solid: mp 81–82°; nmr δ 2.59 (3 H, s, NCH_3), 2.62–3.20 (7 H, m), 3.64 (3 H, s, OCH_3), 3.82 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 5.13 (2 H, s, CH_2Ph), 6.14 (1 H, s), 6.58–6.83 (4 H, m), 7.42 (5 H, s, ArH of benzyl moiety).

Anal. Calcd for $C_{27}H_{31}NO_4$: C, 74.8; H, 7.21; N, 3.23. Found: C, 74.17; H, 7.29; N, 3.07.

(±)-*O*-Methylflavinantine (11a). (i) Laudanosine (200 mg) was oxidized at 1.10 V in the manner described above to give **11a** as a yellow oil in 52% yield: nmr δ 1.93 (2 H, m), 2.44 (3 H, s, NCH_3), 2.49–3.66 (5 H, m), 3.82 (3 H, s, OCH_3), 3.87 (3 H, s, OCH_3), 3.90 (3 H, s, OCH_3), 6.30 (1 H, s), 6.53 (1 H, s), 6.70 (1 H, s), 6.95 (1 H, s); ir (KBr) 1670, 1645, 1625 cm^{-1}; uv max 240 and 283 nm. These data correspond with authentic spectra supplied by Professor T. Kametani.[10]

(ii) Electrolysis in the described fashion of 340 mg of *O*-benzylcodamine (**10c**) at 1.04 V gave **11a** in 53% yield. Spectroscopic data were identical with those of the above specimen.

(iii) Following the described oxidation method at 1.09 V, an equal molar mixture of 321 mg of laudanosine (**10a**) and 242 mg of bis(acetonitrile)palladium(II) chloride yielded **11a** in 63% yield whose spectroscopic properties were identical with those of the above specimen.

(±)-*O*-Benzylflavinantine (11b). **10b** (259 mg) was electrolyzed at 1.05 V in the prescribed manner to yield **11b** as a colorless glass in 53% yield based on quantitative conversion to the methiodide salt. Nmr and ir of the free base compared favorably with literature values:[35] ir ($CHCl_3$) 1660, 1640, 1620 cm^{-1}; nmr δ 1.80 (2 H, m), 2.52 (3 H, s, NCH_3), 2.60–3.52 (5 H, m), 3.65 (3 H, s, OCH_3), 3.87 (3 H, s, OCH_3), 5.18 (2 H, s, CH_2Ph), 6.13 (1 H, s), 6.34 (1 H, s), 6.70 (1 H, s), 6.80 (1 H, s), 7.40 (5 H, s, Ar H of benzyl moiety).

The methiodide salt was recrystallizated from EtOH to a constant melting point of 203–204° (lit.[35] 208–210°); HCl salt, mp 239–240° dec.

2,3-Dimethoxy-6-benzyloxymorphinandienone (11c). **10d** (350 mg) was oxidized in the described manner at 1.10 V to give **11c**[16] in 44% yield: nmr δ 1.84 (2 H, m), 2.42 (3 H, s, NCH_3), 2.58–3.50 (5 H, m), 3.67 (3 H, s, OCH_3), 3.78 (3 H, s, OCH_3), 5.06 (2 H, s, CH_2Ph), 6.33 (1 H, s), 6.40 (1 H, s), 6.45 (1 H, s), 6.62 (1 H, s), 7.28 (5 H, s, ArH of benzyl moiety); ir (neat) 1660, 1640, 1620 cm^{-1}; methiodide salt, mp 227° (lit.[16] 225–227°).

(±)-*O*-Benzylisoflavinantine (11d). **11d** was obtained in 43% yield after 240 mg of **10e** was oxidized at 1.05 V in the prescribed manner: nmr[32] δ 1.86 (2 H, m), 2.44 (3 H, s, NCH_3), 2.48–3.65 (5 H, m), 3.80 (3 H, s, OCH_3), 3.92 (3 H, s, OCH_3), 5.12 (2 H, s, CH_2Ph), 6.30 (1 H, s), 6.40 (1 H, s), 6.72 (1 H, s), 6.88 (1 H, s), 7.37 (5 H, s, ArH of benzyl moiety); ir[33] ($CHCl_3$) 1665, 1640, 1620 cm^{-1}.

Acknowledgment. A portion of this work was supported by Grant No. GM-19234 from the National Institutes of Health, U. S. Public Health Service. We thank Forrest Anderson for technical assistance.

(35) T. Kametani, T. Sugahara, H. Yagi, and K. Fukumoto, *J. Chem. Soc. C*, 1063 (1969).

Nonenzymic Biogenetic-Like Olefinic Cyclizations.[1a] Stereospecific Cyclization of Dienic Acetals[1b]

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Abstract: This paper reports the details of a basic study on a system which has proved to be useful in effecting nonenzymic biogenetic-like olefinic cyclizations. Cyclization of the trans dienic acetal **5** with stannic chloride in benzene gives, in high yield, a mixture of *trans*-octalol ethers, **11a–15a**. The predominant isomer is **12a**, particularly when nitromethane is used as the cyclization solvent (yield of **12a**, *ca.* 80%). Cyclization of the cis dienic acetal **6** gives similar results except that the bicyclic products are cis-fused. The degree of stereoselectivity with respect to the configuration of the ring fusion (cis or trans) is better than 97% for the cyclization of the acetal **5**, and 95% for the acetal **6**. The acetals **5** and **6** were prepared by the Wittig reaction of the phosphorane **8** with the keto acetal **7**. The structures and configurations of the major cyclizations were proved by degradation to the known dimethyloctalins.

This paper contains a description of the details of the basic study which led to the demonstration that the acetal function is particularly useful for initiating biogenetic-like olefinic cyclizations. Further exploitation of the system has culminated in the successful cyclization of a tetraenic acetal to yield the *D*-homosteroid nucleus,[2] an example of the stereospecific formation of six asymmetric centers in a tetracyclic product derived, in a single step, from an acyclic substrate having no centers of asymmetry.

The known susceptibility of certain unsaturated aldehydes of the citronellal type to undergo acid-catalyzed cyclization[3] prompted us to explore the possibility of using the aldehyde group to initiate polycyclization of polyolefinic systems. We first considered it essential to ascertain if unsaturated aldehydes having the olefinic bond in the 5 instead of the 6 position would also cyclize readily. The behavior of 5-methyl-5-hexenal (**1**) was therefore examined.[4] When a solution of this aldehyde in methanol containing (0.02 *N*) hydrogen chloride was allowed to stand for 2 hr at 0°, the acetal **2** was formed in quantitative yield. When this same solution was allowed to stand at room temperature, the aldehyde was completely cyclized, giving a mixture of *cis*- and *trans*-dimethoxymethylcyclohexane (**3**) and the olefinic ethers **4**. The rate of the cyclization process could readily be

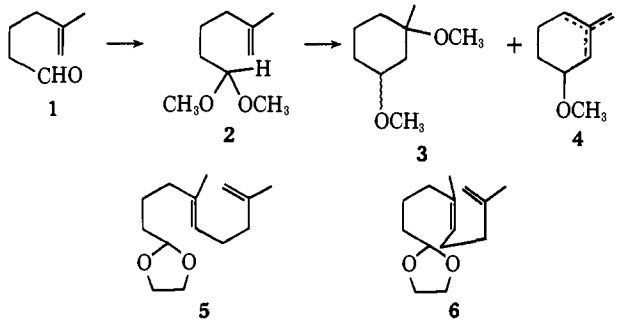
(1) (a) For a recent paper in this series, see G. D. Abrams, W. R. Bartlett, V. A. Fung, and W. S. Johnson, *Bioorg. Chem.*, **1**, 243 (1971). (b) A preliminary account of the present work has appeared: W. S. Johnson, A. van der Gen, and J. J. Swoboda, *J. Amer. Chem. Soc.*, **89**, 170 (1967).

(2) Preliminary report: W. S. Johnson, K. Wiedhaup, S. F. Brady, and G. L. Olson, *ibid.*, **90**, 5277 (1968).

(3) For a short review, see Y. Naves and P. Ochsner, *Helv. Chim. Acta*, **47**, 51 (1964).

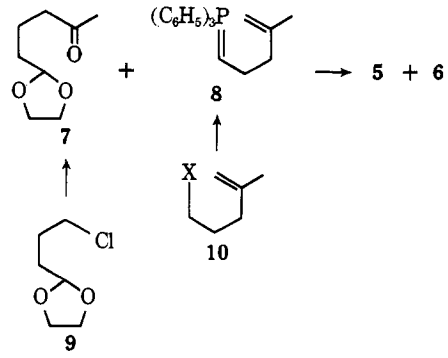
(4) Since this study was carried only to the point of demonstrating that the cyclization did in fact proceed readily, the experimental work was not rigorously refined and the details, therefore, are not reported.

followed, by observing the rate of disappearance of the signal at δ 1.68 ppm (for the C-5 methyl group) in the nmr spectrum of a solution of the acetal **2** in CH_3OD containing (0.12 *N*) hydrogen chloride. The half-life for the process was thus estimated to be 8 ± 2 min at 25°. In view of the promising nature of these preliminary results,[4] we turned our attention to the possibility of utilizing acetals instead of aldehydes for the aforementioned objective of producing fused-ring systems from acyclic substrates. In the present paper, the synthesis and cyclization of the trans and cis dienic acetals **5** and **6** are described.



Synthesis of the Dienic Acetals. Since both the trans (**5**) and cis (**6**) dienic acetals were wanted (see below), we envisaged employing the nonstereoselective Wittig reaction of the keto acetal **7** with the ylide **8**. For the preparation of the keto acetal, we started with 1-ethylenedioxy-4-chlorobutane[5] (**9**), which is readily prepared in quantity by Rosenmund reduction of commercially available γ-chlorobutyryl chloride followed by treatment of the resulting (crude) chloroaldehyde with ethylene glycol and *p*-toluenesulfonic acid. The Grignard reagent of the chloro acetal was prepared in tetrahydrofuran[6] and treated, at −60°, with acetic anhydride[7] to give the keto acetal **7**. The yield for this last step was only about 32%, because the Grignard reagent is unstable and is consumed in part by ring closure to the salt of hydroxyethyl cyclobutyl ether.[6]

5-Bromo-2-methylpentene-1 (**10**, X = Br), which was



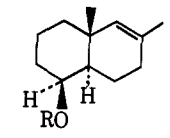
required for formation of the Wittig reagent **8**, was prepared from 4-methyl-4-penten-1-ol[8] (**10**, X = OH) by conversion to its tosylate followed by treatment with lithium bromide in monoglyme. The bromide **10** (X = Br) was transformed, by heating at 100° with triphenylphosphine in benzene, into the triphenylphosphonium bromide, mp 199.5–200°. This salt was treated with methylsulfinylcarbanion in dimethyl sulfoxide according to Corey's procedure[9] to form the Wittig reagent **8** which was allowed to react with the aforementioned keto acetal **7**. The product, obtained in 80% yield after distillation, consisted of a mixture of the trans and cis dienic acetals **5** and **6** in a ratio of 2:3 as estimated by gas chromatographic analysis. This mixture was separated by preparative gas chromatography; thus the cis acetal **6** was obtained as a liquid contaminated with 1.0% of the trans isomer, and the trans acetal **5** also as a liquid contaminated with 0.8% of the cis isomer. The compositional analysis and the spectral properties (see Experimental Section) were all in accord with the indicated structures. The configurations were assigned principally on the basis of the positions of the nmr signals for the C-5 methyl groups, which appeared at δ 1.60 ppm for the trans and 1.68 for the cis isomer. In substances $R^1CH{=}C(CH_3)R^2$ of known configuration, it has been shown that the nmr signal for the methyl group appears in the range δ 1.58–1.60 ppm for the trans isomers and δ 1.64–1.68 for the cis isomers.[10] In addition, the trans exhibited a longer retention time than the cis isomer on gas chromatography, which is consistent with general behavior for such isomers observed in our laboratory.

Cyclization Studies. Of various cyclization catalysts that were examined, stannic chloride[11] appeared to be particularly effective and has been given the most attention. The solvent also has a significant influence on the isomeric distribution of cyclization products. Although we have found solvent systems which yield principally a single cyclization product (see below), we have nevertheless studied the benzene–stannic chloride system of Goldsmith[11] in detail, because it gave significant amounts of the largest number of isomeric cyclization products and therefore promised to afford the greatest amount of information about the course of the reaction. The benzene–stannic chloride cyclization studies are discussed forthwith.

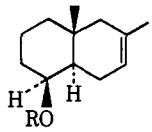
Estimation by gas chromatography of the rate of disappearance of 0.05 *M* solutions of the trans dienic acetal **5** in benzene indicated that cyclization was relatively slow until the stannic chloride concentration reached approximately 0.025 *M* (50 mol %), at which point the reaction became almost too rapid to follow. For preparative purposes 48 mol % of catalyst was employed, and after 5 min at 25°, cyclization was essentially complete. Short-path distillation gave a 97% recovery of material showing that there had been little or no polymerization. The gas chromatogram of the distillate showed six peaks of longer retention time than that of the starting material. These peaks, in order of increasing retention time, were labeled as follows (relative % of total area of peak is given in parentheses): A (4.5%), B (5), C (63), D (3.5), E (1), and F (21). As shown below, peak A probably corresponds to monocyclic material, and peaks B–F all correspond to trans bicyclic material comprising 93% of the total area. By

(5) M. G. Pleshakov, A. E. Vasil'ev, I. K. Sarycheva, and N. A. Preobrashenskii, *J. Gen. Chem. USSR*, **31**, 1433 (1961).
(6) *Cf.* Cl. Feugeas and H. Normant, *Bull. Soc. Chim. Fr.*, 1441 (1963).
(7) *Cf.* M. S. Newman and W. T. Booth, Jr., *J. Amer. Chem. Soc.*, **67**, 154 (1945).
(8) W. S. Johnson and R. Owyang, *ibid.*, **86**, 5593 (1964).
(9) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).
(10) R. B. Bates and D. M. Gale, *J. Amer. Chem. Soc.*, **82**, 5749 (1960); see also ref 1a, footnote 11.
(11) This catalyst has been shown to be useful in promoting the cyclization of epoxy olefins: D. J. Goldsmith, B. C. Clark, Jr., and R. C. Joines, *Tetrahedron Lett.*, 1149 (1966).

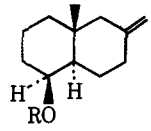
preparative gas chromatography, it was possible to separate these components in the indicated state of purity as estimated by analytical gas chromatography: substance A (purity 80%), B (85), C (96), D (39), E (78), and F (89). The nmr spectrum of substance A showed absorption at δ 4.72 ppm for a terminal methylene group and no signal for an angular methyl group; therefore it was presumably not bicyclic material and was not investigated further. The nmr spectra of substances B–F all showed sharp high-field singlets for the angular methyl group indicating that they were bicyclic products. Evidence for the exact nature of these substances is set forth below.



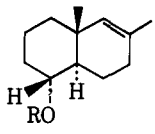
11a, R = CH_2CH_2OH
b, R = H



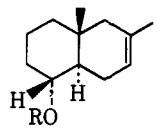
12a
b



13a



14a
b

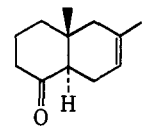


15a
b

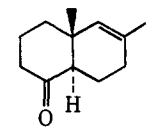
The detailed spectral properties of substances B, C, E, and F (see Experimental Section) were all in accord with the hydroxyethoxydimethyloctalin structures **11a**, **12a**, **14a**, and **15a**, respectively. The nmr spectrum of the low-yield, impure fraction D showed two signals appearing at δ 4.56 and 4.68, indicative of two nonequivalent protons of a $C{=}CH_2$ group, and an angular methyl absorption at δ 0.93 ppm. This fraction D, therefore, was presumed to contain some of the substance **13a**.

Each of the substances B, C, E, and F were degraded to the corresponding octalols **11b**, **12b**, **14b**, and **15b** by conversion to the tosylates followed by treatment with sodium iodide and zinc in glyme, *i.e.*, $ROCH_2CH_2OH \rightarrow ROCH_2CH_2OTs \rightarrow ROCH_2CH_2I \rightarrow ROH + CH_2{=}CH_2$. The nmr spectra of the two octalols with equatorial hydroxy groups, namely **14b** and **15b**, showed sharp signals for the angular methyl group at δ 0.84 and 0.80 ppm, and broad one-proton multiplets for the axial 5β hydrogens centered at 3.55 and 3.43. The spectra of the axial hydroxy isomers **11b** and **12b** showed signals for the angular methyl groups at 1.07 and 1.01 (shifted downfield relative to the equatorial isomers as a result of 1,3-diaxial interactions with the hydroxyl groups[12]), and relatively narrow multiplets for the equatorial 5α hydrogens centered at 3.88 and 3.38. In the case of the two Δ^1 isomers, the width at half-height of the signals for the vinyl proton was 4.7 cps at 5.05 ppm for **11b** and 5.2 cps at 5.12 ppm for **14b**, while for the Δ^2 isomers it was 9.7 cps at 5.38 ppm for **12b** and 9.4 cps at 5.37 ppm for **15b**. The band broadening in the case of the Δ^2 isomers results from additional coupling with the adjacent protons at C-4.

Oxidation of the two C-5 epimers **12b** and **15b** with Jones reagent[13] yielded a single octalone, **16**. Similarly, both C-5 epimers **11b** and **14b** yielded a single octalone, **17**. The nmr spectra of the octalones ex-



16



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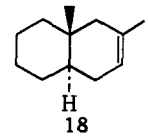
hibited singlets at δ 0.76 and 0.83 ppm, respectively, for the angular methyl groups. Wolff–Kishner reduction of the more abundant Δ^2-octalone **16** gave a mixture of the *trans*- and *cis*-dimethyloctalins **18** and **19** in a ratio



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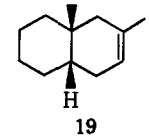

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of about 3:2.[14] These hydrocarbons were isolated by preparative gas chromatography and identified by infrared spectral and gas chromatographic retention time comparisons with authentic material.[15] A rigorous proof of configuration of the ketones **16** and **17** was obtained by hydride reduction of the tosylhydrazones which is described below.

The cyclization of the cis dienic acetal **6** was explored in order to ascertain if the stereochemical course of the reaction is determined by the configuration of the olefinic bonds in the substrate.[16] The product of the reaction of the cis acetal, which appeared to react slightly faster than the corresponding trans isomer under the conditions described above, was similarly mainly composed of bicyclic material (gas chromatographic area 88.5% of total). None of these bicyclic products was the same as B, C, E, or F formed in the trans series, as shown by the nonidentity of the positions of the signals for the angular methyl groups in the nmr spectra. Because of the conformational mobility of bicyclic isomers in the cis series, they were not so readily separated by chromatography, nor was it possible to ascertain by spectroscopy the configuration at C-5. Instead of concerning ourselves with these problems, we submitted the total cyclization mixture to degradation and oxidation as described above for the trans series. The resulting mixture of octalones was obtained in 79% overall yield. Gas chromatographic analysis indicated that this mixture contained 62% of the Δ^2-octalone **21**, 34% of the Δ^1-octalone **20**, and 4.5% of material which appeared to consist, as suggested by nmr, of a mixture of decalones. These fractions were separated by pre-

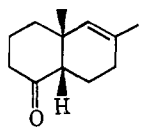
(12) *Cf.* R. F. Zürcher, *Helv. Chim. Acta*, **46**, 2054 (1963).

(13) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(14) Such isomerization during the Wolff–Kishner reduction is an established phenomenon; see, *inter alia*, C. Djerassi, T. T. Grossnickle, and L. B. High, *J. Amer. Chem. Soc.*, **78**, 3166 (1956). The reduction of ketone **16**, by treatment of the thioketal with deactivated Raney nickel, also gave partial isomerization; *cf.* J. W. Huffman, T. Kamiya, L. H. Wright, J. J. Schmid, and W. Herz, *J. Org. Chem.*, **31**, 4128 (1966), and references cited therein.

(15) Prepared by John W. Scott from *cis*- and *trans*-9-methyl-2-decalone by reaction with methyllithium followed by dehydration. In addition to the octalins **18** and **19**, this reaction also yielded small amounts of the corresponding cis and trans Δ^1 isomers. *cis*-9-Methyl-2-decalone: A. J. Birch and R. Robinson, *J. Chem. Soc.*, 501 (1943); W. S. Johnson, P. J. Neustaedter, and K. K. Schmiegel, *J. Amer. Chem. Soc.*, **87**, 5148 (1965). Trans isomer: W. Nagata, I. Kikkawa, and M. Fujimoto, *Chem. Pharm. Bull.*, **11**, 226 (1963); W. Nagata and I. Kikkawa, *ibid.*, **11**, 289 (1963).

(16) *Cf.* W. S. Johnson and J. K. Crandall, *J. Org. Chem.*, **30**, 1785 (1965), and W. S. Johnson, *Accounts Chem. Res.*, **1**, 1 (1968), for a discussion of the general stereochemical problem and its relationship to the Stork–Eschenmoser hypothesis.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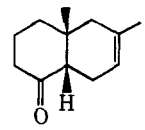
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parative gas chromatography. The positions of the olefinic bonds were determined, as in the trans series, by the widths at half-height of the vinyl proton nmr signals, which were 4.4 cps at δ 5.09 ppm for the Δ^1-octalone **20** and 9.0 cps at 5.33 ppm for the Δ^2 isomer **21**. Evidence that these octalones belonged to the cis series was provided by their nonidentity with the aforementioned trans isomers and by the appearance of the nmr signals for the angular methyl groups at lower field (δ 1.07 ppm for ketone **20** and at 1.06 for **21**) than in the trans series.[17] Treatment of each of the ketones **20** and **21** with potassium hydroxide in methanol effected partial conversion into the respective trans isomers **17** and **16** which were identified by infrared and nmr spectroscopic comparison. The positions of the equilibria were determined by approach from both sides and analyzed by measuring the nmr signals for the angular methyl groups. At equilibrium, the cis:trans ratios were 27:73 for the Δ^2 and 81:19 for the Δ^1 isomer. In the case of the Δ^1 isomers, the position of the equilibrium was also determined by gas chromatography to be 82:18.

Further evidence for the configurations of the octalones was obtained by a study of the line width of the angular methyl signals in the nmr spectra (see Table I).[18] In accordance with theory the angular methyl

Table I. Nmr Line Widths at Half-Height for Angular Methyl Groups

Octalone	Angular CH_3 δ, ppm	Angular CH_3 $W_{h/2}$, cps	TMS $W_{h/2}$, cps	$\Delta W_{h/2}$, cps
trans-Δ^2 (**16**)	0.76	1.41	0.31	1.10
cis-Δ^2 (**21**)	1.06[a]	1.04	0.32	0.72
trans-Δ^1 (**17**)	0.83	0.84	0.32	0.52
cis-Δ^1 (**20**)	1.07	0.54	0.32	0.22

[a] This signal appeared as a doublet, J = 0.45 cps.

absorptions of the trans octalones are appreciably broader than those of the corresponding cis compounds.[18] As expected, these signals for the Δ^1 isomers are much narrower than those for the Δ^2 ketones, because of the difference in extent of the long-range coupling. It is particularly noteworthy that the value for the *trans*-Δ^1-octalone is smaller than for the cis-Δ^2 isomer. This observation shows that an unequivocal configurational assignment can be made only by a comparison of bridgehead epimeric pairs, and that caution must be exercised in drawing conclusions from the line width of only one isomer.

Rigorous chemical proof of the configurations of the octalones **16**, **17**, **20**, and **21** was obtained by conversion to the octalins using a slight modification of the method of Caglioti.[19] Thus, the ketones were converted, on treatment with tosylhydrazine at room temperature in methanol, into the tosylhydrazones which were reduced with sodium borohydride in refluxing dioxane. Under these conditions, epimerization at C-10 did not exceed 10%. The products of this reduction sequence were identified by gas chromatography and ir and nmr comparison with the authentic dimethyloctalins (see above).[15]

Quantitative gas chromatographic and nmr spectral analysis indicated that the total mixture of octalones derived from the trans acetal upon cyclization in benzene or nitromethane (see below) contained 2.5 and 3% of *cis*-octalones, respectively. If this value is corrected for the 0.8% of cis isomer in the starting acetal, the process is better than 97% stereoselective. Similarly, it was shown by nmr analysis that the octalones produced from the cyclization of the cis acetal (contaminated with 1.6% of the trans isomer) contained 6% (or less) of *trans*-octalones corresponding to a stereoselectivity of better than 95%.[20] Hence the cyclization is essentially completely stereospecific.

The cyclization of the trans dienic acetal **5** was examined in a series of solvents. It was found that, in general, the more polar solvents gave higher proportions of the C-5 axial isomers as follows: pentane (axial/equatorial isomer ratio 1.9), carbon tetrachloride (2.2), carbon disulfide (2.5), chloroform (2.6), benzene (2.8), nitroethane (6.9), nitrobenzene (7.2), nitromethane (8.2), ethyl acetate (9.1), and acetonitrile (17). The ratio of Δ^1 to Δ^2 isomers also varied considerably with the different cyclization solvents. Of particular interest was the reaction in nitromethane which gave largely a single product, namely the Δ^2-5β (axial) isomer **12a** (80% of total gas chromatographic area).

Experimental Section

General Considerations. Melting points were determined on a Kofler hot-stage microscope. Nuclear magnetic resonance spectra were determined under the supervision of Dr. L. J. Durham on a Varian A-60 or HA-100 nmr spectrometer. Deuteriochloroform was employed as the solvent with tetramethylsilane as the internal reference. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane = 0. Gas chromatographic analyses were conducted on an Aerograph Hy-Fi gas chromatograph equipped with a hydrogen flame ionizer detector and a disc chart integrator. Nitrogen and hydrogen flow rates were approximately 25 ml/min. Analyses were carried out on a 7.5 ft × 0.125 in. stainless steel column packed with 15% Carbowax on Chromosorb W 60–80 mesh, referred to below as the "Carbowax column." Gas chromatographic separations were carried out on an Aerograph Autoprep 700 with manual injection and collection. The column (20 ft × 0.375 in. stainless steel) was packed with 20% Carbowax on Chromosorb W 60–80 mesh, referred to below as the

(17) The observed differences in chemical shift between the *cis*- and *trans*-octalones are larger than that of 0.13 ppm between *cis*- and *trans*-9-methyldecalin: M. J. T. Robinson, *Tetrahedron Lett.*, 1685 (1965). Insofar as the cis isomers adopt the "steroid" A/B conformation, the carbonyl group will cause an extra downfield shift of about 0.23 ppm relative to the trans isomers (*cf.* ref 12). In their "nonsteroid" conformations, the carbonyl group has no appreciable effect, but in this case the methyl group becomes equatorial to the ring containing the olefinic bond, which also results in a downfield shift: J. W. ApSimon, W. G. Craig, P. V. Demarco, D. W. Mathieson, L. Saunders, and W. B. Whalley, *Chem. Commun.*, 359 (1966).

(18) K. L. Williamson, T. Howell, and T. A. Spencer, *J. Amer. Chem. Soc.*, **88**, 325 (1966).

(19) L. Caglioti and M. Magi, *Tetrahedron*, **19**, 1127 (1963); L. Caglioti and P. Grasselli, *Chem. Ind. (London)*, 153 (1964).

(20) Further experiments have shown that submission of each of the *cis*-octalones **20** and **21** to the conditions of the Jones oxidation effected no increase in the amount of contamination by the corresponding trans isomers. It was discovered, however, that significant isomerization of the cis-Δ^2 isomer **21** does occur during preparative gas chromatography. For determination of isomeric purity, the cyclization product from the cis dienic acetal **6** was therefore processed as described above except that the resulting mixture of ketones **20** and **21** was submitted to short-path distillation and analyzed by nmr spectroscopy.

"preparative Carbowax column." Thin layer chromatography experiments were carried out using silica gel G (E. Merck AG) as adsorbent.

1-Ethylenedioxy-4-chlorobutane (9). The Rosenmund reduction of 4-chlorobutyryl chloride was carried out as previously described.[5] A high flow rate (>200 ml/min) of hydrogen or of a mixture of hydrogen and nitrogen had to be maintained in order to prevent an excessive concentration of hydrogen chloride from accumulating in the reaction mixture. The resulting 4-chlorobutanal was heated in benzene containing excess ethylene glycol and some *p*-toluenesulfonic acid in a system equipped for azeotropic removal of water. Thus, from 200 g of 4-chlorobutyryl chloride there was obtained, after distillation through a 24-in. spinning band column, 145 g (68%) of the chloro acetal **9**, bp 91–92° (18 mm), n^{25}D 1.4512.

1-Ethylenedioxyhexan-5-one (7). The Grignard reagent of the chloro acetal **9** was prepared according to the general procedure of Normant.[6] A total of 68.3 g of the chloro acetal, 160 ml of tetrahydrofuran, and 17 g of magnesium was employed, and altogether 3 ml of ethylene dibromide was used to accelerate the reaction. After the initial vigorous reaction had subsided, external heating was applied to maintain reflux for a total period of 50 min. According to the method of Newman and Booth,[7] the solution was then cooled to −20°, diluted with 250 ml of cold tetrahydrofuran, filtered, and added over a period of 1 hr to a stirred solution of 42 ml of acetic anhydride in 80 ml of tetrahydrofuran at −60°. After the addition was complete, the mixture was stirred for 1 hr, allowed to warm to −30°, and then added to 2 l. of a cold solution of 200 g of ammonium chloride and 200 ml of ammonia in water. This mixture was extracted with ether and the combined organic layers were washed with ammonium chloride–ammonia solution followed by saturated brine. The residue obtained on evaporation of the solvent was distilled through a spinning band column to give 22.5 g (32%) of the keto acetal **7**: bp 124–125° (18 mm); n^{25}D 1.4438; ir (liquid film) 5.84 μ. No impurities were detectable in this fraction by gas chromatographic analysis.

Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.6; H, 8.8.

4-Methyl-4-pentenyltriphenylphosphonium Bromide (10, X = $(C_6H_5)_3$PBr). This material was prepared by John W. Scott. A solution of 320 g of *p*-toluenesulfonyl chloride and 114 g of 4-methyl-4-penten-1-ol[8] (**10**, X = OH) in 465 ml of pyridine was kept at 0° for 2 hr and then refrigerated at 4° overnight. The mixture was diluted with 750 ml of benzene and cooled (ice–water bath) while 2.6 l. of 1:1 concentrated hydrochloride acid–water was added with stirring. During the addition the temperature was not allowed to exceed 10°. The aqueous phase was extracted with ether, and the combined organic layers were washed with water, saturated sodium bicarbonate solution, and saturated brine and dried over anhydrous sodium sulfate. The residue obtained on removal of the solvent at reduced pressure amounted to 249 g of a pale yellow liquid; ir (liquid film) 7.35, 8.45 (sulfonate ester), and 11.2 μ (=CH_2).

This crude *p*-toluenesulfonate was converted into 4-methyl-4-pentenyl bromide (**10**, X = Br) as follows. A mixture of the crude *p*-toluenesulfonate, 180 g of anhydrous lithium bromide, and 2200 ml of 1,2-dimethoxyethane was heated at reflux for 30 min. A white precipitate began to form during the early stage of heating. After cooling, the mixture was poured into saturated sodium bicarbonate solution (3 l.) and extracted with ether. The combined organic layers were washed with saturated sodium bicarbonate solution and saturated brine and dried over anhydrous sodium sulfate. The residue obtained on careful removal of the solvent at reduced pressure was distilled through a 24-in. platinum spinning band column to give 37.0 g (fraction 1) of colorless liquid, bp 45.0–47.0° (19 mm), which appeared to be 95% pure by gas chromatography, and 94.4 g (fraction 2) of colorless liquid: bp 47.0–47.3° (19 mm); n^{20}D 1.4694; ir (liquid film) 6.05 (C=C) and 11.2 μ (=CH_2). This second fraction appeared to have a purity of better than 99% by gas chromatography and was used as an analytical sample.

Anal. Calcd for $C_6H_{11}Br$: C, 44.19; H, 6.76; Br, 48.98. Found: C, 44.0; H, 6.7; Br, 49.1.

A solution of 54.3 g of the aforementioned 4-methyl-4-pentenyl bromide (mixture of distillation fractions 1 and 2) and 83.0 g of triphenylphosphine, mp 80–81°, in 60 ml of anhydrous benzene was sealed under nitrogen in a 125-ml pressure bottle protected by a wire screen and heated at 100° for 45 hr. The bottle was cooled and opened, and the solid was removed by filtration and washed well with benzene and ether. The oily residue obtained on evaporation of the solvent from the filtrate and washings was re-treated as above with 5.0 g of triphenylphosphine in 30 ml of benzene. The solid product from this second treatment was combined with the first and recrystallized from ethanol–ether to give 110 g (crop 1) of cream-colored powder, mp 198–199°, and 17.0 g (crop 2), mp 197–198°. A portion of the first-crop material was recrystallized to give the colorless triphenylphosphonium salt **10** (X = $(C_6H_5)_3$PBr), mp 199.5–200°.

Anal. Calcd for $C_{24}H_{26}PBr$: C, 67.77; H, 6.16; Br, 18.55. Found: C, 67.5; H, 6.1; Br, 18.6.

The two crops of this product were combined for further use.

***trans*- and *cis*-1-Ethylenedioxy-5,9-dimethyldeca-5,9-diene (5 and 6).** A solution of methylsulfinylcarbanion was prepared[9] from 7.7 g of sodium hydride and 300 ml of dimethyl sulfoxide by warming for 10 min at 50° and then for 40 min at 78°. To this was added a solution of 136 g of the aforementioned phosphonium salt in 250 ml of dimethyl sulfoxide. The mixture was stirred at room temperature for 15 min; then 47.5 g of 1-ethylenedioxyhexan-5-one was added with cooling (ice–water bath) and stirring. The mixture was then allowed to stir at room temperature overnight, 1 l. of 30–60° petroleum ether was added, and the mixture was poured into 3 l. of saturated brine. The precipitate (mainly triphenylphosphine oxide) was separated by filtration and the filtrate was extracted with petroleum ether. The precipitate was dissolved in acetone, and this solution was treated with petroleum ether and saturated brine, whereupon the triphenylphosphine oxide again separated. This precipitate was dissolved and reprecipitated once again as above. The combined petroleum ether extracts were concentrated to a volume of 100 ml and chromatographed on 300 g of basic alumina to give, on elution with 500 ml of petroleum ether, 63.7 g of crude acetal fraction. Distillation through a 24-in. spinning band column gave 54 g (80% yield) of a mixture of the trans and cis dienic acetals **5** and **6** as a colorless liquid, bp 138–140° (3.5 mm). The composition of this mixture as indicated by gas chromatography on the Carbowax column was 57% cis and 43% trans isomer. These isomers were separated by gas chromatography on the preparative Carbowax column. With injections of 50 μl at a column temperature of 190° and a flow rate of 200 ml/min, the cis isomer (shorter retention time) was obtained 99.0% pure and the trans isomer (longer retention time) was obtained 99.2% pure: cis isomer n^{25}D 1.4686, ir (liquid film) 6.07 μ (C=C); trans isomer n^{25}D 1.4702, ir (liquid film) 6.06 μ (C=C). For both isomers: nmr ($CDCl_3$) δ 5.15 (m, 1, HC=C), 4.85 (t, 1, J = 4.1 cps, H at C-1), 4.79 (s, 2, =CH_2), 3.90 (m, 2, OCH_2CH_2O), 3.87 (m, 2, OCH_2CH_2O), 1.71 (s, 3, CH_3 at C-9). The signal for the CH_3 group at C-5 appeared at δ 1.68 (s, 3) for the cis isomer and at 1.60 (s, 3) for the trans isomer.

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found for cis isomer: C, 74.0; H, 10.6; for trans isomer: C, 74.75; H, 10.6.

Cyclization of *trans*-1-Ethylenedioxy-5,9-dimethyldeca-5,9-diene (5) with Stannic Chloride in Benzene. A solution of 0.625 g of freshly distilled stannic chloride in 10 ml of anhydrous benzene was added over a period of 30 sec to a rapidly stirred solution of 1.120 g of the aforementioned trans dienic acetal in 90 ml of benzene at 25° (nitrogen atmosphere). After a total reaction time of 300 sec, the mixture was added to a solution of 50 ml of 10% sodium hydroxide in 50 ml of saturated brine, and the aqueous phase was extracted with benzene. The combined organic solutions were washed with water, saturated sodium bicarbonate solution, and saturated brine. The pale yellow oily residue obtained on evaporation of the solvent at reduced pressure was submitted to short-path distillation at 80–120° (0.025 mm) to give 1.084 g of a colorless oil, ir (liquid film) 2.94 (OH) and 9.07 μ (C—O). Analytical gas chromatography on the Carbowax column (column temperature 212°) showed six peaks with retention times: A, retention time 15.3 min, relative area 6%; B, 17.7 min, 8%; C, 19.8 min, 58%; D, 21.5 min, 3%; E, 24.5 min, 1%; and F, 26.8 min, 23%. The values given in the discussion section were obtained from another cyclization experiment and the differences in relative areas indicate the variations to be expected from one run to another.

Separation of 670 mg of a comparable cyclization mixture on the preparative Carbowax column at 210° yielded 27 mg of fraction A (purity 80%), 38 mg of fraction B (contaminated with 10% of C), 235 mg of fraction C (contaminated with 4% of B), 10 mg of fraction D (contaminated with 57% of C), 7 mg of fraction E (contaminated with 20% of C), and 133 mg of F (contaminated with 2% of E and 8% of C).

The first fraction, containing substance A, showed nmr absorption at δ 4.72 (s, 2, =CH_2), while no signal indicative of an angular methyl group was found. The fraction, containing compound D, displayed nmr absorptions at δ 4.56 and 4.68 (=CH_2, nonequivalent) and 0.93 (s, angular CH_3). These observations are regarded as corresponding to the tentative assignments made for A and D in

the discussion section, and the materials were not examined further. Fractions B, C, E, and F were characterized as **11a**, **12a**, **14a**, and **15a**, respectively, by their conversion to the corresponding octalols (see below). The nmr spectra ($CDCl_3$) exhibited singlet signals for the angular methyl group and the vinylic proton (width at half height) respectively as follows: **11a**, 1.02 and 5.11 ppm (4.8 cps); **12a**, 0.97 and 5.36 (9.1); **14a**, 0.85 and 5.15 (5.0); **15a**, 0.80 and 5.35 (9.3).

trans-**2,9-Dimethyl-Δ^2-5β-octalol (12b).** A cooled (−5°) solution of 95 mg of material comparable to fraction C described above, containing mainly the hydroxyethoxydimethyloctalin **12a**, in 0.5 ml of anhydrous pyridine was added to a cold (0°) solution of 100 mg of *p*-toluenesulfonyl chloride in 0.5 ml of pyridine. After 16 hr at −20°, 1 drop of 85% lactic acid was added. The resulting mixture was kept at room temperature for 10 min and then added to 50 ml of a 2% solution of lactic acid in water. The mixture was extracted with ether and the combined organic layers were washed with water, 1 *N* hydrochloric acid, water, saturated sodium bicarbonate solution, water, and finally with saturated brine. The residue obtained on removal of the solvent at reduced pressure amounted to 154 mg of a colorless liquid, ir (liquid film) 8.40 and 8.50 μ (sulfonate ester).

To a stirred solution of this crude tosylate in 1.5 ml of anhydrous 1,2-dimethoxyethane was added under nitrogen 200 mg of zinc powder followed by 200 mg of powdered sodium iodide. The stirred mixture was slowly heated, and upon reaching reflux temperature, the evolution of ethane was measured. Gas formation subsided after 90 min and amounted to 95% of the theoretical volume. The cooled reaction mixture was filtered into 20 ml of a 5% solution of sodium thiosulfate, and the insoluble material was washed thoroughly with ether and water. The aqueous layer was extracted with ether, and the combined organic solutions were washed with 1% sodium thiosulfate, water, saturated sodium bicarbonate solution, water, and saturated brine. The oily residue obtained upon evaporation of the solvent was subjected to short-path distillation at 80–100° (0.05 mm) to yield 73 mg of the octalol **12b** as a colorless oil, which appeared to be about 94% isomerically pure by gas chromatography: ir (liquid film) 2.91 (OH) and 8.90 μ (C—O); nmr ($CDCl_3$) δ 5.38 (s, 1, $W_{h/2}$ = 9.7 cps, vinylic H), 3.38 (s, 1, $W_{h/2}$ = 6.7 cps, H at C-5), 1.01 (s, 3, angular CH_3).[21]

trans-**2,9-Dimethyl-Δ^2-5α-octalol (15b)** was prepared as described above for the isomer **12b**. Thus, treatment of 112 mg of the aforementioned crude hydroxyethoxydimethyloctalin **15a** (fraction F) with 105 mg of *p*-toluenesulfonyl chloride in 1.0 ml of dry pyridine yielded 153 mg of a colorless liquid, ir (liquid film) 8.40 and 8.50 μ (sulfonate ester). Subjection of this material to the side-chain degradation procedure described above afforded, after short-path distillation at 80–100° (0.05 mm), 54 mg of the equatorial octalol **15b** as a colorless liquid. The isomeric purity as estimated by gas chromatography was better than 89%: ir (liquid film) 3.00 (OH) and 9.73 μ (C—O); nmr ($CDCl_3$) δ 5.37 (m, 1, $W_{h/2}$ = 9.4 cps, vinylic H), 3.43 (m, 1, H at C-5), 0.80 (s, 3, angular CH_3).[21]

trans-**2,9-Dimethyl-Δ^1-5β-octalol (11b)** was prepared as described above. Thus, from 33.5 mg of the aforementioned hydroxyethoxydimethyloctalin **11a** (fraction B) and 38 mg of *p*-toluenesulfonyl chloride there was obtained 62 mg of the crude *p*-toluenesulfonate of **11a** as a colorless oil. This on treatment with 60 mg of zinc and 75 mg of sodium iodide in 0.6 ml of dimethoxyethane yielded an oily product which upon short-path distillation at 80–100° (0.1–0.3 mm) gave 17 mg of **11b** as a colorless oil of better than 81% isomeric purity by gas chromatography: nmr ($CDCl_3$) δ 5.05 (s, 1, $W_{h/2}$ = 4.7 cps, vinylic proton), 3.88 (m, 1, $W_{h/2}$ = 7.5 cps, H at C-5), 1.07 (s, 3, angular CH_3).[22]

trans-**2,9-Dimethyl-Δ^1-5α-octalol (14b).** Similarly, reaction between 13 mg of the hydroxyethoxydimethyloctalin **14a** (fraction E) with 19 mg of *p*-toluenesulfonyl chloride in 0.2 ml of pyridine afforded 28 mg of the crude tosyl derivative of **14a** as a colorless oil. Side-chain degradation of this substance with 30 mg of zinc and 40 mg of sodium iodide gave, after short-path distillation at 80–100° (0.02 mm), 8 mg of **14b**, about 65% isomerically pure by gas chromatography: nmr ($CDCl_3$) δ 5.12 (s, 1, $W_{h/2}$ = 5.2 cps, vinylic proton), 3.55 (broad m, 1, H at C-5), 0.84 (s, 3, angular CH_3).[22]

trans-**2,9-Dimethyl-Δ^2-5-octalone (16).** A solution of 54 mg of the aforementioned, purified axial octalol **12b** in 3 ml of degassed acetone was cooled to 0° while 0.09 ml of Jones reagent[13] was added dropwise over a period of 1 min. The orange-brown mixture was stirred at 0° for 4 min, then quenched by the addition of isopropyl alcohol and diluted with water. The aqueous phase was extracted with ether and the combined organic layers were washed with 2 *N* hydrochloric acid, saturated sodium bicarbonate, water, and saturated brine. Upon removal of the solvent, the oily residue was washed through 2 g of neutral alumina and then submitted to short-path distillation at 60–70° (0.1 mm) to afford 51 mg of a colorless oil. Preparative tlc over alumina (40:60 ether-hexane) gave 23 mg of the liquid octalone **16**, purity better than 92% (gas chromatography): ir (liquid film) 5.88 μ (C=O); nmr ($CDCl_3$) δ 5.38 (s, 1, $W_{h/2}$ = 8.2 cps, vinylic proton), 0.76 ppm (s, 3, $W_{h/2}$ = 1.41 cps, angular methyl).[21]

The semicarbazone was obtained as colorless crystals from ethanol–water, mp 210° (dec).

Anal. Calcd for $C_{13}H_{21}ON_3$: C, 66.35; H, 9.00. Found: C, 66.2; H, 9.0.

Treatment of a solution of 18 mg of the aforementioned, purified equatorial octalol **15b** in 1.0 ml of acetone with 0.03 ml of Jones reagent in the way described above gave, after short-path distillation at 60° (0.1 mm), 15 mg of a colorless liquid. R_f values on tlc in three solvent systems, as well as the ir and nmr spectra of this material, were identical with those of the octalone **16**.

trans-**2,9-Dimethyl-Δ^1-5-octalone (17).** Oxidation of 17 mg of the axial octalol **11b** in 1.0 ml of acetone with 0.3 ml of Jones reagent just as described above gave, after short-path distillation at 60° (0.1 mm), 10 mg of the octalone **17** as a colorless oil: ir (liquid film) 5.83 μ (C=O); nmr ($CDCl_3$) δ 5.29 (s, 1, $W_{h/2}$ = 4.7 cps, vinylic proton), 0.83 ppm (s, 3, $W_{h/2}$ = 0.84 cps, angular methyl group).[21]

The semicarbazone was obtained as colorless crystals from ethanol–water; mp 222–225° (dec).

Anal. Calcd for $C_{13}H_{21}ON_3$: C, 66.35; H, 9.00. Found: C, 66.1; H, 8.9.

The 2,4-diphenylhydrazone was crystallized from ethanol–water, mp 163–164°.

Anal. Calcd for $C_{18}H_{22}O_4N_4$: C, 60.32; H, 6.19. Found: C, 60.4; H, 6.15.

Oxidation of 8 mg of the aforementioned equatorial octalol **14b** in 0.5 ml of acetone with 0.01 ml of Jones reagent in the way described above gave, after short-path distillation at 60° (0.1 mm), 6 mg of a colorless oil. The material showed R_f values on tlc in three solvent systems and ir and nmr spectral characteristics identical with those of the octalone **17**.

trans-**2,9-Dimethyl-Δ^2-octalin (18).** **(a)** *Via* **Wolff–Kishner Reduction.** A solution of 213 mg of the aforementioned trans octalone **16** (obtained by cyclization of the acetal **5** in benzene and containing less than 2.5% of cis ketones) in 10 ml of triethylene glycol was added under nitrogen to a solution of 400 mg of sodium hydroxide in 10 ml of triethylene glycol; then 3 ml of 95% hydrazine was added. The resulting mixture was heated under nitrogen at 130–140° for 1 hr, then at 195–210° for a further 3 hr. The cooled mixture was partitioned between 200 ml of water and 150 ml of pentane; then the aqueous phase was acidified with hydrochloric acid and extracted with pentane. The combined organic solutions were washed with water, 10% sodium hydroxide, 2 *N* hydrochloric acid, saturated sodium bicarbonate, water, and finally with saturated brine. Evaporation of the solvent afforded 190 mg of a yellow oil. Preparative tlc on alumina (pentane) gave 131 mg of a colorless oil consisting of two components in a ratio of 63:37 (as estimated by gas chromatography) which were isolated by gas chromatography over the preparative Carbowax column at 100°, and identified as the trans octalin **18** and cis octalin **19**, respectively, on the basis of complete agreement of retention times in gas chromatography and ir spectra with those of samples of authentic material.[15] The nmr ($CDCl_3$) of the trans isomer showed absorption at δ 5.32 (broad s, 1, vinylic proton), 1.63 (broad s, 3, CH_3 at C-2), and 0.77 (s, 3, angular CH_3). For the cis isomer, corresponding absorptions were found at δ 5.24, 1.63, and 0.87 ppm.

(b) *Via* **Reduction of the Tosylhydrazone.**[19] A slight modification was made in the reported procedure,[19] in that the tosylhydrazones of the octalones **16**, **17**, **20**, and **21** were formed at room temperature. Thus, 18 mg of the trans octalone **16** (purity and origin as

(21) A satisfactory combustion analysis was obtained on a comparable (optically active) specimen that was produced in the asymmetrically induced cyclization of an optically active acetal: W. S. Johnson, C. A. Harbert, and R. D. Stipanovic, *J. Amer. Chem. Soc.*, 90, 5279 (1968). The analytical specimen was purified by gas chromatography followed by short-path distillation and its spectral properties were identical with those of the material described in the present work.

(22) Because of its lack of isomeric purity this material was not characterized further, but was converted into the ketone for rigorous characterization (see below).

described under (a)) was treated with 22 mg of tosylhydrazine[23] in 0.25 ml of methanol at room temperature. Inspection of the mixture by tlc (60:40 pentane–ether) indicated the reaction to be essentially complete after 16 hr. The crude tosylhydrazone of **16** was isolated as an oil amounting to 35 mg. A solution of this material in 3 ml of dioxane was stirred with 90 mg of sodium borohydride at room temperature for 4 hr, then at reflux for an additional 14 hr. Following careful addition of 0.5 *N* hydrochloric acid, the mixture was extracted with ether. The combined organic layers were washed, dried, and evaporated to give 13 mg of a colorless oil, which was chromatographed on 2 g of silica gel. Elution with pentane gave 11 mg of material, which by gas chromatographic analysis (95°) appeared to consist of the *trans*- and *cis*-dimethyloctalins **18** and **19**, representing 96 and 2.5% of the total area, respectively. The trans isomer was isolated by preparative gas chromatography, and the ir spectrum was found to be identical with that of the authentic sample.[15]

***trans*-2,9-Dimethyl-Δ¹-octalin.** The procedure described above was followed. From 18 mg of the aforementioned trans octalone **17** (99% pure by gas chromatographic analysis) and 22 mg of tosylhydrazine in 0.2 ml of methanol there was obtained 28 mg of the crystalline tosylhydrazone; melting point after recrystallization from aqueous methanol was 135–136.5°. Reduction of this material with 90 mg of sodium borohydride in 3 ml of dioxane afforded a colorless oil. Chromatography on 2 g of silica gel gave 10.5 mg of material, which was analyzed by gas chromatography (95°) on the Carbowax column. In addition to 4% of a substance, which may have been the 1,5(10)-diene elimination product, the product consisted of 95% of one component and 0.5% of another substance. Comparison of retention times with those of the authentic samples[15] indicated that these latter two compounds were *trans*- and *cis*-2,9-dimethyl-Δ¹-octalin, respectively.

Cyclization of *trans*-1-Ethylenedioxy-5,9-dimethyldeca-5,9-diene (5) with Stannic Chloride in Nitromethane. A stirred solution of 1.95 g (7.5 mmol) of stannic chloride in 75 ml of dry nitromethane under nitrogen was cooled to 0° while a solution of 0.336 g (1.5 mmol) of the trans dienic acetal **5** in 75 ml of nitromethane was added over 30 sec. The mixture was stirred for another 180 sec at 0°, then quenched by the addition of 100 ml of 1 *N* hydrochloric acid, and extracted with ether. The combined organic layers were washed with 2 *N* hydrochloric acid, saturated sodium bicarbonate, water, and saturated brine. The pale yellow oil obtained upon evaporation of the solvent was subjected to short-path distillation at 80–120° (0.05 mm) to yield 0.312 g (93%) of a colorless oil. Gas chromatography over the Carbowax column (212°) indicated the presence of four bicyclic substances representing 97% of the total peak area. By comparison of the retention times with those of the octalin derivatives isolated from the cyclization experiment of **5** in benzene described above, these materials were identified as **11a** (retention time 17.7 min, relative % of total peak area 6.5%), **12a** (19.8 min, 80%), **14a** (24.5 min, 0.5%), and **15a** (26.8 min, 10%).

Without further purification, this mixture was subjected to the side-chain degradation procedure described in detail above, to give 230 mg of a pale yellow oil, which was distilled (short-path) at 80–100° (0.1 mm) to give 214 mg of a mixture of octalols as a colorless liquid. Oxidation of this material with Jones reagent as described above and purification by preparative tlc on alumina (40:60, ether–pentane) followed by short-path distillation at 60–80° (0.05 mm) gave 148 mg (70% yield) of a colorless oil, ir (liquid film) 5.88 (C=O) μ. The nmr ($CDCl_3$) showed a singlet absorption at δ 5.37 ppm (vinylic proton of **16**). The signal of the angular methyl group of **16** appeared as a singlet at 0.76 ppm. In addition, weak singlet absorptions were found at δ 0.83 and 1.06, indicative of the *trans*-Δ¹-octalone **17** and the cis octalones **20** and **21** (see below). The planimetric integration of these angular methyl absorptions indicated the product to consist of 88% of **16**, 8% of **17**, and 3% of a mixture of the cis ketones **20** and **21**.

Cyclization of *trans*-1-Ethylenedioxy-5,9-dimethyldeca-5,9-diene (5) with Stannic Chloride in Other Solvents. The procedure described above for the cyclization of the dienic acetal **5** in nitromethane was applied to a variety of solvents in order to study their effect on the product distribution in the cyclization mixture. Crude reaction mixtures were subjected to short-path distillation at 80–120° (0.01 mm) (recoveries generally better than 90%) and analyzed by gas chromatography over the Carbowax column for the relative amounts of bicyclic material. Thus, the distribution of **11a**, **12a**, **14a**, and **15a**, respectively, in the reaction mixtures obtained from cyclization of **5** in acetonitrile was 20, 68, 0.5, and 4.5%; in pentane, 3, 58, 1, and 32%; in chloroform 9, 54, 1.5, and 23%; in carbon tetrachloride, 4, 61, 2, and 27%; in ethyl acetate, 25, 39, 1, and 6%; in carbon disulfide, 5, 61, 2, and 26%; in nitrobenzene, 7, 74, 1, and 10%; in nitroethane, 7, 76, 1, and 11%.

Cyclization of *cis*-1-Ethylenedioxy-5,9-dimethyldeca-5,9-diene (6) with Stannic Chloride in Benzene. The procedure described above for cyclization of the corresponding trans isomer **5** was followed. Thus, treatment of a solution of 2.02 g (9.0 mmol) of 6 (containing 1.6% of the trans isomer **5** according to gas chromatographic analysis) in 180 ml of benzene with a solution of 2.35 g (9.0 mmol) of stannic chloride in 180 ml of benzene at room temperature afforded 2.02 g of a nearly colorless oily reaction product. Short-path distillation of this material at 80–120° (0.05 mm) gave 1.84 g of a colorless oil: ir (liquid film) 2.88 (OH), 8.9, and 9.4 μ (C–O).

Analysis by gas chromatography (Carbowax column at 212°) indicated starting acetal (retention time 8.1 min, 4% of total area of peaks), 7.5% of low-retention time (8–18 min) material, and four peaks of longer retention times: A′ (retention time 19.7 min, 38%); B′ (22.1 min, 41%); C′ (24.2 min, 5%); and D′ (28.5 min, 4.5%).

***cis*-2,9-Dimethyl-Δ¹-5-octalone (20) and *cis*-2,9-Dimethyl-Δ²-5-octalone (21).** The procedure described above for degradation of the side chain was followed. Thus, treatment of 1.82 g of the aforementioned cyclization mixture obtained from **6** with 2.10 g of *p*-toluenesulfonyl chloride in 20 ml of dry pyridine yielded 3.00 g of a nearly colorless oil, ir (liquid film) 8.40 and 8.48 (sulfonate ester). Treatment of this product in 40 ml of dimethoxyethane with 4 g of zinc and 4 g of sodium iodide afforded, after short-path distillation at 60–100° (0.025 mm), 1.35 g of a mixture of Δ¹- and Δ²-2,9-dimethyl-5-octalols as a colorless oil; ir (liquid film) 2.96 (OH) and 9.39 μ (C–O). Gas chromatography over Carbowax at 165° indicated the presence of four major products with retention times of 12.5, 14.5, 18.0, and 19.5 min and representing *ca.* 5, 30, 45, and 15% of the total gas chromatographic peak area, respectively. A specimen of the material with retention time of 14.5 min was isolated by preparative gas chromatography (Carbowax), and subjected to short-path distillation.

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.7; H, 11.1.

Similarly a sample of the materials with retention times of 18.0–19.5 min was isolated and submitted to short-path distillation.

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.1; H, 11.2.

A solution of 0.700 g of this mixture of octalols in 40 ml of acetone was treated with 1.17 ml of Jones reagent exactly as described above for the trans-octalols. The resulting pale yellow oil was distilled (short-path) at 50–70° (0.03 mm) to give 0.595 g of a mixture of octalones as a colorless liquid, ir (liquid film) 5.85 μ (C=O). Gas chromatography (Carbowax column at 165°) showed three peaks of retention times 19.6, 23.6, and 28.6 min representing 34, 4, and 62% of the total peak area, respectively. These products were separated by subjecting 0.365 g of the mixture to gas chromatography on the preparative Carbowax column at 200°, and isolated in amounts of 0.084, 0.013, and 0.200 g, respectively. Upon short-path distillation at 45–70° (0.03 mm), the first fraction yielded 0.081 g of the pure (gas chromatography) *cis*-Δ¹-octalone **20**: ir (liquid film) 5.84 μ (C=O); nmr ($CDCl_3$) δ 5.09 (s, 1, $W_{h/2}$ = 4.4 cps, vinylic proton), 1.62 (s, 3, CH_3 at C-2), 1.07 (s, 3, $W_{h/2}$ = 0.54 cps, angular CH_3).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.6; H, 10.05.

The semicarbazone of **20** was obtained from comparable material. It crystallized from ethanol–water as colorless needles, mp 200–201°.

Anal. Calcd for $C_{13}H_{21}ON_3$: C, 66.35; H, 9.00. Found: C, 66.25; H, 8.9.

The 2,4-dinitrophenylhydrazone of **20**, prepared from comparable material, crystallized from ethanol–water as yellow needles, mp 131–132.3°.

Anal. Calcd for $C_{18}H_{22}O_4N_4$: C, 60.32; H, 6.19. Found: C, 60.3; H, 6.15.

The third fraction from the gas chromatography was distilled (short-path) at 50–70° (0.03 mm) to give 0.197 g of a colorless oil, which was found to consist of 75% of the *cis*-Δ²-octalone **21** and of 25% of the corresponding trans isomer **16** (see also below). Repeated preparative gas chromatography yielded pure **21**: ir (liquid film) 5.85 μ (C=O); nmr ($CDCl_3$) δ 5.33 (broad singlet,

(23) L. Friedman, R. L. Litle, and W. R. Reichle, *Org. Syn.*, 40, 93 (1960).

1, $W_{h/2}$ = 9.0 cps, vinylic proton), 1.61 (s, 3, CH_3 at C-2), 1.06 (d, 3, $W_{h/2}$ = 1.04, angular CH_3).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.7; H, 10.0.

The semicarbazone of **21** crystallized from ethanol–water as colorless needles, mp 172–174°.

Anal. Calcd for $C_{13}H_{21}ON_3$: C, 66.35; H, 9.00. Found: C, 66.05; H, 9.0.

The 2,4-dinitrophenylhydrazone of **21** melted at 146–150°.

Anal. Calcd for $C_{18}H_{22}O_4N_4$: C, 60.32; H, 6.19. Found: C, 60.25; H, 6.2.

The second fraction from the gas chromatography was distilled (short-path) to yield 0.013 g of material which was shown to be contaminated with the substances **20** and **21**. It was therefore resubmitted to preparative gas chromatography which afforded material showing a single peak in the vpc (relative area 98%), ir (liquid film) 5.85 μ (C=O). The nmr spectrum displayed singlet absorptions at δ 0.83, 0.85, 0.89, and 0.92. There were no signals for vinylic protons. This material, presumably a mixture of cis and trans decalones, was not investigated further.

***cis*-2,9-Dimethyl-Δ^1-octalin.** The procedure described for the trans isomer was followed. From 18 mg of the pure (gas chromatographed) *cis*-Δ^1-octalone **20** and 22 mg of tosylhydrazine there was obtained 34 mg of the oily tosylhydrazone. Reduction with sodium borohydride yielded, after chromatography on 1 g of silica gel, 10 mg of a colorless oil. Gas chromatographic analysis (Carbowax), using authentic samples[15] as reference, showed this material to consist of 85% of the *cis*-2,9-dimethyl-Δ^1-octalin and of 10% of the corresponding trans isomer.

***cis*-2,9-Dimethyl-Δ^2-octalin.** Similarly, 36 mg of the *cis*-Δ^2-octalone **21** (containing 11% of the trans isomer, as estimated by gas chromatography) was converted into 65 mg of the oily tosylhydrazone. Reduction with sodium borohydride gave, after column chromatography on 2 g of silica gel, 24 mg of colorless oil. Analysis by gas chromatography and comparison with authentic samples[15] indicated the mixture to consist of 84% of the *cis*-Δ^2-octalin, 12% of the corresponding trans isomer, and 4% of an unidentified substance.

Equilibration Studies of the *trans*- and *cis*-Octalones 16, 17, 20, and 21. A solution of 35 mg of the *trans*-Δ^2-octalone **16** and 12.5 ml of 1 *N* potassium hydroxide in methanol was refluxed for 45 min, cooled, added to 50 ml of 5% hydrochloric acid, and extracted with ether. The combined organic layers were washed with water, saturated sodium bicarbonate, and saturated brine. The pale yellow oil, obtained upon evaporation of the solvent, was distilled (short-path) at 85° (0.03 mm) to give 33 mg of a colorless ketone mixture. Planimetric integration of the signals at δ 0.76 and 1.06 in the nmr spectrum indicated an equilibrium composition of 72% of the trans octalone **16** and 28% of the cis isomer **21**. In a similar experiment, approach to the equilibrium starting from the cis isomer **21** yielded a mixture containing 73% of **16** and 27% of **21**.

The equilibrium mixture, obtained from the *trans*-Δ^1-octalone **17**, by treatment as described above, was determined by nmr to have a trans:cis ratio of 19:81. In this case, the composition could also be established by integration of the relative peak areas in the gas chromatogram (Carbowax, 150°), which indicated a trans:cis ratio of 18:82. Approaching the equilibrium from the *cis*-Δ^1-octalone **20** gave identical results.

Stereoselectivity of the Cyclization of the Trans Dienic Acetal 5. The degree of stereoselectivity of the cyclization of **5** in nitromethane can be derived from the experiment described above. The amount of the cis octalones **20** and **21** in the total mixture of ketones obtained following side-chain degradation of the cyclization products and subsequent oxidation of the intermediate octalols was found to be 3%. Correcting this value for the 0.8% of cis isomer present in the starting acetal indicates the stereoselectivity of the process to be better than 97%.

The same degree of stereoselectivity was observed for the cyclization of **5** in benzene. Thus, when 0.153 g of the acetal **5** (containing 0.8% of the cis isomer) was cyclized in this solvent, and the total reaction product was subjected to short-path distillation, side-chain degradation, Jones oxidation, and preparative tlc, 0.073 g (60% yield) of a mixture of ketones was obtained, consisting of 9% of the *trans*-Δ^1-octalone **17** and 85% of the *trans*-Δ^2-octalone **16**. The amount of corresponding cis ketones as judged by gas chromatography and nmr was 2.5%.

Stereoselectivity of the Cyclization of the Cis Dienic Acetal 6. Results of the cyclization of the cis acetal **6** and the subsequent conversion of the reaction product to a mixture of octalones have been reported above. As described, the *cis*-Δ^2-octalone **21**, obtained by preparative gas chromatography, was contaminated with 25% of the corresponding trans isomer. Separate experiments showed, however, that appreciable isomerization occurred during gas chromatographic treatment of **21**. Thus, gas chromatography of **21**, containing 12% of the trans isomer over the preparative Carbowax column at 200° (retention time 60 min), yielded material consisting of 79% of cis and 21% of trans isomer. Similarly, at 180° (retention time 100 min), gas chromatographic treatment of a mixture of cis and trans isomers (76:24) afforded a mixture of these components now containing 60% of the trans isomer. The *cis*-Δ^1-octalone **20** was found to be stable under these conditions. Inspection of the nmr spectra of the total ketonic reaction mixtures, partially purified by repeated short-path distillation rather than preparative gas chromatography, indicated the contribution of the signals of the angular methyl groups of **16** and **17** to be 3% of the total area measured for the angular methyl groups of all components. The material, obtained as the second fraction from preparative gas chromatography of the ketonic mixture, and tentatively identified as a mixture of decalones, may possibly contain some trans octalones. However, the total amount could not exceed 3%. Hence, taking into account the fact that the starting cis acetal contained 1.6% of the trans isomer, the stereoselectivity of the cyclization is better than 95%.

Acknowledgment. We thank the U. S. Public Health Service, the National Science Foundation, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.