Tetrahedron Letters No. 9, pp 791 - 794, 1972. Pergamon Press. Printed in Great Britain.

A NEW SYNTHETIC ROUTE TO THE FUNGAL SEX HORMONE ANTHERIDIOL AND THE DETERMINATION OF ITS ABSOLUTE STEREOCHEMISTRY[1]

J. A. Edwards, J. Sundeen[2a], W. Salmond[2b]
T. Iwadare[2c] and J. H. Fried

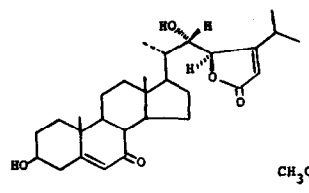
Institute of Organic Chemistry, Syntex Research
3401 Hillview Avenue, Palo Alto, California 94304

(Received in USA 17 January, 1972; received in UK for publication 27 January 1972)

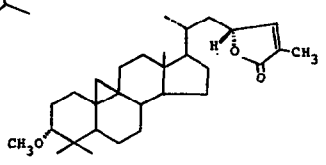
We wish to report another synthesis of the fungal sex hormone antheridiol[3,4] and to provide unequivocal evidence that the absolute stereochemistry of this natural product is as shown in structure 1.

The present synthesis was devised with the objective of first introducing the stereochemistry at C_{22} via the furyl carbinol intermediate 4a and then to elaborate the butenolide system by oxidative methods. Condensation of the 2-lithio derivative[5] of 3-isopropylfuran with 3-tetrahydropyran-2'-yloxy-22,23-bisnorchol-5-en-24-al[4] proceeded in a stereospecific manner to yield the pure carbinol 4a[7] (60%) [mp 161-165°; $[\alpha]_D$ ($CHCl_3$) -46°; ν_{max} (KBr) 3450, 1025 cm^{-1}; nmr ($CDCl_3$) δ 0.67 (18-H), 0.99 (19-H), 1.00 (d, J 6 Hz, 21-H), 1.12, 1.14 (2 x d, J 7 Hz, isopropyl CH_3), 4.90 (22-H), 5.73 (narrow m, 6-H), 6.31, 7.26 ppm (2 x d, J 2 Hz, furyl-H)] which afforded the 22-acetate 4b [mp 152-155°; $[\alpha]_D$ ($CHCl_3$) -13°; ν_{max} (KBr) 1730, 1230, 1025 cm^{-1}] with Ac_2O/Py. Treatment of 4b with 3.3 molar equiv of m-chloroperbenzoic acid furnished the amorphous lactol 5 (81%) [nmr ($CDCl_3$) δ 0.63 (18-H), 1.04 (19-H), 1.01 (d, J 7 Hz, 21-H); 1.16, 1.23 (2 x d, J 7 Hz, isopropyl CH_3), 2.03 (acetoxy-H), 2.85 (d, J 4 Hz, 6-H), 5.26 (22-H), 5.89 ppm (butenolide-H)] which was reduced by $NaBH_4$ in diox-H_2O (19:1) to a mixture of acetoxy butenolides 6[8] (95%). Sequential treatment of the latter products with Zn-NaI-CH_3CO_2H[9] to regenerate the 5,6-double bond and 5% H_2SO_4 to hydrolyze the 22-acetate provided a mixture of dihydroxy butenolides 9. Purification of this mixture by prep. tlc furnished to 22S,23R butenolide 9a[10] (5.5% from 6) [mp 242-247°; $[\alpha]_D$ ($CHCl_3$) -24°; ν_{max} (KBr) 3450, 1740, 1620

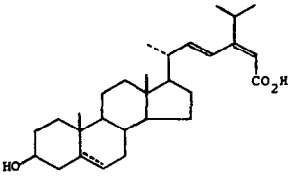
cm^{-1}; nmr ($CDCl_3$) δ 0.69 (18-H), 1.00 (19-H), 1.12, 1.16, 1.21 (21-H and isopropyl CH_3), 4.91 (d, J 9 Hz, 23-H), 5.32 (narrow m, 6-H), 5.75 ppm (24'-H)], the 22R,23S butenolide 9c (13.5% from 6) [mp 210-211°, identical with the previously described γ-lactone[4]] and a mixture of 22R,23R and 22S,23S (threo) butenolides (ca. 8%)[11]. The formation of four hydroxy butenolides starting with a pure furyl carbinol 4a demonstrates that epimerization of the C_{22} center of the lactol 5 via the intermediate keto acid has occurred during the $NaBH_4$ reduction[12].



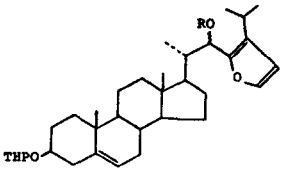
1



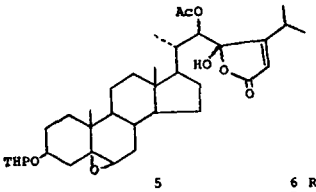
2



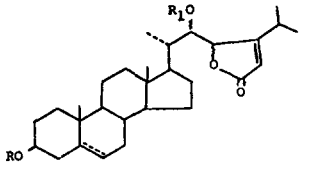
3a with 5,6-double bond
b with 5α,6α-epoxide



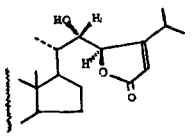
4a R=H
b R=$COCH_3$



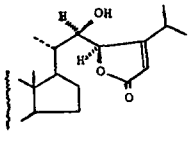
5



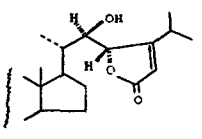
6 R=THP; R_1=$COCH_3$; with 5α,6α-epoxide
7 R=R_1=H; with 5α,6α-epoxide
8 R=H; R_1=$COCH_3$; with 5,6-double bond
9 R=R_1=H; with 5,6-double bond



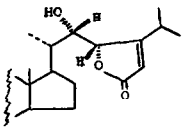
9a



9b



9c



9d

The threo lactones were obtained more efficiently by reaction of the 5α, 6α-epoxydienoic acid 3b[4] with OsO_4/Py followed by reductive removal of the 5,6-epoxide with Zn. Purification of the resulting mixture by fractional crystallization and prep. tlc furnished the 22S,23S butenolide 9d (22%) [mp 266.5-269°; $[\alpha]_D$ [$CHCl_3$-MeOH (3:1)] -20°; ν_{max} (KBr) 3500, 1740, 1630 cm^{-1}; nmr [$CDCl_3$-MeOD (4:1)] δ 0.75 (18-H), 1.01 (19-H), 1.11, 1.18, 1.25 (3 x d, J 7 Hz, 21-H and isopropyl CH_3), 5.06 (23-H), 5.30 (narrow m, 6-H), 5.77 ppm (24'-H)]

and the 22R,23R butenolide 9b (7.5%, admixed with ca. 5% of butenolide 9d) [mp 195.5-201°; nmr ($CDCl_3$) δ 0.72 (18-H), 1.00 (19-H), 1.11 (d, J 7 Hz, 21-H), 1.15, 1.25 (2 x d, J 7 Hz, isopropyl CH_3), 3.9 (m, 22-H), 4.86 (23-H), 5.32 broad d, 6-H), 5.78 ppm (24'-H); MS m/e 456 (M^+)].

The stereochemical assignments follow from a comparison of the circular dichroism spectra of the butenolides 9a-d and of cyclograndisolide (2), a triterpene of known absolute configuration at C_{23}[13] as determined by X-ray crystallographic analysis. As shown in Table 1, butenolides 9a and 9b have the opposite absolute stereochemistry to cyclograndisolide at the C_{23} center. Since butenolide 9b is obtained by cis dihydroxylation of a 22,23-trans double bond, its absolute configuration is 22R,23R. Butenolide 9a must have the opposite stereochemistry to 9b at C_{23} and it is, therefore, assigned the 22S,23R (erythro) stereochemistry. The side chain stereochemistry of butenolides 9c and 9d follows from similar arguments.

Table 1

Butenolide	CD Maximum θ°	nm	Solvent
22S,23R 9a	+35,875	220	diox-MeOH (3:1)
22R,23S 9c[4]	-38,249	222.5	diox-MeOH (3:1)
22S,23S 9d	-20,820	224	diox-MeOH (3:1)
22R,23R 9b	+15,070	224	diox-MeOH (3:1)
Cyclograndisolide[13]	-31,500	220	diox

Finally, hematoporphyrin-sensitized photooxygenation[4,14] of the 22S,23R butenolide 9a followed by treatment of the crude Δ^6-5α-hydroperoxide with $Cu(OAc)_2$ furnished antheridiol 1 (36%) [mp 250-254°], identical in all respects with an authentic sample of the hormone[4]. This shows that antheridiol possesses the 22S,23R ($22\beta_F$,$23\beta_F$) stereochemistry and confirms the tentative predictions made earlier for the absolute configuration of this natural product[4,15].

ACKNOWLEDGEMENTS

We thank Dr. Lewis Throop for the CD spectra and Dr. B. Berkoz for helpful discussions.

REFERENCES

1. Publication No. 395 from the Institute of Organic Chemistry, Syntex Research, Palo Alto, California.

2. Syntex Postdoctoral Fellow: (a) 1968-1969; (b) 1969-1970; (c) 1970-1971.

3. For leading references, see G. P. Arsenault, K. Biemann, A. W. Barksdale and T. C. McMorris, J. Amer. Chem. Soc., 90, 5635 (1968).

4. J. A. Edwards, J. S. Mills, J. Sundeen and J. H. Fried, ibid, 91, 1248 (1969).

5. This reagent was prepared by decarboxylation of 4-isopropyl-5-bromo-2-furoic acid[6] by steam distillation in the presence of mercuric chloride to the liquid 2-bromo-3-isopropylfuran [bp 130° (760 mm) with decomposition; ν_{max}^{film} 1495, 1460, 1380, 1365, 1170, 1160, 1110, 1060, 1005, 890 cm^{-1}; nmr ($CDCl_3$) δ 0.69 (d, J 7 Hz, isopropyl CH_3), 1.68 (m, J 7 Hz, methine H), 3.85 and 4.42 ppm (2 x d, J 2 Hz, furyl-H)]. Since the bromofuran distillate gradually darkened during the course of the distillation, the dried steam distillate was treated directly with n-butyl-lithium in hexane to form the lithio derivative.

6. H. Gilman, N. O. Calloway and R. R. Burtner, J. Amer. Chem. Soc., 57, 906 (1935).

7. Satisfactory elemental analyses were obtained for all fully characterized compounds.

8. During the course of this work, D. Satoh and K. Auyama, Chem. Pharm. Bull. Tokyo, 18, 1239 (1970), described the conversion of a 17β-furylandrostane to an α,β-unsaturated lactone by the same sequence of reactions. See also J. M. Ferland, Y. Lefebvre, R. Deghenghi and K. Wiesner, Tetrahedron Letters, 3617 (1966).

9. J. W. Cornforth, R. H. Cornforth and K. K. Mathew, J. Chem. Soc., 112 (1959).

10. In our first synthesis of antheridiol 1, lactone 9a was not isolated in a pure state. Antheridiol was obtained by treating a γ-lactone fraction rich in 9a by the zinc reduction and photoxygenation procedures. See ref. 4.

11. An alternate synthesis of the butenolide system 9 was achieved by the direct condensation of the anion of 3-isopropylbutenolide with 3-tetrahydropyran-2'-yloxy-22,23-bisnorchol-5-en-24-al[4] followed by acid hydrolysis. This furnished, among other products, the butenolides 9b and 9c in low yield. Unpublished results of W. Salmond from these laboratories. See also T. C. McMorris and R. Seshadri, J. Chem. Soc., D, 1646 (1971).

12. For a related example of the epimerization of asymmetric ketones during $NaBH_4$ reduction, see V. Hach, E. C. Fryberg and E. McDonald, Tetrahedron Letters, 2629 (1971).

13. F. H. Allen, J. P. Kutney, J. Trotter and N. D. Westcott, ibid, 283 (1971).

14. A. Nikon and J. F. Bagli, J. Amer. Chem. Soc., 83, 1498 (1961).

15. D. M. Green, J. A. Edwards, A. W. Barksdale and T. C. McMorris, Tetrahedron, 27, 1199 (1971).