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Enzymatic kinetic resolution of 1-(3′-furyl)-3-buten-1-ol and 2-(2′-furyl)-propan-1-ol†

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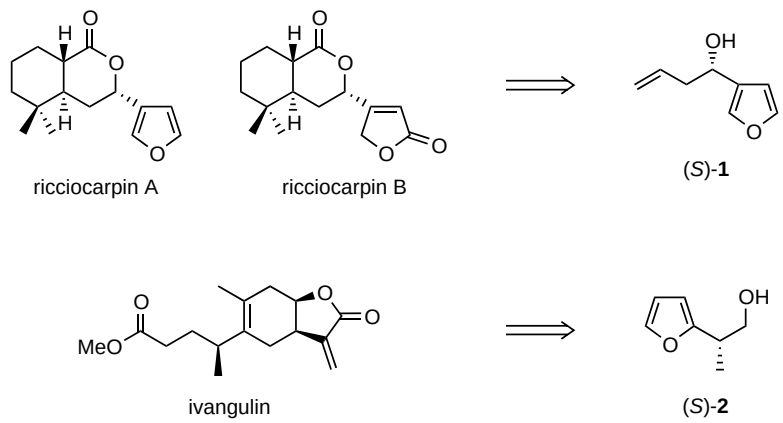
Abstract—The enzymatic kinetic resolution of the racemic alcohols 1-(3′-furyl)-3-buten-1-ol (±)-**1** and 2-(2′-furyl)propan-1-ol (±)-**2** was investigated by screening a range of lipases and esterases for enantioselective transacylation, as well as for enantioselective hydrolysis. For both alcohols, lipase-catalyzed hydrolysis of the derived racemic acetate gave the best results for accessing the desired (*S*)-enantiomers. In the case of the secondary alcohol (±)-**1**, ASL turned out to be the optimum enzyme, whereas PPL was found to be superior in the case of the primary alcohol (±)-**2**. Additionally, an alternative access to (*S*)-**2** via Oppolzer's camphor sultam methodology is described.

1. Introduction

The hydroxyalkyl furans (*S*)-1-(3′-furyl)-3-buten-1-ol (*S*)-**1** and (*S*)-2-(2′-furyl)propan-1-ol (*S*)-**2** are important building blocks for the synthesis of various natural products (Scheme 1).[1–3] We recently communicated a short enantioselective access to the molluscicidal furanosesquiterpene lactones ricciocarpin A and ricciocarpin B by two-fold application of catalytic ring closing metathesis using (*S*)-**1** as the key precursor.[1] Moreover, we have shown that the 1,10-*seco*-eudesmanolide ivangulin is efficiently available in racemic form by means of the thermodynamically controlled intramolecular Diels–Alder reaction of the vinylsulfonate derived from racemic **2** as the crucial step.[2] Thus, the preparation of (*S*)-**2** would constitute a formal total synthesis of the naturally occurring enantiomer of this sesquiterpene lactone.[3] Herein, we report the syntheses of (*S*)-**1** and (*S*)-**2** by enzymatic kinetic resolution[4–6] of the corresponding racemic alcohols and



Scheme 1.

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† Dedicated to Professor Joachim Thiem on the occasion of his 60th birthday.

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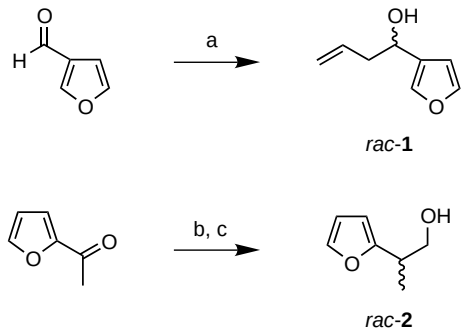
disclose an alternative access to (*S*)-**2** via Oppolzer's camphor sultam[7] methodology.

2. Results and discussion

2.1. Preparation of alcohols (±)-1 and (±)-2

Furan-3-carboxaldehyde, which has already been converted to either enantiomer of the homoallylic alcohol **1** via stoichiometric asymmetric allylborations,[8] was subjected to a Barbier reaction with allyl bromide and zinc[9] to give (±)-**1** in nearly quantitative yield (Scheme 2). The primary alcohol (±)-**2**[10,11] was conveniently secured from 2-acetylfuran by Wittig olefination followed by hydroboration/oxidation.



Scheme 2. (a) Zn, CH_2=$CHCH_2Br$, NH_4Cl/H_2O/THF, rt, 98%; (b) Ph_3P=CH_2, Et_2O, rt to reflux; (c) (i) BH_3·THF, THF, 0°C to rt, (ii) H_2O_2, NaOH, 40–50°C, 64% from 2-acetylfuran.

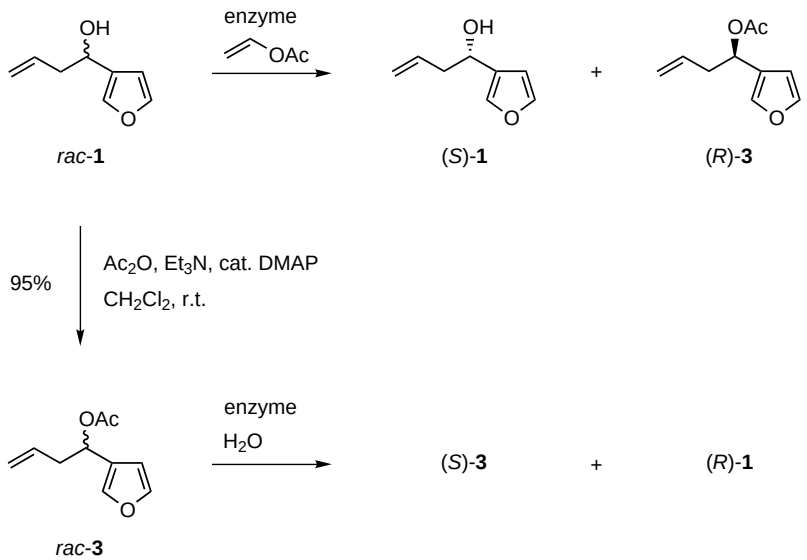
2.2. Enzymatic kinetic resolution of 1-(3′-furyl)-3-buten-1-ol (±)-1

Since the absolute configuration of the ricciocarpins A and B was unknown prior to our work, we were interested in devising a catalytic access to either enantiomer of **1**. To this end, we screened a range of lipases and esterases for enantioselective transacylation of the racemic secondary alcohol (±)-**1**, as well as for enantioselective hydrolysis of the derived acetate (±)-**3** (Scheme 3).

Some of the enzymes tested for transacylation of (±)-**1** with vinyl acetate[12] in pentane containing 1% of water[13] displayed high enantioselectivities on an analytical scale (Table 1). Thus, the lipases from *Pseudomonas fl.* (PSL from Fluka), *Candida antarctica* fraction B (CAL-B), *Thermomyces lanuginosa* (TLL) and *Alcaligines* sp. (ASL) led to high *E* values.[14,15] However, except for ASL, this enhanced selectivity was accompanied by a rather low reaction rate. For all other enzymes listed, low selectivity and/or slow conversion was observed. Unfortunately, we faced severe problems upon attempted scale-up using ASL, which might be due to deactivation of the enzyme under the conditions used. With the exception of the lipase from *C. antarctica* fraction A (CAL-A), all of the enzymes investigated preferentially converted the (*R*)-enantiomer of **1** in accord with the empirical rule of Kazlauskas for secondary alcohols.[16]

Compared to the transesterification experiments described above, the enzymatic hydrolysis of acetate (±)-**3** proceeded with higher reaction rates (Table 2). For ASL, excellent enantioselectivity was also observed. As a consequence, depending on the degree of conversion, ASL-catalyzed hydrolysis of (±)-**3** can be utilized to obtain both (*S*)-**3** and (*R*)-**1** in high enantiomeric purity. Interestingly, CAL-A again did not follow the empirical rule[16] of Kazlauskas.

ASL not only showed the best performance in the analytical runs, but also gave an excellent result for the hydrolysis of (±)-**3** on a multi-gram scale (Scheme 4). By allowing the reaction to proceed for 4 days, (*S*)-**3** (99% e.e. by GC) was efficiently secured next to (*R*)-**1** (88% e.e. by GC). With the aim of isolating the (*S*)-acetate in high yield and extremely high enantiomeric purity, rigorous control of conversion is not necessary,



Scheme 3.

Table 1. Enzyme-catalyzed transesterification of (±)-**1** with vinyl acetate in pentane

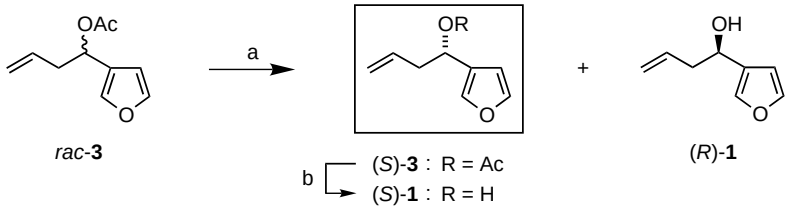
Enzyme[a]	Conversion (%)[b]	Time (h)	E.e. (%)[b]		E[c]
			1	**3**	
PSL[d]	45	69	61 (*S*)	85 (*R*)	35
CAL-B	35	196	50 (*S*)	94 (*R*)	75
CRL	4	72	N.d.[e]	N.d.	N.d.
CRL-pur.	3	98	N.d.	N.d.	N.d.
CAL-A	96	4	88 (*R*)	3 (*S*)	3
PSL	62	25	70 (*S*)	44 (*R*)	5
PPL	5	168	N.d.	N.d.	N.d.
TLL	41	168	39 (*S*)	94 (*R*)	65
MML	<1	46	N.d.	N.d.	N.d.
ASL	55	3	92 (*S*)	95 (*R*)	80
PLE-1	4	70	N.d.	N.d.	N.d.
PLE-2	3	138	N.d.	N.d.	N.d.

[a] Boehringer Mannheim screening set.
[b] Determined by capillary GC.
[c] Enantioselectivity factor.
[d] Purchased from Fluka.
[e] N.d. = not determined.

Table 2. Enzyme-catalyzed hydrolysis of (±)-**3** in aqueous dimethylsulfoxide

Enzyme[a]	Conversion (%)[b]	Time (h)	E.e. (%)[b]		E[c]
			3	**1**	
CAL-B	69	40	96 (*S*)	73 (*R*)	18
CAL-A	93	3	41 (*R*)	6 (*S*)	2
TLL	38	42	5 (*S*)	3 (*R*)	1
ASL	55	7	94 (*S*)	95 (*R*)	80
PLE-1	91	1.5	32 (*S*)	2 (*R*)	1
PLE-2	49	0.5	31 (*S*)	21 (*R*)	2

[a] Boehringer Mannheim screening set.
[b] Determined by capillary GC.
[c] Enantioselectivity factor.



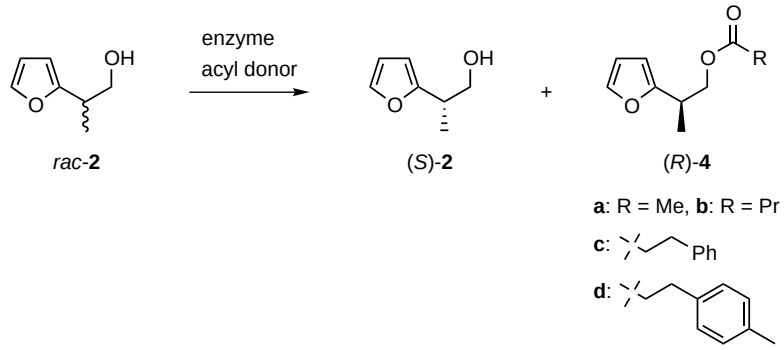
Scheme 4. (a) ASL, H_2O/DMSO (9:1), pH 7, silica gel, 40°C, 4 days, 44% (*S*)-**3** (99% e.e.), 48% (*R*)-**1** (88% e.e.); (b) NaOH, rt, 100%.

since the reaction slows down dramatically after the (*R*)-acetate has been consumed. Saponification of (*S*)-**3** then delivered (*S*)-**1** without erosion of configurational integrity.

The absolute configuration of **1** was unambiguously determined by anomalous X-ray diffraction of a lactone isomer of ricciocarpin B synthesized from (*S*)-**1**.[1] This analysis also confirmed the previous configurational assignment for **1**, which until now relied on analogy with the outcome of related asymmetric allylborations.[8]

2.3. Enzymatic kinetic resolution of 2-(2′-furyl)propan-1-ol (±)-2

In order to access the naturally occurring enantiomer of the 1,10-*sec*-eudesmanolide ivangulin by the route developed in the racemic series,[2] the (*S*)-enantiomer of **2** is required. Using a range of commercially available lipases, we first focused on the kinetic resolution of the primary alcohol (±)-**2**[10,11] by enantioselective transacylation using different acyl donors and organic solvents (Scheme 5).[17]



Scheme 5.

Table 3 lists the results of the transesterification experiments performed with vinyl acetate[12] as the acyl donor in pentane containing 1% of water.[13] The best *E* values were obtained with the lipases from *C. antarctica* fraction B (CAL-B) and *Porcine pancreas* (PPL). However, CAL-B displayed a low conversion rate, and the reaction usually stopped after 20–25% conversion. Except for CAL-A, all of the enzymes checked preferentially transformed the (*R*)-enantiomer in accord with the empirical rule of Kazlauskas for primary alcohols.[18,19] Thus, it was impossible to obtain the desired (*S*)-**2** in high enantiomeric purity by this protocol.

In an attempt to increase the *E* value of the PPL-catalyzed transesterification of (±)-**2**, different acyl donors were tested (Table 4). The use of isopropenyl acetate and vinyl butyrate led to similar reaction rates and enantiomeric excesses as observed with vinyl acetate. Additionally, we also tested two vinyl esters featuring an aromatic ring in the acyl moiety.[20] Unfortunately, vinyl 3-phenylpropanoate and vinyl 3-(4-methylphenyl)-propanoate only brought about lower reaction rates with no increase in enantioselectivity.

As an alternative, we tried to raise the *E* value by variation of the organic solvent containing 1% of water

Table 3. Lipase-catalyzed transesterification of (±)-**2** with vinyl acetate in pentane

Enzyme[a]	Conversion (%)[b]	Time (h)	E.e. (%)[b]		*E*[c]
			2	**4**	
PSL[d]	39	0.5	17 (*S*)	42 (*R*)	2
CAL-B	22	4	11 (*S*)	89 (*R*)	20
CRL	93	2.5	31 (*S*)	3 (*R*)	2
CRL-pur.	43	43	6 (*S*)	24 (*R*)	2
CAL-A	82	0.6	15 (*R*)	7 (*S*)	2
PSL	11	3	5 (*S*)	40 (*R*)	2
PPL	47	7	47 (*S*)	62 (*R*)	8
TLL	15	4	2	1	1
MML	22	4.5	3	3	1
ASL	94	0.5	2	2	1

[a] Boehringer Mannheim screening set.
[b] Determined by capillary GC.
[c] Enantioselectivity factor.
[d] Purchased from Fluka.

Table 4. PPL-catalyzed transesterification of (±)-**2** with various acyl donors in pentane

Acyl donor	Conversion (%)[a]	Time (h)	E.e. (%)[a]		*E*[b]
			2	**4**	
Isopropenyl acetate	35	4	37 (*S*)	70 (*R*)	8
Vinyl butyrate	75	3	81 (*S*)	41 (*R*)	4
Vinyl 3-phenylpropanoate	40	48	N.d.[c]	52 (*R*)	5
Vinyl 3-(4-methylphenyl)-propanoate	52	28	N.d.	63 (*R*)	8

[a] Determined by capillary GC.
[b] Enantioselectivity factor.
[c] N.d. = not determined.

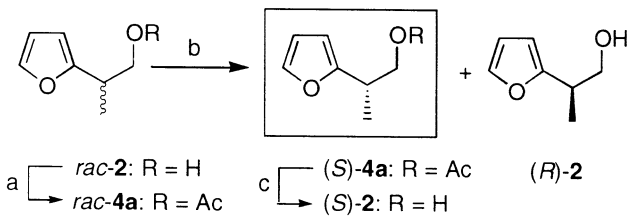
Table 5. Transesterification of (±)-**2** with vinyl acetate in different solvents using PSL and PPL

Solvent	Enzyme[a]	Conversion (%)[b]	Time (h)	E.e. (%)[b]		E[c]
				2	**4**	
Hexane	PSL	58	0.5	28 (*S*)	31 (*R*)	3
	PPL	41	9	41 (*S*)	16 (*R*)	9
Cyclohexane	PSL	71	1.0	41 (*S*)	26 (*R*)	3
	PPL	20	23	18 (*S*)	68 (*R*)	6
Toluene	PSL	7	1.5	17 (*S*)	42 (*R*)	3
	PPL	13	48	10 (*S*)	76 (*R*)	8
Chloroform	PSL	16	27	9 (*S*)	47 (*R*)	3
	PPL	<1	26	N.d.[d]	N.d.	N.d.
Dichloromethane	PSL	48	27	17 (*S*)	34 (*R*)	3
	PPL	<1	26	N.d.	N.d.	N.d.
Tetrahydrofuran	PSL	<1	20	N.d.	N.d.	N.d.
	PPL	<1	40	N.d.	N.d.	N.d.

[a] Boehringer Mannheim screening set.
[b] Determined by capillary GC.
[c] Enantioselectivity factor.
[d] N.d. = not determined.

in experiments performed with PPL, PSL and vinyl acetate (Table 5). PSL was applied in addition to PPL, since this enzyme has been used successfully in lipase-catalyzed reactions of primary alcohols.[21] But again, we did not observe an increase in enantioselectivity.

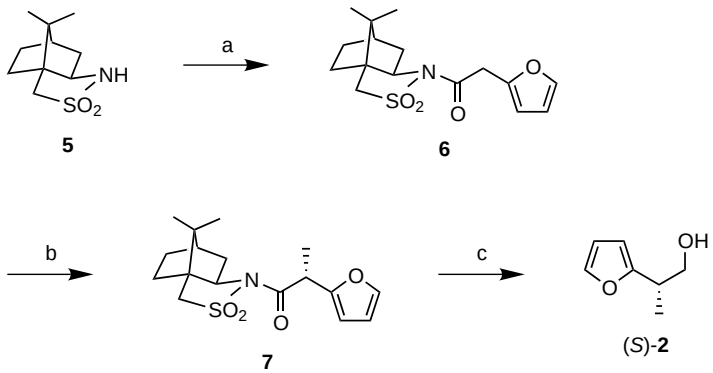
On the other hand, a hydrolytic approach to the kinetic resolution of (±)-**2** turned out to be advantageous (Scheme 6). For the PPL-catalyzed hydrolysis of the derived acetate (±)-**4a** on a preparative scale, an E value of 16 was observed, and (*S*)-**4a** was isolated with 98% e.e., as determined by capillary GC after 81% conversion. Of course, the yield of (*S*)-**4a** has to be rather low at this high conversion. However, considering that (±)-**4a** is a derivative of a primary alcohol with the stereogenic center being three bonds apart from the acyl group attacked, the selectivity attained is not bad at all. Simple saponification of (*S*)-**4a** then provided the virtually enantiopure alcohol (*S*)-**2**, the absolute configuration of which was proven during an alternative chiral auxiliary based route to (*S*)-**2** (vide infra).



Scheme 6. (a) Ac_2O, DMAP, pyridine, rt, 100%; (b) PPL, H_2O/DMSO (9:1), pH 7, silica gel, 40°C, 2 h (81% conversion), 18% (*S*)-**4a** (98% e.e.), 63% (*R*)-**2** (10% e.e.); (c) K_2CO_3, MeOH, rt, 100%.

2.4. Camphor sultam route to (*S*)-2

As an alternative to the enzymatic kinetic resolution approach to (*S*)-**2**, we additionally developed a highly stereoselective access to this hydroxyalkyl furan via Oppolzer's camphor sultam[7] methodology (Scheme 7).[3] After acylation of the sodium salt of (2*R*)-sultam **5** with furan-2-yl-acetyl chloride,[22] the resultant mixed imide **6** was methylated with high diastereoselectivity (97% d.e. by GC). A single recrystallization improved the purity of this material to >99% d.e. (GC). Finally, reductive cleavage of **7** with lithium aluminum hydride yielded the desired (*S*)-**2** in virtually enantiopure form. The absolute configuration was unequivocally proven by X-ray diffraction analysis[23] of sultam **7** (Fig. 1).[24]



Scheme 7. (a) (i) NaH, toluene, rt; (ii) furan-2-yl-acetyl chloride, rt, 76%; (b) (i) $NaN(SiMe_3)_2$, THF, −78°C, (ii) MeI, HMPA, −78°C to rt, (iii) recrystallization, 87% **7** (>99% d.e.); (c) $LiAlH_4$, THF, rt, 89%.

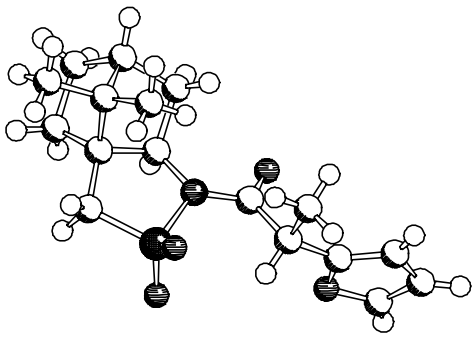


Figure 1. Crystal structure of sultam **7**.[23,25]

3. Experimental

3.1. General experimental information

For general experimental information see Ref. 26. The enzymes were purchased from Boehringer Mannheim (screening set) and stored at 4 and −20°C. Lipase PSL was purchased from Fluka and stored at −20°C. The acyl donors vinyl acetate, vinyl butyrate and isopropenyl acetate are commercially available and were used without further purification. Vinyl 3-phenylpropanoate and vinyl 3-(4-methylphenyl)propanoate were prepared according to the method of Schneider.[27] Conversions of the enzyme-catalyzed reactions were determined using a Shimadzu 14A gas chromatograph equipped with a 25 m×0.25 mm HP 05 capillary column (Hewlett Packard), carrier gas H_2. The conversions were calculated from the peak areas. The enantiomeric excess values were determined using a Varian 3300 gas chromatograph equipped with a 50 m×0.25 mm chiral capillary column Hydrodex®-ß-6-TBDM (Macherey–Nagel), carrier gas H_2. The E values were calculated using Sih's method (irreversible case).[14,15]

3.2. Synthesis of racemic 1-(3′-furyl)-3-buten-1-ol (±)-1

To a vigorously stirred emulsion of sat. aqueous NH_4Cl (45 mL) and THF (9 mL) was added Zn (6.00 g, 91.8 mmol), furan-3-carbaldehyde (4.80 g, 50.0 mmol) and 3-bromopropene (6.65 g, 55.0 mmol). The mixture was stirred for 1 h at room temperature and extracted with ether (3×25 mL), The combined organic extracts were dried over $MgSO_4$, filtered through a pad of silica gel and concentrated in vacuo to give pure (±)-**1** (6.76 g, 98%); bp 58°C (1 mBar); R_f 0.44 (pentane/ether, 1:1); IR (CCl_4): 3620, 3431 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.17 (s, 1H), 2.46–2.52 (m, 2H), 4.69 (apparent t, $J=5.3$ Hz, 1H), 5.15 (d, $J=10.1$ Hz, 1H), 5.16 (d, $J=17.2$ Hz, 1H), 5.81 (apparent tdd, $J_t=7.1$ Hz, $J_d=10.1$ Hz, $J_d=17.2$ Hz, 1H), 6.40 (s, 1H), 7.38 (s, 2H), ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 42.35 (t), 66.04 (d), 108.49 (d), 118.39 (t), 128.43 (s), 134.06 (d), 138.99 (d), 143.20 (d); MS (GC) m/z: 138 (5) [M^+], 97 (100) [$M^+-C_3H_5$].

3.3. Synthesis of racemic 1-(3′-furyl)-3-buten-1-yl acetate (±)-3

To a stirred solution of (±)-**1** (11.9 g, 86.1 mmol) in CH_2Cl_2 (100 mL) was added triethylamine (50 mL, 0.36 mol), acetic anhydride (16.7 g, 164 mmol) and DMAP (1.04 g, 8.51 mmol) at 15°C. The mixture was stirred for 2 h at 15°C and washed with water (2×50 mL), 2N aqueous HCl (50 mL), sat. aqueous $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered through a pad of silica gel and concentrated in vacuo. Distillation of the crude product afforded pure (±)-**3** (14.7 g, 95%); bp 56–57°C (1 mBar); R_f 0.67 (pentane/ether, 1:1); IR (neat): 1738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.98 (s, 3H), 2.46–2.61 (m, 2H), 5.00 (d, $J=10.1$ Hz, 1H), 5.04 (d, $J=17.1$ Hz, 1H), 5.66 (apparent tdd, $J_t=7.1$ Hz, $J_d=10.1$ Hz, $J_d=17.1$ Hz, 1H), 5.76 (apparent t, $J=6.8$ Hz, 1H), 6.33 (s, 1H), 7.31 (s, 1H), 7.35 (s, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 21.16 (q), 39.15 (t), 67.70 (d), 108.91 (d), 118.11 (t), 124.48 (s), 133.14 (d), 140.34 (d), 143.17 (d), 170.31 (s); MS (GC) m/z: 180 (1) [M^+], 43 (100); anal. calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found C, 66.71; H, 6.71%.

3.4. Synthesis of racemic 2-(2′-furyl)propan-1-ol (±)-2

To a suspension of methyltriphenylphosphonium bromide (85.5 g, 239 mmol) in dry ether (1.6 L) was added dropwise a solution of n-BuLi in hexane (1.6 M, 150 mL, 240 mmol) at 0°C. The resultant solution was allowed to warm to room temperature and 2-acetylfuran (27.4 g, 249 mmol) dissolved in dry ether (160 mL) was added dropwise over a period of 60 min. After stirring for 2 h under reflux, the mixture was treated with water (300 mL). The aqueous layer was extracted with ether (3×150 mL), and the combined organic layers were washed with water (60 mL) and dried over $MgSO_4$. The mixture was concentrated by distillation through a Vigreux column to a volume of 200 mL. Distillation of this residue and collection of the fraction (ca. 160 mL) with bp 65–135°C gave a solution of crude 2-(2′-furyl)propene that was immediately used for the subsequent hydroboration/oxidation without further purification. The solution of unpurified 2-(2′-furyl)propene obtained as described above was diluted with dry THF (200 mL), and a solution of BH_3 in THF (0.98 M, 68 mL, 66.6 mmol) was added at 0°C over a period of 45 min. After stirring for an additional 1 h at room temperature, water (7 mL) was added carefully. The mixture was cooled to 0°C, 3 M aqueous NaOH (34 mL) was rapidly added followed by dropwise addition of 30% H_2O_2 (20 mL), and the resultant mixture was stirred for 1 h at 40–50°C. The aqueous layer was saturated with Na_2SO_3, separated and acidified to pH 3 with concentrated HCl. The organic layer was vigorously shaken with this aqueous solution to destroy any peroxides and then it was dried over $MgSO_4$. Removal of the solvent in vacuo afforded pure (±)-**2** (20.1 g, 64% from 2-acetylfuran); bp 113°C (43 mBar); R_f 0.36 (pentane/ether, 1:1); IR (neat): 3348 cm^{-1}; ^1H NMR (300

MHz, $CDCl_3$): δ 1.26 (d, $J=7.0$ Hz, 3H), 1.68 (s, 1H), 3.04 (m, 1H), 3.72 (m, 2H), 6.08 (m, 1H), 6.31 (dd, $J=1.8$ Hz, $J=3.2$ Hz, 1H), 7.34 (dd, $J=0.9$ Hz, $J=1.8$ Hz, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 15.05 (q), 35.97 (d), 66.26 (t), 104.87 (d), 109.92 (d), 141.12 (d), 157.39 (s); MS (GC) m/z: 126 (47) [M^+], 95 (100); anal. calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found C, 66.66; H, 8.12%.

3.5. Synthesis of racemic 2-(2′-furyl)propan-1-yl acetate (±)-4a

To a solution of (±)-**2** (2.52 g, 20.0 mmol) in acetic anhydride (10 mL, 106 mmol) was added pyridine (1.58 g, 20 mmol) and DMAP (244 mg, 2.00 mmol). The mixture was stirred overnight at room temperature and ice cold water was added. The aqueous layer was extracted with ether (3×20 mL), and the combined organic extracts were washed with 2N HCl and sat. aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography over silica gel (pentane/ether, 1:4) to give the acetate (±)-**4a** (3.36 g, 100%); bp 46°C (1 mBar); R_f 0.46 (pentane/ether, 1:4); IR (neat): 1747 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (d, $J=7.0$ Hz, 3H), 2.04 (s, 1H), 3.18 (m, 1H), 4.13 (dd, $J=6.9$ Hz, $J=10.6$ Hz, 1H), 4.26 (dd, $J=6.4$ Hz, $J=10.6$ Hz, 1H), 6.06 (d, $J=3.2$ Hz, 1H), 6.30 (dd, $J=1.8$ Hz, $J=3.2$ Hz, 1H), 7.32 (dd, $J=0.7$ Hz, $J=1.8$ Hz, 1H), ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 15.62 (q), 20.78 (q), 32.81 (d), 67.16 (t), 104.79 (d), 109.96 (d), 141.22 (d), 156.40 (s), 170.86 (s); MS (GC) m/z: 168 (1) [M^+], 108 (100); anal. calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found C, 64.30; H, 7.30%.

3.6. General method for lipase-catalyzed transesterification (analytical scale)

The organic solvent (10 mL), water (0.1 mL), acyl donor (3 mmol) and substrate (1 mmol) were placed in a 100 mL screw-cap bottle and stirred gently at 40°C. The enzyme was added, and the reaction vessel was closed. The progress of the reaction was followed by analysis of samples taken from the reaction mixture at intervals by gas chromatography. When the reaction had stopped or the desired conversion was reached, the reaction mixture was filtered through silica gel and the solvent was removed in vacuo. The acetate and alcohol were separated by flash chromatography over silica gel (pentane/ether, 1:1).

3.7. General method for lipase-catalyzed hydrolysis (analytical scale)

The substrate (1 mmol) was dissolved in a mixture of pH 7.0 phosphate buffer (36 mL) and DMSO (4 mL) containing 5% (w/v) silica gel at 40°C. The enzyme was added, and the pH was maintained at 7.0 by automatic titration with 1N aqueous NaOH using a pHstat Titroline *alpha* (Schott). The progress of the reaction was followed by analysis of samples taken from the reaction mixture at intervals by gas chromatography. When the reaction had stopped or the desired conversion was reached, the reaction mixture was filtered through silica gel and extracted three times with ether. The combined organic extracts were washed with sat. aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated in vacuo. The acetate and alcohol were separated by flash chromatography over silica gel (pentane/ether, 1:1).

3.8. Gram-scale resolution of (±)-1-(3′-furyl)-3-buten-1-ol (±)-1

Similar to the general procedure described above, (±)-**3** (7.28 g, 40.4 mmol) in phosphate buffer pH 7.0 (200 mL) and DMSO (20 mL) in the presence of lipase ASL (450 mg) and silica gel (6 g) afforded after 4 days at 40°C unreacted (*S*)-**3** (3.18 g, 44%; $[\alpha]_D^{25}=-65.9$ (*c* 1.06, CH_2Cl_2), 99% e.e.) and (*R*)-**1** (2.65 g, 48%; $[\alpha]_D^{25}=+26.4$ (*c* 1.96, CH_2Cl_2), 88% e.e.). Upon stirring with 2N aqueous NaOH (400 mL) at room temperature for 16 h, (*S*)-**3** (3.75 g, 20.8 mmol) underwent complete deacylation to give the corresponding alcohol (*S*)-**1** (2.88 g, 100%; $[\alpha]_D^{25}=-30.7$ (*c* 1.72, CH_2Cl_2), >95% e.e.).

3.9. Gram-scale resolution of (±)-2-(2′-furyl)propan-1-ol (±)-2

Similar to the general procedure described above, (±)-**4a** (1.60 g, 9.51 mmol) in pH 7.0 phosphate buffer (36 mL) and DMSO (4 mL) in the presence of lipase PPL (500 mg) and silica gel (2 g) afforded after 2 h at 40°C unreacted (*S*)-**4a** (280 mg, 18%; $[\alpha]_D^{25}=+5.3$ (*c* 1.75, $CHCl_3$), 98% e.e.) and (*R*)-**2** (760 mg, 63%, 10% e.e.). Upon stirring with K_2CO_3 (231 mg, 1.67 mmol) in methanol (5 mL) at room temperature for 2 h, (*S*)-**4a** (280 mg, 1.67 mmol) underwent complete deacylation to give the corresponding alcohol (*S*)-**2** (210 mg, 100%; $[\alpha]_D^{25}=+6.5$ (*c* 1.00, $CHCl_3$), >95% e.e.).

3.10. Camphor sultam route to (*S*)-2-(2′-furyl)propan-1-ol (*S*)-1

3.10.1. (2*R*)-*N*-(1′-Oxy-2′-(2″-furyl)ethyl)bornane-2,10-sultam 6. NaH (400 mg, 16.7 mmol) in dry toluene (10 mL) was treated with (2*R*)-bornane-2,10-sultam **5** (2.85 g, 13.2 mmol) dissolved in dry toluene (35 mL). After stirring for 0.5 h at room temperature, a solution of furan-2-yl-acetyl chloride (2.39 g, 16.5 mmol) in dry toluene (20 mL) was added dropwise. The mixture was stirred for 3 h at room temperature, diluted with water (5 mL) and extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography over silica gel (ethyl acetate/petrol ether, 1:1) to give **6** as a white solid (3.26 g, 76%); mp 108°C (ether); $[\alpha]_D^{20}=-112.3$ (*c* 1.02, $CHCl_3$); R_f 0.59 (ethyl acetate/petrol ether/ether, 2:2:1); IR (KBr): 1701, 1330, 1135 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (s, 3H), 1.13 (s, 3H),

1.32–1.44 (m, 2H), 1.83–1.90 (m, 3H), 1.90–2.17 (m, 2H), 3.44 (d, $J=13.8$ Hz, 1H), 3.51 (d, $J=13.8$ Hz, 1H), 3.87 (dd, $J=5.0$ Hz, $J=7.9$ Hz, 1H), 4.06 (d, $J=17.4$ Hz, 1H), 4.13 (d, $J=17.4$ Hz, 1H), 6.24 (dd, $J=0.9$ Hz, $J=3.1$ Hz, 1H), 6.31 (dd, $J=1.9$ Hz, $J=3.1$ Hz, 1H), 7.35 (dd, $J=0.9$ Hz, $J=1.9$ Hz, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 19.75 (q), 20.65 (q), 26.29 (t), 32.66 (t), 34.87 (t), 38.18 (t), 44.51 (d), 47.68 (s), 48.49 (s), 52.76 (t), 65.05 (d), 108.67 (d), 110.36 (d), 142.12 (d), 146.75 (s), 166.48 (s); MS (GC) m/z: 323 (41) [M^+], 81 (100); anal. calcd for $C_{16}H_{21}NO_4S$: C, 59.42; H, 6.54; N, 4.33. Found C, 59.40; H, 6.61; N, 4.51%.

3.10.2. (2*R*,2′*R*)-*N*-(1′-Oxy-2′-(2″-furyl)propyl)-bornane-2,10-sultam 7. To a solution of **6** (720 mg, 2.23 mmol) in dry THF (10 mL) was added $NaN(SiMe_3)_2$ (428 mg, 2.33 mmol) in dry THF (2.3 mL) dropwise over a period of 30 min at −78°C. The mixture was stirred for 1 h at −78°C, MeI (850 mg, 6.0 mmol) in HMPA (1 mL) was added, and the resultant solution was allowed to warm to room temperature and diluted with water. The aqueous layer was extracted with ethyl acetate, and the combined organic extracts were washed with water, brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography over silica gel (ethyl acetate/petrol ether, 1:3) to give **7** (710 mg, 94%) with 97% d.e. (GC). Recrystallization of this material from ether at room temperature afforded **7** (655 mg, 87%) as a single diastereomer according to capillary GC analysis; mp 130°C (ether); $[\alpha]_D^{20}=-65.7$ (c 0.47, $CHCl_3$); R_f 0.41 (ethyl acetate/petrol ether, 1:3); IR (KBr): 1695, 1317, 1110 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (s, 3H), 1.18 (s, 3H), 1.33–1.44 (m, 2H), 1.58 (d, $J=7.2$ Hz, 3H), 1.87–2.10 (m, 5H), 3.45 (d, $J=13.8$ Hz, 1H), 3.58 (d, $J=13.8$ Hz, 1H), 3.91 (dd, $J=5.3$ Hz, $J=7.4$ Hz, 1H), 4.48 (q, $J=7.2$ Hz, 1H), 6.23 (dd, $J=0.7$ Hz, $J=3.1$ Hz, 1H), 6.30 (dd, $J=1.9$ Hz, $J=3.1$ Hz, 1H), 7.35 (dd, $J=0.7$ Hz, $J=1.9$ Hz, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 17.09 (q), 19.85 (q), 20.83 (q), 26.39 (t), 32.83 (t), 38.29 (t), 39.83 (d), 44.62 (d), 47.79 (s), 48.43 (s), 53.04 (t), 65.31 (d), 106.96 (d), 110.13 (d), 141.97 (d), 152.32 (s), 171.97 (s); MS (GC) m/z: 337 (13) [M^+], 95 (100); anal. calcd for $C_{17}H_{23}NO_4S$: C, 60.51; H, 6.87; N, 4.15. Found C, 60.28; H, 7.06; N, 4.07%.

3.10.3. (*S*)-2-(2′-Furyl)propan-1-ol (*S*)-2 by reduction of 7. To a suspension of $LiAlH_4$ (67 mg, 1.77 mmol) in dry THF (6 mL) was slowly added a solution of **7** (590 mg, 1.75 mmol) in dry THF (12 mL) at room temperature under argon. After stirring for 1 h at room temperature, sat. aqueous Na_2SO_4 was added and the aqueous layer extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was treated with pentane at −30°C, and (2*R*)-bornane-2,10-sultam **5** (318 mg, 84%) was separated from the solution of the alcohol by filtration. After concentration of the pentane solution in vacuo, the crude product was purified by flash chromatography over silica gel (ether/petrol ether, 1:1) to give (+)-(*S*)-**2** (196 mg, 89%).

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group $P2_1$ (No. 4), $\lambda = 1.54178$ Å, $T = 223$ K, $\omega/2\theta$ scans, 5701 reflections collected ($\pm h$, $-k$, $\pm l$), $[(\sin\theta)/\lambda] = 0.62$ Å^{-1}, 3754 independent ($R_{int} = 0.086$) and 3638 observed reflections [$I \geq 2\sigma(I)$], 422 refined parameters, $R = 0.052$, $wR^2 = 0.148$, max. residual electron density 0.63 (–0.55) e Å^{-3}, Flack parameter 0.04(2), two independent molecules in the asymmetric unit, differences in the position of the furyl groups, hydrogens calculated and refined as riding atoms. Data set was collected with an Enraf–Nonius CAD4 diffractometer. Programs used: data collection EXPRESS (Nonius, B. V., 1994), data reduction MolEN (Fair, K. Enraf–Nonius, B. V., 1990), structure solution SHELXS-86 (Sheldrick, G. M. *Acta Crystallogr*. **1990**, *A46*, 467–473), structure refinement SHELXL-97 (Sheldrick, G. M. Universität Göttingen, 1997). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 163835. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: int. code +44(1223)336-033, e-mail: deposit@ccdc.cam.ac.uk].

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