Chloro Olefin Annelation

PETER T. LANSBURY

Department of Chemistry, State University of New York at Buffalo, Buffalo, New York 14214

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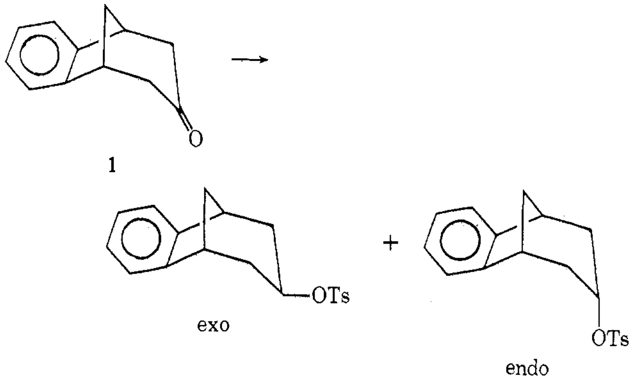
The design of rational syntheses of natural products has increasingly occupied the serious attention of organic chemists, and for good reasons. First, the complex carbocyclic skeletons and functional group diversity of corticosteroids, camptothecin, tetracyclines, and unsaturated sesquiterpene lactones, to name only a few, have challenged synthetic chemists to develop new reactions that are the key to success in a total synthesis. Secondly, many important uses in medicine are being found for such compounds (*e.g.*, in birth control, in cancer chemotherapy, and as broad spectrum antibiotics), and total synthesis often represents the most direct and economical means of preparing them in the needed quantities. Examples are the totally synthetic 19-nor steroids,[1] used as antifertility agents, and the biologically potent prostaglandins.[2]

Although much progress has been made in expanding the options for preparing various classes of compounds, particularly those featuring the ubiquitous carbonyl group,[3–5] comparatively little has been done in developing new annelation procedures. Synthetic organic chemists still rely heavily on Robinson annelations,[3] intramolecular acylations,[3] and Diels–Alder reactions,[4] which are best applied or even restricted to six-membered-ring formation. Similar limitations apply in the recently developed stereospecific biogenetic-like polyene cyclizations,[6] wherein 1,5-diene units lead to fused cyclohexane rings in terpene and steroid intermediates. As a result of this state of affairs, two recent total syntheses[7,8] of the hydroazulenic sesquiterpene bulnesol included lengthy processes of ring expansion and/or contraction of cyclohexanoid or decalinic intermediates, rather than direct construction of a suitable bicyclo[5.3.0]decane intermediate.[9] Hitherto, there have been no efficient methods for generating hydroazulenes. Space limitations prevent the inclusion of some of the novel annelation procedures recently developed in other laboratories. Therefore, we mention only the promising intramolecular coupling of allylic α,ω-dihalides with nickel carbonyl that has led to humulene[10] and medium-ring lactones of the macrolide antibiotic type,[11] Muxfeldt's elegant bis annelation route to Terramycin,[12] and the growing potential of photochemical annelation of enones and olefins in natural products synthesis.[13]

Chloro olefin annelation originated several years ago during an investigation of nucleophilic participation by remote aryl groups. Substantial quantities of 3,5-(*o*-phenylene)cyclohexanone (**1**) were required in order



to study the solvolytic behavior of the derived carbinol arenesulfonates.[14] Handicapped by a multistep, low-yield synthesis of **1**, beginning with dihalocarbene addition to benzonorbornadiene, we considered the possibility of acid-catalyzed diene cyclization,[6] utilizing 1-allylindenes (**2a–c**)[15] which were readily preparable by alkylation of indenylmagnesium bromide.[14b]

Solvolysis of **2a** in 97+% formic acid resulted in substantial skeletal rearrangement to benzobicyclo-

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Peter T. Lansbury received his B.S. degree at Penn State in 1953 and his Ph.D. from Northwestern University. After a brief period with Du Pont, he joined the State University of New York at Buffalo in 1959, and is now Professor of Chemistry. During 1963–1967, he was an Alfred P. Sloan Foundation Fellow. Professor Lansbury's earlier research activities included synthesis and reactions of organolithium reagents, stereochemistry and rearrangements of 7,12-dihydropleiadenes, univalent nitrogen intermediates, and novel reducing agents. More recently, the emphasis has shifted toward developing new reactions and approaches for natural products synthesis.

(1) L. Velluz, J. Mathieu, and L. Nomine, *Tetrahedron Suppl.*, **8**, Part II, 495 (1966), and references cited therein.

(2) (a) J. E. Pike, *Fortschr. Chem. Org. Naturstoffe*, **28**, 313 (1970). (b) For more recent developments, *cf.* J. Fried, C. H. Lin, J. C. Sih, P. Dalven, and G. F. Cooper, *J. Amer. Chem. Soc.*, **94**, 4342 (1972); C. J. Sih, P. Price, R. Sood, R. G. Salomon, G. Peruzzotti, and M. Casey, *ibid.*, **94**, 3643 (1972); E. J. Corey and P. L. Fuchs, *ibid.*, **94**, 4014 (1972).

(3) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, Chapters 9–11.

(4) W. Carruthers, "Some Modern Methods of Organic Synthesis," Cambridge University Press, London, 1971, Chapters 1, 3, and 5.

(5) For novel organometallic routes to aldehydes and ketones, see W. O. Siegl and J. P. Collman, *J. Amer. Chem. Soc.*, **94**, 2516 (1972); J. P. Collman, S. R. Winter, and D. R. Clark, *ibid.*, **94**, 1788 (1972).

(6) W. S. Johnson, *Accounts Chem. Res.*, **1**, 1 (1968).

(7) J. A. Marshall and J. D. Partridge, *Tetrahedron*, **25**, 2159 (1968).

(8) C. Heathcock and R. Ratcliffe, *J. Amer. Chem. Soc.*, **93**, 1746 (1971).

(9) An indirect synthesis of hydroazulenes makes use of transannular solvolytic ring closure of 1,6-cyclodecadiene derivatives (J. A. Marshall and W. F. Huffman, *ibid.*, **92**, 6358 (1970)), but these, in turn, required decalinic precursors for fragmentation (J. A. Marshall, *Synthesis*, 229 (1971)).

(10) E. J. Corey and E. Hamanaka, *J. Amer. Chem. Soc.*, **89**, 2758 (1967).

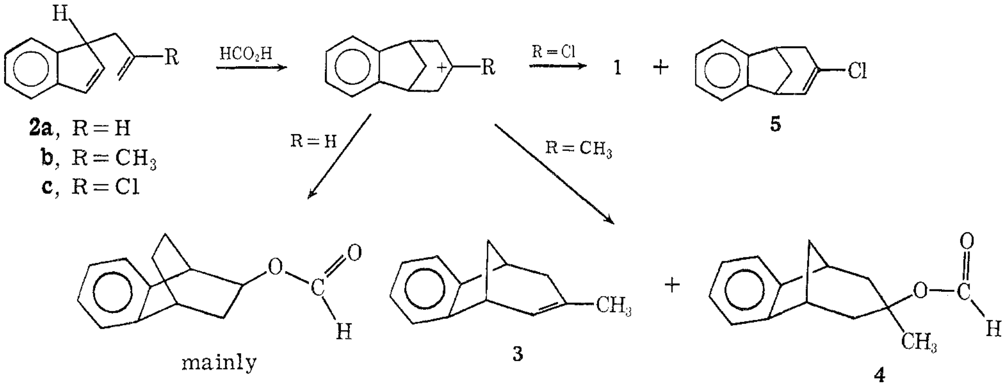
(11) E. J. Corey and H. A. Kirst, *ibid.*, **93**, 667 (1972).

(12) H. Muxfeldt, G. Hardtmann, F. Kathawala, E. Vedejs, and J. B. Mooberry, *ibid.*, **90**, 6534 (1968), and references cited.

(13) P. G. Sammes, *Quart. Rev., Chem. Soc.*, **24**, 37 (1970).

(14) (a) P. T. Lansbury and N. T. Boggs, III, *Chem. Commun.*, 1007 (1967); (b) E. J. Nienhouse, Ph.D. Dissertation, State University of New York at Buffalo, 1967.

(15) P. T. Lansbury and E. J. Nienhouse, *Chem. Commun.*, 1008 (1967).



[2.2.2]octyl formates, whereas **2b** cyclized to **3** and **4** in a ratio of 1:2 without rearrangement; the latter compounds were, however, inappropriate for the desired purpose. Nevertheless, this finding suggested that intramolecular electrophilic attack upon a β-chloroallyl side chain, as in **2c**, would also proceed without rearrangement and that the α-chloro carbonium ion thus produced would capture solvent and ultimately generate the carbonyl group in preference to undergoing β elimination (see further mechanistic discussion below).

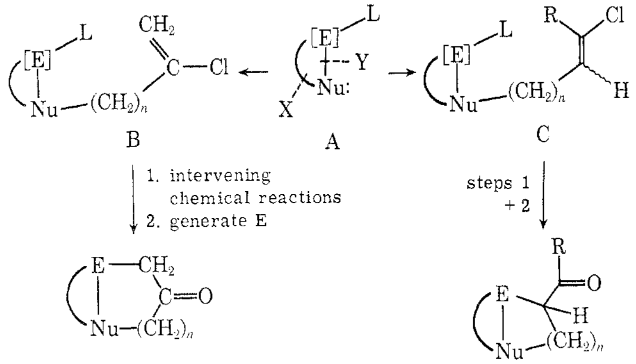
The first formolysis of **2c** indeed afforded exceptionally good results, there being produced 60% of **1** and 30% of **5** (which subsequently gave more **1** when treated with cold 90% sulfuric acid)![16] This stroke of good luck caused us to think in broader terms of possibilities for synthesizing mono- and polycyclic carbonyl-containing isoprenoids. Realistically, had we then been confronted with some of the less favorable results later obtained from supposedly well-conceived experiments, we might have abandoned extending the ideas that have now taken form as a general method of constructing both cycloalkanones[17] and acylcycloalkanes.

It is noteworthy that highly nucleophilic alkenes (*e.g.*, enamines, enol ethers, and enolate and imine anions) have been widely extolled for their synthetic capabilities (alkylation, acylation, Michael additions, etc.), just as anilines and phenols have monopolized synthetic aromatic chemistry. Vinyl chlorides, on the other hand, have received scant attention as substrates for ionic electrophiles because of their alleged inertness.[18,19] We were reassured by a concrete demonstration of their synthetic utility as we contemplated pushing ahead to more complex synthetic challenges. In this Account, we show that the relatively nonnucleophilic chloro olefin moiety[20] can be advantageously employed for annelation in ways entirely different from and complementary to highly concerted processes utilizing electron-rich olefins.

Expectations and Possibilities for Chloro Olefin Annelation

The efficient cyclization of **2c**[16] led immediately to consideration of ways in which terminal and internal vinyl halides,[21] once incorporated into a molecule, could serve as sites for intramolecular electrophilic attack, with orientation according to Markovnikov's rule. The requisite electrophilic center was to be unveiled after any required intermediate steps had been completed (Scheme I).

Scheme I



Formula A represents a potentially bifunctional molecule, either cyclic (no dotted lines) or acyclic (cleave at X or Y), or even a monofunctional compound wherein Nu: is part of the reagent containing the chloro olefin (*e.g.*, $-SCH_2C(Cl){=}CH_2$ and $CH_3(Cl)C{=}CHCH_2CH_2MgBr$ in examples cited below). It was anticipated, and subsequently demonstrated,[17] that the "inert" vinyl chloride bearing side chain would: (1) permit intermediate chemical steps as vigorous as organometallic additions and $LiAlH_4$ reductions;[22] (2) provide thermodynamically controlled stereoselectivity

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[16] P. T. Lansbury and E. J. Nienhouse, *J. Amer. Chem. Soc.*, **88**, 4290 (1966).

[17] P. T. Lansbury, E. J. Nienhouse, D. J. Scharf, and F. R. Hilfiker, *ibid.*, **92**, 5649 (1970).

[18] K. Bott and H. Hellman, *Angew. Chem., Int. Ed. Engl.*, **5**, 870 (1966). These workers observed a number of intermolecular reactions of carbonium ions with 1,1-dichloroethylene to produce carboxylic acids.

[19] M. Hanack, *Accounts Chem. Res.*, **3**, 209 (1970). Recent successful vinyl halide solvolyses are discussed herein.

[20] Few studies of possible π participation by electron-deficient olefinic groups have been reported. In one system, where both methyl and methoxy groups enhanced the nucleophilicity of double bonds during solvolytic cyclization (H. Felkin and C. Lion, *Chem. Commun.*, 60 (1968)), a chlorine substituent retarded rate and uncyclized product predominated (private communication from Professor Felkin).

[21] Vinyl fluorides have not been investigated; they are not only difficult to synthesize but also would be too reactive toward acid. Vinyl bromides and iodides would be *too* reactive in undesirable ways and insufficiently reactive when desired.

[22] Intentional sulfuric acid hydrolysis of ketones such as 2-(β-chloroallyl)cyclohexanone provides a facile furan synthesis *via* intermediate 1,4-diketones,[14b] just as the Wichterle modification of the Robinson annelation affords 1,5-diketones, and hence cyclohexenones, *via* chloride hydrolysis under vigorous conditions.[3]

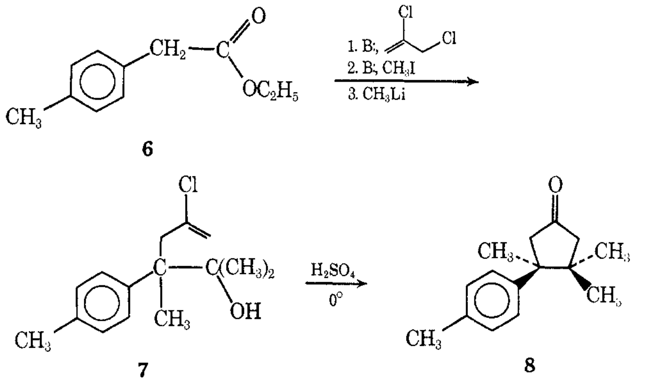
in closure to form a bicyclic (or more complex) ring system, since neighboring group participation was expected to be minimal or absent; (3) allow carbonium ions initially generated in the ring-forming step to rearrange *prior* to closure, especially if a more stable ring would result (*e.g.*, five membered rather than four membered), and (4) minimize complications that could arise from acid-catalyzed double bond migration (*e.g.*, terminal (B) $\rightleftarrows$ internal (C)), which frequently occur in nucleophilic olefins.[23] Experience showed that E must be a relatively stable ion so that its generation can occur under mild enough conditions to ensure preservation of the chloroalkene. This can usually be achieved by formic acid or cold 90% sulfuric acid, our most frequently employed reaction media.

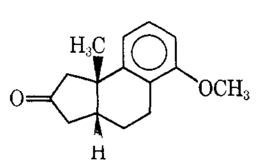
In our work, we have used the commercially available 2,3-dichloropropene and 1,3-dichloro-2-butene and their products of homologation (*via* malonic ester syntheses, acetoacetic ester syntheses, etc.). Ring-opened products from cyclopropyl ketones and phosphorus pentachloride[24] have also found use, as have hydrogen chloride addition products derived from terminal alkynyl halides.[25] Internal vinyl chlorides were used as cis,trans mixtures, since the individual stereoisomers gave comparable results. The major isomer in such mixtures is shown in the formulas used throughout this Account.

Cycloalkanone Synthesis

Five-, six-, and seven-membered cycloalkanones and various bicyclic fused systems derived from them have been successfully generated from electrophilic closure upon 2-chloro-1-enes.[17]

To begin, the sesquiterpene β-cuparenone **8**, previously characterized only tentatively as to the position of the carbonyl group, was unambiguously synthesized in only four steps from ester **6**. Isotopic labeling provided mechanistic insight into the ring-forming step. When CD_3Li was substituted for CH_3Li, cyclization of **7** possessing CD_3 groups only at the carbinol carbon produced **8**-d_6 in which each alkyl-bound methyl group contained *ca.* two-thirds CD_3 (by nmr analysis, with Ar-CH_3 serving as internal standard). This observation established that closure occurs slowly relative to the rapid alkyl and aryl shifts experienced by the intermediate carbonium ions.[26] Nondegenerate rearrangements, particularly those involving hydride shifts and epi sulfonium ions, have been used advantageously to prepare various other ketones (*vide infra*). Fused cyclopentanones of the 2-hydrindanone type such as **9** and **10** have been prepared in yields ranging from 40 to 50%.[27] In these cases, the more stable cis ring fusion was produced when benzylic cations were generated, in spite of the fact that the carbinol precursors were usually epimeric mixtures.





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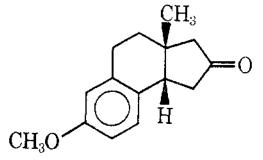

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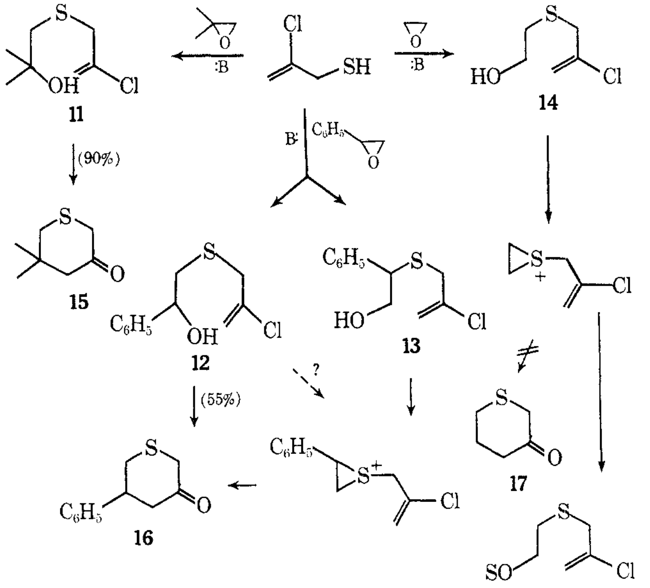
After the successful synthesis of the "pinched" cyclohexanone **1**, it was expected that monocyclic, six-membered ring ketones would present little difficulty. β-Chloroallyl mercaptan was allowed to react with several epoxides, and the products (**11**–**13**) were subjected to cyclization.[28,29] The most interesting finding is that both **12** and **13** cyclize to give only **16**, the latter by prior rearrangement *via* epi sulfonium ions. The parent 3-thianone (**17**) was not obtainable[30] because sulfonium ion **14a** can react only with solvent by bimolecular, backside attack.

Scheme II



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[23] (a) H. O. House, *Rec. Chem. Progr.*, **28**, 99 (1967); (b) G. Stork and P. F. Hudrlik, *J. Amer. Chem. Soc.*, **90**, 4462 (1968).

[24] M. S. Newman and G. Kaugers, *J. Org. Chem.*, **31**, 1379 (1966).

[25] P. Peterson, *Accounts Chem. Res.*, **4**, 407 (1971).

[26] P. T. Lansbury and F. F. Hilfiker, *Chem. Commun.*, 619 (1969).

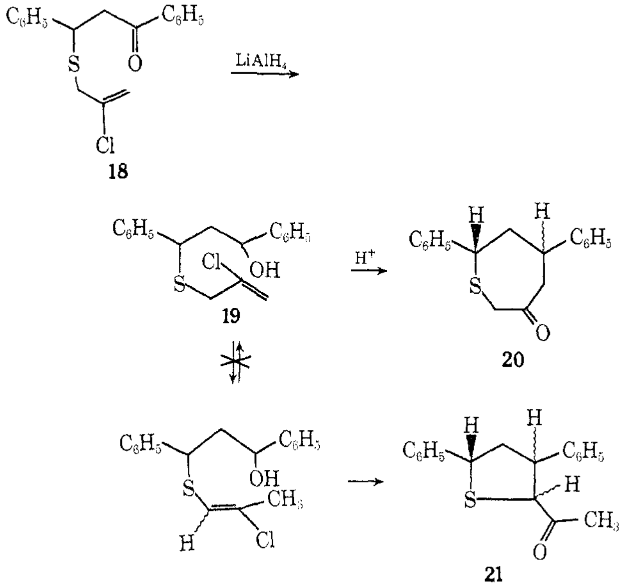
[27] P. T. Lansbury, F. F. Hilfiker, and L. Armstrong, *J. Amer. Chem. Soc.*, **90**, 534 (1968); F. Hilfiker, Ph.D. Dissertation, State University of New York at Buffalo, 1970.

[28] P. T. Lansbury and D. J. Scharf, *J. Amer. Chem. Soc.*, **90**, 536 (1968).

[29] Throughout this Account, yields of reactions are indicated in parentheses over the appropriate arrows in the flow sheets.

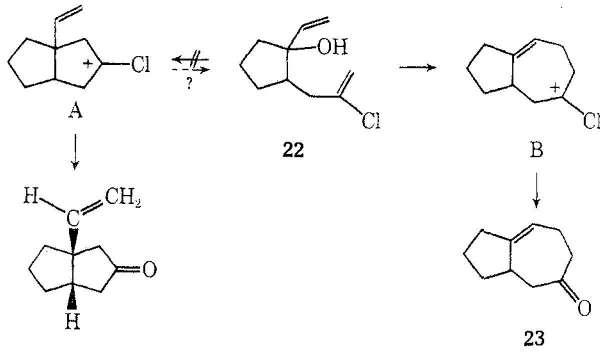
[30] D. J. Scharf, Ph.D. Dissertation, State University of New York at Buffalo, 1969.

Scheme II was applied in efforts to prepare a thiacycloheptanone, using **18** derived from chalcone.[17]

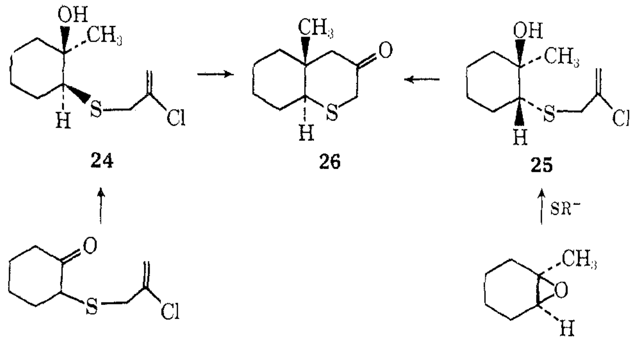


Formolysis of **19** afforded **20** as the sole ketonic product, although in only 20% yield; there was no infrared or nmr evidence for isomer **21**. This experiment demonstrates the stability of terminal chloro olefins in formic acid; had isomerization occurred, **21** would surely have appeared in high yield, judging from subsequent studies with internal chloro olefins.[31] Proctor, *et al.*,[32] have also succeeded in producing seven-membered rings of the azabenzsuberone type.

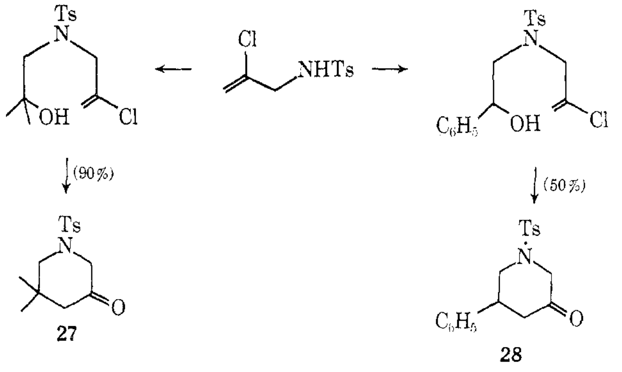
Our most valuable contribution featuring cycloheptanone formation bears on the synthesis of sesquiterpenes having hydroazulenic skeletons. Such compounds have been prepared previously by lengthy, multistep sequences,[7,8] often involving ring expansion or contraction or both. By comparison, a properly functionalized model for bulnesol and related guaianes can be produced *directly* in *ca.* 80% yield from vinylcarbinol **22**, which is readily acquired by Grignard addition to 2-(β-chloroallyl)cyclopentanone.[33] The success of this reaction hinges on the strain required to produce the internal α-chlorocyclopentyl ion A, a problem not shared by isomeric ion B which gives **23**, the only primary ketonic product.

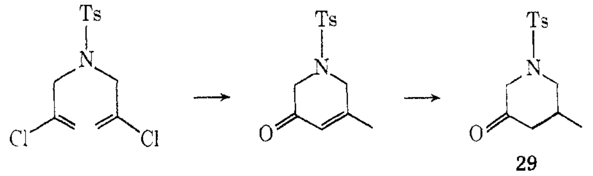


Decalone formation was also assessed by using epimeric cyclohexanols containing β-chloroallylthio substituents, namely **24** and **25**. The expected *trans*-2-decalone **26** was isolated in *ca.* 40% yield from either **24** or **25**.[28]



Several *N*-tosyl-3-piperidones were synthesized[28,30] by approaches similar to those which afforded 3-thianones. Thus, **27** and **28** were readily prepared, provided the normally basic nitrogen was protected as the tosylamide; once again, the parent 3-piperidone was inaccessible, although the 3-methyl derivative **29** was acquired by a different approach.[30]





Acylcycloalkane Syntheses

Initial investigations[31] of internal chloro olefin annelation utilized 1,3-dichloro-2-butene, which was first converted into heteroatom nucleophiles **30** and **31**. These, in turn, were allowed to react with epoxides, and the resultant carbinols were cyclized,[31] as outlined in Scheme III. The intermediacy of epi sulfonium ions again ensures formation of pure **33**, in spite of the formation of isomeric carbinols from **30** and styrene oxide.

The brevity and efficiency of the above results led to consideration of this approach for directly generating the D ring of 20-keto steroids.[34] Construction of the

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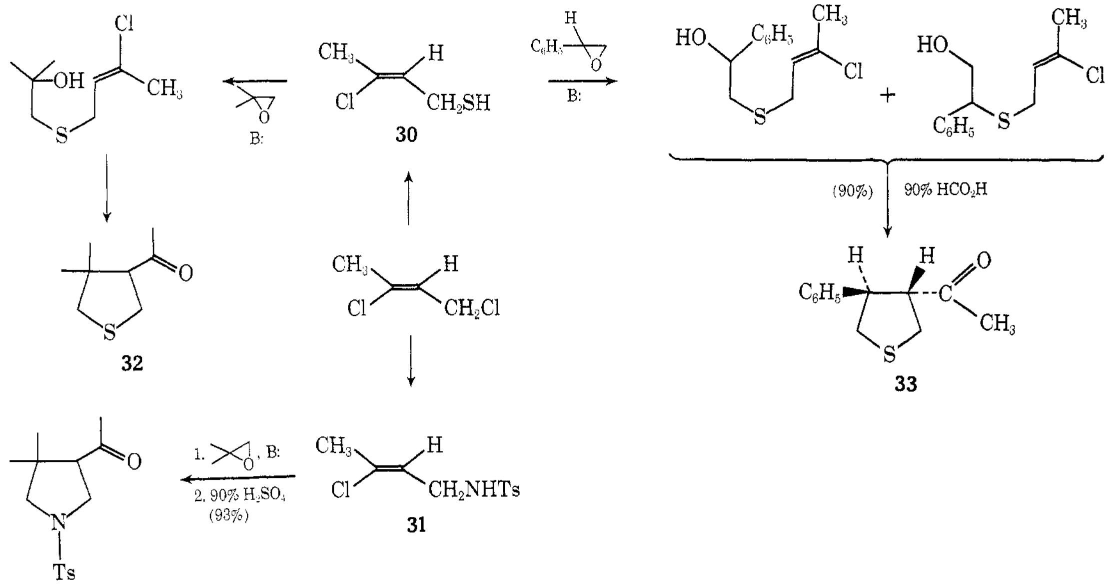
(31) P. Briggs, Ph.D. Dissertation, State University of New York at Buffalo, 1970.

(32) D. N. Gupta, I. McCall, A. McLean, and G. R. Proctor, *J. Chem. Soc. C*, 2191 (1970).

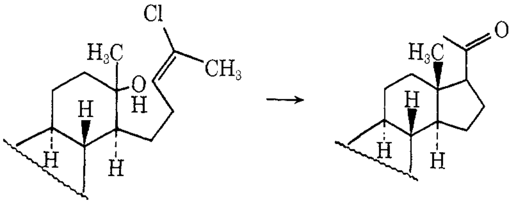
(33) Unpublished results with P. Wovkulich. A similar allylic cation closure constituted the last step in a recent total synthesis of (−)-daucene (M. Yamasaki, *J. Chem. Soc., Chem. Commun.*, 606 (1972)).

(34) P. T. Lansbury, P. C. Briggs, T. R. Demmin, and G. E. DuBois, *J. Amer. Chem. Soc.*, **93**, 1311 (1971).

Scheme III



trans-fused acetylhydrindan portion of these steroids has long been a vexing problem in total synthesis.[35]

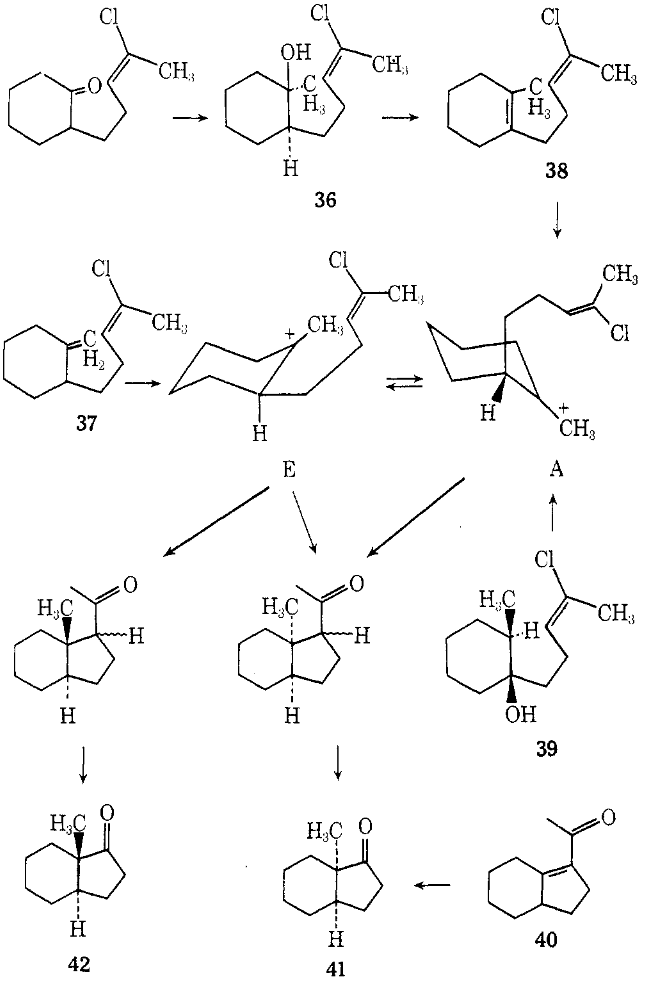


The usual approach has been to contract the D ring after assemblage of an angularly methylated *trans*-decalone.

Our initial efforts utilized carbinol **36**,[34] but similar results were also encountered with **37–39**[36] owing to the facility of deprotonation–reprotonation equilibria, a phenomenon encountered repeatedly with tertiary alcohols that are prone to dehydrate.

Formolysis produced nearly quantitative yields of the four acetylhydrindans, each showing a singlet in the nmr attributable to the angular methyl group.[34] The two epimeric cis-fused ketones, which were the major components, were independently synthesized from the acetylhydrindene **40**; degradation of these epimers produced **41**, whereas the two minor trans-fused ketones produced **42**. The ratio of **41** to **42** was *ca.* 3:1, with even higher cis preferences being obtained with ethyl and vinyl carbinols (C_8–CH_3 replaced by ethyl and vinyl).[36]

Since a major amount of product formation during annelation may occur *via* conformer A, with its axial chloro olefin side chain, we decided to continue work with a conformationally rigid substrate wherein the side chain would hopefully be confined to the desired equatorial position (by preventing ring flipping and perhaps reducing epimerization *via* dehydration–reprotonation). Accordingly, ketone **43** was prepared[34] and converted to carbinol **44**.[37] Formolysis of **44**



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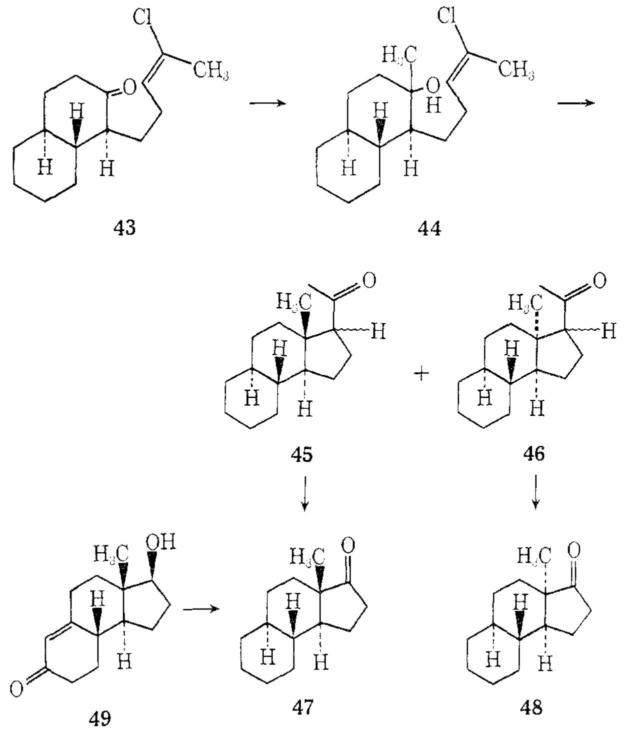
(35) *Cf.* L. Velluz, J. Valls, and G. Nomine, *Angew. Chem., Int. Ed. Engl.*, **4**, 181 (1965).

(36) T. R. Demmin, Ph.D. Dissertation, State University of New York at Buffalo, 1972.

(37) Side-chain epimerization in **44** is less likely than in **36** because the $\Delta^{1,2}$ π bond introduces more strain than the alternative $\Delta^{2,3}$ bond (which does not lead to C_1–R epimerization). Furthermore, reprotonation of Δ^1-octalin, if formed, would go *via* a "pre-chair" transition state, restoring the original stereochemistry.

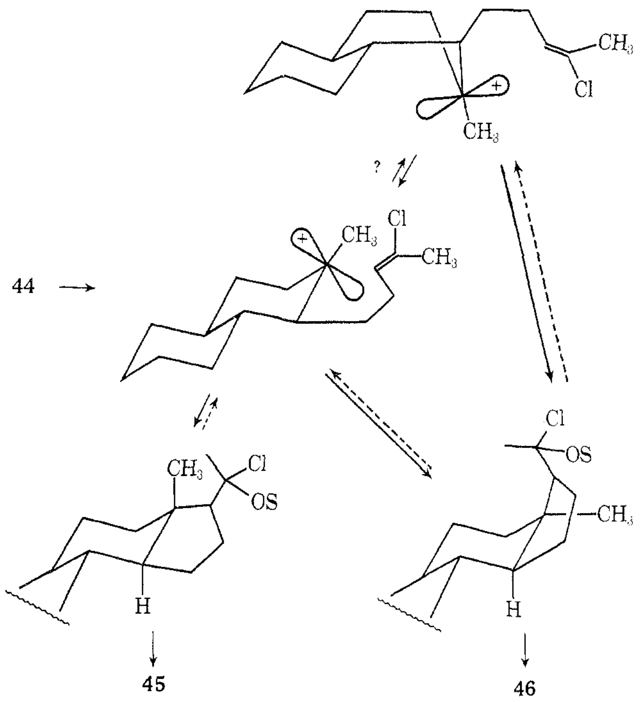
proceeded in $\geq 95\%$ yield, as with **36**, but in this case the nmr spectrum of the tricyclic ketone mixture encouragingly showed[34] a preponderance of trans-fused compound.



43 **44** **45** **46** **49** **47** **48**

As before, degradation of the acyl side chains provided **47** and **48**, the former being independently obtained by standard transformations of **49**, which fortunately became available to us.[38] Ketone **47** was now the major isomer (*ca.* 60% yield of **45**), indicating that the ion derived from **44** had less inclination to undergo axial closure, as had been observed in the conformationally mobile monocyclic ion derived from **36**. Since side-chain epimerzation was considered unlikely,[37] axial closure in **44**-R$^+$ would require a twist-boat cyclohexyl cation, which is improbable but not impossible.[39] Upon varying temperature and reaction times[40] for formolysis of **44**, it became clear that the desired trans stereoselectivity (which reached 65% in most runs) actually diminished at lower temperatures and short reaction times, contrary to expectations, though yields were still $\geq 95\%$.

Thus, when half of an anhydrous formolysis was worked up after 12 hr at 10°, the ratio of **47** to **48** was 50:50 and no reactant or other products were evident; however, when the remaining solution was *refluxed* for 12 hr more, work-up then afforded a 60:40 mixture of the trans- and cis-fused ketones. Apparently, the cyclization is reversible (dotted lines, above), but only under vigorous conditions, and might involve opened vinyl formate as well as vinyl chloride. The postulated cleavage has analogy in the ring-D fragmentation of 17-keto steroid oximes.[41]



At this point, a digression into acetylenic reactions with tertiary carbonium ions (where π participation is unlikely) is appropriate. Carbinol **50**, prepared along the same lines as **44**, was solvolyzed[42] with the expectation that five-membered ring formation (→ **51**) would predominate[43] over closure to the six-membered vinyl formate, leading to **52**.

Since the alkynyl side chain in **50**, although chemically equivalent to that in **44**, was geometrically quite different (linear *vs.* angular), we anticipated that the stereoselectivity in propionylhydrindan formation might be greater. Fortunately, only *ca.* 2–5% of **52** was generally formed during formolyses and trifluoroacetolyses of **50**, and the desired closure gave as much as 82% trans-fused ketone.[42] Johnson and his coworkers[44] have independently demonstrated the utility of alkynyl closures in model ring-D annelations, as well as in a total synthesis of progesterone.[45]

It is too early to say whether chloro olefin or alkynyl cyclizations will be of value in large-scale steroid syntheses. There is certainly sufficient promise to date to warrant further research, particularly in introducing

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(38) Kindly furnished by Dr. G. Nomine, Roussel-Uclaf.

(39) W. H. Saunders, Jr., and K. T. Finley, *J. Amer. Chem. Soc.*, **87**, 1384 (1965); V. J. Shiner, Jr., and J. G. Jewett, *ibid.*, **87**, 1382 (1965).

(40) G. E. DuBois, Ph.D. Dissertation, State University of New York at Buffalo, 1972.

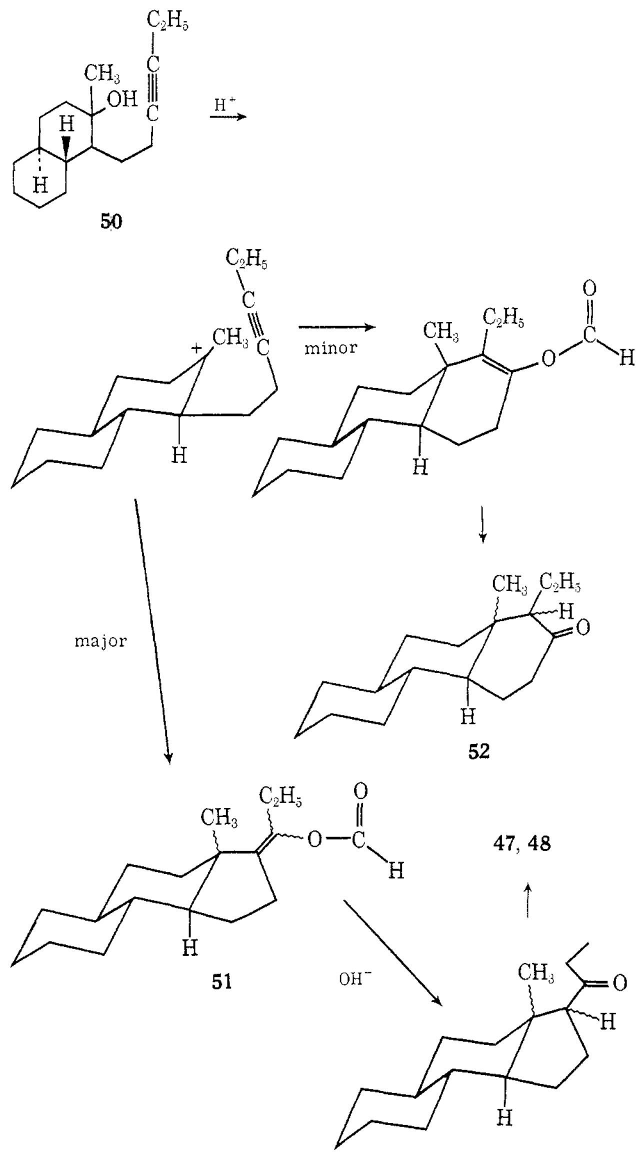
(41) C. W. Shoppee and R. W. Killick, *J. Chem. Soc. C*, 1513 (1970).

(42) P. T. Lansbury and G. E. DuBois, *Chem. Commun.*, 1107 (1971).

(43) The first acetylenic closures investigated were formolysis and trifluoroacetolysis of 2-(2-pentynyl)-1-methylcyclohexanol (each pure isomer was studied separately), whose products were expected to correspond in part with those derived from **36–39** (after vinyl ester hydrolysis). In the event, as much as 40% of the products were derived from six-membered ring formation (*i.e.*, *cis*- and *trans*-1,9-dimethyl-2-decalone); we were not deterred from proceeding to **50**, however, because of conformational mobility in cyclohexyl cations that might favor six- over five-membered ring formation (T. R. Demmin, unpublished results).

(44) W. S. Johnson, M. B. Gravestock, R. J. Parry, R. F. Meyers, T. A. Bryson, and D. H. Miles, *J. Amer. Chem. Soc.*, **93**, 4330 (1971).

(45) W. S. Johnson, M. B. Gravestock, and B. E. McCarry, *ibid.*, **93**, 4332 (1971).



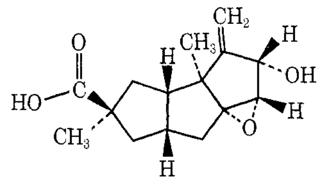
50

52

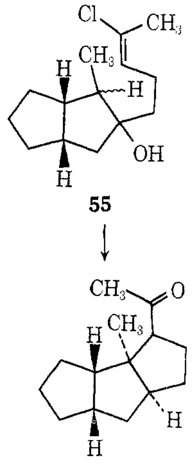
51

47, 48

additional functionality into the side-chain component destined to become ring D (*e.g.*, in the more complex corticosteroids), so that the overall scheme becomes more convergent.

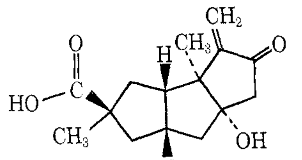


53



55

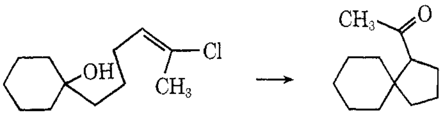
56



54

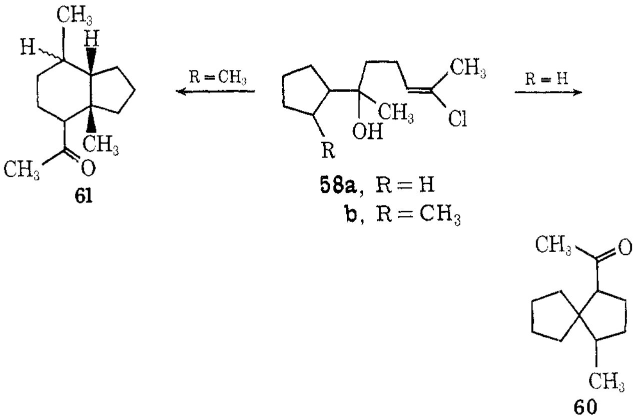
Concurrent with our acylhydrindan work, chloro olefin annelation was employed to generate the basic tricyclic skeleton (*e.g.*, **55** → **56**) in Hirsutic acids C and N, **53** and **54**, respectively.[46] By analogy with carbinol **39**, formolysis of **55** involved planned rearrangement of tertiary ions *via* dehydration–reprotonation,[47] thus providing the requisite carbonium ion for *cis*-bicyclo[3.3.0]octane formation.[48] Moreover, as examination of models made clear, the cis fusion was created from the less-hindered convex side of the bicyclooctyl carbonium ion, generating the overall cis-anti-cis geometry in **56** which corresponds to that in **53** and **54** and hence provides a valuable reference compound for establishing the relative configuration of other synthetic intermediates.[48]

Carbonium ion rearrangements in **39** and **55** led to fused bicyclic systems, rather than affording acylspiroalkanes; however, spirocyclic ketones could be expected if the ring being formed were larger than four-membered. Therefore, the formolytic behavior of carbinols **57** and **58** was examined.[49,50] The clean-cut formation of **59** and **60** (side-chain degradation in all cases afforded cyclopentanones) provides a potentially direct path to sesquiterpenes of the cedrane and acorane types which we are currently exploiting.[49] As in other instances where thermodynamic stabilities controlled product composition, **58b** was able to bypass spiran formation and proceed, *via tert*-alkyl ions, to the more stable **61**.[50]



57

59



61

58a, R = H
b, R = CH$_3$

60

A further example is provided by formolysis of **62**, derived from bis alkylation of anthrone and reduction.[34] This experiment again illustrates the inertness of vinyl chlorides toward formic acid, the noteworthy feature being that the "unused" chlorobutenyl group in **62**

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(46) F. W. Comer, F. McCapra, I. H. Qureshi, and A. I. Scott, *Tetrahedron*, **23**, 4761 (1967).

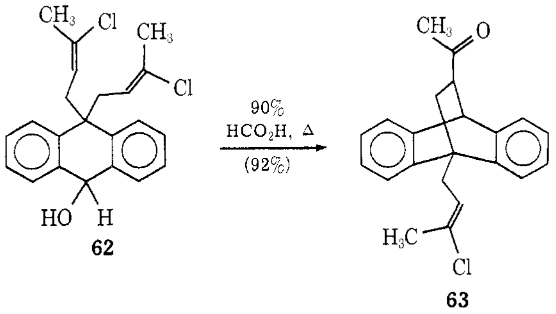
(47) This point was established by employing **55**-d_3 and showing the loss of one D enroute to **56**.

(48) P. T. Lansbury and N. Nazarenko, *Tetrahedron Lett.*, 1833 (1971).

(49) Unpublished results with G. E. DuBois.

(50) Unpublished results with N. Nazarenko.

remained unaltered while the other underwent internal cationic attack, *followed* by hydrolysis.[34]

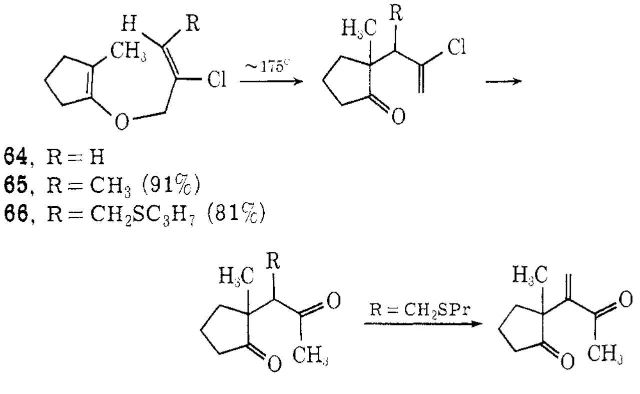


62 **63**

Miscellaneous Annelations

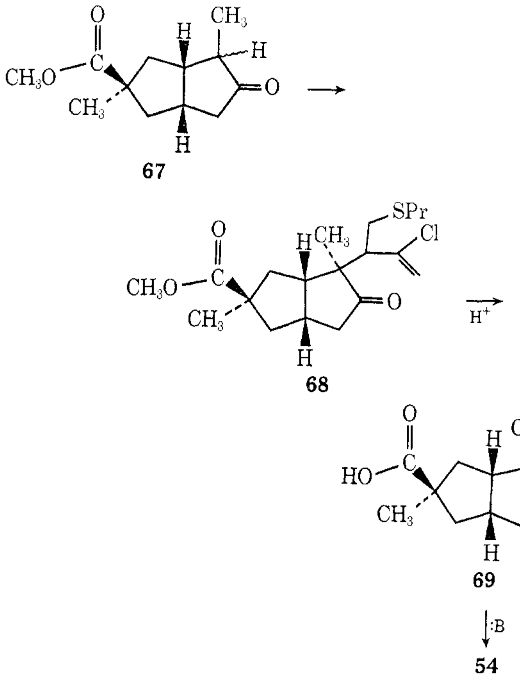
The synthetic utility of Claisen rearrangements[51] of chloroallyl ethers, while not leading directly to cyclic product, deserves mention, since it provides a nonoxidative pathway to acetone side chains.[52] We have examined ketalization of 2-methylcyclopentanone with β-chloroallyl alcohol and several more complex derivatives; dehydration to vinyl ether and *in situ* rearrangement have consistently provided high yields of 2,2-disubstituted cyclopentanones.[53] As Scheme IV shows, it is possible to use an additionally functionalized β-chloroallyl alcohol (*e.g.*, as in **66**) and accomplish the direct incorporation of an α,β-unsaturated ketone (or its masked equivalent) selectively at the more substituted side of an unsymmetrical ketone.

Scheme IV



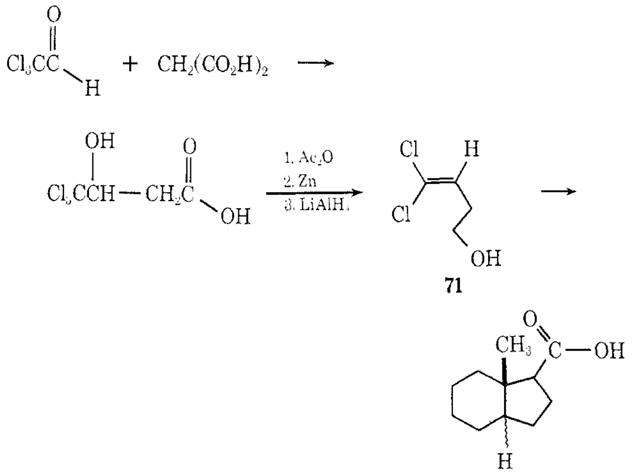
64, R = H
65, R = CH_3 (91%)
66, R = $CH_2SC_3H_7$ (81%)

A convergent, stereocontrolled total synthesis of Hirsutic acid N (**54**) was made possible by the following sequence, wherein Claisen alkylation, which proceeded with proper site selectivity and stereoselectivity,[54] allowed all the required side-chain functionality to be introduced in a single operation.[55] The fact that 1-methylbicyclo[3.3.0]octan-2-one (**70**), a model for **67**, could not be alkylated in straightforward fashion with an appropriate four-carbon reagent[56] makes the "chloro-Claisen" rearrangement especially valuable. Furthermore, our emphasis upon modifications of the allylic portion of Claisen rearrangements involving allyl vinyl ethers complements the various modifications in the vinyl ether portion developed by Johnson,[57] Faulkner,[58] and Lythgoe,[59] and their coworkers.



67 **68** **69** **54**

Returning now to *bona fide* annelation reactions, other chloro olefin bearing side chains have also received attention in our laboratory. Useful reagents for forming cycloalkanecarboxylic acids are typified by **71**, readily available from chloral and malonic acid.[60]



71 **72**

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[51] (a) J. Reucroft and P. G. Sammes, *Quart. Rev., Chem. Soc.*, **25**, 162 (1971); (b) D. J. Faulkner, *Synthesis*, 179 (1971).

[52] This transformation is often carried out by ozonolysis of a β-methallyl side chain (*cf.* F. Sakan, H. Hashimoto, A. Ichihara, H. Shirahma, and T. Matsumoto, *Tetrahedron Lett.*, 1703 (1971)).

[53] Unpublished results with J. E. Rhodes.

[54] P. T. Lansbury, N. Y. Wang, and J. E. Rhodes, *ibid.*, 1829 (1971).

[55] P. T. Lansbury, N. Y. Wang, and J. E. Rhodes, *ibid.*, 2053 (1972).

[56] N. Nazarenko, Ph.D. Dissertation, State University of New York at Buffalo, 1971. Alkylation of **70** with 3-bromo-2-butanone gave O-alkylation, whereas α-methylallyl chloride underwent S_N2′ displacement, but with C-alkylation.

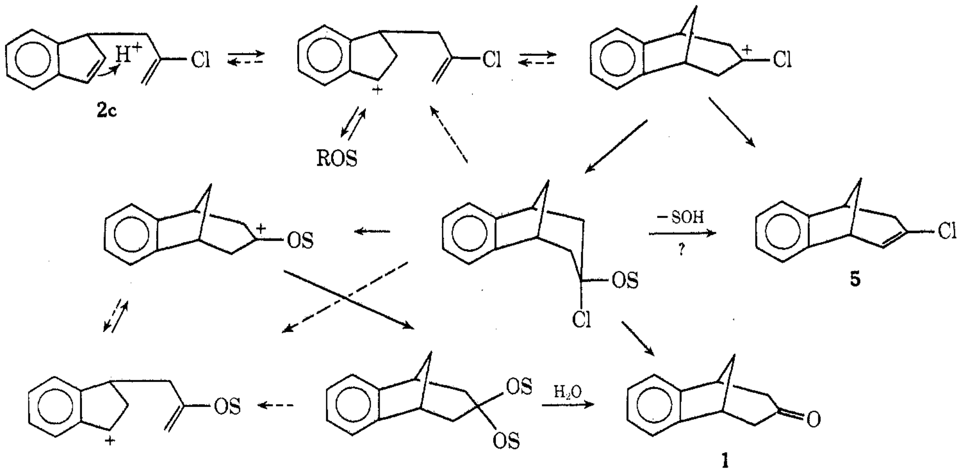
[57] W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, and M. R. Petersen, *J. Amer. Chem. Soc.*, **92**, 741 (1970).

[58] D. J. Faulkner and M. R. Petersen, *Tetrahedron Lett.*, 3243 (1969).

[59] I. J. Bolton, R. G. Harrison, and B. Lythgoe, *Chem. Commun.*, 1512 (1970).

[60] Unpublished results with R. Stewart.

Scheme V



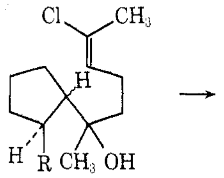
Alkylation of cyclohexanone by **71**-mesylate, followed by methyl Grignard addition and formolysis, provides a modest yield of the hydrindan **72**.

Mechanistic Aspects of Chloro Olefin Annelation

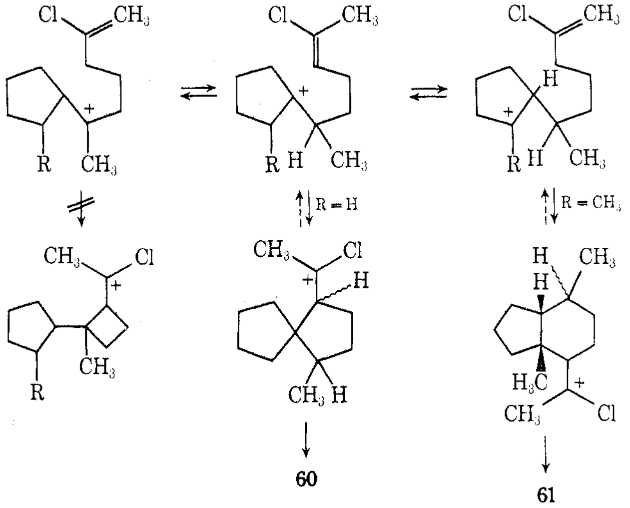
A formolysis scheme, consistent for terminal chloro olefins such as **2c** and corroborated by additional observations mentioned in this Account, is formulated in Scheme V.[61] Protonation of **2c** (or ionization of an equivalent carbinol in other cases) is not accompanied by closure, since a vinyl chloride is a poor π participator[20] and enols are *not* involved; furthermore, several examples of ionic rearrangement of the initial electrophilic center prior to closure have been encountered (*cf.* **8**, **13**, and **39**). Once cyclization has occurred, both **1** and **5** follow by logical steps and do not interconvert (*cf.* **62** → **63**). There is also the possibility that *reopening* of cyclic ions, α-chloro formates, or gem diformates (dotted arrows) may take place in appropriate cases (*cf.* **44** → **45** + **46**, wherein product distribution of a *completed* low-temperature reaction shifts upon heating). This latter process could regenerate a vinyl chloride or ester.

Similar mechanistic pathways can be suggested for substrates bearing *internal* chloro olefin groups, *e.g.*, **58**. The monocyclic ion equilibria which precede cyclization involve deprotonation and reprotonation steps, by analogy with **55**.[47]

More detailed schemes, which would require additional experimental data, must be postponed for now, as is discussion of the situation in 90% aqueous sulfuric acid. In this case, reopening of chlorocarbonium ions is unlikely, since the great proportion of water present ensures direct conversion to ketone and/or its stable conjugate acid. However, there is certainly sufficient information at hand to aid in planning future synthetic experiments.



58a, R = H
b, R = CH_3



Summary and Prognosis

A number of useful aspects of chloro olefin annelations are reiterated in summary: (1) substituents on C_β and more remote from the carbonyl group are introduceable; alkylation at C_α can readily be achieved by various known means; (2) carbonium ion rearrangements prior to intramolecular attack on chloro olefin increase the possible sites for generating electrophilic centers and in a predictable manner; (3) the inertness of vinyl chlorides allows for a great variety of intervening chemical operations before their final capture in the carbonyl-forming step and minimizes double bond migration prior to closure.

Among topics for future investigation are the use of other electrophiles, such as bromonium ion,[62] R^+, and SR^+ donors, to attack reactive double bonds and initiate closure, as well as the synthesis of more complex,

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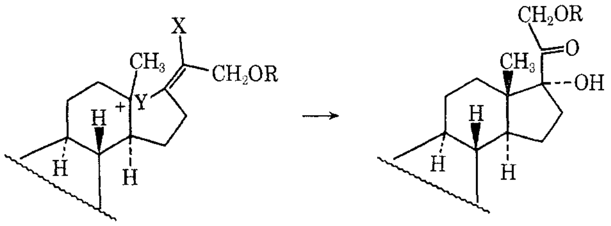
(61) Proton transfers are omitted for the sake of brevity. SOH refers to either formic acid or water, which is present in reagent-grade formic acid.

(62) D. Duffin and J. K. Sutherland, *Chem. Commun.*, 627 (1970).

chloro olefin bearing molecules capable of providing additional functionality directly, such as



Such a development would impart more "convergent" character[35] to a multistep synthesis.

I express my sincere gratitude to my students whose names appear in the references for their frequent ideas and their experimental efforts that culminated in this Account. Financial support from the National Science Foundation and the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.