# On Baldwin's Kinetic Barrier Against 5-(Enol-*endo*)-*exo*-trigonal Closures: a Comparison of Ionic and Analogous Radical Reactions, and a New Synthesis of Cyclopentanones

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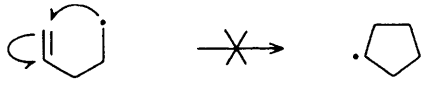
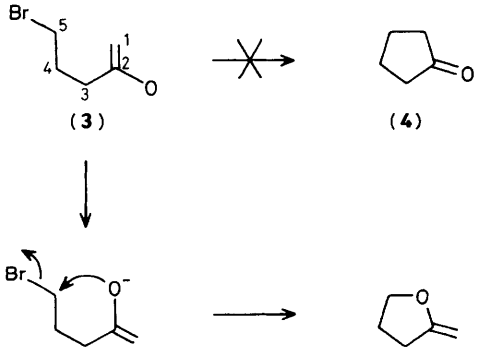
The kinetic barrier that impedes ionic 5-(enol-*endo*)-*exo*-trigonal closures does not play such a dominant role in the case of α-oxo radicals (**17**); these radicals cyclize directly to cyclopentanones in a process that constitutes a synthetic method for converting allylic alcohols (**12**) into bicyclo[*n*.3.0]alkanones (**19**).

The Rules for Ring Closure[1] were formulated at a time when free radical cyclizations were not receiving much attention, at least from synthetic chemists. Nevertheless, these rules and, especially, the prohibition[1a] against simple 5-*endo*-trigonal processes, as in (**1**) → (**2**), are very reliable[2] in the radical domain.[3] This area has been much expanded recently,[4] and, in the course of our own research, we have discovered a general radical cyclization which is analogous in its outcome to the *disfavoured* ionic 5-(enol-*endo*)-*exo* closure.[1c,d]

The C(1)–C(2) bond of enolates [see (**3**)] and corresponding enols has appreciable double-bond character.[5] Therefore, the strong kinetic barrier against 5-*endo*-trigonal cyclizations[1a] serves to interpret the experimental observation that the process (**3**) → (**4**) is much less favourable than the sequence (**3**) → (**5**) → (**6**).[1c,6] The case of intramolecular aldol condensations is similar; the closure shown in (**7**) is also kinetically disfavoured and, at least in competition experi-



(**1**) (**2**)

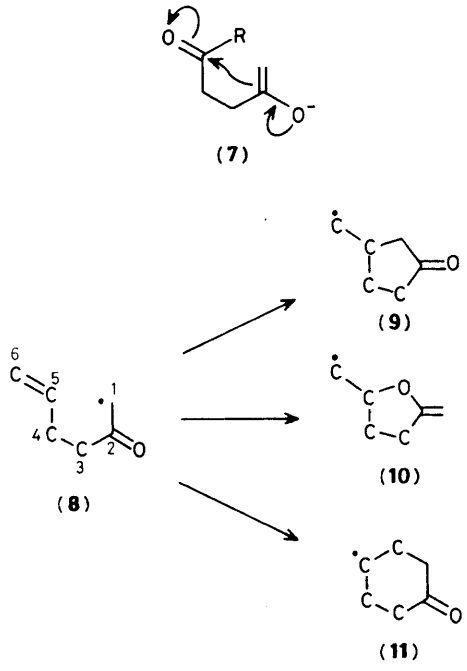


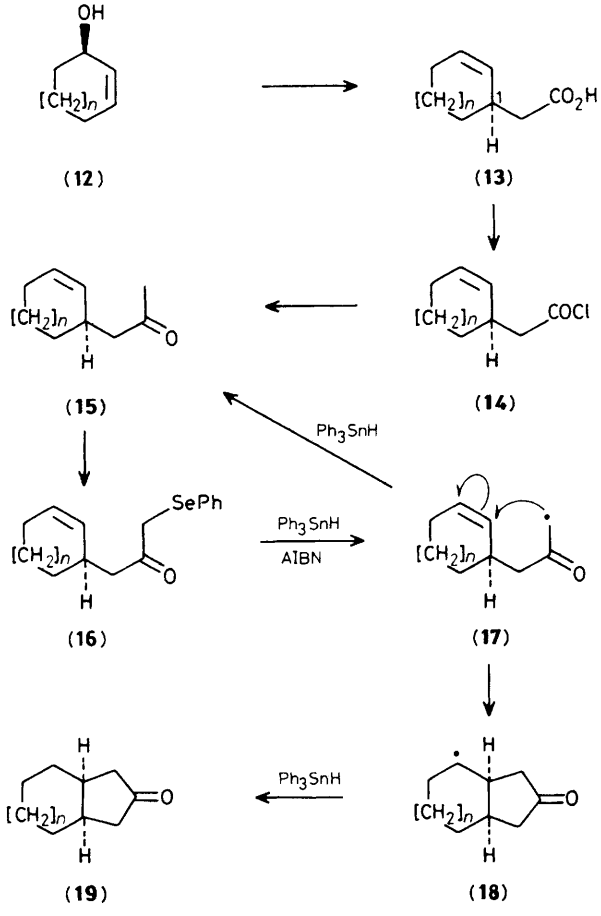
(**3**) (**4**) (**5**) (**6**)

**Table 1.**[a] Results of ring closure reactions.

| Acid | Acid chloride (%) | Methyl ketone (**15**) (%) | α-(Phenylseleno) ketone (**16**) (%) | Radical products combined yield (**19**) + (**15**) (%) | Ratio (**19**) : (**15**) | (**19**) | (%) | (**15**) | (%) |
|---|---|---|---|---|---|---|---|---|---|
| (**13a**) | 84 | 84 | 69 | 79 | 84 : 16[b] | (**19a**) | 64[c] | (**15a**) | 10 |
| (**13b**) | 84 | 67 | 73[d] | 85 | 84 : 16[b] | (**19b**) | 72[e] | (**15b**) | 12 |
| (**13c**) | | 77[f] | 75 | 89 | 79 : 21[g] | (**19c**) | 73[h] | (**15c**) | 16 |
| (**13d**) | | 89[f] | 69[i] | 86 | 100 : 0 | (**19d**) | 86 | (**15d**) | 0 |
| (**13e**) | | 42[f,j] | 68[k] | 83[l] | | (**19e**) | 76[g] | (**15e**) | |

[a] Yields refer to isolated materials except where stated otherwise. [b] By both g.l.c. and $^1$H n.m.r. (400 MHz). [c] *cis*-Isomer; for $^{13}$C n.m.r. data see ref. 17. [d] Contains ≤5% or regioisomeric (phenylseleno) ketone. [e] *cis*-Isomer; for $^{13}$C n.m.r. data see ref. 18. [f] Overall yield from acid. [g] By g.l.c. [h] Both ring-fusion geometries (63 : 38 by g.l.c.). A small amount of bicyclo[4.3.1]decan-3-one (≤6.5%; $^{13}$C n.m.r. at 100.6 MHz) may be present in this material. For $^{13}$C n.m.r. data see ref. 19. [i] Corrected for the fact that (**15d**) contained ($^1$H n.m.r. at 400 MHz) 7% of *exo* isomer; (**16d**) was pure. [j] The low yield is due to the volatility of the compound; the experiments were done on a small scale. [k] Contains ≤10.4% ($^1$H n.m.r. at 400 MHz) of regioisomeric (phenylseleno) ketone. [l] Combined yield of 2,4-dinitrophenylhydrazones of (**19e**) and of (**15e**). The $^1$H n.m.r. spectrum (400 MHz) of the material showed that the amount (10.3% of total) of derivative of (**15e**) corresponded to the undesired regioisomer in (**16**) (see footnote k).




**Scheme 1.** **a**; $n = 0$; **b**; $n = 1$; **c**; $n = 2$.

ments, is not observed when an alternative intramolecular pathway is available which does not involve the barrier that is implicit in (**7**).[1d]

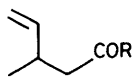
In the area of radical chemistry, the quantum mechanical effects are different and the C(1)–C(2) bond of an α-oxo radical [see (**8**)] is very largely a single bond,[7,8] the main resonance hybrid (85% contribution[7]) being the one shown in (**8**). Therefore, the rotational barrier about C(1)–C(2) in (**8**) is small[7,8] (*ca.* 9 kcal mol$^{-1}$) as compared with that[5] (>27 kcal mol$^{-1}$) which prevails in (**3**) and (**7**). For this reason the stereoelectronic requirements for closure of (**8**) to (**9**) might be easily met and there should probably be no serious geometrical factor that would hinder formation of (**9**) in favour of the thermodynamically much less stable[9] enol ether (**10**).† However, it is not clear from structure (**8**) whether the normal regiochemistry of radical cyclization would be altered to afford (**11**), or whether simple reduction [(**8**) → –$COCH_3$] would be a serious competing pathway.

We report that appropriate α-oxo radicals containing the substructure (**8**) generally close in the manner (**8**) → (**9**),‡ and

† The pent-4-enyloxy radical undergoes 5-*exo* closure with $k_c > 10^8$ s$^{-1}$ at room temperature (ref. 10); its all-carbon analogue, the hex-5-enyl radical, has $k_c$ 1 × 10$^5$ s$^{-1}$ at 25 °C (ref. 11).

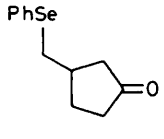
‡ For a related example containing an aryl-conjugated ketone, see ref. 12.


(13d) R = OH
(15d) R = Me
(16d) R = $CH_2SePh$




(13e) R = OH
(15e) R = Me
(16e) R = $CH_2SePh$


(19d)

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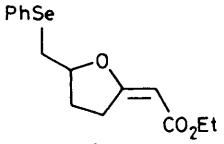
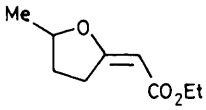



(21)

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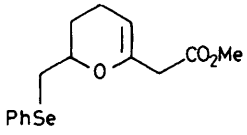


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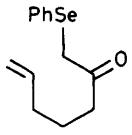


(24)

we have used this property as the basis of a new route to bicyclic cyclopentanones (Scheme 1).

The sequence can be regarded as starting with γ,δ-unsaturated carboxylic acids [*e.g.* (**13**)]. Such compounds are accessible by several methods: in particular, they often can be prepared from allylic alcohols (**12**) by Claisen rearrangement,[13] a process that generates the acids with predictable stereochemistry at C(1) [see (**13**)]. We examined several approaches for transforming such acids into the required α-(phenylseleno) ketones (**16**), but had to accept the following classical method as best. The acids were converted into their acyl chlorides [(**13**) → (**14**); oxalyl chloride, benzene, room temp., 2—3 h], which, on treatment with lithium dimethylcuprate (3 equiv., diethyl ether, −78 °C, 10 min) afforded the methyl ketones (**15**). Kinetic deprotonation [lithium di-isopropylamide (1.1 equiv.), tetrahydrofuran, −78 °C, 10 min] and quenching (−78 °C) with benzeneselenenyl chloride (1.25 equiv.) gave the α-(phenylseleno) ketones (**16**).§ Besides the cycloalkenylacetic acids (**13a—c**) shown in Scheme 1, the bicyclic acid (**13d**)[14] and the acyclic example (**13e**)[15] were also subjected to these reactions so as to produce the corresponding methyl ketones (**15d** and **e**) and the derived α-(phenylseleno) ketones (**16d** and **e**).

Generation of the radical (**16**) → (**17**) (Scheme 1) by treatment with triphenyltin hydride[16] under our standard conditions[4a]¶ led to mixtures of cyclized (**19**) and uncyclized (**15**) products (see Scheme 1) in 76—89% yield and generally in the ratio *ca.* 80 : 20. The uncyclized materials can, of course, be resubjected to phenylselenenylation and ring closure. Our results are collected in Table 1.

As expected on the basis of the rules for ring fusion stereochemistry,[4a,20] (**19a**) and (**19b**) were obtained only as *cis*-ring-fused compounds, but (**19c**) was a mixture of *cis*- and *trans*-isomers. The radical derived from the bicyclic (phenylseleno) ketone (**16d**) closed only ($^{13}C$ n.m.r. at 100.6 MHz) by a 5-*exo* pathway to give 2-isotwistanone (**19d**). In contrast, the radical derived from the conformationally most mobile (phenylseleno) ketone [*i.e.* (**16e**)] closed by a 6-*endo* pathway, giving 3-methylcyclohexanone (76% yield by g.l.c.). We believe this result corresponds to the direct general process (**8**) → (**11**) (see above), because treatment of (**20**)‖ with triphenyltin hydride under our standard conditions gave 3-methylcyclopentanone (84% by g.l.c.) and, little if any (g.l.c.–mass spectrometry) hex-5-en-2-one or cyclohexanone. We take this experiment as evidence that 5-*exo* carbocyclization in our system (**16e**) would not be reversible. Evidently, for (**16e**), the derived radical gives the product of *endo* closure directly. In the cycloheptenyl case (**16c**) the radical cyclization product (**19c**) contains material (≤6.5%) tentatively identified by its $^{13}C$ n.m.r. spectrum[19] as bicyclo[4.3.1]decan-8-one. On this basis, therefore, the example of (**16c**) is also one in which some 6-*endo* closure occurs.

In connection with the possibility that our reactions involve a reversible sequence of the type (**8**) ⇋ (**10**), we note that compound (**21**),[22] and a number of substances like it, are smoothly reduced by stannanes[22,23] in the sense (**21**) → (**22**). Even under our own (high dilution) conditions, (**21**) is converted into (**22**) (80% yield) without rearrangement (by g.l.c.). However, the selenide (**23**),[23] in which the double bond is not conjugated, behaves in a more complex manner. Under our conditions ($Ph_3SnH$) simple reduction ($-CH_2SePh \rightarrow -CH_3$) occurs (69% yield; isolated), but some ring opening (13.7% yield; isolated) to methyl 3-oxo-oct-7-enoate also takes place. No ring-opening was observed when (**23**) was exposed to $Ph_3SnSePh$ (0.7 equiv.) in refluxing benzene (12 h). It appears that, in general, radical species of the type $\dot{C}$–C–O–C=C do not undergo rapid β-elimination.

Finally, we have also examined the oxo selenide (**24**), which was prepared by reaction of pent-4-enylmagnesium bromide with (phenylseleno)acetaldehyde, followed by oxidation (C–OH → C=O; NCS, $Me_2S$).[24] Simple hept-6-enyl radicals cyclize about $10^2$ times more slowly than hex-5-enyl species, and intramolecular allylic hydrogen abstraction is a significant pathway.[25] However, (**24**) produced 3-methylcyclohexanone and cycloheptanone in yields (g.l.c.) of 45 and 41%, respectively.

All isolated new compounds were fully characterized by spectroscopic measurements (including accurate mass) and, with the exception of (**20**), also by combustion analysis.

§ As indicated in Table 1, we sometimes detected small amounts of (phenylseleno) ketone produced from the internal enolate, Such material is simply converted into the parent ketone in the next step.

¶ Solutions in benzene of *freshly prepared* triphenyltin hydride (1.2 equiv.; 0.55 M) and of azoisobutyronitrile (0.2 equiv., 0.008 M) were added over 13 h to a refluxing solution of (phenylseleno) ketone in benzene (0.02 M). Refluxing was continued for 1—2 h more, and the products were then isolated.

‖ Prepared by the action of PhSeNa on 3-(iodomethyl)cyclopentanone (ref. 21).

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