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A novel scalable and stereospecific synthesis of 3α- and 3β-amino-5α-androstan-17-ones and 3α- and 3β-amino-5α-pregnan-20-ones

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ABSTRACT

A novel scalable stereoselective synthesis of 3α- and 3β-amino-5α-androstan-17-ones and 3α- and 3β-amino-5α-pregnan-20-ones has been developed using phthalimide based Mitsunobu chemistry. In all four cases, the products were isolated as single diastereoisomers in high chemical yield and purity without the need for chromatography at any stage in their syntheses.

The 3-aminosteroids represent an important class of organic compounds with therapeutic applications including anti-inflammatory,[1] anti-bacterial,[2] anti-microbial,[3] anti-angiogenic[4] and anti-cancer[5] properties.

Classically, 3-aminosteroids have been prepared by reduction of the corresponding 3-oximes with reducing reagents including $LiAlH_4$,[6] sodium metal in *iso*-propanol[7] and catalytic hydrogenation.[6] Reductive amination has also been employed, allowing for the preparation of 3-aminosteroids from the corresponding 3-ketosteroids.[3] With the exception of sodium metal mediated oxime reduction in *iso*-propanol, the reductive introduction of an amino group at the 3-position of steroids does not proceed in a stereospecific manner because of the lack of facial selectivity exhibited by the reducing agent. For example, the $LiAlH_4$ reduction of a 3-oxime provided a 6:1 diastereomeric mixture of the corresponding 3β:3α aminosteroids,[6] whereas PtO_2-mediated reduction of the same material gave a 1:1 mixture.[6] Furthermore, the $NaBH_3CN$ reductive amination of a 3-ketosteroid provided a 2:1 diastereomeric mixture of the corresponding 3β:3α aminosteroids.[3] It is worthy of note, that in all of these cases, extensive chromatographic purification was required to separate the diastereoisomers, reducing the efficiency of the processes and their amenability to large scale synthesis.

During the course of a recent internal research program, we required multi-gram quantities of diastereomerically pure 3β- and 3α-amino-5α-androstan-17-ones **1** and **2**, and 3β- and 3α-amino-5α-pregnan-20-ones **3** and **4** (Fig. 1).

A survey of the literature revealed that several methods were available for the stereoselective synthesis of 3α-aminosteroids. For example, Reyes et al.[7] reported the stereoselective synthesis of 3β-amino-5α-androstan-17-one (**1**) in a five-step linear sequence starting from 3β-hydroxy-5α-androstan-17-one (**5**). Although the synthesis was reported to occur diastereoselectively in high yield, toxic and hazardous reagents, including chromium oxide and sodium metal, were required in two of the steps, reducing the amenability of the process to large scale synthesis. The required 3β-amino group was obtained stereoselectively by reduction of the corresponding 3-oxime with sodium metal in *iso*-propanol. In our hands, whilst this method provided the desired material, the yield was very low (<10%) and the reaction work-up was extensive and largely inefficient.

In a more recent publication, Kerr and Chisholm[8] disclosed the stereoselective synthesis of 3α-amino-5α-androstan-17-one by a three-step linear sequence involving the S_N2 substitution of a 3β-tosyloxy group with sodium azide, followed by Staudinger reduction to the desired amine. Overall, the process was low yielding (<20%) and involved the use of potentially explosive sodium azide at high temperature. Interestingly, the same publication also disclosed the stereospecific synthesis of 3α-amino-5α-androstanes and 3α-aminocholestene using a Mitsunobu reaction involving diphenylphosphoryl azide, requiring purification by flash column chromatography. The application of the same methodology to the synthesis of 3β-amino-5α-androstan-17-one, however, was not reported.

We were interested in introducing the 3-amino functionality via a Mitsunobu reaction using phthalimide instead of azide, for both practical and thermal stability issues. Whilst there are only

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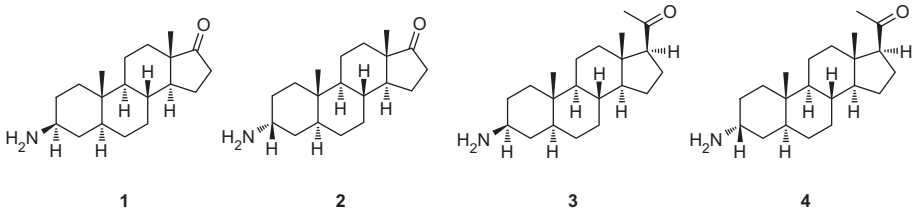

Figure 1. Structures of 3-aminoandrostanones and 3-aminopregnanones.

two examples of phthalimide based Mitsunobu chemistry being successfully applied to the synthesis of diastereomerically pure 3-aminocholestanes,[9,10] to the best of our knowledge, this methodology has not been reported for the stereospecific synthesis of either 3α- and 3β-amino-5α-androstan-17-ones or 3α- and 3β-amino-5α-pregnan-20-ones.

Herein, we describe the stereoselective synthesis of 3α- and 3β-amino-5α-androstan-17-ones and 3α- and 3β-amino-5α-pregnan-20-ones using a phthalimide based Mitsunobu reaction sequence. Linear reaction schemes of six steps delivered both 3β-amino-5α-androstan-17-one (**1**) and 3β-amino-5α-pregnan-20-one (**3**) as hydrochloride salts from the corresponding 3β-hydroxy species **5** and **11**, respectively. The related 3α-amino-compounds, 3α-amino-5α-androstan-17-one (**2**) and 3α-amino-5α-pregnan-20-one (**4**), were prepared in two steps from the corresponding acetal protected 3β-hydroxy species, **6** and **12**, respectively. In all four examples, no chromatographic purification was required and the intermediates and products were invariably isolated from the reaction mixtures in high chemical yields as single diastereoisomers. In each case the stereochemistry was confirmed by comparison with the ^{1}H NMR data reported in the literature.[6–8] Furthermore, values for the line-width at half height (w/2) of the key H-3 resonances were determined from the ^{1}H NMR data to consolidate the stereospecificity of the approach.[11]

The key focus of our synthetic strategy was accessing the acetal protected 3α-hydroxyandrostane (**8**) stereoselectively to enable the subsequent Mitsunobu reaction with phthalimide to introduce the required 3β-amine. Our initial synthetic strategy involved the oxidation/reduction cycle depicted in Scheme 1, path A. Thus, protection of the 17-keto group of 3β-hydroxy-5α-androstan-17-one (**5**) afforded the acetal **6** in excellent yield.[12] The stereochemistry of the 3β-hydroxy group was inverted by a sequential oxidation/reduction[13] process using Dess Martin periodinane (DMP) and K-Selectride®, respectively, to give the 3α-hydroxyandrostane (**8**), stereoselectively. However, this path left some 3β-hydroxy starting material (<5%) representing a significant issue to the proposed telescoping strategy, so the alternative route shown in Scheme 1, path B was developed. The acetal protected 3β-hydroxyandrostane (**6**) was subjected to a Mitsunobu reaction with benzoic acid, inverting the stereochemistry of the 3-hydroxy group cleanly to afford the corresponding benzoate in high yield. It is worthy of note that the benzoate precipitated from the reaction mixture as it formed and was subsequently collected by filtration as a single diastereoisomer with high chemical purity (>98%) by ^{1}H NMR analysis. Subsequent sodium methoxide mediated cleavage of the benzoate group provided the 3α-hydroxyandrostane (**8**) in high yield as a single diastereoisomer.

The amine was then introduced stereoselectively at the 3-position by a Mitsunobu reaction with phthalimide, providing the 3β-phthalimide **9** in high yield. It is important to note that this compound precipitated from methanol during the reaction work-up as a single diastereoisomer and was collected by filtration. The chemical purity was >98% by ^{1}H NMR analysis, with no evidence of any 3α-diastereomer.

Sequential cleavage of the phthalimide and acetal protecting groups was completed by refluxing with hydrazine in ethanol followed by treatment with aqueous hydrochloric acid in THF, respectively, affording the desired 3β-amino-5α-androstan-17-one (**1a**) as the hydrochloride salt. These two deprotection stages were telescoped effectively into a single step. Typically, during the hydrazine-mediated phthalimide cleavage, the phthalizine side-product precipitated from the reaction mixture and the amino product remained in solution. The product solution was collected and distilled to dryness to provide the crude acetal protected 3β-aminoandrostane, which was subsequently dissolved in a 2 N hydrogen chloride/THF/acetone mixture for acetal deprotection. The reaction mixture was then concentrated to a low volume and subsequently diluted with ether leading to precipitation of the 3β-amino-5α-androstan-17-one (**1a**) product as the hydrochloride salt. Pleasingly, the diastereoselectivity of the product was confirmed by preparation of the corresponding acetic acid salt (see Supplementary data) and comparison with the ^{1}H NMR data reported in the literature.[7] Furthermore, the orientation of the H-3 proton was confirmed to be axial (3α-H) from the magnitude of the line-width at half height (w/2 = 23 Hz), which is consistent with that expected for an axial proton in these systems.

The overall yields for the two six-step sequences from 3β-hydroxy-5α-androstan-17-one (**5**) were 37% and 28% for paths A and B, respectively, with the synthetic methodology performing well on scale-up, successfully affording multi-gram quantities of the desired product. It is also important to recognize that these yields do not represent optimized processes and reflect only the robust and efficient nature of the overall strategy, in that generic methodologies responded well when applied to the current synthetic scheme.

Synthesis of the corresponding 3α-amino-5α-androstan-17-one (**2**) was conducted as depicted in Scheme 2. 3β-Hydroxy-5α-androstane (**6**) was subjected to a Mitsunobu reaction with phthalimide affording the 3α-phthalimide **10** in high yield as a single diastereoisomer. As before with the 3β-phthalimide **9**, the 3α-isomer **10** precipitated cleanly from the methanol during the course of the reaction work-up and was collected by filtration. Sequential cleavage of the phthalimide and acetal groups was achieved by initially refluxing the 3α-phalimidoandrostane **10** with hydrazine monohydrate in ethanol followed by treatment with an aqueous 2 N hydrogen chloride solution in THF, to give the desired 3α-amino-5α-androstan-17-one (**2a**) as the hydrochloride salt in an overall yield of 53%. Once again, the diastereoselectivity of the product was confirmed by direct comparison with the ^{1}H NMR data reported for this compound in the literature.[8] Furthermore, the orientation of the H-3 proton was confirmed to be equatorial (3β-H) from the value of the line-width at half height (w/2 = 9 Hz), which is typical for an equatorial proton and considerably smaller than that expected for the corresponding axial proton.

The synthesis of 3β-amino-5α-pregnan-20-one (**3a**) was investigated using the same strategy that had been successfully developed for the synthesis of 3β-amino-5α-androstan-17-one (**1a**) as depicted in Scheme 3. Protection of the 20-keto group in