Synthesis of Spiro-Compounds: Use of Diselenoacetals for Generation of Quaternary Centres by Alkylation and Radical Cyclization

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Ketones are readily converted *via* the corresponding diphenyl diselenoacetals (**2**) into selenides (**5**) which undergo radical 5-*exo* cyclization to spiro-compounds (**7**) on treatment with triphenyltin hydride and azoisobutyronitrile; an analogous sequence serves for the preparation of spiro-lactones (**12**).

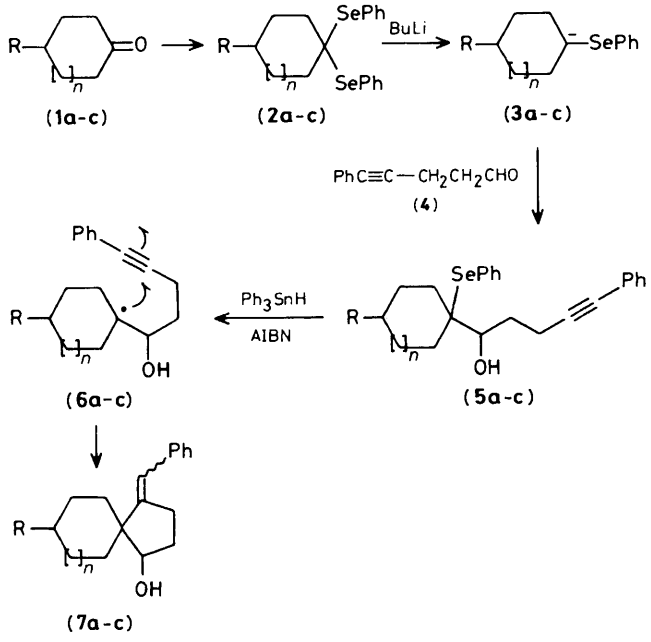
The associated problems of generating spiro-structures and quaternary carbon centres are often difficult and much work has been done in this area in an effort to develop useful synthetic routes.[1] We report a new and general procedure that involves making a carbonyl carbon equivalent first of all to a carbanion and then to a radical. The carbanion is used to attach an acetylenic alkyl chain and, when the radical is generated, it cyclizes in a 5-*exo* manner onto the triple bond (see Scheme 1). The use of diselenoacetals in carbanion-based reactions is, of course, well-known[2] and homolytic cleavage of carbon–selenium bonds is also a firmly established general reaction.[3] We have combined both processes, as in Scheme 1, and our results with several examples are collected in Table 1.

The required diselenoacetals were made from the corre-

Table 1.[a]

Diselenoacetal (2)	Hydroxyselenide (5) Yield from (2) (%)		Cyclization product (7) Yield from (5) (%)	
(2a) R = H, $n = 0$	(5a)	(73)	(7a)	(68)
(2b) R = H, $n = 1$	(5b)	(65)	(7b)	(75)
(2c) R = Bu^t, $n = 1$	(5c)	(86)	(7c)	(86)
(2a)[b]	(5d)	(55)	(7d)	(91)
(2e)	(5e)	(50)	(7e)	(64)

[a] All yields refer to pure, isolated products. [b] 2-(Phenylethynyl)benzaldehyde was used instead of (4).



Scheme 1

sponding ketones by literature methods[4] in yields of about 50%. No attempt was made to optimize this standard reaction.† The carbanions [*cf.* (3) Scheme 1] were generated[5] by the action of BuLi (1 equiv.) in tetrahydrofuran (THF) at −78 °C (*ca.* 5 min), and were then quenched by rapid addition of an aldehyde: 5-phenylpent-4-ynal (4)[6] or 2-(phenylethynyl)benzaldehyde.[7] The desired hydroxyselenides (5) were isolated after a brief reaction period (*ca.* 2 min) in yields of 50—86% (see Table 1). In this work we have confined our attention to acetylenes that lead, after cyclization, to a five-membered ring. The cyclization was carried out by the following general procedure: benzene solutions of triphenyltin hydride [1.1—1.4 mmol per mmol (5), 0.015—0.030 M] and of azoisobutyronitrile (AIBN) [0.10—0.23 mmol per mmol (5), 0.002—0.003 M] were added simultaneously over 7—8 h (syringe pump) to a refluxing solution (0.012—0.021 M) of (5) in the same solvent. After the end of the addition, refluxing was arbitrarily continued for 6 h and the products (7a—e) were then isolated by flash chromatography in the yields shown.

We assigned structures on the basis of precedent,[8] as those resulting from 5-*exo* closure‡ [*cf.* (6) Scheme 1] rather than

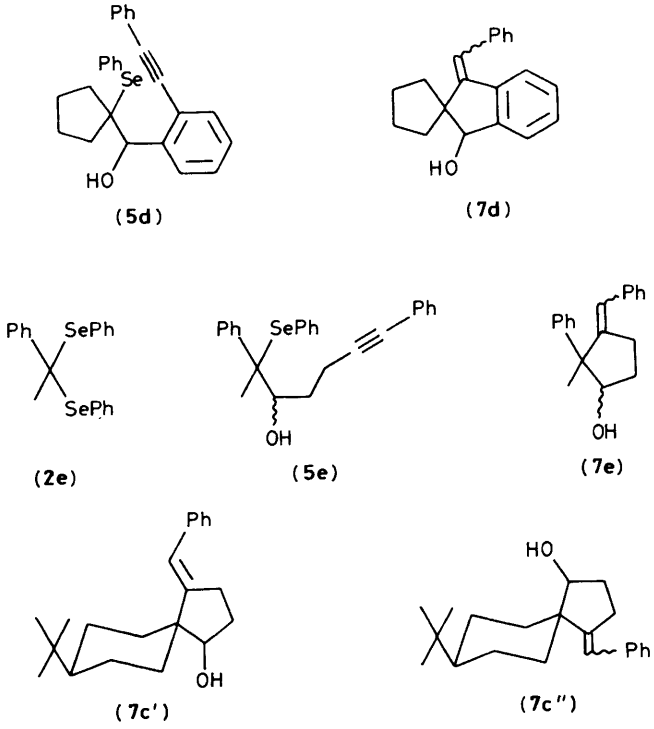
† With care, very high yields can be obtained: *cf.* ref. 4.

‡ We used the entity C≡C–Ph, rather than C≡C–H or C≡C–Me, in order to minimize the potential for problems due to 6-*endo* closure, but it is not yet clear whether this precaution is necessary (*cf* refs. 8a and 8b).

Table 2.[a]

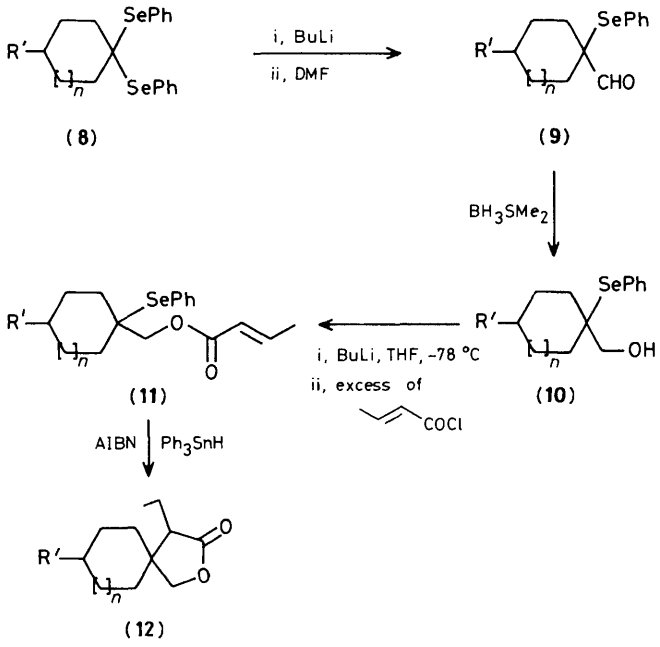
	Yield (%)			
(8)	(9)	(10)	(11)	(12)
a; R′ = H, $n = 0$	84	88	73	73
b; R′ = H, $n = 1$	86	75	75	69
c; R′ = Bu^t, $n = 1$	84[b]	75[b]	76[b,c]	86[d]
d; R′ = H, $n = 2$	37[e,f]	65	71	66
e; R′ = H, $n = 3$	37[e,f]	54[g]	71	59

[a] Except where indicated, yields refer to pure, isolated products. With the indicated values of R′ and n, the numbered compounds refer to Scheme 2. [b] Stereochemistry of (9c), (10c), and (11c) not determined. [c] Esterification conditions to obtain (11c) i, Bu^{t}OK (1.3 equiv., 10 min); 2:1 Et_2O–THF; −25 °C; ii, crotonyl chloride (2 equiv., 10 min). [d] Mixture of isomers (12c). [e] Yield calculated from n.m.r. spectrum. [f] Substantial amounts of aryl-formylated products were obtained, *cf.* ref. 10. [g] Isolated yield of (10e) from mixture of formyl compounds.



6-*endo* cyclization. In the cases of (7a—d) the structural assignments were proved chemically: the first three alcohols (7a—c) were acetylated (88—95% yield§) and ozonized (64—85% yield) to the corresponding cyclopentanones (i.r.). The total ozonolysis products in the sequences using (7a) and (7b) were examined by ^{1}H n.m.r. spectroscopy (200 MHz): only one aldehyde signal (benzaldehyde) was present in each case. The structure of (7d) was proved by oxidation (pyridinium chlorochromate) to a mixture of (*Z*)- and (*E*)-cyclopentanones [83%, $\nu_{max.}$ 1712 cm^{-1} (CCl_4)]. The ^{1}H and ^{13}C n.m.r. spectra (Bruker WH 400 or WH 200) of (7a—e) showed the compounds to be mixtures of geometric isomers. Of course, in the case of (7e) there is an additional stereochemical complication because two asymmetric centres are present. The cyclization product (7c) was separated chromatographically into two components, (7c′) and (7c″) (39

§ (7c″) (see later) was acetylated in 54% yield only.



Scheme 2

and 47% isolated yields, respectively)¶ and the structures were assigned by acetylation (95 and 54%, respectively), ozonolysis (85—86%), and comparison with published[1d] data for the resulting ketones. The stereochemistry of the intermediate hydroxyselenide (**5c**) was not determined. The above experiments to establish structures (**7a—d**) show that the cyclization products are synthetically equivalent to ketones, and were necessary also for another reason: the chemical shift of the $\geq CH$–O– signal proved not to be a reliable indicator of ring size. The methine ^1H signal of cyclopentanol occurs ($CDCl_3$) at δ 4.4 and the value for cyclohexanol is δ 3.7. However, we observed signals in the range δ 3.5—4.9 for the cyclization products even though each one is a cyclopentanol derivative.

The present methodology based on selenoacetals and radical cyclization is likely to be quite versatile; it is certainly not limited to production of spiro-carbocycles. For example, it can be easily adapted (Scheme 2) so as to afford spirolactones[9] and typical results with this modification are summarized in Table 2.

Acknowledgement of financial support is made to the Natural Sciences and Engineering Research Council of Canada.

Received, 17th May 1985; Com. 674

¶ The chair conformations shown and the *E* geometry for (**7c'**) are arbitrary assignments.

References

1 (a) S. F. Martin, *Tetrahedron*, 1980, **36**, 419; (b) A. P. Krapcho, *Synthesis*, 1974, 383; (c) A. P. Krapcho, *ibid.*, 1976, 425; (d) J. Shimada, K. Hashimoto, B. H. Kim, E. Nakamura, and I. Kuwajima, *J. Am. Chem. Soc.*, 1984, **106**, 1759.
2 A. Krief, *Tetrahedron*, 1980, **36**, 2531.
3 D. L. J. Clive, G. J. Chittattu, V. Farina, W. A. Kiel, S. M. Menchen, C. G. Russell, A. Singh, C. K. Wong, and N. J. Curtis, *J. Am. Chem. Soc.*, 1980, **102**, 4438.
4 W. Dumont and A. Krief, *Angew. Chem., Int. Ed. Engl.*, 1977, **16**, 540; D. L. J. Clive and S. M. Menchen, *J. Org. Chem.*, 1979, **44**, 1883; D. L. J. Clive and S. M. Menchen, *ibid.*, 1979, **44**, 4279; L. A. Paquette, T-H. Yan, and G. J. Wells, *ibid.*, 1984, **49**, 3610.
5 D. Van Ende, W. Dumont, and A. Krief, *Angew. Chem., Int. Ed. Engl.*, 1975, **14**, 700; D. Seebach and A. K. Beck, *ibid.*, 1974, **13**, 806; W. Dumont, P. Bayet, and A. Krief, *ibid.*, 1974, **13**, 804; D. Van Ende and A. Krief, *Tetrahedron Lett.*, 1976, 457.
6 W. S. Johnson, L. R. Hughes, J. A. Klock, T. Niem, and A. Shenvi, *J. Am. Chem. Soc.*, 1979, **101**, 1279. We oxidized the corresponding alcohol: M. Yamaguchi, Y. Nobayashi, and I. Hirao, *Tetrahedron*, 1984, **40**, 4261.
7 P. N. Anderson and J. T. Sharp, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1331. 2-Bromodiphenylacetylene was made by a general method: D. C. Owsley and C. E. Castro, *Org. Synth.*, 1972, **52**, 128.
8 (a) *Cf.* J. K. Crandall and W. J. Michaely, *J. Org. Chem.*, 1984, **49**, 4244; (b) D. P. Curran and D. M. Radiewicz, *J. Am. Chem. Soc.*, 1985, **105**, 1448; (c) G. Stork and R. Mook, Jr., *ibid.*, 1983, **105**, 3721; (d) A. G. Angoh and D. L. J. Clive, *J. Chem. Soc., Chem. Commun.*, 1985, 941, 980.
9 *Cf.* D. L. J. Clive and P. L. Beaulieu, *J. Chem. Soc., Chem. Commun.*, 1983, 307; M. Okabe and M. Tada, *J. Org. Chem.*, 1982, **47**, 5382.
10 H. M. J. Gillissen, P. Schipper, P. J. J. M. Van Ool, and M. H. Beck, *J. Org. Chem.*, 1980, **45**, 319.