A New Method for the Synthesis of Normal and Medium Ring Silylated Unsaturated Thiolactones

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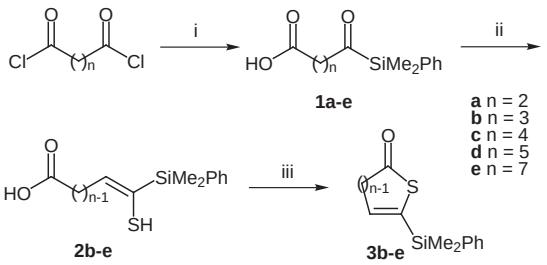
Abstract: Enolizable ω-carboxy acylsilanes are converted *via* (*Z*)-ω-carboxy-α-silyl enethiols into unsaturated silylated thiolactones having a ring size in the range from five to ten.

Key words: ω-carboxy acylsilanes, (*Z*)-ω-carboxy-α-silyl enethiols, thiolactones, polyphosphate esters

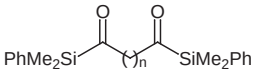
Thiolactones present a particular interest due to the biological activity associated with a number of derivatives such as thiolactomycin,[1] thiotetromycin,[1] thiocoumarins[2] and α_2-macroglobulin.[3] Moreover, the resolution of the crucial problem concerning the alkylation of β-[4] and γ-thiolactones,[5] has considerably increased their utility in synthesis. Despite the importance of this class of compounds, relatively little attention has been given to their preparation. A general approach to γ- and δ-thiolactones has been developed starting from bismetallated derivatives of thioacids and carbonyl compounds.[6] The thioaldeyde Diels-Alder approach provides an access to unsaturated δ-thiolactones[7] and the reaction of *S*-(4-alkenyl)-dithiocarbonates with tri-*n*-butyltin hydride affords γ-thiolactones.[8] More recently, it has been reported[9] that ω-halo acid chlorides give a sulfur transfer reaction, mediated by benzyltriethylammonium tetrathiomolybdate, leading to saturated thiolactones. However, this method does not give satisfactory yields especially in the case of macrocycles (ring size ≥ 12) and the synthesis of mesocycles (ring size in the range 8 to 11) has not been reported.

In connection with our ongoing interest in the chemistry of enolizable thioacylsilanes as a source of sulfur heterocycles,[10] we pursued a new method for the preparation of unsaturated silylated thiolactones **3**, starting from acyl dichlorides *via* acylsilanes **1** and (*Z*)-ω-carboxy-α-silyl enethiols **2** (Scheme 1).



Scheme 1 i) $(PhMe_2Si)_2CuCNLi_2$, THF, -78°C, 1h; ii) H_2S/HCl, Et_2O, -20°C, then solid $NaHCO_3$, r.t.; iii) PPE, $CHCl_3$, r.t. or 40°C.

In the past we developed[10b,11] a generally applicable method for the synthesis of acylsilanes, based on the nucleophilic silylation of an acid chloride with bis(dimethylphenylsilyl)lithium cyano cuprate[12] at -78°C. Following this procedure, starting from commercially available acyl dichlorides and one equivalent of bis(dimethylphenylsilyl)lithium cyano cuprate, we prepared ω-carboxy acylsilanes **1**[13] in moderate yields (Table), due to the competitive formation of the bis(acyl)silanes **4**, obtained in yields ranging from 10% to 13%.



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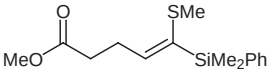

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We have already reported that acylsilanes, containing a hydrogen atom α to the carbonyl group, can be transformed stereoselectively into (*Z*)-α-silyl enethiols[14] by thionation at low temperature with hydrogen sulfide and hydrogen chloride followed by neutralization of the ethereal solution with solid sodium hydrogencarbonate. With this procedure[15] compounds **1** were transformed into (*Z*)-ω-carboxy-α-silyl enethiols **2** in very good yields (Table). The (*Z*)-stereochemistry has been assigned to enethiols **2** by n.O.e. experiments performed on methyl 5-[dimethyl(phenyl)silyl]-5-(methylsulfanyl)-4-pentenoate **5**,[16] obtained from **2b** by reaction with MeI and K_2CO_3 in acetone.

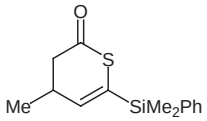
The cyclization can be performed by using polyphosphate ester (PPE) as a condensation reagent, very easily prepared from phosphorus pentoxide and ether.[17] The condensation, carried out[18] both at room temperature and at 40°C, gave the better yields in thiolactones **3** under the latter condition (Table) probably due to the shorter time required for the reaction.

The best yields were obtained in the synthesis of δ- and ε-thiolactones (Table, entries 2 and 3). Starting from 3-methyl glutaryl chloride also the methyl substituted thiolactone **6** could be obtained, working at 40°C, in 85% yield.[20]

Table:[19] Yields of **1**, **2** and **3**

Entry	1-3	Yield (%)				Ring
		1[a,b]	2[a]	3[a] (r.t.[d])	3[a] (40°C[e])	size
1	**a**	15	c	-	-	5
2	**b**	43	75	60	80	6
3	**c**	42	82	51	61	7
4	**d**	41	86	32	52	8
5	**e**	40	85	36	55	10

[a] Yields of pure isolated products. [b] Obtained beside bis(acyl)silanes **4** (see experimental). [c] See text. [d] Reaction time: 12h. [e] Reaction time: 2-4 h.



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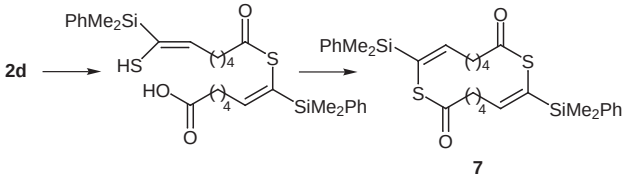
It is known that medium ring compounds are much more difficult to synthesize by cyclization methods than other cyclic compounds including macrocycles.[21] Also in our case the cyclization to eight-and ten-membered rings (Table, entries 4 and 5, respectively), gave to some extent lower yields under the conditions employed.[22] The reaction leading to the 8-membered ring, performed at room temperature, gave the competitive formation of a dimeric product, to whom structure **7** has been assigned on the basis of its spectral data.[23] The formation of a dimeric product is in agreement with other results obtained during the synthesis of 2-silyl-thiacyclooct-2-ene[10c] and of medium rings in general,[24] and can be rationalized through a dimerization of **2d** followed by an intramolecular cyclization to a sixteen-membered ring **7** (Scheme 2).



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Scheme 2

The synthesis of the 5-membered ring thiolactone **3a** proved to be difficult. In fact the ω-carboxy acylsilane **1a**, deriving from succinyl dichoride was obtained in very poor yield (Table, entry 1), besides a large amount of succinic acid and some degradation products. Moreover, the thionation did not afford the expected enethiol **2a** but the thiolactone **8**[25] arising probably from a direct cyclization of **2a**, followed by desilylation and migration of the double bond in the α,β-position.

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The sequence of the events and a mechanistic explanation for the formation of **8** are still under investigation.

In conclusion, this protocol can be successfully applied not only to the synthesis of unsaturated silylated thiolactones having a ring size of six and seven, but also to the synthesis of medium ring thiolactones with a ring sizes in the range 8 to 11 and to the synthesis of thiolactones bearing a substituent. Further optimization of the reaction conditions for the synthesis of acylsilanes **1** and the extension of this strategy towards the synthesis of macrocycles are currently under way.

Acknowledgement

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(12) Fleming, I.; Newton, T.W.; Roessler, F. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2527.
(13) *General procedure for the preparation of* **1**: bis(dimethyl phenylsilyl)copper-cyano cuprate (5.0 mmol) was added slowly at -78 °C under argon to a solution of acyl dichloride (5.0 mmol) in anhydrous THF (5 mL) *via* cannula. The mixture was stirred at -78 °C for 1 h, then was allowed to warm to 0 °C and was stirred for 1 h at 0 °C. The mixture was quenched with saturated aqueous ammonium chloride and extracted with diethyl ether. The organic layer was dried and concentrated under reduced pressure. Column chromatography on silica gel (light petroleum-diethyl ether 5:1 and 1:1 as eluent) gave, as the higher R_f fraction, a product arising from the silylcuprate,

as the second R_f fraction bis(acyl)silane **4** as a yellow oil and as the lower R_f fraction the ω-carboxy acylsilane **1** as a yellow oil.

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(15) *General procedure for the preparation of* **2**: hydrogen chloride and hydrogen sulfide were bubbled into a solution of the ω-carboxy acylsilane **1** (1.0 mmol) in anhydrous diethyl ether (50 mL) at -20 °C, until the starting acylsilane had disappeared (TLC with 1:1 light petroleum-diethyl ether as eluent). The mixture was allowed to warm to room temperature and solid sodium hydrogen carbonate was added to the solution until the evolution of carbon dioxide ceased (10 g), then the reaction was left overnight. The crude, filtered and concentrated under reduced pressure, gave the (*Z*)-ω-carboxy-α-silyl enethiol **2** in a pure form.

(16) **5:** To a solution of **2b** (1 mmol) in acetone (5 mL), solid oven-dried K_2CO_3 (1.5 mmol) and the methyl iodide (2.5 mmol) were added. The mixture was stirred at room temperature for 3h then quenched with water and extracted with diethyl ether. The organic layer was dried and concentrated. Column chromatography on silica gel (light petroleum-ethyl acetate 15:1 as eluent) gave the title product in 65% yield as an oil. I.R. (CCl_4) ν_{max}, cm^{-1}: 1740 (COOMe), 1430 (SiPh), 1260 ($SiMe_2$), 1110 (SiPh); ^{1}H-NMR (200 MHz, $CDCl_3$) δ, ppm: 0.42 (6H, s, $SiMe_2$), 2.0 (3H, s, SMe), 2.45 (2H, t, *J* 7.5 Hz, CH_2), 2.7 (2H, m, CH_2), 3.68 (3H, s, OCH_3), 6.15 (1H, t, *J* 6.0 Hz, vinylic CH), 7.30-7.60 (5H, m, ArH); ^{13}C-NMR (50.28 MHz, $CDCl_3$) δ, ppm: -2.12 ($SiMe_2$), 17.61 (SCH_3), 25.89, 33.20 (CH_2), 51.43 (OCH_3), 127.77, 129.14, 133.90 (ArCH), 145.19 (vinylic CH), 133.02, 138.1 (ArC + vinylic C), 173.29 ($COOCH_3$); MS (m/z): 294 (M^+), 247 (M^+-SCH_3), 135 ($SiMe_2Ph$). Irradiation of the dimethylsilyl signal at 0.62 ppm produced a significant increase (15%) of the intensity of the signal of the vinylic proton at 6.18 ppm.

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(18) *General procedure for the preparation of* **3**: a mixture of (*Z*)-ω-carboxy-α-silyl enethiol **3** (0.5 mmol) and PPE (1 mL) in $CHCl_3$ (8 mL) was stirred at room temperature for 12h or at 40°C for 2h. The reaction mixture was treated with saturated aqueous ammonium chloride and extracted with chloroform. The organic layer was dried with sodium sulfate and concentrated under reduced pressure. Column chromatography on silica gel (light petroleum-ethyl acetate 10:1 as eluent) gave the title product as a yellow oil.

(19) All new compounds gave spectroscopic data in agreement with the assigned structures. Selected data for **1**, **2**, **3**, **4**:
1b: I.R. (CCl_4) ν_{max}, cm^{-1}: 3520 (OH), 1710 (COOH), 1645 ($COSiMe_2Ph$), 1430 (SiPh), 1260 ($SiMe_2$), 1110 (SiPh); ^{1}H-NMR (300 MHz, $CDCl_3$) δ, ppm: 0.50 (6H, s, $SiMe_2$), 1.5 (2H, m, CH_2), 2.2 (2H, t, *J* 7.3 Hz, CH_2), 2.6 (2H, t, *J* 7.3 Hz, CH_2), 7.4-7.8 (5H, m, ArH); ^{13}C-NMR (50.28 MHz, $CDCl_3$) δ, ppm: -4.33 ($SiMe_2$), 17.67 (CH_2), 33.52 (CH_2COOH), 47.81 ($CH_2COSiMe_2Ph$), 128.56, 130.52, 134.65 (ArCH), 129.86 (ArC), 179.71 (COOH), 245.62 ($COSiMe_2Ph$); MS (m/z): 250 (M^+), 233 (M^+-H_2O), 205 (M^+-COOH), 163 ($COSiMe_2Ph$), 135 ($SiMe_2Ph$), 115 (M^+-$SiMe_2Ph$).
2b: I.R. (CCl_4) ν_{max}, cm^{-1}: 3540 (OH), 1720 (COOH), 1430 (SiPh), 1260 ($SiMe_2$), 1110 (SiPh); ^{1}H-NMR (200 MHz, $CDCl_3$) δ, ppm: 0.42 (6H, s, $SiMe_2$), 2.52 (5H, m, SH + 2 CH_2), 5.92 (1H, m, vinylic H), 7.3-7.65 (5H, m, ArH), 9.0 (1H, bs, OH); ^{13}C-NMR (50.28 MHz, $CDCl_3$) δ, ppm: -3.36 ($SiMe_2$), 25.41, 32.69 (CH_2), 127.90, 129.49, 134.06, 136.93 (3ArCH + vinylic CH), 133.2, 137.2 (ArC + vinylic C), 179.07 (COOH); MS (m/z): 266 (M^+), 248 (M^+-H_2O), 233 (248-CH_3), 135 ($SiMe_2Ph$).
3b: I.R. (CCl_4) $\boldsymbol{\nu}_{max}$, cm^{-1}: 1680 (COS), 1430 (SiPh), 1250 ($SiMe_2$), 1130 (SiPh); ^{1}H-NMR (200 MHz, $CDCl_3$) **δ**, ppm: 0.48 (6H, s, $SiMe_2$), 2.55 (4H, m, $2CH_2$), 6.38 (1H, m, vinylic H), 7.35-7.45 (3H, m, ArH), 7.50-7.65 (2H, m, ArH); ^{13}C-NMR (50.28 MHz, $CDCl_3$) **δ**, ppm: -3.37 ($SiMe_2$), 25.53, 38.02 (CH_2), 127.94, 129.69, 132.75, 133.95 (3ArCH + vinylic CH), 134.88, 135.48 (ArC + vinylic C), 200.33 (COS); MS (m/z): 248 (M^+) 233 (M^+- CH_3), 215 (M^+- SH), 191 (M^+-C_3H_5O), 171 (M^+-C_6H_5), 135($SiMe_2Ph$).
3d: I.R. (CCl_4) $\boldsymbol{\nu}_{max}$, cm^{-1}: 1675 (COS), 1430 (SiPh), 1250 ($SiMe_2$) 1110 (SiPh); ^{1}H-NMR (300 MHz, $CDCl_3$) δ, ppm: 0.44 (6H, s, $SiMe_2$), 1.65 (4H, m, $2CH_2$), 2.25 (2H, m, CH_2), 2.48 (2H, t, CH_2), 6.57 (1H, t, *J* 7.2 Hz, vinylic H), 7.30-7.40 (3H, m, ArH), 7.50-7.65 (2H, m, ArH); ^{13}C-NMR (75.4 MHz, $CDCl_3$) δ, ppm: -3.79 ($SiMe_2$), 24.53, 24.88, 29.74, 38.97 (CH_2), 127.91, 129.55, 134.00 (ArCH), 150.96 (vinylic CH), 132.83, 135.73 (ArC + vinylic C), 205.48 (COS); MS (m/z): 276 (M^+) 261 (M^+- CH_3), 247 (M^+- COH), 135 ($SiMe_2Ph$).
4b: I.R. (CCl_4) ν_{max}, cm^{-1}: 1640 ($COSiMe_2Ph$), 1430 (SiPh), 1240 ($SiMe_2$), 1110 (SiPh); ^{1}H-NMR (300 MHz, $CDCl_3$) δ, ppm: 0.5 (6H, s, $SiMe_2$), 1.65 (2H, m, CH_2), 2.5 (4H, t, *J* 7.1 Hz, $2CH_2$), 7.3-7.6 (5H, m, ArH); ^{13}C-NMR (75.4 MHz, $CDCl_3$) δ, ppm: -4.17 ($SiMe_2$), 15.44 (CH_2), 48.34 ($CH_2COSiMe_2Ph$), 128.81, 130.53, 134.60 (ArCH), 129.48 (ArC), 245.71 ($COSiMe_2Ph$); MS (m/z): 368 (M^+), 233 (M^+-$SiMe_2Ph$), 163 ($COSiMe_2Ph$), 135 ($SiMe_2Ph$).

(20) **6**: oil; I.R. (CCl_4) $\boldsymbol{\nu}_{max}$, cm^{-1}: 1690 (COS), 1430 (SiPh), 1250 ($SiMe_2$), 1130 (SiPh); ^{1}H-NMR (300 MHz, $CDCl_3$) **δ**, ppm: 0.48 (6H, s, $SiMe_2$), 1.15 (3H, d, *J* 7.1 Hz, CH_3), 2.35 (1H, dd, J_1 15.18, J_2 11.25 Hz, H_a-CH_2), 2.61 (1H, dd, J_1 15.48, J_2 4.27 Hz, H_b-CH_2), 2.75 (1H, m, CH), 6.22 (1H, d, *J* 3.7 Hz, vinylic H), 7.35-7.45 (3H, m, ArH), 7.50-7.65 (2H, m, ArH); ^{13}C-NMR (75.4 MHz, $CDCl_3$) δ, ppm: -1.98 ($SiMe_2$), 19.52 (CH_3), 31.96 (CH), 45.75 (CH_2), 127.93, 129.75, 132.05 (ArCH), 123.61, 135.83 (ArC + vinylic C), 139.53 (vinylic CH), 200.03 (COS); MS (m/z): 262 (M^+) 247 (M^+- CH_3), 215 (M^+-SH), 205 (M^+- C_3H_5O), 185 (M^+-C_6H_5), 135($SiMe_2Ph$).

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(22) In the attempt of improving the yields of mesocycles, we performed the cyclization in high dilution conditions, by adding slowly products **2d** and **2e** to a solution of the polyphosphate ester in $CHCl_3$, but the reactions failed and we isolated only undesired products among which were the ethyl esters of **2d** and **2e**.

(23) **7**: p.f. = 133-134°C (from methanol); I.R.(CCl_4) $\boldsymbol{\nu}_{max}$, cm^{-1}: 1700 (COS), 1430 (SiPh), 1250 ($SiMe_2$) 1110 (SiPh); ^{1}H-NMR (300 MHz, $CDCl_3$) δ, ppm: 0.34 (6H, s, $SiMe_2$), 1.35 (2H, m, CH_2), 1.62 (2H, m, CH_2), 2.18 (2H, m, CH_2), 2.50 (2H, t, *J* 7.0 Hz, CH_2), 6.52 (1H, t, *J* 7.26 Hz, vinylic H), 7.30-7.40 (3H, m, ArH), 7.50-7.65 (2H, m, ArH); ^{13}C-NMR (75.4 MHz, $CDCl_3$) δ, ppm: -3.03 ($SiMe_2$), 24.57, 27.36, 30.72, 42.97 (CH_2), 127.68, 129.17, 134.14 (ArCH), 155.49 (vinylic CH), 134.05, 137.23 (ArC + vinylic C), 197.23 (COS); MS (m/z): 552 (M^+) 537 (M^+- CH_3), 135 ($SiMe_2Ph$).

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