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Diversity-Oriented Synthesis of 2,5-Disubstituted Tetrahydrofurans Based on a "Cyclization-Hydrogenation-Substitution" Strategy

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A variety of (tetrahydrofuran-2-yl)acetates have been prepared based on hydrogenation and subsequent nucleophilic substitutions of 2-alkylidene-5-(hydroxymethyl)tetrahydrofurans. The latter are readily available by cyclization of 1,3-dicarbonyl dianions ("free dianions") with epibromohydrin.

Introduction

Functionalized tetrahydrofurans occur in a variety of pharmacologically relevant natural products.[1–8] (Tetrahydrofuran-2-yl)acetates[9] are present, for example, in the polyether antibiotics lasalocid A,[2] ferensimycin A and B, and lysocellin.[3] They also represent versatile synthetic building blocks and have been used, for example, during the synthesis of the natural acetogenin solamin isolated from *Annonaceae* (Figure 1).[4] Many acetogenins exhibit remarkable cytotoxic, antitumor, antimalarial, immunosuppressive, pesticidal and antifeedant activities.[1]

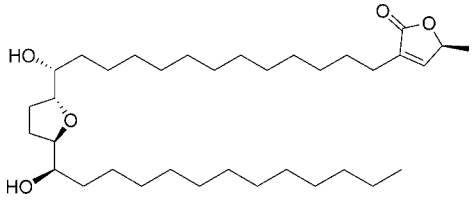

Figure 1. Solamin.

2-Alkylidenetetrahydrofurans[5,6] represent important synthetic building blocks that have been used for the synthesis of natural products. The hydrogenation[5m,6h,6i] of 2-alkylidenetetrahydrofurans has been applied to the synthesis of natural products, such as methyl nonactate which represents a building block of nonactin (Figure 2).[6,7] Some years ago, we reported the synthesis of 2-alkylidene-5-(hydroxymethyl)tetrahydrofurans by cyclization of 1,3-dicarbonyl dianions with epibromohydrin.[10–12] Herein, we report the diastereoselective hydrogenation of these compounds and their functionalization by substitution reactions.

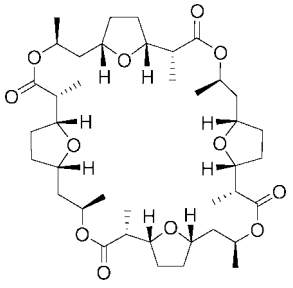

Figure 2. Nonactin.

Results and Discussion

The hydrogenation of 5-hydroxymethyl[dihydrofuran-2(3*H*)-ylidene]acetates **2a**,**b**, prepared by $LiClO_4$-mediated cyclization of dilithiated **1a**,**b** with epibromohydrin,[10] afforded the (tetrahydrofuran-2-yl)acetates **4a**,**b** with very good diastereoselectivity (Scheme 1, Table 1). The hydrogenation of **2c**, available by cyclization of the dilithiated **1c** with epibromohydrin, afforded the (tetrahydrofuran-2-yl)-acetamide **4c** with good diastereoselectivity. The influence of two hydroxy protecting groups on the diastereoselectivity was studied: the hydrogenation of **3a**, containing a *tert*-butyldimethylsilyl (TBS) group, and subsequent hydrolysis of the silyl ether gave **4c** as an inseparable 1:1 mixture of diastereomers. The hydrogenation of trityl-substituted 2-alkylidenetetrahydrofuran **3b** failed.

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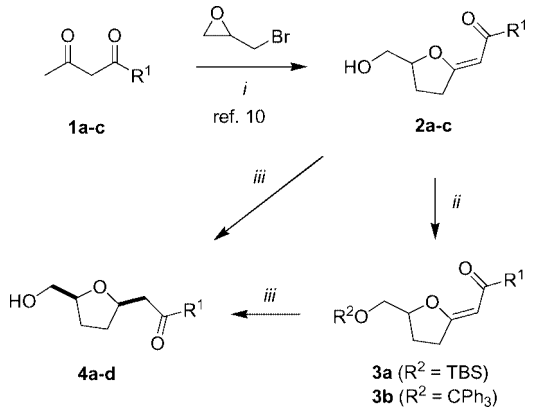


Scheme 1. Synthesis of **4a**–**d**, *i*: 1) NaH, *n*BuLi, THF, 0 °C, 1 h, 2) epibromohydrin, $LiClO_4$, –78 → –40 °C, at –40 °C 8 h, –40 → 20 °C, then at 20 °C 10 h; *ii*: NEt_3, TBSCl (or Ph_3CCl), CH_2Cl_2, 0 → 20 °C, 20 °C, 24 h; *iii*: H_2, Pd/C (0.5 equiv.), MeOH (or EtOH), 20 °C, 48 h.

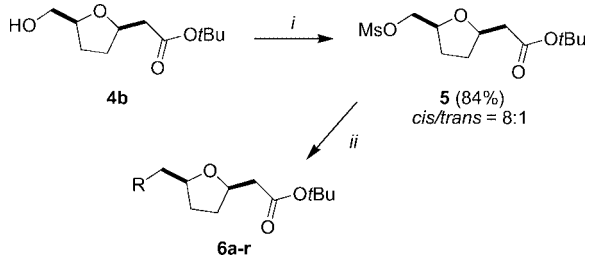
Table 1. Synthesis of (tetrahydrofuran-2-yl)acetates (**4a**–**d**).

Substrate [%][a]	4	R^1	% (4)[a]	*cis*/*trans*[b]
2a (74)[c]	**a**	OMe	67	7:1
2b (68)[c]	**b**	O*t*Bu	87	10:1
2c (96)[c]	**c**	NEt_2	86	5:1
3a (78)	**c**	NEt_2	85	1:1
3b (95)	**d**	O*t*Bu	0	–

[a] Isolated yields. [b] Diastereoselectivity (by ^{1}H NMR). [c] Known compounds (ref.[10]).

Functionalization of (Tetrahydrofuran-2-yl)acetates by S_N2 Reactions

The tetrahydrofuran **4b** was transformed into the mesylate **5** (Scheme 2, Table 2). The diversity-oriented synthesis of tetrahydrofurans by functionalization of **5** was studied. It was expected that S_N2 reactions would require some improvement studies, due to the β-oxygen effect operating in substrate **5**. In fact, the solvent, temperature and reaction time proved to be important parameters during the improvement studies (Table 3). The reaction of **5** with lithium bromide and sodium iodide afforded the [5-(bromomethyl)- and 5-(iodomethyl)tetrahydrofuran-2-yl]acetates **6a**,**b**. [5-(Azidomethyl)tetrahydrofuran-2-yl]acetate **6c** was prepared by reaction of **5** with sodium azide. The hydrogenation of the latter afforded **6d**. Treatment of **5** with dimethylamine, pyrrolidine and morpholine afforded **6e**–**g**, respectively. The tetrahydrofuran **6h** was prepared by reaction of sodium cyanide with **5**. The reaction of **5** with *n*-propyl- and *tert*-butylthiol gave **6i**,**j**, respectively. Likewise, **6k**,**l** were prepared by reaction of **5** with butyl 3-mercaptopropionate and methyl mercaptoacetate, respectively. Treatment of **5** with



Scheme 2. Synthesis of **6a**–**r**, *i*: NEt_3, MsCl, CH_2Cl_2, 0 → 20 °C, 20 °C, 18 h; *ii*: see Table 2.

Table 2. Synthesis of (tetrahydrofuran-2-yl)acetates **6a**–**r**.

6	R	% (6)[a]	*cis*/*trans*[b]	Reaction conditions[d]
a	Br	51	8:1	LiBr, (1)
b	I	48	8:1	NaI, (1)
c	N_3	72	8:1	NaN_3, (2)
d[c]	NH_2	93	7:1	H_2, Pd/C, (3)
e	NMe_2	57	4:1	Me_2NH, (2)
f		63	8:1	Pyrrolidine, (4)
g		65	7:1	Morpholine, (4)
h	CN	58	8:1	NaCN, (2)
i	S(*n*Pr)	45	1.3:1	(*n*Pr)SH, (5)
j	S(*t*Bu)	93	1:1	(*t*Bu)SH, (5)
k	$S(CH_2)_2CO_2(n$Bu)	57	4:1	(*n*Bu)$O_2C(CH_2)_2$SH, (5)
l	SCH_2CO_2Me	68	5:1	MeO_2CCH_2SH, (5)
m	SCH_2Ph	53	5:1	$PhCH_2SH$, (5)
n	SPh	74	6:1	PhSH, (5)
o		77	4:1	*o*-TolSH, (5)
p		76	5:1	*m*-TolSH, (5)
q		77	5.5:1	*p*-TolSH, (5)
r		33	1.5:1	2-hydroxypyridine, (5)

[a] Isolated yields. [b] Diastereoselectivity (by ^{1}H NMR). [c] Compound **6d** prepared by hydrogenation of **6c**. [d] Conditions: (1) acetone, reflux, 12 h; (2) DMF, 60–80 °C, 24–48 h; (3) EtOH, 20 °C, 48 h; (4) 1,4-dioxane, 60 °C, 48 h; (5) NaO*t*Bu, THF, reflux.

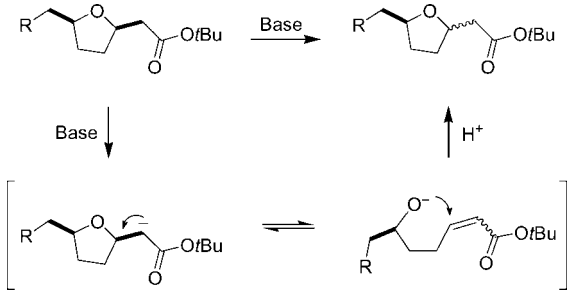
Table 3. Improvement of S_N2 reactions of (tetrahydrofuran-2-yl) acetates.

6	Entry	Reagent	Solvent	Temp. (°C)	Reaction time (h)	Yield (%)
a	1	LiBr	THF	20	24	0[a]
	2	"	DMF	153	8	0[b]
	3	"	Acetone	56	2	14[c]
	4	"	"	56	12	51
	5	"	"	56	24	46
b	1	NaI	THF	20	24	0[a]
	2	"	DMF	153	8	0[b]
	3	"	Acetone	56	2	8[c]
	4	"	"	56	12	48
	5	"	"	56	24	44
d	1	PPh_3	THF	50	16	0
	2	H_2, Pd/C	EtOH	20	24	93
e	1	$HNMe_2$	DMF/EtOH (10:1)	60	48	57
	2	"	"	70	48	53
f	1		1,4-Dioxane	50	24	0[a]
	2		"	65	48	63
	3		"	101	48	41
g	1		1,4-Dioxane	60	48	65
	2		"	65	48	60
h	1	NaCN	1,4-Dioxane	65	48	0
	2	"	DMF	60	24	58
	3	"	"	60	48	51

[a] No conversion, substrate was recovered. [b] Decomposition. [c] A small amount of substrate was recovered.

benzyl-, phenyl-, *o*-tolyl-, *m*-tolyl- and *p*-tolylthiol afforded the tetrahydrofurans **6m**–**q**, respectively. Compound **6r** was prepared from **5** with 2-hydroxypyridine. Treatment of **6n** with boron trifluoride–diethyl ether resulted in hydrolysis of the ester functionality and afforded the [5-(phenylthiomethyl)tetrahydrofuran-2-yl]acetic acid in very low yield (12%).

The diastereomeric ratio of the tetrahydrofurans decreased in several reactions, which can be explained by base-mediated epimerization of carbon atom C-2 based on a ring-opening/ring-closure mechanism (Scheme 3). Epimerizations have been observed especially for the compounds prepared under basic conditions (Table 2). Related epimerizations have been previously observed.[13]



Scheme 3. Epimerization of 2-[(alkoxycarbonyl)methyl]tetrahydrofurans.

Conclusion

A variety of [5-(hydroxymethyl)tetrahydrofuran-2-yl]acetates have been prepared by hydrogenation of 2-alkylidenetetrahydrofurans, readily available by cyclization reactions of 1,3-dicarbonyl dianions ("free dianions") with epibromohydrin. In addition, (tetrahydrofuran-2-yl)acetates have been functionalized by nucleophilic substitution reactions.

Experimental Section

General Comments: All solvents were dried by standard methods and all reactions were carried out under an inert gas. For ^{1}H and ^{13}C NMR spectra, the deuterated solvents indicated were used. Mass spectrometric 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.

General Procedure for the Hydrogenation of 2-Alkylidenetetrahydrofurans: To a H_2-concentrated suspension of Pd/C (0.5 equiv., 10% Pd on charcoal) in methanol (or ethanol) (5–10 mL/mmol) was added 2-alkylidenetetrahydrofuran (**2** or **3**) (1 equiv.). The reaction mixture was concentrated with H_2 and stirred under H_2 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 the (tetrahydrofuran-2-yl)acetate **4**. Notably, the (tetrahydrofuran-2-yl)acetates are 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.

Methyl [5-(Hydroxymethyl)tetrahydrofuran-2-yl]acetate (4a): The general hydrogenation procedure was applied to compound **2a** (0.150 g, 0.80 mmol) with Pd/C (20% Pd, 0.44 g, 0.40 mmol) in ethanol (3 mL), and compound **4a** was isolated after chromatography (silica gel; petroleum ether/Et_2O, 3:1) as a slightly yellowish oil [0.082 g, 67%, an inseparable 7:1 (*cis*/*trans*) mixture of diastereomers]. ^{1}H NMR ($CDCl_3$, 250 MHz, for major diastereomer): δ = 1.61 (m, 2 H, CH_2), 1.84 (m, 2 H, CH_2), 2.50 (m, 2 H, CH_2CO), 3.41 (m, 2 H, C*H*$_2$OH), 3.64 (s, 3 H, OCH_3), 4.03 (m, 1 H, OC*H*-CH_2OH), 4.24 (m, 1 H, OC*H*CH_2CO) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz, for major diastereomer): δ = 25.5 (C-4), 30.3 (C-3), 39.5 (C-1, CH_2), 50.8 (OCH_3), 63.5 (OCH_2), 74.8 (C-2), 79.0 (C-5, OCH), 170.8 (O=C–O) ppm.

***tert*-Butyl [5-(Hydroxymethyl)tetrahydrofuran-2-yl]acetate (4b):** The general hydrogenation procedure was applied to compound **2b** (1.00 g, 4.60 mmol) with Pd/C (10% Pd, 1.22 g, 1.15 mmol) in ethanol (45 mL), and compound **4b** was isolated without further purification as a yellowish oil [0.88 g, 87%, an inseparable 10:1 (*cis*/*trans*) mixture of diastereomers]. ^{1}H NMR ($CDCl_3$, 250 MHz, for major diastereomer): δ = 1.44 (s, 9 H, O*t*Bu), 1.60–2.16 (m, 4 H, 2 CH_2), 2.44 (m, 2 H, CH_2), 3.43 (m, 1 H, C*H*$_2$–OH), 3.75 (m, 1 H, C*H*$_2$–OH), 4.06 (m, 1 H, OCH), 4.28 (m, 1 H, OCH) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz, for major diastereomer): δ = 26.3 (C-4, CH_2), 28.0 (3 CH_3 of O*t*Bu), 31.2 (C-3), 42.1 (C-1, CH_2), 64.5 (CH_2–OH), 76.1 (C-2), 79.9 (C-5, OCH), 80.8 (C of O*t*Bu), 170.8 (O=C–O) ppm. IR (neat): $\tilde{\nu}$ = 3430 (br), 2977 (s), 2934 (m), 2876 (m), 1728 (s), 1393 (m), 1368 (m), 1322 (w), 1299 (w), 1256 (w), 1152 (s), 1100 (m), 1058 (m) cm^{-1}. MS (DCI, NH_3): *m*/*z* (%) = 234 (69) $[M + NH_4]^+$, 178 (100). $C_{11}H_{20}O_4$ (216.3): calcd. C 61.09, H 9.32; found C 61.07, H 9.36.

***N*,*N*-Diethyl-2-[5-(hydroxymethyl)tetrahydrofuran-2-yl]acetamide (4c):** The general hydrogenation procedure was applied to compound **2c** (0.100 g, 0.47 mmol) with Pd/C (20% Pd, 0.49 g, 0.24 mmol) in ethanol (3 mL), and compound **4c** was isolated after chromatography (silica gel; petroleum ether/Et_2O, 3:1) as a slightly yellowish oil [0.087 g, 86%, an inseparable 5:1 (*cis*/*trans*) mixture of diastereomers]. ^{1}H NMR ($CDCl_3$, 250 MHz, for major diastereomer): δ = 1.02 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.11 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.61 (m, 1 H, CH_2), 2.06 (m, 1 H, CH_2), 1.83 (m, 2 H, CH_2), 2.42 (dd, *J* = 6.3, 6.3 Hz, 1 H, CH_2CO), 2.57 (dd, *J* = 6.3, 6.3 Hz, 1 H, CH_2CO), 3.25 [m, 4 H, N(C*H*$_2$CH$_3$)$_2$], 3.58 (m, 2 H, C*H*$_2$OH), 3.96 (m, 1 H, OC*H*CH$_2$OH), 4.14 (m, 1 H, OC*H*CH_2CO) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz, for major diastereomer): δ = 12.8, 14.2 (CH_3), 26.2 (C-4), 31.5 (C-3), 39.1 (C-1, CH_2), 39.9, 41.9 (NCH_2), 64.4 (OCH_2), 76.1 (C-2), 79.8 (C-5, OCH), 169.8 (O=C–O) ppm.

Functionalization of 2-Alkylidentetrahydrofurans and (Tetrahydrofuran-2-yl)acetates by S_N2 Reactions

***N*,*N*-Diethyl-2-{5-[(*tert*-butyldimethylsilyloxy)methyl]tetrahydrofuran-2(3*H*)-ylidene}acetamide (3a):** To a CH_2Cl_2 (10 mL) solution of compound **2c** (0.500 g, 2.30 mmol) were added NEt_3 (0.26 g, 2.6 mol) and *tert*-butyldimethylsilyl chloride (0.36 g, 2.4 mmol) at 0 °C and the reaction mixture was stirred at 20 °C for 20 h. Then 4-(dimethylamino)pyridine (0.024 g, 0.2 mmol) was added at 20 °C and the mixture stirred for 10 h. To the reaction mixture was added H_2O (20 mL) and the resulting mixture extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were washed with concentrated aqueous NH_4Cl (40 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; *n*-pentane/Et_2O, 10:1) to give compound **3a** (0.59 g, 78%) as a yellowish oil. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.03 [s, 3 H, Si(CH_3)$_2$], 0.05 [s, 3 H, Si(CH_3)$_2$], 0.88

(s, 9 H, *t*Bu), 1.14 [m, 6 H, $N(CH_2CH_3)_2$], 2.01 (m, 2 H, CH_2), 2.71 (m, 2 H, CH_2), 3.25 [m, 4 H, $N(CH_2CH_3)_2$], 3.78 (m, 2 H, OCH_2), 4.60 (m, 1 H, OCH), 4.93 (s, 1 H, CH=C) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = –5.6 [2 C, $Si(CH_3)_2$], 13.2, 14.4 (CH_3), 18.1 (C, *t*Bu), 25.1 (C-3, CH_2), 25.7 (3 CH_3, *t*Bu), 31.4 (C-4, CH_2), 39.5, 42.3 (NCH_2), 64.6 (OCH_2), 84.8 (C-5, OCH), 88.2 (*C*H=C–O), 165.7 (O=C–O), 166.8 (O–*C*=CH). MS (EI, 70 eV): *m*/*z* (%) = 327 (9) $[M]^+$, 270 (100), 255 (10).

***tert*-Butyl {5-[(Triphenylmethoxy)methyl]dihydrofuran-2(3*H*)-ylidene}acetate (3b):** To a CH_2Cl_2 (20 mL) solution of compound **2b** (0.20 g, 0.93 mmol) were added NEt_3 (0.19 g, 1.86 mmol), 4-(dimethylamino)pyridine (0.04 g) and triphenylmethyl chloride (0.29 g, 1.03 mmol) at 20 °C, and the mixture stirred for 18 h. To the reaction mixture was added ice/water and the resulting mixture extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were washed with concentrated aqueous NH_4Cl (40 mL) and H_2O (20 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; *n*-pentane/Et_2O, 10:1) to give compound **3b** {0.40 g, 95%, an inseparable 3:1 [(*E*)/(*Z*)] mixture of diastereomers} as a white solid. ^1H NMR ($CDCl_3$, 250 MHz, for major diastereomer): δ = 1.47 (s, 9 H, 3 CH_3), 1.82–2.14 (m, 2 H, CH_2), 2.57 (m, 2 H, CH_2), 3.25 (m, 2 H, CH_2), 4.78 (m, 1 H, OCH) 5.33 (s, 1 H, CH=C), 7.12–7.46 (m, 15 H, 15 CH) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz, for major diastereomer): δ = 26.0 (C-3, CH_2), 28.5 (3 CH_3, *t*Bu), 30.2 (C-4, CH_2), 65.4 (OCH_2), 78.9 (O*t*Bu), 82.2 (C-5, OCH), 86.7 (*C*Ph_3), 91.3 (*C*H=C–O), 127.1, 127.9, 128.6 (CH of Ph), 143.7 (C of Ph), 168.2 (O=C–O), 175.7 (O–*C* = CH) ppm. IR(KBr): $\tilde{\nu}$ = 3466 (br., m), 2976 (w), 2930 (w), 1727 (m), 1705 (m), 1639 (m), 1445 (m), 1368 (m), 1325 (m), 1246 (m), 1155 (s), 1112 (s), 1081 (m), 1032 (m), 1011 (m), 759 (s), 700 (s), 638 (w) cm^{-1}. MS (DCI, NH_3): *m*/*z* (%) = 492 (1) $[M + H_2O + NH_4]^+$, 243 (100), 232 (4), 176 (3).

***tert*-Butyl [5-(Mesyloxymethyl)tetrahydrofuran-2-yl]acetate (5):** To a CH_2Cl_2 (20 mL) solution of compound **4b** (0.32 g, 1.48 mmol) were added NEt_3 (0.30 g, 2.96 mmol) and methanesulfonyl chloride (0.25 g, 2.20 mmol) at 0 °C. The reaction mixture was warmed to 20 °C and stirred at 20 °C for 18 h. To the reaction mixture was added concentrated aqueous $NaHCO_3$ and the resulting mixture extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; petroleum ether/Et_2O, 1:1) to give compound **5** [0.52 g, 84%, an inseparable 8:1 (*cis*/*trans*) mixture of diastereomers] as a colorless oil. ^1H NMR ($CDCl_3$, 250 MHz, for major diastereomer): δ = 1.43 (s, 9 H, 3 CH_3), 1.47–1.88 (m, 2 H, CH_2), 1.96–2.18 (m, 2 H, CH_2), 2.38 (dd, *J* = 16.2, 7.2 Hz, 1 H, CH_2), 2.54 (dd, *J* = 16.2, 7.2 Hz, 1 H, CH_2), 3.04 (s, 3 H, SCH_3), 4.13–4.37 (m, 4 H, CH_2OMs, 2 OCH) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz, for major diastereomer): δ = 27.3 (C-4, CH_2), 28.0 (3 CH_3, *t*Bu), 30.0 (C-3, CH_2), 37.7 (SCH_3), 41.9 (C-1, CH_2), 71.6 (OCH_2), 76.5 (C-2), 76.6 (C-5, OCH), 80.7 (O*t*Bu), 170.2 (O=C–O) ppm. IR (neat): $\tilde{\nu}$ = 3340 (br., m), 3338 (m), 2025 (s), 2975 (s), 2942 (s), 1727 (s), 1450 (m), 1412 (m), 1399 (m), 1350 (s), 1277 (m), 1258 (m), 1174 (s), 1092 (m), 1044 (m), 978 (s), 958 (s), 882 (m), 856 (m), 824 (m), 530 (m), 505 (m) cm^{-1}. MS (DCI, NH_3): *m*/*z* (%) = 606 (16) $[2M + NH_4]^+$, 312 (100) $[M + NH_4]^+$, 256 (63).

***tert*-Butyl [5-(Bromomethyl)tetrahydrofuran-2-yl]acetate (6a):** To an acetone (10 mL) solution of compound **5** (0.22 g, 0.75 mmol) was added LiBr (0.45 g, 5.20 mmol) at 20 °C. The reaction mixture was heated and stirred at reflux for 12 h. After cooling to 20 °C, the precipitate was filtered, washed with acetone and the filtrate was concentrated in vacuo. The residue was dissolved in H_2O/CH_2Cl_2 (1:1, 30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; petroleum ether/Et_2O, 10:1) to give compound **6a** [0.11 g, 51%, an inseparable 8:1 (*cis*/*trans*) mixture of diastereomers] as a yellowish oil. ^1H NMR ($CDCl_3$, 250 MHz, for major diastereomer): δ = 1.43 (s, 9 H, 3 CH_3, *t*Bu), 1.58–1.91 (m, 2 H, CH_2), 2.08 (m, 2 H, CH_2), 2.38 (dd, *J* = 16.2, 7.2 Hz, 1 H, CH_2), 2.59 (dd, *J* = 16.2, 7.2 Hz, 1 H, CH_2), 3.33 (dd, *J* = 11.4, 7.2 Hz, 1 H, CH_2Br), 3.43 (dd, *J* = 11.4, 7.2 Hz, 1 H, CH_2Br), 4.16 (m, 1 H, OCH), 4.29 (m, 1 H, OC*H*CH_2Br) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz, for major diastereomer): δ = 28.1 (3 CH_3, *t*Bu), 29.8 (C-4), 30.7 (C-3, CH_2), 35.7 (CH_2–Br), 42.0 (C-1, CH_2), 76.7 (C-2), 78.3 (C-5, OCH), 80.6 (O*t*Bu), 170.4 (O=C–O) ppm. MS (DCI, NH_3): *m*/*z* (%) = 576 (45) $[2M + NH_4]^+$, 313 (36), 296 (100) $[M + NH_4]^+$, 242 (11). $C_{11}H_{19}BrO_3$ (279.2): calcd. C 47.32, H 6.86; found C 47.35, H 6.90.

***tert*-Butyl [5-(Iodomethyl)tetrahydrofuran-2-yl]acetate (6b):** To an acetone (10 mL) solution of compound **5** (0.20 g, 0.68 mmol) was added NaI (0.71 g, 4.76 mmol) at 20 °C. The reaction mixture was heated and stirred at reflux for 8 h. After cooling to 20 °C, the precipitate was filtered, washed with acetone and the filtrate was concentrated in vacuo. The residue was dissolved in H_2O/CH_2Cl_2 (1:1, 30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; petroleum ether/Et_2O, 10:1) to give compound **6b** [0.07 g, 48%, an inseparable 10:1 (*cis*/*trans*) mixture of diastereomers] as a yellowish oil. ^1H NMR ($CDCl_3$, 250 MHz, for major diastereomer): δ = 1.47 (s, 9 H, 3 CH_3, *t*Bu), 1.72 (m, 2 H, CH_2), 2.08 (m, 2 H, CH_2), 2.41 (dd, *J* = 16.2, 7.2 Hz, 1 H, CH_2), 2.59 (dd, *J* = 16.2, 7.2 Hz, 1 H, CH_2), 3.16 (dd, *J* = 14.4, 7.2 Hz, 1 H, CH_2I), 3.27 (dd, *J* = 14.4, 7.2 Hz, 1 H, CH_2I), 4.23 (m, 1 H, OCH), 4.34 (m, 1 H, OC*H*CH_2I) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz, for major diastereomer): δ = 7.1 (CH_2–I), 28.1 (3 CH_3, *t*Bu), 30.9 (C-3), 31.4 (C-4), 42.2 (C-1, CH_2), 76.9 (C-2), 78.6 (C-5, OCH), 80.6 (O*t*Bu), 170.4 (O=C–O) ppm. IR (neat): $\tilde{\nu}$ = 3436 (br., w), 2975 (m), 2928 (m), 1729 (s), 1646 (w), 1573 (w), 1555 (w), 1526 (w), 1521 (w), 1456 (w), 1412 (w), 1394 (w), 1368 (m), 1348 (w), 1320 (w), 1297 (w), 1256 (w), 1210 (w), 1158 (s), 1125 (w), 1097 (m), 1055 (m), 967 (w), 947 (w), 893 (w), 882 (w), 843 (w), 801 (w), 600 (w) cm^{-1}. MS (DCI, NH_3): *m*/*z* (%) = 670 (100) $[2M + NH_4]^+$, 344 (71) $[M + NH_4]^+$, 288 (14). $C_{11}H_{19}IO_3$ (326.2): calcd. C 40.50, H 5.87; found C 40.46, H 5.93.

***tert*-Butyl [5-(Azidomethyl)tetrahydrofuran-2-yl]acetate (6c):** To a DMF (10 mL) solution of crude compound **5** (0.49 g, 2.05 mmol) was added NaN_3 (0.40 g, 6.16 mmol) at 20 °C. The reaction mixture was heated and stirred at 80 °C for 48 h. After cooling to 20 °C, H_2O (20 mL) was added to the mixture and the resulting mixture extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; petroleum ether/Et_2O, 40:1 → 10:1) to give compound **6c** [0.16 g, 72%, an inseparable 8:1 (*cis*/*trans*) mixture of diastereomers] as a yellowish oil. ^1H NMR ($CDCl_3$, 250 MHz, for major diastereomer): δ = 1.44 (s, 9 H, 3 CH_3, *t*Bu), 1.58–1.79 (m, 2 H, CH_2), 1.92–2.14 (m, 2 H, CH_2), 2.39 (dd, *J* = 16.2, 7.2 Hz, 1 H, CH_2), 2.61 (dd, *J* = 16.2, 7.2 Hz, 1 H, CH_2), 3.18 (dd, *J* = 14.4, 6.3 Hz, 1 H, CH_2N_3), 3.36 (dd, *J* = 14.4, 6.3 Hz, 1 H, CH_2N_3), 4.11 (m, 1 H, OCH), 4.26 (m, 1 H, OC*H*CH_2N_3) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz, for major diastereomer): δ = 27.3 (3 CH_3, *t*Bu), 28.3 (C-4), 30.9 (C-3), 41.9 (C-1, CH_2), 54.8 (CH_2–N_3), 76.4 (C-2),

78.0 (C-5, OCH), 80.6 (O*t*Bu), 170.4 (O=C–O) ppm. MS (DCI, NH_3): *m*/*z* (%) = 259 (100) $[M + NH_4]^+$, 220 (9), 203 (48). $C_{11}H_{19}N_3O_3$ (241.3): calcd. C 54.75, H 7.94; found C 54.71, H 7.93.

***tert*-Butyl [5-(Aminomethyl)tetrahydrofuran-2-yl]acetate (6d):** The general hydrogenation procedure was applied to compound **6c** (0.17 g, 0.70 mmol) with Pd/C (0.37 g, 10% Pd, 0.35 mmol) in ethanol (12 mL), and compound **6d** was isolated without further purification as a yellowish oil [0.13 g, 93%, an inseparable 7:1 (*cis*/*trans*) mixture of diastereomers]. ^{1}H NMR ($CDCl_3$, 250 MHz, for major diastereomer): δ = 1.39 (s, 9 H, 3 CH_3, *t*Bu), 1.51–1.78 (m, 2 H, CH_2), 1.86–2.13 (m, 2 H, CH_2), 2.24–2.59 (m, 2 H, CH_2), 2.61–3.03 (m, 2 H, CH_2), 4.03 (m, 1 H, OCH), 4.18 (m, 1 H, OC*H*CH_2N), 4.92 (br., 2 H, NH_2) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz, for major diastereomer): δ = 28.0 (3 CH_3, *t*Bu), 41.9 (C-4), 42.2 (C-3), 45.3 (C-1, CH_2), 54.3 (CH_2–NH_2), 76.0 (C-2), 78.2 (C-5, OCH), 80.5 (O*t*Bu), 170.6 (O=C–O) ppm. IR (neat): $\tilde{\nu}$ = 3387 (br., s), 2977 (s), 2934 (s), 2879 (s), 1728 (s), 1674 (s), 1573 (m), 1548 (m), 1539 (m), 1455 (s), 1418 (m), 1391 (s), 1368 (s), 1298 (s), 1255 (s), 1212 (s), 1154 (s), 1074 (s), 950 (m), 843 (w) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 215 (2) $[M]^+$, 142 (33), 129 (100), 111 (57), 57 (79). The exact molecular mass *m*/*z* = 215.1521 ± 2 ppm $[M]^+$ for $C_{11}H_{21}NO_3$ was confirmed by HRMS (EI, 70 eV).

***tert*-Butyl {5-[(Dimethylamino)methyl]tetrahydrofuran-2-yl}acetate (6e):** To a DMF (5 mL) solution of compound **5** (0.20 g, 0.68 mmol) was added dimethylamine (2.30 g, 1.70 mmol, 33% in methanol) at 20 °C. The reaction mixture was heated and stirred at 60 °C for 1 d. After cooling to 20 °C, concentrated aqueous $NaHCO_3$ (20 mL) was added and the resulting mixture extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with H_2O (2 × 50 mL) and brine (50 mL), then dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; Et_2O) to give compound **6e** [0.09 g, 57%, an inseparable 4:1 (*cis*/*trans*) mixture of diastereomers] as a colorless oil. ^{1}H NMR ($CDCl_3$, 250 MHz, for major diastereomer): δ = 1.42 (s, 9 H, 3 CH_3, *t*Bu), 1.56 (m, 2 H, CH_2), 2.02 (m, 2 H, CH_2), 2.26 (s, 6 H, 2NCH_3), 2.38 (m, 3 H, CH_2, NCH_2), 2.59 (dd, *J* = 16.2, 7.2 Hz, 1 H, CH_2), 3.97 (m, 1 H, OCH), 4.18 (m, 1 H, OC*H*CH_2N) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz, for major diastereomer): δ = 28.0 (3 CH_3, *t*Bu), 29.8 (C-4), 30.5 (C-3, CH_2), 36.4 (2NCH_3), 42.3 (C-1, CH_2), 64.5 (NCH_2), 75.9 (C-2), 77.3 (C-5, OCH), 80.36 (O*t*Bu), 170.5 (O=C–O) ppm. MS (EI = 70 eV): *m*/*z* (%) = 243 (3) $[M]^+$, 170 (7), 58 (100), 57 (5). The exact molecular mass *m*/*z* = 243.1834 ± 2 ppm $[M]^+$ for $C_{13}H_{25}NO_3$ was confirmed by HRMS (EI, 70 eV).

***tert*-Butyl [5-(Pyrrolidin-1-ylmethyl)tetrahydrofuran-2-yl]acetate (6f):** To a 1,4-dioxane (5 mL) solution of compound **5** (0.27 g, 0.92 mmol) was added pyrrolidine (0.13 g, 1.84 mmol) at 20 °C. The reaction mixture was heated and stirred at 60 °C for 2 d. After cooling to 20 °C, the precipitate was filtered, washed with 1,4-dioxane, and the filtrate was concentrated in vacuo. To the residue was added H_2O (20 mL) and the resulting mixture extracted with Et_2O (2 × 30 mL) and CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with H_2O (50 mL) and brine (50 mL), then dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; Et_2O) to give compound **6f** [0.15 g, 63%, an inseparable 8:1 (*cis*/*trans*) mixture of diastereomers] as a colorless oil. ^{1}H NMR ($CDCl_3$, 250 MHz, for major diastereomer): δ = 1.44 (s, 9 H, 3 CH_3, *t*Bu), 1.57 (m, 2 H, CH_2), 1.75 (m, 4 H, 2 CH_2), 2.01 (m, 2 H, CH_2), 2.32 (dd, *J* = 16.2, 7.2 Hz, 1 H, CH_2), 2.44–2.63 (m, 7 H, CH_2, 3 NCH_2), 3.98 (m, 1 H, OCH), 4.18 (m, 1 H, OC*H*CH_2N) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz, for major diastereomer): δ = 23.3 (2 CH_2), 28.0 (3 CH_3, *t*Bu), 29.8 (C-4), 30.6 (C-3), 42.4 (C-1, CH_2), 54.8 (2 NCH_2), 61.4 (NCH_2), 75.8 (C-2), 78.4 (C-5, OCH), 80.4 (O*t*Bu), 170.6 (O=C–O) ppm. IR (neat): $\tilde{\nu}$ = 3433 (br., w), 2972 (m), 2933 (m), 2877 (m), 2797 (w), 1729 (s), 1654 (w), 1457 (m), 1428 (w), 1392 (m), 1368 (m), 1348 (w), 1319 (m), 1292 (m), 1256 (m), 1154 (s), 1107 (m), 1068 (m) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 269 (2) $[M]^+$, 196 (8), 84 (100). The exact molecular mass *m*/*z* = 269.1991 ± 2 ppm $[M]^+$ for $C_{15}H_{27}NO_3$ was confirmed by HRMS (EI, 70 eV).

***tert*-Butyl [5-(Morpholinomethyl)tetrahydrofuran-2-yl]acetate (6g):** To a 1,4-dioxane (5 mL) solution of compound **5** (0.20 g, 0.68 mmol) was added morpholine (0.12 g, 0.99 mmol) at 20 °C. The reaction mixture was heated and stirred at 60 °C for 2 d. After cooling to 20 °C, the precipitate was filtered, washed with 1,4-dioxane and the filtrate was concentrated in vacuo. To the residue was added H_2O (20 mL) and the resulting mixture extracted with Et_2O (2 × 30 mL) and CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with H_2O (50 mL) and brine (50 mL), then dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; Et_2O) to give compound **6g** [0.12 g, 65%, an inseparable 7:1 (*cis*/*trans*) mixture of diastereomers] as a colorless oil. ^{1}H NMR ($CDCl_3$, 250 MHz, for major diastereomer): δ = 1.43 (s, 9 H, 3 CH_3, *t*Bu), 1.57 (m, 2 H, CH_2), 2.01 (m, 2 H, CH_2), 2.34 (dd, *J* = 16.2, 7.2 Hz, 1 H, CH_2), 2.53 (m, 7 H, CH_2, 3 NCH_2), 3.69 (t, *J* = 5.4 Hz, 4 H, 2 OCH_2), 4.04 (m, 1 H, OCH), 4.21 (m, 1 H, OC*H*CH_2N) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz, for major diastereomer): δ = 28.1 (3 CH_3, *t*Bu), 29.9 (C-4), 30.4 (C-3), 42.4 (C-1, CH_2), 54.3 (2 NCH_2), 63.8 (NCH_2), 66.8 (2 OCH_2), 76.1 (C-2), 77.4 (C-5, OCH), 80.4 (O*t*Bu), 170.5 (O=C–O) ppm. IR (neat): $\tilde{\nu}$ = 3439 (br., w), 2973 (m), 2931 (m), 2859 (w), 1728 (s), 1455 (m), 1391 (w), 1368 (m), 1326 (w), 1295 (m), 1255 (m), 1153 (s), 1117 (s), 1069 (m) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 285 (4) $[M]^+$, 212 (13), 100 (100), 87 (7). The exact molecular mass *m*/*z* = 285.1940 ± 2 ppm $[M]^+$ for $C_{15}H_{27}NO_4$ was confirmed by HRMS (EI, 70 eV).

***tert*-Butyl [5-(Cyanomethyl)tetrahydrofuran-2-yl]acetate (6h):** To a DMF (16 mL) solution of compound **5** (0.20 g, 0.68 mmol) was added NaCN (0.33 g, 6.80 mmol) at 20 °C. The reaction mixture was heated and stirred at 60 °C for 1 d. After cooling to 20 °C, concentrated aqueous $NaHCO_3$ (30 mL) was added and extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with H_2O (2 × 50 mL) and brine (50 mL), then dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; petroleum ether/Et_2O, 5:1) to give compound **6h** [0.09 g, 58%, an inseparable 8:1 (*cis*/*trans*) mixture of diastereomers] as a colorless oil. ^{1}H NMR ($CDCl_3$, 250 MHz, for major diastereomer): δ = 1.44 (s, 9 H, 3 CH_3, *t*Bu), 1.76 (m, 2 H, CH_2), 2.12 (m, 2 H, CH_2), 2.43 (dd, *J* = 16.2, 7.2 Hz, 1 H, CH_2), 2.49–2.65 (m, 3 H, CH_2, CH_2CN), 4.14 (m, 1 H, OCH), 4.26 (m, 1 H, OC*H*CH_2N) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz, for major diastereomer): δ = 24.4 (*C*H_2–CN), 28.0 (3 CH_3, *t*Bu), 30.3 (C-4), 30.6 (C-3), 41.7 (C-1, CH_2), 74.1 (C-2), 76.6 (C-5, OCH), 80.7 (O*t*Bu), 117.3 (CN), 170.2 (O=C–O) ppm. MS (DCI, NH_3): *m*/*z* (%) = 468 (7) $[2M + NH_4]^+$, 457 (5), 243 (100) $[M + NH_4]^+$, 226 (35) $[M + H]^+$, 187 (39). $C_{12}H_{19}NO_3$ (225.3): calcd. C 63.98, H 8.50; found C 64.01, H 8.52.

General Procedure for the S_N2 Reactions of Thiols or Alcohols with *tert*-Butyl [5-(Mesyloxymethyl)tetrahydrofuran-2-yl]acetate (5): Sodium (1.2 equiv.) in *tert*-butyl alcohol (10 mL) was stirred for 12 h and to this suspension was added THF (10 mL) at 0 °C. To the mixture was added the thiol or alcohol (2.5 equiv.) and the resulting mixture stirred until a clear solution had formed. To this solution

was slowly added compound **5** (1.0 equiv.) and the resulting mixture stirred at reflux for 3–24 h. After cooling to ambient temperature, concentrated aqueous $NaHCO_3$ (100 mL) was added and the resulting mixture extracted with diethyl ether repeatedly. The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; *n*-pentane/Et_2O) to give **6i**–**r**.

***tert*-Butyl [5-(Prop-1-ylthiomethyl)tetrahydrofuran-2-yl]acetate (6i):** The general procedure for S_N2 reactions was applied to compound **5** (0.166 g, 0.56 mmol) with Na (0.019 g, 0.84 mmol) and propan-1-thiol (0.130 g, 1.70 mmol). Compound **6i** was isolated after chromatography (silica gel; *n*-pentane/Et_2O, 15:1; R_f = 0.30) as a colorless oil [0.069 mg, 45%, an inseparable 1.3:1 (*cis*/*trans*) mixture of diastereomers]. ^1H NMR ($CDCl_3$, 250 MHz, for both diastereomers): δ = 0.97 (t, J = 7.2 Hz, 3 H, CH_3) 1.44 (s, 9 H, 3 CH_3, *t*Bu), 1.45–1.80 (m, 4 H, CH_2), 1.90–2.20 (m, 2 H, CH_2), 2.32 (dd, J = 7.2, 7.2 Hz, 1 H, CH_2, minor diastereomer), 2.37 (dd, J = 7.2, 7.2 Hz, 1 H, CH_2, major diastereomer), 2.50–2.65 (m, 4 H, 2 CH_2), 2.70 (dd, J = 13.2, 5.4 Hz, 1 H, SCH_2), 4.00–4.10 (m, 1 H, OCH, major diastereomer), 4.10–4.30 (m, 1 H, OCH), 4.30–4.40 (m, 1 H, OCH, minor diastereomer) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz, for both diastereomers): δ = 13.4 (CH_3), 23.0 (CH_2), 28.1 (3 CH_3, *t*Bu), 30.4, 31.2, 34.8, 37.2, 42.0 (CH_2, minor diastereomer), 30.8, 31.7, 34.9, 37.2, 42.3 (CH_2, major diastereomer), 75.6, 78.6 (OCH, minor diastereomer), 76.0, 79.2 (OCH, major diastereomer), 80.5 (O*t*Bu), 170.5 (O=C–O) ppm. IR (neat): $\tilde{\nu}$ = 2968 (s), 2932 (m), 1731 (s), 1459 (m), 1368 (m), 1295 (m), 1255 (m), 1161 (s), 1060 (m), 948 (w), 844 (w) cm^{-1}. MS (EI = 70 eV): *m*/*z* (%) = 274 (5) $[M]^+$, 129 (100), 111 (38), 57 (25). $C_{14}H_{26}O_3S$ (274.4): calcd. C 61.28, H 9.55; found C 61.43, H 9.28.

***tert*-Butyl [5-(*tert*-Butylthiomethyl)tetrahydrofuran-2-yl]acetate (6j):** The general procedure for S_N2 reactions was applied to compound **5** (0.150 g, 0.51 mmol) with Na (0.019 g, 0.84 mmol) and 2-methylpropan-2-thiol (0.153 g, 1.70 mmol). Compound **6j** was isolated without further purification as a slightly yellowish oil [0.137 g, 93%, an inseparable 1:1 (*cis*/*trans*) mixture of diastereomers]. ^1H NMR ($CDCl_3$, 250 MHz, for both diastereomers): δ = 1.30 (s, 9 H, 3 CH_3 of S*t*Bu), 1.43 (s, 9 H, 3 CH_3 of O*t*Bu), 1.55–1.75 (m, 2 H, CH_2), 2.00–2.20 (m, 2 H, CH_2), 2.25–2.40 (m, 1 H, CH_2), 2.50–265 (m, 2 H, CH_2), 2.76 (dd, J = 13.2, 5.4 Hz, 1 H, SCH_2), 3.95–4.05 (m, 1 H, OCH, one diastereomer), 4.05–4.15 (m, 1 H, OCH, one diastereomer), 4.15–4.25 (m, 1 H, OCH, one diastereomer), 4.30–4.40 (m, 1 H, OCH, one diastereomer) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz, for both diastereomers): δ = 28.1 (3 CH_3 of O*t*Bu), 30.9 (3 CH_3 of S*t*Bu), 30.6, 30.8, 31.4, 31.6, 33.7, 33.8, 42.0, 42.1 42.2 (CH_2, S*t*Bu), 75.6, 76.0, 78.3, 78.9 (OCH), 80.5 (O*t*Bu), 170.5 (O=C–O) ppm. IR (neat): $\tilde{\nu}$ = 2971 (s), 1932 (m), 1730 (s), 1459 (m), 1367 (s), 1297 (m), 1255 (m), 1160 (s), 1060 (m), 949 (m), 845 (w) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 288 (6) $[M]^+$, 129 (100), 111 (27), 57 (98), 41 (40). $C_{15}H_{28}O_3S$ (288.4): calcd. C 62.46, H 9.78; found C 62.37, H 9.50.

***tert*-Butyl (5-{[2-(*n*-Butoxycarbonyl)ethyl]thiomethyl}tetrahydrofuran-2-yl)acetate (6k):** The general procedure for S_N2 reactions was applied to compound **5** (0.197 g, 0.67 mmol) with Na (0.021 g, 0.90 mmol) and butyl 3-mercaptopropionate (0.275 g, 1.70 mmol). Compound **6k** was isolated after chromatography (silica gel; *n*-pentane/Et_2O, 5:1; R_f = 0.24) as a slightly yellowish oil [0.137 g, 57%, an inseparable 4:1 (*cis*/*trans*) mixture of diastereomers]. ^1H NMR ($CDCl_3$, 250 MHz, for major diastereomer): δ = 0.92 (t, J = 7.2 Hz, 3 H, CH_3), 1.36 (t, J = 7.2 Hz, 2 H, CH_2), 1.44 (s, 9 H, 3 CH_3, *t*Bu), 1.55–1.75 (m, 4 H, 2 CH_2), 1.95–2.15 (m, 2 H, CH_2), 2.33 (dd, J = 15.0, 7.2 Hz, 1 H, CH_2), 2.45–2.65 (m, 2 H, CH_2), 2.71 (dd, J = 13.2, 6.3 Hz, 1 H, SCH_2), 2.80–2.90 (m, 2 H, CH_2), 4.00–4.10 (m, 1 H, OCH), 4.09 (t, J = 7.2 Hz, 2 H, OCH_2), 4.15–4.25 (m, 1 H, OCH) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz, for major diastereomer): δ = 13.7 (CH_3), 19.1, 27.9 (CH_2), 28.1 (3 CH_3, *t*Bu), 30.4, 30.6, 30.8, 35.0, 37.3, 42.2 (CH_2), 64.5 (OCH_2), 76.1 (C-2), 79.2 (C-5, OCH), 80.5 (O*t*Bu), 170.5, 172.0 (O=C–O) ppm. IR (neat): $\tilde{\nu}$ = 2964 (s), 2934 (s), 1734 (s), 1461 (m), 1366 (s), 1296 (m), 1249 (s), 1162 (s), 1060 (s), 948 (m), 843 (w) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 360 (1) $[M]^+$, 129 (100), 111 (31), 57 (82), 43 (20), 41 (26). $C_{18}H_{32}O_5S$ (360.5): calcd. C 59.97, H 8.95; found C 59.70, H 8.76.

***tert*-Butyl {5-[(Methoxycarbonylmethyl)thiomethyl]tetrahydrofuran-2-yl}acetate (6l):** The general procedure for S_N2 reactions was applied to compound **5** (0.223 g, 0.76 mmol) with Na (0.021 g, 0.93 mmol) and methyl mercaptoacetate (0.180 g, 1.70 mmol). Compound **6l** was isolated after chromatography (silica gel; *n*-pentane/Et_2O, 4:1; R_f = 0.20) as a slightly yellowish oil [0.158 g, 68%, an inseparable 5:1 (*cis*/*trans*) mixture of diastereomers]. ^1H NMR ($CDCl_3$, 250 MHz, for major diastereomer): δ = 1.39 (s, 9 H, 3 CH_3, *t*Bu), 1.55–1.75 (m, 2 H, CH_2), 1.90–2.10 (m, 2 H, CH_2), 2.32 (dd, J = 15.0, 7.2 Hz, 1 H, CH_2), 2.52 (dd, J = 15.0, 7.2 Hz, 1 H, CH_2), 2.65–2.85 (m, 2 H, SCH_2), 3.26 (d, J = 15.0 Hz, 1 H, SCH_2), 3.34 (d, J = 15.0 Hz, 1 H, SCH_2), 3.69 (s, 3 H, OCH_3), 4.00–4.10 (m, 1 H, OCH), 4.10–4.20 (m, 1 H, OCH) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz, for both diastereomers): δ = 28.0 (3 CH_3, *t*Bu), 30.3, 30.7, 34.0, 37.3, 42.1 (CH_2, major diastereomer), 31.1, 31.6, 33.9, 37.3, 41.9 (CH_2, minor diastereomer), 52.2 (OCH_3), 75.6, 78.5 (OCH, minor diastereomer), 76.1, 79.1 (OCH, major diastereomer), 80.4 (O*t*Bu), 170.3, 170.9 (O=C–O) ppm. IR (neat): $\tilde{\nu}$ = 2977 (s), 1732 (s), 1437 (m), 1368 (s), 1282 (s), 1160 (s), 1058 (s), 949 (m), 843(m), 766 (w), 589 (w) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 304 (1) $[M]^+$, 248 (19), 129 (100), 111 (36), 57 (30). $C_{14}H_{24}O_5S$ (304.4): calcd. C 55.24, H 7.95; found C 55.41, H 7.63.

***tert*-Butyl [5-(Benzylthiomethyl)tetrahydrofuran-2-yl]acetate (6m):** The general procedure for S_N2 reactions was applied to compound **5** (0.195 g, 0.66 mmol) with Na (0.026 g, 1.14 mmol) and phenylmethanethiol (0.211 g, 1.70 mmol). Compound **6m** was isolated after chromatography (silica gel; *n*-pentane/Et_2O, 10:1; R_f = 0.23) as a slightly yellowish oil [0.114 g, 53%, an inseparable 5:1 (*cis*/*trans*) mixture of diastereomers]. ^1H NMR ($CDCl_3$, 250 MHz, for both diastereomers): δ = 1.44 (s, 9 H, 3 CH_3, *t*Bu), 1.55–1.75 (m, 2 H, CH_2), 1.90–2.10 (m, 2 H, CH_2), 2.36 (dd, J = 15.0, 7.2 Hz, 1 H, CH_2), 2.45–2.65 (m, 3 H, CH_2), 3.77 (s, 2 H, SCH_2Ph), 4.00–4.10 (m, 1 H, OCH, major diastereomer), 4.10–4.20 (m, 1 H, OCH, minor diastereomer), 4.20–4.30 (m, 1 H, OCH, major diastereomer), 4.30–4.40 (m, 1 H, OCH, minor diastereomer), 7.20–7.35 (m, 5 H, 5 CH of Ph) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz, for both diastereomers): δ = 28.1 (3 CH_3, *t*Bu), 30.4, 30.8, 36.9, 42.3 (CH_2, major diastereomer), 31.2, 31.7, 36.8, 42.0 (CH_2, minor diastereomer), 36.2 (SCH_2), 75.7, 78.7 (OCH, minor diastereomer), 76.1, 79.3 (OCH, major diastereomer), 80.5 (O*t*Bu), 126.9, 128.4, 129.0 (CH of Ph), 138.5 (C of Ph), 170.5 (O=C–O) ppm. IR (neat): $\tilde{\nu}$ = 2975 (m), 2929 (m), 1728 (s), 1455 (m), 1367 (s), 1296 (m), 1254 (m), 1160 (s), 1058 (s), 948 (w), 844 (w), 768 (w), 703 (m) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 322 (2) $[M]^+$, 266 (59), 129 (99), 111 (46), 91 (100), 57 (35). $C_{18}H_{26}O_3S$ (322.5): calcd. C 67.05, H 8.13; found C 66.77, H 7.83.

***tert*-Butyl [5-(Phenylthiomethyl)tetrahydrofuran-2-yl]acetate (6n):** The general procedure for S_N2 reactions was applied to compound **5** (0.180 g, 0.61 mmol) with Na (0.021 g, 0.91 mmol) and thiophenol (0.169 g, 1.53 mmol). Compound **6n** was isolated after

chromatography (silica gel; *n*-pentane/Et_2O, 10:1; R_f = 0.30) as a yellowish oil [0.139 g, 74%, an inseparable 6:1 (*cis*/*trans*) mixture of diastereomers]. ^1H NMR ($CDCl_3$, 250 MHz, for major diastereomer): δ = 1.44 (s, 9 H, 3 CH_3, *t*Bu), 1.55–1.80 (m, 2 H, CH_2), 2.00–2.20 (m, 2 H, CH_2), 2.35 (dd, J = 15.0, 7.2 Hz, 1 H, CH_2), 2.57 (dd, J = 15.0, 6.9 Hz, 1 H, CH_2), 2.93 (dd, J = 14.1, 7.2 Hz, 1 H, SCH_2), 3.18 (dd, J = 14.1, 5.4 Hz, 1 H, SCH_2), 4.00–4.15 (m, 1 H, OCH), 4.15–4.30 (m, 1 H, OCH), 7.10–7.30 (m, 2 H, 2 CH of Ph), 7.36 (d, J = 7.2 Hz, 2 H, 2 CH of Ph), 7.45–7.60 (m, 1 H, CH of Ph) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz, for major diastereomer): δ = 28.1 (3 CH_3, *t*Bu), 30.4 (C-4), 30.8 (C-3), 39.0 (C-1, CH_2), 42.2 (SCH_2), 76.2 (C-2), 78.0 (C-5, OCH), 80.6 (O*t*Bu), 126.0, 128.8, 129.2 (CH of Ph), 136.4 (C of Ph), 170.4 (O=C–O) ppm. IR (neat): $\tilde{\nu}$ = 2926 (s), 2855 (s), 1729 (s), 1583 (w), 1478 (m), 1367 (s), 1298 (m), 1256 (m), 1159 (s), 1061 (s), 949 (w), 844 (w), 741 (s), 692 (m) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 308 (11) $[M]^+$, 252 (31), 129 (100), 111 (50), 57 (44). The exact molecular mass *m*/*z* = 308.1446 ± 2 ppm $[M]^+$ for $C_{17}H_{24}O_3S$ was confirmed by HRMS (EI, 70 eV).

***tert*-Butyl [5-(*o*-Tolylthiomethyl)tetrahydrofuran-2-yl]acetate (6o):** The general procedure for S_N2 reactions was applied to compound **5** (0.236 g, 0.80 mmol) with Na (0.025 g, 1.08 mmol) and 2-methylthiophenol (0.221 g, 1.70 mmol). Compound **6o** was isolated after chromatography (silica gel; *n*-pentane/Et_2O, 12.5:1; R_f = 0.27) as a yellowish oil [0.201 g, 77%, an inseparable 4:1 (*cis*/*trans*) mixture of diastereomers]. ^1H NMR ($CDCl_3$, 250 MHz, for major diastereomer): δ = 1.44 (s, 9 H, 3 CH_3), 1.60–1.85 (m, 2 H, CH_2), 2.00–2.20 (m, 2 H, CH_2), 2.37 (dd, J = 15.0, 7.2 Hz, 1 H, CH_2), 2.37 (s, 3 H, CH_3, CH_3), 2.58 (dd, J = 15.0, 6.9 Hz, 1 H, CH_2), 2.89 (dd, J = 13.2, 8.1 Hz, 1 H, SCH_2), 3.16 (dd, J = 13.2, 5.4 Hz, 1 H, SCH_2), 4.00–4.15 (m, 1 H, OCH), 4.15–4.30 (m, 1 H, OCH), 7.00–7.20 (m, 3 H, 3 CH), 7.32 (d, J = 7.2 Hz, 1 H, CH) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz, for both diastereomers): δ = 20.4 (CH_3), 28.1 (3 CH_3, *t*Bu), 30.5, 30.8, 38.4, 42.2 (CH_2, major diastereomer), 31.3, 31.6, 38.3, 41.9 (CH_2, minor diastereomer), 75.8, 77.3 (OCH, minor diastereomer), 76.2, 77.9 (OCH, major diastereomer), 80.6 (O*t*Bu), 125.7, 126.4, 130.1 (CH), 128.2 (CH, major diastereomer), 128.3 (CH, minor diastereomer), 135.6, 137.6 (C), 170.5 (O=C–O) ppm. IR (neat): $\tilde{\nu}$ = 3060 (w), 2976 (s), 1730 (s), 1590 (m), 1466 (s), 1367 (s), 1298 (s), 1255 (s), 1160 (s), 1062 (s), 948 (m), 844 (m), 747 (s) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 322 (23) $[M]^+$, 266 (35), 129 (100), 111 (42), 108 (40), 107 (29), 57 (31). $C_{18}H_{26}O_3S$ (322.5): calcd. C 67.05, H 8.13; found C 67.07, H 7.86.

***tert*-Butyl [5-(*m*-Tolylthiomethyl)tetrahydrofuran-2-yl]acetate (6p):** The general procedure for S_N2 reactions was applied to compound **5** (0.203 g, 0.69 mmol) with Na (0.019 g, 0.83 mmol) and 3-methylthiophenol (0.221 g, 1.70 mmol). Compound **6p** was isolated after chromatography (silica gel; *n*-pentane/Et_2O, 12.5:1; R_f = 0.24) as a yellowish oil [0.169 g, 76%, an inseparable 5:1 (*cis*/*trans*) mixture of diastereomers]. ^1H NMR ($CDCl_3$, 250 MHz, for both diastereomers): δ = 1.44 (s, 9 H, 3 CH_3, *t*Bu), 1.55–1.85 (m, 2 H, CH_2), 1.95–2.20 (m, 2 H, CH_2), 2.31 (s, 3 H, CH_3), 2.36 (dd, J = 15.0, 7.2 Hz, 1 H, CH_2), 2.58 (dd, J = 15.0, 7.2 Hz, 1 H, CH_2), 2.90 (dd, J = 13.2, 8.1 Hz, 1 H, SCH_2), 3.18 (dd, J = 13.2, 5.4 Hz, 1 H, SCH_2), 4.00–4.15 (m, 1 H, OCH, major diastereomer), 4.15–4.30 (m, 1 H, OCH), 4.30–4.45 (m, 1 H, OCH, minor diastereomer), 6.95–7.05 (m, 1 H, CH), 7.15 (d, J = 8.1 Hz, 2 H, 2 CH), 7.16 (s, 1 H, CH) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz, for both diastereomers): δ = 21.3 (CH_3), 28.1 (3 CH_3, *t*Bu), 30.4, 30.8, 38.9, 42.2 (CH_2, major diastereomer), 31.2, 31.6, 38.9, 41.9 (CH_2, minor diastereomer), 75.7, 77.5 (OCH, minor diastereomer), 76.2, 78.0 (OCH, major diastereomer), 80.5 (O*t*Bu), 126.2, 126.8, 129.8 (CH, major diastereomer), 126.3, 126.9, 129.9 (CH, minor diastereomer), 128.7 (CH), 136.1, 138.6 (C), 170.5 (O=C–O) ppm. IR (neat): $\tilde{\nu}$ = 2976 (s), 2927 (s), 1731 (s), 1593 (m), 1475 (m), 1367 (s), 1298 (m), 1255 (m), 1159 (s), 1059 (s), 949 (m), 852 (w), 775 (m), 689 (m) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 322 (15) $[M]^+$, 129 (60), 108 (100), 107 (77). $C_{18}H_{26}O_3S$ (322.5): calcd. C 67.05, H 8.13; found C 67.33, H 7.92.

***tert*-Butyl [5-(*p*-Tolylthiomethyl)tetrahydrofuran-2-yl]acetate (6q):** The general procedure for S_N2 reactions was applied to compound **5** (0.153 g, 0.52 mmol) with Na (0.029 g, 1.27 mmol) and 4-methylthiophenol (0.300 g, 2.42 mmol). Compound **6q** was isolated after chromatography (silica gel; *n*-pentane/Et_2O, 12.5:1; R_f = 0.30) as a yellowish oil [0.130 g, 77%, an inseparable 5.5:1 (*cis*/*trans*) mixture of diastereomers]. ^1H NMR ($CDCl_3$, 250 MHz, for major diastereomer): δ = 144 (s, 9 H, 3 CH_3, *t*Bu), 1.45–1.75 (m, 2 H, CH_2), 2.00–2.10 (m, 2 H, CH_2), 2.31 (s, 3 H, CH_3), 2.35 (dd, J = 15.0, 7.2 Hz, 1 H, CH_2), 2.57 (dd, J = 15.0, 7.2 Hz, 1 H, CH_2), 2.88 (dd, J = 13.2, 7.2 Hz, 1 H, SCH_2), 3.14 (dd, J = 13.2, 7.2 Hz, 1 H, SCH_2), 3.95–4.10 (m, 1 H, OCH), 4.15–4.30 (m, 1 H, OCH), 7.08 (d, J = 8.1 Hz, 2 H, 2 CH), 7.27 (d, J = 8.1 Hz, 2 H, 2 CH) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz, for major diastereomer): δ = 21.0 (CH_3), 28.1 (3 CH_3, *t*Bu), 30.3 (C-4), 30.8 (C-3), 39.6 (C-1, CH_2), 42.2 (SCH_2), 76.1 (C-2), 78.1 (C-5, OCH), 80.5 (O*t*Bu), 129.6 (2 C), 130.0 (2 C, CH), 132.5, 136.1 (C), 170.5 (O=C–O) ppm. IR (neat): $\tilde{\nu}$ = 2976 (m), 2926 (m), 1729 (s), 1493 (m), 1367 (m), 1298 (m), 1255 (m), 1159 (s), 1059 (m), 948 (m), 805 (m), 492 (w) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 322 (31) $[M]^+$, 266 (41), 129 (100), 111 (43). The exact molecular mass *m*/*z* = 322.1603 ± 2 ppm $[M]^+$ for $C_{18}H_{26}O_3S$ was confirmed by HRMS (EI, 70 eV). $C_{18}H_{26}O_3S$ (322.5): calcd. C 67.05, H 8.13; found C 67.13, H 7.97.

***tert*-Butyl [5-(Pyridin-2-yloxymethyl)tetrahydrofuran-2-yl]acetate (6r):** The general procedure for S_N2 reactions was applied to compound **5** (0.197 g, 0.67 mmol) with Na (0.023 g, 0.99 mmol) and 2-hydroxypyridin (0.168 g, 1.76 mmol, suspended in 5 mL of THF) (reaction time: 26 h; extraction with CH_2Cl_2). Compound **6r** was isolated after chromatography (silica gel; Et_2O/acetone, 10:1; R_f = 0.22) as a slightly yellowish oil [0.064 g, 33%, an inseparable 1.5:1 (*cis*/*trans*) mixture of diastereomers]. ^1H NMR ($CDCl_3$, 250 MHz, for both diastereomers): δ = 1.44 (s, 9 H, 3 CH_3, *t*Bu), 1.50–1.75 (m, 2 H, CH_2), 2.00–2.20 (m, 2 H, CH_2), 2.30–2.50 (m, 2 H, CH_2), 3.75–3.85 (m, 1 H, OCH_2), 4.15–4.45 (m, 3 H, OCH, OCH_2), 6.11 (dd, J = 7.2, 7.2 Hz, 1 H, CH), 6.55 (d, J = 9.3 Hz, 1 H, CH), 7.31 (dd, J = 9.3, 7.2 Hz, 1 H, CH), 7.44 (d, J = 7.2 Hz, 1 H, CH) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz, for both diastereomers): δ = 28.1 (3 CH_3, *t*Bu), 28.3, 30.8, 42.5, 52.6 (CH_2, major diastereomer), 29.0, 31.6, 41.6, 52.0, (CH_2, minor diastereomer), 75.4 (OCH, minor diastereomer), 76.2 (CH, major diastereomer), 77.6 (OCH), 80.6 (O*t*Bu), 105.2, 139.3 (CH, major diastereomer), 105.4, 139.1 (CH, minor diastereomer), 120.4, 139.6 (CH), 162.8 (C), 170.3 (O=C–O, major diastereomer), 170.5 (O=C–O, minor diastereomer) ppm. IR (neat): $\tilde{\nu}$ = 3085 (w), 2977 (s), 2936 (m), 1730 (s), 1664 (s), 15.91 (s), 1540 (s), 14.62 (m), 13.69 (s), 12.54 (s), 1150 (s), 1063 (s), 951 (m), 845 (m), 767 (s), 574 (w), 528 (w) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 293 (2) $[M]^+$, 142 (45), 57 (100), 41 (63). $C_{16}H_{23}NO_4$ (293.4): calcd. C 65.51, H 7.90, N 4.77; found C 65.24, H 7.68, N 4.58.

Synthesis of [5-(Phenylthiomethyl)tetrahydrofuran-2-yl]acetic Acid: To a THF (10 mL) solution of compound **6n** (0.139 g 0.45 mmol) was added boron trifluoride–diethyl ether (0.127 g, 0.90 mmol) at 20 °C, and the resulting mixture stirred for 20 h. To the reaction mixture was added H_2O (60 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; *n*-pentane/Et_2O, 1:2; R_f = 0.27)

to give compound **7** (0.014 g, 12%) as a yellowish solid. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.75–1.90 (m, 2 H, CH_2), 2.05–2.20 (m, 2 H, CH_2), 2.50–2.70 (m, 2 H, CH_2), 2.97 (dd, J = 13.2, 7.2 Hz, 1 H, SCH_2), 3.19 (dd, J = 13.2, 5.4 Hz, 1 H, SCH_2), 4.05–4.20 (m, 1 H, OCH), 4.20–4.35 (m, 1 H, OCH), 7.15–7.40 (m, 1 H, CH of Ph) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 30.2 (C-4), 30.9 (C-3), 38.9 (C-1, CH_2), 40.5 (SCH_2), 75.6 (C-2), 78.4 (C-5, OCH), 126.1, 128.9, 129.3 (CH of Ph), 129.4 (C of Ph), 175.5 (O=C–O) ppm. IR (KBr): $\tilde{\nu}$ = 2924 (m), 1713 (s), 1583 (w), 1479 (m), 1440 (m), 1183 (m), 1088 (m), 1057 (m), 899 (w), 743 (m), 692 (m) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 252 (64) $[M]^+$, 129 (100), 111 (82). The exact molecular mass *m/z* = 252.0820 ± 2 ppm $[M]^+$ for $C_{13}H_{16}O_3S$ was confirmed by HRMS (EI, 70 eV).

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[1] For natural tetrahydrofurans and acetogenins, see: a) S. C. Sinha, E. Keinan, A. Sinha, A. Yazbak, S. C. Sinha, *Pure Appl. Chem.* **1997**, *69*, 423; b) D. A. Evans, A. M. Ratz, B. E. Huff, G. S. Sheppard, *Tetrahedron Lett.* **1994**, *35*, 7171; c) G. Schmid, T. Fukuyama, K. Akasaka, Y. Kishi, *J. Am. Chem. Soc.* **1979**, *101*, 259; d) D. B. Collum, J. H. McDonald, W. C. Still, *J. Am. Chem. Soc.* **1980**, *102*, 2117; e) R. E. Ireland, J. D. Armstrong, J. Lebreton, R. S. Meissner, M. A. Rizzacasa, *J. Am. Chem. Soc.* **1993**, *115*, 7152; f) E. Keinan, S. C. Sinha, *Pure Appl. Chem.* **2002**, *74*, 93; g) A. Bermejo, B. Figadère, M.-C. Zafra-Polo, I. Barrachina, E. Estornell, D. Cortes, *Nat. Prod. Rep.* **2005**, *22*, 269.

[2] Lasalocid A: a) T. Nakata, G. Schmid, B. Vranesic, M. Okigawa, T. Smith-Palmer, Y. Kishi, *J. Am. Chem. Soc.* **1978**, *100*, 2933; b) R. E. Ireland, R. C. Anderson, R. Badoud, B. J. Fitzsimmons, G. J. McGarvey, S. Thaisrivongs, C. S. Wilcox, *J. Am. Chem. Soc.* **1983**, *105*, 1988.

[3] Ferensimycin A and B and lysocellin:D. A. Evans, R. P. Polniaszek, K. M. DeVries, D. E. Guinn, D. J. Mathre, *J. Am. Chem. Soc.* **1991**, *113*, 7613.

[4] Solamin: a) A. R. L. Cecil, R. C. D. Brown, *ARKIVOC* **2002** (xi), 49; for other solamin syntheses, see: b) A. R. L. Cecil, Y. Hu, M. J. Vincent, R. Duncan, R. C. D. Brown, *J. Org. Chem.* **2004**, *69*, 3368; c) T. J. Donohoe, S. Butterworth, *Angew. Chem. Int. Ed.* **2005**, *44*, 4766; d) S. C. Sinha, E. Keinan, *J. Am. Chem. Soc.* **1993**, *115*, 4891.

[5] For cycloadditions, see: a) A. Weichert, H. M. R. Hoffmann, *J. Org. Chem.* **1991**, *56*, 4098; b) P. Tchelitcheff, *Bull. Soc. Chim. Fr.* **1954**, 672; c) R. E. Ireland, D. Haebich, *Chem. Ber.* **1981**, *114*, 1418; d) H. Audrain, J. Thorhauge, R. G. Hazell, K. A. Joergensen, *J. Org. Chem.* **2000**, *65*, 4487; for reactions with amines, see; e) M. R. Detty, *J. Org. Chem.* **1979**, *44*, 2073; f) S. Batra, S. Srivastava, K. Singh, R. Chander, A. K. Khanna, A. Bhaduri, *P. Bioorg. Med. Chem.* **2000**, *8*, 2195; for cyclopropanations, see: g) W. Kirmse, K. Rode, *Chem. Ber.* **1987**, *120*, 847; for oxidative carbonylations, see h) H. C. Strauch, G. Erker, R. Fröhlich, *J. Organomet. Chem.* **2000**, *593–594*, 388; i) K. Kato, A. Nishimura, Y. Yamamoto, H. Akita, *Tetrahedron Lett.* **2001**, *42*, 4203; j) K. Kato, M. Tanaka, Y. Yamamoto, H. Akita, *Tetrahedron Lett.* **2002**, *43*, 1511; for hydrogenations see: k) H. Tsujita, Y. Ura, K. Wada, T. Kondo, T.-A. Mitsudo, *Chem. Commun.* **2005**, 5100; l) G. V. M. Sharma, S. Punna, L. Hymavathi, N. Y. Reddy, P. R. Krishna, M. S. Chorghadeb, S. V. Ley, *Tetrahedron: Asymmetry* **2005**, *16*, 1135; m) T. Ohta, T. Miyake, N. Seido, H. Kumobayashi, H. Takaya, *J. Org. Chem.* **1995**, *60*, 357; see also ref.[6]

[6] Reviews: a) T. L. B. Boivin, *Tetrahedron* **1987**, *43*, 3309; b) J.-C. Harmange, B. Figadère, *Tetrahedron: Asymmetry* **1993**, *4*, 1711; c) Y. S. Rao, *Chem. Rev.* **1976**, *76*, 625; d) G. Pattenden, *Prog. Chem. Nat. Prod.* **1978**, *35*, 133; e) D. W. Knight, *Contemp. Org. Synth.* **1994**, *1*, 287; see also: f) H. Gerlach, H. Wetter, *Helv. Chim. Acta* **1974**, *57*, 2306; g) U. Schmidt, J. Gombos, E. Haslinger, H. Zak, *Chem. Ber.* **1976**, *109*, 2628; h) P. A. Bartlett, J. D. Meadows, E. Ottow, *J. Am. Chem. Soc.* **1984**, *106*, 5304; i) A. G. M. Barrett, H. G. Sheth, *J. Org. Chem.* **1983**, *48*, 5017; j) B. Lygo, *Tetrahedron* **1988**, *44*, 6889.

[7] Methyl nonactate: a) M. Ahmar, C. Duyck, I. Fleming, *Pure Appl. Chem.* **1994**, *66*, 2049; for (–)-nonactic acid, see also: b) B. Fraser, P. Perlmutter, *J. Chem. Soc., Perkin Trans. 1* **2002**, 2896; c) S. Batmangherlich, A. H. Davidson, *J. Chem. Soc., Chem. Commun.* **1985**, 1399.

[8] Spiroketal chalcogran: a) S. V. Ley, B. Lygo, H. M. Organ, A. Wonnacott, *Tetrahedron* **1985**, *41*, 3825; b) P. M. Booth, C. M. J. Fox, S. V. Ley, *J. Chem. Soc., Perkin Trans. 1* **1987**, 121; c) K. Mori, M. Sasaki, S. Tamada, T. Suguro, S. Masuda, *Tetrahedron* **1979**, *35*, 1601.

[9] For the synthesis of (tetrahydrofuran-2-yl)acetates, see: a) D. J. Dixon, S. V. Ley, E. W. Tate, *J. Chem. Soc., Perkin Trans. 1* **2000**, 2385; b) M. Babjak, P. Zálupský, T. Gracza, *ARKIVOC* **2005** (v), 45.

[10] P. Langer, I. Freifeld, *Chem. Eur. J.* **2001**, *7*, 565.

[11] For reviews of cyclization reactions of free and masked dianions, see: a) P. Langer, *Chem. Eur. J.* **2001**, *7*, 3858; b) P. Langer, *Synthesis* **2002**, 441; c) P. Langer, W. Freiberg, *Chem. Rev.* **2004**, *104*, 4125.

[12] Synthesis and reactions of 2-alkylidenetetrahydrofurans: a) P. Langer, E. Holtz, I. Karimé, N. N. R. Saleh, *J. Org. Chem.* **2001**, *66*, 6057; b) P. Langer, E. Bellur, *J. Org. Chem.* **2003**, *68*, 9742; see also; c) G. L. Edwards, D. J. Sinclair, *Tetrahedron Lett.* **1999**, *40*, 3933; d) S. A. Krueger, T. A. Bryson, *J. Org. Chem.* **1974**, *39*, 3167; e) B. Gabriele, G. Salerno, F. De Pascali, M. Costa, G. P. Chiusoli, *J. Organomet. Chem.* **2000**, *593–594*, 409; f) D. Pflieger, B. Muckensturn, *Tetrahedron* **1989**, *45*, 2031; g) E. Bellur, P. Langer, *Synlett* **2004**, 2169; h) E. Bellur, P. Langer, *Eur. J. Org. Chem.* **2005**, 4815; i) E. Bellur, P. Langer, *Synlett* **2004**, 2172; j) E. Bellur, P. Langer, *J. Org. Chem.* **2005**, *70*, 3819; k) E. Bellur, P. Langer, *J. Org. Chem.* **2005**, *70*, 7686; l) E. Bellur, I. Freifeld, P. Langer, *Tetrahedron Lett.* **2005**, *46*, 2185; m) E. Bellur, P. Langer, *J. Org. Chem.* **2005**, *70*, 10013; n) E. Bellur, H. Görls, P. Langer, *Eur. J. Org. Chem.* **2005**, 2074; see also; o) P. Langer, T. Krummel, *Chem. Eur. J.* **2001**, *7*, 1720; p) P. Langer, H. Armbrust, T. Eckardt, J. Magull, *Chem. Eur. J.* **2002**, *8*, 1443.

[13] a) T. Sato, Y. Hayakawa, R. Noyri, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2515; b) H. Ohrui, S. Emoto, *J. Org. Chem.* **1977**, *42*, 1951; c) H. Ohrui, G. H. Jones, J. G. Moffatt, M. L. Maddox, A. T. Christensen, S. K. Byram, *J. Am. Chem. Soc.* **1975**, *97*, 4602.

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