

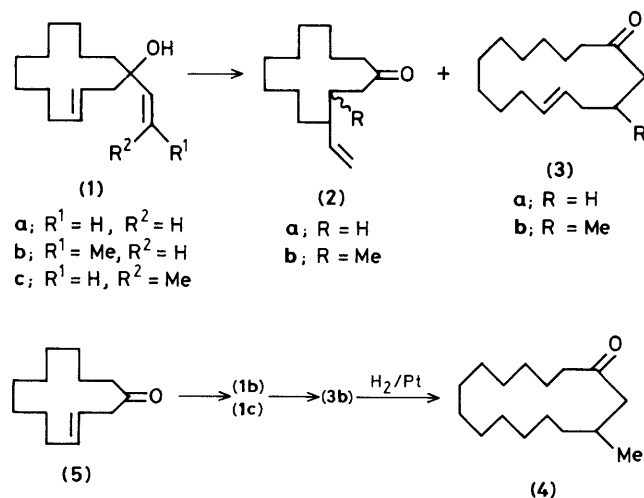
Substituent Control of Periselectivity: Application to the Synthesis of (\pm)-Muscone

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The thermal, [1,3]-shift siloxy-Cope, ring expansion is shown to be highly favoured relative to the [3,3]-shift for the large-ring system required for the synthesis of muscone.

In earlier work,¹ we noted that the trimethylsilyl derivative of compound (**1a**) rearranges thermally at 298.6 °C with both [1,3]- and [3,3]-sigmatropic shifts to give a rather unselective 54 : 46 ratio of (**2a**) and (**3a**) (see Table 1). We now report a striking change in periselectivity when a methyl group is added to the terminal position of the vinyl group. The trimethylsilyl derivatives of both the *trans* and *cis* methyl compounds, (**1b**) and (**1c**), undergo the thermal [1,3]-shift ring expansion to



(**3b**) with <2% of the competing [3,3]-shift. This opens up a rather straightforward route² to muscone, (**4**). Cyclododecene was converted into cyclotridec-3-enone, (**5**), in five steps as outlined earlier.¹ The Grignard reagent formed from prop-1-enyl bromide (mixed isomers) was added to (**5**), which generated a 46% yield of (**1b**) and (**1c**). The 33 : 67 mixture of (**1b**) and (**1c**) was separated by flash chromatography. Thermolysis of the trimethylsilyl derivative of each isomer cleanly produced (**3b**) (see Table 1) which was reduced over Adams catalyst (71%) to give (\pm)-muscone, (**4**). Thus, the separation of (**1b**) and (**1c**) in the above sequence is not necessary since both lead to the desired product.†

The dramatic change in periselectivity of the siloxy-Cope rearrangement of (**1b**) or (**1c**) presumably arises because the methyl group sterically destabilizes the transition state for the [3,3]-shift more than that for the [1,3]-shift. There is some precedent for this in earlier work¹ which demonstrated that the more congested medium-sized rings favoured the [1,3]-shift more than the [3,3]-shift. When the rearrangements of (**1b**) or (**1c**) are carried out by treating with KH in hexamethylphosphoric triamide (HMPA),³ the [1,3]- to [3,3]-shift ratio increases relative to (**1a**) but not to a useful selectivity for synthesis (see Table 1).

† All new compounds gave satisfactory high resolution mass spectra as well as supporting i.r., ¹H n.m.r., and ¹³C n.m.r. data. Mass spectra of the diastereoisomers of (**2b**) were obtained using a g.c. inlet but high resolution was only obtained on the mixture.

Table 1. Thermal rearrangement of compounds (1).

	Conditions	Products†	% Yield
(1a)	298.6 °C, 2 h ^a	54 : 46 ratio of (2a) and (3a)	79
(1b)	318 °C, 5 h ^a	>98% (3b)	55
(1c)	322 °C, 5 h ^a	>98% (3b)	53
(1a)	60 °C, 4.5 h ^b	87 : 13 ratio of (2a) and (3a)	70
(1b)	100 °C, 2 h ^b	52 : 48 ratio of (2b) ^c and (3b)	39
(1c)	102 °C, 1.25 h ^b	61 : 39 ratio of (2b) ^d and (3b)	62

^a The trimethylsilyl derivative of (1) was heated in the gas phase and the resultant enol ether products were hydrolysed as described in ref. 1. ^b The alcohol (1) was treated with KH in HMPA. ^c (2b) is a 70 : 30 mixture of the two diastereoisomers. ^d (2b) is a 56 : 44 mixture of the two diastereoisomers.

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