Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 7132–7139
Tetrahedron

Synthesis of (tetrahydrofuran-2-yl)acetates based on a 'cyclization/hydrogenation/enzymatic kinetic resolution' strategy

Esen Bellur,[a,b] Ilia Freifeld,[a] Dominique Böttcher,[a] Uwe T. Bornscheuer[a,†] and Peter Langer[b,c,*]

[a]*Institut für Chemie und Biochemie, Universität Greifswald, Soldmannstr. 16, 17487 Greifswald, Germany*
[b]*Institut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, 18059 Rostock, Germany*
[c]*Leibniz-Institut für Katalyse e. V. an der Universität Rostock, Albert-Einstein-Str. 29a, 18059 Rostock, Germany*

Received 8 March 2006; revised 20 March 2006; accepted 22 March 2006
Available online 19 May 2006

Abstract—A variety of (tetrahydrofuran-2-yl)acetates and (pyrrolidin-2-yl)acetates have been prepared by hydrogenation of 2-alkylidenetetrahydrofurans and 2-alkylidenepyrrolidines, which are readily available by cyclization reactions of 1,3-dicarbonyl dianions ('free dianions') or 1,3-bis-silyl enol ethers ('masked dianions') with 1,2-dielectrophiles. The enzymatic kinetic resolution of (tetrahydrofuran-2-yl)acetates with recombinant esterase Est56 proceeded with excellent enantioselectivities ($E>100$).

1. Introduction

Functionalized tetrahydrofurans occur in a variety of pharmacologically relevant natural products.[1–4,6–8] (Tetrahydrofuran-2-yl)acetates are present, for example, in the polyether antibiotics lasalocid A (Fig. 1),[2] ferensimycin A, B, and lysocellin (Fig. 2).[3] They also represent versatile synthetic building blocks and have been used, for example, during the synthesis of the natural acetogenin solamin isolated from *Annonaceous*.[4] Many acetogenins exhibit remarkable cytotoxic, antitumor, antimalarial, immunosuppressive, pesticidal, and antifeedant activities.[1]

2-Alkylidenetetrahydrofurans[5,6] represent important synthetic building blocks that have been used for the synthesis of natural products. Numerous synthetic transformations of 2-alkylidenetetrahydrofurans have been reported, which include, for example, cycloadditions,[5a–d] nucleophilic additions,[5e–f] cyclopropanations,[5g] oxidative carbonylations,[5h–j] and codimerizations.[5k] The hydrogenation[5m,6h–i] of 2-alkylidenetetrahydrofurans has been applied to the synthesis of natural products, such as methyl nonactate, which represents a building block of nonactin.[6,7] The spiroketal chalcogran has been prepared from a bicyclic 2-alkylidenetetrahydrofuran.[8] 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,[9] and also by other methods.[10c–f] 2-Alkylidenetetrahydrofurans have been functionalized by lithiation and subsequent alkylations;[10a,b] in addition, the bromination of the exocyclic double bond and subsequent cross-coupling reactions have been reported.[10g,h] Recently, we have reported the synthesis of 6-bromo-3-oxoalkanoates and functionalized benzofurans by reaction of 2-alkylidenetetrahydrofurans with boron tribromide (BBr_3).[11] In addition, furans and benzofurans have been prepared by sequential '[3+2] cyclization/dehydrogenation'[12] and '[3+2] cyclization/elimination'[13] reactions. Herein, we report a convenient approach to racemic (tetrahydrofuran-2-yl)acetates[14] based on a '[3+2] cyclization/hydrogenation'

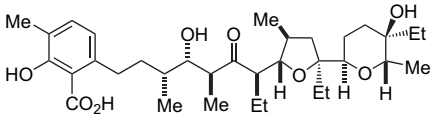


Figure 1. Lasalocid A.

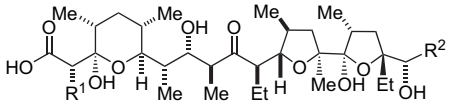


Figure 2. Ferensimycin A, B, and lysocellin.

Keywords: Cyclizations; Tetrahydrofurans; Pyrrolidines; Enzymatic kinetic resolution; Hydrogenation.
* Corresponding author. Tel.: +49 381 4986410; fax: +49 381 4986412; e-mail: peter.langer@uni-rostock.de
† Fax: +49 383 48680066; e-mail: uwe.bornscheuer@uni-greifswald.de.

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.03.077

strategy. In addition, we report the enzymatic kinetic resolution of (tetrahydrofuran-2-yl)acetates. The novel recombinant esterase Est56, extracted from soil samples using the metagenome approach, and supplied by BRAIN AG (Zwingenberg, Germany) has been used for these transformations.[15,16]

In the present manuscript, we also report the synthesis of an ethyl (pyrrolidin-2-yl)acetate by diastereoselective hydrogenation of an ethyl (4-methoxypyrrolidin-2-ylidene)acetate. 2-Alkylidenepyrrolidines[17,18] represent direct precursors for the stereoselective synthesis of pyrrolidine substructures[18] by reduction[18f] of the exocyclic double bond. Pyrrolidines are present in a variety of alkaloids, such as hygrine, hygroline or cuskhygrin, and in non-natural products used in the clinic (e.g., the vasodilator buflomedil).[18] They are ubiquitous structural motifs in drugs and drug candidates displaying antidepressant,[19a,b] antihypertensive,[19a,c] anti-arthritic,[19d,e] antibacterial,[19f–h] antithrombotic,[19i–k] and analgesic[19l,m] activities. Recent drug development incorporating the pyrrolidine motif has identified candidates with promising anti-HIV[19n,o] and antibacterial adjunct[19p,q] activities. Numerous applications in the synthesis of natural products have been reported.[20] Recently, we have reported[21a] the synthesis of 2-alkylidene-4-methoxypyrrolidines by condensation of 1,3-bis-silyl enol ethers with 1-azido-2,2-dimethoxyethane, and cyclization by Staudinger–aza-Wittig reaction.[21b]

2. Results and discussion

2.1. Synthesis of (tetrahydrofuran-2-yl)acetates based on cyclizations of free dianions with 1-bromo-2-chloroethane (*method A*)

The Pd/C catalyzed hydrogenation of the known 2-alkylidenetetrahydrofurans **3a–d**, prepared by cyclization of dilithiated methyl, ethyl, *iso*-propyl and *tert*-butyl acetoacetate (**1a–d**) with 1-bromo-2-chloroethane,[10a,b] afforded the (tetrahydrofuran-2-yl)acetates **5a–d** (Scheme 1, Table 1). 3-Methyl- and 3-ethyl-(tetrahydrofuran-2-yl)acetates **5e** and **5f** were prepared by hydrogenation of the known 2-alkylidenetetrahydrofurans **3e** and **3f**, respectively. The latter are again available by cyclization of 1,3-dicarbonyl dianions **1e,f** with 1-bromo-2-chloroethane.[10a,b] Tetrahydrofurans **5e**,**f** were isolated as inseparable 6:5 mixtures of diastereomers. The hydrogenation of tetrahydro[2,3′]bifuranyliden-2′-one **3g**,[10b] prepared by cyclization of dilithiated α-acetyl-γ-butyrolactone (**1g**) with 1-bromo-2-chloroethane, gave the octahydro[2,3′]bifuranyl-2′-one **5g** as an inseparable 3:2 mixture of diastereomers.

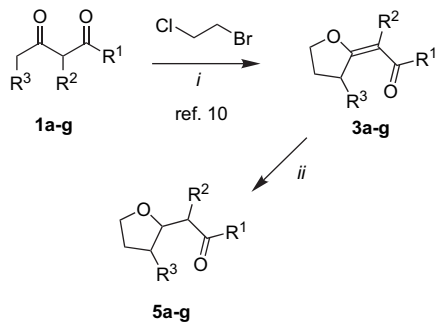
Table 1. Synthesis of (tetrahydrofuran-2-yl)acetates (**5a–g**)

Substrate (%)[a]	5	R^1	R^2	R^3	% (5)[a]	dr[b]
3a (86)[c]	**a**	OMe	H	H	97	—
3b (79)[c]	**b**	OEt	H	H	100	—
3c (77)[d]	**c**	O^{i}Pr	H	H	100	—
3d (77)[c]	**d**	O^{t}Bu	H	H	83	—
3e (72)[c]	**e**	OMe	H	Me	89	6:5
3f (82)[c]	**f**	OEt	H	Et	95	6:5
3g (58)[c]	**g**	OCH_2CH_2		H	86	3:2

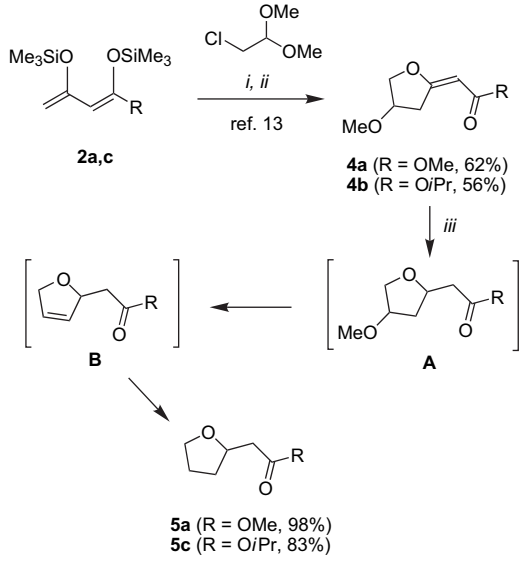
[a] Isolated yields.
[b] Diastereomeric ratio, assignment arbitrary.
[c] Known compounds (Ref. 10a,b).
[d] Combined yield (Ref. 12).

2.2. Synthesis of (tetrahydrofuran-2-yl)acetates based on cyclizations of masked dianions with 1-chloro-2,2-dimethoxyethane (*method B*)

The 4-methoxy-2-alkylidenetetrahydrofurans **4a**,**b** were prepared, following our recently reported procedure,[13] by TMSOTf catalyzed condensation of 1,3-bis-silyl enol ethers **2a**,**c** (available from **1a**,**c** in two steps) with 1-chloro-2,2-dimethoxyethane and subsequent DBU-mediated cyclization (Scheme 2). The hydrogenation of **4a**,**b** afforded the (tetrahydrofuran-2-yl)acetates **5a**,**c** by elimination of methanol and subsequent hydrogenation of the double bond thus formed (*method B*). For the synthesis of **5a**,**c**, *method A* is superior to *method B* because of the higher yields (*method A*: 83 and 77%; *method B*: 61 and 47%) and because less synthetic steps are required (*method A*: two steps; *method B*: five steps).



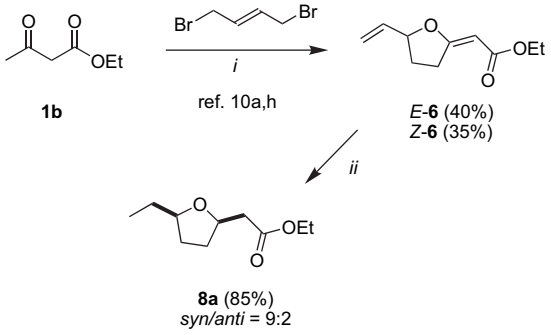
Scheme 1. Synthesis of (tetrahydrofuran-2-yl)acetates **5a–g**: (i) (1) LDA (2.3 equiv), THF, 0 °C, 1 h, (2) $Br(CH_2)_2Cl$, −78→20 °C, 14 h, then reflux, 12 h; (ii) H_2, Pd/C (0.5 equiv; for **5a**: 0.3 equiv), MeOH (or EtOH), 20 °C, 48 h.



Scheme 2. Synthesis of (tetrahydrofuran-2-yl)acetates **5a**,**c**: (i) $ClCH_2CH(OMe)_2$, Me_3SiOTf (0.5 equiv), CH_2Cl_2, −78→20 °C, 14 h, then at 20 °C, 2 h; (ii) DBU (2.0 equiv), THF, 20 °C, 6 h; (iii) H_2, Pd/C (0.5 equiv), MeOH, 20 °C, 48 h.

2.3. Synthesis of (tetrahydrofuran-2-yl)acetates based on cyclizations of free dianions with 1,4-dibromobut-2-ene (*method C*)

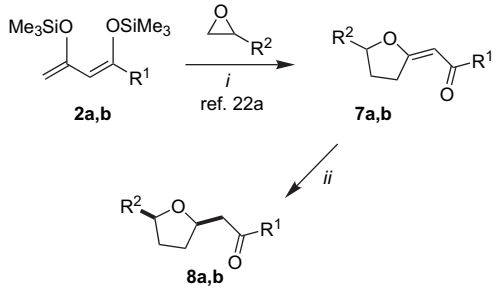
The cyclization of dilithiated ethyl acetoacetate (**1b**) with 1,4-dibromobut-2-ene afforded, following a known procedure,[10a] (5-vinyldihydrofuran-2(3*H*)-ylidene)acetate **6** as a separable mixture of *E*/*Z* isomers (Scheme 3).[10h] The hydrogenation of **6** afforded the (5-ethyltetrahydrofuran-2-yl)acetate **8a** by hydrogenation of the vinyl group and the exocyclic double bond.



Scheme 3. Synthesis of **8a**: (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) H_2, Pd/C (0.5 equiv), EtOH, 20 °C, 48 h.

2.4. Synthesis of (tetrahydrofuran-2-yl)acetates based on cyclizations of masked dianions with epoxides (*method D*)

2-Alkylidenetetrahydrofurans **7a**,**b** were prepared, following a known procedure,[22a] by $TiCl_4$ mediated cyclization of 1,3-bis-silyl enol ethers **2a**,**b** with 1,2-epoxybutane and epichlorohydrin, respectively (Scheme 4, Table 2). The hydrogenation of **7a** afforded the tetrahydrofuran **8a** with moderate diastereoselectivity. The hydrogenation of **7b** afforded (5-chloromethyltetrahydrofuran-2-yl)acetate **8b** with very good diastereoselectivity.



Scheme 4. Synthesis of 5-alkyl-(tetrahydrofuran-2-yl)acetates **8a**,**b**: (i) $TiCl_4$ (2 equiv), 4 Å MS, CH_2Cl_2, −78→20 °C, 14 h, then at 20 °C, 3 h; (ii) H_2, Pd/C (0.5 equiv), MeOH (or EtOH), 20 °C, 48 h.

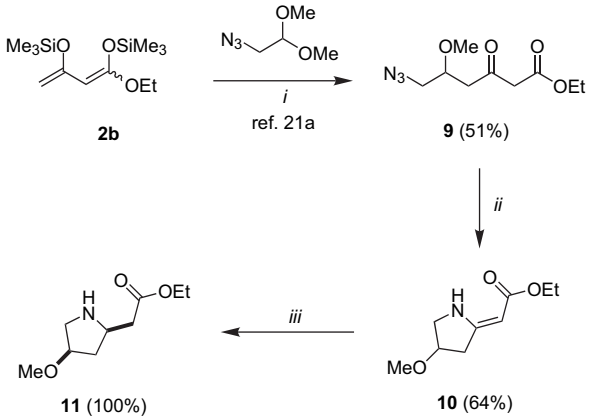
Table 2. Synthesis of 5-alkyl-(tetrahydrofuran-2-yl)acetates (**8a**,**b**)

Substrate (%)[a]	**8**	R^1	R^2	% (**8**)[a]	*syn*/*anti*[b]
7a (62)[c]	**a**	OEt	Et	70	3:1
7b (66)	**b**	OMe	CH_2Cl	100	>10:1

[a] Isolated yields.
[b] Diastereoselectivity (by ^1H NMR).
[c] Known compound (Ref. 22a).

2.5. Synthesis of (pyrrolidin-2-yl)acetates based on [3+2] cyclizations of 1,3-bis-silyl enol ethers with 1-azido-2,2-dimethoxyethane

The ethyl (4-methoxypyrrolidin-2-ylidene)acetate **10** was prepared, following our recently reported procedure,[21a] by TMSOTf catalyzed condensation of 1,3-bis-silyl enol ether **2b**, with 1-azido-2,2-dimethoxyethane and subsequent cyclization of **9** by Staudinger–aza-Wittig reaction. The palladium-catalyzed hydrogenation of **10** afforded ethyl (4-methoxypyrrolidin-2-yl)acetate (**11**) with 10:1 diastereoselectivity (Scheme 5).



Scheme 5. Synthesis of **11**: (i) $N_3CH_2CH(OMe)_2$, Me_3SiOTf (0.5 equiv), CH_2Cl_2, −78→20 °C; (ii) PPh_3, THF, 45 °C, 6 h; (iii) H_2, Pd/C (0.5 equiv), EtOH, 20 °C, 24 h.

2.6. Enzymatic kinetic resolution of (tetrahydrofuran-2-yl)acetates

To monitor the enantioselectivity in the enzymatic kinetic resolution of the (tetrahydrofuran-2-yl)acetates, suitable conditions for gas chromatographic (GC) analysis were developed (Table 3).

The enzymatic kinetic resolutions of these (tetrahydrofuran-2-yl)acetates were next studied (Table 4). The analytical scale enzyme reactions of methyl and ethyl (tetrahydrofuran-2-yl)acetates (**5a**,**b**) were carried out with esterases[15] (Est56, Est63, Est8) and lipases[15] (CAL-B, BCL). For **5a**,**b**, the best resolution results were achieved with the recombinant esterase Est56.

Enzymatic kinetic resolution of **5a** with recombinant esterase Est56 gave (−)-**5a** (40%, >99% ee) and the hydrolysis product (−)-**12** (49%, 87% ee) (Scheme 6, Table 5, entry 4). The preparative scale reaction of **5a** with Est56 was repeated

Table 3. GC analysis of (tetrahydrofuran-2-yl)acetates

Substrate	Temperature (°C)	Retention time (min)[a]			
		Substrate (ester)		Product (acid)[b,c]	
5a	70	18.2	18.8	18.2	18.8
5b	70	29.7	30.5	18.2	18.8

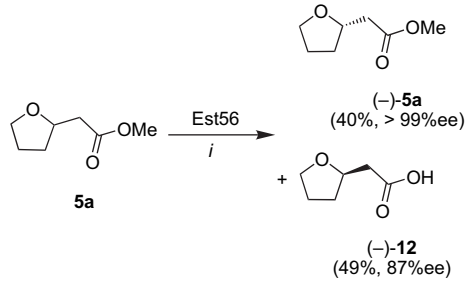
[a] Chiral column: Hydrodex®-β-3P, [Heptakis-(2,6-di-*O*-methyl-3-*O*-pentyl)-β-cyclodextrin].
[b] Product of enzyme reactions.
[c] Retention times for methyl ester of hydrolysis products [acid+diazomethane→methyl ester].

Table 4. Analytical scale enzymatic kinetic resolution reactions

Enzyme	Substrate	Conversion (%)	Reaction time (h)	eeS (%)[a,b]	eeP (%)[a,c]	*E*-value
Est56	**5a**	59	49	>99	70	48
Est56	**5b**	60	53	88	67	15
Est63	**5a**	30	49	33	75	9
Est8	**5a**	18	48	3	2	1
Est8	**5b**	5	48	<1	11	1
CAL-B	**5a**	95	1	—	—	1
CAL-B	**5b**	95	1	—	—	1
BCL	**5a**	35	48	19	35	2
BCL	**5b**	40	48	23	33	2

eeS: enantiomeric excess of substrate; eeP: enantiomeric excess of product.
[a] Calculated from gas chromatograms (GC).
[b] For (−)-**5a**.
[c] For (−)-**12**.

five times and optimized, which finally led to conditions in which excellent enantioselectivities ($E>100$) at high conversions and short reaction times were obtained. The resolution reaction of racemic **5a** with Est56 afforded *both* products with negative (−) optical rotation values. Unfortunately, the absolute configurations of (−)-**5a** and (−)-**12** could *not* be determined by comparison with literature results: Laxmi and Iyengar reported[23] that the lipase (*Candida cylindracea*) mediated enantioselective hydrolysis of **5a** afforded (*S*)-(+)-**5a** and (*R*)-(−)-**12**, which were used for the synthesis of the natural product (*R*)-(+)-α-lipoic acid. Co-injection (GC) of (−)-**5a** and (−)-**12** proved that the products have different configurations.



Scheme 6. Enzymatic kinetic resolution of **5a**: (i) (Table 5, entry 4) recombinant esterase Est56, phosphate buffer (50 mM, pH 7.5), 37 °C, 5 h, the assignment of the absolute configuration is arbitrary.

In conclusion, a variety of (tetrahydrofuran-2-yl)acetates have been prepared by hydrogenation of 2-alkylidenetetrahydrofurans readily available by [3+2] cyclizations of 1,3-dicarbonyl dianions ('free dianions') or 1,3-bis-silyl enol ethers ('masked dianions') with various 1,2-dielectrophiles. Similarly, (4-methoxypyrrolidin-2-yl)acetate has been prepared from 2-alkylidenepyrrolidin. Enzymatic kinetic resolution of (tetrahydrofuran-2-yl)acetates by recombinant esterase Est56 proceeded with excellent enantioselectivity affording these compounds in optically pure form.

Table 5. Preparative scale enzymatic reactions

Entry	Est56[a] (mL)	**5a** (mg)	Conversion (%)	Time (h)	eeS (%)[b,c]	eeP (%)[b,d]	*E*-value
1	2	200	35	216	38	71	9
2	1	4×20	39	187	47	75	11
3	2	50	54	22	>99	83	73
4	1.5	50	54	5	>99	87	>100
5	2	50	54	3	>99	84	100

eeS: enantiomeric excess of substrate; eeP: enantiomeric excess of product.
[a] Crude extract with 50 U/mL (based on a *p*-nitrophenyl acetate assay).
[b] For isolated products.
[c] For (−)-**5a**.
[d] For (−)-**12**.

3. Experimental

3.1. General comments

All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For the ^{1}H and ^{13}C NMR spectra the deuterated solvents indicated were used. The NMR spectra were measured on 300 and 200 MHz instruments. 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. Chiral column used for GC: Hydrodex®-β-3P, [Heptakis-(2,6-di-*O*-methyl-3-*O*-pentyl)-β-cyclodextrin] (25 m, 0.25 mm).

3.2. 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 **2** (1.0 equiv) and the epoxide (1.2 equiv), in the presence of molecular sieves (4 Å), was added $TiCl_4$ (2.0 equiv) at −78 °C. The solution was stirred for 4 h at −78 °C; subsequently, the temperature was allowed to rise to 20 °C during 14 h and the solution was stirred for 3 h at 20 °C. The molecular sieves were filtered-off and washed with CH_2Cl_2. To the solution was added a saturated aqueous solution of $NaHCO_3$, the organic layer was separated and the aqueous layer was repeatedly extracted with CH_2Cl_2. The combined organic extracts were dried (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 **7**. The synthesis of **7a** has been previously reported.[22a]

3.2.1. Methyl (5-chloromethyldihydrofuran-2(3*H*)-ylidene) acetate (7b). Starting with **2a** (7.814 g, 30 mmol), epichlorohydrin (2.82 mL, 36 mmol) and $TiCl_4$ (6.6 mL, 60 mmol) in CH_2Cl_2 (250 mL, 4 Å molecular sieves), **7b** was isolated after chromatography (silica gel, *n*-hexane/EtOAc=100:1→1:1) as a yellowish oil (3.764 g, 66%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.97–2.06 (m, 1H, CH_2), 2.23–2.32 (m, 1H, CH_2), 3.00–3.13 (m, 1H, CH_2), 3.25–3.38 (m, 1H, CH_2), 3.64 (d, J=5.1 Hz, 2H, CH_2–Cl), 3.67 (s, 3H, OCH_3), 4.62–4.70 (m, 1H, OCH), 5.35 (t, J=1.8 Hz, 1H, CH=C). IR (neat, cm^{-1}): $\tilde{\nu}$=2987 (w), 2954 (m), 1704 (s), 1642 (s), 1439 (s), 1365 (s), 1295 (m), 1246 (m), 1189 (s), 1121 (s), 1047 (s), 942 (w), 880 (w), 828 (m), 727 (w). 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).

3.3. General procedure for the hydrogenation of 2-alkylidenetetrahydrofurans

To a H_2 concentrated suspension of Pd/C (0.3–0.5 equiv, 10% Pd on charcoal) in methanol (or ethanol) (5–10 mL/mmol)

was added 2-alkylidenetetrahydrofuran (**3**, **6**, **7** or **10**) (1.0 equiv). The reaction mixture was concentrated with H_2 and stirred under H_2 atmosphere at 20 °C for 48 h. Then the reaction mixture was filtered through Celite, washed with dichloromethane (4×15 mL/mmol), and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc) to give (tetrahydrofuran-2-yl)acetate (**5**, **8** or **11**). Notably, the (tetrahydrofuran-2-yl)acetates were not UV active (neither at short nor at long wavelength); to detect the products on TLC, the following solution was used as a dying agent: MnO_2 (0.3 g/mL) in ethanol.

3.3.1. Methyl (tetrahydrofuran-2-yl)acetate (5a).[23] *Method A*: Starting with **3a** (0.500 g, 3.52 mmol) and Pd/C (10% Pd, 1.123 g, 1.06 mmol) in methanol (20 mL), **5a** was isolated without further purification as a slightly yellowish oil (0.491 g, 97%). *Method B*: Starting with **4a** (0.300 g, 1.74 mmol) and Pd/C (10% Pd, 0.556 g, 0.52 mmol) in methanol (15 mL), **5a** was isolated without further purification as a slightly yellowish oil (0.245 g, 98%). GC (chiral column, 70 °C): retention times (min)=18.2, 18.8. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.50–1.61 (m, 1H, CH_2), 1.87–1.96 (m, 2H, CH_2), 2.04–2.15 (m, 1H, CH_2), 2.49 (dd, J=15.2, 5.8 Hz, 1H, CH_2), 2.61 (dd, J=15.2, 7.2 Hz, 1H, CH_2), 3.70 (s, 3H, OCH_3), 3.72–3.79 (m, 1H, OCH_2), 3.85–3.92 (m, 1H, OCH_2), 4.26 (quint, J=7.2 Hz, 1H, OCH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C=25.0, 30.6, 39.8 (CH_2), 51.1 (OCH_3), 67.4 (OCH_2), 74.6 (OCH), 171.0 (O═C–O). IR (neat, cm^{-1}): $\tilde{\nu}$=2957 (s), 2875 (m), 1741 (s), 1646 (w), 1438 (m), 1417 (w), 1382 (w), 1361 (w), 1322 (w), 1302 (m), 1261 (m), 1201 (m), 1164 (s), 1119 (s), 1100 (m), 1066 (s), 1019 (m), 875 (w), 823 (w), 806 (w). MS (EI, 70 eV): *m*/*z* (%)=143 (M^+, 76), 129 (20), 112 (14), 95 (34), 83 (75), 70 (100). HRMS (ESI): Calcd for $C_7H_{12}O_3$ ([M+1]$^+$): 145.08647; found: 145.08567.

3.3.2. Ethyl (tetrahydrofuran-2-yl)acetate (5b). Starting with **3b** (1.000 g, 6.4 mmol) and Pd/C (10% Pd, 3.407 g, 3.2 mmol) in ethanol (25 mL), **5b** was isolated without further purification as a yellowish oil (1.012 g, 100%). GC (chiral column, 70 °C): retention times (min)=29.7, 30.5. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.15–1.31 (m, 3H, CH_3), 1.55–1.69 (m, 1H, CH_2), 1.88–1.97 (m, 1H, CH_2), 2.05–2.11 (m, 1H, CH_2), 2.28–2.49 (m, 1H, CH_2), 2.54–2.79 (m, 2H, CH_2), 3.43–3.61 (m, 2H, OCH_2), 3.76–3.88 (m, 1H, OCH), 4.12–4.24 (m, 2H, OCH_2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C=14.2 (CH_3), 26.0, 31.5, 39.7 (CH_2), 61.4, 64.5 (OCH_2), 75 (OCH), 166.7 (O═C–O). IR (neat, cm^{-1}): $\tilde{\nu}$=2966 (s), 2875 (w), 1738 (s), 1651 (w), 1446 (m), 1412 (m), 1374 (m), 1304 (m), 1260 (s), 1182 (s), 1164 (s), 1096 (s), 1067 (s), 1030 (s). MS (EI, 70 eV): *m*/*z* (%)=158 (M^+, 2), 144 (13), 130 (51), 114 (31), 97 (13), 84 (21), 71 (100).

3.3.3. *iso*-Propyl (tetrahydrofuran-2-yl)acetate (5c). *Method A*: Starting with **3c** (0.150 g, 0.88 mmol) and Pd/C (10% Pd, 0.469 g, 0.44 mmol) in ethanol (10 mL), **5c** was isolated without further purification as a slightly yellowish oil (0.152 g, 100%). *Method B*: Starting with **4b** (0.250 g, 1.25 mmol) and Pd/C (0.664 g, 10% Pd, 0.62 mmol) in methanol (15 mL), **5c** was isolated without further purification as a slightly yellowish oil (0.179 g, 83%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.24 (d, J=6.3 Hz, 6H, 2×CH_3), 1.50–1.61 (m, 1H, CH_2), 1.85–1.96 (m, 2H, CH_2), 2.03–2.12 (m, 1H, CH_2), 2.43 (dd, J=15.1, 6.3 Hz, 1H, CH_2), 2.58 (dd, J=15.1, 7.0 Hz, 1H, CH_2), 3.70–3.79 (m, 1H, OCH_2), 3.84–3.92 (m, 1H, OCH_2), 4.24 (quint, J=6.8 Hz, 1H, OCH), 5.04 (quint, J=6.3 Hz, 1H, OCH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C=21.1 (2C, CH_3), 24.9, 30.5, 40.3 (CH_2), 66.9 (OCH), 67.4 (OCH_2), 74.6 (OCH), 169.9 (O═C–O). IR (neat, cm^{-1}): $\tilde{\nu}$=2962 (s), 2934 (s), 2874 (m), 1731 (s), 1649 (w), 1457 (m), 1447 (m), 1408 (w), 1379 (m), 1262 (s), 1232 (m), 1180 (s), 1108 (s), 1070 (s), 1022 (m), 967 (w), 801 (m). MS (EI, 70 eV): *m*/*z* (%)=172 (M^+, 1), 157 (3), 142 (3), 129 (11), 112 (8), 102 (28), 97 (4), 89 (48), 84 (16), 71 (100). HRMS (ESI): Calcd for $C_9H_{16}O_3$ ([M+Na]$^+$): 195.09972; found: 195.09889.

3.3.4. *tert*-Butyl (tetrahydrofuran-2-yl)acetate (5d). Starting with **3d** (0.200 g, 1.09 mmol) and Pd/C (10% Pd, 0.580 g, 0.5 mmol) in ethanol (10 mL), **5d** was isolated after chromatography (silica gel, *n*-hexane/EtOAc=100:1→10:1) as a colorless oil (0.170 g, 83%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.45 (s, 9H, O^{t}Bu), 1.51–1.61 (m, 1H, CH_2), 1.84–1.94 (m, 2H, CH_2), 2.01–2.10 (m, 1H, CH_2), 2.36 (dd, J=15.1, 6.7 Hz, 1H, CH_2), 2.53 (dd, J=15.1, 6.7 Hz, 1H, CH_2), 3.70–3.78 (m, 1H, OCH_2), 3.83–3.91 (m, 1H, OCH_2), 4.20 (quint, J=6.7 Hz, 1H, OCH). ^{13}C NMR ($CDCl_3$, 50 MHz): δ_C=25.5 (CH_2), 28.0 (O^{t}Bu), 31.1, 41.8 (CH_2), 68.9 (OCH_2), 75.4 (OCH), 80.4 (O^{t}Bu), 170.6 (O═C–O). IR (neat, cm^{-1}): $\tilde{\nu}$=2976 (m), 2946 (w), 2936 (w), 2874 (w), 1730 (s), 1455 (w), 1390 (w), 1368 (m), 1300 (w), 1288 (w), 1257 (m), 1208 (w), 1154 (s), 1102 (w), 1068 (m), 1020 (w). MS (EI, 70 eV): *m*/*z* (%)=186 (M^+, 1), 157 (12), 141 (4), 129 (49), 114 (17), 102 (16), 73 (10), 72 (96), 70 (45), 57 (100). MS (DCI, NH_3): *m*/*z* (%)=390 ([2×M+NH_4]$^+$, 23), 360 (15), 334 (13), 204 ([M+NH_4]$^+$, 47), 165 (28), 148 (100). The exact molecular mass *m*/*z*=186.1256±2 ppm [M^+] for $C_{10}H_{18}O_3$ was confirmed by HRMS (EI, 70 eV). Anal. Calcd for $C_{10}H_{18}O_3$ (186.248): C 64.49, H 9.74; found: C 64.52, H 9.75.

3.3.5. Methyl (3-methyltetrahydrofuran-2-yl)acetate (5e). Starting with **3e** (0.350 g, 2.24 mmol) and Pd/C (10% Pd, 1.192 g, 1.12 mmol) in methanol (15 mL), **5e** was isolated after chromatography (silica gel, *n*-hexane/EtOAc=100:1→10:1) as a colorless oil (0.316 g, 89%, an inseparable 6:5 mixture of diastereomers). ^{1}H NMR ($CDCl_3$, 200 MHz, for both diastereomers): δ=0.92 (d, J=7.0 Hz, 3H, CH_3), 1.05 (d, J=6.5 Hz, 3H, CH_3), 1.48–1.67 (m, 2H, CH_2), 1.79–1.96 (m, 1H, CH), 2.01–2.19 (m, 2H, CH_2), 2.28–2.39 (m, 1H, CH), 2.42–2.61 (m, 4H, 2×CH_2), 3.70 (s, 6H, 2×OCH_3), 3.71–3.98 (m, 5H, 2×OCH_2, OCH), 4.19–4.29 (m, 1H, OCH). ^{13}C NMR ($CDCl_3$, 50 MHz): Major diastereomer: δ_C=16.8 (CH_3), 34.3 (CH_2), 39.0 (CH), 39.2 (CH_2), 51.6 (OCH_3), 67.0 (OCH_2), 81.7 (OCH), 171.9 (O═C–O). Minor diastereomer: δ_C=14.2, 33.5, 35.3, 36.0, 51.6, 66.4, 77.6, 172.1. IR (neat, cm^{-1}): $\tilde{\nu}$=2961 (s), 2876 (m), 1741 (s), 1455 (m), 1438 (m), 1381 (w), 1325 (w), 1303 (w), 1282 (m), 1257 (w), 1198 (m), 1169 (s), 1128 (w), 1107 (w), 1087 (m), 1043 (w), 1016 (m). MS (EI, 70 eV): *m*/*z* (%)=158 (M^+, 3), 143 (2), 130 (30), 127 (6), 98 (17), 85 (100), 72 (21). The exact molecular mass *m*/*z*=158.0943±2 ppm [M^+] for $C_8H_{14}O_3$ was confirmed by HRMS (EI, 70 eV).

3.3.6. Ethyl (3-ethyltetrahydrofuran-2-yl)acetate (5f). Starting with **3f** (0.280 g, 1.52 mmol) and Pd/C (10% Pd, 0.809 g, 0.76 mmol) in ethanol (15 mL), **5f** was isolated after chromatography (silica gel, *n*-hexane/EtOAc=100:1→10:1) as slightly yellowish oil (0.268 g, 95%, inseparable 6:5 mixture of diastereomers). ^{1}H NMR ($CDCl_3$, 300 MHz, for both diastereomers): δ=0.94 (dt, J=7.2, 4.8 Hz, 6H, 2×CH_3), 1.27 (t, J=7.2 Hz, 6H, 2×OCH_2CH_3), 1.32–1.48 (m, 1H, CH), 1.50–1.66 (m, 4H, 2×CH_2), 1.70–1.82 (m, 1H, CH), 2 00–2.22 (m, 4H, 2×CH_2), 2.36–2.43 (m, 2H, CH_2), 2.45–2.56 (m, 2H, CH_2), 3.73 (q, J=7.8 Hz, 1H, OCH), 3.80 (t, J=6.0 Hz, 2H, OCH_2), 3.84–3.97 (m, 2H, OCH_2), 4.17 (q, J=7.2 Hz, 4H, 2×OCH_2CH_3), 4.37 (q, J=6.6 Hz, 1H, OCH). ^{13}C NMR ($CDCl_3$, 50 MHz): Major diastereomer: δ_C=12.6, 14.1 (CH_3), 25.5, 32.0, 40.1 (CH_2), 46.2 (CH), 60.4 (OCH_2CH_3), 67.1 (OCH_2), 80.3 (OCH), 171.8 (O=C–O). Minor diastereomer: δ_C=12.8, 14.1, 21.9, 30.5, 36.2, 43.3, 60.4, 66.6, 77.4, 171.5. IR (neat, cm^{-1}): $\tilde{\nu}$=2965 (s), 2934 (m), 2876 (m), 1738 (s), 1459 (w), 1377 (w), 1309 (m), 1261 (m), 1172 (s), 1141 (w), 1082 (m), 1036 (s). MS (EI, 70 eV): *m*/*z* (%)=186 (M^+, 1), 158 (44), 143 (22), 130 (5), 116 (10), 110 (13), 99 (100), 84 (16), 70 (31). The exact molecular mass *m*/*z*=186.1256±2 ppm [M^+] for $C_{10}H_{18}O_3$ was confirmed by HRMS (EI, 70 eV).

3.3.7. Octahydro-[2,3′]bifuranyl-2′-one (5g). Starting with **3g** (0.300 g, 1.95 mmol) and Pd/C (10% Pd, 0.500 g, 0.47 mmol) in ethanol (10 mL), **5g** was isolated after chromatography (silica gel, *n*-hexane/EtOAc=50:1→1:1) as a colorless oil (0.261 g, 86%, an inseparable 3:2 mixture of diastereomers). ^{1}H NMR ($CDCl_3$, 300 MHz, for both diastereomers): δ=1.66–1.77 (m, 1H, CH_2), 1.84–2.07 (m, 6H, 3×CH_2), 2.11–2.46 (m, 5H, 3×CH_2), 2.64–7.72 (m, 1H, CH of minor diastereomer), 2.82–2.89 (m, 1H, CH of major diastereomer), 3.72–3.82 (m, 2H, OCH_2), 3.84–3.92 (m, 2H, OCH_2), 4.13–4.20 (m, 2H, OCH_2), 4.21–4.29 (m, 2H, OCH_2), 4.34–4.43 (m, 2H, 2×OCH). ^{13}C NMR ($CDCl_3$, 50 MHz): Major diastereomer: δ_C=25.8, 26.1, 28.0 (CH_2), 42.7 (CH), 67.0, 68.7 (OCH_2), 78.8 (OCH), 177.1 (O=C–O). Minor diastereomer: δ_C=23.9, 25.8, 29.9, 44.0, 66.9, 68.4, 77.4, 177.5. IR (neat, cm^{-1}): $\tilde{\nu}$=2078 (m), 2915 (w), 2876 (m), 1768 (s), 1455 (w), 1380 (m), 1218 (m), 1167 (s), 1133 (w), 1070 (m), 1026 (s), 956 (w). MS (EI, 70 eV): *m*/*z* (%)=155 (M^+, 27), 141 (7), 128 (19), 112 (9), 97 (5), 86 (24), 72 (77), 70 (53), 57 (48), 55 (43), 41 (100). Anal. Calcd for $C_8H_{12}O_3$ (156.181): C 61.52, H 7.74; found: C 61.46, H 7.94.

3.3.8. Ethyl (5-ethyltetrahydrofuran-2-yl)acetate (8a). *Method C*: Starting with **6** (0.500 g, 2.74 mmol) and Pd/C (10% Pd, 1.460 g, 1.37 mmol) in ethanol (30 mL), **8a** was isolated after chromatography (silica gel, *n*-hexane/EtOAc=100:1→3:1) as a colorless oil (0.435 g, 85%, an inseparable 9:2 [*syn*/*anti*] mixture of diastereomers). *Method D*: Starting with **7a** (0.16 g, 0.87 mmol) and Pd/C (10% Pd, 0.469 g, 0.44 mmol) in ethanol (30 mL), **8a** was isolated after chromatography (silica gel, *n*-hexane/EtOAc=100:1→3:1) as a colorless oil (0.11 g, 70%, an inseparable 3:1 [*syn*/*anti*] mixture of diastereomers). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.91 (t, J=7.2 Hz, 3H, CH_3), 1.26 (t, J=7.2 Hz, 3H, CH_3), 1.42–1.52 (m, 2H, CH_2), 1.53–1.65 (m, 2H, CH_2), 1.91–2.11 (m, 2H, CH_2), 2.44 (dd, J=15.0, 6.6 Hz, 1H, CH_2), 2.63 (dd, J=15.0, 6.6 Hz, 1H, CH_2), 3.79 (quint, J=6.6 Hz, 1H, OCH), 4.15 (q, J=7.2 Hz, 2H, OCH_2), 4.24 (quint, J=6.6 Hz, 1H, OCH). ^{13}C NMR ($CDCl_3$, 50 MHz): Major diastereomer: δ_C=9.8, 13.8 (CH_3), 28.5, 30.0, 30.7, 40.9 (CH_2), 59.9 (OCH_2), 74.9, 80.6 (CH), 170.9 (O=C–O). Minor diastereomer: δ_C=9.8, 13.8, 28.3, 30.9, 31.5, 40.6, 59.9, 74.5, 79.9, 170.8. IR (neat, cm^{-1}): $\tilde{\nu}$=2969 (s), 2936 (m), 2877 (m), 1737 (s), 1462 (m), 1376 (m), 1299 (m), 1252 (m), 1193 (s), 1165 (s), 1079 (s), 1036 (s), 957 (w). MS (EI, 70 eV): *m*/*z* (%)=186 (M^+, 4), 171 (4), 157 (64), 141 (6), 130 (78), 126 (5), 114 (27), 110 (100), 99 (78), 83 (54), 70 (76). MS (DCI, NH_3): *m*/*z* (%)=204 ([M+NH_4]$^+$, 100), 192 (43), 187 (M^+, 7), 151 (43), 134 (35), 108 (10). HRMS (ESI): Calcd for $C_{10}H_{18}O_3$ ([M+1]$^+$): 187.13342; found: 187.13281. Anal. Calcd for $C_{10}H_{18}O_3$ (186.248): C 64.49, H 9.74; found: C 64.46, H 9.78.

3.3.9. Methyl (5-chloromethyltetrahydrofuran-2-yl)acetate (8b). Starting with **7b** (0.500 g, 2.62 mmol) and Pd/C (10% Pd, 1.396 g, 1.31 mmol) in methanol (30 mL), **8b** was isolated without further purification as a slightly yellowish oil (0.505 g, 100%, inseparable 10:1 [*syn*/*anti*] mixture of diastereomers). ^{1}H NMR ($CDCl_3$, 300 MHz): Major diastereomer: δ=1.56–1.73 (m, 1H, CH_2), 1.84–1.89 (m, 1H, CH_2), 2.04–2.10 (m, 2H, CH_2), 2.52 (dd, J=15.3, 2.7 Hz, 1H, CH_2), 2.67 (dd, J=15.3, 3.0 Hz, 1H, CH_2), 3.45–3.63 (m, 2H, CH_2–Cl), 3.70 (s, 3H, OCH_3), 4.19 (m, 1H, OCH), 4.34 (m, 1H, OCH). ^{13}C NMR ($CDCl_3$, 75 MHz): Major diastereomer: δ_C=27.8, 29.8, 39.4 (CH_2), 46.0 (CH_2–Cl), 51.0 (OCH_3), 75.1, 77.5 (OCH), 170.1 (O=C–O). IR (neat, cm^{-1}): $\tilde{\nu}$=2955 (m), 2927 (w), 2879 (w), 1739 (s), 1649 (w), 1439 (m), 1390 (w), 1377 (w), 1352 (w), 1320 (w), 1298 (w), 1278 (w), 1260 (w), 1201 (m), 1177 (m), 1093 (m), 1065 (m), 1012 (w), 901 (w), 883 (w), 796 (w), 746 (w). MS (EI, 70 eV): *m*/*z* (%)=192 (M^+, 1), 163 (1), 161 (5), 157 (17), 143 (100), 132 (4), 127 (1), 125 (5), 121 (19), 119 (60), 116 (36), 110 (71), 103 (2), 101 (21), 85 (6), 83 (65), 77 (5), 75 (11), 72 (8), 70 (19). HRMS (ESI): Calcd for $C_8H_{13}ClO_3$ [M^+]: 193.0440 (^{37}Cl), 191.0469 (^{35}Cl); found: 193.0440 (^{37}Cl), 191.0466 (^{35}Cl).

3.3.10. Ethyl (4-methoxypyrrolidin-2-yl)acetate (11). Starting with **10**[21a] (0.200 g, 1.08 mmol) and Pd/C (0.345 g, 10% Pd, 0.32 mmol) in ethanol (10 mL), **11** was isolated without further purification as a yellowish oil (0.202 g, 100%, inseparable 10:1 mixture of diastereomers). ^{1}H NMR ($CDCl_3$, 300 MHz): Major diastereomer: δ=1.26 (dt, J=7.2, 1.8 Hz, 3H, CH_3), 1.94 (dt, J=10.6, 3.4 Hz, 1H, CH_2), 1.92–1.98 (m, 1H, CH_2), 2.87 (dd, J=17.3, 7.4 Hz, 1H, CH_2), 3.22 (dd, J=17.3, 7.2 Hz, 1H, CH_2), 3.33 (s, 3H, OCH_3), 3.40 (dd, J=12.5, 4.9 Hz, 1H, CH_2–NH), 3.54 (d, J=12.5 Hz, 1H, CH_2–NH), 3.71 (q, J=7.04 Hz, 1H, CH–NH), 4.07–4.11 (m, 1H, OCH), 4.18 (dq, J=7.2, 1.8 Hz, 2H, OCH_2), 8.00 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz): Major diastereomer: δ_C=13.9 (CH_3), 35.8, 37.0 (CH_2), 49.1 (CH_2–NH), 54.4 (CH–NH), 56.7 (OCH_3), 60.9 (OCH_2), 78.4 (OCH), 170.2 (O=C–O). IR (neat, cm^{-1}): $\tilde{\nu}$=3419 (m), 2982 (s), 2937 (s), 2831 (m), 2747 (m), 1732 (s), 1640 (w), 1445 (w), 1403 (m), 1381 (m), 1347 (w), 1324 (m), 1259 (m), 1202 (s), 1106 (s), 1068 (m), 1028 (m). MS (EI, 70 eV): *m*/*z* (%)=187 (M^+, 2), 159 (5), 156 (7), 142 (4), 128 (54), 111 (7), 100 (86), 96 (39), 84 (25), 69 (100). HRMS (ESI): Calcd for $C_9H_{17}NO_3$ ([M+1]$^+$): 188.12867; found: 188.12782.

3.4. General procedure for the enzymatic kinetic resolution of (tetrahydrofuran-2-yl)acetates

3.4.1. Analytical scale. For small-scale reactions, (tetrahydrofuran-2yl)acetate (**5a**,**b**) (0.025–0.035 mmol) and recombinant esterase Est56 solution (100 μl) were dissolved in phosphate buffer (ad 1000 μL, 50 mM, pH 7.5) and toluene (10% v/v). The mixture was shaken in a thermoshaker at 37 °C and 1400 rpm. After certain time intervals, to the sample (100 μL) taken, distilled water (100 μL) was added. The sample was acidified by HCl (aq, 1 N) addition, and extracted with diethylether (3×200 μL). The combined organic extracts were dried (Na_2SO_4) and from this solution, enantiomeric excess and conversions were determined by GC analysis. For **5a**,**b**, first substrate (ester) was extracted at neutral to basic pH, and then after acidification, the free acid, which was produced during the enzymatic hydrolysis, was extracted separately.

3.4.2. Preparative scale. The substrate (**5a**) (0.25–0.35 mmol) was added to a solution of recombinant esterase Est56 (crude extract with 50 U/mL, based on a *p*-nitrophenyl acetate assay, 1.0 mL) in phosphate buffer (50 mM, pH 7.5, 9 mL) and the mixture was stirred at 37 °C until 50% conversion (determined by GC analysis) was reached. *Method 1*: To the reaction mixture was added HCl (aq, 10%, 10 mL) and the resulting acidic mixture was extracted with dichloromethane (4×20 mL). The combined organic extracts were dried (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 were added water (10 mL) and aq Na_2CO_3 solution (concd, 1 mL), and the resulting basic mixture was extracted with dichloromethane (or diethylether) (4×20 mL). The combined organic extracts were dried (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 (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 5.

3.4.3. Resolution of (−)-5a and (−)-12. Table 5, entry 4 (*Method 2*) Starting with racemic **5a** (50 mg, 0.35 mmol) and Est56 (1.5 mL), (−)-**5a** (20 mg, 40%) and (−)-**12** (22 mg, 49%) were isolated without further purification as slightly yellowish and colorless oils, respectively. Column chromatography is not recommended due to the invisibility of products on TLC.

3.4.4. Methyl (tetrahydrofuran-2-yl)acetate [(−)-5a].[23] GC (chiral column, 70 °C): retention time (min)=18.6, 99% ee. Rotation ($CDCl_3$): $[\alpha]_D^{20}$ −3.6. Spectral data is the same as given above for racemic **5a**.

3.4.5. (−)-2-(Tetrahydrofuran-2-yl)acetic acid [(−)-12].[23] GC (chiral column, after conversion to the methyl ester by using diazomethane, 70 °C): retention time (min)=18.7, 86.3% ee. Rotation ($CDCl_3$): $[\alpha]_D^{20}$ −6.9. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.52–1.64 (m, 1H, CH_2), 1.89–2.00 (m, 2H, CH_2), 2.08–2.18 (m, 1H, CH_2), 2.58 (d, J=0.9 Hz, 1H, CH_2), 2.60 (d, J=2.1 Hz, 1H, CH_2), 3.77–3.84 (m, 1H, OCH_2), 3.90–3.97 (m, 1H, OCH_2), 4.26 (quint, J=6.9 Hz, 1H, OCH), 9.93 (br s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C=25.5, 31.2, 40.0 (CH_2), 68.2 (OCH_2), 75.0 (OCH), 174.7 (O═C–OH). IR (neat, cm^{-1}): $\tilde{\nu}$=3404 (br), 2926 (m), 2861 (w), 1722 (s), 1433 (w), 1276 (w), 1261 (w), 1255 (w), 1252 (w), 1201 (w), 1171 (w), 1099 (w), 1058 (m). MS (EI, 70 eV): *m*/*z* (%)=130 (M^+, 14), 83 (1), 72 (1), 55 (3), 44 (100), 28 (97). MS (EI, 70 eV): *m*/*z* (%)=130 (M^+, 14), 83 (1), 72 (1), 55 (3), 44 (100), 28 (97).

3.4.6. Co-injection of (−)-5a and (−)-12. GC (chiral column, after conversion of the acid to the methyl ester by using diazomethane, 70 °C): retention times (min)=18.8 and 19.4.

Acknowledgements

Financial support from the DAAD (scholarship for E.B.), the BASF AG, the state of Mecklenburg-Vorpommern (Landesforschungsschwerpunkt 'Neue Wirkstoffe und Screeningverfahren'), the Deutsche Bundesstiftung Umwelt (Osnabrück, Germany, grant no AZ13071), and from the Deutsche Forschungsgemeinschaft is gratefully acknowledged. We thank the BRAIN AG (Zwingenberg, Germany) and Amano Pharmaceuticals (Nagoya, Japan) for the provision of enzymes.

References and notes

1. Tetrahydrofuran natural products, acetogenins: (a) Keinan, E.; Sinha, A.; Yazbak, A.; Sinha, S. C.; Sinha, S. C. *Pure Appl. Chem.* **1997**, *69*, 423; (b) Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *Tetrahedron Lett.* **1994**, *35*, 7171; (c) Schmid, G.; Fukuyama, T.; Akasaka, K.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 259; (d) Collum, D. B.; McDonald, J. H.; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2117; (e) Ireland, R. E.; Armstrong, J. D.; Lebreton, J.; Meissner, R. S.; Rizzacasa, M. A. *J. Am. Chem. Soc.* **1993**, *115*, 7152; (f) Keinan, E.; Sinha, S. C. *Pure Appl. Chem.* **2002**, *74*, 93.
2. Lasalocid A: (a) Nakata, T.; Schmid, G.; Vranesic, B.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. *J. Am. Chem. Soc.* **1978**, *100*, 2933; (b) Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988.
3. Ferensimycin A, B, and lysocellin: Evans, D. A.; Polniaszek, R. P.; DeVries, K. M.; Guinn, D. E.; Mathre, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 7613.
4. Solamin: (a) Cecil, A. R. L.; Brown, R. C. D. *ARKIVOC* **2002**, *xi*, 49; for other solamin syntheses: (b) Cecil, A. R. L.; Hu, Y.; Vincent, M. J.; Duncan, R.; Brown, R. C. D. *J. Org. Chem.* **2004**, *69*, 3368; (c) Donohoe, T. J.; Butterworth, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 4766; (d) Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1993**, *115*, 4891.
5. For cycloadditions, see: (a) Weichert, A.; Hoffmann, H. M. R. *J. Org. Chem.* **1991**, *56*, 4098; (b) Tchelitcheff, P. *Bull. Soc. Chim. Fr.* **1954**, 672; (c) Ireland, R. E.; Haebich, D. *Chem. Ber.* **1981**, *114*, 1418; (d) Audrain, H.; Thorhauge, J.; Hazell, R. G.; Joergensen, K. A. *J. Org. Chem.* **2000**, *65*, 4487; for

reactions with amines, see: (e) Detty, M. R. *J. Org. Chem.* **1979**, *44*, 2073; (f) Batra, S.; Srivastava, S.; Singh, K.; Chander, R.; Khanna, A. K.; Bhaduri, A. P. *Bioorg. Med. Chem.* **2000**, *8*, 2195; for cyclopropanations: (g) Kirmse, W.; Rode, K. *Chem. Ber.* **1987**, *120*, 847; for oxidative carbonylations: (h) Strauch, H. C.; Erker, G.; Fröhlich, R. *J. Organomet. Chem.* **2000**, *593–594*, 388; (i) Kato, K.; Nishimura, A.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2001**, *42*, 4203; (j) Kato, K.; Tanaka, M.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2002**, *43*, 1511; for hydrogenations: (k) Tsujita, H.; Ura, Y.; Wada, K.; Kondo, T.; Mitsudo, T.-A. *Chem. Commun.* **2005**, 5100; (l) Sharma, G. V. M.; Punna, S.; Hymavathi, L.; Reddy, N. Y.; Krishna, P. R.; Chorghadeb, M. S.; Ley, S. V. *Tetrahedron: Asymmetry* **2005**, *16*, 1135; (m) Ohta, T.; Miyake, T.; Seido, N.; Kumobayashi, H.; Takaya, H. *J. Org. Chem.* **1995**, *60*, 357; see also Ref. 6.

6. Reviews: (a) Oivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309; (b) Barrett, A. G. M.; Sheth, H. G. *J. Org. Chem.* **1983**, *48*, 5017; (c) Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625; (d) Pattenden, G. *Prog. Chem. Nat. Prod.* **1978**, *35*, 133; (e) Knight, D. W. *Contemp. Org. Synth.* **1994**, *1*, 287; (f) Gerlach, H.; Wetter, H. *Helv. Chim. Acta* **1974**, *57*, 2306; (g) Schmidt, U.; Gombos, J.; Haslinger, E.; Zak, H. *Chem. Ber.* **1976**, *109*, 2628; (h) Bartlett, P. A.; Meadows, J. D.; Ottow, E. *J. Am. Chem. Soc.* **1984**, *106*, 5304; (i) Lygo, B. *Tetrahedron* **1988**, *44*, 6889.
7. Methyl nonactate: (a) Ahmar, M.; Duyck, C.; Fleming, I. *Pure Appl. Chem.* **1994**, *66*, 2049; also see for (−)-nonactic acid: (b) Fraser, B.; Perlmutter, P. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2896.
8. Spiroketal chalcogran: (a) Ley, S. V.; Lygo, B.; Organ, H. M.; Wonnacott, A. *Tetrahedron* **1985**, *41*, 3825; (b) Booth, P. M.; Fox, C. M. J.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1987**, 121; (c) Mori, K.; Sasaki, M.; Tamada, S.; Suguro, T.; Masuda, S. *Tetrahedron* **1979**, *35*, 1601.
9. For reviews of cyclization reactions of free and masked dianions, see: (a) Langer, P. *Chem.—Eur. J.* **2001**, *7*, 3858; (b) Langer, P. *Synthesis* **2002**, 441; (c) Langer, P.; Freiberg, W. *Chem. Rev.* **2004**, *104*, 4125.
10. (a) Langer, P.; Holtz, E.; Karimé, I.; Saleh, N. N. R. *J. Org. Chem.* **2001**, *66*, 6057; (b) Langer, P.; Bellur, E. *J. Org. Chem.* **2003**, *68*, 9742; see also: (c) Edwards, G. L.; Sinclair, D. J. *Tetrahedron Lett.* **1999**, *40*, 3933; (d) Krueger, S. A.; Bryson, T. A. *J. Org. Chem.* **1974**, *39*, 3167; (e) Gabriele, B.; Salerno, G.; De Pascali, F.; Costa, M.; Chiusoli, G. P. *J. Organomet. Chem.* **2000**, *593–594*, 409; (f) Pflieger, D.; Muckensturn, B. *Tetrahedron* **1989**, *45*, 2031; (g) Bellur, E.; Langer, P. *Synlett* **2004**, 2169; (h) Bellur, E.; Langer, P. *Eur. J. Org. Chem.* **2005**, 4815; (i) Bellur, E.; Langer, P. *Synthesis* **2006**, *3*, 480.
11. (a) Bellur, E.; Langer, P. *Synlett* **2004**, 2172; (b) Bellur, E.; Langer, P. *J. Org. Chem.* **2005**, *70*, 3819; (c) Bellur, E.; Langer, P. *J. Org. Chem.* **2005**, *70*, 7686.
12. (a) Bellur, E.; Freifeld, I.; Langer, P. *Tetrahedron Lett.* **2005**, *46*, 2185; (b) Bellur, E.; Langer, P. *J. Org. Chem.* **2005**, *70*, 10013.
13. (a) Bellur, E.; Görls, H.; Langer, P. *Eur. J. Org. Chem.* **2005**, 2074; see also: (b) Langer, P.; Krummel, T. *Chem.—Eur. J.* **2001**, *7*, 1720.
14. For the synthesis of (tetrahydrofuran-2-yl)acetates see: (a) Dixon, D. J.; Ley, S. V.; Tate, E. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2385; (b) Babjak, M.; Zálupský, P.; Gracza, T. *ARKIVOC* **2005**, *v*, 45.
15. Lorenz, P.; Liebeton, K.; Niehaus, F.; Eck, J. *Curr. Opin. Biotechnol.* **2002**, *13*, 572.
16. Reviews/books about enzymes in organic synthesis: (a) Bornscheuer, U. T.; Kazlauskas, R. J. *Hydrolases in Organic Synthesis—Regio- and Stereoselective Biotransformations*, 2nd ed.; Wiley-VCH: Weinheim, 2005; (b) Davis, B. G.; Boyer, V. *Nat. Prod. Rep.* **2001**, *18*, 618; (c) Faber, K. *Pure Appl. Chem.* **1997**, *69*, 1613.
17. For reviews, see: (a) Lue, P.; Greenhill, J. V. *Adv. Heterocycl. Chem.* **1997**, *67*, 209; (b) Granik, V. G.; Makarov, V. A. *Adv. Heterocycl. Chem.* **1999**, *72*, 283; (c) Sardina, F. J.; Rapoport, H. *Chem. Rev.* **1996**, *96*, 1825, and references cited therein.
18. (a) Folmer, J. J.; Acero, C.; Thai, D. L.; Rapoport, H. *J. Org. Chem.* **1998**, *63*, 8170; (b) Benovsky, P.; Stephenson, G. A.; Still, J. R. *J. Am. Chem. Soc.* **1998**, *120*, 2493; (c) Wang, M.-X.; Miao, W. S.; Cheng, Y.; Huang, Z. T. *Tetrahedron* **1999**, *55*, 14611; (d) Bertschy, H.; Meunier, A.; Neier, R. *Angew. Chem.* **1990**, *102*, 828; *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 777; (e) Montforts, F.-P.; Schwartz, U. M.; Mai, G. *Liebigs Ann. Chem.* **1990**, 1037; (f) Lygo, B. *Synlett* **1993**, 765; (g) Langer, P.; Freifeld, I. *Chem. Commun.* **2002**, 2668.
19. (a) Abbott Lab., WO-8906534; (b) Maryanoff, B. E.; McComsey, D. F.; Gardocki, J. F.; Shank, R. P.; Costanzo, M. J.; Nortey, S. O.; Schneider, C. R.; Setler, P. E. *J. Med. Chem.* **1987**, *30*, 1433; (c) Sankyo Co., JP-1996092207; (d) GlaxoSmithKline, WO-9508534; (e) Glaxo Wellcome, US-5665754; (f) Fukui, H.; Shibata, T.; Naito, T.; Nakano, J.; Maejima, T.; Senda, H.; Iwatani, W.; Tatsumi, Y.; Suda, M.; Arika, T. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2833; (g) Kaken Pharmaceutical Co., US-5668147; (h) Bucsh, R. A.; Domagala, J. M.; Laborde, E.; Sesnie, J. C. *J. Med. Chem.* **1993**, *36*, 4139; (i) Fujisawa Pharmaceuticals Co., US-5514701; (j) Sone, H.; Okuda, Y.; Tsurushima, Y.; Asano, M.; Suzuki, S.; Kawakami, Y.; Yamashita, K. *Prostaglandins* **1997**, *53*, 395; (k) Nitromed, WO-0189519; (l) Vecchietti, V.; Giordani, A.; Giardina, G.; Colle, R.; Clarke, G. D. *J. Med. Chem.* **1991**, *34*, 397; (m) Chang, A.-C.; Cowan, A.; Takemori, A. E.; Portoghese, P. S. *J. Med. Chem.* **1996**, *39*, 4478; (n) Hale, J. J.; Budhu, R. J.; Holson, E. B.; Finke, P. E.; Oates, B.; Mills, S. G.; MacCoss, M.; Gould, S. L.; DeMartino, J. A.; Springer, M. S.; Siciliano, S.; Malkowitz, L.; Schleif, W. A.; Hazuda, D.; Miller, M.; Kessler, J.; Danzeisen, R.; Holmes, K.; Lineberger, J.; Carella, A.; Carver, G.; Emini, E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2741; (o) Merck & Co., US-6166037; (p) Microside Pharmaceuticals, WO-0001714; (q) Microside Pharmaceuticals, US-6399629; (r) Hughes, T. E.; Mone, M. D.; Russell, M. E.; Weldon, S. C.; Villhauer, E. B. *Biochemistry* **1999**, *38*, 11597.
20. Pyrrolidine natural products: (a) Chen, C.; Li, X.; Neumann, C. S.; Lo, M. M.-C.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2005**, *44*, 2249; (b) Pearson, W. H. *Pure Appl. Chem.* **2002**, *74*, 1339; (c) Enders, D.; Thiebes, C. *Pure Appl. Chem.* **2001**, *73*, 573; (d) Donohoe, T. J.; Headley, C. E.; Cousins, R. P. C.; Cowley, A. *Org. Lett.* **2003**, *5*, 999; Pyrrolidine synthesis: (e) Brinner, K. M.; Ellman, J. A. *Org. Biomol. Chem.* **2005**, *3*, 2109; review: (f) Marson, C. M. *ARKIVOC* **2001**, *i*, 1.
21. (a) Bellur, E.; Görls, H.; Langer, P. *J. Org. Chem.* **2005**, *70*, 4751; (b) Montforts, F.-P.; Schwartz, U. M.; Mai, G. *Liebigs Ann. Chem.* **1990**, 1037, and references cited therein.
22. (a) Langer, P.; Armbrust, H.; Eckardt, T.; Magull, J. *Chem.—Eur. J.* **2002**, *8*, 1443; (b) Langer, P.; Freifeld, I. *Chem.—Eur. J.* **2001**, *7*, 565.
23. Laxmi, Y. R. S.; Iyengar, D. S. *Synthesis* **1996**, 594.