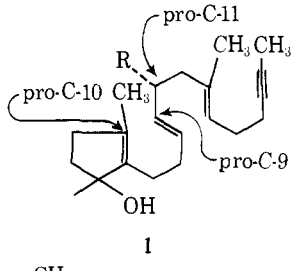
Biomimetic Polyene Cyclizations.[1] Asymmetric Induction by a Chiral Center Remote from the Initiating Cationic Center. 11α-Methylprogesterone

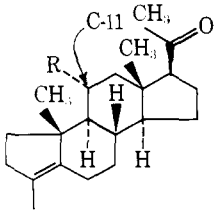
Sir:

As part of a general study aimed at the total synthesis of 11-substituted steroids, e.g., cortisone, via biomimetic polyene cyclization, we chose to examine the cyclization of the trienynol **1** (R = CH_3) in order to (a) ascertain how the new chiral center at pro-C-11[2] would affect the stereochemical course of the reaction and (b) determine its potential for use in the synthesis of 11-methylprogesterone.[3] An analysis of the stereochemical problem follows.

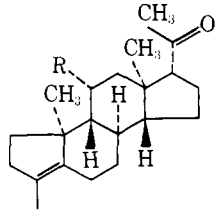
Cyclization of substrate **1** (R = H), without a substituent at pro-C-11[2] is known[4] to be stereospecific giving (71% yield) a single tetracyclic racemic product **2** (R = H) + **3** (R = H) which has been converted into racemic progesterone, **12** (R = H).[5] The stereochemical course of the cyclization of **1** (R = H) is the result of initiation of the stereospecific process by equal amounts of backside and frontside attachment of pro-C-9 to pro-C-10 giving **2** (R = H) and **3** (R = H), respectively.[6] The cyclization of the homologue **1** (R = CH_3) differs in that, because of the chiral center at pro-C-11,[2] it can lead theoretically to two tetracyclic C-11 diastereomers. Thus the enantiomer with the *R* configuration at pro-C-11, shown in formula **1** (R = CH_3), could cyclize by a backside attachment of pro-C-9 to pro-C-10, giving the 11-equatorial methyl substance **2** (R = CH_3) (*R* configuration at C-11 and *R* at C-10), or a frontside attachment giving the 11-axial methyl isomer **3** (R = CH_3) (*R* at C-11 and *S* at C-10). Since cyclization of the pro-C-11 *S* form of the substrate would give an enantiomeric set of results, it became apparent that the question of how the pro-C-11 chiral center would affect the stereochemical course of the cyclization could be answered by working with racemic materials, and determining the ratio of tetracyclic racemic 11-equatorial (**2** plus enantio-**2**) to 11-axial (**3** plus enantio-**3**) diastereomers. The present communication provides a demonstration that the effect of the pro-C-11 chiral center is profound, resulting in production of the 11α-methyl diastereomer **2** (plus its enantiomer) as the only detectable tetracyclic product. This work has not only led to the synthesis of the hitherto unknown 11α-methylprogesterone, in its racemic form, but it also foreshadows the totally asymmetric synthesis of cortisone via a biomimetic polyene cyclization.[7]



1

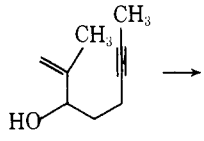


2

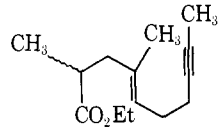


3

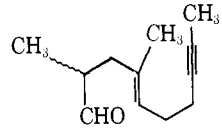
The synthesis of the racemic cyclization substrate **1** (R = CH_3)[5] was carried out by a scheme analogous to that already described for the preparation of the lower homologue **1** (R = H).[4] Thus the known allylic alcohol **4** was converted, by reaction with ethyl orthopropionate involving a Claisen rearrangement,[8] into the enyne ester **5**[9] in 84% yield after distillation[10] at 127-129° (4.7 mm). Saponification afforded the corresponding acid[9] in 97% yield after distillation[10] at 112-115° (0.3 mm). Reduction of this acid with lithium aluminum hydride afforded the corresponding enynol[9] in 85% yield after distillation[10] at 84-91° (0.34 mm). A modified Collins oxidation[11] of the alcohol afforded the aldehyde **6**[9a] in 88% yield after distillation[10] at 120° (2.3 mm) (semicarbazone, mp 83.5-85°[9b]).



4

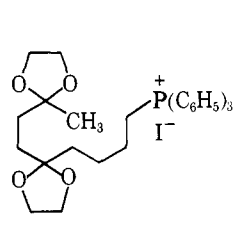


5

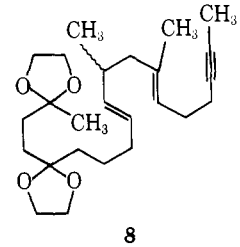


6

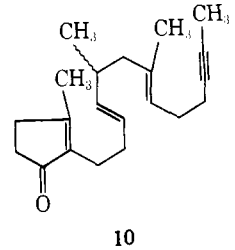
The aldehyde **6** was then allowed to interact in a Wittig-Schlosser condensation with the phosphorane produced from the known phosphonium salt **7**.[4] In order to achieve high trans stereoselectivity some modification of the reported procedure[4] was necessary.[12] The resulting diketal **8**[9a] (90% pure and 97:3 trans:cis isomers by VPC) was used in the next stage without purification. An analytical specimen[9] was prepared by TLC followed by distillation[10] at 210° (6 μ). Hydrolysis of the crude diketal **8** to the dione **9**, followed by base-catalyzed cyclodehydration afforded, after chromatography on basic alumina followed by distillation[10] at 220° (10 μ), the enone **10**[9] in 46% overall yield from aldehyde **6**.



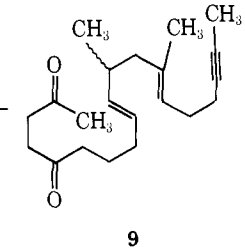
7



8



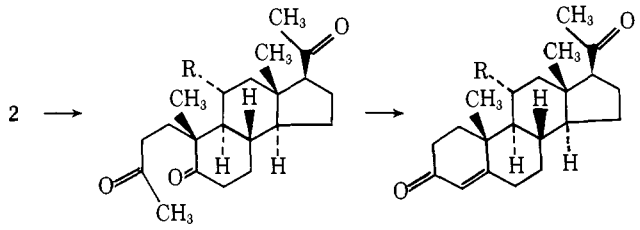
10



9

The enone **10** was treated with excess methyllithium in ether to give the trienynol **1** (R = CH_3)[5] which, being quite unstable, was submitted to cyclization without purification. Treatment with trifluoroacetic acid in dichloroethane, in the presence of ethylene carbonate, under the same conditions described for the cyclization of the lower homologue **1** (R = H),[4] resulted in only a 16% yield of tetracyclic product. Thus the rate of cyclization appears to be attenuated by the methyl substituent at pro-C-11, probably because of steric hindrance. Eventually conditions were discovered, i.e.,

0.30 mmol of substrate, 6 ml of 2,2,2-trifluoroethanol, 3 mmol of trifluoroacetic acid, 0°, 3 h, which afforded, after preparative TLC, a 66% yield of crystalline tetracyclic material **2** (R = CH_3)[5] shown by VPC to be a 9:91 mixture of 17α-17β epimers. Recrystallization from hexane gave the pure 17β form, mp 118.5–119.5°.[9] The NMR signal for the C-18 methyl appeared at δ 0.61 ppm. The total crude tetracyclic fraction (see above) showed no detectable angular methyl absorption in the 0.7 ppm region where the C-18 methyl resonance of the 11β isomer should occur (see below); hence it is concluded that, at most, only a trace amount of the racemic form of the 11β-isomer was formed.



11 **12**

The constitution of the 119° tetracyclic product was established by its conversion,[4] via ozonolysis followed by cyclodehydration of the resulting trione **11** (R = CH_3),[5] into racemic 11α-methylprogesterone, **12** (R = CH_3).[5] Dry column chromatography over basic alumina afforded, in 41% overall yield, a mixture of 17α and 17β epimers in a ratio of 18:82 as determined by VPC. Crystallization from methanol yielded the pure racemic 17β isomer **12**,[5] mp 162–163°,[9] the constitution of which was established unequivocally by single-crystal x-ray diffraction analysis performed by Shenvi and Hodgson.[13] This substance was clearly different from the known[14] 11β-methylprogesterone. In particular the NMR signal for the C-18 methyl of the 11β isomer appeared downfield at δ 0.76 ppm (due to shielding by the axial 11β methyl group) compared with δ 0.68 ppm for the 11α isomer.

The failure to detect any of the 11β-isomer **3** (R = CH_3)[5] in the cyclization of **1** (R = CH_3) must mean that the activation energy for its formation is significantly higher than for the reaction to produce the 11α-epimer. This difference may be due, in part, to the nonbonded interaction, in the transition state for formation of the 11β-isomer, between the methyl groups attached to pro-C-11 and pro-C-10 (and also, possibly, pro-C-13) of **1** (R = CH_3). Insofar as the geometry of the transition states for the cyclization resembles products **3** (R = CH_3) and **2** (R = CH_3), these methyl groups have 1,3-diaxial relationships in the former, but not in the latter, series.

Since cyclization of racemic ***1*** *(R = CH_3)[5] gives a single distereomer, it follows that if this substrate were obtained in a pure enantiomeric form, the tetracyclic product would also be enantiomerically pure.*[15] *Thus the process involves essentially total asymmetric synthesis induced by the pro-C-11 chiral center.*

Acknowledgment. We wish to thank the National Institutes of Health and the National Science Foundation for support of this research.

References and Notes

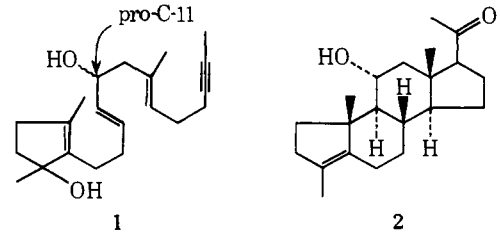
(1) For recent papers in this series see R. A. Volkmann, G. C. Andrews, and W. S. Johnson, *J. Am. Chem. Soc.*, **97**, 4777 (1975); W. R. Bartlett and W. S. Johnson, *Bioorg. Chem.*, in press.
(2) The term "pro-C-11" is meant to refer to that carbon which becomes C-11 (steroid numbering) in the anticipated product **2**.
(3) 11-Methyl steroids are of special biological interest (J. S. Baran, H. D. Lennon, S. E. Mares, and E. F. Nutting, *Experientia*, **26**, 762 (1970)). For example, 11β-methylprogesterone has significant activity when administered orally (J. S. Baran, private communication). Also, 17α-acetoxy-11β-methyl-19-norprogesterone is an exceedingly potent substance. It has been reported to be 300 times as active as progesterone in preventing estrus and ovulation in experimental animals (D. F. Wishart, *J. Reprod. Fertil.*, **30** (2), 333 (1972).
(4) W. S. Johnson, M. B. Gravestock, and B. E. McCarry, *J. Am. Chem. Soc.*, **93**, 4332 (1971).
(5) This formula depicts only one enantiomer of a racemic pair.
(6) It was shown that the substrate **1** (R = H or CH_3) always undergoes facile dehydration prior to cyclization; hence the chirality of the carbon holding the hydroxyl group is lost and cannot influence the stereochemical course of the cyclization.
(7) W. S. Johnson, S. Escher, and B. Metcalf, *J. Am. Chem. Soc.*, following paper in this issue.
(8) Cf. W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T.-t. Li, D. J. Faulkner, and M. R. Peterson, *J. Am. Chem. Soc.*, **92**, 741 (1970).
(9) (a) The NMR and ir spectra were entirely consistent with the assigned structure. (b) Satisfactory C, H analyses were obtained.
(10) Evaporative bulb-to-bulb distillation using a Buchi Kugelrohrofen.
(11) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).
(12) After addition of the second mole equivalent of phenyllithium in THF at −78°, an amount of anhydrous ether equal to the total volume of the reaction solution was added. The bright red solution was then allowed to warm to −15° over a 15-min period, excess methanol was added, and finally the mixture was stirred at room temperature for 30 min.
(13) Details will be reported in the full paper on the subject of the present communication.
(14) 11β-Methylprogesterone has been prepared by partial synthesis starting with an 11-keto steroid (J. S. Baren, unpublished observation). We wish to thank Dr. Baren of Searle Laboratories for providing us with a sample of this substance as well as the NMR spectrum.
(15) Work as yet incomplete (W. S. Johnson, R. Muller, B. Ganem, and J. Calzada, unpublished observations) has shown that the substrate **1** (R = $CH_2CH{=}CH_2$), containing an unknown excess of one enantiomer, does indeed cyclize (>60% yield) to give an optically active product. The synthetic scheme resembled that described in the present study. The carboxylic acid corresponding to the aldehyde **6** ($CH_2CH{=}CH_2$ in place of the α CH_3) was completely resolved as the salt of (+)-α-methylbenzylamine; however it was not possible to avoid partial racemization of the aldehyde during the Wittig condensation.

William S. Johnson,* Grant E. DuBois
Department of Chemistry, Stanford University
Stanford, California 94305
Received November 10, 1975

A Stereospecific Total Synthesis of Racemic 11α-Hydroxyprogesterone via a Biomimetic Polyene Cyclization[1]

Sir:

For several years we have been exploring the possibility of synthesizing an 11-oxy steroid via the cyclization of a polyenic substrate having an oxygen substituent at pro-C-11, e.g., substance **1**. After many failures,[2] we concluded that the resistance to cyclization was probably the result of one or more of the following: (a) steric hindrance due to the substituent at pro-C-11, (b) attenuation of the nucleophilicity of the disubstituted olefinic bond by the inductive effect of the allylic oxygen, and (c) premature destruction of this allylic system by the acidic cyclization conditions. In order to simplify the problem, our attention was turned to a study of the cyclization of substrates in which the pro-C-11 position was substituted by a hydrocarbon residue, e.g., a methyl group.[1a] Although the introduction of such substituents resulted in attenuation of the rate of cyclization (due to steric hindrance), nevertheless over 60% yields of tetracyclic products could be obtained under appropriately modified



1 **2**