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Organo-catalyzed enantioselective synthesis of some β-silyl γ-alkyl γ-butyrolactones as intermediates for natural products

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ABSTRACT

The enantioselective synthesis of some β-silyl γ-alkyl γ-butyrolactones has been achieved by an organo-catalyzed Michael addition of enolizable aldehydes onto a silylmethylene malonate followed by a silicon-facilitated Bayer–Villiger oxidation of the β-silyl aldehyde adducts as the key step. γ-Alkyl γ-butenolides were obtained from the β-silyl γ-alkyl γ-butyrolactones by Fleming–Tamao oxidation of the silyl group to a hydroxy group and subsequent elimination. These butenolides are the advanced intermediates of some natural products such as (+)-γ-caprolactone, (+)-methylenolactocine, and (−)-quercus lactone.

1. Introduction

Chiral γ-substituted γ-butyrolactones are abundant in nature. They are also valuable intermediates for the synthesis of a large variety of molecules containing acyclic and cyclic systems including antibiotics, pheromones, plant growth regulators, antifungal agents, and flavor components.[1–3] A few interesting examples, such as avenaciolide **1**, γ-dodecanolactone **2**, γ-caprolactone **3**, protolichesterinic acid **4**, methylenolactocine **5**, rocellaric acid **6**, quercus lactone **7**, and blastmycinone **8** are shown in Figure 1. β-Hydroxy γ-alkyl γ-butyrolactones are a class of molecules, which have additional features in addition to their occurrences as natural product such as **8**. They can easily be converted into γ-substituted γ-butenolides **9**,[4,5] well known intermediates for functionalized butyrolactone and other molecule syntheses.[4–9]

The syntheses of chiral γ-substituted γ-butyrolactones and butenolides have been an ongoing challenge for synthetic chemists. Although a large number of methods for the preparation of optically active γ-alkyl γ-butyrolactones and γ-substituted γ-butenolides have been reported in the literature,[10–25] substrate generality, stereochemical purities, and high yields are yet to be achieved. Recently, we have reported a highly enantioselective organocatalytic Michael addition of enolizable aldehydes and methyl ketones to a silylmethylene malonate **10**[26] leading to highly functionalized β-silyl aldehydes **11**[27] and β-silyl ketones **12** (Scheme 1).[28,29] These adducts can be easily transformed into medium-sized rings leading to skeletal and stereochemical diversities of complex structures, patterned after δ-valerolactones of types **13** and **14**, piperidines **15**, and pyrrolidines **16** (Scheme 1).[27–29] Herein, we report enantioselective syntheses of some β-silyl γ-alkyl γ-butyrolactones via an organo-catalyzed Michael addition of enolizable aldehydes onto silylmethylene malonate **10** and their conversion to γ-alkyl γ-butenolides via a silicon-facilitated[30] Bayer–Villiger oxidation and Fleming–Tamao oxidation[31,32] as the key steps.

2. Results and discussion

We have recently established that the direct Michael addition of enolizable aldehydes to dimethyl(phenyl)silylmethylene malonate **10** could be catalyzed by (*S*)-diphenylprolinol trimethylsilyl ether **17**/acetic acid combination.[27] The optimized conditions required 1 equiv of silylmethylene malonate **10**, 10 equiv of an aldehyde, a combination of 15 mol % each of (*S*)-diphenylprolinol trimethylsilyl ether **17** and acetic acid as the catalyst system and dichloromethane as the solvent at room temperature for 4 days. Thus, under these optimized *n*-butanal, *n*-hexanal and *n*-heptanal conditions gave β-silyl aldehyde adducts **11a**, **11b**, and **11c** in very good yield, diastereoselectivity, and enantioselectivity (Scheme 2).

The diastereoisomeric mixture of aldehydes **11a–c** was subjected to a β-silicon-facilitated Bayer–Villiger oxidation using 3-chloroperoxybenzoic acid in dichloromethane, resulting in an inseparable mixture of diastereoisomeric formates **18a–c** in very good yield (Scheme 3). In each case, the isomeric formate mixture was then hydrolyzed with KOH in methanol and the resulting hydroxy dicarboxylic acid upon heating at 100 °C underwent decarboxylation and concomitant lactonization leading directly to the desired major lactones **19a–c** in very good yield after chromatographic purification. The minor diastereoisomeric product also was eliminated during this purification step. The dimethyl(phenyl)silyl group in **19a–c** was then converted into a

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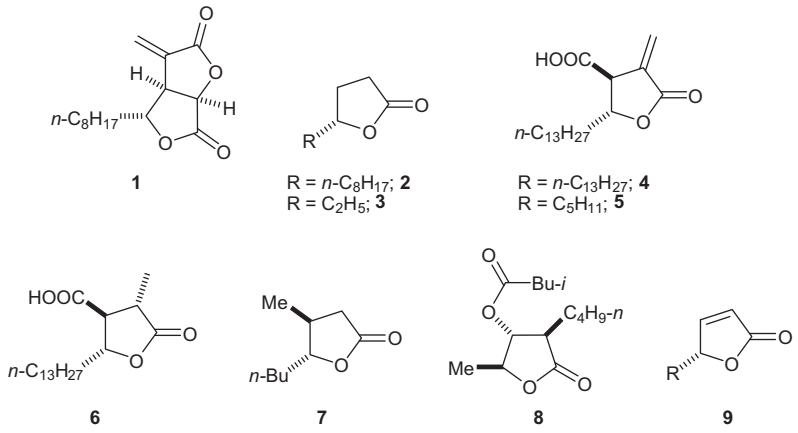
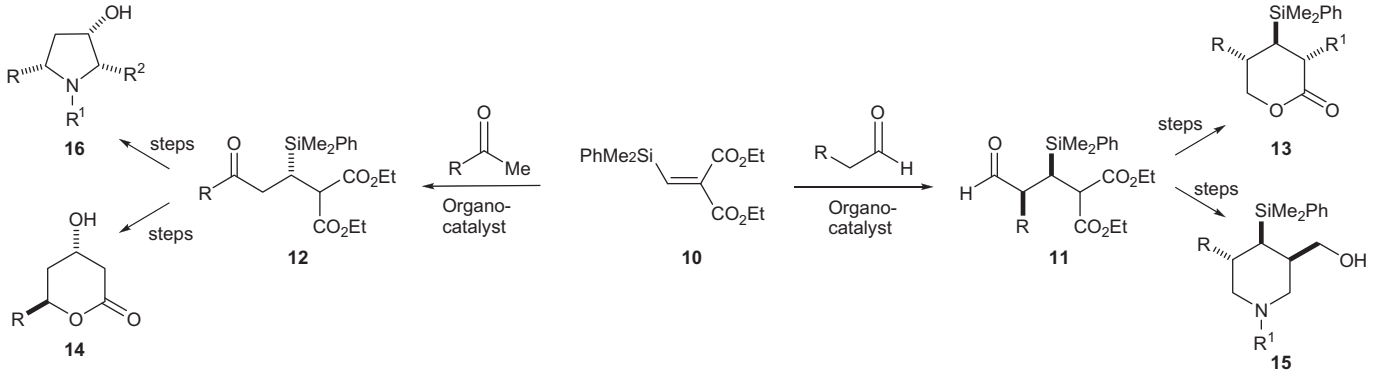
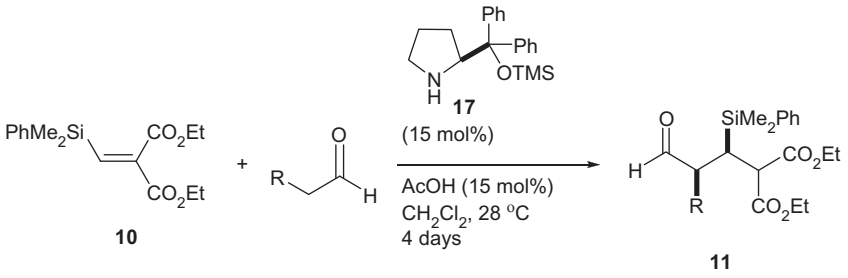


Figure 1. Some γ-substituted butyrolactones.



Scheme 1. Application of aldehyde and ketone adducts of **10** in heterocycle synthesis.

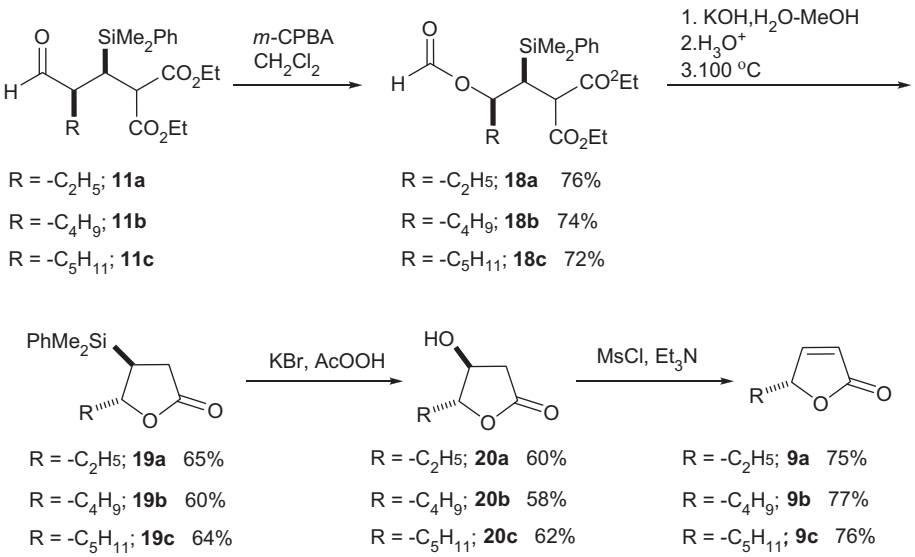


Product	% yield	dr	% ee of major isomer
R = -C_2H_5; **11a**	79	86/14	98
R = -C_4H_9; **11b**	73	84/16	>99
R = -C_5H_{11}; **11c**	75	81/19	98

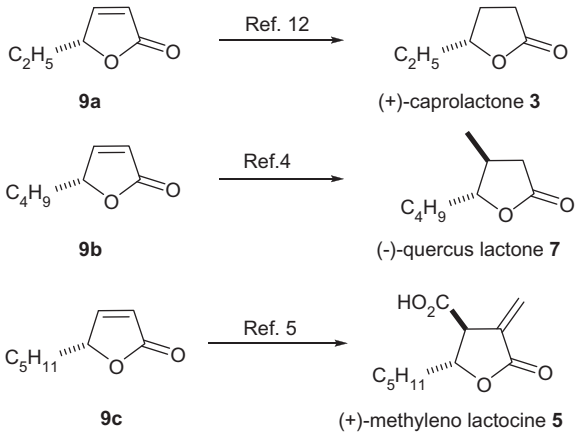
Scheme 2. The addition of unmodified aldehydes to silylmethylene malonate **10**.

hydroxy group following Fleming–Tamao[31,32] oxidation using potassium bromide and peracetic acid with retention of configuration, leading to hydroxy lactones **20a–c**. Butenolides **9a–c** were then prepared from these hydroxy lactones **20a–c** by the treatment with MsCl and NEt_3 at 0 °C.[6]

Butenolides **9a–c** are well known intermediates for the synthesis of many naturally occurring γ-lactones. For example, butenolide **9a** has already been converted[33] into the natural product, (+)-γ-caprolactone **3** (Scheme 4). The absolute configuration of the alkyl group in **9a** was also assigned from the ^1H and ^{13}C chemical shift values, and comparing the specific rotation value {$[\alpha]_D^{28} = -92$ (*c* 1.46, MeOH); lit.[33] $[\alpha]_D^{20} = -94$ (*c* 1.05, CH_2Cl_2)}. (−)-Quercus lactone **7** has been obtained using butenolide **9b** as the key intermediate.[4] The absolute configuration of **9b** was confirmed by comparing the physical and spectroscopic data with the literature values {$[\alpha]_D^{28} = -101.9$ (*c* 2.16, $CHCl_3$); lit.[34] $[\alpha]_D^{25} = -101$ (*c* 1.2, $CHCl_3$)}. The natural product (+)-methylenolactocine **5** has been synthesized from the butenolide **9c** in three steps



Scheme 3. Preparation of chiral γ-alkyl butenolides.



Scheme 4. Formal synthesis of some γ-butyrolactone natural products.

(Scheme 4).[5] The absolute configuration of **9c** was also confirmed by comparing the ^{1}H and ^{13}C chemical shift values as well as the specific rotation value {$[\alpha]_D^{28} = -93$ (*c* 2.53, $CHCl_3$); lit.[5] $[\alpha]_D^{25} = -90.1$ (*c* 1.76, $CHCl_3$)}.

3. Conclusion

In conclusion, we have achieved the enantioselective synthesis of some β-silyl γ-alkyl γ-butyrolactones via an organo-catalyzed Michael addition of enolizable aldehydes onto a silylmethylene malonate and their conversion into γ-alkyl γ-butenolides, potent intermediates for γ-alkyl γ-butyrolactones natural products, via a silicon-facilitated Bayer–Villiger oxidation and Fleming–Tamao oxidation as the key steps. These γ-alkyl γ-butenolides are the advanced intermediates of some natural products, such as (+)-γ-caprolactone **3**, (+)-methylenolactocine **5**, and (−)-quercus lactone **7**.

4. Experimental

HPLC grade acetone, NMP, DMF, toluene, THF, methanol were used as received. Butanal, hexanal, and heptanal were commercially available, and were distilled prior to use. Silylmethylene malonate **10** was prepared following a procedure reported in the literature.[35] Diphenylprolinol was commercially available and its TMS-ether **17** was prepared according to the literature.[36]

Solvent removal was carried out using a rotary evaporator connected to a dry ice condenser. TLC (0.5 mm) was carried out using home made silica plates with a fluorescence indicator. Column chromatography was performed on silica gel (230–400 mesh). ^{1}H and ^{13}C NMR spectra were recorded in a 200 MHz (^{1}H: 200 MHz, ^{13}C: 50 MHz) or 500 MHz (^{1}H: 500 MHz, ^{13}C: 125 MHz) or 700 MHz (^{1}H: 700 MHz, ^{13}C: 175 MHz) spectrometers. ^{1}H and ^{13}C shifts are given in ppm, δ scale and are measured relative to internal $CHCl_3$ and $CDCl_3$ as standards, respectively. Chemical shifts are reported in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), quint (pentet), m (multiplet) and br (broad). Coupling constants, *J*, are reported in Hertz. High resolution mass spectra were recorded at 60–70 eV on a Waters Micromass Q-TOF spectrometer (ESI, Ar). Optical rotations were measured in a JASCO DIP 360 polarimeter. Infrared spectra (IR) were recorded on a JASCO FT IR spectrophotometer in NaCl cells or in KBr disks. Peaks are reported in cm^{-1}. Enantiomeric excess (ee) determinations were carried out by HPLC instrument fitted with a chiralpak AD–H/OD–H column and UV detector with λ fixed at 254 nm.

4.1. Michael addition of aldehydes to 10 using organocatalyst 17 and AcOH additive

General procedure I: The respective aldehyde (5 mmol, 10 equiv) was added to a stirred mixture of silylmethylene malonate **10** (153 mg, 0.5 mmol, 1 equiv), pyrrolidine **17** (25 mg, 0.075 mmol, 0.15 equiv), and acetic acid (4 μL, 0.075 mmol, 0.15 equiv) in dichloromethane (1 mL) at 0 °C. After 4 days at 28 °C, the reaction mixture was diluted with water and extracted with EtOAc/hexane (1/1). The organic extract was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica using hexane/EtOAc (95/5) as eluent to give **11a–c** (73–79%).

4.1.1. Ethyl (3*R*,4*S*)-3-dimethylphenylsilyl-2-ethoxycarbonyl-4-formylhexanoate 11a

Prepared from silylmethylene malonate **10** and *n*-butanal according to *General procedure I*. Yield: 149 mg, 79%. The diastereomeric ratio was determined from ^{1}H NMR spectra; crude (*syn*/

anti = 86/14), after purification (*syn*/*anti* = 86/14). Careful chromatography of a small portion of a sample gave *syn*-**11a** (>95% de, NMR). Data for *syn*-**11a**: ee = 98%. The enantiomeric excess of *syn*-**11a** was determined by HPLC using Daicel OD–H column (λ = 254 nm, hexane/*i*-PrOH = 99.7:0.3, 0.6 mL/min), t_R = 23.58 min (major), t_R = 52.15 min (minor). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.34 (s, 3H), 0.42 (s, 3H), 0.79 (t, *J* = 7.4 Hz, 3H), 1.17–1.27 (m, 6H), 1.35–1.72 (m, 2H), 2.29 (t, *J* = 5.2 Hz, 1H), 2.33–2.43 (m, 1H), 3.52 (d, *J* = 5.0 Hz, 1H), 4.01–4.14 (m, 4H), 7.24–7.35 (m, 3H), 7.53–7.58 (m, 2H), 9.53 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ −2.4, −1.4, 12.4, 13.9 (2C), 21.6, 26.7, 51.4, 53.7, 61.5, 61.6, 127.7 (2C), 129.1, 134.0 (2C), 138.6, 169.6 (2C), 204.1. IR (film): 3071, 2981, 2937, 2877, 1745, 1725, 1462, 1427, 1252, 1110, 909, 820 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{31}O_5Si$ $[M+H]^+$: 379.1941; found: 379.1935.

4.1.2. Ethyl (3*R*,4*S*)-3-dimethylphenylsilyl-2-ethoxycarbonyl-4-formyloctanoate 11b

Prepared from silylmethylene malonate **10** and *n*-hexanal according to *General procedure I*. Yield: 148 mg, 73%. The diastereomeric ratio was determined from ^{1}H NMR spectra; crude (*syn*/*anti* = 84/16), after purification (*syn*/*anti* = 84/16). Careful chromatography of a small portion of sample gave *syn*-**11b** (>95% de, NMR). Data for *syn*-**11b**: ee = 99%. The enantiomeric excess of *syn*-**11b** was determined by HPLC using Daicel AD–H column (λ = 254 nm, hexane/*i*-PrOH = 99.7:0.3, 0.5 mL/min), t_R = 34.56 min (major), t_R = 37.36 min (minor). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.35 (s, 3H), 0.42 (s, 3H), 0.78 (t, *J* = 6.2 Hz, 3H), 1.12–1.39 (m, 12H), 2.27 (t, *J* = 5.2 Hz, 1H), 2.37–2.51 (m, 1H), 3.53 (d, *J* = 5.0 Hz, 1H), 4.01–4.17 (m, 4H), 7.32–7.35 (m, 3H), 7.53–7.58 (m, 2H), 9.52 (d, *J* = 2.0 Hz,1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ −2.5, −1.4, 13.8, 13.9 (2C), 22.4, 26.9, 28.2, 29.8, 51.3, 51.8, 61.4, 61.6, 127.7 (2C), 129.0, 134.0 (2C), 138.7, 169.6 (2C), 204.2. IR (film): 3070, 3048, 2958, 2872, 2721, 1745, 1726, 1465, 1427, 1251, 1110, 912, 820 cm^{-1}. HRMS (ESI) calcd for $C_{22}H_{35}O_5Si$ $[M+H]^+$: 407.2254; found: 407.2236.

4.1.3. Ethyl (3*R*,4*S*)-3-dimethylphenylsilyl-2-ethoxycarbonyl-4-formylnonanoate 11c

Prepared from silylmethylene malonate **10** and *n*-heptanal according to *General procedure I*. Yield: 157 mg, 75%. The diastereomeric ratio was determined from ^{1}H NMR spectra; crude (*syn*/*anti* = 81/19), after purification (*syn*/*anti* = 81/19). Careful chromatography of a small portion of sample gave *syn*-**11c** (>95% de, NMR). Data for *syn*-**11c**: ee = 97.8%. The enantiomeric excess of *syn*-**11c** was determined by HPLC using Daicel AD–H column (λ = 254 nm, hexane/*i*-PrOH = 99.6:0.4, 0.6 mL/min), t_R = 18.63 min (major), t_R = 24.48 min (minor). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.34 (s, 3H), 0.42 (s, 3H), 0.80 (t, *J* = 6.2 Hz, 3H), 1.10–1.57 (m, 14H), 2.66 (t, *J* = 5.2 Hz,1H), 2.42–2.47 (m, 1H), 3.53 (d, *J* = 5.2 Hz, 1H), 4.01–4.17 (m, 4H), 7.31–7.37 (m, 3H), 7.52–7.58 (m, 2H), 9.51 (d, *J* = 2.2 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ −2.4, −1.4, 13.9 (3C), 22.3, 26.9, 27.4, 28.5, 31.5, 51.3, 51.8, 61.4, 61.6, 127.8 (2C), 129.0, 134.0 (2C), 138.7, 169.7 (2C), 204.2. IR (film): 3070, 3048, 2957, 2930, 2858, 1745, 1727, 1465, 1427, 1250, 1152, 1110, 1029, 819 cm^{-1}. HRMS (ESI) calcd for $C_{23}H_{37}O_5Si$ $[M+H]^+$: 421.2410; found: 421.2415.

4.2. Bayer–Villiger oxidation of aldehydes 11a–c

General procedure II: A solution of 3-chloroperoxybenzoic acid (~70%) (375 mg, 1.5 mmol, 1.5 equiv) in dichloromethane (10 mL) was pre-dried over anhydrous $MgSO_4$ and added to a stirred mixture of the respective aldehydes **11a–c** (1 mmol, 1 equiv) and disodium hydrogen phosphate dihydrate (356 mg, 2 mmol, 2 equiv) in dichloromethane (7 mL) at 0 °C. The reaction mixture was brought to room temperature and stirred under those conditions for 4 h. The reaction mixture was quenched with aqueous sodium metabisulfite solution and extracted with dichloromethane. The combined organic extract was washed with $NaHCO_3$ solution followed by water and brine, dried over MgSO4 and evaporated under reduced pressure. The residue was purified by column chromatography on silica using hexane/EtOAc (95/5) as eluent to give the desired formate esters **18a–c** (72–76%).

4.2.1. (2*R*,3*S*)-1,1-Di(ethoxycarbonyl)-2-dimethyl(phenyl)-silylpentan-3-yl formate 18a

Prepared from aldehyde **11a** according to *General procedure II*. Yield: 298 mg, 76% as an oil. The diastereomeric ratio was determined from ^{1}H NMR spectra; crude (*syn*/*anti* = 86/14), after purification (*syn*/*anti* = 92/8). Careful chromatography of a small portion of sample gave *syn*-**18a**. $[\alpha]_D^{25} = +12.5$ (*c* 3.7, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.33 (s, 3H), 0.44 (s, 3H), 0.67 (t, *J* = 7.3 Hz, 3H), 1.20–1.28 (m, 6H), 1.35–1.67 (m, 2H), 2.25 (q, *J* = 3.6 Hz, 1H), 3.65 (d, *J* = 3.6 Hz , 1H), 4.00–4.21 (m, 4H), 5.12–5.19 (m, 1H), 7.32–7.35 (m, 3H), 7.64–7.59 (m, 2H), 7.96 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ −3.5, −1.6, 9.3, 13.8, 13.9, 27.1, 30.6, 50.2, 61.2, 61.5, 74.9, 127.7 (2C), 129.0, 134.0 (2C), 138.7, 160.4, 169.7, 170.0. IR (film): 3070, 3047, 2956, 2932, 2872, 1747, 1729, 1373, 1178, 1110, 1033, 820 cm^{-1}.

4.2.2. (2*R*,3*S*)-1,1-Di(ethoxycarbonyl)-2-dimethyl(phenyl)-silylheptan-3-yl formate 18b

Prepared from aldehyde **11b** according to *General procedure II*. Yield: 312 mg, 74% as an oil. The diastereomeric ratio was determined from ^{1}H NMR spectra; crude (*syn*/*anti* = 84/16), after purification (*syn*/*anti* = 93/7). Careful chromatography of a small portion of sample gave *syn*-**18b**. $[\alpha]_D^{25} = +12.8$ (*c* 1.64, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.33 (s, 3H), 0.44 (s, 3H), 0.71 (t, *J* = 6.6 Hz, 3H), 0.96–1.07 (m, 4H), 1.20–1.28 (m, 6H), 1.35–1.67 (m, 2H), 2.24 (q, *J* = 3.6 Hz, 1H), 3.65 (d, *J* = 3.6 Hz, 1H), 4.00–4.21 (m, 4H), 5.12–5.19 (m, 1H), 7.32–7.35 (m, 3H), 7.64–7.59 (m, 2H), 7.94 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ −3.6, −1.5, 13.7, 13.9, 14.0, 22.1, 27.0, 31.0, 33.9, 50.2, 61.2, 61.5, 73.8, 127.8 (2C), 129.0, 134.0 (2C), 138.8, 160.3, 169.7, 169.9. IR (film): 3070, 3047, 2958, 2934, 2873, 1748, 1729, 1373, 1178, 1111, 1033, 820 cm^{-1}.

4.2.3. (2*R*,3*S*)-1,1-Di(ethoxycarbonyl)-2-dimethyl(phenyl)-silyloctan-3-yl formate 18c

Prepared from aldehyde **11c** according to *General procedure II*. Yield: 314 mg, 72% as an oil. The diastereomeric ratio was determined from ^{1}H NMR spectra; crude (*syn*/*anti* = 81/19), after purification (*syn*/*anti* = 94/6). Careful chromatography of a small portion of sample gave *syn*-**18c**. $[\alpha]_D^{23} = +9.7$ (*c* 1.85, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.33 (s, 3H), 0.44 (s, 3H), 0.76 (t, *J* = 6.8 Hz, 3H), 0.94–1.20 (m, 6H), 1.22–1.35 (m, 6H), 1.39–1.57 (m, 2H), 2.23 (q, *J* = 3.6 Hz, 1H), 3.60 (d, *J* = 3.6 Hz, 1H), 3.98–4.21 (m, 4H), 5.16–5.25 (m, 1H), 7.32–7.35 (m, 3H), 7.54–7.58 (m, 2H), 7.94 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ −3.6, −1.5, 13.7, 13.8, 13.9, 22.3, 24.5, 30.9, 31.2, 34.0, 50.2, 61.2, 61.5, 73.8, 127.7 (2C), 129.0, 134.0 (2C), 138.8, 160.2, 169.7, 169.9. IR (film): 3070, 3047, 2955, 2930, 2871, 1746, 1730, 1372, 1176, 1111, 1033, 821 cm^{-1}.

4.3. Synthesis of butyrolactones from formates 18a–c

General procedure III: Potassium hydroxide (280 mg, 5 mmol, 5 equiv) was added to a stirred solution of the formyl esters **18a–c** (1 mmol) in methanol (7 mL) at room temperature. After 12 h, the solvent was evaporated under reduced pressure and the residue was diluted with water (2 mL), acidified with dilute HCl and extracted with ethyl acetate. The organic extract was dried over

Na_2SO_4 and evaporated under reduced pressure. The residue was heated at 110 °C under a nitrogen atmosphere for 5 h, cooled to room temperature and purified by column chromatography on silica using hexane/EtOAc (95/5) as an eluent to give the desired butyrolactones **19a–c** (60–65%) as a single diastereoisomer.

4.3.1. (4*S*,5*R*)-4-Dimethyl(phenyl)silyl-5-ethyl-4,5-dihydrofuran-2(3*H*)-one 19a

Prepared from formate **18a** according to *General procedure III*. Yield: 160 mg, 65% as an oil. $[\alpha]_D^{25} = +31.8$ (*c* 0.66, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 0.35 (s, 6H), 0.94 (t, *J* = 7.3 Hz, 3H), 1.46–1.69 (m, 3H), 2.28–2.62 (m, 2H), 4.23–4.33 (m, 1H), 7.34–7.48 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$): δ −4.8, −4.5, 9.8, 28.3, 29.0, 31.8, 84.6, 128.1 (2C), 129.7, 133.5 (2C), 135.4, 176.9. IR (film): 3019, 2957, 2930, 2871, 1774, 1426, 1372, 1176, 1111, 821 cm^{-1}. HRMS (ESI) calcd for $C_{14}H_{20}NaO_2Si$ [M+Na]+: 271.1128; found: 271.1130.

4.3.2. (4*S*,5*R*)-4-Dimethyl(phenyl)silyl-5-butyl-4,5-dihydrofuran-2(3*H*)-one 19b

Prepared from formate **18b** according to *General procedure III*. Yield: 165 mg, 60% as an oil. $[\alpha]_D^{25} = +49.0$ (*c* 1.51, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 0.36 (s, 6H), 0.83 (t, *J* = 7.0 Hz, 3H), 1.17–1.31 (m, 3H), 1.36–1.52 (m, 3H), 1.62–1.72 (m, 1H), 2.27–2.61 (m, 2H), 4.27–4.38 (m, 1H), 7.31–7.48 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$): δ −4.8, −4.5, 13.7, 22.2, 27.7, 29.0, 31.8, 35.8, 83.5, 128.1 (2C), 129.8, 133.5 (2C), 135.5, 176.9. IR (film): 3019, 2957, 2932, 2859, 1774, 1427, 1254, 1210, 1112, 836, 758 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{24}NaO_2Si$ $[M+Na]^+$: 299.1443; found: 299.1449.

4.3.3. (4*S*,5*R*)-4-Dimethyl(phenyl)silyl-5-pentyl-4,5-dihydrofuran-2(3*H*)-one 19c

Prepared from formate **18c** according to *General procedure III*. Yield: 185 mg, 64% as an oil. $[\alpha]_D^{25} = +45.1$ (*c* 0.82, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 0.36 (s, 6H), 0.84 (t, *J* = 6.5 Hz, 3H), 1.13–1.32 (m, 5H), 1.37–151 (m, 3H), 1.62–1.72 (m, 1H), 2.27–2.62 (m, 2H), 4.27–4.37 (m, 1H), 7.36–7.48 (m, 5H).^{13}C NMR (50 MHz, $CDCl_3$): δ −4.8, −4.4, 13.8, 22.3, 25.3, 29.0, 31.3, 36.1, 83.6, 128.2 (2C), 129.8, 133.7 (2C), 135.5, 177.0. IR (film): 3019, 2956, 2933, 2859, 1773, 1428, 1254, 1210, 1111, 836, 757 cm^{-1}. HRMS (ESI) calcd for $C_{17}H_{26}NaO_2Si$ $[M+Na]^+$: 313.1600; found: 313.1598.

4.4. Synthesis of β-hydroxy γ-butyrolactones from β-silyl lactones 19a–c

General procedure IV: Potassium bromide (143 mg, 1.2 mmol, 1.2 equiv) was added to a stirred solution of lactones **19a–c** (1 mmol) in freshly prepared peracetic acid (6 mL of a 35% solution in acetic acid) at 0 °C followed by the addition of H_2O_2 (30%, 0.15 mL). The reaction mixture was allowed to return to room temperature and stirred for 24 h. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane. The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure to give the crude hydroxyl lactones **20a–c** (58–62%).

4.4.1. (4*S*,5*R*)-5-Ethyl-4-hydroxy-4,5-dihydrofuran-2(3*H*)-one 20a

Prepared from silylated lactone **19a** according to *General procedure IV*. Yield 78 mg, 60%. $[\alpha]_D^{29} = +40.0$ (*c* 0.8, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 1.02 (t, *J* = 7.2 Hz, 3H), 1.59–1.70 (m, 2H), 2.51 (dd, *J* = 3.0, 18.0 Hz, 1H), 2.81 (dd, *J* = 6.2, 18.2 Hz, 1H), 2.97 (br, 1H), 4.28–4.30 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 9.5, 26.0, 37.7, 71.2, 89.2, 175.6. IR (film): 3736, 3435, 2960, 2934, 2872, 2862, 1770, 1190, 1053, 987, 757 cm^{-1}. HRMS (ESI) calcd for $C_6H_{11}O_3$ $[M+H]^+$: 131.0663; found: 131.0710.

4.4.2. (4*S*,5*R*)-5-Butyl-4-hydroxy-4,5-dihydrofuran-2(3*H*)-one 20b

Prepared from silylated lactone **19b** according to *General procedure IV*. Yield 93 mg, 58%. $[\alpha]_D^{24} = +35.1$ (*c* 0.94, $CHCl_3$). ^1H NMR (700 MHz, $CDCl_3$): δ 0.93 (t, *J* = 6.3 Hz, 3H), 1.38–1.42 (m, 3H), 1.46–1.49 (m, 1H), 1.60–1.68 (m, 2H), 2.50–2.53 (m, 1H), 2.83 (dd, *J* = 6.3, 18.2 Hz, 1H), 3.0 (br, 1H), 4.28–4.3 (m, 1H), 4.36–4.37 (m, 1H). ^{13}C NMR (175 MHz, $CDCl_3$): δ 13.8, 22.3, 27.3, 32.7, 37.7, 71.5, 88.0, 175.6. IR (film): 3738, 3435, 2959, 2934, 2873, 2863, 1771, 1189, 1052, 987, 757 cm^{-1}. HRMS (ESI) calcd for $C_8H_{15}O_3$ $[M+H]^+$: 159.1021; found: 159.1028.

4.4.3. (4*S*,5*R*)-5-Pentyl-4-hydroxy-4,5-dihydrofuran-2(3*H*)-one 20c

Prepared from silylated lactone **19c** according to *General procedure IV*. Yield 107 mg, 62%. $[\alpha]_D^{26} = +36.0$ (*c* 2.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.3 Hz, 3H), 1.29–1.45 (m, 6H), 1.54–1.62 (m, 2H), 2.47 (dd, *J* = 3.5, 18.0 Hz, 1H), 2.79 (dd, *J* = 6.5, 18.0 Hz, 1H), 3.36 (br, 1H), 4.20–4.30 (m, 1H), 4.30–4.40 (m, 1H), ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.8, 22.4, 24.8, 31.4, 32.9, 37.6, 71.4, 88.3, 175.9. IR (film): 3737, 3434, 2960, 2936, 2873, 2860, 1770, 1190, 1052, 985, 758 cm^{-1}. HRMS (ESI) calcd for $C_9H_{17}O_3$ $[M+H]^+$: 173.1133; found: 173.1194.

4.5. Synthesis of γ-butenolides from β-hydroxy butyrolactones 20a–c

General procedure V: Methanesulfonyl chloride (0.05 mL, 0.65 mmol) was added to a stirred solution of the hydroxylactone **20a–c** (0.6 mmol) and triethylamine (0.17 mL, 1.2 mmol) in dichloromethane (4 mL) at 0 °C. After 1 h, the reaction mixture was quenched with saturated ammonium chloride solution. The reaction mixture was extracted with dichloromethane and the extract was evaporated to give the crude butenolide which was purified by column chromatography to give pure **9a–c** (75–77%).

4.5.1. (*R*)-5-Ethyl-2(5*H*)-furanone 9a

Prepared from hydroxy lactone **20a** according to *General procedure V*. Yield: 51 mg, 75% as oil. $[\alpha]_D^{24} = -91.8$ (*c* 1.46, MeOH) lit.[32] $[\alpha]_D^{23} = -94$ (*c* 1.46, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$): δ 0.98 (t, *J* = 7.4 Hz, 3H), 1.59–1.89 (m, 2H), 4.95–5.01 (m, 1H), 6.09 (dd, *J* = 5.7 Hz, *J* = 1.9 Hz, 1H), 7.43 (dd, *J* = 5.7 Hz, *J* = 1.3 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 8.9, 26.3, 84.2, 121.8, 155.8, 173.0. IR (film): 3018, 2957, 2931, 2860, 1754, 1600, 1465, 1334, 1163, 1096, 1024, 819 and 756 cm^{-1}.

4.5.2. (*R*)-5-Buthyl-2(5*H*)-furanone 9b

Prepared from hydroxy lactone **20b** according to *General procedure V*. Yield: 64 mg, 77% as oil. $[\alpha]_D^{24} = -101.8$ (*c* 2.16, $CHCl_3$) lit.[34] $[\alpha]_D^{24} = -101.8$ ($CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.9 Hz, 3H), 1.25–1.51 (m, 4H), 1.55–1.85 (m, 2H), 4.98–5.05 (m, 1H), 6.08 (dd, *J* = 5.7 Hz, *J* = 1.9 Hz, 1H), 7.44 (dd, *J* = 5.8 Hz, *J* = 1.2 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.7, 22.3, 27.0, 32.8, 83.4, 121.5, 156.2, 173.0. IR (film): 3019, 2959, 2933, 2863, 1755, 1600,1466, 1335, 1164, 1097, 1024, 819 and 754 cm^{-1}.

4.5.3. (*R*)-5-Pentyl-2(5*H*)-furanone 9c

Prepared from hydroxy lactone **20c** according to *General procedure V*. Yield: 70 mg, 76% as oil. $[\alpha]_D^{24} = -93.3$ (*c* 2.53, $CHCl_3$) lit.[5] $[\alpha]_D^{25} = -90.1$ (*c* 1.76, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 0.85 (t, *J* = 6.5 Hz, 3H), 1.16–1.48 (m, 7H), 1.53–1.83 (m, 2H), 4.96–5.04 (m, 1H), 6.06 (dd, *J* = 5.6 Hz, *J* = 1.9 Hz, 1H), 7.43 (dd, *J* = 5.7 Hz, *J* = 1.3 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.8, 22.3, 24.6, 31.4,

33.1, 83.4, 121.4, 156.2, 173.0. IR (film): 3018, 2957, 2931, 2858, 1752, 1600,1465, 1334, 1163, 1095, 1024, 819 and 757 cm^{-1}.

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