with his programs, and for many fruitful discussions. Thanks are also due the Research Corporation for financial support and to our Computer Center for extraordinarily generous amounts of computer time.

**Supplementary Material Available.** A listing of structure factor amplitudes will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JACS-74-892.

# Latent Homoallylic Ions in Carbocyclic Ring Construction. α-Cedrene

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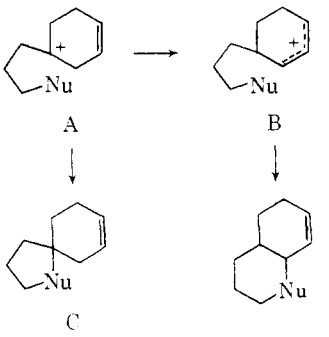
**Abstract:** A synthetically useful concept for construction of complex carbocyclic ring systems by cationic cyclization is developed. Transformations theoretically attributable to homoallylic cations which are unachievable in practice can be performed by *partial* generation and consumption of such bifunctional intermediates in *different* steps. A short and efficient total synthesis of α-cedrene illustrates the approach.

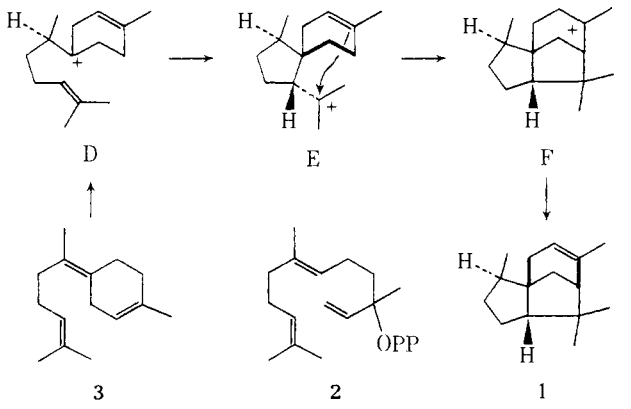
The utilization of latent functionality[1] has become a powerful consideration in total syntheses of complex organic molecules. Whereas the use of blocking groups[2] continues to play an indispensable role in peptide and nucleotide synthesis *inter alia*, latent carbonyl compounds such as furans, anisoles, pyridines, and isoxazoles have become increasingly popular synthetic building blocks for terpenes, steroids, etc. Not only does latent functionality increase efficiency (*e.g.*, by eliminating blocking and deblocking steps) but the possibility exists of partially generating "asymmetric difunctionality" before fully revealing two similar or identical groups. Thus, while hydrogenolysis and hydrolysis of isoxazoles ultimately yield a β-diketone, modified conditions allow a single intermediate β-enamino ketone to form and react selectively.[3] Chloroalkenes are latent ketones which have found use in nonconcerted cationic cyclizations leading stereoselectively to cycloalkanones and acylcycloalkanes, and in [2,3]- and [3,3]-sigmatropic rearrangements.[4] In this paper, such a group is employed along with a *latent* homoallylic cation to facilitate the construction, *via* spiroannelation, of the fascinating sesquiterpene α-cedrene[5-8] (**1**). As will be clear below, actual homoallylic ions can and do rearrange (→B) prior to intended spirocyclization (→C), when only a weakly nucleophilic terminus is present, *e.g.*, see Scheme I.

**Scheme I**




Examination of a proposed biosynthesis of cedrene as depicted in Scheme II indicates that nerolidyl pyro-

**Scheme II**

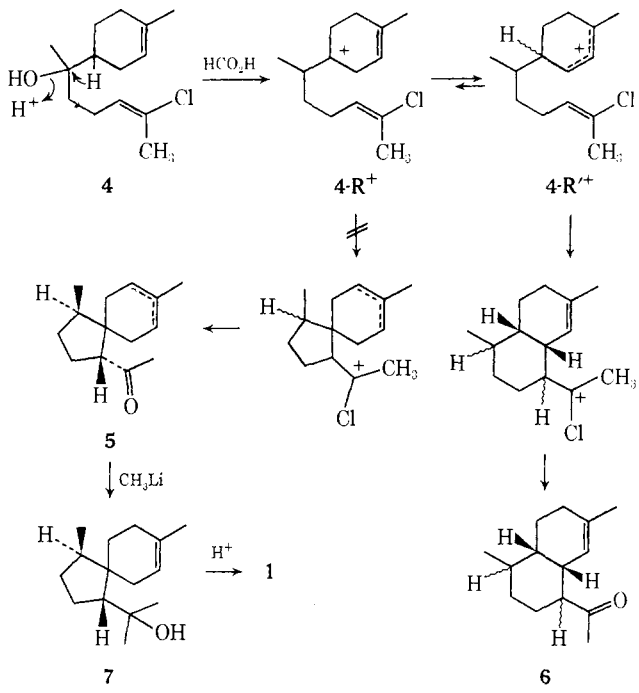



phosphate (**2**), or perhaps *cis*-farnesyl pyrophosphate, cyclizes to γ-bisabolene (**3**) and that subsequent enzyme-catalyzed steps (**3** → D → E → F) should eventually produce **1**. The viability of this scheme has been demonstrated recently by the acid-catalyzed biogenetic-like cyclization of nerolidol to **1**, epicedrene and an aromatic isomer of the curcumenes in comparable yields.[8c] The complexity of the product mixture arises

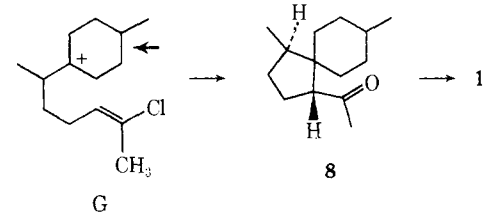
(1) D. Lednicer, *Advan. Org. Chem.*, **8**, 179 (1972).
(2) J. F. W. McOmie, Ed., "Protective Groups in Organic Chemistry," Plenum Press, New York, N. Y., 1973.
(3) G. Stork and J. E. McMurry, *J. Amer. Chem. Soc.*, **89**, 5463 (1967).
(4) P. T. Lansbury, *Accounts Chem. Res.*, **5**, 311 (1972).
(5) Structure: P. Yates, "Structure Determination," W. A. Benjamin, New York, N. Y., 1967, Chapter 1.
(6) Biogenesis: W. Parker, J. S. Roberts, and R. Ramage, *Quart. Rev., Chem. Soc.*, **21**, 331 (1967).
(7) First total synthesis: G. Stork and F. H. Clarke, Jr., *J. Amer. Chem. Soc.*, **83**, 3114 (1961).
(8) Biogenetic-type syntheses: (a) E. J. Corey, N. N. Girotra, and C. T. Mathew, *J. Amer. Chem. Soc.*, **91**, 1557 (1969); (b) T. G. Crandall and R. G. Lawton, *ibid.*, **91**, 2127 (1969); (c) N. H. Andersen and D. D. Syrdal, *Tetrahedron Lett.*, 2455 (1972).

in part because of lack of site and steroselectivity during *in vitro* protonation of **3**, which possesses three equally nucleophilic trisubstituted double bonds. Not surprisingly, when the biogenetic pipeline was entered at a later and safer point, by generating E from preformed spirodecanes[8a,b] **1** was obtained in excellent yield,[8b] but unfortunately many steps were needed to produce such a precursor. Indeed, construction of complex spiro, bridged, and fused carbocyclic intermediates has frequently encumbered synthetic efforts in the terpene area. We initially approached the problem of regioselective protonation of "bisabolene-like" intermediates by introducing a single nonnucleophilic chloroalkene group, as in **4** (Scheme III). Formolysis

**Scheme III**




of **4** resulted in excessive rearrangement (**4**-R$^+$ → **4**-R′$^+$) more rapidly than cyclization, hence yielding the 6/6-cis-fused[9] acetyloctalin **6**, a potential synthetic precursor to muurolanes and amorphanes, instead of spiro ketone **5**.[10] Knowing that *saturated* cyclohexyl cations analogous to **4**-R$^+$ indeed spirocyclize cleanly,[11] it became clear that a correctly protonated γ-bisabolene equivalent (corresponding to D) required two features not present in the parent triene rather than only one (as in **4**). Thus, ion G possesses one vinyl chloride grouping, which we expected to partake only in the crucial closure (as in D → E), and *entirely lacks* the cyclohexenyl π bond (arrow) that would allow diversion to 6/6-fused material. If G is indeed a valid latent

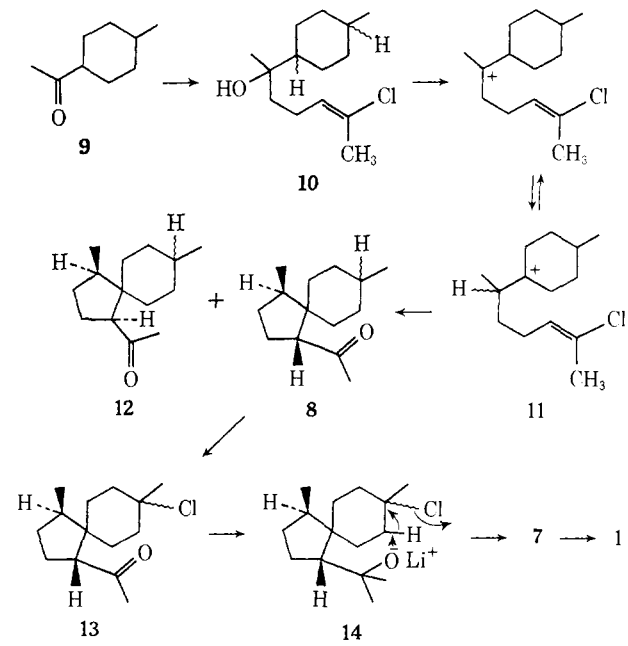



G

homoallylic ion, it must be possible to regioselectively introduce the desired double bond before *or* after methyllithium addition to **8** (affording **5** or **7**, respectively) so as to generate **1** *via* E. We now report successful realization of this scheme in only five steps, several occurring in a single laboratory operation.

The key intermediate, spiro ketone **8**, was assembled in two steps, beginning with addition of 4-chloro-3-pentenyllithium[12] (generated by lithium–halogen exchange at −78°) to 4-methylcyclohexyl methyl ketone[13] (**9**), which afforded carbinol **10** in 97% yield, as a stereomeric mixture.[14] Formolysis converted **10** to ketones **8** and **12** in over 90% yield (Scheme IV); gas

**Scheme IV**




chromatographic analysis revealed that the two possible trans racemates (**8**) amounted to *ca.* 85% of the total after methoxide equilibration[8a,b] and that separation

(9) W. S. Johnson, P. J. Neustaedter, and K. K. Schmiegel, *J. Amer. Chem. Soc.*, **87**, 5148 (1965).

(10) When **4** was formolyzed at room temperature overnight, then subjected to hydrolysis and work-up, there was obtained a 68% yield of oily ketone **6** (epimeric mixture): M$^+$ 206; ir carbonyl absorption at 5.87 μ; salient nmr methyl signals at δ 0.90, 1.60, and 2.04. The structure of **6** was inferred by degrading the acetyl side chain (peroxytrifluoroacetic acid in methylene chloride) to acetate, saponification of the latter grouping, and Jones oxidation of the substituted cyclohexanol to a *six-membered* ring ketone, $\lambda_{film}$ C=O 5.87 μ. When the same series of degradation steps was performed on the spiro ketone mixture of **8** and **12**, the resulting spiro[4.5]decan-1-one had $\lambda_{film}$ C=O 5.77 μ, as expected for a cyclopentanone: R. C. Stewart, M.A. Thesis, State University of New York at Buffalo, 1973.

(11) G. E. DuBois, unpublished results mentioned in ref 4, in which addition of 5-chloro-4-hexenylmagnesium bromide to cyclohexanone produces the *tert*-cyclohexanol that formolyzes to 1-acetylspiro[4.5]-decane in 82% yield. The latter was degraded (ref 10) to the known spiro[4.5]decan-1-one: R. Mayer, G. Wenschuh, and W. Topelman, *Chem. Ber.*, **91**, 1616 (1958).

(12) G. E. DuBois, Ph.D. Dissertation, State University of New York at Buffalo, 1972. The 2-chloro-5-iodo-2-pentene used is obtained in two steps from methyl cyclopropyl ketone ($PCl_5$ fragmentation followed by iodide displacement) as a mixture of *E* and *Z* isomers.

(13) N. Dufort and E. Flammand, *Can. J. Chem.*, **46**, 1073 (1968). In the present work, **9** was prepared by two independent routes: (1) hydrogenation of the Diels–Alder adduct of isoprene and methyl vinyl ketone (*cf.* E. F. Lutz and G. M. Bailey, *J. Amer. Chem. Soc.*, **86**, 3899 (1964)), and (2) hydrogenation of *p*-methylacetophenone over Rh/C and Jones oxidation of the resultant cyclohexylcarbinol. After base equilibration, the cis:trans ratios in **9**, prepared by the two routes, were consistent with the values reported by the Canadian workers (*ca.* 3:1 ratio of *trans*- to *cis*-**9**).

(14) The alternative addition of 6-chloro-5-hepten-2-yl organometallics to 4-methylcyclohexanone would give the immediate carbinol precursor to G (*cf.* ref 11), rather than requiring tertiary cation isomerization, but this proved less practical experimentally.

from **12** would be hard to achieve. This material was used directly for the ensuing steps. Regioselective introduction of the latent double bond into **8** was initiated by photochemical chlorination at the less hindered *cyclohexyl* tertiary C–H bond[15] with iodobenzene dichloride. The crude chloride, which we anticipated would be mainly **13**, was subjected immediately to methyllithium addition, and the derived alkoxide **14** was refluxed for 3 hr to effect dehydrochlorination in the required sense.[8b] Formolysis of the derived carbinol (primarily α-acorenol (**7**)) yielded a complex product mixture (analyzed by glc on SE-30 and Carbowax columns), in which the major component α-cedrene (**1**) was present in *ca.* 80% yield, based on **8**.

In summary, regioselective introduction of unsaturation into **14** *after* utilizing a saturated 1-alkylcyclohexyl cation for spiroannelation prevents the potentially disastrous homoallyl to allyl cation rearrangement during generation of the acorane skeleton. Besides that complication, the closure **4R**$^+$ → **5** (Scheme III) would not have allowed the crucial double bond placement that is made possible in the sequence **13** → **14**. Lastly, we hope that the overall brevity and simplicity realizable by employing the above concepts will find use in other terpene syntheses. Such efforts are under way in these laboratories.

## Experimental Section[16]

**2-Chloro-6-hydroxy-6-(4-methylcyclohexyl)hept-2-ene (10).** 2-Chloro-5-iodo-2-pentene[12] (5.84 g, 25.3 mmol) was dissolved in dry ether (20 ml) under argon and cooled to −78°. *tert*-Butyllithium (12.65% solution in pentane; 21 ml) was added dropwise with stirring over 10 min. 4-Methylcyclohexyl methyl ketone[13] (2.59 g, 18.5 mmol) was added dropwise at −78°, and the mixture was allowed to reach room temperature and stirred overnight under argon. The reaction mixture was poured onto saturated NaCl solution and extracted with ether and the ether extracts were washed with saturated NaCl solution and dried ($MgSO_4$). Evaporation of the solvent and purification by bulb-to-bulb distillation (137° (0.14 mm)) yielded the product as a colorless oil (4.40 g, 97%): nmr δ 5.4 (m, HC=C), 2.04 (br s, $CH_3C$=C), 1.04 (s, $CH_3C(OH)$), 0.85 (d, $J \approx 6$ Hz, $CH_3CH$); ir $\lambda_{max}^{film}$ 2.85 (OH), 3.38, 3.46, 6.02 (C=C), 6.90, 7.21, and 10.90 μ; mass spectrum *m/e* 244 ($M^+$), 226 ($M^+ - 18$). *Anal.* Calcd for $C_{14}H_{25}OCl$: C, 68.69; H, 10.29. Found: C, 68.91; H, 10.47.

**1-Acetyl-4,8-dimethylspiro[4,5]decane (8 and 12). Preparation and Equilibration.** 2-Chloro-6-hydroxy-6-(4-methylcyclohexyl)-hept-2-ene (**10**) (4.0 g, 16.4 mmol) was added under argon to a mixture of formic acid (97%, 140 ml) and acetic anhydride (34 ml), and the reaction mixture was heated on a steam bath for 2 hr. The reaction mixture was poured onto ice and extracted with ether, and the combined ether extracts were washed with saturated NaCl solution, saturated $NaHCO_3$ solution, and saturated NaCl solution, and dried ($MgSO_4$). Removal of solvent yielded the crude product as a yellow oil (quant. yield). Distillation afforded the product as a colorless liquid (2.40 g, 71%): bp 105° (0.14 mm); ir $\lambda_{max}^{film}$ 3.40, 3.44, 3.51, 5.86 (C=O), 6.89, 7.40, and 8.55 μ. *Anal.* Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.51; H, 11.75.

Gas chromatography (6-ft Carbowax, 200°, 60 ml/min) indicated the presence of three components with retention times as follows: a, 8.1 min (24%); b, 9.2 min (18%); and c 10.0 min (58%). Samples of each component were obtained by preparative vpc and shown to have near-identical mass spectral fragmentation pattern: mass spectrum component a, *m/e* 208 (8), 190 (12), 150 (58), 95 (48), 84 (100), 81 (50); component b, *m/e* 208 (7), 190 (10), 150 (43), 95 (43), 84 (100), 81 (38); component c, *m/e* 208 (9), 190 (11), 150 (45), 95 (41), 84 (100), 81 (41); nmr component a, δ 3.06 (m, 1 H, $CHCOCH_3$), 2.12 (s, 3 H, $COCH_3$), 2.4–0.6 (c, 18 H); component b, δ 2.67 (m, 1 H, $CHCOCH_3$), 2.03 (s, 3 H, $COCH_3$), 2.4–0.6 (c, 18 H); component c, δ 2.67 (m, 1 H, $CHCOCH_3$), 2.03 (s, 3 H, $COCH_3$), 2.4–0.6 (c, 18 H).

Equilibration experiments were next conducted with the above stereoisomers. Component a (11 mg) was refluxed with a solution of sodium methoxide in methanol (0.8 *M*, 20 ml) for 4 hr. Standard ether work-up yielded a product (10 mg) shown by vpc to be unchanged pure component a. A mixture containing 6% of b and 94% of c was subjected to equilibration under the same conditions to yield a mixture of 17% b and 83% c. Similarly, a 39:61 mixture of b and c yielded an 18:82 mixture upon equilibration. It was concluded that b and c are epimers, the minor component b having the less stable cis arrangement of methyl and acetyl groups on the cyclopentane ring. Component a differs from b and c in the stereochemistry at the spiro center relative to the 4-methyl group on the cyclohexane, and is assumed to contain only the trans arrangement of methyl and acetyl groups on the five-membered ring or perhaps small unidentifiable amounts of the acetyl epimer.

The original mixture of isomers (1.72 g) was refluxed in sodium methoxide–methanol solution (0.8 *M*, 200 ml) for 24 hr and worked up as usual to yield a product (1.51 g, 88%) shown by vpc to contain components a, b, and c in the ratio 26:13:61, respectively.

Refluxing such a mixture in glacial acetic acid and concentrated HCl (5:2 mixture) did not alter the isomer ratios appreciably. Accordingly, the isomeric mixture (87% *trans*-**8**, and 13% *cis*-**12** was used for subsequent reactions.

**(±)-α-Cedrene (1).** 1-Acetyl-4,8-dimethylspiro[4.5]decane (253 mg, 1.22 mmol) was dissolved in benzene (100 ml) and the solution thoroughly degassed with argon. Iodobenzene dichloride[17] (1.37 g, 4.97 mmol) was added in four portions over 2 hr during irradiation with a 150-W bulb, at temperatures not exceeding 50°. The reaction mixture was irradiated for a further 1 hr and then cooled to 5°. Methyllithium (1.5 *M* in ether, 2.1 ml) was added in small portions until aliquots of the reaction mixture just gave a positive Michler's ketone test. The mixture was allowed to warm to room temperature, then refluxed under argon for 3 hr. The reaction mixture was poured onto saturated NaCl solution and the organic layer was separated, washed with saturated NaCl solution, and dried ($MgSO_4$). Removal of solvent yielded the crude product (773 mg) whose nmr spectrum contained all of the characteristic absorptions of α-acorenol (**7**).[18] The crude product was stirred with formic acid (90%, 80 ml) under argon at room temperature for 1 hr. The reaction mixture was poured onto ice and extracted with pentane, and the pentane extracts were washed (saturated NaCl solution, saturated $NaHCO_3$ solution, and saturated NaCl solution) and dried ($MgSO_4$). Careful evaporation of the solvent yielded the crude product (670 mg) shown by vpc (6 ft SE-30, 185°, 60 ml/min) to contain cedrene as the major component. By the addition of a known weight of a vpc standard (9,10-dihydroanthracene) to an aliquot of the reaction mixture, the yield of cedrene was determined to be approximately 80% based on isomer **8** of 1-acetyl-4,8-dimethylspiro[4.5]decane. Preparative vpc yielded the pure product which was shown to have spectral properties (nmr, mass spectrum) identical with those of an authentic sample of (±)-α-cedrene. It is likely that ~15% of epicedrene, arising from the comparable amount of **12** coexisting with **8**, is present and undetectable.

**Acknowledgment.** We are grateful to the National Science Foundation for financial support of this research.

(15) R. Breslow, J. A. Dale, P. Kalicky, S. Y. Liu, and W. N. Washburn, *J. Amer. Chem. Soc.*, **94**, 3276 (1972).

(16) Boiling points are uncorrected. Vapor phase chromatography (vpc) analytical data and preparative separations were accomplished with a Hewlett-Packard 720 gas chromatograph, using helium as carrier gas. Nmr spectra were obtained on a JEOL-100 Minimar spectrometer, using $CCl_4$ as solvent and TMS as internal standard. The chemical shifts are quoted in ppm downfield from TMS. Infrared spectra were recorded on a Beckman IR-5A spectrophotometer. Mass spectral data were obtained using a Hitachi-Perkin-Elmer RMU-6E mass spectrometer at an ionization potential of 70 eV. Microanalyses were performed by Instranal Laboratory, Inc., Rensselaer, N. Y.

(17) H. J. Lucas and E. R. Kennedy, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 482.

(18) B. Tomita and Y. Hirose, *Tetrahedron Lett.*, 143 (1970).