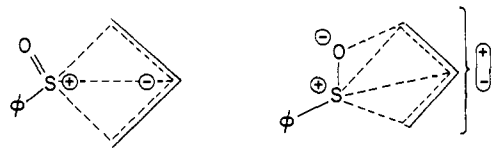
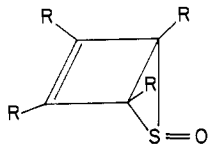


3a **3b**

tween these alternatives awaits the outcome of kinetic studies presently in progress.

The extraordinarily facile automerization of the sulfoxide of perfluorotetramethyl(Dewar thiophene) (**4**), characterized by Ross, Seiders, and Lemal[11] and tentatively favored by these authors to proceed by an unusual pseudopericyclic 1,3-sigmatropic route, merits some comment. On the other hand, cyclobutadiene complexed to phenylthio moieties have been proposed to occur during the isomerization of 2-phenyl- to 3-phenylthiophene in glow discharges[18] and to explain ^{13}C labeling patterns found in electron impact studies.[19] Similar square pyramidal structures have been suggested[4] as possible thiaallylic rearrangement intermediates. Finally, π-face bonding of rectangular, singlet cyclobutadiene with carbon monoxide, hydrogen cyanide, and benzene has been considered in recent theorietical investigations.[20]

However, in view of the dissociative pathway identified for the conversion of **1** → **2** (X = O), the possibility now exists that the automerization of **4** passes through an intermediate with



4 (R = CF_3)

the structure of an ion pair of dipolar or multipolar character, whose geometry is a reflection of charge interactions of considerable complexity.

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(17) The associative model calculations here yield a maximum value of k_{32}/k_{34}. Correction for natural abundance ^{13}C and ^{2}H would result in a slightly lower value.
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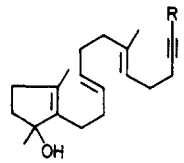
Harold Kwart,* David A. Benko
University of Delaware, Department of Chemistry
Newark, Delaware 19711
Received July 18, 1978

Biomimetic Polyene Cyclizations.[1] Participation of the Phenylacetylenic Group as a Terminator and the Formation of C/D Cis Steroidal Products

Sir:

The participation of the methylacetylenic group as a terminator of biomimetic polyene cyclizations, so as to form directly the five-membered D ring of steroid precursors, has been well documented;[2] e.g., the conversion **1** into **13** (Me in place of C_6H_5) occurs in yields approaching 70%.[3] The remaining

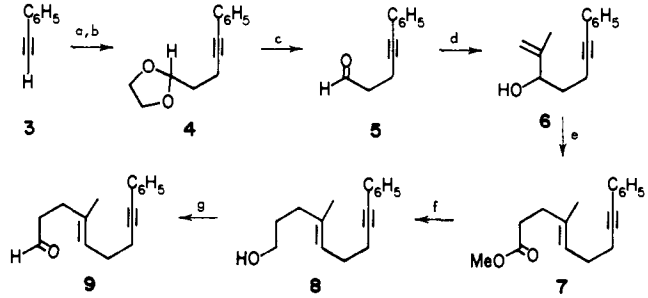


1 (R = Me)
2 (R = C_6H_5)

material consists principally of olefinic byproducts, apparently derived from deprotonation of a tricyclic cation.[4] It was hoped that use of a more nucleophilic terminator, i.e., the phenylacetylenic in place of the methylacetylenic group, would lead to increased yields of tetracyclic material. Therefore an examination of the cyclization of the trienynol **2** was undertaken, and the present communication represents a preliminary report of this study which has yielded some unexpected results.

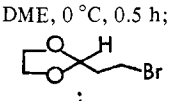
The trienynol **2** was synthesized in a convergent manner, the key step being a Wittig reaction between the aldehyde **9** and the phosphorane formed from the known phosphonium salt **10**.[3] The aldehyde **9** was prepared as outlined in Scheme I. Treatment of the lithium salt of **3** with the ethylene glycol acetal[5] of 3-bromopropanal produced the acetal **4**[6,7] in 82% yield. Hydrolysis of the acetal function gave the aldehyde **5**[6,7] in 78% yield, which was treated with isopropenylmagnesium bromide to produce the allylic alcohol **6**[6,7] in 93% yield. This alcohol was converted to the enyne ester **7**[6,7] in 91% yield by means of the orthoacetate Claisen reaction.[8] Reduction of the

Scheme I[a]



3 **4** **5** **6** **9** **8** **7**

[a] a, BuLi, 1:2 HMPA–DME, 0 °C, 0.5 h; b, compound i, DME,



i

0 °C, 2 h; c, 1:1 5% HCl–$(CH_3)_2CO$, 23 °C, 48 h; d, *i*-C_3H_5MgBr, THF, 0 °C, 1 h; e, $CH_3C(OCH_3)_3$, 0.5% $C_2H_5CO_2H$, 95 °C, 48 h; f, $LiAlH_4$, THF, 0 °C, 1 h; g, $CrO_3 \cdot 2C_5H_5N$, CH_2Cl_2, 23 °C, 0.5 h.

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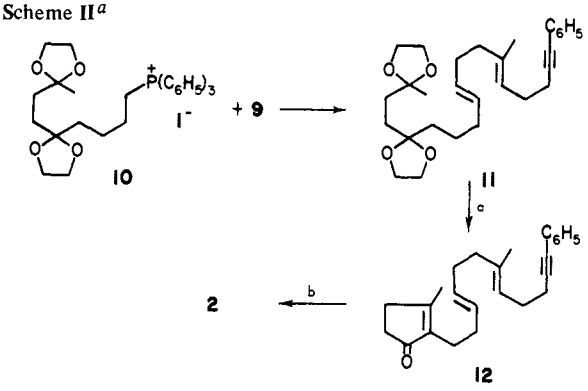
Scheme II[a]



[a] a, 1:4 5% HCl–MeOH, 23 °C, 18 h, and 5:6:2 5% NaOH–MeOH–THF, 70 °C, 3 h; b, MeLi, Et_2O, 0 °C, 10 min.

enyne ester **7** gave an 81% yield of the corresponding alcohol **8**[6,7,9] (homogeneous by VPC on a 6-ft 3% XE-60 column), the NMR spectrum of which included a singlet at δ 1.63 which is characteristic of a methyl group on a trans trisubstituted olefinic bond. Collins oxidation[10] of the enyne alcohol **8** gave the required aldehyde **9**[6,7] in 90% yield.

The aldehyde **9** was condensed with the phosphorane formed from the phosphonium salt **10**[3] (see Scheme II), using the Schlosser[11] modification of the Wittig reaction, to give a 73% yield of the diketal **11**.[6,7,9] Hydrolysis to the corresponding dione followed by base-catalyzed cyclodehydration produced the cyclopentenone **12**[6,7,9] (*pro*-C-8,9 bond, >95% trans by VPC) in 81% yield. Treatment of **12** with excess ethereal methyllithium gave the trienynol **2** which was cyclized immediately without purification.

In a typical experiment, a solution of the substrate **2** (derived from 200 mg of the enone **12**) in 14 mL of methylene chloride was added slowly to a solution of 1.4 mL of trifluoroacetic acid in 26 mL of methylene chloride, containing 800 mg of ethylene carbonate, maintained at −45 °C. After the mixture was stirred at this temperature for 45 min, treatment with methanolic sodium hydroxide resulted in the isolation[9] of a mixture of tetracyclic ketones in yields close to 80%. The exact composition of this mixture depended on the extent of the epimerization at C-17 on basic workup. Partial separation of the mixture could be achieved by column chromatography on Florisil. First eluted was the 13α,17β isomer **15** (mp 122–125 °C after recrystallization from ethanol), followed by fractions containing mixtures of all four isomers **13, 14, 15,** and **16.** Finally the pure 13β,17β isomer **13** (mp 108–110 °C after recrystallization from ethanol) was eluted. Heating **15** under reflux in *tert*-butyl alcohol containing potassium *tert*-butoxide resulted in epimerization of the C-17 position to give virtually complete conversion to the 13α,17α isomer **16** (at equilibrium the ratio of **16:15** was 95:5) which after recrystallization from ethanol melted at 147–149 °C. On similar epimerization **13** gave an equilibrium mixture containing ~40% of the corresponding 13β,17α isomer **14.** Preparative plate chromatography on silica gel gave a pure sample of **14** (mp 110–112 °C after recrystallization from ethanol). Each of the isomers **13, 14, 15,** and **16** was separable by VPC (6-ft 3% XE-60 column, 230 °C, retention times 9.5, 8, 5.5, and 6.5 min, respectively) and each was shown by coinjection to be one of the four components of the original mixture. The VPC trace of the crude mixture, obtained after cyclization and basic workup, also showed that the ratio of 13β (C/D trans) isomers (**13** + **14**) to 13α (C/D cis) isomers (**15** + **16**) was always ~4:1.

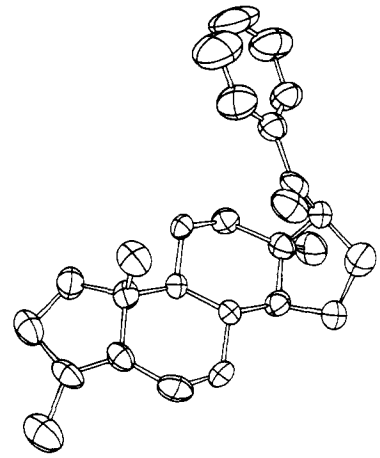
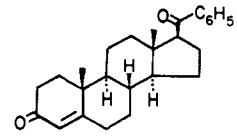


Figure 1. An ORTEP plot of the isomer, mp 122–125 °C, showing it to have the structure **15.**

The structure of 13β (C/D trans) isomer **13** (and hence of **14**) was confirmed by the following transformations. Ozonolysis of **13** (O_3, 1:1 CH_2Cl_2–MeOH, −78 °C, 5 min; zinc and 2 N acetic acid, 0 °C, 4 h) followed by base-catalyzed cyclodehydration (1:2 5% NaOH–MeOH, 23 °C, 40 h) produced the known steroid analogue **17**,[12] which was identical both spectroscopically (NMR, IR, and mass spectra) and chromatographically with that prepared by the reported procedure.[12] Unequivocal proof of the structure of **15** (and hence of **16**) was obtained by a single-crystal X-ray analysis (see Figure 1).



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In conclusion, the phenylacetylenic terminator did indeed give higher yields of tetracyclic material compared with the methylacetylenic case, and there was no evidence of products derived from incomplete cyclization. However, quite unexpectedly, ~20% of the product was found to consist of the unnatural 13α (C/D cis) isomers.[13] This discovery has prompted us to look more critically at all of our cyclizations involving acetylenic terminators, and evidence has been gradually accumulating suggesting that these generally lead to products contaminated with 13α (C/D cis) isomers. Formerly these contaminants were apparently overlooked because they were often present in small amounts and were inadvertantly eliminated by chromatography in early eluants. Moreover, by our VPC technique, the major 13α,17β product generally exhibited the same retention time as, and therefore was mistaken for, the 13β,17α isomer. A solution to the problem of the failure of acetylenic bonds to participate completely stereoselectively in polyene cyclizations is presented in the companion paper.[14]

Acknowledgment. We thank the National Institutes of Health and the National Science Foundation for support of

this research. We are also indebted to Janet L. Carlson for the refinement of several of the procedures described here.

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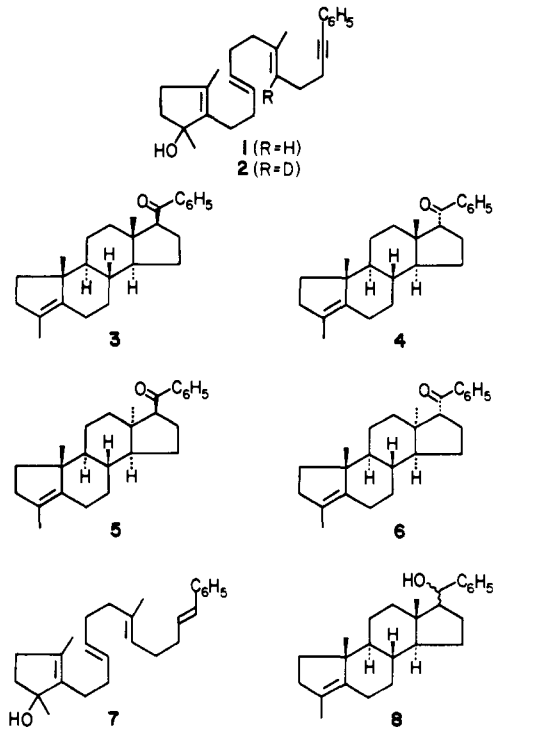
William S. Johnson,* Leslie R. Hughes
James A. Kloek, Tony Niem, Ashok Shenvi
Department of Chemistry, Stanford University
Stanford, California 94305
Received November 1, 1978

Biomimetic Polyene Cyclizations.[1] A Comparison of the Phenylacetylenic and Styryl Terminators in Influencing the Stereoselectivity of Processes Leading to Steroidal Products

Sir:

It has been observed in our laboratory that certain polyene cyclizations in which an acetylenic terminator is used to form the D ring of the steroid nucleus are not always highly stereoselective, yielding tetracyclic products that contain up to 20% 13α isomers having the unnatural C/D cis configuration.[1a] Thus, cyclization of the substrate **1** gives a good yield of tetracyclic products **3, 4, 5,** and **6;** however, the ratio of C/D trans (**3** + **4**) to C/D cis isomers (**5** + **6**) is 4:1. Since this ratio is not affected significantly either by changing reaction conditions or by the introduction of electro-divergent substituents in the phenyl group,[2] we have been prompted to undertake critical examination of the stereochemical outcome of cyclizations involving other types of terminators in the hope of realizing improved stereoselectivity. The present paper describes such a study of the effect of the styryl terminator via a plan which envisaged cyclization of the substrate **7** followed by oxidation of the resulting[3] benzylic alcohols **8** to the known ketones (**3, 4, 5,** and **6**) and determination of the proportion of these compounds in this mixture.

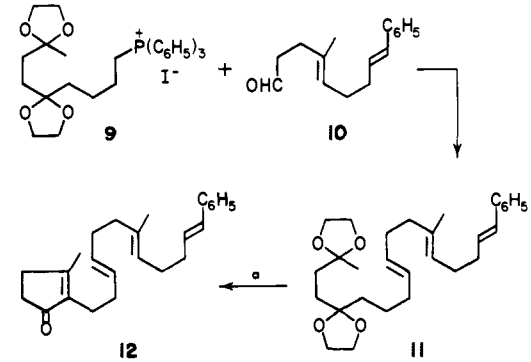
The styryl substrate **7** was prepared by a convergent synthesis (see Scheme I) involving the condensation of the known aldehyde **10**[3a] with the previously described phosphonium salt **9**.[4] Using the Schlosser modification[5] of the Wittig reaction a 50% yield of the bisketal **11**[6-8] was obtained. Hydrolysis to the corresponding dione,[6-8] followed by base-catalyzed cyclodehydration, produced the cyclopentenone **12**,[6-8] in 82% yield (94:6 trans:cis isomers by LC). Treatment of **12** with excess methyllithium gave the unstable cyclopentenol **7.** According



to a procedure developed in these laboratories by F. W. Hobbs, a solution of the crude alcohol **7** (derived from 25 mg of enone **12**) in 7 mL of methylene chloride was added dropwise to a solution of 55 μL of trifluoroacetic acid in 15 mL of methylene chloride maintained at −25 °C. The resulting trifluoroacetates were hydrolyzed with sodium hydroxide in THF and filtered through Florisil to give, in ~80% yield, a mixture of benzylic alcohols **8.** The crude product was then dissolved in hexane and treated with excess activated manganese dioxide[9] to generate the corresponding phenyl ketones.[10] The mixture was analyzed by VPC without further purification and each of the base-line separated peaks identified by coinjection with authentic samples of the tetracyclic ketones **3, 4, 5,** and **6.** In this manner it was possible to show that the 13α (C/D cis) isomers **5** and **6** accounted for <2% of the total ketonic product. Thus, in contrast to the phenylacetylenic terminator, acid-catalyzed cyclization of the substrate **7** containing the styryl terminator appears to be highly stereoselective.[11]

Mechanistic Considerations. The formation of a significant amount of a 13α (C/D cis) isomer has been observed previously in the acid-catalyzed cyclization of **13.** In that case it was demonstrated that the 13α (C/D cis) isomer arose almost exclusively from the acid-catalyzed cyclization of an intermediary tricyclic hydrocarbon **14,** whereas no such partially cyclized intermediate was involved in the formation of the 13β

Scheme I[a]



[a] a, 1:3 5% HCl–acetone, 23 °C, 24 h; 5:6:2 5% NaOH–MeOH–THF, 70 °C, 3 h.

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