Invited Paper

Radical Cyclization in the Control of Regio- and Stereochemistry

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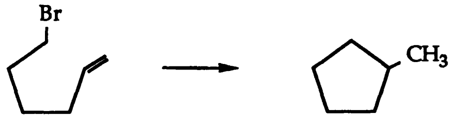
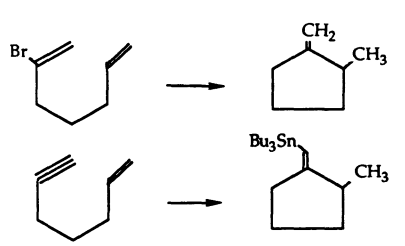
This article presents a review of the control of regio- and stereochemistry which is now possible by the use of the recently introduced haloacetal and the related halosilyl ether cyclizations, starting from a cyclohexenol or a cyclopentenol. The hydroxyl group is the control element which permits the addition of two carbon chains to the double bond of the allylic alcohol system, with complete regiospecificity and stereospecificity at the near end of the double bond, and with complete regiospecificity and high stereoselectivity at the far end of the bond. Examples of the use of the new methodology from the field of alkaloid, steroid and prostaglandin synthesis are given.

It is remarkable that the long-known radical-mediated cyclization of 6-bromo-1-hexene to methylcyclopentane[1] has not seen much application to specific problems of synthesis. Perhaps this is because the process is intrinsically limited to the construction of structures which specifically include a substituted cyclopentane (or, less frequently, a substituted cylcohexane).[2]



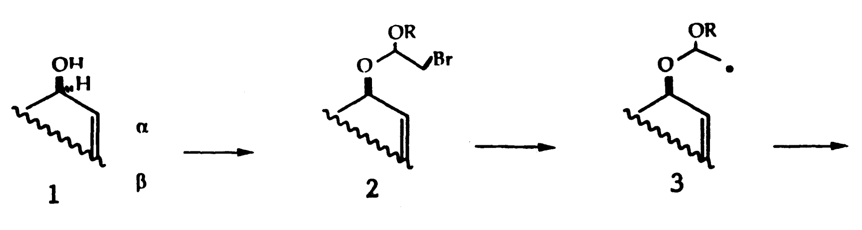
A potentially much broader field of application opened up with the introduction of the vinyl radical cyclization,[3] since the resulting five- or six-membered ring now contains a double bond in a predetermined position, where it can serve as the basis for subsequent synthetic elaboration. A further increase in scope followed the discovery[4] that the vinyl radical which leads to ring formation can be produced not only by the classical removal of a halogen atom, but also by selective addition of a stannyl radical to an alkyne.



These developments have been important. What I wish to review here, however, are radical-mediated cyclizations which we believe to be of much wider application. The new methodology followed the realization that the stereochemistry of the hydroxyl group of a cyclic allylic alcohol, most commonly a cyclopentenol or a cyclohexenol (cf. 1), could be used to add functional carbon chains at the near (α), as well as at the far (β) end of the double bond. And this proceeds with *complete* regiospecificity and stereospecificity at the α end, as well as complete regiospecificity and high stereoselectivity at the β end. In other words, any of the four possible arrangements of two functional chains on adjacent carbon atoms could be produced at will.

The principle of the method involves *connecting to the allylic hydroxyl a detachable radical precursor capable of cyclizing to a five-membered ring.*[5] The *regiospecificity* at the α-center follows because of the great preference (magnified here, for obvious reasons) for the formation of a five-membered ring. The *stereospecificity* at the α-center follows from the Bürgi–Dunitz-like[6] (~109°±) approach of the radical center to the plane of the double bond.[7] When the olefinic double bond is in a six-membered or smaller ring, this necessarily results in the cis fusion of the new ring. Eventual removal of the detachable connection concludes the regio- and stereospecific attachment of the α-chain, cis to the controlling hydroxyl group.

This is illustrated, using an acetal link as the detachable connector.



Obviously, the epimeric stereochemical attachment of the α-chain is accessible by starting with the epimeric allylic alcohol.

Not only can regio- and stereospecific addition of a functional chain be accomplished at the α-center, it can simultaneously be achieved at the β-center. Three requirements had to be met to make this a useful process: a) The radical generated at the β-center by the initial cyclization has to be trapped in an *intermolecular* reaction within the lifetime of that radical. This is not a problem when the required β-substituent is a hydrogen (e.g. from a stannane). It becomes a problem when the trap must be a functional carbon atom or a functional carbon chain. Such a trap should not be so efficient that it would trap the initiator itself (e.g. $Bu_3Sn\cdot$) or the initial primary radical before it cyclizes, but efficient enough to trap the β-center (which may be secondary or tertiary) faster than the latter either acquires a hydrogen from some component of the medium, or disproportionates. b) The species capable of trapping the β-center must be as versatile as possible. The most useful trap would result in the delivery of a one carbon functional species. c) The stereochemistry must be controlled.

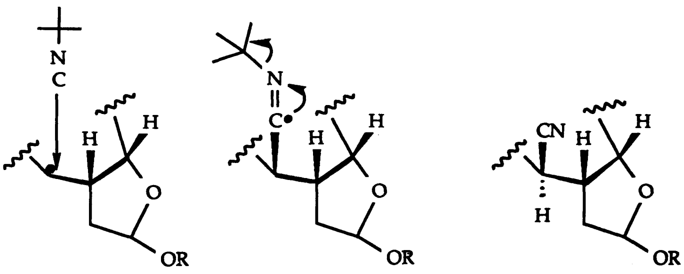
We eventually concluded that *t*-butyl isocyanide would answer the second requirement by transferring a cyano group to the β-center.[8] That this proved successful is fortunate because isocyanides are known to react with stannyl radicals, as shown.[9]

$$R_3Sn\cdot + R'\text{-}N{=}C \rightarrow R_3Sn(C{\equiv}N) + R'\cdot$$

This process is, however, considerably slower than reaction of the stannyl radical with the halo acetal (**2**→**3**). It is, of course, necessary to keep the stannane concentration low enough if one wishes to deliver a carbon species, rather than a hydrogen, at the β-center.

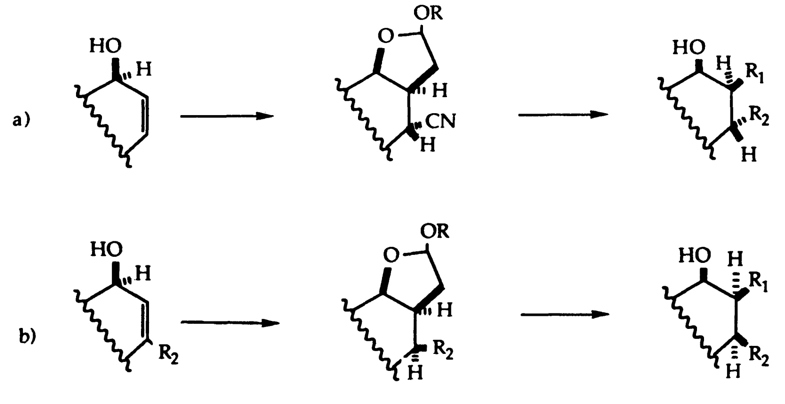
A convenient way to achieve the required low concentration involves producing the necessary stannane by conducting the radical cyclization-trapping in the presence of sodium cyanotrihydroborate in refluxing *t*-butyl alcohol.[10] This procedure regenerates tributylstannane from the small concentration of tributylstannyl halide produced as the reaction proceeds. An important added advantage is that only ~0.1 equiv of halostannane needs to be added to carry out the whole process.

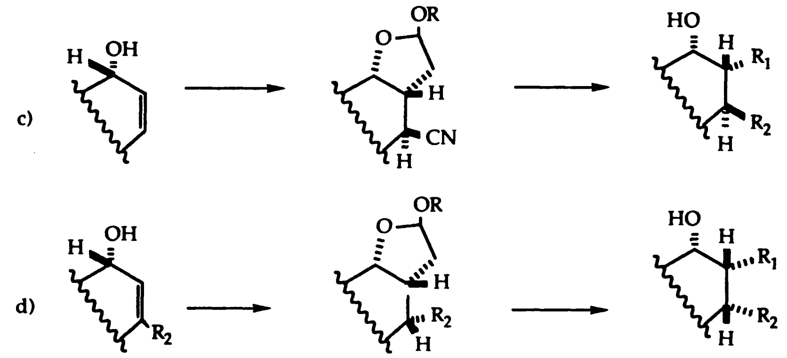
Note that the use of *t*-butyl isocyanide cannot lead to telomer formation because the adduct once formed loses its radical nature simply by ejection of a *t*-butyl radical.



With respect to the final requirement of stereoselectivity at the β-center, we made use of the fact that the cis fusion of the five-membered acetal ring would produce a molecule with a clear-cut differentiation between its convex and its concave faces. As we anticipated, attachment of the trap takes place on the more accessible convex face with high selectivity.

The result of this cyclization-trapping process, therefore, is that the allylic hydroxyl controls the attachment of the vicinal substituent (an acetaldehyde equivalent in the bromo acetal version of the general

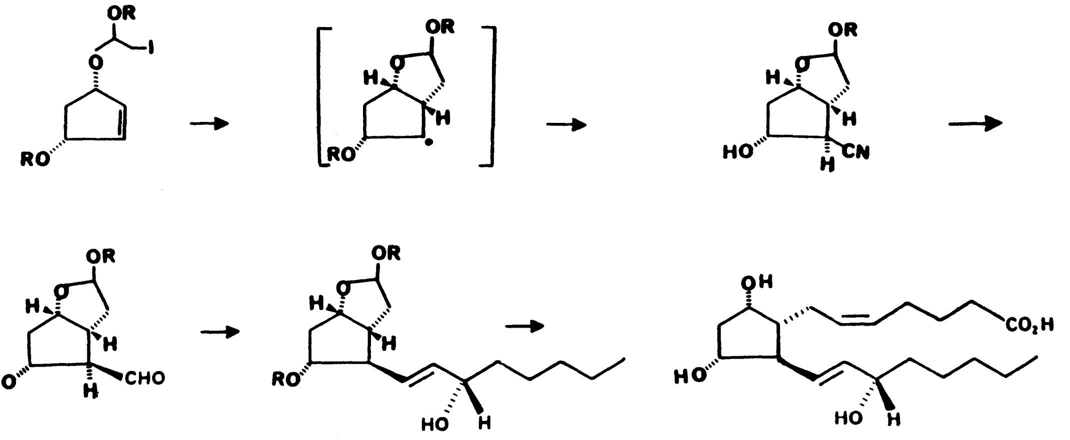




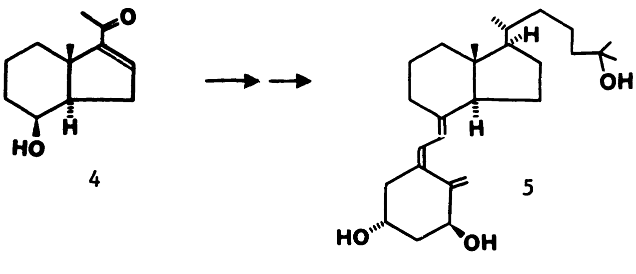
scheme) cis, and that of the substituent at the far end of the double bond trans to it. Because the far end substituent can be either a functional carbon (e.g. cyano group) or a hydrogen (in the absence of carbon trap), all four possible arrangements at the site of the original double bond can be produced at will. This is shown in a)—d) above. Of course, after it has served its control function, the hydroxyl can eventually be kept, inverted, oxidized or removed entirely, as the situation requires.

Note also that the halo acetal sequence delivers the acetaldehyde chain in a protected acetal form. This allows various organometallic transformations to be carried out on the substituent (e.g. cyano) before liberating and elaborating the acetaldehyde chain.

The synthesis of prostaglandins,[11] which is illustrated below, is one of the simplest and most obvious applications of the general principles that have just been outlined.



This is an archetype for this type of construction since it simply requires the addition of two chains of defined stereochemistry to the double bond of a cyclic allyl alcohol. One further illustration, in a less obvious situation, will serve to emphasize the generality of this reaction sequence. Consider the problem of constructing the hydrindan **4** a useful starting material for the synthesis of calcitriol (**5**) and other D vitamins.



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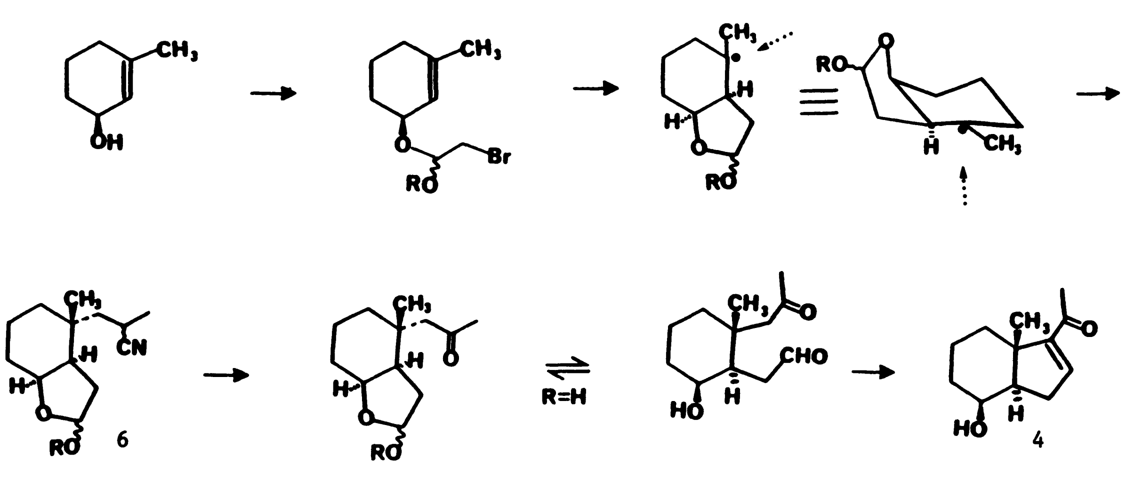
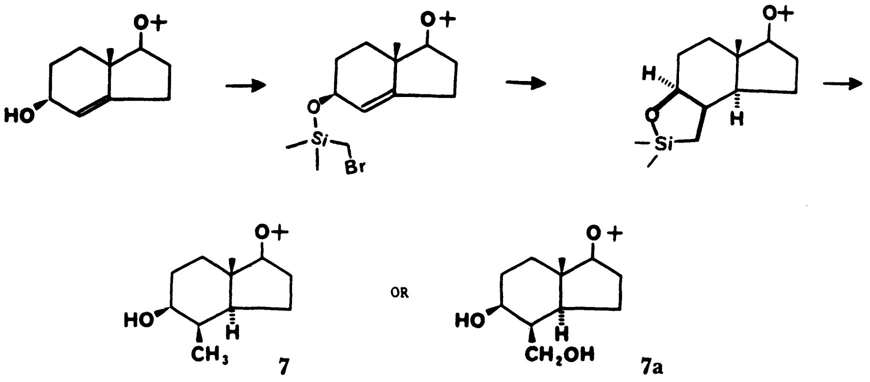
This requires the assembly of a *trans*-hydrindan system, and it is not immediately obvious that this target could, nevertheless, be reached easily by the general bromo acetal route. This is, however, again simply a matter of controlling the regio- and stereochemistry of two vicinal functional chains: only four steps are required to make **4**, starting with 3-methyl-2-cyclohexenol,[12] as is shown below.

In this particular construction, we see again the protection afforded by the acetal function during the transformation (reaction of **6** with LDA, then with oxygen) of the functional chain trapped at the far center (methacrylonitrile, rather than t-butyl isocyanide, was used as the trap in this particular case, as a convenient precursor of the required acetonyl residue).

This is not the only way that the problem of ring junction stereochemistry can be solved using the



principles outlined here. The trapping from the convex side at the far center means that if it is a hydrogen atom which is delivered at that center (no carbon trap present), it will be delivered anti to the controlling allylic hydroxyl (cf. b) and d) above). An important corollary of that simple fact is that cis or trans ring fusions can be generated at will.[13] An example[14] is shown below.



Note that the cis junction would be produced, if desired, merely by starting with the epimeric alcohol.

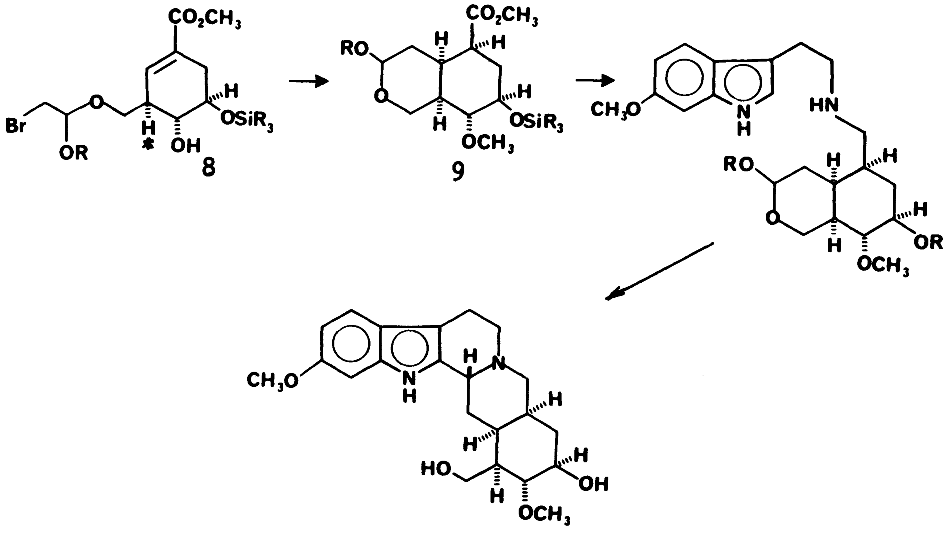
This particular case illustrates the use of a silyl ether rather than an acetal as the detachable connection. This is a useful variant when either a one carbon functional group[15] (cf. **7a**), or even a methyl group, is required adjacent to the original allylic hydroxyl, rather than an acetaldehyde chain.

Two special features should be pointed out here: 1) The ring junction is produced, cis or trans at will, by a process which does not depend on the thermodynamic stability of the particular bicyclic system. Either cis- or trans-hydrindans can thus be produced, as well as cis or trans decalins. 2) The regio- and stereochemistry of the newly added substituent, either hydroxymethyl or methyl, is also kinetically determined so that, in the trans series, it ends up axial even if, as in **7** and **7a** this happens to produce a 1,3-diaxial interaction with an angular methyl group.[16] This is particularly useful because it is often a simple matter to invert the axial substituent to the more stable epimeric position, via the adjacent ketone.

Let us end by showing an example which further emphasizes the variety of synthetic targets which can take advantage of the features that we are illustrating here. This concerns again setting up vicinal stereochemistry on a double bond via the bromo acetal route, but it now involves a homoallylic rather than an allylic alcohol as we see in **8**. This raises a new problem because abstraction of the starred allylic hydrogen by the radical derived from the bromo acetal would now compete with cyclization. This is circumvented by increasing the cyclization rate, in this particular case by making the olefin more electron poor by conjugation with the carbonyl group.

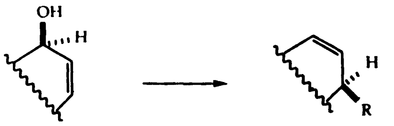
The radical cyclization-trapping process (trapping at the far center is now by a hydrogen; cf. case b above) thus controls the last two centers in ring E of the alkaloid reserpine. That these are correctly placed, as anticipated, is shown by transformation of the major cyclization product **9** to reserpinol.[17]

There are other processes which make use of the stereochemistry of an allylic hydroxyl to direct the formation of a carbon–carbon bond. The best known of these is the Claisen rearrangement (cf. A below). This very important reaction transfers



stereochemistry from an allylic hydroxyl to the far end of the related double bond, but loses the hydroxyl in the process. There are multiple-step schemes which can control two adjacent centers, as the bromo acetal radical process can. The Diels–Alder reaction, for instance, using a conjugated cyclic ketone, leads to a cyclohexene which can be cleaved to give two different chains adjacent to the carbon oxygen bond (cf. **B**). The stereochemistry is, however, not broadly controllable in this special application of a reaction which has, of course, many other important uses. We believe, however, that the concise transformations we have just discussed (cf. a)—d) above) have considerable potential in synthesis.

A.



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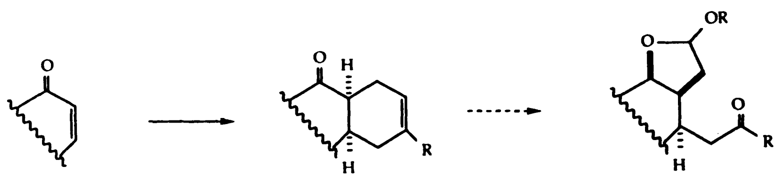

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References

1) C. Walling, J. H. Cooley, A. A. Ponaras, and E. J. Racah, *J. Am. Chem. Soc.*, **88**, 5361 (1966); R. C. Lamb, P. W. Ayers, and M. K. Toney, *ibid.*, **85**, 3483 (1963); C. Walling and A. Cioffari, *ibid.*, **94**, 6059 (1972) and A. L. J. Beckwith and K. U. Ingold, "Rearrangements in Ground and Excited States," ed by P. de Mayo, Academic Press, New York (1980) pp. 182—220.

2) Imaginative application of this "simple" radical cyclization has, however, recently been made by Curran: D. Curran and S. C. Kuo, *J. Am. Chem. Soc.*, **108**, 1106 (1986).

3) G. Stork and N. H. Baine, *J. Am. Chem. Soc.*, **104**, 2321 (1982).

4) G. Stork and R. Mook, Jr., *J. Am. Chem. Soc.*, **109**, 2829 (1987).

5) G. Stork, R. Mook, S. D. Biller, and S. D. Rychnovsky, *J. Am. Chem. Soc.*, **105**, 3741 (1983).

6) H. B. Bürgi, J. D. Dunitz, J. M. Lehn, and G. Wipff, *Tetrahedron*, **30**, 1563 (1974), and earlier papers.

7) Cf. M. J. S. Dewar and S. Olivella, *J. Am. Chem. Soc.*, **100**, 5290 (1978); A. L. J. Beckwith and C. H. Schiesser, *Tetrahedron*, **41**, 3925 (1985); K. N. Houk, M. N. Paddon-Row, D. C. Spellmeyer, N. G. Rondan, and S. Nagase, *J. Org. Chem.*, **51**, 2874 (1986).

8) G. Stork and P. M. Sher, *J. Am. Chem. Soc.*, **105**, 6765 (1983).

9) Cf. D. H. R. Barton, G. Bringmann, and W. B. Motherwell, *Synthesis*, **1980**, 68.

10) G. Stork and P. M. Sher, *J. Am. Chem. Soc.*, **108**, 303 (1986).

11) G. Stork, P. M. Sher, and H. L. Chen, *J. Am. Chem.*

Soc., **108**, 6384 (1986).

12) Unpublished work by T. Zebovitz from this laboratory.

13) G. Stork and M. Kahn, *J. Am. Chem. Soc.*, **107**, 500 (1985).

14) G. Stork and M. J. Sofia, *J. Am. Chem. Soc.*, **108**, 6826 (1986).

15) Cf. K. Tamao, N. Ishida, and M. Kumada, *J. Org. Chem.*, **48**, 2120 (1983).

16) A. J. Burgstahler and I. C. Nordin, *J. Am. Chem. Soc.*, **81**, 3151 (1959); see also R. K. Hill and A. G. Edwards, *Tetrahedron Lett.*, **1964**, 3239.

17) Unpublished work by M. Casey and P. C. Tang from this laboratory.