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Reaction of silyl ketene acetals with epoxides: a new method for the synthesis of γ-butanolides

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Abstract—Titanium tetrachloride promoted reaction of silyl ketene acetals with epoxides, followed by acidic work-up, affords butanolides in moderate/good yields. With epihalohydrins the reaction is regioselective and occurs at the less substituted end of the epoxide; the γ-haloalkyl-γ-butanolides thus obtained can be further transformed into various products.

1. Introduction

Epoxide ring opening with carbon nucleophiles is one of the most useful reactions in organic synthesis.[1] However, the role of nucleophile is usually conferred to organometallics, while the analogous reactions of ketone and ester enolates are generally less efficient. While the group I and II ketone enolates do not react with epoxides at all, γ-hydroxyketones can be obtained when the reaction is performed in the presence of boron trifluoride etherate,[2] scandium triflate,[3] in 5 M etheral solution of lithium perchlorate[4] or, indirectly, with the enolate of the corresponding imine[5] or *N*,*N*-dimethylhydrazone.[6] Similarly, although sporadic examples of epoxide ring opening with lithium mono- and dianions of carboxylic acids and derivatives have been reported,[7] these species are essentially unreactive towards epoxides and their reactions have not found broad synthetic application. Aluminum ester enolates, which can be obtained by transmetallation of their lithium counterperts with chloroalanes are much more reactive and their reactions with epoxides offer an efficient approach to γ-hydroxy carboxylic acid derivatives and butanolides.[8] Reactions of epoxides with enolates have been recently reviewed.[9] Indirect methods for butanolide synthesis have also been devised, relying on reactions of alkoxyalkynilalanes[8a] or, more recently, silylynamines as the reactive intermediates.[10]

Keywords: Epoxides; Ketene acetals; Lactones; Titanium and compounds; Alkylation.

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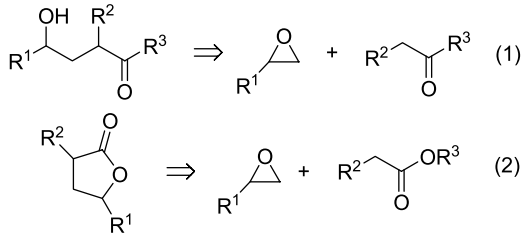
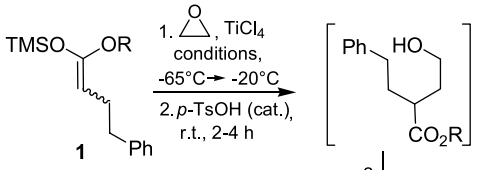
2. Results and discussion

Some time ago, we found that silyl enol ethers react with epoxides under the conditions of the Mukaiyama reaction, to give the homoaldol type products.[11] The reaction, initially suspected to proceed via the titanium enolate, was subsequently shown to involve the catalysis by $TiCl_4$ as a Lewis acid.[12] In this way, the scope of the homoaldol transform, represented by the Eq. (1) in Scheme 1, was enlarged by a new synthetic transformation, complementary to the existing ones. We now wish to report the extension of this method to silyl ketene acetals, which offers an alternative synthetic approach to γ-butanolides (Eq. (2)).



Scheme 1. Homoaldol transforms for γ-hydroxyketones and butanolides.

When a dichloromethane solution of silyl ketene acetal (SKA) **1**, prepared from isopropyl phenylbutanoate,[14] and ethylene oxide was submitted to the action of $TiCl_4$ at −60 °C, the TLC of the reaction mixture indicated the formation of two products which, upon acidic work-up, converged to a single compound—α-(2-phenylethyl)-γ-butanolide **2**—which was isolated in 19% yield (Scheme 2). Other Lewis acids ($BF_3 \cdot Et_2O$, $ZnCl_2$, $Ti(O^iPr)_4$, $SnCl_4$,



Conditions:

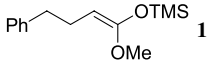
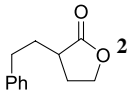
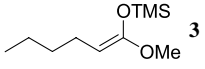
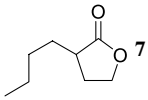
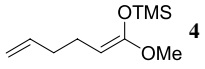
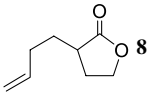
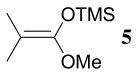
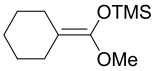
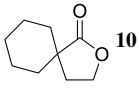
R	Solvent	Yield (%)
^{i}Pr	CH_2Cl_2	19
Me	CH_2Cl_2	38
Me	CH_2Cl_2/ *n*-hexane (1 : 2)	62

Scheme 2. The first experiments with ethylene oxide.

TMSOTf) were ineffective catalysts for this transformation. Reducing the size of the ester alkyl group proved beneficial, as substituting the smaller methyl group for isopropyl in **1** increased the yield to 38%. Further improvements were achieved by performing the reaction in the mixed solvent: *n*-hexane/dichloromethane = 2/1, which resulted in the yield enhancement to 62% (97%, based on the recovered methyl 4-phenylbutanoate). The best results were obtained when the reagents were used in the molar ratio: SKA/ethylene oxide/$TiCl_4$ = 1/2/3; change in the molar ratio, or the alternative order of addition, decreased the yield.

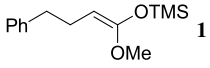
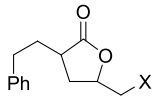
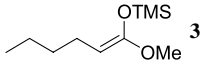
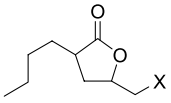
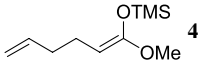
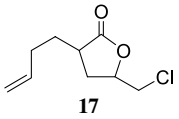
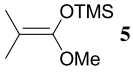
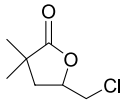
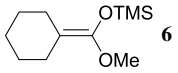
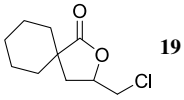
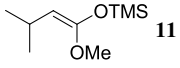
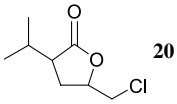
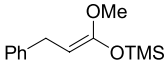
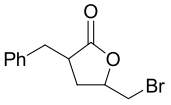
Several other SKA were submitted to these reaction conditions. In all cases the desired γ-butyrolactones were obtained in 53–69% yields, as shown in Table 1. The reaction proved suitable for the preparation of lactones possessing a saturated (entry 2), unsaturated (entry 3) or a side chain with an aromatic unit (entry 1), as well as those possessing a quaternary center in the α-position (entry 4), including spirolactones (entry 5).

Table 1. Reactions of SKA with ethylene oxide

Entry	Reactant	Product	Yield (%)[a]
1.	 **1**	 **2**	62 (97)[b]
2.	 **3**	 **7**	69
3.	 **4**	 **8**	64
4.	 **5**	 **9**	53
5.	 **6**	 **10**	66

[a] Isolated yields of pure products.
[b] Yield calculated on the basis of recovered methyl 4-phenylbutanoate.

Table 2. Reactions with epichloro- and epibromohydrin

Entry	Reactant	Product	Yield (%)[a]
1.	 **1**	 **13** X = Cl	49
2.		**14** X = Br	50
3.	 **3**	 **15** X = Cl	64
4.		**16** X = Br	64
5.	 **4**	 **17**	83
6.	 **5**	 **18**	44
7.	 **6**	 **19**	69
8.	 **11**	 **20**	59
9.	 **12**	 **21**	54

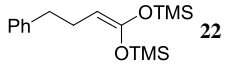
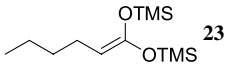
[a] Isolated yields of pure products.

A higher level of product functionalization was obtained when performing the reaction with epihalohydrins. Thus, both epichloro- and epibromohydrin reacted with a range of SKA to afford the corresponding γ-halomethylbutanolides in 44–83% yield (Table 2). Owing to a negative inductive effect of the halide substituent, the epoxide ring opening is regioselective, with the nucleophilic attack occurring exclusively at the less substituted epoxide end. The reaction is not stereoselective, however, as the products were obtained as equimolar mixtures of *cis* and *trans* isomers.

Bis-trimethylsilyl ketene acetals, which can be obtained from carboxylic acids, are also efficient reaction partners. As can be seen from Table 3, the yields in their reactions with ethylene oxide and epihalohydrins compare favourably with those of SKA.

We also examined the reaction of SKA with substituted epibromohydrins of type **24**. These compounds can be

Table 3. Reactions of bis-SKA

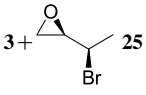
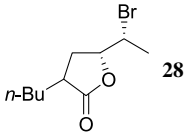
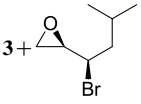
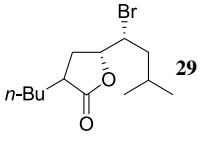
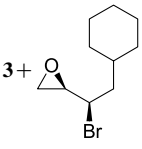
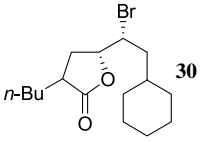
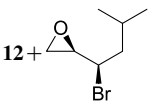
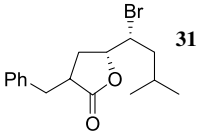
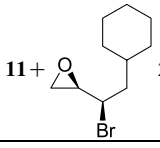
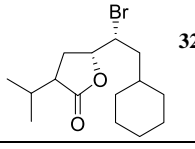
Entry	Reactants	Product	Yield (%)[a]
	 **22**		
1.	**22** + 	**2**	66
2.	**22** + 	**13**	59
3.	**22** + 	**14**	53 (73%[b])
	 **23**		
4.	**23** + 	**7**	80
5.	**23** + 	**15**	67

[a] Isolated yields of pure products.
[b] Yield determined.

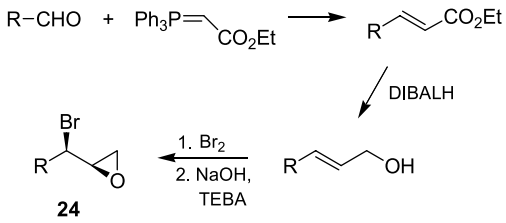
stereoselectively obtained by a four-step sequence displayed in Scheme 3.

The results of SKA alkylation with substituted epibromohydrins of type **24** are displayed in Table 4. No isomerization occurs under the reaction conditions and all the products were obtained as *syn*-isomers, with the retention

Table 4. Alkylations of SKA with substituted epibromohydrins

Entry	Reactants	Product	Yield (%)[a]
1.	**3** +  **25**	 **28**	73
2.	**3** +  **26**	 **29**	66
3.	**3** +  **27**	 **30**	54
4.	**12** +  **26**	 **31**	21
5.	**11** +  **27**	 **32**	69

[a] Isolated yields of pure products.

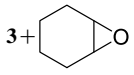
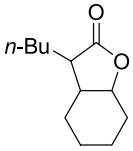
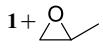
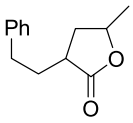
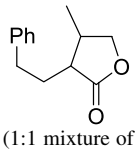
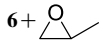
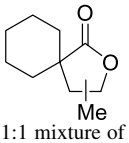
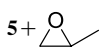
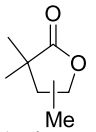
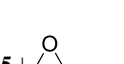
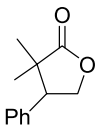


Scheme 3. Synthesis of substituted epibromohydrins.

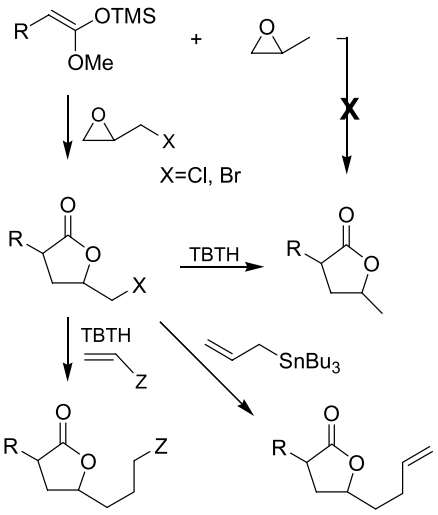
of configuration of the stereocenters originating from the bromohydrin.

Reactions with epoxides that do not possess a halide substituent in the vicinal position were less successful (Table 5). Alkylation of **3** with cyclohexene oxide furnished the condensed bicyclic lactone **33** in an acceptable 48% yield (entry 1), but with the structurally similar SKA **1** and **23** lower yields were obtained. The reactions with propene oxide gave rise to mixtures of regioisomers which were isolated in modest yields (entries 2–4). In the case of styrene oxide, the reaction could be performed in the presence of $BF_3 \cdot Et_2O$, and gave the 3-phenylbutanolide derivative **40** regioselectively (entry 5; this is the only case where the

Table 5. Reactions of SKA with epoxides other than epihalohydrins

Entry	Reactants	Product	Yield (%)[a]
1.	**3** + 	 **33**	48
2.	**1** + 	 **34** +  **35** (1:1 mixture of regioisomers)	29
3.	**6** + 	 **36**+**37** (1:1 mixture of regioisomers)	35
4.	**5** + 	 **38**+**39** (1:1 mixture of regioisomers)	38
5.	**5** + 	 **40**	15, 32[b]

[a] Isolated yields of pure products.
[b] BF_3Et_2O was used instead of $TiCl_4$.



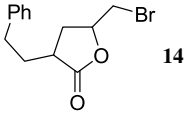
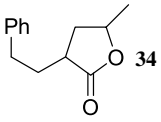
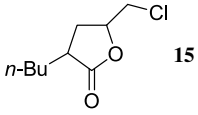
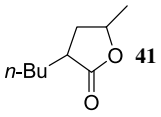
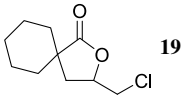
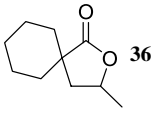
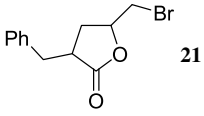
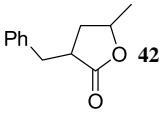
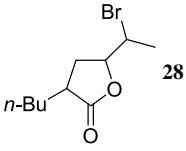
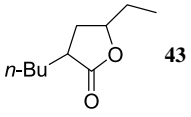
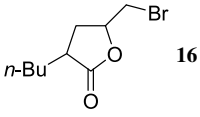
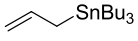
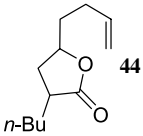
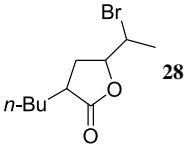
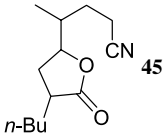
Scheme 4. Transformations of products.

coupling could be achieved with a Lewis acid other than $TiCl_4$).

However, the poor performance of unsymmetrical, non-halogen-containing epoxides, does not necessarily restrict the scope of the reaction to the synthesis of quite simple derivatives, as the products of the coupling with epihalohydrins are amenable to further synthetic transformations (Scheme 4). Thus, the combination of the alkylation with epihalohydrin and the reduction with tributyltinhydride affords regioselectively γ-alkyl substituted butanolides, which are not directly obtainable by the reaction with the corresponding unsymmetrical epoxides (Table 6, entries 1, 3–6). This transformation can also be carried out with hypophosphorous acid as a non-toxic and environmentally-friendly reagent (entry 2).[15] Carbon–carbon bond forming reactions are also possible, and the examples of allylation and of the Giese addition are given in entries 7 and 8, respectively. Radical reactions are particularly well suited for these type of transformations as, in contrast to β-alkoxy organometallics, β-alkoxy radical intermediates are not susceptible to β-elimination. These combinations of reactions are the synthetic equivalents of the alkylation with structurally more complex epoxides.

In conclusion, a new reaction of silyl ketene acetals with epoxides is described, which complements the existing methods for the synthesis of γ-butanolides.

Table 6. Transformations of 4-haloalkylbutanolides

Entry	Reactants		Products	Yield (%)[a]
1.	 **14**	Bu_3SnH	 **34**	73
2.		H_3PO_2		76
3.	 **15**	Bu_3SnH	 **41**	74
4.	 **19**	Bu_3SnH	 **36**	78
5.	 **21**	Bu_3SnH	 **42**	80
6.	 **28**	Bu_3SnH	 **43**	82
7.	 **16**		 **44**	83
8.	 **28**	Bu_3SnH  AIBN	 **45**	76

[a] Yield of the isolated pure compound.

3. Experimental

3.1. General

All chromatographic separations were performed on Silica, 10–18, 60A, ICN Biomedicals. Standard techniques were used for the purification of reagents and solvents. NMR spectra were recorded on a Varian Genmini 200, ^{1}H NMR at 200 MHz, ^{13}C NMR at 50 MHz, for samples in deuterated chloroform. Chemical shifts are expressed in ppm using tetramethylsilane as internal standard, coupling constants (J) are in Hz. IR spectra were recorded on a Perkin–Elmer 457 grating FT instrument, and are expressed in cm^{-1}. Mass spectra were obtained on a Finnigan ITDS 700 instrument. Microanalyses were performed at the Vario EL III instrument CHNOS Elementar Analyzer, Elemantar Analysensysteme GmbH, Hanau-Germany. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. GC analyses were performed on a Varian 3400 instrument, equipped with Varian 4270 integrator, VOCOL™ column (105 m, ID: 0.53 mm, film thickness 3.0 μm, carrier gas H_2, 10 mL/min), FI detector. Preparative gas chromatography was performed on a Varian P-90 instrument, using 2 m long stainless steel column packed with 10% OV-101 on Chromosorb 80, (carrier gas H_2, 10 mL/min).

3.2. General procedure for the synthesis of silyl ketene acetals.[14]

To a cold (−78 °C) solution of LDA (13 mmol) in THF (13 mL) was added a solution of the corresponding ester (10 mmol) in THF (10 mL), dropwise, with stirring. After 30 min, TMSCl (2.16 g; 20 mmol) was added, the mixture was stirred for additional 30 min at −78 °C, then allowed to reach rt. The solvent was removed at the rotary evaporator, the product was extracted from the residue with *n*-hexane, the organic extract was concentrated at the rotavapor and the residue was distilled under reduced pressure.

3.2.1. 4-Phenyl-1-methoxy-1-trimethylsilyloxy-1-butene (1). 82%. Colorless oil, bp 95 °C/0.4 mmHg. Spectroscopic data for this compound have not been reported in the literature.[16] ^{1}H NMR δ: 7.82–7.60 (m, 5H); 4.20–3.90 (m, 4H); 3.20–3.05 (m, 2H); 2.85–2.75 (m, 2H); 0.18 (s, 9H).

3.2.2. 1-Methoxy-1-trimethylsilyloxy-1-hexene (3). 60%. Colorless oil, bp 55–8 °C/2 mmHg; spectroscopic data identical to that reported in the literature.[17]

3.2.3. 1-Methoxy-1-trimethylsilyloxy-1,5-hexadiene (4). 79%. Colorless oil, bp 40 °C/1 mmHg. Spectroscopic data for this compound have not been reported in the literature.[18] ^{1}H NMR δ: 5.90–5.70 (m, 1H); 5.05–4.90 (m, 2H). 3.90–3.80 (m, 1H); 3.50 (s, 3H, major isomer); 3.45 (s, 3H, minor isomer); 2.07–2.04 (m, 4H); 0.22 (s, 9H).

3.2.4. 2-Methyl-1-methoxy-1-trimethylsilyloxy-1-propene (5). 52%. Colorless oil, bp 63 °C/25 mmHg; spectroscopic data identical to that reported in the literature.[14]

3.2.5. (Cyclohexylidene(methoxy)methoxy)trimethylsilane (6). 74%. Colorless oil, bp 80 °C/25 mmHg; spectroscopic data identical to that reported in the literature.[14]

3.2.6. 3-Methyl-1-methoxy-1-trimethylsilyloxy-1-butene (11). 40%. Colorless oil, bp 45 °C/1 mmHg. Spectroscopic data for this compound have not been reported in the literature.[13b] ^{1}H NMR δ: 3.66–3.45 (m, 4H); 2.56–2.45 (m, 1H); 0.93 (d, J=6.8 Hz, 6H); 0.22 (s, 9H).

3.2.7. 3-Phenyl-1-methoxy-1-trimethylsilyloxy-1-propene (12). 53%. Colorless oil, bp 85 °C/1 mmHg; spectroscopic data identical to that reported in the literature.[19]

3.2.8. 4-Phenyl-1,1-bis(trimethylsilyloxy)-1-butene (22). 72%. Colorless oil, bp 130 °C/0.2 mmHg. Due to its lability, compound **22** has not been fully characterized, but was identified only by ^{1}H NMR spectrum. ^{1}H NMR δ: 7.30–7.11 (m, 5H); 3.55 (t, J=7.2 Hz, 1H); 2.64–2.51 (m, 2H); 2.28–2.11 (m, 2H); 0.19 (s, 9H); 0.17 (s, 9H).

3.2.9. 1,1-Bis(trimethylsilyloxy)-1-hexene (23). 95%. Colorless oil, bp 80 °C/1 mmHg. Due to its lability, compound **23** has not been fully characterized, but was identified only by ^{1}H NMR spectrum. ^{1}H NMR δ: 3.55 (t, J=7.2 Hz, 1H); 1.96–1.86 (m, 2H); 1.33–1.22 (m, 4H); 0.92–0.85 (m, 3H); 0.21 (s, 9H); 0.17 (s, 9H).

3.3. Synthesis of γ-butanolides. General procedure for the alkylation of silyl ketene acetals with epoxydes

To a cold (−60 °C) solution of silyl ketene acetal (1 mmol) and epoxide (2 mmol) in a solvent mixture dichloromethane–*n*-hexane=1:2 (3 mL) was added dropwise a solution of $TiCl_4$ in dichloromethane (0.82 mL of the 3.65 M solution; 3 mmol), with stirring under an argon atmosphere. The reaction mixture was allowed to reach −20 °C, then cooled to −30 °C and quenched by the addition of conc. aq NH_4Cl (5 mL). The organic phase was separated, and the aqueous layer was extracted with dichloromethane (3×10 mL). To a combined extract was added *p*-TsOH (20 mg; 0.1 mmol) and the reaction mixture was stirred 3 h at rt. The solution was washed with water, dried over anh. Na_2SO_4 and concentrated under reduced pressure. Purification by dry-flash chromatography afforded the corresponding γ-butanolides.

3.3.1. 2-(2-Phenylethyl)-4-butanolide (2). Purification by dry-flash chromatography was performed using 20% acetone in petroleum–ether as an eluent, to give the title compound in 66% yield when the reaction is performed with 4-phenyl-1,1-bis(trimethylsilyloxy)-1-butene **22**, (when 4-phenyl-1-methoxy-1-trimethylsilyloxy-1-butene **1** was used as the starting compound the yield was 62%). Colorless oil, bp 135–145 °C/0.3 mmHg (Kugelrohr). IR_{film}: 3063, 3029, 2922, 2861, 1769, 1495, 1454, 1376, 1184, 1150, 1026, ^{1}H NMR δ: 7.40–7.10 (m, 5H); 4.34 (ddd, J_1=J_2=9.0 Hz, J_3=2.7 Hz, 1H); 4.16 (ddd, J_1=J_2=9.0 Hz, J_3=6.6 Hz, 1H); 2.85–2.60 (m, 2H); 2.60–2.10 (m, 3H); 2.10–1.60 (m, 2H); ^{13}C NMR δ: 179.3; 140.7; 128.4; 128.3; 126.1; 66.3; 38.2; 33.1; 31.8; 28.6; HRMS (EI): M^+, found 190.0997; $C_{12}H_{14}O_2$ requires 190.0994. MS (EI) *m/z*: 190 (M^+, 17%); 105 (15%); 91 (25%); 85 (100%).

3.3.2. 2-Butyl-4-butanolide (7). Colorless oil, 80% from 1,1-bis(trimetilsilyloxy)-1-hexene, (69% from 1-methoxy-1-trimethylsilyloxy-1-hexene). Spectroscopic data for this compound have not been reported in the literature.[20] IR_{film}: 3053, 2959, 2931, 1773, 1462, 1376, 1168, 1026; ^1H NMR δ: 4.35 (ddd, $J_1=J_2=9.0$ Hz, $J_3=3.0$ Hz, 1H); 4.20 (ddd $J_1=J_2=9.0$ Hz, $J_3=6.4$ Hz, 1H); 2.60–2.30 (m, 2H); 2.10–1.80 (m, 2H); 1.60–1.25 (m, 5H); 1.00–0.80 (m, 3H); ^{13}C NMR δ: 179.6; 66.4; 39.0; 29.8; 29.3; 28.4; 22.2; 13.7.

3.3.3. 2-(3-Butenyl)-4-butanolide (8). Colorless oil, 64%, spectroscopic data identical to that reported in the literature.[21] ^{13}C NMR spectra for this compound have not been reported; ^{13}C NMR δ: 179.2 (C); 136.9 (CH); 115.2 (CH_2); 66.1 (CH_2); 38.1 (CH); 30.9 (CH_2); 29.0 (CH_2); 28.2 (CH_2).

3.3.4. 2,2-Dimethyl-4-butanolide (9). Colorless oil, 53%, spectroscopic data identical to that reported in the literature.[21] ^{13}C NMR spectra for this compound have not been reported; ^{13}C NMR δ: 182.0; 64.4; 38.1; 36.4; 23.6.

3.3.5. 2-Oxa-spiro[4.5]decan-1-one (10). Colorless oil, 66%. ^1H NMR δ: 4.26 (t, $J=7.1$ Hz, 2H); 2.16 (t, $J=7.1$ Hz, 2H); 1.80–1.20 (m, 10H); ^{13}C NMR δ: 181.9; 65.1; 43.0; 32.9; 32.2; 25.2; 22.0; HRMS (EI): M^+, found 154.0976; $C_{12}H_{20}O_2$ requires 154.0994; MS (EI) *m/z*: 154 (M^+, 32%); 99 (100%); 86 (82%); 81 (56%); 67 (32%).

3.3.6. 2-(2-Phenylethyl)-4-chloromethyl-4-butanolide (13). Colorless oil, 60% from 4-phenyl-1,1-bis(trimethylsilyloxy)-1-butene **22** (49% from 4-phenyl-1-methoxy-1-trimethylsilyloxy-1-butene **1**), obtained as a 1:1 mixture of stereoisomers. The isomers were preparatively separated by a second dry-flash chromatography, using 5% acetone in petroleum–ether as an eluent. Anal. Calcd for $C_{13}H_{15}ClO_2$: C 65.41, H 6.33; Found: C 65.88, H 6.34. Isomer **A**: IR_{film}: 3028, 2950, 1773, 1603, 1496, 1453, 1167, 1033; ^1H NMR δ: 7.40–7.10 (m, 5H); 4.74 (ddt, $J_1=J_2=8.6$ Hz, $J_3=4.7$ Hz, 1H); 3.65 (d, $J=4.7$ Hz, 2H); 2.90–2.60 (m, 3H); 2.45–2.25 (m, 1H); 2.25–2.00 (m, 2H); 1.90–1.70 (m, 1H); ^{13}C NMR δ: 178.3 (C); 140.5 (C); 128.5 (CH); 128.3 (CH); 126.2 (CH); 76.1 (CH); 45.9 (CH_2); 38.1 (CH); 33.1 (CH_2); 32.8 (CH_2); 30.9 (CH_2). Isomer **B**: IR_{film}: 3027, 2925, 1775, 1603, 1496, 1453, 1165, 1035; ^1H NMR δ: 7.40–7.20 (m, 5H); 4.57 (ddt, $J_1=J_2=10.2$ Hz, $J_3=5.0$ Hz, 1H); 3.69 (d, $J=5.0$ Hz, 2H); 2.90–2.40 (m, 4H); 2.40–2.20 (m, 1H); 1.90–1.70 (m, 2H); ^{13}C NMR δ: 177.7 (C); 140.5 (C); 128.5 (CH); 128.4 (CH); 126.3 (CH); 76.3 (CH); 45.3 (CH_2); 39.5 (CH); 33.1 (CH_2); 32.2 (CH_2); 31.9 (CH_2).

3.3.7. 2-(2-Phenylethyl)-4-bromomethyl-4-butanolide (14). Colorless oil, 53% from 4-phenyl-1,1-bis(trimethylsilyloxy)-1-butene **22**, (50% from 4-phenyl-1-methoxy-1-trimethylsilyloxy-1-butene **1**), obtained as a 1:1 mixture of stereoisomers. Anal. Calcd for $C_{13}H_{15}BrO_2$: C 55.14, H 5.34; found: C 55.16, H 5.58; IR_{film}: 3020, 2949, 2861, 1768, 1602, 1494, 1454, 1160; ^1H NMR δ: 7.35–7.18 (m, 5H); 4.74 (ddt, $J_1=8.1$ Hz, $J_2=5.7$ Hz, $J_3=4.4$ Hz, 1H, isomer **A**); 4.54 (ddt, $J_1=10.3$ Hz, $J_2=J_3=4.0$ Hz, 1H, isomer **B**); 3.62–3.42 (m, 2H); 2.89–2.48 (m, 3H); 2.41–2.06 (m, 2H); 1.88–1.66 (m, 2H); ^{13}C NMR δ: 178.3; 177.6; 140.5; 128.5; 128.4; 126.3; 76.0; 75.9; 39.7; 38.2; 34.0; 33.6; 33.4; 33.2; 33.1; 32.8; 32.0; 31.8.

3.3.8. 2-Butyl-4-chloromethyl-4-butanolide (15). Colorless oil, 67% from 1,1-bis(trimetilsilyloxy)-1-hexene, (64% from 1-methoxy-1-trimethylsilyloxy-1-hexene), obtained as a 1:1 mixture of stereoisomers. Anal. Calcd for $C_9H_{15}ClO_2$: C 56.69, H 7.93; found: C 56.84, H 7.78; HRMS (EI): M^+, found 190.07821; $C_{12}H_{14}O_2$ requires 190.07606; IR_{film}: 3055, 2959, 2934, 1775, 1461, 1345, 1175; ^1H NMR δ: 4.76 (ddt, $J_1=8.6$ Hz, $J_2=J_3=4.4$ Hz, 1H, diastereoisomer **A**); 4.64 (ddt, $J_1=10.0$ Hz, $J_2=5.6$ Hz, $J_3=5.1$ Hz, 1H, diastereoisomer **B**); 3.80–3.65 (m, 2H); 2.80–2.40 (m, 2H); 2.40–2.00 (m, 1H); 2.00–1.30 (m, 6H); 1.00–0.80 (m, 3H); ^{13}C NMR δ: 178.5; 177.8; 76.3; 76.1; 48.5; 46.1; 45.3; 40.3; 38.8; 31.9; 30.7; 29.8; 29.2; 29.1; 22.2; 13.7.

3.3.9. 2-Butyl-4-bromomethyl-4-butanolide (16). Colorless oil, 64%, obtained as a 1:1 mixture of stereoisomers. Anal. Calcd for $C_9H_{15}BrO_2$: C 45.98, H 6.43; found: C 45.74, H 6.55; IR_{film}: 2958, 2933, 2864, 1777, 1461, 1343, 1174. Isomer **A**: ^1H NMR δ: 4.75 (ddt, $J_1=8.2$ Hz, $J_2=J_3=5.0$ Hz, 1H); 3.55 (d, $J=5.0$ Hz, 2H); 2.82–2.66 (m, 1H); 2.39 (ddd, $J_1=13.4$ Hz, $J_2=9.6$ Hz, $J_3=4.6$ Hz, 1H); 2.17 (ddd, $J_1=13.4$ Hz, $J_2=J_3=7.9$ Hz, 1H); 1.92–1.79 (m, 1H); 1.58–1.27 (m, 5H); 0.95–0.88 (m, 3H); ^{13}C NMR δ: 178.4 (C); 75.9 (CH); 38.8 (CH); 34.3 (CH_2); 31.6 (CH_2); 30.5 (CH_2); 29.0 (CH_2); 22.1 (CH_2); 13.6 (CH_3). Isomer **B**: ^1H NMR δ: 4.60 (ddt, $J_1=10.4$ Hz, $J_2=J_3=5.6$ Hz, 1H); 3.57 (d, $J=5.6$ Hz, 2H); 2.75–2.51 (m, 2H); 1.95–1.65 (m, 2H); 1.52–1.27 (m, 5H); 0.95–0.88 (m, 3H); ^{13}C NMR δ: 177.7 (C); 75.9 (CH); 40.4 (CH); 33.5 (CH_2); 33.1 (CH_2); 29.6 (CH_2); 29.0 (CH_2); 22.1 (CH_2); 13.5 (CH_3).

3.3.10. 2-(3-Butenyl)-4-chloromethyl-4-butanolide (17). Colorless oil, 83%, obtained as a 1:1 mixture of diastereoisomers, which could not be separated by column chromatography, but were separated by preparative gas chromatography. Bp 100–105 °C/0.3 mmHg (Kugelrohr, for the mixture of isomers). Anal. Calcd for $C_9H_{13}O_2$: C 57.30; H 6.95; Found: C 56.98; H 6.98. Isomer **A**: IR_{film}: 3074, 2919, 2862, 1774, 1641, 1347, 1170, 1038; ^1H NMR δ: 5.90–5.70 (m, 1H); 5.15–4.95 (m, 2H); 4.76 (app. hex., $J=4.6$ Hz, 1H); 3.71 (dd, $J_1=J_2=5.4$ Hz, 2H); 2.85–2.65 (m, 1H); 2.60–2.30 (m, 2H); 2.30–1.90 (m, 2H); 1.70–1.50 (m, 2H); ^{13}C NMR δ: 178.6; 136.9; 115.9; 76.2; 46.0; 38.2; 31.2; 30.8; 30.3. Isomer **B**: 3074, 2939, 2864, 1775, 1641, 1345, 1172, 1037; ^1H NMR δ: 5.89–5.69 (m, 1H); 5.15–4.95 (m, 2H); 4.60 (m, 1H); 3.71 (dd, $J_1=5.2$ Hz, $J_2=1.1$ Hz, 2H); 2.80–2.40 (m, 2H); 2.30–2.00 (m, 3H); 1.95–1.50 (m, 2H); ^{13}C NMR δ: 177.8; 137.0; 115.9; 76.3; 45.3; 39.6; 32.2; 31.2; 29.4.

3.3.11. 2,2-Dimethyl-4-chloromethyl-4-butanolide (18). Colorless oil, 44%. Spectroscopic data for this compound have not been reported in the literature.[8c] IR_{film}: 2968, 2933, 1775, 1461, 1385, 1207, 1117; ^1H NMR δ: 4.69 (ddt, $J_1=9.4$ Hz, $J_2=6.5$ Hz, $J_3=5.2$ Hz, 1H); 3.70 (d, $J=5.2$ Hz, 2H); 2.24 (dd, $J_1=12.9$ Hz, $J_2=6.5$ Hz, 1H); 2.00 (dd, $J_1=12.9$ Hz, $J_2=9.4$ Hz, 1H); 1.32 (s. 3H); 1.30 (s. 3H); ^{13}C NMR δ: 180.9; 74.9; 45.5; 40.5; 40.2; 24.9; 24.8.

3.3.12. 3-Chloromethyl-2-oxa-spiro[4.5]decan-1-one (19). Colorless oil, 69%. IR_{film}: 2933, 2859, 1768, 1450, 1344, 1269, 1193, 1162, 1099, 1031; ^1H NMR δ: 4.68 (ddt, $J_1=9.2$ Hz, $J_2=6.9$ Hz, $J_3=4.7$ Hz, 1H); 3.74 (d, $J=4.7$ Hz, 2H); 2.43 (dd, $J_1=13.0$ Hz, $J_2=6.9$ Hz, 1H); 1.90 (dd, $J_1=13.0$ Hz, $J_2=9.2$ Hz, 1H); 1.85–1.20 (m, 10H); ^{13}C NMR δ: 180.4 (C); 75.1 (CH); 45.7 (CH_2); 44.4 (C); 36.0 (CH_2); 33.6 (CH_2); 31.8 (CH_2); 24.8 (CH_2); 21.8 (CH_2); 21.6 (CH_2); HRMS (EI): M^+, found 202.0760; $C_{12}H_{15}ClO_2$ requires 202.0782; MS (EI) *m/z*: 202 (M^+, 44%); 153 (35%); 147 (56%); 134 (82%); 81 (100%); 67 (58%).

3.3.13. 2-Isopropyl-4-chloromethyl-4-butanolide (20). Colorless oil, 59%, obtained as a 1:1 mixture of *cis*- and *trans*-isomers, bp 95 °C/0.8 mmHg. IR_{film}: 2964, 2880, 1774, 1465, 1342, 1173, 1035; HRMS (EI): $[M-CH_3]^+$, found 161.0355; $C_7H_{10}ClO_2$ requires 161.0369 (the intensity of M^+ ion was too low for a high resolution signal). Isomer **A**: ^1H NMR δ: 4.77–4.61 (m, 1H); 3.71–3.68 (m, 2H); 2.71 (ddd, $J_1=9.5$ Hz, $J_2=8.4$ Hz, $J_3=5.0$ Hz, 1H); 2.29–2.06 (m, 3H); 1.04 (d, $J=6.8$ Hz, 3H); 0.95 (d, $J=6.6$ Hz, 3H); ^{13}C NMR δ: 177.8 (C); 76.2 (CH); 46.4 (CH_2); 45.0 (CH); 28.7 (CH); 26.5 (CH_2); 20.1 (CH_3); 18.1 (CH_3). Isomer **B**: ^1H NMR δ: 4.59 (ddd, $J_1=11.2$ Hz, $J_2=6.1$ Hz, $J_3=5.1$ Hz, 1H)m, 1H); 3.72 (d, $J=5.0$ Hz, 2H); 2.67 (ddd, $J_1=12.1$ Hz, $J_2=9.1$ Hz, $J_3=5.0$ Hz, 1H); 2.35 (ddd, $J_1=12.1$ Hz, $J_2=9.1$ Hz, $J_3=6.2$ Hz, 1H); 2.26–2.13 (m, 1H); 2.00–1.83 (m, 1H); 1.06 (d, $J=6.4$ Hz, 3H); 0.94 (d, $J=6.6$ Hz, 3H); ^{13}C NMR δ: 176.9 (C); 75.9 (CH); 46.4 (CH_2); 45.3 (CH); 27.5 (CH_2); 27.4 (CH); 20.3 (CH_3); 18.0 (CH_3).

3.3.14. 2-(2-Phenylmethyl)-4-bromomethyl-4-butanolide (21). Colorless oil, 54%, obtained as a 1:1 mixture of *cis*- and *trans*-isomers, which were separated by column chromatography. Spectroscopic data for this compound have not been reported in the literature.[22] IR_{film}: 2923, 2862, 1777, 1604, 1496, 1341, 1161; HRMS (EI): M^+, found 268.0091; $C_{13}H_{13}BrO_2$ requires 268.0099. Isomer **A**: ^1H NMR δ: 7.37–7.17 (m, 5H); 4.54 (ddt, $J_1=10.7$ Hz, $J_2=J_3=5.2$ Hz, 1H); 3.46 (d, $J=5.2$ Hz, 2H); 3.23–3.02 (m, 1H); 2.92–2.72 (m, 2H); 2.26–2.14 (m, 2H); ^{13}C NMR δ: 178.2 (C); 138.1 (C); 128.8 (CH); 128.7 (CH); 126.8 (CH); 126.7 (CH); 76.1 (CH); 40.7 (CH); 36.4 (CH_2); 34.0 (CH_2); 30.7 (CH_2). Isomer **B**: ^1H NMR δ: 7.37–7.18 (m, 5H); 4.54 (dddd, $J_1=9.5$ Hz, $J_2=J_3=6.2$ Hz, $J_4=4.5$ Hz, 1H); 3.49 (dd, $J_1=12.1$ Hz, $J_2=4.2$ Hz, 1H); 3.38 (dd, $J_1=12.1$ Hz, $J_2=6.2$ Hz, 1H); 3.28 (dd, $J_1=12.0$ Hz, $J_2=4.6$ Hz, 1H); 3.00 (dddd, $J_1=11.4$ Hz, $J_2=J_3=9.0$ Hz, $J_4=4.2$ Hz, 1H); 3.23–3.02 (m, 1H); 2.79 (dd, $J_1=12.1$ Hz, $J_2=9.0$ Hz, 1H); 2.42 (ddd, $J_1=13.1$ Hz, $J_2=9.0$ Hz, $J_3=6.2$ Hz, 1H); 1.76 (ddd, $J_1=13.1$ Hz, $J_2=11.4$ Hz, $J_3=9.5$ Hz, 1H); ^{13}C NMR δ: 177.1 (C); 138.1 (C); 128.8 (CH); 128.7 (CH); 126.8 (CH); 76.2 (CH); 42.5 (CH); 36.0 (CH_2); 33.1 (CH_2); 32.8 (CH_2).

3.3.15. 2-Butyl-4-(1-bromoethyl)-4-butanolide (28). Colorless oil, 73%, obtained as a 1:1 mixture of *cis*- and *trans*-isomers. Anal. Calcd for $C_{10}H_{17}BrO_2$: C 48.21, H 6.88; found: C 47.71, H 6.98; IR_{film}: 2958, 2931, 2865, 1779, 1452, 1355, 1220, 1171; Isomer **A**: ^1H NMR δ: 4.57 (ddd, $J_1=8.5$ Hz, $J_2=4.8$ Hz, $J_3=3.5$ Hz, 1H); 4.20 (dq, $J_1=6.9$ Hz, $J_2=3.5$ Hz, 1H); 2.83–2.70 (m, 1H); 2.34 (ddd, $J_1=13.5$ Hz, $J_2=10.0$, $J_3=4.1$ Hz, 1H); 2.09 (ddd, $J_1=13.5$ Hz, $J_2=8.5$ Hz, $J_3=7.3$ Hz, 1H); 1.93–1.70 (m, 1H); 1.75 (d, $J=6.9$ Hz, 3H); 1.50–1.32 (m, 5H); 0.95–0.85 (m, 3H); ^{13}C NMR δ: 179.0 (C); 80.0 (CH); 50.8 (CH); 39.3 (CH); 31.2 (CH_2); 31.1 (CH_2); 29.3 (CH_2); 22.3 (CH_2); 21.2 (CH_3); 13.8 (CH_3). Isomer **B**: ^1H NMR δ: 4.50–4.39 (m, 1H); 4.28–4.12 (m, 1H); 2.75–2.43 (m, 2H); 1.96–1.81 (m, 1H); 1.75 (d, $J=6.9$ Hz, 3H); 1.53–1.27 (m, 6H); 0.95–0.88 (m, 3H); ^{13}C NMR δ: 178.0 (C); 80.2 (CH); 49.0 (CH); 40.4 (CH); 31.8 (CH_2); 29.6 (CH_2); 29.1 (CH_2); 22.1 (CH_2); 21.0 (CH_3); 13.6 (CH_3).

3.3.16. 2-Butyl-4-(1-bromo-3-methylbutyl)-4-butanolide (29). Colorless oil, 66%, obtained as a 1:1 mixture of *cis*- and *trans*-isomers. Anal. Calcd for $C_{13}H_{23}BrO_2$: C 53.61, H 7.96; found: C 53.32, H 7.84; IR_{film}: 2958, 2868, 1773, 1462, 1362, 1267, 1173; HRMS (EI): M^+, found 324.0736; $C_{16}H_{21}O_2Br$ requires 324.0725. Isomer **A**: ^1H NMR δ: 4.61 (ddd, $J_1=8.7$ Hz, $J_2=4.7$ Hz, $J_3=3.2$ Hz, 1H); 4.12 (dt, $J_1=6.8$ Hz, $J_2=3.2$ Hz, 1H); 2.89–2.73 (m, 1H); 2.38 (ddd, $J_1=13.0$ Hz, $J_2=10.0$ Hz, $J_3=4.6$ Hz, 1H); 2.17–2.06 (m, 1H); 2.02–1.81 (m, 3H); 1.63–1.32 (m, 6H); 0.98–0.88 (m, 9H); ^{13}C NMR δ: 179.2 (C); 79.3 (CH); 56.6 (CH); 43.0 (CH_2); 39.3 (CH); 31.5 (CH_2); 31.3 (CH_2); 29.3 (CH_2); 25.9 (CH); 23.0 (CH_3); 22.4 (CH_2); 20.8 (CH_3); 13.8 (CH_3). Isomer **B**: ^1H NMR δ: 4.47 (ddd, $J_1=10.0$ Hz, $J_2=6.0$ Hz, $J_3=4.0$ Hz, 1H); 4.12 (dt, $J_1=10.4$ Hz, $J_2=3.8$ Hz, 1H); 2.74–2.41 (m, 2H); 2.02–1.78 (m, 4H); 1.63–1.34 (m, 6H); 0.99–0.89 (m, 9H); ^{13}C NMR δ: 178.0 (C); 79.4 (CH); 54.4 (CH); 42.6 (CH_2); 40.4 (CH); 32.1 (CH_2); 29.8 (CH_2); 29.5 (CH_2); 25.9 (CH); 23.1 (CH_3); 22.4 (CH_2); 20.7 (CH_3); 13.8 (CH_3).

3.3.17. 2-Butyl-4-(1-bromo-2-cyclohexylethyl)-4-butanolide (30). Colorless oil, 54%, obtained as a 1:1 mixture of diastereoisomers. IR_{film}: 2923, 2858, 1751, 1449, 1351, 1272, 1181, 1117, 1064, 1032. Isomer **A**: ^1H NMR δ: 4.53–4.41 (m, 1H); 4.16 (ddd, $J_1=10.7$ Hz, $J_2=J_3=3.6$ Hz, 1H); 2.73–2.29 (m, 3H); 2.00–1.50 (m, 12H); 1.47–1.12 (m, 7H); 0.96–0.89 (m, 3H); ^{13}C NMR δ: 178.0 (C); 79.5 (CH); 57.7 (CH); 46.6 (CH_2); 40.5 (CH); 35.1 (CH); 33.7 (CH_2); 32.1 (CH_2); 31.6 (CH_2); 29.8 (CH_2); 29.5 (CH_2); 26.4 (CH_2); 26.1 (CH_2); 25.8 (CH_2); 22.4 (CH_2); 13.8 (CH_3). Isomer **B**: mp 82 °C. Anal. calcd. for $C_{16}H_{27}BrO_2$: C 58.01, H 8.21; found: C 57.65, H 8.18; ^1H NMR δ: 4.60 (ddd, $J_1=8.6$ Hz, $J_2=4.7$ Hz, $J_3=3.1$ Hz, 1H); 4.21–4.11 (m, 1H); 2.88–2.73 (m, 1H); 2.39 (ddd, $J_1=13.3$ Hz, $J_2=10.1$ Hz, $J_3=4.6$ Hz, 1H); 2.09 (ddd, $J_1=13.3$ Hz, $J_2=8.6$ Hz, $J_3=7.4$ Hz, 1H); 1.95–1.51 (m, 10H), 1.45–1.11 (m, 9H); 0.95–0.85 (m, 3H); ^{13}C NMR δ: 179.1 (C); 79.3 (CH); 56.0 (CH); 41.7 (CH_2); 39.3 (CH); 35.2 (CH); 33.6 (CH_2); 31.7 (CH_2); 31.5 (CH_2); 31.3 (CH_2); 29.3 (CH_2); 26.4 (CH_2); 26.1 (CH_2); 25.9 (CH_2); 22.5 (CH_2); 13.8 (CH_3).

3.3.18. 2-(2-Phenylmethyl)-4-(1-bromo-3-methylbutyl)-4-butanolide (31). Colorless oil, 21%, single isomer. IR_{film}: 3032, 2958, 2874, 1774, 1603, 1496, 1459, 1362, 1172, 1038; ^1H NMR δ: 7.37–7.10 (m, 5H); 4.39 (ddd, $J_1=8.2$ Hz, $J_2=5.2$ Hz, $J_3=3.2$ Hz, 1H); 4.03 (ddd, $J_1=J_2=7.0$ Hz, $J_3=3.2$ Hz, 1H); 3.26–3.10 (m, 2H); 2.82 (dd, $J_1=15.0$ Hz, $J_2=10.0$ Hz, 1H); 2.33–2.07 (m, 2H); 1.97–1.77 (m, 2H); 1.58–1.44 (m, 1H); 0.94 (d, $J=6.6$ Hz, 3H); 0.87 (d, $J=6.6$ Hz, 3H); ^{13}C NMR δ: 178.4 (C); 139.0 (C); 129.0 (CH); 128.8 (CH); 126.9 (CH); 79.3 (CH); 56.6 (CH); 43.1

(CH_2); 41.0 (CH); 37.0 (CH_2); 30.6 (CH_2); 25.9 (CH); 22.9 (CH_3); 20.8 (CH_3).

3.3.19. 4-(1-Bromo-2-cyclohexylethyl)-2-isopropyl-4-butanolide (32). Colorless oil, 69%, obtained as a 1:1 mixture of diastereoisomers, which were separated by dry-flash chromatography. IR_{film}: 2926, 2846, 1758, 1448, 1377, 1238, 1160, 1039. Isomer **A**: ^1H NMR δ: 4.55 (ddd, $J_1=7.6$ Hz, $J_2=6.0$ Hz, $J_3=3.0$ Hz, 1H); 4.16 (ddd, $J_1=J_2=6.6$ Hz, $J_3=3.5$ Hz, 1H); 2.77 (ddd, $J_1=J_2=9.0$ Hz, $J_3=5.0$ Hz, 1H); 2.29–2.17 (m, 3H); 1.81–1.51 (m, 8H); 1.35–1.12 (m, 3H); 1.02 (d, $J=6.9$ Hz, 3H); 0.95 (d, $J=6.9$ Hz, 3H); 0.91–0.75 (m, 2H); ^{13}C NMR δ: 178.3 (C); 79.4 (CH); 56.5 (CH); 45.4 (CH); 41.7 (CH_2); 35.2 (CH); 33.6 (CH_2); 31.7 (CH_2); 29.2 (CH); 27.4 (CH_2); 26.3 (CH_2); 26.0 (CH_2); 25.8 (CH_2); 20.2 (CH_3); 18.1 (CH_3); HRMS (EI): M^+, found 316.1043; $C_{15}H_{25}BrO_2$ requires 316.1038. Isomer **B**: ^1H NMR δ: 4.44 (ddd, $J_1=10.1$ Hz, $J_2=6.1$ Hz, $J_3=4.0$ Hz, 1H); 4.18 (ddd, $J_1=J_2=7.4$ Hz, $J_3=3.5$ Hz, 1H); 2.64 (ddd, $J_1=12.2$ Hz, $J_2=9.0$ Hz, $J_3=5.0$ Hz, 1H); 2.40–2.15 (m, 2H); 2.10–1.53 (m, 9H); 1.42–1.11 (m, 3H); 1.05 (d, $J=7.0$ Hz, 3H); 0.95 (d, $J=7.0$ Hz, 3H); 0.89–0.72 (m, 2H); ^{13}C NMR: 176.9 (C); 79.1 (CH); 53.7 (CH); 46.6 (CH); 41.4 (CH_2); 35.1 (CH); 33.7 (CH_2); 31.6 (CH_2); 27.7 (CH_2); 27.6 (CH); 26.4 (CH_2); 26.1 (CH_2); 25.8 (CH_2); 20.5 (CH_3); 18.3 (CH_3); HRMS (EI): M^+, found 316.1053; $C_{15}H_{25}BrO_2$ requires 316.1038.

3.3.20. 3-Butylhexahydrobenzofuran-2-one (33). Colorless oil, 48%, obtained as a 1:1 mixture of stereoisomers which were separated by preparative gas chromatography. HRMS (EI): M^+, found 196.1463; $C_{12}H_{20}O_2$ requires 196.1482; MS (EI) *m/z*: 196 (M^+; 8%); 140 (100%); 95 (8%); 82 (6%); 67 (9%); IR_{film}: 2937, 2864, 1777, 1457, 1389, 1206, 1175, 1124, 1080, 1024. Isomer **A**: ^1H NMR δ: 3.70 (ddd, $J_1=J_2=10.8$ Hz, $J_3=3.8$ Hz, 1H); 2.30–2.15 (m, 2H); 2.10–1.70 (m, 4H); 1.65–1.20 (m, 10H); 0.91 (t, $J=7.0$ Hz, 3H); ^{13}C NMR δ: 178.6; 82.6; 49.9; 46.2; 30.1; 29.2; 28.2; 28.1; 25.3; 24.0; 22.8; 13.9. Isomer **B**: ^1H NMR δ: 3.97 (ddd, $J_1=J_2=10.8$ Hz, $J_3=4.0$ Hz, 1H); 2.50–2.40 (m, 1H); 2.30–2.10 (m, 1H); 2.00–1.80 (m, 4H); 1.60–1.20 (m, 10H) 0.91 (t, $J=7.0$ Hz, 3H); ^{13}C NMR δ: 175.0; 82.0; 47.7; 44.0; 30.7; 29.6; 25.4; 25.0; 24.7; 23.9; 22.6; 13.9.

3.3.21. 2-(2-Phenylethyl)-4-methyl-4-butanolide (34) and 2-(2-phenylethyl)-3-methyl-4-butanolide (35). Colorless oil, 30% (41% yield calculated on the basis of the recovered starting compound), obtained as a mixture of regioisomers in a 7:3 ratio (regioisomer **34** as 1:1 mixture of diastereoisomers; regioisomer **35** as 3:1 mixture of diastereoisomers). Anal. Calcd for $C_{13}H_{16}O_2$: C 76.44, H, 7.90; found: C 76.26; H 8.09; IR_{film}: 3028, 2975, 2932, 1769, 1603, 1496, 1454, 1185; ^{1}HNMR δ: 7.47–7.16 (m, 5H); 4.67 (ddq, $J_1=12.7$ Hz, $J_2=J_3=6.3$ Hz, 1H, **34**, isomer **A**); 4.45 (ddq, $J_1=11$ Hz, $J_2=6.2$ Hz, $J_3=5.5$ Hz, 1H, **34**, isomer **B**); 4.36 (dd, $J_1=8.8$ Hz, $J_2=7.0$ Hz, 1H, **35**, isomer **A**); 3.69 (dd, $J_1=J_2=6.4$ Hz, 1H, **35**, isomer **B**); 2.85–2.40 (m, 4H); 2.30–1.90 (m, 2H); 1.85–1.58 (m, 1H); 1.41 (d, $J=6.3$ Hz, 3H, **34**, isomer **A**); 1.35 (d, $J=6.2$ Hz, 3H, **34**, isomer **B**); 1.13 (d, $J=6.4$ Hz, 3H, **35**, isomer **B**); 1.04 (d, $J=7.0$ Hz, 3H, **35**, isomer **A**); ^{13}C NMR δ: 179.1; 178.8; 140.7; 128.5; 128.4; 126.1; 75.0; 74.8; 73.0; 72.4; 45.8; 40.5; 38.3; 37.0; 36.3; 35.0; 33.2; 33.1; 32.6; 32.3; 31.8; 30.5; 26.5; 21.1; 20.8; 16.4; 13.4.

3.3.22. 3-Methyl-2-oxaspiro[4.5]decane-1-one (36) and 4-methyl-2-oxaspiro[4.5]decane-1-one (37). Mixture of regioisomers in 2:1 ratio, obtained as a colorless oil in 35% yield. The regioisomers were separated by preparative gas chromatography. Physical data for 3-methyl-2-oxaspiro(4.5(decane-1-one (**36**):[23] White crystals, mp 70 °C; IR: 2930, 2859, 1756, 1452, 1391, 1212, 1135, 1086, 1015; ^1H NMR spectra identical to that reported in the literature;[23] ^{13}C NMR δ: 182.0 (C); 73.6 (CH); 45.3 (C); 41.1 (CH_2); 34.3 (CH_2); 31.5 (CH_2); 25.3 (CH_2); 22.1 (CH_2); 22.0 (CH_2); 21.4 (CH_3). Physical data for 4-methyl-2-oxaspiro (4.5(decane-1-one (**37**):[24] Colorless oil; IR and ^1H NMR spectra identical to that reported in the literature;[24] ^{13}C NMR spectra for this compound have not been reported in the literature;^{13}C NMR δ: 181.2 (C); 71.5 (CH_2); 45.1 (C); 38.3 (CH); 31.9 (CH_2); 27.2 (CH_2); 25.4 (CH_2); 21.9 (CH_2); 21.6 (CH_2); 13.5 (CH_3).

3.3.23. 2,2,4-Trimethyl-4-butanolide (38) and 2,2,3-trimethyl-4-butanolide (39). Mixture of regioisomers in 3:2 ratio, obtained as a colorless oil in 38% yield. The regioisomers were separated by preparative gas chromatography. Physical data for 2,2,4-trimethyl-4-butanolide (**38**):[25] White crystals, mp 53 °C; IR: 2975, 2938, 2878, 1766, 1459, 1387, 1186, 1112; ^1H NMR spectra identical to that reported in the literature;[25] ^{13}C NMR δ: 182.1; 73.3; 45.2; 40.8; 25.0; 24.3; 21.1. Physical data for 2,2,3-trimethyl-4-butanolide (**39**):[26] Colorless oil; Spectroscopic data for this compound have not been reported in the literature;[26]IR_{film}: 2971, 2923, 1775, 1462, 1393, 1220, 1109; ^1H NMR δ: 4.37 (dd $J_1=9.0$ Hz, $J_2=7.5$ Hz, 1H); 3.80 (dd, $J_1=J_2=9.0$ Hz, 1H); 2.33 (ddq, $J_1=9.5$ Hz, $J_2=J_3=7.0$ Hz, 1H); 1.25 (s, 3H); 1.09 (s, 3H); 1.05 (d, $J=7.0$ Hz, 3H); ^{13}C NMR δ: 182.6; 71.1; 41.4; 40.6; 23.2; 17.9; 11.1.

3.3.24. 2,2-Dimethyl-3-phenyl-4-butanolide (40). Colorless oil, 15% yield. When the reaction was performed by substituting $BF_3\cdot Et_2O$ for $TiCl_4$, the title compound was isolated in 32% yield. Spectroscopic data for this compound have not been reported in the literature.[27] IR_{film}: 3032, 2977, 2915, 2876, 1774, 1595, 1492, 1457, 1393, 1207, 1108, 1029; ^1H NMR δ: 7.40–7.15 (m, 5H); 4.56 (dd, $J_1=J_2=8.0$ Hz, 1H); 4.50 (dd, $J_1=J_2=8.0$ Hz, 1H); 3.42 (dd, $J_1=J_2=8.0$ Hz, 1H); 1.35 (s, 3H); 0.90 (s, 3H); ^{13}C NMR δ: 181.5 (C); 136.0 (C); 128.7 (CH); 128.0 (CH); 127.4(CH); 68.6 (CH_2); 52.1 (CH); 24.1 (CH_3); 19.6 (CH_3).

3.4. General procedure for the reduction of 4-(1-haloalkyl)-4-butanolides with tributyltin hydride

A solution of the corresponding 4-(1-haloalkyl)-4-butanolide (1 mmol), tributyltin hydride (1.5 mmol) and a catalytic amount of azobis(isobutyronitrile) in benzene (5 mL) was heated to reflux, with stirring, under an argon atmosphere. The course of the reaction was monitored by TLC. Upon completion, the reaction mixture was concentrated under reduced pressure, dissolved in diethyl ether (20 mL), a saturated aqueous solution of sodium fluoride (10 mL) was added and the mixture was vigorously stirred for 24 h at rt. The organic layer was separated, dried over anh. Na_2SO_4,

filtered, concentrated under reduced pressure and the product was purified by dry-flash chromatography.

3.4.1. 2-(2-Phenylethyl)-4-methyl-4-butanolide (34). Colorless oil, 73%, obtained from **14** as a 1:1 mixture of diastereoisomers. Spectroscopic data for this compound have not been reported in the literature.[28] IR_{film}: 3059, 3028, 2978, 2931, 1769, 1604, 1453, 1350, 1186, 1113; ^1H NMR δ: 7.32–7.13 (m, 5H); 4.63 (ddq, $J_1=12.7$ Hz, $J_2=J_3=6.3$ Hz, 1H, isomer **A**); 4.41 (ddq, $J_1=11.0$ Hz, $J_2=6.2$ Hz, $J_3=5.5$ Hz, 1H isomer **B**); 2.75–2.36 (m, 4H); 2.31–1.90 (m, 2H); 1.83–1.61 (m, 1H); 1.38 (d, $J=6.2$ Hz, 3H isomer **A**); 1.35 (d, $J=6.3$ Hz, 3H, isomer **B**); ^{13}C NMR δ: 178.9 (C); 178.6 (C); 140.6 (C); 128.2 (CH); 128.1 (CH); 125.9 (CH); 74.8 (CH); 74.7 (CH); 40.3 (CH); 38.2 (CH); 36.8 (CH_2); 34.7 (CH_2); 33.1 (CH_2); 33.0 (CH_2); 32.1 (CH_2); 31.7 (CH_2); 20.9 (CH_3); 20.6 (CH_3).

3.4.2. 2-Butyl-4-methyl-4-butanolide (41). Colorless oil, 74%, obtained from **15** as a 1:1 mixture of diastereoisomers. Spectroscopic data for this compound have not been reported in the literature.[28] IR_{film}: 2961, 2933, 2865, 1772, 1460, 1346, 1179. ^1H NMR δ: 4.67 (ddq, $J_1=J_2=J_3=6.4$ Hz, 1H, isomer **A**); 4.49 (ddq, $J_1=11.0$ Hz, $J_2=J_3=6.0$ Hz, 1H isomer **B**); 2.70–2.43 (m, 1.5H); 2.11–1.76 (m, 2H); 1.56–1.27 (m, 5.5H); 1.42 (d, $J=6.0$ Hz, 3H isomer **B**); 1.37 (d, $J=6.4$ Hz, 3H, isomer **A**); 0.95–0.88 (m, 3H); ^{13}C NMR δ: 179.3 (C); 179.0 (C); 74.9 (CH); 74.8 (CH); 41.2 (CH); 39.1 (CH); 36.8 (CH_2); 34.8 (CH_2); 30.2 (CH_2); 29.8 (CH_2); 29.3 (CH_2); 22.2 (CH_2); 21.0 (CH_3); 20.7 (CH_3); 13.6 (CH_3).

3.4.3. 3-Methyl-2-oxa-spiro[4.5]decane-1-one (36). White crystals, mp 70 °C, 78%. The spectra of **36** are given in Section 3.3.22.

3.4.4. 2-(2-Phenylmethyl)-4-methyl-4-butanolide (42). From **21A**. Colorless oil, 80%. Spectroscopic data identical to that reported in the literature.[20,29]

3.4.5. 2-Butyl-4-ethyl-4-butanolide (43). From **28A**. Colorless oil, 82%. Spectroscopic data for this compound have not been reported in the literature.[30] IR_{film}: 3050, 2960, 2928, 1770, 1461, 1357, 1180. ^1H NMR δ: 4.50–4.21 (m, 1H); 2.67–2.37 (m, 1H); 2.12–2.01 (m, 2H); 1.93–1.27 (m, 8H); 1.04–0.89 (m, 6H); ^{13}C NMR δ: 178.0 (C); 80.0 (CH); 39.3 (CH); 33.0 (CH_2); 30.6 (CH_2); 29.5 (CH_2); 28.5 (CH_2); 22.4 (CH_2); 13.9 (CH_3); 9.6 (CH_3).

3.5. Reduction of 4-bromoalkyl-4-butanolides with hypophosphorous acid. 2-(2-Phenylethyl)-4-methyl-4-butanolide (34)

To a refluxing solution of **14** (150 mg; 0.53 mmol), hypophosphorous acid (289 μL of the 50% aqueous solution; 2.65 mmol) and triethylamine (295 mg; 2.92 mmol) in dioxane (4.8 mL) was added AIBN (113 mg; 0.7 mmol) in four portions, at 30 min intervals. Upon completion, the reaction mixture was diluted with dichloromethane (50 mL) and washed with water. The organic extract was dried over anh. $MgSO_4$, filtered and concentrated under reduced pressure. Purification by dry-flash chromatography afforded 82 mg (76%) of the title compound **34**, whose physical data are given in Section 3.4.1.

3.6. Allylation of 4-bromomethyl-2-butyl-4-butanolide (16) with allyl tributyltin. 4-(3-Butenyl)-2-butyl-4-butanolide (44)

A solution of 4-bromomethyl-2-butyl-4-butanolide (116 mg; 0.49 mmol), allyl tributyltin (326 mg; 0.99 mmol) and azobis(isobutyronitrile) (catalytic amount) in benzene (1 mL) was heated to reflux, with stirring, under an argon atmosphere. The reaction was monitored by TLC. Work-up of the reaction mixture as described in Section 3.4., followed by purification by dry-flash chromatography, afforded 80 mg (83%) of the title compound **44**, as a colorless oil. Anal. calcd. for $C_{12}H_{20}O_2$: C 73.43, H 10.27; found: C 73.63, H 10.61; IR_{film}: 2933, 2866, 1771, 1458, 1357, 1287, 1178; ^1H NMR δ: 5.81 (ddt, $J_1=17.0$ Hz, $J_2=10.3$ Hz, $J_3=6.6$ Hz, 1H); 5.12–4.99 (m, 2H); 4.51 (ddt, $J_1=7.9$ Hz, $J_2=J_3=6.2$ Hz, 1H); 2.67–2.52 (m, 1H); 2.31–1.98 (m, 4H); 1.92–1.55 (m, 4H); 1.49–1.27 (m, 6H); 0.92 (t, $J=7.6$ Hz, 3H); ^{13}C NMR δ: 172.4 (C); 137.1 (CH); 115.6 (CH_2); 78.0 (CH); 39.2 (CH); 34.8 (CH_2); 33.4 (CH_2); 30.5 (CH_2); 29.5 (CH_2); 29.4 (CH_2); 22.4 (CH_2); 13.9 (CH_3).

3.7. Tributyltin hydride mediated free radical addition of 4-bromomethyl-2-butyl-4-butanolide (28) to acrylonitrile. 4-(4-Cyano-2-butyl)-2-butyl-4-butanolide (45)

To a refluxing solution of 4-bromomethyl-2-butyl-4-butanolide **28A** (120 mg; 0.48 mmol), acrylonitrile (510 mg; 9.6 mmol) and azobis(isobutyronitrile) (catalytic amount) in benzene (24 mL), tributyltin hydride (9 mL of 0.07 M solution in benzene; 0.63 mmol) was added in 4 portions, in 30 min intervals, with stirring, under an argon atmosphere. The reaction was monitored by TLC. Work-up of the reaction mixture as described in Section 3.4, followed by purification by dry-flash chromatography, afforded 82 mg (76%) of the title compound **45**, as a colorless oil (obtained as 1:1 mixture of diastereoisomers). IR_{film}: 2961, 2935, 2870, 2247, 1769, 1463, 1183, 1001; ^1H NMR: 4.46–4.36 (m, 1H, isomer **A**); 4.22 (dd, $J_1=15.3$ Hz, $J_2=6.9$ Hz, 1H, isomer **B**); 2.70–2.55 (m, 1H); 2.53–2.36 (m, 2H); 2.24–1.97 (m, 3H); 1.92–1.75 (m, 3H); 1.67–1.27 (m, 5H); 1.00 (t, $J=6.3$ Hz, 3H); 0.95–0.88 (m, 3H); ^{13}C NMR: 179.2 (C); 179.0 (C); 119.4 (C); 119.2 (C); 82.0 (CH); 80.8 (CH); 39.5 (CH); 39.4 (CH); 37.3 (CH); 36.6 (CH); 31.6 (CH_2); 30.8 (CH_2); 30.7 (CH_2); 30.6 (CH_2); 29.3 (CH_2); 28.6 (CH_2); 28.0 (CH_2); 22.3 (CH_2); 14.9 (CH_2); 14.8 (CH_2); 14.4 (CH_3); 13.7 (CH_3); 13.2 (CH_3); HRMS (EI): M^+, found 223.1564; $C_{13}H_{21}NO_2$ requires 223.1572.

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