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Facile Synthesis of a Steroidal Diyne via D-ring Cleavage

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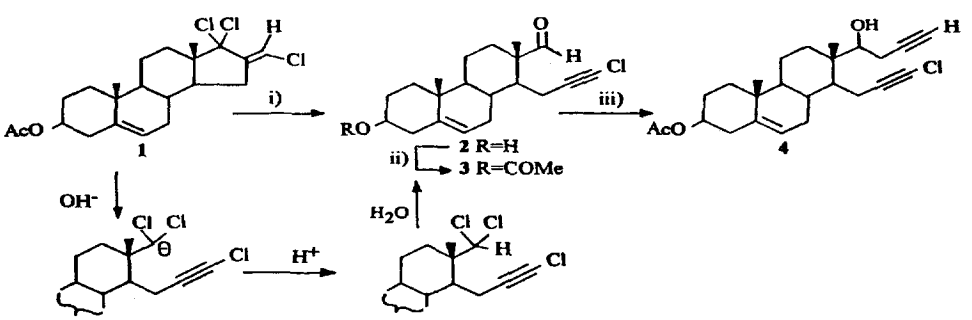
Abstract : A base-promoted conversion of a steroidal D-ring into a formyl alkyne and its conversion to a steroidal diyne is described. © 1997 Published by Elsevier Science Ltd.

The enediyne antitumor antibiotics derived from bacterial sources have generated widespread interest[1,2] due to DNA cleavage. However, the chemical instability and extreme potency of these naturally occuring compounds restrict them from broad use as antitumor agent.[3] As a result synthesis of artificial enediynes attract enormous interests[4,5] aimed at greater chemical stability and enhanced antitumor efficacy. Further, the challenging structural complexities of enediynes has tempted organic chemists in the search of synthetic strategies involving intramolecular cyclisation[4,6] of acetylide with non-enolizable aldehyde group.

The synthesis of estramycin[7] has allowed access to a new class of enediynes by enclosing the diene-diyne moiety within the steroidal core. Recently we have initiated a program[8] in which we manipulate the steroidal D-ring.[9] The geminal dihalides are ideal templates[10] as well as important substrates[11] for a broad range of compounds. In continuation of our interests[12] to explore the versatility of steroidal C-17 geminal dihalides, we wish to report here an efficient one-pot synthesis of a steroidal des-D formyl alkyne and its utility for the synthesis of a novel class of steroidal diynes.



Reagents : i) KOH/MeOH-H_2O(4:1); ii) Ac_2O/Pyridine; iii) Propargyl bromide/Zn/THF

When 3-β-acetoxy-17,17-dichloro-16(E)-chloromethyleneandrost-5-ene **1** was refluxed in methanolic KOH solution (MeOH:H_2O=4:1) for 0.5h, it underwent ring opening to afford the des-D steroidal formyl alkyne **2** in 70% yield. Acetylation of **2** with acetic anhydride and pyridine gave **3** in 92% yield.[13] The appearance of an IR band at ν_{max} 1660 cm^{-1} and a sharp ^{1}HNMR singlet at δ 9.72 support the presence of an aldehyde group in **3**. Finally, treatment[14] of **3** with propargyl bromide and zinc dust in tetrahydrofuran at room temperature for 4h gave the steroidal diyne **4** in 58% yield.[13] The reaction of **1** with $NaHCO_3$ in MeOH-H_2O for 12h afforded[8] exclusively 3-β-hydroxy-16-(E)-chloromethyleneandrost-5-en-17-one.

The steroidal D-ring cleavage of 1 is proposed to follow an inverse Reimer-Tiemann mechanism via initial olefinic proton abstraction by the action of strong base with a concomitant ring cleavage to form a dichloro carbanion and chloroacetylene-bearing intermediate. The dichloro carbanion acquires a proton from the solvent to give a dichloromethyl group which undergoes hydrolysis to give the formyl alkyne 2. Under milder basic conditions, the olefinic proton remains intact resulting simply in hydrolysis of the C-17 geminal dichloride.

In conclusion, we have shown a novel strategy for straightforward synthesis of a steroidal formyl alkyne as a potential candidate for intramolecular acetylide-aldehyde cyclisation. In addition, we demonstrate the synthesis of a novel class of steroidal diyne by attaching an alkyne group to a aldehyde group thereby replacing D-ring with a diyne moiety. Further work on the use of steroidal formyl alkyne to give cyclic enediynes is in progress.

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13. Compound **3** : m.p. 141-142°C (MeOH); IR(KBr) ν 2900, 2200, 1720, 1660 cm^{-1}; ^{1}HNMR($CDCl_3$) : δ 9.72(1H,s), 5.15(1H,bs), 4.30(1H,m), 1.84(3H,s), 0.95(3H,s), 0.84(3H,s), 2.30-1.10(17H,m); MS m/z 316 (M^+- CH_3COOH, 100%), 318 [(M^++2)-CH_3COOH, 33%]. **4** : IR(KBr) ν 3400, 2200, 2130, 3250, 2900, 1720 cm^{-1}; ^{1}HNMR($CDCl_3$) : δ 5.25(1H,bs), 4.72-4.60(1H,m), 3.80-3.65(1H,m), 2.32(1H,t), 2.05(3H,s), 1.05(3H,s), 0.90(3H,s), 2.20-1.20(20H,m); MS m/z 356 (M^+-CH_3COOH, 100%), 358 [(M^++2)-CH_3COOH), 33%].
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