

STEREOCONTROLLED SYNTHESIS OF THE WITHANOLIDE D SIDE CHAIN FROM
20-OXOSTEROID*

Tetsuji Kametani,[†] Masayoshi Tsubuki, and Toshio Honda*

Institute of Medicinal Chemistry, Hoshi University, Ebara
2-4-41, Shinagawa-ku, Tokyo 142, Japan

Abstract — A new procedure for the construction of the withanolide D side chain starting from 20-oxopregnane is described. The key reactions are stereochemical control of C-20 and C-22 positions involving stereoselective hydrogenation of the enone 4, and an efficient transformation of the resulting γ -lactone 5 into the δ -lactone 8. Successful isomerization of the olefin 12 using RhCl_3 is also reported.

Withanolides, a group of naturally occurring ergostane-type steroids possessing a δ -lactone in the side chain, have been isolated from the plants of the Solanaceae family.¹ Synthetic efforts have been paid to the development of an efficient route to withanolides, such as withaferin A (1) and withanolide D (2), because of their attractive biological activities, mainly antitumor and insect antifeedant properties. In connection with our synthetic work on the physiologically active steroids utilizing furan derivatives,² we have investigated the synthesis of withanolides and describe herein an efficient synthesis of the withanolide D side chain from 20-oxopregnane 3 employing a stereoselective reduction of the enone 4 and subsequent homologation of the resulting γ -lactone 5 to the δ -lactone 8 having (20R,22R)-diol functionality.

As outlined in Scheme I, a key intermediate 8 was prepared from the ketone 3. Reaction of 3 with 2-lithio-4-methylfuran³ in tetrahydrofuran (THF) gave the furylcarbinol, whose ring-opening reaction with m-chloroperbenzoic acid (m-CPBA) in dichloromethane (CH_2Cl_2) followed by oxidation of the lactol with pyridinium

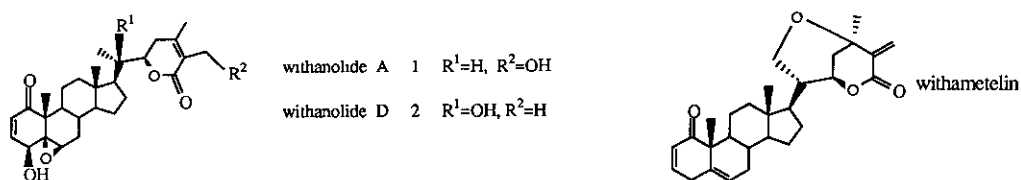
* Dedicated to Sir Derek Barton, Professor of Texas A&M University, on occasion of his 70th birthday.

[†]Deceased October 11, 1988.

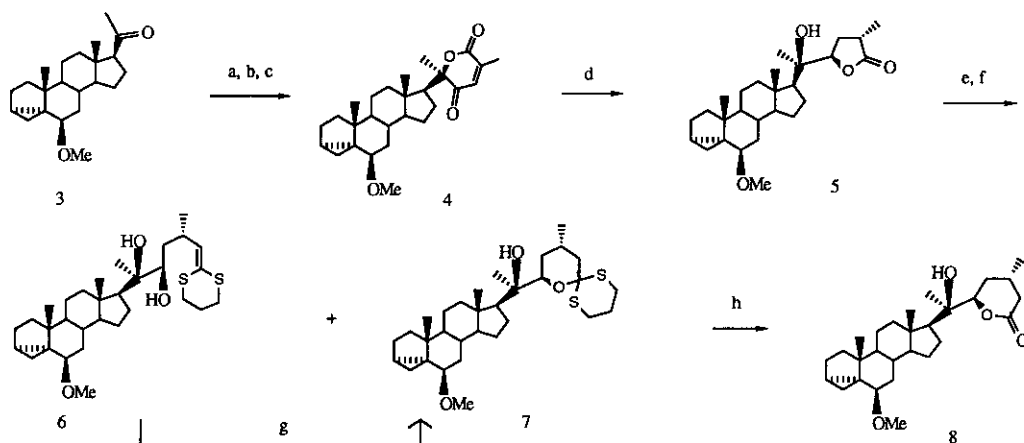
chlorochromate afforded the lactone **4** in 80% overall yield. Catalytic hydrogenation of **4** in the presence of platinum oxide in ethyl acetate (AcOEt) proceeded stereoselectively^{2a} to give the γ -lactone **5** having a (20R,22R,24S)-configuration. Homologation of a lactone moiety was accomplished by application of ketene thioacetal chemistry.⁴ Reduction of **5** with diisobutylaluminum hydride in THF gave the lactol, which was then treated with 2-lithio-2-trimethylsilyl-1,3-dithiane⁵ in THF at 0 °C to afford the ketene thioacetal **6**. Purification of **6** by column chromatography on silica gel using CH₂Cl₂ as an eluent gave **6** and its cyclized compound **7** in a ratio of 1:2. Acid catalyzed cyclization⁶ of **6** was also achieved quantitatively by employing camphorsulfonic acid in THF. The thioacetal **7** was then hydrolyzed with periodic acid⁷ in CH₂Cl₂-methanol to afford the δ -lactone **8** in 94% yield.

Conversion of **8** into the unsaturated lactone **13** was realized by the following sequence of reactions (Scheme II). Methylation of **8** with lithium isopropylcyclohexylamide (LICHA) and methyl iodide in THF at -78 °C gave homogeneous **9**, which was further treated with LICHA and diphenyl disulfide in THF at -78 °C to give the sulfide **10** specifically⁸ in 80% overall yield from **8**. Oxidation of **10** with m-CPBA in chloroform followed by oxidative elimination of the sulfoxide in toluene at 110 °C furnished the desired unsaturated lactone **11** and α -methylene lactone **12** in a ratio of 1:4.2, respectively. The stereochemistry of the side chain in **11**, was established by its conversion into the known acetate **13**, which exhibited the spectroscopic data identical with those of **13**.⁹ Finally, isomerization of the exo-olefin in **12** into the corresponding endo-olefin was carried out employing rhodium chloride (RhCl₃).¹⁰ A solution of **12** and RhCl₃ in absolute ethanol was heated at 100 °C for 8 h in a sealed tube to give the ring opened 3 β -ethoxy compound **14** instead of **11** quantitatively. Therefore, **12** was first transformed into the acetate **15**, which was subjected to the isomerization followed by acetylation to furnish **13** in 81% overall yield.

Thus we developed a new procedure for construction of the withanolide D side chain from 20-oxosteroid employing stereoselective reduction of **4** and subsequent transformation of the γ -lactone **5** to the δ -lactone **8** as key reactions. The α -methylene lactone **12** obtained by this synthesis could be a very important compound because of its applicability to the synthesis of withametelin.¹¹

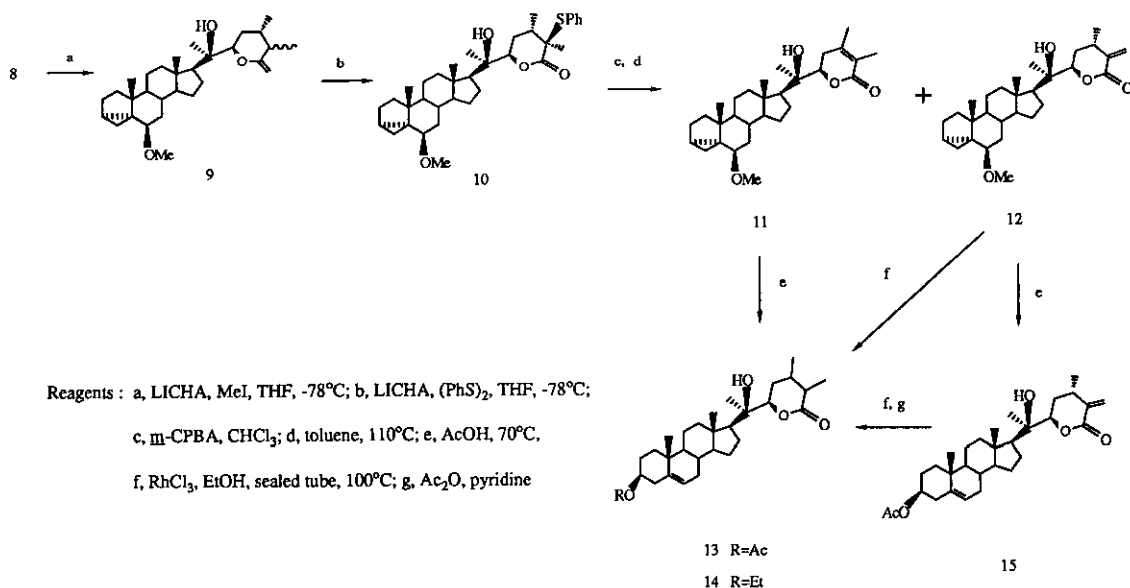


Scheme I



Reagents: a, $\text{Li-O-C}_6\text{H}_5$, THF, -78°C ; b, m-CPBA, AcONa, CH_2Cl_2 , 0°C ; c, PCC, AcONa, CH_2Cl_2 ; d, H_2 , PtO_2 , AcOEt; e, DIBAL, THF, -78°C ; f, Li-SiMe_3 , THF, 0°C , then silica gel, CH_2Cl_2 ; g, CSA, THF; h, HIO_4 , CH_2Cl_2 -MeOH

Scheme II



ACKNOWLEDGEMENT

This work was supported in part by Grant-in-Aid for Special Project Research of Intracellular Processing of Biomolecules for the Expression of their Biological Functions from the Ministry of Education, Science, and Culture, Japan.

REFERENCES AND NOTES

1. For reviews of the isolation and synthesis of withanolides see: N. Ikekawa, M. Hirayama, and K. Gamoh, J. Syn. Org. Chem., Japan, 1983, **41**, 941.; E. Glotter, I. Kirson, D. Lavie, and A. Abraham, "Bio-Organic Chemistry" E. E. van Tamelen Ed., Academic Press: New York, 1978, Vol. 2, pp. 57 - 94.
2. T. Kametani, M. Tsubuki, K. Higurashi, and T. Honda, J. Org. Chem., 1986, **51**, 2932; T. Kametani, M. Kigawa, M. Tsubuki, and T. Honda, J. Chem. Soc., Perkin Trans. I, 1988, 1503.
3. D. W. Knight and D. C. Rustidge, J. Chem. Soc., Perkin Trans. I, 1981, 679.
4. For a review of the ketene thioacetal chemistry see: D. Seebach, Synthesis, 1969, 17, and references cited therein.
5. F. A. Carey and A. S. Court, J. Org. Chem., 1972, **37**, 1926.
6. E. J. Corey and D. J. Beams, J. Am. Chem. Soc., 1973, **95**, 5829; K. Suzuki, K. Tomooka, E. Katayama, T. Matsumoto, and G. Tsuchihashi, ibid., 1986, **108**, 5221; M. Hatanaka, Tetrahedron Lett., 1987, **28**, 83.
7. J. Cairns and R. T. Logan, J. C. S., Chem. Commun., 1980, 886.
8. Since the sulfide 10 was a single isomer and the subsequent desulfenylation proceeded via syn-elimination afforded 11 and 12, the stereochemistry at C-25 of 10 was tentatively assigned as shown in Scheme II.
9. M. Ishiguro, M. Hirayama, H. Saito, A. Kajikawa, and N. Ikekawa, Heterocycles, 1981, **15**, 823; K. Gamoh, M. Hirayama, and N. Ikekawa, J. Chem. Soc., Perkin Trans. I, 1984, 449.
10. P. A. Grieco, M. Nishizawa, N. Marinovic, and W. J. Ehmann, J. Am. Chem. Soc., 1976, **98**, 7102.
11. Y. Oshima, A. Bagchi, H. Hikino, S. C. Sinha, M. Sahai, and A. B. Ray, Tetrahedron Lett., 1987, **28**, 2025.

Received, 27th July, 1988