Reactions of phenyldimethylsilyllithium with β-*N*,*N*-dimethylaminoenones: A convenient synthesis of β-dimethyl(phenyl)silylacrylic acid and its derivatives[1]

Ian Fleming, Elena Marangon, Chiara Roni, Matthew G. Russell, and Sandra Taliansky Chamudis

Abstract: Phenyldimethylsilyllithium reacted with 5,5-dimethyl-3-(*N*,*N*-dimethylamino)cyclohex-2-enone (**7**), 3-(*E*)-*N*,*N*-dimethylaminopropenal (**11**), and 4-*N*,*N*-dimethylaminobut-3-en-2-one (**13**) to give the corresponding β-silyl-α,β-unsaturated carbonyl compounds **8**, **12**, and **14**, in which the dimethylamino group has been displaced by the phenyldimethylsilyl group. Phenyldimethylsilyllithium reacted with ethyl β-*N*,*N*-dimethylaminopropenoate (**15**) by conjugate addition, but, in contrast to the ketones **7** and **13** and the aldehyde **11**, the intermediate enolate **16** was *C*-protonated in the aqueous work-up to give ethyl 3-*N*,*N*-dimethylamino-3-dimethyl(phenyl)silylpropanoate (**17**). When the enolate **16** was instead given a mysteriously brief treatment with methyl iodide before work-up, the product was ethyl 3-(*E*)-dimethy(phenyl)silylpropenoate (**18**). Phenyllithium and methyllithium also added conjugatively to ethyl β-*N*,*N*-dimethylaminoacrylate (**15**) but, in contrast to the silyl case, the intermediate enolate **22** reacted unexceptionally with methyl iodide to give the products **25** and **26** of stereoselective *C*-methylation. This synthesis of the ester **18** was used to synthesize the Oppolzer sultam derivative **30**.

Key words: conjugate addition, elimination, substitution, silyllithium, silylenone.

Résumé : Le phényldiméthylsilyllithium réagit avec la 5,5-diméthyl-3-(*N*,*N*-diméthylamino)cyclohex-2-énone (**7**), le 3-(*E*)-*N*,*N*-diméthylaminopropénal (**11**) et la 4-*N*,*N*-diméthylaminobut-3-én-2-one (**13**) pour conduire à la formation des composés carbonylés β-silyl-α,β-insaturés correspondants, **8**, **12** et **14** dans lesquels le groupe diméthylamino a été remplacé par un groupe phényldiméthylsilyle. Avec le β-*N*,*N*-diméthylaminopropénoate d'éthyle (**15**), le phényldiméthylsilyllithium donne une réaction d'addition conjuguée, mais, par opposition avec ce qui a été observé avec les cétones **7** et **13** et l'aldéhyde **11**, l'intermédiaire énolique **16** la récupération aqueuse des produits provoque une *C*-alkylation qui conduit au 3-*N*,*N*-diméthylamino-3-diméthyl(phényl)silylpropénoate (**17**). Toutefois, lorsque l'énolate **16** est soumis à un mystérieusement court traitement par de l'iodure de méthyle avant la récupération des produits, le produit obtenu est alors le 3-(*E*)-diméthyl(phényl)silylpropénoate d'éthyle (**18**). Le phényllithium et le méthyllithium s'ajoutent aussi de façon conjugue au β-*N*,*N*-diméthylaminopropénoate d'éthyle (**15**) mais, par opposition à ce qui a été observé dans le cas silylé, l'intermédiaire énolique **22** réagit sans surprise avec l'iodure de méthyle pour conduire aux produits **25** et **26** de *C*-méthylation stéréosélective. Cette synthèse de l'ester **18** a été utilisée pour réaliser la synthèse du dérivé sultame d'Oppolzer **30**.

Mots clés : addition conjugue, élimination, substitution, silyllithium, silylénone.

[Traduit par la Rédaction]

Introduction

The phenyldimethylsilyllithium reagent (1) was first made and, along with its triphenylsilyl analogue, quite extensively studied by Gilman in the 1950s and 1960s (2), but it has been relatively little used except as a source of the corresponding cuprate reagent (3), which we introduced in 1978 (4). More recently, we have been engaged in further studies of the silyllithium reagent itself (5), and of its reactions with a number of substrates, including aromatic esters (6), α-silyloxy esters (7), saturated esters (8), amides (9, 10), thioamides (11), nitriles (12), sulfonamides (13), and acid chlorides (14). Most notably, tertiary amides have been a source of several remarkable reactions, which we have to a large

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Dedicated with affection to Professor Ed Piers.

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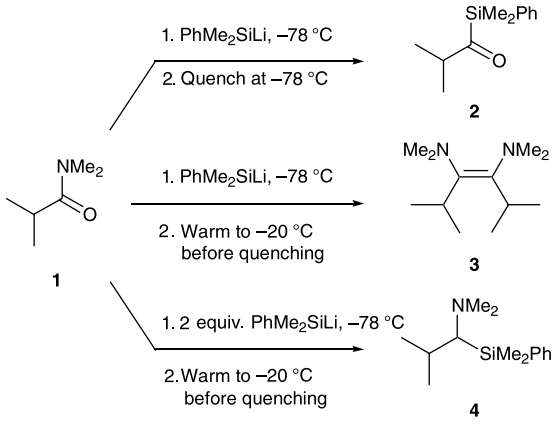
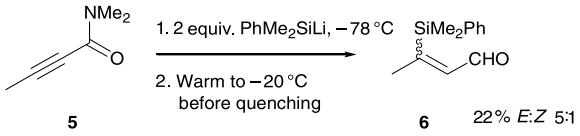
extent unravelled (9, 10). Most strikingly, the simple *N*,*N*-dimethylamide **1** could be induced to give in good yield any one of three distinct products (**2**, **3**, or **4**), depending upon the reaction conditions and (or) the stoichiometry (Scheme 1) (8, 9).

Almost every change we made to the structure of the starting amide led to other surprises, an experience Gilman was not immune to either. Thus, the reaction of the acetylenic amide **5** proved to be different from the saturated amide, not only because conjugate addition was now both possible and what occurred, but also because reduction took place as well, at least in the products **6** that we could recognise (Scheme 2). Conjugate addition is hardly surprising, since silyllithium and stannyllithium reagents can easily react in this way with unsaturated carbonyl compounds in THF (15), although the cuprates are usually rather better, but reduction to an aldehyde had not been a common outcome in our earlier work. The yield, however, was unimpressive, and we did not pursue this unpromising line. More interesting were the results of reactions with vinylogous amide systems, which we reported in a preliminary communication (16), and which we report in full here.

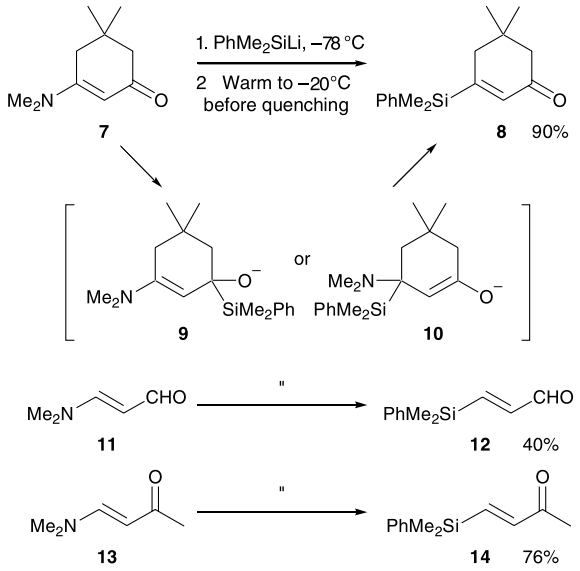
Scheme 1.



Scheme 2.



Scheme 3.



Results and discussion

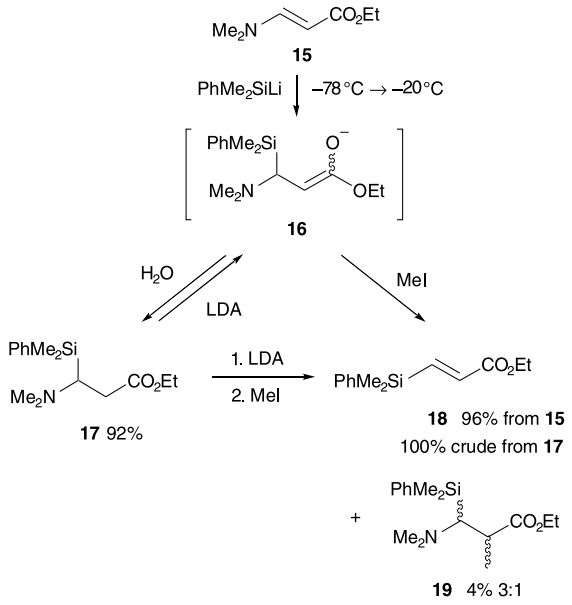
The reaction of phenyldimethylsilyllithium with the enone **7** was unexceptional in giving the β-silylenone **8** in which the dimethylamino group has been replaced by the silyl group (Scheme 3). Two pathways might have been followed. In one, the silyllithium reagent attacked the carbonyl group directly to give the enamine **9**, hydrolysis of which, followed by elimination of water, would give the enone **8**. Alternatively, conjugate attack took place to give the enolate **10**, which underwent elimination of the dimethylamino group. A similar outcome was found for the enal **11** giving the enal **12**, in a less clean reaction with the same two possible pathways. The conjugate addition–elimination pathway is certainly followed in the reaction between the silyllithium reagent and the enone **13**, which gave the β-silylenone **14** in good yield. Furthermore, it is known that a β-amino group encourages conjugate addition by organolithium reagents (17), and trimethylsilyllithium is also known to give conjugate addition, rather than direct attack at the carbonyl group, with cyclohexenones in THF (15). Finally, it is not obvious why the pathway involving direct attack at the carbonyl group should not enter the carbene-forming sequence that we have seen is so accessible in the reactions described earlier, and involved, for example, in the formation of the enediamine **3** and the α-aminosilane **4** (9, 10). It seems likely that the conjugate addition–elimination pathway is followed in all of these reactions.

The products **8**, **12**, and **14** are easily made by other methods (18–20), and so we have not taken this investigation any further. Instead, we investigated the corresponding reaction with the vinylogous carbamate **15**, which gave us a curious result, and, incidentally, a better synthesis of the ester **18** than the one we had been using quite extensively hitherto in our synthetic work.

When we added the silyllithium reagent to the ester **15**, the only product after an aqueous quench was that of conjugate addition **17** (Scheme 4). While this is unsurprising in itself, it raised the first question: why was the dimethylamino group eliminated in the experiments in Scheme 3, and not here? One possibility is that the ketone and aldehyde enolates are kinetically protonated on oxygen. The resultant enols might then live long enough to expel the dimethylamino group in the aqueous medium before they underwent tautomerism to the ketones or the aldehyde. In contrast, it is possible that the ester enolate is protonated directly on carbon, and the dimethylamino group would not then be so easily lost.

However, this was not the most puzzling observation. If, instead of the aqueous quench, we added methyl iodide, and then worked up in the usual way, the major product was the β-silylester **18**. This was not the result that we expected, because the carbon atom of the enolate ion **16** ought to have

Scheme 4.

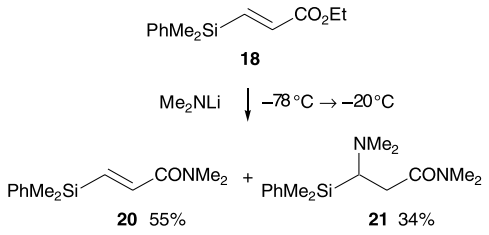


been more nucleophilic towards methyl iodide than the dimethylamino group. The product of enolate methylation **19** was detectable on one occasion, and then only in a small amount. Similarly, when we regenerated the enolate **16** from the ester **17** using LDA, and treated that enolate with methyl iodide, the same unsaturated ester **18** was formed.

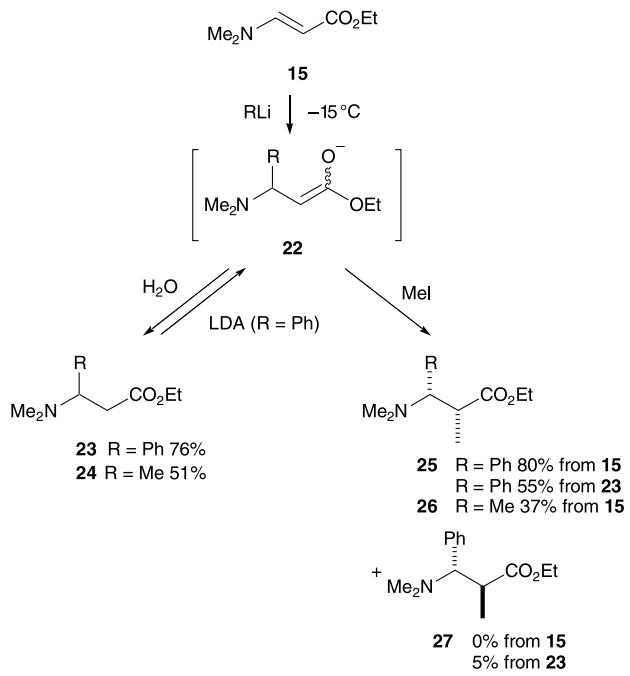
Additionally remarkable is that the elimination of dimethylamine **16** → **18** achieved by the treatment with methyl iodide took only a few minutes at –20 °C. In contrast, if we treated the amine **17** with methyl iodide in THF, little *N*-methylation took place over 18 h at room temperature — we recovered the amine **17** in 86% yield. Evidently, the α-silyl group does not on its own increase the nucleophilicity of the nitrogen lone pair (21) enough to suggest an exceptionally easy *N*-methylation. It seems improbable that coordination by the enolate oxygen to the silyl group could make the nitrogen lone pair more nucleophilic than the carbon atom of the enolate ion, and we have no convincing explanation for the ease with which the elimination took place. It is not specific to using methyl iodide, since benzyl bromide and allyl bromide had the same effect, although not in such good yield. The most obvious explanation would have been that the dimethylamide ion had already been expelled from the enolate **16** before the aqueous quench, and had added back during the aqueous quench giving the saturated ester **17**. The role of the methyl iodide in this scenario would have been to quench the dimethylamide ion, and prevent it from adding back. This is not the explanation, because the unsaturated ester **18**, which would have been the product of that elimination, reacted with lithium dimethylamide to give the amides **20** and **21** (Scheme 5). These products were not present in the reaction mixtures from Scheme 3. Furthermore, quenching the reaction mixture from the conjugate addition by injecting it directly into aqueous hydrochloric acid, which can be expected to protonate the amide ion rapidly, gave largely the ester **17** (67%) and only a little (9%) of the product of elimination **18**.

The easy elimination induced by methyl iodide has something to do with the presence of the silyl group. We repeated

Scheme 5.



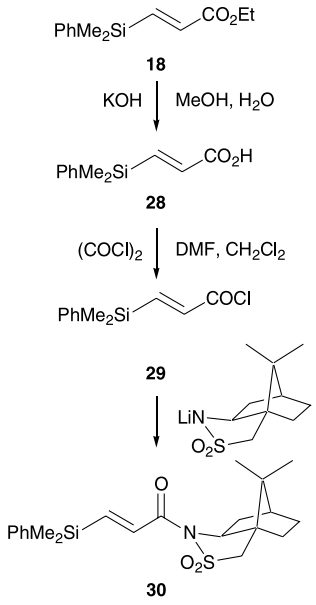
Scheme 6.



the reaction with the ester **15** using phenyllithium instead of phenyldimethylsilyllithium (Scheme 6). Conjugate addition took place to give the enolate **22** (R = Ph); quenching with ammonium chloride solution gave the amino ester **23**, but quenching with methyl iodide gave the expected enolate methylation, with the expected (22) high degree of diastereoselectivity in favour of the known (23) isomer **25**. Regeneration of the enolate **22** (R = Ph) from the ester **23** using LDA, followed by methylation with methyl iodide, gave the same result: *C*-methylation, this time with a detectable but small amount of the diastereoisomer **27** formed as well. In some rather lower yielding, but otherwise similar reactions, methyllithium also added in a conjugate manner, and the enolate **22** (R = Me) could be trapped with either protons or methyl iodide to give the esters **24** and **26**, respectively.

The ester **18** has usually been prepared most economically by hydrosilylation–dehydrogenation of ethyl acrylate (24), but in that otherwise excellent method it is always contaminated with the saturated analogue, no matter how much of an excess of ethyl acrylate is used to limit the amount of hydrosilylation. In our experience, the saturated analogue, although harmless to what we were doing, has frequently been difficult to remove, and we have found ourselves carrying it through the next few steps of our synthetic work until we found a stage at which it could be removed relatively easily.

Schcme 7.



The synthesis reported here is free of this problem. For further development, it was helpful to saponify the crude ester **18**, to separate acidic products from the inevitable silicon-containing by-products. The carboxylic acid was occasionally crystalline, but recrystallization, either of the acid or of various salts was not practical. Since we needed it attached to Oppolzer's sultam, as did he (25), we converted the acid into its acid chloride and joined it onto the auxiliary (Scheme 7), at which point we had a crystalline derivative **30** that could be purified by recrystallization. The overall yield of this useful compound from the amino ester **15** was 41%.

Experimental

^{13}C NMR data from attached proton tests (APT) are given in the form 133.6– when the C atom has an odd number of H atoms attached, and 167.2+ when it has an even number of H atoms attached.

(*E*)- and (*Z*)-3-Dimethyl(phenyl)silybut-2-enal (6)

But-2-ynoic acid *N*,*N*-dimethylamide (26) (0.22 g, 2.00 mmol) in THF (2 mL) was added dropwise to dimethyl-(phenyl)silyllithium (1, 7) (4.8 mL, 1 mol dm^{-3} in THF, 4.8 mmol) at –78 °C, and the mixture was kept at –20 °C for 1 h. Saturated aqueous sodium bicarbonate (5 mL) and diethylether (5 mL) were added. The aqueous portion was removed and the basic products extracted from the organic fraction with dilute hydrochloric acid (3 N). The aqueous layers were basified (10% NaOH) to pH 12 and then extracted with ether (3 × 20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude products (0.24 g). Chromatography (SiO_2, CH_2Cl_2) gave the *aldehydes* (0.09 g, 22%) as an inseparable mixture (*E*:*Z*, 5:1). (*E*)-isomer: ^{1}H NMR (250 MHz, $CDCl_3$) δ: 10.1 (1H, d, *J* = 7.8, CHO), 7.5–7.4 (2H, m, Ph), 7.4–7.2 (3H, m, Ph), 6.3 (1H, dq, *J* = 7.8 and 1.7, C=CH), 2.2 (3H, d, *J* = 1.7, CMe), and 0.4 (6H, s, $SiMe_2$). ^{13}C NMR ($CDCl_3$) δ: 192.9–, 167.2+, 142.9–, 137.5+, 133.6–, 128.3–, 15.9– and –0.9– (1 signal missing). (*Z*)-isomer: ^{1}H NMR (250 MHz, $CDCl_3$) δ: 9.7 (1H, d, *J* = 8.5, CHO), 7.5–7.4 (2H, m, Ph), 7.4–7.2 (3H, m, Ph), 6.5 (1H, dq, *J* = 8.5 and 1.4, C=CH), 2.1 (3H, d, *J* = 1.4, CMe), and 0.5 (6H, s, $SiMe_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 190.2–, 163.9+, 137.8–, 135.4+, 134.0–, 129.7–, 128.1–, 26.8– and –0.4–.

5,5-Dimethyl-3-(dimethylphenylsilyl)cyclohex-2-enone (8)

Dimethyl(phenyl)silyllithium (2.4 mL, 1 mol dm^{-3} in THF, 2.4 mmol) was added dropwise to 5,5-dimethyl-3-(dimethylamino)cyclohex-2-enone (0.37 g, 2.20 mmol) in THF (2 mL) at –78 °C, the mixture stirred at –78 °C for 1 h, and then kept at –20 °C for 1 h. Saturated aqueous sodium bicarbonate solution (5 mL) and diethyl ether (5 mL) were added. The aqueous portion was removed and the basic products removed from the organic fraction with dilute hydrochloric acid. The organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude neutral products (0.65 g) as a yellow oil. Chromatography (SiO_2, CH_2Cl_2) gave the ketone (18) (0.51 g, 90%) as an oil. R_f(CH_2Cl_2) 0.44. IR ν_{max} (film, cm^{-1}): 1675 (C=O), 1589 (C=C), 1249 (SiC), and 1112 (SiC). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.5–7.45 (2H, m, Ph), 7.4–7.35 (3H, m, Ph), 6.30 (1H, t, *J* = 1.8, C=CH), 2.24 (2H, s, CH_2CO), 2.19 (2H, d, *J* = 1.8, CH_2C=C), 0.95 (6H, s, CMe_2), and 0.43 (6H, s, $SiMe_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 199.0+, 163.4+, 136.0–, 135.4–, 133.9–, 129.6–, 128.1–, 51.5+, 42.1+, 34.3+, 28.1– and –4.4–. MS *m*/*z* (EI): 259.1 (50%, MH$^+$), 243.1 (90, M – Me), and 137.0 (100) (found: M$^+$, 258.14402; $C_{16}H_{22}OSi$ requires M, 258.14398).

3-(*E*)-Dimethyl(phenyl)silylpropenal (12)

3-(*E*)-*N*,*N*-Dimethylaminopropenal (90%, 0.5 mL, 4.5 mmol) in THF (4.5 mL) was added dropwise to a solution of dimethyl(phenyl)silyllithium (0.9 mol dm^{-3} in THF, 5.5 mL, 4.95 mmol) under argon at –78 °C. The mixture was stirred for 1 h at this temperature and then at –15 °C for 1 h. Saturated aqueous sodium bicarbonate solution (5 mL) was added. The organic layer was washed with water (2 mL). The combined aqueous layers were extracted with ether (3 × 2 mL). The combined organic layers were washed with aqueous hydrochloric acid (3 N, 2 mL), brine (2 mL), dried ($MgSO_4$), and the solvent evaporated under reduced pressure. The residue was distilled to give the aldehyde (19) (0.342 g, 40%), bp 91 °C at 0.9 mmHg (1 mmHg = 133.322 Pa). R_f(CH_2Cl_2) 0.84. IR ν_{max} (film, cm^{-1}): 1693 (C=O), 1428 (C=C), 1251 (SiC), and 1117 (SiC). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.53 (1H, d, *J* = 7.6, CHO) 7.52–7.50 (2H, m, Ph), 7.40–7.30 (4H, m, Ph and CHSi), 6.54 (1H, dd, *J* = 18.7 and 7.6, CHCO), and 0.47 (6H, s, Si*Me*$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.5–, 156.4–, 145.1–, 135.7+, 133.7–, 129.8–, 128.1– and –3.4–. MS *m*/*z* (EI): found: M$^+$, 190.08271; $C_{11}H_{14}OSi$ requires M, 190.08132.

4-(*E*)-[Dimethyl(phenyl)silyl]but-3-en-2-one (14)

Dimethyl(phenyl)silyllithium (0.9 mol dm^{-3} in THF, 5.25 mL, 4.7 mmol) was added dropwise to a solution of 4-*N*,*N*-dimethylaminobut-3-en-2-one (0.5 mL, 4.3 mmol) in THF (5 mL) at –78 °C under argon. The mixture was stirred at this temperature for 1 h, and then at –10 °C for 1 h. Aque-

ous sodium bicarbonate (saturated, 5 mL) and ether (5 mL) were added and the layers separated. The aqueous layer was extracted with ether (2 × 3 mL). The combined organic layers were washed with dilute hydrochloric acid (3 N, 2 × 3 mL), brine (2 mL), dried ($MgSO_4$), and the solvent evaporated off under reduced pressure. The residue was chromatographed (SiO_2, light petroleum (bp 40–60 °C)) to give the ketone (20) (0.66 g, 76%). R_f(Et_2O) 0.87. IR ν_{max} (Nujol, cm^{-1}): 1678 (C=O), 1217 ($SiMe_2$), 1115 (SiPh), 735 (Ph), and 700 (Ph). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.52–7.49 (2H, m, Ph), 7.40–7.36 (3H, m, Ph), 7.11 (1H, d, *J* = 19.2, SiCH), 6.48 (1H, d, *J* = 19.2, CHCO), 2.28 (3H, s, COMe), and 0.43 (6H, s, $SiMe_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.6+, 145.6–, 144.0–, 136.3+, 133.8–, 129.6–, 127.9–, 26.3–, –3.2–. MS *m*/*z* (ESI): 227 (100%, M^+Na) (found: MNa^+, 227.0871; $C_{12}H_{16}OSi$ requires M + Na, 227.0868).

Ethyl 3-*N*,*N*-dimethylamino-3-dimethyl(phenyl)silylpropanoate (17)

Dimethyl(phenyl)silyllithium (4.1 mL, 1 mol dm^{-3} in THF, 4.1 mmol) was added dropwise to (*E*)-ethyl 3-(dimethylamino)propenoate (0.53 g, 3.72 mmol) in THF (5 mL) at –78 °C. The mixture was stirred at –78 °C for 1 h then kept at –20 °C for 1 h. Saturated aqueous sodium bicarbonate (5 mL) and ether (5 mL) were added. The aqueous portion was removed and the basic products extracted from the organic fraction with dilute hydrochloric acid (3 N). The aqueous extract was basified (10% NaOH) to pH 12 and then extracted with ether (3 × 20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the *ester* (1.17 g, 92%) as an oil. R_f(Et_2O) 0.95. IR ν_{max} (film, cm^{-1}): 1732 (C=O), 1249 (SiC), and 1111 (SiC), 836 (SiC), 734 (Ph), and 701 (Ph). ^1H NMR (250 MHz, $CDCl_3$) δ: 7.57–7.53 (2H, m, Ph), 7.36–7.26 (3H, m, Ph), 4.03 (2H, q, *J* = 7.2, OCH_2Me), 2.92 (1H, dd, *J* = 8.7 and 5.2, CHSiN), 2.56 (1H, dd, *J* = 15.2 and 8.8, CH_AH_BCO), 2.29 (6H, s, NMe_2), 2.26 (1H, dd, *J* = 14.7 and 5.1, CH_AH_BCO), 1.20 (3H, t, *J* 7.2, OCH_2Me), 0.42 (3H, s, $SiMe_AMe_B$), and 0.37 (3H, s, $SiMe_AMe_B$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.2+, 138.2+, 134.5–, 129.1–, 127.8–, 60.3+, 53.6–, 43.9–, 30.8+, 14.1–, 2.4– and –3.32–. LSI-MS m/*z*: found: MH^+, 280.1750; $C_{15}H_{25}NO_2Si$ requires M + H, 280.1727. In various runs, the neutral fraction gave small amounts of the conjugated ester **18** (typically 9%), identical (^1H NMR, ^{13}C NMR) with the sample described below.

A sample of the ester **17** was stirred overnight in iodomethane at room temperature. This gave, on work-up, recovered starting material (86%) and ethyl (*E*)-3-(dimethylphenylsilyl)-propenoate (14%).

Ethyl 3-(*E*)-dimethy(phenyl)silylpropenoate (18)

Method A

Ethyl 3-(*E*)-*N*,*N*-dimethylaminopropenoate (3 mL, 21 mmol) was added dropwise to a solution of dimethyl(phenyl)silyllithium (0.52 mol dm^{-3} in THF, 48 mL, 25 mmol) and toluene (25 mL) under argon at –15 °C keeping the temperature below –10 °C, and then kept at –15 °C for 15 min. Methyl iodide (3.9 mL, 63 mmol) was added dropwise keeping the temperature below –5 °C. The mixture was stirred at room temperature for 20 min and quenched with water (10 mL). The organic layer was washed with water (2 × 10 mL) and the combined aqueous layers extracted with ether (4 × 5 mL). The combined organic layers were washed with aqueous hydrochloric acid (3 N, 7 mL). The aqueous layer was then extracted with ether (4 × 2 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure to give the crude ester (27) (9.9 g, 96%). Chromatography of an earlier run, with some losses, gave pure ester (67%). R_f(Et_2O:light petroleum (bp 40–60 °C), 50:50) 0.85. IR ν_{max} (film, cm^{-1}): 1727 (C=O), 732 (Ph), and 700 (Ph). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.60–7.50 (2H, m, Ph), 7.40–7.32 (3H, m, Ph), 7.28 (1H, d, *J* = 19, CH=), 6.28 (1H, d, *J* = 19, CH=), 4.21 (2H, q, *J* = 7.1, OCH_2), 1.29 (3H, t, *J* = 7.1, CH_2Me), and 0.43 (6H, s, $SiMe_2$). ^1H NMR (100 MHz, $CDCl_3$) δ: 165.7+, 147.3–, 136.4+, 135.4–, 133.8–, 129.5–, 128.0–, 60.6+, 14.2– and –3.2–. MS *m*/*z* (EI): found: M^+, 234.1083; $C_{13}H_{18}O_2Si$ requires 234.1076). MS *m*/*z* (ESI): 257 (100%, Mna^+) (found: MNa^+, 257.0971; $C_{13}H_{18}O_2Si$ requires M + Na, 257.0974). In one run, the basic fraction gave ethyl 2-methyl-3-dimethylamino-3-dimethyl(phenyl)silylpropanoate (**19**) (4%) as an inseparable mixture of isomers (~3:1) characterized only by the definitive ^1H NMR spectrum: (250 MHz, $CDCl_3$) δ major isomer: 7.60–7.55 (2H, m, Ph), 7.35–7.30 (3H, m, Ph), 4.08 (2H, q, *J* = 7.4, CO_2CH_2Me), 2.90–2.70 (2H, m, CHN and C*H*Me), 2.40 (6H, s, NMe_2), 1.23 (3H, t, *J* = 7.1, CO_2CH_2Me), 0.97 (3H, d, *J* = 6.8, CH*Me*), and 0.42 (6H, s, $SiMe_2$); minor isomer: 7.60–7.55 (2H, m, Ph), 7.35–7.30 (3H, m, Ph), 3.91 (1H, q, *J* = 7.1, $CO_2CH_AH_BMe$), 3.91 (1H, q, *J* = 7.1, $CO_2CH_AH_BMe$), 2.90–2.70 (2H, m, CHN and C*H*Me), 2.37 (6H, s, NMe_2), 1.20 (3H, t, *J* = 7.1, CO_2CH_2Me), 0.97 (3H, d, *J* = 6.8, CH*Me*), and 0.41 (6H, s, $SiMe_2$).

Method B

n-Butyllithium (1.45 mol dm^{-3} in hexanes, 5.4 mL, 7.9 mmol) was added slowly to a stirred solution of distilled diisopropylamine (1.1 mL, 7.9 mmol) in dry THF (3.6 mL) at 0 °C under nitrogen. After 15 min, the solution was cooled to –78 °C and ethyl (*E*)-3-(*N*,*N*-dimethylamino)-3-dimethyl(phenyl)silylpropanoate (1.0 g, 3.6 mmol) in dry THF (4.5 mL) added by cannula, and the mixture was stirred for 1 h. Methyl iodide (1.5 mL, 25 mmol) was added slowly, and the mixture stirred for 1 h at –78 °C and warmed over 20 min to 0 °C. Saturated ammonium chloride solution was added, the layers separated, and the aqueous layers extracted with ether. The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated to give ethyl (*E*)-3-dimethyl(phenyl)silylpropenoate (0.88 g, >100%), identical (TLC, ^1H NMR) with the earlier sample. Basification of the aqueous layers (10% NaOH), and extraction with ether gave the basic products (25 mg), which were a complex mixture of several compounds (^1H NMR).

Method C

The procedure of Method A was followed, but benzyl bromide was used in place of methyl iodide. The products were the unsaturated ester **18** (43%) and the conjugate addition product **17** (38%). There was no sign of the product of *C*-benzylation.

Method D

The procedure of Method A was followed, but allyl bromide was used in place of methyl iodide. The products were the unsaturated ester **18** (67%) and the conjugate addition product **17** (3%). There was no sign of the product of *C*-allylation.

(*E*)-*N*,*N*-Dimethyl-3-dimethyl(phenyl)silylpropenamide (20) and *N*,*N*-dimethyl-3-dimethylamino-3-dimethyl(phenyl)silylpropionamide (21)

n-Butyllithium (1.5 mL of a 1.7 mol dm^{-3} solution in hexanes, 2.55 mmol) was added to dimethylamine (2.2 mL of a 1.7 mol dm^{-3} solution in THF, 3.7 mmol) at –78 °C and stirred at this temperature for 1 h to give a solution of lithium dimethylamide. (*E*)-Ethyl 3-dimethyl(phenyl)silylpropenoate (0.39 g, 1.68 mmol) in THF (2.0 mL) was added dropwise at –78 °C and stirred at this temperature for 30 min and then kept at –20 °C for 30 min. Saturated aqueous sodium bicarbonate (5 mL) and ether (5 mL) were added. The aqueous portion was removed and the basic products extracted from the organic fraction with hydrochloric acid (3 N). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give (E)-N,N- *dimethyl*-3-*dimethyl*(*phenyl*)*silylpropenamide* (0.215 g, 55%). R_f(Et_2O) 0.25. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.55–7.52 (2H, m, Ph), 7.39–7.29 (3H, m, Ph), 7.25 (1H, d, *J* = 18.4, SiCH=C*H*), 6.29 (1H, d, *J* = 18.4, C*H*=CH), 3.04 (6H, br s, $CONMe_2$), and 0.39 (6H, s, $SiMe_2$). The aqueous extract was basified (10% NaOH) to pH 12, and then extracted with ether (3 × 20 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give N,N-*dimethyl*-3-(*dimethylamino*)-3-*dimethyl*(*phenyl*)*silylpropionamide* (0.16 g, 34%). R_f(Et_2O) 0.36. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.62–7.54 (2H, m, Ph), 7.36–7.32 (3H, m, Ph), 2.88 (3H, s, $CONMe_AMe_B$), 2.82 (3H, s, $CONMe_AMe_B$), 2.60 (1H, dd, *J* = 13.2 and 5.4, CHNSi), 2.35 (6H, s, $CHNMe_2$), 2.28–1.95 (2H, m, $COCH_2$), 0.40 (3H, s, $SiMe_AMe_B$), and 0.38 (3H, s, $SiMe_AMe_B$).

Ethyl 3-*N*,*N*-dimethylamino-3-phenylpropionate (23)

Phenyllithium (1.8 mol dm^{-3}, 12.5 mL, 22.4 mmol) was added slowly to a solution of ethyl (*E*)-3-*N*,*N*-dimethylaminopropenoate (1.84 g, 2 mL, 14 mmol) in dry ether (17 mL) under argon at –15 °C, keeping the temperature below –5 °C. The mixture was stirred at –10 °C for 0.5 h and at room temperature for 2.5 h. The mixture was quenched with aqueous ammonium chloride solution (25 mL, saturated). The aqueous layer was extracted with ether (3 × 10 mL). The combined organic layers were washed with aqueous hydrochloric acid (3 N, 65 mL). The aqueous layer was extracted with ether (3 × 10 mL), and then basified to pH 11 with sodium hydroxide solution (10%) using universal indicator paper, and the aqueous layer was extracted with ether (3 × 50 mL). The combined organic layers were washed with brine (1 × 30 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give the amine (28) as an oil (2.4 g, 76%). IR ν_{max}(film, cm^{-1}): 1735 (C=O), 1371 (CHCO) and 700 (Ph). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 (2H, m, Ph), 7.27–7.23 (3H, m, Ph), 4.06 (2H, q, *J* = 7.1, OCH_2), 3.86 (1H, dd, *J* = 6.9 and 8.2, C*H*Ph), 2.95 (1H, dd, *J* = 14.8 and 6.9, CH_ACH_B), 2.69 (1H, dd, *J* = 14.8 and 8.2, $CH_AC H_B$), 2.18 (6H, s, NMe_2), and 1.11 (3H, t, *J* = 7.1, CH_2Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.7+, 138.8+, 128.4–, 128–, 127.4–, 68.7–, 66.4+, 42.2–, 38.6+, 14.0–. MS *m*/*z* (EI): 222 (100%, MH^+) (found: MH^+, 222.1493; $C_{13}H_{19}O_2N$ requires M + H, 222.1494); hydrochloride, mp 190 °C (from Me_2CO) (lit. (29) mp 192 °C).

Ethyl (2*SR*,3*RS*)-3-dimethylamino-2-methyl-3- phenylpropionate (25)

Method A

Phenyllithium (12.5 mL, 1.8 mol dm^{-3}, 22.4 mmol) was added slowly to a solution of ethyl (*E*)-*N*,*N*-dimethylaminopropenoate (2 g, 2 mL, 14 mmol) in dry ether (17 mL) under Ar at –15 °C, keeping the temperature below 0 °C. The mixture was stirred at –10 °C for 0.5 h and then kept at room temperature for 1 h. Methyl iodide (2.2 mL, 35 mmol) was added at –15 °C, and the solution kept at room temperature for 15 h. The reaction was quenched with ammonium chloride solution (40 mL). The aqueous layer was extracted with ether (3 × 10 mL). The combined organic layers were acidified with hydrochloric acid (3 N, 65 mL). The aqueous layer was washed with ether (2 × 15 mL), basified with sodium hydroxide solution (10%), and the basic product extracted with ether (4 × 40 mL). The organic layer was washed with brine, dried ($MgSO_4$), and the solvent evaporated under reduced pressure to give the amine (23) (2.52 g, 80%). R_f(Et_2O–light petroleum (bp 40–60 °C), 1:1) 0.55. IR ν_{max} (film, cm^{-1}): 1735 (C=O), 756 (Ph), and 705 (Ph). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 7.36–7.26 (3H, m, Ph), 7.13–7.12 (2H, m, Ph), 4.20 (2H, qd, *J* = 1.9 and 7.1, OCH_2), 3.68 (1H, d, *J* 11.0, PhC*H*), 3.15 (1H, dq, *J* = 11.0 and 6.8, C*H*Me), 2.10 (6H, s, NMe_2), 1.28 (3H, t, *J* 7.1, CH_2Me), and 0.93 (3H, d, *J* 6.8, $CHMe$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.6+, 134.0–, 129.3–, 127.9–, 127.3–, 72.3–, 60.0+, 42.1–, 41.2–, 14.6– and 14.2–. MS *m*/*z* (EI): 236 (2%, MH^+), 191 (8, MH – OEt), and 160 (100, M – Ph) (found: M^+, 236.1649; $C_{14}H_{22}NO_2$ requires M, 236.1645).

Method B

Butyllithium (1.47 mol dm^{-3} in hexane, 50 mL, 1.44 mmol) was added to a solution of diisopropylamine (0.22 mL, 1.58 mmol) in dry THF (7.20 mL) under nitrogen at –78 °C and stirred for 15 min. Ethyl 3-dimethylamino-3-phenylpropionate (0.159 g, 0.718 mmol) was added at –78 °C, and the temperature maintained for 1 h. Methyl iodide (0.11 mL, 1.8 mmol) was added, the mixture stirred at –78 °C for 30 min and then allowed to come to room temperature and kept for 1 h. The reaction was quenched with ammonium chloride solution (10 mL). The aqueous layer was extracted with ether (3 × 3 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and the solvent was evaporated off under reduced pressure. The residue was dissolved in ether (20 mL) and washed with hydrochloric acid (3 N, 20 mL). The aqueous layer was washed with ether (3 × 6 mL) and basified with sodium hydroxide solution (10%), extracted with ether (4 × 10 mL), and the combined organic layers washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give a mixture of the esters (0.117 g, 60%) in a ratio of 10:1. R_f(Et_2O–light petroleum (bp 40–60 °C), 1:1) 0.55. ^{1}H NMR (400 MHz, $CDCl_3$) δ (signals from the major isomer, identical to those reported

above, together with signals from the minor isomer **27**): 7.36–7.26 (3H, m, Ph), 7.13–7.12 (2H, m, Ph), 3.85 (2H, q, J = 7.1, OCH_2), 3.74 (1H, d, J = 11.0, PhC*H*), 3.10 (1H, dq, J = 11.0 and 6.85, C*H*Me), 2.10 (6H, s, NMe_2), 1.35 (3H, d, J = 6.85, CH*Me*), and 0.91 (3H, t, J = 7.1, OCH_2*Me*).

Ethyl 3-*N*,*N*-dimethylaminobutanoate (24)

Methyllithium (1.54 mol dm^{-3} in Et_2O, 18.5 mL, 28.5 mmol) was added to 3-(*E*)-*N*,*N*-dimethylaminopropenoate (2 g, 14 mmol) in dry ether (17 mL) at –15 °C under nitrogen, maintaining the temperature below 0 °C. The reaction was stirred at 0 °C for 30 min and then kept at room temperature for 1 h. The reaction was quenched with ammonium chloride solution (40 mL). The aqueous layer was extracted with ether (3 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and the solvent evaporated under reduced pressure to give the amine (30) (1.14g, 51%). IR ν_{max} (film, cm^{-1}): 1732 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.13 (2H, q, J = 7.1, OCH_2), 3.10 (1H, ddq, J = 8.5, 5.7, and 6.6, C*H*Me), 2.53 (1H, dd, J = 14.4 and 5.7, CH_ACH_BCO), 2.23 (6H, s, NMe_2), 2.18 (1H, dd, J = 14.4 and 8.5, CH_ACH_BCO), 1.24 (3H, t, J 7.1, OCH_2*Me*), and 1.03 (3H, d, J = 6.6, CH*Me*).

Ethyl 3-*N*,*N*-dimethylamino-2-methylbutanoate (26)

Methyllithium (1.54 mol dm^{-3} in Et_2O, 37 mL, 28.5 mmol)) was added to 3-(*E*)-*N*,*N*-dimethylaminopropenoate (4 g, 28 mmol) in dry ether (34 mL) at –15 °C under nitrogen, maintaining the temperature below 0 °C. The reaction was stirred at –15 °C for 30 min and then kept at room temperature for 16 h. The mixture was cooled to –15 °C, methyl iodide (2.2 mL, 35 mmol) was added, and the mixture kept at room temperature for 16 h. The reaction was quenched with ammonium chloride solution (15 mL) and water (10 mL). The aqueous layer was extracted with ether (3 × 10 mL). The combined organic layers were washed with brine and part of the solvent evaporated under reduced pressure. The organic layer was washed with hydrochloric acid solution (3 N), and the aqueous layer was washed with ether (3 × 8 mL). The aqueous layer was basified with sodium hydroxide solution (10%), and extracted with ether (5 × 17 mL). The organic layer was washed with brine, dried ($MgSO_4$), and the solvent evaporated off to give the *amine* (1.80 g, 37%) with only one diastereoisomer detectable, presumably the 2*RS*,3*RS* isomer by analogy with the formation of the known compound **25**. IR ν_{max} (film, cm^{-1}): 1735 (C=O) and 1155 (OC). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.15 (2H, m, OCH_2), 2.75 (1H, dq, J = 9.6 and 6.6, NC*H*Me), 2.51 (1H, dq, J = 9.6 and 6.9, COC*H*Me), 2.19 (6H, s, NMe_2), 1.09 (3H, d, J = 6.9, COCH*Me*), and 0.89 (3H, d, J = 6.6, NCH*Me*). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.1+, 61.8–, 59.8–, 44.6–, 40.6–, 14.2– and 8.5–. MS *m*/*z* (EI): 173 (30%, M^+), 158 (20, M – Me), 128 (13, M – EtO), 73 (39, CO_2Et), and 72 (100, Me_2N=CHMe) (found: M^+, 173.1411; $C_9H_{19}NO_2$ requires M, 173.1416).

3-(*E*)-Dimethyl(phenyl)silylpropenoic acid (28)

The crude ethyl 3-(*E*)-dimethy(phenyl)silylpropenoate (**15**) (9.9 g) in methanol (40 mL) and potassium hydroxide (10 g) in distilled water (9 mL) were stirred at room temperature for 1.5 h. The methanol and ethanol were evaporated off under reduced pressure, and the residue was taken up in distilled water (30 mL), washed with ether (4 × 10 mL), acidified to pH 1 with aqueous hydrochloric acid (3 N, ~50 mL), and extracted with ether (4 × 15 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and the solvent evaporated off under reduced pressure to give the acid (19) (3.2 g, 75% over two steps) as an indeterminately low-melting solid. R_f(Et_2O:light petroleum (bp 40–60 °C), 50:50) 0.43. IR ν_{max} (film, cm^{-1}): 1694 (C=O), 1593 (C=C), 840 ($SiMe_2$), 732 (Ph), and 700 (Ph). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.53–7.48 (2H, m, Ph), 7.51 (1H, d, J = 19, SiCH), 7.42–7.36 (3H, m, Ph), 6.29 (1H, d, J = 19, CHCO), and 0.45 (6H, s, $SiMe_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.9+, 150.8–, 136.0+, 134.5–, 133.8–, 130.4–, 128.0–, and –3.6–. MS *m*/*z* (ESI): 229 (10%, MNa^+). Anal. calcd. for $C_{11}H_{14}O_2Si$ (%): C 64.0, H 6.8; found: C 64.0 H 6.9. Benzylamine salt, mp 130 to 131 °C (from MeOH). N.B. Upon addition of ether to the basic aqueous solution, the formation of three layers was often observed. The dark-coloured middle layer, presumably the carboxylate salt, not completely soluble in the aqueous layer, was combined with the lower aqueous layer, and carried through in the acidification step. This problem was worse when sodium hydroxide was used to hydrolyze the ester, and largely avoided by using potassium hydroxide.

***N*-{*E*-3-[Dimethyl(phenyl)silyl]propenoyl-(7*R*)-2,10-camphorsultam (30)**

Oxalyl chloride (2 mL, 23 mmol), was added to 3-(*E*)-dimethyl(phenyl)silylpropenoic acid (3.2 g, 16 mmol) in dichloromethane (11 mL) under nitrogen at room temperature, followed by *N*,*N*-dimethylformamide (0.55 mL), and the mixture was stirred at this temperature until the bubbling ceased (~1 h). The solvent and the excess oxalyl chloride were evaporated off under reduced pressure at 50 °C and then at 2 mmHg (1 mmHg = 133.322 Pa) for 2 h to give the acid chloride **29**. Meanwhile, *n*-butyllithium (1.6 mol L^{-1}, ~10 mL) was added to (1*R*)-(+)-2,10-camphorsultam (31) (3.23 g, 15 mmol) in THF (15 mL) under nitrogen at –78 °C, using 1-pyreneacetic acid as the indicator. This solution was added by cannula to the solution of the acid chloride **29** in THF (20 mL) at –78 °C, and the mixture stirred at room temperature for 1 h. The mixture was filtered through a silica pad, washing through with ether (50 mL). This filtrate was washed with sodium bicarbonate (30 mL), dried ($MgSO_4$), filtered and the solvent evaporated off under reduced pressure to give the crude product (5.694 g, 90%), which was crystallized from ethanol (3.5 mL) to give a first crop of the *imide* (2.23 g, 35% from the acid) as pale yellow needles, mp 90 to 91 °C (from EtOH). The mother liquors were then evaporated to give a second crop (0.14 g, 2%), mp 88.5–89.5 °C. The mother liquors were chromatographed (SiO_2, light petroleum (bp 40–60 °C) – Et_2O, 9:1) to give a third crop (0.765 g, 12%), mp 89.5–90 °C, making the total yield (3.13 g, 49%). $[\alpha]_D^{20}$ +63.1 (*c* 1.04 in $CHCl_3$). R_f(Et_2O–light petroleum (bp 40–60 °C), 50:50) 0.47. IR ν_{max}(Nujol, cm^{-1}): 1672 (C=O), 1598 (C=C), 1166 (SO_2N), and 1117 (SiPh). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.52–7.50 (2H, m, Ph), 7.48 (1H, d, J = 18.2, SiCH), 7.36–7.35 (3H, m, Ph), 7.01 (1H, d, J = 18.2, CHCO), 3.93 (1H, dd, J = 7.0 and 5.7, NCH), 3.50 (1H, d, J = 13.8, $SO_2CH_AH_B$),

3.44 (1H, d, J = 13.8, $SO_2CH_AH_B$), 2.20–2.03 (2H, m), 2.00–1.84 (3H, m), 1.48–1.32 (2H, m), 1.18 (3H, s, CMe_AMe_B), 0.98 (3H, s, CMe_AMe_B), and 0.44 (6H, s, $SiMe_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.5+, 148.7–, 136.4+, 134.2–, 133.9–, 129.5–, 128.0–, 65.2–. 53.1+, 48.6+, 47.8+, 44.7–, 38.5+, 32.9+, 26.5+, 20.9–, 19.9–, –3.2– and –3.3–. MS *m*/*z* (EI): 403 (47%, M^+), 267 (22, M – $PhMe_2SiH$), 189 (100, M – Me_2N), and 135 (46, $PhMe_2Si^+$) (found: M^+ 403.1640; $C_{21}H_{29}NO_3SSi$ requires M, 403.1637). Anal. calcd. for $C_{21}H_{29}NO_3SSi$(%): C 62.5, H 7.2, N 3.5; found: C 62.5, H 7.3, N 3.4. Although this compound has been described before (25), no mp, and no spectroscopic or analytical data were given.

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