Enzymatic Resolution of 1,2-Diols: Comparison between Hydrolysis and Transesterification Reactions

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A new practical procedure for the enzymatic resolution of 1,2-diols **1a–e** has been developed by lipase-catalysed regio- and enantio-selective esterification using anhydrides as acylating agents in organic solvents.

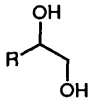
Enantiomerically pure 1,2-diols are valuable synthetic intermediates in asymmetric synthesis. They are widely used as chiral building blocks in a large number of important industrial applications including pharmaceuticals, agrochemicals, pheromones and liquid crystals.

Several routes for the synthesis of chiral 1,2-diols have been reported starting from naturally products, such as L-amino acids, (*S*)-malic acid or D-mannitol.[1] However, these methods require expensive chemical reagents and sometimes laborious experimental procedures.

Recently, lipases have been proposed as catalysts in asymmetric synthesis because they are readily available, inexpensive, stable, and require no cofactor. A number of reports have been published on lipase-catalysed resolutions of racemic alcohols, either *via* enantioselective hydrolysis of the corresponding esters in aqueous solutions,[2] or *via* enantioselective esterification and transesterification in organic solvents.[3,4]

The latter method was extended to the resolution of aliphatic 1,2-diols by using porcine pancreatic lipase (PPL) and aliphatic esters or anhydrides as acylating agents.[5,6] Under these conditions PPL showed remarkable regioselectivity in the esterification of the primary alcohol, but very poor stereoselectivity.[7]

We now describe a new, efficient method for the resolution of 1,2-diols **1a–e** by using a different enzyme: the lipase PS from *Pseudomonas cepacia*.



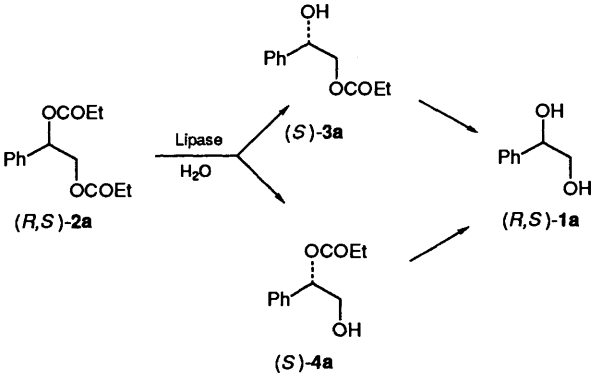
1a-e

a R = Ph
b R = $C_6H_4NO_2$-*p*
c R = C_6H_4Cl-*p*
d R = $TsOCH_2$
e R = Bu

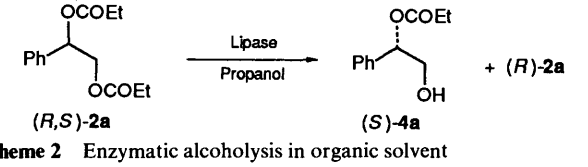
Results and Discussion

We reported[8] that lipase PS, unlike PPL, was an efficient catalyst in the esterification of both primary and secondary alcohols. In order to study the selectivity of this enzyme when both alcohol moieties are present in the same substrate, 1-phenylethane-1,2-diol, **1a**, was selected as a model compound and the enzymatic hydrolysis (Scheme 1) and alcoholysis (Scheme 2) of the corresponding diester **2a** were compared with the esterification of the diol **1a** (Scheme 3).

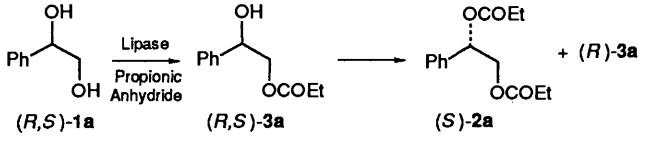
Hydrolyses were carried out in aq. phosphate buffer, pH 7, at 30 °C. The pH was kept constant by addition of 0.5 mol dm^{-3} sodium hydroxide, using a pH-stat. Periodically, aliquots were withdrawn and analysed by HPLC. The reaction was stopped after addition of molar proportions NaOH/**2a** = 0.89. At this stage the amounts of diol **1a**, primary monoester **3a**, secondary monoester **4a** and diester **2a** were quantitatively determined to be 20:22:27:31. The products were separated by column



Scheme 1 Enzymatic hydrolysis



Scheme 2 Enzymatic alcoholysis in organic solvent



Scheme 3 Enzymatic esterification in organic solvent

chromatography on silica gel and the optical purities were determined by chiral stationary-phase HPLC after alkaline hydrolysis to diol **1a** (see Experimental section). The absolute configuration was assigned by comparing the sign of the optical rotation of the diol with that reported.[9]

Kinetic studies showed that the rate of hydrolysis of the primary ester moiety was 2.6-times faster than that of the secondary ester. Both monoesters **3a** and **4a** underwent further hydrolysis to yield the diol **1a**, demonstrating the low regioselectivity of lipase PS under these reaction conditions. As shown in Table 1, the *S* isomer of **2a** was preferentially hydrolysed; however, the low optical purity and the heterogeneity of the products were not satisfactory for practical use.

In a second approach we investigated the alcoholysis of (*R,S*)-**2a** in organic solvents with propan-1-ol as a nucleophile (Scheme 2). The reaction was carried out by suspending lipase PS, supported on Celite, in a solution of (*R,S*)-**2a** and propan-1-ol (molar ratio 1:8) in anhydrous 2-methylbutan-2-ol at 30 °C. The reaction, stopped at 40% conversion, afforded as the only products the unchanged substrate (*R*)-**2a** and the secondary monoester (*S*)-**4a**. As shown in Table 1, both compounds were obtained with moderate optical purity. These findings

Table 1 Lipase PS-catalysed resolution of 1,2-diols **1a–d**

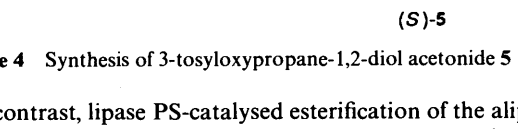
		Diol **1**			Monoester **3**			Monoester **4**			Diester **2**		
Substrate	Reaction	Yield (%)[d]	Confign.	e.e. (%)	Yield (%)	Confign.	e.e. (%)	Yield (%)	Confign.	e.e. (%)	Yield (%)	Confign.	e.e. (%)
2a	*a*	20	*S*	75[d]	22	*S*	75[e]	27	*S*	13[e]	31	*R*	96[e]
2a	*b*							40	*S*	78	60	*R*	36
1a	*c*	50	*R*	16	40	*R*	5				10	*S*	99
1a	*c*				53	*R*	77				47	*S*	93
1b	*c*				55	*R*	75[f]				45	*S*	95[f]
1c	*c*				52	*R*	85[g]				48	*S*	92[g]
1d	*c*	23	*S*	25[h]	42	*S*	71[h]				35	*R*	97[h]
1d	*c*				48	*S*	98				52	*R*	86

[a] Hydrolysis, performed in 0.01 mol dm^{-3} phosphate buffer, pH7 (50 cm^3), substrate (12 mmol), enzyme (270 mg), at 30 °C. [b] Alcoholysis, performed in 2-methylbutan-2-ol (40 cm^3), substrate (5 mmol), enzyme (300 mg), at 30 °C. [c] Esterifications were carried out in 2-methylbutan-2-ol (40 cm^3), substrate (11 mmol), propionic anhydride (24 mmol), enzyme (300 mg), supported on 1 g of Celite), at 25 °C. [d] Determined by HPLC. [e] Determined after transformation into diol **1a** by alkaline hydrolysis. [f] Determined after transformation into diol **1a** by the sequence of (i) reduction of the nitro group (Pd/C, $NaBH_4$)[13] and (ii) reductive deamination ($NaNO_2$/HCl, H_3PO_2).[14] [g] Determined after transformation into diol **1a** by reductive dehalogenation (Pd/C, H_2).[15] [h] Determined by transformation into 3-tosyloxypropane-1,2-diol acetonide **5**.[16]

demonstrated that alcoholysis proceeded with much more regioselectivity than did the hydrolysis, although maintaining the poor stereoselectivity displayed in water.

In a different strategy, we studied the lipase-catalysed esterification of diol **1a** using anhydrides as acylating agents (Scheme 3). The esterification reactions were performed by adding the lipase, supported on Celite, to a solution of diol **1a** and propionic anhydride in 2-methylbutan-2-ol at 25 °C. Surprisingly, the behaviour of lipase PS under these reaction conditions was dramatically different from that in water. As shown in Scheme 3, the diol **1a** was initially quantitatively transformed into the primary monoester **3a**, which was subsequently and stereoselectively acylated to give the diester **2a** in the *S* form, with unchanged monoesters **3a** recovered in the *R* form. No trace of the secondary ester **4a** could be detected. The optical purities of the products, isolated at different degrees of conversion (Table 1), showed that lipase PS is specific for the *S* enantiomer in both steps of esterification of diol **1a**, with the enantiospecificity of the esterification of the secondary hydroxy group being considerably larger than that of the primary one.

On the basis of the marked enentioselectivity expressed by lipase PS in the esterification of diol **1a**, we extended the method to the preparative resolution of racemic 1,2-diols **1b–e**. As shown in Table 1, substrates bearing an aromatic group **1b–d** confirmed the regioselectivity and the stereoselectivity observed for diol **1a**. The diol **1d**, obtained from the corresponding enzymically prepared esters by chemical hydrolysis, was easily converted into optically pure 3-tosyloxypropane-1,2-diol acetonide **5**, an extremely versatile chiral intermediate in synthetic organic chemistry (Scheme 4).



Scheme 4 Synthesis of 3-tosyloxypropane-1,2-diol acetonide **5**

In contrast, lipase PS-catalysed esterification of the aliphatic substrate **1e** afforded, as intermediate products, a mixture of secondary monoester **4e**, primary monoester **3e**, diester **2e** and unchanged diol **1e** with very low optical purities.

These data confirmed the studies reporting that lipase PS requires the presence of bulky groups, such as aromatic or a *tert*-butyl moiety, in order to increase the degree of its stereodifferentiation.[10]

The results obtained using the three above described procedures demonstrate that the choice of reaction conditions plays a crucial role in determining the enantioselectivity of lipase PS.[11] In particular, the lipase-catalysed esterification provides a simple and efficient method for the preparation of optically pure aromatic-group-containing 1,2-diols, with no requirement for previous introduction of protective groups.[12,13]

The synthetic potential of the method has been demonstrated by the synthesis of the acetonide (*S*)-**5** starting from (*S*)-**1d**.

Experimental

^1H NMR spectra were recorded in $CDCl_3$ solution with $SiMe_4$ as internal standard, on a Bruker AC 200 instrument. GLC analyses were carried out on a Carlo Erba HRGC 5300 with a 2 m × 4 mm SP 2100 3% column, at 100–280 °C, and with a flame ionization detector and N_2 as carrier gas. All the hydrolyses were performed with a Methrom pH-stat. Optical purity of compound **1a** was determined by HPLC analysis, performed on a chiral column of Chiralcel OC (Daicel Chemical Industries, Ltd). The eluant was hexane–propan-2-ol (9:1 v/v), while the flow rate was 0.8 cm^3 min^{-1} and readings were made at 254 nm. Lipase Amano PS from *Pseudomonas cepacia* (30 units mg^{-1}) was purchased from Amano Chemical Co. Optical rotations were measured with a Perkin-Elmer 241 polarimeter.* All the organic chemicals used were purchased from Fluka Chemie.

Enzymatic Hydrolysis of 1-*Phenylethane*-1,2-*diol Dipropionate* **2a**.—To a magnetically stirred suspension of (*R*,*S*)-1-phenylethane-1,2-diol dipropionate **2a** (3.0 g, 12 mmol) in 0.01 mol dm^{-3} phosphate buffer, pH 7 (50 cm^3), at 30 °C was added lipase PS (0.270 g, 8100 units). The pH was kept constant at 7 by addition of 0.05 mol dm^{-3} aq. sodium hydroxide. Periodically, aliquots (1 mm^3) of the liquid phase were withdrawn and analysed by HPLC. The hydrolysis was stopped after 6.5 h and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with 5% aq. sodium hydroxide, dried (Na_2SO_4) and then evaporated to dryness. Chromatography on silica gel, with hexane–ethyl acetate (8:2 v/v) as eluant, afforded diester (*R*)-(−)-**2a** (0.9 g, 31%); $[\alpha]_D^{25}$ −62.6 (*c* 1, acetone), ee = 96%; δ_H 1.2 (6 H, t), 2.4 (4 H, q), 4.4 (2 H, m), 6.1 (1 H, m) and 7.4 (5 H, s) (Found: C, 67.1; H, 7.3. Calc. for $C_{14}H_{18}O_4$: C, 67.2; H, 7.25%); monoester 0.509 g of (*S*)-(+)-**3a** (0.509 g, 22%); $[\alpha]_D^{25}$ + 19 (*c* 1, acetone); ee = 75%; δ_H 1.2 (3 H, t), 2.4 (2 H, q), 2.9 (1 H, s), 4.2 (2 H, m, 4.95 (1 H, m) and 7.4 (5 H, s)

* Following a recent IUPAC recommendation, units for $[\alpha]_D^{25}$ are 10^{-1} deg cm^2 g^{-1}.

(Found: C, 68.1; H, 7.3. Calc. for $C_{11}H_{14}O_3$: C, 68.0; H, 7.25%); monoester (*S*)-(+)-**4a** 10.62 g, 27%); $[\alpha]_D^{25}$ +11 (*c* 1, acetone); ee = 13%; δ_H 1.12 (3 H, t), 2.4 (2 H, q), 2.6 (1 H, br s), 3.75 (2 H, d), 5.85 (1 H, t) and 7.34 (5 H, s) (Found: C, 68.1; H, 7.3. Calc. for $C_{11}H_{14}O_3$: C, 68.0; H, 7.25%); and diol (*S*)-(+)-**1a** (0.325 g, 20%); $[\alpha]_D^{25}$ +29.3 (*c* 1, EtOH); ee = 75%; δ_H 3.7 (2 H, m), 4.1 (2 H, br s), 4.75 (1 H, m) and 7.3 (5 H, s) (Found: C, 69.6; H, 7.3. Calc. for $C_8H_{10}O_2$: C, 69.5; H, 7.29%). The ee's of products **2a**, **3a** and **4a** were determined by HPLC after alkaline hydrolysis to the diol **1a**.

Adsorption of Enzyme on Celite.—Celite 577 (2 g) was washed successively with water and 0.3 mol dm^{-3} phosphate buffer and was then added to a solution of lipase Amano PS (0.5 g, 15 000 units) in 0.3 mol dm^{-3} phosphate buffer (10 cm^3). The mixture was spread on a watch glass and left to dry at 25 °C with occasional mixing until visibly dry. At this stage the water content was ~1% as determined by the Fisher method.

Enzymatic Alcoholysis of Diester **2a**.—Lipase PS (0.3 g, 9000 units) supported on Celite 577 (1 g) was added to a solution of diester (*R,S*)-**2a** (1.3 g, 5 mmol) and propan-1-ol (1.47 g, 24.6 mmol) in anhydrous 2-methylbutan-2-ol (40 cm^3). The resulting suspension was shaken on an orbital shaker at 200 rpm at 30 °C. After 24 h the reaction was stopped at 40% conversion, and the supported enzyme was filtered off. The solvent was evaporated off under reduced pressure and the residue was chromatographed on silica gel with hexane–ethyl acetate (9:1 v/v) as eluant to afford diester (*R*)-(−)-**2a** (0.71 g, 54%); $[\alpha]_D^{25}$ −22.5 (*c* = 1, acetone), ee = 36%; and monoester (*S*)-(+)-**4a** (0.34 g, 37%); $[\alpha]_D^{25}$ +66.0 (*c* 1, acetone); ee = 78%.

Enzymatic Esterification of Diols **1a–c**.—The following procedure is representative. (*R,S*)-1-phenylethane-1,2-diol **1a** (1.5 g, 11 mmol) was dissolved in 2-methylbutan-2-ol (40 cm^3). Propionic anhydride (3.1 g, 23.8 mmol) and lipase PS (0.3 g, 9000 units) supported on Celite 577 (1 g) were added to the solution. The reaction mixture was magnetically stirred at 25 °C. Periodically, aliquots (1 mm^3) were withdrawn, and analysed by HPLC. After 22 h, compounds **2a** (47%) and **3a** (53%) were detected and the reaction was stopped. The solid enzyme preparation was filtered off, and the solution was washed with 5% aq. Na_2CO_3, dried (Na_2SO_4), and evaporated to dryness. Chromatography on silica gel with hexane–ethyl acetate (95:5 v/v) as eluant afforded diester (*S*)-(+)-**2a** (1.23 g, 45%); $[\alpha]_D^{25}$ +61.4 (*c* 1, acetone); ee = 93%; and monoester (*R*)-(−)-**3a** 0.885 g, 42%); $[\alpha]_D^{25}$ −18.5 (*c* 1, acetone); ee = 77%.

By use of the above procedure starting from diol (*R,S*)-**1b**, the corresponding monoester (*R*)-(−)-**3b** (42%); δ_H 1.2 (3 H, t), 2.35 (2 H, q), 2.9 (1 H, br p), 4.3 (2 H, m), 5.0 (1 H, m) and 7.35 (4 H, s); $[\alpha]_D^{25}$ −15.1 (*c* 1, acetone); ee = 75% (Found: C, 55.1; H, 5.55; N, 5.7. Calc. for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.47; N, 5.85%); and the diester (*S*)-(+)-**2b** (53%); δ_H 1.2 (6 H, q), 2.3 (4 H, m), 4.3 (2 H, m), 5.7 (1 H, m) and 7.35 (4 H, s); $[\alpha]_D^{25}$ +40 (*c* 1, acetone); ee = 95% (Found: C, 56.9; H, 5.9; N, 4.7. Calc. for $C_{14}H_{17}NO_6$: C, 56.94; H, 5.80; N, 4.74%) were obtained. Furthermore, optically active monoester (*R*)-(−)-**3c** (50%); δ_H 1.15 (3 H, t), 2.35 (2 H, q), 3.1 (1 H, s), 4.2 (2 H, m), 4.9 (1 H, 2 d) and 7.3 (4 H, s); $[\alpha]_D^{25}$ −11.9 (*c* 1, acetone); ee = 85% (Found: C, 57.7; H, 5.8 (Calc. for $C_{11}H_{13}ClO_3$: C, 57.77; H, 5.73%) and diester (*S*)-(+)-**2c** (46%); δ_H 1.15 (6 H, m), 2.3 (4 H, m), 4.25 (2 H, d), 5.8 (1 H, 2 d) and 7.3 (4 H, s); $[\alpha]_D^{25}$ +57.5 (*c* 1, acetone); ee = 92% (Found: C, 59.0; H, 6.0. Calc. for $C_{14}H_{17}ClO_4$: C, 59.05; H, 6.02%) were prepared from the corresponding diol (*R,S*)-**1c** by the same method. The optical purities of these compounds were determined after their chemical conversion into the diol **1a**, following known procedures.[14–16]

Alkaline Hydrolysis of Esters **2a–c** *and* **3a–c**.—The following procedure is representative. (*S*)-(+)-1-Phenylethane-1,2-diol dipropionate **2a** {1.23 g, 5 mmol; $[\alpha]_D^{25}$ +61.4 (*c* 1, acetone)} was dissolved in methanol (15 cm^3). A solution of sodium hydroxide (0.44 g, 11 mmol) in methanol (15 cm^3) was added dropwise to the magnetically stirred solution at 0 °C. The mixture was then allowed to react at 25 °C. The hydrolysis proceeded to complete conversion into diol after 3 h. The reaction mixture was evaporated under reduced pressure, diluted with CH_2Cl_2, and washed with water. The organic layer was dried (Na_2SO_4) and then evaporated to dryness to afford diol (*S*)-(+)-**1a** (0.61 g, 90%); $[\alpha]_D^{25}$ +36.5 (*c* 1, EtOH); ee = 93%.

Enzymatic Esterification of Diol **1d**.—(*R,S*)-3-Tosyloxypropane-1,2-diol **1d** (5 g, 19 mmol) was dissolved in 2-methylbutan-2-ol (125 cm^3). Propionic anhydride (5.41 g, 41.6 mmol) and lipase PS (0.75 g, 22 500 units) supported on Celite 577 (2.5 g) were added to the solution. The reaction mixture was magnetically stirred at 25 °C. Periodically, aliquots (1 mm^3) were withdrawn and analysed by HPLC. After 5 h, compounds **3d** (48%) and **2d** (52%) were detected and the reaction was stopped. The enzyme was filtered off and the solution was washed with 5% aq. Na_2CO_3, dried (Na_2SO_4), and evaporated to dryness. Chromatography on silica gel with hexane–ethyl acetate (80:20 v/v) as eluant afforded diester (*R*)-(+)-**2d** (3.48 g, 49%); $[\alpha]_D^{25}$ +7.57 (*c* 1, $CHCl_3$); ee = 86%; δ_H 1.1 (6 H, t), 2.3 (4 H, q), 2.45 (3 H, s), 4.15 (4 H, m), 5.1 (1 H, m) and 7.35 and 7.75 (4 H, 2 d) (Found: C, 53.75; H, 6.2; S, 8.9. Calc. for $C_{16}H_{22}O_7S$: C, 53.62; H, 6.19; S, 8.95%); and monoester (*S*)-(+)-**3d** (2.73 g, 45%); $[\alpha]_D^{25}$ +1.8 (*c* 1, $CHCl_3$); ee = 98%; δ_H 1.1 (3 H, t), 2.3 (2 H, q), 2.45 (3 H, s), 4.1 (5 H, m) and 7.35 and 7.75 (4 H, 2 d) (Found: C, 51.5; H, 6.0; S, 10.7. Calc. for $C_{13}H_{18}O_6S$: C, 51.64; H, 6.0; S, 10.6%).

The optical purities and configuration of esters **2d** and **3d** were determined *via* chemical transformation into the corresponding optically active 3-tosyloxypropane-1,2-diol acetonide **5**.

Chemical Hydrolysis of Esters **2d** *and* **3d**.—(*R*)-(+)-3-Tosyloxypropane-1,2-diol dipropionate **2d** {1 g, 2.6 mmol; $[\delta]_D^{25}$ +7.6 (*c* 1, $CHCl_3$)} was dissolved in a solution of toluene-*p*-sulfonic acid (PTSA) (0.01 g, 0.05 mmol) in methanol (30 cm^3). The solution was magnetically stirred at 60 °C. After 3 h the solution was diluted with brine and extracted wth CH_2Cl_2. The organic layer was dried (Na_2SO_4) and the solvent was evaporated off under reduced pressure. Chromatography on silica gel with 50:50 (v/v) hexane–ethyl acetate as eluant afforded (*R*)-(−)-3-tosyloxypropane-1,2-diol **1d** (0.6 g, 85%); $[\alpha]_D^{25}$ −8.0 (*c* 1, MeOH) {lit.,[17] $[\alpha]_D^{25}$ −9.3 (*c* 1, MeOH)}; ee = 86%; δ_H 2.4 (3 H, s), 3.6–4.1 (5 H, m) and 7.35 and 7.75 (4 H, 2 d)}.

Following the above procedure, optically active diol (*S*)-(+)-**1d** (82%); $[\alpha]_D^{25}$ +9.2 (*c* 1, MeOH); ee = 98% (Found: C, 48.8; H, 5.8; S, 13.0. Calc. for $C_{10}H_{14}O_5S$: C, 48.77; H, 5.73; S, 13.02%) was prepared from the corresponding enzymatically produced ester (*S*)-(+)-**3d** {$[\alpha]_D^{25}$ +1.8 (*c* 1, $CHCl_3$)}.

Preparation of (S)-(+)-3-*Tosyloxypropane*-1,2-*diol Acetonide* **5**.—To a flask fitted with a Dean–Stark trap and condenser were added acetone (15 cm^3, 200 mmol), light petroleum (45–70 °C) (15 cm^3), (*S*)-(+)-3-tosyloxypropane-1,2-diol **1d** {5 g, 19 mmol; $[\alpha]_D^{25}$ +9.2 (*c* 1, MeOH)} and PTSA (0.055 g, 0.29 mmol). The magnetically stirred reaction mixture was refluxed for 4 h. The solution was then cooled, sodium acetate (0.025 g, 0.3 mmol) was added, and the contents were stirred for 30 min. The salts were filtered off and the solution was evaporated to dryness. The residue, purified by silica gel chromatography with ethyl ether–hexane (80:20 v/v) as eluant, afforded acetonide (*S*)-(+)-**5** (4.3 g, 80%); $[\alpha]_D^{25}$ +4.5 (*c* 1, EtOH) {lit.,[18] $[\alpha]_D^{25}$

+4.5 (*c* 1, EtOH)}; ee = 98%; δ_H 1.35 (6 H, s), 2.45 (3 H, s), 3.7–4.25 (5 H, m) and 7.35 and 7.8 (4 H, 2 d).

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