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Tetrahedron: *Asymmetry* 18 (2007) 1077–1084

# Preparation of enantiomerically pure (3*E*)-alkyl-4-(hetero-2-yl)-2-hydroxybut-3-enoates by *Candida parapsilosis* ATCC 7330 mediated deracemisation and determination of the absolute configuration of (3*E*)-ethyl-4-(thiophene-2-yl)-2-hydroxybut-3-enoate

T. Vaijayanthi[a] and Anju Chadha[b,*]

[a]*Department of Chemistry, Indian Institute of Technology Madras, Chennai 600 036, India*
[b]*Laboratory of Bioorganic Chemistry, Department of Biotechnology and National Center for Catalysis Research, Indian Institute of Technology Madras, Chennai 600 036, India*

Received 14 March 2007; accepted 26 April 2007
Available online 1 June 2007

**Abstract**—Deracemisation of racemic (3*E*)-alkyl-4-(hetero-2-yl)-2-hydroxybut-3-enoates using *Candida parapsilosis* ATCC 7330 resulted in the formation of one enantiomer in high enantiomeric excess [up to >99% ee] and isolated yields [up to 79%]. The absolute configuration of the enantiomerically pure (3*E*)-ethyl-4-(thiophene-2-yl)-2-hydroxybut-3-enoate as determined by $^1$H NMR of the Mosher esters was found to be (*S*).


## 1. Introduction

Several chemical[1] and enzymatic[2] methods are known for the synthesis of enantiomerically pure α-hydroxy esters, which are important and useful chiral synthons.[3] Of these, the resolution of racemates can result in a maximum theoretical yield of only 50% for each enantiomer.[4] In order to increase the yield of one enantiomer beyond 50%, the racemic substrate can be deracemised.[5] Deracemisation is a methodology, which can, in principle, provide a single enantiomer from a racemate in high yield and high enantiomeric excess.[6] Deracemisation can be carried out by re-racemisation, dynamic kinetic resolution or stereoinversion, chemically, chemo-enzymatically or enzymatically by using either isolated enzymes or whole cells.[2c–i,7] Among the other strategies for deracemisation,[8] stereoinversion using *Candida parapsilosis* has been well illustrated for 1,2-diols and 1,3-diols.[9] Deracemisation of racemic aryl α- and β-hydroxy esters to the corresponding enantiomerically pure (*S*)-hydroxy esters in high chemical yields (up to 85%) and up to >99% ee by *C. parapsilosis* ATCC 7330 was previously reported by our group.[2c,d–i] The asymmetric synthesis of (3*E*)-isopropyl-4-(furan-2-yl)-2-hydroxybut-3-enoate and (3*E*)-isopropyl-4-(thiophene-2-yl)-2-hydroxybut-3-enoate using the asymmetric catalyst Ru-TsDPEN gives low ee (59–65%).[10] Herein we report the deracemisation, by *C. parapsilosis* ATCC 7330, of hetero-aryl compounds, that is, (3*E*)-alkyl-4-(hetero-2-yl)-2-hydroxybut-3-enoates, where the hetero atom is either oxygen, sulfur or nitrogen. These chiral synthons are required for the synthesis of important pharmaceutical compounds such as 6-(1-arylmethylpyrrol-2-yl)-1,4-dioxo-5-hexenoic acids, 4-[5-(benzoylamino)thien-2-yl]-2,4-dioxobutanoic acid and 1-[5-(4-fluorobenzyl)furan-2-yl]-3-hydroxy-3-(1*H*-1,2,4-triazol-3-yl)propene which are found to possess antiviral activity.[11–13] The synthesis of racemic (3*E*)-alkyl-4-(hetero-2-yl)-2-hydroxybut-3-enoates is included along with the biocatalytic deracemisation to obtain the enantiomerically pure (3*E*)-alkyl-4-(hetero-2-yl)-2-hydroxybut-3-enoates in high yields. The determination of the absolute configurations of enantiomerically pure (3*E*)-ethyl-4-(thiophene-2-yl)-2-hydroxybut-3-enoate, which is obtained from its racemate by *C. parapsilosis* ATCC 7330 mediated deracemisation is reported here for the first time.

* Corresponding author. Tel.: +91 44 2257 4106; fax: +91 44 2257 4102; e-mail: anjuc@iitm.ac.in

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doi:10.1016/j.tetasy.2007.04.029

## 2. Results and discussion

### 2.1. Synthesis of substrates

Racemic (3*E*)-alkyl-4-(hetero-2-yl)-2-hydroxybut-3-enoates **3a**–**3i** (Table 1, Scheme 1) were synthesised by reported procedures[14] to obtain high yields of the target esters. (3*E*)-4-(Hetero-2-yl)-2-oxobut-3-enoic acids **1a**–**1i** (Scheme 1) were obtained in 90–95% yields by condensing the precursor aldehydes with pyruvate. Previous reports on the synthesis of (3*E*)-ethyl-4-(furan-2-yl)-2-oxobut-3-enoate, (3*E*)-methyl-4-(furan-2-yl)-2-oxobut-3-enoate, (3*E*)-ethyl-4-(thiophene-2-yl)-2-oxobut-3-enoate and (3*E*)-methyl-4-(thiophene-2-yl)-2-oxobut-3-enoate **2a**–**2d** (Scheme 1, Table 1) had used the Wittig reaction.[15–17] In order to improve the above reaction conditions such as refluxing with triphenyl phosphine for 3 days, various (3*E*)-alkyl-4-(hetero-2-yl)-2-oxobut-3-enoates **2a**–**2i** (Scheme 1, Table 1) were prepared within 3 h by esterification of the corresponding acids using concentrated hydrochloric acid as a catalyst. With the exception of (3*E*)-ethyl-4-(furan-2-yl)-2-hydroxybut-3-enoate **3a** and its derivatives which are known,[18] the synthesis of the racemic α-hydroxy heteroaryl carbonyl compounds **3b**–**3i** (Scheme 1, Table 1) is reported here for the first time. The sodium borohydride reduction of the (3*E*)-alkyl-4-(hetero-2-yl)-2-oxobut-3-enoates **2a**–**2i** (Scheme 1, Table 1) resulted in the corresponding racemic (3*E*)-alkyl-4-(hetero-2-yl)-2-hydroxybut-3-enoates **3a**–**3i** (Scheme 1, Table 1) in moderate to good yields (75–90%).

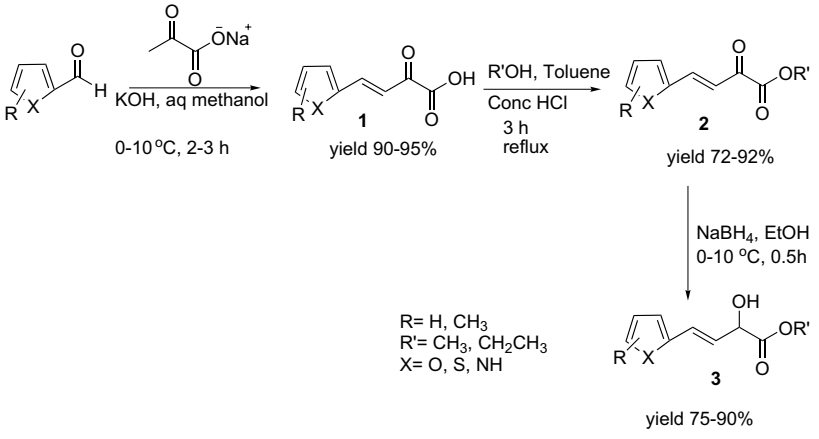
**Table 1.** Synthesis of racemic (3*E*)-alkyl-4-(hetero-2-yl)-2-hydroxybut-3-enoates **3a**–**3i**

| Entry | X | R | R′ | Yield (%) **2** | Yield (%) **3** |
|---|---|---|---|---|---|
| **a** | O | H | Et | 85 | 80 |
| **b** | O | H | Me | 87 | 75 |
| **c** | S | H | Et | 92 | 85 |
| **d** | S | H | Me | 90 | 83 |
| **e** | O | 5-Me | Et | 75 | 85 |
| **f** | O | 5-Me | Me | 72 | 82 |
| **g** | S | 5-Me | Et | 84 | 90 |
| **h** | S | 5-Me | Me | 86 | 89 |
| **i** | NH | H | Et | 73 | 76 |

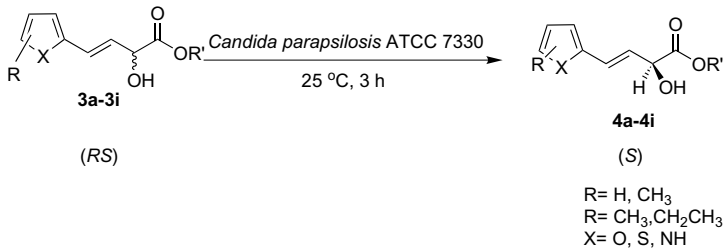
### 2.2. Deracemisation of racemic (3*E*)-alkyl-4-(hetero-2-yl)-2-hydroxybut-3-enoates using *C. parapsilosis* ATCC 7330

The deracemisation of the ethyl and methyl esters of racemic (3*E*)-4-(hetero-2-yl)-2-hydroxybut-3-enoic acids **3a**–**3i** (Scheme 2, Tables 2 and 3) by *C. parapsilosis* ATCC 7330 provided the enantiomerically pure ethyl and methyl esters of (*S*)-(3*E*)-4-(hetero-2-yl)-2-hydroxybut-3-enoic acids, respectively, **4a**–**4i** (Scheme 2, Tables 2 and 3) in excellent enantiomeric excess (90–>99%) and good isolated yields (52–79%) as described in Section 4. At the end of the reaction, that is, after the ee reached a constant value, as monitored by HPLC, the cells were filtered and the aqueous layer extracted with ethyl acetate. The enantiomeric excess of products **4a**–**4i** (Scheme 2, Tables 2 and 3) was determined by HPLC using a chiral stationary phase.

*C. parapsilosis* ATCC 7330 mediated deracemisation of the methyl and ethyl esters of racemic (3*E*)-4-(furan-2-yl)-2-hydroxybut-3-enoic acid, (3*E*)-4-(thiophene-2-yl)-2-hydroxybut-3-enoic acid and (3*E*)-4-(pyrrole-2-yl)-2-hydroxybut-3-enoic acid **3a**–**3d** and **3i** (Scheme 2, Tables 2 and 3) gave only one enantiomer in good yields (52–70%) and ee (95–>99%) **4a**–**4d** and **4i** (Scheme 2, Tables 2 and 3). The introduction of a 5-methyl group in the methyl and ethyl esters of (3*E*)-4-(furan-2-yl)-2-hydroxybut-3-enoic acid and (3*E*)-4-(thiophene-2-yl)-2-hydroxybut-3-enoic acid **3e**–**3h** (Scheme 2, Tables 2 and 3) improved the yields of the product enantiomer to 75–79% with good ee (92–97%) **4e**–**4h** (Scheme 2, Tables 2 and 3). Thus the biocatalyst *C. parapsilosis* ATCC 7330 deracemises (3*E*)-alkyl-4-(hetero-2-yl)-2-hydroxybut-3-enoates **3a**–**3i** (Scheme 2, Tables 2 and 3) into their enantiomerically pure product enantiomers **4a**–**4i** (Scheme 2, Tables 2 and 3) in good isolated yields (52–79%) and high ee (90–>99%), accepting the methyl substituents on these heteroaryl esters thus suggesting a wide substrate tolerance of the enzyme. In addition to the high enantioselectivity, the biocatalyst displays chemoselectivity in that the *C. parapsilosis* ATCC 7330 mediated deracemisation of β,γ-unsaturated α-hydroxy esters occurs without affecting the C=C bond. Hence, multifunctional enantiomerically pure chiral synthons (3*E*)-alkyl-4-




**Scheme 1.** Synthesis of racemic (3*E*)-alkyl-4-(hetero-2-yl)-2-hydroxybut-3-enoates **3a**–**3i**.




**Scheme 2.** Deracemisation of racemic (3*E*)-alkyl-4-(hetero-2-yl)-2-hydroxybut-3-enoates **3a**–**3i**.

**Table 2.** Deracemisation of racemic (3*E*)-alkyl-4-(hetero-2-yl)-2-hydroxybut-3-enoates **4a**–**4i**

| Compound | X | R | R′ | Yield | ee[a] | $[\alpha]_D^{25}$ | Lit. value | Abs conf |
|---|---|---|---|---|---|---|---|---|
| **4a** | O | H | Et | 70 | >99 | +25.6 (*c* 1, MeOH)[b] | −28.2 (MeOH, 200 mM)[c] | (*S*) |
| **4b** | O | H | Me | 52 | >99 | +25.1 (*c* 1, MeOH)[b] | −28.2 (MeOH, 200 mM)[c] | (*S*) |
| **4c** | S | H | Et | 70 | >99 | +97.6 (*c* 1, MeOH)[b] | −98.0 (MeOH, 97 mM)[c] | (*S*) |
| **4d** | S | H | Me | 65 | >99 | +96.9 (*c* 1, MeOH)[b] | −98.0 (MeOH, 97 mM)[c] | (*S*) |
| **4e** | O | 5-Me | Et | 78 | 90 | +35.2 (*c* 1, MeOH) | — | (*S*)[d] |
| **4f** | O | 5-Me | Me | 75 | 92 | +41.7 (*c* 1, MeOH) | — | (*S*)[d] |
| **4g** | S | 5-Me | Et | 77 | 95 | +61.4 (*c* 1, MeOH) | — | (*S*)[d] |
| **4h** | S | 5-Me | Me | 79 | 97 | +65.9 (*c* 1, MeOH) | — | (*S*)[d] |
| **4i** | NH | H | Et | 60 | 95 | +52.1 (*c* 1, MeOH) | — | (*S*)[d] |

[a] Enantiomeric excess was determined by using chiral HPLC (Chiracel ODH, solvent: hexane–IPA (98:2), flow rate: 1 ml/min).
[b] Specific rotations were measured after hydrolysis of the esters and compared with literature reported values.
[c] Ref. 19.
[d] Compounds **4e**–**4i** showed that the deracemised product had the same elution profile as compounds **4a**–**4d**, that is, the '*R*' enantiomer is the late eluting enantiomer, while '*S*' is the early eluting enantiomer (refer Table 3).

**Table 3.** Retention times of enantiomerically pure (3*E*)-alkyl-4-(heteroar-2-yl)-2-hydroxybut-3-enoates **4a**–**4i**

| Entry | X | R | R′ | Elution of HPLC peaks (retention time in minutes) | |
|---|---|---|---|---|---|
| | | | | Early (major) | Later (minor) |
| **4a** | O | H | Et | 13.95 | 17.19 |
| **4b** | O | H | Me | 19.71 | 23.85 |
| **4c** | S | H | Et | 15.89 | 19.60 |
| **4d** | S | H | Me | 22.35 | 28.76 |
| **4e** | O | 5-Me | Et | 13.44 | 14.56 |
| **4f** | O | 5-Me | Me | 17.41 | 18.88 |
| **4g** | S | 5-Me | Et | 20.27 | 22.53 |
| **4h** | S | 5-Me | Me | 20.55 | 22.53 |
| **4i** | NH | H | Et | 14.56 | 17.58 |

(hetero-2-yl)-2-hydroxybut-3-enoates **4a**–**4i** (Scheme 2, Tables 2 and 3) are obtained after 3 h.

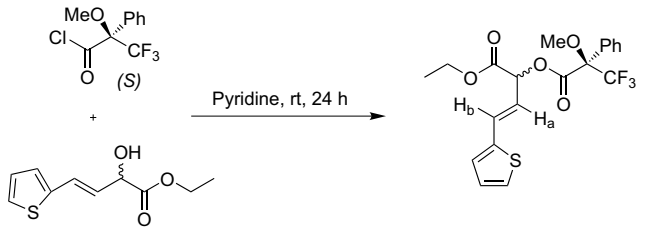
It was observed that upon deracemisation, the racemic (3*E*)-ethyl-4-(furan-2-yl)-2-hydroxybut-3-enoate **3a** (Scheme 2, Tables 2 and 3) results in the predominant formation of the (*S*)-enantiomer and a small amount (27%) of the corresponding (3*E*)-4-(furan-2-yl)-2-hydroxybut-3-enoic acid [92% ee][19] $\{[\alpha]_D^{25} = +23.0\ (c\ 1.0\ CH_3OH)\}$ as a side product. A control experiment revealed that the ester was stable under experimental conditions and in all likelihood enzymatic hydrolysis follows the deracemisation resulting in the formation of acid.

The mechanism of the deracemisation of the racemic (3*E*)-alkyl-4-(hetero-2-yl)-2-hydroxybut-3-enoates **3a**–**3i** (Scheme 2, Tables 2 and 3) as seen in aryl-2-hydroxy esters,[2g] which may involve a keto ester as an intermediate can be explained by a redox mechanism (stereoinversion) mediated by oxidoreductases. In order to verify the mechanism the following experiment was carried out with (3*E*)-ethyl-4-(furan-2-yl)-2-hydroxybut-3-enoate **3a** (Scheme 2, Tables 2 and 3). The time course of the deracemisation of the racemic (3*E*)-ethyl-4-(furan-2-yl)-2-hydroxybut-3-enoate **3a** (Scheme 2, Tables 2 and 3) was monitored by HPLC using a reverse phase column. Aliquots of the reaction mixture were taken every 15 min for 3 h. The keto ester intermediate was detected at 15 and 30 min, after which time it did not show up as a peak in the HPLC. The possible reasons for this observation could be (i) the first step which involves the formation of a keto ester intermediate is irreversible and (ii) the second step (reversible) which involves the enantioselective reduction of the keto ester intermediate (forward reaction) is considerably faster than the backward reaction, leading to a negligible concentration of the keto ester intermediate at any point during the reaction.[20] The presence of (3*E*)-ethyl-4-(furan-2-yl)-2-oxobut-3-enoate was confirmed by spiking it with the standard substrate **2a** (Scheme 1, Table 2).

### 2.3. Determination of the absolute configuration of (3*E*)-ethyl-4-(thiophene-2-yl)-2-hydroxybut-3-enoate 4c

Circular dichroism[21] and lanthanide shift reagents[22] can be employed for the determination of the absolute

configuration, but $^1$H NMR of Mosher esters is still the most widely used method.[23] In the present study, the absolute configuration of enantiomerically pure (3*E*)-ethyl-4-(thiophene-2-yl)-2-hydroxybut-3-enoate **4c** (Tables 2 and 3) was determined by a detailed $^1$H NMR study of the Mosher derivatives of **4c**. (*R*)-MTPA esters of (*RS*)-(3*E*)-ethyl-4-(thiophene-2-yl)-2-hydroxybut-3-enoate **3c** (Table 2) and enantiomerically pure ethyl-4-(thiophene-2-yl)-2-hydroxybut-3-enoate **4c**, whose absolute configuration was unknown, were also prepared (Scheme 3). The structure of the diastereomer [MTPA-(*S*,*R* or *R*,*R*)-**4c**, Scheme 3] was confirmed by $^1$H NMR spectroscopy as per the following discussion:




**Scheme 3.** Synthesis of (*R*)-MTPA esters of (*R*,*S*)-**3c** and (*R* or *S*)-**4c**.

(a) Determination of the absolute configuration of enantiomerically pure aryl β,γ-unsaturated α-hydroxy esters using $^1$H NMR of Mosher esters is reported.[24] The only structural difference between the reported[24] ethyl-2-hydroxy-4-phenyl-but-3-enoate enantiomer and the enantiomer (3*E*)-ethyl-4-(thiophene-2-yl)-2-hydroxybut-3-enoate **4c**, of which the absolute configuration was to be determined, is the thiophene moiety instead of a benzene ring which was assumed to have no effect on the protons under consideration for this study.

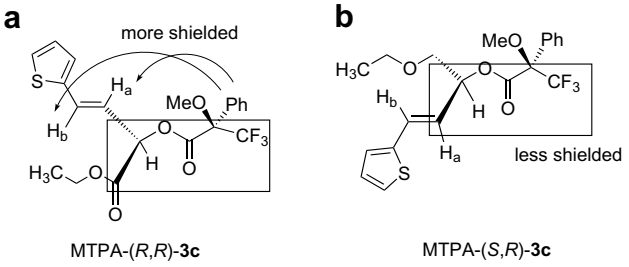


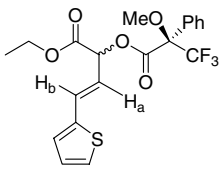
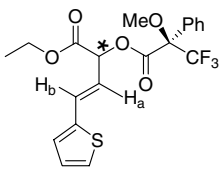

**Figure 1.** (*R*)-MTPA derivatives of ester (*R*,*R* and *S*,*R*)-**3c**.

(b) Figure 1a and b represent the absolute configurations of the diastereomers of MTPA-(*R*,*R*)-**3c** and MTPA-(*S*,*R*)-**3c** obtained from (*S*)-Mosher's acid chloride with (*RS*)-**3c**. The benzene ring of the Mosher's ester moiety can be assigned either *cis* or *trans* with regards to the olefinic protons ($H_a$ and $H_b$) of (*R*)-**3c** and (*S*)-**3c**. Thus in MTPA-(*R*,*R*)-**3c** (Fig. 1a) the benzene ring is *cis* and in MTPA-(*S*,*R*)-**3c** (Fig. 1b) it is *trans* with respect to the olefinic protons—$H_a$ and $H_b$. In the ester MTPA-(*R*,*R*)-**3c**, $H_a$ ($\delta$ 5.95–6.01 ppm) and $H_b$ ($\delta$ 6.70–6.74 ppm) are more shielded when compared to the $H_a$ ($\delta$ 6.02–6.08 ppm) and $H_b$ ($\delta$ 6.75–6.79 ppm) in MTPA-(*S*,*R*)-**3c** (Fig. 1, Table 4). This is due to the diamagnetic effect of the phenyl ring of Mosher's ester, as shown in Figure 1a and b.

(c) The $^1$H NMR spectrum of MTPA ester-(*S*,*R* or *R*,*R*)-**4c** [$H_a$ ($\delta$ 6.02–6.08 ppm), $H_b$ ($\delta$ 6.75–6.79 ppm)] was compared with the $^1$H NMR spectrum of the MTPA esters of the racemic mixture (*R*,*R* and *S*,*R*)-**3c** [$H_a$ ($\delta$ 5.95–6.01 and 6.02–6.08 ppm), $H_b$ ($\delta$ 6.70–6.74 and 6.75–6.79 ppm)]. The chemical shift ($\delta$) values for $H_a$ and $H_b$ protons of MTPA-(*S*,*R* or *R*,*R*)-**4c** match with those of the MTPA-(*S*,*R*)-**3c** (less shielded or where benzene and olefinic protons $H_a$ and $H_b$ are *trans*) as shown in Figure 2 indicating that the enantiomerically pure deracemised product **4c** is the (*S*)-enantiomer (Table 4).

(d) The specific rotation values for esters **4a**–**4b** and **4d** were measured after hydrolysis and compared with those reported in the literature[19] based on which the absolute configuration was assigned as (*S*). For compounds **4e**–**4i**, the specific rotations are reported herein for the first time. The other deracemised compounds **4e**–**4i** (Scheme 2, Tables 2 and 3) have identical chromatographic behaviour (elution order on the chiral stationary phase column) as the suggested (*S*) enantiomer.

**Table 4.** Chemical shift values of $H_a$ and $H_b$ in MTPA ester-(*R*,*R* and *S*,*R*)-**3c**, MTPA ester-(*R*,*R* or *S*,*R*)-**4c** (refer Scheme 3)

| Entry | Product Mosher's ester | Absolute configuration | $H_a$ ($\delta$ ppm) | $H_b$ ($\delta$ ppm) |
|---|---|---|---|---|
| MTPA ester-**3c** |  | (*R*,*R*) and (*S*,*R*) | 5.95–6.01 and 6.02–6.08 | 6.70–6.74 and 6.75–6.79 |
| MTPA ester-**4c** |  | (*R*,*R*) or (*S*,*R*) | 6.02–6.08 | 6.75–6.79[a] |

[a] These values are very similar to the ethyl-2-hydroxy-4-phenyl-but-3-enoate. Hence, we established that is was most likely (*S*).

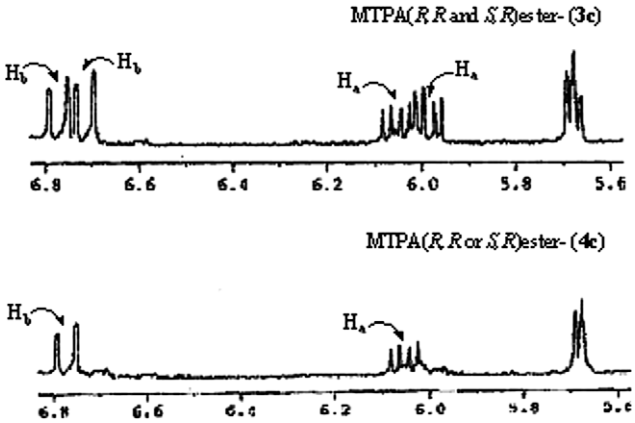



**Figure 2.** $^{1}H$ NMR signals of $H_a$ and $H_b$ in MTPA-(*R*,*R* and *S*,*R*)-**3c**, MTPA-(*R*,*R* or *S*,*R*)-**4c**.

## 3. Conclusion

Deracemisation by the biocatalyst, *C. parapsilosis* ATCC 7330 was found to be highly chemo- and enantioselective towards heteroaryl β,γ-unsaturated α-hydroxy esters resulting in the synthesis of multifunctional important chiral synthons, enantiomerically pure (*S*)-(3*E*)-alkyl-4-(hetero-2-yl)-2-hydroxybut-3-enoates **4a**–**4i** (Scheme 2, Tables 2 and 3) in high yields (up to 79%) and in high ee (up to >99%). The absolute configuration of the enantiomerically pure (3*E*)-ethyl-4-(thiophene-2-yl)-2-hydroxybut-3-enoate **4c** was determined as (*S*) using $^{1}H$ NMR of the Mosher ester.

## 4. Experimental

### 4.1. General methods

*C. parapsilosis* ATCC 7330 was purchased from ATCC, Manassas, VA 20108, USA. All chemicals used for media preparation were purchased locally. All substrates were synthesised as shown in the given schemes. $^{1}H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ on a JEOL GSX400 and Bruker AV-400 spectrometers operating at 400 MHz. Chemical shifts are expressed in ppm values using TMS as an internal standard. Infrared spectra were recorded on a Shimadzu IR 470 Instrument. Mass spectra were recorded on a Q TOF micromass spectrometer. The enantiomeric excess (ee%) were determined by HPLC analysis. HPLC using a chiral column analysis was done on a Jasco PU-1580 liquid chromatograph equipped with PDA detector. The chiral column used was Chiralcel OD-H (Daicel, 4.6 × 250 mm). The solvent used was hexane/isopropanol (98/2) at a flow rate of 1 ml $min^{-1}$ and the absorbance monitored using a PDA detector at 254 nm. The formation of the keto ester as intermediate in the mechanistic study was detected by HPLC using a reverse phase column ($R_t$: 3.97 min; column: Sil C-18, solvent system: acetonitrile–water (70/30), flow rate: 1 ml $min^{-1}$, detector: PDA). Optical rotations were determined on an Autopal$^{R}$ digital polarimeter. TLC was done using Kieselgel 60 $F_{254}$ aluminium sheets (Merck 1.05554).

### 4.2. Synthesis of substrates

**4.2.1. Preparation of (3*E*)-4-(hetero-2-yl)-2-oxobut-3-enoic acids 1a–1i. Typical reaction procedure of compound 1a.** Treatment of furan-2-aldehyde (0.862 ml, 0.010 mol) with sodium pyruvate (1.145 g, 0.010 mol) with 50% aqueous methanolic potassium hydroxide (0.841 g, 0.015 mol) at 0–10 °C with stirring for 3 h, resulted in the production of yellow salts that were neutralised with dilute HCl and extracted using ethyl acetate (3 × 10 ml). The combined organic extracts were dried over anhydrous sodium sulfate, then concentrated to afford (3*E*)-4-(furan-2-yl)-2-oxobut-3-enoic acid as a yellow solid in 90% yield. The same procedure was followed for compounds **1b**–**1i** (Scheme 1).

**4.2.2. Preparation of (3*E*)-alkyl-4-(hetero-2-yl)-2-oxobut-3-enoates 2a–2i. Typical reaction procedure of compound 2a.** Esterification of (3*E*)-4-(furan-2-yl)-2-oxobut-3-enoic acid **1a** (Scheme 1) (3 mmol, 500 mg) was carried out with ethanol (5 ml) in the presence of concentrated hydrochloric acid (0.2 ml) as a catalyst in dry toluene (10 ml) for 3 h at 95 °C. After esterification was complete, the toluene and excess ethanol were removed. Compound (3*E*)-ethyl-4-(furan-2-yl)-2-oxobut-3-enoate **2a** was obtained as a brownish yellow solid in 85% yield (2.5 mmol, 495 mg) after column purification using hexane–ethyl acetate (95/5) as solvent. The same procedure was followed for compounds **2b**–**2i** (Scheme 1 and Table 1).

**4.2.3. Preparation of (3*E*)-alkyl-4-(hetero-2-yl)-2-hydroxybut-3-enoates 3a–3i. Typical reaction procedure of compound (3*E*)-ethyl-4-(furan-2-yl)-2-hydroxybut-3-enoate 3a.** Reduction of (3*E*)-ethyl-4-(furan-2-yl)-2-oxobut-3-enoate **2a** (Scheme 1) (2.3 mmol, 450 mg) was carried out with sodium borohydride (2.3 mmol, 86 mg) in ethanol (5 ml) for 0.5 h at 0–10 °C. After completion of the reaction, the ethanol was removed. Compound (3*E*)-ethyl-4-(furan-2-yl)-2-hydroxybut-3-enoate **3a** was obtained as a brownish yellow liquid in 80% yield (1.8 mmol, 362 mg) after column purification using hexane–ethyl acetate (95/5) as the solvent. The same procedure was followed for compounds **3b**–**3i** (Scheme 1 and Table 1).

### 4.3. Deracemisation of various racemic (3*E*)-alkyl-4-(hetero-2-yl)-2-hydroxybut-3-enoates

**4.3.1. Culture medium for the growth of *C. parapsilosis* ATCC 7330.** Cells of the yeast, *C. parapsilosis* ATCC 7330 were grown as reported earlier[2i] and harvested after 44 h and used for the deracemisation reaction.

**4.3.2. A typical procedure for the deracemisation reaction of (3*E*)-ethyl-4-(furan-2-yl)-2-hydroxybut-3-enoate 3a using the whole cells of *C. parapsilosis* ATCC 7330.** Deracemisation of racemic (3*E*)-ethyl-4-(furan-2-yl)-2-hydroxybut-3-enoate **3a** (3 mg, 0.015 mmol) mediated by resting cells of *C. parapsilosis* ATCC 7330 was carried out using the reported procedure.[2i] In order to determine the isolated chemical yield, the deracemisation of **3a** was carried out with 72 mg of the substrate. The rest of the racemic (3*E*)-alkyl-4-(hetero-2-yl)-2-hydroxybut-3-enoates **3b**–**3i** were also used as substrates in the same manner (Scheme 2 and Table 2).

### 4.4. Preparation of MTPA esters

(*R*)-MTPA esters of (*RS*)-(3*E*)-ethyl-4-(thiophene-2-yl)-2-hydroxybut-3-enoate **3c** (Table 2) and enantiomerically pure ethyl-4-(thiophene-2-yl)-2-hydroxybut-3-enoate **4c** (Table 2) were prepared (Scheme 3) by using the reported method.[24]

#### 4.4.1. Analytical data

**4.4.1.1. (3*E*)-Ethyl-4-(furan-2-yl)-2-oxobut-3-enoate 2a.** Yellow solid: mp 70 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ ppm: 1.31 (t, $J = 7.4$ Hz, 3H), 4.29 (q, $J = 7.4$ Hz, 2H), 6.45 (dd, $J = 2.0$, 3.5 Hz, 1H), 6.75 (d, $J = 3.5$ Hz, 1H), 7.12 (d, $J = 15.6$ Hz, 1H), 7.50 (d, $J = 2.0$ Hz, 1H), 7.52 (d, $J = 15.6$ Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ ppm: 13.8, 62.2, 113.0, 117.7, 118.5, 133.3, 146.2, 150.8, 161.8, 182.1; IR $\nu_{max}$: 625.4, 705.1, 801.0, 1023.8, 1086.8, 1377.9, 1561.9, 1603.0, 1733.7, 2956.0 cm$^{-1}$; HRMS (ESI): *m/z* 195.0657, $C_{10}H_{11}O_4$ $[M+H]^+$ requires 195.0649.

**4.4.1.2. (3*E*)-Ethyl-4-(5-methylfuran-2-yl)-2-oxobut-3-enoate 2e.** Orange yellow solid: mp 87 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ ppm: 1.30 (t, $J = 7.0$ Hz, 3H), 2.30 (s, 3H), 4.28 (q, $J = 7.0$ Hz, 2H), 6.08 (d, $J = 3.6$ Hz, 1H), 6.65 (d, $J = 3.6$ Hz, 1H), 7.05 (d, $J = 15.6$ Hz, 1H), 7.46 (d, $J = 15.6$ Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ ppm: 13.0, 14.4, 61.2, 109.0, 115.3, 119.7, 132.5, 148.8, 156.7, 161.3, 181.3; IR $\nu_{max}$: 623.1, 733.1, 879.5, 1045.1, 1086.8, 1377.9, 1560.9, 1604.2, 1737.6, 2883.3, 2972.7 cm$^{-1}$; HRMS (ESI): *m/z* 231.0638, $C_{11}H_{12}O_4Na$ $[M+Na]^+$ requires 231.0633.

**4.4.1.3. (3*E*)-Methyl-4-(5-methylfuran-2-yl)-2-oxobut-3-enoate 2f.** Yellow solid: mp 84 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ ppm: 2.46 (s, 3H), 3.85 (s, 3H), 6.08 (d, $J = 3.5$ Hz, 1H), 6.65 (d, $J = 3.5$ Hz, 1H), 7.05 (d, $J = 15.6$ Hz, 1H), 7.46 (d, $J = 15.6$ Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ ppm: 14.1, 52.9, 110.1, 116.1, 121.0, 133.7, 149.8, 157.8, 162.6, 181.8; IR $\nu_{max}$: 625.4, 705.1, 801.0, 973.5, 1023.8, 1085.3, 1141.0, 1184.3, 1249.1, 1285.4, 1370.3, 1437.5, 1515.9, 1561.1, 1603.3, 1682.5, 1733.7, 2956.0 cm$^{-1}$; HRMS (ESI): *m/z* 217.0480, $C_{10}H_{10}O_4Na$ $[M+Na]^+$ requires 217.0477.

**4.4.1.4. (3*E*)-Ethyl-4-(5-methylthiophen-2-yl)-2-oxobut-3-enoate 2g.** Yellow solid: mp 102 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ ppm: 1.32 (t, $J = 6.7$ Hz, 3H), 2.45 (s, 3H), 4.29 (q, $J = 6.7$ Hz, 2H), 6.70 (d, $J = 2.9$ Hz, 1H), 6.93 (d, $J = 15.6$ Hz, 1H), 7.15 (d, $J = 2.9$ Hz, 1H), 7.83 (d, $J = 15.6$ Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ ppm: 14.0, 16.0, 62.3, 117.9, 127.3, 134.7, 137.8, 140.9, 147.1, 162.2, 182.0; IR $\nu_{max}$: 466.1, 592.8, 733.2, 781.7, 790.2, 848.4, 862.6, 882.4, 913.4, 989.6, 1048.1, 1083.4, 1092.4, 1202.0, 1237.8, 1261.6, 1283.3, 1311.4, 1372.6, 1420.7, 1586.9, 1731.7, 2957.0 cm$^{-1}$; HRMS (ESI): *m/z* 247.0409, $C_{11}H_{12}O_3SNa$ $[M+Na]^+$ requires 247.0405.

**4.4.1.5. (3*E*)-Methyl-4-(5-methylthiophen-2-yl)-2-oxobut-3-enoate 2h.** Yellow solid: mp 95 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ ppm: 2.46 (s, 3H), 3.85 (s, 3H), 6.71 (d, $J = 2.8$ Hz, 1H), 6.95 (d, $J = 15.6$ Hz, 1H), 7.19 (d, $J = 2.8$ Hz, 1H), 7.85 (d, $J = 15.6$ Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ ppm: 16.1, 53.0, 117.7, 127.4, 135.0, 137.8, 141.1, 147.4, 162.6, 181.6; IR $\nu_{max}$: 498.1, 544.3, 663.2, 706.5, 795.0, 971.5, 1050.1, 1083.3, 1198.4, 1256.0, 1528.9, 1582.1, 1654.4, 1682.0, 1731.3, 2953.1 cm$^{-1}$; HRMS (ESI): *m/z* 233.0247, $C_{10}H_{10}O_3SNa$ $[M+Na]^+$ requires 233.0248.

**4.4.1.6. (3*E*)-Ethyl-4-(pyrrole-2-yl)-2-oxobut-3-enoate 2i.** Brown yellow liquid; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ ppm: 1.31 (t, $J = 7.2$ Hz, 3H), 4.15 (q, $J = 7.2$ Hz, 2H), 4.92 (s, br, 1H), 6.08–6.18 (m, 2H), 6.57 (d, $J = 3.1$ Hz, 1H), 6.72 (d, $J = 15.4$ Hz, 1H), 7.60 (d, $J = 15.4$ Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ ppm: 14.1, 61.0, 109.2, 114.8, 120.4, 130.4, 131.5, 147.4, 162.6, 181.6; IR $\nu_{max}$: 498.1, 544.3, 663.2, 706.5, 795.0, 971.5, 1050.1, 1083.3, 1198.4, 1256.0, 1528.9, 1582.1, 1654.4, 1682.0, 1731.3, 2953.1 cm$^{-1}$; HRMS (ESI): *m/z* 216.0010, $C_{10}H_{11}NO_3Na$ $[M+Na]^+$ requires 216.0007.

**4.4.1.7. (3*E*)-Methyl-4-(furan-2-yl)-2-hydroxybut-3-enoate 3b.** Yellow liquid; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ ppm: 3.11 (s, 1H), 3.82 (s, 3H), 4.82 (d, $J = 5.4$ Hz, 1H), 6.21 (dd, $J = 5.4$ and 15.7 Hz, 1H), 6.28 (d, $J = 3.2$ Hz, 1H), 6.36 (dd, $J = 1.2$ and 3.2 Hz, 1H), 6.63 (d, $J = 15.7$ Hz, 1H), 7.35 (d, $J = 1.2$ Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ ppm: 53.0, 70.8, 109.0, 111.3, 120.1, 123.7, 142.3, 159.0, 173.1; IR $\nu_{max}$: 594.4, 702.1, 731.0, 884.0, 923.9, 965.0, 1013.8, 1125.3, 1264.8, 1438.4, 1735.8, 2359.8, 2955.5, 3480.7 cm$^{-1}$; HRMS (ESI): *m/z* 205.0476, $C_9H_{10}O_4Na$ $[M+Na]^+$ requires 205.0477.

**4.4.1.8. (3*E*)-Ethyl-4-(thiophen-2-yl)-2-hydroxybut-3-enoate 3c.** Yellow liquid; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ ppm: 1.21 (t, $J = 6.9$ Hz, 3H), 3.1 (s, br, 1H), 4.1 (q, $J = 6.9$ Hz, 2H), 4.70 (d, $J = 5.2$ Hz, 1H), 5.90 (dd, $J = 5.2$ and 15.6 Hz, 1H), 6.83 (d, $J = 1.6$ Hz, 1H), 6.88 (d, $J = 15.6$ Hz, 1H), 6.90 (dd, $J = 1.6$ and 5.2 Hz, 1H), 7.10 (d, $J = 5.2$ Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ ppm: 16.2, 53.1, 70.8, 124.6, 124.9, 125.5, 126.6, 127.3, 141.1, 173.6; IR $\nu_{max}$: 486.7, 545.4, 698.7, 753.4, 826.3, 855.2, 957.1, 1020.5, 1040.7, 1040.7, 1118.9, 1199.4, 1257.1, 1368.6, 1644.9, 1728.8, 2981.5, 3466.0 cm$^{-1}$; HRMS (ESI): *m/z* 235.0408, $C_{10}H_{12}O_3SNa$ $[M+Na]^+$ requires 235.0405.

**4.4.1.9. (3*E*)-Methyl-4-(thiophen-2-yl)-2-hydroxybut-3-enoate 3d.** Yellow liquid; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ ppm: 3.89 (s, 3H), 4.86 (d, $J = 5.2$ Hz, 1H), 6.14 (dd, $J = 5.2$ and 15.6 Hz, 1H), 6.99 (d, $J = 15.6$ Hz, 1H), 7.02 (d, $J = 1.6$ Hz, 1H), 7.05 (dd, $J = 1.6$, 4.7 Hz, 1H), 7.24 (d, $J = 4.7$ Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ ppm: 53.0, 70.9, 124.5, 124.8, 125.4, 126.5, 127.4, 141.0, 173.5; IR $\nu_{max}$: 494.4, 699.2, 809.2, 852.9, 956.7, 1040.6, 1119.6, 1206.2, 1435.2, 1585.2, 1656.5, 1727.4, 2952.0, 3436.4 cm$^{-1}$; HRMS (ESI): *m/z* 221.0245, $C_9H_{10}O_3SNa$ $[M+Na]^+$ requires 221.0248.

**4.4.1.10. (3*E*)-Ethyl-4-(5-methylfuran-2-yl)-2-hydroxybut-3-enoate 3e.** Yellow liquid; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ ppm: 1.37 (t, $J = 7.1$ Hz, 3H), 3.09 (s, br, 1H), 3.72 (s, 3H), 4.2 (q, $J = 7.1$ Hz, 2H), 4.82 (d, $J = 5.2$ Hz, 1H), 6.0–6.21 (2H, m), 6.47 (dd, $J = 5.2$ and 15.6 Hz,

1H), 6.59 (d, $J = 15.6$ Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ ppm: 13.6, 14.1, 62.2, 70.9, 107.4, 110.2, 120.3, 122.1, 150.4, 150.8, 173.3; IR $\nu_{max}$: 701.4, 729.7, 785.4, 858.2, 1021.2, 1081.0, 1243.5, 1370.4, 1444.5, 1467.6, 1514.2, 1563.4, 1603.8, 1642.0, 1727.3, 2983.2, 3452.4 $cm^{-1}$; HRMS (ESI): $m/z$ 211.0969, $C_{11}H_{15}O_4$ $[M+H]^+$ requires 211.0970.

**4.4.1.11. (3*E*)-Methyl-4-(5-methylfuran-2-yl)-2-hydroxybut-3-enoate 3f.** Yellow liquid; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ ppm: 2.0 (s, 3H), 3.75 (s, 3H), 4.71 (d, $J = 5.4$ Hz, 1H), 5.88 (d, $J = 1.6$ Hz, 1H), 6.02 (dd, $J = 5.4$ and 15.6 Hz, 1H), 6.08 (d, $J = 1.6$ Hz, 1H), 6.47 (d, $J = 15.6$ Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ ppm: 13.6, 52.9, 70.9, 107.5, 110.3, 120.4, 121.9, 150.3, 152.4, 173.7; IR $\nu_{max}$: 701.6, 732.2, 786.1, 965.8, 1021.3, 1086.1, 1265.2, 1437.8, 1516.7, 1562.6, 1603.2, 1732.6, 2954.9, 3473.7 $cm^{-1}$; HRMS (ESI): $m/z$ 219.0638, $C_{10}H_{12}O_4Na$ $[M+Na]^+$ requires 219.0633.

**4.4.1.12. (3*E*)-Ethyl-4-(5-methylthiophen-2-yl)-2-hydroxybut-3-enoate 3g.** Yellow liquid; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ ppm: 1.3 (t, $J = 6.8$ Hz, 3H), 2.4 (s, 3H), 4.19 (q, $J = 6.8$ Hz, 2H), 4.74 (d, $J = 5.6$ Hz, 1H), 6.25 (dd, $J = 5.6$ and 15.4 Hz, 1H), 6.61 (d, $J = 1.6$ Hz, 1H), 6.65 (d, $J = 15.4$ Hz, 1H), 6.68 (d, $J = 1.6$ Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ ppm: 14.0, 16.2, 61.1, 73.3, 126.8, 127.0, 127.5, 127.9, 145.0, 135.2, 172.0; IR $\nu_{max}$: 702.3, 733.2, 801.0, 1021.2, 1106.9, 1192.4, 1266.3, 1448.5, 1725.7, 2832.6, 2943.4, 3333.7 $cm^{-1}$; HRMS (ESI): $m/z$ 249.0565, $C_{11}H_{14}O_3SNa$ $[M+Na]^+$ requires 249.0561.

**4.4.1.13. (3*E*)-Methyl-4-(5-methylthiophen-2-yl)-2-hydroxybut-3-enoate 3h.** Yellow liquid; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ ppm: 2.4 (s, 3H), 3.5 (s, 3H), 4.72 (d, $J = 5.5$ Hz, 1H), 6.23 (dd, $J = 5.5$ and 15.4 Hz, 1H), 6.62 (d, $J = 1.7$ Hz, 1H), 6.65 (d, $J = 15.4$ Hz, 1H), 6.69 (d, $J = 1.7$ Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ ppm: 16.5, 52.4, 73.0, 126.8, 127.0, 127.5, 127.7, 135.5, 143.6, 173.0; IR $\nu_{max}$: 750.3, 801.4, 956.2, 1035.2, 1095.6, 1216.7, 1366.4, 1444.4, 1642.9, 1738.7, 1991.2, 2210.0, 2854.1, 2925.4, 3455.8 $cm^{-1}$; HRMS (ESI): $m/z$ 213.0592, $C_{10}H_{13}O_3S$ $[M+H]^+$ requires 213.0585.

**4.4.1.14. (3*E*)-Ethyl-4-(pyrrole-2-yl)-2-hydroxybut-3-enoate 3i.** Brown yellow liquid; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ ppm: 1.3 (t, $J = 7.3$ Hz, 3H), 2.8 (s, br, 1H), 4.15 (q, $J = 7.3$ Hz, 2H), 4.77 (d, $J = 5.5$ Hz, 1H), 6.12 (d, $J = 2.5$ Hz, 1H), 6.14–6.18 (m, 1H), 6.27 (dd, $J = 5.5$ and 15.6 Hz, 1H), 6.64 (d, $J = 15.6$ Hz, 1H), 6.68 (d, $J = 2.5$ Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ ppm: 14.2, 16.9, 74.3, 109.5, 112.5, 119.7, 126.8, 127.5, 130.1, 172.0; IR $\nu_{max}$: 702.3, 733.2, 801.0, 1021.2, 1106.9, 1192.4, 1266.3, 1448.5, 1725.7, 2832.6, 2943.4, 3333.7 $cm^{-1}$; HRMS(ESI): $m/z$ 218.0900, $C_{10}H_{13}NO_3Na$ $[M+Na]^+$ requires 218.0909.

**4.4.1.15. MTPA-(*R*,*R* and *S*,*R*)-3c.** Yellow liquid; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ ppm: 1.28 (2t, $J = 6.9$ Hz, 6H), 3.51 (s, 3H), 3.62 (s, 3H), 4.32 (2q, $J = 6.9$ Hz, 4H), 5.79 (2d, $J = 5.1$ Hz, 2H), 5.98 (dd, $J = 5.1$ and 15.2 Hz, 1H), 6.05 (dd, $J = 5.1$ and 15.2 Hz, 1H), 6.72 (d, $J = 15.2$ Hz, 1H), 6.77 (d, $J = 15.2$ Hz, 1H), 6.90–7.65 (m, 16H).

**4.4.1.16. MTPA-(*S*,*R*)-4c.** Yellow liquid; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ ppm: 1.28 (t, $J = 6.9$ Hz, 3H), 3.62 (s, 3H), 4.25 (q, $J = 6.9$ Hz, 2H), 5.79 (d, $J = 5.1$ Hz, 1H), 6.06 (dd, $J = 5.1$ and 15.2 Hz 1H), 6.76 (d, $J = 15.2$ Hz, 1H), 7.0–7.7 (m, 8H).

## Acknowledgements

We thank the DST, Government of India, for providing financial assistance and Sophisticated Analytical Instrumentation Facility (SAIF), Indian Institute of Technology Madras, Chennai, for NMR data.

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