Construction of *trans*-Ring-fused Compounds by Radical Cyclization

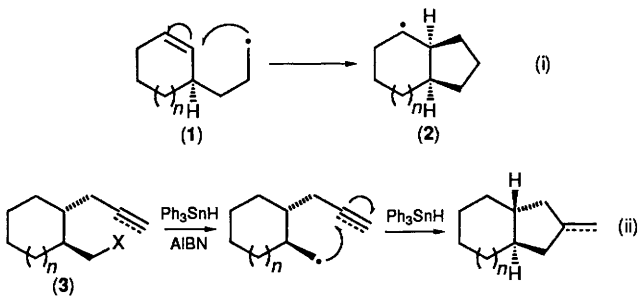
Derrick L. J. Clive,* Hartford W. Manning, and Taryn L. B. Boivin

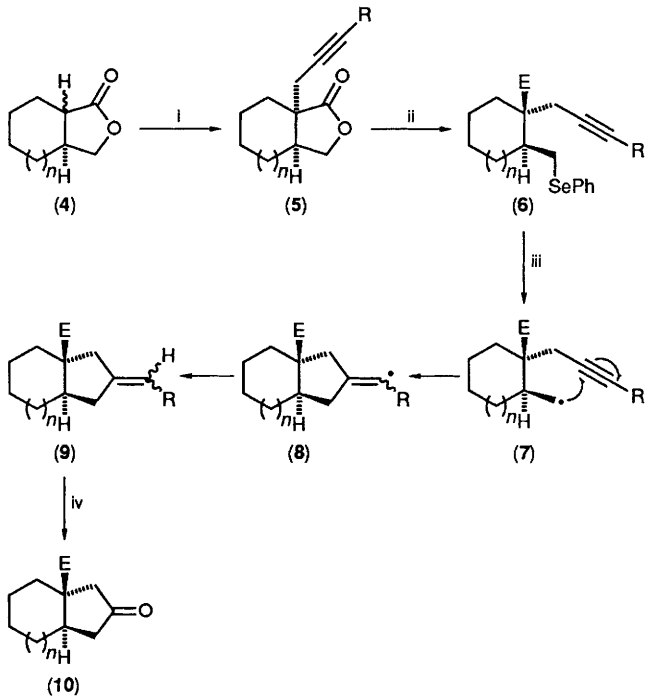
Department of Chemistry, University of Alberta, Edmonton, Alberta, T6G 2G2, Canada

Enolates derived from bicyclic lactones of type (**4**) are alkylated with prop-2-ynylic (and allylic) bromides to give products (**5**) in which the unsaturated alkyl group is *syn* to the remaining ring-fusion hydrogen; prop-2-ynylic aldehydes can be used instead of halides and, in both cases, lactone opening with sodium phenyl selenide, esterification, and treatment with a stannane then leads to *trans*-ring-fused bicyclic compounds.

Formation of bicyclic compounds by radical ring closure [(**1**) → (**2**), equation (i)] gives products with *cis* ring-fusion for n = 1,2.[1] In order to generate the *trans*-ring fused isomers[2] the last bond to be formed should *not* be a bond to a ring junction atom.[1a] This restriction can be accommodated [equation (ii)] by attaching to a ring a pair of *trans*-disposed substituents [as in (**3**)], one carrying a homolysable group (X) and the other a radical trap (C=C, or C≡C). Such an approach depends on methods for making the intermediates of type (**3**) [see equation (ii)].

We report in this context an alkylation/lactone-opening sequence (Scheme 1) that leads, after radical cyclization, to *trans*-ring-fused compounds. The starting lactones (**4**) are easily available by a number of convenient methods,[3] and the key step of Scheme 1 is the alkylation, (**4**) → (**5**). In the cases we have examined (Table 1) the unsaturated chain in the product (**5**) is *syn* to the remaining ring fusion hydrogen.[7] This stereochemical result ensures that, after lactone opening,



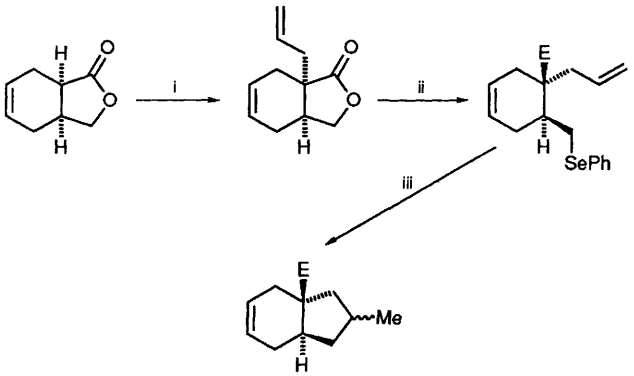


Scheme 1. *Reagents and conditions*: i, lithium di-isopropylamide (LDA); $RC{\equiv}CCH_2Br$; ii, $PhSe^-$, tetrahydrofuran–hexamethylphosphoric triamide (THF–HMPA), 70 °C; CH_2N_2, ether; iii, Ph_3SnH, azoisobutyronitrile (AIBN), benzene, reflux; iv, oxidative cleavage (E = CO_2Me).

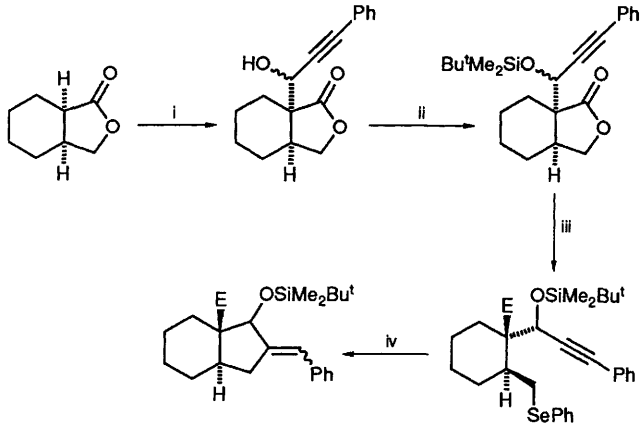
Table 1.[a]

Entry	Lactone (**4**)	Alkylated lactone (**5**)	Selenide (**6**)	Bicyclic product (**9**)	Ketone (**10**)
(i)	(**4a**) $n = 0$[b,c]	(**5a**) $n = 0$, R = Pr, 63%	(**6a**) $n = 0$, R = Pr, 81%	—[d]	—[e]
(ii)	(**4b**) $n = 1$[b,f]	(**5b**) $n = 1$, R = Ph, 97%	(**6b**) $n = 1$, R = Ph, 72% (100%)[g]	(**9b**) $n = 1$, R = Ph, 96%[h]; 87%[i]	(**10b**) $n = 1$, 64%[j]; 60%[k]
(iii)	(**4b**) $n = 1$	(**5b**) $n = 1$, R = Pr, 88%	(**6b**) $n = 1$, R = Pr, 77%, (87%)[g]	(**9b**) $n = 1$, R = Pr, 82%[h]	(**10b**) $n = 1$, 73%[j]
(iv)	(**4c**) $n = 2$[l,m]	(**5c**) $n = 2$, R = Pr, 89%[n]	(**6c**) $n = 2$, R = Pr, 66%, (86%)[g]	(**9c**) $n = 2$, R = Pr, 79%[h], 95%[i]	—[e]
(v)	(**4d**) $n = 3$[o,p]	(**5d**) $n = 3$, R = Pr, 72%	(**6d**) $n = 3$, R = Pr, 74%	(**9d**) $n = 3$, R = Pr, 77%[h], 87%[i]	(**10d**) $n = 3$, 82%[j]

[a] All yields refer to pure isolated compounds. [b] *cis*-geometry. [c] Made by reduction (ref. 3b) of the corresponding anhydride (ref. 4). [d] Reduction product (**6a**, $n = 0$, R = Pr, H instead of PhSe) was isolated in about 14% yield, but not characterized beyond measurement of its ^{1}H NMR (400 MHz) spectrum. [e] Experiment not tried. [f] Made by reduction (ref. 3b) of the corresponding anhydride, itself available by Diels–Alder chemistry and hydrogenation. [g] Yield corrected for recovered starting material. [h] Ph_3SnH/AIBN used for radical cyclization. The product is a mixture of *Z*- and *E*-isomers. [i] Ph_3SnH/Et_3B used for radical cyclization. The product is a mixture of *Z*- and *E*-isomers. [j] Ozonolysis (O_3/CH_2Cl_2/MeOH/−78 °C; Ph_3P). [k] OsO_4 (2 mol%)/$NaIO_4$ (2 equiv.)/THF–H_2O/room temperature/17 h. [l] Mixture of *cis*- and *trans*-isomers. [m] Made by reduction (ref. 3b) of the corresponding anhydride (*cf.* ref. 5), itself available analogously to (**4a**). [n] A small amount (about 0.6% yield) of the *trans*-isomer (ring fusion hydrogen and hexynyl group *trans*) was isolated. [o] Single isomer. [p] Made by reduction (ref. 3b) of the corresponding anhydride (*cf.* ref. 5), itself available analogously to (**4a**) from 2-ethoxycarbonylcyclononanone (ref. 6).



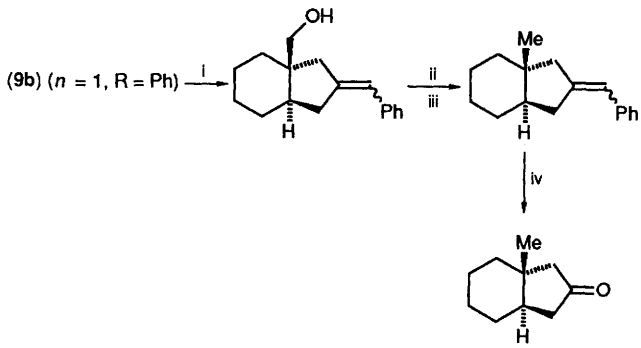
Scheme 2. *Reagents and conditions*: i, LDA, THF, allyl bromide, −78 to 0 °C, 89%; ii, $PhSe^-$, THF–HMPA, 70 °C; CH_2N_2, ether, 74%; iii, Ph_3SnH, AIBN, benzene, reflux, 92%. (E = CO_2Me. Starting lactone prepared by method of ref. 3a.)



Scheme 3. *Reagents and conditions*: i, LDA, THF, PhC≡CCHO, −78 °C, 94%; ii, Bu^{t}Me$_2$SiCl, Et_3N, 4-dimethylaminopyridine (DMAP), dimethylformamide (DMF), 50 °C, 85%; [at this stage the diastereoisomers (about 1 : 1) were separated and characterized, but only one of them was taken further]; iii, $PhSe^-$, THF–HMPA, 70 °C; CH_2N_2, ether, 65%; iv, Ph_3SnH, AIBN, benzene, reflux, 78%.

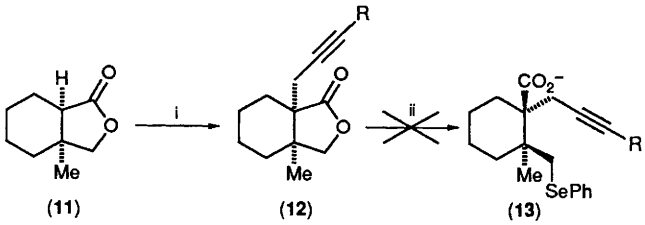
(**5**) → (**6**), the chain carrying the radical precursor (CH_2SePh) and the unsaturated pendant ($CH_2C{\equiv}C$–R) [see (**6**)] are *trans* to one another. The penultimate step of the scheme, (**6**) → (**7**) → (**8**) → (**9**), is a conventional 5-*exo* closure of the radical, generated by reaction with a stannane.†

The present method is suitable for constructing 5/6, 5/7, and 5/8 systems (see Table 1), but the radical cyclization does not work when the initial ring is five-membered [Table 1, entry (i)]. The unsaturated pendant is not limited to an acetylene; we have also examined an alkene, as summarized in Scheme 2.



Scheme 4. *Reagents and conditions*: i, $LiAlH_4$, 95%; ii, 2,4,6-triisopropylbenzenesulphonyl chloride, NaH, 80 °C, 81%; iii, Et_3BHLi, THF, reflux, 94%; iv, O_3, MeOH–CH_2Cl_2, −78 °C, Ph_3P, 60%.

† Two methods were used. (A) Benzene solutions of triphenyltin hydride (0.14 M; 1.5 equiv.) and of azoisobutyronitrile (0.01 M; 0.1 equiv.) were added during 10 h to a refluxing benzene solution of the substrate (0.026 M; 1 equiv.), and refluxing was continued 2 h after the end of the addition. (B) (*cf.* ref. 8). Triethylborane (1 M in hexane; 1 equiv.) was added to a stirred solution of the substrate (0.01 M; 1 equiv.) and triphenyltin hydride (0.012 M; 1.2 equiv.) in hexane, which had been dried but not protected from atmospheric oxygen. The mixture was stirred overnight with protection from atmospheric moisture (calcium sulphate drying tube).



Scheme 5. *Reagents and conditions*: i, LDA, THF, $PhC{\equiv}CCH_2Br$, −78 to 0 °C, 90%; ii, $PhSe^-$, THF–HMPA, 70 °C, <14%, 87% corrected for recovered (**12**).

Aldol condensation (Scheme 3) can be used instead of alkylation, but the hydroxy group must be protected (*e.g.*, by silylation) before the lactone is opened.

The radical cyclization products (see Table 1) are, of course, amenable to further modification such as oxidative cleavage of the double bond [Table 1, entries (ii), (iii), (v)] and/or conversion of the ester into a methyl group (*e.g.*, Scheme 4).

It was necessary in this work to prove the stereochemistry of the initial alkylation (or aldol) process, and the structures for (**5b**) (R = Ph), (**5c**), (**5d**), (**12**) (see below, and Scheme 5), and (**16**) (see below, and Scheme 6) were established by chemical correlation with appropriate reference samples of defined geometry;‡ the stereochemistry for the other key substances (of Schemes 1, 2, and 3) was then assigned by analogy.

We have also demonstrated that alkylation still occurs in the desired stereochemical sense when a substituent is present adjacent to the alkylation site [see Scheme 5, (**11**)[9] → (**12**); Scheme 6, (**15**) → (**16**)].‡

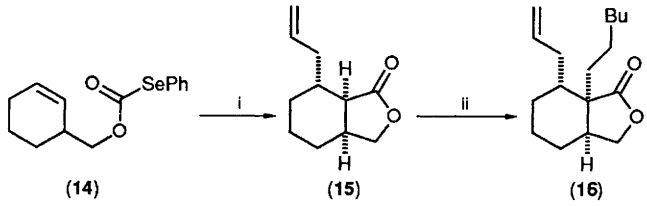
One restriction on the general method of Scheme 1 is evident from our preliminary experiments: when the ring fusion hydrogen in (**5**) (see Scheme 1) is replaced [as in (**11**),[9] Scheme 5] by a methyl group, then the lactone opening [see Scheme 5, (**12**) → (**13**)] is too sluggish to be useful, at least under the standard conditions that we have tried.[10]

All new compounds were fully characterized by spectroscopic and/or combustion analytical measurements, with the exception specified in footnote d of Table 1.

Acknowledgement of financial support is made to the Natural Sciences and Engineering Research Council of Canada and the University of Alberta. H. W. M. holds an NSERC Graduate Studentship.

Received, 27th March 1990; Com. 0/01344G

‡ Details of the stereochemical assignments will be given in the full paper.



Scheme 6. *Reagents and conditions*: i, allyltributyltin, $Bu_3SnSnBu_3$, benzene, photolysis, 72%; ii, LDA, THF–HMPA, $n\text{-}C_6H_{13}Br$, −78 °C to room temperature, about 75%. [Compound (**14**) was prepared ($COCl_2$, Et_3N; PhSeH, pyridine; 84%) from cyclohex-2-enylmethanol, which was made by reduction ($LiAlH_4$) of methyl (cyclohex-2-enyl)acetate (ref. 11)].

References

1 (a) D. L. J. Clive, D. R. Cheshire, and L. Set, *J. Chem. Soc., Chem. Commun.*, 1987, 353; (b) A. Y. Mohammed and D. L. J. Clive, *ibid.*, 1986, 588.
2 Construction of *trans* hydrindanes is a classical problem. For recent approaches, see (a) G. Stork and M. J. Sofia, *J. Am. Chem. Soc.*, 1986, **108**, 6826; (b) P. A. Zoretic, B. C. Yu, and M. L. Casper, *Synth. Commun.*, 1989, **19**, 1859.
3 *E.g.*, (a) Partial reduction of anhydrides: D. M. Bailey and R. E. Johnson, *J. Org. Chem.*, 1970, **35**, 3574; (b) cyclization of acyl radicals [*cf.* (**14**) → (**15**), Scheme 6]: M. D. Bachi and E. Bosch, *Heterocycles*, 1989, **28**, 579; (c) homochiral lactones: I. J. Jakovac, H. B. Goodbrand, K. P. Lok, and J. B. Jones, *J. Am. Chem. Soc.*, 1982, **104**, 4659.
4 L. N. Owen and A. G. Peto, *J. Chem. Soc.*, 1955, 2383; A. Svendsen and P. M. Boll, *Tetrahedron*, 1973, **29**, 4251; D. Wilkening and B. P. Mundy, *Synth. Commun.*, 1984, **14**, 227.
5 J. Sicher, F. Šipoš, and J. Jonáš, *Coll. Czech. Chem. Commun.*, 1961, **26**, 262.
6 W. L. Mock and M. E. Hartman, *J. Org. Chem.*, 1977, **42**, 459.
7 Recent work on the stereochemistry of alkylation: (a) B. Herradón and D. Seebach, *Helv. Chim. Acta*, 1989, **72**, 690; (b) K. Tomioka, H. Kawasaki, K. Yasuda, and K. Koga, *J. Am. Chem. Soc.*, 1988, **110**, 3597; (c) K. Tomioka, H. Kawasaki, and K. Koga, *Tetrahedron Lett.*, 1985, **26**, 3027; (d) V. G. Matassa, P. R. Jenkins, A. Kümin, L. Damm, J. Schreiber, D. Felix, E. Zass, and A. Eschenmoser, *Israel J. Chem.*, 1989, **29**, 321; (e) A. I. Meyers, M. Harre, and R. Garland, *J. Am. Chem. Soc.*, 1984, **106**, 1146; (f) A. I. Meyers and B. A. Lefker, *Tetrahedron*, 1987, **43**, 5663. Review: D. A. Evans, in 'Asymmetric Synthesis,' ed. J. D. Morrison, Academic Press, New York, 1984, vol. 3, p. 1.
8 K. Nozaki, K. Oshima, and K. Utimoto, *Tetrahedron Lett.*, 1988, **29**, 6127.
9 J. J. Bloomfield and S. L. Lee, *J. Org. Chem.*, 1967, **32**, 3919.
10 P. Dowd and P. Kennedy, *Synth. Commun.*, 1981, **11**, 935; D. Liotta and H. Santiesteban, *Tetrahedron Lett.*, 1977, 4369; R. M. Scarborough, Jr., and A. B. Smith, III, *ibid.*, 1977, 4361.
11 C. A. Bunnell and P. L. Fuchs, *J. Am. Chem. Soc.*, 1977, **99**, 5184.