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Kinetic resolution of primary 2-methyl-substituted alcohols *via* *Pseudomonas cepacia* lipase-catalysed enantioselective acylation

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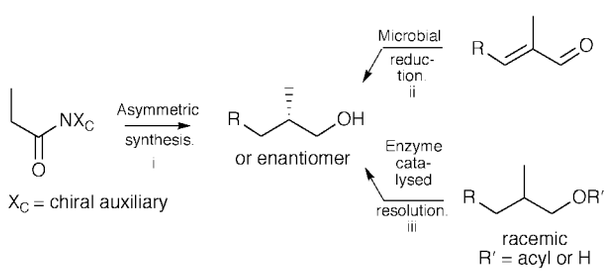
The enantioselectivities of lipases from *Pseudomonas cepacia* (PFL, Amano PS, *etc.*) towards a series of primary 2-methyl-substituted alcohols using vinyl acetate as the acyl donor in transesterifications in organic solvents were studied. In terms of enantioselectivity, the best results were found for 3-aryl-2-methylpropan-1-ols with enantiomeric ratios (*E*-values) over 100 in most cases, whereas other 3-substituted primary 2-methylpropan-1-ols generally displayed lower enantioselectivities: 3-cycloalkyl-2-methylpropan-1-ols ($E \approx 20$) and 2-methylalkan-1-ols ($E \approx 10$). Moving the aryl group closer or further away from the chiral centre resulted in low enantioselectivities: 2-arylpropan-1-ols ($E < 10$), 2-methyl-4-(2-thienyl)butan-1-ol ($E = 12$), 2-methyl-5-(2-thienyl)pentan-1-ol ($E = 3.2$) and 2-methyl-6-(2-thienyl)hexan-1-ol ($E = 3.8$).

One of the most attractive approaches for obtaining chiral nonracemic compounds is *via* enantioselective catalysis. Within this area biocatalysis has evolved as one of the most efficient methods and both whole-cell systems and isolated enzymes are widely used as catalysts.[1–5]

A large number of hydrolytic enzymes, especially lipases, have been used successfully for the kinetic resolution of racemic secondary alcohols *via* enantioselective acylation or hydrolysis of their esters.[5–7] However, a very limited number of enzymes are capable to resolve racemates of primary alcohols or their esters. Thus, only lipases from *Pseudomonas* and Porcine Pancreas (PPL) are known to efficiently resolve these substrates.[5]

Enantiomerically pure 2-methyl-branched, primary alcohols are valuable synthetic building blocks for, *e.g.*, pheromone synthesis[8,9] and many methods have been developed for their preparation (Scheme 1). They can be obtained *via* chemical



Scheme 1 Some examples of synthetic strategies for the preparation of enantiomerically pure 2-methylalkan-1-ols. *Reagents and conditions*: i, base then remove Xc, then reduction; ii, baker's yeast reduction provides one enantiomer; iii, lipase catalysed kinetic resolution then product separation provides the pure enantiomers (one as ester).

methods, *e.g.* auxiliary-based ones such as the widely used diastereoselective alkylation of amide enolates which, after removal of the chiral auxiliary followed by reduction, gives nonracemic 2-methyl-substituted alcohols.[10,11] Biocatalysts have also been found very useful for the preparation of such alcohols. Thus baker's yeast reduction of (*E*)-3-aryl-2-methylpropenals provides moderate to good yields of (*S*)-3-aryl-2-methylpropan-1-ols.[12–17] However, if both enantiomers are needed, lipase-catalysed kinetic resolutions are preferred. Although a few examples are available of moderately successful

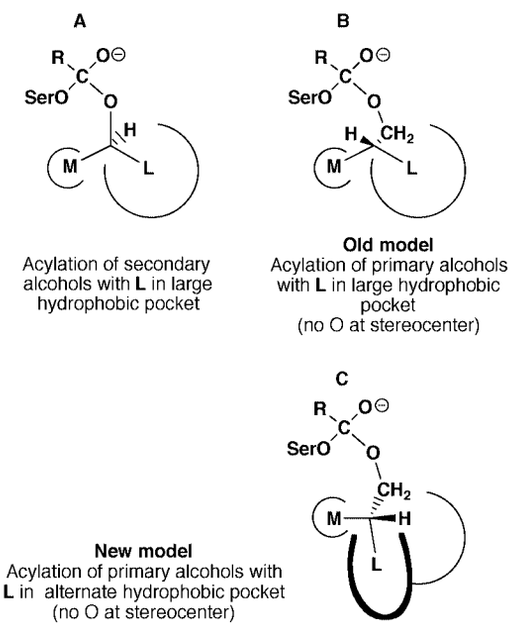


Fig. 1 Empirical rules for the enantiopreferences of *Pseudomonas* lipases.[25,26] Models **A** and **B** describe the situation for secondary and primary alcohols, respectively, assuming the latter employ the same pockets. **M** and **L** symbolise medium sized and large substituents, *e.g.* methyl and phenyl, respectively. The rules for models **B** and **C** do not hold if either **M** or **L** is equal to OR.[21]

PPL-catalysed kinetic resolutions of racemic 2-methyl-substituted alcohols or esters,[18–20] *Pseudomonas*-derived lipases are the biocatalysts of choice for these transformations today.[5,21–24]

Predictive rules have been derived for the enantiopreference of *Pseudomonas* lipases towards secondary alcohols and also for primary alcohols branched in the 2-position (**A** and **B**, respectively, in Fig. 1) without oxygen atoms at the stereogenic centre.[25,26] These rules postulate that primary alcohols dock into the same pockets as secondary alcohols. Assuming that this is the case, additional models, including box models, have been presented, describing the active site of *Pseudomonas* lipases.[27–29] For *Pseudomonas cepacia* lipase (PCL, see introductory remark under Experimental section), the X-ray crystal structure of the

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open conformation has recently been reported.[30,31] Molecular-modelling studies of transition-state analogues bound to the active site of PCL, have been performed starting from the X-ray structure of PCL and two large hydrophobic pockets have been identified.[21] From these studies it appears that primary alcohols bind to PCL in a different mode than do secondary ones.[21] Thus, for 2-methyl-3-phenylpropan-1-ol (**2g**, see structures in Table 2) the large benzyl group binds to an alternative hydrophobic pocket in a narrow groove not used by secondary alcohols (see Fig. 1, **C**).[21] The enantioselectivity of PCL toward the *S*-enantiomer arises from binding of the methyl group at the stereogenic centre to a small hydrophobic pocket.[21] This interaction is absent with the slow reacting *R*-enantiomer.[21] It must be pointed out that if the enzyme employs different docking modes for primary and secondary alcohols, box models derived from reactions of both types of alcohols must be used with caution.

We have long been interested in the preparation of enantiomerically pure 2-methyl-1-alkyl building blocks for the syntheses of highly pure stereoisomers of pine sawfly pheromones.[9,32–34] For 2-methylalkanols, we have studied baker's yeast-mediated reductions[14] and *Candida rugosa* lipase-catalysed kinetic resolution by esterification of 2-methylalkanoic acids followed by reduction.[35,36] Although the latter sequence is quite satisfactory for obtaining both enantiomers of a 2-methylalkan-1-ol, we wished to develop alternative strategies. Therefore we decided to study the use of PCL as the catalyst for the kinetic resolution of a number of 2-methyl-substituted alcohols *via* transesterification of vinyl acetate. The results of our investigations are summarised here (preliminary accounts of parts of this work: Högberg *et al.*,[9] Nguyen *et al.*[22] and Nordin *et al.*[23]).

Results and discussion

Preparation of substrates

In order to explore the enantioselectivity of the PCL-catalysed transesterification as a function of the substrate structure we have studied a number of new substrates of types **1**–**6** (Chart 1).

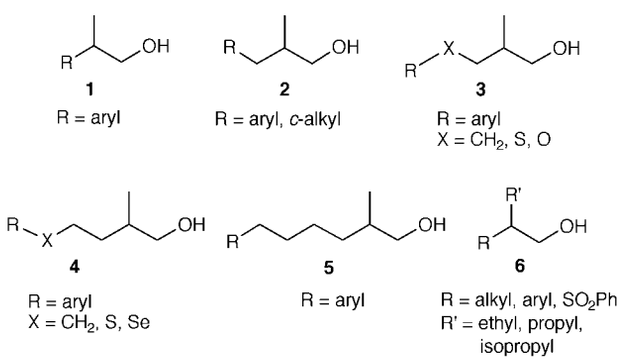
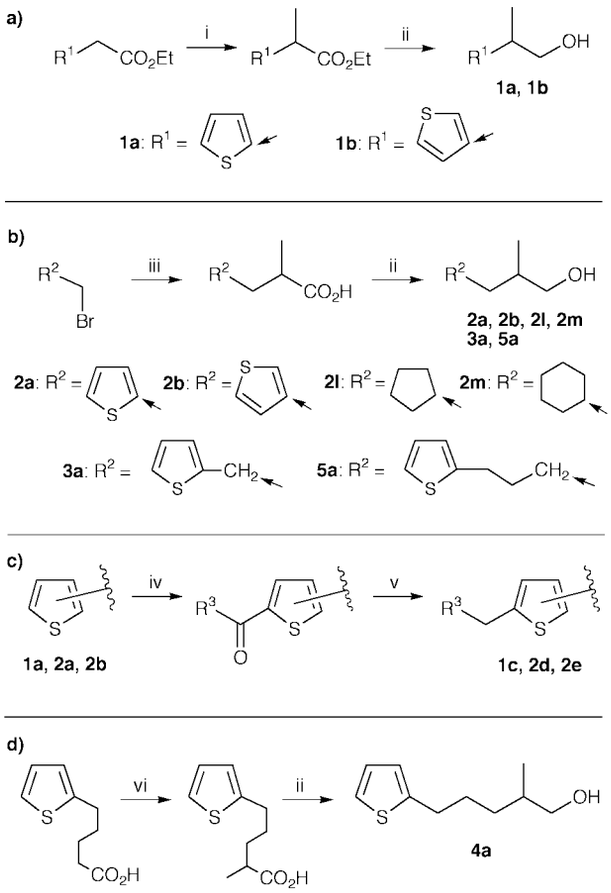


Chart 1 2-Alkylalkan-1-ols studied as substrates for PCL-catalysed transesterifications.

The syntheses of these are summarised below and details of the preparative procedures can be found in the Experimental section.

For comparison with other 2-methyl-ω-(2-thienyl)alkan-1-ols we prepared some thiophene derivatives **1a**–**c**, **2b**, **3a**, **4a** and **5a** as described in Scheme 2. Thus ethyl thiophene-2-acetate was alkylated[37] with methyl iodide and reduced to give 2-(2-thienyl)-propan-1-ol **1a** (Scheme 2a). 2-(3-Thienyl)propan-1-ol **1b** was obtained in a similar way from ethyl thiophene-3-acetate. The two 2-methyl-3-thienylpropan-1-ols **2a** and **2b** were prepared *via* alkylation of diethyl methylmalonate followed by hydrolysis to the diacid, decarboxylation and LAH reduction (Scheme 2b). 2-(2-Thienyl)propan-1-ol **1a** was transformed into 2-(5-butyl-2-thienyl)propan-1-ol **1c** *via* Friedel–Crafts acylation followed by Huang-Minlon reduction (Scheme 2c).[14] 2-Methyl-3-(5-propyl-2-thienyl)propan-1-ol **2d**, its precursor **2c**, and 3-(5-ethyl-3-thienyl)-2-methylpropan-1-ol[34] **2e** were obtained in a similar way from compounds **2a** and **2b**.



Scheme 2 Preparation of substrates containing thienyl and cycloalkyl moieties. For R^1 and R^2, arrows indicate points of attachment. *Reagents and conditions*: i, LDA then MeI; ii, LAH then H_2O; iii, Anion of diethyl methylmalonate then NaOH, EtOH, H_2O then H_3O^+, H_2O then heat (decarboxylation); iv, R^3COCl, $SnCl_4$, CH_2Cl_2; v, N_2H_4, NaOH, diethylene glycol, 120 to >200 °C; vi, 2 eq. LDA then MeOTs.

2-Methyl-4-(2-thienyl)butan-1-ol **3a** and 2-methyl-6-(2-thienyl)hexan-1-ol **5a** were prepared from 2-(2-bromoethyl)-thiophene and 2-(4-bromobutyl)thiophene, respectively, using the methylmalonate method described above (Scheme 2b). Deprotonation of 5-(2-thienyl)pentanoic acid with 2 mole equiv. of LDA followed by alkylation with methyl toluene-*p*-sulfonate in the presence of 1,3-dimethylpropylene urea (DMPU) gave, after acidification, 2-methyl-5-(2-thienyl)pentanoic acid which, when subjected to LAH reduction, furnished 2-methyl-5-(2-thienyl)pentan-1-ol **4a** (Scheme 2d).

Some additional substrates were also prepared (see Schemes 2 and 3) and used in this study. Thus 3-cyclopentyl- and 3-cyclohexyl-2-methylpropan-1-ol, **2l** and **2m**, respectively, were prepared using the methylmalonate route (Scheme 2b). Secondly, 2-methoxybenzaldehyde was condensed with propanal. After reduction of the double bond of the aldol condensation product followed by borohydride reduction of the resulting aldehyde, 3-(*o*-methoxyphenyl)-2-methylpropan-1-ol **2h** was obtained (Scheme 3a). Racemisation of 2-methylalkanols can be performed by treatment with sodium and benzophenone in hot toluene.[24] Application of this method to (*S*)-3-(2-furyl)-2-methylpropan-1-ol (*S*)-**2f**, which can be obtained from 3-(2-furyl)-2-methylpropenal *via* baker's yeast reduction,[12] furnished 3-(2-furyl)-2-methylpropan-1-ol **2f** (Scheme 3b). Finally, conjugate addition of thiophenol to methacrolein furnished an

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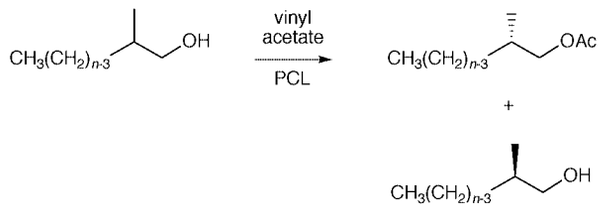
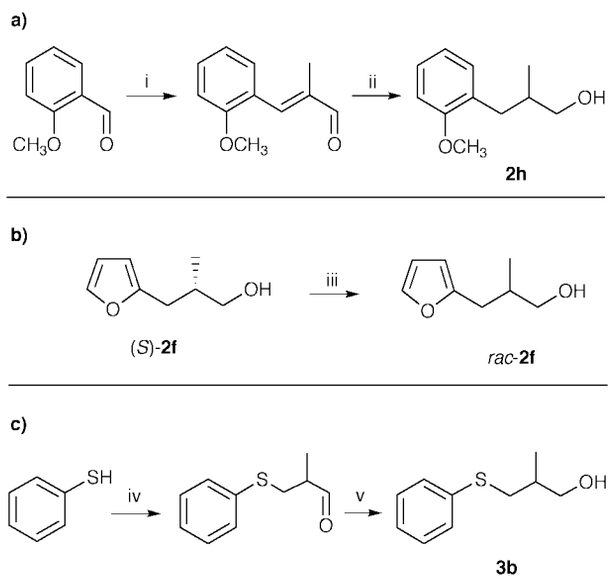
Table 1 PCL-catalysed kinetic resolution of 2-methylalkan-1-ols by transesterification with vinyl acetate



Substrate n =	Enzyme	Solvent	c/%	ee$_p$/%	ee$_s$/%	E	Ref.
5	Amano PS	CH_2Cl_2	80.2	28.7	98	5.9	24
6	Amano PS	CH_2Cl_2	74.6	33.7	99	8.7	24
8	Amano PS	CH_2Cl_2	78.0	27.4	96.2	5.7	24
8	PFL (Fluka)	$CHCl_3$	39.5	60.0		5.8	23
10	Amano PS	CH_2Cl_2	70.0	42.4	98.1	9.9	24
10	Amano PS	$CHCl_3$	40.6	73.4		10.7	23
10	Amano AK	$CHCl_3$	39.3	72.5		9.9	23
10	PFL (Fluka)	$CHCl_3$	38.3	73.8		10.4	23
12	PFL (Fluka)	$CHCl_3$	39.4	74.4		10.9	23
14	PFL (Fluka)	$CHCl_3$	42.7	72.4		10.6	23

aldehyde which, after borohydride reduction, gave 2-methyl-3-(phenylthio)propan-1-ol **3b** (Scheme 3c).[38]



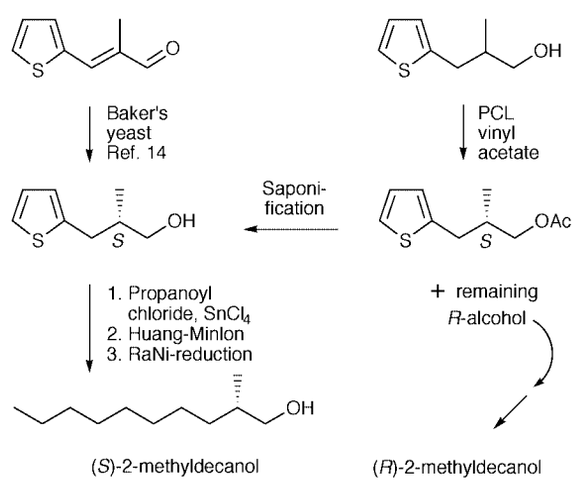
Scheme 3 Preparation of substrates without thienyl or cycloalkyl moieties. *Reagents and conditions*: i, Propanal, NaOH, EtOH, H_2O; ii, Pd, H_2 then $NaBH_4$; iii, Na, toluene, reflux; iv, 2-methylprop-2-enal, Cupric acetate [catalyst]; v, $NaBH_4$.

Kinetic resolutions by transesterifications catalysed by PCL

2-Methylalkan-1-ols. The kinetic resolution of 2-methylalkan-1-ols with alkanol chain lengths from 5 to 14 by transesterification with vinyl acetate in the presence of PCL gives E-values[1–4] (*i.e.*, reaction rate ratios of the enantiomers in a racemic starting material) of between 6 and 11 (see Table 1).[23,24] We studied the possibility of increasing the E-values in this reaction for some long-chain 2-methylalkanols using PCL [PFL (Fluka), Amano PS or AK] by changing the solvent, by immobilising the enzyme, by changing the temperature and water activity. However, only small effects were registered.[23] Because these low E-values were unsatisfactory for preparative purposes, an alternative approach had to be used for the preparation of such 2-methylalkan-1-ols of high enantiomeric excesses (ees).

Substrates of type 2 (see Chart 1). We have earlier shown that baker's yeast reduction of 2-methyldec-2-enal (Scheme 1, R = C_7H_{15}) provides (*S*)-2-methyldecan-1-ol albeit in both unsatisfactory ee and yield.[14] To circumvent this problem we have utilised a thiophene ring as a masked -$(CH_2)_4$- group, which is easily revealed by Raney nickel reduction (Scheme 4, left).[14]

It is known that 2-methyl-3-phenylpropan-1-ol **2g** can be efficiently resolved by PCL-catalysed kinetic acylation with vinyl acetate.[9,39,40] Therefore, it occurred to us that the heterocyclic analogue 2-methyl-3-(2-thienyl)propan-1-ol **2a** could behave in a similar way. An efficient approach to both of the pure enantiomers of 2-methylalkanols would then be available, using either of the pure enantiomers of 2-methyl-3-(2-thienyl)propan-1-ol **2a** as the starting material (Scheme 4, right). Using racemic



Scheme 4 Synthetic strategies for the preparation of the enantiomers of 2-methyldecan-1-ol using thiophene as a masked -$(CH_2)_4$- group either *via* baker's yeast reduction (left) or *via* PCL-catalysed kinetic resolution by transesterification of vinyl acetate (right).

2-methyl-3-(2-thienyl)propan-1-ol **2a** as the substrate in a PFL-catalysed transesterification of vinyl acetate in chloroform with an initial water activity of $a_w = 0.32$, we found, to our satisfaction, that this reaction was highly enantioselective ($E \approx 200$). The same reaction has also been studied by others using PCL.[15] They showed that both enantiomers can be used as building blocks using a similar Friedel–Crafts acylation–Huang-Minlon–Raney nickel reduction sequence to that described in Scheme 4, to prepare both enantiomers of the antimicrobial and cytostatic alkaloid niphatesine C.[41]

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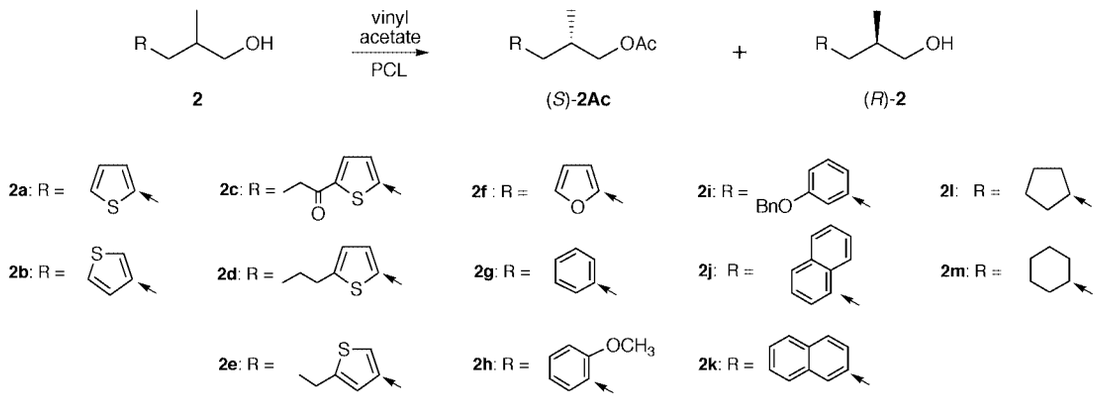
Table 2 PCL-catalysed kinetic resolution of 3-substituted 2-methylpropan-1-ols by transesterification with vinyl acetate



Substrate	Enzyme	Solvent	*c*/%	ee_p/%	ee_s/%	*E*	Ref.
2a	PFL (Fluka)	$CHCl_3$	39.3	98.2		200	*a*, 9
2a	Amano PS	$CHCl_3$	37.9	97.3		130	*a*, 9
2a	Amano PS	TBME	42.2	97.5		170	*a*, 9
2b	Amano PS	$CHCl_3$	38.9	96.6		108	*a*
2c	Amano PS	TBME	40.2	97.3		144	*a*, 22
2d	Amano PS	TBME	43.5	98.5		300	*a*, 22
2e	Amano PS	TBME	38.5	95.1		75	*a*
2f	Amano PS	$CHCl_3$	31.0	97.1		105	*a*
2g	PFL	CH_2Cl_2				172	42
2g	Amano PS	$CHCl_3$	40.9	96.6		116	*a*, 9
2g	Amano PS	TBME	40.5	96.6		90	*a*, 9
2h	Amano PS	TBME	41.2	94.2		67	*a*
2i	Amano PS	EtOAc[b]	45	98	79	≥100[c]	13
2j	PFL	$CHCl_3$				150	43
2k	PFL	$CHCl_3$				45	43
2l	Amano PS	TBME	41.2	81.9		18	*a*
2m	Amano PS	TBME	39.4	83.2		18	*a*

[a] This work. [b] Anhydrous ethyl acetate (EtOAc) was used both as solvent and acyl donor. [c] $E = 29$ was reported by Bianchi *et al.*[13] but from the ee_p, ee_s and conversion given by the authors, $E = 240$ was calculated by using Sih's and Rakels' formulae.[44,45]

In order to establish how the nature of the substituent R in compounds of type **2** (see Chart 1) affects the *E*-value a number of these were prepared as described above and resolved according to the standard procedure (see Experimental section). The results are summarised in Table 2 and compared with some earlier results[13,43] obtained by other groups.

When comparing the *E*-values presented in Table 2 it was evident that there were two categories of substrates. One group was the 3-aryl-2-methylpropan-1-ols, *e.g.* **2a**–**h** which were resolved with high *E*-values ($E \approx 70$–300). The *E*-values obtained were roughly independent of whether the ring was 2-furyl, 3-thienyl or phenyl. They all gave $E \geq 100$. An interesting observation was that substitution in the 5-position of the thienyl ring in the 2-methyl-3-(3-thienyl)propan-1-ols gave a lower *E*-value for **2e** compared with the unsubstituted **2b**, $E = 75$ and $E = 108$, respectively. On the other hand, the 3-(2-thienyl)propanol **2a**, which gave $E = 170$, on substitution in the 5-position showed the opposite effect on *E*. Thus, substrate **2d** gave $E = 300$.

The second category of substrates in Table 2 consisted of the 3-cycloalkyl-2-methylpropan-1-ols **2l** and **2m** which had cycloalkane rings instead of aromatic rings in their structures. In these cases, the *E*-values were much lower, $E \approx 18$, but not as low as those observed for 2-methylalkan-1-ols, *E* between 6 and 11 (Table 1). This difference between the substrates containing cycloalkyl and aryl substituents indicated that the aromatic systems interacted in a favourable way with, *e.g.*, aromatic moieties in the enzyme.

Thus, for substrates of type **2** containing aromatic rings, the *E*-values were good to excellent in most cases. However, this does not mean that the aromatic ring in the substrate is located in the optimal position for achieving high *E*-values. Therefore a series of new substrates were studied.

Substrates of type 1 (see Chart 1). Some substrates of type **1** have been studied before and generally give rather low *E*-values in PCL-catalysed kinetic resolutions.[42,43] However, some sterically demanding substrates, *e.g.* naphthyl derivatives **1e** and **1f**, give improved *E*-values.[43] The new compounds studied here also gave similar results (see Table 3). It is interesting to note that for substrates of type **1**, the 2-thienyl-substituted compound **1a** gave a better *E*-value than the corresponding 3-thienyl and phenyl derivatives **1b** and **1d**, *i.e.* similar to the corresponding substrates of type **2**. Increasing the bulk of the substrate by using 5-butyl-2-thienyl compound **1c** also gave a higher *E*-value.

Substrates of type 3 (see Chart 1). Some derivatives of type **3** (Chart 1) with X = O and with very bulky R-groups [R = TBDMS or Bu^tPh_2Si (TBDPS)] have been efficiently resolved with vinyl acetate and PCL.[46,47] Since oxygen directly linked to the stereocentre alters the enantioselectivity of primary alcohols,[21,25] it might also have unpredictable effects when located further away. Because a sulfur atom, on the other hand, is similar in size and polarity to a CH_2 group we considered it worthwhile to study the phenylthio derivative of **3** (X = S, R = Ph), *i.e.* compound **3b** (Scheme 3d). Resolution of this produced the acetate in 67.3% ee at 34.0% conversion, corresponding to an *E*-value of 3.4. To our knowledge the case with X = CH_2 and R = aryl has not been studied previously. Therefore, we prepared 2-methyl-4-(2-thienyl)butan-1-ol (**3a**, Scheme 2b) and subjected it to transesterification under the standard condi-

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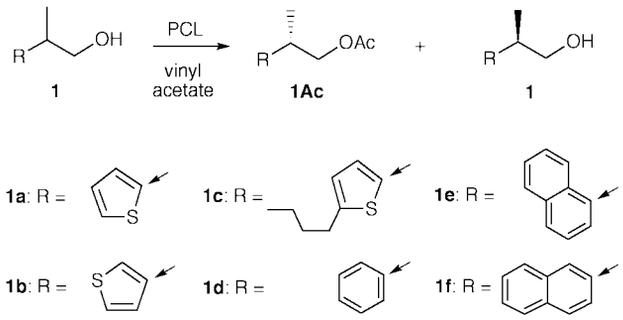
Table 3 PCL-catalysed kinetic resolution of 2-substituted 2-methylethanols by transesterification with vinyl acetate



Substrate	Enzyme	Solvent	c/%	ee_p/%	ee_s/%	E	Ref.
1a	Amano PS	$CHCl_3$	39.9	31.0	20.5	2.3	*a*, 22
1b	Amano PS	$CHCl_3$		12.6	6.2	1.2	*a*
1c	Amano PS	$CHCl_3$	39.9	68.8	42.2	8.1	*a*, 22
1d	PFL	CH_2Cl_2				1.8	42
1e	PFL	$CHCl_3$				9.0	43
1f	PFL	$CHCl_3$				6.0	43

[a] This work.

tions. At 40% conversion the acetate (*S*)-**3aAc** was produced (ee_p = 76.6%) and the remaining alcohol (*R*)-**3a** (ee_s = 45.6%) which gave E = 12. Thus, the E-values obtained with substrates of type **3** (Chart 1) were clearly inferior to those of type **2**. Therefore, studies with these substrates were not pursued further.

Substrates of type 4 (see Chart 1). Only a very limited number of compounds of this type with R = Aryl has been studied. Both 2-methyl-4-phenylthiobutan-1-ol as well as the corresponding phenylseleno derivative, **4** (R = Ph) and X = S and X = Se, respectively, have been successfully resolved.[48] No E-values were given but have been estimated to be around 20.[25] We prepared **4a** (R = 2-thienyl, X = CH_2, Scheme 2d) and resolved it with PCL and vinyl acetate in *tert*-butyl methyl ether (TBME) as solvent. At 42% conversion, the acetate (*S*)-**4aAc** (ee_p = 42.8%) and the remaining alcohol (*R*)-**4a**, (ee_s = 27.7%) were obtained, corresponding to E = 3.2.

Substrates of type 5 (see Chart 1). No example of this case with R = aryl is, to our knowledge, known. We prepared (Scheme 2b) and kinetically resolved compound **5a** using PCL and vinyl acetate. The acetate produced at 43.5% conversion was of 45.9% ee, corresponding to an E-value of 3.8.

Substrates of type 6 (see Chart 1). Some examples have been reported of *Pseudomonas* lipase-catalysed resolution of primary 2-alkyl-substituted alcohols having larger substituents than methyl in the 2-position. The fast reacting enantiomer of these alcohols are shown in Chart 2. Using lipase catalysis, the

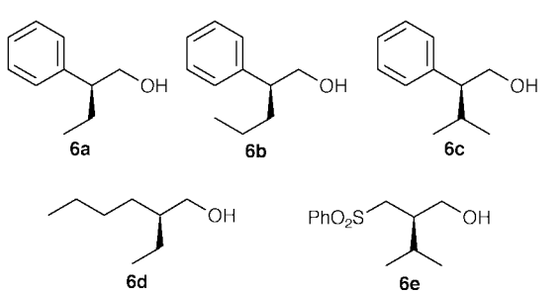
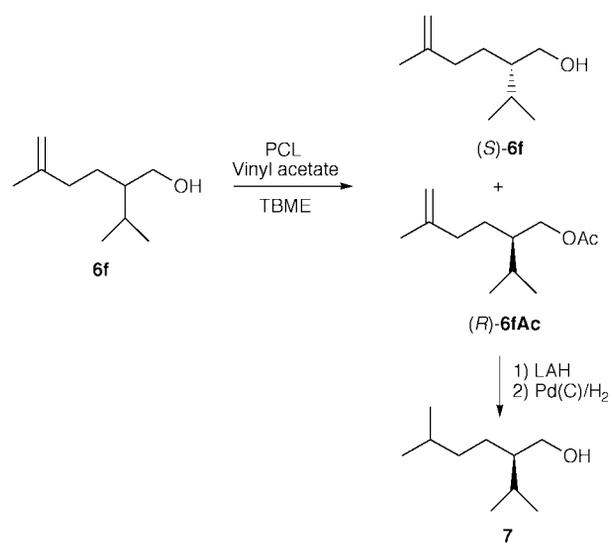


Chart 2 Some 2-alkylalkan-1-ols with larger substituents than methyl that have been prepared by *Pseudomonas* lipase-catalysed kinetic resolution. The fast reacting enantiomer in each case is shown.

alcohols **6a**–**d** were obtained from the racemic alcohols *via* kinetic resolution by transesterification[24,49] and the alcohol **6e** was obtained after hydrolysis of the corresponding racemic chloroacetate.[50] The E-values for the two 2-isopropyl substituted alcohols **6c**[49] and **6e**[5] are 29 and 11, respectively.

2-Isopropyl-5-methylhex-5-en-1-ol **6f** could serve as a building block for the total synthesis of germacra-1,6-dien-5-ol, a major constituent of the defence secretion of the pine sawfly *Neodiprion sertifer* and of the needle resin of Scots pine.[51] Therefore, we subjected the racemic alcohol **6f** to PCL-catalysed transesterification with vinyl acetate in TBME, as shown in Scheme 5. The E-value was found to be E = 14 for



Scheme 5 PCL-catalysed transesterification of the 2-isopropyl alcohol **6f** with vinyl acetate as acyl donor and TBME as solvent. Enantiomeric ratio E = 14. The *R* configuration of the fast reacting enantiomer (+)-**6f** was established after conversion to **7**.

this reaction and at 40% conversion the acetate (*R*)-**6fAc** (ee_p = 80%) was obtained and at 60% conversion the alcohol (*S*)-**6f** (ee_s = 95%) remained, corresponding to E =14. The *R* configuration of the fast reacting enantiomer (+)-**6f** was established after conversion to (*R*)-(+)-tetrahydrolavandulol **7** with known configuration[52] (Scheme 5). The preparation of the racemic substrate **6f** will be published elsewhere.

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Conclusions

When comparing racemic substrates containing aromatic rings from the groups **1**–**5**, it was evident that the location of this ring in a substrate was crucial for achieving a successful resolution. Indeed, only substrates of type **2** were more efficiently resolved than straight-chain 2-methylalkan-1-ols. Thus, 2-methyldecan-1-ol gave $E \approx 11$ whereas the series of 2-methyl-(5-substituted 2-thienyl)alkan-1-ols with the same number of carbon atoms, *i.e.* compounds **1c**, **2d** and **5a**, gave $E \approx 8$, 300 and 4, respectively. The same trend was observed in the series of 2-methyl-ω-(2-thienyl)alkan-1-ols **1a**, **2a**, **3a**, **4a** and **5a** ($E \approx 2$, 200, 12, 3 and 4). For both substrates of type **1** and **2** the enantioselectivities varied roughly in the same direction for the substituents 3-thienyl < phenyl < 2-thienyl. Thus both the nature of the aromatic ring and, especially, its position relative to the stereogenic centre are important for achieving high *E*-values.

The alternative large pocket in PCL (see Fig. 1, **C**) has been proposed to bind the benzyl group of the primary alcohol **2g**.[21] This pocket is lined with the hydrophobic amino acid residues Tyr-23, Leu-27, Tyr-29, Phe-146, Ile-290 and Leu-293.[21] It is interesting to note that both tyrosine and phenylalanine are aromatic amino acids. A tentative explanation for our results is that the aromatic amino acids in this pocket most likely are loosely bound *via* π–π interactions to suitably located aryl groups in a substrate alcohol, *e.g.* phenyl or thienyl in **2g** or **2a**, respectively. These types of π–π interactions may give additional stability to 'normal' hydrophobic interactions present. Such π–π interactions are absent for the 3-cycloalkyl-2-methylpropan-1-ols **2l** and **2m** and, of course, also for the 2-methylalkanols, hence should lead to lowered *E*-values. The observed values were $E \approx 20$ and $E \leq 11$, respectively. Similarly, moving the aromatic ring away from the π–π interaction sites of the protein could explain the low *E*-values observed for the substrate groups **1**, **3**, **4** and **5**.

We have demonstrated that among substrates carrying 2-thienyl substituents in the series **1**–**5**, only those of type **2**, *e.g.* 2-methyl-3-(2-thienyl)propan-1-ols **2a**, **2c**, and **2d**, were resolved with very high enantioselectivity. Thus, among the substrates investigated, only the latter substrates can serve as useful starting materials for Raney nickel reduction to enantiomerically pure, long-chain 2-methyl alcohols.

Experimental

Pseudomonas cepacia was previously named *Pseudomonas fluorescens*. Thus, in earlier reports PCL is called PFL. The old abbreviation PFL is still used by some authors. *P. cepacia* has been reclassified again and is now called *Burkholderia cepacia*.[5,21] Different abbreviations and trade names have been used by different authors and manufacturers for PCL: Lipase P, Lipase PS, Amano P, Amano PS, Amano P-30, PFL, *etc*.[5] In this paper we use the old name PCL for this lipase and, if necessary, Amano PS and PFL (Fluka) are used to specify the reaction conditions. Amano PS (PCL) from *Pseudomonas cepacia* was obtained from Amano Pharmaceutical Company. The specific activity was 30.0 U mg^{-1} and the enzyme was stored at 4 °C over dried silica. Unless otherwise stated, starting materials and solvents were used as received from commercial suppliers. Dry THF was distilled from a mixture of potassium and benzophenone and dry diethyl ether was distilled from $LiAlH_4$ before use. Dry diisopropylamine was distilled from CaH_2. Air-sensitive reagents were handled with gas-tight syringes and the reactions were performed under argon. Preparative liquid chromatography (medium-performance liquid chromatography, MPLC) was performed on straight-phase silica gel (Merck 60, 230–400 mesh) employing a gradient of an increasing concentration of diethyl ether in *n*-pentane as eluent. Mps were measured in glass capillaries in a Tottoli type hot bath (Büchi). Bps were registered as air bath temperatures in Büchi Kugelrohr apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL EX 270 spectrometer or a Bruker DMX 250 spectrometer. Optical rotation was measured on a Perkin-Elmer 241 polarimeter. Mass spectra were recorded using GC-MS (Varian 3300 GC and an ion-trap detector, Finnigan ITD 800 or Varian 3800 GC and an ion-trap detector, Varian Saturn 2000). IR spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer. Exact masses (HRMS) were obtained using a VG-70E mass spectrometer. Refractive indices were measured on a Pleuger refractometer.

Transesterification reactions at initial $a_w = 0.32$

The procedure described earlier[23] was slightly modified. Amano PS (10.0 mg) and a racemic alcohol **1**–**6** (1.0 mmol) were mixed with solvent (1.8 ml) in the reaction flask containing a magnetic stirring bar. The mixture in the open flask was stirred for 24 h in a sealed container over saturated $MgCl_2$ ($a_w = 0.32$[53]). After 24 h pre-equilibrated solvent was added to the reaction flask to compensate for loss by evaporation. Vinyl acetate (0.34 ml, 3.7 mmol) was added to the reaction flask, which was immediately sealed with a septum. The mixture was stirred at 400 rpm at rt. The conversion was followed by GC. When the reaction had reached the desired conversion (≈ 40%) the mixture was filtered through a filter of low porosity and the solid collected was washed with *n*-pentane (3 ml). The components were separated by MPLC.

Reduction of the enantiomerically enriched acetates

The chemically pure, enantiomerically enriched esters (*R*)-**1aAc**, (*S*)-**1bAc**, (*R*)-**1cAc**, (*S*)-**2a**–**hAc**, (*S*)-**2l**,**mAc**, (*S*)-**3aAc**, (*R*)-**3bAc**, (*S*)-**4aAc**, (*S*)-**5aAc** and (*R*)-**6fAc** were obtained as described above (0.3–0.4 mmol). One of them was dissolved in anhydrous diethyl ether (1 ml) and added to a stirred suspension of $LiAlH_4$ (30 mg) in anhydrous diethyl ether (3 ml) under argon. The mixture was stirred at rt for 1 h and then quenched with water–THF (1 : 1; 60 µl) followed by 15% NaOH (30 µl) and water (20 µl). After refluxing for 10 min the mixture was filtered, washed with diethyl ether and dried ($MgSO_4$). After evaporation of the solvent either pure (*R*)-**1a**, (*S*)-**1b**, (*R*)-**1c**, (*S*)-**2a**–**h**, (*S*)-**2l**,**m**, (*S*)-**3a**, (*R*)-**3b**, (*S*)-**4a**, (*S*)-**5a** or (*R*)-**6f** was obtained in quantitative yield. For optical rotation values for these compounds, see Table 4.

Determination of conversion

The conversions in the transesterification reactions were determined by capillary GC. The conversions were calculated from the area of the ester peak relative to that of the alcohol peak after calibration against the racemic ester.

Determination of enantiomeric excess

The ees of the alcohols **1**–**6**, except **2f** and **3b**, were determined by analysing the diastereomeric mixture of their corresponding 2-alkylacyl-1-phenylethylamides.[54] Baseline separation was readily obtained using a Carbowax®-coated capillary column and He as carrier gas. The ees of the alcohols **2f** and **3b** were determined by analysing both the ^{1}H and ^{19}F NMR spectra[12,14] of their corresponding 'α-methoxy-α-(trifluoromethyl)phenylacetate' (MTPA) esters.

2-(2-Thienyl)propan-1-ol 1a. 2-(2-Thienyl)propanoic acid[37] was reduced using general procedure A (see below). MPLC and distillation (82 °C/0.02 mbar†) gave the title compound (95% yield, >99% by GC), n_D^{20} 1.5903 (HRMS: Calc. for $C_7H_{10}OS$: *M*, 142.045. Found: M^+, 142.043); ν_{max} (neat, NaCl) 3371, 3355, 3105, 2930, 2360, 1382, 1077, 824, 695, 432 cm^{-1}; δ_H (270 MHz;

† 1 bar = 10^5 Pa.

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Table 4 Optical rotations of the fast reacting alcohol enantiomers

Alcohol	ee_p/%	$[\alpha]_D^{25}$ [a]	$[\alpha]_D$ (literature)
(*R*)-**1a**	31.0	−6.2 *c* 19 [b]	
(*S*)-**1b**	12.6	−2.0 *c* 11 [b]	
(*R*)-**1c**	68.8	−11.4 *c* 57 [b]	
(*S*)-**2a**	98	−19.0 neat	−19.3 neat [14]
(*S*)-**2b**	96.6	−16.0 *c* 0.8 [c]	−14.9 *c* 1.8 [c,d]
(*S*)-**2d**	98.5	−17.3 *c* 1.9 [c]	−17.4 *c* 1.5 [c,14]
(*S*)-**2f**	81.9	−15.4 *c* 0.7 [b]	
(*S*)-**2g**	83.2	−10.1 *c* 0.8 [b]	
(*S*)-**2h**	94.2	−10.8 *c* 1.1 [c]	
(*S*)-**2i**	97.1	−17.6 *c* 0.7 [c]	−18.5 *c* 8.0 [c,12]
(*S*)-**3a**	76.6	−16.4 *c* 36 [b]	
(*R*)-**3b**	67.3	−19.9 *c* 1.4 [e]	−18.9 *c* 3.9 [e,65]
(*S*)-**4a**	42.8	−7.3 *c* 1.1 [c]	+24.6 neat [f,60]
(*S*)-**5a**	45.9	−6.4 *c* 1.3 [c]	
(*R*)-**6f**	79.9	+8.3 *c* 1.0 [c]	
(*S*)-**6f** [g]	95	−14.3 *c* 1.2 [c]	

[a] The optical rotation was measured on the alcohols obtained after reduction of the produced esters. [b] Chloroform as solvent. [c] Methanol as solvent. [d] The optical rotation reported previously by us [14] was corrected. [e] Dichloromethane as solvent. [f] The literature value [60] is for the *R*-enantiomer of **4a**. [g] Remaining substrate (slow reacting enantiomer).

$CDCl_3$) 1.38 (3H, d, $J = 7$ Hz), 1.68 (1H, s), 3.22 (1H, m), 3.68 (2H, m), 6.85–7.00 (2H, m), 7.18 (1H, m); δ_C (67.8 MHz; $CDCl_3$) 18.60, 38.11, 68.93, 123.48, 123.86, 126.79, 147.42.

2-(3-Thienyl)propan-1-ol 1b. 2-(3-Thienyl)propanoic acid [55] was reduced using general procedure A (see below). Distillation (77 °C/0.02 mbar) gave the alcohol **1b** (99.6% purity by GC), n_D^{20} 1.5405 (HRMS: Calc. for $C_7H_{10}O$: *M*, 142.045. Found: M^+, 142.045); ν_{max} (neat, NaCl) 3357, 3348, 2962, 2928, 2875, 2360, 2342, 1377, 688, 656 cm^{-1}; *m*/*z* (relative intensity) 142 (M^+, 24%), 111 (100), 97 (6), 85 (6), 77 (27), 67 (16), 59 (13), 51 (5); δ_H (270 MHz; $CDCl_3$) 1.29 (3H, d, $J = 7$ Hz), 1.42 (1H, s), 3.07 (1H, m), 3.68 (2H, m), 7.03 (2H, m), 7.30 (1H, m); δ_C (67.8 MHz; $CDCl_3$) 17.47, 37.94, 68.32, 120.45, 125.89, 126.76, 144.55.

2-(5-Butyl-2-thienyl)propan-1-ol 1c. Following the method described for (*S*)-**2d** [14] but starting with 2-(2-thienyl)propan-1-ol **1a** and butyryl chloride, $SnCl_4$-catalysed acylation followed by Huang-Minlon reduction, MPLC and distillation (95 °C/0.02 mbar) gave the title compound (54% overall yield, 99% pure by GC), n_D^{20} 1.5159 (HRMS: Calc. for $C_{11}H_{18}OS$: *M*, 198.108. Found: M^+, 198.111); ν_{max} (neat, NaCl) 3363, 2872, 2853, 2360, 1465, 1451, 1379, 1042, 1030, 798 cm^{-1}; *m*/*z* (relative intensity) 198 (M^+, 9%), 167 (100), 155 (2), 137 (2), 125 (18), 111 (21), 105 (3), 91 (11), 79 (5), 77 (5), 59 (5); δ_H (270 MHz; $CDCl_3$) 0.91 (3H, t, $J = 7$ Hz), 1.31 (3H, d, $J = 7$ Hz), 1.38 (2H, m), 1.61 (1H, s), 1.63 (2H, m), 2.76 (2H, t, $J = 8$ Hz), 3.15 (1H, m), 3.65 (2H, m), 6.61 (1H, d, $J = 3$ Hz), 6.67 (1H, d, $J = 3$ Hz); δ_C (67.8 MHz; $CDCl_3$) 13.79, 18.42, 22.21, 29.81, 33.73, 38.30, 68.88, 123.45 (intense), 144.10, 144.51.

General procedure A

Representative procedure for the reduction of 2-methylalkanoic acids.

2-Methyl-3-(2-thienyl)propan-1-ol 2a. 2-Methyl-3-(2-thienyl)-propanoic acid [56] (0.5 g, 2.9 mmol) dissolved in dry diethyl ether (10 ml) was added dropwise, under argon, to a stirred suspension of $LiAlH_4$ (0.3 g, 8 mmol) in dry diethyl ether (20 ml) at rt. After stirring of the mixture for 2 h at rt, water (0.3 ml) was added dropwise, followed by 15% NaOH (0.3 ml) and water (0.2 ml). The mixture was refluxed for 20 min and cooled to rt. After filtration, drying ($MgSO_4$), and filtration, the solvent was evaporated *in vacuo*. Bulb-to-bulb distillation (132–135 °C/0.65 mbar) gave the title compound (0.39 g, 86% yield, >99% pure by GC). The spectroscopic data were in good agreement with those reported for (*S*)-2-methyl-3-(2-thienyl)propan-1-ol (*S*)-**2a**.[14]

2-Methyl-3-(3-thienyl)propan-1-ol 2b. The title compound was prepared by general procedure A (see above) from 2-methyl-3-(3-thienyl)propanoic acid obtained by general procedure B (see below). The spectroscopic data were in good agreement with those reported for (*S*)-2-methyl-3-(3-thienyl)-propan-1-ol (*S*)-**2b**.[14]

2-Methyl-3-(5-propyl-2-thienyl)propan-1-ol 2d. This was prepared by the method described for (*S*)-**2d** [14] but from 2-methyl-3-(2-thienyl)propan-1-ol **2a** *via* $SnCl_4$-catalysed propionylation followed by Huang-Minlon reduction. The spectroscopic data was in good agreement with literature data.[14]

3-(5-Ethyl-3-thienyl)-2-methylpropan-1-ol 2e. This was obtained from the batch prepared by Karlsson and Hedenström.[34]

3-(2-Furyl)-2-methylpropan-1-ol 2f. The procedure described for racemisation of primary 2-methylalkanols was used.[24] Thus, (*S*)-2-methyl-3-(2-furyl)propan-1-ol [12] (2.5 g, 17.9 mmol), $[\alpha]_D^{25}$ −12.1 ‡ (*c* 1.35, $CHCl_3$), and Na (25 mg, 1.1 mmol) were added to a solution of toluene (50 ml) and benzophenone (0.18 g, 1.0 mmol) in a round-bottom flask. The reaction mixture was refluxed for 24 h and then water (50 ml) was added. The mixture was extracted with diethyl ether (3 × 50 ml). The combined extracts were washed with water (100 ml) and dried with $MgSO_4$. The solvent was evaporated and the residue was subjected to MPLC (120 g silica), giving the title compound (1.98 g, 79% yield, 99.8% by GC), $[\alpha]_D^{25}$ −0.3 (*c* 1.5, $CHCl_3$, corresponds to 2% *S*). The spectroscopic data were identical with those reported for (*S*)-**2f**.[12]

3-(*o*-Methoxyphenyl)-2-methylpropan-1-ol 2h. Prepared by KBH_4 reduction of 3-(*o*-methoxyphenyl)-2-methylpropionaldehyde [57] as described for **3b** below. Bulb-to-bulb distillation (108–110 °C/0.06 mbar) gave the alcohol at 80% yield and 97% pure by GC, n_D^{20} 1.604 (HRMS: Calc. for $C_{11}H_{16}O_2$: *M*, 180.115. Found: M^+, 180.114); *m*/*z* (relative intensity) 180 (M^+, 32%), 162 (12), 147 (15), 121 (95), 93 (50), 91 (100), 77 (20); ν_{max} (neat, NaCl) 2950, 2870, 1707, 1459, 1417, 1380, 1293, 1244, 1180, 1096 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 0.95 (3H, d, $J = 7$ Hz), 1.95 (1H, m), 2.05 (1H, br s), 2.54 (1H, dd, $J = 14$ and 7 Hz), 2.71 (1H, dd, $J = 14$ and 7 Hz), 3.39 (2H, apparent t, $J = 5$ Hz), 3.83 (3H, s), 6.85–6.92 (2H, m), 7.10–7.22 (2H, m) ppm; δ_C (67.8 MHz; $CDCl_3$) 16.95, 33.14, 36.73, 55.45, 66.94, 110.44, 120.65, 127.28, 128.75, 131.19, 157.46.

General procedure B

Representative procedure for preparation of 2-methylalkanoic acids.

3-Cyclopentyl-2-methylpropanoic acid. A slightly modified version of the method described for 2-methyldodecanoic acid.[58] Sodium (0.54 g 23.4 mmol) was dissolved in absolute ethanol (18 ml) under an atmosphere of argon. When all the sodium had dissolved, diethyl methylmalonate (4.2 ml, 24.8 mmol) was added and the solution was refluxed for 5 min. After cooling of the mixture to room temperature, (bromomethyl)cyclopentane (3.46 g, 21.2 mmol) was added followed by reflux for 5 h. In order to neutralise the excess of base a few drops of glacial acetic acid were added at room temperature.

‡ Specific optical rotations are given in units of 10^{-1} deg cm^2 g^{-1}.

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The solvent was evaporated off and the residue was dissolved in water (100 ml) and extracted with diethyl ether (3 × 50 ml). The combined organic phases were washed successively with 10% Na_2CO_3 (25 ml) and brine (50 ml), and dried ($MgSO_4$). After solvent evaporation the crude diester was added to a solution of KOH in 95% ethanol (2 M; 50 ml) and refluxed for 4 h (or longer if needed). After cooling to room temperature, the solvent was evaporated off and the residue was dissolved in water (50 ml) and washed with diethyl ether (2 × 25 ml). Acidification with conc. hydrochloric acid at 0 °C and extraction with diethyl ether (3 × 50 ml) was followed by successive washings of the combined ether phases with water (25 ml) and brine (15 ml). After drying over $MgSO_4$ the mixture was evaporated to yield the crude diacid (4.42 g, 22.1 mmol), which was decarboxylated neat in an open flask at 190 °C for 3 h. After cooling, the product was dissolved in 10% aq. Na_2CO_3 (100 ml) and washed with diethyl ether (30 ml) followed by acidification at 0 °C with conc. hydrochloric acid. Extraction with diethyl ether (3 × 50 ml) and washing with brine (30 ml) followed by drying over $MgSO_4$, filtration and concentration *in vacuo* gave the crude acid (2.23 g, 14.3 mmol). After bulb-to-bulb distillation (135 °C/0.65 mbar), the title compound was obtained (2.0 g, 60% yield, >99% purity by GC), n_D^{20} 1.603 (HRMS: Calc. for $C_9H_{16}O_2$: *M*, 156.115. Found: M^+, 156.116); *m*/*z* (relative intensity) 157 (M^+ + 1, 53%), 139 (91), 137 (28), 111 (45), 109 (22), 83 (100), 74 (55) 69 (44), 67 (51), 55 (65); δ_H (270 MHz; $CDCl_3$) 1.08 (2H, m), 1.17 (3H, d, *J* = 7 Hz), 1.34–1.63 (5H, m), 1.71–1.86 (4H, m), 2.49 (1H, m), 11.7 (1H, br s); δ_C (67.8 MHz; $CDCl_3$) 17.27, 25.03, 25.09, 32.53, 32.69, 37.92, 38.74, 40.00, 183.70.

3-Cyclopentyl-2-methylpropan-1-ol 2l. Using general procedure A (see above), 3-cyclopentyl-2-methylpropanoic acid (0.8 g, 5.1 mmol) gave the alcohol **2l** (0.45 g, 63% yield, >99% purity by GC) after bulb-to-bulb distillation (80 °C/0.35 mbar), n_D^{20} 1.603 [HRMS: ($M^+ - H_2O$)§ Calc. for C_9H_{16}: *m*/*z* 124.125. Found: *m*/*z* 124.125]; *m*/*z* (relative intensity) 141 ($M^+ - 1$, 0.1%), 123 (2), 109 (7), 95 (21), 82 (56), 69 (100), 67 (97); ν_{max} (neat, NaCl) 3341, 2950, 2868, 2357, 1447, 1379, 1034, 984 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 0.91 (3H, d, *J* = 7 Hz), 0.99–1.19 (3H, m), 1.29–1.39 (2H, m), 1.46–1.88 (8H, m), 3.39–3.50 (2H, m); δ_C (67.8 MHz; $CDCl_3$) 16.80, 25.11, 32.56, 33.37, 34.86, 37.50, 39.75, 68.68.

3-Cyclohexyl-2-methylpropan-1-ol 2m. Using general procedure B (see above) the corresponding acid was prepared from (bromomethyl)cyclohexane (46.3 mmol) and diethyl methylmalonate (54 mmol). The acid was reduced using general procedure A (see above) and, after bulb-to-bulb distillation (90 °C/0.02 mbar), the title compound was obtained at >99% purity, n_D^{20} 1.466 [HRMS: ($M^+ - H_2O$)[59] Calc. for $C_{10}H_{18}$: *m*/*z*, 138.141. Found: *m*/*z*, 138.140]; *m*/*z* (relative intensity) 155 ($M^+ - 1$, 9%), 137 (21), 123 (9), 109 (14), 96 (53), 95 (40), 83 (92), 81 (100), 69 (21), 67 (41); δ_H (270 MHz; $CDCl_3$) 0.77–1.01 (3H, m), 0.88 (3H, d, *J* = 7 Hz), 1.10–1.35 (6H, m), 1.65–1.75 (6H, m), 3.41 (2H, m); δ_C (67.8 MHz; $CDCl_3$) 16.84, 26.33, 26.44, 26.69, 32.60, 33.03, 34.27, 34.81, 41.10, 68.77.

2-Methyl-4-(2-thienyl)butanoic acid.[59] This was prepared from 2-(2-bromoethyl)thiophene according to general procedure B (see above). Distillation (140–143 °C/0.15 mbar) gave the title acid, n_D^{20} 1.5189; ν_{max} (neat, NaCl) 2975, 2936, 1705, 1465, 1441, 1339, 941, 849, 823, 695 cm^{-1}; δ_H (270 MHz) 1.23 (3H, d, *J* = 7 Hz), 1.80 (1H, m), 2.12 (1H, m), 2.54 (1H, m), 2.90 (2H, t, *J* = 8 Hz), 6.80 (1H, d, *J* = 3 Hz), 6.91 (1H, m), 7.11 (1H, m), 11.35 (1H, br s); δ_C (67.8 MHz) 16.80, 27.42, 35.20, 38.55, 123.16, 124.44, 126.74, 144.08, 182.84.

§ Note: We were unable to distinguish the M^+ peak from the background so the detected peak is $M^+ - H_2O$.

2-Methyl-4-(2-thienyl)butan-1-ol 3a. Reduction of 2-methyl-4-(2-thienyl)butanoic acid[59] according to general procedure A (see above), followed by distillation (115 °C/0.02 mbar), gave the title alcohol (81% yield, 99% purity by GC), n_D^{20} 1.5272; ν_{max} (neat, NaCl) 3355, 3106, 2926, 2360, 1460, 1440, 1034, 848, 821, 692 cm^{-1}; *m*/*z* (relative intensity) 170 (M^+, 15%), 152 (8), 137 (20), 123 (17), 110 (71), 97 (100), 85 (5), 73 (5), 59 (16), 53 (24); δ_H (270 MHz) 0.98 (3H, d, *J* = 7 Hz), 1.44 (1H, s), 1.52 (1H, m), 1.67–1.90 (2H, m), 2.89 (2H, m), 3.50 (2H, m), 6.79 (1H, m), 6.91 (1H, m), 7.10 (1H, m); δ_C (67.8 MHz) 16.35, 27.39, 35.15 (intense), 68.00, 122.84, 123.95, 126.67, 145.43.

2-Methyl-3-(phenylthio)propanal.[38] Methacrolein (21 ml, 0.25 mol) was stirred with $Cu(OAc)_2$ (50 mg) in a round-bottom flask on an ice-bath. Thiophenol (20 ml, 0.19 mol) was added dropwise for 30 min. The mixture was heated to 40 °C for 2 h. A distillation set-up was connected to the reaction flask and the product was distilled (110 °C/2 mmHg) from the reaction mixture to give the title compound in 92% yield. Spectroscopic data were identical with those in the literature.[38]

2-Methyl-3-(phenylthio)propan-1-ol 3b.[38] A mixture of $NaBH_4$ (5.5 g) and 2M NaOH (5.5 ml) in water (50 ml) was added dropwise to a solution of 2-methyl-3-(phenylthio)-propanal (31 g, 0.18 mol) in methanol (100 ml). After the addition was complete (1.5 h) the reaction mixture was poured into water and extracted with diethyl ether twice and the combined extracts were washed successively with saturated aq. $NaHCO_3$ and brine, and dried with $MgSO_4$. After solvent evaporation and distillation (115–116 °C/1 mmHg) the title alcohol was obtained (23 g, 84% yield, 99% by GC). The spectroscopic data were identical with those in the literature.[38]

2-Methyl-5-(2-thienyl)pentan-1-ol 4a.[60] Using a slightly modified version of the method described for the preparation of 2-methyldodecanoic acid,[61] 2-methyl-5-(2-thienyl)pentanoic acid[59] was prepared. *n*-Butyllithium in hexane (1.6 M; 20.0 ml, 32.0 mmol) was added slowly (60 min) to a solution of dry diisopropylamine (4.5 ml, 32 mmol) in dry THF (25 ml) at −5 °C. After stirring of the mixture for 30 min at 0 °C, 5-(2-thienyl)pentanoic acid (3.0 g, 16 mmol) in dry THF (14 ml) was added slowly during 50 min at 0 °C. After stirring of the mixture for 30 min at 0 °C, dry DMPU (1.8 ml, 15 mmol) was added and the solution was stirred at rt for 1 h. After cooling (−5 °C) of the mixture, methyl toluene-*p*-sulfonate (3.0 g, 16 mmol) was added and the mixture was stirred at rt overnight. A mixture of the starting acid and the desired product (30 : 70) was obtained. After acidification with 10% HCl, extraction with diethyl ether (4 × 40 ml), drying ($MgSO_4$), and evaporation off of the solvent the resulting mixture of the two acids was reduced according to general procedure A (see above). The produced alcohols **4a** and 5-(2-thienyl)pentan-1-ol were separated with MPLC using 113 g of silica gel. Bulb-to-bulb distillation (130 °C/0.74 mbar) gave the alcohol **4a** (1.3 g, 6.6 mmol, 41% overall yield, >99% pure according to GC), n_D^{20} 1.5202 [lit.,[60] $n_D^{16.5}$ 1.5245 for the *R*-(+) enantiomer]; ν_{max} (neat, KBr) 3346, 2932, 2872, 1460, 1440, 1380, 1238, 1038, 850, 820 cm^{-1}; *m*/*z* (relative intensity) 184 (30%), 166 (21), 156 (14), 137 (12), 123 (24), 111 (17), 110 (73), 98 (34), 97 (100), 53 (16); δ_H (250 MHz; $CDCl_3$) 0.93 (3H, d, *J* = 6.7 Hz), 1.10–1.25 (1H, m), 1.42–1.57 (1H, m), 1.45 (1H, s), 1.58–1.82 (3H, m), 2.83 (2H, t, *J* = 7.6 Hz), 3.43 (1H, dd, *J* = 10.5 and 6.3 Hz) 3.49 (1H, dd, *J* = 10.5 and 5.8 Hz), 6.78 (1H, dd, *J* = 3.4 and 1.0 Hz), 6.92 (1H, dd, *J* = 5.1 and 3.4 Hz), 7.11 (1H, dd, *J* = 5.1 and 1.2 Hz); δ_C (62.9 MHz; $CDCl_3$) 16.51, 29.23, 30.16, 32.54, 35.57, 68.20, 122.84, 124.03, 126.67, 145.49.

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2-(4-Bromobutyl)thiophene.[62,63] 4-(2-Thienyl)butyl toluene-*p*-sulfonate[64] (16.3 g, 52.6 mmol) dissolved in dry acetone (66 ml) was added to a suspension of anhydrous LiBr (20.63 g, 237 mmol) in dry acetone (165 ml) and heated to reflux for 36 h. The mixture was cooled to rt followed by addition of water (300 ml) and extraction with diethyl ether (3 × 400 ml). The organic phase was washed successively with water (300 ml) and brine (300 ml), followed by drying ($MgSO_4$) and solvent evaporation. MPLC (114 g of silica gel) using an ethyl acetate–cyclohexane gradient as eluent followed by bulb-to-bulb distillation (85–87 °C/0.15 mbar) gave the title compound (10.3 g, 89%). Spectroscopic data were in good agreement with those in the literature.[62,63]

2-Methyl-6-(2-thienyl)hexanoic acid. This was prepared from 2-(4-bromobutyl)thiophene using general procedure B (see above). The acid was obtained (60% yield, 99% by GC) after bulb-to-bulb distillation (137–138 °C/0.3 mbar), mp 39–40 °C (HRMS: Calc. for $C_{11}H_{16}O_2S$: *M*, 212.087. Found: M^+, 212.087); ν_{max} (neat, NaCl) 2927, 2849, 1700, 1459, 1257, 1231, 965, 852, 828, 706 cm^{-1}; *m*/*z* (relative intensity) 212 (M^+, 31%), 194 (3), 166 (2), 151 (2), 139 (7), 136 (9), 111 (28), 98 (32), 97 (100), 53 (12); δ_H (270 MHz; $CDCl_3$) 1.18 (3H, d, $J = 7$ Hz), 1.43 (3H, m), 1.70 (3H, m), 2.46 (1H, m), 2.83 (2H, t, $J = 7$ Hz), 6.76 (1H, d, $J = 4$ Hz), 6.90 (1H, m), 7.09 (1H, d, $J = 5$ Hz), 11.7 (1H br s); δ_C (67.8 MHz; $CDCl_3$) 16.80, 26.58, 29.67, 31.59, 33.14, 39.27, 122.82, 124.01, 126.65, 145.30, 183.20.

2-Methyl-6-(2-thienyl)hexan-1-ol 5a. Reduction of 2-methyl-6-(2-thienyl)hexanoic using general procedure A (see above) followed by distillation (109–109.5 °C/0.45 mbar), gave the title alcohol (88% yield, 99% by GC), n_D^{20} 1.517 (HRMS: Calc. for $C_{11}H_{18}OS$: *M*, 198.108. Found: M^+, 198.104); ν_{max} (neat, NaCl) 3323, 2925, 2851, 1461, 1438, 1377, 1233, 1035, 850, 821, 691 cm^{-1}; *m*/*z* (relative intensity) 198 (M^+, 11%), 181 (4), 170 (25), 137 (7), 123 (19), 111 (19), 110 (32), 98 (43), 97 (100), 53 (13); δ_H (270 MHz; $CDCl_3$) 0.91 (3H, d, $J = 7$ Hz), 1.14 (1H, m), 1.31–1.47 (4H, m), 1.55–1.73 (3H, m), 2.83 (2H, t, $J = 8$ Hz), 3.43 (2H, m), 6.77 (1H, m), 6.90 (1H, m), 7.09 (1H, m); δ_C (67.8 MHz; $CDCl_3$) 16.57, 26.43, 29.85, 32.02, 32.83, 35.69, 68.27, 122.77, 123.95, 126.65, 145.62.

(*R*)-(+)-Tetrahydrolavandulol 7.[52] (*R*)-(+)-**6f** {$[\alpha]_D^{25}$ +8.3 (*c* 1.0, MeOH), ee 79.9%} was obtained after reduction (general method) of the corresponding acetate produced in the PCL transesterification. This (30 mg) was hydrogenated in methanol (2 ml) with Pd(C) (5 mg, 10% Pd) as catalyst. After 6 h the catalyst was filtered off, and washed with methanol. After drying ($MgSO_4$) and evaporation off of the solvent the title compound was obtained, $[\alpha]_D^{25}$ +12 (*c* 0.4, MeOH) {lit.,[52] $[\alpha]_D^{20}$ +12.8 (neat)}. Spectroscopic data were in good agreement with those in the literature.[52]

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