mary amines and hydrazines are linear and of slope = 1.0. In this case changes in ΔF° are quantitatively reflected in $\Delta F^\ddagger$. Thus, it appears that in the reaction of some α-effect nucleophiles with certain substrates the change in $\Delta F^\ddagger$ cannot be solely related to changes in ΔF°.

Acknowledgment. This work was supported by a grant from the National Institutes of Health.

Experiments Directed toward the Total Synthesis of Terpenes. XVII. Development of Methods for the Synthesis of Pentacyclic Triterpenes Based on a Mechanistic Interpretation of the Stereochemical Outcome of the Friedel–Crafts Cyclialkylation Reaction[1]

Robert E. Ireland,* Steven W. Baldwin,[2] and Steven C. Welch[3]

Contribution No. 4306 from the Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California 91109.
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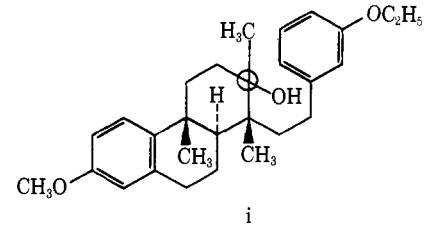
Abstract: The α-methylene ketone **11** was prepared and found to undergo conjugate addition with *m*-methoxybenzylmagnesium chloride with great facility. The initial adduct was trapped with acetic anhydride, and the resulting enol acetate **12** was used either in methylation experiments to prepare vicinal-dimethylated ketone **13** or to generate the ketone **16** by saponification. Cyclization of the former ketone **13** with polyphosphoric acid served to delineate a route to β-amyrin-type triterpenes, while polyphosphoric acid cyclization of the product from methyllithium and the latter ketone **16** provided a means for the construction of friedelin-type triterpenes. The stereochemical outcome of the latter cyclialkylation reaction is interpreted in the light of recent mechanistic concepts.

In plans developed for the total synthesis of such pentacyclic triterpenes as β-amyrin (**1**) and friedelin (**3**) the alcohol **2** and the diether **4**, respectively, were selected as the initial pentacyclic objectives.[4] In both cases the aromatic rings were proposed not only as suitable substrates from which to build the terpenoid substitution pattern in the terminal rings, but also to facilitate construction of the key intermediates themselves through use of the Friedel–Crafts type cyclodehydration[5a] or cyclialkylation[5b] reaction. From a logistic standpoint the ideal precursors for these pentacyclic aromatic intermediates are tricyclic systems that bear β-(*m*-alkoxyphenyl)ethyl side chains and already include the requisite angular methyl groups. The alcohol **2** would thus be made from the diketone **5**, and the diether **4** might in principle be prepared from the tricyclic alcohol **6**.[6]

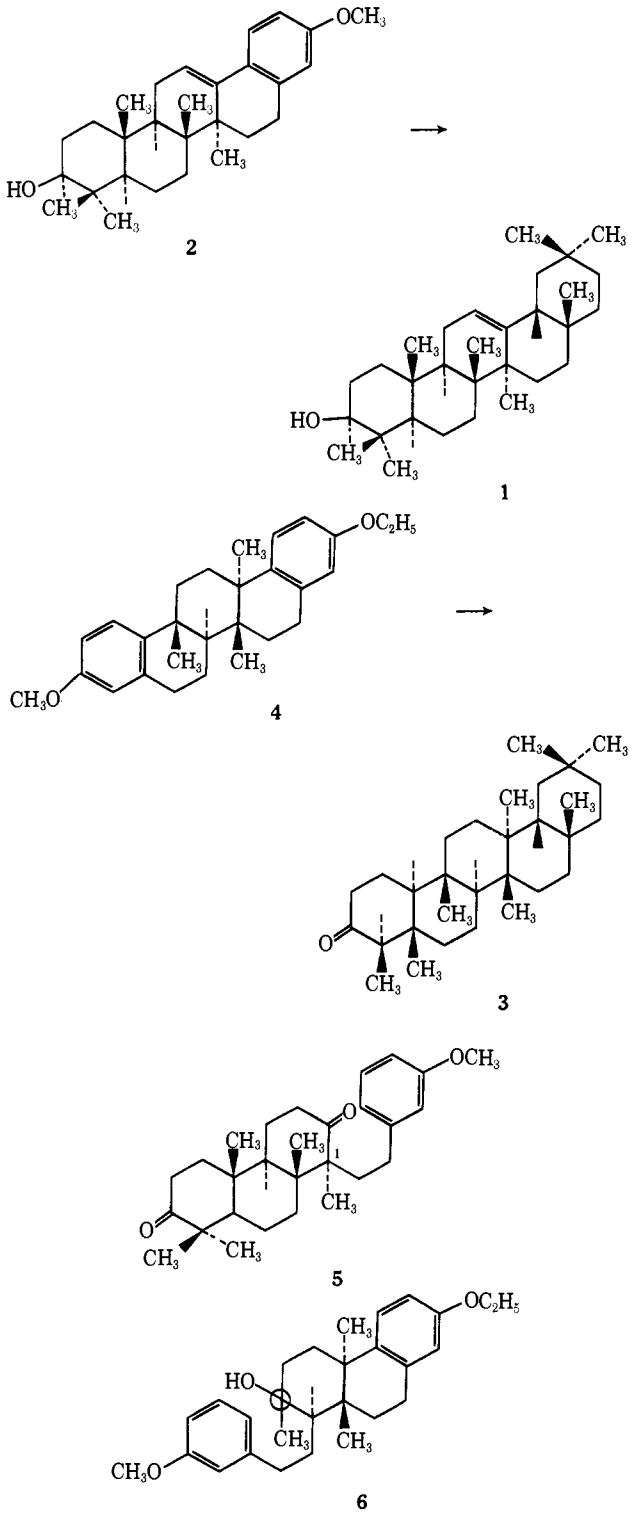
The decision to direct these synthetic effects through the tricyclic derivatives **5** and **6** was predicted on the results of some preliminary work on a model system that foreshadowed the viability of the approach. In particular, two problems had to be faced: (1) for the synthesis through the diketone **5** means had to be developed for the stereoselective incorporation at Cl of the β-(*m*-methoxyphenyl)ethyl and methyl side chains, and (2) the synthesis through the alcohol **6** was only possible if the stereochemical outcome of the Friedel–Crafts cyclialkylation reaction was at least predominantly the required B/C trans fused diether **4** and not the isomeric cis derivative. Favorable answers to both of these questions were found through the study of the synthesis of the tetracyclic model systems **15** and **20**.

The central feature of both of these syntheses is the α-methylene ketone **11**. The high reactivity of α,β-unsaturated ketones toward conjugate addition of carbon nucleophiles (Michael reaction) and, under certain circumstances, the ability to trap and alkylate the re-

(1) This work was made possible by a grant (GP 7810) from the National Science Foundation.
(2) Trainee of the Public Health Service, National Institute of General Medical Services.
(3) Postdoctoral Fellow (5FO2A135418) of the National Institute of Allergy and Infectious Diseases, 1968–1970.
(4) R. E. Ireland, D. A. Evans, D. Glover, G. M. Rubottom, and H. Young, *J. Org. Chem.*, 34, 3717 (1969).
(5) For reviews, see (a) W. J. Johnson, *Org. React.*, 2, 114 (1944); (b) L. R. C. Barclay, "Friedel-Crafts and Related Reactions," Vol. II, Part 2, G. A. Olah, Ed., Interscience, New York, N. Y., 1964, Chapter 22.
(6) The alternate alcohol i which might also be expected to serve this purpose was prepared (D. A. Evans, unpublished results) and found to undergo skeletal rearrangement rather than cyclialkylation on treatment with *p*-toluenesulfonic acid in boiling benzene. For mechanistic reasons discussed later in this paper, in retrospect even had the alcohol i cyclized the stereochemistry of the expected product would be the undesired trans-anti-cis.



i

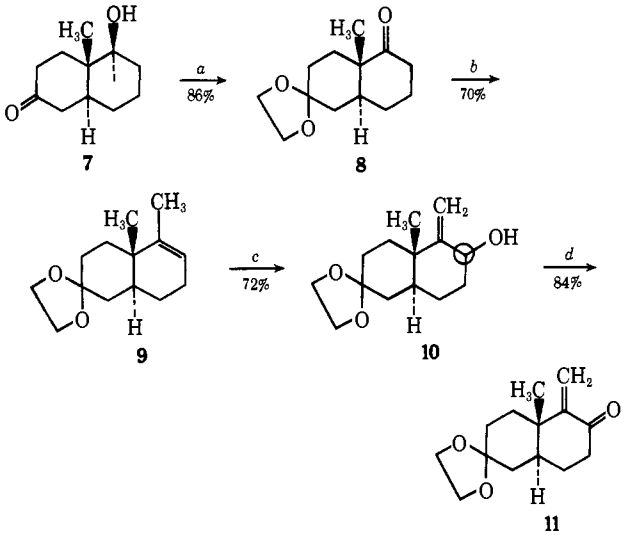


sulting enolate anion,[7] suggested that an α-methylene ketone grouping would serve as a means for the introduction of two dissimilar alkyl residues α to a ketone. This is the transformation required for the synthesis of the tricyclic diketone **5** and the model diketone **14**. The same conjugate addition process with an α-methylene ketone grouping but followed by protolysis of the intermediate enolate anion and then methyl Grignard addition to the resulting saturated ketone provides a and magnesium reagents rather extensively. Several pathway to the tricyclic alcohol **6** and the model alcohol **19**.

The problems forseen in the use of the α-methylene ketone synthon for these synthesis were the known lability of such systems toward Diels–Alder type dimerization,[8] and the ability to prepare only the desired one of the two possible α-methylene derivatives of an unsymmetrical ketone. The former problem proved to be of no concern, for, probably due to the size and complexity of the α-methylene ketones prepared for this and later studies, dimerization was a slow and noncompetitive process.

The method used to prepare the specifically desired α-methylene ketone synthon is shown in Scheme I.

Scheme I. Synthesis of α-Methylene Ketone **9**



[a] $(CH_2OH)_2$, H^+, C_6H_6; 8 *N* H_2CrO_5, acetone. [b] CH_3Li, ether; I_2, Δ. [c] O_2, rose bengal, $(CH_3)_2CHOH$, *hν*; $LiAlH_4$, ether. [d] CrO_3–Py_2, CH_2Cl_2.

Utilization of the photooxygenation[9] of a methyl olefin (**9**) provided an excellent means for the introduction of the allylic alcohol system (**10**) which in turn was readily oxidized to the desired α-methylene ketone grouping (**11**). For molecules of interest to this work the requisite methyl olefins **9** were readily and specifically prepared from the corresponding saturated ketone system **8**[10] through the addition of methyllithium and then dehydration. This specificity, of course, is a function of the saturated ketone used, and the scheme used here relies on the α',α'-disubstitution of the decalone **8**. Alternative means have been developed[11] for the preparation of the methyl olefins required in the photooxygenation step where Grignard addition and subsequent dehydration of the resulting alcohol would lead to a mixture of olefins. The complementarity of these methods provides a general scheme for the synthesis of such useful α-methylene ketone intermediates in good overall yield from readily available precursors.

We investigated the conjugate addition reaction between the α-methylene ketone **11** and benzylic lithium

(7) H. O. House and V. Kramar, *J. Org. Chem.*, **28**, 3362 (1963); H. O. House and B. M. Trost, *ibid.*, **30**, 1341, 2502 (1965).

(8) C. Mannich, *Ber.*, 74, 557 (1941); E. Romann, A. J. Frey, P. A. Stadler, and A. Eschenmoser, *Helv. Chim. Acta*, 40, 1900 (1957).

(9) The procedure developed by P. S. Wharton, G. A. Hiegel, and R. V. Coombs, *J. Org. Chem.*, **28**, 3217 (1963), was used; see also A. Nickon and J. F. Bagli, *J. Amer. Chem. Soc.*, **83**, 1498 (1961), for an alternate procedure.

(10) R. F. Church, R. E. Ireland, and D. R. Shridhar, *J. Org. Chem.* **27**, 707 (1962); M. Los, U. S. Patent 3,344,169 (1967).

(11) R. E. Ireland and G. Pfister, *Tetrahedron Lett.*, 2145 (1969).

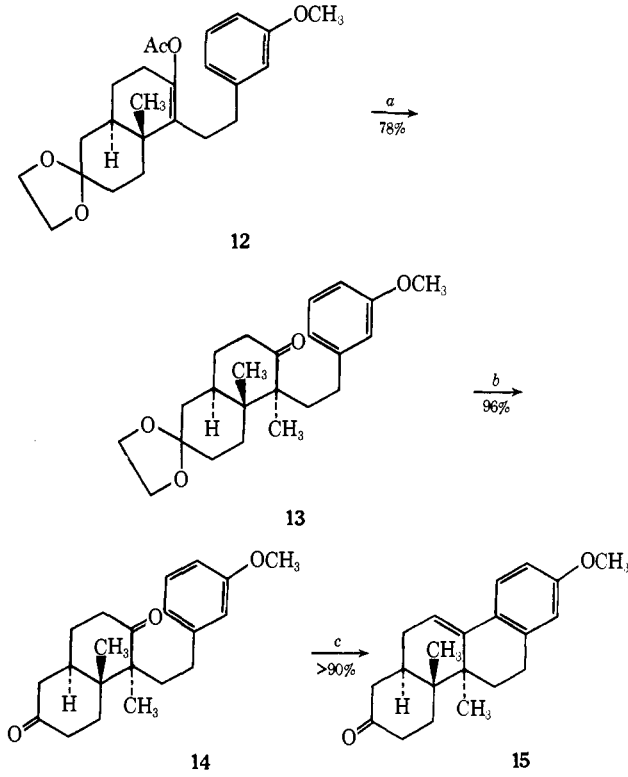
interesting facts emerged from this study, the results of which are presented in Table I (see Experimental Section). The propensity of the α-methylene ketone system to undergo conjugate addition in preference to carbonyl addition is apparent from those cases (runs 3, 5, 7, and 9) in which the catalytic effect of added copper salts is absent. Such is, of course, not the general result from the reaction between an α,β-unsaturated ketone and an organolithium or magnesium derivative,[12] and must be attributed to the structure of the substrate enone used here. Interestingly, even the organolithium reagents (3 and 5) gave significant amounts of conjugate addition products in the absence of added copper salts, although the organomagnesium reagents (7 and 9) resulted in higher yields of these products under similar conditions. Indeed, the desired preparative result (73% yield of the enol acetate **12**) was best obtained by utilization of *m*-methoxybenzylmagnesium chloride *without* the addition of copper salts (**9**).

Another result of this study was the observation that the generation of *m*-methoxybenzyllithium from the triphenyltin derivative[13] is *not* a quantitative process in spite of the precipitation of tetraphenyltin from the reaction mixture (1, 2, and 3). Even when the ratio of phenyllithium to *m*-methoxybenzyltriphenyltin was significantly less than one to one (2, 3) a large portion of the product was represented by the conjugate addition of the phenyl residue. This result implies either random cleavage of the initial *m*-methoxybenzyltriphenyltin reagent or, more likely, an equilibrium between *m*-methoxybenzyllithium, phenyllithium, and the respective tin derivatives. This was unexpected in view of the reported[13] and observed insolubility of tetraphenyltin in the reaction medium, and the observation rendered the generation of *m*-methoxybenzyllithium in this manner useless for preparative purposes.

Another interesting facet of these experiences was the observation that the most effective way to isolate and purify these conjugate addition reaction products was through O-acetylation of the enolate anions generated. When the reaction mixture was quenched with either aqueous ammonium chloride or methyl iodide, the ketonic components of the mixture (products and starting material) were virtually impossible to separate in pure form; as their enol acetates the products of conjugate addition were readily separated by chromatography of silica gel from the other reaction products. Since such enol acetates are ideal intermediates for the subsequent synthetic operations that were planned, the requirement that they be formed in this reaction was in no way a handicap.

Thus the conversion of the enol acetate **12** (Scheme II) to the desired dicyclic ketone ketal **13** was effected in 78% yield by methylation according to the procedure of House.[7] That the newly introduced methyl group was in the required α (axial) orientation was evident from the shift of the nmr signal of this methyl group from 78 Hz in deuteriochloroform to 60 Hz in benzene—a shift[14] due to the benzene collision complex of +18 Hz.

Scheme II. Conversion of α-Methylene Ketone **11** to Tetracyclic Ketone **15**



[a] CH_3Li, DME; CH_3I. [b] H_3O^+. [c] PPA, 60°.

Satisfactory completion of this phase of the model study was stymied only briefly by the fact that the ketal function of the ketone ketal **13** not only did not survive the polyphosphoric acid cyclodehydration conditions,[15] but also was responsible for the formation of a complex mixture of products. The problem was readily overcome by hydrolysis of the ketal prior to cyclization, whereupon the diketone **14** readily cyclized to the desired tetracyclic ketone **15** on mild polyphosphoric acid treatment. This sequence developed for the conversion of ketone ketal **8** through the α-methylene ketone **11** to the anti vicinally dimethylated tetracyclic ketone **15** is quite efficient (21% overall yield in seven steps) and has proved useful in the synthesis of *dl*-germanicol,[16] a member of the β-amyrin (**1**) type pentacyclic triterpenes.

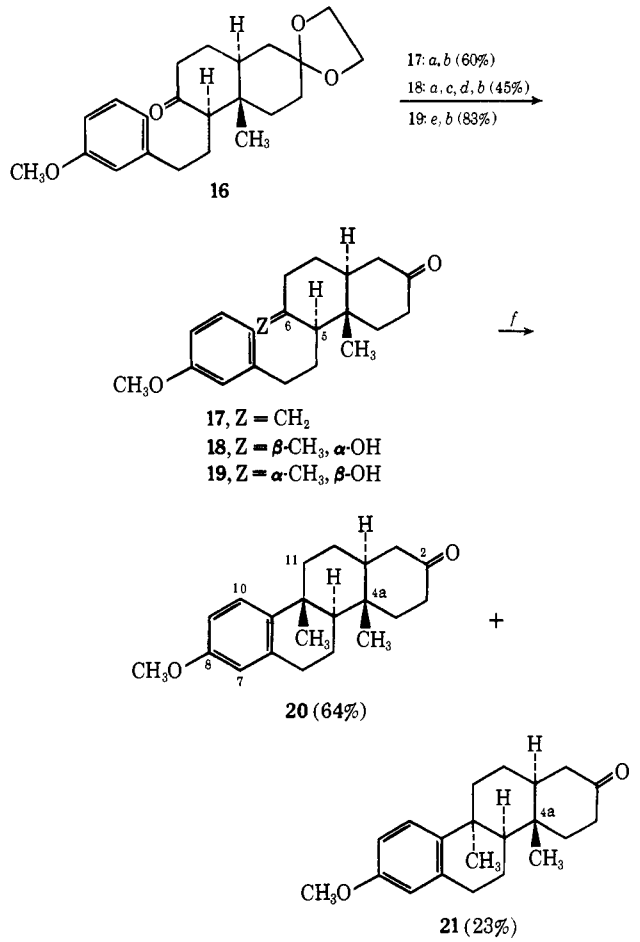
The enol acetate **13** also served as the precursor for systems with which to investigate the stereochemical outcome of the cyclialkylation of the anisole ring, and hence the formation of the tetracyclic ketone **20**, a model for the friedelin (**2**) type syntheses. Saponification of the enol acetate **13** afforded the ketone ketal **16** in 95% yield; the 69% overall yield of this ketone ketal **16** from the α-methylene ketone **11** by this two-step procedure was significantly better than that available from direct protolysis of the conjugate addition reaction mixture.

In order to ascertain whether the stereochemical result of the cyclialkylation reaction was in any way a

(12) H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 2138 (1966).
(13) H. Gilman and S. Rosenberg, *ibid.*, 24, 2063 (1959).
(14) N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 159–176; P. C. Cherry, W. R. T. Cottrel, G. D. Meakins, and E. E. Richards, *J. Chem. Soc.*, 181 (1967); J. Ronayne and D. H. Williams, *Chem. Commun.*, 712 (1966).
(15) G. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. J. McLoughlin, J. Siddall, and H. Smith, *J. Chem. Soc.*, 5072 (1963).
(16) R. E. Ireland, S. W. Baldwin, D. J. Dawson, M. I. Dawson, J. E. Dolfini, J. Newbold, W. S. Johnson, M. Brown, R. J. Crawford, P. F. Hudrlik, G. H. Rasmussen, and K. K. Schmiegel, *J. Amer. Chem. Soc.*, **92**, 5743 (1970).

function of the stereochemistry or character of the precursor to the intermediate C-6 cationic center required for cyclialkylation, the ketone ketal **16** was converted (Scheme III) into the olefin **17** and the isomeric alcohols

Scheme III. Conversion of α-Methylene Ketone **11** to Tetracyclic Ketone **20**



[a] $(C_6H_5)_3PCH_2$. [b] HO^+. [c] *m*-$ClC_6H_4CO_3H$, CH_2Cl_2. [d] $LiAlH_4$, Et_2O. [e] CH_3Li, Et_2O. [f] PPA, 60°.

18 and **19**. The results of the cyclization of these substances in polyphosphoric acid bear out the recorded[17] insensitivity of the product stereochemistry to that of the precursor, for in each instance two tetracyclic products were formed in high yield and in the same 3:1 ratio (determined from the crude product by nmr analysis as well as on isolation by chromatography).

A priori this cycliaklylation reaction might lead to the production of the four tetracyclic ketones which are isomeric about the carbons of the B/C ring fusion. The highly strained trans-syn-trans isomer, however, may be excluded at the outset, since the ring C boat cation necessary for its production must certainly be of higher energy than other likely intermediates. Of the remaining three possible stereoisomers, the cis-anti-trans structure **21** was assigned to the minor component of the product mixture after inspection of the nmr spectrum. The 1,3-diaxial relationship between the aromatic ring and the C-4a methyl group in this B/C cis structure[18] was manifest in the shielding of this methyl group, and the signal for these protons appeared at 27 Hz.

The major product of the cyclization must then have either the trans-anti-trans or the cis-syn-trans structure. The trans fused D ring in both possible stereoisomers assures a rigid conformation for each isomer and thereby provides a means for the distinction between the two on the basis of the nmr chemical shift difference between the aromatic C-10 and C-7 protons ($\Delta\delta_{10,7}$). Nagata[19] has shown that the steric compression between the equatorial C-11 proton and the aromatic C-10 proton of the trans-anti-trans isomer (type A)[19] results in a marked deshielding of this proton that is not present in a rigid cis-syn-trans structure (type C)[19] where the protons are too far apart to interact. Using the chemical shift of the unaffected C-7 aromatic proton as a reference, Nagata showed that in the nmr spectra of type A structures the value of $\Delta\delta_{10,7}$ was 0.60 ppm and in the spectra of type C compounds the lack of steric compression results in a $\Delta\delta_{10,7}$ value of 0.39 ppm. The spectrum of the major component from these cyclization experiments showed an aromatic pattern in which the C-10 proton was centered at δ 7.19 ppm and the C-7 proton at δ 6.60 ppm—a $\Delta\delta_{10,7}$ of 0.59 ppm, which agrees well with that expected for the trans-anti-trans (type A)[19] structure **20**. Thus, of the three reasonable stereoisomers that might result from this cyclization, the product mixture is made up entirely of the two shown, and there is no evidence for the formation of the cis-syn-trans isomer. Moreover, the desired trans-anti-trans tetracyclic ketone **20** is the major product from the cyclization reaction and is available in 53% yield from the dicyclic ketone ketal **16** in two steps through the alcohol **19**. The information gained in this model study was used in designing a successful synthesis of the diether **4** and thence *dl*-alnusenone,[20] a friedelin (**3**) type pentacyclic triterpene.

Mechanism of Cyclialkylation Reaction

The stereochemical result of this cyclialkylation study is particularly interesting in view of the concepts[5] previously developed to explain the observations made on the formation of octahydrophenanthrene derivatives by a similar process. The extensive work of Barnes[21] and others[22] on the mechanism of this acid-catalyzed reaction led to the conclusion that in a kinetically controlled process (mild acid conditions) the predominant formation of cis-fused isomers will result in cases that involve an activated aromatic nucleus and generate an octahydrophenthanthrene with an angular methyl group. This is exactly the situation that pertains in the system studied here, and yet the major product is the trans-fused isomer. This apparent dichotomy between these two series actually provides the key to the stereochemical nuances of such cyclialkylation reactions, and with the aid of some recently developed concepts a new, compatible explanation of the observed results is possible.

In the formation, for example, of an octahydrophenanthrene structure from the cationic intermediate **22**,[23]

(17) Numerous studies cited by Barclay,[5b] including that of Barnes[21] and Ireland,[29] bear this out.

(18) R. E. Ireland, P. S. Grand, R. E. Dickerson, J. Bordner, and D. R. Rydjeski, *J. Org. Chem.*, **35**, 570 (1970); B. L. Shapiro, M. J. Gattuso, N. F. Hepfinger, R. H. Shone, and W. L. White, *Tetrahedron Lett.*, 219 (1971).

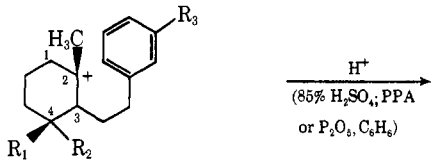
(19) W. Nagata, T. Teresawa, and K. Tori, *J. Amer. Chem. Soc.*, **86**, 3742 (1964).

(20) R. E. Ireland and S. C. Welch, *ibid.*, **92**, 7232 (1970).

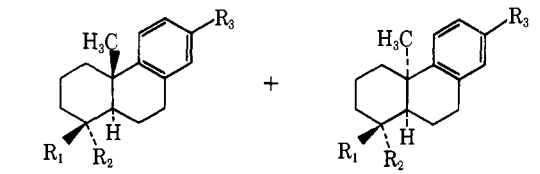
(21) R. A. Barnes, *ibid.*, **75**, 3004 (1953).

(22) W. E. Parham, E. L. Wheeler, and R. M. Dodson, *ibid.*, 77, 1166 (1955); E. Wenkert and B. G Jackson, *ibid.*, **80**, 211 (1958).

which may be formed by acid treatment of a structurally similar system with a hydroxyl function of C-3,[24] the trans (**23**) and/or cis (**24**) isomers may result. Since the initial stereochemistry of the side chain at C-3 will have no bearing[24] on that of the product formed in this flexible system, and the transition state geometry of the kinetically controlled process will resemble that of the cation **22**,[23] only the three interconvertible chair conformations $\mathbf{A}^{\ddagger}_{eq}$, $\mathbf{E}^{\ddagger}_{eq}$, and $\mathbf{A}^{\ddagger}_{ax}$[25] need be considered

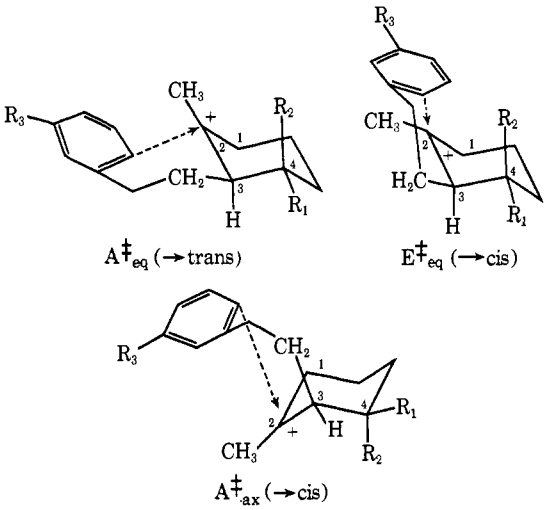


22, $R_1, R_2, R_3 = H$
25, $R_1, R_2 = CH_3$; $R_3 = OCH_3$
28, $R_1 = CH_3$; $R_2 = CO_2CH_3$; $R_3 = H$



23, $R_1, R_2, R_3 = H$ (<20%)
24, $R_1, R_2, R_3 = H$ (>76%)
26, $R_1, R_2 = CH_2$; $R_3 = OCH_3$ (24%)
27, $R_1, R_2 = CH_3$; $R_3 = OCH_3$ (>60%)
29, $R_1 = CO_2H$; $R_2 = CH_3$; $R_3 = H$ (30%)
30, $R_1 = CH_3$; $R_2 = CO_2H$; $R_3 = H$ (~30%)

for this transition state. The $A_{1,2}$ strain[26] between the C-2 methyl group and the C-3 side chain in conformations $\mathbf{A}^{\ddagger}_{eq}$ and $\mathbf{E}^{\ddagger}_{eq}$ will result in a higher energy for these forms than that of conformation $\mathbf{A}^{\ddagger}_{ax}$ with an axial C-3 side chain. In this case which lacks any substituents at C-4 the Felkin principle[27] suggests that the energy barrier to cyclization will be minimal through the transition state that resembles conformation $\mathbf{E}^{\ddagger}_{eq}$, which experiences only small steric strain between the entering aromatic ring and the axial hydrogens at C-4 and C-6. In the transition states that resemble $\mathbf{A}^{\ddagger}_{eq}$ and $\mathbf{A}^{\ddagger}_{ax}$ the torsional strain associated with cyclization should be similar,[28] and the lower energy of conformation $\mathbf{A}^{\ddagger}_{ax}$ suggests that the preferred path will be through the transition state that resembles this conformation. The stereochemistry of the product that results from the cyclization of the cation **22**[23] will be predominately the consequence of reaction paths that use transition states that resemble conformations $\mathbf{A}^{\ddagger}_{ax}$ and $\mathbf{E}^{\ddagger}_{eq}$ and will thus be predominately the cis isomer **24**. The experimental evidence[24] is in accord with this analysis.



In the case of the carbonium ion **25**[23] which may be generated by acid treatment of the system with a hydroxyl group at C-1[29] or C-3,[30] the addition of the gem-dimethyl groups at C-4 will raise the energy of the conformation $\mathbf{E}^{\ddagger}_{eq}$ significantly as a result of the added nonbonded interaction between the C-3 side chain and the methyl group at R_2. In addition the Felkin principle[27] suggests that the steric strain associated with cyclization through the transition state that resembles this conformation $\mathbf{E}^{\ddagger}_{eq}$ will be large, and, therefore, it may be dropped from consideration in this instance.

The energy difference between conformations $\mathbf{A}^{\ddagger}_{eq}$ and $\mathbf{A}^{\ddagger}_{ax}$ will again slightly favor conformation $\mathbf{A}^{\ddagger}_{ax}$ in spite of the two axial substituents present, due to the lack of the $A_{1,2}$ strain[26] that is part of conformation $\mathbf{A}^{\ddagger}_{eq}$ with only one less axial substituent. Since again the torsional strain associated with the cyclization reaction through transition states that resemble conformations $\mathbf{A}^{\ddagger}_{eq}$ and $\mathbf{A}^{\ddagger}_{ax}$ will be comparable,[28] the lower energy path to products will be through the transition state similar to conformation $\mathbf{A}^{\ddagger}_{ax}$, and the predominant product will be the cis isomer **27**. Again this analysis is in accord with the experimental findings.[29,30]

This type of analysis may also be used to explain the stereochemistry of the products formed on cyclization of cation **28**,[23] which may in principle lead to four racemates due to the asymmetry at C-4. This asymmetry also means that in the generation of the cation **28**[23] from a precursor with a hydroxyl group at C-2[31] or C-3[32] or from the equivalent C-2(3) olefin,[31,33] the stereochemical result of the proton addition to C-3 *will*

(23) The graphic simplicity of the carbonium ion representation for the positively charged reaction intermediate in these cyclialkylations does not imply that hydrogen bridged ions, solvated ions or the like may not be involved. It is implied that any such intermediate will have similar reactivity and steric properties.

(24) R. A. Barnes and R. T. Gottesman, *J. Amer. Chem. Soc.*, 74, 35 (1952); Barnes[21] also found that both 2-β-(2′,5′-dimethoxyphenyl)-ethyl-1-methylcyclohexanol and 1-β-(2′,5′-dimethoxyphenyl)-ethyl-2-methylcyclohexanol afforded the same cis-fused octahydrophenanthrene on cyclization in warm polyphosphoric acid in yields of 81 and 57%, respectively, and concluded that the location of the hydroxyl group in the reactant was not an important factor in the determination of the stereochemistry of the octahydrophenanthrene formed.

(25) This nomenclature was introduced by Felkin[27] and describes the transition state for reaction at a ketonic carbonyl in terms of the stereochemistry of the product that results. The mechanistic similarity between that process and the one discussed here suggests the adoption of the same form here.

(26) S. K. Malhotra and F. Johnson, *J. Amer. Chem. Soc.*, 87, 5492, 5493 (1965).

(27) M. Chérest and H. Felkin, *Tetrahedron Lett.*, 2205 (1968).

(28) Torsional strain is known to be relatively insensitive to the bulk of the groups involved; the rotational barrier of propene, for example, is barely larger than that of ethane: J. Dale, *Tetrahedron*, 22, 3373 (1966).

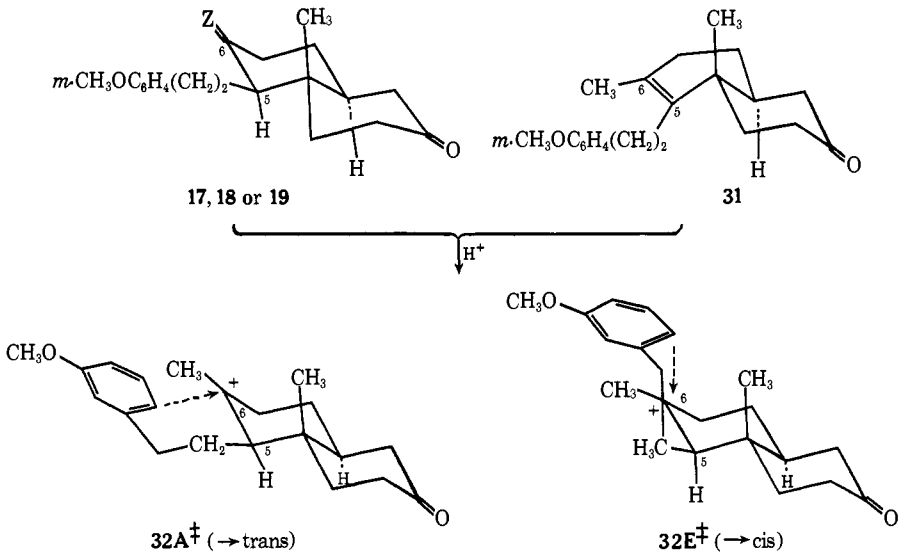
(29) R. F. Church, R. E. Ireland, and J. A. Marshall, *Tetrahedron Lett.*, No. 17, 1 (1960).

(30) J. A. Barltrop and N. A. J. Rogers, *J. Chem. Soc.*, 2566 (1958); repetition of the cyclization of this alcohol in these laboratories (R. A. Partyka, unpublished work) under the reported conditions afforded the trans-fused octahydrophenanthrene in 24% yield and the cis-fused isomer as an ion in >60% yield.

(31) U. R. Ghatak, D. K. Datta, and S. C. Ray, *J. Amer. Chem. Soc.*, 82, 1728 (1960).

(32) R. A. Barnes, unpublished work quoted by Barclay;[5] see also F. E. King, T. J. King, and J. G. Topliss, *Chem. Ind. (London)*, 118 (1956).

(33) R. D. Haworth and B. P. Moore, *J. Chem. Soc.*, 633 (1946).



have a bearing on that of the cyclization process. While the cyclohexane portion of the system is still flexible, cation conformation $A^{\mp}_{ax}$ is no longer merely the flip form of conformations $A^{\mp}_{eq}$ and $E^{\mp}_{eq}$ but a stereoisomer in which the C-3 proton has been added cis to the carbomethoxyl group (R_2) rather than trans. Since the ratio of cyclization products is invariant regardless of which precursor is used for the generation of the cation **28**,[23] proton addition and elimination must be a rapid preequilbrium to the cyclialkylation, and therefore the two C-3 α and β protonated cations must be considered. In spite of this the product determining conformations of these two cations will still be the ones shown above, since it is only in these forms that the C-4 carbomethoxyl group (R_2) is axial and capable of stabilizing the developing positive charge at C-2 through π-bonding (incipient lactone formation). The three other conformational forms that result from the flip of the cyclohexane ring will have the carbomethoxyl group (R_2) equatorially oriented so that interaction with the C-2 positive charge will be sterically impossible. These forms will be of higher energy *per se*. Thus, while it is expected that any reaction path that entails the addition of a proton to C-3 will take place so as to generate initially that conformation of the cation **28**[23] with an axial[34] hydrogen at C-3, in the situation where this protonation takes place cis to the C-4 carbomethoxyl group, the resulting conformer with this group equatorial will flip to the more stable conformer $A^{\mp}_{ax}$. This conformer only appears to be the result of equatorial protonation.

The stabilization of the charge at C-2 in the cation **28**[23] by incipient lactone formation with the C-4 carbomethoxyl group will necessitate attack at C-2 by the aromatic ring from the side opposite the carbomethoxyl group. This, together with the obvious high steric strain[27] that will prohibit reaction through the transition state that resembles conformation $E^{\mp}_{eq}$, means that cyclization will proceed through the transition states most closely represented by conformations $A^{\mp}_{eq}$ and $A^{\mp}_{ax}$. The only cyclization products predicted by this analysis are the acids **29** and **30**, and these are indeed just the isomers observed[31-33] experimentally.

(34) J. Volls and E. Toromanoff, *Bull. Soc. Chim. Fr.*, 758 (1961).

Under what appears to be a thermodynamically controlled process ($AlCl_3$, HCl) dehydroabietic acid is transformed[32] into the same cis acid **30** by a cleavage–recyclization process that is attended by deisopropylation. This result is not inconsistent with the above analysis of the kinetically controlled cyclization, but merely implies that in this series the cis-fused isomer **30** has the lower energy and will be formed under equilibrium conditions.

The foregoing analysis of the stereochemical results observed in the formation of octahydrophenanthrenes from the cations[23] **22**, **25**, and **28** also adequately accommodates the observations made in the present work on dodecahydrochrysene formation by cationic cyclization of the dicyclic precursors **17**, **18**, and **19**. In this case, however, the addition of the second trans-fused saturated ring restricts both the structures and conformations available to the intermediate cation and results in a significantly different stereochemical outcome. Consistent with the observations[21] made in the octahydrophenanthrene series, the stereochemistry of the products formed in the dodecahydrochrysene series is independent of the nature of the precursor of the product determining cationic intermediate. Therefore, the stereochemistry present in the alcohols **17** and **18** at C-6 must be lost on generation of a cation by acid treatment and lead to the same intermediate available from the olefin **19** under similar conditions.[35] Unless deprotonation regenerates a mixture of olefinic starting materials that contains the olefin **31** at a rate commensurate with cyclization, the intermediate cation involved will have the structure **32**.[23] Generation of this cation will preserve the more stable equatorial (β) orientation of the C-5 side chain that exists in the precursors, since this C-5 asymmetric center will remain undisturbed during this process.

If the tetrasubstituted olefin **31** is regenerated by deprotonation of the cation **32**, reprotonation of the double bond will occur readily in this reaction medium and take place in an antiparallel[34] manner at C-5 in a trans relationship to the adjacent axial angular methyl group.

(35) A similar result is observed on conversion of 3α- and 3β-methylcholestanol and 3-methyl-2-cholestene to 3α-methyl-3β-chlorocholestane with hydrochloric acid; D. H. R. Barton, A. da S. Campos-Neves, and R. C. Cookson, *J. Chem. Soc.*, 3500 (1956).

The alternative parallel[34] protonation at this center will be a much higher energy process due to the steric hindrance of the then cis-angular methyl group and the attendant initial formation[34] of a twist-boat conformation of the cationic ring. The absence of any products from this cyclization reaction with a trans-syn-cis or trans-syn-trans backbone implies that should the olefin **31** exist in the reaction mixture, the energy barrier to parallel[34] (equatorial, β) protonation is higher than that for antiparallel[34] (axial, α) protonation *and* subsequent cyclization of the cation.

This same relationship between parallel and antiparallel attack of cyclohexene systems by electrophiles of numerous different types is a general observation,[34] and in the absence of specific steric effects, the antiparallel[34] process is expected to prevail. Therefore, even if the olefin **31** is generated during the reaction by proton loss from the initially formed cation **32**,[23] the same cation will be regenerated by protonation, and the mode of cyclization of this species will determine the stereochemistry of the observed products.

The trans fusion of the present dicyclic system also excludes conformational interchanges such as were possible in the flexible cyclohexane series. Without invoking high energy boat conformations, it is not possible for the present dicyclic cationic intermediate to adopt a conformation similar to the $\mathbf{A}^{\mp}_{ax}$ one available to cations[23] **22**, **25**, and **28**. Therefore, the transition state for cyclization will resemble conformations $\mathbf{32A}^{\mp}$ and/or $\mathbf{32E}^{\mp}$, and the ratio of B/C trans to cis-fused products will reflect the energetics associated with each. The lower energy path to products from these two conformations will be that through the transition state that resembles conformation $\mathbf{32A}^{\mp}$ since the steric strain[27] associated with transition through conformation $\mathbf{32E}^{\mp}$ will be greater than the torsional strain[27] associated with the cyclization through the conformation related to $\mathbf{32A}^{\mp}$. As a result the stereochemistry of the tetracyclic products will reflect this propensity for conformation $\mathbf{32A}^{\mp}$ in the transition state, and the composition of the product mixture will favor the trans-fused B/C isomer. The fact that the experimental observations show that the ratio of products formed is indeed 3:1 in favor of the trans-anti-trans tetracyclic ketone **20** is satisfying justification of the applicability of these principles[26,27,34] to such problems.

The foregoing analysis should prove useful for prediction of the stereochemical outcome of other Friedel–Crafts cyclialkylation reactions as well as related cationic cyclization processes. The validity of this point as it relates to aliphatic polyene cyclizations is under investigation.

Experimental Section[36]

4′,4′a,6′,7′,8′,8′aα-Hexahydro-4′aβ-methylspiro[1,3-dioxolane-2,2′(1′*H*)-naphthalen]-5′(3′*H*)-one (8). A stirred solution of 79.4 g (0.44 mol) of the keto alcohol **7**,[37] 150 ml of ethylene glycol, and 1.0 g of *p*-toluenesulfonic acid in 2.5 l. of benzene was heated at reflux under a nitrogen atmosphere for 3 hr. After cooling, the mixture was washed with water and saturated aqueous sodium bicarbonate solution and dried (Na_2SO_4). Removal of the benzene at reduced pressure afforded 99.1 g of crude ketal alcohol. This material was dissolved in 1 l. of reagent acetone, cooled to 0°, and treated with 122 ml of Jones' reagent[38] (2 equiv), while the temperature was maintained below 3° with cooling. After dilution with 200 ml of water and removal of the bulk of the acetone on a rotary evaporator, the aqueous mixture was extracted with ether. The ethereal solution was washed with water and saturated brine and then dried ($MgSO_4$). After removal of the drying agent and then evaporation of the ether at reduced pressure, there remained 83.6 g (86%) of the ketal ketone **8**, mp 45–47° (lit.[10] mp 47–48°).

3′,4′,4′a,7′,8′,8′aα-Hexadyro-4′aβ,5′-dimethylspiro[1,3-dioxolane-2,2′(1′*H*)-naphthalene] (9). A solution of 98.7 g (0.44 mole) of ketal ketone **8** in 1 l. of dry ether under a nitrogen atmosphere was cooled to 0°, and then 400 ml of 2 *M* ethereal methyllithium (0.8 mol) was added dropwise with stirring. The resulting solution was stirred at room temperature for 1 hr, and then treated with saturated aqueous ammonium chloride solution. The ethereal layer was separated, washed with water and saturated brine, and then dried ($MgSO_4$). After filtration to remove the drying agent and evaporation of the ether at reduced pressure, there was obtained 100.8 g (95%) of the crude tertiary alcohol.

To a melt of 99.9 g (0.41 mol) of this crude material maintained at 140°[10] was added 1.9 g of iodine in three portions over a 1-hr period. The dark reaction mixture was cooled, diluted with ether, washed with 10% aqueous sodium thiosulfate, and then dried ($MgSO_4$). After removal of the drying agent, evaporation of the ether at reduced pressure left 94.0 g of crude olefin **9**, which on distillation afforded 69.0 g (70%) of a clear oil that boiled at 99–100° (0.35 mm). A small sample was evaporatively distilled (90–95° at 0.04 mm) for analytical purposes: ir ($CHCl_3$) 1375 (CH_3) and 1130–1050 cm^{-1} (ketal); nmr ($CDCl_3$) δ 1.02 (s, 3, C-4′aβ CH_3), 1.65 (d, 3, J = 2 Hz C-5′ CH_3), 3.94 (s, 4, $-OCH_2CH_2O-$), and 8.59 (m, 1, C-6′ vinyl H).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 76.22; H, 9.74. Found: C, 76.04; H, 9.76.

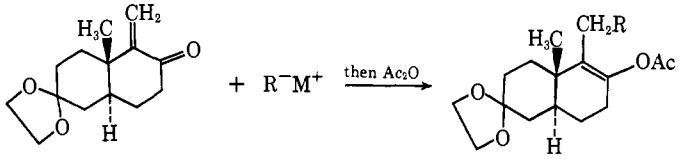
3′,4′,4′a,6′,7′,8′,8′aα-Heptahydro-6′-hydroxy-4′aβ-methyl-5-methylenespiro[1,3-dioxolane-2,2′(1′*H*)-naphthalene] (10). After the procedure of Wharton,[9] a solution of 15.0 g (67.5 mmol) of the olefin **9**, bp 99–100° (0.35 mm), and 3.0 g of rose bengal in 200 ml of isopropyl alcohol was placed in an immersion-type photoreaction vessel with a stream of oxygen bubbling through the solution from a glass frit in the bottom. Irradiation with a Hanovia 450-W medium-pressure light source through a Pyrex filter sleeve was carried out over a 7-hr period. The solvent was removed on a rotary evaporator, 500 ml of ether was added, and the solution was treated with excess $LiAlH_4$. After this mixture was stirred for 6 hr, it was treated with saturated aqueous ammonium sulfate solution and stirred for 2 hr. Filtration and concentration of this ethereal solution afforded 16.5 g of a yellow oil that was chromatographed on 300 g of Florisil. Elution with 2 l. of 15% ether–petroleum ether separated residual starting material and other low-boiling components. Further elution with 3 l. of 60% ether–petroleum ether afforded 11.8 g (72%) of solid material that consisted of a 1:10 mixture of the epimeric alcohols of the hydroxyl ketal **9**. Two crystallizations of a sample of this mixture from ether–*n*-hexane afforded white needles of the pure 6′α-hydroxy derivative which melted at 93–94.5°: ir ($CHCl_3$) 3600, 3450 (OH), 1640 (C=C), and 1130–1050 cm^{-1} (ketal); nmr ($CDCl_3$) δ 0.99 (s, 3, C-4′aβ CH_3), 3.94 (s, 4, $-OCH_2CH_2O-$, 4.33 (m, 1, C-6′, H), and 4.78, 5.07 (m, 1, C=C H_2).

(36) All melting points were determined on a Kofler hot state and are uncorrected. All boiling points are uncorrected. Infrared spectra (ir) were taken on a Perkin-Elmer infrared spectrometer, Model 237B, and ultraviolet spectra (uv) were taken on a Cary recording spectrometer, Model 11M. Nuclear magnetic resonance (nmr) spectra were taken on a Varian Associates Model A60-A or F60. All gas chromatographic analyses (vpc) were carried out on an F&M Model 810 gas chromatograph which was equipped with a 6 ft × 1/8 in. column packed with 3% silicon gum rubber (SE30) on Chromosorb Q (NAW), 60–80 mesh. The carrier gas (helium) was maintained at 60 ml/min. Preparative thin layer chromatography (ptlc) was performed on 20 cm × 20 cm plates coated with a 1-mm layer of silica gel $PF_{254+366}$ (Brinkman Instruments Co.). Anhydrous solvents were dried immediately prior to use. Ether, benzene, tetrahydrofuran (THF), and dimethoxyethane (DME) were distilled from lithium aluminum hydride; *tert*-butyl alcohol was distilled from calcium hydride; pyridine was stored over barium oxide and distilled from calcium hydride. Petroleum ether, unless otherwise noted, refers to that hydrocarbon fraction boiling in the range 30–60° that is supplied by J. T. Baker Co., Phillipsburg, N. J., and labeled "Analyzed Reagent." All microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(37) A. J. Birch, E. Pride, and H. Smith, *J. Chem. Soc.*, 4688 (1958).

(38) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *ibid.*, **39** (1946); see also C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

Table I. Reactions of Organometallic Reagents with α-Methylene Ketone **11**



A. Organolithium Reagents: m-$CH_3OC_6H_4CH_2Sn(C_6H_5)_3 + C_6H_5Li \rightleftharpoons m$-$CH_3OC_6H_4CH_2Li + (C_6H_5)_4Sn$

	11, mmol	Sn reag, mmol	C_6H_5Li, mmol	CuI, mmol	Total solvent vol, ml[a]	T, C_6H_5Li (T, CuI–**11**) addn, °C	Isolated yield, %[b] 1,4-Benzyl addn	Isolated yield, %[b] 1,4-Phenyl addn
1	0.85	2.57	2.09	1.28	57	−30 (−20)	51	25
2	0.84	3.40	2.54	1.27	75	0 (0)	31	50
3	0.40	1.20	0.82	0.0	30	−35 (−20)	36	12
4	0.85	0.0	2.47	1.27	40	−20 (−20)		89
5	0.85	0.0	1.70	0.0	48	−15		32

B. Organomagnesium Reagents: $RCH_2Cl + Mg \rightarrow RCH_2MgCl$

	11, mmol	RCH_2Cl, mmol	Mg, mmol	$Cu(OHc)_2 \cdot 2H_2O$, mmol	Total solvent vol, ml[a]	T, ketone addn, °C	Isolated yield 1,4 adduct, %[b]
6	0.85	4.25[c]	5.10	0.26	26	0	71
7	0.85	4.25[c]	5.10	0.0	25	0	71
8	0.85	4.25[d]	5.10	0.26	23	0	68
9	1.70	8.50[d]	10.20	0.0	40	0	73

[a] The solvent in every case was anhydrous ether; anhydrous dimethoxyethane showed no advantage and anhydrous THF completely inhibited 1,4 addition, [b] 1,2 adduct and/or recovered ketone **11** accounted for the remainder of the product. [c] Benzyl chloride. [d] m-Methoxybenzyl chloride.

Anal. Calcd for $C_{14}H_{18}O_3$: C, 70.53; H, 9.30. Found: C, 70.40; H, 9.22.

3′,4′,4′a,7′,8′,8′a-Hexahydro-4′aβ-methyl-5′-methylenespiro-[1,3-dioxolane-2,2′(1′*H*)-naphthalen]-6′(5′*H*)-one (11). To a solution of 46.4 g (0.18 mol) of Collins reagent[39] in 1 l. of dry dichloromethane was added over a 5-min period with efficient stirring a solution of 6.98 g (0.029 mol) of the alcohol mixture **10** in 125 ml of dry dichloromethane. The dark reaction mixture was allowed to stir an additional 10 min at 23° and then filtered through 277 g of neutral alumina (Woelm, Activity I). The alumina was washed with dichloromethane (ten 100-ml portions), and then evaporation of the combined dichloromethane fractions at reduced pressure afforded 5.8 g (84%) of the α-methylene ketone **11**, mp 89–91°. The analytical sample, obtained after crystallization from ether, melted at 94–69°: ir ($CHCl_3$) 1685 (>C=O), 1610 (>C=C<), and 1130–1050 cm^{-1} (ketal); nmr ($CDCl_3$) δ 0.95 (s, 3, C-4′aβ CH_3), 3.96 (s, 4, $-OCH_2CH_2O-$), 5.12 (d, 1, J = 1.5 Hz, >C=CH), and 5.68 (d, 1, J = 1.5 Hz, >C=CH).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 71.16; H, 8.53. Found: C, 71.22; H, 8.51.

***m*-Methoxybenzyltriphenyltin.** A solution of 5.0 g (12.9 mmol) of triphenyltin chloride and 3.15 g (20.2 mmol) of m-methoxybenzyl chloride in 15 ml of dry THF was slowly added to a stirred, vigorously refluxing (bath 61°) suspension of 1.0 g (41 mg-atoms) of magnesium turnings in 20 ml of dry ether under a nitrogen atmosphere. When the addition was completed (0.5 hr), 10 ml of dry benzene was added, and the reaction mixture was heated at reflux for 10.5 hr. The reaction mixture was then cooled and treated with 3 ml of saturated brine solution and finally dried ($MgSO_4$). After removal of the drying agent and evaporation of the solvents at reduced pressure, there remained a clear oil that deposited 5.75 g (94%) of a white solid, mp 57–59°, on trituration with cold petroleum ether. Recrystallization of this material from petroleum ether gave 5.41 g (88%) of m-methoxybenzyltriphenyltin as white cubes, mp 60–61°. A further recrystallization of a sample from n-hexane afforded material for analysis: mp 61–61.5°; nmr ($CDCl_3$), δ 2.92 (s, 2, $-CH_2-$), 3.48 (s, 3, OCH_3), and 6.4–7.8 (m, 19, Ar H).

Anal. Calcd for $C_{26}H_{24}OSn$: C, 66.28; H, 5.14; Sn, 25.19. Found: C, 66.11; H, 5.19; Sn, 25.07.

General Procedure for the Reaction of Lithium Organocopper and Organolithium Derivatives with the Methylene Ketone 11. m-Methoxybenzyllithium was prepared from the corresponding triphenyltin compound by reaction with phenyllithium.[13] A 100-ml three-neck flask (flask A) was fitted with a serum cap and a nitrogen inlet. A piece of glass tubing (5-mm o.d.) passing through a rubber stopper was placed so that the end of the tube came to within 5 mm of the bottom of flask A. Several glass wool plugs were placed in the tube to filter out the solid tetraphenyltin formed. The other end of the tube passed through a stopcock and another rubber stopper into a second 100-ml three-neck flask (flask B) similarly equipped with a serum cap and nitrogen inlet. The desired amount of m-methoxybenzyltriphenyltin in 75% of the total solvent volume indicated in Table I was placed in flask A and cooled to the desired temperature. The calculated amount of a standardized solution of phenyllithium in benzene was added by syringe to flask A. Within 2 min a heavy white precipitate of tetraphenyltin formed. After 0.5 hr at the indicated temperature, the bright yellow supernatant liquid was forced through the connecting tube by a positive nitrogen pressure into flask B. The residual solution in flask A was washed into flask B with one portion of 10% of the total solvent volume. Flask B was brought to the desired temperature, and if required (Table I) a weighed amount of solid copper(I) iodide was added. After 0.5 hr the methylene ketone **11** in the remaining 15% of the solvent was added by syringe, and the solution was kept at the indicated temperature for 1 hr before it was quenched with acetic anhydride. Isolation of the products was accomplished after the addition of water. The organic layer was separated, washed with water and then saturated brine solution, and then dried ($MgSO_4$). After removal of the drying agent and evaporation of the solvents, the crude product was purified by ptlc.

3′,4′,4′a,7′,8′,8′aα-Hexahydro-5′-(2′-*m*-methoxyphenylethyl)-4′aβ-methylspiro[1,3-dioxolane-2,2′(1′*H*)-naphthalene] (12). A. **From Organolithium Reagent (Table I, Part A).** A solution of m-methoxybenzyllithium from 1.21 g (2.57 mmol) of m-methoxybenzyltriphenyltin and 2.09 mmol of phenyllithium in 36 ml of ether was prepared and transferred to flask B as described above (8 ml of ether for wash). Then 242 mg (1.28 mmol) of solid copper(I) iodide was added at −20°, and the solution was stirred for 0.5 hr. A solution of 200 mg (0.85 mmol) of the methylene ketone **11** in 7 ml of dry ether was then added by syringe. After 0.9 hr at −20 to −15°, the solution was brought to reflux and quenched with 4 ml (43 mmol) of acetic anhydride. After 0.3 hr the reaction mixture was cooled and worked up as described above. Purification by ptlc (25% ether–petroleum ether, double development) afforded 82 mg (25%) of the phenyl adduct, mp 69–70°. The major slower moving band amounted to 173 mg (51%) of the m-methoxybenzyl

(39) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

adduct **12**, mp 72–74°. The analytical sample, obtained after crystallization from *n*-hexane, had mp 72–74°; ir ($CHCl_3$) 1740 (acetate C=O), 1675 (enol C=C), 1600, 1580, 1490 (aromatic), and 1140–1070 cm^{-1} (ketal); nmr ($CDCl_3$) δ 1.02 (s, 3, C-4aβ CH_3), 2.10 (s, 3, $-COCH_3$), 3.76 (s, 3, Ar OCH_3), 3.89 (s, 4, $-OCH_2CH_2O-$), and 6.6–7.4 (m, 4, Ar H).

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.99; H, 8.02.

The experiments which were conducted at higher temperatures (2) and without added copper(I) iodide (3) were conducted and analyzed in a similar fashion with the recorded (Table I) variations in quantities of reagents.

B. **From Organomagnesium Reagent (Table I, Part B).** A solution of 0.668 g (4.25 mmol) of *m*-methoxybenzyl chloride in 4 ml of dry ether was added to a stirred suspension of 0.124 g (5.10 mg-atoms) of magnesium turnings in 10 ml of ether under a nitrogen atmosphere over 0.25 hr. After stirring at room temperature for 1 hr, the solution was cooled to 0°, 52 mg (0.26 mmol) of cupric acetate monohydrate (recrystallized from acetic acid) was added in one lot, and the mixture was stirred for 6 min. Then 200 mg (0.85 mmol) of the methylene ketone **11** in 9 ml of dry ether was added over a 10-min period. A transient orange color was visible as a drop of the enone solution came in contact with the Grignard surface. After the addition was completed, the reaction mixture was stirred at room temperature for 1 hr and then quenched with 4 ml (43 mmol) of acetic anhydride. After 45 min the reaction mixture was diluted with aqueous ammonium chloride solution; the ether layer was separated and washed with water and saturated brine solution and then dried ($MgSO_4$). Removal of the drying agent and evaporation of the ether left a clear oil that on purification by ptlc (25% ether–petroleum ether, double development) afforded 231 mg (68%) of pure enol acetate **12**, which melted at 71–73°, alone or in admixture with a sample prepared by the procedure above. The nmr and solution ir spectra of the two samples were identical.

The same procedure was used for the reaction between the methylene ketone **11** and *m*-methoxybenzylmagnesium chloride in the absence of copper(II) acetate, and the results are recorded in Table I, run 9.

When benzyl chloride was used in place of *m*-methoxybenzyl chloride (Table I, runs 6 and 7), the same procedure was followed with the results indicated. A sample of the corresponding enol acetate for analysis was obtained after crystallization from *n*-hexane and melted at 77–79°; ir ($CHCl_3$) 1735 (acetate >C=O), 1675 (>C=C<), 1600 and 1495 (aromatic), and 1140–1030 cm^{-1} (ketal); nmr ($CDCl_3$) δ 1.02 (s, 3, C-4′aβ CH_3), 2.13 (s, 3, $COCH_3$), 3.95 (s, 4, $-OCH_2CH_2O-$), and 7.28 (s, 5, Ar H).

Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.57; H, 8.23.

3′,4′,4′a,7′,8′,8′aα-Hexahydro-5′-benzyl-4′aβ-methylspiro[1,3-dioxolane-2,2′(1′*H*)-naphthalene]. A solution of 1.54 ml of phenyllithium solution (1.65 *M* in benzene, 2.47 mmol) in 35 ml of dry ether under a nitrogen atmosphere was cooled to −20° and 242 mg (1.27 mmol) of copper(I) iodide added. The green solution was stirred for 0.5 hr and then 201 mg (0.85 mmol) of the methylene ketone **11** in 5 ml of dry ether was added by syringe. After 1 hr 4 ml (43 mmol) of acetic anhydride was added, and the solution was stirred at room temperature for 1 hr. The mixture was then treated with water, and the ethereal layer was separated, washed with water and then saturated with brine solution, and dried ($MgSO_4$). Removal of the desiccant and evaporation of the ether left a light oil that on purification by ptlc (25% ether–petroleum ether, double development), gave 268 mg (89%) of an oil that crystallized on trituration with ether–*n*-hexane (1:5). This material melted at 69–70°: ir ($CHCl_3$) 1740 cm^{-1} (acetate C=O), 1650 (enol C=C), 1600 and 1495 (aromatic), and 1140–1030 cm^{-1} (ketal); nmr ($CDCl_3$) δ 0.94 (s, 3, C-4′aβ CH_3), 1.95 (s, 3, $COCH_3$), 3.36 (s, 2, Ar CH_2) and 7.05 (s, 5, Ar H).

Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.16; H, 7.85.

When this experiment was performed in the same manner, except that the addition of copper(I) iodide was omitted (Table I, run 5), the same 1,4 adduct was isolated in significantly lower yield.

3′,4′,4′a,7′,8′,8′aα-Hexahydro-4′aβ,5′α-dimethyl-5′β-(2′-*m*-methoxyphenylethyl)spiro[1,3-dioxolane-2,2′(1′*H*)-naphthalen]-6′-(5′*H*)-one (13). In an adaptation of the procedure of House and Trost[7] 93 mg (0.23 mmol) of the enol acetate **12** in 0.8 ml of dimethyloxyethane was added under a nitrogen atmosphere to a solution of 0.27 ml of ethereal methyllithium solution (1.7 *N*, 0.46 mmol) in 1.2 ml of anhyrous dimethoxyethane. After stirring for 0.5 hr at room temperature, this mixture was treated with 1.0 ml (16.1 mmol) of methyl iodide, and the solution was stirred for an additional 5 min. The reaction mixture was then diluted with water and extracted with ether. The ethereal extract was washed with water and saturated brine solution and then dried ($MgSO_4$). Removal of the desiccant and evaporation of the ether afforded 85 mg (99%) of a yellow oil which deposited 66 mg (78%) of white crystals, mp 63–68°, from cold *n*-hexane. Recrystallization of a portion of this material from ether–*n*-hexane gave a sample for analysis: mp 69–70°; ir ($CHCl_3$) 1700 (C=O), 1600, 1580, 1490 (aromatic), 1380 (CH_3) and 1150–1040 cm^{-1} (ketal); nmr ($CDCl_3$) δ 0.75 (s, 3, C-4′aβ CH_3), 1.30 (s, 3 C-5′α CH_3), 3.81 (s, 3, Ar OCH_3), 3.95 (s, 4, $-OCH_2CH_2O-$), and 6.6–7.3 (m, 4, Ar H); nmr (C_6H_6) δ 0.50 (s, C-4′aβ CH_3) and 1.00 (C-5′α CH_3).

Anal. Calcd for $C_{22}H_{23}O_4$: C, 74.16; H, 8.66. Found: C, 74.26; H, 8.67.

1α,8aβ-Dimethyl-3,4,4aα,7,8,8a-hexahydro-1β-(2′-*m*-methoxyphenylethyl)-2,6(1*H*,5*H*)-naphthalenedione (14). A solution of 56 mg (0.15 mmol) of the ketone **13** in 5 ml of reagent acetone and 1 ml of 10% hydrochloric acid was allowed to stand 0.75 hr at room temperature. This solution was then diluted with water and extracted with ether. The ethereal extract was washed with water and saturated brine solution and then dried (Na_2SO_4). Removal of the drying agent and evaporation of the ether afforded 47 mg (96%) of the diketone **14**, mp 111–114°. The analytical sample, obtained after crystallization from acetone–*n*-hexane, melted at 127.5–128.5°; ir ($CHCl_3$) 1710 (C=O), 1600, 1585, 1490 (aromatics), 1380 (CH_3), and 1040 cm^{-1} (methoxyl); nmr ($CDCl_3$) δ 0.95 (s, 3, C-8a CH_3), 1.28 (s, 3, C-1 CH_3), 4.63 (s, 3, Ar OCH_3), and 6.6–7.3 (m, 4, Ar H).

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.77; H, 8.48.

4aβ,4bα-Dimethyl-8-methoxy-3,4,4a-4b,5,6,12,12aα-octahydro-2(1*H*)-chrysenone 15. Into a test tube reaction flask equipped with a nitrogen inlet and a mechanical stirrer with a screw-type blade was placed 28 mg (0.085 mmol) of the diketone **14**. To this was added 15 ml of polyphosphoric acid which was freshly prepared from 30 ml of 85% phosphoric acid and 34 g of phosphorus pentoxide. The thick solution was vigorously stirred at 65–70° for 40 min, and then the mixture poured onto ice and extracted with ether. The ethereal extract was washed with water and saturated aqueous sodium bicarbonate solution and then dried ($MgSO_4$). After removal of the drying agent and evaporation of the ether at reduced pressure, there remained 28 mg (quantitative) of a light brown solid, mp 185–189°, that was composed of >97% of a single volatile component, vpc (oven temperature 290°, R_f 2.4 min). The analytical sample of the tetracyclic ketone **15**, obtained after two recrystallizations from acetone, melted at 192–194°; ir ($CHCl_3$) 1710 (C=O), 1640 (C=C—Ar), 1610, 1570, 1495 (aromatic), 1375 (methyls), and 1035 cm^{-1} (methoxyl); nmr ($CDCl_3$) δ 1.00 (s, 3, C-4a CH_3), 1.08 (s, 3, C-4b CH_3), 3.78 (s, 3, Ar OCH_3), 6.15 (t, 1, J = 5 Hz, C-11 vinyl hydrogen), 6.61 (s, 1, C-7 Ar H), 6.73 (dd, 1, J = 9 and 3 Hz, C-9 Ar H) and 7.56 (d, 1, J = 9 Hz, C-10 Ar H).

Anal. Calcd for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 81.31; H, 8.45.

When the cyclodehydration of ketone **14** was attempted in boiling toluene with a catalytic amount of *p*-toluenesulfonic acid present, extensive decomposition occurred.

3′,4′,4′a,7′,8′,8′aα-Hexahydro-5′β-(2′-*m*-methoxyphenylethyl)-4′aβ-methylspiro[1,3-dioxolane-2,2(1′*H*)-naphthalen]-6′(5′*H*)-one (16). The enol acetate **12** (0.310 g, 0.774 mmol) was dissolved in a solution of potassium hydroxide (85%, 0.495 g, 7.51 mmol) in anhydrous methanol (50 ml) under nitrogen. The resulting pale yellow solution was allowed to stir at room temperature under nitrogen for 16 hr, and then it was transferred to a separatory funnel with ether (100 ml). An equal volume of water (100 ml) was added. The aqueous layer was separated and extracted with ether (three 25-ml portions). The combined ethereal extracts were dried (Na_2SO_4) and concentrated at reduced pressure to give 0.265 g (95%) of nearly colorless liquid ketal ketone **16**. The analytical sample, prepared by bulb-to-bulb distillation, was a colorless liquid: bp 192–201° (0.07 mm); ir ($CHCl_3$) 705 cm^{-1} (C=O), 1600, 1580, 1490 cm^{-1} (aromatic); nmr ($CDCl_3$) δ 3.91 (s, 4, $-OCH_2CH_2O-$), 3.76 (s, 3, Ar OCH_3), 0.64 (s, 3, C-4′aβ CH_3).

Anal. Calcd for $C_{22}H_{30}O_4$: C, 74.71; H, 8.44. Found: C, 73.86; H, 8.45.

4aβ-Methyl-6-methylene-5β-(2′-*m*-methoxyphenylethyl)-3,4,4a-5,7,8,8aα-heptahydronaphthalen-2(1*H*)-one (17). Triphenylphosphonium bromide (0.335 g, 0.939 mmol, dried at 60° for 18 hr at 0.05 mm) was stirred in anhydrous ether (20 ml) at 0° under dry

nitrogen while a solution of phenyllithium (0.44 ml, 0.94 mmol, 2.14 *M* solution in 70:30 benzene–ether) was added. The resulting bright orange-yellow solution was allowed to stir with continued cooling for 15 min. The ketal ketone **16** (0.164 g, 0.457 mmol) dissolved in dry ether (20 ml) was then added rapidly. The cooling bath was removed, and the slurry was allowed to stir at room temperature for 19 hr. The resulting reaction mixture was filtered, and the residue was washed with hexane (50 ml). The combined organic solutions were concentrated at reduced pressure, and the residue was partitioned between 1:3 aqueous methanol (75 ml) and hexane (50 ml). The aqueous methanol layer was separated and extracted with hexane (three 50-ml portions). The combined organic solutions were washed with 1:3 aqueous methanol (two 50-ml portions) and water (two 50-ml portions), dried (Na_2SO_4), and concentrated at reduced pressure.

This crude product (0.143 g of a colorless liquid) was dissolved in a solution of reagent acetone (100 ml) and 5% hydrochloric acid (0.5 ml). The resulting clear solution was stirred at room temperature under nitrogen for 2.5 hr. The reaction mixture was neutralized with saturated aqueous sodium bicarbonate solution, concentrated at reduced pressure, and then partitioned between water (50 ml) and ether (50 ml). The aqueous layer was separated and extracted with ether (three 25-ml portions). The combined ethereal extracts were washed with saturated aqueous sodium bicarbonate solution (10 ml) and saturated aqueous sodium chloride solution (two 70-ml portions), dried (Na_2SO_4), and concentrated at reduced pressure to a pale yellow liquid (0.134 g). Preparative thin layer chromatography on silica gel using 50% ether–petroleum ether eluent and double elution gave 0.086 g (60.4%) of the exocyclic methylene ketone **11** (R_f 0.51), mp 77–78°. The analytical sample, prepared by recrystallization from ether–hexane, melted at 78.2–78.6°; ir ($CHCl_3$) 3070, 1640, 890 (=CH_2), 1705 (C=O), 1605, 1600, 1580, 1480 (aromatic), and 1040 cm^{-1} (CH_3OAr); nmr ($CDCl_3$) δ 6.6–7.5 (m, 4, Ar H), 4.91 (broad d, 2, >C=CH_2), 3.78 (s, 3, ArOCH_3), and 0.82 (s, 3, C-4aβ CH_3).

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.66; H, 9.02.

4aβ,6β-Dimethyl-6α-hydroxy-5β-(2′-*m*-methoxyphenylethyl)-3,4,-4a,5,6,7,8,8aα-octahydronaphthalen-2(1*H*)-one (18). A solution of *m*-chloroperbenzoic acid (85%, 0.272 g, 1.34 mmol) in 6 ml of dichloromethane was added to a stirred solution of the exocyclic methylene ketal **17** (0.182 g, 0.511 mmol) in 12 ml of dichloromethane at 0° under nitrogen. This solution was allowed to stir at 0° for 4 hr. The excess peracid was destroyed with 10% aqueous sodium sulfite solution, and the organic solution was washed with 5% aqueous sodium hydroxide solution (three 10-ml portions) and saturated aqueous sodium chloride solution (three 10-ml portions), dried (Na_2SO_4), and concentrated at reduced pressure to a viscous yellow liquid. Preparative thin layer chromatography in silica gel using 50% ether–petroleum ether eluent and a single elution gave 0.172 g (91%) of a mixture of epoxides (R_f 0.31) as a colorless liquid; ir ($CHCl_3$) 3050 (terminal oxirane) and 1605, 1600, 1580 cm^{-1} (aromatic); nmr ($CDCl_3$) δ 6.57–7.60 (m, 4, Ar H), 3.91 (s, 4, $-OCH_2CH_2O-$), 3.75 (s, 3, Ar OCH_3), and 0.80 (two singlets, 3, C-4aβ CH_3, ratio *ca.* 25:75) indicates a mixture of epoxides in which the equatorial oxygen isomer is predominant).

A solution of this oxirane mixture in 10 ml of anhydrous ether was added to a stirred suspension of lithium aluminum hydride (0.240 g, 6.33 mmol) in 50 ml of dry ether at room temperature under nitrogen. The resulting gray slurry was allowed to stir at room temperature for 16 hr. The reaction mixture was quenched with 10% aqueous sodium hydroxide solution, filtered through anhydrous magnesium sulfate, and concentrated at reduced pressure to give a pale yellow liquid. Preparative thin layer chromatography on silica gel using 50% ether–petroleum ether eluent and a single elution gave 0.091 g of a colorless liquid (R_f 0.31). A solution of this product in 50 ml of acetone and 0.5 ml of 5% hydrochloric acid was stirred at room temperature under nitrogen for 4 hr. Water (25 ml) and 10% aqueous sodium hydroxide solution (0.25 ml) were added, and the acetone was removed at reduced pressure. The residue was extracted with ether (five 20-ml portions) and the combined ethereal extracts were washed with saturated aqueous sodium bicarbonate solution (three 10-ml portions) and saturated aqueous sodium chloride solution (three 10-ml portions), dried (Na_2SO_4), and concentrated at reduced pressure. In this manner there was obtained 0.076 g (45% overall) of the keto alcohol **18** as light yellow crystals, mp 67–70°. The analytical sample, prepared by recrystallization from ether–hexane, was a white crystalline solid that melted at 73.0–73.5°; ir ($CHCl_3$) 3585 (sharp, OH), 3460 (broad, OH), 1705 (C=O), 1605, 1600, 1585, 1485, (aromatic), and 1035 cm^{-1} (CH_3OAr); nmr ($CDCl_3$), δ 6.55–7.42 (m, 4, Ar H) 3.78 (s, 3, Ar OCH_3), 1.22, (s, 3, C-6β CH_3) and δ 0.93 (s, 3, C-4aβ CH_3).

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15. Found: C, 74.43; H, 9.25.

4aβ,6α-Dimethyl-6β-hydroxy-5β-(2′-*m*-methoxyphenylethyl)-3,-4,4a,5,6,7,8,8aα-octahydronaphthalen-2(1*H*)-one (19). A solution of the ketone ketal **16** (0.445 g, 1.24 mmol) in 30 ml of anhydrous ether was added dropwise with stirring to an ethereal solution of methyllithium (10.0 ml of a 2.3 *M* solution, 23 mmol) at 0° under nitrogen. The resulting clear solution was allowed to warm to room temperature over a period of 1 hr.

The solution was then cooled to 0° and carefully quenched with 5 ml of saturated aqueous ammonium chloride solution. The mixture was transferred to a separatory funnel with ether (25 ml) and water (25 ml), and the aqueous layer was separated and extracted with ether (three 10-ml portions). The combined ethereal extracts were washed with saturated aqueous sodium chloride solution (three 25-ml portions), dried (Na_2SO_4), and concentrated at reduced pressure to a colorless liquid (0.403 g).

A solution of this product in 50 ml of acetone was treated with 1.0 ml of 10% hydrochloric acid, and the resulting solution was allowed to stir at room temperature for 4 hr.

Water (25 ml) was added, and the mixture was extracted with ether (five 30-ml portions). The combined ethereal extracts were washed with saturated aqueous sodium bicarbonate solution (three 10-ml portions), water (10 ml), and saturated aqueous sodium chloride solution (three 10-ml portions), dried ($NaSO_4$) and concentrated at reduced pressure to a slightly yellow crystalline solid (0.340 g, 83%, mp 134–136°). The analytical sample of the axial hydroxy ketone **19**, prepared by recrystallization from ether–hexane, was obtained as white crystals that melted at 136–136.5°; ir ($CHCl_3$) 3600 (sharp, OH), 3450 (broad, OH), 1705 (C=O), 1600, 1585, 1485, (aromatic), and 1035 cm^{-1}; nmr (Ar OCH_3) 1.25 (s, 3, CH_3CO), 1.11 (s, 3, C-6α CH_3), and 1.26 (s, 3, C-4aβ CH_3).

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15. Found: C, 76.33; H, 9.19.

4aβ,10bβ-Dimethyl-8-methoxy-3,4,4a,4bα,5,6,10b,11,12,12α-decahydrochrysene-2(1*H*)-one (20) and 4aβ,10bα-Dimethyl-8-methoxy-3,4,4a,5bα,5,6,10b,11,12,12aα-decahydrochrysen-2(1*H*)-one (21). **(a) From Hydroxy Ketone 19.** A solution of the axial hydroxy ketone **19** (0.467 g, 1.41 mmoles) in 24 ml of freshly prepared polyphosphoric acid was stirred under nitrogen at 60° (bath temperature) for 1 hr. The orange-red solution was cooled to room temperature, poured onto ice (100 g), and extracted with ether (five 25-ml portions); the ether layer was dried (Na_2SO_4) and concentrated at reduced pressure to a light yellow liquid (0.436 g). Preparative thin layer chromatography on silica gel using 30% ether–petroleum ether eluent and triple elution gave the following two compounds.

(1) B/C trans tetracyclic ketone **20** (R_f 0.51), 0.280 g (64%), mp 130–130.8°. The analytical sample was prepared by recrystallization from ether–hexane and melted at 130.6–131.1°; ir ($CHCl_3$) 1705 (C=O), 1605, 1570, 1490 (3,4-disubstituted anisole), and 1030 cm^{-1} (CH_3OAr); nmr ($CDCl_3$) δ 7.19 (d, 1, J = 9 Hz, C-10 H), 6.75 (d, 1, J = 3 Hz, C-9 H), 6.60 (s, 1, C-7 H) [$\Delta\delta_{10,7}$ = 0.59 (type A)], 3.73 (s, 3, C-8 OCH_3), 1.21 (s, C-10bβ CH_3), and 1.05 (s, 3, C-4aβ CH_3).

Anal. Calcd for $C_{21}H_{26}O_2$: C, 80.73; H, 9.03. Found: C, 80.63; H, 9.11.

(2) B/C cis tetracyclic ketone **21** (R_f 0.59), 0.100 g (23%), mp 114–115°. The analytical sample was prepared by recrystallization from ether–hexane and melted at 115–116°; ir ($CHCl_3$) 1705 (C=O), 1605, 1575, 1495 (3,4-disubstituted anisole), and 1030 cm^{-1} (CH_3OAr); nmr ($CDCl_3$) δ 7.19 (d, 1, J = 9 Hz, C-10 H), 6.75 (d, 1, J = 3 Hz, C-9 H), 6.61 (s, 1, C-7 H) [$\Delta\delta_{10,7}$ = 0.58 (type B)],[19] 3.77 (s, 3, C-8 OCH_3), 1.14 (s, C-10bα CH_3), and 0.45 (s, 3, C-4aβ CH_3).

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.56; H, 9.01.

The ratio of these two isomers in the crude reaction products was 71:29 trans–cis tetracyclic ketones **20** and **21** by vpc at 290° and integration of the methyl signals in the nmr spectrum.

(b) From Hydroxy Ketone 18. In a similar fashion a solution of the equatorial hydroxy ketone **18** (0.028 g, 0.085 mmol) in 12 ml of freshly prepared polyphosphoric acid under a nitrogen atmosphere was allowed to stir at 60° (bath temperature) for 1.5 hr. The pale yellow solution was cooled to room temperature and worked up as described above; the resulting pale yellow liquid amounted to 0.026 g. The ratio of the two isomeric ketones **20** and **21** deter-

mined by vpc and nmr analysis as above was 72:78. The assignments of the peaks in the vpc were verified by peak enhancement using the pure isomers from the preceding experiment.

(c) **From Olefinic Ketone.** In the same fashion **a** solution of 0.041 g (0.13 mmol) of the exocyclic methylene ketone **17** in 12 ml of freshly prepared polyphosphoric acid under a nitrogen atmosphere was allowed to stir at 60° (bath temperature) for 1.5 hr. The orange solution was cooled to room temperature and worked up as described above. The crude product (0.040 g) was again analyzed by vpc and nmr, and the two isomeric ketones **20** and **21** were found to be present in a ratio of 75:25. Again peak enhancement with samples of the pure isomers was used to verify assignments.

Stereochemistry of Low-Spin Iron Porphyrins. I. Bis(imidazole)-α,β,γ,δ-tetraphenylporphinatoiron(III) Chloride[1]

D. M. Collins, R. Countryman, and J. L. Hoard*

Contribution from the Department of Chemistry, Cornell University, Ithaca, New York 14850. *Received August 27, 1971*

Abstract. Bis(imidazole)-α,β,γ,δ-tetraphenylporphinatoiron(III) chloride [written $(Im_2FeTPP)^+Cl^-$] crystallizes as the 1:1 solvate from methanol solution. The monoclinic unit cell containing $4[(Im_2FeTPP)^+Cl^-]CH_3OH$ has a = 14.265, b = 16.390, and c = 18.121 Å, and β = 90.83° ($\bar{\lambda}$ = 1.54178 Å). Calculated and experimental densities are 1.367 and 1.36 g/ml, respectively, at 19°; the space group is $P2_1/n$. Measurement of diffracted intensities employed θ–2θ scanning with Cu Kα radiation on a four-circle diffractometer. Of the 6800 independent reflections scanned for $(\sin\theta)/\lambda < 0.562$ Å^{-1}, the 5299 retained as observed were used for the determination and anisotropic least-squares refinement of the 559 structural parameters; conventional and weighted R values of 0.076 and 0.077 were obtained. The octahedral FeN_6 coordination group in the $(Im_2FeTPP)^+$ ion is dimensionally quasitetragonal. Equatorial Fe–N bond lengths are constrained by the porphinato core to the relatively high averaged value of 1.989 Å, with a mean deviation of 0.005 Å and an (individual) esd of 0.004 Å. Axial Fe–N bond lengths are 1.957 (4) and 1.991 (5) Å to, respectively, well-oriented and badly oriented imidazole ligands; the latter is strongly hydrogen bonded through its N–H group to the chloride ion, and is involved in substantial steric repulsions with porphinato nitrogen atoms. Stereochemical parameters of the porphinato core are consistent with the structural data from earlier and concurrent studies of iron porphyrins.

Inasmuch as each of the four possible combinations of ferrous(II) or ferric(III) iron in a *high-* or a *low-*spin ground state is realized in one or more of the naturally occurring iron porphyrins (the hemes in the hemoproteins), elucidation of the structural principles governing iron porphyrin stereochemistry carries many biologically significant implications. A five-coordinate square-pyramidal geometry, with the Fe^{3+} ion displaced ~0.50 Å out-of-plane from the porphinato core (see Figures 1 and 2 for diagrams of the porphinato skeleton), was established early as typical for the coordination group in a high-spin ferric porphyrin.[2,3] Explicit recognition of the pervasive role taken by the porphinato core in modulating the geometry of the coordination group, together with existing structural data for simpler iron complexes, led to the formulation of the overall pattern of iron porphyrin stereochemistry[3] that was freely employed for discussion of the anticipated configurational and conformational alterations attending the reversible oxygenation of the protohemes in hemoglobin and myoglobin.[3-6]

This stereochemical pattern[3] calls for square-pyramidal five-coordination in a high-spin ferrous porphyrin, with a substantially larger out-of-plane displacement of the Fe^{2+} ion than that of the smaller Fe^{3+} in a high-spin ferric porphyrin. It specifies further that addition to the five-coordinate high-spin iron ion, ferrous or ferric, of any sixth ligand effecting the transition to the low-spin state must bring the iron and the four porphinato nitrogen atoms into near or exact coplanarity with much shortened bonds.[7] It then led to the suggestion[4] that just such stereochemical alterations at a heme center accompanying the oxygenation of hemoglobin could require cooperative movements (translations and rotations of groups) in the protein framework, and thus provide a starting point for a mechanism to account for the cooperative interactions of the four subunits.[8]

Experimental confirmation of the proposed stereochemical pattern and of its direct applicability to the hemes in the hemoproteins has been delayed for about 5 years by untoward circumstances. Only recently have representative low-spin iron porphyrins, the bis(imidazole)-α,β,γ,δ-tetraphenylporphinatoiron(III) chloride (written hereinafter as $(Im_2FeTPP)^+Cl^-$)

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