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An approach to open-chain 1,5-stereocontrol using a silyl group

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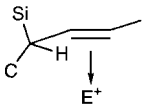
Nucleophilic attack by an ethylcuprate on the α,β-unsaturated ketone 3 takes place *anti* to the silyl group to give largely (96:4) a single product 4, fragmentation of which removes the silyl group, and reveals a pair of stereogenic centres having an open-chain 1,5 relationship 9.

We have developed a substantial body of chemistry in which a stereogenic centre carrying a silyl group controls the stereochemistry of electrophilic attack on a C=C double bond in the sense **1**,[1] and we have also adapted these reactions to control

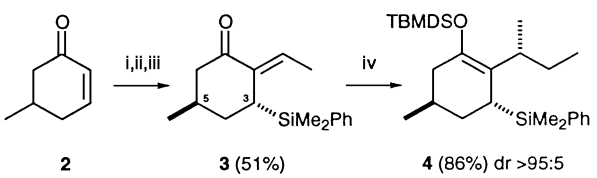


1

more distant open-chain relationships, including 1,4 in the course of syntheses of tetrahydrolipstatin[2] and of nonactin,[3] and 1,6 in an S_E2'' reaction.[4] The use of a silyl group to control 1,4-relationships has also been exploited by Procter[5] and by Panek.[6] We have now developed a method for the control of a 1,5-relationship, which we describe here. The essence of our approach is successively to set up two 1,3-relationships, moving the stereochemistry three atoms along the chain each time. By using a silyl group in the middle, we can remove the intervening functionality and stereochemistry to reveal the open-chain 1,5-relationship.

We began with the well established 1,3-control seen in conjugate additions to 5-substituted cyclohexenones,[7] which we already knew was well behaved when the nucleophile was a silyl group.[8] On this occasion we used the phenyldimethylsilylzincate reagent[9] with 5-methylcyclohex-2-enone **2** (Scheme 1), and the intermediate zinc enolate readily underwent an aldol reaction with acetaldehyde to give a β-hydroxy ketone as a mixture of diastereoisomers. Dehydration gave, as far as we could tell, a single α,β-unsaturated ketone **3** with the C-5 methyl and C-3 silyl groups *trans* to each other and the exocyclic double bond with a *Z* configuration (COSY and NOESY). This set up the first 1,3-relationship, and we set up the second by conjugate addition of an ethylcuprate reagent in the presence of *tert*-butyldimethylsilyl chloride. This gave a silyl enol ether **4** as a single diastereoisomer (^{1}H-NMR, >95:5), which proved (see below) to have the relative configuration illustrated.

We carried out the complementary sequence, trapping the zinc enolate with propionaldehyde instead of acetaldehyde, and adding a methylcuprate to the α,β-unsaturated ketone **5**, which gave largely (86:14) the alternative stereoisomer **6** (Scheme 2).



2 **3** (51%) **4** (86%) dr >95:5

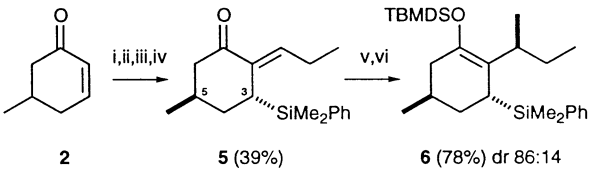
Scheme 1 *Reagents and conditions*: i, $PhMe_2SiZnMe_2$ Li, THF, −78 °C, 1 h; ii, MeCHO, −78 °C, 2 h; iii, MsCl, Py, $CHCl_3$, reflux, 16 h; iv, TBDMSCl, Et_2CuLi LiCN, THF, −78 °C, 1 h.

This time we could clearly see the signals (^{1}H-NMR) of the minor isomer, which were identical to those we had already seen for the isomer **4**. Clearly, the reaction had been stereochemically highly controlled, and either stereoisomer, **4** or **6**, could be obtained with nearly equal ease.

We hydrolysed the silyl enol ether **4**, and obtained a single diastereoisomer of the ketone **7**, which was unaffected by treatment with sodium methoxide, suggesting that it was the thermodynamically favourable isomer (Scheme 3). We then applied a fragmentation reaction developed by Nishiyama and Itoh,[10] using the oxime acetate **8**, and obtained the alkene **9** with the 1,5-relationship between C-3 and C-7 revealed in an open chain. That the alkene had a *trans* double bond showed that the relative stereochemistry assigned (COSY and NOESY) to C-2 in the ketone **7** was correct, since Itoh has shown that this type of fragmentation is stereospecifically *anti*.

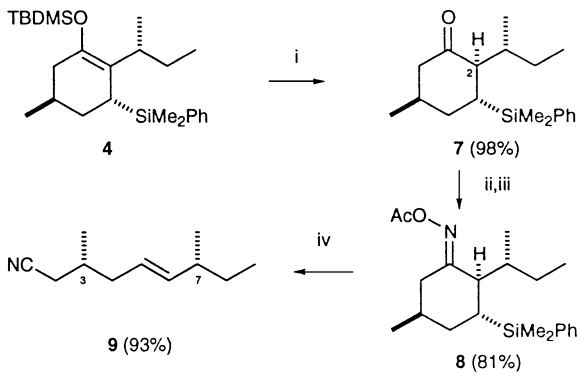
We proved the relative stereochemistry between the 1,5-related centres, by carrying out the same sequence using enantiomerically pure (5*R*)-methylcyclohex-2-enone **1**,[11] and obtained the nitrile **9** enantiomerically pure at C-3. Ozonolysis and borohydride reduction gave 2-methylbutanol, derivatisation of which with Mosher's acid gave us the known esters (Scheme 4).[12] The major component **10** was the *R*,*R*-diastereoisomer (^{1}H-NMR), and a minor component (4%) was now detectable and identifiable as the *R*,*S*-diastereoisomer, allowing us to measure, more accurately than it had been possible to from the earlier NMR spectra, the degree to which we had been successful in the conjugate addition step **3** → **4**.

We suggest that, if the silyl group in the α,β-unsaturated ketone **3** were equatorial **11**, it would suffer from steric compression with the methyl group on the exocyclic double



2 **5** (39%) **6** (78%) dr 86:14

Scheme 2 *Reagents and conditions*: i, $PhMe_2SiZnMe_2$ Li, THF, −78 °C, 1 h; ii, EtCHO, −78 °C, 2 h; iii, MsCl, Et_3N, CH_2Cl_2, 0 °C, 2 h; iv, DBU, toluene, reflux, 4 h, or NaH, THF, 0 °C → rt, 12 h; v, Me_2CuLi LiCN, THF, −78 °C, 40 min; vi, TBDMSCl, HMPA, Et_3N, −78 °C, 1 h.



4 **7** (98%) **8** (81%) **9** (93%)

Scheme 3 *Reagents and conditions*: i, HCl, H_2O, THF, rt, 14 h; ii, NH_2OH HCl, Py, EtOH, reflux, 12 h; iii, Ac_2O, Py, CH_2Cl_2, 0 °C → rt, 4 h; iv, Me_3SiOTf, CH_2Cl_2, 0 °C, 4 h.

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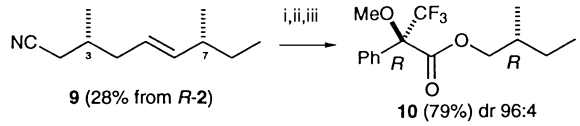
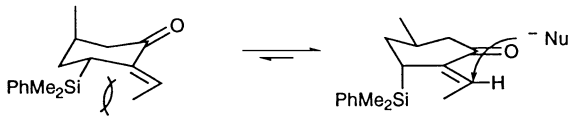


9 (28% from *R*-**2**) **10** (79%) dr 96:4

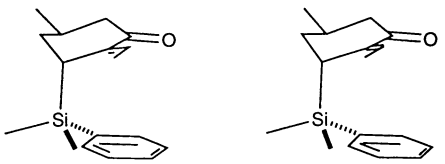
Scheme 4 *Reagents and conditions*: i, O_3, Et_2O, −78 °C, 10 min; ii, $NaBH_4$, H_2O, 0 °C, 1 h; iii, Mosher's *R*-acid, DCC, DMAP, CH_2Cl_2, rt, 16 h.



11 **12**

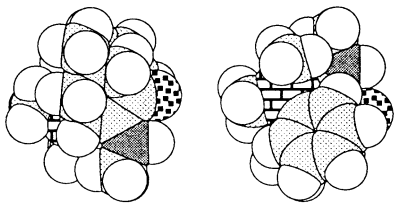
bond. In consequence, even though a trimethylsilyl group has a larger A-value than a methyl group (2.5[13] and 1.74, respectively), the lower-energy conformation of the enone **3** probably has the methyl group equatorial and the silyl group axial **12**, where, in any case, it only has one 1,3-diaxial interaction. With the silyl group held on the lower surface, nucleophilic attack can be expected to take place on the top surface *anti* to the bulky group **12** (arrow), and hence give the silyl enol ether with the relative configuration **4**.

To support this argument, we carried out molecular modelling calculations (Macromodel), which confirmed that the conformation with the silyl group axial **12** had the lowest energy,[14] with the stereo drawings **13** giving a more accurate



13

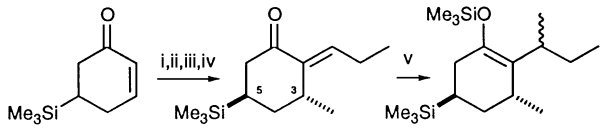
picture of the minimised structure. Looking at the space-filling versions **14** (from above) and **15** (from below) illustrates the difference between the two surfaces of the enone **3**—the β-carbon (darker grey) in the top view is exposed, but in the bottom view it is hindered by the substituents on the silyl group.[15]



14 top view **15** bottom view

Furthermore, the calculation for the second α,β-unsaturated ketone **5** revealed why it suffered a lower degree of stereocontrol in the conjugate addition step—the methyl group of the ethyl group was oriented upwards, hindering the top surface more than the top surface of the α,β-unsaturated ketone **3** = **12** = **13**.

The stereocontrol in this system is interesting from two points of view. In the first place, it shows that the silyl group is not so hindering that it cannot adopt the axial position, and yet simultaneously it does hinder the approach of the incoming nucleophile. The long Si–C bond takes the silyl group far enough away from the cyclohexane ring to make 1,3-diaxial interactions less severe than they would be for a carbon-based group, and yet the length of the Si–C bonds to the three other substituents on the silicon atom causes them to occupy much of the space below the double bond. In the second place, this is the first reaction that we have studied in which the double bond



16 **17** (41%) **18** (74%) dr 50:50

Scheme 5 *Reagents and conditions*: i, Me_2CuLi, THF, −78 °C, 1 h; ii, TBDMSCl, HMPA, Et_3N, −78 °C → rt, 1 h; iii, EtCHO, $TiCl_4$, CH_2Cl_2 −78 °C, 2 h; iv, TsOH, toluene, reflux, 1 h; v, Me_2CuLi, THF, −78 °C, 1 h; vi, TMSCl, HMPA, Et_3N, −78 °C → rt, 1 h.

adjacent to the stereogenic centre carrying a silyl group has undergone *nucleophilic* attack. All our work in the past has involved electrophilic attack. Since the sense of attack, *anti* to the silyl group **1**, is the same, it may be that we have here some indication that the stereocontrol is largely steric in origin. This conclusion stems from the prejudice that nucleophilic attack and electrophilic attack would take place in opposite senses if purely electronic effects were operative.

Although this may be a little too simplistic, we can be sure that the silyl group is an important component in ensuring the high levels of diastereocontrol that we have seen, for we have carried out a similar set of reactions with the C-5 methyl group and the C-3 silyl group in **5** interchanged (Scheme 5). Starting with the silicon-containing cyclohexenone **16**,[16] and using a methylcuprate to set up the 1,3-related centres in the enone **17**. This time, the conjugate addition of the methylcuprate gave both possible diastereoisomers **18** in equal amounts. Presumably a methyl group on C-3, although surely held axial, shields the bottom surface from attack to the same extent as the upturned methyl group on the side chain shields the top surface.

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Notes and references

1 Summarised in: I. Fleming, *J.. Chem. Soc., Perkin Trans. 1*, 1992, 3363.
2 I. Fleming and N. J. Lawrence, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2679.
3 M. Ahmar, C. Duyck and I. Fleming, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2721; I. Fleming and S. K. Ghosh, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2733.
4 I. Fleming and C. P. Leslie, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1197.
5 G. Procter, A. T. Russell, P. J. Murphy, T. S. Tan and A. N. Mather, *Tetrahedron*, 1988, **44**, 3953.
6 C. E. Masse and J. S. Panek, *Chem. Rev.*, 1995, **95**, 1293.
7 N. L. Allinger and C. K. Riew, *Tetrahedron Lett.*, 1966, 1269. For the most recent discussion, see S. Mori and E. Nakamura, *Chem. Eur. J.*, 1999, **5**, 1534. For the first application in synthesis, see G. Stork, R. A. Kretchmer and R. H. Schlessinger, *J. Am. Chem. Soc.*, 1968, **90**, 1647; G. Stork, *Pure Appl. Chem.*, 1968, **17**, 383.
8 I. Fleming, R. Henning, D. C. Parker, H. E. Plaut and P. E. J. Sanderson, *J. Chem. Soc., Perkin Trans. 1*, 1995, 317.
9 R. A. N. C. Crump, I. Fleming and C. J. Urch, *J. Chem. Soc., Perkin Trans. 1*, 1994, 701.
10 H. Nishiyama, K. Sakuta, N. Osaka, H. Arai, M. Matsumoto and K. Itoh, *Tetrahedron*, 1988, **44**, 2413.
11 D. Caine, K. Procter and R. A. Cassell, *J. Org. Chem.*, 1984, **49**, 2647.
12 H. Oikawa, I. Matsuda, T. Kagawa, A. Ichihara and K. Kohmoto, *Tetrahedron*, 1994, **50**, 13 347.
13 W. Kitching, H. A. Olszowy, G. M. Drew and W. Adcock, *J. Org. Chem.*, 1982, **47**, 5153.
14 The chair conformation with the silyl group equatorial is 46.5 kJ mol^{-1} higher in energy, and there are two families of boat conformations in between, at 13 and 40 kJ mol^{-1} above the minimum.
15 Although the calculation places the phenyl group under the carbonyl group, a methyl group would be nearly as much hindrance at the β-carbon; we do not think that the high degree of selectivity is dependent upon the presence of the phenyl group on silicon.
16 M. Laguerre, J. Dunoguès R. Calas and N. J. Duffaut, *J. Organomet. Chem.*, 1975, **93**, C17; M. Asaoka, K. Shima and H. Takei, *Tetrahedron Lett.*, 1987, **28**, 5669.