Repetitive Ring Expansion of Cyclic Ketones by a Method Allowing Regiochemical Control

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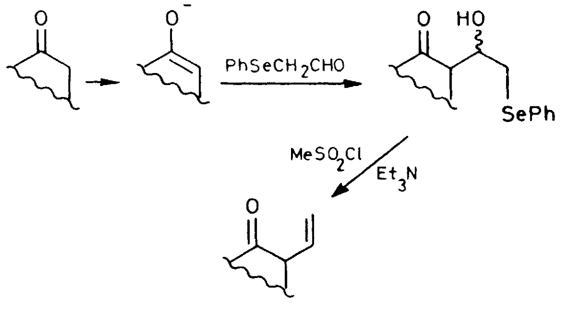
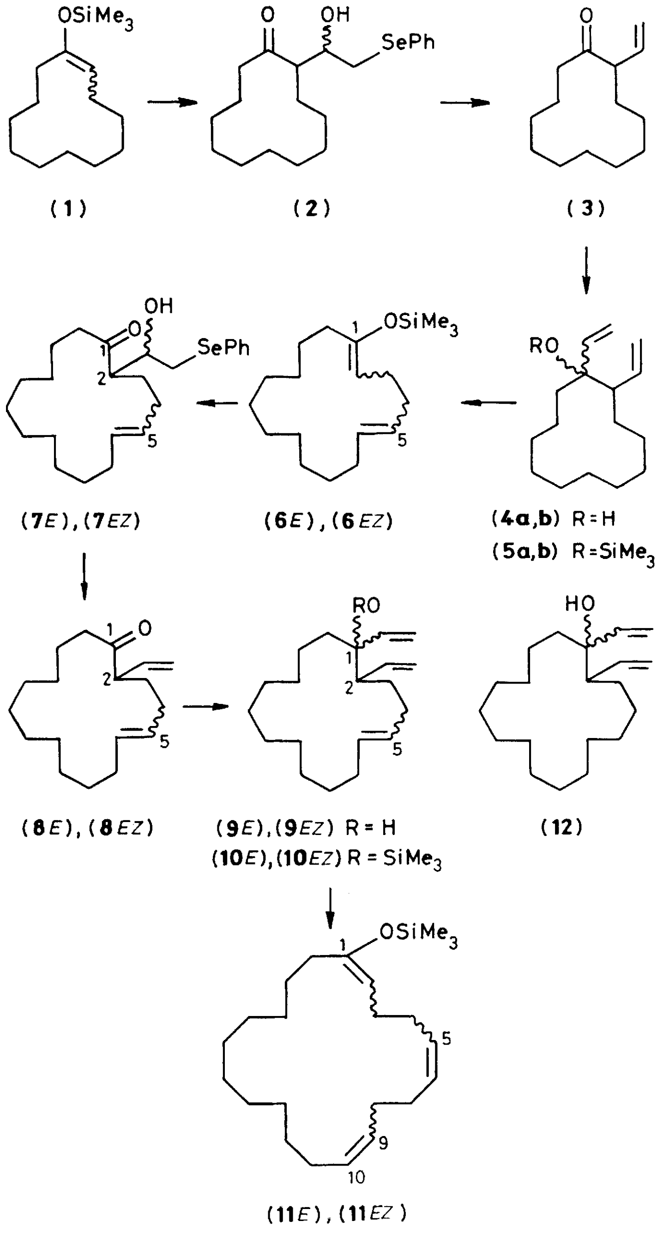
Cyclododecanone was converted into the 20-membered cycloalkenes (**11***E*) and (**11***EZ*) and into (*Z,E*)-cycloeicosadec-5-en-1-one to illustrate a method for repetitive ring expansion based on the use of (phenylseleno)acetaldehyde and the siloxy-Cope rearrangement.

We report a procedure for ring expansion of ketones in a repetitive fashion. This type of methodology calls for regeneration in each cycle of a member of the same compound class, or, of a substance easily converted into it. There is, however, the further requirement that the regiochemical bias of the starting material be preserved during the homologation.[1] As described below, (phenylseleno)acetaldehyde, which is a synthetic equivalent of the vinyl carbonium ion[2,3] (Scheme 1), can be used in a sequence for ring expansion that satisfies the stated criteria. The reactions are summarized in Scheme 2.

Treatment[2b] of the silyl enol ether (**1**)[4] with MeLi [in ether–glyme (*ca.* 1 : 1.5)] to generate the enolate, and then with $ZnCl_2$[2b] and (phenylseleno)acetaldehyde[2b] gave (88%) the diastereoisomeric alcohols (**2**). Without separation, the



Scheme 1



Scheme 2

alcohols were converted by the action of Et_3N and $MeSO_2Cl$[2b,5] into 2-vinylcyclododecanone (**3**) (80%).† Addition of (**3**) to vinyl-lithium[7] in tetrahydrofuran (THF) at −55 °C gave two alcohols (**4a**) and (**4b**) (*ca.* 2.3 : 1; 94%) without problems due to competitive enolization.

For exploratory purposes the alcohols were separated by chromatography but this is not essential to the scheme. Both undergo anionic oxy-Cope rearrangement on heating with KH in THF but condensation with (phenylseleno)acetaldehyde did not proceed cleanly, at least in our preliminary experiments, and it may be relevant that under the ring-expansion conditions extensive equilibration of regioisomeric enolates can occur.[8]‡ The problem with the condensation was avoided as follows: Each tertiary alcohol was silylated [Me_3SiCl, $(Me_3Si)_2NH$][9] in Me_2SO and the individual products (**5a**) [from (**4a**); 93%] and (**5b**) [from (**4b**); 91%] underwent siloxy-Cope rearrangement[10] on heating under nitrogen (200 °C; 15 min). Compound (**5a**) gave a product (**6***E*) (98%) with 5*E*-geometry while (**5b**) gave (**6***EZ*) (98%) containing both 5*E*- and 5*Z*-isomers (*ca.* 1 : 1).§ The stereochemical assignment[11] was made by converting (**6***E*) and (**6***EZ*) into the corresponding cyclohexadec-5-enones[6a] by the action of $Bu_4N^+F^-$ in THF. The experiment starting from (**5a**) gave the 5*E*-enone (82%) while that starting from (**5b**) gave a mixture of the 5*E*- (40%) and 5*Z*- (48%) isomers. N.m.r. spectroscopy (^{13}C, ^1H) showed that (**6***E*) was a single compound while (**6***EZ*) was a mixture of geometric isomers.

Reaction of (**6***E*) with MeLi in glyme was too sluggish to be useful but, in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA; 1 equiv.), the corresponding enolate was generated efficiently (in Et_2O) and condensation with (phenylseleno)acetaldehyde under the standard conditions[2b] afforded the corresponding hydroxyselenides (**7***E*) (93%).§ Likewise, (**6***EZ*) was converted (92%) into (**7***EZ*).§ Both (**7***E*) and (**7***EZ*) were then individually subjected to the early stages of the sequence: treatment with Et_3N and $MeSO_2Cl$ gave the corresponding 2-vinylcyclohexadec-5-enones (**8***E*) (82%) and (**8***EZ*) (85%), respectively.§ ^{13}C N.m.r. measurements (50.323 MHz) showed, as expected, that (**8***E*) was a single compound while (**8***EZ*) was a mixture of two isomers. The action of vinyl-lithium (THF; −80 °C) produced the divinyl alcohols (**9***E*) [from (**8***E*); 89%]§ and (**9***EZ*) [from (**8***EZ*); 85%],§ bringing the sequence to a stage where, except for the presence of endocyclic unsaturation, it overlaps with the first cycle. Silylation[9] of (**9***E*) gave (**10***E*)§ (95%), thermolysis (200 °C; 15 min) of which produced (92%) the 20-membered ring system (**11***E*).§ The corresponding stages with (**9***EZ*) [→ (**10***EZ*) → (**11***EZ*)]§ were effected in yields of 92 and 95%, respectively.

In principle, systems of type (**11**) can undergo ring contraction by [3,3] rearrangement involving the 5,9-diene system, but no evidence for this could be detected spectroscopically (^1H n.m.r., 400 MHz). However, in order to accommodate situations where ring contraction might occur and also because the isomers in (**11***E*) and (**11***EZ*) could not be separated for individual characterization, the following variation of the ring expansion process was developed. The selenides (**7***E*) and (**7***EZ*) were individually hydrogenated (both in 80% yield) in benzene at room temperature using Wilkinson's catalyst in order to saturate the 5,6-double bond. The product was converted in the usual way (Et_3N, $MeSO_2Cl$) into 2-vinylcyclohexadecanone (80%), and treatment with vinyl-lithium (−80 °C, THF) gave (85%) the *cis*- and *trans*-divinyl alcohols (**12**).§ The reaction sequence was terminated at this stage by treating (**12**) with KH in warm THF to produce (78%) cycloeicosadec-5-en-1-one as a 5*Z*,5*E*-mixture.

In summary, the transformations (**1**) → (**11***E*), (**11***EZ*) (34—35%) and (**1**) → cycloeicosadec-5-en-1-one (23%) serve to illustrate the repetitive ring expansion process.

All new compounds were characterized spectroscopically

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† This compound has been prepared from 2-chlorocyclododecanone (ref. 6a) by a method that works well (ref. 6b) for 2-chlorocyclohexanones and 2-chlorocycloheptanones. The present method has been applied to 5-, 6-, 8-, 10-, 12-, and 16-membered rings.

‡ Under these conditions ring expansion of 12-methyl-1,2-divinyl-cyclododecanol and condensation with $PhSeCH_2CHO$ gave some material resulting from reaction at the methyl-substituted carbon.

§ (**6***E*), (**7***E*), (**8***E*), (**9***E*), and (**10***E*) have 5*E*-geometry while (**6***EZ*), (**7***EZ*), (**8***EZ*), (**9***EZ*), and (**10***EZ*) are mixtures of 5*E*- and 5*Z*-isomers. (**9***E*), (**9***EZ*), (**10***E*), (**10***EZ*), and (**12**) are mixtures of *cis*- and *trans*-divinyl compounds. (**11***E*) has 9*E*-geometry and (**11***EZ*) is a mixture of 9*E*- and 9*Z*-species.

(including mass measurement) and, apart from (**8***E*) and (**8***EZ*), satisfactory analytical data were also obtained, isomer mixtures beyond the stage of compounds (**5**) (Scheme 2) being examined as such.

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