α-Silylation of Lithium Ester Enolates
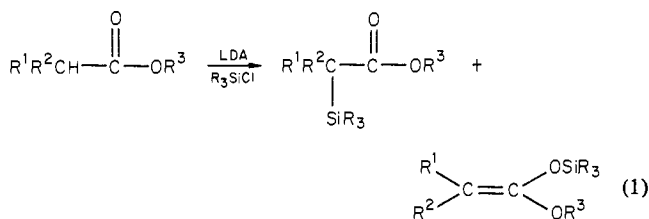
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The synthetic utility of α-silylated esters and lactones has been amply demonstrated.[1,2] Although these systems have been generated in a variety of ways, the majority of these preparations suffer from less than readily available starting materials and/or a lack of generality.[3] The most general current route to these interesting systems involves the reaction of trimethylsilyl triflate with esters or lactones to give the α-trimethylsilyl esters in moderate to good yield with some contamination from O-silylated and bis-silylated products.[4] In addition, Grieco and co-workers[2a] have prepared α-(trimethylsilyl)-γ-butyrolactones via the reaction of the dilithium salt of α-(trimethylsilyl)acetic acid with epoxides followed by lactonization.

An obvious desirable entry into α-silyl esters and lactones would be the direct C-silylation of ester enolates, particularly the readily available lithium ester enolates.[5] All reports to date on the silylation of ester enolates have shown that the predominant product is that of O-silylation[6,7] (eq 1). The two exceptions to

$$R^1R^2CH\!\!-\!\!\overset{\overset{\displaystyle O}{\|}}{C}\!\!-\!\!OR^3 \xrightarrow[R_3SiCl]{LDA} R^1R^2C\!\!-\!\!\overset{\overset{\displaystyle O}{\|}}{C}\!\!-\!\!OR^3 \ + $$

$$\underset{R^2}{\overset{R^1}{>}}C\!=\!C\!\underset{OR^3}{\overset{OSiR_3}{<}} \qquad (1)$$

this general observation are acetates,[6a,c] particularly *tert*-butyl acetates ($R^1 = R^2 = H$; $R^3 = t$-Bu), which can be attributed to a larger steric effect in the O-silylated material than in the C-silylated isomer, and esters of cyclopropane carboxylic acid[6d] ($R^1 = R^2 = CH_2$), which can be explained by the strain of the double bond in the O-silylated isomer. No good examples of C-silylation of the enolates of α-substituted esters have been reported to date.[7]

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
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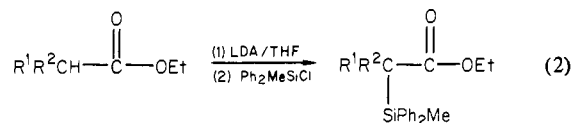
(7) The preparation of ethyl 2-(trimethylsilyl)-2-methylpropionate from the sodium enolate of ethyl 2-methyl-1-propionate has been reported, but this seems doubtful since the product was readily solvolyzed by ethanol, a reaction consistent with the O-silylated isomer but not the C-silylated product. Hance, C. R.; Hauser, C. R. *J. Am. Chem. Soc.* **1953**, *75*, 994.

Table I. Products and Yields of the Diphenylmethylsilylation of Lithium Ester Enolates in THF

entry	ester	product[a]	yield,[b] %
1	CH_3CO_2-t-Bu	$Ph_2MeSiCH_2CO_2$-t-Bu (1)	91.1
2	CH_3CO_2Et	$Ph_2MeSiCH_2CO_2Et$ (2)	93.1
3	$CH_3CH_2CO_2Et$	$Ph_2MeSiCHCO_2Et$ (3) $\vert$ CH_3	93.3
4	$PhCH_2CO_2Et$	$Ph_2MeSiCHCO_2Et$ (4)[10] $\vert$ Ph	50[c]
		$PhCH{=}C(OEt)(OSiPh_2Me)$ (5)[10]	50[c]
5	(γ-butyrolactone)	(6, α-SiMePh_2 lactone)	94.9
6	(α-Me γ-butyrolactone)	(7, α-SiMePh_2, α-Me lactone)	85[c]
7	(δ-valerolactone)	(8, α-SiMePh_2 lactone)	93.9
8	$(-)$-α-NpPhMeSiCl	$(+)$-α-NpPhMeSiCH_2COEt (9)	83.5

[a] All products were characterized by ^{1}H NMR, ^{13}C NMR, IR, mass spectra, and C, H analysis (C ±0.17%; H ±0.05%).[18] [b] Isolated yield after chromatography on silica gel. [c] Yield of the crude material.

We felt that it should be possible to influence the regiochemistry of the silylation by changing the nature of the silylating agent and wish to report herein on the successful synthesis of α-diphenylmethylsilyl esters and lactones based on the above concept. The success of the procedure lies in the use of the silylating agent, diphenylmethylchlorosilane (eq 2). We feel that the difference

$$R^1R^2CH\!\!-\!\!\overset{\overset{\displaystyle O}{\|}}{C}\!\!-\!\!OEt \xrightarrow[(2)\ Ph_2MeSiCl]{(1)\ LDA/THF} R^1R^2C\!\!-\!\!\overset{\overset{\displaystyle O}{\|}}{C}\!\!-\!\!OEt \qquad (2)$$
$$\underset{SiPh_2Me}{}$$

in the regiochemistry shown by the diphenylmethylsilyl group as opposed to the trimethyl or *tert*-butyldimethylsilyl groups is due to its being a softer acid and therefore more reactive toward the carbon terminus of the ambident nucleophile.[8] The fact that the reaction is essentially quantitative and much faster than the reaction with *tert*-butyldimethylchlorosilane[9] rules against an argument involving steric effects. The results are shown in Table I.

Reaction of ethyl lithiopropionate with diphenylmethylchlorosilane followed by an aqueous workup and elution chromatography on silica gel gave ethyl 2-(diphenylmethylsilyl)-propionate in excellent yield. The same reaction with 20% HMPA added as cosolvent and a nonaqueous workup gave a 60:40 mixture of O- and C-silylated material in greater than 95% overall yield (^{1}H NMR). Thus, the use of HMPA as cosolvent leads to considerable O-silylation. When ethyl lithiopropionate was quenched at −78 °C with phenyldimethylchlorosilane in THF followed by a nonaqueous workup, a 60:40 mixture of O- and C-silylated material was obtained in 94% overall yield. This indicates that at least two phenyl groups on the silicon are required to completely direct the silylation toward carbon.

Although the C-silylation of the lithium enolate of ethyl propionate proceeds without problem, the reaction with ethyl lithiophenylacetate (entry 4) gives an equimolar mixture of C- and
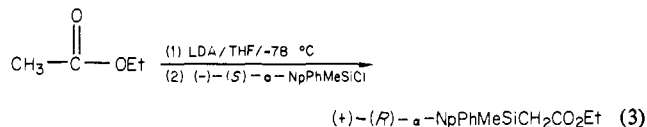
(8) Several studies indicate that aryl groups attached to silicon donate electron density to the silicon via p_π–d_π overlap. This would lower the positive charge density on silicon and make it a softer acid. Among them: Nagy, J.; Réffy, J. *J. Organomet. Chem.* **1970**, *23*, 71. Angelelli, J. M.; Maire, J. C.; Vignollet, Y. *Ibid.* **1970**, *22*, 313.

(9) Rathke and Sullivan[6a] have reported that *tert*-butyldimethylchlorosilane reacts very slowly with lithium ester enolates in THF in the absence of HMPA.

O-silylated material, **4** and **5**, respectively in quantitative yield (crude product). Moreover it was not possible to purify the desired C-silylated isomer (**4**) due to either decomposition or hydrolysis during all attempts.[10]
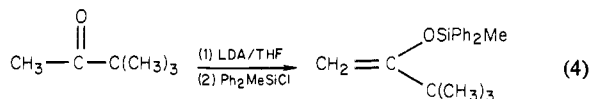
The C-silylation of butyrolactone and valerolactone proceeds exceedingly well to give the C-silylated lactones in high isolated yield. However, the product from the reaction with α-methyl butyrolactone (**7**) proved impossible to purify without the occurrence of decomposition or hydrolysis.[11]

The displacement of the chloride on silicon by the enolate ion occurs with inversion of configuration at silicon as seen by entry **8**[12] (eq 3). This inversion of configuration at silicon is expected

$$CH_3-\overset{\overset{O}{\|}}{C}-OEt \xrightarrow[\text{(2) } (-)-(S)-\alpha-NpPhMeSiCl]{\text{(1) LDA/THF/-78 °C}}$$

$$(+)-(R)-\alpha-NpPhMeSiCH_2CO_2Et \quad (3)$$

on the basis of Sommer's results on the nucleophilic displacement of the chloride leaving group from silicon.[14] Thus, we now have a route to α-silylated esters optically active at silicon from ester lithium enolates.

Finally, an attempt to prepare 1-(diphenylmethylsilyl)-3,3-dimethyl-2-butanone via diphenylmethylsilylation of the lithium enolate of pinacolone gave only the enol silyl ether in 90% isolated yield (eq 4). Thus under the present conditions the reaction does

$$CH_3-\overset{\overset{O}{\|}}{C}-C(CH_3)_3 \xrightarrow[\text{(2) } Ph_2MeSiCl]{\text{(1) LDA/THF}} CH_2=C\overset{OSiPh_2Me}{\underset{C(CH_3)_3}{}} \quad (4)$$

not serve to C-silylate the lithium enolates of ketones.[15]

The silylation of ethyl propionate is representative of the general procedure. A dry, 100 mL, round-bottom flask equipped with magnetic stirring, cold bath, and a nitrogen inlet was charged with 10 mL of THF, 1.55 mL of diisopropylamine (12.0 mmol) and at -78 °C 6.70 mL (12.0 mmol) of 1.79 M *n*-butyllithium in hexane. The resulting solution was warmed to 25 °C for 15 min, cooled to -78 °C again, and 1.02 g (10.0 mmol) of ethyl propionate in 2 mL of THF added via syringe. The clear solution was stirred for 30 min at -78 °C and 2.33 g (10.0 mmol) of diphenylmethylchlorosilane in 10 mL of THF added dropwise via syringe. The reaction mixture was stirred at -78 °C for 1.5 h, warmed to 25 °C for 2 h, and hydrolyzed with 10 mL of 1.5 N HCl. The organic layer was dried over sodium sulfate, concentrated, and the crude sample purified by flash chromatography[16] on silica gel by utilizing 2% ethyl acetate/hexane to give 2.78 g (93.3%) of ethyl (diphenylmethylsilyl)propionate.

The results presented here should inspire greater use of α-silylated esters and lactones in organic synthesis[17] and a greater

(10) Gentle hydrolysis (H$_2$O/pentane) of a 50:50 mixture of **4** and **5** gave a mixture of ethyl phenylacetate and diphenylmethylsilanol. Attempts to purify **4** by chromatography on a variety of silica gels and florisil at temperatures down to -30 °C resulted in hydrolysis. Kugelrohr distillation resulted in decomposition as did gas chromatography. The mixture of **4** and **5** showed a singlet at δ 3.28 for the α proton of **4** and resonances at δ 4.55 and 4.43 (2:1) for the two isomers of **5**. The IR spectrum showed bands at 1735 and 1650 cm^{-1}.

(11) Chromatography on silica gel or florisil even at low temperature resulted in hydrolysis. Attempted distillation gave decomposition. The NMR spectrum of the crude product showed resonances at δ 3.62 (m) for the oxygenated methylene, 1.22 (s) for the alpha methyl and 0.47 (s) for the silyl methyl group. The IR showed a strong carbonyl band at 1770 cm^{-1}. We have been able to prepare and purify *tert*-butyl 2-(diphenylmethylsilyl)-2-methylpropionate (**10**), by methylation of the lithium enolate of *tert*-butyl 2-(diphenylmethylsilyl)propionate (**11**), in 93.1% yield. **11** was prepared also in 93.1% yield from methylation of the lithium enolate of **1**.

(12) Compound **9** showed $[\alpha]_D$ -4.69° (c 10.75, cyclohexane) which compared to Brook's $[\alpha]_D$ +4.65° for the compound formed from the reaction of (+)-α-naphthylphenylmethylchlorosilane and ethyl diazoacetate.[13]

(13) Brook, A. G.; Duffand, J. M.; Anderson, D. G. *J. Am. Chem. Soc.* **1972**, *92*, 7567.

(14) Sommer, L. H. "Stereochemistry, Mechanism and Silicon"; McGraw-Hill: New York, 1965.

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(16) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

appreciation of the potential of the electronic nature of a silicon moiety as opposed to the more commonly invoked steric factors.

(17) Studies related to the utility of α-silylated esters in synthesis are under way in our laboratory. Treatment of the lithium enolate of **2** (LDA/THF/-78 °C) with isobutyraldehyde gives an 85% yield of ethyl 4-methyl-2-butenoate (cis/trans 16:84). 2-(*tert*-butyldimethylsilyloxy)cyclopentanone gave ethyl (2-*tert*-butyldimethylsiloxy-(Z)-cyclopentylidene)acetate in 30% isolated yield. Thus, these α-(diphenylmethylsilyl) esters are useful precursors for a Peterson-type reaction to prepare α,β-unsaturated esters.

(18) **1**: ^{1}H NMR (CCl$_4$, Me$_4$Si) δ 7.1 (m, 10 H), 2.14 (s, 2 H), 1.13 (s, 9 H), 0.62 (s, 3 H); ^{13}C NMR (CDCl$_3$/Me$_4$Si) δ 171.0, 135.0, 134.3, 129.3, 127.6, 79.4 27.7, 25.9, -4.0; IR 1712 cm^{-1}. **2**: ^{1}H NMR (CDCl$_3$/Me$_4$Si) δ 7.58 (m, 4 H), 7.36 (m, 6 H), 3.93 (q, 2 H, J = 7 Hz), 2.40 (s, 2 H), 0.97 (t, 3 H, J = 7 Hz), 0.68 (s, 3 H); ^{13}C NMR (CDCl$_3$/Me$_4$Si) δ 171.9, 134.9, 134.3, 129.5, 127.8, 59.8, 24.8, 13.9, -3.9; IR 1721 cm^{-1}. **3**: ^{1}H NMR (CDCl$_3$, Me$_4$Si) δ 7.60 (m, 4 H), 7.42 (m, 6 H), 3.92 (d, 2 H, J = 7.1 Hz), 2.58 (q, 1 H, J = 8 Hz), 0.59 (d, 3 H, J = 8 Hz), 0.94 (t, 3 H, J = 7.1 Hz), 0.66 (s, 3 H); ^{13}C NMR (CDCl$_3$, Me$_4$Si) δ 175.7, 134.8, 134.3, 129.5, 127.8, 127.7, 59.8, 28.8, 13.9, 11.9, -5.6; IR 1720 cm^{-1}. **6**: ^{1}H NMR (CCl$_4$/Me$_4$Si) δ 7.3 (m, 10 H), 4.28-3.31 (m, 2 H), 2.81-1.80 (m, 3 H), 0.76 (s, 3 H); ^{13}C NMR (CDCl$_3$/Me$_4$Si) δ 179.0, 134.6, 129.8, 127.9, 127.5, 67.1, 28.5, 25.0, -4.7; IR 1765 cm^{-1}. **8**: ^{1}H NMR (CDCl$_3$/Me$_4$Si) δ 7.30 (m, 10 H), 3.90-3.66 (m, 2 H), 2.86-1.40 (m, 4 H), 1.06 (t, 1 H), 0.63 (s, 3 H); ^{13}C NMR (CDCl$_3$/Me$_4$Si) 178.5, 134.8, 129.8, 128.1, 127.9, 75.6, 32.9, 30.4, 21.3, -4.5; IR 1765 cm^{-1}. **9**: ^{1}H NMR (CCl$_4$/Me$_4$Si) δ 6.92-8.02 (m, 12 H), 3.75 (q, 2 H, J = 7 Hz), 2.43 (s, 2 H), 0.80 (t, 3 H, J = 7 Hz), 0.76 (s, 3 H); IR 1735 cm^{-1}. $[\alpha]^{25}_D$ -4.69° (c 2.13, cyclohexane). Brook and co-workers[13] report +4.65° for the other enantiomer.

Indole Alkaloid Synthesis via Claisen Rearrangement. Total Synthesis of Secodine[1]

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It has been over a decade since dehydrosecodine (**1**) was postulated[2] as a key intermediate both in the later stages of the biosynthesis of *Aspidosperma* and *Iboga* alkaloids[3] and in the biomimetic interconversion of certain alkaloids.[4] To date, presumably due to its inherent lability, **1** has not been isolated from natural sources or synthesized as a discrete, isolable substance; however, a number of more highly reduced alkaloids related to **1** have been isolated from *Rhazya* species.[5] These alkaloids include secodine (**2**), 16,17-dihydrosecodin-17-ol (**3**), and 16,17-dihydrosecodine (**4**).[5]

We now wish to report the total synthesis of **2**, utilizing a synthetic strategy which is based upon the Claisen ortho ester

† Fellow of the Alfred P. Sloan Foundation, 1980-1982.
‡ Chevron Graduate Fellow, 1980.

(1) Synthesis via Sigmatropic Rearrangements. 6. For previous paper in this series, see: Raucher, S.; Burks, J. E., Jr.; Hwang, K.-J.; Svedberg, D. P. *J. Am. Chem. Soc.* **1981**, *103*, 1853.

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