 127.8, 128.5, 129.0, 131.1, 135.0, 137.9, 149.4.

*4.2.8. Synthesis of (2-(4-isopropylphenyl)-1,3-dithian-2-yl)(phenyl) methanol [(R,S)-**5b**].* White solid (657 mg, 90% yield). Anal. Calcd for $C_{20}H_{24}OS_2$: C, 69.72; H, 7.02; S, 18.61. Found: C, 69.05; H, 6.10; S, 18.32. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.18 (d, 6H, J=6.85 Hz), 1.80–1.89 (m, 2H), 2.56–2.67 (m, 4H), 2.84 (h, 1H, J=6.85 Hz), 4.88 (s, 1H), 6.77–6.84 (m, 2H), 6.95–7.15 (m, 5H), 7.50 (d, 2H, J=8.92 Hz). ^{13}C NMR (63 MHz, $CDCl_3$): δ 23.9, 24.0, 24.8, 26.9, 27.2, 33.5, 77.1, 81.0, 126.2, 126.9, 127.5, 128.0, 128.1, 128.6, 130.3, 134.5, 137.3, 148.3.

*4.2.9. Synthesis of (4-ethoxyphenyl)(2-phenyl-1,3-dithian-2-yl) methanol [(R,S)-**5c**].* White solid (683 mg, 93% yield). Anal. Calcd for $C_{19}H_{22}O_2S_2$: C, 65.86; H, 6.40; S, 18.51. Found: C, 65.40; H, 6.18; S, 18.22. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.30 (t, 3H, J=7.03 Hz), 1.77–1.89 (m, 2H), 2.50–2.69 (m, 4H), 3.90 (q, 2H, J=7.03 Hz), 4.88 (s, 1H), 6.55–6.72 (m, 4H), 7.21–7.27 (m, 3H), 7.57–7.64 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 14.7, 24.7, 26.9, 27.2, 63.2, 66.5, 80.6, 112.9, 127.1, 128.1, 129.1, 129.2, 130.5, 137.3, 158.7.

*4.2.10. Synthesis of (4-chlorophenyl)(2-phenyl-1,3-dithian-2-yl) methanol [(R,S)-**5e**].* White solid (621 mg, 87% yield). Anal. Calcd for $C_{17}H_{17}ClOS_2$: C, 60.61; H, 5.09; S, 19.04. Found: C, 59.65; H, 4.75; S, 18.52. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.5 (s, 1H), 1.77–1.96 (m, 2H), 2.50–2.73 (m, 4H), 4.88 (s, 1H), 6.68–6.74 (m, 2H), 6.99–7.05 (m, 2H), 7.19–7.29 (m, 3H), 7.56–7.63 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.6, 26.8, 27.2, 75.6, 89.0, 127.1, 127.7, 128.3, 129.4, 130.3.

*4.2.11. Synthesis of (2-(4-chlorophenyl)-1,3-dithian-2-yl)(phenyl) methanol [(R,S)-**5f**].* White solid (644 mg, 90% yield). Anal. Calcd for $C_{17}H_{17}ClOS_2$: C, 60.61; H, 5.09; S, 19.04. Found: C, 59.80; H, 4.83; S, 18.76. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.51 (s, 1H), 1.80–1.90 (m, 2H), 2.44–2.72 (m, 4H), 4.92 (s, 1H), 6.77–6.83 (m, 2H), 7.04–7.21 (m, 5H), 7.53 (d, 2H, J=8.97 Hz). ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.6, 26.9, 27.1, 65.7, 80.9, 127.1, 128.1, 128.3, 132.2, 133.5, 135.9, 136.9.

*4.2.12. Synthesis of (3,4-dichlorophenyl)(2-phenyl-1,3-dithian-2-yl) methanol [(R,S)-**5g**].* White solid (684 mg, 87% yield). Anal. Calcd for $C_{17}H_{16}Cl_2OS_2$: C, 54.98; H, 4.34; S, 17.27. Found: C, 54.38; H, 4.10; S, 16.89. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.60 (s, 1H), 1.89–2.03 (m, 2H), 2.62–2.83 (m, 4H), 4.94 (s, 1H), 6.69 (dd, 1H, J=2.04, 8.32 Hz), 6.92 (d, 1H, J=2.04 Hz), 7.20 (d, 1H, J=8.32 Hz), 7.31–7.39 (m, 3H), 7.65–7.72 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.5, 26.8, 27.2, 66.1, 79.7, 127.4, 127.9, 128.4, 128.7, 130.1, 131.1, 136.9, 137.3.

*4.2.13. Synthesis of (2-(3,4-dichlorophenyl)-1,3-dithian-2-yl)(phenyl) methanol [(R,S)-**5h**].* White solid (660 mg, 84% yield). Anal. Calcd for $C_{17}H_{16}Cl_2OS_2$: C, 54.98; H, 4.34; S, 17.27. Found: C, 54.25; H, 4.05; S, 16.85. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.69 (s, 1H), 1.88–2.11 (m, 2H), 2.59–2.85 (m, 4H), 5.01 (s, 1H), 6.88–6.95 (m, 2H), 7,16–7.27 (m, 3H), 7.34–7.39 (m, 1H), 7.51 (dd, 1H, J=2.31, 8.56 Hz), 7.81 (d, 1H, J=2.31 Hz). ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.4, 26.9, 27.1, 65.1, 77.1, 127.2, 128.1, 128.5, 129.7, 130.3, 132.8.

*4.2.14. Synthesis of (4-(methylthio)phenyl)(2-phenyl-1,3-dithian-2-yl)methanol [(R,S)-**5i**].* White solid (628 mg, 85% yield). Anal. Calcd for $C_{18}H_{20}OS_3$: C, 62.03; H, 5.78; S, 27.60. Found: C, 61.65; H, 5.25; S, 27.15. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.68–1.78 (m, 2H), 2.23 (s, 3H), 2.23–2.60 (m, 4H), 4.76 (s, 1H), 6.57 (d, 2H, J=8.2 Hz), 6.82 (d, 2H, J=8.2 Hz), 7.08–7.16 (m, 3H), 7.46–7.52 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 15.5, 24.7, 26.9, 27.2, 66.4, 80.6, 124.8, 127.6, 128.2, 128.5, 130.5, 133.9, 137.2, 138.3.

*4.2.15. Synthesis of (2-methoxyphenyl)(2-phenyl-1,3-dithian-2-yl) methanol [(R,S)-**5j**].* White solid (640 mg, 90% yield). Anal. Calcd for $C_{18}H_{20}O_2S_2$: C, 65.02; H, 6.06; S, 19.29. Found: C, 64.54; H, 5.65; S, 18.90. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.86–2.04 (m, 2H), 2.52–2.85 (m, 4H), 3.29 (s, 3H), 5.32 (s, 1H), 6.65 (d, 1H, J=8.29 Hz), 6.84–6.90 (m, 1H), 7.09–7.13 (m, 1H), 7.19–7.34 (m, 4H), 7.74–7.78 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.8, 26.9, 27.2, 54.7, 66.7, 78.6, 109.9, 119.5, 127.0, 127.8, 129.1, 130.2, 130.7, 137.6, 157.1.

*4.2.16. Synthesis of (4-isopropylphenyl)(2-(thiophen-2-yl)-1,3-dithian-2-yl)methanol [(R,S)-**5k**].* White solid (608 mg, 82% yield). Anal. Calcd for $C_{18}H_{22}OS_3$: C, 61.67; H, 6.33; S, 27.44. Found: C, 60.95; H, 5.94; S, 26.87. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.13 (d, 6H, J=6.93 Hz), 1.74–1.97 (m, 2H), 2.65–3.06 (m, 5H), 4.90 (s, 1H), 6.84–6.90 (m, 4H), 7.24 (dd, 1H, J=1.58, 0.73 Hz). ^{13}C NMR (63 MHz,

$CDCl_3$): δ 23.8, 24.6, 27.3, 27.5, 33.6, 62.0, 81.4, 125.2, 127.0, 127.4, 127.7, 130.0, 134.5, 148.9.

*4.2.17. Synthesis of (4-fluorophenyl)(2-phenyl-1,3-dithian-2-yl) methanol [(R,S)-**5l**].* White solid (625 mg, 92% yield). Anal. Calcd for $C_{17}H_{17}FOS_2$: C, 63.72; H, 5.35; S, 20.01. Found: C, 63.15; H, 5.05; S, 19.70. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.65 (s, 1H), 1.94–2.06 (m, 2H), 2.63–2.90 (m, 4H), 5.04 (s, 1H), 6.84–6.92 (m, 4H), 7.31–7.43 (m, 3H), 7.68–7.77 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.6, 26.8, 27.2, 66.4, 80.3, 113.6, 114.0, 127.6, 128.2, 129.7, 129.8, 130.3, 137.2.

*4.2.18. Synthesis of (5-ethylthiophen-2-yl)(2-phenyl-1,3-dithian-2-yl)methanol [(R,S)-**5m**].* White solid (506 mg, 71% yield). Anal. Calcd for $C_{17}H_{20}OS_3$: C, 60.67; H, 5.99; S, 28.58. Found: C, 60.03; H, 5.15; S, 28.05. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.46 (t, 3H, *J*=6.95 Hz), 1.89–1.99 (m, 2H), 2.26 (s, 1H), 2.61–2.78 (m, 4H), 4.07 (c, 2H, *J*=6.95 Hz), 4.99 (s, 1H), 6.80–6.94 (m, 3H), 7.13–7.25 (m, 3H), 7.57–7.61 (m, 1H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 14.8, 24.8, 26.9, 27.2, 63.4, 66.0, 81.0, 113.8, 125.8, 126.9, 128.0, 128.2, 128.4, 128.8, 131.8, 137.3, 158.2.

*4.2.19. Synthesis of 3-methyl-1-(2-phenyl-1,3-dithian-2-yl)butan-1-ol [(R,S)-**5n**].* White solid (443 mg, 74% yield). Anal. Calcd for $C_{15}H_{22}OS_2$: C, 63.78; H, 7.85; S, 22.70. Found: C, 63.54; H, 7.50; S, 22.45. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.81 (d, 3H, *J*=6.61 Hz), 0.89 (d, 3H, *J*=6.69 Hz), 1.15–1.41 (m, 2H), 1.68–1.79 (m, 1H), 1.90–2.00 (m, 2H), 2.66–2.80 (m, 4H), 3.93 (dd, 1H, *J*=2.26, 10.03 Hz), 7.31–7.47 (m, 3H), 7.93–8.00 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 21.1, 23.7, 24.7, 25.0, 27.0, 27.2, 40.3, 65.9, 76.6, 127.3, 128.5, 129.9, 138.6.

*4.2.20. Synthesis of 1-(4-hydroxyphenyl)-2-hydroxy-2-phenylethanone [(R,S)-**1d**].* BF_3OEt_2 (389 μL, 3.1 mmol) was dissolved in 1 mL of THF/H_2O (85/15) and HgO (636 mg, 3.1 mmol) was added. This mixture was stirred at 0 °C for 5 min and a solution of **5d** (471 mg, 1.36 mmol) in 10 mL of THF/H_2O (85/15) was added. The reaction was stirred at room temperature under argon. After 5 h, 25 mL of CH_2Cl_2 were added and the solution was filtered and washed with brine. The organic phase was collected and dried over anhydrous Na_2SO_4. CH_2Cl_2 was filtered and evaporated under reduced pressure. The product was purified by column chromatography (SiO_2, CH_2Cl_2) affording 322 mg of a white solid (1.26 mmol, 93% yield). Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.72; H, 6.27. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.43 (t, 3H, *J*=6.97 Hz), 4.07 (c, 2H, *J*=6.97 Hz), 5.91 (s, 1H), 6.85–6.89 (m, 2H), 7.35–7.37 (m, 5H), 7.90–7.94 (d, 2H, *J*=6.34 Hz). ^{13}C NMR (63 MHz, $CDCl_3$): δ 14.5, 63.8, 75.7, 114.3, 125.9, 127.7, 128.4, 129.0, 131.6, 139.6, 163.5, 197.1.

*4.2.21. Synthesis of 2-hydroxy-2-(4-isopropylphenyl)-1-phenylethanone [(R,S)-**1a**].* White solid (330 mg, 94% yield). Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.19; H, 7.14. HPLC analysis (*n*-hexane/2-propanol, 90/10; flow 1 mL/min; Chiralcel OD-H): retention time: (*S*)-**1a**=6.25 min; (*R*)-**1a**=7.58 min. UV analysis: λ_{max}=246 nm. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.18 (d, 6H, *J*=6.94 Hz), 2.77–2.93 (m, 1H), 3.58 (s, 1H), 5.94 (s, 1H), 7.15–7.25 (m, 3H), 7.34–7.43 (m, 2H), 7.47–7.56 (m, 1H), 7.87–8.01 (m, 3H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.2, 34.5, 76.6, 127.7, 128.1, 129.1, 130.4, 134.3, 136.7, 150.3, 199.6.

*4.2.22. Synthesis of 2-hydroxy-1-(4-isopropylphenyl)-2-phenylethanone [(R,S)-**1b**].* White solid (305 mg, 87% yield). Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.21; H, 7.10. HPLC analysis (*n*-hexane/2-propanol, 90/10; flow 1 mL/min; Chiralcel OD-H): retention time: (*S*)-**1b**=6.39 min; (*R*)-**1b**=7.48 min. UV analysis: λ_{max}=258 nm. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.24 (d, 6H, *J*=6.95 Hz), 1.603 (s, 1H), 2.90 (sept, 1H, *J*=6.95 Hz), 6.00 (s, 1H), 7.21–7.43 (m, 7H), 7.86–7.94 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 23.5, 34.3, 76.0, 126.8, 127.7, 128.5, 129.1, 129.4, 131.1, 155.6, 193.0.

*4.2.23. Synthesis of 2-(4-ethoxyphenyl)-2-hydroxy-1-phenylethanone [(R,S)-**1c**].* White solid (336 mg, 96% yield). Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 73.78; H, 6.27. HPLC analysis (*n*-hexane/2-propanol, 90/10; flow 1 mL/min; Chiralcel OD-H): retention time: (*S*)-**1c**=8.18 min; (*R*)-**1c**=10.68 min. UV analysis: λ_{max}=231 nm, 248 nm. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.26 (t, 3H, *J*=7.10 Hz), 3.20 (s, 1H), 3.90 (q, 2H, *J*=7.10 Hz), 5.83 (s, 1H), 6.75 (d, 2H, *J*=8.69 Hz), 7.16 (d, 2H, *J*=8.69 Hz), 7.28–7.34 (m, 2H), 7.39–7.47 (m, 1H), 7.76–7.89 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 15.1, 63.8, 76.1, 115.4, 129.0, 129.5, 129.6, 131.4, 133.9, 134.2, 159.5, 199.4.

*4.2.24. Synthesis of 2-(4-chlorophenyl)-2-hydroxy-1-phenylethanone [(R,S)-**1e**].* White solid (303 mg, 90% yield). Anal. Calcd for $C_{14}H_{11}ClO_2$: C, 68.16; H, 4.49. Found: C, 67.94; H, 4.47. HPLC analysis (*n*-hexane/2-propanol, 90/10; flow 1 mL/min; Chiralcel OD-H): retention time: (*S*)-**1e**=6.74 min; (*R*)-**1e**=8.47 min. UV analysis: λ_{max}=247 nm. ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.86 (s, 1H), 7.17–7.25 (m, 4H), 7.31–7.40 (m, 2H), 7.44–7.51 (m, 1H), 7.79–7.88 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 75.8, 129.2, 129.5, 129.7, 133.6, 134.6, 134.9, 137.9, 199.0.

*4.2.25. Synthesis of 1-(4-chlorophenyl)-2-hydroxy-2-phenylethanone [(R,S)-**1f**].* White solid (325 mg, 96% yield). Anal. Calcd for $C_{14}H_{11}ClO_2$: C, 68.16; H, 4.49. Found: C, 68.05; H, 4.48. HPLC analysis (*n*-hexane/2-propanol, 90/10; flow 1 mL/min; Chiralcel OD-H): retention time: (*S*)-**1f**=8.10 min; (*R*)-**1f**=9.14 min. UV analysis: λ_{max}=258 nm. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.92 (s, 1H, OH), 5.93 (s, 1H), 7.27–7.42 (m, 7H), 7.85–7.90 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 76.2, 127.7, 128.7, 129.0, 129.2, 130.4, 138.2, 140.4, 197.5.

*4.2.26. Synthesis of 2-(3,4-dichlorophenyl)-2-hydroxy-1-phenylethanone [(R,S)-**1g**].* White solid (350 mg, 91% yield). Anal. Calcd for $C_{14}H_{10}Cl_2O_2$: C, 59.81; H, 3.59. Found: C, 59.75; H, 3.57. HPLC analysis (*n*-hexane/2-propanol, 90/10; flow 1 mL/min; Chiralcel OD-H): retention time: (*S*)-**1g**=6.78 min; (*R*)-**1g**=8.71 min. UV analysis: λ_{max}=248 nm. ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.94 (s, 1H), 7.16–7.19 (m, 1H), 7.38–7.50 (m, 4H), 7.57–7.65 (m, 1H), 7.90–7.95 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 74.8, 126.9, 129.0, 129.6, 131.0, 132.8, 132.9, 133.2, 134.4, 139.0, 198.0.

*4.2.27. Synthesis of 1-(3,4-dichlorophenyl)-2-hydroxy-2-phenylethanone [(R,S)-**1h**].* White solid (340 mg, 89% yield). Anal. Calcd for $C_{14}H_{10}Cl_2O_2$: C, 59.81; H, 3.59. Found: C, 59.70; H, 3.60. HPLC analysis (*n*-hexane/2-propanol, 90/10; flow 1 mL/min; Chiralcel OD-H): retention time: (*S*)-**1h**=8.48 min; (*R*)-**1h**=9.68 min. UV analysis: λ_{max}=258 nm. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.63 (s, 1H), 5.80 (s, 1H), 7.21–7.32 (m, 5H), 7.39 (d, 1H, *J*=8.48 Hz), 7.62 (dd, 1H, *J*=2.03, 8.48 Hz), 7.94 (d, 1H, *J*=2.03 Hz) ^{13}C NMR (63 MHz, $CDCl_3$): δ 76.9, 127.7, 127.9, 128.9, 129.3, 130.8, 130.9, 132.9, 133.5, 138.1, 138.5, 196.9.

*4.2.28. Synthesis of 2-hydroxy-2-(4-methylthiophenyl)-1-phenylethanone [(R,S)-**1i**].* White solid (340 mg, 96% yield). Anal. Calcd for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46; S, 12.41. Found: C, 69.68; H, 5.43; S, 12.37. HPLC analysis (*n*-hexane/2-propanol, 90/10; flow 1 mL/min; Chiralcel OD-H): retention time: (*S*)-**1i**=8.15 min; (*R*)-**1i**=10.15 min. UV analysis: λ_{max}=249 nm. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.36 (s, 3H), 4.45 (d, 1H, *J*=5.63 Hz), 5.84 (d, 1H, *J*=5.63 Hz), 7.06–7.21 (m, 4H), 7.28–7.38 (m, 2H), 7.41–7.51 (m, 1H), 7.79–7.86 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 15.8, 76.1, 127.2, 128.6, 129.1, 129.5, 133.8, 134.4, 136.0, 139.7, 199.2.

*4.2.29. Synthesis of 2-hydroxy-2-(2-methoxyphenyl)-1-phenylethanone [(R,S)-**1j**].* White solid (303, 92% yield). Anal.

Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.25; H, 5.80. HPLC analysis (*n*-hexane/2-propanol, 90/10; flow 1 mL/min; Chiralpak AD): retention time: (*S*)-**1j**=23.94 min; (*R*)-**1j**=26.47 min. UV analysis: λ_{max}=246 nm. ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.13 (s, 1H), 3.73 (s, 3H), 6.13 (s, 1H), 6.73–6.81 (m, 2H), 7.03–7.16 (m, 2H), 7.20–7.26 (m, 2H), 7.32–7.40 (m, 1H), 7.78–7.85 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 56.0, 71.3, 111.9, 121.6, 128.1, 128.9, 129.1, 129.5, 130.4, 134.0, 134.1, 156.9, 199.8.

*4.2.30. Synthesis of 2-hydroxy-2-(4-isopropylphenyl)-1-(thiophen-2-yl)ethanone [(R,S)-**1k**].* White solid (315 mg, 89% yield). Anal. Calcd for $C_{15}H_{16}O_2S$: C, 69.20; H, 6.19; S, 12.32. Found: C, 69.09; H, 6.17; S, 12.28. HPLC analysis (*n*-hexane/2-propanol, 90/10; flow 1 mL/min; Chiralcel OD-H): retention time: (*S*)-**1k**=7.57 min; (*R*)-**1k**=8.88 min. UV analysis: λ_{max}=264 nm, 280 nm. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.24 (d, 6H, *J*=0.83 Hz), 1.61 (s, 1H), 2.91 (sept, 1H, *J*=0.83 Hz), 5.76 (s, 1H), 7.07–7.11 (m, 1H), 7.22–7.35 (m, 5H), 7.66–7.68 (m, 1H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 23.8, 33.8, 76.7, 127.2, 127.7, 128.2, 134.0, 134.8, 136.5, 139.6, 149.6, 191.6.

*4.2.31. Synthesis of 2-(4-fluorophenyl)-2-hydroxy-1-phenylethanone [(R,S)-**1l**].* White solid (305 mg, 97% yield). Anal. Calcd for $C_{14}H_{11}FO_2$: C, 73.03; H, 4.82. Found: C, 72.91; H, 4.83. HPLC analysis (*n*-hexane/2-propanol, 90/10; flow 1 mL/min; Chiralcel OD-H): retention time: (*S*)-**1l**=6.93 min; (*R*)-**1l**=8.83 min. UV analysis: λ_{max}=247 nm. ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.71 (s, 1H), 5.99 (s, 1H), 6.99–7.09 (m, 2H), 7.26–7.38 (m, 2H), 7.40–7.51 (m, 2H), 7.53–7.63 (m, 1H), 7.88–7.97 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 75.3, 128.7, 129.3, 133.1, 134.1, 134.5, 137.4, 198.8.

*4.2.32. Synthesis of 2-(5-ethylthiophen-2-yl)-2-hydroxy-1-phenylethanone [(R,S)-**1m**].* White solid (290 mg, 86% yield). Anal. Calcd for $C_{14}H_{14}O_2S$: C, 68.26; H, 5.73; S, 13.02. Found: C, 68.15; H, 5.70; S, 12.98. HPLC analysis (*n*-hexane/2-propanol, 90/10; flow 1 mL/min; Chiralcel OD-H): retention time: (*R*)-**1m**=9.82 min; (*S*)-**1m**=13.81 min. UV analysis: λ_{max}=245 nm. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.27 (t, 3H, *J*=7.44 Hz), 2.80 (c, 2H, *J*=7.44 Hz), 6.17 (s, 1H), 6.62 (d, 1H, *J*=3.44 Hz), 6.81 (d, 1H, *J*=3.44 Hz), 7.45–7.51 (m, 2H), 7.58–7.65 (m, 1H), 7.99–8.04 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 15.6, 23.4, 70.8, 123.4, 126.5, 129.2, 133.3, 134.0, 138.8, 149.1, 197.3.

*4.2.33. Synthesis of 2-hydroxy-4-methyl-1-phenylpentan-1-one [(R,S)-**1n**].* White solid (220 mg, 83% yield). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39; S, 16.64. Found: C, 74.79; H, 8.26; S, 16.48. HPLC analysis (*n*-hexane/2-propanol, 90/10; flow 1 mL/min; Chiralcel OD-H): retention time: (*S*)-**1m**=5.43 min; (*R*)-**1m**=7.78 min. UV analysis: λ_{max}=243 nm. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.95 (d, 3H, *J*=6.60 Hz), 1.11 (d, 3H, *J*=6.60 Hz), 1.34–1.66 (m, 2H), 1.94–2.20 (m, 1H), 3.15 (s, 1H), 5.14 (dd, 1H, *J*=2.48, 10.18 Hz), 7.46–7.58 (m, 2H), 7.60–7.71 (m, 1H), 7.86–7.99 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 21.7, 24.0, 25.5, 45.5, 72.1, 128.9, 129.3, 133.9, 134.3, 202.9.

4.3. Typical procedure for benzoins kinetic resolution (KR)

Substrate (0.2 mmol) was dissolved in 2 mL of freshly distilled THF. Lipase TL® (40 mg) and vinyl butyrate (152 μL, 1.2 mmol) were added and the reaction was stirred at room temperature under argon. The reaction progress was monitored by HPLC and after reaching maximum conversion the transesterification process was stopped by filtering the reaction medium. THF was evaporated and the products were purified by column chromatography. The following compounds were isolated and characterized through this methodology.

*4.3.1. (S)-2-(4-Isopropylphenyl)-2-oxo-1-phenylethyl butyrate [(S)-(**2b**)].* White solid (30 mg, 46% yield). Anal. Calcd for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.62; H, 7.21. HPLC analysis (*n*-hexane/2-propanol, 90/10; flow 1 mL/min; Chiralcel OD-H): retention time: (*S*)-**2b**=4.85 min; UV analysis: λ_{max}=256 nm. $[\alpha]_D^{20}$ +118.3 (*c* 1.03, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.89 (t, 3H, *J*=7.35 Hz), 1.14 (d, 6H, *J*=6.92 Hz), 1.63 (sext, 2H, *J*=7.35 Hz), 2.26–2.50 (m, 2H), 2.75–2.93 (m, 1H), 6.71 (s, 1H), 7.16 (s, 1H), 7.23–7.29 (m, 3H), 7.38–7.46 (m, 3H), 7.81 (d, 2H, *J*=8.32 Hz). ^{13}C NMR (63 MHz, $CDCl_3$): δ 13.6, 18.3, 23.5, 30.9, 34.2, 35.8, 76.4, 124.7, 125.6, 126.7, 128.6, 129.0, 129.1, 132.3, 133.9, 155.0, 173.1, 193.3.

*4.3.2. (S)-2-(4-Ethoxyphenyl)-2-oxo-1-phenylethyl butyrate [(S)-(**2d**)].* White solid (30 mg, 47% yield). Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.46; H, 6.78. HPLC analysis (*n*-hexane/2-propanol, 90/10; flow 1 mL/min; Chiralcel OD-H): retention time: (*S*)-**2d**=5.26 min; UV analysis: λ_{max}=256 nm. $[\alpha]_D^{20}$ +124.9 (*c* 0.8, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.99 (t, 3H, *J*=7.41 Hz), 1.42 (t, 3H, *J*=6.97 Hz), 1.73 (sext, 2H, *J*=7.41 Hz), 2.36–2.58 (m, 2H), 4.07 (q, 2H, *J*=6.97 Hz), 6.84–6.87 (m, 2H), 6.89 (s, 1H), 7.33–7.41 (m, 3H), 7.45–7.52 (m, 2H), 7.91–7.98 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 13.5, 14.5, 18.3, 35.8, 63.6, 76.9, 114.1, 127.1, 128.4, 128.9, 129.0, 131.0, 134.1, 163.0, 173.0, 192.1.

*4.3.3. (S)-2-(4-Chlorophenyl)-2-oxo-1-phenylethyl butyrate [(S)-(**2f**)].* White solid (30 mg, 47% yield). Anal. Calcd for $C_{18}H_{17}ClO_3$: C, 68.25; H, 5.41. Found: C, 68.10; H, 5.39. HPLC analysis (*n*-hexane/2-propanol, 90/10; flow 1 mL/min; Chiralcel OD-H): retention time: (*S*)-**2f**=5.20 min; UV analysis: λ_{max}=255 nm. $[\alpha]_D^{20}$ +116.8 (*c* 1.06, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.90 (t, 3H, *J*=7.11 Hz), 1.66 (sext, 2H, *J*=7.11 Hz), 2.22–2.50 (m, 2H), 6.71 (s, 1H), 7.24–7.41 (m, 7H), 7.80 (d, 2H, *J*=8.86 Hz). ^{13}C NMR (63 MHz, $CDCl_3$): δ 13.6, 18.3, 35.8, 76.4, 128.5, 128.9, 129.1, 129.4, 130.1, 132.9, 133.3, 139.9, 173.1, 192.8.

*4.3.4. (S)-1-(3,4-Dichlorophenyl)-2-oxo-2-phenylethyl butyrate [(S)-(**2g**)].* White solid (33 mg, 47% yield). Anal. Calcd for $C_{18}H_{16}Cl_2O_3$: C, 61.55; H, 4.59. Found: C, 61.34; H, 4.58. HPLC analysis (*n*-hexane/2-propanol, 90/10; flow 1 mL/min; Chiralcel OD-H): retention time: (*S*)-**2g**=5.54 min; UV analysis: λ_{max}=243 nm. $[\alpha]_D^{20}$ +102.4 (*c* 0.96, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.99 (t, 3H, *J*=7.27 Hz), 1.73 (sext, 2H, *J*=7.27 Hz), 2.36–2.57 (m, 2H), 6.82 (s, 1H), 7.29–7.34 (m, 1H), 7.40–7.51 (m, 3H), 7.54–7.64 (m, 2H), 7.90–7.99 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 13.6, 18.3, 35.8, 76.4, 115.9, 116.3, 128.4, 128.9, 129.5, 130.1, 130.4, 130.5, 131.4, 133.5, 134.5, 173.1, 193.8.

*4.3.5. (S)-2-(3,4-Dichlorophenyl)-2-oxo-1-phenylethyl butyrate [(S)-(**2h**)].* White solid (33 mg, 47% yield). Anal. Calcd for $C_{18}H_{16}Cl_2O_3$: C, 61.55; H, 4.59. Found: C, 61.40; H, 4.60. HPLC analysis (*n*-hexane/2-propanol, 90/10; flow 1 mL/min; Chiralcel OD-H): retention time: (*S*)-**2h**=5.23 min; UV analysis: λ_{max}=256 nm. $[\alpha]_D^{20}$ +92.0 (*c* 0.7, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.90 (t, 3H, *J*=7.37 Hz), 1.56–1.71 (m, 2H), 2.25–2.49 (m, 2H), 6.66 (s, 1H), 7.25–7.43 (m, 6H), 7.66 (dd, 1H, *J*=2.06, 8.36 Hz), 7.94 (d, 1H, *J*=2.06 Hz). ^{13}C NMR (63 MHz, $CDCl_3$): δ 13.5, 18.3, 35.7, 76.5, 127.6, 128.5, 129.3, 129.6, 130.7, 132.8, 133.4, 134.1, 138.0, 173.2, 191.9.

4.4. Typical procedure for benzoins dynamic kinetic resolution (DKR)

The substrate (2 mmol) was dissolved in 2 mL of THF and 40 mg of Lipase TL® and vinyl butyrate (152 μL, 1.2 mmol) were added. The mixture was stirred at 50 °C under argon. The reaction progress was followed by HPLC and the mixture was filtered after reaching 40% conversion. Then THF and the remnant acyl donor were evaporated under vacuum. Shvo's catalyst (6 mg), a new amount of Lipase TL

(40 mg) and freshly distilled THF were added. The reaction was restarted by addition of trifluoroethyl butyrate (180 μL, 1.2 mmol) and it was stirred at 50 °C under argon for 24 h. The following compounds were isolated and characterized through this methodology.

*4.4.1. (S)-1-(4-Isopropylphenyl)-2-oxo-2-phenylethyl butyrate [(S)-(**2a**)].* White solid (59 mg, 90% yield). Anal. Calcd for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.45; H, 7.43. HPLC analysis (*n*-hexane/2-propanol, 90/10; flow 1 mL/min; Chiralcel OD-H): retention time: (*S*)-**2a**=5.33 min; UV analysis: λ_{max}=243 nm. $[\alpha]_D^{20}$ +132.9 (*c* 0.7, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.90 (t, 3H, *J*=7.32 Hz), 1.13 (d, 6H, *J*=6.94 Hz), 1.53–1.71 (m, 2H), 2.24–2.48 (m, 2H), 2.71–2.93 (m, 1H), 6.76 (s, 1H), 7.06–7.56 (m, 7H), 7.80–8.01 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 13.6, 18.3, 23.7, 33.8, 35.8, 77.2, 127.2, 128.5, 128.6, 128.8, 130.8, 133.3, 134.7, 150.1, 173.3, 194.0.

*4.4.2. (S)-1-(4-Ethoxyphenyl)-2-oxo-2-phenylethyl butyrate [(S)-(**2c**)].* White solid (60 mg, 92% yield). Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.35; H, 6.71. HPLC analysis (*n*-hexane/2-propanol, 90/10; flow 1 mL/min; Chiralcel OD-H): retention time: (*S*)-**2c**=5.32 min; UV analysis: λ_{max}=244 nm. $[\alpha]_D^{20}$ +149.1 (*c* 0.9, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.98 (t, 3H, *J*=7.20 Hz), 1.39 (t, 3H, *J*=6.86 Hz), 1.72 (sext, 2H, *J*=7.20 Hz), 2.34–2.56 (m, 2H), 4.00 (q, 2H, *J*=6.86 Hz), 6.82–6.91(m, 3H), 7.34–7.44 (m, 4H), 7.46–7.56 (m, 1H), 7.90–7.97 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 13.6, 14.7, 18.3, 35.9, 63.8, 77.2, 115.8, 125.4, 128.5, 128.7, 130.1, 133.2, 134.7, 159.7, 173.3, 194.0.

*4.4.3. (S)-1-(4-Chlorophenyl)-2-oxo-2-phenylethyl butyrate [(S)-(**2e**)].* White solid (46 mg, 73% yield). Anal. Calcd for $C_{18}H_{17}ClO_3$: C, 68.25; H, 5.41. Found: C, 68.04; H, 5.42. HPLC analysis (*n*-hexane/2-propanol, 90/10; flow 1 mL/min; Chiralcel OD-H): retention time: (*S*)-**2e**=5.55 min; UV analysis: λ_{max}=243 nm. $[\alpha]_D^{20}$ +132.7 (*c* 0.9, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.90 (t, 3H, *J*=7.22 Hz), 1.56–1.71 (m, 2H), 2.30–2.47 (m, 2H), 6.76 (s, 1H), 7.22–7.40 (m, 6H), 7.42–7.48 (m, 1H), 7.84 (dd, 2H, *J*=1.41, 8.10 Hz). ^{13}C NMR (63 MHz, $CDCl_3$): δ 13.5, 18.1, 35.7, 77.2, 128.4, 128.7, 128.9, 129.3, 129.8, 130.1, 131.4, 132.1, 133.6, 134.4, 135.3, 173.0, 193.6.

*4.4.4. (S)-1-(4-(Methylthio)phenyl)-2-oxo-2-phenylethyl butyrate [(S)-(**2i**)].* White solid (40 mg, 61% yield). Anal. Calcd for $C_{19}H_{20}O_3S$: C, 69.48; H, 6.14; S, 9.76. Found: C, 69.28; H, 6.05; S, 9.73. HPLC analysis (*n*-hexane/2-propanol, 90/10; flow 1 mL/min; Chiralcel OD-H): retention time: (*S*)-**2i**=5.91 min; UV analysis: λ_{max}=246 nm. $[\alpha]_D^{20}$ +173.5 (*c* 1.59, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.90 (t, 3H, *J*=7.36 Hz), 1.62 (sext, 2H, *J*=7.36 Hz), 2.24–2.46 (m, 5H), 6.75 (s, 1H), 7.10–7.19 (m, 1H), 7.26–7.47 (m, 6H), 7.81–7.88 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 13.6, 15.2, 18.3, 35.9, 76.9, 124.3, 126.4, 129.4, 129.9, 133.4, 134.5, 140.3, 173.8, 193.7.

*4.4.5. (S)-1-(2-Methoxyphenyl)-2-oxo-2-phenylethyl butyrate [(S)-(**2j**)].* White solid (37 mg, 59% yield). Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 72.76; H, 5.47. HPLC analysis (*n*-hexane/2-propanol, 90/10; flow 1 mL/min; Chiralpak AD): retention time: (*S*)-**2j**=11.78 min; UV analysis: λ_{max}=243 nm. $[\alpha]_D^{20}$ +138.9 (*c* 1.56, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.01 (t, 3H, *J*=7.39 Hz), 1.75 (sext, 2H, *J*=7.39 Hz), 2.35–2.57 (m, 2H), 3.93 (s, 3H), 6.91–7.00 (m, 2H), 7.30–7.45 (m, 4H), 7.46–7.57 (m, 1H), 7.96–8.04 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 13.5, 18.3, 35.8, 55.5, 70.8, 111.1, 122.1, 128.3, 128.5, 129.7, 130.6, 133.2, 134.5, 156.4, 173.2, 194.1.

*4.4.6. (S)-1-(4-Isopropylphenyl)-2-oxo-2-(thiophen-2-yl)ethyl butyrate [(S)-(**2k**)].* White solid (58 mg, 88% yield). Anal. Calcd for $C_{19}H_{22}O_3S$: C, 69.06; H, 6.71; S, 9.70. Found: C, 68.93; H, 6.70; S, 9.68. HPLC analysis (*n*-hexane/2-propanol, 90/10; flow 1 mL/min; Chiralcel OD-H): retention time: (*S*)-**2k**=5.56 min; UV analysis: λ_{max}=264 nm, 280 nm. $[\alpha]_D^{20}$ +138.6 (*c* 0.69, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.99 (t, 3H, *J*=7.40 Hz), 1.24 (d, 6H, *J*=6.95 Hz), 1.73 (sext, 2H, *J*=7.40 Hz), 2.25–2.52 (m, 2H), 2.90 (sept, 1H, *J*=6.95 Hz), 6.65 (s, 1H), 7.09 (dd, 1H, *J*=3.81, 4.90 Hz), 7.25 (d, 2H, *J*=8.13 Hz), 7.44 (d, 2H, *J*=8.13 Hz), 7.64 (dd, 1H, *J*=1.12, 4.90 Hz), 7.78 (dd, 1H, *J*=1.12, 3.81 Hz). ^{13}C NMR (63 MHz, $CDCl_3$): δ 13.3, 18.4, 23.8, 33.9, 35.9, 77.8, 127.2, 128.7, 131.0, 132.6, 134.1, 150.0, 172.3, 186.6.

*4.4.7. (S)-1-(4-Fluorophenyl)-2-oxo-2-phenylethyl butyrate [(S)-(**2l**)].* White solid (47 mg, 77% yield). Anal. Calcd for $C_{18}H_{17}FO_3$: C, 71.99; H, 5.71. Found: C, 71.83; H, 5.73. HPLC analysis (*n*-hexane/2-propanol, 90/10; flow 1 mL/min; Chiralcel OD-H): retention time: (*S*)-**2l**=5.33 min; UV analysis: λ_{max}=245 nm. $[\alpha]_D^{20}$ +118.0 (*c* 0.6, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.90 (t, 3H, *J*=7.15 Hz), 1.64 (sext, 2H, *J*=7.15 Hz), 2.27–2.45 (m, 2H), 6.77 (s, 1H), 6.94–7.03 (m, 2H), 7.28–7.43 (m, 5H), 7.83–7.87 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 13.6, 18.3, 35.8, 115.9, 116.3, 128.5, 128.7, 130.4, 130.6, 133.6, 134.5, 161.1, 172.9, 194.0.

*4.4.8. (R)-1-(5-Ethylthiophen-2-yl)-2-oxo-2-phenylethyl butyrate [(R)-(**2m**)].* White solid (54 mg, 85% yield). Anal. Calcd for $C_{18}H_{20}O_3S$: C, 68.33; H, 6.37; S, 10.13. Found: C, 68.24; H, 6.34; S, 10.10. HPLC analysis (*n*-hexane/2-propanol, 90/10; flow 1 mL/min; Chiralcel OD-H): retention time: (*R*)-**2m**=7.13 min; UV analysis: λ_{max}=242 nm. $[\alpha]_D^{20}$ +135.6 (*c* 0.92, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.01 (t, 3H, *J*=7.33 Hz), 1.30 (t, 3H, *J*=7.55 Hz), 1.64–1.84 (m, 2H), 2.37–2.60 (m, 2H), 2.77–2.92 (m, 2H), 6.69 (s, 1H), 6.96 (d, 1H, *J*=3.46 Hz), 7.06 (s, 1H), 7.40–7.68 (m, 3H), 8.01 (d, 2H, *J*=7.38 Hz). ^{13}C NMR (63 MHz, $CDCl_3$): δ 14.0, 16.0, 18.7, 36.2, 72.8, 124.0, 129.1, 129.3, 132.5, 134.0, 134.8, 151.2, 173.8, 193.3.

*4.4.9. (S)-4-Methyl-1-oxo-1-phenylpentan-2-yl butyrate [(S)-(**2n**)].* White solid (48 mg, 92% yield). Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.15; H, 8.34. HPLC analysis (*n*-hexane/2-propanol, 90/10; flow 1 mL/min; Chiralcel OD-H): retention time: (*S*)-**2n**=5.36 min; UV analysis: λ_{max}=241 nm. $[\alpha]_D^{20}$ +65.0 (*c* 0.35, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.90–1.19 (m, 9H), 1.54–1.95 (m, 5H), 2.44 (t, 2H, *J*=7.54 Hz), 5.96 (dd, 1H, *J*=3.14, 10.35 Hz), 7.37–7.71 (m, 3H), 7.97 (d, 2H, *J*=8.60 Hz). ^{13}C NMR (63 MHz, $CDCl_3$): δ 14.0, 18.8, 21.8, 23.6, 25.5, 36.3, 40.4, 74.1, 128.8, 129.2, 133.9, 135.1, 173.8, 197.5.

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Supplementary data

NMR data of compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.07.030.

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