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An efficient method for the synthesis of methyl 11α-amino-3α,7α-diacetoxy-12-oxo-5β-cholan-24-oate

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Abstract—The synthesis of methyl 11α-azido-3α,7α-diacetoxy-12-oxo-5β-cholan-24-oate, methyl 11β-azido-3α,7α-diacetoxy-12-oxo-5β-cholan-24-oate and methyl 11α-amino-3α,7α-diacetoxy-12-oxo-5β-cholan-24-oate have been achieved. Mechanistic aspects for the decomposition of steroidal azidoketones to its enamines are discussed.

1. Introduction

Among the numerous HIV-1 protease inhibitors, the most active inhibitors contain hydroxyethylamine or the related carbonyl equivalent. Marples and co-workers have designed[1] novel steroidal inhibitors of HIV-1 protease, having such types of amino-alcohols and amino-ketones namely, 11-amino-12-hydroxy/keto-steroids **1** and **2** based upon bile acids and estra 1,3,5 (10)-trienes, respectively, with the help of X-ray crystallographic data[2] and molecular modeling (Fig. 1). The attempted synthesis of these amino-steroids failed[1] due to problems in the decomposition of α-azidoketones. Such types of decomposition is observed in both alicyclic[3,4] as well as steroidal[1,4–6] α-azidoketones.

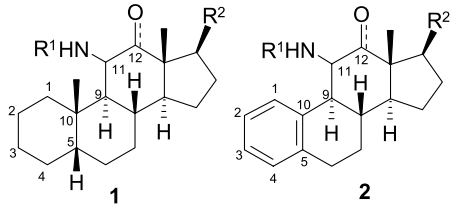

Figure 1. Proposed HIV-1 protease inhibitors.

Steroids with C-11 functionality are crucial for biological activity and are observed in a number of drug molecules including steroid hormones.[7] Stereoselective C-11 functionalization in the steroids is one of the challenging targets for synthetic organic chemists as it involves severe steric interactions caused by the C-18 and C-19 angular methyl groups. In this paper, we wish to report a successful synthesis of methyl 11α-amino-3α,7 α-diacetoxy-12-oxo-5β-cholan-24-oate **18** from the corresponding methyl 11α-azido-3α,7 α-diacetoxy-12-oxo-5β-cholan-24-oate **13** and unstable methyl 11β-azido-3α,7 α-diacetoxy-12-oxo-5β-cholan-24-oate **14**. A generalized mechanism for the decomposition of steroidal azidoketones **13** and **14** is also discussed.

2. Results and discussion

Recently, Marples and co-worker reported[1] the synthesis of a steroidal enamine, methyl 11-amino-3α-benzyloxy-12-oxo-5β-chol-9, 11-en-24-oate **7** from 11α-bromo compound **3**. Compound **3** on treatment with NaN_3 in DMSO at 100 °C for 48 h afforded the steroidal enamine **7** instead of the expected β-azido compound **4** (Fig. 2). They proposed the formation of enamine **7** through the intermediates **4**, **5** and **6** with the expulsion of nitrogen gas. Thus, the synthesis of 11-aminosteroids with a specific stereogenic center at C-11 was not realized by Marples et al. This compound **7** is reported[1] to possess modest activity against HIV-1 protease.

In the course of our studies on the synthesis of steroidal protease inhibitors we prepared methyl 11α-bromo-3α,7α-diacetoxy-12-oxo-5β-cholan-24-oate **10** (71% yield) and

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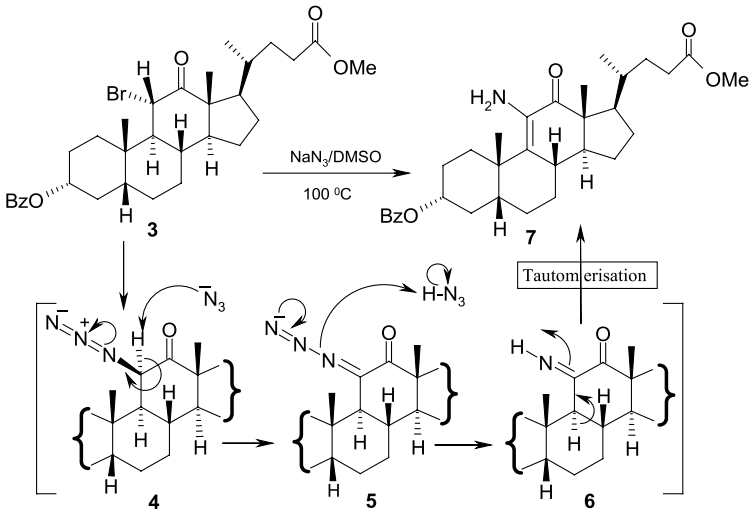
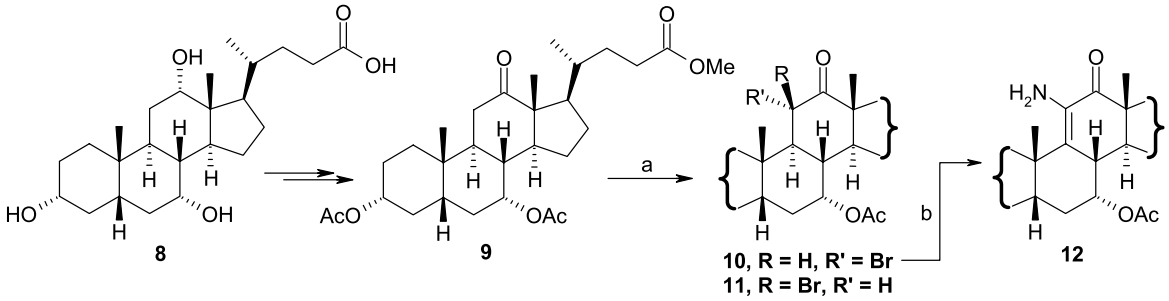


Figure 2. Proposed mechanism for the formation of steroidal enamine **7**.



Scheme 1. Reagents and conditions: (a) Br_2, benzene, 28 °C, 96 h, 95%. (b) NaN_3 (12 equiv), DMF, 100 °C, 48 h, 72%.

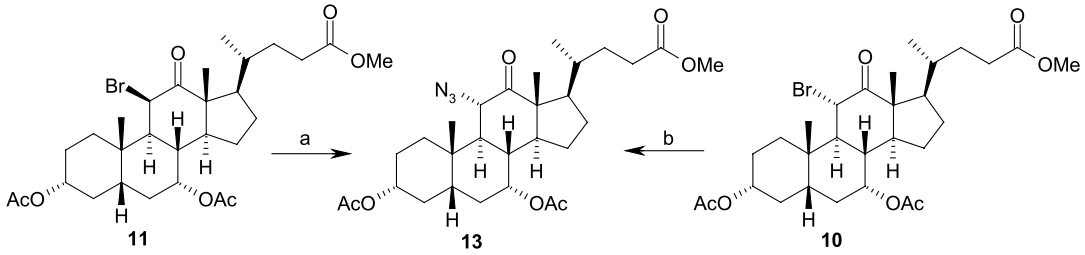
methyl 11β-bromo-3α,7α-diacetoxy-12-oxo-5β-cholan-24-oate **11** (24% yield) from cholic acid **8** following the literature procedures[8–12] (Scheme 1).

Starting from the α-bromo ketone **10** and following the procedure of Marples et al.,[1] using DMF as solvent in place of DMSO we synthesized steroidal enamine, methyl 11-amino-3α,7α-diacetoxy-12-oxo-5β-chol-9, 11-en-24-oate **12** in 72% yield (Scheme 1). However, our main aim was to synthesize the hitherto unknown 11-amino steroids.

Substitutions α to carbonyl groups are known to follow S_N2 mechanism[13,14] and exposure of compound **11** with 5 equiv of NaN_3 in DMF at 28 °C for 8 h furnished the azido compound **13** in 85% yield (Scheme 2). Treatment of epimeric α-bromo compound **10** with 5 equiv of NaN_3 in DMF at 60 °C for 16 h surprisingly resulted in the formation of the same azido compound **13** in 98% yield.

The assignment of the stereochemistry at C-11 of compound **13** was supported by the ^{1}H NMR spectrum in which the C-11 proton appeared as a doublet (δ 4.06 ppm, $J=10.8$ Hz) due to *trans* diaxial coupling between the C-11 and C-9 protons (Table 1). This was confirmed by single crystal X-ray analysis (Fig. 3).

In addition, 11α-bromo-12-keto compound **10** under mild reaction conditions [slight excess of NaN_3 (1.2 equiv) at 60 °C for 4 h] afforded the unstable 11β-azido-12-keto compound **14** in 64% yield (Scheme 3). The assignment of stereochemistry at C-11 of compound **14** was supported by the ^{1}H NMR spectrum in which the C-11 proton appeared as



Scheme 2. Reagents and conditions: (a) NaN_3 (5 equiv), DMF, 28 °C, 8 h, 85%. (b) NaN_3 (5 equiv), DMF, 60 °C, 16 h, 98%.