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Application of Sharpless asymmetric dihydroxylation to thienyl- and benzothienyl acrylates and crotonates

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Abstract—Optimized conditions for the catalytic asymmetric dihydroxylation have been applied to thiophene and benzothiophene containing acrylates and crotonates to afford the corresponding diols in good overall yields and good to excellent enantiomeric excess. The products obtained were revealed to be useful intermediates in peptidomimetic synthesis.

1. Introduction

Chiral vicinal diols are interesting and useful synthetic frameworks due to their presence in many biologically active compounds as well as in synthetic HIV-protease inhibitors.[1] Moreover, they can be easily transformed into 1,2-aminoalcoholic subunits,[2] common structural components in a large group of naturally occurring and synthetic molecules.

Among several asymmetric methodologies,[3] such diols can be easily obtained by the Sharpless asymmetric dihydroxylation[2a] that has been extensively applied to different *E*-olefins. However, with the exception of a few cases, it has never been applied to thiophene containing olefins.[4]

Herein we focused our attention on the preparation of chiral 1,2-diol subunits starting from several thienyl and benzothienyl substituted acrylates and crotonates (Fig. 1), useful new building blocks for peptidomimetic chemistry.

To the best of our knowledge, only a few examples of asymmetric oxidation of heteroaromatic acrylates as well as crotonates, have been reported,[4,5] mainly with pyridine and pyrrole substituted olefins. This is probably due to the lower reactivity of the electron deficient olefin and/or to the reactivity of the thiophene ring under the usual reaction conditions.

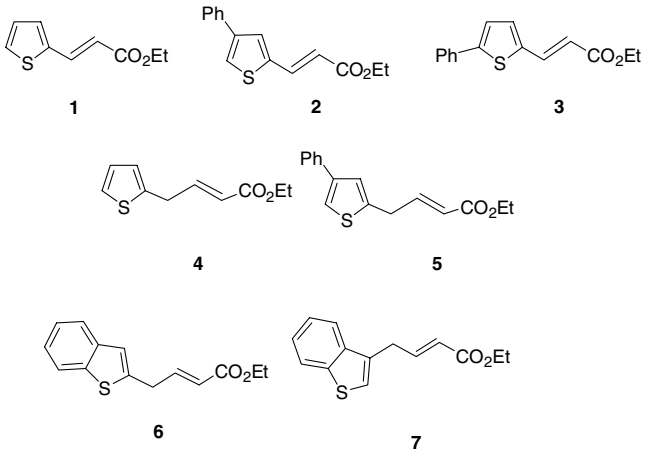

Figure 1.

We have previously reported the first use of the Sharpless asymmetric dihydroxylation on a thiophene containing acrylate[4] and herein we report an extension of the protocol to other substituted thiophene and benzothiophene acrylates and crotonates to afford interesting chiral 1,2-diols.

2. Results and discussion

The starting *trans* olefins **1**–**7** (Fig. 1) were readily prepared in two different ways depending upon the length of the aliphatic chain. Acrylates **1**–**3** were obtained by a Wittig–Horner reaction[6] from the corresponding heteroaryl

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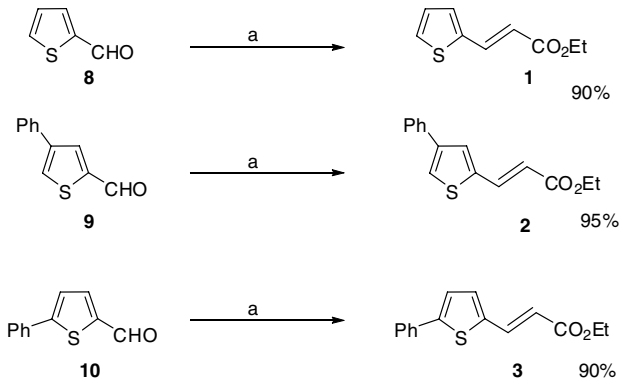
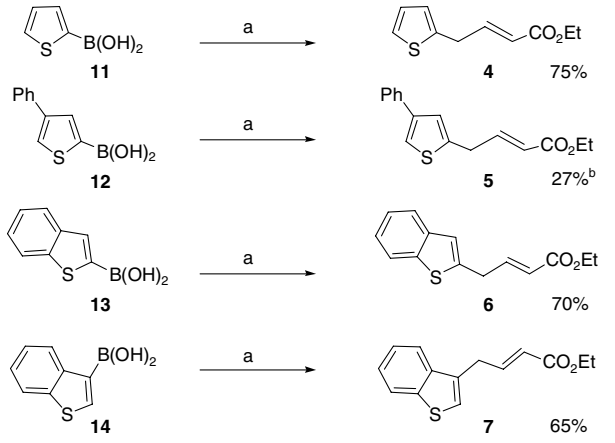


Scheme 1. Reagents and conditions: (a) triethyl phosphonoacetate, toluene, NaH 60%, rt, 16 h.

aldehydes (Scheme 1), while crotonates **4**–**7** were synthesized via Suzuki coupling[7] between commercially available heteroaryl boronic acids **11**, **13** and **14**[8] and ethyl 4-bromocrotonate (Scheme 2).



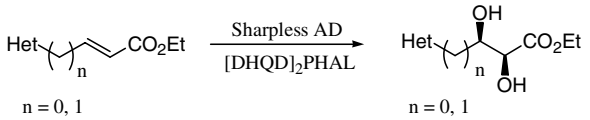
Scheme 2. Reagents and conditions: (a) ethyl 4-bromocrotonate, $Pd(PPh_3)_4$, Na_2CO_3, dioxane, reflux, 18–20 h; (b) overall yield from 3-phenyl thiophene.

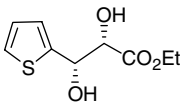
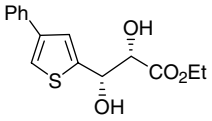
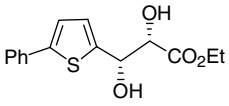
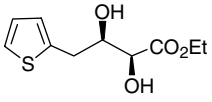
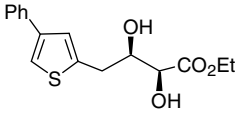
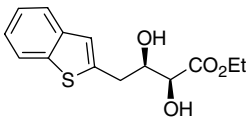
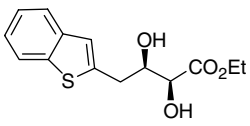
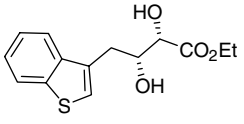
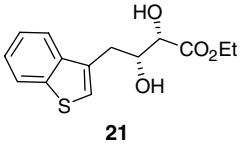
All olefins were obtained in good yields except for compound **5** (27% in yield), probably due to the low regioselectivity of the reaction affording the appropriate boronic acid **12**.[8] The conditions of the Suzuki coupling reaction have been carefully studied: an excess of the starting boronic acid was always necessary to completely consume the ethyl 4-bromo crotonate. This was found to be very important because of a difficult separation of the ethyl 4-bromo crotonate and the final olefins during column chromatography on silica gel.

On all these substrates, the Sharpless asymmetric dihydroxylation (Table 1) was extensively studied under different conditions by varying the temperature, reaction time and catalyst amount (vide infra).

As already reported,[4] the standard conditions for AD (1 mol % of ligand respect to the olefin)[2a] have been changed by increasing the ligand to 2.4 mol %: we obtained the desired diol within about 50% chemical yield and with excellent ee (99%).

Table 1. Sharpless asymmetric dihydroxylation on heteroaryl acrylates and crotonates **1**–**7**



Entry	Olefin	T (°C)	t (h)	Product	Yield (%)	ee[a] (%)
1	**1**	0/15	16	 **15**	60	>98
2	**2**	0/rt	21	 **16**	78	>98
3	**3**	rt	120	 **17**	22	98[b]
4	**4**	0	18	 **18**	90	94
5	**5**	0	40	 **19**	65	88
6	**6**	0	28	 **20**	47	88
7	**6**	rt	24	 **20**	70	84
8	**7**	0	48	 **21**	47	82
9	**7**	rt	20	 **21**	47	81

[a] Evaluated by chiral HPLC.
[b] Evaluated on acetonide derivative of diol.

In a subsequent paper,[5a] where AD was reported to be applied to various heteroaryl acrylates, the amount of ligand was increased further from 2% to 3% affording improved yields and similar ees.

Recently[9] we have reported a further improvement in the synthesis of diol **15** obtained by increasing either the AD-mix catalyst (from 1.40 to 1.64 g/mmol of olefin) and ligand (from 2.0 to 2.4 mol %): such conditions were therefore applied to all olefins **1**–**7** described here.

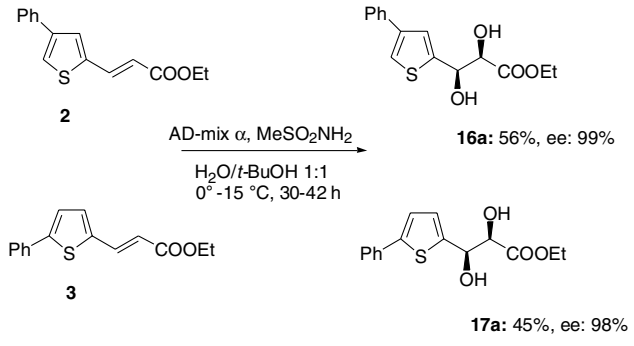
In Table 1, we report the results of our studies with respect to the reaction time, temperature, yield and ee (evaluated by HPLC).

As can be seen in Table 1, the ee was found to be excellent for the acrylates (entries 1–3), with varying chemical yields. The low chemical yield for the dihydroxylation of olefin **3** was probably due to the high electron deficiency of the olefinic double bond conjugated with the thiophene bearing the phenyl group at the α-position. Moreover, the evaluation of the ee of diol **17** by HPLC analysis was very difficult, therefore, it was made via the corresponding 1,3-dioxolane (see Experimental).[10]

Different and unpredictable results were obtained for crotonates **4**–**7**. Noteworthy are the chemical and optical yields for the AD on crotonate **4** to give diol **18**, in the presence of an unsubstituted thiophene ring. On the contrary, with olefins **5**, **6** and **7**, we noticed a slight decrease in the ee values with respect to the other ones.

An increase in the reaction temperature from 0 °C to room temperature for diol **20** led to an enhanced yield, while diol **21** was obtained in similar amount under both temperature conditions (0 and 25 °C). Remarkably, either at 0 °C or at room temperature, the thienyl ring was found unaltered under the reaction conditions.

Finally, we attempted to reproduce the Sharpless asymmetric dihydroxylation on compounds **2** and **3** by using the AD-mix α reagent with ligand DHQ, as reported in Scheme 3.



Scheme 3.

As shown, the change of the ligand did not give any substantial difference in chemical yields and in ees for diols **16a** and **17a**. Therefore, we can conclude that the thienyl substrates reacted in a similar way both with AD-mix α or AD-mix β reagents.

3. Conclusions

Herein we have applied the Sharpless asymmetric dihydroxylation on several acrylates and crotonates with thienyl and benzothienyl substituents with the aim of obtaining novel chiral 1,2-diols. With the thienyl ring containing acrylates the ees are excellent even if the chemical yields are not always satisfactory. Indeed, on the crotonates we can obtain the desired diols in good chemical and optical yields under different reaction conditions.

It is noteworthy that during the reaction, no oxidation by-products of the thienyl ring were detected.

The new 1,2-diols synthesized represent very interesting compounds because they are present in many natural products, in drugs and in peptidomimetics. In particular, they can be easily transformed into aminoalcohols with a high chemoselectivity, as has already been demonstrated.[9]

4. Experimental

4.1. General

Column chromatography was carried out on Merck silica gel (0.063–0.200 mm particle size) by progressive elution with petroleum ether/ethyl acetate mixtures. Mass spectra were obtained by GC/MS with electron impact ionization. ^{1}H and ^{13}C NMR spectra were normally carried out in $CDCl_3$ solutions on a VARIAN INOVA 500 and/or on Bruker AM 300. Chemical shifts (δ) were expressed in ppm and coupling constant (J) in hertz. Optical rotations were determined operating at the sodium D line at 25 °C. HPLC analyses were conducted using a Chiralcel OJ-H column with UV detection at 235 nm.

Unless otherwise specified, the materials were purchased from commercial suppliers and used without further purification. Tetrahydrofuran, toluene, diethyl ether were distilled from sodium/benzophenone ketyl immediately before use. Dichloromethane was distilled from P_2O_5. Moisture-sensitive reactions were conducted in oven- or flame-dried glassware under an argon atmosphere.

The synthesis and characterization of compounds **1** and **15** has already been reported.[4,9]

4.2. Synthesis of olefins 2 and 3

These compounds were synthesized by Wittig–Horner reaction according to the reported experimental procedure.[4,9]

4.2.1. 3-(4-Phenyl-thiophen-2-yl)-acrylic acid ethyl ester 2. Obtained as a yellow powder in 95% yield. $R_f = 0.5$ (petroleum ether/EtOAc 9:1). Mp: 79–81 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, $J = 16$ Hz, 1H), 7.58 (d, $J = 7.5$ Hz, 2H), 7.54 (s, 1H), 7.49 (s, 1H), 7.44 (t,

$J = 7.5$ Hz, 2H), 7.35 (t, $J = 7$ Hz, 1H), 6.30 (d, $J = 16$ Hz, 1H), 4.28 (q, $J = 7.5$ Hz, 2H), 1.36 (t, $J = 7.5$ Hz, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 166.8, 143.2, 140.1, 137.0, 134.9, 129.7, 128.9, 127.6, 126.2, 123.0, 117.3, 60.5, 14.3. EI-MS *m/z*: M^+, 258. Anal. Calcd for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46; O, 12.39; S, 12.41. Found: C, 70.01; H, 5.51; O, 12.34; S, 12.37.

4.2.2. 3-(5-Phenyl-thiophen-2-yl)-acrylic acid ethyl ester 3. Obtained as a yellow powder in 90% yield. $R_f = 0.45$ (petroleum ether/Et_2O 85:15). Mp: 81–83 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, $J = 16$ Hz, 1H), 7.59 (d, $J = 7$ Hz, 2H), 7.32 (m, 3H), 7.23 (d, $J = 3.7$ Hz, 1H), 7.18 (d, $J = 3.7$ Hz, 1H), 6.23 (d, $J = 16$ Hz, 1H), 4.27 (q, $J = 7$ Hz, 2H), 1.34 (t, $J = 7$ Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 166.7, 147.1, 138.6, 136.9, 133.4, 132.1, 128.9, 128.0, 125.8, 123.8, 116.4, 60.3, 14.2. EI-MS *m/z*: M^+, 258. Anal. Calcd for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46; O, 12.39; S, 12.41. Found: C, 69.70; H, 5.44; O, 12.36; S, 12.43.

4.3. Synthesis of olefins 4–7: general procedure

To a solution of ethyl 4-bromocrotonate (4 mmol) in dry dioxane (36 mL) under an argon atmosphere, palladium tetrakis phosphine (0.2 mmol) was added. The solution was stirred at room temperature and after 0.15 h boronic acid (8 mmol) and Na_2CO_3 (20 mmol) were added. The solution was stirred at reflux and monitored on TLC: after about 18 h the ethyl 4-bromocrotonate disappeared completely from the reaction mixture. The mixture was cooled to room temperature, dissolved in ethyl acetate and washed twice with H_2O (100 mL × 2). The organic phase was dried over Na_2SO_4 and the solvent evaporated under *vacuum* and the crude purified on silica gel giving the product as a yellow oil.

4.3.1. 4-Thiophen-2-yl-but-2-enoic acid ethyl ester 4. Obtained in 75% yield. $R_f = 0.6$ (petroleum ether/EtOAc 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (dt, $J = 7$ Hz, $J = 15$ Hz, 1H), 7.03 (m, 3H), 5.90 (dt, $J = 2$ Hz, $J = 15$ Hz, 1H), 4.21 (q, $J = 7.0$ Hz, 2H), 3.74 (d, $J = 2$ Hz, 2H), 1.30 (t, $J = 7.0$ Hz, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 166.3, 146.0, 139.7, 127.1, 125.6, 124.3, 122.6, 60.4, 32.3, 14.3. EI-MS *m/z*: M^+, 196, 100%, 123. Anal. Calcd for $C_{10}H_{12}O_2S$: C, 61.20; H, 6.16; O, 16.30; S, 16.34. Found: C, 61.17; H, 6.18; O, 16.31; S, 16.33.

4.3.2. 4-(4-Phenyl-thiophen-2-yl)-but-2-enoic acid ethyl ester 5. Obtained in 27% after two steps starting from 3-phenyl thiophene. $R_f = 0.5$ (petroleum ether/Et_2O 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, $J = 8$ Hz, 2H), 7.27 (m, 4H), 7.32 (s, 1H), 7.16 (s, 1H), 5.96 (d, $J = 16$ Hz, 1H), 4.23 (q, $J = 7$ Hz, 2H), 3.76 (d, $J = 6$ Hz, 2H), 1.32 (t, $J = 7$ Hz, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 166.6, 146.0, 142.6, 140.9, 136.0, 129.1, 127.4, 126.6, 125.3, 123.3, 123.1, 119.4, 60.7, 38.5, 32.9, 30.0, 14.5. EI-MS *m/z*: M^+, 272. Anal. Calcd for $C_{16}H_{16}O_2S$: C, 70.56; H, 5.92; O, 11.75; S, 11.77. Found: C, 70.54; H, 5.95; O, 11.71; S, 11.76.

4.3.3. 4-Benzo[*b*]thiophen-2-yl-but-2-enoic acid ethyl ester 6. Obtained in 70% yield. $R_f = 0.7$ (petroleum ether/EtOAc 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81–7.27 (m, 4H), 7.14 (dd, $J_1 = 6$ Hz, $J_2 = 15$ Hz, 1H), 7.08 (s, 1H), 4.97 (d, $J = 15$ Hz, 1H), 4.22 (q, $J = 7$ Hz, 2H), 3.80 (d, $J = 6$ Hz, 2H), 1.30 (t, $J = 7$ Hz, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 166.2, 145.0, 140.8, 139.9, 139.6, 124.3, 123.9, 123.2, 123.0, 60.4, 38.2, 33.0, 29.5, 14.2. Anal. Calcd for $C_{14}H_{14}O_2S$: C, 68.26; H, 5.73; O, 12.99; S, 13.02. Found: C, 68.28; H, 5.70; O, 12.97; S, 13.05.

4.3.4. 4-Benzo[*b*]thiophen-3-yl-but-2-enoic acid ethyl ester 7. Obtained in 65% yield. $R_f = 0.3$ (petroleum ether/Et_2O 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.9 (d, $J = 4.4$ Hz, 1H), 7.71 (d, $J = 8.6$ Hz, 1H), 7.41 (m, 2H), 7.25 (m, 2H), 5.92 (d, $J = 15.0$ Hz, 1H), 4.18 (q, $J = 7.0$ Hz, 2H), 3.75 (d, $J = 6.0$ Hz, 2H), 1.28 (t, $J = 7.0$ Hz, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 166.3, 145.4, 140.4, 138.3, 132.1, 124.4, 124.0, 123.2, 122.9, 122.9, 121.6, 60.3, 31.2, 14.2. Anal. Calcd for $C_{14}H_{14}O_2S$: C, 68.26; H, 5.73; O, 12.99; S, 13.02. Found: C, 68.24; H, 5.75; O, 12.97; S, 13.05.

4.4. General procedure for synthesis of diols 15–21

All these compounds were prepared according to the standard procedure for AD,[2a] except for diols **16**, **17** and **19** where 1.68 g of commercial AD-mix β reagent and 9.6 mg of $(DHQD)_2PHAL$ for 1 mmol of olefin were used. Diols **16a** and **17a** were synthesized according to the standard procedure for AD[2a] using the commercial AD-mix α reagent. The crude was purified by column chromatography on silica gel and all the compounds were characterized by MS, ^{1}H and ^{13}C NMR spectra. The data are reported as follows.

4.4.1. (−)-(2*S*,3*S*)-2,3-Dihydroxy-3-thiophen-2-yl-propionic acid ethyl ester 15. Obtained in 60% yield. $R_f = 0.2$ ($CHCl_3$/MeOH 98:2); $[\alpha]_D^{20} = -2.7$ (*c* 4, MeOH); ee = 99.87 (Chiralcel OJ-H, hexane/*i*-PrOH 95:5, 0.5 mL/min, $\lambda = 235$ nm, $t_R = 59.76$, $t_R = 65.16$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, $J = 4.8$ Hz, 1H), 7.11 (d, $J = 3.4$ Hz, 1H), 7 (m, 1H), 5.27 (d, $J = 1.8$ Hz, 1H), 4.44 (d, $J = 2.4$ Hz, 1H), 4.31 (q, $J = 7$ Hz, 2H), 1.32 (t, $J = 7$ Hz, 3H), 2.85 (br s, 1H), 3.3 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 143.8, 126.8, 125.8, 125.4, 74.6, 71.1, 62.5, 14.3. EI-MS *m/z*: M^+, 216 (100), 113. Anal. Calcd for $C_9H_{12}O_4S$: C, 49.99; H, 5.59. Found: C, 50.01; H, 6.02.

4.4.2. (−)-(2*S*,3*S*)-2,3-Dihydroxy-3-(4-phenyl-thiophen-2-yl)-propionic acid ethyl ester 16. Obtained as pale yellow powder in 78% yield. Mp: 79–81 °C. $R_f = 0.35$ (petroleum ether/EtOAc 8:2); $[\alpha]_D^{20} = -8.74$ (*c* 0.91, EtOAc); ee = 98% (Chiracel OJ, hexane/*i*-PrOH 80:20, 0.8 mL/min, $\lambda = 235$ nm, $t_R = 23.45$, $t_R = 33.90$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.6–7.2 (m, 5H), 7.57 (d, $J = 7.5$, 2H), 5.29 (s, 1H), 4.47 (s, 1H), 4.30 (q, $J = 7.5$ Hz, 2H), 3.65 (br s, 1H), 3.30 (br s, 1H), 1.31 (t, $J = 7.5$, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 172.6, 144.4, 142.1, 135.9, 129.1, 127.5, 126.5, 124.8, 120.7, 74.6, 71.3, 62.7, 14.4. Anal. Calcd for $C_{15}H_{16}O_4S$: C, 61.62; H, 5.52; O, 21.89; S, 10.97. Found: C, 61.59; H, 5.54; O, 21.85; S, 10.99.

4.4.3. (+)-(2*S*,3*S*)-2,3-Dihydroxy-3-(5-phenyl-thiophen-2-yl)-propionic acid ethyl ester 17. Obtained in 27% yield ($R_f = 0.32$ in petroleum ether/EtOAc 6:4); $[\alpha]_D^{20} = +6.6$ (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, $J = 8.0$ Hz, 2H), 7.38 (t, $J = 7.0$ Hz, 2H), 7.28 (m, 1H), 7.20 (d, $J = 3.6$ Hz, 1H), 7.08 (d, $J = 3.6$ Hz, 1H), 5.25 (d, $J = 2.4$ Hz, 1H), 4.47 (d, $J = 2.4$ Hz, 1H), 4.34 (q, $J = 7.0$ Hz, 2H), 1.33 (t, $J = 7.0$ Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 174.2, 148.9, 140.1, 136.2, 129.6, 128.5, 126.3, 124.3, 121.9, 75.4, 72.1, 61.5, 14.0. Anal. Calcd for $C_{15}H_{16}O_4S$: C, 61.62; H, 5.52; O, 21.89; S, 10.97. Found: C, 61.59; H, 5.55; O, 21.91; S, 10.95.

4.4.4. (+)-(2*S*,3*R*)-2,3-Dihydroxy-4-thiophen-2-yl-butyric acid ethyl ester 18. Obtained in 90% yield $R_f = 0.33$ (petroleum ether/EtOAc 6:4); $[\alpha]_D^{20} = +24.4$ (*c* 1.5, $CHCl_3$); ee = 94% (Chiracel OB, hexane/*i*-PrOH 95:5, 0.6 mL/min, $\lambda = 235$ nm, $t_R = 30.46$, $t_R = 36.75$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.03 (m, 3H), 4.29 (q, $J = 7$ Hz, 2H), 4.18 (m, 2H), 3.20 (br s, 1H), 3.19 (d, $J = 7.5$ Hz, 2H), 3.28 (br s, 1H), 1.32 (t, $J = 7.0$ Hz, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 173.3, 139.5, 127.0, 126.2, 124.3, 73.3, 72.0, 62.1, 34.1, 14.1. EI-MS *m*/*z*: M^+, 230, 100%, 97. Anal. Calcd for $C_{10}H_{14}O_4S$: C, 52.16; H, 6.13; O, 27.79; S, 13.92. Found: C, 52.17; H, 6.10; O, 27.81; S, 13.94.

4.4.5. (+)-(2*S*,3*R*)-2,3-Dihydroxy-4-(4-phenyl-thiophen-2-yl)-butyric acid ethyl ester 19. Obtained as pale yellow powder in 65% yield. Mp: 127–130 °C; $R_f = 0.46$ (petroleum ether/EtOAc 6:4). $[\alpha]_D^{20} = +26.6$ (*c* 0.5, $CHCl_3$); ee = 88% (Chiracel OJ, hexane/*i*-PrOH 90:10, 0.8 mL/min, $\lambda = 235$ nm, $t_R = 71.97$, $t_R = 89.92$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, $J = 8.5$ Hz, 2H), 7.41 (t, $J = 8.0$ Hz, 2H), 7.31 (m, 2H), 7.33 (s, 1H), 4.31 (q, $J = 7.0$ Hz, 2H), 4.22 (m, 2H), 3.25 (br s, 1H), 3.22 (d, $J = 6.5$ Hz, 2H), 2.32 (br s, 1H), 1.32 (t, $J = 6.5$ Hz, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 173.5, 142.5, 140.7, 136.0, 129.1, 127.4, 126.6, 126.4, 126.1, 119.6, 119.5, 73.5, 72.2, 62.6, 34.8, 14.5. Anal. Calcd for $C_{16}H_{18}O_4S$: C, 62.72; H, 5.92; O, 20.89; S, 10.47. Found: C, 62.70; H, 5.91; O, 20.92; S, 10.45.

4.4.6. (+)-(2*S*,3*R*)-4-Benzo[*b*]thiophen-2-yl-2,3-dihydroxy-butyric acid ethyl ester 20. This compound was obtained in different yield at different reaction temperatures: 47% and 70% yield; $[\alpha]_D^{20} = +36.7$ (*c* 1.8, $CHCl_3$) and 32.9 (*c* 1.9, $CHCl_3$); ee = 88% and 84% (Chiracel OB, hexane/*i*-PrOH 90:10, 0.8 mL/min, $\lambda = 235$ nm, $t_R = 39.39$, $t_R = 50.89$) at 0 °C and at rt, respectively. $R_f = 0.55$ (petroleum ether/EtOAc 6:4); ^1H NMR (500 MHz, $CDCl_3$) δ 7.54 (m, 4H), 7.17 (s, 1H), 4.25 (m, 4H), 3.28 (br s, 1H), 3.26 (d, $J = 7$ Hz, 2H), 1.31 (t, $J = 7$ Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 173.2, 140.6, 139.9, 139.7, 124.2, 123.8, 123.0, 123.0, 122.1, 72.9, 71.9, 62.3, 35.1, 14.1. Anal. Calcd for $C_{14}H_{16}O_4S$: C, 59.98; H, 5.75; O, 22.83; S, 11.44. Found: C, 59.96; H, 5.77; O, 22.81; S, 11.43.

4.4.7. (+)-(2*S*,3*R*)-4-Benzo[*b*]thiophen-3-yl-2,3-dihydroxy-butyric acid ethyl ester 21. Obtained in 47% yield. $R_f = 0.4$ (petroleum ether/EtOAc 7:3); $[\alpha]_D^{20} = +18.8$ (*c* 1.05, $CHCl_3$); ee = 82% (Chiracel OB, hexane/*i*-PrOH 80:20, 0.8 mL/min, $\lambda = 235$ nm, $t_R = 11.60$, $t_R = 16.66$); ^1H NMR (300 MHz, $CDCl_3$) 7.88 (m, 2H), 7.43 (m, 2H), 7.32 (s, 1H), 4.33 (br s, 1H), 4.25 (q, $J = 7.0$ Hz, 2H), 4.14 (br s, 1H), 3.25 (br s, 1H), 3.23 (d, $J = 6.6$ Hz, 2H), 2.48 (br s, 1H), 1.28 (t, $J = 7.0$ Hz, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 173.3, 140.4, 138.9, 131.9, 124.3, 124.1, 123.9, 122.9, 121.7, 72.1, 71.8, 62.2, 32.8, 14.1. Anal. Calcd for $C_{14}H_{16}O_4S$: C, 59.98; H, 5.75; O, 22.83; S, 11.44. Found: C, 59.96; H, 5.77; O, 22.86; S, 11.45.

4.4.8. (+)-(2*R*,3*R*)-2,3-Dihydroxy-3-(4-phenyl-thiophen-2-yl)-propionic acid ethyl ester 16a. Obtained in 56% yield. $[\alpha]_D^{20} = +7.3$ (*c* 1.66, EtOAc); ee = 99% (Chiracel OJ, hexane/*i*-PrOH 80:20, 0.8 mL/min, $\lambda = 235$ nm, $t_R = 23.45$, $t_R = 33.90$).

4.4.9. (−)-(2*R*,3*R*)-2,3-Dihydroxy-3-(5-phenyl-thiophen-2-yl)-propionic acid ethyl ester 17a. Obtained in 45% yield. $[\alpha]_D^{20} = -3.3$ (*c* 1.13, EtOAc).

4.5. Synthesis of acetonide derivatives of diols 17 and 17a

These compounds were synthesized according to the literature procedure.[10]

4.5.1. (+)-(2*S*,2*S*)-2,2-Dimethyl-5-(5-phenyl-thiophen-2-yl)-[1,3]-dioxolane-4-carboxylic acid ethyl ester. Obtained in 96% yield. $R_f = 0.6$ (petroleum ether/EtOAc, 8:2); ee = 98% (Chiracel OJ, hexane/*i*-PrOH 95:5, 0.8 mL/min, $\lambda = 235$ nm, $t_R = 9.91$, $t_R = 11.37$); $[\alpha]_D^{20} = +86.7$ (*c* 1.75, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, $J = 7$ Hz, 2H), 7.40 (dd, $J = 7$ Hz, 2H), 7.32 (d, $J = 7$ Hz, 1H), 7.21 (d, $J = 4$ Hz, 1H), 7.09 (d, $J = 4$ Hz, 1H), 5.20 (d, $J = 3$ Hz, 1H), 4.50 (d, $J = 3$ Hz, 1H), 4.32 (q, $J = 7.5$ Hz, 2H), 1.61 (s, 3H), 1.58 (s, 3H), 1.33 (t, $J = 7.5$ Hz, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 169.7, 144.9, 140.3, 134.2, 128.9, 127.7, 126.8, 125.8, 122.7, 111.9, 81.1, 77.3, 61.7, 26.9, 26.0, 14.2. Anal. Calcd for $C_{18}H_{20}O_4S$: C, 65.04; H, 6.06; O, 19.25; S, 9.65. Found: C, 65.06; H, 6.08; O, 19.22; S, 9.66.

4.5.2. (−)-(2*R*,2*R*)-2,2-Dimethyl-5-(5-phenyl-thiophen-2-yl)-[1,3]-dioxolane-4-carboxylic acid ethyl ester. Obtained in 96% yield. ee = 98% (Chiracel OJ, hexane/*i*-PrOH 95:5, 0.8 mL/min, $\lambda = 235$ nm, $t_R = 9.91$, $t_R = 11.37$).

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