

STEREOCONTROLLED SYNTHESIS OF THE WITHANOLIDE D SIDE CHAIN FROM
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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

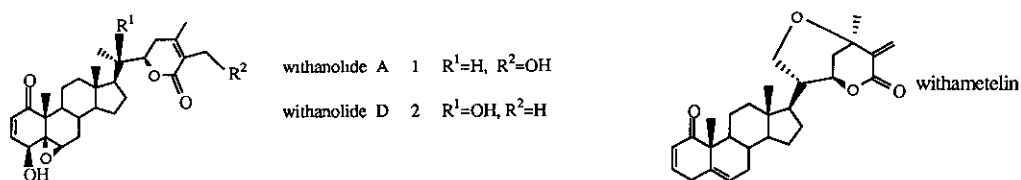
* Dedicated to Sir Derek Barton, Professor of Texas A&M University, on occasion of his 70th birthday.

[†] Deceased October 11, 1988.

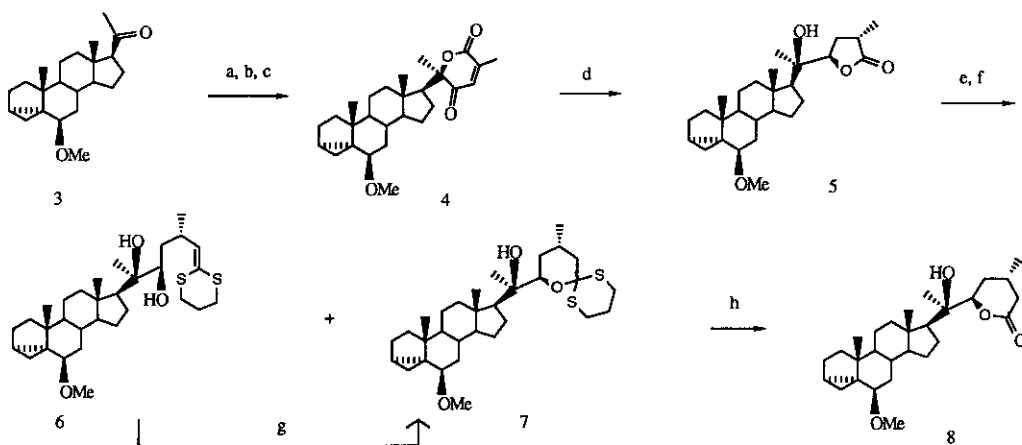
chlorochromate afforded the lactone **4** in 80% overall yield. Catalytic hydrogenation of **4** in the presence of platinum oxide in ethyl acetate (AcOEt) proceeded stereoselectively^{2a} to give the γ -lactone **5** having a (20R,22R,24S)-configuration. Homologation of a lactone moiety was accomplished 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

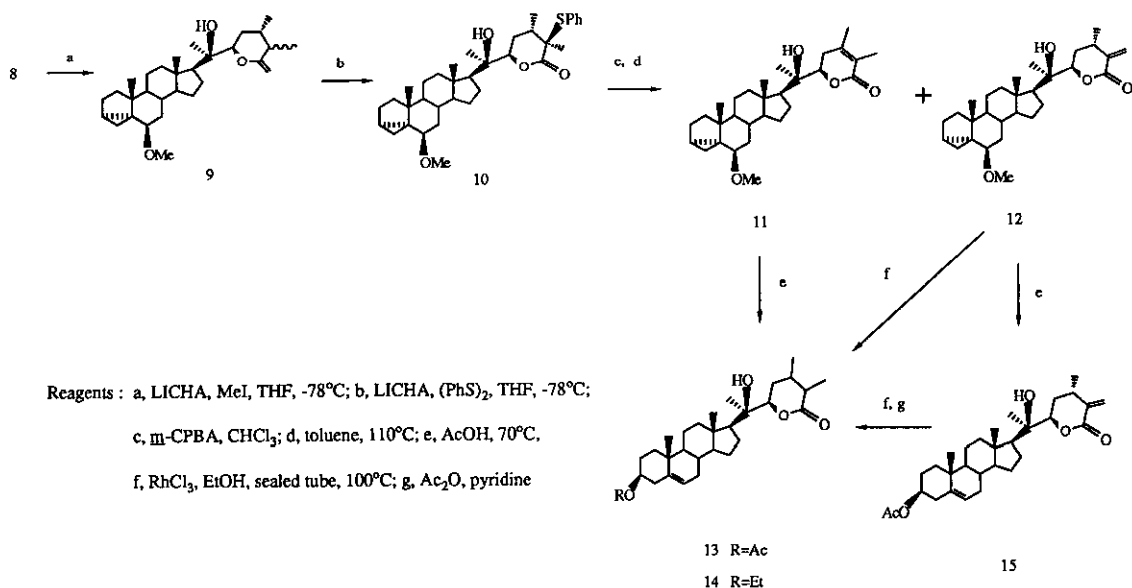


Scheme I



Reagents : a, $\text{Li-O} \begin{array}{c} \diagup \\ \diagdown \end{array}$, THF, -78°C ; b, $m\text{-CPBA}$, AcONa, CH_2Cl_2 , 0°C ; c, PCC, AcONa, CH_2Cl_2 ; d, H_2 , PtO_2 , AcOEt; e, DIBAL, THF, -78°C ,
 f, $\text{Li} \begin{array}{c} \diagup \\ \diagdown \end{array} \text{S} \begin{array}{c} \diagdown \\ \diagup \end{array} \text{S}$, THF, 0°C , then silica gel, CH_2Cl_2 ; g, CSA, THF; h, HIO_4 , $\text{CH}_2\text{Cl}_2\text{-MeOH}$

Scheme II



Reagents : a, LICHA, MeI, THF, -78°C ; b, LICHA, $(\text{PhS})_2$, THF, -78°C ;
 c, $m\text{-CPBA}$, CHCl_3 ; d, toluene, 110°C ; e, AcOH, 70°C .
 f, RhCl_3 , EtOH, sealed tube, 100°C ; g, Ac_2O , pyridine

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