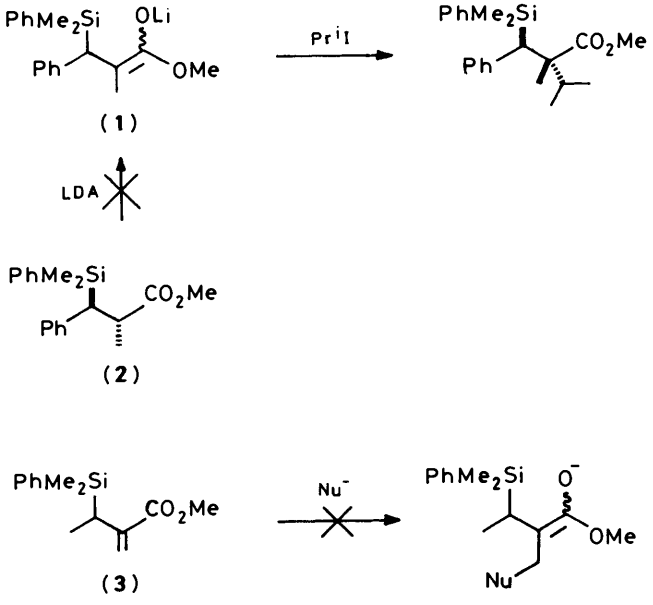
Effect of a β-Silyl Group on the Regiochemistry of Enolisation of Ketones†

Wolfhard Engel, Ian Fleming*, and Roger H. Smithers
University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW

1-Dimethyl(phenyl)silylpentan-3-one (**4**), 3-dimethyl(phenyl)silylcyclopentanone (**10**) and 3-dimethyl-(phenyl)silylcyclohexanone (**16**) are deprotonated by lithium di-isopropylamide in favour of enolate formation away from the silyl group to the extent of 70:30, 70:30, and >95:5, respectively. The effect of the silyl group appears to be largely steric in origin.

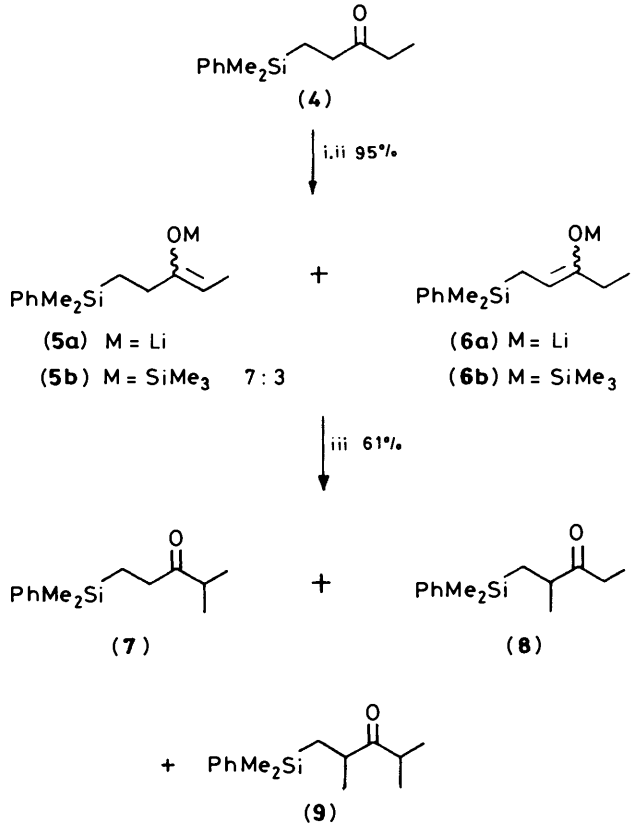
The cation-stabilising effect of a trimethylsilylmethyl group is well-known.[1] It is not known whether the same group is correspondingly destabilising of an anion, but, in the course of our work on β-silyl enolates, we have come across three pieces of evidence which support this expectation. In the first place, these enolates react relatively well with alkyl halides compared to enolates lacking the silyl group, as in the reaction of the enolate (**1**) with isopropyl iodide,[2] an electrophile rarely effective with simple enolates. Secondly, we have found[3] it impossible to regenerate the enolate (**1**) from the corresponding ester (**2**) using lithium di-isopropylamide (LDA), a base usually effective in generating ester enolates with this level of substitution. Finally, we find the αβ-unsaturated ester (**3**) to be extraordinarily resistant to conjugate addition of nucleophiles like malonate, acetoacetate, amines, and even our silyl-cuprate reagent, all of which are usually able to add to unsaturated esters. The only nucleophile we could add was sodium benzenethiolate.[4]



With these suggestive, but inconclusive observations in mind, we considered that it might be possible to use a silyl group in the β-position of a ketone to direct enolisation to the other side of the ketone, away from the silyl group. We now report that the effect of a β-silyl group on the kinetic ease of enolisation is detectable but it is only minimally effective in controlling the direction of base-catalysed enolisation of an unsymmetrical ketone.

† No reprints available

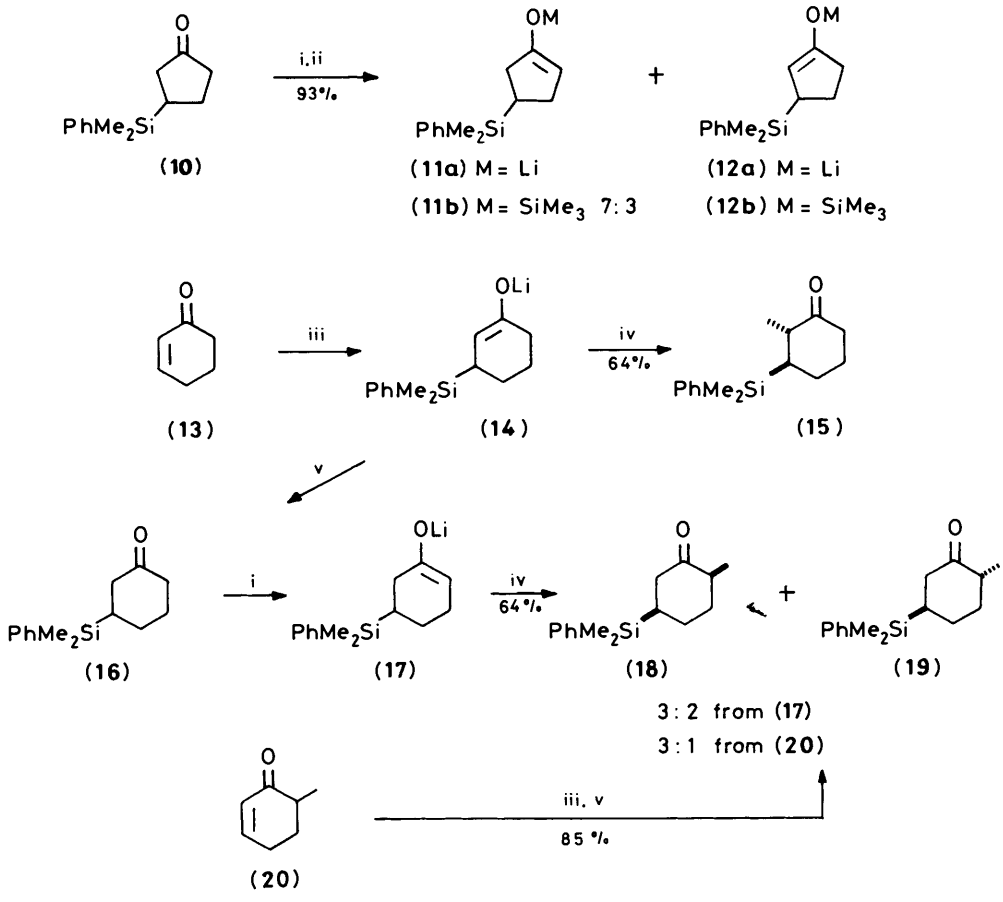
As far as acid-catalysed enolisation is concerned, we already knew[5] that there was no difficulty in enolisation on the side of the ketone which carried the silyl group: bromination of such ketones appeared, on the whole, to take place more rapidly towards the silyl group than away from it.



Reagents: i, LDA; ii, Me_3SiCl; iii, MeI

Results and Discussion

The β-silyl ketone (**4**) and LDA gave a mixture of four enolates *Z*- and *E*-(**5a**) and *Z*- and *E*-(**6a**), which we analysed by gas chromatography of the corresponding silyl enol ethers (**5b**) and (**6b**) and assigned by highfield ^1H n.m.r. spectroscopy. The analysis was aided by our being able to make a mixture of the enolates *Z*- and *E*-(**6a**) by conjugate addition of our silyl-cuprate reagent to pent-1-en-3-one followed by silylation. While the assignment of *Z* and *E* geometry is a little less secure (see Experimental section), the 70:30 ratio of (**5**):(**6**) is



Reagents: i, LDA; ii, Me_3SiCl; iii, $(PhMe_2Si)_2CuLi$; iv, MeI; v, NH_4Cl

unambiguously in favour of kinetic enolisation away from the silyl group. Furthermore, we confirmed it by methylating the mixture of enolates (**5a**) and (**6a**), prepared either directly from the ketone or by treating the silyl enol ethers (**5b**) and (**6b**) with methyl-lithium. The result was a mixture of monomethylated products (**7**) and (**8**), together with some unavoidable dimethylated product (**9**) in varying amounts, generally with the formation of twice as much of the ketone (**7**) as of the ketone (**8**). A representative run is described in the Experimental section. Similarly described there is the methylation of the corresponding ketones with a trimethylsilyl group in place of the phenyldimethylsilyl group. The ratio of the trimethylsilyl ketones corresponding to (**7**) and (**8**) was again close to 2:1, showing that the more convenient phenyldimethylsilyl group is not significantly different from the trimethylsilyl group.

In an attempt to measure the thermodynamic ratio of the same enolates, we treated the ketone (**4**) with a slight deficiency of potassium hydride, followed by chlorotrimethylsilane. The ratio of silyl enol ethers (**5b**):(**6b**) was between 1:5 and 1:6, surprisingly in favour of enolisation towards the silyl group. The yield was not high, never better than 28%, but the ratio was essentially the same in several runs, and independent of the yield. This implies that we are seeing the thermodynamic ratio, and not the result of selective loss of the silyl enol ethers (**5b**), but we have not rigorously proved that it is the thermodynamic ratio.

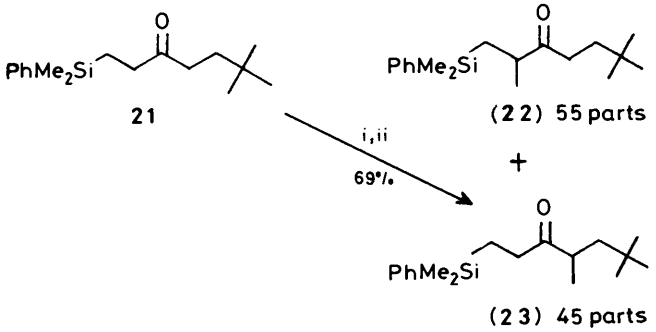
It seemed likely that the rate of enolisation was so little influenced by the presence of the silyl group because the silicon–carbon bond was not constrained to overlap with the developing enolate π-orbitals. We examined, therefore, two cyclic systems where that constraint might be present. The cyclopentanone (**10**) gave the enolates (**11a**) and (**12a**) in a ratio of 70:30, as determined by g.l.c. analysis of the silyl enol ethers (**11b**) and (**12b**). The structures were again assigned by conjugate addition of the silyl-cuprate reagent to cyclopentenone followed by silylation, which gave only the silyl enol ether (**12b**).

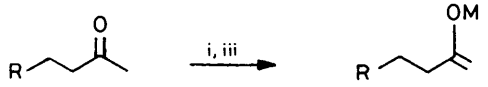
The corresponding cyclohexanone (**16**), however, gave only the enolate (**17**), although in this case we did not carry out g.l.c. analysis. Methylation of the enolate gave the monomethylated products (**18**) and (**19**) in a ratio of 3:2, reflecting the preferred axial attack of the methyl iodide on a pseudo-chair enolate with the silyl group in an equatorial position, and none of the ketone (**15**). We prepared the ketone (**15**) cleanly by conjugate addition methylation, (**13**) ⟶ (**14**) ⟶ (**15**), and can therefore set a lower limit of 5% on its presence in the mixture of (**18**) and (**19**). We also prepared a mixture of the ketones (**18**) and (**19**) by conjugate addition of the silyl-cuprate reagent to 6-methylcyclohexenone (**20**). The ratio of (**18**) to (**19**) was 3:1, reflecting the axial attack of the cuprate reagent on a pseudo-chair enone with the methyl group equatorial. We assigned relative configurations to (**18**) and (**19**) principally by ^1H n.m.r. spectroscopy on the separated compounds, but confirmed it by equilibration, in which the *cis* isomer (**18**) was converted essentially completely into the *trans* isomer (**19**).

Clearly, these results imply only a small influence of the silyl group in the cyclopentanone, where it is most constrained to overlap with the developing enolate π-bond, but a substantial influence in the cyclohexanone case. This may well be largely a steric effect, for it is known that bulky substituents in the 3-position of cyclohexanones significantly affect the regioselectivity of enolate formation.[6] There is much less information about cyclopentanones, but kinetic enolisation appears to be

controlled to about the same extent by 3-substituents as it is in cyclohexanones.[7]

To provide further evidence that the effect of the silyl group is largely steric in origin, we prepared the ketone (**21**). On treatment successively with 1 equiv. of lithium di-isopropylamide and 1 equiv. of methyl iodide, this ketone gave a 55:45 mixture of the monomethylated ketones (**22**) and (**23**) in 69% yield. In this case, it seems, a silyl group and a t-butyl group are having very comparable effects. This is supported by their being equally effective in driving kinetically controlled enolate formation in the ketones (**24**), (**25**), and (**26**) completely, as far as





(**24**) R = Me_3Si (**27**) R = Me_3Si, M = Li

(**25**) R = $PhMe_2Si$ (**28**) R = $PhMe_2Si$ M = $SiMe_3$ 80%

(**26**) R = Bu^t (**29**) R = Bu^t, M = $SiMe_3$ 64%

Reagents: i, LDA; ii, MeI; iii, Me_3SiCl

we can tell (n.m.r.), towards the methyl group. With methyl n-alkyl ketones the selectivity for enolisation in this direction is only 84:16.[8]

We conclude that a silyl group has a small but detectable effect on the kinetic acidity of C–H bonds β to it.

Experimental

Gas chromatographic analyses were carried out on a Carlo Erba machine at 130 °C with a 15 m capillary column of SE 54.

Conjugate Addition of the Dimethyl(phenyl)silylcuprate Reagent to αβ-Unsaturated Ketones.—Typically, dimethyl(phenyl)silyl-lithium[9] in tetrahydrofuran (THF) (8.8 ml of a 0.68M solution, 6 mmol) was added to copper(I) cyanide (270 mg, 3 mmol) in THF (5 ml) under argon at 0 °C, and stirred for 20 min. The resulting wine coloured solution was cooled to −78 °C and freshly distilled αβ-unsaturated ketone (2 mmol) in THF (2 ml) was added from a syringe and the mixture stirred for 2 h. Three procedures were used from this point on.

In the first, the mixture was added to aqueous ammonium chloride at 0 °C, extracted with ether (4 × 50 ml), and the combined ether layers washed with brine (50 ml), dried (3A molecular sieve powder[10]) and evaporated; the residue was then chromatographed (SiO_2, EtOAc–hexane) and distilled. The following ketones were prepared in this way. 1-*Dimethyl(phenyl)silylpentan-3-one* (**4**) (47%), b.p. 120—130 °C/0.1 mmHg (Kugelrohr) (Found: C, 71.1; H, 8.90. $C_{13}H_{20}OSi$ requires C, 70.9; H, 9.15%), R_F (10% EtOAc–hexane) 0.31, $\nu_{max.}$(film) 1 710 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 7.5—7.3 (5 H, m, Ph), 2.41—2.31 (4 H, m), 1.04—1.00 (5 H, m), and 0.27 (6 H, s); *m/z* 205 (80%, *M* − Me), 143 (60, *M* − Ph), and 135 (100, $PhMe_2Si$).

3-*Dimethyl(phenyl)silylcyclopentanone* (**10**) (75%), b.p. 120—130 °C/0.07 mmHg (Kugelrohr) (Found: C, 71.2; H, 8.65. $C_{13}H_{18}OSi$ requires C, 71.5; H, 8.30), R_F (EtOAc–hexane 15:85) 0.31, $\nu_{max.}$(film) 1 725 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 7.6—7.3 (6 H, m, Ph), 2.4—1.2 (7 H, m, ring), and 0.34 (6 H, s, $SiMe_2$).

cis-*and*trans-3-*Dimethyl(phenyl)silyl-6-methylcyclohexanone* (**18**) and (**19**) (85%) from 6-methylcyclohex-2-ene-1-one[11] as a 77:23 mixture (Found: C, 73.2; H, 9.10. $C_{15}H_{22}PSi$ requires C, 73.1; H, 9.00%), *m/z* 246 (M^+) and 135 (100%, $PhMe_2Si$); the mixture was separated by flash chromatography giving the *cis*-isomer (**18**) R_F (10% EtOAc–hexane) 0.31, $\nu_{max.}$(film) 1 710 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 7.5—7.3 (5 H, m, Ph), 2.50 (1 H, m, MeC*H*), 2.40—2.20 (2 H, m, CH_2CO), 1.9—1.63 (4 H, m, CH_2CH_2), 1.35 (1 H, m, SiCH), 1.06 (3 H, d, *J* 7 Hz, *Me*CH), and 0.29 (6 H, s, $SiMe_2$); $\delta_C(CDCl_3)$ 215.7, 136.9, 133.8, 129.2, 127.8, 44.0 (C-2), 39.2 (C-6), 34.4 (C-5), 26.0 (C-4), 21.9 (Me), 16.2 (3-C), −4.9 (MeSi), and −5.1 (MeSi); and the *trans*-isomer (**19**) R_F (10% EtOAc–hexane) 0.24, $\nu_{max.}$(film) 1 710 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 7.5—7.3 (5 H, m, Ph), 2.40—2.00 (3 H, m, CH_2COCH), 1.80—1.25 (5 H, m, CH_2CH_2CH), 0.97 (3 H, d, *J* 6.5 Hz, *Me*CH), and 0.29 (6 H, s, $SiMe_2$) (irradiation of the doublet at 0.97 caused collapse of a multiplet centred at 2.35 to 4 lines, *J* 12.0 and 5.7 Hz); $\delta_C(CDCl_3)$ 213.9, 136.7, 133.9, 129.2, 127.9, 45.4 (C-2), 42.6 (C-6), 39.4 (C-5), 29.0 (C-4), 26.7 (Me), 14.6 (C-3), −5.2 (MeSi), and −5.4 (MeSi). The downfield shifts experienced by Me, C-2, C-4, and C-6 compared to the *cis* diastereoisomer (**18**) are consistent with the diequatorial nature of (**19**).[12]

Alternatively, methyl iodide (0.62 ml, 10 mmol) was added and stirring continued for a further 4 h at −78 °C. The reaction was then briefly warmed to 0 °C (5 min), recooled to −78 °C, and quenched by addition of saturated aqueous ammonium chloride (5 ml) previously made slightly basic (pH 8) with aqueous ammonia. Work-up as above gave the following methylated ketones: 2-*methyl*-1-*dimethyl(phenyl)silylpentan-3-one* (**8**) (48%) R_F (10% EtOAc–hexane) 0.32, $\nu_{max.}$(film) 1 705 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 7.5—7.3 (5 H, m, Ph), 2.56 (2 H, q, *J* 7 Hz), 2.33 (1 H, m), 1.22 (1 H, dd, *J* 14.8 and 6.3 Hz, CH_AH_BSi), 1.03 (3 H, d, *J* 7 Hz), 0.96 (3 H, t, *J* 7 Hz), 0.78 (1 H, dd *J* 14.8 and 7.9 Hz, CH_AH_B), and 0.29 (6 H, s) (Found: *M* − Me, 219.1205. $C_{14}H_{22}OSi$ requires *M* − Me 219.1205), *m/z* 219 (24%, *M* − Me), 205 (20, *M* − C_2H_5), and 135 (100, $PhMe_2Si$).

trans-2-*Methyl*-3-*dimethyl(phenyl)silylcyclopentanone* (44%) needles, m.p. 38.5—39.0 °C (from ether) (Found: C, 72.4; H, 8.85, $C_{14}H_{20}OSi$ requires C, 72.4; H, 8.70) R_F (EtOAc–hexane 15.85 v/v) 0.32, $\nu_{max.}$(film) 1 720 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 7.6—7.3 (5 H, m, Ph), 2.4—1.5 (5 H, m, CH_2CH_2 and CHCO) 1.3—1.0 (1 H, m, CHSi), 1.02 (3 H, dd, *J* 1 and 7 Hz, CH*Me*), and 0.36 and 0.31 (3 H each, s, $SiMe_2$).

trans-3-*Dimethyl(phenyl)silyl-2-methylcyclohexanone* (**15**) (64%) (Found: C, 73.1; H, 9.1. $C_{15}H_{22}OSi$ requires C, 73.1; H, 9.0%) R_F (10% EtOAc–hexane) 0.22, $\nu_{max.}$(film) 1 075 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 7.5—7.3 (5 H, m, Ph), 2.4—2.1 (3 H, m, $CHCOCH_2$), 1.8—1.5 (4 H, m, CH_2CH_2), 1.12—1.10 (1 H, dt, *J* 3.5 and 10 Hz, CHSi), 0.96 (3 H, d, *J* 7 Hz CH*Me*), and 0.37 and 0.35 (3 H each, s, $SiMe_2$) (irradiation of the doublet at 0.96 resulted in collapse of a multiplet centred at 2.30 to a doublet, $J_{ax,ax}$ 10.8 Hz, C*H*Me), *m/z* 246 (M^+), 231 (*M* − Me), and 135 (100%, $PhMe_2Si$).

For the preparation of the silyl enol ethers, dry triethylamine (22 mmol) and chlorotrimethylsilane (22 mmol) were added and stirring continued at −78 °C for 1 h. The mixture was brought to room temperature, diluted with hexane (40 ml), and filtered through Celite. The solvents were evaporated off and the residue distilled to give the silyl enol ethers *Z*- and *E*-(**6b**) b.p. 130 °C/0.1 mmHg, $\nu_{max.}$ 1 645 cm^{-1} and (**12b**) b.p. 125—130 °C/0.05 mmHg, $\nu_{max.}$ 1 625 $cm.^{-1}$ These compounds had the following salient properties: *Z*-(**6b**) (30% of mixture) R_f 8.5 min,

$\delta_H(CDCl_3)$ 4.47 (1 H, tt, *J* 7.8 and 1 Hz, =CH); *E*-(**6b**) (70% of mixture) R_t 9.5 min, $\delta(CDCl_3)$ 4.62 (1 H, t, *J* 8.6 Hz); (**12b**) R_t 8.9 min, $\delta_H(CDCl_3)$ 4.61 (1 H, br m). The assignment of *Z* and *E* configuration was by the presence of the allylic coupling in the former.[13]

Generation of Enolates from the Saturated Ketones.—Typically, the ketone (5 mmol) in THF (10 ml) was added over 20 min by syringe to LDA (6 mmol), prepared from di-isopropylamine (6 mmol) and butyl-lithium (6 mmol) in THF (20 ml), at −78 °C under argon, and stirred for 1 h. Two procedures were used from this point on.

For the preparation of the silyl enol ethers, chlorotrimethylsilane (8.7 mmol) was added and the mixture allowed to come to room temperature. Hexane was added and work up carried out as described above, to give the mixtures of silyl enol ethers. The mixture of (**5b**) and (**6b**) (95%), b.p. 130—135 °C/0.05 mmHg (Kugelrohr), showed four peaks by g.l.c. at R_t 8.65 (12%) *Z*-(**6b**), 9.6 min (19%) *E*-(**6b**), 9.92 min (40%) *E*-(**5b**), and 10.7 min (29%) *Z*-(**5b**). Diagnostic signals in the ^1H n.m.r. spectrum at δ 4.62 (t), 4.59 (q, *J* 6.9 Hz), and 4.47 (tt) integrated to 20:73:7, respectively, supporting these ratios, if the signal at 4.59 is from *E*- and *Z*-(**5b**). The relative configuration of *E*- and *Z*-(**5b**) was assigned by the allylic coupling of the latter.[13] The mixture of silyl enol ethers (**11b**) and (**12b**) (93%) showed peaks at R_t 8.6 min (69%) and 7.5 min (31%), respectively; co-injection of the mixture with authentic (**12b**) identified these isomers.

For the methylation reactions, methyl iodide (5 × excess) was added at −78 °C, the mixture stirred for 30 min and allowed to warm to room temperature. Work-up as before gave the methylated ketones. We analysed the ketones (**7**), (**8**), and (**9**) by g.l.c., R_t 6.4 min (61%), 5.9 min (25%), and 7.1 min (14%), respectively, identified by comparison with authentic (**8**) and enriched samples of (**7**) and (**9**) (separated by preparative t.l.c. from the mixture): 4-*methyl*-1-*dimethyl*(*phenyl*)*silylpentan*-3-*one* (**7**) (Found: C, 72.0; H, 9.30. $C_{14}H_{22}OSi$ requires C, 71.7; H, 9.5%), R_F (10% EtOAc–hexane) 0.32, $\nu_{max.}$(film) 1 705 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 7.5—7.3 (5 H, m, Ph), 2.50 (1 H, sept, *J* 7 Hz), 2.4—2.3 (2 H, m), 1.04 (6 H, d, *J* 7 Hz), 0.96 (2 H, t, *J* 8 Hz), and 0.28 (6 H, s) (Found: *M* − Me, 219.1205. $C_{14}H_{22}OSi$ requires *M* − Me 219.1205), *m/z* 219 (12%, *M* − Me) 205 (20, *M* − C_2H_5), and 135 (100, $PhMe_2Si$). The dimethylated product (**9**) had $\nu_{max.}$(film) 1 700 cm^{-1}; $\delta_H(CDCl_3)$ 7.55—7.3 (5 H, m, Ph), 2.8—2.55 (2 H, m, CHCOCH), 1.21 (1 H, dd, *J* 5.5 and 14.8 Hz, CH_AH_BSi), 1.05 (3 H, d, *J* 6.9 Hz, $CHMe_AMe_B$), 1.04 (3 H, d, *J* 6.8 Hz, $CHMe_AMe_B$), 0.99 (3 H, d, *J* 6.8 Hz, CH*Me*CO), 0.81 (1 H, dd, J 8.4 and 14.8 Hz, CH_AH_BSi), 0.32 and 0.31 (3 H each, 2 × s, $SiMe_2$); *m/z*, 248 (3%, M^+), 233 (73, *M* − Me), and 135 (100, $PhMe_2Si$).

We analysed the mixture of ketones (**18**) and (**19**) (64%), prepared from the ketone (**16**),[9] by their ^1H n.m.r. spectra; they were present in the ratio of 60:40, and had spectra identical with the earlier samples. The ketone (**15**) was not detectable (^1H n.m.r.) in the mixture.

We analysed the mixture of ketones (**22**) and (**23**) (69%) by the ^1H n.m.r. spectrum of the mixture, which could not be separated chromatographically, but which gave signals easily associated with each isomer, $\nu_{max.}$(film) 1 705 cm^{-1} (CO); $\delta_H(CDCl_3)$ (**22**) (55% of the mixture) 7.51—7.25 (5 H, m, Ph), 2.58 (1 H, m, $SiCH_2CH$), 2.52—2.16 (2 H, m), 1.35 (2 H, t, *J* 7.6 Hz, $COCH_2CH_2$), 1.25 (1 H, dd, *J* 14.8 and 6.2 Hz, $SiCH_ACH_B$), 1.02 (3 H, d, *J* 6.7 Hz), 0.85 (9 H, s), 0.81 (partially obscured) (1 H, dd, *J* 14.8 and 6.2 Hz, $SiCH_ACH_B$), 0.305 (3 H, s), and 0.30 (3 H, s); and (**23**) (45% of the mixture) 7.51—7.25 (5 H, m, Ph), 2.52—2.16 (3 H, m), 1.84 (1 H, dd, *J* 15.0 and 7.6 Hz, $CH_ACH_BBu^t$), 1.06 (partially obscured) (1 H, dd, *J* 15.0 and 7.6 Hz, $CH_ACH_BBu^t$), 1.02 (obscured) (2 H, $SiCH_2CH_2$), 1.01 (3 H, d, *J*, 7.0 Hz), 0.82 (9 H, s), and 0.29 (6 H, s) (Found: *M* − Me 275.1831. $C_{18}H_{30}OSi$ requires *M* − Me 275.1831), *m/z* 275 (18%, *M* − Me) and 35 (100, $PhMe_2Si$). Irradiation at 1.02 decoupled the multiplet at 2.58 reducing it to a triplet (*J* 6.5 Hz).

Preparation of the Thermodynamic Mixture of Enolates.—1-Dimethyl(phenyl)silylpentan-3-one (1.05 g, 4.7 mmol) in THF (4 ml) was added to a suspension of potassium hydride (0.173 g, 4.13 mmol) in THF (25 ml) at room temperature. After 30 min, the reaction mixture was cooled to −78 °C and triethylamine (0.9 ml, 6.5 mmol) and chlorotrimethylsilane (0.82 ml, 6.5 mmol) were added successively. The mixture was kept at −78 °C for 30 min, allowed to come to room temperature, and stirred for 1 h. Work-up was essentially the same as for the silyl enol ethers above, except that after removal of hexane the oil (1.23 g) was further purified by column chromatography (SiO_2, 100 g, EtOAc–hexane, 1:9) and distilled to give the silyl enol ether (0.36 g, 28%), b.p. 125—130 °C/0.05 mmHg (Kugelrohr). Analysis by g.l.c. gave four peaks (R_t 8.6, 9.5, 9.8, and 10.6 min, respectively, in the proportions 79:4:1:16 identifiable as *Z*-(**6b**), *E*-(**6b**), *E*-(**5b**), and *Z*-(**5b**). The n.m.r. spectra, with identifiable peaks at $\delta_H(CDCl_3)$ 4.62 (t), 4.58 (tq, *J* 1.0 and 6.7 Hz), and 4.47 (tt), ascribed to *E*-(**6b**), *Z*-(**5b**), and *Z*-(**6b**), respectively, with relative intensities 8:19:73, supported these figures. A second run gave only 20% (Found: C, 65.6; H, 9.7. $C_{16}H_{28}OSi$ requires C, 65.7; H, 9.65%) and the same isomers in the proportion 69:17:1:13 (g.l.c.). In a similar way, the cyclopentanone (**10**) gave the silyl enol ethers (**11b**) and (**12b**) in a ratio of 60:40 but only in 7% yield.

1-*Trimethylsilylpentan*-3-*one*.—This analogue of (**4**) was prepared (45%) from 4-trimethylsilylbutan-2-one (**24**)[14] by methylation with methyl iodide of the enolate (**27**) generated using LDA as described above. This compound is known,[15] R_F (5% EtOAc–hexane) 0.22, $\nu_{max.}$(film) 1 710 (C=O), and 1 245 cm^{-1} ($SiMe_3$); $\delta_H(CDCl_3)$ 2.6—2.3 (4 H, m) 1.10 (3 H, t, *J* 7.1 Hz), 0.80 (2 H, t, *J* 10 Hz), and 0.06 (9 H, s, $SiMe_3$). We could detect no trace of the alternative product of methylation.

Methylation of 1-*Trimethylsilylpentan*-3-*one*.—This was carried out, as described for the earlier methylations. The 66:34 mixture of 4-methyl to 2-methyl product was measured from the ^1H n.m.r. spectrum of the inseparable mixture, R_F (5% EtOAC–hexane) 0.28, $\nu_{max.}$(film) 1 705 (C=O) and 1 240 cm^{-1} ($SiMe_3$); $\delta_H(CDCl_3)$ the spectrum of the known 4-methyl isomer [5] plus (2-Me isomer) 2.40 (3 H, m, partially obscured), 1.08 (d, 3 H, *J* 6.9 Hz), 1.03 (3 H, t, *J* 7.3 Hz, partially obscured), 0.89 (1 H, dd, *J* 15.5 and 6.5 Hz, $SiCH_AH_B$), and 0.56 (1 H, dd, *J* 15.5 and 8.5 Hz, Si CH_AH_B and −0.01 (9 H, s).

6,6-*Dimethyl*-1-*dimethyl*(*phenyl*)*silylheptan*-3-*one* (**21**).—A catalytic amount of anhydrous zinc bromide (*ca.* 25 mg) was added to a mixture of 2-(trimethylsilyloxy)buta-1,3-diene[16] (2.3 g, 16 mmol) and 1-chloro-2,2-dimethylpropyl phenyl sulphide[17] (4.1 g, 19.2 mmol) in dichloromethane (25 ml) at 25 °C and the reaction stirred for 1.5 h. The liquid was then filtered through neutral alumina (5 g), the solvent evaporated, and the residue flash chromatographed (SiO_2, 500 g, 7.5% EtOAc–hexane) to give 6,6-*dimethyl*-5-*phenylthiohept*-1-*en*-3-*one* (2.51 g, 63%), R_F (7.5% EtOAc–hexane) 0.23, $\nu_{max.}$(film) 1 680 (C=O), 1 605, and 1 580 cm^{-1} (aryl); $\delta_H(CDCl_3)$ 7.55—7.15 (5 H, m, Ph), 6.35 (2 H, m), 5.80 (1 H, dd, *J* 9 and 3 Hz), 3.75 (1 H, t, *J* 6 Hz, PhSC*H*), 2.95 (2 H, d, *J* 6 Hz), and 1.05 (9 H, s) (Found: M^+ 248.1235. $C_{15}H_{20}OS$ requires *M* 248.1235), *m/z* 248 (15%, M^+), 110 (35, PhSH), and 55 (100, CH_2=CHC=O). The silyl-cuprate reagent was added to this ketone by the method described above to give 6,6-*dimethyl*-1-*dimethyl*(*phenyl*)*silyl*-5-*phenylthioheptan*-3-*one* (34%), R_F (10% EtOAc–hexane) 0.34, $\nu_{max.}$(film) 1 705 (C=O), 1 580, and 1 480 cm^{-1} (aryl); $\delta_H(CDCl_3)$ 7.80—7.15 (10 H, m,

aryl), 3.6 (1 H, t, *J* 6 Hz), 2.65 (2 H, d, *J* 6 Hz), 2.3 (2 H, t, *J* 8 Hz), 1.02—0.90 (11 H, s and m, t-butyl and $SiCH_2$), and 0.2 (6 H, s) (Found: M^+ 384.1943, $C_{23}H_{32}OSSi$ requires *M* 384.1944), *m/z* 384 (2%, M^+), 135 (100, $PhMe_2Si$), 110 (30, PhSH). This ketone was desulphurised[18] with W-2 Raney nickel in acetone–EtOH (9:1) for 20 min with a sonnicator to give the *ketone* (**21**) (68%), b.p. 100—110 °C/0.02 mmHg (Kugelrohr) (Found: C, 73.7; H, 10.25. $C_{17}H_{28}OSi$ requires C, 73.8; H, 10.20%), R_F (7.5% EtOAc–hexane) 0.35, $\nu_{max.}$(film) 1 705 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 7.5—7.25 (5 H, m, Ph), 2.40—2.25 (4 H, m), 1.41 (2 H, t, *J* 8.2 Hz), 0.99 (2 H, t, *J* 8.3 Hz), 0.99 (2 H, t, *J* 8.3 Hz), 0.85 (9 H, s), and 0.27 (6 H, s); *m/z* 276 (M^+), 261 (*M* − Me), and 135 ($PhMe_2Si$).

Generation of Enolates from the Ketones (**25**) *and* (**26**).—4-Dimethyl(phenyl)silylbutan-2-one (**25**)[9] and 5,5-dimethylhexan-2-one (**26**)[19] were separately treated with LDA and chlorotrimethylsilane, as described above, to give the silyl enol ethers (**28**) (80%) b.p. 130 °C/0.05 mmHg (Kugelrohr), $\nu_{max.}$(film) 1 630 (C=C) and 1 260 cm^{-1} ($SiMe_3$); $\delta_H(CDCl_3)$ 7.7—7.2 (5 H, m, Ph), 4.05 (2 H, d, *J* 6 Hz), 2.0 (2 H, m), 0.9 (2 H, m), 0.25 (6 H, s), and 0.15 (9 H, s); and 5,5-*dimethyl*-2-(*trimethylsilyloxy*)*hex*-1-*ene* (**29**) (64%), b.p. 73—75 °C/21 mmHg, (Found: C, 66.0; H, 12.0. $C_{11}H_{24}OSi$ requires C, 66.0; H; 12.10%), $\nu_{max.}$(film) 1 640 (C=C), and 1 260 cm^{-1} ($SiMe_3$), $\delta_H(CDCl_3)$ 4.05 (2 H, d, *J* 3 Hz), 2.0 (2 H, m), 1.39 (2 H, m), 0.9 (9 H, s), and 0.2 (9 H, s, $SiMe_3$). Neither compound was contaminated with any trace (^1H n.m.r.) of its regioisomer.

Acknowledgements

We thank the Royal Society for a grant to R. H. S. and Dr. Karl Thomae GmbH., Biberach, West Germany, for leave of absence to W. E.

References

1 C. Eaborn, *J. Chem. Soc., Chem. Commun.*, 1972, 1255 and references therein.
2 I. Fleming, J. H. M. Hill, D. Parker, and D. Waterson, *J. Chem. Soc., Chem. Commun.*, 1985, 318.
3 I. Fleming, J. H. M. Hill, and D. Waterson, unpublished results.
4 I. Fleming and J. D. Kilburn, unpublished results.
5 I. Fleming and J. Goldhill, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1493.
6 E. Friedrich and W. Lutz, *Chem. Ber.*, 1980, **113**, 1245; D. Caine, K. Procter, and R. A. Cassell, *J. Org. Chem.*, 1984, **49**, 2647; D. A. Lightner, T. D. Bouman, J. K. Gawronski, K. Gawronska, J. L. Chappuis, B. V. Crist, and A. E. Hansen, *J. Am. Chem. Soc.*, 1981, **103**, 5314; B. M. Trost, K. Hiroi, and L. N. Jungheim, *J. Org. Chem.*, 1980, **45**, 1839.
7 G. H. Posner and C. M. Lentz, *J. Am. Chem. Soc.*, 1979, **101**, 934.
8 H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, 1969, **34**, 2324.
9 D. J. Ager, I. Fleming, and S. K. Patel, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2520.
10 D. R. Burfield and R. H. Smithers, *J. Chem. Educ.*, 1982, **59**, 703.
11 I. Fleming and I. Paterson, *Synthesis*, 1979, 736.
12 E. Breitmaier and W. Voelter in '^{13}C NMR Spectroscopy,' Verlag Chemie, Weinheim, 2nd. edn., 1978, p. 74.
13 R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, 1976, **98**, 2868.
14 J. Dunogués, A. E. Ekouya, R. Calas, and N. Duffaut, *J. Organomet. Chem.*, 1975, **87**, 151.
15 P. F. Hudrlik and G. P. Withers, *Tetrahedron Lett.*, 1976, 29.
16 P. Cazeau, F. Moulines, O. Laporte, and F. Duboudin, *J. Organomet. Chem.*, 1980, **201**, C9.
17 I. Paterson and I. Fleming, *Tetrahedron Lett.*, 1979, 2179.
18 I. Paterson and I. Fleming, *Tetrahedron Lett.*, 1979, 995.
19 E. H. Man, F. C. Frostick, and C. R. Hauser, *J. Am. Chem. Soc.*, 1952, **74**, 3228.

Received 28*th November* 1985; *Paper* 5/2071