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Kinetic resolution of tropic acid ethyl ester and its derivatives by lipase PS

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Abstract—The first kinetic resolution of tropic acid ethyl ester (TAEE) with lipase PS and vinyl acetate as an acylating agent is reported. The resulting (*S*)-(−)-3-acetoxy tropic acid ethyl ester and (*R*)-(+)-tropic acid ethyl ester are produced in high yields and in excellent ee (87–94%). The method has been extended to resolve a variety of tropic acid ester derivatives. In addition, an improved method for the preparation of racemic mixtures of tropic acid ethyl ester and its derivatives from 3-hydroxy-2-phenyl-acrylic acid ethyl ester using $NaBH_4$ in methanol is reported. This procedure is better than the previous ones because it is cleaner, safer and can be worked up easily. An improved method of deacylating the chiral 3-acetoxy tropic acid ethyl ester without any loss of stereochemical integrity using HCl/CH_3OH is also reported.

1. Introduction

(*S*)-(−)-Tropic acid is an important building block for biologically active tropane alkaloids, such as hyoscyamine and scopolamine[1–3] (Fig. 1). The use of these alkaloids has its roots in ancient times and they continue to be valuable drugs in the pharmaceutical field. Scopolamine is used as an anesthetic during surgery, for treatment of mental illnesses and as a vomiting inhibitor.[4] Hyoscyamine is used to treat cardiacarythmia and is also as an anesthetic.[5–7] Motofen,[8] which contains difenoxin hydrochloride and atropine sulfate, is used as adjunctive therapy in the management of acute diarrhea. Atrovent,[9] another commercial drug, is used to treat chronic bronchitis and emphysema. Furthermore, the presence of the two functional groups (hydroxyl and acid) in the tropic acid greatly aids in the further modification of the molecule, thus permitting several important derivatives to be made from this single chiral building block. As there are many important uses for chiral tropic acid, an efficient method for synthesizing this compound is greatly desired.

Since 1881, several methods have been developed to synthesize the racemic tropic acid, some of which have been patented.[1–3,10–15] In 1919, the first method of chemical resolution of tropic acid using quinine as the resolving reagent was reported,[12] and later, Watson determined the configuration of natural tropic acid.[15] More recently, two methods of synthesizing the (*R*)-(+)-tropic acid ester in excellent ee with low yield were published.[16,17] Until now, the biosynthesis of tropic acid has been the only means of obtaining the enantiomerically pure (*S*)-enantiomer.[1,3] Herein, we report the first lipase-catalyzed kinetic enzymatic resolution of tropic acid ethyl ester and its derivatives (±)-**2a**–**i** in high yields and with excellent ee (Schemes 1 and 6). As primary alcohols (±)-**2a**–**i** acylation takes place without much hindrance, making the kinetic resolution procedure is simple and efficient. We also report a method of synthesizing racemic tropic acid ethyl esters (±)-**2a**–**i** that improves on one previously patented by Sletzinger and Paulsen.[13]

Enzymatic resolution is a well-investigated area of research in resolving α-hydroxy compounds.[16,18–27] However, not many examples of resolution of β-hydroxy compounds like tropic acid esters are known. The presence of the two functional groups (hydroxyl and ester) in the tropic acid ester greatly aids in the further modification of the molecule, thus permitting several important derivatives to be made from this single building block. Unlike its α-hydroxy counterpart, protonation of the hydroxyl group on this β-hydroxy compound does not destroy the stereogenic center. Furthermore, the acylation of primary alcohols **2a**–**i**, can easily take place without

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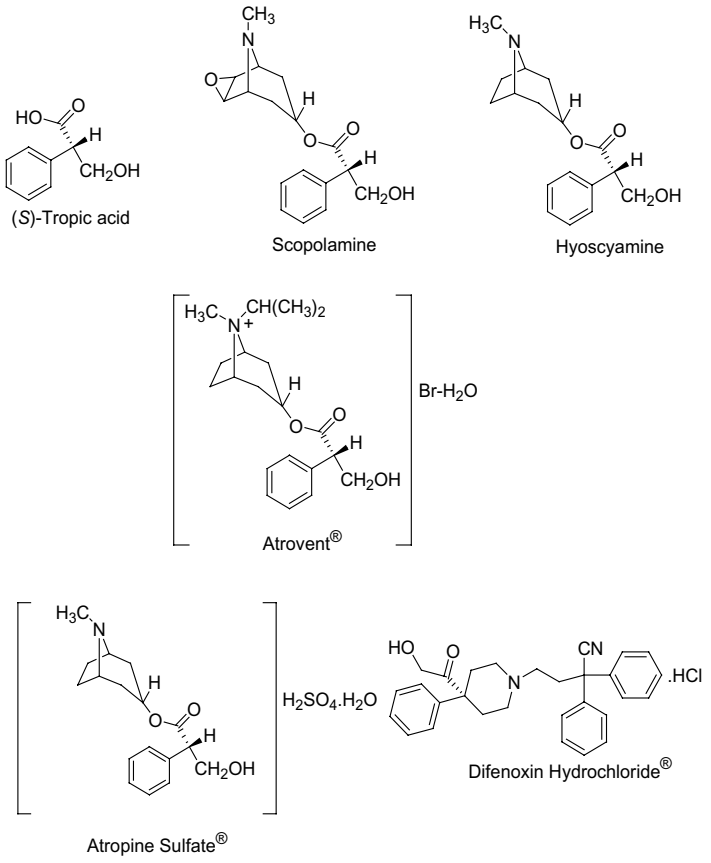
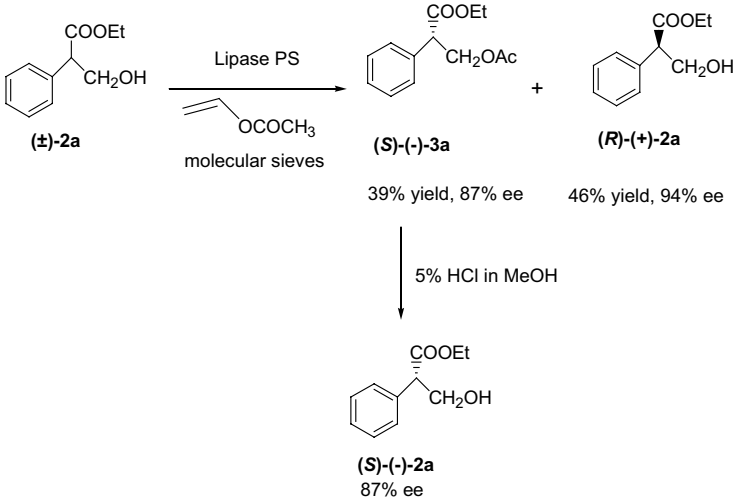


Figure 1. Biologically active compounds and drugs derived from (*S*)-(−)-tropic acid.



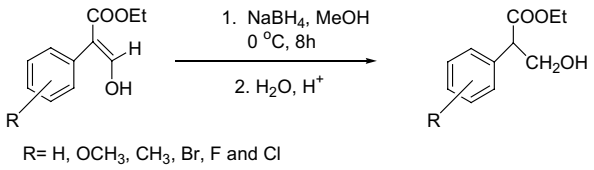
Scheme 1. Enzymatic kinetic resolution of tropic acid ethyl ester with lipase PS.

much hindrance, thereby making the kinetic resolution procedure simple and efficient.

2. Results and discussion

2.1. Synthesis of the racemic mixtures of tropic acid ethyl ester and its derivatives (±)-2b–i

The tropic acid ethyl ester, **2a**[28,29] and its derivatives (±)-**2b**–**i** were easily prepared by the reduction of 3-hydroxy-2-phenylacrylic acid ethyl ester[30] **1a**–**i** with sodium borohydride in methanol (Scheme 2; Table 1). The reduction was performed for 8 h at 0–25 °C, and the resulting alcohol isolated by column chromatography in high yield. Better yields were obtained with the introduction of electron-donating substituents (Table 1, entries 1–6). The yields of the products decrease with electron-withdrawing substituents (Table 1, entries 8 and 9). These results support the notion that electronic effects rather than steric effects play the major role in lower product yields.



Scheme 2. Reduction of 3-hydroxy-2-arylacrylic acid ethyl esters **1a**–**i** with sodium borohydride.

Table 1. Isolated yields of racemic tropic acid ethyl esters from $NaBH_4$ reduction

Entry	Substrate	R group	*T* (°C)	*t* (h)	%Yield
1	**1a**	H	0	8	90
2	**1b**	3,5-$(OCH_3)_2$	0	8	95
3	**1c**	4-OCH_3	0	8	92
4	**1d**	2,5-$(CH_3)_2$	0	8	84
5	**1e**	4-CH_3	0	8	80
6	**1f**	5-Br-2-OCH_3	0	8	83
7	**1g**	4-Br	0	8	79
8	**1h**	6-Cl-2-F	0	8	74
9	**1i**	4-F	0	8	62

2.2. Enzymatic acetylation and screening of enzymes. Lipase-catalyzed acylation of tropic acid ethyl ester (±)-2a

2.2.1. Screening of enzymes. Initially, 30 enzymes were screened to resolve the racemic tropic acid ester. Each of the reaction mixtures was subjected to similar experimental conditions (solvent, temperature, and time) and vinyl acetate used as the acylating agent. Each mixture was monitored at 1, 4, 8, and 24 h by TLC and GC. Of these 30 enzymes, five (*porcine liver esterase*, *Pseudomonas cepacia lipase*, *porcine pancreatic lipase*, *chiro CLEC-CR* and *Candida rugosa esterase*) (entries 1–3 and 5–6) were able to resolve the tropic acid ester with 35–50% conversion in a reasonable time of 4–8 h (Table 2).

2.2.2. Enzymatic kinetic resolution with lipase PS. Of these five enzymes, *Pseudomonas cepacia* lipase (entry 2), commercially known as lipase PS, was found to be the best at resolving the tropic acid ethyl ester (±)-**2a** (~50% conversion) at a reasonable rate (4–8 h), in high yields and with excellent % ee. As shown in Scheme 1, the racemic tropic acid ethyl ester was resolved to provide (*S*)-(−)-3-acetoxy tropic acid ethyl ester **3a** in 39% yield with 87% ee and (*R*)-(+)-tropic acid ethyl ester **2a** in 42% yield with 94% ee.

For an easier work-up, the enzyme-catalyzed reactions were performed with a Celite-supported enzyme. The Celite support aids the ease of separation by filtration of the enzyme once the reaction is complete. Molecular sieves were used to enhance the rate and yields of the product.[31,32]

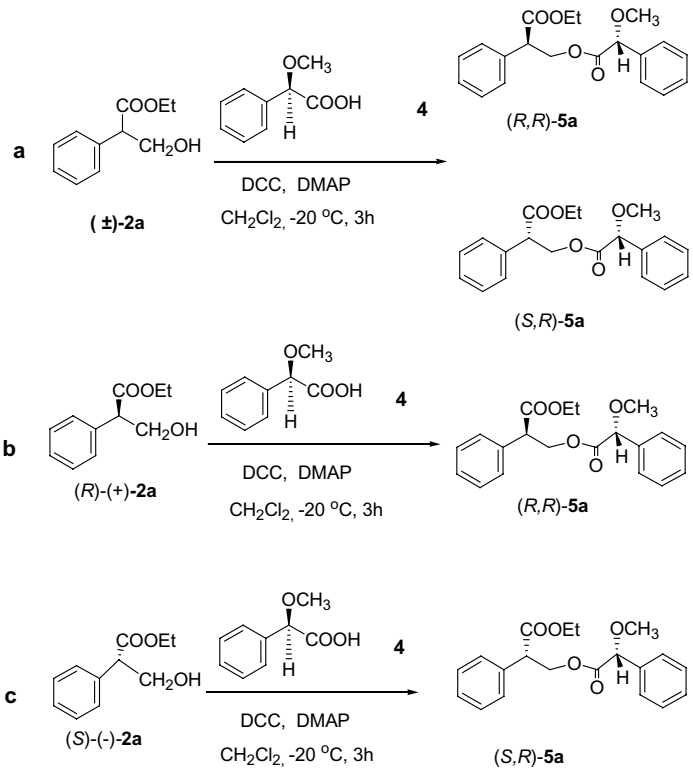
Lipase PS was found to resolve the tropic acid ester better with vinyl acetate (94% ee) than acetic anhydride (51% ee) as the acylating reagent. The decrease in % ee in the acetic anhydride could have been due to the formation of acetic acid, which may have racemized the product, as observed in a previous study.[31]

Table 2. Summary of the results from the screening of enzymes

Entry	Enzyme	Percent conversion at			
		1 h	4 h	8 h	24 h
1	*Porcine liver esterase*	10	30	38	40
2	*Pseudomonas cepacia lipase*	30	37	~50	100
3	*Porcine Pancreatic lipase*		25	35	80
4	*Candida rugosa lipase*			25	100
5	*Candida rugosa esterase*	20	25	35	90
6	*Pseudomonas species lipase*	10	25	30	60
7	*ChiroCLEC-CR (dry)*		15	30	35
8	*Aspergillus oryzae protease*			0	34
9	*Candida antarctica 'B' lipase*			0	24
10	*Candida antarctica 'A' lipase*			25	
11	*Candida lipolytica lipase*	NR			
12	*Subtilisin carlsberg*	NR			
13	*Humicola lanuginosa lipase*	NR			
14	*Bacillus species protease*	NR			
15	*alpha-Chymotrypsin*	NR			
16	*ChiroCLEC-BL (dry)*	NR			
17	*ChiroCLEC-PC (dry)*	NR			
18	*Rhiiopus delmar lipase*	NR			
19	*Rhizopus niveus lipase*	NR			
20	*Rhizo2us oryzae lipase*	NR			
21	*Chromobacterium viscosum lipase*	NR			
22	*Alcaligenes species lipase*	NR			
23	*Geotricurn candidum lipase*	NR			
24	*Mucoijavanicus lipase*	NR			
25	*Mucormeihei lipase*	NR			
26	*Penicillin acyldse*	NR			
27	*Papain*	NR			
28	*Aspergillus species protease*	NR			
29	*PeptiCEC-TR (dry)*	NR			
30	*Aspergillus niger lipase*	NR			

2.2.3. Determination of the enantiomeric excess of (*R*)-(+)-tropic acid ethyl ester (*R*)-(+)-2a. The ee of (*R*)-(+)-tropic acid ethyl ester (*R*)-(+)-**2a** was determined by analysis of the ^1H NMR spectrum of its (*R*)-(−)-α-methoxyphenyl acetic acid derivative.[33] First, racemic tropic acid ethyl ester (±)-**2a** was reacted with enantiomerically pure (*R*)-(−)-α-methoxyphenyl carboxylic acid in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP). The reaction was run in CH_2Cl_2 at −20 °C for 3 h. After work-up, the 1:1 diastereomeric mixture of esters (*R*,*R*)-**5a** and (*S*,*R*)-**5a** was determined by the ^1H NMR spectrum (Scheme 3). A 1:1 peak area ratio of the methoxyphenyl ester methine proton peaks of the two diastereoisomers was observed at 3.720 and 3.385 ppm in $CDC1_3$ (Fig. 2a).

Under identical conditions, the chiral (2*R*)-(+)-tropic acid ethyl ester **2a** isolated from the enzymatic reaction was treated with (*R*)-(−)-α-methoxyphenyl carboxylic acid **4** (Scheme 3, reaction B). The same two proton NMR peaks were observed (Fig. 2b) and a 94% ee for the chiral acid ester (2*S*,2*R*)-**5a** calculated, based on peak areas.



Scheme 3. Synthesis of (*R*,*R*)-**5a** and (*S*,*R*)-**5a** (2-methoxy-2-phenyl-propionic acid 2-phenyl-2-ethoxy carbonyl ethyl ester), that is, diastereoisomers from racemic and non-racemic tropic acid ethyl esters using chiral derivatizing agent[33–37] (Scheme 3 and Fig. 2 have parallel information).

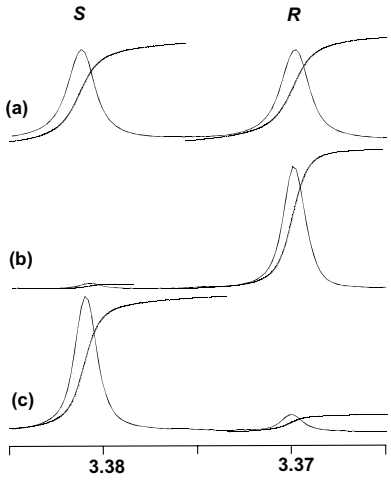
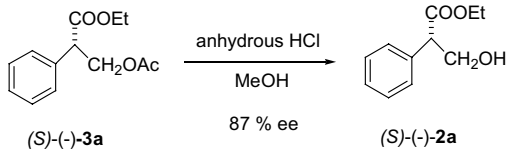


Figure 2. ^{1}H NMR spectra of diastereomeric mixture of the phenyl-methoxy ester; (a) reference spectrum of 1:1 diastereomeric mixture of **5a**; (b) spectra of the diastereomers obtained from the kinetically resolved (*R*)-(+)-**2a**; (c) diastereomers from (*S*)-(−)-**2a** (which was obtained from (*S*)-(−)-**3** after deacylation).

2.3. Deacylation of (*S*)-(−)-3-acetoxy tropic acid ethyl ester (*S*)-(−)-3a and determination of (*S*)-(−)-tropic acid ethyl ester (*S*)-(−)-2a % ee

2.3.1. Determination of ee of (*S*)-(−)-3-acetoxy tropic acid ethyl ester (*S*)-(−)-3a. For the determination of the ee of the (*S*)-(−)-3-acetoxy tropic acid ethyl ester

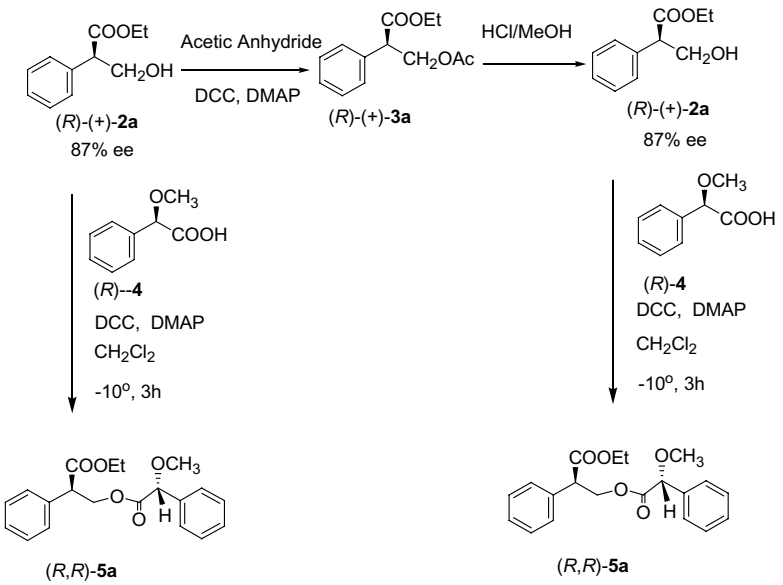


Scheme 4. Deacylation of (*S*)-(−)-3-acetoxy tropic acid ethyl ester (*S*)-(−)-**3a**.

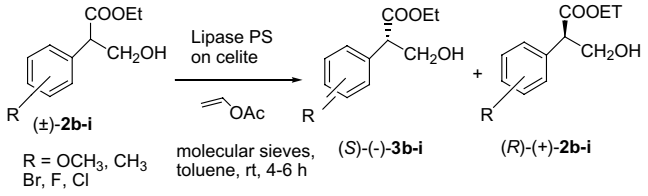
(*S*)-(−)-**3a**,[†] the compound was hydrolyzed to the tropic acid ethyl ester (*S*)-(−)-**2a** in the presence of anhydrous HCl in methanol (Scheme 4). The ee of the converted (*S*)-(−)-**2a** was determined by the derivatization, as previously described for the (*R*)-(+)-**2a** enantiomer, and was found to be 87% ee (Fig. 2c). Resolution followed by the deacylation provided the tropic acid ethyl ester (*S*)-(−)-**2a** in high % ee, which is the building block of several naturally occurring biologically active compounds (Fig. 1).

2.3.2. Confirmation of the effectiveness of the acid hydrolysis. It is reasonable to assume that during the hydrolysis under acidic conditions, some of the (*S*)-(−)-3-acetoxy tropic acid ethyl ester may have been

[†] The use of shift reagents such as Europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphoratel], Praseodymium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] and Europium tris[(heptafluoropropylhydroxymethylene)-(+)-camphorate] to resolve this ester was unsuccessful.



Scheme 5. Acylation and deacylation reactions.



Scheme 6. Kinetic resolution of the derivatives of tropic acid ethyl ester **2b**–**i**.

racemized. In order to determine if any racemization occurred during the acid hydrolysis (deacylation), the following control reaction was performed. First, the optically active (*R*)-(+)-tropic acid ester **2a** with known % ee was converted to the (*R*)-(+)-3-acetoxy tropic acid ethyl ester **3a** by reacting (*R*)-(+)-**2a** with acetic anhydride in the presence of DCC and DMAP (Scheme 3b). This (*R*)-(+)-3-acetoxy tropic acid ethyl ester was then hydrolyzed back to the (*R*)-(+)-**2a** in the presence of 5% HCl in methanol and derivatized to form diastereomer **5a** (Scheme 5). The resulting ee of (*R*)-(+)-tropic acid ester **2a** indicated that no loss of ee occurred during the hydrolysis reaction (Fig. 3). Consequently, an improved and easy procedure of hydrolyzing the chiral 3-acetoxy-2-arylpropanoic acid ester to 3-hydroxy-2-arylpropanoic acid ester without any racemization at the stereogenic center has been found.

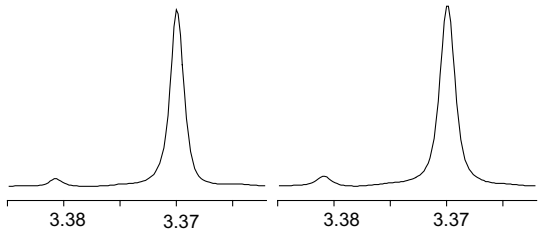


Figure 3. ^{1}H NMR spectrum of (a) diastereomeric mixture **5a** of (*R*)-(+)-**2a** before acylation; (b) diastereomeric mixture **5a** of (*R*)-(+)-**2a** after acylation and deacylation.

Selective hydrolysis of (*S*)-(−)-3-acetoxy tropic acid ester **3a** to (*S*)-(−)-tropic acid ester **2a** without any loss of enantiomeric excess proved to be a real challenge. In one case, the use of a known method of selective hydrolysis with methanolic potassium carbonate[38] (a mild base) was found to be unsuccessful, yielding only 2-phenyl-propenoic acid ester. In another case, there was no reaction when scandium trifluoromethanesulfonate[39] was used for the hydrolysis of the 3-acetoxy tropic acid ester **3a**.

2.4. Kinetic resolution of tropic acid ethyl ester derivatives 2b–i

After accomplishing the enzymatic kinetic resolution of **2a**, we proceeded to resolve the racemic mixture of the derivatives **2b**–**i**. Indeed, we obtained (*R*)-(−)-**2b**–**i** and (*S*)-(−)-**3b**–**i** using lipase PS with vinyl acetate as the acylating agent (Scheme 6). The results of the enzymatic resolution of the eight compounds, **2b**–**i** are listed in Table 3.

The substituted compounds bearing electron-donating substituents gave excellent yields and % ee (entries 1–5), except for the methyl substituent (entry 6), which gave good yields but low % ee. The compounds bearing electron-withdrawing substituent gave high yields of both products, but only gave moderate enantiomeric excesses (entries 7–9).

3. Conclusion

In summary, we have successfully resolved racemic tropic acid ethyl ester and a number of its derivatives by lipase PS in high yield and excellent % ee. We have also prepared the derivatives of racemic tropic acid ethyl

Table 3. Kinetic resolution of the derivatives of tropic acid ethyl ester

Entry	Starting material	R group	(*S*)-(−)-**3b–i**			(*R*)-(+)-**2b–i**		
			Product	% Yield	% Ee	Product	% Yield	% Ee
1	**2b**	3,5-$(OCH_3)_2$	**3b**	49	94	**2b**	43	94
2	**2c**	4-OCH_3	**3c**	~40	98	**2c**	48	>99
3	**2d**	2,5-$(CH_3)_2$	**3d**	~30	83	**2d**	44.5	87
4	**2e**	4-CH_3	**3e**	39	65	**2e**	40.5	50
5	**2f**	5-Br-2-OCH_3	**3f**	42	81	**2f**	41.5	81
6	**2g**	4-Br	**3g**	46	64	**2g**	47	67
7	**2h**	6-CI-2-F	**3h**	31	65	**2h**	38	67
8	**2i**	4-F	**3i**	~40	50	**2i**	44	55

ester by using an improved method over the previous patented one. During our studies, we have developed a more efficient procedure for deacylating the chiral 3-acetoxy tropic acid ethyl esters (*S*)-(−)-**3a–i** to the corresponding ethyl esters (*S*)-(−)-**2a–i** with no detectable loss of ee.

4. Experimental

4.1. General methods

All the glassware was oven dried and purged with nitrogen before use. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ on a Bruker 300 or 250 MHz NMR spectrometer. Chemical shifts are expressed in ppm relative to tetramethylsilane and $CDCl_3$ was used as the lock solvent. Optical rotations were recorded on a Jasco DIP-370 digital polarimeter at 25 °C. Mass spectra were obtained on a Hewlett–Packard 5985B (H/P). GC(FID) were obtained on a Shimadzu Gas Chromatograph-2GC-14A. GC/MS system, operated in DIP (direct insertion probe) CI IE-70 eV.

Column chromatography was performed using EM Science silica gel 60 (70–230 mesh). Thin layer chromatography was performed using EM Science F254 silica gel 60. Celite 521 was obtained from Across Chemicals. Molecular sieves, 3 Å, 1–2 mm beads was obtained from Lancaster Synthesis. HPLC grade CH_2Cl_2 and tetrahydrofuran (EM Science) were freshly distilled under a nitrogen atmosphere from sodium benzophenone sodium under nitrogen prior to use. Vinyl acetate and acetic anhydride were obtained from Aldrich Chemical Co. (*R*)-(−)-methoxyphenyl acetic acid, 4-dimethylaminopyridine, (DMAP), and 1,3-dicyclohexylcarbodimime (DCC) were purchased from Acro Chemicals. Phosphate buffer (pH 7) was obtained from Fisher Scientific. Lipase Amano PS was a gift from Amano Chemicals. Lipase VII was purchased from Aldrich Chemicals. Chiro-Screen TE kit was purchased from Altus Biologies Inc. The 3-hydroxy-2-phenylacrylic acid ethyl esters **1a–i** were prepared by the method described in the literature.[30]

4.2. Reduction of 3-hydroxy-2-phenylacrylic acid ethyl ester 1a–i to 2a–i

4.2.1. Tropic acid ethyl ester (±)-2a.[28,29] 3-Hydroxy-2-phenylacrylic acid ethyl ester **1a** (250 mg, 1.30 mmol) was dissolved in methanol (25 mL) and the solution cooled to 0 °C. Sodium borohydride (59.3 mg, 1.56 mmol) was added slowly over a period of 15 min and the reaction continued to stir at 0 °C for 6–8 h. After the solvent was removed under reduced pressure, ether (20 mL) and water (10 mL) were added to the viscous, crude semi-solid. This semi-solid was extracted with ether (4 × 20 mL) and the combined ether extracts washed with water (20 mL), brine (20 mL), and then dried over Na_2SO_4. After removal of the solvent under reduced pressure, the oil was purified via column chromatography (silica gel, 5–20% ether in pentane) to provide (±)-**2a** as a colorless oil (177 mg, 0.911 mmol, 70%): ^1H NMR ($CDCl_3$, 300 MHz): δ 7.26–7.10 (m, 5H), 4.23 (t, 1H), 4.18, (dd, 1H), 4.14 (q, 2H), 3.85 (m, 1H), 2.71 (s b, 1H), 1.21 (t, 3H, $J = 7.14$ Hz); ^{13}C NMR ketyl. HPLC grade methanol (EM Science) was distilled under nitrogen from magnesium iodide. Reagent grade benzene (EM Science) was distilled from ($CDC1_3$, 300 MHz): δ 173.15, 135.55, 128.47, 128.10, 126.57, 64.58, 61.09, 50.65, 14.02.

4.2.2. 3-Hydroxy-2-(3,5-dimethoxyphenyl) propionic acid ethyl ester (±)-2b. Prepared according to the general procedure described above in Section 4.2.1 for (±)-**2a** from 3-hydroxy-2-(3,5-dimethoxyphenyl)-acrylic acid ethyl ester (250.2 mg, 0.991 mmol) and sodium borohydride (59.3 mg 1.56 mmol). The products were separated by column chromatography on silica gel (5–20% ether/pentane). Compound (±)-**2b** was isolated as a tan color oil (240 mg, 0.941 mmol, 95% yield). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.30 (s, H), 7.16 (dd, 2H, $J = 4.2$ and 2.93 Hz), 4.54 (t, 1H, $J = 9.65$ Hz), 4.27, (q, 2H, $J = 5.62$ Hz), 4.14 (dd, 2H, $J = 5.0$ and 2.2 Hz), 3.85 (s, 6H), 2.24 (br s, 1H), 1.25 (t, 3H $J = 7.14$ Hz); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 171.62, 162.83, 148.30, 126.65, 126.15, 121.48, 112.99, 110.74, 110.53, 108.16, 60.86, 55.77,14.61; MS (EI, *m*/*z*%): 254(M+, 43), 224(100), 195(72), 181(67), 167(30), 151(70), 137(38), 121(64), 139(5), 109(10), 103(6); HRMS (EI, *m*/*z*%): calcd for $C_{13}H_{18}O_5$ $[M]^+$ 254.1154. Observed: 254.1174. Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.41, H, 7.14. Observed: C, 61.08, H, 6.84.

4.2.3. 3-Hydroxy-2-(4-methoxyphenyl)-propionic acid ethyl ester (±)-2c.[40–42] Prepared according to the general procedure described above in Section 4.2.1 for (±)-**2a** from 3-hydroxy-2-(4-methoxyphenyl)-acrylic acid ethyl ester **1c** (250.2 mg, 1.124 mmol) and sodium borohydride (59.3 mg, 1.56 mmol). The products were

separated by column chromatography on silica gel (5–20% ether/pentane). Compound (±)-**2c** was isolated as a light orange oil (240 mg, 1.070 mmol, 95% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.20 (d, 2H, J = 8.9 Hz), 6.89 (d, 2H, J = 8.8 Hz), 4.20 (m, 3H), 3.85 (dd, 2H, J = 5.52 and 10.65 Hz), 3.80 (s, 3H, OCH_3), 2.18 (br s, 1H), 1.21 (t, 3H, J = 7.14 Hz CH_3); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 173.15, 135.55, 128.47, 128.10, 117.21, 126.57, 64.58, 61.09, 50.48, 14.02. HRMS: (EI, *m*/*z*%) 224(M+, 24), 194(98), 180(8), 165(99), 151(64), 137(44), 134(16), 121(100), 109(30), 105(14); HRMS: (EI, *m*/*z*%): calcd for $C_{13}H_{18}O_5$ $[M]^+$ 224.1049. Observed: 224.1044.

4.2.4. 3-Hydroxy-2-(2,5-dimethylphenyl)-propionic acid ethyl ester (±)-2d. Prepared according to the general procedure described above in Section 4.2.1 for (±)-**2a** from 3-hydroxy-2-(2,5-dimethylphenyl)-acrylic acid ethyl ester **1d** (250.2 mg, 1.30 mmol) and sodium borohydride (59.3 mg 1.56 mmol). The products were separated by column chromatography on silica gel (5–20% ether/pentane). Compound (±)-**2d** was isolated as a colorless oil (190 mg, 0.855 mmol, 84% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26 (dd, 2H, J = 5.4 Hz), 7.10 (dd, 2H, J = 8.7 Hz), 4.23 (t, 1H, J = 6.2 Hz), 4.18 (dd, 1H), 4.14 (q, 2H, J = 5.3 Hz), 3.85 (dd, 1H, J = 5.7 Hz), 2.71 (br s, 1H), 1.21 (t, 3H, J = 7.14 Hz); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 173.74, 138.93, 135.89, 129.81, 123.49, 66.47, 65.20, 61.47, 54.33, 52.62, 21.68, 14.51; MS (EI, *m*/*z*%) 222(M+, 21) 222(21), 208(4), 192(80), 178(3), 163(22), 149(28), 146(100), 135(3), 131(20), 119(44), 107(55), 105(27), 137(21), 103(12). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24, H, 8.16. Observed: C, 69.58, H, 8.04.

4.2.5. 3-Hydroxy-2-(4-tolylphenyl)-propionic acid ethyl ester (±)-2e.[41] Prepared according to the general procedure described above in Section 4.2.1 for (±)-**2a** from 3-hydroxy-2-(4-methylphenyl)-acrylic acid ethyl ester **1e** (250.2 mg, 1.30 mmol) and sodium borohydride (59.3 mg 1.56 mmol). The products were separated by column chromatography on silica gel (5–20% ether/pentane). Compound (±)-**2e** was isolated as a colorless oil (202 mg, 0.970 mmol, 80% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.15 (d, 2H, J = 5.4 Hz), 7.10 (d, 2H, J = 8.7 Hz), 4.23 (t, 1H, J = 6.2 Hz), 4.18 (dd, 1H), 4.14 (q, 2H, J = 5.3 Hz), 3.85 (dd, 1H, J = 5.7 Hz), 2.71 (br s, 1H), 1.21 (t, 3H, J = 7.14 Hz); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 173.19, 135.89, 129.93, 116.78, 104.22, 65.20, 61.46, 50.29, 48.47, 14.02.

4.2.6. 3-Hydroxy-2-(5-bromo-2-methoxyphenyl)-propionic acid ethyl ester (±)-2f. Prepared according to the general procedure described above in Section 4.2.1 for **2a** from 3-hydroxy-2-(5-bromo-2-methoxyphenyl)-acrylic acid ethyl ester **1f** (250.2 mg, 1.30 mmol) and sodium borohydride (59.3 mg, 1.56 mmol). The products were separated by column chromatography on silica gel (5–20% ether/pentane). Compound (±)-**2f** was isolated as a golden oil (199 mg, 0.728 mmol, 83% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.4 (d, 2H, J = 3.12 and 13 Hz), 6.77 (d, 2H, J = 8.7 Hz), 4.45 (dd, 1H, 10.78 and J = 12.4 Hz), 4.23 (t, 1H, J = 6.2 Hz), 4.18 (dd, 1H, J = 9.6 and 5.3 Hz), 4.14 (q, 2H, J = 5.3 Hz), 3.85 (dd, 1H, J = 9.9 and 11.5 Hz), 2.24 (br s, 1H), 1.24 (t, 3H, J = 7.1 Hz); ^{13}CNMR ($CDCl_3$, 300 MHz): δ 175, 160, 157, 130, 117, 116, 104, 99, 63, 61, 55, 51, 48, 47, 29, 14: MS (EI, *m*/*z*%): 304/302(M+, 31), 274/272(100), 258(6), 245(11), 228/226(60), 213(31), 199(30), 187(23), 185(27), 164(11), 150(60), 134(13), 121(64), 118(340), 1079(17). Anal. Calcd for $C_{12}H_{15}BrO_4$, 47.54, H, 4.99. Observed: C, 46.88, H, 4.41.

4.2.7. 3-Hydroxy-2-(4-bromophenyl)-propionic acid ethyl ester (±)-2g. Prepared according to the general procedure described above in Section 4.2.1 for (±)-**2a** from 3-hydroxy-2-(4-bromophenyl)-acrylic acid ethyl ester **1g** (250.2 mg, 1.30 mmol) and sodium borohydride (59.3 mg 1.56 mmol). The products were separated by column chromatography on silica gel (5–20% ether/pentane). Compound (±)-**2g** was isolated as a light yellow oil (199 mg, 0.728 mmol, 79% yield): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26 (d, 2H, J = 5.36 Hz), 7.10 (dd, 2H, J = 8.65 Hz), 4.23 (t, 1H), 4.18 (dd, 1H), 4.14 (m, 1H), 3.85 (s, 3H, OCH_3), 2.7 (br s, 1H, OH), 1.25 (t, 3H, J = 7.14 Hz); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 173.10, 137.31, 132.81, 130.34, 129.68, 65.76, 61.02, 53.54, 14.97; MS (EI, *m*/*z*%) 272/270(M+, 20), 256/258(5), 242/244(3), 224/226(68.4), 196/198(19), 183/185(100), 170/172(15), 155/153(37), 155/153(37), 89(90), 75/(36), 63(24).

4.2.8. 3-Hydroxy-2-(2-chloro-6-fluorophenyl)-propionic acid ethyl ester (±)-2h. Prepared according to the general procedure described above in Section 4.2.1 for (±)-**2a** from 3-hydroxy-2-(2-chloro-6-fluorophenyl)-acrylic acid ethyl ester **1h** (250.2 mg, 1.30 mmol) and sodium borohydride (59.3 mg, 1.56 mmol). The products were separated by column chromatography on silica gel (5–20% ether/pentane). Compound (±)-**2h** was isolated as a colorless oil (185 mg, 0.756 mmol, 74% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26 (m, 2H and 1F), 7.10 (m, 1H and 1F), 4.25 (dd, 1H, 1F, J = 4.38 and 8.43 Hz), 4.23 (m, 3H), 3.74 (dd, 1H and 1F J = 4.38 and 11.31 Hz), 2.71 (br s, 1H), 1.21 (t, 3H, J = 7.14 Hz); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 172.62, 162.89, 159.59, 135.07, 129.29, 123.10, 114.43, 63.32, 61.71, 46.27, 13.89; MS (EI, *m*/*z*%): 246(M+, 1), 228(3), 218(30), 216(100), 188(60), 173/170/(65), 154/156(50), 143(70), 142(15), 125(50), 109(65), 107(68), 95(5), 83(10), 75(50, 57(5). Anal. Calcd for $C_{11}H_{12}ClFO_3$: C, 53.56, H, 4.90. Observed: C, 53.53, H, 4.76.

4.2.9. 3-Hydroxy-2-(4-fluorophenyl) propionic acid ethyl ester (±)-2i.[43,44] Prepared according to the general procedure described above in Section 4.2.1 for (±)-**2a** from 3-hydroxy-2-(4-fluorophenyl)-acrylic acid ethyl ester **1i** (250.2 mg, 1.30 mmol) and sodium borohydride (59.3 mg 1.56 mmol). The products were separated by column chromatography on silica gel (5–20% ether/pentane). Compound (±)-**2i** was isolated as a colorless oil (156 mg, 0.737 mmol, 62% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.30 (d, 2H and 1F, J = 5.94 and 10.17 Hz), 7.26 (dd, 2H and 1F, J = 8.72 and 5.7 Hz), 4.18 (m, 2H), 4.14 (q, 2H, J = 7.12 Hz), 3.82 (dd, 1H

and 1F, $J = 3.70$ Hz), 2.45 (br s, 1H, -OH), 1.23 (t, 3H, $J = 7.14$ Hz CH_3); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 172.92, 163.80, 160.53, 135.48, 129.61, 115.46, 64.67, 61.11, 52.18, 13.93; MS (EI, *m*/*z*%): 212(M+, 8), 198(5), 182(92), 168(21), 165(2), 154(60), 136(48), 121(44), 109(100), 97(38), 91(30), 83(18), 75(12), 57(10), 51(6).

4.3. Kinetic resolution of racemic tropic acid ethyl esters 2a

4.3.1. Screening of enzymes. Racemic tropic acid ethyl ester (±)-**2a** (50 mg, 0.258 mmol) was dissolved in toluene (50 mL). An aliquot (1 mL) of this solution was added to each of the 30 vials containing different enzymes and an aliquot (1 mL) of **2a** was also added to a vial without any enzyme to act as the control. Vinyl acetate (two drops) was then added to each vial. All solution transfers were accomplished using disposable pipettes and vial caps were immediately replaced after each addition in order to avoid cross-contamination. The reaction mixtures were stirred at rt and monitored for the presence of tropic acid ester and 3-acetoxy tropic acid ester by TLC and GC at 1, 4, 8, and 24 h.

4.3.2. Preparation of lipase PS on Celite support. Celite 521 (0.5 g) was washed with distilled water (10 mL), followed by 0.1 M phosphate buffer (10 mL, pH 7). Lipase PS (0.17 g, activity 3000 u/g) was mixed with the Celite and suspended in 0.1 M phosphate buffer (2 mL, pH 7). This suspension was allowed to air dry completely at rt.

4.3.3. Kinetic resolution of racemic tropic acid ethyl ester using vinyl acetate as the acylating agent. In a 100 mL side-arm round-bottom flask, racemic tropic acid ethyl ester **2a** (100 mg, 0.515 mmol) was dissolved in freshly distilled benzene or toluene (15 mL). After lipase PS supported on Celite (1.2 g) and the molecular sieves (2 g) were added to the solution, vinyl acetate (0.05 mL, 0.62 mmol, 1.2 equiv) was added. The reaction mixture was stirred at rt and monitored by TLC or GC. After about 20 min, a second spot appeared and the reaction was stopped when the intensity of the two spots were almost equal (approx. 3–4 h at rt). The Celite-supported enzyme and molecular sieves were then filtered from the mixture and the solvent was removed under reduced pressure. The resulting residue was purified via column chromatography (silica gel, 5–20% ether/pentane) to afford (+)-**2a** (43 mg, 0.222 mmol, 43% yield, 94% ee) and (−)-**3a** (48 mg, 203 mmol, 39.45% yield, 87% ee) as colorless oils. Compound **2a**: $[\alpha]_D^{25} = +42$ (*c* 0.5, $CHCl_3$); **3a**:[39] $[\alpha]_D^{25} = -32.5$ (*c* 1.31, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.26–7.20 (m, 5H), 4.71 (t, 1H), 4.52 (dd, 1H), 4.32 (q, 2H), 3.92 (dd, 1H), 2.01 (s, 3H), 1.21 (t, 3H).

4.3.4. Kinetic resolution of racemic tropic acid ethyl ester using acetic anhydride as the acylating agent. Resolution was performed using the same procedure previously described for vinyl acetate. Racemic (±)-**2a** (100 mg, 0.52 mmol), lipase PS supported on Celite (0.75 g), molecular sieves (2 g) and acetic anhydride (0.04 mL. 0.75 equiv) were combined. The reaction was stirred at rt and monitored by TLC. At 50% completion, as determined by TLC, the Celite-supported lipase PS and molecular sieves were filtered and the remaining solvent was removed under reduced pressure. The resulting residue was purified via column chromatography (silica gel, 5–10% ether/pentane) to furnish **2a** (42 mg, 0.216 mmol, 42%) and **3a** (46 mg, 0.195 mmol, 37.81%) as colorless oils. Compound **2a**: $[\alpha]_D^{25} = +24$ (*c* 2.17, $CHCl_3$), 51.3% ee; **3a**: $[\alpha]_D^{25} = -28$ (*c* 1.65, $CHCl_3$), 83% ee.

4.3.5. Preparation of (*R*)-(+)-3-acetoxytropic acid ethyl ester 3a. The (*R*)-(+)-tropic acid ethyl ester (120 mg, 0.62 mmol) was dissolved in dichloromethane (15 mL), DCC (130 mg, 0.62 mmol), DMAP (76 mg, 0.62 mmol) and acetic anhydride (0.10 mL, 0.93 mmol) added to the reaction mixture. The solution was then stirred for 2–3 h at rt, and the solvent removed under reduced pressure. Water (15 mL) was then added to the resulting residue and the mixture extracted with diethyl ether (3×15 mL). The combined organic phases were washed with saturated sodium bicarbonate solution, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to provide (*R*)-**3a** (139 mg, 0.589 mmol, 96%) as a colorless oil.

4.4. Deacylation of (*R*)-(+)-3-acetoxy tropic acid ester 3a

A sample of (*R*)-(+)-3-acetoxy tropic acid ester **3a** (52 mg, 0.24 mmol, 92% ee) was dissolved in dry methanol (5 mL) and anhydrous HCl (23 mg, 0.631 mmol) in methanol (2.5 mL) then added to the solution. The reaction was monitored by TLC and stirred until the starting material had completely hydrolyzed to tropic acid ethyl ester (2 h at rt). After the solvent was removed under reduced pressure, the pale yellow oil was extracted with diethyl ether (4×10 mL) and the combined organic phases washed with water and dried over Na_2SO_4. The ether was then removed under reduced pressure to provide (*R*)-(+)-**2a** (45 mg, 96% yield, and 92% ee).

4.5. Determination of enantiomeric excess of chiral 3-hydroxy-2-phenyl-propionic acid ethyl esters 2a–i and corresponding acetoxy ethyl esters 3a–i

4.5.1. (*R*)-(+)-Tropic acid ethyl ester (*R*)-(+)-2a. A sample (0.390 g, 0.20 mmol) of (*R*)-(+)-**2a** and dicyclohexylcarbodiimide (46 mg, 0.20 mmol) were added to a solution of (*R*)-(−)-α-methoxyphenyl acetic acid **4** (33 mg, 0.20 mmol) and 4-dimethylaminopyridine (0.847 mg, 0.04 mmol) in methylene chloride (5 mL) at −10 °C. After the mixture was stirred at −10 °C for 3 h, the precipitated urea was removed by filtration and the solvent removed under reduced pressure. The sample was further dried under vacuum pump and the ^1H NMR spectrum of the crude product, which was obtained in $CDCl_3$, indicated a split peak (δ 3.43) corresponding to the methine proton of (*S*)-(−)-tropic acid ethyl ester. The integration ratio of these methine peaks was used to calculate the % ee. The corresponding 1:1 diastereomeric mixture of (*R*)-(−)-α-methoxyphenyl ester derivative was prepared from the (±)-**2a** analogous to the procedure described for the individual enantiomers.

4.5.2. Enantiomeric excesses of 2b–i. The same procedure as described for compound (*R*)-(+)-**2a** was used to determine the enantiomeric excess of compounds **2b**–**i**.

4.5.3. Enantiomeric excesses of (*S*)-(−)-3a–i. All acetoxy propanoic acid esters were converted to corresponding hydroxy phenyl propanoic acid ethyl esters (*S*)-(−)-**2a**–**i** and the % ee determined by derivatization with (*R*)-(−)-α-methoxyphenyl acetic acid using the same procedure as described above in Section 4.5.1 for (*R*)-(+)-**2a**.

4.6. Enzymatic kinetic resolution reactions 2b–i and 3b–i

4.6.1. (*R*)-(+)-3-Hydroxy-2-(3,5-dimethoxyphenyl)-propionic acid ethyl ester (*R*)-(+)-2b and (*S*)-(−)-3-acetoxy-2-(3,5-dimethoxyphenyl)-propionic acid ethyl ester (*S*)-(−)-3b. Racemic (±)-**2b** (100 mg, 0.393 mmol) was resolved according to the general procedure as described in Section 4.3.3. Compound (*R*)-(+)-**2b** was isolated as a light yellow-brown oil (49 mg, 0.204 mmol, 49.0%), 94%; $[\alpha]_D^{25} = +38.7$ (*c* 1.5, $CHCl_3$); same spectroscopic characteristics as of the racemic one (Section 4.1.2). Compound (*S*)-(−)-**3b** was isolated as a light yellow oil (50.05 mg, 0.169 mmol, 43.3%); 94% ee, $[\alpha]_D^{25} = -32.5$ (*c* 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26–7.20 (m, 3H), 4.59 (t, 1H, *J* = 10.9 and 9.5 Hz), 4.35, (dd, 1H, *J* = 10.89 and 5.7 Hz), 4.22, (dd, 1H, *J* = 7.14 Hz), 3.92 (dd, 1H, *J* = 9.5 and 5.7 Hz), 3.85 (s, 6H), 2.01 (s, 3H, $COCH_3$), 1.21 (t, 3H, *J* = 7.14 Hz); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 171.65, 170.60, 149.02, 148.66, 127.24, 120.29, 111.19, 110.90, 65.18, 61.03, 55.80, 55.82, 50.16, 20.75, 14.02. (EI, *m*/*z*%): 296(M+, 8), 237(21), 236(100), 223(16), 195(10), 181(9), 163(17), 151(13), 139(5), 119(5), 107(3), 91(5), 77(7), 51(1).

4.6.2. (*R*)-(+)-3-Hydroxy-2-(4-methoxyphenyl)-propionic acid ethyl ester (*R*)-(+)-2c and (*S*)-(−)-3-acetoxy-2-(4-methoxphenyl)-propionic acid ethyl ester (*S*)-(−)-3c. Racemic (±)-**2c** (100 mg, 0.45 mmol) was resolved according to the general procedure as described in Section 4.3.3. Compound (*R*)-(+)-**2c**[42] was isolated as a light brown oil (48 mg, 0.214 mmol, 48%), >99% ee; $[\alpha]_D^{25} = +44.2$ (*c* 2.44, $CHCl_3$); same spectroscopic characteristics as of the racemic one (Section 4.1.3.). The (*S*)-(−)-**3c**[42] was isolated as colorless oil (47.4 mg, 0.178 mmol, 39.9%); 98% ee, $[\alpha]_D^{25} = -38.2$ (*c* 1.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26–7.20 (m, 4H,), 4.71 (t, 1H, *J* = 9.45 and 10.86 Hz), 4.52, (dd, 1H, *J* = 5.76 and 10.89 Hz), 4.32 (m, 2H), 3.92 (dd, 1H, *J* = 5.64 and 9.40 Hz), 3.80 (s, 3H, OCH_3), 2.01 (s, 3H, $COCH_3$), 1.21 (t, 3H, *J* = 7.14 Hz CH_3). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 173.41, 168.08, 159.09, 129.68, 128.99, 114.12, 113.18, 66.11, 55.08, 47.54, 29.28, 14.30. MS (EI, *m*/*z*%): 266(M+, 6) 221(1), 205(17), 206(100), 193(23), 165(33), 162(27), 151(29), 137(19), 133(66), 121(37), 109(7), 105(4).

4.6.3. (*R*)-(+)-3-Hydroxy-2-(2,5-dimethylphenyl)-tropic acid ethyl ester (*R*)-(+)-2d and (*S*)-(−)-3-acetoxy-2-(2,5-dimethylphenyl)-propionic acid ethyl ester (*S*)-(−)-3d. Racemic (±)-**2d** (100 mg, 0.38 mmol) was resolved according to the general procedure as described in Section 4.3.3. Compound (*R*)-(+)-**2d** was isolated as a colorless oil (44.5 mg, 0.204 mmol, 44.5%), 87% ee; $[\alpha]_D^{25} = +45.7$ (*c* 0.25, $CHCl_3$); same spectroscopic characteristics as of the racemic one (Section 4.1.4). Compound (*S*)-(−)-**3d** was isolated as light yellow oil (71 mg, 0.269 mmol, 30%); 83% ee, $[\alpha]_D^{25} = -30.5$ (*c* 1.35, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26–7.20 (m, 3H), 4.61 (t, 1H, *J* = 9.42 and 10.89 Hz), 4.34 (dd, 1H, *J* = 5.7 and 10.81 Hz), 4.21 (m, 2H), 3.92 (dd, 1H, *J* = 5.6 and 9.41 Hz), 2.32 (s, 6H), 2.01 (s, 3H, $COCH_3$), 1.21 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$) 300 MHz): δ 173.19, 160.45, 138.91, 135.89, 129.93, 123.49, 116.78, 104.22, 65.20, 61.46, 54.34, 50.29, 48.47, 29.68, 14.02.

4.6.4. (*R*)-(+)-3-Hydroxy-2-(4-methylphenyl)-propionic acid ethyl ester (*R*)-(+)-2e and (*S*)-(−)-3-acetoxy-2-(4-methylphenyl)-propionic acid ethyl ester (*S*)-(−)-3e. Racemic (±)-**3e** (100 mg, 0.48 mmol) was resolved accordingly to the general procedure as described in Section 4.3.3. Compound (*R*)-(+)-**2e**[41] was isolated as a colorless oil (40.5 mg, 0.194 mmol, 40.5%) 50% ee; $[\alpha]_D^{25} = +27.8$ (*c* 2.11, $CHCl_3$) same spectroscopic characteristics as that of the racemic one (Section 4.1.5). The (*S*)-(−)-**3e** was isolated as a colorless oil (47 mg, 0.188 mmol, 39.1%); 65% ee, $[\alpha]_D^{25} = -31.8$ (*c* 1.31, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26–7.20 (m, 5H, *J* = 6.24 Hz), 4.71 (t, 1H, *J* = 6.23 Hz), 4.52, (dd, 1H, *J* = 6.24 Hz), 4.32 (q, 2H, *J* = 5.72 Hz), 3.92 (dd, 1H, *J* = 5.60 Hz), 2.01 (s, 3H), 1.21 (t, 3H, *J* = 7.12 Hz); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 173.19, 160.45, 135.89, 129.93, 116.78, 104.22, 65.20, 61.46, 50.29, 48.47, 29.68, 14.02. MS (EI, *m*/*z* %): 250(M+, 3), 205(4), 190(100), 176(83), 164(11), 150(17), 146(66), 132(40), 117(98), 105(49), 91(54), 77(41), 65(17), 51(12).

4.6.5. (*R*)-(+)-3-Hydroxy-2-(5-bromo-2-methoxyphenyl)-propionic acid ethyl ester (*R*)-(+)-2f and (*S*)-(−)-3-acetoxy-2-(5-bromo-2-methoxyphenyl)-propionic acid ethyl ester (*S*)-(−)-3f. Racemic (±)-**2f** (100 mg, 0.33 mmol) was resolved according to the general procedure as described in Section 4.3.3. Compound (*R*)-(+)-**2f** was isolated as a light brown oil (41.5 mg, 0.137 mmol, 41.5%), 81% ee; $[\alpha]_D^{25} = +38.7$ (*c* 1.5, $CHCl_3$); same spectroscopic characteristics as of the racemic one (Section 4.1.6). (*S*)-(−)-**3f** was isolated an a light brown oil (48 mg, 0.139 mmol, 42.2%); 81% ee, $[\alpha]_D^{25} = -28.5$ (*c* 1.62, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26–7.20 (m, 3H), 4.45 (dd 1H, 10.78 and *J* = 12.44) 4.23 (t, 1H, *J* = 6.21 Hz), 4.18 (dd, 1H *J* = 9.63 and 5.34 Hz), 4.14 (m, 2H), 3.85 (dd, 1H, *J* = 9.91 and 11.53 Hz), 2.24 (br s, 1H), 1.24 (t, 3H, *J* = 7.141 Hz); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 175.23, 160.17, 157.35, 130.43, 117.27, 116.35, 104.45, 99.19, 63.38, 61.04, 55.70, 51.04, 48.23, 47.47, 29.23, 14.31. HRMS (EI, *m*/*z*%): calcd for $C_{14}H_7BrO_5$ $[M]^+$ 346.0238/344.0259. Observed: 346.0243/344.0259.

4.6.6. (*R*)-(+)-3-Hydroxy-2-(4-bromophenyl)-propionic acid ethyl ester (*R*)-(+)-2g and (*S*)-(−)-3-acetoxy-2-(4-bromophenyl)-propionic acid ethyl ester (*S*)-(−)-3d. Racemic (±)-**2g** (100 mg, 0.41 mmol) was resolved

according to the general procedure as in Section 4.3.3. Compound (*R*)-(+)-**2g** was obtained as a light yellow oil (47 mg, 0.172 mmol, 47%), 67% ee, $[\alpha]_D^{25} = +30.5$ (*c* 2.31, $CHCl_3$). The (*S*)-(−)-**3g** was isolated as a light brown oil (51.1 mg, 0.162 mmol, 45.9%); 64% ee, $[\alpha]_D^{25} = -27.5$ (*c* 2.31, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.26–7.20 (m, 4H, $J = 6.2$ Hz), 4.59 (t, H, $J = 9.45$ and 10.89 Hz), 4.52, (dd, 1H, 5.7 and 10.89 Hz), 4.32 (m, 2H), 3.92 (dd, 1H, $J = 5.6$ and 9.35 Hz), 2.32 (s, 3H, $COCH_3$), 1.21 (t, 3H, $J = 7.14$ Hz). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 171.10, 165.32, 137.31, 132.81, 130.34, 129.68, 65.76, 61.02, 53.54, 27.97, 14.97.

4.6.7. (*R*)-(+)-3-Hydroxy-2-(6-fluoro-2-chlorophenyl)-propionic acid ethyl ester (*R*)-(+)-2h and (*S*)-(−)-3-acetoxy-2-(6-fluoro-2-chlorophenyl)-propionic acid ethyl ester (*S*)-(−)-3h. Racemic (±)-**2h** (100 mg, 0.41 mmol) was resolved according to the general procedure as in Section 4.3.3. Compound (*R*)-(+)-**2h** was isolated as a colorless oil (48 mg, 0.204 mmol, 48%) 67% ee; $[\alpha]_D^{25} = +37$ (*c* 0.5, $CHCl_3$); same spectroscopic characteristics as of the racemic one (Section 4.1.7). Compound (*S*)-(−)-**3h** was isolated as a colorless oil (73 mg, 0.296 mmol, 31%); 65% ee, $[\alpha]_D^{25} = -29.7$ (*c* 2.35, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.30 (dd, 2H and 1F, $J = 5.5$ and 8.8 Hz), 7.05 (t, HF $J = 8.8$ Hz), 4.44 (dd, 1H, $J = 9.30$ and 10.89 Hz), 4.34 (q, 1H, $J = 5.78$ and 10.89 Hz), 4.19 (m, 2H), 3.92 (dd, 1H, $J = 5.8$ and 9.2 Hz), 2.84 (s, 3H, $COCH_3$), 2.71 (br s, 1H), 1.21 (t, 3H, $J = 7.14$ Hz); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 172.62, 170.33, 162.89, 159.59, 135.07, 129.29, 123.10, 114.43, 63.32, 61.71, 46.27, 29.36, 13.89. MS (EI, *m*/*z*%): 288(M+, 1), 253(7), 245(8), 228(13), 218(15), 216(37), 193(100), 170(16), 156(58), 143(34), 142(33), 121(18), 107(28), 101(10), 81(3), 75(7), 57(4).

4.6.8. (*R*)-(+)-3-Hydroxy-2-(4-fluorophenyl)-propionic acid ethyl ester (*R*)-(+)-2i and (*S*)-(−)-3-acetoxy-2-(4-fluorophenyl)-propionic acid ethyl ester (*S*)-(−)-3i. Racemic (±)-**2i** (100 mg, 0.47 mmol) was resolved according to the general procedure as in Section 4.3.3. The (*R*)-(+)-**2i** was isolated as a light yellow oil (44 mg, 0.207 mmol, 44%), 67% ee; $[\alpha]_D^{25} = +39$ (*c* 0.5, $CHCl_3$); same spectroscopic characteristics as of the racemic one (Section 4.1.8). (*S*)-(−)-3-acetoxy-2-(4-fIuorophenyl)-propionic acid ethyl ester **3i** was isolated as colorless oil (48.5 mg, 0.191 mmol, 40.5%), 50% ee; $[\alpha]_D^{25} = -32.5$ (*c* 1.31, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.30 (dd, 2H and 1F, $J = 5.5$ and 8.8 Hz), 7.05 (t, 2HF $J = 8.8$ Hz), 4.44 (dd, 1H, $J = 9.30$ and 10.89 Hz), 4.34 (q, 1H, $J = 5.78$ and 10.89 Hz), 4.19 (m, 2H), 3.92, (dd 1H, $J = 5.81$ and 9.24 Hz), 2.04 (s, 3H), 1.24 (t, 3H, $J = 7.14$Hz); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 175.23, 163.97, 160.70, 130.57, 129.70, 115.82, 64.94, 61.29, 49.8, 20.68, 13.97.

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