A Short, General, Organoselenium-mediated Synthesis of Cyclic Acetals

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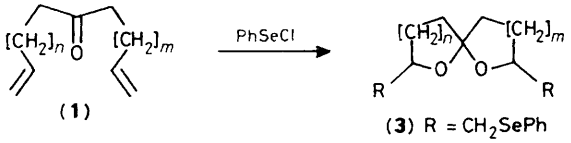
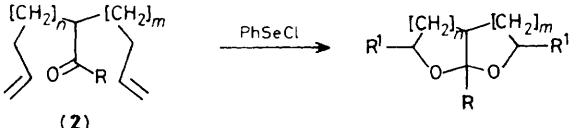
Readily available substrates containing a strategically placed carbonyl group and two isolated double bonds can be coaxed into cyclic acetal formation in a single step employing phenylselenenyl chloride in aqueous acetonitrile.

The cyclic acetal moiety is ubiquitous among natural products of such diversity as pheromones, insect antifeedants, polyether antibiotics, and toxins of marine and fungal origin. The structural complexity and biological activity of these compounds has led to extensive synthetic efforts towards them in recent years and several strategies for generating diverse cyclic acetal functionalities have been devised.[1] We describe here a direct acetal-forming reaction of the readily available dialkenyl ketones (**1**) and α,α-dialkenylated ketones (**2**) to give commonly encountered cyclic acetal moieties (**3**) and (**4**), respectively, in one step, employing a commercially available organoselenium reagent and reaction conditions recently reported by Toshimitsu *et al.*[2]

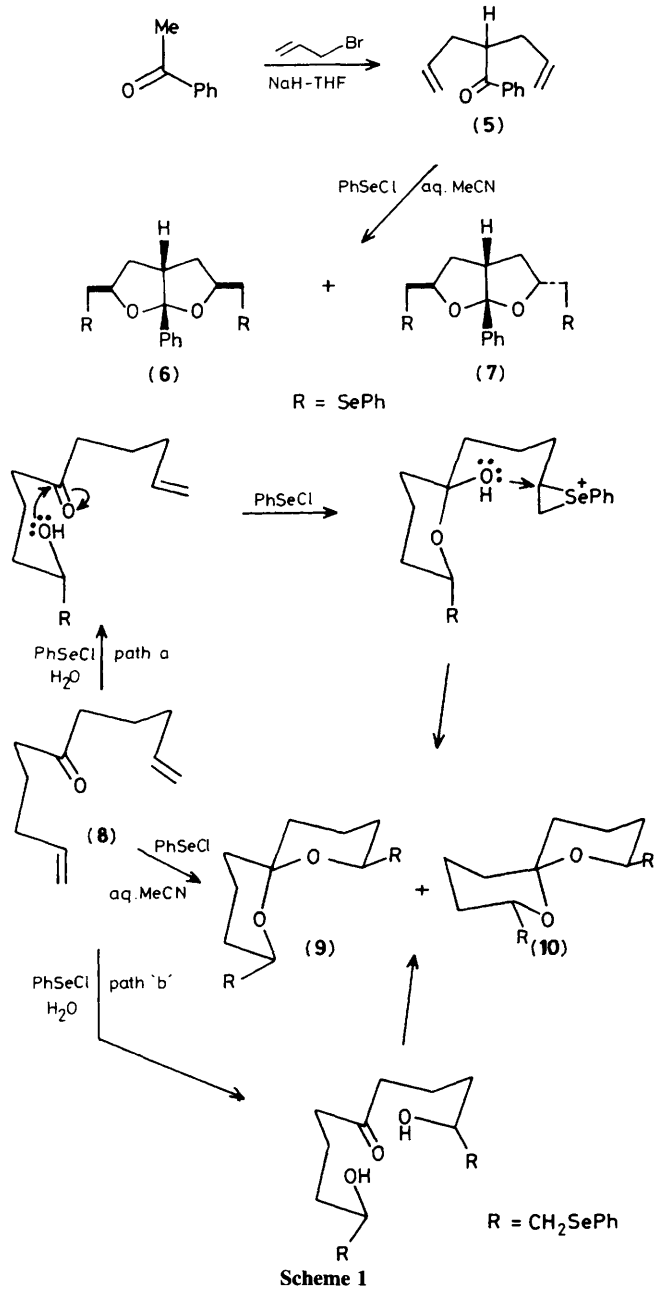
To start with, construction of the saturated furo[2,3-*b*]furan system (**4**) ($n = m = 1$) present in important natural products of current interest like asteltoxin,[3] clerodin,[4] and aflatoxins[5] was undertaken. Bisalkenylation of acetophenone with allyl bromide in the presence of NaH in tetrahydrofuran (THF) furnished 4-benzoylhepta-1,6-diene (**5**) (80%), which on exposure to phenylselenenyl chloride (2 equiv.) in aqueous acetonitrile[2] gave a readily separable 1 : 1 mixture of (**6**) and



(**1**) (**3**) R = CH_2SePh



(**2**) (**4**) R^1 = CH_2SePh, R = H, Me, Ph *etc.*

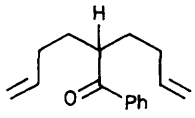
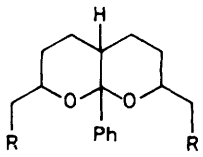
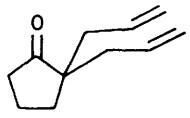
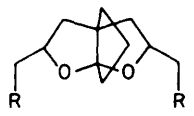
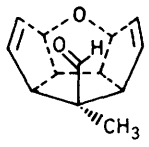
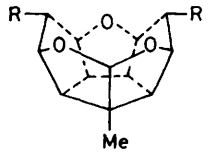
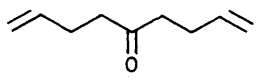
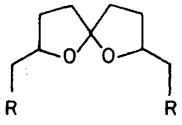
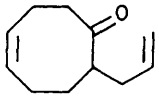
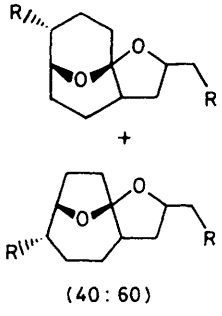


Scheme 1

(7) in 70% yield. The presence of 5 and 8 signals due to non-aromatic carbon atoms in the ^{13}C n.m.r. spectra of (**6**)† and (7),† respectively, enabled firm structural assignments to be made. Several reports[1j—l] have appeared recently on the synthesis of the furo[2,3-*b*]furan system but our construction of (**6**) and (**7**) from acetophenone in two steps is the shortest, and the generality of our synthetic technology is indicated through further examples in Table 1 (entries a—c).

Construction of spiroacetals was demonstrated next and in particular the 1,7-dioxaspiro[5.5]undecane (**3**) ($n = m = 2$) moiety present in the milbemycin–avermectin group[6] of potent anti-parasitic agents. Undeca-1,10-dien-6-one (**8**), available[1m] in two steps from 5-bromopent-1-ene and ethyl formate, on reaction with phenylselenenyl chloride (2 equiv.) in aqueous acetonitrile gave (**9**)† and (**10**)† in a ratio of 70 : 30 (75%). Structural assignment to (**9**) and (**10**) followed from

Table 1.

Entry	Starting material[a]	% Yield[b]	Product(s)[c]
a		70	
b		73	
c		45	
d		62	
e		60	 (40 : 60)

R = SePh

[a] All starting materials were prepared according to literature procedures and characterised. [b] Reactions were generally carried out on a 2—3 mmol scale with 2 equiv. of phenylselenenyl chloride in MeCN–H_2O (5 : 1) at ambient temperature (30 °C). The reactions were monitored by t.l.c. and were complete within 15 min in all the cases reported here. The work-up procedure and other experimental details as reported by Toshimitsu *et al.*[2] were followed. [c] Wherever stereochemistry is not explicitly shown, a mixture of epimers was obtained.

† Compound (**6**) ^1H n.m.r. ($CDCl_3$, 100 MHz): δ 7.1—7.7 (15H, m), 4.3—4.7 (2H, m), 2.8—3.4 (5H, m), and 1.8—2.0 (4H, m); ^{13}C n.m.r. ($CDCl_3$, 25 MHz): δ 117.6, 79.8, 50.6, 39.3, 32.5, and aromatic signals. Compound (**7**): ^1H n.m.r. ($CDCl_3$, 100 MHz): δ 7.1—7.7 (15H, m), 4.0—4.3 (2H, m), 2.6—3.3 (5H, m), and 1.8—2.0 (4H, m); ^{13}C n.m.r. ($CDCl_3$, 25 MHz): δ 117.5, 117.1, 78.3, 77.8, 50.9, 50.6, 39.2, 38.2, 32.5, 31.3, and aromatic signals. Compound (**9**): ^1H n.m.r. ($CDCl_3$, 100 MHz): δ 7.1—7.7 (10H, m), 4.8—5.2 (2H, m), 3.7—4.2 (4H, m), and 1.0—2.0 (12H, m); ^{13}C n.m.r. ($CDCl_3$, 25 MHz): δ 96.8, 69.4, 35.1, 34.1, 30.3, 18.7, and aromatic signals. Compound (**10**): ^1H n.m.r. ($CDCl_3$, 100 MHz); δ 7.1—7.7 (10H, m), 3.9—4.3 (2H, m), 2.8—3.3 (4H, m), and 1.1—2.6 (12H, m); ^{13}C n.m.r. ($CDCl_3$, 25 MHz); δ 98.8, 69.8, 69.2, 34.9, 34.1, 33.4, 32.5, 27.3, 25.8, 19.2, 18.8, and aromatic signals.

the symmetry element present in (**9**) as revealed by its ^{13}C n.m.r. spectrum as well as ^{1}H n.m.r. similarities with related systems.[1a] Further examples of this spiroacetal-forming reaction are given in Table 1 (entries d and e). It may also be mentioned that the $-CH_2SePh$ group generated during these cyclic acetal-forming reactions is very handy for elaboration to either a methyl group *via* reduction or other functionalities through radical reactions.[7]

The mechanistic details of this organoselenium-mediated cyclic acetal formation have not been investigated but path 'a' involving inter- and intra-molecular hydroxyselenations in tandem seems preferable to path 'b' involving two hydroxyselenations and intramolecular acetal formation, Scheme 1. We are presently extending the scope of this simple and versatile reaction to the synthesis of polyether antibiotics by building the olefinic and carbonyl groups within a 'macro' ring and generating the cyclic acetal moiety under macrocyclic stereocontrol.[8]

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