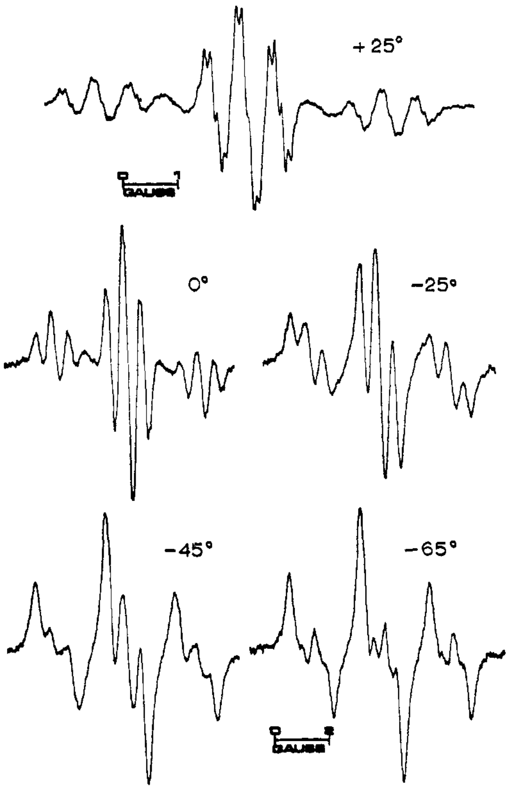

Figure 1. Esr first-derivative spectra of bicyclo[3.3.2]decane-9,10-semidione in DMSO solution at 25° and in a 4:1 DMF–DMSO mixture at lower temperature.

between −75 and 100°. At high temperature the two forms are rapidly interconverting[6] and the hfsc are population averaged, with a^{H} (2 H) 1.95, a^{H} (2 H) 1.55, a^{H} (2 H) 1.40, and a^{H} (1 H) 0.80 G. As the temperature is lowered, the large triplet, from the flexible portion of the molecule, coalesces, and at −65°, when ring inversion has been slowed, increases to 2.75 G. The magnitude of this splitting indicates[4] that the spectrum is due to **4c** where the seven-membered ring with the semidione group is in the chair form.

Thus, the seven-membered ring containing the semidione group prefers the chair conformation to a slightly greater extent than does the saturated seven-membered ring, at least at −65°. Relating this to **3**, it would seem that **3** would have a greater preference for conformation **3c** than would the parent hydrocarbon. Since **3** does not assume the conformation **3c** it would be unlikely for the saturated parent system to do so. The instability of **3c** must then be due to the (unfavorable) "saddle" conformation of the eight-membered ring.[8]

The semidiones were generated from known compounds, *i.e.*, **3** from the diester,[9] and **4** also from the diester prepared by oxidation of bicyclo[3.2.2]non-6-ene obtained by the bisdecarboxylation[10] of the hydrogenated Diels–Alder adduct of cycloheptadiene and maleic anhydride,[11] using methods which have previously been discussed.[12]

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(6) Thus this system possesses a small energy of activation for interconversion as does the bicyclo[3.2.2]nona-6,8-diene system.[7]

(7) A. J. Baker, A. M. Chalmers, W. W. Flood, D. D. MacNicol, A. B. Penrose, and R. A. Raphael, *Chem. Commun.*, 166 (1970).

(8) This is contrary to the suggestion of J. Dale, I. Laszlo, and W. Ruland, *Proc. Chem. Soc.*, 190 (1964).

(9) A. C. Cope, E. S. Graham, and D. J. Marshall, *J. Amer. Chem. Soc.*, **76**, 6159 (1954).

(10) C. M. Cimarusti and J. Wolinski, *ibid.*, **90**, 113 (1968).

(11) E. P. Kohler, M. Tischler, H. Potter, and H. T. Thompson, *ibid.*, **61**, 1057 (1939).

(12) G. A. Russell and P. R. Whittle, *ibid.*, **89**, 6781 (1967).

(13) National Science Foundation Predoctoral Fellow, 1967–1970.

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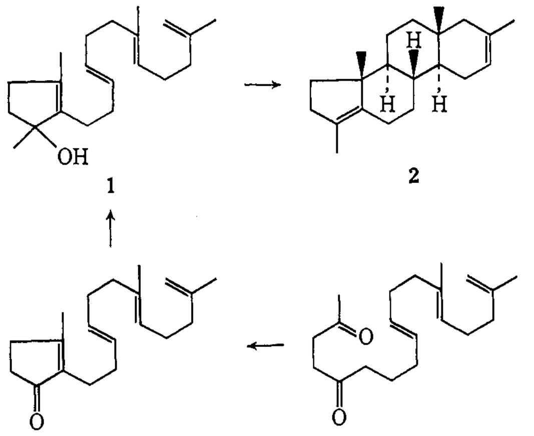
Further Developments in the Nonenzymic Biogenetic-like Steroid Synthesis

Sir:

We have previously shown that the tetraenol **1**, on acid-catalyzed cyclization, is transformed stereospecifically into the crystalline tetracyclic diene **2** which, on oxidative cleavage followed by a double intramolecular aldol cyclodehydration, affords *dl*-16,17-dehydroprogesterone.[1] The substrate **1** is readily produced from the dione **4** by cyclodehydration (to give **3**), followed by treatment with methyllithium. The dione **4** was previously produced by a multistep linear synthesis.[1] We now report a much improved synthesis of **4**, which is *convergent* and depends upon the use of the $\mathrm{S_Ni'}$ reaction of thionyl chloride with an allylic alcohol for the stereospecific production of the *trans*-trisubstituted olefinic bond.[2]



The olefinic aldehyde **5**, which is easily produced by Claisen rearrangement of the vinyl ether of methallyl alcohol, afforded the dienol **6** (mass spectrum *m/e* 140, M^+) on treatment with isopropenyllithium. The dienol, on treatment in anhydrous ether for 1 hr at 25° with 1.3–1.9 equiv of thionyl chloride, gave the *trans* diene chloride **7** contaminated with about 9% of the secondary chloride arising from direct substitution and 3–7% of an unidentified impurity. Fortu-

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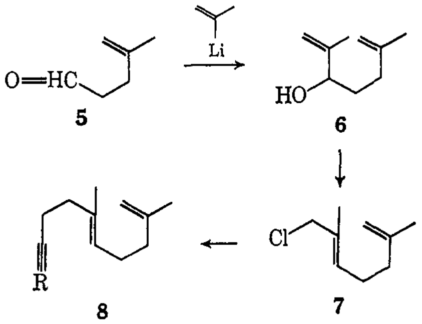
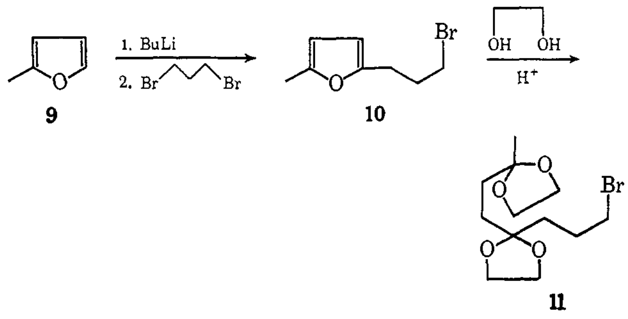
(1) W. S. Johnson, M. F. Semmelhack, M. U. S. Sultanbawa, and L. A. Dolak, *J. Amer. Chem. Soc.*, **90**, 2994 (1968).

(2) This reaction was shown by F. F. Caserio, G. E. Dennis, R. H. DeWolfe, and W. G. Young, *ibid.*, **77**, 4182 (1955), to be stereospecific for the production of *trans*-disubstituted olefinic bonds, *e.g.*, $CH_3CHOHCH{=}CH_2 \rightarrow CH_3CH{=}CHCH_2Cl$ (100% *trans*). In addition to the present case, we have found that the method is applicable to the stereospecific production of *trans*-trisubstituted olefins in two other instances.

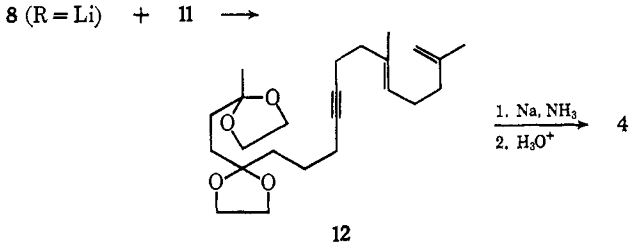
nately these two impurities were relatively volatile and could be eliminated simply by fractionally distilling them from the mixture. The residue,[3] on coupling with excess propargylmagnesium bromide,[4] gave the dienyne **8** (R = H) in about 50% yield overall from the dienol **6**. The dienyne is an unstable compound and, although a pure specimen could be obtained by fractional distillation (attended by considerable decomposition), it was found best to use material that had been simply evaporatively distilled (120° (20 mm)) for continuing the synthesis as described below. It is noteworthy that the dienyne, prepared as described above, was shown by ir, nmr, and vpc to be identical with an authentic specimen of **8** (R = H) isolated by vpc from a 3:2 mixture of *cis* and *trans* isomers resulting from a Wittig reaction between 5-hexyn-2-one and the phosphorane **5** ($(C_6H_5)_3P$ in place of O). The 60-MHz nmr spectrum of the pure dienyne (in $DCCl_3$ TMS internal standard) showed a broad multiplet (1 H) at δ 5.16 (C-6 vinyl proton), a broad singlet (2 H) at 4.70 (terminal vinyl protons), several bands (8 H) at 2.23–2.04 (methylene protons), a sharp multiplet (1 H) at 1.91 (acetylenic proton), a "singlet" (3 H) at 1.72 (C-9 methyl protons), and a singlet (3 H) at 1.62 (C-5 methyl protons).



The bromo bisketal **11**, the other fragment required for reaction with the dienyne, was easily prepared as follows. 2-Methylfuran (**9**) was treated with *n*-butyllithium followed by excess 1,3-dibromopropane giving the bromo compound **10**, bp 70–72° (1.8 mm), *m/e* 202, M^+, in 59% yield.[5] The acid hydrolysis of such compounds is known to give γ-diketones, but this reaction generally results in a dark impure product from which satisfactory material can be isolated in only fair yield. In the present work we have found that substances like **10**, on treatment with ethylene glycol and *p*-toluenesulfonic acid in benzene (refluxing about 4 days), give good (70–90%) yields of the corresponding bisketals. The substance **11** was obtained by flash distillation in 76% yield (purity estimated by tlc and vpc to be about 90%). A specimen was purified by tlc followed by bulb-to-bulb distillation at 140° (0.015 mm), n^{24}D 1.4859.



The lithium salt **8** (R = Li), prepared by the action of methyllithium on the crude dienyne, underwent alkylation with the bromo ketal **11** (39 hr, refluxing in THF) to give the bisketal **12** in yields approaching 50% ($\lambda_{\max}^{\text{film}}$ of chromatographed specimen 3.25, 6.08, and 11.25 μ ($C{=}CH_2$)). This substance, on reduction of the acetylenic bond with sodium in liquid ammonia followed by hydrolysis of the bisketal with dilute methanolic hydrochloric acid, afforded, in >90% yield, the known[1] *trans,trans* dione **4**. The ir spectrum of the intermediary trienic bisketal, after purification by tlc followed by evaporative distillation at 115–120° (10^{-6} mm), was similar to that of **12** except for additional absorption at 10.30 μ (*trans* CH=CH).



Even though the yields have not been optimized, the aforementioned transformations render the tetraenol **1** easily accessible.

Further cyclization studies have revealed that the tetraenol **1**, on treatment with 4 equiv of anhydrous stannic chloride in nitromethane (4.5 ml/mmol of **1**) at −23° for 3 hr, can be converted into crystalline tetracyclic hydrocarbon **2**, mp 67–72°, in about 70% yield (isolated by filtration through Florisil), which represents a dramatic improvement over the previously reported results.[1]

Similar cyclization conditions, applied to the secondary alcohol arising from reduction of **3** with lithium aluminum hydride in ether at 0°, gave comparable yields of crystalline 19-nor-**2**, which is convertible,[6] in two steps, into *dl*-19-nor-16,17-dehydroprogesterone.

According to the present state of the art the yields in this synthesis are such that one may expect to obtain approximately 10 g of *dl*-16,17-dehydroprogesterone (or of the 19-nor compound) starting with 100 g of methallyl alcohol.[7]

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(3) An analytical sample (mass spectrum *m/e* 158, M^+) was prepared by preparative vpc. Condensation of the crude product with diethyl sodiomalonate (16 hr in THF at 75°), followed by treatment with excess tetramethylammonium acetate in DMSO for 12 hr at 92° to effect decarbethoxylation, gave the diene ester **7** (CH_2CO_2Et in place of Cl) which was shown to be identical with the material produced by the orthoacetate Claisen reaction on **6** (W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, and M. R. Petersen, *J. Amer. Chem. Soc.*, **92**, 741 (1970)). The product obtained in the present work showed, by vpc, a trace (<1%) of the *cis* isomer.

(4) R. E. Ireland, M. I. Dawson, and C. A. Lipinski, *Tetrahedron Lett.*, in press. We thank Professor Ireland for making his procedure available to us prior to publication.

(5) *Cf.* G. Büchi and H. Wüest, *J. Org. Chem.*, **31**, 977 (1966).

(6) S. J. Daum, R. L. Clarke, S. Archer, and W. S. Johnson, *Proc. Nat. Acad. Sci. U. S.*, **62**, 333 (1969).

(7) All new compounds reported in this paper have been fully characterized by nmr, ir, and mass spectrometry as well as combustion analysis.

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.

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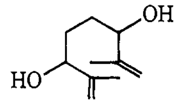
Received April 14, 1970

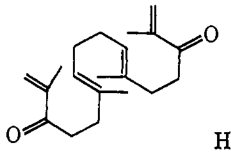
Olefinic Ketal Claisen Reaction. A Facile Route to Juvenile Hormone[1]

Sir:

The methoxyisoprene Claisen method[2] for the production of successive head-to-tail isoprene units with *trans* olefinic bonds has been used in connection with a stereoselective synthesis of squalene.[3] Thus the dienediol **1** on heating at 140° in xylene with excess 3-methoxyisoprene and catalytic amounts of hydroquinone and perchlorohomocubanecarboxylic acid for 25 hr gave the tetraenedione **2**, which was reduced with sodium borohydride to give the tetraenediol **3** in 53% yield.[4] The rearrangement almost certainly involves vinyl allylic ethers like **4**, which are produced *in situ.*



1



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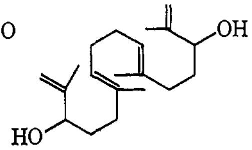

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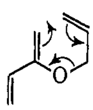

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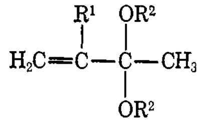
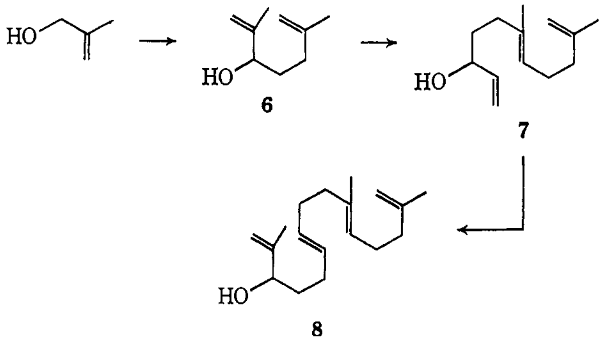


$$H_2C{=}\overset{\overset{\displaystyle R^1}{|}}{C}{-}\underset{\underset{\displaystyle OR^2}{|}}{\overset{\overset{\displaystyle OR^2}{|}}{C}}{-}CH_3$$

5a, $R^1 = H; R^2 = Et$
b, $R^1 = Me; R^2 = Me$
c, $R^1 = Me; R^2 = Et$
d, $R^1 = Et; R^2 = Me$

Some time ago we noted that the ketal from ethylene glycol and mesityl oxide, on heating with geraniol at 192° for 2 days, produced a product with nmr, ir, and mass spectral properties that were consistent with an α,β-unsaturated ketone structure resulting from a Claisen rearrangement involving an intermediary species like **4**. This discovery prompted us to undertake a detailed study of the use of olefinic ketals in the Claisen rearrangement and has led to the development of a procedure for effecting the transformation in good yield under relatively mild conditions.

In order to allow a direct comparison of the olefinic ketal Claisen reaction with the aforementioned method, we have examined the conversion of **1** → **2** using the ketal **5b**. Our currently favored procedure involves heating at 100° for about 8 hr a solution of 1.18 mmol of **1** in 2.6 ml of toluene containing 1.19 mmol of 2,4-dinitrophenol[5] and a total of 13 mmol of **5b**.[6] Chromatography on Florisil afforded diketone **2** which was reduced with sodium borohydride in methanol at 0° to give the diol **3** in 62% yield after distillation[7] at 145° (0.01 mm) (97% pure by vpc, with no detectable *cis* isomers).[8] This procedure has advantages over the former method:[3] the ketals **5**, prepared by direct ketalization (orthoformate and excess alcohol) of the corresponding α,β-unsaturated ketones, are more readily accessible than the corresponding dienol ethers. Also the considerably lower temperature, shorter heating period, and weaker acidity of the reaction mixture give a relatively clean product which is readily purified and afford somewhat better yields. There are no appreciable competing Diels–Alder additions or polymerizations; hence the hydroquinone can be omitted. Moreover these milder conditions minimize tendency for geometric isomerization in sensitive systems (see below).



An interesting application of a succession of olefinic ketal Claisen reactions (combined with the reduction step) is exemplified by the conversion of methallyl alcohol into **6** using the ketal **5b**, of **6** into **7**[8] (*m/e* 194, M+) using the ketal **5a**, and of **7** into **8** using the ketal **5b** or **5c**. The first two stages have been studied in only a preliminary way, but sufficiently to ascertain that products of very high stereochemical purity were produced. The last step, **7** → **8**, has been examined more thoroughly. Under conditions similar to those described above (4 equiv of ketal), yields as high as 81% of distilled[7] (150° (0.35 mm)) tetraenol **8** (98% pure by vpc; *m/e* 262, M+) have been realized. Hence the olefinic ketal Claisen reaction is useful for preparing *trans*-disubstituted as well as *trans*-trisubstituted olefinic bonds.

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[1] This work was reported, in essence, at the Metrochem Organic Synthesis Symposium at Stevens Institute of Technology, Hoboken, N. J., March 25, 1970.

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

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

[4] This represents the yield of material after distillation (footnote 7) at 145° (0.01 mm).

[5] Ammonium nitrate is also effective as a catalyst, as are propionic, diphenylacetic, trimethylacetic, or mesitoic acids. The carboxylic acids, however, are gradually esterified under the reaction conditions.

[6] In the preparation of **2** the olefinic ketal was added in three portions and the methanol removed by distillation as the reaction progressed; however, in other instances comparable results were obtained when the ketal was added all at once or when the methanol was not removed. Also the ethyl ketal **5c** seemed to be as effective as **5b**.

[7] Evaporative bulb-to-bulb distillation using a Büchi kugelrohrofen.

[8] This substance was compared (vpc, tlc, nmr, and ir) and shown to be identical with that from the orthoester Claisen sequence.[3]