

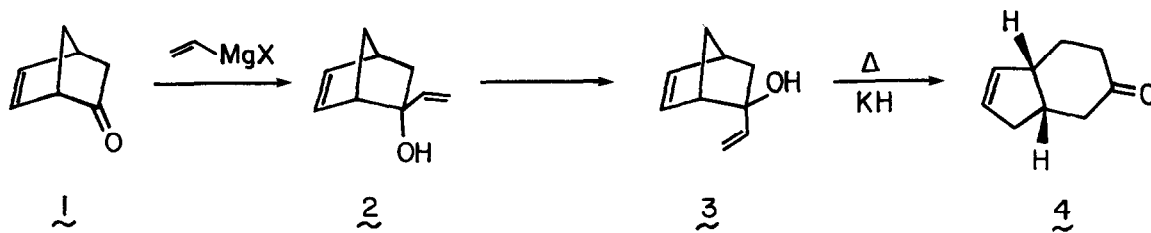
EPIMERIZATION OF BICYCLIC VINYL TERTIARY-ALCOHOLS
VIA [2,3] SIGMATROPIC REARRANGEMENT

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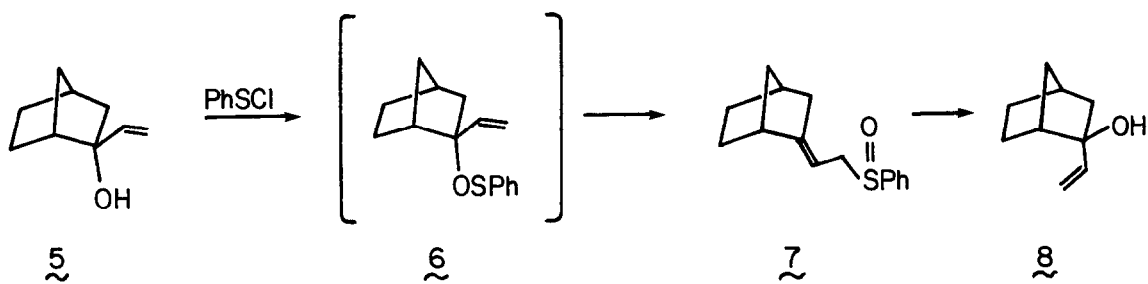
Summary: General methods for inverting the stereochemistry of vinyl tertiary-alcohols such as 2 and 5 into 3 and 8 respectively are described. The procedures employ a [2,3] sulfoxide rearrangement and will facilitate the extended use of the oxy-Cope rearrangement to a variety of related ring systems.

There is considerable current interest in the anionic oxy-Cope rearrangement and it has been applied to a number of natural product syntheses with notable success. Recent examples included the generation of the ophiobolin¹ and steroid^{2,3} skeletons and the total syntheses of juvabione⁴ and poitediol⁵. Obviously successful [3,3] sigmatropic rearrangement requires that the 1,5 diene unit bear a cis relationship. In cyclic systems this has frequently required the insertion of additional groups to control the stereochemistry. It is well established that nucleophilic addition to 2-norbornanones occurs preferentially from the exo face although products from endo attack predominate when an appropriate C-7 substituent is present. This procedure has been used by Jung in their approach to steroids^{2,3}. An alternative, more general solution would involve the epimerization of the undesired isomer to afford the required stereochemistry. We wish to report a general procedure to accomplish this transformation via a [2,3] sigmatropic rearrangement as illustrated for the case of bicyclo[2.2.1]hept-5-en-2-one (1).



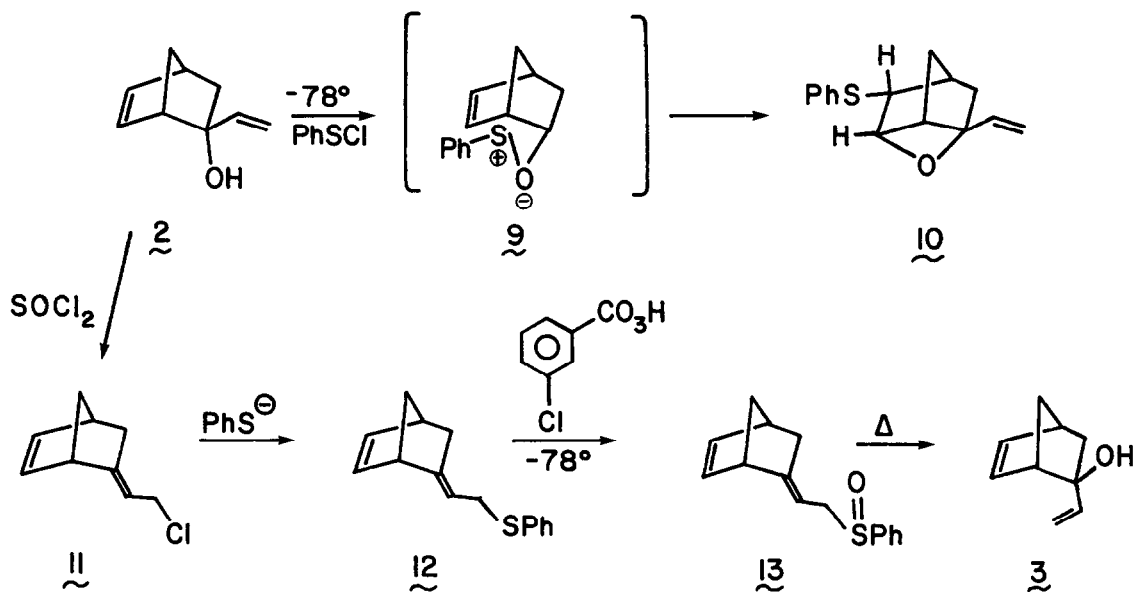
At the outset of these studies, it seemed likely, in view of earlier work by Evans and collaborators⁶⁻⁸ on *tert*-butyl substituted cyclohexanes, that the allylic sulfoxide 7 should rearrange preferentially across the *exo* surface. This was confirmed as follows.

Addition of vinyl magnesium bromide to norcamphor in tetrahydrofuran at 0°C gave the *endo* alcohol 5 exclusively in quantitative yield. Treatment of 5 with *n*-butyllithium followed by freshly distilled phenyl sulfenyl chloride at -78°C afforded the sulfoxide 7 in 45% yield after flash chromatography. Temperatures above -40°C resulted in rapid addition across the double bond. Thermal rearrangement occurred smoothly in refluxing methanol containing trimethyl phosphite as a thiophile, to the desired *exo* alcohol 8 (ratio of *exo* alcohol 8 to *endo* alcohol 5 was 8:1).



Similar Grignard addition of vinyl magnesium bromide to norbornenone (1) at -78°C gave only the *endo* alcohol 2 in 62% yield. In contrast to the results above, none of the sulfoxide 13 was formed when either the lithium or potassium alkoxide corresponding to 2 was exposed to PhSCI at -78°C. Instead the tricyclic oxetane 10 was formed in 60% yield. The structure of this material was established by analogy with related examples of this ring system reported previously,⁹ and ruled out the alternative twistane isomer.¹⁰ The ¹H nmr coupling constant (*J* = 5 Hz) established that the thiophenyl and oxygen substituents bore a *cis* relationship. This suggested that 10 arose *via syn* addition of the polarized ester intermediate 9, which was not detected, rather than by thiophenoxide displacement of a secondary chloride.¹¹ (Phenyl sulfenyl chloride added instantaneously to norbornene at -78°C in THF). Unfortunately other sulfur transfer reagents (dimethyl disulfide, *N*-thiophenyl phthalimide and succinimide) were not effective. Thus, although not suitable for the desired transformation compounds related to 10 hold considerable synthetic promise in other areas since straightforward differential functionalization of bicyclo[2.2.1]heptenes is difficult.

To circumvent these difficulties the following general solution has been developed. Treatment of the vinyl alcohol 2 with thionyl chloride in hexane afforded the unstable primary chloride 11 in 40% yield after chromatography. The chlorine was displaced with sodium benzenethiolate to give 12 and this thioether oxidized at -78°C with *m*-chloroperbenzoic acid to the desired sulfoxide 13 (86%). Under these conditions no epoxides were detected although the sulfoxide was accompanied by some of the corresponding sulfone (7%). This allylic sulfoxide was heated in refluxing methanol containing sodium benzenethiolate to give the vinyl alcohols 3 and 2 in a 9:1 ratio, 51% yield. Trimethyl phosphite was less effective as a thiophile and resulted in lower yields and significant decomposition. The *cis*-hydrindenone 4 was obtained in 70% yield when the potassium anion of alcohol 3 was refluxed in THF for 20 minutes. As expected, treatment of the *endo*-alcohol 2 under the same conditions caused no reaction.



In summary, these procedures are of general synthetic utility for adjusting the stereochemistry of vinyl alcohols. They will facilitate the extended use of the oxy-Cope rearrangement to a variety of related ring systems, and direct rearrangement *via* a sulfenate ester intermediate may still be feasible with less reactive double bonds than norbornene. These concepts are under further investigation and their application is being developed for the total syntheses of the sesterterpenes gascardic¹² and retigeranic acid.

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REFERENCES

1. L.A. Paquette, D.R. Andrews and J.P. Springer, *J. Org. Chem.*, 48, 1147 (1983).
2. M.E. Jung and J.P. Hudspeth, *J. Am. Chem. Soc.*, 100, 4309 (1978).
3. M.E. Jung and G.L. Hatfield, *Tetrahedron Lett.*, 24, 2931 (1983).
4. D.A. Evans and J.V. Nelson, *J. Am. Chem. Soc.*, 102, 774 (1980).
5. R.C. Gadwood, R.M. Lett and J.E. Wissinger, *J. Am. Chem. Soc.*, 106, 3869 (1984).
6. D.A. Evans, G.C. Andrews and C.L. Sims, *J. Am. Chem. Soc.*, 93, 4956 (1971).
7. D.A. Evans and G.C. Andrews, *J. Am. Chem. Soc.*, 94, 3672 (1972).
8. D.A. Evans and G.C. Andrews, *Acc. Chem. Res.*, 7, 147 (1974).
9. M. Shibasaki, A. Nishida and S. Ikegami, *Tetrahedron Lett.*, 3061 (1980).
10. A.K. Saksena, P. Mangiaracina and R. Brambilla, *Tetrahedron Lett.*, 1729 (1978).
11. We are grateful to P. Lavallée (Sherbrooke) and T. Durst (Ottawa) for a useful mechanistic discussion. For leading references on the addition of PhSeCl and PhSCl to alkenes see D.G. Garratt and A. Kabo, *Can. J. Chem.*, 58, 1030 (1980) and G.H. Schmid and D.G. Garratt, *The Chemistry of the Functional Groups: Supplement A: The Chemistry of Double-Bonded Functional Groups*, S. Patai (Ed.), J. Wiley and Sons, London 1977, pp., 825-854.
12. S.J. Alward and A.G. Fallis, *Can. J. Chem.*, 62, 121 (1984).

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