Folding Strain Control for Remote Stereocontrol: Diastereoselectivity in the Ring Closure Reactions of 2-(6′-Trimethylsilylhex-4′-enyl)cyclohex-2-enones with Alkyl Groups at Various Positions in the Side Chain

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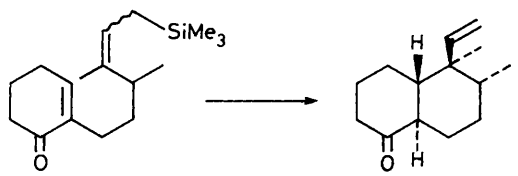
The general utility of the folding strain control concept for remote stereocontrol has been examined in the ring closure reaction of 2-(6′-trimethylsilylhex-4′-enyl)cyclohex-2-enones with various alkyl-substituted side chains.

Recently we reported a doubly stereocontrolled cyclization of the substituted cyclohexenone (**1**) to the decalone derivative (**2**) (Scheme 1).[1] One of the factors leading to stereocontrol is associated with diastereoface selection in the cyclization which is determined by the conformational preference of the 3′-substituent with respect to the diastereoisomeric chain-folding of the acyclic chain in the transition state. Generally in the ring closure reaction of an acyclic chain, in which the bond-forming atom is diastereotopic with respect to a remote chiral centre, two diastereoisomeric transition states A and B are possible (Scheme 2). The energy difference between these of a few kcal/mol (1 cal = 4.184 J) is sufficient to make the reaction diastereoselective. In other words, even if the chiral centre is remote from the bond-forming atom, there would be sufficient possibility that the energy difference between A and B could be large enough for the diastereoface selection to be effective,[2] since the strain energy affecting the energy balance of the diastereoisomeric chain-foldings A and B arises from many factors.[1] We proposed the term folding strain control for this concept.[1] In order to exemplify the utility of this, we investigated the stereoselectivity in the ring closure reaction of 2-(6′-trimethylsilyl-4′-enyl)cyclohex-2-enones with the various alkyl-substituted side chains.†

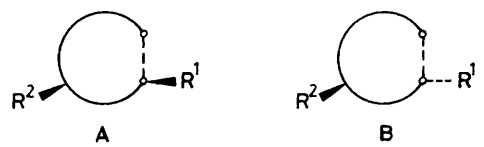
In the cyclization of the 1′-substituted compounds (**3**) and (**4**), two major counteracting factors are possible for the diastereoface selectivity in the transition state.‡ One is the *peri*-interaction with the co-ordinated carbonyl group which favours the axial-like disposition and the other is the increase in extent of steric interactions (mainly *gauche*) inherent such a conformation. The experimental results in Table 1§ conform with the prediction as a whole.¶ The larger substitutent tends to favour the formation of the axial rather than the equatorial product (entries 4 *vs.* 2).

In the case of the 2′-substituted substrate, the preference for the equatorial cyclization product (**12**) over the axial one (**11**) is reasonably predicted, in view of the additional *gauche* interaction in the transition state leading to the latter product. In fact the products (**12a**) and (**12b**) were obtained with good to excellent selectivity from (**5a**) and (**5b**) respectively (entries 6 and 7). The better selectivity for (**5b**) than for (**5a**) arises from the nonbonded interaction between the 2′ and 4′ dimethyl groups which are juxtaposed in the process of the chain-folding leading to the transition state. In this connection the steric energy (SE) difference between the diastereoisomeric products calculated by molecular mechanics techniques (MM-2) for the primary product enols (ΔSE = 1.24 and 3.54 kcal/mol without and with 5-methyl group respectively) is suggestive, even if the assumption of an early transition state is justified for the present reaction. Strain factors may operate to more or less similar degree in both transition state and product.

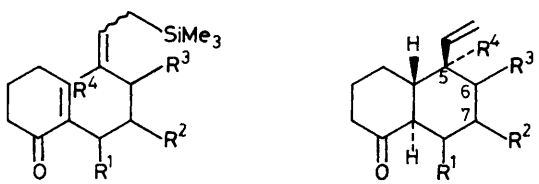


(**1**) (**2**)

Scheme 1. *Reagents*: $TiCl_4/CH_2Cl_2$, then NaOMe/MeOH.



Scheme 2



a; R^4 = H
b; R^4 = Me

	R^1	R^2	R^3		R^1	R^2	R^3
(**3**)	Me	H	H	(**7**)	α-Me	H	H
(**4**)	Bu^n	H	H	(**8**)	β-Me	H	H
(**5**)	H	Me	H	(**9**)	α-Bu^n	H	H
(**6**)	H	*anti*-Me		(**10**)	β-Bu^n	H	H
				(**11**)	H	α-Me	H
				(**12**)	H	β-Me	H
				(**13**)	H	α-Me	α-Me
				(**14**)	H	β-Me	β-Me

† The 1′-substituted substrates were synthesized by the eliminative conjugate addition[3] of suitable cuprate reagents to 2-(6′-trimethylsilylhex-4′-enylidene)-3-phenylsulphenylcyclohexanones prepared from cyclohexenone and stereoselectively constructed 6-trimethylsilylhex-4-enals by Nozaki's method.[4] The 2′- and 2′,3′-anti-substituted substrates were obtained by the coupling[5] of stereoselectively prepared 6-trimethylsilylhex-4-enyl iodides with 2-lithio-3-ethylenedioxycyclohex-1-ene.

‡ Only the chair-like conformation is assumed throughout the discussion in this communication.

§ The cyclization was performed in the presence of $TiCl_4$ in CH_2Cl_2 solution at −78 °C and the mixture of the product stereoisomers was analysed by capillary g.l.c. The structure assignment of the products giving the g.l.c. peaks was possible in most cases with the aid of equilibration experiments (NaOMe) and n.m.r. spectroscopy (^1H and ^{13}C; ^1H homonuclear spin decoupling; nuclear Overhauser enhancement).

¶ In all the cyclization reactions listed, no products isomeric with respect to simple diastereoselection were detected (orientation control).[1]

Table 1. Diastereoselectivity in the cyclization of 2-(6′-trimethylsilylhex-4′-enyl)-cyclohexenones.

	Cyclization substrate						Cyclization product		
Entry		R^1	R^2	R^3	R^4	A/B	Yield (%)	Diastereoisomer ratio	ΔSE(A − B)/ kcal/mol
1	(**3a**) *Z*	Me	H	H	H	(**7a**)/(**8a**)	100	1:1.0	1.13
2	(**3a**) *E*	Me	H	H	H	(**7a**)/(**8a**)	79	1:1.8	1.13
3	(**3b**) *E*[a]	Me	H	H	Me		75[d]		2.43
4	(**4a**) *E*[b]	Bu^n	H	H	H	(**9a**)/(**10a**)	80	1:4.0	
5	(**4b**) *E*[c]	Bu^n	H	H	Me	(**9b**)/(**10b**)	99	1:1.7	
6	(**5a**) *E*	H	Me	H	H	(**11a**)/(**12a**)	47.2[e]	1:18.7	1.24
7	(**5b**) *E*	H	Me	H	Me	(**11b**)/(**12b**)	44.5[e]	1:>500	3.54
8	(**6a**) *E*	H	Me	Me	H	(**13a**)/(**14a**)	84.2[e]	6.9:1	−1.13
9	(**6b**) *E*	H	Me	Me	Me	(**13b**)/(**14b**)	82.6[e]	1:8.7	3.53

[a] *E*/*Z* = 7:1. [b] *E*/*Z* = 16:1. [c] *E*/*Z* = 7:1. [d] Complex mixture. The analysis failed. [e] After treatment with NaOMe/MeOH.

The substrate pair examined next is the 2′,3′-*anti*-disubstituted compounds (**6a**) and (**6b**), where the influence of the two substituents is opposing, both tending to hold the equatorial disposition. The number of *gauche* interactions is similar in both diastereoisomeric transition states, provided that the energy arising from the methyl group being staggered with respect to two alkyl groups is counted as twice that derived from the simple *gauche* interaction.[6] In the case of the substrate (**6a**), the additional $A^{1,3}$-interaction experienced by the 3′-methyl group in the transition state leading to the 7-equatorial product (**14a**) suggests the preponderance of the 6-equatorial product (**13a**). However in the case of the 4′-substituted substrate (**6b**), the severe 1,3-diaxial-like interaction between 2′- and 4′-methyl groups might outweigh the effect described for (**6a**) and lead to a predominant formation of 7-equatorial product (**14b**). With regard to the stability relationship of the product enols, the 6-*eq*., 7-*ax*.-decalone (**13a**) has a lower calculated steric energy than (**14a**) by 1.13 kcal/mol and with the methyl group at the 5α-position the 6-*ax*., 7-*eq*.-decalone (**14b**) become more stable than (**13b**) by 3.53 kcal/mol. In practice, the cyclization of (**6a**) yielded (**13a**) and (**14a**) in a ratio of 6.9:1 and the substrate (**6b**) with the 4′-methyl group gave a 1:8.7 ratio of (**13b**) to (**14b**), the selectivity thus being reversed.

The cyclization studies described above indicate that remote stereocontrol based on the folding strain control principle may afford the cyclization product in excellent diastereoface selectivity in favourable cases and this possibility may be predicted by gross analysis of the strain factors in the folding of the acyclic chain. Force field calculations on the primary products may be indicative to some extent, but such techniques have to be applied with utmost care. Although more examples and the developement of more suitable calculation methods are necessary, we believe that the concept of folding strain control is useful as a strategy for stereoselective ring formation.

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