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The asymmetric synthesis of β-aryl-α-hydroxy esters from β-aryl-α,β-dihydroxy esters

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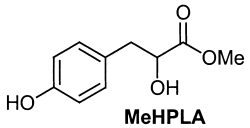
Abstract—α,β-Dihydroxy-β-aryl esters obtained via Sharpless asymmetric dihydroxylation (AD) of substituted cinnamate esters are reduced by sequential reaction with trimethyl orthoacetate and acetyl bromide followed by catalytic hydrogenolysis in methanol to give enantiomerically enriched β-aryl-α-hydroxy esters.

1. Introduction

α-Hydroxy esters are frequently encountered as parts of natural products and also serve as useful intermediates in organic synthesis.[1] As part of a study of the anticancer properties of α,β-unsaturated carbonyl compounds[2] and related analogues we had needed to synthesize materials related to the α-hydroxy ester methyl 4-hydroxyphenyllactate (MeHPLA) which possesses anticancer properties[3] by binding to the nuclear type II estrogen receptor.[4]



MeHPLA

A useful strategy for the preparation of such α-hydroxy esters[5] involves the oxidation of ester enolates with reagents such as MoOPH[6] and other oxidants.[7] To probe the estrogen receptor binding properties of MeHPLA analogues we required a stereoselective method for the synthesis of the required β-aryl-α-hydroxy esters.

The stereoselective oxidation of enolates (yielding α-hydroxy acids) can be achieved in a diastereoselective fashion by the reaction of chiral esters[8] with MoOPH. The corresponding enantioselective process can be achieved by the oxidation of pro-chiral enolates by camphoryl-sulfonyl-oxaziridine.[9] Other methods for the asymmetric synthesis of α-hydroxy esters include the alkylation of chiral glycolate enolates;[10] the catalytic hydrogenation of enol esters;[11] reduction of α-keto esters using a bakers' yeast keto ester reductase,[12] or rhodium catalysts.[13] Enantiomerically enriched α-hydroxy acids can also be prepared by dynamic kinetic resolution using a lipase.[14] The asymmetric method we adopted is an oxidative one, although overall the transformation is effectively the regio- and enantioselective hydration of an alkene. Our synthesis is based on the Sharpless catalytic asymmetric dihydroxylation (AD) reaction of substituted cinnamates. Cinnamates have proved to be exceptionally good substrates for the AD reaction. The resulting α,β-dihydroxy esters are obtained with high enantiomeric excesses. To access the β-hydroxy acid we therefore required a selective method for the reductive replacement of the β-hydroxyl group. We knew through our interest in the C-13 paclitaxel side-chain syntheses[15] that the diol **2a** derived from methyl cinnamate (**1a**) could be transformed into the β-bromo-α-acetoxy ester **3a**.[6,17] This ester now possesses a group at the β position that can be easily reduced. A related process involving the reduction of α-hydroxy-β-iodo esters, (generated by the regiospecific ring-opening of α,β-epoxy esters with $MgI_2{\cdot}Et_2O$), using tributyltin hydride is efficient.[18] We were reluctant to use tributyltin hydride to reduce **3a**, as tin-containing residues[19] would make the assessment of anticancer activity (via the MTT cell growth inhibition assay) unreliable. A more attractive procedure was hydrogenolysis and we report our results in full herein.[20]

2. Results and discussion

The diol **2a** was prepared, with an enantiomeric excess of 89%, by the catalytic AD of methyl cinnamate (**1a**) using a protocol of Sharpless, modified by the use of OsO_4.[16] We found that in this case the reaction was significantly faster than the reaction using $K_2OsO_2(OH)_4$ as the source of the osmium. The α-acetoxy-β-bromo ester **3a** was obtained, again using a procedure developed by Sharpless,[21] by treating the diol with trimethyl orthoacetate and acetyl

Keywords: α-hydroxy esters; asymmetric dihydroxylation; hydrogenolysis; reduction; anticancer agents.

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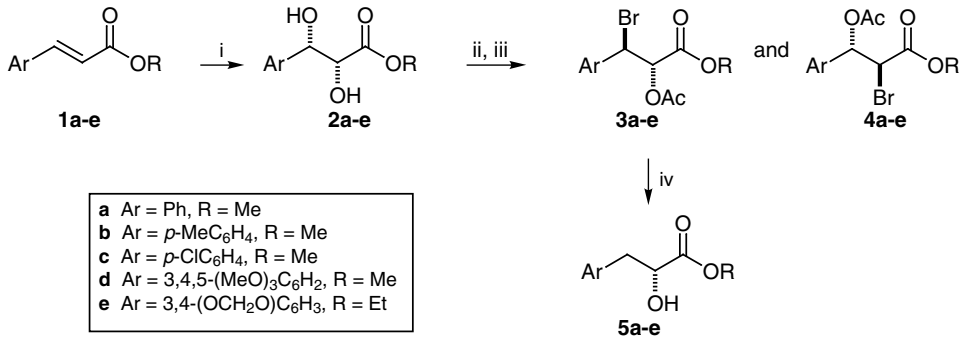
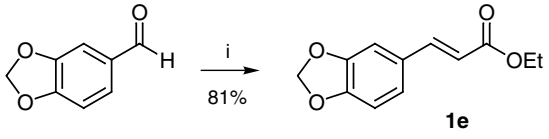


Scheme 1. *Reagents and conditions*: (i) OsO_4/DHQ_2PHAL, NMNO, *tert*-BuOH; (ii) $MeC(OMe)_3$, TsOH (cat.); (iii) AcBr; (iv) H_2, Pd/C, MeOH (EtOH for **5e**).

bromide. Fortunately the bromoester **3a** is easily separated from its regioisomer **4a** simply by recrystallisation. The catalytic hydrogenation of the bromoacetate **3a** with hydrogen and 10% Pd/C, resulted in the hydrogenolysis of the carbon–bromine bond and unexpectedly the methanolysis of the acetate group. The enantiomeric excess of the hydroxy ester **5a** was 89% (as determined by HPLC), indicating there was no loss in stereochemical integrity of the α-stereogenic centre; the optical rotation indicated that the centre was configured *R*.[8] The simultaneous cleavage of the α-acetate group is a result of the generation of hydrogen bromide, which is a by-product of this hydrogenolysis reaction. It should be noted that the palladium catalysed hydrogenation of **3a** in the presence of NaOAc/AcOH in ethyl acetate gives the acetate of **5a**[22] (Scheme 1).

To assess the generality of the procedure, a series of substituted cinnamic esters **1b–e** was prepared and subjected to Sharpless dihydroxylation. The Cinnamates **1b–d** were prepared by acid-catalysed Fischer–Speier esterification of the corresponding available cinnamic acids. The ethyl ester **1e** was prepared in 81% yield by the DBU/LiCl mediated Horner–Wadsworth–Emmons reaction of piperonal and triethyl phosphonoacetate (Scheme 2).[23]

Sharpless dihydroxylation of the cinnamates was performed as before to yield the corresponding diols **2b–e** in good to high enantiomeric excess, as determined by HPLC (Scheme 1 and Table 1). Racemic samples of the **2b–e** were prepared to ensure that the minor peak observed in the HPLC traces was actually the enantiomer of each diol. These racemic samples were prepared by the same AD reaction but substituting the DHQ_2PHAL ligand with pyridine. Sequential treatment of the diols with triethyl orthoacetate/TsOH and acetyl bromide led to mixtures of regioisomeric bromoacetates **3b–e** and **4b–e**. The ratio of **3/4** in each case was determined by integration of the peaks corresponding to H-2 and H-3 in the ^1H NMR spectrum of the crude reaction mixture. This ratio varied from good (12:1) for the *p*-methyl substituted series (**b**) to poor (1:1) for the methylenedioxy substituted series. The pattern of regioselectivity in general matches the electron releasing nature of the *para* substituent. Such an electron-donating group would weaken the C-3–O bond of the intermediate acetoxonium ion **6** (Scheme 3). The *p*-methoxy group of **5d** is presumably not as electron releasing as the methyl group of **5b** because of the buttressing effects of the two flanking methoxyl groups. The conformational restriction imposed by the 5-membered ring presumably reduces the electron

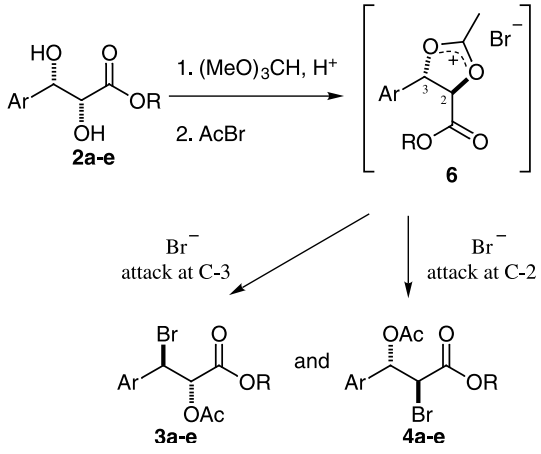


Scheme 2. *Reagents and conditions*: (i) $EtO_2CCH_2P(O)(OEt)_2$, DBU, LiCl, MeCN, rt 48 h.

Table 1. Yields and enantiomeric excesses in the transformations **1→5**

	1→2		**2→3** and **4**		**3→5**	
	Yield (%)	ee (%)	Yield (%)	**3/4**	Yield (%)	ee (%)
a	75	89[a]	52[b]	3:1	67	89[c]
b	74	92[c]	–	12:1	84[d]	–[e]
c	66	68[c]	–	6:1	70[d]	–[e]
d	34	91[f]	–	2:1	61[d]	93[g]
e	81	89[c]	–	1:1	35[d]	84[c]

[a] Enantiomeric excesses determined by GC: β-cyclodextrin dimethyl; 164°C, mean flow 25 mL s^{-1}.
[b] Enantiomeric excesses determined by yield of pure **4a**.
[c] Enantiomeric excesses determined by HPLC: Chiracel OB; 90:10 hexane/IPA; 1 mL min^{-1}.
[d] Enantiomeric excesses determined by yield of **5** from **2**.
[e] Enantiomeric excesses not determined.
[f] Enantiomeric excesses determined by HPLC: Chiracel OD; 80:20 hexane/IPA; 1 mL min^{-1}.
[g] Enantiomeric excesses determined by HPLC: Chiracel OD; 90:10 hexane/IPA; 1 mL min^{-1}.



Scheme 3.

donating effects of the substituents of **5e**. However in this case the comparison with the other members of the series is only rough since **5e** is an ethyl ester. The mixtures of **3b–e** and **4b–e** proved difficult to separate either by chromatography or by crystallization. However it was not essential to separate these regioisomers, as it was possible to cleanly isolate the α-hydroxy ester **5b–e** after hydrogenolysis of the mixture. The hydrogenation reactions were performed as before except in the case of the mixture of **3e** and **4e**. Because this series incorporated an ethyl ester, ethanol was chosen as the reaction solvent to avoid complications of transesterification. The overall yields of the α-hydroxy esters **3b–d** are good. Only the yield of **5e** is low, reflecting the lack of regioselectivity in the reaction of **2e**. The enantiomeric excess of the esters **5d** and **5e** corresponded closely, within experimental error, to that of the diols **2d** and **2e**, respectively. This provides further evidence that the transformation **1→3** and **4** does not affect the stereochemical integrity of the stereogenic centre adjacent to the ester group. Unfortunately we were not able to effect the analytical HPLC separation of the enantiomers of **5b** or **5c**. We have to assume that these are similar to those of **2b** and **2c**, respectively.

The esters **5b–e** showed no in vitro cytotoxicity (all IC_{50}s>50 μM) against K562 (human Caucasian chronic myelogenous leukaemia), BT20 (human breast cancer) and MCF7 (human breast cancer) cell lines. The MCF7 cell line is estrogen positive whilst the BT20 cell line is estrogen negative. Differential activity against these cell lines is indicative of antiestrogenic activity. However, the lack of any activity is disappointing and probably points to the importance of the *para*-hydroxyl group in determining the activity of MeHPLA. The results may also support the assumption that endogenous MeHPLA is the L-form (*S* enantiomer).[24] Racemic samples of **5a**, **5b** and **5d** were also inactive against the K562 cell line. Further work to study the relationship between the activity and stereochemistry of MeHPLA is underway.

3. Conclusions

In summary, we have successfully demonstrated that it is possible to synthesize α-hydroxy esters from *syn*-1,2-diols, starting from readily available materials that are inexpensive. The reduction avoids the use of tributyltin hydride. The method is also a good example of a serendipitous one-pot, two-step synthesis. The sequence is a curious tandem process, since the hydrogen bromide that is released in the hydrogenolysis reaction catalyses the subsequent methanolysis of the acetyl group. The inactivity of the esters **5a–e** illustrates that the presence of the *p*-hydroxy group of MeHPLA contributes to its anticancer properties.

4. Experimental

4.1. General

200 MHz ^{1}H NMR spectra were recorded using a Bruker AC 200 spectrometer using $CHCl_3$ as an internal standard. A Bruker AC 300 spectrometer was used to record 300 MHz ^{1}H and 75 MHz ^{13}C NMR spectra. Coupling constant (*J*) values are given in Hz. Chemical ionisation, (CI), and electron impact, (EI), mass spectra were recorded using a Kratos MS25 mass spectrometer; fast atom bombardment (FAB) mass spectra were recorded using a Kratos MS50 mass spectrometer using a *meta*-nitrobenzyl-alcohol matrix. Accurate mass determinations were performed using a Kratos Concept IS mass spectrometer. Elemental analysis was performed using a Carlo–Erba 1106 elemental analyser. Infra red spectra were recorded using a Phillips Analytical PU9625 pulsed-FT spectrometer. Melting points were determined using a Büchi 510 melting point apparatus and are not corrected. Kugelrühr distillation was performed using a Büchi GKR-51 apparatus. Column chromatography was conducted using silica gel 60 (230–400 mesh, Merck and Co.) and silica TLC was conducted on pre-coated aluminium sheets (60 F_{254}) with a 0.2 mm thickness (Aldrich Chemical Co.). Ether refers to diethyl ether and was distilled prior to use. Hexane used for column chromatography was also distilled prior to use. Anhydrous ether, anhydrous dichloromethane, anhydrous methanol and anhydrous *N*,*N*-dimethylformamide (DMF) were obtained from the Aldrich Chemical Co. and used as supplied. Anhydrous toluene was distilled from sodium metal and stored under nitrogen in the presence of 4 Å molecular sieves. Anhydrous dimethyl sulfoxide was distilled under reduced pressure and stored under nitrogen in the presence of 4 Å molecular sieves. THF was distilled from sodium metal in the presence of benzophenone immediately prior to use. Commercially available (Lancaster) methyl cinnamate (**1a**) was used without purification.

4.2. General method for the synthesis of cinnamates 1

Cinnamates **1b**, **c** and **d** were prepared by esterification (MeOH, H_2SO_4 (cat.)); **1b**: (4.44 g, 58%); mp 56–58°C {lit.[25] mp 57–58°C}; (Found: C, 75.3; H, 7.1. $C_{11}H_{12}O_2$ requires C, 75.0; H, 6.8%); **1c**: (4.85 g, 63%); mp 72–74°C (lit.[26] mp 73–75°C); (Found: C, 61.0; H, 4.7; Cl, 18.4. $C_{10}H_9O_2Cl$ requires C, 61.1; H, 4.6; Cl, 18.1%); **1d**: (5.91 g, 78%); mp 94–95°C (lit.[27] mp 94–97°C); (Found: C, 61.6; H, 6.4. Requires C, 61.9; H, 6.4%).

4.2.1. Ethyl 3-[(3′,4′-methylenedioxy)phenyl]propenoate (1e). This was prepared using the general method of Masamune and co-workers.[23] Triethyl phosphonoacetate (12.3 g, 55 mmol) and then DBU (7.48 mL, 55 mmol) were added to a mixture of piperonal (7.49 g, 50 mmol) and lithium chloride (2.22 g, 52 mmol) in dry acetonitrile (160 mL). The mixture was stirred at rt for 48 h then poured into water (500 mL) and extracted with chloroform (3×150 mL). The combined organic extracts were dried (magnesium sulfate) and evaporated to leave a yellow waxy solid. The crude material was recrystallised from toluene to afford **1e** as colourless crystals (8.85 g, 81%); mp 66–67°C; (Found: C, 65.2; H, 5.5. $C_{12}H_{12}O_4$ requires C, 65.5; H, 5.5%); ν_{max} (KBr disc) 3000 (w), 2900 (w), 1700 (s), 1650 (m), 1610 (m), 1510 (s), 1490 (s), 1370 (m), 1360 (m), 1300 (w), 1250 (bs), 1180 (m), 1100 (w), 1030 (m), 860 (w), 800 (m) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.32 (3H, t, *J*=7.2 Hz, CH_3), 4.24 (2H, q, *J*=7.2 Hz, CH_2CH_3), 6.00 (2H, s, OCH_2O), 6.25 (1H, d, *J*=16.0 Hz, H2), 6.80 (1H,

d, J=1.7 Hz, H2′), 6.98–7.03 (2H, m, H5′ and H6′), 7.58 (1H, d, J=16.0 Hz, H3); δ_C (75 MHz, $CDCl_3$) 14.4 (CH_3), 60.5 (CH_2CH_3), 101.6 (C7′), 106.5 (C5′), 108.6 (C1′), 116.3 (C2), 124.5 (C6′), 128.9 (C1′), 144.4 (C3), 148.4 (C4′), 149.6 (C3′), 167.3 (C1); m/z (FAB) 221 (85%, $[M+H]^+$), 220 (100, M^+), 175 (80%, $[M-OEt]^+$).

4.2.2. Methyl (2*R*,3*S*)-2,3-dihydroxy-3-phenylpropionate (2a). This was prepared according to the method of Sharpless and co-workers.[16] NMO (31 mL, 60% in water) and OsO_4 (4 mL, of a solution made from 1 g in *t*-BuOH (100 mL)) were added to (*E*)-methyl cinnamate (20.55 g, 127 mmol) and DHQ_2PHAL (500 mg, 0.64 mmol) in *t*-BuOH (62 mL). The mixture was stirred vigorously at rt for 8 h, then quenched with saturated aqueous sodium sulfite solution (100 mL) and then stirred at rt for a further 1 h. Water (100 mL) was added and the mixture was extracted with EtOAc (2×150 mL). The combined organic extracts were washed with HCl_{aq}. (4×50 mL, 1 M) then dried ($MgSO_4$) and evaporated to leave a cream coloured solid (20.30 g). The crude material was purified by crystallisation from toluene to afford the diol **2a** as colourless crystals (18.65 g, 75, 89% ee). The enantiomeric excess was measured by GC; β-cyclodextrin dimethyl (B-DM), 164°C, mean flow rate ca. 25 mL s^{-1}. Retention times: major enantiomer 21.94 min, minor enantiomer 25.17 min); mp 84–85°C (lit.[16], mp 84–86°C); $[\alpha]_D$=+5.9 (*c* 1.0 in EtOH) {lit.[16], $[\alpha]_D$=+3.4 (*c* 1.2 in EtOH); lit.[28] $[\alpha]_D$=+8.2 (*c* 1.2 in EtOH)}; (Found: C, 61.2; H, 6.3. $C_{10}H_{12}O_4$ requires C, 61.2; H, 6.1%); R_f 0.22 (silica; 3:1; hexane/EtOAc, v/v); ν_{max} (KBr disc) 3500 (vs), 3400 (vs), 2960 (w), 1715 (s), 1460 (m), 1400 (m), 1325 (m), 1220 (s), 1110 (s), 720 (m) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.70 (1H, d, J=7.0 Hz, OH), 3.08 (1H, d, J=7.0 Hz, OH), 3.83 (3H, s, CH_3), 4.38 (1H, dd, J=3.0, 7.0 Hz, PhCH), 5.03 (1H, dd, J=3.0, 7.0 Hz, CH), 7.30–7.43 (5H, m, aromatic); δ_C (75 MHz, $CDCl_3$) 52.7 (CH_3), 74.4 (CH), 74.8 (CH), 126.2 (CH), 127.9 (CH), 128.4 (CH), 139.9 (C), 173.1 (C=O); m/z (FAB) 197 (20%, $[M+H]^+$), 179 (100, $[M-OH]^+$), 119 (40, $[M-Ph]^+$).

4.2.3. Methyl (2*S*,3*R*)-2-acetoxy-3-bromo-3-phenylpropionate (3a). This was prepared according to the method of Sharpless and co-workers.[16] Trimethyl orthoacetate (38 mL) was added to the diol **2a** (20.30 g, 104 mmol) and TsOH (292 mg, 1.7 mmol) in dry CH_2Cl_2 (80 mL). The mixture was stirred at rt for 2 days. The volatile components were evaporated in vacuo to leave a yellow oil that was dissolved in CH_2Cl_2 (80 mL). Acetyl bromide (7.8 mL, 105 mmol) was added to the mixture at 0°C, and stirred for a further 2 h at 0°C then stored at 4°C for 16 h. The solvent was then evaporated to leave a pale brown solid that was stirred in a mixture of hexane and ether (70 mL, 6:4, v/v) for 40 min and then filtered. The residue was washed with more of the same solvent to afford the bromo ester **3a** as pale orange crystals. The filtrate was concentrated and recrystallised a second time to give further **3a** (16.32 g, 52% combined yield); mp 85–86°C {lit.[16] mp 86–87°C}; $[\alpha]_D$=−105 (*c* 1.0 in EtOH) {lit.[16] $[\alpha]_D$=−113 (*c* 1.3 in EtOH)}; (Found: C, 47.9; H, 4.3; Br, 26.6. $C_{12}H_{13}BrO_4$ requires C, 47.8; H, 4.3; Br, 26.5%); ν_{max} (KBr disc) 2980 (w), 1750 (vs), 1450 (m), 1380 (m), 1220 (s), 1190 (s), 900 (w), 700 (m) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.11 (3H, s, CH_3C=O), 3.71 (3H, s, CH_3), 5.34 (1H, d, J=7.0 Hz, PhCH), 5.64 (1H, d, J=7.0 Hz, CH), 7.32–7.47 (5H, m, aromatic); δ_C (75 MHz, $CDCl_3$) 20.4 (CH_3C=O), 49.1 (PhCH), 52.6 (CH_3), 75.1 (COAc), 128.5 (CH), 128.6 (CH), 129.0 (CH), 136.6 (C), 167.2 (C=O), 169.4 (C=O); m/z (FAB) 303 {30%, $[M(^{81}Br)+H]^+$}, 301 {30%, $[M(^{79}Br)+H]^+$}, 243 {100, $[M(^{81}Br)-AcOH]^+$}, 241 {90, $[M(^{79}Br)-AcOH]^+$}.

4.2.4. Methyl (2*R*)-2-hydroxy-3-phenylpropanoate (5a). A mixture of methyl ester **3a** (148 mg, 0.49 mmol) and palladium (10%) on carbon (10 mg) was stirred in dry MeOH (5 mL) under H_2 (1 atm.) at rt for 2 days. The mixture was then filtered through Celite® and concentrated to leave an orange oil (94 mg). The crude material was purified by chromatography (silica; $CHCl_3$) to afford **5a** as a colourless solid (73 mg, 67%); mp 36–38°C; $[\alpha]_D$=+9.7 (*c* 1.0 in $CHCl_3$), −3.0 (*c* 1.0 in MeOH) and +8.7 (*c* 1.3 in acetone) {lit.[8] $[\alpha]_D$=−2.4 (*c* 2.7 in MeOH) and +8.5 (*c* 3.9 in acetone)}; (Found: C, 66.5; H, 6.5. $C_{10}H_{12}O_3$ requires C, 66.6; H, 6.7%); R_f 0.35 (silica; $CHCl_3$); ν_{max} (KBr disc) 3500–3200 (bw), 1750 (vs), 1500 (w), 1450 (bw), 1275 (bw), 1110 (bs), 750 (s), 705 (s) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.66 (1H, d, J=6.7 Hz, OH), 2.96 (1H, dd, J=6.7, 13.9 Hz, CH_aH_b), 3.14 (1H, dd, J=4.4, 13.9 Hz, CH_aH_b), 3.77 (3H, s, OMe), 4.46 (1H, dt, J=4.4, 6.7 Hz, CH), 7.18–7.34 (5H, m, aromatic); δ_C (75 MHz, $CDCl_3$) 40.5 (CH_2), 52.4 (CH), 71.2 (CH_3), 127.2 (CH), 128.4 (CH), 129.4 (CH), 136.2 (C), 174.5 (C=O); m/z (FAB) 181 (40%, $[M+H]^+$), 162 (40, $[M-H_2O]^+$).

4.2.5. Methyl (2*R*,3*S*)-2,3-dihydroxy-3-(4′-methylphenyl)propanoate (2b). Dihydroxylation of the propenoate **1b** (1.99 g, 11.31 mmol) was performed as described earlier (reaction time 24 h). The crude material was recrystallised from toluene to afford **2b** as colourless plate-like crystals (1.76 g, 74, 92% ee). The ee was determined by HPLC: Chiracel OB; 90:10 hexane/IPA; 1 mL min^{-1}; mp 92–94°C; $[\alpha]_D$=+9.28 (*c* 1.0 in $CHCl_3$); (Found: C, 62.9; H, 6.8. $C_{11}H_{14}O_4$ requires C, 62.8; H, 6.7%); ν_{max} (KBr disc) 3500 (vs), 3390 (bs), 3020 (w), 2960 (w), 1740 (vs), 1520 (w), 1450 (m), 1320 (m), 1230 (m), 1110 (vs), 1055 (m), 990 (w), 890 (w) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.34 (3H, s, Me), 2.64 (1H, bd, J=6.5 Hz, OH), 3.06 (1H, bd, J=5.6 Hz, OH), 3.82 (3H, s, OMe), 4.36 (1H, bs, H2), 4.99 (1H, bs, H3), 7.18 (2H, bd, J=8.0 Hz, aromatic), 7.29 (2H, bd, J=8.0 Hz, aromatic); δ_C (75 MHz, $CDCl_3$) 21.0 (CH_3), 52.5 (OMe), 74.3 (CH), 74.7 (CH), 125.6 (CH), 128.9 (CH), 136.9 (C), 137.5 (C), 173.1 (C=O); m/z (FAB) 233 (70%, $[M+Na]^+$), 209 (20, $[M-H]^+$), 193 (100, $[M-OH]^+$), 133 (80), 121 (30), 105 (60).

4.2.6. Methyl (2*R*,3*S*)-2,3-dihydroxy-3-(4′-chlorophenyl)-propanoate (2c). This was prepared in the same way as diol **2b**, from the propenoate **1c** (2.74 g, 13.94 mmol). Recrystallisation of the crude material from toluene gave **2c** as fine colourless crystals (2.11 g, 66, 68% ee). The enantiomeric excess was determined by HPLC: Chiracel OB; 90:10 hexane/IPA; 1 mL min^{-1}; mp 113–115°C; $[\alpha]_D$=7.42 (*c* 1.3 in $CHCl_3$); (Found: C, 51.7; H, 5.3; Cl, 15.5. $C_{10}H_{11}O_4Cl$ requires C, 52.1; H, 4.8; Cl, 15.4%); ν_{max} (KBr disc) 3540 (m), 3470 (bm), 2960 (w), 2900 (w), 1910

(w), 1740 (vs), 1500 (s), 1445 (w), 1225 (bs), 1110 (s), 1060, (m), 1020 (m), 940 (w), 830 (w), 790 (w) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.74 (1H, bs, OH), 3.11 (1H, bs, OH), 3.83 (3H, s, CH_3), 4.34 (1H, bs, H2), 4.99 (1H, bs, H3), 7.35 (4H, bs, aromatic); δ_C (75 MHz, $CDCl_3$) 53.1 (CH_3), 73.9 (CH), 74.8 (CH), 127.8 (CH), 128.7 (CH), 134.0 (C), 138.0 (C), 173.1 (C=O); *m/z* (FAB) 255 {20%, $[M(^{37}Cl)+Na]^+$}, 253 {60, $[M(^{35}Cl)+Na]^+$}, 215 {30, $[M(^{37}Cl)-OH]$}, {100, $[M(^{35}Cl)-OH]$}.

4.2.7. Methyl (2*R*,3*S*)-2,3-dihydroxy-3-(3′,4′,5′-trimethoxyphenyl)propanoate (2d). This was prepared in the same way as diol **2b**, from the propenoate **1d** (2.018 g, 8.01 mmol). Recrystallisation of the crude material from toluene gave **2d** as fine colourless needles (0.773 g, 34, 91% ee). The enantiomeric excess was determined by HPLC: Chiracel OD; 80:20 hexane/IPA; 1 mL min^{-1}; mp 126–128°C; $[\alpha]_D$=+2.88 (*c* 1.1 in $CHCl_3$); (Found: C, 54.6; H, 6.5. $C_{13}H_{18}O_7$ requires C, 54.6; H, 6.3%); ν_{max} (KBr disc) 3550 (s), 3500 (s), 3000 (w), 2975 (w), 2950 (w), 2850 (w), 1745 (vs), 1600 (vs), 1515, (s), 1470 (s), 1430 (s), 1340 (s), 1140 (vs), 1110 (vs), 1075 (s), 1005 (s), 845 (m), 765 (m) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.63 (1H, bs, OH), 3.03 (1H, bs, OH), 3.83 (3H, s, OMe), 3.84 (3H, s, OMe), 3.86 (6H, s, OMe), 4.37 (1H, d, *J*=2.6 Hz, H2), 4.96 (1H, d, *J*=2.6 Hz, H3), 6.63 (2H, s, aromatic); δ_C (75 MHz, $CDCl_3$) 52.6 (OMe), 56.1 (OMe), 60.8 (OMe), 74.5 (CH), 74.9 (CH), 103.3 (CH), 135.9 (C), 137.4 (C), 153.2 (C), 173.1 (C=O); *m/z* (FAB) 309 (20%, $[M+Na]^+$), 286 (40, M^+), 269 (85, $[M-OH]^+$), 197(100).

4.2.8. Ethyl (2*R*,3*S*)-2,3-dihydroxy-3-[(3′,4′-methylenedioxy)phenyl]propanoate (2e). This was prepared in the same way as diol **2b**, from the propenoate **1e** (2.285 g, 10.3 mmol). The crude material was purified by chromatography (silica; 3:1; hexane/EtOAc, v/v) to afford **2e** as a white solid (2.130 g, 81, 89% ee). The enantiomeric excess was determined by HPLC: Chiracel OB; 90:10 hexane/IPA; 1 mL min^{-1}; mp 77–78°C; $[\alpha]_D$=+1.7 (*c* 1.5 in $CHCl_3$); (Found: C, 56.5; H, 5.6. $C_{12}H_{14}O_6$ requires C, 56.7; H, 5.6%); R_f 0.11 (silica; 3:1; hexane/EtOAc, v/v); ν_{max} (KBr disc) 3520 (m), 3380 (bs), 3000 (w), 2980 (w), 2900 (w), 1720 (s), 1490 (m), 1450 (s), 1320 (m), 1290 (m), 1220 (s), 1110 (s), 1050 (m), 930 (w), 750 (w) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.28 (3H, t, *J*=7.0 Hz, CH_3), 2.73 (1H, d, *J*=6.0 Hz, OH), 3.15 (1H, d, *J*=5.9 Hz, OH), 4.26 (2H, q, *J*=7.0 Hz, CH_2CH_3), 4.28 (1H, bs, H2), 4.89 (1H, bs, H3), 5.95 (2H, s, H7′), 6.76–6.86 (2H, m, H5′,6′), 6.93 (1H, d, *J*=1.2 Hz, H2′); δ_C (75 MHz, $CDCl_3$) 14.0 (CH_3), 62.0 (CH_2), 74.3 (CHOH), 74.9 (CHOH), 101.0 (C7′), 107.0 (C2′), 107.9 (C5′), 119.7 (C6′), 133.9 (C1′), 147.2 (C4′), 147.6 (C3′), 172.6 (C=O); *m/z* (FAB) 254 (40%, M^+), 253 (70, $[M-H]^+$), 237 (100, $[M-OH]^+$).

4.2.9. Methyl (2*S*,3*R*)-2-acetoxy-3-bromo-3-(4′-methylphenyl)propanoate (3b) and methyl (2*S*,3*S*)-2-bromo-3-acetoxy-3-(4′-methylphenyl)propanoate (4b). These were prepared in the same way as bromo ester **3a**, from the diol **2b** (810 mg, 3.85 mmol). The crude reaction product was purified quickly by column chromatography (silica; $CHCl_3$) to afford **3b** and **4b** as a colourless solid (721 mg, 59%), as a (12:1, **3b/4b**) mixture of regioisomers (determined by ^1H NMR); mp 45°C (dec); R_f 0.60 (silica; $CHCl_3$); δ_H (300 MHz, $CDCl_3$) (isomer **3b**) 2.11 (3H, s, CH_3), 2.33 (3H, s, CH_3), 3.70 (3H, s, CH_3), 5.33 (1H, d, *J*=6.3 Hz, H3), 5.63 (1H, d, *J*=6.3 Hz, H2), 7.12 (2H, d, *J*=8.0 Hz, aromatic), 7.29 (2H, d, *J*=8.0 Hz, aromatic); δ_H (300 MHz, $CDCl_3$) (isomer **4b**) 2.00 (3H, s, CH_3), 2.35 (3H, s, CH_3), 3.78 (3H, s, CH_3), 4.50 (1H, d, *J*=9.9 Hz, H3), 6.05 (1H, d, *J*=9.9 Hz, H2), 7.10–7.75 (4H, aromatic); δ_C (75 MHz, $CDCl_3$) (isomer **3b**) 20.3 (CH_3), 21.1 (CH_3), 49.2 (CH_3), 52.6 (CH), 75.3 (CH), 128.0 (CH), 129.2 (CH), 133.7 (C), 139.0 (C), 167.2 (C=O), 169.4 (C=O); (Found: M^+, 314.0144. $C_{13}H_{15}BrO_4$ requires M^+, 314.0154); *m/z* (FAB) 317 {85%, $[M(^{81}Br)+H]^+$}, 315 {100, $[M(^{79}Br)+H]^+$}, 285 (40), 283 (45), 257 (35), 255 (35), 235 (50), 193 (100).

4.2.10. Methyl (2*S*,3*R*)-2-acetoxy-3-bromo-3-(4′-chlorophenyl)propanoate (3c) and methyl (2*S*,3*S*)-2-bromo-3-acetoxy-3-(4′-chlorophenyl)propanoate (4c). These were prepared in the same way as bromo ester **3a** from the diol **2c** (867 mg, 3.76 mmol). The crude product was purified quickly by column chromatography (silica; 5:1; hexane/ethyl acetate, v/v) to afford **3c** and **4c** as a colourless solid (813 mg, 64%) as a (6.5:1, **3c/4c**) mixture of regioisomers (determined by ^1H NMR); mp 54–56°C (dec.); R_f 0.39 (silica; 5:1 hexane/EtOAc, v/v); ν_{max} (KBr disc) 3000 (m), 2940 (m), 1750 (bs), 1590 (m), 1490 (m), 1440 (m), 1360 (m), 1200 (bs), 1090 (m), 1000 (m), 820 (m) cm^{-1}; δ_H (300 MHz, $CDCl_3$) (isomer **3c**) 2.12 (3H, s, CH_3), 3.69 (3H, s, OMe), 5.32 (1H, d, *J*=6.1 Hz, H3), 5.62 (1H, d, *J*=6.1 Hz, H2), 7.26 (4H, m, aromatic); δ_H (300 MHz, $CDCl_3$) (isomer **4c**) 2.02 (3H, s, CH_3), 3.81 (3H, s, OMe), 4.43 (1H, d, *J*=9.8 Hz, H3), 6.08 (1H, d, *J*=9.8 Hz, H2), 7.26–7.42 (4H, m, aromatic); δ_C (75 MHz, $CDCl_3$) 20.4, 20.5, 45.6, 47.9, 52.6, 53.1, 74.6, 74.9, 128.2, 128.3, 128.4, 129.1, 129.8, 130.1, 134.9, 135.0, 167.8, 169.3, 170.7, 172.1; (Found: $[M+NH_4]^+$, 351.9945. $C_{12}H_{12}BrClO_4$ requires $[M+NH_4]^+$, 351.9951); *m/z* (CI) 352 {70%, $[M(^{79}Br^{35}Cl)+NH_4]^+$}, 354 {100, $[M(^{81}Br^{35}Cl$ and $^{79}Br^{37}Cl)+NH_4]^+$}, 356 {20, $[M(^{81}Br^{37}Cl)+NH_4]^+$}.

4.2.11. Methyl (2*S*,3*R*)-2-acetoxy-3-bromo-3-(3′,4′,5′-trimethoxyphenyl)propanoate (3d) and methyl (2*S*,3*S*)-2-bromo-3-acetoxy-3-(3′,4′,5′-trimethoxyphenyl)propanoate (4d). These were prepared in the same way as the bromo ester **3a** from the diol **2d** (439 mg, 1.53 mmol). The crude material was purified quickly by column chromatography (silica; $CHCl_3$) to afford **3d** and **4d** as a colourless oil (543 mg, 90%) as a (2:1, **3d/4d**) mixture of regioisomers (determined by ^1H NMR); mp 62–64 °C; R_f 0.34 (silica; $CHCl_3$); ν_{max} (KBr disc) 3000 (bw), 2950 (bw), 2840 (w), 1755 (vs), 1595 (s), 1510 (s), 1465 (bs), 1435 (m), 1375 (m), 1220 (bs), 1130 (s), 1010 (m), 915 (bw), 735 (m) cm^{-1}; δ_H (300 MHz, $CDCl_3$) (isomer **3d**) 2.09 (3H, s, CH_3), 3.74 (3H, s, OMe), 3.75–3.77 (6H, s, OMe), 5.28 (1H, d, *J*=6.7 Hz, H3), 5.65 (1H, d, *J*=6.7 Hz, H2), 6.58 (2H, s, aromatic); δ_H (300 MHz, $CDCl_3$) (isomer **4d**) 2.21 (3H, s, CH_3), 3.70 (3H, s, OMe), 3.75–3.77 (6H, s, OMe), 5.31 (1H, d, *J*=5.1 Hz, H2), 5.43 (1H, d, *J*=5.1 Hz, H3), 6.58 (2H, s, aromatic); δ_C (75 MHz, $CDCl_3$) 20.4, 20.5, 49.6, 51.3, 52.7, 52.9, 56.0, 56.1, 60.8, 75.0, 75.6, 77.6, 105.5, 105.8, 107.2, 107.5, 132.4, 139.6, 152.9, 153.1, 167.3, 169.3, 169.6; (Found: $[^{79}Br]$ M^+, 390.0313. $C_{15}H_{19}BrO_7$ requires $[^{79}Br]$ M^+ 390.0315); *m/z* (FAB) 392 [40%, $M(^{81}Br)^+$], 390 [40,

M(^{79}Br)$^+$], 311 (100), 279 (50), 269 (100), 252 (70), 237 (70).

4.2.12. Ethyl (2*S*,3*R*)-2-acetoxy-3-bromo-3-[(3′4′-methylenedioxy)phenyl]propanoate (3e) and ethyl (2*S*,3*S*)-2-bromo-3-acetoxy-3-[(3′,4′-methylenedioxy)phenyl]propanoate (4e). These were prepared in the same way as the bromo ester **3a** from the diol **2e** (439 mg, 1.53 mmol). The crude material was then purified by flash column chromatography (silica; 4:1; hexane/EtOAc, v/v) to afford **3e** and **4e** as a pale yellow oil (1.434 g, 95%) as a (1:1, **3e/4e**) mixture of regioisomers. This material was not rigorously purified and was used immediately in the next step; R_f 0.23 (silica; 4:1; hexane/EtOAc, v/v); δ_H (300 MHz, $CDCl_3$) 1.17 (3H, t, J=7.1 Hz, CH_3), 1.21 (3H, t, J=7.1 Hz, CH_3), 2.17 (3H, s, CH_3), 2.22 (3H, s, CH_3), 4.10–4.20 (4H, m, CH_2CH_3), 5.30 (1H, d, J=5.5 Hz), 5.32 (1H, d, J=5.9 Hz), 5.36 (1H, d, J=5.5 Hz), 5.57 (1H, d, J=5.9 Hz), 5.97 (4H, s, H7′), 6.70 (1H, d, J=7.1 Hz), 6.72 (1H, d, J=7.0 Hz), 6.85 (1H, dd, J=1.8, 7.0 Hz, H6′), 6.86 (1H, dd, J=1.9, 7.1 Hz, H6′), 7.00 (1H, d, J=1.9 Hz), 7.04 (1H, d, J=1.8 Hz); δ_C (75 MHz, $CDCl_3$) 13.8 (CH_3), 13.9 (CH_3), 20.3 (CH_2), 20.3 (CH_2), 49.6 (C2 or C3), 51.3 (C2 or C3), 61.8 (OAc), 61.9 (OAc), 75.3 (C2 or C3), 75.8 (C2 or C3), 101.4 (C10), 101.5 (C10), 107.6 (C5), 107.8 (C5), 108.9 (C8), 109.1 (C8), 121.8 (C9), 122.3 (C9), 130.4 (C4), 130.7 (C4), 147.7 (C6 or C7), 147.8 (C6 or C7), 147.9, (C6 or C7), 148.2 (C6 or C7), 166.3 (OAc), 166.6 (OAc), 169.3 (C1), 169.6 (C1); (Found: M^+, 358.0052. $C_{14}H_{15}BrO_6$ requires M^+, 358.0052); *m/z* (FAB) 361 {10%, [M(^{81}Br)+H]$^+$}, 360 [30, M(^{81}Br)$^+$], 359 {30, [M(^{79}Br)+H]$^+$}, 358 [80, M(^{79}Br)$^+$], 279 (100, [M−Br]$^+$), 237 (90).

4.2.13. Methyl (2*R*)-2-hydroxy-3-(4′-methylphenyl)propanoate (5b). The bromo acetates **3b/4b** (1.63 g, 5.18 mmol) and palladium on carbon (10 mg, 10%) were stirred vigorously in dry MeOH (4 mL) under H_2 (1 atm.) at rt for 24 h. The mixture was filtered through Celite®, poured into water (100 mL) and extracted with chloroform (3×50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to leave an orange coloured oil. The crude material was purified by column chromatography (silica; $CHCl_3$) to afford **5b** as a colourless oil (0.780 g, 78%); $[\alpha]_D$=+7.9 (*c* 1.5 in $CHCl_3$); R_f 0.36 (silica; $CHCl_3$); ν_{max} (KBr disc) 3500 (wb), 2960 (m), 2920 (m), 1740 (vs), 1520 (s), 1440 (m), 1270 (bs), 1220 (bs), 1120 (s), 1100 (s), 1030 (w), 810 (m), 790 (w) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.31 (3H, s, CH_3), 2.66 (1H, d, J=6.5 Hz, OH), 2.92 (1H, dd, J=6.5, 14.0 Hz, H_aH_b), 3.08 (1H, dd, J=4.4, 14.0 Hz, H_aH_b), 3.78 (3H, s, OMe), 4.44 (1H, dt, J=4.4, 6.5 Hz, CH), 7.10 (4H, s, aromatic); δ_C (75 MHz, $CDCl_3$) 21.1 (CH_3), 40.2 (CH_2), 52.4 (CH_3), 71.4 (CH), 129.2 (CH), 129.4, (CH), 133.3 (C), 136.4 (C), 174. 7 (C=O); (Found: [M+NH_4]$^+$, 212.1288. $C_{11}H_{15}O_3$ requires [M+NH_4]$^+$, 212.1286); *m/z* (CI) 212 (100%, [M+NH_4]$^+$), 204 (80), 198 (60), 194 (10, M^+).

4.2.14. Methyl (2*R*)-2-hydroxy-3-(4′-chlorophenyl)propanoate (5c). This was prepared in the same way as **5b** from **3c/4c** to afford **5c** as a colourless solid (68 mg, 70%); $[\alpha]_D$=+11.6 (*c* 1.0 in $CHCl_3$); (Found: C, 55.8; H, 5.0; Cl, 16.4. $C_{10}H_{11}O_3Cl$ requires C, 56.0; H, 5.2; Cl, 16.5%); R_f 0.40 (silica; $CHCl_3$); ν_{max} (KBr disc) 3250 (wb), 2960 (w), 1750 (vs), 1500 (s), 1440 (s), 1410 (w), 1350 (w), 1290 (m), 1220 (s), 1180 (m), 1110 (s), 1100 (s), 1020 (s), 980 (w), 810 (s), 710 (m) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.76 (1H, d, J=6.7 Hz, OH), 2.91 (1H, dd, J=6.7, 14.0 Hz, CH_aH_b), 3.10 (1H, dd, J=4.3, 14.0 Hz, CH_aH_b), 3.77 (3H, s, OMe), 4.43 (1H, dt, J=4.3, 6.7 Hz, CH), 7.16 (2H, d, J=8.4 Hz, aromatic), 7.29 (2H, d, J=8.4 Hz, aromatic); δ_C (75 MHz, $CDCl_3$) 39.9 (CH_2), 46.9 (OMe), 71.1 (CH), 128.5 (CH), 131.1 (CH), 132.9 (C), 135.0 (C), 174.6 (C=O); (Found: [M+H]$^+$, 215.0480. $C_{10}H_{11}ClO_3$ requires [M+H]$^+$, 215.0475); *m/z* (FAB) 239 {10%, [M(^{37}Cl)+Na]$^+$}, 237 {30, [M(^{35}Cl)+Na]$^+$}, 217 {25, [M(Cl^{37})+H]$^+$}, 215 {75, [M(Cl^{35})+H]$^+$}, 196 (45), 165 (25), 155 (100), 137 (35), 125 (50).

4.2.15. Methyl (2*R*)-2-hydroxy-3-(3′,4′,5′-trimethoxyphenyl)propanoate (5d). This was prepared in the same way as **5b** from **3d/4d** to afford **5d** as a white solid (126 mg, 61, 93% ee). The enantiomeric excess was determined by HPLC: Chiracel OD; 90:10 hexane/IPA; 1 mL min^{-1}; mp 75–76°C; $[\alpha]_D$=+8.2 (*c*1.0 in $CHCl_3$); (Found: C, 57.7; H, 6.7. $C_{13}H_{18}O_6$ requires C, 57.7; H, 6.7%); R_f 0.13 (silica; $CHCl_3$); ν_{max} (KBr disc liquid film) 3400 (s), 3000 (m), 2950 (m), 2820 (m), 1730 (s), 1600 (s), 1510 (s), 1450 (m), 1430 (m), 1370 (w), 1340 (w), 1290 (m), 1250 (m), 1220 (m), 1130 (vs), 1020 (m), 830 (s) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.76 (1H, d, J=6.1 Hz, OH), 2.89 (1H, dd, J=6.1, 14.0 Hz, CH_aH_b), 3.07 (1H, dd, J=4.1, 14.0 Hz, CH_aH_b), 3.79 (3H, s, OMe), 3.82 (3H, s, OMe), 3.86 (6H, s, OMe), 4.45 (1H, dt, J=6.1, 4.1 Hz, CHOH), 6.43 (2H, s, aromatic); δ_C (75 MHz, $CDCl_3$) 40.6 (CH2), 52.3 (CH), 55.9 (OMe), 60.7 (OMe), 71.2 (OMe), 106.3 (CH), 131.7 (C), 136.8 (C), 153.1 (C), 174.3 (C=O); (Found: M^+, 270.1104. $C_{13}H_{18}O_6$ requires M^+, 270.1103); *m/z* (FAB) 270 (60%, M^+), 252 (40, [M−H_2O]$^+$), 211 (40), 181 (100).

4.2.16. Ethyl (2*R*)-2-hydroxy-3-[(3′,4′-methylenedioxy)-phenyl]propanoate (5e). This was prepared in the same way as **5b** from **3e/4e** to afford **5e** as a colourless oil (313 mg, 35, 84% ee). The enantiomeric excess was determined by HPLC: Chiracel OB; 90:10 hexane/IPA; 1 cm^{-3} min^{-1}; $[\alpha]_D$=+23.7 (*c* 1.0 in $CHCl_3$); R_f 0.22 (silica; 3:1; hexane/EtOAc, v/v); ν_{max} (KBr disc) 3500 (bs), 3000 (m), 2900 (m), 1740 (vs), 1510 (s), 1490 (s), 1450 (s), 1370 (w), 1250 (bs), 1200 (bs), 1100 (bs), 1040 (s), 940 (s), 810 (m) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.29 (3H, t, J=7.2 Hz, CH_3), 2.77 (1H, d, J=5.2 Hz, OH), 2.88 (1H, dd, J=6.6, 14.0 Hz, CH_aH_b), 3.24 (1H, dd, J=4.4, 14.0 Hz, CH_aH_b), 4.22 (2H, q, J=7.2 Hz, CH_2CH_3), 4.34–4.41 (1H, m, H2), 5.92 (2H, s, H7′), 6.64–6.74 (3H, m, H2′,5′,6′); δ_C (75 MHz, $CDCl_3$) 14.2 (CH_3), 40.2 (CH_2CH_3), 61.7 (C3), 71.3 (C2), 100.9 (C7′), 108.1 (C2′), 109.9 (C5′), 122.5 (C6′), 130.0 (C1′), 146.5 (C4′), 147.5 (C3′), 174.1 (C1); (Found: M^+, 224.0685. $C_{12}H_{14}O_5$ requires [M−CH_2]$^+$, 224.0684); *m/z* (CI) 242 (100%, [M−CH_2+NH_4]$^+$), 225 (20, [M−CH_2+H]$^+$), 224 (5, [M−CH_2]$^+$).

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