The dienynol **12** also underwent facile cyclization at −30° (30 min) in acetonitrile containing 1% trifluoroacetic acid. The acetonitrile served as the nucleophile as well as the solvent and the product, which appeared by vpc to be formed in almost quantitative yield, was shown to be the enamide **14**:[4] λ_{max}^{film} 6.0 μ; mass spectrum *m/e* 289, base peak (M^+), 274 (M − 15), 246 (M − 43), 236 (M − 49), 215 (M − 74). The nmr spectrum included, in addition to the three-proton singlets at δ 0.95, 1.11, 1.27, 1.70, and 1.80 (see above), singlets at 1.97 (3 H) for the methyl on the olefinic carbon holding the amido residue, at 2.00 (3 H) for the methyl attached to the amido carbonyl carbon, and at 6.34 (1 H, disappearing on treatment with D_2O) for the proton on the nitrogen atom. This product appeared to be oxygen-sensitive and a satisfactory analytical sample was not obtained. Ruthenium tetroxide degradation of the enamide gave the dione **5**, and treatment of the enamide with 1:1 2 *N* hydrochloric acid–methanol for 8 hr at 23° gave the methyl ketone **15** (β:α ratio 11:1 by vpc).

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William S. Johnson,* Michael B. Gravestock, Ronald J. Parry
Robert F. Myers, Thomas A. Bryson, D. Howard Miles
Department of Chemistry, Stanford University
Stanford, California 94305
Received May 21, 1971

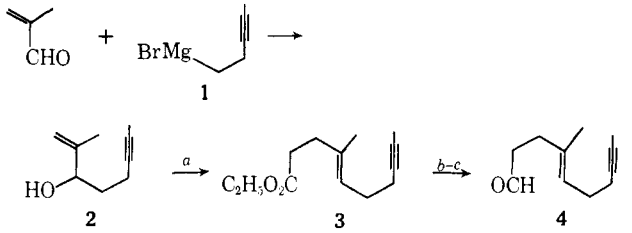
Acetylenic Bond Participation in Biogenetic-Like Olefinic Cyclizations. II. Synthesis of *dl*-Progesterone

Sir:

In an accompanying communication we have disclosed that an appositely placed acetylenic bond can participate in an olefinic cyclization so as to produce a trans-fused five-membered ring; thus the *trans*-hydrindan ring system was formed stereospecifically in one step from an acyclic substrate.[1] In the present communication we report on an extension of this work, *i.e.*, the stereospecific cyclization of the trienynol **11** to give a tetracyclic substrate **12** which in turn is readily converted into *dl*-progesterone (**14**).

The trienynol **11** was produced by a convergent synthesis, the key step being a stereoselective Wittig condensation of the aldehyde **4** with the ylide **7** to produce the diketal **8**. The aldehyde **4** was prepared as outlined in Scheme I. Thus, the Grignard reagent **1**

Scheme I



[a] $CH_3C(OC_2H_5)_3$, 0.3% $CH_3CH_2CO_2H$, 138°, 2.5 hr. [b] $LiAlH_4$, ether, 0°, 1 hr. [c] $CrO_3 \cdot 2C_5H_5N$, CH_2Cl_2, 23°, 1.2 hr.

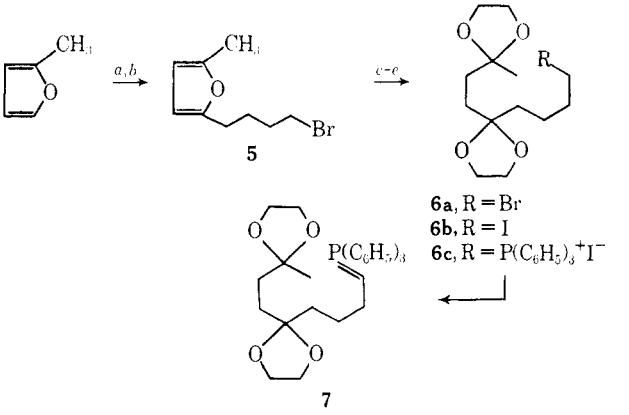
(1) W. S. Johnson, M. B. Gravestock, R. J. Parry, R. F. Myers, T. A. Bryson, and D. H. Miles, *J. Amer. Chem. Soc.*, **93**, 4330 (1971).

from 1-bromo-3-pentyne,[2] on interaction with methacrolein, gave the allylic alcohol **2** which (without purification) was converted, by the ortho acetate Claisen reaction,[3] into the enyne ester **3** in 55% overall yield after distillation[4] at 90° (0.025 mm) (*Anal.* Found: C, 75.2; H, 9.8). The nmr spectrum[5] included a singlet at δ 1.62 (3 H) characteristic of a methyl group on a trans-trisubstituted olefinic bond, and a triplet (J = 2 Hz) at 1.76 (3 H) for the methylacetylenic residue. A sample of the aforementioned allylic alcohol **2** was purified by distillation[4] at 60° (0.05 mm) (*Anal.* Found: C, 78.1; H, 10.15). The nmr spectrum[5] included the triplet (J = 2 Hz) at δ 1.76 (3 H) characteristic of the methylacetylenic residue.

The reduction of the ester **3** gave, in 90% yield, the corresponding enyne alcohol which was 98% pure as ascertained by vpc. A sample was purified by distillation[4] at 80° (0.025 mm) (*Anal.* Found: C, 78.5; H, 10.7). The nmr spectrum,[5] like that of **3**, included a singlet at δ 1.64 (3 H) and a triplet (J = 2 Hz) at 1.77. The unpurified enyne alcohol, on oxidation with Collins reagent,[6] was converted (86% yield) into the aldehyde **4** which was 98% pure by vpc. A sample was purified by distillation[4] at 70° (0.025 mm) (*Anal.* Found: C, 80.7; H, 9.75). The nmr spectrum,[5] like that of **3**, included a singlet at δ 1.57 (3 H) and a triplet (J = 2 Hz) at 1.71 (3 H). In addition there was a singlet at 9.80 (1 H) for the aldehyde proton.

The diketal bromide **6a** (Scheme II) was prepared by a

Scheme II



[a] *n*-BuLi, THF, 4 hr, −30 to −20°. [b] 2.9 equiv of $Br(CH_2)_4Br$, 2.5 hr, −20 to 23°, 14 hr at 23°. [c] (To give **6a**) 3.2 mol equiv of $HOCH_2CH_2OH$, C_6H_6, 0.026 mol equiv of *p*-$CH_3C_6H_4SO_3H$, hydroquinone (trace), 43-hr reflux with removal of H_2O. [d] (To give **6b**) 1.4 equiv of NaI, trace of MgO, $CH_3CH_2COCH_3$, N_2, 40 min, 80°. [e] (To give **6c**) 1.4 equiv of $(C_6H_5)_3P$, C_6H_6, 16 hr, 80°.

method like that already described for producing a homolog.[7] Thus, 2-methylfuran was alkylated with 1,4-dibromobutane to give, after fractional dis-

(2) K. E. Schulte and K. P. Reiss, *Chem. Ber.*, **87**, 964 (1954).
(3) *Cf.* W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T-t. Li, D. J. Faulkner, and M. R. Petersen, *J. Amer. Chem. Soc.*, **92**, 741 (1970).
(4) Evaporative bulb-to-bulb distillation using Büchi kugelrohrofen.
(5) The nmr spectrum at 60 MHz, TMS internal standard, $CDCl_3$ solvent, was entirely consistent with the assigned structure. Details are not recorded here, except for absorptions of particular significance.
(6) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).
(7) W. S. Johnson, T-t. Li, C. A. Harbert, W. R. Bartlett, T. R. Herrin, B. Staskun, and D. H. Rich, *J. Amer. Chem. Soc.*, **92**, 4461 (1970).

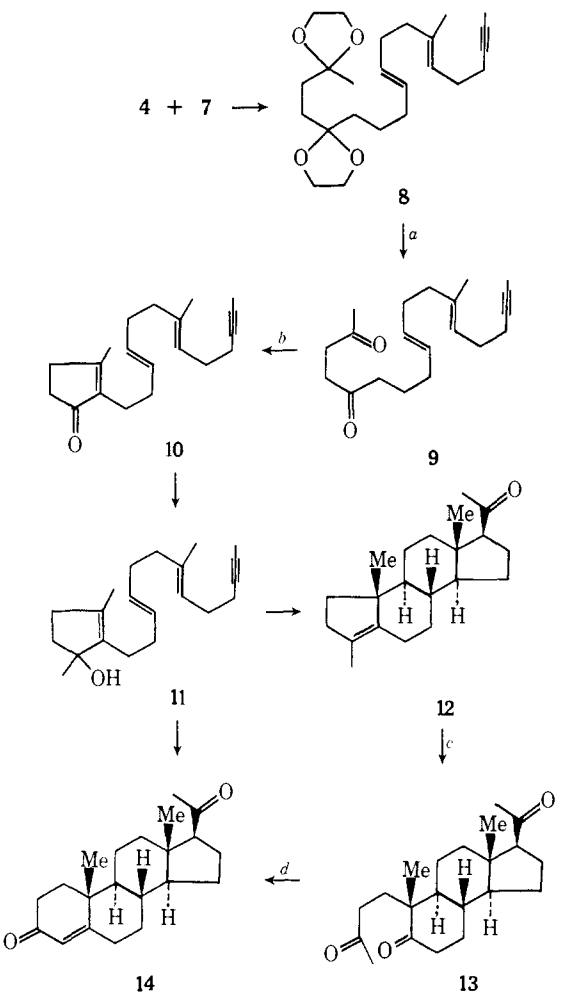
tillation, the bromide **5**, bp 47–48.5° (0.03 mm), in 75% yield (*Anal.* Found: C, 49.8; H, 6.1; Br, 36.8). The nmr spectrum[5] included a singlet at δ 2.12 (3 H) for the methyl group, a triplet (J = 6 Hz) at 3.37 (2 H) for the protons α to the bromine, and a singlet at 5.82 (2 H) for the protons at C-3 and C-4 on the furan ring. In the ketalization step, **5** → **6a**, a trace of hydroquinone was introduced in order to suppress the formation of polymeric material. Chromatography on Florisil afforded (71% conversion) the diketal bromide **6a** (99% pure by vpc). The yield, accounting for recovered **5**, was 88%. A sample was purified by distillation[4] at 140° (0.05 mm) (*Anal.* Found: C, 48.4; H, 7.2; Br, 28.8). The nmr spectrum[5] included a singlet at δ 1.22 (3 H) for the methyl group, a singlet at 1.56 (4 H) for the two methylene groups flanked by the ketal residues, a triplet (J = 6 Hz) at 3.35 (see above), and a pair of singlets at 3.83 and 3.85 (8 H) for the four ketal methylene groups. The crude iodide **6b**, obtained from **6a** in 99% yield, was used directly for preparation of the phosphonium salt **6c**. The nmr spectrum[5] of a sample of **6b**, distilled[4] at 145° (0.05 mm) (*Anal.* Found: C, 42.4; H, 6.1; I, 34.5), was similar to that of **6a**, including a triplet (J = 6 Hz) at δ 3.20 (2 H) for the protons α to the iodine. The phosphonium iodide **6c** was crystallized from acetone as colorless microcrystals, mp 135–140° (*Anal.* Found: C, 59.0; H, 6.0; P, 4.8; I, 19.5). The nmr spectrum[5] included many similar features to that of the bromide **6a** and, in addition, a multiplet ($W_{h/2}$ = 24 Hz) at δ 3.62 for the CH_2P^+ protons and a multiplet at 7.7–8.1 (15 H) for the aromatic protons. The yield of crystalline **6c** was 94%, or 61% overall from 2-methylfuran.

The phosphonium iodide, in THF, was treated[8] with 1 equiv of phenyllithium in ether. The resulting red solution of the ylide **7** was cooled to −70°, 1 mol equiv of the enyne aldehyde **4** was added, and the temperature was raised to −30°; then a second equivalent of phenyllithium was added, followed by excess methanol (−30°). The crude product **8** (see Scheme III), containing $(C_6H_5)_3PO$, was used for the next step. A sample of the diketal dienyne **8** was purified by tlc on silica gel (3:7 EtOAc–pentane) followed by distillation[4] at 190° (0.01 mm) (*Anal.* Found: C, 74.1; H, 9.7). As shown below, this product contained about 3% of the isomer with the cis-disubstituted olefinic bond. The nmr spectrum[5] included a singlet at δ 1.39 (3 H) for the methyl on the ketal carbon, a singlet at 1.63 (3 H), a triplet (J = 2 Hz) at 1.75 (3 H), a singlet at 3.94 (8 H) for four ketal methylene groups, an unresolved triplet (J = 6 Hz) at 5.19 and a multiplet at 5.41 (2 H) for the vinyl hydrogens of the trans-disubstituted olefinic bond. Hydrolysis of the crude diketal **8**[9] afforded the crude dienyne diketone **9** which was used directly for conversion to **10**. A sample of **9** was purified by tlc on silica gel (3:7 EtOAc–pentane) followed by distillation[4] at 190° (0.01 mm) (*Anal.* Found: C, 79.4; H, 9.9). The nmr spectrum[5] included a singlet at δ 2.21 (3 H) for the methyl ketone group. The crude diketone **9** was converted into the

(8) According to the procedure of M. Schlosser and K. F. Christmann, *Angew. Chem., Int. Ed. Engl.*, **5**, 126 (1966).

(9) According to the method described for an analogous substance: W. S. Johnson, M. F. Semmelhack, M. U. S. Sultanbawa, and L. A. Dolak, *J. Amer. Chem. Soc.*, 90, 2994 (1968).

Scheme III



[a] 3:10 aqueous 0.1 *N* HCl-MeOH, N_2, 6 hr, 40°. [b] 3:7 EtOH–2% NaOH in H_2O, N_2, 18-hr reflux. [c] CH_3OH–CH_2Cl_2, 0.55 mol equiv of O_3, 2 min, −70°, followed by excess aqueous HOAc and Zn, 30 min, −15 to 23°. [d] 5:2 H_2O–5% KOH, 20 hr, 23°, N_2.

unsaturated ketone **10** which, after chromatography on Florisil, was isolated in 40% overall yield from the enyne aldehyde **4**. Analysis by vpc indicated that this product consisted of 97% of the trans,trans isomer and 3% of the cis,trans isomer. A sample was distilled at 190° (0.05 mm) (*Anal.* Found: C, 84.3; H, 9.8); mass spectrum (*m/e* 284, M^+; 269, M − 15; 163, M − 121).

The unsaturated ketone **10** was treated with excess methyllithium in ether to give the trienynol **11** which, being quite unstable, was submitted to cyclization without purification. Thus the crude carbinol **11** (from 210 mg of **10**) in 22 g of 1,2-dichloroethane containing 2.2 g of ethylene carbonate (to trap the vinyl cation) was treated with 2.03 g of trifluoroacetic acid for 3 hr at 0° under N_2. Excess potassium carbonate in aqueous methanol was added in order to neutralize the mixture and to hydrolyze the enol complex. Chromatography gave 158 mg (71% yield) of tetracyclic material which by vpc was a 5:1 mixture of the 17β (formula **12**) and the 17α epimeric ketones. A sample was distilled[4] at 190° (0.05 mm) (*Anal.* Found: C, 83.8; H, 10.6); mass spectrum (*m/e* 300, M^+; 285, M − 15 (base peak); 257, M − 43). The nmr spec-

trum[5] included singlets at δ 0.65 (3 H) for the C-19 methyl, 0.92 (3 H) for the C-18 methyl, 1.58 (3 H) for $CH_3C{=}C$, and 2.13 (3 H) for the C-21 methyl. Crystallization from pentane gave material mp 88–89°, which contained <5% of the 17α form by vpc.

The tetracyclic ketone **12** was submitted to ozonolysis to give the triketone **13** which, without purification, was treated so as to induce intramolecular aldol condensation. Preparative tlc of the product on silica gel (40% EtOAc in pentane) gave (45% overall yield from **12**) a crystalline product which contained 85% of the 17β (**14**) and 15% of the 17α isomer. Two recrystallizations gave *dl*-progesterone, mp 182–185°, undepressed on admixture with authentic material,[10] mp 182–185.5°. The solution ir, nmr, and mass spectra of the former specimen were identical with the respective spectra of the latter as well as of natural progesterone. It is to be noted that many of the yields recorded in this paper have not yet been optimized.

Acknowledgments. We are indebted to the National Institutes of Health and the National Science Foundation for support of this research.

(10) W. S. Johnson, J. A. Marshall, J. F. W. Keana, R. W. Franck, D. G. Martin, and V. J. Bauer, *Tetrahedron, Suppl.*, **8** (2), 541 (1966).

William S. Johnson,* Michael B. Gravestock, Brian E. McCarry
Department of Chemistry, Stanford University
Stanford, California 94305
Received May 21, 1971

A Correlation of Some Structural Parameters of Pyrimidine Nucleosides. A Nuclear Magnetic Resonance Study

Sir:

A number of workers have drawn attention to the apparent correlation between the nature of the sugar–ring puckering and the sugar–base torsion angle (ϕ_{CN}) of crystalline nucleosides as determined by X-ray studies.[1-3] Prestegard and Chan[4] described correlations between the chemical shift of the H_6 hydrogen and the $J_{1'2'}$ coupling constant of pyrimidine nucleosides which suggest that this torsion angle–ring puckering relationship may exist in aqueous solution as well. Wilson and Rahman[5] pointed out that there may in some cases be a mutual relation between ring puckering and the nucleoside conformation about the exocyclic $C_{4'}$–$C_{5'}$ bond. It was to investigate the possibility of the existence of this latter relationship in aqueous solution that the present pmr study of a variety of pyrimidine nucleosides was initiated. Our data demonstrate that the gauche–gauche conformation is favored if the ribose, or deoxyribose, is in the $C_{3'}$ endo conformation and less favored if the sugar is puckered $C_{2'}$ endo.

The nucleosides were purchased from Calbiochem and the Sigma Chemical Co.; 0.1 *M* aqueous (D_2O) solutions containing 0.05 *M* internal reference (2,2,3,3-tetradeuterio-3-(trimethylsilyl)propionic acid sodium salt) were lyophilized three times. Spectra were obtained at 220 MHz (23°) and analyzed using LAME.[6] The spectral assignments were carried out by comparison of the shift data in the ribose and deoxyribose series with consideration of published work.[4,7] Some of the data for the correlation were taken from the literature. The literature sources are indicated in the caption of Figure 2.

The $J_{1'2'}$ and $J_{3'4'}$ couplings provide a means of monitoring the average conformation of the sugar ring. They can be related, *via* the Karplus equation,[8] to the dihedral angles $\phi_{1'2'}$ and $\phi_{3'4'}$ in the relevant HCC′H′ fragments (Figure 1). Smith and Jardetzky[9] have estimated the dihedral angles and corresponding coupling constants for a number of possible puckered conformations of ribose and deoxyribose rings. From their table we can make the following qualitative predictions: (a) with increasing proportion of the $C_{3'}$ endo (and/or $C_{2'}$ exo) conformation $\phi_{3'4'}$ and $J_{3'4'}$ increase whereas $\phi_{1'2'}$ and $J_{1'2'}$ decrease and (b) the reverse of (a) is the case for increasing proportion of the $C_{2'}$ endo (and/or $C_{3'}$ exo) conformation.[10]

Newman projection formulas along the $C_{4'}$–$C_{5'}$ bond are shown in Figure 1. Clearly, in the gauche–gauche rotamer in which the 5′ hydroxyl lies above the sugar ring the magnitudes of the vicinal coupling constants $J_{4'5'B}$ and $J_{4'5'C}$[11] are predicted by the Karplus equation to be small (*ca.* 2 Hz), since the coupled nuclei are in a gauche configuration ($\phi_{4'5'B}$ and $\phi_{4'5'C}$ = 60°). However, if the 5′ hydroxyl lies off the ring in either the trans–gauche or gauche–trans rotamer, the 4′ hydrogen is trans to one methylene hydrogen (ϕ = 180°) and the corresponding vicinal J is predicted to be large (*ca.* 10 Hz). Thus any perturbation resulting in a *decrease* in the proportion of the gauche–gauche rotamer should be manifest in an increase in the observed *sum* of $J_{4'5'B} + J_{4'5'C}$.[12]

In Figures 2 and 3 we have plotted this sum *vs.* $J_{3'4'}$ and $J_{1'2'}$, respectively. Clearly, a good correlation exists for the nucleosides indicated by ×. Further, we note that the sum decreases smoothly with increasing $J_{3'4'}$, but increases with increasing $J_{1'2'}$. Both trends are consistent with a correlated decrease in the gauche–gauche population with an increasing proportion of the $C_{2'}$ endo (and/or $C_{3'}$ exo) conformation in this series of ribo- and deoxyribonucleosides. The molecules on the correlation lines have the following common structural features: (a) they are β anomers, (b) they have a C—H and C=O at the ortho positions of the base, and (c) they most certainly exist in their anti conformation in solution.[13-26]

(1) A. E. V. Haschmeyer and A. Rich, *J. Mol. Biol.*, **27**, 369 (1967).
(2) M. Sundaralingam, *Biopolymers*, **7**, 821 (1969).
(3) A. V. Lakshminarayanan and V. Sasisekharan, *Biochim. Biophys. Acta*, **204**, 49 (1970).
(4) J. H. Prestegard and S. I. Chan, *J. Amer. Chem. Soc.*, **91**, 2843 (1969).
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(6) C. W. Haigh and J. M. Williams, *J. Mol. Spectrosc.*, **32**, 398 (1969).
(7) R. U. Lemieux, *Can. J. Chem.*, **39**, 116 (1961).
(8) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).
(9) M. Smith and C. D. Jardetzky, *J. Mol. Spectrosc.*, **28**, 70 (1968).
(10) Endo means the atom is located on the same side of the plane defined by $C_{1'}$, $O_{1'}$, and $C_{4'}$ as the $C_{4'}$–$C_{5'}$ bond. Exo means that it is found on the opposite side.
(11) In the spectral analyses the 4′ and 5′ hydrogens are treated as an ABC subsystem, hence the subscripts B and C.
(12) We realize that the actual rotamers about the $C_{4'}$–$C_{5'}$ bond may be somewhat distorted from the ϕ = 60° values due to O–O repulsion. Qualitatively identical trends are predicted on a distorted rotamer model. Further, since an absolute assignment of the magnetically nonequivalent methylene hydrogens cannot be made at this time, the sum of the two vicinal couplings must be used as a qualitative measure of the relative rotamer populations.
(13) B. J. Blackburn, A. A. Grey, I. C. P. Smith, and F. E. Hruska, *Can. J. Chem.*, **48**, 2866 (1970).