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Lipase-catalyzed kinetic resolution of (*RS*)-hydroxy tellurides

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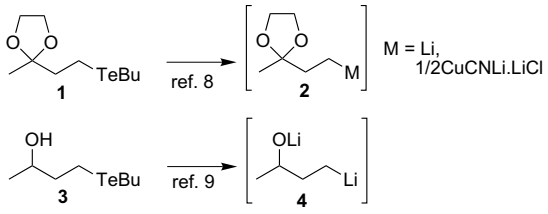
Abstract—The enzymatic resolution of racemic mixtures of hydroxy tellurides with a range of lipases has been investigated. Lipase-B from *Candida antarctica* (CALB) gave the best conversions, providing both enantiomers with high enantiomeric purity. A comparative study of the effect of solvent and substrate on the enzymatic kinetic resolution was performed.

1. Introduction

Several synthetic methods based on tellurium reagents are available for the transformation of functional groups and for the creation of carbon–carbon bonds.[1,2] Most of these processes included in the latter category involve the stereoselective synthesis of olefins through the appropriate manipulation of vinyl tellurides.[3] In recent years, these reagents have been employed in the total stereoselective synthesis of natural products.[4] In contrast, the alkyl tellurides have been less exploited owing to negative reports concerning their instability in light and air, their toxicity and their unpleasant odour.[5] Recent studies in our laboratory, however, have shown that such disadvantageous properties do not always apply.[6]

Functionalized tellurides **1** and **3** have previously been prepared[7–9] and used as a source of homoenolates **2**[8] and 1,4-dianions **4**[9] via a tellurium/lithium exchange reaction (Scheme 1).[1,2,8–11]

This peculiar reactivity of the functionalized alkyl tellurides makes them potential precursors of enantiomerically pure building blocks for organic synthesis. Among the methods available for preparing enantiomerically pure reagents, biocatalysis,[12] particularly involving enzymatic kinetic resolution,[13] is most often employed. In this context, lipases offer a number of distinct advantages since they tolerate unnatural substrates, perform enantioselective hydrolyses and catalyze the formation of ester and amide bonds.[14] Recently, we have reported the enzymatic resolution in organic media of a range of hydroxy selenides.[15] As an extension of, and a complement to, our previous biocatalytic studies of chalcogen-based compounds, we here report an investigation concerning the enzymatic resolution of hydroxy tellurides in organic media (Scheme 2). To the best of our knowledge, enzymatic kinetic resolution has not previously been used for this purpose.



Scheme 1. Homoenolates and 1,4-dianions derived from alkyl tellurides.

2. Results and discussion

2.1. Preparation of hydroxy tellurides 5a–f

Hydroxy tellurides **5a–f** were prepared according to published procedures as summarized in Figure 1. Sodium phenyltellurolate, formed from diphenyl ditelluride and sodium borohydride,[16] gave **5a** in 81% isolated yield upon

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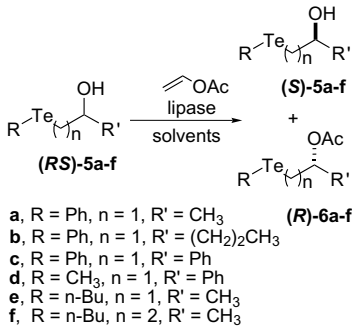


Scheme 2. Lipase-catalyzed transesterification of the (*RS*)-hydroxy tellurides **5a**–**f** in organic media.

Telluride	Procedure
5a, c	Ph_2Te_2 + $NaBH_4$ + oxirane
5b	$PhTeCH_2TePh$ + BuLi + aldehyde
5d, e	RLi + Te^0 + oxirane
5f	[$BuTeLi/H_2O$] + MVK, carbonyl reduction

Figure 1. General procedure for the preparation of hydroxy tellurides **5a**–**f**.

reaction with propylene oxide, and **5c** in 60% isolated yield upon reaction with styrene oxide.

Telluride **5b** was prepared in 61% yield through tellurium/lithium exchange reaction between bis-(phenyltellanyl)-methane and *n*-butyllithium, followed by the 1,2-addition of the resulting phenyltellanyl-methyl lithium to butyraldehyde.[17] Reaction of the appropriate lithium alkyl tellurolate with styrene oxide or propylene oxide furnished the hydroxy tellurides **5d** and **5e** in isolated yields of 60% and 80%, respectively.

Telluride **5f** was prepared by the conjugate addition of *n*-butyltellurol to methylvinyl ketone followed by reduction of the carbonyl with sodium borohydride. Alternatively, **5f** could be obtained in 70% isolated yield by sequential 1,4-addition of *n*-butyltellurol to methylvinyl ketone and carbonyl reduction in a one-pot operation.[9]

The tellurides described in the present work were light yellow oils and were either odourless or presented odours that were no more unpleasant than many other reagents used in organic synthesis. The compounds were stable to ambient light and could be manipulated in air with no appreciable decomposition. However, prolonged contact with air, especially when dissolved in hexane or ethyl acetate, should be avoided. Decomposition of the tellurides in solution can be minimized by using deoxygenated solvents.

2.2. Enzymatic resolution of hydroxy tellurides 5a–f

The enantioselectivity of the enzyme-catalyzed *trans*-esterification of hydroxy telluride was evaluated in organic media with (*RS*)-**5a** as substrate and vinyl acetate as acetate donor. Three free lipases, PPL (*Porcine pancreatic* lipase), PSL (*Pseudomonas* sp. lipase) and CRL (*Candida rugosa* lipase), and one immobilized lipase, CALB (*Candida antarctica* lipase-B), were employed in the assays.

In a typical experiment, lipase was added to a solution of a racemic mixture of alcohol (*RS*)-**5a** and vinyl acetate in hexane. The mixture was maintained at 30 °C and the course of conversion was followed by chiral-GC analysis. The best enantioselectivity was achieved with CALB, which yielded both (*S*)-**5a** and (*R*)-**6a** in enantiomeric excesses (ee) greater than 98% (Table 1, entry 7) within 2 h.

High stereoselectivity was also obtained with PSL, yielding (*R*)-**6a** in 98% ee (Table 1, entry 3) within 2 h and (*S*)-**5a** in 94% ee (Table 1, entry 4) after 24 h. The enantiopreference of CALB, PSL and PPL was for (*R*)-**5a**, whilst that of CRL was for (*S*)-**5a** (Table 1, entries 5 and 6).

In view of these results, the influence of the solvent on the resolution of the racemic mixture of the alcohol **5a** was studied using CALB, as the most efficient lipase, and CRL, since it presented an inverse enantiopreference. The solvents employed were those commonly used in kinetic resolution studies. Conversion experiments were performed at 30 °C, and product yields determined after a 3 h reaction for CLR and after a 1 h reaction for CALB (Fig. 2).

It is clear that, whilst the solvent exerted a significant influence on the level of conversion of substrate, it exhibited no

Table 1. Enzymatic resolution[a] of (*RS*)-1-(phenyltellanyl)-2-propanol **5a** using different lipases

Entry	Lipase	Time (h)	Conversion (%)	ee **5a**[b] (%)	ee **6a**[c] (%)	Absolute configuration[d]	*E*[e]
1	PPL	6	32	44	93	(*R*)	
2		24	41	63	91	(*R*)	40
3	PSL	6	36	56	98	(*R*)	
4		24	49	94	96	(*R*)	174
5	CRL	1	21	13	48	(*S*)	
6		3	46	35	41	(*S*)	3.3
7	CALB	2	50	>99	98	(*R*)	>200

[a] The reactions were performed with 0.5 mmol of (*RS*)-**5a** and PPL (1 g), PSL (300 mg), CRL (75 mg) or CALB (30 mg) in hexane (10 mL) and vinyl acetate (2.5 mmol, 0.23 mL).
[b] Enantiomeric excess (ee) of the recovered alcohol **5a**.
[c] Enantiomeric excess (ee) of the acetate **6a**.
[d] Absolute configuration of the acetate **6a**.
[e] This parameter describes the enantioselectivity of the enzyme.

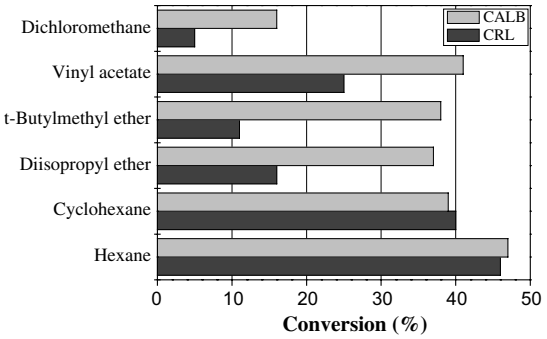


Figure 2. Effect of the solvent on the lipase-catalyzed kinetic resolution of (*RS*)-1-(phenyltellanyl)-2-propanol **5a** at 30 °C.

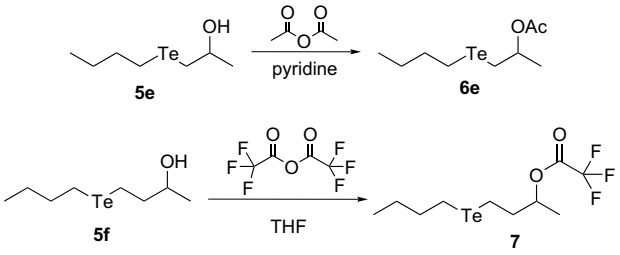
effect on either the enantioselectivity or enantiopreference of the enzyme. Thus, in all solvents CALB showed a preference for (*R*)-**5a**, and (*R*)-**6a** was obtained in >99% ee. In contrast, the preference of CRL was for the (*S*)-**5a** enantiomer, and the enantioselectivity was low ($E < 4$) in all solvents.

Since the most efficient resolution of (*RS*)-**5a** was obtained with CALB in hexane at 30 °C, this system was employed in order to study the influence of the substituent groups R and R′ (Scheme 2) on the kinetic resolution of the racemic alcohols. No acetylated products were obtained when **5b**, **5c** or **5d** were substrates (data not shown). These findings are in agreement with the results of a recent study with CALB in which it was shown that poor enantioselectivities (*E*) were obtained with secondary alcohols bearing a medium-sized substituent smaller than an *n*-propyl group.[18]

According to Kazlauskas's rule,[19] and from a previous study with CALB,[18] the present results indicate that in (*RS*)-**5a**–**d**, the tellanyl group behaves as a large substituent. Hence, for a successful resolution by CALB, the hydroxy tellurides require R′ to be a medium-sized substituent smaller than an ethyl group, such as, for example, the methyl group in (*RS*)-**5a**. Accordingly, the enzymatic resolution of the hydroxy tellurides (*RS*)-**5e** and (*RS*)-**5f** was attempted by mixing the substrate (0.5 mmol), CALB (30 mg) and vinyl acetate (5 equiv, 2.5 mmol) in deoxygenated hexane and incubating at 30 °C. Under these conditions, the racemic mixture of alcohols **5e** and **5f** were resolved with the usual stereochemical preference for the (*R*)-configuration in the stereogenic carbinolic centre being observed. For each substrate, the unreacted (*S*)-enantiomers could be obtained with ⩾90% ee (Table 2, entries 2 and 4), whilst the acetylated products, (*R*)-**6e** and (*R*)-**6f**, could be obtained with ⩾96% ee (Table 2, entries 1, 2 and 3). However, the isolated yield was very low (<5%) following the enzymatic resolution of **5f** owing to the instability of the substrate even in deoxygenated hexane. During the course of the reaction, a white powder was formed that was presumed to be a telluroxide. The kinetic resolution of **5f** with CALB was thus carried out with dry THF as solvent. Under these conditions, the enzymatic resolution of **5f** was achieved with an improved isolated yield (36%) and with high enantioselectivity (Table 2, entries 5 and 6), even though the enzymatic activity of CALB is lower in polar solvents. The results obtained with **5a**, **5e** and **5f** confirmed that hydroxy tellurides bearing a medium-sized substituent (R′) smaller than an ethyl group (Scheme 2) can be successfully resolved using CALB.

2.3. Determination of the enantiomeric excess of hydroxy tellurides 5e and 5f

The ee values of the alcohols **5a**, **5e** and **5f** and of the corresponding esters (**6a**, **6e** and **6f**) were calculated from the chiral-GC chromatograms by comparison with racemic samples. Direct analyses were not, however, possible for **5e** and **5f** owing to the poorly resolved chiral chromatograms obtained. Thus, **5e** was transformed into its acetate **6e**, and **5f** was transformed into its corresponding trifluoroacetate **7**, prior to chiral-GC analysis (Scheme 3).



Scheme 3. Derivatization reactions to determine the enantiomeric excess of hydroxy tellurides **5e** and **5f**.

Table 2. Enzymatic resolution[a] of hydroxy tellurides with CALB at 30 °C

Entry	Substrate	Solvent	Time (h)	Conversion (%)	ee (*S*)-**5** (%)[b]	ee (*R*)-**6** (%)[c]	Yield (%)[d]	*E*[e]
1	(*RS*-**5e**)	Hexane	1	47	87	>99		
2		Hexane	2	49	97	>99	39	>200
3	(*RS*-**5f**)	Hexane	1	45	80	96		
4		Hexane	4	49	90	95	<5	120
5		THF	8	48	93	99		
6		THF	12	50	99	98	36	>200

[a] The reactions were performed with (*RS*)-**5e** (0.5 mmol) or (*RS*)-**5f** (0.5 mmol) and CALB (30 mg) in hexane (10 mL) or CALB (50 mg) in THF (10 mL) and vinyl acetate (2.5 mmol, 0.23 mL).
[b] Enantiomeric excess (ee) of the recovered alcohol **5e** or **5f**.
[c] Enantiomeric excess (ee) of the acetate **6e** or **6f**.
[d] Isolated yield of the acetate **6e** or **6f**.
[e] This parameter describes the enantioselectivity of the enzyme.

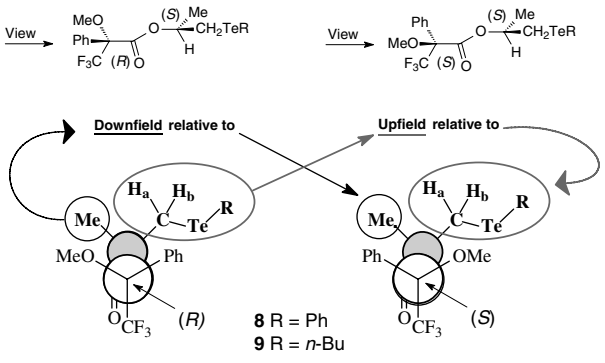
2.4. Determination of the absolute configuration of resolved compounds

The absolute stereochemistries of the unreacted substrates **5a** (>99% ee) and **5e** (>98% ee), derived from kinetic resolution with CALB were determined by NMR. The alcohols were derivatized with the two stereoisomers of α-methoxy-α-(trifluoromethyl)phenyl acetic acid (MTPA), and the resulting diastereoisomeric derivatives **8** and **9** presented different chemical shifts in their ^{1}H NMR spectra. According to Mosher's model,[20] the differences originated from the anisotropic effect of the aromatic ring in the preferred conformation. In the case of isomers (*S*,*S*)-**8** and (*S*,*S*)-**9**, the methyl group linked to the carbinolic carbon is shielded by the phenyl group, whereas in isomers (*R*,*S*)-**8** and (*R*,*S*)-**9**, the phenyl substituent shields the methylene group (protons Ha and Hb). Thus, the signal associated with the methyl group in (*R*,*S*)-**8** and (*R*,*S*)-**9** appeared downfield compared with that of the methyl group in (*S*,*S*)-**8** and (*S*,*S*)-**9**. The inverse trend was observed for the respective methylene group (Fig. 3). Moreover, the same effect in chemical shifts was found in the ^{13}C and ^{125}Te NMR spectra (Fig. 3). From these considerations, the absolute stereochemistries of alcohols **5a** and **5e** were determined as (*S*).

In order to determine the stereochemistry of **5f**, the hydroxy telluride was converted into the corresponding di-lithium salt (1,4-dianion) and reacted with carbon dioxide to form valerolactone **10** (Scheme 4). The absolute stereochemistry was then determined by comparison of the specific rotation of **10** with the literature data.[21] In this way, the absolute stereochemistry of alcohol **5f** was determined as (*S*).

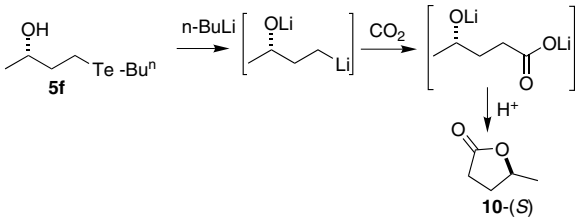
3. Conclusions

It has been demonstrated that the presence of a tellanyl group in the structure of a secondary alcohol does not inhibit lipase activity. Moreover, enzymatic resolution with CALB of the racemic hydroxy tellurides **5a**, **5e** and **5f** yielded (*R*)- and (*S*)-enantiomers in high enantiomeric purity. This simple method affords enantiomerically enriched hydroxy tellurides, which are promising building blocks in organic synthesis by virtue of their facile Te/M exchange reaction.[1,2,9–11]



	(*R*,*S*)-**8** / (*R*,*S*)-**9**	(*S*,*S*)-**8** / (*S*,*S*)-**9**
δ_{Ha}(ppm) =	3.14 / 2.70	3.17 / 2.79
δ_{Hb}(ppm) =	2.98 / 2.86	3.06 / 2.91
$\delta_{H\text{-}Me}$(ppm) =	1.45 / 1.48	1.38 / 1.40
δ_{Te}(ppm) =	440.9 / 204.9	441.9 / 206.3
$\delta_{C\text{-}Te}$(ppm) =	13.35 / 7.23	13.40 / 7.30
$\delta_{C\text{-}Me}$(ppm) =	20.86 / 20.70	20.71 / 20.56

Figure 3. Mosher's model for compounds **8** and **9**.



Scheme 4. Determination of the absolute configuration of hydroxy telluride **5f**.

4. Experimental

4.1. General

CALB (Novozym 435®; immobilized lipase-B from *C. antarctica*; 10,000 PLU/g) and PSL (free *Pseudomonas* sp. lipase; 30,000 u/g) were kindly donated by Novozyms Inc. and Amano Pharmaceutical Co., respectively. PPL (free *P. pancreatic* lipase; 147 units/mg protein), and CRL (free *C. rugosa* lipase; 1440 units/mg protein) were purchased from Sigma-Aldrich Chemical CO. The solvents used in the enzymatic resolutions were deoxygenated by sonication under nitrogen bubbling. NMR spectra were recorded on Bruker models AC-200 and DRX-500, and Varian model FT-300, spectrometers with samples dissolved in $CDCl_3$. The internal references were TMS (^{1}H NMR), the central peak of the $CDCl_3$ signal (^{13}C NMR) and a capillary of diphenyl ditelluride 1 M (^{125}Te NMR). IR spectra were recorded on a Bomem MB-100 spectrophotometer, and optical rotations were determined on a Jasco DIP 370 digital polarimeter. Chiral GC analyses were performed on a Shimadzu GC-17A instrument coupled to a flame ionization detector (FID) and equipped with Supelco® BetaDex™ 120 (β-cyclodextrin packing) or GamaDex™ 120 (γ-cyclodextrin packing) capillary columns (30 m × 0.25 mm i.d.; 0.25 μm) or with a Varian Chromopack™ Chirasil-Dex CB (β-cyclodextrin packing) capillary column (25 m × 0.25 mm i.d.; 0.25 μm). In each case, the carrier gas was H_2. Mass spectra were recorded by coupling the GC to a Shimadzu model QP 5050A mass spectrometer.

4.2. Synthesis

4.2.1. General procedure for the preparation of racemic mixture of substrates (*RS*)-5a and (*RS*)-5c. Diphenyl ditelluride (2.252 g, 5.5 mmol) was placed in a two-necked flask and dissolved in dry ethanol (30 mL) under a nitrogen atmosphere. Sodium borohydride was added slowly at room temperature until the solution became colourless. Following the addition of the appropriate epoxide

(propylene oxide or styrene oxide, 11 mmol), the reaction mixture was stirred for 2 h at room temperature. Aqueous Na_2CO_3 (10%, 20 mL) was added to the mixture and the whole was extracted with ethyl acetate (3×20 mL). The organic phase was washed with brine, dried with $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography over silica gel eluting with hexane/ethyl acetate (9:1).

4.2.1.1. (*RS*)-1-(Phenyltellanyl)-propan-2-ol, (*RS*)-5a. Oil; yield 2.13 g (81%); CAS NR. 133617-20-6. ^{1}H NMR (300 MHz; $CDCl_3$) δ 1.30 (3H, d, $J = 6.1$ Hz), 2.16 (1H, s), 2.96 (1H, dd, $J = 12.2$, 7.6 Hz), 3.14 (1H, dd, $J = 12.2$, 4.5 Hz), 3.89–3.95 (1H, m), 7.17–7.28 (3H, m), 7.72–7.76 (2H, m). ^{13}C NMR (75 MHz; $CDCl_3$) δ 21.5 ($J^1_{^{13}C-^{125}Te} = 163$ Hz), 23.7, 67.4, 111.2, 127.7, 129.2, 138.4. ^{125}Te NMR (157 MHz, 300 K, $CDCl_3$) δ 367.1; IR (ν/cm^{-1}) 3371, 3061, 2968, 2924, 2891, 2873, 1573, 1472, 1451, 1433, 1405, 1320, 1058, 732, 692. MS m/z (rel int.): 264 [M$^+$] (21), 222 (19), 207 (18), 130 (10), 91 (26), 77 (100), 59 (96), 51 (60), 45 (10).

4.2.1.2. (*RS*)-1-Phenyl-2-(phenyltellanyl)ethanol, (*RS*)-5c. Oil; yield 1.92 g (60%); CAS NR. 55136-89-5. ^{1}H NMR (300 MHz; $CDCl_3$) δ 2.59 (1H, d, $J = 3.5$ Hz), 3.26 (1H, dd, $J = 12.1$, 8.1 Hz), 3.32 (1H, dd, $J = 12.3$, 5.0 Hz), 4.84–4.90 (1H, m), 7.15–7.35 (8H, m), 7.69–7.72 (2H, m). ^{13}C NMR (75 MHz; $CDCl_3$) δ 20.6, 73.6, 111.5, 125.6, 127.7, 128.4, 129.2, 138.3, 143.4. IR (ν/cm^{-1}) 3407, 3059, 3029, 2989, 2930, 2874, 1574, 1493, 1475, 1452, 1434, 1047, 734, 697. MS m/z (rel int.) 326 (14), 325 [M$^+$] (3), 220 (16), 205 (15), 121 (18), 103 (33), 91 (50), 77 (100), 51 (58).

4.2.2. General procedure for the preparation of racemic mixture of substrate (*RS*)-5b. Bis-(phenyltellanyl)-methane[22] (0.847 g, 2 mmol) was placed in a two-necked flask and dissolved in dry THF (8 mL) under a nitrogen atmosphere. A solution of *n*-butyl lithium in hexane (1.4 mol L^{-1}, 1.43 mL, 2 mmol) was added slowly at -78 °C, and the resulting mixture stirred for 30 min. Butyraldehyde (0.18 mL, 0.144 g, 2 mmol) was added and the whole solution stirred again for 20 min at -78 °C and them for 1 h at room temperature. Following the addition of saturated aqueous NH_4Cl solution (2 mL), the reaction mixture was extracted with ethyl acetate (3×5 mL), the organic phase washed with brine (5 mL), dried over $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography over silica gel eluting with hexane/ethyl acetate (9:1).

4.2.2.1. (*RS*)-1-(Phenytellanyl)-2-pentanol, (*RS*)-5b. Oil; yield 0.355 g (61%). Found: C, 45.62; H, 5.66. Calcd for $C_{11}H_{16}OTe$: C, 45.27; H, 5.53. ^{1}H NMR (500 MHz; $CDCl_3$) δ 0.89 (3H, t, $J = 7.32$ Hz), 1.32–1.37 (1H, m), 1.50–1.61 (2H, m), 2.14 (1H, s), 2.98 (1H, dd, $J = 12.26$, 7.94 Hz), 3.16 (1H, dd, $J = 12.26$, 4.03 Hz), 3.69–3.74 (1H, m), 7.17–7.29 (3H, m), 7.73–7.76 (2H, m); ^{13}C NMR (125 MHz; $CDCl_3$) δ 13.9, 19.2, 20.4, 40.1, 70.8, 111.2, 127.8, 129.3, 138.5. MS m/z (rel int.): 292 [M$^+$] (40), 222 (40), 207 (45), 130 (18), 91 (43), 77 (93), 69 (63), 45 (100), 43 (64).

4.2.3. General procedure for the preparation of racemic substrates (*RS*)-5d and (*RS*)-5e. *n*-Methyllithium in diethyl ether (1.1 mol L^{-1}, 4.54 mL, 5 mmol) or *n*-butyl lithium in hexane (1.4 mol L^{-1}, 3.57 mL, 5 mmol), as appropriate, was added to a suspension of elemental tellurium (0.638 g, 5 mmol) in dry THF (25 mL) under nitrogen and with magnetic stirring. The appropriate epoxide (styrene oxide (0.57 mL, 5 mmol) or propylene oxide [0.70 mL, 10 mmol]) was added and the mixture heated at reflux for 6 h. The reaction mixture was cooled to room temperature, treated with saturated aqueous NH_4Cl (5 mL) solution and extracted with ethyl acetate (3×5 mL). The organic phase was washed with brine (5 mL), dried over $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography over silica gel eluting with hexane/ethyl acetate (85:15).

4.2.3.1. (*RS*)-1-Phenyl-2-(methyltellanyl)-ethanol, (*RS*)-5d. Oil; yield 0.791 g (60%). Found: C, 40.71; H, 4.36. Calcd for $C_9H_{12}OTe$: C, 40.98; H, 4.59. ^{1}H NMR (200 MHz; $CDCl_3$) δ 1.77 (3H, s), 2.98–3.03 (2H, m), 4.78–4.84 (1H, m); 7.27–7.22 (5H, m). ^{13}C NMR (75 MHz; $CDCl_3$) δ 17.3, 73.8, 125.7, 127.8, 128.4, 143.8. ^{125}Te NMR (157 MHz, 300 K, $CDCl_3$) δ 25,1. MS m/z (rel int.) 226 (32), 160 (61), 140 (9), 121 (71), 103 (73), 91 (44), 77 (100), 65 (14), 43 (80).

4.2.3.2. (*RS*)-1-(*n*-Butyltellanyl)-2-propanol, (*RS*)-5e. Oil; yield 0.794 g (80%); CAS NR. 414902-88-8. Found: C, 34.33; H, 6.32. Calcd for $C_7H_{16}OTe$: C, 34.49; H, 6.61. ^{1}H NMR (200 MHz; $CDCl_3$) δ 0.92 (3H, t, $J = 7.5$ Hz), 1.29 (3H, d, $J = 5.7$ Hz), 1.32–1.47 (2H, m), 1.72 (2H, quint., $J = 7.5$ Hz), 2.54–2.91 (4H, m), 3.86 (1H, sext, $J = 5.7$ Hz), ^{13}C NMR (50 MHz; $CDCl_3$) δ 3.16, 13.2, 15.6, 23.5, 24.8, 34.1, 67.4. ^{125}Te NMR (157 MHz, 300 K, $CDCl_3$) δ 118.5; MS m/z (rel int.) 246 (13), 204 (5), 186 (2), 168 (10), 145 (3), 126 (2), 57 (55), 55 (29), 41 (100).

4.2.4. One-pot procedure for the preparation of (*RS*)-1-(*n*-butyltellanyl)-3-butanol (*RS*)-5f. Elemental tellurium (0.638 g, 5 mmol) and THF (10 mL) were added sequentially to a dry two-necked flask under a nitrogen atmosphere. A solution of *n*-butyl lithium in hexane (1.4 mol L^{-1}, 3.5 mL, 5 mmol) was added dropwise with vigorous stirring to produce a light yellow coloured solution to which deoxygenated H_2O (0.18 mL, 10 mmol) was added. The mixture was stirred for 5 min, after which freshly distilled methylvinyl ketone (0.4 mL, 0.35 g, 5 mmol) was added in one portion. The resulting red coloured mixture was stirred for 30 min, after which an aqueous solution of $NaBH_4$ (1 mol L^{-1}, 6 mL, 6 mmol) was added by means of a dropping funnel. When the reaction had reached completion (monitored by TLC), the mixture was diluted with H_2O (20 mL) and ethyl acetate/hexane (1:1, 50 mL). The phases were separated, the aqueous phase washed twice with ethyl acetate/hexane (1:1, 50 mL). The organic phases were then combined, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography over silica gel eluting with hexane/ethyl acetate (15:1).

4.2.4.1. (*RS*)-1-(*n*-Butyltellanyl)-3-butanol, (*RS*)-5f. Oil; yield 0.901 g (70%); CAS NR. 861399-10-2; ^{1}H NMR (200 MHz; $CDCl_3$) δ 0.85 (3H, t, $J = 6.2$ Hz), 1.13 (3H, d, $J = 6.3$ Hz), 1.31 (2H, sext, $J = 7.2$ Hz); 1.65 (2H, quint, $J = 7.2$ Hz), 1.76–1.85 (2H, m), 2.53–2.69 (4H, m), 3.75 (1H, sext, $J = 6$ Hz). ^{13}C NMR (50 MHz; $CDCl_3$) δ 2.3, 2.7, 13.4, 23.2, 25.0, 34.2, 41.1, 69.1. ^{125}Te NMR (157 MHz, 300 K, $CDCl_3$) δ 251.43. MS *m*/*z* (rel int.) 260 [M^++2] (13), 258 [M^+] (13), 256 (7), 255 (3), 254 (2), 215 (3), 186 (8), 72 (5), 57 (73), 55 (100), 45 (44).

4.2.5. General procedure for the preparation of racemic mixture of esters. Hydroxy telluride (3.6 mmol) was placed in a two-necked flask and dissolved in dry pyridine (5 mL) under a nitrogen atmosphere. Acetic anhydride (2 mL, 21 mmol) was slowly added at 0 °C and the mixture was stirred at room temperature whilst the reaction was monitored by TLC. After 4 h, aqueous HCl (10% v/v, 5 mL) was added and the reaction mixture was extracted with ethyl acetate (10 mL). The organic phase was washed three times with saturated aqueous $CuSO_4$ solution (15 mL) and brine (5 mL), dried over $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography over silica gel eluting with hexane/ethyl acetate (9:1).

4.2.5.1. (*RS*)-*O*-Acetyl-1-(phenyltellanyl)-2-propanol, (*RS*)-6a. Oil; yield 0.925 g (84%). Found: C, 43.10; H, 4.61. Calcd for $C_{11}H_{14}O_2Te$: C, 43.20; H, 4.61. ^{1}H NMR (300 MHz; $CDCl_3$) δ 1.34 (3H, d, $J = 6.24$ Hz), 1.93 (3H, s), 3.08 (2H, d, $J = 6.2$ Hz), 5.03–5.13 (1H, m), 7.17–7.28 (3H, m), 7.73–7.76 (2H, m). ^{13}C NMR (75 MHz; $CDCl_3$) δ 14.8, 21.1, 21.2, 71.4, 111.5, 127.8, 128.2, 138.5, 170.3. ^{125}Te NMR (157 MHz, 300 K, $CDCl_3$) δ 440.5. IR (*v*/cm^{-1}) 3059, 2979, 2932, 2870, 1735, 1574, 1434, 1372, 1241, 733, 692. MS *m*/*z* (rel int.) 306 [M^+] (5), 249 (2), 222 (1), 207 (5), 101 (36), 77 (26), 43 (100).

4.2.5.2. (*RS*)-*O*-Acetyl-1-(*n*-butyltellanyl)-2-propanol, (*RS*)-6e. Oil; yield 0.875 g (85 %). Found: C, 37.80; H, 6.38. Calcd for $C_9H_{18}O_2Te$: C, 37.82; H, 6.35. ^{1}H NMR (500 MHz; $CDCl_3$) δ 0.92 (3H, t, $J = 7.4$ Hz), 1.35 (3H, d, $J = 6.2$ Hz), 1.36–1.42 (2H, m), 1.73 (3H, sext, $J = 7.4$ Hz), 2.04 (3H, s), 2.69 (2H, t, $J = 7.4$ Hz), 2.77 (1H, dd, $J = 12.2$, 7.2 Hz), 2.83 (1H, dd, $J = 12.2$, 5.6 Hz), 5.00 (1H, sext, $J = 6.2$Hz). ^{13}C NMR (125 MHz; $CDCl_3$) δ 3.7, 8.7, 13.4, 20.9, 21.3, 25.0, 34.2, 72.0, 170.4. ^{125}Te NMR (157 MHz, 300 K, $CDCl_3$) δ 189.0. MS *m*/*z* (rel int.) 288 (6), 258 (2), 187 (3), 172 (8), 101 (29), 57 (18), 43 (100).

4.2.5.3. (*RS*)-*O*-Acetyl-1-(*n*-butyltellanyl)-3-butanol, (*RS*)-6f. Oil; yield 0.993 g (92%). Found: C, 40.02; H, 6.53. Calcd for $C_{10}H_{20}O_2Te$: C, 40.05; H, 6.72. ^{1}H NMR (300 MHz; $CDCl_3$) δ 0.92 (3H, t, $J = 7.5$ Hz), 1.23 (3H, d, $J = 6.3$ Hz), 1.38 (2H, sext, $J = 7.5$ Hz), 1.72 (2H, quint, $J = 7.5$ Hz), 2.04 (3H, s), 1.87–2.11 (2H, m), 2.49–2.67 (4H, m). ^{13}C NMR (125 MHz; $CDCl_3$) δ −3.6, 2.8, 13.4, 19.5, 21.3, 25.0, 34.2, 38.8, 72.2, 170.6. ^{125}Te NMR (157 MHz, 300 K, $CDCl_3$) δ 270.15.

4.3. General procedure for the enzymatic resolution

Lipase (0.03–1 g, Tables 1 and 2) and vinyl acetate (5 equiv, 2.5 mmol, 0.23 mL) were added to a solution of the appropriate hydroxy telluride (0.5 mmol) dissolved in the appropriate solvent (10 mL). The reaction mixture was stirred and the course of the reaction monitored by chiral GC. After ca. 50% conversion had been achieved, the enzymes (free or immobilized) were removed by filtration and the resulting solution concentrated. The organic residues were subjected to column chromatography over silica gel in order to obtain the acetylated product and the unreacted enantiomer.

4.3.1. (*S*)-1-(Phenyltellanyl)-2-propanol, (*S*)-5a. Oil; $[\alpha]_D^{28} = +5$ (*c* 1.0, CH_2Cl_2); ee >99%.

4.3.2. (*R*)-*O*-Acetyl-1-(phenyltellanyl)-2-propanol, (*R*)-6a. Oil; $[\alpha]_D^{22} = -6$ (*c* 1.0, CH_2Cl_2); ee >99%.

4.3.3. (*S*)-1-(Butyltellanyl)-2-propanol, (*S*)-5e. Oil; $[\alpha]_D^{23} = +33$ (*c* 1.0, CH_2Cl_2), ee >99%.

4.3.4. (*R*)-*O*-Acetyl-1-(butyltellanyl)-2-propanol, (*R*)-6e. Oil; yield 0.056 g (39%); $[\alpha]_D^{23} = +4$ (*c* 1.0, CH_2Cl_2); ee = 98%.

4.3.5. (*S*)-1-(Butyltellanyl)-3-butanol, (*S*)-5f. Oil; $[\alpha]_D^{22} = +7$ (*c* 1.0, CH_2Cl_2); ee >99%.

4.3.6. (*R*)-*O*-Acetyl-1-(butyltellanyl)-3-butanol, (*R*)-6f. Oil; yield 0.054 g (36%); $[\alpha]_D^{22} = +18$ (*c* 1.0, CH_2Cl_2); ee = 98%.

4.4. Determination of the enantiomeric excesses

The conditions for chiral GC analyses were—(*RS*)-**5a**: Gama Dex column at 120 °C, 100 min hold, 90 kPa; $t_R1 = 84.4$ min, $t_R2 = 85.4$ min; (*RS*)-**5e**: Gama Dex column at 65 °C, 150 min hold, 65–98 °C at 0.5 °C min^{-1}, 90 kPa; $t_R1 = 198.4$ min, $t_R2 = 200.2$ min; (*RS*)-**6a**: Chirasil-Dex CB column at 120 °C, 40 min hold, 100 kPa; $t_R1 = 35.3$ min, $t_R2 = 39.6$ min; (*RS*)-**6e**: Chiralsil-Dex CB column at 80 °C, 120 min hold, 80–110 °C at 2 °C min^{-1}, 125 kPa; $t_R1 = 102.2$ min, $t_R2 = 125.1$ min; (*RS*)-**6f**: Chiralsil-Dex CB column at 60 °C, 3 min hold, 60–190 °C at 5 °C min^{-1}, 100 kPa; $t_R1 = 22.0$ min, $t_R2 = 22.6$ min; (*RS*)-**7**: Chiralsil-Dex CB column at 80 °C, 90 min hold, 80–140 °C at 1 °C min^{-1}, 120 kPa; $t_R1 = 78.6$ min, $t_R2 = 82.0$ min; (*RS*)-**10**: Chirasil-Dex CB column at 60 °C, 3 min hold, 60–190 °C at 5 °C min^{-1}, 100 kPa; $t_R1 = 10.1$ min, $t_R2 = 10.4$ min. *E* values were calculated from the enantiomeric excesses of product (ee_p) and substrate (ee_s) according to the Sih, Sharpless and Fajans equation, namely, $E = \ln\{[1 - c(1 + ee_p)]/\ln[1 - c(1 - ee_p)]\}$, where $c = [ee_s/(ee_s + ee_p)]$.[23]

4.4.1. General procedure for the hydrolysis of acetates 6. The appropriate acetoxy telluride (1 mmol) was dissolved in methanol (5 mL), and H_2O (2 mL) and K_2CO_3 (0.2 mmol) added. The mixture was stirred overnight and then extracted with ethyl acetate (2 × 5 mL). The organic

phase was washed with brine (2 mL), dried and then concentrated to yield a residue that was purified by flash chromatography over silica gel.

4.5. Determination of the absolute configuration

4.5.1. Esterification of (*S*)-1-(phenyltellanyl)-2-propanol (*S*)-5a and (*S*)-1-(*n*-butyltellanyl)-2-propanol (*S*)-5e with Mosher's acid. The appropriate alcohol (*S*)-**5a** or (*S*)-**5e** (0.1 mmol), Et_3N (1.2 mmol) and DMAP (0.1 mmol) were dissolved in dry CH_2Cl_2 (10 mL) under a nitrogen atmosphere, and α-methoxy-α-trifluoromethyl-phenyl acetyl chloride (0.5 mmol) dissolved in dry CH_2Cl_2 (5 mL) added. After 15 min reaction time, the solution was washed with H_2O (3 × 2 mL), dried and concentrated to yield a residue, which was purified by flash chromatography on silica gel. Derivatives were, however, unstable on silica gel and were purified by rapid and simple filtration over silica gel, initially with hexane and then with ethyl acetate.

4.5.1.1. (1*S*,2*R*)-1-Methyl-2-(phenyltellanyl)ethyl 3,3,3-trifluoro-2-methoxy-2-phenylpropionate (1*S*,2*R*)-8. Oil; yield 0.025 g (52%); ^{1}H NMR (500 MHz; $CDCl_3$) δ 1.45 (3H, d, $J = 6.23$ Hz), 2.98 (1H, dd, $J = 12.32$, 7.32 Hz), 3.14 (1H, dd, $J = 12.32$, 5.84 Hz), 3.56 (3H, s), 5.30–5.36 (1H, m), 7.27–7.64 (10H, m). ^{13}C NMR (125 MHz; $CDCl_3$) δ 13.35, 20.86, 55.50, 74.80, 111.38, 127.34, 128.41, 129.39, 129.60, 130.02, 138.50, 165.84. ^{125}Te NMR (157 MHz, 300 K, $CDCl_3$) δ 440.9.

4.5.1.2. (1*S*,2*S*)-1-Methyl-2-(phenyltellanyl)ethyl 3,3,3-trifluoro-2-methoxy-2-phenylpropionate (1*S*,2*S*)-8. Oil; yield 0.024 g (50%); ^{1}H NMR (500 MHz; $CDCl_3$) δ 1.38 (3H, d, $J = 6.21$ Hz), 3.06 (1H, dd, $J = 12.35$, 7.05 Hz), 3.17 (1H, dd, $J = 12.35$, 6.25 Hz), 3.56 (3H, s), 5.29–5.34 (1H, m), 7.26–7.59 (10H, m). ^{13}C NMR (125 MHz; $CDCl_3$) δ 13.39, 20.72, 55.63, 74.92, 111.32, 127.71, 128.41, 129.43, 129.60, 130.03, 138.55, 165.94. ^{125}Te NMR (157 MHz, 300 K, $CDCl_3$), δ 441.9.

4.5.1.3. (1*S*,2*R*)-1-Methyl-2-(*n*-butyltellanyl)ethyl 3,3,3-trifluoro-2-methoxy-2-phenylpropionate (1*S*,2*R*)-9. Oil; ^{1}H NMR (500 MHz; $CDCl_3$) δ 0.90 (3H, t, $J = 7.3$ Hz), 1.31–1.38 (2H, m), 1.48 (3H, d, $J = 6.2$ Hz), 1.65–1.71 (2H, m), 2.57–2.67 (2H, m), 2.70 (1H, dd, $J = 12.3$, 7.9 Hz), 2.86 (1H, dd, $J = 12.3$, 5.3 Hz), 3.57 (3H, s), 5.23–5.30 (1H, m), 7.38–7.43 (3H, m), 7.53–7.55 (2H, m). ^{13}C NMR (125 MHz; $CDCl_3$) δ 4.1, 7.2, 13.4, 20.7, 24.9, 34.1, 55.5, 75.4, 84.5, 127.3, 128.4, 129.5, 132.4, 165.9. ^{125}Te NMR (157 MHz, 300 K, $CDCl_3$) δ 204.9.

4.5.1.4. (1*S*,2*S*)-1-Methyl-2-(*n*-butyltellanyl)ethyl 3,3,3-trifluoro-2-methoxy-2-phenylpropionate (1*S*,2*R*)-9. Oil; ^{1}H NMR (500 MHz; $CDCl_3$) δ 0.91 (3H, t, $J = 7.3$ Hz), 1.32–1.39 (2H, m), 1.40 (3H, d, $J = 6.2$ Hz), 1.68–1.74 (2H, m), 2.67–2.70 (2H, m), 2.79 (1H, dd, $J = 12.3$, 7.7 Hz), 2.91 (1H, dd, $J = 12.3$, 5.7 Hz), 3.57 (3H, s), 5.23–5.28 (1H, m), 7.39–7.45 (3H, m), 7.53–7.56 (2H, m). ^{13}C NMR (125 MHz; $CDCl_3$) δ 4.2, 7.3, 13.4, 20.6, 25.0, 34.1, 55.5, 75.6, 84.5, 127.5, 128.4, 129.6, 132.3, 166.0. ^{125}Te NMR (157 MHz, 300 K, $CDCl_3$) δ 206.3.

4.5.2. Procedure for the preparation of valerolactone 10. A solution of *n*-butyl lithium in hexane (1.4 mol L^{-1}, 1.57 mL, 2.2 mmol) was added dropwise with continuous stirring to hydroxy telluride **5e** (0.25 g, 1 mmol) dissolved in THF (5 mL) while maintaining at −70 °C in a round-bottomed flask. The reaction mixture was stirred for 20 min at −70 °C and then saturated with dry CO_2, warmed to room temperature and stirred for 1 h. Aqueous HCl (50% v/v, 5 mL) was added, the mixture extracted with diethyl ether (3 × 5 mL), the organic phase washed with brine (5 mL), dried with $MgSO_4$ and the solvent removed by distillation. The residue was purified by column chromatography over silica gel eluting with hexane:diethyl ether (9:1).

4.5.2.1. Valerolactone. Oil; $[\alpha]_D^{23} = +30$ (*c* 1.0; $CHCl_3$); ee = 98%; lit.[21] (*S*)-enantiomer: $[\alpha]_D = -26.7$ (*c* 1.0, $CHCl_3$) ee 74%; CAS NR. 58917-25-2; ^{1}H NMR (300 MHz; $CDCl_3$) δ 1.43 (3H, d, $J = 6.3$ Hz), 1.78–1.91 (1H, m), 2.54–2.59 (2H, m), 4.6–4.71 (1H, m). ^{13}C NMR (75 MHz; $CDCl_3$) δ 21.0, 29.1, 29.8, 77.4, 177.6. IR (*v*/cm^{-1}) 2998, 1777, 1432, 1130. MS *m*/*z* (rel int.): 41 (47), 43 (34), 56 (100), 85 (45), 100 (8).

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