Rules for Ring-fusion Geometry and the Preparation of *trans*- or *cis*-Fused Bicyclic Compounds by Radical Closure

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Aldol condensation with (phenylseleno)acetaldehyde and radical cyclization leads to *cis*-fused bicyclic compounds when applied (Scheme 1) to esters of cycloalk-2-enylacetic acid; *trans*-isomers are formed when the reactions are used (Scheme 2) in conjunction with organocuprate-mediated addition to cycloalkenones.

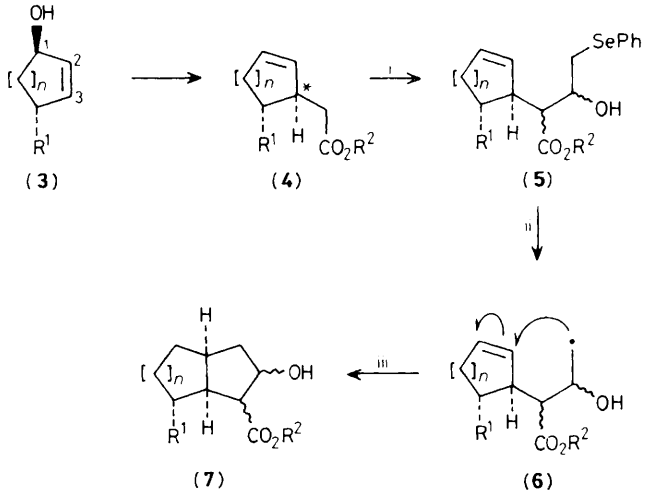
The construction of bicyclic compounds *via* radical closure proceeding under conditions of kinetic control [as in (**1**) → (**2**)] has stereochemical consequences for the ring-fusion geometry that are predictable by empirical rules.[1] The processes (**1**) → (**2**) for n = 1,2,3 may be described[1] as 5-*exo*-[*endo*-5], 5-*exo*-[*endo*-6], and 5-*exo*-[*endo*-7] cyclizations, respectively, and the preferred stereochemistry of the reaction is as indicated:

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

Process	*trans*-Ring-fusion
5-*exo*-[*endo*-5]	Disfavoured
5-*exo*-[*endo*-6]	Disfavoured†
5-*exo*-[*endo*-7]	Allowed

A corollary to these rules is that *trans*-ring-fused compounds, *trans*-(**2**), n = 1,2, are best prepared by reactions in which the last bond to be made in the ring-forming process is *not* a bond to one of the ring junction atoms. We report that an aldol reaction with (phenylseleno)acetaldehyde followed by radical cyclization can be used, in conformity with these ideas, to prepare either *cis*- or *trans*-ring-fused bicyclic compounds.

The route to *cis*-materials (Scheme 1) is based on esters of cycloalkenylacetic acid (**4**). These are readily available by several routes,[4,5] but their preparation from allylic alcohols (**3**) by methods based[5] on the Claisen rearrangement are particularly convenient in the present context. The suprafacial nature of the rearrangement means that the stereochemistry of the esters [see (**4**) starred atom] is controllable by proper choice of stereochemistry at C-1 of the alcohol. The esters are deprotonated by addition to lithium di-isopropylamide (LDA) (1.1 equiv.) [tetrahydrofuran (THF), −78 °C, 20 min] and the resulting carbanions give aldol products, (**4**) → (**5**), with (phenylseleno)acetaldehyde[6] [1.25 equiv., −78 °C, 5 min; quench with AcOH (1.5 equiv.) in THF]. Treatment of the hydroxyselenides (**5**) with triphenyltin hydride (1.30 equiv.) and azoisobutyronitrile (AIBN) (0.10 equiv.) in refluxing benzene under our standard conditions[1] generates a radical, (**5**) → (**6**), which furnishes the bicyclic products (**7**). Both stages (**4**) → (**5**) and (**5**) → (**7**) are efficient, and our results[8]



(**3**) (**4**) (**5**) (**7**) (**6**)

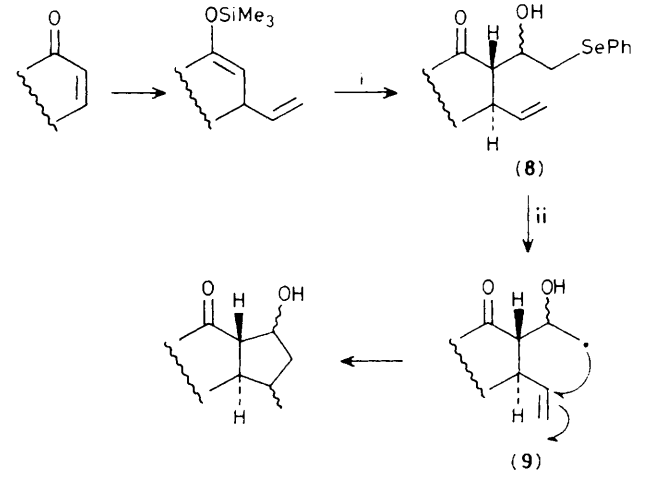
Scheme 1. *Reagents:* i, LDA then $PhSeCH_2CHO$; ii, Ph_3SnH, AIBN; iii, Ph_3SnH.

Table 1. Results for *cis*-ring fusion based on cyclization of the radical (**6**).[a]

(**4**)	R^1	R^2	n	% Yield	
a;	H	Me	1[b]	(**5a**), 74	(**7a**), 89[c]
b;	H	Me	2[b]	(**5b**), 84	(**7b**), 91[d]
c;	Bu[t]	Et	2[e]	(**5c**), 93	(**7c**), 71[f]

[a] All yields refer to isolated and pure materials and isomer ratios were determined by ^1H n.m.r. spectroscopy (400 MHz). All compounds are racemic. [b] Made by esterification ($MeOH–H_2SO_4$) of the appropriate acid. [c] Isomer ratio: 49:27:10:14. [d] Isomer ratio: 44:40:10:6. [e] Prepared in two steps (89%; 56%) by the general method of ref. 5b, starting from *trans*-4-t-butylcyclohex-2-enol (ref. 7). [f] 2 major isomers.

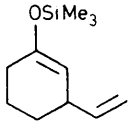
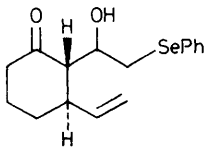
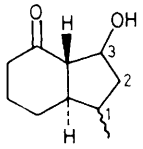
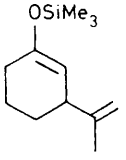
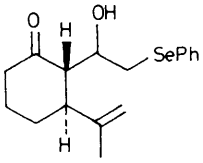
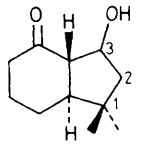
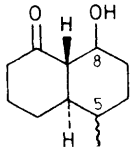
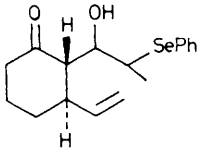
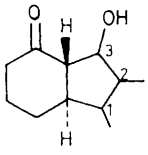
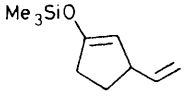
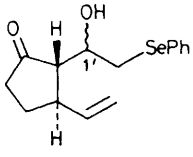
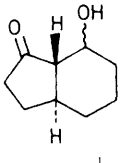
† For MM2 force-field calculations on 5-*exo*-[*endo*-6] and 6-*exo*-[*endo*-6] processes see ref. 2. For an example of a 6-*exo*-[*endo*-6] reaction (leading to *cis*-fusion) see ref. 3.



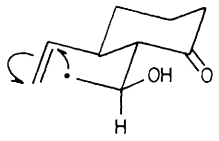
(**8**) (**9**)

Scheme 2. *Reagents:* i, MeLi, then $ZnCl_2$, followed by $PhSeCH_2CHO$; ii, Ph_3SnH, AIBN.

Table 2. Results for *trans*-ring fusion based on cyclization of the radical (**9**).[a]

Starting material	Aldol product, % yield	Cyclization product(s), % yield
 (**10a**)	 (**10bβ**),[b,c] 56 (**10cα**), 25	 (**10cβ**), 58[d] (**10cα**), 56[e]
 (**11a**)	 (**11bβ**),[b,c] 56 (**11bα**), 25	 (**11cβ**), 40 (**11cα**), (81)[g] +  (**11dβ**), 29[f] (**11dα**), (81)[g]
(**12a**) ≡ (**10a**)	 (**12b**), 53[h] 83[i]	 (**12c**), 51[j]
 (**13a**)	 (**13b**), 73[k]	 (**13c**), 34[l]

[a] Except where otherwise indicated, yields refer to isolated and pure compounds. All compounds with asymmetric centres are racemic. [b] α and β (with their usual meaning) define the orientation of the hydroxy group. [c] The β- and α-epimers were isolated, in the yields shown, from the same aldol condensation. Each epimer was cyclized separately. [d] As a mixture of two compounds (>80:20, ^{13}C n.m.r.) isomeric at C-1. [e] Two isomers (*ca.* 9:1, ^1H n.m.r.) epimeric at C-1. [f] Two isomers (*ca.* 2:3, ^1H n.m.r.) epimeric at C-5. [g] Combined yield of (**11cα**) and (**11dα**) which were chromatographically inseparable; ratio (**11cα**) to (**11dα**) 1:1.6 (^1H n.m.r.). [h] As a *single* isomer. Stereochemistry in side chain not established. *trans*-Relationship of side chains assigned by analogy. [i] As a mixture of isomers. [j] Two isomers (*ca.* 1:3.2, ^1H n.m.r.), both with same stereochemistry at C-3. [k] Two isomers (*ca.* 1:1) epimeric at C-1'. [l] Calculated from the ^1H n.m.r. spectrum of a mixture of (**13c**) and the non-cyclized reduction product [PhSe replaced by H in (**13b**)].



(**14**)

with several examples are collected in Table 1. The *cis*-ring-fusion for (**7b**) was proved by deoxygenation[9] (thiocarbonyldiimidazole; tributyltin hydride, AIBN, THF, 70 °C) to give the known epimeric *cis*-esters.[1] In the case of (**7c**) the ring junction stereochemistry was assigned by nuclear Overhauser effect (n.O.e) measurements.

The intermediates (**6**) are β-hydroxy radicals and must have a different level of reactivity[10] from corresponding species lacking the adjacent hydroxy function. However, as expected,[11] no problems were met on this account and the cyclizations proceed smoothly, even for the third example, (**5c**) → (**7c**), in which the pendant side chain is restrained (at least in the ground state) pseudo-equatorially by the strong conformational preference of the t-butyl group.

Preparation of *trans*-ring-fused compounds involves the sequence of Scheme 2, in which the *trans*-disposition of the side chains [as in (**8**)] is set up by conjugate addition and aldol condensation, a sequential process known[6] to give this stereochemical result. Treatment with triphenyltin hydride and AIBN, again under standard conditions,[1] generates the desired radical, (**8**) → (**9**), which then cyclizes. The mode of closure [5-*exo* (as shown in Scheme 2) or 6-*endo*] depends on the substitution pattern of the double bond. Our results with (phenylseleno)acetaldehyde and with 2-(phenylseleno)propanal are summarized in Table 2. For an unsubstituted double bond, (**10b**) → (**10c**); (**12b**) → (**12c**), 5-*exo* closure takes place, but internal monosubstitution [as in (**11b**)] leads to a mixture resulting from both *exo* and *endo* closure. When the *trans*-disposed side chains are appended to a five-membered ring, (**13b**), then cyclization is not the main pathway and that which does occur follows mainly, if not exclusively, the 6-*endo* route.[2,12]

The transformations (**10bβ**) → (**10cβ**) and (**10bα**) → (**10cα**) are highly stereoselective. The ratio of the isomers of (**10cβ**) is >80:20 and, for (**10cα**), the ratio is *ca.* 9:1. An *X*-ray crystallographic analysis of the 3,5-dinitrobenzoate derivative (m.p. 167—168 °C) of (**10cβ**) showed that the preferred pathway in the radical cyclization must resemble the all chair conformation (**14**), which leads to the observed (*X*-ray) 1α-Me,3β-OH stereochemistry of the major product.

In summary, we have shown that bicyclic compounds, suitably functionalized to permit further modification, can be made with predictable *cis*- or *trans*-ring-fusion geometry by a judicious use of conjugate addition, aldol condensation with an α-(phenylseleno)aldehyde, and radical cyclization.

Satisfactory combustion analysis and full spectroscopic data were obtained for all new compounds, with the reservation that some materials were analysed as isomer mixtures when separation was not possible.

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