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

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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-methylfuran[3] 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

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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 diisolbutylaluminum hydride in THF gave the lactol, which was then treated with 2-lithio-2-trimethylsilyl-1,3-dithiane[5] in THF at 0 ℃ to afford the ketene thioacetal **6**. Purification of **6** by column chromatography on silica gel using CH_2Cl_2 as an eluent gave **6** and its cyclized compound **7** in a ratio of 1:2. Acid catalyzed cyclization[6] of **6** was also achieved quantitatively by employing camphorsulfonic acid in THF. The thioacetal **7** was then hydrolyzed with periodic acid[7] in CH_2Cl_2-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 ℃ gave homogeneous **9**, which was further treated with LICHA and diphenyl disulfide in THF at -78 ℃ to give the sulfide **10** specifically[8] 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 ℃ 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 ($RhCl_3$).[10] A solution of **12** and $RhCl_3$ in absolute ethanol was heated at 100 ℃ for 8 h in a sealed tube to give the ring opened 3β-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]

withanolide A 1 R^1=H, R^2=OH

withanolide D 2 R^1=OH, R^2=H

withametelin

Scheme I

Reagents : a,  , 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,  , THF, 0°C, then silica gel, CH_2Cl_2 ; g, CSA, THF ; h, HIO_4, CH_2Cl_2-MeOH

Scheme II

Reagents : a, LICHA, MeI, THF, -78°C; b, LICHA, $(PhS)_2$, THF, -78°C;

c, m-CPBA, $CHCl_3$; d, toluene, 110°C; e, AcOH, 70°C,

f, $RhCl_3$, EtOH, sealed tube, 100°C; g, Ac_2O, pyridine

13 R=Ac

14 R=Et

15

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