THE TOTAL SYNTHESIS OF THE WATER MOLD SEX HORMONE OOGONIOL

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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.

Oogoniols (1a - d), 1-3 steroidal sex hormones of the water mold, Achlya, 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,16α-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

Conditions: (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, by adopting the procedure established by Clark, I. M. et al. The Wittig reaction of 10 with Ph₃P(Et)Br/LDA in THF 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 with Li(Et₃C)₃AlH 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.
Treatment of the deep purple colored organocyanocuprate solution in THF, prepared by adding the Grignard reagent \( \text{b} \) generated from bromide \( 15 \) (2.88 equiv) to CuCN (2.85 equiv), with the vinyl epoxide \( \text{e} \) resulted in the stereo- and regioselective formation of the desired 1,4-adduct \( \text{f} \) in 93% yield (eq. 1).\(^{14}\) The stereochemistry at C-15, 20, and 24 was judged homogeneous based on the high field \( ^1\text{H} \) (360 MHz) and \( ^{13}\text{C} \) (90.56 MHz) NMR data. Following selective hydrogenation of the adduct \( \text{f} \) and protection of the 15R-hydroxyl as TMS ether, the \( \alpha\)-keto group was introduced using Salmond's reagent \( \text{g} \) (Scheme III). Deprotection of the enone \( \text{i} \) 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 \(^1\text{H}\), and 90.56 MHz \(^{13}\text{C}\) NMR spectra) of the synthetic oogoniol were identical with those, kindly provided by Professor McMorris, of the natural product.

Scheme III

1. \( \text{H}_2, \text{PtO}_2/\text{AcOEt}, \text{rt}, 12\text{h} \) (92%)
2. TMSOTf, 2,6-lutidine
   \( \text{CH}_2\text{Cl}_2, 0^\circ\text{C}, \text{5 min} \) (89%)
3. 3,5 dimethylpyrazole/\( \text{CrO}_3 \)
   \( \text{CH}_2\text{Cl}_2/-20^\circ\text{C} - 10^\circ\text{C} \)
   \( \text{4h} \) (71%)

\[ \text{CH}_3\text{CH}_2\text{O} \]

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\(^{a}\) Conditions: (a) 5% Pt/C, \( \text{H}_2 \), 40 psi (86%); (b) HCOOH/H\(_2\text{O}_2\), \( 35^\circ\text{C}, 2\text{h} \); (c) KOH/\( \text{EtOH} \), \( \text{rt}, 3\text{h} \); (d) NaIO\(_4\)/acetone, \( \text{H}_2\text{O}, \text{rt}, 4\text{h} \) (60% overall for b, c, and d); (e) Li(\( \text{Et}_3\text{CO}_3\))\(_\text{AlH}/\text{THF}, -78^\circ\text{C}, \text{1h} \) (78%); (f) TBDPSCI/imidazole/DMF, \( \text{rt}, 3\text{h} \) (94%); (g) MCPBA/\( \text{NaHCO}_3 \), \( \text{CH}_2\text{Cl}_2\), reflux, 48h (60% yield plus 33% recovery of the starting ketone); (h) \( \text{K}_2\text{CO}_3/\text{MeOH}, 0^\circ\text{C}, \text{1h} \) (98%); (i) \( \text{Ph}_3\text{P/NBS/CH}_2\text{Cl}_2, 0^\circ\text{C}, \text{1h} \) (98%)
In summary, the water mold sex hormone oogoniol (1a) has been synthesized from adrenosterone (3) 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

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References and Footnotes
7. TBDMS = t-butyldimethylsilyl; TBDPS = t-butyldiphenylsilyl.
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 derivative.
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.


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