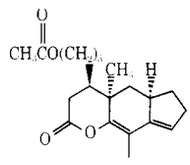


iii

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).

Robert K. Boeckman, Jr.,*[23,24] James P. Bershas
Department of Chemistry, Wayne State University
Detroit, Michigan 48202

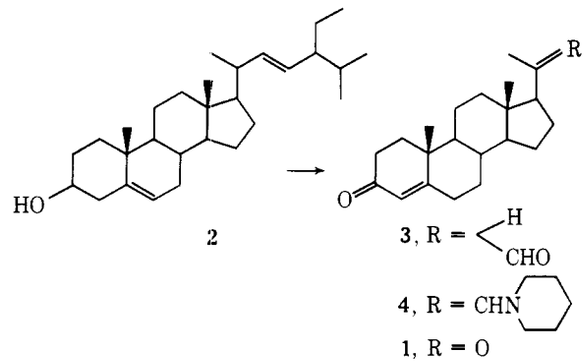
Jon Clardy,*[25] Barbara Solheim
Ames Laboratory USERDA and Department of Chemistry
Iowa State University
Ames, Iowa 50011

Received July 18, 1977

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

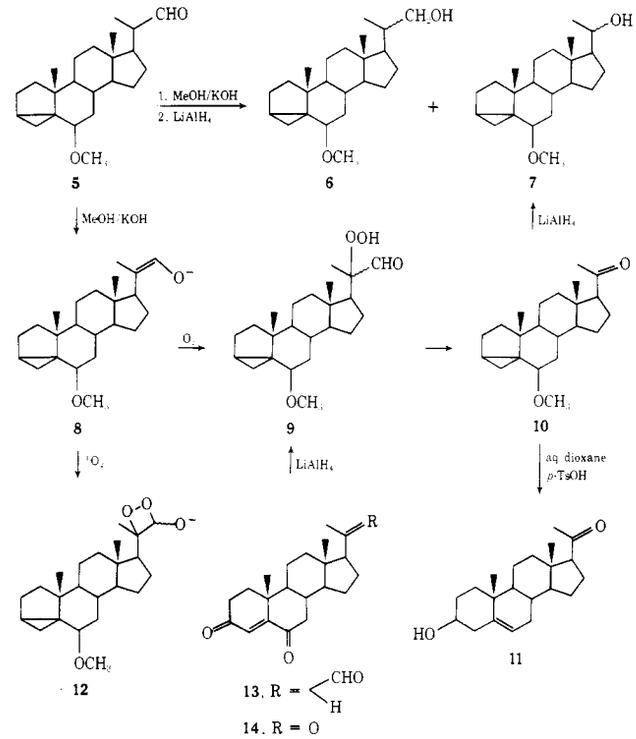


2 3, R = H, CHO 4, R = CHN 1, R = O

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)

and to the Upjohn Company (Kalamazoo, Mich.) for steroid starting materials.

References and Notes

(1) F. W. Heyl and M. E. Herr, *J. Am. Chem. Soc.*, **72**, 2617 (1950); G. Slomp, Jr., and J. L. Johnson, *ibid.*, **80**, 915 (1958); J. E. Huber, *Tetrahedron Lett.*, 3271 (1968).
(2) D. J. Vanderah and C. Djerassi, *Tetrahedron Lett.*, 683 (1977); D. J. Vanderah and C. Djerassi, *J. Org. Chem.*, in press.
(3) F. G. Bordwell, R. G. Scamehorn, and A. C. Knipe, *J. Am. Chem. Soc.*, **92**, 2172 (1970).
(4) J. A. Steele and E. Mosettig, *J. Org. Chem.*, **28**, 571 (1963); W. G. Salmond and M. C. Sobala, *Tetrahedron Lett.*, 1695 (1977).
(5) For leading references see L. F. Fieser and M. Fieser, "Steroids", Reinhold, New York, N.Y., 1959, p 539.
(6) J. C. Ouannes and T. Wilson, *J. Am. Chem. Soc.*, **90**, 6527 (1968).
(7) A. P. Schaap, "Singlet Molecular Oxygen", Dowden, Hutchinson and Ross, Stroudsburg, Pa., 1976, p 290.
(8) 3,6-Dioxobisnor-4-cholenaldehyde (**13**): mp 142–145 °C; $[\alpha]_D$ −15° [*c* 4.12, $CHCl_3$] (mixture of epimers at C-20); NMR signals (100 MHz) at 6.13 (1 H, H-5), 1.175 (3 protons, C-19 methyl), 1.124 and 1.057 (d, J = 5 Hz, together 3 protons, C-21 methyl), 0.772 and 0.733 ppm (s, together 3 protons, C-18 methyl); UV_{EtOH} λ_{max} (nm) 312 (ϵ 0.3 × 10^4), 250 (ϵ 1.0 × 10^4); CD_{EtOH} [θ] 297 [14 360], and 238.5 nm [41 180]; MS *m/e* 342 (37, M^+), 327 (16), 324 (11), 314 (33), 300 (15), 285 (14), 243 (27), 191 (28), 175 (10), 173 (11), 165 (12), 163 (17), 161 (12), 152 (20), 151 (10), 149 (12), 148 (11), 147 (19), 137 (100), 136 (67), 135 (14), 134 (16), 133 (30), 131 (11), 123 (11), 122 (12), 121 (15), 119 (14), 110 (14), 109 (29), 108 (20), 107 (26), 105 (23), 95 (22), 94 (11), 93 (27), 91 (34), 81 (38), 80 (50), 79 (45), 78 (10), 77 (26), 69 (15), 68 (11), 67 (28), 66 (16), 65 (11), 56 (15), 55 (50), 53 (21); structural assignment based on comparison of the spectral data with compound **14**.
(9) R. J. Langenbach and H. W. Knoche, *Steroids*, **11**, 123 (1968).

Padmanabhan Sundararaman, Carl Djerassi*
Department of Chemistry, Stanford University
Stanford, California 94305

Received July 25, 1977