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A facile synthesis of 5,5-dideutero-4-dimethyl (phenyl)silyl-6-undecyl-tetrahydropyran-2-one as a deuterium labeled synthon for (−)-tetrahydrolipstatin and (+)-δ-hexadecanolide†

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Deuterium-labeled biologically active compounds are gaining importance because they can be utilized as tracers or surrogate compounds to understand the mechanism of action, absorption, distribution, metabolism, and excretion. Deuterated drug molecules (heavy drugs) become novel as well as popular because of better stability and bioavailability compared with their hydrogen analogs. Labeling of organic molecules with deuterium at specific positions is thus gaining popularity. In this work, we have exploited a highly regioselective and enantioselective direct Michael addition of methyl-d_3 alkyl ketones to dimethyl (phenyl)silylmethylene malonate that was catalyzed by (*S*)-*N*-(2-pyrrolidinylmethyl)pyrrolidine/trifluoroacetic acid/ D_2O combination with high yield and isotopic purity. The 5,5-dideutero-4-dimethyl(phenyl)silyl-6-undecyl-tetrahydropyran-2-one was obtained from the adduct of methyl-d_3 undecanyl ketone and dimethyl(phenyl)silylmethylene malonate by a silicon controlled diastereoselective ketone reduction, lactonization, and deethoxycarbonylation. The dideuterated silylated tetrahydropyran-2-one is the precursor for *geminal* $^2H_2$-labeled (+)-4-hydroxy-6-undecyl-tetrahydropyran-2-one, an advanced intermediate for *gem*-dideutero (–)-tetrahydrolipstatin and (+)-δ-hexadecanolide syntheses.

Keywords: deuterium labeling; organocatalysis; Michael addition; 5,5-dideutero-4-dimethyl(phenyl)silyl-6-undecyl-tetrahydropyran-2-one; methyl-d_3 alkyl ketones, dimethyl(phenyl)silylmethylene malonate; 4,4-dideuterated 3-silyl-5-keto ester

Introduction

There are significant advancements in the analytical techniques for the detection of stable isotopes (e.g., ^2H and ^{13}C) attached to organic molecules by NMR or mass spectrometry. Therefore, there is a surge of interest in applications of stable isotope-labeled compounds in general and deuterium (^2H or D)-labeled compounds, in particular, in a variety of scientific fields. Deuterium-labeled biologically active compounds are utilized as tracers or surrogate compounds to understand the mechanism of action, absorption, distribution, metabolism, and excretion.[1–3] Compounds labeled with deuterium at specific positions are used in the investigation of chemical and enzymatic reaction mechanisms,[4,5] kinetics,[6–10] and the structural elucidation of biological macromolecules.[11]

The difference in physical and chemical properties between H and D is very small but measurable. Deuteration increases lipophilicity of organic molecules. A C–D bond is shorter than a C–H bond. There is a slight increase in basicity of deuterated amines and a slight decrease in acidity of deuterated phenols and carboxylic acids. The primary use of D substitution in place of H in drug discovery is to use the kinetic isotope effect (KIE), which usually ranges from onefold to sevenfold, with exceptions. Thus, site specific substitution of hydrogen with D where H atom abstraction is the rate determining step that can impede metabolism and also can reduce toxicity. Because of KIE, deuterium slows epimerization thus enhances stereochemical stability.

Recently, deuterated drug molecules (heavy drugs) become novel as well as popular drugs that exhibit better stability and bioavailability compared with their hydrogen analogs.[12,13] Deuterated paroxetine,[14,15] an antidepressant (Figure 1) altered the drug's metabolism and prolonged its activity *in vivo*. The metabolism rate of deuterated analog of venlafaxine,[16] dual serotonin/norepinephrine reuptake inhibitor dropped to 50%. The nephrotoxicity of efavirenz (Figure 1), an HIV-1 non-nucleoside reverse transcriptase inhibitor got reduced to a good extent.[17] The chiral center next to α-ketoamide (*S*-configuration) in telaprevir (Figure 1) tends to epimerize (*R*-configuration), which was suppressed through the deuteration at the specified position of telaprevir.[18]

The 4-hydroxytetrahydropyran-2-one (commonly known as β-hydroxy-δ-lactone) subunit is present in a large number of

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biologically important molecules[19–21] (Figure 2) and it has been shown[22] from structure activity relationship (SAR) studies that the lactone moiety is essential for the biological activity. The synthesis of 4-hydroxytetrahydropyran-2-ones can be achieved from the corresponding 4-dimethyl(phenyl)silyl-tetrahydropyran-2-ones by a stereospecific Fleming–Tamao[23,24] oxidation of dimethyl (phenyl)silyl group to a hydroxyl group with retention of configuration. Labeled 4-dimethyl(phenyl)silyltetrahydropyran-2-ones with deuterium at specific positions would therefore be useful for detailed biological studies for such kind of molecules. The H–D exchange reactions are often carried out at C–Hs α to a carbonyl or OH groups, aryl-C–Hs and benzylic C–Hs because of the reactivity of these positions.[25–27] Inactivated positions do not undergo H–D exchange so easily, although some efforts have been made for perdeuteration of alkanes.[28–30] We propose a selective deuterium labeling strategy at the unreactive 5-position of the tetrahyropyran-2-one as shown in Scheme 1. The 5,5-dideutero-4-dimethyl(phenyl)silyl-tetrahydropyran-2-ones **1**-d_2 could be obtained from the 4,4-dideuterated 3-silyl-5-keto ester **2**-d_2 which in turn could be prepared by a regioselective and enantioselective Michael addition of methyl-d_3 alkyl ketones **3** to a silylmethylene malonate **4**. Herein, we report enantioselective organo-catalyzed Michael addition of methyl-d_3 alkyl ketones **3** to silylmethylene malonate **4** and conversion of one of the adducts to 5,5-

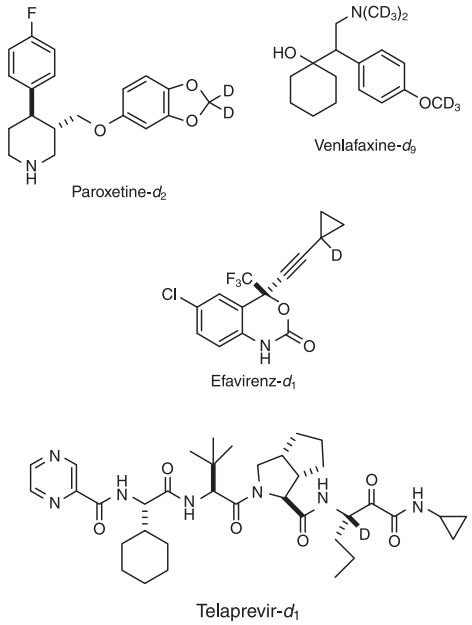
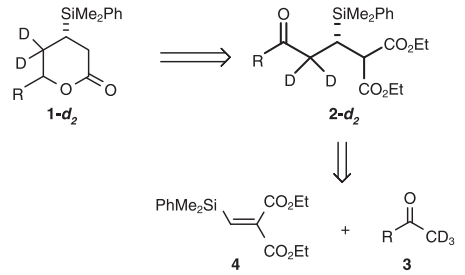


Figure 1. Some D-labeled pharmaceuticals.



Scheme 1. Retro synthetic analysis of 6-alkyl-5,5-dideutero-4-dimethyl(phenyl) silyl-tetrahydropyran-2-ones.

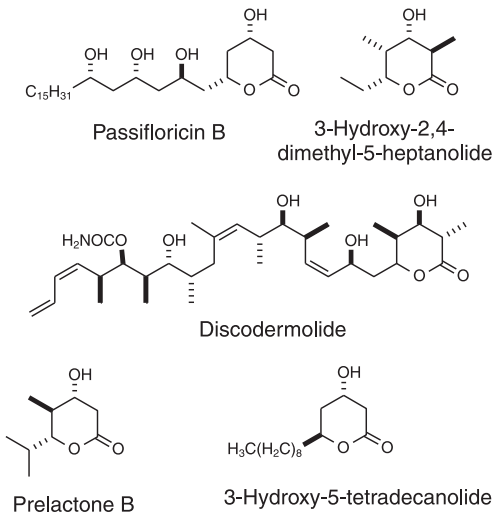
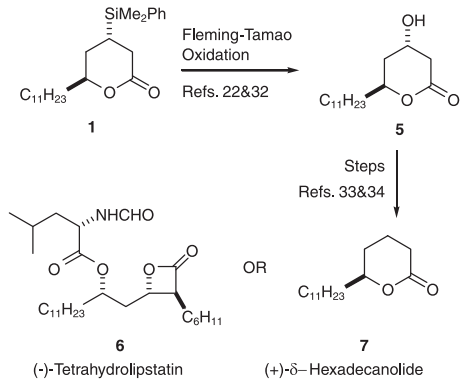
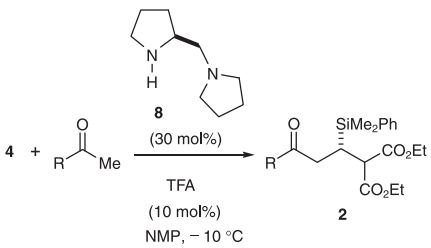


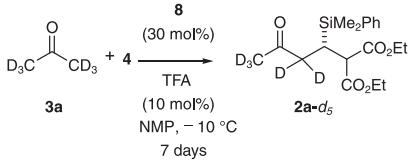
Figure 2. Some biologically active β-hydroxy-δ-lactones.



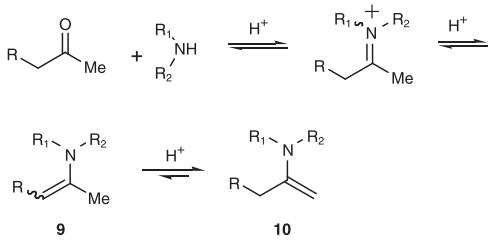
Scheme 2. Synthesis of 4-hydroxy-6-undecyl-tetrahydropyran-2-one **5**, the known intermediate for (–)-tetrahydrolipstatin **6** and (+)-δ-hexadecanolide **7**.



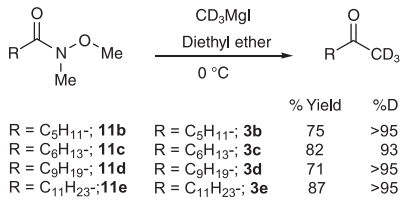
Scheme 3. Michael addition of methyl ketones to malonate **4**.



Scheme 4. Michael addition of acetone-d_6 to malonate **4**.



Scheme 5. Prototropy of the enamines.



Scheme 6. Synthesis of methyl-d_3 alkyl ketones.

dideuterated 4-silyl-tetrahydropyran-2-one **1**-d_2 via a Si-directed carbonyl reduction,[31] lactonization, and deethoxycarbonylation as the key steps. The corresponding proteo analog **1** (R=$C_{11}H_{23}$−) is the precursor[32] for 4-hydroxy-6-undecyl-tetrahydropyran-2-one **5**, the known intermediate for (–)-tetrahydrolipstatin **6**[33] and (+)-δ-hexadecanolide **7**[34] syntheses (Scheme 2).

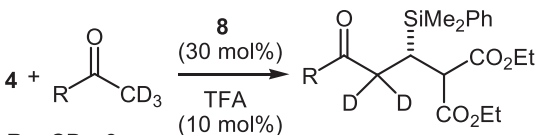
Result and discussion

Recently, we have shown[35] a highly regioselective Michael addition of alkyl methyl ketones to silylmethylene malonate **4** using *N*-(2-pyrrolidinylmethyl)pyrrolidine **8**[36] (Scheme 3) and Trifluoroacetic acid combination as the catalyst system of choice and *N*-methyl-2-pyrrolidone (NMP) as the solvent. A large number of alkyl methyl ketones with varying steric or electronic nature were reacted with malonate **4** to give exclusively the adducts **2** with high yield, regioselectivity and enantioselectivity (Scheme 3). The optimized conditions were to use 4–12 equiv of alkyl methyl ketone with respect to silylmethylene malonate **4** and 30 mol% of catalyst **8** in combination with 10 mol% of TFA in NMP (0.25 M) at −10 °C for 3–7 days providing the adducts **2** in very good yield (>76%) and with high enantiomeric excess (>90%). The formation of the regioisomeric addition product could not be detected in any of the cases.

When we replaced ordinary acetone with acetone-d_6 **3a** (99.5 atom% D) in the aforementioned optimized conditions, we obtain our desired product **2a**-d_5 (Scheme 4) in 64% yield but with deteriorated deuterium content (CD_2:71 atom% D, CD_3:61 atom% D).

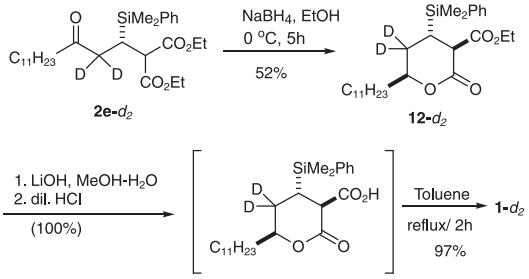
Although, the result was slightly disappointing, it was not totally unexpected. Barbas III[37] has suggested that these reactions proceeded through enamine intermediates[38,39] of the

Table 1. Conjugate addition of methyl-d_3 ketones **3a-e** to silyl malonate **4**



Entry	Ketone (equiv)	Time (d)/ Temp (°C)	Product	Yield[a]	%ee[b]	atom% D (CD_2)[c]
1	**3a** (10)	4/−10	**2a**-d_5	64	77	>95
2	**3b** (5)	2/−10	**2b**-d_2	82	99	93
3	**3c** (4)	4/−10	**2c**-d_2	80	86	82
4	**3d** (5)	3/−10	**2d**-d_2	88	96	93
5	**3e** (5)	3/4	**2e**-d_2	95	90	82

Ee, enantiomeric excess.
[a]Yield of chromatographically homogeneous product.
[b]Determined by HPLC.
[c]From ^{1}H NMR spectra by comparing integration of the scrambled CD_2 peaks with terminal Me or ester Me groups.



Scheme 7. Synthesis of 5,5-dideutero substituted tetrahydropyran-2-one **1**-d_2.

carbonyl donors. It is well-established[40,41] that in the presence of acid, the prototropy of the reactive enamine is more favorable, and the equilibration between the more and less substituted enamines **9** and **10** (Scheme 5) could occur. Thus, the moisture content of the solvent and the use of non-deuterated TFA might have scrambled the D–H in donor acetone-d_6 or in the product resulting in the lowering of deuterium content in the product. The deuterium content of the product **2a**-d_5 could be improved to a good extent (CD_2:>95 atom% D, CD_3:>95 atom% D) by using dry NMP and adding a small amount of D_2O in to the reaction mixture.

To see the generality of this process, a few methyl-d_3 alkyl ketones *viz.* 2-heptanone **3b**, 2-octanone **3c**, 2-undecanone **3d**, and 2-tridecanone **3e** were synthesized from commercially available starting materials as depicted in Scheme 6. An addition of an ethereal solution of methyl magnesium iodide-d_3 (99 atom% D) to Weinreb's amides **11b–e**[42] directly gave methyl-d_3 ketones **3b–e** in very good yield and isotopic purity (Scheme 6).

When this methyl alkyl ketones **3a–d** were reacted with the silyl malonate **4** under optimal conditions, we obtained only one regioisomeric product in very good yield and with good to excellent enantioselectivity as depicted in Table 1. The deuterium content at the specified site was also very high (82–>95% atom% D) in all cases. The reaction requires excess amount of ketones (4–10 equiv) to obtain appreciable rate of reaction and completion within a period mentioned in Table 1. Valuable ketones that have been used in excess can be recovered partially during isolation of products.

We next carried out a Si-directed reduction[31] of the carbonyl group in **2e**-d_2 to intermediate alcohol that could not be isolated but provided directly the lactone **12**-d_2 without any loss of D (Scheme 7). The ester group in **12**-d_2 was hydrolyzed with lithium hydroxide to give the intermediate acid, which on refluxing in toluene gave 5,5-dideutero analog of the 4-silyl-6-undecyl-tetrahydropyran-2-one **1**-d_2. The relative and absolute stereochemistry of the silyl and the alkyl groups in **1**-d_2 were assigned from the ^1H and ^{13}C chemical shift values[32] and comparing the specific rotation value $[\alpha]_D^{25} = -30.8$ (*c* 2.6, $CHCl_3$); *lit.*[32] $[\alpha]_D^{25} = -39.9$, *c* 1.93, $CHCl_3$). The proteo analog **1** has already been converted[32] to 4-hydroxy-6-undecyl-tetrahydropyran-2-one **5**, an advanced intermediate for (–)-tetrahydrolipstatin **6**[33] and (+)-δ-hexadecanolide **7**[34] syntheses.

Conclusions

In conclusion, we have developed a directly organocatalytic asymmetric Michael addition of alkyl methyl-d_3 ketones to a silylmethylene malonate in good yields and with high regioselectivity and enantioselectivity. The deuterium content of the products at the specified position is appreciably high. This is also the first successful attempt to engage unsymmetrical alkyl methyl-d_3 ketones to add via methyl terminal of acetyl group in such reactions. One of the ketone adducts thus obtained has already been converted to *gem*-dideutero substituted tetrahydropyran-2-one, the precursor for deuterated analog of 4-hydroxy-6-undecyl-tetrahydropyran-2-one, an advanced intermediate for (–)-tetrahydrolipstatin and (+)-δ-hexadecanolide syntheses. The 4-silyl-6-alkyl-tetrahydropyran-2-ones hold promise for *O*-and *N*-heterocyclic natural/pharmaceutical products with deuterium labeling at specific positions.

Experimental

General experimental

High-performance liquid chromatography grade acetone and NMP were used as received. Dimethyl(phenyl)silyl chloride, CD_3MgBr (1 M solution in ether) and (*S*)-*N*-(benzyloxycarbonyl)proline were obtained from Aldrich (MO, USA). Silylmethylene malonate **4** was prepared following a procedure reported by us.[43] The catalyst **8** was prepared following the literature procedures.[36]

Solvent removal was carried out using a rotary evaporator connected to a dry ice condenser. TLC (0.5 mm) was carried out using homemade silica plates with fluorescence indicator. Column chromatography was performed on silca gel (230–400 mesh).

^1H and ^{13}C NMR spectra were recorded in a 200 MHz (^1H: 200 MHz, ^{13}C: 50 MHz) or 500 MHz (^1H: 500 MHz, ^{13}C: 125 MHz) or 600 MHz (^1H: 600 MHz, ^{13}C: 150 MHz) or 700 MHz (^1H: 700 MHz, ^{13}C: 175 MHz) spectrometers. ^1H and ^{13}C shifts are given in ppm, δ scale and are measured relative to internal $CHCl_3$ and $CDCl_3$ as standards, respectively. Enantiomeric excess determinations were carried out by HPLC using a JASCO PU-2080 instrument (Japan) fitted with a Daicel chiralpak AD-H column and UV-2075 detector with λ fixed at 254 nm. Optical rotations were measured in a JASCO DIP Polarimeter (Japan).

General procedure I: preparation of *N*-methoxy-*N*-methylamides 11b–e

In a typical procedure, an acyl chloride (10 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (1.1 g, 11 mmol) was dissolved in dichloromethane (100 mL) at room temperature. The solution was cooled to 0 °C, and pyridine (1.9 mL, 22 mmol) was added to it. The reaction mixture was stirred at room temperature for 1 h and evaporated under reduced pressure. The residue was partitioned between brine and dichloromethane. The organic extract was dried over $MgSO_4$ and evaporated under reduced pressure to afford the amides **11b–e** in 93–96% yield which were sufficiently pure and used directly for the next step.

N-Methoxy-*N*-methylhexanamide 11b

Yield: 94%; IR (neat): 3433, 2959, 1653, 1463, 1416 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, J = 6.6 Hz, 3H, CH_3CH_2), 1.24–1.37 (m, 4H, 2 × CH_2), 1.53–1.68 (m, 2H, CH_2), 2.39 (t, J = 7.5 Hz, 2H, CH_2CH_2CO), 3.16 (s, 3 H, *N*-CH_3), 3.66 (s, 3H, *O*-CH_3); ^{13}C NMR (50 MHz, CDCl3): δ 13.7, 22.3, 24.1, 31.4, 31.7, 32.0, 61.0, 174.5; EI-MS: *m/z* 160 (2%, M + 1), 99 (44), 71 (52), 61 (100).

N-Methoxy-*N*-methylheptanamide 11c

Yield: 93%; IR (neat): 3453, 2949, 1656, 1468, 1418 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.86 (t, J = 6.6 Hz, 3H, CH_3CH_2), 1.20–1.40 (m, 6H, 3 × CH_2), 1.53–1.67 (m, 2H, CH_2), 2.39 (t, J = 7.2 Hz, 2H, CH_2CH_2CO), 3.16 (s, 3H, *N*-CH_3), 3.66 (s, 3H, *O*-CH_3); ^{13}C NMR (50 MHz, CDCl3): δ 13.8, 22.3, 24.4, 28.9, 31.4, 31.7, 32.0, 61.0, 174.5; EI-MS: *m/z* 113 (30%), 103 (8), 85 (35), 73 (5), 61 (100).

N-Methoxy-*N*-methyldecanamide 11d

Yield: 95%; IR (neat): 3443, 2958, 1653, 1478, 1412 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.85 (t, $J = 6.2$ Hz, H, CH_3CH_2), 1.24 (s, broad, 12H, $6 \times CH_2$), 1.57–1.66 (m, 2H, CH_2), 2.39 (t, $J = 7.4$ Hz, 2H, CH_2CH_2CO), 3.16 (s, 3H, *N*-CH_3), 3.66 (s, 3H, O-CH_3); ^{13}C NMR (50 MHz, CDCl3): δ 13.9, 22.5, 24.4, 29.1, 29.3 (3C), 31.7 (2C), 32.0, 61.0, 174.5.

N-Methoxy-*N*-methyldodecanamide 11e

Yield: 96%; IR (neat): 3443, 2959, 1654, 1478, 1408 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.83 (t, $J = 6.6$ Hz, 3H, CH_3CH_2), 1.21 (s, broad, 18H, $9 \times CH_2$), 1.50–1.61 (m, 2H, CH_2), 2.36 (t, $J = 7.4$ Hz, 2H, CH_2CH_2CO), 3.13 (s, 3H, *N*-CH_3), 3.63 (s, 3H, *O*-CH_3); ^{13}C NMR (50 MHz, CDCl3): δ 13.8, 22.4, 24.4, 29.0, 29.1 (2C), 29.2, 29.3 (2C), 31.6, 31.9, 61.8, 174.4; EI-MS: *m/z* 244 (0.5%, M + 1), 183 (8), 109 (8), 85 (15), 71 (35), 61 (100).

General procedure II: preparation of alkyl methyl-d_3 ketones 3b–3e

An ethereal solution of CD_3MgI (1 *M*, 11 mL, 11 mmol) was added drop wise to a stirred solution of *N*-methoxy-*N*-methylamides **11b–e** (10 mmol) in ether (15 mL) at 0 °C. After 1.5 h, the reaction mixture were poured into ice-cold 0.5 *M* aqueous HCl (25 mL) and extracted with dichloromethane. The organic extract was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was distilled to give the respective ketones **3b–e** in 70–87% yield.

1,1,1,-Trideuterioheptan-2-one 3b

Yield: 75%; IR (neat): 2925, 2855, 2253, 1714, 1465, 1410 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.86 (t, $J = 6.6$ Hz, 3H, CH_3CH_2), 1.21–1.34 (m, 4H, $2 \times CH_2$), 1.47–1.62 (2H, CH_2), 2.39 (t, $J = 7.2$ Hz, 2H, CH_2CH_2CO); ^{13}C NMR (50 MHz, CDCl3): δ 13.8, 22.3, 23.4, 31.2, 43.6, 209.3; EI-MS: *m/z* 117 (2%, M^+), 99 (40), 71 (68), 61 (100).

1,1,1,-Trideuteriooctan-2-one 3c

Yield: 82%; IR (neat): 2926, 2855, 2253, 1714, 1465, 1411 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.85 (t, $J = 6.6$ Hz, 3H, CH_3CH_2), 1.25–1.28 (m, 6H, $3 \times CH_2$), 1.46–1.57 (m, 2H, $CH_2CH_2CH_2CO$), 2.35–2.42 (t, $J = 7.5$ Hz, 2H, CH_2CH_2CO); ^{13}C NMR (50 MHz, CDCl3): δ 13.9, 22.4, 23.7, 28.7, 31.5, 43.6, 209.4; EI-MS: *m/z* 131 (8%, M^+), 113 (5), 88 (6) 74 (20), 61 (100).

1,1,1,-Trideuterioundecan-2-one 3d

Yield: 70%; IR (neat): 2925, 2855, 2253, 1714, 1465, 1410 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 0.89 (t, $J = 6$ Hz, 3H, CH_3CH_2), 1.28–1.32 (m, 14H, $7 \times CH_2$), 1.57–1.60 (m, 2H, $CH_2CH_2CH_2CO$), 2.42 (t, $J = 6.6$ Hz, 2H, CH_2CH_2CO); ^{13}C NMR (50 MHz, CDCl3): δ 13.9, 22.0, 22.5, 23.8, 29.1, 29.2 (2C), 29.3, 31.7, 43.6, 208.8; EI-MS: *m/z* 173 (5%, M^+), 112 (5), 74 (26), 61 (100)

1,1,1,-Trideuteriotridecan-2-one 3e

Yield: 87%; IR (neat): 2926, 2855, 2253, 1714, 1465, 1410 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.87 (t, $J = 6$ Hz, 3H, CH_3CH_2), 1.25 (s, broad, 16H, $8 \times CH_2$), 1.52–1.64 (m, 2H, $CH_2CH_2CH_2CO$), 2.4 (t, $J = 7.2$ Hz, 2H, CH_2CH_2CO); ^{13}C NMR (50 MHz, CDCl3): δ 13.6, 22.3, 23.4, 28.8, 29.0, 29.1 (2C), 29.3 (2C), 31.5, 43.2, 208.1; EI-MS: *m/z* 201 (2%, M^+), 74 (20), 61 (100).

General procedure III. Michael addition of methyl-d_3 ketones 3a–e to silylmethylene malonate 4 using organocatalyst 8

Acetone-d_6 *or* respective alkyl methyl-d_3 ketone (2–5 mmol, 4–10 equiv) was added to a stirred mixture of silylmethylene malonate **4** (153 mg, 0.5 mmole, 1 equiv), pyrrolidine **8** (23 mg, 0.15 mmol, 0.3 equiv), TFA (4 μL, 0.05 mmol, 0.1 equiv), and D_2O (20 μL, 1 mmol, 2 equiv) in dry NMP (1 mL) at −10 °C. After 2–4 d at −10 °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 either **2a**-d_5 (64%) or **2b-e**-d_2 (80–95%).

Ethyl (3*S*)-3-dimethyl(phenyl)silyl-4,4-dideutero-2-ethoxycarbonyl-5-oxohexanoate 2a-d_5

Yield: 119 mg, 64%; HPLC: Daicel chiralpak AD-H, 2-propanol/hexane (1/99), flow rate = 1.0 mL/min, t_R(3*S*)-**2a**-d_5 14.5 min (88.3%), t_R(3*R*)-**2a**-d_5 21.05 min (11.7%); Opt. Rot.: $[\alpha]_D^{24} = +1.3$ (*c* 1.55, $CHCl_3$), *lit.*[35] for preteo analog $[\alpha]_D^{25} = +4.78$ (*c* = 2.31, MeOH); IR (film): 3070, 3029, 2957, 2931, 2855, 1747, 1729, 1465, 1427, 1370, 1301, 1250, 1152, 1032, 817 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.31 (s, 3H, CH_3Si), 0.32 (s, 3H, CH_3Si), 1.20 (t, $J = 7.2$ Hz, 6H, $2 \times CH_3CH_2OCO$), 2.28 (d, $J = 5.6$ Hz, 1H, SiC*H*), 3.47 (d, $J = 5.6$ Hz, 1H, *CH*CHSi), 3.95–4.11 (m, 4H, $2 \times CH_3CH_2OCO$), 7.30–7.35 (m, 3H, Ph), 7.47–7.52 (m, 2H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ −3.6, −3.4, 13.8 (2C), 20.0, 51.5, 61.0, 61.1, 127.6 (2C), 129.0, 134.0 (2C), 137.0, 169.3, 169.7, 207.6.

Ethyl (3*S*)-3-dimethyl(phenyl)silyl-4,4-dideutero-2-ethoxycarbonyl-5-oxodecanoate 2b-d_2

Yield: 174 mg, 82%; HPLC: Daicel chiralpak AD-H, 2-propanol/ hexane (0.7/99.3), flow rate = 1.0 mL/min, t_R(3*S*)-**2b**-d_2 14.0 min (99.51%), t_R(3*R*)-**2b**-d_2 23.5 min (0.49%); Opt. Rot.: $[\alpha]_D^{25} = +1.94$ (*c* 3.1, $CHCl_3$), *lit.*[35] for preteo analog $[\alpha]_D^{25} = +1.92$ (*c* = 2.61, MeOH); IR (neat): 3070, 3028, 2956, 2930, 2853, 1746, 1729, 1465, 1426, 1370, 1301, 1249, 1151, 1032, 817 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.32 (s, 3H, CH_3Si), 0.33 (s, 3H, CH_3Si), 0.85 (t, $J = 6.6$ Hz, 3H, CH_2CH_3), 1.16–1.26 (m, 10H, $2 \times CH_2$ and $2 \times CH_3CH_2OCO$), 1.35–1.46 (m, 2H, CH_2), 2.08–2.22 (m, 2H, $COCH_2$), 2.26–2.31 (m, 1H, SiCH), 3.49 (d, $J = 5.8$ Hz, 1H, *CH*CHSi), 4.00–4.11 (q, $J = 7.2$ Hz, 4H, $2 \times CH_3CH_2OCO$), 7.30–7.34 (m, 3H, Ph), 7.47–7.52 (m, 2H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ −3.5, −3.2, 13.8 13.9 (2C), 20.0, 22.4, 23.4, 31.3, 42.4, 51.8, 61.0, 61.3, 127.6 (2C), 129.1, 134.2 (2C), 137.0, 169.5, 169.9, 210.0; EI-MS: *m/z* 407 (M^+-CH_3, 12%), 345 (18), 246 (14), 135 (100), 75 (35).

Ethyl (3*S*)-3-dimethylphenylsilyl-4,4-dideutero-2-ethoxycarbonyl-5-oxoundecanoate 2c-d_2

Yield: 175 mg, 80%; HPLC: Daicel chiralpak AD-H, 2-propanol/ hexane (0.7/99.3), flow rate = 1.0 mL/min, t_R(3*S*)-**2c**-d_2 7.41 min (92.91%), t_R(3*R*)-**2c**-d_2 11.4 min (7.09%); Opt. Rot.: $[\alpha]_D^{25} = +1.92$ (*c* 2.61, $CHCl_3$); IR (neat): 3070, 3029, 2957, 2931, 2855, 1747, 1729, 1465, 1427, 1370, 1301, 1250, 1152, 1032, 817 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.31 (s, 3H, CH_3Si), 0.33 (s, 3H, CH_3Si), 0.85 (t, $J = 6.4$ Hz, 3H, CH_2CH_3), 1.16–1.23 (m, 12H, $3 \times CH_2$ and $2 \times CH_3CH_2OCO$), 1.31–1.45 (m, 2H, CH_2), 2.08–2.23 (m, 2H, $COCH_2$), 2.26–2.31 (m, 1H, SiCH), 3.50 (d, $J = 5.6$ Hz, 1H, *CH*CHSi), 4.00–4.11 (m, 4H, $2 \times CH_3CH_2OCO$), 7.28–7.33 (m, 3H, Ph), 7.47–7.52 (2H, m, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ −3.5, −3.2, 13.9 (2C), 20.0, 20.1, 22.4, 23.6, 28.8, 31.5, 42.5, 51.8, 61.1, 61.2, 127.6 (2C), 129.1, 134.2 (2C), 137.3, 169.5, 169.8, 209.9; EI-MS: *m/z* 421 (M^+-CH_3, 12%), 359 (17), 261 (12), 199(18) 135 (100), 144(24) 75 (35).

Ethyl (3*S*)-3-dimethylphenylsilyl-4,4-dideutero-2-ethoxycarbonyl-5-oxotetradecanoate 2d-d_2

Yield: 210 mg, 88%; HPLC: Daicel chiralpak AD-H, 2-propanol/ hexane (0.7/99.3), flow rate = 1.0 mL/min, t_R(3*S*)-**2d**-d_2 9.1 min (98.11%), t_R(3*R*)-**2d**-d_2 15.5 min (1.89%); Opt. Rot.: $[\alpha]_D^{24} = +2.0$ (*c* 1.49, $CHCl_3$), *lit.*[35] for preteo analog $[\alpha]_D^{28} = +4.81$ (*c* = 2.91, MeOH); IR (neat): 3070, 3028, 2956, 2930, 2853, 1746, 1729, 1465, 1426, 1370, 1301, 1249, 1151, 1032, 817 cm^{-1} ; H NMR (500 MHz, $CDCl_3$): δ 0.41 (s, 3H, CH_3Si), 0.42 (s, 3H, CH_3Si), 0.96 (t, $J = 7$ Hz, 3H, $CH_2[CH_2]_3CH_3$), 1.25–1.36 (m, 18H, $[CH_2]_6CH_3$ and $2 \times CH_3CH_2OCO$), 1.49–1.52 (m, 2H, $CH_2CH_2[CH_2]_6CH_3$) 2.21–2.34 (m, 2H, $COCH_2[CH_2]_4CH_3$), 2.37 (d, $J = 5.5$ Hz, 1H, SiC*H*), 3.57 (d, $J = 5.5$ Hz,1H, *CH*CHSi), 4.13–4.17 (m, 4H, $2 \times CH_3CH_2OCO$), 7.34–7.42 (m, 3H, Ph), 7.59–7.60 (2H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$): δ −3.4, −3.1, 13.9 (2C), 14.0, 20.1, 22.6, 23.7, 29.1, 29.2, 29.3 29.4, 31.8, 42.5, 51.8, 61.1, 61.3, 127.6 (2C), 129.1,

134.2 (2C), 137.3, 169.4, 169.8, 209.9; EI-MS: *m/z* 343 (M^+-$SiMe_2Ph$, 13%), 327 (19), 249 (17), 181 (20) 135 (100), 75 (34).

Ethyl (3*S*)-3-dimethylphenylsilyl-4,4-dideutero-2-ethoxycarbonyl-5-oxohexadecanoate 2e-d_2

Yield: 240 mg, 95%; HPLC: Daicel chiralpak AD-H, 2-propanol/ hexane (0.7/99.3), flow rate = 1.0 mL/min, *t*R(3*S*)-**2e**-d_2 19.7 min (94.99%), *t*R(3*R*)-**2e**-d_2 26.19 min (5.01%); Opt. Rot.: $[\alpha]_D^{22}$ = +1.67 (*c* 1.9, $CHCl_3$), *lit.*[32] for preteo analog $[\alpha]_D^{23}$ +4.67 (*c* 1.07, MeOH); IR (neat): 3070, 3028, 2956, 2930, 2853, 1746, 1729, 1465, 1426, 1370, 1301, 1249, 1151, 1032, 817 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.32 (s, 3H, CH_3Si), 0.33 (s, 3H, CH_3Si), 0.87 (t, *J* = 6Hz, 3H, $[CH_2]_8CH_3$), 1.16–1.24 (m, 22H, $CH_2[CH_2]_8CH_3$, 2 × CH_3CH_2OCO), 1.38–1.45 (m, 2H, $CH_2CH_2[CH_2]_8CH_3$), 2.08–2.22 (m, 2H, $COCH_2[CH_2]_9CH_3$) 2.26–2.31 (m, 1H, SiCH), 3.48 (d, *J* = 5.8 Hz, 1H, CHCHSi), 4.00–4.12 (m, 4H, 2 × CH_3CH_2OCO), 7.30–7.33 (m, 3H, Ph), 7.47–7.52 (m, 2H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ −3.5, −3.1, 13.9, 14.0 (2C), 20.0, 22.6, 23.7, 29.1, 29.2, 29.3, 29.4, 29.5 (2C) 31.8, 42.5, 51.8, 61.1, 61.2, 127.6 (2C), 129.1, 134.2 (2C), 137.3, 169.4, 169.8, 209.9; EI-MS: *m/z* 491 (M^+-CH_3, 4%), 429 (10), 249 (12), 135 (100), 75 (14).

(3*S*,4*S*,6*S*)-5,5-Dideutero-4-dimethyl(phenyl)silyl-3-ethoxycarbonyl-6-undecyl-tetrahydro-2*H*-pyran-2-one 12-d_2

Sodium borohydride (29 mg, 0.76 mmol) was added portion wise to a stirring solution of **2e**-d_2 (190 mg, 0.38 mmol) in EtOH (2.0 mL) at 0 °C. After 5 h, the mixture was quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2. The organic extract was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography to give lactone **12**-d_2 (91 mg, 52%). IR (film): 3069, 3048, 2926, 2853, 1751, 1736, 1465, 1427, 1371, 1041, 776, 735 cm^{-1}; Opt. Rot.: $[\alpha]_D^{25}$ = −10.7 (*c* 3.38, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 0.32 (s, 3H, CH_3Si), 0.33 (s, 3H, CH_3Si), 0.87 (t, *J* = 6.4 Hz, 3H, CH_2CH_3), 1.21–1.29 (m, 21H, 9 × CH_2 and $CO_2CH_2CH_3$), 1.38–1.54 (m, 2H, CH_2), 1.92–2.02 (m, 1H, SiCH), 3.34 (d, *J* = 11.4 Hz, 1H, $CHCO_2CH_2CH_3$), 3.79–3.81 (m, 1H, CHOCO), 4.00–4.17 (m, 2H, $CHCO_2CH_2CH_3$), 7.34–7.40 (m, 3H, Ph), 7.46–7.51 (m, 2H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.1, −4.8, 13.9, 14.1, 17.7, 22.6, 24.9, 29.2, 29.3, 29.4, 29,5, 29.6 (2C), 31.8, 34.7, 47.3, 61.6, 78.6, 128.1 (2C), 129.8, 134.0 (2C), 135.1, 169.3, 169.8; EI-MS: *m/z* 462 (M^+ 4), 429 (15), 135 (100), 75 (18).

(4*S*,6*S*)-5,5-Dideutero-4-dimethyl(phenyl)silyl-6-undecyl-tetrahydro-2*H*-pyran-2-one 1-d_2

Solid $LiOH.2H_2O$ (11 mg, 0.26 mmol, 2 equiv) was added portion wise to a stirred solution of **12**-d_2 (60 mg, 0.13 mmol) in 95% aqueous methanol (1.0 mL) at room temperature. The mixture was stirred overnight, and the solvent was evaporated under reduced pressure. The residue was diluted with water, acidified with dil HCl, and extracted with EtOAc. The organic extract was dried (Na_2SO_4) and evaporated under reduced pressure to give the crude acid, which was dissolved in toluene (5 mL) and heated under reflux under nitrogen. After 2 h, the solvent was removed under reduced pressure, and the residue was purified by column chromatography to give lactone **1**-d_2 (49 mg, 97%).

IR (film): 2960, 2931, 2859, 2250, 1740, 1427, 1256, 1113, 1064, 834, 812, 701 cm^{-1}; Opt. Rot.: $[\alpha]_D^{25}$ = −30.8 (*c* 2.6, $CHCl_3$), *lit.*[32] for preteo analog $[\alpha]_D^{25}$ = −39.9 (*c* 1.93, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 0.32 (s, 6H, $[CH_3]_2Si$), 0.87 (t, *J* = 6.4 Hz, 3H, CH_2CH_3), 1.24 (s, broad, 18H, 9 × CH_2), 1.38–1.48 (m, 3H, CH_2 and SiCH), 2.21 (dd, *J* = 13.2, 15.8 Hz, 1H, $CH_AH_BCO_2$-), 2.42 (dd, *J* = 5.7, 15.8 Hz, 1H, $CH_AH_BCO_2$-), 3.97–4.09 (m, 1H, CHOCO), 7.35–7.39 (m, 3H, Ph), 7.44–7.49 (m, 2H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.5, −5.4, 14.2, 14.8, 22.7, 25.2, 29.4 (2C), 29.5, 29.6, 29.7 (2C), 30.1, 31.9, 35.0, 78.3, 128.2 (2C), 129.7, 133.9 (2C), 135.8, 173.9; EI-MS: *m/z* 390 (M^+ 2), 235 (5), 135 (100), 116 (25), 75 (18).

Conflict of Interest

The authors did not report any conflict of interest.

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