The Total Synthesis of Analogues of Withanolide F

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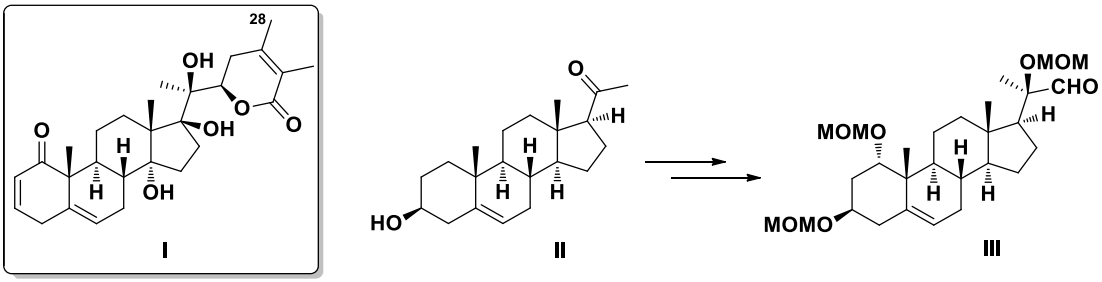
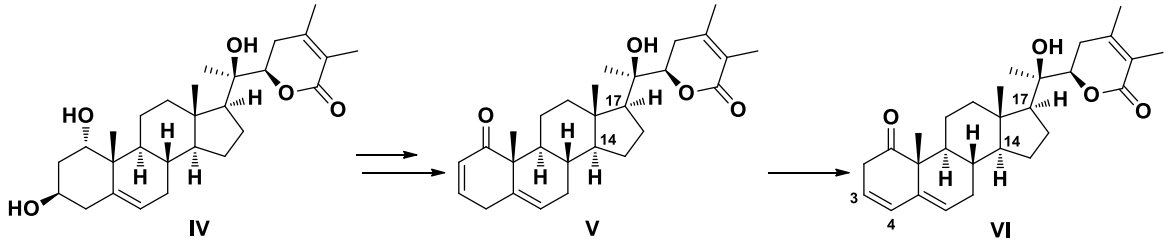
Abstract

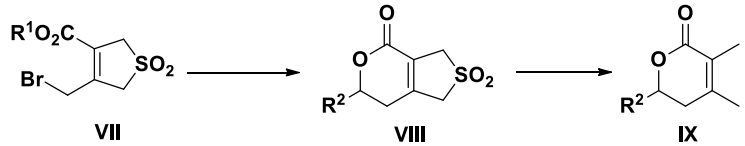
The total synthesis of analogues of withanolide F **I**, a highly oxygenated C-28 steroidal lactone natural product isolated from the leaves of the plant *Withania adpressa* is discussed herein. Chapter 1 describes the classification of the withanolides, their biological activity and previous studies towards the synthesis of the withanolides. Based on well-established chemistry, commercially available pregnenolone **II** was transformed into the key aldehyde **III** in nine steps, two steps fewer than previously published routes, with an optimised 14% yield as summarised in Chapter 2



Chapter 3 outlines the synthetic efforts towards the construction of the δ-lactone side chain in compound **IV**. The synthesis of 14,17-dideoxy-17-*epi*-withanolide F **V** was then completed *via* a straightforward acetylation-oxidation-elimination sequence from triol **IV**. Isomerisation of the 2,3-double bond delivered a novel analogue of withanolide F **I**, 3,4-dihydro-$\Delta^{3,4}$-14,17-dideoxy-17-*epi*- withanolide F **VI**, as reported in Chapter 4.



The development of new methodology to form δ-lactone side chain **IX**, a key structural feature of natural products **I**, **V** and **VI**, from cyclic sulfone **VII** *via* the heterocyclic lactone **VIII** based on the Dreiding-Schmidt reaction was investigated. Chapter 5 discusses the studies towards the synthesis of strategic sulfone **VII**.



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Declaration

The research in this Thesis was carried out at the University of York and at AnalytiCon Discovery GmbH between October 2011 and October 2013. The work is, to the best of my knowledge, original except where due reference has been made to other workers.

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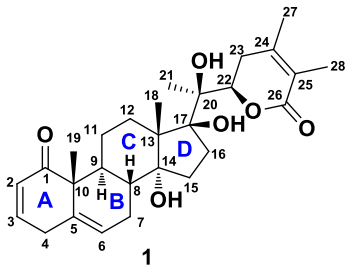
Chapter 1. Introduction: Withanolide Natural Products.

1.1. Withanolide F (1)

1.1.1. Isolation and biological activity

Withanolide F (**1**) (**Figure 1i**) is a natural compound first extracted in 1977 by Glotter and co-workers as a minor component of *Withania somnifera* Dunal.[1] It has also been extracted from other *Withania* species such as the aerial parts of *Withania coagulans*,[2] and the leaves of *Withania adpressa* (**Figure 1ii**).[3] This molecule presents interesting biological properties including strong immunosuppressive activity expressed as the inhibition of B- and T-cell proliferation on murine spleen cells (1.66 μM).[4] Furthermore, withanolide F (**1**) exhibits potent cytotoxicity against Hep2 human cancer cell lines (4.4 μg/mL) reinforcing its potential as an antiproliferative agent and thus, its great interest in cancer chemotherapy.[5]



1

i **ii**

Figure 1 i. Structure of withanolide F (**1**), **ii**. Withania species.

1.1.2. Structural features and assignment

The structural features and assignments of withanolide F (**1**) have been determined through ^{1}H-NMR and ^{13}C-NMR spectroscopy (in conjunction with COSY and HMBC experiments) together with IR, UV and mass spectrometry. This compound was described as a colourless solid with a melting point of 159-160 °C and UV (MeOH) maximum at 226 nm which is characteristic for an α,β-unsaturated carbonyl chromophore. The ^{1}H-NMR spectrum of withanolide F (**1**) showed three downfield signals at δ 5.79-5.74 (m), δ 6.88

(ddd, $J_{3,2}$ = 9.8 Hz, $J_{3,4\beta}$ = 4.9 Hz, $J_{3,4\alpha}$ = 2.2 Hz) and δ 5.60-5.56 (m) representative of protons H-2, H-3 and H-6, respectively, and a downfield methine signal at δ 4.65 (dd, $J_{22,23\alpha}$ = 12.7 Hz, $J_{22,23\beta}$ = 3.6 Hz) representative of proton H-22 characteristic of the δ-lactone side chain.[3]

1.2. Structurally Related Natural Products

1.2.1. General overview of withanolides

Withanolides are a class of natural compounds isolated from plants of the family *Solanaceae* which show a rich array of biological properties. More specifically, they are secondary metabolites of the genus *Withania*. From a structural point of view, the withanolides are characterised by a highly oxygenated A/B-ring system of a steroid skeleton which is based on an ergostane core structure. They are also distinguished by the presence of a δ-lactone side chain (**Figure 2**).[6]

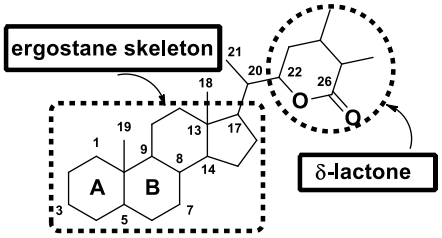


Figure 2. Withanolide skeleton.

1.2.2. Withanolide classification

The core of these interesting molecules can occur in several modifications and withanolides extracted from different species present diverse differences, albeit some of them seem to follow common patterns for the A/B-ring substitution (**Figure 3**).[6]

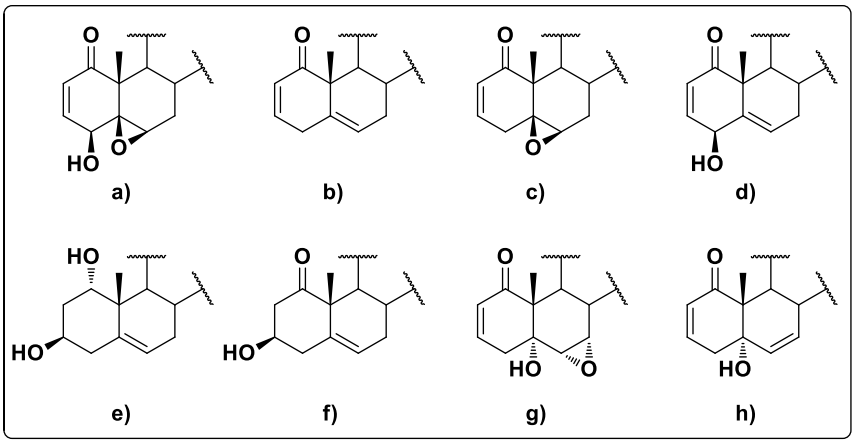


Figure 3. Common substitution patterns of the A/B-ring in withanolides.

From the discovery of the first withanolide, isolated in 1965,[7] to the end of 1989, almost 170 different compounds were isolated and characterised.[8] More recently, between 1996 and 2010 another major investigation campaign was conducted during which over 360 new withanolides were identified.[8] Considering the large number of molecules, it became necessary to establish an accurate classification of these compounds. Investigations on compounds extracted from *Withania somnifera* Dunal growing in Israel in 1968 by Glotter and Lavie led to the identification of three chemotypes, a chemically distinct entity within the same species, that helped classify the withanolides.[9] The common structural features of these three new chemotypes are shown in **Figure 4**:

- Chemotype I: 20-H withanolides (*e.g.*: Nic-11 (**2**)[10]).
- Chemotype II: 20-OH and β-oriented side chain withanolides (*e.g.*: withanolide G (**3**)[11]).
- Chemotype III: 20-OH and α-oriented side chain withanolides (*e.g.*: withanolide S (**4**)[1]).

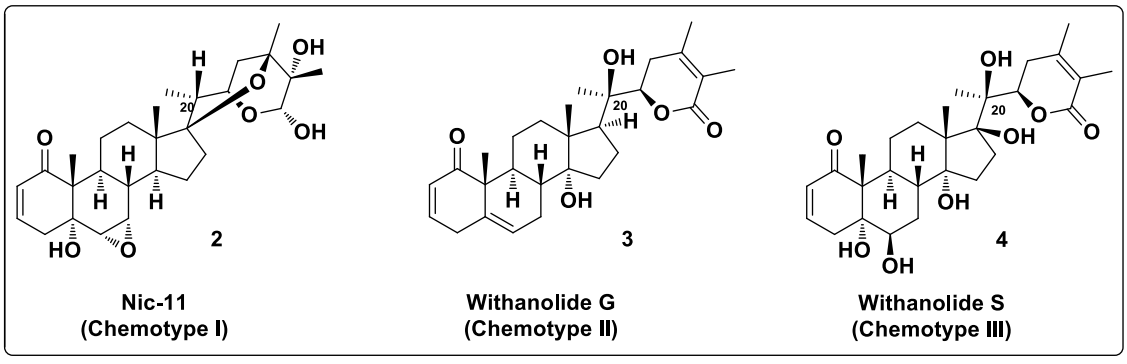


Figure 4. Chemotype classification of withanolides.

1.2.3. Withanolide bioactivity

Recent studies have showed that embryonic patterning pathways, such as Wnt, Hh (Hedgehog) and Notch, play critical roles in human cancer. Inhibition of these pathways can lead to tumour cell proliferative arrest and death.[12] Therefore, the investigation of natural small molecules that have anti-tumoural effects *in vitro* would be a promising therapeutic strategy in cancer treatment. Many natural compounds extracted from medicinal plants are an invaluable source of complex molecules with a number of pharmacological properties. Amongst them are withanolides which have been thoroughly studied since 1965 and highly appreciated for their biological activities including anticancer activity *in vitro*, antifeedant, immunosuppressive, antimicrobial and anti-inflammatory activities.[13] **Figure 5** shows a selection of structurally different withanolides exhibiting these diverse biological activities.

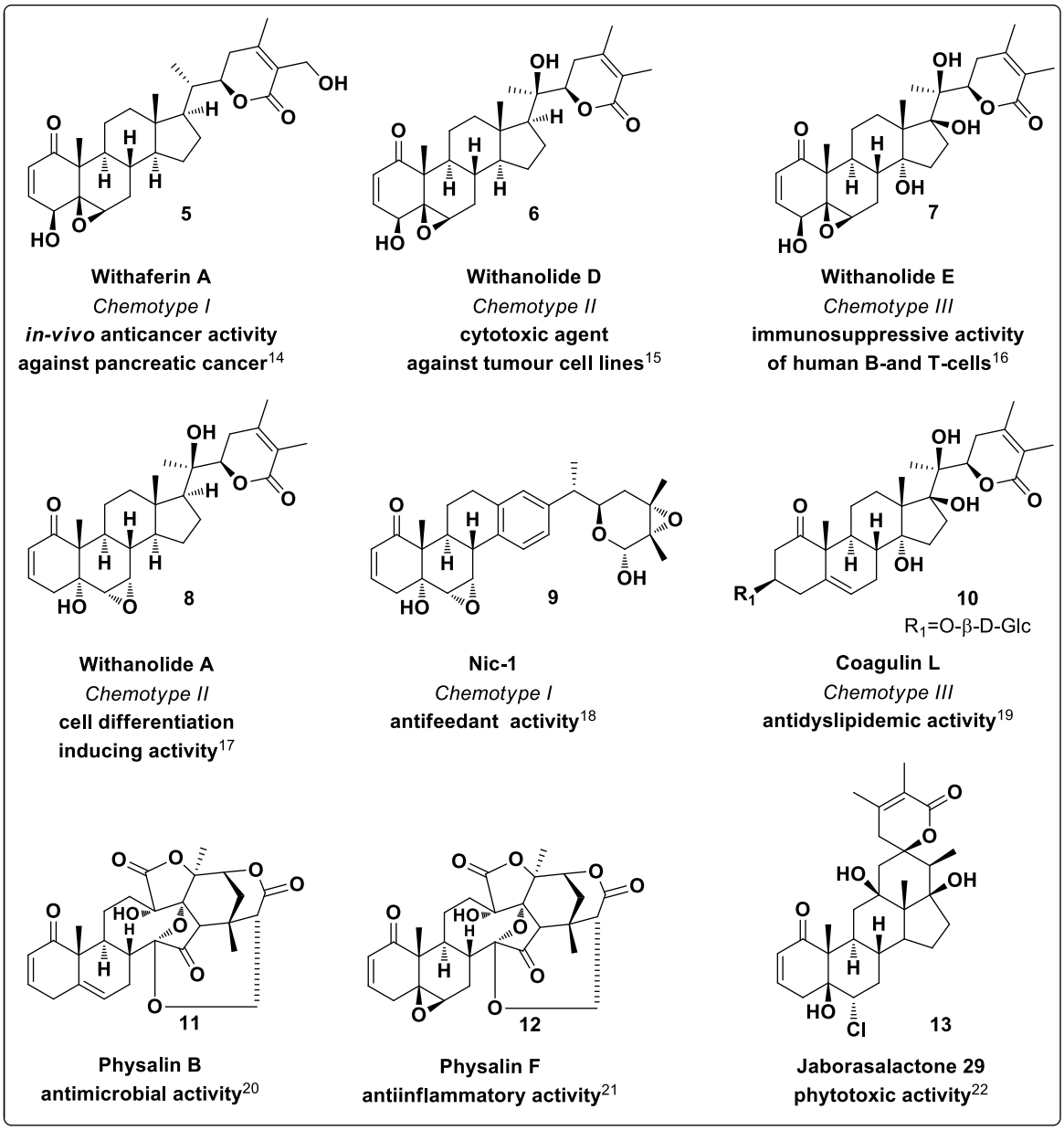


Figure 5. Examples of well-known withanolides and their biological properties.

Furthermore, *in vitro* screening of cardiac glycosides, natural compounds that belong to the same plant steroids as withanolides, has produced strong inhibitors of Hh/Gli signalling pathway expressed in human pancreatic cancer cells (**Figure 6**).[12] Interestingly, these two families of natural products present structural similarities, including a lactone side chain and the aglycone functionality, which might be helpful in future SAR studies.

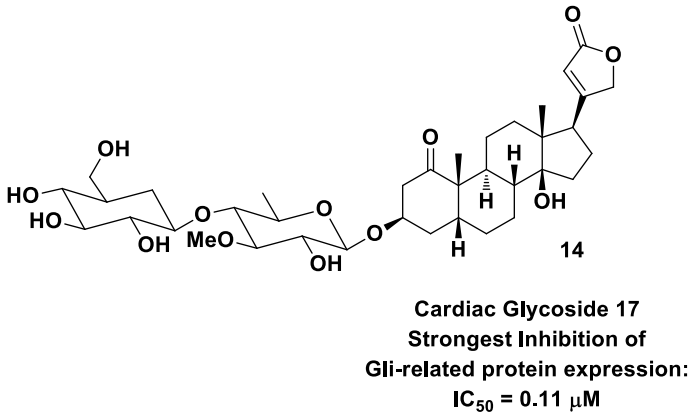


Figure 6. Structure of cardiac glycoside 17 (**14**).

Due to this broad spectrum of biological activity and their intriguing structural features, the investigation of withanolides would be a promising starting point in the development of new therapeutic agents.

1.3. Biosynthesis

The biogenetic aspects of withanolides have not been studied in detail and there is very little information on their biosynthesis. In 1976, Goodwin *et al*. suggested that 24-methylene-cholesterol (**15**) could be a sterol precursor of withanolides based on studies using radiolabelled 24-methylene-cholesterol (**15**) which was incorporated into withanolides such as withaferin A (**5**) and withanolide D (**6**) (**Figure 7**).[23]

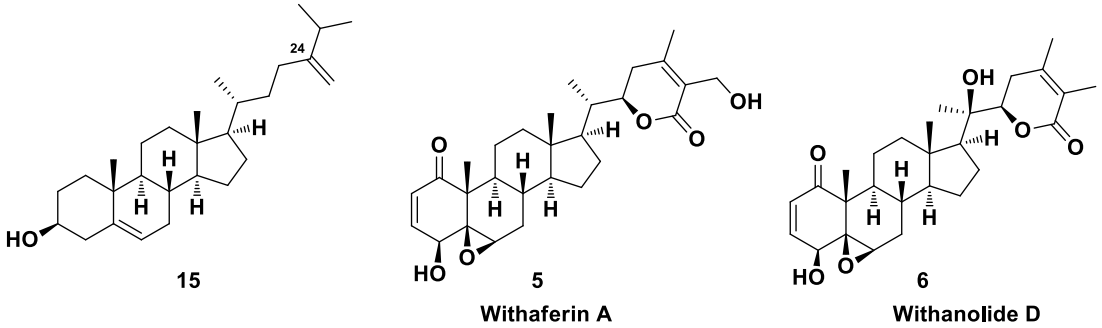
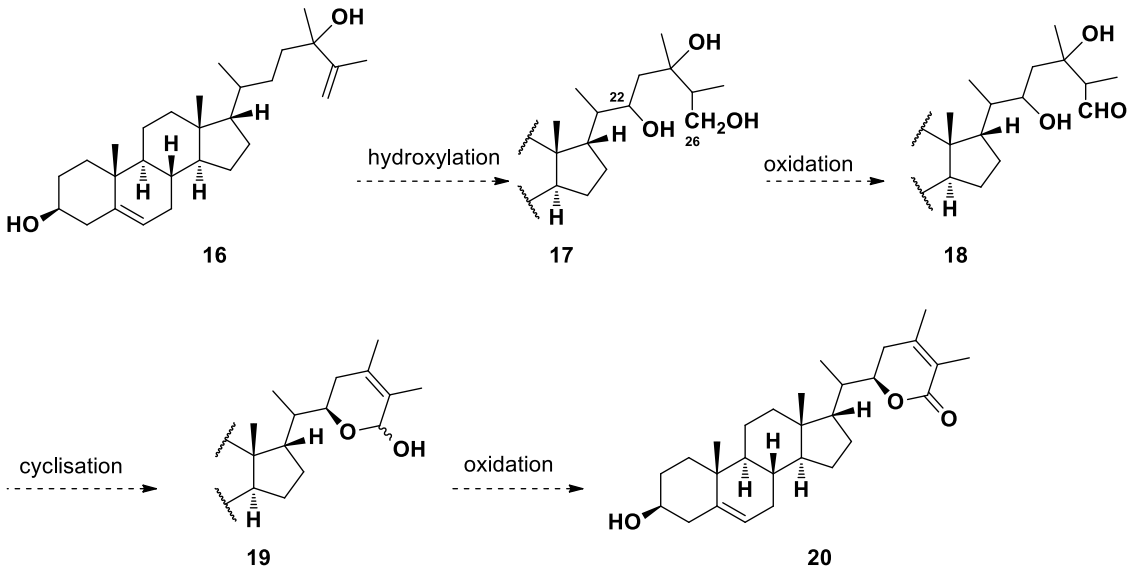


Figure 7. Structure of 24-methylene-cholesterol (**15**), withaferin A (**5**) and withanolide D (**6**).

Based on crossbreeding studies by Lavie's group in 1977,[24] Garg and co-workers identified the ergostene diol **16** as a potential intermediate in the biosynthetic sequence leading to the

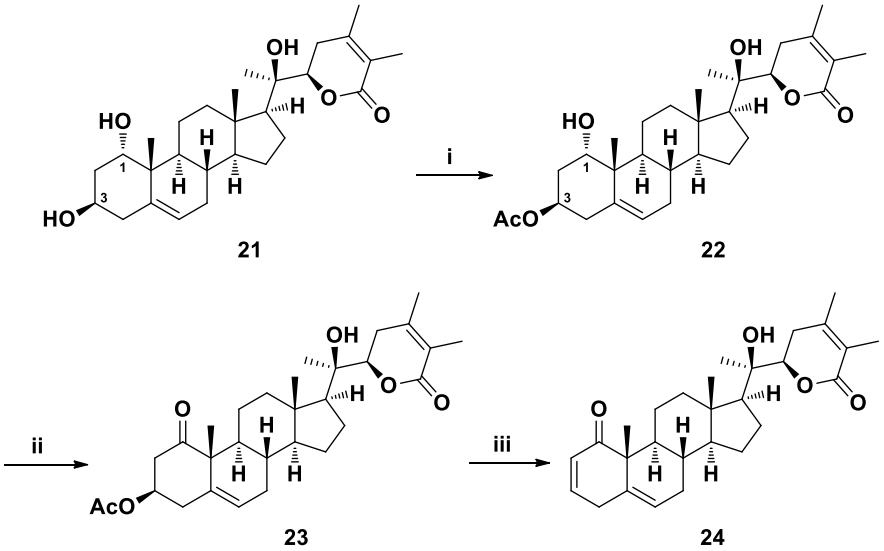
formation of the side chain lactone of withanolides.[2] Their biosynthetic proposal suggested that the appropriate hydroxylation of C-22 and C-26 and subsequent cyclisation would form the key lactol side chain **19** which has been reported to be present in various withanolides. The final oxidation step of C-26 hydroxyl group would furnish the desired unsaturated δ-lactone side chain characteristic of withanolides (**Scheme 1**).



Scheme 1. Proposed intermediates in the biogenesis of the δ-lactone side chain of the withanolides.

In 1981, Lavie and co-workers proposed that a new withanolide **21**, an analogue of withanolide E (**7**) extracted from *Withania somnifera* Dunal (**Figure 8**), could be a key intermediate in the biogenesis of the withanolides.[25] This compound **21** was then submitted to biomimetic reactions involving the formation of a C-1-oxo derivative followed by the elimination of the C-3β hydroxyl group in order to build the 2-en-1-one substitution pattern of the A-ring, characteristic of various withanolides. By analogy with the synthetic sequence using 1α,3β-hydroxycholesterol developed by Ikekawa and co-workers in 1975,[26] the biomimetic synthesis began with the selective acetylation of the C-3β hydroxyl function of **21** to form monoacetate **22**. The 1α-hydroxyl group of compound **22** was subsequently oxidised using Jones' reagent followed by elimination of the 3β-acetate **23** under alkaline conditions to afford 2,5-dien-1-one **24** (**Scheme 2**). Unfortunately, no yields were reported for these steps.

Figure 8. *Withania somnifera* Dunal species.



Scheme 2. Biomimetic synthesis of 2,5-dien-1one **24**.

Reagents and conditions: ***i****.* Ac_2O*, AcOH, 80 °C, 4 h,* ***ii****.* CrO_3*, acetone, rt,* ***iii****. 1.5% aq. NaOH, 1,4-dioxane, rt, 6 h.*

Furthermore, Lavie's group concluded that the presence of the δ-lactone side chain in the isolated compound **21** implied that the formation of the unsaturated side chain of withanolides *in vivo* occurred prior to the oxidation reactions of the A-ring.[25] This interesting observation might be useful for the development of future synthetic methods.

1.4. Previous Total Synthesis of Withanolides

Synthetic achievements on the withanolides have been mainly focused on the three well-known withanolides extracted from the *Withania somnifera* Dunal plant by Lavie *et al.* (**Figure 9**): the first withanolide isolated in 1965 was withaferin A (**5**) (chemotype I),[7] followed by withanolide D (**6**) (chemotype II) isolated in 1968[9] and withanolide E (**7**) (chemotype III) isolated in 1972. [27]

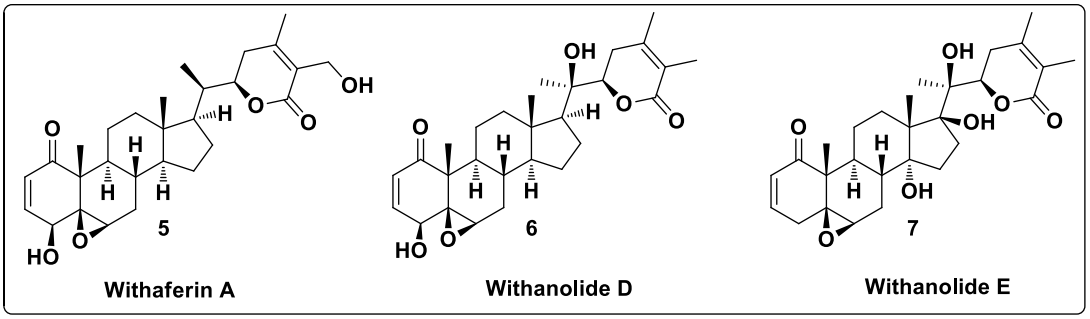
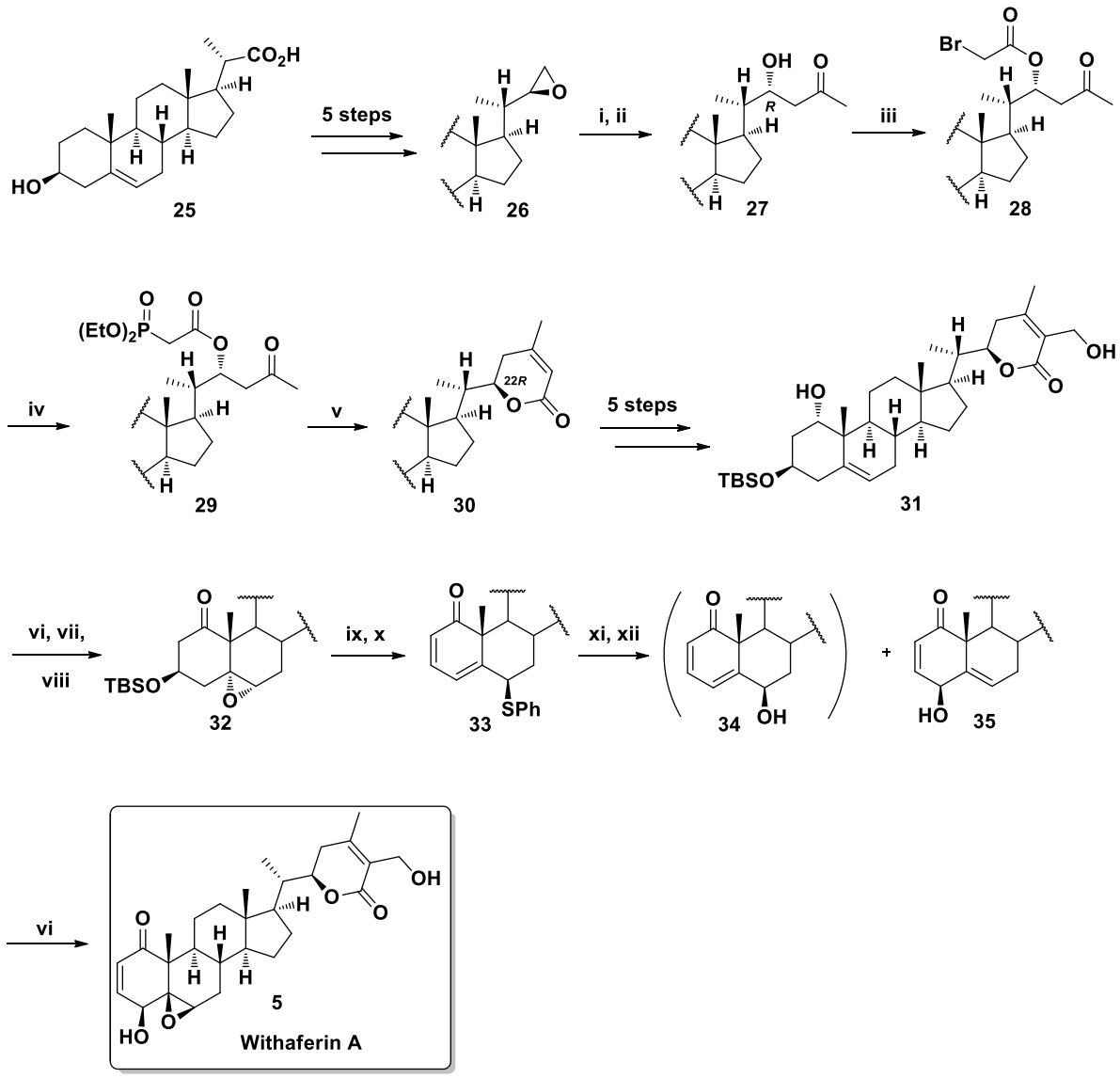


Figure 9. Well-known withanolides.

1.4.1. The synthesis of withaferin A (**5**)

The first stereoselective synthesis of withaferin A (**5**) was carried out by Ikekawa's group and was based on their own previous work on the withanolides.[28] Epoxide **26** was obtained from 3β-hydroxybisnorchol-5-enoic acid (**25**) in 5 steps in 7% yield and was converted into diethyl phosphonate **29**, key precursor for the δ-lactone formation, *via* a bromoacetylation step followed by an Arbuzov reaction (**Scheme 3**). The subsequent intramolecular Wittig-Horner condensation allowed the synthesis of the desired δ-lactone side chain **30**. The introduction of the hydroxymethyl group at C-25 was achieved using standard reaction conditions. Thus, the δ-lactone moiety **31** was synthesised in 14% yield over 10 steps from carboxylic acid **25**. The key step of this total synthesis was the allyl sulfoxide-sulfenate rearrangement of 6β-phenylthio-2,4-dienone **33**. Hence, the rearrangement of the conjugated 2,4-dienone **33** under rigorous conditions, *i.e*. no oxygen and light, enabled the formation of the desired 4β-hydroxy-2,5-dien-1-one **35**, in 52% yield which after further epoxidation gave (+)-withaferin A (**5**) in an overall 0.09% yield.

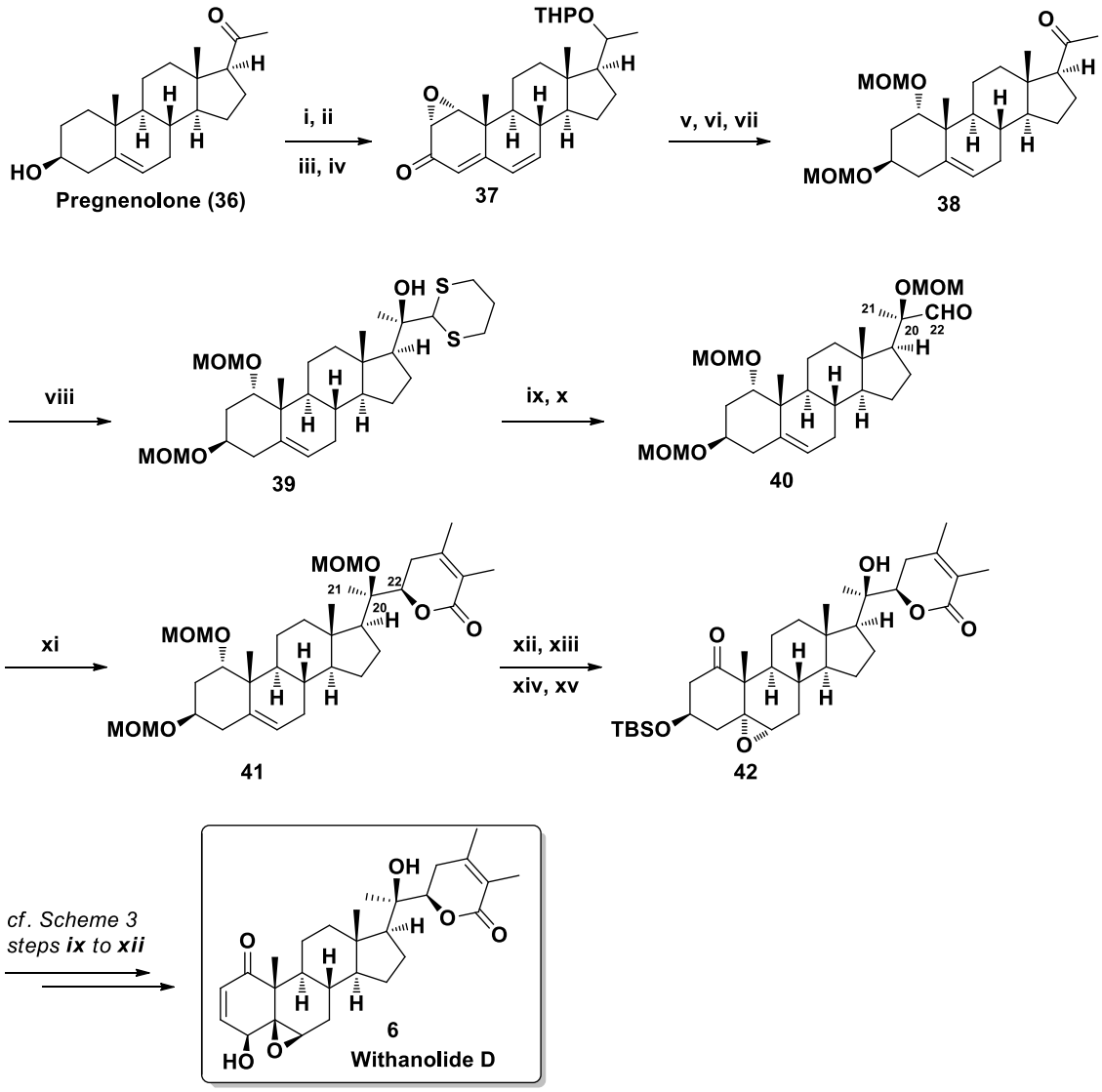


Scheme 3. Synthesis of withaferin A (**5**).

Reagents and conditions: ***i****. 2-Me-1,3-dithiane,* ^{n}*BuLi, THF, −78 °C;* ***ii****. HgO,* BF_3•Et_2O*, rt (76% over two steps);* ***iii****.* $BrCH_2COBr$*, pyridine,* Et_2O*, 0 °C;* ***iv****.* $P(OEt)_3$*, 100 °C, 50 min;* ***v****. NaH, THF, rt, 30 min (79% over three steps);* ***vi****. m-CPBA,* $CHCl_3$*;* ***vii****. TBDMSCl, imidazole, DMF;* ***viii****. PDC, DMF (49% over three steps);* ***ix****. PhSH,* Al_2O_3*,* Et_2O *(37%);* ***x****. p-TsOH;* H_2O*, benzene, 60 °C (100%);* ***xi****. m-CPBA,* $CHCl_3$*;* ***xii****. excess* $P(OMe)_3$*, MeOH, THF, rt, absence of light (52% of* ***35****).*

1.4.2. The synthesis of withanolide D (**6**)

The first stereocontrolled synthesis of withanolide D (**6**) was reported in 1984 by Ikekawa and co-workers.[29] The key steps of the synthesis were similar to those discussed for Ikekawa's synthesis of withaferin A (**5**) (**Scheme 3**) such as the functionalisation of the A/B-ring. The construction of the side chain of withanolide D (**6**) involved a stereocontrolled γ-coupling reaction of a lithium enolate with protected 20-hydroxy-22-aldehyde **40** (**Scheme 4**).[30] The latter **40** was prepared from commercially available pregnenolone (**36**) in 11 steps in 10% yield *via* an interesting Birch reduction using unusual conditions (lithium metal and ammonium chloride in THF) developed by Barton and co-workers in 1973.[31] The key step of the synthesis was the installation of the δ-lactone **41** achieved in very good yield *via* an interesting aldol condensation method. Subsequent modifications of the A/B-ring system allowed the formation of epoxyketone **42** in 45% yield over four steps. The concluding part of the synthesis, which followed the sequence of reactions described in step **vii** to **xii** in **Scheme 3** enabled the formation of (+)-withanolide D (**6**) in an overall 0.96% yield from pregnenolone (**36**).

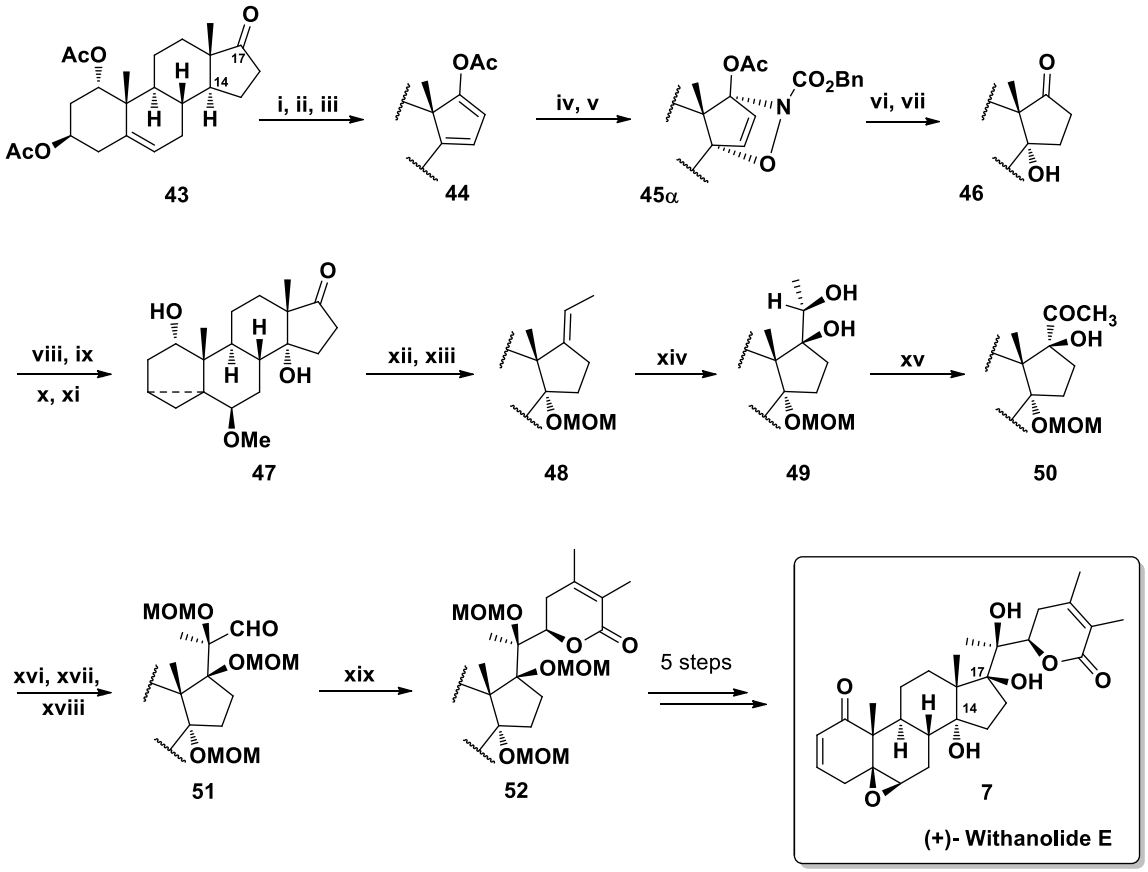


Scheme 4. Synthesis of withanolide D (**6**).

Reagents and conditions: ***i****. $NaBH_4$, MeOH, THF, 0 °C, 40 min;* ***ii****. DDQ, 1,4-dioxane, reflux, 8 h;* ***iii****. DHP, p-TsOH, CH_2Cl_2, rt, 3 h;* ***iv****. H_2O_2 (30% w/w), 10% NaOH in MeOH, MeOH, 15 °C, overnight (51% over four steps);* ***v****. Li/NH_3, NH_4Cl, THF, −40 °C, 4 h (76%);* ***vi****. 1) MOMCl, diethylcyclohexylamine, 1,4-dioxane, reflux, 6 h, 2) 2 M aq. HCl, MeOH, rt, 2 h (60%);* ***vii****. PCC, NaOAc, CH_2Cl_2, rt, 3 h (80%);* ***viii****. 1,3-dithiane, ^{n}BuLi, THF, −5 °C, 8 h (78%);* ***ix****. HgO, BF_3•Et_2O, aq. THF, reflux, 30 min;* ***x****. MOMCl, diethylcyclohexylamine, 1,4-dioxane, reflux, 8 h (69% over two steps);* ***xi****. ethyl 2,3-dimethylbut-2-enoate, LDA, THF/DMPU, − 78 °C, 6 h (86%) ;* ***xii****. 6 M aq. HCl, THF, rt, 3 h ;* ***xiii****. TBSCl, imidazole, DMF, rt, 1 h;* ***xiv****. m-CPBA, CH_3Cl, −5 °C, 40 min;* ***xv****. PDC, DMF, −5 °C, 8 h (45% over four steps).*

1.4.3. The synthesis of withanolide E (**7**)

(+)-Withanolide E (**7**) was first synthesised in 1991 by Grieco and Medrano using a hetero-Diels-Alder reaction between benzyl nitrosoformate and dienol acetate **44** as the key step.[32] This strategy enabled the introduction of the correct stereochemistry at the C-14 position, *i.e.* an α-hydroxyl group. Diacetate **43** was first converted into a silyl enol ether following Miller's procedure,[33] and was then transformed into dienol acetate **44** *via* a Saegusa reaction and by exposure to isopropenyl acetate (**Scheme 5**).[34] Compound **44** was then treated with benzyl nitrosoformate to undergo a 1,4-cycloaddition and allowed the formation of the isomeric cycloadducts **45α** and **45β** in a 2:1 ratio. The minor adduct **45β** was converted into the desired adduct **45α** *via* brief refluxing in toluene. Thus, cycloadduct **45α** was synthesised in an overall 85% yield. Once the stereochemistry of the C-14 hydroxyl group was established, the synthesis focused on establishing the β-configuration of the C-17 hydroxyl group which proved to be less simple than expected. To address the difficulties of this strategy, the (17*Z*)-ethylidene steroid **48**, obtained from ketone **47** in 85% yield over two steps, was treated with osmium tetroxide to afford a 1.4:1 mixture of glycols **49α** and **49β** which were readily separated by column chromatography on silica**.** A straightforward route was proposed to complete the functionalisation of the A/B-ring and the construction of the side chain lactone **52** through a similar aldol type reaction as used in the total synthesis of withanolide D (**6**) (**Scheme 4**) allowing the synthesis of (+)-withanolide E (**7**) in a 2.4% overall yield over 25 steps.

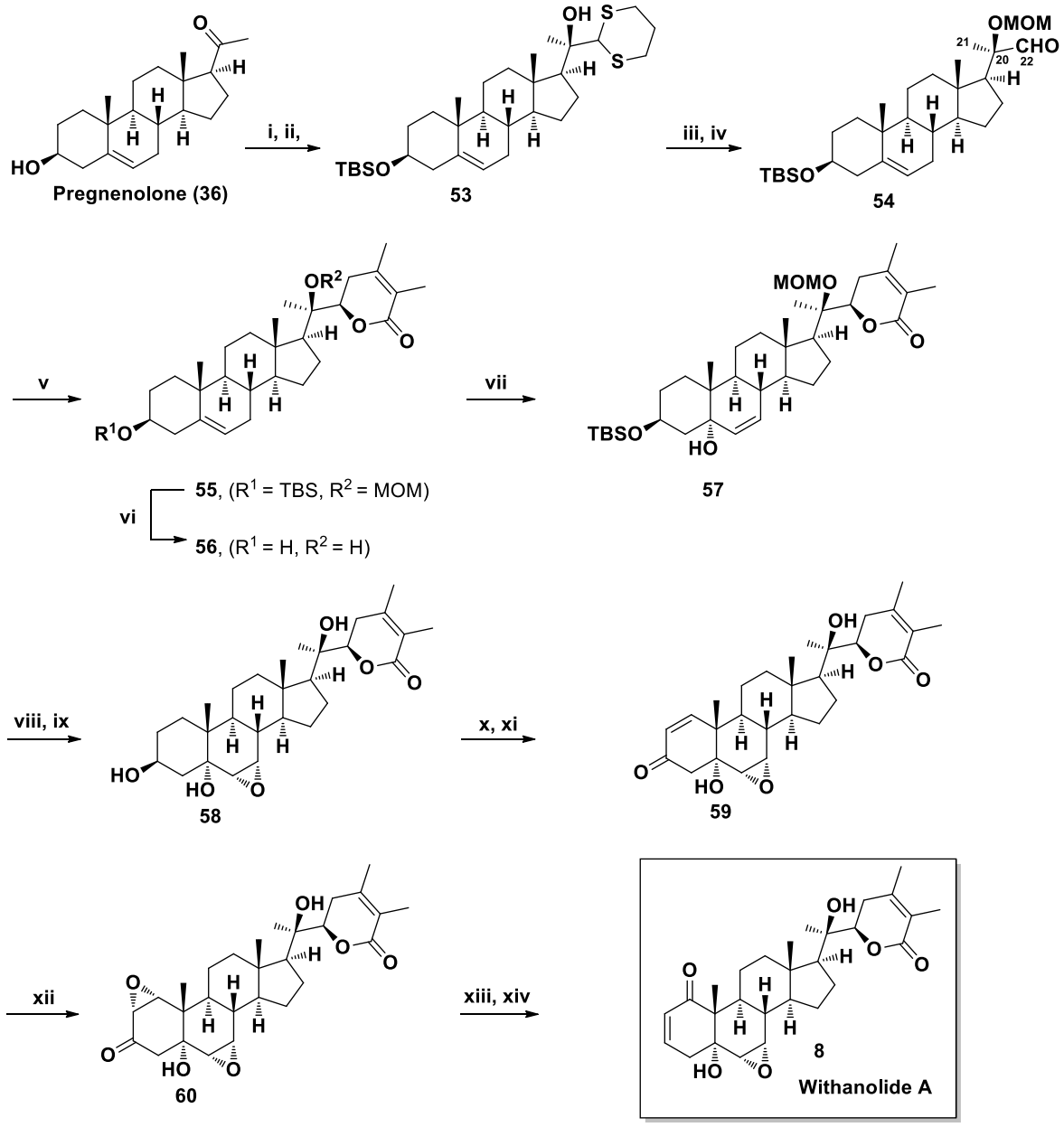


Scheme 5. Synthesis of withanolide E (**7**).

Reagents and conditions: ***i****. TMSI, $(TMS)_2NH$, Et_3N, $ClCH_2CH_2Cl$, −23 °C, 45 min;* ***ii****. $Pd(OAc)_2$, K_2CO_3, CH_3CN, 12 h;* ***iii****. $^{i}PrOAc$, TsOH, reflux (86% over three steps);* ***iv****. benzyl nitrosoformate;* ***v****. toluene, reflux (85% over two steps);* ***vi****. H_2, 5% Pd-Ba_2SO_4, EtOH, 3 h;* ***vii****. 1) $CuCl_2$•$2H_2O$, H_2O, THF, 4 h (79% over two steps), 2) 5% KOH, MeOH, reflux, 2 h (100%);* ***viii****. TsCl, pyridine, 12 h;* ***ix****. TBSOTf, Et_3N, CH_2Cl_2, 0 °C. 30 min;* ***x****. KOAc, MeOH, reflux, 12 h;* ***xi****. TBAF, THF, 4 d (50% over four steps);* ***xii****. Ph_3PCHCH_3, THF;* ***xiii****. MOMCl, $^{i}Pr_2NEt$, dioxane, 80 °C, sealed tube (85% over two steps);* ***xiv****. OsO_4, pyridine (80%);* ***xv****. TFAA, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1.5 h (89%);* ***xvi.*** *CH_2CHLi, THF, −78 °C, 1 h (97%);* ***xvii****. MOMCl, $^{i}PrNEt_2$, dioxane, 90 °C, 24 h, sealed tube;* ***xviii****. 1) O_3, MeOH, −100 °C, 2) Me_2S, 30 min (70%);* ***xix****. ethyl 2,3-dimethylbut-2-enoate, LDA, THF/HMPA, −78 °C to rt, 1.5 h (86%).*

1.4.4. The synthesis of withanolide A (**8**)

It was only recently (2011) that the first total synthesis of withanolide A (**8**) was reported by Gademann and co-workers (**Scheme 6**).[35] They observed that the α,β-unsaturated ketone in the A-ring was a chemically sensitive fragment towards lactonisation reaction conditions whereas the δ-lactone side chain and the hydroxyepoxide in the B-ring were considerably more stable functionalities of the molecule. The main features of the synthetic strategy were a singlet-oxygen ene reaction and a Wharton carbonyl transposition. The synthesis started with pregnenolone (**36**), also used as precursor in the synthesis of withanolide D (**6**), as a cheap and commercially available reagent. The first five steps of the reaction sequence served to stereoselectively construct the δ-lactone side chain in 49% yield using the same vinylogous aldol condensation method as developed by Ikekawa for the synthesis of withanolide D (**6**).[30] The next key step was the regioselective introduction of the hydroxyepoxide moiety in the B-ring. This was achieved by a singlet-oxygen-mediated photooxygenative olefin migration that led to the formation of an allylic tertiary alcohol **57** which was in turn submitted to stereoselective epoxidation conditions forming the epoxyalcohol **58** in 61% yield.[36] The required enone functionality in the A-ring was established *via* treatment of triol **58** with IBX under optimised conditions developed by Nicolaou and co-workers.[37] Further epoxidation of enone **59** enabled the synthesis of the diepoxide **60** in good yield (60%). The next key step of the synthesis was the Wharton carbonyl transposition which allowed the conversion of epoxy ketone **60** into the rather sensitive α,β-unsaturated ketone functionality of the molecule.[38] Thus, (+)-withanolide A (**8**) was synthesised in 14 steps in a 4.5% overall yield.



Scheme 6. Synthesis of withanolide A (**8**).

Reagents and conditions: ***i****. TBSCl, imidazole, THF, rt, (98%);* ***ii****. 1,3-dithiane,* ^{n}*BuLi, THF, −78 °C to rt (84%);* ***iii****. NCS,* CH_2Cl_2*, rt (73%);* ***iv****. MOMCl, NaI, DIPEA, DME, reflux (94%);* ***v****. ethyl 2,3-dimethylbut-2-enoate, LiHMDS, THF/DMPU, −78 °C to rt (87%);* ***vi****. HCl, THF/*H_2O*, rt (87%);* ***vii****.* O_2*, TPP, hγ 589 nm, pyridine,* PPh_3*, rt (61%);* ***viii****. m-CPBA,* CH_2Cl_2*, 0 °C to rt (96%);* ***ix****. HCl, THF/*H_2O*, rt (80%);* ***x****. TPAP, NMO,* CH_2Cl_2*, rt (95%);* ***xi****. IBX, MPO, DMSO, 40 °C (81%);* ***xii****.* H_2O_2*, triton B, THF, 0 °C (60%);* ***xiii****.* N_2H_4*•HCl,* Et_3N*, 0 °C to rt (62% over two steps);* ***xiv****. PDC,* CH_2Cl_2*, rt (80%).*

1.5. Structure Activity Relationship (SAR) Studies

In recent years, investigation of the bioactivity of the withanolides in diverse biological fields led to speculations about the structure-activity relationship of these complex molecules. In 2003, Nair and co-workers showed that the presence of an α,β-unsaturated δ-lactone side chain was critical for the selective inhibition of the COX-2 enzyme.[39] Another interesting observation was that the 2-en-1-one and the 5β,6β-epoxy functionalities had a positive influence on some biological properties such as the cytotoxicity and the cell differentiation induction (**Figure 10**).[39]

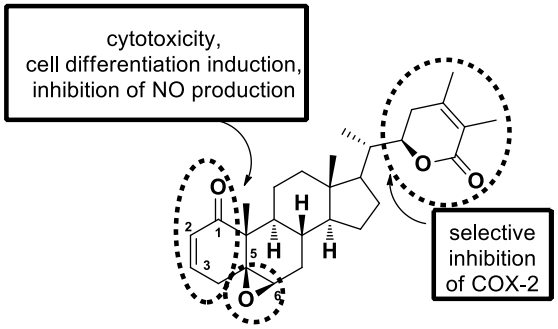


Figure 10. Pharmacophoric features for different bioactivities of withanolides.

In 2009, studies on the inhibition of T- and B-cell proliferation by withanolides and withacoagulins extracted from *Withania coagulans* resulted in important conclusions regarding the SAR (**Figure 11**).[4]

Figure 11. *Withania coagulans* Dunal species.

Thus, comparisons of the bioactivities of these compounds outlined the following interesting suggestions (**Figure 12**):

- Withanolides with a 2,5-dien-1-one functionality in the A/B-ring showed stronger activities than their 3,5-dien-1-one isomers.

- The presence of the 17β-hydroxyl group increases the inhibition of T-cell proliferation.
- The presence of a methyl group at the C-27 position enhances the bioactivity compared to withanolides with a CH_2OH functionality at the same carbon.
- The 15α-hydroxyl group lowers the bioactivity. Whereas the 14α-hydroxyl functionality did not show any significant effect in the activity of withanolides.

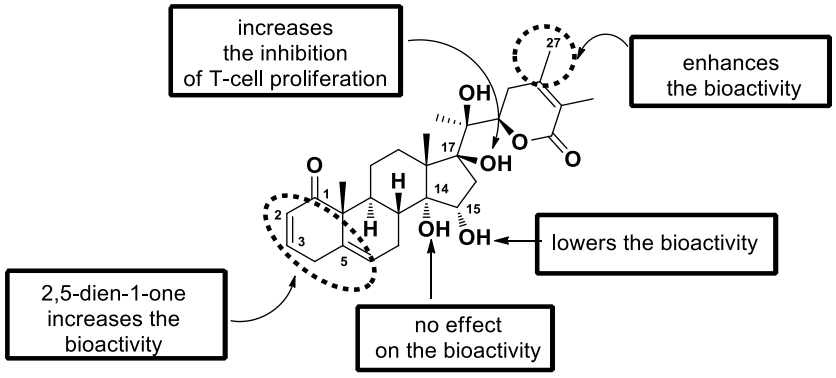
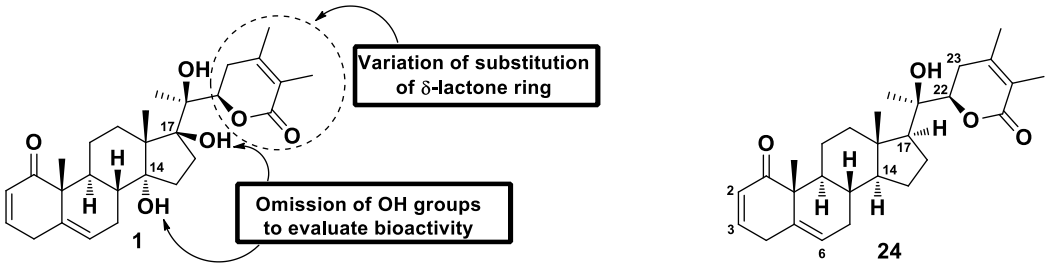


Figure 12. SAR of withanolides.

1.6. Project Aims

Although withanolide F (**1**) may be considered a direct precursor of withanolide E (**7**), to date there have been no reported syntheses of withanolide F (**1**) in the literature. The investigation of analogues of this compound would not only enable a better evaluation of its biological activity but also facilitate the development of the total synthesis of withanolide F (**1**).

In the course of our synthetic studies towards the framework of the steroid withanolide F (**1**) and taking into consideration the prior SAR evaluation of withanolides (**Figure 13i**), we became interested in the influence of the C-14 and the C-17 hydroxyl groups and the stereochemistry of the C-17 side chain on the biological activity. In order to develop synthetic access to these structures, we set molecule **24** lacking these hydroxyl groups and with a β-orientated side chain at C-17 as our first target (**Figure 13ii**).



i **ii**

Figure 13 i. SAR evaluation of withanolide F (**1**), **ii**. Structure of 14,17-dideoxy-17-*epi*-withanolide F (**24**).

The target molecule named 14,17-dideoxy-17-*epi*-withanolide F (**24**) is known and was isolated from *Withania coagulans* Dunal plant by Choudhary *et al*. in 2003.[40] The structure was determined through ^{1}H-NMR and ^{13}C-NMR spectroscopy together with mass spectrometry. Key features included three downfield signals at δ 5.85 (dd, $J_{2,3}$ = 9.8 Hz, $J_{2,4}$ = 3.0 Hz), 6.74 (m) and 5.58 (br d, $J_{6,7}$ = 6.0 Hz) which represented three protons H-2, H-3 and H-6, respectively, and a downfield signal at δ 4.20 (dd, $J_{22,23\alpha}$ = 13.2 Hz, $J_{22,23\beta}$ = 3.4 Hz) which was assigned to H-22 methine proton of the δ-lactone side chain. As previously mentioned, 14,17-dideoxy-17-*epi*-withanolide F (**24**) has been synthesised by Lavie *et al*. in 1981 in three steps from triol **21** *via* a biomimetic synthesis which included a acetylation-oxidation-elimination sequence (**Scheme 2**).[25] Unfortunately, no yields and details on the scale and the reproducibility of this synthesis were reported in the literature.

Moreover, during the course of our research, the formation of the δ-lactone side chain of the target system revealed to be more challenging than expected given the extensive successful work previously published towards its synthesis. Therefore, this synthetic challenge required to develop a new method to build the δ-lactone side chain, a key structural feature characteristic of withanolides.

Thus, the core project aims were as follow:

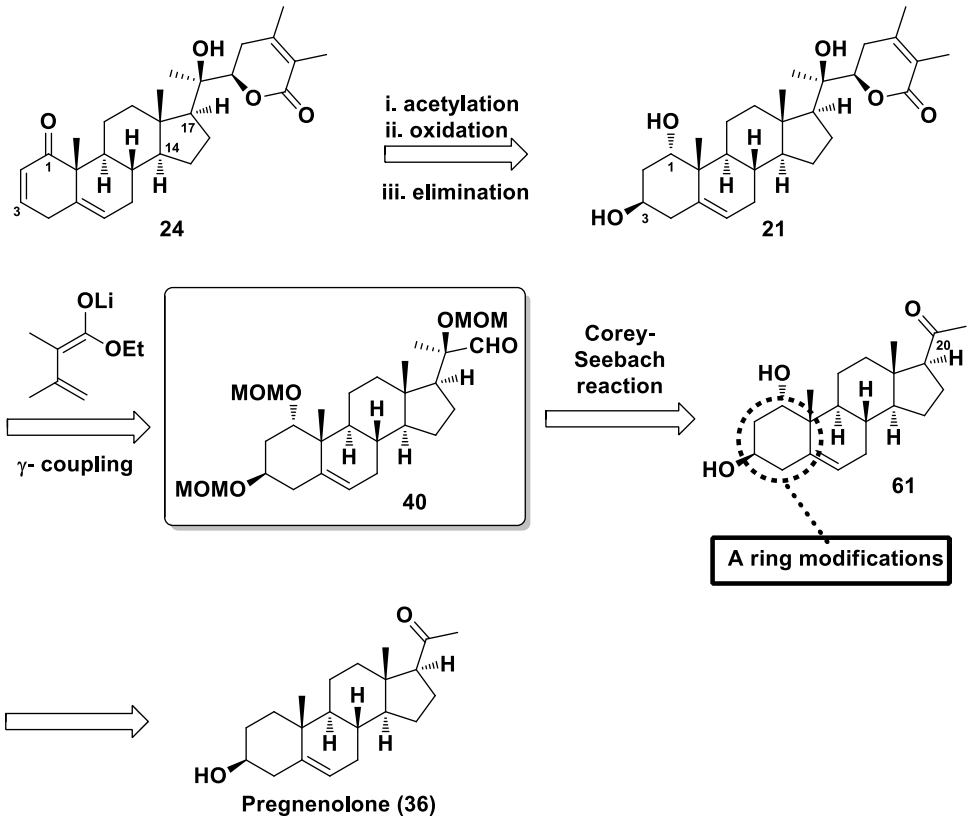
(**i**) to synthesise 14,17-dideoxy-17-*epi*-withanolide F (**24**).

(**ii**) to devise a new method towards the construction of δ-lactone side chain and apply it to the total synthesis of analogues of withanolide F (**1**).

Chapter 2. Synthesis of the Key Aldehyde for Withanolide Synthesis.

2.1. Retrosynthesis of 14,17-Dideoxy-17-*Epi*-Withanolide F (24)

As previously discussed, the synthesis of target compound **24**, an analogue of withanolide F (**1**) lacking the C-14 and C-17 hydroxyl functionalities and with an inverted configuration at C-17, was targeted to develop a general synthetic access to the core structure of withanolide F (**1**). The retrosynthesis of the 14,17-dideoxy-17-*epi*-withanolide F (**24**) was based on established chemistry on structurally related withanolides and in particular the syntheses of withanolide D (**6**)[29] and withanolide E (**7**).[32] From a retrosynthetic point of view, enone **24** can be obtained by selective acetylation of the C-3 hydroxyl group and oxidation of the C-1 hydroxyl functionality of diol **21**, followed by the selective elimination of the C-3 acetyl group.



Scheme 7. Proposed retrosynthesis of 14,17-dideoxy-17-*epi*-withanolide F (**24**) *via* key aldehyde **40**.

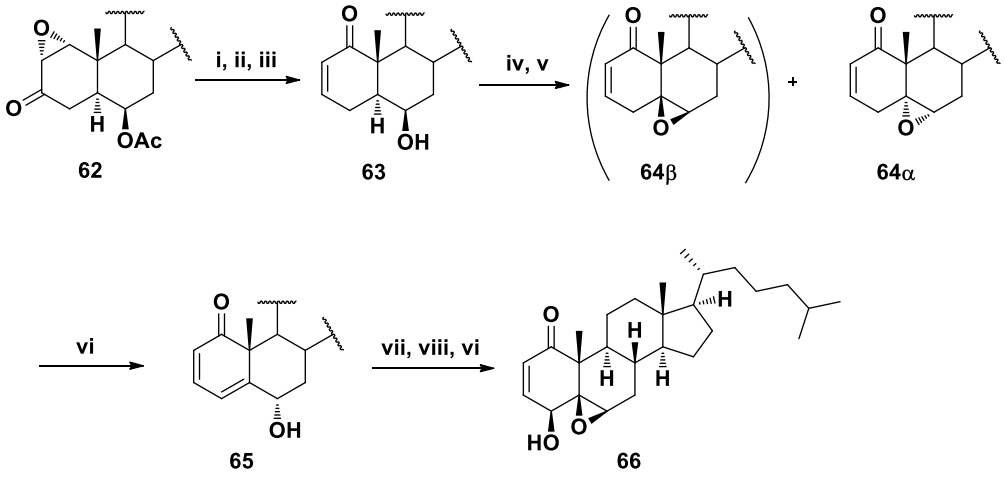
The retrosynthetic strategy relies on the formation of the δ-lactone side chain of compound **21** *via* a nucleophilic attack of a lithium enolate on the key aldehyde **40**. In turn, aldehyde **40** was envisioned to arise from ketone **61** *via* a Corey-Seebach reaction. Finally, diol **61** could be accessed from commercially available pregnenolone (**36**) *via* a key Birch reduction step (**Scheme 7**).

2.2. Oxidation of the A/B-Ring System: Literature Routes

The withanolides differ from other natural polyhydroxysteroids having the δ-lactone side chain and complex functional groups on the A/B-ring system. Therefore, the synthesis of such complex structures necessitated the development of new synthetic methods for establishing those particular functionalities of the A/B-ring of the withanolides.

2.2.1. 5β,6β-Epoxy-1-oxo-2-en-4β-ol: literature examples

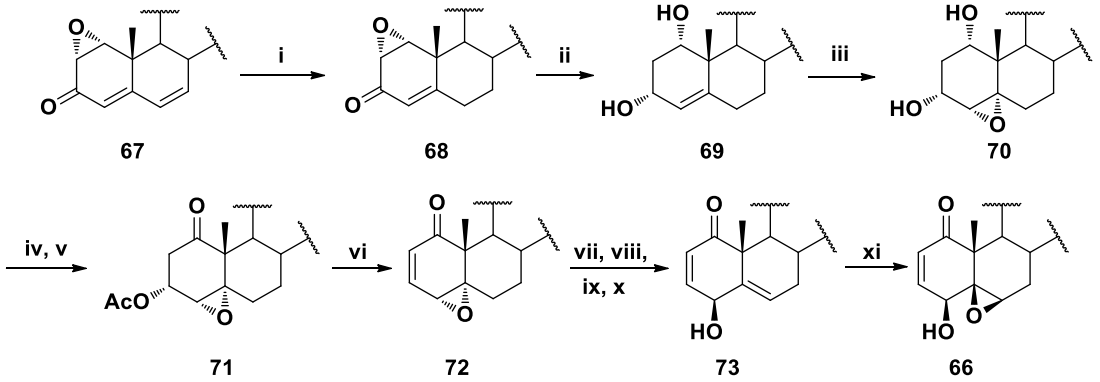
Initial studies towards the modification of the A/B-ring focused on the synthesis of the 5β,6β-epoxy-1-oxo-2-en-4β-ol fragment common to various withanolides, including withaferin A (**5**) and withanolide D (**6**). As part of studies towards the development of new synthetic methods, model compounds based on cholesterol (**74**) were used by Ikekawa's group. They synthesised a cholestane derivative possessing the same epoxide and quinoid-like moiety in the A/B-ring.[41] Appropriate modifications of 6β-acetoxy-1α,2α-epoxycholestan-3-one (**62**) *via* the sequence of reactions shown in **Scheme 8** afforded 5β,6β-epoxy-1-oxo-cholest-2-en-4β-ol (**66**) in 26% yield over 9 steps.



Scheme 8. Synthesis of 5β,6β-epoxy-1-oxo-cholest-2-en-4β-ol (**66**).

Reagents and conditions: ***i****.* N_2H_4*;* ***ii****.* CrO_3*;* ***iii****. KOH;* ***iv****.* $POCl_3$*, pyridine (45% over four steps);* ***v****. m-CPBA (69% of* ***64β*** *and 25% of* ***64α****);* ***vi****. NaOH (97%);* ***vii****. MsCl,* $NaHCO_3$*-pyridine;* ***viii****.* OsO_4*, NaOH (85%).*

An alternative synthesis of related cholestane derivatives was developed by Weissenberg and co-workers which started from 1α,2α-epoxycholestan-4-en-3-one (**67**) and allowed the formation of the 5β,6β-epoxy-1-oxo-cholest-2-en-4β-ol (**66**) in 10 steps in a 53% overall yield (**Scheme 9**).[42]

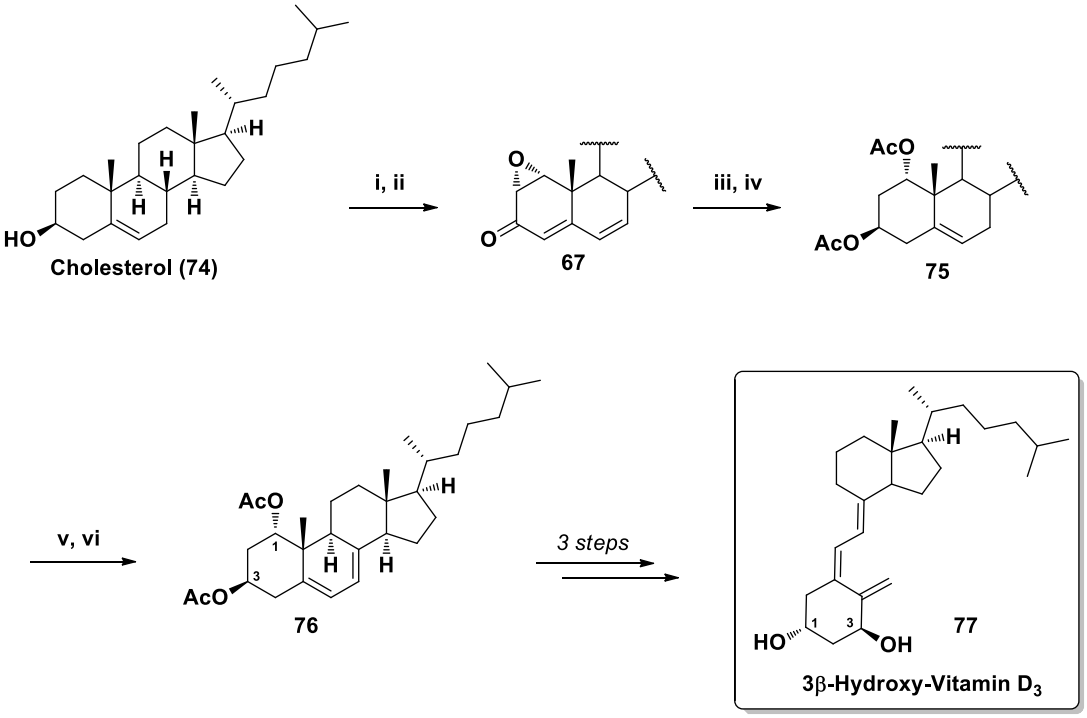


Scheme 9. Alternative synthesis of 5β,6β-epoxy-1-oxo-cholest-2-en-4β-ol (**66**).

Reagents and conditions: ***i****.* H_2*, 5%* $Pd\text{-}CaCO_3$ *(100%);* ***ii****.* $LiAlH_4$*;* ***iii****.* $PhCO_3H$*;* ***iv****.* Ac_2O*, pyridine;* ***v****.* CrO_3*;* ***vi****.* Al_2O_3 *(70% over five steps);* ***vii****.* H_2SO_4*, AcOH;* ***viii****.* Ac_2O*, pyridine, (75% over two steps);* ***ix****.* $SOCl_2$*;* ***x****.* $Ba(OMe)_2$*;* ***xi****.* $PhCO_3H$ *(100% over three steps).*

2.2.2. 1α,3β-Dihydroxy-5-pregnene system: literature examples

1α,3β-Dihydroxy-5-pregnene systems were key intermediates in numerous total syntheses of various natural products. The synthetic strategy was first established by Barton *et al*. during their studies towards the synthesis of 3β-hydroxy-vitamin D_3 (**77**).[31] It involved the oxidation of the A/B-ring to the corresponding 1,4,6-trien-3-one followed by epoxidation under alkaline conditions which led to the formation of 1α,2α-epoxycholesta-4,6-dien-3-one (**67**) in poor yield (45% over two steps). The synthesis relied on the key Birch reduction step using a large excess of lithium metal in liquid ammonia to afford the desired 1α,3β-dihydroxy-5-pregnene structure (**75**) in an acceptable 60% yield (**Scheme 10**).

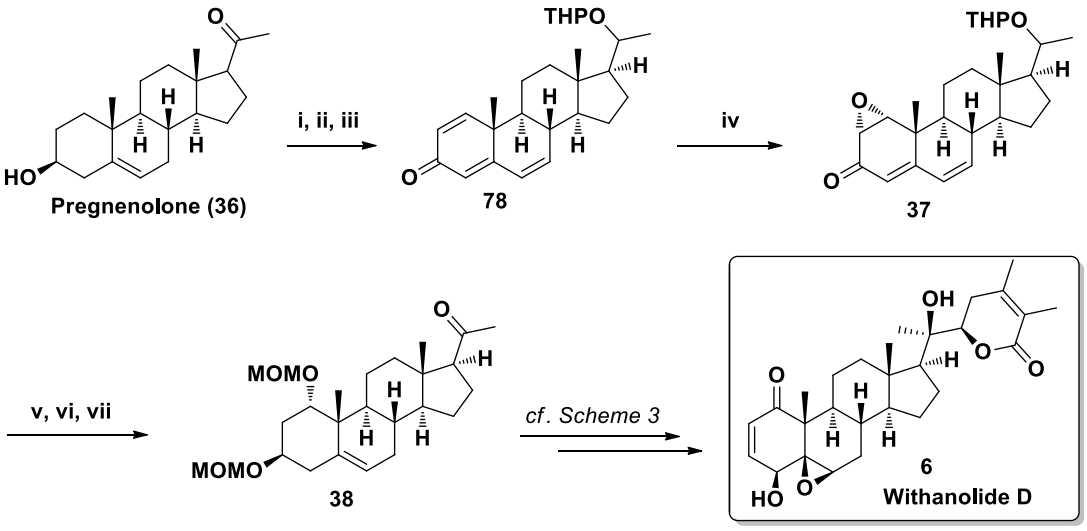


Scheme 10. Synthesis of 3β-hydroxyl-vitamin D_3 (**77**).

Reagents and conditions: ***i****. DDQ, 1,4-dioxane, reflux;* ***ii****.* H_2O_2 *(30% wt), 10% NaOH in MeOH, MeOH, 15 °C, overnight (45% over two steps);* ***iii****.* Li/NH_3*,* NH_4Cl*, THF, −40 °C, (60%);* ***iv****.* Ac_2O*, DMAP, pyridine, rt;* ***v****. DBDMH, hexane;* ***vi****.* $(MeO)_3P$*, xylene, reflux, (34% over three steps).*

In 1984, Ikekawa's group applied this previously described method in the synthesis of withanolide D (**6**), a natural product structurally related to our target **24**.[29] Thus, 1,4,6-trien-3-one **78** was obtained from commercially available pregnenolone (**36**) by

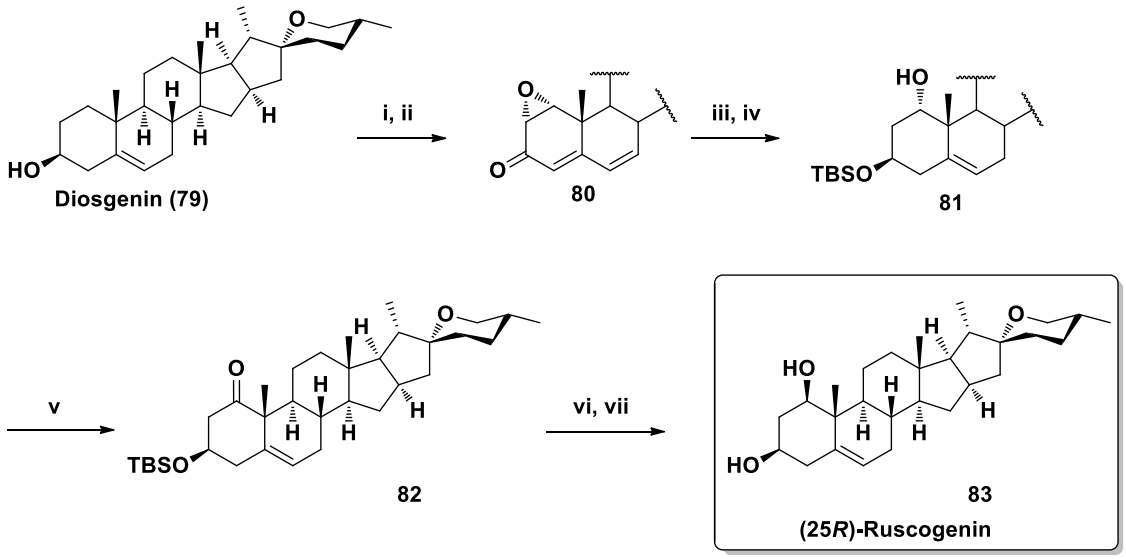
oxidation of the A/B-ring system using DDQ in 61% yield. The next steps included protecting the C-20 hydroxyl with a THP group and epoxidation of the 1,2-double bond of the A-ring using hydrogen peroxide. In turn, 1α,2α-epoxy-4,6-dien-3-one **37** was reduced using Birch reduction conditions previously developed by Barton and co-workers and allowed the synthesis of the key 1α,3β-dihydroxy-5-pregnene **38** in very good yield (76%) (**Scheme 11**).



Scheme 11. Synthesis of withanolide D (**6**).

Reagents and conditions: ***i****. $NaBH_4$, MeOH, THF, 0 °C, 40 min;* ***ii****. DDQ, 1,4-dioxane, reflux, 8 h (61% over two steps);* ***iii****. DHP, p-TsOH, CH_2Cl_2, rt, 3 h;* ***iv****. H_2O_2 (30% wt), 10% NaOH in MeOH, MeOH, 15 °C, overnight (83% over two steps);* ***v****. Li/NH_3, NH_4Cl, THF, −40 °C, 4 h (76%);* ***vi****. 1) MOMCl, diethylcyclohexylamine, 1,4-dioxane, reflux, 6 h, 2) 2 M aq. HCl, MeOH, rt, 2 h (60%);* ***vii****. PCC, NaOAc, CH_2Cl_2, rt, 3 h (80%).*

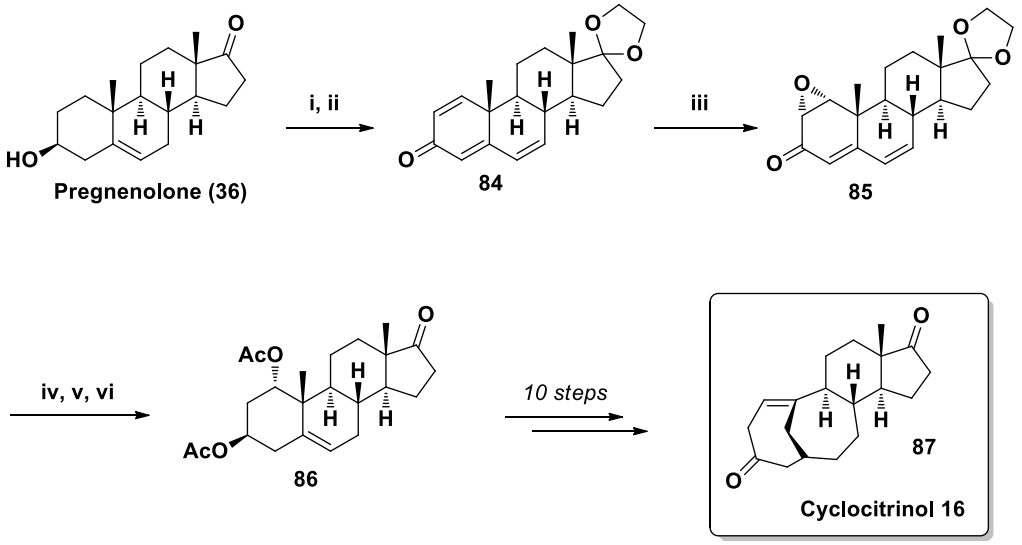
During their work on the total synthesis of (25*R*)-ruscogenin (**83**), Liu *et al*. reported that the key Birch reduction required carefully controlled reaction conditions in order to avoid side products such as Δ^6-1α,3β-diol (**Scheme 12**).[43] Later, inspired by Liu's work, Saito and co-workers showed during their studies towards the synthesis of an analogue of vitamin D that performing the Birch reduction with sodium in liquid ammonia, instead of lithium, led to a mixture of the desired 1α,3β-diol **81** and its C-3 α-epimer in a 9:1 ratio in favour of the 1α,3β-diol **81**.[44]



Scheme 12. Synthesis of (25*R*)-ruscogenin (**83**).

Reagents and conditions: ***i****. DDQ, 1,4-dioxane, reflux, 8 h;* ***ii****.* H_2O_2 *(30% wt), NaOMe, MeOH, rt, overnight (47% over two steps);* ***iii****.* Li/NH_3*,* NH_4Cl*, THF, −40 °C, 3 h;* ***iv****. TBSCl, imidazole, DMF, rt, overnight (53% over two steps);* ***v****. PDC,* CH_2Cl_2*, rt, 1 h;* ***vi****.* $NaBH_4$*, THF, 6 h (64% over two steps);* ***vii****. 5 M HCl, acetone, rt, 1 h (96%).*

This method to install the 1α,3β-dihydroxy-5-pregnene functionality in the A/B-ring system was also applied by El Sheik *et al.* in the synthesis of cyclocitrinols, another class of natural products characterised by a steroid core structure and a unique bicyclo[4.4.1]undecane A/B-ring system (**Scheme 13**).[45] They observed that during the Birch reduction step, the reaction temperature should not be re-cooled to −78 °C after addition of the epoxide **85** as suggested in previously reported procedures, in order to avoid the formation of 1α-hydroxyl-4,5-en-3-one as the major product of the reaction.



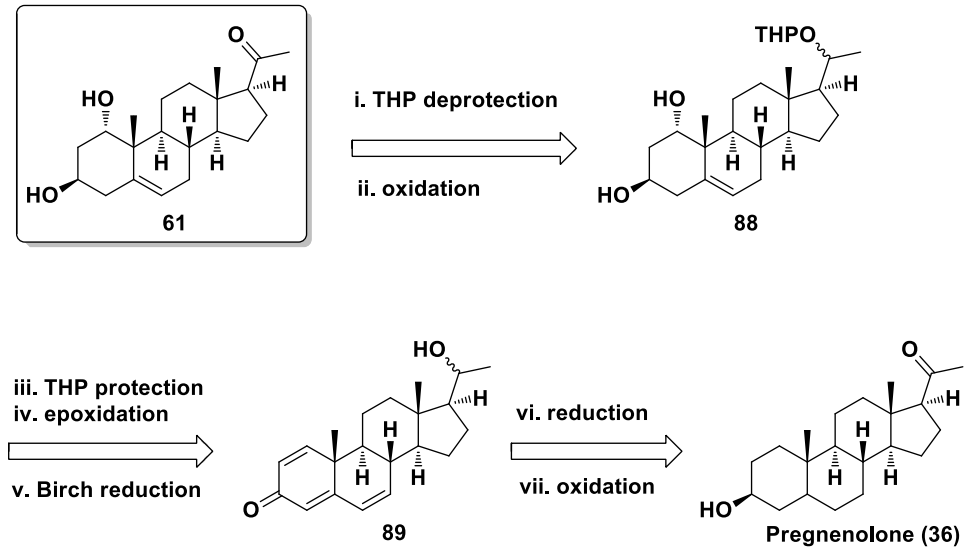
Scheme 13. Synthesis of cyclocitrinol 16 (**87**).

Reagents and conditions: ***i****.* *$(CH_2OH)_2$, TsOH, benzene, reflux;* ***ii****. DDQ, 1,4-dioxane, reflux, 8 h (56% over two steps);* ***iii****.* *H_2O_2 (30% wt), 10% NaOH in MeOH, MeOH, 10 °C, overnight (68%);* ***iv****.* *Li/NH_3, NH_4Cl, THF, −40 °C, 4 h;* ***v****.* *Ac_2O, DMAP, pyridine, rt;* ***vi****.* *TsOH, H_2O, THF, rt (56% over three steps).*

2.3. Oxidation of the A/B-Ring System: Results and Discussion

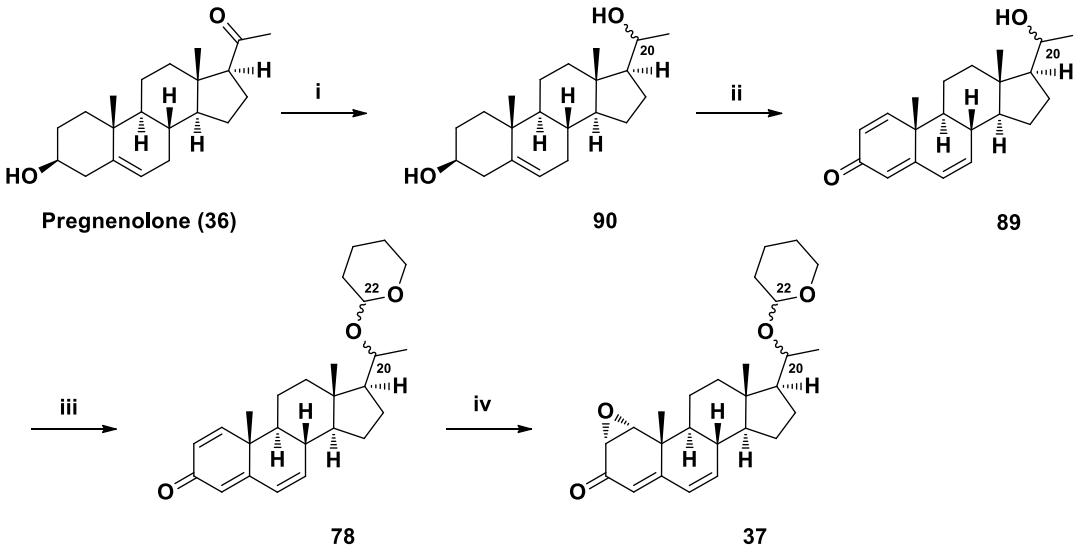
2.3.1. 1α,3β-Dihydroxy-5-pregnene system: initial synthetic route

We devised a first retrosynthetic route for the synthesis of the key 1α,3β-dihydroxy-5-pregnene (**61**) intermediate based on precedent published by Ikekawa *et al*. in their total synthesis of withanolide D (**6**) (**Scheme 14**).[29]



Scheme 14. Proposed retrosynthesis of 1α,3β-dihydroxy-5-pregnene (**61**) *via* THP protection.

As shown in **Scheme 15**, commercially available pregnenolone (**36**) was first reduced using sodium borohydride to form diol **90** in quantitative yield as an inseparable mixture of two diastereoisomers at C-20, which was subsequently oxidised with DDQ to afford trienone **89** in poor yield (38%) compared to the published yield (61%).[29] This modest yield may in part be due to the purification which included two column chromatography steps in order to properly purify the trienone **89**. The published procedure also suggested to purify the crude mixture by column chromatography twice, first on alumina and then on silica gel, but in our hands this led to substantial loss of material.[45] Next, the C-20 alcohol **89** was protected as its THP ether giving an inseparable mixture of four diastereoisomers at C-20 and C-22 (**78**). The crude mixture was exposed to alkaline hydrogen peroxide to provide stereoselectively the α-epoxide **37** as another mixture of four diastereoisomers at C-20 and C-22 in poor yield (30%) compared to the 86% yield reported by Ikekawa's group in the literature.[29]



Scheme 15. Initial synthetic route to epoxide **37**.

Reagents and conditions: ***i****. $NaBH_4$, MeOH, THF, 0 °C, 40 min;* ***ii****. DDQ, 1,4-dioxane, reflux, 8 h (38% over two steps);* ***iii****. DHP, p-TsOH, CH_2Cl_2, rt, 3 h (86%);* ***iv****. H_2O_2 (30% w/w), 10% NaOH in MeOH, MeOH, 15 °C, 12 h (30%).*

The presence of a doublet at δ 3.70 ($J_{1,2}$ = 4.3 Hz) and a doublet doublet at δ 3.38 ($J_{2,1}$ = 4.3 Hz and $J_{2,4}$ = 2.0 Hz) in the ^{1}H-NMR spectrum attributed to H-1 and H-2, respectively, supported the assigned structure of the epoxide in the A-ring. Furthermore, the "W-coupling" between H-2 and H-4 protons (^4J = 2.0 Hz) confirmed the α-configuration of the epoxide **37** (**Figure 14**). These ^{1}H-NMR data are consistent with those previously reported in the literature.[29]

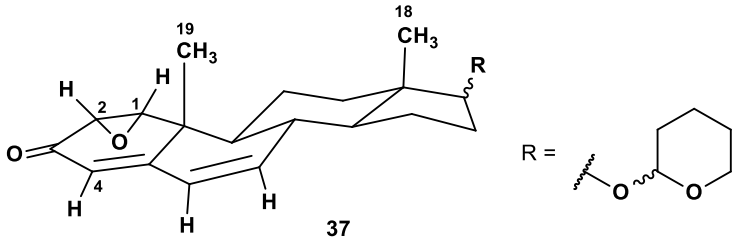
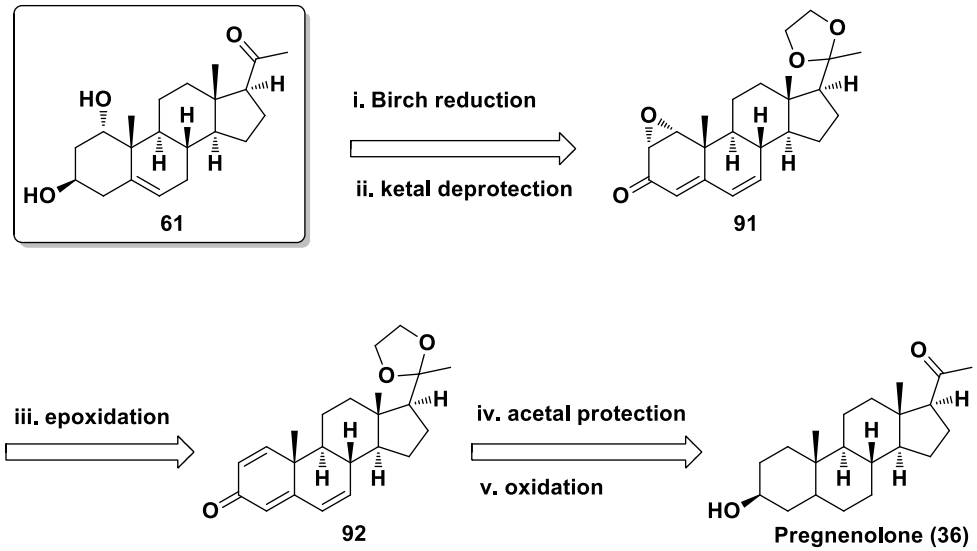


Figure 14. "W-coupling" between H-2 and H-4 of epoxide **37**.

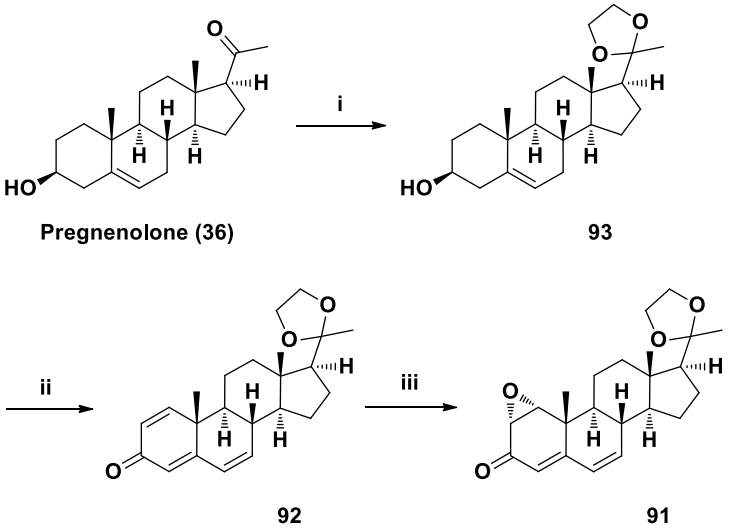
2.3.2. 1α,3β-Dihydroxy-5-pregnene system: revised synthetic route

A thorough examination of the synthetic strategy led to the conclusion that changing the protected C-20 hydroxyl functionality to a ketal would allow access to the key intermediate 1α,3β-diol **61** in two steps fewer than the previously published synthesis by Ikekawa *et al*. (**Scheme 14**).[29] Furthermore, this route avoids the problematic formation of mixtures of inseparable diastereoisomers. With this in mind, a new synthetic route was designed (**Scheme 16**).



Scheme 16. Revised retrosynthesis of 1α,3β-dihydroxy-5-pregnene (**61**) *via* ketal protection.

Based on work by El Sheik *et al.* described in **Scheme 13**,[45] the C-20 ketal **93** was synthesised by protection of commercially available pregnenolone (**36**) with ethylene glycol under standard conditions. Subsequently, oxidation using DDQ furnished the corresponding 1,4,6-trien-3-one **92** in a moderate 38% yield over two steps compared to 56% reported in the literature using same procedures on a similar substrate.[45] In turn, trienone **92** was converted into epoxide **91** using hydrogen peroxide under alkaline conditions in a slightly improved 72% yield compared to the 68% yield published in the literature (**Scheme 17**).[45] Unfortunately, the scale-up of steps **ii** and **iii** from 0.150 mmol to 1.00 mmol resulted in poorer yields (22% and 25%, respectively).

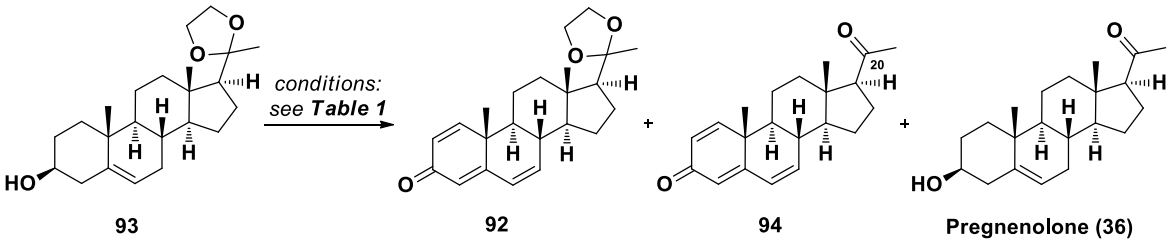


Scheme 17. Revised synthetic route to epoxide **91**.

Reagents and conditions: ***i****. ethylene glycol, p-TsOH, toluene, 130 °C, 12 h (90%);* ***ii****. DDQ, 1,4-dioxane, reflux, 8 h (22%);* ***iii****.* H_2O_2 *(30% w/w), 10% NaOH in MeOH, MeOH, 15 °C, 12 h (25%).*

2.3.3. Optimisation studies of the oxidation step

Unfortunately, this new synthetic route presented a recurring problem concerning low yields during the scale-up of the oxidation step which had been already encountered in the first synthetic route. In this new scheme, the low yield may be attributed to the deprotection of the C-20 ketal group of the starting material **93** and of the final product **92** by DDQ, as it is a mildly acidic reagent. This is supported by the fact that varying amounts of starting pregnenolone (**36**) and C-20 ketone **94** could be isolated from this reaction (**Scheme 18**). In order to address this problem, several conditions were tried, including working under rigorously anhydrous and under basic conditions. Nevertheless, none of these attempts were successful in improving the outcome of the reaction as summarised in **Table 1**.



Scheme 18. Synthesis of trienone **92**.

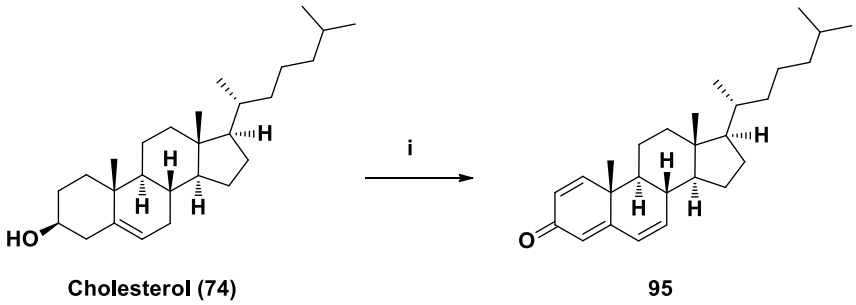
*Reagents and conditions: DDQ (5.0 eq.), conditions see **Table 1**.*

Table 1. Optimisation study of the DDQ oxidation of compound **93**.

Entry	Conditions*	Outcome
1	pyridine (excess), 1,4-dioxane, 110 °C, 24 h	rsm **93**
2	KOH (excess), 1,4-dioxane, 110 °C, 24 h	decomposed mixture
3	benzene, 90 °C, 72 h	**92**: 13% **36**: 15%
4	4 Å molecular sieves, 1,4-dioxane, 110 °C, 48 h	**92**: 19% **94**: 6%
5	K_2CO_3 (excess), 1,4-dioxane, 100 °C, 48 h	**93**: 24% **94**: 23%
6	1,4-dioxane, 110 °C, 24 h	**92**: 28% **94**: 16%

* Anhydrous conditions and under an argon atmosphere.

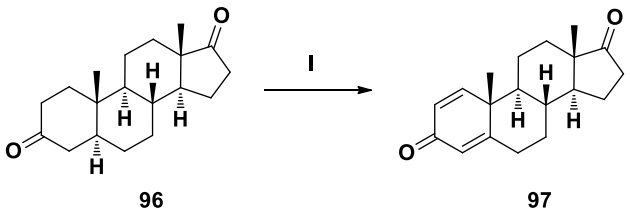
Considering that none of the aforementioned conditions gave satisfactory results, we decided to turn to alternative and more recently developed literature oxidation conditions. Shvo and co-workers reported a new method to transform cyclic ketones and alcohols into their α,β-unsaturated derivatives under mild reaction condition in good yields using $Pd(OAc)_2$ and diethyl allyl phosphate (ADP) as the hydrogen source (**Scheme 19**).[46]



Scheme 19. Catalytic oxidation of cholesterol (**74**) to trienone **95**.

Reagents and conditions: ***i.*** *$Pd(OAc)_2$, ADP, Na_2CO_3, THF, 80 °C, 40 h (75%).*

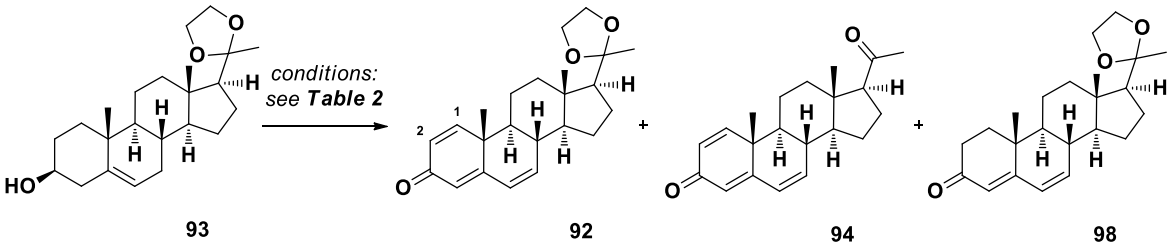
Furthermore, in 2000, Nicolaou *et al*. developed an IBX-mediated dehydrogenation process which was applicable to steroid systems and allowed oxidation in high yields and under mildly acidic conditions (**Scheme 20**).[47]



Scheme 20. Catalytic oxidation of C-3-oxo-androsterone (**96**) to dienone **97**.

Reagents and conditions: ***i.*** *IBX, ADP, Na_2CO_3, toluene/DMSO (2:1), 85 °C, 48 h (72%).*

Based on these previously published results, a screen of various oxidative conditions was undertaken as shown in **Table 2**. An interesting outcome of the reaction was the isolation of the dienone intermediate **98** as a side product which suggests that the last step of the catalytic cycle may be the formation of the 1,2-double bond (**Scheme 21**).



Scheme 21. Oxidation of ketal **93**.

Table 2. Alternative oxidation conditions to form trienone **92**.

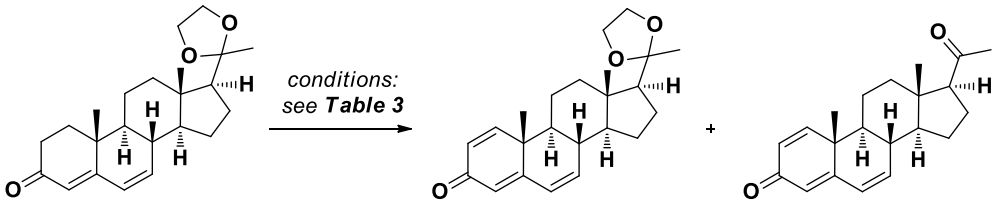
Entry	Reagents	Conditions*	Outcome
1	IBX (4.0 eq.), Na_2CO_3 (4.0 eq.)[47]	toluene/DMSO (2:1), 85 °C, 48 h	**98**: 14% **93**: 27% complex mixture
2	IBX (4.0 eq.), K_2CO_3 (4.0 eq.)	toluene/DMSO (2:1), 85 °C, 48 h	**98**: 18% **93**: 13% complex mixture
3	$Pd_2(dba)_3$•$CHCl_3$ (0.04 eq.), ADP (3.5 eq.), Na_2CO_3 (4.2 eq.)	THF, 86 °C, 72 h	**98**: 22% **93**: 72%
4	$Pd_2(dba)_3$•$CHCl_3$ (0.04 eq.), ADP (3.5 eq.), K_2CO_3 (4.2 eq.)	DMF, 86 °C, 72 h	**98**: 31% **93**: 61%
5	$Pd(OAc)_2$ (0.04 eq.), ADP (3.5 eq.), Na_2CO_3 (4.2 eq.)[46]	THF, 85 °C, 72 h	**98**: 47% **93**: 16%
6	$Pd(OAc)_2$ (0.1 eq.), ADP (8.8 eq.), Na_2CO_3 (10.5 eq.)	THF, 86 °C, 72 h	**98**: 53% **93**: 17%
7	$Pd(OAc)_2$ (0.04 eq.), ADP (3.5 eq.), K_2CO_3 (4.2 eq.)	DMF, 86 °C, 72 h	**98**: 71% **93**: 26%
8	$Pd(OAc)_2$ (0.04 eq.), ADP (3.5 eq.), Na_2CO_3 (4.2 eq.)	(g scale) DMF, 180 °C, 72 h	**92**: 20% decomposed mixture
9	$Pd(OAc)_2$ (0.04 eq.), ADP (3.5 eq.), Na_2CO_3 (4.2 eq.)[48]	DMF, 160 °C, 72 h	**92**: 27% **98**: 46%
10	$Pd(OAc)_2$(0.04 eq.), ADP (3.5 eq.), Na_2CO_3 (4.2 eq.)	DMF, 180 °C, 72 h	**92**: 50% **98**: 25%
11	$Pd(OAc)_2$ (0.04 eq.), ADP (3.5 eq.), Na_2CO_3 (4.2 eq.)	DMSO, 190 °C, 72 h	rsm **93**
12	$Pd(OAc)_2$ (0.1 eq.), ADP (8.8 eq.), Na_2CO_3 (10.5 eq.)	(g scale) DMF, 160 °C, 72 h	**92**: 62% **98**: 7% **94**: 3%

* Anhydrous conditions and under an argon atmosphere.

The use of IBX as an oxidising agent returned complex mixtures of products and therefore, the investigation of these reaction conditions was not pursued (**Table 2**, entries **1** and **2**). The optimisation study of the oxidation step relied on repeating the work of Shvo *et al*. work on cholesterol (**74**),[46] by varying the conditions in order to obtain an optimal yield and purity of the desired trienone **92**. The next four experiments were run at low temperature (85-86 °C) and only led to the formation of intermediate **98** in low yields (**Table 2**, entries **5** to **7**) except for entry **6** in which a 53% yield of dienone **98** was isolated which implied that increasing the amount of the catalyst complex could potentially push the reaction towards completion. Moreover, changing parameters such as the catalyst, the solvent or the base did not show any positive effect (**Table 2**, entries **3** and **4**).

The conditions assayed in entry **9** (DMF at reflux) have been disclosed by a Chinese patent[48] using C-17 ketal protected pregnenolone as the substrate which, in their case, gave trienone **84** in excellent yield (85%). Disappointingly, in our hands these conditions allowed the formation of trienone **92** in poor yield (27%). Nevertheless, under the same conditions only at higher temperature, trienone **92** was isolated in an improved 50% yield (**Table 2**, entry **10**). Based on the previous result, it was thought that increasing the temperature could positively influence the outcome of the reaction. In order to validate this hypothesis, solvents with higher boiling points were used. Unfortunately, this experiment led to the recovery of the starting material **93** (**Table 2**, entry **11**). At this point, the best result developed in entry **9** was scaled up but mostly led to poor yields. Indeed, as shown in entry **8**, scaling up the reaction at an oil bath temperature of 180 °C in DMF led to low yield (20%). Decomposition of DMF at vigorous reflux was assumed to be the problem. In order to avoid this situation, this reaction was run at a more gentle reflux (oil bath temperature at 160 °C) which led to a more acceptable yield on gram scale (entry **12**, 62% yield). Considering that entry **12** gave the best outcome in terms of yield (62% yield) and purity (>99%), these conditions were adopted as the preferred procedure for the second step of the synthesis.

In order to improve the overall yield of the oxidation step, dienone **98** was submitted to different oxidation conditions (**Scheme 22**, **Table 3**).



98 **92** **94**

Scheme 22. Oxidation of dienone **98** in trienone **92**.

Table 3. Oxidation of 1,2-double bond of dienone **98**.

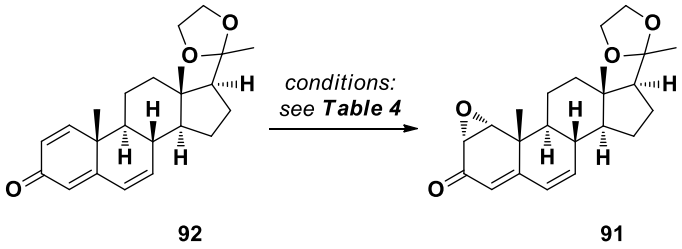
Entry	Reagents	Conditions*	Outcome
1	IBX (4.0 eq.), K_2CO_3 (4.0 eq.)	toluene/ DMSO (2:1), 85 °C, 48 h	rsm **98**
2	$Pd(OAc)_2$ (0.04 eq.), ADP (3.5 eq.), Na_2CO_3 (4.2 eq.)	DMF, 160 °C, 72 h	**92**: 46% **98**: 33%
3	DDQ (3.5 eq.)	1,4-dioxane, 110 °C, 48 h	**92**: 58% **94**: 23%

* Anhydrous conditions and under an argon atmosphere.

The conversion of dienone **98** into trienone **92** proceeded in an acceptable yield when the reaction was run under the DDQ-mediated oxidation conditions (**Table 3**, entry **3**) and hence, these conditions were used when repeating this reaction.

2.3.4. Optimisation studies of the epoxidation reaction

There are a number of reports in the literature for the nucleophilic epoxidation of the 1,2-double bond of the A-ring of steroids using peroxide-containing reagents in acceptable to good yields (up to 85%) and on various scales.[49,50,51] Unfortunately, in our hands this step proceeded in low yield upon scale-up. This was partly because of recovery of unreacted trienone **92**, and prompted a screening of different epoxidation conditions (**Scheme 23**, **Table 4**).



92 **91**

Scheme 23. Synthesis of epoxide **91**.

Table 4. Screening of epoxidation conditions.

Entry	Reagents	Conditions	Outcome
1	^{t}BuOOH (70% w/w in H_2O) (30.0 eq.), DBU (cat.)	MeOH, 0 °C → rt, 24 h	**91**: 27% + mixture*
2	^{t}BuOOH (70% w/w in H_2O) (30.0 eq.), triton B (cat.)	THF, 0 °C → rt, o/n	**91**: 45% + mixture*
3	[H_2O_2.urea] (30.0 eq.), TBD (cat.)	CH_2Cl_2, 0 °C → 20 °C, 24 h	rsm **92**
4	H_2O_2 (30% w/w) (30.0 eq.) K_2CO_3 (3.0 eq.)	MeOH, 15 °C → rt, o/n	rsm **92**
5	H_2O_2 (30% w/w) (30.0 eq.) NaOH (5% in MeOH) (cat.)	MeOH, 15°C → rt, o/n	rsm **92**
6	H_2O_2 (30% w/w) (30.0 eq.) triton B (0.05 eq.)	THF/H_2O, 0 °C → rt, o/n	**91**: 47% **92**: 10%
7	H_2O_2 (30% w/w) (27.0 eq.) NaOH (10% in MeOH) (cat.)	MeOH , 15 °C → rt, 24 h	**91**: 46% **92**: 20%
8	H_2O_2 (30% w/w) (30.0 eq.) NaOH (10% in MeOH) (cat.)	MeOH, 15 °C → rt, 24 h	**91**: 48% **92**: 24%

Table 4 (continued). Screening of epoxidation conditions.

Entry	Reagents	Conditions	Outcome
9	H_2O_2 (30% w/w) (40.0 eq.), NaOH (10% in MeOH) (cat.)	(g scale) MeOH, 15 °C → rt, 24 h	**91**: 51% + mixture*
10	H_2O_2 (30% w/w) (40.0 eq.), NaOH (10% in MeOH) (cat.)	^{i}PrOH, 15 °C → rt, 24 h	**91**: 72% **92**: 16%

* Another fraction of at least four by-products, that could not be separated and characterised, was collected.

As shown in entries **1** to **3**, using sterically hindered reagents such as ^{t}BuOOH and [H_2O_2.urea] complex with DBU or triton B and TBD, respectively, as the base did lead to an improvement in the yield. The use of a milder base in order to avoid multiple epoxidation returned only the recovery of trienone **92** (**Table 4**, entries **4** and **5**), whilst using triton B as the base produced the desired epoxide in a moderate yield (**Table 4**, entry **6**). Entries **7** to **9** showed that increasing the number of equivalents of hydrogen peroxide significantly improved the yield. Thus, increasing the equivalents of hydrogen peroxide to 40 equivalents (entry **9**) gave the best result in terms of yield (51%) and purity (> 99%). It was hypothesised that methanol could either react with the dienone functionality of the A/B-ring system *via* a conjugate addition or cleave the epoxide ring accounting for the lower yield. Therefore, the reaction was run in ^{i}PrOH, a less nucleophilic solvent and this lead to the formation of epoxide **91** in an improved yield (72%) on small scale (53 mg, 0.150 mmol) (entry **10**). Furthermore, this result was fairly reproducible on a larger scale (up to 5.00 g, 14.1 mmol) albeit with a slight drop of the yield to 60%.

2.3.5. Discussion of the stereoselectivity of the epoxidation step

The prefered α-configuration of the epoxide was assumed based on the favoured nucleophilic attack of the 1,2-double bond in the A-ring, from the bottom face of the molecule as the top face was sterically hindered by the axial bridgehead C-19 methyl group. In addition, a small ^{4}J (2.0 Hz) "W-coupling" between H-2 and H-4 was observed, consistent with the α-configuration (**Figure 15**). The structure of epoxide **91** was confirmed through single crystal X-ray analysis. This crystal structure confirmed the α-configuration of the epoxide and the consequent "W-type" alignment of the H-2 and H-4 protons (**Figure 14**).

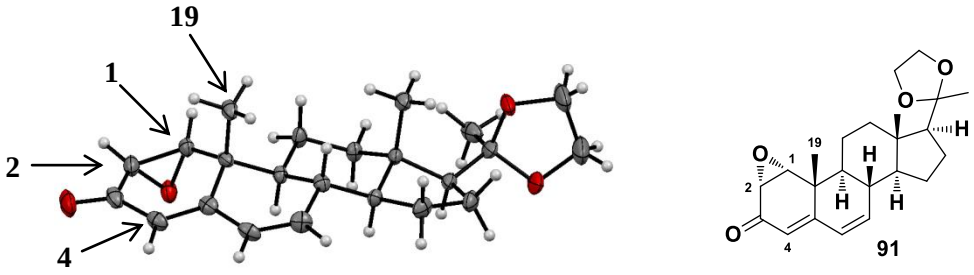
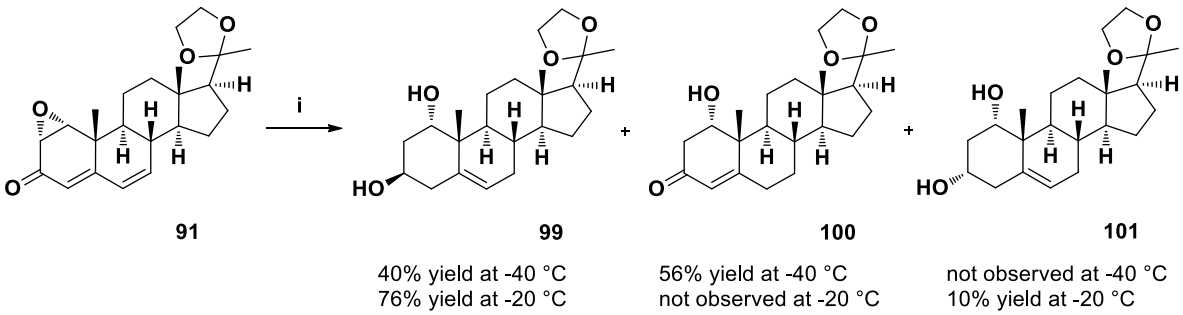


Figure 15. X-ray crystal structure of 1α,2α-epoxyketal **91** depicted using Mercury 3.0. ORTEP representation shown with ellipsoid at 50% probability. (CCDC 983154, **Appendix I)**.

2.3.6. The Birch reduction

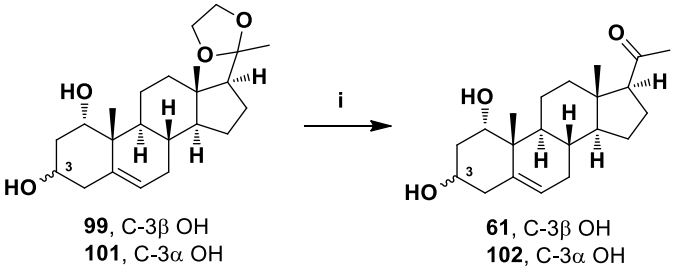
The next key step of the total synthesis was the conversion of epoxide **91** into 1α,3β-diol **99** *via* a Birch reduction using lithium in ammonia and ammonium chloride. Repeating the procedure used in the total synthesis of withanolide D (**6**)[29] afforded 1α,3β-diol **99** in 40% yield alongside with hydroxyenone **100** in 56% yield (**Scheme 24**). In a previous study of this reaction by El Sheikh for the synthesis of the core structure of the cyclocitrinol,[45] it was hypothesised that quenching the reaction mixture at low temperature (−78 °C) led to the formation of undesired hydroxyenone as the major product. Taking this suggestion into consideration, the scale-up of the reaction was carried out at higher temperature, *i.e.* the reaction mixture was quenched between −10 °C and −20 °C. This experiment enabled the formation of 1α,3β-diol **99** in good yields on a one gram scale (76%) along with the diastereoisomer 1α,3α-diol **101** (10%) separable by column chromatography; and without the formation of hydroxyenone **100**.



Scheme 24. Birch reduction of epoxide **91**.

Reagents and conditions: ***i.*** *Li/NH_3, THF, 4 h then NH_4Cl.*

The diastereoisomers 1α,3β-diol **99** and 1α,3α-diol **101** were each subjected to Corey's acidic conditions to cleave the C-20 ketal protecting group and gave the corresponding C-20 ketone **61** and C-20 ketone **102**, respectively, in quantitative yields (**Scheme 25**).[52]



Scheme 25. Synthesis of C-20 ketones **61** and **102** under acidic conditions.

Reagents and conditions: ***i.*** *AcOH/H_2O/THF (65:35:10), rt, 12 h (100% of* ***61*** *and 100% of* ***102****).*

2.3.7. Structural assignment of ketones **61** and **102**

At this point, the structure of 1α,3β-diol **61** was proved through single crystal X-ray analysis (**Figure 16**). This X-ray crystallography gave an insight into the stereochemistry of the molecule showing the axial and equatorial configurations of C-1 hydroxyl and C-3 hydroxyl groups, respectively.

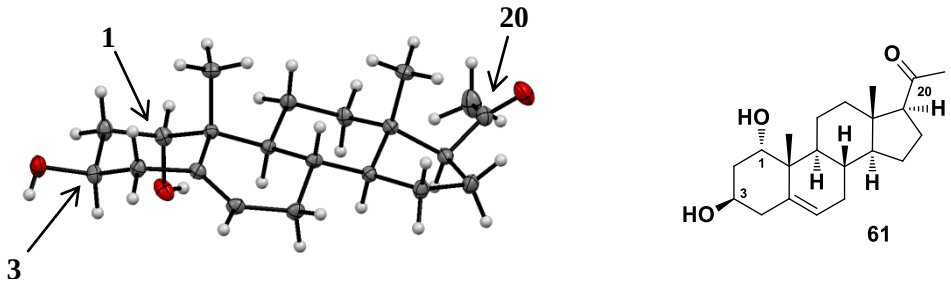


Figure 16. X-ray crystal structure of 1α,3β-diol **61** depicted using Mercury 3.0. ORTEP representation shown with ellipsoid at 50% probability. (CCDC 983153, **Appendix I)**.

The stereochemistry of 1α,3α-diol **102** was further supported by strong nOe interactions between H-2α (δ 1.99-1.96, m) and H-3 and between H-4α (δ 2.69-2.67, m) and H-3, suggesting that H-3 is in an equatorial position (**Figure 17**).

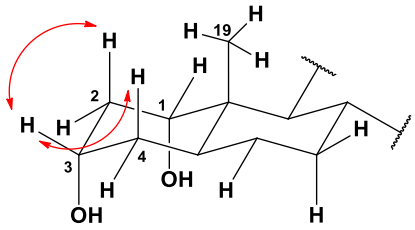
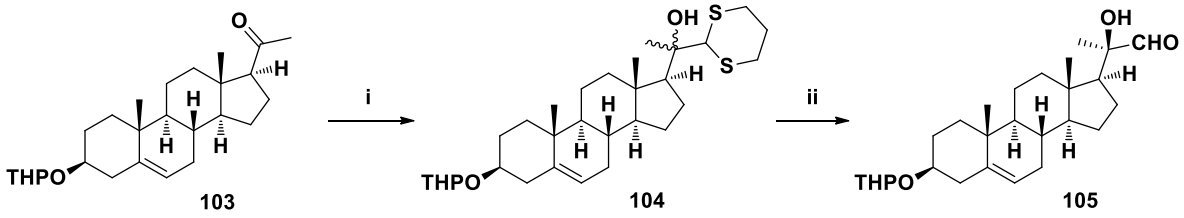


Figure 17. Key nOe interactions of 1α,3α-diol **102** (**Appendix II**).

2.4. C-1 Homologation of Ketone 61 to Aldehyde 40

2.4.1. The Corey-Seebach umpolung methodology: literature examples

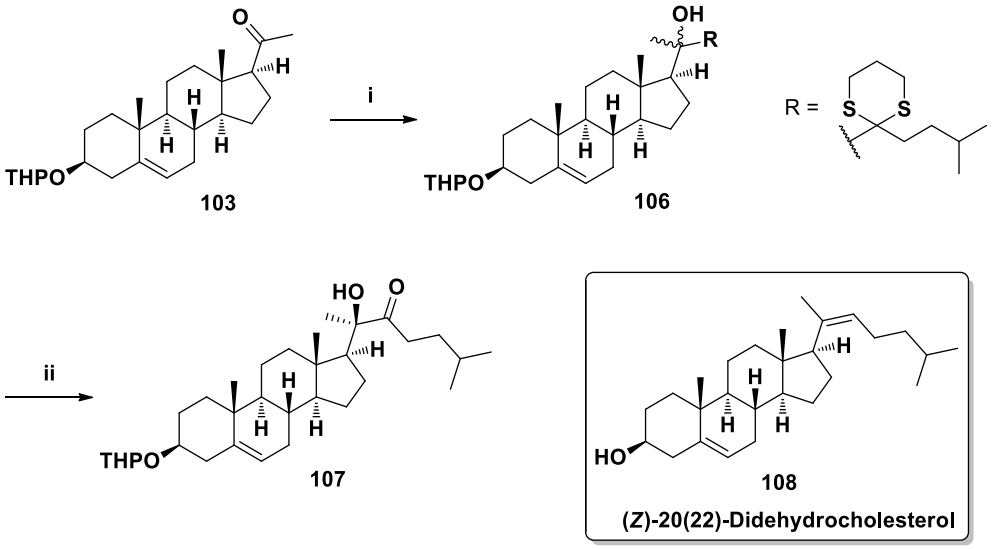
In 1972, Lettré *et al.* investigated the synthesis of 20-hydroxyaldehydes *via* the addition of 1,3-dithiane to derivatives of pregnenolone (**36**).[53] Under standard reaction conditions using 1.0 eq. of 1,3-dithiane and ^{n}BuLi, ketone **103** was converted into dithiane adduct **104** in good yield as a mixture of diastereoisomers at C-20 (**Scheme 26**). Unfortunately, no ratio of the diastereoisomers was reported in the literature. Subsequent hydrolysis of the dithiane adduct **104** afforded the corresponding 20*R*-aldehyde **105** in a moderate 63% yield.



Scheme 26. Synthesis of dithiane adduct **104** by Lettré *et al*.

Reagents and conditions: ***i****. 1.0 eq. 1,3-dithiane, 1.0 eq.* ^{n}*BuLi, THF, −30 °C to 0 °C, 24 h (77%);* ***ii****.* $HgCl_2/HgO$*,* CH_3CN*, reflux, 5 h (63%).*

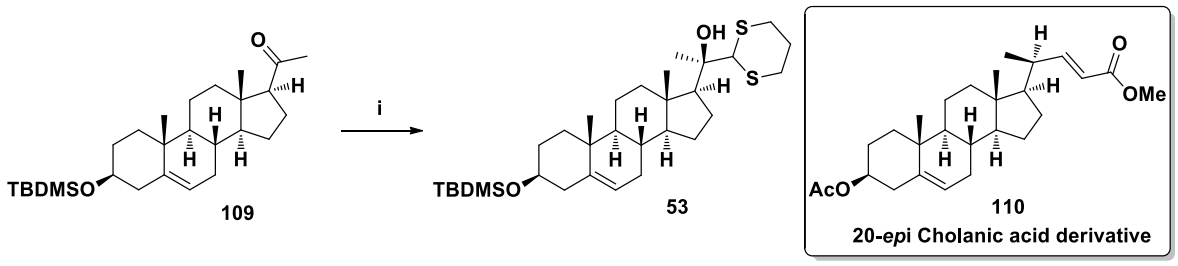
Since then, this synthetic route has been used successfully to synthesise and/or extend the side chain of steroid-related compounds in moderate to good yields.[30,54,55,56] For example, during the synthesis of (*Z*)-20(22)-didehydrocholesterol (**108**), Koreeda *et al*. applied similar reactions conditions as Lettré's group to form dithiane adduct **106** in 70% yield (**Scheme 27**).[54]



Scheme 27. Synthesis of dithiane adduct **106** by Koreeda *et al*.

Reagents and conditions: ***i****. 1.0 eq. 2-isopropyl-1,3-dithiane, 1.0 eq.* ^{n}*BuLi, THF, −25 °C, 7 h (70%);* ***ii****.* $HgCl_2$*-*$CaCO_3$*,* $CH_3CN/THF/H_2O$*, reflux, 50 h (51%).*

More recently (2007), Shingate *et al*. successfully used the Corey-Seebach umpolung methodology during their stereoselective syntheses of 20-*epi*-cholanic acid derivatives, *e.g*. **110**.[56] Thus, ketone **109** was treated with 1.5 eq. of 1,3-dithiane and 1.8 eq. of ^{n}BuLi at low temperature to afford the corresponding 20*R*-hydroxydithiane adduct **53** in 82% yield (**Scheme 28**).

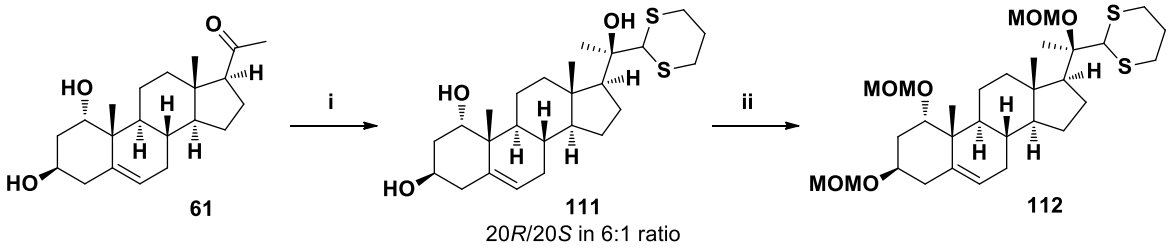


Scheme 28. Synthesis of dithiane adduct **53** by Shingate *et al*.

Reagents and conditions: ***i****. 1.5 eq. 1,3-dithiane, 1.8 eq.* ^{n}*BuLi, THF, −25 °C, 7 h (82%).*

2.4.2. Synthesis of dithiane adduct **112**

We decided to explore this dithiane chemistry using similar reaction conditions on the unprotected 1α,3β-dihydroxyketone **61**, but unfortunately, the synthesis of dithiane adduct **111** was low yielding and led mostly to the recovery of unreacted ketone **61**. Indeed, the dithioacetal **111** was obtained as a mixture of C-20*R*- and C-20*S*-diastereoisomers in a 6:1 ratio in 44% yield (91% brsm). Subsequently, the hydroxyl groups in triol **111** were protected as tris-MOM derivatives in good yield (83%) (**Scheme 29**).[29] Therefore, the dithiane adduct **112** was synthesised from the C-20 ketone **61** in 37% yield over two steps. Both dithiane adducts **111** and **112** were novel compounds and therefore, fully characterised.

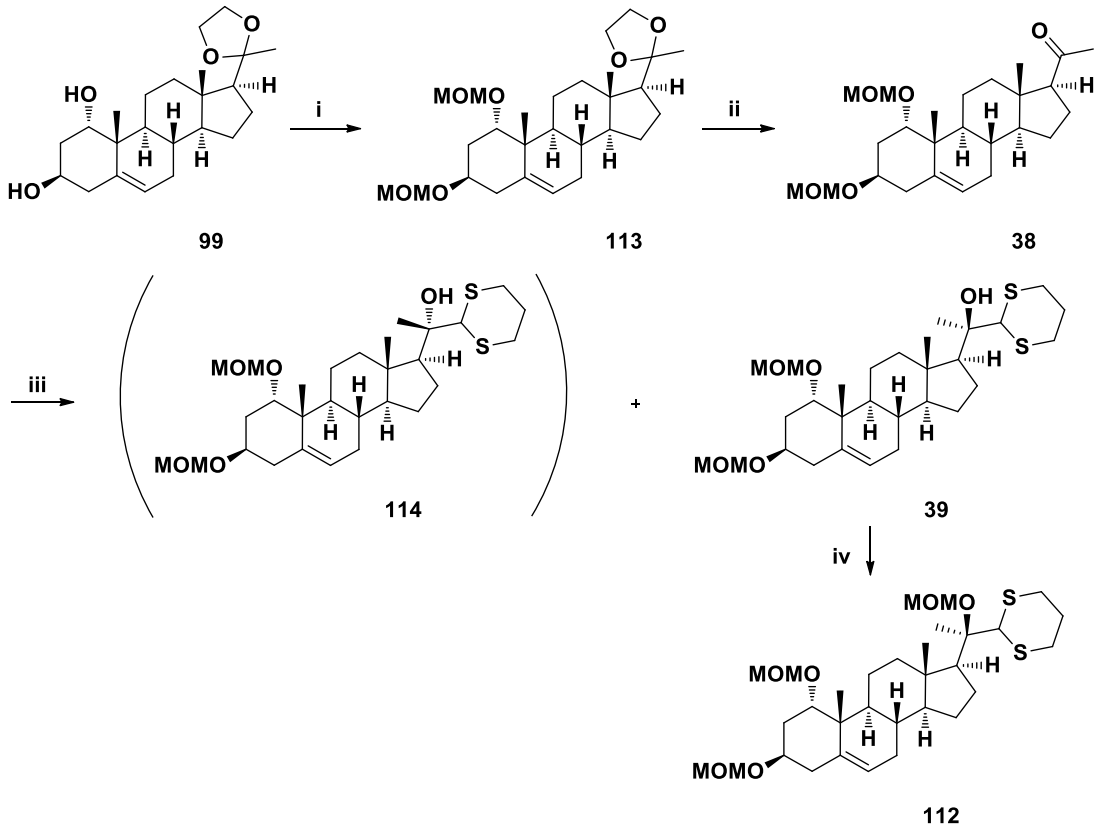


Scheme 29. Synthesis of dithiane adduct **112**.

Reagents and conditions: ***i****. 5.0 eq. 1,3-dithiane, 5.0 eq.* ^{n}*BuLi, THF, −5 °C, 8 h (44%, 91% brsm);* ***ii****. MOMCl,* $^{i}Pr_2EtN$*, 1,4-dioxane, reflux, 12 h (83%).*

2.4.3. Alternative route to dithiane **112**

It was proposed that by protecting diol **61** as a bis-MOM the yield of the Corey-Seebach reaction may be improved. MOM-protected ketal **113** was therefore prepared and submitted to Corey's deprotection conditions to afford ketone **38** in 92% yield over two steps.[52] The next key step was the Corey-Seebach dithiane reaction which was carried out using standard conditions and provided a 6:1 mixture of C-20 hydroxydithioacetal diastereoisomers **39** and **114** which were readily separated by column chromatography and gave the dithiane adduct **39** in 71% yield. This reaction has also been disclosed by Ikekawa *et al*. in a comparable yield (78%).[29] Subsequently, the C-20 hydroxyl **39** was protected as a methoxymethylene ether in very good yield (85%) (**Scheme 30**). Thus, the dithiane adduct **112** was synthesised in a slightly improved 42% yield over four steps.



Scheme 30. Revised synthetic route to dithiane adduct **112**.

Reagents and conditions: ***i****. 7.4 eq. MOMCl, 1,4-dioxane, reflux, 6 h (92%);* ***ii****. AcOH/H_2O/THF (65:35:10), rt, 12 h (100%);* ***iii****. 5.0 eq. 1,3-dithiane, 5.0 eq.* ^{n}*BuLi, THF, −5 °C, 8 h (71% of* ***39*** *and 4% of* ***114****);* ***iv****. MOMCl,* $^{i}Pr_2EtN$*, 1,4-dioxane, reflux, 12 h (85%).*

2.4.4. Discussion of the stereoselectivity of the Corey-Seebach reaction

The stereochemical aspects of different approaches to construct and/or extend the side chain of steroid-related molecules have been reviewed previously by Piatak and Wicha.[57] Here, they reported that the stereochemistry at C-20 was assumed to be *R* according to the preferential nucleophilic attack of the bulky 2-lithio-1,3-dithiane on the less sterically hindered face of ketone **38**, *i.e.* from the C-16 side and therefore, the opposite face of the steroid core structure as illustrated by the Felkin-Ahn model described in **Figure 18**.

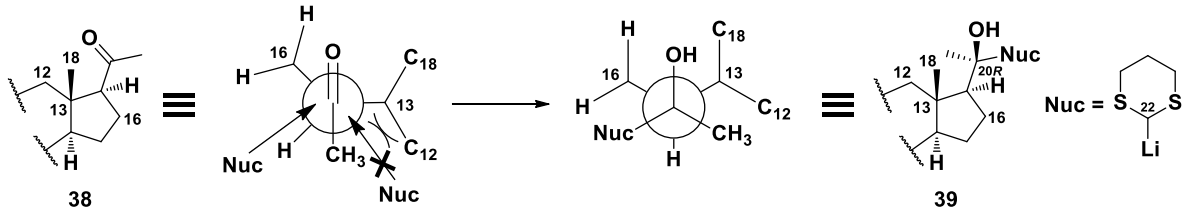


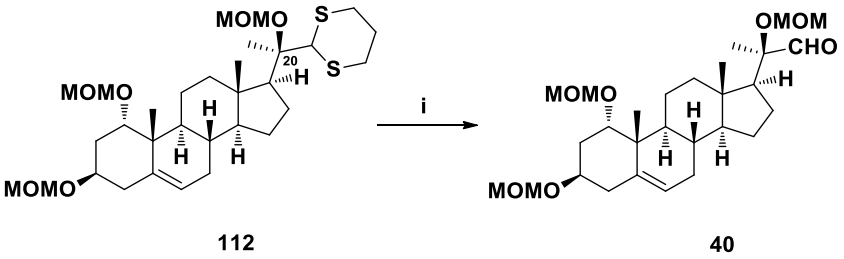
Figure 18. Felkin-Ahn model for diastereoselective attack of 2-lithio-1,3-dithiane on ketone **38**.

Furthermore, it was expected that the diagnostic ^{1}H-NMR signals at C-21 and C-22 offered the best option for the confirmation of the stereochemistry at C-20. Indeed, it was anticipated that the H-21 of the C-20β isomer would show a signal more downfield than its C-20α diastereoisomer.[57] In our case, the ^{1}H-NMR spectrum of the desired 20*R*-hydroxydithiane **39** presented a downfield signal at δ 1.42 (s) representative of H-21 whereas the ^{1}H-NMR spectrum of the undesired 20*S*-hydroxydithiane **114** showed a signal at δ 1.32 (s). Likewise, H-22 of the undesired C-20*S*-diastereoisomer was expected to show a signal more downfield due to interactions between H-22 and the C-20α hydroxyl group. Thus, the H-22 of the undesired 20*S*-hydroxydithiane **114** was observed in the ^{1}H-NMR spectrum at δ 4.33 (s) whereas the ^{1}H-NMR spectrum of the desired 20*R*-hydroxydithiane **39** showed a signal at δ 4.13 (s). From these observations and precedent, it was concluded that 20*R*-hydroxydithiane **39** was the major product in the Corey-Seebach reaction (**Scheme 30**).

Similar arguments were used to assign the *R*- and *S*-diastereoisomers of adduct **111**. Thus, in the ^{1}H-NMR spectrum of adduct **111**, H-22 and H-21 of the desired 20*R*-hydroxydithiane showed signals at δ 4.19 (s) and δ 1.40 (s), respectively; H-22 and H-21 of the 20*S*-hydroxydithiane were observed at δ 4.35 (s) and δ 1.38 (s), respectively.

2.4.5. Dithiane adduct cleavage: synthesis of the model system **117**

The next key step in the total synthesis was the hydrolysis of dithiane adduct **112** to form the corresponding aldehyde **40**. This reaction was carried out on a similar substrate 20*R*-hydroxydithiane **39** in good yield (85%) under standard mercuric oxide conditions as reported by Ikekawa's group during the synthesis of withanolide D (**6**).[29] Unfortunately, using the same procedure with MOM-protected C-20 hydroxydithiane **112** gave the desired aldehyde **40** in poor yield (27%) and mostly led to decomposition (**Scheme 31**).



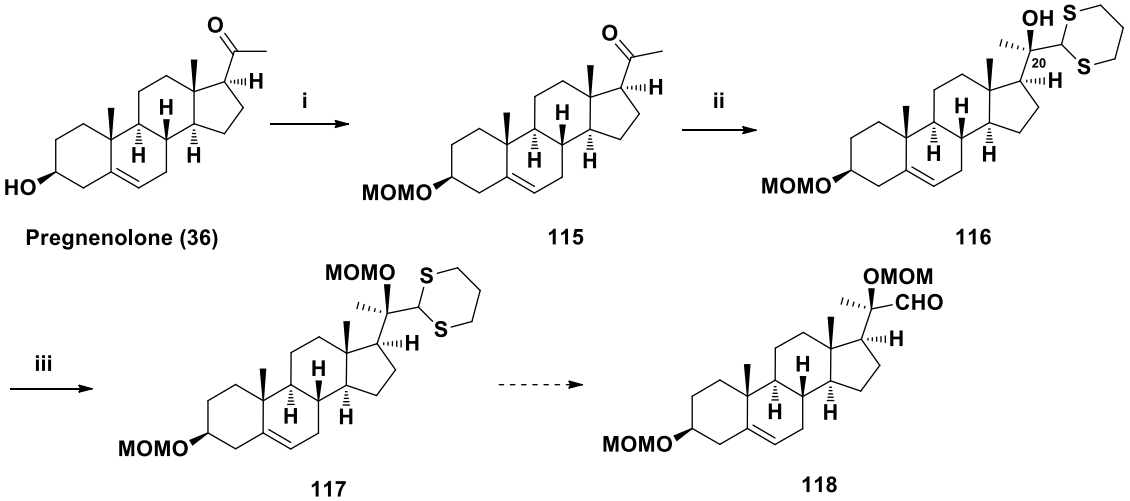
112 40

Scheme 31. Hydrolysis of dithiane adduct **112** under mercuric oxide conditions.

.

Reagents and conditions: ***i.*** *HgO, BF_3•Et_2O, THF/H_2O (1:1), reflux, 4 h (27%).*

This step required an extensive optimisation study and in order not to use all the dithiane adduct material **112**, we proposed to screen a range of conditions for the cleavage step on a model steroid system **117** which was a novel compound and easily accessible from pregnenolone (**36**). Towards this aim, the C-3 hydroxyl group of commercially available pregnenolone (**36**) was protected as the methoxymethylene ether **115** in very good yield on gram scale. In turn, ketone **115** was treated under Corey-Seebach reaction conditions to afford the dithiane adduct **116** in 78% yield as a mixture of diastereoisomers at C-20 in a 6:1 ratio. Finally, the tertiary alcohol was protected using standard conditions which afforded compound **117** in excellent yield (**Scheme 32**). Both of these dithiane adducts **116** and **117** were novel and therefore, fully characterised.



Pregnenolone (36) 115 116

117 118

Scheme 32. Synthesis of the model steroid system **117**.

Reagents and conditions: ***i.*** *MOMCl, $^{i}Pr_2EtN$, 1,4-dioxane, reflux, 12 h (88%);* ***ii.*** *1,3-dithiane, $^{n}BuLi$, THF, −5 °C, 8 h (78%, 6:1 ratio at C-20);* ***iii.*** *MOMCl, $^{i}Pr_2EtN$, 1,4-dioxane, reflux, 12 h (92%).*

2.4.6. Structural assignment of dithiane adducts **116** and **117**

Similar arguments previously discussed to confirm the structural assignment of dithiane adducts **111** and **39** were used to assign the *R*- and *S*-diastereoisomers of adduct **116**. Hence, H-21 and H-22 showed a downfield signal at δ 1.44 (s) and a highfield signal at δ 4.13 (s), respectively, which is characteristic of the desired C-20*R*-diastereoisomer **116**. Likewise, the H-21 and H-22 of the undesired C-20*S*-diastereoisomer of adduct **116** were observed at δ 1.33 (s) and δ 4.36 (s), respectively.

Furthermore, an X-ray crystal structure was obtained of the dithiane adduct **117** in order to confirm its structure and stereochemistry (**Figure 19**). Pleasingly, the assigned C-20*R*-configuration was confirmed with the C-21 methyl group pointing "down". Likewise, the C-3β configuration of the protected alcohol was verified as the H-3 is clearly in an axial position. We are therefore confident of earlier assignments.

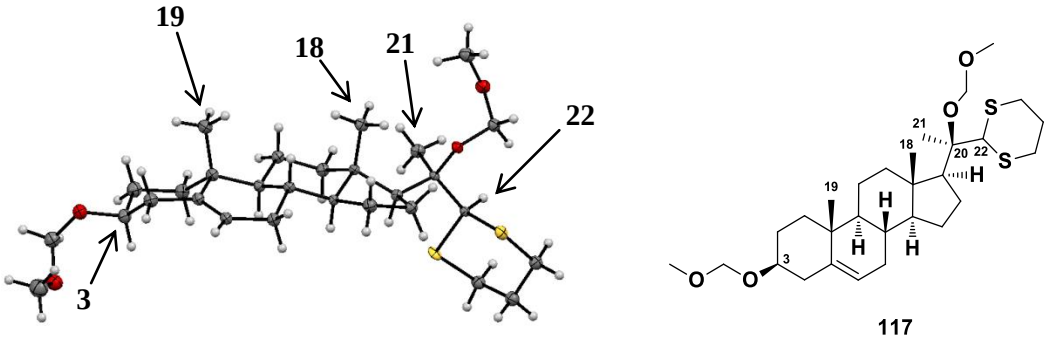
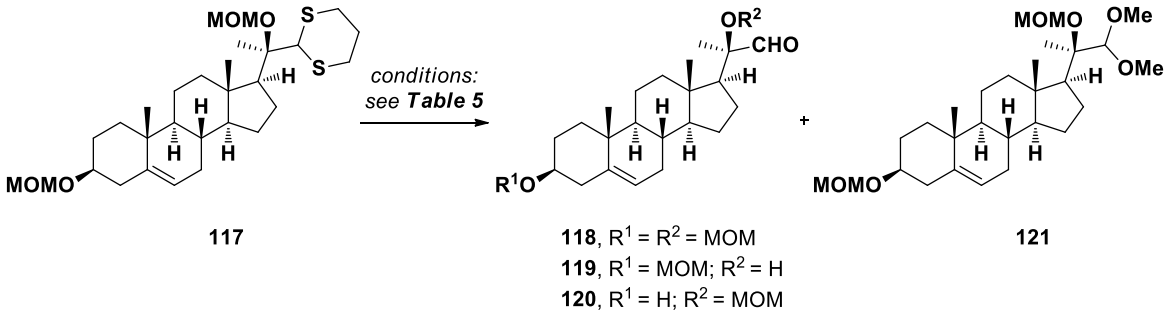


Figure 19. X-ray crystal structure of *R*-enantiomer of dithiane adduct **117** depicted using Mercury 3.0. ORTEP representation shown with ellipsoid at 50% probability. (CCDC 983152, **Appendix I**).

2.4.7. Completion of the synthesis of aldehyde **40**

Several successful methods for the hydrolysis of the dithiane moiety have been investigated in the past few years.[58,59,60] Therefore, model dithiane **117** was subjected to a series of these different reaction conditions in order to form the corresponding aldehyde **118** as listed in **Table 5** (**Scheme 33**).



117

118, $R^1 = R^2 = MOM$
119, $R^1 = MOM$; $R^2 = H$
120, $R^1 = H$; $R^2 = MOM$

121

Scheme 33. Hydrolysis of dithiane **117**.

Table 5. Screening of conditions for the cleavage of dithiane **117**.

Entry	Reagents	Conditions	Outcome
1	DMP (2.0 eq.), $NaHCO_3$ (1.0 eq.)	$CH_3CN/H_2O/CH_2Cl_2$ (8:1:1), rt, 48 h	rsm **117**
2	DMP (2.0 eq.), Na_2CO_3 (1.0 eq.)	$CH_3CN/H_2O/CH_2Cl_2$ (8:1:1), rt, 48 h	rsm **117**
3	DMP (2.0 eq.), K_2CO_3 (1.0 eq.)	$CH_3CN/H_2O/CH_2Cl_2$ (8:1:1), rt, 48 h	rsm **117**
4	NaI (0.01 eq.), *p*-benzoquinone (1.2 eq.)[67]	CH_3CN/H_2O (10:1), 100 °C, 48 h	rsm **117**
5	NCS (4.0 eq.), $AgNO_3$ (4.5 eq.), 2,6-lutidine (10 eq.)[64]	MeOH/THF (1:1), rt, o/n	**118**: 5% **121**: 68%
6	PIDA (2.0 eq.)[61]	CH_3CN/H_2O (9:1), rt, o/n	**118**: 9% decomposed mixture
7	NCS (4.0 eq.), $AgNO_3$ (4.5 eq.), 2,6-lutidine (10 eq.)	THF, rt, o/n	**118**: 20% decomposed mixture
8	HgO (2.2 eq.), BF_3•Et_2O (2.2 eq.)[29]	THF/H_2O (1:1), 70 °C, 30 min	**118**: 35% **119**: 27% **120**: 49%
9	NCS (4.0 eq.), $AgNO_3$ (4.5 eq.), 2,6-lutidine (10 eq.)	H_2O/THF (1:1), rt, o/n	**118**: 40% decomposed mixture
10	NCS (2.1 eq.)[35]	CH_2Cl_2/H_2O (10:1), rt, 2 h	**118**: 54%
11	DMP (2.0 eq.)[62]	$CH_3CN/H_2O/CH_2Cl_2$ (8:1:1), rt, o/n	**118**: 70%

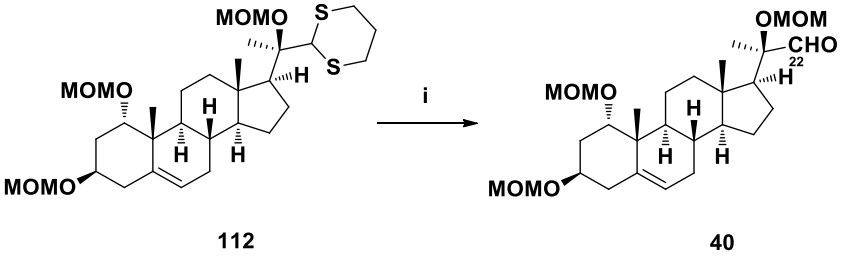
Table 5 (**continued**). Screening of conditions for the cleavage of dithiane **117**.

Entry	Reagents	Conditions	Outcome
12	NCS (3.9 eq.), $AgNO_3$ (4.4 eq.)[65]	CH_3CN/H_2O (4:1), 0 °C, 30 min	**118**: 77%
13	NBS (6.0 eq.), 2,6-lutidine (12 eq.) [63]	CH_3CN/H_2O (4:1), 0 °C → rt, o/n	decomposed mixture
14	NCS (4.0 eq.), $AgNO_3$ (4.5 eq.), 2,6-lutidine (10 eq.)	CH_3CN/THF (1:1), rt,o/n	decomposed mixture
15	NCS (4.0 eq.), $AgNO_3$ (4.5 eq.), 2,6-lutidine (10 eq.)	CH_2Cl_2/THF (1:1), rt, o/n	decomposed mixture
16	$NaClO_2$ (10.0 eq.), $NaH_2PO_4.H_2O$ (5.0 eq.), 2-Me-2-butene (10.0 eq.)[66]	MeOH/H_2O (3:1), rt, 1 h	decomposed mixture

Traditionally, the deprotection of dithiane moieties has required drastic hydrolysis conditions or the use of toxic mercury salts.[68] Nevertheless, as seen in entry **8**, using mercuric oxide resulted in the formation of compound **118** in poor yield (35%). Moreover, it was found that the reaction conditions were too acidic and resulted in the deprotection of either the C-3 or the C-20 methoxymethylene ether group. Therefore, a screening of more recently developed conditions was undertaken. The conditions assayed in entry **6** (DMP) gave a good yield (70%).[62] Unfortunately, the use of $NaHCO_3$, $NaCO_3$ and K_2CO_3 as bases typically resulted in no reaction at all which might suggests that the acidity of the reagent positively influenced the outcome of the reaction (entries **1** to **3**). Likewise, conditions assayed in entry **5** using NCS gave promising results.[64] It was thought that changing the solvent system could help avoid the formation of the undesired acetal **121** and favor the reaction towards the formation of the corresponding aldehyde **118**. Unfortunately, this was not observed, at best it gave aldehyde **118** in 40% yield (entries **7**, **9 14** and **15**). Pleasingly, the Smith reaction conditions (NCS and $AgNO_3$, entry **12**) gave a very good yield (77%).[65] The conditions of entry **10** have been disclosed by Gademann *et al*. in the total synthesis of withanolide A (**5**) and delivered the aldehyde **54** in 73% yield.[35] Disappointingly, in our case, the yield was not improved when compared to entry **12** (54%). Similarly, none of the reaction conditions recently developed on related substrates tested on the dithiane adduct **117** were successful (entries **4** and **16**).[66, 67]

Entry **12** constitutes the best option for the hydrolysis of the dithiane adduct **117** in terms of yield and safety, although, these conditions led to a lower yield on a gram scale (57% yield). Fortunately, when applied to target dithiane adduct **112**, these reaction

conditions worked successfully and pleasingly delivered the corresponding aldehyde **40** in a very good yield (85%) which was reliably reproducible on a gram scale without MOM hydrolysis (**Scheme 34**). Compound **40** exhibited the typical aldehyde peaks in ^{1}H- and ^{13}C-NMR spectra, *i.e.* a downfield signal at δ 9.68 (s) and a downfield signal at δ 205.4 which represented H-22 and C-22, respectively, and was fully characterised.



112 40

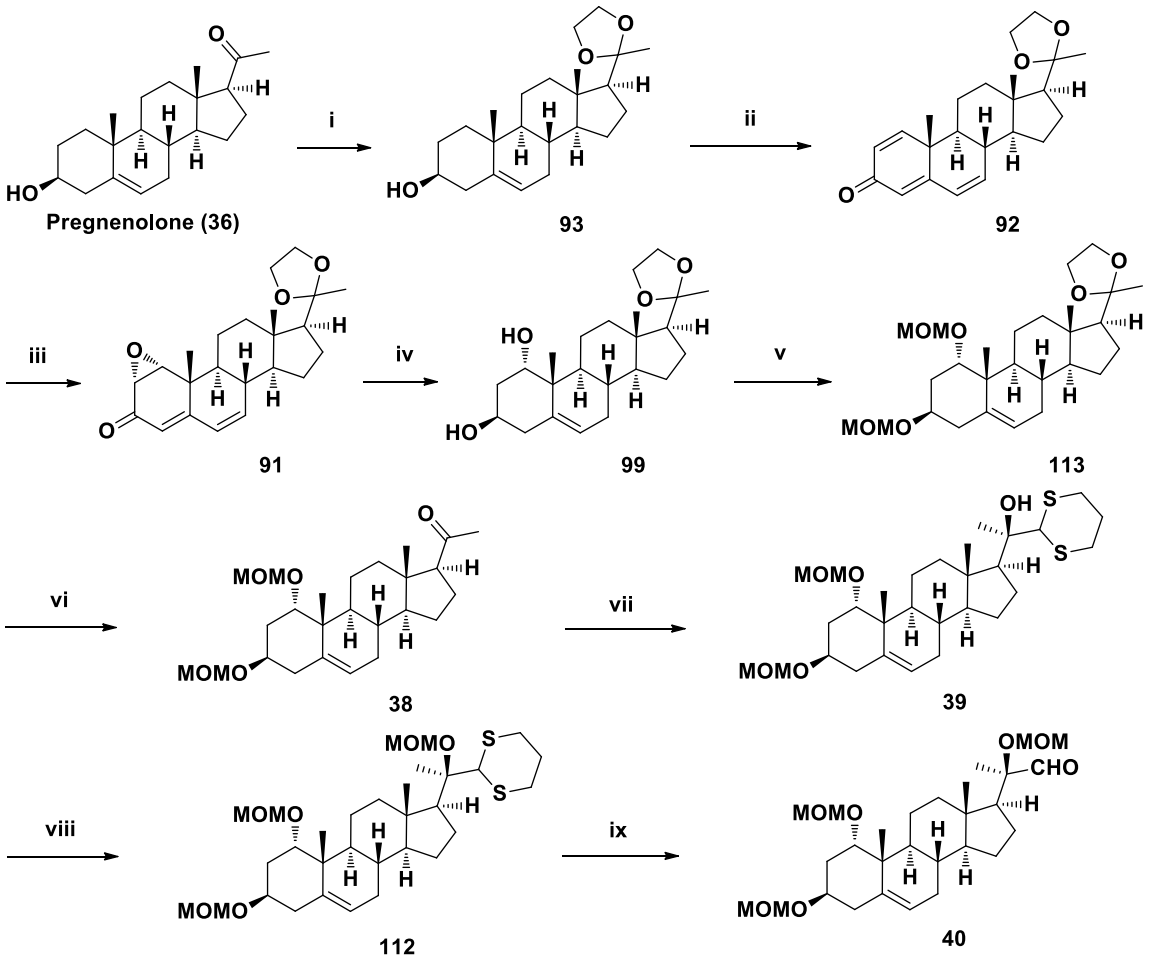
Scheme 34. Synthesis of aldehyde **40**.

Reagents and conditions: ***i****. NCS, $AgNO_3$, CH_3CN/H_2O (4:1), 0 °C, 30 min (85%).*

2.5. Summary and Future Work

2.5.1. Summary

Initial efforts towards the total synthesis of 14,17-dihydro-17-*epi*-withanolide F (**24**) concerned the synthesis of aldehyde **40**, a key intermediate in the proposed retrosynthesis (**Scheme 7**). Pleasingly, aldehyde **40** was synthesised in nine steps and an overall 14% yield from pregnenolone (**36**) (**Scheme 35**).



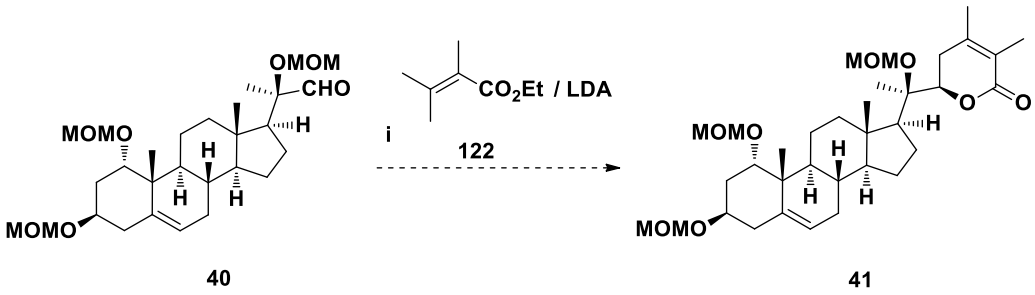
Scheme 35. Optimised synthetic route to aldehyde **40**.

Reagents and conditions: ***i****. ethylene glycol, p-TsOH, toluene, 130 °C, 12 h (90%);* ***ii****. Pd(OAc)$_2$, ADP, Na$_2$CO$_3$, DMF, 160 °C, 72 h (62%);* ***iii****. H$_2$O$_2$ (30% w/w), 10% NaOH in MeOH, ^{i}PrOH, 15 °C, 12 h (72%);* ***iv****. Li/NH$_3$, NH$_4$Cl, THF, −78 °C to −40 °C to −20 °C, 4 h (76%);* ***v****. MOMCl, 1,4-dioxane, reflux, 6 h (92%);* ***vi****. AcOH/H$_2$O/THF (65:35:10), rt, 12 h (100%);* ***vii****. 1,3-dithiane, ^{n}BuLi, THF, −5 °C, 8 h (71%);* ***viii****. MOMCl, ^{i}Pr$_2$EtN, 1,4-dioxane, reflux, 12 h (85%);* ***ix****. NCS, AgNO$_3$, CH$_3$CN/H$_2$O (4:1), 0 °C, 30 min (85%).*

The key steps of the synthesis included a Pd(OAc)$_2$-mediated catalytic oxidation process, a Birch reduction, a C-1 homologation *via* a Corey-Seebach reaction and an efficient dithiane hydrolysis

2.5.2. Future work

With aldehyde **40** in hand, further studies towards the construction of the δ-lactone side chain were planned. It was envisioned that the key α,β-unsaturated lactone in the side chain could be installed *via* a stereoselective vinylogous aldol reaction using a procedure developed by Ikekawa *et al.*[69] The strategy outlined previously would involve the condensation of the steroidal aldehyde **40** with the lithium enolate derived from ester **122** (**Scheme 36**). This investigation is discussed in **Chapter 3**



Scheme 36. Construction of δ-lactone **41**.

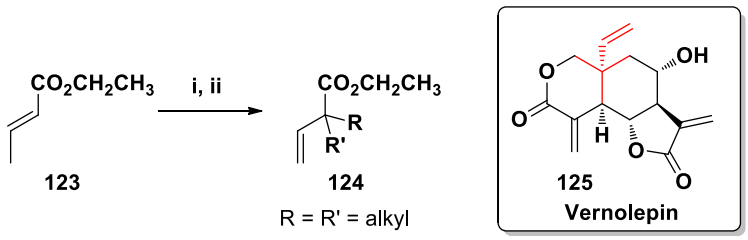
*Suggested reagents and conditions: **i**. LDA, THF/DMPU, −78 °C, 6 h.*

Chapter 3. Construction of the δ-Lactone Side Chain

As discussed in **Chapter 2**, the key step in the total synthesis of 14,17-dideoxy-17-*epi*-withanolide F (**24**) was the δ-lactone side chain formation. The installation of this structural feature, which is unique to the withanolides in steroid synthesis, has been thoroughly investigated over the past few years and has led to the development of a number of different methods for its construction.

3.1. δ-Lactone Construction: Literature Examples

In 1973, Hermann *et al*. developed a deconjugative alkylation method to form a quaternary carbon center bearing a vinyl substituent, a key structural feature found in a number of natural compounds such as vernolepin (**125**), as sesquiterpene lactone.[70] A non-nucleophilic form of LDA as a complex with HMPA was used in order to avoid any Michael addition of the base to the ethyl crotonate **123** and gave the desired alkylated crotonate **124** in high yields (88% - 98%) using a broad range of alkyl halides (**Scheme 37**).

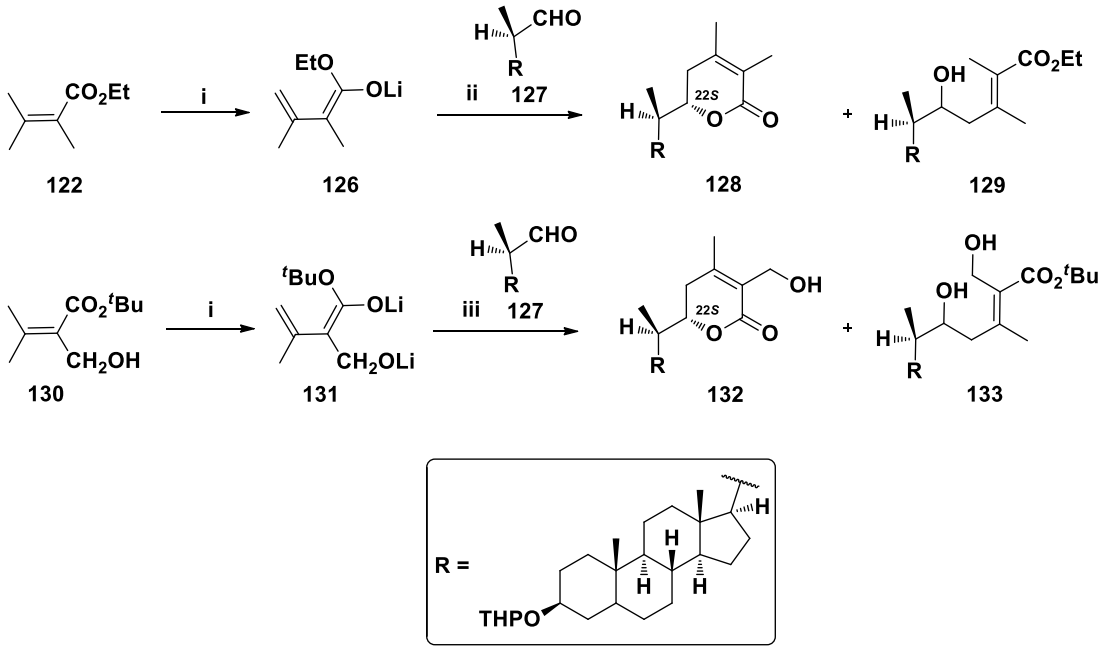


Scheme 37. Deconjugative alkylation to form quaternary carbon center.

Reagents and conditions: ***i****. LDA/HMPA (1:1), RX, THF, −78 °C;* ***ii****. LDA/HMPA (1:1), R'X, THF, −78 °C (88% up to 98%).*

The first studies on the construction of the α,β-unsaturated δ-lactone side chain of withanolides were conducted by Ikekawa's group in 1975.[69] Using the method of Herrmann's group outlined above,[70] esters **122** and **130** were reacted with LDA/HMPA and the resulting dienolates **126** and **131**, respectively, were treated with steroidal aldehyde **127** (**Scheme 38**). Their studies led to the discovery of exclusive γ-coupling in the aldol reaction of tetrasubstituted esters to give the corresponding α,β-unsaturated lactones **128** and **132**, respectively. The steroidal lactones thus formed were structurally identical to the

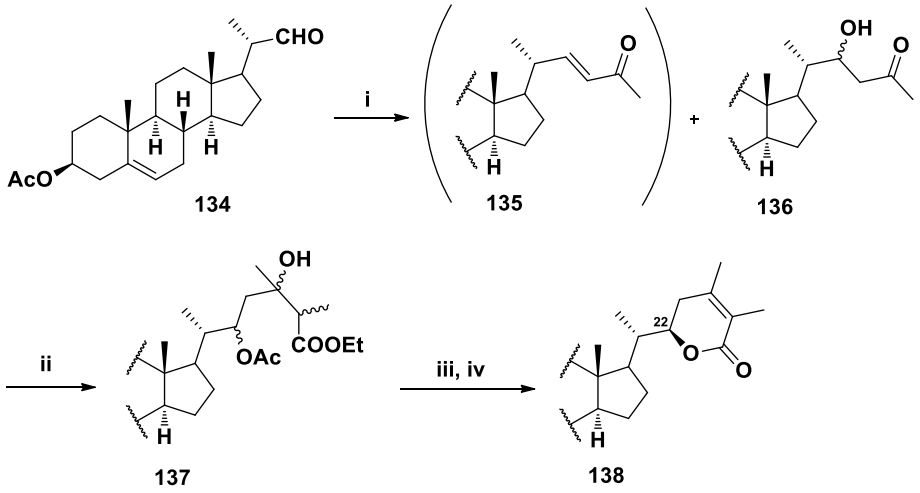
side chains of withanolides but with the C-22*S* stereochemistry instead of the C-22*R*-configuration.



Scheme 38. δ-Lactone formation *via* γ-coupling of lithium enolates.

Reagents and conditions: ***i****. LDA, THF, −78 °C, 20 min;* ***ii****. THF, −78 °C, 1 h (56% of* ***128*** *and 22% of* ***129****):* ***iii****. THF, −78 °C, 1 h (11% of* ***132*** *and 55% of* ***133****).*

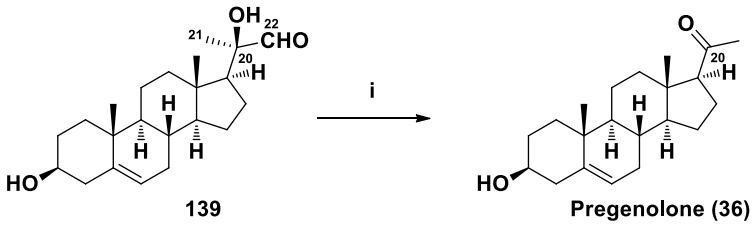
Later, Gonzalez *et al*. investigated an aldol condensation of aldehyde **134** with acetone under alkaline conditions which allowed the formation of α,β-unsaturated ketone **135** and hydroxyketone **136** (no yields were reported in the paper).[71] The alcohol **136** was acetylated and treated under Reformatsky conditions using ethyl α-bromopropionate to form the corresponding ester **137**. After alkaline hydrolysis of the ester **137**, the corresponding carboxylic acid cyclised under acidic conditions. The concomitant dehydration of the tertiary C-24 hydroxy group gave the δ-lactone **138** (**Scheme 39**). It was suggested that the product formed was a mixture of epimers at C-22 with *S*-configuration as the major one according to the Cotton effect of the lactone ($\Delta\epsilon_{258}$ −3.72).[69]



Scheme 39. δ-Lactone formation *via* aldol condensation.

Reagents and conditions: ***i****. acetone, 10% aq. NaOH;* ***ii****. 1) Ac_2O, 2) ethyl α-bromopropionate, zinc;* ***iii****. 1 M NaOH, MeOH, rt ;* ***iv****. 2 M HCl, MeOH, 60 °C, 24 h.*

Ikekawa *et al*. subsequently investigated the construction of the lactone side chain by the condensation of the C-20 hydroxyaldehyde **139** with the lithium enolate of α,β-unsaturated ester **122** and obtained ketone **36** in 80% yield, which was suggested to arise from elimination of the C-20 formyl group under basic conditions (**Scheme 40**).[30]

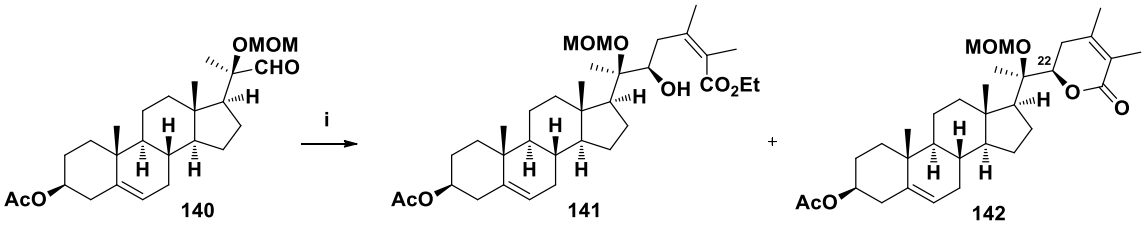


Scheme 40. Deformylation under lactone-forming conditions.

Reagents and conditions: ***i****. ethyl 2,3-dimethylbutenoate (**122**), LDA/HMPA, THF, −78 °C, 3 h, rt, 19 h (80%).*

On the other hand, the condensation of the corresponding C-20 methoxymethylene ether protected aldehyde **140** with a lithium enolate of α,β-unsaturated ester **122** allowed the formation of the desired C-22*R*-lactone **142** in 16% yield and the hydroxyester **141** in 44% yield (**Scheme 41**). These results have demonstrated the importance of protecting the C-20 hydroxyl functionality in order to avoid subsequent deformylation during the

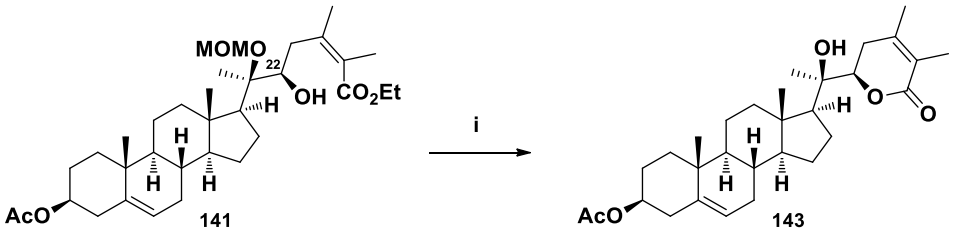
condensation step and to promote the formation of lactone **142** with the desired C-22*R*-configuration.



Scheme 41. δ-Lactone formation with the desired C-22*R*-configuration.

Reagents and conditions: ***i****. ethyl 2,3-dimethylbutenoate (**122**), LDA/HMPA, THF, −78 °C to −35 °C, 8 h (44% of **141** and 16% of **142**).*

Cleavage of the MOM protecting group also promoted the lactonisation of hydroxy ester **141** to form the final compound **143** in good yield (83%) (**Scheme 42**). In the literature,[30] it was proposed that this result suggested that the C-22 alcohol was hindered by the MOM functionality which, consequently, did not favour the lactonisation step.

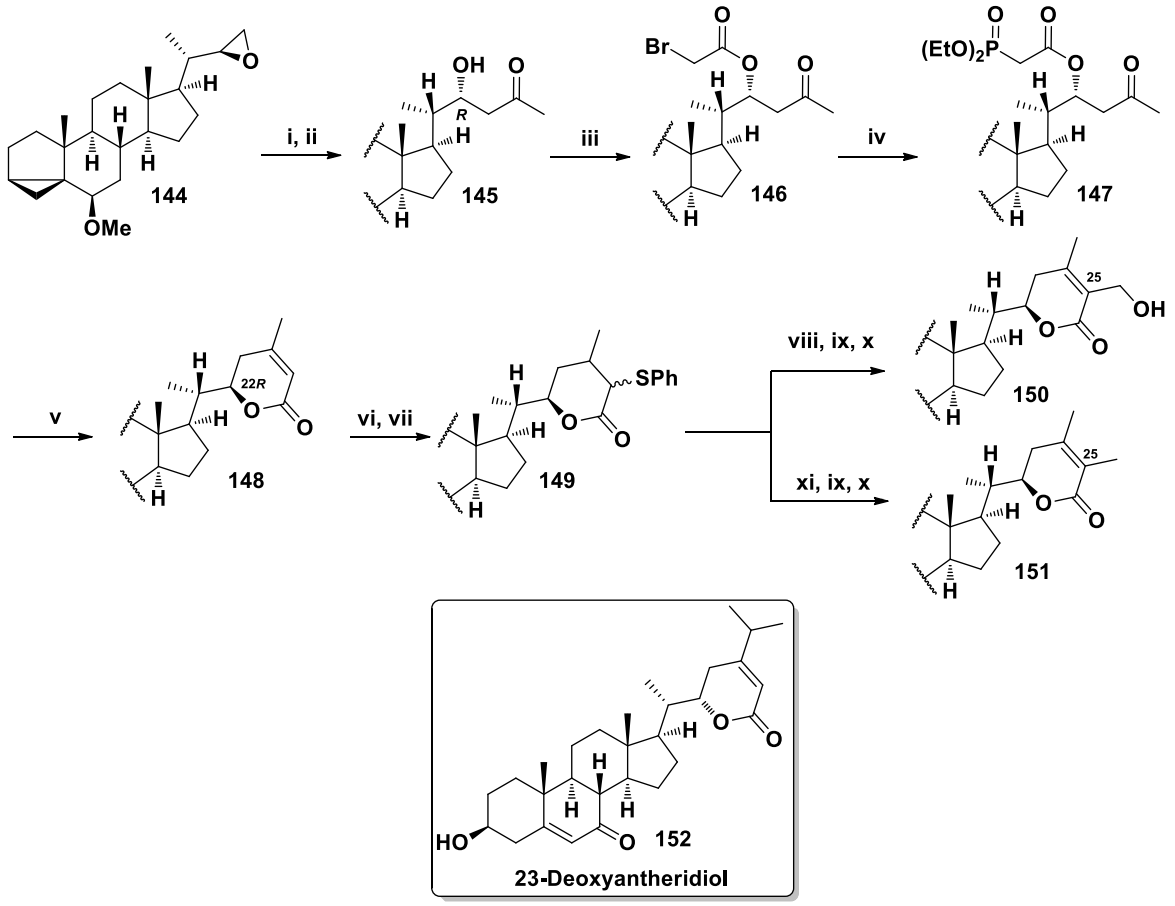


Scheme 42. MOM deprotection using iodine.

Reagents and conditions: ***i****. I_2, THF, 50 - 60 °C, 16 h (83%).*

Ikekawa and co-workers developed an alternative procedure to obtain the C-22*R*-configuration for the δ-lactone following the synthetic strategy developed by McMorris for the synthesis of the 23-deoxyantheridiol (**152**).[72,73] As shown in **Scheme 43**, after alkylation of the epoxide **144** using 2-methyl-1,3-dithiane followed by deprotection of the hydroxythioketal with mercury(II) oxide, hydroxyketone **145** was treated with bromoacetyl bromide which following the McMorris procedure, gave the lactone **148** with the correct C-22*R*-configuration. The C-25 hydroxymethyl was introduced *via* formation of phenylthio-lactone **149** as a mixture of diastereoisomers at C-25 in a 2:1 in favour of the

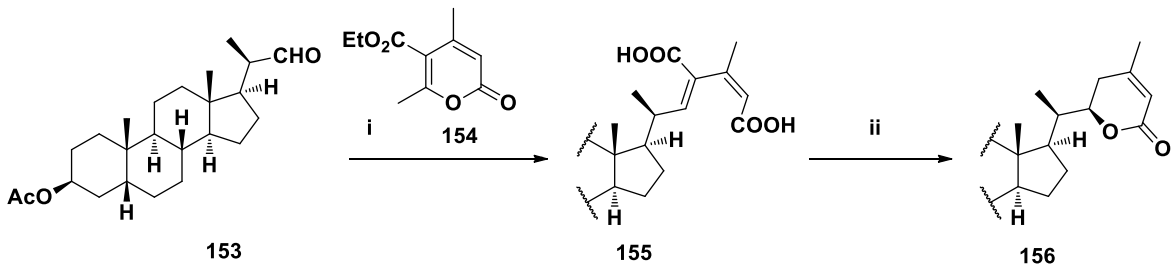
α-configuration separable by column chromatography. Subsequent exposure of the latter **149** to an excess of formaldehyde, *m*-CPBA oxidation of the sulfide **149** to the corresponding sulfoxide and desulfenylation at high temperature allowed the formation of the unsaturated lactone **150** in 14% yield over 10 steps. The latter **150** possesses the same δ-lactone side chain as found in the well-known withanolide, withaferin A (**5**). The dimethyl-lactone **151** was also prepared by this route (**Scheme 43**).



Scheme 43. Stereoselective synthesis of the δ-lactone side chain.

Reagents and conditions: ***i****. 2-methyl-1,3-dithiane,* ^{n}*BuLi, THF, −78 °C;* ***ii****. HgO,* BF_3•Et_2O*, rt (76% over two steps);* ***iii****.* $BrCH_2COBr$*, pyridine,* Et_2O*, 0 °C;* ***iv****.* $P(OEt)_3$*, 100 °C, 50 min;* ***v****. NaH, THF, rt, 30 min (79% over three steps);* ***vi****.* H_2*, Pd-C,* $NaHCO_3$*, 1,4-dioxane, rt (100%);* ***vii****. 1) LiCHA, THF, −78 °C, 30 min, 2)* $(PhS)_2$*, HMPA, THF, −78 °C, 20 min (28% of* ***149α*** *and 15% of* ***149β****);* ***viii****. 1) LiCHA, THF, −78 °C, 1 h, 2)* CH_2O*, THF, −78 °C, 30 min (76%);* ***ix****. m-CPBA,* $CHCl_3$*, 0 °C, 10 min;* ***x****. 100 °C (70% over two steps);* ***xi****. 1) LiCHA, THF, −78 °C, 1 h, 2) MeI, −78 °C, 1 h.*

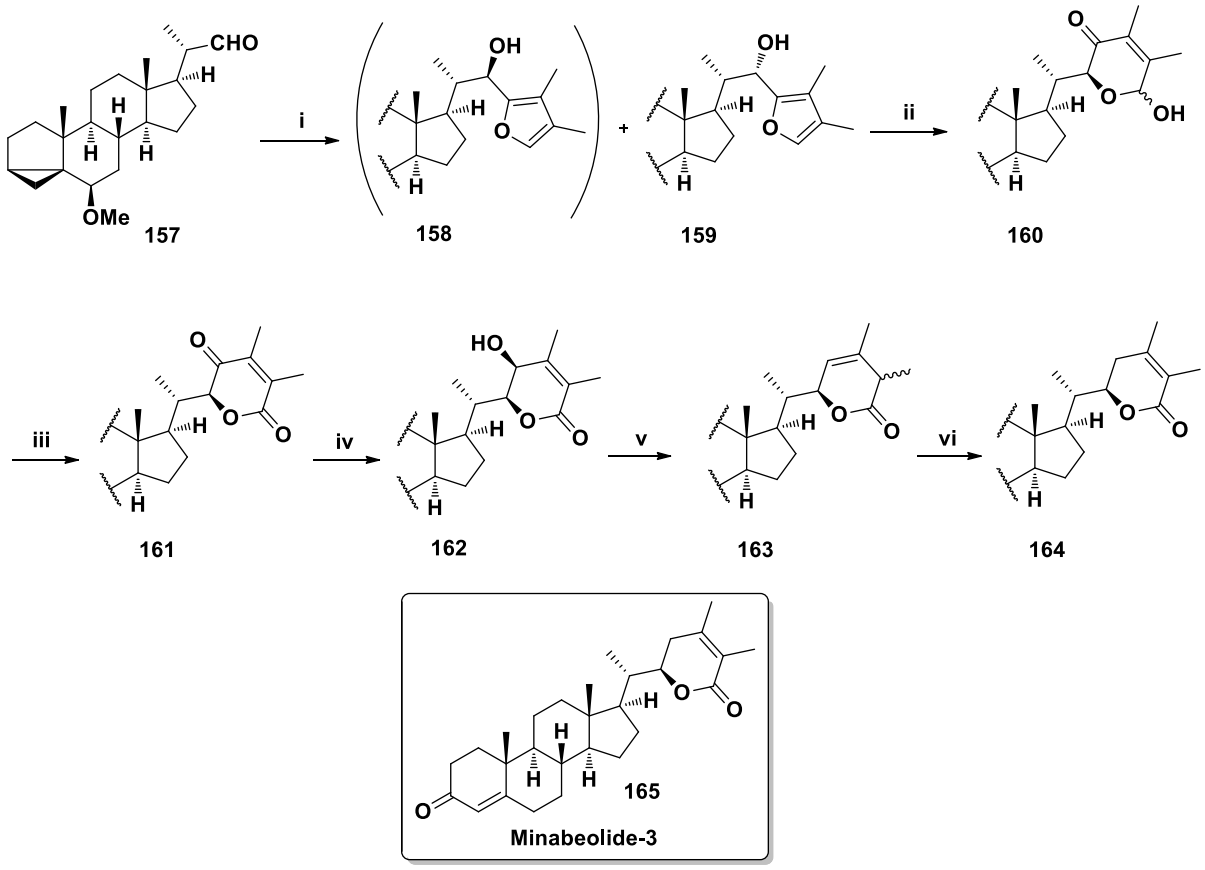
Casinovi *et al*. proposed a synthesis of the δ-lactone moiety of the withanolides *via* the condensation of the steroidal aldehyde **153** with ethyl 4,6-dimethyl-2-oxo-2H-pyran-5-carboxylate (**154**) under alkaline conditions.[74] The diacid **155** thus formed in good yield (75%) was then decarboxylated by heating and simultaneously lactonisation took place to give the desired δ-lactone **156** in 33% yield (**Scheme 44**).



Scheme 44. δ-Lactone formation *via* decarboxylation of diacid **155**.

Reagents and conditions: ***i****. ethyl 4,6-dimethyl-2-oxo-2H-pyran-5-carboxylate (****154****), NaOH, MeOH, reflux, 1 h (75%);* ***ii****. 2,4-dimethylpyridine, toluene, 100 °C, 1 h (33%).*

Another strategy was proposed by Honda and co-workers for the construction of the side chain characteristic of the withanolides.[75] Their method was based on the ring-enlargement of a furylcarbinol type of compound. The stereoselective synthesis of C-22*S*-furylcarbinol **159** was achieved in good yield *via* the addition of 2-lithio-3,4-dimethylfuran to the aldehyde **157**. The next key step was the ring-enlargement *via* an Achmatowicz reaction using NBS to give the lactol **160** in 84% yield. The following reactions using standard chemistry gave access to the desired lactone **164** in 13% yield over four steps (**Scheme 45**). This synthetic approach was successfully applied in the total synthesis of minabeolide-3 (**165**) achieved in 30% yield over 12 steps.



Scheme 45. δ-Lactone formation *via* ring-enlargement of the C-22*S*-furylcarbinol **159**.

Reagents and conditions: ***i****. 3,4-dimethylfuran,* ^{n}*BuLi, methylaluminium bis(2,4,6-tri-tert-butylphenoxide),* CH_2Cl_2*, rt, 2 h (80%);* ***ii****. NBS, anhydrous NaOAc, aq. THF, 0 °C, 30 min (84%);* ***iii****. PCC, celite, anhydrous NaOAc,* CH_2Cl_2*, rt, 2 h;* ***iv****.* $NaBH_4$*, MeOH, 0 °C, 30 min (73% over two steps);* ***v****. 1)* Ac_2O*, DMAP, pyridine,* CH_2Cl_2*, 0 °C, 1 h (95%), 2) zinc-amalgam, HCl,* Et_2O*, −15 °C, 15 min (21%, 77% brsm);* ***vi****. DBU, THF, rt, 2 h (91%).*

3.2. Synthesis of Ethyl 2,3-Dimethylbutenoate (122)

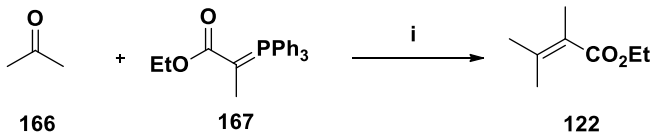
Based on the previous literature precedents, the most straightforward method and valid in terms of obtaining the desired C-22*R*-configuration was the one step synthesis conducted by Ikekawa's group.[30] It consisted of a nucleophilic attack of the lithium dienolate of ester **122** onto the steroidal aldehyde **40** as shown in **Scheme 36**.

Unfortunately, the ethyl 2,3-dimethylbutenoate (**122**) is not commercially available; therefore, its synthesis was investigated.

3.2.1. Synthesis of ethyl 2,3-dimethylbutenoate (**122**): literature routes

The synthesis of ethyl 2,3-dimethylbutenoate (**122**) has been exhaustively examined by many groups over the years and we herein describe the most successful results.

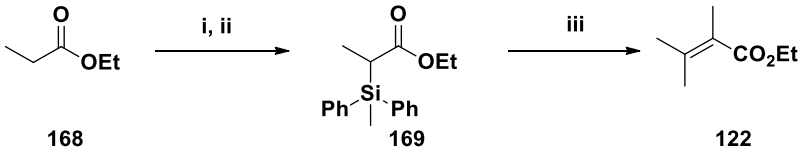
Initially, Gallagher *et al*. achieved the synthesis of ethyl 2,3-dimethylbutenoate (**122**) *via* a Wittig reaction with triphenylphosphorane **167** using standard conditions (**Scheme 46**).[76] Unfortunately, the yield of the reaction was not reported in the publication. Furthermore, later on Isaacs and El-Din reported that the same reaction conditions delivered the desired unsaturated ester **122** in only 1% yield. In their case, the Wittig reaction required very high pressure conditions (P = 9 kbar) to be able to access ethyl 2,3-dimethylbutenoate (**122**) in good yield (80%).[77]



Scheme 46. Synthesis of ethyl 2,3-dimethylbutenoate (**122**) *via* a Wittig reaction.

Reagents and conditions: ***i****.* CH_2Cl_2*, reflux, 12 h.*

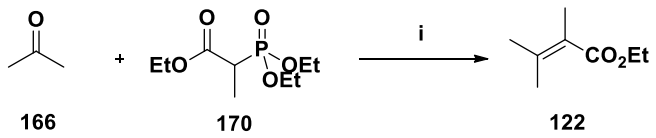
Another interesting approach was the direct silylation of lithium enolate derived from ester **168** followed by a Peterson-type of reaction to afford the corresponding ethyl 2,3-dimethylbutenoate (**122**) in 54% yield (**Scheme 47**).[78]



Scheme 47. Synthesis of ethyl 2,3-dimethylbutenoate (**122**) *via* a Peterson reaction.

Reagents and conditions: ***i****. LDA, THF, −78 °C, 30 min,* ***ii****.* Ph_2CH_3SiCl*, −78 °C, 1.5 h, rt, 2 h (93% over two steps);* ***iii****. acetone, LDA, THF, −78 °C, 1.5 h, reflux, 1.5 h (54%).*

Skibbie *et al*. were able to prepare the desired ester **122** *via* a Horner-Wadsworth-Emmons reaction using triethyl phosphonopropionate (**170**) with sodium hydride in DME in 69% yield (**Scheme 48**).[79]



166 170 122

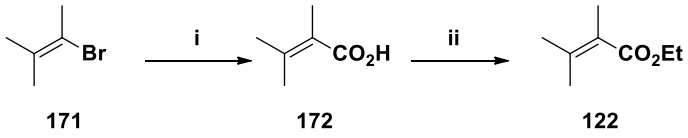
Scheme 48. Synthesis of ethyl 2,3-dimethylbutenoate (**122**) *via* a Horner-Wadsworth-Emmons reaction.

Reagents and conditions: ***i****. NaH, DME, 0 °C then reflux, 12 h (69%).*

3.2.2. Synthesis of ethyl 2,3-dimethylbutenoate (**122**): results and discussion

Unfortunately, in our hands any attempts to repeat the procedure developed by Skibbie *et al.* only led to the recovery of triethyl phosphonopropionate (**170**) (**Scheme 48**).[79] Other bases (^{n}BuLi, LiHMDS) and solvent (THF) were screened but none of these conditions resulted in the formation of the desired product **122**. Likewise, the synthesis of ethyl 2,3-dimethylbutenoate (**122**) *via* a Wittig reaction with triphenylphosphorane **167** using standard conditions only led to recovery of the starting material **166** after purification (**Scheme 46**).

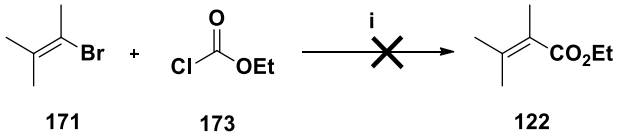
The synthesis of ethyl 2,3-dimethylbutenoate (**122**) was considered *via* a Br/Li exchange. Lithiation of commercially available bromobutene **171** and trapping with CO_2 delivered the desired carboxylic acid **172** in 36% yield (**Scheme 49**). This reaction has been disclosed in the literature in a comparable 34% yield.[80] Further esterification was attempted using different reaction conditions (EtOH with $SOCl_2$ or H_2SO_4). Thus, the reaction mixture needed to be stirred for a long period of time (3 days) and at 50 °C in order to push the reaction to completion. Pleasingly, the desired ethyl 2,3-dimethylbutenoate (**122**) was observed in the crude ^{1}H-NMR spectrum, in conjunction with ethanol. Unfortunately, ester **122** is very volatile and concentration as well as distillation of the solvent did not offer a good separation; therefore, no conclusive yield can be reported.



Scheme 49. Synthesis of ethyl 2,3-dimethylbutenoate (**122**) *via* esterification.

Reagents and conditions: ***i****. Li, CO_2, THF, −30 °C to −78 °C to rt (36%);* ***ii****. $SOCl_2$ or H_2SO_4, EtOH, 50 °C, 3 d.*

Considering that none of the aforementioned conditions were useful, another method for the synthesis of ethyl α,β-dimethylbutenoate (**122**) was considered *via* a Br/Li exchange. It was proposed that lithiation of commercially available bromobutene **171** and trapping with ethyl chloroformate (**173**) would give the desired crotonate **122** directly (**Scheme 50**).[81] Unfortunately, upon purification by column chromatography, decomposition of the crude residue was observed. Likewise, the use of ^{s}BuLi led only to a decomposed mixture.

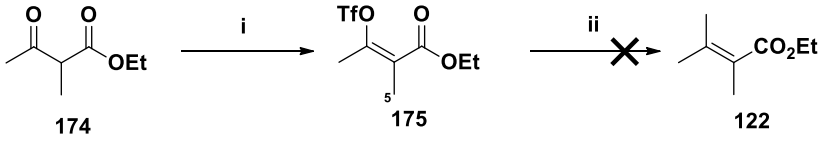


Scheme 50. Synthesis of ethyl 2,3-dimethylbutenoate (**122**) *via* lithiation of bromobutene **171**.

Reagents and conditions: ***i****. ^{n}BuLi or ^{s}BuLi, Et_2O, −78 °C to rt, 3 h.*

Another method for the synthesis of α,β-unsaturated ester **122** was based on the treatment of enol triflate **175** accessible from the commercially available *β*-ketoester **174** with a cuprate reagent. Thus, *β*-ketoester **174** was treated with triflic anhydride under Schotten-Baumann type conditions to furnish the corresponding (*Z*)-enol triflate **175** in an increased yield when compared to the literature (100% vs. 67%).[82] The (*Z*)-configuration of the product **175** was established by the presence of the high field signal of the C-5 methyl group at δ 2.15 in the ^{1}H-NMR spectrum which was consistent with ^{1}H-NMR data previously published in the literature.[82] Indeed, the C-5 methyl group in the (*E*)-enol triflate was expected to show at δ 2.42 according to the literature.[83]

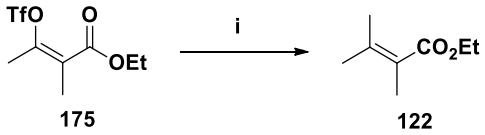
Lipshutz and Elworthy described in the literature that for the coupling between vinyl triflates and allylic cuprates, cyanocuprates presented the highest reactivity.[84] Therefore, (*Z*)-enol triflate **175** was treated with methyl cyanocuprate in order to synthesise the desired α,β-unsaturated ester **122**. Disappointingly, the outcome of the reaction was a decomposed mixture (**Scheme 51**).



Scheme 51. Synthesis of ethyl 2,3-dimethylbutenoate (**122**) *via* a cuprate coupling.

Reagents and conditions: ***i****. Tf_2O, aq. LiOH, toluene, 5 - 10 °C, 30 min (100%);* ***ii****. CuCN, MeLi , Et_2O, −78 °C, 1 h.*

A screening of different cuprate reagents was therefore undertaken as summarised in **Table 6** (**Scheme 52**).



Scheme 52. Coupling between (*Z*)-enol triflate **175** and an organocuprate.

Reagents and conditions: ***i****. 1.0 eq. CuX, 2.0 eq. MeLi, Et_2O, −78 °C, 1 h.*

Table 6. Screening of cuprate reagents.

Entry	CuX	Outcome
1	CuOAc	decomposed mixture
2	CuCl	rsm **175**
3	CuOTf	decomposed mixture
4	CuI	**122**: 87%

Most of the reaction conditions assayed led to decomposition or recovery of the starting material **175** (**Scheme 52**, **Table 6**, entries **1** to **3**). Fortunately, the use of copper iodide

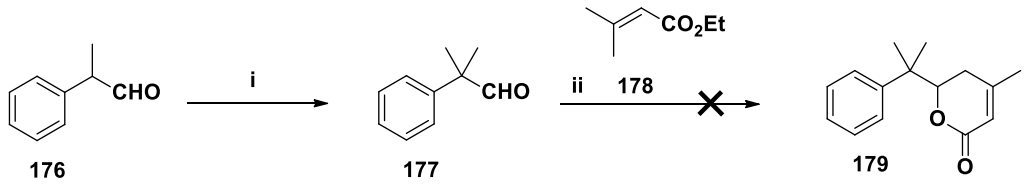
delivered ethyl 2,3-dimethylbutenoate (**122**) in very good yield (87%) (**Table 6**, entry **4**). This result was pleasingly reproducible on large scale (up to 4 g, 9.56 mmol).

The absence of signal at δ 118 (q, J_{CF} = 318 Hz) in ^{13}C-NMR spectrum characteristic of the CF_3 group of the triflate functionality of the starting material **175** along with the presence of a third methyl group at δ 1.82-1.80 (m) in the ^{1}H-NMR spectrum confirmed the structural assignment of ethyl 2,3-dimethylbutenoate (**122**).

3.3. Studies Towards the Construction of δ-Lactone 41

3.3.1. Studies using ethyl 3,3-dimethylbutenoate (**178**)

Our first approach was to test the vinylogous aldol type reaction using conditions developed by Ikekawa *et al*. on a simple and easily accessible model system such as 2,2-dimethylphenylacetaldehyde (**177**) using commercially available ethyl 3,3-dimethylacrylate (**178**). Hence, 2,2-dimethylphenylacetaldehyde (**177**) was obtained from 2-phenylpropionaldehyde (**176**) repeating a published procedure in very good yield (87% vs 77% in the literature).[85] Unfortunately, submitting 2,2-dimethylphenylacetaldehyde (**177**) to the previously described aldol condensation conditions resulted exclusively in the recovery of the starting material **177** (**Scheme 53**).

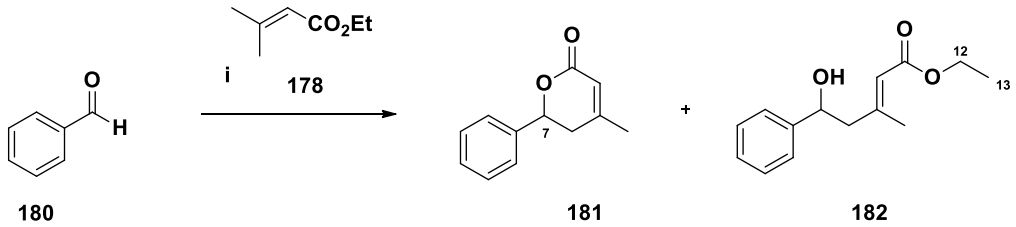


Scheme 53. Attempted δ-lactone formation using a model aldehyde **177**.

Reagents and conditions: ***i****. NaH, MeI, THF, 0 °C, 1 h (87%);* ***ii****. LDA, DMPU, THF, −78 °C to rt, 6 h.*

The δ-lactone synthesis was attempted on benzaldehyde (**180**) repeating the same literature procedure developed by Ikekawa *et al*. using commercially available ethyl 3,3-dimethylbutenoate (**178**).[30] Pleasingly, this reaction delivered the desired lactone product **181** in excellent yield (78%) along with the hydroxyester **182** in 8% yield

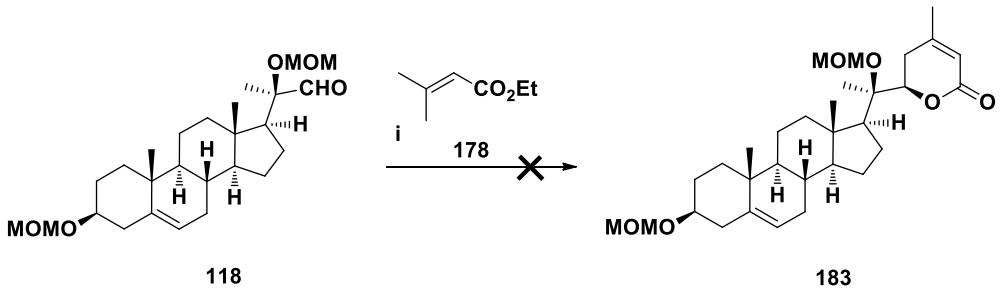
(**Scheme 54**). ^{1}H-NMR data of these two compounds **181** and **182** were consistent with those previously published in the literature.[86,87]



Scheme 54. δ-Lactone **181** formation using benzaldehyde (**180**).

Reagents and conditions: ***i****. LDA, DMPU, THF, −78 °C to rt, 5.5 h (78% of* ***181*** *and 8% of* ***182****).*

Unfortunately, these reaction conditions were unsuccessful when applied to the steroidal model system **118** and only led to decomposition (**Scheme 55**).

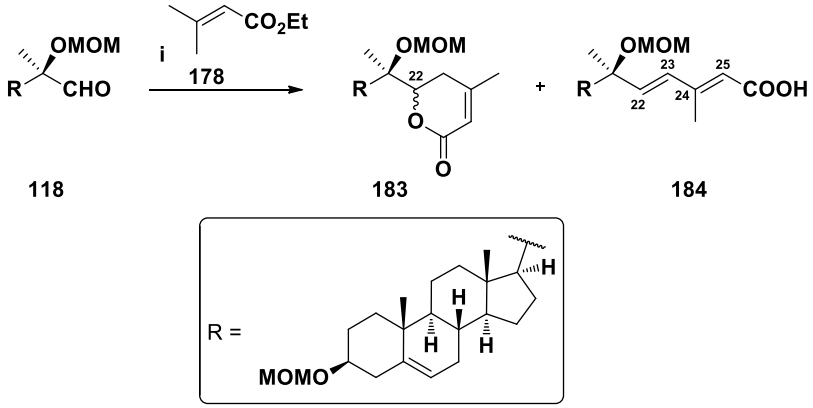


Scheme 55. Attempted δ-lactone **183** formation upon deprotonation with LDA.

Reagents and conditions: ***i****. LDA, DMPU, THF, −78 °C to rt, 12 h.*

Another option was the optimised reaction conditions for the δ-lactone formation developed by Gademann *et al*. during their synthesis of withanolide A (**8**).[35] To this end, aldehyde **118** was treated with ethyl 3,3-dimethylbutenoate (**178**) and LiHMDS in THF/DMPU at low temperature (**Scheme 56**). The δ-lactone **183** was isolated as a mixture of diastereoisomers at C-22 in a 1:1 ratio in poor yield (9%). The structural assignment of lactone **183** will be discussed later in this Chapter. The major product isolated was the α,β,γ,δ-dienoic acid **184** (25% yield). Mechanistically, it was thought that the open chain lactone was first synthesised as a hydroxyester which underwent subsequently dehydration

to give the isolated dienoic acid **184**. The latter **184** was a novel compound and as such was fully characterised. Its structure was confirmed by key signals in the ^{1}H-NMR spectrum including three downfield signals at δ 7.55 (d, $J_{22,23}$ = 16.4 Hz), δ 6.26 (d, $J_{22,23}$ = 16.4 Hz) and at δ 5.68 (s) representative of the vinylic protons H-23, H-22 and H-25, respectively, along with downfield signals in the ^{13}C-NMR spectrum at δ 153.1 (C-24), δ 144.1 (C-22), δ 125.9 (C-23), δ 116.6 (C-25) characteristic of the α,β,γ,δ-unsaturated diene. The carboxylic acid moiety was confirmed by IR spectroscopy, namely by the presence of typical peaks at 2934 cm^{-1} and at 1714 cm^{-1} representative of the O-H stretch and the C=O stretch, respectively.



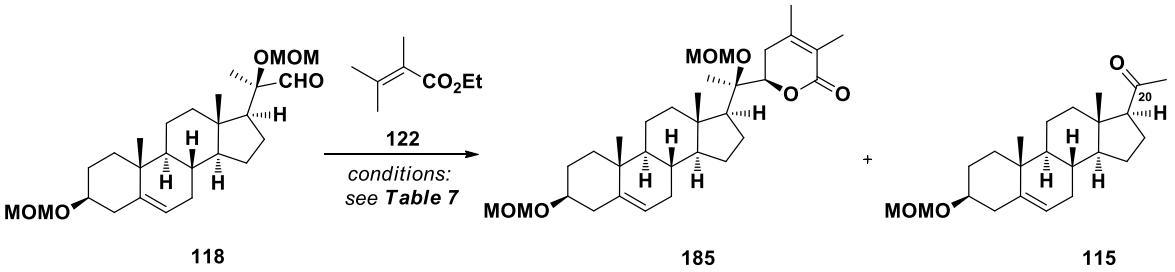
Scheme 56. δ-Lactone **183** formation upon deprotonation with LiHMDS.

Reagents and conditions: ***i****. LiHMDS, THF, DMPU, −78 °C to rt, 18 h (9% of* ***183*** *and 25% of* ***184****).*

Given the side reaction encountered when using ethyl 3,3-dimethylbutenoate (**178**), it was proposed that the latter **178** did not constitute a good model system to use for this type of sensitive reaction. Therefore, the studies towards the δ-lactone formation were henceforth carried out exclusively using ethyl α,β-dimethylbutenoate (**122**).

3.3.2. Studies using ethyl 2,3-dimethylbutenoate (**122**)

Initially, the studies towards the unsaturated lactone side chain construction were focused on the steroidal model aldehyde **118** (**Scheme 57**). A screening of reaction conditions were run in order to optimise the synthesis of the desired lactone **185** as summarised in **Table 7**.



Scheme 57. Synthesis of δ-lactone using the model aldehyde **118**.

Table 7. Screening of conditions for the δ-lactonisation on model system **118**.

Entry	Deprotonation step conditions	Addition step conditions	Outcome
1	**122** (2.7 eq.), LDA (3.0 eq.), THF/DMPU* (8:2), −78 °C, 1.5 h	**118** (1.0 eq.), −78 °C → rt, o/n	decomposed mixture
2	**122** (2.7 eq.), NaHMDS (3.0 eq.), THF, −78 °C, 1.5 h	**118** (1.0 eq.), −78 °C, 5 h	decomposed mixture
3	**122** (2.7 eq.), KHMDS (3.0 eq.), THF/DMPU* (8:2), −78 °C, 1.5 h	**118** (1.0 eq.), −78 °C, 5 h	decomposed mixture
4	**122** (2.7 eq.), LiHMDS (3.0 eq.), THF, −78 °C, 1.5 h	**118** (1.0 eq.), −78 °C, 5 h	**115**: 48%
5	**122** (1.5 eq.), LiHMDS (1.4 eq.) THF/DMPU* (8:2), −78 °C, 1.5 h	**118** (1.0 eq.), −78 °C, 5 h	**118**: 12% **115**: 35%
6	**122** (2.7 eq.), LiHMDS (3.0 eq.), THF/DMPU* (8:2), −78 °C, 1.5 h	**118** (1.0 eq.), −100 - −90 °C, 5 h	**185**: 11% **115**: 52%
7	**122** (2.7 eq.), LiHMDS (3.0 eq.), THF/DMPU* (8:2), −78 °C, 1.5 h	**118** (1.0 eq.), −78 °C, 6 h	**185**: 33% **115**: 8%
8	**122** (2.7 eq.), LiHMDS (3.0 eq.), THF/DMPU* (8:2), −78 °C, 1.5 h	**118** (1.0 eq.), −78 → −40 °C, 6 h	**185**: 38% **115**: 12%
9	**122** (2.7 eq.), LiHMDS (3.0 eq.) THF/DMPU* (8:2), −78 °C, 1.5 h	**118** (1.0 eq.), −78 → −40 °C, 1 h	**185**: 61% **115**: 10%
10[i]	**122** (2.7 eq.), LiHMDS (3.0 eq.) THF/DMPU* (8:2), −78 °C, 1.5 h	**118** (1.0 eq.), −78 °C, 6 h	**185**: 73% **115**: 15%

*: DMPU freshly distilled over CaH_2.

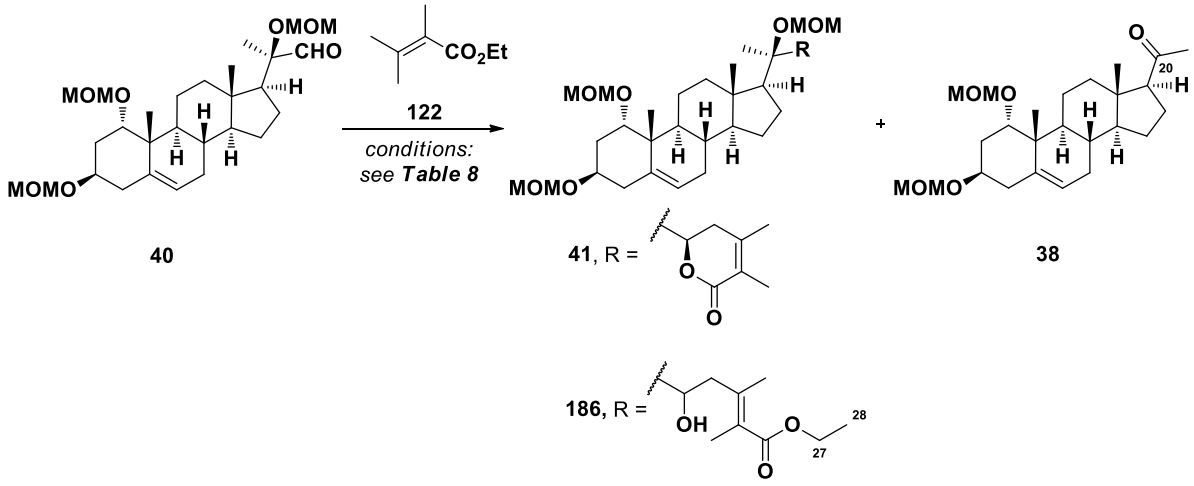
[i]: inverted addition, *i.e.* a solution of the lithium dienolate derived from **122** was added to the aldehyde **118** at –78 °C.

When applied to steroidal aldehyde **118**, the conditions developed by Ikekawa *et al*. led to decomposition as predicted by the test reaction run on the model system **118** using ethyl 3,3-dimethylbutenoate (**178**) (**Scheme 55**) (**Table 7**, entry **1**).[30] Subsequently, the δ-lactone **185** synthesis was attempted using the optimised reaction conditions developed by

Gademann *et al.* as previously described.[35] To this end, ethyl 2,3-dimethylbutenoate (**122**) was deprotonated using LiHMDS in THF/DMPU (8:2) at low temperature, subsequently, aldehyde **118** was added slowly over 15 min. Fortunately, these conditions led to formation of the desired δ-lactone **185** in 33% yield along with ketone **115** in 8% yield (**Table 7**, entry **7**). In order to optimise the yield, the reaction was run at higher temperature (−40 °C) so that the nucleophilic attack would be favoured (**Table 7**, entry **8**). After noticing by TLC that the desired product **185** was formed predominantly within the first hour of the reaction and then decomposed into other products after 5 h, the reaction was repeated at −40 °C for one hour. Pleasingly, a significant improvement of the yield was observed (**Table 7**, entry **9**). Moreover, in order to try a broad range of temperatures, the reaction was attempted at very low temperature (between –100 °C and –90 °C) which surprisingly delivered a small amount of the desired product **185** in poor yield (11%) and predominantly afforded the C-20 ketone **115** (52% yield, **Table 7**, entry **6**). One hypothesis to explain the recurring low yield of this reaction was that the initial deprotonation step was not complete, leaving an excess of base in the reaction mixture upon addition of the aldehyde **118**. The base may be involved in the cleavage of the methoxymethylene ether protecting group of the C-20 alcohol **118** which followed by a deformylation step would lead to the formation of the C-20 ketone **115** as the major product. With this in mind, it was thought that reducing the number of equivalents of the base and of the ethyl 2,3-dimethylbutenoate (**122**) could positively influence the reaction and help avoid the synthesis of the C-20 ketone **115**. Unfortunately, this was not observed (**Table 7**, entry **5**). Other bases such as NaHMDS and KHMDS did not improve the outcome of the reaction either (**Table 7**, entries **2** and **3**). Additionally, the presence of DMPU seemed to be determining for the formation of the δ-lactone side chain as shown in entry **9**. Fortunately, the desired δ-lactone **185** was obtained in very good yield (73%) when using the standard conditions but transferring the dienolate into a solution of aldehyde **118** *via* canula at –78 °C (**Table 7**, entry **10^{i}**). The desired δ-lactone **185** was a novel compound, and therefore, fully characterised. Its structural assignment will be discussed later in this Chapter.

3.3.3. Synthesis of δ-lactone **41**

Considering the aforementioned optimisation study, the most promising reaction conditions to form the unsaturated lactone side chain were tested using the target aldehyde **40** as described in **Table 8** (**Scheme 58**).



Scheme 58. Synthesis of δ-lactone using the target aldehyde system **40**.

Table 8. Screening of conditions for the δ-lactonisation of steroidal aldehyde **40**.

Entry	Deprotonation step conditions	Addition step conditions	Outcome
1	**122** (2.7 eq.), LiHMDS (3.0 eq.) THF/DMPU* (8:2), −78 °C, 1.5 h	**40** (1.0 eq.), −78 → −40 °C, 1 h	**40**: 68% **38**: 11%
2	**122** (2.7 eq.), LiHMDS (3.0 eq.) THF/DMPU* (8:2), −78 °C, 1.5 h	**40** (1.0 eq.), −78 °C, 6 h	**41**: 33% **38**: 41%
3[i]	**122** (2.7 eq.), LiHMDS (3.0 eq.) THF/DMPU* (8:2), −78 °C, 1.5 h	**40** (1.0 eq.), −78 °C, 6 h	**41**: 67% **38**: 4% **186**: 3%

*: DMPU freshly distilled over CaH_2.

[i]: inverted addition, *i.e.* a solution of the lithium dienolate derived from **122** was added to the aldehyde **40** at –78 °C.

When applying the conditions developed by Gademann *et al*. to the target system **40**,[35] the desired lactone **41** was formed in 33% yield along with 41% of the deformylated side product **38** (**Table 8**, entry **2**). Therefore, the same strategy as with the model system **118** was used and the reaction was repeated at –40 °C for 1 h using the target aldehyde steroid **40**. Unfortunately, in this case, most of the starting material **40** was recovered along with

some C-20 ketone **38** (**Table 8**, entry **1**). Fortunately, inverting the order of addition of the reagents helped once again to deliver the desired lactone **41** in an improved 67% yield along with 4% yield of the C-20 ketone **38** and 3% yield of the hydroxyl ester **186** both of which were readily separable by column chromatography (**Table 8**, entry **3^{i}**). Hence, these conditions were used when repeating this reaction.

3.3.4. Discussion of the stereoselectivity of the δ-lactonisation step

The structural assignment of δ-lactone **41** was confirmed by the presence of a downfield signal at δ 4.23 as a doublet doublet ($^{3}J_{22,\ 23ax}$ = 13.3 Hz and $^{3}J_{22,\ 23eq}$ = 3.2 Hz) in the ^{1}H-NMR spectrum characteristic of a methine proton of the δ-lactone side chain. The C-22 configuration of the δ-lactone side chain was anticipated to be *R*. Indeed, according to Cram's rules, the condensation of the lithium dienolate with the aldehyde **40** was assumed to occur through a Cram chelate cyclic model. Therefore, the nucleophilic attack would arise along the less hindered face, *i.e.* on opposite face of the steroid core structure to deliver the C-22*R*-configuration as shown in **Figure 20**.

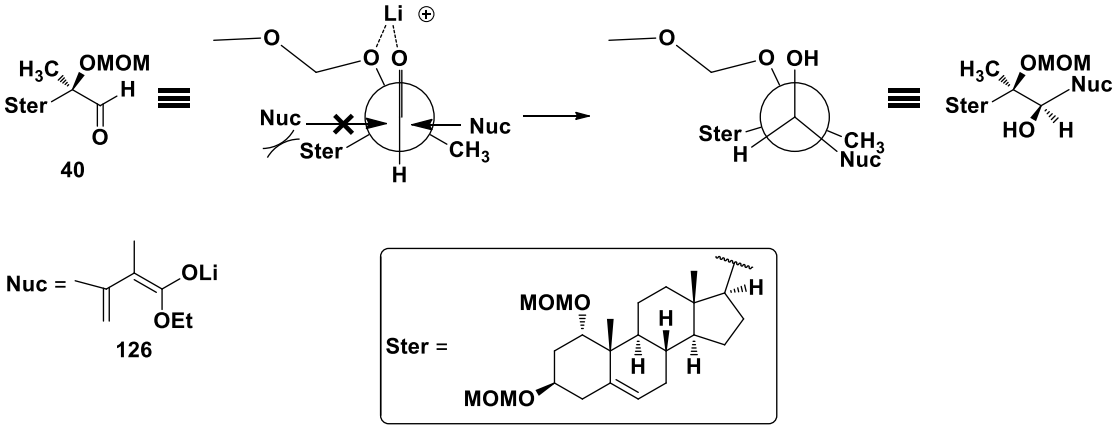


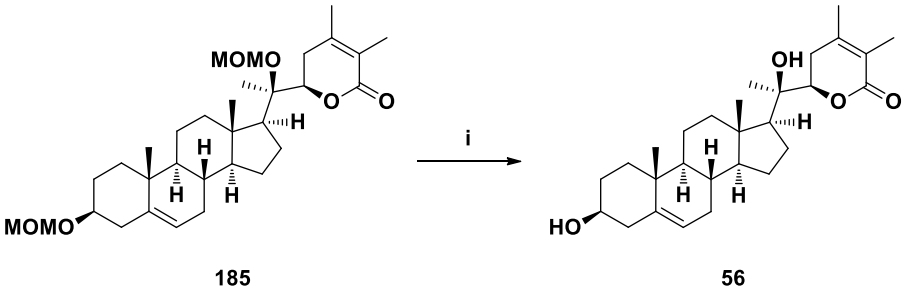
Figure 20. Cram chelate cyclic model for diastereoselective vinylogous aldol condensation of lithium dienolate **126** with aldehyde **40**.

Similar arguments were used to confirm the structural assignment of δ-lactones **185** and **183** which both presented key downfield methine proton signals in their ^{1}H-NMR spectra. Hydroxyester **186** exhibited typical ethyl peaks in ^{1}H-NMR spectrum, *i.e.* a downfield signal at δ 4.16 (br q, $J_{27,28}$ = 7.1 Hz) assigned to the CH_2 group of the ethyl functionality and a high field signal at δ 1.25 (t, $J_{27,28}$ = 7.1 Hz), the methyl group of the ethyl moiety of ester **186**.

3.4. Synthesis of Triol 21

3.4.1. Study on model system **185**

The next step in the total synthesis of 14,17-dideoxy-17-*epi*-withanolide F (**24**) was the cleavage of the methoxymethylene ether protecting groups at C-1, C-3 and C-20 using strongly acidic conditions.[29] The 6 M aq. HCl in THF conditions were first tested on the model steroid system **185** and proceeded to give the desired diol **56** in quantitative yield (**Scheme 59**). The structure of diol **56** was confirmed by ^{1}H- and ^{13}C-NMR spectra missing the signals characteristic of MOM group, namely two downfield signals at ~ δ 5.0 representative of the CH_2 groups and two singlets at ~ δ 3.35 characteristic of the methyl groups of the MOM functionality. These data were consistent with those previously published in the literature.[35]



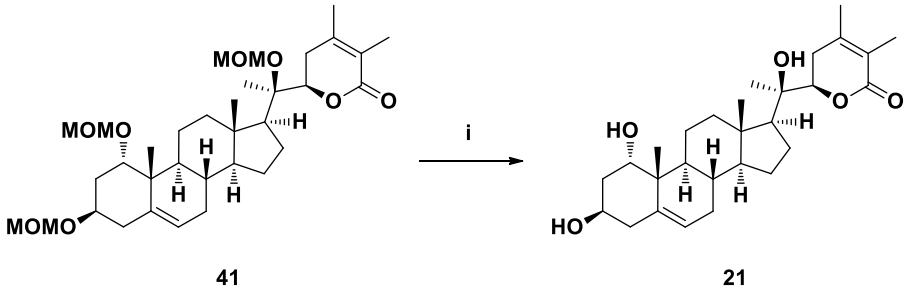
185 56

Scheme 59. MOM deprotection under acidic conditions.

Reagents and conditions: ***i****. 6 M aq. HCl, THF, rt, 3 h (100%).*

3.4.2. Application to target system **41**

In the same manner, lactone **41** was submitted to 6 M aq. HCl conditions to deliver quantitatively the corresponding triol **21** (**Scheme 60**). This reaction has been previously disclosed in the literature in a lower yield (82%) using the exact same reaction conditions and substrate **41** as reported by Ikekawa *et al*. during the synthesis of withanolide D (**6**).[29] Moreover, the absence of ^{1}H-NMR signals characteristic of MOM group of the starting material **41** confirmed the structure of triol **21** which was fully characterised.



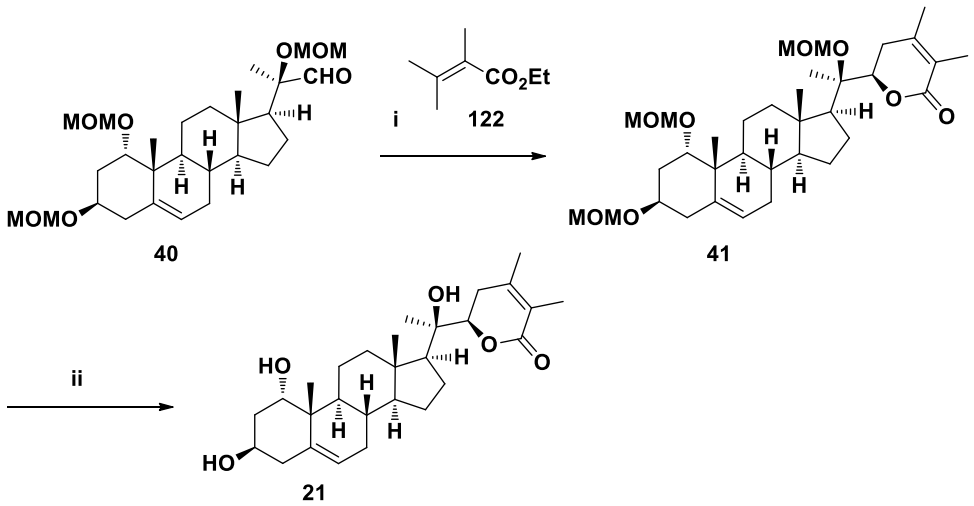
Scheme 60. MOM deprotection of lactone **41**.

Reagents and conditions: ***i****. 6 M aq. HCl, THF, rt, 7 h (100%).*

3.5. Summary and Future Work

3.5.1. Summary

The δ-lactone side chain of 14,17-dideoxy-17-*epi*-withanolide F (**24**) was successfully introduced using methodology developed during the synthesis of the model compound **185**. Extensive optimisation studies were required to obtain the desired lactone **41** upon aldol condensation of aldehyde **40** with lithium dienolate derived from ester **122**, readily prepared from a coupling with vinyl triflate **175** as previously outlined in Scheme **52**. Subsequent cleavage of the methoxymethylene ether groups of lactone **41** under strongly acidic conditions allowed the synthesis of triol **21**, a key intermediate in the suggested retrosynthetic strategy (**Scheme 7**), in 67% yield over two steps (**Scheme 61**).

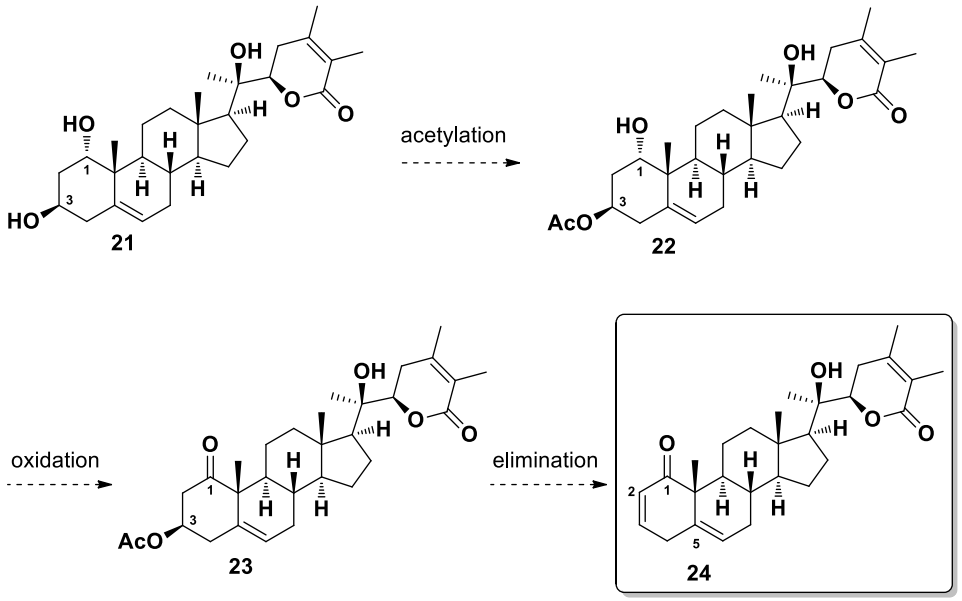


Scheme 61. Synthesis of triol **21**.

Reagents and conditions: ***i****.* ***122****, LiHMDS, THF/DMPU (8:2), −78 °C, 6 h;* ***ii****. 6 M aq. HCl, THF, rt, 7 h (67% over two steps).*

3.5.2. Future work

Future work was focused on completing the total synthesis of 14,17-dideoxy-17-*epi*-withanolide F (**24**) *via* A/B-ring functionalisation to construct the desired 2,5-dien-1-one fragment. Namely, it was proposed to selectively acetylate triol **21** at C-3 and the C-1 hydroxyl functionality would then be oxidised under standard conditions. Finally, the desired target compound **24** could be accessed *via* the elimination of the C-3 acetate group of compound **23** (**Scheme 62**). The culmination of the total synthesis is further detailed in **Chapter 4**.



Scheme 62. Construction of A/B-ring 2,5-dien-1-one fragment.

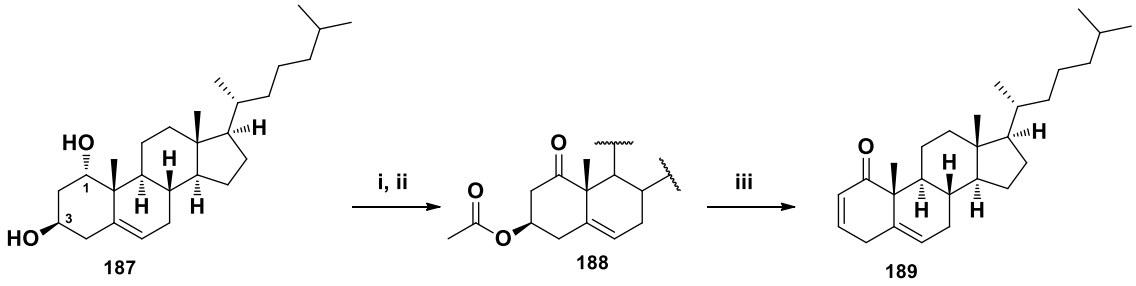
Chapter 4. A/B-Ring Functionalisation: The Synthesis of 14,17-Dideoxy-17-Epi-Withanolide F (24)

4.1. A/B-Ring Functionalisation: Synthesis of 2,5-Dien-1-One Fragment

4.1.1. 2,5-Dien-1-ones: literature examples

As previously mentioned in **Chapter 1**, the 2,5-dien-1-one fragment is common for the A/B-rings of different withanolides (**Figure 3**). Several syntheses of this key structure have been disclosed in the literature.[88-90] Most of them followed the same synthetic strategy; namely the conversion of the 1,3-diol functionality in the A-ring into the corresponding α,β-unsaturated ketone, *via* a selective protection of the C-3 alcohol, oxidation of the C-1 hydroxyl group and elimination of the C-3 leaving group.

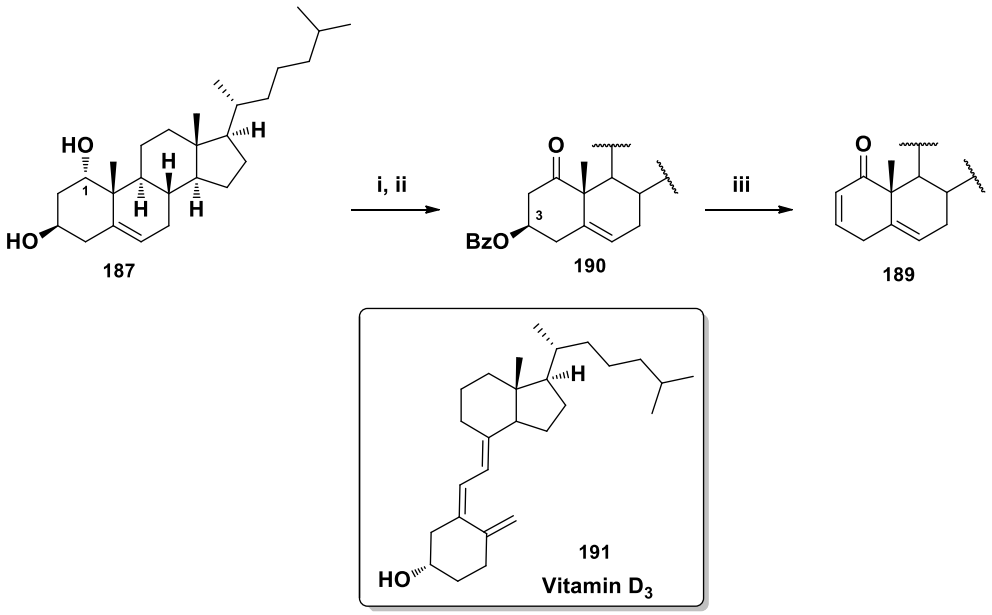
In 1975, Ikekawa *et al*. developed a synthetic sequence to convert 1α-hydroxycholesterol (**187**) into the corresponding cholesta-2,5-dien-1-one (**189**) in 54% yield over three steps. A selective acetylation at C-3 under standard conditions and the oxidation of C-1 alcohol **187** using Jones' reagent were followed by elimination with aq. NaOH in dioxane (**Scheme 63**).[26]



Scheme 63. Synthesis of cholesta-2,5-dien-1-one (**189**).

Reagents and conditions: ***i.*** *Ac_2O, AcOH, 80 °C, 4 h (60%),* ***ii.*** *CrO_3, acetone, rt,* ***iii.*** *1.5% aq. NaOH, 1,4-dioxane, rt, 6 h (90% over two steps).*

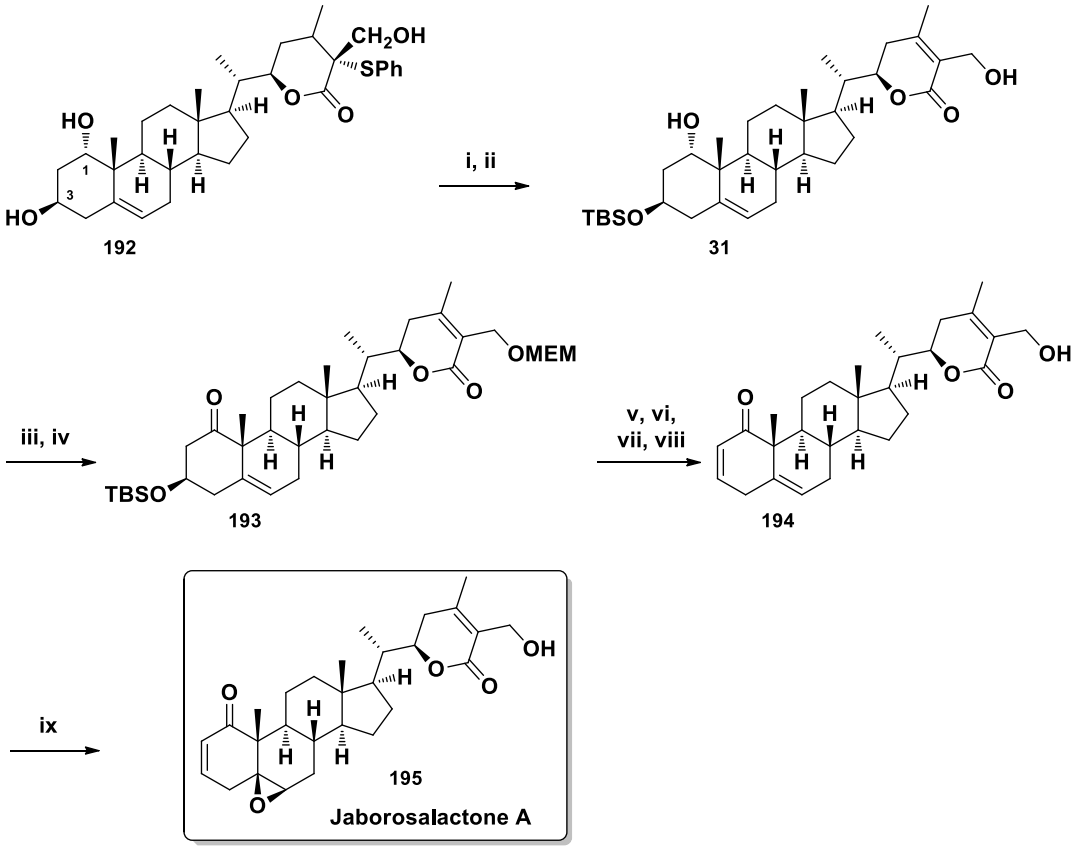
Okamura *et al*. used the same strategy when studying the synthesis of vitamin D_3 (**191**) and analogues with modified A-rings.[88] Thus, selective benzoylation at C-3 under standard conditions was achieved in good yield. Subsequent oxidation with Jones' reagent and elimination of the C-3 benzoyl group using DBN as the base delivered the desired 2,5-dien-1-one **189** in 36% yield over two steps (**Scheme 64**).



Scheme 64. Synthesis of 2-en-1-one fragment *via* selective benzoylation of diol **187**.

Reagents and conditions: ***i****. BzCl, pyridine, 0 °C, 15 - 20 min (72%);* ***ii****.* CrO_3*, acetone, 10 min (98%);* ***iii****. DBN,* Et_2O*, rt, 1.5 h (37%).*

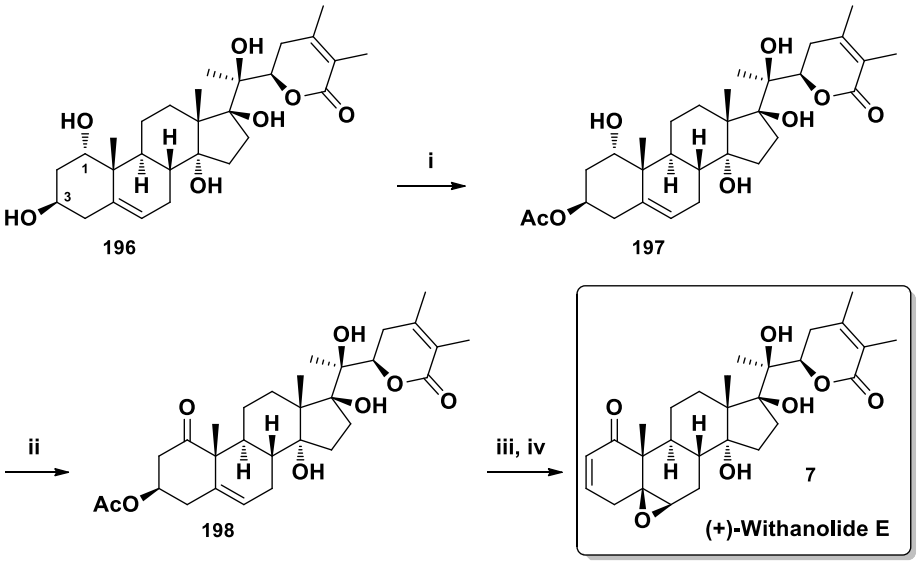
In 1982, Ikekawa *et al*. applied the same synthetic approach during the synthesis of jaborosalactone A (**195**).[89] Hence, diol **192** was selectively protected at C-3 with a TBDMS group followed by oxidation of the C-1 alcohol in moderate yield under standard conditions. The final sequence of reactions of the synthesis involved cleavage of the silyl ether protecting group under acidic conditions, acetylation of the corresponding C-3 alcohol and subsequent elimination which was achieved under mildly basic conditions using alumina to deliver 2,5-dien-1-one **194** in 13% yield over eight steps (**Scheme 65**).



Scheme 65. Synthesis of jaborosalactone A (**195**).

Reagents and conditions: ***i****. TBDMSCl, imidazole, DMF (63%);* ***ii****. 1) m-CPBA, $CHCl_3$, −78 °C, 2) 100 °C (63%);* ***iii****. MEMCl, $^{i}Pr_2NEt$, CH_2Cl_2;* ***iv****. PDC, DMF (41% over two steps);* ***v****. AcOH, H_2O, THF;* ***vi****. Ac_2O, pyridine;* ***vii****. Al_2O_3, benzene;* ***viii****. H_2SO_4, THF (81% over four steps);* ***ix****. m-CPBA, CH_2Cl_2 (71%).*

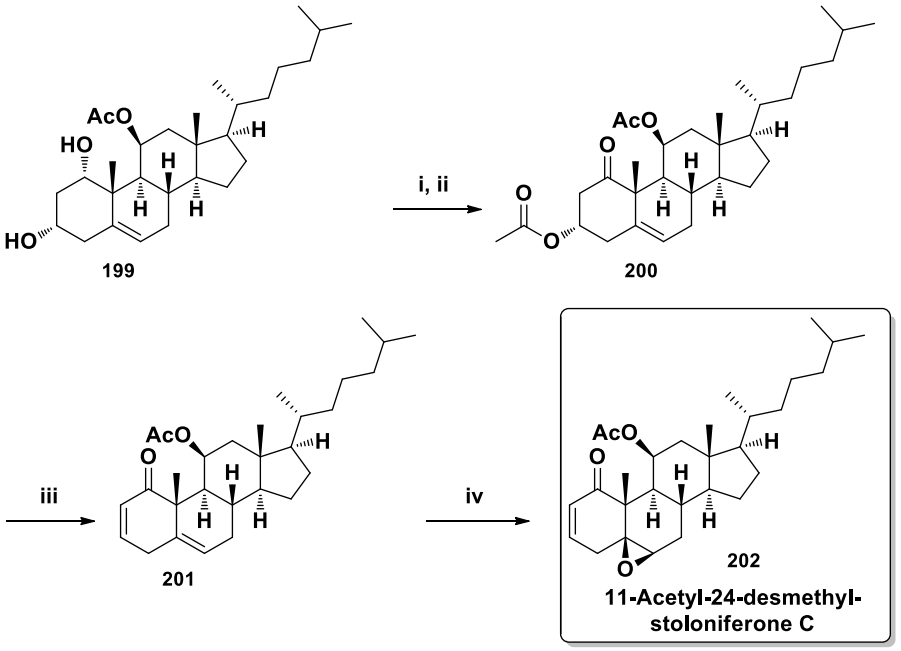
Another similar example was reported by Grieco and co-workers during the total synthesis of (+)-withanolide E (**7**).[32] Thereby, the selective acetylation of 1α,3β-diol **196** at C-3 and subsequent Swern oxidation of C-1 hydroxyl group furnished ketone **198** in 56% yield over two steps. The elimination of C-3 acetyl group was successfully achieved using DBN and the final epoxidation step using peracid delivered (+)-withanolide E (**7**) in 71% yield over two steps (**Scheme 66**).



Scheme 66. Synthesis 2,5-dien-1-one fragment *via* selective acetylation.

Reagents and conditions: ***i****.* Ac_2O*, DMAP, pyridine, rt, 15 h (72%);* ***ii****.* $(COCl)_2$*, DMSO,* Et_3N*,* CH_2Cl_2*, −78 °C to rt, 1.5 h (78%);* ***iii****. DBN,* CH_2Cl_2*, rt, 40 min;* ***iv****. m-CPBA,* $NaHCO_3$*,* CH_2Cl_2*, 18 h (71% over two steps).*

More recently (2001), Sodano's group was able to similarly synthesise 2,5-dien-1-one **201** in 55% yield from diol **199** over three steps during the total synthesis of 11-acetyl-24-desmethyl-stoloniferone C (**202**), a bioactive secondary metabolite from a marine invertebrate (**Scheme 67**).[90]

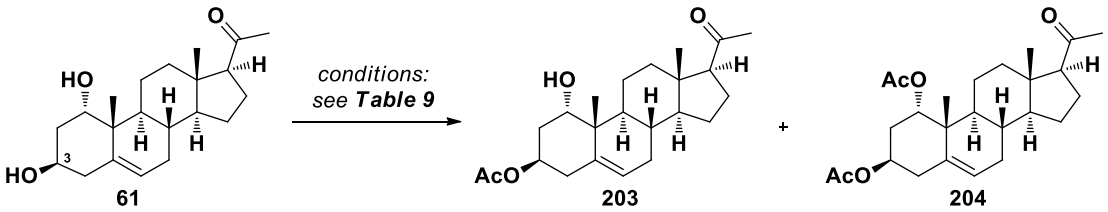


Scheme 67. Synthesis of 11-acetyl-24-desmethyl-stoloniferone C (**202**).

Reagents and conditions: ***i****.* Ac_2O*, pyridine, rt, 12 h (91%);* ***ii****. PDC, 3 Å molecular sieves,* CH_2Cl_2*, rt, 6 h (75%);* ***iii****.* Al_2O_3*, benzene, reflux (80%);* ***iv****. m-CPBA,* $NaHCO_3$*,* CH_2Cl_2*, 0 °C, 5 h (28%).*

4.1.2. Studies of the A-ring functionalisation using a model system

In order to investigate the A-ring functionalisation, an optimisation study was undertaken using ketone **61** as a model system. The first step was the selective acetylation of diol **61** at C-3, to this aim several conditions were attempted and are summarised in **Table 9** (**Scheme 68**).



Scheme 68. Attempted selective acetylation of diol **61**.

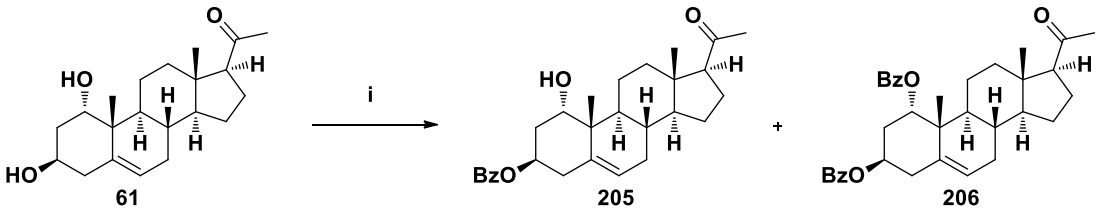
Table 9. Screening of conditions for the selective acetylation of diol **61**.

Entry	Reagents	Conditions	Outcome
1	Ac_2O (2.2 eq.), pyridine (5.0 eq.), DMAP (0.1 eq.),	CH_2Cl_2, rt, 1.5 h	**203**: 8% **204**: 62%
2	Ac_2O (3.6 eq.), NEt_3 (2.6 eq.), DMAP (0.1 eq.),	CH_2Cl_2, rt, o/n	**203**: 24% **204**: 67%
3	Ac_2O (1.8 eq.), NEt_3 (1.3 eq.), DMAP (0.1 eq.),	CH_2Cl_2, rt, o/n	**203**: 43% **204**: 24%
4	Ac_2O (3.6 eq.), NEt_3 (2.6 eq.), DMAP (0.1 eq.)	CH_2Cl_2, 0 °C, o/n	**203**: 44% **204**: 19%
5	Ac_2O (1.8 eq.), NEt_3 (1.3 eq.), DMAP (0.1 eq.),	CH_2Cl_2, rt, 1.5 h	**203**: 49%, 85% brsm **204**: 10%
6	Ac_2O (2.2 eq.), pyridine (5.0 eq.),	CH_2Cl_2, rt, o/n	**203**: 50%
7	Ac_2O (3.6 eq.), NEt_3 (2.6 eq.), DMAP (0.05 eq.)	CH_2Cl_2, rt, o/n	**203**: 65% **204**: 20%

As outlined in **Scheme 67** for the synthesis of 11-acetyl-24-desmethyl-stoloniferone C (**202**), the selective acetylation of C-3 hydroxyl group has been reported in the literature in good yield.[90] Unfortunately, in our hands these reaction conditions only led to moderate yield (**Table 9**, entry **6**). Similarly, the conditions used by Gademann's group for the total synthesis of withanolide A (**8**) (**Scheme 6**) were attempted and unfortunately, the major compound isolated was the diacetylated product **204** in 67% yield, probably because of the excess of acetic anhydride used (**Table 9**, entry **2**).[35] Therefore, a screening study was undertaken based on the variation of the previous reaction conditions such as changing the base, decreasing the number of equivalent of the reagents, varying the time and the temperature of the reaction (**Table 9**, entries **1**, **3**, **4** and **5**). Disappointingly, none of these reaction conditions significantly improved the yield of the reaction. Fortunately, decreasing the number of equivalent of the DMAP catalyst helped deliver the desired compound **203** in an acceptable 65% yield (**Table 9**, entry **7**). Hence, these conditions were used when applying this reaction to the target steroidal system **21**. The desired acetate **203** was a novel compound and therefore, fully characterised. ^{1}H- and ^{13}C-NMR data of diacetate **204** were consistent with those previously published in the literature.[91]

It was considered that the protection of diol **61** could be achieved with better selectivity using bulkier protecting groups. Therefore, diol **61** was selectively protected at C-3 with the benzoyl functionality using benzoyl chloride under standard reaction conditions

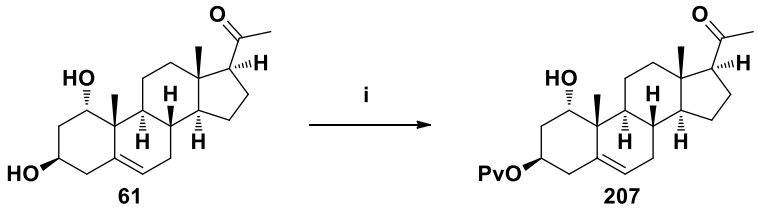
allowing the formation of the desired product **205** in 68% yield alongside with the dibenzoylated product **206** in 19% yield (**Scheme 69**).[92]



Scheme 69. Selective benzoylation of diol **61**.

Reagents and conditions: ***i****. BzCl, pyridine, CH_2Cl_2, rt, 12 h (68% of* ***205*** *and 19% of* ***206****).*

Another option was to protect diol **61** with a pivaloyl group. This reaction was run under standard conditions and unfortunately, led mostly to the recovery of the starting material **61** alongside formation of the desired compound **207** selectively but in poor yield (14%) (**Scheme 70**).[93]

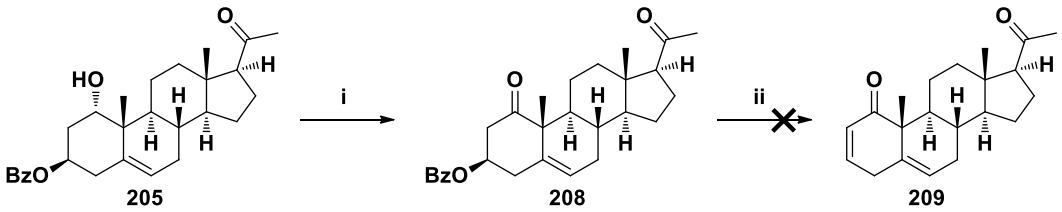


Scheme 70. Selective pivaloylation of diol **61**.

Reagents and conditions: ***i****. PvCl, pyridine, CH_2Cl_2, rt, 12 h (14%).*

These three last compounds **205**, **206** and **207** were novel and therefore, fully characterised.

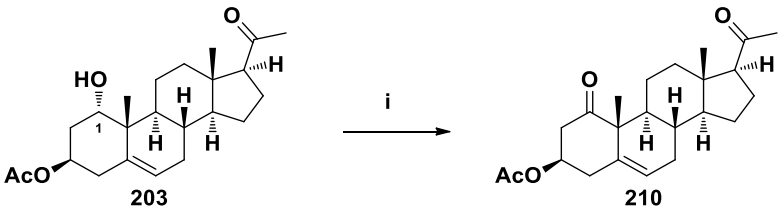
The next key step was the oxidation of C-1 alcohol **205** to the corresponding ketone using Dess-Martin reaction conditions. Unfortunately, decomposition reactions competed and the desired ketone **208** was only formed in poor yield (32%). Furthermore, the following elimination step using KOH was unsuccessful in this instance and only led to recovery of the starting material **208** (**Scheme 71**).



Scheme 71. Synthesis of 2,5-dien-1-one **209** *via* elimination of C-3 benzoyl group.

Reagents and conditions: ***i****. DMP, CH_2Cl_2, rt, 12 h (32%);* ***ii****. 0.1 M KOH, dioxane, rt, 15 min.*

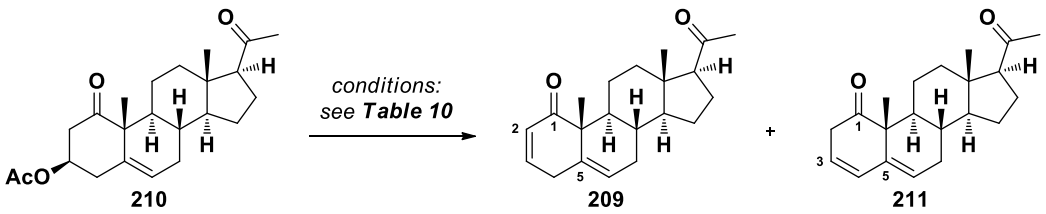
Given the previous results, it was suggested that using this benzoyl protecting group was not the best option. Fortunately, the Dess-Martin oxidation of the acetoxy protected C-1 alcohol **203** was successful and pleasingly delivered the desired ketone **210** quantitatively (**Scheme 72**). Ketone **210** was a novel compound and therefore, fully characterised.



Scheme 72. Dess-Martin oxidation of alcohol **203**.

Reagents and conditions: ***i****. DMP, CH_2Cl_2, rt, 12 h (100%).*

The elimination step of acetate **210** to obtain the corresponding 2-en-1-one **209** was investigated next (**Scheme 73**, **Table 10**).



Scheme 73. Synthesis of 2,5-dien-1-one **209**.

Table 10. Screening of conditions for the elimination of C-3 acetate group **210**.

Entry	Conditions	Outcome
1	0.1 M KOH (0.5 mL), dioxane, rt, 3 h	**209**: 76%, 100% brsm
2	DBN (2.0 eq.), rt, 40 min	**211**: 89% yield
3	DBN (0.5 eq.), rt, 10 min	**211**/**209**: (1:0.12)
4	Al_2O_3 (25 eq.), benzene, rt → 55 °C, 5 h	**209**: 95%

Considering that a related elimination was reported in the literature using DBN as the base, these reaction conditions were the first to be tested with our model system **210**.[32,88] Surprisingly, upon elimination of the acetate group, 3,5-dien-1-one **211** was isolated as the major compound in a very good yield (**Table 10**, entry **2**). It was initially proposed that the prolonged time of the reaction might have facilitated isomerisation of the double bond from the 2,3- to the 3,4-position. Therefore, the previous reaction was run under the same conditions but for 10 min which led to an inseparable mixture of 3,5-dien-1-one **211** and 2,5-dien-1-one **209** in a 1:0.12 ratio (**Table 10**, entry **3**). Fortunately, other basic conditions using less hindered bases delivered the desired 2-en-1-one **209** in very good to excellent yields (**Table 10**, entries **1** and **4**).

Both dienone products **209** and **211** were novel compounds and therefore, fully characterised.

4.1.3. Discussion of the elimination step

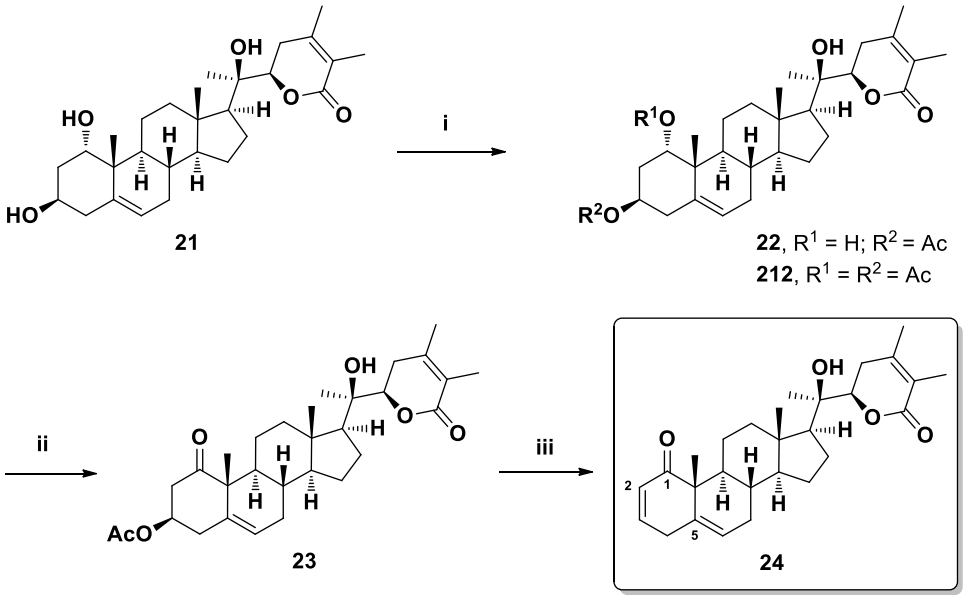
It is likely that the elimination step in **Scheme 73** proceeded by an $E1_{CB}$ type of elimination leading to give the 2-en-1-one substitution in the A-ring. The assignment of enone **209** was supported by typical peaks in its ^{1}H- and ^{13}C-NMR spectrum indicating the presence of an α,β-unsaturated ketone, namely a signal at δ 6.77 (ddd, $J_{3,2}$ = 10.0 Hz, $J_{3,4\beta}$ = 4.9 Hz, $J_{3,4\alpha}$ = 2.5 Hz) and at δ 5.87 (dd, $J_{3,2}$ = 10.0 Hz, $J_{2,4\beta}$ = 2.1 Hz) assigned to the vinylic protons H-3 and H-2, respectively; and peaks at δ 204.4, δ 145.2, δ 127.9 attributed to C-1, C-3, and C-2, respectively.

Given the aforementioned results of the screening of different bases for the elimination reaction leading to two different substitution patterns in the A-ring, we initially thought that alkene isomerisation of **209** led to the formation of **211**, but an alternative hypothesis

is that the steric hindrance between DBN and the C-19 axial methyl group may lead to E2-type elimination of H-4 rather than an $E1_{CB}$ elimination. The structural assignment of the 3,5-dien-1-one **211** was verified by the presence of distinctive peaks in the ^{1}H- and ^{13}C-NMR spectra, *i.e*. two downfield signals at δ 6.03 (br d, $J_{3,4}$ = 9.3 Hz), δ 5.61-5.59 (m) assigned to the vinylic protons H-4 and H-3, respectively, and two high field peaks at δ 129.4 and at δ 121.6 attributed to C-4 and C-3, respectively.

4.1.4. "The End Game": the synthesis of 14,17-dideoxy-17-*epi*-withanolide F (**24**)

Given the aforementioned optimisation studies on the model system **61** towards the synthesis of the 2-en-1-one fragment in the A-ring, the best results were applied to the desired steroidal target; thus, diol **21** was selectively acetylated at C-3 in good yield (only 17% of the bisacetylated compound **212** was isolated). Subsequent Dess-Martin oxidation of C-1 hydroxyl group **22** delivered ketone **23** in 84% and the final elimination step using basic alumina allowed the formation of the desired target 2,5-dien-1-one **24** in excellent yield (**Scheme 74**). The data of acetate **22**, the undesired diacetate **212** and ketone **23** were consistent with those previously published in the literature.[25]



Scheme 74. Construction of A-ring 2-en-1-one fragment of target compound **24**.

Reagents and conditions: ***i****. Ac_2O, Et_3N (50% in CH_2Cl_2), DMAP, CH_2Cl_2, rt, 6 h (72%);* ***ii****. DMP, CH_2Cl_2, rt, 2 h (84%);* ***iii****. Al_2O_3, benzene, 50 °C, 3.5 h (90%).*

4.1.5. Characterisation of 14,17-dideoxy-17-*epi*-withanolide F (**24**)

Once the total synthesis of 14,17-dideoxy-17-*epi*-withanolide F (**24**) was completed, ^{1}H- and ^{13}C-NMR spectral data of the synthetic sample (see **Appendix III** for copies of NMR spectra) were compared to the data previously reported in the literature by Choudhary *et al*.[40] Although most of the signals match, some errors were noticed in the published literature. The incorrect peaks reported in the literature are highlighted in **Tables 11** and **12**.

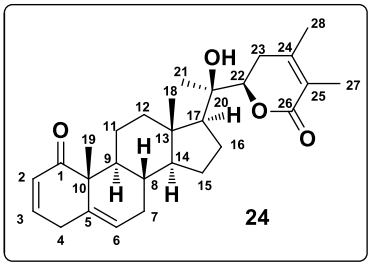


Table 11. Comparison of ^{1}H-NMR spectral data. 400 MHz, $CDCl_3$.

Atom	δ (ppm) Reported*	δ (ppm) Synthetic
2	5.89 (dd, 9.8, 3.0)	5.87 (dd, 9.9, 3.0)
3	6.74 (m)	6.75 (ddd, 9.9, 4.6, 3.0)
4	2.79 (dd, 21.6, 4.8)	3.27 (dd, 21.4, 2.4), 2.85 (dd, 21.4, 4.6)
6	5.58 (br d, 6.0)	5.55 (br d, 6.10)
7	1.98 (m), 1.90 (m)	1.97-1.94 (m), 1.52-1.45 (m)
8	1.52 (m)	1.42-1.37 (m)
9	1.60 (m)	1.64-1.59 (m)
11	1.50 (m)	2.18 (br dd, 13.1, 3.4)
12	1.69 (m)	2.04 (br d, 12.8)
14	3.65 (m)	1.11-1.07 (m)
15	1.25-1.09 (m)	1.62-1.59(m)
16	2.01 (m)	1.98-1.95(m)
17	1.58 (m)	1.47-1.43 (m)
18	1.21	1.21
19	0.89	0.89
21	1.28	1.29
22	4.20 (dd, 13.2, 3.4)	4.20 (dd, 13.4, 3.3)
23	2.38 (m), 2.10 (m)	2.39 (br dd, 15.6, 15.0)
27	1.86	1.87
28	1.93	1.97

*^{1}H-NMR spectral data recorded at 500 MHz in $CDCl_3$.

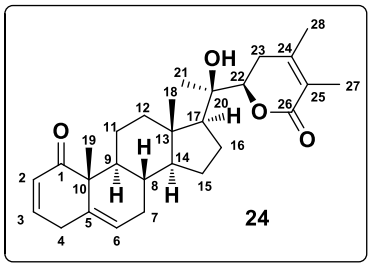


Table 12. Comparison of ^{13}C-NMR spectral data. 125 MHz, $CDCl_3$.

Atom	δ (ppm) Reported*	δ (ppm) Synthetic
1	204.5	204.4
2	127.9	127.9
3	145.2	145.1
4	33.4	33.5
5	135.9	135.9
6	124.7	124.7
7	31.6	30.7
8	39.7	32.6
9	40.1	42.8
10	50.1	50.5
11	21.9	23.4
12	23.4	40.2
13	49.6	42.9
14	54.7	56.7
15	29.6	23.9
16	42.9	21.8
17	56.6	54.7
18	18.9	19.0
19	13.6	13.6
20	75.2	75.2
21	20.5	21.0
22	81.0	81.0
23	30.6	31.6
24	149.0	148.8
25	122.0	122.0
26	166.2	166.0
27	12.7	12.4
28	21.7	20.5

*^{13}C-NMR spectral data recorded at 125 MHz in $CDCl_3$.

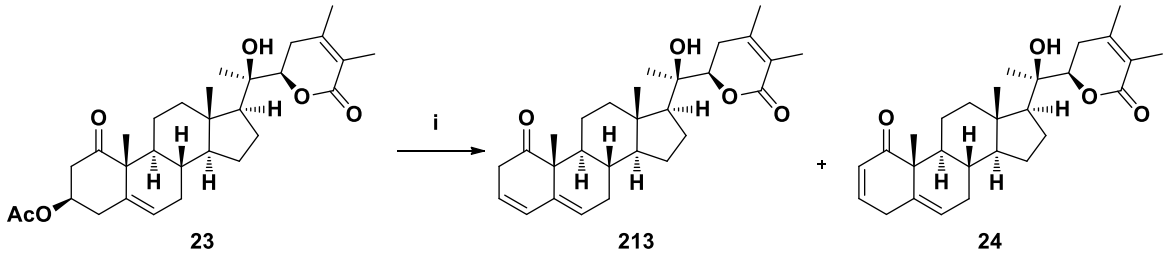
As can be seen in the above tables (**Tables 11** and **12**), our spectroscopic data for 14,17-dideoxy-17-*epi*-withanolide F (**24**) fail to match that reported by Choudhary *et al*. in the original isolation paper. In order to gather a clearer conclusion as to the discrepancies observed in the ^{1}H- and ^{13}C-NMR spectra, a sample of 14,17-dideoxy-17-*epi*-withanolide F (**24**) or the original NMR spectroscopic data will be requested directly from the authors of the isolation paper. Only upon receipt and processing of the raw data will we be able to confirm that the hypothesis that original structural assignement was incorrect.

4.2. Synthesis of Other Analogues of Withanolide F (1)

As mentioned in **Chapter 1**, biological properties of analogues of withanolide F (**1**) have not been studied in detail yet. Therefore, in order to broaden the SAR studies of compound (**1**), the syntheses of other withanolide F (**1**) analogues were investigated.

4.2.1. The first synthesis of 3,4-dihydro-$\Delta^{3,4}$-14,17-dideoxy-17-*epi*-withanolide F (**213**)

An interesting outcome of the optimisation study on the model system **61** was the formation of the 3-en-1-one compound **211** when using DBN as the base. These basic conditions were attempted on acetate **23** and led to a mixture of 3-en-1-one **213** and 2-en-1-one **24** in a 1:0.18 ratio and in excellent yield (91%) (**Scheme 75**). Unfortunately, these two compounds **213** and **24** were not separable by column chromatography.

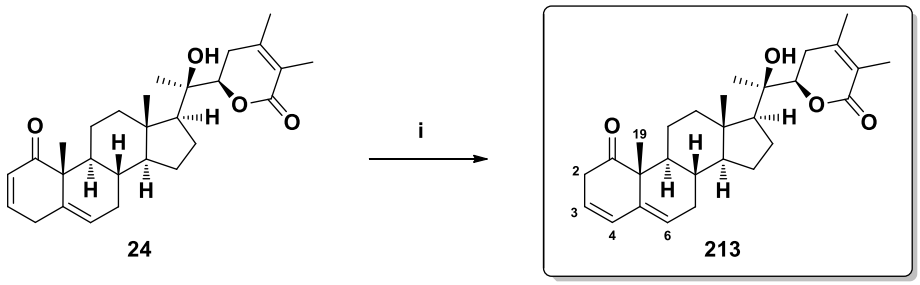


Scheme 75. Synthesis of 3,5-dien-1-one **213** *via* elimination of acetate group **23**.

Reagents and conditions: ***i****. DBN, CH_2Cl_2, rt, 45 min (91% of* ***213/24*** *in 1:0.18 ratio).*

In the literature, the migration of the A-ring double bond from a 2,3-position to the 3,4-position has been disclosed by Lavie *et al*. strictly under acidic conditions (both in nature and under synthetic conditions).[25] Fortunately, in our hands, isomerisation of the

2,3-double bond in the A-ring was successful under basic conditions and delivered the desired 3,4-dihydro-$\Delta^{3,4}$-14,17-dideoxy-17-*epi*-withanolide F (**213**) as a single product in excellent yield (**Scheme 76**).



Scheme 76. Synthesis of 3,5-dien-1-one **213** *via* isomerisation of 2,3-double bond.

Reagents and conditions: ***i****. DBN, CH_2Cl_2, rt, 3 h (98%).*

This constitutes the first total synthesis of 3,4-dihydro-$\Delta^{3,4}$-14,17-dideoxy-17-*epi*-withanolide F (**213**), an interesting analogue of withanolide F (**1**), that is novel and was never been isolated. It has been reported in the literature by Lavie *et al*. that this 3-en-1-one substitution pattern is rarely observed in nature and the only isolated withanolides that possess it are withanolide I (**214**)[11] and withanolide K (**215**)[94] (**Figure 21**).

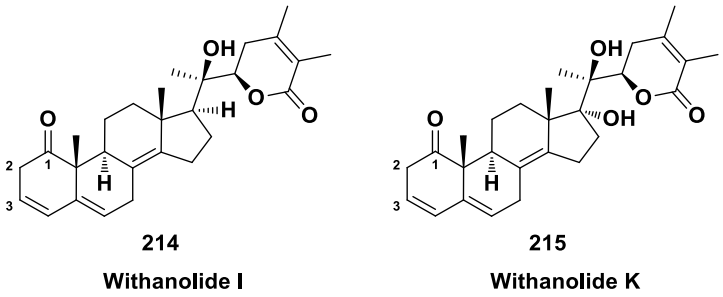


Figure 21. Structures of withanolide I (**214**) and withanolide K (**215**).

4.2.2. Characterisation of 3,4-dihydro-$\Delta^{3,4}$-14,17-dideoxy-17-*epi*-withanolide F (**213**)

Based on comparison of the ^{1}H- and ^{13}C-NMR signals of withanolide I (**214**) and K (**215**) that possess the same 3,5-dien-1-one system, the structure of 3,4-dihydro-$\Delta^{3,4}$-14,17-dideoxy-17-*epi*-withanolide F (**213**) was confirmed (see **Appendix IV** for copies of NMR spectra).[11] Thus, the coupling pattern of the olefinic protons H-3 (δ 5.60-5.58, m), H-4 (δ 6.03, d, $J_{4,3}$ = 9.2 Hz), H-6 (δ 5.63, br d, J = 3.1 Hz) and of the CH_2 group H-2

(δ 3.28, br d, J = 19.5 Hz and δ 2.73, dd, J = 19.5 Hz, $J_{2,3}$ = 4.3 Hz) together with the high value of C-19 methyl signal at δ 1.35 were consistent with a 3,5-dien-1-one substitution pattern.

4.2.3. Attempted synthesis of glycoside **216**

Promising results of cardiac glycosides that produced strong inhibitors of Hh/Gli signalling pathway expressed in human pancreatic cancer cells during their *in vitro* screening were previously outlined in **Chapter 1**.[12] Moreover, a sugar derivative of withanolide F (**1**) was isolated from *Withania adpressa* by AnalytiCon Discovery GmbH and showed some interesting bioactivity during the *in vivo* testing (these results cannot be reported here for confidentiality reasons). Given these previous observations, it became clear that it would be interesting to synthesise a similar C-3 aglycone analogue **216** (**Figure 22**).

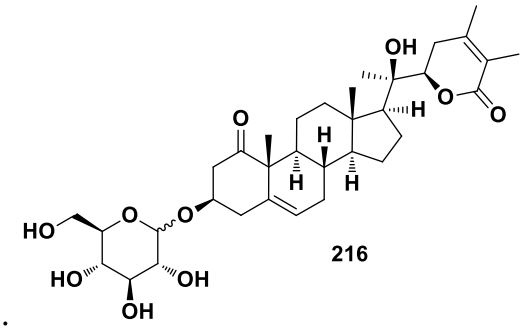
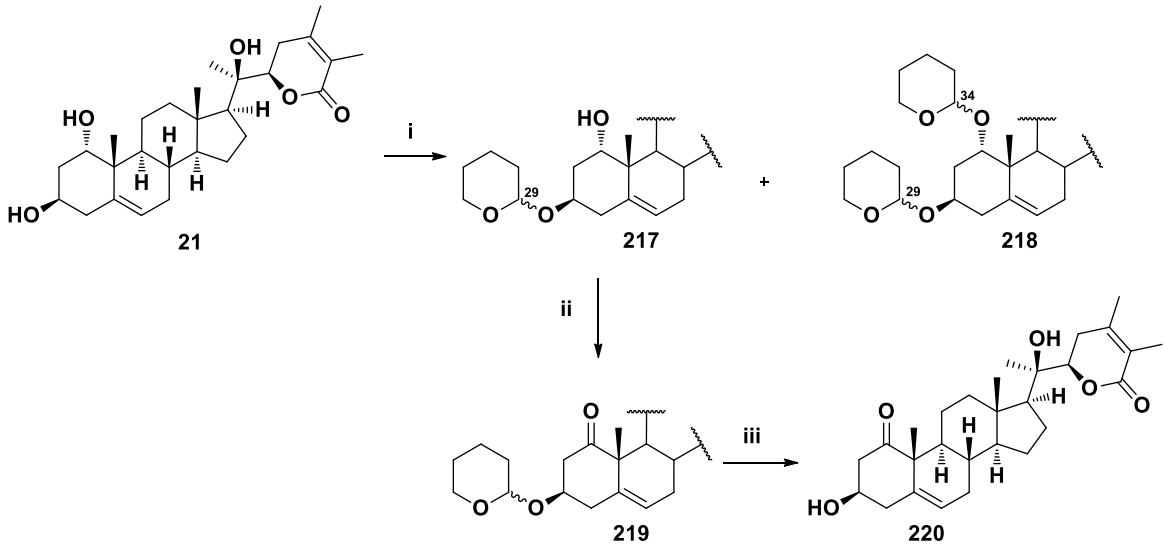


Figure 22. Structure of C-3 aglycone analogue **216**.

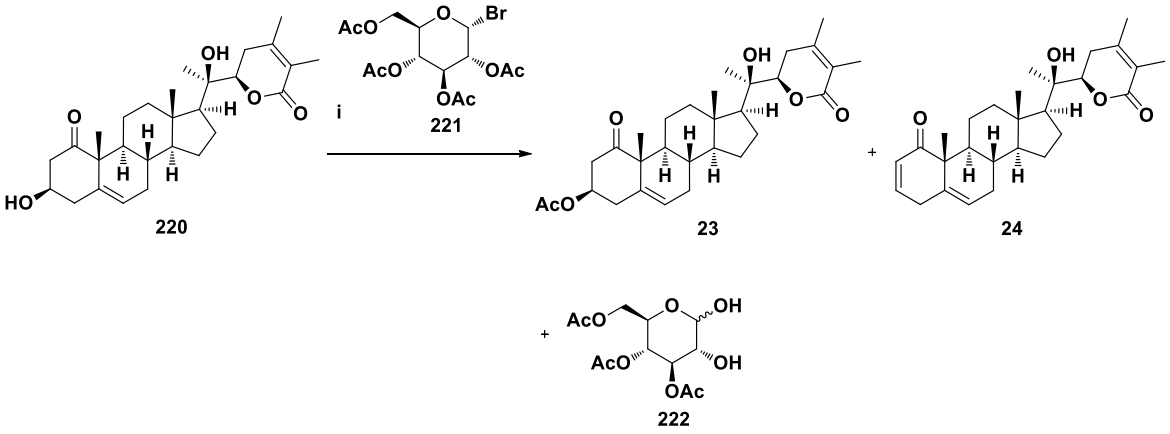
To this aim, a synthetic route was designed using a key intermediate from the total synthesis previously described. Triol **21** was selectively protected at C-3 using a THP ether protecting group. Under standard reaction conditions and at room temperature the reaction was not selective; the bis-THP protected compound **218** was obtained as an inseparable mixture of four diastereoisomers at C-29 and C-34.[29] However, pleasingly the desired C-3 THP protected compound **217** was obtained in 57% yield as a mixture of inseparable two diastereoisomers at C-29 when carrying out the reaction at low temperature with fewer equivalents of DHP (**Scheme 77**). The following oxidation step allowed the formation of ketone **219** in 61% yield under Dess-Martin reaction conditions. The subsequent cleavage of THP protecting group using standard acidic conditions led to the desired C-3 alcohol **220** quantitatively.[29] These three key intermediates **217**, **219** and **220** in the synthesis of C-3 aglycone analogue **216** were novel, and therefore, fully characterised.



Scheme 77. Synthesis of hydroxyketone **220**.

Reagents and conditions: ***i****. DHP, p-TsOH, CH_2Cl_2, rt, 3 h (57% of* ***217*** *and 19% of* ***218****);* ***ii****. DMP, CH_2Cl_2, rt, 3 h (61%);* ***iii****. 2 M HCl, MeOH, rt, 2 h (100%).*

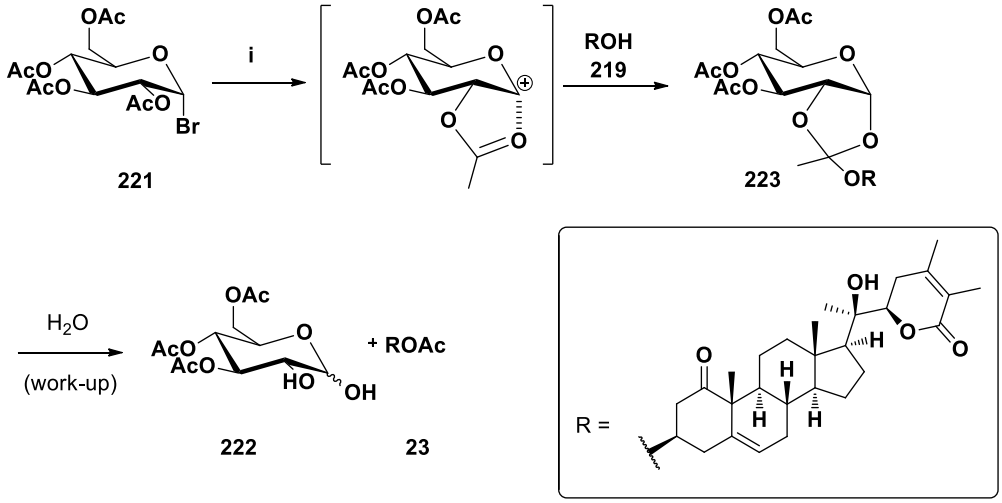
Unfortunately, an attempted glycosylation of alcohol **220** with commercially available acetobromo-α-D-glucose (**221**) and CF_3SO_3Ag promotion was unsuccessful.[95] This reaction only led to the synthesis of acetate **23** and 2,5-dien-1one **24**, which probably resulted from the elimination of C-3 acetate **23** under basic conditions (**Scheme 78**). This reaction was run on a very small scale (~ 15 mg, 0.0329 mmol), therefore, no conclusive yields were obtained.



Scheme 78. Attempt to glycosylate alcohol **220**.

Reagents and conditions: ***i****. CF_3SO_3Ag, 4 Å molecular sieves, CH_2Cl_2, 0 °C to rt, 6 h.*

The competing hydrolysis of glucose derivative **221** *via* ortho-ester formation was previously reported in the literature by Polt *et al*. during their synthesis of *O*-linked glycopeptides analogues of encephalin (**Scheme 79**).[95]



Scheme 79. Ortho-ester formation.

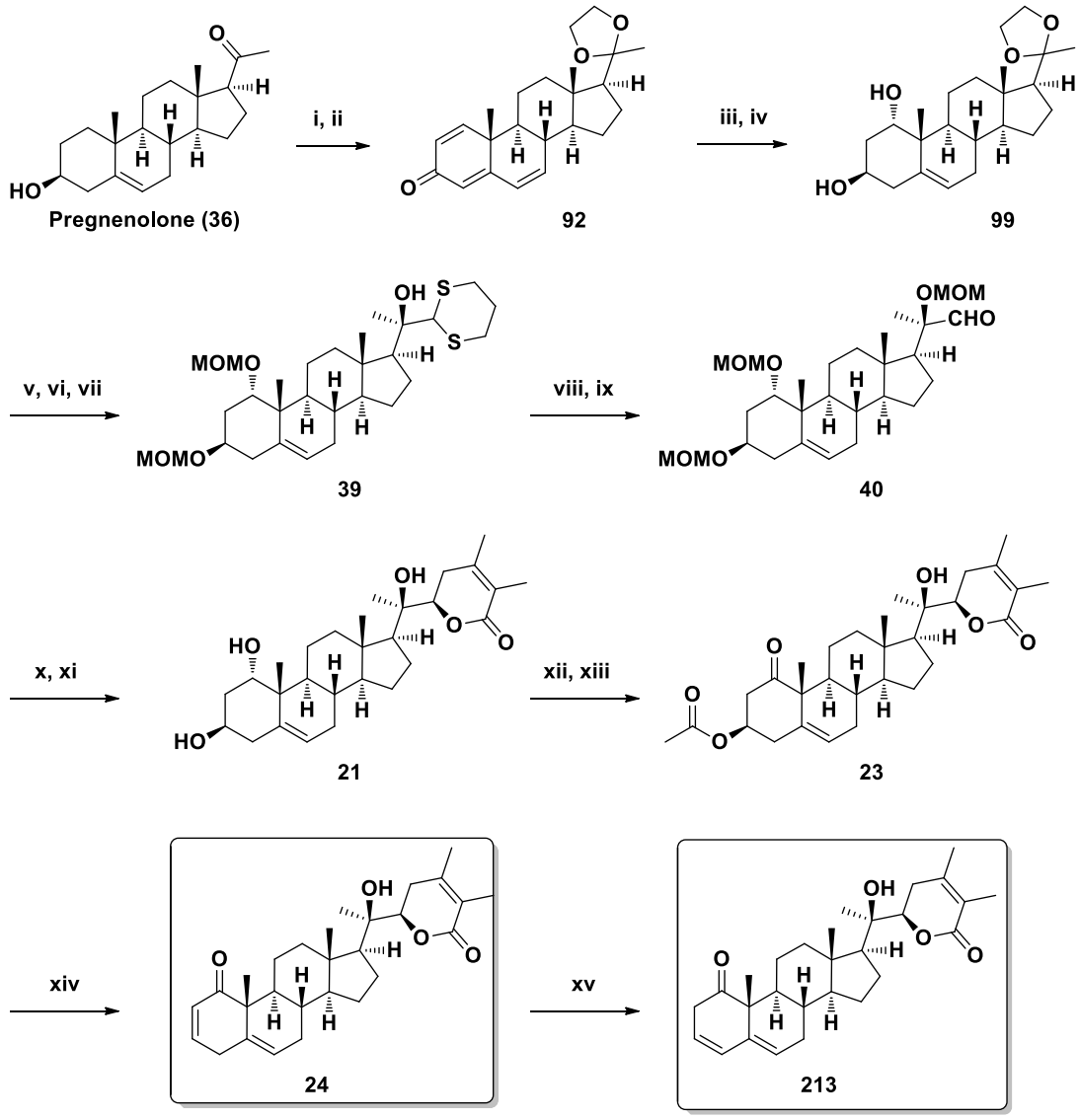
Reagents and conditions: ***i****. CF_3SO_3Ag, 4 Å molecular sieves, 0 °C to rt, 6 h.*

They suggested that using a sugar protected with benzyl groups could help avoid this side reaction. Unfortunately, in our case, there is a good chance that the subsequent deprotection of the benzyl groups under hydrogenation conditions would also hydrogenate the 5,6-double bond of the desired target molecule **216**.

4.3. Summary and Future Work

4.3.1. Summary

In summary, the acetylation-oxidation-elimination sequence enabled the total synthesis of 14,17-dideoxy-17-*epi*-withanolide F (**24**) to be achieved in 14 steps and in an overall 5.3% yield (**Scheme 80**). The key features of the total synthesis included a Birch reduction, a C-1 homologation process through a Corey-Seebach reaction, an efficient dithiane cleavage and a vinylogous aldol reaction to build the key δ–lactone side chain. Pleasingly, a novel analogue of withanolide F (**1**), 3,4-dihydro-$\Delta^{3,4}$-14,17-dideoxy-17-*epi*-withanolide F (**213**), was synthesised in 15 steps and in 5.2% overall yield (**Scheme 80**). The key step of the total synthesis was the migration of the 2,3-double bond of 14,17-dideoxy-17-*epi*-withanolide F (**24**) under basic conditions.

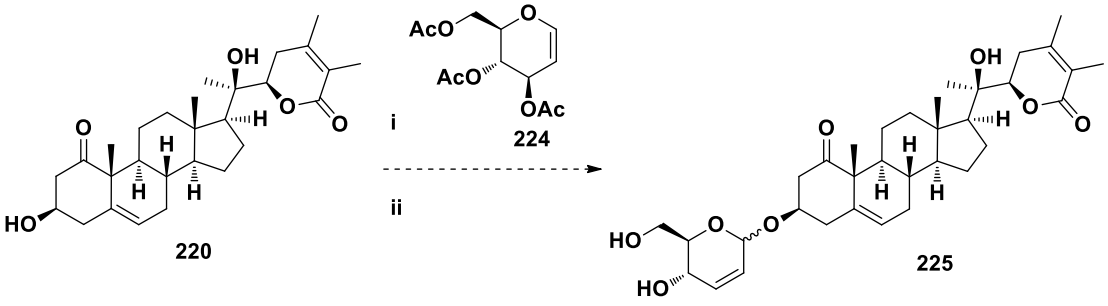


Scheme 80. Total syntheses of 14,17-dideoxy-17-*epi*-withanolide F (**24**) and 3,4-dihydro-$\Delta^{3,4}$-14,17-dideoxy-17-*epi*-withanolide F (**213**).

Reagents and conditions: ***i****. ethylene glycol, p-TsOH, toluene, 130 °C, 12 h (90%);* ***ii****. $Pd(OAc)_2$, ADP, Na_2CO_3, DMF, 160 °C, 72 h (62%);* ***iii****. H_2O_2 (30% w/w), 10% NaOH in MeOH, ^{i}PrOH, 15 °C, 12 h (72%);* ***iv****. Li/NH_3, NH_4Cl, THF, −78 °C to −40 °C to −20 °C, 4 h (76%);* ***v****. MOMCl, 1,4-dioxane, reflux, 6 h (92%);* ***vi****. $AcOH/H_2O$/THF (65:35:10), rt, 12 h (100%);* ***vii****. 1,3-dithiane, ^{n}BuLi, THF, −5 °C, 8 h (71%);* ***viii****. MOMCl, $^{i}Pr_2EtN$, 1,4-dioxane, reflux, 12 h (85%);* ***ix****. NCS, $AgNO_3$, CH_3CN/H_2O (4:1), 0 °C, 30 min (85%);* ***x****. LiHMDS, THF/DMPU (8:2), −78 °C, 6 h;* ***xi****. 6 M aq. HCl, THF, rt, 7 h (67% over two steps);* ***xii****. Ac_2O, Et_3N (50% in CH_2Cl_2), DMAP, CH_2Cl_2, rt, 6 h (72%);* ***xiii****. DMP, CH_2Cl_2, rt, 2 h (84%);* ***xiv****. Al_2O_3, benzene, 50 °C, 3.5 h (90%);* ***xv****. DBN, CH_2Cl_2, rt, 3 h (98%).*

4.3.2. Future work

Future work will focus on building a library of other analogues of withanolide F (**1**) using 14,17-dideoxy-17-*epi*-withanolide F (**24**) and 3,4-dihydro-$\Delta^{3,4}$-14,17-dideoxy-17-*epi*-withanolide F (**213**) *via* A/B-ring functionalisation and variation of the side chain. Many variants should be available using standard chemistry such as, for example, epoxidation to form a 5β,6β-epoxide;[29] this is a key feature that has showed some positive influence on the bioactivity of some withanolides (see SAR studies in **Chapter 1**).[39] Completing the synthesis of the C-3 aglycone analogue **216** by using other sugars that possess different protecting groups should also be investigated.[96] Other methods could be studied in order to synthesise different sugar derivatives, for example, *via* the Ferrier reaction using commercially available tri-O-acetyl-D-glucal (**224**) to form glycoside **225**, another novel analogue of withanolide F (**1**) (**Scheme 81**).[97,98]



Scheme 81. Synthesis of glycoside analogue **225** *via* Ferrier reaction.

Suggested reagents and conditions: ***i****.* BF_3•Et_2O, CH_2Cl_2, −20 °C *to rt, 1 h;* ***ii****.* K_2CO_3, *MeOH/*H_2O *(4:1), rt, 1 h.*

As mentioned in **Chapter 1**, the main purpose of building a library of analogues of withanolide F (**1**) is to allow a better understanding of their possible biological activity and to develop SAR studies. Therefore, the next step of this project should be the biological testing of the compounds **24** and **213** so far synthesised along with intermediates of the total syntheses previously described. These tests should mainly be focused on the influence of these molecules and their structural features on the Hh-Gli and Wnt-TCF biological pathways.[99,100] The experiments would involve Luciferase reporter assays which would be performed on three different cancer cell types and the level of target gene expression for

both signalling pathways would be examined. These experiments should indicate whether the tested compounds are Gli and/or TCF agonists or antagonists.

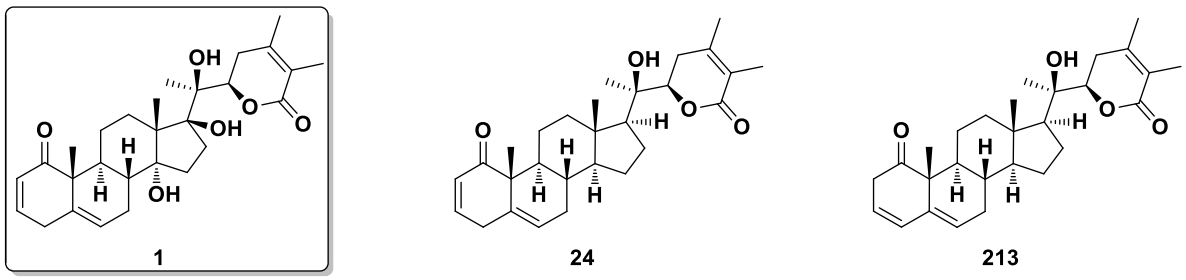


Figure 23. Structures of withanolideF (**1**) and analogues **24** and **213**.

Moreover, given the low yields encountered during the synthesis of the δ-lactone side chain of the target molecule **24**, a new synthetic approach to the synthesis of the side chain and later a methodology towards the construction of other type of heterocycles as side chains is needed. To this end, a new general methodology for the construction of the δ-lactone side chain is discussed in **Chapter 5**

Chapter 5. Methodology Towards the Construction of δ-Lactones

5.1. Overview of Published Routes to δ-Lactones

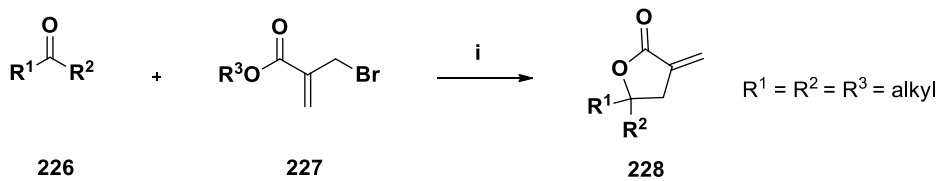
An overview of published routes to δ-lactone has been described in **Chapter 3**. From all the methods to construct the δ-lactone side chain developed so far, the one step vinylogous condensation of an enolate with an aldehyde developed by Ikekawa *et al.* was the most efficient in terms of stereospecificity and yield. As shown in **Scheme 4**, this reaction has been disclosed in the literature to deliver the desired C-22*R* δ-lactone **41** in a very good yield (86%) during the total synthesis of withanolide D.[29] More recently (2011), this procedure has been repeated by Gademann *et al.* using slightly optimised reaction conditions to deliver C-22*R* δ-lactone **55** in 87% yield (**Scheme 6**).[35]

Unfortunately, as discussed earlier in **Chapter 3**, problems were encountered when trying to repeat these literature procedures to form the δ-lactone side chain, [29,35] Another future project would be to develop improved procedures. A very short study was carried out to evaluate a new variant of the Dreiding-Schmidt reaction for this purpose.[101]

5.2. The Dreiding-Schmidt Reaction

5.2.1. The Dreiding-Schmidt reaction: literature examples

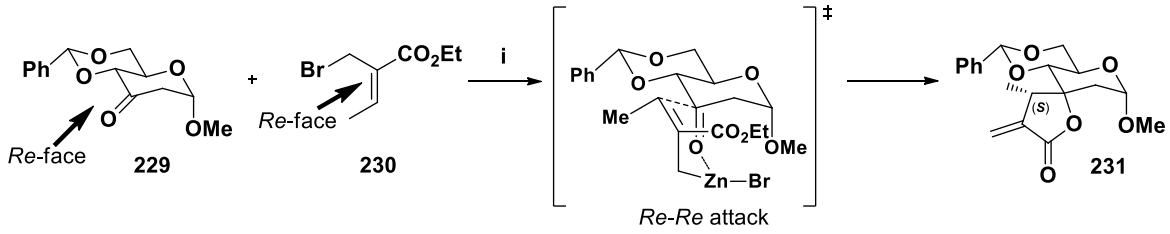
In 1970 using Dreiding's previous work on the treatment of cyclohexanone with γ-bromo and β'-bromo-tiglic esters under Reformatsky's conditions,[102] Schmidt's group developed a zinc-mediated reaction between a ketone **226** and a bromomethyl acrylic ester **227** to give α-methylene-γ-lactones **228** in good yields (42% to 100%) (**Scheme 82**).[101]



Scheme 82. Synthesis of α-methylene-γ-lactone **228** *via* the Dreiding-Schmidt reaction.

Reagents and conditions: ***i****. Zn, THF, 50 °C, 1 h (42% to 100%).*

Csuk *et al.* investigated the stereoselectivity of the Dreiding-Schmidt reaction with carbohydrates.[103] They achieved the formation of spiroanellated butyrolactones **231** with an additional stereocentre in the β-position of the anellated lactone ring. The yield and the stereoselectivity were significantly improved by using the highly reactive zinc-silver/graphite surface reagent when compared to using standard carbohydrate reaction conditions (24% yield reported in the literature).[104] It was suggested that the favoured transition state of the reaction proceeds through a *Re-Re* attack which avoids 1,3-diaxial interactions between the substituents (**Scheme 83**).

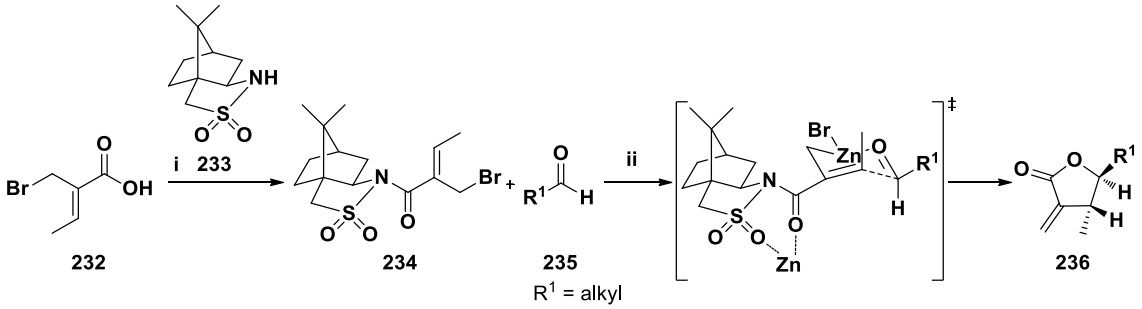


Scheme 83. Synthesis of spiroanellated butyrolactone **231** *via* the Dreiding-Schmidt reaction.

Reagents and conditions: ***i****. Zn-Ag/graphite, THF, −30 °C (74%).*

Csuk's group was also able to perform an asymmetric synthesis of α-methylene-γ-butyrolactones **236** *via* an diastereotioselective Dreiding-Schmidt reaction.[105] Thus, non-racemic bromomethyl acrylate reagents were tested for their potential use as chiral reagents. Carboxylic acid **232** was transformed into amide **234** by using the amino moiety of (+)-Oppolzer's sultam (**233**) in good yield (74%). The *syn*-orientation of the chiral bromomethylacrylate **234** was favoured by the zinc chelation of the carbonyl functionalities present in the methacrylamide **234**. The methacrylamide **234** thus formed was submitted to the Dreiding-Schmidt reaction conditions which allowed the formation of the corresponding disubstituted butyrolactone **236**. The scope of the reaction was extended to a broad range of aldehydes **235** and allowed the formation of the desired products **236** in very good yield (up to 95%) and e.e. (up to 82%) (**Scheme 84**). The chiral auxiliary **234** was recovered in good yields. It was suggested that the favoured six-membered chair-like transition state would go through a $Si_{zn\text{-}reagent}$-$Re_{aldehyde}$ attack. Indeed, the attack of the *Si*-face of the zinc reagent **234** was preferred due to the steric hindrance of the camphor skeleton and the attack of the aldehyde **235** through its *Re*-face would bring

the R^1 functional group into a favourable equatorial position and avoid any 1,3-diaxial interactions with the other substituents.

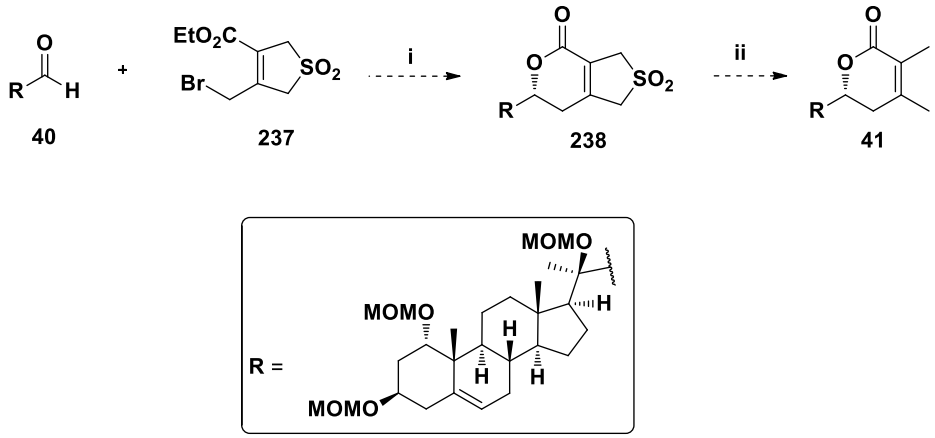


Scheme 84. The Dreiding-Schmidt reaction *via* methacrylamide **234**.

Reagents and conditions: ***i****. NaH, toluene, 25 °C, 2 h (74%);* ***ii****. Zn/Ag-graphite, THF, 0 °C (68% up to 95% yield, 69% up to 82% ee).*

5.2.2. Possible new route to δ-lactones *via* the Dreiding-Schmidt reaction

An mentioned earlier, given the problems we initially encountered with the published routes to build dimethylated δ-lactones (**Scheme 58**),[29,35] we decided to devise a novel route. The plan was to use the Dreiding-Schmidt reaction of bromoester **237** and aldehyde **40** to generate an intermediate lactone **238** in a one-step reaction. The cyclic sulfone moiety would ensure that there would be no *E*/*Z* issues; subsequent reductive removal of the sulfone group would reveal the α,β-dimethyl substitution of the desired δ-lactone **41** (**Scheme 85**).



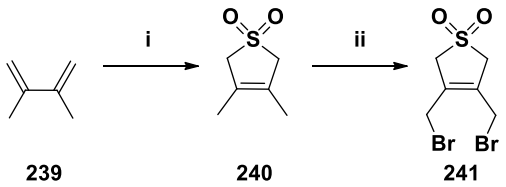
Scheme 85. Synthesis of δ-lactone **41** synthesis *via* the Dreiding-Schmidt reaction.

Suggested reagents and conditions: ***i****. Zn-Ag/graphite, THF, 0 °C;* ***ii****. Raney nickel.*

Unfortunately, bromoester **237** is not commercially available. Therefore, its synthesis was investigated.

5.2.3. Literature routes to bromoester **237**

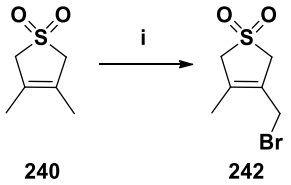
Unfortunately, to date, the synthesis of bromoester **237** has not been reported in the literature. On the other hand, Takayama *et al*. disclosed a synthetic approach to form dibromide **241** from commercially available 2,3-dimethylbuta-1,3-diene (**239**) in 75% yield over two steps (**Scheme 86**).[106]



Scheme 86. Synthesis of dibromide **241**.

Reagents and conditions: ***i****.* SO_2*, hydroquinone, MeOH, rt (99%);* ***ii****.* *NBS,* CH_2Cl_2*, reflux (76%).*

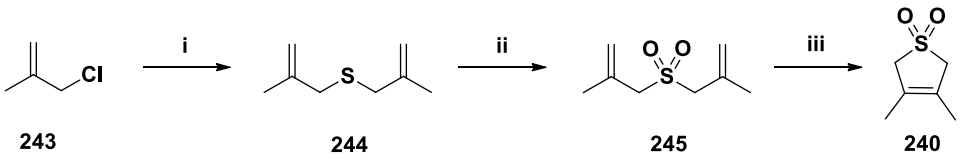
Later, Ito *et al*. synthesised mono-bromide **242** from cyclic sulfone **240** in moderate yield by refluxing NBS and catalytic amounts of benzoyl peroxide in benzene (**Scheme 87**).[107]



Scheme 87. Synthesis of mono-bromide **242**.

Reagents and conditions: ***i****.* *NBS,* $(PhCO_2)_2$*, benzene, reflux, 3 h (50%).*

More recently (2011), Jain *et al*. described the synthesis of sulfone **245** in 88% yield over two steps from commercially available 3-chloro-2-methylpropene (**243**).[108] The final ring-closing metathesis step to synthesise cyclic sulfone **240** has been disclosed by Yao in excellent yield (**Scheme 88**).[109]

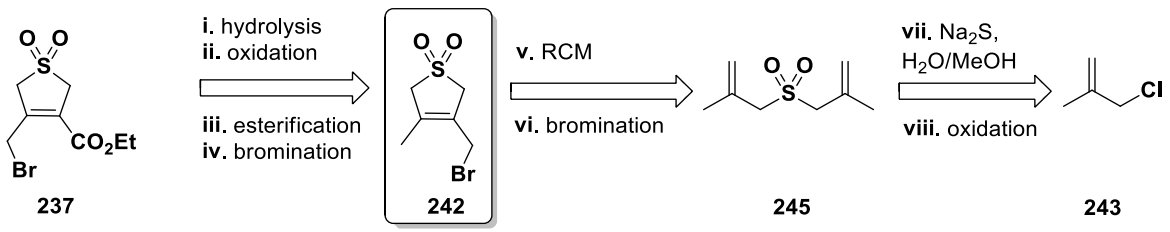


Scheme 88. Synthesis of cyclic sulfone **240**.

Reagents and conditions: ***i****. Na_2S, H_2O, MeOH, rt to reflux, 8 h (88%);* ***ii****. m-CPBA, CH_2Cl_2, 0 °C, 45 min (100%);* ***iii****. 0.05 eq. of Grubbs II generation cat., CH_2Cl_2, reflux, 24 h (99%).*

5.2.4. Proposed retrosynthesis of bromoester **237**

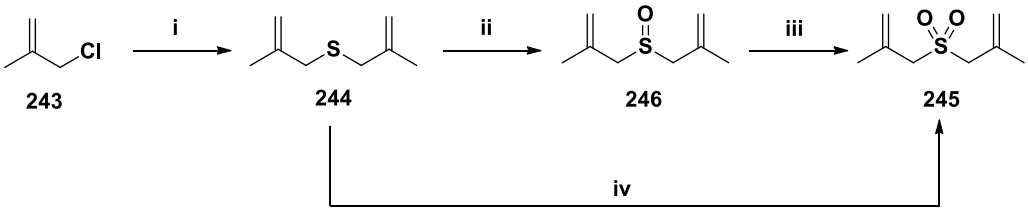
Based on the reactions outlined above, a retrosynthetic route for bromoester **237** was designed. Thus, from a retrosynthetic point of view bromoester **237** could be obtained from the key mono-bromide **242** *via* oxidation of the bromide functionality to give the corresponding aldehyde and subsequently, the carboxylic acid which, in turn, could be treated under standard conditions to form the ester moiety of the final compound **237**. Finally, the latter could be submitted to standard bromination reaction conditions to form bromoester **237**. This synthetic approach relies on a ring-closing metathesis of sulfone **245** using Grubbs' second generation catalyst, followed by treatment with NBS to give mono-bromide **242**. In turn, it was envisaged that sulfone **245** could be prepared from commercially available 3-choro-2-methylpropene (**243**) (**Scheme 89**).



Scheme 89. Proposed retrosynthesis of bromoester **237**.

5.2.5. Synthesis of the key mono-bromide **242**

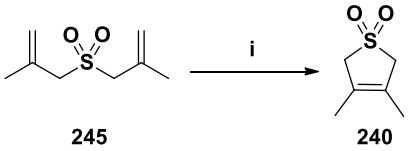
The initial efforts of the synthesis were focused on accessing mono-bromide **242**, a key intermediate in the proposed retrosynthesis of bromoester **237** (**Scheme 89**). Thus, methallyl sulfide (**244**) was synthesised from commercially available 3-choro-2-methylpropene (**243**) in an improved yield compared to the literature (100% vs. 88%).[108] Standard hydrogen peroxide conditions led only to the formation of the sulfoxide **246**[110] which in turn was oxidized to the corresponding sulfone **245** in quantitative yield using *m*-CPBA. Fortunately, methallyl sulfide (**244**) could be oxidized using three equivalents of *m*-CPBA to deliver directly sulfone **245** in good yield as previously reported in the literature (**Scheme 90**).[108]



Scheme 90. Synthesis of sulfone **245**.

Reagents and conditions: ***i****.* *Na_2S, MeOH/H_2O (1:1), reflux, 12 h (100%);* ***ii****.* *H_2O_2 (30% w/w), AcOH, rt, 12 h, (46%);* ***iii****.* *m-CPBA, CH_2Cl_2, 0 °C, 45 min (100%);* ***iv****.* *m-CPBA, CH_2Cl_2, 0 °C, 45 min (81%).*

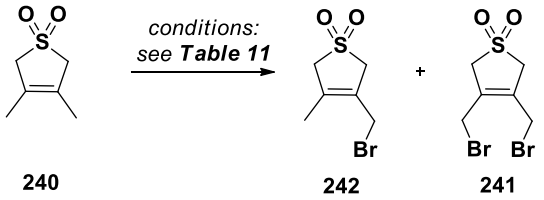
The next key step of the synthesis was the ring-closing metathesis reaction using Grubbs' second generation catalyst. As outlined in **Scheme 88**, this reaction was reported to work in excellent yield (99%) when using 5 mol% of the catalyst.[109] Unfortunately, in our hands these reaction conditions delivered cyclic sulfone **240** in only 45% yield (79% brsm). During optimisation studies, it was observed that using 8 mol% of the catalyst added portion-wise over 4 h ensured the reaction went to completion. Pleasingly, the cyclic sulfone **240** was obtained in quantitative yield (**Scheme 91**).



Scheme 91. Synthesis of cyclic sulfone **240** *via* ring-closing metathesis.

Reagents and conditions: ***i****. Grubbs II generation cat., CH_2Cl_2, reflux, 24 h (100%).*

With the cyclic sulfone **240** in hand, the mono-bromination was attempted using similar reaction conditions as described by Takayama *et al*. to form dibromide **241**.[106] Unfortunately, in our hands the reaction led only to recovery of the starting material **240** (**Table 13**, entry **1**). Therefore, the reaction was thoroughly investigated in order to find the optimum conditions (**Scheme 92**, **Table 13**).



Scheme 92. Bromination of cyclic sulfone **240**.

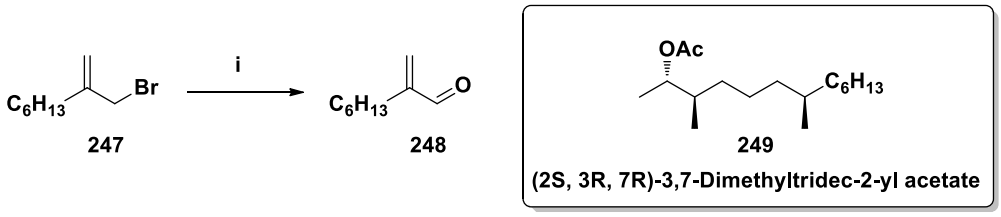
Table 13. Optimisation study of the bromination step.

Entry	Reagents	Conditions	Outcome
1	NBS (1.0 eq.)	CH_2Cl_2, 45 °C, o/n	rsm **240**
2	NBS (1.6 eq.), $(PhCO_2)_2$ (0.05 eq.)	$CHCl_3$, 60 °C, o/n	**242**: 22%, 73% brsm decomposed mixture
3	NBS (3.2 eq.), $(PhCO_2)_2$ (0.1 eq.)	$CHCl_3$, 60 °C, o/n	**242**: 26%, 48% brsm decomposed mixture
4	NBS (1.2 eq.), $(PhCO_2)_2$ (0.08 eq.)	benzene, 80 °C, o/n	decomposed mixture
5	NBS (1.6 eq.), $(PhCO_2)_2$ (0.05 eq.)	chlorobenzene, 100 °C, o/n	**242**: 29%, **241**: 14% decomposed mixture
6	NBS (1.0 eq.), $(PhCO_2)_2$ (0.05 eq.)	CCl_4, 80 °C, o/n	**240**/**242**: (1:1)
7	NBS (1.5 eq.), $(PhCO_2)_2$ (0.05 eq.)	CCl_4, 80 °C, o/n	**240**/**242**: (1:6)
8	NBS (2.0 eq.), $(PhCO_2)_2$ (0.05 eq.)	CCl_4, 80 °C, o/n	**240**/**242**/**241**: (0.29:1:0.14)

It was first suggested that using catalytic amounts of benzoyl peroxide could help initiate the reaction. The reaction was run in chloroform which allowed the formation of the desired mono-bromide **242** in low yield (22%) (**Table 13**, entry **2**). Increasing the quantity of the reagents did not improve the yield (**Table 13**, entry **3**). Unfortunately, repeating the procedure previously published by Ito *et al*. to from mono-bromide **242** only led to decomposition in our case (**Table 13**, entry **4**).[107] Changing to a higher boiling solvent such as chlorobenzene resulted in a slight increase of the yield to 29% along with the isolation of dibromide **241** (**Table 13**, entry **5**). Given the mixed decomposition fractions isolated previously, it was suggested that the brominated compounds **241** and **242** were not stable upon purification by column chromatography. The bromination step was attempted under Wohl-Ziegler reaction conditions,[111] *i.e*. using CCl_4 as the solvent, and varying the number of equivalents of NBS in order to allow the reaction to go to completion and to use the resulting mono-bromide **242** as crude mixture in the next step. As shown in entries **6** to **8** (**Table 13**), when up to 1.5 eq. of NBS was used, no dibromide **241** was formed. Therefore, the best conditions were obtained by refluxing a mixture of cyclic sulfone **240** and 1.5 eq. of NBS (**Table 13**, entry **6**). The structure assignment of mono-bromide **242** was supported by the presence of typical peaks in the ^{1}H- and ^{13}C-NMR spectrum indicating the presence of three CH_2 groups at δ 4.06 (br s), δ 3.95-3.93 (m), δ 3.84-3.82 (m) attributed to H-6, H-4 and H-1, respectively. Furthermore, the assignment of mono-bromide **242** was reinforced by the presence of one bromine atom in mass spectrometry (ESI) analysis. These data were consistent with those previously described in the literature.[107]

5.2.6. Studies towards the synthesis of bromoester **237**

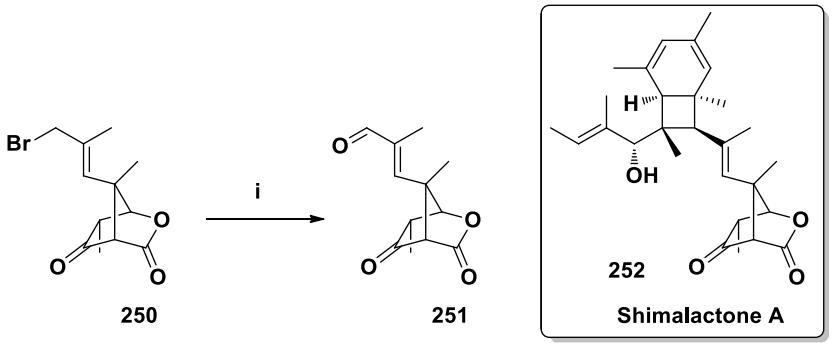
The next key step towards the synthesis of bromoester **237** was the synthesis of aldehyde **253** which was attempted *via* the Kornblum oxidation of mono-bromide **242**. This reaction has been disclosed in the literature using allylic halides in moderate to good yields.[112,113] A good example was reported recently (2006) by Kulinkovich *et al*. during the synthesis of (2*S*,3*R*,7*R*)-3,7-dimethyltridec-2-yl acetate (**249**), an insect pheromone, where they synthesised aldehyde **248** in 71% yield under standard reaction conditions (**Scheme 93**).[112]



Scheme 93. Kornblum oxidation of allyl-bromide **247**.

Reagents and conditions: ***i****. DMSO, $NaHCO_3$, rt, 48 h (71%).*

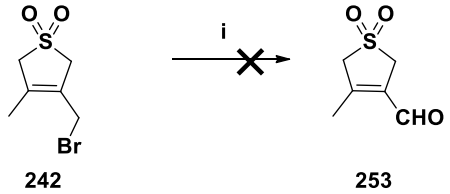
The oxidation of allyl-bromide **250** has also been reported in the literature by Trauner *et al*. using IBX and DMSO in very good yield during the synthesis of shimalactone A (**252**), a neuritogenic natural product (**Scheme 94**).[113]



Scheme 94. Oxidation of allyl-bromide **250** using IBX.

Reagents and conditions: ***i****. IBX, DMSO, 50 °C, 12 h (84%).*

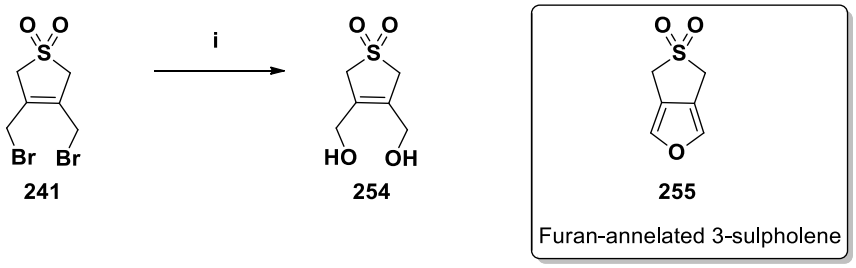
Unfortunately, in our hands, these reaction conditions applied to our mono-bromide substrate **242** only led to decomposition (**Scheme 95**).[112,113]



Scheme 95. Kornblum oxidation of allyl-bromide **242**.

Reagents and conditions: ***i****. DMSO, $NaHCO_3$, rt, 12 h or IBX, DMSO, 50 °C, 12 h.*

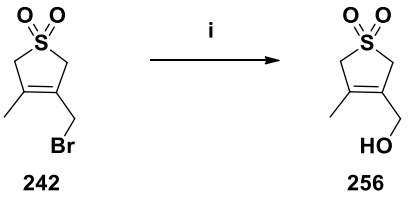
Considering that oxidation of allyl-bromide **242** to the aldehyde **253** was unsuccessful, an alternative synthetic route was designed and mono-bromide **242** was first hydrolysed to the corresponding alcohol **256** prior to the oxidation to form aldehyde **253**. A similar reaction has been disclosed in the literature by Takayama *et al*. in the course of their studies towards the construction of furan-annelated 3-sulpholene (**255**).[114] Thus, the hydrolysis of dibromide **241** by treatment with CF_3CO_2Ag delivered diol **254** in excellent yield (**Scheme 96**).



Scheme 96. Synthesis of diol **254**.

Reagents and conditions: ***i****. CF_3CO_2Ag, H_2O, rt, 3 d (93%).*

Based on the reaction conditions described above, hydrolysis of mono-bromide **242** was attempted but only delivered the desired allylic alcohol **256** in poor yield (**Scheme 97**). Therefore, a screening of conditions was conducted as summarised in **Table 14**.



Scheme 97. Synthesis of allyl-alcohol **256**.

Reagents and conditions: ***i****. 2.0 eq. CF_3CO_2Ag, H_2O, rt, 12 h (15%).*

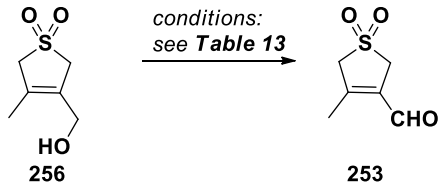
Table 14. Screening of conditions for the hydrolysis of mono-bromide **242**.

Entry	Reagent	Conditions	Outcome
1	$AgNO_3$ (1.0 eq.)	H_2O, rt, o/n	rsm **242**
2	AgO (2.0 eq.)	H_2O, rt, o/n	**256**: 83%
3*	CF_3CO_2Ag (2.0 eq.)	H_2O, rt, o/n	**256**: 100%

*: Inverted addition, mono-bromide **242** was added to a solution of CF_3CO_2Ag in H_2O at rt.

A screening of different silver salts was undertaken and the desired allyl-alcohol **256** was obtained in good yield when using silver oxide (**Table 14**, entry **2**). It was suggested that the yield of the reaction could be improved by inverting the addition of the reagents and applying a vigorous stirring as the mono-bromide **242** was not soluble in water. Pleasingly, the reaction conditions described in entry **3*** allowed the formation of novel alcohol **256** quantitatively.

The next step was the oxidation of alcohol **256** to aldehyde **253** which was carried out using standard reaction conditions as summarised in **Table 15** (**Scheme 98**).



256 **253**

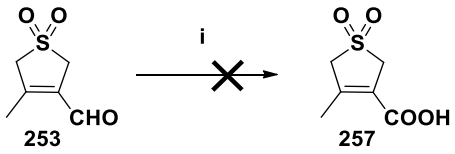
Scheme 98. Synthesis of aldehyde **253** *via* oxidation of alcohol **256**.

Table 15. Screening of conditions for the oxidation of alcohol **256**.

Entry	Conditions	Outcome
1[115]	MnO_2 (5.0 eq.), CH_2Cl_2, rt, o/n	**253**: 40%, 96% brsm
2[116]	DMP (2.0 eq.), CH_2Cl_2, rt, o/n	**253**: 49%

Disappointingly, aldehyde **253** was synthesised in only moderate yields up to 49% under standard reaction conditions (**Table 15**, entries **1** and **2**). Aldehyde **253** was a novel compound and therefore, fully characterised.

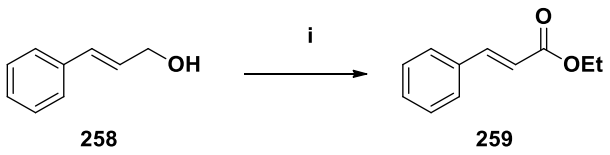
Unfortunately, attempt to access carboxylic acid **257** from aldehyde **253** was unsuccessful under Pinnick's oxidation conditions and only led to decomposition (**Scheme 99**).[117,118]



Scheme 99. Synthesis of carboxylic acid **257** *via* Pinnick oxidation.

Reagents and conditions: ***i****. $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, CH_3CN/H_2O (3:1), rt, 12 h.*

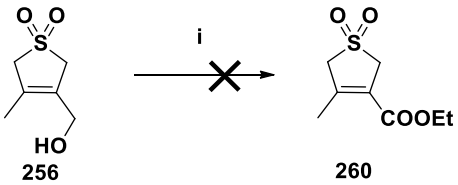
In order to address previous issues to synthesise the ester moiety of bromoester **237**, another synthetic approach was investigated. One option was the one-pot tandem oxidation process developed by Taylor's group to synthesise esters and amides from activated alcohols which was reported in moderate to excellent yield (**Scheme 100**).[119]



Scheme 100. Synthesis of ester **259** *via* tandem oxidation process.

Reagents and conditions: ***i****. MnO_2, NaCN, EtOH, THF, rt, 7 d (49%).*

Unfortunately, in our case, these reaction conditions only led to recovery of the starting material **256** (**Scheme 101**).



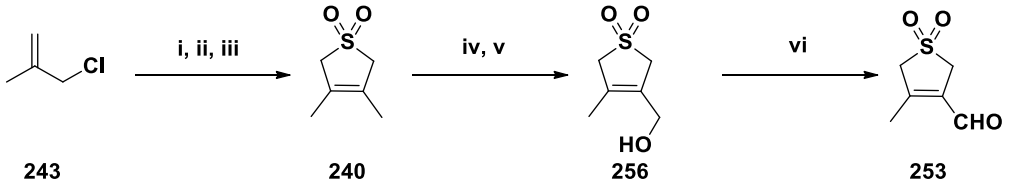
Scheme 101. Synthesis of ester **260** *via* tandem oxidation process.

Reagents and conditions: ***i****. MnO_2, NaCN, EtOH, THF, rt, 3 d.*

5.3. Summary and Future Work

5.3.1. Summary

Although not yet completed, good progress has been made towards the first synthesis of bromoester **237**, a key reagent for the Dreiding-Schmidt reaction. The synthesis of aldehyde **253** was achieved in 40% yield over six steps (**Scheme 102**). The key features of the synthesis included an efficient *m*-CPBA oxidation, a ring-closing metathesis and a silver salt promoted hydrolysis of bromide moiety.

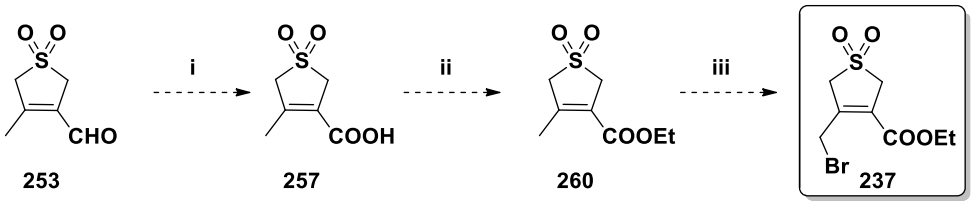


Scheme 102. Synthesis of aldehyde **253**.

Reagents and conditions: ***i****. Na_2S, MeOH/H_2O (1:1), reflux, 12 h (100%);* ***ii****. m-CPBA, CH_2Cl_2, 0 °C, 45 min (81%);* ***iii****. Grubbs II generation cat., CH_2Cl_2, reflux, 24 h (100%);* ***iv****. 1.5 eq. NBS, $(PhCO_2)_2$, chlorobenzene, 100 °C, 12 h;* ***v****. CF_3CO_2Ag, H_2O, rt, 12 h;* ***vi****. DMP, CH_2Cl_2, rt, 12 h (49% over three steps).*

5.3.2. Future work

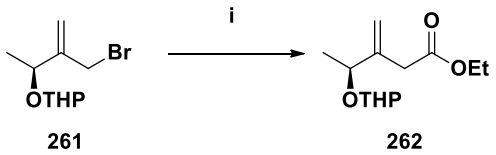
The next key steps of the synthesis of bromoester **237** involve a screening of reaction conditions to oxidize aldehyde **253** to carboxylic acid **257** including using $KMnO_4$, AgO, PDC.[120,121,122] In turn, carboxylic acid **257** could be converted into the corresponding ester **260** using standard esterification conditions.[123] Finally, the desired bromoester **237** would be obtained using previously described Wohl-Ziegler reaction conditions (**Scheme 103**).[111]



Scheme 103. Synthesis of the key bromoester **237**.

Suggested reagents and conditions: ***i****. $KMnO_4$ or AgO or PDC;* ***ii****. H_2SO_4, EtOH, reflux;* ***iii****. NBS, CCl_4, reflux, 12 h.*

On the other hand, Kulinkovich *et al*. has reported recently the synthesis of ester **262** from allyl-bromide **261** quantitatively in one step possibly *via* a Dreiding-Schmidt type reaction (**Scheme 104**).[124]

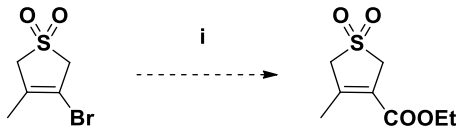


261 **262**

Scheme 104. Synthesis of ester **262** from bromide **261**.

Reagents and conditions: ***i****. Zn, CuCl, 1,2-dibromoethane,* $ClCO_2Et$*,* THF/Et_2O*, reflux, 1.5 h (100%).*

This reaction outlined above would constitute an interesting option to access ester **260** directly from mono-bromide **242** (**Scheme 105**).

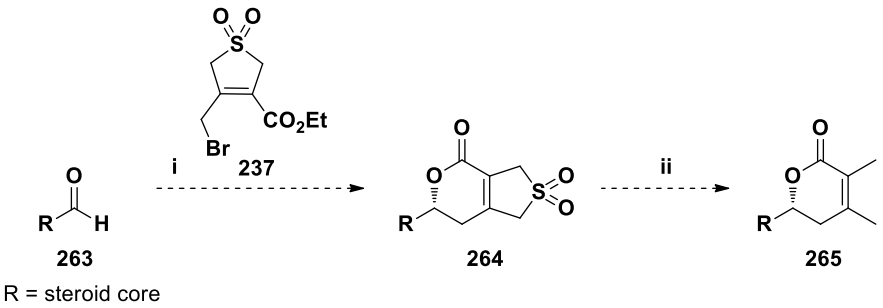


242 **260**

Scheme 105. Synthesis of ester **260** from allyl-bromide **242**.

Suggested reagents and conditions: ***i****. Zn, CuCl, 1,2-dibromoethane,* $ClCO_2Et$*,* THF/Et_2O*, reflux, 1.5 h.*

With bromoester **237** in hand, a range of different aldehydes **263** including the model system aldehyde **118** synthesised in **Chapter 2**, could be submitted to the standard Dreiding-Schmidt reaction conditions to form the corresponding heterocyclic δ-lactones **264**. In turn, the sulfone moitey of compound **264** could be reduced using standard Raney nickel conditions to allow the formation of the desired δ-lactone **265** (**Scheme 106**).



Scheme 106. Synthesis of δ-lactone **265** *via* the Dreiding-Schmidt reaction using bromoester **237**.

Suggested reagents and conditions: ***i****. Zn-Ag/graphite, THF, 0 °C;* ***ii****. Raney nickel.*

From this screening of conditions on model steroid systems, optimum reaction conditions could be developed and implemented in the total synthesis of 14,17-dideoxy-17-*epi*-withanolide F (**24**) in order to improve the yield of the δ-lactone side chain construction as described in **Scheme 85**.

Another focus of the project in the future could involve variations of the side chain, in particular the substitution of the δ-lactone by other heterocycles. Lactams, carbamates, cyclic ethers and amines are options, as well as variation of the ring size to construct the corresponding γ-lactone or ε-lactone (**Figure 23**).

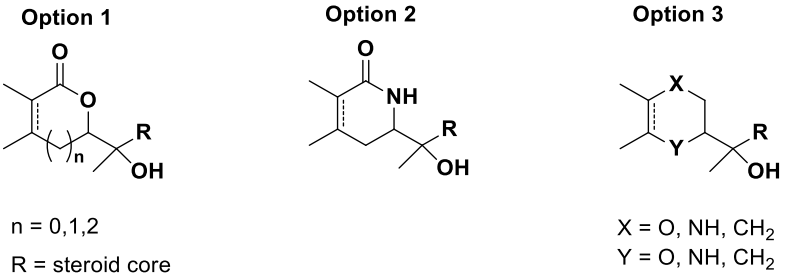


Figure 24. Variation of the δ-lactone side chain.

Variation of the side chains would give the opportunity to expand the library of analogues of withanolide F (**1**) and allow a better understanding of their possible biological activities.

Chapter 6. Experimental

6.1. General Experimental Procedures

NMR spectra were recorded on a Jeol ECX 400 instrument (^{1}H: 400 MHz and ^{13}C: 100 MHz) at the University of York and on a Bruker DPX 400 (^{1}H: 400 MHz and ^{13}C: 100 MHz) or a Bruker DRX 500 (^{1}H: 500 MHz and ^{13}C: 125 MHz) spectrometer at AnalytiCon Discovery GmbH, and measured at rt. Chemical shifts are quoted in ppm, they are calibrated to the residual non-deuterated solvent peak (^{1}H, $CHCl_3$: δ = 7.25 ppm, MeOH: δ = 3.31 ppm; ^{13}C, $CHCl_3$: δ = 77.0 ppm, MeOH: δ = 49.0 ppm) and are reported as follows: chemical shift δ/ppm (number of protons, multiplicity, coupling constant *J*/Hz, assignment) [br, broad; s, singlet; d, doublet; t, triplet; m, multiplet]. Coupling constants, *J*, are reported to the nearest 0.1 Hz. Structural assignments were verified by COSY, NOESY, HMBC and HSQC spectroscopy where necessary. The numbering of compounds is for characterisation purposes and, while it conforms to IUPAC where possible, it may vary from the numbering in the compound name. Infra-red spectra were recorded neat on a ThermoNicolet IR-100 spectrometer. Spectra were analysed as thin films on NaCl plates dispersed from $CDCl_3$. Only structurally important absorptions are quoted. Absorption maxima (υ_{max}) are quoted in wavenumbers (cm^{-1}). Optical rotations were determined using a JASCO DIP-370 Digital polarimeter using a sodium lamp at a wavelength of 589 nm and are quoted in units of 10^{-1} deg cm^2 g^{-1}. Concentrations are quoted in g/100 mL. Mass-spectra (low and high resolution) were obtained by the University of York Mass Spectrometry Service, using electrospray ionization (ESI) on a Bruker Daltonics, Micro-tof spectrometer. Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. Thin layer chromatography (TLC) was performed on aluminium plates coated with Merck Silica gel 60 F_{254}, and visualisation was achieved by UV light (λ_{max} = 254 nm) and/or by staining with anisaldehyde or potassium permanganate. Flash column chromatography was carried out using Fluka flash silica gel 60 using head pressure by means of bellows and the specified eluent. Petroleum ether (PE) refers to the fraction boiling in the range 40-60 °C. When required, diethyl ether, THF, CH_2Cl_2, acetonitrile and toluene were obtained dry from an Innovative Technology Inc. PureSolv Purification System. Degassed solvent refers to solvent

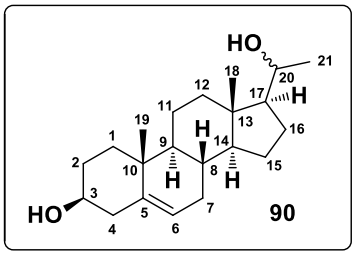
which has been purged with argon for at least 2 h. All reactions were carried out in oven-dried glassware and under an inert atmosphere of argon unless stated otherwise. All commercially available reagents and solvents were used as supplied unless stated otherwise.

The literature reference above the compound titles corresponds to known procedures either from the identical substrate or as a general procedure. The literature references corresponding to the data are included within the text.

6.2. Experimental Procedures

6.2.1 Chapter 2. Synthesis of the key aldehyde for withanolide synthesis

20-Hydroxypregnolone (90)[29]

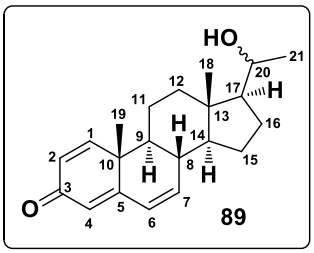


$NaBH_4$ (130 mg, 3.30 mmol, 1.0 eq.) was added over 5 min to a solution of pregnenolone (**36**) (1.00 g, 3.20 mmol, 1.0 eq.) in MeOH (10 mL) and THF (6 mL) at 0 °C. After 50 min, the reaction mixture was carefully quenched with water (10 mL) and adjusted to pH 2 with 1 M aq. HCl. The mixture was then extracted with CH_2Cl_2 (20 mL). The organic fraction was dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo* to give the title compound **90** (1.12 g, 3.51 mol, 100%) as a white foam and as an inseparable mixture of two diastereoisomers at C-20 in a 4:1 ratio: **mp** 188-191 °C decomposed (Lit.[125] 184-185 °C decomposed); $\boldsymbol{R_f}$ 0.39 (1:1 heptane/EtOAc); $\boldsymbol{[\alpha]_D^{23}}$ −79.0 (*c* 1.0, $CHCl_3$) (Lit.[126] $\boldsymbol{[\alpha]_D^{20}}$ −68.5, c 0.8, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3374 (O-H stretch), 2895 (C-H stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, **MeOD**) 5.34 (1 H, br d, *J* 4.8, *H-6*), 3.67-3.59 (1 H, m, *H-20*), 3.43-3.37 (1 H, m, *H-3*), 2.27-2.15 (3 H, m, *H-4*, *H-12a*), 2.00-1.77 (3 H, m, *H-1a*, *H-2a*, *H-7a*), 1.68-1.43 (7 H, m, *H-2b, H-7b, H-8, H-11, H-16*), 1.37-1.28 (1 H, m, *H-17*), 1.24-1.14 (3 H, m, *H-12b, H-15*), 1.10 (3 H, s, *H-21*), 1.08-1.07 (1 H, m, *H-1b*), 1.04-1.03 (1 H, m, *H-14)*, 1.03 (3 H, s, *H-19*), 0.99-0.92 (1 H, m, *H-9*), 0.78 (3 H, s, *H-18*), 0.62 (3 H, s, *H-18**); $\boldsymbol{\delta_C}$ (**125 MHz**, **MeOD**) 142.8 (*C-5*), 122.2 (*C-6*), 72.1 (*C-3*), 70.5 (*C-20*), 59.1 (*C-17*), 58.7 (*C-8*), 57.5 (*C-14*), 51.7 (*C-9*), 43.4 (*C-13*), 42.7 (*C-4*), 40.4 (*C-12*), 38.4

(*C-1*), 37.2 (*C-10*), 32.8 (*C-7*), 31.9 (*C-2*), 26.0 (*C-16*), 26.0 (*C-15*), 23.5 (*C-21*), 21.7 (*C-11*), 19.6 (*C-19*), 12.2 (*C-18*); **m/z** (**ESI**) 341 $[MNa]^+$. Calcd. for $C_{21}H_{34}NaO_2$: 341.2451. Found: $[MNa]^+$, 341.2462 (−3.3 ppm error). *: signal of minor diastereoisomer. Data consistent with those previously reported in the literature.[127]

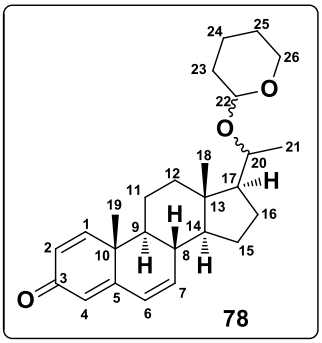
Lab. Book: ***LNB0084-001-01***.

20-Hydroxypregna-1,4,6-trien-3-one (89)[29]



A solution of diol **90** (202 mg, 0.634 mmol, 1.0 eq.) and DDQ (475 mg, 2.09 mmol, 3.3 eq.) in 1,4-dioxane (7 mL) was stirred at reflux temperature for 8 h. The reaction mixture was cooled to room temperature, filtered through Celite® and washed with CH_2Cl_2 (15 mL). The filtrate was concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (6:4 to 3:7 heptane/EtOAc) to afford the title compound **89** (75.0 mg, 0.240 mmol, 38%) as a yellow solid and as an inseparable mixture of two diastereoisomers at C-20 in a 9:1 ratio: **mp** 129-132 °C decomposed (Lit.[29] 131-134 °C decomposed); $\boldsymbol{R_f}$ 0.27 (1:1 heptane/EtOAc); $\boldsymbol{[\alpha]_D^{23}}$ −21.0 (*c* 0.1, $CHCl_3$) (Lit.[128] $\boldsymbol{[\alpha]_D^{20}}$ −19.6, *c* 0.5, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 2932 (O-H stretch), 1646 (C=O stretch), 1598 (C=C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, **MeOD**) 7.08 (1 H, d, *J* 10.2, *H-1*), 6.25 (1 H, br d, *J* 10.2, *H-2*), 6.23 (1 H, dd, *J* 10.0, 2.7, *H-6*), 6.03 (1 H, br d, *J* 10.0, *H-7*), 6.00 (1 H, br s, *H*-4), 3.78-3.73 (1 H, m, *H-20*), 2.30 (1 H, dd, *J* 10.3, 10.2, *H-8*), 2.21 (1 H, ddd, *J* 13.0, 3.4, 3.2, *H-12a*), 1.86-1.62 (4 H, m, *H-11*, *H-16*), 1.49-1.43 (1 H, m, *H-9*), 1.40-1.23 (5 H, m, *H-12b*, *H-14*, *H-15*, *H-17*), 1.20 (3 H, s, *H-19*), 1.16 (3 H, d, *J* 6.1, *H-21*), 0.88 (3 H, s, *H-18*), 0.76 (3 H, s, *H-18**); $\boldsymbol{\delta_C}$ (**125 MHz**, **MeOD**) 187.2 (*C-3*), 162.7 (*C-5*), 152.7 (*C-1*), 138.4 (*C-7*), 127.6 (*C-2*), 125.6 (*C-6*), 123.7 (*C-4)*, 70.2 (*C-20*), 57.9 (*C-17*), 53.2 (*C-14*), 48.3 (*C-9*), 42.5 (*C-13*), 41.2 (*C-10*), 39.4 (*C-12*), 37.8 (*C-8*), 26.0 (*C-16*), 25.8 (*C-15*), 23.7 (*C-21*), 21.6 (*C-11*), 20.7 (*C-19*), 12.2 (*C-18*); **m/z** (**ESI**) 313 $[MH]^+$. Calcd. for $C_{21}H_{29}O_2$: 313.2162. Found: $[MH]^+$, 313.2156 (2.1 ppm error). *: signal of minor diastereoisomer. Data consistent with those previously reported in the literature.[29] **Lab. Book**: ***LNB0084-019-08***.

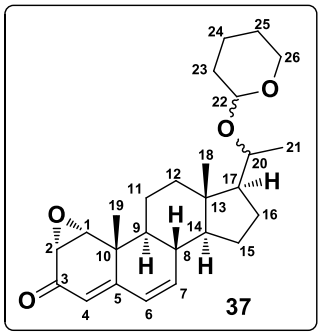
20-Tetrahydropyranyloxypregna-1,4,6-trien-3-one (78)[29]



A solution of hydroxy trienone **89** (156 mg, 0.499 mmol, 1.0 eq.), dihydropyran (0.123 mL, 1.45 mmol, 2.9 eq.) and *p*-TsOH (1.00 mg, 0.007 mmol, 0.013 eq.) in CH_2Cl_2 (4 mL) was stirred at room temperature for 3 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (10 mL). The aqueous layer was back extracted with CH_2Cl_2 (10 mL), the combined organic extracts were dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo* to give the title compound **78** (170 mg, 0.430 mmol, 86%) as a white solid and as an inseparable mixture of four diastereoisomers at C-20 and C-22: $\boldsymbol{R_f}$ 0.62 (1:1 heptane/EtOAc + 1.5% Et_3N); $\boldsymbol{\delta_H}$ (**400 MHz**, **MeOD**) 7.29 (1 H, dd, *J* 5.2, 5.2, *H-1*), 6.30 (1 H, br d, *J* 9.6, *H-6*), 6.21 (1 H, dd, *J* 5.2, 5.2, *H-2*), 6.14 (1 H, d, *J* 9.6, *H-7*), 5.98 (1 H, br s, *H-4*), 4.48 (1 H, dd, *J* 3.5, 3.4, *H-22*), 3.88-3.82 (1 H, m, *H-26a*), 3.73-3.64 (1 H, m, *H-20*), 3.55-3.49 (1 H, m, *H-26b*), 2.42-2.34 (1 H, m, *H-8*), 2.26 (1 H, ddd, *J* 12.9, 3.4, 3.2, *H-12a*), 1.88-1.39 (13 H, m, *H-9*, *H-11*, *H-15*, *H-16*, *H-23*, *H-24*, *H-25*), 1.37-1.31 (1 H, m, *H-17*), 1.31-1.25 (2 H, m, *H-12b*, *H-14*), 1.23 (3 H, s, *H-19*), 1.11 (3 H, d, *J* 6.1, *H-21*), 0.91 (3 H, s, *H-18*), 0.84 (3 H, s, *H-18*)*; $\boldsymbol{\delta_C}$ (**125 MHz**, **MeOD**) 187.5 (*C-3*), 165.5 (*C-5*), 155.3 (*C-1*), 140.5 (*C-7*), 127.0 (*C-2*), 126.9 (*C-6*), 122.5 (*C-4),* 100.2 (*C-22),* 69.5 (*C-20*), 61.8 (*C-26*), 58.0 (*C-17*), 53.9 (*C-14*), 49.0 (*C-9*), 43.0 (*C-13*), 41.6 (*C-10*), 39.2 (*C-12*), 38.4 (*C-8*), 30.6 (*C-16*), 30.0 (*C-23*), 25.0 (*C-25*), 25.0 (*C-15*), 25.0 (*C-11*), 22.9 (*C-21*), 19.9 (*C-19*), 19.5 (*C-24*), 11.2 (*C-18*); **m/z** (**ESI**) 397 $[MH]^+$. Calcd. for $C_{26}H_{37}O_2$: 397.2737. Found: $[MH]^+$, 397.2733 (1.1 ppm error). *: signal of one of the minor diastereoisomers. Data consistent with those previously reported in the literature.[29]

Lab. Book: ***LNB0084-013-01***.

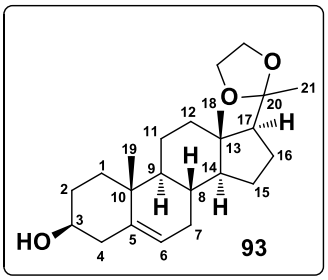
1α,2α-Epoxy-20-tetrahydropyranyloxypregna-4,6-dien-3-one (37)[29]



To a solution of trienone **78** (170 mg, 0.400 mmol, 1.0 eq.) in MeOH (4 mL) containing 10% NaOH in MeOH (0.050 mL, cat.) was added hydrogen peroxide (30% w/w, 0.320 mL, 0.010 mol, 25.0 eq.) at 0 °C. The reaction mixture was stirred 12 h at 15 °C. The resulting solution was diluted with Et_2O (10 mL) and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (9:1 heptane/EtOAc) to afford the title compound **37** (50.0 mg, 0.121 mmol, 30%) as a white solid and as a mixture of four diastereoisomers at C-20 and C-22: $\boldsymbol{R_f}$ 0.68 (1:1 heptane/EtOAc + 1.5% Et_3N); $\boldsymbol{\delta_H}$ (**400 MHz**, **MeOD**) 6.17-6.12 (2 H, m, *H-6*, *H-7*), 5.61 (1 H, br s, *H-4*), 4.66-4.64 (1 H, m, *H-22*), 3.96-3.93 (1 H, m, *H-26a*), 3.86-3.84 (1 H, m, *H-20*), 3.70 (1 H, d, *J* 4.3, *H-1*), 3.51-3.48 (1 H, m, *H-26b*), 3.38 (1 H, dd, *J* 4.3, 2.0, *H-2*), 2.32 (1 H, dd, *J* 10.8, 10.6, *H-8*), 2.19 (1 H, ddd, *J* 13.3, 3.1, 3.2, *H-12a*), 1.86-1.27 (16 H, m, *H-9*, *H-11*, *H-12b*, *H-14*, *H-15*, *H-16*, *H-17*, *H-23*, *H-24*, *H-25*), 1.21 (3 H, s, *H-19*), 1.08 (3 H, d, *J* 5.9, *H-21*), 0.90 (3 H, s, *H-18*), 0.83 (3 H, s, *H-18**); $\boldsymbol{\delta_C}$ (**125 MHz**, **MeOD**) 197.0 (*C-3*), 162.1 (*C-5*), 142.0 (*C-7*), 128.1 (*C-6*), 119.7 (*C-4*), 102.3 (*C-22*), 73.7 (*C-20*), 64.2 (*C-26*), 60.3 (*C-1*), 57.8 (*C-17*), 55.3 (*C-2*), 54.2 (*C-14*), 47.6 (*C-9*), 43.9 (*C-13*), 40.4 (*C-12*), 39.7 (*C-10*), 38.6 (*C-8*), 32.6 (*C-16*), 32.5 (*C-23*), 26.5 (*C-25*), 26.5 (*C-15*), 22.0 (*C-21*), 21.8 (*C-11*), 21.0 (*C-24*), 18.7 (*C-19*), 12.7 (*C-18**), 11.7 (*C-18*); **m/z** (**ESI**) 413 $[MH]^+$. Calcd. for $C_{26}H_{37}O_4$: 413.2686. Found: $[MH]^+$, 413.2687 (−0.1 ppm error). *: signal of one of the minor diastereoisomers. Data consistent with those previously reported in the literature.[29]

Lab. Book: ***LNB0084-014-02***.

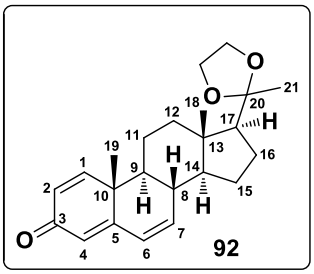
3β-Hydroxy-20,20-ethylenedioxypregn-5-ene (93)



To a solution of pregnenolone (**36**) (10.0 g, 0.032 mol, 1.0 eq.) in toluene (130 mL) were added ethylene glycol (8.80 mL, 0.160 mol, 5.0 eq.) and *p*-TsOH (42.6 mg, 0.224 mmol, cat.) and the resulting mixture was stirred 12 h at 135 °C. The reaction mixture was quenched with sat. aq. $NaHCO_3$ (100 mL) and extracted with EtOAc (100 mL). A white solid precipitated in the extraction funnel and was filtered afterwards on a Büchner funnel; it was a part of the title compound **93** which was stored in a separate flask. The organic layer was washed with H_2O (60 mL) and brine (60 mL). The aqueous phase was back extracted with EtOAc (60 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo* to give the title compound **93** (10.3 g, 0.029 mol, 90%) as a white powder which required no further purification: **mp** 164-165 °C decomposed (Lit.[129] 163-166 °C decomposed); $\boldsymbol{R_f}$ 0.45 (1:1 heptane/EtOAc + 1.5% NEt_3); $\boldsymbol{[\alpha]_D^{23}}$ −43.9 (*c* 1.0, $CHCl_3$) (Lit.[129] $\boldsymbol{[\alpha]_D^{26}}$ −39.0, *c* 0.5, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3241 (O-H stretch), 2887 (C-H stretch), 1633 (C=O stretch), 1037 (C-O-C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, **MeOD**) 5.34 (1 H, br d, *J* 5.0, *H-6*), 3.98-3.82 (4 H, m, *H-22*, *H-23*), 3.41-3.35 (1 H, m, *H-3*), 2.25-2.16 (2 H, m, *H-4*), 2.08 (1 H, ddd, *J* 12.8, 3.2, 3.1, *H-12a*), 1.98-1.95 (1 H, m, *H-7a*), 1.85-1.78 (1 H, m, *H-1a*), 1.78-1.69 (4 H, m, *H-8, H-11, H-17*), 1.64-1.61 (1 H, m, *H-16a),* 1.57-1.44 (5 H, m, *H-7b, H-2, H-15*), 1.26 (3 H, s, *H-21*), 1.22-1.19 (2 H, m, *H-12b, H-16b*), 1.09-1.06 (1 H, m, *H-1b*), 1.02-1.01 (1 H, m, *H-14*), 1.01 (3 H, s, *H-19*), 0.96-0.91 (1 H, m, *H-9*), 0.79 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**125 MHz**, **MeOD**) 142.5 (*C-5*), 122.6 (*C-6*), 112.8 (*C-20*), 72.3 (*C-3*), 65.9 (*C-23*), 63.9 (*C-22*), 59.4 (*C-17),* 58.0 (*C-14*), 51.6 (*C-9*), 42.8 (*C-4*), 42.6 (*C-13*), 40.6 (*C-12*), 38.3 (*C-1*), 37.4 (*C-10*), 32.7 (*C-7*), 32.3 (*C-2*), 31.9 (*C-8*), 24.6 (*C-21*), 24.5 (*C-16*), 23.8 (*C-11*), 21.5 (*C-15*), 19.7 (*C-19*), 13.3 (*C-18*); **m/z** (**ESI**) 361 $[MH]^+$. Calcd. for $C_{23}H_{37}O_3$: 361.2737. Found: $[MH]^+$, 361.2740 (−0.8 ppm error). Data consistent with those previously reported in the literature.[128]

Lab. Book: ***LNB0107-008-11***.

20,20-Ethylenedioxypregn-1,4,6-trien-3-one (92)



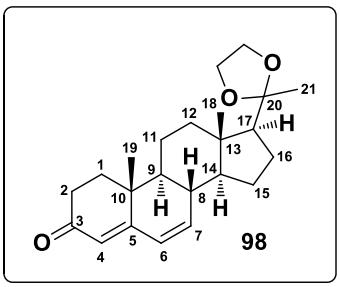
DDQ procedure:[29] A solution of ketal **93** (50.0 mg, 0.139 mmol, 1.0 eq.) and DDQ (110 mg, 0.485 mmol, 3.5 eq.) in 1,4-dioxane (3 mL) was stirred at 115 °C for 8 h. The reaction mixture was cooled to room temperature, filtered through Celite® and washed with EtOAc (15mL). The filtrate was concentrated to dryness *in vacuo*. The crude mixture was purified by column chromatography on silica gel (7:3 heptane/EtOAc + 7.5% NEt_3) to afford the title compound **92** (20.7 mg, 0.058 mmol, 42%) as a yellow solid.

Lab. Book: ***LNB0084-029-02***.

$Pd(OAc)_2$ procedure:[46] To a solution of $Pd(OAc)_2$ (405 mg, 1.80 mmol, 0.1 eq.) and ADP (28.3 mL, 0.159 mol, 8.8 eq.) stirred beforehand in DMF (12 mL) at room temperature for 30 min was added Na_2CO_3 (20.1 g, 0.189 mol, 10.5 eq.) and ketal **93** (6.50 g, 0.018 mol, 1.0 eq.) in DMF (13 mL) and the reaction mixture was stirred for 72 h at 160 °C under argon atmosphere. The resulting mixture was cooled to room temperature, diluted with EtOAc (50 mL) and concentrated *in vacuo*. The crude residue was dissolved in EtOAc (300 mL). A 100 mL portion of this solution was diluted with EtOAc (350 mL) and washed three times with ice-cold water (150 mL). This procedure was repeated three times (one time for each third of the crude). All the combined organic extracts were dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (9:1 to 6:4 heptane/EtOAc + 7.5% NEt_3) to afford the title compound **92** (3.95 g, 0.011 mol, 62%) as a yellow solid: **mp** 164-165 °C decomposed (Lit.[128] 162-163 °C decomposed); $\boldsymbol{R_f}$ 0.57 (1:1 heptane/EtOAc + 1.5% NEt_3); $\boldsymbol{[\alpha]_D^{23}}$ 11.9 (*c* 1.0, $CHCl_3$) (Lit.[128] $\boldsymbol{[\alpha]_D^{20}}$ 13.6, *c* 0.5, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 2921 (C-H stretch), 1651 (C=O stretch), 1599 (C=C stretch), 1049 (C-O-C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, **MeOD**) 7.29 (1 H, d, *J* 10.3, *H-1*), 6.31 (1 H, br d, *J* 9.8, *H-6*), 6.22 (1 H, br d, *J* 10.3, *H-2*), 6.16 (1 H, d, *J* 9.8, *H-7*), 5.98 (1 H, br s, *H-4*), 4.01-3.82 (4 H, m, *H-22*, *H-23*), 2.36 (1 H, dd, *J* 10.7, 10.1, *H-8*), 2.16 (1 H, ddd, *J* 13.0, 3.2, 3.1, *H-12a*), 1.87-1.67 (6 H, m, *H-11*, *H-15a*, *H-16*, *H-17*), 1.45-1.33 (2 H, m, *H-9*, *H-15b*), 1.27 (3 H, s, *H-19*), 1.24-1.23 (2 H, m, *H-12b*,

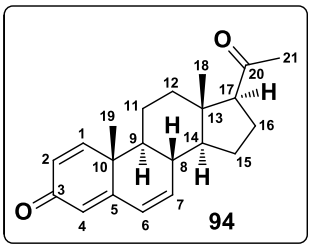
H-14), 1.23 (3 H, s, *H-21*), 0.91 (3 H, s, *H-18*); **δ_C** (**125 MHz**, **MeOD**) 188.2 (*C-3*), 166.2 (*C-5*), 156.1 (*C-1*), 140.9 (*C-7*), 127.9 (*C-6*), 127.7 (*C-2*), 123.3 (*C-4)*, 112.5 (*C-20*), 65.6 (*C-23*), 63.7 (*C-22*), 59.1 (*C-17*), 54.7 (*C-14*), 49.8 (*C-9*), 43.1 (*C-13*), 43.0 (*C-10*), 40.2 (*C-12*), 38.8 (*C-8*), 24.4 (*C-19*), 23.8 (*C-15*), 23.2 (*C-16*), 21.5 (*C-11*), 20.6 (*C-21*), 13.0 (*C-18*); **m/z** (**ESI**) 355 $[MH]^+$. Calcd. for $C_{23}H_{31}O_3$: 355.2268. Found: $[MH]^+$, 355.2263 (1.2 ppm error). Data consistent with those previously reported in the literature.[128]

Lab. Book: ***LNB0107-033-08***.



Also isolated was 20,20-ethylenedioxypregna-4,6-dien-3-one (**98**) (475 mg, 1.33 mmol, 7%) as a yellow solid: **mp** 166-168 °C decomposed (Lit.[130] 164-166 °C decomposed); $\boldsymbol{R_f}$ 0.60 (1:1 heptane/EtOAc + 1.5% NEt_3); $\boldsymbol{[\alpha]_D^{24}}$ 57.9 (*c* 1.0, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3381 (O-H stretch), 2899 (C-H stretch), 1636 (C=O stretch), 1593 (C=C stretch), 1033 (C-O-C stretch); **δ_H** (**400 MHz**, **MeOD**) 6.24 (1 H, br d, *J* 9.8, *H-6*), 6.17 (1 H, dd, *J* 9.8, 2.5, *H-7*), 5.64 (1 H, br s , *H-4*), 4.01-3.84 (4 H, m, *H-22, H-23*), 2.67-2.59 (1 H, m, *H-2a*), 2.40-2.35 (1 H, m, *H-1a*), 2.27 (1 H, dd, *J* 10.8, 10.7, *H-8*), 2.13 (1 H, ddd, *J* 13.0, 3.2, 3.1, *H-12a*), 2.08-2.04 (1 H, m, *H-1b*), 1.89-1.77 (1 H, m, *H-17*), 1.76-1.70 (1 H, m, *H-2b*), 1.59-1.30 (5 H, m, *H-11*, *H-15*, *H-16a*), 1.27 (3 H, s, *H-21*), 1.26-1.19 (4 H, m, *H-9*, *H-12b*, *H-14*, *H-16b*), 1.14 (3 H, s, *H-19*), 0.87 (3 H, s, *H-18*); **δ_C** (**125 MHz**, **MeOD**) 202.6 (*C-3*), 167.6 (*C-5*), 143.2 (*C-6*), 128.3 (*C-7*), 123.5 (*C-4*), 112.8 (*C-20*), 65.6 (*C-23*), 63.9 (*C-22*), 58.9 (*C-17*), 54.8 (*C-14*), 54.3 (*C-10*), 52.3 (*C-9*), 43.6 (*C-13*), 40.5 (*C-12*), 38.3 (*C-8*), 34.6 (*C-1*), 34.4 (*C-2*), 24.6 (*C-21*), 24.2 (*C-16*), 24.1 (*C-15*), 21.4 (*C-11*), 16.1 (*C-19*), 13.3 (*C-18*); **m/z** (**ESI**) 357 $[MH]^+$. Calcd. for $C_{23}H_{33}O_3$: 357.2424. Found: $[MH]^+$, 357.2422 (0.5 ppm error). Data consistent with those previously reported in the literature.[130]

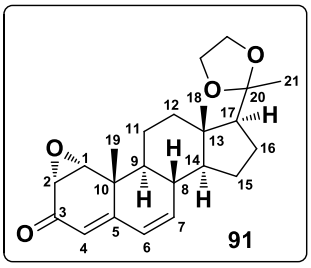
Lab. Book: ***LNB0107-033-06***.



Further elution gave pregn-1,4,6-trien-3,20-dione (**94**) (155 mg, 0.499 mmol, 3%) as an orange solid: **mp** 136-140 °C decomposed (Lit.[131] 144-146 °C decomposed); $\boldsymbol{R_f}$ 0.44 (1:1 heptane/EtOAc + 1.5% NEt_3); $\mathbf{[\alpha]_D^{23}}$ 45.2 (*c* 1.0, $CHCl_3$); $\mathbf{\upsilon_{max}/cm^{-1}}$ (neat) 2937 (C-H stretch), 1701 (C=O stretch), 1651 (C=O stretch), 1602 (C=C stretch); $\mathbf{\delta_H}$ (**400 MHz**, **MeOD**) 7.29 (1 H, d, *J* 10.1, *H-1*), 6.32 (1 H, dd, *J* 9.8, 2.4, *H-6*), 6.23 (1 H, br d, *J* 10.1, *H-2*), 6.14 (1 H, d, *J* 9.8, *H-7*), 5.99 (1 H, br s, *H-4*), 2.66 (1 H, t, *J* 9.2, *H-17*), 2.38-2.33 (1 H, dd, *J* 10.5, 10.1, *H-8*), 2.21-2.19 (1 H, m, *H-12a*), 2.16-2.14 (1 H, m, *H-12b*), 2.12 (3 H, s, *H-21*), 1.95-1.85 (4 H, m, *H-11*, *H-15a*, *H-16a*), 1.57-1.43 (3 H, m, *H-9*, *H-14*, *H-15b*), 1.24-1.23 (1 H, m, *H-16b*), 1.23 (3 H, s, *H-19*), 0.74 (3 H, s, *H-18*); $\mathbf{\delta_C}$ (**125 MHz**, **MeOD**) 211.8 (*C-20*), 188.6 (*C-3*), 166.3 (*C-5*), 156.3 (*C-1*), 140.4 (*C-7*), 128.6 (*C-6*), 128.3 (*C-2*), 124.0 (*C-4*), 64.1 (*C-17*), 55.0 (*C-14*), 49.9 (*C-9*), 45.4 (*C-13*), 43.0 (*C-10*), 39.6 (*C-8*), 39.5 (*C-12*), 31.6 (*C-21*), 23.8 (*C-15*), 23.0 (*C-16*), 21.2 (*C-11*), 20.9 (*C-19*), 13.6 (*C-18*); **m/z** (**ESI**) 311 $[MH]^+$. Calcd. for $C_{21}H_{27}O_2$: 311.2006. Found: $[MH]^+$, 311.2009 (−1.0 ppm error). Data consistent with those previously reported in the literature.[132]

Lab. Book: ***LNB0107-011-06***.

1α,2α-Epoxy-20,20-ethylenedioxypregna-4,6-dien-3-one (91)[29]

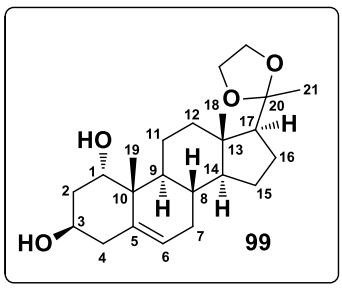


To a solution of trienone **92** (53.0 mg, 0.150 mmol, 1.0 eq.) in ^{i}PrOH (4 mL) containing 10% NaOH in MeOH (0.03 mL, cat.) was added hydrogen peroxide (30% w/w, 0.180 mL, 5.98 mmol, 40.0 eq.) at 0 °C. The resulting mixture was stirred overnight allowing to reach room temperature. The reaction mixture was diluted with Et_2O (10 mL), quenched with brine (10 mL) and the organic layer was washed with H_2O (2 × 10 mL). The combined

organic extracts were dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (9:1 heptane/EtOAc + 7.5% NEt_3) to afford the title compound **91** (40.0 mg, 0.108 mmol, 72%) as a white solid: **mp** 140-141 °C decomposed (Lit.[128] 137-138 °C decomposed); $\boldsymbol{R_f}$ 0.37 (1:1 heptane/EtOAc + 1.5% NEt_3); $\boldsymbol{[\alpha]_D^{23}}$ 212.2 (*c* 1.0, $CHCl_3$) (Lit.[128] $\boldsymbol{[\alpha]_D^{20}}$ 233.6, *c* 0.5, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3346 (O-H stretch), 2888 (C-H stretch), 1633 (C=O stretch), 1592 (C=C stretch), 1031 (C-O-C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, **MeOD**) 6.18-6.13 (2 H, m, *H-7*, *H-6*), 5.61 (1 H, br s, *H-4*), 4.01-3.83 (4 H, m, *H-22*, *H-23)*, 3.69 (1 H, br d, *J* 4.1, *H-1*), 3.37 (1 H, dd, *J* 4.1, 1.9, *H-2*), 2.34-2.30 (1 H, m, *H-8*), 2.19 (1 H, ddd, *J* 13.0, 3.1, 3.0, *H-12*), 1.89-1.70 (5 H, m, *H-11*, *H-16*, *H-17*), 1.62-1.57 (1 H, m, *H-9*), 1.40-1.31 (3 H, m, *H-12*, *H-15*), 1.29-1.28 (1 H, m, *H-14*), 1.28 (3 H, s, *H-21*), 1.20 (3 H, s, *H-19*), 0.90 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**125 MHz**, **MeOD**) 196.8 (*C-3*), 161.7 (*C-5*), 142.0 (*C-7*), 128.6 (*C-6*), 119.8 (*C-4*), 111.5 (*C-20*), 65.8 (*C-23*), 64.1 (*C-22*), 60.4 (*C-1*), 59.1 (*C-17*), 55.6 (*C-2*), 54.6 (*C-14*), 47.8 (*C-9*), 43.4 (*C-13*), 40.4 (*C-12*), 40.0 (*C-10*), 38.3 (*C-8*), 24.6 (*C-15*), 24.5 (*C-21*), 24.2 (*C-16*), 22.1 (*C-11*), 18.7 (*C-19*), 13.1 (*C-18*); **m/z** (**ESI**) 371 $[MH]^+$. Calcd. for $C_{23}H_{31}O_4$: 371.2217. Found: $[MH]^+$, 371.2213 (1.2 ppm error). X-Ray crystallography: CCDC 983154 contains the supplementary crystallographic data for this compound, see **Appendix I**. Crystals were grown by slow evaporation of EtOAc. Data consistent with those previously reported in the literature.[128]

Lab. Book: ***LNB0107-022-02***.

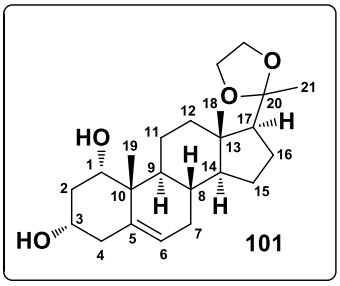
<u>1α,3β-dihydroxyl-20,20-ethylenedioxypregn-5-ene (99)</u>[29]



In a three-necked flask, argon was swept through the system for 15 min and NH_3 (95 mL) was trapped in the flask at −78 °C. Lithium ribbons (1.62 g, 0.234 mol, 89.9 eq.) were cut into short pieces and slowly added: the reaction mixture became instantly dark blue. After 1 h, a solution of epoxide **91** (0.970 g, 2.62 mmol, 1.0 eq.) in THF (95 mL) was added dropwise over 20 min. The reaction was cooled at −40 °C and stirred for 20 min. NH_4Cl

(28.0 g, 0.524 mol, 200 eq.) was added portionwise over 1 h at reflux temperature (external temperature between −20 °C and −10 °C): the reaction mixture became white and pasty. Most of the NH_3 was removed in a stream of argon. The residue was diluted with Et_2O (100 mL) and washed with brine (2 × 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (1:1 to 4:6 heptane/EtOAc + 7.5% NEt_3) to afford the title compound **99** (745 mg, 1.98 mmol, 76%) as a white solid: **mp** 201-205 °C decomposed (Lit.[128] 203-207 °C decomposed); $\boldsymbol{R_f}$ 0.20 (1:1 heptane/EtOAc + 1.5% NEt_3); $\boldsymbol{[\alpha]_D^{23}}$ −49.2 (*c* 1.0, $CHCl_3$) (Lit.[128] $\boldsymbol{[\alpha]_D^{20}}$ −47.0, *c* 0.5, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3380 (O-H stretch), 2929 (C-H stretch), 2894 (C-H stretch), 1046 (C-O-C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, **MeOD**) 5.48 (1 H, br d, *J* 5.5, *H-6*), 4.03-3.81 (5 H, m, *H-3, H-22, H-23*), 3.79 (1 H, br s, *H-1*), 2.32-2.21 (2 H, m, *H-4*), 2.09-1.92 (4 H, m, *H-2a*, *H-7*, *H-12a*), 1.81-1.43 (9 H, m, *H-2b, H-8, H-9*, *H-11*, *H-15, H-16a, H-17*), 1.28 (3 H, s, *H-21*), 1.23-1.04 (3 H, m, *H-12b*, *H-14, H-16b*), 1.00 (3 H, s, *H-19*), 0.79 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**125 MHz**, **MeOD**) 138.0 (*C-5*), 124.2 (*C-6*), 111.9 (*C-20*), 72.6 (*C-1*), 65.2 (*C-3*), 64.9 (*C-23*), 63.0 (*C-22*), 59.2 (*C-17*), 57.0 (*C-14*), 43.6 (*C-10*), 42.5 (*C-13*), 41.9 (*C-9*), 41.3 (*C-4*), 40.4 (*C-12*), 38.5 (*C-2*), 32.6 (*C-7*), 32.5 (*C-8*), 24.9 (*C-21*), 24.8 (*C-15*), 23.1(*C-16*), 20.5 (*C-11*), 19.0 (*C-19*), 12.4 (*C-18*); **m/z** (**ESI**) 399 $[MNa]^+$. Calcd. for $C_{23}H_{36}NaO_4$: 399.2506. Found: $[MNa]^+$, 399.2507 (−0.4 ppm error). Data consistent with those previously reported in the literature.[128]

Lab. Book: ***LNB0170-082-04***.

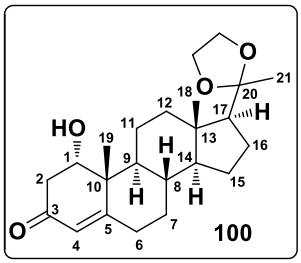


Also isolated was *1α,3α-dihydroxyl-20,20-ethylenedioxypregn-5-ene* (**101**) (97.6 mg, 0.259 mmol, 10%) as an amorphous white solid: **mp** 147-150 °C decomposed; $\boldsymbol{R_f}$ 0.56 (6:4 PE/EtOAc + 1.5% NEt_3); $\boldsymbol{[\alpha]_D^{24}}$ 47.3 (*c* 1.0, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3249 (O-H stretch), 2928 (C-H stretch), 1055 (C-O-C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, **MeOD**) 5.54 (1 H, br d, *J* 5.3, *H-6*), 4.07-4.05 (1 H, m, *H-3*), 4.01-3.83 (4 H, m, *H-22, H-23*), 3.73 (1 H, br s, *H-1*), 2.64-2.58 (1 H, m, *H-4a*), 2.23-2.18 (1 H, m, *H-4b*), 2.10-2.05 (1 H, dt, *J* 12.7, 3.3, 3.3, *H-7a*), 2.02-1.42 (11 H, m, *H-2, H-7b, H-8, H-9*, *H-11*, *H-15*, *H-16a*, *H-17*), 1.27 (3 H, s, *H-21*),

1.23-1.06 (4 H, m, *H-12, H-14, H-16b*), 0.99 (3 H, s, *H-19*), 0.80 (3 H, s, *H-18*); **δ_C** (**125 MHz**, **MeOD**) 135.7 (*C-5*), 125.5 (*C-6*), 111.8 (*C-20*), 73.2 (*C-1*), 68.1 (*C-3*), 64.8 (*C-23*), 62.9 (*C-22*), 58.2 (*C-17*), 56.7 (*C-14*), 42.6 (*C-10*), 41.6 (*C-13*), 41.4 (*C-9*), 39.2 (*C-4*), 39.0 (*C-12*), 32.7 (*C-2*), 31.7 (*C-7*), 31.6 (*C-8*), 24.0 (*C-15*), 23.6 (*C-21*), 23.0 (*C-16*), 20.5 (*C-11*), 18.3 (*C-19*), 12.1 (*C-18*); **m/z** (**ESI**) 399 $[MNa]^+$. Calcd. for $C_{23}H_{36}NaO_4$: 399.2506. Found: $[MNa]^+$, 399.2499 (1.6 ppm error).

Lab. Book: ***LNB0170-078-03***.

<u>20,20-Ethylenedioxy-1α-hydroxy-4-pregnen-3-one (100)</u>

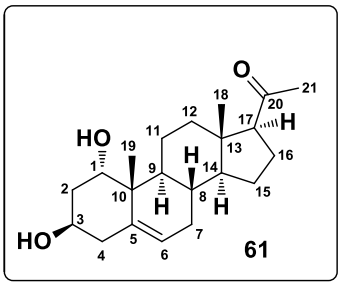


In a three-necked flask, argon was swept through the system for 15 min and NH_3 (5 mL) was trapped in the flask at −78 °C. Lithium ribbons (77.5 mg, 11.2 mmol, 89.3 eq.) were cut into short pieces and slowly added: the reaction mixture became instantly dark blue. After 1 h, a solution of epoxide **91** (46.3 mg, 0.125 mmol, 1.0 eq.) in THF (5 mL) was added dropwise over 20 min. The reaction was cooled at −40 °C and stirred for 20 min. The reaction was cooled back at −78 °C and NH_4Cl (0.775 g, 0.014 mol, 116 eq.) was added portionwise over 1 h: the reaction mixture became white and pasty. Most of the NH_3 was removed in a stream of argon. The residue was diluted with Et_2O (10 mL) and washed with brine (2 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (1:1 to 4:6 heptane/EtOAc + 7.5% NEt_3) to afford the *title compound* **100** (26.1 mg, 0.07 mmol, 56%) as a white solid: **mp** 222-223 °C decomposed; $\boldsymbol{R_f}$ 0.41 (1:1 heptane/EtOAc + 1.5% NEt_3); $\mathbf{[\alpha]_D^{24}}$ 30.1 (*c* 0.93, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3380 (O-H stretch), 2924 (C-H stretch), 1672 (C=O stretch), 1052 (C-O-C stretch); **δ_H** (**400 MHz**, **MeOD**) 5.70 (1 H, br s, *H-4*), 4.06-4.04 (1 H, m, *H-1*), 3.99-3.84 (4 H, m, *H-22, H-23*), 2.80 (1 H, dd, *J* 16.9, 2.5, *H-2a*), 2.46 (1 H, dd, *J* 16.9, 2.5, *H-2b*), 2.11 (1 H, d, *J* 12.5, *H-12a*), 1.84-1.45 (11 H, m, *H-6a*, *H-7*, *H-8*, *H-9*, *H-11*, *H-15a*, *H-16*, *H-17*), 1.41-1.38 (1 H, m, *H-6b*), 1.30-1.27 (2 H, m, *H-12b*, *H-15b*), 1.29 (3 H, s, *H-21*), 1.22

(3 H, s, *H-19*), 1.15-1.11 (1 H, m, *H-14*), 0.85 (3 H, s, *H-18*); **δ_C** (**125 MHz**, **MeOD**) 199.5 (*C-3*), 140.2 (*C-5*), 123.4 (*C-4*), 112.7 (*C-20*), 71.6 (*C-1*), 63.3 (*C-23*), 63.0 (*C-22*), 59.1 (*C-17*), 56.3 (*C-14*), 45.2 (*C-9*), 43.6 (*C-10*), 43.4 (*C-13*), 42.4 (*C-2*), 40.1 (*C-12*), 33.1 (*C-6*), 31.8 (*C-8*), 31.4 (*C-7*), 30.1 (*C-21*), 23.7 (*C-15*), 22.2 (*C-16*), 19.9 (*C-11*), 18.1 (*C-19*), 12.4 (*C-18*); **m/z** (**ESI**) 375 $[MH]^+$. Calcd. for $C_{23}H_{35}O_4$: 375.2530. Found: $[MH]^+$, 375.2510 (5.3 ppm error).

Lab. Book: ***LNB0084-121-02***.

1α,3β-Dihydroxy-5-pregnen-20-one (61)[52]

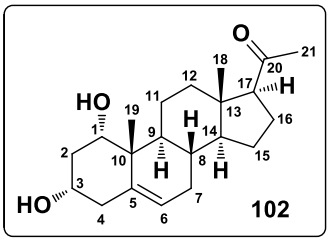


A solution of ketal **99** (65.0 mg, 0.172 mmol, 1.0 eq.) in AcOH/H_2O/THF (65:35:10, 33 mL) was stirred overnight at room temperature. The reaction mixture was diluted with EtOAc (50 mL) and slowly quenched with sat. aq. $NaHCO_3$ (20 mL). The organic phase was adjusted to pH 8 by washing with sat. aq. $NaHCO_3$. The organic extract was dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo* to give the title compound **61** (57.2 mg, 0.172 mmol, 100%) as white solid which required no further purification: **mp** 222-225 °C decomposed (Lit.[133] 232-236 °C decomposed); $\boldsymbol{R_f}$ 0.05 (1:1 heptane/EtOAc); $\boldsymbol{[\alpha]_D^{23}}$ 46.3 (*c* 1.0, $CHCl_3$) (Lit.[128] $\boldsymbol{[\alpha]_D^{20}}$ 49.2, *c* 0.16, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3337 (O-H stretch), 2894 (C-H stretch), 1671 (C=O stretch); **δ_H** (**400 MHz**, **MeOD**) 5.49 (1 H, br d, *J* 5.2, *H-6*), 3.90-3.87 (1 H, m, *H-3*), 3.80 (1 H, br s, *H-1*), 2.64 (1 H, dd, *J* 9.2, 9.1, *H-17*), 2.29-2.15 (3 H, m, *H-4, H-16a*), 2.12 (3 H, s, *H-21*), 2.03-1.21 (14 H, m, *H-2, H-7, H-8, H-9, H-11, H-12, H-14, H-15, H-16b*), 1.01 (3 H, s, *H-19*), 0.62 (3 H, s, *H-18*); **δ_C** (**125 MHz**, **MeOD**) 209.9 (*C-20*), 137.6 (*C-5*), 125.8 (*C-6*), 73.2 (*C-1*), 66.9 (*C-3*), 64.0 (*C-17*), 57.2 (*C-14*), 44.1 (*C-13*), 42.0 (*C-10*), 41.5 (*C-9*), 41.4 (*C-4*), 38.9 (*C-12*), 38.6 (*C-2*), 32.0 (*C-7*), 31.8 (*C-8*), 31.6 (*C-21*), 24.5 (*C-15*), 23.2 (*C-16*), 20.3 (*C-11*), 19.7 (*C-19*), 13.5 (*C-18*); **m/z** (**ESI**) 333 $[MH]^+$. Calcd. for $C_{21}H_{33}O_3$: 333.2424. Found: $[MH]^+$, 333.2422 (0.8 ppm error). X-Ray crystallography: CCDC 983153 contains the supplementary crystallographic data for this compound, see **Appendix I**. Crystals were

grown by slow evaporation of CH_2Cl_2. Data consistent with those previously reported in the literature.[128]

Lab. Book: ***LNB0107-018-01***.

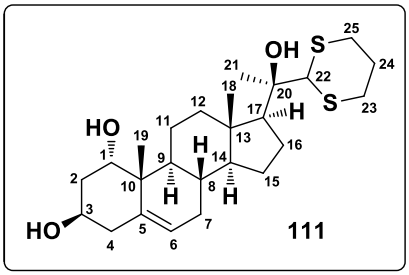
1α,3α-Dihydroxy-5-pregnen-20-one (102)



A solution of ketal **101** (50.0 mg, 0.133 mmol, 1.0 eq.) in AcOH/H_2O/THF (65:35:10) (3 mL) was stirred overnight at room temperature. The reaction mixture was diluted with EtOAc (10 mL) and slowly quenched with sat. aq. $NaHCO_3$ (10 mL). The organic phase was adjusted to pH 8 by washing with sat. aq. $NaHCO_3$. The organic extract was dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo* to give the *title compound* **102** (44.2 mg, 0.133 mmol, 100%) as a yellow solid which required no further purification: **mp** 147-150 °C decomposed; $\boldsymbol{R_f}$ 0.21 (1:1 heptane/EtOAc); $\boldsymbol{[\alpha]_D^{23}}$ 36.7 (*c* 1.0, $CHCl_3$); (Found: C, 75.67; H, 9.73; $C_{27}H_{44}O_6$ requires C, 75.86; H, 9.70%); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3317 (O-H stretch), 2925 (C-H stretch), 1706 (C=O stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, **$CDCl_3$**) 5.57 (1 H, br d, *J* 5.4, *H-6*), 4.16 (1 H, br s, *H-3*), 3.75 (1 H, br s, *H-1*), 2.64 (1 H, ddd, *J* 15.0, 4.9, 2.7, *H-4a*), 2.54 (1 H, dd, *J* 9.3, 9.0, *H-17*), 2.23-2.19 (1 H, m, *H-4b*), 2.11 (3 H, s, *H-21*), 2.06-1.88 (5 H, m, *H-2, H-7a, H-9, H-12a*), 1.72-1.33 (8 H, m, *H-7b, H-8, H-11, H-12b, H-15a, H-16)*, 1.23-1.21 (2 H, m, *H-14, H-15b)*, 0.96 (3 H, s, *H-19*), 0.61 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**100 MHz**, **$CDCl_3$**) 209.8 (*C-20*), 135.2 (*C-5*), 126.3 (*C-6*), 73.2 (*C-1*), 68.5 (*C-3*), 63.7 (*C-17*), 56.7 (*C-14*), 44.0 (*C-13*), 42.8 (*C-10*), 41.3 (*C-9*), 39.7 (*C-4*), 38.5 (*C-12*), 33.5 (*C-2*), 31.9 (*C-7*), 31.8 (*C-8*), 31.7 (*C-21*), 24.5 (*C-15)*, 22.8 (*C-16*), 19.9 (*C-11*), 19.2 (*C-19*), 13.2 (*C-18*); **m/z** (**ESI**) 355 $[MNa]^+$. Calcd. for $C_{21}H_{32}NaO_3$: 355.2244. Found: $[MNa]^+$, 355.2230 (3.9 ppm error).

Lab. Book: ***LNB0189-009-01***.

1α,3β-Dihydroxy-(20*R*)-20-hydroxydithianepregn-5-ene (111)



To a solution of 1,3-dithiane (696 mg, 5.79 mmol, 5.0 eq.) in THF (8 mL) was added ^{n}BuLi (1.6 M in hexane, 3.62 mL, 5.79 mmol, 5.0 eq.) at −5 °C under argon. To the resulting solution was added dropwise a solution of ketone **61** (385 mg, 1.16 mmol, 1.0 eq.) in THF (8 mL). The reaction mixture was stirred for 5 h at −5 °C, diluted with Et_2O (20 mL) and quenched with sat. aq. NH_4Cl (10 mL). The organic phase was adjusted to pH 7 by washing with H_2O, dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (2:8 heptane/EtOAc) to afford the *title compound* **111** (230 mg, 0.506 mmol, 44%) as a white solid as a mixture of two diastereoisomers at C-20 in a 6:1 ratio in favor of the C-20β diastereoisomer: **mp** 148-151 °C decomposed; $\boldsymbol{R_f}$ 0.11 (1:1 heptane/EtOAc + 1.5% Et_3N); $\boldsymbol{[\alpha]_D^{23}}$ −57.0 (*c* 1.0, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3338 (O-H stretch), 2890 (C-H stretch), 2856 (S-H stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, **MeOD**) 5.48 (1 H, br d, *J* 4.8, *H-6*), 4.35 (1 H, s, *H-22**), 4.19 (1 H, s, *H-22*), 3.91-3.85 (1 H, m, *H-3*), 3.78 (1 H, br s, *H-1*), 2.92-2.79 (4 H, m, *H-23, H-25*), 2.30-2.20 (2 H, m, *H-4*), 2.09-2.04 (1 H, m, *H-2a*), 1.96-1.47 (13 H, m, *H-2b, H-7, H-9, H-11, H-12a, H-15, H-16a, H-17, H-24)*, 1.40 (3 H, s, *H-21**), 1.39 (3 H, s, *H-21*), 1.24-1.03 (4 H, m, *H-8, H-12b, H-14, H-16b*), 1.00 (3 H, s, *H-19*), 0.88 (3 H, s, *H-18*), 0.83 (3 H, s, *H-18**); $\boldsymbol{\delta_C}$ (**125 MHz**, **MeOD**) 138.4 (*C-5*), 124.2 (*C-6*), 76.8 (*C-20*), 72.4 (*C-1*), 60.7 (*C-22*), 60.0 (*C-3*), 57.3 (*C-14*), 55.4 (*C-17*), 42.7 (*C-13*), 41.4 (*C-4*), 41.1 (*C-9*), 40.9 (*C-10*), 40.2 (*C-12*), 38.4 (*C-2*), 31.8 (*C-7*), 31.5 (*C-8*), 31.0 (*C-23, C-25*), 26.4 (*C-24*), 24.9 (*C-15*), 23.0 (*C-21**), 22.8 (*C-21*), 21.2 (*C-16*), 20.0 (*C-11*), 18.9 (*C-19*), 13.5 (*C-18**), 12.9 (*C-18*); **m/z** (**ESI**) 475 $[MNa]^+$. Calcd. For $C_{25}H_{40}NaO_3S_2$: 475.2311. Found: $[MNa]^+$, 475.2304 (1.6 ppm error). *: signals of the other diastereoisomer.

Lab. Book: ***LNB0170-048-01***

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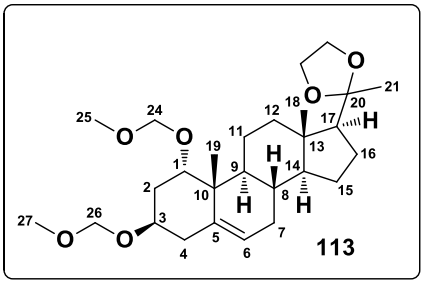
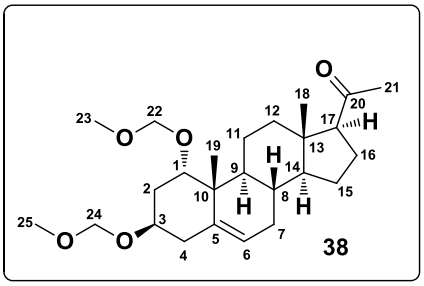
20,20-Ethylenedioxy-1α,3β-bismethoxymethylenoxypregn-5-ene (113)



To a solution of diol **99** (2.90 g, 7.70 mmol, 1.0 eq.) in 1,4-dioxane (65 mL) were added Hünig's base (10.1 mL, 0.058 mmol, 7.6 eq.) and chloromethyl methyl ether (4.30 mL, 0.057 mmol, 7.4 eq.) and the resulting mixture was stirred overnight at reflux temperature. After cooling to room temperature, the reaction mixture was diluted with EtOAc (50 mL), quenched with sat. aq. NH_4Cl (30 mL) and stirred vigorously for 5 min. The organic phase was washed with H_2O (30 mL) and brine (30 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (8:2 heptane/EtOAc + 7.5% NEt_3) to afford the *title compound* **113** (3.31 g, 7.12 mmol, 92%) as a white solid: **mp** 84-87 °C decomposed; $\boldsymbol{R_f}$ 0.50 (7:3 heptane/EtOAc + 1.5% NEt_3); $\mathbf{[\alpha]_D^{23}}$ −9.6 (*c* 1.0, $CHCl_3$); (Found: C, 69.64; H, 9.51; $C_{27}H_{44}O_6$ requires C, 69.79; H, 9.54%); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3368 (O-H stretch), 2881 (C-H stretch), 1614 (C=C stretch), 1025 (C-O-C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, **MeOD**) 5.46 (1 H, br d, *J* 5.2, *H-6*), 4.72 (1 H, d, *J* 7.0, *H-24a*), 4.66 (1 H, d, *J* 6.7, *H-26a*), 4.63 (1 H, d, *J* 6.7, *H-26b*), 4.56 (1 H, d, *J* 7.0, *H-24b*), 4.00-3.76 (5 H, m, *H-3*, *H-22*, *H-23*), 3.71 (1 H, br s, *H-1*), 3.37 (3 H, s, *H-25*), 3.34 (3 H, s, *H-27*), 2.40-1.44 (16 H, m, *H-2*, *H-4*, *H-7*, *H-8*, *H-9*, *H-12a*, *H-11*, *H-14*, *H-15*, *H-16a*, *H-17*), 1.27 (3 H, s, *H-21*), 1.20-1.15 (2 H, m, *H-12b*, *H-16b*), 1.03 (3 H, s, *H-19*), 0.81 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**125 MHz**, **MeOD**) 138.3 (*C-5*), 124.0 (*C-6*), 111.8 (*C-20*), 95.8 (*C-24*), 94.8 (*C-26*), 79.5 (*C-1*), 72.7 (*C-3*), 65.1 (*C-23*), 63.1 (*C-22*), 58.6 (*C-8*), 58.5 (*C-17*), 57.1 (*C-14*), 55.2 (*C-25*), 54.2 (*C-27*), 41.8 (*C-13*), 41.3 (*C-10*), 41.1 (*C-9*), 39.9 (*C-12*), 39.0 (*C-4*), 32.7 (*C-2*), 31.9 (*C-15*), 31.6 (*C-7*), 23.8 (*C-21*), 23.6 (*C-16*), 19.9 (*C-11*), 19.1 (*C-19*), 12.4 (*C-18*); **m/z** (**ESI**) 487 $[MNa]^+$. Calcd. for $C_{27}H_{44}NaO_6$: 487.3030. Found: $[MNa]^+$, 487.3032 (−0.4 ppm error).

Lab. Book: ***LNB0170-120-02***.

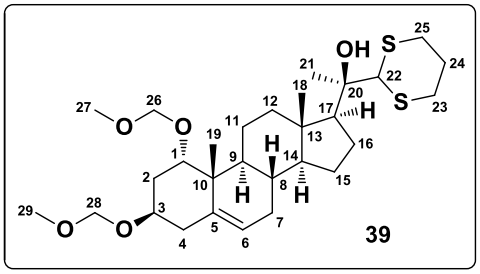
1α,3β-Bismethoxymethylenoxypregn-5-en-20-one (38)[52]



A solution of ketal **113** (267 mg, 0.575 mmol, 1.0 eq.) in AcOH/H_2O/THF (65:35:10) (18 mL) was stirred overnight at room temperature. The reaction mixture was diluted with EtOAc (40 mL) and slowly quenched with sat. aq. $NaHCO_3$ (20 mL). The organic phase was adjusted to pH 8 by washing with sat. aq. $NaHCO_3$. The organic extract was dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo* to give the title compound **38** (247 mg, 0.575 mmol, 100%) as an orange solid which required no further purification: **mp** 125-127 °C decomposed (Lit.[29] 128-129 °C decomposed); $\boldsymbol{R_f}$ 0.44 (1:1 heptane/EtOAc); $\boldsymbol{[\alpha]_D^{23}}$ 48.0 (*c* 1.0, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 2901 (C-H stretch), 1706 (C=O stretch), 1042 (C-O-C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, **MeOD**) 5.48 (1 H, br d, *J* 5.4, *H-6*), 4.74 (1 H, d, *J* 7.0, *H-22a*), 4.66 (1 H, d, *J* 6.7, *H-24a*), 4.63 (1 H, d, *J* 6.7, *H-24b*), 4.58 (1 H, d, *J* 7.0, *H-22b*), 3.85-3.78 (1 H, m *H-3*), 3.73 (1 H, br s, *H-1*), 3.40 (3 H, s, *H-23*), 3.34 (3 H, s, *H-25*), 2.64 (1 H, dd, *J* 9.1, 9.1, *H-17*), 2.42-2.24 (3 H, m, *H-2a, H-4*), 2.12 (3 H, s, *H-21*), 2.09-1.24 (14 H, m, *H-2b, H-7, H-8, H-9, H-11, H-12, H-14, H-15, H-16)*, 1.04 (3 H, s, *H-19*), 0.64 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**125 MHz**, **MeOD**) 210.2 (*C-20*), 138.7 (*C-5*), 124.4 (*C-6*), 96.9 (*C-22*), 95.8 (*C-24*), 80.2 (*C-1*), 73.3 (*C-3*), 64.7 (*C-17*), 58.3 (*C-8*), 57.9 (*C-14*), 56.4 (*C-23*), 55.2 (*C-25*), 44.7 (*C-13*), 42.3 (*C-10*), 42.2 (*C-9*), 39.9 (*C-4*), 39.5 (*C-12*), 33.3 (*C-2*), 32.4 (*C-7*), 31.3 (*C-21*), 25.2 (*C-16*), 20.9 (*C-11*), 20.8 (*C-15*), 19.9 (*C-19*), 13.4 (*C-18*); **m/z** (**ESI**) 443 $[MNa]^+$. Calcd. for $C_{25}H_{40}NaO_5$: 443.2768. Found: $[MNa]^+$, 443.2763 (1.1 ppm error). Data consistent with those previously reported in the literature.[29]

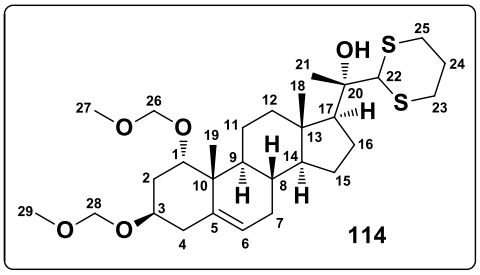
Lab. Book: ***LNB0107-010-01***.

1α,3β-Bismethoxymethylenoxy-(20*R*)-20-hydroxydithianepregn-5-ene (39)[29]



To a solution of 1,3-dithiane (8.23 g, 0.069 mol, 10.0 eq.) in THF (30 mL) was added ^{n}BuLi (1.6 M in hexane, 42.8 mL, 0.069 mol, 10.0 eq.) at −20 °C under argon. To the resulting solution was added dropwise a solution of ketone **38** (2.88 g, 6.85 mol, 1.0 eq.) in THF (30 mL). The reaction mixture was stirred for 7 h at −20 °C, diluted with Et_2O (60 mL) and quenched with sat. aq. NH_4Cl (60 mL). The organic phase was adjusted to pH 7 by washing with H_2O (4 × 15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to dryness. The crude residue was purified by column chromatography on silica gel (8:2 heptane/EtOAc) to afford the title compound **39** (2.63 g, 4.86 mmol, 71%) as a white solid: **mp** 150-153 °C decomposed (Lit.[29] 154-156 °C decomposed); $\boldsymbol{R_f}$ 0.68 (1:1 heptane/EtOAc + 1.5% Et_3N); $\boldsymbol{[\alpha]_D^{23}}$ −27.8 (*c* 0.5, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3480 (O-H stretch), 2931 (C-H stretch), 2843 (S-H stretch), 1037 (C-O-C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, **$CDCl_3$**) 5.54 (1 H, br d, *J* 4.9, *H-6*), 4.73 (1 H, d, *J* 6.7, *H-26a*), 4.66 (1 H, d, *J* 6.9, *H-28a*), 4.63 (1 H, d, *J* 6.9, *H-28b*), 4.58 (1 H, d, *J* 6.7, *H-26b*), 4.13 (1 H, s, *H-22*), 3.86-3.82 (1 H, m, *H-3*), 3.72 (1 H, br s, *H-1*), 3.38 (3 H, s, *H-27*), 3.34 (3 H, s, *H-29*), 2.97-2.81 (4 H, m, *H-23*, *H-25*), 2.44 (1 H, ddd, *J* 13.5, 5.0, 1.6, *H-4a*), 2.36-2.31 (1 H, m, *H-4b*), 2.22 (1 H, br d, *J* 13.4, *H-2a*), 2.10-2.07 (1 H, m, *H-12a*), 1.95 (1 H, dd, *J* 17.7, 2.4, *H-7a*), 1.91-1.47 (13 H, m, *H-2b*, *H-7b*, *H-8*, *H-9*, *H-11*, *H-15*, *H-16*, *H-17*, *H-24)*, 1.42 (3 H, s, *H-21*), 1.24-1.13 (2 H, m, *H-12b*, *H-14*), 1.02 (3 H, s, *H-19*), 0.88 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**125 MHz**, **$CDCl_3$**) 137.9 (*C-5*), 124.1 (*C-6*), 95.6 (*C-26*), 95.1 (*C-28*), 78.7 (*C-1*), 77.0 (*C-20*), 72.5 (*C-3*), 61.2 (*C-22*), 56.9 (*C-14*), 56.2 (*C-29*), 55.2 (*C-17*), 55.1 (*C-27*), 43.0 (*C-13*), 41.6 (*C-9*), 41.1 (*C-10*), 40.0 (*C-12*), 38.9 (*C-4*), 32.5 (*C-2*), 31.6 (*C-7*), 31.5 (*C-8*), 31.3 (*C-23*), 30.9 (*C-25*), 26.0 (*C-24*), 24.2 (*C-15*), 23.8 (*C-21*), 21.7 (*C-16*), 20.2 (*C-11*), 19.7 (*C-19*), 13.5 (*C-18*); **m/z** (**ESI**) 563 $[MNa]^+$. Calcd. for $C_{29}H_{48}NaO_5S_2$: 563.2835. Found: $[MNa]^+$, 563.2820 (2.8 ppm error). Data consistent with those previously reported in the literature.[29]

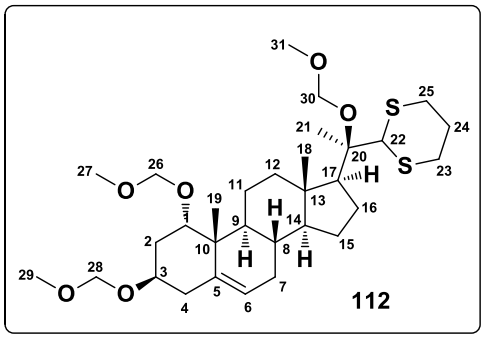
Lab. Book: ***LNB0170-123-02***.



Further elution gave 1α,3β-bismethoxymethylenoxy-(20*S*)-20-hydroxydithianepregn-5-ene (**114**) (16.0 mg, 0.030 mmol, 4%) as a white solid: **mp** 142-146 °C decomposed (Lit.[29] 148-150 °C decomposed); R_f 0.60 (1:1 heptane/EtOAc + 1.5% Et_3N); $[\alpha]_D^{23}$ −29.4 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3472 (O-H stretch), 2928 (C-H stretch), 2853 (S-H stretch), 1040 (C-O-C stretch); δ_H (**400 MHz**, **$CDCl_3$**) 5.54 (1 H, br d, *J* 5.5, *H-6*), 4.73 (1 H, d, *J* 7.3, *H-26a*), 4.66 (1 H, d, *J* 7.1, *H-28a*), 4.63 (1 H, d, *J* 7.1, *H-28b*), 4.59 (1 H, d, *J* 7.3, *H-26b*), 4.33 (1 H, s, *H-22*), 3.88-3.81 (1 H, m, *H-3*), 3.71 (1 H, br s, *H-1*), 3.38 (3 H, s, *H-29*), 3.34 (3 H, s, *H-27*), 2.96-2.80 (4 H, m, *H-23, H-25*), 2.43 (1 H, ddd, *J* 13.9, 5.3, 2.0, *H-4a*), 2.35-2.29 (1 H, m, *H-4b*), 2.21 (1 H, br d, *J* 14.0, *H-2a*), 2.08-1.41 (14 H, m, *H-2b, H-7, H-9, H-11, H-12a, H-15, H-16, H-17, H-24)*, 1.32 (3 H, s, *H-21*), 1.21-1.08 (3 H, m, *H-8, H-12b, H-14*), 1.01 (3 H, s, *H-19*), 0.89 (3 H, s, *H-18*); δ_C (**125 MHz**, **$CDCl_3$**) 137.8 (*C-5*), 124.1 (*C-6*), 95.9 (*C-26*), 95.1 (*C-28*), 79.0 (*C-1*), 77.7 (*C-20*), 72.5 (*C-3*), 61.1 (*C-22*), 56.6 (*C-14*), 56.1 (*C-29*), 55.1 (*C-17*), 55.0 (*C-27*), 43.4 (*C-13*), 41.6 (*C-10*), 41.1 (*C-9*), 39.7 (*C-12*), 38.9 (*C-4*), 32.8 (*C-2*), 31.5 (*C-7*), 31.3 (*C-8*), 31.2 (*C-23*), 30.8 (*C-25*), 29.7 (*C-24*), 25.9 (*C-15*), 25.0 (*C-21*), 23.9 (*C-16*), 20.3 (*C-11*), 19.7 (*C-19*), 13.9 (*C-18*); **m/z** (**ESI**) 563 $[MNa]^+$. Calcd. for $C_{29}H_{48}NaO_5S_2$: 563.2835. Found: $[MNa]^+$, 563.2843 (−1.4 ppm error). Data consistent with those previously reported in the literature.[29]

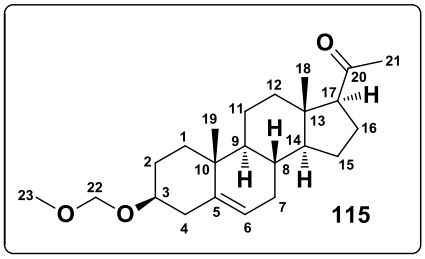
Lab. Book: ***LNB0170-115-04***.

(20*R*)-20-Dithiane-1α,3β,20*R*-trismethoxymethylenoxy-pregn-5-ene (112)



To a solution of alcohol **39** (1.12 g, 2.07 mmol, 1.0 eq.) in 1,4-dioxane (55 mL) were added Hünig's base (2.74 mL, 0.016 mol, 7.6 eq.) and chloromethyl methyl ether (1.16 mL, 0.015 mol, 7.4 eq.). The resulting mixture was stirred overnight at 80 °C. After cooling to room temperature, the reaction mixture was diluted with EtOAc (50 mL), quenched with sat. aq. NH_4Cl (20 mL) and stirred vigorously for 5 min. The organic phase was washed with H_2O (20 mL) and brine (20 mL). The organic extract was dried over $MgSO_4$, filtered and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (7:3 PE/EtOAc) to afford the *title compound* **112** (1.03 g, 1.76 mmol, 85%) as a yellow solid: **mp** 188-191 °C decomposed; $\boldsymbol{R_f}$ 0.84 (1:1 PE/EtOAc); (Found: C, 63.69; H, 8.92; $C_{31}H_{52}O_6S_2$ requires C, 63.66; H, 8.96%); $\boldsymbol{[\alpha]_D^{22}}$ –49.0 (*c* 1.0, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3361 (O-H stretch), 2894 (C-H stretch), 2849 (S-H stretch), 1020 (C-O-C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, **MeOD**) 5.48 (1 H, br d, *J* 4.8, *H-6*), 4.93 (1 H, d, *J* 6.6, *H-30a*), 4.72 (1 H, d, *J* 7.3, *H-26a*), 4.70 (1 H, d, *J* 6.6, *H-30b*), 4.66 (1 H, d, *J* 6.8, *H-28a*), 4.64 (1 H, d, *J* 6.8, *H-28b*), 4.57 (1 H, d, *J* 7.3, *H-26b*), 4.37 (1 H, s, *H-22*), 3.84-3.79 (1 H, m, *H-3*), 3.71 (1 H, br s, *H-1*), 3.40 (3 H, s, *H-27*), 3.38 (3 H, s, *H-29*), 3.34 (3 H, s, *H-31*), 2.91-2.82 (4 H, m, *H-23*, *H-25*), 2.40 (1 H, ddd, *J* 13.4, 5.5, 2.1, *H-4a*), 2.33-2.22 (2 H, m, *H-2a*, *H-4b*), 2.11-1.46 (15 H, m, *H-2b*, *H-7*, *H-8*, *H-9*, *H-12a*, *H-11*, *H-14*, *H-15*, *H-16*, *H-17*, *H-24*), 1.56 (3 H, s, *H-21*), 1.28-1.19 (2 H, m, *H-12b*, *H-16*), 1.03 (3 H, s, *H-19*), 0.90 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**100 MHz**, **MeOD**) 137.8 (*C-5*), 123.8 (*C-6*), 111.8 (*C-20*), 95.6 (*C-26*), 94.6 (*C-28*), 91.8 (*C-30*), 79.1 (*C-1*), 72.2 (*C-3*), 61.5 (*C-22*), 56.8 (*C-14*), 55.5 (*C-17*), 55.5 (*C-27*), 55.2 (*C-29*), 54.1 (*C-31*), 41.3 (*C-13*), 41.3 (*C-9*), 41.1 (*C-10*), 40.2 (*C-12*), 39.0 (*C-4*), 32.5 (*C-2*), 31.8 (*C-8*), 31.3 (*C-7*), 31.3 (*C-23*, *C-25*), 26.5 (*C-24*), 23.8 (*C-15*), 22.1 (*C-16*), 21.8 (*C-21*), 21.2 (*C-11*), 18.8 (*C-19*), 12.8 (*C-18*); **m/z** (**ESI**) 607 $[MNa]^+$. Calcd. for $C_{31}H_{52}NaO_6S_2$: 607.3098. Found: $[MNa]^+$, 607.3086 (1.9 ppm error). **Lab. Book**: ***LNB0149-116-03***.

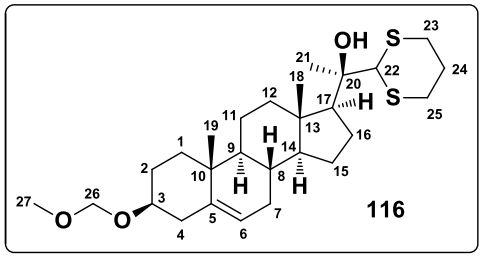
3β-Methoxymethylenoxypregn-5-ene (115)[29]



To a solution of pregnenolone (**36**) (1.00 g, 3.16 mmol, 1.0 eq.) in 1,4-dioxane (20 mL) were added Hünig's base (4.17 mL, 24.0 mmol, 7.6 eq.) and chloromethyl methyl ether (1.76 mL, 23.4 mmol, 7.4 eq.). The resulting mixture was stirred overnight at reflux temperature. After cooling to room temperature, the reaction mixture was diluted with EtOAc (20 mL), quenched with sat. aq. NH_4Cl (10 mL) and stirred vigorously for 5 min. The organic phase was washed with H_2O (10 mL) and brine (10 mL). The organic extract was dried over $MgSO_4$, filtered and concentrated to dryness *in vacuo* to afford the title compound **115** which required no further purification (1.00 g, 2.77 mmol, 88%) as an amorphous orange solid: **mp** 105-107 °C decomposed (Lit.[134] 109-111 °C decomposed); $\boldsymbol{R_f}$ 0.74 (8:2 PE/EtOAc); $\boldsymbol{[\alpha]_D^{23}}$ 15.0 (*c* 1.0, $CHCl_3$) (Lit.[134] $\boldsymbol{[\alpha]_D}$ 13.0, c 0.254); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3375 (O-H stretch), 2894 (C-H stretch), 1679 (C=O stretch), 1028 (C-O-C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, $\boldsymbol{CDCl_3}$) 5.36 (1 H, br d, *J* 5.3, *H-6*), 4.69 (2 H, s, *H-22*), 3.47-3.39 (1 H, m, *H-3*), 3.37 (3 H, s, *H-23*), 2.53 (1 H, dd, *J* 9.2, 9.2, *H-17*), 2.38-2.19 (3 H, m, *H-2*, *H-4*), 2.13 (3 H, s, *H-21*), 2.06-1.04 (15 H, m, *H-1*, *H-2*, *H-7*, *H-8*, *H-9*, *H-11*, *H-12*, *H-15*, *H-16*), 1.01 (3 H, s, *H-19*), 0.99-0.97 (1 H, m, *H-14*), 0.63 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**100 MHz**, $\boldsymbol{CDCl_3}$) 209.6 (*C-20*), 140.7 (*C-5*), 121.3 (*C-6*), 95.3 (*C-22*), 76.3 (*C-3*), 63.8 (*C-17*), 56.9 (*C-14*), 55.4 (*C-23*), 50.1 (*C-9*), 44.1 (*C-13*), 39.6 (*C-12*), 38.8 (*C-4*), 37.3 (*C-1*), 36.8 (*C-10*), 31.9 (*C-7*), 31.8 (*C-21*), 31.5 (*C-8*), 28.9 (*C-2*), 24.6 (*C-15*), 22.9 (*C-16*), 21.1 (*C-11*), 19.5 (*C-19*), 13.2 (*C-18*); **m/z** (**ESI**) 361 $[MH]^+$. Calcd. for $C_{23}H_{37}O_3$: 361.2737. Found: $[MH]^+$, 361.2728 (2.6 ppm error). Data consistent with those previously reported in the literature.[134]

Lab. Book: ***LNB0107-142-01***.

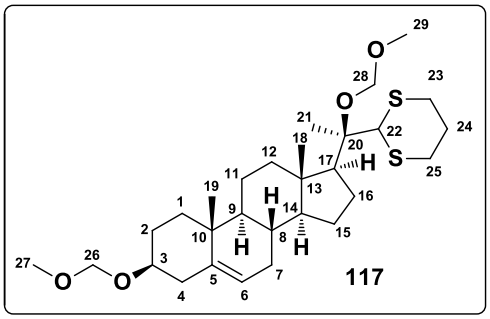
(20*R*)-20-Hydroxydithiane-3β-methoxymethylenoxypregna-5-ene (116)



To a solution of 1,3-dithiane (1.67 g, 13.9 mmol, 5.0 eq.) in THF (5 mL) was added ^{n}BuLi (1.6 M in hexane, 8.67 mL, 13.9 mmol, 5.0 eq.) at −5 °C under argon. To the resulting solution was added dropwise a solution of ketone **115** (1.00 g, 2.77 mmol, 1.0 eq.) in THF (15 mL). The reaction mixture was stirred for 6 h at −5 °C, diluted with Et_2O (15 mL) and quenched with sat. aq. NH_4Cl (10 mL). The organic phase was adjusted to pH 7 by washing with H_2O (4 × 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to dryness. The crude residue was purified by column chromatography on silica gel (90:10 to 85:15 PE/EtOAc): the product containing fractions were concentrated and dried *in vacuo* to afford the *title compound* **116** (1.04 g, 2.16 mmol, 78%) as a mixture of diastereoisomers at C-20 in a 6:1 ratio as a white solid: **mp** 190-194 °C; $\boldsymbol{R_f}$ 0.50 (8:2 PE/EtOAc); (Found: C, 66.63; H, 9.16; $C_{27}H_{44}O_3S_2$ requires C, 67.45; H, 9.22%); $\boldsymbol{[\alpha]_D^{24}}$ −51.7 (*c* 1.0, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3422 (O-H stretch), 2931 (C-H stretch), 2888 (S-H stretch), 1032 (C-O-C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, $\boldsymbol{CDCl_3}$) 5.36 (1 H, br d, *J* 5.2, *H-6*), 4.69 (2 H, s, *H-26*), 4.36 (1 H, s, *H-22**), 4.15 (1 H, s, *H-22*), 3.44-3.40 (1 H, m, *H-3*), 3.38 (3 H, s, *H-27*), 3.00-2.82 (4 H, m, *H-23, H-25*), 2.38-2.27 (2 H, m, *H-4*), 2.12-1.50 (16 H, m, *H-1*, *H-2*, *H-7*, *H-9*, *H-11*, *H-15*, *H-16*, *H-17*, *H-24)*, 1.44 (3 H, s, *H-21*), 1.33 (3 H, s, *H-21**), 1.34-1.06 (4 H, m, *H-8*, *H-12*, *H-14*), 1.02 (3 H, s, *H-19*), 0.89 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**100 MHz**, $\boldsymbol{CDCl_3}$) 140.8 (*C-5*), 121.6 (*C-6*), 94.4 (*C-26*), 77.3 (*C-20*), 77.0 (*C-3*), 60.8 (*C-22*), 56.8 (*C-14*), 55.4 (*C-27*), 55.2 (*C-17*), 50.1 (*C-9*), 43.0 (*C-13*), 40.0 (*C-12*), 39.5 (*C-4*), 37.3 (*C-1*), 36.8 (*C-10*), 31.8 (*C-7*), 31.6 (*C-23*), 31.5 (*C-25*), 31.4 (*C-8*), 31.0 (*C-24*), 28.8 (*C-2*), 24.4 (*C-21*), 23.8 (*C-15*), 21.7 (*C-16*), 21.0 (*C-11*), 19.4 (*C-19*), 13.4 (*C-18*); **m/z** (**ESI**) 463 $[M-H_2O]^+$. Calcd. for $C_{27}H_{43}O_2S_2$: 463.2699. Found: $[M-H_2O]^+$, 463.2706 (−1.4 ppm error). *: signals of the other diastereoisomer.

Lab. Book: ***LNB0107-144-04***.

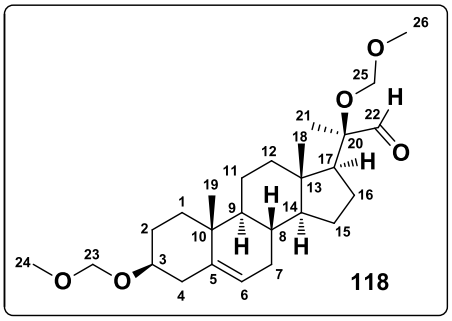
(20*R*)-20-Dithiane-3β,20*R*-bismethoxymethylenoxypregn-5-ene (117)



To a solution of alcohol **116** (3.00 g, 6.25 mmol, 1.0 eq.) in 1,4-dioxane (90 mL) were added Hünig's base (8.26 mL, 0.047 mol, 7.6 eq.) and chloromethyl methyl ether (3.49 mL, 0.046 mol, 7.4 eq.) and the resulting mixture was stirred overnight at reflux. After cooling to room temperature, the reaction mixture was diluted with EtOAc (40 mL), quenched with sat. aq. NH_4Cl (20 mL) and stirred vigorously for 5 min. The organic phase was washed with H_2O (20 mL) and brine (20 mL). The organic extract was dried over $MgSO_4$, filtered and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (9:1 PE/Et_2O) to afford the *title compound* **117** (3.00 g, 5.72 mmol, 92%) as an amorphous orange solid: **mp** 108-110 °C*;* $\boldsymbol{R_f}$ 0.34 (8:2 PE/Et_2O); (Found: C, 66.04; H, 9.12; $C_{29}H_{48}O_4S_2$ requires C, 66.37; H, 9.22%); $\boldsymbol{[\alpha]_D^{23}}$ –24.5 (*c* 1.0, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3345 (O-H stretch), 2889 (C-H stretch), 2849 (S-H stretch), 1022 (C-O-C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, $\mathbf{CDCl_3}$) 5.34 (1 H, br d, *J* 5.2, *H-6*), 4.92 (1 H, d, *J* 6.8, *H-28a*), 4.75 (1 H, d, *J* 6.8, *H-28b*), 4.69 (2 H, s, *H-26*), 4.27 (1 H, s, *H-22*), 3.45-3.40 (1 H, m, *H-3*), 3.42 (3 H, s, *H-29*), 3.37 (3 H, s, *H-27*), 2.90-2.80 (4 H, m, *H-23*, *H-25*), 2.36 (1 H, ddd, *J* 13.0, 6.6, 1.8, *H-4a*), 2.29-2.24 (1 H, m, *H-4b*), 2.10-1.44 (18 H, m, *H-1*, *H-2*, *H-7*, *H-8*, *H-9*, *H-12a*, *H-11*, *H-14*, *H-15*, *H-16a*, *H-17*, *H-24*), 1.57 (3 H, s, *H-21*), 1.32-1.28 (2 H, m, *H-12b*, *H-16b*), 1.00 (3 H, s, *H-19*), 0.87 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**100 MHz**, $\mathbf{CDCl_3}$) 140.7 (*C-5*), 121.7 (*C-6*), 94.7 (*C-26*), 92.3 (*C-28*), 81.8 (*C-20*), 77.0 (*C-3*), 61.7 (*C-22*), 56.8 (*C-17*), 56.6 (*C-14*), 56.7 (*C-29*), 55.1 (*C-27*), 50.1 (*C-9*), 43.1 (*C-13*), 40.2 (*C-12*), 39.6 (*C-4*), 37.3 (*C-1*), 36.7 (*C-10*), 32.4 (*C-23*), 31.8 (*C-7*), 31.8 (*C-25*), 31.4 (*C-8*), 28.9 (*C-2*), 26.5 (*C-24*), 24.0 (*C-15*), 22.5 (*C-16*), 21.0 (*C-11*), 21.9 (*C-21*), 19.5 (*C-19*), 13.5 (*C-18*); **m/z** (**ESI**) 547 $[MNa]^+$. Calcd. for $C_{29}H_{48}NaO_4S_2$: 547.2886. Found: $[MNa]^+$, 547.2878 (1.5 ppm error). X-Ray crystallography: CCDC 983152 contains the supplementary crystallographic data for this compound, see **Appendix I**. Crystals were grown by slow evaporation of PE.

Lab. Book: ***LNB0107-145-03***.

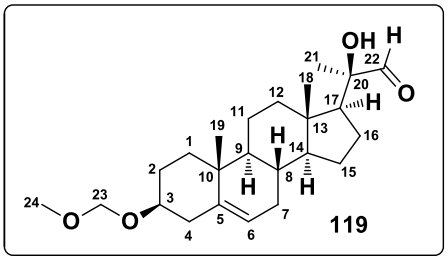
3β-(20*R*)-20-Bismethoxymethylenoxy-22-oxopregn-5-ene (118)



To a solution of dithiane adduct **117** (30.0 mg, 0.057 mmol, 1.0 eq.) in CH_3CN/H_2O (4:1, 3.3 mL) was added a solution of $AgNO_3$ (42.7 mg, 0.252 mmol, 4.4 eq.) and NCS (30.5 mg, 0.229 mmol, 4.0 eq.) in CH_3CN/H_2O (4:1, 1.4 mL) at 0 °C. The reaction mixture was protected from light and stirred for 30 min. After warming to room temperature, the reaction mixture was quenched with sat. aq. Na_2SO_3 (1 mL) then with sat. aq. $NaHCO_3$ (1 mL) and with brine (1 mL). The reaction mixture was stirred vigorously for 5 min and filtered through Celite®. The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (8:2 PE/Et_2O) to afford the *title compound* **118** (19.0 mg, 0.044 mmol, 77%) as a white amorphous solid: **mp** 106-107 °C; $\boldsymbol{R_f}$ 0.52 (7:3 PE/Et_2O); $\boldsymbol{[\alpha]_D^{23}}$ −17.5 (*c* 1.0, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3350 (O-H stretch), 2895 (C-H stretch), 1693 (C=O stretch), 1019 (C-O-C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, **$CDCl_3$**) 9.70 (1 H, s, *H-22*), 5.35 (1 H, br d, *J* 5.2, *H-6*), 4.85 (1 H, d, *J* 7.5, *H-25a*), 4.69 (2 H, s, *H-23*), 4.62 (1 H, d, *J* 7.5, *H-25b*), 3.45-3.40 (1 H, m, *H-3*), 3.42 (3 H, s, *H-26*), 3.37 (3 H, s, *H-24*), 2.35 (1 H, ddd, *J* 13.2, 5.0, 2.0, *H-4a*), 2.28-2.22 (1 H, m, *H-4b*), 2.21-2.18 (2 H, m, *H-2*), 1.98-1.39 (13 H, m, *H-1*, *H-7*, *H-8*, *H-11*, *H-12a*, *H-15*, *H-16*, *H-17)*, 1.37 (3 H, s, *H-21*), 1.24-1.19 (1 H, m, *H-9*), 1.06-1.01 (2 H, m, *H-12b*, *H-14*), 1.01 (3 H, s, *H-19*), 0.78 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**100 MHz**, **$CDCl_3$**) 205.4 (*C-22*), 140.8 (*C-5*), 121.6 (*C-6*), 94.8 (*C-23*), 91.9 (*C-25*), 85.7 (*C-20*), 77.0 (*C-3*), 58.5 (*C-17*), 56.1 (*C-14*), 56.1 (*C-26*), 55.3 (*C-24*), 50.1 (*C-9*), 43.4 (*C-13*), 40.1 (*C-12*), 39.6 (*C-4*), 37.3 (*C-1*), 36.8 (*C-10*), 31.8 (*C-7*), 31.7 (*C-8*), 29.0 (*C-2*), 24.0 (*C-15*), 22.0 (*C-16*), 20.9 (*C-11*), 19.4 (*C-19*), 18.9 (*C-21*), 14.8 (*C-18*); **m/z** (**ESI**) 457 $[MNa]^+$. Calcd. for $C_{26}H_{42}NaO_5$: 457.2924. Found: $[MNa]^+$, 457.2920 (0.9 ppm error).

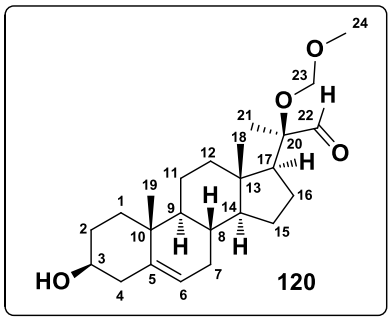
Lab. Book: ***LNB0107-158-03***.

(20*R*)-20-Hydroxyformyl-3β-methoxymethylenoxypregn-5-ene (119)



A solution of dithiane adduct **117** (100 mg, 0.191 mmol, 1.0 eq.) in THF (1 mL) was added dropwise to a suspension of HgO (90.7 mg, 0.419 mmol, 2.2 eq.) and BF_3•Et_2O (0.052 mL, 0.419 mmol, 2.2 eq.) in THF/H_2O (1:1, 1.3 mL). The reaction was stirred at reflux for 4 h. The reaction mixture was cooled to room temperature and filtered through Celite® and washed with Et_2O (5 mL). The organic phase was washed with sat. aq. $NaHCO_3$ (2 × 5 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (7:3 to 1:1 PE/EtOAc) to afford the *title compound* **119** (20.0 mg, 0.051 mmol, 27%) as a white amorphous solid: **mp** 125-127 °C; $\boldsymbol{R_f}$ 0.33 (7:3 PE/Et_2O); $\boldsymbol{[\alpha]_D^{24}}$ −77.2 (*c* 1.0, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3409 (O-H stretch), 2889 (C-H stretch), 1698 (C=O stretch), 1024 (C-O-C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, **$CDCl_3$**) 9.57 (1 H, s, *H-22*), 5.35 (1 H, br d, *J* 5.2, *H-6*), 4.69 (2 H, s, *H-23*), 3.47-3.40 (1 H, m, *H-3*), 3.38 (3 H, s, *H-24*), 2.36 (1 H, ddd, *J* 12.8, 4.6, 1.5, *H-4a*), 2.30-2.24 (1 H, m, *H-4b*), 1.98-1.34 (16 H, m, *H-1*, *H-2*, *H-7*, *H-9*, *H-11*, *H-12a*, *H-14*, *H-15*, *H-16*, *H-17*), 1.36 (3 H, s, *H-21*), 1.27-1.03 (2 H, m, *H-8*, *H-12b*), 1.02 (3 H, s, *H-19*), 0.80 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**100 MHz**, **$CDCl_3$**) 203.6 (*C-22*), 140.9 (*C-5*), 121.5 (*C-6*), 94.8 (*C-23*), 79.6 (*C-20*), 77.0 (*C-3*), 56.6 (*C-17*), 55.5 (*C-24*), 55.3 (*C-14*), 50.2 (*C-9*), 43.4 (*C-13*), 40.1 (*C-12*), 39.6 (*C-4*), 37.3 (*C-1*), 36.8 (*C-10*), 31.8 (*C-7*), 31.4 (*C-8*), 29.0 (*C-2*), 24.2 (*C-15*), 23.1 (*C-21*), 22.2 (*C-16*), 21.0 (*C-11*), 19.5 (*C-19*), 13.9 (*C-18*); **m/z** (**ESI**) 413 $[MNa]^+$. Calcd. for $C_{24}H_{38}NaO_4$: 413.2662. Found: $[MNa]^+$, 413.2674 (−2.8 ppm error).

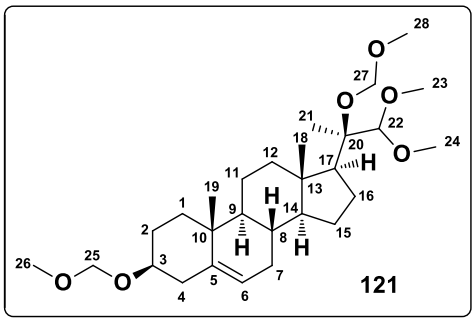
Lab. Book: ***LNB0107-148-04***.



Further elution gave *(20R)-20-formyl-3β-hydroxyl-20-methoxymethylenoxypregn-5-ene* (**120**) (36.3 mg, 0.093 mmol, 49%) as a white amorphous solid: **mp** 118-120 °C decomposed; $\boldsymbol{R_f}$ 0.16 (6:4 PE/Et_2O); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3345 (O-H stretch), 2889 (C-H stretch), 1700 (C=O stretch), 1013 (C-O-C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, $\boldsymbol{CDCl_3}$) 9.70 (1 H, s, *H-22*), 5.35 (1 H, br d, *J* 5.5, *H-6*), 4.85 (1 H, d, *J* 7.2, *H-23a*), 4.62 (1 H, d, *J* 7.2, *H-23b*), 3.51-3.46 (1 H, m, *H-3*), 3.42 (3 H, s, *H-24*), 2.33-2.23 (2 H, m, *H-4*), 2.00-1.94 (1 H, m, *H-7*), 1.89-1.46 (16 H, m, *H-1*, *H-2*, *H-7*, *H-9*, *H-11*, *H-12a*, *H-14*, *H-15*, *H-16*, *H-17)*, 1.37 (3 H, s, *H-21*), 1.27-1.03 (2 H, m, *H-8*, *H-12b*), 1.01 (3 H, s, *H-19*), 0.79 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**100 MHz**, $\boldsymbol{CDCl_3}$) 205.4 (*C-22*), 140.9 (*C-5*), 121.6 (*C-6*), 92.0 (*C-23*), 85.7 (*C-20*), 71.8 (*C-3*), 58.5 (*C-17*), 56.1 (*C-14*), 55.9 (*C-24*), 50.1 (*C-9*), 43.5 (*C-13*), 42.3 (*C-12*), 40.0 (*C-4*), 37.3 (*C-1*), 36.6 (*C-10*), 31.7 (*C-7*), 31.6 (*C-2*), 31.5 (*C-8*), 23.9 (*C-15*), 21.9 (*C-16*), 20.9 (*C-11*), 19.5 (*C-19*), 18.8 (*C-21*), 14.7 (*C-18*); **m/z** (**ESI**) 391 $[MH]^+$. Calcd. for $C_{24}H_{39}O_4$: 391.2843. Found: $[MH]^+$, 391.2858 (−3.9 ppm error).

Lab. Book: ***LNB0107-148-05***.

3β-(20*R*)-20-Bismethoxymethylenoxy-22-dimethoxypregn-5-ene (121)

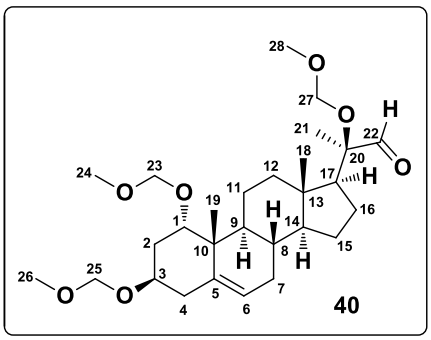


To a solution of $AgNO_3$ (72.8 mg, 0.429 mmol, 4.5 eq.) in MeOH (0.61 mL) was added NCS (50.9 mg, 0.381 mmol, 4.0 eq.) and 2,6-lutidine (0.111 mL, 0.952 mmol, 10 eq.) at room temperature. The reaction mixture was protected from light. After 30 min, a solution of dithiane adduct **117** (50 mg, 0.095 mmol, 1.0 eq.) in THF (0.61 mL) was added

dropwise and the reaction mixture was stirred overnight. After cooling to 0 °C, the reaction mixture was quenched with sat. aq. Na_2SO_3 (1 mL) then with sat. aq. $NaHCO_3$ (1 mL) and with H_2O (1 mL). The reaction mixture was stirred vigorously for 5 min and diluted with Et_2O (1 mL). The aqueous layer was extracted with Et_2O (2 × 1 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (8:2 PE/Et_2O) to afford the *title compound* **121** (31.3 mg, 0.065 mmol, 68%) as a white solid: **mp** 103-105 °C; $\boldsymbol{R_f}$ 0.53 (7:3 PE/Et_2O); $\boldsymbol{[\alpha]_D^{24}}$ −26.6 (*c* 1.0, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3387 (O-H stretch), 2891 (C-H stretch), 1702 (C=O stretch), 1022 (C-O-C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, $\boldsymbol{CDCl_3}$) 5.35 (1 H, br d, *J* 5.3, *H-6*), 4.99 (1 H, d, *J* 6.6, *H-27a*), 4.69 (2 H, s, *H-25*), 4.66 (1 H, d, *J* 6.6, *H-27b*), 4.02 (1 H, s, *H-22*), 3.53 (3 H, s, *H-24*), 3.46 (3 H, s, *H-23*), 3.45-3.41 (1 H, m, *H-3*), 3.41 (3 H, s, *H-28*), 3.38 (3 H, s, *H-26*), 2.36 (1 H, ddd, *J* 13.2, 4.9, 1.6, *H-4a*), 2.30-2.23 (1 H, m, *H-4b*), 2.07-1.41 (15 H, m, *H-1*, *H-2*, *H-7*, *H-8*, *H-11*, *H-12a*, *H-15*, *H-16*, *H-17)*, 1.33 (3 H, s, *H-21*), 1.25-1.01 (2 H, m, *H-12b*, *H-14*), 1.01 (3 H, s, *H-19*), 0.92-0.88 (1 H, m, *H-9*), 0.88 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**100 MHz**, $\boldsymbol{CDCl_3}$) 140.9 (*C-5*), 121.8 (*C-6*), 111.2 (*C-22*), 94.8 (*C-25*), 92.5 (*C-27*), 81.0 (*C-20*), 77.0 (*C-3*), 59.0 (*C-24*), 57.5 (*C-23*), 56.7 (*C-14*), 56.4 (*C-28*), 55.3 (*C-26*), 55.1 (*C-17*), 50.2 (*C-9*), 42.8 (*C-13*), 40.3 (*C-12*), 39.6 (*C-4*), 37.1 (*C-1*), 36.8 (*C-10*), 31.8 (*C-7*), 31.3 (*C-8*), 28.9 (*C-2*), 23.9 (*C-15*), 21.7 (*C-16*), 20.8 (*C-11*), 19.4 (*C-19*), 15.9 (*C-21*), 13.5 (*C-18*); **m/z** (**ESI**) 503 $[MNa]^+$. Calcd. for $C_{28}H_{48}NaO_6$: 503.3346. Found: $[MNa]^+$, 503.3336 (1.3 ppm error).

Lab. Book: ***LNB0107-156-03***.

(20*R*)-20-Formyl-1α,3β,20-trismethoxymethylenoxypregn-5-ene (40)[65]



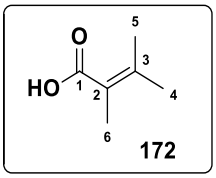
To a solution of dithiane adduct **112** (500 mg, 0.855 mmol, 1.0 eq.) in CH_3CN/H_2O (4:1, 54 mL) was added a solution of $AgNO_3$ (644 mg, 3.79 mmol, 4.4 eq.) and NCS (451 mg, 3.38 mmol, 4.0 eq.) in CH_3CN/H_2O (4:1, 22 mL) at 0 °C. The reaction mixture was protected from light and stirred for 30 min. After warming to room temperature, the

reaction mixture was quenched with sat. aq. Na_2SO_3 (5 mL) then with sat. aq. $NaHCO_3$ (5 mL) and with brine (5 mL). The reaction mixture was stirred vigorously for 5 min and filtered through Celite®. The aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (8:2 PE/Et_2O) to afford the title compound **40** (358 mg, 0.724 mmol, 85%) as an amorphous yellow solid: **mp** 115-117 °C decomposed (Lit.[29] 118-120 °C decomposed); $\boldsymbol{R_f}$ 0.69 (7:3 PE/EtOAc); $\boldsymbol{[\alpha]_D^{23}}$ –18.8 (*c* 1.0, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3389 (O-H stretch), 2889 (C-H stretch), 1701 (C=O stretch), 1025 (C-O-C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, **$CDCl_3$**) 9.68 (1 H, s, *H-22*), 5.54 (1 H, br d, *J* 5.2, *H-6*), 4.83 (1 H, d, *J* 7.2, *H-27a*), 4.73 (1 H, d, *J* 7.1, *H-23a*), 4.66 (1 H, d, *J* 7.0, *H-25a*), 4.64 (1 H, d, *J* 7.0, *H-25b*), 4.60 (1 H, d, *J* 7.1, *H-23b*), 4.56 (1 H, d, *J* 7.2, *H-27b*), 3.87-3.78 (1 H, m, *H-3*), 3.72 (1 H, br s, *H-1*), 3.39 (3 H, s, *H-24*), 3.38 (3 H, s, *H-26*), 3.33 (3 H, s, *H-28*), 2.43 (1 H, ddd, *J* 13.6, 5.3, 1.8, *H-4a*), 2.35-2.29 (1 H, m, *H-4b*), 2.25-2.20 (1 H, m, *H-2a*), 1.98-1.90 (1 H, m, *H-7a*), 1.74-1.39 (11 H, m, *H-2b, H-7b, H-8, H-9, H-11, H-12a, H-15a, H-16, H-17),* 1.34 (3 H, s, *H-21*), 1.24-1.03 (3 H, m, *H-12b, H-14, H-15b*), 1.01 (3 H, s, *H-19*), 0.77 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**100 MHz**, **$CDCl_3$**) 205.4 (*C-22*), 138.0 (*C-5*), 124.1 (*C-6*), 95.7 (*C-23*), 95.2 (*C-25*), 92.0 (*C-27*), 85.7 (*C-20*), 78.8 (*C-1*), 72.6 (*C-3*), 58.6 (*C-17*), 56.3 (*C-26*), 56.2 (*C-14*), 55.9 (*C-28*), 55.2 (*C-24*), 43.5 (*C-13*), 41.6 (*C-10*), 41.2 (*C-9*), 39.9 (*C-12*), 39.0 (*C-4*), 32.6 (*C-2*), 31.5 (*C-7*), 31.5 (*C-8*), 24.0 (*C-15*), 21.9 (*C-16*), 20.2 (*C-11*), 19.8 (*C-19*), 18.8 (*C-21*), 14.8 (*C-18*); **m/z** (**ESI**) 517 $[MNa]^+$. Calcd. for $C_{28}H_{46}NaO_7$: 517.3136. Found: $[MNa]^+$, 517.3121 (2.8 ppm error). Data consistent with those previously reported in the literature.[29]

Lab. Book: ***LNB0170-148-02/03***.

6.2.2. Chapter 3. Construction of the δ-lactone side chain

2,3-Dimethyl-2-butenoic acid (172)[80]

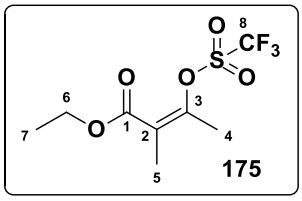


172

To a suspension of lithium (32.6 mg, 4.70 mmol, 2.8 eq.) in THF (0.5 mL) was added dropwise a solution of 2-bromo-3-methyl-2-butene (**171**) (250 mg, 1.68 mmol, 1.0 eq.) in THF (0.5 mL) over 5 min at –30 °C. The reaction mixture was warmed to –5 °C and stirred for 5 min. The reaction mixture was cooled down to –78 °C and an excess of CO_2 was added (bubbling through the reaction mixture). After 30 min, the reaction mixture was warmed to 0 °C, quenched with ice-cold water (1 mL) and diluted with heptane (3 mL). The aqueous phase was acidified with 1 M aq. HCl (1 mL) and extracted with heptane (5 mL). The organic phase was separated, dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo* to afford the title compound **172** (69.7 mg, 0.611 mmol, 36%) as yellow needdles: **mp** 70-74 °C decomposed (Lit.[80] 71 °C decomposed); $\boldsymbol{R_f}$ 0.70 (15:1 PE/EtOAc); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 2822 (O-H stretch), 1670 (C=O stretch), 1655 (C=C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, **$CDCl_3$**) 2.11 (3 H, s, *H-5*), 1.88 (3 H, s, *H-6*), 1.86 (3 H, s, *H-4*); $\boldsymbol{\delta_C}$ (**100 MHz**, **$CDCl_3$**) 174.9 (*C-1*), 148.4 (*C-3*), 121.5 (*C-2*), 23.5 (*C-5*), 23.4 (*C-4*), 15.7 (*C-6*); **m/z** (**ESI**) 115 $[MH]^+$. Calcd. for $C_6H_{11}O_2$: 115.0754. Found: $[MH]^+$, 115.0754 (−0.5 ppm error). Data consistent with those previously reported in the literature.[80]

Lab. Book: ***LNB0149-047-01***.

Ethyl 2-methyl-3-trifluorosulfonatebut-2-enoate (175)[82]



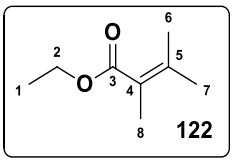
175

To a solution of ethyl 2-methylacetoacetate (**174**) (0.580 mL, 0.004 mol, 1.0 eq.) in toluene (20 mL) was added 5 M aq. LiOH (6.0 mL, 0.030 mol, 7.5 eq.) at 10 °C and the reaction mixture was stirred vigorously for 5 min. Triflic anhydride (1.7 mL, 0.010 mol, 2.5 eq.) was added dropwise maintaining the temperature of the reaction between 5 °C and 15 °C.

After 30 min, the biphasic solution was diluted with H_2O (15 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (20 mL). The combined organic layers were washed with H_2O (15 mL) and brine (15 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to dryness *in vacuo* to give the title compound **175** (1.15 g, 0.004 mol, 100%) as an orange liquid which required no further purification: $\boldsymbol{R_f}$ 0.42 (15:1 PE/EtOAc); $\boldsymbol{\delta_H}$ (**400 MHz**, $\mathbf{CDCl_3}$) 4.28 (2 H, q, *J* 7.2, *H-6*), 2.15-2.13 (3 H, m, *H-5*), 1.98 (3 H, q, *J* 1.2, *H-4*), 1.34 (3 H, t, *J* 7.2, *H-7*); $\boldsymbol{\delta_C}$ (**100 MHz**, $\mathbf{CDCl_3}$) 165.3 (*C-1*), 147.6 (*C-3*), 121.8 (*C-2*), 118.3 (q, J_{CF} 319, *C-8*), 61.7 (*C-6*), 17.6 (*C-5*), 15.2 (*C-4*), 13.8 (*C-7*); **m/z** (**ESI**) 277 $[MH]^+$. Calcd. for $C_8H_{12}F_3O_5S$: 277.0352. Found: $[MH]^+$, 277.0350 (0.7 ppm error). Data consistent with those previously reported in the literature.[83]

Lab. Book: ***LNB0107-104-01***.

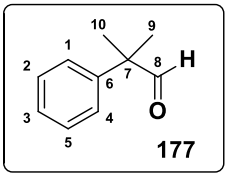
Ethyl 2,3-dimethylbutenoate (122)[135]



To a suspension of CuI (2.76 g, 0.015 mol, 1.0 eq.) in Et_2O (65 mL) was added MeLi (1.6 M in Et_2O, 18.0 mL, 0.029 mol, 2.0 eq.) at 0 °C and the reaction mixture was stirred for 5 min to give a clear solution. A solution of the (*Z*)-enol triflate **175** (4.00 g, 0.015 mol, 1.0 eq.) in Et_2O (65 mL) was added to the cuprate solution at −78 °C. After 1 h, a solution of NH_4Cl/NH_3 (50 mL), prepared by mixing a sat. aq. solution of NH_4Cl (15 mL), MeOH (10 mL) and 25% aq. NH_3 (4 mL) was poured into the reaction mixture at −78 °C. The reaction mixture was then poured into a separating funnel, the reaction flask was washed consecutively with NH_4Cl/NH_3 (50 mL) and Et_2O (50 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL), the combined organic layers were washed with H_2O (50 mL), dried over $MgSO_4$, filtered and concentrated to dryness *in vacuo* to give the title compound **122** (1.80 g, 0.013 mol, 87%) as a yellow liquid: $\boldsymbol{R_f}$ 0.70 (15:1 PE/EtOAc); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 2944 (O-H stretch), 1670 (C=O stretch), 1618 (C=C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, $\mathbf{CDCl_3}$) 4.19 (2 H, q, *J* 7.1, *H-2*), 2.02-2.00 (3 H, m, *H-6*), 1.88-1.86 (3 H, m, *H-8*), 1.82-1.80 (3 H, m, *H-7*), 1.30 (3 H, t, *J* 7.1, *H-1*); $\boldsymbol{\delta_C}$ (**100 MHz**, $\mathbf{CDCl_3}$) 169.9 (*C-3*), 142.8 (*C-5*), 122.7 (*C-4*), 60.1 (*C-2*), 22.9 (*C-6*), 22.4 (*C-7*), 15.7 (*C-8*), 14.4 (*C-1*). Data consistent with those previously reported in the literature.[136]

Lab. Book: ***LNB0149-123-07***.

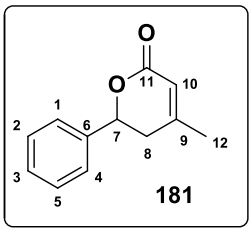
2,2-(Dimethyl)-2-phenylacetaldehyde (177)[85]



To a solution of aldehyde **176** (250 mg, 1.86 mmol, 1.0 eq.) in THF (0.8 mL) was added a solution of NaH (49.2 mg, 2.05 mmol, 1.1 eq.) in THF (0.8 mL) dropwise over 5 min at 0 °C. After 10 min, MeI (0.233 mL, 3.77 mmol, 2.2 eq.) was added carefully maintaining the temperature around 0 °C. After 1 h, the reaction was quenched with sat. aq. $NaHCO_3$ (2 mL) and extracted with Et_2O (3 × 2 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated to dryness *in vacuo* to afford the title compound **177** (240 mg, 1.62 mmol, 87%) as a yellow oil which required no further purification: $\boldsymbol{R_f}$ 0.86 (8:2 PE/EtOAc); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 2986 (C-H stretch), 1722 (C=O stretch), 1420 (C=C stretch), 1393 (CH_3 bend); $\boldsymbol{\delta_H}$ (**400 MHz**, **$CDCl_3$**) 9.51 (1 H, s, *H-8*), 7.41-7.37 (3 H, m, *H-2*, *H-3*, *H-5*), 7.31-7.27 (2 H, m, *H-1*, *H-4*), 1.47 (6 H, s, *H-9*, *H-10*); $\boldsymbol{\delta_C}$ (**100 MHz**, **$CDCl_3$**) 202.4 (*C-8*), 141.3 (*C-6*), 129.0 (*C-2*, *C-3*, *C-5*), 126.8 (*C-1*, *C-4*), 50.6 (*C-7*), 22.6 (*C-9*, *C-10*); **m/z** (**ESI**) 149 $[MH]^+$. Calcd. for $C_{10}H_{13}O$: 149.0961. Found: $[MH]^+$, 149.0961 (−0.2 ppm error). Data consistent with those previously reported in the literature.[137]

Lab. Book: ***LNB0107-109-01***.

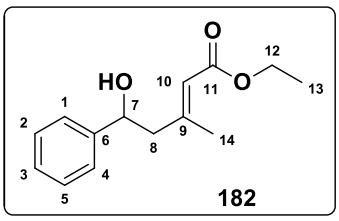
(6*S*)-4-Methyl-6-phenyl-5,6-dihydro-2*H*-pyran-2-one (181)[30]



To a solution of $^{i}Pr_2NH$ (0.632 mL, 4.50 mmol, 2.4 eq.) in THF (10 mL) was added ^{n}BuLi (1.6 M in hexane, 2.59 mL, 4.15 mmol, 2.2 eq.) dropwise at –78 °C and the resulting mixture was stirred for 30 min. A solution of 3,3-dimethylbutenoate (**178**) (507 mg, 3.96 mmol, 2.1 eq.) in THF/DMPU (9:1, 6 mL) was added dropwise and stirred for 1 h. A solution of benzaldehyde (**180**) (200 mg, 1.88 mmol, 1.0 eq.) in THF (10 mL) was added dropwise at –78 °C and the reaction mixture was

stirred for 5.5 h. The reaction mixture was warmed to room temperature, quenched with sat. aq. NH_4Cl (10 mL) and extracted with Et_2O (15 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (9:1 to 7:3 PE/EtOAc) to afford the title compound **181** (277 mg, 1.47 mmol, 78%) as a yellow amorphous solid: **mp** 73-75 °C decomposed; $\boldsymbol{R_f}$ 0.38 (7:3 PE/EtOAc); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3000 (C-H stretch), 1689 (C=O stretch), 1655 (C=C stretch), 1039 (C-O-C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, $\mathbf{CDCl_3}$) 7.35-7.25 (5 H, m, *H-1*, *H-2*, *H-3*, *H-4*, *H-5*), 5.82-5.81 (1 H, m, *H-10*), 4.91 (1 H, dd, *J* 12.2, 4.1, *H-7*), 2.55 (1 H, ddq, *J* 17.9, 12.2, 0.9, *H-8b*), 2.38 (1 H, dd, *J* 17.9, 4.1, *H-8a*), 1.94 (3 H, d, *J* 1.1, *H-12*); $\boldsymbol{\delta_C}$ (**100 MHz**, $\mathbf{CDCl_3}$) 164.6 (*C-11*), 157.2 (*C-9*), 138.4 (*C-6*), 128.3 (*C-2*, *C-5*), 128.2 (*C-3*), 125.7 (*C-1*, *C-4*), 116.2 (*C-10*), 78.3 (*C-7*), 36.4 (*C-8*), 22.6 (*C-12*); **m/z** (**ESI**) 189 $[MH]^+$. Calcd. for $C_{12}H_{13}O_2$: 189.0910. Found: $[MH]^+$, 189.0915 (−2.9 ppm error). Data consistent with those previously reported in the literature.[86]

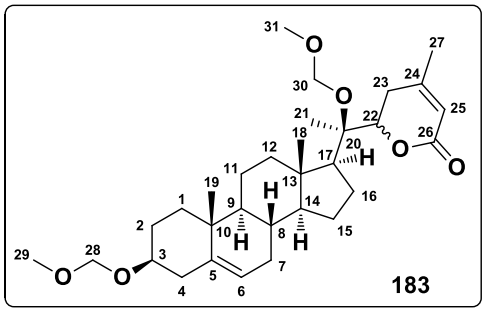
Lab. Book: ***LNB0149-004-03***.



Also isolated was ethyl 5-hydroxy-3-methyl-5-phenylpent-2-enoate (**182**) (34.0 mg, 0.145 mmol, 8%) as an orange oil: $\boldsymbol{R_f}$ 0.93 (7:3 PE/EtOAc); $\boldsymbol{\delta_H}$ (**400 MHz**, $\mathbf{CDCl_3}$) 7.37-7.28 (5 H, m, *H-1*, *H-2*, *H-3*, *H-4*, *H-5*), 5.78 (1 H, dd, *J* 2.3, 1.2, *H-10*), 4.91 (1 H, dd, *J* 8.7, 5.0, *H-7*), 4.15 (2 H, q, *J* 7.3, *H-12*), 2.57 (1 H, dd, *J* 14.0, 8.7, *H-8a*), 2.51 (1 H, dd, *J* 14.0, 5.0, *H-8b*), 2.23 (3 H, d, *J* 1.2, *H-14*), 1.28 (3 H, t, *J* 7.3, *H-13*); $\boldsymbol{\delta_C}$ (**100 MHz**, $\mathbf{CDCl_3}$) 166.4 (*C-11*), 155.6 (*C-9*), 143.7 (*C-6*), 128.6 (*C-2*, *C-5*), 127.8 (*C-3*), 125.6 (*C-1*, *C-4*), 118.5 (*C-10*), 72.1 (*C-7*), 59.7 (*C-12*), 50.7 (*C-8*), 19.0 (*C-14*), 14.4 (*C-13*); **m/z** (**ESI**) 257 $[MNa]^+$. Calcd. for $C_{14}H_{18}NaO_3$: 257.1148. Found: $[MNa]^+$, 257.1140 (2.4 ppm error). Data consistent with those previously reported in the literature.[87]

Lab. Book: ***LNB0149-004-02***.

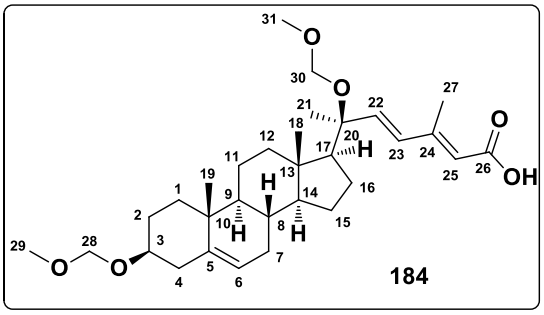
3β,20*R*-Bismethoxymethylenoxy-1,14,17-trisdeoxy-17-*epi*-25-desmethyl-withanolide F (183)



To a solution of LiHMDS (1.0 M in toluene, 1.38 mL, 1.38 mmol, 3.0 eq.) in THF (1.2 mL) was added a solution of 3,3-dimethylbutenoate (**178**) (0.174 mL, 1.24 mmol, 2.7 eq.) in THF/DMPU (1:1, 1.2 mL) dropwise at −78 °C and the resulting mixture was stirred for 1 h. A solution of aldehyde **118** (200 mg, 0.460 mmol, 1.0 eq.) in THF (2 mL) was added dropwise and the reaction mixture was stirred for 6 h at −78 °C. The reaction mixture was stirred overnight allowing the temperature to reach room temperature, quenched with sat. aq. NH_4Cl (5 mL) and extracted with Et_2O (3 × 5 mL). The combined organic phases were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (8:2 to 1:1 PE/Et_2O) to afford the *title compound* **183** (22.0 mg, 0.043 mmol, 9%) as a mixture of diastereoisomers at C-22 in a 1:1 ratio and as a yellow oil: $\boldsymbol{R_f}$ 0.22 (4:6 PE/Et_2O); $\boldsymbol{\delta_H}$ (**400 MHz**, **$CDCl_3$**) 5.80 (1 H, s, *H-25*), 5.35 (1 H, br d, *J* 4.6, *H-6*), 4.98 (1 H, d, *J* 6.7, *H-28a*), 4.81 (1 H, d, *J* 6.7, *H-28b*), 4.80 (1 H, d, *J* 7.8, *H-28a**), 4.69 (2 H, s, *H-30*), 4.68 (3 H, br s, *H-30**, *H 28b**), 4.32 (1 H, dt, *J* 13.1, 3.3, *H-22*), 3.46-3.19 (1 H, m, *H-3*), 3.39 (6 H, s, *H-29*, *H-31*), 2.51-2.42 (1 H, m, *H-23a*), 2.36-2.32 (1 H, m, *H-23b*), 2.30-2.22 (3 H, m, *H-2a*, *H-4*), 1.99 (3 H, br d, *J* 3.6, *H-27*), 1.89-1.45 (14 H, m, *H-1*, *H-2b*, *H-7*, *H-8*, *H-11*, *H-12a*, *H-15*, *H-16*, *H-17)*, 1.42 (3 H, s, *H-21**), 1.40 (3 H, s, *H-21*), 1.30-1.28 (1 H, m, *H-12b*), 1.06-1.04 (1 H, m, *H-14*), 1.00 (3 H, s, *H-19*), 0.94-0.89 (1 H, m, *H-9*), 0.86 (3 H, s, *H-18**), 0.81 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**100 MHz**, **$CDCl_3$**) 165.2 (*C-26*), 158.4 (*C-24*), 140.9 (*C-5*), 120.6 (*C-6*), 116.4 (*C-25*), 94.8 (*C-28*), 92.8 (*C-30*), 91.8 (*C-28**), 83.2 (*C-22*), 80.7 (*C-20*), 77.0 (*C-3*), 56.8 (*C-14*), 55.5 (*C-17*), 55.3 (*C-29, C-31*), 50.1 (*C-9*), 43.1 (*C-13*), 40.2 (*C-12*), 39.6 (*C-4*), 37.3 (*C-1*), 36.8 (*C-10*), 31.8 (*C-7*), 31.3 (*C-8*), 30.8 (*C-23*), 28.9 (*C-2*), 23.9 (*C-15*), 23.2 (*C-27*), 22.0 (*C-16*), 20.8 (*C-11*), 19.4 (*C-19*), 18.0 (*C-21*), 16.9 (*C-21**), 13.9 (*C-18**),

13.7 (*C-18*); **m/z** (**ESI**) 539 $[MNa]^+$. Calcd. for $C_{31}H_{48}NaO_6$: 539.3343. Found: $[MNa]^+$, 539.3345 (−0.4 ppm error). *****: signals of the other diastereoisomer.

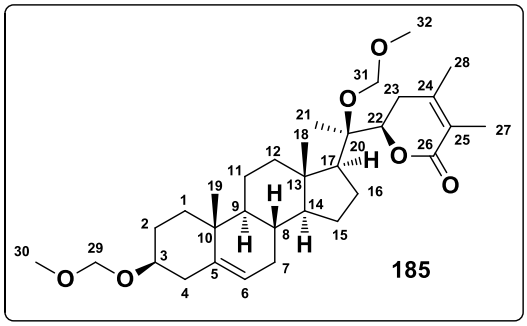
Lab. Book: ***LNB0149-025-09***.



Also isolated was *3β,20R-bismethoxymethylenoxy-22-(3'-carboxy-2'-methylpropenylenyl)-pregn-5-ene* (**184**) (60.0 mg, 0.116 mmol, 25%) as an amorphous yellow solid: **mp** 132-134 °C decomposed; $\boldsymbol{R_f}$ 0.35 (4:6 PE/Et_2O); $\boldsymbol{[\alpha]_D^{23}}$ 15.7 (*c* 0.5, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 2934 (O-H stretch), 1714 (C=O stretch), 1682 (C=C stretch), 1599 (C=C stretch), 1449 (O-H bend), 1252 (C-O stretch), 1032 (C-O-C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, $\boldsymbol{CDCl_3}$) 7.55 (1 H, d, *J* 16.4, *H-23*), 6.26 (1 H, d, *J* 16.4, *H-22*), 5.68 (1 H, s, *H-25*), 5.33 (1 H, br s, *H-6*), 4.67 (2 H, s, *H-28*), 4.63 (2 H, s, *H-30*), 3.44-3.39 (1 H, m, *H-3*), 3.37 (3 H, s, *H-31*), 3.35 (3 H, s, *H-29*), 2.35-2.25 (2 H, m, *H-4*), 2.00 (3 H, br d, *J* 1.1, *H-27*), 1.91-1.47 (15 H, m, *H-1*, *H-2*, *H-7*, *H-8*, *H-11*, *H-12a*, *H-15*, *H-16*, *H-17*), 1.44 (3 H, s, *H-21*), 1.18-1.04 (2 H, m, *H-12b*, *H-14*), 0.98 (3 H, s, *H-19*), 0.93-0.87 (1 H, m, *H-9*), 0.80 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**100 MHz**, $\boldsymbol{CDCl_3}$) 170.8 (*C-26*), 153.1 (*C-24*), 144.1 (*C-22*), 140.8 (*C-5*), 125.9 (*C-23*), 121.7 (*C-6*), 116.6 (*C-25*), 94.7 (*C-28*), 91.8 (*C-30*), 81.7 (*C-20*), 77.0 (*C-3*), 60.6 (*C-17*), 56.6 (*C-14*), 55.6 (*C-31*), 55.3 (*C-29*), 50.2 (*C-9*), 43.2 (*C-13*), 40.2 (*C-12*), 39.6 (*C-4*), 37.3 (*C-1*), 36.8 (*C-10*), 31.9 (*C-7*), 31.5 (*C-8*), 29.1 (*C-2*), 23.9 (*C-15*), 23.5 (*C-21*), 22.5 (*C-16*), 21.4 (*C-27*), 21.0 (*C-11*), 19.4 (*C-19*), 14.3 (*C-18*); **m/z** (**ESI**) 539 $[MNa]^+$. Calcd. for $C_{31}H_{48}NaO_6$: 539.3343. Found: $[MNa]^+$, 539.3327 (3.0 ppm error).

Lab. Book: ***LNB0149-025-02***.

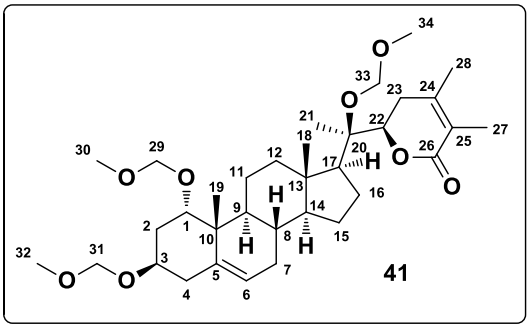
3β,20*R*-Bismethoxymethylenoxy-1,14,17-trisdeoxy-17-*epi*-withanolide F (185)



To a solution of LiHMDS (1.0 M in THF, 0.359 mL, 0.359 mmol, 3.0 eq.) in THF (0.417 mL) was added a solution of ethyl-2,3-dimethylbutenoate (**122**) (45.9 mg, 0.323 mmol, 2.7 eq.) in THF/DMPU (1:1, 0.834 mL) dropwise at −78 °C and the resulting mixture was stirred for 1.5 h. This reaction mixture was canulated dropwise to a solution of aldehyde **118** (52.0 mg, 0.120 mmol, 1.0 eq.) in THF (0.834 mL) and the reaction mixture was stirred for 5 h at −78 °C. The reaction mixture warmed to room temperature, quenched with sat. aq. NH_4Cl (3 mL), extracted with Et_2O (3 × 3 mL). The combined organic phases were washed with brine (3 mL), dried over $MgSO_4$, filtered and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (85:15 heptane/EtOAc) to afford the *title compound* **185** (46.6 mg, 0.088 mmol, 73%) as a white solid: **mp** 80-83 °C decomposed; $\boldsymbol{R_f}$ 0.29 (7:3 heptane/EtOAc); (Found: C, 72.23; H, 9.56; $C_{32}H_{50}O_6$ requires C, 72.42; H, 9.50%); $\mathbf{[\alpha]_D^{23}}$ 20.8 (*c* 1.0, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 2932 (C-H stretch), 1709 (C=O stretch), 1034 (C-O-C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, $\mathbf{CDCl_3}$) 5.33 (1 H, br d, *J* 4.3, *H-6*), 4.96 (1 H, d, *J* 6.7, *H-29a*), 4.81 (1 H, d, *J* 6.7, *H-29b*), 4.66 (2 H, s, *H-31*), 4.23 (1 H, dd, *J* 13.1, 3.4, *H-22*), 3.42-3.38 (1 H, m, *H-3*), 3.35 (3 H, s, *H-32*), 3.34 (3 H, s, *H-30*), 2.46 (1 H, br dd, *J* 15.9, 15.2, *H-23a*), 2.32 (1 H, br dd, *J* 12.7, 3.0, *H-4a*), 2.24 (1 H, br dd, *J* 12.7, 11.4, *H-4b*), 2.12 (1 H, br d, *J* 15.8, 1.96, *H-23b*), 1.99-1.95 (2 H, m, *H-7a*, *H-16a*), 1.91 (3 H, s, *H-28*), 1.89-1.86 (1 H, m, *H-2a*), 1.85 (3 H, s, *H-27*), 1.72-1.46 (10 H, m, *H-1*, *H-2b*, *H-7b*, *H-8*, *H-11*, *H-12a*, *H-15a*, *H-16b*), 1.57 (1 H, br dd, *J* 9.7, 9.5, *H-17*), 1.38 (3 H, s, *H-21*), 1.33-1.28 (1 H, m, *H-12b*), 1.17-1.10 (1 H, m, *H-15b*), 0.98 (3 H, s, *H-19*), 0.90-0.86 (2 H, m, *H-9*, *H-14*), 0.85 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**125 MHz**, $\mathbf{CDCl_3}$) 166.1 (*C-26*), 148.7 (*C-24*), 138.0 (*C-5*), 121.8 (*C-25*), 121.5 (*C-6*), 94.6 (*C-29*), 92.7 (*C-31*), 82.1 (*C-22*), 79.8 (*C-20*), 76.7 (*C-3*), 56.3 (*C-14*), 56.2 (*C-32*), 55.2 (*C-30*), 54.4 (*C-17*), 50.0 (*C-9*), 42.9 (*C-13*), 42.4 (*C-10*), 40.1 (*C-12*), 39.5 (*C-4*), 37.1 (*C-1*), 32.0 (*C-23*), 31.8 (*C-7*), 31.3 (*C-8*), 28.8 (*C-2*), 23.9 (*C-15*), 21.8 (*C-16*), 20.8

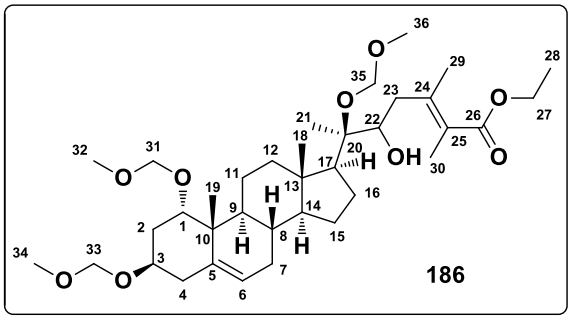
(*C-11*), 20.4 (*C-28*), 19.3 (*C-19*), 17.8 (*C-21*), 13.8 (*C-18*), 12.4 (*C-27*); **m/z** (**ESI**) 553 [MNa]+. Calcd. for $C_{32}H_{50}NaO_6$: 553.3500. Found: [MNa]+, 553.3481 (3.4 ppm error).
Lab. Book: ***LNB0170-018-05***.

1α,3β,20*R*-Trismethoxymethylenoxy-14,17-dideoxy-17-*epi*-withanolide F (41)[35]



To a solution of LiHMDS (1.0 M in THF, 1.09 mL, 1.09 mmol, 3.0 eq.) in THF (1.27 mL) was added a solution of ethyl-2,3-dimethylbutenoate (**122**) (140 mg, 0.982 mmol, 2.7 eq.) in THF/DMPU (1:1, 2.54 mL) dropwise at −78 °C and the resulting mixture was stirred for 1.5 h. This reaction mixture was canulated dropwise to a solution of aldehyde **40** (180 mg, 0.364 mmol, 1.0 eq.) in THF (2.54 mL), the reaction mixture was stirred for 5 h at −78 °C. The reaction mixture was quenched with sat. aq. NH_4Cl (5 mL), extracted with Et_2O (3 × 5 mL). The combined organic phases were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (9:1 to 8:2 heptane/EtOAc) to afford the title compound **41** (145 mg, 0.245 mmol, 67%) as a white solid: **mp** 215-218 °C decomposed (Lit.[29] 220-222 °C decomposed); $\boldsymbol{R_f}$ 0.40 (1:1 heptane/EtOAc); $\boldsymbol{[\alpha]_D^{23}}$ 30.4 (*c* 0.1, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 2932 (C-H stretch), 1710 (C=O stretch), 1027 (C-O-C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, **$CDCl_3$**) 5.54 (1 H, br d, *J* 4.9, *H-6*), 4.98 (1 H, d, *J* 6.5, *H-33a*), 4.81 (1 H, d, *J* 6.5, *H-33b*), 4.73 (1 H, d, *J* 7.1, *H-29a*), 4.66 (2 H, br s, *H-31*), 4.58 (1 H, d, *J* 7.1, *H-29b*), 4.23 (1 H, dd, *J* 13.3, 3.2, *H-22*), 3.86-3.83 (1 H, m, *H-3*), 3.72 (1 H, br s, *H-1*), 3.39 (3 H, s, *H-30*), 3.37 (3 H, s, *H-34*), 3.34 (3 H, s, *H-32*), 2.48-2.42 (2 H, m, *H-4a*, *H-23a*), 2.35-2.31 (1 H, m, *H-4b*), 2.22 (1 H, br d, *J* 13.0, *H-2a*), 2.12 (1 H, br d, *J* 17.2, 2.3, *H-23b*), 1.98-1.95 (2 H, m, *H-7a*, *H-16a*), 1.92 (3 H, s, *H-28*), 1.87 (3 H, s, *H-27*), 1.72-1.47 (8 H, m, *H-2b*, *H-7b*, *H-8*, *H-9*, *H-11a*, *H-12a*, *H-15a*, *H-16b*), 1.64 (1 H, br dd, *J* 10.7, 9.0, *H-17*), 1.40 (3 H, s, *H-21*), 1.30-1.27 (1 H, m, *H-12b*), 1.19-1.14 (2 H, m, *H-11b*, *H-15b*), 1.07-1.05 (1 H, m, *H-14*), 1.01 (3 H, s, *H-19*), 0.87 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$

(**100 MHz**, **$CDCl_3$**) 166.1 (*C-26*), 148.7 (*C-24*), 138.0 (*C-5*), 124.1 (*C-6*), 121.1 (*C-25*), 95.6 (*C-29*), 95.1 (*C-31*), 92.8 (*C-33*), 82.3 (*C-22*), 79.8 (*C-20*), 78.7 (*C-1*), 72.5 (*C-3*), 56.7 (*C-14*), 56.3 (*C-30*), 56.2 (*C-34*), 55.1 (*C-32*), 54.6 (*C-17*), 43.8 (*C-13*), 41.8 (*C-10*), 41.1 (*C-9*), 40.2 (*C-12*), 38.9 (*C-4*), 32.5 (*C-23*), 32.2 (*C-2*), 31.5 (*C-7*), 31.2 (*C-8*), 24.0 (*C-15*), 21.7 (*C-16*), 20.5 (*C-11*), 20.1 (*C-28*), 19.7 (*C-19*), 17.9 (*C-21*), 13.8 (*C-18*), 12.4 (*C-27*); **m/z** (**ESI**) 613 [MNa]+. Calcd. for $C_{34}H_{54}NaO_8$: 613.3711. Found: [MNa]+, 613.3690 (3.4 ppm error). Data consistent with those previously reported in the literature.[29]
Lab. Book: ***LNB0170-126-02***.

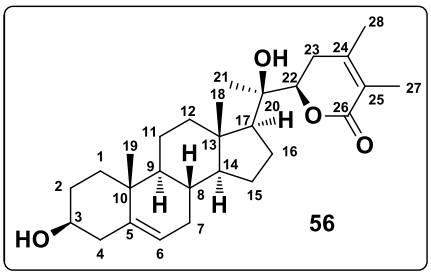


Also isolated was *1α,3β,20R-trismethoxymethylenoxy-22-hydroxy-(2',3'-dimethylbutenoate)-pregn-5-ene* (**186**) (7.10 mg, 0.011 mmol, 3%) as a yellow oil: $\boldsymbol{R_f}$ 0.42 (1:1 heptane/EtOAc); $\boldsymbol{[\alpha]_D^{23}}$ −32.9 (*c* 0.44, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3429 (O-H stretch), 2932 (C-H stretch), 1709 (C=O stretch), 1027 (C-O-C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, **$CDCl_3$**) 5.58 (1 H, br d, *J* 4.6, *H-6*), 4.87 (1 H, d, *J* 7.1, *H-35a*), 4.73 (1 H, d, *J* 7.0, *H-31a*), 4.65 (2 H, br s, *H-33*), 4.58 (1 H, d, *J* 7.0, *H-31b*), 4.52 (1 H, d, *J* 7.1, *H-35b*), 4.16 (2 H, br q, *J* 7.1, *H-27*), 3.84-3.82 (1 H, m, *H-3*), 3.72-3.69 (2 H, m, *H-1*, *H-22*), 3.38 (6 H, s, *H-32*, *H-36*), 3.34 (3 H, s, *H-34*), 2.44 (1 H, dd, *J* 13.1, 4.2, *H-4a*), 2.40-2.35 (1 H, m, *H-4b*), 2.29-2.10 (4 H, m, *H-2*, *H-23*), 2.03 (3 H, s, *H-29*), 2.02-1.99 (1 H, m, *H-12a*), 1.96-1.93 (1 H, m, *H-7a*), 1.90 (3 H, s, *H-30*), 1.71-1.39 (9 H, m, *H-7b*, *H-8*, *H-9*, *H-11*, *H-15a*, *H-16*, *H-17*), 1.29 (3 H, s, *H-21*), 1.25 (3 H, t, *J* 7.1 *H-28*), 1.21-1.14 (2 H, m, *H-12b*, *H-15b*), 1.02 (3 H, s, *H-19*), 1.01-0.98 (1 H, m, *H-14*), 0.78 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**125 MHz**, **$CDCl_3$**) 169.8 (*C-26*), 143.9 (*C-24*), 137.9 (*C-5*), 124.4 (*C-6*), 124.1 (*C-25*), 95.6 (*C-31*), 95.2 (*C-33*), 91.0 (*C-35*), 84.7 (*C-20*), 78.7 (*C-1*), 74.0 (*C-22*), 72.5 (*C-3*), 60.0 (*C-27*), 57.7 (*C-14*), 56.4 (*C-32*), 56.3 (*C-34*), 56.0 (*C-36*), 54.2 (*C-17*), 43.4 (*C-13*), 41.6 (*C-10*), 41.2 (*C-9*), 39.7 (*C-12*), 38.9 (*C-4*), 38.0 (*C-23*), 32.5 (*C-2*), 31.5 (*C-8*), 31.1 (*C-7*), 24.1 (*C-15*), 21.4 (*C-16*), 20.4 (*C-29*), 20.2 (*C-11*), 19.7 (*C-19*), 15.8 (*C-21*), 15.4 (*C-30*), 14.6 (*C-28*), 13.6

(*C-18*); **m/z** (**ESI**) 659 $[MNa]^+$. Calcd. for $C_{36}H_{60}NaO_9$: 659.4130. Found: $[MNa]^+$, 659.4122 (1.2 ppm error).

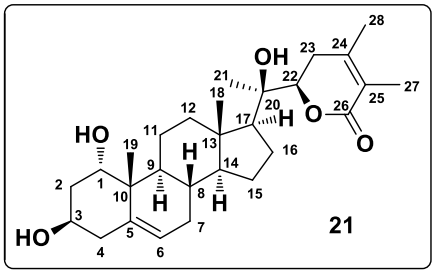
Lab. Book: ***LNB0170-126-05***.

3β,20*R*-Bishydroxy-1,14,17-trisdeoxy-17-*epi*-withanolide F (56)[29]



To a solution of MOM protected diol **185** (39.0 mg, 0.074 mmol, 1.0 eq.) in THF (1 mL) was added 6 M aq. HCl (0.94 mL). The reaction was stirred at room temperature for 3 h, quenched with sat. aq. $NaHCO_3$ (1 mL) and extracted with EtOAc (5 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (7:3 heptane/EtOAc) to afford the title compound **56** (32.8 mg, 0.074 mmol, 100%) as an amorphous white solid: **mp** 240-244 °C decomposed (Lit.[35] 243-245 °C decomposed); $\boldsymbol{R_f}$ 0.25 (7:3 heptane/EtOAc); $\boldsymbol{[\alpha]_D^{23}}$ 18.7 (*c* 1.0, $CHCl_3$) (Lit.[35] $\boldsymbol{[\alpha]_D^{20}}$ 16.7, *c* 0.62, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3396 (O-H stretch), 2926 (C-H stretch), 1694 (C=O stretch), 1058 (C-O-C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, **$CDCl_3$**) 5.33 (1 H, br d, *J* 4.4, *H-6*), 4.21 (1 H, dd, *J* 13.3, 3.2, *H-22*), 3.53-3.49 (1 H, m, *H-3*), 2.47-2.40 (1 H, m, *H-23a*), 2.28 (1 H, br dd, *J* 12.7, 3.7, *H-4*a), 2.22 (1 H, br dd, *J* 12.7, 11.6, *H-4b*), 2.11 (1 H, br dd, *J* 15.4, 3.2, *H-23b*), 2.04-2.00 (1 H, m, *H-12a*), 1.97-1.95 (2 H, m, *H-7a*, *H-11a*), 1.94 (3 H, s, *H-28*), 1.87 (3 H, s, *H-27*), 1.83-1.81 (2 H, m, *H-1a*, *H-2a*), 1.62-1.41 (7 H, m, *H-2a*, *H-7b*, *H-8*, *H-11b*, *H-15a*, *H-16a*, *H-17*), 1.27 (3 H, s, *H-21*), 1.25-1.20 (3 H, m, *H-12b*, *H-15b*, *H-16b*), 1.07-1.03 (1 H, m, *H-1b*), 0.99 (3 H, s, *H-19*), 0.98-0.96 (1 H, m, *H-14*), 0.91-0.89 (1 H, m, *H-9*), 0.85 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**100 MHz**, **$CDCl_3$**) 166.1 (*C-26*), 148.9 (*C-24*), 140.8 (*C-5*), 122.0 (*C-6*), 121.5 (*C-25*), 80.9 (*C-22*), 75.2 (*C-20*), 71.7 (*C-3*), 56.8 (*C-14*), 54.7 (*C-17*), 50.5 (*C-9*), 43.0 (*C-13*), 42.3 (*C-4*), 40.1 (*C-12*), 37.2 (*C-1*), 36.5 (*C-10*), 31.9 (*C-2*), 31.8 (*C-8*), 31.6 (*C-7*), 31.3 (*C-23*), 23.8 (*C-15*), 22.0 (*C-16*), 20.9 (*C-21*), 20.8 (*C-11*), 20.6 (*C-28*), 19.4 (*C-19*), 13.6 (*C-18*), 12.5 (*C-27*); **m/z** (**ESI**) 465 $[MNa]^+$. Calcd. for $C_{28}H_{42}NaO_4$: 465.2975. Found: $[MNa]^+$, 465.2974 (0.3 ppm error). Data consistent with those previously reported in the literature.[35] **Lab. Book**: ***LNB0189-007-02***.

1α,3β,20*R*-Trihydroxy-14,17-dideoxy-17-*epi*-withanolide F (21)[29]

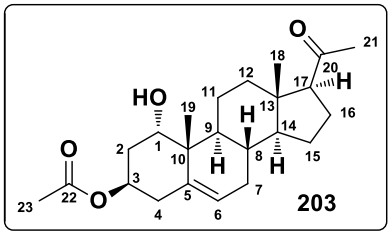


To a solution of MOM protected triol **41** (11.8 mg, 0.020 mmol, 1.0 eq.) in THF (0.5 mL) was added 6 M aq. HCl (0.40 mL). The reaction was stirred at room temperature for 7 h, quenched with sat. aq. $NaHCO_3$ (1 mL) and extracted with EtOAc (5 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (15:85 heptane/EtOAc) to afford the title compound **21** (10.2 mg, 0.022 mmol, 100%) as an amorphous pale pink solid: **mp** 264-269 °C decomposed (Lit.[29] 270-272 °C decomposed); $\boldsymbol{R_f}$ 0.13 (2:8 heptane/EtOAc); $\boldsymbol{[\alpha]_D^{23}}$ 17.3 (*c* 1.0, $CHCl_3$) (Lit.[29] $\boldsymbol{[\alpha]_D}$ 19.4, *c* 0.14); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3396 (O-H stretch), 2926 (C-H stretch), 1692 (C=O stretch), 1052 (C-O-C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, $\boldsymbol{CDCl_3}$) 5.58 (1 H, br d, *J* 4.8, *H-6*), 4.21 (1 H, dd, *J* 13.3, 3.3, *H-22*), 4.01-3.94 (1 H, m, *H-3*), 3.84 (1 H, br s, *H-1*), 2.43 (1 H, br d, *J* 15.9, *H-23a*), 2.37 (1 H, br dd, *J* 13.7, 3.2, *H-4*a), 2.28 (1 H, br dd, *J* 13.7, 12.1, *H-4b*), 2.13-2.00 (2 H, m, *H-2a*, *H-23b*), 2.00-1.97 (2 H, m, *H-7a*, *H-16a*), 1.94 (3 H, s, *H-28*), 1.87 (3 H, s, *H-27*), 1.73 (1 H, br ddd, *J* 12.4, 12.0, 2.3, *H-2b*), 1.66-1.45 (6 H, m, *H-7b*, *H-11a*, *H-12a*, *H-15a*, *H-16b*, *H-17*), 1.30-1.28 (2 H, m, *H-8*, *H-12b*), 1.27 (3 H, s, *H-21*), 1.20-1.14 (2 H, *H-9*, *H-15b*), 1.08-1.06 (2 H, m, *H-11b*, *H-14*), 1.02 (3 H, s, *H-19*), 0.86 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**125 MHz**, $\boldsymbol{CDCl_3}$) 166.1 (*C-26*), 148.9 (*C-24*), 137.4 (*C-5*), 125.4 (*C-6*), 122.0 (*C-25*), 81.0 (*C-22*), 75.2 (*C-20*), 72.1 (*C-1*), 66.4 (*C-3*), 56.7 (*C-14*), 54.7 (*C-17*), 43.0 (*C-13*), 41.7 (*C-10*), 41.5 (*C-9*), 41.4 (*C-4*), 39.8 (*C-12*), 38.3 (*C-2*), 31.6 (*C-23*), 31.5 (*C-7*), 31.3 (*C-8*), 23.9 (*C-15*), 22.7 (*C-16*), 20.8 (*C-21*), 20.5 (*C-11*), 20.1 (*C-28*), 19.4 (*C-19*), 13.6 (*C-18*), 12.4 (*C-27*); **m/z** (**ESI**) 459 $[MH]^+$. Calcd. for $C_{28}H_{43}O_5$: 459.3105. Found: $[MH]^+$, 459.3117 (−2.6 ppm error). Data consistent with those previously reported in the literature.[29]

Lab. Book: ***LNB0149-125-03***.

6.2.3. Chapter 4. A/B-ring functionalisation: the synthesis of 14,17-dideoxy-17-*epi*-withanoldie F (**24**)

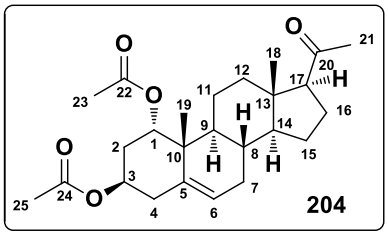
3β-Acetate–1α-hydroxy-5-pregnen-20-one (203)



To a solution of diol **61** (30.0 mg, 0.090 mmol, 1.0 eq.) in CH_2Cl_2 (5 mL) was added NEt_3 (50% in CH_2Cl_2, 37.8 μL, 0.237 mmol, 2.6 eq.), DMAP (0.500 mg, 0.008 mmol, 0.05 eq.) and Ac_2O (30.9 μL, 0.328 mmol, 3.6 eq.). The reaction was stirred at room temperature overnight, quenched with 0.1 M aq. HCl (2 mL) and extracted with CH_2Cl_2 (5 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (7:3 heptane/EtOAc) to afford the *title compound* **203** (21.9 mg, 0.059 mmol, 65%) as an amorphous white solid: **mp** 175-179 °C decomposed; $\boldsymbol{R_f}$ 0.34 (1:1 heptane/EtOAc); $\boldsymbol{[\alpha]_D^{23}}$ 13.6 (*c* 1.0, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3444 (O-H stretch), 2931 (C-H stretch), 1742 (C=O stretch), 1706 (C=O stretch), 1035 (C-O-C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, **$CDCl_3$**) 5.59 (1 H, br d, *J* 5.2, *H-6*), 5.05-4.98 (1 H, m, *H-3*), 3.85 (1 H, br s, *H-1*), 2.52 (1 H, t, *J* 8.9, *H-17*), 2.42 (1 H, ddd, *J* 13.2, 5.3, 1.9, *H-4a*), 2.33 (1 H, br dd, *J* 13.2, 11.9, *H-4b*), 2.18-2.14 (1 H, m, *H-16a*), 2.10 (3 H, s, *H-21*), 2.08-2.05 (1 H, m, *H-2a*), 2.04-2.01 (1 H, m, *H-12a*), 2.01 (3 H, s, *H-23*), 1.98-1.95 (1 H, m, *H-7a*), 1.85 (1 H, td, *J* 11.6, 1.9, *H-2b*), 1.72-1.56 (5 H, m, *H-7b*, *H-9, H-11a, H-15a, H-16b*), 1.50-1.39 (3 H, m, *H-8*, *H-11b*, *H-12b*), 1.21-1.17 (2 H, m, *H-15b*, *H-14*), 1.02 (3 H, s, *H-19*), 0.61 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**125 MHz**, **$CDCl_3$**) 209.5 (*C-20*), 170.5 (*C-22*), 136.3 (*C-5*), 126.1 (*C-6*), 72.4 (*C-1*), 69.4 (*C-3*), 63.5 (*C-17*), 56.6 (*C-14*), 43.9 (*C-13*), 41.7 (*C-10*), 41.3 (*C-9*), 38.5 (*C-12*), 37.2 (*C-4*), 34.6 (*C-2*), 31.7 (*C-21*), 31.6 (*C-7*), 31.5 (*C-8*), 24.5 (*C-15*), 22.8 (*C-16*), 21.3 (*C-23*), 20.2 (*C-11*), 19.3 (*C-19*), 13.2 (*C-18*); **m/z** (**ESI**) 397 $[MNa]^+$. Calcd. for $C_{23}H_{34}NaO_4$: 397.2349. Found: $[MNa]^+$, 397.2343 (1.6 ppm error).

Lab. Book: ***LNB0170-079-03***.

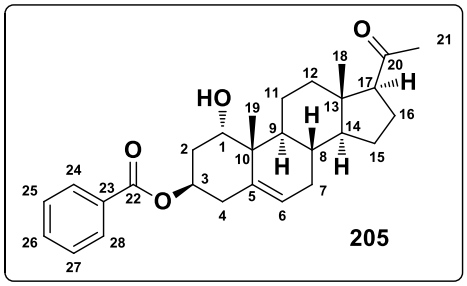
1α,3β-Bisacetate-5-pregnen-20-one (204)[35]



To a solution of diol **61** (30.0 mg, 0.090 mmol, 1.0 eq.) in CH_2Cl_2 (5 mL) was added NEt_3 (50% in CH_2Cl_2, 37.8 μL, 0.237 mmol, 2.6 eq.), DMAP (1.10 mg, 9.02 μmol, 0.10 eq.) and Ac_2O (30.9 μL, 0.328 mmol, 3.6 eq.). The reaction was stirred at room temperature overnight, quenched with 0.1 M aq. HCl (2 mL) and extracted with CH_2Cl_2 (5 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (7:3 heptane/EtOAc) to afford the title compound **204** (25.0 mg, 0.060 mmol, 67%) as an amorphous white solid: **mp** 155-159 °C decomposed (Lit.[91] 141-142 °C decomposed); $\boldsymbol{R_f}$ 0.50 (1:1 heptane/EtOAc); $\boldsymbol{[\alpha]_D^{23}}$ 27.1 (*c* 1.0, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 2940 (C-H stretch), 1733 (C=O stretch), 1703 (C=O stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, **$CDCl_3$**) 5.51 (1 H, br d, *J* 5.0, *H-6*), 5.04 (1 H, br s, *H-1*), 4.92-4.86 (1 H, m, *H-3*), 2.51 (1 H, t, *J* 9.0, *H-17*), 2.46 (1 H, ddd, *J* 13.2, 4.8, 2.0, *H-4a*), 2.32 (1 H, br dd, *J* 12.0, 11.2, *H-4b*), 2.19-2.12 (1 H, m, *H-16a*), 2.08 (3 H, s, *H-21*), 2.07-2.05 (1 H, m, *H-2a*), 2.04 (3 H, s, *H-25*), 1.99 (3 H, s, *H-23*), 1.98-1.95 (2 H, m, *H-7a*, *H-12a*), 1.80 (1 H, td, *J* 11.9, 2.0, *H-2b*), 1.69-1.55 (3 H, m, *H-7b*, *H-15a*, *H-16b*), 1.48-1.31 (5 H, m, *H-8*, *H-9*, *H-11*, *H-12b*), 1.19-1.14 (2 H, m, *H-14*, *H-15b*), 1.05 (3 H, s, *H-19*), 0.58 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**125 MHz**, **$CDCl_3$**) 209.3 (*C-20*), 170.3 (*C-24*), 170.2 (*C-22*), 136.0 (*C-5*), 124.8 (*C-6*), 74.5 (*C-1*), 69.2 (*C-3*), 63.5 (*C-17*), 56.8 (*C-14*), 43.8 (*C-13*), 42.0 (*C-9*), 40.4 (*C-10*), 38.6 (*C-12*), 37.2 (*C-4*), 31.9 (*C-2*), 31.6 (*C-8*), 31.5 (*C-21*), 31.4 (*C-7*), 24.4 (*C-15*), 22.7 (*C-16*), 21.3 (*C-25*), 21.1 (*C-23*), 20.4 (*C-11*), 19.3 (*C-19*), 13.2 (*C-18*); **m/z** (**ESI**) 417 $[MH]^+$. Calcd. for $C_{25}H_{37}O_5$: 417.2636. Found: $[MH]^+$, 417.2633 (0.6 ppm error). Data consistent with those previously reported in the literature.[91]

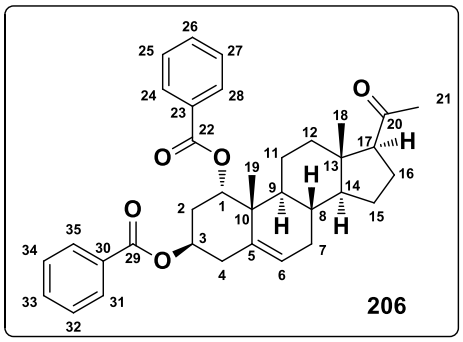
Lab. Book: ***LNB0170-065-02***.

3β-Benzoyl–1α-hydroxy-5-pregnen-20-one (205)



To a solution of diol **61** (20.0 mg, 0.060 mmol, 1.0 eq.) in CH_2Cl_2 (0.5 mL) was added pyridine (24.2 μL, 0.301 mmol, 5.0 eq.) and BzCl (15.4 μL, 0.132 mmol, 2.2 eq.) at 0 °C. The reaction was stirred at room temperature overnight, quenched with sat. aq. $NaHCO_3$ (1 mL) and extracted with EtOAc (5 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (8:2 to 7:3 heptane/EtOAc) to afford the *title compound* **205** (17.7 mg, 0.041 mmol, 68%) as an amorphous white solid: **mp** 228-230 °C decomposed; $\boldsymbol{R_f}$ 0.27 (1:1 heptane/EtOAc); $\boldsymbol{[\alpha]_D^{23}}$ 18.6 (*c* 1.0, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3483 (O-H stretch), 2967 (C-H stretch), 1714 (C=O stretch), 1684 (C=O stretch), 1453 (C=C stretch), 711 (C-H bend); $\boldsymbol{\delta_H}$ (**400 MHz**, **$CDCl_3$**) 8.02 (2 H, d, *J* 7.3, *H-24*, *H-28*), 7.54 (1 H, t, *J* 7.0, *H-26*), 7.42 (2 H, t, *J* 7.6, *H-25*, *H-27*), 5.64 (1 H, br d, *J* 4.8, *H-6*), 5.30-5.26 (1 H, m, *H-3*), 3.93 (1 H, br s, *H-1*), 2.58-2.49 (3 H, m, *H-4*, *H-17*), 2.25 (1 H, br d, *J* 12.3, *H-2a*), 2.18-2.16 (1 H, m, *H-16a*), 2.12 (3 H, s, *H-21*), 2.04-1.98 (3 H, m, *H-2a*, *H-7a*, *H-12a*), 1.77-1.47 (8 H, m, *H-7b*, *H-8*, *H-9*, *H-11*, *H-12b*, *H-15a*, *H-16b*), 1.32-1.24 (2 H, m, *H-14*, *H-15b)*, 1.08 (3 H, s, *H-19*), 0.64 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**125 MHz**, **$CDCl_3$**) 209.5 (*C-20*), 170.5 (*C-22*), 136.3 (*C-5*), 132.8 (*C-26*), 130.6 (*C-23*), 129.5 (*C-25, C-27*), 128.3 (*C-24, C-28*), 126.1 (*C-6*), 72.4 (*C-1*), 69.4 (*C-3*), 63.5 (*C-17*), 56.6 (*C-14*), 43.9 (*C-13*), 41.7 (*C-10*), 41.3 (*C-9*), 38.5 (*C-12*), 37.2 (*C-4*), 34.6 (*C-2*), 31.7 (*C-21*), 31.6 (*C-7*), 31.5 (*C-8*), 24.5 (*C-15*), 22.8 (*C-16*), 20.2 (*C-11*), 19.3 (*C-19*), 13.2 (*C-18*); **m/z** (**ESI**) 459 $[MNa]^+$. Calcd. for $C_{28}H_{36}NaO_4$: 459.2506. Found: $[MNa]^+$, 459.2508 (−0.4 ppm error).

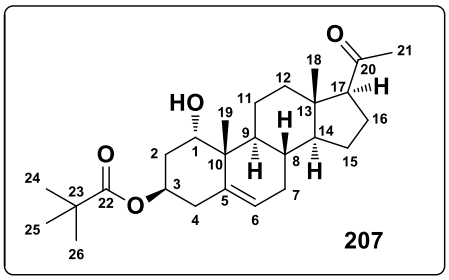
Lab. Book: ***LNB0170-089-03***.



Also isolated was *1α,3β-bisbenzoyl-5-pregnen-20-one* (**206**) (6.30 mg, 0.012 mmol, 19%) as a white solid: **mp** 234-236 °C decomposed; $\boldsymbol{R_f}$ 0.45 (1:1 heptane/EtOAc); $\boldsymbol{[\alpha]_D^{23}}$ 50.3 (*c* 0.8, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 2939 (C-H stretch), 1713 (C=O stretch), 1450 (C=C stretch), 709 (C-H bend); $\boldsymbol{\delta_H}$ (**400 MHz**, **$CDCl_3$**) 8.05 (2 H, d, *J* 7.3, *H-24*, *H-28*), 7.99 (2 H, d, *J* 7.2, *H-31*, *H-35*), 7.57 (1 H, t, *J* 7.4, *H-26*), 7.53 (1 H, t, *J* 7.4, *H-33*), 7.47 (2 H, t, *J* 7.7, *H-25*, *H-27*), 7.41 (2 H, t, *J* 7.7, *H-32*, *H-34*), 5.68 (1 H, br d, *J* 5.2, *H-6*), 5.40 (1 H, br s, *H-1*), 5.28-5.25 (1 H, m, *H-3*), 2.73 (1 H, br ddd, *J* 13.5, 5.6, 1.8, *H-4a*), 2.58-2.54 (1 H, m, *H-4b*), 2.45 (1 H, br t, *J* 9.1, *H-17*), 2.38-2.35 (1 H, m, *H-2a*), 2.19-2.07 (2 H, m, *H-2b*, *H-16a*), 2.05 (3 H, s, *H-21*), 2.05-2.03 (1 H, m, *H-7a*), 1.98-1.96 (1 H, m, *H-12a*), 1.68-1.32 (8 H, m, *H-7b*, *H-8*, *H-9*, *H-11*, *H-12b*, *H-15a*, *H-16b*), 1.14-1.09 (2 H, m, *H-14*, *H-15b*), 1.21 (3 H, s, *H-19*), 0.61 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**125 MHz**, **$CDCl_3$**) 209.4 (*C-20*), 165.8 (*C-22*), 165.5 (*C-29*), 136.1 (*C-5*), 133.1 (*C-26*), 132.9 (*C-33*), 130.4 (*C-23*), 130.2 (*C-30*), 129.7 (*C-25*, *C-27*), 129.5 (*C-32*, *C-34*), 128.6 (*C-24*, *C-28*), 128.3 (*C-31*, *C-35*), 125.2 (*C-6*), 74.9 (*C-1*), 70.3 (*C-3*), 63.5 (*C-17*), 56.7 (*C-14*), 43.9 (*C-13*), 42.3 (*C-10*), 41.0 (*C-9*), 38.5 (*C-12*), 37.4 (*C-4*), 32.1 (*C-2*), 31.8 (*C-21*), 31.7 (*C-7*), 31.5 (*C-8*), 24.8 (*C-15*), 22.7 (*C-16*), 20.9 (*C-11*), 19.5 (*C-19*), 13.3 (*C-18*); **m/z** (**ESI**) 563 $[MNa]^+$. Calcd. for $C_{35}H_{40}NaO_5$: 536.2768. Found: $[MNa]^+$, 563.2779 (−1.9 ppm error).

Lab. Book: ***LNB0170-089-02***.

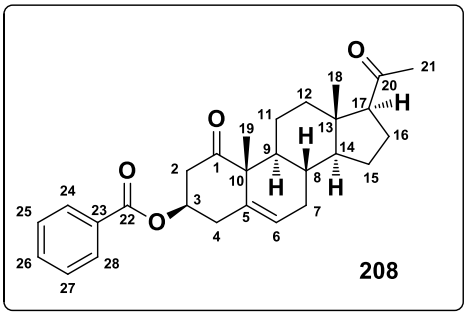
1α-Hydroxy-3β-pivaloyl 5-pregnen-20-one (207)



To a solution of diol **61** (20.0 mg, 0.060 mmol, 1.0 eq.) in CH_2Cl_2 (0.5 mL) was added pyridine (24.2 μL, 0.301 mmol, 5.0 eq.) and PvCl (16.3 μL, 0.132 mmol, 2.2 eq.) at 0 °C. The reaction was stirred at room temperature overnight, quenched with sat. aq. $NaHCO_3$ (2 mL) and extracted with EtOAc (5 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (7:3 heptane/EtOAc) to afford the *title compound* **207** (3.40 mg, 8.16 μmol, 14%) as an amorphous white solid: **mp** 222-225 °C decomposed; $\boldsymbol{R_f}$ 0.30 (1:1 heptane/EtOAc); $\boldsymbol{[\alpha]_D^{22}}$ 24.7 (*c* 0.19, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3383 (O-H stretch), 2923 (C-H stretch), 1723 (C=O stretch), 1700 (C=O stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, $\boldsymbol{CDCl_3}$) 5.60 (1 H, br d, *J* 5.1, *H-6*), 5.00-4.97 (1 H, m, *H-3*), 3.87 (1 H, br s, *H-1*), 2.53 (1 H, t, *J* 9.1, *H-17*), 2.42 (1 H, ddd, *J* 13.4, 5.3, 1.7, *H-4a*), 2.31 (1 H, br dd, *J* 13.4, 12.8, *H-4b*), 2.20-2.15 (1 H, m, *H-16a*), 2.11 (3 H, s, *H-21*), 2.05-1.98 (3 H, m, *H-2a*, *H-7a*, *H-12a*), 1.83 (1 H, td, *J* 12.3, 1.8, *H-2b*), 1.70-1.41 (5 H, m, *H-7b*, *H-9*, *H-11a*, *H-15a*, *H-16b*), 1.32-1.17 (5 H, m, *H-8*, *H-11b*, *H-12b*, *H-14*, *H-15b*), 1.17 (9 H, s, *H-24*, *H-25*, *H-26*), 1.04 (3 H, s, *H-19*), 0.62 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**125 MHz**, $\boldsymbol{CDCl_3}$) 209.6 (*C-20*), 178.3 (*C-22*), 136.0 (*C-5*), 126.2 (*C-6*), 72.6 (*C-1*), 69.2 (*C-3*), 63.6 (*C-17*), 56.7 (*C-14*), 43.8 (*C-13*), 41.8 (*C-10*), 41.4 (*C-9*), 38.5 (*C-12*), 38.1 (*C-23*), 37.2 (*C-4*), 34.0 (*C-2*), 31.7 (*C-7*), 31.6 (*C-21*), 31.5 (*C-8*), 27.2 (*C-24*, *C-25*, *C-26*), 23.2 (*C-15*), 22.6 (*C-16*), 20.3 (*C-11*), 19.4 (*C-19*), 13.2 (*C-18*); **m/z** (**ESI**) 439 $[MNa]^+$. Calcd. for $C_{26}H_{40}NaO_4$: 439.2819. Found: $[MNa]^+$, 439.2830 (−2.7 ppm error).

Lab. Book: ***LNB0170-090-02***.

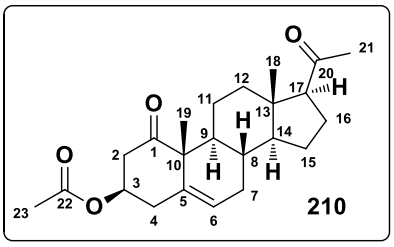
3β-Benzoyl-1-oxo 5-pregnen-20-one (208)



To a solution of alcohol **205** (13.6 mg, 0.031 mmol, 1.0 eq.) in CH_2Cl_2 (0.5 mL) was added DMP (39.6 mg, 0.094 mmol, 3.0 eq.). The reaction was stirred at room temperature overnight, quenched with 1 M aq. Na_2CO_3 (2 mL) and extracted with CH_2Cl_2 (5 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (7:3 heptane/EtOAc) to afford the *title compound* **208** (4.36 mg, 0.010 mmol, 32%) as an amorphous white solid: **mp** 242-243 °C decomposed; $\boldsymbol{R_f}$ 0.40 (1:1 heptane/EtOAc); $\boldsymbol{[\alpha]_D^{23}}$ 25.0 (*c* 0.28, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 2918 (C-H stretch), 1702 (C=O stretch), 1113 (C-O-C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, **$CDCl_3$**) 8.02 (2 H, d, *J* 7.2, *H-24*, *H-28*), 7.57 (1 H, t, *J* 7.4, *H-26*), 7.44 (2 H, t, *J* 7.7, *H-25*, *H-27*), 5.71 (1 H, br d, *J* 5.4, *H-6*), 5.21-5.13 (1 H, m, *H-3*), 2.86-2.76 (4 H, m, *H-2*, *H-4*), 2.56 (1 H, t, *J* 9.1, *H-17*), 2.13 (3 H, s, *H-21*), 2.03-2.00 (2 H, m, *H-7a*, *H-12a*), 1.85-1.81 (1 H, m, *H-16a*), 1.72-1.44 (8 H, m, *H-7b*, *H-8*, *H-9*, *H-11*, *H-12b*, *H-15a*, *H-16b*), 1.28-1.21 (2 H, m, *H-15b*, *H-14*), 1.33 (3 H, s, *H-19*), 0.64 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**125 MHz**, **$CDCl_3$**) 210.1 (*C-1*), 209.5 (*C-20*), 165.7 (*C-22*), 134.5 (*C-5*), 133.3 (*C-26*), 130.6 (*C-23*), 129.7 (*C-25*, *C-27*), 128.5 (*C-24*, *C-28*), 126.8 (*C-6*), 70.6 (*C-3*), 63.7 (*C-17*), 58.6 (*C-14*), 52.8 (*C-10*), 44.1 (*C-2*), 44.0 (*C-13*), 42.7 (*C-9*), 38.7 (*C-12*), 37.4 (*C-4*), 31.9 (*C-21*), 31.7 (*C-8*), 31.2 (*C-7*), 24.5 (*C-15*), 22.8 (*C-16*), 22.5 (*C-11*), 18.9 (*C-19*), 13.5 (*C-18*); **m/z** (**ESI**) 457 $[MNa]^+$. Calcd. For $C_{28}H_{34}NaO_4$: 457.2349. Found: $[MNa]^+$, 457.2351 (−0.3 ppm error).

Lab. Book: ***LNB0170-097-02***.

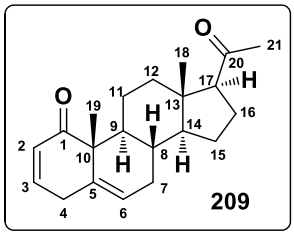
3β-Acetate-1-oxo 5-pregnen-20-one (210)



To a solution of alcohol **203** (50.0 mg, 0.134 mmol, 1.0 eq.) in CH_2Cl_2 (1.25 mL) was added DMP (113 mg, 0.267 mmol, 2.0 eq.). The reaction was stirred at room temperature overnight, quenched with 1 M aq. Na_2CO_3 (2 mL) and extracted with CH_2Cl_2 (5 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (7:3 heptane/EtOAc) to afford the title compound **210** (50 mg, 0.134 mmol, 100%) as an amorphous yellow solid: **mp** 146-150 °C decomposed (Lit.[138] 154-156 °C decomposed); $\boldsymbol{R_f}$ 0.45 (1:1 heptane/EtOAc); $\boldsymbol{[\alpha]_D^{23}}$ 65.6 (*c* 0.68, $CHCl_3$) (Lit.[138] $\boldsymbol{[\alpha]_D}$ 73.5, $CHCl_3$); 2922 (C-H stretch), 1739 (C=O stretch), 1703 (C=O stretch), 1032 (C-O-C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, **$CDCl_3$**) 5.65 (1 H, br d, *J* 5.4, *H-6*), 4.92-4.86 (1 H, m, *H-3*), 2.73-2.61 (3 H, m, *H-2*, *H-4a*), 2.54 (1 H, t, *J* 8.9, *H-17*), 2.50-2.47 (1 H, m, *H-4b)*, 2.11 (3 H, s, *H-21*), 2.03 (3 H, s, *H-23*), 2.02-1.98 (1 H, m, *H-12a*), 1.78 (1 H, dd, *J* 13.1, 3.4, *H-16a*), 1.70-1.41 (7 H, m, *H-7a*, *H-8*, *H-9*, *H-11a*, *H-12b*, *H-15a*, *H-16b*), 1.26 (3 H, s, *H-19*), 1.25-1.22 (4 H, m, *H-7b*, *H-11b*, *H-14*, *H-15b*), 0.62 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**125 MHz**, **$CDCl_3$**) 210.0 (*C-1*), 209.4 (*C-20*), 170.1 (*C-22*), 134.4 (*C-5*), 126.5 (*C-6*), 70.0 (*C-3*), 63.6 (*C-17*), 56.7 (*C-14*), 52.7 (*C-10*), 43.9 (*C-2*), 43.9 (*C-13*), 42.5 (*C-9*), 38.6 (*C-12*), 37.2 (*C-4*), 31.8 (*C-8*), 31.5 (*C-21*), 31.0 (*C-7*), 24.4 (*C-15*), 22.7 (*C-16*), 22.4 (*C-11*), 21.1 (*C-23*), 18.7 (*C-19*), 13.3 (*C-18*); **m/z** (**ESI**) 373 $[MH]^+$. Calcd. for $C_{23}H_{33}O_4$: 373.2373. Found: $[MH]^+$, 373.2358 (4.0 ppm error). Data consistent with those previously reported in the literature.[138]

Lab. Book: ***LNB0170-100-03***.

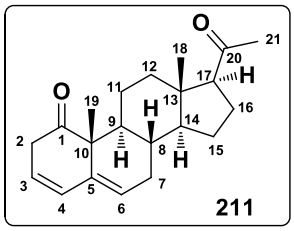
2,5-Pregnen-1,20-dione (209)



To a solution of acetate **210** (17.6 mg, 0.047 mmol, 1.0 eq.) in benzene (0.5 mL) was added Al_2O_3 (120 mg, 1.18 mmol, 25.0 eq.) at room temperature. The reaction was heated at 55 °C, stirred for 5 h, filtered through Celite® and washed with EtOAc (5 mL). The filtrate was concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (7:3 heptane/EtOAc) to afford the *title compound* **209** (14.0 mg, 0.045 mmol, 95%) as an amorphous white solid: **mp** 132-136 °C decomposed $\boldsymbol{R_f}$ 0.58 (1:1 heptane/EtOAc); $\mathbf{[\alpha]_D^{23}}$ 27.5 (*c* 0.71, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 2965 (C-H stretch), 1701 (C=O stretch), 1682 (C=O stretch), 1665 (C=C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, $\mathbf{CDCl_3}$) 6.78-6.75 (1 H, ddd, *J* 10.0, 4.9, 2.5, *H-3*), 5.87 (1 H, dd, *J* 10.0, 2.1, *H-2*), 5.56 (1 H, br d, *J* 6.1, *H-6*), 3.27 (1 H, dd, *J* 21.4, 2.4, *H-4a*), 2.82 (1 H, dd, *J* 21.4, 4.9, *H-4b*), 2.57 (1 H, t, *J* 9.2, *H-17*), 2.29 (1 H, dd, *J* 13.4, 3.1, *H-16a*), 2.19-2.15 (1 H, m, *H-11a*), 2.12 (3 H, s, *H-21*), 2.03-1.95 (2 H, m, *H-7a*, *H-12a*), 1.72-1.41 (7 H, m, *H-9*, *H-7b*, *H-8*, *H-11b*, *H-12b*, *H-15a*, *H-16b*), 1.28-1.24 (2 H, m, *H-14*, *H-15b*), 1.22 (3 H, s, *H-19*), 0.63 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**125 MHz**, $\mathbf{CDCl_3}$) 209.6 (*C-20*), 204.4 (*C-1*), 145.2 (*C-3*), 135.9 (*C-5*), 127.9 (*C-2*), 124.6 (*C-6*), 63.8 (*C-17*), 56.8 (*C-14*), 50.5 (*C-10*), 43.8 (*C-13*), 42.8 (*C-9*), 38.9 (*C-12*), 33.5 (*C-8*), 33.2 (*C-4*), 31.6 (*C-21*), 30.7 (*C-7*), 24.5 (*C-15*), 23.7 (*C-16*), 22.5 (*C-11*), 19.0 (*C-19*), 13.4 (*C-18*); **m/z** (**ESI**) 313 $[MH]^+$. Calcd. for $C_{21}H_{29}O_2$: 313.2162. Found: $[MH]^+$, 313.2151 (3.5 ppm error).

Lab. Book: ***LNB0170-114-01***.

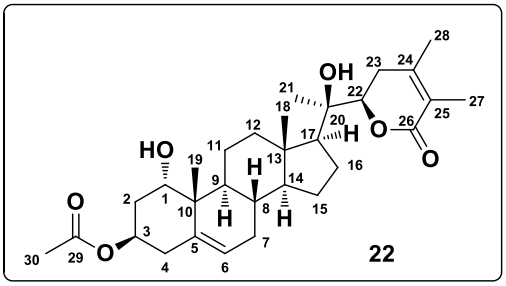
3,5-Pregnen-1,20-dione (211)



To a solution of acetate **210** (14.3 mg, 0.038 mmol, 1.0 eq.) in CH_2Cl_2 (0.5 mL) was added DBN (9.49 μL, 0.077 mmol, 2.0 eq.). The reaction was stirred at room temperature for 40 min, quenched with sat. aq. NH_4Cl (2 mL) and extracted with CH_2Cl_2 (5 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (7:3 heptane/EtOAc) to afford the *title compound* **211** (10.7 mg, 0.034 mmol, 89%) and as an amorphous white solid: **mp** 150-153 °C decomposed; $\boldsymbol{R_f}$ 0.58 (1:1 heptane/EtOAc); $\boldsymbol{[\alpha]_D^{23}}$ 90.9 (*c* 0.6, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 2930 (C-H stretch), 1721 (C=O stretch), 1702 (C=O stretch), 1690 (C=C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, **$CDCl_3$**) 6.03 (1 H, br d, *J* 9.3, *H-4*), 5.63 (1 H, dd, *J* 5.8, 2.3, *H-6*), 5.61-5.59 (1 H, m, *H-3*), 3.29 (1 H, br d, *J* 19.5, *H-2a*), 2.74 (1 H, dd, *J* 19.8, 4.6, *H-2b*), 2.57 (1 H, t, *J* 9.2, *H-17*), 2.21-2.14 (2 H, m, *H-7a*, *H-11a*), 2.12 (3 H, s, *H-21*), 1.98 (1 H, dt, *J* 12.2, 3.6, *H-12a*), 1.91-1.85 (1 H, m, *H-11b*), 1.82 (1 H, dd, *J* 11.9, 4.0, *H-9*), 1.71-1.50 (5 H, m, *H-7b*, *H-8*, *H-12b*, *H-15a*, *H-16a*), 1.35 (3 H, s, *H-19*), 1.34-1.32 (1 H, m, *H-16b*), 1.28-1.22 (2 H, m, *H-14*, *H-15b*), 0.63 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**125 MHz**, **$CDCl_3$**) 210.8 (*C-20*), 209.4 (*C-1*), 141.0 (*C-5*), 129.4 (*C-4*), 126.9 (*C-6*), 121.6 (*C-3*), 63.7 (*C-17*), 56.7 (*C-14*), 52.1 (*C-10*), 44.1 (*C-13*), 40.9 (*C-9*), 39.8 (*C-2*), 38.7 (*C-12*), 31.7 (*C-8*), 31.6 (*C-21*), 30.9 (*C-7*), 24.4 (*C-15*), 22.6 (*C-16*), 22.5 (*C-11*), 20.4 (*C-19*), 13.4 (*C-18*); **m/z** (**ESI**) 313 $[MH]^+$. Calcd. for $C_{21}H_{29}O_2$: 313.2162. Found: $[MH]^+$, 313.2153 (2.8 ppm error).

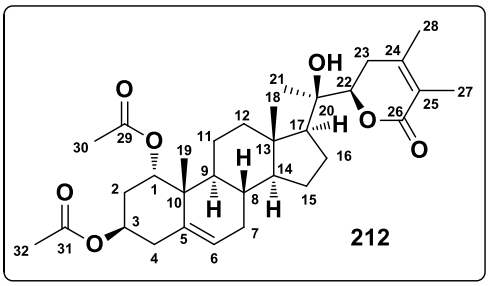
Lab. Book: ***LNB0170-093-02***.

3β-Acetate-1α,20*R*-bishydroxy-14,17-dideoxy-17-*epi*-withanolide F (22)[35]



To a solution of triol **21** (100 mg, 0.218 mmol, 1.0 eq.) in CH_2Cl_2 (11 mL) was added NEt_3 (50% in CH_2Cl_2, 80.0 μL, 0.574 mmol, 2.6 eq.), Ac_2O (74.9 μL, 0.792 mmol, 3.6 eq.) and DMAP (1.33 mg, 0.011 mmol, 0.05 eq.). The reaction was stirred at room temperature for 6 h, quenched with 0.1 M aq. HCl (1 mL) and extracted with CH_2Cl_2 (10 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (2:8 heptane/EtOAc) to afford the title compound **22** (78.4 mg, 0.157 mmol, 72%) as an amorphous white solid: **mp** 144-147 °C decomposed (Lit.[25] 144-146 °C decomposed); $\boldsymbol{R_f}$ 0.63 (1:9 heptane/EtOAc); $\boldsymbol{[\alpha]_D^{23}}$ 5.3 (*c* 1.0, $CHCl_3$) (Lit.[139] $\boldsymbol{[\alpha]_D^{23}}$ 6.9, *c* 0.44, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3481 (O-H stretch), 2928 (C-H stretch), 1709 (C=O stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, **$CDCl_3$**) 5.60 (1 H, br d, *J* 5.4, *H-6*), 5.05-4.99 (1 H, m, *H-3*), 4.21 (1 H, dd, *J* 13.3, 3.3, *H-22*), 3.85 (1 H, s, *H-1*), 2.45-2.41 (1 H, m, *H-23a*), 2.37-2.30 (2 H, m, *H-4*), 2.13-2.00 (3 H, m, *H-2a*, *H-12a*, *H-23b*), 2.02 (3 H, s, *H-30*), 1.96-1.94 (1 H, m, *H-16a*), 1.94 (3 H, s, *H-28*), 1.93-1.90 (1 H, m, *H-7a*), 1.87 (3 H, s, *H-27*), 1.65-1.40 (8 H, m, *H-2b*, *H-7b*, *H-8*, *H-9*, *H-11a*, *H-15a*, *H-16b*, *H-17*), 1.29-1.27 (1 H, m, *H-12b*), 1.28 (3 H, s, *H-21*), 1.08-1.05 (3 H, m, *H-11b*, *H-14*, *H-15b*), 1.03 (3 H, s, *H-19*), 0.87 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**125 MHz**, **$CDCl_3$**) 170.4 (*C-29*), 166.1 (*C-26*), 148.9 (*C-24*), 136.3 (*C-5*), 126.2 (*C-6*), 122.0 (*C-25*), 81.0 (*C-22*), 75.2 (*C-20*), 72.5 (*C-1*), 69.4 (*C-3*), 56.6 (*C-14*), 54.6 (*C-17*), 43.0 (*C-13*), 41.7 (*C-10*), 41.7 (*C-9*), 39.8 (*C-12*), 37.2 (*C-4*), 34.5 (*C-2*), 31.8 (*C-7*), 31.6 (*C-23*), 31.2 (*C-8*), 23.9 (*C-15*), 21.9 (*C-16*), 21.4 (*C-11*), 20.9 (*C-30*), 20.5 (*C-21*), 20.1 (*C-28*), 19.3 (*C-19*), 13.5 (*C-18*), 12.4 (*C-27*); **m/z** (**ESI**) 501 $[MH]^+$. Calcd. for $C_{30}H_{45}O_6$: 501.3211. Found: $[MH]^+$, 530.3218 (−1.6 ppm error). Data consistent with those previously reported in the literature.[25]

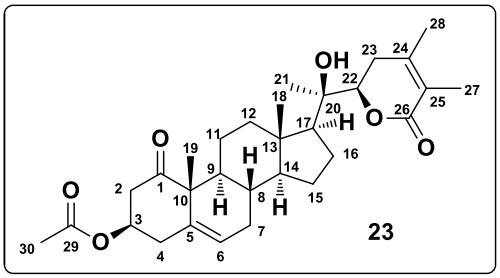
Lab. Book: ***LNB0170-133-03***.



Also isolated was 1α,3β-bisacetate-20*R*-hydroxy-14,17-dideoxy-17-*epi*-withanolide F (**212**) (19.8 mg, 0.037 mmol, 17%) as a white solid: **mp** 140-142 °C decomposed (Lit.[140] 135 °C decomposed); $\boldsymbol{R_f}$ 0.72 (1:9 heptane/EtOAc); $\mathbf{[\alpha]_D^{23}}$ 16.2 (*c* 0.96, $CHCl_3$) (Lit.[25] $\mathbf{[\alpha]_D^{25}}$ 17.6, *c* 0.11, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3489 (O-H stretch), 2941 (C-H stretch), 1713 (C=O stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, **$CDCl_3$**) 5.53 (1 H, br d, *J* 4.9, *H-6*), 5.05 (1 H, br s, *H-3*), 4.93-4.89 (1 H, m, *H-1*), 4.21 (1 H, dd, *J* 13.3, 3.3, *H-22*), 2.46 (1 H, br ddd, *J* 13.4, 5.0, 1.8, *H-4a*), 2.43-2.30 (3 H, m, *H-4b*, *H-23*), 2.11-2.06 (1 H, m, *H-2a*), 2.04 (3 H, s, *H-30*), 2.02 (3 H, s, *H-32*), 1.95-1.93 (2 H, m, *H-7a*, *H-12a*), 1.93 (3 H, s, *H-28*), 1.88 (3 H, s, *H-27*), 1.63-1.29 (11 H, m, *H-2b*, *H-7b*, *H-8*, *H-9*, *H-11*, *H-15*, *H-16*, *H-17*), 1.28 (3 H, s, *H-21*), 1.19-1.11 (1 H, m, *H-12b*), 1.08 (3 H, s, *H-19*), 1.03-0.99 (1 H, m, *H-14*), 0.85 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**125 MHz**, **$CDCl_3$**) 170.4 (*C-31*), 170.3 (*C-29*), 166.0 (*C-26*), 148.7 (*C-24*), 136.1 (*C-5*), 125.0 (*C-6*), 122.0 (*C-25*), 80.9 (*C-22*), 75.1 (*C-20*), 74.6 (*C-3*), 69.3 (*C-1*), 56.7 (*C-14*), 54.5 (*C-17*), 43.0 (*C-13*), 42.0 (*C-10*), 40.4 (*C-9*), 39.9 (*C-12*), 37.3 (*C-4*), 31.9 (*C-8*), 31.6 (*C-2*), 31.5 (*C-7*), 31.1 (*C-23*), 23.8 (*C-15*), 21.9 (*C-16*), 21.3 (*C-32*), 21.1 (*C-30*), 20.8 (*C-21*), 20.5 (*C-11*), 20.2 (*C-28*), 19.4 (*C-19*), 13.6 (*C-18*), 12.4 (*C-27*); **m/z** (**ESI**) 565 $[MNa]^+$. Calcd. for $C_{32}H_{46}NaO_6$: 565.3136. Found: $[MH]^+$, 565.3142 (−1.1 ppm error). Data consistent with those previously reported in the literature.[25]

Lab. Book: ***LNB0170-133-02***.

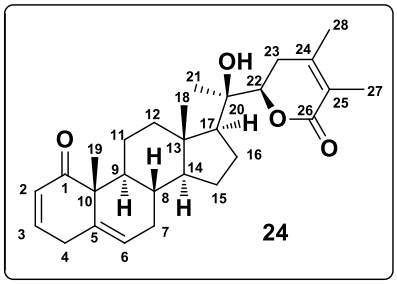
3β-Acetate–20*R*-hydroxy-1-oxo-14,17-dideoxy-17-*epi*-withanolide F (23)



To a solution of diol **22** (78.0 mg, 0.156 mmol, 1.0 eq.) in CH_2Cl_2 (1.5 mL) was added DMP (132 mg, 0.312 mmol, 2.0 eq.). The reaction was stirred at room temperature for 2 h, quenched with 1 M aq. Na_2CO_3 (5 mL) and extracted with CH_2Cl_2 (10 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (4:6 heptane/EtOAc) to afford the title compound **23** (65.0 mg, 0.130 mmol, 84%) as an amorphous yellow solid: **mp** 166-168 °C decomposed (Lit.[25] 169-171 °C decomposed); $\boldsymbol{R_f}$ 0.44 (1:1 heptane/EtOAc); $\boldsymbol{[\alpha]_D^{23}}$ 34.5 (*c* 1.0, $CHCl_3$) (Lit.[25] $\boldsymbol{[\alpha]_D}$ 29.8, *c* 0.13); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3500 (O-H stretch), 2927 (C-H stretch), 1708 (C=O stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, $\boldsymbol{CDCl_3}$) 5.63 (1 H, br d, *J* 5.1, *H-6*), 4.94-4.86 (1 H, m, *H-3*), 4.20 (1 H, dd, *J* 13.3, 3.3, *H-22*), 2.70 (1 H, dd, *J* 13.2, 6.3, *H-2a*), 2.69-2.60 (2 H, m, *H-2b*, *H-4a*), 2.49 (1 H, br dd, *J* 12.5, 11.7, *H-4b*), 2.40 (1 H, br dd, *J* 16.0, 13.3, *H-23a*), 2.10 (1 H, dd, *J* 16.0, 3.3, *H-23b*), 2.05-2.03 (2 H, m, *H-7a*, *H-12a*), 2.03 (3 H, s, *H-30*), 1.94 (3 H, s, *H-28*), 1.88 (3 H, s, *H-27*), 1.70-1.44 (7 H, m, *H-7b*, *H-9*, *H-11a*, *H-15a*, *H-16*, *H-17*), 1.35-1.32 (1 H, m, *H-12b*), 1.28 (3 H, s, *H-21*), 1.27 (3 H, s, *H-19*), 1.27-1.25 (1 H, m, *H-8*), 1.20-1.15 (1 H, m, *H-15b*), 1.08-1.03 (2 H, m, *H-11b*, *H-14*), 0.88 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**125 MHz**, $\boldsymbol{CDCl_3}$) 210.1 (*C-1*), 170.1 (*C-29*), 165.9 (*C-26*), 148.8 (*C-24*), 134.4 (*C-5*), 126.5 (*C-6*), 122.0 (*C-25*), 81.0 (*C-22*), 75.2 (*C-20*), 70.0 (*C-3*), 56.7 (*C-14*), 54.8 (*C-17*), 52.7 (*C-10*), 43.9 (*C-2*), 43.1 (*C-9*), 42.6 (*C-13*), 39.9 (*C-12*), 37.2 (*C-4*), 31.8 (*C-8*), 31.6 (*C-7*), 31.1 (*C-23*), 23.8 (*C-15*), 21.9 (*C-16*), 21.5 (*C-30*), 21.2 (*C-11*), 20.9 (*C-21*), 20.5 (*C-28*), 18.7 (*C-19*), 13.6 (*C-18*), 12.5 (*C-27*); **m/z** (**ESI**) 521 $[MNa]^+$. Calcd. for $C_{30}H_{42}NaO_6$: 521.2874. Found: $[MNa]^+$, 521.2874 (−0.1 ppm error). Data consistent with those previously reported in the literature.[25]

Lab. Book: ***LNB0149-131-03***.

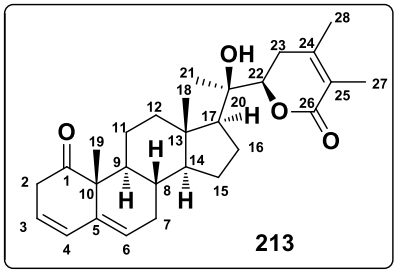
14,17-Dideoxy-17-*epi*-withanolide F (24)[89]



To a solution of acetate **23** (40 mg, 0.080 mmol, 1.0 eq.) in benzene (1 mL) was added Al_2O_3 (205 mg, 2.01 mmol, 25.0 eq.). The reaction was stirred at 50 °C for 4 h, filtered through Celite® and washed with EtOAc (10 mL). The filtrate was concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (75:25 heptane/EtOAc) to afford the title compound **24** (31.5 mg, 0.072 mmol, 90%) as an amorphous white solid: **mp** 194-195 °C decomposed; $\boldsymbol{R_f}$ 0.30 (6:4 heptane/EtOAc); $\boldsymbol{[\alpha]_D^{23}}$ 18.6 (*c* 1.0, $CHCl_3$) (Lit.[40] $\boldsymbol{[\alpha]_D^{20}}$ 34.0, *c* 0.0053, $CHCl_3$); **UV** $\boldsymbol{\lambda_{max}}$ (MeOH) 222 nm (Lit.[40] **UV** $\boldsymbol{\lambda_{max}}$ (MeOH) 218 nm); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3463 (O-H stretch), 2926 (C-H stretch), 1705 (C=O stretch), 1682 (C=O stretch), 1666 (C=C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, $\boldsymbol{CDCl_3}$) 6.75 (1 H, ddd, *J* 9.9, 4.6, 3.0, *H-3*), 5.87 (1 H, dd, *J* 9.9, 3.0, *H-2*), 5.55 (1 H, br d, *J* 6.1, *H-6*), 4.20 (1 H, dd, *J* 13.4, 3.3, *H-22*), 3.27 (1 H, dd, *J* 21.4, 3.0, *H-4a*), 2.85 (1 H, dd, *J* 21.4, 4.6, *H-4b*), 2.39 (1 H, br dd, *J* 15.6, 15.0, *H-23a*), 2.18 (1 H, br dd, *J* 13.1, 3.4, *H-11a*), 2.11 (1 H, br dd, *J* 17.4, 2.8, *H-23b*), 2.04 (1 H, br d, *J* 12.8, *H-12a*), 1.98-1.95 (2 H, m, *H-7a*, *H-16a*), 1.97 (3 H, s, *H-28*), 1.87 (3 H, s, *H-27*), 1.64-1.34 (8 H, m, *H-7b*, *H-8*, *H-9*, *H-11b*, *H-12b*, *H-15a*, *H-16b*, *H-17*), 1.29 (3 H, s, *H-21*), 1.21 (3 H, s, *H-19*), 1.17-1.04 (2 H, m, *H-14*, *H-15b*), 0.89 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**125 MHz**, $\boldsymbol{CDCl_3}$) 204.4 (*C-1*), 166.0 (*C-26*), 148.8 (*C-24*), 145.1 (*C-3*), 135.9 (*C-5*), 127.9 (*C-2*), 124.7 (*C-6*), 122.0 (*C-25*), 81.0 (*C-22*), 75.2 (*C-20*), 56.7 (*C-14*), 54.7 (*C-17*), 50.5 (*C-10*), 42.9 (*C-13*), 42.8 (*C-9*), 40.2 (*C-12*), 33.5 (*C-4*), 32.6 (*C-8*), 31.6 (*C-23*), 30.7 (*C-7*), 23.9 (*C-15*), 23.4 (*C-11*), 21.8 (*C-16*), 21.0 (*C-21*), 20.5 (*C-28*), 19.0 (*C-19*), 13.6 (*C-18*), 12.4 (*C-27*); **m/z** (**ESI**) 461 $[MNa]^+$. Calcd. for $C_{28}H_{38}NaO_4$: 461.2662. Found: $[MNa]^+$, 461.2666 (−0.7 ppm error). Data consistent with those previously reported in the literature.[40]

Lab. Book: ***LNB0170-138-02***.

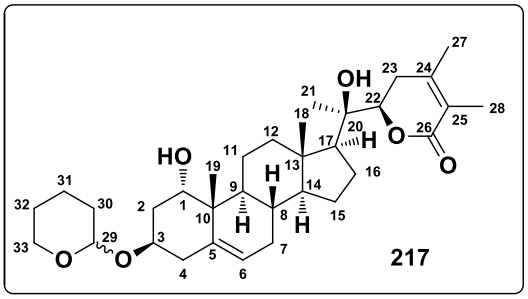
3,4-Dihydro-$\Delta^{3,4}$-14,17-dideoxy17-*epi*-withanolide F (213)



To a solution of 2,5-dienone **24** (20.0 mg, 0.046 mmol, 1.0 eq.) in CH_2Cl_2 (0.5 mL) was added DBN (11.3 μL, 0.091 mmol, 2.0 eq.). The reaction was stirred at room temperature for 3 h, quenched with sat. aq. NH_4Cl (2 mL) and extracted with CH_2Cl_2 (5 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (75:25 heptane/EtOAc) to afford the *title compound* **213** (19.5 mg, 0.044 mmol, 98%) as an amorphous white solid: **mp** 215-218 °C decomposed; $\boldsymbol{R_f}$ 0.30 (6:4 heptane/EtOAc); $\boldsymbol{[\alpha]_D^{23}}$ 64.4 (*c* 0.5, $CHCl_3$); **UV** $\boldsymbol{\lambda_{max}}$ (MeOH) 225 nm; $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3483 (O-H stretch), 2942 (C-H stretch), 1713 (C=O stretch), 1660 (C=C stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, **$CDCl_3$**) 6.03 (1 H, d, *J* 9.2, *H-4*), 5.63 (1 H, br d, *J* 3.1, *H-6*), 5.60-5.58 (1 H, m, *H-3*), 4.20 (1 H, dd, *J* 13.4, 3.7, *H-22*), 3.28 (1 H, br d, *J* 19.5, *H-2a*), 2.73 (1 H, dd, *J* 19.5, 4.3, *H-2b*), 2.43-2.36 (1 H, m, *H-23a*), 2.16-2.10 (3 H, m, *H-7a*, *H-23b*), 2.04-2.00 (1 H, m, *H-12a*), 1.95 (3 H, s, *H-28*), 1.88 (3 H, s, *H-27*), 1.81-1.38 (10 H, m, *H-7b*, *H-8*, *H-9*, *H-11*, *H-12b*, *H-15a*, *H-16*, *H-17*), 1.35 (3 H, s, *H-19*), 1.30 (3 H, s, *H-21*), 1.15-1.09 (2 H, m, *H-14*, *H-15b*), 0.90 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**125 MHz**, **$CDCl_3$**) 209.3 (*C-1*), 166.5 (*C-26*), 149.2 (*C-24*), 141.5 (*C-5*), 129.7 (*C-4*), 127.4 (*C-6*), 122.2 (*C-25*), 122.0 (*C-3*), 80.6 (*C-22*), 75.4 (*C-20*), 57.0 (*C-14*), 55.0 (*C-17*), 52.7 (*C-10*), 43.3 (*C-13*), 41.1 (*C-9*), 40.1 (*C-12*), 39.6 (*C-2*), 31.6 (*C-7*), 31.1 (*C-8*), 30.9 (*C-23*), 23.8 (*C-15*), 22.3 (*C-11*), 21.8 (*C-16*), 21.4 (*C-19*), 20.9 (*C-28*), 20.6 (*C-21*), 14.3 (*C-18*), 12.8 (*C-27*); **m/z** (**ESI**) 461 $[MNa]^+$. Calcd. for $C_{28}H_{38}NaO_4$: 461.2662. Found: $[MNa]^+$, 461.2663 (−0.0 ppm error).

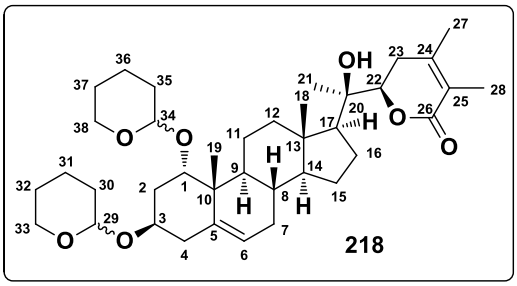
Lab. Book: ***LNB0170-157-02***.

1α,20*R*-Bishydroxy-3β-tetrahydropyranyloxy-14,17-dideoxy-17-*epi*-withanolide F (217)



To a solution of triol **21** (38.8 mg, 0.085 mmol, 1.0 eq.) in CH_2Cl_2 (2.5 mL) was added DHP (5.76 μL, 0.064 mmol, 0.75 eq.) and *p*-TsOH (cat.) at 0 °C. The reaction was stirred for 3 h, quenched with sat. aq. $NaHCO_3$ (3 mL) and extracted with CH_2Cl_2 (10 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (7:3 heptane/EtOAc) to afford the *title compound* **217** (26.0 mg, 0.048 mmol, 57%) as an inseparable mixture of two diastereoisomers at C-29 in a 1:1 ratio and as an amorphous white solid: $\boldsymbol{R_f}$ 0.19 (1:1 heptane/EtOAc); $\boldsymbol{\delta_H}$ (**400 MHz**, **$CDCl_3$**) 5.58 (1 H, br d, *J* 6.1, *H-6*), 4.68 (1 H, br d, *J* 12.7, *H-29*), 4.21 (1 H, dd, *J* 13.2, 2.9, *H-22*), 3.99-3.94 (1 H, m, *H-3*), 3.91-3.88 (1 H, m, *H-33a*), 3.83-3.80 (1 H, m, *H-1*), 3.51-3.46 (1 H, m, *H-33b*), 2.44-2.25 (4 H, m, *H-2a*, *H-4*, *H-23a*), 2.12-1.98 (4 H, m, *H-2b*, *H-7a*, *H-12a*, *H-23b*), 1.94 (3 H, s, *H-28*), 1.87 (3 H, s, *H-27)*, 1.85-1.32 (17 H, m, *H-7b*, *H-8*, *H-9*, *H-11*, *H-12b*, *H-15*, *H-16*, *H-17*, *H-30*, *H-31*, *H-32*), 1.27 (3 H, s, *H-21*), 1.09-1.04 (1 H, m, *H-14*), 1.02 (3 H, s, *H-19*), 0.86 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**125 MHz**, **$CDCl_3$**) 166.5 (*C-26*), 148.5 (*C-24*), 137.8 (*C-5*), 125.6 (*C-6*), 121.6 (*C-25*), 97.3 (*C-29*), 81.1 (*C-22*), 75.2 (*C-20*), 73.1 (*C-1*), 70.9 (*C-3*), 63.1 (*C-33*), 57.3 (*C-14*), 54.9 (*C-17*), 43.3 (*C-13*), 41.8 (*C-10*), 41.6 (*C-9*), 39.8 (*C-12*), 39.6 (*C-2*), 37.5 (*C-4*), 31.5 (*C-7*), 31.3 (*C-8*), 31.2 (*C-30*, *C-31*, *C-32*), 31.1 (*C-23*), 24.4 (*C-15*), 22.1 (*C-16*), 21.4 (*C-28*), 21.1 (*C-21*), 20.5 (*C-11*), 19.3 (*C-19*), 13.9 (*C-18*), 12.9 (*C-27*); **m/z** (**ESI**) 565 $[MNa]^+$. Calcd. for $C_{33}H_{50}NaO_6$: 565.3500. Found: $[MNa]^+$, 565.3502 (−0.5 ppm error).

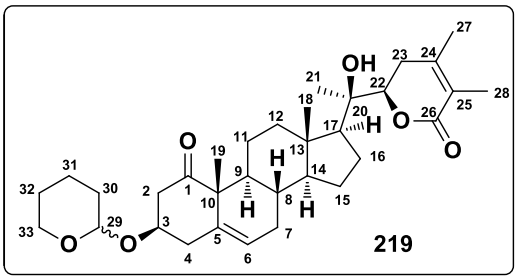
Lab. Book: ***LNB0189-002-04***.



Also isolated was *1α,3β-bistetrahydropyranyloxy-20R-hydroxy-14,17-dideoxy-17-epi-withanolide F* (**218**) (9.05 mg, 0.014 mmol, 19%) as an inseparable mixture of four diastereoisomers at C-29 and C-34 and as an amorphous white solid: $\boldsymbol{R_f}$ 0.49 (1:1 heptane/EtOAc); $\boldsymbol{\delta_H}$ (**400 MHz**, **$CDCl_3$**) 5.45 (1 H, br d, *J* 5.3, *H-6*), 4.72-4.56 (4 H, m, *H-29*, *H-29**, *H-34*, *H-34**), 4.19 (1 H, dd, *J* 13.2, 3.0, *H-22*), 4.07-3.99 (1 H, m, *H-3*), 3.92-3.81 (5 H, m, *H-3*, *H-33a*, *H-33a**, *H-38a*, *H-38a**), 3.78 (1 H, br s, *H-1*), 3.64 (1 H, br s, *H-1**), 3.52-3.43 (4 H, m, *H-33b*, *H-33b**, *H-38b*, *H-38b**), 2.42-2.36 (3 H, m, *H-2a*, *H-4a*, *H-23a*), 2.25-2.18 (2 H, m, *H-2b*, *H-4b*), 2.13-2.10 (1 H, m, *H-23b*), 2.04-2.02 (1 H, m, *H-12a*), 1.92 (3 H, s, *H-28*), 1.90-1.88 (1 H, m, *H-7a*), 1.86 (3 H, s, *H-27*), 1.80-1.30 (23 H, m, *H-7b*, *H-8*, *H-9*, *H-11*, *H-12b*, *H-15*, *H-16*, *H-17*, *H-30*, *H-31*, *H-32*, *H-35*, *H-36*, *H-37*), 1.27 (3 H, s, *H-21*), 1.09-1.04 (1 H, m, *H-14*), 1.00 (3 H, s, *H-19**), 0.97 (3 H, s, *H-19*), 0.86 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**125 MHz**, **$CDCl_3$**) 166.7 (*C-26*), 148.8 (*C-24*), 138.2 (*C-5*), 123.4 (*C-6*), 122.2 (*C-25*), 101.1 (*C-29*), 98.3 (*C-29**), 96.2 (*C-34*), 95.1 (*C-34**), 81.8 (*C-1*), 80.7 (*C-22*), 76.2 (*C-1**), 75.7 (*C-20*), 71.7 (*C-3*), 70.6 (*C-3**), 62.5 (*C-33*, *C-33**), 61.7 (*C-38*, *C-38**), 56.8 (*C-14*), 54.3 (*C-17*), 43.4 (*C-13*), 42.8 (*C-10*), 41.2 (*C-9*), 40.0 (*C-12*), 39.5 (*C-2*), 39.3 (*C-4*), 32.1-30.1 (*C-30*, *C-31*, *C-32*, *C-35*, *C-36*, *C-37*), 31.5 (*C-7*), 31.2 (*C-8*), 31.1 (*C-23*), 24.5 (*C-15*), 22.2 (*C-16*), 21.4 (*C-21*), 21.0 (*C-28*), 20.4 (*C-11*), 20.3 (*C-19**), 19.3 (*C-19*), 13.9 (*C-18*), 12.7 (*C-27*); **m/z** (**ESI**) 649 $[MNa]^+$. Calcd. for $C_{38}H_{58}NaO_7$: 649.4075. Found: $[MNa]^+$, 649.4076 (−0.3 ppm error). *: signal of other diastereoisomers.

Lab. Book: ***LNB0170-158-02***.

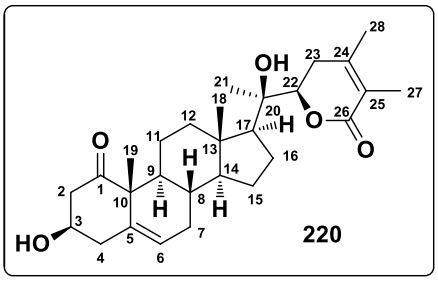
3β-Tetrahydropyranyl-20*R*-hydroxy-1-oxo-14,17-dideoxy-17-*epi*-withanolide F (219)



To a solution of hydroxyl **217** (27.0 mg, 0.050 mmol, 1.0 eq.) in CH_2Cl_2 (1 mL) was added DMP (42.2 mg, 0.100 mmol, 2.0 eq.). The reaction was stirred at room temperature overnight, quenched with 1 M aq. Na_2CO_3 (2 mL) and extracted with CH_2Cl_2 (5 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (75:25 heptane/EtOAc) to afford the *title compound* **219** (16.4 mg, 0.030 mmol, 61%) as an inseparable mixture of two diastereoisomers at C-29 in a 1:1 ratio and as an amorphous white solid: $\boldsymbol{R_f}$ 0.58 (1:1 heptane/EtOAc); $\boldsymbol{\delta_H}$ (**400 MHz**, **$CDCl_3$**) 5.59 (1 H, br d, *J* 5.6, *H-6*), 4.72 (1 H, br s, *H-29*), 4.63 (1 H, br s, *H-29**), 4.20 (1 H, dd, *J* 13.3, 3.0, *H-22*), 3.89-3.84 (1 H, m, *H-33a*), 3.83-3.77 (1 H, m, *H-3*), 3.49-3.46 (1 H, m, *H-33b*), 2.83-2.78 (1 H, m, *H-2a*), 2.72-2.52 (3 H, m, *H-2b*, *H-4*), 2.43-2.37 (1 H, m, *H-23a*), 2.16-1.99 (3 H, m, *H-7a*, *H-12a*, *H-23b*), 1.94 (3 H, s, *H-28*), 1.87 (3 H, s, *H-27*), 1.81-1.32 (17 H, m, *H-7b*, *H-8*, *H-9*, *H-11*, *H-12b*, *H-15*, *H-16*, *H-17*, *H-30*, *H-31*, *H-32*), 1.28 (6 H, s, *H-19*, *H-21*), 1.09-1.03 (1 H, m, *H-14*), 0.87 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**125 MHz**, **$CDCl_3$**) 210.7 (*C-1*), 166.0 (*C-26*), 148.8 (*C-24*), 135.1 (*C-5*), 125.9 (*C-6*), 122.0 (*C-25*), 97.2 (*C-29*, *C-29**), 81.0 (*C-22*), 75.2 (*C-20*), 73.1 (*C-3*), 62.5 (*C-33*), 56.7 (*C-14*), 54.7 (*C-17*), 52.6 (*C-10*), 46.4 (*C-2*), 43.1 (*C-13*), 42.4 (*C-9*), 40.0 (*C-12*), 38.2 (*C-4*), 31.6 (*C-8*), 31.4 (*C-30*), 31.3 (*C-32*), 31.1 (*C-23*), 31.0 (*C-7*), 29.7 (*C-31*), 23.9 (*C-15*), 21.9 (*C-16*), 21.0 (*C-11*), 20.5 (*C-28*), 19.4 (*C-19, C-21*), 13.6 (*C-18*), 12.5 (*C-27*); **m/z** (**ESI**) 563 $[MNa]^+$. Calcd. for $C_{33}H_{48}NaO_6$: 563.3343. Found: $[MNa]^+$, 563.3358 (−2.6 ppm error). *: signal of other diastereoisomers.

Lab. Book: ***LNB0170-160-02***.

3β,20*R*-Dihydroxy-1-oxo-14,17-dideoxy-17-*epi*-withanolide F (220)[29]

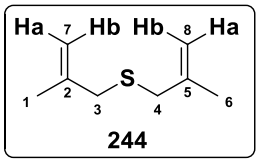


To a solution of THP protected alcohol **219** (15.6 mg, 0.029 mmol, 1.0 eq.) in MeOH (0.5 mL) was added 2 M aq. HCl (0.1 mL). The reaction was stirred at room temperature for 1 h, quenched with sat. aq. $NaHCO_3$ (2 mL) and extracted with EtOAc (5 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (7:3 heptane/EtOAc) to afford the title compound **220** (14.0 mg, 0.031 mmol, 100%) as an amorphous pale pink solid: **mp** 184-187 °C decomposed (Lit.[29] 189-190 °C decomposed); $\boldsymbol{R_f}$ 0.55 (9:1 heptane/EtOAc); $\boldsymbol{[\alpha]_D^{23}}$ 25.6 (*c* 0.28, $CHCl_3$) (Lit.[25] $\boldsymbol{[\alpha]_D^{24}}$ 30.0, *c* 0.13, $CHCl_3$); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3429 (O-H stretch), 2981 (C-H stretch), 1709 (C=O stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, **$CDCl_3$**) 5.60 (1 H, br d, *J* 4.4, *H-6*), 4.19 (1 H, dd, *J* 13.2, 2.9, *H-22*), 3.85-3.82 (1 H, m, *H-3*), 2.73-2.70 (1 H, m, *H-2a*), 2.63 (1 H, dd, *J* 12.4, 5.3, *H-2b*), 2.54-2.50 (2 H, m, *H-4*), 2.43-2.37 (1 H, m, *H-23a*), 2.10 (1 H, br d, *J* 15.9, *H-23b*), 1.99-1.96 (2 H, m, *H-7a*, *H-12a*), 1.94 (3 H, s, *H-28*), 1.87 (3 H, s, *H-27*), 1.62-1.31 (10 H, m, *H-7b*, *H-8*, *H-9*, *H-11*, *H-12b*, *H-15a*, *H-16*, *H-17*), 1.30 (3 H, s, *H-19*), 1.29 (3 H, s, *H-21*), 1.19-1.15 (1 H, m, *H-15b*), 1.08-1.02 (1 H, m, *H-14*), 0.87 (3 H, s, *H-18*); $\boldsymbol{\delta_C}$ (**125 MHz**, **$CDCl_3$**) 210.6 (*C-1*), 166.1 (*C-26*), 148.9 (*C-24*), 135.1 (*C-5*), 126.0 (*C-6*), 122.0 (*C-25*), 81.0 (*C-22*), 75.2 (*C-20*), 69.1 (*C-3*), 56.6 (*C-14*), 54.5 (*C-17*), 52.4 (*C-10*), 48.0 (*C-2*), 43.1 (*C-13*), 42.4 (*C-9*), 41.2 (*C-4*), 39.9 (*C-12*), 31.6 (*C-7*), 31.3 (*C-23*), 31.1 (*C-8*), 23.9 (*C-15*), 22.3 (*C-16*), 21.8 (*C-21*), 20.9 (*C-28*), 20.5 (*C-11*), 19.3 (*C-19*), 13.7 (*C-18*), 12.5 (*C-27*); **m/z** (**ESI**) 479 $[MNa]^+$. Calcd. for $C_{28}H_{40}NaO_5$: 479.2768. Found: $[MNa]^+$, 479.2759 (1.9 ppm error). Data consistent with those previously reported in the literature.[29]

Lab. Book: ***LNB0189-001-01***.

6.2.4. Chapter 5. Methodology towards the construction of δ-lactones

Methallyl sulfide (243)[108]

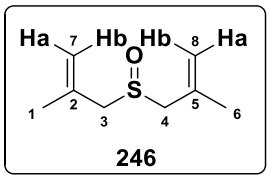


244

To a solution of Na_2S (2.00 g, 8.33 mmol, 1.0 eq.) in MeOH/H_2O (1:1, 11.0 mL) was added 3-chloro-2-methylpropene (**243**) (2.04 mL, 0.021 mol, 2.5 eq.) and the solution was vigorously stirred at room temperature for 1 h. The reaction mixture was stirred overnight at reflux temperature, quenched with sat. aq. NH_4Cl (10 mL) and extracted with Et_2O (10 mL). The organic phase was adjusted to pH 7 by washing with H_2O (5 × 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound **244** (1.19 g, 8.37 mmol, 100%) as a colourless liquid which required no further purification: $\boldsymbol{R_f}$ 0.73 (100% PE); $\boldsymbol{\delta_H}$ (**400 MHz**, **$CDCl_3$**) 4.87-4.85 (2 H, m, *H-7a*, *H-8a*), 4.82-4.80 (2 H, m, *H-7b*, *H-8b*), 3.04-3.02 (4 H, m, *H-3*, *H-4*), 1.83-1.80 (6 H, m, *H-1*, *H-6*); $\boldsymbol{\delta_C}$ (**100 MHz**, **$CDCl_3$**) 141.1 (*C-2*, *C-5*), 113.5 (*C-7*, *C-8*), 38.0 (*C-3*, *C-4*), 20.9 (*C-1*, *C-6*); **m/z** (**ESI**) 143 $[MH]^+$. Calcd. for $C_8H_{15}S$: 143.0889 Found: $[MH]^+$, 143.0898 (−6.3 ppm error). Data consistent with those previously reported in the literature.[110]

Lab. Book: ***LNB0107-139-01***.

Methallyl sulfoxide (246)[110]



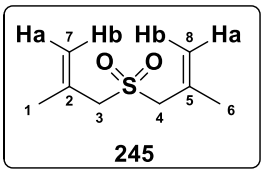
246

To a solution of methallyl sulfide **244** (119 mg, 0.838 mmol, 1.0 eq.) in glacial acetic acid (1.4 mL) was added dropwise H_2O_2 (30% w/w, 0.150 mL, 5.02 mmol, 6.0 eq.) at 0 °C and the reaction mixture was stirred overnight. Upon completion of the reaction, the reaction mixture was quenched with sat. aq. $NaHCO_3$ (2 mL) and diluted with CH_2Cl_2 (2 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (2 mL), dried over $MgSO_4$, filtered and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (7:3 PE/EtOAc) to afford the title compound **246** (61.2 mg, 0.387 mmol, 46%) as colorless crystals: **mp** 25 °C decomposed (Lit.[110] rt decomposed);

***R*$_f$** 0.43 (7:3 PE/EtOAc); **υ$_{max}$/cm^{-1}** (neat) 2973 (C-H stretch), 1650 (C=C stretch), 1378 (CH_3 bend), 1035 (S=O stretch); **δ$_H$** (**400 MHz**, **$CDCl_3$**) 5.12-5.09 (2 H, m, *H-7a*, *H-8a*), 5.03 (2 H, br s, *H-7b*, *H-8b*), 3.46-3.38 (4 H, m, *H-3*, *H-4*), 1.91-1.89 (6 H, m, *H-1*, *H-6*); **δ$_C$** (**100 MHz**, **$CDCl_3$**) 135.8 (*C-2*, *C-5*), 118.4 (*C-7*, *C-8*), 61.5 (*C-3*, *C-4*), 23.0 (*C-1*, *C-6*); **m/z** (**ESI**) 159 $[MH]^+$. Calcd. for $C_8H_{15}OS$: 159.0838. Found: $[MH]^+$, 159.0837 (0.5 ppm error). Data consistent with those previously reported in the literature.[110]

Lab. Book: ***LNB0107-131-02***.

Methallyl sulfone (245)[108]

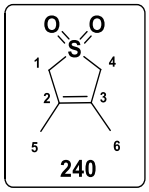


245

To a solution of methallyl sulfide **244** (1.19 g, 8.38 mmol, 1.0 eq.) in CH_2Cl_2 (10 mL) was added *m*-CPBA (4.34 g, 25.1 mmol, 3.0 eq.) portionwise over 1 h at 0 °C and stirred vigorously for 1 h. The reaction mixture was warmed to room temperature over 4 h, diluted with Et_2O (20 mL) and quenched with sat. aq. $Na_2S_2O_4$ (10 mL). The organic phase was washed with sat. aq. $Na_2S_2O_4$ (5 × 10 mL) and with sat. aq. $NaHCO_3$ (2 × 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (9:1 to 7:3 PE/EtOAc) to afford the title compound **245** (1.18 g, 6.77 mmol, 81%) as a white amorphous solid: **mp** 29-31 °C decomposed (Lit.[110] 32 °C decomposed); ***R*$_f$** 0.66 (7:3 PE/EtOAc); **υ$_{max}$/cm^{-1}** (neat) 1405 (CH_3 bend), 1304 (S=O stretch), 1118 (S=O stretch), 820 (CH_2 bend); **δ$_H$** (**400 MHz**, **$CDCl_3$**) 5.24-5.22 (2 H, m, *H-7a*, *H-8a*), 5.10 (2 H, br s, *H-7b*, *H-8b*), 3.71 (4 H, s, *H-3*, *H-4*), 1.98-196 (6 H, m, *H-1*, *H-6*); **δ$_C$** (**100 MHz**, **$CDCl_3$**) 133.7 (*C-2*, *C-5*), 120.7 (*C-7*, *C-8*), 59.8 (*C-3*, *C-4*), 22.7 (*C-1*, *C-6*); **m/z** (**ESI**) 175 $[MH]^+$. Calcd. for $C_8H_{15}O_2S$: 175.0787. Found: $[MH]^+$, 175.0789 (−1.1 ppm error). Data consistent with those previously reported in the literature.[110]

Lab. Book: ***LNB0107-141-02***.

3,4-Dimethyl-2,5-dihydrothiophene-1,1-dioxide (240)[109]

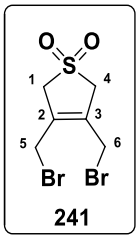


240

To a solution of sulfone **245** (1.00 g, 5.74 mmol, 1.0 eq.) in degassed CH_2Cl_2 (40 mL) was added Grubbs second generation catalyst (388 mg, 0.459 mmol, 0.08 eq.) portionwise (4 × 2 mol% over 4 h, *i.e.* 97.2 mg added per hour). The reaction mixture was stirred overnight at reflux temperature, cooled to room temperature and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (95:5 to 7:3 heptane/EtOAc) to afford the title compound **240** (851 mg, 5.82 mmol, 100%) as a grey amorphous solid: **mp** 109-113 °C decomposed (Lit.[141] 135 °C decomposed); $\boldsymbol{R_f}$ 0.38 (7:3 PE/EtOAc); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 1404 (CH_3 bend), 1289 (S=O stretch), 1107 (S=O stretch), 719 (CH_2 bend); $\boldsymbol{\delta_H}$ (**400 MHz**, **$CDCl_3$**) 3.73 (4 H, s, *H-1*, *H-4*), 1.78 (6 H, s, *H-5*, *H-6*); $\boldsymbol{\delta_C}$ (**100 MHz**, **$CDCl_3$**) 125.9 (*C-2*, *C-3*), 61.0 (*C-4*, *C-1*), 14.9 (*C-5*, *C-6*); **m/z** (**ESI**) 169 $[MNa]^+$. Calcd. for $C_6H_{10}NaO_2S$: 169.0294. Found: $[MNa]^+$, 169.0293 (0.3 ppm error). Data consistent with those previously reported in the literature.[110]

Lab. Book: ***LNB0149-067-03***.

3,4-Di(bromomethylene)-2,5-dihydrothiophene-1,1-dioxide (241)[106]



241

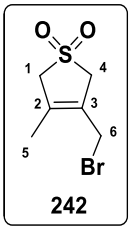
To a solution of cyclic sulfone **240** (67.0 mg, 0.458 mmol, 1.0 eq.) in chlorobenzene (0.48 mL) was added NBS (130 mg, 0.733 mmol, 1.6 eq.) and benzoyl peroxide (1:1 with plasticiser dicyclo phthalate, 11.1 mg, 0.023 mmol, 0.05 eq.). The reaction mixture was stirred at reflux overnight, cooled to room temperature, diluted with CH_2Cl_2 (5 mL) and concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (9:1 to 8:2 PE/EtOAc) to afford the title compound **241** (19.5 mg, 0.065 mmol, 14%) as a brown amorphous solid: **mp** 115-118 °C decomposed

(Lit.[142] 118-120 °C decomposed); $\boldsymbol{R_f}$ 0.31 (7:3 PE/EtOAc); $\boldsymbol{\delta_H}$ (**400 MHz**, $\mathbf{CDCl_3}$) 4.08 (4 H, br s, *H-5*, *H-6*), 4.02 (4 H, br s, *H-1*, *H-4*); $\boldsymbol{\delta_C}$ (**100 MHz**, $\mathbf{CDCl_3}$) 131.6 (*C-2*, *C-3*), 58.8 (*C-1*, *C-4*), 24.3 (*C-5*, *C-6*); **m/z** (**ESI**) 302 $[MH]^+$. Calcd. for $C_6H_9{}^{79}Br{}^{79}BrO_2S$: 302.8685. Found: $[MH]^+$, 302.8695 (−3.3 ppm error). Data consistent with those previously reported in the literature.[142]

Lab. Book: ***LNB0149-012-03***.

Further elution gave 3-bromomethylene-4-methyl-2,5-dihydrothiophene-1,1-dioxide (**242**) (29.8 mg, 0.133 mmol, 29%) as a brown amorphous solid.

3-Bromomethylene-4-methyl-2,5-dihydrothiophene-1,1-dioxide (242)[106]

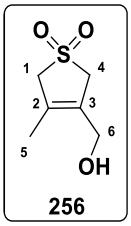


242

To a solution of cyclic sulfone **240** (100 mg, 0.680 mmol, 1.0 eq.) in CCl_4 (2.5 mL) was added NBS (181.6 mg, 1.02 mmol, 1.5 eq.) and benzoyl peroxide (1:1 with plasticiser dicyclo phthalate, 8.30 mg, 0.034 mmol, 0.05 eq.). The reaction mixture was stirred at reflux overnight, cooled to room temperature, diluted with CH_2Cl_2 (10 mL) and quenched with H_2O (10 mL). The aqueous layer was further extracted with CH_2Cl_2 (2 × 10 mL), the organic phase was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo* to give the title compound **242** as a mixture with cyclic sulfone in a 6:1 ratio which was used without further purification: **mp** 83-85 °C decomposed (Lit.[107] 81-82 °C decomposed); $\boldsymbol{R_f}$ 0.29 (7:3 PE/EtOAc); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 1380 (CH_3 bend), 1289 (S=O stretch), 1108 (S=O stretch), 823 (CH_2 bend), 564 (C-Br stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, $\mathbf{CDCl_3}$) 4.06 (2 H, br s, *H-6*), 3.95-3.93 (2 H, m, *H-4*), 3.84-3.82 (2 H, m, *H-1*), 1.90 (3 H, s, *H-5*); $\boldsymbol{\delta_C}$ (**100 MHz**, $\mathbf{CDCl_3}$) 131.9 (*C-2*), 126.6 (*C-3*), 61.2 (*C-1*), 58.0 (*C-4*), 26.0 (*C-6*), 14.9 (*C-5*); **m/z** (**ESI**) 246 $[MNa]^+$. Calcd. for $C_6H_9{}^{79}BrNaO_2S$: 246.9399. Found: $[MNa]^+$, 246.9382 (6.9 ppm error). Data consistent with those previously reported in the literature.[107]

Lab. Book: ***LNB0149-012-04/05***.

3-Hydroxymethylene-4-methyl-2,5-dihydrothiophene-1,1-dioxide (256)

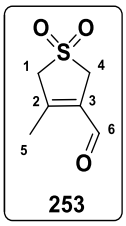


256

To a solution of CF_3CO_2Ag (42.9 mg, 0.194 mmol, 2.0 eq.) in H_2O (0.350 mL) was added mono-brominated compound **242** (21.8 mg, 0.097 mmol, 1.0 eq.). The reaction mixture was stirred at room temperature overnight. The reaction mixture was filtered through a PVC filter (0.45 μm), washed with EtOAC (3 mL) and the filtrate was concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (2:8 heptane/EtOAc) to afford the *title compound* **256** (16.2 mg, 0.100 mmol, 100%) as a yellow oil: $\boldsymbol{R_f}$ 0.20 (2:8 heptane/EtOAc); $\boldsymbol{\upsilon_{max}/cm^{-1}}$ (neat) 3490 (O-H stretch), 1407 (CH_3 bend), 1294 (S=O stretch), 1253 (C=O stretch), 1160 (S=O stretch); $\boldsymbol{\delta_H}$ (**400 MHz**, **$CDCl_3$**) 4.31 (2 H, br s, *H-6*), 3.92 (2 H, br s, *H-4*), 3.78 (2 H, br s, *H-1*), 1.84 (3 H, br s, *H-5*); $\boldsymbol{\delta_C}$ (**125 MHz**, **$CDCl_3$**) 128.4 (*C-3*), 126.6 (*C-2*), 60.9 (*C-1*), 58.3 (*C-6*), 57.6 (*C-4*), 14.7 (*C-5*); **m/z** (**ESI**) 185 $[MNa]^+$. Calcd. for $C_6H_{10}NaO_3S$: 185.0243. Found: $[MNa]^+$, 185.0242 (0.6 ppm error).

Lab. Book: ***LNB0149-074-03***.

3-Formyl-4-methyl-2,5-dihydrothiophene-1,1-dioxide (253)



253

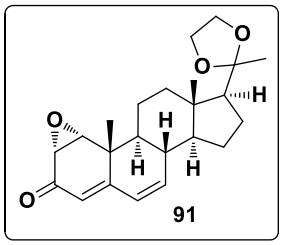
To a solution of allylic alcohol **256** (10.9 mg, 0.067 mmol, 1.0 eq.) in CH_2Cl_2 (0.5 mL) was added DMP (57.0 mg, 0.134 mmol, 2.0 eq.). The reaction mixture was stirred at room temperature overnight, filtered through Celite® and washed with Et_2O (5 mL). The filtrate was concentrated to dryness *in vacuo*. The crude residue was purified by column chromatography on silica gel (2:3 heptane/EtOAc) to afford the *title compound* **253** (5.30 mg, 0.033 mmol, 49%) as a yellow solid: **mp** 106-108 °C decomposed; $\boldsymbol{R_f}$ 0.31 (2:8 heptane/EtOAc); $\boldsymbol{\delta_H}$ (**400 MHz**, **$CDCl_3$**) 10.1 (1 H, s, *H-6*), 4.03 (2 H, br s, *H-4*), 3.99

(2 H, br s, *H-1*), 2.33 (3 H, br s, *H-5*); **δ_C** (**125 MHz**, **$CDCl_3$**) 184.9 (*C-6*), 149.4 (*C-2*), 131.8 (*C-3*), 62.5 (*C-1*), 54.7 (*C-4*), 15.1 (*C-5*); **m/z** (**ESI**) 183 $[MNa]^+$. Calcd. for $C_6H_8NaO_3S$: 183.0086. Found: $[MNa]^+$, 183.0078 (4.5 ppm error).

Lab. Book: ***LNB0189-003-02***.

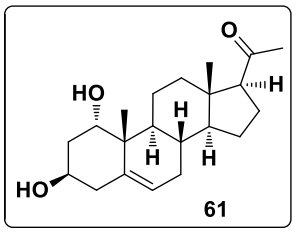
Appendix I. X-Ray Crystallography Data

1α,2α-Epoxy-20,20-ethylenedioxypregn-4,6-dien-3-one (**91**) (CCDC 983154)



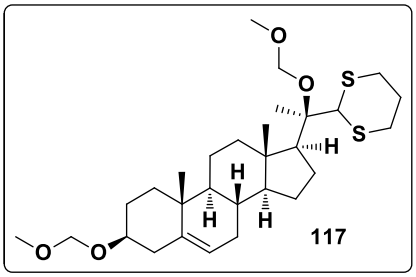
Identification code	rjkt1311a
Empirical formula	$C_{23}H_{30}O_4$
Formula weight	370.47
Temperature/K	110.00(14)
Crystal system	monoclinic
Space group	C2
a/Å, b/Å, c/Å	19.5214(8), 7.3857(2), 28.3837(11)
α/°, β/°, γ/°	90.00, 109.574(5), 90.00
Volume/Å^3	3855.8(3)
Z	8
ρ_{calc}mg/mm^3	1.276
m/mm^{-1}	0.086
F(000)	1600.0
Crystal size/mm^3	0.2645 × 0.1023 × 0.0675
2Θ range for data collection	5.94 to 56.28°
Index ranges	$-19 \le h \le 25$, $-5 \le k \le 9$, $-35 \le l \le 21$
Reflections collected	7868
Independent reflections	5739[R(int) = 0.0227]
Data/restraints/parameters	5739/1/493
Goodness-of-fit on F^2	1.091
Final R indexes [I>=2σ (I)]	R_1 = 0.0494, wR_2 = 0.1195
Final R indexes [all data]	R_1 = 0.0569, wR_2 = 0.1245
Largest diff. peak/ hole/ e Å^{-3}	0.30/−0.25

1α,3β-Dihydroxy-5-pregnen-20-one (**61**) (CCDC 983153)



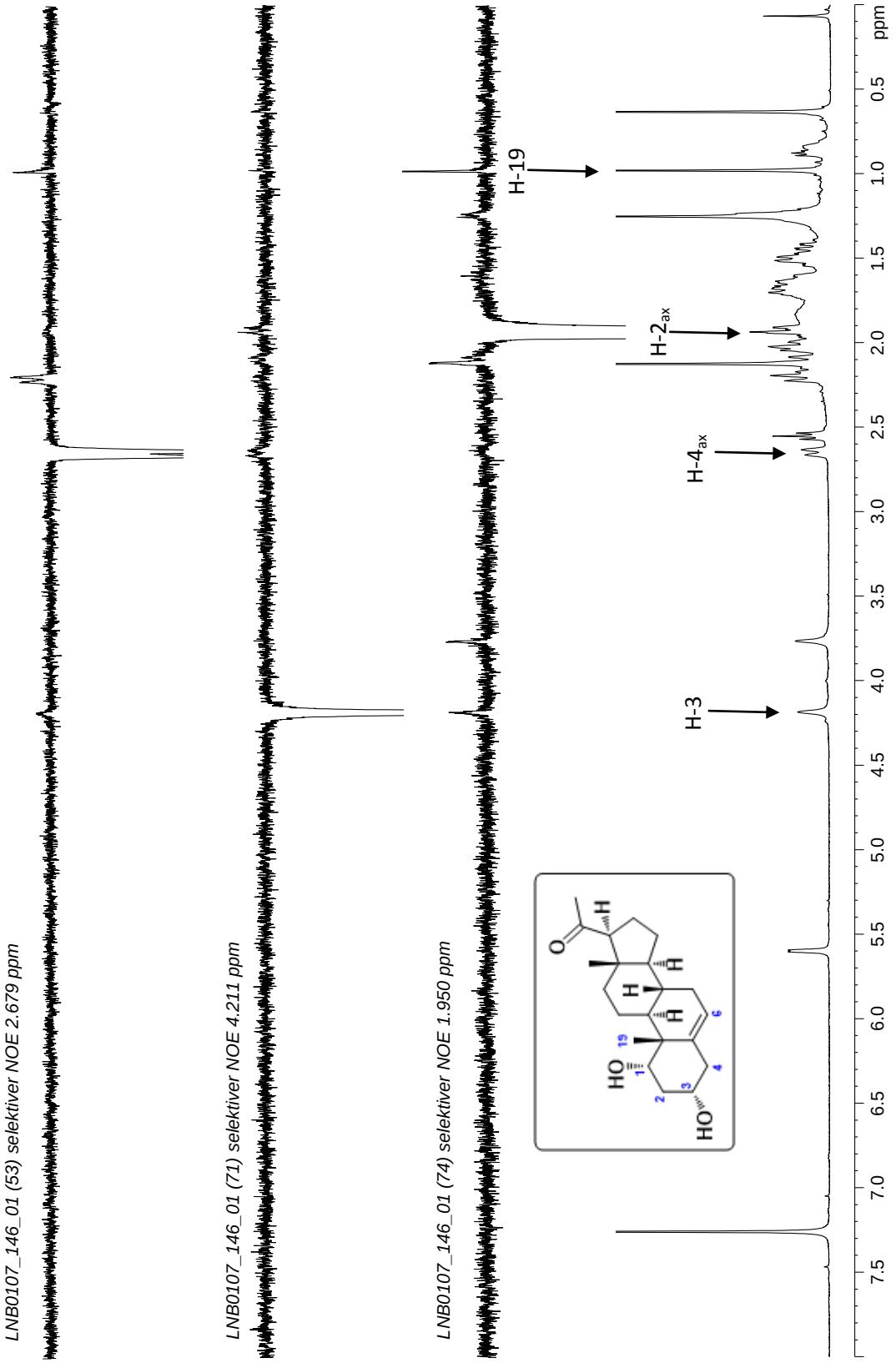
Identification code	rjkt1310
Empirical formula	$C_{21}H_{32}O_3$
Formula weight	332.47
Temperature/K	110.05(10)
Crystal system	tetragonal
Space group	$P4_32_12$
a/Å, b/Å, c/Å	11.48385(11), 11.48385(11), 27.9202(4)
α/°, β/°, γ/°	90.00, 90.00, 90.00
Volume/Å^3	3682.08(7)
Z	8
ρ_{calc}mg/mm^3	1.199
m/mm^{-1}	0.078
F(000)	1456.0
Crystal size/mm^3	0.3692 × 0.2032 × 0.1302
2Θ range for data collection	5.8 to 64.16°
Index ranges	$-15 \leq h \leq 15$, $-16 \leq k \leq 13$, $-41 \leq l \leq 41$
Reflections collected	18861
Independent reflections	5919[R(int) = 0.0343]
Data/restraints/parameters	5919/0/228
Goodness-of-fit on F^2	1.095
Final R indexes [I>=2σ (I)]	R_1 = 0.0443, wR_2 = 0.1142
Final R indexes [all data]	R_1 = 0.0501, wR_2 = 0.1175
Largest diff. peak/ hole/ e Å^{-3}	0.42/−0.20

(20*R*)-20-Dithiane-3β,20*R*-bismethoxymethylenoxypregn-5-ene (**117**) (CCDC 983152)



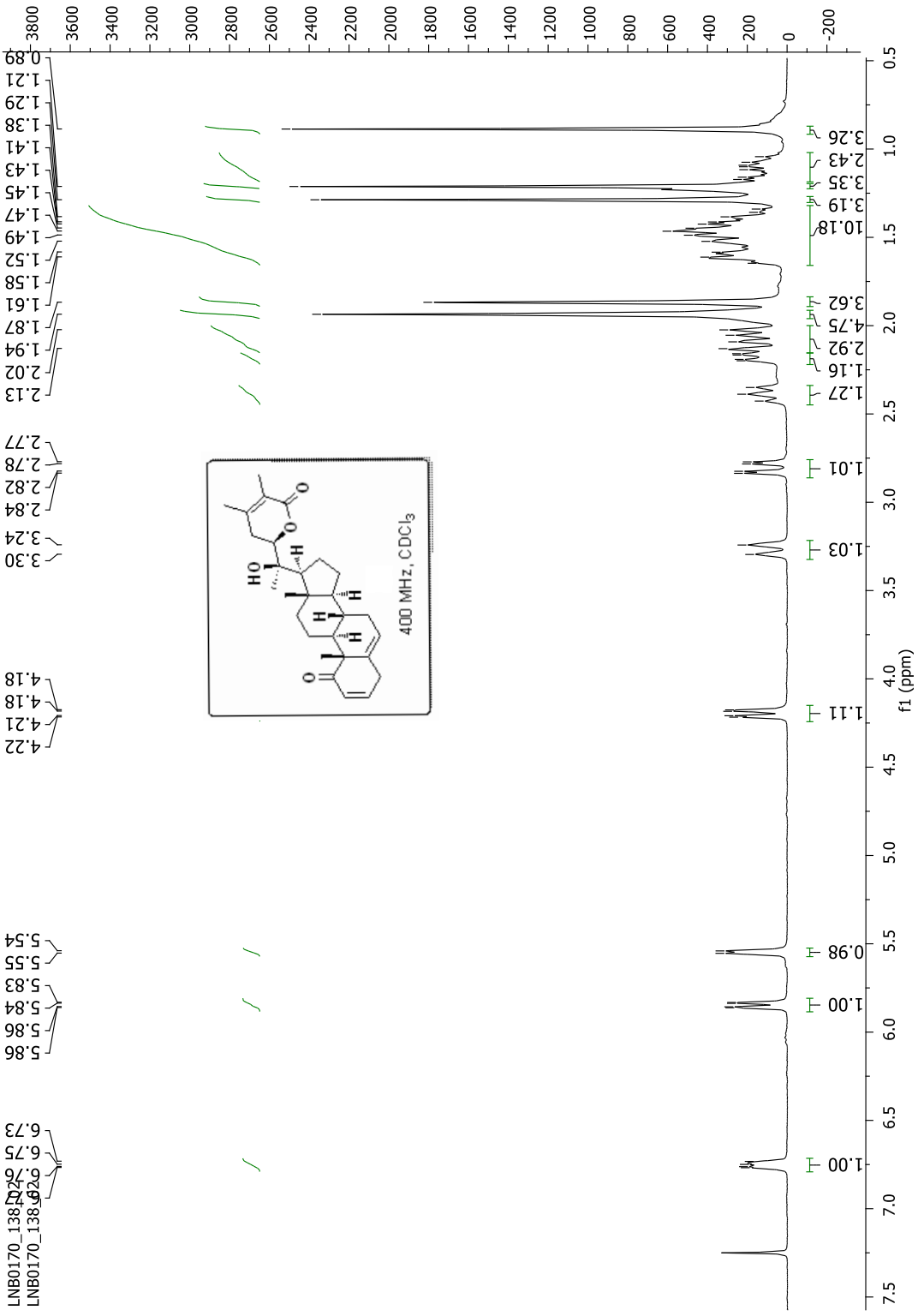
Identification code	rjkt1208
Empirical formula	$C_{29}H_{48}O_4S_2$
Formula weight	524.79
Temperature/K	110.00(10)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å, b/Å, c/Å	6.79761(16), 9.1752(3), 45.2097(12)
α/°, β/°, γ/°	90.00, 90.00, 90.00
Volume/Å^3	2819.71(14)
Z	4
ρ_{calc}mg/mm^3	1.236
m/mm^{-1}	0.221
F(000)	1144.0
Crystal size/mm^3	0.3417 × 0.2004 × 0.0263
2Θ range for data collection	6.06 to 60.06°
Index ranges	$-9 \le h \le 9$, $-8 \le k \le 12$, $-35 \le l \le 63$
Reflections collected	13133
Independent reflections	8139[R(int) = 0.0474]
Data/restraints/parameters	8139/36/321
Goodness-of-fit on F^2	1.146
Final R indexes [I>=2σ (I)]	R_1 = 0.1145, wR_2 = 0.2431
Final R indexes [all data]	R_1 = 0.1211, wR_2 = 0.2463
Largest diff. peak/ hole/ e Å^{-3}	1.30/−0.86

Appendix II. nOe Spectra for 1α,3α-Dihydroxy-5-Pregnen-20-One (102)

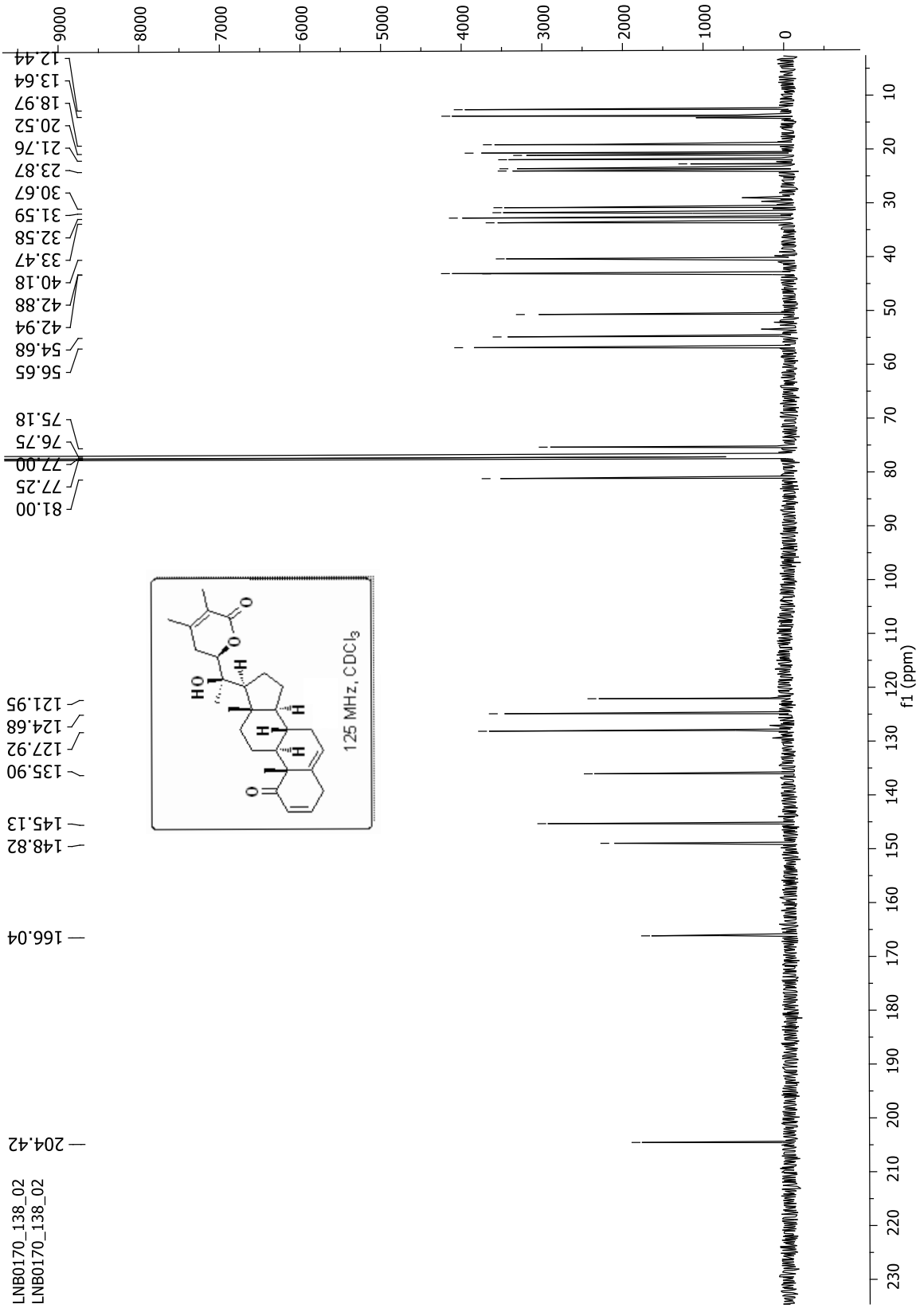


Appendix III. ^{1}H- and ^{13}C-NMR Spectra for 14,17-Dideoxy-17-Epi-Withanolide F (24)

^{1}H-NMR spectrum of 14,17-dideoxy-17-*epi*-withanolide F (**24**)

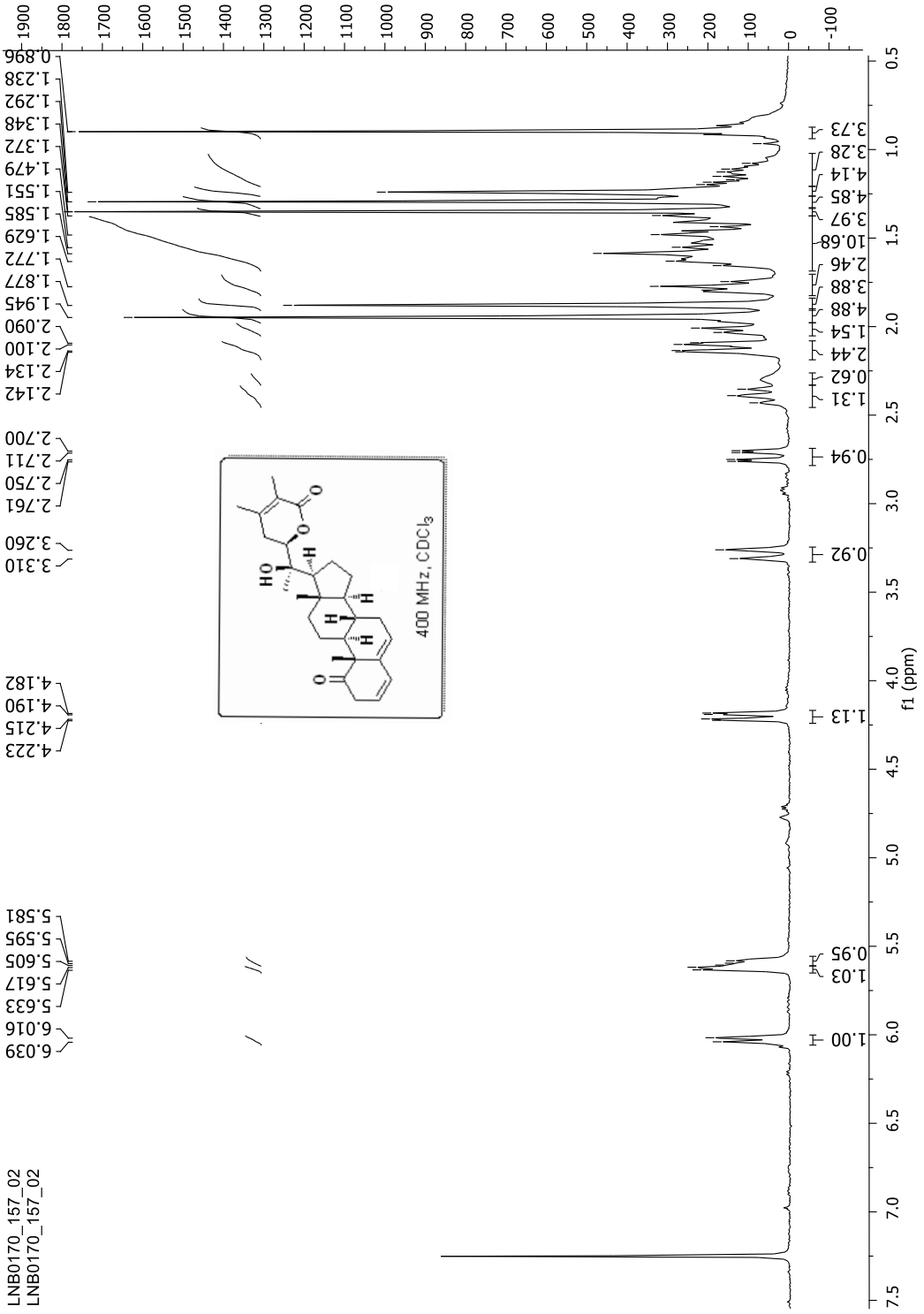


^{13}C-NMR spectrum of 14,17-dideoxy-17-*epi*-withanolide F (**24**)

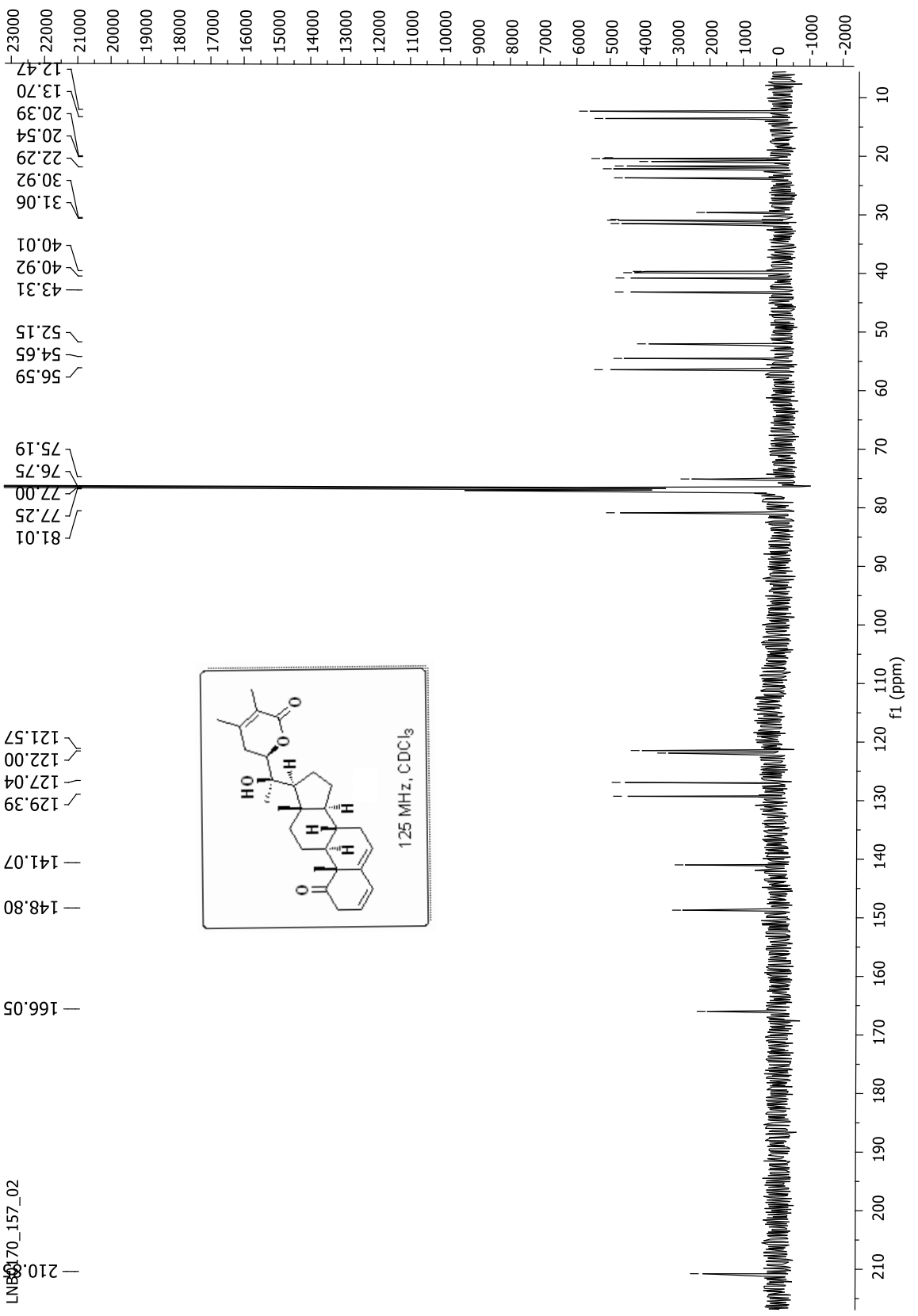


Appendix IV. ^{1}H- and ^{13}C-NMR Spectra for 3,4-Dihydro-$\Delta^{3,4}$-14,17-Dideoxy-17-Epi-Withanolide F (213)

^{1}H-NMR spectrum of 3,4-dihydro-$\Delta^{3,4}$-14,17-dideoxy-17-*epi*-withanolide F (**213**)



^{13}C-NMR spectrum of 3,4-dihydro-$\Delta^{3,4}$-14,17-dideoxy-17-*epi*-withanolide F (**213**)



Abbreviations

The following abbreviations are used within the dissertation:

Ac	Acetyl
AcOH	Acetic acid
ADP	Allyl diethyl phosphate
aq.	Aqueous
br	Broad
brsm	Based on recovered starting material
Bz	Benzoyl
Bu	Butyl
°C	Degrees Celsius
cat.	Catalytic
CCDC	Cambridge Crystallographic Data Centre
COSY	COrrelated SpectroscopY
δ	Chemical shift
d	Day
d	Doublet
dba	Dibenzylideneacetone
DBDMH	Dibromodimethylhydantoin
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-*p*-benzoquinone
DHP	Dihydropyran
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DME	Dimethylether or Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	Dimethyl sulfoxide
E	Entgegen, *trans*

$E1_{CB}$	Unimolecular conjugate base elimination
E2	Bimolecular elimination
e.e.	Enantiomeric excess
eq.	Equivalent
ESI	Electrospray ionisation
Et	Ethyl
g	Gram(s)
Glc	Glucose
h	Hour(s)
Hh	Hedgehog
HMBC	Heteronuclear Multiple Bond Correlation
HMPA	Hexamethylphosphoramide
HRMS	High Resolution Mass Spectrometry
HSQC	Heteronuclear Single Quantum Coherence
HWE	Horner-Wadsworth-Emmons
Hz	Hertz
i	*iso*
IBX	2-Iodoxybenzoic acid
IC_{50}	Half maximal Inhibition Concentration
IR	Infra-red (spectroscopy)
IUPAC	International Union of Pure and Applied Chemistry
J	Coupling constant in Hertz
LDA	Lithium diisopropylamide
LiCHA	Lithium isopropyl cyclohexylamide
LiHMDS	Lithium hexamethyldisilazane
Lit.	Literature
m	*meta*
m	Multiplet
M	Molarity
***m*-CPBA**	3-Chloroperbenzoic acid
Me	Methyl
mg	Milligram(s)
MHz	Mega Hertz
min	Minute(s)

mL	Milliliter(s)
mmol	Millimole(s)
mp	Melting point
MPO	4-Methoxypyridine-*N*-oxide
mol	Mole(s)
MOM	Methoxymethyl ether
Ms	Methanesulfonyl
m/z	Mass to charge ratio
n	Normal
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
nm	Nanometre
NMO	*N*-Methylmorpholine N-oxide
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
o/n	Overnight
p	*p*ara
PCC	Pyridinium chlorochromate
Pd/C	Palladium on carbon
PDC	Pyridinium dichromate
PE	Petroleum Ether (40 - 60 °C)
Ph	Phenyl
PIDA	(Diacetoxyiodo)benzene
PPh_3	Triphenylphosphine
ppm	Parts per million
Pr	Propyl
Pv	Pivaloyl
***p*-TsOH**	*p*-Toluenesulfonic acid
RCM	Ring-closing metathesis
R_f	Retention factor
rsm	Recovered starting material
rt	Room temperature
s	Singlet

s	*sec*
sat.	Saturated
t	*tert*
TBAF	Tributylammonium fluoride
TBD	Triazabicyclodecene
TBDMS	*tert*-Butyldimethylsilyl
TBS	*tert*-Butyldimethylsilyl
TBSOTf	*tert*-Butyldimethylsilyl- trifluoromethane sulfonate
Tf	Trifluoromethanesulfonyl
TFAA	Trifluoroacetic anhydride
Tf_2O	Trifluoromethanesulfonic anhydride
THF	Tetrahydrofuran
THP	Tetrahydropyran
TLC	Thin Layer Chromatography
TMSI	Trimethylsilyliodide
$(TMS)_2NH$	Bis(trimethylsilyl)amine
TPAP	Tetrapropylammonium perruthenate
TPP	*meso*-tetraphenylporphyrin
Triton B	Benzyltrimethylammonium hydroxide
Ts	Toluenesulfonyl
***p*-$TsOH.H_2O$**	*p*-Toluenesulfonic acid monohydrate
UV	Ultra-Violet
υ	Wavenumbers
w/w	Weight per weight
Z	Zusammen, *cis*

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