5-*endo*-Trigonal Radical Cyclisation—a General Procedure for Making Five-Membered Rings

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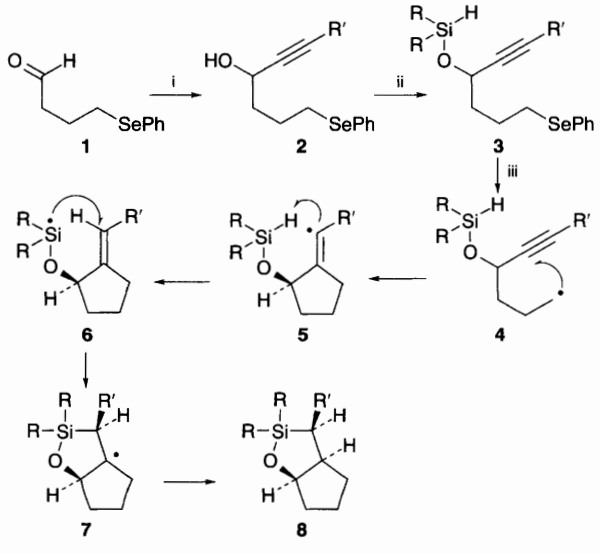
Silicon-centred radicals, derived from alkoxy dialkyl silanes by intramolecular hydrogen transfer, undergo 5-*endo*-trigonal closure.

The 5-*exo*-trigonal pathway is the characteristic regiochemical result in radical cyclisation, and there are few examples[1] of 5-*endo*-trigonal closure.[2] We report that silicon-centred radicals of type **6** generally close by the 5-*endo*-trigonal pathway (**6** → **7**, Scheme 1)—at least when the stannane and initiator are added slowly. The starting radicals **6** are easily generated by the cyclisation–hydrogen transfer process **4** → **5** → **6** and the subsequent cyclisation (**6** → **7** → **8**) proceeds with the stereochemical result shown, implying a direct *endo* pathway rather than rearrangement from the product of initial 4-*exo* closure. The alkoxy silanes **3** are available from alcohols **2** by silylation with R_2SiHCl or related reagents,[3] and the alcohols are themselves accessible by reaction of a lithium acetylide with an aldehyde (**1** → **2**). Typical results are shown in Table 1.

In most cases it was convenient to trigger the whole sequence by homolysis of a C–Se bond,but a C–Br bond is also suitable (**14b** → **c**). On the basis of preliminary experiments with **9b** and **15**, the (di-*tert*-butyl)silane starting materials are judged to work best in the radical-induced sequence and, unlike **15** (R = Me or Ph), they are stable† to chromatography. The overall sequence is less efficient for R = Ph, Me, or Pr^i, but we have not established for each case whether the intramolecular hydrogen transfer or the 5-*endo* closure, or both, are inefficient. In the methyl series **15** (R = Me), use of Bu_3SnD gave alcohol **16** (of undetermined geometry) in 38–45% yield (after treatment with methanolic K_2CO_3, H_2O_2, KF), indicating appreciable intermolecular reduction of the vinyl radical before intramolecular hydrogen transfer. In another labelling experiment, **9b** (Table 1) was treated with Bu_3SnD to produce (64%) the C-3a deuterated analogue of **9c**, as expected from the mechanism shown in Scheme 1.

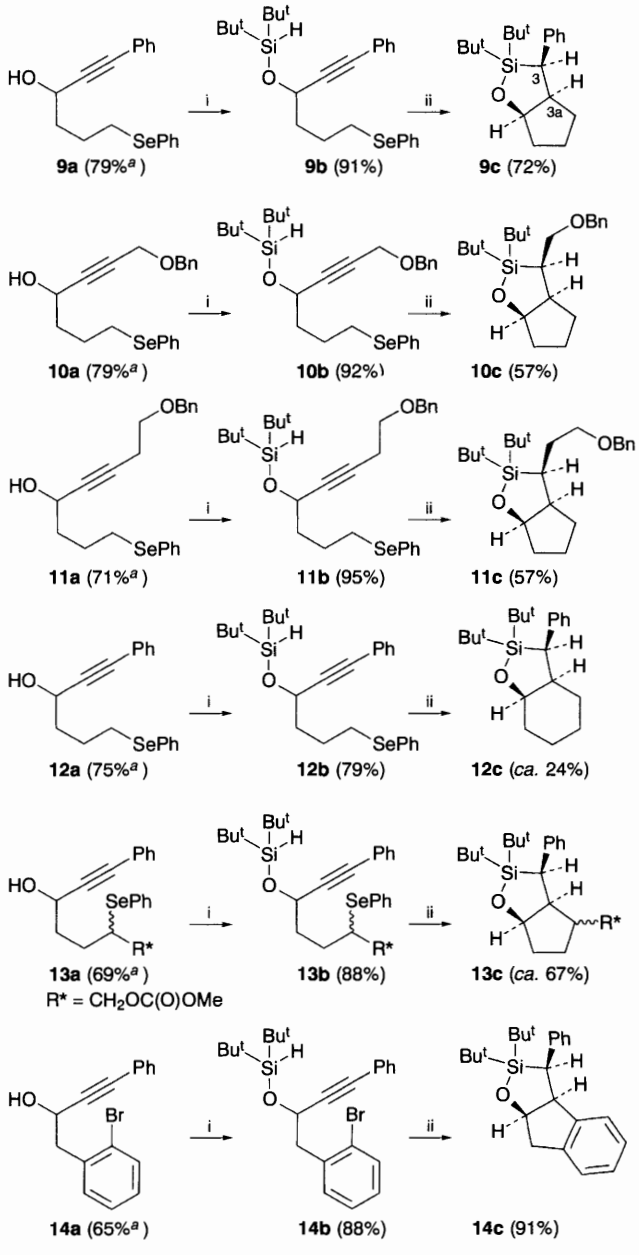
In the cyclisation products, the (di-*tert*-butyl)silyl unit is difficult to cleave from its attached carbon in the absence of certain structural features described below, and results of attempts to effect the cleavage are summarised in Scheme 2.



Scheme 1 *Reagents and conditions*: i, R′C≡CLi, THF, −78 °C; ii, R_2SiHCl, base, THF, reflux; iii, Slow addition (2 h) of Ph_3SnH and AIBN; benzene, reflux

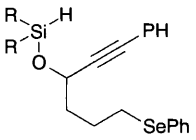
Standard conditions (K_2CO_3, MeOH, H_2O_2, THF, KF),[4] did not work on substrate **9c**, although they were successful for the corresponding diphenyl- and dimethyl-series.‡ For the di-*tert*-butyl compounds, however, a suitably located oxygen function makes it possible to cleave the crucial silicon–carbon bond (Scheme 3) under a variety of conditions.

Table 1 Intramolecular hydrogen transfer–radical cyclisation

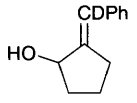


[a] Yield for coupling of acetylide with appropriate aldehyde. *Reagents and conditions*: i, But_2SiHCl, imidazole; ii, Ph_3SnH, AIBN.

The structure of **9c** (Table 1), first established spectroscopically, was confirmed by X-ray analysis of the derivative **9d** (Scheme 2), and the stereochemistry of the other cyclisation



15 (R = Ph, Me, Pr^i)



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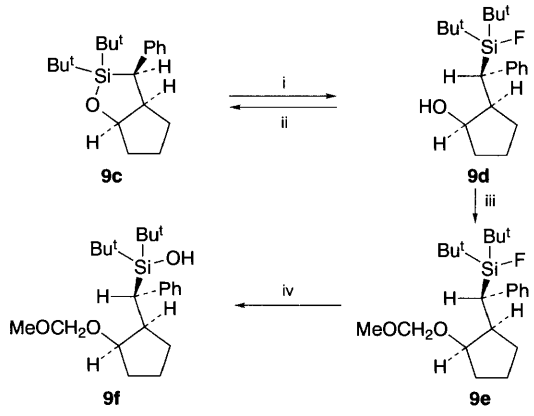
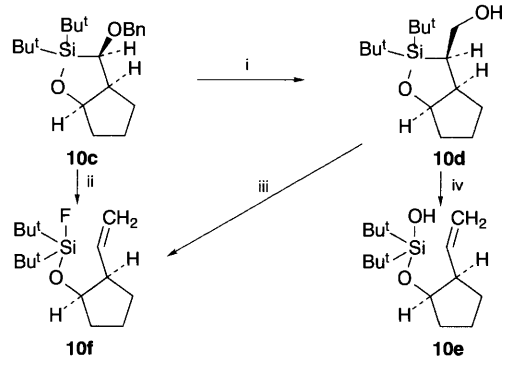


Scheme 2 *Reagents and conditions*: i, $BF_3{\cdot}Et_2O$, 80%; ii, MEOH–K_2CO_3, 94%; iii, $MeOCH_2Cl$, Et_2NPr^i, 60%; iv, H_2O_2–KF, K_2Co_3, 80%



Scheme 3 *Reagents and conditions*: i, H_2/PdC, 95%; ii, $BF_3{\cdot}Et_2O$, 77%; iii, $BF_3{\cdot}Et_2O$, 69%; iv, Bu^{t}OK, 83%

products **10c–14c** was assigned on the basis of appropriate coupling constants for $J_{3,3a}$, except in the case of **11c**, where the assignment was made by analogy.

As prop-2-ynyl alcohols (*cf.* **2**) are available in optically pure form[5] our results suggest that the present methodology can be applied also to the synthesis of optically pure cyclopentanoids.

Acknowledgement is made to the Natural Sciences and Engineering Research Council of Canada and to Merck Frosst for financial support. M. C. held a Killam Postgraduate Fellowship.

Received, 26th October 1994; Com. 4/06560C

Footnotes

† The same is true for **15** (R = Pr^i).

‡ Yield of diol in the dimethyl series, starting from **15** (R = Me), was 27–35%; the corresponding yield in the diphenyl series (**15**, R = Ph) was 14% but, as indicated above, for the former case, the intramolecular hydrogen transfer was shown to be especially inefficient.

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