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Master Thesis

Synthesis of 20βOH-NorMD, a long-term urinary metandienone metabolite

Submitted at the

Institute of Applied Synthetic Chemistry
of the Vienna University of Technology

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> Do the difficult things while they are easy and do the great things while they are small. A journey of a thousand miles must begin with a single step.
>
> Lao Tzu

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1 Introduction

The goal of this thesis was a good-yielding chemical synthesis of a metandienone metabolite which is of interest in doping analysis. Compound 20βOH-NorMD (IUPAC: 17β-hydroxymethyl-17α-methyl-18-norandrosta-1,4,13-triene-3-one) has been identified as a long-term urinary metabolite which can be detected and attributed to metandienone up to almost 3 weeks after exposure. The structure is depicted in Figure 1.

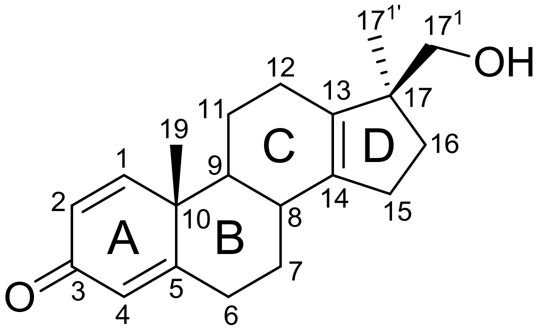
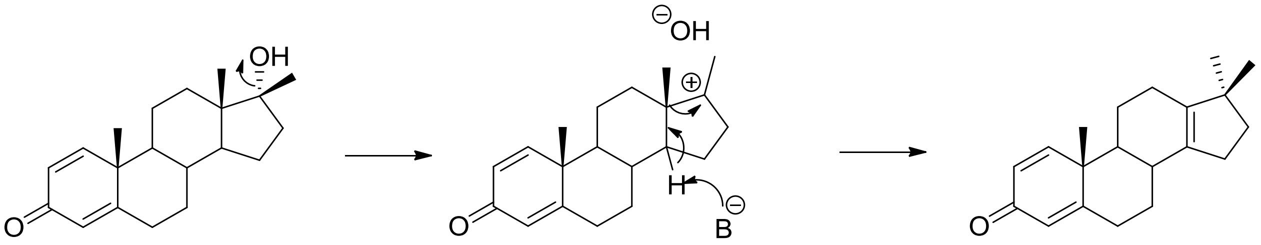


Figure 1.

The nature of this metabolite and the reason why it is traceable for such a long time lie within MD's ability to undergo not only enzymatic transformations *in vivo*, but also a Wagner-Meerwein rearrangement of the 13-methyl with consecutive elimination to give rise to a 17-dimethyl analogue which can be further hydroxylated at either methyl (Scheme 1.).[1]



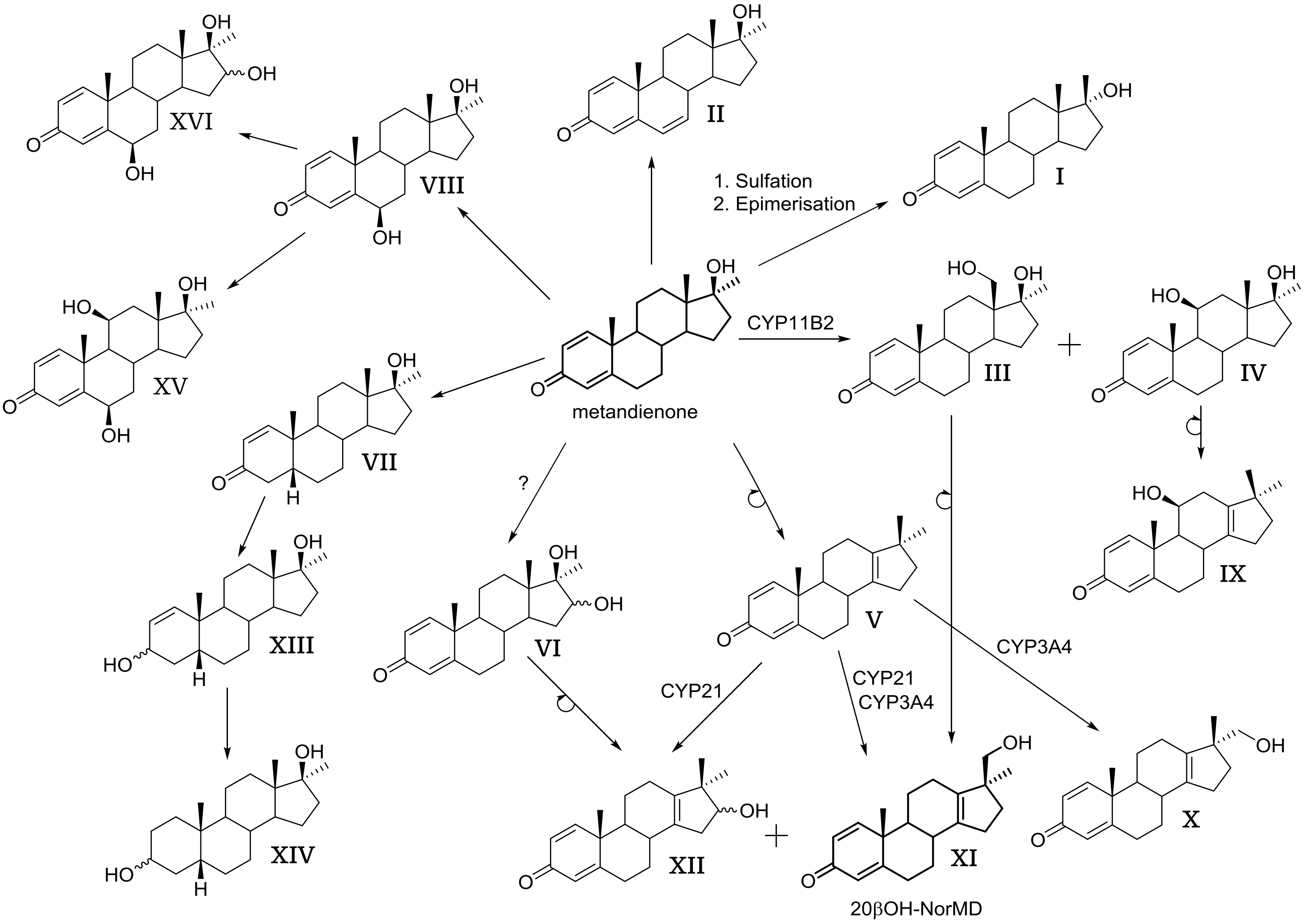
Scheme 1.

The chemical synthesis of the other isomer: 20αOH-NorMD has been described before by Parr et al in 2012.[2] Zöllner *et al.* reported a chemoenzymatic way to 20βOH-NorMD but no chemical synthesis was yet published.[3]

2 State of the art

2.1 Metandienone metabolism

Metandienone is an anabolic androgenic steroid (AAS) that is used to improve performance of athletes and is prohibited by the World Anti-Doping Association (WADA). It was first synthesized by Vischer *et al.*[4] in 1955 and the first metabolite (compound VIII) was found by Rongone and Segaloff in 1963.[5] Since then the metabolism of this important AAS has been extensively studied.[6,7,8,9,10,11]



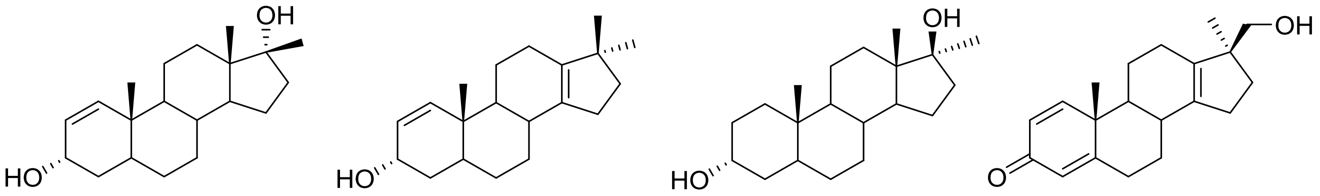
Scheme 2.

The most important metabolites are depicted in the scheme above. Two interesting reactions that can occur on a variety of different metabolites are sulfation of the 17-hydroxy group which leads to hydrolysis in urine and subsequent epimerisation of this carbon (e.g. I)[8] and Wagner-Meerwein rearrangement to the 18-normetandienone derivatives (e.g. V, IX).

Urinary excretion occurs through glucuronidation or sulfation of the hydroxyl functionalities (Phase II metabolites). These metabolites can be traced back to their Phase I counter-parts by enzymatic cleavage with β-glucuronidase and subsequent GC/MS analysis.[7]

Most of the metabolites in Scheme 2 are excreted within a week at most. There's evidence that sulphate conjugation and epimerisation can prolong detectability. For example the sulphate conjugate of 20βOH-NorMD is detectable up to 26 days after a single administration of 5 mg metandienone.

Below some prominent metabolites of MD and their detection limits are depicted. Before the discovery of XI, XIV was used as a long-term metabolite. The two epimers X and XI have identical retention times.



XIII
7 days

XVIII
5 days

XIV
5 days

XI
19 days

Figure 2.

2.2 20βOH-NorMD discovery and analysis

The metabolite was first discovered by Schänzer *et al.* in 2006.[12] Before this work the focus lay on hydroxylated metabolites, which were derivatized and analysed *via* GC/MS to identify metandienones presence in doping specimen. In his work Schänzer used liquid chromatography coupled with tandem mass spectrometry and found a new metabolite.

The compound was isolated by solid-phase extraction of urine specimens, extraction with TBME (to remove unconjugated steroids) and column chromatography. Additionally 17-trideuteromethyl metandienone was also administered and the deuterated metabolite was isolated in the same fashion.

GC/MS/MS analysis was done after derivatization as TMS ether.

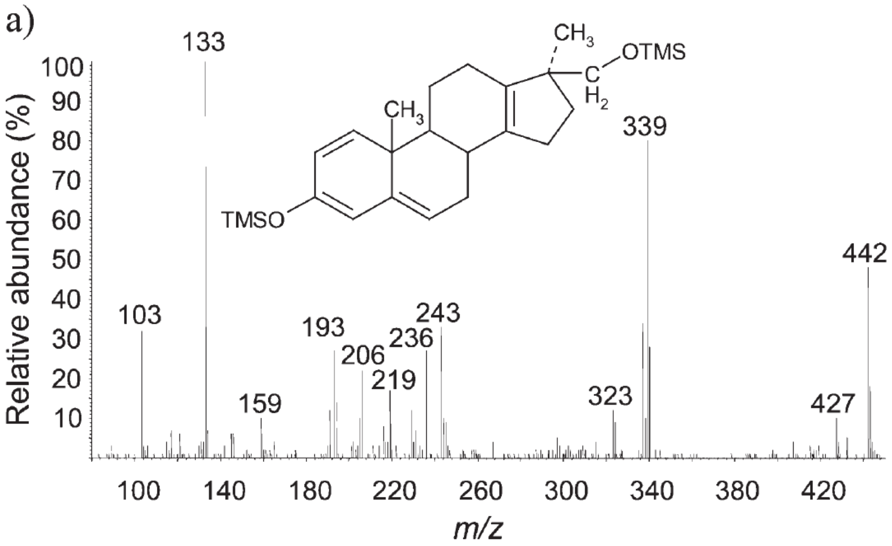
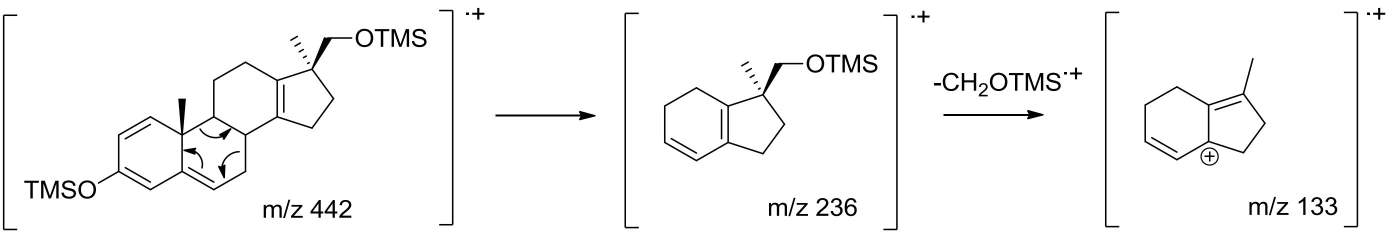


Figure 3.

M/z 133 was suggested to be originating from a loss of CH_2OTMS-radical after a retro Diels-Alder takes place at the C ring (Scheme 3.).



Scheme 3.

This proves that hydroxylation took place on one of the 17-methyls. Moreover the deuterated metabolite shows a shifted m/z of 239 instead of 236.

Since all three deuterium atoms are present no hydroxylation of the deuterated methyl group took place. This defines the stereochemistry on C-17.

The structural confirmation of its A/B-ring structure was obtained by LC/ESI-MS(/MS) analysis using high-resolution/high-accuracy measurements as well as low resolution tandem MS (Figure 4).

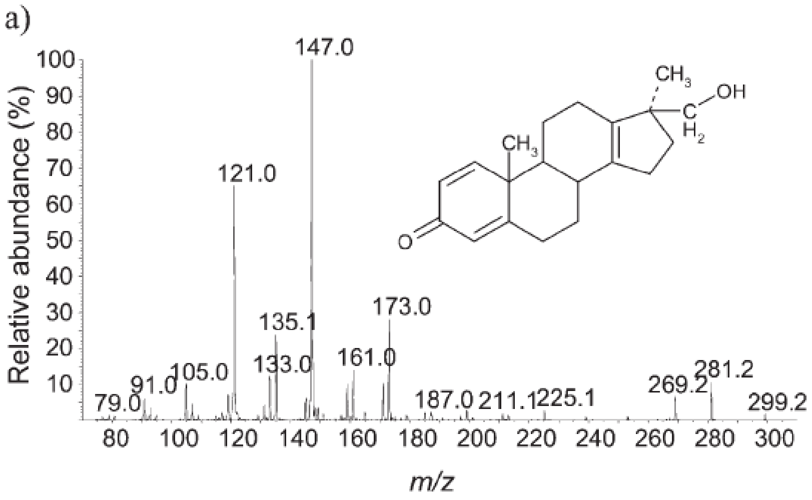


Figure 4.

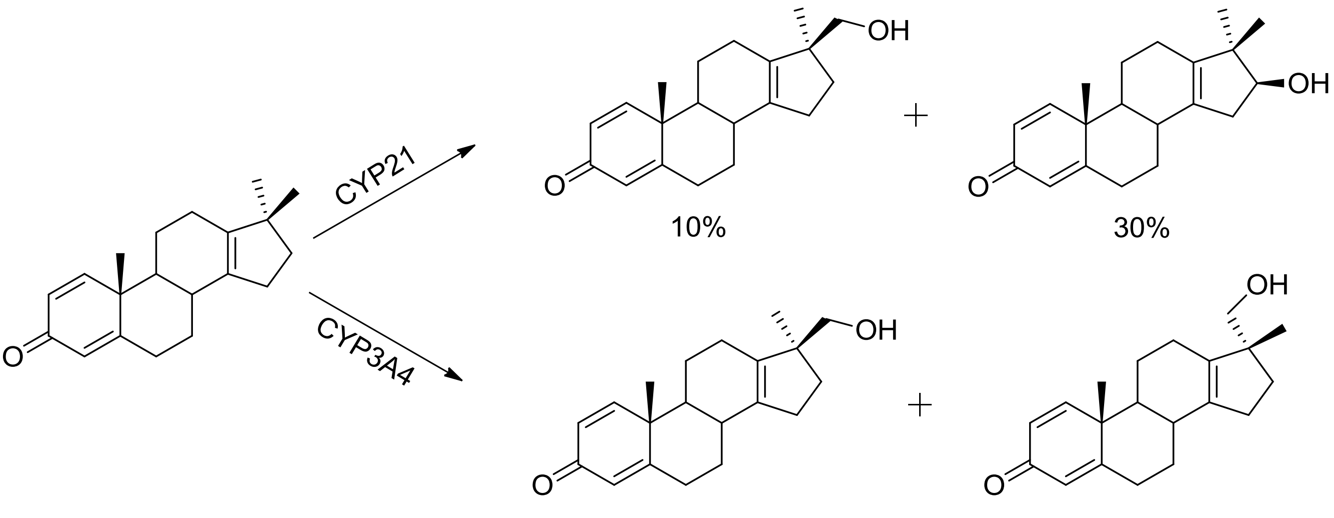
M/z 121, 135.1 and 147 indicate 1,4-dien-3-one functionality, this ensures the A/B-ring structure is derived from metandienone. Hydroxylation is indicated again by m/z 269.2 which stems from neutral loss of formaldehyde of the protonated species m/z 299.2

2.3 Enzymatic synthesis of 20βOH-NorMD

Cytochromes P450 (abbreviation: CYP) are responsible for a variety of different metabolic reactions and can react with very different substrates. Their purpose is biodegradation of xenobiotics during first-pass metabolism in the liver. Reactions include dealkylation, hydroxylation, sulfoxidation, epoxidation and deamination. They are of great interest in many fields of research and can also be utilised in synthesis.

In 2010 Zöllner *et al.* presented an enzymatic transformation that gave access to 20βOH-NorMD.[3] Eleven hepatic or steroidogenic CYPs (CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A7*2, CYP4Z1, CYP11B1, CYP11B2, CYP17 and CYP21) were tested by recombinant expression through fission yeast strains. After a screening essay it was confirmed that CYP21 and CYP3A4 (most abundant in the human liver and responsible for 6β-hydroxylation of testosterone) metabolize the substrate to the desired product.

Additionally CYP21 forms larger quantities of a 16β-hydroxylated side-product and CYP3A4 can transform either methyl into a hydroxymethyl moiety (Scheme 4). In another work by Zöllner it was confirmed that the 17β-hydroxymethyl epimer is formed preferably.[2]



Scheme 4.

CYP2C19 transformed the substrate into a different metabolite although no structural elucidation was performed due to lack of significant amounts of material.

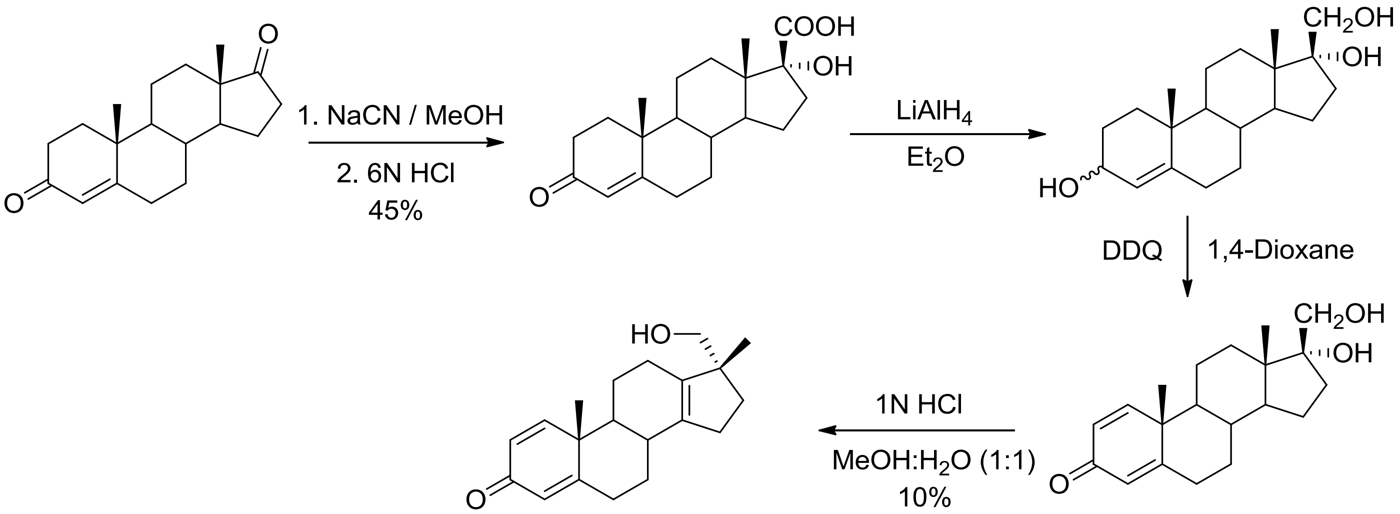
The actual synthesis was carried out in a 5L fed-batch fermentation experiment using the CYP21 expressing strain CAD 75. Glucose levels were held at 1 g/L during the growth period and increased when substrate was added (in two portions of 150 mg at an interval of 24 hours). The optimal substrate concentration was evaluated in previous experiments to be between 175 and 225 µM, higher concentrations resulting in CYP inhibition. Product formation was monitored by GC/MS with metandienone as the internal standard. After five days the product concentration was constant at about 10% and 30% of the byproduct was formed.

After fermentation the product was extracted with ethyl acetate and final purification was done *via* semi-preparative HPLC. The best results were obtained using a $N(CH_3)_2$ column with *n*-hexane:isopropanol as solvent system. Thus they obtained 17β-hydroxymethyl-17α-methyl-18-norandrosta-1,4,13-triene-3-one as well as 16β-hydroxy-17,17-dimethyl-18-norandrosta-1,4,13-triene-3-one in pure form (10 mg each).

The fact that 20αOH-NorMD was found in urine samples after metandienone administration proves the involvement of CYP3A4 in the synthesis of 20βOH-NorMD in humans. The *in vivo* involvement of CYP21 was shown by Parr in 2012 by synthesis of 16βOH-NorMD as reference material and comparison with urine samples.

2.4 Chemical synthesis of 20αOH-NorMD

In 2012 Parr and Zöllner[2] reported a synthesis of the 17-epimer 20αOH-NorMD from androst-4-ene-3,17-dione:



Scheme 5.

Selective addition to the 17-carbonyl could be achieved by precipitation of the wanted androstenedione cyanohydrine from the solution as described by Nitta *et al.*[13] After hydrolysis with 6N hydrochloric acid the impurities were easily removed by extraction at basic pH. The product was isolated by extraction under acidic conditions.

Reduction with lithium aluminium hydride gave a mixture of both diastereomers of 17β-hydroxymethylandrost-4-en-3β,17α-diol. This was oxidised with DDQ in dioxane under inert atmosphere to introduce the 1,4-dien-3-one functionality.

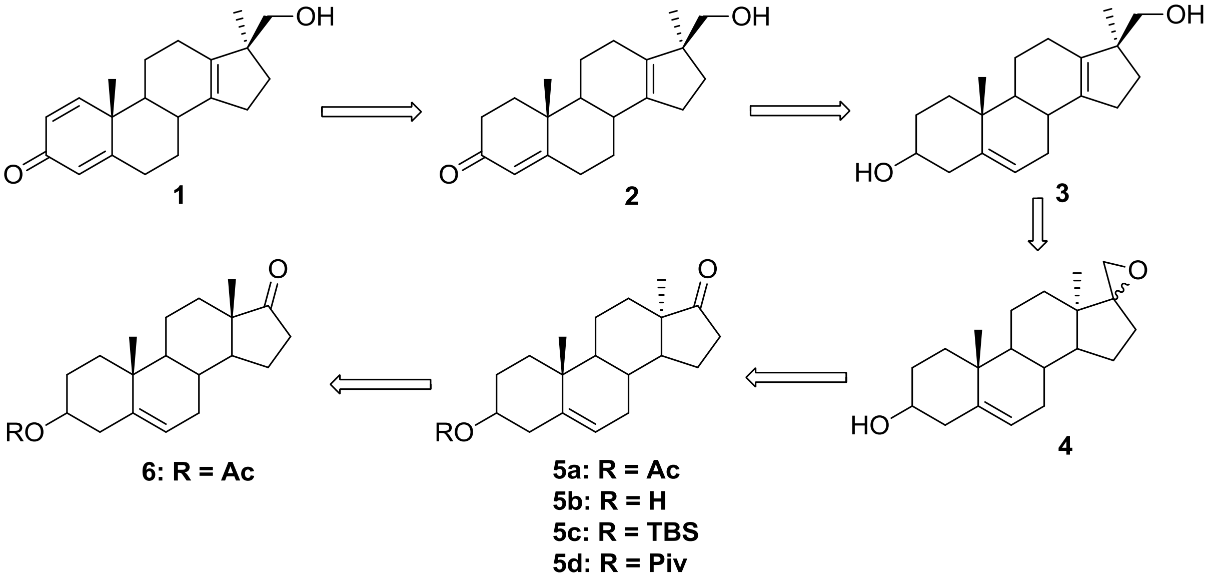
The final step was the Wagner-Meerwein rearrangement which was performed with hydrochloric acid in methanol/water. Roughly one gram of raw product from this reaction was purified by column chromatography with hexanes/ethyl acetate and subsequent crystallisation from hexanes/ethyl acetate to give 87 mg of final product which was characterized with NMR and GC/MS (bis-TMS-derivatized). NOESY experiments confirmed the stereochemistry on C-17.

The reason why a similar route to this was not published for 20βOH-NorMD will be addressed in this work (see 3.2)

3 Own synthetic work

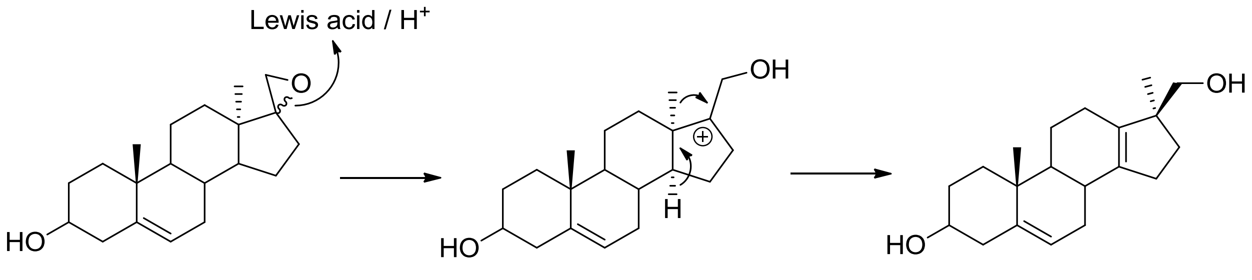
3.1 Retrosynthetic analysis

The goal of this work was an efficient, scalable synthesis of 20βOH-NorMD from commercially available dehydroepiandrosterone acetate. The aforementioned Wagner-Meerwein rearrangement is a useful tool to get to the fully substituted 13-olefin. Since a hydroxyl group has to remain on a 17-methyl an epoxide opening was chosen. An alternative way could be addition of cyanide to the 13α-methyl isomer of dehydroepiandrosterone, like in the synthesis of 20αOH-NorMD, but addition to the 17-carbonyl proved to be very difficult and in most cases no reaction took place or the yield was miniscule.



Scheme 6.

The highest substituted olefin should be, in theory, the favoured product of the rearrangement though full regioselectivity of the rearrangement is not to be expected.



Scheme 7.

The carbocation on C-17 can react to form a variety of products. Elimination can take place from C-12, C-14 and C-16 and a 1,2-hydride shift from C-20 would give the 17-carbaldehyde.

The crucial steps in this synthesis are the isomerisation at C-13 as well as the Wagner-Meerwein rearrangement of the epoxide at C-17/C-20 for the D ring and full oxidation of the 3-OH to the dienone at the A ring. The chronology of these steps can be altered depending on favourable experimental results,

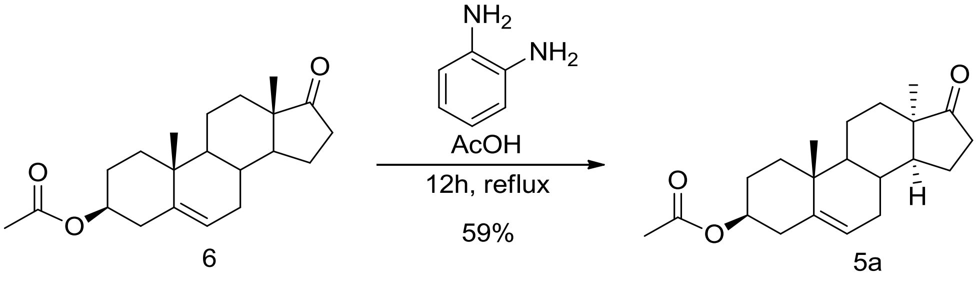
Nevertheless, oxidising the A ring first in this case could lead to problems: Epoxidation can now occur competitively on the 3- or the 17-carbonyl. Although an α,β-saturated ketone should act as a worse electrophile the geometry at C-17 is quite sterically demanding by the cis-configuration of the ring junction as well as the inverted methyl group.

Completing the D ring first also has its challenges: There are some strategies for selective oxidation of secondary alcohols on steroids[14] but oxidation of the 3-OH could form an aldehyde at the primary 20-OH which then needs to be selectively reduced.. Alternatively protecting group strategies could be employed but in any case, some additional steps are necessary.

3.2 Corey-Chaykovsky approach

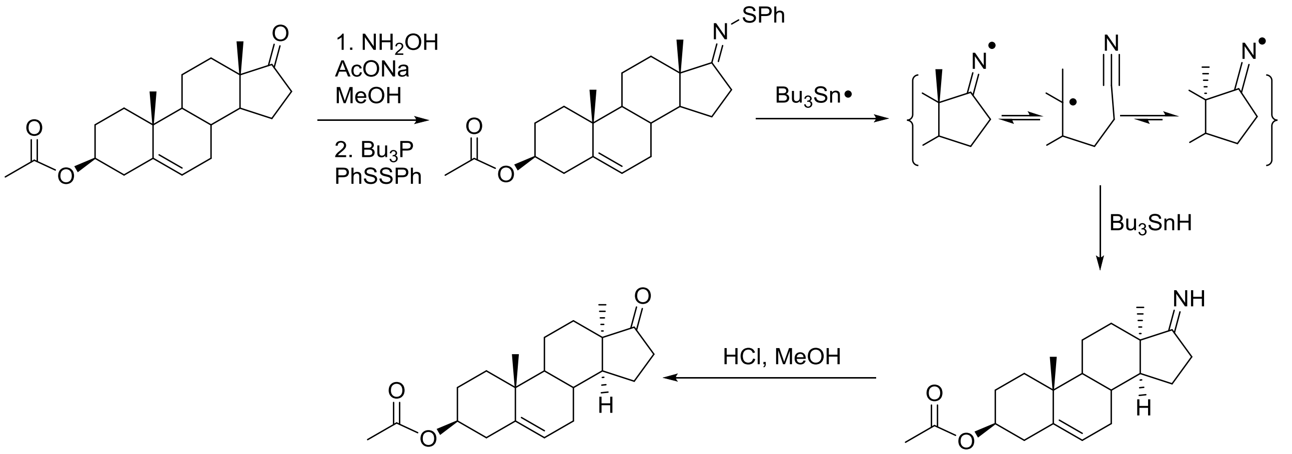
First of all when starting with this project the hypothesis of the Wagner-Meerwein rearrangement needed to be validated as soon as possible. This step is crucial for the construction of the molecule and needs to deliver the right stereochemistry and regioselectivity.

Thus the latter of previously described strategies was chosen and work on the D ring begun by methyl epimerization of dehydroepiandrosterone acetate in acetic acid with 1,2-phenylendiamine.[15]



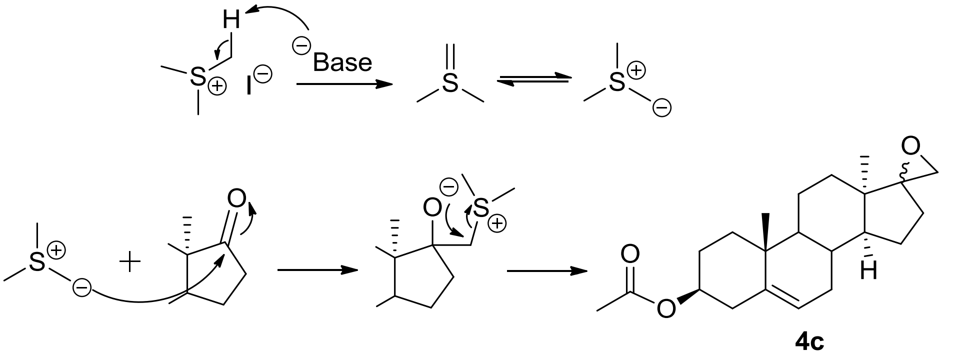
Scheme 8.

The mechanism of this particular reaction has not been extensively explored but the original authors suggested an ion-radical mechanism taking place, indicated by the dark blue color of the boiling solution. In related work Boivin *et al.* present a mechanism for the 13-epimerisation of DHEA with a sulfur-imine under radical conditions.[16]



Scheme 9.

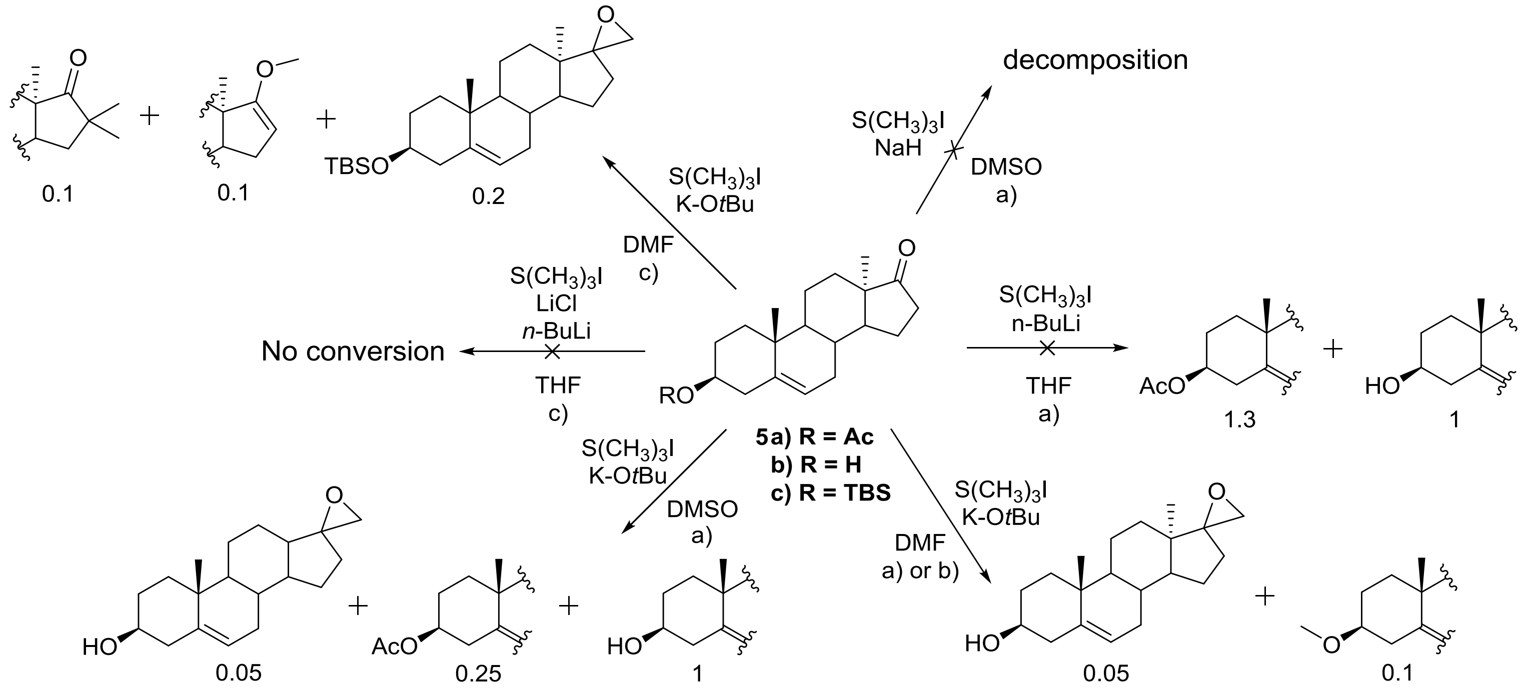
The next step was already the epoxidation of the 17-ketone. The Corey-Chaykovsky reaction[17] uses sulfur ylid chemistry, reminiscing of the Wittig reaction but with a different outcome. The lower oxophilicity of sulfur causes insertion, elimination of the sulfur as divalent species and gives rise to a methylenepoxide. In fact, as depicted in Scheme 10, there is not even the formation of an oxathiethan, the transition state is believed to be a zwitterionic species.



4c

Scheme 10.

A variety of reaction conditions (base, temperature, solvent) was tested on 5a - 5c and most of them gave no conversion, deprotection of the acetate or other side products, none of which were epoxidised (Scheme 11). Deprotection with K_2CO_3 and protection with TBSCl did help with protecting group stability but only moderately pushed the yields from ~10% to ~20% conversion (15% isolated yield at best).



Scheme 11.

The low reactivity of the ketone towards the ylid nucleophile is suspected to stem from the sterically demanding environment as well as good enolizability with strong bases at C-16. A calculated 3D-model of the ketone 5b is depicted in Figure 5.

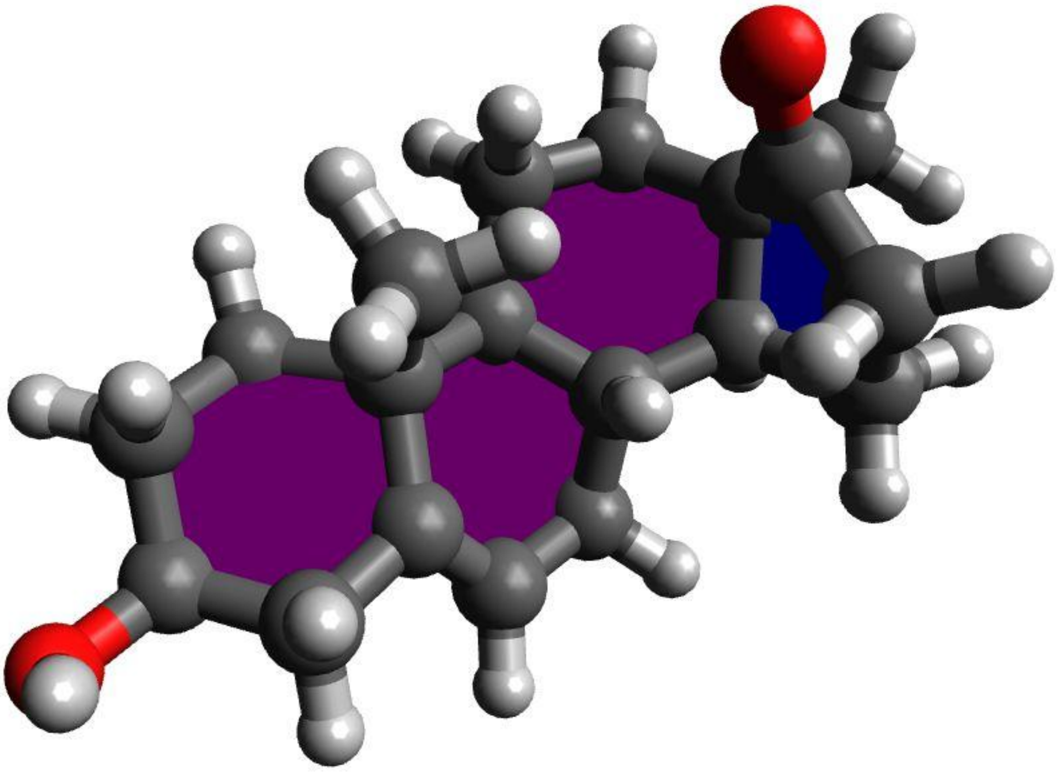
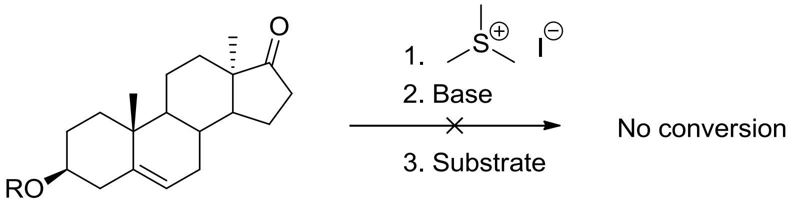


Figure 5.

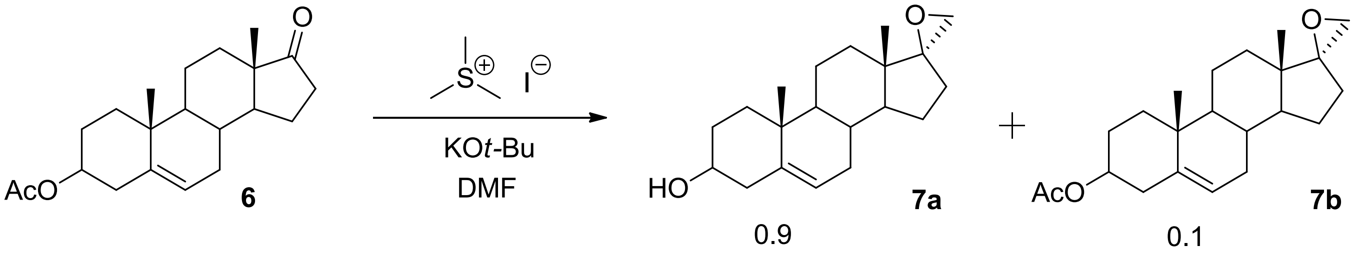
The backside is restricted by the 13α-methyl and the cis-junction of the C/D-rings[18] (13α, 14β half-chair conformation) prevents larger molecules to get into the tight space between the C-19 and the carbonyl. Contrary to this the back side of the corresponding 13β-methylandrostenone is easily accessible. This also provides a plausible explanation as to why no analogous route to Parr's synthesis of 20αOH-NorMD has been published.

The only way to avoid enolization is by preparing the ylid before. Interestingly, there was no reaction observed when the sulfur-ylid was prepared previously to addition of the substrate. Only when the base was added directly to the substrate/reagent solution conversion was observed.



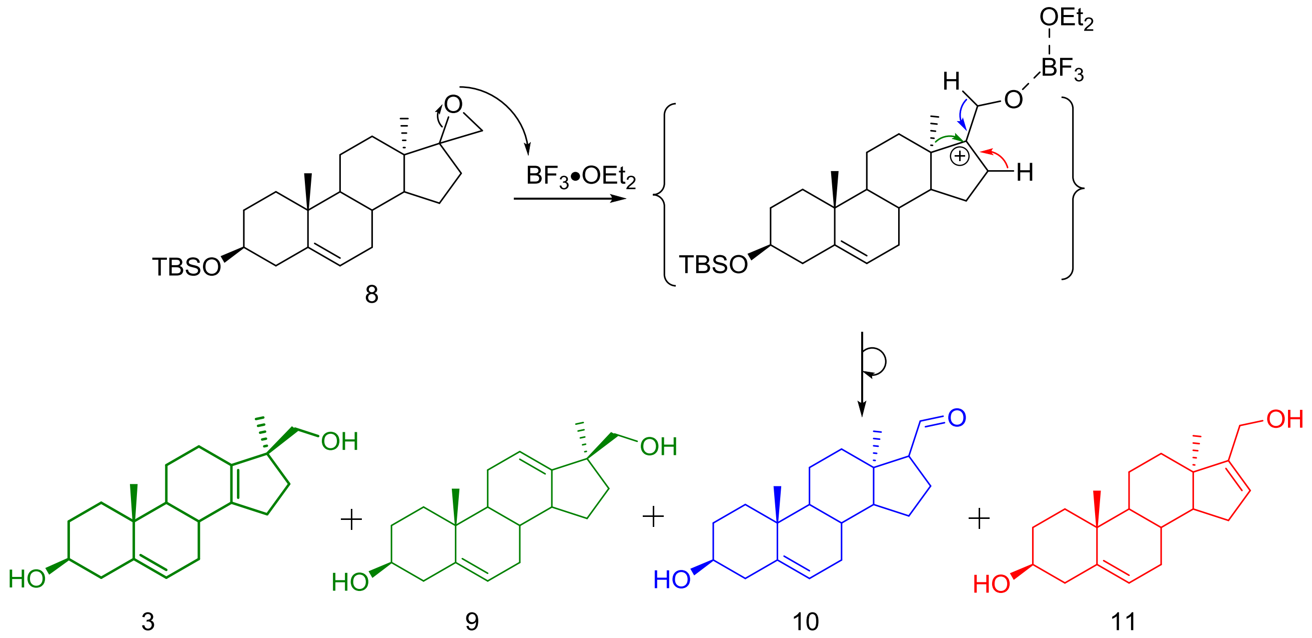
Scheme 12

The same reaction conditions when employed in the reaction of 6 gave – as was expected - full conversion to just one diastereomer of epoxide.



Scheme 13.

At this point it was obvious that this reactivity problem at C-17 has to be addressed some other way as this path resulted in only 15% yield and difficult purification: The 16-dimethyl derivative depicted in Scheme 11 has an R_f value directly between the two diastereomers of the product epoxide. This made the isolation of one of the diastereomers impossible, since no pure fraction could be obtained from chromatography. Another route to get to these spiroepoxides had to be developed in order to produce significant amounts of material.



Scheme 14.

However the synthesized material was used to investigate the Wagner-Meerwein rearrangement in the next step. The first try used $BF_3{\cdot}OEt_2$ as a Lewis acid in THF and gave a complex mixture of products, which was not at all surprising given the number of possible reactions.

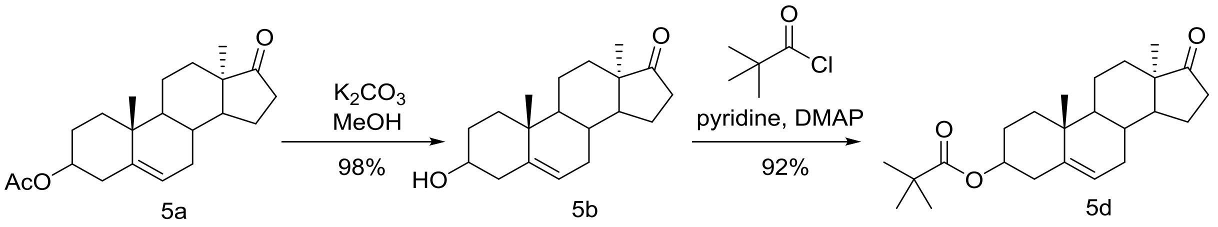
Structures 9-11 were not confirmed as column chromatography yielded mostly mixtures. Diol 3 was isolated and the structure confirmed. The yield of product was very low but these experiments showed that, in principle this reaction can occur as planned. However further optimizations are necessary to maximize the conversion to the desired product.

To prevent oxidation at the newly formed 20-OH selective protection of the primary alcohol was pursued, however a mixture of di-, monoprotected and unprotected ensued which was deprotected completely again. After Oppenauer oxidation under standard conditions (toluene, cyclohexanone, aluminium isopropoxide) was unsuccessful further experiments were not carried out due to lack of material and inefficiency of the route as whole. Thus, other methods to get to the epoxide were investigated.

3.3 Methylenation approach

The idea behind this approach was getting to an *exo*-methylene double bond from C-17 to C-20 and afterwards epoxidize this electron-rich double bond selectively to keep the conjugated olefins intact.

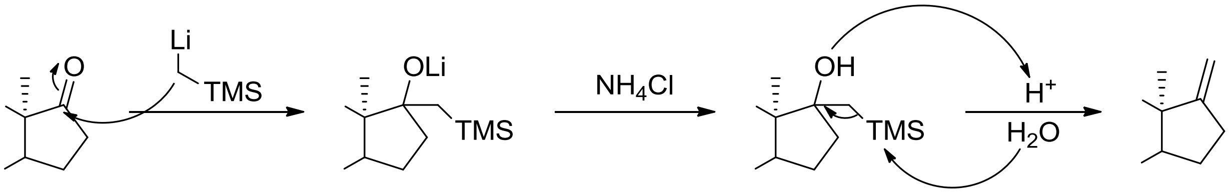
The first few steps were identical: epimerization, then cleavage of the acetate and installing a viable protecting group (in this case pivalate instead of TBS).



Scheme 15.

After this different methylenation strategies were investigated. Wittig reaction was ruled out from the beginning because of the steric bulk of the triphenylphosphin as well as the lack of reactivity towards the sulfur ylid before.

Thus, first Peterson olefination[19] was employed, using (trimethylsilyl)methyllithium. The mechanism for this olefination proceeds over a stable adduct intermediate. Under hydrolysis the olefin is liberated under basic or acidic conditions, the difference being the formed stereochemistry. In this case, as it is a terminal olefin, both methods could be employed.



Scheme 16.

However the adduct was never formed. Under standard literature conditions only starting material was recovered. Ketone activation with anhydrous cerium(III)-chloride as described by Johnson *et al.*[20] as well as a soluble lanthanium(III)-chloride/lithium chloride complex in THF discovered by Knochel *et al.*[21] were unsuccessful. The latter required the corresponding Grignard reagent which was also used in all protocols but to no avail.

A test reaction using cyclohexanone gave full conversion to the product. It is suspected that the TMS group may be too bulky to get close enough to the ketone for addition.

Next the Tebbe[22] and the Nysted[23] reagents were tested, both known in literature to react with demanding substrates and with good functional group tolerance.[24]

Unfortunately Tebbe reagent, probably due to its rather bulky Cp ligands on the titanium, gave no conversion.

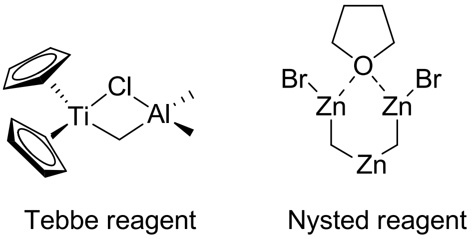
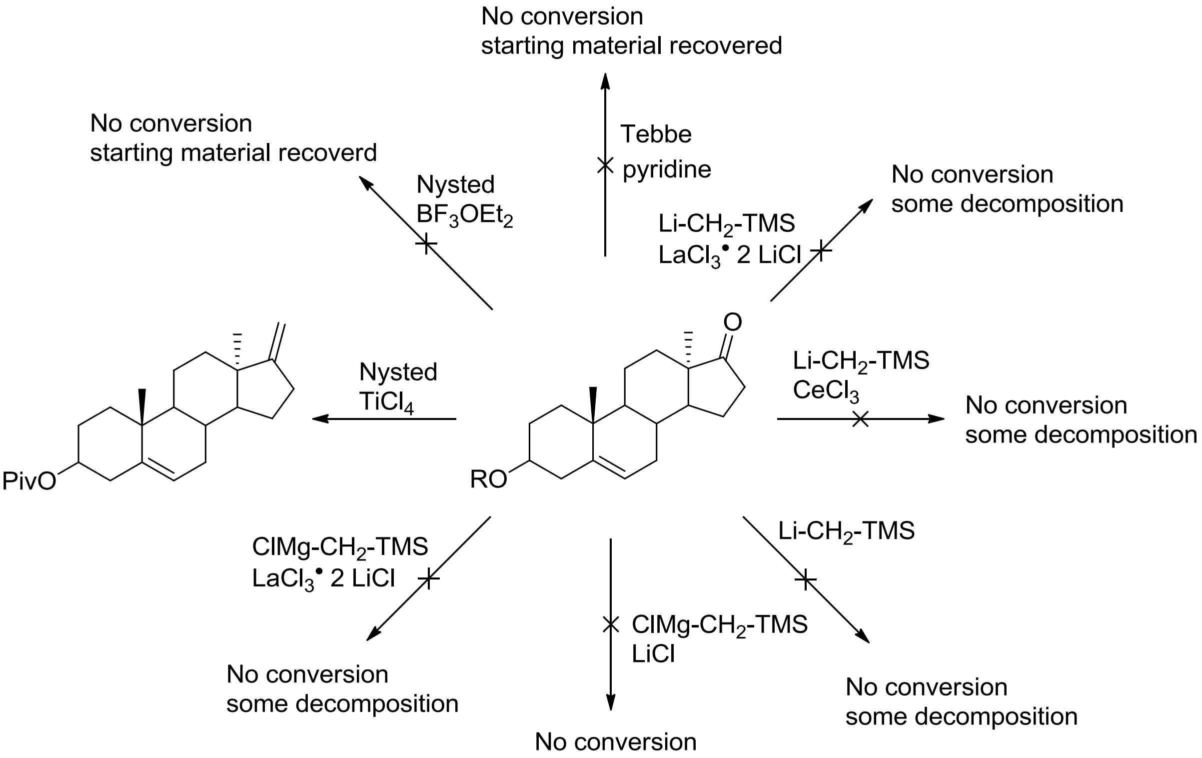


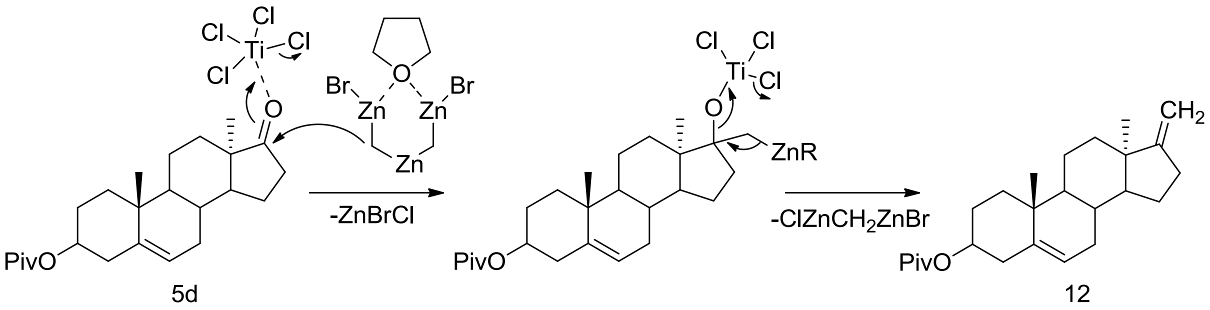
Figure 6.

The Nysted reagent finally efficiently olefinated the substrate under activation with $TiCl_4$; using $BF_3{\cdot}OEt_2$ as Lewis acid resulted in no conversion.



Scheme 17.

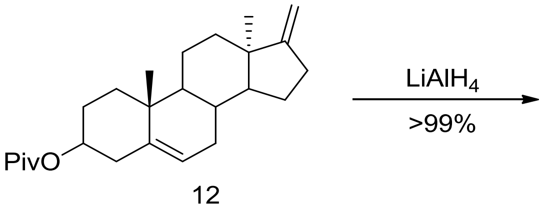
Nysted reagent is known to effectively methylenate sterically crowded ketones under Lewis acid mediation. The activated ketone is attacked by the zinc-substituted methylene. Two chloride ions are liberated from the $TiCl_4$ which can further drive the reaction by interaction with the zinc ions. The mechanism of the reaction is depicted in Scheme 18.



Scheme 18.

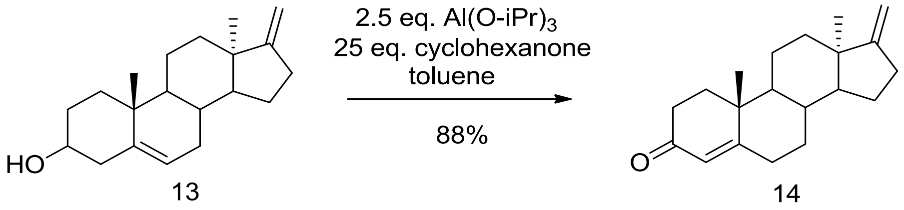
The acetate group was cleaved during this reaction and lowered the yield but the pivalate stayed intact. Conversion is dependent on the quality of $TiCl_4$, with a fresh reagent full conversion and >90% isolated yield was possible, after the first use this dropped to 60% and 50% on the third use.

With the olefin in the right position, work on the A ring was resumed. Cleavage of the pivalate was accomplished quantitatively by reduction with $LiAlH_4$.



Scheme 19.

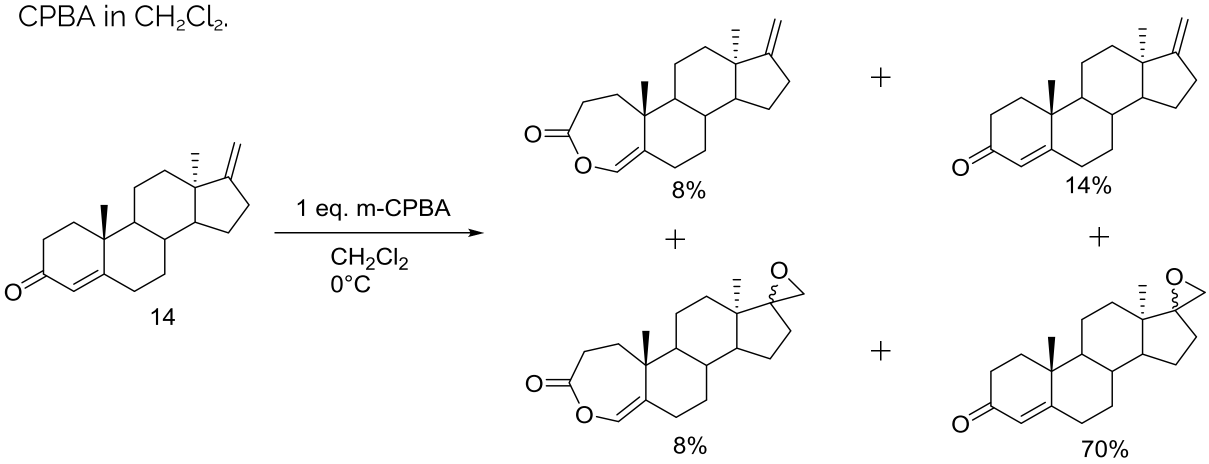
Next Oppenauer oxidation[25] was chosen instead of more modern oxidation methods like Swern or Dess-Martin because literature suggests that the 5-olefin isomerizes into conjugation under these conditions. Indeed the transformation was successful and provided enone 13 in good yield. Using 1-methyl-4-piperidone[26] instead of cyclohexanone (to circumvent chromatographic purification) resulted in longer reaction times without reaching full conversion.



Scheme 20.

Since selectivity of the epoxidation has to be addressed, two possibilities were evaluated. Either α,β-oxidation of the enone to the dienone followed by epoxidation. In this case there are three double-bonds which can be attacked. Epoxidising 14 first and oxidising the A ring afterwards would be the alternative.

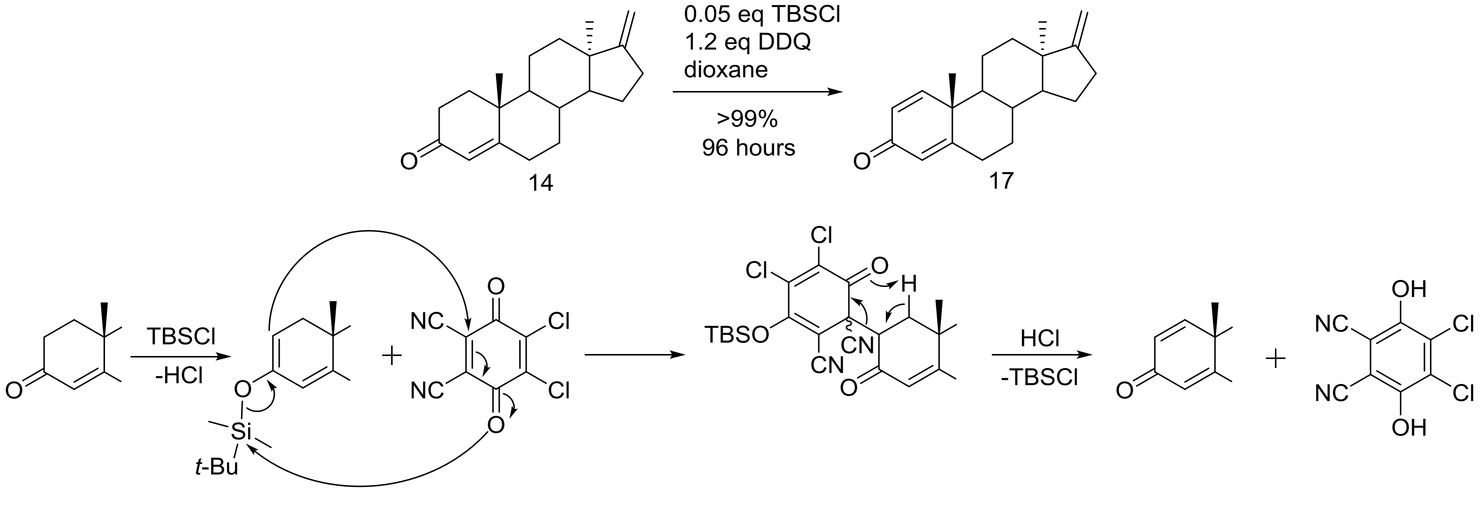
Enone 14 formed considerable amounts of Baeyer-Villiger-oxidation products with *m*-CPBA in CH_2Cl_2.



Scheme 21.

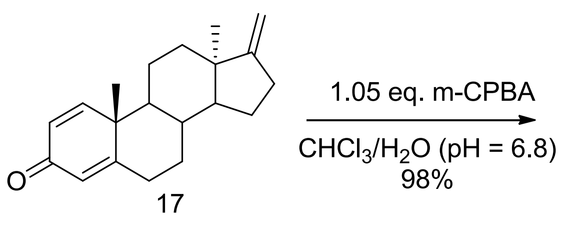
Using excess of *m*-CPBA would probably even lower the yield. Instead a biphasic system of chloroform and aqueous buffer solution (pH = 6.8) was used. This lowered the side product formation (ca. 8%) and also allowed *exo*-methylene conversion to reach 90%.

We suspected the double α,β-unsaturated ketone to be less electrophilic on the carbonyl and thereby perform even better in terms of selectivity. Oxidation was carried out according to literature with DDQ and catalytic TBSCl in dioxane at room temperature.[27] No side-reactions occurred and the yield was excellent.



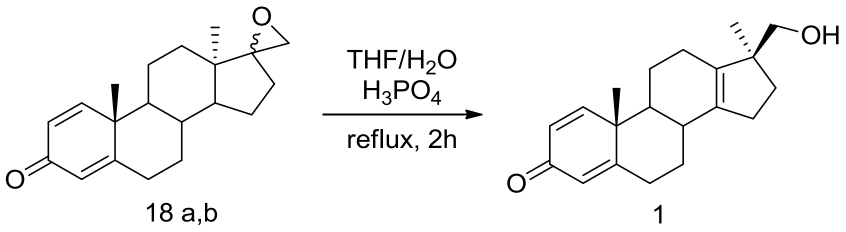
Scheme 22.

With this trienone 17 in hand the epoxidation experiments were repeated and this time the reaction was selective towards the 17-olefin.



Scheme 23.

Next we decided to take a second look at the epoxide opening. Since anhydrous epoxide opening with $BF_3{\cdot}OEt_2$ as Lewis acid provided the wanted isomer as a minor product, aqueous conditions were tested. Phosphoric acid was chosen as H^+-source because of the low nucleophility of its corresponding base as well as its non-oxidative properties (in contrast to sulphuric acid).

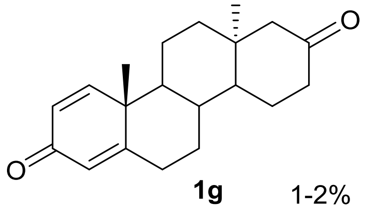
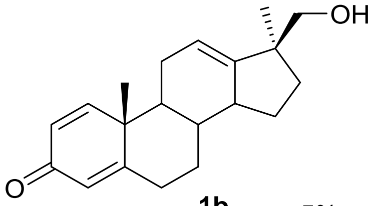
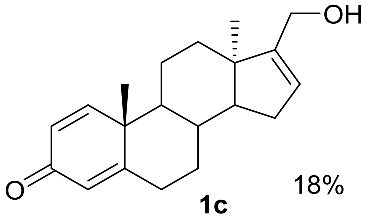
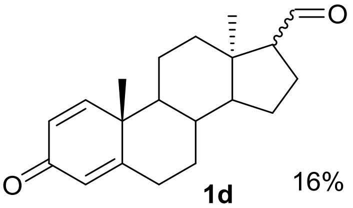
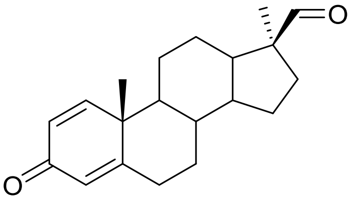
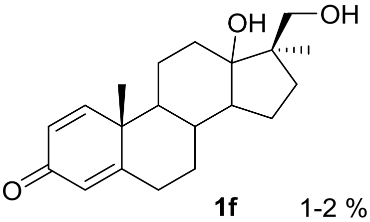
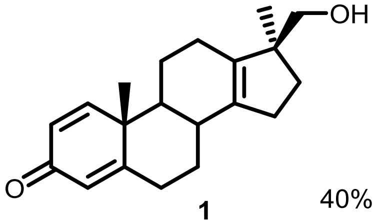


Scheme 24.

The by-products formed were found to be similar regioisomers but the ratio was shifted towards the desired product 1 with this protocol. Running the reaction over 8-12 hours at room temperature gave the same ratio of products. Unfortunately the purification and separation of the isomers proofed difficult, likely because of their similar structure and functionality. In the end reverse phase preparative HPLC was chosen but even though crude NMR indicated about 40% conversion to the product only 22% isolated yield could be achieved; the reason being that the first few product fractions were always contaminated with isomer 1b.

Consecutive purification of this *via* preparative HPLC results in significant losses of product on the column due to mixed fractions. With a different column, capable of base-line separation of this mixture in one run, a better yield could be achieved. The different isomers and their ratios are depicted in Table 1.

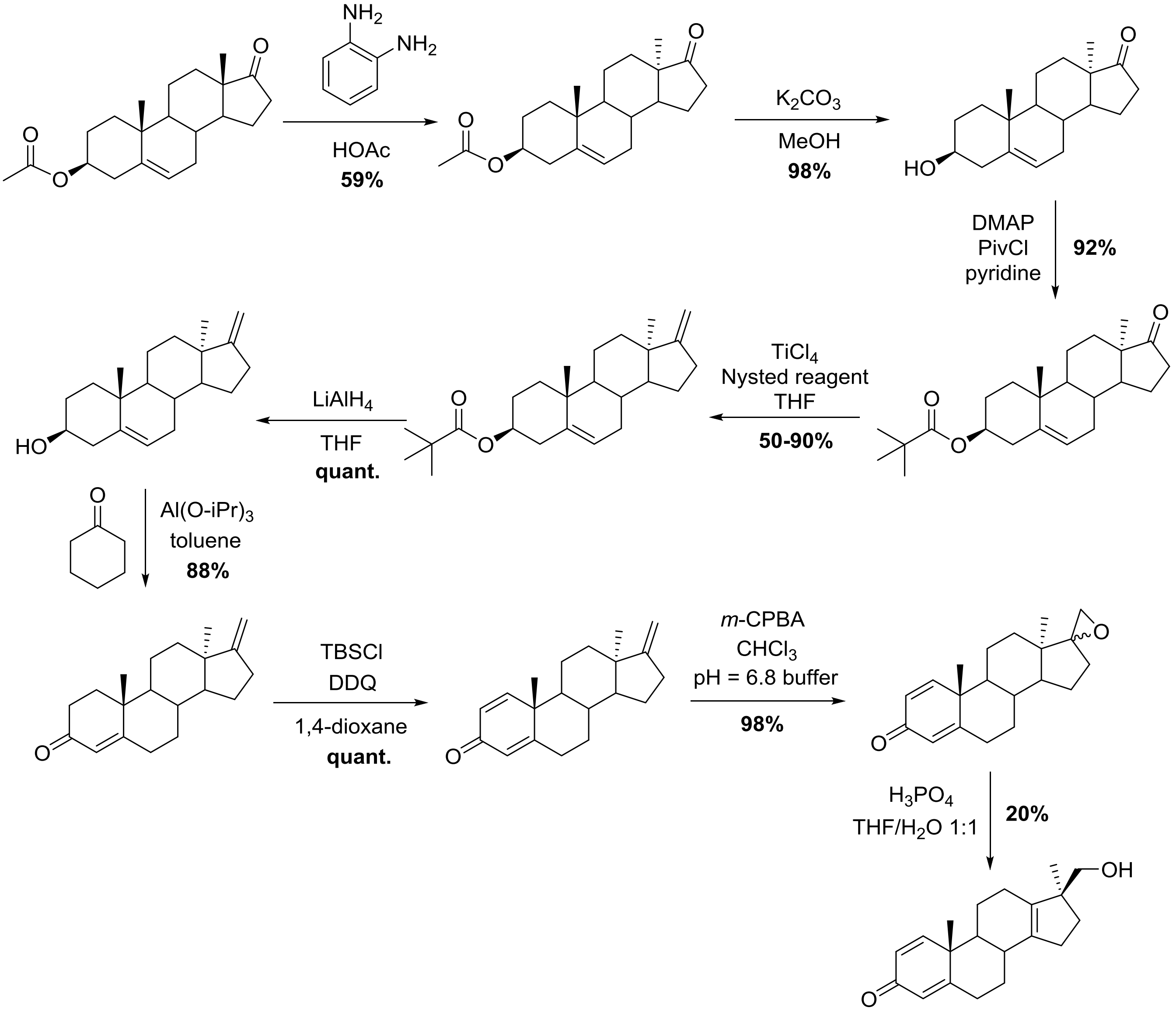
Table 1.

 **1g** 1-2%	 **1b** 5%
 **1c** 18%	 **1d** 16%  **1e**
 **1f** 1-2 %	
 **1** 40%	

Only structures 1 and 1c were obtained in pure form and characterized fully. The other structures are derived from the ^{1}H and ^{13}C-NMR spectra that were obtained upon isolation of material, many times consisting of a mixture of two products that were inseparable by the methods applied.

3.4 Final synthetic route

To summarize the optimized synthetic route is depicted in Scheme 25. Up to the oxidation with DDQ all experiments have been scaled up to quantities of one gram. The bottle-neck of this synthesis is primarily the difficult purification after the rearrangement at the last step.



Scheme 25.

4 Conclusio

We were able to successfully synthesize metabolite 1 in a nine step synthesis with an overall yield of 5.5%. The sequence used olefination and epoxidation followed by a Wagner-Meerwein-rearrangement to install the functionalities with the correct stereochemistry.

After some issues with reactivity at C-17 this work provides a useful strategy for introducing the 17β-hydroxymethyl-17α-methyl substitution pattern to the D ring of steroids.

This gives access to a range of different long-term metabolites of popular doping agents. Any 17-methylated testosterone derivative (many of which have been used as AAS) will likely produce similarly hydroxylated metabolites *in vivo*.

5 Experimental Part

5.1 General

The following general procedures were used in all reactions unless otherwise noted. Glassware was oven-dried at 110 °C and assembled while still hot. Schlenk flasks were flame-dried. Oxygen- and moisture sensitive reactions were carried out under a slight argon overpressure using Schlenk techniques and in dry solvents. Sensitive liquids and solutions were transferred *via* syringes through rubber septa. All reactions were stirred magnetically unless otherwise stated.

The solvents used were purified and dried according to common procedures as follows.

- Dry methylene chloride, diethyl ether and toluene were retrieved from an Innovative Technologies PureSolv system.
- Dry tetrahydrofuran was pre-dried using an Innovative Technologies PureSolv system, refluxed over sodium/benzophenone and freshly distilled.
- Dry DMF and DMSO were used as purchased.
- Ethyl acetate, petroleum ether and diethyl ether (technical grade) were distilled prior to use.
- All other solvents used were p.a. or HPLC grade.
- $CDCl_3$ was passed through a column filled with basic aluminium oxide.

All reagents were used as received, except boron trifluoride diethyletherate and 4-methylpiperidone, which were freshly distilled.

^{1}H and ^{13}C NMR spectra were recorded on a *Bruker AC* 200 at 200 and 50 MHz or on a *Bruker AC* 400 at 400 and 100 MHz, using the solvent peak as reference. ^{13}C NMR spectra were run in proton-decoupled mode. Multiplicities of ^{1}H signals were referred to as s (singlet), d (doublet), t (triplet), q (quartet), p (pentet). sext (sextet), h (heptet) and m (multiplet). All coupling constants are listed in Hz.

IR spectra were recorded on a *Perkin Elmer Spectrum* 65 FT IR spectrometer, equipped with a *MK II Golden Gate Single Reflection* ATR unit.

TLC-analysis was done with precoated aluminium-backed plates (Silica gel 60 F_{254}, Merck). Compounds were visualized by submerging in an acidic phosphormolybdic acid / Cerium sulphate solution and heating.

Melting points of crystalline compounds were determined with a Kofler hot-stage apparatus and are uncorrected.

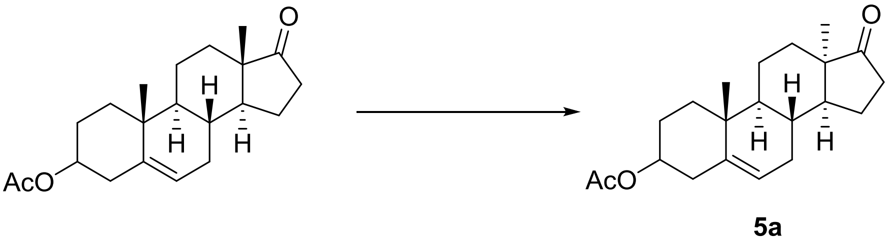
Specific rotations were measured on an *Anton Parr* MCP 500 polarimeter in a 10 cm cell at 20°C and 589 nm. The concentration c is given in g/100ml.

HPLC analysis was done on a *JASCO* system using the PU-2089 pump, AS-2057 autosampler, CO-2060 column oven and an MD-2018 photo-diode array detector with a *ReproSil®* 100, C18, 5 µm (250 x 4.6 mm) column.

Preparative HPLC was carried out on a *Reveleris® Prep* system by *Grace Discovery Sciences* with 3 channel variable UV/Vis and ELS detectors using a *Luna®* 10 µm, C18 (TMS endcapping) 100 Å, LC Column (250 x 21.2 mm).

Preparative flash chromatography was done manually using glass columns and compressed air or with an automated *Büchi Sepacore* chromatography system (MPLC). In either case silica gel 60 (0.04 - 0.063 mm, 230 - 400 mesh, Merck) was used as stationary phase.

5.2 3β-Hydroxy-13α-methylandrost-5-en-17-one acetate (5a)



Ketone 6 (10 g, 30.26 mmol) was dissolved in 125 ml acetic acid and 5.43 g (= 50.2 mmol, 1.66 eq.) *o*-phenylenediamine was added. The mixture was refluxed for 24 hours. The color changed from light brown to dark green in about 2 h and then proceeded to turn very dark with blue complexion which disappeared after cooling the reaction. The solution was then flooded with 150 ml dH_2O upon which a beige precipitate formed. This was extracted with 150 ml EtOAc and the organic phase washed ten times with small portions of water and four times with saturated $NaHCO_3$, dried over Na_2SO_4 and the solvent evaporated *in vacuo*. The crude mixture was purified by MPLC (3x 180g SiO_2, 70 ml/min, 15% → 30% Et_2O in LP) to give 5.91 g (59%) of 5a as well as 1.98 (19.8%) of starting material as white crystalline solids.

R_f: (LP/Et_2O 3:1) 0.55

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.33 (1H, tt, *J* = 2.56), 4.53 (1H, h, *J* = 5.4), 2.18 – 2.38 (4H, m), 2.0 – 2.19 (3H, m), 1.96 (3H, s), 1.68 – 1.87 (3H, m), 1.45 – 1.63 (3H, m) 1.15 (1H, td, *J* = 13.44, 3.61), 0.98 – 1.1 (2H, m), 0.93 (3H, s), 0.92 (1H, m), 0.80 (3H, s), 0.8 (1H, m).

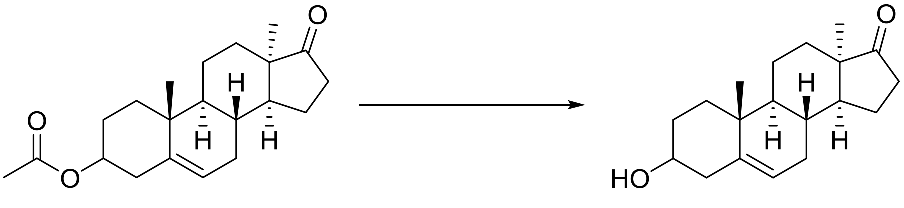
^{13}C-NMR (100MHz, $CDCl_3$): δ = 222.09, 170.43, 139.19, 121.88, 73.72, 50.98, 50.02, 47.86, 37.86, 36.81, 36.61, 34.12, 34.05, 33.03, 31.56, 27.56, 25.12, 22.91, 22.04, 21.39, 19.05

IR [cm^{-1}]: 2965, 2935, 2909, 2875, 1731, 1467, 1441, 1407, 1363, 1318, 1235, 1201, 1124, 1097, 1086, 1024, 1001, 958, 939, 903, 881, 853, 837, 803, 712, 660, 610, 566, 536, 518, 505

m.p.: 141 – 143 °C

$[\alpha]^{20}_D$ = -154.3 (c 0.78, CH_2Cl_2)

5.3 3β-Hydroxy-13α-methylandrost-5-en-17-one (5b)



Ketone 5a (1.15 g, 3.48 mmol) was dissolved in 50 ml methanol, and 1 g (7.24 mmol, 2 eq.) potassium carbonate in methanol were added. The mixture was refluxed for an hour and TLC showed full conversion. The reaction mixture was diluted with dH_2O and extracted with CH_2Cl_2. The pooled extracts were washed with brine, dried over Na_2SO_4 and evaporated to give 982 mg (98%) of 5b as white crystals.

R_f: (LP/EtOAc 5:1) 0.24

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.35 (1H, tt, J = 5.10, 2.55), 3.50 (1H, h, J = 5.28), 2.25 – 2.41 (3H, m), 2.03 – 2.24 (4H, m), 1.71 – 1.91 (4H, m), 1.41 – 1.67 (4H, m), 1.19 (1H, td, J = 13.56, 4.04), 1.0 – 1.14 (2H, m), 0.97 (3H, s), 0.94 (1H, td, J = 11.94, 2.1), 0.85 (1H, td, J = 12.9, 3.55), 0.83 (3H, s).

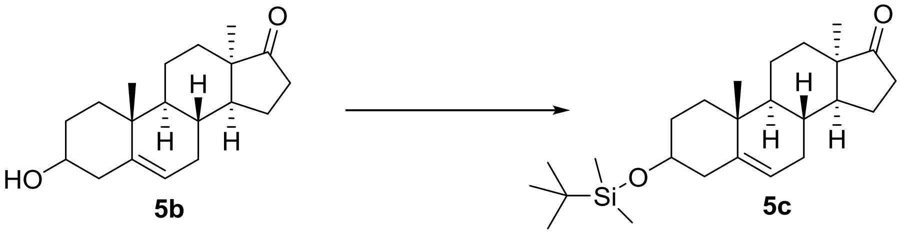
^{13}C-NMR (100MHz, $CDCl_3$): δ = 222.50, 140.44, 121.03, 71.74, 51.18, 50.18, 48.07, 42.12, 36.98, 36.85, 34.29, 34.21, 33.17, 31.73, 31.57, 25.26, 23.09, 22.17, 19.25.

IR [cm^{-1}]: 3456, 2932, 2890, 2849, 1722, 1472, 1450, 1406, 1376, 1304, 1263, 1234, 1199, 1171, 1133, 1107, 1087, 1066, 1057, 1044, 1020, 1001, 962, 940, 875, 839, 817, 807, 738, 716, 614, 566, 515.

m.p.: 180 – 181 °C

$[\alpha]^{20}_D$ = -167.4 (c 0.81, CH_2Cl_2)

5.4 3β-(*tert*-Butyldimethylsilyl)oxy-13α-methylandrost-5-en-17-one (5c)



Ketone 5b (173 mg, 0.6 mmol) was dissolved in 2 ml DMF. To this were added 90.4 mg TBSCl (0.6 mmol, 1 eq.) and 82 mg imidazole (1.2 mmol, 2 eq.). After stirring for 48 hours all the starting material had been consumed and the solution was evaporated to dryness. The residue was dissolved in 0.1 M HCl and EtOAc. After separation of the layers the aqueous phase was extracted three times more with EtOAc. The pooled organic phases were washed with water and brine, dried over Na_2SO_4 and the solvent evaporated to give 237 mg (98%) product as off-white solid. Further purification was not necessary since spectral data indicated absence of impurities.

R_f: (LP/EtOAc 10:1) 0.54

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.31 (1H, tt, *J* = 5.10, 2.55), 3.45 (1H, h, *J* = 4.61), 2.26 – 2.40 (2H, m), 2.00 – 2.26 (5H, m), 1.73 – 1.86 (2H, m), 1.44 – 1.72 (5H, m), 1.17 (1H, td, *J* = 13.37, 3.54), 1.0 – 1.14 (2H, m), 0.96 (3H, s), 0.89 (1H, m), 0.86 (9H, s), 0.81 (3H, s), 0.03 (6H, s).

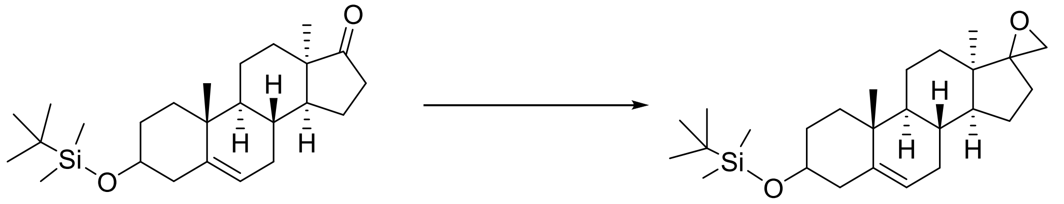
^{13}C-NMR (100MHz, $CDCl_3$): δ = 222.26, 141.12, 120.51, 72.59, 51.19, 50.11, 48.14, 42.66, 37.08, 36.90, 34.25, 34.19, 33.19, 31.97, 31.76, 26.02, 25.25, 23.04, 22.15, 19.25, 18.31.

IR [cm^{-1}]: 2933, 2895, 2854, 1729, 1471, 1438, 1405, 1381, 1368, 1249, 1078, 1044, 1006, 975, 962, 938, 886, 865, 836, 819, 809, 798, 771, 726, 699, 666, 614, 557, 528, 512.

m.p.: 113 – 115 °C

$[\alpha]^{20}_{D}$ = 118.5 (c 1.05, CH_2Cl_2)

5.5 Spiro(13α-methylandrost-5-en-17,2'-oxirane)-3-ol (8a, 8b)



5c **8a, 8b**

Ketone 5c (518 mg, 1.3 mmol) and trimethylsulfonium iodide (525 mg, 2.6 mmol, 2 eq.) were dissolved in DMF and stirred for 60 minutes at room temperature, then 1 equivalent of KO*t*-Bu (289 mg, 1.3 mmol) was added and TLC was taken at T+5 and T+30 minutes. Then the other equivalent of base was added and TLC was taken at T+60 and T+120 minutes and as no continuation of the reaction past 60 minutes was observed there was added solid ammonium chloride and the solvent was evaporated. The solids were dissolved in 20 ml water and 20 ml CH_2Cl_2 and the aqueous phase extracted three times with CH_2Cl_2. The pooled organic phases were washed three times with water and dried over Na_2SO_4.

The crude product (550 mg) was separated *via* column chromatography (60 g silica gel, LP/Et_2O 14:1) to give 186 mg (~110 mg epoxides = 20%) of a mixture of both diastereomers of the product as well as side product 19 (See 3.2). Only a few milligrams of the epoxide 8a were isolated in pure form. There were recovered 233 mg of starting material.

8a:

R_f: (LP/Et_2O 10:1) 0.45

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.33 (1H, t, *J* = 2.69), 3.48 (1H, h, *J* = 4.87), 2.7 (1H, d, *J* = 4.64), 2.61 (1H, d, *J* = 4.64), 2.09 – 2.37 (4H, m), 1.76 – 1.98 (3H, m), 1.61 – 1.76 (2H, m), 1.39 – 1.5 (3H, m), 1.28 – 1.38 (3H, m), 0.97 – 1.18 (2H, m), 0.94 (3H, s), 0.93 (3H, s), 0.88 (9H, s), 0.05 (6H, s).

^{13}C-NMR (100MHz, $CDCl_3$): δ = 141.35, 120.85, 72.77, 68.49, 54.55, 48.06, 47.87, 42.81, 41.23, 37.29, 37.00, 33.47, 33.24, 32.16, 31.47, 30.52, 28.42, 26.09, 25.01, 22.85, 19.49, 18.41.

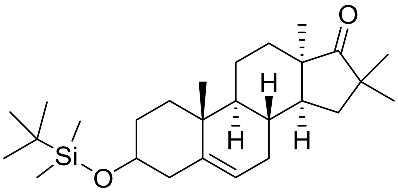
m.p.: 156 – 158 °C

8b:

R_f: (LP/Et_2O 10:1) 0.4

^1H-NMR (200 MHz, $CDCl_3$): δ = 5.33 (1H, m), 3.48 (1H, h, *J* = 4.82), 2.80 (2H, dd, *J* = 13.6, 4.95), 2.1 – 2.38 (4H, m), 1.93 – 2.1 (2H, m), 1.65 – 1.9 (3H, m), 1.4 – 1.6 (5H, m), 1.2 – 1.4 (2H, m), 1.05 – 1.2 (2H, m), 0.99 (3H, s), 0.91 (3H, s), 0.88 (9H, s), 0.05 (6H, s).

19:

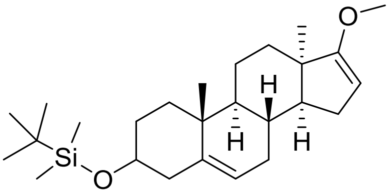


Yield: 70mg (13%)

R_f: (LP/Et_2O 10:1) 0.43

^1H-NMR (200 MHz, $CDCl_3$): δ = 5.33 (1H, s), 3.47 (1H, h, J = 5.08), 1.95 – 2.45 (6H, m), 1.4 – 1.9 (8H, m), 1.18 (3H, s), 1.15 (3H, s), 0.93 (3H, s), 0.88 (9H, s), 0.82 (3H, s), 0.05 (6H, s).

20:

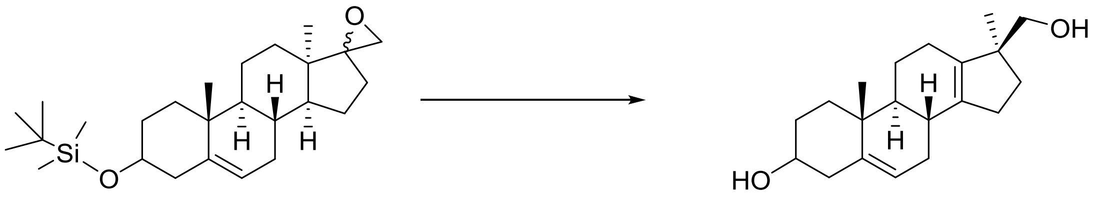


.Yield: 54 mg (10%)

R_f: (LP/Et_2O 10:1) 0.88

^1H-NMR (200 MHz, $CDCl_3$): δ = 5.32 (1H, s), 4.28 (1H, s), 3.58 (3H, s), 3.47 (1H, h, *J* = 4.98), 2.38 – 2.6 (1H, m), 2.05 – 2.3 (3H, m), 1.76 - 2 (3H, m), 1.41 – 1.72 (5H, m), 1.13 – 1.4 (4H, m), 0.98 (3H, s), 0.88 (12H, s), 0.05 (6H, s).

5.6 17β-Hydroxymethyl-17α-methyl-18-norandrosta-5,13-dien-3-ol (3)


8a, 8b

3

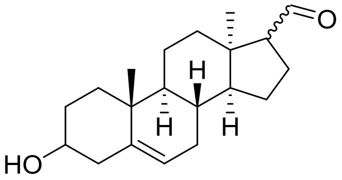
Epoxide 8a (55 mg, 0.13 mmol) was dissolved in 4 ml CH_2Cl_2 and cooled to 0°C. To this there were added 19 mg boron trifluoride diethyletherate (0.13 mmol, 1 eq.) in 0.5 ml CH_2Cl_2 dropwise. The solution was stirred in an ice-bath and the color changed slowly to a light purple over the course of 30 minutes. After 30 more minutes the reaction was quenched with $NaHCO_3$ solution, washed with $NaHCO_3$ and brine, dried over Na_2SO_4 and evaporated to dryness. The crude product was light green. This was separated *via* column chromatography (5 g SiO_2, LP/EtOAc 5:1 → 1:1) to give 3.5 mg (8%) product as orange oil as well as 10.

R_f: (LP/EtOAc 1:1) 0.38

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.41 (1H, tt, *J* = 2.55), 3.54 (1H, h, *J* = 5.30), 3.49 (1H, d, *J* = 10.5), 3.32 (1H, d, *J* = 10.5), 2.10 – 2.35 (4H, m), 1.91 – 2.03 (2H, m), 1.81 – 1.9 (2H, m), 1.49 – 1.68 (5H, m), 1.2 – 1.36 (4H, m), 1.04 – 1.17 (3H, m), 0.99 (3H, s), 0.95 (3H, s).

^{13}C-NMR (100MHz, $CDCl_3$): δ = 141.44, 140.62, 137.0, 72.13, 69.01, 49.06, 42.23, 37.21, 34.13, 33.05, 31.59, 31.32, 30.69, 23.04, 22.38, 21.96, 18.89

10:

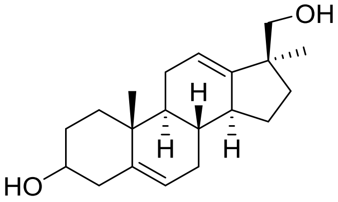


When the same protocol was applied exclusively to the other diastereomer of epoxide (8b) this product was mainly (> 50%) formed.

R_f: (LP/EtOAc 1:1) 0.5

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 9.71 (1H, d, J = 2.6), 5.36 (1H, m), 3.52 (1H, m), 2.81 (1H, t, J = 8.6), 2.26 (4H, m), 1.88 (4H, m), 1.56 (6H, m), 1.2 (6H, m), 0.96 (3H, s), 0.92 (3H, s).

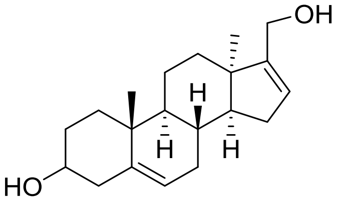
9 (not isolated):



R_f: (LP/EtOAc 1:1) 0.35

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 5.33 (2H, m), 3.53 (1H, m), 3.31 (2H, dd, *J* = 16.16, 10.88) 2.56 (2H, m), 2.1 – 2.35 (4H, m), 1.8 – 2.02 (5H, m), 1.36 – 1.66 (6H, m), 1.1 – 1.34 (6H, m), 1.08 (3H, s), 0.99 (3H, s).

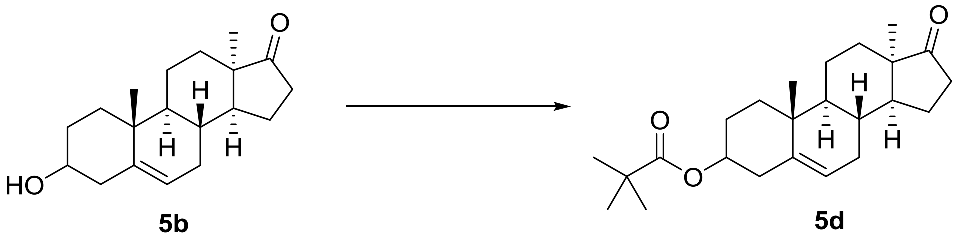
11 (not isolated):



R_f: (LP/EtOAc 1:1) 0.35

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 5.54 (1H, s), 5.36 (1H, p, *J* = 2.21), 4.16 (2H, qq, *J* = 14.54, 2.07), 3.53 (1H, m), 2.56 (2H, m), 2.1 – 2.35 (4H, m), 1.8 – 2.02 (5H, m), 1.36 – 1.66 (6H, m), 1.1 – 1.34 (6H, m), 0.91 (3H, s), 0.87 (3H, s).

5.7 3β-Hydroxy-13α-methylandrost-5-en-17-one pivalate (5d)



Hydroxyketone 5b (1.63 g, 5.64 mmol) was dissolved in 10 ml pyridine and about 5 mg DMAP was added. This was cooled in an ice-bath and stirred until fully dissolved and then 815 mg trimethylacetyl chloride (6.77 mmol, 1.2 eq.) was added dropwise. The mixture was stirred for 3 hours. The solvent was evaporated in vacuo and the residue dissolved in CH_2Cl_2 and $NaHCO_3$ solution. After phase separation the aqueous layer was extracted three times with small portions of CH_2Cl_2, the pooled organic phases washed with dH_2O and brine and dried over Na_2SO_4 to give 1.94 g (92%) as off-white solid.

R_f: (LP/EtOAc 7:1) 0.55

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.38 (1H, tt, *J* = 2.58), 4.56 (1H, h, *J* = 5.42), 2.04 – 2.42 (7H, m), 1.74 – 1.93 (3H, m), 1.49 – 1.7 (5H, m), 1.21 (1H, td, *J* = 13.37, 3.59), 1.17 (9H, s), 1.04 – 1.13 (1H, m), 0.98 (3H, s), 0.98 (1H, td, *J* = 11.54, 2.73), 0.87 (1H, td, *J* = 13.29, 3.53), 0.85 (3H, s)

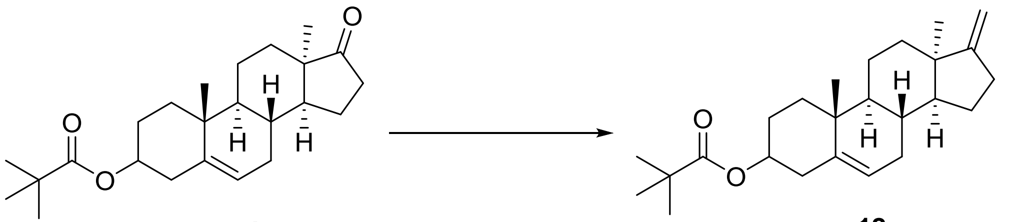
^{13}C-NMR (100MHz, $CDCl_3$): δ = 222.45, 178.17, 139.49, 121.86, 73.48, 51.15, 50.20, 47.99, 38.75, 37.89, 36.97, 36.74, 34.30, 34.20, 33.18, 31.70, 27.58, 27.28, 25.26, 23.07, 22.16, 19.23.

IR [cm^{-1}]: 2957, 2870, 1732, 1717, 1480, 1406, 1372, 1284, 1161, 1086, 1033, 1004, 989, 941, 898, 883, 852, 827, 798, 770, 712, 624.

m.p.: 166 – 170 °C

$[\alpha]^{20}_D$ = -131 (c 0.96, CH_2Cl_2)

5.8 17-Methylene-13α-methylandrost-5,17-dien-3-ol pivalate (12)



5d **12**

Nysted reagent suspension (30.6 g, 20 wt%, 13.42 mmol, 5 eq.) in THF was stirred in a schlenk flask at 0 °C and 8 ml 1M $TiCl_4$ (8.05 mmol, 3 eq.) in dichloromethane were added dropwise. The white milky suspension turned yellow and then light brown over the course of 10 minutes. Ketone 5d (1 g, 2.7 mmol, 1 eq.) was added after formation of the reagent and the reaction mixture was taken out of the cooling bath. The reaction was complete after stirring at RT for 18 hours and was quenched with 100 ml 2M HCl and extracted with Et_2O. The pooled organic phases were washed with brine, dried over Na_2SO_4 and evaporated to dryness. A yellow oil (1.28 g) was obtained as crude product. This was purified over a 60 g silica gel column with 15:1 LP/EtOAc as eluent to give 586 mg (59%) of product as colorless crystals as well as 230 mg (23%) starting material.

R_f: (LP/EtOAc 15:1) 0.34

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.37 (1H, t, *J* = 4.65), 4.84 (1H, t, *J* = 2.02), 4.69 (1H, t, *J* = 2.02), 4.57 (1H, h, *J* = 4.65), 2.18 – 2.54 (5H, m), 1.78 – 1.95 (4H, m), 1.39 – 1.63 (5H, m), 1.36 (1H, dd, 13.4, 3.24), 1.27 (1H, dd, 9.64, 6.2), 0.98 – 1.20 (3H, m), 1.17 (9H, s), 0.95 (3H, s), 0.89 (3H, s).

^{13}C-NMR (100MHz, $CDCl_3$): δ = 178.15, 157.51, 139.36, 122.47, 103.05, 73.66, 54.52, 48.93, 46.08, 38.75, 37.95, 37.02, 36.86, 34.12, 33.42, 33.19, 31.54, 29.85, 27.70, 27.30, 25.30, 21.55, 19.36.

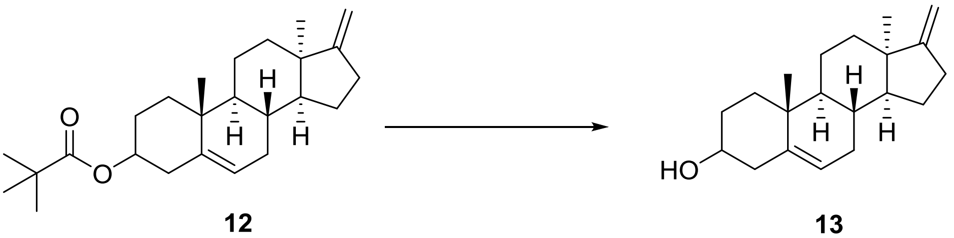
IR [cm^{-1}]: 2957, 2870, 1732, 1717, 1480, 1406, 1372, 1284, 1161, 1086, 1033, 1004, 989, 941, 898, 883, 852, 827, 798, 770, 712, 624.

m.p.: 111 – 114 °C

$[\alpha]^{20}_D$ = -118.6 (c 0.42, CH_2Cl_2)

HRMS:

5.9 17-Methylene-13α-methylandrost-5,17-dien-3-ol (13)


12 **13**

Pivalate (12) (506 mg, 1.37 mmol) was dissolved in approximately 15 ml THF and LiAlH4 (129 mg, 3.41 mmol, 2.5 eq.) was added at room temperature under stirring. Foam was formed and after 1 hour TLC indicated complete consumption of starting material. The grey suspension was quenched with water, dried over Na_2SO_4 and the solids filtered and thoroughly washed with Et_2O. Evaporation of the pooled organic phases gave 392 mg (100%) product as colorless solid.

R_f: (LP/EtOAc 5:1) 0.17

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.35 (1H, tt, *J* = 2.51), 4.84 (1H, t, *J* = 2.23), 4.69 (1H, t, *J* = 2.23), 3.51 (1H, h, *J* = 5.28), 2.13 – 2.53 (5H, m), 1.77 – 1.95 (4H, m), 1.38 – 1.6 (6H, m), 1.35 (1H, dd, *J* = 13.40, 3.28), 0.99 – 1.29 (5H, m), 0.94 (3H, s), 0.93 (1H, m), 0.86 (3H, s).

^{13}C-NMR (100MHz, $CDCl_3$): δ = 157.47, 140.30, 121.69, 121.86, 103.06, 71.92, 54.57, 49.03, 46.05, 42.23, 37.11, 36.90, 34.17, 33.44, 33.18, 31.70, 31.55, 29.84, 25.30, 21.57, 19.37.

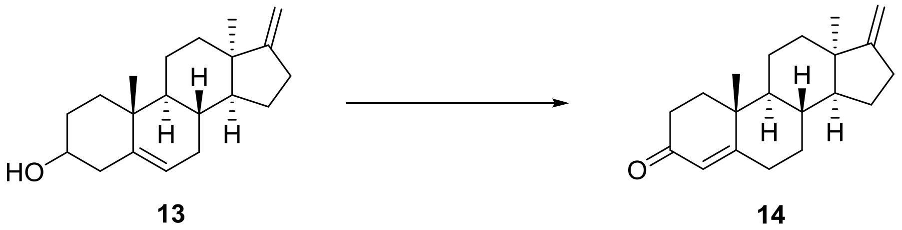
IR [cm^{-1}]: 3229, 2936, 2893, 2865, 2846, 1651, 1466, 1451, 1350, 1261, 1230, 1162, 1137, 1093, 1071, 1054, 1012, 959, 945, 885, 850, 836, 804, 613.

m.p.: 150 – 152 °C

$[\alpha]^{20}_{D}$ = -168.9 (c 0.7, CH_2Cl_2)

HRMS:

5.10 17-Methylene-13α-methylandrost-4-en-3-one (14)



Alcohol (13) (393 mg, 1.37 mmol) was dissolved in 30 ml toluene and 2 g cyclohexanone (34.3 mmol, 25 eq.) as well as aluminium *iso*-propoxide (0.7 g, 3.43 mmol, 2.5 eq.) were added. The suspension was refluxed for two hours and turned increasingly yellow. It was then washed with 15 ml water and 0.5 M H_2SO_4, dried over Na_2SO_4 and the now clear solution evaporated *in vacuo*. The oily residue was purified *via* column chromatography on 25 g silica gel with 5:1 LP/EtOAc as eluent. There were obtained 345 mg (88%) as white solid.

R_f: (LP/EtOAc 5:1) 0.33

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.7 (1H, t, *J* = 0.68), 4.86 (1H, t, *J* = 2.34), 4.71 (1H, t, *J* = 2.34), 2.21 – 2.57 (6H, m), 2.0 – 2.1 (2H, m), 1.96 (1H, dt, *J* = 13.54, 3.19), 1.8 – 1.92 (1H, m), 1.52 – 1.75 (3H, m), 1.44 (1H, dq, *J* = 12.3, 3.15), 1.35 (1H, td, *J* = 19.73, 3.55), 1.13 – 1.27 (2H, m), 1.05 (3H, s), 0.97 – 1.03 (1H, m), 0.94 (3H, s), 0.91 – 0.97 (1H, m).

^{13}C-NMR (100MHz, $CDCl_3$): δ = 199.78, 171.59, 156.87, 123.78, 103.35, 53.35, 52.71, 45.90, 38.90, 37.40, 35.67, 34.30, 34.06, 33.28, 32.95, 31.28, 29.46, 24.76, 21.35, 17.85.

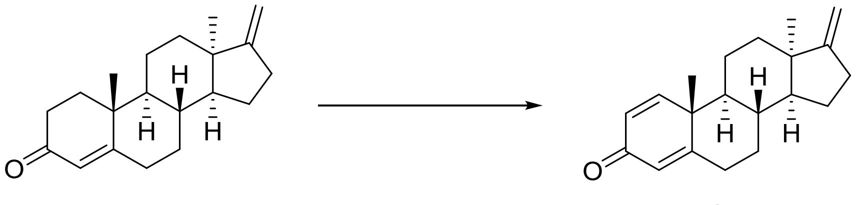
IR [cm^{-1}]: 2932, 2846, 1663, 1615, 1438, 1413, 1367, 1357, 1328, 1270, 1229, 1183, 1095, 1022, 956, 927, 886, 857, 777, 747, 685.

m.p.: 166 – 167 °C

$[\alpha]^{20}_D$ = 72.9 (c 1.01, CH_2Cl_2)

HRMS:

5.11 17-Methylene-13α-methylandrost-1,4-dien-3-one (17)



To Enone (14) (232 mg, 0.82 mmol) dissolved in 5 ml 1,4-dioxane was added TBSCl (6 mg, 0.04 mmol, 0.05 eq.) neat and then the mixture was cooled to 0 °C. To the solidified solution there was added DDQ in two portions. The mixture was slowly allowed to reach room temperature and was stirred for 96 hours. The solution was evaporated, the residue dissolved in CH_2Cl_2 and washed with aqueous $Na_2S_2O_3$, $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4 and evaporated in vacuo to give 227 mg (99%) of a yellow solid which was used in the next step without further purification.

R_f: (LP/EtOAc 3:1) 0.75

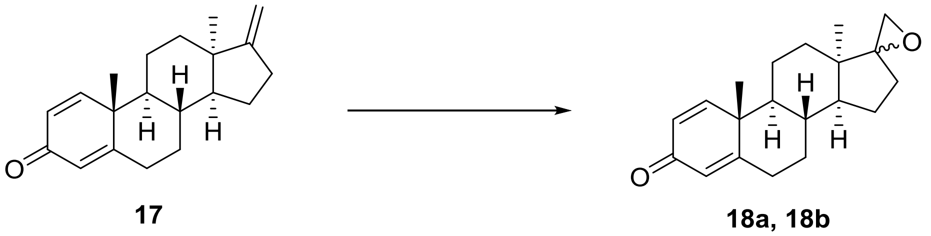
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.07 (1H, d, *J* = 10.12), 6.23 (1H, dd, *J* = 10.14, 1.86), 6.06 (1H, t, *J* = 1.52), 4.89 (1H, t, J = 2.06), 4.75 (1H, t, J = 2.38), 2.3 – 2.59 (4H, m), 2.14 – 2.22 (1H, m), 1.95-2.01 (1H, m), 1.81 – 1.94 (1H, m), 1.6 – 1.67 (1H, m), 1.35 – 1.42 (2H, m), 1.13 – 1.28 (2H, m), 1.1 (3H, s), 0.97 – 1.13 (3H, m), 0.95 (3H, s).

^{13}C-NMR (100MHz, $CDCl_3$): δ = 186.54, 169.46, 156.63, 155.81, 127.66, 123.80, 103.55, 53.30, 50.82, 46.09, 43.58, 37.24, 34.59, 34.12, 33.14, 31.10, 29.33, 24.84, 22.83, 18.93

m.p.: 108 – 110 °C

$[\alpha]^{20}_D$ = -9.1 (c 1.02, CH_2Cl_2)

5.12 Spiro(13α-methylandrost-1,4-dien-17,2'-oxirane)-3-one (18 a,b)



To a solution of Dienone (17) (200 mg, 0.71 mmol) in 3 ml $CHCl_3$ and 2 ml 6.88 pH buffer solution at 0°C there was added *m*-CPBA (218 mg, 0.88 mmol, 1.2 eq.) in 1 ml $CHCl_3$ dropwise. The temperature was held under vigorous stirring for 3 hours. The reaction was quenched with aqueous $NaHCO_3$ and $Na_2S_2O_3$ solution and washed twice with aqueous $NaHCO_3$. After back extraction of the aqueous phases the pooled organic phases were dried over Na_2SO_4 and evaporated *in vacuo* to give 209 mg (99%) epoxides 18 a,b as colorless solids which were used without further purification.

An analytical sample was purified *via* column chromatography: 50 mg crude product on 5 g silica gel, 3:1 LP/EtOAc as eluent yielded the two diastereomers as pure compounds.

18 a:

R_f: (LP/EtOAc 3:1) 0.33

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.06 (1H, d, *J* = 10.12), 6.22 (1H, dd, *J* = 10.12, 1.88), 6.07 (1H, t, *J* = 1.56), 2.73 (1H, d, *J* = 4.56), 2.64 (1H, d, *J* = 4.64), 2.32 – 2.52 (2H, m), 2.19 – 2.3 (2H, m), 1.87 – 1.97 (1H, m), 1.59 – 1.86 (4H, m), 1.43 (1H, td, *J* = 16.88, 3.67), 1.19 – 1.41 (3H, m), 1.17 (3H, s), 0.95 – 1.13 (2H, m), 0.92 (3H, s).

^{13}C-NMR (100MHz, $CDCl_3$): δ = 186.55, 169.60, 155.96, 127.59, 123.69, 68.35, 53.16, 49.75, 47.54, 43.58, 41.43, 37.21, 34.77, 32.96, 31.50, 30.00, 27.96, 24.68, 24.34, 18.98.

IR [cm^{-1}]: 3402, 2924, 2847, 1652, 1610, 1597, 1443, 1409, 1375, 1352, 1301, 1241, 1218, 1143, 1095, 1043, 1032, 1013, 985, 950, 936, 922, 886, 839, 802, 747, 710, 690.

m.p.: 128 – 130 °C

$[\alpha]^{20}_D$ = -65.8 (c 0.6, CH_2Cl_2)

HRMS:

18 b:

R_f: (LP/EtOAc 3:1) 0.18

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.04 (1H, d, *J* = 10.12), 6.24 (1H, dd, *J* = 10.14, 1.9), 6.08 (1H, t, *J* = 1.50), 2.83 (2H, dd, J = 18.54, 4.94), 2.34 – 2.5 (2H, m), 2.18 – 2.27 (1H, m), 2.02 – 2.14 (2H, m), 1.88 – 2 (1H, m), 1.68 – 1.77 (1H, m), 1.56 – 1.67 (2H, m), 1.18 – 1.41 (5H, m), 1.15 (3H, s), 1 – 1.13 (1H, m), 0.99 (3H, s).

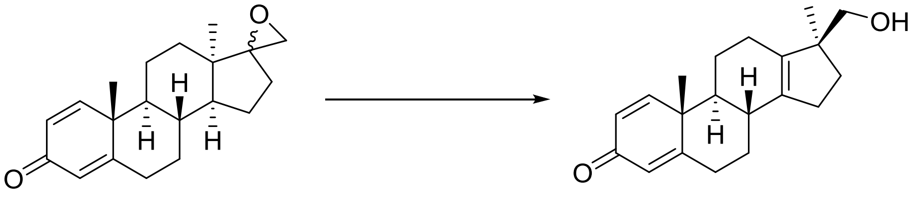
^{13}C-NMR (100MHz, $CDCl_3$): δ = 186.38, 168.91, 155.28, 127.88, 123.94, 66.58, 55.19, 53.14, 49.70, 43.33, 41.11, 37.62, 34.65, 32.88, 31.79, 29.36, 26.23, 24.34, 23.58, 18.92.

IR [cm^{-1}]: 2930, 2900, 2848, 1667, 1627, 1602, 1490, 1440, 1406, 1363, 1294, 1243, 1112, 1085, 1056, 1027, 979, 951, 905, 881, 841, 817, 778, 706, 690, 614.

m.p.: 132 – 133 °C

$[\alpha]^{20}_D$ = -11 (c 0.6, CH_2Cl_2)

5.13 17β-Hydroxymethyl-17α-methyl-18-norandrosta-1,4,13-triene-3-one (1)



18a, 18b **1**

To a mixture of epoxides 18a and 18b (210 mg, 0.7 mmol) in 5 ml THF/H_2O 1:1 were added 5 drops of phosphoric acid and heated to reflux for 2 hours. After completion the THF was evaporated and the aqueous phase extracted with CH_2Cl_2, washed with $NaHCO_3$ solution and brine and dried over Na_2SO_4. The organic solvent was evaporated to yield 209 mg crude product as oily crystals. This was separated on the preparative HPLC (water + 0.1 % TFA / methanol = 2:3) to give 47 mg (22%) as light yellow oily solid.

R_f: (LP/EtOAc 1:1) 0.44

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.14 (1H, d, *J* = 10.16), 6.26 (1H, dd, *J* = 10.16, 1.88), 6.09 (1H, t, *J* = 1.6), 3.48 (1H, d, *J* = 10.54), 3.34 (1H, d, *J* = 10.54), 2.52 (1H, tdd, *J* = 20.09, 5.03, 1.51), 2.37 – 2.47 (2H, m), 2.14 – 2.34 (3H, m). 1.86 – 2.1 (4H, m), 1.5 – 1.72 (4H, m). 1.30 (1H, td, J = 11.3, 2.06), 1.21 (3H, s), 0.92 (3H, s).

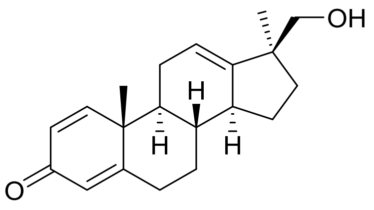
^{13}C-NMR (100MHz, $CDCl_3$): δ = 186.44, 168.76, 155.62, 138.95, 137.60, 127.83, 124.51, 69.02, 51.67, 49.51, 43.45, 36.74, 33.96, 33.36, 32.62, 30.82, 24.03, 22.48, 21.82, 18.65

IR [cm^{-1}]: 3395, 2923, 2855, 1655, 1615, 1600, 1451, 1376, 1295, 1241, 1151, 1040, 942, 888, 815, 687, 578, 558, 532, 511.

$[\alpha]^{20}_D$ = 17.4 (c 0.88, CH_2Cl_2)

HRMS:

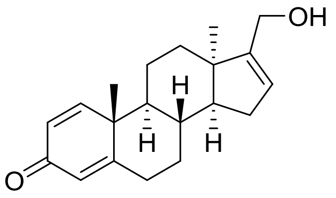
1b:



R_f: (toluene/MeOH 10:1) 0.32

^{1}H-NMR (400 MHz, CDCl$_3$): δ = 6.93 (1H, d, *J* = 9.98), 6.17 (1H, dd, *J* = 11.10, 1.97), 6.04 (1H, t, *J* = 1.73), 5.33 (1H, q, *J* = 3.09), 3.38 (1H, d, *J* = 11.1), 3.29 (1H, d, *J* = 11.1) 2.4 – 2.55 (1H, m), 2.3 – 2.47 (2H, m), 2 – 2.16 (2H, m), 1.9 – 1.98 (1H, m), 1.72 – 1.8 (1H, m), 1.62 (2H, broad s), 1.42 (2H, m), 1.01 – 1.3 (2H, m), 1.14 (3H, s), 0.86 (3H, s).

1c:

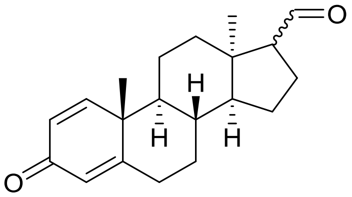


R_f: (toluene/MeOH 10:1) 0.26

^{1}H-NMR (400 MHz, CDCl$_3$): δ = 7.07 (1H, d, *J* = 10.12), 6.23 (1H, dd, *J* = 10.10, 1.86), 6.07 (1H, t, *J* = 1.54), 3.48 (1H, d, J = 10.54), 5.60 (1H, s), 4.12 – 4.25 (2H, m), 2.53 – 2.63 (1H, m), 2.3 – 2.47 (2H, m), 2 – 2.16 (2H, m), 1.9 – 1.98 (1H, m), 1.72 – 1.8 (1H, m), 1.62 (2H, broad s), 1.42 (1H, m), 1.01 – 1.3 (3H, m), 1.10 (3H, s), 0.98 (3H, s).

^{13}C-NMR (100MHz, CDCl$_3$): 186.55, 169.28, 155.67, 149.67, 127.69, 124.52, 123.95, 60.13, 53.10, 49.83, 47.95, 43.58, 39.04, 35.61, 35.16, 33.58, 33.30, 27.85, 23.96, 18.86.

1d:

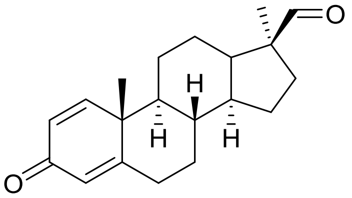


R_f: (LP/EtOAc 1:1) 0.61

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.7 (1H, d, *J* = 3.11), 7.09 (1H, d, *J* = 10.16), 6.25 (1H, dd, *J* = 10.16, 1.88), 6.08 (1H, m), 2.77 (1H, td, *J* = 13.82, 2.77), 2.31 – 2.5 (2H, m), 2.1 – 2.28 (2H, m), 1.85 – 2.08 (4H, m), 1.72 – 1.84 (1H, m), 1.5 – 1.7 (2H, m), 1.34 – 1.47 (1H, m), 1.0 – 1.3 (3H, m), 1.18 (3H, s), 0.94 (3H, s).

^{13}C-NMR (100MHz, $CDCl_3$): δ = 205.59, 186.3, 168.8, 155.3, 127.8, 123.8, 55.0, 53.5, 50.3, 46.3, 43.3, 37.4, 34.3, 34.2, 32.8, 26.9, 24.9, 21.9, 21.6, 18.8.

1e:

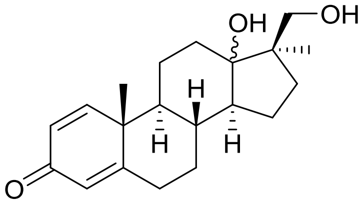


R_f: (LP/EtOAc 1:1) 0.61

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.85 (1H, s), 6.99 (1H, d, J = 10.16), 6.25 (1H, dd, J = 10.16, 1.88), 6.08 (1H, m), 2.31 – 2.5 (2H, m), 2.1 – 2.28 (2H, m), 1.85 – 2.08 (4H, m), 1.72 – 1.84 (1H, m), 1.5 – 1.7 (2H, m), 1.34 – 1.47 (1H, m), 1.0 – 1.3 (4H, m), 1.25 (3H, s), 1.19 (3H, s).

^{13}C-NMR (100MHz, $CDCl_3$): δ = 205.38, 186.3, 169.0, 155.5, 127.7, 123.7, 61.14, 54.24, 53.7, 50.5, 43.4, 37.6, 34.3, 34.2, 32.8, 26.9, 24.9, 21.9, 21.6, 18.8.

1f:



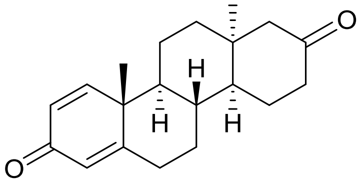
Mixture of 1f and 1g and other minor byproducts was isolated. This mixture is suspected to consist of about 4:1 f:g.

R_f: (LP/EtOAc 1:1) 0.15

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.1 (1H, d, *J* = 10.12), 6.24 (1H, dd, *J* = 10.11, 1.83), 6.08 (1H, m), 3.65 (2H, dd, J = 63.26, 11.28), 2.31 – 2.53 (3H, m), 2.2 – 2.3 (1H, m), 1.94 – 2.2 (5H, m), 1.8 – 1.91 (2H, m), 1.41 – 1.51 (1H, m), 1.33 – 1.43 (1H, m), 1.19 – 1.30 (1H, m), 1.01 – 1.13 (1H, m), 1.23 (3H, s), 0.83 (3H, s).

^{13}C-NMR (400 MHz, $CDCl_3$): δ =186.2, 169.3, 155.7, 127.2, 123.6, 82.3, 67.8, 51, 50.94, 47.24, 42.6, 35.3, 33.2, 32.5, 31.8, 31.45, 24.75, 22.9, 21.77, 18.5,

1g:



R_f: (LP/EtOAc 1:1) 0.15

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.08 (3H, s), 0.98 (3H, s)

^{13}C-NMR (400 MHz, $CDCl_3$): δ = 221, 186, 168.2, 154.9, 127.4, 123.6, 51, 49.4, 42.8, 39.2, 37.6, 35.6, 34.5, 34.0, 32.7, 31.2, 23.6, 22.9, 21.17, 18.3.

6 References

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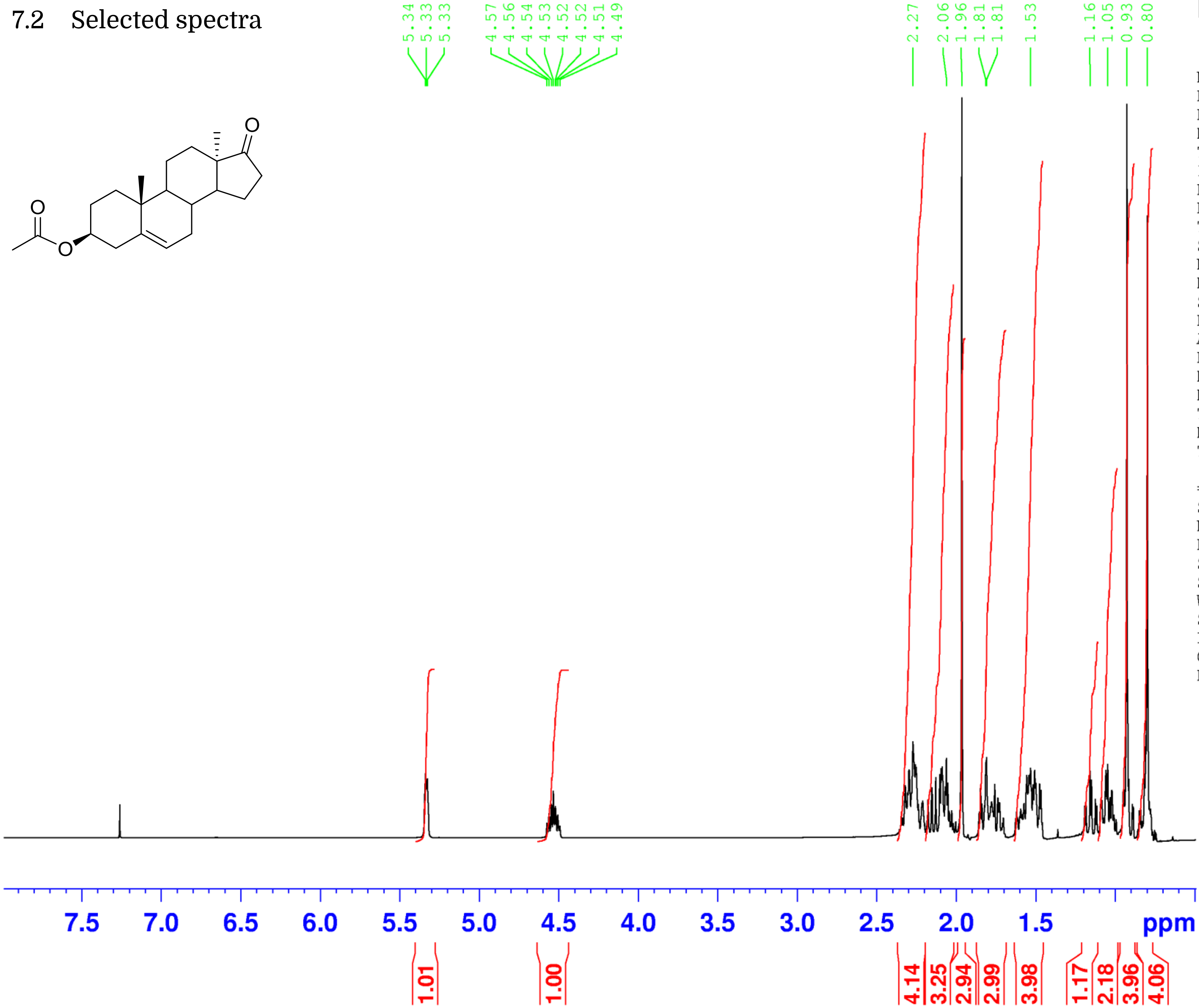
7 Appendix

7.1 Abbreviations

AAS	anabolic androgenic steroid
AcONa	sodium acetate
Al(O-*i*Pr)$_3$	aluminium(III)-*iso*propoxide
BF_3OEt_2	boron trifluoride diethyletherate
Bu	butyl
Bu_3P	tributylphosphine
Bu_3SnH	tributyltinhydride
CAN	Cerium ammonium nitrate
$CeCl_3$	cerium(III)-chloride
CH_2Cl_2	dichloromethane
$CHCl_3$	chloroform
CYP	Cytochrom P450
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
eq.	equivalents
ESI-MS	Electronspray ionisation mass spectrometry
Et_2O	diethyl ether
EtOAc	ethyl acetate
GC/MS	Gas chromatography / mass spectrometry
H_3PO_4	phosphoric acid
HCl	hydrochloric acid
*i*Pr	isopropyl
K2CO3	potassium carbonate

KO*t*Bu	potassium *tert*-butoxide
$LaCl_3$	lanthanum(III)-chloride
$LiAlH_4$	Lithium aluminium hydride
LiCl	lithium chloride
LP	light petroleum
m-CPBA	*meta*-chlorperbenzoic acid
MD	metandienone
MeOH	methanol
$Na_2S_2O_3$	sodium thiosulphate
Na_2SO_4	sodium sulphate
NaCN	sodium cyanide
NaH	sodium hydride
$NaHCO_3$	sodium bicarbonate
n-BuLi	*n*-Butyllithium
NH_2OH	hydroxylamine
NH_4Cl	ammonium chloride
PhSSPh	Diphenylsulfide
pivalate	2,2,2-trimethylacetate
$S(CH_3)_3I$	trimethylsulfonium iodide
SiO_2	silicium dioxide (silica gel)
TBME	*tert*-butyl methyl ether
TBSCl	*tert*-butyldimethylsilylchloride
*t*Bu	*tert*-butyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
$TiCl_4$	titanium(IV)-chloride
TMS	trimethylsilyl

7.2 Selected spectra



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FIDRES            0.195125 Hz
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RG                   12.55
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TE                   297.4 K
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SFO1           400.1330010 MHz
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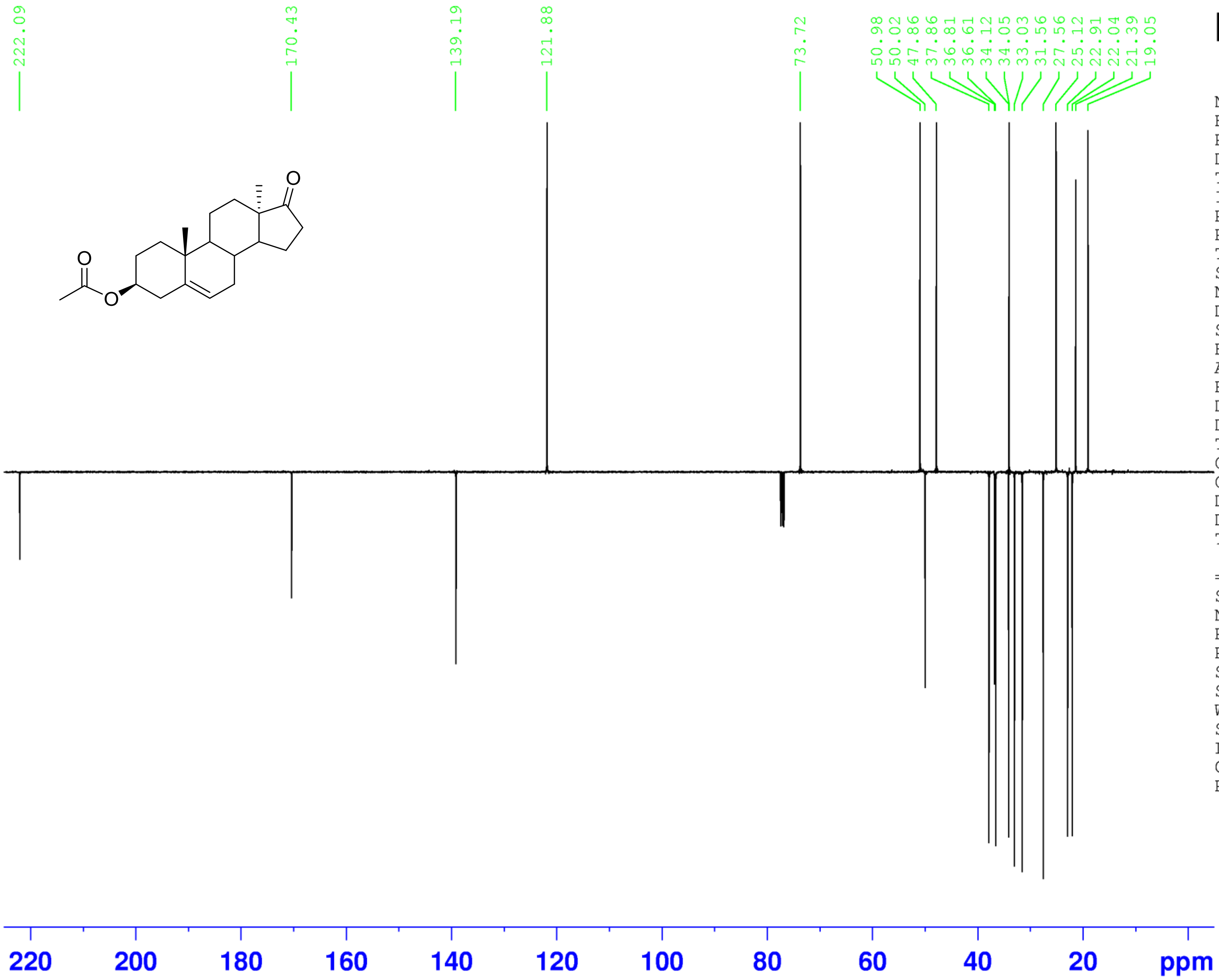

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FIDRES	0.353213 Hz
AQ	1.4156276 sec
RG	201.19
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DE	6.50 usec
TE	298.5 K
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CNST11	1.0000000
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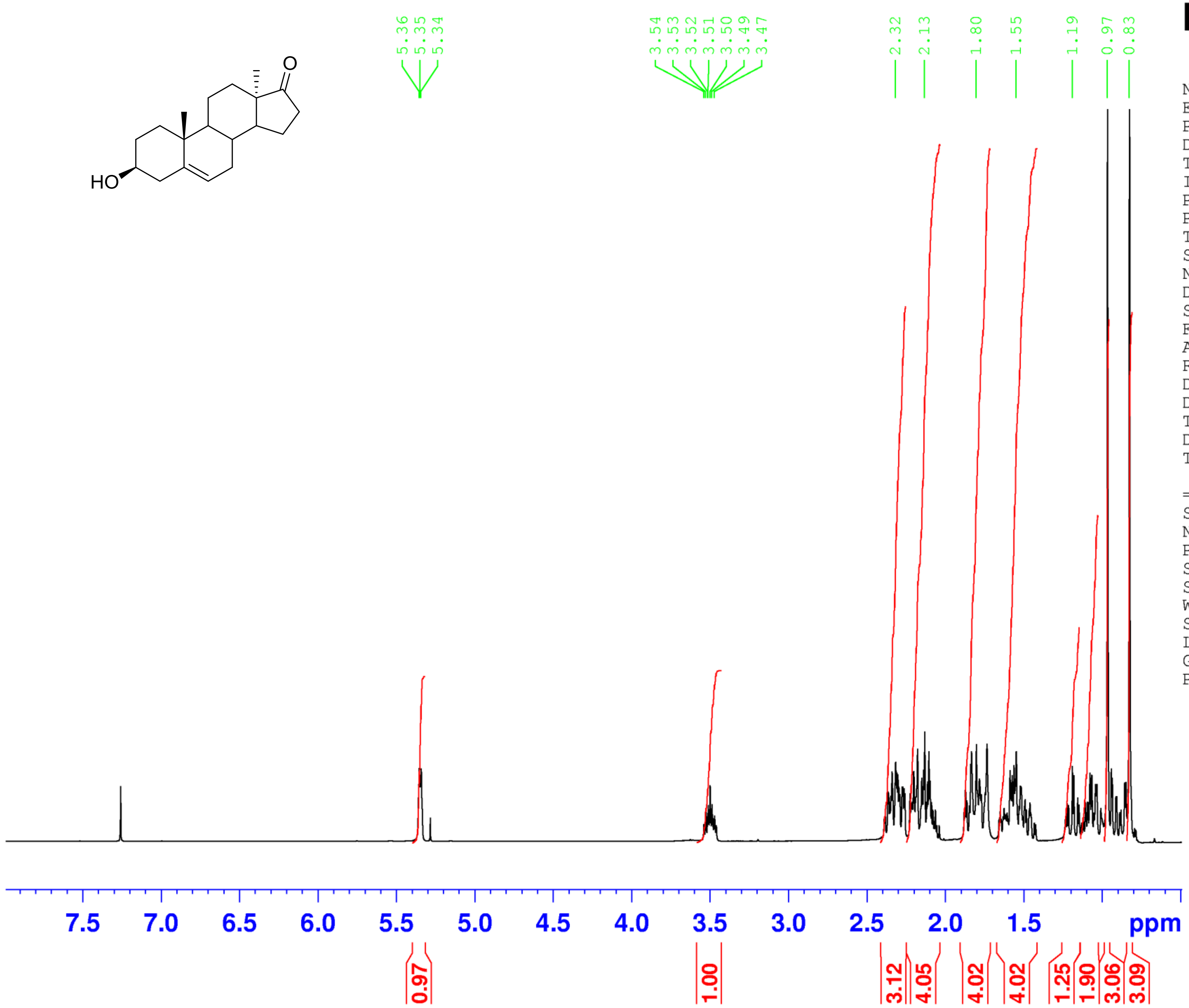

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SWH                   6393.862 Hz
FIDRES                0.195125 Hz
AQ                   2.5625076 sec
RG                       39.08
DW                      78.200 usec
DE                        6.50 usec
TE                       297.2 K
D1                  1.00000000 sec
TD0                          1

======== CHANNEL f1 ========
SFO1               400.1330010 MHz
NUC1                        1H
P1                        9.75 usec
SI                       16384
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WDW                         EM
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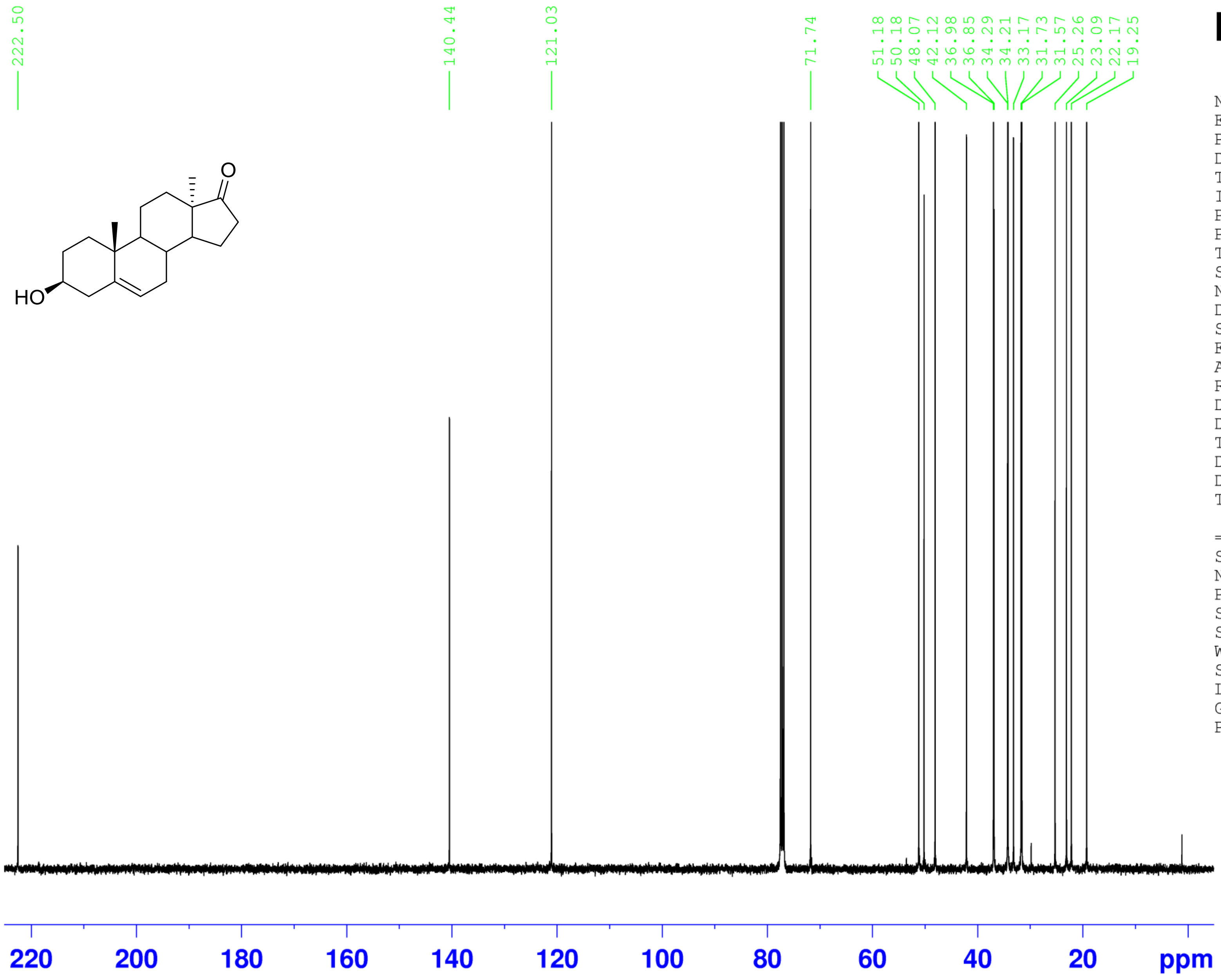

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FIDRES           0.353213 Hz
AQ              1.4156276 sec
RG                 201.19
DW                 21.600 usec
DE                   6.50 usec
TE                  298.0 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                     1

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SI                  32768
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SSB                     0
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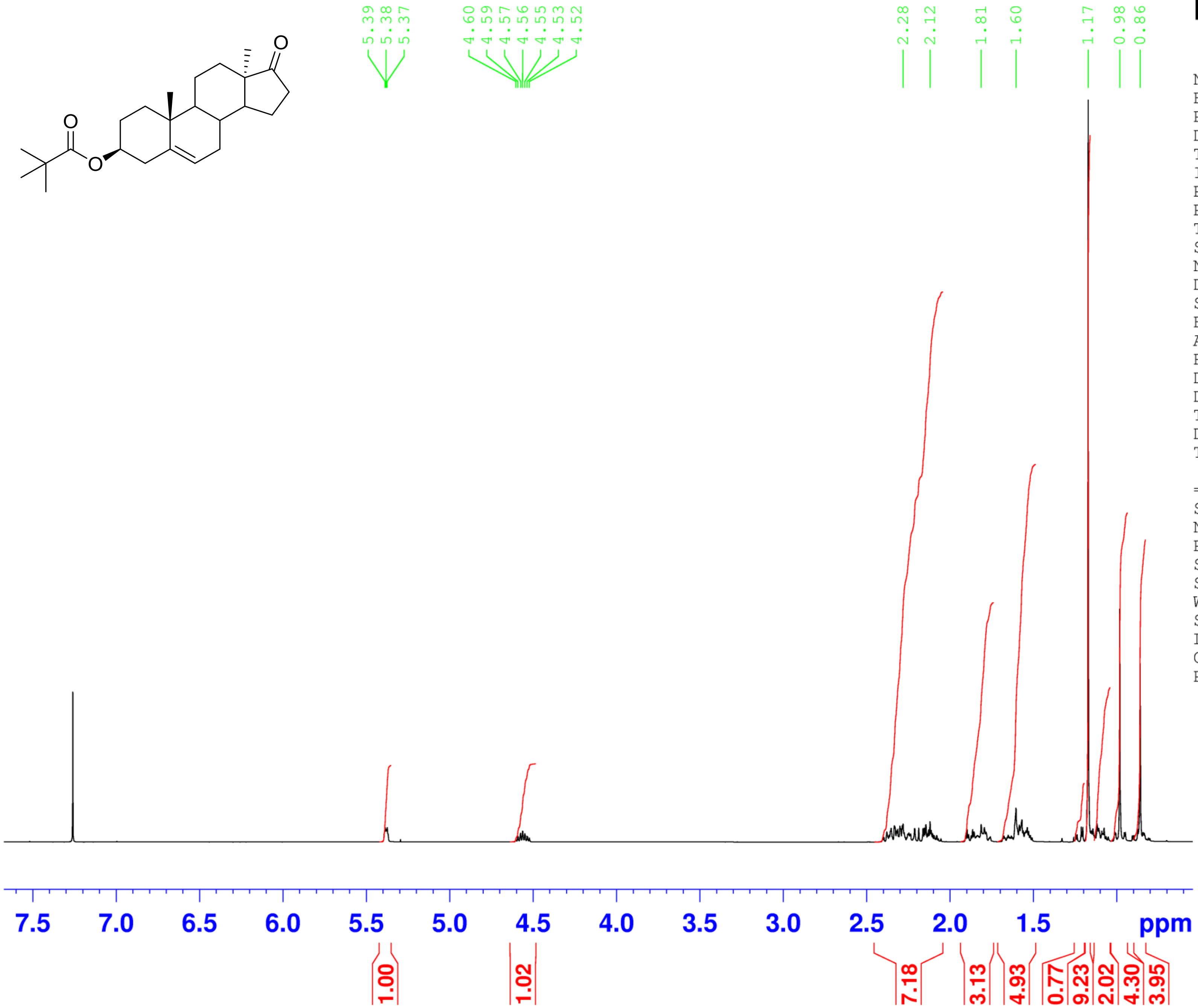

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PULPROG	zg30	
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SOLVENT	CDCl3	
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DS	0	
SWH	6393.862	Hz
FIDRES	0.195125	Hz
AQ	2.5625076	sec
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DW	78.200	usec
DE	6.50	usec
TE	297.1	K
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TD0	1	

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P1	9.75	usec
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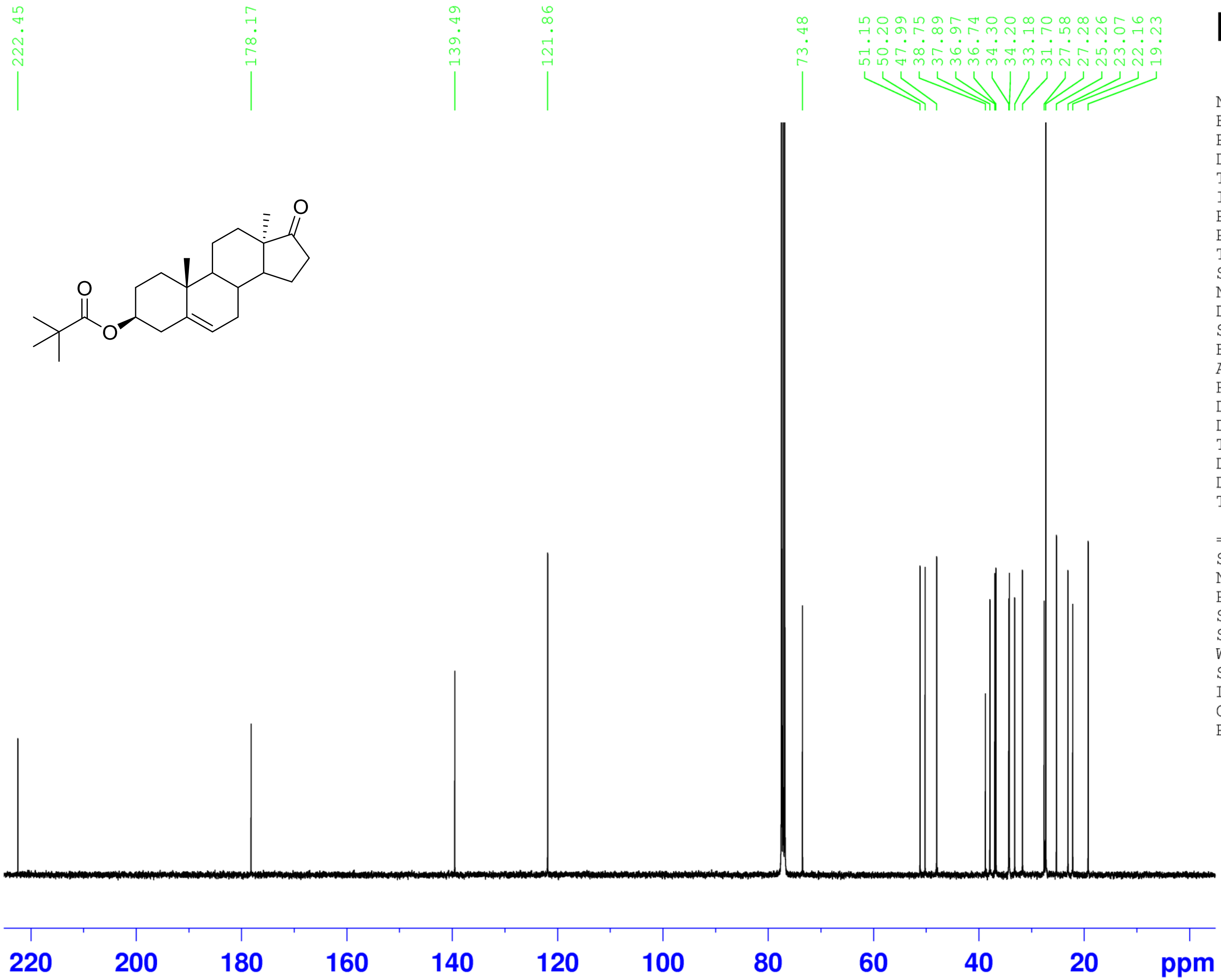

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NS                   5120
DS                      4
SWH             23148.148 Hz
FIDRES           0.353213 Hz
AQ              1.4156276 sec
RG                 201.19
DW                 21.600 usec
DE                   6.50 usec
TE                  297.8 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                     1

======== CHANNEL f1 ========
SFO1          100.6238359 MHz
NUC1                  13C
P1                   9.00 usec
SI                  32768
SF            100.6127558 MHz
WDW                    EM
SSB                     0
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PC                   1.40
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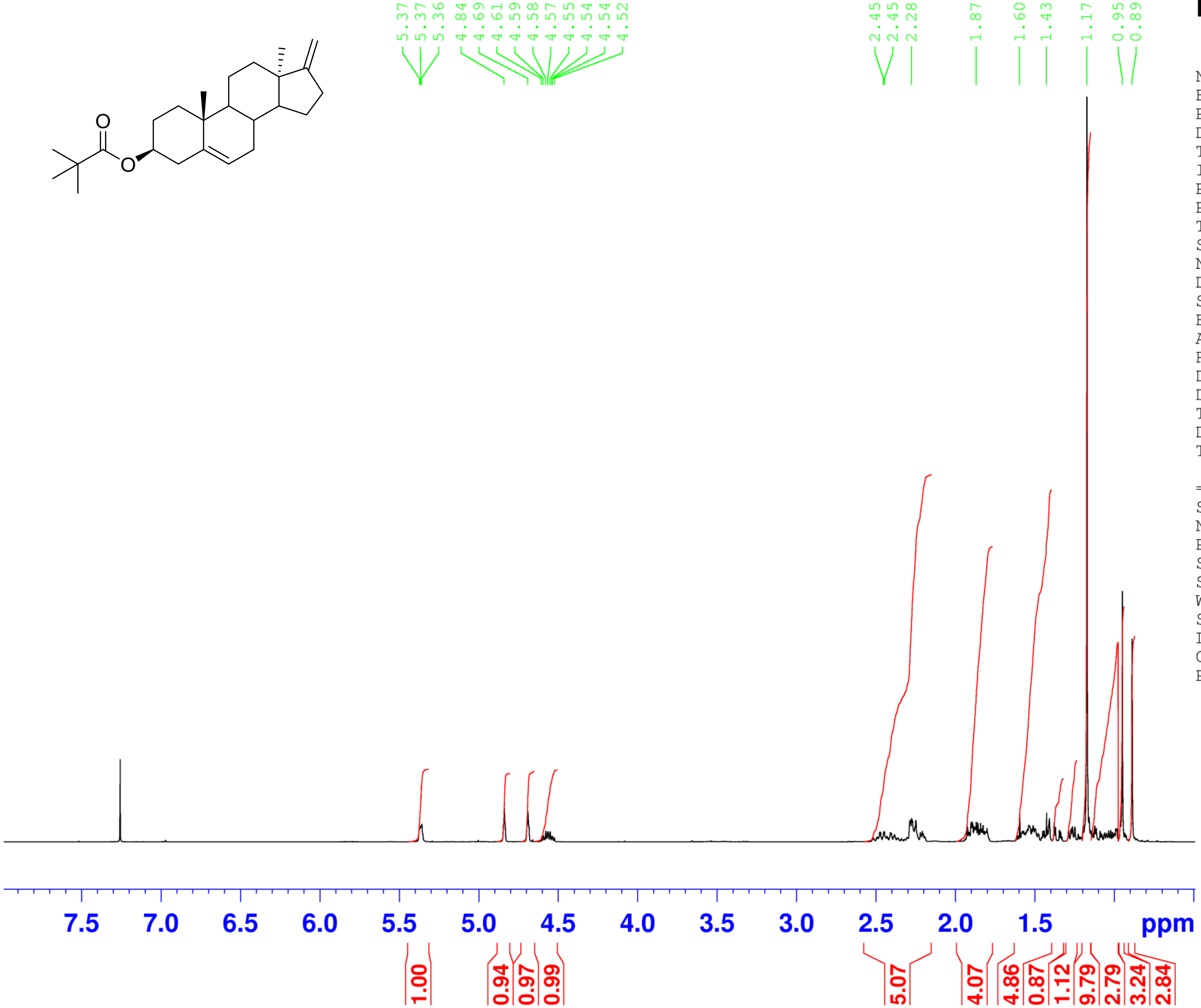

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PULPROG	zg30	
TD	32768	
SOLVENT	CDCl3	
NS	64	
DS	0	
SWH	6393.862	Hz
FIDRES	0.195125	Hz
AQ	2.5625076	sec
RG	45.28	
DW	78.200	usec
DE	6.50	usec
TE	297.0	K
D1	1.00000000	sec
TD0	1	

======== CHANNEL f1 ========

SFO1	400.1330010	MHz
NUC1	1H	
P1	9.75	usec
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SF	400.1300105	MHz
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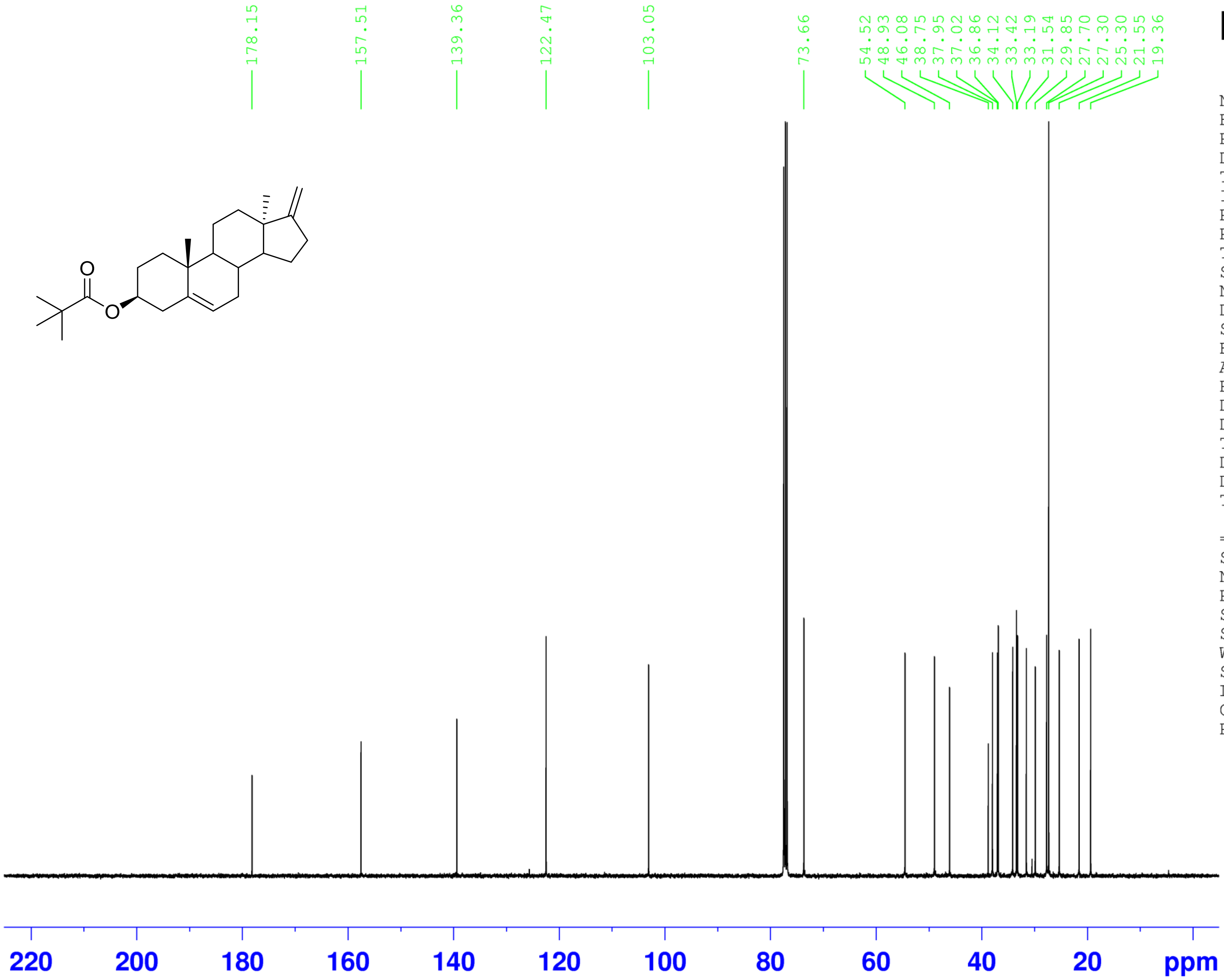

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SOLVENT	CDCl3
NS	3072
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SWH	23148.148 Hz
FIDRES	0.353213 Hz
AQ	1.4156276 sec
RG	201.19
DW	21.600 usec
DE	6.50 usec
TE	297.8 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1

======== CHANNEL f1 ========

SFO1	100.6238359 MHz
NUC1	13C
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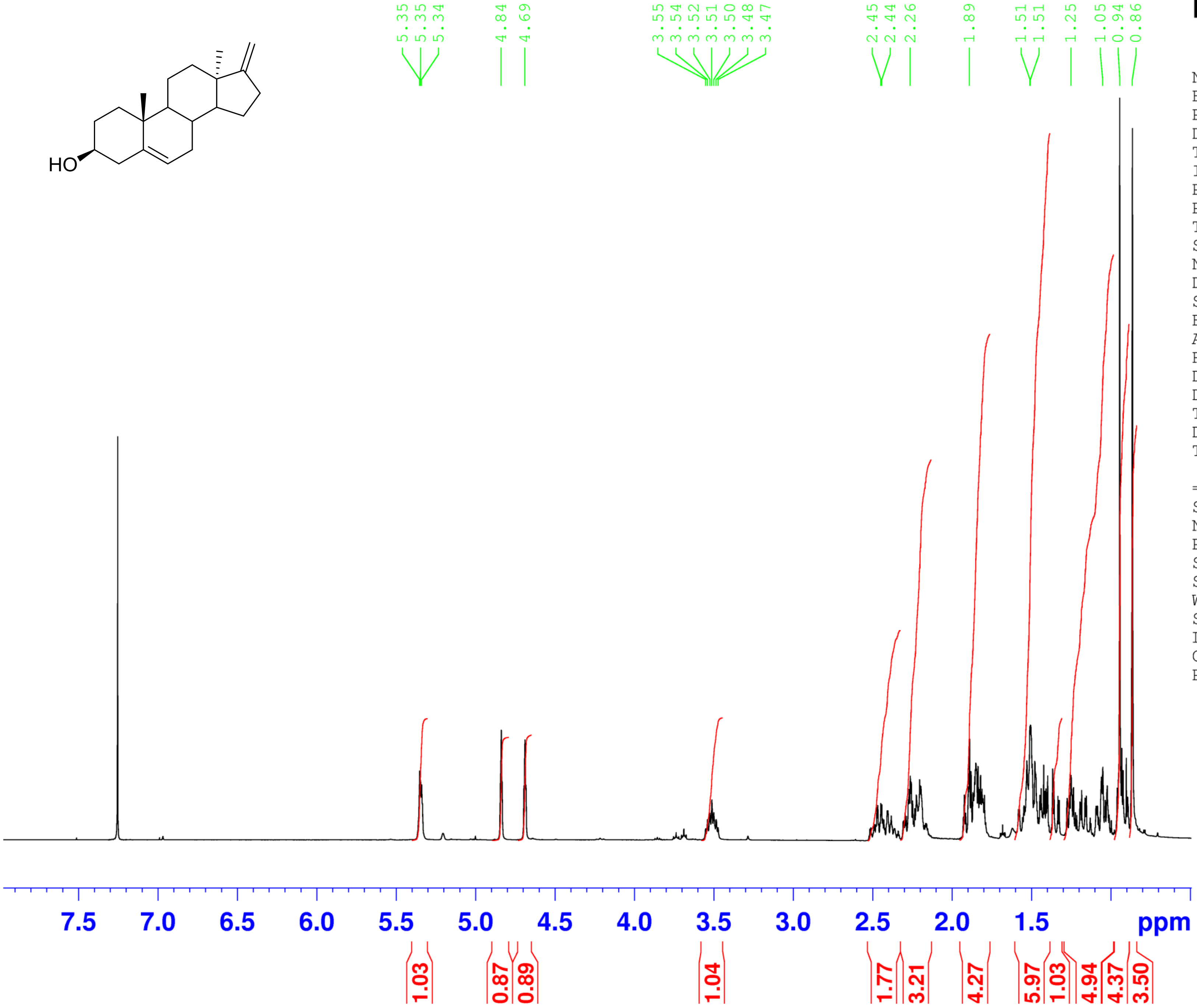

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SOLVENT              CDCl3
NS                      16
DS                       0
SWH               6393.862 Hz
FIDRES            0.195125 Hz
AQ               2.5625076 sec
RG                   54.95
DW                  78.200 usec
DE                    6.50 usec
TE                   297.0 K
D1              1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
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NUC1                    1H
P1                    9.75 usec
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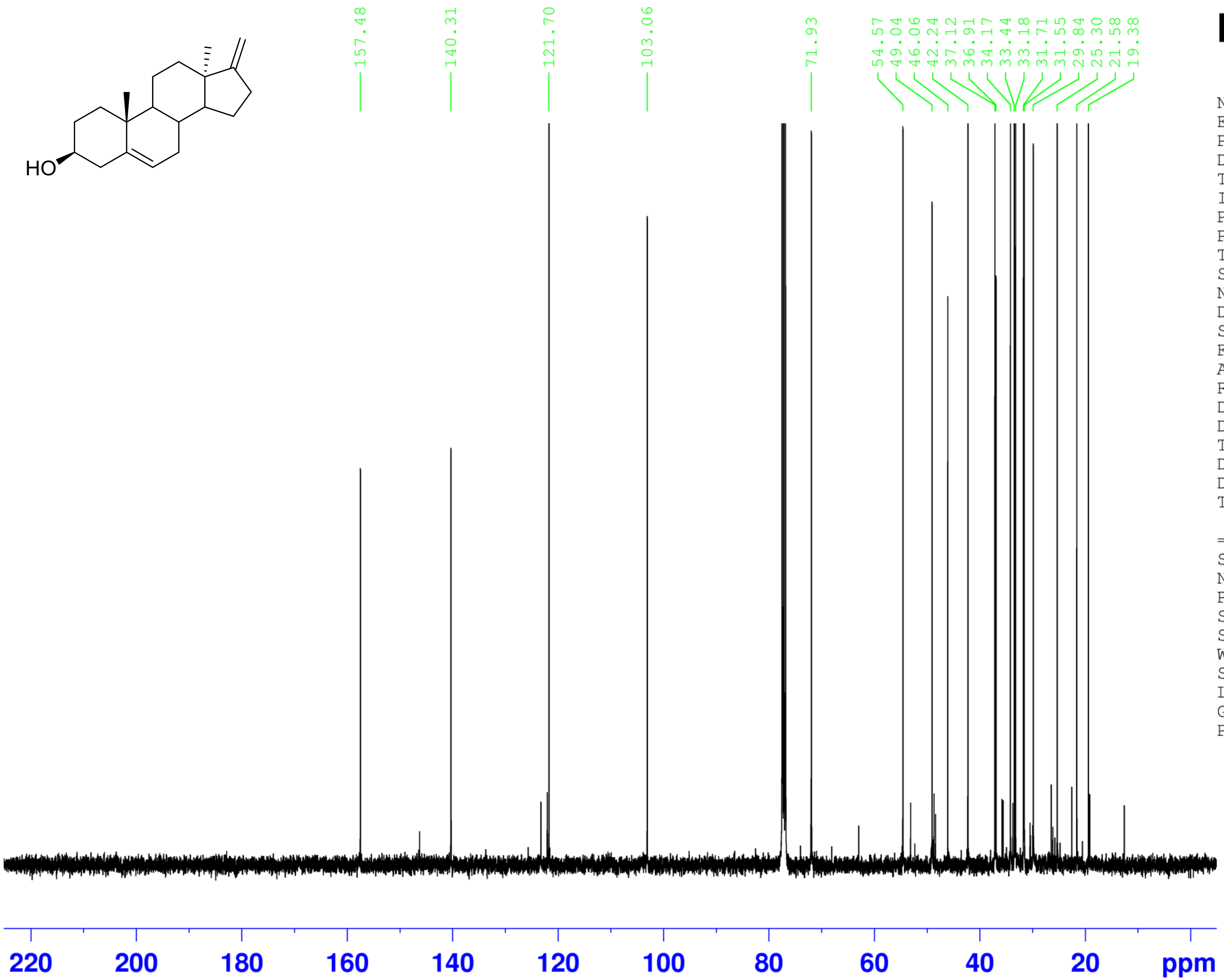

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SWH	23148.148	Hz
FIDRES	0.353213	Hz
AQ	1.4156276	sec
RG	201.19	
DW	21.600	usec
DE	6.50	usec
TE	297.9	K
D1	2.00000000	sec
D11	0.03000000	sec
TD0	1	

======== CHANNEL f1 ========

SFO1	100.6238359	MHz
NUC1	13C	
P1	9.00	usec
SI	32768	
SF	100.6127562	MHz
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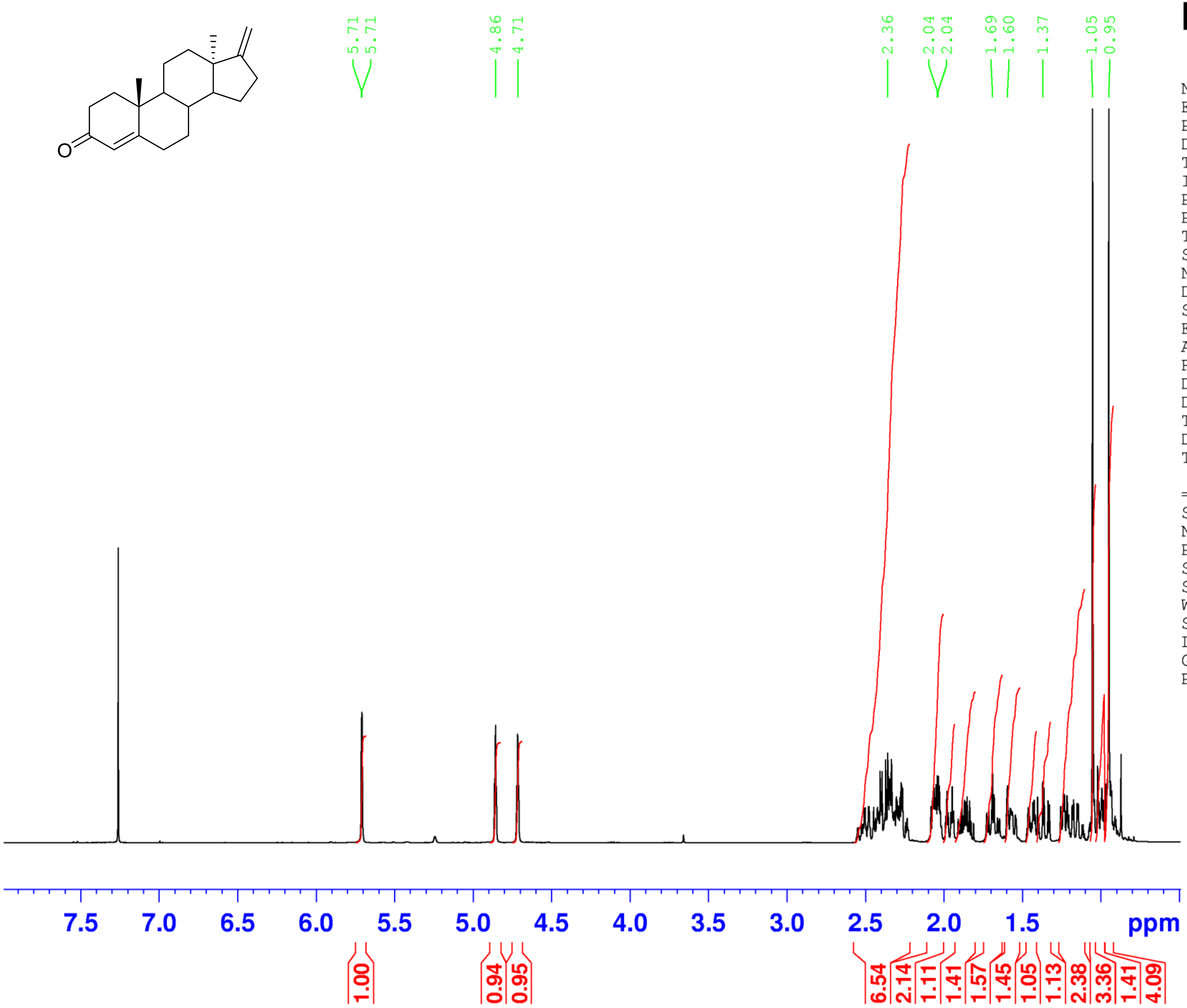

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NS                      16
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FIDRES            0.195125 Hz
AQ               2.5625076 sec
RG                   49.08
DW                  78.200 usec
DE                    6.50 usec
TE                   297.4 K
D1             1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1           400.1330010 MHz
NUC1                    1H
P1                    9.75 usec
SI                   16384
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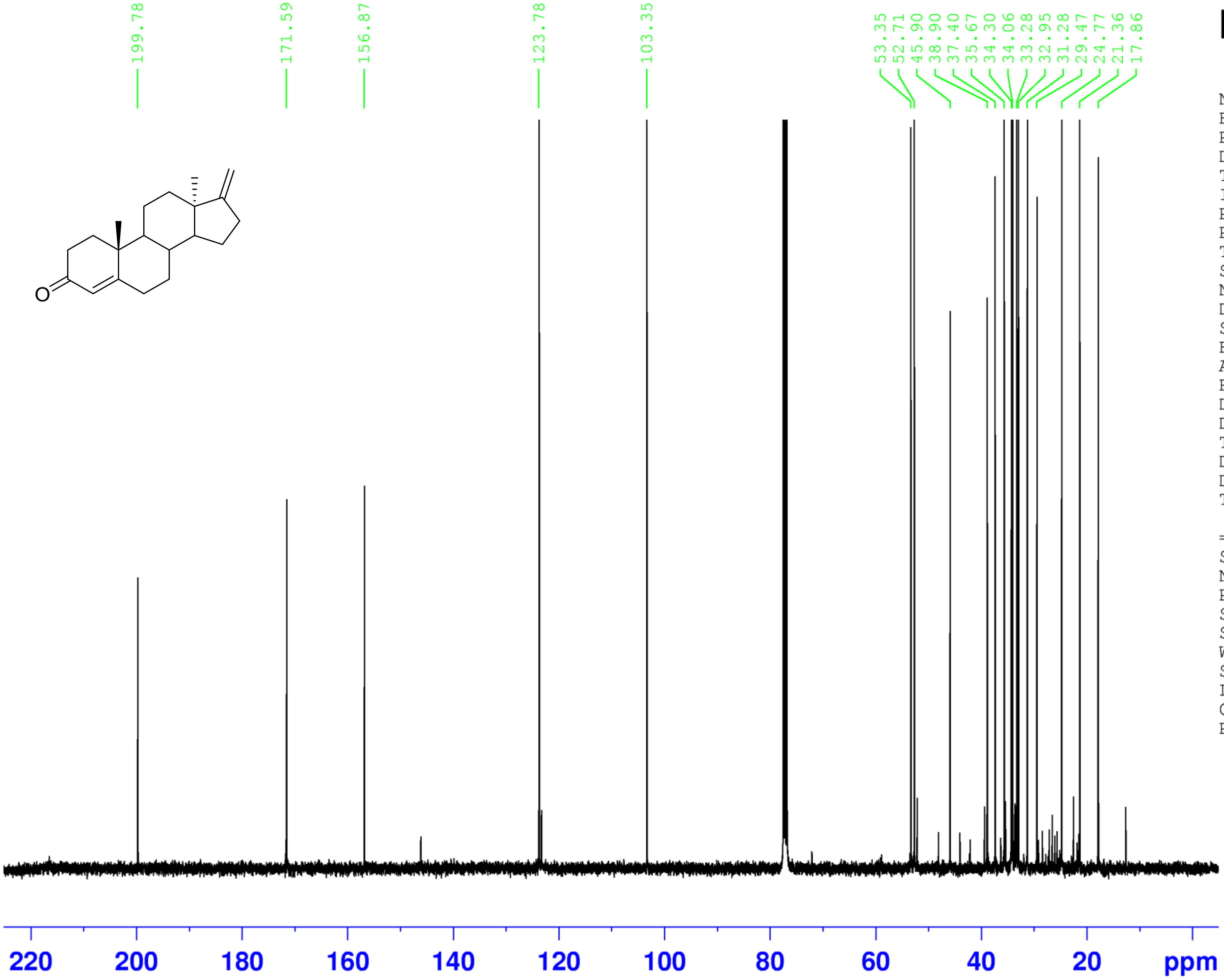

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PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                  2048
DS                     4
SWH            23148.148 Hz
FIDRES          0.353213 Hz
AQ             1.4156276 sec
RG                201.19
DW                21.600 usec
DE                  6.50 usec
TE                 298.0 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         100.6238359 MHz
NUC1                 13C
P1                  9.00 usec
SI                 32768
SF           100.6127555 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
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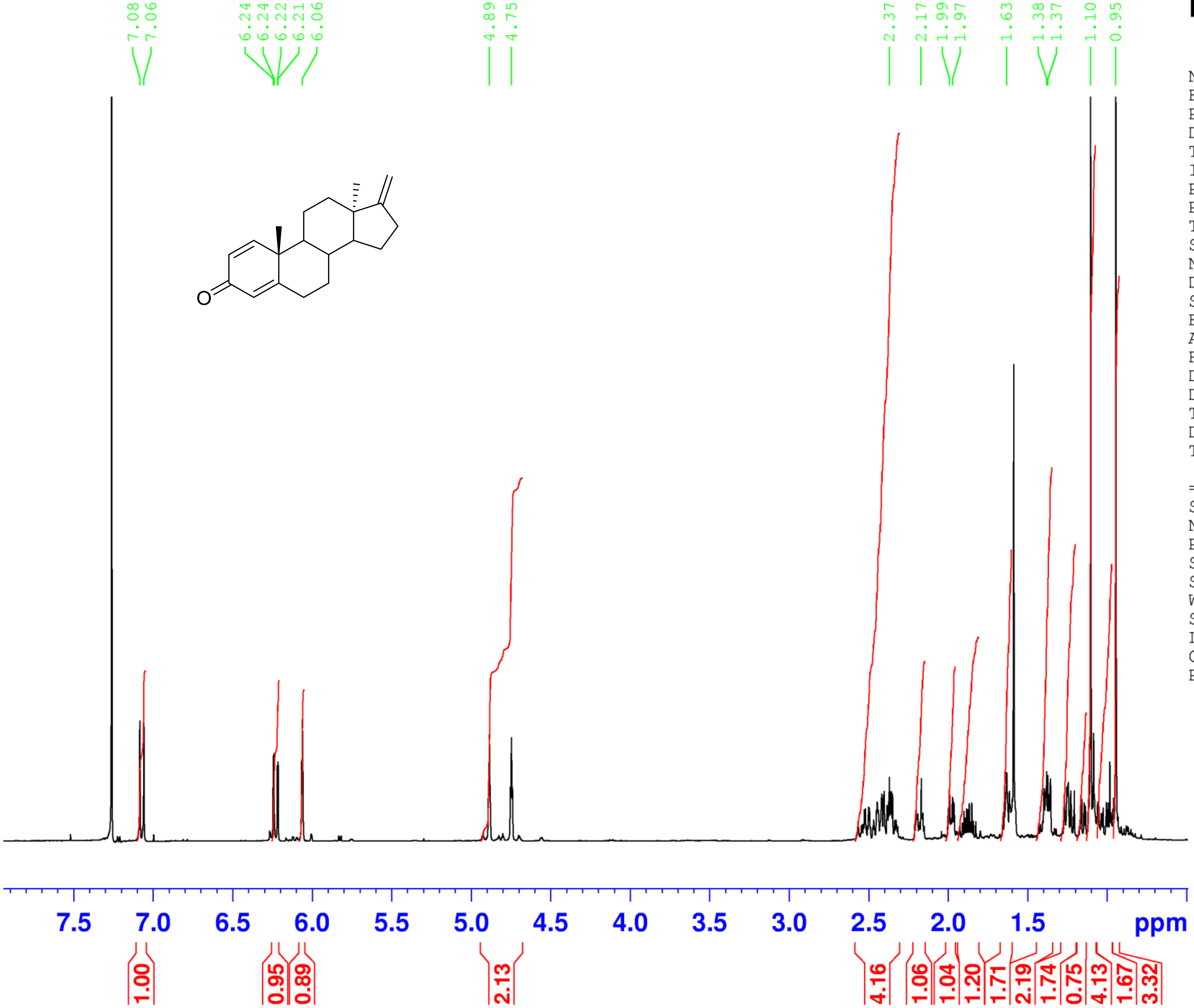

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FIDRES            0.195125 Hz
AQ               2.5625076 sec
RG                  201.19
DW                  78.200 usec
DE                    6.50 usec
TE                   296.9 K
D1              1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
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NUC1                    1H
P1                    9.75 usec
SI                   16384
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WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
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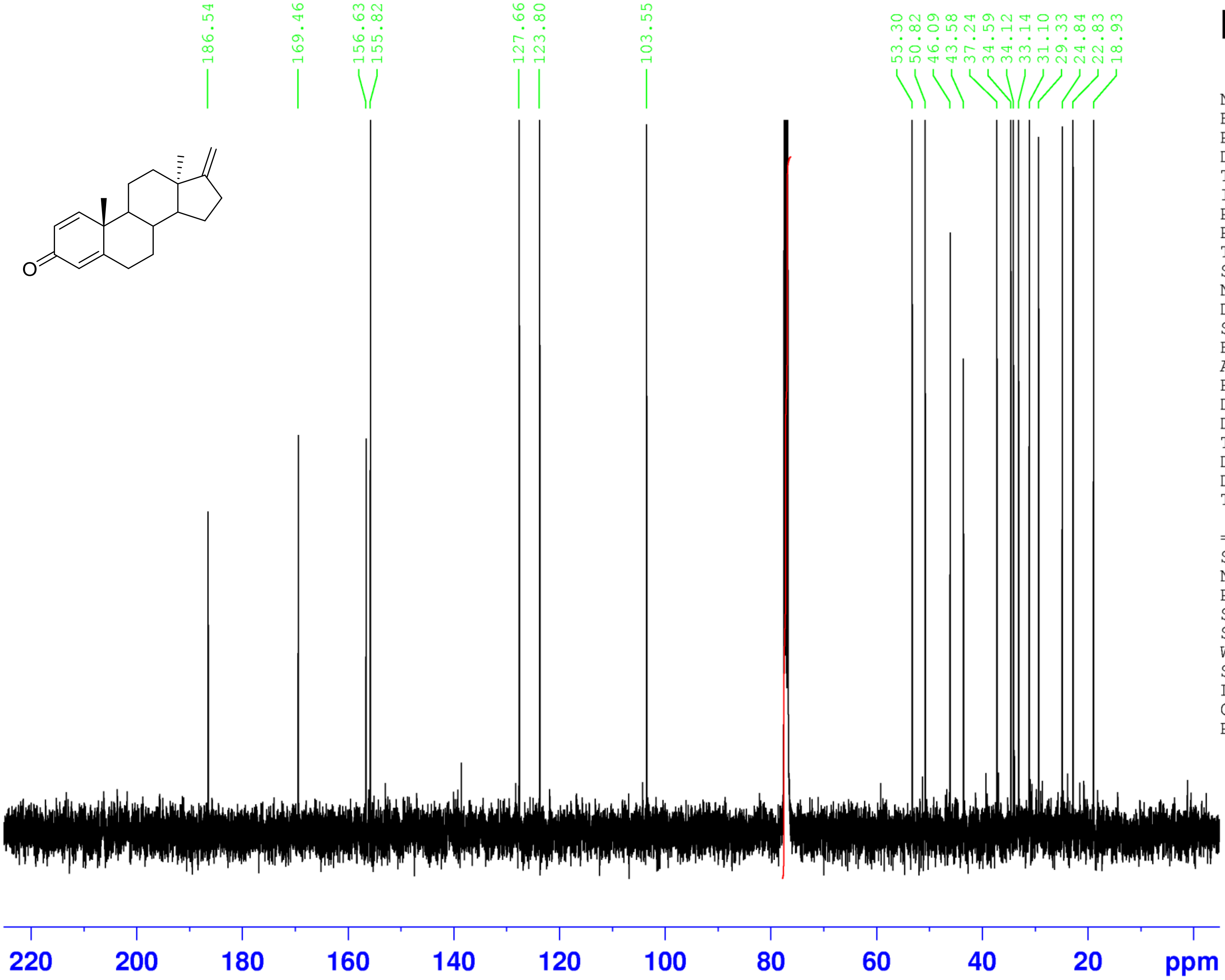

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FIDRES	0.353213 Hz
AQ	1.4156276 sec
RG	201.19
DW	21.600 usec
DE	6.50 usec
TE	297.8 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1

======== CHANNEL f1 ========

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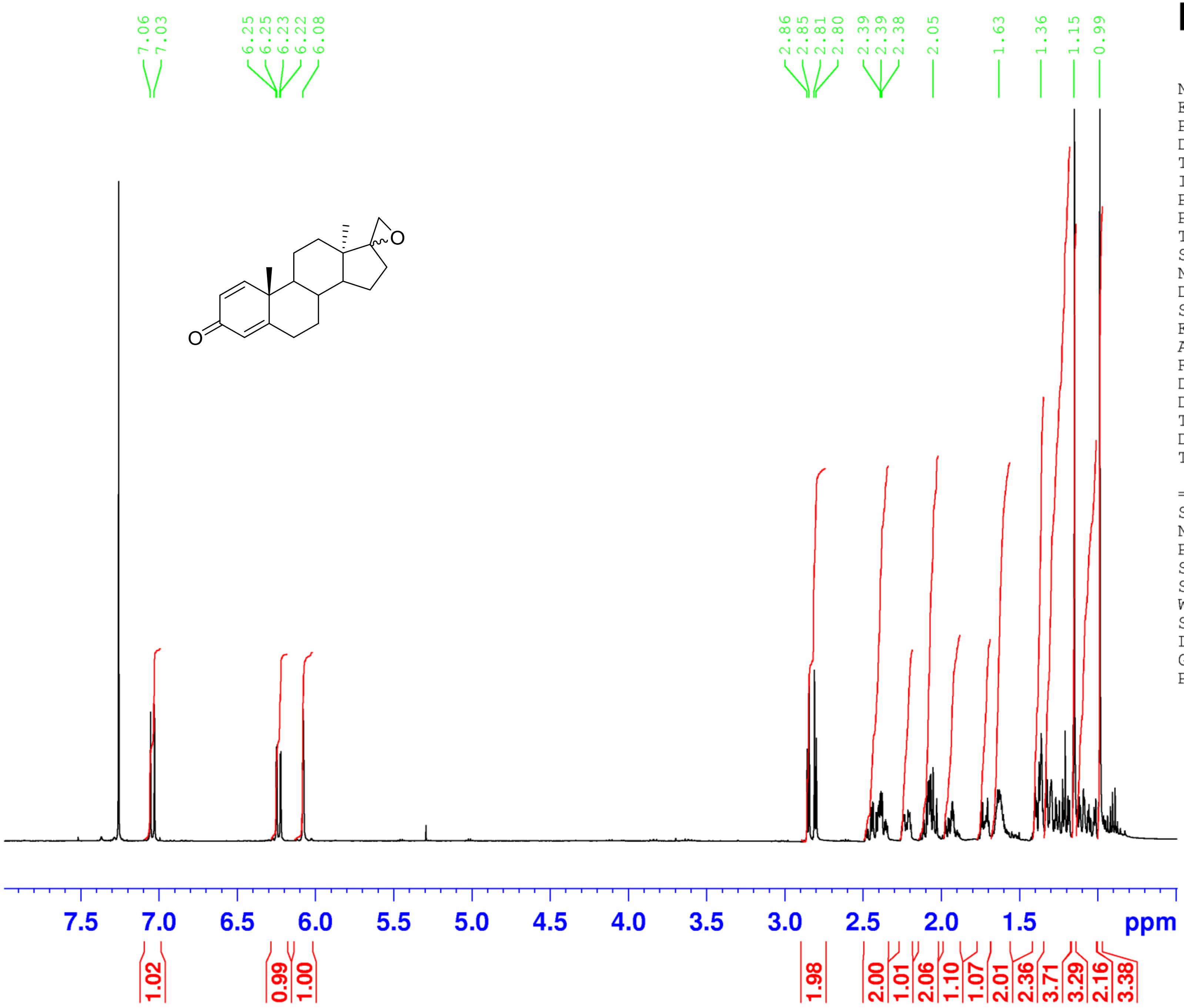

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DE                     6.50 usec
TE                    296.8 K
D1               1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
SFO1            400.1330010 MHz
NUC1                     1H
P1                     9.75 usec
SI                    16384
SF              400.1300098 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
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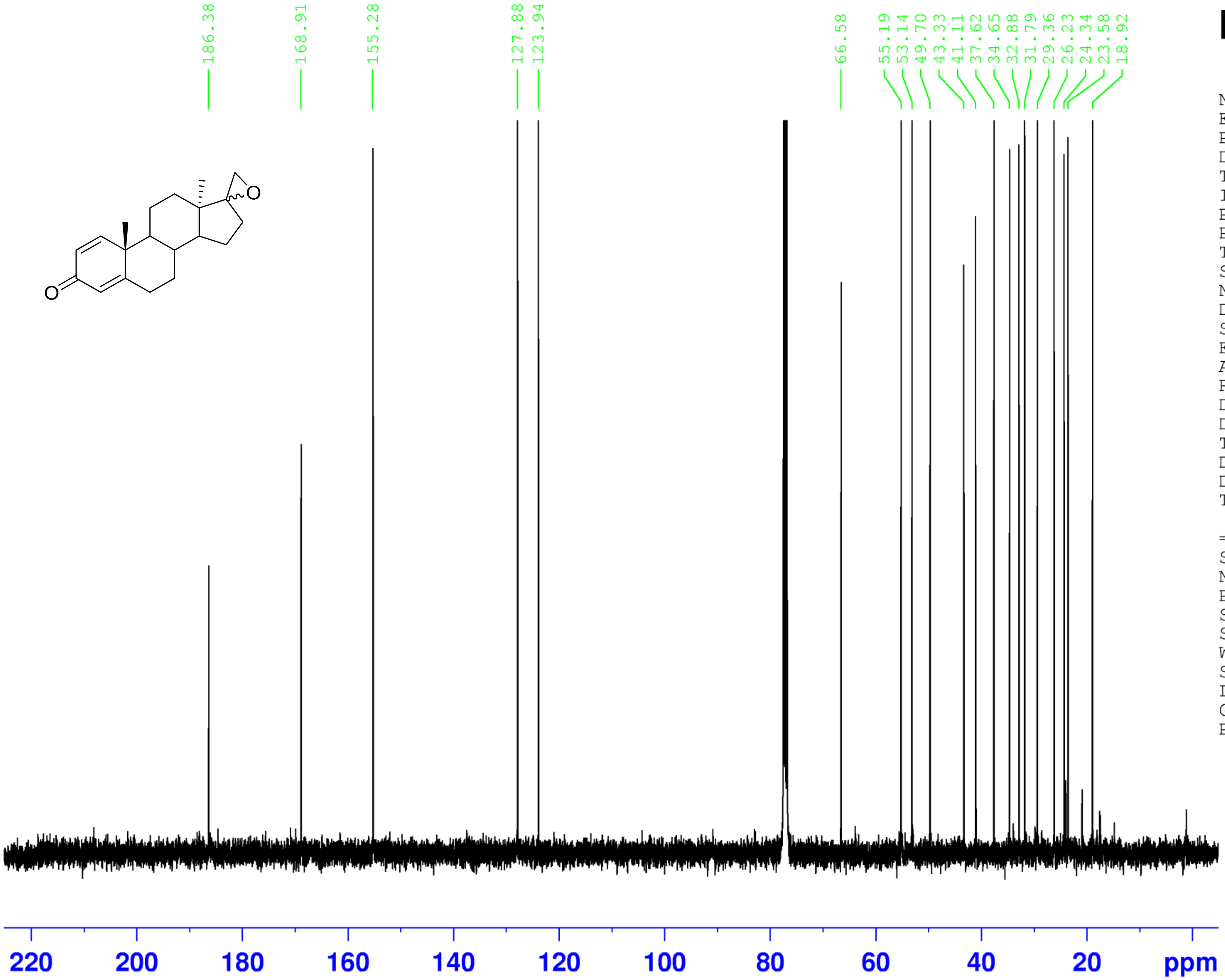

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SOLVENT             CDCl3
NS                   3000
DS                      4
SWH             23148.148 Hz
FIDRES           0.353213 Hz
AQ              1.4156276 sec
RG                 201.19
DW                 21.600 usec
DE                   6.50 usec
TE                  297.8 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                     1

======== CHANNEL f1 ========
SFO1          100.6238359 MHz
NUC1                  13C
P1                   9.00 usec
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SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
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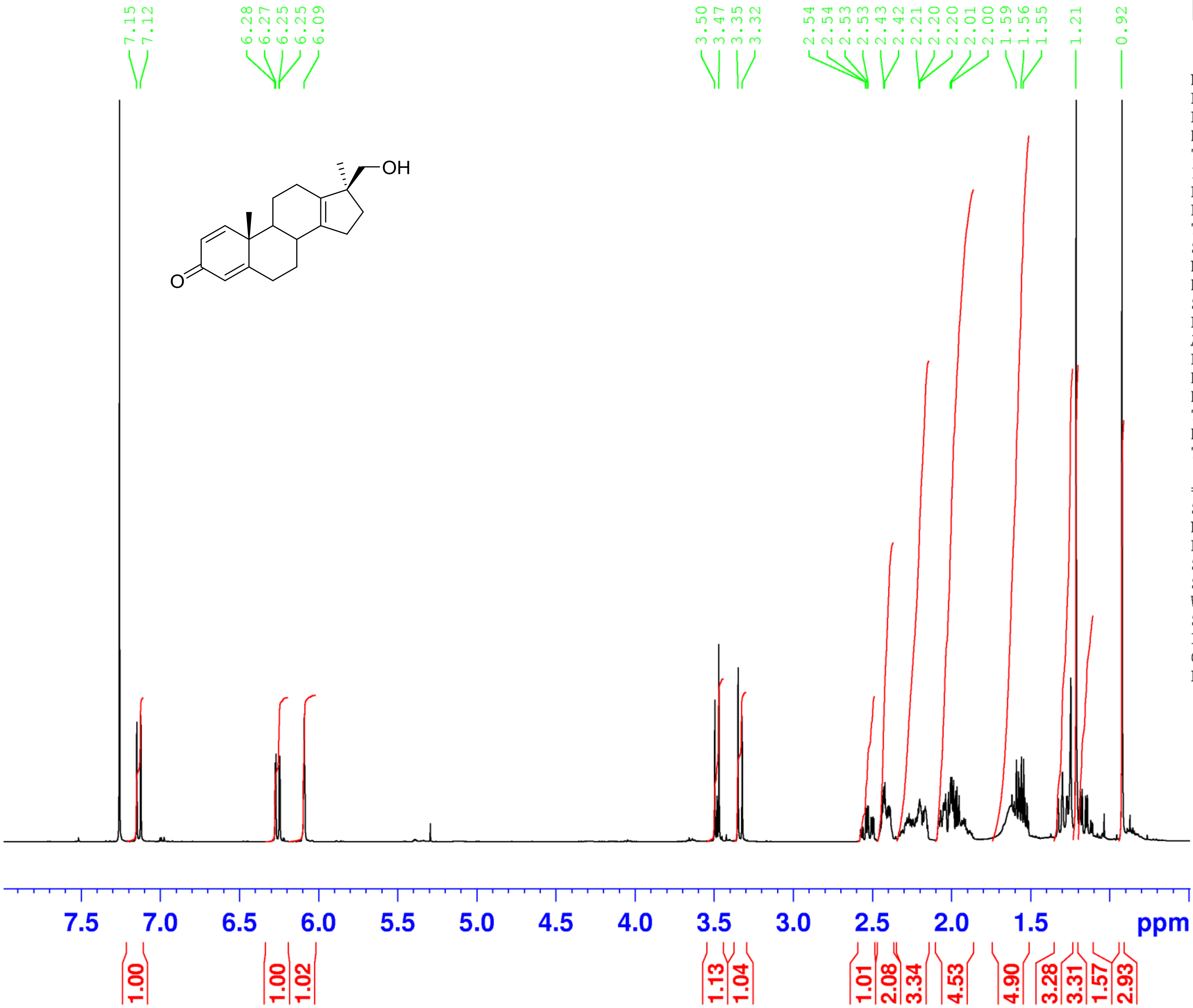

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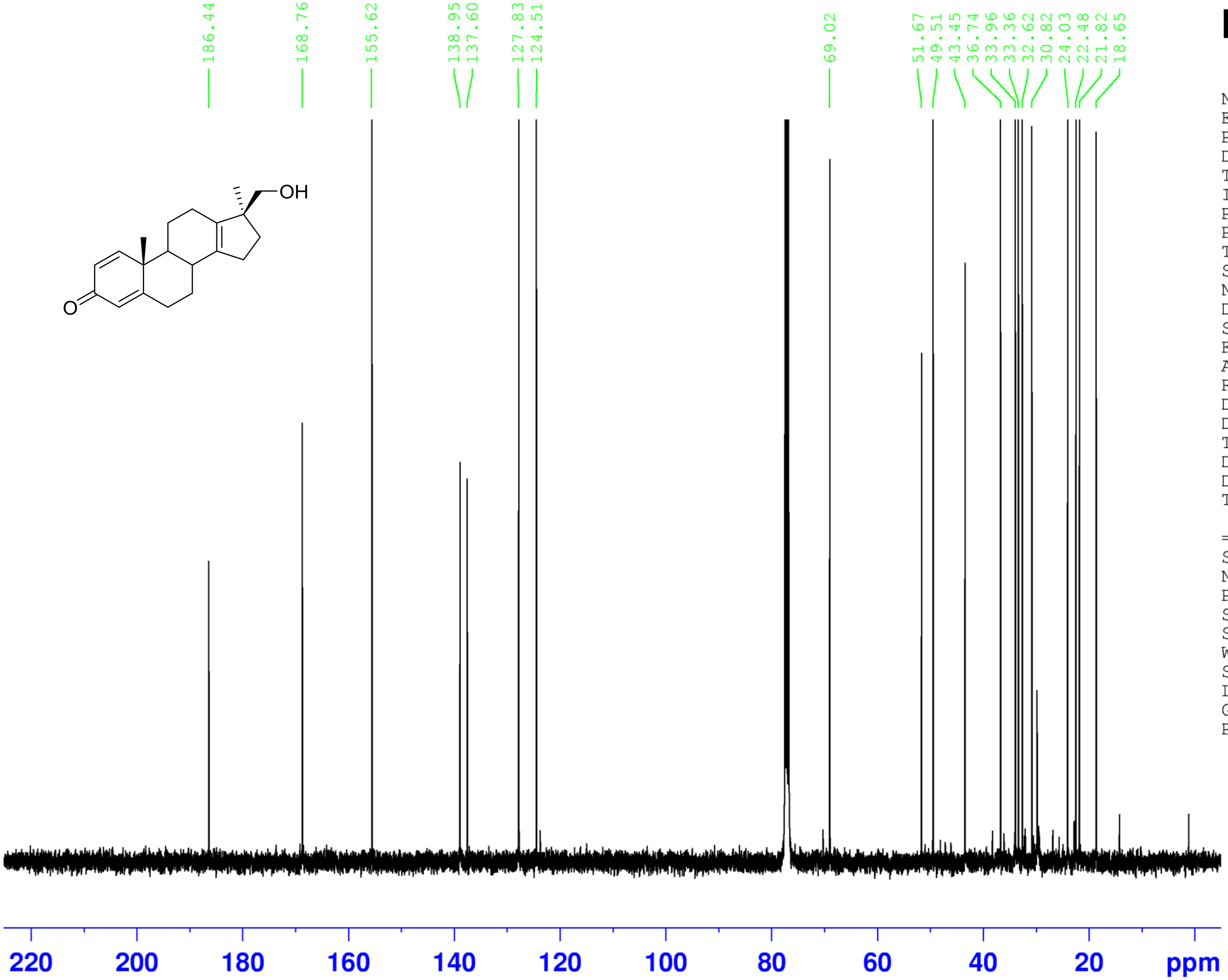
TD                   32768
SOLVENT              CDCl3
NS                      64
DS                       0
SWH               6393.862 Hz
FIDRES            0.195125 Hz
AQ               2.5625076 sec
RG                  127.26
DW                  78.200 usec
DE                    6.50 usec
TE                   297.3 K
D1              1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1          400.1330010 MHz
NUC1                   1H
P1                    9.75 usec
SI                   16384
SF            400.1300098 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```



```
NAME                NK-076
EXPNO                    2
PROCNO                   1
Date_             20150516
Time                  2.44
INSTRUM              spect
PROBHD   5 mm PABBO BB/
PULPROG            zgpg30
TD                   65536
SOLVENT              CDCl3
NS                    8192
DS                       4
SWH              23148.148 Hz
FIDRES            0.353213 Hz
AQ               1.4156276 sec
RG                  201.19
DW                  21.600 usec
DE                    6.50 usec
TE                   297.9 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1         100.6238359 MHz
NUC1                 13C
P1                  9.00 usec
SI                 32768
SF           100.6127553 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```