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Synthesis of new (*R*)-secondary carbinols with different structures via enzymatic resolution

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ABSTRACT

The present study deals with the biocatalytic enantioselective synthesis of 19 new chiral alcohols with alkyl (C_{11}–C_{19}) and phenyl, substituted phenyl, heteroaromatic, and naphthyl groups **4a**–**4z** with an (*R*)-configuration and high enantiomeric excess (~100%). The corresponding ketones **1a**–**1z** were synthesized and then reduced with $NaBH_4$ to their racemic alcohols **2a**–**2z**, which were converted into their racemic acetyl derivatives **3a**–**3z**. Enzymes of four different types were used for the enantioselective hydrolysis of these acetyl compounds **3a**–**3z**. The optimal reaction conditions for these four enzymes were established by investigating the enantiomeric excesses by chiral HPLC. *Amano lipase from Burkholderica cepacia* (*Pseudomonas cepacia*) **AL-PS** was determined as the best enzyme in this work. This study presents an environmentally friendly and green chemistry method for the synthesis of these new (*R*)-chiral carbinols **4a**–**4z**.

1. Introduction

Enantiomerically pure or enriched carbinols are of very high importance as intermediates for the synthesis of a wide variety of targets, such as pharmaceuticals, pesticides, and so on. Therefore, a number of highly selective methods for their synthesis have been developed.[1–4]

Enzymes are widely recognized as being among the most active and selective catalysts for the preparation of optically active compounds,[5–8] because of their chemo-, regio-, stereoselective, and environmentally friendly features. The mild reaction conditions and the small number of side reactions make enzymatic processes more popular than non-enzymatic processes.

The enzymatic enantioselective hydrolysis of esters is a well-established technique for obtaining optically active alcohols and hydrolases are one of the classes of enzymes most used in asymmetric synthesis.[9–12] Therefore, ketones **1a**–**1z** were used as starting materials and then reduced by $NaBH_4$ to their racemic carbinols **2a**–**2z**, which were converted by acetic anhydride into their acetyl derivatives **3a**–**3z** (Scheme 1).

We envisioned that enzymatic hydrolysis of racemic acetyl carbinols with lipases might afford the desired enantiomerically pure secondary carbinols. However, the lack of literature information on the enzymatic hydrolysis of fatty acetyl carbinols prompted us to synthesise a series of 19 different chiral fatty alcohols **4a–4z**, and to screen them for selective hydrolysis with four different commercially available lipase enzymes. The new (*R*)-enantiomers of the 18 chiral alcohols were synthesized for the first time by the enzymatic method reported herein. The (*S*)-enantiomers of these alcohols were synthesized before via an asymmetric reduction method with chiral borane catalysts;[13] and **4a** has been synthesized as its (*R*)- and (*S*)-enantiomers;[14] **4s** as its (*S*)-enantiomer;[15] and **4t** as its (*S*)-enantiomer.[16]

These new (*R*)-alcohols **4a**–**4z** could be used as chiral starting materials for the synthesis of several natural bioactive compounds and as chiral auxiliaries and chiral ligands in asymmetric synthesis.

2. Results and discussion

Nineteen chiral alcohols with an (*R*)-configuration with alkyl (C_{11}–C_{19}) and phenyl, substituted phenyl, heteroaromatic, and naphthyl groups **4a**–**4z** were synthesized via the enzymatic resolution of their corresponding ketones **1a**–**1z**.

Several commercial lipases have an enantioselective hydrolyzing ability on acetyl compounds to synthesise chiral secondary alcohols in the water phase. The lipases used in this study are *Porcine pancreatic lipase*[17] **PPL**, *Lipase from Candida cylindracea*[18] **CCL**, *Lipase from Candida rugosa*[19] **CRL,** and *Amano lipase from Burkholderica cepacia* (*Pseudomonas cepacia*)[20] **AL-PS**.

To determine of the best chiral enzyme, acetyl carbinol **3c** was hydrolyzed by four lipases. The screening was performed by using the enzymes in a phosphate buffer at ambient temperature. Table 1 shows the results of the synthesis of 1-phenyl-1-tetradecanol **4c** under different reaction conditions and in appropriate pH values.

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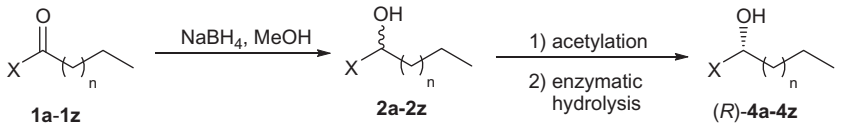


Ketone	Chiral Alcohol	X	n
1a	**4a**	Ph	9
1b	**4b**	Ph	10
1c	**4c**	Ph	11
1d	**4d**	Ph	12
1e	**4e**	Ph	13
1f	**4f**	Ph	16
1g	**4g**	Ph	17
1h	**4h**	*p*-Tolyl	10
1j	**4j**	*p*-$MeOC_6H_4$	11
1k	**4k**	*p*-BrC_6H_4	11
1m	**4m**	*p*-HOC_6H_4	11
1n	**4n**	2-Furyl	13
1p	**4p**	2-Thienyl	13
1r	**4r**	2-Naphthyl	10
1s	**4s**	Ph	*
1t	**4t**	Me	15
1x	**4x**	Et	13
1y	**4y**	*n*-Pr	11
1z	**4z**	*n*-Pr	15

* *p*-$C(CH_3)_3C_6H_4$

Scheme 1. Structures of the ketones and the enantioselective synthesis of the new (*R*)-alcohols.

The selectivities of the hydrolysis of **3c** with the lipases from **PPL**, **CRL,** and **CCL** were low. Conversely, better results were obtained for the hydrolysis of **3c** with the lipase from *Amano lipase from B. cepacia* **AL-PS**. Lipase **AL-PS** exhibited the best enantioselectivity and the highest activity with *E*-values of >400 (Table 1, entry 8).

Next, **AL-PS** was used as the hydrolysis agent in the enantioselective hydrolysis of the other acetyl carbinols **3a**–**3z** (Scheme 2). With the exception of **3m**, in which the phenyl and naphthyl derivatives were hydrolyzed with high selectivity by the lipase, heteroaryl derivatives **3n**–**3p** showed less selectivity. The results are summarized in Table 2.

Chiral alkyl aryl alcohols **4a**, **4b**, **4c**, **4e**, **4h**, **4j,** and **4r** were obtained with >99% ee and the *E*-values were >200. However, dialkyl carbinols **4t**–**4z** did not give better results compared to alkyl aryl carbinols. Among the dialkyl carbinols, **4x** showed the best *E*-value (104). All of these carbinols were formed with an (*R*)-configuration in high enantiomeric excess by the lipase-catalyzed enantioselective hydrolysis using **AL-PS** lipase (Scheme 2).

The absolute configuration of the novel chiral alcohols was assigned by comparing the sign of their specific rotations with the literature values of similar chiral alcohols (**4a–4g**,[14] **4h–4j**,[22] **4k–4m**,[23] **4n–4r**,[24] **4s,**[15] and **4t–4z**[25]).

The (*S*)-enantiomers of these chiral secondary carbinols were previously synthesized by us with chiral borane catalysts[13] in good yield and an average ee of 95%. With this enzymatic resolution, only the (*R*)-enantiomers were obtained with 15–49% yield and an average ee of 92%. However, this enzymatic method is a better alternative method than the chemical method because of the inexpensive and mild reaction conditions, in addition to being more environmentally friendly.

The ee values and the conversions of the new chiral alcohols **4a**–**4z** were determined by chiral HPLC and were analyzed by IR, NMR (^1H and ^{13}C), MS, elemental analysis and specific rotation values. The enantiomeric ratios (*E*) were calculated as: $\ln [1 - c(1 + ee_p)]/\ln [1 - c(1 - ee_p)]$.[21]

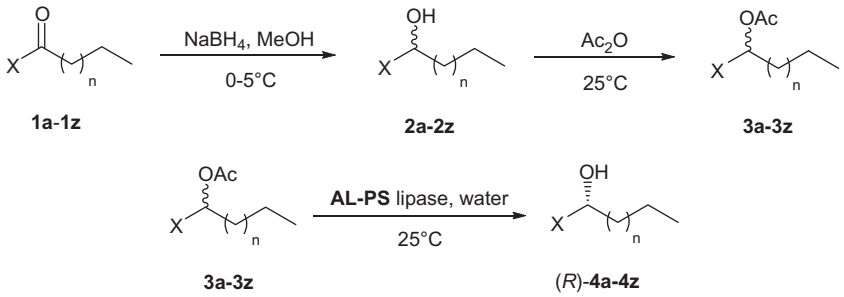
3. Conclusion

In conclusion, *Porcine pancreatic lipase* **PPL**, *lipase from C. cylindracea* (**CCL**), *lipase from C. rugosa* **CRL,** and *Amano lipase from B. cepacia* (*P. cepacia*) **AL-PS** have been used for the first time as resolution enzymes for the synthesis of the chiral carbinols **4a**–**4z**. The enzyme-catalyzed enantioselective hydrolysis of acetyl derivatives **3a**–**3z** was performed under different experimental

Table 1
Enantioselective hydrolysis of **3c** with four different lipases

Entry	Lipase	Stirring method	Time (days)	pH	Conversion[a] (%)	ee[a] (%)	Absolute configuration[b]	*E*[c]
1	**PPL**	Ultrasonic bath	8	7.6	5	91	(*R*)	22
2	**PPL**	Magnetic stirrer	10	7.6	0	—	—	0
3	**CCL**	Ultrasonic bath	4	8.0	1	77	(*R*)	8
4	**CCL**	Magnetic stirrer	6	8.0	20	81	(*R*)	12
5	**CRL**	Ultrasonic bath	4	7.7	0	—	—	0
6	**AL-PS**	Ultrasonic bath	4	6.8	10	70	(*R*)	6
7	**AL-PS**	Ultrasonic bath	4	7.2	35	96	(*R*)	83
8	**AL-PS**	Magnetic stirrer	4	7.2	45	>99	(*R*)	>400

[a] Determinated by HPLC on a chiral phase.
[b] The absolute configuration of the products was assigned by comparing the sign of their specific rotation with the literature value of similar chiral alcohols.[14]
[c] *E* = enantiomeric ratio calculated as previously reported.[21]



Scheme 2. Enantioselective synthesis of chiral alcohols **4a**–**4z** via enzymatic hydrolysis.

Table 2
Enzymatic asymmetric synthesis of secondary alcohols with **AL-PS** lipase

Entry	Product alcohol	Conversion[a] (%)	$[\alpha]_D^{25}$[b]	ee[a] (%)	Absolute configuration[c]	E[d]
1	**4a**	23	+31	>99	(*R*)	>200
2	**4b**	25	+36.6	>99	(*R*)	>200
3	**4c**	45	+42.6	>99	(*R*)	>400
4	**4d**	48	+18.9	>92	(*R*)	150
5	**4e**	15	+21.3	>99	(*R*)	>200
6	**4f**	10	+22	86	(*R*)	15
7	**4g**	20	+17.4	92	(*R*)	30
8	**4h**	20	+28.4	>99	(*R*)	>200
9	**4j**	32	+17.9	>99	(*R*)	>200
10	**4k**	32	+13.9	92	(*R*)	37
11	**4m**	60	+4.6	22	(*R*)	2
12	**4n**	32	+8.3	72	(*R*)	9
13	**4p**	19	+11.7	70	(*R*)	124
14	**4r**	32	+52.1	>99	(*R*)	>200
15	**4s**	30	+52.9	90	(*R*)	28
16	**4t**	48	−10	80	(*R*)	20
17	**4x**	52	−18	91	(*R*)	104
18	**4y**	45	−8	57	(*R*)	6
19	**4z**	48	−15	60	(*R*)	7

[a] Determinated by HPLC on a chiral phase.
[b] Specific rotations were measured in hexane for **4a**–**4g** or chloroform for **4h**–**4z**.
[c] The absolute configuration of the products was assigned by comparing of the sign of their specific rotation with the literature value of similar chiral alcohols (**4a–4g**,[14] **4h–4j**,[22] **4k–4m**,[23] **4n–4r**,[24] **4s**,[15] and **4t–4z**[25]).
[d] E = enantiomeric ratio calculated as previously reported.[21]

conditions. The best reaction media and the best enzyme were thus determined; perfect reactivity and enantioselectivity were observed for **AL-PS** (Table 1). One important advantage of the method is that the reaction can be performed in the water phase and so this method is more environmentally friendly than chemical processes. Lipase **AL-PS** can be used as a valuable catalyst for the resolution of 1-aryl-1-alkanols with linear alkyl chains. We have thus developed an environmentally friendly method for the synthesis of these new chiral carbinols **4a**–**4z**.

4. Experimental

4.1. General

The chemicals used in this work were commercially available from Merck or Aldrich. The prochiral ketones used as starting materials were synthesized by Friedel–Craft acylation.[26] The racemic alcohols were prepared by the reduction of the corresponding ketones with $NaBH_4$ in methanol–THF. The reactions were monitored by TLC using silica gel plates and the products were purified by flash column chromatography on silica gel (Merck; 230–400 mesh) with hexane–ethyl acetate. NMR spectra were recorded at 500 MHz for ^1H and 125 MHz for ^{13}C using Me4Si as the internal standard in $CDCl_3$. GC–MS were recorded on Shimadzu/QP2010 Plus. Optical rotations were measured with an Optical Activity AA-55 digital polarimeter at room temperature. IR spectra were recorded on a Mattson 1000. Melting points were determinated with a Bühi Melting Point B-540. Enantiomeric excesses (ee) of the chiral alcohols were determined with Shimadzu/DGU-20A_5 HPLC apparatus fitted with 25 cm Chiralcel OD and OD-H (Daicel) chiral columns.

4.2. General procedure for the enzymatic asymmetric synthesis of chiral alcohols

4.2.1. General procedure for the acetylation of the racemic alcohols

The acetylation of the racemic alcohols was performed with acetic anhydride using an acidic ion exchanger (Amberlist 15) at room temperature and stirred for 30 min. The crude acetates obtained were purified by column chromatography (*n*-hexane–EtOAc 8:2). The yields of the reactions were higher than 99.5%.

4.2.2. General procedure for the lipase-catalyzed hydrolysis of the acetyl compounds

The racemic acetyl compound (200 mg) was dissolved in acetone (5 mL) and then added to a phosphate buffer (25 mL, pH values were showed in Table 1) in a 50 mL round bottomed flask. To this reaction mixture was added the enzyme catalyst (100 mg) and the reaction flask was capped to prevent the loss of co-solvent due to evaporation. The reaction mixture was stirred at

25 °C. The progress of the reaction was monitored by TLC until no further change was detected (4–10 days). The products were isolated by extraction of the reaction mixture with ether. The hydrolyzed product (the secondary alcohol) and the acetyl derivative were separated by column chromatography (*n*-hexane–EtOAc 8:2).

4.3. Spectroscopic data of the chiral alcohols synthesized

4.3.1. (*R*)-1-Phenyl-1-dodecanol 4a

Mp 34.4–35.2 °C (lit.[14] mp 34.4–35.4 °C), $[\alpha]_D^{25} = +31$ (*c* 1.1, hexane) {lit.[14] $[\alpha]_D^{25} = +31$ (*c* 1.0, hexane)}, ee = >99%. HPLC analysis: Chiralcel OD chiral column, mobile phase *iso*-PrOH/hexane: 2/98, flow rate: 1.0 mL/min, wavelength: 210 nm; t_R (retention time): 9.924 min for the (*R*)-isomer, not observed (for racemic 10.338 min) for the (*S*)-isomer. IR (neat, cm^{-1}): 3400, 3023, 2930, 2853, 1623, 1469, 1407, 1315, 769, 707 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.80 (t, 3H, *J* = 6.3 Hz), 1.12–1.39 (m, 18H), 1.58–1.74 (m, 2H), 1.80 (br s, 1H), 4.58 (t, 1H, *J* = 6.3 Hz), 7.18–7.22 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.07, 23, 26, 28.80–30.01, 32.20, 38.6, 75.01, 126.00, 126.85, 128.90, 145.2. MS *m/z*: 41, 79, 91, 104, 107, 120, 133, 244, 260, 262 (M^+). Anal. Calcd for $C_{18}H_{30}O$: C, 82.38; H, 11.52. Found: C, 82.38; H, 11.19.

4.3.2. (*R*)-1-Phenyl-1-tridecanol 4b

Mp 28.2–29.3 °C, $[\alpha]_D^{25} = +36.6$ (*c* 1.1, hexane), ee = >99%. HPLC analysis: Chiralcel OD chiral column, mobile phase *iso*-PrOH/hexane: 2/98, flow rate: 1.0 mL/min, wavelength: 210 nm; t_R (retention time): 9.847 min for the (*R*)-isomer, not observed (for racemic 12.222 min) for the (*S*)-isomer. IR (neat, cm^{-1}): 3400, 3023, 2930, 2853, 1623, 1469, 1407, 1315, 1050, 779, 725 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.82 (t, 3H, *J* = 6.3 Hz), 1.22–1.27 (m, 20H), 1.62–1.71 (m, 2H), 1.80 (br s, 1H), 4.58 (t, 1H, *J* = 7.3 Hz), 7.28–7.39 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.30, 22.89, 26.05, 28.80–30.01, 32.20, 38.6, 75.01, 126.00, 126.85, 128.90, 145.2. MS *m/z*: 43, 55, 79, 91, 107, 120, 133, 258, 274, 276 (M^+). Anal. Calcd for $C_{19}H_{32}O$: C, 82.54; H, 11.66. Found: C, 82.54; H, 12.12.

4.3.3. (*R*)-1-Phenyl-1-tetradecanol 4c

Mp 52.8–53.2 °C, $[\alpha]_D^{25} = +42.6$ (*c* 1.1, hexane), ee = >99%. HPLC analysis: Chiralcel OD chiral column, mobile phase *iso*-PrOH/hexane: 2/98, flow rate: 1.0 mL/min, wavelength: 210 nm; t_R (retention time): 10.499 min for the (*R*)-isomer, not observed (for racemic 12.015 min) for the (*S*)-isomer. IR (neat, cm^{-1}): 3369, 3023, 2923, 2853, 1691, 1469, 1384, 1269, 1123, 1038, 738, 707 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.82 (t, 3H, *J* = 6.3 Hz), 1.14–1.40 (m, 22H), 1.62–1.78 (m, 2H), 1.50 (br s, 1H), 4.58 (t, 1H, *J* = 7.3 Hz), 7.18–7.30 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.20, 23.89, 26.05, 29.50–30.01, 32.20, 38.6, 75.01, 126.00, 126.85, 128.90, 145.2. MS *m/z*: 43, 57, 79, 91, 107, 120, 133, 272, 274, 288, 290 (M^+). Anal. Calcd for $C_{20}H_{34}O$: C, 82.69; H, 11.80. Found: C, 82.51; H, 11.57.

4.3.4. (*R*)-1-Phenyl-1-pentadecanol 4d

Mp 36.8–37.3 °C, $[\alpha]_D^{25} = +18.9$ (*c* 1.1, hexane), ee = 92%. HPLC analysis: Chiralcel OD chiral column, mobile phase *iso*-PrOH/hexane: 2/98, flow rate: 1.0 mL/min, wavelength: 210 nm; t_R (retention time): 9.305 min for the (*R*)-isomer, 11.463 min for the (*S*)-isomer. IR (neat, cm^{-1}): 3372, 3030, 2946, 2865, 1675, 1483, 1402, 1316, 1050, 779, 698 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.82 (t, 3H, *J* = 6.8 Hz), 1.12–1.29 (m, 24H), 1.62–1.70 (m, 2H), 1.85 (br s, 1H), 4.56 (t, 1H, *J* = 7.8 Hz), 7.16–7.27 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.31, 22.90, 26.05, 29.56–29.90, 32.14, 39.35, 74.94, 126.11, 127.69, 128.64, 145.19. MS *m/z*: 43, 69, 79, 91, 107, 120, 133, 286, 304, 305 (M^+). Anal. Calcd for $C_{21}H_{36}O$: C, 82.83; H, 11.92. Found: C, 82.99; H, 12.94.

4.3.5. (*R*)-1-Phenyl-1-hexadecanol 4e

Mp 60.5–61.2 °C, $[\alpha]_D^{25} = +21.3$ (*c* 1.1, hexane), ee = >99%. HPLC analysis: Chiralcel OD chiral column, mobile phase *iso*-PrOH/hexane: 2/98, flow rate: 1.0 mL/min, wavelength: 210 nm; t_R (retention time): 9.090 min for the (*R*)-isomer, not observed (for racemic 11.189 min) for the (*S*)-isomer. IR (neat, cm^{-1}): 3372, 3043, 2946, 2854, 1669, 1483, 1402, 1316, 1023, 779, 698 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.85 (t, 3H, *J* = 6.8 Hz), 1.12–1.30 (m, 26H), 1.72–1.82 (m, 2H), 1.95 (br s, 1H), 4.68 (t, 1H, *J* = 7.3 Hz), 7.28–7.36 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.31, 22.90, 26.05, 29.56–29.90, 32.14, 39.35, 74.94, 126.11, 127.69, 128.64, 145.19. MS *m/z*: 43, 55, 69, 79, 107, 120, 133, 207, 316, 318 (M^+). Anal. Calcd for $C_{22}H_{38}O$: C, 82.95; H, 12.03. Found: C, 82.84; H, 13.45.

4.3.6. (*R*)-1-Phenyl-1-nonadecanol 4f

Mp 50.5–51 °C, $[\alpha]_D^{25} = +22$ (*c* 1.1, hexane), ee = 86%. HPLC analysis: Chiralcel OD chiral column, mobile phase *iso*-PrOH/hexane: 2/98, flow rate: 1.0 mL/min, wavelength: 210 nm; t_R (retention time): 8.115 min for the (*R*)-isomer, 10.232 min for the (*S*)-isomer. IR (neat, cm^{-1}): 3407, 3025, 2947, 2861, 1686, 1483, 1409, 1325, 1077, 752, 698 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.80 (t, 3H, *J* = 6.8 Hz), 1.12–1.25 (m, 32H), 1.56–1.68 (m, 2H), 1.82 (br s, 1H), 4.60 (t, 1H, *J* = 7.3 Hz), 7.17–7.27 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.31, 22.90, 26.05, 29.57–30.01, 32.14, 39.35, 74.95, 126.11, 127.69, 128.64, 145.19. MS *m/z*: 43, 69, 79, 91, 107, 120, 147, 207, 342, 358 (M^+). Anal. Calcd for $C_{25}H_{44}O$: C, 82.26; H, 12.30. Found: C, 81.39; H, 12.82.

4.3.7. (*R*)-1-Phenyl-1-Eicosanol 4g

Mp 70.2–71 °C, $[\alpha]_D^{25} = +17.4$ (*c* 1.1, hexane), ee = 92%. HPLC analysis: Chiralcel OD chiral column, mobile phase *iso*-PrOH/hexane: 2/98, flow rate: 1.0 mL/min, wavelength: 210 nm; t_R (retention time): 7.957 min for the (*R*)-isomer, 10.034 min for the (*S*)-isomer. IR (neat, cm^{-1}): 3407, 3040, 2946, 2871, 1685, 1483, 1409, 1325, 1050, 752, 698 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.85 (t, 3H, *J* = 6.8 Hz), 1.15–1.30 (m, 34H), 1.44 (br s, 1H), 1.61–1.72 (m, 2H), 4.70 (t, 1H, *J* = 7.3 Hz), 7.27–7.37 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.31, 22.90, 26.05, 29.57–30.01, 32.14, 39.35, 74.94, 126.11, 127.69, 128.64, 145.19. MS *m/z*: 43, 57, 79, 91, 107, 120, 147, 207, 356, 374 (M^+). Anal. Calcd for $C_{26}H_{46}O$: C, 83.35; H, 12.66. Found: C, 83.19; H, 13.36.

4.3.8. (*R*)-1-(*p*-Methylphenyl)-1-tridecanol 4h

Mp 39.1–39.7 °C, $[\alpha]_D^{25} = +28.4$ (*c* 1.1, $CHCl_3$), ee = >99%. HPLC analysis: Chiralcel OD chiral column, mobile phase *iso*-PrOH/hexane: 1/99, flow rate: 1.0 mL/min, wavelength: 210 nm; t_R (retention time): 15.007 min for the (*R*)-isomer, not observed (for racemic 15.869 min) for the (*S*)-isomer. IR (neat, cm^{-1}): 3392, 3038, 2923, 2853, 1646, 1469, 1269, 1261, 1107, 1046, 823, 738 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.80 (t, 3H, *J* = 6.8 Hz), 1.14–1.40 (m, 20H), 1.50 (br s, 1H), 1.58–1.80 (m, 2H), 2.28 (s, 3H), 4.68 (t, 1H, *J* = 7.3 Hz), 7.09 (d, 2H, *J* = 7.8 Hz), 7.16 (d, 2H, *J* = 7.8 Hz). ^{13}C NMR ($CDCl_3$): δ 14.20, 21.30, 23.01, 26.20, 29.00–30.01, 32.20, 39.35, 74.80, 126.01, 129.69, 136.54, 142.19. MS *m/z*: 41, 57, 77, 93, 121, 131, 145, 272, 288, 290 (M^+). Anal. Calcd for $C_{20}H_{34}O$: C, 82.69; H, 11.80. Found: C, 82.41; H, 11.63.

4.3.9. (*R*)-1-(*p*-Methoxyphenyl)-1-tetradecanol 4j

Mp 44.9–45.4 °C, $[\alpha]_D^{25} = +17.9$ (*c* 1.1, $CHCl_3$), ee = >99%. HPLC analysis: Chiralcel OD chiral column, mobile phase *iso*-PrOH/hexane: 2/98, flow rate: 1.0 mL/min, wavelength: 210 nm; t_R (retention time): 14.250 min for the (*R*)-isomer, not observed (for racemic 15.277 min) for the (*S*)-isomer. IR (neat, cm^{-1}): 3307, 3069, 2923, 2853, 1623, 1461, 1307, 1253, 1107, 1046, 807, 723 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.82 (t, 3H, *J* = 6.3 Hz), 1.12–1.35 (m, 22H), 1.50 (br s, 1H), 1.58–1.75 (m, 2H), 3.72 (s, 3H), 4.55 (t,

1H, J = 6.8 Hz), 6.80 (dd, 2H, J_1 = 1.9, J_2 = 6.8 Hz), 7.16 (dd, 2H, J_1 = 1.9, J_2 = 6.8 Hz). ^{13}C NMR ($CDCl_3$): δ 14.40, 23.01, 26.20, 29.40–30.01, 32.20, 39.05, 55.03, 75.00, 114.01, 115.09, 125.54, 139.19, 159.20. MS *m/z*: 43, 44, 69, 94, 121, 137, 147, 320 (M^+), 321. Anal. Calcd for $C_{21}H_{36}O_2$: C, 78.70; H, 11.32. Found: C, 78.16; H, 10.97.

4.3.10. (*R*)-1-(*p*-Bromophenyl)-1-tetradecanol 4k

Mp 42.7–43.1 °C, $[\alpha]_D^{25} = +13.9$ (*c* 1.1, $CHCl_3$), ee = 92%. HPLC analysis: Chiralcel OD chiral column, mobile phase *iso*-PrOH/hexane: 2/98, flow rate: 1.0 mL/min, wavelength: 210 nm; t_R (retention time): 10.521 min for the (*R*)-isomer, 10.994 min for the (*S*)-isomer. IR (neat, cm^{-1}): 3353, 3069, 2923, 2846, 1600, 1476, 1353, 1223, 1130, 1076, 823, 723 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.80 (t, 3H, J = 6.8 Hz), 1.12–1.34 (m, 22H), 1.54–1.72 (m, 2H), 1.80 (br s, 1H), 4.53 (t, 1H, J = 7.3 Hz), 7.14 (dd, 2H, J_1 = 1.9, J_2 = 6.3 Hz), 7.39 (dd, 2H, J_1 = 1.9, J_2 = 6.3 Hz). ^{13}C NMR ($CDCl_3$): δ 14.50, 23.50, 26.20, 29.80–30.01, 32.20, 39.40, 74.00, 121.01, 127.90, 131.80, 144.19. MS *m/z*: 43, 55, 77, 106, 120, 157, 185, 368, 369 (M^+). Anal. Calcd for $C_{20}H_{33}BrO$: C, 65.03; H, 9.00. Found: C, 65.41; H, 9.09.

4.3.11. (*R*)-1-(*p*-Hydroxyphenyl)-1-tetradecanol 4m

Mp 66.2–67.1 °C, $[\alpha]_D^{25} = +4.6$ (*c* 1.1, $CHCl_3$), ee = 22%. HPLC analysis: Chiralcel OD chiral column, mobile phase *iso*-PrOH/hexane: 5/95, flow rate: 1.0 mL/min, wavelength: 210 nm; t_R (retention time): 20.772 min for the (*R*)-isomer, 23.017 min for the (*S*)-isomer. IR (neat, cm^{-1}): 3407, 3030, 2923, 2853, 1630, 1469, 1307, 1284, 1123, 1053, 807, 723 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.82 (t, 3H, J = 6.8 Hz), 1.12–1.34 (m, 22H), 1.49 (br s, 1H), 1.56–1.76 (m, 2H), 4.45 (t, 1H, J = 6.8 Hz), 4.70 (br s, 1H), 6.74 (dd, 2H, J_1 = 1.9, J_2 = 6.3 Hz), 7.18 (dd, 2H, J_1 = 1.9, J_2 = 6.3 Hz). ^{13}C NMR ($CDCl_3$): δ 15.00, 23.10, 26.00, 29.40–30.01, 31.20, 38.30, 73.50, 114.20, 126.20, 136.10, 154.19. MS *m/z*: 41, 65, 77, 95, 107, 123, 133, 305, 306 (M^+). Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18. Found: C, 78.22; H, 11.57.

4.3.12. (*R*)-1-(2-Furyl)-1-hexadecanol 4n

Mp 58.5–59.4 °C, $[\alpha]_D^{25} = +8.3$ (*c* 1.1, $CHCl_3$), ee = 72%. HPLC analysis: Chiralcel OD chiral column, mobile phase *iso*-PrOH/hexane: 1.5/98.5, flow rate: 1.0 mL/min, wavelength: 210 nm; t_R (retention time): 10.441 min for the (*R*)-isomer, 11.301 min for the (*S*)-isomer. IR (neat, cm^{-1}): 3346, 3023, 2923, 2853, 1607, 1476, 1276, 1153, 1107, 1046, 846, 753 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.82 (t, 3H, J = 6.8 Hz), 1.14–1.42 (m, 27H), 1.74–1.82 (m, 2H), 4.70 (t, 1H, J = 6.8 Hz), 6.15 (dd, 1H, J_1 = 0.9, J_2 = 3.4 Hz), 6.26 (dd, 1H, J_1 = 1.9, J_2 = 3.4 Hz), 7.30 (dd, 1H, J_1 = 0.9, J_2 = 1.9 Hz). ^{13}C NMR ($CDCl_3$): δ 14.25, 23.10, 25.90, 29.80–30.01, 32.10, 36.10, 68.00, 106.20, 111.01, 142.10, 157.20. MS *m/z*: 41, 69, 81, 97, 107, 121, 135, 290, 308 (M^+), 309. Anal. Calcd for $C_{20}H_{36}O_2$: C, 77.86; H, 11.76. Found: C, 77.01; H, 11.86.

4.3.13. (*R*)-1-(2-Thenyl)-1-hexadecanol 4p

Mp 44.9–45.4 °C, $[\alpha]_D^{25} = +11.7$ (*c* 1.1, $CHCl_3$), ee = 70%. HPLC analysis: Chiralcel OD chiral column, mobile phase *iso*-PrOH/hexane: 1.5/98.5, flow rate: 1.0 mL/min, wavelength: 210 nm; t_R (retention time): 13.557 min for the (*R*)-isomer, 15.578 min for the (*S*)-isomer. IR (neat, cm^{-1}): 3423, 3092, 2923, 2853, 1630, 1479, 1392, 1276, 1084, 1046, 800, 707 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.82 (t, 3H, J = 6.3 Hz), 1.12–1.42 (m, 26H), 1.48 (br s, 1H), 1.70–1.85 (m, 2H), 4.70 (t, 1H, J = 7.3 Hz), 6.88–6.92 (m, 2H), 7.16 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 14.20, 23.10, 25.90, 29.40–30.01, 32.20, 36.60, 74.20, 124.20, 125.50, 126.40, 147.20. MS *m/z*: 55, 79, 97, 113, 123, 139, 151, 281, 306, 324 (M^+). Anal. Calcd for $C_{20}H_{36}OS$: C, 74.01; H, 11.18; S, 9.88. Found: C, 75.32; H, 10.82; S, 7.83.

4.3.14. (*R*)-1-(Naphthlalen-2-yl)-1-tridecanol 4r

Mp 26–27 °C, $[\alpha]_D^{25} = +52.1$ (*c* 1.1, $CHCl_3$), ee = >99%. HPLC analysis: Chiralcel OD chiral column, mobile phase *iso*-PrOH/hexane: 10/90, flow rate: 1.0 mL/min, wavelength: 210 nm; t_R (retention time): not observed (for racemic 6.112 min) for the (*S*)-isomer, 10.069 min for the (*R*)-isomer. IR (neat, cm^{-1}): 3346, 3023, 2923, 2853, 1607, 1476, 1276, 1153, 1107, 1046, 846, 753 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.80 (t, 3H, J = 6.3 Hz), 1.14–1.54 (m, 21H), 1.70–1.92 (m, 2H), 4.75 (t, 1H, J = 6.8 Hz), 7.40–8.20 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 14.40, 23.10, 26.60, 29.80–30.01, 32.20, 38.80, 72.00, 123.00, 123.40, 125.10, 125.20, 126.20, 128.20, 129.20, 130.10, 134.10, 149.02. MS *m/z*: 43, 57, 77, 97, 115, 157, 181, 193, 221, 308, 326 (M^+). Anal. Calcd for $C_{23}H_{34}O$: C, 84.60; H, 10.50. Found: C, 84.52; H, 10.23.

4.3.15. (*R*)-(4-*t*-Butylphenyl)(phenyl)methanol 4s

Mp 79.7–80.5 °C, $[\alpha]_D^{25} = +52.9$ (*c* 1.1, $CHCl_3$), ee = 90%. HPLC analysis: Chiralcel OD chiral column, mobile phase *iso*-PrOH/hexane: 10/90, flow rate: 1.0 mL/min, wavelength: 210 nm; t_R (retention time): 8.807 min for the (*S*)-isomer, 9.884 min for the (*R*)-isomer. IR (neat, cm^{-1}): 3229, 3030, 2959, 2855, 1599, 1449, 1339, 1270, 1110, 1011, 755, 630 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.12 (s, 9H), 2.20 (br s, 1H), 5.70 (s, 1H), 7.10–7.40 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 32.14, 34.35, 76.04, 125.20, 126.50, 126.70, 127.50, 128.50, 141.00, 144.19, 150.80. MS *m/z*: 41, 51, 77, 91, 105, 119, 134, 183, 209, 225, 240 (M^+). Anal. Calcd for $C_{17}H_{20}O$: C, 84.96; H, 8.39. Found: C, 85.15; H, 8.12.

4.3.16. (*R*)-2-Nonadecanol 4t

Mp 53.2–53.9 °C, $[\alpha]_D^{25} = -10$ (*c* 0.97, $CHCl_3$) ee = 80%. HPLC analysis: The enantiomeric excess was determined by HPLC analysis using a chiral column after derivatization to the corresponding benzoate. Chiralcel OD-H chiral column, mobile phase *iso*-PrOH/hexane: 0.2/99.8, flow rate: 0.5 mL/min, wavelength: 230 nm; t_R (retention time): 10.158 min for the (*S*)-isomer, 10.783 min for the (*R*)-isomer. IR (neat, cm^{-1}): 3325, 2947, 1483, 1375, 1158, 806, 752 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.82 (t, 3H, J = 6.8 Hz), 1.12 (d, 3H, J = 5.8 Hz), 1.2 (m, 30H), 1.36 (m, 2H), 1.52 (s, 1H), 3.68 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 14.32, 22.91, 23.70, 25.99, 29.57, 29.82–29.91, 32.14, 39.62, 68.43. MS *m/z*: 43, 45, 57, 71, 97, 111, 125, 207. Anal. Calcd for $C_{19}H_{40}O$: C, 80.21; H, 14.17. Found: C, 79.63; H, 15.40.

4.3.17. (*R*)-3-Octadecanol 4x

Mp 45–47 °C, $[\alpha]_D^{25} = -18$ (*c* 0.95, $CHCl_3$), ee = 91%. HPLC analysis: The enantiomeric excess was determined by HPLC analysis using a chiral column after derivatization to the corresponding benzoate. Chiralcel OD-H chiral column, mobile phase *iso*-PrOH/hexane: 0.2/99.8, flow rate: 0.5 mL/min, wavelength: 230 nm; t_R (retention time): 10.523 min for the (*S*)-isomer, 11.030 min for the (*R*)-isomer. IR (neat, cm^{-1}): 3325, 2919, 1483, 1375, 1077, 806, 725 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.82 (t, 3H, J = 7.5 Hz), 0.86 (t, 3H, J = 7.1 Hz), 1.2 (m, 26H), 1.3 (m, 2H), 1.4 (m, 2H), 1.47 (s, 1H), 3.43 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 10.03, 14.31, 22.97, 25.88, 29.57, 29.84–30.37, 32.14, 37.21, 73.58. MS *m/z*: 43, 57, 69, 83, 97, 111, 125, 239, 252. Anal. Calcd for $C_{18}H_{38}O$: C, 79.93; H, 14.16. Found: C, 79.21; H, 14.12.

4.3.18. (*R*)-4-Heptadecanol 4y

Mp 44–45 °C, $[\alpha]_D^{25} = -8$ (*c* 0.85, $CHCl_3$), ee = 57%. HPLC analysis: The enantiomeric excess was determined by HPLC analysis using a chiral column after derivatization to the corresponding benzoate. Chiralcel OD-H chiral column, mobile phase *iso*-PrOH/hexane: 0.2/99.8, flow rate: 0.5 mL/min, wavelength: 230 nm; t_R (retention time): 10.154 min for the (*S*)-isomer, 10.845 min for the (*R*)-isomer. IR (neat, cm^{-1}): 3353, 2920, 1483, 1375, 1158, 1077, 860,

725 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.90 (t, 3H, J = 6.8 Hz), 0.96 (t, 3H, J = 6.8 Hz), 1.24–1.38 (m, 24H), 1.40–1.50 (m, 5H), 3.85 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 14.31, 14.33, 19.51, 22.90, 25.87, 29.57, 29.83–29.94, 32.14, 32.14, 37.75, 39.91, 71.98. MS *m/z*: 43, 55, 73, 83, 97, 111, 153, 166, 211, 238. Anal. Calcd for $C_{17}H_{34}O$: C, 79.61; H, 14.15. Found: C, 79.64; H, 15.47.

4.3.19. (*R*)-4-Henicosanol 4z

Mp 54–55 °C, $[\alpha]_D^{25} = -15$ (*c* 1.1, $CHCl_3$), ee = 60%. HPLC analysis: The enantiomeric excess was determined by HPLC analysis using a chiral column after derivatization to the corresponding benzoate. Chiralcel OD-H chiral column, mobile phase *iso*-PrOH/hexane: 0.2/99.8, flow rate: 0.5 mL/min, wavelength: 230 nm; t_R (retention time): 9.148 min for the (*S*)-isomer, 9.676 min for the (*R*)-isomer. IR (neat, cm^{-1}): 3355, 2924, 1483, 1357, 1157, 1079, 725 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.85 (t, 3H, J = 6.8 Hz), 0.91 (t, 3H, J = 6.8 Hz), 1.24–1.38 (m, 32H), 1.35–1.44 (m, 4H), 1.51 (s, 1H), 3.82 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 14.31, 14.33, 19.05, 22.90, 25.87, 29.58, 29.84–29.94, 32.14, 32.14, 37.75, 39.91, 71.97. MS *m/z*: 44, 55, 73, 83, 97, 111, 125, 207, 269. Anal. Calcd for $C_{21}H_{44}O$: C, 80.69; H, 14.19. Found: C, 80.64; H, 14.45.

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