Preparation of tetrahydrofuran, γ-lactone, chromanol and pyrrolidine systems by sequential 5-*exo*-digonal radical cyclization, 1,5-hydrogen transfer from silicon, and 5-*endo*-trigonal cyclization

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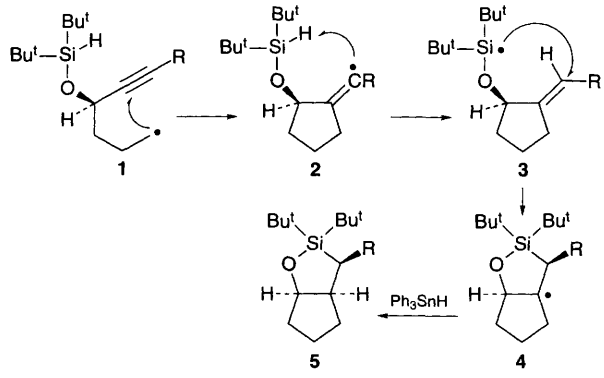
Sequential 5-*exo*-digonal radical closure, intramolecular 1,5-hydrogen transfer from silicon to carbon, and 5-*endo*-trigonal closure of the resulting silicon-centred radicals are used to make five- and six-membered heterocycles containing oxygen or nitrogen.

Substituted cyclopentanes can be prepared by an unusual, but general, sequence of radical reactions based on successive 5-*exo*-digonal cyclization (**1** ⟶ **2**), 1,5-hydrogen transfer from silicon (**2** ⟶ **3**), 5-*endo*-trigonal closure (**3** ⟶ **4**), and intermolecular hydrogen transfer from stannane (**4** ⟶ **5**).[1] 5-*endo*-Trigonal closures are not often observed in synthetic radical chemistry,[2] but are permitted here because the presence of a second row element in the ring being formed avoids the kinetic barrier that would otherwise be predicted.[3] This step (**3** ⟶ **4**) can be suppressed, however, by suitable choice of radical precursor—iodide[4] instead of selenide[1]—but for many purposes the *endo* closure is an especially useful feature (Scheme 1). Here we report an extension of our methodology to the preparation of heterocycles containing oxygen or nitrogen (Table 1).

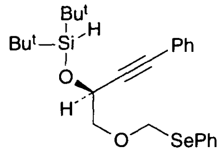
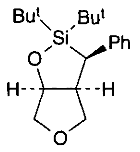
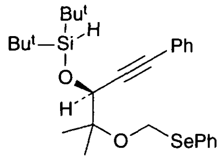
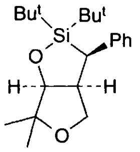
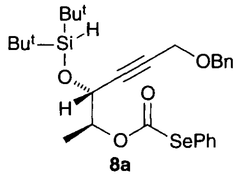
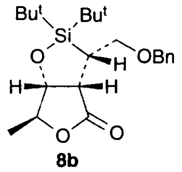
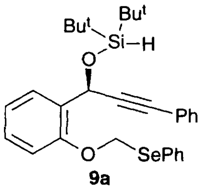
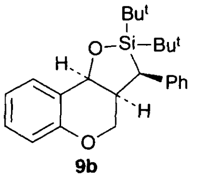
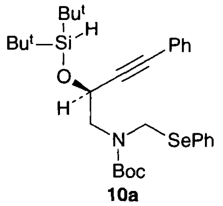
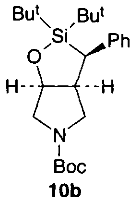
All of the starting materials used in this work are readily available. In the case of entries 1 and 2 (Table 1), the sequence of Scheme 2 was used to prepare **6a** and **7a** *via* the known[5] dioxolanones **12a** and **12b**, respectively. Ordinary lactones have often been opened[6a,b] by treatment with phenylselenide anion;[6] and we found that the same reagent is very convenient here for opening dioxolanones (see **12a,b** ⟶ **13a,b**, Scheme 2). Compound **8a** was made by the route[7] summarized in Scheme 3, while the phenol derivative **9a** (Table 1) was made by *O*-(phenylseleno)methylation of salicylaldehyde (DBU, $PhSeCH_2Cl$, $AgNO_3$, THF; 80%), reaction of the aldehyde groupwith lithium phenylacetylide (PhC≡CLi; 83%), and silylation (Bu^t_2SiHCl, Et_3N, cat. DMAP, CH_2Cl_2, 95%). The nitrogen-containing example **10a** was available from **18**[9] by a similar route to that shown in Scheme 1, *i.e.* successive reaction with PhSeNa (THF, reflux) and diazomethane (80% overall), partial reduction (DIBAL, Et_2O, 83%), treatment with lithium phenylacetylide (THF, −78 °C, 79%), and silylation (Bu^t_2-SiHCl, imidazole, THF, reflux, 93%).



Scheme 1

Each of the experiments summarized in Table 1 was conducted by simultaneous slow addition (over *ca.* 5 h) of Ph_3SnH (1.5 mol per mol substrate, 0.006 mol dm^{-3} in PhH) and AIBN (azobisisobutyronitrile) (0.3 mol per mol substrate, 0.0015 mol dm^{-3} in PhH) to a refluxing benzene solution (0.005 mol dm^{-3}) of the radical precursor **6a**–**10a**. After the addition, refluxing was continued for an arbitrary period of 0.5–12 h. Our stereochemical assignments were based on mechanistic considerations[1] and ^1H NMR decoupling and/or NOE measurements. Compound **9b** was also desilylated[10] (TBAF, DMF, 75%) to the known *cis*-benzylchroman-4-ol.[11]

Table 1 Cyclization results

Entry	Alkyne	Heterocycle	Yield (%)
1	 **6a**	 **6b**	85
2	 **7a**	 **7b**	88
3	 **8a**	 **8b**	85
4	 **9a**	 **9b**	85
5	 **10a**	 **10b**	95

All compounds are racemic, except for **8a** and **8b**.

Our results show that substituted tetrahydrofuran, γ-lactone, pyrrolidine and chromanol systems are accessible by the present method. The carbon–silicon bond in the products is, of course, also amenable to further modification. Since the stereochemistry of the radical reaction is determined by the stereochemistry at the carbon bearing the silyloxy group, optically pure heterocycles are readily available from appropriate optically pure alcohols (Table 1, example 3).

The results summarized in Table 1 have a number of noteworthy features. Alkoxymethyl radicals, which are intermediates in examples 1–4 (Table 1), are expected to cyclize slowly relative to the hexenyl radical;[12] nonetheless, the reactions proceed in good yield. The case of **9a** indicates that intramolecular transfer[13,14] of H_a (see **19**) does not occur to any appreciable extent,[14] if at all, even though the C–H_a bond should be weakened by the surrounding structural units. The facility of such hydrogen transfer would depend not only on the accessible geometries[14a] of the system, and the strength of the C–H_a bond, but also on certain characteristics of the radical (here $ArOCH_2^\bullet$), such as resonance stabilization.[12] We have not established the relative importance of these factors, but note that efficient 6-*exo*-trigonal closures of alkoxymethyl radicals have also been observed,†,[15] and the absence of intramolecular transfer during these reactions or in the 6-*exo*-digonal closure reported here,[14f] may be a general‡ and synthetically useful characteristic of alkoxymethyl radicals.

All new compounds were fully characterized by spectroscopic methods, including accurate mass measurements.

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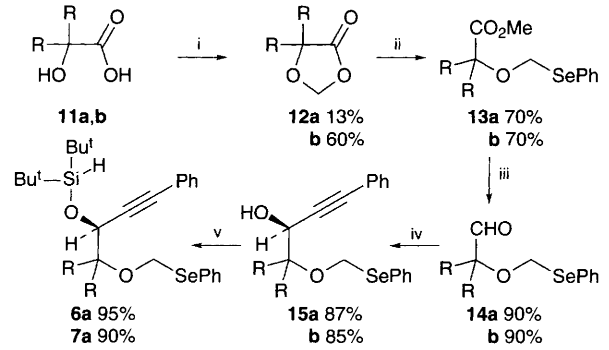
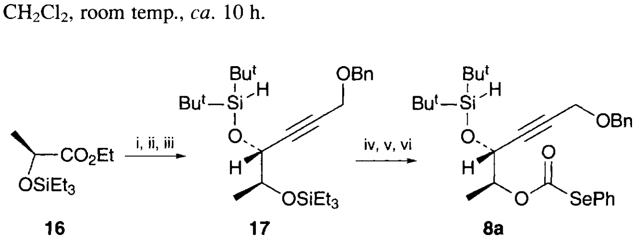
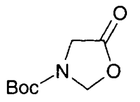


Scheme 2 For compounds **11a–15a** and **6a**, R = H; for **11b–15b** and **7a**, R = Me. *Reagents and conditions*: i, $(CH_2O)_n$, cat. toluene-*p*-sulfonic acid, refluxing benzene, Dean–Stark apparatus, overnight, for **12a**; *s*-trioxane, cat. toluene-*p*-sulfonic acid, refluxing benzene, Dean–Stark apparatus, 10 h, for **12b**; ii, (*a*) PhSeSePh, NaH, HMPA, refluxing THF, 6 h; (*b*) refluxing MeOH, cat. conc. H_2SO_4, overnight; iii, DIBAL-H, CH_2Cl_2, −78 °C, 5 h; iv, PhC≡CH, BuLi, −78 °C to room temp; v, Bu^t_2SiHCl, Et_3N, cat. DMAP, CH_2Cl_2, room temp., *ca.* 10 h.



Scheme 3 *Reagents and conditions*: i, DIBAL-H, CH_2Cl_2, −78 °C, 4 h, 80%; ii, $BnOCH_2C{\equiv}CH$, BuLi, THF, −78 °C, 4 h, chromatographic separation of the isomers; iii, Bu^t_2SiHCl, Et_3N, cat. DMAP, CH_2Cl_2, 10 h; iv, 8 : 8 : 1 THF–AcOH–H_2O, overnight, 52% over three steps (*cf.* ref. 8); v, (*a*) $(COCl)_2$ solution in toluene, THF, room temp., 4 h; (*b*) PhSeH, pyridine, 5 h, 80% over two steps



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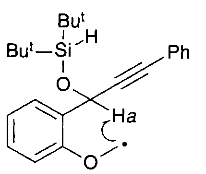

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Footnotes

† These systems lack the additional activating features of H_a in **9a**.

‡ Hydrogen transfer is also insignificant or absent in the cyclization of acyl (see ref. 16) or 1,1-difluoroalkyl (see ref. 17) radicals.

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