Enantioselective Route to β-Silyl-δ-keto Esters by Organocatalyzed Regioselective Michael Addition of Methyl Ketones to a (Silylmethylene)malonate and Their Use in Natural Product Synthesis

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Abstract: The direct Michael addition of alkyl methyl ketones through the acetyl methyl terminal to diethyl {[dimethyl(phenyl)silyl]methylene}malonate was catalyzed by the (*S*)-*N*-(pyrrolidin-2-ylmethyl)pyrrolidine/trifluoroacetic acid combination with high yield and excellent regio- and enantioselectivity. The ketone adducts can easily undergo de-ethoxycarbonylation to give β-silyl-δ-keto esters with excellent synthetic potential. This has been demonstrated by the synthesis of a suitably substituted β-silyl-δ-keto ester as an advanced intermediate for a chiral hydroxylated pyrrolidine natural product, (+)-preussin. Silicon-controlled diastereoselective reduction of the ketone functionality of β-silyl-δ-keto esters followed by lactonization of the resulting hydroxy esters gave disubstituted δ-valerolactones. Advanced intermediates for the antipodes of natural products, namely (+)-massoialactone and (+)-mevinolin analogue, and natural products, namely (–)-tetrahydrolipstatin and (+)-5-hexadecanolide, have been achieved.

Key words: Michael addition, organosilicon compounds, methyl ketone, organocatalysis, regioselective, natural product

The unique properties of silicon[1] have led to its wide utilization in organic chemistry these range in general from protecting functional groups[2] to a temporary tether,[3] and specifically from masking the hydroxy group,[4] to highly controlled and selective organic reactions.[1,5] Carbonyl compounds having a silyl group at the β-position are popular targets because of their versatile nature[6] and they are also an excellent surrogate for the acetate aldol[7] reaction. We are interested in the asymmetric synthesis of intermediates of type **1** or **2** (Figure 1) containing a silicon group positioned at β to both a ketone and an ester functionalities because they are potential synthons[8] for privileged structures containing chiral N- and O-heterocycles. The synthesis of β-silyl-δ-keto esters **1** has been reported[9,10] by asymmetric desymmetrization of 3-[dimethyl(phenyl)silyl]glutaric anhydride **3** followed by selective alkylation of one of the carboxy functionalities. Although high selectivity[10] was achieved in the desymmetrization process, it required specially designed SuperQuat[11] oxazolidin-2-ones. The choice of the dimethyl(phenyl)silyl group was made due to its easy incorporation into the carbon framework and also it can be easily converted into the corresponding alcohol under oxidative conditions (Fleming–Tamao)[12] with complete retention of stereochemistry. The desymmetrization of anhydrides with a limited type of carbon nucleophiles[13,14] has been reported recently to produce keto esters. Enantio/diastereoselective conjugative silylation of simple unsaturated carbonyl compounds are also well known.[15] However, such types of reactions have not been applied to the synthesis of β-silyl-δ-keto esters. We envisage an alternate and straightforward method that involves an atom-economic,[16] regio- and enantioselective, direct Michael addition of an alkyl methyl ketone to the β-silylacrylate **4** or (silylmethylene)malonate **5**[17] (Figure 1).

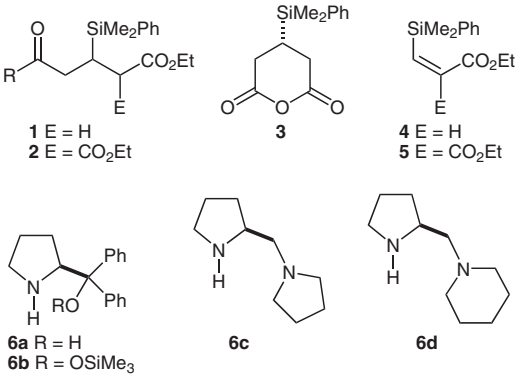

Figure 1 Structures of substrates and catalysts

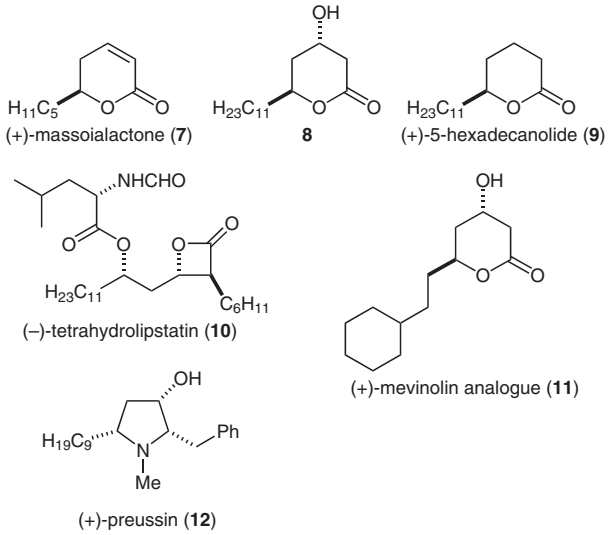

Figure 2 Structures of N- and O-heterocycles

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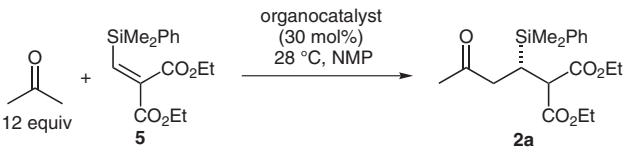
The Michael addition[18] is one of the most frequently used reactions because of its efficiency and effectiveness. Significant development has been made in the asymmetric version of this reaction, providing adducts with high enantiomeric purity.[19] Aldehydes and ketones have generally been used as donors after their modification to more activated species such as enolates or enamines.[20,21] The major drawbacks for the use of enolates/enamines are the addition of extra synthetic step(s) and stoichiometric use of a chiral induction reagent. In recent times, an organocatalysis[22] route has been developed for the direct addition of ketones or aldehydes to activated alkenes, especially to nitroalkenes with satisfactory results. However, the addition of the same donors[23] to alkylidenemalonates is less successful. Barbas and co-workers[24] for the first time demonstrated that acetone can add to various (arylmethylene)- and alkylidenemalonates under organocatalysis with moderate yields and enantioselectivities. Natural proline-catalyzed[25] direct addition of acetone to an (arylmethylene)malonate took place with good yield, but poor enantioselectivity. Recent reports showed that *N*-(pyrrolidin-2-ylmethyl)trifluoromethanesulfonamide[26] and pyrrolidinyl-camphor[27] derivatives can catalyze the Michael addition between ketones and (arylmethylene)malonates; the adducts were formed in moderate to good yields and good to high enantioselectivities, depending upon the substituents present on the ketones and the (arylmethylene)malonates. Alkylidenemalonates were not good acceptors for this reaction. Although cyclic ketones reacted with good diastereo- and enantioselectivities, acyclic ketones gave poor results.[24,26] Despite some success with these methodologies, reaction with acyclic unsymmetrical ketones, especially methyl ketones, remains very challenging. Besides yield and enantioselectivity, the regioselectivity of the addition is also an important issue.[28] Herein, we report a full account[29] of our efforts for the development of an efficient, highly regio- and enantioselective organocatalytic conjugate addition of acyclic methyl ketones to (silylmethylene)malonate **5** (Figure 1) providing β-silyl-δ-keto diesters **2**, and their application in the synthesis of intermediates for O-and N-heterocyclic natural products or their counterparts, viz. (+)-massoialactone (**7**), (+)-5-hexadecanolide (**9**), (–)-tetrahydrolipstatin (**10**), and (+)-mevinolin analogue (**11**) (Figure 2).

As discussed above, direct addition of cyclic and acyclic ketones to nitroalkenes and few more activated alkenes has been well studied. Although alkylidenemalonates are well known for their Michael acceptor properties and useful functionalities for further elaboration, direct addition of various ketones to them have not been studied in detail. Especially, the reactivity and regioselectivity issues were not addressed in case of unsymmetrical ketones. We resolved these issues one-by-one using (silylmethylene)malonate **5** as the acceptor. We first chose acetone as the model ketone to obviate the regioselectivity issue and concentrated our effort on optimization of the yield and enantioselectivity of the adduct. The direct addition of acetone to (silylmethylene)malonate **5** using a catalytic amount of racemic amino acids for the synthesis of silylated keto diester *rac*-**2a** has already been demonstrated,[30] as a part of a goal to develop silicon-based linkers for solid-phase organic synthesis.[31] We, therefore, began our studies for the asymmetric version of this reaction using a few natural amino acid catalysts with *N*-methylpyrrolidin-2-one as the solvent at room temperature. The result with (*S*)-proline as the catalyst resulted in the formation of **2a** in good yield but very poor enantioselectivity (Table 1, entry 1). With (*S*)-arginine and (*S*)-tryptophan, the reaction was slow and also the enantioselectivity was very poor (entries 2 and 3). Simple pyrrolidines derived from proline, viz. diphenylprolinol **6a**[32] and its silyl ether **6b**,[33] are well-known catalysts for the addition of aldehydes and ketones to nitroalkenes. The silyl ether **6b** has recently been found to be an efficient catalyst for direct addition of unmodified aldehydes to (silylmethylene)malonate **5**[34a] and (trifluoroethylidene)malonates[34b] with adducts formed in good yields and diastereo- and enantioselectivities. Unfortunately, both **6a** and **6b** were not effective for this addition (entries 4 and 5). Pyrrolidine-based diamines derived from natural proline such as *N*-(pyrrolidin-2-ylmethyl)pyrrolidine **6c** and *N*-(pyrrolidin-2-ylmethyl)piperidine **6d** (Figure 1) are popular organocatalysts for aldol,[35] Michael,[24,36] and Mannich reactions.[37] They can be easily made from proline[38] and also, Barbas has used such catalysts for the asymmetric addition of ketones to alkylidenemalonates.[24] When pyrrolidine **6c** was used under the reported conditions,[24] the addition of acetone to (silylmethylene)malonate **5** was very slow and the desired keto diester adduct **2a** was formed in poor yield, but with mod-

Table 1 Catalyst Screening for Direct Acetone Addition on (Silylmethylene)malonate **5**



Entry	Catalyst	Temp, time	Yield[a] (%)	ee[b] (%)
1	(*S*)-Pro	28 °C, 1 d	75	<5
2	(*S*)-Trp	28 °C, 1 d	56	<5
3	(*S*)-Arg	28 °C, 5 d	42[c]	12
4	**6a**	28 °C, 7 d	trace	–[d]
5	**6b**	28 °C, 7 d	trace	–[d]
6	**6c**	28 °C, 6 d	10[e]	66
7	**6c**	28 °C, 3.5 d	61	55
8	**6d**	28 °C, 3.5 d	40[c]	55

[a] Yield of chromatographically homogeneous product.
[b] Determined by HPLC.
[c] Incomplete reaction.
[d] Not determined.
[e] Reaction was performed in THF as reported in ref. 24b.

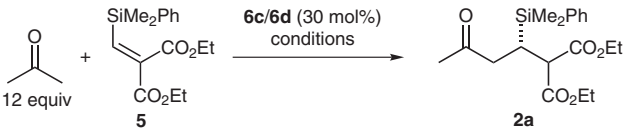
erate enantioselectivity (entry 6). The catalytic ability of pyrrolidine **6c** was increased substantially with slight erosion of enantioselectivity by changing the solvent to *N*-methylpyrrolidin-2-one (entry 7). Similarly, pyrrolidine **6d** also showed moderate yield and selectivity in *N*-methylpyrrol idin-2-one (entry 8).

We next planned to introduce different additives in association with catalysts **6c** and **6d** to improve the yield and the enantioselectivity of adduct **2a**. Many research groups have used varying amounts of Bronsted acids as additives to accelerate the amine-catalyzed Michael addition of aldehydes and ketones to nitroalkenes[36,39] resulting in good yields and stereoselectivities. Barbas[24] has suggested that these reactions proceed through enamine intermediates[20a,b] of the carbonyl donors. It is well known that enamine formation between an amine and a carbonyl compound is facilitated by acids. Hine[40] in his seminal work has shown that the process was 15 times faster with protonated primary amines than the free base. Therefore, the Michael addition of acetone with (silylmethylene)malonate **5** was next examined with the pyrrolidine catalysts **6c** and **6d** in the presence of organic acids such as acetic acid and 4-nitrobenzoic acid (PNBA) in *N*-methylpyrrolidin-2-one.

The addition of 10 mol% of acetic acid or 4-nitrobenzoic acid and 30 mol% of catalyst **6c** at 4 °C provided the desired product **2a** in good yield (Table 2, entries 1 and 2) with a significant improvement of enantioselectivity. Next, the temperature of the reaction was lowered for further enhancement of selectivity. Therefore, the reactions using catalyst **6c** and with or without 10 mol% acetic acid were carried out at –10 °C for seven days. Although this improved the enantioselectivity, the conversion was abysmally poor (entries 3 and 4). Interestingly, trifluoroacetic acid appeared to be a better additive and using 10 mol% of it with 30 mol% of catalyst **6c** at –10 °C for seven days gave a decent yield of the product **2a** with excellent enantioselectivity (entry 5). Additional experiments with varying amounts of trifluoroacetic acid (5–30%) (entries 5–8) established 10 mol% of trifluoroacetic acid to be optimum for the reaction. We also wanted to see the effect of solvents on the enantioselectivity and examined the reaction in *N*,*N*-dimethylformamide and toluene. Although the yield was comparable in these solvents, the enantioselectivity was lower (entries 9 and 10). The other catalyst **6d** turned out to be poor (entry 11). Therefore, the optimized conditions are to use 12 equivalents of acetone with respect to (silylmethylene)malonate **5** and 30 mol% of catalyst **6c** in combination with 10 mol% of trifluoroacetic acid in *N*-methylpyrrolidin-2-one (0.25 M) at –10 °C for seven days providing the adduct **2a** in 76% yield and with 90% ee (Table 2, entry 5).

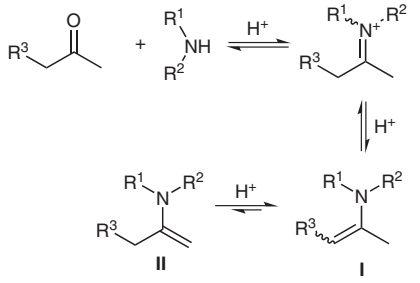
With optimal catalyst, additive, and reaction conditions established with acetone, we went one step further by introducing unsymmetrical alkyl methyl ketones as donors. Unlike acetone, alkyl methyl ketones introduce the problem of regioselectivity. Barbas[24] has suggested that these reactions proceed through enamine intermediates[20a,b] of the carbonyl donors. It is well established[36] that in the presence of acid, the prototropy of the reactive enamine is more favorable and the equilibration between the more and the less-substituted enamines **I** and **II** (Scheme 1) could occur. This leads to the formation of the more stable substituted enamine **I** on thermodynamic grounds. However, the regiocontrol of the reaction is often governed by Curtin–Hammett kinetics. Therefore, the balance between Curtin–Hammett kinetics and acidity decides the regioselectivity. Many research groups have addressed the issue of regioselectivity during aldol[41] and Michael[42] additions involving unsymmetrical ketone donors, by tuning the acidity of the α and α′ protons with suitable functional groups. When methyl isopropyl ketone was reacted with (silylmethylene)malonate **5** under the optimized conditions as described in Table 2, we obtained only one regioisomeric product **2b**, as revealed by the ^{1}H NMR spectrum of the crude reaction product, in very high yield and with excellent enantioselectivity (Table 3, entry 2). Initially it was envisaged that the high regioselectivity might be an outcome of the steric crowding by the isopropyl group. However, this was discounted from the results with several other ketones lacking any such steric congestion. In all the cases (Table 3) the adducts **2c–k** were formed only by reaction at the methyl terminal of the acetyl group of the ketones. Also, the adducts were obtained in very good yields and enantioselectivities. The reactions required excess amount of the ketone (2–12 equiv) to get an appreciable rate of reaction and completion within the time period

Table 2 Optimization of Direct Acetone Addition on (Silylmethylene)malonate **5** Using Additives



Entry	Catalyst/additive (mol%)	Solvent, temp, time	Yield[a] (%)	ee[b] (%)
1	**6c**/AcOH (10)	NMP, 4 °C, 5 d	72	84
2	**6c**/PNBA (10)	NMP, 4 °C, 5 d	79	80
3	**6c**/nil	NMP, –10 °C, 7 d	<5[c]	80
4	**6c**/AcOH (10)	NMP, –10 °C, 7 d	<5[c]	88
5	**6c**/TFA (10)	NMP, –10 °C, 7 d	76	90
6	**6c**/TFA (5)	NMP, –10 °C, 7 d	56	88
7	**6c**/TFA (15)	NMP, –10 °C, 7 d	57	88
8	**6c**/TFA (30)	NMP, –10 °C, 7 d	44[c]	90
9	**6c**/TFA (10)	DMF, –10 °C, 7 d	78	84
10	**6c**/TFA (10)	toluene, –10 °C, 7 d	88	82
11	**6d**/TFA (10)	NMP, –10 °C, 10 d	44[c]	84

[a] Yield of chromatographically homogeneous product.
[b] Determined by HPLC.
[c] Incomplete reaction.



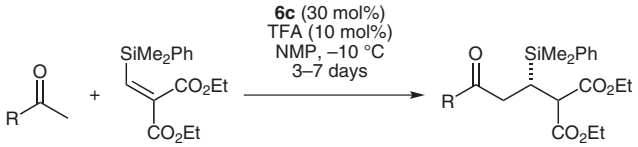
Scheme 1 Enamines of alkyl methyl ketones

mentioned. Valuable ketones can be recovered as other byproduct formations were not observed.

We next attempted to generalize this regio- and enantioselective methyl ketone addition to (arylmethylene)- and alkylidenemalonates. Therefore, diethyl benzylidene-, 4-fluorobenzylidene-, and (3-phenylpropylidene)malonates **13a–c** were reacted with methyl ethyl ketone in the presence of catalyst **6c** under the optimized conditions described for (silylmethylene)malonate **5**; no reaction took place with any of these methylenemalonates. Even at higher temperature (28 °C), the reaction between diethyl 4-fluorobenzylidenemalonate (**13b**) and methyl ethyl ketone catalyzed by **6c** and trifluoroacetic acid in *N*-methylpyrrolidin-2-one was very sluggish. The reaction was incomplete even after five days. Moreover, it produced a 3:2 regioisomeric mixture of adducts **14** and **15** in 18% yield and with the acetyl terminal adduct as the major product[43] (Scheme 2). The internal adduct **15** also appeared to be the *syn*-diasteroisomer[24b] as judged by ^{1}H NMR spectroscopy (J_{HaHb} = 7 Hz). In addition, a substantial amount (32%) of an unsaturated ketone **16** was also produced. The source of this ketone **16** could be the retro-Knoevenagel of 4-fluorobenzylidenemalonate (**13b**) producing 4-fluorobenzaldehyde followed by its organocatalyzed aldol dehydration[24,44] with methyl ethyl ketone. This study clearly indicated that silyl substitution is crucial for the reactivity of the (silylmethylene)malonate **5** as well as for the regioselectivity of the addition.

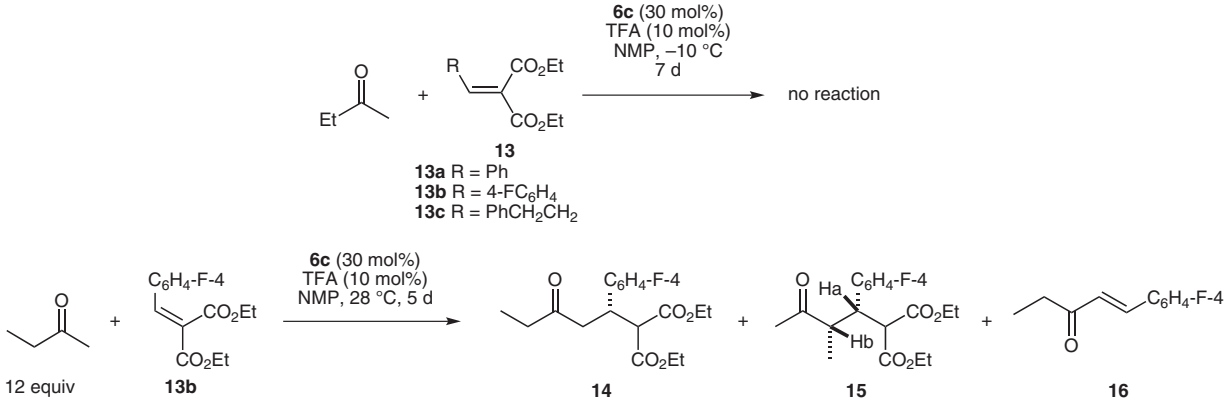
To show the utility of these adducts, a few keto diesters **2f–i** were subjected to Krapcho de-ethoxycarbonylation[45] leading to keto esters **1f–i**, respectively (Scheme 3) in very good yields. The keto esters can further be transformed into natural products with well-known biological activity. For example, keto ester **1f** (Scheme 4) was hydrolyzed with lithium hydroxide followed by esterification with diazomethane to give the keto methyl ester **17**. By comparing the sign and magnitude of the optical rotation value of **17** {$[\alpha]_D^{24}$ –0.8 (*c* 0.8, $CHCl_3$)} with the reported[8a] value {$[\alpha]_D^{21}$ –0.8 (*c* 0.79, $CHCl_3$)}, the silyl-bearing chiral center was concluded to be of *S*-configuration. This also confirmed the absolute stereochemistry of the adduct **2f**. This keto ester **17** can be converted into a pyrrolidine skeleton easily and has already been trans-

Table 3 Regioselective Addition of Alkyl Methyl Ketone to (Silylmethylene)malonate **5**



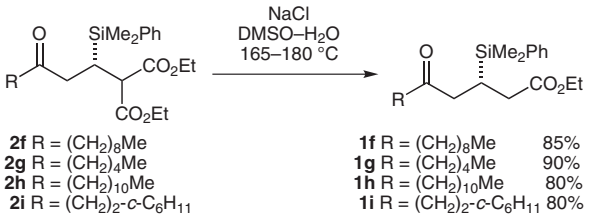
Entry	R	Equiv of ketone	Time (d)	Product	Yield[a] (%)	ee[b] (%)
1	Me	12	7	**2a**	76	90.0
2	*i*-Pr	12	7	**2b**	82	99.5
3	*i*-Bu	5	6	**2c**	82	96.7
4	Et	12	7	**2d**	81	92.8
5	Pr	12	7	**2e**	85	91.2
6	$(CH_2)_8Me$	5	3	**2f**	88	91.1
7	$(CH_2)_4Me$	5	3	**2g**	94	99.6
8	$(CH_2)_{10}Me$	6	6	**2h**	80	87[c]
9	$(CH_2)_2$-*c*-C_6H_{11}	5	5	**2i**	76	90.5
10	$(CH_2)_6OBn$	2	6	**2j**	92	91.3
11	$CH(OMe)_2$	6	7	**2k**	78	85.4

[a] Yield of chromatographically homogeneous product.
[b] Determined by HPLC.
[c] Reaction performed at 4 °C.

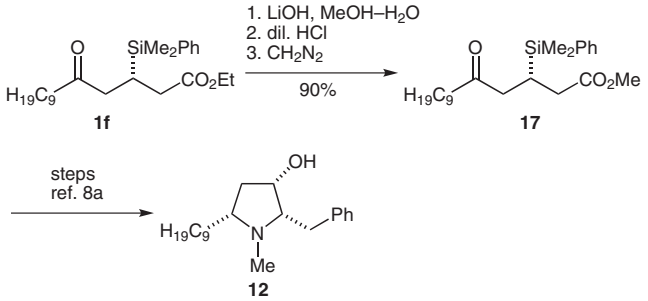


Scheme 2 Addition of methyl ethyl ketone to (arylmethylene)- and alkylidenemalonates

formed into (+)-preussin (**12**), a hydroxylated pyrrolidine natural product in a few steps.[8a,b] The absolute configuration of other products **2a–e** and **2j**,**k** were tentatively assigned in analogy with **2f**.

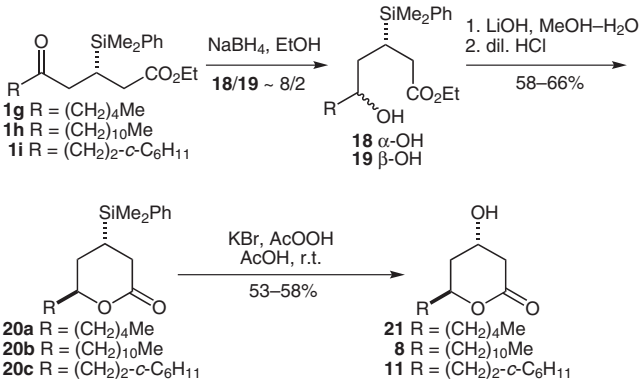


Scheme 3 Synthesis of δ-keto-β-silyl esters

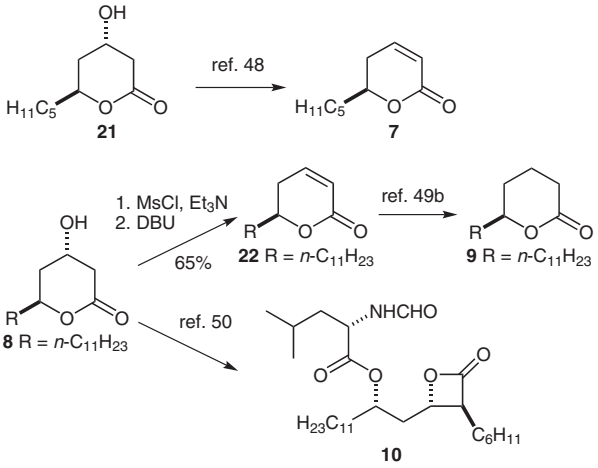


Scheme 4 Synthesis of (+)-preusssin

The absolute configurations of other products **2g–i** were assigned by converting them into keto esters **1g–i** and then into known chiral valerolactone intermediates (Scheme 5). These valerolactones are known to be used for the synthesis of natural products having a large spectrum of biological properties including important pharmacological activity. For this, a silicon-directed stereoselective reduction[46] of the ketones **1g–i** with sodium borohydride gave an inseparable mixture of diastereomeric alcohols **18a–c** and **19a–c** (**18/19** ~ 80:20) in very good yield (Scheme 5). The diastereomeric hydroxy ester mixture in each case was then hydrolyzed and the intermediate hydroxy acids underwent smooth cyclization to give the major lactones **20a–c**.[47] The dimethyl(phenyl)silyl group in **20a–c** was then converted into the hydroxy group following Fleming oxidation[12c] using potassium bromide and peracetic acid with retention of configuration leading to hydroxy lactones **21**, **8**, and **11**, respectively. Lactone (–)-**21** is the antipode of the hydroxy lactone that has already been converted into the natural product (+)-massoialactone (**7**) (Figure 2, Scheme 6). The relative and absolute stereochemistry of the hydroxy and the alkyl groups in **21** were assigned from the ^{1}H and ^{13}C chemical shift values, and comparing the specific rotation value {$[\alpha]_D^{28}$ –34.7 (*c* 1.5, $CHCl_3$) [Lit.[48] $[\alpha]_D$ +29.4 (*c* 1.4, $CHCl_3$) for the antipode of **21**}. The hydroxy valerolactone **8** was converted into the intermediate unsaturated lactone **22** which has already been converted[49] into (*S*)-hexadecanolide. The absolute stereochemistry of alkyl bearing stereocenter of **8** was assigned to be *S* by comparing the specific rotation value {$[\alpha]_D^{29}$ +57 (*c* 1, THF) [Lit.[49] $[\alpha]_D^{25}$ +78.7 (*c* 1, THF)}. (–)-Tetrahydrolipstatin (**10**) has also been prepared from the lactone **8**[50] (Scheme 6). Lactone **11** is the antipode of a reported mevinolin analogue. The relative and absolute stereochemistry of **11** was further confirmed from the physical and spectral data {mp 74–75 °C, Lit. [51] 72–74 °C for the antipode of **11**; $[\alpha]_D^{27}$ –32.9 (*c* 0.94, $CHCl_3$) [Lit.[51] $[\alpha]_D^{25}$ +29 (*c* 0.28, $CHCl_3$) for the antipode of **11**}.



Scheme 5 Synthesis of hydroxy lactones



Scheme 6 Synthesis of valerolactone based natural products

Considering the enamine mechanism proposed by Barbas,[24b] the stereochemical outcome for the formation of **2g–i** can be explained by the transition-state assembly[26] depicted in Figure 3. The (silylmethylene)malonate **5** approaches the enamine from the less hindered *Si* face. The hydrogen bonding interaction of tertiary nitrogen, one of the carbonyl group of (silylmethylene)malonate and trifluoroacetic acid activated the substrates by bringing them

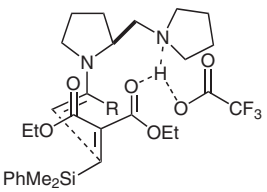


Figure 3 Potential transition state

to proximity, explaining well that a catalytic amount of trifluoroacetic acid can speed up the reaction.

In conclusion, we have developed a directly organocatalytic asymmetric Michael addition of alkyl methyl ketones to a (silylmethylene)malonate with high regio- and enantioselectivity. This is the first successful attempt to engage unsymmetrical methyl ketones to add via methyl terminal of acetyl group in such reactions. The ketone adducts thus obtained can easily undergo de-ethoxycarbonylation to give variety of β-silylated keto esters which can be further transformed to O- and N-heterocyclic natural products.

HPLC-grade acetone, NMP, DMF, toluene, THF, MeOH were used as received. Isopropyl methyl ketone, MEK, methyl propyl ketone, isobutyl methyl ketone, heptan-2-one, tridecan-2-one, and pyruvaldehyde dimethyl acetal were distilled prior to use. Characterization data for the products **2a–g,j,k** are available in the Supporting Information of a previous publication[29] hence they are not included here. Silylmethylene malonate **5** was prepared following a procedure reported by us.[17] Diphenylprolinol **6a** was commercially available and its TMS ether **6b** was prepared according to the literature[37] procedure. All the amino acids were purchased from commercial sources. The catalysts **6c** and **6d** were prepared following literature procedures.[38]

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 fluorescence indicator. Column chromatography was performed on silica gel (230–400 mesh).

^{1}H and ^{13}C NMR spectra were recorded on 200 MHz (^{1}H: 200 MHz, ^{13}C: 50 MHz), 500 MHz (^{1}H: 500 MHz, ^{13}C: 125 MHz) or 700 MHz (^{1}H: 700 MHz, ^{13}C: 175 MHz) spectrometers relative to internal $CHCl_3$ and $CDCl_3$ as standards, respectively. HRMS were recorded at 60–70 eV on a Q-TOF spectrometer (ESI, Ar). Enantiomeric excess (ee) determinations were carried out by HPLC with a Chiralpak AD-H/OD-H column and UV detector at λ = 254 nm. Optical rotations were measured in a polarimeter.

Ethyl (3S)-3-[Dimethyl(phenyl)silyl]-2-(ethoxycarbonyl)-5-oxoalkanoates 2a–k; General Procedure 1

Respective alkyl methyl ketone (1–6 mmol, 2–12 equiv) was added to a stirring mixture of (silylmethylene)malonate **5** (153 mg, 0.5 mmol, 1 equiv), pyrrolidine **6c** (23 mg, 0.15 mmol, 0.3 equiv) and TFA (4 μL, 0.05 mmol, 0.1 equiv) in NMP (2 mL) at –10 °C. After 3–7 d at –10 °C, the mixture was diluted with H_2O 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 (silica gel, hexane–EtOAc, 95:5) to give **2a–k** (76–94%).

Ethyl (3*S*)-3-[Dimethyl(phenyl)silyl]-2-(ethoxycarbonyl)-5-oxohexadecanoate (2h)

Following general procedure 1 using tridecan-2-one (595 mg, 3 mmol), malonate **5** (153 mg, 0.5 mmol), pyrrolidine **6c** (23 mg, 0.15 mmol, 0.3 equiv), and TFA (4 μL, 0.05 mmol, 0.1 equiv) in NMP (2 mL) at 4 °C for 6 d gave **2h** (201 mg, 80%); HPLC (Daicel Chiralpak AD-H, *i*-PrOH–hexane, 0.7:99.3, flow rate = 0.6 mL/min): t_R = 17.2 (93.55%) [(3*S*)-**2h**], 27.4 min (6.45%) [(3*R*)-**2h**].

$[\alpha]_D^{23}$ +4.67 (*c* 1.07, $CHCl_3$).

IR (neat): 2981, 1748, 1730, 1465, 1367, 1249, 1151, 1111, 1034, 819 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.32 (s, 3 H, $SiCH_3$), 0.33 (s, 3 H, $SiCH_3$), 0.87 [t, *J* = 6.3 Hz, 3 H, $CH_3(CH_2)_{10}CO$), 1.16–1.30 [m, 22 H, 2 $CO_2CH_2CH_3$, $CH_3(CH_2)_8CH_2CH_2CO$], 1.34–1.51 [m, 2 H, $CH_3(CH_2)_8CH_2CH_2CO$], 2.04–2.44 [m, 3 H, $CH_3(CH_2)_9CH_2CO$, SiCH], 2.57 [dd, *J* = 6.0, 18.6 Hz, 1 H, $CH_3(CH_2)_9CH_2COCH_AH_B$], 2.71 [dd, *J* = 6.2, 18.6 Hz, 1 H, $CH_3(CH_2)_9CH_2COCH_AH_B$], 3.48 (d, *J* = 5.8 Hz, 1 H, $CH(CO_2CH_2CH_3)_2$], 4.06 (q, *J* = 7 Hz, 4 H, 2 CH_3CH_2OCO), 7.28–7.33 (m, 3 H, Ph), 7.47–7.52 (m, 2 H, Ph).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –3.4, –3.2, 13.8 (2 C), 13.9, 20.3, 22.6, 23.8, 29.1, 29.2, 29.3, 29.4, 29.5 (2 C), 31.8, 40.9, 42.5, 51.9, 61.0, 61.1, 127.6 (2 C), 129.0, 134.2 (2 C), 137.4, 169.4, 169.8, 209.6.

Anal. Calcd for $C_{29}H_{48}O_5Si$: C, 69.00; H, 9.58. Found: C, 69.21; H, 9.61.

Ethyl (3*S*)-3-[Dimethyl(phenyl)silyl]-2-(ethoxycarbonyl)-7-cyclohexyl-5-oxoheptanoate (2i)

Following general procedure 1 using 4-cyclohexylbutan-2-one (386 mg, 2.5 mmol), malonate **5** (153 mg, 0.5 mmol), pyrrolidine **6c** (23 mg, 0.15 mmol, 0.3 equiv), and TFA (4 μL, 0.05 mmol, 0.1 equiv) in NMP (2 mL) at –10 °C for 5 d gave **2i** (175 mg, 76%); HPLC: (Daicel Chiralpak AD-H, *i*-PrOH–hexane, 0.7:99.3), flow rate = 1.0 mL/min): t_R = 14.0 (95.27%) [(3*S*)-**2i**], 23.7 min (4.73%) [(3*R*)-**2i**].

$[\alpha]_D^{23}$ +3.62 (*c* 2.76, $CHCl_3$).

IR (neat): 2980, 1745, 1729, 1448, 1369, 1249, 1151, 1111, 1034, 818 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.30 (s, 3 H, $SiCH_3$), 0.32 (s, 3 H, $SiCH_3$), 0.69–0.86 (m, 2 H, *c*-C_6H_{11}), 0.96–1.35 (m, 12 H, 2 $CO_2CH_2CH_3$, *c*-$C_6H_{11}CH_2CH_2CO$, *c*-C_6H_{11}), 1.50–1.61 (m, 5 H, *c*-C_6H_{11}), 2.04–2.33 (m, 3 H, *c*-$C_6H_{11}CH_2CH_2CO$, SiC*H*), 2.57 (dd, *J* = 6.0, 18.6 Hz, 1 H, *c*-$C_6H_{11}CH_2CH_2COCH_AH_B$), 2.71 (dd, *J* = 6.4, 18.6 Hz, 1 H, *c*-$C_6H_{11}CH_2CH_2COCH_AH_B$), 3.48 [d, *J* = 5.6 Hz, 1 H, $CH(CO_2CH_2CH_3)_2$], 4.04 (q, *J* = 7.2 Hz, 4 H, 2 CH_3CH_2OCO), 7.27–7.32 (m, 3 H, Ph), 7.46–7.50 (m, 2 H, Ph).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –3.5, –3.1, 13.8 (2 C), 20.3, 26.2 (2 C), 26.5, 31.0, 33.0 (3 C), 40.0, 40.9, 51.9, 61.0, 61.1, 127.6 (2 C), 129.0, 134.2 (2 C), 137.4, 169.4, 169.8, 210.0.

Anal. Calcd for $C_{26}H_{40}O_5Si$: C, 67.79; H, 8.75. Found: C, 67.75; H, 8.72.

Ethyl (3*S*)-3-[Dimethyl(phenyl)silyl]-5-oxoalkanoates 1f–i; General Procedure 2

A stirring soln of **2f–i** (0.8 mmol), NaCl (58 mg, 1.0 mmol), and H_2O (1.5 mL) in DMSO (40 mL) was heated at 165–180 °C under N_2 for 6 h. The mixture was diluted with H_2O (200 mL) and extracted with Et_2O. The organic extract was washed with H_2O and brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was chromatographed (silica gel, hexane–EtOAc, 95:5) to give **1f–i** (80–90%).

Ethyl (3*S*)-3-[Dimethyl(phenyl)silyl]-5-oxotetradecanoate (1f)

Following general procedure 2 using **2f** (170 mg, 0.357 mmol), NaCl (40 mg, 0.68 mmol), H_2O (1 mL), and DMSO (28 mL) gave **1f** (123 mg, 85%); HPLC (Daicel Chiralpak AD-H, *i*-PrOH–hexane, 1:99, flow rate = 1.0 mL/min): t_R = 9.9 (94.87%) [(3*S*)-**1f**], 15.3 min (5.13%) [(3*R*)-**1f**].

$[\alpha]_D^{25}$ –6.93 (*c* 2.31, $CHCl_3$).

IR (neat): 2956, 2927, 2855, 1724, 1718, 1216, 1112, 1036, 816, 754 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.29 (s, 3 H, $SiCH_3$), 0.30 (s, 3 H, $SiCH_3$), 0.87 [t, *J* = 6.5 Hz, 3 H, $(CH_2)_8CH_3$], 1.10–1.33 [m, 15 H, $(CH_2)_7CH_3$, CH_3CH_2OCO], 1.40–1.52 (m, 2 H, CH_2), 1.87–2.01 (m, 1 H, SiCH), 2.12–2.44 (m, 6 H, CH_2COCH_2, CH_2CO_2Et), 4.00 (q, *J* = 7.2 Hz, 2 H, CH_3CH_2OCO), 7.32–7.37 (m, 3 H, Ph), 7.46–7.51 (m, 2 H, Ph).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –4.5, –4.3, 14.1, 17.2, 22.7, 23.8, 29.2 (2 C), 29.3 (2 C), 29.4 (2 C), 31.9, 34.7, 42.7, 60.3, 127.8 (2 C), 129.2, 133.9 (2 C), 136.9, 173.6, 210.5.

MS (EI, 70eV): *m*/*z* (%) = 389 (13), 371 (13), 327 (20), 135 (100), 78 (43).

Ethyl (3*S*)-3-[Dimethyl(phenyl)silyl]-5-oxodecanoate (1g)

Following general procedure 2 using **2g** (360 mg, 0.857 mmol), NaCl (60 mg, 1 mmol), H_2O (1.5 mL), and DMSO (40 mL) gave **1g** (268 mg, 90%).

$[\alpha]_D^{27}$ –7.62 (*c* 0.63, $CHCl_3$).

IR (film): 3070, 3019, 2957, 2931, 2872, 1730, 1715, 1216, 1112, 1041, 836, 817, 758 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.29 (s, 3 H, $SiCH_3$), 0.32 (s, 3 H, $SiCH_3$), 0.85 [t, *J* = 7.3 Hz, 3 H, $(CH_2)_4CH_3$], 1.28–1.59 [m, 7 H, $CH_3(CH_2)_2CH_2CH_2CO$, CH_3CH_2OCO], 1.38–1.53 [m, 2 H, $CO(CH_2)_3CH_2CH_3$], 1.90–2.00 (m, 1 H, SiCH), 2.11–2.43 [m, 6 H, $CH_2COCH_2(CH_2)_3CH_3$, $CH_2CO_2CH_2CH_3$], 4.00 (q, *J* = 7 Hz, 2 H, CH_3CH_2OCO), 7.32–7.35 (m, 3 H, Ph), 7.45–7.50 (m, 2 H, Ph).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –4.6, –4.3, 13.8, 14.0, 17.2, 22.3, 23.4, 31.2, 34.6, 42.5, 42.6, 60.2, 127.7 (2 C), 129.1, 133.9 (2 C), 136.9, 173.5, 210.0.

MS (EI, 70eV): *m*/*z* (%) = 333 (15), 271 (25), 249 (15), 135 (100).

Ethyl (3*S*)-3-[Dimethyl(phenyl)silyl]-5-oxohexadecanoate (1h)

Following general procedure 2 using **2h** (600 mg, 1.19 mmol), NaCl (100 mg, 1.7 mmol), H_2O (2 mL), and DMSO (60 mL) gave **1h** (412 mg, 80%).

$[\alpha]_D^{26}$ –6.0 (*c* 2.97, $CHCl_3$).

IR (film): 2957, 2932, 2871, 1730, 1715, 1212, 1112, 1041, 836, 817, 758 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.29 [s, 6 H, $Si(CH_3)_2$], 0.86 (t, *J* = 6.4 Hz, 3 H, $[CH_2]10CH_3$), 1.16–1.23 [m, 19 H, CH_3CH_2OCO, $COCH_2CH_2(CH_2)_8CH_3$], 1.38–1.53 [m, 2 H, $COCH_2CH_2(CH_2)_8CH_3$], 1.87–2.00 (m, 1 H, SiCH), 2.11–2.35 [m, 4 H, $CH_2COCH_2(CH_2)_9CH_3$], 2.40–2.44 (m, 2 H, $CH_2CO_2CH_2CH_3$), 4.00 (q, *J* = 7 Hz, 2 H, CH_3CH_2OCO), 7.27–7.35 (m, 3 H, Ph), 7.46–7.50 (m, 2 H, Ph).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –4.7, –4.4, 13.8, 13.9, 17.2, 22.5, 23.6, 29.0, 29.1, 29.2, 29.3, 29.4 (2 C), 31.7, 34.5, 42.4, 42.6, 60.0, 127.6 (2 C), 128.9, 133.7 (2 C), 136.9, 173.1, 209.8.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{45}O_3Si$: 433.3138; found: 433.3141.

Ethyl (3*S*)-3-[Dimethyl(phenyl)silyl]-7-cyclohexyl-5-oxoheptanoate (1i)

Following general procedure 2 using **2i** (827 mg, 1.79 mmol), NaCl (130 mg, 2.24 mmol), H_2O (2 mL), and DMSO (60 mL) gave **1i** (555 mg, 80%).

$[\alpha]_D^{25}$ –6.4 (*c* 2.64, $CHCl_3$).

IR (film): 2958, 2931, 2871, 1731, 1715, 1216, 1112, 1041, 836, 817, 759 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.29 [s, 6 H, $Si(CH_3)_2$], 0.72–0.89 (m, 3 H, *c*-C_6H_{11}), 1.01–1.23 (m, 6 H, *c*-C_6H_{11}, $CO_2CH_2CH_3$), 1.29–1.40 (m, 2 H, $COCH_2CH_2C_6H_{11}$), 1.50–1.67 (m, 5 H, *c*-C_6H_{11}), 1.87–2.00 (m, 1 H, SiCH), 2.11–2.35 (m, 4 H, $CH_2COCH_2CH_2C_6H_{11}$), 2.41–2.50 (m, 2 H, $CH_2CO_2CH_2CH_3$), 4.00 (q, *J* = 7 Hz, 2 H, CH_3CH_2OCO), 7.30–7.36 (m, 3 H, Ph), 7.45–7.50 (m, 2 H, Ph).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –4.6, –4.3, 14.0, 17.3, 26.1 (2 C), 26.5, 31.0, 33.0 (2 C), 34.6, 37.2, 40.1, 42.7, 60.1, 127.7 (2 C), 129.1, 133.9 (2 C), 137.0, 173.3, 210.4.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{36}O_3NaSi$: 411.2331; found: 411.2329.

Methyl (3*S*)-3-[Dimethyl(phenyl)silyl]-5-oxotetradecanoate (17)

$LiOH·H_2O$ (20 mg, 0.43 mmol) was added to a stirring soln of **1f** (92 mg, 0.228 mmol) in 5% aq MeOH (2 mL) at r.t. After 6 h, the solvent was evaporated under reduced pressure and the residue was diluted with H_2O (1 mL), acidified with dil. HCl and extracted with EtOAc. The extract was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was esterified with ethereal diazomethane, the solvent was evaporated, and the residue was chromatographed to give the methyl ester **17** (80 mg, 90%).

$[\alpha]_D^{24}$ –0.8 (*c* 0.8, $CHCl_3$) [Lit.[8a] $[\alpha]_D^{21}$ –0.8 (*c* 0.79, $CHCl_3$)].

IR (neat): 2952, 2925, 2854, 1736, 1715, 1250, 1112, 816, 774, 701 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.29 [s, 6 H, $Si(CH_3)_2$], 0.86 (t, *J* = 6.4 Hz, 3 H, $CH_3CH_2CH_2$), 1.12–1.38 [br s, 12 H, $CH_2(CH_2)_6CH_3$], 1.41–1.50 (m, 2 H, $COCH_2CH_2$), 1.87–2.00 (m, 1 H, SiCH), 2.12–2.43 (m, 6 H, CH_2COCH_2, $CH_2CO_2CH_3$), 3.55 (s, 3 H, OCH_3), 7.33–7.36 (m, 3 H, Ph), 7.45–7.5 (m, 2 H, Ph).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –4.6, –4.4, 14.0, 17.2, 22.6, 23.7, 29.1, 29.2, 29.3 (2 C), 31.8, 34.5, 42.6 (2 C), 51.4, 127.8 (2 C), 129.2, 133.9 (2 C), 136.8, 173.9, 210.4.

(4*S*,6*S*)-4-[Dimethyl(phenyl)silyl]-6-pentyl-tetrahydro-2*H*-pyran-2-one (20a)

$NaBH_4$ (30 mg, 0.78 mmol) was added portionwise to a stirring soln of **1g** (109 mg, 0.31 mmol) in EtOH (1.5 mL) at 0 °C. After 5 h, the mixture was quenched with sat. NH_4Cl soln and extracted with CH_2Cl_2. The organic extract was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure to give an inseparable diastereomeric mixture of alcohols **18a** and **19a** (**18a**/**19a** 80:20) (86 mg). The alcohol mixture was dissolved in 10% aq MeOH (1 mL) and LiOH (42 mg 1.0 mmol, 4 equiv) was added portionwise at r.t. The mixture was stirred overnight and the solvent was evaporated under reduced pressure. The residue was diluted with H_2O (1 mL), acidified with dil. HCl and extracted with EtOAc. The organic extract was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography to give **20a** (55 mg, 58%).

$[\alpha]_D^{28}$ –52.0 (*c* 1.75, $CHCl_3$).

IR (film): 3010, 2960, 2931, 2859, 1740, 1427, 1256, 1113, 1064, 834, 812, 701 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.32 [s, 6 H, $Si(CH_3)_2$], 0.86 [t, *J* = 6.5 Hz, 3 H, $(CH_2)_4CH_3$], 1.25–1.51 [m, 7 H, SiCH, $CH_2(CH_2)_3CH_3$], 1.59–1.83 [m, 4 H, $COCH_2$, $CH_3(CH_2)_3CH_2$], 2.22 (dd, *J* = 11.2, 16.0 Hz, 1 H, $SiCHCH_AH_BCHOCO$), 2.42 (dd, *J* = 5.6, 16.0 Hz, 1 H, $SiCHCH_AH_BCHOCO$), 3.97–4.09 (m, 1 H, CHOCO), 7.35–7.38 (m, 3 H, Ph), 7.44–7.49 (m, 2 H, Ph).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.6, –5.5, 13.9, 14.9, 22.4, 24.8, 28.0, 29.9, 31.4, 34.9, 78.2, 128.0 (2 C), 129.5, 133.7 (2 C), 135.6, 173.6.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{29}O_2Si$: 305.1934; found: 305.1931.

(4*S*,6*S*)-4-Hydroxy-6-pentyl-tetrahydro-2*H*-pyran-2-one (21)

To a stirring soln of **20a** (150 mg, 0.49 mmol) and AcOOH (35% soln in AcOH, 3 mL) at 0 °C was added KBr (72 mg, 0.6 mmol), then H_2O_2 (30%, 0.1 mL). The mixture was allowed to attain r.t. and stirred for 24 h. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2. The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure. The residue

was purified by column chromatography to give **21** (53 mg, 58%) as an oil.

$[\alpha]_D^{28}$ –34.7 (*c* 1.5, $CHCl_3$) [Lit.[48] value for the antipode of **21** $[\alpha]_D$ +29.4 (*c* 1.4, $CHCl_3$)].

IR (film): 3419, 3015, 2956, 2930, 2860, 1715, 1376, 1256, 1035 758 cm^{-1}.

^1H NMR (700 MHz, $CDCl_3$): δ = 0.90 [t, *J* = 7 Hz, 3 H, $(CH_2)_4CH_3$], 1.28–1.34 [m, 4 H, $CH_2CH_2(CH_2)_2CH_3$], 1.36–1.43 [m, 1 H, $CH_2CH_AH_B(CH_2)_2CH_3$], 1.48–1.55 [m, 1 H, $CH_2CH_AH_B(CH_2)_2CH_3$], 1.57–1.62 [m, 1 H, $CH_AH_BCH_2(CH_2)_2CH_3$], 1.69–1.77 [m, 2 H, $CH_AH_BCH_2(CH_2)_2CH_3$, OCHCH_AH_BCHOH], 1.96 (m, 1 H, OCHCH_AH_BCHOH), 2.13 (br s, 1 H, OH), 2.62 (dd, *J* = 4, 18 Hz, 1 H, CH_AH_BCOO), 2.73 (dd, *J* = 5, 18 Hz, 1 H, CH_AH_BCOO), 4.36–4.40 (m, 1 H, C*H*OH), 4.65–4.72 (m, 1 H, CHOCO).

^{13}C NMR (175 MHz, $CDCl_3$): δ = 13.9, 22.5, 24.5, 31.5, 35.4, 35.8, 38.6, 62.6, 76.0, 170.9.

MS (EI, 70 eV): *m*/*z* (%) = 187 (3) $[M + H]^+$, 169 (2), 140 (7), 115 (79), 97 (100), 73 (42).

(4*S*,6*S*)-4-[Dimethyl(phenyl)silyl]-6-undecyl-tetrahydro-2*H*-pyran-2-one (20b)

$NaBH_4$ (88 mg, 2.3 mmol) was added portionwise to a stirring soln of **1h** (400 mg, 0.92 mmol) in EtOH (4.5 mL) at 0 °C. After 5 h, the mixture was quenched with sat. NH_4Cl soln and extracted with CH_2Cl_2. The organic extract was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure to give an inseparable diastereomeric mixture of alcohols **18b** and **19b** (**18b/19b** 80:20) (370 mg). The alcohol mixture was dissolved in 10% aq MeOH (4 mL) and LiOH (144 mg 3.4 mmol, 4 equiv) was added portionwise at r.t. The mixture was stirred overnight and the solvent was evaporated under reduced pressure. The residue was diluted with H_2O (4 mL), acidified with dil. HCl, and extracted with EtOAc. The organic extract was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography to give **20b** (235 mg, 66%).

$[\alpha]_D^{25}$ –39.9 (*c* 1.93, $CHCl_3$).

IR (film): 3010, 2960, 2930, 2860, 1741, 1425, 1256, 1113, 1064, 834, 812, 701 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.30 [s, 6 H, $Si(CH_3)_2$], 0.87 [t, *J* = 6.2 Hz, 3 H, $(CH_2)_{10}CH_3$], 1.24 [br s, 18 H, $(CH_2)_9CH_3$], 1.33–1.51 [m, 3 H, SiCH, $CH_2(CH_2)_9CH_3$], 1.66–1.81 (m, 2 H, CHOCH_2CHSi), 2.21 (dd, *J* = 13, 16 Hz, 1 H, CH_AH_BCOO), 2.42 (dd, *J* = 7.6, 16 Hz, 1 H, CH_AH_BCOO), 3.97–4.09 (m, 1 H, CHOCO), 7.33–7.39 (m, 3 H, Ph), 7.44–7.49 (m, 2 H, Ph).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.7, –5.6, 13.8, 14.9, 22.5, 24.9, 27.9, 29.1 (2 C), 29.2, 29.3, 29.4 (2 C), 29.9, 31.7, 34.9, 77.9, 127.8 (2 C), 129.4, 133.6 (2 C), 135.6, 173.0.

(4*S*,6*S*)-4-Hydroxy-6-undecyl-tetrahydro-2*H*-pyran-2-one (8)

To a stirring soln of **20b** (235 mg, 0.6 mmol) and AcOOH (35% soln in AcOH, 4 mL) at 0 °C was added KBr (88 mg, 0.74 mmol), then H_2O_2 (30%, 0.1 mL). The mixture was allowed to attain r.t. and stirred for 24 h. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2. The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography to give **8** (87 mg, 53%) as an oil.

$[\alpha]_D^{25}$ –22.9 (*c* 2.1, $CHCl_3$).

IR (film): 3420, 3017, 2956, 2930, 2853, 1715, 1376, 1256, 1035, 758 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.86 [t, *J* = 6.0 Hz, 3 H, $(CH_2)_{10}CH_3$], 1.47 [br s, 18 H, $(CH_2)_9CH_3$], 1.45–2.06 [m, 4 H, $CH_2(CH_2)_9CH_3$, CHOHCH_2CHOCO], 2.61 (dd, *J* = 3.8, 17.6 Hz, 1 H, CH_AH_BCOO), 2.72 (dd, *J* = 5.0, 17.6 Hz, 1 H, CH_AH_BCOO), 4.32–4.39 (m, 1 H, C*H*OH), 4.60–4.74 (m, 1 H, CHOCO).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.9, 22.6, 24.8, 29.3, 29.4, 29.5, (2 C), 29.6 (2 C), 31.8, 35.5, 35.8, 38.5, 62.2, 76.2, 171.3.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{31}O_3$: 271.2273; found: 271.2282.

(*S*)-6-Undecyl-5,6-dihydro-2*H*-pyran-2-one (22)

MsCl (23 μL, 0.32 mmol) was added to a stirring soln of **8** (80 mg, 0.29 mmol) and Et_3N (40 μL, 0.64 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C. After 1 h, the mixture was quenched with sat. NH_4Cl soln. The mixture was extracted with CH_2Cl_2 and the extract was evaporated to give the crude mesylate. The mesylate and DBU (185 μL, 1.24 mmol) were dissolved in anhyd CH_2Cl_2 (1 mL) and the mixture was stirred overnight. The mixture was diluted with CH_2Cl_2 and washed with sat. NH_4Cl soln. The organic layer was separated, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel) to give **22** (47 mg, 65%); mp 48–51 °C [Lit.[49a] 45–47 °C].

$[\alpha]_D^{29}$ +57.0 (*c* 1.0, THF) [Lit.[49b] $[\alpha]_D^{25}$ +78.7 (*c* 1.0, THF)].

^1H NMR (200 MHz, $CDCl_3$): δ = 0.86 [t, 3 H, $(CH_2)_{10}CH_3$], 1.24 [br s, 20 H, $(CH_2)_{10}CH_3$], 2.26–2.34 (m, 2 H, CH_2CHOCO), 4.33–4.46 (m, 1 H, CHOCO), 6.00 (dt, *J* = 1.6, 9.8 Hz, 1 H, CH_2CH=CHCO), 6.86 (dt, *J* = 4.4, 9.6 Hz, 1 H, CH_2CH=C*H*CO).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 22.6, 24.8, 29.2, 29.3, 29.4 (2 C), 29.5, 29.6 (2 C), 31.9, 34.9, 78.0, 121.5, 144.8, 164.5.

(4*S*,6*S*)-6-(2-Cyclohexylethyl)-4-[dimethyl(phenyl)silyl]-tetrahydro-2*H*-pyran-2-one (20c)

$NaBH_4$ (115 mg, 3 mmol) was added portionwise to a stirring soln of **1i** (455 mg, 1.17 mmol) in EtOH (5 mL) at 0 °C. After 5 h, the mixture was quenched with sat. NH_4Cl soln and extracted with CH_2Cl_2. The organic extract was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure to give an inseparable diastereomeric mixture of alcohols **18c** and **19c** (**18c/19c** 80:20) (394 mg). The alcohol mixture was dissolved in 10% aq MeOH (4 mL) and LiOH (170 mg 4 mmol) was added portionwise it at r.t. The mixture was stirred overnight and the solvent was evaporated under reduced pressure. The residue was diluted with H_2O (4 mL), acidified with dil. HCl and extracted with EtOAc. The organic extract was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography to give **20c** (250 mg, 62%).

$[\alpha]_D^{23}$ –49.5 (*c* 2.0, $CHCl_3$).

IR (film): 3011, 2922, 2850, 1743, 1448, 1256, 1113, 1066, 834, 815, 736 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.32 [s, 6 H, $Si(CH_3)_2$], 0.76–0.95 (m, 2 H, *c*-C_6H_{11}), 1.01–1.54 (m, 7 H, SiCH, CH_2CH_2-*c*-C_6H_{11}, *c*-C_6H_{11}), 1.62–1.83 (m, 9 H, SiCHCH_2CHOCO, CH_2CH_2-*c*-C_6H_{11}, *c*-C_6H_{11}), 2.21 (dd, *J* = 13, 15.8 Hz, 1 H, CH_AH_BCOO), 2.42 (dd, *J* = 5.6, 15.8 Hz, 1 H, CH_AH_BCOO), 3.94–4.06 (m, 1 H, CHOCO), 7.33–7.39 (m, 3 H, Ph), 7.39–7.49 (m, 2 H, Ph).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.7, –5.6, 14.9, 26.0 (2 C), 26.4, 27.9, 29.9, 32.2, 32.5, 32.9, 33.0, 37.3, 78.4, 127.9 (2 C), 129.4, 133.6 (2 C), 135.6, 173.2.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{33}O_2Si$: 345.2250; found: 345.2236.

(4*S*,6*S*)-6-(2-Cyclohexylethyl)-4-hydroxy-tetrahydro-2*H*-pyran-2-one (11)

To a stirring soln of **20c** (232 mg, 0.67 mmol) and AcOOH (35% soln in AcOH, 4 mL) at 0 °C was added KBr (102 mg, 0.86 mmol),

then H_2O_2 (30%, 0.1 mL). The mixture was allowed to attain r.t. and stirred for 24 h. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2. The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography to give **11** (84 mg, 56%); mp 74–75 °C [Lit.[50] 72–74 °C].

$[\alpha]_D^{27}$ –32.9 (*c* 0.94, $CHCl_3$) [Lit.[50] value for the antipode of **11** $[\alpha]_D^{25}$ +29 (*c* 0.28, $CHCl_3$)].

IR (film): 3419, 3019, 2955, 2930, 2853, 1717, 1066, 758 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.78–0.94 (m, 2 H, *c*-C_6H_{11}), 1.00–1.52 (m, 6 H, CH_2CH_2-*c*-C_6H_{11}, *c*-C_6H_{11}), 1.57–1.78 (m, 7 H, CHOHCH_2CHOCO, C$H_2$$CH_2$-*c*-$C_6H_{11}$, *c*-$C_6H_{11}$), 1.91–2.03 (m, 3 H, *c*-C_6H_{11}, OH), 2.59 (dd, *J* = 2.8, 17.8 Hz, 1 H, C$H_A$$H_B$COO), 2.71 (dd, *J* = 4.8, 17.8 Hz, 1 H, $CH_A$$H_B$COO), 4.32–4.40 (m, 1 H, CHOH), 4.57–4.71 (m, 1 H, CHOCO).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.2 (2 C), 26.6, 32.3, 32.9, 33.2, 33.3, 35.9, 37.5, 38.6, 62.6, 76.4, 170.9.

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