Tandem ring-closing metathesis–radical cyclization based on 4-(phenylseleno)butanal and methyl 3-(phenylseleno)propanoate — a route to bicyclic compounds

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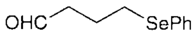
α,ω-(Phenylseleno) carbonyl compounds, such as 4-(phenylseleno)butanal (1) and methyl 3-(phenylseleno)propanoate (2), are easily converted by anionic reactions into substances that undergo sequential ring-closing metathesis and radical cyclization, affording bicyclic products.

The usefulness of radical cyclization is often determined by the ease with which the cyclization substrates can be made. In this regard, the nature of the homolyzable group is, of course, important, because this determines the stages at which it may be introduced. In particular, early introduction can avoid the extra steps involved in replacing a non-homolyzable group by one that is homolyzable. For radical generation, phenyl selenides have the distinct advantage that the PhSe group is usually inert to basic or nucleophilic reagents[1] and, among the common transformations, care need be exercised only in the choice of oxidizing agent[2,3] when selenium is present. We have found that the PhSe group is compatible with the Grubbs catalyst $(Cy_3P)_2Cl_2Ru{=}CHPh$,[4–8] and we report that α,ω-(phenylseleno) carbonyl compounds, such as 4-(phenylseleno)butanal (**1**[9]) and methyl 3-(phenylseleno)propanoate (**2**[10]) are useful for the



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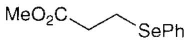

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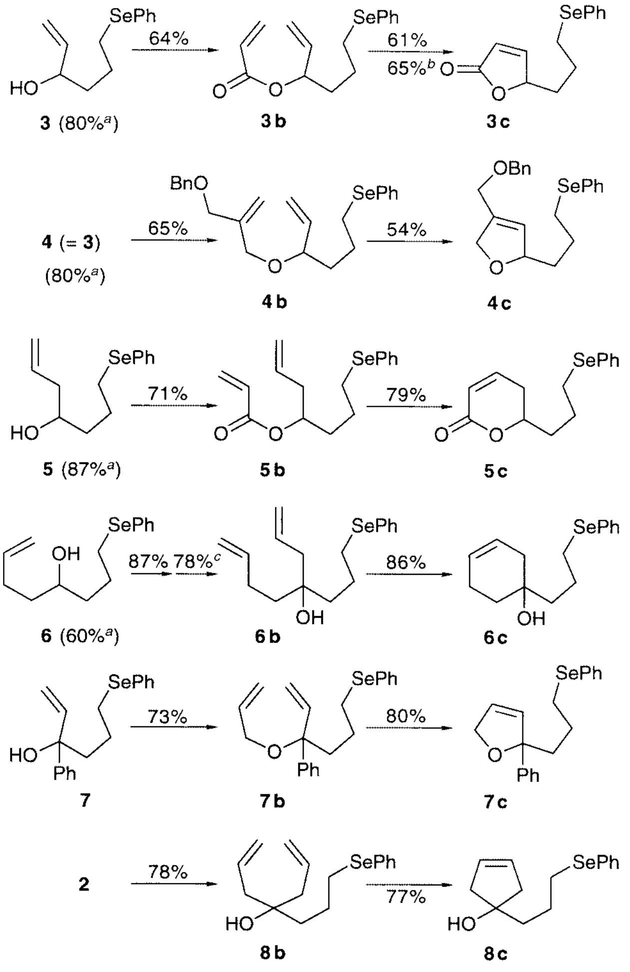
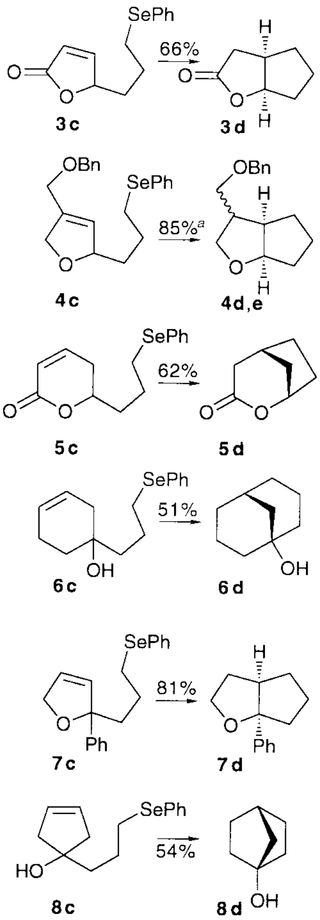
construction of substances that undergo sequential ring-closing metathesis[11] and radical cyclization. The PhSe group allows the use of anionic chemistry that would not be suitable in the



Scheme 1 (*a*) Yield from **1**. (*b*) Corrected for recovered **3b**. (*c*) First yield is for the oxidation of **6** to the corresponding ketone; second yield for reaction of the ketone with allylmagnesium bromide.



Scheme 2 (*a*) Yield of more polar isomer [(3α,3aβ,6aβ)-stereochemistry] 60%; yield of less polar isomer [(3α,3aα,6aα)-stereochemistry] 25%.

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presence of halogen or carboxy groups as the eventual source of radicals.[12] Several publications have reported that the catalyst is usually not compatible with sulfide substrates.[4,5]

The starting materials **3b–8b** (Scheme 1) for the metathesis–radical closure sequence were made as follows. Aldehyde **1** was converted into alcohols **3** (80%), **5** (87%), and **6** (60%) (Scheme 1) by reaction with vinyllithium, allylmagnesium bromide, and but-3-enylmagnesium bromide, respectively. Reaction of **1** with phenyllithium (50%), oxidation, using pyridine·SO_3 in DMSO[2] (87%), and treatment of the resulting ketone with vinyllithium afforded alcohol **7** (85%).

The alcohols **3**, **5**, **6** and **7** were easily converted into substrates for ring-closing metathesis by simple ionic reactions. Acylation of **3** and **5** with acryloyl chloride (Et_3N, DMAP, CH_2Cl_2) gave **3b** (64%) and **5b** (71%), respectively (Scheme 1), and the ethers **4b** (65%) and **7b** (73%) were made by alkylation (NaH, THF) of **3** with 2-chloromethyl-3-[(phenylmethyl)-oxy]prop-1-ene[13,14] and of **7** with allyl bromide, respectively.

The metathesis substrate **6b** was prepared by oxidation of **6** (87%), again using the pyridine·SO_3–DMSO system—which is an excellent reagent for selective oxidation of phenylseleno alcohols—and treatment with allylmagnesium bromide (78%).

The bis-allyl selenide **8b** was obtained directly from ester **2** by the action of allylmagnesium bromide (78%).

Each of the bis-olefins shown in Scheme 1 underwent ring-closing metathesis in the presence of $(Cy_3P)_2Cl_2Ru{=}CHPh$ (8–12 mol%; 22% for **3b**), and the products were isolated by flash chromatography. The reactions were usually run in PhH at 50 °C for 12 h [**4b**, **6b** (65 °C), **7b**, **8b** (refluxing PhH,[15] 8 h)], or in refluxing CH_2Cl_2 in the presence of Ti(OPr-*i*)$_4$,[16] (42 h,[17] **3b**, 8 h, **5b**). In the case of the acrylates (**3b**, **5b**), Ti(OPr-*i*)$_4$ must be added to complex the ester carbonyl and prevent unproductive complexation of carbenoid intermediates.[18]

The radical cyclization step (see Scheme 2), leading to **3d**, **4d**,**e**, **5d–8d**, was carried out under standard conditions by syringe pump addition (over *ca*. 10 h) of a PhH solution of Bu_3SnH (1.4–2.2 equiv., 0.01–0.08 M) and AIBN (0.2–0.4 equiv., 0.006–0.03 M) to a refluxing solution (0.01–0.02 M) of the substrate (1 equiv.) in the same solvent. In the case of **6c** we isolated only the product of 6-*exo* cyclization, and not the isomeric alcohol resulting from 7-*exo* closure.[19]

The above experiments establish that the PhSe group, which serves as a very convenient radical source, can be introduced at an early stage in synthetic routes that involve ionic reactions and that end with sequential application of two powerful bond-forming processes, ring-closing metathesis and radical cyclization.

All new compounds were characterized spectroscopically, including high resolution mass measurements.

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Notes and references

1 A. Y. Mohammed and D. L. J. Clive, *J. Chem. Soc., Chem. Commun.*, 1986, 588.

2 *Cf.* J. R. Parikh and W. von E. Doering, *J. Am. Chem. Soc.*, 1967, **89**, 5505.

3 Other oxidation methods: (*a*) R. Baudat and M. Petrzilka, *Helv. Chim. Acta*, 1979, **62**, 1406; (*b*) D. H. R. Barton, D. J. Lester, W. B. Motherwell and M. T. B. Papoula, *J. Chem. Soc., Chem. Commun.*, 1980, 246; (*c*) G. H. Posner and M. J. Chapdelaine, *Tetrahedron Lett.*, 1977, 3227; (*d*) M. Shimizu, H. Urabe and I. Kuwajima, *Tetrahedron Lett.*, 1981, **22**, 2183; (*e*) J. Lucchetti and A. Krief, *C. R. Acad. Sci., Ser. C*, 1979, **288**, 537.

4 Sulfides and disulfides have been subjected to ring-closing metathesis, using a *molybdenum* catalyst; in some experiments a ruthenium catalyst [$(Cy_3P)_2Cl_2Ru{=}CHCH{=}CPh_2$] was unsatisfactory (Ref. 5), as was $(Cy_3P)_2Cl_2Ru{=}CHPh$ (Ref. 6).

5 *E.g.* (*a*) S.-Y. Shon and T. R. Lee, *Tetrahedron Lett.*, 1997, **38**, 1283; (*b*) S. K. Armstrong and B. A. Christie, *Tetrahedron Lett.*, 1996, **37**, 9373.

6 A. G. M. Barrett, M. Ahmed, S. P. Baker, S. P. D. Baugh, D. C. Braddock, P. A. Procopiou, A. J. P. White and D. J. Williams, *J. Org. Chem.*, 2000, **65**, 3716.

7 For a rare example of ring-closing metathesis of a sulfide, using $(Cy_3P)_2Cl_2Ru{=}CHPh$, see: A. G. M. Barrett, S. P. D. Baugh, D. C. Braddock, K. Flack, V. C. Gibson, M. R. Giles, E. L. Marshall, P. A. Procopiou, A. J. P. White and D. J. Williams, *J. Org. Chem.*, 2000, **63**, 7893.

8 For an extensive table of functional group-catalyst compatibility, see: S. K. Armstrong, *J. Chem. Soc., Perkin Trans. 1*, 1998, 371.

9 (*a*) D. L. J. Clive and R. J. Bergstra, *J. Org. Chem.*, 1990, **55**, 1786; (*b*) C. Bigogno, B. Danieli, G. Lesma and D. Passarella, *Heterocycles*, 1995, **41**, 973.

10 K. Hiroi, J. Abe, K. Suya, S. Sato and T. Koyama, *J. Org. Chem.*, 1994, **59**, 203.

11 For one of several recent reviews, see: R. H. Grubbs and S. Chang, *Tetrahedron*, 1998, **54**, 4413.

12 For synthesis of bridgehead bicyclic sultams by tandem ring-closing metathesis–radical cyclization (in which the radical is derived from a halomethylsulfonyl group), see: L. A. Paquette and S. M. Leit, *J. Am. Chem. Soc.*, 1999, **121**, 8126.

13 T. Konosu, Y. Furukawa, T. Hata and S. Oida, *Chem. Pharm. Bull.*, 1991, **39**, 2813.

14 In the alkylation with this reagent, NaI was added to generate the iodide *in situ*.

15 Reaction was very slow in refluxing CH_2Cl_2. *Cf.* A. Fürstner, O. R. Thiel, L. Ackermann, H.-J. Schanz and S. P. Nolan, *J. Org. Chem.*, 2000, **65**, 2204.

16 A solution of the substrate was refluxed in the presence of Ti(OPr-*i*)$_4$ before adding the Grubbs catalyst.

17 A fresh portion of catalyst was added after 30 h.

18 (*a*) A. Fürstner and K. Langemann, *J. Am. Chem. Soc.*, 1997, **119**, 9130; (*b*) A. K. Gosh, J. Cappiello and D. Shin, *Tetrahedron Lett.*, 1998, **39**, 4651.

19 *Cf.* A. L. J. Beckwith, *Tetrahedron*, 1981, **37**, 3073.