to nitrogen.[5] Therefore, in order to prove this hypotesis we monitored the course of the reaction of *O,O*-diisopropylphosphoroselenoic acid (**1f**) with DCC (Figure 1)[11] by the low-temperature ^{31}P NMR. Thus, a solution of DCC in ether was treated with an equimolar amount of **1f** at −80 °C and the resulting mixture was examined at 24.3 MHz using ^{31}P Fourier transform NMR with proton noise decoupling.[6] Two signals of high intensity were observed at $\delta_{^{31}P}$ −48.5 and −10.3 ppm. The first of them was attributed to the salt of seleno acid **1f** with DCC. It is interesting to point out that the coupling between phosphorus and selenium, $^1J_{^{31}P-^{77}Se}$ = 789 Hz, was observed, providing additional support of this assignment.[7] The δ −10.3 signal with the characteristic coupling constant $^1J_{^{31}P-^{77}Se}$ = 410 Hz corresponds undoubtedly to the expected *Se*-diisopropylphosphoryl-*N,N'*-dicyclohexylisoselenourea (**2f**).[8] The spectrum showed also the low intensity signal at +2.2 ppm corresponding to the already characterized *N*-diisopropylphosphoryl-*N,N'*-dicyclohexylselenoura (**3f**) and two doublets centered at −52 and +16.5 ppm due to tetraisopropyl monoselenopyrophosphate. Then we raised the temperature to −50 °C and observed the spectrum every 10 min. It showed gradual decrease of the signals at δ −48.5 and −10.3 ppm and at the same time fast increase of the signal due to **3f**. The signals due to **3f** and selenopyrophosphate in a ratio 4:1 were the only signals in the spectrum at room temperature.

The unstable adducts **2** and **4** were observed similarly using other acids **1** as the reaction components.[9] Their spectral characteristics are given in Table II.[10,11]

The mechanism of the phosphorylation by means of *N*-phosphorylthio(seleno)ureas **3** is under current investigation.

Supplementary Material Available. Tables I and II, including physical and spectral properties of the adducts **2, 3, 4,** and **5,** and Figure 1, showing the low-temperature FT ^{31}P NMR study of the reaction between DCC and **1f** (3 pages). Ordering information is given on any current masthead page.

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(4) The natural abundance of ^{77}Se is 7.58%. For the application of $^{31}P-^{77}Se$ coupling in structural and stereochemical studies see: I. A. Nuretdinov and E. I. Loginova, *J. Gen. Chem. USSR*, 2380 (1971); Perkin-Elmer NMR Quarterly, **1** (November), 6; W. McFarlane and J. A. Nash, *Chem. Commun.*, 913 (1969); W. J. Stec, A. Okruszek, B. Uznański, and J. Michalski, *Phosphorus*, **2,** 97 (1972); W. J. Stec, *Z. Naturforsch. B*, **31,** 393 (1976).
(5) Similar rearrangement has been observed by Chupp and Leschinsky in the reaction between isocyanides and phosphorus thio acids: J. P. Chupp and K. L. Leschinsky, *J. Org. Chem.*, **40,** 66 (1975).
(6) ^{31}P NMR spectra were obtained with a Jeol-JNM-FX60 Fourier transform NMR spectrometer. Chemical shifts are given in parts per million downfield from external 85% H_3PO_4.
(7) Triethylammonium salt of seleno acid **1f** has $\delta_{^{31}P}$ −50.4 ppm and $^1J_{^{31}P-^{77}Se}$ = 808 Hz, whereas the free acid **1f** absorbs at $\delta_{^{31}P}$ −60.8 ppm with $^1J_{^{31}P-^{77}Se}$ = 910 Hz.
(8) The proton-undecoupled ^{31}P NMR spectrum revealed that the signals at −48.5 and −10.3 ppm are triplets ($^3J_{POCH}$ = 7.3 Hz), whereas the resonance signal at +2.2 ppm is a double triplet due to an additional coupling $^3J_{PNCH}$ = 23 Hz, discussed earlier.
(9) We were not able to detect under similar conditions the 1:1 adducts of type **2** or **3** from *O*-isopropylmethylphosphonothioic acid and diethylphosphinothioic acid with DCC. The low-temperature FT ^{31}P NMR spectra of the mixtures of *O,O*-diethylphosphoric acid, *O,O*-dineopentylphoric acid, and *O,O*-diphenylphosphoric acid with DCC revealed the formation of corresponding *O*-phosphorylisoureas having $\delta_{^{31}P}$ +10.1 (10.9), +10.2, and +20.7 (21.6) ppm, respectively. However, in contrast to *S*-phosphorylisothioureas they did not undergo rearrangement to *N*-phosphorylureas, but reacted further to form pyrophosphates. These results and mechanistic differences will be discussed in a full paper.
(10) It is interesting to note that in some instances small, minor peaks (given in Table II in parantheses) are seen in the region characteristic of the adducts **2** and **4** which may be interpreted as evidence of syn–anti isomerism.
(11) See paragraph at the end of paper about supplementary material.

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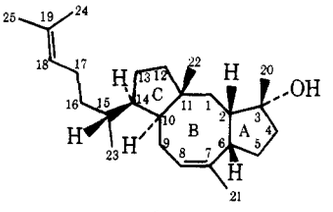
Received July 22, 1977

Sesterterpenes. 1. Stereospecific Construction of the Ceroplastol and Ophiobolin Ring Systems via a Common Bicyclic Intermediate

Summary: The ring systems present in the two major classes of ophiobolane sesterterpenes have been obtained via a common bicyclic intermediate. In each case, the eight-membered ring was constructed by fragmentation of an appropriately functionalized bicyclo[3.3.1]nonane ring system.

Sir: We have been investigating, for some time, the development of protocols for the synthesis of various classes of sesterterpenes. Among those under study are the two major stereochemical subclasses of the ophiobolane system exemplified by ophiobolin F (**1**)[1] and ceroplastol I (**2**).[2] Recent reports from other laboratories have prompted us to report our studies in this area.[3,4]



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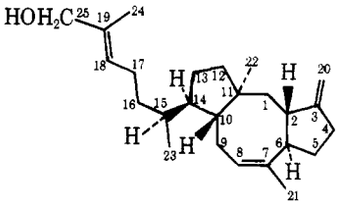

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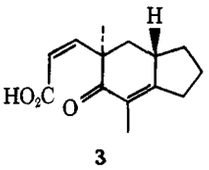
The structures of **1** and **2** present considerable synthetic challenges, since they possess four asymmetric centers about the central eight-membered ring. We were intrigued, however, by the fact that the systems differ in relative stereochemistry at only one center (C-2) about the eight-membered ring, although they possess different absolute stereochemistry. To exploit this observation, we undertook the construction of a bicyclic intermediate, ketone **3,** which we felt might be readily elaborated to intermediates of either stereochemical series. It was hoped that the trienol lactones **4,** which were plausibly derived from **3,** would serve as efficient precursors of bicyclo[3.3.1]nonanones of general structure **5,** and ultimately of



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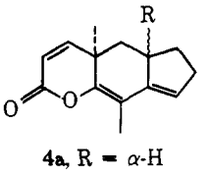
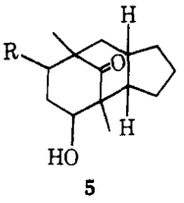


4a, R = α-H
b, R = β-H



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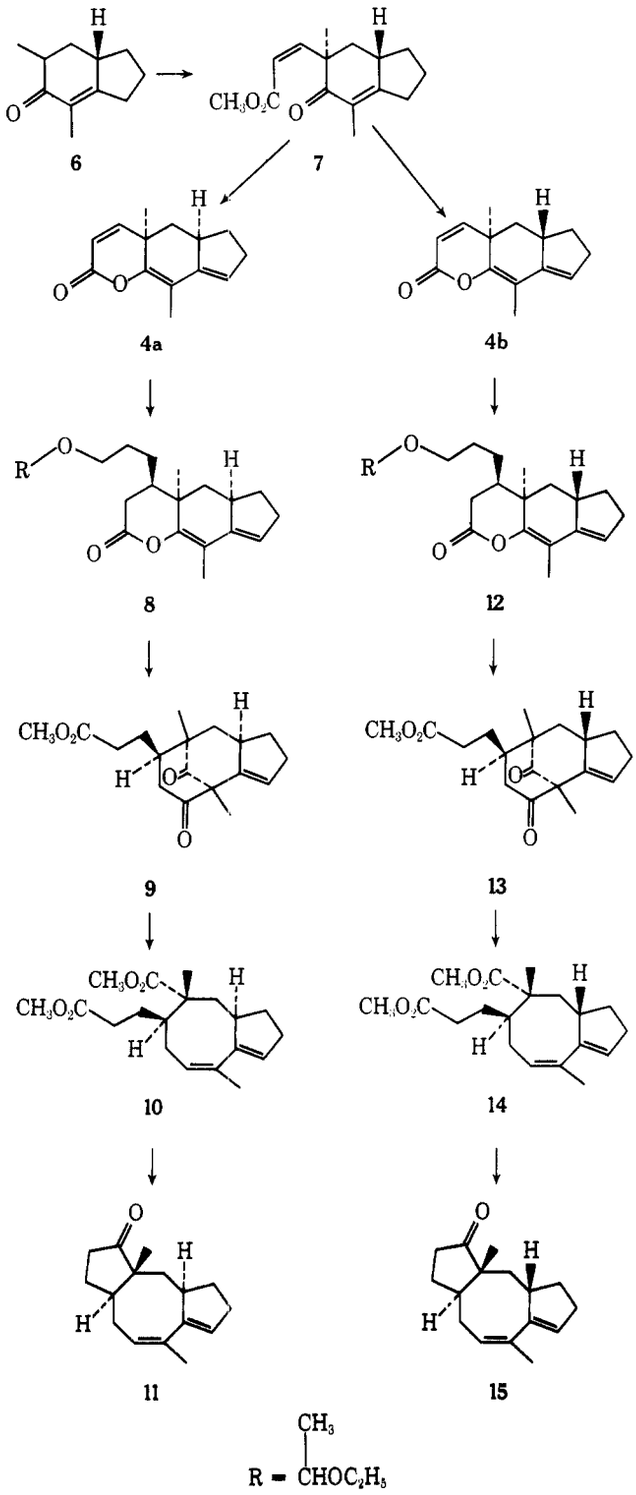
Scheme I



the required functionalized cyclooctenes by fragmentation. We have demonstrated the successful application of this strategy as described below.

Treatment of the pyrrolidine enamine of cyclopentanone with isopropenyl ethyl ketone under modified conditions provided bicyclic ketone **6** [bp 84–88 °C (1.5 mm)] in 59% yield (Scheme I).[5,6] To produce the required *cis*-acrylate side chain, we employed the cross-conjugated enolate of **6** (LiICA, −28 °C) to control regiochemistry.[7] Quenching with *cis*-3-chloroacrylate (1.1 equiv, −78 °C, 5 h) afforded, by addition–elimination, the required *cis*-acrylate ester **7** [bp 125 °C (0.4 mm)], NMR δ 5.90 (s, 2 H), 3.65 (s, 3 H), in 74% yield. This is the first example of addition–elimination to a cross-conjugated enolate, and it proceeds with clean retention (for the trans isomer also). It appears that use of the *cis*- and *trans*-chloroacrylates will be a valuable method for stereospecific introduction of an acrylate side chain in some cases. After saponification of **7** (1.1 equiv of KOH, 25 °C 48 h) which provided **3**,[8] the crystalline (mp 72.5–75 °C) enol lactone **4a** [NMR δ 6.7 (d, J = 10 Hz, 1 H)] was obtained as the major product (3:1) under acidic lactonization conditions [$HClO_4$-(cat), 10 equiv of Ac_2O, 0 °C, 2 m] in ~80% yield.[9] Epimerization occurs during lactone formation, leading to **4a** in the ceroplastol series.[10] Isolation of the intermediate mixed anhydride and completion of lactonization under basic conditions, shown not to equilibrate the epimers, led to the same major product, suggesting equilibration prior to cyclization. Alternatively, **4b** [NMR δ 6.6 (d, J = 10 Hz, 1 H)] is produced as the major isomer (7:1) upon lactonization under basic conditions ($NaOAc/Ac_2O$, 150 °C).[11]

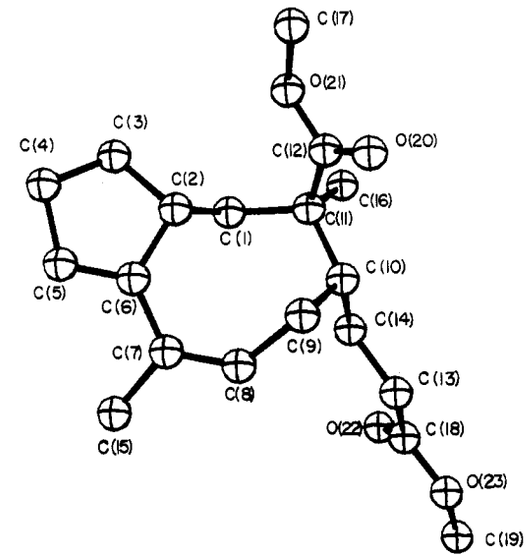


Figure 1. A computer-generated perspective drawing of **10**. Hydrogens are omitted for clarity.

Control of stereochemistry during introduction of the three-carbon side chain must be assured as this operation sets the geometry of the key trans BC ring junction required for *both* series. Treatment of **4a** with the mixed cuprate derived from *tert*-butylacetyene and the ethyl vinyl ether protected 1-bromo-3-propanol (1.7 equiv, −40 → 0 °C, 18 h) provided the diene lactone **8** (56%).[12] Lactone **8** was reductively rearranged (1.5 equiv of DIBAL, 0 °C, 2 h) to a mixture of ketols, which upon Jones oxidation and esterification (CH_2N_2) afforded the crystalline (mp 114.5–115 °C) diketo ester **9** (~35% from **7**).[12,13] Reduction of **9** with $Li(O\text{-}t\text{-}Bu)_3H$ (1.5 equiv), tosylation (0 °C, py), and fragmentation (4.0 equiv of $NaOCH_3$, 65 °C) provided the crystalline diester **10** (mp 111–112.5 °C) in approximately 33% overall yield.[14] The structure of **10** was confirmed by single-crystal x-ray analysis to have the stereochemistry shown[15] (Figure 1). The ring system was completed by Dieckmann cyclization (3.0 equiv of LiHMDS, 115 °C, 4 h) of **10** to **11** (~40%) [NMR δ 5.3–5.9 (m, 2 H); M^+ calcd for $C_{16}H_{22}O$ 230.1670, found 230.1660].

The stereochemical outcome of the conjugate addition is in accord with the expected stereoelectronic control usually observed in organocuprate chemistry.[19] We have found in this case, as well as a number of related systems, that enol lactones serve as excellent acceptors, although the corresponding open-chain esters are sluggish and few examples of additions to lactones have been recorded. The addition to lactone **4b** required for the ophiobolin series is, however, somewhat more

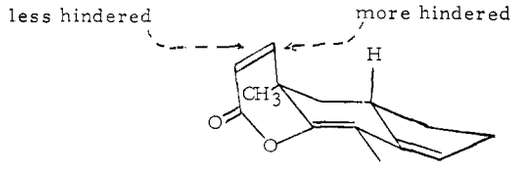
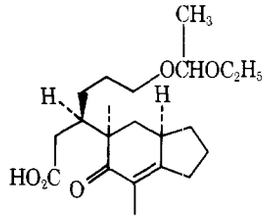


Figure 2.

difficult. Examination of a model (Figure 2) suggests that the required mode of addition, while favored stereoelectronically, is rather more hindered than addition from the outside of the concave ring system. Precedent exists that steric hindrance to approach of the reagent can markedly influence the stereochemical outcome.[20]

Treatment of **4b** under comparable conditions with the mixed cuprate described above (1.7 equiv, $-40 \rightarrow 0$ °C, 18 h) provided adduct **12** as the major product (50%).[21] In this case, stereoelectronic control still dominates in spite of the steric hindrance. Lactone **12** was then elaborated to ketone **15** by a comparable series of steps as those described for **8** to **11** (Scheme I).

We have examined two methods for introduction of the final asymmetric center in the ceroplastol series. Treatment of lactone **8** with KOH in ethanol (1.8 equiv, 25 °C, 18 h) afforded **16.** Reduction of **16** with Li/NH_3 (excess) and reoxidation (CrO_3/acetone, 0 °C) gave **17** in ~60% overall yield.[22] As can



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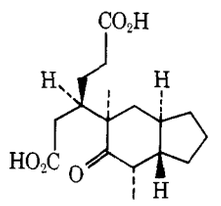

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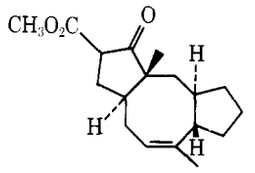

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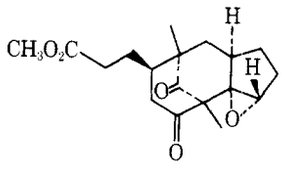
be seen, transformation of acid **17** via the lactone rearrangement–fragmentation sequence would be expected to lead to ester **18** possessing the correct relative asymmetry for the ceroplastols.[10,13] Alternatively, diketo ester **9** undergoes stereoselective epoxidation (MCPBA/CH_2Cl_2, 25 °C), affording ester **19** in ~70% yield. Rearrangement of **19** with boron trifluoride etherate (1.05 equiv, CH_2Cl_2, −78 °C) gave the desired triketone **20** [IR (cm^{-1}) 1740, 1735, 1715] in which the



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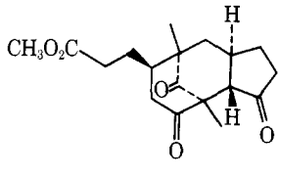

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final asymmetric center is introduced stereospecifically by migration of the adjacent β hydrogen. Again, triketone **20** possesses all the asymmetry required for the ceroplastol system.[10,13]

We are currently exploiting this methodology in our approaches to the natural substances **1** and **2.**

Acknowledgment. This research was generously supported by a grant (AI-11662) from the Allergy and Infectious Diseases Institute of the National Institutes of Health, to whom we are grateful.

Supplementary Material Available: Fractional coordinates and temperature factors (Table I), bond distances (Table II), and bond angles (Table III) for compound **10** (4 pages). Ordering information is given on any current masthead page.

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(5) R. Silverstein, W. Gore, and G. T. Pearce, *J. Org. Chem.*, **40,** 1705 (1975).
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(7) W. Ruesch, R. A. Lee, C. McAndrews, and K. M. Patel, *Tetrahedron Lett.*, 965 (1973).
(8) The use of hot base resulted in production of substantial amounts of equilibrated acid. The fact that no epimerization had occurred was demonstrated by reesterification to **7** with ethereal diazomethane.
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(10) In the interests of clarity of presentation, all structures of synthetic intermediates (racemic) are represented in the ophiobolin absolute stereochemical series.
(11) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, **74,** 4223 (1952).
(12) P. Eaton, G. Cooper, R. Johnson, and R. Mueller, *J. Org. Chem.*, **37,** 1947 (1972).
(13) Note that the apparent epimerization which occurs upon transformation of **8** → **10** is the result of the change in the stereochemical plane of reference from the six-membered ring in **8** to the eight-membered ring in **10.** No actual change of configuration occurs.
(14) R. A. Raphael, J. Martin, and W. Parker, *J. Chem. Soc.*, 289 (1964).
(15) Compound **10** crystallized in the triclinic crystal class with unit cell dimensions $a = 8.334$ (2), $b = 9.753$ (3), $c = 11.466$ (3) Å, $\alpha = 78.10$ (2), $\beta = 92.47$ (2), and $\gamma = 78.04$ (2)°. An approximate density of 1.20 g/cm^3 indicated two molecules of $C_{19}C_{19}H_{28}O_4$ per unit cell of either $P\bar{1}$ or $P1$. All unique reflection data with $2\theta \leq 114°$ were collected using graphite monochromated Cu Kα (1.54178 Å) x rays. A total of 2690 diffraction maxima were surveyed and after correction for Lorentz, polarization, and background effects 2371 (91%) were judged observed ($F_o^2 \leq 3\sigma(F_o^2)$).
Intensity statistics[16] suggested the centric space group $P\bar{1}$, and solution of the crystal structure was undertaken in this space group. Signs were determined for the 200 largest normalized structure factors using a multisolution, weighted sign determining procedure.[17] All nonhydrogen atoms were located in three-dimensional *E* synthesis from the most consistent set. Full-matrix least-squares refinement followed by a difference synthesis revealed all of the hydrogen atoms.[18] Further refinement with anisotropic thermal parameters for the nonhydrogen atoms and isotropic thermal parameters for the hydrogens have currently reached a minimum of 0.047 for the observed reflections. Bond distances and angles generally agree well with accepted values. Additional crystallographic details may be found in the supplementary material.
Figure 1 is a computer-generated drawing of the final x-ray model without hydrogens. Both enantiomers are present in the unit cell. The important point is the relative configurations at the three asymmetric centers C(2), C(1), and C(10). With reference to the eight-membered ring the hydrogens at C(2) and C(10) and the carbomethoxy group at C(11) are all on the same side.
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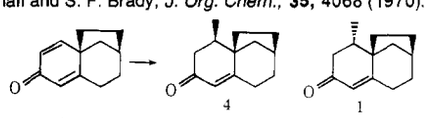
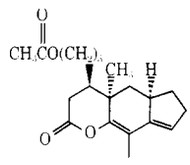


i ii

(21) Adduct **12** was compared to **8** by saponification and relactonization under equilibrating conditions. This procedure provided a lactone iii which was



iii

identical with the lactone prepared from **8** by hydrolysis and acetylation. This confirms the trans relationship between the methyl and side chain in **12**.

(22) G. Stork and S. D. Darling, *J. Am. Chem. Soc.*, **82**, 1512 (1960).
(23) Recipient of a Career Development Award (CA-00273) from the National Cancer Institute of the National Institutes of Health (1976–1981).
(24) Fellow of the Alfred P. Sloan Foundation (1976–1978).
(25) Camille and Henry Dreyfus Award (1972–1977).

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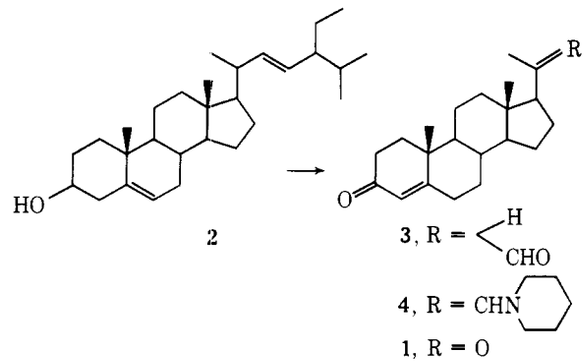
A Convenient Synthesis of Progesterone from Stigmasterol

Summary: A convenient synthesis of progesterone from stigmasterol is described involving as the key step the high yield photooxygenation of the 20-aldehyde **5** to the 20-ketone **10**.

Sir: One of the most important manufacturing processes[1] of the female sex hormone progesterone (**1**), which is also a key intermediate in the synthesis of corticosteroids, starts with stigmasterol (**2**). The final steps involve selective conversion of the aldehyde **3** to the 22-enamine **4**, followed by oxidation

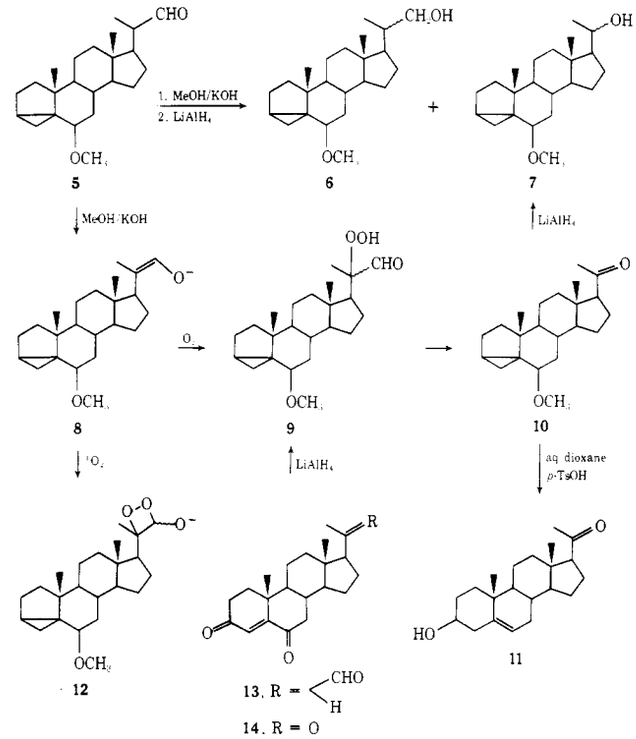


2 3, R = H, CHO 4, R = CHN 1, R = O

under a variety of conditions (ozonization, photooxidation) to progesterone.

During a recent synthesis[2] of novel marine sterols, we encountered an unexpected oxidation reaction: epimerization of aldehyde **5** with methanolic potassium hydroxide for 60 h, followed by reduction with lithium aluminum hydride yielded, in addition to the expected mixture of alcohols **6**, the epimeric 20-hydroxy pregnane derivatives **7** in 35% yield (Scheme I). This side reaction, which probably proceeds via the intermediate hydroperoxide[3] **9**, prompted a more detailed study which has now resulted in a simple one-step conversion of the aldehyde **5** into the corresponding 20-ketone **10** and thence to progesterone (**1**).

Scheme I



Stigmasterol (**1**) can be converted in excellent overall yield[4] to the 22-aldehyde **5**, 1.0 g of which was dissolved in 50 mL of 10% methanolic potassium hydroxide solution and cooled to 0 °C. After the addition of 15 mg of rose bengal sensitizer, oxygen was bubbled through the solution for 10 min with continuous irradiation from a 1000 W tungsten lamp. The reaction mixture was poured into water, extracted with ether, and washed successively with dilute hydrochloric acid, saturated sodium bicarbonate solution, and water. Evaporation of the dried ether extract gave the 20-ketone **10**, which was directly hydrolyzed by heating for 15 min under reflux in 20% aqueous dioxane containing 100 mg of *p*-toluenesulfonic acid, to afford the standard progesterone precursor pregn-5-en-3β-ol-20-one (**11**) in 94% overall yield (based on **5**). The Oppenauer oxidation of **11** to progesterone (**1**) is a standard commercially utilized operation.[5]

When the reaction was carried out in the absence of light or of the sensitizer no detectable amount of the ketone **10** was formed. Under identical conditions, but in the presence of Dabco,[6] a singlet oxygen quencher, only a 35% conversion (GC analysis) to **10** was realized. These reactions confirm that the 20-ketopregnane **10** is formed by a photooxidation process probably via the dioxetane intermediate **12** formed from the enol **8** by a (2 + 2) cycloaddition process[7] with singlet oxygen.

The reaction sequence outlined in this communication, coupled with the facile high-yield conversion[4] of stigmasterol (**2**) to the 22-aldehyde **5**, provides a very efficient and relatively inexpensive method for the synthesis of pregnenolone (**11**) and hence of progesterone.

An attempt was also made to eliminate the need for the *i*-methyl ether protecting group of **5** by carrying out the sensitized photooxygenation directly on the unprotected keto aldehyde **3**. While progesterone (**1**) was formed in 60% yield, it was invariably contaminated by ~10% each of the 6-keto aldehyde **13**[8] and the trione **14**,[9] thus making this alternative and much shorter synthesis of progesterone (**1**) a less efficient one.

Acknowledgment. We are grateful to the National Institutes of Health for financial assistance (Grant No. GM-06840)