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# One-Pot Multistep Synthesis of C19 Androgen Steroids Enabled by a Reagent Free Electrochemical Side Chain Cleavage

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## AFFIDAVIT

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# Abstract

This thesis is focused on the implementation of electrochemical transformations for reactions currently performed in a multi-step manner with classical chemical transformations. Thus, producing high amounts of waste and using mostly non ecologically friendly reagents. Furthermore, dealing with the intrinsic problem of a required workup before continuing with further transformations tends to decrease overall yields of multistep processes.

Steroids are one class of chemicals that can benefit from electrochemical transformations. As many different important drugs are synthesized from standard steroids. A method that increases not only yield but also decreases the environmental impact is highly favorable nowadays. One class of important steroids are C19 androgens.

The synthesis of many valuable C19 androgens can be accomplished by removal of the C17 side chain from more abundant corticosteroids, followed by further derivatization of the resulting 17-keto derivative. Conventional chemical reagents pose significant drawbacks for this synthetic strategy, as large amounts of waste are generated and quenching of the reaction mixture and purification of the 17-ketosteroid intermediate are typically required. Herein, it is possible to present a mild, safe and sustainable electrochemical strategies for the preparation of C19 steroids. A reagent and catalyst free protocol for the removal of the C17 side-chain of corticosteroids via anodic oxidation has been developed, enabling several one-pot, multistep procedures for the synthesis of androgen steroids. In addition, simultaneous anodic C17 side-chain cleavage and cathodic catalytic hydrogenation of a steroid has been demonstrated, rendering a convenient and highly atom economic procedure for the synthesis of saturated androgens. With all reactions of the side chain cleavage generating yields above 90% and the application of further one pot reactions with yields over 70% proofs this method superior to the classical methods used up to now.

# Zusammenfassung

Der Fokus der vorliegenden Arbeit liegt auf der Implementierung von elektrochemischen Transformationen für Reaktionen, die bisher in mehrstufigen Prozessen mit Hilfe klassischer Transformationen vollzogen wurden. Daher produzieren derartige Prozesse meist große Mengen an Abfall und nutzen keine umweltfreundlichen Reagenzien. Ein weiteres Problem ist die problematische Aufarbeitung bevor weiter Reaktionen durchgeführt werden können. Dies wiederum führt zu einer Abnahme der Gesamtausbeute in mehrstufigen Reaktionen.

Steroide sind eine Chemikalienklasse, die von elektrochemischen Umwandlungen profitieren kann. Viele wichtige Medikamente werden ausgehend von Standard-Steroiden hergestellt. Hier wäre eine Methode, die nicht nur die Ausbeute erhöht, sondern auch die ökologischen Auswirkungen möglichst gering hält zu bevorzugen. Eine Klasse dieser wichtigen Steroide sind C19 Androgene.

Die Synthese von vielen C19 Androgenen kann mit Hilfe einer Abspaltung der C17 Seitenkette von häufig vertretenen Corticosteroiden erreicht werden. Von denen ausgehend weitere Umwandlungen leicht durchgeführt werden können. Konventionelle Chemikalien weisen hier signifikante Nachteile auf. Nicht nur werden große Mengen an Abfall produziert, auch die Aufreinigung der 17C-Ketosteroidintermediate ist notwendig. Hier ist es möglich unter Verwendung von Elektrochemie Strategien zu entwickeln die sicher und nachhaltig sind und dabei unter milden Bedingungen ablaufen und damit eine gute Möglichkeit bieten C19 Steroide herzustellen. Eine reagenzien- und katalysatorfreie Methode zur Abspaltung der C17 Seitenkette von Corticosteroiden wurde entwickelt. Genutzt wird hierfür eine anodische Oxidation, die mehrstufige Reaktionen im selben Gefäß, ohne weiter Aufarbeitung möglich macht. Zusätzlich wurde eine Methode entwickelt, die es ermöglicht die anodische Seitenkettenspaltung mit einer Hydrierung zu koppeln, welche den an der Kathode erzeugten Wasserstoff direkt nutzt. Dies bietet eine praktische und atomeffiziente Möglichkeit gesättigte Androgene herzustellen. Alle Reaktionen der Seitenkettenspaltung generieren Ausbeuten über 90% und die nachfolgen Reaktionen konnten mit Ausbeuten von mehr als 70% optimiert werden. Damit konnte gezeigt werden, dass diese elektrochemische Methode den derzeitigen überlegen ist.

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# 1 Introduction

## 1.1 Synthetic Organic Electrochemistry – Basics and Instrumentation

Electrochemistry is a useful, but often neglected tool in synthetic organic chemistry. Electrochemical transformations are based on the exchange of electrons between electrodes immersed in a solution and the organic compounds dissolved in it (Figure 1). This enables redox processes and electron-transfer-based transformations to take place in the absence of external reagents under mild and safe conditions. Even though some of the largest scale chemical reactions are electrochemical (e.g., chloralkali process), this way of synthesizing is not common for complex organic compounds.[1] Although many organic syntheses are based on redox transformations, stoichiometric amounts of oxidizing or reducing agents are most often used.

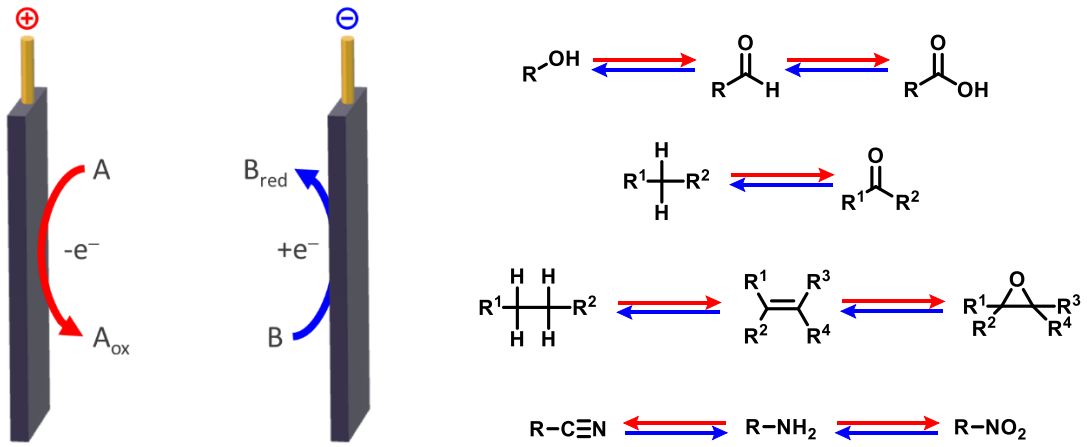



*Figure 1: Schematic view of electron transfer between electrodes and compounds in solution (left) and some typical redox organic transformations (right)[2]*

As electrochemistry uses electrons as “traceless reagents”, electroorganic synthesis is a very efficient, green and safe alternative strategy for synthesizing compounds. Electricity is easily available and its production is becoming more sustainable from renewable resources. This makes electrochemistry both economically as well as

environmentally. Moreover, as stoichiometric amounts of reagents are not needed, the amount of waste generated is very low compared with conventional methods.

In comparison to standard organic synthesis techniques, electrochemistry requires a few devices not commonly found in a chemistry laboratory. Most importantly, a suitable DC power supply is needed, as well as electrodes with a known shape and composition. Other electrical components such as cable connections and multimeters are also required (Figure 2).


*Figure 2: Typical electroorganic synthesis labware and equipment*

To avoid issues with reproducibility, the implementation of standardized reaction vessels and electrodes is recommended. The commercially available IKA ElectraSyn 2.0, which includes a potentiostat with stirring capabilities, electrochemical cells and electrodes are an easy way to achieve this (Figure 3). A ElectraSyn 2.0 reactor was used in this thesis to perform all the experimental work. Figure 3 shows the two different Systems, setup for an experiment.

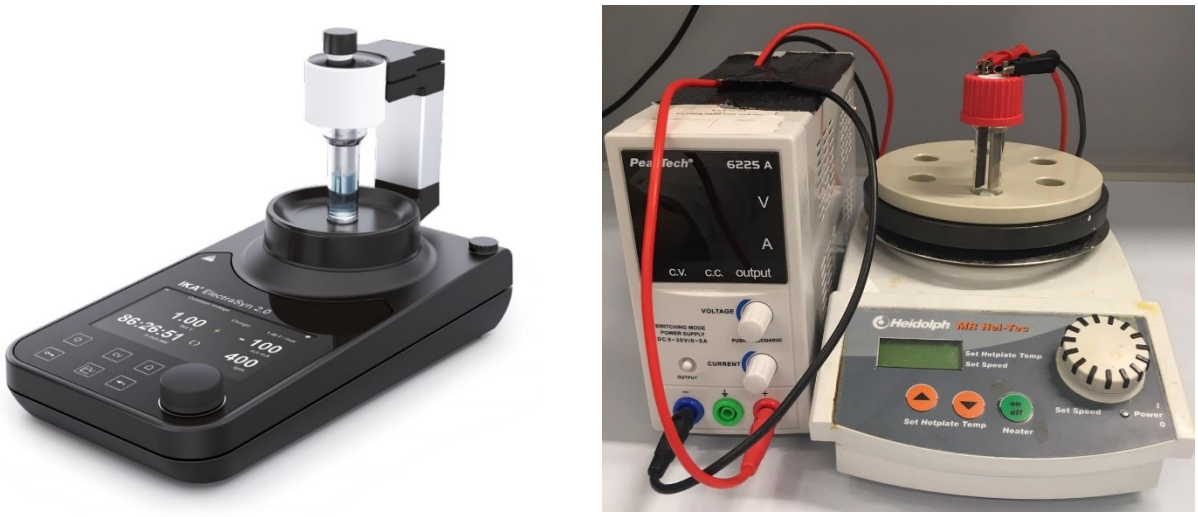



*Figure 3: IKA ElectraSyn 2.0[3] and DIY setup*

The electrode where the desired reaction is taking place is referred to as the working electrode. The other electrode is called counter electrode. An oxidation takes place at the anode (+) and, simultaneously, a reduction occurs at the cathode (-). These two simultaneous processes are required to generate the flow of electrons, which is aided by the power supply.

Knowledge of the required potential of a reaction is important to design an electrochemical transformation (Figure 4). Notably, appropriate selectivity can be attained both under potentiostatic and galvanostatic conditions (via control of the current density).

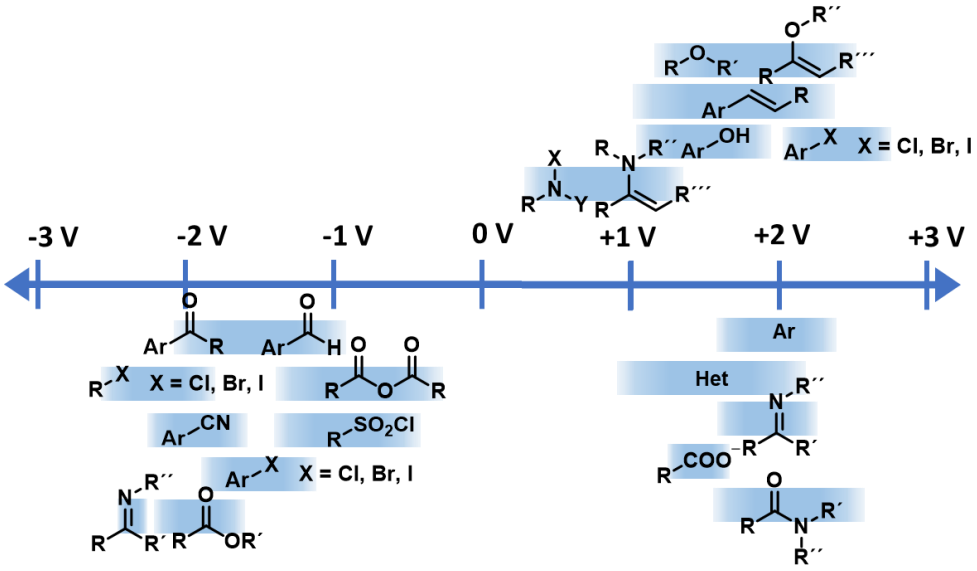



*Figure 4: Redox potentials of different functional groups*[4]

The choice of solvent is also very important (Figure 5). Commonly used are non protic polar solvents. The solvent of choice needs to be electrochemically inert within the voltage range of the target reaction. This is known as “solvent window”. Non-polar to avoid the solvent reacting to easily and hindering the reaction and polar to reduce the use of supporting electrolytes. Supporting electrolytes are required to make the solution conductive. Low conductivity of the solution leads to an increase in potential because the resistance of the solution increases. This can lead to two problems:

increase of the cell potential (and thus the energy consumption) and reducing the current efficiency. Several salts, soluble in organic solvent, can be used as supporting electrolyte. Importantly, they need to be electrochemically inert.

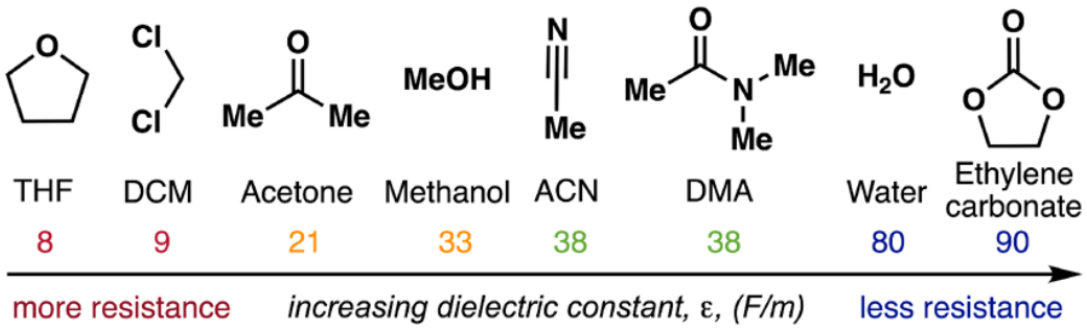



*Figure 5: Different solvents for use in electrochemistry*[5]

It should be pointed out that, in addition to direct electrolysis of the starting materials on the electrode surface (see Figure 1), in direct electrolysis with redox mediators can also be performed. A mediator is added in catalytic amounts, and its active form is recovered via its direct electrolysis (Figure 6).

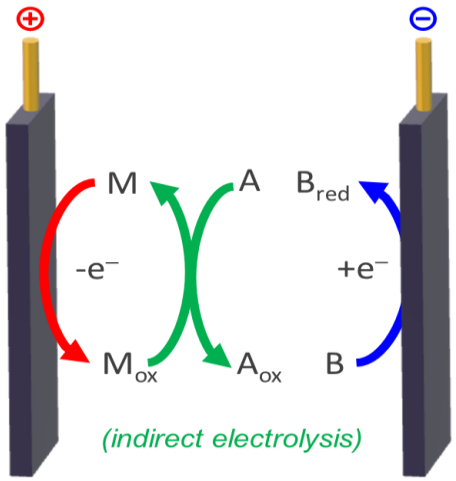



*Figure 6: General scheme of indirect electolysis*

## 1.2 Electrode materials and setting

During this thesis, a few different electrode materials have been implemented. Electrode are conducting materials that are chemically resistant and electrochemically inert. They can be made of many metals as well as several semiconductors. Some materials that are suitable as cathode may not be suitable as anode if they are reductively inert but prone to oxidation and vice versa. Common anode materials include platinum and several forms of carbon such as graphite, glassy carbon or boron-

*Figure 7: Different electrodes materials by IKA*[3]

doped diamond. Typical cathode materials include platinum, graphite or steel, among many others.

When cathodic reductions are desired, metal anodes are occasionally oxidized. In such cases the term sacrificial electrode is used. If a reaction works with a sacrificial electrode, one benefit is the regeneration of new surface during the reaction. However, the electrode is consumed over time. Electrode fouling can occur when materials deposit on their surface. This can lead to decrease on the reaction efficiency and ultimately the reaction may stop. This effect can be somewhat minimized by using a mediator in the reaction. A difference approach, commonly used is to invert the polarity of the reaction after certain time intervals.

Before starting a reaction, it is important to check the alignment of the electrodes. Poor alignment will greatly influence reproducibility (Figure 8).

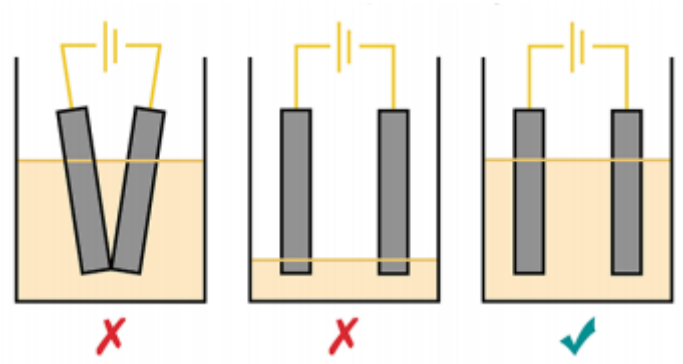


*Figure 8: Orientation of the electrodes*[5]

Both for the anode and cathode, a good cleaning procedure is crucial to maintain the reaction reproducibility. Metal electrodes can simply be polished with sandpaper and rinsed with solvent to restore the original surface.

## 1.3 Electrochemical cell types

The most simple electrochemical cell consist of a single chamber in which all electrodes are immersed in a solution. This is called undivided cell. Using such simple setup a large number of reaction can be executed, but there are limitations. If the desired product reacts on the counter electrode or the substrate is decomposed there, both electrode environments need to be separated. This separation can be done using a divided cell. Divided cell feature two separate reaction vessels. Each of the vessels is outfitted with one of the electrodes. The two parts are connected by a membrane or a frit, allowing only the flux of charge carrying species. A divided cell setup is more complex not only because the separation of both sides must work sufficiently. In addition, the distance between the electrodes is larger in most cases and the separator increases the overall resistance of the cell. This increases again the potential at a fixed current and therefore decreases the cell efficiency.

*Figure 9: Divided electrochemical cell*

## 1.4 Current density and double layer formation[6]

To understand how current density affects electrochemical reactions, current and potential must be understood. Potential is the force that moves electrons. This movement is described by the so-called potential difference between two points. It is also often referred as voltage. In electrochemistry, those two points are the two electrodes immersed the solution. The flux of electrons moving due to the potential is the current. Current density refers to the amount of flux at a given point. In electrochemistry, it is a value connected to the current of the cell and the surface of the electrodes. When applying electricity to a solution another effect is can be observed: the formation of a Helmholtz double layer. This layer is formed by ions and solvent molecules on the electrode surface. The thickness and the formation of the layer depends on different factors and it is a rather complex phenomenon in organic solvents. As the layer is formed directly on the electrode surface it is also involved in creating a uniform current and potential over the electrode. The double layer can be beneficial in a way that it protects the electrode surface from corrosion or passivation.

## 1.5 Steroids

Steroids constitute a very large and important class of natural compounds and pharmaceutical ingredients. Their biosynthesis by plants and animals is fundamental for many physiological processes, as steroids play key roles in signalling, as hormones, and as membrane constituents.[7] Due to their key biological properties, a significant number medicines have been developed based on steroid derivatives, with a wide range of applications including anti-inflammatory, contraceptive, antibiotic or antihistamine treatments.[8] The vital importance of steroids in modern medicine is underscored by the fact that many of them are among the top selling drugs[9] and several are also included in the WHO list of essential medicines.[10] It is therefore not surprising that, over the past few decades, important research efforts have focused on the discovery of novel steroid drugs and the development of more efficient methods for their synthesis.[11]

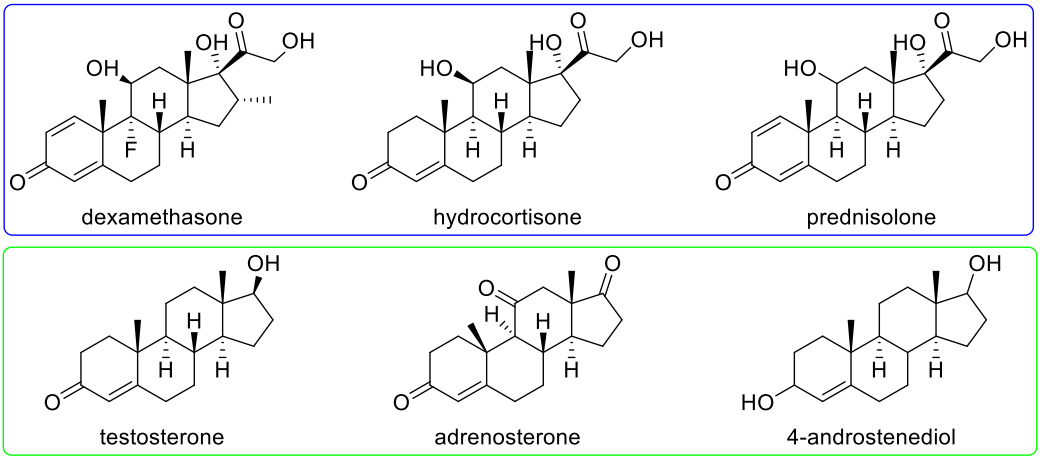



*Figure 10: Steroids listed as essential medicines by the WHO (top)[10] and examples of androgen medicines.*

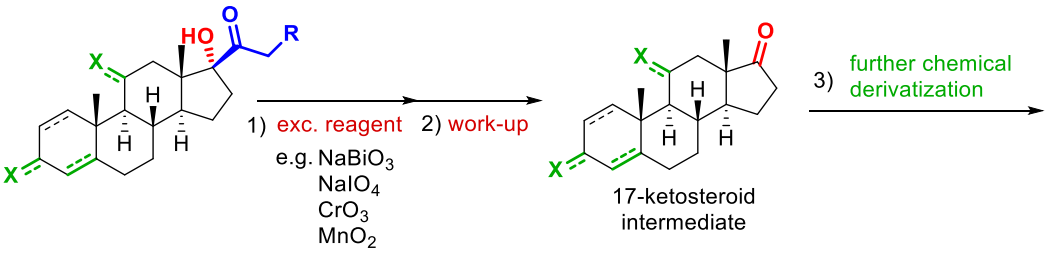
Within the large family of steroidal compounds, C19 steroids, based on the androstane skeleton, are also relevant natural hormones and synthetic or semisynthetic active ingredients, with over 40 marketed drugs[12]. As an example compounds like adrenosterone and 4-androstenediol are used as supplements for Testosterone deficiency. Their almost similar size and shape allows them to fit the active sides of their physiological counterparts and therefore allows an efficient method of controlling the hormone levels of patients.

# 2 Aim of this thesis

The aim of this thesis is the development of a convenient strategy for the synthesis of C19 steroids via the generation of 17-ketosteroid precursors, which in turn are obtained by removal of the side-chain of more abundant corticosteroids.[13] Removal of the C17 side-chain of corticosteroids has traditionally involved the use of excess amounts of strong oxidizing agents such as $NaBiO_3$,[14] $NaBH_4/NaIO_4$,[15] $CrO_3$[16] or $MnO_2$. Additional methods involving excess $I_2/NH_3$[17] and strong bases[18] have also been developed, although with either moderate yields or limited applicability. More recently, cleavage of hydroxyacetone side-chains with bismuth(III) catalysts has been reported.[19] Due to the important shortcomings of these methods and the difficulties associated with the selective side-chain removal without degradation of the androstane skeleton, microbial approaches have been intensely investigated.[20] However, the low solubility of steroids in aqueous systems severely limits their product yield and productivity.[21]

The classical chemical methods for the removal of the C17 side-chain outlined above typically require quench or neutralization of the excess of reagents, in addition to work-up and purification steps to isolate the corresponding 17-ketosteroid before it can be further derivatized to the target compound (Figure 11a).[13,22] We hypothesized that cleavage of the α-hydroxyketone C17-C20 bond might be possible via anodic oxidation in a catalyst- and reagent-free fashion (Figure 11b).[23,24] Such methodology for the generation of 17-ketosteroids, in the absence of external reagents, would permit direct derivatization of the intermediate without additional work-up or purification steps, resulting in a convenient and sustainable one-pot procedure for the multistep preparation of essential C19 steroids.

(a) Classical multistep synthesis of C19 steroids with cleavage of the side-chain




(b) **This Thesis**: one pot multistep strategy via electrochemical side-chain cleavage

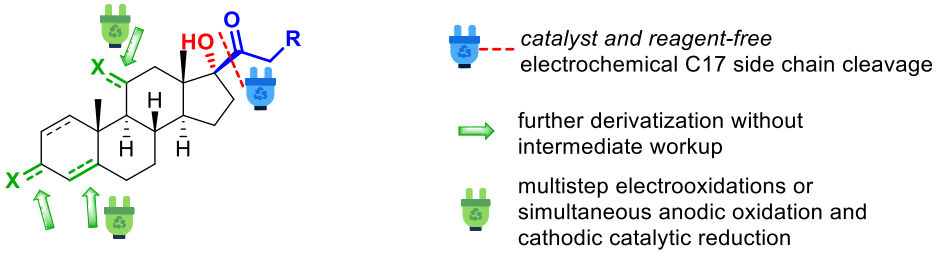



*Figure 11: Synthesis of C19 steroids. Classical and electrochemical approach*

# 3 Results and Discussion

## 3.1 Optimization of the electrolysis

### 3.1.1 General information on the optimization of the electrochemical C17 side-chain cleavage

In a 5 mL IKA ElectraSyn vial (undivided cell) equipped with a stir bar, the supporting electrolyte (0.3 mmol) and the corresponding amount of hydrocortisone **1a** were placed. Then, 3 mL of solvent and any additional liquid additive (e.g., water) were added. The electrochemical cell was capped and the mixture stirred for 10 min. Then, constant current was applied under a stirring speed of 1000 rpm until the desired amount of charge had been applied. The reaction outcome was monitored by HPLC chromatography. HPLC samples were prepared by diluting 20 µL aliquots of the crude reaction mixture in 1 mL MeCN. Conversion was determined by HPLC peak area percent (254 nm). Selectivity was determined by HPLC peak area percent (254 nm) as the percentage of product with respect to all other peaks except the substrate.

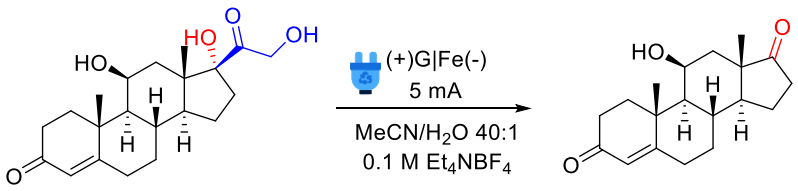



*Figure 12:Model reaction for the C17 cleavage of corticosteroids using hydrocortisone (**1a**)*

### 3.1.2 Optimization of the solvent system

The first test reaction (Entry 1, table 1) already showed promising results. Graphite and stainless steel were chosen as the electrode materials. A current of 5 mA was applied to avoid selectivity issues due to an increase in potential and potential losses in current efficiency. $Et_4NBF_4$ is one of the most widely used electrolytes and was therefore selected for the initial test. A conversion of 79% and an excellent selectivity of almost 100% were observed. In the absence of water both the selectivity and conversion were lower compared to the initial conditions (entry 2). Further testing with severalsolvent mixtures (entries 3-6) revealed that MeCN and $H_2O$ seemed to be optimal. Selectivity was reasonably good for all screened solvents, but lower conversion were obtained with other solvent systems. The amount of water was also optimized (entries 7 and 8, table 1). In the end the initial system proofed to be the optimal one.

*Table 1: Optimization of the solvent system for the electrolysis of hydrocortisone (1a)*

| Entry | Conditions | Conversion (%)[a] | Selectivity (%)[b] |
|---|---|---|---|
| 1 | MeCN:$H_2O$ (40:1), $Et_4NBF_4$, (+)G/Fe(-), 5 mA, 2 F/mol | 79 | 99 |
| 2 | **MeCN**, $Et_4NBF_4$, (+)G/Fe(-), 5 mA, 2 F/mol | 57 | 95 |
| 3 | **MeOH,** $Et_4NBF_4$, (+)G/Fe(-), 5 mA, 2 F/mol | 65 | 92 |
| 4 | **THF:$H_2O$ (10:1),** $Et_4NBF_4$, (+)G/Fe(-), 5 mA, 2 F/mol | 78 | 91 |
| 5 | **Acetone:$H_2O$ (40:1),** $Et_4NBF_4$, (+)G/Fe(-), 5 mA, 2 F/mol | 68 | 95 |
| 6 | **EtOH,** $Et_4NBF_4$, (+)G/Fe(-), 5 mA, 2 F/mol | 51 | 99 |
| 7 | **MeCN:$H_2O$ (20:1),** $Et_4NBF_4$, (+)G/Fe(-), 5 mA, 2 F/mol | 73 | 87 |
| 8 | **MeCN:$H_2O$ (10:1),** $Et_4NBF_4$, (+)G/Fe(-), 5 mA, 2 F/mol | 69 | 88 |

[a] Determined by HPLC peak area percent (254 nm). [b] Determined by HPLC peak area percent (254 nm) as the percentage of product with respect to all other peaks except the substrate. G = graphite anode, GC = glassy carbon, RVC = reticulated vitreous carbon, Fe = stainless steel.

### 3.1.3 Optimization of current and supporting electrolyte

To decrease reaction time the current increased. Notably, increased current decreased the conversion by at least a third and the selectivity decreased slightly (Table 2, entry 1 & 2). This was an indication that the cleavage is current sensitive. Continuing with 5mA, $NaClO_4$ and $LiClO_4$ were also evaluated as supporting electrolyte. As both showed a decrease in selectivity and conversion, no further electrolytes were screened and the amount of $Et_4NBF_4$ was altered instead. Also here the initial conditions proofed to be the best ones.

*Table 2: Optimization of current and supporting electrolyte for the electrolysis of hydrocortisone (1a)*

| Entry | Conditions | Conversion (%)[a] | Selectivity (%)[b] |
|---|---|---|---|
| 1 | MeCN:$H_2O$ (40:1), $Et_4NBF_4$, (+)G/Fe(-), **10 mA**, 2 F/mol | 53 | 96 |
| 2 | MeCN:$H_2O$ (40:1), $Et_4NBF_4$, (+)G/Fe(-), **20 mA**, 2 F/mol | 44 | 97 |
| 3 | MeCN:$H_2O$ (40:1), **$NaClO_4$,** (+)G/Fe(-), 5 mA, 2 F/mol | 47 | 73 |
| 4 | MeCN:$H_2O$ (40:1), **$LiClO_4$,** (+)G/Fe(-), 5 mA, 2 F/mol | 35 | 73 |
| 5 | MeCN:$H_2O$ (40:1), **$Et_4NBF_4$ (0.05 molar),** (+)G/Fe(-), 5 mA, 2 F/mol, | 66 | 87 |
| 6 | MeCN:$H_2O$ (40:1), **$Et_4NBF_4$ (0.025 molar),** (+)G/Fe(-), 5 mA, 2 F/mol | 45 | 86 |

[a] Determined by HPLC peak area percent (254 nm). [b] Determined by HPLC peak area percent (254 nm) as the percentage of product with respect to all other peaks except the substrate. G = graphite anode, GC = glassy carbon, RVC = reticulated vitreous carbon, Fe = stainless steel.

### 3.1.4 Optimization of electrode material

After optimization of the components of the reaction mixture, other electrode materials were also evaluated. First, stainless steel was swapped with Ni as a cathode. Lower conversion and selectivity was observed. Reticulated vitreous carbon (RVC) and glassy carbon (GC) were tested as anode materials (entries 2 and 3). Notably, no conversion was observed with GC and the electrode surface was covered with a layer of a tarry, unidentified substance. RVC showed similar issues. Graphite on the other hand gave excellent results, leading to the conclusion that the surface of the compressed graphite powder in this electrode is favorable in this chemical transformation. Platinum also gave poor results. By polishing the anode surface between reactions, it was possible to run an unlimited amount of reactions without noticing a change in conversion or selectivity.

*Table 3: Optimization of the electrode material for the electrolysis of hydrocortisone (1a)*

| Entry | Conditions | Conversion (%)[a] | Selectivity (%)[b] |
|---|---|---|---|
| 1 | MeCN:$H_2O$ (40:1), $Et_4NBF_4$, **(+)G/Ni(-),** 5 mA, 2 F/mol | 62 | 91 |
| 2 | MeCN:$H_2O$ (40:1), $Et_4NBF_4$, **(+)GC/Fe(-),** 5 mA, 2 F/mol | <1 | - |
| 3 | MeCN:$H_2O$ (40:1), $Et_4NBF_4$, **(+)RVC/Fe(-),** 5 mA, 2 F/mol | 9 | 67 |
| 4 | MeCN:$H_2O$ (40:1), $Et_4NBF_4$, **(+)Pt/Fe(-),** 5 mA, 2 F/mol | 11 | 75 |

[a] Determined by HPLC peak area percent (254 nm). [b] Determined by HPLC peak area percent (254 nm) as the percentage of product with respect to all other peaks except the substrate. G = graphite anode, GC = glassy carbon, RVC = reticulated vitreous carbon, Fe = stainless steel.

### 3.1.5 Optimization of the required charge

The final part of the optimization was identifying the correct amount of charge required. The table below (entry 1 to 3) shows the increase in conversion to the optimal of 4 F/mol. A further increase of charge led to a decrease in selectivity. The optimized optimal conditions for the electrochemical C17 side-chain cleavage with hydrocortisone result in 99% conversion and 98% selectivity.

*Table 4: Optimization of the required charge for the electrolysis of hydrocortisone (1a)*

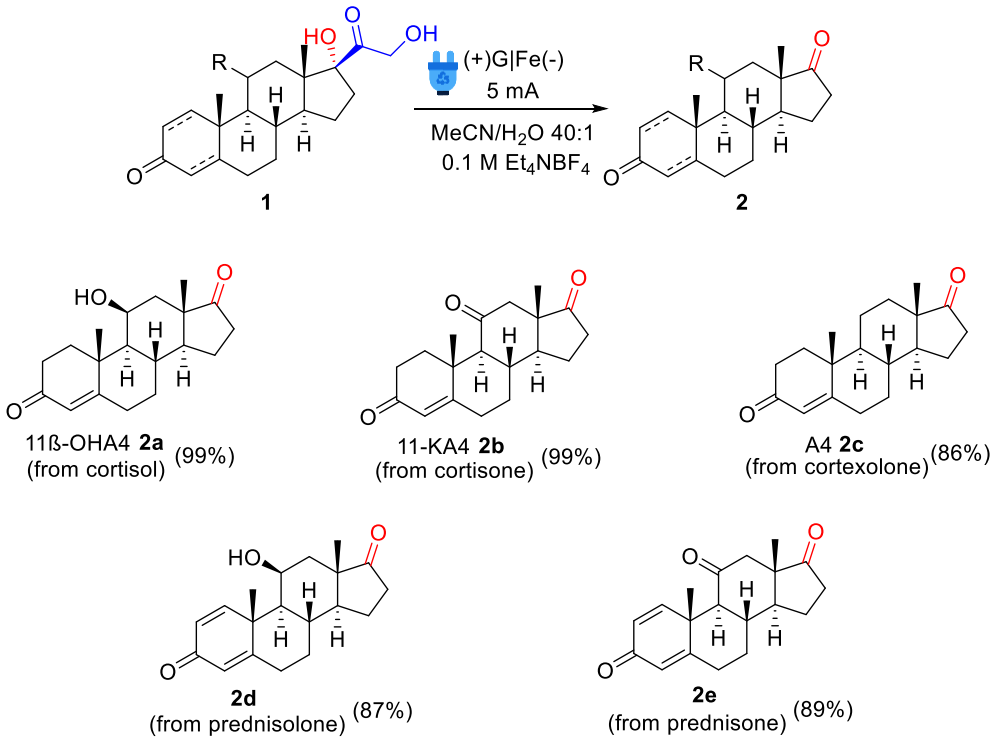
| Entry | Conditions | Conversion (%)[a] | Selectivity (%)[b] |
|---|---|---|---|
| 1 | MeCN:$H_2O$ (40:1), $Et_4NBF_4$, (+)G/Fe(-), 5 mA, **3 F/mol** | 84 | 98 |
| 2 | MeCN:$H_2O$ (40:1), $Et_4NBF_4$, (+)G/Fe(-), 5 mA, **3.5 F/mol** | 93 | 98 |
| 3 | MeCN:$H_2O$ (40:1), $Et_4NBF_4$, (+)G/Fe(-), 5 mA, **4 F/mol** | 99 | 98 |
| 4 | MeCN:$H_2O$ (40:1), $Et_4NBF_4$, (+)G/Fe(-), 5 mA, **4.2 F/mol** | 98 | 94 |
| 5 | MeCN:$H_2O$ (40:1), $Et_4NBF_4$, (+)G/Fe(-), 5 mA, **4.5 F/mol** | 99 | 88 |

[a] Determined by HPLC peak area percent (254 nm). [b] Determined by HPLC peak area percent (254 nm) as the percentage of product with respect to all other peaks except the substrate. G = graphite anode, GC = glassy carbon, RVC = reticulated vitreous carbon, Fe = stainless steel.

## 3.2 Scope of the electrochemical C17 side chain cleavage

The scope and applicability of this electrochemical C17 side-chain cleavage protocol was next investigated. Thus, several key 17-ketosteroids **2** were prepared from their corresponding corticosteroid precursors (Figure 9). As mentioned above, 11β-hydroxyandrostenedione **2a** was obtained in quantitative yield (Figure 9a). When cortisone and cortexolone were used as starting materials, the Reichstein's substance G (adrenosterone) **2b** and androstenedione **2c** were obtained with quantitative and excellent yield, respectively. Anodic side-chain cleavage of the more sensitive prednisone and prednisolone also provided satisfactory results, and 17-ketosteroids **2d** and **2e** were obtained in excellent yields. Importantly, it could also be shown that this reagent-free electrochemical procedure does not require the presence of a hydroxyketone side-chain, a rather common limitation of some conventional chemical cleavage methods. Thus, 17α-hydroxyprogesterone **3**, which contains a methylketone side-chain, could be cleanly electrolyzed to the corresponding 17-ketosteroid **2c** in quantitative yield (Figure 9b). The mechanism of this α-hydroxyketone C-C bond cleavage is a 2-electron process, which could involve the hydrate form of the ketone in the presence of water (see suggested mechanism in chapter 3.3). The vicinal diols have been shown to undergo C-C bond cleavage under anodic oxidation.[25]

(a) Corticosteroids hydroxyacetone side chain cleavage




(b) Cleavage of a non-hydroxyl-containing side-chain

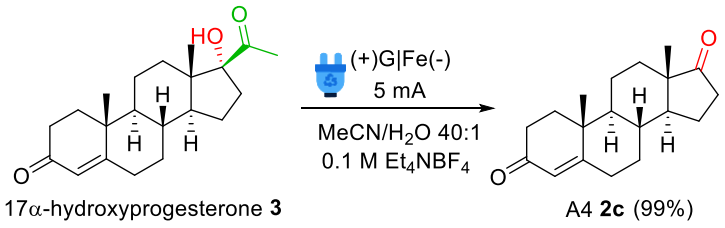



*Figure 13: Scope of the C17 side-chain cleavage*

## 3.3 Proposed mechanism of the electrochemical C17 side-chain cleavage of steroids

The proposed mechanism for the C17 side-chain cleavage (Figure 14) starts with the generation of the hydrate I of the starting ketone (**1**) in the presence of water. This is supported by the fact that the reaction performed best with water as additive compared with other less nucleophilic protic solvents ($H_2O$ > MeOH > EtOH) (Table 1). One electron anodic oxidation followed by loss of one proton would release glycolic acid as byproduct and radical III. Rapid anodic oxidation of III with loss of a second proton results in the product **2**. Simultaneously, reduction of two protons with release of hydrogen gas takes place on the cathode surface.

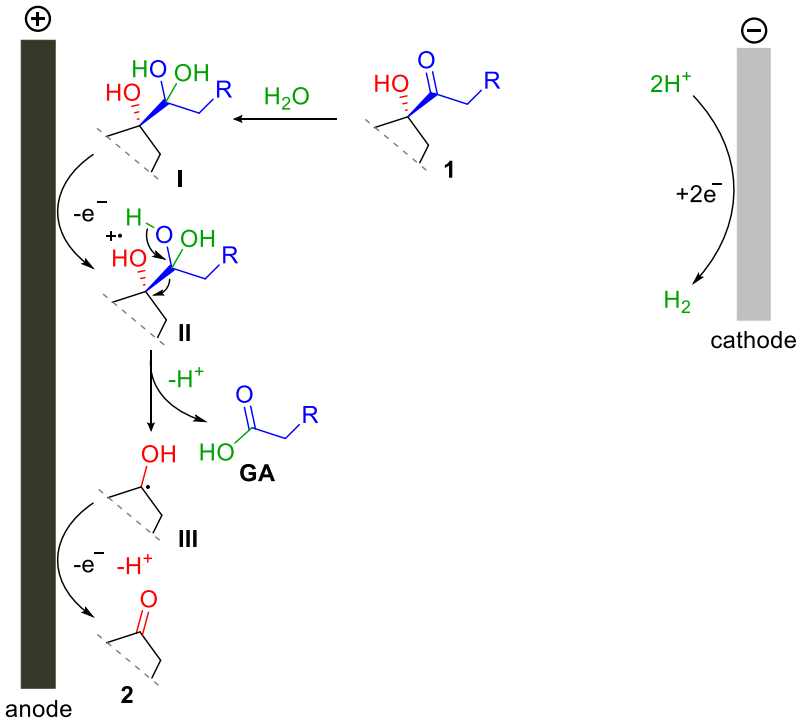



*Figure 14: Proposed mechanism for the C17 side-chain cleavage of steroids*

## 3.4 One-pot multistep preparation of C19 androgens

As mentioned in chapter 1.5, the preparation of many C19 androgen steroids require several reaction steps. Side-chain cleavage with conventional chemicals complicate these multistep synthetic routes, as quench and workup procedures for the purification of the 17-ketosteroid intermediates are required. The catalyst and reagent free electrochemical procedure presented herein permitted the execution of several multistep C19 steroid syntheses in one pot, by simply adding additional reagents or catalysts to the electrochemical cell

### 3.4.1 One-pot side-chain cleavage followed by a carbonyl reduction using $NaBH_4$

The anodic oxidation of cortisone (**1b**) followed by addition of $NaBH_4$ to the undivided cell directly unlocked a simple and convenient one-pot procedure for the synthesis of 11-ketotestosterone (**4**), an important androgen (Figure 15).[26] By simple extraction the product could be isolated with 82 % yield. Implementation of a similar strategy was used for the transformation of cortexolone (**1c**). Addition of $NaBH_4$ generated 4-androstenediol (**5**) also with high yields (76 %). This molecule is a precursor for testosterone[27], making this strategy an easy procedure to excess different androgen precursors.

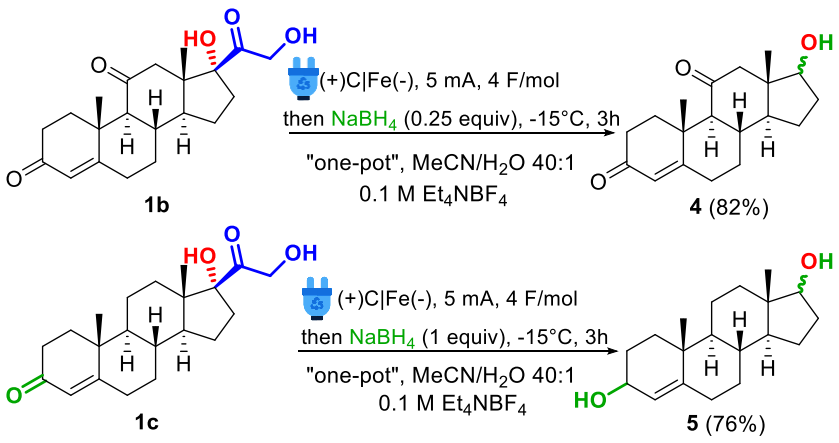



*Figure 15: One-pot side-chain cleavage followed by carbonyl reduction*

### 3.4.2 One-pot multistep electrooxidation of hydrocortisone to adrenosterone

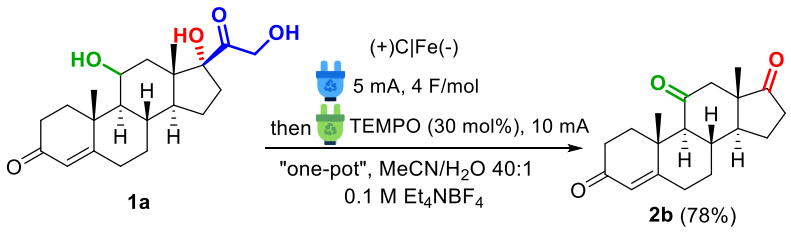



*Figure 16: One-pot multistep electrooxidation of hydrocortisone to andrenosterone*

A open-pot two-step electrooxidative transformation for the synthesis of adrenosterone (**2b**) from hydrocortisone (**1a**) was also developed. In this transformation, anodic side-chain cleavage of hydrocortisone **1a**, directly followed by electrocatalytic oxidation of the alcohol moiety in intermediate **2a** by simple adding TEMPO as electrocatalyst[28a] to the ongoing electrolysis (after 4 F/mol), was attempted (see Figure 16). TEMPO catalyzed anodic oxidations are favored by moderately basic pH.[28b] As this transformation proved challenging, the reaction conditions for the electrocatalytic step were initially screened using the oxidation of cyclohexanol as model (Table 5, entries 1-9). For this purpose, an electrolysis reaction mixture was emulated by adding 1 equiv glycolic acid to the solution of cyclohexanol in MeCN/$H_2O$ 40:1. This is due to the fact that during the electrochemical cleavage of a hydroxyketone C17 side-chain is released (see mechanism in chapter 3.3). Electrocatalytic oxidation of alcohols with TEMPO is favored by basic conditions. Thus, addition of 2,6-lutidine and $NaHCO_3$/$Na_2CO_3$ as basic additives were evaluated. The amount of base needed to be sufficient to neutralize the glycolic acid that is generated during the side-chain cleavage. While 2,6-lutidine did not lead to any conversion to the ketone (entries 1-4), combinations of aqueous solutions of Na2CO3 ultimately led to excellent conversion and selectivity. Conversion in both tables below is determined by GC-FID peak area percent for the model reaction and for the Steroid reaction with HPLC area percent (254 nm). Selectivity was determined in both tables via GC-FID peak area integration for the model reaction and for the steroids via HPLC peak area integration (254 nm). Selectivity refers to the area percentage of product with respect to all other peaks except the substrate.

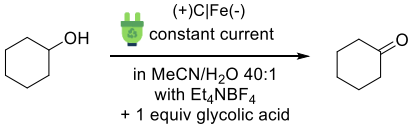



*Figure 17: Emulated reaction mixture for optimization*

*Table 5: Optimization of the alcohol oxidation with TEMPO in an emulated reaction mixture*

| Entry | Conditions | Conversion (%) | Selectivity (%) |
|---|---|---|---|
| 1 | 10 mol% TEMPO, no base added, 2 F | <1 | - |
| 2 | 10 mol% TEMPO, 2 equiv 2,6-lutidine, 2 F | <1 | - |
| 3 | 10 mol% TEMPO, 3 equiv 2,6-lutidine, 2 F | <1 | - |
| 4 | 30 mol% TEMPO, 3 equiv 2,6-lutidine, 2F | <1 | - |
| 5 | 30 mol% TEMPO, 1 equiv $Na_2CO_3$ in 75 µl $H_2O$, 2 F/mol | <5 | 100 |
| 6 | 30 mol% TEMPO, 1 equiv $Na_2CO_3$ in 75 µl $H_2O$, 8 F/mol | 15 | 100 |
| 7 | 30 mol% TEMPO, 1 equiv $Na_2CO_3$ in 75 µl $H_2O$, 12 F/mol | 66 | 100 |
| **8** | **30 mol% TEMPO, 1 equiv $Na_2CO_3$ in 75 µl $H_2O$, 16 F/mol** | **91** | **100** |
| 9 | 30 mol% TEMPO, 1 equiv $Na_2CO_3$ in 75 µl $H_2O$, 18 F/mol | 91 | 98 |

Once the reaction conditions had been optimized, the conditions were applied to the steroid example hydrocortisone (Table 6; entries 1 & 2). An experimental procedure for the complete one-pot procedure is given in section 5.6. As can be seen in the table below. The optimal conditions form the emulated reaction mixture did not give sufficient conversion. This is probably caused by the passivation of the electrode in the first electrolysis step. Therefore, the amount of charge must be higher than in the optimal conditions of the emulated reaction. It is also possible that during the TEMPO electrolysis something else is cladding the electrode because the selectivity is lower than in the model. Therefore, there is definitely formation of side-product that could passivate the surface too.

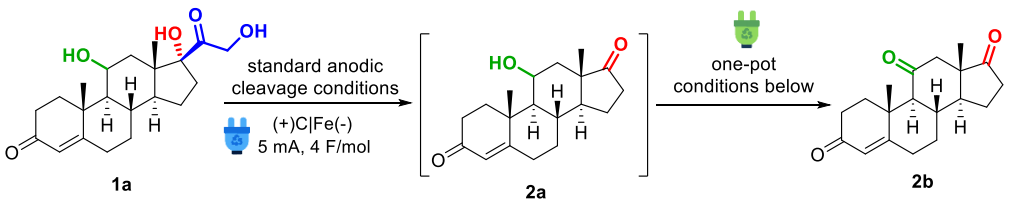



*Figure 18: Reaction procedure for the final TEMPO telescoping reaction*

*Table 6: Optimization for the alcohol oxidation with the real reaction mixture*

| Entry | Conditions | Conversion (%) | Selectivity (%) |
|---|---|---|---|
| 1 | 30 % TEMPO, 1 equiv $Na_2CO_3$ in 75 µl $H_2O$, 16 F | 65 | 92 |
| **2** | **30 % TEMPO, 1 equiv $Na_2CO_3$ in 75 µl $H_2O$, 25 F** | **99** | **85** |

### 3.4.3 Simultaneous anodic removal of the C17 side-chain and cathodic catalytic hydrogenation of Cortisone

Starting from the hydroxyketone side-chain cleavage of cortisone (**1b**), androstane-3,11,17-trione (**6**) was prepared by Pd/C catalyzed hydrogenation of the C4-C5 double bond (Figure 19). In this case, once the electrolysis had ended, 10 mol% Pd/C was added to the electrochemical cell and the mixture stirred under $H_2$ atmosphere at room temperature for 2 h. Filtration and extraction with aqueous $NaHCO_3$/DCM provided an excellent yield (91%) of the reduced androgen **6**.

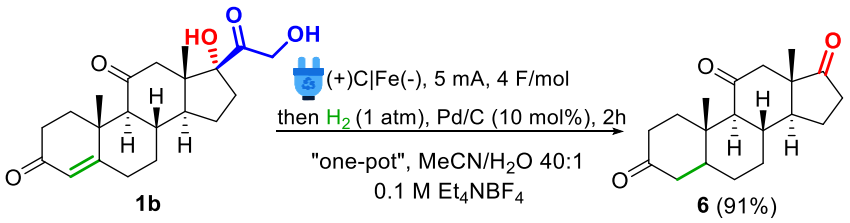



*Figure 19: Simultaneous anodic removal of the C17 side-chain and cathodic catalytic hydrogenation of cortisone*

The above successful preparation of androstane-3,11,17-trione (**6**), following a one-pot electrochemical side-chain cleavage/catalytic hydrogenation sequence, led us to infer that the same transformation could probably be accomplished in a single electrochemical reaction. This is due to the fact, that during the anodic side-chain cleavage $H_2$ gas is produced at the cell cathode (the proposed mechanism can be seen in chapter 3.3). Such synthetic strategy would result in a highly convenient and atom economic procedure for the synthesis of **6** and other analogue saturated androgens. To test this hypothesis, cortisone (**1b**) was electrolyzed under the optimal reaction conditions for the cleavage of the side-chain in the presence of a suspension of 10 mol% Pd/C (Figure 14). In this experiment, the reaction vial was tightly closed to ensure that the $H_2$ generated at the cathode could not easily escape the cell. To our delight, HPLC monitoring of the reaction mixture revealed disappearance of both the starting steroid **1b** and the 17-ketosteroid intermediate **2b**. Compound **6**, generated by simultaneous anodic oxidation and cathodic catalytic hydrogenation of **1b** was obtained in nearly quantitative yield (97%).

It should be emphasized that, while examples of “ex-cell” exploitation of the $H_2$ generated in electrochemical reactions have been reported,[29] in situ utilization “in-cell” for the catalytic reduction of a molecule that is simultaneously being oxidized is unique.

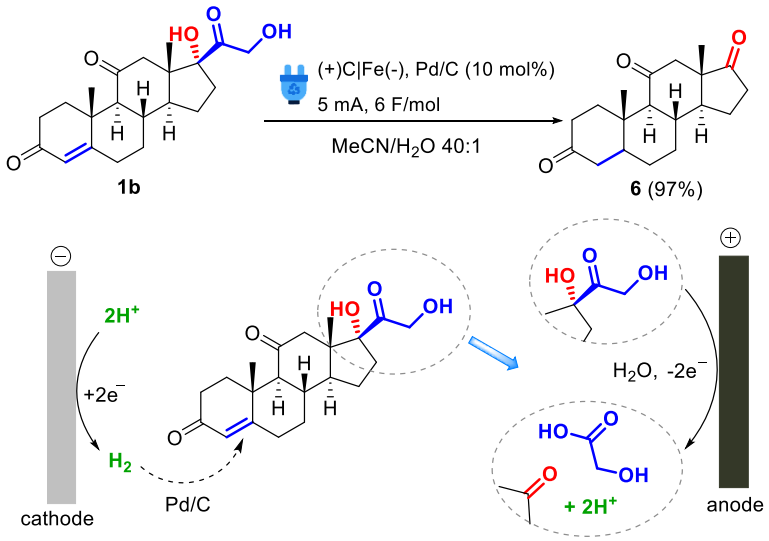



*Figure 20: Simultaneous anodic removal of the C17 side-chain and cathodic catalytic hydrogenation of cortisone (1b)*

# 4 Conclusion and Outlook

In summary, it was possible to develop a method that allows the safe sustainable electrochemical synthesis of C19 androgen steroids based on the anodic oxidative cleavage of the C17 side-chain from corticosteroids. With this remarkable method it was demonstrated that a wide variety of different corticosteroids can be transformed into the desired androgens. Several of those steroids were synthetized with quantitative yields and a very easy workup could be implemented to obtain the desired androgens. This not only decreases the amount of chemicals and solvents needed for the preparation of the steroids, but also the overall reaction and workup time as compared with conventional chemical methods. All multistep reaction examples show how easy it is to transform multiple different follow up reactions without isolation or even transferring the reaction mixture into another vessel. Especially the simultaneous C17 side chain cleavage on the anode and the direct hydrogenation using the hydrogen generated on the cathode show superior atom efficiency compared to standard chemical methods. Therefore, the presented generation of saturated androgens is remarkably easy to do in one step instead of using a complicated multistep reaction methodology.

For future applications, this methodology will allow an easy and economical way to synthesize a wide variety of C19 androgens. Making it an excellent option for the production, of steroidal drugs. Not only is the purity already very high directly after the reaction, as electricity is the main reagent the overall cost of the process is can be significantly lower than with standard chemical methods.

# 5 Experimental

## 5.1 General Information

$^{1}H$ NMR spectra were recorded on a 300 MHz instrument from Bruker. $^{13}C$ NMR spectra were recorded on the same instrument at 75 MHz. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet, respectively. Analytical HPLC analysis was carried out on a C18 reversed-phase (RP) analytical column (150 × 4.6 mm, particle size 5 mm) at 37 °C by using mobile phases A [water/acetonitrile 90:10 (v/v) + 0.1% TFA] and B (acetonitrile + 0.1% TFA) at a flow rate of 1.5 mL/min. The following gradient was applied: linear increase from solution 3% B to 100% B within 10 min. Tetraethylammonium tetrafluoroborate (Aldrich, Code: 242144, Lot: BCBV4670; Acros, Code: AC22161025, Lot: A0416770), hydrocortisone (Aldrich, Code: H4001, Lot: SLCB9138), prednisolone (Aldrich, Code: P6004, Lot: SLBT9873), cortisone (TCI, Code: C1317, Lot: BDF8F-FT), cortexolone (TCI, Code: C1478, Lot: OKOYF-RH), prednisone (TCI, Code: P1276, Lot: MK5EB-EG) and 17α-hydroxyprogesterone (TCI, Code: H1250, Lot: JCDVM-KO) were acquired from the vendors stated and used without any further purification. HPLC grade acetonitrile and water were used in all experiments. All electrochemical reactions were carried out in IKA ElectraSyn 2.0 undivided cells (5 mL vials) equipped with standard IKA ElectraSyn 2.0 electrodes. Graphite and stainless steel electrodes were polished with sand paper (3000 grit) before each electrolysis experiment.

## 5.2 General procedure for the electrochemical C17 side-chain cleavage of steroids

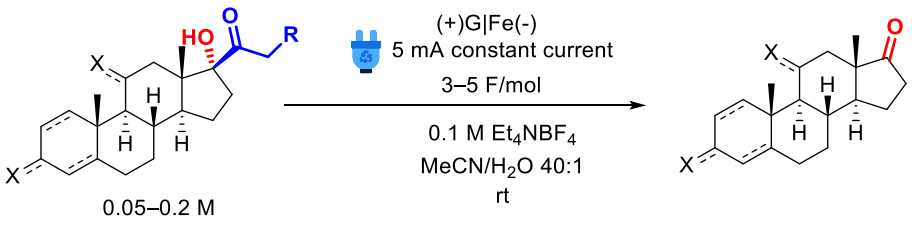



*Figure 21: General reaction procedure for the C17 side-chain cleavage of steroids*

In a 5 mL IKA ElectraSyn vial (undivided cell) equipped with a stir bar, $Et_4NBF_4$ (65 mg, 0.3 mmol) and the steroid starting material (0.15 to 0.6 mmol) were placed. Then, 3 mL of MeCN and 75 µL of water were added and the vial was capped with the cell head equipped with a standard IKA ElectraSyn graphite anode and stainless steel cathode. The suspension was stirred for 10 min and then a constant current of 5 mA was applied under a stirring speed of 1000 rpm. After 3-5 F/mol of charge had been passed, the reaction mixture was evaporated under reduced pressure. The residue was diluted with a saturated aqueous solution of $NaHCO_3$ and extracted with DCM. The organic phase was dried over $Na_2SO_4$ and evaporated under reduced pressure, yielding the target 17-ketosteroid.

## 5.3 Preparation and analytical data of all electrolysis products

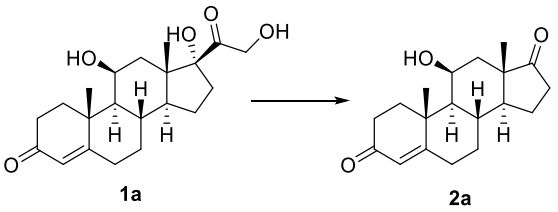



*Figure 22: 1a to 2a*

**11β-Hydroxyandrost-4-ene-3,17-dione (2a).** Following the general procedure with hydrocortisone (**1a**) (217 mg, 0.6 mmol) as the substrate and applying 4 F/mol of charge, the title compound was obtained as a white solid (181 mg, 99%); m.p. 178-180 °C (lit.[20] 185-188 °C); $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 5.58 (s, 1H), 4.54 (bs, 1H), 4.24 (m, 1H), 2.46 - 2.40 (m, 3H), 2.26 - 2.16 (m, 3H), 2.09 - 2.05 (m, 2H), 2.00 - 1.79 (m, 5H), 1.39 (s, 3H), 1.29 - 1.21 (m, 4H), 1.05 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 219.1, 198.5, 172.5, 122.1, 66.6, 56.2, 51.9, 46.8, 35.3, 34.5, 33.9, 31.8, 31.6, 31.1, 21.8, 20.9, 15.9; MS (ESI+) m/z: 344 (M + $H^+$ + MeCN); IR (ATR, $cm^{-1}$) 3414, 2924, 1731, 1654, 1230, 1093, 1049, 899. These data are in agreement with those reported previously in the literature.[20]

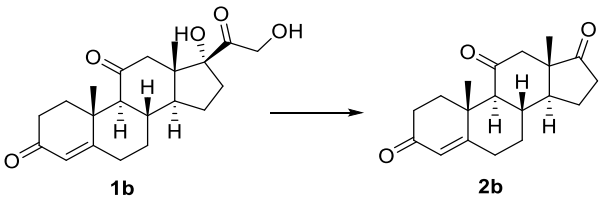



*Figure 23: 1b to 2b*

**4-Androstene-3,11,17-trione (2b).** Following the general procedure with cortisone (**1b**) (108 mg, 0.3 mmol) as the substrate and applying 4 F/mol of charge, the title compound was obtained as a white solid (90 mg, 99%); m.p. 209-210 °C (lit.[20] 214-217 C); $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 5.67 (s, 1H), 2.59 - 2.54 (m, 1H), 2.46 - 2.38 (m, 3H), 2.32 - 1.99 (m, 10H), 1.68 - 1.60 (m, 2H), 1.35 (s, 3H), 1.28 - 1.14 (m 1H), 0.75 (s, 3H). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 217.6, 209.0, 198.7, 169.4, 124.2, 62.1, 50.4, 50.3, 48.6, 38.3, 36.1, 35.9, 34.4, 33.8, 31.8, 30.9, 21.5, 17.3, 14.8. MS (ESI+) m/z: 342 (M + $H^+$ + MeCN); IR (ATR, $cm^{-1}$) 2909, 1740, 1703, 1663, 1225, 1050, 893. These data are in agreement with those reported previously in the literature.[20]

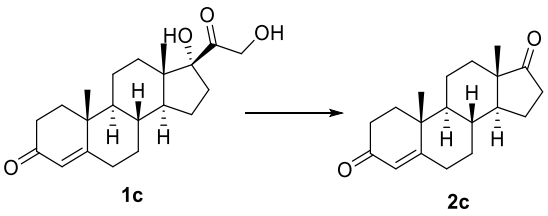



*Figure 24: 1c to 2c*

**Androst-4-ene-3,17-dione (2c).** Following the general procedure with cortexolone (**1c**) (156 mg, 0.45 mmol) as the substrate and applying 4 F/mol of charge, the title compound was obtained as a white solid (111 mg, 86 %); m.p. 159-160 °C (lit.[19b] 169-171 °C); $^{1}$H NMR (300 MHz, $CDCl_3$) δ 5.76 (s, 1H), 2.51 - 2.37 (m, 5H), 2.17 - 1.85 (m, 6H), 1.73 - 1.54 (m, 4H), 1.50 - 1.29 (m, 3H), 1.22 (s, 3H), 1.18 - 1.01 (m, 1H), 0.93 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 220.4, 199.3, 170.3, 124.2, 53.8, 50.8, 47.5, 38.6, 35.7, 35.7, 35.2, 33.9, 32.6, 31.3, 30.8, 21.7, 20.3, 17.4, 13.7. MS (ESI+) m/z: 328 (M + $H^+$ + MeCN); IR (ATR, $cm^{-1}$) 2942, 2853, 1738, 1666, 1612, 1226, 858. These data are in agreement with those reported previously in the literature.[19b]

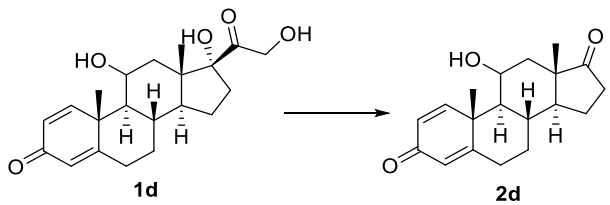



*Figure 25: 1d to 2d*

**1,4-Androstadien-11β-ol-3,17-dione (2d).** Following the general procedure with prednisolone (**1d**) (54 mg, 0.15 mmol) as the substrate and applying 4.5 F/mol of charge, the title compound was obtained as a white solid (39 mg, 87 %); m.p. 178-181 °C (lit.[20] 184-186 °C); $^{1}$H NMR (300 MHz, $CDCl_3$) δ 7.30 – 7.27 (d, 1H), 6.30 - 6.27 (d, 1H), 6.04 (s, 1H), 4.50 (m, 1H), 3.36 - 3.29 (m, 1H), 2.67 - 2.23 (m, 5H), 2.18 - 1.92 (m, 4H), 1.78 - 1.64 (m, 3H), 1.49 (s, 3H), 1.47 - 1.36 (m, 2H), 1.26 – 1.24 (m, 1H) 1.19 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 218.9, 186.5, 169.6, 156.0, 128.0, 122.6, 69.8, 55.9, 51.7, 46.9, 44.1, 40.9, 35.2, 32.7, 31.8, 30.9, 21.9, 21.2, 15.8. MS (ESI+) m/z: 342 (M + $H^+$ + MeCN); IR (ATR, $cm^{-1}$) 2316, 2927, 1732, 1654, 1614, 1599, 1064, 1014, 885. These data are in agreement with those reported previously in the literature.[20]

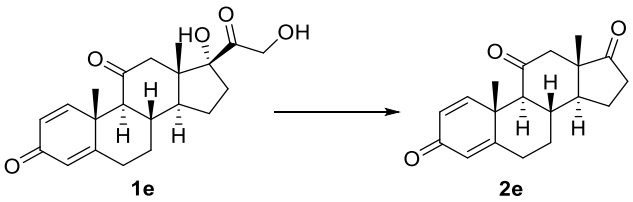



*Figure 26: 1e to 2e*

**Androsta-1,4-diene-3,11,17-trione (2e).** Following the general procedure with prednisone (**2e**) (54 mg, 0.15 mmol) as the substrate and applying 3 F/mol of charge, the title compound was obtained as a white solid (40 mg, 89 %); m.p. 190-191 °C (lit.[30] 195 - 197 °C); $^{1}$H NMR (300 MHz, $CDCl_3$) δ 7.68 - 7.65 (d, 1H), 6.25 - 6.21 (d, 1H), 6.11 (s, 1H), 2.62 - 2.55 (m, 2H), 2.51 - 2.46 (m, 2H), 2.35 - 2.24 (m, 2H), 2.20 - 2.12 (m, 2H), 2.02 - 1.70 (m, 4H), 1.48 (s, 3H), 1.34 - 1.26 (m, 1H), 0.93 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 216.3, 207.3, 186.1, 165.6, 154.6, 127.9, 124.9, 60.9, 50.5, 50.1, 49.7, 42.3, 36.0, 35.9, 32.2, 31.9, 21.7, 18.9, 14.8. MS (ESI+) m/z: 340 ($M + H^+ + MeCN$); IR (ATR, $cm^{-1}$) 1739, 1705, 1660, 1622, 1225, 886. These data are in agreement with those reported previously in the literature.[31]

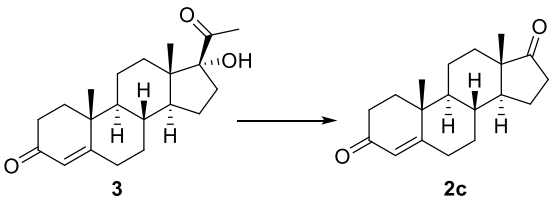



*Figure 27: 3 to 2c*

**Androst-4-ene-3,17-dione (2c) (from 17α-hydroxyprogesterone).** Following the general procedure with 17α-hydroxyprogesterone (**3**) (149 mg, 0.45 mmol) (0.15 M substrate concentration) as the substrate and applying 5 F/mol of charge, the title compound was obtained as a white solid (130 mg, 99 %); m.p. 159-160 °C (lit.[19b] 169-171 °C); $^{1}$H NMR (300 MHz, $CDCl_3$) δ 5.76 (s, 1H), 2.53 - 2.38 (m, 5H), 2.14 - 1.84 (m, 6H), 1.73 - 1.54 (m, 4H), 1.49 - 1.29 (m, 3H), 1.22 (s, 3H), 1.18 - 1.01 (m, 1H), 0.92 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 220.4, 199.3, 170.3, 124.1, 53.8, 50.8, 47.5, 38.6, 35.7, 35.7, 35.1, 33.9, 32.6, 31.3, 30.7, 21.7, 20.3, 17.4, 13.7; MS (ESI+) m/z: 328 ($M + H^+ + MeCN$); IR (ATR, $cm^{-1}$) 2942, 1738, 1663, 1226, 858. These data are in agreement with those reported previously in the literature.[19b]

## 5.4 One-pot synthesis of 11-oxotestosterone from cortisone via an anodic oxidation/ketone reduction sequence

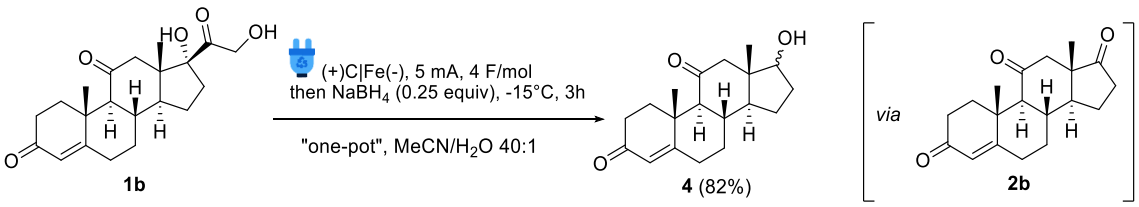



*Figure 28: One-pot synthesis of 11-oxotestosterone (4) from cortisone (1b) via anodic oxidation/ketone reduction sequence*

In a 5 ml IKA ElectraSyn vial (undivided cell) equipped with a stir bar, $Et_4NBF_4$ (65 mg, 0.3 mmol) and cortisone (**1b**) (108 mg, 0.3 mmol) were placed. Then, 3 mL of MeCN and 75 µL of water were added and the vial was capped with the cell head equipped with a standard IKA Electrasyn graphite anode and a stainless steel cathode. The suspension was stirred for 10 min and then a constant current of 5 mA was applied under a stirring speed of 1000 rpm. After 4 F/mol of charge had been passed the electrical current was stopped. Then, the electrochemical cell was immersed in an ice/acetone bath (-15 °C) and a solution of $NaBH_4$ (0.25 equiv) in 1 mL MeOH was added to the crude electrolysis reaction mixture under vigorous stirring. After 3 h, the reaction was quenched with an excess of water and extracted with DCM. The organic phase was dried over $Na_2SO_4$, filtered, and evaporated under reduced pressure, yielding 11-oxotestosterone **4** (74 mg, 82%) as a white solid. M.p. 180-181 °C (lit.[32] 186-187 °C); $^1$H NMR (300 MHz, $CDCl_3$) δ 5.73 (s, 1H), 3.89 - 3.86 (m, 1H), 2.82 – 2.74 (m, 1H), 2.56 - 2.43 (m, 3H), 2.34 -2.18 (m, 5H), 1.99 - 1.88 (m, 3H), 1.76 - 1.59 (m, 4H), 1.44 (s, 3H), 1.29 - 1.19 (m, 2H), 0.77 - 0.73 (d, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 208.9, 199.8, 168.8, 124.6, 79.8, 62.8, 54.7, 49.6, 46.9, 38.3, 37.5, 34.7, 33.7, 32.2, 31.7, 30.7, 22.8, 17.2, 11.8. MS (ESI+) m/z: 344 (M + $H^+$ + MeCN); IR (ATR, $cm^{-1}$) 3276, 2929, 1702, 1663, 1614, 1347, 1220, 1063,1026, 684. These data are in agreement with those reported previously in the literature.[32]

## 5.5 One-pot synthesis of 4-androstenediol from cortexolone via an anodic oxidation/ketone reduction sequence

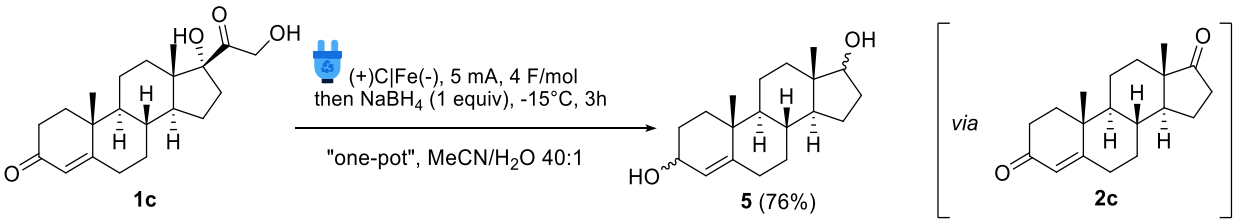



*Figure 29: One-pot synthesis of 4-androstenediol (5) from cortexolone (1c) via an anodic oxidation/ketone reduction sequence*

In a 5 ml IKA ElectraSyn vial (undivided cell) equipped with a stir bar, $Et_4NBF_4$ (65 mg, 0.3 mmol) and cortexolone (**1c**) (156 mg, 0.45 mmol) were placed. Then, 3 mL of MeCN and 75 µL of water were added and the vial was capped with the cell head, equipped with a standard IKA Electrasyn graphite anode and a stainless steel cathode. The suspension was stirred for 10 min and then a constant current of 5 mA was applied under a stirring speed of 1000 rpm. After 4 F/mol of charge had been passed the electrical current was stopped. Then, the electrochemical cell was immersed in an ice/acetone bath (-15 °C) and a freshly prepared solution of $NaBH_4$ (17 mg, 1 equiv) in 1 mL MeOH was added to the crude electrolysis reaction mixture under vigorous stirring. After 3 h, the reaction was quenched with an excess of water and extracted with DCM. The organic phase was dried over $Na_2SO_4$, filtered and evaporated under reduced pressure, yielding 4-androstenediol (**5**) (100 mg 76 %) as a white solid. M.p. 105-106 °C (lit.[33] 32 84-85 °C); $^1$H NMR (300 MHz, $CDCl_3$) δ 5.30 - 5.29 (d, 1H) , 4.18 - 4.13 (m, 1H), 3.66 - 3.60 (m, 1H), 2.21 – 2.15 (m, 1H), 2.06 - 2.00 (m, 2H), 1.80 - 1.71 (m, 4H), 1.58 - 1.50 (m, 4H), 1.47 - 1.38 (m, 3H), 1.32 -1.27 (m, 3H) 1.07 (s, 3H), 1.04 - 0.83 (m, 2H), 0.77 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 147.4 123.5, 81.8, 67.9, 54.6, 50.7, 42.9, 37.4, 36.6, 36.0, 35.4, 32.6, 32.1, 30.5, 29.5, 23.4, 20.6, 18.9, 11.1. MS (ESI+) m/z: 332 (M + $H^+$ + MeCN); IR (ATR, $cm^{-1}$) 2647, 2919, 2846, 1732, 1659, 1614, 1226, 1055, 1015, 870. These data are in agreement with those reported previously in the literature.[33]

## 5.6 One-pot synthesis of adrenosterone from hydrocortisone via a two-step anodic oxidation sequence

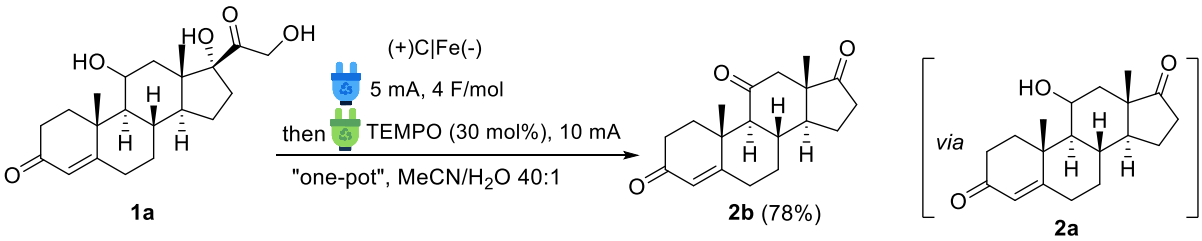



*Figure 30: One-pot synthesis of adrenosterone (2b) from hydrocortisone (1a) via a two step anodic oxidation sequence*

In a 5 ml IKA ElectraSyn vial (undivided cell) equipped with a stir bar, $Et_4NBF_4$ (65 mg, 0.3 mmol) and hydrocortisone (**1a**) (54 mg, 0.15 mmol) were placed. Then, 3 mL of MeCN and 75 µL of water were added and the vial was capped with the cell head, with a standard IKA Electrasyn graphite anode and a stainless steel cathode attached. The suspension was stirred for 10 min and then a constant current of 5 mA was applied under a stirring speed of 1000 rpm. After 4 F/mol of charge had been passed, TEMPO (28 mg, 30 mol%) and a solution of 16 mg of Na2CO3 in 75 µL of water were added to the vial. The cell current was increased to 10 mA and the mixture was electrolyzed with an additional 25 F/mol. Then, the electrical current was stopped, and the crude reaction mixture was evaporated under reduced pressure. The residue was diluted with a saturated aqueous solution of $NaHCO_3$ and extracted with DCM. The organic phase was dried over $Na_2SO_4$ and evaporated under reduced pressure, yielding adrenosterone (**2b**) (35 mg, 78%) as a white solid. M.p. 206-208 °C (lit.[20] 214-217 °C); $^1$H NMR (300 MHz, DMSO) δ 5.66 (s, 1H), 2.60 - 2.56 (m, 1H), 2.46 - 2.37 (m, 3H), 2.24 - 2.00 (m, 10H), 1.67 - 1.56 (m, 2H), 1.35 (s, 3H), 1.33 - 1.27 (m, 1H), 0.75 (s, 3H). $^{13}$C NMR (75 MHz, DMSO) δ 217.6, 209.0, 198.7, 169.4, 124.2, 62.1, 50.4, 50.3, 48.6, 38.3, 36.1, 35.9, 34.4, 33.8, 31.8, 30.9, 21.5, 17.3, 14.8. IR (ATR, $cm^{-1}$) 2909, 1740, 1703, 1663, 1225, 1050, 893. These data are in agreement with those reported previously in the literature.[20]

## 5.7 Simultaneous anodic side-chain cleavage and cathodic catalytic hydrogenation of cortisone

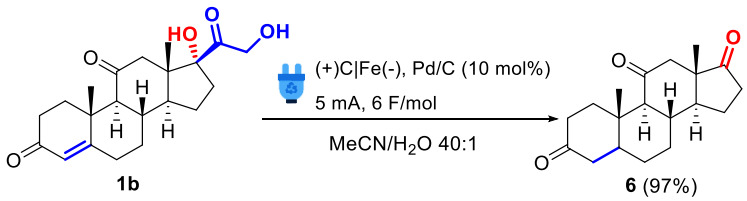



*Figure 31: Simultaneous anodic side-chain cleavage and cathodic cytalytic hydrogenation of cortisone (1b) generating androstane-3,11,17-trione*

In a 5 ml IKA ElectraSyn vial (undivided cell) equipped with a stir bar, $Et_4NBF_4$ (65 mg, 0.3 mmol), cortisone (108 mg, 0.3 mmol) and 10% Pd/C (32 mg, 10 mol%) were placed. Then, 3 mL of MeCN and 75 µL of water were added and the vial was capped with the cell head, with a standard IKA Electrasyn graphite anode and a stainless steel cathode. The cell cap was tightly closed with Parafilm and the suspension was stirred for 10 min. Then a constant current of 5 mA was applied under a stirring speed of 1000 rpm. After 6 F/mol of charge had been passed, the reaction mixture was filtered using a syringe filter and was evaporated under reduced pressure. The residue was diluted with a saturated aqueous solution of $NaHCO_3$ and extracted with DCM. The organic phase was dried over $Na_2SO_4$ and evaporated under reduced pressure, yielding androstane-3,11,17-trione (**6**) as a white solid (88 mg, 97%). The product was obtained as a mixture of the α and β isomers resulting from the hydrogenation. M.p. 176 °C (lit.[34] 174-176 °C); $^1$H NMR (300 MHz, DMSO-$d_6$) δ 2.91 - 2.54 (m, 3H), 2.47 - 2.23 (m, 4H), 2.17 - 2.07 (m, 2H), 1.99 - 1.84 (m, 5H), 1.69 -1.48 (m, 3H)p, 1.43 - 1.19 (m, 3H), 1.15 (s, 3H), 0.72 (s, 3H). $^{13}$C NMR (α-Isomer) (75 MHz, DMSO-$d_6$) δ 217.9, 210.5, 210.2, 51.1, 50.5, 50.4, 49.2, 49.0, 44.9, 42.2, 37.4, 36.3, 35.8, 34.6, 25.9, 24.9, 21.5, 14.8, 14.8. $^{13}$C NMR (β-Isomer) (75 MHz, DMSO-$d_6$) δ 217.7, 212.1, 209.7, 63.2, 50.5, 50.4, 50.4, 46.4, 44.2, 37.9, 36.7, 36.2, 36.0, 35.4, 30.9, 28.0, 22.4, 21.6, 11.3. IR (ATR, cm$^{-1}$) 3448, 2929, 1738, 1702, 1664, 1224,1049, 1015. These data are in agreement with those reported previously in the literature.[35]

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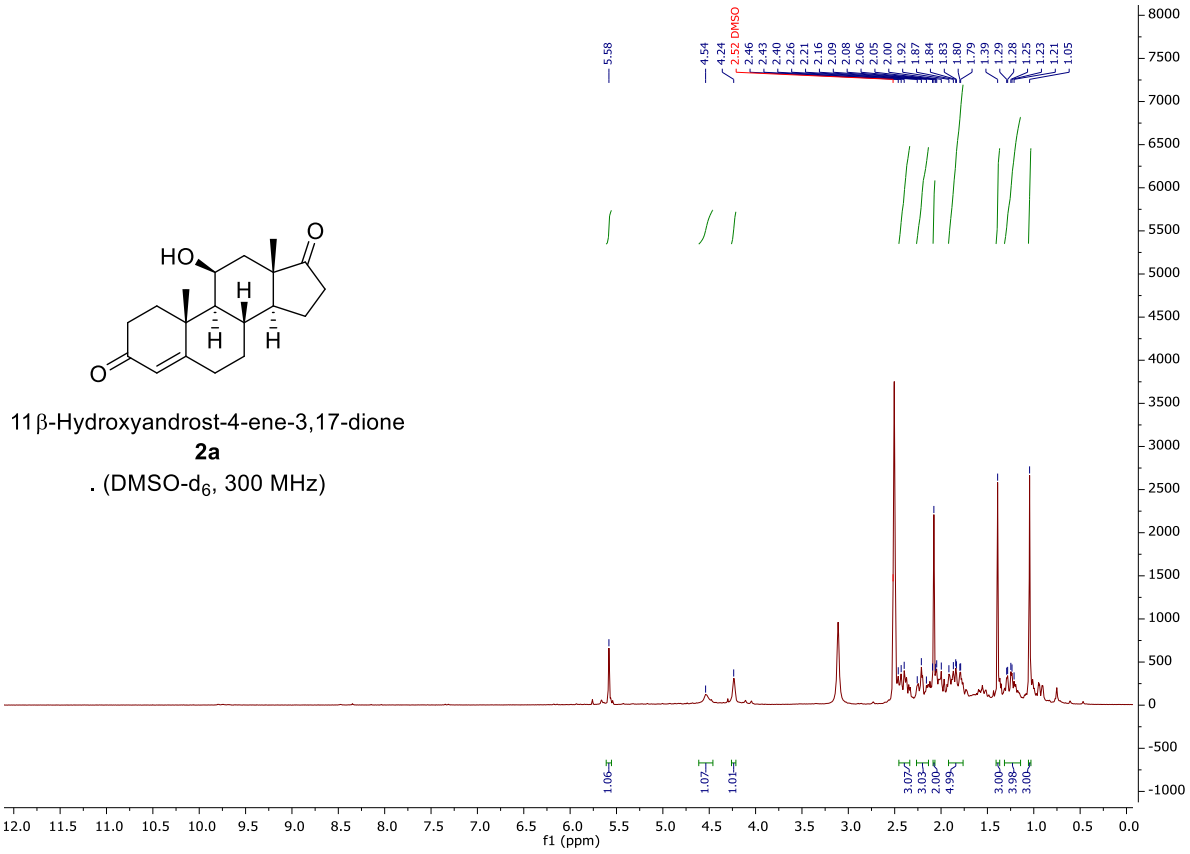
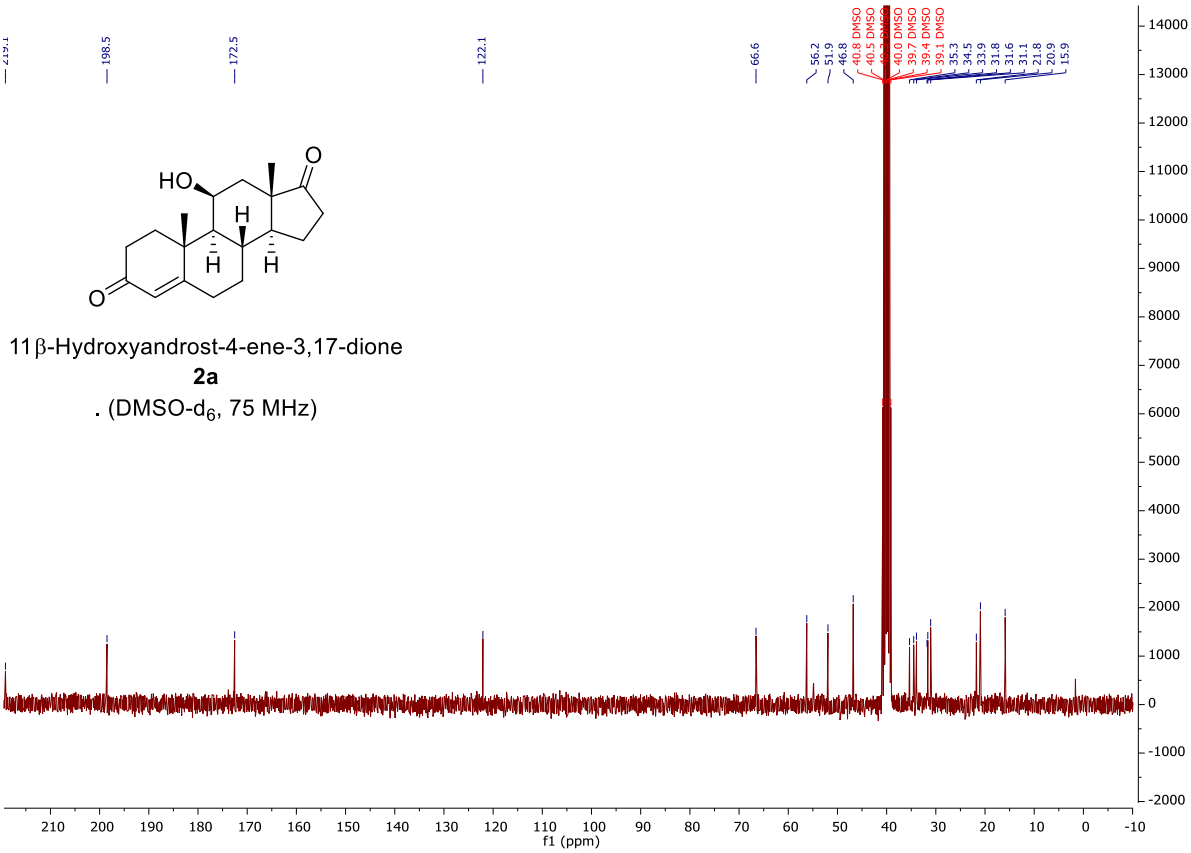
# 7 Appendix


HO
O
O
H
H
H
11β-Hydroxyandrost-4-ene-3,17-dione
2a
. (DMSO-d6, 300 MHz)
f1 (ppm)


HO
O
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H
H
H
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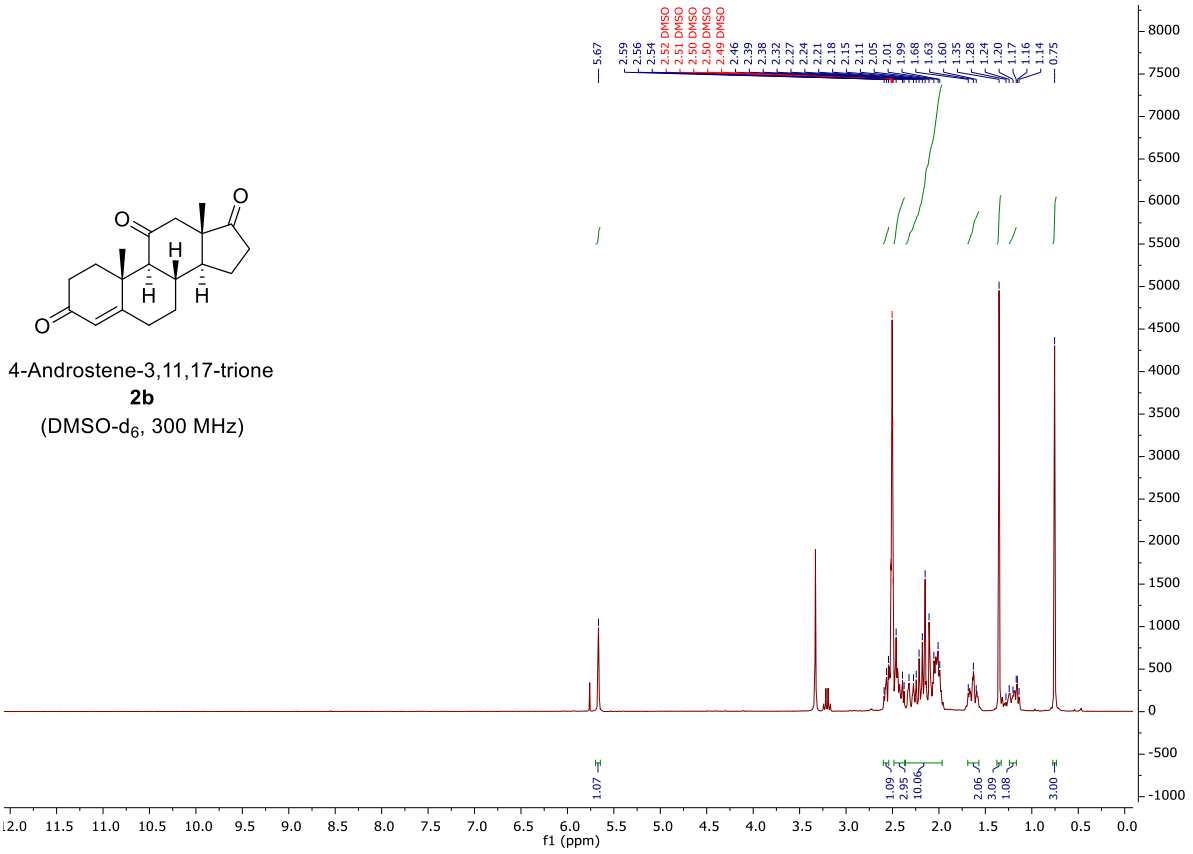
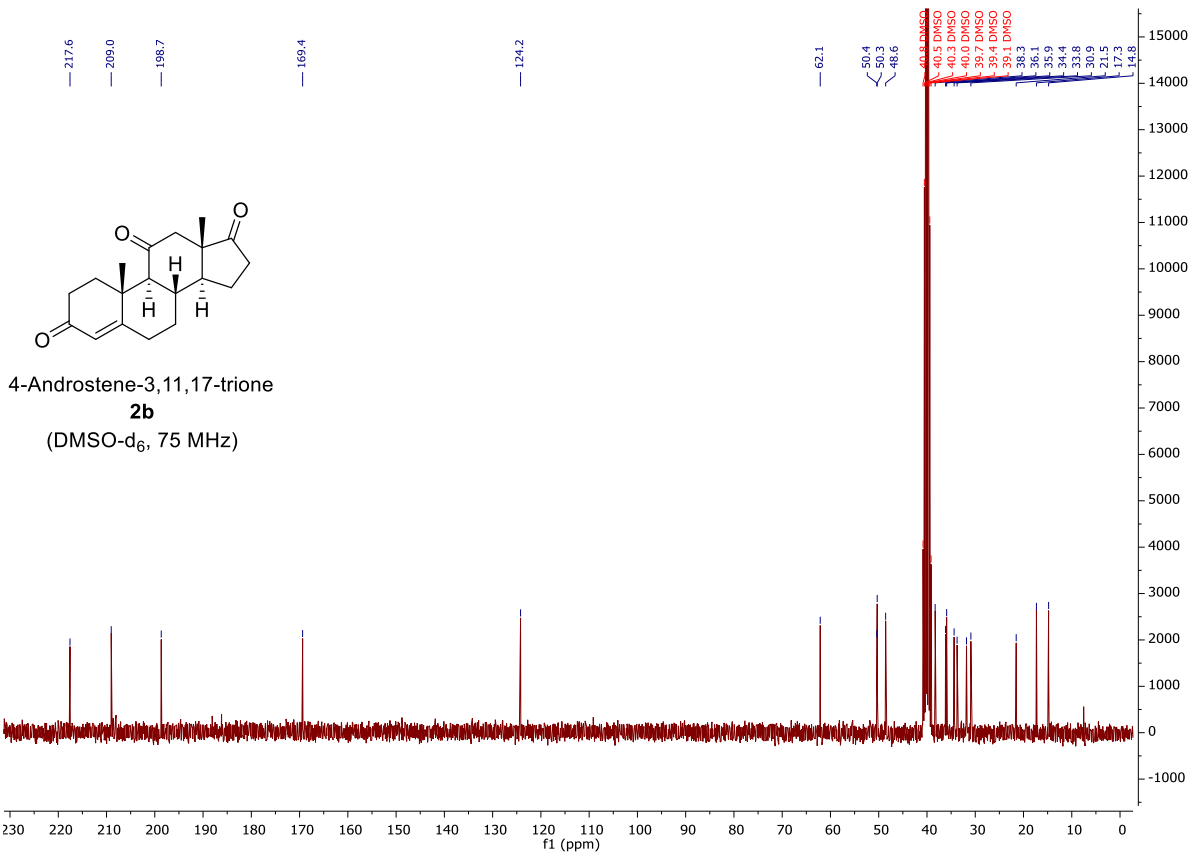
2a
. (DMSO-d6, 75 MHz)
f1 (ppm)




4-Androstene-3,11,17-trione

**2b**

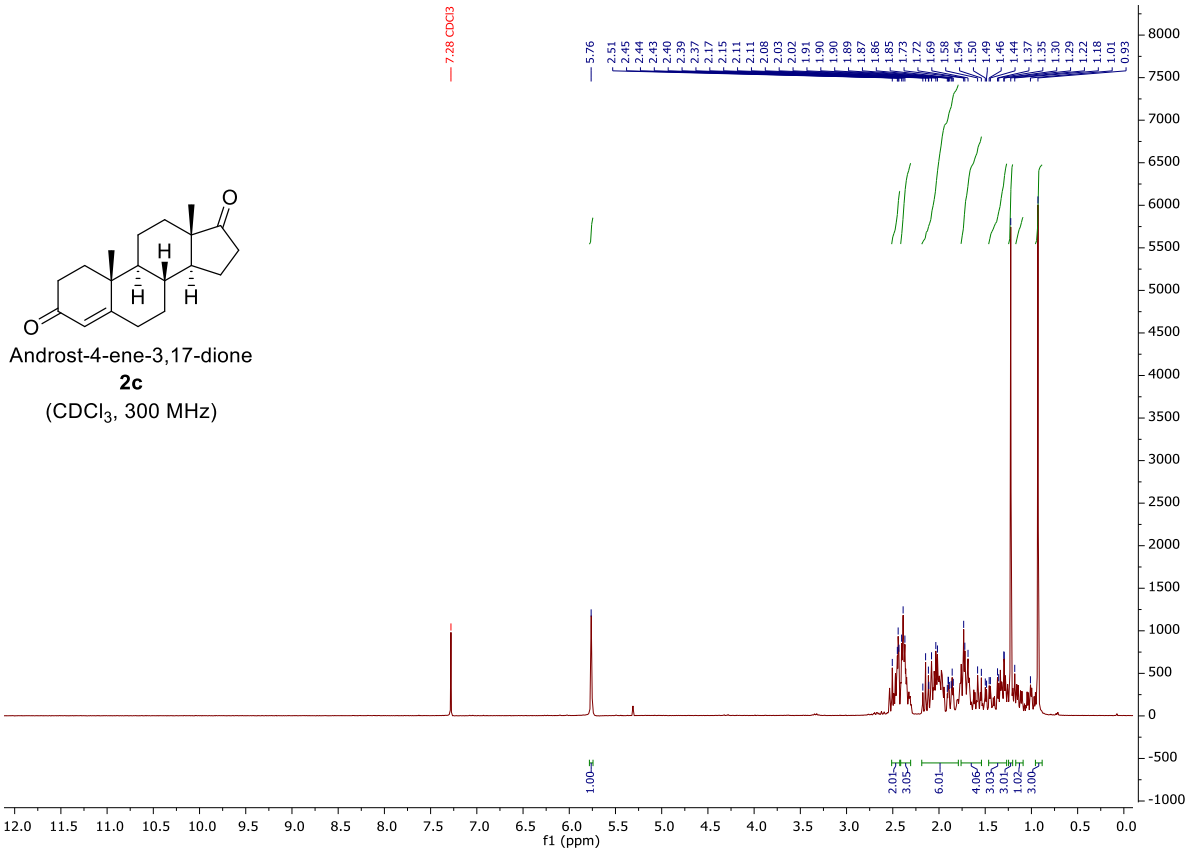
(DMSO-$d_6$, 300 MHz)




4-Androstene-3,11,17-trione

**2b**

(DMSO-$d_6$, 75 MHz)






Androst-4-ene-3,17-dione

**2c**

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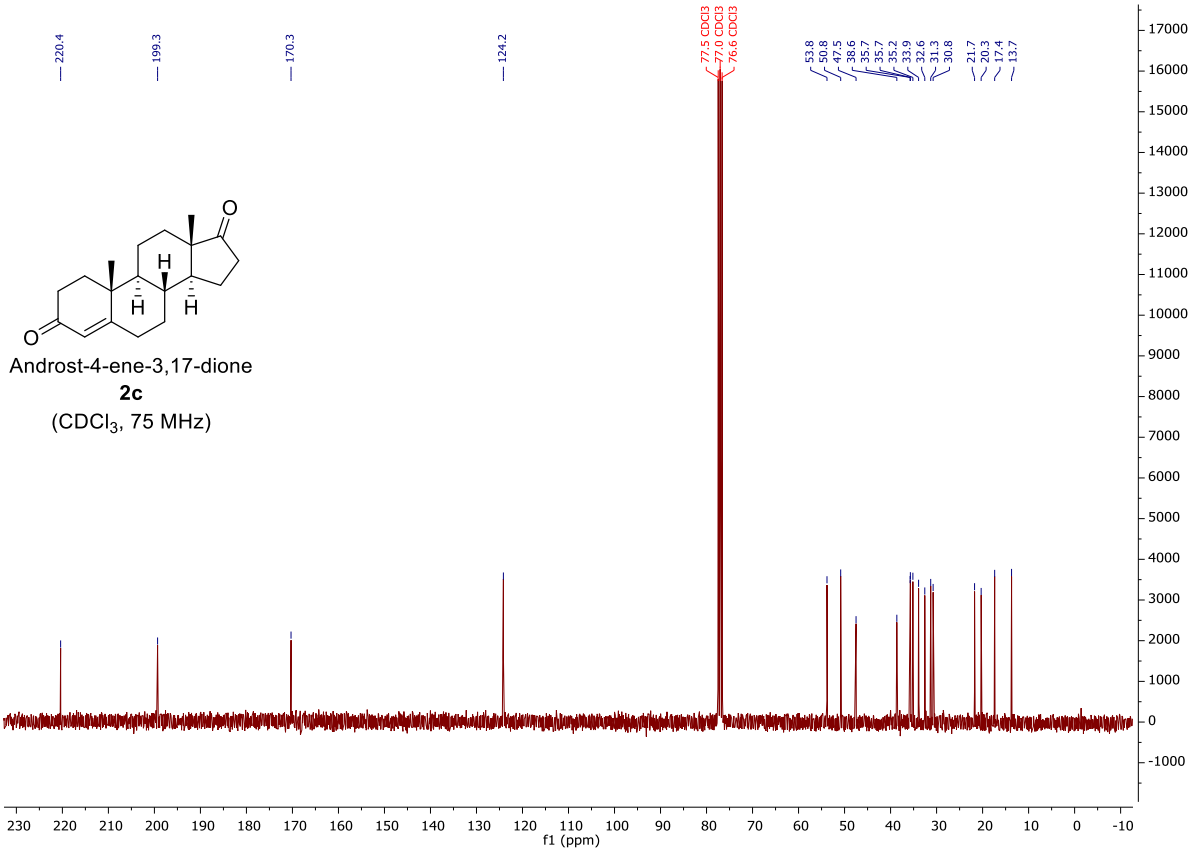
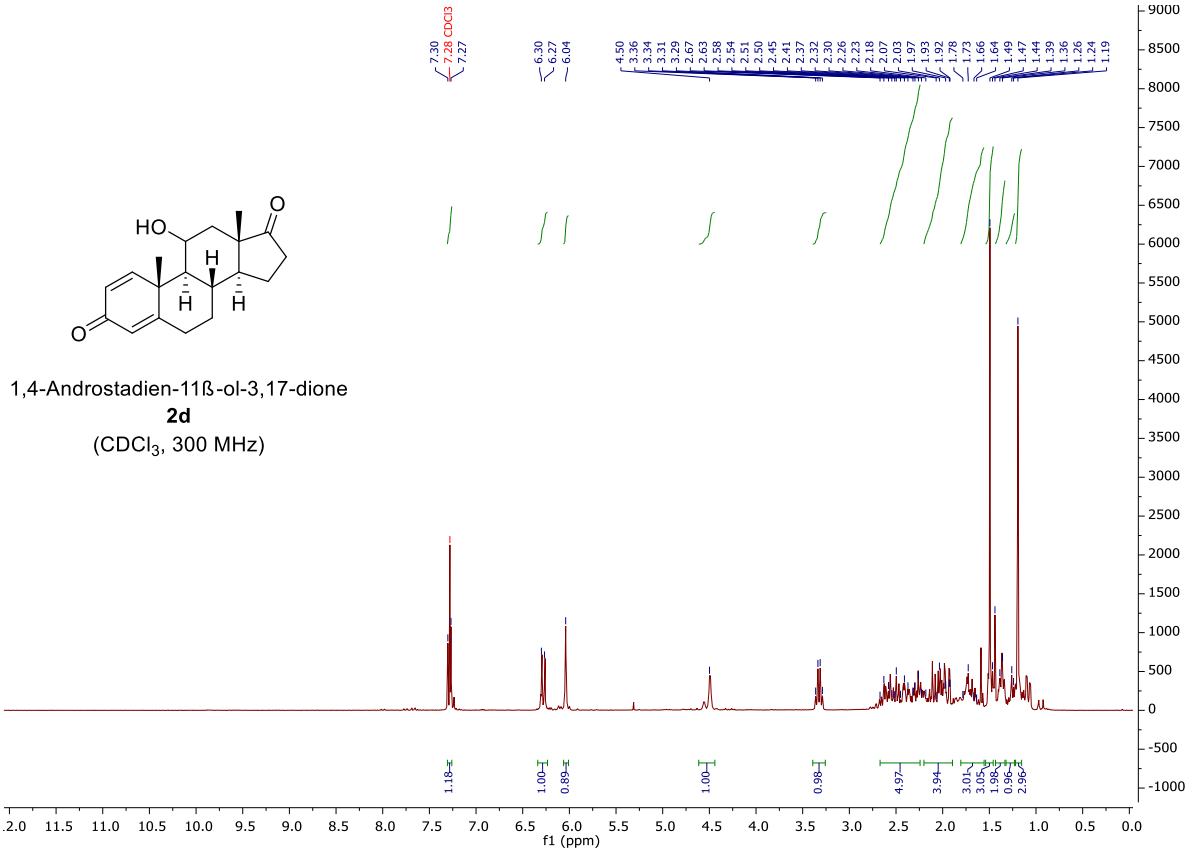





Androst-4-ene-3,17-dione

**2c**

($CDCl_3$, 75 MHz)




1,4-Androstadien-11ß-ol-3,17-dione

**2d**

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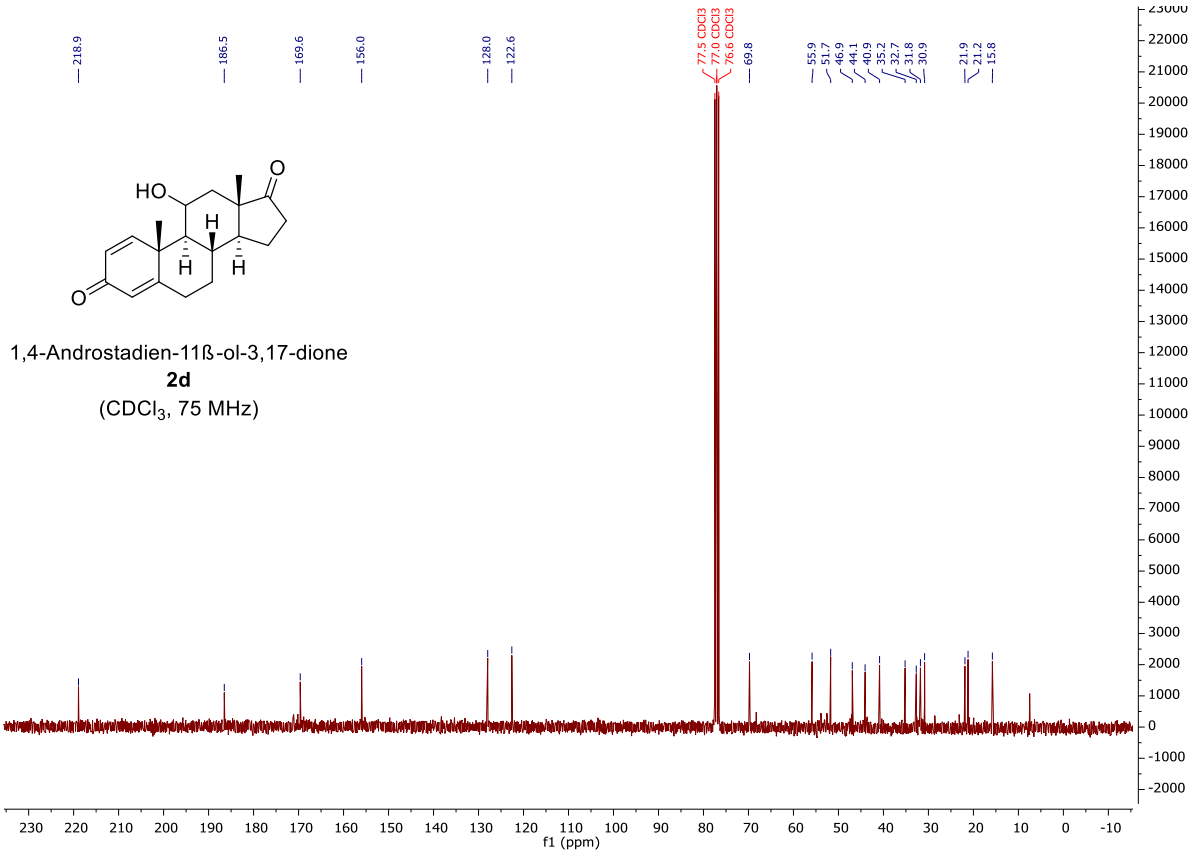


1,4-Androstadien-11ß-ol-3,17-dione

**2d**

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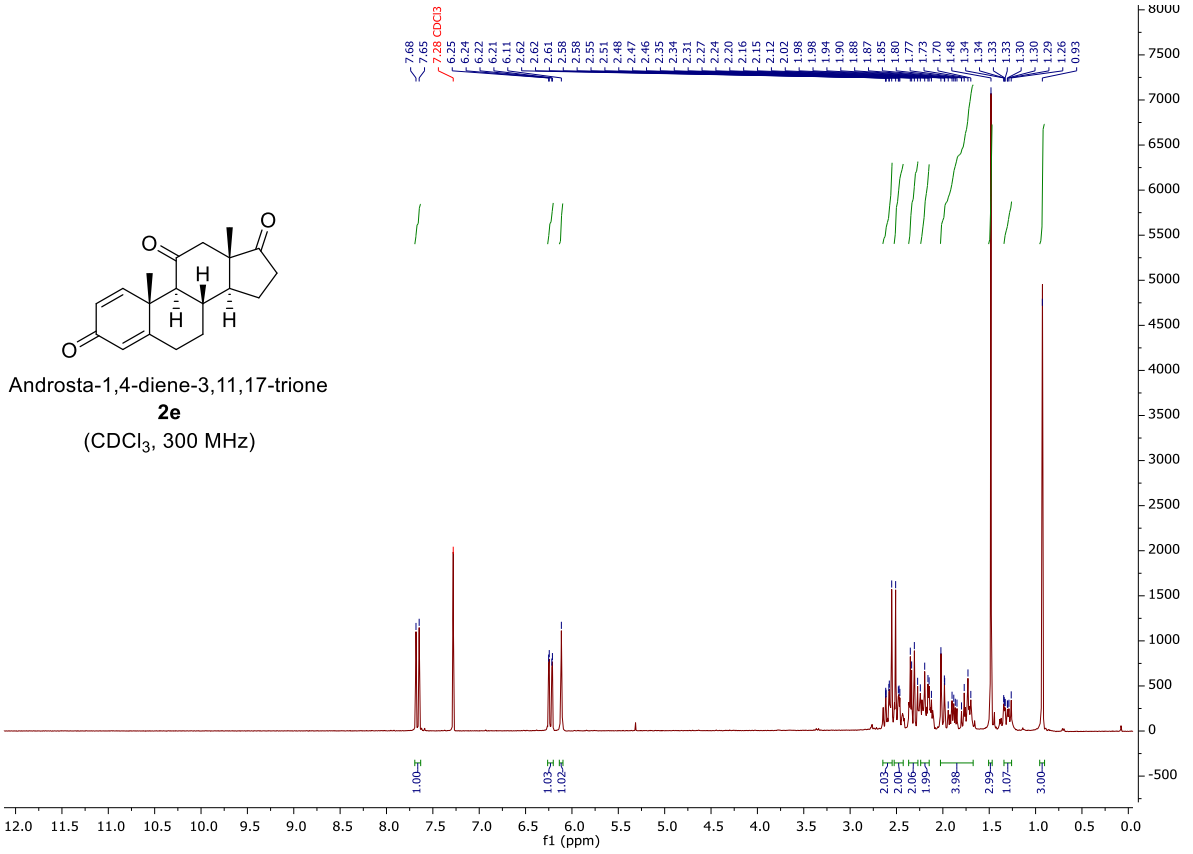
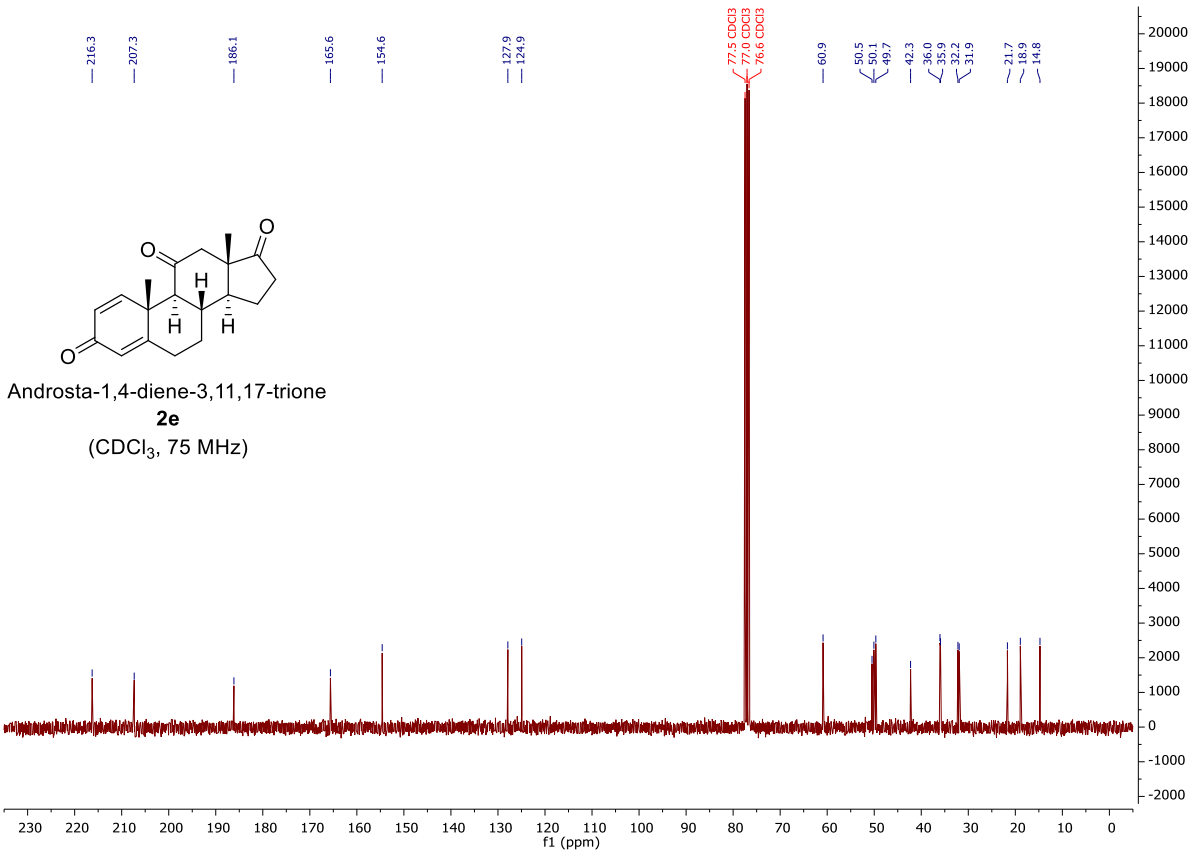
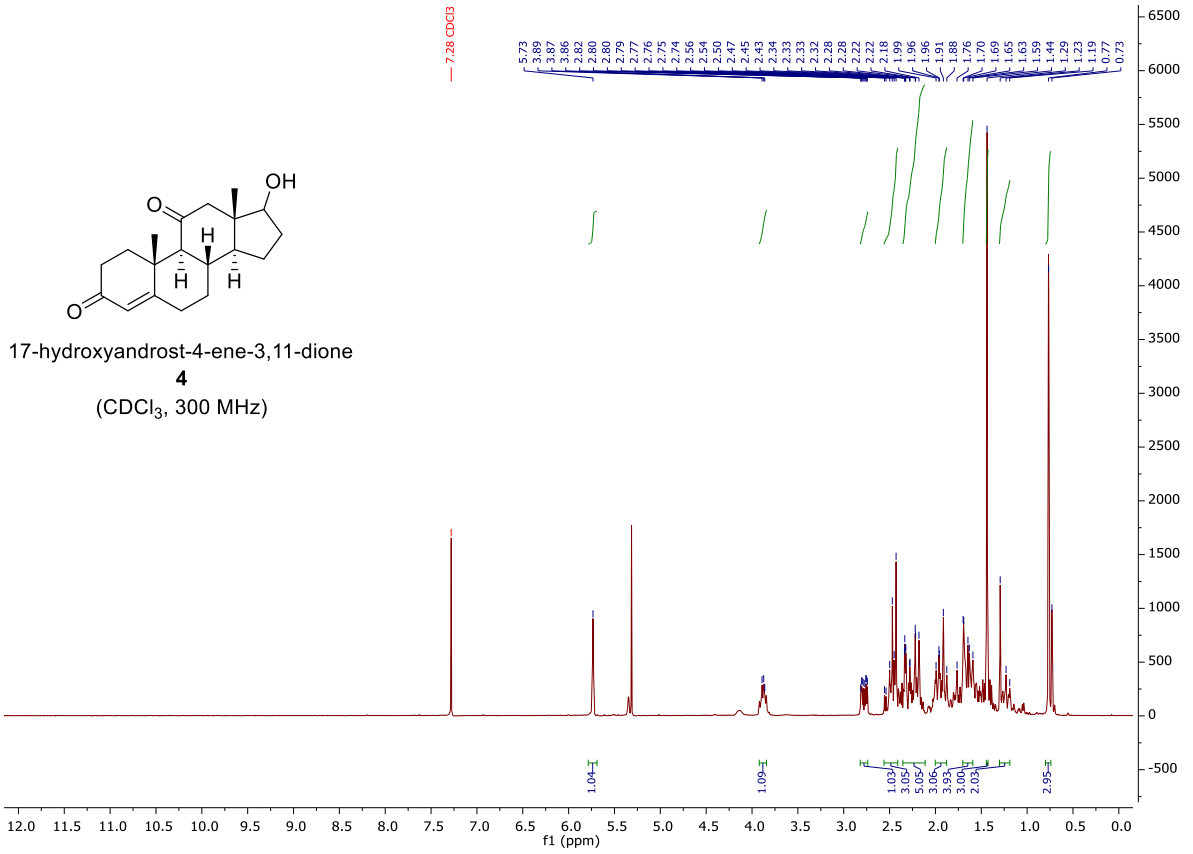


Androsta-1,4-diene-3,11,17-trione
**2e**
($CDCl_3$, 300 MHz)



Androsta-1,4-diene-3,11,17-trione
**2e**
($CDCl_3$, 75 MHz)



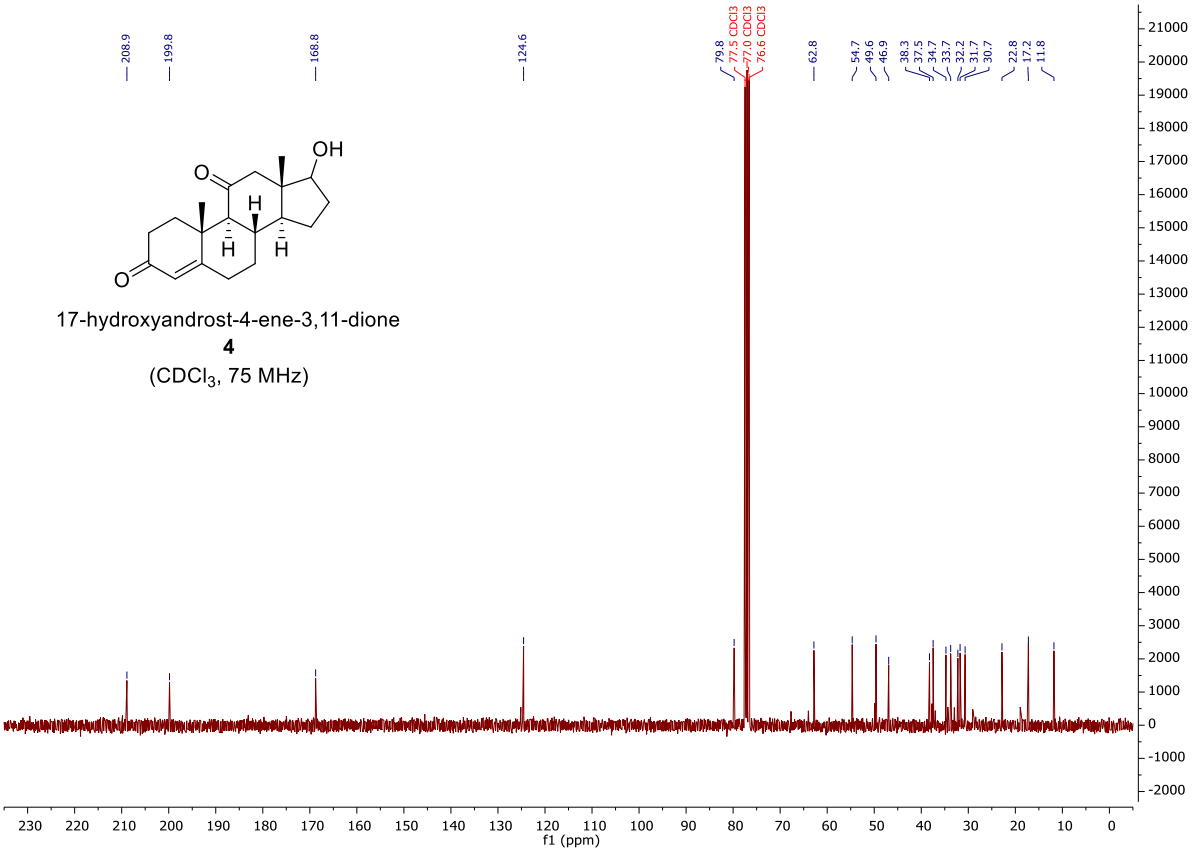




17-hydroxyandrost-4-ene-3,11-dione

**4**

($CDCl_3$, 300 MHz)



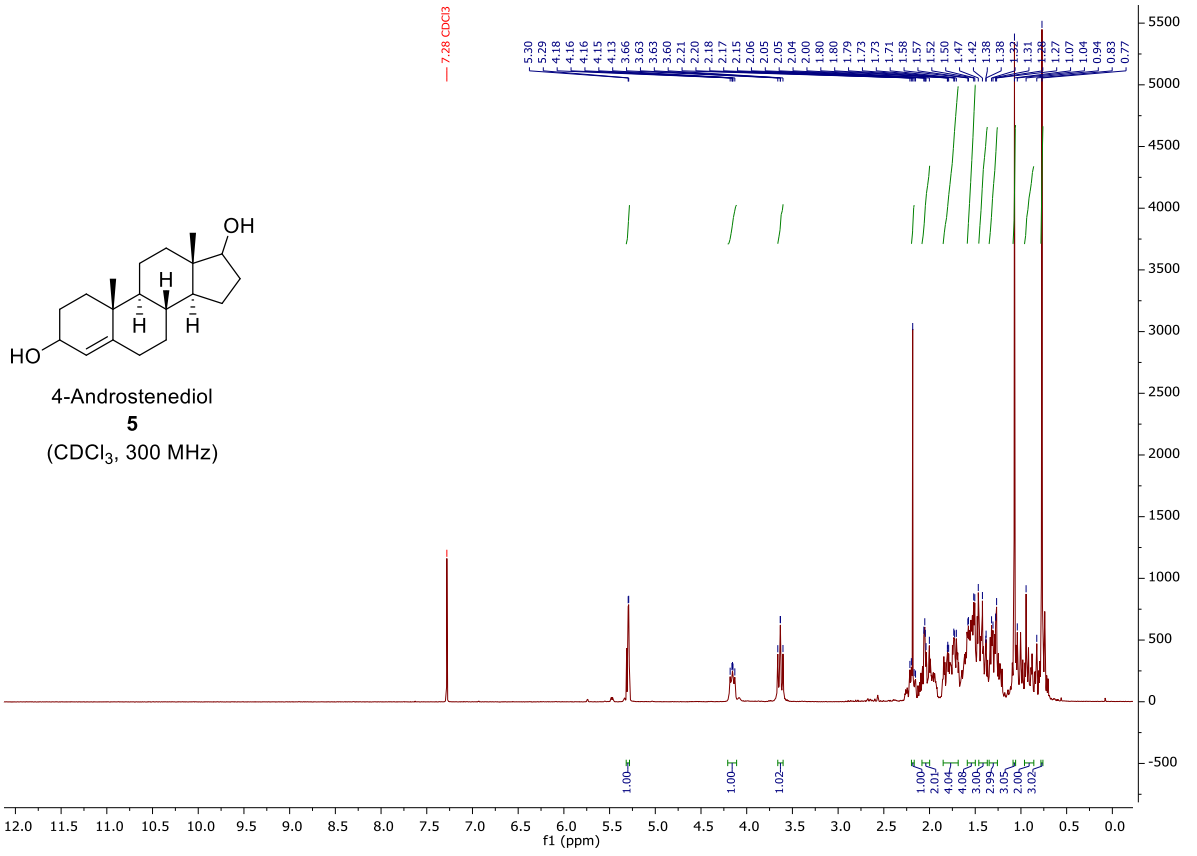




17-hydroxyandrost-4-ene-3,11-dione

**4**

($CDCl_3$, 75 MHz)




4-Androstenediol

**5**

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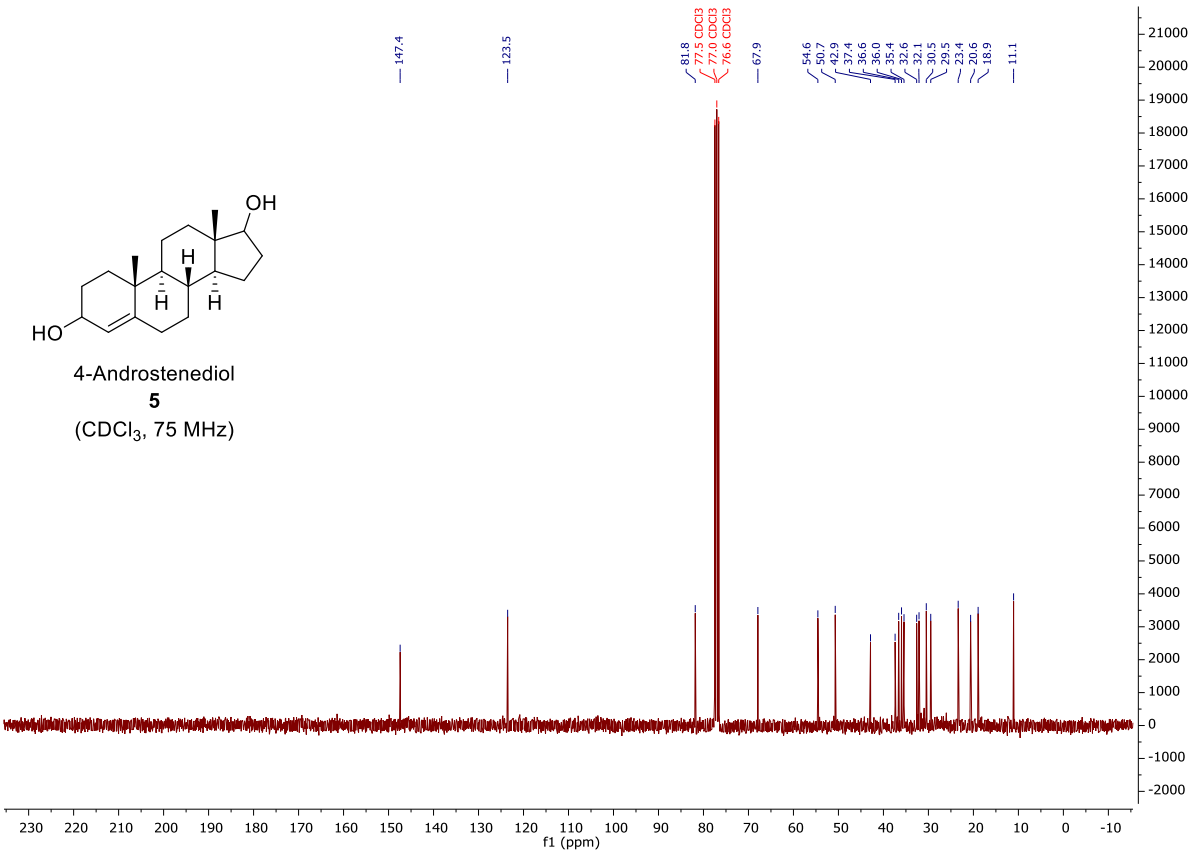
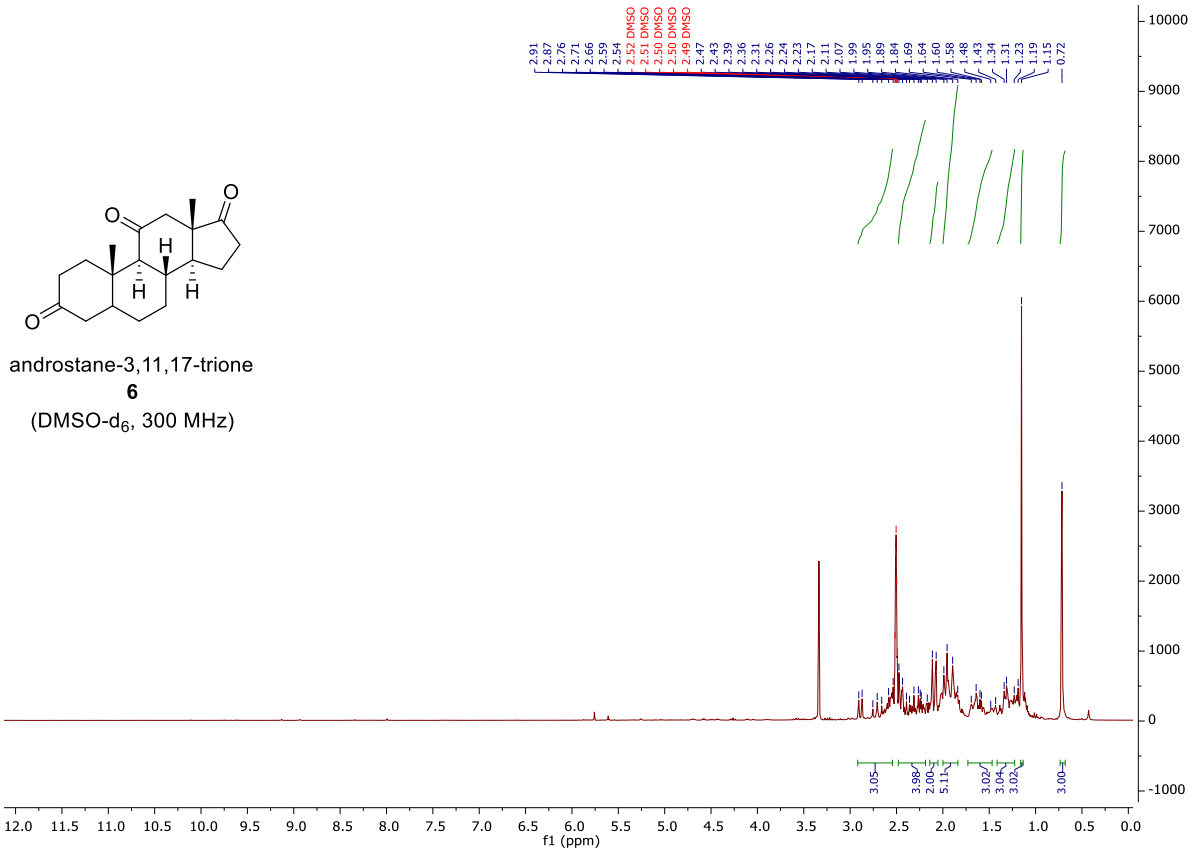
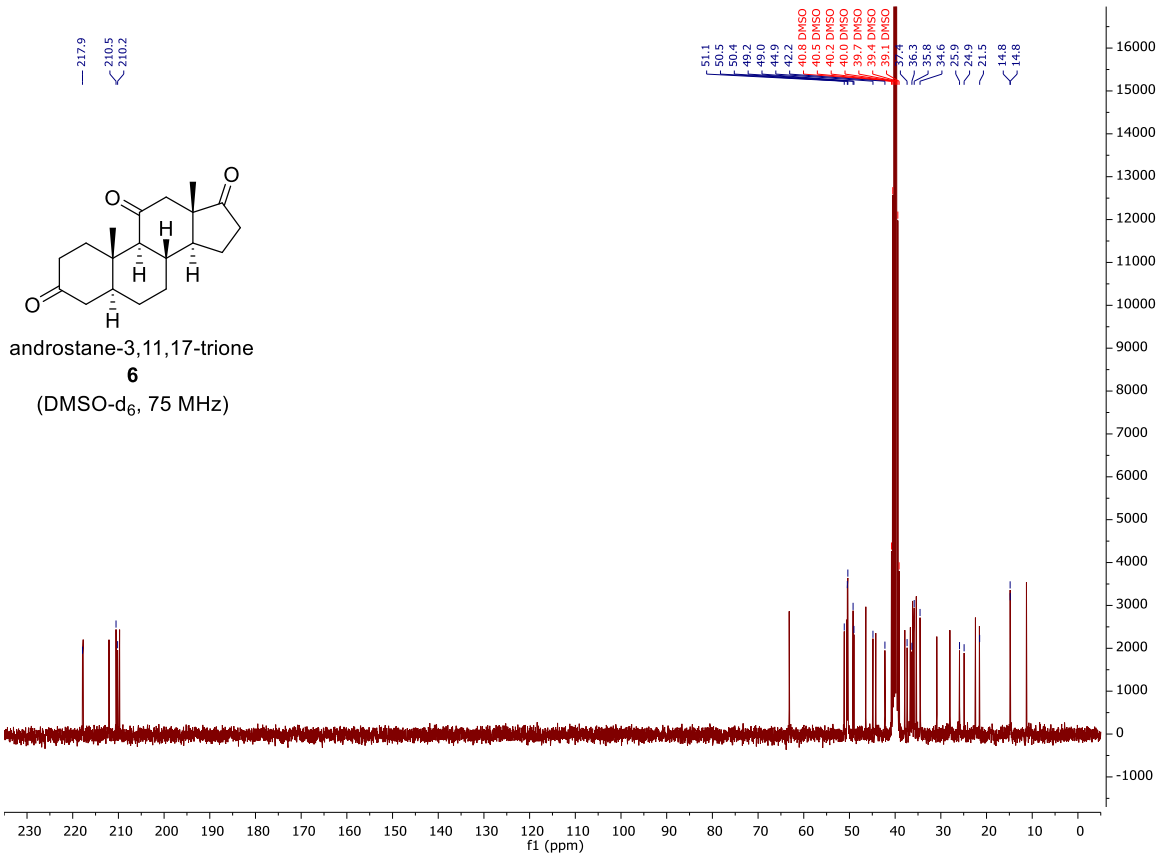



4-Androstenediol

**5**

($CDCl_3$, 75 MHz)


androstane-3,11,17-trione
6
(DMSO-d6, 300 MHz)
f1 (ppm)


androstane-3,11,17-trione
6
(DMSO-d6, 75 MHz)
f1 (ppm)