THE TOTAL SYNTHESIS OF THE WATER MOLD SEX HORMONE OOGONIOL

Toshiaki Mase, Junji Ichita, Joseph P. Marino, and Masato Koreeda*

Department of Chemistry, The University of Michigan
Ann Arbor, Michigan 48109

Summary: The water mold sex hormone oogoniol (1a) has been synthesized from adrenosterone in 18 steps in 7.0% overall yield.   The crucial step introduces the stereochemistry at C-15 and C-20 through a highly efficient 1,4-addition of the organocyanocuprate generated from the side chain Grignard reagent (4) and CuCN to the steroidal 15β,16β-epoxy-17(20)(E)-ethylidene 2.
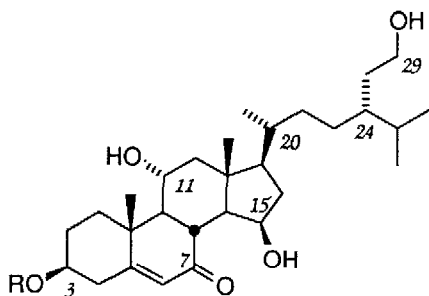
1a R = H   oogoniol
1b R = i-PrCO-   oogoniol - 1
1c R = C₂H₅CO- oogoniol - 2
1d R = CH₃CO-   oogoniol - 3

Oogoniols (1a - d),[1-3] steroidal sex hormones of the water mold, Achyla, possess a unique 15β-hydroxy steroid nucleus with a (24R)-29-hydroxy side chain. Introduction of a hydroxyl at C-15[4] in the steroid nucleus remains a challenging synthetic problem.[5]   Previously, we have shown that the reaction of the 15β,16β-epoxy-17(20)(E)-ethylidene with mixed cuprates gives the 1,4-addition product at C-20, simultaneously establishing two chiral centers at C-15 and C-20.[6]   In this paper, we now report that oogoniol (1a) has been synthesized from adrenosterone (5) using a modified version of this approach for the crucial, stereo- and regiocontrolled introduction of the side chain (see eq. 1).[7]
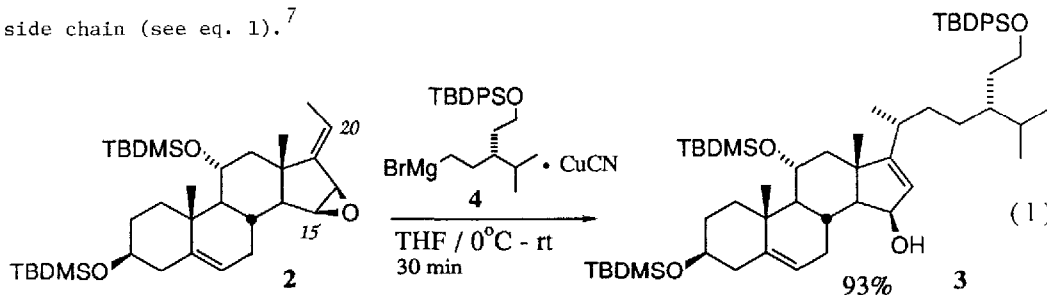

The requisite vinyl epoxide 2 was synthesized from adrenosterone (5)[8] in 13 steps in 28.8% overall yield (Scheme I).   The 3-acetoxy-3,5-diene[9] obtained from adrenosterone was selectively ketalized at C-17 to afford 3-acetoxy-17-ethylenedioxyandrosta-3,5-dien-11-one, which was reduced with NaBH₄ in t-BuOH/THF/H₂O[10] to the 3β,11β-diol 6.   Following the selective acetylation of the 3β-hydroxyl of 6, the stereochemistry at C-11 was inverted to the desired α-hydroxyl.   Both introduction of the C-15/16 double bond (see 8 → 9) and its epoxidation to the

Scheme I^a

adrenosterone **(5)**
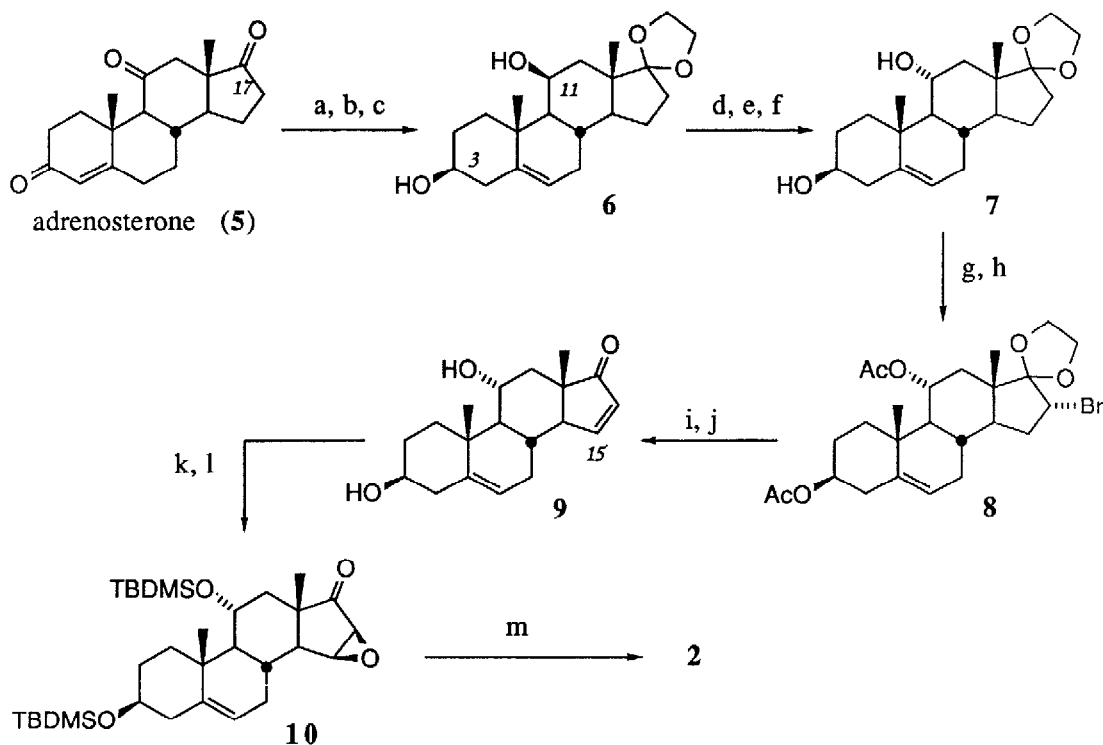
^aConditions: (a) AcCl/Ac₂O, reflux, 6h (92%); (b) (CH₂OH)₂, p-TsOH, HC(OEt)₃, reflux, 1h (83%);
(c) NaBH₄/t-BuOH, THF, H₂O, 0°C - r t, 5h (88%); (d) Ac₂O/py, r t, 4h (95%); (e) PCC, CH₂Cl₂, r t,
2h (99%); (f) Li/liq NH₃, dioxane, MeOH, -30°C (99%); (g) Ac₂O/py, r t , 8h (94%); (h) C₅H₅N Br₂-HBr/
THF, r t , 2h (work-up with NaI, Na₂S₂O₃) (94%); (i) t-BuOK (excess)/DMSO, 40°C, 24h (86%);
(j) PPTS/acetone/H₂O, r t , 24h (88%); (k) TBDMSOTf/2,6-lutidine, CH₂Cl₂, 0°C, 10 min (89%);
(l) 30% H₂O₂, 4MNaOH/t-BuOH, THF, r t , 1h (85%); (m) Ph₃P(Et)Br/LDA/THF, 0°C, 30 min (90%)

15β,16β-epoxy-17-one (see **9** → **10**) were achieved, as in our previous study,[6] by adopting the

procedure established by Clark, I. M. et al.[11] Wittig reaction of **10** with Ph₃P(Et)Br/LDA in

THF[6] afforded cleanly the key intermediate 17(20)(**E**)-ethylidene **2** (mp 137 - 139°C) in 90% yield.

The synthesis of the side chain bromide **15** was achieved from (**R**)-(+)-limonene (**11**) in 9

steps in 21.8% overall yield (Scheme II). Selective reduction of the keto-aldehyde **12**[12] with

Li(Et₃CO)₃AlH[13] followed by protection of the resulting primary alcohol provided the ketone **13**

in 73% overall yield from **11**. The use of the TBDPS group over the more commonly used TBDMS

was necessary because of the observed propensity for deprotection of the latter during the

ensuing Baeyer-Villiger reaction.

Scheme II[a]
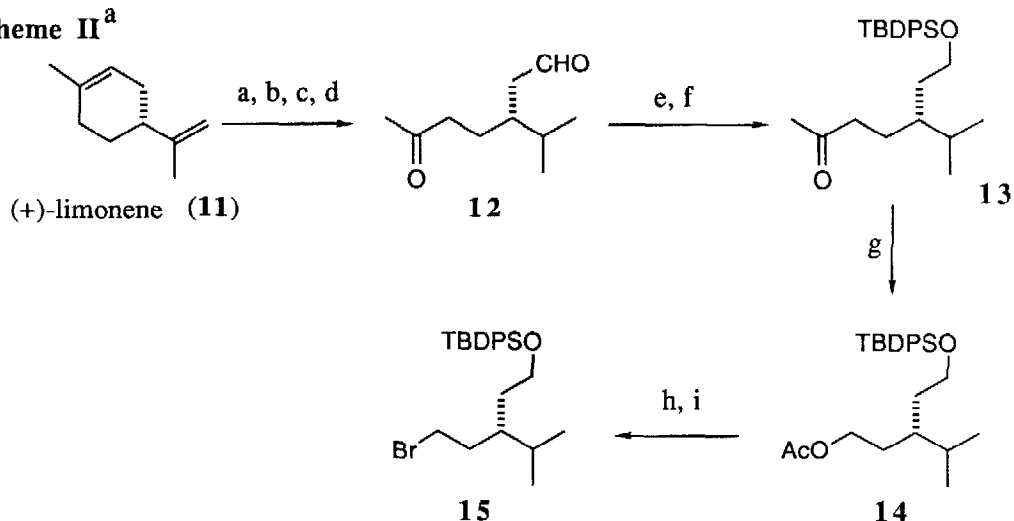
[a] Conditions: (a) 5% Pt/C, H₂, 40 psi (86%); (b) HCOOH/H₂O₂, 35°C, 2h; (c) KOH/EtOH, r t, 3h;
(d) NaIO₄/acetone, H₂O, r t, 4h (60% overall for b, c, and d); (e) Li(Et₃CO)₃AlH/THF, -78°C, 1h (78%);
(f) TBDPSCl/imidazole/DMF, r t, 3h (94%); (g) MCPBA/NaHCO₃, CH₂Cl₂, reflux, 48h (60% yield plus
33% recovery of the starting ketone); (h) K₂CO₃/MeOH, 0°C, 1h (98%); (i) Ph₃P/NBS/CH₂Cl₂, 0°C, 1h (98%)

Treatment of the deep purple-colored organocyanocuprate solution in THF, prepared by adding
the Grignard reagent **4** generated from bromide **15** (2.88 equiv) to CuCN (2.85 equiv), with the
vinyl epoxide **2** resulted in the stereo- and regioselective formation of the desired 1,4-adduct
3 in 93% yield (eq. 1).[14] The stereochemistry at C-15, 20, and 24 was judged homogeneous
based on the high field ¹H (360 MHz) and ¹³C (90.56 MHz) NMR data. Following selective hydro-
genation of the adduct **3** and protection of the 15β-hydroxyl as TMS ether, the 7-keto group was
introduced using Salmond's reagent[15,16] (Scheme III). Deprotection of the enone **16** with HF,
followed by purification using silica gel chromatography, provided oogoniol (**1a**) as a single
stereoisomer in 85% yield as a white crystalline powder (mp 101 - 103°C). The spectroscopic
properties (FTIR, 360 MHz ¹H, and 90.56 MHz ¹³C NMR spectra) of the synthetic oogoniol were
identical with those, kindly provided by Professor McMorris, of the natural product.

Scheme III

1. H₂, PtO₂/ AcOEt, r t, 12h (92%)
2. TMSOTf, 2,6-lutidine
   CH₂Cl₂, 0°C, 5 min (89%)
3. 3,5-dimethylpyrazole/CrO₃
   CH₂Cl₂/ - 20°C - - 10°C
   4h (71%)

50% aq HF/CH₃CN/THF
(1/19/19)
r t, 3h
85%
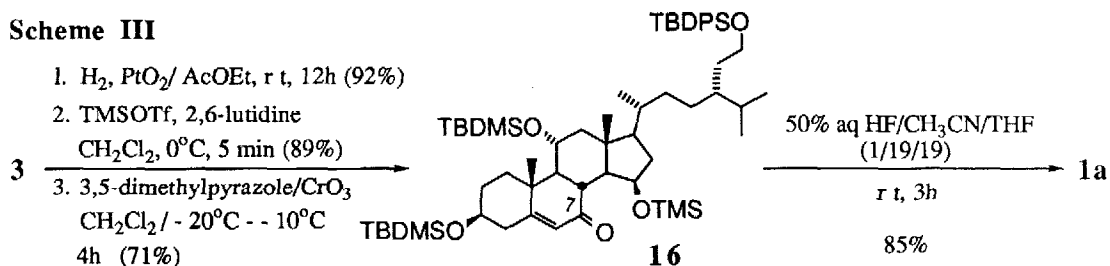
In summary, the water mold sex hormone oogoniol (**1a**) has been synthesized from adreno-sterone (**5**) in 18 steps in 7.0% overall yield. The use of the Grignard-reagent derived cyanocuprate for the 1,4-addition instead of more conventional organolithium-cyanocuprate reagents is particularly noteworthy. Current efforts from these laboratories include the synthesis of oogoniols-1-3 (**1b** - **d**).[17]

References and Footnotes

1. McMorris, T. C.; Schow, S. R.; Weihe, G. R. Tetrahedron Lett. **1978**, 335.

2. Preus, M. W.; McMorris, T. C. J. Am. Chem. Soc. **1979**, **101**, 3066.

3. Wiersig, J. R.; Waespe-Sarcevic, N.; Djerassi, C. J. Org. Chem. **1979**, **44**, 3374.

4. For recent examples of other naturally occurring C-15 hydroxylated steroids, see: Minale, L.; Pizza, C.; Riccio, R.; Zollo, F. Experientia **1983**, **39**, 567 and Tachibana, K.; Sakaitani, M.; Nakanishi, K. Tetrahedron **1985**, **41**, 1027.

5. (a) Taylor, E. J.; Djerassi, C. J. Org. Chem. **1977**, **42**, 3571. (b) Anastasia, M.; Fiecchi, A.; Gariboldi, P.; Scala, A. Ibid. **1979**, **44**, 4447. (c) McMorris, T. C.; Le, P. H.; Preus, M. W.; Schow, S. R.; Weihe, G. R. Ibid. **1983**, **48**, 3370. (d) Liu, D.; Stuhmiller, L. M.; McMorris, T. C. J. Chem. Soc. Perkin Trans. I **1988**, 2161.

6. Marino, J. P.; Abe, H. J. Am. Chem. Soc. **1981**, **103**, 2907.

7. TBDMS = t-butyldimethylsilyl; TBDPS = t-butyldiphenylsilyl.

8. Purchased from Fine Chemical Division, The Upjohn Company, Kalamazoo, Michigan.

9. Kelly, R. W.; McClenaghan, I.; Sykes, P. J. J. Chem. Soc. (C) **1967**, 2375.

10. Edwards, J. A.; Calzada, M. C.; Ibanez, L. C.; Bowers, A. Steroids **1965**, **6**, 371.

11. Clark, I. M.; Denny, W. A.; Jones, E. R. H.; Meakins, G. D.; Pendlebury, A.; Pinhey, J. T. J. C. S. Perkin I **1972**, 2765.

12. Kishida, Y. Chem. Ind. **1960**, 465. See also: Nicotra, F.; Penza, L.; Ronchetti, F.; Russo, G.; Toma, L. J. Org. Chem. **1986**, **51**, 1272.

13. Krishnamurthy, S. J. Org. Chem. **1981**, **46**, 4628.

14. Our initial efforts for adding the side chain moiety to **2** using the cyanocuprate generated from the lithium derivative of the bromide **15** under a variety of conditions were not successful due to the difficulties encountered during the formation of the lithium deriva-tive.

15. Salmond, W. G.; Barta, M. A.; Havens, J. L. J. Org. Chem. **1978**, **43**, 2057.

16. This oxidation did not proceed to completion even under prolonged treatment; 10 - 15% of the starting compound was recovered.

17. After completion of this work, we learned that Professor T. C. McMorris (University of California, San Diego) has also achieved the total synthesis of oogoniol (**1a**) using the similar approach described in this report. We thank Professor McMorris for this information.

Note Added in Proof. The synthesis of oogoniol by Professor McMorris (see footnote 17) has just appeared; Moon, S.-S.; Stuhmiller, L. M.; McMorris, T. C. *J. Org. Chem.* **1989**, *54*, 26.