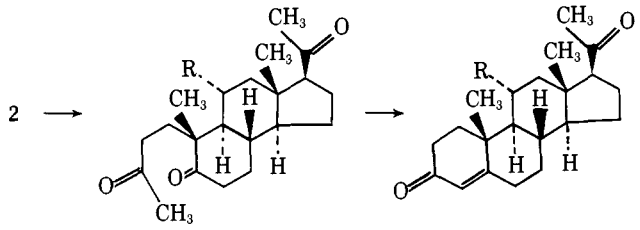
0.30 mmol of substrate, 6 ml of 2,2,2-trifluoroethanol, 3 mmol of trifluoroacetic acid, 0°, 3 h, which afforded, after preparative TLC, a 66% yield of crystalline tetracyclic material **2** (R = CH_3)[5] shown by VPC to be a 9:91 mixture of 17α-17β epimers. Recrystallization from hexane gave the pure 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.

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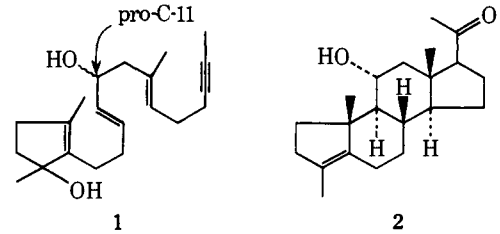
A Stereospecific Total Synthesis of Racemic 11α-Hydroxyprogesterone via a Biomimetic Polyene Cyclization[1]

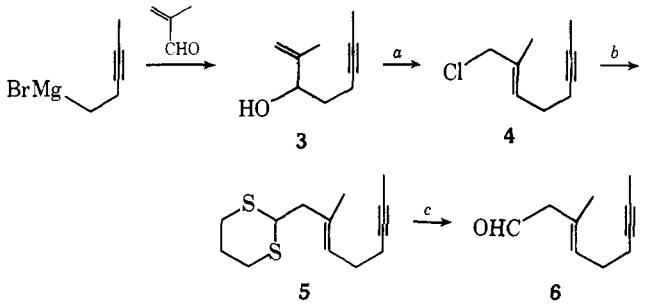
Sir:

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



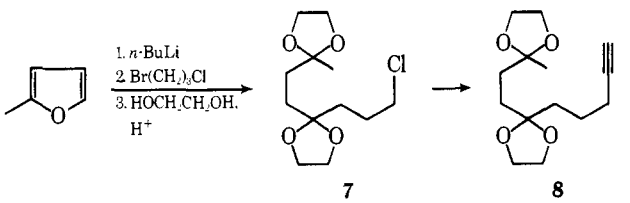
1 2

Scheme I



[a] 1.5 mol equiv of $SOCl_2$ in CCl_4, N_2 stream to sweep out HCl, 16 h, 25°. [b] 0.9 mol equiv of dithiane in THF, 0.9 mol equiv of *n*-BuLi in hexane, 2 h, −30°; 90% 4 added at −70°; 11 h at −20°. [c] 10 mol equiv of MeI, 4 mol equiv of $CaCO_3$, 4:1 CH_3CN:H_2O, 14 h, 25°, N_2.

Scheme II



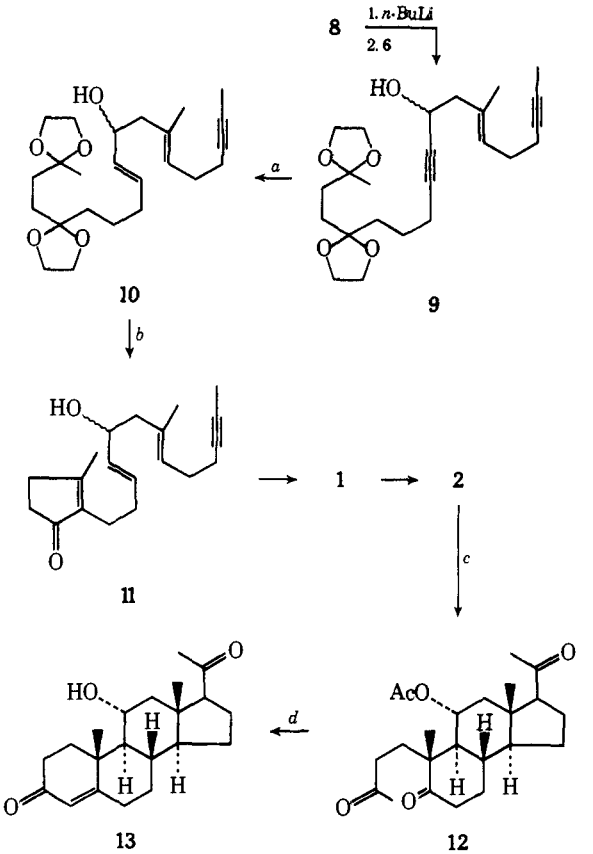
conditions. We were, therefore, prompted to reexamine the pro-C-11-oxy system with the view of exploring the use of the newer and more strenuous cyclization conditions. The present communication discloses the successful stereospecific cyclization, **1**[3] → **2**,[3] and the conversion of the latter substance into racemic 11α-hydroxyprogesterone, **13**,[3] the (+)-enantiomer of which is a key intermediate in the commercial production of hydrocortisone acetate.[4]

Substrate **1** was produced by a convergent synthesis, the key step being the addition of the lithium salt of the acetylene **8** to aldehyde **6** to give the propargylic alcohol **9**. The aldehyde **6** was prepared as outlined in Scheme I. Thus the known enynol **3**,[5] derived (61% yield) from 3-pentynylmagnesium bromide and methacrolein, was allowed to interact with thionyl chloride, under conditions known to induce the stereoselective SNi′ reaction,[6] to give after distillation[7] at 70–80° (0.7 mm) an 87% yield[8] of the allylic chloride **4**[9] contaminated with about 11% of the unrearranged secondary allylic chloride as shown by VPC analysis. Although these isomers could be separated by fractional distillation, we found conditions whereby 2-lithiodithiane reacted preferentially with the primary halide, giving on chromatography (silica gel) recovered secondary chloride and an 85% yield of the thioacetal **5**.[10] Distillation[7] at 140° (0.05 mm) gave a sample[9] which was 98% pure by VPC. Hydrolysis[11] of the chromatographed thioacetal gave the crude aldehyde **6**[9a] in 99% yield. Since this product was quite sensitive to rearrangement to the α,β unsaturated isomer, it was used directly without purification.

The acetylene **8** was produced as outlined in Scheme II. The diketal chloride **7** was prepared[12] by a method analogous to that described for the corresponding bromide.[6] Thus alkylation of methylfuran with 1-bromo-3-chloropropane followed by ethylene glycolysis, gave **7**,[9] after distillation at 120–125° (0.10 mm), in 74% overall yield from methylfuran. This material was used to alkylate lithium acetylide-ethylenediamine complex (2 mol equiv) in Me_2SO (1 h, 25°) giving, after chromatography on silica gel, an 86% yield of the acetylene **8** (homogeneous by VPC).[12] Distillation at 120° (0.05 mm) gave an analytical specimen of **8**.[9]

As outlined in Scheme III, the convergent step was performed by treating the acetylene **8** in dimethoxyethane with 1 mol equiv of *n*-butyllithium in hexane followed by 0.9 mol

Scheme III



[a] 2 mol equiv of $LiAlH_4$ in THF, reflux 4 h. [b] Ac_2O, C_5H_5N, 16 h, 25°; acetone, H_2O, TsOH, 76 h, 25°; 5:3 MeOH:5% NaOH, 5 h, 70°. [c] Ac_2O and $C_5H_{11}N$, to give acetate of **2**; 1:1 MeOH:CH_2Cl_2, −78°, excess O_3; Zn, HOAc 0–25°, 4 h. [d] MeOH–H_2O, KOH, N_2, 1 h, 25°; 2 h, 70°.

equiv of the aldehyde at −20 to 25°. Chromatography of the product on alumina gave substance **9** in 95% yield.[9a,13] Rechromatography on silica gel followed by distillation[7] at 186° (0.01 mm) gave an analytical sample of **9**.[9] The crude propargylic alcohol **9** was reduced with lithium aluminum hydride in THF to give, after chromatography on alumina, the trans allylic alcohol **10**[9a,14] in 90% yield. Rechromatography on silica gel followed by distillation[7] at 195° (0.025 mm) gave an analytical sample of **10**.[9] Substance **10** was acetylated, then treated[5] so as to effect (a) hydrolysis of the ketal residues and (b) cyclodehydration of the resulting 1,4-dione system (with concomitant saponification of the acetate group). Thus the hydroxy enone **11**[9a] was isolated, after chromatography on silica gel, in 95%[13] overall yield from crude **10**. Rechromatography and distillation[7] at 180° (0.01 mm) gave an analytical sample of **11**.[9] Treatment of the enone **11** with methyllithium in ether gave the trienyndiol **1** which, being quite unstable, was submitted directly to cyclization without purification.

The diol **1** proved to be significantly less susceptible to cyclization than the pro-C-11 methyl analogue.[1a] After considerable experimentation conditions were found for producing the tetracyclic product **2**,[3] as a mixture of 17α and 17β epimers, in 29–35% yield.[15] In a typical experiment, a solution of crude substrate **1** (derived from 300 mg of enone **11**) in 14 ml of 2,2,2-trifluoroethanol at 0°, was added to a solution of 19 ml of trifluoroacetic acid in 40 ml of trifluoroethanol, and the mixture was then stirred at 25° for 42 h. After treatment with aqueous potassium hydroxide, the crude product was distilled[7] at 210° (6 μ) affording 185 mg of volatile material which was chromatographed on

silica gel. Trituration of the fraction enriched in the 17 β isomer with hexane gave 62 mg of pure substance **2**,[3] mp 133–134°.[9] The remaining fraction of tetracyclic material (30 mg) consisted of a mixture of 17α and 17β epimers. Both epimers could be used for the succeeding steps of the synthesis. The failure to detect any 11β-hydroxy tetracyclic product indicates a stereochemical behavior like that observed in the 11-methyl series.[1a] The stereoselectivity of the cyclization portends well for obtaining a single optically active cyclization product from enantiomerically pure substrate.[16]

The 17β epimer **2**[3] was acetylated (pure acetate, mp 108–110°[9]), then submitted to ozonolysis[5] to give the trione **12**,[3] followed by cyclodehydration.[5] The alkaline conditions of this last step effected saponification of the acetate and equilibration at C-17 giving, after chromatography on silica gel, an 84% yield[8,13] of racemic 11α-hydroxyprogesterone **13**[3] admixed with its 17α epimer (ratio ca. 76:24 by VPC). Crystallization from methanol gave the 17β form, mp 190–196°.[9] The NMR, solution ir, mass spectrum, and VPC (coinjection) behavior were identical with the corresponding properties of authentic (+)-11α-hydroxyprogesterone.

Thus a total synthesis of racemic 11α-hydroxyprogesterone has been achieved in ca. 15% overall yield in 16 steps from simple compounds. This represents approximately a 7% overall (22 steps) yield of ("racemic") hydrocortisone acetate.[4] Our synthesis may be compared with a well-known[17] total synthesis, which leads to optically active cortisone in "1% overall yield in 27 steps."[18]

Acknowledgment. We wish to thank the National Institutes of Health and the National Science Foundation for support of this research. We are also grateful to the Swiss National Foundation and Richardson-Merrell, Inc. for fellowship grants in support of S.E. and B.W.M., respectively.

References and Notes

(1) For recent papers in this series see (a) W. S. Johnson and G. E. DuBois, *J. Am. Chem. Soc.*, preceding paper in this issue; (b) R. A. Volkmann, G. C. Andrews, and W. S. Johnson, *Ibid.*, **97**, 4777 (1975); (c) W. R. Bartlett and W. S. Johnson, *Bioorg. Chem.*, in press.
(2) In our first exploratory study (W. S. Johnson and T. A. Bryson, unpublished observations) involving attempts to cyclize the benzyl ether of **1**, a trace of tetracyclic material seemed to be formed; however, follow-up experiments were not promising.
(3) This formula depicts only one enantiomer of a racemic pair.
(4) In a personal communication, Dr. Philip F. Beal, III, of the Upjohn Company has indicated that the commercial conversion of **13** into hydrocortisone acetate is accomplished in ca. 50% yield according to a simplified and refined version of the published method: J. A. Hogg, P. F. Beal, A. H. Nathan, F. H. Lincoln, W. P. Schneider, B. J. Magerlein, A. R. Hanze, and R. W. Jackson, *J. Am. Chem. Soc.*, **77**, 4436 (1955). We assume that this conversion would work as well starting from the 17α epimer of **13**.
(5) W. S. Johnson, M. B. Gravestock, and B. E. McCarry, *J. Am. Chem. Soc.*, **93**, 4332 (1971).
(6) W. S. Johnson, T-t. Li, C. A. Harbert, W. R. Bartlett, T. R. Herrin, B. S. Staskun, and D. H. Rich, *J. Am. Chem. Soc.*, **92**, 4461 (1970).
(7) Evaporative bulb-to-bulb distillation using a Buchi Kugelrohrofen.
(8) From an experiment performed by A. J. Lewis.
(9) (a) The NMR and ir spectra were entirely consistent with the assigned structure. (b) Satisfactory C, H analyses were obtained.
(10) Procedure developed by R. S. Brinkmeyer. The first specimen of the thioacetal **5** was prepared by T. A. Bryson from pure primary chloride.
(11) Cf. R. L. Markezich, W. E. Willy, B. E. McCarry, and W. S. Johnson, *J. Am. Chem. Soc.*, **95**, 4414 (1973).
(12) Procedure developed by M. Hendrick. The first specimen of **8** was prepared by B. E. McCarry.
(13) From an experiment performed by J. Calzada.
(14) For the stereospecificity of reduction of propargylic alcohols, see B. Grant and C. Djerassi, *J. Org. Chem.*, **39**, 968 (1974), and references cited therein.
(15) This yield has not yet been optimized. R. S. Brinkmeyer has recently found conditions (50% TFA in TFE, 6 h, 25°) which gave the tetracyclic product in 39% yield.
(16) See ref 1a for a discussion of this problem. In preliminary experiments by R. S. Brinkmeyer, optically active **1**, of unknown enantiomeric composition, was obtained by asymmetrically induced hydride reduction of the ketone prepared by Jones oxidation of **1**.[3] This sample of **1** did indeed give optically active **2**; hence the chiral center at pro-C-11 is not racemized completely (if at all) during cyclization. Work in progress is aimed at obtaining optically active intermediates efficiently at an early stage of a revised synthesis of **1**.
(17) L. Velluz, G. Nomine, and J. Mathieu, *Angew. Chem.*, **72**, 725 (1960); L. Velluz, G. Nomine, J. Mathieu, E. Toromanoff, D. Bertin, R. Bucourt, and J. Tessler, *C. R. Acad. Sci.*, **250**, 1293 (1960).
(18) K. Nakanishi, T. Goto, S. Ito, S. Natori, and S. Nozoe, "Natural Products Chemistry", Vol. 1, Academic Press, New York, N.Y., 1974, pp 499–500.

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Determination of Signs of Long-Range Carbon–Carbon Coupling Constants. The SPT-Difference Spectroscopy Method

Sir:

In a recent investigation on correlations between long-range ^{13}C–^{13}C, ^{13}C–^{1}H, and ^{1}H–^{1}H NMR spin–spin couplings in geometrically equivalent systems, Marshall et al.[1] synthesized a tri-^{13}C-labeled methyl tetrolate (15-step scheme) in order to determine the signs of the ^{13}C–^{13}C coupling constants involving the labeled sites using double or triple resonance techniques. Although the preparation of multiply ^{13}C-labeled compounds is both tedious and expensive, it was indicated that such multiple labeling work is being extended to other compounds for determination of signs of J_{CC} and J_{CC}/J_{CH}. We wish to demonstrate that the signs of ^{13}C–^{13}C couplings may often be obtained most conveniently from *mono*-^{13}C-labeled compounds[2] using various ^{13}C–{^{1}H} double resonance techniques. For small molecules, such as methyl [1-^{13}C]tetrolate (**1**), with first-order ^{1}H and ^{13}C spectra both (1) the selective population transfer (SPT) method[3] and (2) the off-resonance (selective) proton decoupling technique[4] are useful whereas for second-order systems method 2 is in general preferable.[5]

1

The methyl tetrolate **1**, enriched with >90% ^{13}C at position C1 only and synthesized in three steps from propyne and >90% ^{13}C-enriched barium carbonate, serves to illustrate the determination of signs of ^{13}C–^{13}C couplings from monolabeled compounds. Magnitudes of the ^{13}C–^{13}C and ^{13}C–^{1}H couplings were obtained from first-order analysis of the proton decoupled and/or coupled ^{13}C spectra.[6]

The signs of $^{1}J_{C1-C2}$, $^{2}J_{C1-C3}$, and $^{3}J_{C1-C4}$ (127.5, 20.28, and 1.90 Hz, respectively) were all determined relative to that of $^{4}J_{C1-H5}$ using ^{13}C–{^{1}H} SPT experiments;[3] i.e., selective SPT π pulses were applied to transitions in the H5 proton region (corresponding to definite spin states for carbon C1) prior to observing the C2, C3, and C4 spectra, respectively. For all three cases J_{C1-CX} (X = 2, 3, and 4) and $^{4}J_{C1-H5}$ were found to be of opposite sign. The determination of $^{2}J_{C3-C1} \times {}^{4}J_{C1-H5} < 0$ from the C3 spectrum (doublets of quartets, $|^{2}J_{C3-C1}|$ = 20.28 Hz and $|^{2}J_{C3-H5}|$ = 10.74 Hz) is illustrated in Figure 1. Application of selective π pulses to the high frequency transition in the $^{13}C3$–H5 proton satellite spectrum (doublet of doublets, $|^{2}J_{C3-H5}|$ = 10.74 Hz and $|^{4}J_{C1-H5}|$ = 1.96 Hz) gives rise to emission and enhanced absorption within the low frequency quartet of the C3 spectrum (Figure 1b). The same effects are observed in the high frequency quartet when the gated perturbation is applied at 2.0 Hz *lower* frequency (Figure 1c). Thus $^{2}J_{C3-C1} \times {}^{4}J_{C1-H5} < 0$.