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Enantioselective synthesis of 2-alkylidenetetrahydrofurans based on a 'cyclization/enzymatic resolution' strategy

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Abstract—Enantiomerically pure 2-alkylidenetetrahydrofurans have been prepared by $TiCl_4$ mediated enantiospecific reactions of 1,3-bis-silyl enol ethers with enantiomerically pure epichlorohydrin. In addition, the enzymatic kinetic resolution of 2-alkylidenetetrahydrofurans, using *Candida antarctica* lipase B (CAL-B), was studied. Enzymatic kinetic resolution of monocyclic 5-vinyl-2-alkylidenetetrahydrofuran with CAL-B afforded the enantiomerically pure ester with 97% ee. For a bicyclic 2-alkylidenetetrahydrofuran, this proceeded with excellent enantioselectivity (E >100) affording the enantiomerically pure acid with 98% ee. 2-Alkylidenetetrahydrofurans were prepared by [3+2] cyclization reactions of 1,3-dicarbonyl dianions ('free dianions') or 1,3-bis-silyl enol ethers ('masked dianions').

1. Introduction

2-Alkylidenetetrahydrofurans represent useful synthetic building blocks.[1,2] A variety of synthetic transformations of 2-alkylidenetetrahydrofurans have been reported: for example, cycloadditions,[1a–d] nucleophilic additions,[1e,f] cyclopropanations,[1g] and oxidative carbonylations.[1h–j] The hydrogenation[1k,2h,i] of 2-alkylidenetetrahydrofurans has been applied to the synthesis of natural products, such as methyl nonactate and nonactin.[2,3] The spiroketal chalcogran has been prepared from a bicyclic 2-alkylidenetetrahydrofuran.[4] In recent years, we and others have reported a number of one-pot syntheses of 2-alkylidenetetrahydrofurans by cyclization of 1,3-dicarbonyl dianions or 1,3-bis-silyl enol ethers with 1,2-dielectrophiles,[5,6a,b] as well as using other methods.[6c–h] 2-Alkylidenetetrahydrofurans have been functionalized by lithiation and subsequent alkylations[6b] and by bromination of the exocyclic double bond and subsequent cross-coupling reactions.[7] Recently, the synthesis of 6-bromo-3-oxoalkanoates and functionalized benzofurans by reaction of 2-alkylidenetetrahydrofurans with boron tribromide (BBr_3) has been reported.[8] In addition, furans and benzofurans have been prepared by oxidation[9] and elimination[10] reactions of 2-alkylidenetetrahydrofurans. To date, we have reported the synthesis of nonchiral or racemic 2-alkylidenetetrahydrofurans. Herein, we report, for the first time, the synthesis of enantiomerically pure 2-alkylidenetetrahydrofurans by enantiospecific $TiCl_4$-mediated cyclization of 1,3-bis-silyl enol ethers with enantiomerically pure epichlorohydrin; these transformations provide a significant extension of our methodology reported some years ago.[11] In addition, we report what is, to the best of our knowledge, the first enzymatic kinetic resolution of 2-alkylidenetetrahydrofurans. In these reactions, *Candida antarctica* lipase B (CAL-B) has been used. The basidomycetous yeast *C. antarctica* produces two different lipases named A and B. CAL-B is very active toward a broad range of esters, amides and thiols and catalyzes a variety of regio- and enantioselective reactions. In particular, CAL-B was shown to be a very versatile biocatalyst for the synthesis of enantiomerically pure compounds.[12]

2. Results and discussion

2.1. Reaction of 1,3-bis-silyl enol ethers with enantiomerically pure epichlorohydrin

2-Alkylidenetetrahydrofurans by $TiCl_4$ mediated the cyclization of 1,3-bis-silyl enol ethers with racemic epoxides.[11]

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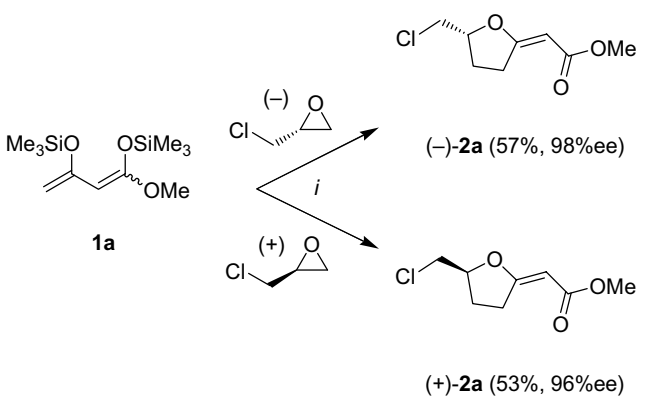


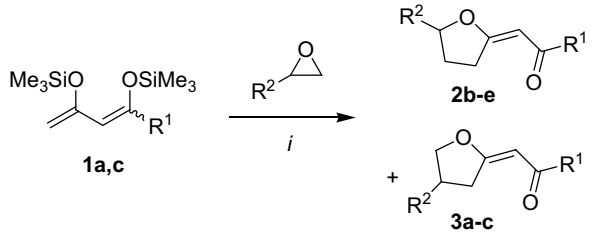
Scheme 1. Cyclizations of 1,3-bis-silyl enol ethers with enantiomerically pure epichlorohydrin. Reagents and conditions: (i) $TiCl_4$ (2 equiv), 4 Å MS, CH_2Cl_2, −78→20 °C, 14 h, then at 20 °C, 4 h.

We have shown that, in most cases, the asymmetric carbon atom of chiral racemic epoxides is not involved in the mechanism of the reaction. Therefore, we studied stereospecific reactions of enantiomerically pure epoxides. The $TiCl_4$ mediated cyclization of 1,3-bis-silyl enol ether **1a** with commercially available (*R*)-(−)- and (*S*)-(+)-epichlorohydrin afforded the enantiomerically pure methyl (5-chloromethyldihydrofuran-2(3*H*)-ylidene)acetates (*R*)-(−)-**2a** and (*S*)-(+)-**2a**, respectively, with excellent enantiospecificity. No loss of enantiomeric excess was observed during the cyclization. As expected from our previous results,[11] the cyclizations proceeded with very good chemo-, regio-, and *E*-diastereostereoselectivity (Scheme 1).

2.2. Enzymatic kinetic resolution of racemic 2-alkylidenetetrahydrofurans

The $TiCl_4$ mediated cyclization of 1,3-bis-silyl enol ether **1a** with propeneoxide, 1,2-epoxybutane, and 1,2-epoxyhexane afforded the racemic 2-alkylidenetetrahydrofurans **2b–d**; the regioisomers **3a–c** were also obtained (Scheme 2 and Table 1). The formation of regioisomers **3** strongly depended on the reaction conditions and quality of the starting materials. We have reported earlier the synthesis of **2e** by regioselective cyclization of 1,3-bis-silyl enol ether **1c** with epichlorohydrin.[11]

The cyclization of 1-bromo-2-chloroethane **4** with dilithiated ethyl 3-oxoheptanoate **5**, prepared by the condensation of ethyl acetoacetate with 1-iodopropane,[6b] afforded

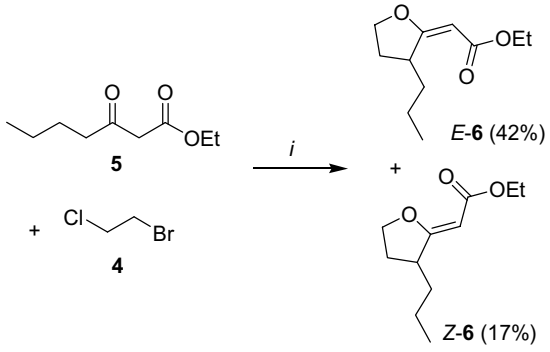


Scheme 2. Synthesis of **2b–e** and **3a–c**. Reagents and conditions: (i) $TiCl_4$ (2 equiv), 4 Å MS, CH_2Cl_2, −78→20 °C, 14 h, then at 20 °C, 4 h.

Table 1. Products and yields of **2b–e** and **3a–c**

2	3	R^1	R^2	% *E*-**2**[a]	% *Z*-**2**[a]	% **3**[a]
b	**a**	OMe	Me	33	9	18
c	**b**	OMe	Et	48	9	13
d	**c**	OMe	Bu	36	—	23
e		OEt	CH_2Cl	52[b]	—	—

[a] Isolated yields.
[b] Known compound (Ref. 11).



Scheme 3. Synthesis of **6**. Reagents and conditions: (i) (1) LDA (2.3 equiv), THF, 0 °C, 1 h; (2) $Br(CH_2)_2Cl$, −78→20 °C, 14 h, then at 20 °C, 24 h.

the 2-alkylidenetetrahydrofuran **6**, as a separable mixture of *E*/*Z* isomers (Scheme 3).

For the enzymatic kinetic resolution reactions[13] of 2-alkylidenetetrahydrofurans, several hydrolases were studied (Table 2). Reactions of 5-alkyl-2-alkylidenetetrahydrofurans *E*-**2c** with CAL-B and BCL (AmanoPS) and **2e** with pig liver esterase (PLE) and CAL-B were carried out. Unfortunately, none of these enzyme reactions gave satisfactory kinetic resolutions for *E*-**2c** and **2e**.

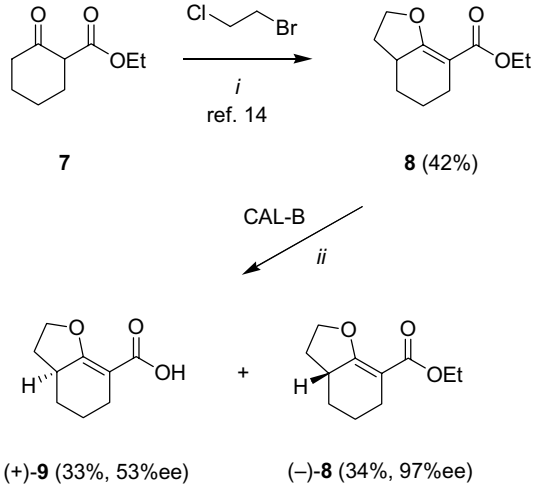
The cyclization of dilithiated ethyl 2-oxocyclohexanecarboxylate **7** with 1-bromo-2-chloroethane afforded the known[9] ethyl 2,3,3a,4,5,6-hexahydrobenzofuran-7-carboxylate **8** (Scheme 4). The analytical-scale enzymatic kinetic resolution of **8** was highly enantioselective using CAL-B (Table 2). The preparative scale enzymatic kinetic resolution of **8** was then studied (Scheme 4 and Table 3): CAL-B-catalyzed enantioselective hydrolysis of bicyclic 2-alkylidenetetrahydrofuran **8** afforded (−)-**8** (34%, 97% ee) and the acid (+)-**9** (33%, 53% ee) (entry 3). The reaction was repeated three times on a preparative scale and better ee (enantiomeric excess) values have been observed for reactions 1 and 2. Unfortunately, the resolution products of entries 1 and 2 racemized during purification by column chromatography (silica gel). The racemization presumably proceeds by activation of (−)-**8** by silica gel (intermediate **A**) and subsequent double bond migration to form intermediate **B** (Scheme 5). For entry 3, separation of the resolution products was successfully carried out by simple extraction at optimized pH ranges without racemization.

The reaction of dilithiated ethyl acetoacetate with 1,4-dibromobut-2-ene afforded, as reported earlier, 5-vinyl-2-alkylidenetetrahydrofuran **10** as a separable mixture of

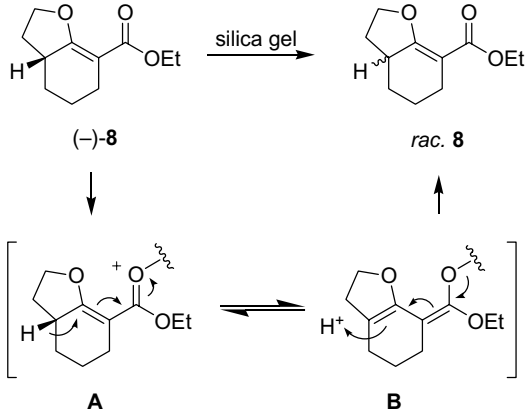
Table 2. Analytical-scale enzymatic kinetic resolution reactions

Enzyme	Substrate	Conversion (%)	Time (h)[a]	eeS (%)[b]	eeP (%)[b]	*E*-Value
PLE	**2e**	50	48	4	1	1
CAL-B	*E*-**2c**	36	25	16	28	2
CAL-B	**2e**	7	25	<1	9	1
CAL-B	**8**	34	25	51	98	>100
CAL-B	*E*-**10**	—	25	>99	n.d.[c]	—
AmanoPS	*E*-**2c**	20	48	<1	3	1
AmanoPS	*E*-**10**	5	48	<1	9	5

[a] Reaction time.
[b] Calculated from gas chromatograms (GC).
[c] n.d.: not detected.



Scheme 4. Enzymatic kinetic resolution of **8**. Reagents and conditions: (i) (1) LDA (2.3 equiv), THF, 0 °C, 1 h; (2) $Br(CH_2)_2Cl$, −78→−20 °C, 6 h; (3) −20 °C, 12 h; (4) −20→20 °C, 12 h; (5) 20 °C, 12 h; (ii) (Table 3, entry 3) CAL-B, phosphate buffer (50 mM, pH 7.5), toluene (10% v/v), 37 °C, 96 h, assignment of the absolute configuration is arbitrary.



Scheme 5. Possible mechanism for the racemization of (−)-**8** on silica gel.

E/*Z* isomers (Scheme 6).[6a] The *Z*-configured isomer was formed first and subsequently underwent an isomerization into the thermodynamically more stable *E*-configured isomer. The analytical-scale enzyme reactions of *E*-**10** (Table 2) were carried out with CAL-B and AmanoPS. Again, only CAL-B gave an excellent kinetic resolution, affording the remaining substrate with >99% ee. The preparative scale enzymatic kinetic resolution of *E*-**10** with CAL-B afforded (−)-*E*-**10** (48%, 97% ee) and acid (−)-**11** (36%) (Scheme 6 and Table 3, entry 5). The enantiomeric excess of acid (−)-**11** could not be determined by GC measurements, due to reaction of the vinyl functionality with diazomethane.[14] The latter has been used to monitor the hydrolysis products on GC by conversion of the acid to the corresponding methyl ester [acid+diazomethane→methyl ester].

To monitor the enantioselectivity in the enzymatic kinetic resolution of the 2-alkylidenetetrahydrofurans, gas chromatography (GC) analysis was developed (Table 4).

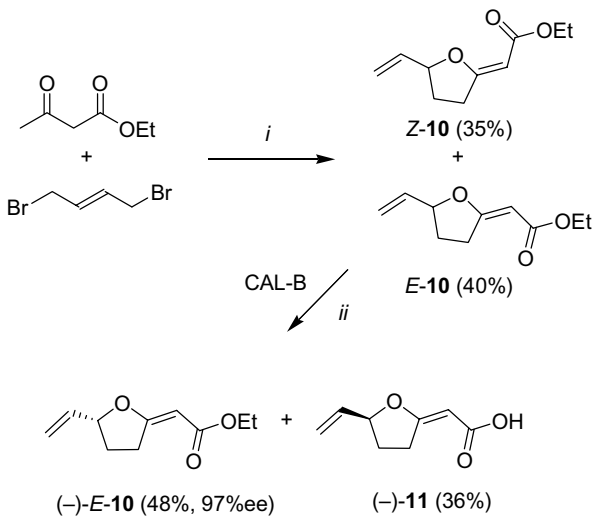
3. Conclusion

In conclusion, enantiomerically pure 2-alkylidenetetrahyrofurans have been prepared by stereospecific reactions of 1,3-bis-silyl enol ethers with enantiomerically pure epoxides. Analytical-scale enzymatic kinetic resolution of 2-alkylidenetetrahydrofurans, prepared by [3+2] cycliza-

Table 3. Preparative scale enzymatic resolution reactions

Entry	Substrate (mg)	CAL-B (mg)	Conversion (%)	Time (h)	eeS (%)[a]	eeP (%)[a,b]	*E*-Value
1[c]	**8** (50)	22	52	96	23 (92)	n.d. (84)	38
2[c]	**8** (50)	25	52	96	(98)	n.d. (87)	68
3	**8** (50)	25	64	96	>97	53	12
4	*E*-**10** (50)	20	—	168	93	n.d.	—
5	*E*-**10** (50)	25	—	200	97	n.d.	—

[a] For isolated products.
[b] n.d.: not detected.
[c] Ee of crude product, racemization during purification by column chromatography.



Scheme 6. Enzymatic kinetic resolution of *E*-**10**. Reagents and conditions: (i) (1) LDA (2.3 equiv), THF, 0 °C, 1 h; (2) $BrCH_2CH{=}CHCH_2Br$, −78→20 °C, 14 h, then at 20 °C, 24 h; (ii) (Table 3, entry 5) CAL-B, phosphate buffer (50 mM, pH 7.5), toluene (10% v/v), 37 °C, 200 h, the assignment of absolute configuration is arbitrary.

Table 4. GC-analysis of 2-alkylidenetetrahydrofurans

Substrate	Chiral column[a]	Temperature (°C)	Retention time (min)[d]			
			Substrate (ester)		Product (acid)[b,c]	
E-**2b**	2	140	7.6	11.2	—	—
E-**2c**	2	140	9.3	13.0	—	—
2d	2	140	18.6	21.1	—	—
2e	2	120 °C//5°/min// 180 °C, 15 min	16.3	17.2	5.2	5.4
3c	2	140	24.4	27.5	—	—
E-**6**	1	120	12.7	13.8	—	—
8	1	150	16.8	17.6	14.2	15.1
E-**10**	2	140	12.2	15.3	6	7

[a] Hydrodex®-β-3P 1. [Heptakis-(2,6-di-*O*-methyl-3-*O*-pentyl)-β-cyclodextrin]; 2. [Heptakis-(2,3)-di-*O*-acetyl-6-*O*-TBDMS-β-cyclodextrin].
[b] Product of enzyme reactions.
[c] Retention times for methyl ester of hydrolysis products [acid+diazomethane→methyl ester].
[d] The absolute configurations of all compounds are unknown.

tions of 1,3-dicarbonyl dianions ('free dianions') or 1,3-bis-silyl enol ethers ('masked dianions') with various 1,2-dielectrophiles, has been studied with various esterases and lipases. These results were confirmed by the preparative scale kinetic resolution of 2-alkylidenetetrahydrofurans using *C. antarctica* lipase B (CAL-B).

4. Experimental

4.1. General experimental

All solvents were dried by standard methods and all reactions carried out under an inert atmosphere. For the ^1H and ^{13}C NMR spectra, the deuterated solvents indicated were used. Mass spectral data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, H_2O or DCI, NH_3), or electrospray ionization (ESI). For preparative scale chromatography, silica gel (60–200 mesh) was used. For analytical-scale enzymatic reactions, thermo-shaker (Eppendorf, Hamburg, Germany) was used. GC-14A gas chromatograph, C-R5A and C-R3A Chromatopac/Integrator, Shimadzu (Duisburg, Germany) were used for analytical gas chromatograms (GC). Chiral columns used for GC: Hydrodex®-β-3P 1. [Heptakis-(2,6-di-*O*-methyl-3-*O*-pentyl)-β-cyclodextrin] (25 m, 0.25 mm), 2. [Heptakis-(2,3)-di-*O*-acetyl-6-*O*-TBDMS-β-cyclodextrin] (25 m, 0.25 mm). Polarimeter type 241, Perkin Elmer was used for optical rotation measurements.

4.2. General procedure for the reaction of 1,3-bis-silyl enol ethers with epoxides

To a CH_2Cl_2-solution (4 mL/mmol) of 1,3-bis-silyl enol ether **1** (1.0 equiv) and the epoxide (1.2 equiv), in the presence of molecular sieves (4 Å), $TiCl_4$ (2.0 equiv) was added at −78 °C. The solution was stirred for 4 h at −78 °C; subsequently, the temperature was allowed to rise to 20 °C for 14 h and the solution stirred for 3 h at 20 °C. The molecular sieves were filtered-off and washed with CH_2Cl_2. To the solution, a saturated aqueous solution of $NaHCO_3$ was added, the organic layer was separated, and the aqueous layer repeatedly extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc) to give either **2** or **3**.

4.2.1. Methyl (−)-(2*E*)-[(5*R*)-5-(chloromethyl)dihydrofuran-2(3*H*)-ylidene]acetate (*R*)-(−)-2a. Starting with **1a** (2.605 g, 10 mmol), (*R*)-(−)-epichlorohydrin (1.110 g, 12 mmol), and $TiCl_4$ (2.2 mL, 20 mmol) in CH_2Cl_2 (75 mL, 4 Å molecular sieves), (*R*)-(−)-**2a** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 100:1→1:1) as a colorless oil (1.079 g, 57%). GC (column 2, 140 °C): retention time (min) = 17.1, 98.3% ee. $[\alpha]_D^{20} = -66.1$ (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 1.97$–2.06 (m, 1H, CH_2 at C-4), 2.23–2.32 (m, 1H, CH_2 at C-4), 3.00–3.13 (m, 1H, CH_2 at C-3), 3.25–3.38 (m, 1H, CH_2 at C-3), 3.64 (d, $J = 5.1$ Hz, 2H, CH_2–Cl), 3.67 (s, 3H, OCH_3), 4.62–4.70 (m, 1H, OCH at C-5), 5.35 (t, $J = 1.8$ Hz, 1H, CH=C). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta_C = 25.8$ (C-3), 29.1 (C–4, CH_2), 44.5 (CH_2Cl), 49.8 (OCH_3), 81.2 (C-5, OCH), 89.0 (*C*H=C), 167.8 (O=C—O), 174.7 (O—*C*=CH). IR (neat, cm^{-1}): $\tilde{\nu} = 2954$ (m), 1704 (s), 1642 (s), 1439 (s), 1365 (s), 1295 (m), 1246 (m), 1189 (s), 1121 (s), 1047 (s), 828 (m). MS (EI, 70 eV): *m*/*z* (%) = 192 (M^+ [^{37}Cl], 5), 190 (M^+ [^{35}Cl], 17), 161 (16), 159 (49), 155 (2), 141 (4), 123 (10), 109 (5), 69 (100). HRMS (ESI): Calcd for $C_8H_{11}ClO_3$ [M^+]: 192.9885 (^{37}Cl), 190.0391 (^{35}Cl). Found: 192.9883 (^{37}Cl), 190.0387 (^{35}Cl).

4.2.2. Methyl (+)-(2*E*)-[(5*S*)-5-(chloromethyl)dihydrofuran-2(3*H*)-ylidene]acetate (*S*)-(+)-2a. Starting with **1a** (2.605 g, 10 mmol), (*S*)-(+)-epichlorohydrin (1.110 g, 12 mmol), and $TiCl_4$ (2.2 mL, 20 mmol) in CH_2Cl_2 (75 mL, 4 Å molecular sieves), (*S*)-(+)-**2a** was isolated after

chromatography (silica gel, *n*-hexane/EtOAc = 100:1→1:1) as a colorless oil (1.005 g, 53%). GC (column 2, 140 °C): retention time (min) = 16.3, 96.1% ee. $[\alpha]_D^{20} = +63.5$ (*c* 1, $CHCl_3$). Spectral data are the same as given above for (*R*)-(−)-**2a**.

Synthesis of **2b** and **3a**: Starting with **1a** (7.814 g, 30 mmol), propenoxide (2.112 g, 36 mmol), and $TiCl_4$ (6.6 mL, 60 mmol) in CH_2Cl_2 (250 mL, 4 Å molecular sieves), **3a** (0.826 g, 18%), *E*-**2b** (1.546 g, 33%), and *Z*-**2b** (0.437 g, 9%) were isolated after chromatography (silica gel, *n*-hexane/EtOAc = 100:1→1:1) as pale yellow, pale yellowy and yellow oils, respectively.

4.2.3. Methyl (4-methyldihydrofuran-2(3*H*)-ylidene)acetate 3a. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.11$ (d, $J = 6.3$ Hz, 3H, CH_3), 2.52 (oct, $J = 6.9$ Hz, 1H, CH at C-4), 2.69 (ddd, $J = 17.7$, 6.9, 1.8 Hz, 1H, CH_2 at C-3), 3.33 (dd, $J = 6.9$, 1.8 Hz, 1H, CH_2 at C-3), 3.66 (s, 3H, OCH_3), 3.78 (dd, $J = 8.4$, 6.6 Hz, 1H, OCH_2 at C-5), 4.29 (dd, $J = 8.4$, 6.9 Hz, 1H, OCH_2 at C-5), 5.30 (t, $J = 1.8$ Hz, 1H, CH=C). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta_C = 17.2$ (CH_3), 31.8 (C-3, CH_2), 38.3 (C–4, CH), 50.5 (OCH_3), 77.7 (C-5, OCH_2), 89.6 (*C*H=C), 168.9 (O=C—O), 176.7 (O—*C*=CH). IR (neat, cm^{-1}): $\tilde{\nu} = 2975$ (m), 1704 (s), 1640 (s), 1441 (m), 1389 (m), 1244 (m), 1181 (m), 1120 (s), 1046 (s), 826 (m). MS (EI, 70 eV): *m*/*z* (%) = 156 (M^+, 50), 139 (27), 125 (89), 111 (45), 69 (100). Anal. Calcd for $C_8H_{12}O_3$ (156.179): C, 61.52; H, 7.74. Found: C, 61.41; H, 7.40.

4.2.4. Methyl (5-methyldihydrofuran-2(3*H*)-ylidene)acetate *E*-2b. GC (column 2, 140 °C): retention times (min) = 7.6, 11.2. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.36$ (d, $J = 6.3$ Hz, 3H, CH_3), 1.60–1.72 (m, 1H, CH_2 at C-4), 2.17–2.29 (m, 1H, CH_2 at C-4), 2.90–3.02 (m, 1H, CH_2 at C-3), 3.26–3.39 (m, 1H, CH_2 at C-3), 3.66 (s, 3H, OCH_3), 4.53 (sext, $J = 6.3$ Hz, 1H, OCH at C-5), 5.27 (t, $J = 1.5$ Hz, 1H, CH=C). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta_C = 20.3$ (CH_3), 30.7 (C-3), 31.0 (C–4, CH_2), 50.6 (OCH_3), 80.3 (C-5, OCH), 88.7 (*C*H=C), 169.1 (O=C—O), 176.8 (O—*C*=CH). IR (neat, cm^{-1}): $\tilde{\nu} = 2968$ (m), 1740 (s), 1708 (s), 1638 (s), 1442 (m), 1362 (m), 1242 (s), 1194 (s), 1175 (s), 1121 (s), 1048 (s). MS (EI, 70 eV): *m*/*z* (%) = 156 (M^+, 45), 139 (23), 125 (87), 111 (35), 69 (100). Anal. Calcd for $C_8H_{12}O_3$ (156.179): C, 61.52; H, 7.74. Found: C, 61.42; H, 7.56.

4.2.5. Methyl (5-methyldihydrofuran-2(3*H*)-ylidene)acetate *Z*-2b. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.45$ (d, $J = 6.3$ Hz, 3H, CH_3), 1.61–1.70 (m, 1H, CH_2 at C-4), 2.15 (m, $J = 6.9$ Hz, 1H, CH_2 at C-4), 2.71–2.77 (m, 2H, CH_2 at C-3), 3.67 (s, 3H, OCH_3), 4.74 (dsext, $J = 6.3$, 1.8 Hz, 1H, OCH at C-5), 4.84 (t, $J = 1.2$ Hz, 1H, CH=C). IR (neat, cm^{-1}): $\tilde{\nu} = 2978$ (m), 2884 (m), 1651 (s), 1440 (s), 1405 (s), 1124 (s). MS (EI, 70 eV): *m*/*z* (%) = 156 (M^+, 20), 125 (30), 69 (100). HRMS (EI): Calcd for $C_8H_{12}O_3$ [M^+]: 156.0781. Found: 156.0783.

Synthesis of **2c** and **3b**: Starting with **1a** (7.814 g, 30 mmol), 1,2-epoxybutane (3.1 mL, 36 mmol), and $TiCl_4$ (6.6 mL, 60 mmol) in CH_2Cl_2 (300 mL, 4 Å molecular sieves), **3b** (0.656 g, 13%), *E*-**2c** (2.467 g, 48%) and *Z*-**2c** (0.458 g, 9%) were isolated after chromatography (silica gel, *n*-hexane/EtOAc = 100:1→1:1) as pale yellow, pale yellowy and yellow oils, respectively.

4.2.6. Methyl (4-ethyldihydrofuran-2(3*H*)-ylidene)acetate 3b. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.96$ (t, $J = 7.5$ Hz, 3H, CH_3), 1.46 (quint, $J = 7.5$ Hz, 2H, CH_2CH_3), 2.32 (sept, $J = 7.5$ Hz, 1H, CH at C-4), 2.66–2.75 (ddd, $J = 18.0$, 7.5, 1.8 Hz, 1H, CH_2 at C-3), 3.27–3.37 (ddd, $J = 18.0$, 8.1, 1.5 Hz, 1H, CH_2 at C-3), 3.66 (s, 3H, OCH_3), 3.85 (dd, $J = 8.7$, 7.2 Hz, 1H, OCH_2 at C-5), 4.31 (dd, $J = 8.7$, 7.2 Hz, 1H, OCH_2 at C-5), 5.29 (t, $J = 1.8$ Hz, 1H, CH=C). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta_C = 13.3$ (CH_3), 23.5, 30.4 (C-3, CH_2), 38.3 (C–4, CH), 50.5 (OCH_3), 76.4 (C-5, OCH_2), 88.7 (*C*H=C), 168.9 (O=C—O), 176.7 (O—*C*=CH). IR (neat, cm^{-1}): $\tilde{\nu} = 2963$ (m), 1706 (m), 1644 (s), 1439 (m), 1121 (s), 1046 (m). MS (EI, 70 eV): *m*/*z* (%) = 170 (M^+, 18), 141 (99), 109 (34), 81 (13), 69 (100). HRMS (EI): Calcd for $C_9H_{14}O_3$ [M^+]: 170.0937. Found: 170.0937.

4.2.7. Methyl (5-ethyldihydrofuran-2(3*H*)-ylidene)acetate *E*-2c. GC (column 2, 140 °C): retention times (min) = 9.3, 13.0. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.98$ (t, $J = 7.5$ Hz, 3H, CH_3), 1.55–1.76 (m, 3H, CH_2CH_3, CH_2 at C-4), 2.11–2.22 (m, 1H, CH_2 at C-4), 2.89–3.02 (m, 1H, CH_2 at C-3), 3.25–3.38 (m, 1H, CH_2 at C-3), 3.66 (s, 3H, OCH_3), 4.29–4.36 (m, 1H, OCH at C-5), 5.27 (t, $J = 1.5$ Hz, 1H, CH=C). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta_C = 9.4$ (CH_3), 27.5, 28.4 (C-3), 30.2 (C–4, CH_2), 50.2 (OCH_3), 85.2 (C-5, OCH), 88.7 (*C*H=C), 168.8 (O=C—O), 176.8 (O—*C*=CH). IR (neat, cm^{-1}): $\tilde{\nu} = 2974$ (m), 1703 (s), 1641 (s), 1374 (m), 1115 (s), 1048 (m). MS (EI, 70 eV): *m*/*z* (%) = 170 (M^+, 70), 125 (100), 83 (81). Anal. Calcd for $C_9H_{14}O_3$ (170.206): C, 63.51; H, 8.29. Found: C, 63.80; H, 7.99.

4.2.8. Methyl (5-ethyldihydrofuran-2(3*H*)-ylidene)acetate *Z*-2c. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.02$ (t, $J = 7.5$ Hz, 3H, CH_3), 1.60–1.73 (m, 2H, CH_2CH_3), 1.80–1.91 (m, 1H, CH_2 at C-4), 2.08–2.18 (m, 1H, CH_2 at C-4), 2.70–2.75 (m, 2H, CH_2 at C-3), 3.67 (s, 3H, OCH_3), 4.48–4.57 (m, 1H, OCH at C-5), 4.83 (t, $J = 1.2$ Hz, 1H, CH=C). IR (neat, cm^{-1}): $\tilde{\nu} = 2972$ (m), 2938 (m), 1738 (s), 1704 (s), 1641 (m), 1458 (m), 1376 (m), 1228 (m), 1114 (s), 1046 (s). MS (EI, 70 eV): *m*/*z* (%) = 170 (M^+, 11), 142 (65), 125 (76), 81 (19), 69 (100). HRMS (EI): Calcd for $C_9H_{14}O_3$ [M^+]: 170.0937. Found: 170.0937.

Synthesis of **2d** and **3c**: Starting with **1a** (7.814 g, 30 mmol), 1,2-epoxyhexane (3.718 g, 36 mmol), and $TiCl_4$ (6.6 mL, 60 mmol) in CH_2Cl_2 (250 mL, 4 Å molecular sieves), **3c** (1.359 g, 23%), and **2d** (2.133 g, 36%) were isolated after chromatography (silica gel, *n*-hexane/EtOAc = 100:1→1:1) as pale yellowy oils.

4.2.9. Methyl (4-butyldihydrofuran-2(3*H*)-ylidene)acetate 3c. GC (column 2, 140 °C): retention times (min) = 24.4, 27.5. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.40$ (t, $J = 7.2$ Hz, 3H, CH_3), 1.75–1.95 (m, 6H, $3 \times CH_2$ of *n*-Bu), 2.87 (sept, $J = 7.2$ Hz, 1H, CH at C-4), 3.12–3.22

(ddd, $J = 18.3$, 7.8, 1.8 Hz, 1H, CH_2 at C-3), 3.78–3.87 (ddd, $J = 18.3$, 7.8, 1.5 Hz, 1H, CH_2 at C-3), 4.14 (s, 3H, OCH_3), 4.31 (dd, $J = 8.4$, 7.2 Hz, 1H, OCH_2 at C-5), 4.79 (dd, $J = 8.4$, 7.2 Hz, 1H, OCH_2 at C-5), 5.77 (t, $J = 1.8$ Hz, 1H, CH=C). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta_C = 13.8$ (CH_3), 22.5, 30.0, 32.1, 36.6 (C-3, CH_2), 37.2 (C–4, CH), 50.5 (OCH_3), 76.3 (C-5, OCH_2), 89.3 (*C*H=C), 169.0 (O=C—O), 176.9 (O—*C*=CH). IR (neat, cm^{-1}): $\tilde{\nu} = 2956$ (s), 2932 (m), 1707 (m), 1692 (m), 1643 (s), 1438 (m), 1253 (s), 1129 (s), 1048 (m), 1011 (s), 846 (s), 789 (s). MS (EI, 70 eV): m/z (%) = 198 (M^+, 100), 183 (7), 167 (40), 140 (33), 125 (29). The exact molecular mass $m/z = 198.1256 \pm 2$ ppm [M^+] for $C_{11}H_{18}O_3$ was confirmed by HRMS (EI, 70 eV).

4.2.10. Methyl (5-butyldihydrofuran-2(3*H*)-ylidene)acetate 2d. GC (column 2, 140 °C): retention times (min) = 18.6, 21.1. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.92$ (t, $J = 7.2$ Hz, 3H, CH_3), 1.25–1.47 (m, 4H, $2 \times CH_2$ of *n*-Bu), 1.50–1.75 (m, 3H, CH_2 of *n*-Bu, CH_2 at C-4), 2.12–2.24 (m, 1H, CH_2 at C-4), 2.88–3.01 (m, 1H, CH_2 at C-3), 3.25–3.36 (m, 1H, CH_2 at C-3), 3.66 (s, 3H, OCH_3), 4.38 (quint, $J = 7.8$ Hz, 1H, OCH at C-5), 5.27 (t, $J = 1.5$ Hz, 1H, CH=C). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta_C = 13.9$ (CH_3), 22.5, 27.7, 29.1, 30.5 (C-3), 34.6 (C–4, CH_2), 50.1 (OCH_3), 84.3 (C-5, OCH), 89.1 (*C*H=C), 168.8 (O=C—O), 176.6 (O—*C*=CH). IR (neat, cm^{-1}): $\tilde{\nu} = 2963$ (s), 2932 (s), 1710 (s), 1687 (m), 1648 (s), 1365 (m), 1215 (m), 1170 (s), 1142 (s), 1029 (s). MS (EI, 70 eV): m/z (%) = 198 (M^+, 24), 183 (43), 167 (46), 125 (31), 69 (100). Anal. Calcd for $C_{11}H_{18}O_3$ (198.259): C, 66.64; H, 9.15. Found: C, 66.34; H, 9.35.

4.2.11. Ethyl (5-chloromethyldihydrofuran-2(3*H*)-ylidene)-acetate 2e. The synthesis of **2e** has been previously reported.[11] GC (column 2, 120 °C//5°/min//180 °C, 15 min): retention times (min) = 16.3, 17.2.

4.3. General procedure for the [3+2] cyclization of 1,3-dicarbonyl dianions with 1-bromo-2-chloroethane and *trans*-1,4-dibromo-2-butene[6a,b]

A THF solution of LDA was prepared by addition of *n*-BuLi (2.5 equiv) to a THF solution (10 mL/mmol) of diisopropylamine (2.5 equiv) at 0 °C. To the LDA solution, the 1,3-dicarbonyl compound (1.0 equiv) was added at 0 °C and the solution was stirred at 0 °C for 2 h. To the solution, 1-bromo-2-chloroethane (or *trans*-1,4-dibromo-2-butene) (1.2 equiv) was added at −78 °C. Subsequently, the temperature was allowed to rise to 20 °C over 14 h and the solution stirred at 20 °C for 12 h. To the reaction mixture, an aqueous solution of HCl (10%, 10 mL/mmol) was added and the mixture was extracted with diethylether (2×10 mL/mmol) and dichloromethane (3×10 mL/mmol). The combined organic extracts were dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc) to give 2-alkylidenetetrahydrofuran.

4.3.1. Ethyl (3-propyldihydrofuran-2(3*H*)-ylidene)acetate 6. Starting with ethyl 3-oxoheptanoate **5** (3.200 g, 18.6 mmol), diisopropylamine (6.53 mL, 46.5 mmol), *n*-BuLi (29.2 mL, 46.5 mmol, 15% in *n*-hexane), and 1-bromo-2-chloroethane (1.85 mL, 22.3 mmol) in THF (100 mL), *E*-**6** (1.546 g, 42%), and *Z*-**6** (0.636 g, 17%) were isolated after chromatography (silica gel, *n*-hexane/EtOAc = 100:1→1:1) as yellow oils (combined yield: 59%). Compound *E*-**6**: GC (column 1, 120 °C): retention times (min) = 12.7, 13.8. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.96$ (t, $J = 7.2$ Hz, 3H, CH_3 of *n*-Pr), 1.25 (t, $J = 7.2$ Hz, 3H, OCH_2CH_3), 1.31–1.49 (m, 3H, $2 \times CH_2$ of *n*-Pr), 1.62–1.71 (m, 1H, CH_2 of *n*-Pr), 1.97 (dd, $J = 12.6$, 6.3 Hz, 1H, CH_2 at C-4), 2.04–2.15 (m, 1H, CH_2 at C-4), 3.60–3.65 (m, 1H, CH at C-3), 4.09–4.20 (m, 3H, OCH_2CH_3, OCH_2 at C-5), 4.26–4.32 (m, 1H, OCH_2 at C-5), 5.23 (s, 1H, CH=C). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta_C = 13.9$, 14.4 (CH_3), 20.7, 29.4, 34.6 (C–4, CH_2), 43.6 (C-3, CH), 59.2 (OCH_2), 70.1 (C-5, OCH_2), 89.2 (*C*H=C—O), 168.0 (O=C—O), 180.7 (O—*C*=CH). IR (neat, cm^{-1}): $\tilde{\nu} = 2959$ (s), 2934 (s), 1740 (s), 1644 (s), 1455 (m), 1406 (m), 1117 (s), 1033 (m). MS (EI, 70 eV): m/z (%) = 198 (M^+, 24), 169 (45), 153 (100). The exact molecular mass $m/z = 198.1256 \pm 2$ ppm [M^+] for $C_{11}H_{18}O_3$ was confirmed by HRMS (EI, 70 eV). Compound *Z*-**6**: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.95$ (t, $J = 7.2$ Hz, 3H, CH_3 of *n*-Pr), 1.26 (t, $J = 7.2$ Hz, 3H, OCH_2CH_3), 1.31–1.49 (m, 4H, $2 \times CH_2$ of *n*-Pr), 1.60–1.77 (m, 1H, CH_2 at C-4), 2.14–2.25 (m, 1H, CH_2 at C-4), 2.75–2.85 (m, 1H, CH at C-3), 4.15 (q, $J = 7.2$ Hz, 2H, OCH_2CH_3), 4.26–4.34 (m, 1H, OCH_2 at C-5), 4.45–4.52 (m, 1H, OCH_2 at C-5), 4.85 (d, $J = 1.5$ Hz, 1H, CH=C). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta_C = 14.0$, 14.4 (CH_3), 22.5, 30.2, 32.1 (C–4, CH_2), 41.4 (C-3, CH), 59.2 (OCH_2), 69.9 (C-5, OCH_2), 87.6 (*C*H=C—O), 166.2 (O=C—O), 175.5 (O—*C*=CH). IR (neat, cm^{-1}): $\tilde{\nu} = 2954$ (m), 1704 (s), 1642 (s), 1436 (m), 1379 (m), 1351 (m), 1118 (s), 1045 (m). MS (EI, 70 eV): m/z (%) = 198 (M^+, 5), 183 (1), 169 (20), 156 (100), 153 (61), 141 (10), 128 (6), 114 (17), 109 (14), 97 (8), 84 (35). HRMS (EI): Calcd for $C_{11}H_{18}O_3$ [M^+]: 198.1256. Found: 198.1259.

4.3.2. Ethyl 2,3,3a,4,5,6-hexahydrobenzofuran-7-carboxylate 8.[9] Starting with ethyl 2-oxocyclohexanecarboxylate **7** (1.400 g, 8.23 mmol), diisopropylamine (5.3 mL, 37.5 mmol), *n*-BuLi (23.6 mL, 37.5 mmol, 15% in *n*-hexane), and 1-bromo-2-chloroethane (0.87 mL, 10.5 mmol) in THF (50 mL), **8** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 100:1→1:1) as a yellow oil (0.683 g, 42%). GC (column 1, 150 °C): retention times (min) = 16.8, 17.6. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.29$ (t, $J = 7.2$ Hz, 3H, CH_3), 1.38–1.55 (m, 1H, CH_2 at C-4), 1.57–1.77 (m, 1H, CH_2 at C-3), 1.90–1.99 (m, 1H, CH_2 at C-5), 2.07–2.15 (m, 1H, CH_2 at C-5), 2.17–2.34 (m, 2H, CH_2 at C–4, CH_2 at C-3), 2.36–2.44 (m, 1H, CH_2 at C–6), 2.55–2.67 (m, 2H, CH_2 at C–6, CH at C-3a), 4.11–4.27 (m, 1H, OCH_2 at C–2), 4.17 (q, $J = 7.2$ Hz, 2H, OCH_2CH_3), 4.45 (t, $J = 8.4$ Hz, 1H, OCH_2 at C–2). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta_C = 14.2$ (CH_3), 22.1 (C-5), 23.7 (C–6), 27.3 (C-4), 30.5 (C-3, CH_2), 40.9 (C-3a, CH), 59.2 (OCH_2CH_3), 71.0 (C–2, OCH_2), 96.7 (*C*=C—O), 166.8 (O=C—O), 168.0 (O—*C*=C). IR (neat, cm^{-1}): $\tilde{\nu} = 2937$ (m), 1738 (m), 1711 (s), 1681 (s), 1651 (s), 1303 (m), 1297 (m), 1270 (m), 1245 (m), 1197 (s), 1180 (m), 1163 (m), 1145 (s), 1108 (m), 1075 (s). MS (EI, 70 eV): m/z (%) = 196 (M^+, 49), 168

(97), 150 (82), 122 (100). Anal. Calcd for $C_{11}H_{16}O_3$ (196.246): C, 67.32; H, 8.22. Found: C, 66.96; H, 8.38.

4.3.3. Ethyl (5-vinyldihydrofuran-2(3*H*)-ylidene)acetate 10.[6a] Starting with ethyl acetoacetate (6.32 mL, 50 mmol), diisopropylamine (17.6 mL, 125 mmol), *n*-BuLi (78.5 mL, 125 mmol, 15% in *n*-hexane), and *trans*-1,4-dibromo-2-butene (12.834 g, 60 mmol) in THF (300 mL), *E*-**10** (3.633 g, 40%), and *Z*-**10** (3.213 g, 35%) were isolated after chromatography (silica gel, *n*-hexane/EtOAc = 100:1→1:1) as yellow oils (combined yield: 75%). Compound *E*-**10**: GC (column 2, 140 °C): retention times (min) = 12.2, 15.3. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.26$ (t, $J = 7.2$ Hz, 3H, CH_3), 1.82–1.91 (m, 1H, CH_2 at C-4), 2.22–2.31 (m, 1H, CH_2 at C-4), 2.99–3.08 (m, 1H, CH_2 at C-3), 3.21–3.32 (m, 1H, CH_2 at C-3), 4.13 (q, $J = 7.2$ Hz, 2H, OCH_2CH_3), 4.80 (q, $J = 7.5$ Hz, 1H, OCH at C-5), 5.23 (dt, $J = 10.5$, 1.2 Hz, 1H, CH_2=CH), 5.31 (dt, $J = 9.9$, 1.2 Hz, 1H, CH_2=CH), 5.36 (t, $J = 1.2$ Hz, 1H, CH=C), 5.80–5.91 (m, 1H, CH=CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta_C = 14.1$ (CH_3), 29.4 (C-3), 29.8 (C–4, CH_2), 58.7 (OCH_2), 83.4 (C-5, OCH_2), 89.3 (CH=C–O), 116.9 (CH_2=CH), 135.7 (CH=CH_2), 168.0 (O=C–O), 175.6 (O–C=CH). IR (neat, cm^{-1}): $\tilde{\nu} = 2983$ (s), 2941 (m), 1707 (s), 1644 (s), 1459 (m), 129 (m), 1392 (m), 1372 (s), 1348 (s), 1321 (m), 1284 (m), 1239 (m), 1164 (s), 1111 (s), 1047 (s), 1007 (s), 993 (s), 934 (m), 886 (s), 825 (s). MS (EI, 70 eV): *m*/*z* (%) = 182 (M^+, 58), 153 (4), 137 (100), 108 (27), 95 (24). Anal. Calcd for $C_{10}H_{14}O_3$ (182.219): C, 65.92; H, 7.74. Found: C, 65.30; H, 7.88. The synthesis of *Z*-**10** has been previously reported.[6a]

4.4. General procedure for the enzymatic resolution reactions

4.4.1. Analytical scale. For small-scale reactions, substrate (0.025–0.035 mmol) and *C. antarctica* lipase B (CAL-B) (2.5 mg, 120 U/mg, based on pH-stat assay against tributyrin) were dissolved in phosphate buffer (ad 1000 μL, 50 mM, pH 7.5) and toluene (10% v/v). The mixture was shaken in a thermo-shaker at 37 °C and 1400 rpm. After a certain time interval, a 100 μL sample was taken and 100 μL distilled water was added. The sample was acidified by HCl (aq, 1 M) addition and extracted with diethylether (3 × 200 μL). The combined organic extracts were dried over Na_2SO_4 and from this solution, the enantiomeric excess (ee) and conversions were determined by GC analysis. For **8** and *E*-**10**, the resolution products acid and ester were extracted together.

4.4.2. Preparative scale. Substrate **8** or *E*-**10** (0.25–0.35 mmol) was added into a solution of CAL-B (25 mg, 120 U/mg, based on pH-stat assay against tributyrin) in phosphate buffer (50 mM, pH 7.5, 9 mL) and toluene (1 mL). The mixture was stirred at 37 °C until 50% conversion (determined by GC analysis) was reached. *Method 1*: To the reaction mixture, HCl (aq, 10%, 10 mL) was added and the resulting acidic mixture extracted with dichloromethane (4 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc) to give the enantiomerically pure ester and hydrolysis product (acid), respectively. *Method 2*: To the reaction mixture was added water (10 mL) and aq Na_2CO_3 solution (concd, 1 mL), and the resulting basic mixture extracted with dichloromethane (or diethylether) (4 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo to give the enantiomerically pure ester without further purification. The aqueous layer was acidified by HCl addition (aq, 10%) and extracted with dichloromethane (4 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo to give the enantiomerically pure hydrolysis product (acid) without further purification. In some cases, the residues were purified by column chromatography (silica gel, *n*-hexane/EtOAc) for better rotation values. Purity and structure of compounds were confirmed by ^{1}H NMR. For reaction details, see Table 3.

4.4.2.1. Compounds (−)-8 and (+)-9. Table 3, entry 3 (Method 2): Starting with racemic **8** (50 mg, 0.25 mmol) and CAL-B (25 mg), (−)-**8** (17 mg, 34%), and (+)-**9** (14 mg, 33%) were isolated without further purification as yellow and pale yellow oils, respectively. Column chromatography (silica gel) is not recommended due to the racemization.

4.4.2.2. Compound (−)-8. GC (column 1, 150 °C): retention time (min) = 17.0, 97.4% ee. $[\alpha]_D^{20} = -109.7$ (*c* 1, $CDCl_3$). Spectral data are the same as given above for racemic **8**.

4.4.2.3. (+)-2,3,3a,4,5,6-Hexahydrobenzofuran-7-carboxylic acid (+)-9. GC (column 1, after conversion to the methyl ester by using diazomethane, 150 °C): retention time (min) = 15.0, 53.3% ee. $[\alpha]_D^{20} = +28.5$ (*c* 1, $CDCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.20$–1.33 (m, 2H, CH_2 at C–4, CH_2 at C-3), 1.44–1.53 (m, 1H, CH_2 at C-5), 1.60–1.78 (m, 2H, CH_2 at C-5, CH_2 at C-4), 1.95–2.02 (m, 1H, CH_2 at C-3), 2.14–2.49 (m, 2H, CH_2 at C–6), 2.65–2.70 (m, 1H, CH at C-3a), 4.20–4.35 (m, 1H, OCH_2 at C–2), 4.54 (t, $J = 8.4$ Hz, 1H, OCH_2 at C–2). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta_C = 22.1$ (C-5), 23.3 (C–6), 27.4 (C-4), 30.6 (C-3, CH_2), 40.3 (C-3a, CH), 72.2 (C–2, OCH_2), 98.6 (C=C–O), 167.8 (O=C–OH), 167.9 (O–C=C). IR (neat, cm^{-1}): $\tilde{\nu} = 3411$ (br), 2978 (m), 2863 (m), 1653 (m), 1447 (m), 1407 (m), 1391 (m), 1124 (s). MS (EI, 70 eV): *m*/*z* (%) = 150 ($[M\text{-}H_2O]^+$, 100), 123 (17), 93 (33). HRMS (ESI): Calcd for $C_9H_{12}O_3$ [M^+]: 168.0786. Found: 168.0789.

4.4.2.4. Compound (−)-*E*-10 and (−)-11. Table 3, entry 5 (Method 2): Starting with racemic *E*-**10** (50 mg, 0.27 mmol) and CAL-B (25 mg), (−)-*E*-**10** (24 mg, 48%), and (−)-**11** (15 mg, 36%) were isolated without further purification as pale yellow oils.

4.4.2.5. Compound (−)-*E*-10. After purification by column chromatography (silica gel, *n*-hexane/EtOAc = 100:1→3:1). GC (column 2, 140 °C): retention time (min) = 12.8, 97% ee. $[\alpha]_D^{20} = -93.8$ (*c* 1, $CDCl_3$). Spectral data are the same as given above for racemic *E*-**10**.

4.4.2.6. (−)-(2*E*)-(5-Vinyldihydrofuran-2(3*H*)-ylidene)-acetic acid (−)-11. GC (column 2, diazomethane, 140 °C): retention time (min) = not detected, % ee: not detected. $[\alpha]_D^{20} = -16.0$ (*c* 1, $CDCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 1.79$–1.92 (m, 1H, CH_2 at C-4), 2.20–2.32 (m, 1H, CH_2 at C-4), 2.97–3.09 (m, 1H, CH_2 at C-3), 3.22–3.35 (m, 1H, CH_2 at C-3), 4.86 (q, $J = 7.5$ Hz, 1H, OCH), 5.11–5.37 (m, 3H, CH=C, CH_2=CH), 5.80–5.91 (m, 1H, CH=CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta_C =$ 29.7 (C-3), 30.4 (C–4, CH_2), 83.5 (C-5, OCH_2), 89.1 (*C*H=C—O), 114.9 (*C*H_2=CH), 140.6 (*C*H=CH_2), 177.2 (O=C—OH), 178.8 (O—*C*=CH). IR (neat, cm^{-1}): $\tilde{\nu} = 3412$ (br), 3086 (w), 2956 (m), 2926 (s), 1712 (s), 1661 (w), 1459 (m), 1425 (m). MS (EI, 70 eV): *m*/*z* (%) = 154 (M^+, 10), 137 (19), 121 (23), 109 (14), 96 (51), 82 (57), 69 (100). HRMS (ESI): Calcd for $C_8H_{10}O_3$ [M^+]: 154.0630. Found: 154.0628.

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