

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

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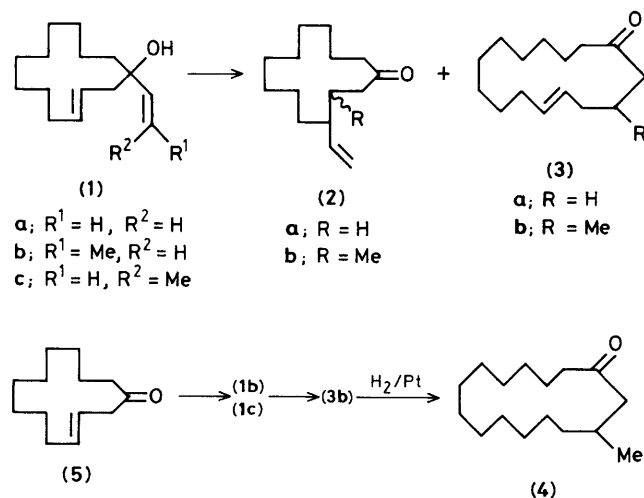
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The thermal, [1,3]-shift siloxy-Cope, ring expansion is shown to be highly favoured relative to the [3,3]-shift for the large-ring system required for the synthesis of muscone.

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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