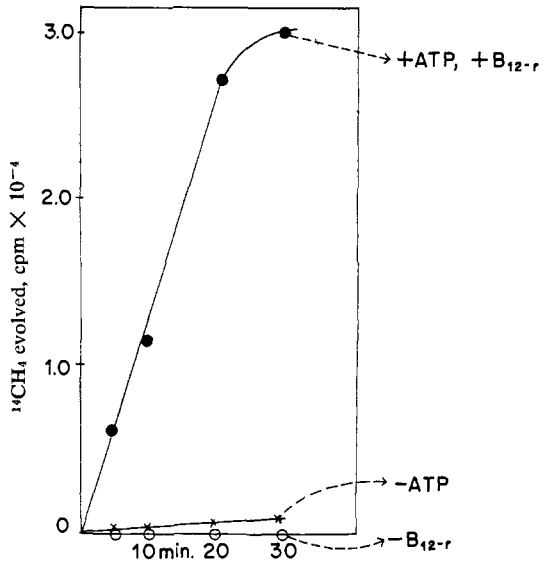
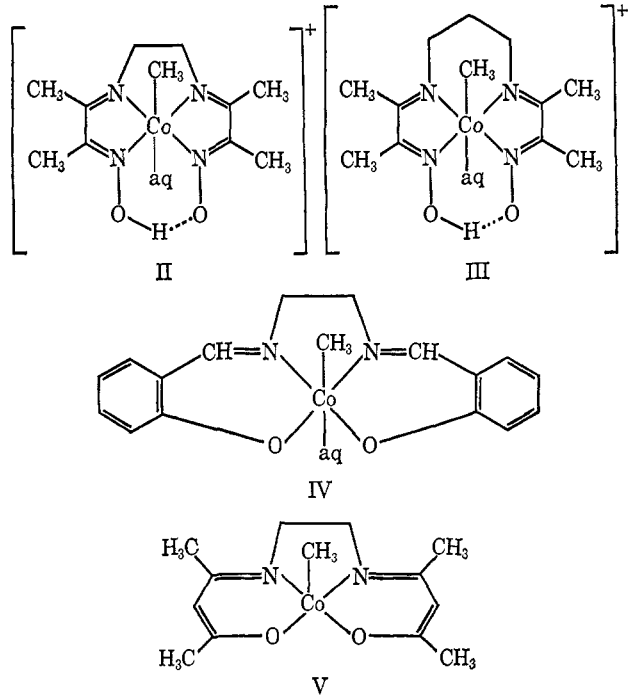


Figure 1. Dependence of $^{14}CH_4$ formation from $^{14}CH_3$-Co(dmg)$_2$·H_2O on vitamin B_{12r} and ATP. Reactions contained: extracts, 27.5 mg of protein; ATP, 10.0 μmol (where indicated); B_{12r}, 1.0 μmol (where indicated); methyl-^{14}C-(aquo)bis(dimethylcobaloxime) (0.22 Ci/mmol), 3.5 μmol; and TES buffer, pH 7.0, 100 μmol. Reactions were run under H_2 at 40°. Total reaction volume 1.25 ml.

components. The greatest activity is found in cobaloximes containing easily displaceable axial ligands such as water or pyridine (Table I).

In order to demonstrate the cofactor requirements for the reaction $^{14}CH_3$-Co(dmg)$_2$·H_2O (dmg = dimethylglyoximato monoanion) was synthesized and $^{14}CH_4$ was assayed[10] in the presence and absence of ATP and B_{12r}. The results of this experiment show the absolute requirement for these two components (Figure 1). When reaction flasks in which ATP had been omitted were taken and the contents submitted to gel filtration on Sephadex G-10, a small amount of methyl-^{14}C-cobalamin was detected and characterized by high-voltage electrophoresis in 4% formic acid followed by radioautography. This experiment shows that some (presumably indirect) methyl transfer from $^{14}CH_3$-Co(dmg)$_2$·H_2O to vitamin B_{12} occurs under the reaction conditions but does not prove that this transfer reaction is important in the catalytic methane formation. The methane system also causes vitamin B_{12r} to become alkylated if excess ethyl or *n*-propyl iodide is added. Ethyl- and *n*-propylcobalamin are formed in stoichiometric yields. Ethyl- and *n*-propylcobaloximes do not produce ethane or propane. Hence, a specificity similar to that observed with the cobalamin derivatives is also observed with the cobaloxime model compounds.



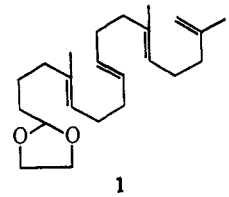
Acknowledgment. This work was supported by National Science Foundation Grants GB 6174, GB 5813, and GB 4481 and U. S. Public Health Service Grant UI-SW 0045.

B. C. McBride, J. M. Wood
Department of Chemistry, University of Illinois Urbana, Illinois 61801
J. W. Sibert, G. N. Schrauzer
Department of Chemistry, University of California, San Diego Revelle College, La Jolla, California 92037
Received June 24, 1968

The Nonenzymic, Biogenetic-Like Cyclization of a Tetraenic Acetal

Sir:

We wish to announce that the tetraenic acetal **1** can be induced to undergo cyclization so as to afford tetracyclic material, namely substances **2a** and **2b**, in about 30% yield.[1] The process is highly stereoselective giving, as far as we have been able to ascertain, tetracyclic products with the rings fused exclusively in the *trans,anti,trans,anti,trans* configuration. Thus we have been able to realize for the first time the nonenzymic stereoselective conversion of an acyclic molecule having no centers of asymmetry into a product with four carbocyclic rings and a multiplicity of asymmetric centers. This process bears a formal resemblance to the enzymic production of tetracyclic triterpenoids from squalene.



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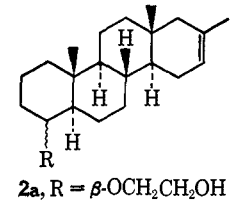
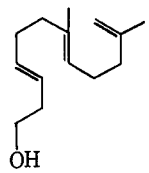


2a, R = β-OCH_2CH_2OH
b, R = α-OCH_2CH_2OH
c, R = β-OH
d, R = α-OH
e, R = H

(1) *Cf.* previous studies on the cyclization of dienic and trienic acetals to give bi- and tricyclic products, respectively: (a) W. S. Johnson, A. van der Gen, and J. J. Swoboda, *J. Am. Chem. Soc.*, **89**, 170 (1967); (b) W. S. Johnson and R. B. Kinnel, *ibid.*, **88**, 3861 (1966).

(10) J. M. Wood, A. M. Allam, W. J. Brill, and R. S. Wolfe, *J. Biol. Chem.*, 240, 3564 (1965).

The tetraenic acetal **1** was prepared as follows. The mesylate of the trienol **3**[2] was treated with sodioacetylacetone in dimethylformamide and benzene to give the dione **4** (R = H). Reaction of this dione with cupric chloride in dimethylformamide containing lithium chloride[3] afforded the chlorodione **4** (R = Cl) which, on treatment with a suspension of barium hydroxide in 95% ethanol at 0°, was smoothly transformed into the chloro ketone **5**. The Cornforth olefin synthesis[4] was used for the elaboration of the remainder of the molecule. Thus the chloro ketone **5** and the Grignard reagent[5] from 1-ethylenedioxy-4-chlorobutane[6] were allowed to interact in tetrahydrofuran at −95°.[7] Treatment of the resulting chlorohydrin by the described sequence[4] afforded the tetraenic acetal **1** which, after purification by a combination of short-path distillation and preparative tlc, was obtained as a colorless oil (*Anal.* Found: C, 79.5; H, 10.8). This material appeared, by vpc analysis, to consist of about 95% of the all-*trans* isomer **1** and 5% of the Δ^5-*cis* isomer.



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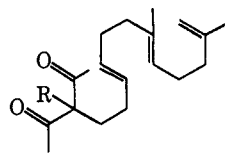

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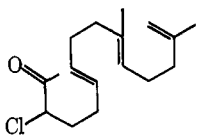

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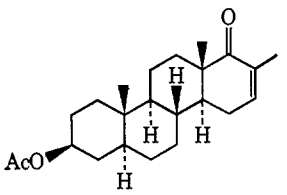
Cyclization studies were performed on the distilled tetraenic acetal **1** (purity 90–92% by vpc). A solution of the substrate (0.05 *M*) and stannic chloride (0.20 *M*) in pentane was stirred for 15 min at 0°, then for 5 min after removal of the cooling bath. Two semicrystalline fractions were separated by chromatography of the crude product on acid-washed alumina. Fraction a, obtained in 23% yield, was recrystallized from methanol to give **2a**: mp 161–163.5°; nmr ($CDCl_3$), δ 0.75 (C-18 methyl), 0.96 (C-19 methyl),[8] 1.61 (vinyl methyl), and 5.33 (broad, vinyl H) ppm. The slower moving chromatographic fraction (b), obtained in 26% yield, contained the 4α isomer **2b**. Recrystallization from methanol gave material: mp 120–125°; nmr ($CDCl_3$), δ 0.77 (C-18 and C-19 methyls), 1.61 (vinyl methyl), and 5.35 (broad, vinyl H) ppm. There was no nmr evidence (*i.e.*, sharper, higher field vinyl H absorption) for the presence of the $\Delta^{17,17a}$ isomer in either epimeric series.[9] The absolute yields of tetracyclic compounds **2a** and **2b** were estimated by vpc analysis of the aforementioned crude fractions a and b to be about 14 and 13%, respectively. The remainder of the material in these crude fractions had shorter retention times on vpc and appeared to be mainly incompletely cyclized products as suggested by ir and nmr absorption bands characteristic of the terminal methylene group.

The side chain of the tetracyclic substances was degraded by the method employed in the bicyclic series.[1a] Thus substance **2a** was converted into **2c**: mp 125–126° (crystallized from methanol); nmr ($CDCl_3$), δ 0.77 (C-18 methyl), 1.02 (C-19 methyl),[8] 1.61 (vinyl methyl), 3.81 (narrow multiplet, equatorial C-4 H), and 5.34 (vinyl H) ppm. Similarly the epimer **2b** was transformed into **2d**: mp 150–153°; nmr ($CDCl_3$), δ 0.78 (C-18 and C-19 methyls), 1.62 (vinyl methyl), 3.44 (broad multiplet, axial C-4 H), and 5.34 (vinyl H) ppm. That these two secondary alcohols (**2c** and **2d**) were epimers was proved by their oxidation to the same ketone: mp 133.5–135° (*Anal.* Found: C, 84.0; H, 10.5); nmr ($CDCl_3$), δ 0.766 and 0.718 (angular methyls), 1.60 (vinyl methyl), and 5.30 (vinyl H) ppm. Wolff–Kishner reduction of this ketone gave a mixture of hydrocarbons containing about 85% of the substance **2e** and 15% of the A/B *cis* isomer[9,10] as estimated by vpc analysis as well as by the relative intensities of the nmr signal for the C-19 methyl at δ 0.76 and 0.89 ppm, respectively. Recrystallization from methanol gave the pure isomer **2e**: mp 95–97°; nmr ($CDCl_3$), δ 0.76 (C-18 and C-19 methyls), 1.60 (vinyl methyl), and 5.30 (vinyl H) ppm; when benzene was used as solvent, the angular methyl signals were resolved, appearing at 0.74 and 0.82 ppm.

The structures and configurations of the tetracyclic products described above were unequivocally proved by comparison of the racemic hydrocarbon **2e** with an authentic specimen of the enantiomer derived by partial synthesis from a steroid as follows. The known acetoxy unsaturated ketone **6**,[11] obtainable in several steps from pregnenolone acetate, was reduced with lithium aluminum hydride. The resulting diol **7** (R^1 = R^2 = OH, mixture of C-17a epimers) was acetylated with acetic anhydride and pyridine, and the diacetate was reduced with lithium in ethylamine[12] to effect hydrogenolysis of the allylic acetoxy group giving a mixture of the 3-hydroxy-Δ^{16} substance **7** (R^1 = OH, R^2 = H) and the $\Delta^{17,17a}$ isomer in a ratio of 3:2 as estimated by nmr. The former substance was presumably derived from the 17aβ (pseudoequatorial) acetoxy isomer, and the latter from the 17aα epimer.[12] This mixture of double bond isomers was oxidized with Jones reagent to the 3-keto compound which was converted, by Wolff–Kishner reaction, into the mixture of Δ^{16} and $\Delta^{17,17a}$ hydrocarbons. The components of this mixture were cleanly separated by preparative tlc on silica gel impreg-



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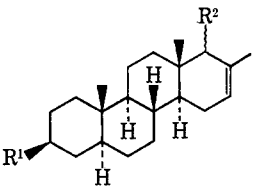

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(2) W. S. Johnson, M. F. Semmelhack, M. U. S. Sultanbawa, and L. A. Dolak, *J. Am. Chem. Soc.*, **90**, 2996 (1968).
(3) E. M. Kosower, W. J. Cole, G.-S. Wu, D. E. Cardy, and G. Meisters, *J. Org. Chem.*, **28**, 630 (1963).
(4) J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 112, 2539 (1959).
(5) *Cf.* C. Feugeas and H. Normant, *Bull. Soc. Chim. France*, 1441 (1963).
(6) M. G. Pleshakov, A. E. Vasil'ev, I. K. Sarycheva, and N. A. Preabrazhenskii, *J. Gen. Chem. USSR*, **31**, 1433 (1961).
(7) The low temperature was used to enhance the stereoselectivity of the Grignard addition reaction and hence of the introduction of the Δ^5 double bond. See S. F. Brady, M. A. Ilton, and W. S. Johnson, *J. Am. Chem. Soc.*, **90**, 2882 (1968).
(8) The β (axial) group at C-4 is responsible for the downfield shift of the C-19 methyl group, just as in the case described in ref 1a.
(9) *Cf.* ref 1a.
(10) Such isomerization during the Wolff–Kishner reduction is an established phenomenon; see, *inter alia*, C. Djerassi, T. T. Grossnickle, and L. B. High, *J. Am. Chem. Soc.*, **78**, 3166 (1956).
(11) D. K. Fukushima, S. Dobriner, and R. S. Rosenfeld, *J. Org. Chem.*, **26**, 5025 (1961).
(12) *Cf.* A. S. Hallsworth, H. B. Henbest, and T. I. Wrigley, *J. Chem. Soc.*, 1969 (1957).

nated with 10% silver nitrate. The desired naturally derived Δ^{16} isomer **2e** melted at 108.5–110° after crystallization from methanol–ethyl acetate. The nmr, solution ir, and mass spectra (molecular ion peak at *m/e* 286) of this material were identical with the corresponding spectra of the hydrocarbon prepared from the product of cyclization of the tetraenic acetal.

Acknowledgment. We wish to 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.

William S. Johnson, Koenraad Wiedhaup, Stephen F. Brady, Gary L. Olson
Department of Chemistry, Stanford University
Stanford, California 94305
Received August 5, 1968

Asymmetric Induction of an Olefinic Acetal Cyclization

Sir:

The enzymatic cyclization of squalene proceeds with total asymmetric induction to produce only one enantiomeric form of the polycyclic products. It has been our general aim to simulate this result in our nonenzymic olefinic cyclizations.[1]

We have described the stannic chloride catalyzed cyclization of the *trans* dienic acetal **1** (R = H) which proceeds in high yield and essentially stereospecifically with respect to the ring fusion.[2] Thus when the reaction was conducted in nitromethane solution,[1] the major product (about 80% yield) was the *dl* mixture **2a,b** (R = CH_2CH_2OH). The *dl* mixture **3a,b** (R = CH_2CH_2OH), with the epimeric (equatorial) side chain, was the main constituent of the remainder of the product. Degradation of the side chain to the hydroxyl group, followed by oxidation, gave a single racemic ketone (**4a,b**) from both epimers. The present investigation was undertaken to see if the cyclization of the optically active acetal **1** (R = CH_3) derived from *l*-2,3-butanediol (*R,R* configuration) would proceed with asymmetric induction to produce, after the side-chain degradation, ketone that was rich in either **4a** or **4b**. This objective has been realized; indeed the degree of asymmetric induction observed was exceedingly high. We have been able, moreover, to ascertain the absolute configuration of the products.

The acetal **1** (R = CH_3) was prepared as follows. The *trans*-bromodiene **5**,[3] on condensation with sodiomalonic ester, gave the dienic malonic ester **6** (R = CO_2Et) which, upon heating with sodium cyanide in dimethyl sulfoxide,[4] suffered decarbethoxylation giving **6** (R = H). The alcohol **7**, obtained by reduction of **6** (R = H) with lithium aluminum hydride, was transformed in 94% yield into the corresponding aldehyde simply by treatment at room temperature for 15 min with about 6 mol equiv of Collins reagent.[5] This aldehyde, on treatment with excess *l*-butane-2,3-diol[6] in the presence of boron trifluoride etherate, was converted into the acetal **1** (R = CH_3), ORD $[\alpha]^{20}_{300}$ −84.0° (*c* 0.699, dioxane).[7]

A solution of the acetal **1** (R = CH_3) (0.02 *M*) and stannic chloride (0.04 *M*) in benzene was allowed to stand for 7 min at room temperature. At the end of this period cyclization was complete. When nitromethane was used as the solvent cyclization was complete in 3 min at 0°. In pentane the reaction took about 4 hr at room temperature, and in ultradry pentane it required 9 days for completion.[8]

The major products of the cyclization, namely **2a,b** (R = $CH(CH_3)CH(OH)CH_3$) and **3a,b** (R = $CH(CH_3)$-$CH(OH)CH_3$), were easily separated by chromatography on Florisil. The side chain was removed very efficiently as follows: oxidation with Collins reagent[5] gave the corresponding keto ether (R = $CH(CH_3)COCH_3$) which, on treatment with lithium and ethylamine, underwent cleavage affording the octalols **2a,b** (R = H) and **3a,b** (R = H). Traces of impurities were removed from these last substances by submitting them to preparative tlc and vpc. In the case of the cyclization in benzene, the axial octalol **2a,b** (R = H), on oxidation with Jones reagent, yielded a specimen of octalone **4a,b**, ORD[9a] (*c* 0.261, dioxane) $[\Phi]_{589}$ +118°, $[\Phi]_{315}$ +594°, $[\Phi]_{222}$ +9278°, which, as shown below, corresponds to a composition of 92% **4b** and 8% **4a**. In contrast, the ORD curve of the octalone derived from the equatorial octalol proved to be the enantiomeric counterpart, corresponding to 8% **4b** and 92% **4a**.[9a] In the case of the cyclizations conducted in ultradry pentane and in nitromethane, the ORD curves of the octalones derived from the axial octalols indicated that **4b** was present to the extent of 86[9b] and 75%,[9a] respectively. These ORD curves were abnormal and could not be used to deduce the absolute configurations of the products.

The aforementioned enantiomeric ratios were determined as follows. A sample of axially derived octalone obtained from the cyclization in benzene was reduced by the Wolff–Kishner method and the pure *trans*-octalin was separated from the *cis* isomer[10] by preparative vpc. This octalin, in methanol, was treated with excess ozone at −78° followed by hydrogen peroxide in acetic acid to give the keto acid **8** (R = CH_3).[11] Further oxidation with sodium hypobromite[12] afforded the diacid **8** (R = OH),[11] which was trans-

(1) *Cf.* W. S. Johnson, *Accounts Chem. Res.*, **1**, 1 (1968).
(2) W. S. Johnson, A. van der Gen, and J. J. Swoboda, *J. Am. Chem. Soc.*, **89**, 170 (1967).
(3) S. F. Brady, M. A. Ilton, and W. S. Johnson, *ibid.*, **90**, 2882 (1968).
(4) A. P. Krapcho, G. A. Glynn, and B. J. Grenon, *Tetrahedron Letters*, 215 (1967).
(5) J. C. Collins, W. W. Hess, and F. J. Frank, *ibid.*, 3363 (1968).
(6) We wish to thank Dr. Karl L. Smiley, Head of Industrial Products Investigations, Fermentation Laboratory, U. S. Department of Agriculture, Peoria, Ill., for a generous gift of a sample of this material. The absolute configuration of this diol is known to be *R,R*; see, *inter alia*, L. J. Rubin, H. A. Lardy, and H. O. L. Fischer, *J. Am. Chem. Soc.*, **74**, 425 (1952).
(7) The optical activity was not attenuated upon prolonged extension of the time of reaction; hence no appreciable racemization of the optically active centers had occurred.
(8) The effect of traces of water to enhance the rate of reactions involving Lewis acid catalysts has been well documented: G. A. Olah, "Friedel-Crafts and Related Reactions," Vol. I, Interscience Publishers, Inc., New York, N. Y., 1963, pp 205–215.
(9) (a) Average of three determinations; (b) average of two determinations.
(10) The amount of *cis* isomer, formed during the Wolff–Kishner reaction (see ref 2), can be suppressed to about 20% by first conducting the hydrazone formation at 0° for 12 hr.
(11) As shown below, this substance contained about 92% of that enantiomeric form depicted by the formula.
(12) According to a modification of the procedure of C. Djerassi and J. Staunton, *J. Am. Chem. Soc.*, **83**, 736 (1961), in which the dioxane was omitted.