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Journal of Organometallic Chemistry 690 (2005) 2172–2179
Journal of Organometallic Chemistry
www.elsevier.com/locate/jorganchem

Two-carbon homologation of ketones via sily ketene acetals: Synthesis of α,β-unsaturated acids and α-trimethylsilyl δ-ketoacids

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Received 15 November 2004; accepted 25 January 2005
Available online 14 April 2005

Abstract

The reaction of C,O,O-tris(trimethylsilyl)ketene acetal **1** with saturated, cyclic and aromatic ketones **2** proceeds smoothly in the presence of titanium chloride to give (*E*)-α,β-unsaturated carboxylic acids **3** with fairly good stereoselectivity. With α,β-unsaturated ketones **4**, α-trimethylsilyl δ-ketoacids **5** (*syn* + *anti*) are obtained according to Michael-type 1,4 addition. These diastereoisomers are separated and the configurations of **5a** are achieved by X-ray molecular analysis.

Keywords: Trimethylsilyl acetate; Silyl ketene acetal; α,β-Unsaturated acids; α-Silyl ketoacids

1. Introduction

We have shown in a previous work [1] that C,O,O-tris(trimethylsilyl)ketene acetal **1** is a versatile organosilicon reagent for the conversion of aldehydes into (*E*)-α,β-alkenoic acids with two-carbon unit introduction (Scheme 1). Recently, we have reported the study of stereochemical control in alkenoic acids formation [2].

In this paper, we show that this study can be also applied to ketones. This complementary study is justified by the fact that ketones are generally less reactive than aldehydes. Moreover, in contrast to unsaturated aldehydes, α,β-unsaturated ketones lead to Michael-type 1,4 addition products.

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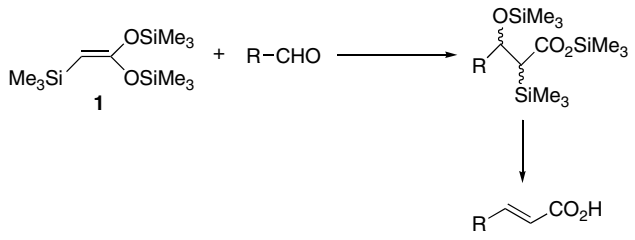
doi:10.1016/j.jorganchem.2005.01.049

2. Results and discussion

2.1. Reaction with saturated, cyclic and aromatic ketones

The reaction has been initially performed with acetophenone and various catalysts in order to determinate the best conditions for this condensation-elimination reaction. The results are listed in Table 1.

The attempts carried with Lewis acids (entries 1 to 5) show that only $AlCl_3$ and $TiCl_4$ lead to the expected acids **3a**. However, with $TiCl_4$, acetophenone conversion is complete whatever the reaction temperature is (entries 4 and 5). Unfortunately in this case, a (*Z* + *E*) mixture of the acids **3a** is obtained. $ZnBr_2$ and HgI_2, which have given very interesting results with aldehydes [1,2], are totally inactive (entries 1, 2). Electrophilic assistance of the carbonyl by complexation with these Lewis acids seems to be insufficient to allow nucleophilic addition of the trisilylated reagent **1**. With KOH, and CsF (entries 6,7), the acetophenone conversion is very slow and does not occur with



Scheme 1.

NaF (entry 8). In fluoride catalyzed reaction (entries 7 and 8), we have observed in the reaction mixture, before hydrolysis, the silylated enolate derived from acetophenone. This enol arises from an exchange between this highly enolizable ketone and the trisilylated reagent **1**. Therefore, $TiCl_4$ seems to be the best catalyst for this reaction.

To determine the scope and limitations of this new direct synthesis of α,β-unsaturated β-disubstitued acids **3**, several saturated, cyclic and aromatic ketones were used. Results are reported in Table 2.

Firstly, it is to be noticed that with ketones, we have never isolated the intermediates that lead to the corresponding alkenoic acids **3** by Peterson-type elimination. Condensation and elimination reactions must both be fast, even at very low temperature (−70 °C). Entry 3 shows that benzophenone is completely inactive at low temperature, even after six days. Nevertheless, at room temperature, a good yield of the corresponding ethylenic acid is obtained (entry 4). Meanwhile, with unsymmetrical ketones, the reaction gave a (*Z* + *E*) mixture of the acids **3**.

2.2. Reaction with α,β-unsaturated ketones

Several groups were interested in silylated enol ethers condensation with α,β-unsaturated ketones using Lewis acids. These reactions were extended to alkylsilylketene acetals. Michael-type 1,4 addition products were then obtained [9–12].

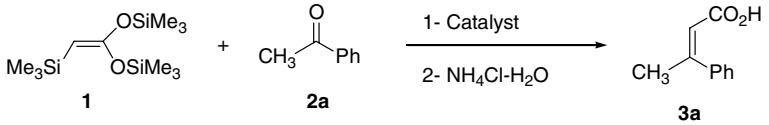
Regarding trisilylated reagent **1** condensation with α,β-ethylenic ketones, we have found that $TiCl_4$ was the best catalyst for this reaction. α-Trimethylsilyl δ-ketoacids **5**, unknown in the literature, are obtained in good yields (entries 1–3, Table 3). With cyclohexenone **4d**, the expected δ-ketoacid **5d** was obtained along with the by-product **6d** issued from a double 1,4 Michael-type condensation (Scheme 2). Proportion of **6d** depends on the way of introduction of the trisilylated reagent **1** versus cyclohexenone. The intermediate **A** that arises from condensation of **1** on **4d**, reacts on cyclohexenone to give **6d**. The proportion of the latter is lowered when cyclohexenone is added very slowly to the mixture of trisilylated reagent **1** and $TiCl_4$ (entry 5).

This kind of double Michael-type 1,4 addition (Michael–Michael tandem reaction) has already been reported in the literature [13] for alkylsilylketene acetals.

δ-Ketoacids **5a**, **5b** and **5d** are obtained as mixture of diastereoisomers which were separated by cold precipitation (**5a**) or column chromatography (**5b** and **5d**). Separation of diastereoisomers **5a** leads to two solids. One of them is crystalline, which allowed us to find out its configuration using X-ray crystallography and therefore to conclude on the configuration of the other diastereoisomer (Scheme 3).

Structure assigned by X-ray (Fig. 1) shows that stereoisomer $\mathbf{5a_1}$, which coupling constant $J_{a,b} = 11.25$

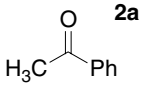
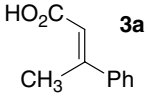
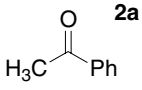
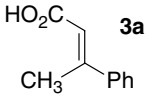
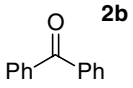
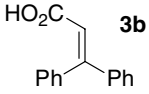
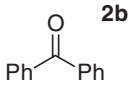
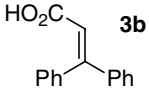
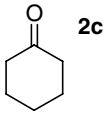
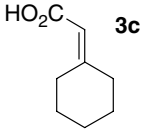
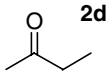
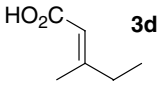
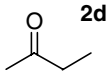
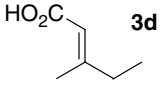
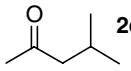
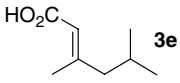
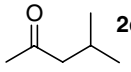
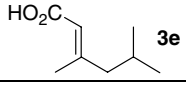
Table 1
Reaction of C,O,O-tris(trimethylsilyl)ketene acetal **1** with acetophenone in the presence of various catalysts



Entry	Catalyst	Solvent	Temp. (°C)	Time (h)	**2a/3a**[a]
1	10% $ZnBr_2$	THF	rt	5.5	100/0
2	10% HgI_2	Toluene	rt	5.0	100/0
3	1 eq $AlCl_3$	CH_2Cl_2	rt	5.0	48/52
4	1 eq $TiCl_4$	CH_2Cl_2	−70	9.0	0/100[b]
5	1 eq $TiCl_4$	CH_2 Cl_2	−70 (1 h) → rt	6.5	0/100[b]
6	1% KOH	DMF	rt	5.5	92/8
7	10% CsF	DMF	rt	5.0	95/5
8	10% NaF	DMSO	rt	24.0	100/0

[a] Estimated by ^{13}H NMR on the crude reaction mixture.
[b] Mixture of (*E* + *Z*) isomers.

Table 2
Synthesis of β-disubstitued ethylenic acids **3** using trisilylated reagent **1**

Entry	Ketones **2**	Temp. (°C)	Time (h)	Acids **3**	Yield[a] (%)	*E*/*Z*[b]	Ref.
1	 **2a**	−70	9.0	 **3a**	95	78/22	[3]
2	 **2a**	−70 → rt	3.0	 **3a**	89	80/20	[3]
3	 **2b**	−70	144.0	 **3b**	0	–	[4,5]
4	 **2b**	−70 → rt	120.0	 **3b**	80	–	[4,5]
5	 **2c**	−70 → rt	4.0	 **3c**	95	–	[5]
6	 **2d**	−70	1.5	 **3d**	88	70/30	[6,7]
7	 **2d**	−70 → rt	3.0	 **3d**	90	70/30	[6,7]
8	 **2e**	−70	36.0	 **3e**	85	88/12	[8]
9	 **2e**	−70 → rt	3.0	 **3e**	95	70/30	[8]

[a] Isolated yields.
[b] The stereochemistry of each compound was determined by the ^{13}H RMN spectrum of the crude product.

Hz, corresponds to the *anti* isomer. Indeed, Fig. 1 shows that phenyl and trimethylsilyl groups are positioned in *anti* one by the other. By means of this assignment, it can be settled that the configuration of the second diastereoisomer **5a$_2$** ($J_{a,b}$ = 11.52 Hz) is *syn*.

Unfortunately, determination of the other δ-ketoacids (**5b** and **5d**) configuration using X-ray spectroscopy was not possible since diastereoisomers **5b** are in a powder form and diastereoisomers **5d** are oils.

2.3. Reduction of α-silyl-δ-ketoacids 5

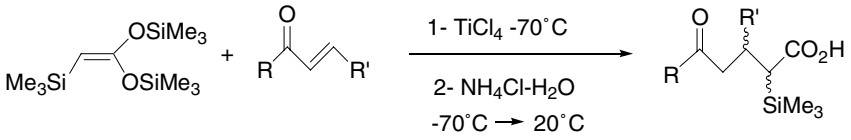
It is known that δ-ketoacids leads, after carbonyl reduction, to the corresponding lactones. The latters belong to an important class of natural compounds. Lactones are also very useful intermediates in total synthesis of biologically active products. Since α-silyl-δ-ketoacids **5** are not described in the literature, it strikes us as interesting to study their potentiality in α-silyl lactones synthesis.

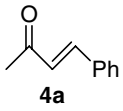
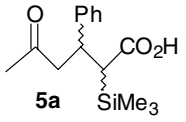
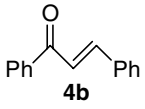
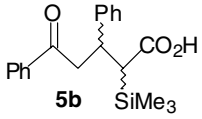
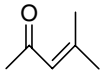
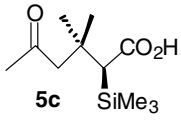
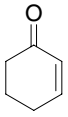
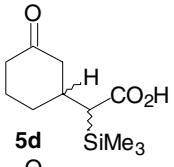
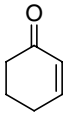
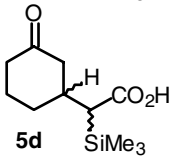
We firstly reduced the α-silyl-δ-ketoacid **5a** mixture (*syn*/*anti* = 53/47) using sodium borohydride in ethanol (Scheme 4). We obtained, after acid hydrolysis, the desilylated lactones **8a** as two diastereoisomers along with the δ-hydroxy-α-trimethylsilyl acid **7a** (one diastereoisomer).

In order to determine which of the two stereoisomers **5a** (*syn* or *anti*) gave the δ-hydroxy-α-trimethylsilyl acid **7a** and which gave the two lactones **8a**, we have reduced each diastereoisomer **5a** separately.

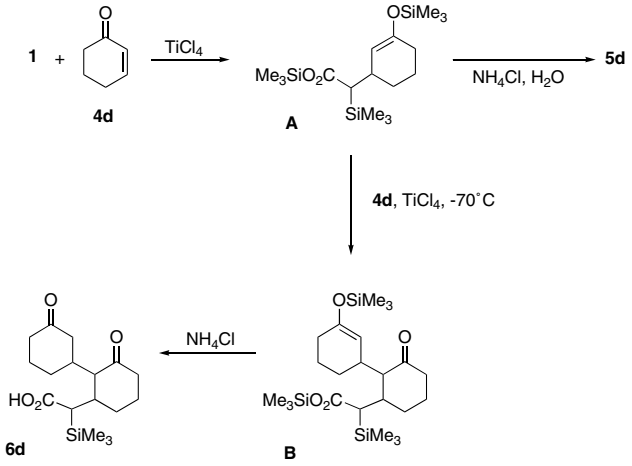
Reduction of δ-ketoacid **5a** *anti* afforded the two lactones **8a** *syn* and *anti* in a 20/80 ratio (Scheme 5). Their

Table 3
Reaction of trisilylated reagent **1** with various α,β-unsaturated ketones



Entry	Ketones **4**	Time (h)	Acids **5**	Yield (%)[a]	Diastereoisomeric ratio[b]
1	 **4a**	3.0	 **5a**	81	53/47
2	 **4b**	7.0	 **5b**	80	50/50
3	 **4c**	3.5	 **5c**	80	–
4	 **4d**	1.5	 **5d**	54 (26)[c]	67/33
5	 **4d**	1.5	 **5d**	41 (8)[c,d]	67/33

[a] Isolated yield.
[b] Estimated by ^{13}H NMR on the crude reaction mixture.
[c] Formation of a by-product **6d**.
[d] Reverse order addition: ketone diluted in dichloromethane is added to a solution of trisilylated reagent **1** and $TiCl_4$ in dichloromethane.



Scheme 2.

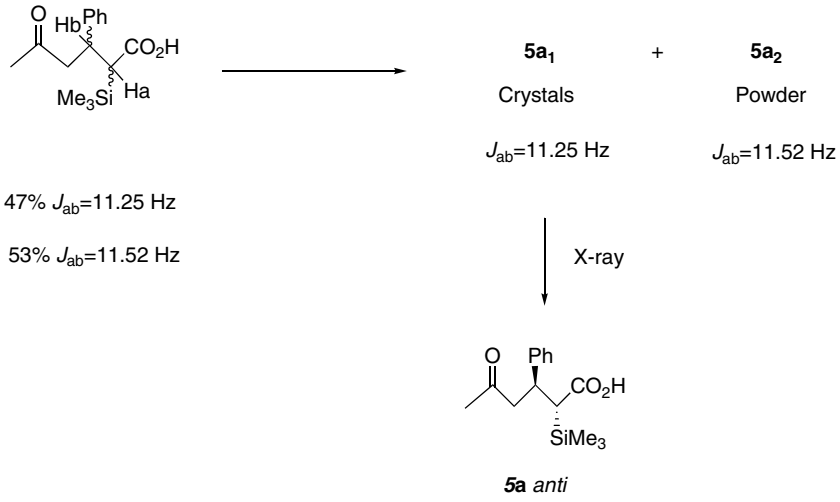
configuration assignments were done using the literature data [14].

We have next reduced the δ-ketoacid **5a** *syn* (Scheme 6).

This reduction gave exclusively one diastereoisomer of δ-hydroxy-α-trimethylsilyl acid **7a** (white powder) which is unknown in the literature. The determination of its configuration and the reduction of the other δ-ketoacids **5** are currently being investigated in our laboratory. The results will be reported in due course.

3. Conclusion

In conclusion, reaction of the organosilicon reagent 1 with saturated, cyclic and aromatic ketones leads to α,β-ethylenic acids **3** in good yields. *E* isomer is the major



Scheme 3.

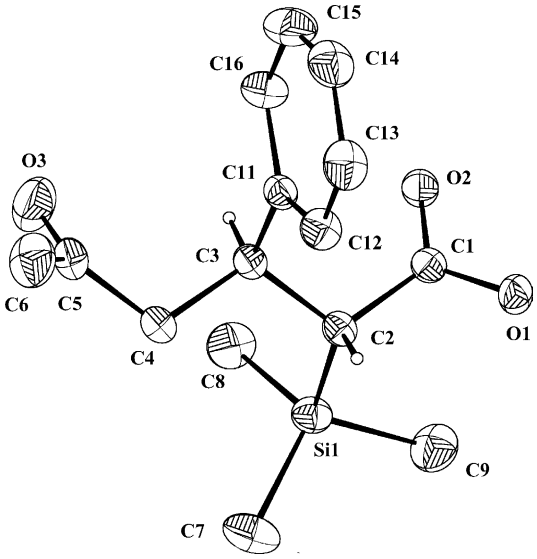


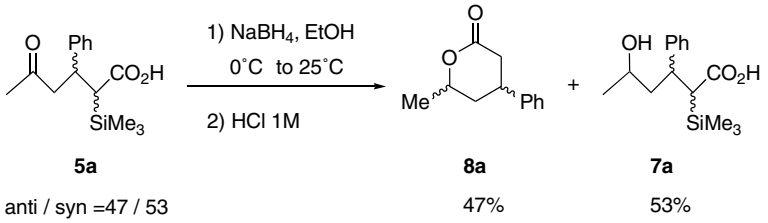
Fig. 1. Cameron view of **5a**. (Ellipsoid at 30% probability level.)

reaction product. Attempts to study the relationship between (*Z*,*E*) isomers of the alkenoic acids **3** obtained and the configuration (*syn*, *anti*) of the intermediates failed. The latter compounds could not be isolated, even at low temperature. The reaction of 1 with α,β-ethylenic ketones affords exclusively the expected δ-ketoacids **5** according to Michael-type 1,4 addition. These compounds are obtained as a mixture of two diastereoisomers (*syn* + *anti*) which were separated and the configurations of **5a** were achieved by X-ray analysis.

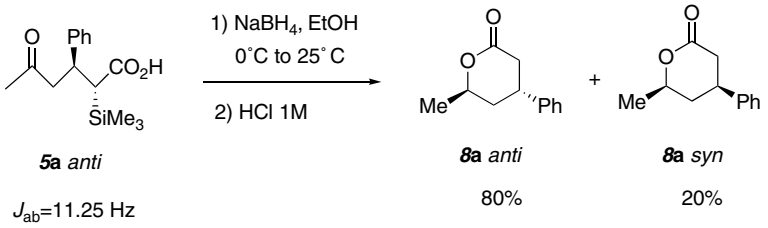
4. Experimental

4.1. General information

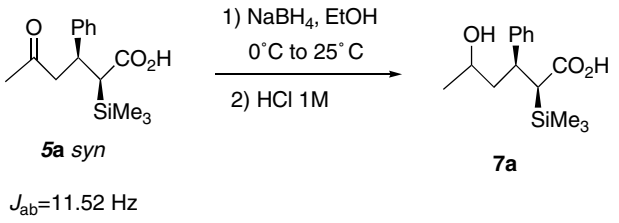
All reactions involving water-sensitive compounds were carried out in oven-dried glassware and under



Scheme 4.



Scheme 5.



5a *syn* **7a**

J_{ab}=11.52 Hz

Scheme 6.

nitrogen atmosphere. Unless otherwise noted, starting materials were purchased from commercial sources and used as received. C,O,O-Tris(tri-methylsilyl)ketene acetal **1** was prepared according to our previously reported procedure [1]. Zinc bromide was prepared by heating ground zinc and 1,2-dibromoethane in THF at reflux [15]. All the solvents were dried and distilled prior to use.

^{1}H and ^{13}C NMR spectra were recorded at 250 MHz using $CDCl_3$ or acetone-d_6 as solvent. Chemical shifts are given in ppm (J in Hz) relative to chloroform or acetone. Melting points are uncorrected. Flash chromatography was done on Merck grade 60 silica gel (230–400 mesh) using mixtures of cyclohexane and ethyl acetate as eluent.

4.2. Preparation of unsaturated acids **3** and δ-keto-α-trimethylsilyl acids **5**

4.2.1. General procedure

To a dichloromethane (20 mL) solution of ketone (1.7 mmol) is added $TiCl_4$ (1.7 mmol) at −70 °C. Trisilylated reagent **1** (2 mmol) is added dropwise at the same temperature. Reaction is checked using TLC until disappearance of the starting ketone. The resulting red solution is then quenched with a saturated NH_4Cl solution (20 mL) at −70 °C and the mixture is raised to room temperature. The aqueous layer is extracted by dichloromethane (3 × 20 mL). The organic layers are washed with H_2O (20 mL) and dried over $MgSO_4$. The solvent is removed under reduced pressure. Acid–base workup, to remove any remaining nonacidic organic material, gives acids **3** (or **5**) which are purified by recrystallization or flash chromatography. Physical, spectral and analytical data for all compounds follow.

4.2.2. (*E*)-3-Phenyl but-2-enoic acid (**3a**)

Recrystallized in petroleum ether; mp = 97 °C (Lit. [3], mp = 95–97 °C).

^{13}H NMR ($CDCl_3$) δ 2.57 (d, 3H, J = 1.22 Hz, CH_3), 6.14 (d, 1H, J = 1.22 Hz, H-2), 7.33–7.37 (m, 3H, ArH), 7.44–7.48 (m, 2H, ArH), 11.55 (s, 1H, COOH); ^{13}C NMR ($CDCl_3$) δ 18.29, 116.50, 126.38, 128.53, 129.32, 141.98, 158.49, 172.50.

IR (KBr): 3500–2500 (OH), 1680 (C=O); MS: $M^{\cdot+}$ = 162. Anal. Calc. for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 74.21; H, 6.08.

4.2.3. (*Z*)-3-Phenyl but-2-enoic acid (**3a**)

Data from (*Z* + *E*) mixture:

^{13}H NMR ($CDCl_3$) δ 2.17 (d, 3H, J = 1.21 Hz, CH_3), 5.93 (d, 1H, J = 1.21 Hz, H-2), 7.16–7.37 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ 27.55, 117.02, 126.81, 127.89, 127.93, 140.22, 158.28, 171.37.

IR (KBr): 3500–2500 (OH), 1680 (C=O); MS (*Z* + *E* mixture): $M^{\cdot+}$ = 162.

4.2.4. 3,3-Diphenyl prop-2-enoic acid (**3b**)

Recrystallized in ethanol; mp = 158 °C (Lit. [5], mp = 158–160 °C). ^{13}H NMR ($CDCl_3$) δ 6.28 (s, 1H, H-2), 7.11–7.32 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$) δ 116.43, 127.88, 128.37, 128.41, 128.50, 129.23, 129.70, 138.36, 140.80, 158.98, 171.18.

IR (KBr): 3600–2500 (OH), 1680 (C=O). MS: $M^{\cdot+}$ = 224. Anal. Calc. for $C_{15}H_{12}O_2$: C, 80.34; H, 5.39. Found: C, 80.09; H, 5.25.

4.2.5. Cyclohexylidene ethanoic acid (**3c**)

Recrystallized in petroleum ether; mp = 88–89 °C (Lit. [5], mp = 90–91.5 °C).

^{13}H NMR ($CDCl_3$) δ 1.54 (m, 6H, H-β, H-β′, H-γ), 2.22 (m, 2H, H-α), 2.73 (m, 2H, H-α′), 5.55 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$) δ 26.16, 27.85, 28.63, 30.06, 38.23, 112.45, 166.77, 172.20.

IR (KBr): 3600–2400 (OH), 1700 (C=O). MS: $M^{\cdot+}$ = 140. Anal. Calc. for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.40; H, 8.50.

4.2.6. (*E*)-3-Methylpent-2-enoic acid (**3d**)

Column flash chromatography was done using cyclohexane/ethyl acetate (90/10) as eluent. Oil.

Data from (*Z* + *E*) mixture:

^{13}H NMR ($CDCl_3$) δ 1.05 (t, 3H, J = 7.46 Hz, H-5), 2.14 (d, 3H, J = 1.16 Hz, H-4′), 2.17 (q, 2H, J = 7.46 Hz, H-4), 5.66 (q, 1H, J = 1.16 Hz, H-2).

IR (KBr): 3500–2500 (OH), 1686 (C=O); MS (*E* + *Z* mixture): $M^{\cdot+}$ = 114.

4.2.7. (*Z*)-3-Methylpent-2-enoic acid (**3d**)

Data from (*Z* + *E*) mixture:

^{13}H NMR ($CDCl_3$) δ 1.04 (t, 3H, J = 7.56 Hz, H-5), 1.89 (d, 3H, J = 1.33 Hz, H-4′), 2.61 (q, 2H, J = 15.11 Hz, J = 7.56 Hz, H-4), 5.62 (q, 1H, J = 1.33 Hz, H-2).

IR (KBr): 3500–2500 (OH), 1686 (C=O); MS (*Z* + *E* mixture): $M^{\cdot+}$ = 114.

4.2.8. (*E*)-3,5-Dimethylhex-2-enoic acid (**3e**)

Column flash chromatography was done using cyclohexane/ethyl acetate (90/10) as eluent. Oil.

Data from ($Z + E$) mixture:

^{13}H NMR ($CDCl_3$) δ 0.87 (d, 6H, $J = 6.34$ Hz, H-6, H-6′), 1.85 (m, 1H, H-5), 2.01 (d, 2H, $J = 7.21$ Hz, H-4), 2.12 (s, 3H, CH_3), 5.64 (s, 1H, H-2).

IR (KBr): 3500–2500 (OH), 1690(C=O); MS ($E + Z$ mixture): $M^{\cdot+} = 142$.

*4.2.9. (Z)-3,5-Dimethylhex-2-enoic acid (**3e**)*

Data from ($Z + E$) mixture:

^{13}H NMR ($CDCl_3$) δ 0.89 (d, 6H, $J = 6.24$ Hz, H-6, H-6′), 1.85 (m, 1H, H-5), 1.88 (s, 3H, CH_3), 2.55 (d, 2H, $J = 7.45$ Hz, H-4), 5.70 (s, 1H, H-2).

IR (KBr): 3500–2500 (OH), 1690(C=O); MS ($E + Z$ mixture): $M^{\cdot+} = 142$.

*4.2.10. 5-Oxo-3-phenyl-2-trimethylsilyl hexanoic acid (**5a**)*

4.2.10.1. Anti. Recrystallized in pentane/carbon tetrachloride (60/40); mp = 139–140 °C.

^{13}H NMR ($CDCl_3$) δ 0.10 (s, 9H, $SiMe_3$), 1.80 (s, 3H, H-6), 2.41 (d, 1H, $J = 11.25$ Hz, H-2), 2.69 (dd, 2H, $J = 8.75$ Hz, $J = 6.25$ Hz, H-4), 3.54 (ddd, 1H, $J = 11.25$ Hz, $J = 8.75$ Hz, $J = 6.25$ Hz, H-3), 7.04–7.16 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ −1.44, 30.84, 40.53, 44.17, 49.42, 126.72, 127.71, 128.30, 143.14, 179.07, 206.92.

IR (KBr): 1713 (C=O acid), 1680 (C=O ketone). MS: $MH^+ = 279$. Anal. Calc. for $C_{15}H_{22}O_3Si$: C, 64.71; H, 7.96. Found: C, 64.90; H, 7.83.

X-ray crystal data of **5a**: $C_{15}H_{22}O_3Si$; $M = 278.4$; space group = $P2_1/c$; $a = 10.553(3)$ Å; $b = 14.121(4)$ Å; $c = 11.758(8)$ Å; $V = 1672(1)$ Å^3; $Z = 4$; $T = 295$ K; $\mu = 0.136$ mm^{-1}; reflections total 3268; reflections observed ($I > 3\sigma(I)$) 1529; parameters refined 174; final values, $R_{obs} = 0.0500$; $wR_{all} = 0.0753$; GOF = 1.088.

4.2.10.2. Syn. Recrystallized in pentane/carbon tetrachloride (60/40); mp = 115–117 °C.

^{13}H NMR ($CDCl_3$) δ −0.21 (s, 9H, $SiMe_3$), 1.86 (s, 3H, H-6), 2.40 (d, 1H, $J = 11.5$ Hz, H-2), 2.82 (ddd, 2H, $J = 15.5$ Hz, $J = 10.4$ Hz, $J = 3.7$ Hz, H-4), 3.61 (ddd, 1H, $J = 11.5$ Hz, $J = 10.4$ Hz, $J = 3.7$ Hz, H-3), 7.11–7.27 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ −2.24, 30.57, 40.25, 44.58, 51.13, 127.13, 128.34, 128.51, 141.77, 181.11, 207.13.

IR (KBr): 1720 (C=O acid), 1685 (C=O ketone). MS: $MH^+ = 279$. Anal. Calc. for $C_{15}H_{22}O_3Si$: C, 64.71; H, 7.96. Found: C, 64.48; H, 7.82.

*4.2.11. 5-Oxo-3,5-diphenyl-2-trimethylsilylhexanoic acid (**5b**)*

The two diastereoisomers were separated by column flash chromatography using cyclohexane/ethyl acetate (80/20) as eluent.

4.2.11.1. Isomer I. White powder; mp = 132–134 °C.

^{13}H NMR ($CDCl_3$) δ −0.20 (s, 9H, $SiMe_3$), 2.67 (d, 1H, $J = 11.5$ Hz, H-2), 3.36 (ddd, 2H, $J = 15.8$ Hz, $J = 10.3$ Hz, $J = 3.6$ Hz, H-4), 3.83 (td, 1H, $J = 11.5$ Hz, $J = 10.3$ Hz, $J = 3.6$ Hz, H-3), 7.05–7.46 (m, 8H, ArH), 7.75–7.78 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ −2.17, 40.52, 44.41, 46.38, 127.04, 127.88, 128.06, 128.49, 132.81, 136.96, 141.84, 180.48, 198.24.

IR (KBr): 1700 (C=O acid), 1695 (C=O ketone). MS: $MH^+ = 341$. Anal. Calc. for $C_{20}H_{24}O_3Si$: C, 70.55; H, 7.10. Found: C, 70.70; H, 7.22.

4.2.11.2. Isomer II. White powder; mp = 150–151 °C.

^{13}H NMR ($CDCl_3$) δ 0.22 (s, 9H, $SiMe_3$), 2.67 (d, 1H, $J = 10.8$ Hz, H-2), 3.38 (ddd, 2H, $J = 16.35$ Hz, $J = 10.1$ Hz, $J = 3.9$ Hz, H-4), 3.91 (ddd, 1H, $J = 10.8$ Hz, $J = 10.1$ Hz, $J = 3.9$ Hz, H-3), 7.09–7.57 (m, 8H, ArH), 7.78–7.81 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ −1.31, 40.17, 44.07, 44.40, 126.51, 127.90, 128.13, 128.45, 132.92, 137.08, 143.57, 178.91, 198.03.

IR (KBr): 1689 (C=O acid), 1674 (C=O ketone). MS: $MH^+ = 341$. Anal. Calc. for $C_{20}H_{24}O_3Si$: C, 70.55; H, 7.10. Found: C,70.41; H, 7.19.

*4.2.12. 3,3-Dimethyl-5-oxo-2-trimethylsilylhexanoic acid (**5c**)*

Column flash chromatography was done using cyclohexane/ethyl acetate (70/30) as eluent. Oil.

^{13}H NMR ($CDCl_3$) δ 0.12 (s, 9H, $SiMe_3$), 1.16 (s, 6H, CH_3), 2.07 (s, 3H, H-6), 2.36 (d, 1H, $J = 15.8$ Hz, H-4), 2.37 (s, 1H, H-2), 2.78 (d, 1H, $J = 15.8$ Hz, H-4′); ^{13}C NMR ($CDCl_3$) δ 0.22, 27.42, 28.02, 32.19, 35.86, 48.68, 53.85, 180.84, 208.45.

IR (KBr): 1718 (C=O acid), 1683 (C=O ketone). MS: $MH^+ = 231$. Anal. Calc. for $C_{11}H_{22}O_3Si$: C, 57.35; H, 9.63. Found: C, 57.57; H, 9.40.

*4.2.13. 2-(3-Oxocyclohexyl)-2-trimethylsilylethanoic acid (**5d**)*

The two diastereoisomers were separated by column flash chromatography using cyclohexane/ethyl acetate (90/10) as eluent.

4.2.13.1. Isomer I. Oil: ^{13}H NMR ($CDCl_3$) δ 0.08 (s, 9H, $SiMe_3$), 1.43–2.50 (m, 10H); ^{13}C NMR ($CDCl_3$) δ −1.62, 24.87, 30.91, 38.06, 40.74, 44.04, 47.27, 180.14, 210.87.

IR (KBr): 1716 (C=O acid), 1685 (C=O ketone). MS: $MH^+ = 229$. Anal. Calc. for $C_{11}H_{20}O_3Si$: C, 57.85; H, 8.83. Found: C, 57.50; H, 8.72.

4.2.13.2. Isomer II. Oil: ^{13}H NMR ($CDCl_3$) δ 0.09 (s, 9H, $SiMe_3$), 1.43–2.50 (m, 10H); ^{13}C NMR ($CDCl_3$) δ −1.67, 24.63, 31.02, 37.99, 40.89, 44.29, 47.56, 180.40, 211.03.

IR (KBr): 1716 (C=O acid), 1685 (C=O ketone). MS: $MH^+ = 229$. Anal. Calc. for $C_{11}H_{20}O_3Si$: C, 57.85; H, 8.83. Found: C, 57.39; H, 8.61.

4.2.14. 2-[3′-Oxocyclohexyl-2-(3-oxocyclohexyl)]-2-trimethylsilyl acid (**6d**)

Column flash chromatography was done using cyclohexane/ethyl acetate (70/30) as eluent. White powder.

^{13}H NMR ($CDCl_3$) δ 0.12 (s, 9H, $SiMe_3$), 0.79–2.40 (m, 18H); ^{13}C NMR ($CDCl_3$) δ −1.5, 22.4, 23.2, 25.1, 29.2, 37.8, 38.9, 39.1, 39.8, 41.1, 45.7, 179.9, 210.7, 213.4.

MS: $MH^+ = 325$.

4.3. Reduction of δ-keto-α-trimethylsilyl acids **5a**

1.2 mmol of *syn* **5a** (0.335 g) is dissolved in ethanol (6 mL) and the solution cooled at 0 °C. Sodium borohydride (0.054 g, 1.44 mmol) is added portionwise. The mixture is then stirred for 1.5 h at this temperature and hydrolyzed by 5 mL of hydrochloric acid 1 M. The alcohol is removed under reduced pressure and the resulting aqueous layer is extracted by ethyl acetate (3×20 mL). The organic layer is dried over magnesium sulphate and the solvent is removed under reduced pressure.

When **5a** *anti* is reduced, the resulting lactones **8a** are separated by flash chromatography using a mixture of ethyl acetate/ cyclohexane (10/90) as eluent.

4.3.1. 5-Hydroxy-3-phenyl-2-trimethylsilyl hexanoic acid (**7a**)

White powder; mp = 149–151 °C.

^{13}H NMR (acetone-d_6) δ −0.21 (s, 9H, $SiMe_3$), 1.16 (d, 3H, $J = 6.15$ Hz, CH_3), 1.85 (ddd, 1H, $J = 4.12$ Hz, $J = 7.44$ Hz, $J = 11.6$ Hz, H-4), 1.99 (ddd, 1H, $J = 5.57$ Hz, $J = 11.6$ Hz, $J = 13.27$ Hz, H-4′), 2.42 (d, 1H, $J = 11.6$ Hz, H-2), 3.12 (ddd, 1H, $J = 11.60$ Hz, $J = 4.1$ Hz, H-3), 3.48 (m, 1H, H-5), 7.2–7.4 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ −1.9, 22.4, 42.9, 46.0, 48.22, 65.4, 127.5, 129.2, 129.4, 144.0, 176.0.

IR (KBr): 1718 (C=O acid). MS: $M^{\cdot +} = 280$. Anal. Calc. for $C_{15}H_{24}O_3Si$: C, 64.24; H, 8.63. Found: C, 64.57; H, 8.31.

4.3.2. 6-Methyl-4-phenyltetrahydropyran-2-one (**8a**)

4.3.2.1. Anti. Oil: ^{13}H NMR ($CDCl_3$) δ 1.39 (d, 3H, $J = 6.3$ Hz, CH_3), 2.02 (m, 2H, H-5), 2.74 (m, 2H, H-3), 3.33 (m, 1H, H-4), 4.53 (m, 1H, H-6), 7.13–7.35 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ 21.2, 34.6, 35.8, 36.7, 73.8, 126.6, 127.0, 128.9, 143.0, 171.7.

IR (KBr): 1733 (C=O). MS: $MH^+ = 191$. Anal. Calc. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.32; H, 7.66.

4.3.2.2. Syn. Oil: ^{13}H NMR ($CDCl_3$) δ 1.42 (d, 3H, $J = 6.28$ Hz, CH_3), 1.70 (m, 1H, H-5), 2.13 (m, 1H, H-5), 2.50 (dd, 1H, $J = 17.8$ Hz, $J = 11.5$ Hz, H-3), 2.87 (ddd, 1H, $J = 17.8$ Hz, $J = 5.9$ Hz, $J = 2.0$ Hz, H-3), 3.16 (m, 1H, H-4), 4.54 (m, 1H, H-6), 7.12–7.38 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ 21.9, 37.4, 37.6, 38.0, 73.9, 126.5, 127.2, 129.0, 143.0, 170.9.

IR (KBr): 1734 (C=O). MS: $MH^+ = 190$. Anal. Calc. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.32; H, 7.65.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.jorganchem.2005.01.049.

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