Facial Selectivity in Nucleophilic Reactions of Spirocyclic Ketones can be controlled by a Distant, Orthogonal Double Bond

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Spiro[4.5]dec-7-ene-1,4-dione and derivatives substituted at C-7, C-8, and/or C-9 gave products of reaction with methyllithium and with sodium borohydride that in every instance favoured nucleophilic carbonyl attack on the face *syn* to the double bond; the results are consistent with stereoelectronic control, and the selectivity correlates with a difference in the abilities of the orthogonal C–C bonds to donate electron density.

Some synthetic studies in our laboratories have used spirocyclic diketones as key synthetic intermediates.[1] Facial selectivity in the reactions of these ketones will be important in establishing the stereochemistry in future synthetic endeavours.

There is growing evidence to indicate that facial selectivity in the reactions of carbonyl compounds can be controlled by stereoelectronic factors.[2,3] With this in mind the spirodiketone **1** was prepared, by geminal acylation using 1,2-bis(trimethylsilyloxy)cyclobutene and the requisite unsaturated ketal,[4] to ascertain if there would be significant facial selectivity in its (single) reactions. Treatment with methyllithium† gave **2a** and **3a** in a ratio of 5:1, and sodium borohydride provided **2b** and **3b** in a ratio of 6:1. Thus, the preferred pathway in both reactions was by attack onto the face of the carbonyl *syn* to the distant double bond.

The influence of remote substituents (on C-7, C-8 and C-9) was investigated with methyl derivatives **4**, **5** and **6** (Table 1). Substitution on C-7 and C-9 enhanced *syn*-addition very marginally, except **6** was considerably more selective in its $NaBH_4$ reduction. (The double bond of **6** must have played a role in enhancing the *syn*-addition because its reduced form **7** was less selective than **6**.) In contrast, **5**, with a methyl group at C-8, was a little less selective than **1**. However, the combination of the *syn*-favouring features of **4** and **6** in **8** led to a dramatic, synthetically useful, improvement in the facial selectivity such that NMR signals for an *anti*-product were not noted in the spectra of the crude products. (After the MeLi reaction of **8** a small amount of the *anti*-adduct was discovered in a single chromatographic fraction.[5] Some $NaBH_4$ *anti*-product was prepared for chromatographic and NMR comparison by reduction to the *trans*-diol and partial reoxidation).

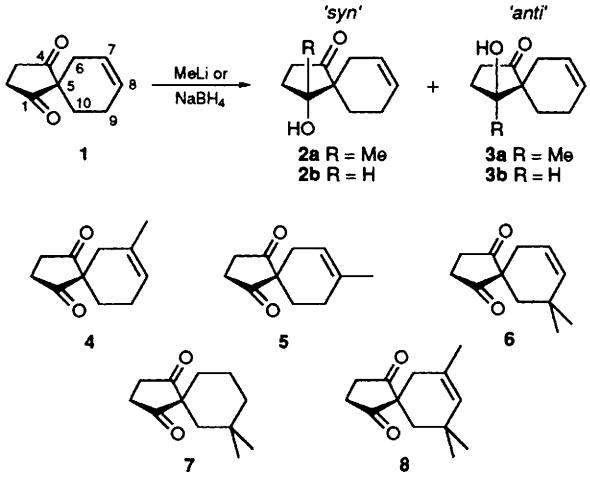


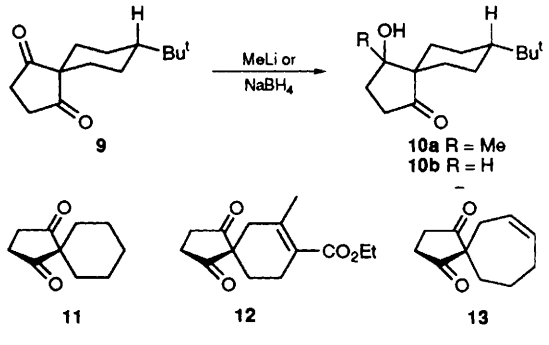
Table 1 Facial selectivity in the reactions of spiro-diketones

	MeLi[a]		$NaBH_4$[b]	
Diketone	Yield (%)	*syn*:*anti*[c]	Yield (%)	*syn*:*anti*[c]
1	86	5:1	94	6:1
4	86	6:1	92	7:1
5	89	4:1	89	2.5:1
6	91	6:1	94	14:1
7	86	3:1[d]	82	7:1[d]
8	87	63:1[e]	80	>99:1

[a] MeLi (2–5 mol. equiv.) in diethyl ether at −78 °C. [b] $NaBH_4$ (0.25–0.3 mol. equiv.) in MeOH at room temp. [c] Ratios were determined by careful integration of 300 MHz ^1H NMR spectra of the crude products. Relative stereochemistries were assigned based on nuclear Overhauser effect difference spectra and in some instances X-ray crystal structures. The products of **7** were correlated with those of **6** by catalytic hydrogenation. [d] *Syn* is defined as addition to the face opposite the dimethyls. [e] Ratio of isolated products.[5]

Diketones **1** and **4–8** are nominally symmetrical, but their cyclohexene moieties must be rapidly interchanging half-chair conformers in which the two carbonyl groups are distinct. The conformationally locked diketone **9** reacted with methyllithium and with sodium borohydride to give almost exclusively the products of attack on the equatorial carbonyl (with respect to the cyclohexane ring), *i.e.* **10a** and **10b**. A similar preference can be expected in **1** and **4–8**. Models show that substituents on C-7 or C-9 cannot directly influence the facial selectivity of an equatorial carbonyl by steric hindrance. (Also, diketone **4**, which bears a methyl at C-7, was marginally more selective for the *syn*-face than was **1**, and **7**, which has no double bond, does indeed react with facial selectivity.) Thus, any steric control of facial selectivity would have to arise from the small differences in the positions of the C-6 hydrogens *vs.* the C-10 hydrogens in **1**, and the changes in facial selectivity, however significant, seen in Table 1 would have to reflect differences in the C-6 and C-10 hydrogens. To address this possibility a few rates of $NaBH_4$ reduction were compared competitively. Diketone **1** was reduced 1.5 times faster than the saturated diketone **11**, and **6**, which is more substituted than **1**, was reduced 5 times faster than **11**. Thus, it appeared that the distant double bond and the methyl groups on C-9 influenced the reacting carbonyl in a facially biased manner by a rate-accelerating phenomenon, whereas one would have expected steric hindrance to result in a retardation of rate.

Stereochemical information was probably transmitted from the cyclohexene ring to the reacting carbonyl through the C–C bonds adjacent, and orthogonal, to the carbonyl. Our results correlated with the ability of these adjacent bonds to donate electron density to the face opposite the incoming nucleophile as, for instance, the Cieplak model for selectivity[3] would predict (*i.e.* C-5,10 > C-5,6). *syn*-Selectivity was somewhat enhanced by methyls (electron-donating groups) at C-7 and C-9. These must have increased the electron density on the *anti*-



face, and, by induction, C-5,10 became more able to donate electron density. In contrast, methyl substitution at C-8 would have increased electron-density on the *syn*-face; consequently *syn*-selectivity decreased as the two adjacent bonds became more similar in their electron-donating abilities. This rationalization suggested that electron-withdrawal would have the reverse effect on facial selectivity. Indeed, $NaBH_4$ reduction of compound **12** gave a ratio of 12:1 of the *syn*- and *anti*-reaction products, respectively, which was more selective than **4**. Finally, reactions of **13** showed less facial selectivity than did those of **1** (1.5:1 with MeLi, 2:1 with $NaBH_4$, both favouring the *syn*-product). In spite of the conformational mobility of the cycloheptene ring, the results with **13** were in agreement with a 'through-bonds' facial phenomenon with the homo-allylic nature of C-10 in the cyclohexene-derived diketones being important.

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Footnote

† Excess of methyllithium was necessary to obtain a good yield without any doubly methylated product. D_2O quench of a MeLi reaction gave a product with two D's per molecule. Thus, it appeared that the nonreactivity of the second carbonyl was due to enolization. (In contrast, reductions were monitored closely by TLC so that diol formation could be prevented.)

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