

## Diastereoselective Aldol Reactions of $\beta$ -Silylenolates†

Ian Fleming\* and Jeremy D. Kilburn

University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.

$\beta$ -Silylenolates react with aldehydes with high diastereoselectivity with respect to both new chiral centres, the relative stereochemistry in the aldol relationship being dependent upon the geometry of the enolate double bond.

In our earlier work,<sup>1</sup> we showed that a wide range of  $\beta$ -silylenolates, generated by conjugate addition of our silylcuprate reagent to  $\alpha,\beta$ -unsaturated esters (**1**), could be alkylated with high diastereoselectivity. In that work, the electrophile was always an alkyl halide, and only two chiral centres were set up. We now report the control of a third chiral centre: aldehydes react with the same high diastereoselectivity shown by alkyl halides, but the aldol stereochemistry between C-2 and C-3 is also well controlled, in either the *syn* (*erythro*) or *anti* (*threo*) sense. This control is possible, because, as we reported earlier, *we have easy access to both geometrical isomers of the enolates* (**2**) and (**3**), as shown in Scheme 1. These isomers give different aldol products (**4**) and (**5**) in high yield and with high selectivity (Table 1).

We proved the relative stereochemistry between C-2 and C-3 by reducing the purified products (**4b**) and (**5b**) with lithium aluminium hydride and forming the acetone of the 1,3-diols. These gave easily interpretable <sup>1</sup>H n.m.r. spectra, which established that the stereochemistry between C-2 and C-3 was that expected for lithium enolates with sterically demanding groups attached to C-2 of the enolate structure.<sup>2</sup>

We assigned the relative stereochemistry between C-1 and C-2 in two ways. First, we checked that trigonal electrophiles which do not introduce a third chiral centre generally react in the same sense as the alkyl halides we had used earlier. Thus

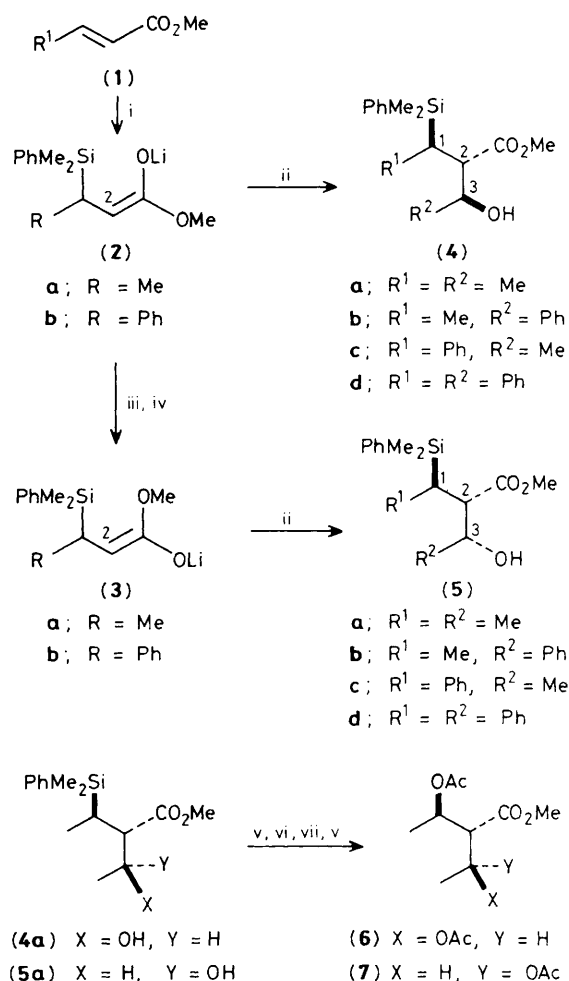
phenylthiomethyl chloride reacted with the silyl enol ethers (**2a**) or (**3a**) (SiMe<sub>3</sub> for Li) in the presence of zinc bromide,<sup>3</sup> to give largely (82:18 or 87:13) one diastereoisomer. Desulphurisation of the mixture of products gave a mixture of diastereoisomers in the same ratios, and with the same major isomer as we had seen earlier when we alkylated the enolate

**Table 1.** Diastereoselectivity in aldol reactions of the  $\beta$ -silylenolates (**2**) and (**3**).

Enolate	Aldehyde	Major product	Isolated yield (%) of major product <sup>a</sup>	Ratio <sup>b</sup> ( <b>4</b> ):( <b>5</b> )
( <b>2a</b> )	MeCHO	( <b>4a</b> )	73	89:11
( <b>3a</b> )	MeCHO	( <b>5a</b> )	81	6:94
( <b>2a</b> )	PhCHO	( <b>4b</b> )	90	94:6
( <b>3a</b> )	PhCHO	( <b>5b</b> )	79	9:91
( <b>2b</b> )	MeCHO	( <b>4c</b> )	81 <sup>c</sup>	85:15
( <b>3b</b> )	MeCHO	( <b>5c</b> )	78	9:91
( <b>2b</b> )	PhCHO	( <b>4d</b> )	81	91:9
( <b>3b</b> )	PhCHO	( <b>5d</b> )	79	10:90

<sup>a</sup> Except where otherwise stated, free (<sup>1</sup>H n.m.r.) of diastereoisomers. <sup>b</sup> Determined by <sup>1</sup>H n.m.r. spectroscopy. Except where otherwise stated, the minor products, with opposite relative configuration between C-1 and C-2, were not detectable by <sup>1</sup>H n.m.r. spectroscopy. <sup>c</sup> Contaminated with about 4% of one of the diastereoisomers isomeric between C-1 and C-2.

† No reprints available.



**Scheme 1.** Reagents: i,  $(PhMe_2Si)_2CuLi$ ; ii,  $R^2CHO$ ,  $-78^\circ C$ ; iii,  $NH_4Cl$ ,  $H_2O$ ; iv, lithium di-isopropylamide, tetrahydrofuran,  $-78^\circ C$ ; v,  $Ac_2O$ ,  $Et_3N$ ; vi,  $BF_3 \cdot 2AcOH$ ; vii, *m*-chloroperbenzoic acid,  $Et_3N$ ,  $Et_2O$ .

(**2a**) with methyl iodide.<sup>1</sup> Furthermore, we found that a range of trigonal electrophiles (formaldehyde, Eschenmoser's salt,<sup>4</sup> and 2-trimethylsilylbut-1-ene-3-one<sup>5</sup>) reacted with the enolates (**2a**) and (**3a**) with high diastereoselectivity, and that two other trigonal electrophiles (the 1,3-dithienium cation<sup>6</sup> and methoxymethyl chloride with zinc bromide<sup>7</sup>) reacted with the trimethylsilyl enol ethers corresponding to the enolates (**2a**) and (**3a**). It is most unlikely that the sense of the diastereoselectivity has inverted for any of these reactions, which all gave diastereoselectivity better than 70:30, with most close to 90:10. Secondly, we converted the alcohol (**4b**) into the chloride ( $SOCl_2$ ,  $Et_3N$ ) and hydrogenolysed the chloride ( $H_2$ , Pd, C, 45 psi). The product was the same diastereoisomer that we had obtained earlier by benzylation of the enolate (**2a**).<sup>1</sup>

Finally, we proved the relative stereochemistry between C-1 and C-3 by converting the alcohols (**4a**) and (**5a**) into the diacetates (**6**) and (**7**), using the two steps we had earlier developed to convert phenyldimethylsilyl groups into hydroxy groups with retention of configuration.<sup>8</sup> The products (**6**) and (**7**) were readily distinguished; the symmetry of the former and the asymmetry of the latter were evident from their  $^1H$  n.m.r. spectra.

Received, 18th November 1985; Com. 1626

## References

- 1 I. Fleming, J. H. M. Hill, D. Parker, and D. Waterson, *J. Chem. Soc., Chem. Commun.*, 1985, 318.
- 2 D. A. Evans, J. V. Nelson, and T. R. Taber, *Top. Stereochem.*, 1982, **13**, 1.
- 3 I. Fleming and I. Paterson, *Tetrahedron Lett.*, 1979, 993.
- 4 J. Schreiber, M. Haag, N. Hashimoto, and A. Eschenmoser, *Angew. Chem., Int. Ed. Engl.*, 1971, **10**, 330; J. C. Roberts, P. S. Borromeo, and C. D. Poulter, *Tetrahedron Lett.*, 1977, 1621.
- 5 G. Stork and B. Ganem, *J. Am. Chem. Soc.*, 1973, **95**, 6152; R. K. Boekman, D. M. Blum, B. Ganem, and N. Halbey, *Org. Synth.*, 1978, **58**, 152.
- 6 I. Paterson and L. G. Price, *Tetrahedron Lett.*, 1981, **22**, 2829.
- 7 I. Paterson, *Tetrahedron Lett.*, 1979, 1519; T. Shono, I. Nishiguchi, T. Komamura, and M. Sasaki, *J. Am. Chem. Soc.*, 1979, **101**, 984.
- 8 I. Fleming, R. Henning, and H. Plaut, *J. Chem. Soc., Chem. Commun.*, 1984, 29.